Clinical Trials: Targeted Therapy

Clinical Cancer Research

A Phase I Study of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody–Drug Conjugate, in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma

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Abstract

Purpose: ADCT-402 (loncastuximab tesirine) is an antibody–drug conjugate comprising a CD19-targeting antibody and pyrrolobenzodiazepine dimers. A first-in-human study evaluated the safety and preliminary clinical activity of loncastuximab tesirine in patients with B-cell non-Hodgkin lymphoma (NHL).

Patients and Methods: A multicenter, phase I, dose-escalation and dose-expansion study enrolled patients ages ≥18 years with relapsed/refractory (R/R) B-cell NHL. Patients received loncastuximab tesirine every 3 weeks at doses assigned by a 3+3 dose-escalation design. Dose escalation was used to assess the safety and tolerability of loncastuximab tesirine to determine the dose for expansion. Secondary objectives evaluated clinical activity, characterized the pharmacokinetic profile, and evaluated antidrug antibodies.

Results: During dose escalation, 88 patients with R/R B-cell NHL were treated with loncastuximab tesirine at doses 15 to 200 μg/kg. Treatment-emergent adverse events (TEAEs) were experienced by 87/88 (98.9%) patients. Most common TEAEs (≥20% of patients) were hematologic abnormalities, fatigue, edema, liver test abnormalities, nausea, rash, and dyspnea. Grade ≥3 TEAEs (≥5% of patients) included hematologic abnormalities, liver test abnormalities, fatigue, and dyspnea. Overall response rate at doses ≥120 μg/kg was 59.4% (41 of 69 patients; 40.6% complete response; 18.8% partial response). Median duration of response, progression-free survival, and overall survival (all doses) were 4.8, 5.5, and 11.6 months, respectively. Drug exposure increased with increasing dose, showing moderate accumulation with multiple doses ≥150 μg/kg. There was no evidence of immunogenicity.

Conclusions: Loncastuximab tesirine had promising activity with acceptable safety in this dose-escalation study. A phase II study with initial dosing at 150 μg/kg has been initiated based on these results.

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Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of biologically and clinically diverse lymphoid malignancies, ranging from indolent to clinically aggressive forms (1). NHL is the seventh most commonly diagnosed cancer among men and women in the United States with an estimated 74,680 new cases and 19,910 deaths in 2018 (2). Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive subtype of NHL, accounting for approximately one-third of all newly diagnosed cases (3). First-line treatment of DLBCL is curative for 60% to 70% of patients (4). Of those who fail to achieve remission or who experience early relapse, a proportion of young, fit patients may be cured with high-dose therapy and autologous stem cell transplantation (ASCT; ref. 5). An additional fraction achieves remission with chimeric antigen receptor therapy (CAR-T; refs. 6, 7). For all other patients, outcomes with salvage therapy remain poor. The poor outcomes demonstrated in a multicohort retrospective NHL research study (SCHOLAR-1) in patients with refractory DLBCL highlight the need for more effective therapeutic options in this cohort, with a complete response (CR) rate of only 7% to the next line of therapy, and median overall survival (OS) of 6.3 months, with similar results across all trials included (8).

Translational Relevance

Overexpression of the transmembrane glycoprotein CD19 contributes to the pathogenesis of B-cell malignancies, making it a valid therapeutic target for $CD19^+$ hematological B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL). In patients with relapsed/refractory (R/R) DLBCL ineligible for autologous stem cell transplantation or chimeric antigen receptor T-cell therapy, novel therapies with sustained efficacy are urgently required. ADCT-402 (loncastuximab tesirine) is an antibody–drug conjugate comprising a humanized monoclonal antibody directed against CD19, stochastically conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin. PBD dimers are distinguished from conventional DNA cross-linking agents as their interstrand cross-links do not distort the DNA structure; protecting them against DNA repair mechanisms and maintaining their biological activity. Here, loncastuximab tesirine shows promising single-agent activity in R/R $CD19^+$ B-cell non-Hodgkin lymphoma with a notable 55% response rate in R/R DLBCL at doses $\geq$120 μg/kg. Side effects were generally manageable.

Antibody–drug conjugates (ADCs) directed against tumor-associated surface antigens permit specific targeting of cancer cells with cytotoxic agents, with the potential to maximize efficacy while minimizing systemic toxicities (9). The human CD19 antigen is a transmembrane glycoprotein expressed on the majority of malignant B cells at normal to high levels (10). In normal human cells, expression of CD19 continues through pre-B and mature B-cell differentiation until it is finally downregulated during terminal differentiation into plasma cells (11); however, expression of CD19 is maintained in hematologic B-cell malignancies, including DLBCL (10, 12).

ADCT-402 (loncastuximab tesirine) is an ADC comprising a humanized monoclonal antibody directed against CD19, stochastically conjugated through a cathepsin-cleavable valine-alanine linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer toxin (13). PBD dimers are sequence-selective DNA cross-linking agents that are distinguished from conventional DNA cross-linking agents (such as the nitrogen mustards and platinum drugs), in that the interstrand cross-links formed between PBD and cellular DNA (minor groove) do not cause distortion of the DNA structure. Less DNA distortion may hide PBD dimers from DNA repair mechanisms, and appears to help in maintaining their biological activity and persistence in cells (14). The PBD dimer SG3199 has shown picomolar activity against panels of human hematologic tumor cell lines in *in vitro* studies (15). Loncastuximab tesirine has demonstrated potent dose-dependent antitumor activity against CD19-expressing B-cell malignancies in both *in vitro* and *in vivo* preclinical models (13). Moreover, loncastuximab tesirine has shown an acceptable safety and pharmacokinetic (PK) profile, with excellent stability and tolerability in preclinical studies, supporting further investigation in clinical trials (13).

