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Final Results of a Phase 1 Study of Loncastuximab Tesirine in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma

Tracking no: BLD-2020-007512R1

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Abstract:
The prognosis for patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) remains poor, with a need for alternatives to current salvage therapies. Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin. Presented here are final results of a Phase 1 dose-escalation and dose-expansion study in patients with R/R B-NHL. Objectives were to determine the maximum tolerated dose (MTD) and recommended dose(s) for expansion and to evaluate safety, clinical activity, pharmacokinetics, and immunogenicity of loncastuximab tesirine. Overall, 183 patients received loncastuximab tesirine, with 3+3 dose escalation at 15–200 µg/kg and dose expansion at 120 and 150 µg/kg. Dose-limiting toxicities (all hematologic) were reported in 4 patients. The MTD was not reached, although cumulative toxicity was higher at 200 µg/kg. Hematologic treatment-emergent adverse events were most common, followed by fatigue, nausea, edema, and liver enzyme abnormalities. Overall response rate (ORR) in evaluable patients was 45.6%, including 26.7% complete responses (CR). ORRs in patients with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, and follicular lymphoma were 42.3%, 46.7%, and 78.6%, respectively. Median duration of response in all patients was 5.4 months and not reached in patients with DLBCL (doses ≥120 µg/kg) who achieved CR. Loncastuximab tesirine had good stability in serum, notable anti-tumor activity, and an acceptable safety profile, warranting continued study in B-NHL. The recommended dose for Phase 2 was determined as 150 µg/kg every 3 weeks (Q3W) for 2 doses followed by 75 µg/kg Q3W. Study: NCT02669017.

Conflict of interest: COI declared - see note

COI notes: M. Hamadani has received research support from Takeda Pharmaceutical Company; Spectrum Pharmaceuticals; Astellas Pharma. Consultancy: Janssen R&D; Incyte Corporation; ADC Therapeutics; Celgene Corporation; Pharmacyclics, Omeros, AbGenomics, Verastem, TeneoBio. Speaker's Bureau: Sanofi Genzyme, AstraZeneca. J. Radford has acted in a consultant/advisory role for Takeda, ADC Therapeutics, Bristol Myers Squibb, Novartis, and Kite Pharma; as a speaker for Takeda, ADC Therapeutics, and Seattle Genetics; received research funding from Takeda; provided expert testimony for Takeda and ADC Therapeutics; and holds stocks/shares in AstraZeneca and GlaxoSmithKline (spouse). C. Carlo-Stella has received research support from ADC Therapeutics and Rhizen Pharmaceuticals; has served as consultant or advisor for Servier, Novartis, Genenta Science srl, ADC Therapeutics, Roche, Boehringer Ingelheim, and Sanofi; and has received honoraria for speaker engagements from Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen Oncology, AstraZeneca. P. F. Caimi, E. Reid, O. A. O'Connor, and M. Solh have received research support from ADC Therapeutics. K. M. Ardeshna is supported by the University College London (UCL)/UCL Hospitals (UCLH) Biomedical Research Unit and has received honoraria or attended advisory boards for Celgene, Gilead, Takeda, Roche and Beigene. W. Townsend has received research support from ADC Therapeutics and honoraria from Roche and Gilead. L. T. Heffner has received institutional research funding from Pharmacyclics, Genentech, Kite, and ADC Therapeutics, and honorarium from Kite. B. S. Kahl has received research support from ADC Therapeutics and acted as a consultant for Seattle Genetics and Genentech. J. M. Feingold, D. Ungar, L. Wang, J. Boni, K. Havenith, and Y. Qin are employees of ADC Therapeutics with stock options.

Preprint server: No;

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Author contributions and disclosures: M.H., J.R., C.C.-S., P.C., E.R., O.A.O., K.M.A., W.T., M.S., L.T.H. and B.K. were involved in designing the study and data acquisition. J.M.F., D.U., J.B. and Y.Q. were involved in designing the study. K.H. and L.W. were involved in collecting and assembling the study data. All authors were involved in data analysis and interpretation. All authors named in the manuscript meet the International Committee of Medical Journal Editors criteria for authorship, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval of the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis

Non-author contributions and disclosures: Yes; Editorial assistance was provided by Becky Salisbury, PhD and Louise Gildea, PhD at Fishawack Communications Ltd, funded by ADC Therapeutics.

Agreement to Share Publication-Related Data and Data Sharing Statement: For original data, please contact clinical.trials@adctherapeutics.com.

Clinical trial registration information (if any): https://clinicaltrials.gov/ct2/show/NCT02669017

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Short running title: Loncastuximab tesirine in B-cell NHL

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Word count:

- Abstract: 250
- Body text: 3999

Figure/table count: 4 tables, 4 (multipanel) figures

Reference count: 35

Chosen scientific categories: Clinical Trials and Observations; Lymphoid Neoplasia

Key points

- Loncastuximab tesirine demonstrated manageable safety and notable anti-tumor activity in relapsed/refractory B-cell non-Hodgkin lymphoma
- A Phase 2 study employing a dosing regimen based on cumulative safety, PK, and efficacy data from this study has been conducted

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Abstract

The prognosis for patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) remains poor, with a need for alternatives to current salvage therapies. Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin. Presented here are final results of a Phase 1 dose-escalation and dose-expansion study in patients with R/R B-NHL. Objectives were to determine the maximum tolerated dose (MTD) and recommended dose(s) for expansion and to evaluate safety, clinical activity, pharmacokinetics, and immunogenicity of loncastuximab tesirine. Overall, 183 patients received loncastuximab tesirine, with 3+3 dose escalation at 15–200 µg/kg and dose expansion at 120 and 150 µg/kg. Dose-limiting toxicities (all hematologic) were reported in 4 patients. The MTD was not reached, although cumulative toxicity was higher at 200 µg/kg. Hematologic treatment-emergent adverse events were most common, followed by fatigue, nausea, edema, and liver enzyme abnormalities. Overall response rate (ORR) in evaluable patients was 45.6%, including 26.7% complete responses (CR). ORRs in patients with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, and follicular lymphoma were 42.3%, 46.7%, and 78.6%, respectively. Median duration of response in all patients was 5.4 months and not reached in patients with DLBCL (doses ≥120 µg/kg) who achieved CR. Loncastuximab tesirine had good stability in serum, notable anti-tumor activity, and an acceptable safety profile, warranting continued study in B-NHL. The recommended dose for Phase 2 was determined as 150 µg/kg every 3 weeks (Q3W) for 2 doses followed by 75 µg/kg Q3W. Study: NCT02669017.

