Interim Data from a Phase 1 Study Evaluating Pyrrolobenzodiazepine-Based Antibody Drug Conjugate ADCT-402 (Loncastuximab Tesirine) Targeting CD19 for Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

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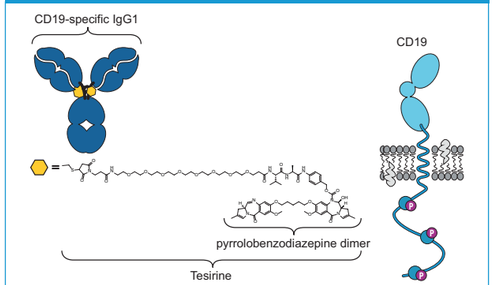
INTRODUCTION

- Outcomes of patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) remain dismal, with 5-year survival rates <20%.[1]
- CD19, which is normally expressed during B-cell development, is universally present in B-cell leukemias.[2]
- ADCT-402 (loncastuximab tesirine [Lonca-T]) is an antibody drug conjugate composed of a human CD19-targeting monoclonal antibody conjugated to tesirine, a pyrrolobenzodiazepine (PBD) dimer cytotoxin (**Figure 1**).

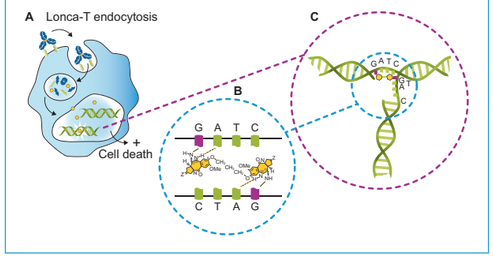
Figure 1. Structure of Lonca-T (left) and CD19 (right)



Lonca-T, loncastuximab tesirine.

- Lonca-T binds to the CD19 antigen on the tumor cell surface (**Figure 2**).
  - Once antibody-bound, CD19 is rapidly internalized by the cell,[3] the protease-sensitive linker is cleaved, and the PBD dimers are released inside the cell and migrate to the nucleus
  - PBD dimers covalently bind discrete sequences of base pairs in the minor groove of DNA and form DNA cross-links, resulting in a stalled DNA replication fork blocking cell division and causing cancer cell death.[4]

Figure 2. Targeted delivery of PBD. **(A)** The ADC is internalized and releases the PBD toxin into the lysosomes of the tumor cell; **(B)** the toxin cross-links DNA; and **(C)** DNA replication stalls, causing cell death



ADC, antibody drug conjugate; Lonca-T, loncastuximab tesirine; PBD, pyrrolobenzodiazepine.

- In preclinical studies, Lonca-T demonstrated potent anti-tumor activity in mouse models of B-cell malignancies.[5]
- Lonca-T has excellent stability in preclinical in vivo models.[5]
- Interim data from a Phase 1 study evaluating Lonca-T in patients with R/R B-ALL are presented.

OBJECTIVES

- Primary objective:
  - Assess the tolerability and safety of Lonca-T in patients with R/R B-ALL.
- Secondary objectives include:
  - Evaluation of clinical activity, characterization of the pharmacokinetic (PK) profile, and evaluation of anti-drug antibodies.

METHODS

- A Phase 1, open-label, dose-escalation (part 1) and dose-expansion (part 2), multicenter, US study is enrolling patients with R/R B-ALL (**Table 1**).

Table 1. Key inclusion and exclusion criteria for the study

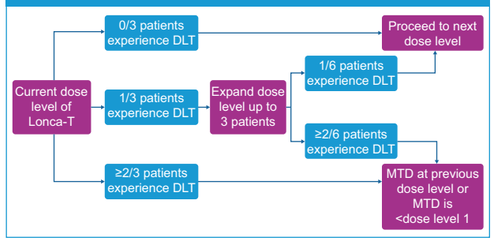
Key inclusion criteria	Key exclusion criteria
• Patients aged 12 years and older with R/R B-ALL who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available[a] • Eastern Cooperative Oncology Group performance status 0–2 • White blood cell count <15,000 cells/μL prior to Day 1	• Known active central nervous system leukemia[b] or Burkitt's leukemia/lymphoma • Autologous or allogenic transplant within 60 days prior to screening or active graft-versus-host disease • Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment • Active autoimmune disease

[a]In the opinion of the investigator. [b]Defined as morphological evidence of lymphoblasts in the cerebrospinal fluid.

