# Camidanlumab tesirine in relapsed/refractory lymphoma: A Phase 1, multicenter, open-label, dose-escalation, dose-expansion study

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## Summary

**Background—**Novel approaches are required to improve outcomes in relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma (NHL). The study aimed to evaluate camidanlumab tesirine, an anti-CD25 antibody-drug conjugate, in this patient population.

**Methods—**This now-complete, Phase 1, open-label, dose-escalation (Part 1), dose-expansion (Part 2), multicenter trial was conducted across 12 hospital sites (seven US, five UK). Adults with performance status 0–2, pathologically-confirmed R/R cHL or NHL, and no suitable established therapy were enrolled. Camidanlumab tesirine was administered intravenously (3–150 µg/kg) once every 3 weeks. Primary objectives were to assess dose-limiting toxicity (DLT), determine maximum-tolerated dose (MTD) and recommended expansion dose(s), and assess safety/tolerability. Safety was assessed in all treated patients; efficacy in treated patients with ≥1 valid baseline and post-baseline disease assessment or disease progression/death after first study-drug dose. This trial was registered at ClinicalTrials.gov (NCT02432235).

**Findings—**During Oct 5, 2015–Jun 30, 2019, 133 patients enrolled: cHL, n=77; NHL, n=56. Median (IQR) follow-up was 9·15 months (4·17–14·32). Eight DLTs were reported in 5/86 (5·8%) patients; the MTD was not reached. Dose-expansion was based on available data. Grade ≥3 treatment-emergent AEs (TEAEs) (≥10% of 133 patients) included gamma-glutamyltransferase increased (n=20 [15·0%]), maculopapular rash (n=16 [12·0%]), and anemia (n=15 [11·3%]); 74 (55·6%) patients experienced serious TEAEs, most commonly pyrexia (n=16 [12·0%]).There was 1/133 (0·8%) fatal TEAE and 2/133 (1·5%) deaths outside the reporting period considered at least possibly study-drug related. Overall response rates were: 71·4% (55/77 patients; 95% CI: 60·0–81·2) in cHL overall and 86·5% (32/37 patients; 71·2–95·5) at 45 µg/kg camidanlumab tesirine, 37·7% (20/53 patients; 24·8–52·1) in NHL overall, and 48·4% (15/31 patients; 30·2–66·9) in T-cell NHL.

**Interpretation—**These results warrant further evaluation of camidanlumab tesirine as a potential treatment option for R/R lymphoma, particularly cHL.

**Funding—**ADC Therapeutics SA.

## Research in context

**Evidence before this study**

CD25 is expressed on the surface of various hematologic tumor cell types and is therefore a promising target for antitumor therapies in lymphoma. To ascertain the treatment landscape for CD25-directed therapies in lymphoma prior to study initiation in 2015, a PubMed search was conducted (Nov 23, 2020) using the terms “lymphoma”, “CD25” and “clinical trial” for studies published from Jan 1, 2010 to Jan 1, 2015. Of the studies identified, the majority were early phase trials and patient population sizes were generally small, with fewer than 40 patients in 75% of the studies. CD25-directed treatments evaluated for lymphoma were limited to an anti-CD25 monoclonal antibody assessed in combination with chemotherapy and an immunotoxin targeting IL-2 receptors. Objective response rates were between 18% and 53% but patient populations varied widely.

Camidanlumab tesirine is a CD25-targeted antibody-drug conjugate (ADC) with antitumor activity against CD25-expressing hematologic malignancies in preclinical models.

**Added value of this study**

Although CD25 is a recognized therapeutic target in hematologic malignancies and other therapies have previously been shown to have efficacy, to our knowledge, there are no CD25-directed therapies currently in widespread use for lymphoma. Our study shows that a CD25-directed ADC can produce high response rates in heavily pre-treated relapsed or refractory classical Hodgkin lymphoma (cHL) or non-Hodgkin lymphoma (NHL), with particularly encouraging responses in patients with cHL, where notably three-quarters of patients had received both prior brentuximab vedotin (BV) and a checkpoint inhibitor (CHPi), and in T-cell NHL (T‑NHL) at the doses selected for expansion. Furthermore, we extend understanding of multiple putative modes of antitumor activity and immune-mediated toxicity of CD25-directed therapies, through evaluation of T-cell population changes and the relationship between CD25 expression and response.

**Implications of all the available evidence**

This study provides strong evidence that a CD25-directed ADC is effective in lymphoma. Within the context of the limited therapeutic options available to patients with multiply relapsed or refractory lymphoma following a high number of prior therapies, including autologous hematopoietic cell transplantation, BV, and CHPi, the findings of this study suggest that camidanlumab tesirine could offer a novel treatment option for cHL and T-NHL. Based on this evidence, a pivotal Phase 2 trial of camidanlumab tesirine in patients with relapsed or refractory cHL is currently in progress.

