# Results from an Ongoing Phase 1 Study Indicate ADCT-301 (Camidanlumab Tesirine) Is Well Tolerated in Patients with Relapsed or Refractory CD25-Positive Acute Leukemia

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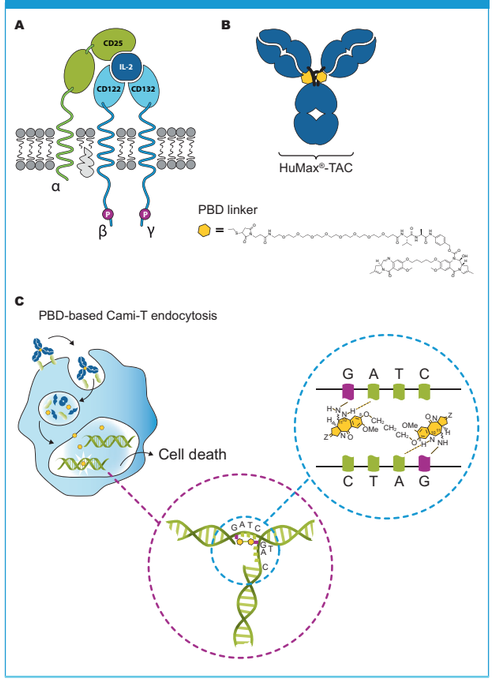
## INTRODUCTION

- There is a significant need for improved therapeutics for patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).
- Cell surface expression of CD25 (IL-2R, α-chain; **Figure 1A**) on AML and ALL blast cells is associated with adverse outcomes, including induction failure, relapse, and shorter overall survival.[1,2,3]
- ADCT-301 (camidanlumab tesirine [Cami-T]) is an antibody drug conjugate composed of a human CD25-targeting monoclonal antibody conjugated to tesirine, a pyrrolobenzodiazepine (PBD) dimer cytotoxin (**Figure 1B**).
- Cami-T has demonstrated anti-tumor efficacy in mouse xenograft models of CD25-expressing hematologic malignancies.[4]
  - The mode of action of Cami-T is presented in **Figure 1C**.
- Here, we present interim data from a Phase 1 study of Cami-T treatment in patients with relapsed or refractory (R/R) CD25-positive (CD25+) acute leukemia.

**Figure 1.** Schematic Representation and Mechanism of Action of Cami-T




**A.** The IL-2 receptor is a heterotrimeric receptor composed of alpha (α; CD25), beta (β), and gamma (γ) chains. **B.** Camidanlumab tesirine (Cami-T) comprises HuMax®-TAC, a human IgG1 anti-CD25 antibody, stochastically conjugated via a cathepsin-cleavable valine-alanine linker to a PBD warhead to allow targeted PBD delivery to CD25+ B- and T-cells. **C.** The PBD-conjugated ADC binds to the CD25 antigen on the tumor cell. Upon binding, the ADC is internalized and releases PBD dimers after the protease-sensitive linker is cleaved in the lysosomes. The released PBD molecules migrate into the nucleus and sequence-selectively bind to the DNA minor groove forming interstrand cross-links that block tumor cell division and, hence, directly kill the cell.

ADC, antibody drug conjugate; PBD, pyrrolobenzodiazepine, HuMax®-TAC, anti-CD25 human monoclonal antibody.

## OBJECTIVES

### Primary objectives

- Part 1: Evaluate the safety and tolerability, and define a maximum tolerated dose (MTD) of Cami-T to recommend for part 2.
- Part 2: Evaluate the safety and tolerability of Cami-T at the dose level recommended in part 1.

### Secondary objectives

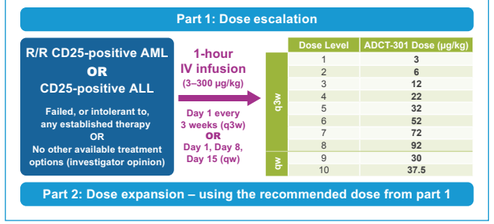
- Evaluate the clinical activity of Cami-T as measured by overall response rate, duration of response, progression-free survival, and overall survival.
- Characterize the pharmacokinetic (PK) profile of Cami-T.
- Evaluate anti-drug antibodies in blood before, during, and after Cami-T treatment.

