Masonic Cancer Center, University of Minnesota
Cancer Experimental Therapeutics Initiative

DT2219 Immunotoxin for the Treatment of Relapsed or Refractory CD19 (+) and/or CD 22 (+) B-Lineage Leukemia or Lymphoma

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Revision History

Revision #	Version Date	Summary Of Changes	Consent Changes
	12/18/2014	original to CPRC	
	01/20/2015	In response to CPRC's initial review, original to FDA and IRB: Section 11 – correct stopping rule calculations Page 19 – clarify requirements and procedures for an individual patient to continue on DT2219ARL after experiencing a DLT or stopping rule event, edit elsewhere in the protocol to match changes Other edits as detailed in the CPRC stip response letter Additional edits: • Replace DT2219ARL with DT2219 in title and throughout document, replace treatment course with treatment cycle • Section 7.2 Simplify the research related lab draws • Clarify follow-up ends at 1 year for all patients	n/a
n/a	03/30/2015	In response to FDA's review (interim version not submitted to CPRC/IRB): • Revise the Phase II component to use Simon's Optimum two-stage design with each disease assessed independently. Stage 1 will enroll 9 lymphoma patients and 9 leukemia patients (including any treated at MTD during phase I and completed 1 cycle) and if 1 more responses, stage 2 will be activated enrolling an additional 8 patients per disease cohort – previous version stratified by diagnosis enrolling 19 patients per type. • Section 2.4 – update table 1 • Revise definition of dose limiting toxicity • Add that a grade 3 or higher hypersensitivity reaction to DT2219 will result in permanent discontinuation of the study drug • Clarify to be eligible for Re-Treatment a patient must meet the eligibility criteria in section 4 and test negative for antibodies to be eligible and that treatment will be per section 6 of the protocol and the schedule of tests and procedures will be guided by section 7 with follow-up for survival thorough 1 year after 1st re-treatment dose • Add toxicity assessment to the standard of care chart in section 7.1 to occur at every patient encounter • Add a final treatment visit at day 50 (approximately 30 days after the last dose of DT2219) • Define in section 9.2 that all adverse events grade 3 or greater, regardless of attribution or expectedness, will be documented in OnCore on the AE log form • Limit targeted toxicity collection to the 1st cycle of DT2219 • Clarify the process for DLT and stopping rule events form processing in section 9.2 based on MCC CTO SOPs • Recalculate the stopping rule to be more stringent • Add antibody testing to cycle 3, previously 1 and 2 only	yes
n/a	04/28/2015	In response to FDA review (interim version not submitted to CPRC/IRB) • Sections 6.2.1 and 11.1 – delete grade 4 transaminase elevations and the selected grade 3 events occurring after completion of the DT2219 infusion from the definition of DLT • Sections 6.1, 6.3, and 6.5 - update to read if a grade 2 or greater hypersensitivity reaction occurs despite pre-medication, the patient will be permanently discontinued. • Section 9.2 – revise to record all adverse events regardless of grade, attribution and expectedness in the Cancer Center's clinical database (OnCore) from the 1st infusion until 30 days after the last infusion or the start of a new therapy, whichever comes 1st; expanded the procedure for potential serious adverse event recording and reporting • Section 11.5 – delete the exclusion that grade 4 transaminase elevations need to persist for more than 2 weeks to be considered excessive toxicity for the early study stopping rule • Appendix IV – replace anaphylaxis with hypersensitivity reaction in targeted toxicity	
1	07/28/2015	1st submission to the IRB/CPRC since January 2015 version – all FDA mandated changes summarized in the 3/30/2015 and 4/28/2015 are incorporated in this version, plus the following additional changes:	yes

Revision #	Version Date	Summary Of Changes	Consent Changes
		• Synopsis and Section 1.3 – update correlative objective regarding neutralizing antibody from "measure level of" to "test for presence of" neutralizing antibody • Section 4.5 inclusion criteria clarification of recovery from previous treatments by specifying "acute" toxicities and must have recovered to "grade 1 or better". Also removed waiting period since last treatment in patients with rapidly progressing disease as defined in section 4.5. • Section 4.13 exclusion criteria – replace "uncontrolled" with "untreated" systemic infection • Section 6.5 – replace "despite pre-medication" in regards to grade 3 toxicity as all patients are pre medicated and clarify with a reoccurrence of toxicity despite pre-medication "with methylprednisone • Section 7.1 – add BM Bx to the 30 day screening window, tweak day 1 tests and procedures to indicate specific days rather than "x" • Section 9.2 – add disease progression (in addition to start of new therapy) as a situation when AE monitoring and follow-up would end • Section 11.3 – Correlative endpoints: add "documentation of neutralizing antibody presence" in addition to measuring its level. • Minor edits section 4.7 replace PFTs with DLCOcorr; section 4.10 expand consent statement to include "with appropriate parent/guardian consent and minor information sheet for participants < 18 years of age" since minors may be enrolled; sections 5.4, 9.2, and 10.2 - replace Study Nurse with Study Coordinator; Section 6.1 minor edits including deletion of duplicative language • Update to current protocol template – section 9.2 and 10.3 • Update appendix I – Eligibility checklist	
	12/15/2015	Interim version – not submitted to IRB Remove Jeffrey Miller as a co-investigator	no
2	05/10/2016	• Modify treatment schedule to allow flexibility using guidelines of at least 48 hours, but not more than 72 hours between doses within a 4 dose set with further modification to accommodate rare instances (e.g. Monday holiday) • Section 4.8 – remove requirement to stay for 48 hours after the 4 and 8th doses from eligibility • Section 4.12 – simplify active CNS leukemia exclusion • Section 6.1 – criteria for additional treatment cycles – clarify presence of neutralizing antibodies at any time (not just after the 1st cycle) will deem patient ineligible for future treatment courses • Section 7.1 add footnote to day 10 and 24 visits that only apply to phase I cycle 1 • Section 7.2 – revise and update research related testing - Reduce the number of days PK samples will be collected, but increase the number of samples - Delete days 10 and 29 as sample collection days, replace it with day 22-24 time point - Increase neutralizing ab sample from 2 ml to 5 ml, except at baseline collect 10 ml - Add 2 green top tubes for immune environment assessment - Add additional bone marrow sample for research at the time of each SOC BM biopsy - Add a tumor or lymph node biopsy pre-treatment and optional post-treatment - Revise and add footnotes to match table - All samples to go to TTL (previously Vallera's lab) - Add new sections detailing neutralizing antibody testing (sect 7.2.2), pre-treatment tumor biopsy (sect 7.2.3), and post-treatment tumor biopsy (sect 7.2.4) Additional clarifications and edits including: • Synopsis and section 1.3 – re-word correlative objective to match endpoint in section 11.3 • Section 4.2, Appendix I – reword for clarity • Section 6.1 – clarify DT2219 will be piggy backed onto an existing line and dosing will be based on Day 1 (-3 days) weight • Section 7.1 – SOC table of events – clarify PET/CT requirements for lymphoma pts, clarify footnote #1, clarify which baseline tests can be done within 30 days of start • Section 9.2 – edit adverse event collection for clarity	yes

Revision #	Version Date	Summary Of Changes	Consent Changes
		• Section 11.5 – edit for clarity • Update title page, page 2 and sections 6.6 and 10.3 : IND sponsor transferred to V. Bachanova (PI) – paperwork previously submitted to FDA, retain Dr. Vallera on cover page as study agent design and production	
3	11/10/2016	Begin enrollment at 80 mcg/kg per protocol design with the following adjustments: • Add a separate screening consent form to collect 10 cc of blood to test for the presence of diphtheria antibodies prior to full work-up • Schema and section 6.1 - shorten duration of infusion by half – 1st infusion over 2 hours (previously 4 hours) and all subsequent infusions as 1 hour (previously 2 hours), Section 6.1 only - reduce post infusion monitoring to 30 minutes; remove post-DT2219 normal saline infusion language, and cut back on hydrocortisone pre-med dose (from 100 mg to 25-50mg) • Section 4 – remove from eligibility the requirement to stay in the Twin Cities metropolitan area during treatment – will be reiterated at time of consent • Section 7.2: Reduce PK times to mid infusion and end of infusion • Section 9.2 update targeted toxicity time points to match 30 minute post-infusion monitoring and clarify time points may be adjusted or eliminated to match SOC visits in section 7.1 • Update co-investigators on cover page – replace M Verneris who left the institution with Peter Gordon, MD/PhD • Other minor edits and updates to protocol template	Yes and add screening consents for antibody testing
4	03/06/2017	Declare DT2219 MTD at 60 µg/kg/dose and proceed to Phase II expansion • Section 4 - In response to liver function related toxicity seen at 80 µg/kg/dose, revise patient eligibility to stricter liver function requirements and exclude patients with active Hepatitis B or Hepatitis C (virus detectable by PCR) • Section 6.1 – correct pediatric dose conversion for hydrocortisone • Section 6.3 - Add management of increased liver function tests • Section 7: Add hepatitis B and C screening at baseline • Other minor edits	yes
5	07/10/2017	• Section 6.1 - clarify use of allopurinol is at the treating physician's discretion as part of good medical care and is not required as part of the study treatment plan. • Minor edits including correcting CPRC number in section 1 of the footer, update expediting reporting table in section 9.3, add new DSMP link in section 10.3	yes, treatment consent

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Table of Contents

Protocol Synopsis

DT2219 Immunotoxin for the Treatment of Relapsed or Refractory CD19 (+) and/or CD 22 (+) B-Lineage Leukemia or Lymphoma

Study Design:

This is a phase I/II study of DT2219 for the treatment of relapsed or refractory CD19 (+) and/or CD 22 (+) B-lineage leukemia and lymphoma. The study consists of two phases - a phase I dose/schedule finding component using the maximum tolerated dose identified during the previous phase I study, but with a higher number of doses and a two-stage phase II extension component to confirm safety and make a preliminary determination of the activity level by disease using the dose identified in phase I.

Patients will receive a minimum of one cycle of DT2219 as an intravenous infusion days 1, 3, 5, 8 and days 15, 17, 19 and 22 of a 28 day treatment cycle. A disease reassessment will be done at day 29. If a patient has clinical benefit and no unacceptable side effects, they may receive up to 2 additional cycles of DT2219 until disease progression, unacceptable toxicity and/or development of antibodies.

The primary goal of the dose/schedule finding component is to determine if the maximum tolerated dose (MTD) of DT2219 identified in our previous dose escalation study can be repeated after a short break. Enrollment will begin at the DT2219 dose of 60 µg/kg/dose using an eight dose schedule with the ability to move up or down a dose level (40 or 80 µg/kg/dose) in subsequent patients based on the tolerance of 60 µg/kg. Tolerance is evidenced by an inability to receive at least 6 out of 8 planned doses at the assigned dose level. If toxicity develops, an individual patient may move to a lower dose-level to allow administration of 8 doses. A minimum of 6 patients will be enrolled to confirm that the previous MTD is tolerable when used on an 8 dose schedule. The phase I component was completed in March 2017 with 60 µg/kg/dose declared as the MTD.

The MTD from phase I will be carried forward into a two-stage phase II component to confirm safety and make a preliminary determination of the activity level for non-Hodgkin lymphoma (NHL) patients (Arm 1) and leukemia (Leukemia) patients (Arm 2).

