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Interim Results from a Phase 1 Study of ADCT-301 (Camidanlumab Tesirine) Show Promising Activity of a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate in Relapsed/Refractory Hodgkin/Non-Hodgkin Lymphoma

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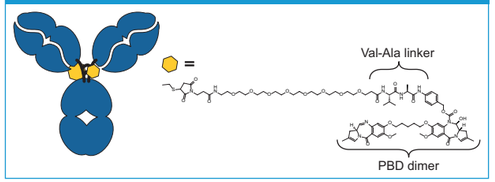
INTRODUCTION

- CD25 (IL-2R-α) is expressed on the cell surface of many lymphomas, including Hodgkin lymphoma (HL), peripheral T-cell lymphoma, cutaneous T-cell lymphoma, and diffuse large B-cell lymphoma.[1–3]
- ADCT-301 (camidanlumab tesirine [Cami-T]) is an antibody drug conjugate comprising a human monoclonal antibody against CD25 stochastically conjugated via a cleavable valine-alanine linker to tesirine, a potent pyrrolobenzodiazepine (PBD) dimer toxin (**Figure 1**).
- Cami-T binds to the CD25 antigen on tumor cells and is internalized via endocytosis.
  - The protease-sensitive linker is cleaved in the lysosome and the free PBD dimers migrate into the nucleus
  - PBD dimers sequence-selectively bind to the DNA minor groove, blocking cell division and resulting in cell death.[4]
- Cami-T has demonstrated potent antitumor activity against CD25-expressing mouse xenograft lymphoma models.[4]
- Here, we report the latest interim data from the ongoing first-in-human clinical trial of Cami-T in patients with relapsed/refractory (R/R) HL and non-Hodgkin lymphoma (NHL).

Figure 1. Cami-T structure



PBD, pyrrolobenzodiazepine

STUDY OBJECTIVES

- In part 1 (dose escalation), to assess the safety and tolerability of Cami-T, and define a maximum tolerated dose (MTD) and the recommended dose of Cami-T for part 2.
- In part 2 (dose expansion), to evaluate the safety and tolerability of the Cami-T dose recommended in part 1.
- Both parts will also assess efficacy (overall response rate [ORR; per 2014 Lugano Classification[5]], duration of response, progression-free survival, and overall survival), pharmacokinetics (PK), and anti-drug antibody activity.

STUDY DESIGN

- In this Phase 1, open-label, multicenter study, eligible patients (**Table 1**) with R/R HL or NHL receive 1-hour intravenous infusions of Cami-T every 3 weeks (1 cycle).
- In part 1, the initial cohort received a starting dose of 3 μg/kg, with subsequent cohorts enrolled at escalating doses up to a maximum of 300 μg/kg according to a continual reassessment method, which allows expansion at different doses for different lymphoma subtypes.
  - The dose-limiting toxicity (DLT) observation period is Cycle 1, with cumulative DLTs occurring through Cycle 3 incorporated into the adaptive dose-escalation algorithm
  - No more than 10 patients can be treated at any dose level unless at least 3/10 patients have documented a partial response or better
  - The MTD will be the highest dose that has at least a 60% probability of the DLT rate being <30%.
- Part 2 will further evaluate safety, tolerability, PK and clinical activity at the dose recommended from part 1.

Table 1. Study inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Age 18 years or older • Histologically confirmed relapsed or refractory lymphoma, including stage ≥Ib cutaneous T-cell lymphoma • Failed, or intolerant to, any established therapy known to provide clinical benefit at current state of disease • Eastern Cooperative Oncology Group performance status 0 to 2	• 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 Cami-T • History of symptomatic autoimmune disease • Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment

RESULTS

Patient characteristics

- As of November 1, 2017, 86 patients have been treated with Cami-T.
  - Median number of cycles: 2 [min, max: 1, 15], with a median treatment duration of 43 days [min, max: 7, 375]
  - 71 patients have been treated with doses ranging from 3 to 150 μg/kg during part 1
  - 15 patients have been treated with dose 45 μg/kg in part 2
  - Baseline characteristics are shown in **Table 2**.
- Histological subtypes treated include HL, n=50 and NHL, n=36.

