

Protocol Number: ADCT-402-102

**Official Title: A Phase 1, Open-label, Dose-Escalation, Multicenter Study to Evaluate the
Tolerability, Safety, Pharmacokinetics, and Anti-tumor Activity of ADCT-402
in Patients with Relapsed or Refractory B-cell Lineage Acute Lymphoblastic
Leukemia (B-ALL)**

NCT Number: NCT02669264

Document Date: 19 April 2017

CLINICAL STUDY PROTOCOL
IND: 126138

A Phase 1, Open-label, Dose-Escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Anti-tumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Acute Lymphoblastic Leukemia (B-ALL)

PROTOCOL NO.: ADCT-402-102
EudraCT Number: 2016-000953-10

Sponsor:

ADC Therapeutics SA
[Redacted]

Sponsor Contact:

[Redacted]

Medical Monitor:

[Redacted]

Date of Original Protocol: 18 September 2015
Date of Protocol Amendment 1: 8 December 2015
Date of Protocol Amendment 2: 14 March 2016
Date of Protocol Amendment 3: 19 April 2017

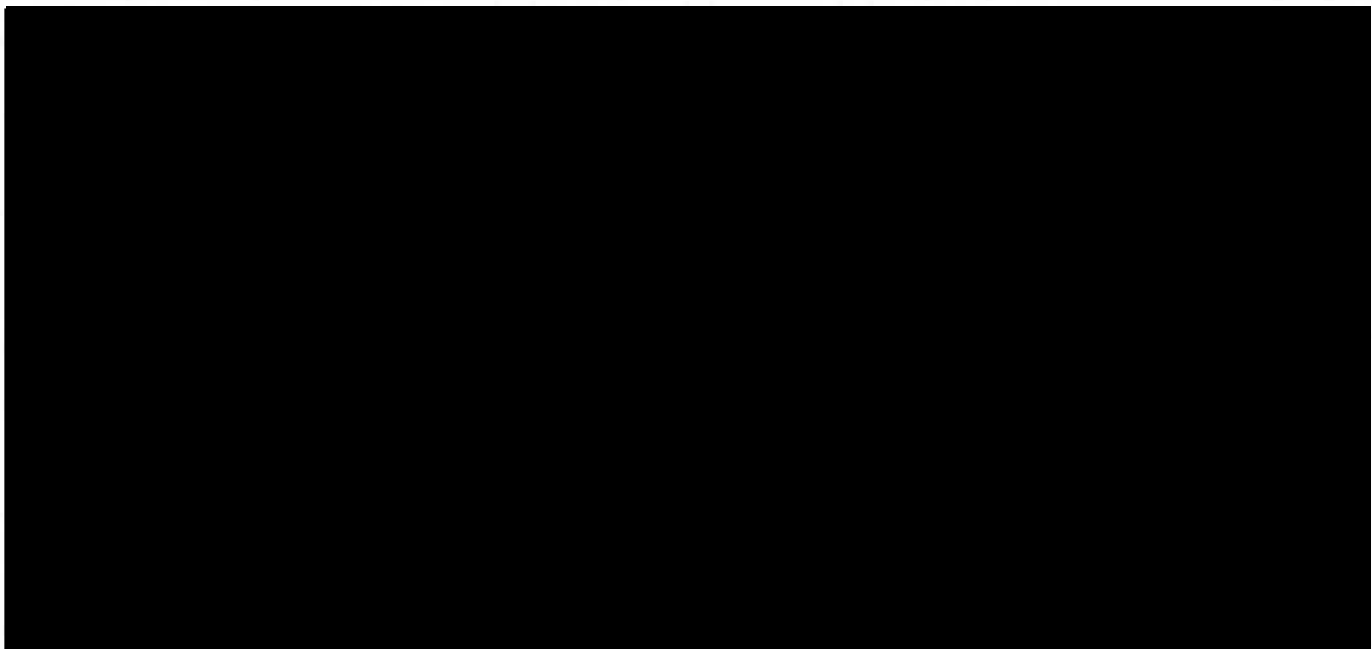
Confidentiality Statement

All financial and non-financial support for this study will be provided by ADC Therapeutics SA. The concepts and information contained in this document or generated during the study are

considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of ADC Therapeutics SA. The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R1), Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 1, Open-label, Dose-Escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Anti-tumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Acute Lymphoblastic Leukemia (B-ALL)
Protocol Number	ADCT-402-102
Date of Original Protocol:	18 September 2015
Protocol Amendment 1:	8 December 2015
Protocol Amendment 2:	14 March 2016
Protocol Amendment 3:	19 April 2017



Declaration of Investigator

I have read and understood all sections of the protocol entitled “A Phase 1, Open-label, Dose-Escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Anti-tumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Acute Lymphoblastic Leukemia (B-ALL)” and the accompanying Investigator Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 3, dated 19 April 2017, the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics SA or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.


I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ADC Therapeutics SA.

Signature of Principal Investigator


Date


Printed Name of Principal Investigator

Table of Contents

Table of Contents	5
List of Tables.....	8
List of Figures.....	9
Protocol Synopsis.....	10
List of Abbreviations.....	20
1 Introduction and Study Rationale.....	23
1.1 Description of ADCT-402.....	23
1.2 Study Rationale.....	24
1.2.1 Clinical Background	24
1.2.2 Biology of CD19.....	24
1.2.3 Non-clinical Efficacy and Safety of ADCT-402.....	25
1.3 Safety of Commercially Available Antibodies Directed against CD19	26
2 Study Objectives.....	27
2.1 Primary Objectives.....	27
2.2 Secondary Objectives.....	27
	
3 Investigational Plan and Patient Selection	28
3.1 Study Design.....	28
3.2 Dose-Escalation	28
3.3 Selection of Study Population.....	31
3.3.1 Inclusion Criteria	31
3.3.2 Exclusion Criteria	32
4 Study Procedures	35
4.1 Procedures by Study Day – Every 3-Week (Q3W) Dosing Schedule	35
4.1.1 Screening Period (Day –28 to –1)	35
4.1.2 Day 1 (+ 3 days) of Each Cycle.....	36
4.1.3 Day 2 (Cycles 1 and 2)	39
4.1.4 Day 3 (Cycles 1 and 2)	39
4.1.5 Day 5 (Cycles 1 and 2)	39

4.1.6	Day 8 (\pm 2 days) of Each Cycle.....	39
4.1.7	Day 15 (\pm 2 days) of Cycles 1 and 2	40
4.1.8	End of Treatment Visit.....	40
4.1.9	12-week Follow-up Visit	41
4.1.10	Long-term Follow-up.....	41
4.2	Withdrawal of Patients from the Study.....	41
4.2.1	Reasons for Withdrawal/Discontinuation	41
4.2.2	Handling of Withdrawals.....	42
4.2.3	Patient Replacements.....	43
5	Study Treatments	44
5.1	Method of Assigning Patients to Treatment.....	44
5.2	Prophylactic Treatments for Hypersensitivity	44
5.3	Treatments Administered	45
5.4	Dose Delays and Modifications	46
5.5	Identity of Investigational Product.....	46
5.5.1	ADCT-402 Drug Product.....	46
5.6	Management of Clinical Supplies.....	47
5.6.1	Study Drug Packaging and Storage.....	47
5.6.2	Study Drug Preparation and Administration.....	47
5.6.3	Study Drug Accountability	47
5.7	Overdose Management	47
5.8	Treatment Compliance.....	47
5.9	Concomitant Treatment.....	48
5.9.1	Prohibited During Study	48
5.9.2	Permitted During Study	48
6	Study Assessments and Procedures	50
6.1	Efficacy Assessments.....	50
6.2	Pharmacokinetic, Pharmacodynamic and XXXXXXXXXX	51
6.2.1	Pharmacokinetic Assessments	51
6.2.2	Pharmacodynamic and Other Assessments	51
6.3	Safety and Tolerability Assessments.....	52
6.3.1	Definition of Dose-Limiting Toxicities	52

6.3.2	Safety Oversight by the Dose-Escalation Steering Committee	52
6.3.3	Adverse Events	53
6.3.4	Pregnancy	56
6.3.5	Clinical Laboratory Analyses	56
6.3.6	Electrocardiograms	57
6.3.7	Physical Examination	57
6.3.8	Vital Sign Measurements	57
6.3.9	Weight	57
6.3.10	Eastern Cooperative Oncology Group Performance Status	57
6.4	Sample Handling, Storage and Shipment	58
7	Statistical and Analytical Plan	59
7.1	Safety Endpoints	59
7.2	Endpoints	59
7.2.1	Primary Endpoints	59
7.2.2	Secondary Endpoints	59
		
7.3	Sample Size Calculations	59
7.4	Analysis Sets	60
7.5	Description of Subgroups to be Analyzed	60
7.6	Statistical Analysis Methodology	60
7.6.1	Safety Analyses	60
7.6.2	Efficacy Analysis	61
7.6.3	Pharmacokinetic and Pharmacodynamic Analyses	62
7.6.4	Study Drug Exposure	63
7.7	Data Quality Assurance	63
7.7.1	Data Management	63
8	Ethics	65
8.1	Independent Ethics Committee or Institutional Review Board	65
8.2	Ethical Conduct of the Study	65
8.3	Patient Information and Consent	65
9	Investigator's Obligations	66
9.1	Confidentiality	66

9.2	Financial Disclosure and Obligations	66
9.3	Adverse Events and Study Report Requirements	66
9.4	Investigator Documentation	67
9.5	Study Conduct.....	67
9.6	Adherence to Protocol.....	67
9.7	Investigator’s Final Report	67
9.8	Records Retention.....	67
		
10	Study Management.....	69
10.1	Monitoring	69
10.1.1	Monitoring of the Study.....	69
10.1.2	Inspection of Records	69
10.2	Management of Protocol Amendments and Deviations.....	69
10.2.1	Modification of the Protocol.....	69
10.2.2	Protocol Deviations	70
10.3	Study Termination.....	70
10.4	Final Report	70
11	Reference List.....	71
12	Appendices	74
12.1	Appendix: Schedule of Events	74
12.2	Appendix: CTCAE Immune System Hypersensitivity Grades.....	84

List of Tables

Table 1.	Planned Dose Levels for ADCT-402 (Q3W Administration)	29
Table 2.	Planned Dose Levels for ADCT-402 (QW Administration)	29
Table 3.	Definition of Severity Grades for Common Terminology Criteria for Adverse Events (CTCAE).....	55
Table 4.	Definition of Eastern Cooperative Oncology Group (ECOG) Performance Status Grades	58
Table 5.	Schedule of Study Procedures: Every 3-Week (Q3W) Dosing.....	75
Table 6.	Central Laboratory Sample Collection Schedule: Every 3-Week (Q3W) Dosing.....	78
Table 7.	Schedule of Study Procedures: Weekly (QW) Dosing	79

Table 8. Central Laboratory Sample Collection Schedule: Weekly (QW) Dosing, Cycle 1.....82

Table 9. Central Laboratory Sample Collection Schedule: Weekly (QW) Dosing, Cycle 2+83

Table 10. CTCAE Immune System Hypersensitivity Grades.....84

List of Figures

Figure 1. Schematic Representation and Chemical Structure of ADCT-40223

Figure 2. Schematic Representation for Dose-Escalation (3+3) Design30

Protocol Synopsis

Protocol Number: ADCT-402-102

Title: A Phase 1, Open-label, Dose-Escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Anti-tumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-lineage Acute Lymphoblastic Leukemia (B-ALL).

Sponsor: ADC Therapeutics SA

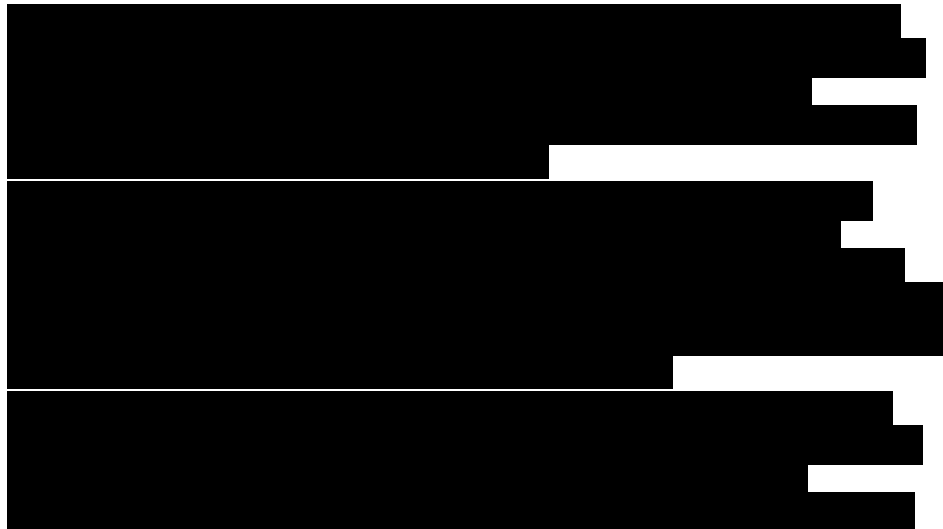
Study Phase: 1

Study Sites: Approximately 10 sites during dose-escalation (Part 1) and 25 sites during dose expansion (Part 2).

Indication: Patients with relapsed or refractory B-cell lineage acute lymphoblastic leukemia (B-ALL) who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available, in the opinion of the Investigator.

Rationale: More than 6,000 new cases of ALL are diagnosed yearly in the U.S., with more than half (58%) occurring in patients <20 years of age. Children younger than 15 years have the best prognosis, with an expected 5-year survival rate of 88%, compared with 61% for adolescents and young adults and 40 to 45% for adults >40 years of age. ALL in older patients is more often associated with poor prognostic factors, including a higher relapse rate, higher incidence of minimal residual disease (MRD), and poorer tolerance to induction therapy.

In normal human tissue, expression of cluster of differentiation 19 (CD19) is limited to the developmental stages of the B-cell and is lost in terminally differentiated plasma cells. Expression of CD19 is maintained in hematologic B-cell malignancies, including B-ALL.



[REDACTED]

Objectives:

Primary objectives:

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-402 in patients with relapsed or refractory B-ALL (Part 1).
- Determine the recommended dose of ADCT-402 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCT-402 in Part 2 (expansion) at the dose level recommended in Part 1.