A first-in-human study was conducted to evaluate the safety and efficacy of loncastuximab tesirine in patients with relapsed/refractory (R/R) B-cell NHL. Here, we report on the safety, tolerability, PK profile, and preliminary clinical activity of loncastuximab tesirine during the dose-escalation part of this study.

Patients and Methods

Study design

This was an open-label, single-arm, phase I study conducted at 12 international study centers in patients with R/R B-cell NHL (clinicaltrials.gov: NCT02669017). The study was conducted in two parts, part 1 (dose escalation) followed by part 2 (dose expansion). Part 1 of the study was designed to determine the recommended dose(s) and schedule for part 2 of the study.

The primary objective of the dose-escalation portion of the study was to investigate the safety and tolerability of loncastuximab tesirine to determine the maximum tolerated dose (MTD) and the recommended dose for expansion cohorts. Secondary objectives were to evaluate the clinical activity based on the 2014 Lugano Classification Criteria [measured by overall response rate (ORR), duration of response (DoR), progression-free survival (PFS), and OS], characterize the PK profile, and evaluate antidrug antibodies (ADA) in patients with R/R B-cell NHL.

Study population

Male or female patients ($\geq$18 years of age) with histologically confirmed R/R B-cell NHL, who had failed or were intolerant to established therapies, or for whom no other established treatment options were available, were included in the study. Other key criteria for eligibility included measurable disease as defined by the 2014 Lugano Classification (16) Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, absolute neutrophil count $\geq$1,000/μL, platelet count $\geq$75,000/μL, hemoglobin $\geq$9.0 g/dL without transfusion within the 2 weeks prior to day 1, serum/plasma creatinine $\leq$1.5 mg/dL or creatinine clearance >60 mL/min, serum/plasma alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate transaminase (AST) $\leq 2\times$ the upper limit of normal (ULN), and serum/plasma total bilirubin $\leq 1.5\times$ ULN. Key exclusion criteria included were active graft-versus-host disease, prior autologous, or allogeneic transplant within 60 days before screening, and congenital long QT syndrome or a corrected QTc interval of $\geq$450 milliseconds at screening unless secondary to a pacemaker or bundle branch block.

Treatment and dose-escalation design

Loncastuximab tesirine was administered intravenously over 1 hour, once every 3 weeks (one cycle). Patients were assigned to dose cohorts according to a 3+3 dose-escalation design, which was overseen by a Dose Escalation Steering Committee. Intrapatient dose escalation was not permitted. In accordance with the 3+3 design, the MTD was defined as the highest dose level at which none of the first three treated patients, or no more than one of the first six treated patients, experienced a dose-limiting toxicity (DLT). The DLT observation period was one cycle. A hematologic DLT was defined as any grade 3 or 4 febrile neutropenia or neutropenic infection, grade 4 neutropenia lasting more than 7 days, grade 4 thrombocytopenia, grade 3 thrombocytopenia with clinically significant bleeding or requiring a platelet transfusion, or grade 4 anemia. A nonhematologic DLT was defined as any grade 4 tumor lysis syndrome, grade 3 or higher adverse events (AEs; including nausea, vomiting, diarrhea, and electrolyte

imbalances lasting more than 48 hours despite optimal therapy), grade 3 or higher hypersensitivity reaction, or grade 2 or higher skin ulceration.

During dose escalation, enrollment at any dose level could be expanded if three patients had completed the DLT observation period and at least one patient achieved a partial response (PR) or better. No more than 10 patients could be treated at any dose level unless $\geq$3 of the 10 patients had achieved a PR or better.

Patients were treated until there was evidence of disease progression, patient withdrawal due to a serious or intolerable AE, or the patient withdrew from the study for other reasons. Doses could be delayed for up to 21 days for any toxicity until resolution to grade 1 or lower. Patients could then resume treatment if they were deriving clinical benefit. Patients who resumed treatment following a dose delay could have their dose of study drug reduced by 50%. If toxicity occurred again at the reduced dose, the patient was discontinued from the study. Patients who discontinued treatment for any reason other than disease progression were followed with imaging every 12 weeks until disease progression or initiation of new anticancer treatment, and thereafter by telephone for up to 12 months after the last dose of study drug to collect survival information.

Study assessments

Safety was assessed based on physical examination, electrocardiogram, vital signs, ECOG performance status, hematology, coagulation panel, biochemistry, and urinalysis. AEs were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and collected until 12 weeks after the last dose of the drug or initiation of new anticancer treatment.

Disease assessments were conducted every other cycle for the first two evaluations [6 weeks (end of cycle 2) and 12 weeks (end of cycle 4)], and every third cycle (every 9 weeks) thereafter until progression, or more frequently if clinically indicated. Patient response to treatment was determined by the investigator with PET-CT or CT as CR, PR, stable disease (SD), or progressive disease (PD), based on the 2014 Lugano Classification criterion (16).

PK assessments of loncastuximab tesirine and free warhead SG3199 in serum were conducted using validated bioanalytical methods. PK parameters included maximum concentration (C_{max}) and AUC as determined from peripheral blood samples. In addition, potential immunogenicity was evaluated by assessing serum ADAs against loncastuximab tesirine using validated bioanalytical methods.

