A phase 1 dose-escalation study to evaluate the tolerability, safety, pharmacokinetics, and antitumor activity of ADCT-402 in patients with relapsed or refractory B-cell lineage non-Hodgkin lymphoma (B-NHL)

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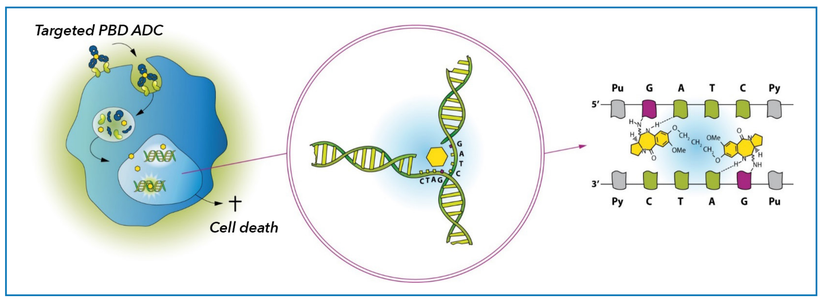
Background and Rationale

- Human cluster of differentiation 19 (CD19) expression is typically restricted to the early development of B-cells.[1] However, CD19 expression is maintained in malignant B-cells,[2] making it a promising target for B-NHL treatment.
- The ADCT-402 antibody–drug conjugate (ADC) is a humanized anti-CD19 antibody conjugated to a pyrrolobenzodiazepine (PBD) 'warhead' dimer, via a cleavable linker, allowing targeted delivery of PBD to CD19+ B-cells (Figure 1).
- ADCT-402 has demonstrated complete responses (CR) in several mouse xenograft models of B-NHL,[3] suggesting this may be a novel and efficacious method to specifically deliver anticancer agents to malignant B-NHL cells.
- This is the first clinical study of ADCT-402 (ADCT-402-101; NCT02669017) that has been designed to determine the safety, tolerability, pharmacokinetics, and antitumor activity of ADCT-402 as monotherapy in patients with B-NHL.

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



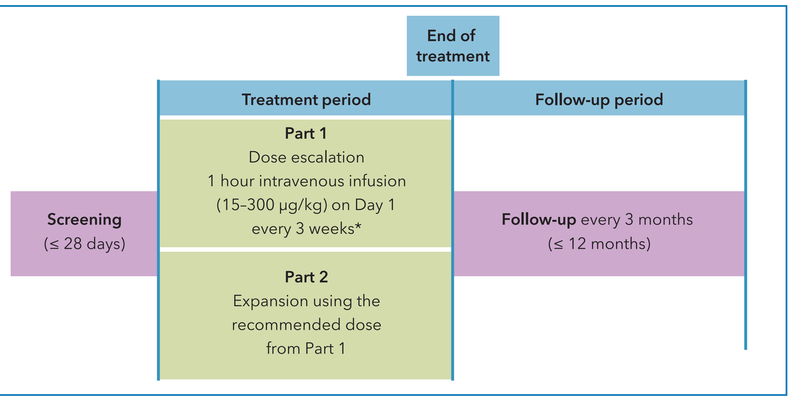
Following the binding of the PBD-based ADC to the target antigen on the cancer cell and its internalization, the PBD dimers are released in the lysosomes. From here, the PBD molecules can diffuse into the nucleus where they sequence-selectively bind to the minor groove of DNA, blocking cancer cell division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

Study Design and Objectives

- Phase 1, open-label, dose escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of ADCT-402 monotherapy, in patients with relapsed or refractory B-cell NHL (NCT02669017, Figure 2).
- The study will determine the maximum tolerated dose (MTD), preliminary clinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and other exploratory assessments of ADCT-402.
- Number of dose levels is decided by Dose Escalation Screening Committee (DESC). Potential dose levels are described in Table 1.
- If the maximum allowed dose is reached without MTD identified; no further dose escalation allowed pending safety analysis.
- Key eligibility and exclusion criteria are shown in Tables 2 and 3, respectively.
- Trial is continuously monitored for safety.*
- 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, and 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-402 trial design



*Dose escalation will be conducted according to a Fibonacci 3+3 design. Disease assessments every other cycle for first 2 evaluations (6 weeks [end of Cycle 2 ± 1 week] and 12 weeks [end of Cycle 4 ± 1 week]), and every third cycle (every 9 weeks [e.g., end of Cycles 7, 10, 13, etc., ± 1 week]) thereafter until progression, or as clinically indicated. Response to treatment determined according to 2014 Lugano Classification Criteria.

