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ORIGINAL PAPER

Haematological Malignancy – Clinical

Targeting CD25+ lymphoma cells with the antibody–drug conjugate camidanlumab tesirine as a single agent or in combination with targeted agents

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Summary
Camidanlumab tesirine (ADCT-301) is a CD25-specific antibody-drug conjugate (ADC) employing SG3199, a highly cytotoxic DNA minor groove cross-linking pyrrolobenzodiazepine dimer. The ADC has shown early clinical antitumour activity in various cancers, including B- and T-cell lymphomas. We assessed its preclinical activity as a single agent in 57 lymphoma cell lines and in combination with selected drugs in T-cell lymphoma-derived cell lines. Cells were exposed to increasing concentrations of the ADC or SG3199 for 96 h, followed by an MTT proliferation assay. CD25 expression was measured at cell surface and RNA levels. Experiments with PDX-derived cell lines were used for validation studies. Camidanlumab tesirine presented more potent single agent in vitro cytotoxic activity in T- than B-cell lymphomas. In vitro activity was correlated with CD25 cell surface and RNA expression. In vitro activity was correlated with CD25 cell surface and RNA expression. When camidanlumab tesirine-containing combinations were evaluated in four T-cell lymphoma models, the most active partners were everolimus, copanlisib, venetoclax, vorinostat, and pralatrexate, followed by bortezomib, romidepsin, bendamustine, and 5-azacytidine. The strong camidanlumab tesirine single-agent anti-lymphoma activity and the in vitro synergisms with targeted agents identify potential combination partners for future clinical studies.

KEYWORDS
antibody-drug conjugate, camidanlumab tesirine, CD25, lymphomas, T-cell lymphoma

INTRODUCTION

Antibody-drug conjugates (ADCs) allow the delivery of potent cytotoxic agents to tumour cells.[1–3] The regulatory approval of various ADCs for patients with haematological cancers or solid tumours demonstrates their clinical relevance.[1–3] A significant factor contributing to their therapeutic window is the choice of the target.[2,3] The IL-2 receptor (IL2R) exists in two functional forms.[4] While the low-affinity form is a dimer, made of a β- (CD122) and a γ-chain (CD132), the high-affinity receptor is a trimeric complex, also including an α-chain (CD25).[4] High levels of the high-affinity IL2R are transiently expressed by CD4+ and CD8+ T cells following T-cell receptor (TCR)

activation.[5] Unlike other T-cell subsets, most regulatory T cells (T_{regs}) express high levels of CD25 and lower levels of CD122 and CD132. Different types of haematological cancers also express CD25. All human adult T-cell leukaemia/lymphoma and hairy cell leukaemia constitutively express CD25.[6,7] In addition, CD25 expression has been observed in approximately 60% of chronic lymphocytic leukaemia (CLL), 60%–90% of Hodgkin lymphomas (HL), 40% of diffuse large B-cell lymphomas (DLBCL), up to 85% of peripheral T-cell lymphomas (PTCL) and 15% of follicular lymphomas.[6,8–15] Due to its expression pattern, CD25 represents a therapeutic target for antibody and cellular therapy-based approaches in oncology and autoimmune disorders.[16–18]

Camidanlumab tesirine, previously known as ADCT-301, is an ADC composed of the human IgG1 HuMax-TAC directed against CD25, stochastically conjugated through a protease cleavable dipeptide linker to a pyrrolobenzodiazepine (PBD) dimer warhead (SG3199).[19] Upon binding to CD25, camidanlumab tesirine internalizes and traffics to the lysosomes where the PBD dimers are released, forming highly cytotoxic DNA interstrand cross-links, causing cell death.[19]

Phase 1 and phase 2 studies have been conducted exploring camidanlumab tesirine in advanced solid tumours, acute myeloid leukaemia (AML), and relapsed refractory Hodgkin and non-Hodgkin lymphoma.[20–22] In the phase 1 study, conducted in relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma, 133 patients were enrolled (77 classical HL and 56 non-Hodgkin lymphoma). The most observed adverse events, including elevated liver enzymes, rash, fatigue, oedema or effusion, and nausea, appeared typical of PBD-containing ADCs and were generally reversible and manageable with dose delays or reductions.[21] Notably, anti-tumoural activity was seen in classical HL and non-Hodgkin lymphomas.[21] In a phase 2 trial, in patients with R/R cHL who had received ≥3 prior systemic therapies, including brentuximab vedotin and anti-PD-1, camidanlumab tesirine showed an overall response rate (ORR) of 70%, with 33% of patients achieving a complete response (CR).[23]

This study aimed to assess the preclinical activity of camidanlumab tesirine as a single agent in an extensive collection of lymphoma cell lines and its potential role as a combination partner.

METHODS

Cell lines

Lymphoma cell lines were cultured according to the recommended conditions, as previously described.[24] All media were supplemented with foetal bovine serum (FBS) (10% or 20%) and penicillin–streptomycin–neomycin (≈5000 units penicillin, 5 mg streptomycin and 10 mg neomycin/mL; Sigma-Aldrich, Darmstadt, Germany). Human cell line identities were confirmed by short tandem repeat DNA fingerprinting using the Promega GenePrint 10 System kit (B9510). Cells were periodically tested for mycoplasma negativity using the MycoAlert Mycoplasma Detection Kit (Lonza, Visp, Switzerland).