## Introduction

Lymphomas are a heterogeneous group of malignancies of the lymphatic system comprising Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).1 The different subtypes of NHL, including B-cell (B-NHL), T-cell (T-NHL), and NK-cell lymphomas, have considerable variation in prognosis.1,2 In contrast, ~95% of HLs are classical HL (cHL).3 Although cHL generally has a favorable prognosis, 5–10% of patients are refractory to initial treatment and 10–30% relapse after achieving initial complete remission.4 Despite salvage therapy and autologous hematopoietic cell transplantation (autoHCT) consolidation, durable disease control is achieved in only 50–60% of patients with relapsed or refractory (R/R) cHL. 4,5

Novel approaches to improve outcomes for R/R lymphomas include chimeric antigen receptor T-cell (CAR-T) therapy, small molecule inhibitors, antibody-drug conjugates (ADCs) such as brentuximab vedotin (BV), and/or checkpoint inhibitors (CHPi).6-10 However, some patients do not respond to these treatments or relapse after initial remission, leaving an unmet need for effective therapies to improve outcomes and minimize long-term treatment toxicities.3,6,7,10

CD25 (interleukin-2 receptor subunit alpha) is a marker of T-cell activation and its expression on the surface of various hematologic tumor cell types is well established.11 Camidanlumab tesirine, an ADC comprising HuMax®-TAC, a human IgG1 anti-CD25 monoclonal antibody, stochastically conjugated to a pyrrolobenzodiazepine (PBD) dimer warhead via a cleavable linker, causes cell death through formation of cytotoxic DNA interstrand cross-links.12

In preclinical models, camidanlumab tesirinehas targeted antitumor activity against CD25-expressing hematologic malignancies and exhibits bystander killing of CD25-negative cells.13 Anti-CD25 therapies may also modify the tumor microenvironment and facilitate induction of antitumor immunity by depleting CD25-positive regulatory T cells (Tregs).11,12,14

Here, we report results of the first-in-human clinical trial of camidanlumab tesirinein adults with histologically confirmed R/R lymphoma.

## Methods

### Study design and participants

This was a Phase 1, open-label, dose-escalation (Part 1), dose-expansion (Part 2), multicenter study conducted across 12 hospital sites (seven US; five UK; **Table S1** appendix p3). Adults (≥18 years) with pathologically confirmed R/R NHL (including stage ≥1b cutaneous T-cell lymphoma [CTCL]) or cHL who had no therapies available to them with established clinical benefit for their current disease stage and measurable disease (2014 Lugano Classification/Global Response Score and modified Severity-Weighted Assessment Tool [mSWAT] for CTCL)15,16 were recruited by investigators. Prior treatment with BV and CHPi was added during the study (Jan 19, 2018) as a requirement for cHL patients. Patients had Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 and adequate laboratory tests (creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and bilirubin for all patients; absolute neutrophil count, platelets, and hemoglobin for all except patients with adult T-cell leukemia/lymphoma [ATLL]).

Key exclusion criteria included allogeneic transplantation or autoHCT ≤60 days prior to Day 1 of Cycle 1, active graft-versus-host disease or history of symptomatic autoimmune disease, neuropathy, or other central nervous system disease considered autoimmune. Full criteria are provided (appendix, p28).

The study was performed per the International Council for Harmonization, Good Clinical Practice guidelines, and Declaration of Helsinki. The protocol and amendments were approved by each institutional review board. All patients provided written informed consent.

### Procedures

Camidanlumab tesirine was given intravenously over 30–60 minutes once every 3 weeks (Q3W; Day 1 of each 21-day cycle). Dose escalation (Part 1) was conducted per continual reassessment method, from a starting dose of 3 µg/kg Q3W, with a minimum of two patients required per dose-escalation cohort (see appendix p28 for increment rules). If no dose-limiting toxicities (DLTs) were observed in the first two patients, up to ten additional patients could be enrolled for further exploration of that dose level during Part 1, provided at least one patient had documented stable disease (SD). Further patients could be included if 3/10 had documented partial response (PR) or better. The maximum tolerated dose (MTD) was defined as the highest tolerated dose that could be delivered to patients with at least a 60% probability that the DLT rate would be under 30%. The DLT observation period was initially two treatment cycles but subsequently shortened to one (Nov 8, 2016; Protocol Amendment 4; appendix p28) based on ongoing safety and pharmacokinetic (PK) evaluation showing tolerability and relatively short half-life of camidanlumab tesirine. Data were reviewed by the Dose Escalation Steering Committee, who also determined recommended dose(s) of camidanlumab tesirine for dose expansion (Part 2). Patients were to be treated until disease progression, new anticancer treatment initiation, or significant toxicity.

Dexamethasone prophylaxis (4 mg twice-daily, 1 day prior, on day of, and 1 day post-treatment) was administered. Study drug dosing could be withheld for ≤21 days for any patient who experienced toxicity of any grade at the discretion of the Investigator. Treatment could resume following recovery to Grade ≤1. On resumption of treatment, doses could be reduced by one dose level at the investigator’s discretion. Dosing delays of >21 days were allowed if there was potential benefit to the patient in resuming treatment. In the event of disease progression, Grade ≥3 hypersensitivity reactions, or recurrent Grade ≥3 non-hematological toxicity, patients were to be withdrawn from treatment with camidanlumab tesirine.