Table 1. ADCT-402 planned dose levels

Dose level	Dose of ADCT-402, µg/kg
1	15
2	30
3	60
4	90
5	120
6	150
7	200
8	250
9	300

Primary objectives

- Part 1 (dose escalation):
  - safety, tolerability, and determination of the MTD
  - determination of the recommended dose of ADCT-402 for Part 2.
- Part 2 (expansion):
  - safety and tolerability at the dose level recommended in Part 1.

Secondary objectives

- Clinical activity of ADCT-402 (overall response rate, duration of response, overall survival, and progression-free survival).
- PK profile of ADCT-402 (total antibody; drug-to-antibody ratio [DAR] ≥ 0), PBD-conjugated antibody (DAR ≥ 1), and free 'warhead'.
- Evaluate anti-drug antibodies (ADAs) to ADCT-402.

Exploratory objectives

- Obtain preliminary data on correlation between the clinical activity and PK profile of ADCT-402:
  - baseline expression level of CD19 in tumor tissue
  - DNA cross-links in blood using the Comet assay.
- Evaluate the dynamic change in peripheral blood white blood cell (WBC) populations and expression of CD markers (e.g., CD19, CD20, CD21, CD22) before, during, and after treatment with ADCT-402 (Cycles 1 and 2).
- Obtain preliminary data on influence of ADAs (to ADCT-402) on the clinical activity and PK profile of ADCT-402.
- Explore the influence of ADCT-402 and free 'warhead' concentrations on the corrected QT (QTc) interval.

Table 2. Key eligibility criteria

Key eligibility criteria
≥ 18 years of age
Refractory or relapsed B-cell NHL (per WHO Classification system)[4]
Availability of formalin-fixed paraffin-embedded tumor tissue block
Measurable disease, as defined by the 2014 Lugano Classification
ECOG PS ≤ 2
Absolute neutrophil count (ANC) ≥ 1000/µL, platelet count of ≥ 75000/µL, hemoglobin ≥ 9.0 g/dL (without transfusion within the 2 weeks prior to Day 1), serum creatinine ≤ 1.5 mg/dL
Serum alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase ≤ 2 times the upper limit of normal (ULN); ≤ 5 times ULN if there is liver or bone involvement
Total serum bilirubin ≤ 1.5 times ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤ 3 times ULN)

Table 3. Key exclusion criteria

Key exclusion criteria
Evidence of active graft-versus-host disease
Autologous or allogenic transplant within the 60 days prior to the screening visit
History of immunogenicity or hypersensitivity to a CD19 antibody
Evidence of myelodysplasia or myeloid leukemia
Known history of positive serum human ADA
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., hypertension, unstable angina, congestive heart failure)
Concurrent treatment with other experimental drugs (within 14 days or 5 half-lives prior to start of study treatment on Cycle 1, Day 1)
Steroid use ≥ 20 mg of prednisone within 4 weeks prior to Day 1
Major surgery, chemotherapy, systemic therapy (excluding steroids), radiotherapy, or biotherapy targeted therapies within 21 days prior to Cycle 1, Day 1 treatment
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 I study with a maximum total sample size of 60 patients.
  - Part 1: ≤ 30 patients at 8 sites
  - Part 2: ≤ 30 patients at 12 sites (in cohorts of 10).
- 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 disease 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 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 March 2016.
- Enrollment has been completed at Dose Level 1 (15 µg/kg) with no DLTs observed.
- Patient accrual is ongoing.

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References

1. Haas KM and Tedder TF. *Adv Exp Med Biol* 2005;560:125–139.
2. Wang K, *et al. Exp Hematol Oncol* 2012;1:36.
3. Zammarchi F, *et al. Poster presented at 57th ASH Annual Meeting and Exposition. Orlando (USA).* 2015 [Poster 1564].
4. Swerdlow SH, *et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* 2008; 4th ed., Lyon, France.