# Interim Data from the First Clinical Study of ADCT-301, a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory Hodgkin/Non-Hodgkin Lymphoma

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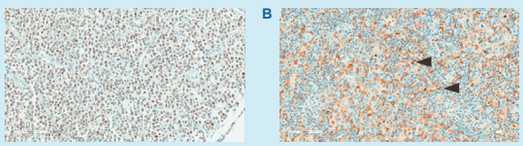
## BACKGROUND

- Expression of CD25 (IL-2R-α) occurs in many lymphomas, including Hodgkin lymphoma (HL), peripheral T-cell lymphoma, cutaneous T-cell lymphoma, and diffuse large B-cell lymphoma (DLBCL).[1]

**Figure 1.** CD25 immunohistochemical staining of tissue microarrays of lymph node tissue from a patient with **A.** DLBCL and **B.** Classical HL. Black arrows indicate Reed-Sternberg cells.




- ADCT-301 is an antibody drug conjugate (ADC) comprising a human monoclonal antibody against CD25, stochastically conjugated via a cathepsin-cleavable valine-alanine linker to a potent pyrrolobenzodiazepine (PBD) dimer toxin.

**Figure 2.** IL-2R complex that includes CD25 (left). ADCT-301 structure (right).

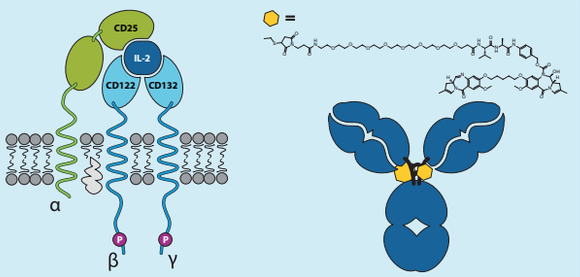
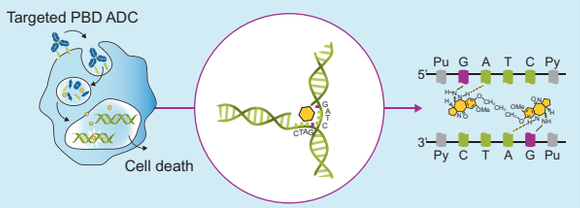



**Figure 3.** Targeted PBD delivery to CD25+ B- and T-cells.




The PBD-based ADC binds to the CD25 antigen on the tumor cell, becomes internalized, and the PBD dimers are released in the lysosomes. The PBD molecules then diffuse into the nucleus, where they sequence-selectively bind to the DNA minor groove forming interstrand cross-links, which block tumor cell division and directly kill the cell.

- ADCT-301 has demonstrated potent anti-tumor activity against CD25-expressing hematological malignancies in mouse xenograft models.[2]
- This first in-human clinical trial of ADCT-301 is currently enrolling patients (pts) with relapsed HL and Non-Hodgkin lymphoma (NHL).
- Interim data from the latest data cut are reported here.

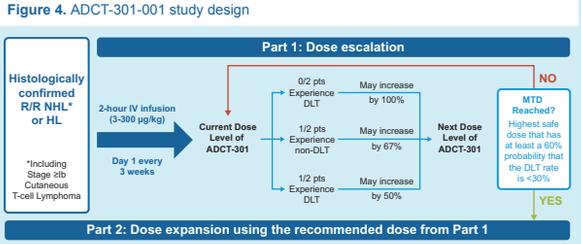
## STUDY OBJECTIVES

- This phase I, open-label, dose-escalation (Part 1) and dose-expansion (Part 2) study will:
  - Assess the safety and tolerability of ADCT-301 monotherapy in pts with relapsed/refractory HL or NHL and define a maximum tolerated dose (MTD) of ADCT-301 to recommend for Part 2 (Part 1)
  - Evaluate the safety and tolerability of ADCT-301 at this recommended dose (Part 2).
- Efficacy, pharmacokinetics, pharmacodynamics, and anti-drug antibody activity are also being assessed.

## STUDY DESIGN

- Patients with relapsed/refractory HL/NHL are receiving IV infusions of ADCT-301 every 3 weeks (1 cycle).
- The initial dose cohort was 3 µg/kg and subsequent cohorts are being enrolled at escalating doses according to a continual reassessment method (**Figure 4**).
- No intra-patient dose escalation is allowed.