Disease assessments used diagnostic computed tomography (CT) and/or positron emission tomography-CT (18F-fluorodeoxyglucose-avid lymphomas) at baseline, prior to Day 1 of Cycles 3 and 5, then every third cycle thereafter until progression, and response was assessed by investigators. mSWAT was used for post-baseline assessments of skin-limited CTCL. Safety (including adverse events [AEs] and laboratory tests) was monitored at every visit: at least weekly in Cycles 1 and 2, and on Day 1 and 8 of subsequent cycles. Whole blood samples for PK, immunogenicity, and pharmacodynamic analyses were collected per protocol. Patients were followed for up to 12 months after treatment discontinuation.

### Outcomes

The primary objective was to assess DLTs, determine the MTD and recommended dose(s) for expansion (RDE), and to evaluate safety and tolerability of camidanlumab tesirine in lymphoma. Safety endpoints included AEs graded per CTCAE v4·0, serious AEs (SAEs), discontinuations due to AEs, and laboratory abnormalities.

Secondary efficacy endpoints were overall response rate (ORR), duration of response (DoR), overall survival (OS), and progression-free survival (PFS), based on Investigator’s assessment of response.15,16 Other secondary endpoints included PK of camidanlumab tesirine total antibody, PBD-conjugated antibody, and SG3199 (unconjugated warhead), based on validated bioanalytical methods, and immunogenicity, assessed via anti-drug antibodies (ADA) against camidanlumab tesirine in serum.

Exploratory endpoints included correlation between clinical activity and CD25 expression, potential relationships between PK and pharmacodynamic (PD) characteristics, and change in white blood cell populations.

### Statistical analysis

No hypothesis testing was conducted. Maximum total sample size was 140 patients, based on empirical estimates. The study was not formally powered to detect differences between treatment groups. Simulations were conducted assuming scenarios with different dose–toxicity relationships to evaluate the probability of selecting the MTD during dose escalation (Section 13.5.2 of protocol, appendix p28), and doses were expanded to determine doses for Part 2, with ~80 patients expected to be required during Part 1. Part 2 was conducted at dose levels recommended following dose escalation, with up to 60 patients planned.

No formal interim analysis was planned. However, as the MTD was not reached at the initially planned maximum dose of 33 µg/kg, safety data were reviewed and submitted to regulatory authorities for Protocol Amendment 4; the highest dose permitted for dose escalation was increased to 300 µg/kg. One patient received an unplanned overdose of 300 µg/kg for the first dose but continued in the study with subsequent dosing, as planned, at 30 µg/kg. All patients were analyzed according to their actual starting dose of camidanlumab tesirine.

Primary and secondary analyses were conducted following study termination, not due to safety reasons but because all patients had completed or were in follow‑up, except one who had a treatment delay for 44 days prior to study end. Descriptive statistics and listings were used to report safety, efficacy, and PK parameters. Unless otherwise stated, all analyses were performed using SAS® v9.4 (SAS Institute Inc., Cary, NC, USA) or higher.

The safety analysis set comprised all patients who received study drug. The DLT-evaluable analysis set consisted of all patients who received study drug during dose escalation except those who discontinued from the study without experiencing a DLT during the first 21-day cycle. Treatment-emergent AEs (TEAEs) were defined as any event not present prior to study-drug exposure or any event already present that worsened in intensity or frequency after exposure to study drug until either 12 weeks post-last-dose or initiation of new anticancer treatment, whichever came first.

The efficacy analysis set comprised all patients who had received ≥1 dose of study drug with ≥1 valid baseline and post-baseline disease assessment or who had documented disease progression/death any time after first dose of study drug. Patients who started subsequent anticancer therapy before their first post-baseline disease assessment were not assessable for response. ORRs were defined as the proportion of patients with best overall response of complete response (CR) or PR at the time each patient discontinued camidanlumab tesirine and estimates are presented with corresponding 95% confidence intervals (CIs). Kaplan–Meier estimates (SAS® PROC LIFETEST [SAS Institute Inc., Cary, NC, USA]) were used for DoR, OS, PFS, and time-to-first AE leading to dose modification. Time-to-event data are reported by cohort due to heterogeneity in populations. DoR, OS, and PFS for B-NHL could not be reported owing to the low number of responders (data could be misinterpreted). Prespecified subgroup analyses of ORR by dose, histology cohorts, sex, country, age, disease stage at study entry, number of prior therapies, prior therapy type (BV, CHPi and HCT), response to first-line therapy, and response to most recent therapy, were conducted for cHL, but are not reported for all patients due to heterogeneity of the population, or for other disease cohorts due to small sample sizes. Post-hoc subgroup analyses for ORR were conducted for T-cell and B-cell NHL histologies.

The PK/PD analysis sets included all patients receiving ≥1 dose of study drug, and who had ≥1 post-treatment sample and/or sufficient data for reliable exposure estimation. PK parameters were calculated by non-compartmental method17 (Phoenix® WinNonlin® v8·2 [Certara USA, Inc., Princeton, NJ]). The immunohistochemistry analysis set included patients for whom archival tumor tissue or pretreatment biopsies for CD25 protein expression were available, and who had at least one value for a correlative endpoint, and analyses used R v4·0·3 (R Foundation for Statistical Computing, Vienna, Austria).

See appendix for the Statistical Analysis Plan. The study was registered at ClinicalTrials.gov (NCT02432235).

