CLINICAL STUDY PROTOCOL

# An Open-label Pilot Study to Evaluate the Safety and Efficacy of ADCT-301 in Patients with Relapsed or Refractory Acute Myeloid Leukemia, myelodysplastic syndrome, or myeloproliferative neoplasms.

Sponsor/Coordinating Center: Duke Cancer Institute

Protocol Chair:
Gwynn Long, MD Professor of Medicine
Duke University Medical Center, DCI
[redacted]

ADC Therapeutics Contact:
Jens Wuerthner, MD PhD
VP, Head of Global Clinical Development – Oncology
ADC Therapeutics
[redacted]

Coordinating Statistician: Zhiguo Li, PhD, Duke

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# 1 Introduction- Study Agent

Camidanlumanb tesirine, ADCT-301 is an antibody-drug conjugate (ADC), composed of the human monoclonal antibody, HuMax®-TAC, directed against human cluster of differentiation 25 (CD25), and conjugated through a 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.16 The schematic representation of ADCT-301, and the different components that may be formed following the administration of this ADC to humans, are presented in Figure 1.

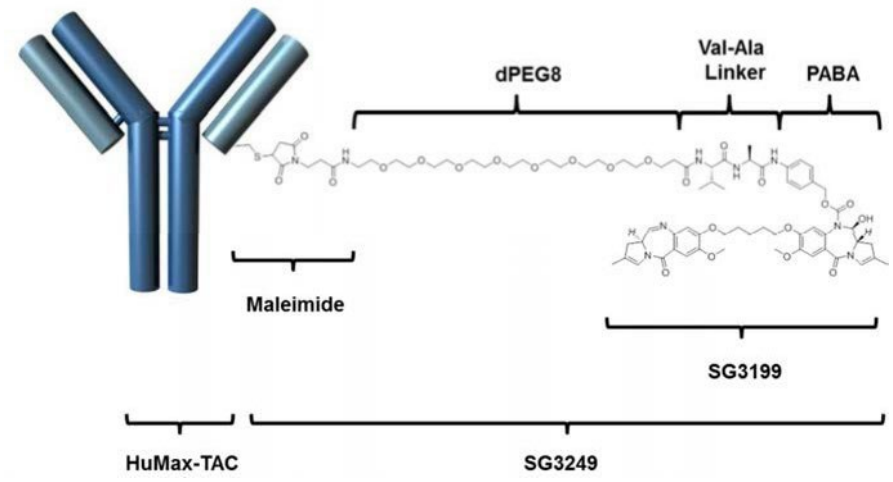


Figure 1. Schematic Representation and Chemical Structure of ADCT-301

Abbreviations: Ala, alanine; PABA, para-aminobenzoic acid; PEG, polyethylene glycol; HuMax®-TAC, human monoclonal antibody being studied; Val, valine.

The make-up of ADCT-301 includes:

1. HuMax®-TAC: A human monoclonal antibody of the IgG1, kappa isotype, specific for human CD25.
2. 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 paraaminobenzoic acid (PABA) self-immolative group.
3. SG3199: A PBD dimer cytotoxin, which is a highly efficient anti-cancer drug due to its interstrand cross-linking, a consequence of its specifically designed strong binding to the minor groove of DNA.

The interleukin-2 receptor (IL-2R) is made up of 3 subunits: α (CD25), β (CD122) and γ (CD132). CD25, or T-cell activation antigen (TAC), is the alpha-chain of IL-2R.5,6 ADCT-301 binds with picomolar affinity to human CD25. After binding and internalization, ADCT-301 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 in a sequence-selective manner, and form highly cytotoxic DNA interstrand cross-links.16 The cross-links formed by PBD dimers are relatively nondistorting of the DNA structure, making them hidden to repair mechanisms, allowing for a longer effective period.1

## 2 Study Rationale and Justification

### 2.1 Clinical Background

AML

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized bythe clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common

leukemia in adults and results in the largest number of deaths due to leukemia in the USA. The diagnosis will account for 38% of an estimated 54,270 new cases of leukemia and 42% of estimated deaths due to leukemia in 2015.2 It is more common in older adults (median age at onset, 67 years), with 72% of cases diagnosed at ages 55 years and older.

The overall 5-year survival rate for AML is 26%, with younger patients (age <45 years) having a higher survival rate (>50%) compared with older patients (~10% for patients 65-74 years). 23 Cytotoxic induction therapy is associated with high rates of complete response/remission, especially for younger patients who are able to tolerate treatment. The discrepancy between the high response rates achieved with induction therapy and poor long-term survival is due to the inability to prevent or overcome disease relapse.4,14 The majority of patients with AML will eventually relapse or develop refractory disease. The prognosis for these patients is poor and most patients will die from progressive disease (PD).

CD25 Expression
CD25, or TAC, is the 55-kilodalton (kDa) alpha-chain of IL-2R.6 In normal human tissue, expression of CD25 is mainly limited to activated T- and B-cells.5,6 It is not expressed on normal human hematopoietic stem cells,29 but has been demonstrated in subpopulations of chemotherapy-resistant human leukemic stem cells (LSC).10 Survival of quiescent, chemotherapy-resistant LSCs may play a role in the development of relapsed or refractory disease in AML.10,19

CD25 expression has been demonstrated in newly diagnosed and relapsed AML 7,13,33 and in late-stage myelodysplastic syndrome related AML.20 Expression of CD25 by AML blast cells is associated with adverse outcomes, including induction failure, relapse, and shortened OS.7,13,20,33 Expression of cluster of differentiation 25 (CD25) independently confers a poor prognosis for patients with ALL and is commonly found in patients with Ph+ ALL.

It is not yet understood what biological role, if any, CD25 may play in the development of adverse outcomes. However, the availability of treatment specifically targeted to cells expressing CD25 may provide additional therapeutic options for these patients.

Additionally, CD25 is expressed on T-regulatory cells of the immune system, a cell type noted to suppress immune responses. This may be beneficial in some aspects such as preventing autoimmune disease, however it may be detrimental in the cancer patient as up regulation is known to occur. Thus, suppression of T regs with ADCT-301-002 (Camidanlumab tesirine) may be another avenue in this setting that may allow for improved tumor surveillance and agent efficacy. 22

## 2.2 Non-human clinical Efficacy and Safety of ADCT-301, Camidanlumab tesirine

The potential for ADCT-301 in treating hematological malignancies, which demonstrate CD25 overexpression, has been shown by complete responses in mouse xenograft models following single, lowdose administration. The efficacy of ADCT-301 in these models is due to targeted delivery of the PBD cytotoxin SG3199.