Secondary objectives:

- Evaluate the clinical activity of ADCT-402, based on the patient's response to treatment (complete response [CR], CR with incomplete blood count recovery [CRi], partial response [PR], progressive disease [PD], no response [NR]) and determination of the overall response rate (ORR), duration of response (DOR), overall survival (OS), and progression-free survival (PFS).
- Characterize the pharmacokinetic (PK) profile of ADCT-402 (total antibody, drug-to-antibody ratio [DAR] ≥ 0), PBD-conjugated antibody (DAR ≥ 1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) against ADCT-402 in serum before, during, and after treatment with ADCT-402.

[REDACTED]

Patient Selection:

Inclusion Criteria:

1. Male or female patients, ages 12 years and older, with relapsed or refractory B-ALL who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available, in the opinion of the Investigator.

Note: Diagnosis and classification as per World Health Organization (WHO) classification of B-ALL ([Swerdlow, 2008](#)).

2. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
3. Serum/plasma creatinine ≤ 1.5 mg/dL. If the patient has a serum/plasma creatinine > 1.5 mg/dL, creatinine clearance must be > 60 mL/min/1.73 m², as calculated by the Cockcroft and Gault equation ([Cockcroft and Gault, 1976](#)).
4. Serum/plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 times the upper limit of normal (ULN); ≤ 5 times ULN if there is liver or bone involvement.
5. Total serum/plasma bilirubin ≤ 1.5 times ULN. Patients with known Gilbert's syndrome may have a total bilirubin up to ≤ 3 times ULN).
6. Negative urine or serum beta-human chorionic gonadotropin (β -HCG) pregnancy test within 7 days prior to the Cycle 1, Day 1 visit, for women of child-bearing potential.
7. Women of child-bearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-402. Men with female partners who are of child-bearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-402.

* Defined as: Sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

** Defined as: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.
Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus

interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

8. WBC value of <15,000 cells/ μ L prior to Cycle 1 Day 1.

Exclusion Criteria:

1. Patients who, in the opinion of the Investigator, have an option for other treatment for B-ALL at the current state of disease.
2. Known active central nervous system (CNS) leukemia, defined as morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF), use of CNS-directed intrathecal treatment for active disease within 28 days prior to Screening, or symptomatic CNS leukemia (i.e., cranial nerve palsies or other significant neurologic dysfunction) within 28 days prior to Screening.

Note: Patients may have a history of CNS leukemic involvement if they have received prior treatment for CNS involvement and no evidence of active disease (defined as ≥ 2 consecutive spinal fluid assessments with no evidence of disease) is present at Screening. Prophylactic intrathecal chemotherapy is not a criterion for exclusion.

3. Patients with Burkitt's leukemia/lymphoma.
4. Active graft-versus-host disease.
5. Autologous or allogenic transplant within the 60 days prior to Screening.
6. Known history of immunogenicity or hypersensitivity to a CD19 antibody.
7. Known history of positive serum human ADA.
8. Active autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barré syndrome and myasthenia gravis); other CNS autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
9. Known seropositive for human immunodeficiency (HIV) virus, hepatitis B surface antigen (HBsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy.

Note: Testing is not mandatory to be eligible. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).

10. History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome.
11. Pregnant or breastfeeding women.
12. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure > 115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary

- disease, coronary angioplasty, myocardial infarction within 6 months prior to Screening, or uncontrolled atrial or ventricular cardiac arrhythmias.
13. Use of any other experimental medication(s) within 14 days or 5 half-lives but, in no case <14 days prior to start of study treatment on Cycle 1, Day 1, except if approved by the Sponsor.
 14. Major surgery, chemotherapy, systemic therapy (excluding hydroxyurea, steroids and any targeted small molecules or biologics), or radiotherapy within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1, Day 1 treatment, except if approved by the Sponsor.
 15. Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE Version 4.0] Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades of alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to the Screening visit.
 16. Isolated extramedullary relapse (i.e. testicular, CNS).
 17. Congenital long QT syndrome or a corrected QTc interval of ≥ 450 ms at the Screening visit (unless secondary to pacemaker or bundle branch block).
 18. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast, or other malignancy that the Sponsor's Medical Monitor and the Investigator agree and document should not be exclusionary.
 19. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.

Study Design:

This is a Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of ADCT-402, used as monotherapy, in patients with relapsed or refractory B-ALL. The study will determine the MTD, as well as evaluate the preliminary activity, PK, pharmacodynamics (PD), and [REDACTED] of ADCT-402.

In Part 1, patients will be assigned to treatment according to a 3+3 dose-escalation design (see below) and oversight by a Dose-Escalation Steering Committee (DESC). In Part 2 (expansion), all patients will be assigned to the dose level of ADCT-402 identified in Part 1.

**Estimated
Duration of Patient
Participation and
Study Duration:**

For each patient, the study will include a Screening period (up to 28 days), a treatment period (until withdrawal), and a follow-up period to assess disease progression and survival for up to 12 months after the last dose of study drug. The total study duration will be dependent on overall patient tolerability to the study drug and response to treatment. It is anticipated that the duration of the entire study (Parts 1 and 2) could be approximately 3 years from first patient treated to last patient completed.

Patients who discontinue treatment for any reason other than disease progression will continue to be followed approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anti-cancer treatment. After documentation of disease progression or start of new treatment, patients will be followed (by telephone contact or chart review) approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.

Patients may withdraw from the study at any time and for any reason, without prejudice to their future medical care, by the Investigator or others at the study site.

**Efficacy
Assessments:**

The Investigator's assessment of response to treatment will be based on bone marrow samples (aspirate or biopsy if aspirate unattainable) obtained during the study. Determination of ORR, DOR, OS, and PFS will be determined based on the Investigator's assessment of the patient's response to ADCT-402 as CR, CRi, PR, PD, or NR.

- Complete response is defined as achieving each of the following:
 - Bone marrow differential showing $\leq 5\%$ blast cells.
 - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$.
 - Absence of extramedullary disease.
 - Patient is independent of red blood cell transfusions.
- Complete response with incomplete blood count recovery is defined as achieving all CR criteria except that values for ANC may be $< 1.0 \times 10^9/L$ and/or values for platelets may be $< 100 \times 10^9/L$.
- Partial response is defined as achieving each of the following:
 - ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$.
 - Bone marrow differential showing a $\geq 50\%$ decrease from baseline in the percentage of bone marrow blast cells to a level $> 5\%$ and $\leq 25\%$,
or
bone marrow differential showing $< 5\%$ blast cells.
- No response is defined as not achieving CR, CRi, or PR.
- PD is defined as:

- For patients with CR or CRi, the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level $\geq 5\%$, or development of extramedullary disease.
- For patients with PR, the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR.

DOR and ORR will be defined among responders (CR, CRi, PR); OS and PFS will also be determined.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Safety Assessments:

Safety will be assessed based on the evaluation of adverse events (AEs), serious AEs (SAEs), treatment discontinuations due to AEs, dose-limiting toxicities (DLTs), periodic 12-lead electrocardiogram (ECG) recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, coagulation panel, biochemistry, pregnancy (for women of child-bearing potential), and urinalysis test results obtained at various timepoints during the study. Adverse events will be graded according to CTCAE Version 4.0.

Definition of DLT:

A DLT is defined as any of the following events, except those that are clearly due to underlying disease or extraneous causes:

- A hematologic DLT is defined as:
 - Grade 3 or higher event of neutropenia or thrombocytopenia, or a Grade 4 anemia, with a hypocellular bone marrow lasting for 6 weeks or more after the start of a cycle, in the absence of residual leukemia (i.e., with

<5% blasts). In case of a normocellular bone marrow with <5% blasts, 8 weeks with \geq Grade 3 pancytopenia will be considered a DLT.

- A non-hematologic DLT is defined as:
 - Grade 4 tumor lysis syndrome (Grade 3 TLS will not constitute DLT unless it leads to irreversible end-organ damage).
 - Grade 3 or higher AE (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grades of alopecia).
 - CTCAE Grade 3 or higher hypersensitivity reaction (regardless of premedication).
 - CTCAE Grade 3 or higher skin ulceration.

The protocol-defined DLT observation period for dose-escalation will be 1 cycle.

Note: Patients who experience a DLT during Cycle 1 are to be permanently discontinued from the study.

**Investigational
Product, Dosage,
and Mode of
Administration:**

ADCT-402 is a sterile formulation containing PBD-conjugated humanized monoclonal IgG1 antibody (DAR \geq 1), humanized monoclonal IgG1 antibody (DAR = 0), and SG3249. It is provided pre-formulated in 10 mL single-use, glass vials containing approximately 16 mg ADCT-402 per vial (deliverable volume 3.2 mL, with an additional 0.3 mL overfill at 5 mg/mL).

Patients will receive a 1-hour intravenous (IV) infusion of ADCT-402 on Day 1 of Cycle 1. If ADCT-402 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion.

Every 3-Week (Q3W) Administration

Patients will be given ADCT-402 on Day 1 of each 3-week (21-day) treatment cycle.

Weekly (QW) Administration

Patients will be given ADCT-402 QW on Days 1, 8, and 15 of each 3-week (21-day) treatment cycle.

A patient will maintain the same treatment schedule throughout the duration of the trial.

Once a patient achieves CR/CRi, frequency or dose may be adjusted by the DESC based on emerging safety, efficacy and PK profile.

The trial will be continuously monitored for emerging safety, efficacy and/or PK profile, and the DESC will determine if it is appropriate to maintain a QW

**Dose-Escalation
Design:**

schedule, revert to an every 3-week (Q3W) schedule, or test other dosing regimens.

In Part 1, patients will be assigned to treatment with ADCT-402 at escalating doses according to a 3+3 study design. The initial dose of ADCT-402 will be 15 µg/kg (Dose Level 1), and the highest allowed dose will be 600 µg/kg. The DLT observation period for dose-escalation is 1 cycle. Patients will be entered sequentially to each dose level.

The first dose level for the QW dosing will be based on the safety and tolerability of patients who have been treated on the Q3W schedule. The first 3 patients will be given a cumulative dose each cycle that is comparable to (but not higher than) the highest dose tested at the Q3W dosing schedule at which 3 patients completed the DLT observation period without a DLT. For example, if the highest Q3W dose tested at which 3 patients did not experience a DLT was cohort 150 µg/kg, the first cohort to receive QW dosing will receive 50 µg/kg each week for 3 weeks.

For each dose level, if none of the first 3 patients at that level experiences a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experiences a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD; therefore, is defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experiences a DLT.

During Part 1, the DESC may expand enrollment at doses below the current dose level as part of the dose-escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient who has achieved a PR (or better). No more than 10 patients in total can be treated at any dose level unless ≥ 3 of the 10 patients have achieved a PR or better.

During dose expansion, patients will be monitored for safety using the same DLT criteria employed during dose-escalation. If during the treatment period, > 30% of patients experience safety events that would meet the criteria that define a DLT in the dose-escalation phase of the study, enrollment in the expansion cohort(s) may be paused and the study data reviewed to determine whether additional monitoring or other action (such as alternate dose levels) should be evaluated prior to further enrollment.

Sample Size:

This is a Phase 1 study with a maximum sample size of approximately 70 patients. It is estimated that Part 1 (dose-escalation) will enroll up to approximately 40 patients and Part 2 (dose expansion) will enroll up to approximately 30 patients.

Date of Protocol:

18 September 2015

**Date of Protocol
Amendment 1:**

8 December 2015

**Date of Protocol
Amendment 2:**

14 March 2016

**Date of Protocol
Amendment 3:**

19 April 2017

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADC	Antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AI	accumulation index
Ala	alanine
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC _{0-∞}	area under the concentration-time curve from time zero to infinity
AUC _{0-last}	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC _{0-τ}	area under the concentration-time curve from time zero to the end of the dosing interval
B-ALL	B-cell lineage acute lymphoblastic leukemia
β-HCG	beta human chorionic gonadotropin
BMA	bone marrow aspirate
BSA	body surface area
BSI	before start of infusion
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
C _L	clearance
C _{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRi	complete response with incomplete blood count recovery
CRO	contract research organization
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% dextrose in water
DAR	drug-to-antibody ratio

Abbreviation	Definition
DESC	Dose-Escalation Steering Committee
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EWOC	escalation with overdose control
eCRF	electronic case report form
EOI	end of infusion
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest non-severe toxic dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	International Normalized Ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
IVF	intravenous fluid
kDa	kilodalton
MNC	mononuclear cells
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
NR	no response
ORR	overall response rate
OS	overall survival
PABA	para-aminobenzoic acid

Abbreviation	Definition
PBD	pyrrolbenzodiazepine
PD	pharmacodynamics
PEG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3-week
QTc	corrected QT interval
QW	every week
QWBA	quantitative whole-body autoradiography
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
λ_z	terminal elimination phase rate constant
T_{max}	time to maximum concentration
$T_{1/2}$	terminal half-life
ULN	upper limit of normal
V_{ss}	volume of distribution at steady-state
Val	valine
V_Z	volume of distribution
WB	whole blood
WBC	white blood cell
WHO	World Health Organization

1 Introduction and Study Rationale

1.1 Description of ADCT-402

ADCT-402 is an antibody-drug conjugate (ADC) composed of a humanized antibody (RB4v1.2) directed against human cluster of differentiation 19 (CD19), attached with a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin.

The PBD dimers are highly efficient anti-cancer drugs that bind in the minor groove of DNA and form highly cytotoxic DNA interstrand cross-links. The schematic representation of ADCT-402 is presented in [Figure 1](#).

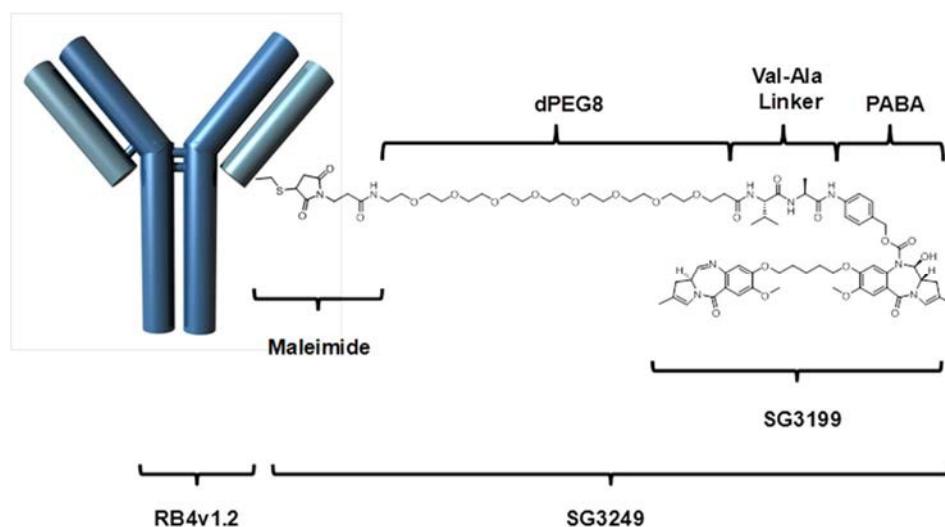


Figure 1. Schematic Representation and Chemical Structure of ADCT-402

Abbreviations: Ala, alanine; PABA, para-aminobenzoic acid; PEG, polyethylene glycol; RB4v1.2, human monoclonal antibody directed against human CD19; Val, valine.