R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia.

- In part 1, patients are assigned to treatment according to a 3+3 dose-escalation design (**Figure 3**) to determine the maximum tolerated dose (MTD).
  - The initial dose of Lonca-T was 15 μg/kg (dose level 1).

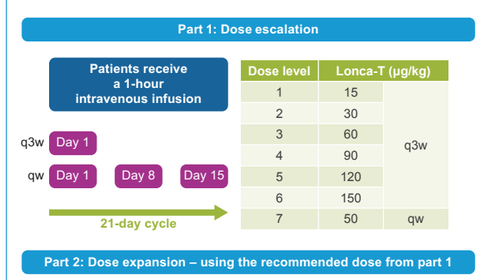
Figure 3. Schematic diagram of dose escalation



DLT, dose-limiting toxicity; Lonca-T, loncastuximab tesirine; MTD, maximum tolerated dose.

- Lonca-T is given intravenously on Day 1 of each 21-day cycle for patients treated every 3 weeks, and on Days 1, 8, and 15 for patients assigned to a weekly dosing regimen (**Figure 4**).
- Part 2 will further evaluate the safety, tolerability, PK, and clinical activity of Lonca-T at the dose recommended from part 1.
- Complete response is defined as achieving each of the following:
  - Bone marrow differential showing ≤5% blast cells
  - Absolute neutrophil count ≥1.0 x 10^9/L and platelet count ≥100 x 10^9/L
  - Absence of extramedullary disease
  - Patient is independent of red blood cell transfusions.

Figure 4. Study design



Lonca-T, loncastuximab tesirine; qw, once weekly; q3w, once every 3 weeks.

RESULTS

Patient characteristics

- As of October 30, 2017, 29 patients (18 male, 11 female) with B-ALL have been treated with Lonca-T (**Table 2**).
  - Patients had received a median (min, max) of 2 (1, 12) previous chemotherapies
  - Eleven (37.9%) patients had received prior allogeneic stem cell transplantation
  - No dose-limiting toxicities (DLTs) have been observed up to the highest evaluated dose of 150 μg/kg once every 3 weeks (q3w).
    - The most recently treated cohort received Lonca-T at a dose of 50 μg/kg once weekly.

Table 2. Patient baseline characteristics (safety analysis set)

Patient characteristic	Total (N=29)
Sex, n (%)	
Female	11 (37.9)
Male	18 (62.1)
Age, years	
Median (min, max)	50.0 (20, 80)
Race, n (%)	
White	24 (82.8)
Black or African American	0
Asian	1 (3.4)
Native Hawaiian or Pacific	1 (3.4)
Other	3 (10.3)
Number of previous chemotherapies	
Median (min, max)	2.0 (1.0, 12.0)
White blood cell count, mean (SD) (x10^9/L)	4.09 (4.25)
Platelet count, mean (SD) (x10^9/L)	45.69 (50.03)
Bone marrow blasts[a]	
≤5%	2 (6.9)
≥5 to ≤25%	5 (17.2)
≥50%	12 (41.4)

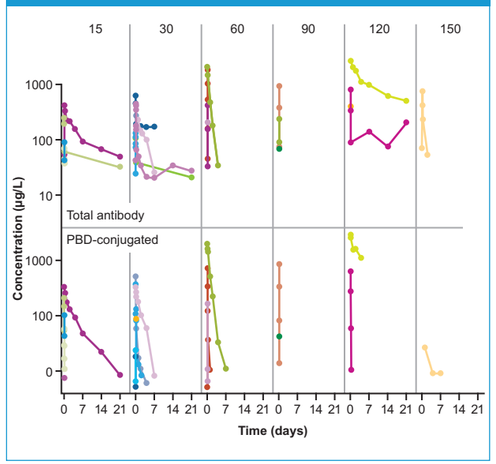
[a]n=19, data not available for all patients.

SD, standard deviation.

Lonca-T PK data

- PK data show PBD-conjugated antibody and total antibody concentrations below quantifiable levels of 5.0 and 20 ng/L, respectively, well before end of the 21-day treatment cycle (**Figure 5**). PBD dimer concentrations were largely below measurable levels throughout the time course, justifying a change to weekly dosing.

Figure 5. Total antibody and PBD-conjugated antibody concentrations versus time by patient and dose (Cycle 1)



PBD, pyrrolobenzodiazepine.