The safety of ADCT-301 has been assessed in non-clinical testing. In mice, ADCT-301 is well tolerated at doses up to 9 mg/kg. A repeat-dose Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys investigated doses ranging from 0.15 to 0.9 mg/kg. Systemic exposure to total ADCT-301 was consistent with the intravenous (IV) infusion route and increased in a generally dose-proportional manner. No marked sex-related differences in exposure were noted. No evidence of accumulation or changes in median time to maximum concentration (Tmax) and in mean terminal half-life (t1/2), clearance (CL), and volume of distribution (Vz) estimates were observed with increasing dose or on repeat dosing (where total ADCT-301 was sufficiently quantifiable). The average Day 1 ADCT-301 maximum concentration (Cmax) (N = 2 at each dose level) at 0.3 mg/kg, 0.6 mg/kg, and 0.9 mg/kg was
4,520 ng/mL, 12,450 ng/mL and 15,950 ng/mL, respectively. The t1/2 value for ADCT-301 ranged from 4.25 days to 7.54 days for doses 0.3 mg/kg to 0.9 mg/kg.

Toxicities included body weight loss, nephrotoxicity, and cutaneous adverse events (AEs). The highest non-severe toxic dose (HNSTD) in the GLP-compliant study in cynomolgus monkeys was determined to be 0.15 mg/kg. As per guidance from the Food and Drug Administration (FDA), a starting dose of 10 µg/kg (1/6 of the HNSTD, based on body surface area [BSA]) could be proposed for this first study in patients with AML. However, based on anomalous exposure data observed on some dosing days at the 0.15 mg/kg dose level, a lower starting dose of 3 µg/kg was chosen for this study to offset any uncertainty associated with the 0.15 mg/kg dose level and to increase the margin of safety.

See the Investigator Brochure for ADCT-301 for additional information, including guidance for the Investigator.

### 2.3 Prior Clinical Study in Leukemia Patient Population

We have recently completed a multicenter study in patients with AML. 35 patients were enrolled and received 3-92ug/kg every 3 weeks or 30 or 37.5 ug/kg weekly. MTD was not reached. Fever, cytopenia, and fatigue were the main side effects. No serious immune- related events such as Guillain-Barré or polyradiculopathy occurred. The half life was noted as under 2 days, thus the weekly infusion has been chosen for further evaluation. Two of 9 patients with the weekly dosing achieved a CR/CRi and both had a prior alloBMT. Given that all doses were well tolerated, we have chosen the higher dose to evaluate in this study. In addition, given the pace of AML progression can be rapid, the weekly therapy rather than 3 week regimen has been chosen for this study. Thus, this is the focus for the patient population in this pilot efficacy study.39

## 3 Study Objectives

### 3.1 Primary Objective:

1. Assess the morphologic complete response rate of ADCT-301given to patients who have relapsed/persistent AML , MDS, or MDS/MPN following allogeneic transplantation.
2. Assess the safety of ADCT-301given to patients who have relapsed/persistent AML , MDS, or MDS/MPN following allogeneic transplantation.

### 3.2 Exploratory Secondary Objectives

1. Assess the molecular complete remission rate of study patients.
2. Assess Duration of Response in responding patients
3. Assess impact on CD25 T cell subset and thus occurrence of GVHD 4. Assess impact of infusions on measures of immune reconstitution

# 4 Investigational Plan and Patient Selection

## 4.1 Study Design

This is a Phase 2, open-label, fixed dose pilot study of the efficacy and safety of ADCT-301 (Camidanlumab tesirine), used as monotherapy, in patients with relapsed or refractory AML, MDS, or MDS/MPN post allogeneic stem cell transplantation. The study will follow a decision rule to determine if a larger confirmatory study is warranted.

Patients will receive a 1-hour IV infusion of ADCT-301 on Day 1 of Cycle 1. If ADCT-301 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent doses cycles for that patient, at the Investigator's discretion. Weekly (QW) administration will be evaluated.

For each patient, the study will include a Screening period (up to 28 days), a treatment period of up to 6, 3 week cycles, and a follow-up period to assess disease progression and survival for up to 12 months after the first 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 could be approximately 4 years from first patient treated to last patient completed in follow up.

The first 5 patients will be followed for efficacy and if the trial is not closed for futility (see statistical assessment decision rule below) accrual will continue.
The first 6 patients will be followed for safety and if the trial is not closed due to safety accrual will continue to the full 10 (see statistical assessment decision rule below).

## 4.2 Dosing and modifications

No intra-patient dose-escalation is allowed.

1.Weekly Administration
Patients will receive ADCT-30137.5 ug/kg infused day 1,8, and 15 q3weeks of a 21 day cycle. Patients will have up to 2 cycles to assess response and safety to therapy and if they are not progressing may continue for up to 6 cycles. Day of administration may be +/1 1 day due to logistical issues without being a deviation.

2. 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.

3. Prophylactic antiemetic medications, electrolyte supplementation, and other standard supportive care measures may also be administered according to standard treatment center protocols

4. Dose Modifications
- Patients will receive the first 2 cycles, irrespective of blood count recovery. For patients achieving a CR/CRi or MLFS, the subsequent cycles would be delayed until peripheral blood count recovery (absolute neutrophil count [ANC] >0.5 x109/L and platelets >50 x109/L).

Dosing may be delayed (but is not required) in cycles 1-2 for up to 3 weeks for non-hematologic toxicity that has worsened by at least 1 grade from baseline but not meeting the 'unacceptable toxicity' definition AND if deemed warranted by the treating physician.

Patients who withdraw before 2 cycles for reasons other than protocol defined unacceptable toxicity will be replaced to allow for evaluation of overall efficacy.

The Investigator should suspend ADCT-301 dosing for any patient who experiences a non hematologic toxicity that meets the protocol-defined 'unacceptable toxicity' during any treatment cycle 3-6. Resumption of dosing post toxicity with ADCT-301 is at the discretion of the Investigator following recovery to CTCAE Grade 1 or to baseline grade.
If 'unacceptable toxicity' occurs during the first 2 cycles, the patient will not resume further therapy on study.