Statistical analysis

Descriptive statistics and listings were used to report the safety, efficacy, and PK parameters. The safety population comprised all patients who received any dose of loncastuximab tesirine. Patients were evaluable for efficacy if they had received at least one dose of loncastuximab tesirine or had documented progression of disease at any time after the first dose. The population for PK analysis comprised all treated patients with sufficient concentration data available for PK analysis.

Ethics statement

The study was initiated after approval from each institutional review board and performed in accordance with the International Council for Harmonisation good clinical practice guidelines and the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment.

Results

Patient demographics

A total of 88 patients were enrolled during the dose-escalation part of the study (part 1); of these, all 88 patients were included in the safety analysis and 86 patients were included in the efficacy analysis. Two patients did not have available disease assessment data as they discontinued the study prior to disease assessment, due to DLT and withdrawal of consent, respectively. Baseline demographics and clinical characteristics of patients are reported in Table 1. DLBCL was the most common subtype enrolled [63 of 88 (71.6%)]. In both the overall population and the subpopulation of patients with DLBCL, slightly more patients had refractory disease than had relapsed following the last line of prior therapy.

Table 1. Baseline demographics and clinical characteristics of the study patients

Characteristic	All patients, *n* = 88	Patients with DLBCL, *n* = 63
Sex, *n* (%)		
Male	60 (68.2)	40 (63.5)
Female	28 (31.8)	23 (36.5)
Median age, years (range)	65.5 (24, 85)	67 (24, 85)
ECOG score, *n* (%)		
0–1	78 (88.6)	53 (84.1)
≥2	10 (11.4)	10 (15.9)
NHL subtype, *n* (%)		
DLBCL group	63 (71.6)	63 (100)
Double-hit (myc and bcl-2)	8 (9.1)	8 (12.7)
Triple-hit (myc, bcl-2, and bcl-6)	1 (1.1)	1 (1.6)
Bulky disease (≥7 cm)	7 (8.0)	7 (11.1)
Mantle cell lymphoma group	9 (10.2)	NA
Follicular lymphoma group	8 (9.1)	NA
Marginal zone B-cell lymphoma	4 (4.5)	NA
CLL/SLL	3 (3.4)	NA
Waldenström macroglobulinemia	1 (1.1)	NA
Status at enrollment, *n* (%)[a]		
Relapsed after responding to last therapy line	35 (39.8)	26 (41.3)
Refractory to last therapy line	50 (56.8)	36 (57.1)
Other	3 (3.4)	1 (1.6)
Number of previous systemic therapies, *n* (%)		
Median (range)	3 (1, 13)	3 (1, 10)
≤3	51 (58)	40 (63.5)
4–6	27 (30.7)	19 (30.2)
7–10	9 (10.2)	4 (6.3)
>10	1 (1.1)	0 (0)
Prior hematopoietic cell transplantation, *n* (%)		
Yes	23 (26.1)	14 (22.2)
No	65 (73.9)	49 (77.8)
Type of transplant, *n* (%)		
Autologous	19 (21.6)	12 (19.0)
Allogeneic	2 (2.3)	1 (1.6)
Both	2 (2.3)	1 (1.6)
Serum LDH, U/L, median (range)	246 (109, 5912)	264 (109, 5763)

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, U/L, lactate dehydrogenase units per liter; NOS: not otherwise specified; SLL: small lymphocytic lymphoma.

[a]Relapsed defined as best response to last therapy of CR or PR. Refractory defined as best response to last therapy of PD or SD. Other defined as best response to last therapy missing or not evaluable.

Table 2. Any grade hematologic and nonhematologic TEAEs reported by ≥10% of patients (safety analysis set)

