Combination of camidanlumab tesirine, a CD25-targeted ADC, with gemcitabine elicits synergistic anti-tumor activity in preclinical tumor models (Abstract #1178)

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Introduction

Camidanlumab tesirine (a.k.a as cami and previously known as ADCT-301) is an antibody-drug conjugate (ADC) comprised of HuMax®-TAC, a monoclonal antibody directed against human CD25, conjugated to the pyrrolobenzodiazepine dimer payload tesirine[1]. Currently, camidanlumab tesirine is being evaluated in a pivotal Phase 2 clinical trial in patients with relapsed or refractory Hodgkin lymphoma (HL) (NCT04052997) and in a Phase 1b clinical trial in patients with advanced solid tumors (NCT03621982). In pre-clinical studies, camidanlumab tesirine demonstrated strong and durable single agent activity in CD25-expressing lymphoma xenograft models[1] and in vitro it synergised with selected targeted agents[2]. Moreover, CD25-ADC, a mouse CD25 cross-reactive surrogate of camidanlumab tesirine, induced potent anti-tumor immunity against established syngeneic solid tumor models by depleting CD25-positive tumor-infiltrating T regulatory cells (Tregs) and it showed synergistic activity when combined with PD-1 blockade[3].

Aim of the study

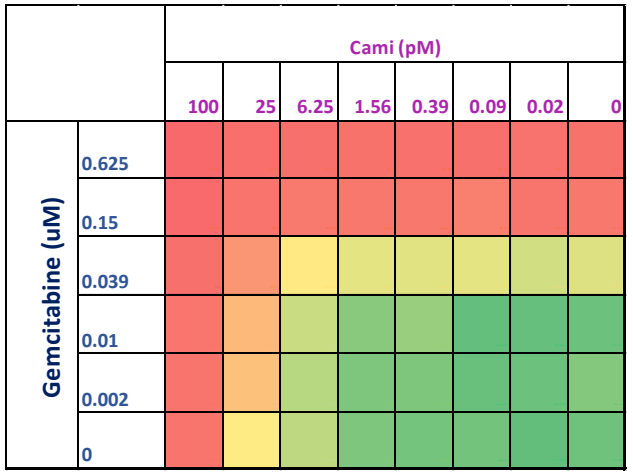
Here, we investigated the *in vitro* and *in vivo* anti-tumor activity of camidanlumab tesirine combined with gemcitabine, a common standard-of-care chemotherapeutic agent used both in a hematological and solid tumor clinical setting.

References

1. Flynn, M.J., et al., ADCT-301, a Pyrrolobenzodiazepine (PBD) Dimer-Containing Antibody-Drug Conjugate (ADC) Targeting CD25-Expressing Hematological Malignancies. Mol Cancer Ther, 2016. 15(11): p. 2709-2721.
2. Spriano, F., et al., The anti-CD25 antibody-drug conjugate camidanlumab tesirine (ADCT-301) presents a strong preclinical activity both as single agent and in combination in lymphoma cell lines. Hematological Oncology, 2019. 37(S2): p. 323-324.
3. Zammarchi, F., et al., A CD25-targeted antibody-drug conjugate depletes regulatory T cells and eliminates established syngeneic tumors via antitumor immunity. Journal for ImmunoTherapy of Cancer, 2020; 8.