Patient-derived tumour xenograft-derived cell lines

To obtain patient-derived tumour xenograft (PDXs), samples from primary anaplastic large-cell lymphoma (ALCL) were implanted subcutaneously (two fragments, 1 mm^3 each) in 4- to 6-week-old (male/female ratio: 1:1) NSG B2m/NSG-MHC I/II DKO mice (Jackson Laboratories, Bar Harbour, ME, USA). Successful engraftments were then serially propagated. Correspondence of PDX with primary samples was confirmed using multicolour flow cytometry, molecular profiling (whole-exome sequencing, RNA-Seq) and drug response.[25–27] De-identified patients' samples were obtained with informed consent under Institutional Review Boards (IRB)-approved protocols, according to the Declaration of Helsinki. Mice were initially purchased, then bred in-house and handled according to the Weill Medical College Institutional Animal Care and Use Committee.

To generate PDX-derived cell lines (PDX-Dlines), PDX tumour tissues were minced and digested for 30–45 min at 37°C. Digestion media were composed of RPMI1640 (Sigma-Aldrich) and digestion buffer (4:1). The digestion buffer was prepared according to the following: 140 nM NaCl (Sigma-Aldrich), 5 mM KCl (Sigma-Aldrich), 2.5 mM phosphate buffer pH 7.4 (prepared solving 3.1 g of NaH_2PO_4–H_2O and 10.9 g of Na_2HPO_4 anhydrous in 1 L of sterile cell culture grade water), 10 mM Hepes (Sigma-Aldrich), 2 mM $CaCl_2$ (Sigma-Aldrich), 1.3 mM $MgCl_2$ (Sigma-Aldrich), 25 mg/mL of collagenase A (Roche, Basel, Switzerland), 25 mg/mL dispase II (Sigma-Aldrich) and 250 mg/mL DNAase (Roche). Digested tissue was then passed through 70 µm nylon filters (Corning, New York, NY, USA), and the resulting cell suspension was washed twice with PBS (Sigma-Aldrich). Cells were resuspended in RPMI1640 (Sigma-Aldrich) plus 20% FBS (Gibco) and seeded at 1 million/mL in T150 flasks (Corning) overnight. T-cell suspensions were cultured (RPMI1640 20% FBS—Sigma/Corning) and eventually passed (1:2) over time. Media were supplemented with 20% FBS (Corning), 100 U/mL glutamine (Sigma), normocin 1:500 (InvivoGen, San Diego, CA, USA), 100 µg/mL streptomycin (Sigma-Aldrich) and initially supplemented with exogenous IL-2 (50 U/mL), IL7 (20 µg/mL) and IL15 (10 µg/mL, R&D). Exogenous lymphokines were ultimately excluded when possible. The correspondence of PDX-Dlines with the donor PDXs was confirmed by flow cytometry and molecular assays (whole-exome sequencing and RNAseq).[25,26] Genotyping was performed once a year (Bio-Synthesis Inc, Lewisville, TX, USA). PDX and PDX-Dlines were produced in the context of protocols approved by Cornell University (IRB: 107004999, 0201005295 and 1 410 015 560; Universal consent: 1302013582; in vivo protocol 2014-0024).

To determine the expression of CD25, 1 × 106 cells were pre-incubated with FcR blocking reagent (catalogue no. 130-059-901; Miltenyi Biotec, Bisley, UK) to prevent unspecific binding of staining antibodies, following manufacturer's instructions and then stained with anti-Hu-CD25 antibody (PE-CF594 mouse anti-human CD25-562694; BD Biosciences, Allschwil, Switzerland) and compared to unstained cells. Median fluorescence intensities were acquired in a BD LSRFortessa instrument (BD Biosciences), and data were analysed using FlowJo software (TreeStar Inc., Ashland, OR USA).

Compounds

Camidanlumab tesirine, SG3199 (warhead), and B12-SG3249 (isotype control ADC) were provided by ADC Therapeutics. Everolimus, pralatrexate, vorinostat, bortezomib, venetoclax, copanlisib, romidepsin, bendamustine and 5-azacytidine were purchased from Selleckchem (Houston, TX, USA).

Cytotoxic activity in single and combination

Anti-proliferative activity after treatment was assessed as previously described.[28] Briefly, cells were exposed to ADCT-301, B12-SG3249 or SG3199 for 96 hours and assayed by MTT [3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazoliumbromide]. Synergism assessment was done by exposing cells (96 h) to increasing doses (0.005 pM up to 50 nM) of camidanlumab tesirine and of other agents alone or in combination, followed by MTT assay and determination of the Chou-Talalay combination index (CI)[29] or ZIP, HAS, Loewe and Bliss parameters using SynergyFinder software.[30,31] Concentrations of compounds that, after 96 h of treatment, left 10% or less of proliferating cells already with the single agent were discarded from further analyses. Combinations were defined as synergistic (median CI < 0.9), additive (median CI, 0–9–1.1), or of no benefit/antagonist (median CI > 1.1). The range of drug concentrations for combination screening were as follows: camidanlumab tesirine (from 100 pM to 0.02 nM, 1:4 dilutions); 5-azacytidine (from 500 to 0.70 nM, 1:3 dilutions); bendamustine (from 20 μM to 5 nM, 1:4 dilutions); bortezomib (from 2 nM to 0.003 nM, 1:3 dilutions); copanlisib (from 2 μM to 0.5 nM, 1:4 dilutions); everolimus (from 1 μM to 0.25 nM, 1:4 dilutions); pralatrexate (from 10 to 0.01 nM, 1:3 dilutions); romidepsin (10 nM to 0.16 nM; 1:2 dilutions); venetoclax (from 10 μM to 2.44 nM, 1:4 dilutions); and vorinostat (from 2 μM to 31 nM, 1:2 dilutions).