TEAE, *n* (%)	Dose (μg/kg)				
	≤90 (*n* = 17)	120 (*n* = 16)	150 (*n* = 19)	200 (*n* = 36)	Total (*N* = 88)
Any TEAE	16 (94.1)	16 (100)	19 (100)	36 (100)	87 (98.9)
Hematologic TEAEs					
Platelet count decreased[a]	11 (64.7)	10 (62.5)	15 (78.9)	29 (80.6)[b]	65 (73.9)[b]
Neutrophil count decreased[a]	10 (58.8)	9 (56.3)	10 (52.6)	26 (74.3)[b]	55 (62.5)[b]
Anemia	4 (23.5)	1 (6.3)	7 (36.8)	13 (36.1)	25 (28.4)
Nonhematologic TEAEs					
Fatigue	7 (41.2)	11 (68.8)	8 (42.1)	17 (47.2)	43 (48.9)
Peripheral edema	1 (5.9)	7 (43.8)	9 (47.4)	14 (38.9)	31 (35.2)
GGT increased	5 (29.4)	4 (25.0)	3 (15.8)	17 (47.2)	29 (33.0)
Nausea	3 (17.6)	4 (25.0)	5 (26.3)	16 (44.4)	28 (31.8)
Rash	2 (11.8)	4 (25.0)	8 (42.1)	9 (25.0)	23 (26.1)
Dyspnea	1 (5.9)	4 (25.0)	5 (26.3)	8 (22.2)	18 (20.5)
ALT increased	3 (17.6)	1 (6.3)	3 (15.8)	10 (27.8)	17 (19.3)
Pleural effusion	2 (11.8)	4 (25.0)	3 (15.8)	8 (22.2)	17 (19.3)
Pyrexia	2 (11.8)	0 (0)	3 (15.8)	12 (33.3)	17 (19.3)
AST increased	3 (17.6)	0 (0)	1 (5.3)	12 (33.3)	16 (18.2)
Decreased appetite	2 (11.8)	0 (0)	2 (10.5)	12 (33.3)	16 (18.2)
Blood alkaline phosphatase increased	4 (23.5)	0 (0)	2 (10.5)	8 (22.2)	14 (15.9)
Myalgia	1 (5.9)	3 (18.8)	1 (5.3)	9 (25.0)	14 (15.9)
Abdominal pain	1 (5.9)	1 (6.3)	4 (21.1)	7 (19.4)	13 (14.8)
Cough	0 (0)	3 (18.8)	2 (10.5)	8 (22.2)	13 (14.8)
Diarrhea	2 (11.8)	3 (18.8)	3 (15.8)	5 (13.9)	13 (14.8)
Rash maculo-papular	3 (17.6)	3 (18.8)	2 (10.5)	5 (13.9)	13 (14.8)
Constipation	2 (11.8)	2 (12.5)	2 (10.5)	6 (16.7)	12 (13.6)
Pruritus	2 (11.8)	2 (12.5)	2 (10.5)	6 (16.7)	12 (13.6)
Vomiting	1 (5.9)	2 (12.5)	2 (10.5)	7 (19.4)	12 (13.6)
Dizziness	1 (5.9)	1 (6.3)	4 (21.1)	4 (11.1)	10 (11.4)
Headache	1 (5.9)	2 (12.5)	2 (10.5)	5 (13.9)	10 (11.4)
Hypokalemia	1 (5.9)	2 (12.5)	3 (15.8)	4 (11.1)	10 (11.4)
Skin hyperpigmentation	1 (5.9)	3 (18.8)	2 (10.5)	4 (11.1)	10 (11.4)
Erythema	1 (5.9)	2 (12.5)	2 (10.5)	4 (11.1)	9 (10.2)
Hyperglycemia	1 (5.9)	0 (0)	3 (15.8)	5 (13.9)	9 (10.2)
Hypotension	2 (11.8)	1 (6.3)	1 (5.3)	5 (13.9)	9 (10.2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Platelet count decreased and neutrophil decreased are reported from laboratory abnormality.
[b]One patient had missing data post-baseline.

Patients received a median of three doses (range, 1–24) of loncastuximab tesirine, ranging from 15 to 200 μg/kg for a median treatment duration of 43.5 days (range, 1–511).

Safety

Overall, 87 of 88 (98.9%) patients experienced at least one treatment-emergent adverse event (TEAE). Commonly experienced TEAEs (reported by ≥10% of patients) are summarized in Table 2. Among these, the most common were hematologic abnormalities (platelet count decreased, neutrophil count decreased and anemia), fatigue, edema, liver test abnormalities [elevated gamma-glutamyl transferase levels (GGT)], nausea, rash, and dyspnea. Skin-related toxicities have been reported with other investigational agents containing the same PBD warhead (17). In this study, skin-related toxicities (predominantly rash, and including maculopapular rash, hyperpigmentation, and skin ulcers) were mild to moderate and reversible or generally manageable with dose delays. GGT increase was generally asymptomatic but required delays/reductions for some patients, which generally allowed patients to continue treatment. Peripheral edema was reported by 31 of 88 (35.2%) of patients and additional TEAEs related to edema/effusion included pleural effusion [17 of 88 (19.3%)], pericardial effusion [4 of 88 (4.5%)], and ascites [2 of 88 (2.3%)]. These events were generally delayed, occurring after at least two cycles. Loop diuretics were ineffective in the management of edema/effusion-related AEs. One patient was reported to experience an infusion-related reaction.

Overall, 65 of 88 (73.9%) patients experienced a TEAE of grade 3 or higher. The most commonly experienced grade ≥3 TEAEs reported in ≥5% of patients are presented in Table 3; and grade ≥3 TEAEs reported by <5% of patients are provided in Supplementary Table S1. The most common grade ≥3 TEAEs comprised hematologic abnormalities (decreased neutrophil and platelet counts, anemia, and febrile neutropenia), liver test abnormalities (increased GGT and alkaline phosphatase), fatigue, and dyspnea. A total of 32 of 88 (36.4%) patients experienced a serious TEAE (any grade) and seven of 88 (8%) patients had a TEAE with fatal outcome. A total of 13 patients (14.8%) had TEAEs that resulted in treatment discontinuation. TEAEs that led to dose delay or reduction were observed in 29 of 88 (33.0%) patients. In this study, patients who experienced grade ≥3 TEAEs often had dose delays, allowing AEs to resolve to grade ≤1, and the majority were able to resume treatment at a reduced dose. The proportion of patients requiring dose delays and reductions increased with increasing cycles of loncastuximab tesirine, but most patients could tolerate at least two cycles at full dose (Supplementary Fig. S1). Accumulating toxicity was apparent at the 200 μg/kg dose, supporting the choice of the 150 μg/kg dose for further investigation. For example, there were 21 instances of ≥ grade 3 GGT increased reported in 17 patients (six patients treated with doses

Table 3. Grade ≥3 TEAEs reported by ≥5% of patients (safety analysis set)