Primary Objective:

Phase I Dose/Schedule Confirmation: To determine if the maximum tolerated dose (MTD) of DT2219 dose of 60 µg/kg/dose identified during the previous phase I study is well tolerated on an 8 dose schedule of day 1, 3, 5, 8 and day 15, 17, 19 and 22

Phase II Component: To establish a preliminary estimate of overall response at day 29 while gaining a more detailed toxicity profile of repeat dosing of DT2219

Secondary Objectives:

- To determine incidence of serious adverse events through day 29
- To determine duration of response for up to 1 year
- To evaluate 1 year disease-free survival
- To evaluate 1 year overall survival
- To determine time to relapse/progression for up to 1 year

Correlative Objectives:

- To determine the pharmacokinetic (PK) profile (Cmax, T1/2, AUC, Cl, Vd) of DT2219
- To document presence and to measure levels of human anti-DT2219 antibodies and correlate with response
- To determine if there is a correlation between PK parameters and toxicity or response
- To determine if the expression of the CD19 and CD22 cell surface antigens is affected by treatment with DT2219 using flow cytometric analysis of lymphoblasts in peripheral blood and bone marrow and B-lymphocytes in peripheral blood
- To correlate CD19 and CD22 surface antigen expression on patient blasts or lymphoma cells with response

Population:

Patients ≥ 12 years with relapsed or refractory CD19+ and/or CD22+ B-lineage leukemia/ lymphoma

Enrollment:

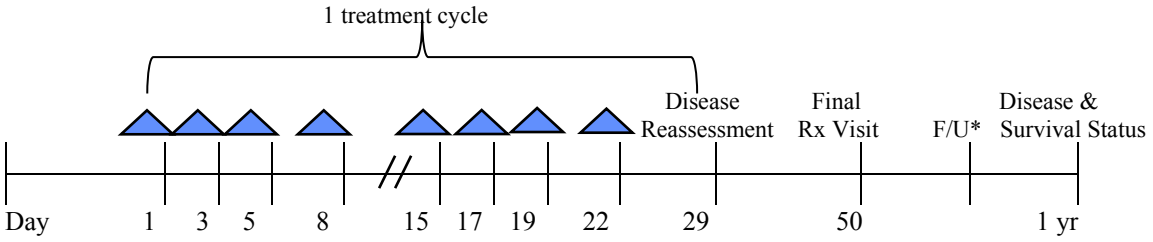
Phase I: Standard 3+3 design requiring 6 to 12 patients (completed March 2017)

Phase II: Two stage design by disease – assigned to Arm 1(NHL) or Arm 2 (Leukemia)

stage 1: enroll a total of 9 patients (including all treated at the MTD in phase I and evaluable after 1st cycle of treatment)

If 1 or more responds within the Arm, activate stage 2 enrolling an additional 8 patients to that Arm

Schema



DT2219 at assigned dose IV on day 1, 3, 5, and 8 and day 15, 17, 19, and 22

The day 1, 3, 5, 8 and day 15, 17, 19 and 22 dosing schedule is based on a Monday start day; however this is not always feasible. Therefore, general dosing rules will be followed within a 4 dose set: 1) each dose will be separated by a minimum 48 hours but 2) no more than 72 hours will lapse between doses except in cases where it is unavoidable (e.g. Monday holidays). Situations where the dosing falls outside of these guidelines will be discussed with and approved by the PI or her designee. No deviation will be filed in these cases.

The 1st dose will be administered over 2 hours; if well tolerated, subsequent doses may be given over 1 hour.

Adults may be treated in the outpatient setting (Early Phase Unit with Masonic Clinic or BMT Clinic, as appropriate for back-up). Pediatric patients will be admitted through the Journey Clinic to Masonic Children's Hospital for treatment.

Additional Treatment Cycles:
For patients experiencing clinical benefit (CR, PR, or SD per disease specific response criteria) at the time of re-assessment, up to 2 additional cycles of DT2219 may be given on the same schedule at the same or lower dose beginning no sooner than 7 days after the last dose of the previous cycle provided they meet the criteria in section 6.1

Final Treatment Visit – Day 50 or 30 days after the last dose of DT2219, whichever is shorter

F/U* – if in remission at the time of treatment end, patients will be followed every 3 months for disease re-assessment until relapse or progression or the start of a new treatment for a maximum of 1 year from the 1st dose.
Retreatment with DT2219 may be an option.

Phase I Component: (Completed March 2017 – MTD = 60 µg/kg/dose)
The phase I component will follow standard 3 or 6 patients per dose level. Enrollment will begin at dose level 1. Dose level -1 will be used only if dose limiting toxicity is encountered with the 1st group.

Dose Cohort	DT2219 Dose
-1	40 µg/kg/dose
1	60 µg/kg/dose
2	80 µg/kg/dose

Patients will receive a minimum of one cycle of DT2219. Dose escalation will proceed within each cohort according to the scheme found in section 11.1. Escalation to dose level 2 may not occur before the last patient in dose level 1 is at least 7 days from the last dose of the 1st treatment cycle to rule out dose limiting toxicity (DLT).

Dose limiting toxicity (DLT) is defined as any of the following occurring from study day 1 through 7 days after the last dose of DT2219 of cycle 1 and clearly not attributed to the primary malignancy or intercurrent illness**:**
- Any Grade 5 adverse event
- Grade 4 neutropenia or thrombocytopenia lasting for more than 7 days
- Grade 3 thrombocytopenia with bleeding
- Any Grade 4 non-hematologic adverse event during the DT2219 infusion
- Any Grade 3 non-hematologic adverse event occurring after completion of DT2219 infusion

Maximum tolerated dose (MTD) is defined as the dose level where no more than 1 out 6 patients experience DLT when at least 6 out of 8 planned DT2219 doses are given over 28 days

Phase II Component (stratify by diagnosis: Arm 1 - NHL, Arm 2 - Leukemia):
Two stage design – Stage 1: enroll 9 patients (including any from phase I treated at MTD and evaluable after 1st cycle of treatment), if 1 or more respond within a diagnosis, activate Stage 2 for that diagnosis: enroll 8 additional patients

1 Objectives

1.1 Primary Objectives

Phase I Dose/Schedule Confirmation: To determine if the MTD of DT2219 dose of 60 μg/kg/dose identified during the previous phase I study is well tolerated on an 8 dose schedule of day 1, 3, 5, 8 and day 15, 17, 19 and 22 of a 28 day treatment cycle.

Phase II Component: To establish a preliminary estimate of overall response at day 29 while gaining a more detailed toxicity profile of repeat dosing of DT2219

1.2 Secondary Objectives

- To determine incidence of serious adverse events through day 29
- To determine duration of response for up to 1 year
- To evaluate 1 year disease-free survival
- To evaluate 1 year overall survival
- To determine time to relapse/progression for up to 1 year

1.3 Correlative Objectives

- To determine the pharmacokinetic (PK) profile (Cmax, T1/2, AUC, Cl, Vd) of DT2219
- To document presence and to measure levels of human anti-DT2219 antibodies and correlate with response
- To determine if there is a correlation between PK parameters and toxicity or response
- To determine if the expression of the CD19 and CD22 cell surface antigens is affected by treatment with DT2219 using flow-cytometric analysis of lymphoblasts in peripheral blood and bone marrow and blood B-lymphocytes.
- To correlate CD19 and CD22 surface antigen expression on patient blasts or lymphoma cells with response

2 Background and Rationale

2.1 The Disease

The incidence of acute lymphoblastic leukemia (ALL) is 5,200 cases in 2007 including 2,400 children and adolescents and 2,800 adults. While 95% of children and 70% of adults achieve remission with aggressive induction combination chemotherapy, only 85% of children and 35% of adults are cured of their disease. Salvage treatments include further chemotherapy, tyrosine kinase inhibitors, antibody therapy and stem cell transplantation, but most relapsed patients suffer severe morbidities and death from chemo-resistant disease. Non-Hodgkin

lymphoma is the 6th most common malignancy in adults. Although curable by chemotherapy for over 60-70% of patient, patients refractory to chemotherapy have a poor prognosis.

An effective biologically based, molecularly targeted therapy for these patients is needed. One therapeutic approach would be to use recombinant immunotoxins (ITs). We have recently developed DT2219, a new recombinant bispecific antibody-targeted toxin with reactivity with most ALL blasts. The anti-CD19 Mab hybridoma HD37 and the anti-CD22 hybridoma RFB4 were used to create the IT. DT2219 was constructed using a hybrid gene encoding the first 390 amino acids of the diphtheria toxin (DT) and the VH and VL regions of anti-CD22 (sFv) and anti-CD19 (sFv). This IT takes advantage of the high level of expression of both the CD19 and CD22 antigens present on the surface of B-lineage leukemia cells. CD19 molecules expressing the HD37 epitope and CD22 molecules expressing the RFB4 epitope are present on a mean of 80% and 50% of B-precursor ALL blasts, respectively. We have demonstrated that DT2219 binds to B-lineage ALL cells and has potent *in vitro* anticancer activity against B-lineage lymphoma cells. In addition, our *in vivo* model significantly prolonged the survival of mice with established B-cell leukemia. Based on these results, we propose to conduct a phase I trial utilizing DT2219 in adults and adolescents with relapsed or refractory B-lineage leukemia or lymphoma.

2.2 The Treatment - DT2219

Monoclonal antibodies (MoAbs) when linked to toxic moieties form highly specific and potent anti-cancer agents called immunotoxins (ITs). Plant toxins and bacterial toxins including diphtheria toxin are highly potent such that even one single molecule in the cytoplasm is sufficient to kill a tumor cell. A variety of these agents are currently undergoing development for the treatment of hematologic malignancies [2]. Importantly, investigators have determined that when two ITs targeting two different cell surface receptors on the same tumor cell are combined, the anti-tumor effect is often superior than when the agents are used individually [3 - 5]. A mixture of two ITs targeting CD19 and CD22 using a deglycosylated ricin-A chain moiety as the toxin (Combotox) was recently proven to be effective in killing Pre-B ALL cells *in vitro* [6] and in curing SCID mice of disseminated leukemia *in vivo* [7].

Diphtheria toxin has recently been used in the development of several ITs currently undergoing testing for treating leukemia. A truncated form of diphtheria toxin conjugated to a single chain of IL2 known as DAB386IL2 tested in 22 patients with chronic lymphocytic leukemia (CLL) yielded a 27% response rate [8]. Another example is the recombinant diphtheria toxin fusion protein, DT388IL3, composed

of the translocation domain of diphtheria toxin fused to human interleukin-3. DT388IL3 has produced remissions in patients with acute myeloid leukemia at tolerable doses [9]. DT388 has also been fused to granulocyte-macrophage colony stimulating factor (GMCSF) and again produced remissions in acute myeloid leukemia but at doses producing hepatic injury [10].

2.3 Preclinical Studies

DT2219 has undergone *in vitro* testing on the Daudi Burkitt's lymphoma cell line known to highly express both CD19 and CD22. It was cytotoxic to Daudi cells with an IC50 of 0.3 nmol/L. DT2219 was also found to be reactive with leukemia cells obtained from two children with newly diagnosed Pre-B ALL. The cytotoxic effect was specific and reproducible. The cytotoxicity and reactivity of DT2219 was greater than the anti-cancer activity of either monovalent or bivalent ITs made with the anti-CD19 and anti-CD22 sFv alone prompting us to propose the use of the bispecific IT for this study [11].

In vivo, when DT2219 was given to SCID mice with established flank tumors, as i.p. injections of 20 μg (2.8 mg/m^2) for four doses, there was a significant reduction in tumor volume. To simulate leukemia, the investigators injected the same cells i.v. into mice resulting in the infiltration of all major organs. The mice were given nine daily injections of 20 μg of DT2219. The mice receiving treatment survived significantly longer than control mice receiving an irrelevant control.

2.4 Clinical Experience

In a phase 1 study conducted at Baylor Scott and White Medical Center, MD Anderson Cancer Center and the Masonic Cancer Center, University of Minnesota, patients received DT2219 in a single course at doses ranging from 0.5 μg/kg/day (1/500th of the MTD in rabbits) to 80 μg/kg/day intravenously (IV) over 2 hours (4 hours for 1st dose) every other day for 4 total doses (days 1, 3, 5 and 8). The dose was escalated in 9 cohorts until a dose limiting toxicity (DLT) was observed (Table 1). The first 15 patients were treated by rapid escalation design (dose cohorts 1-3) or by standard 3+3 dose escalation design (cohorts 4-7) at Baylor. The study then transferred to the University of Minnesota where the Continual Reassessment Method [12] was applied to the last 10 patients (dose cohorts 7 (last dose level at Baylor), 8, 9) with the goal to identify the dose level which corresponds to a desired toxicity rate of 33% or less using grade 3 or greater DT2219 related toxicity except blood pressure changes and fever as the targeted toxicity (based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4).

