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 and CD25-positive acute lymphoblastic leukemia

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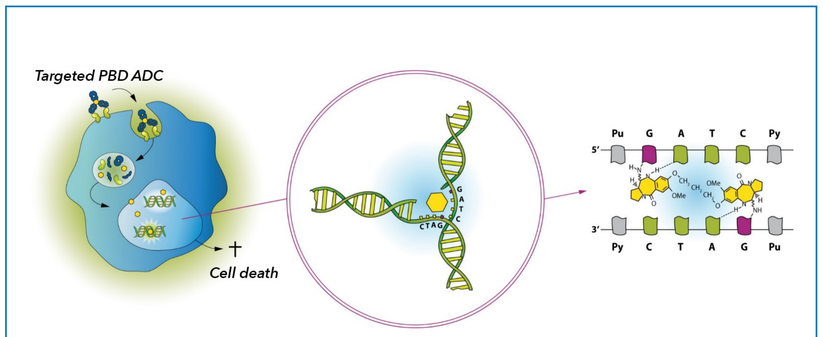
Background and Rationale

- ADCT-301 is an antibody–drug conjugate (ADC) under investigation for:
  - CD25+ acute myeloid leukemia (AML)
  - CD25+ acute lymphoblastic leukemia (ALL)
- Expression of CD25 (IL-2R-α) 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,[2-4] and confers a poor prognosis for patients with ALL.[5]
- The ADCT-301 ADC is a humanized anti-CD25 antibody (HuMax®-TAC) conjugated to a pyrrolobenzodiazepine (PBD) 'warhead' dimer, via a cleavable linker, allowing targeted delivery of PBD to CD25+ B- and T-cells (Figure 1).
- ADCT-301 has demonstrated complete responses (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

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 molecules 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.

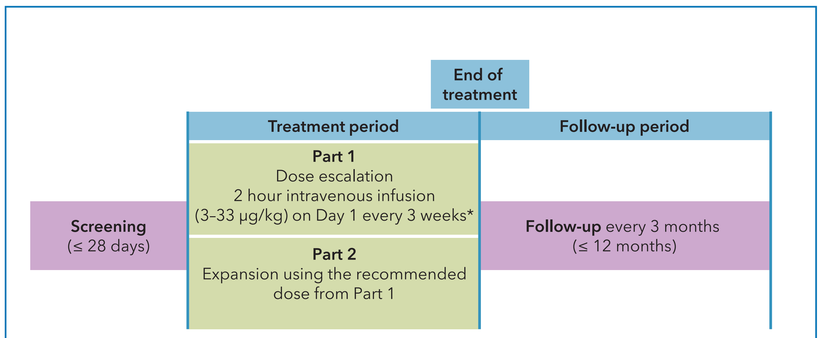
Study Design and Objectives

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).
  - Study was amended in February 2016 to include patients with CD25+ ALL
- The study will determine the maximum tolerated dose (MTD) and evaluate preliminary activity, pharmacokinetics (PK), and pharmacodynamics (PD).
- Number of dose levels decided by the Dose Escalation Screening Committee (DESC).
- If maximum allowed dose (33 µg/kg) is reached without MTD identified, no further dose escalation is permitted pending safety analysis.
- Key eligibility and exclusion criteria are shown in Tables 1 and 2, respectively.
- Trial will be continuously monitored for safety.*
- Commonly reported AEs associated with anti-CD25 monoclonal antibodies are gastrointestinal disorders, including abdominal pain, constipation, diarrhea, nausea, and vomiting.
- Patients treated until disease progression, unacceptable toxicity, or consent withdrawal.
- Study duration is dependent on patient tolerability to study drug and response to treatment.

* Adverse events (AEs), serious adverse events , treatment-emergent adverse events , periodic 12-lead ECG recordings, physical examinations, vital signs measurements, Eastern Cooperative Oncology Group performance status (ECOG PS) and hematological and biochemical tests will be performed. These events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, v4.03).