Grade ≥3 TEAE, n (%)	Dose (μg/kg)				
	≤90 (*n* = 17)	120 (*n* = 16)	150 (*n* = 19)	200 (*n* = 36)	Total (*N* = 88)
Any grade ≥3 TEAE	9 (52.9)	12 (75.0)	13 (68.4)	31 (86.1)	65 (73.9)
Any TEAE leading to dose delay or reduction	2 (11.8)	8 (50.0)	8 (42.1)	11 (30.6)	29 (33.0)
Any serious TEAE	6 (35.3)	4 (25.0)	6 (31.6)	16 (44.4)	32 (36.4)
Any TEAE leading to treatment discontinuation	1 (5.9)	2 (12.5)	3 (15.8)	7 (19.4)	13 (14.8)
Any TEAE with fatal outcome	1 (5.9)	1 (6.3)	1 (5.3)	4 (11.1)	7 (8.0)
Neutrophil count decreased[a]	6 (35.3)	4 (25.0)	7 (36.8)	19 (54.3)[b]	36 (41.4)[b]
Platelet count decreased[a]	1 (5.9)	2 (12.5)	6 (31.6)	15 (42.9)[b]	26 (27.6)[b]
GGT increased	4 (23.5)	1 (6.3)	1 (5.3)	11 (30.6)	17 (19.3)
Anemia	3 (17.6)	1 (6.3)	3 (15.8)	4 (11.1)	11 (12.5)
Fatigue	0 (0)	1 (6.3)	2 (10.5)	3 (8.3)	6 (6.8)
Alkaline phosphatase increased	4 (23.5)	0 (0)	0 (0)	2 (5.6)	6 (6.8)
Febrile neutropenia	1 (5.9)	1 (6.3)	1 (5.3)	2 (5.6)	5 (5.7)
Dyspnea	0 (0)	2 (12.5)	0 (0)	3 (8.3)	5 (5.7)

[a]Platelet count decreased and neutrophil decreased are based on laboratory abnormality.
[b]One patient had missing data post-baseline.

≤150 μg/kg and 11 patients treated with 200 μg/kg). Eight instances of GGT elevation improved to ≤ grade 2 prior to the end of study treatment in a median of 35.5 days (range, 11–63). Thirteen instances of GGT elevation were still ≥ grade 3 at the time the patients discontinued study treatment.

The DLT evaluable analysis set consisted of 73 patients. Overall, three patients reported a DLT, comprising one case of grade 3/4 febrile neutropenia in the 150 μg/kg group and two cases of grade 4 thrombocytopenia in the 200 μg/kg group. The MTD was not reached.

Clinical activity

All patients. A total of 86 patients had posttreatment disease assessments and could be evaluated to measure clinical activity. The best overall response (OR) by dose is reported in Table 4. Response was achieved by 41 of 69 patients (59.4%) treated with ≥120 μg/kg of loncastuximab tesirine, and of these, 28 of 69 (40.6%) and 13 of 69 (18.8%) patients achieved CR and PR, respectively. Tumor regression was observed for 53 of 76 (69.7%) evaluable patients (Supplementary Fig. S2A). After a median follow-up of 7.5 months, the overall DoR was 5.5 months but patients achieving CR had a durable response, with median DoR not reached compared with 3.1 months for patients achieving PR (Fig. 1A). The median PFS (Fig. 1B) and OS (Fig. 1C) were 4.8 and 11.6 months, respectively. The median time to response was 6.14 weeks (range, 4.4–24.0).

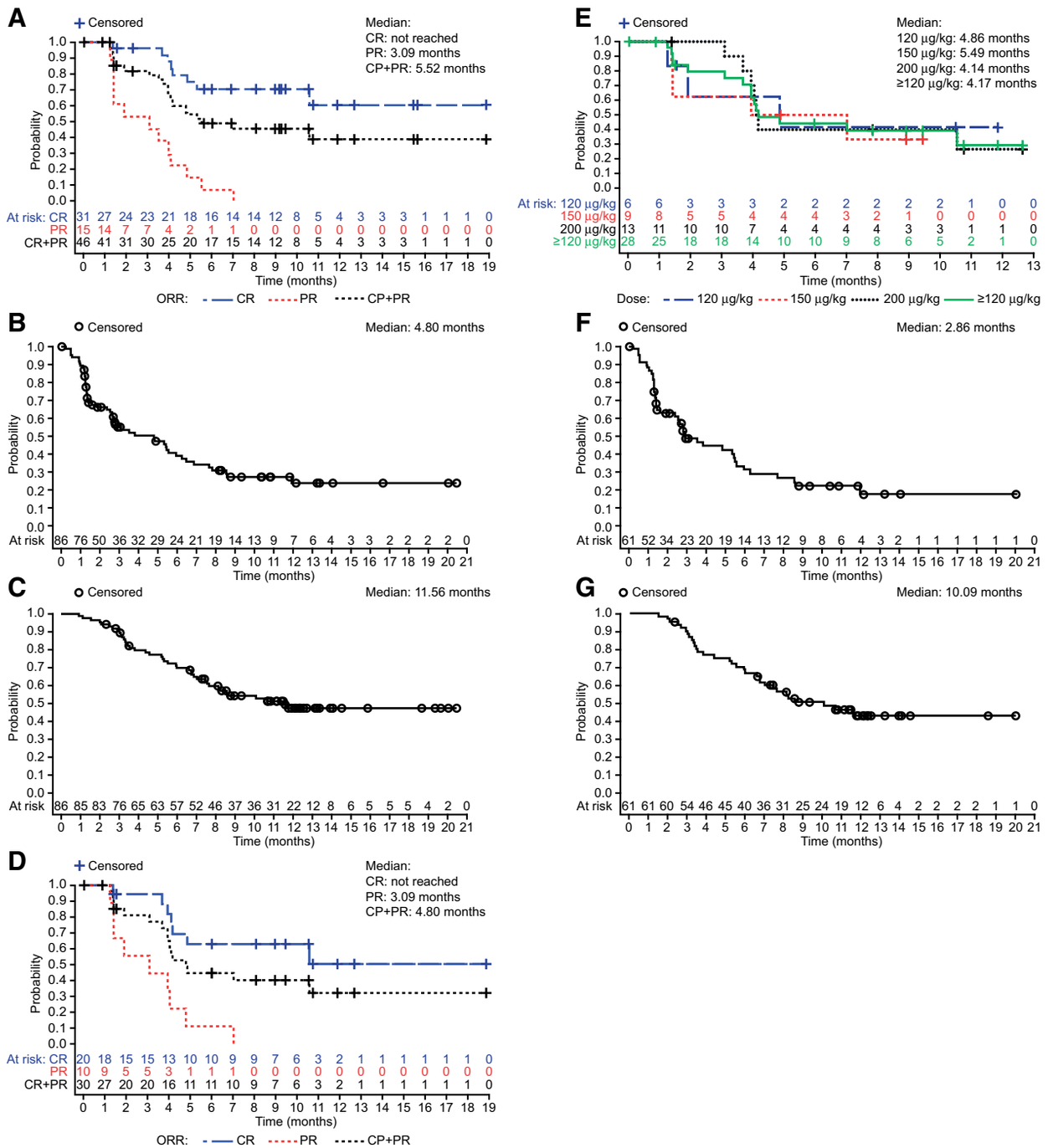
Notably, seven patients treated at higher dose levels responded to loncastuximab tesirine but discontinued treatment to proceed to stem cell transplant; five patients underwent stem cell transplant.