Physician Guidance: Skin rash has been reported in the ADCT-301 program, as well as with another investigational agent containing the same pyrollobenzodiazepine warhead.28 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.

Dose delays: Patients may have doses altered +/- 2 days for logistic or other issues. If this occurs: -in the event of an early or late drug delivery the pt will plan to resume subsequent weekly doses on the ORIGINAL schedule if feasible.

## 4.3 Selection of Study Population

A maximum of 10 Patients evaluable for efficacy will be treated. An evaluable patient for efficacy is one who meets all eligibility criterion and also receives at least one dose of study agent and receives 2 cycles of therapy (unless withdraws earlier for safety, thus will be evaluated for best response at time of withdrawal). Those who are enrolled but are not evaluable for efficacy will be replaced. All subjects who receive at least 1 dose of study agent will be evaluable for safety however.

### 4.3.1 Inclusion Criteria

1. Patients ≧ 18 years of age with persistence or relapse/progression of leukemia/MDS, i.e. AML, MDS, or MDS/MPN following allogeneic stem cell transplantation.

2. ≦grade 1 overall GVHD at time of inclusion with stable immune suppression for at least 2 weeks pre infusion on study and planned stable immune suppression dose for at least 8 weeks (the safety evaluation period)
3. Calculated creatinine clearance ≥ 60.0 ml/min as estimated by Cockcroft Gault and not dialysis dependent.
4. AST, ALT <3 x ULN unless documented due to medications (ie azole or other common therapy for such patients). Total bilirubin ≤3.0 mg/dl unless there is a history of Gilbert's syndrome in which case the T bili should be < 5.0 mg/dl.
5. Females cannot be pregnant or breast-feeding from time of enrollment till 16 weeks post final agent exposure on this study.
6. Immune suppression not greater than 20mg prednisone daily or equivalent dosing of alternative GVHD prophylaxis/therapy
7. Patients are at least 30 days from most recent allogeneic stem cell infusion
8. Patients may have had other therapy post alloBMT and other donor lymphocyte infusions but they must be at least 60 days from the last infusion of such cell therapy products
9. Patients should not be on other active anti-leukemia therapies at the time of infusion on this study and for the duration of the safety evaluation period.
10. Patients must have other anti-leukemia therapies stopped 2 weeks prior to infusion on this study. Hydrea or pheresis ARE allowed prior to this study and may continue until 14 days following the first infusion on this study if deemed to be needed to assist in count control.
11. Patients must be willing to take adequate contraceptive measures during treatment and for at least 6.5 months after discontinuation (as per recommendations in the Sponsor's Investigator's Brochure).

4.3.2 Exclusion Criteria

1. Patients with progressive infections at time of first infusion (patients with treated infections documented as controlled by the treating team are eligible).
2. Known active CNS disease at time of enrollment
3. Patients with other cancers treated within 3 years
4. Known history of immunogenicity or hypersensitivity to a CD25 antibody or a component of ADCT-301.
5. 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 Dr. Rizzieri.
6. Patients with proven, progressive severe autoimmune disease such as multiple sclerosis, active Guillain Barré syndrome, poliomyelitis, sjogren's are not eligible. Given the immediate, life threatening nature of the relapsed cancer in this patient population, those with other stable and non-immediate non-threatening autoimmune disorders such as thyroid disease or diabetes and others are eligible.
7. Patients with a known infection/reactivation of any of the following within 28 days of the first dose of this agent on study are not eligible: measles, influenza A, Zika, Chikungunya, mycoplasma pneumonia, Campylobacter jejuni, enterovirus B68, or SARS-CoV-2. If they have reactivation of one of these and need active treatment, they will not be eligible until the titre is below the level of clinical concern as documented by the treating team. If they have patients have not been vaccinated against SARS-CoV-2, screening

performed based on symptoms or formal testing will be documented. Patients will have evaluation for HSV1, HSV2, VZV, EBV, CMV as part of screening studies. Additionally, screening based on clinical concern and/or symptoms will be conducted for measles, influenza A, Zika, Chikungunya, mycoplasma pneumonia, Campylobacter jejuni, enterovirus B68.

# 5 Study Procedures

## 5.1

The following procedures will be performed during the study. The
Schedule of Procedures are shown in Appendix 13.1.

Concurrent therapy: Patients with a WBC value >15,000 cells/µL at the Screening Visit may receive hydroxyurea prior to and during the first cycle of treatment and/or leukopheresis to lower the WBC value to <10,000 cells/µL as a goal when initiating therapy.
It is the goal to have the total WBC count under 15,000 at the initiation of study agent, though not required on this protocol.

Study drug administration will occur at Days 1, 8, and 15. Safety evaluations will occur in an ongoing fashion with formal lab and safety assessments on the days patient is receiving weekly therapy (weekly though may vary +/- 2 days due to logistical issues).

### 5.1.1 Screening Period (Day –28 to 0)

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) approved informed consent form (ICF). Results (clinical laboratory, etc.) obtained prior to the date of informed consent, but within the allowed timeframe for screening, may be used for if obtained as part of the patient's standard of care.

1. Medical history, disease characteristics and risk criterion if known (ie molecular data) and prior therapies.
2. Serum β-HCG pregnancy testing (women of child-bearing potential only).
3. Physical examination with assessment for any baseline skin rashes and active infections.
4. Baseline laboratory values: parameters include at a minimum complete blood count with differential, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, AST, ALT, total bilirubin, calcium, phosphorous, magnesium, albumin, LDH
5. EKG
6. Confirmation of disease, as per the WHO classification of acute leukemias, at the treating center at some point in the patient's disease course.
7. Percentage of blast cells expressing CD25 and/or fluorescence intensity of CD25 on blast cells.