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Introduction

B-cell non-Hodgkin lymphomas (B-NHL) include both aggressive types, most commonly diffuse large B-cell lymphoma (DLBCL), and indolent types, most commonly follicular lymphoma (FL).[1-4] Approximately 60% of patients with DLBCL can be cured with first-line chemoimmunotherapies.[5,6] Options for patients with relapsed or refractory (R/R) DLBCL include salvage chemotherapy with autologous hematopoietic cell transplantation (auto-HCT) or chimeric antigen receptor T-cell (CAR-T) therapy.[7] However, outcomes with salvage therapy for patients who are refractory to treatment or relapse remain poor,[8] highlighting the need for new therapeutic options. Indolent forms of B-NHL, such as FL, generally respond to treatment but are infrequently curable, and patients with early relapse have particularly poor outcomes.[3] Novel approaches, such as antibody-based treatments, immune checkpoint inhibitors and small molecule inhibitors, could improve outcomes for those with R/R B-NHL, and/or reduce toxicities seen with standard treatments.[2]

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) comprising a humanized anti-CD19 monoclonal antibody stochastically conjugated through a cathepsin-cleavable valine-alanine linker to a pyrrolobenzodiazepine (PBD) dimer toxin, SG3199.[9] CD19 is a suitable target for immunotherapy of B-NHL as it is normally expressed during B-cell development, but only after B-lineage commitment and thus not on hematopoietic stem cells,[10,11] and CD19 expression is lost during terminal plasma cell differentiation but maintained in hematologic B-cell malignancies.[10-12]

PBD dimers are sequence-selective, non-distorting, and potent cytotoxic DNA crosslinking agents.[13-15] The inter-strand crosslinks formed between DNA in the minor groove and PBD are relatively non-distorting of the DNA structure, preventing detection by repair mechanisms and appearing to contribute to the persistence and potent biological activity of PBD in cells.[15,16] Preclinically, loncastuximab tesirine showed highly targeted anti-tumor effects in vitro and in vivo with DNA-PBD crosslinks persisting for up to 36 hours.[9]

Data from the dose-escalation part (Part 1) of the first-in-human study of loncastuximab tesirine in adults with R/R B-NHL demonstrated promising single-agent activity and acceptable safety in patients with R/R B-NHL.[17] Here, we report results for the full study population in Part 1 and Part 2 (dose expansion).

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Methods

Patients

Adults (≥18 years) with histologically-confirmed R/R B-NHL (WHO, 2008[18]) who had failed or were intolerant to established therapy or for whom no other treatment options were available in the opinion of the investigator, were eligible to participate. Inclusion and exclusion criteria are presented in **Supplemental Information**.

The clinical study was performed per the International Council for Harmonization good clinical practice guidelines and the ethical principles of the Declaration of Helsinki, and was approved by each institutional review board. All patients provided written informed consent.

Study Design and Treatment

This Phase 1, open-label 2-part (dose escalation [Part 1] and dose expansion [Part 2]) study of loncastuximab tesirine monotherapy was conducted in patients with R/R B-NHL at 11 centers in 3 countries (US, UK, Italy; enrollment 9 March 2016–8 May 2018; NCT02669017). Primary objectives of Part 1 were to evaluate safety and tolerability of loncastuximab tesirine in R/R B-NHL and to determine the maximum tolerated dose (MTD) and recommended dose(s) for expansion (Part 2). Primary objectives for Part 2 were to evaluate safety and tolerability at the recommended dose(s). Secondary objectives included evaluation of anti-tumor activity, characterization of exposure to total antibody, PBD-conjugated antibody, and free warhead at different doses and cycles using standard PK parameters, and evaluation of induction of anti-drug antibodies (ADA) to loncastuximab tesirine. Exploratory assessments included evaluation of changes in peripheral white blood cell (WBC) counts and CD markers, and correlations between baseline CD19 levels in archival tumor tissue and the PK and clinical activity of loncastuximab tesirine.

Loncastuximab tesirine was given by intravenous infusion over 60 minutes once every 3 weeks (Q3W; Day 1 of each 21-day cycle). In Part 1, patients were assigned to doses using a 3+3 dose-escalation design (starting dose 15 μg/kg Q3W), overseen by a Dose Escalation Steering Committee (DESC). No intra-patient dose escalation was permitted. In Part 2, patients were assigned to recommended dose level(s) and regimen(s) of loncastuximab tesirine identified in Part 1, based on safety, efficacy, and PK data, with ongoing DESC-directed enrollment to enable evaluation of different dosing regimens for doses identified for further evaluation in Part 1. No formal sample size justification was performed as the primary objective was to evaluate safety. Treatment administration is described in **Supplemental Information**.

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Dose-limiting toxicities (DLT) were as defined in the **Supplemental Information** during Cycle 1 in Part 1 (DLT observation period), except when events were clearly due to underlying disease or extraneous causes. Based on the 3+3 design, the MTD was the highest dose level at which 0 of the first 3 patients treated, or ≤1 of the first 6 patients treated, had a DLT during Cycle 1 of Part 1.

Patients received loncastuximab tesirine until disease progression, unacceptable toxicity, initiation of new anti-cancer treatment, or withdrawal from the study. Patients who discontinued treatment for a reason other than progressive disease (PD) were followed every 12 weeks until PD or initiation of new anti-cancer treatment, and survival was followed for ≤12 months after last dose of study drug.

Assessments

Safety assessments included adverse events (AEs), serious AEs, DLTs, periodic 12-lead electrocardiograms, physical examinations, vital signs, Eastern Cooperative Oncology Group performance status, and laboratory tests (hematology, coagulation panel, biochemistry, pregnancy testing [women of childbearing potential], and urinalysis). AEs were classified using the Medical Dictionary for Regulatory Activities, v22.0. Treatment-emergent AEs (TEAEs) were defined as AEs that began or worsened during or after the first dose of study drug until 12 weeks post last dose, or the initiation of new anti-cancer treatment. TEAEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

Anti-tumor activity measures were overall response rate (ORR), duration of response (DOR), overall survival (OS), and progression-free survival (PFS). Disease assessments occurred every other cycle for the first 2 evaluations (6 weeks [end of Cycle 2±1 week]; 12 weeks [end of Cycle 4±1 week]), then every third cycle (end of Cycle 7, 10, etc.) until PD, or more frequently if indicated clinically, according to local site imaging requirements (positron emission tomography-computed tomography [PET-CT] or CT), with the same method used for all assessments in each patient. Investigators classified patients' response to treatment as complete response (CR), partial response (PR), stable disease, or PD (Lugano Classification, 2014).[19]

Blood samples for PK analysis were collected per **Supplemental Table 1**. Blood samples for ADA analysis were collected on Days 1 (pre-infusion) and 21 of each cycle, end of treatment, and during follow-up. Validated bioanalytical methods were used to determine standard PK parameters for loncastuximab tesirine total antibody, PBD-conjugated antibody, and free warhead SG3199, and to determine ADAs to loncastuximab tesirine. Exploratory

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assessments included immunohistochemistry of archival/pre-treatment tumor samples for CD19 protein expression and flow cytometry for peripheral WBC changes.

Statistical Analysis

Safety was analyzed in patients who received study drug, and DLTs in all patients who completed at least 1 cycle in Part 1, or who discontinued before cycle end but had complete DLT information. Evaluation set descriptions are provided in **Supplemental Information**.

Descriptive statistics and data were used to report endpoints. Data are reported for each patient's starting dose of loncastuximab tesirine. DOR, PFS, and OS were estimated using Kaplan–Meier methods with censoring. Efficacy endpoints were analyzed in all patients with B-NHL, and by histology. ORR was also analyzed by predefined subgroups. Non-compartmental analysis was used to determine PK parameters. Population PK modeling used serum concentrations of PBD-conjugated antibody to obtain individual patient metrics of drug exposure. Relationships between exposure and TEAEs were analyzed and binomial logistic regression performed to predict probability of events for a given degree of exposure where event severity had an apparent relationship with drug exposure (**Supplemental Information**). Relationships between CD19 expression in pre-treatment/archival tumor tissue samples and exposure to PBD-conjugated antibody in Cycle 1 and correlations between PK exposure and peripheral CD19+ B cells were evaluated using linear regression analysis.

