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Safety and Efficacy of ADCT-402 (Loncastuximab Tesirine), a Novel Antibody Drug Conjugate, in Relapsed/Refractory Follicular Lymphoma and Mantle Cell Lymphoma: Interim Results From the Phase 1 First-in-Human Study

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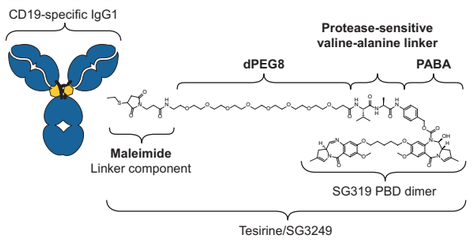
INTRODUCTION

- Patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (NHL), including follicular lymphoma (FL) and mantle cell lymphoma (MCL), have poor clinical outcomes and limited therapy options.[1]
- In the USA, FL is the most common indolent form of lymphoma, constituting approximately 20% of all lymphomas, while MCL is rare and represents approximately 5% of all lymphomas.[2]
- CD19, a B-cell transmembrane antigen, is expressed ubiquitously in B-cell NHL, making it a potential therapeutic target.[3,4]
- ADCT-402 (loncastuximab tesirine) is an antibody drug conjugate comprising a humanized monoclonal antibody directed against human CD19 conjugated through a cathepsin-cleavable valine-alanine linker to SG3199, a pyrrolobenzodiazepine dimer toxin (**Figure 1**).[5]
- Loncastuximab tesirine has demonstrated potent antitumor activity against CD19-expressing mouse models of B-cell malignancies. Moreover, it has shown an acceptable safety and pharmacokinetic (PK) profile with excellent stability in preclinical in vivo models.[5]
- Here we present the latest interim data from the ongoing first-in-human trial of loncastuximab tesirine in a subgroup of patients with R/R FL or MCL.

Figure 1. Loncastuximab tesirine structure



CD19, cluster of differentiation 19; IgG1, immunoglobulin G1; PABA, para-aminobenzoic acid; PBD, pyrrolobenzodiazepine; PEG, polyethylene glycol.

STUDY OBJECTIVES

Primary objective

- To evaluate the safety and tolerability of loncastuximab tesirine, and determine, as appropriate, the maximum tolerated dose (MTD).

Secondary objectives

- To evaluate the clinical activity (measured by overall response rate [ORR], duration of response [DoR], progression-free survival [PFS], and overall survival).
- To characterize the PK profile and evaluate antidrug antibodies (ADA).

STUDY DESIGN

- This is a Phase 1, multicenter, open-label, single-arm, dose-escalation (Part 1) and dose-expansion (Part 2) study in eligible patients (**Table 1**) with R/R B-cell NHL who have failed or are intolerant to established therapies or have no other treatment options available.
- Patients receive 30–60 minute intravenous infusions of loncastuximab tesirine every 3 weeks (Q3W; 1 cycle) at doses ranging from 15 to 200 µg/kg.
- In Part 1, patients are assigned to treatment using a 3+3 dose-escalation study design, based on the assessment of dose-limiting toxicities (DLT) during Cycle 1.
- Treatment for patients in Part 2 is based on the dose(s) determined in Part 1.

Table 1. Study key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Aged 18 years or older • Pathologically confirmed, relapsed/refractory B-cell non-Hodgkin lymphoma • Failed or intolerant to any established therapy, or no other treatment options available • Measurable disease, as defined by the 2014 Lugano Classification • Eastern Cooperative Oncology Group performance status 0–2 • Absolute neutrophil count ≥1000/µL; platelet count ≥75,000/µL; and hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Cycle 1 Day 1 • Creatinine ≤1.5 mg/dL or creatinine clearance >60 mL/min, ALP, ALT, and AST ≤2 x ULN, and total bilirubin ≤1.5 x ULN	• Active graft-versus-host disease • Autologous or allogeneic transplant within the 60 days prior to screening • Known seropositive for human immunodeficiency virus, hepatitis B surface antigen, or antibody to hepatitis C virus • Major surgery, chemotherapy, systemic therapy, or radiotherapy; within 14 days or 5 half-lives prior to Cycle 1 Day 1 treatment

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; ULN, upper limit of normal.