Patients with DLBCL. Of 63 enrolled patients with DLBCL, 61 patients had posttreatment disease assessments and were evaluable for efficacy. Responses at doses ≥120 μg/kg were seen in 28 of 51 (54.9%) patients, and of these, 19 of 51 (37.3%) and nine of 51 (17.6%) patients achieved CR and PR, respectively (Table 4). Tumor regression was observed for 38 of 54 (70.4%) evaluable patients with DLBCL (Supplementary Fig. S2B). After a median follow-up of 7.5 months, the pattern of DoR was similar for the DLBCL population as for the overall population, with a durable response observed in patients achieving CR (median DoR not reached) and a median DoR of 3.1 months in patients achieving PR (Fig. 1D). When DoR was analyzed by dose groups for the higher dose groups. median DoR was highest at the 150 μg/kg dose at 5.5 months compared with 4.9 and 4.1 months in the 120 and 200 μg/kg dose groups, respectively (Fig. 1E). The median PFS and OS in patients with DLBCL were 2.9 and 10.1 months, respectively (Fig. 1F and G).

Table 4. Best overall responses[a] at each loncastuximab tesirine dose (efficacy analysis set)

	Dose (μg/kg)					
	≤90	120	150	200	≥120	Total
Response, n (%)	**All patients (*n* = 86)**					
	17	**16**	**19**	**34**	**69**	**86**
CR	3	6	7	15	28	31 (36.0%)
PR	2	3	5	5	13	15 (17.4%)
SD	4	4	1	2	7	11 (12.8%)
PD	8	3	6	12	21	29 (33.7%)
ORR	5 (29.4%)	9 (56.3%)	12 (63.2%)	20 (58.8%)	41 (59.4%)	46 (53.5%)
	DLBCL sub-group (*n* = 61)					
	10	**11**	**15**	**25**	**51**	**61**
CR	1	4	5	10	19	20 (32.8%)
PR	1	2	4	3	9	10 (16.4%)
SD	2	3	0	2	5	7 (11.5%)
PD	6	2	6	10	18	24 (39.3%)
ORR	2 (20.0%)	6 (54.5%)	9 (60.0%)	13 (52.0%)	28 (54.9%)	30 (49.2%)

[a]Best visit response based on the 2014 Lugano Classification Criteria.



CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; OS, overall survival; PR, partial response; PFS, progression-free survival

Figure 1.

Kaplan–Meier curves showing (**A**) median DoR in all patients, (**B**) median PFS in all patients, (**C**) median OS in all patients, (**D**) median DoR in patients with DLBCL (**E**) median DoR in patients with DLBCL in dose groups ≥120 µg/kg, (**F**) median PFS in patients with DLBCL, (**G**) median OS in patients with DLBCL and (efficacy analysis set).

ORR was higher for patients who responded to their last line of treatment compared with those who were refractory: 69.2% and 32.4%, respectively. However, 10 of 26 patients with relapsed disease (38.5%) and nine of 34 (26.5%) patients with refractory disease had a CR to loncastuximab tesirine (Supplementary Table S2). Only one of six (16.7%) patients with bulky disease responded to loncastuximab tesirine.

Table 5. Summary of Loncastuximab tesirine pharmacokinetic parameters in serum following intravenous administration of 150 μg/kg dose once every 3 weeks

Cycle	Analyte	C_{max} (μg/L)	AUC (μg*day/L)	$t_{1/2}$ (day)	CL (L/day)	V_{ss} (L)	AI
1	PBD-conj. Ab	2995 (55%)	15,245 (103%)	7.15 (88%)	0.75 (105%)	7.19 (39%)	nc
	Total Ab	3685 (60%)	20,327 (111%)	9.07 (113%)	0.64 (120%)	7.43 (43%)	nc
	SG3199	0.04 (–)	—	—	—	—	nc
2	PBD-conj. Ab	3155 (53%)	22,823 (67%)	12.5 (75%)	0.50 (70%)	8.34 (46%)	1.57 (28%)
	Total Ab	3450 (27%)	24,333 (73%)	13.1 (91%)	0.54 (77%)	9.68 (40%)	1.65 (36%)
	SG3199	—	—	—	—	—	—

NOTE: Data shown as geometric mean (geometric CV%). For cycle 2, AUC denoted by AUC extrapolated to infinity for cycle 1 and AUC_{tau} for cycle 2 where tau is the duration of the dosage interval.