CD25 expression

The Quantum simply cellular (QSC) anti-human IgG beads (Bangs Laboratories, Fishers, IN USA) were used to establish A calibration curve for determining the absolute CD25 surface expression. Subsequently, the antibody binding capacity (ABC) values were normalized to the control isotype antibody B12.

CD25 RNA expression values were extracted from previously reported datasets obtained using Illumina HT-12 arrays (GSE94669[32]), HTG EdgeSeq Oncology Biomarker Panel (GSE103934[32]), and total-RNA-Seq (GSE221770[24]).

Data analysis

Pearson correlation (r) was calculated for IC50 values, cell surface CD25 expression levels versus RNA levels, and all other correlations. *BCL2* and/or *MYC* translocations and *TP53* inactivation were retrieved from our previous publication.[32] Differences in IC50 values among lymphoma subtypes were calculated using the non-parametric Mann–Whitney t-test. p values of 0.05 or less defined statistical significance. Statistical analyses, correlations, and boxplots were performed using GraphPad Prism.

RESULTS

The in vitro antitumour activity of camidanlumab tesirine is dependent on CD25 expression

A panel of lymphoma cell lines were exposed to increasing concentrations of the CD25-targeting ADC camidanlumab tesirine for 96 h. The human lymphoma cell lines were derived from activated B-cell-like (ABC; $n = 7$) and germinal centre B-cell-like (GCB) DLBCL ($n = 19$), mantle cell lymphoma (MCL; $n = 10$), marginal-zone lymphoma (MZL; $n = 6$), ALK+ ALCL ($n = 4$), cutaneous T-cell lymphoma (CTCL; $n = 4$), CLL ($n = 2$), HL ($n = 3$), primary mediastinal B-cell lymphoma and ALK– ALCL ($n = 1$).

The median IC50 of camidanlumab tesirine was 650 pM across all cell lines (Table 1; Table S1). On the contrary, the isotype control ADC B12-SG3249 did not show activity in cell lines sensitive to camidanlumab tesirine (Table S1). The cytotoxic activity of camidanlumab tesirine was highly dependent on CD25 expression as demonstrated by a negative correlation between IC50 values and both CD25 protein levels on the cell surface ($n = 57$, Pearson $r = -0.369$, $p = 0.0047$) as well as CD25 RNA levels ($n = 50$, Pearson $r = -0.56$, $p < 0.0001$ [Illumina arrays]; $n = 36$, Pearson $r = -0.59$, $p < 0.0001$ [HTG]; and $n = 53$, Pearson $r = -0.65$, $p < 0.0001$ [total RNA-seq]) (Figure 1). Cell lines could be divided into two groups based on their CD25 expression and sensitivity to camidanlumab tesirine to underline this association further. Cells having IC50 below 5 pM had a significantly higher CD25 expression compared to cells with IC50 higher than 5 pM ($p < 0.0001$) (Figure 2).

Among the individual lymphoma histotypes, the most sensitive cell lines derived from ALK+ and ALK– ALCL (Table 1) are the two subtypes with the highest CD25 surface expression (Figure 2). Indeed, CD25 surface expression was much higher in T- ($n = 9$, median antibody-binding capacity 212 921; 95% C.I., 10 915–334 885) than in B-cell

TABLE 1 Camidanlumab tesirine has in vitro anti-proliferative activity in lymphoma cell lines. Median IC50 values of two independent experiments in 60 lymphoma cell lines. MTT proliferation assay and IC50 calculation on cell lines exposed (96 h) to increasing camidanlumab tesirine concentrations.

Histotype	Number of cell lines	Median IC50 (pM)	95% CI (pM)
ABC DLBCL	7	750	550–4100
ALK– ALCL	1	3	n/a
ALK+ ALCL	4	3.5	1.8–7.4
Canine B-cell lymphoma	1	225	n/a
CLL	2	2629	7.25–5250
CTCL	4	845	198–30 000
GCB DLBCL	19	1250	6.3–4000
HL	3	3500	350–20 000
MCL	10	825	400–2750
Murine B-cell lymphoma	2	1475	500–2450
MZL	6	75.63	0.225–800
PMBCL	1	2	n/a

Abbreviations: ABC, activated B cell; ALCL, anaplastic large-cell lymphoma; CLL, chronic lymphocytic leukaemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B cell; HL, Hodgkin's lymphoma; MCL, mantle cell lymphoma; MZL, marginal-zone lymphoma; PMBCL, primary mediastinal large B-cell lymphoma.

lymphomas ($n = 48$, median antibody-binding capacity 6511 95% C.I., 2055–17 910) ($p = 0.0024$) (Figure 3). Among T-cell lymphomas, CTCL cell lines showed low CD25 expression at levels of B-cell lymphoma. The difference in CD25 expression between B- and T-cell lymphomas was matched with the more potent cytotoxic activity of camidanlumab tesirine in cell lines derived from T-cell-expressing CD25 ($n = 6$, median IC50 = 3 pM; 95% C.I., 1.5 pM–0.9 nM) than from B-cell lymphomas ($n = 48$, 725 pM; 95% C.I., 350 pM–2.5 nM) ($p = 0.0024$) (Figure 3).