All 25 patients received a single course of therapy. One patient attained partial response after the 1st cycle and received an additional 4 dose course after the

protocol was amended with FDA and IRB approval. Twelve patients treated at doses ranging from 0.5 ug/kg/day to 20 ug/kg/day exhibited no or minimal adverse reactions (Table 1). All 13 patients treated at dose levels ≥40 ug/kg/day experienced adverse events (AE) attributed to drug treatment. No infusional toxicity was observed. The most common transient grade 1-2 AEs included weight gain (range 5-14% of baseline), peripheral edema, and hypoalbuminemia consistent with capillary leak syndrome, grade 1-2 fever and fatigue (Table 1). Most AEs were recognized during routine monitoring before the 2nd or 3rd dose of DT2219. All AEs were brief and resolved completely within one week. **TABLE 1. Treatment detail and adverse events**

Cohort	Escalation detail	DT2219 dose µg/kg/day	Doses received	Total dose per cycle (µg)	N	Drug related adverse effects (CTCAE v4.03 toxicity grade)	DLT
1	Rapid escalation	0.5	4	2.0	1	None	No
2		1.25	4	5.0	1	None	No
3		2.5	4	10	1	Gr 1 fever (n=1)	No
4	Standard escalation	5.0	4	20	3	None	No
5		10.0	4	40	4[a]	None	No
6		20.0	4	80	3	Gr 1 ALT elevation (n=1) Gr 2 ALT, AST elevation (n=1)	No
7		40.0	4[b]	160	3	Gr 1 AST, Gr 2 hypoalbuminemia (n=1) Gr 2 capillary leak syndrome (n=1) Gr 1 fatigue (n=1) Gr 3 legs weakness (n=1)	1
7	Continual Reassessment	40.0	4	160	2	Gr 2 hypoalbuminemia (n=1) Gr 2 capillary leak syndrome (n=1) Gr 1 hypokalemia (n=1)	No
8		60.0	4 [c,d]	240	5	Gr 1-2 capillary leak syndrome (n=2) Gr 3 capillary leak syndrome (n=1) Gr 2 anemia (n=1) Gr 3 or thrombocytopenia (n=2) Gr 2 fever (n=2) Gr 4 neutropenia (n=1) Gr 3 capillary leak sy (n=1) Gr 3 neutropenic fever (n=1) Gr 2 hearing loss (n=1) Gr 1 hypocalcemia (n=1)	1
9		80.0	4	320	3	Gr 1 hypokalemia (n=1) Gr 1-2 capillary leak syndrome (n=2) Gr 1 vomiting (n=1) Gr 3 hypokalemia (n=1) Gr 1 AST ALT elevation (n=2) Gr 2 fatigue (n=2)	No

[a]1 patient at the 10 µg/kg/day was less than 12 years old and enrolled after receiving permission from the local IRB [b] patient with DLT received 3 doses of DT2219 [c]1 patient at the 60 µg/kg/day was retreated 8 weeks later with 2nd cycle at dose 40 µg/kg/day.
[d] 1 patient was dose reduced for 4th injection to 40 µg/kg/day due to capillary leak syndrome

Two patients experienced DLTs: the first DLT occurred at the 40 µg/kg dose level in a 71-year-old patient with ALL who developed back pain along with acute lower

extremity weakness after the 3rd dose of study drug. While the patient had a recent history of CNS leukemia prior to enrollment, brain magnetic resonance imaging and cerebrospinal fluid studies at the time of AE were negative for leukemic CNS involvement. This patient died of rapidly progressive disease. No neurologic adverse effects of any grade occurred in the next 10 patients treated at this or higher doses (40-80 ug/kg). The second DLT event occurred at the 60 μg/kg dose level in a 55-year-old patient who developed grade 3 capillary leak manifested as hypoxemia, hypotension, pulmonary edema, and hypoalbuminemia in combination with febrile neutropenia. The patient was hospitalized and treated with oxygen, IV antibiotics, hydration and diuresis. Her symptoms improved with supportive care to grade 2 after 2-3 days and completely resolved in 10 days.

Twenty-five patients were evaluable for response, recognizing that only 9 patients in the highest dose cohorts had measurable drug levels. Treatment produced an objective tumor response in two of these patients. After a single course of DT2219 at dose level 40 μg/kg/day x 4, a 77-year-old patient with chemotherapy-refractory CLL experienced a 40% reduction in cervical and axillary adenopathy with decrease of an abdominal tumor mass at day 28 after treatment. A second response occurred in a 53-year-old patient with relapsed $CD19^{+}CD22^{+}$ diffuse large B cell lymphoma (dose level 60 μg/kg) who experienced a 75% reduction in size of lymphoma lesion after a single course complicated by a grade 3 capillary leak syndrome. Eight weeks later, after FDA approval, this patient received a second DT2219 course at a reduced dose of 40 μg/kg/dose x 4 which resulted in a complete resolution of a subcutaneous mass and pelvic lymphadenopathy. Both patients are alive and in remission, currently at 7 and 8 months after therapy.

2.5 Pharmacology

The diphtheria toxin component of DT2219 is a genetically engineered fusion toxin protein consisting of the amino acid sequences for the enzymatically-active portion of diphtheria fused to the sequence of the single chain Fv fragments of the antibodies targeting the CD19 and CD22 cell surface receptors.

The anti-CD19 and anti-CD22 sFv fragments replaced the native binding domain of diphtheria toxin and allow for the specificity of DT2219. The anti-CD19 sFv fragment recognizes an epitope present on the CD19 antigen. CD19 is a 95 KD glycosylated Type I integral membrane protein, highly expressed on B-cells at all stages of their maturation including B-precursor lymphoblasts and ALL patient blasts and mature B cell lymphoma cells. The anti-CD22 sFv fragment recognizes an epitope present on the CD22 antigen. CD22 is a 135 KD glycoprotein present on normal Pre-B and resting B cells, as well as a spectrum of B-cell tumors. It is

expressed on the majority of ALL lymphoblasts and some mature B cell lymphoma cells.

DT2219 pharmacokinetic data in rats showed a two compartment behavior with a first distribution half-life of 2 hours and a second phase half-life of 14 hours.

At the time of enrollment in our previous phase I study, most patients exhibited low peripheral blood (PB) B-cells counts (median B cell count 3.5% (<0.1 $x10^6$ cells/μL); range 0-52%; n=10) often associated with prior rituximab, corticosteroids and chemotherapy. The effect of DT2219 on B lymphocytes in a patient with an extramedullary ALL relapse shortly after allogeneic HCT was observed with gradual decline in number of PB CD19- and CD22-expressing cells after 4 doses of DT2219 (Figure 1A). The possibility that DT2219 may interfere with fluorochrome-labeled anti-CD19 and anti-CD22 was excluded by examining CD20-positive cells, which also declined over time. The B cell depletion was specific as CD3-positive T cell levels remained constant during the testing interval.

The circulating concentration of DT2219 was also measured in a functional pharmacokinetic bioassay. Patients treated at dose levels 0.5-20 μg/kg/day had no detectable drug in serum when sampled on day 1 and 8 at 15, 30, 45, 60, and 120 minutes post-infusion. All evaluable patients at the University of Minnesota treated with ≥40 μg/kg/dose (n=10) demonstrated detectable levels of DT2219 with the exception of one with preexisting antibodies to DT. The median area under the curve (AUC) after the 1st dose (4 hours infusion) was lower at a median of 285 μg/mL x minutes; (range 0-2020; n=8) compared to drug levels after the 4th dose (2 hours infusion; AUC median 1249 μg/ml x minutes; range 0-1692; n=7). A representative AUC is shown in Figure 1B. The drug half-life ranged from 59-110 minutes (n=4).

Because the recombinant immunotoxin contains a bacterial toxin, immunogenicity is expected and can be a major barrier to the potential activity of bacterial toxin-based drugs. We measured serum neutralizing antibodies (NAs) in all patients treated with ≥40 μg/kg/dose at days 1,8,15,29,35 and 42 (n=9). NAs developed in 3 evaluable patients (30%) at dose levels between 40-80 ug/kg at median of one week (range 1-2 weeks) after the 1st dose of DT2219. One patient had pre-formed anti-diphtheria toxin antibody which we detected at screening and attributed to prior DT immunization. In some patients the presence of NA inversely correlated with the serum concentration of DT2219 (Figure 1C), however no consistent pattern was recognized.

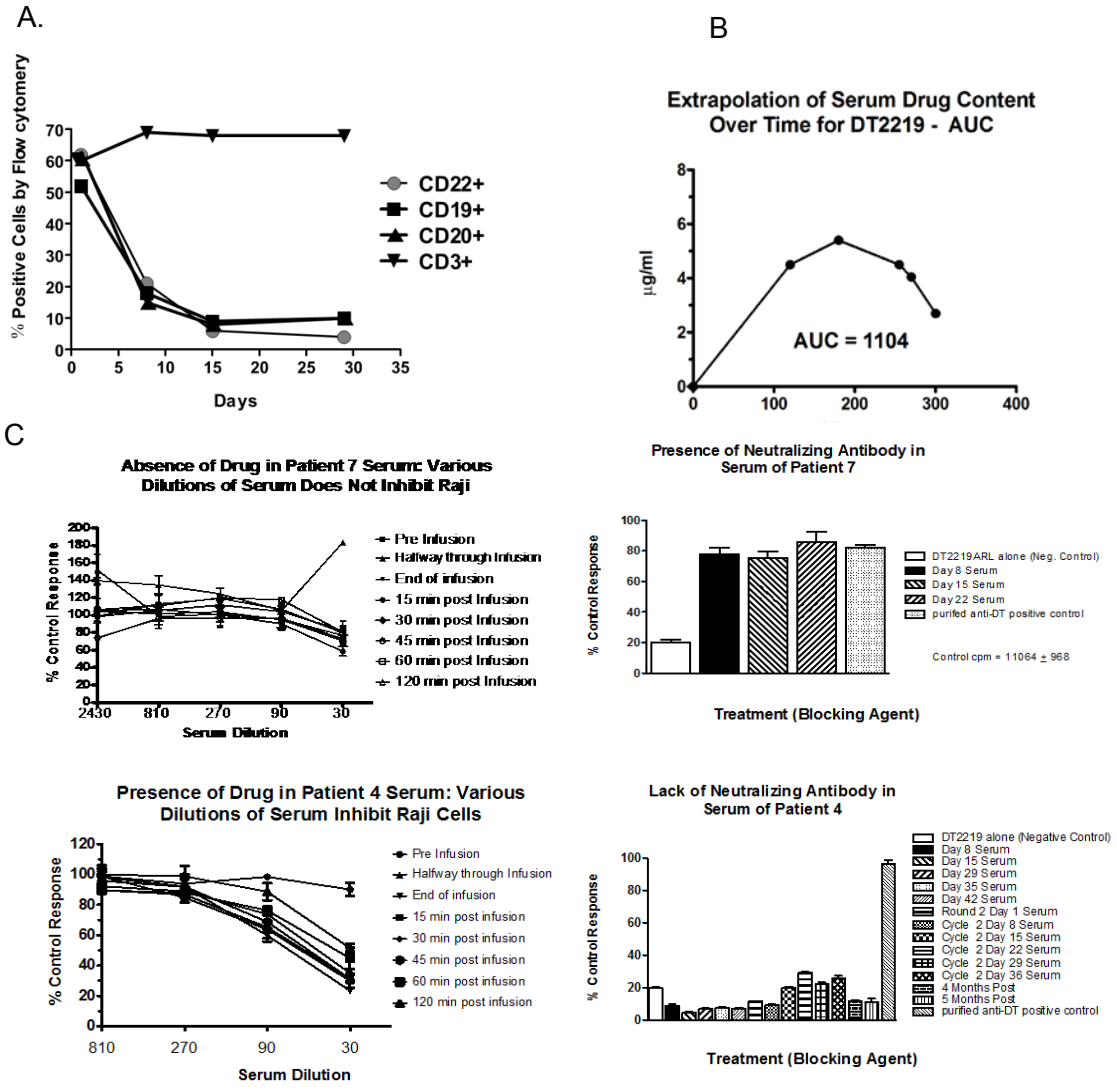


Figure 1

2.6 Study Rationale

In our previous phase I study we established the safety and dosing feasibility of DT2219. We also demonstrated that the current dosing schedule and route of administration achieves drug levels capable of biological and clinical response against CD19/22-expressing lymphoid malignancies refractory to standard therapies with a surprisingly low incidence of neutralizing antibody responses. The previous study also showed that, although MTD was not reached, the drug can be administered safely up to 80 ug/kg/day on a every other day schedule (day 1, 3, 5 and 8) for total of 4 doses. The first dose was infused over 4 hours as a safety precaution was always well tolerated. All other doses were administered over 2 hours. Interestingly, the AUC measured for the first dose was almost always lower than the AUC measured for the 4th dose suggesting the importance of shorter