## METHODS

### Study design

- Phase 1, open-label, multicenter dose-escalation (part 1) and dose-expansion (part 2) study in patients with R/R CD25+ AML or ALL.
- Patients receive Cami-T as an intravenous (IV) infusion with a starting dose cohort at 3 µg/kg every 3 weeks (q3w) (**Figure 2**).

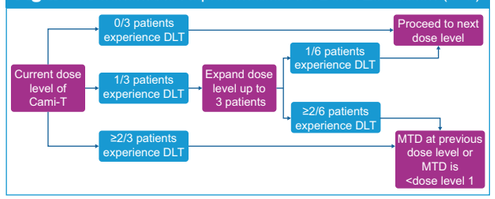
**Figure 2.** Phase 1 Study Design




ADCT-301, camidanlumab tesirine; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; IV, intravenous; q3w, every 3 weeks; qw, once weekly; R/R, relapsed or refractory.

- In part 1, patients are assigned to treatment using a 3+3 dose-escalation design (**Figure 3**), based on assessment of dose-limiting toxicities (DLTs) during Cycle 1, to determine the MTD.
  - Dose frequency in subsequent cohorts may increase to once weekly (qw) based on emerging safety, efficacy, and PK profile.

**Figure 3.** Schematic Representation for Dose Escalation (3+3)




Cami-T, camidanlumab tesirine; DLT, dose-limiting toxicity, MTD, maximum tolerated dose.

- Part 2 will further evaluate safety, tolerability, PK, and clinical activity at the dose recommended from part 1.
- Key inclusion and exclusion criteria are presented in **Table 1**.

**Table 1.** Key Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Age 18 years or older<br>• Pathologically confirmed relapsed or refractory CD25-positive[a] AML or ALL<br>• Eastern Cooperative Oncology Group performance status 0 to 2<br>• WBC count <15,000 cells/µL prior to Cycle 1, Day 1. Patients with WBC ≥15,000 cells/µL could receive hydroxyurea to lower WBC count. | • Active graft-versus-host disease<br>• Known active central nervous system leukemia<br>• Known history of positive serum human anti-drug antibody, or known allergy to any component of Cami-T<br>• Active autoimmune disease<br>• Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment<br>• Autologous or allogenic transplant within the 60 days prior to screening |

[a]CD25-positive AML or ALL is defined as CD25 expression on ≥5% of leukemic cells within bone marrow aspirate or biopsy.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Cami-T, camidanlumab tesirine; WBC, white blood cell.

## RESULTS

### Patient characteristics

- As of October 31, 2017, 33 patients have been treated with Cami-T.
- Baseline characteristics and demographic data of enrolled patients are shown in **Table 2**.
  - Baseline CD25 expression was present in 5% to 100% of local blast cells.

**Table 2.** Patient Demographics and Baseline Characteristics

| Patient Characteristic | Total (N=33) |
|---|---|
| Gender, n (%) | |
| Female | 10 (30.3) |
| Male | 23 (69.7) |
| Age, years | |
| Mean (SD) | 64.6 (14.6) |
| Median (min, max) | 67.0 (22, 82) |
| Race, n (%) | |
| White | 31 (93.9) |
| Black or African American | 0 |
| Asian | 1 (3.0) |
| Missing | 1 (3.0) |
| Diagnosis, n | |
| AML | 32 |
| ALL | 1 |
| Number of previous chemotherapies | |
| Mean (SD) | 3.1 (2.1) |
| Median (Min, Max) | 3.0 (1.0, 9.0) |
| Stem cell transplantation, n (%) | |
| Yes | 6 (18.2) |
| No | 27 (81.8) |
| Total number of cycles dosed | |
| Mean (SD) | 2.0 (1.2) |
| Median (min, max) | 2.0 (1.0, 7.0) |

[a]n=32.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; SD, standard deviation.

### Cami-T safety

- No DLTs were observed up to the highest evaluated q3w dose of 92 µg/kg.
- Upon switching to weekly dosing, one DLT (maculopapular rash) was reported in the 30 µg/kg dose group.
- During exposure, a total of 391 treatment-emergent adverse events (TEAEs) were reported in 31/33 (94%) patients.
  - Most common TEAEs were fatigue (n=10) and nausea (n=8) followed by febrile neutropenia and pneumonia (both n=7).