8. Whole blood sample collection for correlative analysis pre therapy and prior to cycle 2 and at end of cycle 2.
9. Consideration for underlying infection should be given with attention to assure noted infections /reactivation of any of the following are not present within 28 days of the first dose of this agent on study: HSV1, HSV2, VZV, EBV, CMV, measles, influenza A, Zika, Chikungunya, mycoplasma pneumonia, Campylobacter jejuni, enterovirus B68, or SARS-CoV-2. In particular, titres for HSV1, HSV2, VZV, EBV, CMV should be documented as below an infectious level and the other infectious agents be considered if there is evidence of infection of unknown source prior to initiating therapy on this study. Patients will have SARS-CoV-2 screening performed if at all possible during the screening process. If screening is not available, then screening based on symptoms will be documented. Additionally, screening based on clinical concern and/or symptoms will be conducted for measles, influenza A, Zika, Chikungunya, mycoplasma pneumonia, Campylobacter jejuni, enterovirus B68. Terms for considering the tests indicative for active infection needing intervention and thereby excluding the patient for enrolling at that time:
    a. If CMV PCR testing is over 500IU/ml or the treating physician feels a level below this warrants active therapy
    b. If EBV PCR testing is over 500IU/ml or the treating physician feels a level below this warrants active therapy
    c. If HSV 1 PCR is over 50 copies/ml or the treating physician feels a level below this warrants active therapy
    d. If HSV2 PCR is over 50 copies/ml or the treating physician feels a level below this warrants active therapy
    e. If VZV is culture + or seen on viral electron microscopy from a lesion of concern or the treating physician feels on clinical exam there to be an active VZV infection warranting therapy (skin outbreak for instance)

5.1.2 Day 1 (± 2 days) of Each Cycle

Day 1 of each cycle occurs on infusion day. The following procedures will be performed prior to ADCT301 infusion at each cycle, unless otherwise specified.

1. Serum or urine pregnancy test (women of child-bearing potential, Cycle 1 only) required if the screening pregnancy test was obtained >7 days prior to Day 1.
2. Physical examination
3. On Day 1 of Cycle 1, vital signs are to be measured before the start of the infusion and at the end of infusion and again 1 hour later prior to discharge from clinic.
   Note: Timing of measurements is ± approximately 15 minutes.
4. Hematology and biochemistry parameters will be measured prior to dosing unless the last sample was collected:

o <24 hours before the start of ADCT-301 infusion on Day 1 of Cycle 1, or o <48 hours before the start of ADCT-301 infusion on Day 1 of Cycle 2 and subsequent cycles and deemed as not needed by the treating provider team.
The parameters include at a minimum complete blood count with differential, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, AST, ALT, total bilirubin, calcium, phosphorous, magnesium, albumin, LDH

5. Collection of AE information on days of agent infusion and 30 days post last dose (end of therapy evaluation, if patient is available).
6. Correlative collections: pre therapy sample, pre cycle 2, and post cycle 2.

5.1.3 Day 8 and 15 (± 2 day) of Each Cycle- prior to infusion of next dose

1. Physical examination
2. Vital signs.
3. Hematology and biochemistry parameters.
The parameters include at a minimum complete blood count with differential, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, AST, ALT, total bilirubin, calcium, phosphorous, magnesium, albumin, LDH

4. Collection of AE information.

5.1.4 Bone Marrow Aspirate or Biopsy

A BMA (or biopsy if aspirate unattainable) will be obtained at the end of cycle 2/before cycle 3 dose is given (±3 days) for assessment of response, if it appears from the peripheral blood evaluation that there has been a response. Once CR/CRi is achieved, sampling will be only as indicated.

5.1.5 End of Treatment Visit

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

Physical examination,
Weight and vital signs measurements.
WBC, hemoglobin, platelet count
Collection of AE information
Determination of reason to discontinue therapy: toxicity, no response, therapy completed, or patient choice.

5.1.6 Long-term Follow-up

Patients will continue to be followed approximately every 12 weeks from the last disease assessment (may be via phone contact with patient or local provider) until disease progression or initiation of new anti-cancer treatment for up to 1 year from completion of therapy.

## 5.2 Subject withdrawal/discontinuation

### 5.2.1 Reasons for Withdrawal/Discontinuation

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

A patient may be withdrawn from treatment for any of the following reasons:

Disease progression.

unacceptable toxicity following the protocol defined definition Withdrawal of consent.

Major protocol deviation.

Required treatment delay >21 days (except in case of potential patient benefit). Non-compliance, including lost to follow-up.

Pregnancy

Other (e.g., development of contraindications).

Discontinuation of the study by the Sponsor.

Death.

### 5.2.2 Patient Replacements

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

# 6 Study Treatments

## 6.1 Prophylactic Treatments for Hypersensitivity

If 1 patient experiences a CTCAE Grade 2 or higher infusion-related hypersensitivity reaction at any time during study due to the infusions, they will be offered prophylactic treatment, as described below, to reduce the risk of hypersensitivity reactions (may be altered at treating physician discretion).

1. 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 each ADCT-301 infusion. When necessary, 12 and 6 hours before the first infusion may be defined as “immediately before sleeping” and “immediately after waking up.”
2. On Day 1 of each cycle, patients will be given 25-50 mg IV of diphenhydramine hydrochloride at 10-60 minutes before the start of ADCT-301 infusion.
3. On Day 1 of each cycle, patients will be given 50 mg of ranitidine (or equivalent) IV or oral at 10-60 minutes before the start of ADCT-301 infusion.
4. For 2 days following administration of ADCT-301 on Day 1, pt should take dexamethasone 4 mg orally, twice per day.

Other doses and 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.

## 6.2 Identity of Investigational Product

ADC Therapeutics will provide and distribute adequate supplies of ADCT-301 to the study sites. The following drug supplies will be used in the study:

Product Supplied As
a lyophilized white to off-white powder in 2 mL glass vials (5 mg camidanlumab tesirine per vial)

### 6.2.1 ADCT-301 Drug Product

The lyophilized camidanlumab tesirine is formulated in 20 mM histidine, 175 mM sucrose, and 0.04% polysorbate 20, at pH 6.0.

Prior to use, the study drug is reconstituted with 1.2 mL of sterile water for injection to deliver 1.0 mL at a concentration of 5 mg/mL. After reconstitution, the vial should be gently swirled (do not shake the vial) to ensure complete dissolution and homogeneity, and visually inspected prior to use. Sterile water for injection is to be provided by study sites.

Management of Clinical Supplies
Detailed instructions regarding study drug shipment, handling, storage, preparation and administration are included in the pharmacy manual.

### 6.3.1 Study Drug Packaging and Storage

The study drug will be supplied by the Manufacturer through the designated packaging, labeling, and distribution center.

All study drugs must be stored according to the pharmacy manual, in a secure area.

The lyophilized formulation of camidanlumab tesirine should be protected from long-term exposure to light and stored refrigerated (2 to 8°C).

Light protection is not required for dose preparation and during administration of the diluted drug in the IV bag.