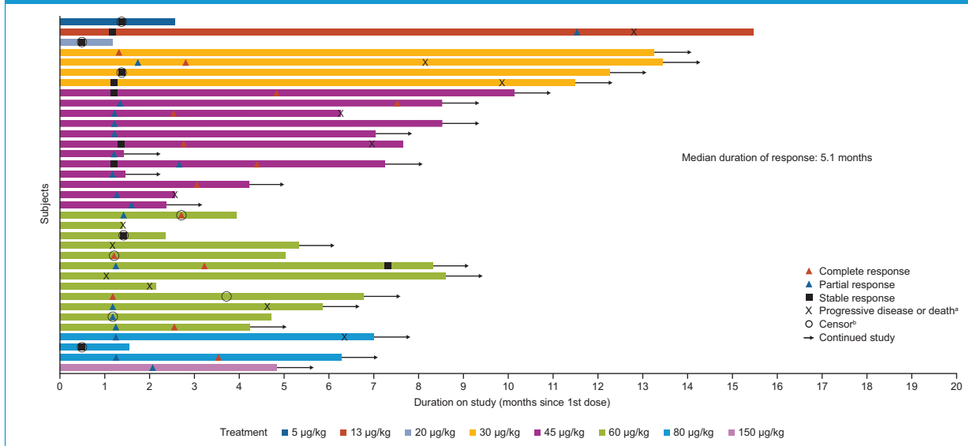
Table 2. Patient baseline characteristics

Patient characteristic	Total (N=86)
Sex, n (%)	
Female	31 (36.0)
Male	55 (64.0)
Age, years	
Median (min, max)	53 (19, 88)
Race, n (%)	
White	70 (81.4)
Black or African American	6 (7.0)
Asian	4 (4.7)
Other	6 (7.0)
Diagnosis, n (%)	
Hodgkin lymphoma	50 (58.1)
Non-Hodgkin lymphoma	36 (41.9)
Cutaneous T-cell lymphoma	7 (8.1)
Diffuse large B-cell lymphoma	14 (16.3)
Mantle cell lymphoma	3 (3.5)
Peripheral T-cell lymphoma	3 (3.5)
Other	9 (10.5)
Number of previous chemotherapies	
Median (min, max)	4 (1, 14)

Cami-T PK data

- Exposure (C_{max} and area under the curve) increased with dose; accumulation was not apparent by Cycle 2 (**data not shown**).

Figure 2. Swimmer plot showing responses by patient (efficacy analysis set; HL)



Each bar represents 1 patient. [a]Study drug was discontinued at "x" for progression but patients continued to be followed. [b]Exclude censors by cutoff date.

Cami-T safety data

- DLTs have been reported in 4 patients:
  - Oral mucositis and small bowel enteritis at 20 μg/kg
  - Elevated creatine phosphokinase at 30 μg/kg
  - Maculopapular rash and pruritus at 30 μg/kg
  - Lip ulceration and skin infection at 45 μg/kg.
- The most common treatment-emergent adverse events (TEAEs) were fatigue, rash, elevated gamma-glutamyltransferase and pyrexia (**Table 3**).
- The most common Grade ≥3 TEAEs were elevated gamma-glutamyltransferase, decreased platelet count, elevated alanine aminotransferase, anemia and rash (**Table 4**).
- Drug dose was delayed or reduced following a TEAE for 28/86 patients (32.6%).
- TEAEs leading to treatment discontinuation occurred in 12/86 patients (14.0%).
- There have been 3 cases of autoimmune neurotoxicity:
  - Two cases of Guillain-Barré syndrome (GBS)
  - One case of polyradiculopathy in a patient with concurrent thyroiditis.
- The MTD has not been reached, but no further dose escalation is planned for patients with HL.

Table 3. Any Grade TEAEs (safety analysis set; N=86)

TEAEs (any grade) reported by ≥20% of patients, n (%)	Camidanlumab tesirine dose (μg/kg) q3w ≤30 μg/kg (n=16)	45[a] (n=30)	60 (n=20)	80 (n=15)	100 (n=3)	150 (n=2)	Total (N=86)
Patients with TEAE (any grade)	15 (93.8)	26 (86.7)	20 (100)	15 (100)	3 (100)	2 (100)	81 (94.2)
Fatigue	4 (25.0)	7 (23.3)	9 (45.0)	5 (33.3)	1 (33.3)	0	26 (30.2)
Rash maculopapular	6 (37.5)	5 (16.7)	7 (35.0)	4 (26.7)	0	0	22 (25.6)
Gamma-glutamyltransferase increased	3 (18.8)	4 (13.3)	5 (25.0)	5 (33.3)	1 (33.3)	1 (50.0)	19 (22.1)
Pyrexia	2 (12.5)	5 (16.7)	6 (30.0)	5 (33.3)	0	0	18 (20.9)

[a]Includes 15 patients from part 1 and 15 patients from part 2. q3w, once every 3 weeks; TEAE, treatment-emergent adverse event.