infusion time for immunotoxins with brief half-life. Early on-target saturation also may play a role in low AUC at the onset of therapy, yet the DT2219 dosing in 4 infusions 1-2 days apart resulted to adequate drug levels, biological effectiveness, and tolerable toxicity. **Although clinical responses to DT2219 were observed at doses of 40 and 60 ug/kg/day, the 4 doses as administered in this trial maybe inadequate to induce deeper remissions.** In one patient who achieved partial remission after 1 cycle, an additional cycle led to complete tumor elimination. The rationale for improved efficacy with repetitive dosing is supported by others who are developing immunotoxin conjugates using bacterial toxins, such as the anti-CD22 moxetumomab pasudotox for hairy cell leukemia or SL-401, an interleukin 3 receptor-diphteria toxin fusion protein for myeloid malignancies [13-15].

In our experience, increasing the number of consecutive doses per cycle is unlikely to be tolerated; however the treatment schedule as proposed in this study with repetitive cycles of four every other day doses at least a week apart is worthy of exploration.

This study will begin at the lowest dose of DT2219 where clinical response was observed (60 ug/kg/day) and apply an 8 dose schedule over the same 28 day treatment cycle tested during the previous phase I study. If no dose limiting toxicity is encountered, a second cohort of patients will be treated at 80 ug/kg/day. The maximum tolerated dose from the phase I component will be used for an expansion disease based (NHL vs Leukemia) two stage phase II component as it is felt based on the previous phase I study a higher number of disease responses will be seen in NHL.

3 Study Design

This is a phase I/II study of DT2219 for the treatment of relapsed or refractory CD19 (+) and/or CD 22 (+) B-lineage leukemia and lymphoma. The study consists of two phases - a phase I dose/schedule finding component and a two-stage phase II component to confirm safety and make a preliminary determination of the activity level by diagnosis using the dose identified in phase I.

Patients will receive a minimum of one cycle of DT2219 given as a 1-2 hour infusion days 1, 3, 5, 8 and days 15, 17, 19 and 22. A disease reassessment will be done at day 29. If a patient has clinical benefit up to two additional cycles of DT2219 may be given until disease progression, unacceptable toxicity and/or development of antibodies. A final post-treatment visit will occur 30 days (approximately day 50) after the final dose of DT2219. Patients in a response at the time treatment is discontinued will be followed until disease progression or the start of a new therapy for a maximum of 1 year.

All patients, regardless of disease status will be followed for survival for 1 year from the 1st dose of study therapy.

The primary goal of the dose/schedule finding component is to determine if the maximum tolerated dose (MTD) of DT2219 identified in our previous dose escalation study can be repeated after a short break. Enrollment will begin at the DT2219 dose of 60 µg/kg/dose using an eight dose schedule with the ability to move up or down a dose level (40 or 80 µg/kg/dose) in subsequent patients based on the tolerance of 60 µg/kg. Tolerance is evidenced by an inability to receive at least 6 out of 8 planned doses at the assigned dose level. If toxicity develops, an individual patient may move to a lower dose-level to allow administration of 8 doses. A minimum of 6 patients will be enrolled to confirm that the previous MTD is tolerable when used on an eight dose schedule.

Once the MTD is determined, the final dose will be carried forward into a two-stage phase II component to confirm safety and make a preliminary determination of the activity level for Non-Hodgkin Lymphoma (NHL) patients (Arm 1) and B-cell lineage leukemia (Leukemia) patients (Arm 2). We will employ Simon's Optimum two-stage design [16] with the possibility to discontinue after the 1st stage if the response rate is low.

With the March 2017 revision, DT2219 at 60 µg/kg/dose was declared the maximum tolerated dose (MTD) and the study moved to phase II enrollment.

4 Patient Selection

Study entry is open to persons 12 years and older regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of a similar studies at the University of Minnesota.

Inclusion Criteria

4.1 Histologic verification of B-cell lineage leukemia or B cell non-Hodgkin lymphoma and evidence of relapse/refractory disease with the presence of CD19 and/or CD22 by flow cytometry or immunohistochemistry of bone marrow aspirate, peripheral blood or node/tumor biopsy

4.2 Relapsed/refractory disease that has failed conventional therapy and other therapies of higher priority

4.3 Age ≥ 12 years

4.4 Karnofsky Performance status of ≥ 60% or, if less than 16 years of age Lansky Play Score of ≥ 60 (appendix II)

4.5 At least 2 weeks should have elapsed since the last dose of chemotherapy and must have recovered from the acute effects of prior therapy (grade 1 or better); however patients who have a >50% rise in peripheral blast count (confirmed twice) or > 50%

growth of lymph nodes are immediately eligible. Patients who have relapsed following autologous or allogeneic BMT are eligible

4.6 In order to prevent tumor lysis syndrome, acute leukemia patients must have a peripheral blast count under 50 x 10^9/L. This may be achieved with hydroxyurea cytoreduction, prior to starting DT2219

4.7 Adequate organ function within 14 days (30 days for cardiac and pulmonary) of treatment start defined as:

- Creatinine: ≤ 1.5 x upper limit of institutional normal (ULN)
- Hepatic: SGOT (AST) and SGPT (ALT) ≤1.5 x ULN and total bilirubin ≤ 1.5 x ULN
- General health: Serum albumin ≥ 3.0g/dL
- Pulmonary: $DLCO_{corr}$ > 50% if symptomatic or prior known impairment
- Cardiac: LVEF by ECHO or MUGA or MRI ≥ 40%

4.8 Women of childbearing potential and men should be advised and agree to practice effective methods of contraception during the course of study

4.9 Voluntary written consent with appropriate parent/guardian consent and minor information sheet for participants < 18 years of age

Exclusion Criteria

4.10 Presence of leukemic or infectious pulmonary parenchymal disease

4.11 Presence of active CNS leukemia

4.12 Presence of any untreated systemic infection

4.13 Documented uncontrolled seizure disorder – a seizure disorder controlled with medication (i.e. no seizures in the previous 6 months) will not exclude a patient

4.14 Active neurologic disorder (i.e. weakness, altered mental status) – peripheral neuropathy alone does not exclude a patient

4.15 Active Hepatitis B or Hepatitis C (virus detectable by PCR)

4.16 Documented penicillin or cephalosporin allergies

4.17 Pregnant or lactating – Women of child bearing potential must have a negative pregnancy test within 14 days of study treatment start

5 Patient Registration/DT2219 Dose Level Assignment

Registration will occur after the patient has signed the treatment consent and eligibility is confirmed but prior to the first dose DT2219. To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist (appendix I) is under attachments within the study in OnCore.

5.1 Registration with the Masonic Cancer Center Clinical Trials Office

Upon completion of the screening evaluation, eligibility confirmation and obtaining written consent, the Study Coordinator or designee will register the patient.

In the phase II component, patients will be assigned to the disease specific arm (Arm 1 – NHL or Arm 2 – Leukemia).

5.2 DT2219 Dose Level Assignment

The Study Coordinator or designee will assign each patient to the current dose level of DT2219. Refer to section 6.2.

5.3 Patient Re-Treatment (Compassionate)

If a patient completes treatment with DT2219 in a response and later progresses, there may be an opportunity for re-treatment provide the patient continues to meet the original eligibility criteria and tests negative for study drug antibody. Refer to section 6.6 for complete details.

After confirmation of eligibility and signing of a re-treatment consent, the patient will be registered in Oncore on the compassionate treatment study arm.

5.4 Patients Who Are Registered and Do Not Receive Study Treatment

If a patient is registered to the study, and is later found not able to begin DT2219, for whatever reason, the patient will be removed from study and treated at the physician's discretion.

The Study Coordinator or designee will update OnCore of the patient's non-treatment status and notify the Principal Investigator. Study data will be collected until the time the patient is off study. The reason for removal from study will be clearly documented in OnCore. The patient will be replaced.

6 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.).

6.1 DT2219 Administration

Patients may begin on prophylactic allopurinol 300 mg po the day of the 1st dose of DT2219 and continue daily until 24 hours after the last dose of DT2219 or as medically indicated. Use of allopurinol is at the discretion of the treating physician as part of good medical care and is not required for this study.

DT2219 will be administered at the assigned dose via a syringe pump piggy backed onto an established normal saline 1L IV (20mL/kg for weight < 50 kg) on days 1, 3, 5, 8 and days 15, 17, 19 and 22. Dosing will be based on a weight obtained day 1 (-3 days) of each treatment cycle.

The day 1, 3, 5, 8 and day 15, 17, 19 and 22 dosing schedule is based on a Monday start day; however this is not always feasible. Therefore, general dosing rules will be followed within a 4 dose set: 1) each dose will be separated by a minimum 48 hours but 2) no more than 72 hours will lapse between doses except in cases where it is unavoidable (e.g. Monday holidays). Situations where the dosing falls outside of these guidelines will be discussed with and approved by the PI or her designee. No deviation will be filed for these cases.

The 1st dose of treatment cycle 1 will be given over 2 hours (+/- 45 minutes) beginning approximately 30 to 60 minutes after the normal saline is started (run at 200ml/hour) and pre-meds (see below) have been given.

For those who tolerate the 1st dose without incidence, subsequent doses may be infused via a syringe pump over 1 hour beginning approximately 30 minutes after the normal saline infusion has been started (run at 200ml/hour with adjustments as needed for peds) and the pre-meds (see below) have been given.

Pre-meds: 30 minutes prior to each infusion, patients will receive acetaminophen 325 mg po, diphenhydramine 25mg PO/IV (12.5mg PO/IV for weight <25kg), hydrocortisone 25-50 mg IV (25 mg IV for weight <25kg), rantidine 50 mg IV (1mg/kg for weight <50kg)

Patient Monitoring: Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry will be measured as follows:

- every 15 minutes (+/- 10 minutes) during the 1st hour of the DT2219 infusion
- every 30 minutes (+/- 10 minutes) during the 2nd hour, if applicable (and subsequent hours, if infusion runs longer) of the DT2219 infusion

A final set of vitals will be recorded 30 minutes (+/- 10 minutes) after the end of the infusion (end of required post-DT2219 monitoring).

Targeted toxicities (appendix IV) and unexpected adverse events will be collected at the time points listed in section 9.2.