Cami shows *in vitro* synergistic efficacy in combination with gemcitabine

A



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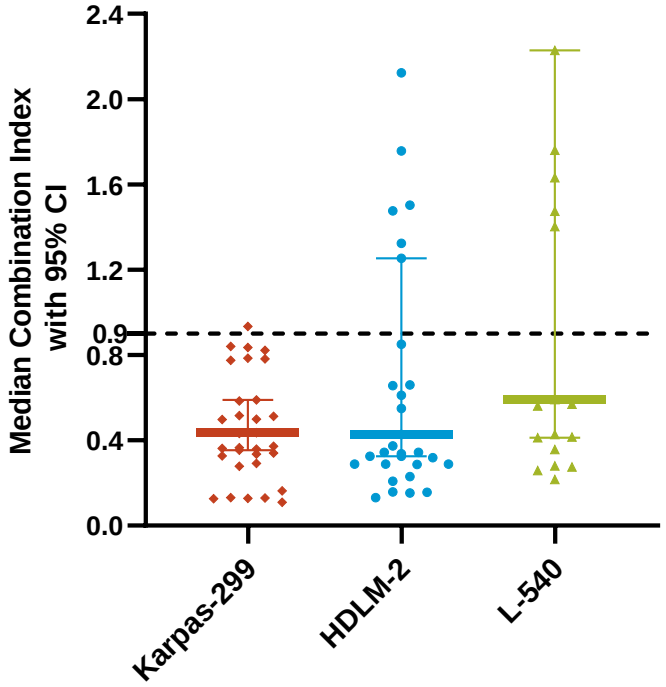
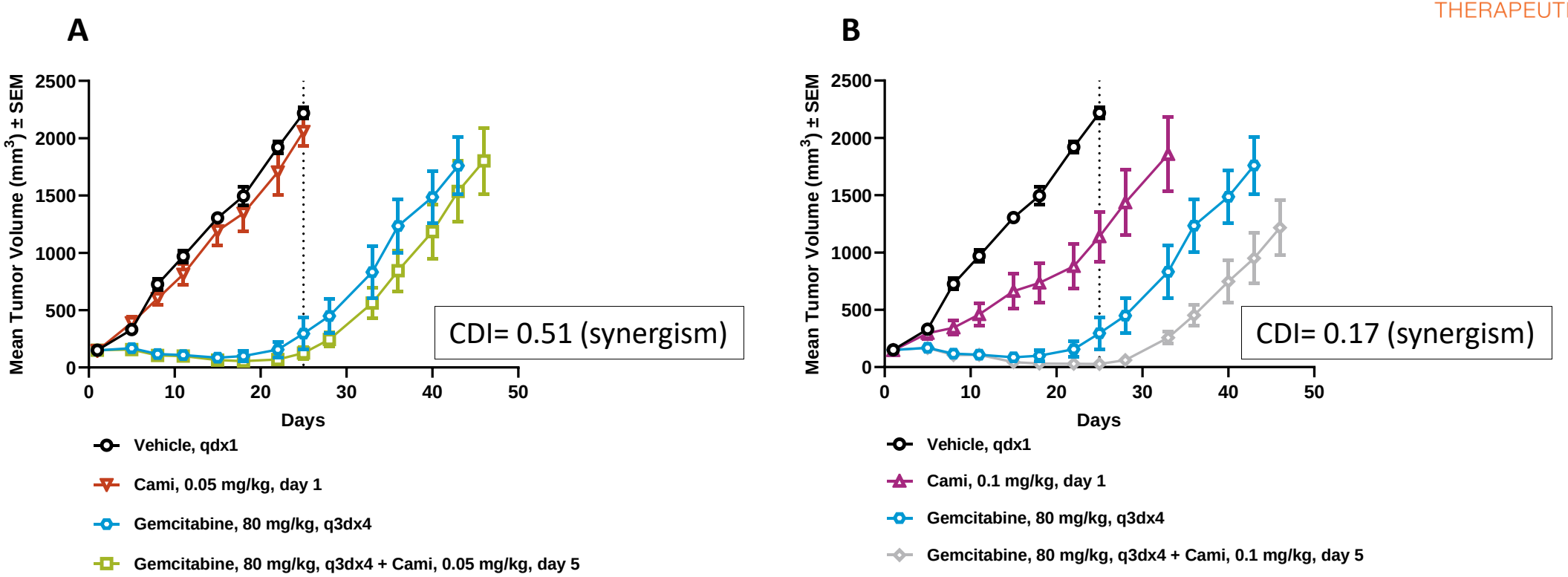


C

	Cami + gemcitabine	
	Median Combination index	95%, confidence interval
Karpas-299	0.44	0.35-0.59
HDLM-2	0.43	0.33-1.25
L540	0.59	0.41-2.23

A. Cami and gemcitabine combination matrix design. Single drugs and 35 dose combinations were tested on each cell line (21 only for L-540). **B.** Distribution of Chou-Talalay Combination Index (C.I.) values obtained combining Cami with gemcitabine in Karpas299, HDLM-2 and L-540 cell lines. In each plot, the horizontal line indicates median CI and the whiskers represent 95% confidence interval values. Dotted horizontal line indicates threshold for synergy. Outside values have been omitted from the figure. **C**. Table summarizing median CI values with 95% confidence interval values.