Data Sharing Statement

Study design is available at clinicaltrials.gov: NCT02669017. For original data, contact clinical.trials@adctherapeutics.com.

Results

Patient Disposition and Characteristics

In total, 183 patients received loncastuximab tesirine. In Part 1, 88 patients were treated with doses of 15–200 µg/kg Q3W (15, 30 or 60 µg/kg: n=4 each; 90 µg/kg: n=5; 120 µg/kg: n=16; 150 µg/kg: n=19; 200 µg/kg: n=36). Cumulative toxicity observed at 200 µg/kg Q3W led to a protocol amendment, with 22 patients assigned 200 µg/kg receiving loncastuximab tesirine every 6 weeks (Q6W) during Part 1.

Based on an increase in cumulative toxicities at 200 µg/kg and evidence of activity at 120 and 150 µg/kg during Part 1, 120 µg/kg Q3W and 150 µg/kg Q3W doses were selected for Part 2, with some patients in the 150 µg/kg group reducing their dose to 75 µg/kg Q3W after

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3 cycles. In Part 2, 26 patients received loncastuximab tesirine 120 µg/kg (Parts 1 + 2: n=42) and 69 patients received 150 µg/kg (Parts 1 + 2: n=88). Patient disposition is shown in **Figure 1**. The most common reason for treatment discontinuation was disease progression (83/183; 45.4%); the most common reason for study discontinuation was death (111/183; 60.7%).

Baseline characteristics for all patients and those with DLBCL are presented in **Table 1**; most patients had DLBCL (139/183; 76.0%), 15 (8.2%) had mantle cell lymphoma (MCL), 14 (7.7%) had FL, and 15 (8.2%) had B-NHL of other histologies. Patients had received a median of 3 prior lines of systemic therapy (range 1–13); 42 (23%) had received prior HCT and 3 (1.6%) had received prior CAR-T therapy. Forty-three patients (23.5%) were primary refractory and 109 (59.6%) were refractory to their most recent systemic therapy.

Safety

Safety and DLT analysis sets comprised 183 and 73 patients, respectively. Patients received a median of 2 doses (range 1–24) of loncastuximab tesirine, with a median weight-adjusted dose per cycle of 129.9 µg/kg (range 14.6–204.4) for a median duration of 64 days (range 22–532).

Four patients experienced DLTs during Part 1: Grade 4 thrombocytopenia in 1 patient receiving 120 µg/kg (1/16), Grade 3 febrile neutropenia in 1 patient receiving 150 µg/kg (1/16), and Grade 4 thrombocytopenia in 2 patients receiving 200 µg/kg (2/25). The MTD was not reached.

In the safety analysis set, 181 patients (98.9%) had at least 1 TEAE. TEAEs (≥10% of patients; **Table 2**) were consistent with those reported previously for loncastuximab tesirine.[17] Hematologic TEAEs were common, including platelet count decreased, neutrophil count decreased (both based on laboratory abnormality reporting), and anemia. Fatigue was the most common non-hematological TEAE (78/183; 42.6%), followed by nausea (59/183; 32.2%), peripheral edema (58/183; 31.7%), and gamma-glutamyltransferase (GGT) increased (57/183; 31.1%). Accumulating toxicity was apparent with loncastuximab tesirine 200 µg/kg, with many TEAEs more common in the 200 µg/kg group than lower dose groups, including hematological abnormalities, peripheral edema, and liver test abnormalities (**Table 2**).

Laboratory values for platelet, neutrophil, and GGT levels are presented in **Supplemental Figure 2**. Generally, platelet counts followed a pattern of decrease and recovery, which was most pronounced at 200 µg/kg, with limited partial platelet recovery reflective of

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accumulating toxicity at this dose. Grade 3/4 platelet count decreases were most common during the first 2 cycles; patients with prolonged events had treatment withdrawn. Neutrophil counts decreased from baseline to Cycle 1, Day 15; further decreases were not apparent except for slight decreases at 90 µg/kg up to Cycle 3, Day 1. GGT levels appeared to increase over time, particularly at higher doses.

Skin- or nail-related toxicities were reported in 98 (53.6%) patients (most commonly rash [45/183; 24.6%], erythema [21/183; 11.5%], pruritus [20/183; 10.9%], and maculopapular rash [19/183; 10.4%]) and were generally mild-to-moderate and reversible but were sometimes prolonged. Rash was most common in sun-exposed areas and most affected patients continued treatment as planned; a minority were managed with dose delays (1.6% each of patients with rash and maculopapular rash) and 2 patients (1.1%) discontinued treatment. Edema or effusion were reported in 86 (47.0%) patients, including peripheral edema in 58 (31.7%) patients and pleural effusion in 39 (21.3%). These events generally occurred after at least 2 cycles. Most patients continued treatment, though some required dose delays. Introducing dexamethasone premedication reduced incidence of edema or effusion in Part 2 (120 µg/kg: 34.6%; 150 µg/kg: 47.8%) versus Part 1 (120 µg/kg: 68.8%; 150 µg/kg: 63.2%). One patient who received loncastuximab tesirine 120 µg/kg had a Grade 2 infusion-related reaction during Cycle 1, Day 1 in Part 2 that resolved on the same day; dosing was not modified, and the patient received 8 further cycles of loncastuximab tesirine.

Grade ≥3 TEAEs (≥5% of all patients) are shown in **Table 3**. Grade ≥3 TEAEs were reported in 141 (77%) patients, most commonly hematologic or liver test abnormalities, and hypokalemia. Consistent with the overall pattern of TEAEs, several Grade ≥3 TEAEs were more common with loncastuximab tesirine 200 µg/kg than lower doses, including GGT increased, neutrophil count decreased, and platelet count decreased.

At least 1 serious TEAE was reported in 85 (46.4%) patients. Excluding disease progression, the most common serious TEAEs were febrile neutropenia (10/183; 5.5%), pyrexia and pleural effusion (7/183; 3.8% each), dyspnea (6/183; 3.3%), sepsis (5/183; 2.7%), and abdominal pain (4/183; 2.2%). Thirty-five (19.1%) patients had TEAEs with a fatal outcome during the study, most commonly (20/35) due to progression of underlying B-NHL; 6 were considered treatment-related, all of which were infections. The pattern of TEAEs among patients with DLBCL was generally similar to that in all patients.

Dose delays of ≤21 days could be used to manage toxicities per protocol, and 68 (37.2%) patients had dose delays due to TEAEs, most commonly (≥5% of patients) GGT increased (19/183; 10.4%) and neutropenia (10/183; 5.5%). Eleven (6.0%) patients had dose

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reductions due to TEAEs and 35 (19.1%) patients had TEAEs leading to treatment discontinuation, most commonly due to GGT increase (7 [3.8%] patients), followed by thrombocytopenia (5 [2.7%] patients). Few patients with DLBCL (<15%, all doses) had dose modifications (treatment discontinuation, delay or dose reduction) during the first 2 cycles. The probability of a dose modification increased to ~30% and ~50% at the third and fourth dose, respectively.