If receiving treatment as an outpatient, upon discharge from clinic after each dose, a member of the research staff will review the time of the next visit with the patient

and the caregiver(s) reiterating the need to contact the study staff during clinic hours or physician on call with any questions or concerns. If there is any concern regarding the patient's general status, a hospital admission will be arranged.

Supportive measures will include acetaminophen for fevers, meperidine for chills, anti-emetics for nausea and vomiting, normal saline or furosemide to maintain fluid balance/blood pressure/pulmonary function, electrolyte replacement, albumin to maintain serum albumin at 3 g/dL or greater.

Anaphylactoid reactions will be treated with 100 mg methylprednisolone IV, diphenhydramine 25 mg IV, or 0.3cc epinephrine (1:1000) IV and transfer to an ICU or inpatient setting for monitoring if clinically indicated.

If grade 2 hypersensitivity reaction occurs, we will use methylprednisolone 100mg pre-med prophylactically prior to subsequent doses. If a grade 2 or greater hypersensitivity reaction re-occurs despite pre-medication, the patient will be permanently discontinued from DT2219.

Any patient experiencing a Grade 3 or greater hypersensitivity reaction related to the DT2219 infusion despite pre-medication will be permanently discontinued from DT2219.

Dose Level Reduction for Toxicity: A one level dose reduction is permitted within a treatment cycle on an individual patient basis if a lower dose allows administration of all 8 doses. This dose reduction is at the discretion of the treating physician in discussion with the PI or designee. For the -1 dose level (if tested), a one level reduction would be 30 µg/kg/dose.

If the event meets the definition of DLT (phase I) or the early stopping rule (phase II), treatment may continue only if the following conditions are met: 1) clinical benefit is observed, 2) the patient is interested in continuing treatment and 3) the DLT or stopping event has resolved to grade 1 or better. In such situations two senior hematology/oncology faculty members must concur with the decision to resume treatment decreasing by 1 dose level. Subsequent toxicity in these patients will not count toward additional DLTs or stopping rule events; however if a second DLT/stopping rule event occurs in the same patient, treatment will be permanently discontinued.

As a guideline, the dose of DT2219 will be decreased by 1 dose level for a grade 3 treatment related event (except for hypersensitivity as detailed above) either within the treatment cycle or at the start of next treatment cycle. No more than 1 dose level reduction is permitted within an individual.

Up to 2 Additional Treatment Cycles may be given if a patient:

- experiences clinical benefit (CR, PR, or stable disease per disease specific response criteria – refer to appendix III) AND
- toxicity from previous treatment cycle has resolved to a grade 1 or 0 and has not experience a grade 3 or higher hypersensitivity reaction to DT2219 despite pre-medication or re-occurrence of a grade 2 hypersensitivity reaction despite pre-medication
- patient continues to meet study eligibility criteria for kidney function (serum creatinine ≤ 1.5 x ULN) and liver function SGOT (AST) and SGPT (ALT) ≤ 1.5 x ULN and total bilirubin ≤ 1.5 x ULN
- Neutralizing antibody against DT2219 was not detected after the current cycle

The above criteria must be met for each subsequent cycle. Subsequent cycles will be given no sooner than 7 days after the last DT2219 dose on the same schedule and at the same or a lower per kg dose of DT2219 as the 1st cycle. The start of a new treatment cycle may be delayed for up to 8 additional weeks.

6.2 DT2219 Dose Level Assignment

6.2.1 Phase I – DT2219 Dosing Confirmation (Completed March 2017)

The phase I component will follow standard 3 or 6 patients per dose level. Enrollment will begin at dose level 1. Dose level -1 will be used only if dose limiting toxicity is encountered with the 1st group. A total of 6 patients will be enrolled at the maximum tolerated dose (MTD) before moving to the expansion component.

Dose Cohort	DT2219 Dose
-1	40 µg/kg/dose
1	60 µg/kg/dose
2	80 µg/kg/dose

Patients will receive a minimum of one cycle of DT2219 using an 8 dose schedule (day 1, 3, 5, 8 and day 15, 17, 19 and 22) over 4 weeks. Dose escalation will proceed within each cohort according to the scheme found in section 11.1. Escalation to dose level 2 may not occur until no sooner than 7 days after the last DT2219 treatment of the last patient in dose level 1 to rule out dose limiting toxicity (DLT). **Dose limiting toxicity (DLT)** is defined as any of the following occurring from day 1 through 7 days after the last dose of DT2219 of the 1st cycle and not attributed to primary malignancy or intercurrent illness**:**

- any Grade 5 adverse event
- any Grade 4 neutropenia or thrombocytopenia lasting more for than 7 days

- any Grade 3 thrombocytopenia with bleeding
- any Grade 4 non-hematologic adverse event during DT2219 infusion
- any Grade 3 non-hematologic adverse event occurring after completion of DT2219 infusion

No single patient can trigger more than one DLT event. If a DLT occurs in a patient, further DT2219 should be only administered if the investigator, in discussion with the PI or designee, feels the benefit of continuing treatment.

6.2.2 Phase II – Simon's Optimum Two-Stage Design

With the March 2017 protocol revision, enrollment moved to phase II using the DT2219 at 60 µg/kg/dose.

Once the MTD for DT2219 using an eight dose schedule is determined, the study will move to a two stage phase II. Patients will be assigned to Arm 1 (NHL) or Arm 2 (Leukemia) based on their diagnosis. Enrollment will proceed independently by diagnosis.

Stage 1: Enroll a total of 9 patients (including all with the relevant diagnosis treated at the MTD in phase I and evaluable after 1st cycle of DT2219). If 1 or more responds, the trial will continue to stage 2 for that diagnosis.
Stage 2: Enroll an additional 8 patients.

If 3 or more patients out of total 17 patients respond then DT2219 will be considered promising for further investigation.

6.3 Guidelines for the Management of Selected Toxicities

See section 8.6 for a complete list of expected toxicities.

Chills associated with study drug administration may be treated with meperidine or morphine sulfate.

Nausea and vomiting may be treated with anti-emetics and IV fluids.

Diarrhea may be treated with loperamide and fluids after stool testing.

Hyperuricemia may be treated with allopurinol, rasburicase and fluids as clinically indicated.

Anaphylaxis and hypersensitivity reactions associated with rash, fever, urticaria, bronchospasm, and angioedema will be treated with IV methylprednisolone (may substitute for dexamethasone or hydrocortisone at equipotent doses), IV diphenhydramine, or, if more severe, epinephrine once. Any patient experiencing a

grade 3 or greater hypersensitivity reaction despite pre-medication or reoccurrence of a grade 2 hypersensitivity reaction despite pre-medication will be permanently discontinued from DT2219.

Vascular leak syndrome is associated with vascular endothelial injury related to fusion protein administration and occurs 3-8 days after initiation of treatment. Patients note symptoms of hypotension, weight gain, edema, nausea, anorexia, shortness of breath, and, at times, confusion and muscle injury. Exam findings include hypoalbuminemia, reductions in blood oxygen saturation, and chest x-ray pulmonary edema. Patients with grade 3 respiratory compromise or grade 4 vascular leak toxicity due to the study drug, will be permanently discontinued from the study drug and will be admitted to the hospital, if indicated, for monitoring and treatment.

Symptomatic hypotension will be treated with boluses of normal saline and a hold on further drug infusion until resolution. If the BP fails to improve with two normal saline boluses, the drug infusion will not be resumed. If low BP persists through the next day, no further drug will be given.

Elevated prothrombin times (PT; INR >1.2) in the absence of other abnormalities consistent with DIC may receive vitamin K IV daily x3. Greater elevations of PT (INR>1.5) may be treated with fresh frozen plasma after the last DT2219 infusion on day 22. If the PT is prolonged to INR >2, the patient may receive fresh frozen plasma daily.

Elevated liver function tests (ALT, AST and/or total bilirubin) guidelines based on CTCAE grading:
Grade 1 or 2: continue therapy per protocol
Grade 3: hold therapy until drops to Grade 1 and resume at lower dose (40mcg/kg)
Grade 4: permanently discontinue therapy

6.4 Supportive Care and Prohibited Therapies

Supportive care will be provided per institutional guidelines. Guidelines may be updated based on current data/drugs without requiring a protocol amendment or be considered a protocol deviation.

Hematopoietic growth factors (e.g., erythropoietin, G-CSF) will be permitted as per institutional pathways.

Appropriate antibiotics, blood products, fluids, electrolytes and general supportive care may be used as medically appropriate.

No other cancer chemotherapy or radiation therapy is permitted during the study period (through day 29 or disease progression).

Use of intravenous immunoglobulin through day 29 is not permitted.

6.5 Duration of Treatment

Treatment may continue on DT2219 for up to 3 treatment cycles unless the patient experiences one or more of the following.

- Has grade 3 or higher hypersensitivity reaction related to DT2219 administration or re-occurrence of a grade 2 or greater hypersensitivity reaction despite pre-medication with methylprednisone
- Develops neutralizing antibody against DT2219
- Has unacceptable toxicity
- Requires more than 1 dose level reduction due to toxicity
- Refuses further treatment or is non-compliant
- Continuing DT2219 is not in the best interest of the patient in the opinion of the treating physician
- More than 8 weeks elapse between treatment cycles

Patients receiving fewer than 6 doses for reasons other than dose limiting toxicity will be replaced.

6.6 Duration of Study Participation

A final study visit will occur at day 50 or 30 days after the last dose (whichever is shorter) of their last treatment cycle. If at the 50 day visit, drug related toxicities have not resolved to < grade 2, follow-up will continue weekly until resolution or stabilization or the start of a new treatment.

If in remission at the time of treatment end, patients will be followed every 3 months for standard of care disease assessment until relapse or progression or the start of a new treatment or for a maximum of 1 year.

Opportunity for Re-Treatment: If a patient completes DT2219 treatment per protocol in a disease response and later relapses, re-treatment may be an option to be discussed with Dr. Bachanova. The subject has to fulfill the eligibility criteria in Section 4. In addition the patient will be tested for the anti-DT2219 antibody and will not be eligible for re-treatment if anti-drug antibody is detected.

Eligible patients will receive DT2219 at the same or a lower dose level and on the same schedule (8 doses over 22 days) as initially treated. Treatment guidelines will be followed per section 6.1. Tests and evaluations during and after treatment would follow those in section 7. This includes frequent assessments for toxicity and survival follow-up through 1 year from the 1st dose off the re-treatment.

Such situations would be considered compassionate and would not be included in the statistical analysis.

7 Schedule of Patient Activities

Scheduled evaluations after screening and up to day 29 of each treatment cycle may be performed +/-1 day from the targeted date; assessments to be performed day 29 and later may be performed +/-3 days from the targeted date. Ongoing follow-up for disease response may be performed +/-30 days.

If Day 1 Does Not Fall on a Monday:

The day 1, 3, 5, 8 and day 15, 17, 19 and 22 dosing schedule is based on a Monday start day; however this is not always feasible. Therefore, general dosing rules will be followed within a 4 dose set: 1) each dose will be separated by a minimum 48 hours but 2) no more than 72 hours (+2 hours) will lapse between doses except in cases where it is unavoidable (e.g. Monday holidays). Situations where the dosing falls outside of these guidelines will be discussed with and approved by the PI or her designee. No deviation will be filed for these cases.