**Table 3.** Summary of Grade ≥3 Treatment-Emergent Adverse Events (TEAEs)

| | Dose Escalation | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | q3w | | | | | | | | qw | | |
| | 3 µg/kg N=4 | 6 µg/kg N=3 | 12 µg/kg N=3 | 22 µg/kg N=3 | 32 µg/kg N=3 | 52 µg/kg N=3 | 72 µg/kg N=3 | 92 µg/kg N=4 | 30 µg/kg N=6 | 37.5 µg/kg N=1 | Total N=33 (%) |
| Any TEAE for Grade ≥3 | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 6 | 0 | 27 (81.8) |
| Febrile neutropenia | 0 | 0 | 2 | 0 | 1 | 0 | 1 | 0 | 3 | 0 | 7 (21.2) |
| Thrombocytopenia | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 5 (15.2) |
| Fatigue | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 4 (12.1) |
| Neutrophil count decreased | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 4 (12.1) |
| Pneumonia | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 4 (12.1) |

- A summary of Grade ≥3 TEAEs that occurred in ≥10% patients are presented in **Table 3**.
  - Grade ≥3 TEAEs were reported by 27/33 (81.8%) patients
  - Eight deaths from TEAEs were recorded (disease progression and AML [both n=3], and cardiac arrest and pneumonia [both n=1])
  - One case each of increased QTc and palpitations was evaluated to be infusion-related by the investigator
  - Four patients experienced TEAEs leading to a dose delay or reduction (2 cases of skin rash, 1 case each of pericarditis and supraventricular tachycardia)
  - Three patients discontinued treatment due to Grade 2 and 3 skin rash (1 and 2 cases, respectively) and 1 patient due to Grade 3 gamma-glutamyltransferase increase.
- In 6 patients who underwent prior allogeneic stem cell transplantation, no cases of graft-versus-host disease were observed.
- In a separate study of Cami-T in patients with Hodgkin lymphoma, there have been 2 reports of Guillain-Barré syndrome and 1 report of polyradiculopathy.
  - To date, no such cases have been observed in patients with leukemia treated with Cami-T.

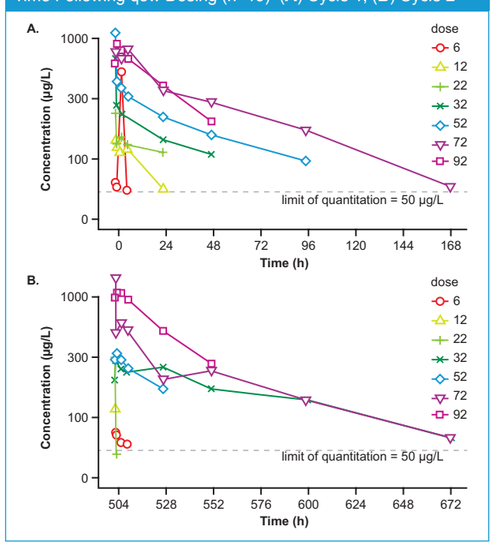
### Cami-T efficacy

- One patient had complete response with incomplete blood count recovery.
- Transient CD25+ blast clearance in 2 patients who received 2 and 7 cycles, respectively, of Cami-T 32 µg/kg q3w, was observed, supporting on-target activity of Cami-T.
  - One patient had 6.25% CD25+ blasts in the marrow prior to Cycle 1, which was reduced to 0% after 2 cycles of Cami-T, despite overall disease progression
  - A second patient had 10% CD25+ blasts in the marrow prior to Cycle 1, which was reduced to 0% after 2 cycles, with a total marrow blast count of 5%. CD25+ blasts remained at 0% until after cycle 7 when the patient had disease progression with CD25+ blasts.

### PK data

- PK data show increasing concentrations of PBD-conjugated antibody with dose (**Figure 4**).
- No drug accumulation is apparent with a q3w regimen.
- Rapid systemic clearance of the drug with levels below limit of quantitation suggests that q3w dosing may be insufficient for therapeutic efficacy.

**Figure 4.** Cami-T PBD-Conjugated Antibody Exposure *versus* Time Following q3w Dosing (n=19) (**A**) Cycle 1; (**B**) Cycle 2




## CONCLUSIONS

- In this ongoing Phase 1 study in patients with CD25+ R/R AML or ALL, single-agent Cami-T has shown an acceptable safety profile thus far.
- The study is continuing to explore the safety profile of weekly dosing.

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### Disclosures

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- **D Ungar, S He, J Boni** – employees of ADC Therapeutics with stock option interests.