The make-up of ADCT-402 includes:

- RB4v1.2: A humanized monoclonal antibody specific for human CD19 of the immunoglobulin G1 (IgG1), kappa isotype, generated by the variable domain resurfacing of the murine monoclonal anti-B4 (anti-CD19) antibody ([Roguska, 1996](#)).
- SG3249: A PBD linker that comprises the PBD dimer SG3199 and all linker components, including the maleimide, 8-polyethylene glycol, a protease-sensitive valine-alanine linker and a para-aminobenzoic acid (PABA) self-immolative group.

ADCT-402 binds with picomolar affinity to human CD19. After binding and internalization, ADCT-402 is transported to the lysosomes, where the protease-sensitive linker is cleaved and free PBD dimers are released inside the target cell. The released PBD dimers bind into the minor groove of DNA and form highly cytotoxic DNA interstrand cross-links ([Hartley, 2011a](#)). The cross-links formed by PBD dimers are relatively non-distorting of the DNA structure, making them hidden to repair mechanisms, allowing for a longer effective period ([Adair, 2012](#)) and making them effective in multiple cancer cell lines resistant to other chemotherapy.

1.2 Study Rationale

Study ADCT-402-102 is the first clinical study with ADCT-402 in patients with B-cell lineage acute lymphoblastic leukemia (B-ALL).

1.2.1 Clinical Background

Acute lymphoblastic leukemia is a hematologic malignancy characterized by the clonal expansion of lymphoid blast cells (B- or T-cell lineage) in the peripheral blood, bone marrow, and/or other tissues. As per the US Surveillance Epidemiology and End Results (SEER) statistical fact sheets, an estimated 6,250 new cases of ALL will be diagnosed in the U.S. in 2015 (0.4% of all cancer cases). It is the most common leukemia diagnosed in children with more than half (58%) of all new cases occurring in patients younger than 20 years of age. The expected overall 5-year survival rate for ALL is approximately 68% ([National Cancer Institute, 2015](#)).

Due to advances in therapy and supportive care, survival rates for ALL have been improving across all age groups. Children younger than 15 years have the best prognosis, with an expected 5-year survival rate of 88%. However, survival rates for older patients have not improved to the same extent. The expected 5-year survival for adolescents and young adults (ages 15 to <20 years) with ALL is approximately 61%, which decreases to approximately 40 to 45% for adults older than 40 years of age ([National Cancer Institute, 2015](#)).

Compared with children, ALL in older patients is more often associated with poor prognostic factors, including a higher relapse rate, cell markers associated with poor outcomes, low incidence of favorable subtypes, higher incidence of minimal residual disease (MRD), and poorer tolerance to induction therapy ([Inaba, 2013](#); [Moorman, 2007](#); [Schafer and Hunger, 2011](#)).

1.2.2 Biology of CD19

Human CD19 is a 95 kilodalton (kDa) type I transmembrane glycoprotein belonging to the immunoglobulin super family ([Carter and Barrington, 2004](#); [Tedder, 2009](#)). In normal human tissue, expression of CD19 is restricted to the various stages of B-cell development (from early pre-B stage to mature B-cells), but it is lost in terminally differentiated plasma cells ([Haas and Tedder, 2005](#); [Scheuermann and Racila, 1995](#)). Once bound to an antibody, CD19 is rapidly internalized by the cell ([Gerber, 2009](#); [Blanc, 2011](#)). It is not shed into the circulation to the

extent observed with other CD antigens¹ (Cooper et al, 2004); therefore, low to no levels of soluble CD19 are present to compete with binding at the target tissue.

Expression of CD19 is maintained in hematologic malignancies of B-cell lineage (e.g., B-ALL, hairy cell leukemia, Burkitt's lymphoma, follicular lymphoma, diffuse large B-cell lymphoma) (Anderson, 1984; Scheuermann and Racila, 1995; Wang, 2012). It is not expressed in most cases of chronic myelogenous leukemia, acute myelogenous leukemia, T-cell ALL, or multiple myeloma (Wang, 2012).

1.2.3 Non-clinical Efficacy and Safety of ADCT-402

The potential for ADCT-402 in treating B-cell hematologic malignancies expressing CD19 has been shown by complete responses in mouse xenograft models of human-derived B-cell leukemias and lymphomas following single, low-dose administration. The efficacy of ADCT-402 in these models is due to targeted delivery [REDACTED].

ADCT-402 is not pharmacologically cross-reactive (active) in any standard species used for non-clinical safety assessment (Blanc, 2011). In the absence of CD19 target engagement in the rat and monkey, it is not possible to non-clinically evaluate the safety consequences associated with possible B-cell depletion. However, the impact and overall safety of B-cell depletion has been investigated clinically and non-clinically with other B-cell deleting agents and been shown to be generally safe and well tolerated (Chen and Cohen, 2012; Kimby, 2005).

The safety studies therefore assessed the potential off-target effects of ADCT-402 and the impact of ADCT-402 on the tissues normally associated with antibody clearance. In rats, ADCT-402 is well tolerated at doses up to 2 mg/kg [REDACTED]

As per guidance from the Food and Drug Administration (FDA), the starting dose of ADCT-402 chosen for this study is 15 µg/kg. See the Investigator Brochure for ADCT-402 for additional information, including guidance for the Investigator.

¹ Note: A report of soluble CD19 detected in the cerebrospinal fluid of patients with certain types of B-cell lymphoma was recently published (Muniz, 2014).

1.3 Safety of Commercially Available Antibodies Directed against CD19

Although several antibodies targeted against CD19 are currently in clinical development with different manufacturers ([Jabbour, 2015](#)), only one is commercially available in the U.S.

Blinatumomab (Blincyto™, Amgen, Thousand Oaks, CA) is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative, relapsed or refractory B-ALL. The antibody binds to CD19 on B-lineage cells and to CD3 on T cells. The most commonly reported adverse reactions reported with its use include pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, and constipation ([Amgen, 2014](#)).

2 Study Objectives

2.1 Primary Objectives

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-402 in patients with relapsed or refractory B-ALL in Part 1.
- Determine the recommended dose of ADCT-402 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCT-402 in Part 2 (expansion) at the dose level recommended in Part 1.

2.2 Secondary Objectives

- Evaluate the clinical activity of ADCT-402, based on the patient's response to treatment (complete response [CR], CR with incomplete blood count recovery [CRi], partial response [PR], progressive disease [PD], no response [NR]) and determination of the overall response rate (ORR), duration of response (DOR), overall survival (OS), and progression-free survival (PFS).
- Characterize the pharmacokinetic (PK) profile of ADCT-402 (total antibody, drug-to-antibody ratio [DAR] ≥ 0), PBD-conjugated antibody (DAR ≥ 1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) to ADCT-402 in blood before, during, and after treatment with ADCT-402.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3 Investigational Plan and Patient Selection

3.1 Study Design

This is a Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of ADCT-402, used as monotherapy, in patients with relapsed or refractory B-ALL. The study will determine the MTD, as well as evaluate the preliminary activity, PK, pharmacodynamics (PD), and [REDACTED] for ADCT-402.

Patients will receive a 1-hour intravenous (IV) infusion of ADCT-402 on Day 1 of Cycle 1. If ADCT-402 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion. Weekly (QW) administration will be evaluated as described in [Section 3.2](#). Additional treatment schedules may be considered based on emerging data.

For each patient, the study will include a Screening period (up to 28 days), a treatment period (until withdrawal, [Section 4.2.1](#)), and a follow-up period to assess disease progression and survival for up to 12 months after the last dose of study drug. The total study duration will be dependent on overall patient tolerability to the study drug and response to treatment. It is anticipated that the duration of the entire study (Parts 1 and 2) could be approximately 3 years from first patient treated to last patient completed.

In Part 1, patients will be assigned to treatment according to a 3+3 dose-escalation design ([Section 3.2](#)) and oversight of a Dose-Escalation Steering Committee (DESC) ([Section 6.3.2](#)). In Part 2, (expansion), all patients will be assigned to the dose level of ADCT-402 identified in Part 1.

Patients who discontinue treatment for any reason other than disease progression will continue to be followed approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anti-cancer treatment. After documentation of disease progression or start of new treatment, patients will be followed (by telephone contact or chart review) approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.

3.2 Dose-Escalation

In Part 1, dose-escalation will be conducted according to a 3+3 design ([Figure 2](#)). The initial dose of ADCT-402 will be 15 µg/kg (Dose Level 1), and the highest allowed dose will be 600 µg/kg. The potential dose levels are described in [Table 1](#) and [Table 2](#).

Table 1. Planned Dose Levels for ADCT-402 (Q3W Administration)

Dose Level	Dose of ADCT-402	Dose Level	Dose of ADCT-402
1	15 µg/kg	9	300 µg/kg
2	30 µg/kg	10	350 µg/kg
3	60 µg/kg	11	400 µg/kg
4	90 µg/kg	12	450 µg/kg
5	120 µg/kg	13	500 µg/kg
6	150 µg/kg	14	550 µg/kg
7	200 µg/kg	15	600 µg/kg
8	250 µg/kg		

Table 2. Planned Dose Levels for ADCT-402 (QW Administration)

Dose Level	Dose of ADCT-402	Dose Level	Dose of ADCT-402
1	5 µg/kg	7	75 µg/kg
2	10 µg/kg	8	100 µg/kg
3	20 µg/kg	9	125 µg/kg
4	30 µg/kg	10	150 µg/kg
5	40 µg/kg	11	175 µg/kg
6	50 µg/kg	12	200 µg/kg

The dose-limiting toxicity (DLT, [Section 6.3.1](#)) observation period for dose-escalation is 1 cycle. The first patient enrolled into the study at 15 µg/kg (Dose Level 1) must be observed for 7 days for occurrence of adverse events (AEs) prior to treating the second patient in the study. Patients will be entered sequentially to each dose level.

For each dose level, if none of the first 3 patients at that level experiences a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experiences a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD;

therefore, is defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experiences a DLT.

No intra-patient dose-escalation is allowed.

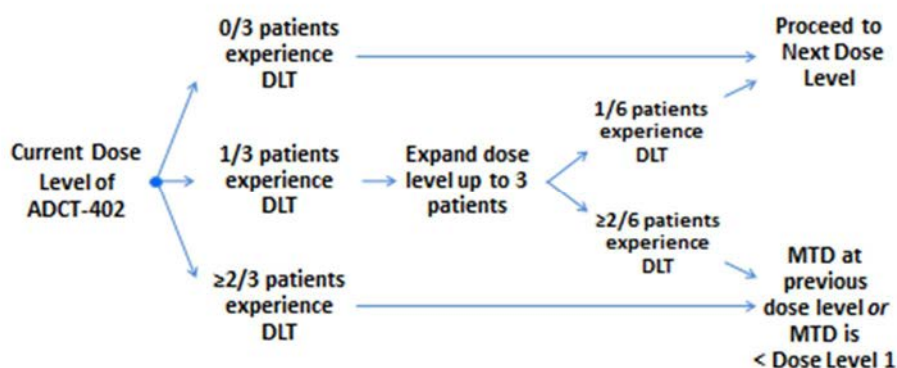


Figure 2. Schematic Representation for Dose-Escalation (3+3) Design

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose; <, less than; ≥ greater than or equal to.

The number of dose levels will depend on the emergent toxicity profile of ADCT-402 and will be decided by the DESC (Section 6.3.2); PK, and PD evaluations may also inform decision making.

Every 3 Week (Q3W) Administration

Patients will be given ADCT-402 on Day 1 of each 3-week treatment cycle.

Weekly (QW) Administration

Patients will be given ADCT-402 QW on Days 1, 8 and 15 of each 3-week (21-day) treatment cycle.

The first dose level for the QW dosing will be based on the safety and tolerability of patients who have been treated on the every 3-week (Q3W) schedule. The first 3 patients will be given a cumulative dose each cycle that is comparable to (but not higher than) the highest dose tested at the Q3W dose schedule at which 3 patients completed the DLT observation period without a DLT. For example, if the highest Q3W dose tested at which 3 patients did not experience a DLT was cohort 150 µg/kg, the first cohort to receive QW dosing will receive 50 µg/kg each week for 3 weeks.

A patient will maintain the same treatment schedule throughout the duration of the trial.

Weekly dosing will be implemented at the discretion of the DESC (and in accordance with local ethics committee approvals). Once a patient achieves CR/CRi, frequency or dose may be adjusted by the DESC based on emerging safety, efficacy and PK profile.

The trial will be continuously monitored for emerging safety, efficacy and/or PK profile and the DESC will determine if it is appropriate to maintain a QW schedule, revert to a Q3W schedule, or test other dosing regimens.

During Part 1, the DESC may expand enrollment at doses below the current dose level as part of the dose-escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient who has achieved a PR ([Section 6.1](#)) or better. No more than 10 patients in total can be treated at any dose level unless ≥ 3 of the 10 patients have achieved a PR or better.

During dose expansion, patients will be monitored for safety using the same DLT criteria employed during dose-escalation. If during the treatment period, $> 30\%$ of patients experience safety events that would meet the criteria that define a DLT in the dose-escalation phase of the study, enrollment in the expansion cohort(s) may be paused and the study data reviewed to determine whether additional monitoring or other action (such as alternate dose levels) should be evaluated prior to further enrollment.

3.3 Selection of Study Population

This is a Phase 1 study with a sample size of up to 70 patients. It is estimated that Part 1 (dose-escalation) will enroll approximately 40 patients at 10 sites and Part 2 (dose expansion) will enroll approximately 30 patients at 25 sites. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

3.3.1 Inclusion Criteria

1. Male or female patients, ages 12 years and older, with relapsed or refractory B-ALL who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available, in the opinion of the Investigator.