RESULTS

Patient characteristics

- As of October 16, 2018, 14 patients with FL (11 males, 3 females) and 15 patients with MCL [11 males, 4 females]) have been treated with loncastuximab tesirine.
  - Baseline characteristics and demographic data are shown in **Table 2.**
- Patients with FL and MCL received a median 3 [range 2–12] and 2 [range 1–11]) cycles of loncastuximab tesirine, respectively.

Loncastuximab tesirine safety data

- Treatment-emergent adverse events (TEAEs) were reported in 96.6% (28/29) of patients with FL and MCL.
  - The most common all-grade TEAEs (≥20% patients), regardless of relationship to study treatment, are presented in **Table 3.**

Table 2. Baseline characteristics and demographic data of study population (safety analysis set)

Patient characteristic	FL (n=14)	MCL (n=15)
Sex, n (%)		
Female	3 (21.4)	4 (26.7)
Male	11 (78.6)	11 (73.3)
Race, n (%)		
White	12 (85.7)	14 (93.3)
Black or African American	1 (7.1)	1 (6.7)
Asian	0	0
Other	1 (7.1)	0
Median age (min, max), years	60.5 (40, 75)	64.0 (51, 87)
Disease stage, n (%)		
I	0	2 (13.3)
II	3 (21.4)	1 (6.7)
III	2 (14.3)	1 (6.7)
IV	9 (64.3)	11 (73.3)
Last line prior chemotherapy response status, n (%)		
Relapsed	9 (64.3)	7 (46.7)
Refractory	5 (35.7)	8 (53.3)
Number of prior systemic therapies, median (min, max)	4 (1, 9)	4 (1, 13)
Prior stem cell transplantation, n (%)		
Yes	4 (28.6)	9 (60.0)
No	10 (71.4)	6 (40.0)
Prior Ibrutinib, n (%)		
Yes	2 (14.3)	11 (73.3)
No	12 (85.7)	4 (26.7)

FL, follicular lymphoma; MCL, mantle cell lymphoma.

Table 3. Any grade TEAEs reported by ≥20% of patients with FL and MCL (safety analysis set; n=29)

TEAE	n (%)
Any TEAE	28 (96.6)
GGT increased	13 (44.8)
Fatigue	12 (41.4)
Anemia	10 (34.5)
Edema peripheral	10 (34.5)
ALP increased	9 (31.0)
Myalgia	9 (31.0)
Nausea	9 (31.0)
Pleural effusion	8 (27.6)
Abdominal pain	7 (24.1)
ALT increased	7 (24.1)
AST increased	7 (24.1)
Dyspnea	7 (24.1)
Erythema	7 (24.1)
Neutrophil count decreased	7 (24.1)
Constipation	6 (20.7)
Headache	6 (20.7)

ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; FL, follicular lymphoma; GGT, gamma-glutamyltransferase; MCL, mantle cell lymphoma; TEAE, treatment-emergent adverse event.

- Overall, 72.4% (21/29) of patients with FL and MCL reported grade ≥3 TEAEs.
  - The most common grade ≥3 TEAEs (≥10% of patients) are shown in **Table 4**.

Table 4. Grade ≥3 TEAEs reported by ≥10% of patients with FL and MCL (safety analysis set; n=29)

TEAE	n (%)
Any grade ≥3 TEAE	21 (72.4)
Neutrophil count decreased*	12 (41.4)
GGT increased	9 (31.0)
Platelet count decreased*	7 (24.1)
Anemia	4 (13.8)
ALP increased	3 (10.3)
Dyspnea	3 (10.3)
Lymphocyte count decreased	3 (10.3)

*Platelet and neutrophil count decreased TEAEs are reported from laboratory hematology data
ALP, alkaline phosphatase; FL, follicular lymphoma; GGT, gamma-glutamyltransferase; MCL, mantle cell lymphoma; TEAE, treatment-emergent adverse event.

- TEAEs leading to treatment discontinuation occurred in 20.7% (6/29) of patients with FL and MCL.
- Immunogenicity assessment of data available from 29 patients demonstrated no potential for ADA induction (0/29 pre- or post-dose cases of ADA positivity).