Anti-tumor Activity

ORR in all patients with B-NHL (180 evaluable) was 45.6% (95% CI 38.1, 53.1), including 48 (26.7%) CRs and 34 (18.9%) PRs.

ORR by histology (**Table 4**) was 42.3% (95% CI 33.9, 51.1) in patients with DLBCL (137 evaluable), 46.7% (95% CI 21.3, 73.4) in patients with MCL (15 evaluable), and 78.6% (95% CI 49.2, 95.3) in patients with FL (14 evaluable). ORR by loncastuximab tesirine dose is shown in **Supplemental Table 2**: ORR for 15–90 µg/kg doses was 29.4% compared with 47.2% for 120–200 µg/kg doses.

Median time to tumor response for all patients with B-NHL who achieved CR or PR was 43.0 days (range 31–323); best percent change from baseline in tumor size is shown by dose and histology in **Figure 2**.

Median DOR with loncastuximab tesirine in all patients with B-NHL was 5.4 months (95% CI 4.0, not reached); it was 4.5 months (95% CI 3.9, 9.5) in patients with DLBCL and not reached in patients with MCL or FL (**Figure 3A**). Similar DORs were achieved in patients with DLBCL receiving 120 µg/kg, 150 µg/kg, and 200 µg/kg doses (**Figure 3B)**. Median DOR was not reached in patients with DLBCL (doses ≥120 µg/kg) who achieved CR (**Figure 3C**).

Median PFS was 3.1 months (95% CI 2.7, 4.2) in all patients with B-NHL, 2.8 months (95% CI 1.9, 3.8) in patients with DLBCL, 4.8 months (95% CI 1.1, 7.8) in patients with MCL, and could not be determined in those with FL due to the low number of events (**Figure 3D**). Median OS was 8.3 months (95% CI 6.7, 10.7) in all patients with B-NHL, 7.5 months (95% CI 6.0, 9.8) in patients with DLBCL, and was not reached in patients with MCL or FL due to low number of events (**Figure 3E**).

A total of 96 (52.5%) patients received subsequent anti-cancer treatment after receiving loncastuximab tesirine, most commonly systemic therapy (n=66), radiotherapy (n=13), and HCT (n=12). One patient had subsequent CAR-T therapy (n=1).

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ORRs for subgroups of patients with DLBCL with high-risk characteristics (**Supplemental Table 3**) were noteworthy in patients ≥75 years-old (55.6%) and responses were observed in other difficult-to-treat populations, including patients refractory to first- or last-line therapy (23.3% and 35.8%, respectively) and those with double- or triple-hit lymphoma (21.7%).

Pharmacokinetics

The numbers of patients with sufficient data for PK analysis of PBD-conjugated antibody, total antibody, and free warhead SG3199 were 161, 160, and 37, respectively, across all Q3W dosing regimens. PK of loncastuximab tesirine administered Q3W during Cycle 1 and Cycle 2 are shown in **Supplemental Tables 4** and **5**. PK exposure similarity between loncastuximab tesirine total antibody and PBD-conjugated antibody indicated good stability in serum. Generally, exposure (area under the concentration-time curve [AUC] and maximum observed concentration [C_{max}]) to loncastuximab tesirine was dose-related and higher in Cycle 2 than Cycle 1. As may be expected due to differing CD19 levels between patients, there was substantial variability in PK exposure and PK parameters assessed for PBD-conjugated antibody, total antibody, and SG3199. At 150 µg/kg, the mean half-life of PBD-conjugated antibody increased from 4.46 days in Cycle 1 to 9.77 days in Cycle 2, indicating likely moderate accumulation with multiple Q3W treatment cycles. As expected, accumulation by Cycle 2 for patients on a Q6W dosing regimen was lower than that of those on Q3W dosing: mean accumulation of 1.22 and 1.33 for PBD-conjugated antibody and total antibody on Q6W regimens compared with 1.72 and 1.74 on Q3W regimens.

Exposure-response modeling of the relationship between PBD-conjugated antibody exposure and TEAEs for 139 patients with available data (**Supplemental Table 6; Equation 1**) showed a higher probability of Grade ≥3 edema and liver enzyme abnormalities in the 200 µg/kg compared with 150 µg/kg dose cohorts, with smaller comparative differences in probability of these events seen with 120 µg/kg compared with 150 µg/kg.

Immunogenicity

Of 183 patients tested for ADAs, 5 exhibited confirmed-positive ADAs pre-dose with low $\log_2$ titers (≤3), and 1 exhibited confirmed-positive ADAs post-dose, with very low $\log_2$ titers (<1), indicating ADA was not induced by loncastuximab tesirine.

Exploratory Analysis

CD19+ tumor cells in tumor tissue ranged from 0 to 99%. No correlation was observed for CD19 expression in tumor tissue with PK exposure, or with clinical response to treatment (**Supplemental Figure 1**). From limited data on peripheral WBC changes (only US patients with ≥2 measurements), preliminary analysis suggests that CD19+ B cells are reduced

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compared with other cells upon treatment with loncastuximab tesirine. Baseline median numbers of peripheral CD19+ B cells/μL in serum were 58.0, 22.0, and 5.0 cells/μL, for 120, 150, and 200 μg/kg doses, respectively. In 13 patients available for analysis who received doses of loncastuximab tesirine >90 μg/kg, median number of peripheral CD19+ B cells/μL in serum was reduced by ~100% 7 days after the second dose, and the reduction was sustained until end-of-treatment. The percentage of peripheral CD19+ B cells significantly correlated with C_{max} and AUC for PBD-conjugated antibody (**Figure 4A and B**). However, no relationship between CD19+ B-cell counts and clinical response was observed.

Discussion

In this Phase 1 study of the ADC loncastuximab tesirine in patients with R/R B-NHL, a dosing regimen associated with reduction of tumor burden and an acceptable safety profile was established for further study. Four patients had DLTs (all hematologic), including 2 who received loncastuximab tesirine 200 μg/kg; the MTD was not reached. TEAEs of hematological abnormalities, peripheral edema, and liver test abnormalities were more common in the 200 μg/kg group than lower dose groups. The safety profile of loncastuximab tesirine was consistent with that previously reported for Part 1,[17] with no additional safety concerns during Part 2. Toxicities were generally reversible and manageable in most patients with dose delays. Toxicities considered likely related to the PBD warhead were common, including edema and effusions, rash, and liver enzyme elevations.[20,21] Incidences of edema and effusion were reduced in Part 2 following introduction of dexamethasone premedication and this approach is being employed to mitigate PBD-related toxicities in further studies of loncastuximab tesirine, together with management with spironolactone. More stringent recommendations on sun exposure are intended to reduce rash.

Tumor burden was assessed, and tumor was found to be responsive to loncastuximab tesirine, with durable responses seen in a proportion of patients with DLBCL, MCL, and FL. Response rates with loncastuximab tesirine were generally lower in subgroups previously reported to have poorer prognosis, such as bulky disease, double-hit, and refractory DLBCL.[2,8,22-25] However, a substantial proportion of patients with high-risk features had encouraging responses to loncastuximab tesirine and characteristics of responders are being further elucidated in Phase 2 studies, including analysis of response in activated B-cell versus germinal center B-cell subtypes, for which there was insufficient information for analysis in this Phase 1 study.