Note: Diagnosis and classification as per World Health Organization (WHO) classification of B-ALL ([Swerdlow, 2008](#)).

2. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
3. Serum/plasma creatinine ≤ 1.5 mg/dL. If the patient has a serum/plasma creatinine > 1.5 mg/dL, creatinine clearance must be > 60 mL/min/1.73 m², as calculated by the Cockcroft and Gault equation ([Cockcroft and Gault, 1976](#)).
4. Serum/plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 times the upper limit of normal (ULN); ≤ 5 times ULN if there is liver or bone involvement.

5. Total serum/plasma bilirubin ≤ 1.5 times ULN. Patients with known Gilbert's syndrome may have a total bilirubin up to ≤ 3 times ULN).
6. Negative urine or serum beta-human chorionic gonadotropin (β -HCG) pregnancy test within 7 days prior to the Cycle 1, Day 1 visit for women of child-bearing potential.
7. Women of child-bearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-402. Men with female partners who are of child-bearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-402.

* Defined as: Sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

** Defined as: Hormonal contraceptives (oral, injectable, patch, intrauterine devices, male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient. **Note:** The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

8. WBC value of $< 15,000$ cells/ μ L prior to Cycle 1 Day 1.

3.3.2 Exclusion Criteria

1. Patients who, in the opinion of the Investigator, have an option for other treatment for B-ALL at the current state of disease.
2. Known active central nervous system (CNS) leukemia, defined as morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF), use of CNS-directed intrathecal treatment for active disease within 28 days prior to Screening, or symptomatic CNS leukemia (i.e., cranial nerve palsies or other significant neurologic dysfunction) within 28 days prior to Screening.

Note: Patients may have a history of CNS leukemic involvement if they have received prior treatment for CNS involvement and no evidence of active disease (defined as ≥ 2 consecutive spinal fluid assessments with no evidence of disease) is present at Screening. Prophylactic intrathecal chemotherapy is not a criterion for exclusion.

3. Patients with Burkitt's leukemia/lymphoma.
4. Active graft-versus-host disease.
5. Autologous or allogenic transplant within the 60 days prior to the Screening visit.

6. Known history of immunogenicity or hypersensitivity to a CD19 antibody.
7. Known history of positive serum human ADA.
8. Active autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barré syndrome and myasthenia gravis); other CNS autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
9. Known seropositive for human immunodeficiency (HIV) virus, hepatitis B surface antigen (HBsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy.

Note: Testing is not mandatory to be eligible. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).

10. History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome.
11. Pregnant or breastfeeding women.
12. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure >115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty, myocardial infarction within 6 months prior to Screening, or uncontrolled atrial or ventricular cardiac arrhythmias.
13. Use of any other experimental medication(s) within 14 days or 5 half-lives, but in no case <14 days prior to the start of study treatment on Cycle 1, Day 1, except if approved by the Sponsor.
14. Major surgery, chemotherapy, systemic therapy (excluding hydroxyurea, steroids and any targeted small molecules or biologics), or radiotherapy within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1, Day 1 treatment, except if approved by the Sponsor.
15. Failure to recover (to [CTCAE Version 4.0] Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades of alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening.
16. Isolated extramedullary relapse (i.e., testicular, CNS).
17. Congenital long QT syndrome, or a corrected QTc interval of ≥ 450 ms, at the Screening visit (unless secondary to pacemaker or bundle branch block).
18. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast, or other malignancy that the Sponsor's Medical Monitor and the Investigator agree and document should not be exclusionary.

- 19.** Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.

4 Study Procedures

4.1 Procedures by Study Day – Every 3-Week (Q3W) Dosing Schedule

The following procedures will be performed during the study. Regardless of dosing schedule, all patients will complete the same Screening procedures described in [Section 4.1.1](#), as well as the same procedures described for End of Treatment (EOT; [Section 4.1.8](#)), 12-Week Follow-up Visit ([Section 4.1.9](#)) and Long-term Follow-up ([Section 4.1.10](#)).

Visit procedures described in [Sections 4.1.2 - 4.1.7](#) are for patients on the Q3W dosing schedule.

The Schedule of Events for the Q3W and QW dosing schedules are shown in [Table 5](#) and [Table 7](#), respectively, in [Appendix 12.1](#).


For QW dosing, most assessments remain uniform, with the following exceptions:

- Study Drug Administration occurs at Days 1, 8, and 15.
- Note: Bone Marrow Aspirate (BMA) or Biopsy for QW patients is still performed within 6 days prior to the first dose of the next cycle.
- Pharmacokinetic and Pharmacodynamics, ADA, WBC population, and additional renal function studies sampling schedule is adjusted according to the prescribed dosing schedule.

4.1.1 Screening Period (Day –28 to –1)

The following procedures will be performed within 28 days prior to the Day 1 visit of Cycle 1, unless otherwise specified:

- A signed and dated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF) is to be obtained prior to performing any study evaluations. Results (clinical laboratory, etc.) obtained prior to the date of informed consent, but within the allowed timeframe for screening, may be used for determination of patient eligibility only if obtained as part of the patient's standard of care.
- Demographic characteristics.
- Medical history (to include a complete history of all surgeries, significant diagnoses, and all cancer treatment [including surgery, radiation therapy, chemotherapy, etc.]).
- Serum or urine β -HCG pregnancy testing (women of child-bearing potential only).
- Physical examination, including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist. However, any unexplained lesion is to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted.

- Vital signs (arterial blood pressure, heart rate, respiratory rate, body temperature).
- Height.
- Weight.
- ECOG performance status.
- Bone marrow samples:
 - Bone marrow aspirate (or biopsy if aspirate is unattainable) for confirmation of disease, as per the WHO classification of ALL ([Swerdlow, 2008](#)), at an approved local clinical laboratory.
- Mononuclear cell (MNC) samples:
 - Whole blood (WB) sample collection with subsequent MNC isolation for retrospective central laboratory evaluation of CD19 and other CD markers (e.g., CD20, CD21, CD22).
 - 
- Hematology, coagulation panel, biochemistry, and urinalysis parameters.
- Patients with a WBC value >15,000 cells/μL may receive cytoreduction treatment with steroids (up to 4 days) or hydroxyurea, and/or leukopheresis, to lower the WBC value to <15,000 cells/μL prior to Cycle 1, Day 1 dosing ([Section 5.3](#)). Hydroxyurea may be used during Cycle 1 to control WBC count at Investigator discretion.

Note: Patients are not to receive treatment with study drug until their WBC value is $\leq 15,000$ cells/μL.

- 12-lead electrocardiogram (ECG).
- Collection of AE information.
- Collection of information on medications used (including prescription or over-the-counter medication, herbal or naturopathic products) within the 14 days prior to the Day 1 visit.

4.1.2 Day 1 (\pm 3 days) of Each Cycle

Day 1 of each cycle occurs on infusion day. The following procedures will be performed prior to ADCT-402 infusion (unless otherwise indicated) at each cycle.

- Serum or urine β -HCG pregnancy test (women of child-bearing potential, Cycle 1 only) required if the screening pregnancy test was obtained >7 days prior to Day 1.
- Physical examination, including whole body skin assessment, unless an assessment was performed within 3 days prior to Day 1.

- Vital signs: On Day 1 of Cycles 1 and 2, vital signs are to be measured before the start of ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of infusion. If no clinically significant changes occur during the Cycles 1 and 2, vital sign measurements are to be obtained prior to the start of and at the end of ADCT-402 infusion for all subsequent cycles. If clinically significant changes in vital signs are observed at Cycle 1 and/or 2 infusion, that patient will be required to have vital signs measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion for all subsequent cycles.
- Weight, unless an assessment was performed within 3 days prior to Day 1.
- ECOG performance status.
- Hematology, coagulation panel, and biochemistry parameters, will be measured prior to dosing unless the last sample was collected:
 - <24 hours before the start of ADCT-402 infusion on Day 1 of Cycle 1, or
 - <72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.
- Sample collection for
 - Additional renal function studies
 - UrinalysisPrior to dosing unless the last sample was collected:
 - <24 hours before the start of ADCT-402 infusion on Day 1 of Cycle 1, or
 - <72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.
- 12-lead ECG (Cycles 1 and 2) before the start of the ADCT-402 infusion, within 30 minutes of the end of infusion, and 3 hours (\pm 30 minutes) and 24 (\pm 2.4) hours after the end of infusion ([Table 5](#) and [Table 7](#) in [Appendix 12.1](#)). For Cycle 3 and subsequent cycles, a 12-lead ECG is to be performed before the start of ADCT-402 infusion.
- Sample collection for central laboratory analysis of ADA (all cycles).
- Sample collection (Cycles 1 and 2) for central laboratory analysis of PK parameters before the start of the ADCT-402 infusion, at the end of the infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion. For Cycle 3 and subsequent cycles, samples will be collected before the start of the ADCT-402 infusion and at the end of the infusion.
- Whole blood sample collection for central laboratory analysis of peripheral WBC populations and evaluation of CD19 and other CD markers (e.g., CD20, CD21, CD22) before the start of, and 3 hours after, ADCT-402 infusion on Day 1 (Cycles 1 and 2).

- MNC samples:

- [REDACTED]

- [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Urine sample collection for central laboratory assessment of additional renal function studies.
- Collection of AE information.
- Collection of concomitant medication information.
- Premedication administration, if applicable ([Section 5.2](#)).
- ADCT-402 administration.

4.1.2.1 Bone Marrow Sample

Within 6 days prior to Day 1 of Cycle 3, a bone marrow sample (aspirate or biopsy if aspirate unattainable) will be obtained for assessment of response to treatment and determination of MRD (via flow cytometry) by an approved clinical laboratory. Results must be available to the Investigator before the next dose of study drug is administered.

A bone marrow sample will then be obtained within 6 days prior to the Day 1 visit of Cycle 5 and at each subsequent cycle until CR or CRi ([Section 6.1](#)) is achieved or until disease progression. Once CR/CRi is achieved, sampling will be repeated at least every 3 cycles, or as clinically indicated.

A bone marrow sample will also be collected at the EOT visit ([Section 4.1.8](#)) for those patients who have not demonstrated disease progression and if their most recent sample was obtained more than 12 (± 1) weeks prior to the EOT visit.

Bone marrow aspirate sample collection with subsequent MNC isolation should follow the same collection schedule as above. Mononuclear cells from BMA will be used for retrospective central laboratory evaluation of CD19 and other CD markers (e.g., CD20, CD21, CD22).

Samples obtained during treatment and at the EOT visit are to be saved for biobanking (see Laboratory Manual). Additionally, when available, results from other analyses conducted as part of the institution's standard of care will also be collected.

4.1.3 Day 2 (Cycles 1 and 2)

The following procedures will be performed 24 hours ($\pm 10\%$) after the end of the ADCT-402 infusion:

- 12-lead ECG.
- Vital signs.
- Sample collection for central laboratory analysis of PK parameters.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.4 Day 3 (Cycles 1 and 2)

The following procedures will be performed 48 hours ($\pm 10\%$) after the end of infusion:

- Vital signs.
- Sample collection for central laboratory analysis of PK parameters.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.5 Day 5 (Cycles 1 and 2)

The following procedures will be performed 96 hours (± 1 day) after the end of infusion:

- Sample collection for central laboratory analysis of PK parameters.
- Vital signs.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.6 Day 8 (± 2 days) of Each Cycle

The following procedures will be performed at this visit:

- Physical examination including whole body skin assessment (Cycles 1 and 2).
- Weight (Cycles 1 and 2).
- Vital signs.
- Hematology and biochemistry parameters.
- Urinalysis.
- Urine sample collection for central laboratory assessment of additional renal function studies.
- Sample collection for central laboratory analysis of PK parameters (Cycles 1 and 2).

- Collection of AE information.
- Collection of concomitant medication information.

4.1.7 Day 15 (\pm 2 days) of Cycles 1 and 2

The Day 15 visit will be conducted during Cycles 1 and 2 only; the following procedures will be performed at this visit:


- Physical examination, including whole body skin assessment.
- Weight.
- Vital signs.
- Hematology and biochemistry parameters.
- Urinalysis.
- Urine sample collection for central laboratory assessment of additional renal function studies.
- Sample collection for central laboratory analysis of PK.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.8 End of Treatment Visit

The following procedures will be performed within 30 days (+ 7 days) after study treatment discontinuation:

- Serum or urine pregnancy test.
- Physical examination including whole body skin assessment.
- Weight and vital signs.
- ECOG performance status.
- Hematology, coagulation panel, and biochemistry parameters.
- Urinalysis and sample collection for assessment of additional renal function studies.
- 12-lead ECG.
- Sample collection for central laboratory assessment of PK and ADA.
- Whole blood sample collection for central laboratory analysis of peripheral WBC populations and evaluation of CD19 and other CD markers (e.g., CD20, CD21, CD22).
- MNC) samples:
 - Whole blood (WB) sample collection with subsequent MNC isolation for retrospective central laboratory evaluation of CD19 and other CD markers (e.g., CD20, CD21, CD22).

○

- 
- Collection of AE information.
 - Collection of concomitant medication information.
 - Bone marrow sample for disease assessment (see [Section 4.1.2.1](#)).

4.1.9 12-week Follow-up Visit

Each patient will have a sample taken for assessment of PK and ADA at 12 (± 1) weeks after their last dose of ADCT-402.

Blood Sample Collection and Adverse Event Monitoring During Long-Term Follow-up

For all patients, a PK and ADA blood sample collection will be performed 12 weeks (± 1 week) following the last dose of ADCT-402.

For all patients, collection of AEs and SAEs will continue for up to 84 days (12 weeks) after the last dose of study drug or initiation of new anti-cancer treatment (see [Section 6.3.3.2](#)).

4.1.10 Long-term Follow-up

Patients who discontinue treatment for any reason other than disease progression will continue to be followed by telephone contact approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anti-cancer treatment.

After documentation of disease progression or start of new treatment, patients will be followed (by telephone contact or chart review) approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.

4.2 Withdrawal of Patients from the Study

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent through the completion of the follow-up period or withdrawal of consent.

4.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason, without prejudice to their future medical care, by the Investigator or others at the study site.

A patient may be withdrawn from treatment with ADCT-402 for any of the following reasons:

- Disease progression.
- AE.

