A phase 1, open-label, dose-escalation, multicenter study to evaluate the tolerability, safety, pharmacokinetics, and activity of ADCT-301 in patients with relapsed or refractory CD25-positive acute myeloid leukemia (AML) and CD25-positive acute lymphoblastic leukemia (ALL) participating patients and their families

CD25+ acute myeloid leukemia (AML)

CD25+ acute lymphoblastic leukemia (ALL)

Expression of CD25 (IL-2r-a) is mainly limited to activated T- and B-cells and is not expressed on hematopoietic stem cells. CD25+ human leukemic stem cells that are chemotherapy-resistant may be important in development of relapsed or refractory AML.1,2

CD25 expression has been demonstrated in newly diagnosed and relapsed AML,3 and confers a poor prognosis for patients with ALL.4

The ADCT-301 ADC is a humanized anti-CD25 antibody (HuMax-TAC) conjugated to a pyrrolobenzodiazepine (PBD) ‘warhead’ dimmer, via a cleavable linker, allowing targeted delivery of PBD to CD25+ T- and B-cells (Figure 1).5

ADCT-301 has demonstrated complete response (CR) in mouse xenograft models, suggesting this may be a novel and efficacious method to specifically deliver anticancer agents to tumour cells.6

This is the first clinical study of ADCT-301 (ADCT-301-002; NCT02588092) that aims to determine the safety and tolerability of ADCT-301, used as monotherapy, in patients with AML or ALL.

CD25 = human cluster of differentiation 25

Background and Rationale

ADCT-301 is an antibody–drug conjugate (ADC) under investigation for:

- CD25+ acute myeloid leukemia (AML)
- CD25+ acute lymphoblastic leukemia (ALL)

Secondary objectives

- Clinical activity of ADCT-301
  - CR, CRi, PR, progressive disease, NR
- Determination of optimal dose of ADCT-301 for Part 2

Study Design and Objectives

Study design

- Phase 1, open-label, dose escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of ADCT-301 monotherapy, in patients with relapsed or refractory CD25+ AML (NCT02588092).
- Part 1: Dose escalation
  - 3 µg/kg to 33 µg/kg on Day 1 every 3 weeks*

Primary objectives

- Part 1 (dose escalation):
  - safety, tolerability, and determination of the MTD
- Part 2 (expansion):
  - safety and tolerability at the dose level recommended in Part 1

Secondary objectives

- Clinical activity of ADCT-301
  - CR, CRi, PR, progressive disease, NR
- Determination of optimal dose of ADCT-301 for Part 2

Exploratory objectives

- Obtain preliminary data on correlation between clinical activity and PK profile of ADCT-301:
  - baseline expression of CD25 on blast cells from whole blood and bone marrow
  - DNA cross-links in blood using Comet assay
- Obtain preliminary data on influence of ADCT-301 and free ‘warhead’ concentration on corrected QT interval (QTc).

Study duration is dependent on patient tolerability to study drug and response to treatment.

The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Duke University Medical Center, Durham, NC, USA; University of Wisconsin Cancer Center, Madison, WI, USA; Emory University Winship Cancer Institute, Atlanta, GA, USA; Northside Hospital, Atlanta, GA, USA; ADCTherapeutics, Fort Lauderdale, FL, USA; Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Figure 1. Schematic of the unique PBD-based ADC’s mode of action

Following the binding of the PBD-based ADC to the target antigen on the cancer cell and its internalization, the PBD dimers are released in the lysosomes. From here the PBD molecule can diffuse into the nucleus where they sequence-selectively bind to the minor groove of DNA, blocking cancer cell division and killing the cell directly.

Statistical Considerations

Study size

- Phase 1 study with maximum sample size of 60 patients.
  - Part 1: ≤ 30 patients from 10 study sites
  - Part 2: ≤ 30 patients from 10 study sites (in cohorts of 10, with the first cohort enrolled at the dose level recommended in Part 1).

- Based on a true AE rate of 15%, there is 80% confidence that ≥ 1 AE will be observed for the 10 patients.
- A DESC will recommend enrollment of additional cohorts for different subtypes or dose levels based on review of safety and efficacy data from previous cohorts.

Analysis populations

- Safety analysis set
  - All patients who receive the study drug.
- Dose-limiting toxicity (DLT)-evaluable analysis set
  - All patients in Part 1 who receive study drug, excluding patients who discontinue drug during Cycle 1 without experiencing a DLT.
- Efficacy analysis set
  - All patients with valid baseline data who receive ≥ 2 doses of study drug.
- PK, PD, and exploratory analysis sets
  - All patients who receive the study drug and have sufficient concentration data.

Current Enrollment

- The first patient was dosed in February 2016.
- Enrollment has been completed at Dose Level 1 (3 µg/kg) with no DLTs observed.
- Patient accrual is ongoing.

Acknowledgements

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- participating patients and their families
- study co-investigators and research coordinators.
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Table 2. Key exclusion criteria

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<th>Key exclusion criteria</th>
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<tr>
<td>Known active or symptomatic central nervous system leukemia within 28 days prior to screening</td>
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<td>Active graft-versus-host disease</td>
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<td>Autologous or allogeneic transplant within the 60 days prior to the screening visit</td>
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<td>Known history of immunogenicity or hypersensitivity to a CD25 antibody</td>
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<tr>
<td>Known history of positive serum human ADA, or known allergy to any component of ADCT-301</td>
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<tr>
<td>Active autoimmune disease</td>
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<tr>
<td>Known seropositivity for human immunodeficiency virus, hepatitis B surface antigen or antibody to hepatitis C virus</td>
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<tr>
<td>History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome</td>
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<td>Presence of significant medical comorbidities (e.g., uncontrolled hypertension, unstable angina, congestive heart failure)</td>
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<td>Concurrent treatment with other experimental drugs (within 14 days or ≤ 5 half-lives but in no case ≤ 14 days prior to start of the study treatment)</td>
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<td>Active secondary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast</td>
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Table 1. Key eligibility criteria

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<tr>
<td>≥ 18 years of age</td>
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<td>Relapsed or refractory CD25+ AML patients who have failed, or are intolerant to, any established therapy</td>
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<td>Myelodysplastic syndrome patients who have received treatment with hypomethylating agents and who failed, or are ineligible for standard induction therapy</td>
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<tr>
<td>Relapsed or refractory CD25+ ALL patients who have failed, or are intolerant to, any established therapy</td>
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<td>ECOG PS ≤ 2</td>
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<td>Serum creatinine ≤ 1.5 mg/dL, or if the patient has a serum creatinine &gt; 1.5 mg/dL, creatinine clearance must be ≥ 50 mL/min/1.73 m²</td>
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<td>Serum alanine aminotransferase (ALT) ≤ 2 times the upper limit of normal (ULN), or ≤ 5 times ULN if liver or bone involvement</td>
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References