A large proportion of the study population had R/R DLBCL, which is likely reflective of the unmet need for these patients due to lack of approved therapies at time of recruitment,

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together with higher incidence of this subtype. A number of treatments for patients with R/R DLBCL have been approved in recent years, including CAR-T therapies, polatuzumab vedotin-piiq with bendamustine and rituximab, selinexor, and tafasitamab-cxix with lenalidomide; however unmet need remains as these therapies have substantial toxicities and many patients do not have a durable response.[27-30]

Exposure to loncastuximab tesirine increased with dose. The similarity of conjugated and total antibody moieties in serum demonstrates good stability that could minimize systemic non-specific toxicities that can occur with more labile ADCs.

Characterizing the effects of WBC levels on drug exposure provides a fundamental understanding of drug action since B cells bear the cognate target of loncastuximab tesirine. Both C_{max} and AUC for PBD-conjugated antibody were significantly correlated with baseline CD19 expression. These significant relationships may explain, in part, the marked variability of PK exposure, due to differences in baseline CD19 expression between patients. Exploratory analyses of target presence and response suggest target-mediated disposition may contribute to higher clearance, especially at the lower doses tested. The time-dependent component of clearance, which is thought to relate to clearance of CD19-expressing cells, is abrogated or eliminated by 5 cycles (~15 weeks). Notably, there was no relationship between CD19 expression and clinical response to loncastuximab tesirine. Similar results have been reported for CD19- and CD30-directed therapies (tisagenlecleucel and brentuximab vedotin)[31,32] in patients with B-NHL, with no correlation observed between target expression in tumor cells and clinical response. Consequently, determining the percentage of CD19+ tumor cells in tumor types known to express CD19 may have limited prognostic value.

Based on cumulative safety, PK, and efficacy data, the recommended dose of loncastuximab tesirine for Phase 2 is 150 µg/kg Q3W for 2 doses followed by 75 µg/kg Q3W for subsequent doses. The 150 µg/kg dose was selected as a dose with encouraging responses but lower frequency of AEs than observed with the 200 µg/kg dose. Exposure-response modeling also demonstrated a higher probability of Grade ≥3 edema and liver enzyme abnormalities in the 200 µg/kg compared with 150 µg/kg dose cohorts. Smaller comparative differences in predicted probability were apparent between the 120 µg/kg and 150 µg/kg doses. Moderate accumulation of loncastuximab tesirine together with frequent dose delays and 50% dose reductions following prolonged delays required during this study supported a strategy of planned dose reduction of 50% after 2 cycles to mitigate onset of late-developing and difficult-to-manage toxicities, such as edema, which generally developed following ≥2 cycles. Selection of this dosing regimen is further supported by the rapid onset

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of response (median 2 cycles), and it is expected to optimize the frequency of objective response while reducing the need for dose delay or further dose reductions.

As demonstrated in this study, loncastuximab tesirine has substantial single-agent anti-tumor activity and is a promising “off-the-shelf” treatment option with outpatient administration for patients who have failed multiple lines of therapy, including patients failing or unsuitable for HCT or CAR-T therapy,[26] or as a bridge to such treatments. Notably, favorable outcomes have been reported in patients with R/R DLBCL treated with CAR-T therapy after previous loncastuximab tesirine treatment.[26] As such, loncastuximab tesirine is being further investigated as monotherapy and in combination with other therapies.[33-35]

Acknowledgments

The study was supported by ADC Therapeutics. Editorial assistance was provided by Becky Salisbury, PhD and Louise Gildea, PhD at Fishawack Communications Ltd, funded by ADC Therapeutics.

Authorship Contributions

M.H., J.R., C.C.-S., P.C., E.R., O.A.O., K.M.A., W.T., M.S., L.T.H. and B.S.K. were involved in designing the study and data acquisition. J.M.F., D.U., J.B. and Y.Q. were involved in designing the study. K.H. and L.W. were involved in collecting and assembling the study data. All authors were involved in data analysis and interpretation. All authors named in the manuscript meet the International Committee of Medical Journal Editors criteria for authorship, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval of the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Conflicts of Interest Disclosures

M. Hamadani has received research support from Takeda Pharmaceutical Company, Spectrum Pharmaceuticals and Astellas Pharma. Consultancy: Janssen R&D, Incyte Corporation, ADC Therapeutics, Celgene Corporation, Pharmacyclics, Omeros, AbGenomics, Verastem and TeneoBio. Speaker’s Bureau: Sanofi Genzyme and AstraZeneca. J. Radford has acted in a consultant/advisory role for Takeda, ADC Therapeutics, Bristol Myers Squibb, Novartis and Kite Pharma; as a speaker for Takeda, ADC Therapeutics and Seattle Genetics; received research funding from Takeda; provided expert testimony for Takeda and ADC Therapeutics; and holds stocks/shares in AstraZeneca and GlaxoSmithKline (spouse). C. Carlo-Stella has received research support

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from ADC Therapeutics and Rhizen Pharmaceuticals; has served as consultant or advisor for Servier, Novartis, Genenta Science srl, ADC Therapeutics, Roche, Boehringer Ingelheim and Sanofi; and has received honoraria for speaker engagements from Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen Oncology and AstraZeneca. P. F. Caimi, E. Reid, O. A. O'Connor, and M. Solh have received research support from ADC Therapeutics. K. M. Ardeshna is supported by the University College London (UCL)/UCL Hospitals (UCLH) Biomedical Research Unit and has received honoraria or attended advisory boards for Celgene, Gilead, Takeda, Roche and Beigene. W. Townsend has received research support from ADC Therapeutics and honoraria from Roche and Gilead. L. T. Heffner has received institutional research funding from Pharmacyclics, Genentech, Kite, and ADC Therapeutics, and honorarium from Kite. B. S. Kahl has received research support from ADC Therapeutics and acted as a consultant for Seattle Genetics and Genentech. J. M. Feingold, D. Ungar, L. Wang, J. Boni, K. Havenith, and Y. Qin are employees of ADC Therapeutics with stock options.