- Withdrawal of consent.
- Major protocol deviation.
- Required treatment delay of >21 days (except in case of potential patient benefit, which must be approved by the Sponsor).
- Non-compliance, including lost to follow-up.
- Pregnancy.
- Other (e.g., development of contraindications).
- The Investigator determines that it is in the best interest of the patient to discontinue the patient's participation in the study.
- Discontinuation of the study by the Sponsor.
- Death.

Patients who experience the following significant toxicities will be immediately and permanently withdrawn from treatment with ADCT-402:

- Any patient who experiences a Grade 3 or higher hypersensitivity reaction ([Appendix 12.2](#)), regardless of premedication, during any cycle of treatment
- Any patient who experiences a protocol-defined DLT beyond Cycle 1 (except in the case of potential patient benefit, which must be approved by the Sponsor).
- Any patient who experiences a recurrent Grade 3 or 4 toxicity, excluding hematological toxicity.
- Any patient who requires a dosing delay >21 consecutive days from the planned Day 1 dosing at any time during treatment (except in case of potential patient benefit, which must be approved by the Sponsor).

4.2.2 Handling of Withdrawals

The Investigator will confer with the Sponsor if a patient experiences a serious or intolerable AE. If a patient discontinues from the study because of an AE, the patient will be followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable ([Section 6.3.3.6](#)).

For each patient who is withdrawn from treatment with ADCT-402 and withdraws from the study, the Investigator will record the reason(s) for discontinuation on the relevant page of the eCRF. Whenever possible, each patient who discontinues study treatment will undergo an EOT visit and all EOT assessments ([Section 4.1.8](#)). Patients who fail to return for final assessments are to be contacted by the investigative site. Following a minimum of 2 documented unsuccessful telephone calls, the investigative site will send a registered letter to the patient in a final attempt to ensure protocol compliance.

Note: Once withdrawn from the study, for any reason, patients are not permitted to be re-enrolled into the study.

4.2.3 Patient Replacements

Any patient in Part 1 who discontinues before completion of the first treatment cycle, for any reason other than a DLT, is to be replaced.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment

In Part 1 (dose-escalation), patients will receive an IV infusion of ADCT-402, according to their assigned schedule. The first patient receiving the first dose of ADCT-402 in the study must be observed for 7 days for occurrence of AEs prior to treating a second patient. Patients will be entered sequentially to each dose level. The dose-escalation procedure is described in [Section 3.2](#). If the highest allowed dose (600 µg/kg) is reached and the MTD is not identified, no further dose-escalation will be allowed, pending a safety analysis and accordingly, an amendment to the protocol

In Part 2 (expansion), all patients will be assigned to the dose level of ADCT-402 identified in Part 1 by the DESC. Once the recommended Part 2 dose is determined, patients receiving lower dose levels of ADCT-402 may be offered continued treatment at the recommended dose.

5.2 Prophylactic Treatments for Hypersensitivity

If 1 patient experiences a Grade 2 or higher infusion-related hypersensitivity reaction ([Appendix 12.2](#)) at any time during Part 1 (dose-escalation), all subsequent patients must receive prophylactic treatment, as described below or as per the institution's standard of care, to reduce the risk of hypersensitivity reactions.

- On Day 1 of each cycle, patients will be instructed to take 20 mg orally of dexamethasone, at 12 and 6 hours before the start of ADCT-402 infusion. When necessary, 12 and 6 hours before the first infusion may be defined as “immediately before sleeping” and “immediately after waking up”.
- On Day 1 of each cycle, patients will be given 50 mg IV of diphenhydramine hydrochloride at 30 minutes before the start of ADCT-402 infusion.
- On Day 1 of each cycle, patients will be given 50 mg of ranitidine (or equivalent) IV at 30 minutes before the start of ADCT-402 infusion.
- For 2 days following administration of ADCT-402 on Day 1, all patients are to take dexamethasone 4 mg orally, twice per day.

Other medications for prophylaxis and treatment of hypersensitivity or infusion reactions may be administered, according to standard treatment center protocols. Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, should be available for immediate use.

If a patient experiences a Grade 1 or 2 hypersensitivity reaction, the following medications (or equivalent) should be administered for 48 hours after ADCT-402 infusion:

- Ranitidine 150 mg orally, 2 times per day.
- Diphenhydramine hydrochloride 50 mg orally, 3 times per day.

Any patient who experiences a Grade 3 or higher hypersensitivity reaction ([Appendix 12.2](#)) should be withdrawn from treatment with ADCT-402 and immediately treated according to institutional standard of care and determined by the treating Investigator. These patients must be carefully observed after the treatment. Additional therapy, as per the institution's standard of care, should also be followed.

5.3 Treatments Administered

In Part 1 (dose-escalation), each patient will be assigned a dose level as described in [Section 3.2](#). In Part 2 (expansion), all patients will be assigned to the dose level identified in Part 1 by the DESC.

ADCT-402 will be administered on investigational product (IP) administration day of each cycle as a 1-hour IV infusion. If ADCT-402 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent infusions, on an individual patient basis, at the Investigator's discretion. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.


Prophylactic antiemetic medications, electrolyte supplementation, and other standard supportive care measures may also be administered according to standard treatment center protocols, or as in [Section 5.2](#) and [Section 5.9.2](#).

Because of non-clinical observations related to nephropathy and adrenal gland changes, adequate patient hydration (e.g., 8 to 10 glasses of water or equivalent per day) is recommended for patients receiving ADCT-402.

New or worsening edema and / or new or worsening pleural effusion have been observed. Therefore patients are advised to monitor their weight on a daily basis ([Sections 5.9.2](#) and [6.3.8](#)).

As non-clinical testing indicates testicular toxicity (atrophy with reduced spermatogenesis), male patients are advised to consider cryopreservation of sperm prior to treatment with ADCT-402, where applicable.

Available pre-clinical data on ADCT-402 does not suggest a photosensitivity concern, based on the lack of any signals in the rat and monkey toxicology studies with ADCT-402 and the



However, skin rash has been reported in another program conducted by this Sponsor, as well as with another investigational agent containing the same pyrrollobenzodiazepine warhead ([Rudin 2016](#)). The rash has been limited to areas at risk for sun exposure, it is therefore recommended that precautions are taken to avoid prolonged exposure of skin to direct sunlight.

5.4 Dose Delays and Modifications

Patients will receive the first 2 cycles of ADCT-402, irrespective of blood count recovery. For patients achieving a CR/CRi, the subsequent cycle would be delayed until peripheral blood count recovery (absolute neutrophil count [ANC] $>500 \times 10^9/L$ and/or platelets $>50 \times 10^9/L$).

The Investigator may suspend ADCT-402 dosing for up to 21 days for any patient who experiences a protocol-defined DLT after Cycle 1 (the defined DLT observation period). At the discretion of the Investigator, the dose may also be delayed for up to 21 days for any toxicity that does not meet DLT criteria. Resumption of dosing with ADCT-402 after suspension is at the discretion of the Investigator, based on assessment of the patient's clinical condition and whether or not the patient is deriving potential clinical benefit from treatment with ADCT-402. Following recovery to Grade 1 or to baseline Grade, treatment with ADCT-402 may resume at the Investigator's discretion.

Patients who resume treatment following a dose delay may, at the discretion of the Investigator, have their dose reduced by 1 dose level. If toxicity recurs at a severity that would mandate a dose delay, then the dose may be further reduced 1 dose level. If toxicity recurs at such level, then the patient is to be discontinued from treatment. Dose re-escalation is allowed at the Investigator's discretion, at maximum to the dose level the patient was initially assigned to.

Dose frequency may be adjusted according to individual patient response as described in [Section 3.2](#).

5.5 Identity of Investigational Product

ADC Therapeutics will provide and distribute adequate supplies of ADCT-402 to the study sites. The following drug supplies will be used in the study:

Product	Supplied As
ADCT-402	10-mL single-use, glass vial at a deliverable volume of 3.2 mL (with an additional 0.3 mL overfill) at 5 mg/mL (equivalent to 16 mg ADCT-402)

5.5.1 ADCT-402 Drug Product

ADCT-402 is a sterile formulation containing PBD-conjugated RB4v1.2 (DAR ≥ 1), RB4v1.2 (DAR = 0), and SG3249. It is provided pre-formulated in 10-mL single-use, glass vials containing approximately 16 mg ADCT-402 per vial (deliverable volume 3.2 mL, with an additional 0.3 mL overfill, at 5 mg/mL).

5.6 Management of Clinical Supplies

5.6.1 Study Drug Packaging and Storage

ADCT-402 will be supplied in a labeled 10-mL stoppered glass vial and shipped to the investigational site. Once the package arrives, the receiving site pharmacy will complete the enclosed forms to acknowledge receipt.

All study drugs must be stored in a secure area (e.g., a locked cabinet). ADCT-402 should be protected from light and stored frozen (-65°C or below). ADCT-402 should be thawed under ambient conditions.

5.6.2 Study Drug Preparation and Administration

After the vials have been completely thawed, they should be gently mixed by swirling to ensure homogeneity and visually inspected before use. The appropriate quantity of ADCT-402 will be removed from the vial with a syringe and diluted into a 50 mL IV bag containing 5% dextrose in water (D5W). The amount of the product to be diluted will depend on the dose level and the body mass of the patient. Once the ADCT-402 has been transferred, the bag should be mixed to ensure homogeneity of the dosing solution. The contents of the IV bag will then be administered to the patient with a dosing pump per institutional guidelines for intravenous fluid (IVF) administration.

Additional instructions regarding study drug handling, storage, and preparation are included in the pharmacy manual.

5.6.3 Study Drug Accountability

The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. All study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.7 Overdose Management

An overdose is any dose of study treatment given to a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor. There are no data available to determine what effects and whether effects of an overdose can be reversed. Symptomatic treatment and standard supportive care measures for the management of this toxicity should be applied.

5.8 Treatment Compliance

Administration of the study treatments will be performed by the Investigator or a qualified designee; therefore, compliance will be verified by the study drug administration information.

5.9 Concomitant Treatment

All medications used within 14 days prior to the Day 1 visit and during the treatment period are to be recorded in the eCRF. Concomitant medication information will be collected for 30 days following the patient's last dose of ADCT-402. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

5.9.1 Prohibited During Study

- Other anti-cancer therapy, with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Hydroxyurea is not permitted after Cycle 1 unless approved by the Sponsor.
- Other investigational agents.
- Chronic treatment with corticosteroids (prednisone ≥ 12.5 mg/day or dexamethasone ≥ 2 mg/day, excluding inhaled steroids).
- Live vaccines.

5.9.2 Permitted During Study

After confirmation and documentation of eligibility, supportive care treatments (transfusions, etc.) can be prescribed as medically appropriate. Hematopoietic growth factors are permitted as per the American Society of Clinical Oncology guidelines ([Smith, 2006](#)); however, prophylactic use of growth factors is not allowed during the first treatment cycle.

Patients with a WBC value $>15,000$ cells/ μL may receive cytoreduction treatment with steroids (up to 4 days) or hydroxyurea prior to and during the first cycle of treatment, and/or leukopheresis, to lower the WBC value to $<15,000$ cells/ μL prior to Cycle 1, Day 1 dosing.

Note: Patients are not to receive treatment with study drug until their WBC value is $\leq 15,000$ cells/ μL .

If a Grade 2 or higher infusion-related hypersensitivity reaction is observed in 1 patient at any time during Part 1 of the study, all subsequent patients must receive prophylactic treatment ([Section 5.2](#)).

Concomitant steroid use is permitted as follows:

- Replacement doses of steroids for patients with adrenal insufficiency.
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection).
- Intrathecal medication for CNS prophylaxis (not for active disease) per institutional standard of care practices.
- Prophylactic treatment with dexamethasone as follows may be instituted by the DESC based on emerging safety and PK profile:

- Dexamethasone 4 mg oral BID the day before investigational product (IP) administration, the day of IP administration, and the day after IP administration (Week 1/Day 1 of each cycle only, regardless of treatment schedule).
- A 2-day course of dexamethasone 4 mg PO BID will be given (Week 1/Days 1 and 2 of each cycle). If possible, the first dose should be given at least 2 hours prior to IP administration. Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator.
- Spironolactone, at standard doses, may be instituted at any time for patients with weight gain greater than 1 kg (2.2 lbs) from Cycle 1 Day 1, new or worsening edema and/or new or worsening pleural effusion. The dose of spironolactone may be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema or pleural effusion.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator.

6 Study Assessments and Procedures

Patients will undergo the procedures at the time points specified in [Section 4.1](#) and the Schedule of Procedures and Central Laboratory Sample Collection for the Q3W and QW dosing schedules ([Table 5](#) through [Table 9](#)) in [Appendix 12.1](#).

6.1 Efficacy Assessments

Assessment of response to treatment with ADCT-402 will be based on bone marrow samples (aspirate, or biopsy if aspirate unattainable). Bone marrow samples will be obtained as described in [Section 4.1.2.1](#).

The activity of ADCT-402 will be evaluated based on the Investigator's evaluation of the patient's response to ADCT-402 as CR, CRi, PR, PD, or NR ([Cheson, 2003](#); [Döhner, 2010](#)).

- Complete response is defined as achieving each of the following:
 - Bone marrow differential showing $\leq 5\%$ blast cells,
 - Absolute neutrophil count $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$,
 - Absence of extra-medullary disease,
 - Patient is independent of red blood cell (RBC) transfusions.
- Complete response with incomplete blood count recovery is defined as achieving all CR criteria except that values for ANC may be $< 1.0 \times 10^9/L$ and/or values for platelets may be $< 100 \times 10^9/L$.
- Partial response is defined as achieving each of the following:
 - ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$,
 - Bone marrow differential showing a $\geq 50\%$ decrease from baseline in the percentage of bone marrow blast cells to a level $> 5\%$ and $\leq 25\%$.
- No response is defined as not achieving CR, CRi, or PR.
- PD is defined as:
 - For patients with CR or CRi, the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level $\geq 5\%$, or development of extramedullary disease.
 - For patients with PR, the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR.

As defined in [Section 7.6.2](#), DOR and ORR will be defined among responders (CR, CRi, PR); OS and PFS will also be determined.

6.2.1 Pharmacokinetic Assessments

The PK profile of ADCT-402 (total antibody; $\text{DAR} \geq 0$), PBD-conjugated antibody ($\text{DAR} \geq 1$), and free warhead SG3199 will be assessed by a central laboratory in Cycles 1 and 2. Additional PK and ADA samples will be collected, at the discretion of the Investigator, during any visit where toxicity is observed. A PK and ADA sample will also be collected concurrently with any other blood draw to assess safety (e.g., Unscheduled Visit), if possible. All PK samples will be evaluable as long as the actual collection times are recorded.