7.1 Standard of Care

	Pre-Treatment within 14 days of treatment start (within 30 days if marked by *)	**During each DT2219 Treatment Cycle**				**Day 50 (+/-3 days) or 30 days after last DT2219 infusion**	**Follow-up through 1 year from 1st dose[2]**
		Prior to each DT2219 dose (days 1,3,5,8 and 15,17,19,22) – refer to previous page if day 1 is not a Monday	**Day 10[4]**	**Day 24[4]**	**Day 29 (+/-3 days)**		
consent	X						
medical history	X						
physical exam	X	X	X	X	X	X	
neurological assessment[3]	X	day 1, 8, 15, 22	X	X	X	X	
toxicity assessment	X	X	X	X	X	X	
Monitor for stopping rules per section 11.5 (expansion only)							
Monitor for DLT per section 11.1 (dose finding only)		X					
vital signs (including 02 sat)	X	per section 6.1	X	X	X	X	
weight	X	X			X	X	
performance status	X	day1, 15			X	X	
CBC, diff, plt	X	X	X	X	X	X	
basic metabolic plus uric acid, mg, phos, LDH	X	on days comprehensive metabolic is not done	X	X			
comprehensive metabolic plus uric acid, mg, phos, LDH	X	day 1, 8, 15, 22			X	X	
PT, PTT, fibrinogen	X	day 1, 15					
hepatitis B and C screening	X*						
Pregnancy test, serum or urine for females of child bearing potential	X*						
EKG	X*						
Ejection Fraction by MUGA or echo or MRI	X*						
PFT's if symptomatic or known impairment	X*						
Bone marrow aspirate +/- biopsy (per SOC)[1]	X*[1]				X[1]		every 3 months[1]
PET/CT OR CAP CT	X*				X (CT only) [5]		
Lumbar Puncture if clinically indicated	X*						

* within 30 days of treatment start

1- For ALL and CLL patients only; however it maybe skipped if there is evidence of progression based upon peripheral blasts count rise or lymph node growth. See section 7.2 – collect additional sample for research purposes at the time of each BM done for SOC.

2- Patients who end treatment while in disease response will be followed per standard of care until relapse, progression, or start of new treatment or for a maximum of 1 year, otherwise follow for survival only at 1 year per section 6.6

3- Neurological assessment weekly including basic motor (gait), coordination (steadiness) and cognitive function (alert and oriented) - any abnormalities should be followed up with a detailed neurologic exam.

4- Day 10 and Day 24 evaluation needed for patients on Phase 1 cycle 1 only

5- PET will be obtained only in NHL patients with no detectable disease on CT scan at C1D29 only OR at time of progression

7.2 Research Related Procedures and Activities

	Pre-treatment within 14 days of treatment start	**Day 8 and 22 cycle 1 only**	**Day 22 or 24**	**End of Treatment (Cycle 1, D29 only)***
Toxicity Notation		per section 9.2		
DT2219 serum levels (PKs) – one 2ml red top tube per time point		X[3]		
Neutralizing antibody against - DT2219 Ig - red top tube(s)	X[1] (10 ml)		X (5 m1 per time point) - cycle 1, 2 and 3)[4]	
peripheral blood immunophenotyping – two 10 ml green top tubes	X		X (cycle 1 only)	X
peripheral blood for immune environment assessment two 10 ml green top tubes	X		X (cycle 1 only)	X
10 ml green top bone marrow for CD19 and CD22 by flow cytometry	At time of SOC BM Bx			
tumor or lymph node biopsy	X[2]			X[5]

* only for patients who have completed 1 full cycle

1 Antibody testing will occur prior to treatment, and in the event of antibody presence, it will be determined on a case by case basis whether the patient will receive DT2219.

2 Pre-treatment tumor or lymph node biopsy – if patient refuses, a planned deviation will be filed.

3 PK time points: Prior to infusion start, at mid-infusion (i.e. 30 minutes if given over 1 hour) and at the end of the infusion (a ± 5 min window is permitted with the actual time of the sample collected recorded.)

4 Presence of neutralizing antibody will deem the patient ineligible for additional treatment cycles or re-treatment per sections 6.5 and 6.6

5 Optional post-treatment tumor or lymph node biopsy – requires a separate consent – adults only

All samples to will go to TTL except tumor or lymph node biopsies which are processed through BioNet.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples for a total of 60 ml of blood may be drawn at additional time points that are not specified above.

7.2.1 Circulating DT2219 in the Blood

Measurement of the Cmax and half-life of DT2219 in the blood of patients will permit correlation of drug levels and leukemia cell exposure (time x concentration) with clinical toxicities and response. Further, different patient leukemia and lymphoma burdens may influence drug pharmacodynamics.

A 2 mL venous blood sample (red top tube) will be drawn on cycle 1 day 8 and 22 (4^{th} and 8^{th} dose) of DT2219 at the following time points: prior to infusion start at mid-infusion (i.e. 30 minutes if given over 1 hour) and at the end of the infusion (a ± 5 min window is permitted) with the actual time of the sample collected recorded.

Samples will be processed in TTL and stored frozen until batch transfer to the Vallera Lab.

7.2.2 Neutralizing Antibody Against DT2219

At study screening: Antibody testing will be done and the results reviewed prior to beginning DT2219 but its result is not part of the inclusion/exclusion criteria. In the event of antibody presence, it will be determined on a case by case basis whether the patient will receive DT2219.

During treatment: a sample will be collected on day 22 (+2 days) of each treatment course and tested in TTL with the results available before the start of the next treatment cycle. Per section 6.5, the antibody result must be negative prior to the start of a new treatment cycle or re-treatment per section 6.6.

7.2.3 Pre-Treatment Tumor/Lymph Node Biopsy

A fresh biopsy of tumor or lymph node will be performed during screening. Part will go to the Fairview Clinical Flow Lab for CD19 and CD22 expression (bill to research) with the remainder retained in BIONET for frozen tissue storage. If a patient does not have accessible tumor or refuses, a planned deviation will be filed.

7.2.4 Post-Treatment Tumor/Lymph Node Biopsy (optional)

A post-treatment tumor/lymph node biopsy of palpable node will be optional for patients with accessible tumor or lymph nodes. Part will go to the Fairview clinical Flow Lab for CD19 and CD22 expression (bill to research) with the remainder retained in BIONET for frozen tissue storage.

8 DT2219

8.1 Procurement

DT2219 is an experimental drug produced by Dr. Daniel A. Vallera at the University of Minnesota Masonic Cancer Center, Minneapolis, Minnesota with approval of the FDA for the purpose of this study (IND #100780).

DT2219 will be supplied by Dr. Vallera for the purposes of this study.

8.2 Formulation

DT2219 protein is supplied frozen in sterile 1 mL colorless, type I glass vials with an 11mm rubber stopper and an aluminum seal ring and is formulated at 1 mg drug in 1 mL of 0.15 M NaCl/10 mM sodium phosphate + 0.5% Polysorbate 80, pH 7.4. Vials used in drug preparation were sterile pyrogen-free, 1 mL (Hollister Stier, Miles Inc. #280090-M01).

8.3 Reconstitution

Vials are to be thawed at room temperature for 15 minutes. Do not shake the vial during thawing. Vials may be gently swirled. The solution must be clear, colorless and without visible particulate matter. Immediately draw the thawed drug into a 3 cc syringe and filter sterilize using a 0.22 um filter (PALL Life Sciences #PN 4192). The drug is transferred to a sterile 5 mL vial and the correct dose volume for the patient aspirated with a 18 x 1-½ "(BD305196) needle into a 30 ml disposable plastic sterile syringe adding enough sterile saline to reach a total volume of 20 ml.

Ideally the drug will be administered within one hour of thawing.

8.4 Storage and Stability

Intact vials should be stored at -80^{o}C and are stable for over 12 months.

8.5 Administration

DT2219 is injected via a syringe pump into a free flowing normal saline 1L IV (20mL/kg for weight < 50 kg) over the prescribed infusion time per section 6.1 on days 1, 3, 5, 8 and day 15, 17, 19 and 22 of a 28 day treatment cycle.

8.6 Toxicity

In the previous first in human phase I study 25 patients were given a one 4-dose treatment course (on days 1, 3, 5, and 8). The first 12 patients were treated at doses ranging from 0.5 ug/kg/day to 20 ug/kg/day exhibited no or minimal adverse reactions (lower than what is used in this study). All 13 patients treated at dose levels ≥40 ug/kg/day experienced adverse events (AE) attributed to drug treatment. A patient by patient summary of events can be found in table 1 of section 2.4.

No infusional toxicity was observed.

The most common transient grade 1-2 AEs included weight gain (range 5-14% of baseline), peripheral edema, and hypoalbuminemia consistent with capillary leak syndrome, grade 1-2 fever and fatigue. Seven patients experienced isolated mild elevation of liver function tests (1.1-2.1 x ULN) without hyperbilirubinemia, which resolved within 3-7 days. Thrombocytopenia and anemia occurred in 5 patients; however, marrow involvement by underlying lymphoma or leukemia often contributed to cytopenias. Whereas lactate dehydrogenase (2-2.3-fold) transiently increased in 4 patients after the 1st dose; clinical tumor lysis or acute cytokine release syndrome did not occur. Most AEs were recognized during routine monitoring before the 2nd or 3rd dose of DT2219. All AEs were brief and resolved completely within one week.

Two patients experienced DLTs.

1) The first DLT occurred at the 40 µg/kg dose level in a 71-year-old patient with ALL who developed back pain along with acute lower extremity weakness after the 3rd dose of study drug. While the patient had a recent history of CNS leukemia prior to enrollment, brain magnetic resonance imaging and cerebrospinal fluid studies at the time of AE were negative for leukemic CNS involvement. This patient died of rapidly progressive disease. No neurologic adverse effects of any grade occurred in the next 10 patients treated at this or higher doses (40-80 ug/kg).
2) The second DLT event occurred at the 60 µg/kg dose level in a 55-year-old patient who developed grade 3 capillary leak manifested as hypoxemia, hypotension, pulmonary edema, and hypoalbuminemia in combination with febrile neutropenia. The patient was hospitalized and treated with oxygen, IV antibiotics, hydration and diuresis. Her symptoms improved with supportive care to grade 2 after 2-3 days and completely resolved in 10 days.

In March 2017, the MTD for DT2219 was declared as 60 µg/kg/dose when given as an 8 dose block (day 1, 3, 5, and 8 and day 15, 17, 19, and 22). Two patients at 80 µg/kg/dose experienced elevated liver function tests that met the criteria for dose limiting. The 6th patient at this level experienced grade 3 capillary leak syndrome with the 1st dose.

9 Adverse Event Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded

from the CTEP home page http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf8.1

9.1 Definitions

Note: throughout this section the generic term "drug" refers to the DT2219.

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Treatment-Emergent Adverse Event: Any event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment. A treatment emergent AE refers to an event temporally related to the study treatment regardless of the causality assessment by the investigator.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: 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.

Serious Adverse Event Or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A 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 serious 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. Note: a grade 4 CTCAE toxicity does not necessarily equate to serious.

If either the IND sponsor or the investigator believes the event is life-threatening or serious, the event must be evaluated by the sponsor for expedited reporting (21CRF 312.32(a)).

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, adverse events that occur as part of the disease process or underlying medical conditions are considered unexpected; however, they will not be reportable per section 9.3.

Unanticipated (unexpected) problems/events as defined by the University Of Minnesota IRB are those that are not already described as potential risks in the consent form, not listed in the Investigator's Brochure or not part of an underlying disease.

Note: The major discord between the FDA and IRB definitions is whether or not the underlying disease is included when considering expectedness.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB, FDA) as detailed in section 9.3. For the IRB this is within 5 business days of discovery. For studies under an IND, it is 7 or 15 calendar days.

9.2 Adverse Event Monitoring and Documentation

For the purposes of this study adverse event monitoring will begin with the 1st dose of DT2219 and continue through 30 days after the last infusion, disease progression, or the start of a new therapy, whichever occurs first.

A toxicity assessment will be done at each time point in section 7 including prior to each dose of DT2219 and at each follow-up visit. Each assessment will cover the time period from the previous assessment with the worse grade of the toxicity noted. All toxicities (regardless of grade, attribution and expectedness) will be recorded in OnCore in the AE log case report form for the duration of the treatment period and for 30 days after the last infusion or the start of a new therapy, whichever occur first.