### Role of the funding source

This study was sponsored by ADC Therapeutics SA and designed by the sponsor in collaboration with investigators, who collected data that were analyzed by the sponsor’s statisticians. All authors were involved in data analysis and interpretation. All drafts were prepared by the authors with editorial support from Fishawack Communications Ltd, part of Fishawack Health. All authors had full access to all data and final responsibility for the decision to submit for publication.

## Results

A total of 133 patients enrolled during Oct 5, 2015–Jun 30, 2019; 77 with cHL and 56 with NHL. The study was terminated on Oct 24, 2019 and data cut-off date was Mar 31, 2020. During dose escalation, patients received camidanlumab tesirine in dose cohorts at 3–150 µg/kg. The following dose levels were expanded based on dose-escalation data: 30 and 45 µg/kg for patients with cHL; 80 μg/kg for patients with T-NHL. Patient disposition is provided (**Figure 1**). Patients received a median (interquartile range; IQR) of 3·0 (2·0–5·0) and mean (standard deviation) of 3·5 (2·43) cycles of camidanlumab tesirine. Median (IQR) duration of follow-up was 9·15 months (4·17–14·32).

Baseline characteristics are provided (**Table 1**).Most patients were heavily pretreated, with a median (IQR) of 5·0 (3·0–7·0) prior systemic therapies. At enrollment, 81 (60·9%) of 133 patients were refractory (stable or progressive disease) to their most recent line of treatment.

In the dose-escalation part, 86 (98·9%) of 87 patients were evaluable for DLT; one patient was not evaluated due to disease progression before completing the DLT period (enrolled pre-Amendment 4 [see Methods]); however, this patient had no DLTs and no treatment-related AEs prior to withdrawal on Cycle 1, Day 15. Five (5·8%) of 86 patients reported eight DLTs in total. One cHL patient treated at 20 µg/kg had DLTs of small bowel enteritis and oral mucositis, both Grade 3; two cHL patients treated at 30 µg/kg experienced DLTs of Grade 3 elevated creatine phosphokinase and Grade 3 skin-related DLT (pruritus and maculopapular rash), respectively; one NHL patient treated at 45 µg/kg had Grade 3 DLTs of herpes infection and worsening back pain; and one NHL patient treated at 80 µg/kg had Grade 4 platelet count decreased. All DLTs were considered at least possibly related to study drug and all resolved.

The MTD was not reached. Given the balance between toxicity and antitumor activity observed at the RDE, dose escalation beyond 150 μg/kg had the potential to cause more toxicity with repeated dosing without increasing antitumor activity, thus it was decided to stop dose escalation despite absence of a defined MTD. The RDE were based on safety with multiple doses, PK, and efficacy data, and were 30 µg/kg and 45 µg/kg for patients with cHL and 80 µg/kg for patients with T-NHL. No RDE were defined for B-NHL.

Overall, 132 (99·2%) of 133 patients experienced a TEAE of any grade(**Table S2** appendix p4). TEAEs are shown by grade in **Table 2.** The most common all-grade TEAEs (≥20% of patients) includedfatigue, pyrexia, maculopapular rash, diarrhea, cough, gamma-glutamyltransferase (GGT) increase, nausea, and anemia (**Table S3** appendix p5).

Grade ≥3 TEAEs occurred in 102 (76·7%) of 133 patients, most commonly (≥10%) GGT increased (20 [15·0%] patients), maculopapular rash (16 [12·0%] patients), and anemia (15 [11·3%] patients) (**Table S4** appendix p7), and 74 (55·6%) patients experienced serious TEAEs, most commonly pyrexia (16 [12·0%] patients) (**Table S5** appendix p9). In both cHL and NHL cohorts, <10% of patients experienced hematological events of thrombocytopenia and neutropenia, and only 1/133 patients had leukopenia (Grade 1; **Table S6** appendix p11).

Fifteen patients (11·3%) had TEAEs with a fatal outcome, comprising two patients (2·6%) with cHL who died of reasons unrelated to study drug (disease progression and unspecified reason; the latter 83 days post-last infusion) and 13 patients (23·2%) with NHL; 12 of whom had TEAEs unrelated to study treatment, and one patient (treated at 150 μg/kg) had neutropenic sepsis, considered probably study-drug related (**Table S2** appendix p4).

Two cHL patients had fatal events after the TEAE-reporting period: immune system disorder and multiple cranial nerve palsy (preferred terms), both considered at least possibly related to study drug. The first patient had recurring pleural effusions and high inflammatory markers during and following treatment with study drug and was diagnosed with immune system disorder (acquired immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) 9 months after study drug termination, featuring worsening third-spacing of fluids and acute kidney injury. The latter patient experienced eyelid ptosis ~9 months after last dose of camidanlumab tesirine, which worsened ~3·5 months later, concurrent with additional cranial nerve palsies that began 7 days after a second cycle of BV and resulted in death due to progressive polyneuropathy.