To understand the metabolic disposition of ADCT-402 in humans, samples remaining after PK analysis is complete may be pooled among patients for potential metabolite identification.

The PK profile will include determination of: maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration ($\text{AUC}_{0\text{-last}}$), area under the concentration-time curve (AUC) from time zero to the end of the dosing interval ($\text{AUC}_{0\text{-}\tau}$), area under the concentration-time curve from time zero to infinity ($\text{AUC}_{0\text{-}\infty}$), accumulation index (AI), volume of distribution at steady-state (V_{ss}), mean residence time (MRT), terminal elimination phase rate constant (λ_z), terminal half-life ($T_{1/2}$), clearance (C_L), and volume of distribution (V_z).

6.2.2 Pharmacodynamic and Other Assessments

The following assessments will be performed at varying time points in the study:

- Flow cytometric assessment of CD19 and other CD marker expression in MNCs isolated from BMA and WB, tested retrospectively by a central laboratory in samples collected before treatment with ADCT-402.
- Level of ADAs against ADCT-402 in serum before, during, and after treatment with ADCT-402.
- Analysis of peripheral WBC populations and CD marker panel expression (e.g., CD19, CD20, CD21 and CD22) before, during, and after treatment with ADCT-402 (Cycles 1 and 2) by flow cytometry in WB.
- Serum concentrations of ADCT-402 and free warhead SG3199, QTc interval.
- Evaluation of MRD, by flow cytometry in bone marrow.

6.3 Safety and Tolerability Assessments

Safety will be assessed based on AEs, serious AEs (SAEs), treatment discontinuation due to AEs, DLTs, periodic 12-lead ECG recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, coagulation panel, biochemistry, pregnancy (for women of child-bearing potential), and urinalysis test results. Adverse events will be graded according to CTCAE Version 4.0. The Schedule of Events for the Q3W and QW dosing schedules are shown in [Table 5](#) and [Table 7](#), respectively, in [Appendix 12.1](#).

6.3.1 Definition of Dose-Limiting Toxicities

A DLT is defined as any of the following events, except those that are clearly due to underlying disease or extraneous causes:

- A hematologic DLT is defined as:
 - Grade 3 or higher event of neutropenia or thrombocytopenia, or a Grade 4 anemia, with a hypocellular bone marrow lasting for 6 weeks or more after the start of a cycle, in the absence of residual leukemia (i.e., with <5% blasts). In case of a normocellular bone marrow with <5% blasts, 8 weeks with \geq Grade 3 pancytopenia will be considered a DLT.
- A non-hematologic DLT is defined as:
 - Grade 4 tumor lysis syndrome (Grade 3 TLS will not constitute DLT unless it leads to irreversible end-organ damage).
 - Grade 3 or higher AE (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grades of alopecia).
 - CTCAE Grade 3 or higher hypersensitivity reaction (regardless of premedication).
 - CTCAE Grade 3 or higher skin ulceration.

The DLT observation period for dose-escalation will be 1 cycle.

Note: Patients who experience a DLT during Cycle 1 are to be permanently discontinued from the study.

6.3.2 Safety Oversight by the Dose-Escalation Steering Committee

A DESC will be responsible for safety monitoring and overall supervision of the study. Membership of the DESC will include:

- Medical monitor(s)/Pharmacovigilance representative(s) (Sponsor and/or designee)
- Investigator(s) from each participating site
- Biostatistician(s)
- Ad-hoc members (e.g., project manager, study coordinators, regulatory representatives, etc.)

In general, the DESC will make any substantial decisions regarding the conduct of the study, such as:

- Monitor the safety of the study and review its progress at monthly intervals or more frequent intervals as required.
- Determine dose levels to be administered and the MTD based on assessment of safety findings and determination of DLTs.
- Approve any amendments or administrative changes to the protocol, when required.
- Determine if it is appropriate to maintain a QW schedule, revert to a Q3W schedule, or test other dosing regimens.

Each DESC meeting and the decisions made will be documented in writing and provided to all participating DESC members and Investigators. Meeting documents may be submitted to IRBs/IECs or competent authorities according to institutional or local requirements.

The DESC will be maintained during Part 2 (expansion) of the study to continue to monitor and evaluate patient safety.

6.3.3 Adverse Events

6.3.3.1 Definitions of Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the Investigator at any time after assignment to the treatment group if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Hospitalization for elective procedures or for protocol compliance is not considered an SAE.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, the event may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.3.3.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient signs the ICF up to 84 days (12 weeks) days after the last dose of study drug or initiation of new anti-cancer treatment.

Any SAEs that occur > 84 days (12 weeks) after the last dose of study drug do not need to be reported unless the Investigator considers them to be related to study drug.

At every study visit, patients will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

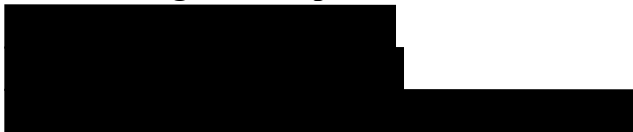
In addition to patient observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., clinically significant changes in laboratory values, physical examination, ECG changes, etc.) or identified from review of other documents that are relevant to patient safety.

6.3.3.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, dose, event terminology, date of onset, CTCAE Version 4.0 assessment of severity and relationship to study drug, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome. With the exception of disease progression, AEs resulting from concurrent illnesses, reactions to concurrent illnesses, and reactions to concurrent medications also must be reported. All AEs will be followed to adequate resolution. CTCAE Version 4.0 will be used to grade all AEs ([Section 6.3.3.4](#)).

Any AE that meets SAE criteria ([Section 6.3.3.1](#)) must be reported to the contract research organization (CRO) immediately (i.e., within 24 hours after the time site personnel first learn about the event). The following contact information is to be used for SAE reporting:

Pharmacovigilance Department



6.3.3.4 Assessment of Severity

Adverse events will be graded according to CTCAE Version 4.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5, as shown in [Table 3](#).

Table 3. Definition of Severity Grades for Common Terminology Criteria for Adverse Events (CTCAE)

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL ^a
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^b
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

a Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.3.3.5 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the eCRF. All AEs, regardless of assessment of causality, are reported in the eCRF.

All SAEs considered at least possibly related to the study drug will be considered unexpected; and therefore, reported as suspected unexpected serious adverse reactions (SUSARs).

6.3.3.6 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

6.3.4 Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical study Pregnancy Report Form. To ensure patient safety, each pregnancy must be reported as described for reported AEs in [Section 6.3.3.3](#), upon learning of its occurrence. The pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was withdrawn from the study. The outcome of the pregnancy will be reported on the Pregnancy Outcome Form. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study treatment must be promptly reported ([Section 6.3.3.3](#)).

6.3.5 Clinical Laboratory Analyses

Samples will be collected at the time points specified in the Schedule of Events for the Q3W and QW dosing schedules ([Table 5](#) and [Table 7](#), respectively) [Appendix 12.1](#).

Any clinically significant abnormal laboratory test results are to be recorded as AEs or SAEs, per CTCAE Version 4.0.

6.3.5.1 Hematology

The complete blood count (CBC) includes WBC with a 5-part differential, platelet count, hemoglobin, hematocrit, and ANC. Peripheral blasts will be included in the hematology analysis for Part 2 only. If the WBC value is $<400 \times 10^6/L$, a differential is not required. The coagulation panel must include partial thromboplastin time (PTT) and International Normalized Ratio (INR); prothrombin time (PT) expressed in seconds is optional. Patients taking coumarin-derivative anticoagulants should be monitored closely and their anticoagulant dose adjusted as needed.

6.3.5.2 Biochemistry

Tests for clinical biochemistry include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, sodium, potassium, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, chloride, creatinine, creatine phosphokinase, total protein, albumin, glucose, triglycerides, total cholesterol, phosphorus, and lactate dehydrogenase. Biochemistry will also include creatinine clearance ([Cockcroft and Gault, 1976](#)).

6.3.5.3 Urinalysis

Urinalysis analytes will include pH, specific gravity, protein, glucose, ketones, bilirubin, nitrites and occult blood. The urinalysis may be performed using a urine dipstick.

6.3.5.4 Additional Renal Function Studies

Urine will be collected for central laboratory testing of biomarkers suggestive of potential renal injury (aquaporin-2, calbindin D28, and clusterin). Analysis of this additional urine sample will be performed at a central laboratory (instructions provided in the Laboratory Manual).

6.3.6 Electrocardiograms

A 12-lead ECG is to be performed at the time points identified in the Schedule of Events for the Q3W and QW dosing schedules ([Table 5](#) and [Table 7](#), respectively) in [Appendix 12.1](#).

Any abnormalities, including those that worsen from baseline, believed to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

Measurement of the QTc interval may be obtained according to the formula used by the institution, however, the Fridericia formula is preferred ([Fridericia, 1920](#)). The same formula used to confirm eligibility must be applied within a patient for the duration of the study.

6.3.7 Physical Examination

Physical examinations will include a complete review of body systems, including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist. However, any unexplained lesion is to be referred to a dermatologist for further evaluation and biopsy if clinically warranted. Any clinically significant abnormalities, including those that worsen from baseline, are to be recorded as AEs or SAEs.

6.3.8 Vital Sign Measurements

Vital signs measurements will include arterial blood pressure, heart rate, respiratory rate, and temperature. Any clinically significant abnormalities, including those that worsen from baseline, are to be recorded as AEs or SAEs.

6.3.9 Weight

If possible, patients are advised to monitor their weight daily starting Cycle 1 Day 1 and inform their investigator if their weight increase more than 1 kg (2.2 lbs) from Cycle 1 Day 1.

6.3.10 Eastern Cooperative Oncology Group Performance Status

The patient's performance status will be assessed according to the time points in the Schedule of Events for the Q3W and QW dosing schedules ([Table 5](#) and [Table 7](#), respectively) in [Appendix 12.1](#) using ECOG performance status grades ([Table 4](#); [Oken, 1982](#)).

Table 4. Definition of Eastern Cooperative Oncology Group (ECOG) Performance Status Grades

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

As per [Oken, 1982](#).

6.4 Sample Handling, Storage and Shipment

Detailed instructions for central laboratory sample collection, labeling, processing, storage, and shipping will be provided to the site in the Laboratory Manual.

Samples will be collected for PK, ADA, peripheral WBC population, CD marker expression, and additional renal function studies. For PK and ADA, WB is to be collected with subsequent serum isolation. Serum samples should be aliquoted and transferred as frozen (-20°C or below, -70°C preferred), according to the Laboratory Manual.

For the analysis of peripheral WBC populations and cell surface markers, WB is to be collected and shipped (ambient), as per the Laboratory Manual, directly to the selected vendor for immediate processing.

Each sample tube should be clearly labeled with : Study number, study center number, patient number, tube identification, and the scheduled sampling time by day (and hour, when necessary).

7 Statistical and Analytical Plan

Full details of the analysis plan, including a more technical and detailed elaboration of the statistical analyses will be provided in the statistical analysis plan (SAP).

7.1 Safety Endpoints

Safety will be assessed based on AEs, SAEs, treatment discontinuations due to AEs, DLTs, periodic 12-lead ECG recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, coagulation panel, biochemistry, pregnancy (for women of child-bearing potential), and urinalysis test results.

7.2 Endpoints

7.2.1 Primary Endpoints

- Assessment of DLTs (Section 6.3.1) and determination of the MTD (Section 3.2) for ADCT-402 during Part 1.
- Determination of the recommended dose of ADCT-402 for Part 2 by the DESC.
- Assessment of safety parameters for Part 1 and Part 2 (Section 7.6.1).

7.2.2 Secondary Endpoints

- Determination of ORR, DOR, OS, and PFS (Section 7.6.2).
- Determination of PK parameters (Section 7.6.3) for ADCT-402 (total antibody; $DAR \geq 0$), PBD-conjugated antibody ($DAR \geq 1$), and free warhead SG3199.
- Measurement of ADAs to ADCT-402 before, during, and after treatment with ADCT-402 (Section 7.6.3).

[REDACTED]

7.3 Sample Size Calculations

This is a Phase I study with a maximum total sample size of 70 patients. It is expected that Part 1 will enroll up to 40 patients and Part 2 will enroll up to 30 patients. Patients will be enrolled in Part 2 of the study in cohorts of approximately 10. Based on a true AE rate of 15%, there is 80% confidence that one AE will be observed for the 10 patients enrolled. The DESC will make

recommendations with regard to the intended differences between these cohorts, e.g. tumor subtypes, dosing regimen or dose levels, as well as the number of these cohorts, taking into account the limit on the overall number of patients as specified above and safety/efficacy data observed up to that decision point.

7.4 Analysis Sets

Six analysis sets will be used in this study:

- The Safety analysis set will consist of all patients who receive study drug.
- The DLT-evaluable analysis set will consist of all patients in Part 1 who receive study drug and excludes patients who discontinue from the study drug during Cycle 1 without experiencing a DLT.
- The Efficacy analysis set will consist of all patients with valid baseline data who receive at least 2 doses of study drug or who have documented progression of disease at any time after the first dose of study drug.
- The PK analysis set will consist of all patients who receive study drug and have sufficient concentration data for PK analysis.
- The PD analysis set will consist of all patients who receive study drug and have sufficient data available for analysis.



7.5 Description of Subgroups to be Analyzed

Subgroup analyses, if planned, will be described in the SAP.

7.6 Statistical Analysis Methodology

7.6.1 Safety Analyses

7.6.1.1 Analyses of Adverse Events

An AE will be considered to be a TEAE if it begins or worsens on or after the patient's first study medication dose date and before the last dose date up to 84 days (12 weeks). Planned summaries of TEAEs will be detailed in the SAP and will include:

- All TEAEs.
- All serious TEAEs.
- All treatment-related TEAEs.
- All treatment-related serious TEAEs.
- All TEAEs resulting in study drug discontinuation.
- All DLTs.

Other AE analyses of interest will be specified in the SAP.

The incidence of deaths and the primary cause of death will be summarized.

7.6.1.2 Clinical Laboratory Results

Clinical hematology, coagulation panel, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Numeric hematology and biochemistry results will be summarized using change from baseline. All results will be summarized using shift from baseline. Shifts for clinical laboratory results that can be graded according to CTCAE Version 4.0 will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in “worst case post baseline” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the SAP.