In addition, for the 1st cycle only, the targeted toxicity form (appendix IV) will be collected at the following time points. The advantage of this form is that it requires

an assessment for each event of interest with a "0" indicating not present or no compliant.

- Before the each dose of DT2219 during cycle 1
- 30 minutes after the each dose of DT2219 during cycle 1
- Day 10, 24 and 29 of cycle 1

All of the above time points are based on the assumption the patient receives treatment as planned. The assessment day(s) may be altered or eliminated if the standard of care visit(s) for a specific time point in section 7.1 is altered or does not occur.

After the final treatment visit approximately 30 days after the last DT2219 infusion, formal AE documentation will end, however; the investigator must report upon knowledge any study treatment related event meeting the criteria for expedited reporting in section 9.3.

Events that potentially meet the definition of serious (SAE): Upon identifying or being notified of a potential serious adverse event (SAE), the Study Coordinator or designee will review the current IRB approved protocol to determine the protocol definition of an SAE and the reporting requirements. The Study Coordinator will notify the study PI and IND sponsor and initiate an SAE report in OnCore within 24 hours of knowledge. The Study Coordinator will forward the partially completed SAE report and the IND specific spreadsheet of "Similar Suspected Adverse Events" to the Principal Investigator who will assign attribution, expectedness, risk and expand upon the clinical information as needed and sign/date the report. The IND sponsor will review the SAE report and if in agreement with the report (if not, a discussion between the PI and Sponsor will occur to resolve any differences and the report edited appropriately), the Study Coordinator will forward the SAE report to the Regulatory Specialist. The Regulatory Specialist will determine if the SAE meets the criteria for expedited reporting to the University of Minnesota Institutional Review Board (IRB) and/or FDA within the required timeframe per section 9.3. In addition, a copy will be forwarded to the Masonic Cancer Center SAE Coordinator at the time it is submitted to the IRB and/or FDA per section 9.3.

Dose Limiting Toxicity (During phase I only): The following events occurring from study day 1 through 7 days after the last dose of DT2219 of the 1st cycle and not clearly attributed to the primary malignancy or intercurrent illness meet the definition of dose limiting toxicity during the phase I (dose escalation component):

- any Grade 5 adverse event
- any Grade 4 neutropenia or thrombocytopenia lasting more for than 7 days
- any Grade 3 thrombocytopenia with bleeding

- any Grade 4 non-hematologic adverse event during DT2219 infusion
- any Grade 3 non-hematologic adverse event occurring after completion of DT2219 infusion

Within 24 hours of identifying or being notified of a potential DLT event, the study's Study Coordinator will gather the relevant clinical data to initiate the Event Form in OnCore. With the study PI and biostatistician, if applicable, the current DLT event, all previously reported DLTs and the protocol dose escalation schema will be reviewed to determine if the dose escalation schema is impacted.

A copy of the completed Event Form will be provided to the study's Regulatory Specialist for submission within 24 hours of receipt to the Masonic Cancer Center's SAE Coordinator (Data and Safety Monitoring Committee) and other entities with study oversight (i.e. IRB, FDA) if applicable. A copy will be filed in the study's regulatory binder. If enrollment to the study is impacted, the Regulatory Specialist or designee, will update the study status in OnCore.

Stopping Rule Events (Phase II only): The following events count towards the study stopping rule during cycle 1 of the phase II (extension) component per section 11.5. Arm 1 and Arm 2 will be monitored separately.

Excess toxicity defined as grade 4 non-hematologic or grade 4 neutropenia or thrombocytopenia lasting for more than 7 days or treatment related toxicity attributed to the study drug occurring within 7 days of the last dose.

If any grade 5 toxicity (death) possibly, probably or definitely related to DT2219 occurs accrual will be temporarily suspended in order to allow comprehensive case review.

Within 24 hours of identifying or being notified of a potential stopping rule event, the Study Coordinator will gather the relevant clinical data to initiate the Event Form in OnCore. With the study PI and biostatistician, the current event, all previously reported stopping rule events for the rule and the current IRB approved protocol will be reviewed to determine if a stopping rule event has occurred and if it results in the early stop of the study.

A copy of the completed Event Form will be provided to the study's Regulatory Specialist for submission within 24 hours of receipt to the Masonic Cancer Center's SAE Coordinator (Data and Safety Monitoring Committee) and other entities with study oversight (i.e. IRB, FDA) if applicable. A copy will be filed in the study's

regulatory binder. If enrollment to the study is impacted, the Regulatory Specialist or designee, will update the study status in OnCore.

Events that count toward dose limiting toxicity or the early stopping rule do not necessarily constitute a serious adverse event requiring expedited reporting and should be reported as such only if they meet the criteria for expedited reporting to the IRB as defined in section 9.3.

In addition, although not always an event requiring expedited reporting, deaths with cause will be recorded in OnCore upon knowledge in the follow-up tab.

9.3 Required Reporting: FDA, IRB, and MCC's SAE Coordinator

Agency	Criteria for Reporting	Time-frame	Form to Use	Submission address/ fax numbers
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	Report Form	irb@umn.edu
FDA	Unexpected and fatal or life threatening suspected adverse reaction	As soon as possible but no later than 7 Calendar-Days	MCC SAE	Submit as an amendment to IND
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	As soon as possible but no later than 15 Calendar-Days		
	All other events per CRF 312.33	At time of IND annual report	Summary format	Submit as part of the IND annual report
	Note: Events clearly determined to be unrelated to DT2219 and felt due to the disease under treatment or an underlying medical condition will not require expedited reporting to the FDA for the purposes of this study			
Masonic Cancer Center Regulatory Specialist	Events that count toward a dose limiting toxicity or stopping rule	within 24 hours	Event Form	SAE Coordinator mcc-saes@umn.edu

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of the previous, similar reports.

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

10 Study Data Collection and Monitoring

10.1 Data Management

This study will report clinical data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms. Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore. Patient demographics, patient specific study treatment calendars, adverse events and other information required for IND annual reporting will be placed in OnCore and other databases maintained by the Cancer Center.

10.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

10.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the study's progress at least quarterly.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 9.3 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, and the FDA.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the sponsor/investigator (Dr. Bachanova) with assistance from the MCC Clinical Trials Office (CTO) will submit

a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect.

10.4 Study Monitoring and Audits

The investigator will permit study-related monitoring, audits, and inspections by the sponsor and/or sponsor designee, IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

10.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

11 Statistical Considerations

11.1 Study Design

A phase I/II design will be used to determine the maximum tolerated dose (MTD) of the DT2219 when administered using an 8 dose schedule for the treatment of relapsed or refractory CD19 (+) and/or CD 22 (+) B-lineage leukemia and lymphoma.

The phase I component will follow a standard 3 or 6 patients per dose level. Enrollment will begin at dose level 1. Dose level -1 will be used only if dose limiting toxicity is encountered with the 1st group.

Dose Cohort	DT2219 Dose
-1	40 µg/kg/dose
1	60 µg/kg/dose
2	80 µg/kg/dose

Patients will receive a minimum of one cycle of DT2219 using an 8 dose schedule (day 1, 3, 5, 8 and day 15, 17, 19 and 22). A disease reassessment will be done at day 29+/- 3 days. Each dose cohort must be separated by at least 7 days to rule out dose limiting toxicity (DLT). Dose escalation will proceed within each cohort according to the following scheme:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 new patients at the next higher dose level
$\geq$ 2 out of 3	This dose level is declared to be above the maximum tolerated dose (MTD) and dose escalation is stopped. Declare the next lower dose the MTD if 6 patients have already been treated at that dose. Enter 3 additional patients at the next lower dose level if only 3 patients have been treated at that dose, and if $\leq$ 1 out of 6 patients has DLT then declare this dose the MTD. If $\geq$ 2 out of 6 patients have DLT then dose de-escalation continues according to the same scheme.
1 out of 3	Enter 3 additional patients at this dose level. • If 0 of these 3 patients (i.e. 1 out of all 6 patients) experience DLT, proceed to the next higher level. • If $\geq$ 1 of these 3 patients (i.e.$\geq$ 2 out of all 6 patients) experience DLT, then this dose is declared to be above the MTD and dose escalation is stopped. Declare the next lower dose the MTD if 6 patients have already been treated at that dose. Enter 3 additional patients at the next lower dose level if only 3 patients have been treated at that dose, and if $\leq$ 1 out of 6 patients has DLT then declare this dose the MTD. If $\geq$ 2 out of 6 patients have DLT then dose de-escalation continues according to the same scheme.

Dose limiting toxicity (DLT) is defined as any of adverse events occurring from study day 1 through 7 days after the last dose of DT2219 of the 1st treatment cycle and not clearly attributed to the primary malignancy or intercurrent illness:

- any Grade 5 adverse event
- any Grade 4 neutropenia or thrombocytopenia lasting more for than 7 days
- any Grade 3 thrombocytopenia with bleeding
- any Grade 4 non-hematologic adverse event during DT2219 infusion
- any Grade 3 non-hematologic adverse event occurring after completion of DT2219 infusion

Each dose cohort must be separated by at least 7 days after the last dose of the last patient in the current dose level.

Evaluable for response: Patients receiving fewer than 6 doses of DT2219 for reasons other than dose limiting toxicity will be replaced.

The design will continue until the MTD is declared or until the first dose is declared to be above the MTD.

Once the MTD is determined, the final dose will be carried forward into a two-stage phase II component to confirm safety and make a preliminary determination of the activity level for Non-Hodgkin Lymphoma (NHL) patients (Arm 1) and Leukemia (Leukemia) patients (Arm 2). We will employ Simon's Optimum two-stage design [16] with the possibility to discontinue after the 1st stage if the response rate is low. The 6 patients treated under MTD in phase I will be included in the phase II component if they are evaluable after the 1st cycle of treatment. They will be assigned to Arm 1 or Arm 2 based on their diagnosis.

- Stage 1: Enroll a total of 9 patients (including all treated at the MTD in phase I and evaluable after 1st cycle of treatment). If 1 or more responds, the trial will continue to stage 2.
- Stage 2: Enroll an additional 8 patients. If 3 or more patients out of total 17 patients respond then DT2219 will be considered promising for further investigation.

Based on the historical data, we expect to complete the enrollment within 12-18 months.

11.2 Rationale for Sample Size

For Phase I Component, 6 to 12 patients will be enrolled. An additional 28-34 patients will be enrolled in the phase II component to obtain 17 lymphoma patients (Arm 1) and 17 leukemia patients (Arm 2) treated at MTD including the 6 patients treated at MTD in phase I and evaluable after the 1st cycle of treatment. For each arm, the phase II trial using Simon's two-stage Optimum design will require 17 patients to test the null hypothesis that the Complete Response (CR) and Partial Response (PR) at day 29 is ≤5% versus the alternative that the CR and PR rate is ≥30% after assuming 90% power and a significance level of 0.05 and using maximum of 17 patients.

Based on the historical data, we expect to complete the enrollment within 12-18 months.

11.3 Study Endpoints

Primary Endpoints

Phase I component is to determine safety and tolerability of the DT2219 for the treatment of relapsed or refractory CD19 (+) and/or CD 22 (+) B-lineage leukemia and lymphoma.

The primary endpoint for Phase II is the overall response at day 29.