Camidanlumab tesirine was also tested in three non-human lymphoma cell lines. IC50 values were 2.5 nM and 500 pM in two mouse cell lines and 225 pM in a canine DLBCL cell line (Table S1), indicating that camidanlumab tesirine is not cross-reactive with mouse and dog CD25. Indeed, a mouse CD25 cross-reactive surrogate ADC for camidanlumab tesirine has been developed to perform ADC studies in syngeneic mouse models.[33]

Within the group of DLBCL cell lines, there was no association between sensitivity to camidanlumab tesirine and the presence of *BCL2* and *MYC* translocations or *TP53* inactivation (Figure S1), similarly reported for other ADCs containing new generations of DNA-targeting payloads.[34,35] The activity of camidanlumab tesirine was finally tested in two PDX-Dlines derived from ALK+ (DN03) and

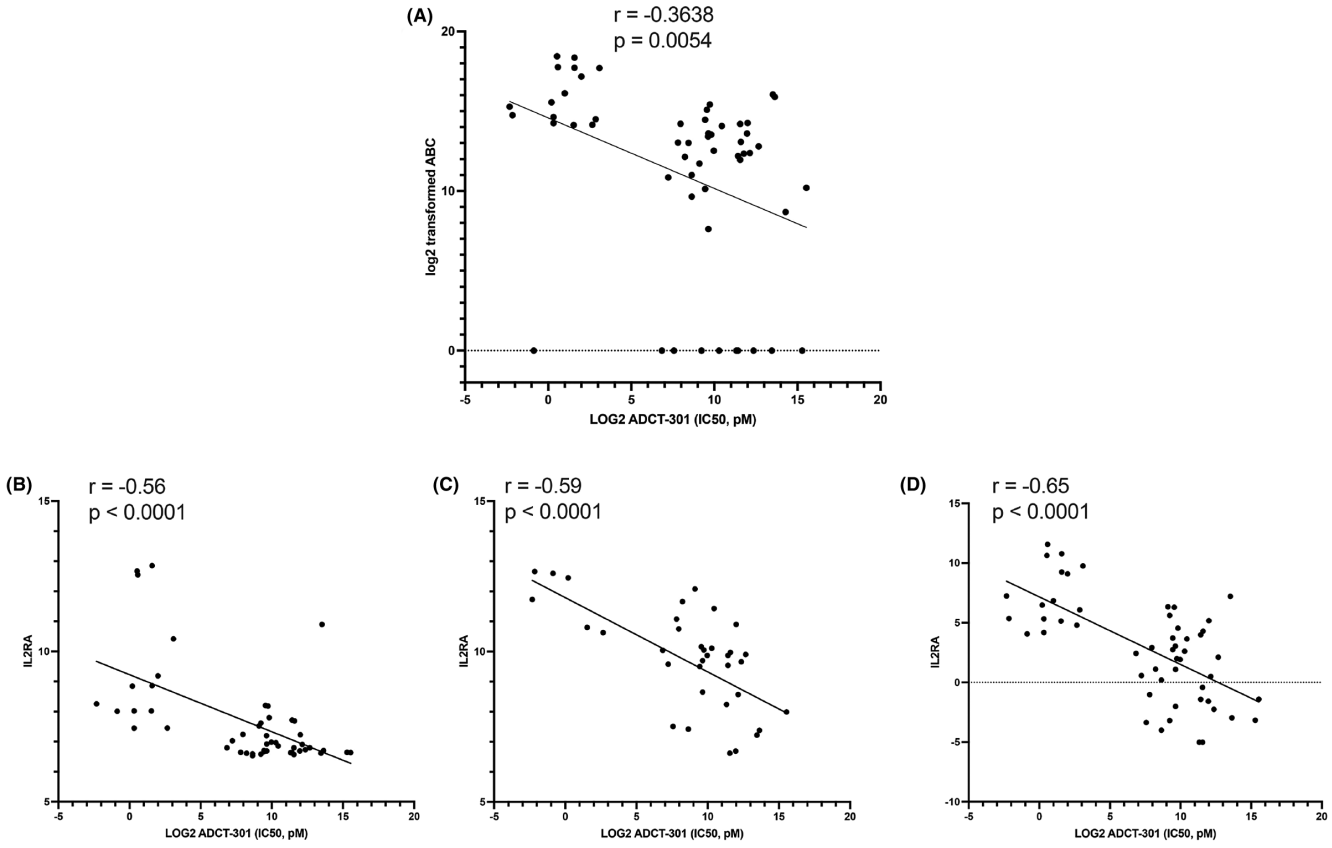

FIGURE 1 Correlation between camidanlumab tesirine (ADCT-301) IC50 and CD25 protein surface or RNA expression. (A) Correlation between camidanlumab tesirine (ADCT-301) IC50 and CD25 surface expression. (B–D) Correlation between camidanlumab tesirine (ADCT-301) IC50 and CD25 (*IL2RA*) RNA expression analysed by Illumina arrays, HTG or total RNA-seq respectively. Pearson correlation performed. ABC, antibody-binding capacity.