TEAEs leading to dose delay occurred in 59 (44·4%) of 133 patients, comprising 38/77 (49·4%) of the cHL cohort, and 21/56 (37·5%) of the NHL cohort, and 8/133 (6·0%) patients had dose reductions. Overall, 34/133 (25·6%), 24/77 (31·2%), and 10/56 (17·9%) of the total, cHL, and NHL populations, respectively, discontinued treatment due to TEAEs (**Table S2** appendix p4) and 31/133 (23·3%) patients had ≥1 treatment-related TEAE leading to camidanlumab tesirine discontinuation. Time to first AE leading to dose modification is shown (**Figure S1** appendix p21).

Infusion-related reactions occurred in 6/133 (4·5%), 5/77 (6·5%), and 1/56 (1·8%) patients of the total, cHL, and NHL populations, respectively (**Table S2** appendix p4). Common PBD-related AEs included skin-related AEs (84/133; 63·2%) and liver function test abnormalities (51/133; 38·3%). Other potentially PBD-related TEAEs included fatigue (51/133; 38·3%), edema or effusion (35/133; 26·3%), and nausea (28/133; 21·1%; **Table S6** appendix p11).

Five of 133 patients (3·8%) developed serious neurologic events of Guillain–Barré syndrome (GBS)/polyradiculopathy (**Table S6** appendix p11), considered likely immune-related and at least possibly study-drug related. There was no clear relationship with dose, with events occurring at 30 (n=1), 45 (n=3), and 60 μg/kg (n=1), but all occurred in cHL patients; 3/5 (60·0%) patients had received prior CHPi treatment and 5/5 (100%) had prior BV. In three patients, GBS/polyradiculopathy resolved following medical management; one patient experienced slow recovery with GBS that was ongoing at study end; and one patient had almost-complete neurologic recovery but died due to hospital-acquired pneumonia following allogeneic HCT.

In total, 130 (97·7%) of 133 patients had post-treatment assessments and were thus evaluable for efficacy; three patients (2·3%) were excluded (no valid post-baseline disease assessment or documented disease progression prior to starting new anticancer therapy, or died). ORRs (95% CI) for all patients, and cHL and NHL cohorts were 57·7% (75/130 patients [48·7–66.3]; CR: 28·5%), 71·4% (55/77 patients [60·0–81·2]; CR: 41·6%), and 37·7% (20/53 patients [24·8–52·1]; CR: 9·4%), respectively; **Figure 2**.

In the cHL cohort, ORR (95% CI) was 86·5% at 45 µg/kg (32/37 patients [71·2–95·5]) and 55·0% at 30 µg/kg (11/20 patients [31·5–76·9]); 48·6% (18/37 patients) and 35·0% (7/20 patients) achieved CR, respectively (**Table S7** appendix p13). Notably, in prespecified and post-hoc subgroup analyses, ORRs (95% CI) at 45 µg/kg remained comparable in patients who received prior BV (32/37 patients, 86·5% [71·2–95·5]), both BV and a CHPi (23/26 patients, 88·5% [69·8–97·6]), HCT (14/16 patients, 87·5% [61·7–98·4]), or all three (11/12, 91·7% [(61·5–99·8]). High response rates were observed in other subgroups analyzed (**Table S8** appendix p14**)**.

Median (95% CI) DoR for the cHL population was 6·64 months (5·06–8·11), and was 7·16 months (4·57–8·51) in patients treated at 45 μg/kg (**Figure 3A**). For patients with CR, median DoR (95% CI) was 8·11 months (5·06–12·16) (17 events). Median (95% CI) PFS was 6·83 months (5·75–8·54) for all doses, and 6·97 months (5·75–9·69) at 45 μg/kg (**Figure 3B**). Median OS was not reached (**Figure 3C**).

In total, 43/77 patients (55·8%) received subsequent anticancer therapy, including three (3·9%) who received CAR-T therapy and ten (13·0%) who received HCT (nine allogeneic) as their next treatment after camidanlumab tesirine.

Notably, responses for four cHL patients (4/77; 5·2%) improved from PR to CR at disease assessments ≥6 weeks post-last infusion despite no further treatment (**Figure 2A**).

ORR (95% CI) in B-NHL was 22·7% (5/22 patients [7·8–45·4]) overall. In diffuse large B-cell lymphoma (DLBCL; including one patient with mediastinal [thymic] large B-cell lymphoma), ORR (95% CI) at doses ≥60 µg/kg was 30·8% (4/13, including two patients with CR [9·1–61·4]; **Table S9** appendix p15); 7/13 (53·8%) had received high-dose chemotherapy and HCT prior to the study; none had received prior CAR-T therapy. Although antitumor activity in B-NHL was observed at doses ≥60 μg/kg, ORRs were lower than observed in a concurrent study with loncastuximab tesirine (CD19-targeted ADC),18 thus dose expansion in NHL was restricted to T-NHL.

ORRs (95% CI) in all patients with T-NHL overall, and at 60, 80, and 100 μg/kg doses, were 48·4% (15/31 patients [30·2–66·9]), 60% (6/10 patients [26·2–87·8]), 57·1% (8/14 patients [28·9–82·3]), and 100% (1/1 patient [2·5–100]) respectively; CRs were reported for 6·5% (2/31 patients), 10% (1/10 patients), 7·1% (1/14 patients), and 0% (0/1 patient), respectively. ORRs (95% CI) at doses ≥60 µg/kg for patients with CTCL, ATLL, peripheral T-cell lymphoma not otherwise specified, or other T-NHLs (hepatosplenic or angioimmunoblastic) were 77·8% (7/9 patients [40·0–97·2]), 42·9% (3/7 patients [9·9–81·6]), 33·3% (2/6 patients [4·3–77·7]) and 100% (3/3 patients [29·2–100·0]), respectively (**Table S9** appendix p15).