Lonca-T safety

- Treatment-emergent adverse events (TEAEs) were reported by 28/29 (96.6%) patients with 265 TEAEs reported in total. Twelve (41.4%) patients reported adverse events deemed to be possibly or probably related to Lonca-T. The most common TEAEs were:
  - Nausea (n=9)
  - Fatigue (n=7)
  - Febrile neutropenia (n=7)
  - Headache (n=7).
- Grade ≥3 TEAEs were reported in 24/29 (82.8%) patients, of which febrile neutropenia (n=7) and neutrophil count decrease (n=4) were the most common (**Table 3**).
- Two patients experienced TEAEs with fatal outcomes (lung infection and sepsis), both from the 120 μg/kg q3w dosing group.
- Four patients experienced TEAEs leading to a dose delay or reduction, but no TEAEs led to treatment withdrawal.
  - Liver toxicity events were recorded in 7 patients, leading to dose delay in 1 patient (owing to hyperbilirubinemia)
    - Four patients experienced Grade 3 liver toxicity events, including during Cycle 1; all were reversible (median [range] duration: 11.5 [5–36] days) and not related to veno-occlusive disease.
  - There were 3 infusion-related reactions, including 1 case each of Grade 2 infusion-related reaction and cytokine release syndrome, and 1 case of Grade 1 tachycardia.
- The MTD has not yet been reached.

Table 3. Grade ≥3 TEAEs by preferred term (safety analysis set)

TEAEs (Grade ≥3)	Loncastuximab tesirine dose (μg/kg) q3w 15 (n=5)	30 (n=7)	60 (n=3)	90 (n=4)	120 (n=5)	150 (n=4)	qw 50 (n=1)	Total (N=29)
Grade ≥3 TEAE reported by ≥10% of patients, n (%)	5 (100)	4 (57.1)	3 (100)	3 (75.0)	5 (100)	4 (100)	0	24 (82.8)
Febrile neutropenia	0	1 (14.3)	1 (33.3)	2 (50.0)	1 (20.0)	2 (50.0)	0	7 (24.1)
Neutrophil count decreased	1 (20.0)	2 (28.6)	0	0	1 (20.0)	0	0	4 (13.8)
Abdominal pain	0	1 (14.3)	0	1 (25.0)	0	1 (25.0)	0	3 (10.3)
Bacteremia	0	0	0	2 (50.0)	1 (20.0)	0	0	3 (10.3)
Lung infection	0	1 (14.3)	1 (33.3)	0	1 (20.0)	0	0	3 (10.3)
Sepsis	0	2 (28.6)	0	0	1 (20.0)	0	0	3 (10.3)

qw, once weekly; q3w, once every 3 weeks; TEAE, treament-emergent adverse event.

Lonca-T efficacy

- Two patients achieved a complete response with no minimal residual disease (MRD), at a dose of 30 μg/kg and 120 μg/kg q3w after 5 and 2 treatment cycles, respectively.
  - Both responders had previously received blinatumomab.
- A third patient achieved a complete response with positive MRD at a dose of 150 μg/kg q3w.
- A fourth patient achieved a complete marrow response with an incomplete blood count response and progression of extramedullary disease at a dose of 150 μg/kg q3w.

CONCLUSIONS

- In this Phase 1 study in patients with R/R B-ALL, single-agent Lonca-T was well tolerated with no DLTs and showed 2 MRD-negative complete remissions in a heavily pretreated population.
- Dose escalation will continue to find the MTD for a weekly regimen.
- A dose-expansion phase in part 2 of the study is planned to further evaluate the tolerability, safety, PK, and activity of Lonca-T.

Acknowledgments

- The authors would like to thank and acknowledge the participating patients and their families, and all study co-investigators and research coordinators.
- Study sponsored by ADC Therapeutics. https://clinicaltrials.gov/ct2/show/NCT02669264.
- Editorial support was provided by Louise Gildea, PhD, at Fishawack Communications Ltd, funded by ADC Therapeutics.

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Disclosures

- **N Jain, R Klisovic, W Stock, A Zeidan, E Atallah, J McCloskey, B Tomlinson, HM Kantarjian, MJ Wieduwilt** – research support, ADC Therapeutics; **L Heffner** – research support, ADC Therapeutics, Pharmacyclics, Genentech, Kite; **D Ungar, S He, J Boni** – employees of ADC Therapeutics with stock option interests.

Presented at the 59th American Society of Hematology Annual Meeting & Exposition, December 9–12, 2017, Atlanta, GA, USA