### 6.3.2 Study Drug Preparation and Administration

The amount of the product to be diluted will depend on the dose level and the body mass of the patient. Of note, a cap on the administered dose is to be applied for patients with a body mass index ≥35 kg/m2. Additional details are included in the pharmacy manual.

Administration of ADCT-301will be performed by the Investigator or a qualified designee according to the pharmacy manual.

Extravasation of ADCT-301 may be associated with local irritation, swelling, pain, or tissue damage. The IV infusion site should be monitored for signs of IV infiltration or drug extravasation, and patients should be instructed to report immediately any signs of IV infiltration or drug extravasation during or after the infusion. Suspected extravasation of ADCT-301should be managed according to institutional protocol for management of extravasation

For patients who have a central line, administration of ADCT-301via this central line should be considered, though not required.

Investigational Product:
Patients will receive a 1-hour intravenous (IV) infusion of ADCT-301 on the first dose and over 30 minutes if well tolerated on subsequent doses, ie no hypersentivitiy reactions requiring intervention as in section 6.1 or infusion related tachycardia or systolic or diastolic blood pressure increase by more than 25% or infusion related temperature change to over 38.3 degrees Celcius.

### 6.3.3 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.

## 6.4 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 IRB and ADC Therapeutics. There are no data available to determine what effects and whether effects of an overdose can be reversed.

## 6.5 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 the investigator’s preference but not planned.

# 7 Study Assessments and Procedures

Patients will undergo the procedures at the time points specified in schedule of events (Appendix).

## 7.1 Efficacy Assessments

Assessment of response to treatment with ADCT-301 will be based on bone marrow samples (aspirate or biopsy if aspirate unattainable) and peripheral blood or other sites known to be involved. Bone marrow samples will be obtained as described for patients who appear to have responded by evaluation of the peripheral blood and justifying the marrow exam as a standard disease assessment. This is anticipated after cycle 2 and at end of cycle 6 or end of therapy in responding patients. If a patient appears to have had a response to cycle 1 based on blood count evaluation, the marrow may also be done prior to cycle 2 at the investigator's discretion.

The activity of ADCT-301 will be evaluated based on the Investigator's evaluation of the patient's response to ADCT-301 as CR, CRi, PR, mlfs, PD or NR using standardized NCCN criterion.8,11 (NCCN published, 2019)40

## 7.2 Exploratory Assessments

1. The following exploratory assessments will be performed at various time points in the study: Percentage of blast cells expressing CD25 and/or fluorescence intensity of CD25 on blast cells (bone marrow or blood) and on lymphocyte subsets by immunohistochemisty or flow cytometry standard clinically available tests (marrow or blood).
2. Immune reconstitution panel with attention to T regs and NK cells as well as T cell exhaustion (marrow preferred, but may be on blood).

## 7.3 SAFETY MONITORING AND REPORTING

Safety will be described using AEs, serious AEs (SAEs), treatment discontinuations due to AEs, and 'unacceptable toxicities'. Adverse events will be graded according to CTCAE Version 5.0.
Formal evaluations will occur weekly on the days of agent infusion.
The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below.

### 7.3.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to use of the study drug. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.
From the time the subject receives first dose of study agent through 30 days post last dose of study agent, all AEs must be recorded. AEs will be assessed according to the CTCAE version 5.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

7.3.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

7.3.3 Reporting of SAEs

Any reaction that is reportable (serious, unexpected and related/possibly related to the study) must be reported using the FDA #3500 MedWatch form and the Duke University Health System (DUHS) Institutional Review Board (IRB) Office SAE form. These reactions will be reported to ADC Therapeutics and IQVIA using the FDA #3500 MedWatch form at the time of regulatory submission (15 calendar days) via secure email to the following addresses: drugsafety@adctherapeutics.com
PhV_clinicaltrials_RZA05954_SO@IQVIA.com

a. Sponsor must submit event of Guillain-Barré syndrome (GBS, including variants such as acute motor and sensory axonal neuropathy), radiculopathy, or polyradiculopathy to ADCT regardless of causality or seriousness within 1 business day via secure email to the following address: drugsafety@adctherapeutics.com

b. Sponsor must send to ADCT a listing of all SAEs at least quarterly

Pregnancy cases will be reported to ADC Therapeutics within 3 business days after the site personnel first learn of the pregnancy via secure email to the following address:
drugsafety@adctherapeutics.com

7.3.3.1 ADCT-301Adverse Events of Special Interest (AESIs)

In company sponsored clinical trials, ADC Therapeutics has designated the following as Adverse Events of Special Interest (AESIs), irrespective of causality, because of clinical importance, known class effects, or based on preclinical signals: :

- GBS (including variants such as acute motor and sensory axonal neuropathy)

- Polyradiculopathy
- Autonomic imbalance, worsening tremors
- Autoimmune-mediated events (including such as but not limited to pneumonitis, hepatitis, colitis, thyroiditis, and nephritis)

It is recognized that these patients with a history of leukemia and an allogeneic stem cell transplant will likely have some degree of baseline neurologic deficit such as autonomia and radiculopathy. For this study, these AESIs that worsen by more than 1 grade from pre-study baseline will be reported to the company using the same process as if it were and SAE (above). AESI may require more frequent patient monitoring and/or intervention. Early recognition of signs and symptoms related to a potential neurological or immune mediated event is important for proper treatment and management of these toxicities.

In order to support the overall evaluation of safety across the ADCT-301clinical development program, the sponsor will submit a listing of all > grade 1 AEs at least annually to ADC Therapeutics.

7.4.1 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsorinvestigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

# 8 Data Quality and Assurance

## 8.1 Endpoints

Primary Objective:

1. Response Rate: Assess the morphologic complete response rate of ADCT-301to patients who have relapsed/persistent AML , MDS, or MDS/MPN following allogeneic transplantation.
2. Safety: Assess the safety of ADCT-301to patients who have relapsed/persistent AML , MDS, MDS/MPN, or ALL following allogeneic transplantation.

Exploratory Secondary Objectives:

1. Assess the molecular complete remission rate of study patients using standard clinical available test based MRD assessment.
2. Assess Duration of Response in responding patients
3. Assess impact on CD25 T cell subset and thus occurrence of GVHD via flow analysis.