Secondary Endpoints

- To determine incidence of serious adverse events through day 29
- To determine duration of response for up to 1 year
- To evaluate 1 year disease-free survival
- To evaluate 1 year overall survival
- To determine time to relapse/progression for up to 1 year

Correlative Endpoints

- To determine the pharmacokinetic (PK) profile (Cmax, T1/2, AUC, Cl, Vd) of DT2219
- To document presence and measure levels of human anti-DT2219 antibodies and correlate with response
- To determine if there is a correlation between PK parameters and toxicity or response
- To determine if the expression of the CD19 and CD22 cell surface antigens is affected by treatment with DT2219 using flow cytometric analysis of lymphoblasts in peripheral blood and bone marrow. B-lymphocytes in peripheral blood
- To correlate CD19 and CD22 surface antigen expression on patient blasts or lymphoma cells with response

11.4 Statistical Analysis

The MTD of DT2219 will be determined by the design. The primary trial endpoint of response will be estimated by simple proportions with confidence intervals calculated from asymptotic standard errors. Kaplan-Meier curves will estimate PFS and log-rank test will be used to compare PFS between disease groups (lymphoma vs. leukemia) and disease status groups (relapsed/refractory vs. post-allogeneic transplant). [17] Competing rusk analysis will be used to estimate relapse/progression rate and Gray-Fine test will be used to test disease effect and disease status effect.[18] Other secondary endpoints will be described with simple descriptive statistics such as medians, ranges, interquartile ranges, proportions,

charts and plots. Correlation between various biomarkers will be estimated with Spearman's rank-order correlation coefficient along with correlation plots.

All analyses will be conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC). Results will be deemed statistically significant at the 0.05 significance level unless otherwise specified.

11.5 Early Stopping Rules for Excessive Toxicity During Expansion Component

Stopping rules will be employed to monitor excess toxicity outside of the phase I trial. The stopping rule was developed using Pocock stopping boundaries. [18] The stopping rule will be monitored for Arm 1 and Arm 2 separately.

If any grade 5 toxicity (death) possibly, probably or definitely related to DT2219 occurs accrual will be temporarily suspended in order to allow comprehensive case review.

Excess toxicity will be defined as **grade 4 non-hematologic or grade 4 neutropenia or thrombocytopenia lasting for more than 7 days treatment related toxicity attributed to the study drug occurring within 7 days of the last dose.** The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 50% if the true rate of toxicity is equal to 15% and our sample size is 17 for each disease cohort (lymphoma vs. leukemia). The stopping rule will be monitored for each cohort separately. This means the enrollment will be stopped and the study re-evaluated if there are 2 out of first 3 subjects, 3 out of 8 subjects, 4 at any time. If the true toxicity rate is 30% then the chance of early stopping is 90% and the expected sample size is 5.68.

12 Conduct of the Study

12.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress

reports, and any revisions to these documents will be provided to the IRB by the investigator.

12.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

13 References

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Appendix I – Eligibility Checklist

DT2219 Immunotoxin for the Treatment of Relapsed or Refractory CD19 (+) and/or CD 22 (+) B-Lineage Leukemia or Lymphoma

HM2014-26

Eligibility Checklist – page 1 of 2

Patient initials ☐☐☐☐ Patient ID ☐☐

1st 2 initials of first name + 1st 2 initials of last name Seq # (i.e. 01, 02, 03, etc.)

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the patient from study entry.

		Yes	No
1.	Histologic verification of B-cell lineage leukemia or B cell non-Hodgkin lymphoma and evidence of relapse/refractory disease with the presence of CD19 and/or CD22 by flow cytometry or immunohistochemistry of bone marrow aspirate, peripheral blood or node/tumor biopsy	☐	☐
2.	Relapsed/refractory disease that has failed conventional therapy and other therapies of higher priority	☐	☐
3.	Age ≥ 12 years	☐	☐
4.	Karnofsky Performance status of ≥ 60% or, < 16 years of age, Lansky Play Score of ≥ 60	☐	☐
5.	At least 2 weeks should have elapsed since the last dose of chemotherapy and must have recovered from the acute effects of prior therapy (Grade 1 or better); however patients who have a >50% rise in peripheral blast count (confirmed twice) or > 50% growth of lymph nodes are immediately eligible - Patients who have relapsed following autologous or allogeneic BMT are eligible	☐	☐
6.	In order to prevent tumor lysis syndrome, leukemia patients must have a peripheral blast count under 50 x 10^9/L. This may be achieved with hydroxyurea cytoreduction, prior to starting DT2219	☐	☐
7.	Adequate organ function within 14 days (30 days for cardiac and pulmonary) of enrollment defined as:	☐	☐

test	requirement
SGOT	≤1.5 x UNL
SGPT	≤1.5 x UNL
total bilirubin	≤ 1.5 x ULN
creatinine	≤ 1.5 mg/dl
serum albumin	≥ 3.0g/dL
Pulmonary, if sxs or known impairment	$DLCO_{corr}$ > 50% ☐ check if n/a
Cardiac	LVEF ≥ 40%

8.	Women of childbearing potential and men should be advised and agree to practice effective methods of contraception during the course of study	☐	☐
9.	Voluntary written consent	☐	☐

DT2219 Immunotoxin for the Treatment of Relapsed or Refractory CD19 (+) and/or CD 22 (+) B-Lineage Leukemia or Lymphoma

HM2014-26

Eligibility Checklist – page 2 of 2

Patient initials ☐☐☐☐

EXCLUSION CRITERIA

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
10.	Presence of leukemic or infectious pulmonary parenchymal disease	☐	☐
11.	Active CNS leukemia.	☐	☐
12.	Presence of any untreated systemic infection	☐	☐
13.	Documented seizure disorder or abnormal neurological examination	☐	☐
14.	Active neurologic disorder (i.e. weakness, altered mental status) – peripheral neuropathy alone does not exclude a patient	☐	☐
15.	Active Hepatitis B or Hepatitis C (virus detectable by PCR)	☐	☐
16.	Documented penicillin or cephalosporin allergies	☐	☐
17.	Pregnant or lactating – Women of child bearing potential must have a negative pregnancy test within 14 days of study treatment start	☐	☐

Diagnosis if enrolled in Phase II: ☐ lymphoma ☐ leukemia

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is eligible.

_____

Signature of enrolling investigator

Appendix II – Performance Status Criteria

For patients 16 years of age and older:

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

For patients < 16 years of age:

Lansky Score	Play Score
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Appendix III – Disease Specific Response Criteria

ACUTE LYMPHOCYTIC LEUKEMIA (ALL) RESPONSE CRITERIA

Bone Marrow:

A1.Maturation of all cell lines: and <5% blasts.
A2. Same as A1, except blasts ≥ 5% and < 25%.
A3. Failure to meet the criteria for A1 or A2.

Peripheral Blood:

B1. Neutrophils > 1,000/mcl; and platelets > 100,000/mcl; and no leukemia blasts in the peripheral blood.
B2. Failure to meet the criteria for B1.

Extramedullary Disease:

C1. None
C2. Any

CR	Attainment of A1 marrow status and B1 peripheral blood status and C1 extramedullary disease status for a period of at least 28 days.
CRi	CR with incomplete blood count recovery: Same as CR but platelets ≤ 100,000/mcl and/or neutrophils ≤ 1,000/mcl.
PR	Partial Response: All of the above criteria for CR must be met, except that the bone marrow may contain ≥ 5% but less than 25% blasts, or ≤ 5% blasts with abnormal morphology
Failure – resistant disease	Resistant Disease: Patient survives ≥ 7 days following completion of initial treatment course with persistent leukemia in the last peripheral blood smear or bone marrow, or with persistent extramedullary disease.
Failure – aplasia	Aplasia: Patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow aplastic or hypoplastic (i.e. < 20% cellularity) and without leukemia blasts.
Failure - indeterminate	Indeterminate: (a) Patient survives < 7 days after completion of initial treatment course; or (b) patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination.
relapse from CR	Relapse: Reappearance of leukemia blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia); or appearance or reappearance of extra-medullary disease.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) RESPONSE CRITERIA

Complete Remission

CR requires all of the following criteria as assessed at least 3 months after completion of therapy:

- Absence of clonal lymphocytes in the peripheral blood.
- Absence of significant lymphadenopathy (e.g., lymph nodes > 1.5 cm in diameter) by physical examination or CT scan.
- No hepatomegaly or splenomegaly by physical examination or by CT scan.
- Absence of constitutional symptoms.
- Blood counts above the following values:
    - Polymorphonuclear leukocytes 1.5 x 10^9/L or more.
    - Platelets more than 100 x 10^9/L
    - Hemoglobin more than 11.0 g/dL; untransfused.

A bone marrow aspirate and biopsy should be performed at least 3 months after the last treatment if clinical and laboratory results demonstrate a CR. The marrow should be analyzed by flow cytometry and/or immunohistochemistry to demonstrate that the marrow is free of clonal B-CLL cells. Cases with residual CLL cells by conventional flow cytometry or immunohistochemistry are defined as partial remission (PR).

In some cases, lymphoid nodules can be found (formerly used to define nodular PR), which often reflect residual disease. Therefore, these nodules should be assessed by immunohistochemistry to define whether they are comprised of CLL cells.

CR with Incomplete Bone Marrow Recovery (CRi)

For the definition of this category, CRi, the marrow evaluation should be performed with scrutiny and not show any clonal infiltrate.

Partial Remission

PR is defined by at least one of these parameters and needs to be documented for a minimal duration of 2 months:

• A decrease in the number of blood lymphocytes by less than 50% or more from the value before therapy.

• A decreased lymph node size by 50% or more in the sum products of up to 6 lymph nodes, or in one lymph node diameter if only a single lymph node was present before therapy, as assessed by CT scan.

• No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2 cm), an increase of less than 25% is not considered to be significant.

• A decrease in the size of the liver and/or spleen by 50% or more as defined by CT scan.

• The blood count should show one of the following results:

- Polymorphonuclear leukocytes at 1.5 x 10^9/L or more or 50% improvement over baseline without granulocyte colony-stimulating factor (G-CSF) support.
- Platelet counts greater than 100 x 10^9/L or 50% improvement over baseline.
- Hemoglobin greater than 11.0 g/dL or 50% improvement over baseline without red blood cell transfusions or erythropoietin support.

Progressive Disease

Progressive disease is characterized by at least one of the following:

- Constitutional symptoms persisting for more than 1 month.
- Progression of lymphadenopathy.
- Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
- An increase by 50% or more in greatest determined diameter of any previous site.
- A lymph node of 1 to 1.5 cm must increase by 50% or more to a size greater than cm in the longest axis. A lymph node of more than 1.5 cm must increase to more than 2.0 cm in the longest axis.
- An increase of 50% or more in the sum of the product of diameters of multiple nodes.
- An increase in the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (e.g., Richter syndrome).

Whenever possible, this diagnosis should be established by lymph node biopsy.
After treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease
Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease.

REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA [19]

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		
		(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Appendix IV –Targeted Toxicity Form (CTCAE 4.0)

See section 9.2 for time points Cycle 1 only

Patient Initials: _____ Date of Assessment: _____ Assessment Time Point: _____

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyper-sensitivity reaction	None	Mild transient reaction; infusion interruption not indicated; intervention not indicated……	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medications indicated for ≤24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening and urgent intervention indicated
Capillary leak syndrome	None	……	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated
Dyspnea	None	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Hypoxia	None	……	Decreased O_2 saturation with exercise (e.g., pulse oximeter < 88%) intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or PaO_2 ≤ 55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated
Fever	None	38.0 - 39.0 degrees C (100.4 -102.2 degrees F)	> 39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	> 40.0 degrees C (>104.0 degrees F) for ≤ 24 hours	> 40.0 degrees C (>104.0 degrees F) for > 24 hours
Chills	None	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	……
Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	……
Vomiting	None	1- 2 episodes (separated by 5 minutes) in 24 hours	3 - 5 episodes (separated by 5 minutes) in 24 hours	>=6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalization indicated	Life-threatening and urgent intervention indicated
Hypotension	None	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Edema	None	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	……
Rash	None	Covering < 10% body surface area (BSA)	Covering 10-30% body surface area (BSA)	>30% body surface area (BSA)	Generalized exfoliative, ulcerative, or bullous dermatitis
Weight Gain	None	5 - <10% from baseline	10 - <20% from baseline	≥20% from baseline	……

Record all other adverse events on the AE log eCRF in OnCore

Person Completing Form: _____ ADL = activities of daily living