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Tables

Table 1. Baseline demographics and clinical characteristics of patients with B-NHL who received loncastuximab tesirine (safety analysis set)

Characteristic	All patients with B-NHL N=183	Patients with DLBCL n=139
Sex, n (%)		
Female	69 (37.7)	59 (42.2)
Male	114 (62.3)	80 (57.6)
Median age, years (range)	63.0 (20–87)	63.0 (20–86)
ECOG score, n (%)		
0–1	160 (87.4)	119 (85.6)
2	21 (11.5)	18 (12.9)
3	2 (1.1)	2 (1.4)
B-NHL subtype, n (%)		
DLBCL group[a]		
Double-hit (myc plus bcl-2 and/or bcl-6 rearrangement)		20 (14.4)
Triple-hit (myc plus bcl-2 and bcl-6 rearrangement)		3 (2.2)
Transformed		37 (26.6)
MCL	15 (8.2)	–
FL	14 (7.7)[b]	–
CLL	6 (3.3)	–
Marginal zone B-cell lymphoma	6 (3.3)	–
Burkitt lymphoma	1 (0.5)	–
Waldenström's macroglobulinemia	1 (0.5)	–
Other	1 (0.5)[c]	–
Number of lines of prior systemic therapy, median (range)	3 (1–13)	3 (1–10)
First-line prior systemic therapy response, n (%)		
Relapsed after initial response	115 (62.8)	90 (64.7)
Refractory to first-line therapy	43 (23.5)	30 (21.6)
Last-line prior systemic therapy response, n (%)		
Relapsed after initial response	66 (36.1)	49 (35.3)
Refractory to last therapy line	109 (59.6)	83 (59.7)
Prior hematopoietic cell transplantation, n (%)		
Autologous	31 (16.9)	22 (15.8)
Allogeneic	5 (2.7)	2 (1.4)
Both	4 (2.2)	2 (1.4)
Other[d]	2 (1.1)	1 (0.7)

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Prior CAR-T therapy, n (%)		
Yes	3 (1.6)	2 (1.4)
No	180 (98.4)	137 (98.6)
Serum LDH, U/L, median (range)	323.0 (109, 9348)	-

[a]DLBCL subtypes (n) comprised DLBCL (134); high-grade BCL (2); aggressive BCL with features intermediate between DLBCL and Burkitt lymphoma (1); Mediastinal (thymic large BCL; 1); and primary mediastinal BCL (1). In the DLBCL category, transformed comprised (n) follicular (26), marginal zone B-cell lymphoma (2), lymphoplasmacytic (1), nodular lymphocyte-predominant Hodgkin lymphoma (2), and Richter's transformation (6); [b]one patient with FL also had CLL/SLL recurrence; [c]this patient had a history of DLBCL and was enrolled based on imaging consistent with recurrence. The patient was subsequently biopsied after enrollment and lesion determined to be sarcoid; [d]one patient with DLBCL had a peripheral stem cell harvest transplant and one patient with FL received a double cord transplant.

BCL, B-cell lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Oncology Cooperative Group; FL, follicular lymphoma; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma; U/L, upper/lower

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Table 2. All grade TEAEs reported in ≥10% of patients with B-NHL who received loncastuximab tesirine in order of incidence by system order class (safety analysis set)

TEAE, n (%)	≤90 µg/kg (n=17)	120 µg/kg (n=42)	150 µg/kg (n=88)	200 µg/kg (n=36)	Total (N=183)
Any TEAE	16 (94.1)	42 (100)	87 (98.9)	36 (100)	181 (98.9)
Hematologic TEAEs					
Platelet count decreased[a]	11 (64.7)	28 (68.3)	62 (71.3)	27 (77.1)	128 (71.1)
Neutrophil count decreased[a]	10 (58.8)	21 (51.2)	50 (58.1)	25 (71.4)	106 (59.2)
Anemia	4 (23.5)	10 (23.8)	32 (36.4)	14 (38.9)	60 (32.8)
WBC count decreased	0	7 (16.7)	6 (6.8)	9 (25.0)	22 (12.0)
Non-hematologic TEAEs					
General disorders and administration site conditions					
Fatigue	7 (41.2)	22 (52.4)	33 (37.5)	16 (44.4)	78 (42.6)
Edema peripheral	1 (5.9)	12 (28.6)	31 (35.2)	14 (38.9)	58 (31.7)
Pyrexia	2 (11.8)	7 (16.7)	13 (14.8)	11 (30.6)	33 (18.0)
Gastrointestinal disorders					
Nausea	3 (17.6)	12 (28.6)	28 (31.8)	16 (44.4)	59 (32.2)
Constipation	2 (11.8)	12 (28.6)	20 (22.7)	6 (16.7)	40 (21.9)
Vomiting	1 (5.9)	7 (16.7)	17 (19.3)	7 (19.4)	32 (17.5)
Abdominal pain	1 (5.9)	9 (21.4)	12 (13.6)	7 (19.4)	29 (15.8)
Diarrhea	2 (11.8)	5 (11.9)	16 (18.2)	5 (13.9)	28 (15.3)
Investigations					
GGT increased	5 (29.4)	13 (31.0)	22 (25.0)	17 (47.2)	57 (31.1)
Blood ALP increased	4 (23.5)	6 (14.3)	18 (20.5)	9 (25.0)	37 (20.2)
AST increased	3 (17.6)	5 (11.9)	15 (17.0)	11 (30.6)	34 (18.6)
ALT increased	3 (17.6)	6 (14.3)	14 (15.9)	9 (25.0)	32 (17.5)
Skin and subcutaneous tissue disorders					
Rash	2 (11.8)	7 (16.7)	27 (30.7)	9 (25.0)	45 (24.6)
Erythema	1 (5.9)	5 (11.9)	11 (12.5)	4 (11.1)	21 (11.5)
Pruritus	2 (11.8)	4 (9.5)	7 (8.0)	7 (19.4)	20 (10.9)
Rash maculopapular	3 (17.6)	4 (9.5)	7 (8.0)	5 (13.9)	19 (10.4)
Metabolism and nutrition disorders					
Decreased appetite	2 (11.8)	7 (16.7)	13 (14.8)	12 (33.3)	34 (18.6)
Hypokalemia	1 (5.9)	3 (7.1)	15 (17.0)	4 (11.1)	23 (12.6)
Hyperglycemia	1 (5.9)	3 (7.1)	10 (11.4)	5 (13.9)	19 (10.4)
Respiratory, thoracic, and mediastinal disorders					
Dyspnea	1 (5.9)	11 (26.2)	21 (23.9)	8 (22.2)	41 (22.4)

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Pleural effusion	2 (11.8)	10 (23.8)	19 (21.6)	8 (22.2)	39 (21.3)
Cough	0	10 (23.8)	16 (18.2)	8 (22.2)	34 (18.6)
Nervous system disorders					
Dizziness	1 (5.9)	6 (14.3)	9 (10.2)	4 (11.1)	20 (10.9)

[a]Platelet count decreased and neutrophil count decreased are based on laboratory abnormality reporting and are reported out of number of patients with post-baseline test value; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg and 1 at 200 µg/kg) were missing for neutrophil count decreased and data for 3 patients (1 each at 120, 150 and 200 µg/kg) were missing for platelet count decreased.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B-NHL, B-cell non-Hodgkin lymphoma; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell

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Table 3. Grade ≥3 TEAEs reported in ≥5% of patients with B-NHL who received loncastuximab tesirine (safety analysis set)

TEAE, n (%)	≤90 µg/kg (n=17)	120 µg/kg (n=42)	150 µg/kg (n=88)	200 µg/kg (n=36)	Total (N=183)
Any Grade ≥3 TEAE	9 (52.9)	32 (76.2)	69 (78.4)	31 (86.1)	141 (77.0)
Neutrophil count decreased[a]	6 (35.3%)	12 (29.3)	35 (40.7)	18 (51.4)	71 (39.7)
Platelet count decreased[a]	1 (5.9%)	7 (17.1)	25 (28.7)	15 (42.9)	48 (26.7)
GGT increased	4 (23.5)	9 (21.4)	15 (17.0)	11 (30.6)	39 (21.3)
Anemia	3 (17.6)	4 (9.5)	16 (18.2)	5 (13.9)	28 (15.3)
Blood ALP increased	4 (23.5)	3 (7.1)	3 (3.4)	2 (5.6)	12 (6.6)
Lymphocyte count decreased	0	4 (9.5)	6 (6.8)	2 (5.6)	12 (6.6)
Disease progression	0	2 (4.8)	9 (10.2)	0	11 (6.0)
Febrile neutropenia	1 (5.9)	2 (4.8)	6 (6.8)	1 (2.8)	10 (5.5)
Hypokalemia	0	0	8 (9.1)	2 (5.6)	10 (5.5)