**Figure 4.** ADCT-301-001 study design




### Key Inclusion Criteria

- Age 18 years or older
- Pathologically confirmed relapsed or refractory lymphoma
- Failed, or intolerant to, any established therapy known to provide clinical benefit at current state of disease
- Measurable disease, defined by the 2014 Lugano Classification Criteria
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Absolute neutrophil count ≥1500/µL
- Platelet count of ≥75,000/µL
- Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1
- Creatinine ≤1.5 mg/dL
- Alkaline phosphatase, alanine, and aspartate aminotransferase ≤2 times the upper limit of normal or ≤5 times ULN if liver or bone involvement
- Total serum bilirubin ≤1.5 times ULN.

### Key Exclusion Criteria

- Active graft-versus-host disease
- Evidence of myelodysplasia or myeloid leukemia
- Known history of positive serum human anti-drug antibody, or known allergy to any component of ADCT-301
- History of symptomatic autoimmune disease
- Known seropositive for human immunodeficiency (HIV) virus, hepatitis B surface antigen (HbsAg), or antibody to hepatitis C virus (anti-HCV)
- Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment
- Congenital long QT syndrome or a corrected QTc interval ≥470 ms at screening
- Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, or ductal or lobular carcinoma in situ of the breast.

## RESULTS

### Patient Characteristics

- As of May 3, 2017, 37 pts have been treated with ADCT-301 doses ranging from 3 to 80 µg/kg.
- The median number of previous therapies in these pts was 4 (range 1–14).

**Table 1.** ADCT-301-001 patient baseline characteristics

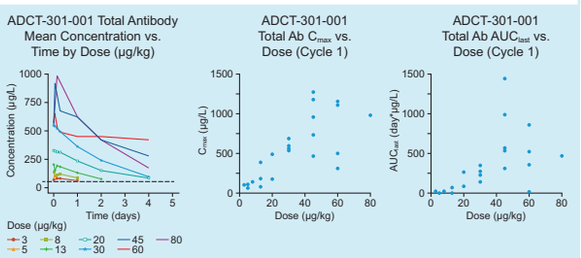
| Patient Characteristic | Total (N=41) |
|---|---|
| **Pts enrolled (n)** | |
| Pts treated, safety analysis set (n[%]) | 37 (90.2) |
| DLT-evaluable analysis set (n[%]) | 25 (61.0) |
| Efficacy analysis set (n[%]) | 25 (61.0) |
| **Race (n[%])*** | |
| White | 27 (73.0) |
| Black or African American | 4 (10.8) |
| Asian | 1 (2.7) |
| American Indian or Alaskan | 0 |
| Native Hawaiian or Pacific | 0 |
| Other | 5 (13.5) |
| **Ethnicity (n[%])*** | |
| Hispanic or Latino | 3 (8.1) |
| Non-Hispanic or Latino | 34 (91.9) |
| **Sex*** | |
| Female | 11 (29.7) |
| Male | 26 (70.3) |
| **Age (years)** | |
| n | 37 |
| Mean | 47.1 |
| SD | 17.41 |
| Median | 46.0 |
| Min, Max | 19, 79 |
| **Body Mass Index (kg/m²)** | |
| n | 36 |
| Mean | 27.69 |
| SD | 8.882 |
| Median | 25.79 |
| Min, Max | 18.3, 64.2 |
| **Diagnosis*** | |
| Hodgkin lymphoma | 23 (62.2) |
| Cutaneous T-cell lymphoma | 4 (10.8) |
| Diffuse Large B-cell lymphoma | 3 (8.1) |
| Mantle cell lymphoma | 3 (8.1) |
| Peripheral T-cell lymphoma | 1 (2.7) |
| Other | 3 (8.1) |

*Safety analysis set

### ADCT-301 Exposure and Pharmacokinetics

- The median number of ADCT-301 cycles received to date is 2 (range 1–14).
- The median duration of treatment is 43 days (range 9–298 days).
- The ADCT-301 PK exposure increased with dose.
- Accumulation was not apparent with multiple doses.
- ADCT-301 was below quantifiable limits before the end of the 3-week cycle.
- As expected, variability increased at ADCT-301 exposure.
- ADCT-301's PBD-antibody conjugate PK profile (not shown) was generally comparable to its total antibody profile.

**Figure 5.** ADCT-301 total antibody pharmacokinetic (PK) profile




### ADCT-301 Safety Data

- 5 pts have reported DLTs:
  - 1 with maculopapular rash at 8 µg/kg
  - 1 with oral mucositis and small bowel enteritis at 20 µg/kg
  - 1 with elevated creatine phosphokinase at 30 µg/kg
  - 1 with maculopapular rash and pruritus at 30 µg/kg
  - 1 with lip ulceration and skin infection at 45 µg/kg.
- The most commonly reported treatment-emergent adverse events (TEAEs) were:
  - Fatigue (8 [21.6%] pts)
  - Rash (7 [18.9%] pts)
  - Anemia (6 [16.2%] pts)
  - Nausea (6 [16.2%] pts)
  - Maculopapular rash (6 [16.2%] pts).