4. Assess impact of infusions on measures of immune reconstitution (correlative samples)

## 8.2 QUALITY CONTROL AND QUALITY ASSURANCE

### 8.2.1 Monitoring

This clinical research study will be monitored both internally by the PI, and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI Protocol Review and Monitoring systems (PRMS) review of this protocol begins with an initial review by the Cancer Protocol Committee (CPC). CPC new protocol review focuses on scientific relevance, study design, adequacy of biostatistical input, protocol prioritization, feasibility of completing the study within a reasonable time frame and risk assessment of the trial. The PI will abide by CPC assessment of the level of risk, which will determine the intensity of subsequent DCI monitoring. CPC also conducts annual scientific progress reviews on protocols that are open to enrollment and focus on protocol prioritization, accrual and scientific progress. These reviews are conducted at the time of IRB annual renewals and documentation of all CPC reviews will be maintained in eIRB/iRIS systems.

A determination for the degree of monitoring conducted by the DCI monitoring team is made at the time of initial CPC approval to commensurate with the type and level of intervention, phase, endpoints, degree of risk, size and complexity of the protocol. A formal, independent monitoring will be conducted by the DCI monitoring team according to the risk level and monitoring plan assigned by the CPC until the study is closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the
IRB.

### 8.2.2 Audits

The Duke University Office of Audit, Risk and Compliance - Human Subjects Research Compliance (HSRC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the HSRC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the HSRC auditor(s) in order to discuss findings and any relevant issues.

HSRC audits are designed to protect the rights and well-being of human research subjects. HSRC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.
HSRC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

8.2.3 Data Management and Processing

8.2.3.1 Case Report Forms (CRFs)

An electronic CRF maintained in a Microsoft Office Access database will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only approved study staff (data coordinators), are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management. Designated personnel will complete user training, as required or appropriate per regulations.

8.2.3.2 Data Management Procedures and Data Verification

Designated personnel using the electronic CRF will have access based on their specific roles in the protocol. Regulatory and nursing coordinators will have read-only access. Data Coordinators will have edit access.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and/or data coordinator back-up will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).
The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

8.2.3.3 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

## 9.0 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

### 9.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

### 9.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).
The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

### 9.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

### 9.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

A case report form (CRF) (please indicate whether a paper or electronic CRF will be used) will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. Only approved study staff (data coordinators), are permitted to make entries, changes, or corrections in the CRF. For paper CRFs, errors will crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The Principal Investigator or authorized key personnel will maintain a record of the changes and corrections. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system (please indicate what eCRF management system is being used).

### 9.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room.

All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database (Microsoft Access), which is housed in an encrypted and password-protected DCI file server (\\cancerlan6\adultbmt_pro). Access to electronic databases will be limited to staff of the division of Cellular Therapy. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

### 9.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 8.

### 9.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.). Amendments will be sent to ADCT for review as well.

### 9.8 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least two years after the date on which a New Drug Application is approved by the FDA (if an IND is involved)
- at least two years after formal withdrawal of the IND associated with this protocol (if an IND is involved)
- at least six years after study completion (Duke policy)

## 10 Statistical Analysis Methodology

### 10.1 Safety Analyses

Assessments of Safety:

Safety will be described using AEs, serious AEs (SAEs), treatment discontinuations due to AEs, and 'unacceptable toxicities'. Adverse events will be graded according to CTCAE Version 5.0. Adverse events will be tabled by grade, and rates of the events and unacceptable toxicities will be calculated.

Decisions Rule for Safety:
6 patients will be treated and monitored with attention to the definition for unacceptable toxicity and continue for 2 cycles before final safety determination is made. If 2 or less patients have unacceptable toxicity within the first 2 cycles then we will expand to 10 total patients. If 3 or less of these 10 have 'unacceptable toxicity' the study will be considered safe at the dosing regimen chosen in this setting.

Toxicity will continue to be monitored for the additional cycles beyond the 2 delivered for formal safety analysis, but the information will not be used to determine an early study stoppage or overall study safety. Occurrence in a subsequent cycle (3-6) of an 'unacceptable toxicity' though would necessitate stopping the therapy and not receiving more agent on study. If in subsequent cycles 3-6 there is agent related death or other unacceptable toxicity, in more than 2 subjects, then continuation beyond cycle 2 for subsequent patients will be reassessed after data is resubmitted to the CPC and IRB for review. Patients currently on therapy and deriving benefit will be provided the information and be offered a chance to continue if they so choose while this review is ongoing to determine if total number of cycles should be further limited.

Definitions: A hematologic 'unacceptable toxicity' will apply to all patients with no evidence of active leukemia and will be defined as an adverse event (AE) in the first 2 cycles (and up to 21 days following the start of 2nd cycle) that is felt to be at least possibly related to treatment agent related and: Toxicity
will be deemed 'unacceptable' if there is new occurrence (post agent infusion) ≥Grade 3 thrombocytopenia or neutropenia for ≥6 weeks in patients with normocellular bone marrow (and <5% blasts). It is expected that patients will have cytopenias induced by this agent as part of the response and due to the underlying disease. The above definition is intended to define the duration of cytopenia felt to be at least possibly related to the agent, not a process of response and/or disease activity. Cycles 1 and 2 will not be delayed or altered due to low counts.

A non-hematologic unacceptable toxicity will be defined as Grade 2 peripheral sensory or motor neuropathy due to agent lasting longer than 3 weeks or grade 3 or 4 lasting longer than 2 weeks despite therapy or >=grade 3 for longer than 1 week of drug related GI, renal, cardiac, neurologic or pulmonary systems despite appropriate therapy or grade 4 skin lasting longer than 1 week. Febrile neutropenia will not be considered 'unacceptable' in this patient population for this study.
Worsening of overall GVHD by at least 1 grade and overall >= grade 3 for more than 2 weeks despite appropriate therapy will also be considered unacceptable toxicity for this study. Grade 1 or 2 GVHD will not be considered 'unacceptable' due to the severe nature of the diagnosis and that if this therapy works some GVHD may be an expected and required part of immune reconstitution and anti-leukemia response. In addition, the occurrence of Guillian-Barre like or Guillan-Barre Syndrome (GBS) of any grade are considered to meet the definition of unacceptable toxicity and require discontinuing treatment. Other non-hematologic toxicities: Any other toxicities that the investigators deem as at least possibly related to the study agent and should be deemed as 'unacceptable" may be counted in this definition as well.
Toxicity will use the current CTC criterion 5.0.