[a]Platelet count decreased and neutrophil count decreased are based on laboratory abnormality reporting; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg and 1 at 200 µg/kg) were missing for neutrophil count decreased and data for 3 patients (1 each at 120, 150 and 200 µg/kg) were missing for platelet count decreased. ALP, alkaline phosphatase; B-NHL, B-cell non-Hodgkin lymphoma; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event

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Table 4. Overall response rate in B-NHL subgroups treated with loncastuximab tesirine doses 15–200 µg (efficacy analysis set)

	B-NHL Subgroup		
	DLBCL (n=137)	**MCL (n=15)**	**FL (n=14)**
ORR, n (%)	58 (42.3)	7 (46.7)	11 (78.6)
[95% CI]	[33.9, 51.1]	[21.3, 73.4]	[49.2, 95.3]
CR, n (%)	32 (23.4)	5 (33.3)	9 (64.3)
PR, n (%)	26 (19.0)	2 (13.3)	2 (14.3)

B-NHL, B-cell non-Hodgkin lymphoma; CI, confidence interval; CR, complete response; DLBCL diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; ORR, overall response rate; PR, partial response

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Figure Legends and Figures

Figure 1. Patient disposition

[a]A patient was considered completed in the study after 12 months post-treatment follow-up data had been obtained. DLT, dose-limiting toxicity

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Figure 2. **Best percent change from baseline in tumor size by dose in (A) patients with B-NHL, (B) patients with DLBCL, (C) patients with MCL, and (D) patients with FL**

B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma

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Figure 3. **Duration of response to loncastuximab tesirine (A) by B-NHL subtype, (B) for patients with DLBCL by dose, and (C) for patients with DLBCL by response); (D) PFS for all patients with B-NHL and those with DLBCL, MCL, and FL; and (E) OS for all patients with B-NHL and those with DLBCL, MCL, and FL**

B-NHL, B-cell non-Hodgkin lymphoma; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; PR, partial response

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Figure 4. Correlation between C_{max} (A) and AUC (B) of loncastuximab tesirine-conjugated antibody during Cycle 1 and baseline peripheral CD19+ B cells

Linear regression models were used with natural log of baseline peripheral CD19+ B cell values as the independent variable and natural log of C_{max} or AUC as the dependent variable. Zero baseline CD19+ cells was set to 0.1 cells/μL and LN(0.1)=-2.30. The estimated slope (standard error) for C_{max} was -0.0617 (0.0239) [95% CI −0.109, −0.0143) and for AUC was −0.232 (0.0370) [95% CI −0.305, −0.158].

AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum observed concentration

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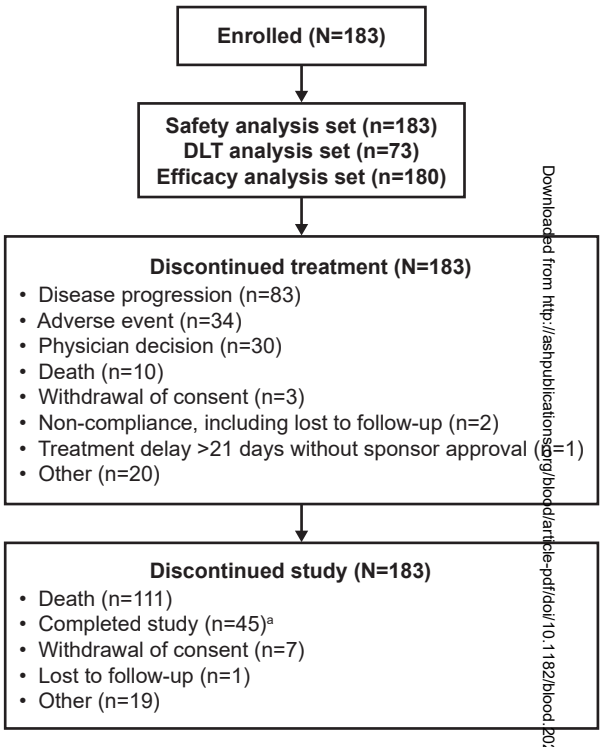

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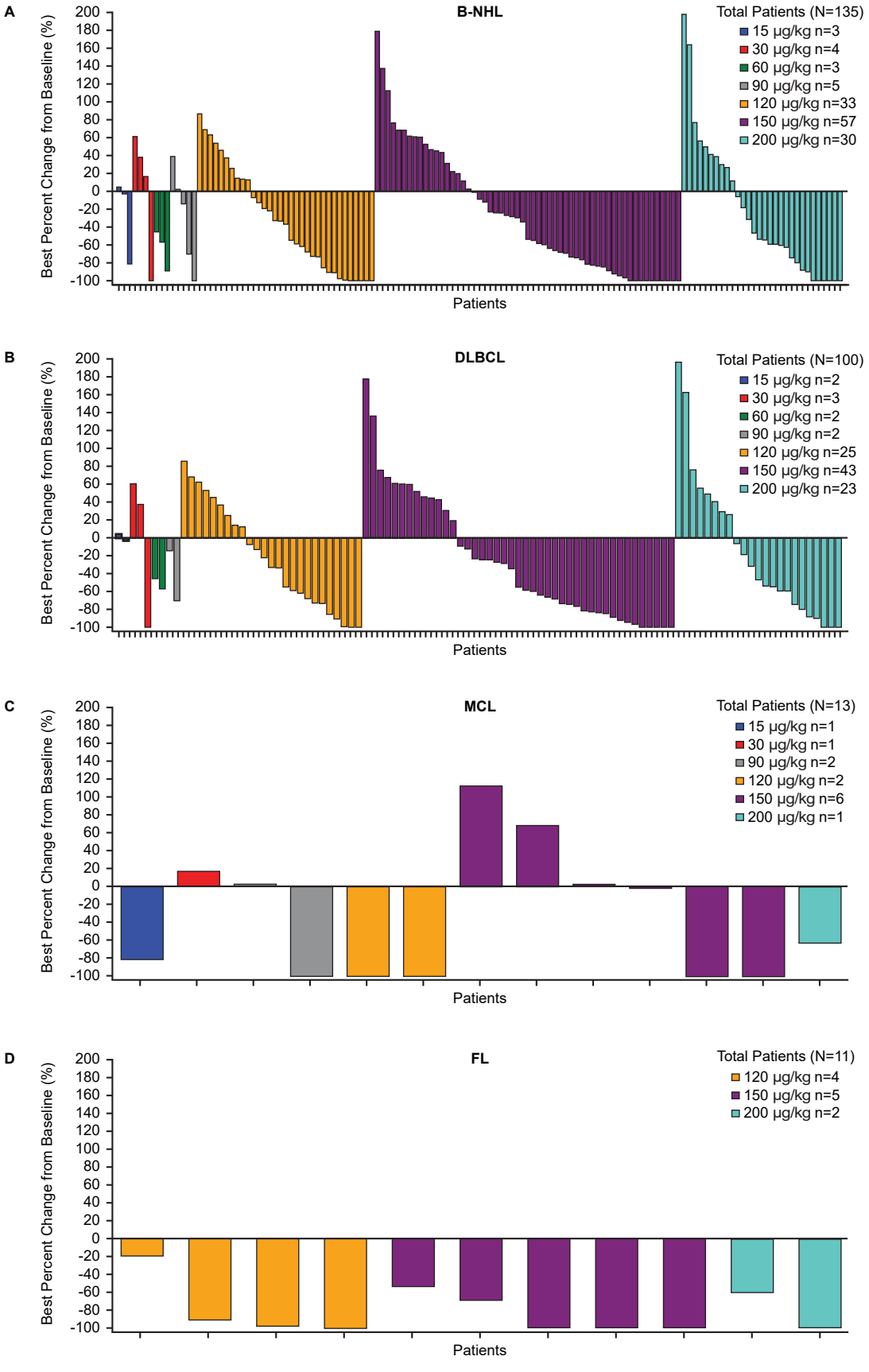