7.6.1.3 Additional Safety Assessments

The results of scheduled assessments of cytokine levels, vital signs, physical examinations, ECOG performance status, and 12-lead ECGs will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in “worst case” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. All data will be listed. Further details will be provided in the SAP.

7.6.2 Efficacy Analysis

Determination of DOR and ORR will be based on the Investigator’s evaluation of the patient’s response to ADCT-402 ([Section 6.1](#)). Overall survival and PFS will also be determined.

7.6.2.1 Overall Response Rate

The ORR will be defined as the proportion of patients with a best overall response of CR, CRi or PR at the time each patient discontinues treatment with ADCT-402. Percentage of ORR with its 95% confidence interval (CI) will be presented.

7.6.2.2 Duration of Response

Duration of response will be defined among responders (CR, CRi, PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. The date of disease progression is defined for patients with CR or CRi as the first date of reappearance of blast cells in bone marrow to a level $\geq 5\%$, or development of extramedullary disease. In patients with PR, this is defined as the first date of an increase in blast cells in bone

marrow such that the patient does not continue to meet the criteria for PR (Section 6.1). For patients whose disease has not progressed or who have not died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. In addition, patients with disease progression or who have died after an extended loss to follow-up by the investigative site will be censored at the date of the last disease assessment prior to the extended loss to follow-up. The data will be analyzed by Kaplan-Meier method. The median DOR and 95% CI will be presented. Further details will be outlined in the SAP.

7.6.2.3 Overall Survival

Overall survival will be defined as the time from the first dose of study drug treatment until the date of death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. The data will be analyzed by Kaplan-Meier method. The median survival time and 95% CI will be presented. Further details will be outlined in the SAP.

7.6.2.4 Progression-Free Survival

Progression-free survival will be defined among the efficacy population (Section 7.4) as the time from first dose of study drug until the first date of either disease progression or death due to any cause. For patients whose disease has not progressed or who have not died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. In addition, patients with disease progression or who have died after an extended loss to follow-up by the investigative site will be censored at the date of the last disease assessment prior to the extended loss to follow-up. The data will be analyzed by Kaplan-Meier method. The median PFS time and 95% CI will be presented. Further details will be outlined in the SAP.

7.6.3 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic endpoints (Section 6.2) for RB4v1.2, PBD-conjugated RB4v1.2, and free warhead SG3199 will be calculated for all patients using non-compartmental analysis. Data for PK will be summarized in tables and individual data will be listed.

[REDACTED]



7.6.4 Study Drug Exposure

Study drug exposure will be summarized by dose level and overall. Duration of treatment, total number of cycles dosed, and total dose received will be summarized. The number of patients dosed by cycle will also be summarized using frequency counts and percentages.

Duration of treatment will be calculated as date of last dose of study drug – date of first dose of study drug + 1.

7.7 Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of a qualified Investigator and appropriate study site, review of protocol procedures with the Investigator and associated personnel before the study and periodic monitoring visits by the clinical research associate. Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples.

The eCRFs will be provided to the clinical contact and the clinical research associate will review them with site personnel.

The clinical research associate will review eCRFs for accuracy and completeness by remote monitoring, during on-site monitoring visits, and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After entry of the data into the clinical study database they will be verified for accuracy.

7.7.1 Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, and patient diaries.

Investigative site personnel will enter patient data into Medidata Rave. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events will be coded using the Medical Dictionary for

Regulatory Activities Version 18.0. Concomitant medications will be coded using WHO Drug Dictionary 01 June 2015.

After database lock, each study site will receive information about all of their site-specific eCRF data as entered into electronic data capture system for the study, including full discrepancy and audit history. Additionally, a copy of all of the study site's data from the study will be created and sent to the Sponsor for storage. The CRO will maintain a duplicate copy for its records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC.

Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted. The Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written ICF, in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50, shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF.

Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study [REDACTED]

9 Investigator's Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, regulatory authorities (e.g., FDA), or the IRB/IEC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor the CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

9.3 Adverse Events and Study Report Requirements

By participating in this study the Investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

The Sponsor will ensure that all relevant safety information (SAEs and SUSARs) is reported to the FDA and competent authorities of EU Member States, and to the IEC, in accordance with current legislation (US 21CFR.316 and EU Directive 2001/20/EC).

9.4 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval.
- Original Investigator-signed Investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the Investigator and each sub-Investigator listed on Form FDA 1572.
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian.

9.5 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

9.6 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

9.7 Investigator's Final Report

Upon completion of the study, where applicable, the Investigator should provide the IRB/IEC with a summary of the study outcome and the Sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the

Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.



10 Study Management

10.1 Monitoring

10.1.1 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and written contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and the CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any change in the study plan requires a protocol amendment. An Investigator may not make any changes to the study without IRB/IEC and Sponsor approval, except those necessary to remove an apparent immediate hazard to the patient. A protocol change intended to eliminate an apparent immediate hazard to a patient(s) may be implemented immediately, but the circumstances of the change must be documented and submitted to the IRB/IEC and to the Sponsor for further evaluation. If the protocol is in need of substantial changes, the Sponsor will amend the protocol and seek approval from the appropriate regulatory authority(ies) before implementation. All amendments to the protocol must be reviewed and approved following the same process as the original protocol before the amended protocol can be implemented.

10.2.2 Protocol Deviations

The Investigator will make every attempt to avoid deviations from the protocol, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. The Investigator will inform the governing IRB/IEC of all protocol changes issued by the Sponsor in accordance with the IRB/IEC's established procedure.

10.3 Study Termination

The Sponsor has every intention of completing the study; however, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last EOT visit to the study site.

10.4 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s).

An Investigator will be identified to act as the signatory for the clinical study report. The Investigator will be provided access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

11 Reference List

- Adair JR, Howard PW, Hartley JA, Williams DG, and Chester KA (2012). Antibody-drug conjugates - a perfect synergy. *Expert Opin Biol Ther* 12(9): 1191-1206.
- Amgen, Thousand Oaks, California USA (2014). Prescribing information for blinatumomab (Blincyto™), Accessed on 21 May 2015 at http://pi.amgen.com/united_states/blincyto/blincyto_pi_hcp_english.pdf.
- Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, and Nadler LM (1984). Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. *Blood* 63(June):1424-1433.
- Blanc V, Bousseau A, Caron A, Carrez C, Lutz RJ, and Lambert JM (2011). SAR3419: an anti-CD19-maytansinoid immunoconjugate for the treatment of B-cell malignancies. *Clin Cancer Res* 17(20):6448-6458.
- Carter RH and Barrington RA (2004). Signaling by the CD19/CD21 complex on B cells. *Curr Dir Autoimmun.* 7:4–32.
- Chen DR and Cohen PL (2012). Living life without B cells: is repeated B-cell depletion a safe and effective long-term treatment plan for rheumatoid arthritis? *Int J Clin Rheumatol* 7(2): 159-166.
- Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al, (2003). Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *Clin Oncol* 21:4642-4649.
- Cockcroft DW and Gault MH (1976). Prediction of creatinine clearance from serum creatinine. *Nephron* 16(1):31-41.
- Cooper LJ, Al-Kadhimi Z, DiGiusto D, Kalos M, Colcher D, Raubitschek A, et al. (2004). "Development and application of CD19-specific T cells for adoptive immunotherapy of B cell malignancies." *Blood Cells Mol Dis* 33(1): 83-89.
- Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al, (2010). Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 115(3):453-474.
- Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. *Act Med Scand* 1920, 53:469–486. Translation published in 2003 in *Annals Noninvasive Electrophysiology* 8(4):343-351.
- Gerber HP, Kung-Sutherland M, Stone I, Morris-Tilden C, Miyamoto J, McCormick R, et al (2009). Potent antitumor activity of the anti-CD19 auristatin antibody drug conjugate hBU12-vcMMAE against rituximab-sensitive and -resistant lymphomas. *Blood* 113(18):4352-4361.
- Haas KM and Tedder TF, (2005). Role of the CD19 and CD21/35 receptor complex in innate immunity, host defense and autoimmunity. *Adv Exp Med Biol.*;560:125–139.

- Hartley JA (2011a). The development of pyrrolobenzodiazepines as antitumour agents. *Expert Opin Investig Drugs* 20(6): 733-744.
- Inaba H, Greaves M, and Mullighan CG (2013). Acute lymphoblastic leukaemia. *Lancet* June 1; 381(9881): doi:10.1016/S0140-6736(12)62187-4.
- Jabbour E, O'Brien S, Ravandi F, and Kantarjian H (2015). Monoclonal antibodies in acute lymphoblastic leukemia. *Blood* 125(26):4010-4015.
- Kimby E (2005). Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 31(6):456-473.
- Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, et al, (2007). Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood* Apr 15;109(8):3189-97. Epub 2006 Dec 14.
- Muniz C, Martin-Martin L, Lopez A, Sanchez-Gonzalez B, Salar A, Almeida J, et al (2014). Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome. *Blood* 123(12): 1864-1869.
- National Cancer Institute (2015). SEER Cancer Statistics Factsheets: Acute Lymphocytic Leukemia (ALL) 2015. Accessed on 1 July 2015, at <http://seer.cancer.gov/statfacts/html/aly1.html>.
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5(6):649-55.
- Roguska MA, Pedersen JT, Henry AH, Searle SM, Roja CM, Avery B, et al, (1996). A comparison of two murine monoclonal antibodies humanized by CDR-grafting and variable domain resurfacing. *Protein Eng* 9(10): 895-904.
- Rudin CM, Pietanza MC, Bauer TM, Spigel DR, Ready N, Morgansztern D, et al. Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC). *J Clin Oncol* 34 (2016) (suppl: abstr LBA8505).
- Schafer ES and Hunger SP, (2011). Optimal therapy for acute lymphoblastic leukemia in adolescents and young adults. *Nat Rev Clin Oncol* 8:417-24, published online 31 May 2011; doi:10.1038/nrclinonc.2011.77
- Scheuermann RH and Racila E (1995). CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. *Leuk Lymphoma* 18(5-6): 385-397.
- Smith TJ (Chair), Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al, (2006). 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Onc* 24(19):3187-3286.

Swerdlow SH, Campo E, Harris NL, et al, eds. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC.

Tedder TF (2009). CD19: a promising B cell target for rheumatoid arthritis . *Nat. Rev. Rheumatol.* 5, 572–577 (2009); doi:10.1038/nrrheum.2009.184

Wang K, Wei G, and Liu D (2012). CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. *Exp Hematol Oncol* 1(1): 36.

12 Appendices

12.1 Appendix: Schedule of Events

The Schedule of Events for the Q3W and QW dosing schedules are shown in ([Table 5](#) and [Table 7](#), respectively) of this appendix. Timings for sample collections for assessment of PK, PD, and other parameters for the Q3W dosing schedule are shown in [Table 6](#), and for the QW dosing schedule in [Table 8](#) and [Table 9](#).

Table 5. Schedule of Study Procedures: Every 3-Week (Q3W) Dosing

Procedure	Screening D-28 to -1	Cycle 1					Cycle 2					Cycle 3 until PD/DC		EOT 30 (+7)days ³	12 Week Follow Up Visit (±1) week ⁴	Follow- Up 12 (± 1) week
		D1	D2 ¹	D3&5 ²	D8	D15	D1	D2 ¹	D3&5 ²	D8	D15	D1	D8			
		±3d			±2d	±2d	±3d			±2d	±2d	±3d	±2d			
Informed consent	X															
Demography	X															
Medical history ⁵	X															
Serum or urine β-HCG pregnancy test	X	X ⁶												X		
Physical examination ⁷	X	X			X	X	X		X	X	X		X			
Vital signs ⁸	X	X ⁹	X	X	X	X	X ⁹	X	X	X	X	X	X	X		
Height	X															
Weight	X	X			X	X	X		X	X	X		X			
ECOG performance status	X	X					X				X		X			
Bone marrow aspirate/biopsy ¹⁰	X										X ¹¹		X ¹²			
Hematology ¹³	X	X ¹⁴			X	X	X ¹⁴		X	X	X ¹⁴	X	X			
Coagulation Panel ¹⁵	X	X ¹⁴					X ¹⁴				X ¹⁴		X			
Biochemistry ¹⁶	X	X ¹⁴			X	X	X ¹⁴		X	X	X ¹⁴	X	X			
Urinalysis ¹⁷	X	X ¹⁴			X	X	X ¹⁴		X	X	X ¹⁴	X	X			
12-lead ECG	X	X ¹⁸	X				X ¹⁸	X			X ¹⁹		X			
Concomitant Medications ²⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Premedication ²¹		X					X				X					
ADCT-402 Administration ²²		X					X				X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²³	
Survival information															X ²⁴	X ²⁴
New anti-cancer treatment information															X ²⁵	X ²⁵

Abbreviations: D = Day(s); d = day(s); DC = discontinue; PD, progressive disease; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment visit; β-HCG, beta-human chorionic gonadotropin.

Refer to [Table 6](#) for Central Lab Sample Collection Schedule.