ALK– (Belli-CD30) ALCL. Both PDX-Dlines were confirmed to express high levels of CD25 (Figure S2). Camidanlumab tesirine showed potent activity in the two PDX cell lines tested, DN03 and Belli-CD30, with IC50 below 0.05 pM and around 0.2 pM, respectively (Figure S2).

The in vitro cytotoxic activity of camidanlumab tesirine is correlated with its warhead

In parallel to the ADC, all the cell lines were also exposed to SG3199, camidanlumab tesirine's warhead. (Table S1) When we correlated the IC50 obtained with camidanlumab tesirine against the antitumour activity of SG3199, cell lines appeared divided into two clusters, driven by the sensitivity to camidanlumab tesirine in line with what was observed regarding CD25 expression (Figure 4). For both the camidanlumab tesirine-sensitive and the camidanlumab tesirine-resistant cell lines, the pattern of activity of the ADC was correlated to its warhead. The correlations were weaker among the sensitive (SG3199; $r = 0.62$, $p = 0.01$), while they appeared more robust in the resistant group (SG3199, $r = 0.8$, $p < 0.0001$) (Figure 4). Differently from camidanlumab tesirine, SG3199 was also active in the murine and canine cell lines (Table S1).

Camidanlumab tesirine-based combinations are active in T-cell lymphoma models

Next, we explored camidanlumab tesirine-based combinations in T-cell lymphoma models. Four cell lines derived from ALK+ ALCL (Karpas-299, KI-JK), CTCL (MAC-1), and ALK– ALCL (FE-PD) were exposed to camidanlumab tesirine in combination with drugs known to have clinical activity against T-cell lymphomas[36] (Table 2; Table S1). Camidanlumab tesirine plus the mTOR inhibitor everolimus showed synergism/additivity in all four cell lines tested. The combination with the folate antagonist pralatrexate showed synergism/benefit in the two ALK+ ALCL cell lines tested. A combination of class I and II HDAC inhibitor vorinostat was synergistic or additive in all four cell lines tested. The combination with bortezomib led to synergism in the CTCL and ALK– ALCL cells and additivity in the two ALK+ ALCL cells. Combinations with the BCL2 inhibitor venetoclax were synergistic in the ALK+ALCL and CTCL models but not beneficial in the ALK– ALCL. Based on the CI

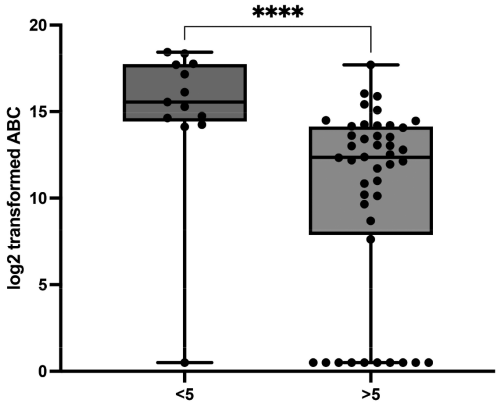

FIGURE 2 CD25 surface expression in cell lines where camidanlumab tesirine has IC50 higher or lower than 5 pM. ABC, antibody-binding capacity. Mann–Whiney test performed; ****$p < 0.0001$.

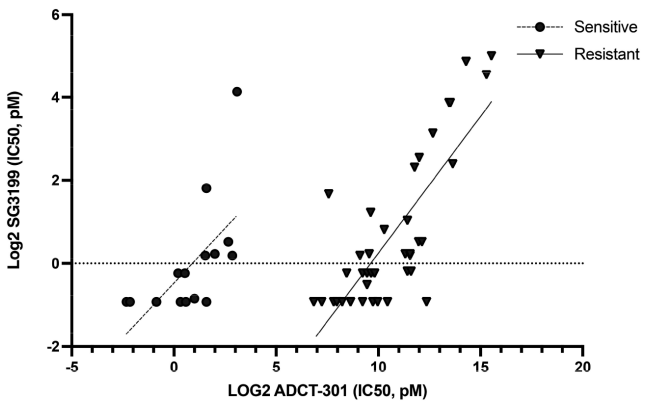

FIGURE 4 Correlation between IC50 values of camidanlumab tesirine (ADCT-301) and its warhead SG3199.

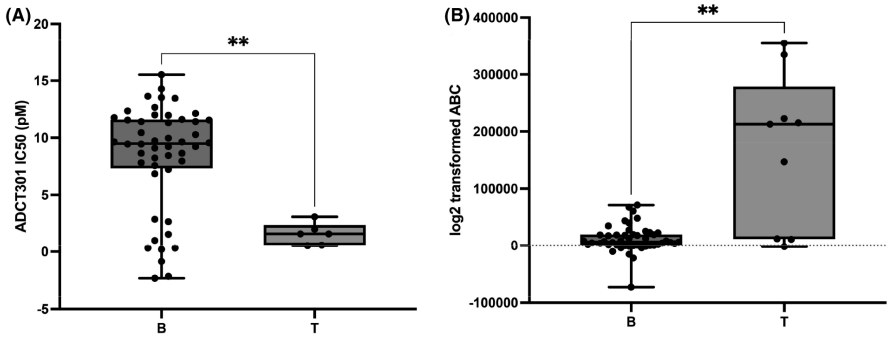

FIGURE 3 Sensitivity to camidanlumab tesirine (ADCT-301) and CD25 expression in B- versus T-cell lymphoma. (A) Camidanlumab tesirine (ADCT-301) IC50 (pM) in B-cell lymphoma compared to T-cell lymphoma cell lines. (B) CD25 surface expression in B-cell lymphoma compared to T-cell lymphoma cell lines. ABC, antibody-binding capacity. Mann–Whiney test performed; ns = non-significant; **$p < 0.01$.