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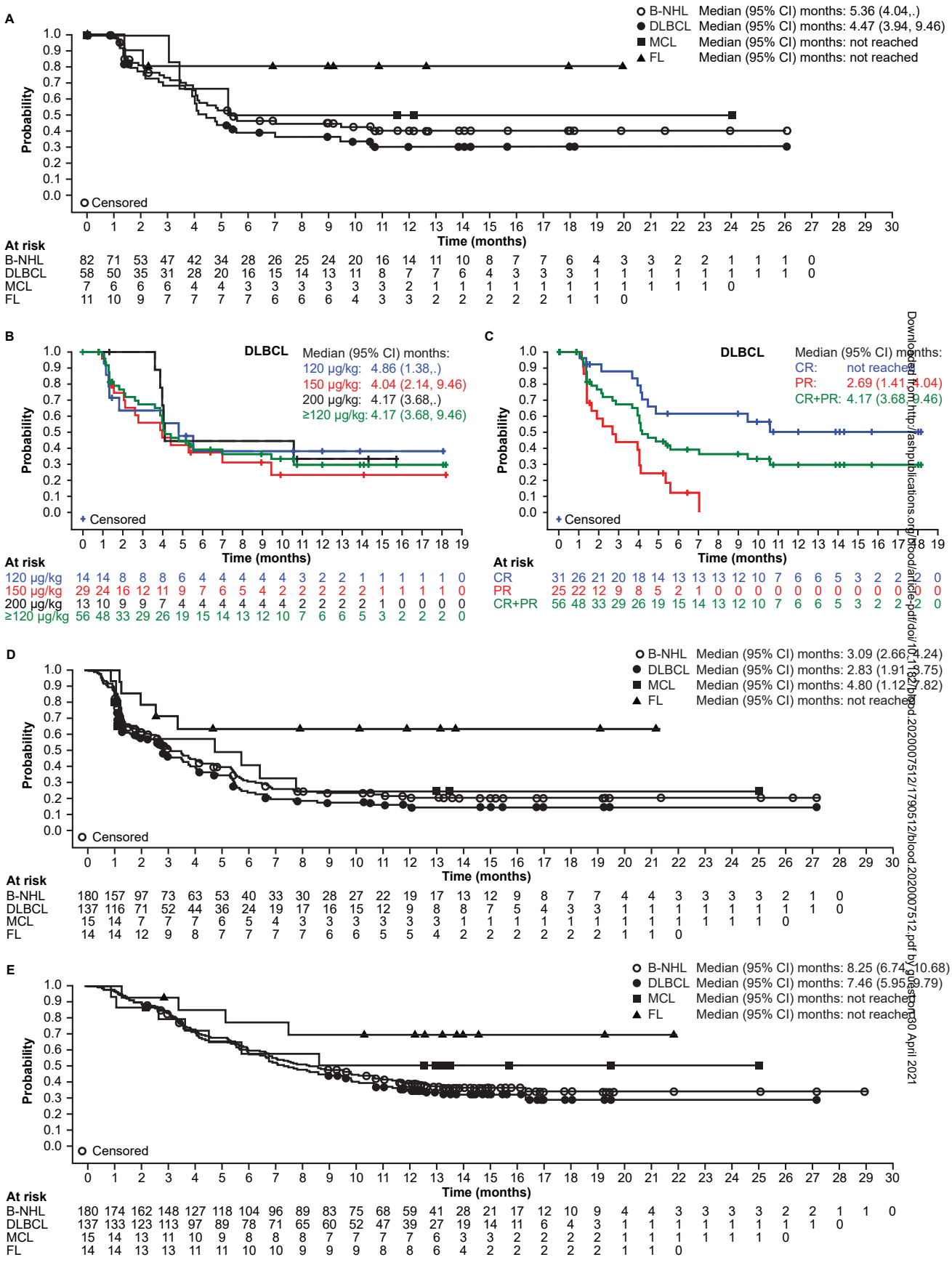

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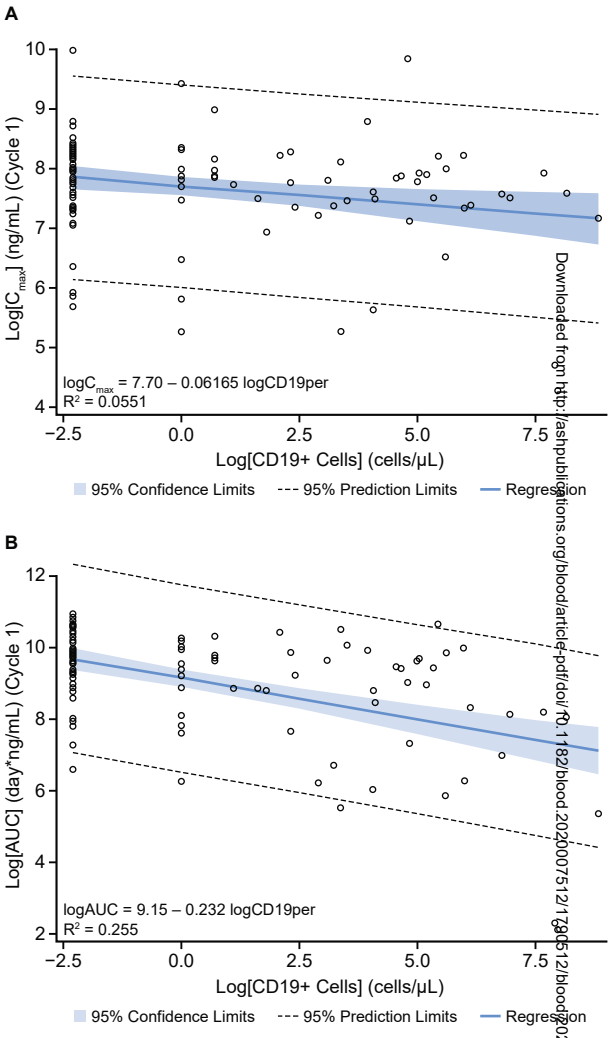

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