Table 4. Grade ≥3 TEAEs (safety analysis set; N=86)

TEAEs (Grade ≥3) reported by ≥5% of patients, n (%)	Camidanlumab tesirine dose (μg/kg) q3w ≤30 μg/kg (n=16)	45[a] (n=30)	60 (n=20)	80 (n=15)	100 (n=3)	150 (n=2)	Total (N=86)
Patients with TEAE Grade ≥3	10 (62.5)	12 (40.0)	11 (55.0)	13 (86.7)	3 (100)	2 (100)	51 (59.3)
Gamma-glutamyltransferase increased	2 (12.5)	1 (3.3)	3 (15.0)	4 (26.7)	0	1 (50.0)	11 (12.8)
Platelet count decreased	1 (6.3)	1 (3.3)	2 (10.0)	2 (13.3)	1 (33.3)	1 (50.0)	8 (9.3)
Alanine aminotransferase increased	0	1 (3.3)	2 (10.0)	1 (6.7)	0	1 (50.0)	5 (5.8)
Anemia	2 (12.5)	1 (3.3)	0	2 (13.3)	0	0	5 (5.8)
Rash maculopapular	4 (25.0)	0	0	1 (6.7)	0	0	5 (5.8)

[a]Includes 15 patients from part 1 and 15 patients from part 2. q3w, once every 3 weeks; TEAE, treatment-emergent adverse event.

Cami-T efficacy data

- Response data for 35 patients with HL are shown in **Figure 2**. The ORR for all doses was 71.4% (25/35 patients).
  - 27 patients with HL have been treated with doses ≥45 μg/kg in part 1, with an ORR of 77.8% (21/27) that comprises a CR rate of 44.4% (12/27) and PR rate of 33.3% (9/27).
  - Of the 12 patients with HL who have been treated with dose 45 μg/kg in parts 1 and 2, 6 patients each have achieved a CR or PR, respectively, resulting in an ORR of 100% (12/12).
  - In part 1 and 2 at doses ≥45 μg/kg, a CR or PR was achieved by:
    - 21/27 patients (77.8%) with prior brentuximab vedotin
    - 13/18 patients (72.2%) with prior checkpoint inhibitor
    - 9/14 patients (64.3%) who had prior stem cell transplantation
    - 4/8 patients (50.0%) who had received all three of the above treatments.
  - Median duration of response was 5.1 months.
- Responses were also seen in patients with NHL (all doses; partial response: 18.2% [6/33]; complete response: 6.1% [2/33]) (**Table 5**).
  - Dose escalation will continue for patients with NHL.

Table 5. Best overall responses[a] (efficacy analysis set)

n (%)	HL: Part 1 only: ≥45 μg/kg (n=27)	HL: Parts 1 & 2: All doses (n=35)	HL: Parts 1 & 2: 45 μg/kg (n=12)	NHL: T-cell lymphoma (n=12)	NHL: B-cell lymphoma (n=21)
ORR	21 (77.8)	25 (71.4)	12 (100)	4 (33.3)	4 (19.0)
CR	12 (44.4)	14 (40.0)	6 (50)	0	2 (9.5)
PR	9 (33.3)	11 (31.4)	6 (50)	4 (33.3)	2 (9.5)
SD	1 (3.7)	4 (11.4)	0	1 (8.3)	0
PD	4 (14.8)	4 (11.4)	0	6 (50.0)	15 (71.4)
NE	1 (3.7)	2 (5.7)	0	1 (8.3)	2 (9.5)

[a]Best visit response based on the 2014 Lugano Classification Criteria.[5]
CR, complete response; HL, Hodgkin lymphoma; NE, not evaluable; NHL, non-Hodgkin lymphoma; OR, overall response (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease.

CONCLUSIONS

- In patients with R/R HL, Cami-T was active with the safety profile as described during dose escalation and expansion.
- The ORR in this heavily pretreated population is very promising and HL expansion cohorts are underway.
- Dose escalation will continue to identify the MTD in NHL, with planned subtype-specific expansion cohorts at the MTD.
- Cami-T has shown high levels of activity in HL, T- and B-cell lymphomas.
- Characterization of the dosing regimen is ongoing to maximize the therapeutic window for Phase 2 in HL.

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