1. Day 2 to occur 24 hours ($\pm 10\%$) after EOI.
2. Day 3 to occur 48 hours ($\pm 10\%$) after EOI. Day 5 to occur 96 (± 24) hours after EOI.
3. After last dose of ADCT-402. EOT window is + 7 days.
4. Follow-up to occur 12 (± 1) week after last dose of ADCT-402. Patients who discontinue treatment for any reason other than disease progression will continue to be followed approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anti-cancer treatment. After documentation of disease progression or start of new treatment, patients will be followed (by telephone contact or chart review) approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.
5. Medical history: To include a complete history of all surgeries, significant diagnoses, cancer history, immunophenotyping and all cancer treatments.
6. Serum or urine pregnancy test: For women of child-bearing potential. Not required if negative screening β -HCG pregnancy test was obtained within 7 days prior to Cycle 1, Day 1.
7. Physical examination to include whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist. Any unexplained lesion is to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. Does not have to be repeated on Day 1, if last performed within 3 days prior to dosing with ADCT-402.
8. Vital signs to include arterial blood pressure, heart rate, respiratory rate, and body temperature.
9. Vital signs: On Day 1 of Cycles 1 and 2, vital signs are to be measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the infusion. If no clinically significant changes occur during Cycles 1 and 2, vital sign measurements are to be obtained prior to infusion start and end of infusion for all subsequent infusions. If clinically significant changes in vital signs are observed at Cycle 1 and/or 2 infusion, that patient will be required to have vital signs measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion for all subsequent cycles. Note: Timing of measurements is approximately ± 15 minutes.
10. A bone marrow sample, via aspirate or biopsy if an aspirate is unattainable, will be obtained at Screening for confirmation of disease (as per WHO classification of ALL [[Swerdlow, 2008](#)]), at an approved clinical laboratory.
11. A bone marrow sample will be obtained within 6 days prior to the Day 1 visit of Cycles 3 and 5 and at each subsequent cycle until CR or CRi is achieved or until disease progression. Assessment of response to treatment and determination of MRD (via flow cytometry) are to be done by an approved clinical laboratory. Results must be available to the Investigator before the next dose of study drug is administered. Once CR/CRi is achieved, sampling will be repeated at least every 3 cycles, or, as clinically indicated.
12. A bone marrow sample will be obtained at the EOT visit for those patients who have not demonstrated disease progression and if their most recent sample was obtained more than 12 (± 1) weeks prior to the EOT visit.
13. Hematology: CBC to include WBC with a 5-part differential, platelet count, hemoglobin, hematocrit, and ANC. Peripheral blasts will be included in the hematology analysis for Part 2 only. If WBC is $< 400 \times 10^6/L$ differential is not required.
14. Samples for hematology, coagulation panel, biochemistry, and urinalysis will be collected prior to dosing unless the last sample was collected:
<24 hours before the start of ADCT-402 infusion on Day 1 of Cycle 1, or
<72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.
15. Coagulation panel: PTT and INR; PT expressed in seconds is optional.
16. Biochemistry: Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, sodium, potassium, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, chloride, creatinine, creatine phosphokinase, total protein, albumin, glucose, triglycerides, total cholesterol, phosphorus, and lactate dehydrogenase. At Day 1 of each cycle, biochemistry will include creatinine clearance (calculated using the Cockcroft and Gault formula [[Cockcroft and Gault, 1976](#)]).
17. Urinalysis to include: pH, specific gravity, protein, glucose, ketones, nitrites, occult blood and bilirubin. The urinalysis may be performed using a urine dipstick.

18. 12-lead ECG: On Days 1 and 2 of Cycles 1 and 2, a 12-lead ECG is to be performed before the start of the ADCT-402 infusion, within 30 minutes of the end of infusion, and 3 hours (\pm 30 minutes) and 24 (\pm 2.4) hours after the end of infusion.
19. 12-lead ECG: On Day 1 of Cycle 3 and subsequent cycles, a 12-lead ECG is to be performed before the start of ADCT-402 infusion.
20. Concomitant medications to include prescription or over-the-counter medication, herbal or naturopathic products within the 14 days prior to the Cycle 1, Day 1 visit, during the study and 30 days following the patient's last dose of ADCT-402.
21. Premedication to be performed if a CTCAE Grade 2 or higher infusion-related hypersensitivity reaction is observed in 1 patient at any time during Part 1 of the study. All subsequent patients must receive prophylactic treatment on Day 1 of each cycle thereafter to reduce the risk of hypersensitivity reaction ([Section 5.2](#)).
22. ADCT-402: Patients will receive a 1-hour IV infusion of ADCT-402, at escalating doses, each 3-week (21-day) cycle. If ADCT-402 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent infusions for that patient, at the Investigator's discretion. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation. The IP window is +15 minutes.
23. For all patients, collection of AEs and SAEs will continue for up to 12 weeks (84 days) after the last dose of study drug or initiation of new anti-cancer treatment. Any SAEs that occur more than 84 days after the last dose of study drug do not need to be reported unless the Investigator considers the event to be related to study drug.
24. After documentation of disease progression or start of new anti-cancer treatment, patients will be contacted by telephone approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.
25. Information on anti-cancer treatment initiated after discontinuation of ADCT-402 to be recorded in the eCRF.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 7. Schedule of Study Procedures: Weekly (QW) Dosing

Procedure	Screen	Cycle 1					Cycle 2					Cycles 3 until PD/DC			EOT 30 (+7) days ³	12 Week Follow- Up Visit (± 1) week ⁴	Follow- Up 12 (± 1) week
		D1	D2 ¹	D3& ²	D8	D15	D1	D2 ¹	D3&5 ²	D8	D15	D1	D8	D15			
		±3d			±2d	±2d	±3d			±2d	±2d	±3d	±2d	±2d			
Informed consent	X																
Demography	X																
Medical history ⁵	X																
Serum or urine β-HCG pregnancy test	X	X ⁶												X			
Physical examination ⁷	X	X			X	X	X			X	X	X		X			
Vital signs ⁸	X	X ⁹	X	X	X	X	X ⁹	X	X	X	X	X	X	X	X		
Height	X																
Weight	X	X			X	X	X			X	X	X	X	X			
ECOG performance status	X	X					X					X		X			
Bone marrow aspirate/biopsy ¹⁰	X											X ¹¹		X ¹²			
Hematology ¹³	X	X ¹⁴			X	X	X ¹⁴			X	X	X ¹⁴	X	X	X		
Coagulation Panel ¹⁵	X	X ¹⁴					X ¹⁴					X ¹⁴			X		
Biochemistry ¹⁶	X	X ¹⁴			X	X	X ¹⁴			X	X	X ¹⁴	X	X	X		
Urinalysis ¹⁷	X	X ¹⁴			X	X	X ¹⁴			X	X	X ¹⁴	X	X	X		
12-lead ECG	X	X ¹⁸	X				X ¹⁸	X				X ¹⁹			X		
Concomitant medications ²⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Premedication ²¹		X			X	X	X			X	X	X	X	X			
ADCT-402 administration ²²		X			X	X	X			X	X	X	X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²³	
Survival information																X ²⁴	X ²⁴
New anti-cancer treatment information																X ²⁵	X ²⁵

Abbreviations: D = day(s); d = day(s); ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment visit; β-HCG, beta-human chorionic gonadotropin.

Refer to Table 8 and Table 9 for Central Lab Sample Collection Schedule.

1. Day 2 to occur 24 hours ($\pm 10\%$) after EOI.
2. Day 3 to occur 48 hours ($\pm 10\%$) after EOI. Day 5 to occur 96 (± 24) hours after EOI.
3. After last dose of ADCT-402. EOT window is + 7 days.
4. Follow-up to occur 12 (± 1) week after last dose of ADCT-402. Patients who discontinue treatment for any reason other than disease progression will continue to be followed approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anti-cancer treatment. After documentation of disease progression or start of new treatment, patients will be followed (by telephone contact or chart review) approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.
5. Medical history: To include a complete history of all surgeries, significant diagnoses, cancer history, immunophenotyping and all cancer treatments.
6. Serum or urine pregnancy test: For women of child-bearing potential. Not required if negative screening β -HCG pregnancy test was obtained within 7 days prior to Cycle 1, Day 1.
7. Physical examination to include whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist. Any unexplained lesion is to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. Does not have to be repeated on Day 1, if last performed within 3 days prior to dosing with ADCT-402.
8. Vital signs to include arterial blood pressure, heart rate, respiratory rate, and body temperature.
9. Vital signs: On Day 1 of Cycles 1 and 2, vital signs are to be measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the infusion. If no clinically significant changes occur during Cycles 1 and 2, vital sign measurements are to be obtained prior to infusion start and end of infusion for all subsequent infusions. If clinically significant changes in vital signs are observed at Cycle 1 and/or 2 infusion, that patient will be required to have vital signs measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion for all subsequent cycles. Note: Timing of measurements is approximately ± 15 minutes.
10. A bone marrow sample, via aspirate or biopsy if an aspirate is unattainable, will be obtained at Screening for confirmation of disease (as per WHO classification of ALL [[Swerdlow, 2008](#)]), at an approved clinical laboratory.
11. A bone marrow sample will be obtained within 6 days prior to the Day 1 visit of Cycles 3 and 5 and at each subsequent cycle until CR or CRi is achieved or until disease progression. Assessment of response to treatment and determination of MRD (via flow cytometry) are to be done by an approved clinical laboratory. Results must be available to the Investigator before the next dose of study drug is administered. Once CR/CRi is achieved, sampling will be repeated at least every 3 cycles, or, as clinically indicated.
12. A bone marrow sample will be obtained at the EOT visit for those patients who have not demonstrated disease progression and if their most recent sample was obtained more than 12 (± 1) weeks prior to the EOT visit.
13. Hematology: CBC to include WBC with a 5-part differential, platelet count, hemoglobin, hematocrit, and ANC. Peripheral blasts will be included in the hematology analysis for Part 2 only. If WBC is $< 400 \times 10^6/L$ differential is not required.
14. Samples for hematology, coagulation panel, biochemistry, and urinalysis will be collected prior to dosing unless the last sample was collected:
<24 hours before the start of ADCT-402 infusion on Day 1 of Cycle 1, or
<72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.
15. Coagulation panel: PTT and INR; PT expressed in seconds is optional.
16. Biochemistry: Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, sodium, potassium, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, chloride, creatinine, creatine phosphokinase, total protein,

albumin, glucose, triglycerides, total cholesterol, phosphorus, and lactate dehydrogenase. At Days 1, 8 and 15 of each cycle, biochemistry will include creatinine clearance (calculated using the Cockcroft and Gault formula [[Cockcroft and Gault, 1976](#)]).

17. Urinalysis to include: pH, specific gravity, protein, glucose, ketones, nitrites, occult blood and bilirubin. The urinalysis may be performed using a urine dipstick.
18. 12-lead ECG: On Days 1 and 2 of Cycles 1 and 2, a 12-lead ECG is to be performed before the start of the ADCT-402 infusion, within 30 minutes of the end of infusion, and 3 hours (\pm 30 minutes) and 24 (\pm 2.4) hours after the end of infusion.
19. 12-lead ECG: On Day 1 of Cycle 3 and subsequent cycles, a 12-lead ECG is to be performed before the start of ADCT-402 infusion.
20. Concomitant medications to include prescription or over-the-counter medication, herbal or naturopathic products within the 14 days prior to the Cycle 1, Day 1 visit, during the study, and 30 days following the patient's last dose of ADCT-402.
21. Premedication to be performed if a CTCAE Grade 2 or higher infusion-related hypersensitivity reaction is observed in 1 patient at any time during Part 1 of the study. All subsequent patients must receive prophylactic treatment on Days 1, 8 and 15 of each cycle thereafter to reduce the risk of hypersensitivity reaction ([Section 5.2](#)).
22. ADCT-402: Patients will receive a 1-hour IV infusion of ADCT-402, at escalating doses, on Days 1, 8 and 15 of each 3-week (21-day) cycle. If ADCT-402 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent infusions for that patient, at the Investigator's discretion. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation. The IP window is +15 minutes.
23. For all patients, collection of AEs and SAEs will continue for up to 12 weeks (84 days) after the last dose of study drug or initiation of new anti-cancer treatment. Any SAEs that occur more than 84 days after the last dose of study drug do not need to be reported unless the Investigator considers the event to be related to study drug.
24. After documentation of disease progression or start of new anti-cancer treatment, patients will be contacted by telephone approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.
25. Information on anti-cancer treatment initiated after discontinuation of ADCT-402 to be recorded in the eCRF.

[Redacted]

[Redacted]

[Redacted]

[Redacted]

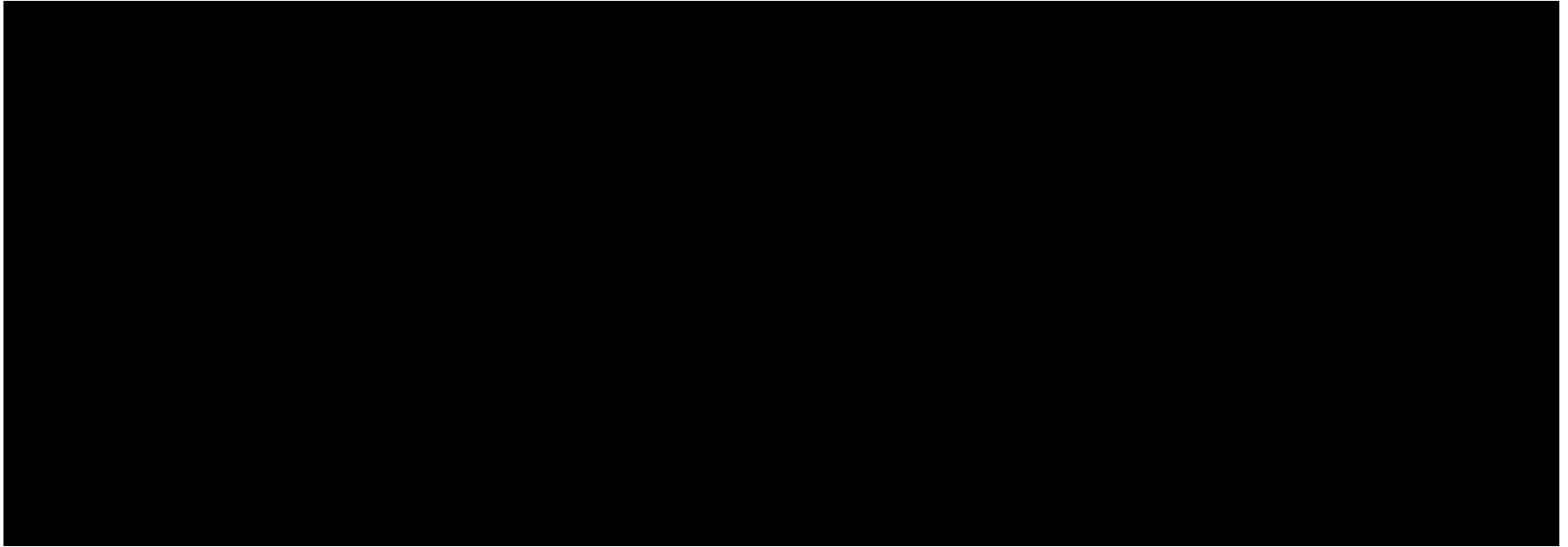
[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]



12.2 Appendix: CTCAE Immune System Hypersensitivity Grades

Table 10. CTCAE Immune System Hypersensitivity Grades

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours	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 (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
<p>Definition: A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.</p>					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, intravenous fluids); prophylactic medications indicated for ≤24 hours	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 (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
<p>Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.</p>					

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or intravenous fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
<p>Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately 6 to 21 days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort, and dyspnea.</p>					
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Abbreviations: ADL, Activities of daily living; NSAIDs, non-steroidal anti-inflammatory drugs. Adapted from CTCAE 4.0 – June 14, 2010, Immune system disorders.