Median (95% CI) DoRs for all patients with T-NHL (31 at risk) and for NHL overall (53 at risk) were 2·45 months (1·41–9·79) (12 events) and 2·50 months (1∙68–4∙73) (16 events), respectively. Median (95% CI) PFS and OS were 2·66 months (1·18–4·80) (27 events) and 5·22 months (3·22–8·77) (25 events) for T-NHL, and 1·38 months (1·18–2·73) (47 events) and 5·22 months (3·25–8·05) (39 events) for NHL overall.

PK parameters are presented for the 45 µg/kg dose (**Table S10** appendix p16). PK exposure increased with dose. Mean apparent clearance displayed moderate-to-marked inter-patient variability (CV~50·3% based on PBD-conjugated antibody Cycle 1 AUCinf at 45 µg/kg). Profiles appeared generally biphasic and comparable between conjugated- and total-antibody moieties. Apparent terminal half-life was ~2·3 days (CV 45·5%) following the 45 μg/kg dose. Unconjugated-warhead SG3199 exposures were below the LLOQ in serum for most patients, generally precluding characterization. In Cycle 2, no accumulation of conjugated or total antibodies was observed at Q3W dosing. No confirmed ADA responses were observed (133 patients tested).

**Figure S2** (appendix p23)presents baseline sCD25 concentration versus area under the concentration–time curve in serum of cHL patients and shows a decreasing trend of drug exposure with higher sCD25, with p=0·098 for patients with CR versus patients with PR, SD, progressive disease, or not evaluable. CRs appeared among patients with lower baseline sCD25 up to ~10,000 ng/L.

While significance was not assessed as analyses were exploratory, trends in suppression of Tregs (CD25+/CD12low/FoxP3+[CD3+/CD4+]) but not total T cells (CD4+) in blood following camidanlumab tesirine versus baseline occurred in most patients, although clear differences by response or sCD25 concentration were not apparent (**Figures S3A–S3B** appendix p24).

Archival tumor biopsies were available for 104/133 (78·2%) patients (cHL: 66; NHL: 38); pre-treatment tumor biopsies were available for 19/133 (14·3%) patients, (cHL: 6; NHL: 13). Immunohistochemistry staining of CD25 on tumor and non-tumor cells from biopsies of cHL patients showed no significant difference (p=0·49) in histoscore for tumor versus non-tumor cells; however, biopsies of patients with B-NHL and T-NHL showed a significant difference between tumor and non-tumor cells, with higher histoscores seen in tumor cells (p=0·00081 and p=0·015 for B-NHL and T-NHL, respectively; **Figure S4A** appendix p26; **Table S11A** appendix p17). In non-tumor cells from patients with cHL, B-NHL, or T-NHL, no significant relationship was seen between CD25 histoscore and clinical response(p=0·90, p=0·26, and p=0·36, respectively; **Figure S4B** appendix p26**;** **Table S11B** appendix p17). Contrary to prior initial exploratory analysis,19 final analysis showed that, in tumor cells from cHL patients, a significantly higher histoscore was observed for responders (those with CR or PR) versus non-responders (progressive disease, SD, or not evaluated) (p=0·0068). This significant difference was not apparent for tumor cells from B-NHL and T-NHL patients (p=0·34 and p=0·70, respectively) (**Figure S4C** appendix p26; **Table S11C** appendix p17).

## Discussion

In this open-label, dose-escalation, dose-expansion, Phase 1 study, camidanlumab tesirine demonstrated a high level of activity in patients with multiply R/R lymphoma; MTD was not reached.

The most commonly observed AEs, such as elevated liver enzymes (without hepatic synthetic dysfunction), rash, fatigue, edema or effusion,and nausea appear typical of PBD dimer-containing ADCs and have been reported in other studies using the same payload, such as Phase 1 and 2 studies of loncastuximab tesirine in NHL.18,20-22 These events were generally reversible and manageable in most patients with dose delays or reductions. Dexamethasone premedication limited incidence of edema and effusion; as previously reported in Part 2 of a trial of loncastuximab tesirine, which has the same payload.18 Of note, PK of SG3199 suggest it is highly unlikely that unbound drug contributes appreciably to toxicity in non-CD25 expressing tissues. Many common TEAEs, such as rash, fatigue, diarrhea, and pyrexia are also reported to occur with approved drugs for cHL, such as BV23 and CHPis.9,24

Autoimmune toxicities were observed at low levels; peripheral sensory neuropathy was seen in 9/133 patients (6·8%) and hypothyroidism in 8/133 patients (6·0%). However, notably 5/77 (6·5%) cHL patients experienced GBS/polyradiculopathy. No NHL patients developed GBS/polyradiculopathy, and no GBS/polyradiculopathy events were observed in a Phase 1 study of camidanlumab tesirine in 35 patients with acute leukemia,25 suggesting cHL patients may be predisposed to GBS/polyradiculopathy when treated with camidanlumab tesirine. The association of immune‐mediated neuropathies with cHL, including paraneoplastic and inflammatory demyelinating neuropathies, such as GBS, is well described in the literature.26 Aimed at improving understanding of the etiology of these events, subgroup analyses demonstrated GBS/polyradiculopathy in camidanlumab tesirine-treated cHL patients was not associated with dose, cycle number, or prior CHPi treatment.27 Targeting the immune system with camidanlumab tesirine in cHL patients could plausibly modulate CD25-positive Tregs, causing immune system changes, rendering these patients more susceptible to GBS/polyradiculopathy. No specific prior therapies associated with increased or reduced GBS risk were identified.