TABLE 2 Camidanlumab tesirine containing combinations in T-cell lymphoma cell lines.

Combination partner	Histology	Cell line	Median combination index	95% C.I.	ZIP	HSA	Loewe	Bliss
Bendamustine	ALK– ALCL	FE-PD	0.91	0.45–1.75	−3.57	−3.78	−5.04	−5.39
	ALK+ ALCL	Karpas-299	0.57	0.29–0.84	2.08	4.84	4.46	3.01
	ALK+ ALCL	KI-JK	1.17	0.57–2.42	−2.16	−0.17	−1.66	−1.06
	CTCL (CD30+)	MAC1	1.73	0.33–5.71	−10.76	0.50	1.51	−12.34
Copanlisib	ALK– ALCL	FE-PD	0.66	0.22–1.47	1.85	5.83	−3.40	3.23
	ALK+ ALCL	Karpas-299	0.84	0.47–2.31	2.35	3.79	3.00	0.46
	ALK+ ALCL	KI-JK	1.26	0.84–1.9	−1.13	3.15	0.37	−1.32
	CTCL (CD30+)	MAC1	0.38	0.17–0.96	4.60	6.70	6.37	3.84
Venetoclax	ALK– ALCL	FE-PD	1.68	0.67–2.1	0.87	4.66	0.17	2.94
	ALK+ ALCL	Karpas-299	0.44	0.27–0.68	3.18	6.08	4.18	4.26
	ALK+ ALCL	KI-JK	0.55	0.38–0.67	4.54	6.06	5.43	5.93
	CTCL (CD30+)	MAC1	0.42	0.32–0.57	−0.71	7.41	6.41	−0.54
Everolimus	ALK– ALCL	FE-PD	0.05	0.03–0.07	0.26	6.58	4.19	0.42
	ALK+ ALCL	Karpas-299	0.03	0.02–0.04	−0.45	6.81	6.46	−0.80
	ALK+ ALCL	KI-JK	0.03	0.02–0.05	2.93	13.19	12.85	2.44
	CTCL (CD30+)	MAC1	0.74	0.27–1.18	−0.68	6.03	5.95	−0.60
5-Azacytidine	ALK– ALCL	FE-PD	>3	>3	−2.38	−1.04	−0.47	−2.99
	ALK+ ALCL	Karpas-299	0.6	0.36–0.97	−5.85	3.60	3.24	−6.52
	ALK+ ALCL	KI-JK	>3	0.38 to >3	−1.79	−1.49	−2.28	−2.26
	CTCL (CD30+)	MAC1	1.87	0.70 to >3	−4.14	−1.31	−2.79	−3.58
Bortezomib	ALK– ALCL	FE-PD	0.13	0.06–0.1985	1.91	4.98	4.94	2.11
	ALK+ ALCL	Karpas-299	0.93	0.4412–1.31	9.96	12.42	11.61	10.01
	ALK+ ALCL	KI-JK	1.03	0.62–1.73	2.67	6.93	6.13	2.14
	CTCL (CD30+)	MAC1	0.31	0.17–0.41	2.68	6.60	6.03	2.71
Pralatrexate	ALK– ALCL	FE-PD	1.49	1.2–1.594	1.06	6.24	−26.25	0.83
	ALK+ ALCL	Karpas-299	0.5	0.19–1.44	−3.65	1.68	0.42	−3.84
	ALK+ ALCL	KI-JK	0.5	0.18–1.28	−3.67	1.02	−0.40	−3.90
	CTCL (CD30+)	MAC1	1.22	0.85–1.38	−3.93	0.33	−6.33	−4.00
Romidepsin	ALK– ALCL	FE-PD	1.16	0.81–8.3	0.56	1.44	−23.02	−0.83
	ALK+ ALCL	Karpas-299	0.85	0.64–1.1	3.33	4.61	3.65	3.28
	ALK+ ALCL	KI-JK	0.89	0.79–1.19	4.97	7.90	0.42	5.36
	CTCL (CD30+)	MAC1	1.25	0.43 to >3	5.41	−0.94	−10.12	2.55
Vorinostat	ALK– ALCL	FE-PD	0.85	0.64–2.08	0.10	2.80	−2.17	−1.70
	ALK+ ALCL	Karpas-299	0.96	0.43–1.44	1.70	3.37	−13.54	0.79
	ALK+ ALCL	KI-JK	0.55	0.47–0.59	5.31	7.86	3.31	4.88
	CTCL (CD30+)	MAC1	0.4	0.11–0.72	8.37	10.88	5.75	8.16

Note: Synergism, additive and no-benefit effects were defined using the Chou–Talalay combination index (CI) or ZIP, HAS, Loewe and Bliss parameters. Synergism, CI < 0.9 or ZIP, HAS, Loewe, Bliss >10 (red); additive effect, 0.9 < CI < 1.1 or ZIP, HAS, Loewe, Bliss between −10 and 10 (yellow); no benefit, CI >1.1 or ZIP, HAS, Loewe, Bliss < −10 (blue).