Abbreviations: AI, accumulation index; C_{max}, observed maximum concentration; CL, steady-state clearance; h, hour; L, liter; nc, not calculated; tau, duration of dosage interval; $t_{1/2}$, apparent half-life; μg, microgram; V_{ss}, steady-state volume of distribution; "—", value not available.

Patients with MCL/FL. All nine enrolled patients with MCL were evaluable for efficacy. Responses were seen in four of nine (44.4%) patients with MCL; of these, three of nine (33.3%) and one of nine (11.1%) patients achieved a CR and PR, respectively. The median DoR in patients with MCL was 5.3 months. The median PFS for patients with MCL was 4.8 months and the median OS was not reached.

All eight patients classified with FL were evaluable for efficacy. A response was seen in seven of eight (87.5%) patients with FL; of these, six of eight (75%) and one of eight (12.5%) patients achieved a CR and PR, respectively. Median DoR, PFS and OS in patients with FL were not reached (data not shown).

Pharmacokinetic profile

PK parameters were available to be calculated from 85 patients each for PBD-conjugated antibody (Ab) and total Ab, and from 10 patients for SG3199 unconjugated warhead, spanning a loncastuximab tesirine dosing range of 15 to 200 μg/kg administered every 3 weeks. For PBD-conjugated antibody and total Ab, exposure increased with increasing dose. Following the 150 μg/kg dose (Table 5), PBD-conjugated antibody mean C_{max} increased from 2,995 during cycle 1 to 3,155 μg/L by cycle 2, AUC increased from 15,245 to 22,823 μg·day/L, and clearance decreased from 0.75 to 0.50 L/day. Interpatient variability was marked. The mean half-life for the PBD-conjugated antibody was 7.2 days during cycle 1, and 12.5 days during cycle 2, indicating that at least moderate (~60%) accumulation, compared with cycle 1, may be expected with multiple cycles of treatment. The apparent volume of distribution was modestly higher than the total blood volume. As expected, exposure to total antibody was nominally higher than the PBD-conjugated form, which is attributable to the relatively long half-life of total antibody. For the SG3199 unconjugated moiety, the levels for most patients and time points were below the limit of quantification (25 ng/L). Limited PK parameters were calculated for the 10 patients for whom SG3199 was quantifiable, with no accumulation observed from cycle to cycle, and a relatively short mean half-life of approximately 21 hours during cycle 1 in two patients treated at 200 μg/kg.

For ADA, 504 observations were available from 88 patients. With the exception of two patients, all observations were found to be negative for the presence of ADAs or ADA induction. For the two patients exhibiting a low level (<3×) confirmed positive titer, both also exhibited a positive ADA titer at baseline, and the ADA titer resolved to baseline before the end of treatment for both patients.

Discussion

Loncastuximab tesirine is a novel ADC, targeting CD19 and delivering PBD dimers to CD19 expressing cells (13). CD19 has rapid internalization upon binding and is not shed into the circulation, making it a desirable target for ADCs. The PBD warhead is more potent than tubulin inhibitors commonly utilized in ADCs and avoids cumulative peripheral neuropathy (18–20).

The toxicity of loncastuximab tesirine appears to be secondary to the PBD component as similar toxicities have been observed in other studies using PBDs as the cytoxin (21–25). In particular, third-spacing of fluids manifesting as peripheral edema, pleural and pericardial effusions, and ascites were prominent for some patients and generally occurred after several cycles rather than immediately on treatment. The mechanism of this toxicity is not precisely clear but may be related to vascular injury. Loop diuretics were not effective in mitigating the edema. Future trials will incorporate dexamethasone as a premedication and recommend spironolactone for management. Fatigue and rash were also common. The rash was most pronounced in sun-exposed areas. Patient education to avoid direct sun exposure was the most helpful strategy for mitigating this toxicity and in future trials more stringent recommendations on sun exposure should reduce these events further. Another common toxicity was an asymptomatic increase in GGT. Myelosuppression was modest, although there was a dose-response relationship as the frequency and severity were most pronounced at the 200 μg/kg dose. The most common grade ≥3 TEAEs were typical in this patient population (e.g., hematological abnormalities, fatigue) or were expected with this drug and generally reversible and manageable with dose delays/reductions. The MTD was not established during the trial due to the low level of DLTs, but accumulating toxicity at the 200 μg/kg dose supported the choice of the 150 μg/kg dose for expansion and phase 2.

Data from PK analysis indicated that exposure to PBD-conjugated antibody increased with dose and was sustained throughout the duration of every 3 weeks dosage interval. Given the PBD-conjugated antibody half-life by cycle 2 of 12.5 days, drug accumulation for subsequent cycles is likely modestly higher than 60%. The ability to characterize the disposition for SG3199 unconjugated warhead was somewhat limited, as most patients receiving the 150 μg/kg dose had levels below the limit of quantification. The relatively short half-life of SG3199 suggests that any premature release in the circulation would not result in accumulation of SG3199 to levels that cause systemic toxicity (15), and no accumulation is apparent with treatment at 150 μ/kg to steady state on the Q3W regimen. Moreover, no significant accumulation of SG3199 was observed in preclinical

animal models (13). Loncastuximab tesirine showed typical IgG1 kinetics and excellent stability *in vivo* in rat and cynomolgus monkeys (13). Induction of immunogenicity from loncastuximab tesirine appears to be minimal.