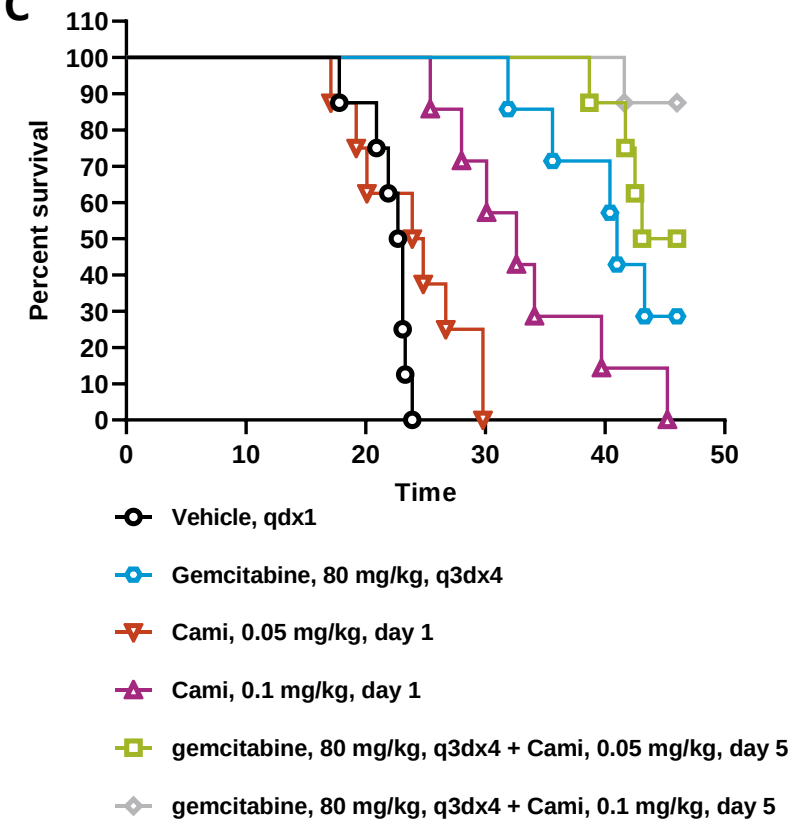
Cami anti-tumor activity synergizes with gemcitabine in the Karpas299 lymphoma xenograft model



- Karpas299 is an anaplastic large cell lymphoma xenograft model expressing CD25.
- Treatments started at mean TV of 150 mm^3. Cami was administered on day 1 as single dose (**A**, 0.05 mg/kg; **B**, 0.1 mg/kg). Gemcitabine was administered from day 1, every 3 days, 4 times (at 80 mg/kg). In the combination group, Cami was administered as single dose on day 5 (24 hours after second dose of gemcitabine).
- Dotted line indicates day when the Coefficient of Drug Interaction (CDI) was calculated (last day at least half of the animals remain in the study).
- All treatments were well tolerated from the animals.