Figure 2. ADCT-301 trial design



*Dose escalation conducted according to a Fibonacci 3+3 design. A bone marrow aspirate (or biopsy if aspirate unattainable) obtained at each cycle, beginning with Cycle 2, and repeated at each subsequent cycle, until disease progression, CR, or complete response with incomplete blood count recovery (CRi) is achieved. Once CR/CRi is achieved, sampling will be repeated every 2 to 3 cycles or as clinically indicated. Activity of ADCT-301 will be evaluated based on the investigator's response evaluation as CR, CRi, partial response (PR), progressive disease or no response (NR).[7,8]

Primary objectives

- Part 1 (dose escalation):
  - safety, tolerability, and determination of the MTD
  - determination of the recommended dose of ADCT-301 for Part 2.
- 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 duration of response, overall response rate, overall survival, and progression-free survival.
- Characterize PK profile of ADCT-301
  - total antibody, drug-to-antibody ratio [DAR] ≥ 0, PBD-conjugated antibody (DAR ≥ 1), and free 'warhead'
  - evaluate anti-drug antibodies (ADAs) to ADCT-301.

Exploratory objectives

- Obtain preliminary data on correlation between clinical activity and PK profile of ADCT-301:
  - baseline expression of CD25 in blast cells from whole blood and bone marrow
  - DNA cross-links in blood using Comet assay.
- Obtain preliminary data on influence of ADAs (to ADCT-301) and soluble CD25 on clinical activity and PK profile.
- Explore influence of ADCT-301 and free 'warhead' concentration on corrected QT interval (QTc).
- Determine baseline expression of other cell surface antigens/biomarkers (e.g., CD34) on blast cells within whole blood and bone marrow and explore correlation with CD25 expression.
- Explore correlation of FMS-like tyrosine kinase 3 (FLT3) related mutations, specifically FLT3 internal tandem duplications (FLT3-ITD) with CD25 expression.
- Evaluate change in peripheral blood white blood cell (WBC) populations before, during, and after treatment with ADCT-301 (Part 2 only).

Table 1. Key eligibility criteria

Key eligibility criteria
≥ 18 years of age
Relapsed or refractory CD25-positive* AML† patients who have failed, or are intolerant to, any established therapy
Myelodysplastic syndrome patients who have received treatment with hypomethylating agents and who failed, or are ineligible for standard induction therapy
Relapsed or refractory CD25-positive* ALL† patients who have failed, or are intolerant to, any established therapy
ECOG PS ≤ 2
Serum creatinine ≤ 1.5 mg/dL or if the patient has a serum creatinine > 1.5 mg/dL, creatinine clearance must be > 60 mL/min/1.73 m^2
Serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2 times the upper limit of normal (ULN); ≤ 5 times ULN if liver or bone involvement
Total serum bilirubin ≤ 1.5 times the ULN. Patients with known Gilbert's syndrome may have a total bilirubin up to ≤ 3 times ULN

*CD25-positive AML is defined as the expression of CD25 by ≥5% of blast cells within the bone marrow (aspirate or biopsy), assessed at an approved clinical laboratory. †Diagnosis and classification as per World Health Organization (WHO) classification of acute leukemias[9]

Table 2. Key exclusion criteria

Key exclusion criteria
Known active or symptomatic central nervous system leukemia within 28 days prior to screening
Active graft-versus-host disease
Autologous or allogenic transplant within the 60 days prior to the screening visit
Known history of immunogenicity or hypersensitivity to a CD25 antibody
Known history of positive serum human ADA, or known allergy to any component of ADCT-301.
Active autoimmune disease
Known seropositivity for human immunodeficiency virus, hepatitis B surface antigen or antibody to hepatitis C virus
History of Stevens–Johnson syndrome or toxic epidermal necrolysis syndrome
Presence of significant medical comorbidities (e.g., uncontrolled hypertension, unstable angina, congestive heart failure)
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 on Cycle 1, Day 1)
Major surgery, chemotherapy, systemic therapy (excluding hydroxyurea and steroids), radiotherapy, or biotherapy targeted therapies within 21 days prior to the Day 1 visit
Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast

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.

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References

1. Ding L, *et al. Nature* 2012;481:506–510.
2. Cerny J, *et al. Br J Haematol* 2013;160:262–266.
3. Gönen M, *et al. Blood* 2012;120:2297–2306.
4. Terwijn M, *et al. Eur J Cancer* 2009;45:1692–1699.
5. Nakase K, *et al. Leukemia* 2007;21:326–332.
6. Flynn MJ, *et al. Poster presented at 57th ASH Annual Meeting and Exposition. Orlando (USA).* 2015 [Poster 1559].
7. Cheson BD, *et al. Clin Oncol* 2003;21:4642–4649.
8. Döhner H, *et al. Blood* 2010;115:453–474.
9. Vardiman J, *et al. Blood* 2009;114:937–951.