Abbreviations: 95% C.I., 95% confidence interval; ALCL, anaplastic large cell lymphoma; CTCL, cutaneous T-cell lymphoma.

index, the PI3K inhibitor copanlisib synergized with camidanlumab tesirine in the CTCL, the ALK– ALCL, and only one ALK+ALCL (Karpas-299). The latter two also achieved synergy by adding the class I HDAC inhibitor romidepsin, while no benefit was seen in the other cell lines. The combination with the chemotherapy agent bendamustine showed synergy/additivity in one ALK+ ALCL (Karpas-299) and the ALK– ALCL but no or marginal benefit in the other models. Finally, the demethylating agent 5-azacytidine was synergistic/additive only in one ALK+ ALCL (Karpas-299), and it was of no or marginally beneficial in the remaining three cell lines (Table 2; Table S1). Since vorinostat and romidepsin are already approved for the treatment of T-cell lymphomas, we tested them in the two PDX-derived cell lines, showing

synergism/additivity with vorinostat and mild or no benefit with romidepsin depending on the synergy parameter (Figure S3).

DISCUSSION

In this manuscript, we show that camidanlumab tesirine has potent in vitro cytotoxic activity in models of CD25-positive lymphomas, and its antitumour activity increases when combined with a series of additional anti-cancer agents.

Camidanlumab tesirine has been initially studied in four CD25-positive cell lines (two ALCL and two HL) and three CD25-negative cell lines (two Burkitt lymphoma and one CTCL).[19] In this publication, camidanlumab tesirine had cytotoxic activity only in the CD25-positive cell lines, and no correlation between expression and activity among the CD25-positive cell lines could be established.[19] Here, we extended the analysis to a broader panel of cell lines derived from B- and T-cell mature lymphomas with different CD25 expression levels. Increasing the number of cell lines led to a strong association between CD25 expression and camidanlumab tesirine antitumour activity. The antitumour activity was highly dependent on CD25 expression, both at the protein level on the cell surface and, even more, at the RNA level, independently from the technologies employed to measure it. The latter also included a targeted RNA-Seq approach designed explicitly for formalin-fixed paraffin-embedded materials, thus easily transferrable to clinical specimens. The higher correlation with CD25 RNA levels might be due to technical issues that make the flow cytometry measurements to assess CD25 protein levels less robust than RNA-based techniques.

In line with the pattern of CD25 expression in clinical specimens,[7,10] we observed a higher expression of CD25 in cell lines derived from mature T-cell lymphomas. This was reflected by a higher in vitro camidanlumab tesirine antitumour activity in T- than B-cell lymphomas. This finding supports what was observed in the phase 1 study, in which the ORR in patients with T-cell lymphoma was twice as high as that observed in the B-cell lymphoma population (48% vs. 23%).[21] In the phase 1 study, the highest ORR and CR rates were seen in r/r HL (71% and 42%, respectively),[21] later confirmed in the phase 2 study (70% and 33%, respectively).[23] Notably, the three HL-derived cell lines tested in our research, which differed from the ones previously tested,[19] were not sensitive to camidanlumab tesirine. In the phase 1 study, a higher CD25 histoscore was associated with higher ORR among HL patients.[21] A correlation between the antitumour activity of an ADC and its target expression is often, but not always, observed due to complex interaction between characteristics of the ADC and its target in the tumour cells.[35,37–45]

Both among the camidanlumab tesirine-sensitive and the camidanlumab tesirine-resistant cell lines, the pattern of activity of the ADC was correlated with that of its warhead SG3199. The correlation was weaker among the sensitive models and appeared more robust in the resistant group. These data suggest that CD25 expression levels and the intrinsic degree of sensitivity of each tumour to the PBD dimer warhead SG3199 are the most decisive factors in driving sensitivity to camidanlumab tesirine. The latter point highlights the importance of optimizing the warheads as a fundamental step to fully exploit the potential offered by the targeted delivery that an ADC allows. The direct effect of camidanlumab tesirine on tumoural cells might not be the only mechanism of action, but it can also exploit a modulation of the immune microenvironment. CD25 is highly expressed in tumour-infiltrating T_{regs} and on activated CD8+ T_{eff} cells. Indeed, camidanlumab tesirine has been shown to exploit its anti-tumoural activity by depleting tumour-infiltrating T_{regs} in favour of CD8+ Teff cells that were unaffected.[33]

Although we can expect the target down-regulation to be a mechanism of resistance, the fact that the activity of camidanlumab tesirine is strictly dependent on CD25 reduces the possibility of an off-target effect. Moreover, the phase 1 study has shown an encouraging safety profile without reaching a maximum tolerated dose.[22]