## 10.2 Efficacy Analysis

Assessment of Efficacy (following NCCN criterion):
Assessment of response to treatment with ADCT-301be based on bone marrow samples or peripheral blood if lack of response is evident. The activity will be evaluated based on the Investigator's evaluation of the patient's response as CR, CRi, PR, MLFS following standard NCCN definitions. Responses will be tabled by category, and rates of responses will be calculated.

Decision Rule for Efficacy:
Five patients will be treated, and if at least 1 of the 5 has a CR or CRi (NCCN criterion) then the study will continue to accrue to the full 10 patients. If at least 4 of the 10 patients attain a CR or CRi, the study will be considered successful and worthy of further combination studies.

Under the proposed stopping rule, the probability of declaring the treatment is unsafe is listed as follows assuming different true rates of toxicity:

| True toxicity rate | probability of declaring safe |
|---|---|
| 0.2 | 0.85 |
| 0.3 | 0.61 |
| 0.4 | 0.35 |
| 0.5 | 0.15 |

Performance of the Efficacy Rule:

| True response rate | probability of declaring success |
|---|---|
| 0.2 | 0.12 |
| 0.3 | 0.35 |
| 0.4 | 0.61 |
| 0.5 | 0.82 |
| 0.6 | 0.94 |

## 10.3 Secondary Analyses

-Assess and calculate the molecular complete remission rate of ADCT-301given to patients who have relapsed/persistent AML, MDS/MPN or following allogeneic transplantation.
Patients will have standard of care assessment for cytogenetic, flow, and when applicable, molecular markers of disease at the same time as morphologic remission I assessed.

-Assess Duration of Response in responding patients.
Duration of response will be assessed using the Kaplan-Meier curve, and the median duration of response will be calculated.
-Assess impact on CD25 T cell subsets

Assess impact of infusions on measures of immune reconstitution: These will be evaluated using flow markers for immune reconstitution with measures of lymphocyte numbers, T reg numbers, T cell exhaustion, and NK cell activity.

11 Reference List


1. Adair JR, PW Howard, JA Hartley, DG Williams, and KA Chester (2012). Antibody-drug conjugates - a perfect synergy. Expert Opin Biol Ther 12(9): 1191-1206.
2. American Cancer Society, (2015). Cancer facts & figures 2015. Accessed on 20 May 2015 at http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/.
3. Angelini DF, T Ottone, G Guerrera, S Lavorgna, M Cittadini, F Buccisano, et al (2015). A leukemia-associated CD34/CD123/CD25/CD99-positive immunophenotype identifies FLT3mutated clones in acute myeloid leukemia. Clin Cancer Res. May 8. pii:clincanres.3186.2014.
4. Breems DA, WL Van Putten, PC Huijgens, GJ Ossenkoppele, GE Verhoef, LF Verdonck, et al (2005). Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 23:1969–1978.
5. Buckner, JH (2010). Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases. Nat Rev Immunol 10(12): 849-859.
6. Burchill MA, J Yang, KB Vang and MA Farrar (2007). Interleukin-2 receptor signaling in regulatory T cell development and homeostasis. Immunol Lett 114(1): 1-8.
7. Cerny J, H Yu, M Ramanathan, GD Raffel, WV Walsh, N Fortier, et al (2013). Expression of CD25 independently predicts early treatment failure of acute myeloid leukaemia (AML). Br J Haematol 160(2): 262-266.
8. Cheson BD, JM Bennett, KJ Kopecky, T Buchner, CL Willman, EH Estey, 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.
9. Cockcroft DW and MH Gault (1976). Prediction of creatinine clearance from serum creatinine. Nephron 16(1):31-41.
10. Ding L, TJ Ley, DE Larson, et al (2012). Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature 481(7382):506-510.
11. Döhner H, EH Estey, S Amadori, FR Appelbaum, T Büchner, AK Burnett, 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.
12. Fridericia LS (1920). The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Act Med Scand 53:469–486.
13. Gönen M, Z Sun, ME Figueroa, JP Patel, O Abdel-Wahab, and J Racevskis, (2012). CD25 expression status improves prognostic risk classification in AML independent of established biomarkers: ECOG phase 3 trial, E1900. Blood 120(11):2297-2306.
14. Grimwade D, H Walker, G Harrison, F Oliver, S Chatters, CJ Harrison, et al, for the Medical Research Council Adult Leukemia Working Party (2001). The predictive value of hierarchical cytogenetic

classification in older adults with acute myeloid leukemia (AML): Analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood 98:1312–1320.

15. Gu Y, Menzies AM, Long GV, Fernando SL, Herkes G (2017) Immune mediated neuropathy following checkpoint immunotherapy. J Clin Neurosci. Nov;45:14-17

16. Hartley JA (2011[1]). The development of pyrrolobenzodiazepines as antitumour agents. Expert Opin Investig Drugs 20(6): 733-744.
17. Inaba H, Greaves M, and Mullighan CG (2013). Acute lymphoblastic leukaemia. Lancet June 1; 381(9881): doi:10.1016/S0140-6736(12)62187-4.
18. Jing Y, H Chen, M Liu, et al. (2014). Susceptibility of Ph-Positive ALL to TKI Therapy Associated with BCR-ABL Rearrangement Patterns: A Retrospective Analysis. PLoS ONE 9(11):doi: 10.1371/journal.pone.0110431.
19. Ishikawa F, S Yoshida, Y Saito, A Hijikata, H Kitamura, S Tanaka, et al (2007). Chemotherapy-resistant human AML stem cells home to and engraft within the bone- marrow endosteal region. Nat Biotechnol 25:1315–1321.
20. Miltiades P, E Lamprianidou, TP Vassilakopoulos, SG Papageorgaiou, AG Galanopoulos, and S Vakalopoulou, for the Hellenic MDS Study Group (2014). Expression of CD25 antigen on CD34+ cells is an independent predictor of outcome in late-stage MDS patients treated with azacitidine. Blood Cancer Journal, 4, e187; doi:10.1038/bcj.2014.9 (Letter to the Editor).
21. 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.
22. Tanak A, and Sakaguchi S. (2019) Europ J Immunology 49: 1140-1146.
23. National Cancer Institute (2015 [1]). SEER Stat Fact Sheets: Acute Myeloid Leukemia (AML), 2015. Accessed on 1 June 2015, at http://seer.cancer.gov/statfacts/html/amyl.html.
24. National Cancer Institute (2015 [2]). SEER Cancer Statistics Factsheets: Acute Lymphocytic Leukemia (ALL) 2015. Accessed on 1 July 2015, at http://seer.cancer.gov/statfacts/html/alyl.html.
25. Goldberg, Atallah, Rizzieri et al . (2020). Camidanlumab tesirine, an antibody drug conjugate, in relapsed/refractory CD25 positive AML or AL: a phase 1 study (in submission)
26. Oken MM, RH Creech, DC Tormey, et al, (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649-55.
27. additional leuk ref
28. Rudin CM, Pietanza MC, Bauer TM, Spigel DR, Ready N, Morgansztern D, et al. Safety and efficacy of single-agent rovolpituzumab 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).
29. Saito Y, H Kitamura, A Hijikata, Tomizawa-Murasawa1, S Tanaka, S Takagi, et al, (2010). Identification of therapeutic targets M for quiescent, chemotherapy-resistant human leukemia stem cells. Sci Transl Med February 3; 2(17): 17ra9. doi:10.1126/scitranslmed.3000349.