Ongoing and planned studies incorporate measures to mitigate risk and rapidly identify autoimmune/neurological events (e.g. exclusion of patients with history of infections ≤4 weeks pre-trial initiation or history of autoimmune neuropathy, regular on-study neurological assessments, and guidelines for early identification of autoimmune/neurological events). TEAEs of special interest being evaluated in the ongoing Phase 2 trial of camidanlumab tesirine in patients with R/R cHL include GBS, polyradiculopathy, autonomic nervous system imbalance, nerve palsy, Grade ≥3 neurologic toxicities/immune-mediated toxicities, and autoimmune-mediated events (e.g. pneumonitis, hepatitis, and colitis).

Camidanlumab tesirine showed high response rates in a heavily pre-treated cHL population. Conversely, lower activity was observed in B-NHL, hence no dose expansion was conducted for B-NHL in this study, and DoR could not be reported owing to the low number of responders.

At 45 µg/kg, 32 (86·5%) of 37 patients with cHL exhibited objective responses, and 18/37 (48·6%) had CRs. Median DoR was 7·16 months. In comparison, 76 (75%) of 102 patients treated with BV exhibited objective responses, with 35/102 (34%) CRs and median DoR of 6·7 months in a Phase 2 study in a similar population of heavily pre-treated patients post-autoHCT,10 but notably all cHL patients treated with camidanlumab tesirine at 45 µg/kg had received prior BV, 70.3% had previously received CHPi , and 43.2% had received HCT. A dosing regimen with reduction from 45 µg/kg to 30 µg/kg camidanlumab tesirine after the first two cycles is being evaluated in a Phase 2 study and is anticipated to increase the proportion of patients able to continue treatment, which could translate into longer DoR.

ORRs were high across other subgroups analyzed, suggesting robust antitumor activity across the R/R cHL population.

Notable single-agent activity was also observed in T-NHL at doses ≥60 µg/kg.

Clinical activity of camidanlumab tesirine may be attributed to multiple putative modes of antitumor activity, including direct targeting of tumor cells expressing CD25, bystander killing and depletion of CD25-positive Tregs, whichregulate intra-tumoral Teff:Treg populations and upregulate antitumor immune responses.11,14

Comparable exposures between conjugated- and total-antibody moieties suggest good linker stability of the immunoconjugate in circulation. Despite the relatively short half-life of camidanlumab tesirine and no accumulation in serum with Q3W treatment, long-lasting effects of PBD dimers on tumors were observed in some cases, with continued tumor shrinkage without further dosing or long AE resolution time.

The response rate and duration should be considered in the context of CD25 levels. CD25 is expressed in the majority of cHL tissue samples, regardless of cHL subtype, and is expressed in some Reed–Sternberg (RS) cells (the main marker of cHL) and rosetting T cells.28,29 However, RS cells represent <1% of the lymphoid population in cHL.29 CD25 expression in other lymphomas is variable.11 In our study, CD25 expression was significantly higher in tumor versus non-tumor cells for B-NHL and T-NHL, but not cHL, with CD25 expression significantly associated with clinical response in only cHL, which we speculate suggests that camidanlumab tesirine acts on malignant RS cells in cHL. Yet high CD25 levels may not be the sole factor contributing to camidanlumab tesirine efficacy; it may potentially exert a bystander effect, with *in vitro* data suggesting that PBD warhead released from dying CD25-expressing cells could contribute to a reduction in surrounding CD25-negative tumor cells.12 Notably, the CD25-directed fusion protein denileukin diftitox showed efficacy (ORR: 30·6%) in patients with CTCL who had only CD25 expression on <20% of malignant T cells.30

While common in Phase 1 studies, the single-arm design and small sample size are potential limitations of this study, in addition to the lack of statistical comparison between subgroups and T-cell profiles, and paucity of time-to-event data for patients with B-NHL. Notwithstanding these considerations, based on the encouraging results, further evaluation of camidanlumab tesirine in cHL and T-NHL is warranted. A pivotal Phase 2 trial of camidanlumab tesirine is evaluating initial dosing at 45 μg/kg for two cycles, followed by dose reduction to 30 μg/kg for remaining cycles to maintain responses whilst minimizing risks of potential toxicity in patients with R/R cHL (NCT04052997).

### Data sharing statement

Study Protocol and Statistical Analysis Plan are available (see appendix). Summary data for study NCT02432235 are available at [ClinicalTrials.gov](https://protect-eu.mimecast.com/s/cy_SCjqVjsjNRYvURA0U1?domain=clinicaltrials.gov). Requests regarding data collected for the study may be sent to clinical.trials@adctherapeutics.com.