**Table 2.** Grade ≥3 TEAEs by Preferred Term

| TEAEs (Grade ≥3) By Preferred Term | Dose (µg/kg) 3 (n=2) | 5 (n=2) | 8 (n=2) | 13 (n=3) | 20 (n=2) | 30 (n=5) | 45 (n=11) | 60 (n=5) | 80 (n=5) | Total (N=37) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Patients with any Grade ≥3 TEAE** | **1 (50.0)** | **1 (50.0)** | **1 (50.0)** | **2 (66.7)** | **1 (50.0)** | **4 (80.0)** | **4 (36.4)** | **1 (20.0)** | **1 (20.0)** | **16 (43.2)** |
| Anemia | | | | | 1 (50.0) | 1 (20.0)* | | | | 2 (5.4) |
| Neutropenia | 1 (50.0) | | | | | | 1 (9.1) | | | 2 (5.4) |
| Colitis | | | | | | | 1 (9.1) | | | 1 (2.7) |
| Cardiac Arrest | | 1 (50.0)* | | | | | | | | 1 (2.7) |
| Enteritis | | | | | 1 (50.0) | | | | | 1 (2.7) |
| Lip ulceration | | | | | | | 1 (9.1) | | | 1 (2.7) |
| Nausea | | | | | | | 1 (9.1)* | | | 1 (2.7) |
| Stomatitis | | | | | 1 (50.0) | | | | | 1 (2.7) |
| Vomiting | | | | | | | 1 (9.1)* | | | 1 (2.7) |
| Skin infection | | | | | | | 1 (9.1) | | | 1 (2.7) |
| Sepsis | | | | | | | 1 (9.1)* | | | 1 (2.7) |
| Blood alkaline phosphatase decreased | | | | | | | | | 1 (20.0)* | 1 (2.7) |
| Blood creatine phosphokinase increased | | | | | | 1 (20.0) | | | | 1 (2.7) |
| Gamma-glutamyltransferase increased | | | | | | 1 (20.0) | | | 1 (20.0)* | 2 (5.4) |
| Platelet count decreased | | | | | | | | 1 (20.0)* | | 1 (2.7) |
| Neutrophil count decreased | | | | | | | 1 (9.1)* | | | 1 (2.7) |
| Dehydration | | | | | | | 2 (18.2)* | | | 2 (5.4) |
| Hypercalcemia | | | | 1 (33.3)* | | | 1 (9.1)* | | | 2 (5.4) |
| Back pain | | | | 1 (33.3)* | | | 1 (9.1)* | | | 2 (5.4) |
| Acute kidney injury | | | | | | | 1 (9.1)* | | | 1 (2.7) |
| Pulmonary embolism | | | | 1 (33.3)* | | | | | | 1 (2.7) |
| Pruritus | | | | | | 1 (20.0) | 1 (9.1)* | | | 2 (5.4) |
| Maculopapular rash | | | 1 (50.0) | | | 1 (20.0) | | | | 2 (5.4) |

* Not considered to be ADCT-301-related

### ADCT-301 Efficacy Data

- All efficacy assessments to date have been investigator-determined.
- 5/13 HL pts (38.5%) at ≥30 µg/kg have had an overall response (i.e. a complete response [CR] or a partial response [PR]):
  - 2 classical HL (cHL) pts at 30 µg/kg have had a CR
  - 2 cHL pts at 45 µg/kg have had a CR and PR, respectively
  - 1 cHL pt at 60 µg/kg has had a PR.
- 8 pts (32.0%) have had stable disease as their best response:
  - 1 cHL pt at 13 µg/kg has remained progression-free for >42 weeks (>14 cycles).
- Stable disease or better has been reported in:
  - 9/11 pts (81.8%) who have received a checkpoint inhibitor
  - 11/16 pts (68.8%) who have received brentuximab
  - 7/11 pts (63.6%) who have received stem cell transplantation
  - 3/5 pts (60.0%) who have received all three types of the above listed treatment.

## CONCLUSIONS

- This dose escalation and expansion study will identify the MTD of ADCT-301 and provide a preliminary assessment of its single-agent anti-tumor activity and toxicity profile in R/R HL and NHL.
- Dose escalation (part 1) is continuing; the MTD has not yet been reached.
- To date, toxicities have been manageable and responses have been encouraging.
- Further initial safety, tolerability, and efficacy results are expected later this year.

### ACKNOWLEDGMENTS

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