Finally, focusing on the T-cell lymphoma models, we explored the potential benefit of adding camidanlumab tesirine to drugs approved by the US Food and Drug Administration (FDA) for patients with T-cell lymphomas[46] or with antitumour activity reported in lymphomas.[47–50] We observed synergism, especially when we combined camidanlumab tesirine with everolimus, vorinostat, bortezomib, copanlisib, venetoclax and pralatrexate. The activity data in two CD25+ two PDX-Dlines derived from ALK+ and ALK– ALCL obtained with vorinostat and romidepsin further suggest the HDAC inhibitors as the most exciting combination partners to be prioritized for future clinical trials with camidanlumab tesirine in patients with T-cell lymphomas in which they are approved as single agents.[47–50] Furthermore, data from AML patients show the clinical feasibility of combining an ADC containing a DNA-damaging toxin with class I and II HDAC inhibitors.[51,52] Conversely, the combination of camidanlumab tesirine with the mTOR inhibitor everolimus appeared in vitro very active. Still, it might be challenging to translate in the clinical setting based on the toxicity observed in a phase 1 study that explored the combination of another mTOR inhibitor, temsirolimus, with inotuzumab ozogamicin, a CD22-targeting ADC containing a DNA-damaging toxin.[53]

PI3K inhibitors are potentially interesting agents for T-cell lymphoma patients.[54,55] Our in vitro data show the benefit of combining them with camidanlumab tesirine. Furthermore, this combination might also be boosted by the depletion of the tumour-infiltrating T_{regs} expected with both classes of drugs.[24,33,56]

Pralatrexate has been safely combined with standard CHOP (Fol-CHOP) in a phase 1 study for first-line PTCL patients, making the combination with camidanlumab tesirine to be considered for clinical evaluation. Venetoclax has shown low clinical activity in PTCL patients,[57] but it might work more in combination,[58] as observed here with camidanlumab tesirine. Hints on the feasibility of this combination

will come from the ongoing phase 1 trial exploring the CD19-targeting ADC loncastuximab tesirine (ADCT-402) based on the same payload as camidanlumab tesirine and venetoclax for R/R lymphoma patients (NCT05053659).

The benefit previously reported for combining the BCMA-targeting, PBD-containing MEDI2228, with bortezomib in multiple myeloma models[59] supports our data with camidanlumab tesirine and the same proteasome inhibitor. So far, clinical safety data are only available for combining bortezomib with the BCMA-targeting belantamab mafodotin, which has a tubulin-damaging payload.[60]

The results obtained for camidanlumab tesirine in combination with bendamustine are perhaps slightly worse than what has been reported for the combination of camidanlumab tesirine with gemcitabine in three lymphoma models (synergism in two HL and one ALCL cell lines).[61]

One limitation of our combination screening is the absence of PTCL and CD30- CTCL, which comprise a majority compared to CD30+ CTCL. In some cases, the tested combinations showed a benefit that was mainly cell-dependent and not subtype-specific, probably due to the high heterogeneity of T-cell lymphomas. For this reason, it will be important to test the most promising combinations from a clinical perspective (vorinostat, pralatrexate, and romidepsin) also in other T-cell lymphoma models, such as PTCL and CD30- CTCL.

In conclusion, our results show a single solid agent in vitro anti-tumour activity for camidanlumab tesirine in CD25-expressing lymphoma models, especially in T-cell lymphomas. Our data also identified possible combination partners that could be clinically explored, including HDAC inhibitors, PI3K and BCL2 inhibitors, and folate antagonists.

AUTHOR CONTRIBUTIONS

Filippo Spriano: performed experiments, data mining, interpreted data and co-wrote the manuscript. Chiara Tarantelli and Eugenio Gaudio: performed experiments and interpreted data. Luciano Cascione: performed data mining. Gaetanina Golino, Lorenzo Scalise and Maria Teresa Cacciapuoti: performed experiments. Giorgio Inghirami: provided advice, characterized PDX cells and provided resources. Emanuele Zucca and Anastasios Stathis: provided advice. Patrick H. Van Berkel and Francesca Zammarchi: co-designed the study, provided reagents and supervised the study. Francesco Bertoni: co-designed the study, performed data mining, interpreted data, supervised the study and co-wrote the manuscript. All authors reviewed and accepted the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Patrick H. Van Berkel and Francesca Zammarchi: ADC Therapeutics employees and stock owners. Chiara Tarantelli: travel grant from iOnctura. Luciano Cascione: travel grant from HTG Molecular Diagnostics. Gaetanina Golino: currently an employee at Daiichi Sankyo Italia. Lorenzo Scalise: presently an employee at SFL, a Veristat company. Emanuele Zucca: institutional research funds from Celgene, Roche and Janssen; advisory board fees from Celgene, Roche, Mei Pharma, Astra Zeneca and Celltrion Healthcare; travel grants from Abbvie and Gilead; and he has provided expert statements to Gilead, Bristol-Myers Squibb and MSD. Anastasios Stathis: institutional research funds from Bayer, ImmunoGen, Merck, Pfizer, Novartis, Roche, MEI Pharma and ADC Therapeutics, and travel grants from AbbVie and PharmaMar. Francesco Bertoni: institutional research funds from ADC Therapeutics, Bayer AG, BeiGene, Floratek Pharma, Helsinn, HTG Molecular Diagnostics, Ideogen AG, Idorsia Pharmaceuticals Ltd., Immagene, ImmunoGen, Menarini Ricerche, Nordic Nanovector ASA, Oncternal Therapeutics and Spexis AG; consultancy fee from BIMINI Biotech, Helsinn and Menarini; advisory board fees to institution from Novartis; expert statements provided to HTG Molecular Diagnostics; travel grants from Amgen, Astra Zeneca and iOnctura. The other authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Gene expression data used in the work are available at the National Centre for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo) database with accession numbers GSE94669, GSE221770 and GSE103934.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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