### Contributions

All authors met ICMJE criteria for authorship.

MH, GPC, PFC, FS, AS, AD, JR, TM, AK, JMZ, PF, and SHo were Principal Investigators with the following contributions: provision of patient care; data acquisition and interpretation; development and critical revision of the manuscript; and provision of final approval of the submitted content and have agreed to be accountable for all aspects of the work, including its accuracy and integrity.

The contributions of KH, HGC, SHe, JB, JF, and JW were as follows: conception or design of the study; data analysis and interpretation; development and critical revision of the manuscript; and provision of final approval of the submitted content, and they have agreed to be accountable for all aspects of the work, including its accuracy and integrity.

SHe, HGC, and SHo had full access to, and verified, the data.

Statistical analyses were provided by SHe. Analyses of PK/PD profiles and parameters were conducted by JB and KH.

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**Figure 1. Trial profile**

**164 patients screened**

**31 ineligible**

**133 patients enrolled and treated**

**Part 1 – Dose escalation and exploration (n=87)**

**Dose escalation (n=31)**

3 µg/kg (n=2)

5 µg/kg (n=2)

8 µg/kg (n=2)

13 µg/kg (n=2)

20 µg/kg (n=2)

30 μg/kg (n=5)

45 µg/kg (n=2)

60 µg/kg (n=4)

80 µg/kg (n=5)

100 µg/kg (n=3)

150 µg/kg (n=2)

**Dose exploration (n=56)**

13 µg/kg (n=1)

30 μg/kg (n=6\*)

45 µg/kg (n=13)

60 µg/kg (n=25)

80 µg/kg (n=11)

**Part 2 – Dose expansion (n=46)**

**NHL**

80 µg/kg (n=10)

**cHL**

30 µg/kg (n=10)

45 µg/kg (n=26)

**Patient disposition by cohort**

**cHL cohort: 77 enrolled and treated**

**NHL cohort: 56 enrolled and treated**

**56 discontinued treatment**

Disease progression (n=34)

Adverse events (n=10)

Death (n=5)

Physician decision (n=2)

Withdrawal by patient (n=1)

Other‡ (n=4)

**77 discontinued treatment**

Disease progression (n=27)

Adverse events (n=23)

Physician decision (n=7)

Withdrawal by patient (n=5)

Study terminated by sponsor (n=1)

Death (n=2)

Other† (n=12)

**77 discontinued study**

Completed (n=39)

Death (n=15)

Withdrawal by patient (n=11)

Lost to follow-up (n=2)

Other§ (n=10)

**56 discontinued study**

Death (n=40)

Completed (n=9)

Withdrawal by patient (n=1)

Other|| (n=6)

**5 excluded from IHC analysis**

 Biopsy/correlative

 endpoint not available

**77 analyzed for primary endpoint**

**56 analyzed for primary endpoint**

**1 excluded from DLT analysis**

 Disease progression prior to completion of DLT period. No DLTs

**3 excluded from efficacy analysis#**

 No valid post-baseline

 disease assessment prior

 to subsequent therapy

**5 excluded from IHC analysis**

 Biopsy/correlative

 endpoint not available

\*One patient received an unplanned overdose of 300 µg/kg for the first dose but continued in the study with subsequent dosing, as planned, at 30 µg/kg.

†Other reasons for treatment discontinuation in the cHL cohort included transition to transplant (n=7), decision by patient (n=2), per protocol temporary halt on the study (screening and dosing) (n=2), and treatment discontinuation due to GBS risk (n=1).

‡Other reasons for treatment discontinuation in the NHL cohort included decision by patient (n=2), lack of response (n=1), and partial clinical hold by the US FDA (n=1).

§Other reasons for study discontinuation in the cHL cohort included study terminated by the Sponsor (n=8), toxicity (n=1), and transition to palliative care (n=1).

||Other reasons for study discontinuation in the NHL cohort included decision by Sponsor (n=3), toxicity (n=1), transition to palliative care (n=1), and partial clinical hold by the US FDA (n=1).

#Progressive disease or death was not reported for these three patients.

cHL, classical Hodgkin lymphoma; DLT, dose-limiting toxicity; FDA, Food and Drug Administration; GBS, Guillain–Barré syndrome; IHC, immunohistochemistry; NHL, non-Hodgkin lymphoma.

**Figure 2. Swimmer plot showing treatment responses for patients with (A) cHL and (B) NHL (efficacy analysis set)**





Each bar represents one patient. \*Only for censored patients who discontinued trial due to reasons other than progression or who go on to a different anticancer treatment.
cHL, classical Hodgkin lymphoma; NHL, non-Hodgkin lymphoma

**Figure 3**. **Kaplan–Meier curves showing: A) median DoR and B) median PFS for all doses and for the 45 μg/kg dose cohort; and C) median OS for all doses in patients with cHL**



Number of patients at risk includes patients who remained for observation at a specific time point, while censored numbers include patients censored cumulatively prior to that time point.

cHL, classical Hodgkin lymphoma; DoR, duration of response; OS, overall survival; PFS, progression-free survival**.**