Loncastuximab tesirine efficacy data

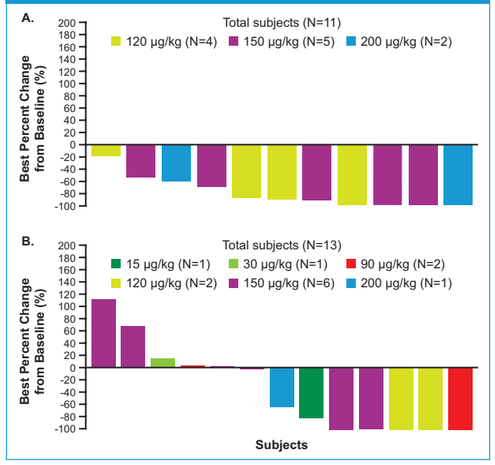
- Best overall responses are reported in **Table 5**. Tumor responses in individual patients are shown in **Figure 2**.
  - In patients with FL:
    - ORR was 78.6% (11/14).
    - Median DoR and PFS (responders and nonresponders) were not reached after a median follow-up time of 11.6 months.
  - In patients with MCL:
    - ORR was 46.7% (7/15).
    - Median DoR was not reached and PFS was 4.8 months after a median follow-up time of 8.7 months.
    - 1 patient with MCL (90 µg/kg group) and 2 patients with FL (150 and 200 µg/kg) went to transplant.

Table 5. Best overall responses* (efficacy analysis set)

Response (%)	FL subgroup (n=14)	MCL subgroup (n=15)
ORR	11 (78.6)	7 (46.7)
CR	9 (64.3)	4 (26.7)
PR	2 (14.3)	3 (20.0)
SD	0	3 (20.0)
PD	2 (14.3)	5 (33.3)
NE	1 (7.1)	0

*Best visit response based on 2014 Lugano Criteria.
CR, complete response; FL, follicular lymphoma; MCL, mantle cell lymphoma; NE, not evaluable; ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Waterfall plot showing nodal regression (best percent change from baseline) for patients with follicular lymphoma (A) and mantle cell lymphoma (B) (efficacy analysis set)



Bars represent individual patients.

CONCLUSIONS

- In this Phase 1 study, loncastuximab tesirine has demonstrated encouraging single-agent antitumor activity and manageable toxicity in patients with R/R FL and MCL.

Acknowledgments

- The authors would like to thank and acknowledge the participating patients and their families, and all study co-investigators and research coordinators.
- This study is sponsored by ADC Therapeutics SA. (NCT02669017).
- The authors received editorial/writing support in the preparation of this poster provided by Eshvendar Reddy Kasala, PhD, of Fishawack Communications Ltd., funded by ADC Therapeutics.

Disclosures

- **P Caimi** has received research support from ADC Therapeutics, has taken part in speaker bureaus for Celgene, and has been an advisory board member for Kite Pharmaceuticals and Genentech. **B Kahl** has received research support from ADC Therapeutics and has acted as a consultant for Seattle Genetics and Genentech. **M Hamadani** has received research support from Otsuka, Takeda, Sanofi Genzyme, MedImmune, Merck, and ADC Therapeutics; has taken part in speaker bureaus for Sanofi Genzyme; and has acted as a consultant for MedImmune, Janssen, Celgene, and Cellerant Therapeutics. **C Carlo-Stella** has received research support from ADC Therapeutics; has taken part in speaker bureaus for Genenta Science, Bristol-Myers Squibb, Amgen, and Janssen; and has acted as a consultant for Boehringer Ingelheim and Sanofi. **KM Ardeshna** has received research support from ADC Therapeutics and has been an advisory board member for Celgene, Roche, Takeda, and ADC Therapeutics. **J Radford** and **OA O'Connor** have received research support from ADC Therapeutics. **M Solh** has received research support from ADC Therapeutics and has taken part in speaker bureaus for Amgen and Celgene. **L Heffner** has received research funding from Pharmacyclics, Genentech, Kite Pharmaceuticals, and ADC Therapeutics. **S He, D Ungar**, and **J Feingold** are employees of ADC Therapeutics with equity interest.

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Presented at the 60th American Society of Hematology Annual Meeting & Exposition, December 1–4, 2018, San Diego, CA, USA