The activity of loncastuximab tesirine in this phase I study was sufficiently promising to warrant phase II trials. At dose levels above 120 μg/kg, 55% of patients with DLBCL exhibited objective responses, with durable responses observed in patients achieving CR. The response rate of 55% is noteworthy in this population and CRs were observed in the subset of patients with refractory disease (defined as best response of SD or PD to last line of therapy), where outcomes are particularly poor. Other novel single agents under investigation for DLBCL generally have response rates below 50% and a short duration of survival (26). High response rates were also observed in FL and in MCL, although the patient numbers are small, and more experience is needed in these subtypes. The DoR was highest at the 150 μg/kg dose. The occurrence of DLTs, as defined in the protocol, were low and therefore the MTD could not be determined. However, accumulating toxicity was apparent at the 200 μg/kg dose and the 150 μg/kg dose was recommended as initial dosing for phase II studies. Most patients could tolerate at least two cycles at this dose. The median number of cycles delivered in this study was 3. To improve the tolerability of the regimen and the ability to administer repeated doses, future trials will explore a reduced dose beginning with cycle 3. The dose-expansion portion of this study has completed enrollment, and a phase II study (NCT03589469) in R/R DLBCL has been initiated.

There is growing interest in combining ADCs with other therapies to improve efficacy, and several studies are evaluating ADCs in combination therapy with immunomodulatory agents (e.g., lenalidomide), conventional chemotherapy (e.g., bendamustine), and/or monoclonal antibodies (e.g., rituximab) for the treatment of R/R DLBCL. The combination of polatuzumab vedotin with bendamustine and rituximab (P + BR) recently received accelerated approval from the FDA for the treatment of R/R DLBCL after at least two prior therapies. This approval was based on promising results from the GO29365 trial, which reported an ORR of 63% (CR = 40%) for the combination compared with 25% (CR = 18%) for BR alone; median OS was 11.8 months compared with 4.7 months (27, 28). Polatuzumab vedotin is associated with a high incidence of peripheral neuropathy, and patients with grade $\geq$2 peripheral neuropathy were excluded from the study of P-BR versus BR. Dose reductions, dose interruptions, and permanent discontinuation of treatment were required for 18%, 51%, and 31% of patients treated with P-BR, respectively, suggesting that tolerability may be an issue with prolonged exposure. Another combination in development for R/R DLBCL, tafasitamab (MOR208) and lenalidomide, had an ORR rate of 58% (CR = 33%) and median PFS of 16.2 months in patients who had received one to three prior therapies in the L-MIND trial (29, 30). Although these results are promising, the lack of a control arm in the L-MIND trial makes it difficult to determine the contribution of tafasitamab to the regimen.

Activity of loncastuximab tesirine monotherapy in part 1 of this study was encouraging compared with these combination trials, considering the heavily pretreated population. It has a different adverse event profile, which may make it more suitable for patients with certain comorbid conditions such as underlying peripheral neuropathy. Moreover, the efficacy of loncatuximab tesrine in combination with other treatments is being explored in two ongoing trials of loncastuximab tesirine in combination with ibrutinib in DLBCL and mantle cell lymphoma (NCT03684694) and loncastuximab tesirine in combination with durvalumab in DLBCL, mantle cell lymphoma or follicular lymphoma (NCT03685344).

If the activity of loncastuximab tesirine can be confirmed in phase II studies, it could prove valuable as an "off the shelf" therapeutic, serving as effective palliative therapy for individuals with incurable lymphomas or as bridging therapy to ASCT or CAR-T therapy.

Disclosure of Potential Conflicts of Interest

B. Kahl is an employee/paid consultant for ADCT, Seattle Genetics, Roche, Celgene, and Morphosys, and reports receiving commercial research grants from ADCT, Genentech, and Celgene. M. Homadani is an employee/paid consultant for ADC Therapeutics, Incyte, and Pharmacyclics; reports receiving commercial research grants from Spectrum; and reports receiving speakers bureau honoraria from Celgene and Sanofi. J.A. Radford reports receiving speakers bureau honoraria from Takeda and ADC Therapeutics, and has immediate family members who hold ownership interest (including patents) in GlaxoSmithKline and AstraZeneca. C. Carlo-Stella is an employee/paid consultant for Boehringer Ingelheim and Sanofi; reports receiving commercial research grants from ADCT and Rhizen Pharmaceuticals; and is an unpaid consultant/advisory board member for ADCT, Sanofi, Servier, Roche, Geneta Science, Novartis, Bristol-Myers Squibb, MSD, and Janssen. P.F. Caimi is an employee/paid consultant for Kite Pharmaceuticals and Genentech; reports receiving commercial research grants from Genentech; and reports receiving speakers bureau honoraria from Celgene. J.M. Feingold is an employee/paid consultant for ADC Therapeutics. K.M. Ardeshna is an unpaid consultant/advisory board member for ADCT Therapeutics. D. Ungar is an employee/paid consultant for ADC Therapeutics. S. He is an employee/paid consultant for ADC Therapeutics. J.P. Boni is an employee/paid consultant for and holds ownership interest (including patents) in ADC Therapeutics. K.E.G. Havenith is an employee/paid consultant for ADC Therapeutics (UK). No potential conflicts of interest were disclosed by the other authors.

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