30. 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.
31. Sejvar JJ, Koohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al, (2011) Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine; 29(3): 599-612.
32. Smith TJ (Chair), J Khatcheressian, GH Lyman, H Ozer, JO Armitage, L Balducci, 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.
33. Terwijn M, N Feller, A van Rhenen, A Kelder, G Westra, S Zweegman, G Ossenkoppele, and GJ Schuurhuis, (2009). Interleukin-2 receptor alpha-chain (CD25) expression on leukaemic blasts is predictive for outcome and level of residual disease in AML. Eur J Cancer Jun;45(9):1692-9. doi: 10.1016/j.ejca.2009.02.021. Epub 2009 Mar 25.
34. Vardiman J, J Thiel, D Arber, R Brunning, M Borowitz et al. (2009). The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 114(5):937-951. doi: 10.1182/blood-2 009-03-209262. Epub 2009 Apr 8.
35. Rizzieri DA, Dev P, Long GD, Gasparetto C, Sullivan KM, Horwitz M, Chute J, Chao NJ. Response and toxicity of donor lymphocyte infusions following T-cell depleted non-myeloablative allogeneic hematopoietic SCT from 3-6/6 HLA matched donors. Bone Marrow Transplant. 2009. 43(4):327-333
36. Ghobadi et al Leuk Res 2016
37. Schroeder et al Biol Blood and Marrow Trans 2015;
38. Schroeder et al Ann Hematol 2018)
39. Goldberg A, Atallah E, Rizzieri D, et al Camidanulab tesirine, an antibody drug conjugate in relapsed refractory CD25+ AML or ALL: a phase 1 study, Leukemia. in press 2020
40. NCCN Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia. NCCN.org Version 1.0, 15 May 2019

# 12 Appendices

## 12.1 Schedule of Events

The Schedule of Procedures for the QW dosing schedule is shown below.

| | Screening Day -28 to -1 | Cycle 1 | | | Cycle 2 -until 6 or progression[1] | | | End of Treatment |
|---|---|---|---|---|---|---|---|---|
| | | W1 | W2 | W3 | W1 | W2 | W3 | |
| | | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | 30 Days |
| | | (±2days) | (±2 days) | (±2 days) | (±2 days) | (±2 days) | (±2 days) | (+ 7 days) |
| Informed Consent | X | | | | | | | |
| Medical History | X | | | | | | | |
| β-HCG pregnancy test (serum or urine)[3] | X | X | | | | | | |
| Physical Examination including baseline rash | X | X | X | X | X | X | X | X |
| Vitals: BP, temperature, respiratory rate | X | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X |
| Height | X | | | | | | | |
| Weight | X | | | | | | | X |
| Laboratory Evaluation see "2" for details | X | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X |
| Evaluation of CD25 on expression on disease and lymphocytes (IHC or FLOW) | X | | | | | | | |
| Confirmation of Disease at treatment site | X | | | | | | | |
| ECOG Performance Status | X | | | | | | | |
| ADCT-301 Administration[6] | | X | X | X | X | X | X | |
| Adverse Events [7] | | X | X | X | X | X | X | X |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Survival Follow-up | | | | | | | | |
| Bone Marrow Aspirate/Biopsy | X | | | | | | X[9] | |
| Correlative study labs | X | | | | X | | X[10] | |

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; β-HCG, beta-human chorionic gonadotropin.

1. After treatment discontinuation. EOT window is up to +7 days.
2. Hematology and biochemistry parameters will be measured prior to dosing unless the last sample was collected:
   - <24 hours before the start of ADCT-301 infusion on Day 1 of Cycle 1, or ○ <72 hours before the start of ADCT-301 infusion all other doses
   - The parameters include at a minimum complete blood count with differential, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, AST, ALT, total bilirubin (ULN = 1.5 mg/dL), calcium, phosphorous, magnesium, albumin, LDH
3. For women of child-bearing potential. Not required if negative screening β-HCG pregnancy test was obtained within 7 days prior to Day 1, Cycle 1.
4 Not to be repeated on Day 1, Cycle 1 if last performed within 3 days prior to dosing.
5. On Day 1 of Cycle 1, vital signs measured before the start of the infusion, every 30 minutes during the infusion, and at the end of infusion. If no clinically significant changes occur during this first infusion, vital sign measurements are obtained prior to infusion start and end of infusion for all subsequent infusions. For Cycles 1 and 2, patients will have vital signs measured 1 hour after the end of infusion and at discharge. Note: Timing of measurements is ± approximately 15 minutes.
6. Patients to receive ADCT-301 IV for 1 hour. If ADCT-301 is well-tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent doses 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 administration window is ±15 minutes.
7. 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.
8. After documentation of disease progression or start of new anti-cancer treatment, patients will be contacted if not seen in person then by telephone approximately every 12 weeks for up to 12 months after the first dose of study drug to collect survival information.
9. Local Laboratory Sample Collection: A BMA (or biopsy if aspirate unattainable) sample will be obtained at Screening, and end Cycle 2 and before cycle 3 delivery if there appears to be a

response based on peripheral counts. CR/CRi patients will have marrow repeated when counts change suggesting need for evaluation, following standards of care.

10. Correlative study lab drawn – end of Cycle 2/pre Cycle 3