Cami anti-tumor activity synergizes with gemcitabine in the Karpas299 lymphoma xenograft model

C



D

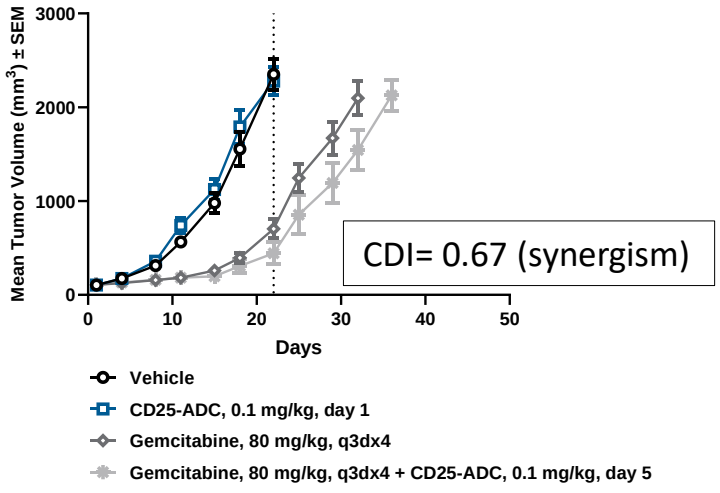
RESPONSE SUMMARY	PR	CR	TFS
Vehicle	0	0	0
Gemcitabine	1	2	0
Cami, 0.05 mg/kg, day 1	0	0	0
Cami, 0.1 mg/kg, day 1	0	0	0
Gemcitabine + Cami, 0.05 mg/kg	4	2	1
Gemcitabine + Cami, 0.1 mg/kg	4	4	1

C. Kaplan-Meier analysis of survival.

D. Response summary. PR, partial responder; CR, complete responder; TFS, tumor-free survivor.

CD25-ADC anti-tumor activity synergizes with gemcitabine in the CT26 colorectal cancer model

A



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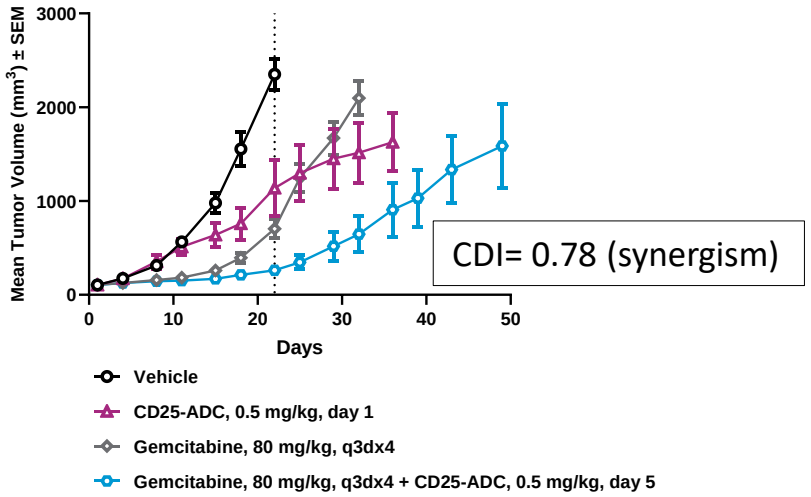

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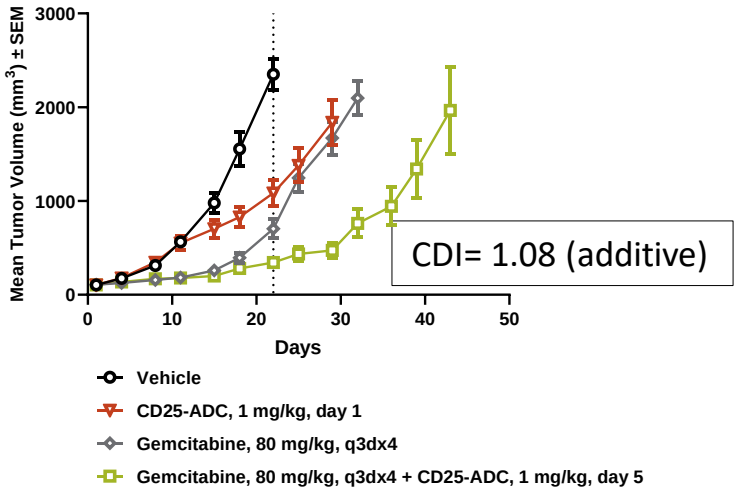
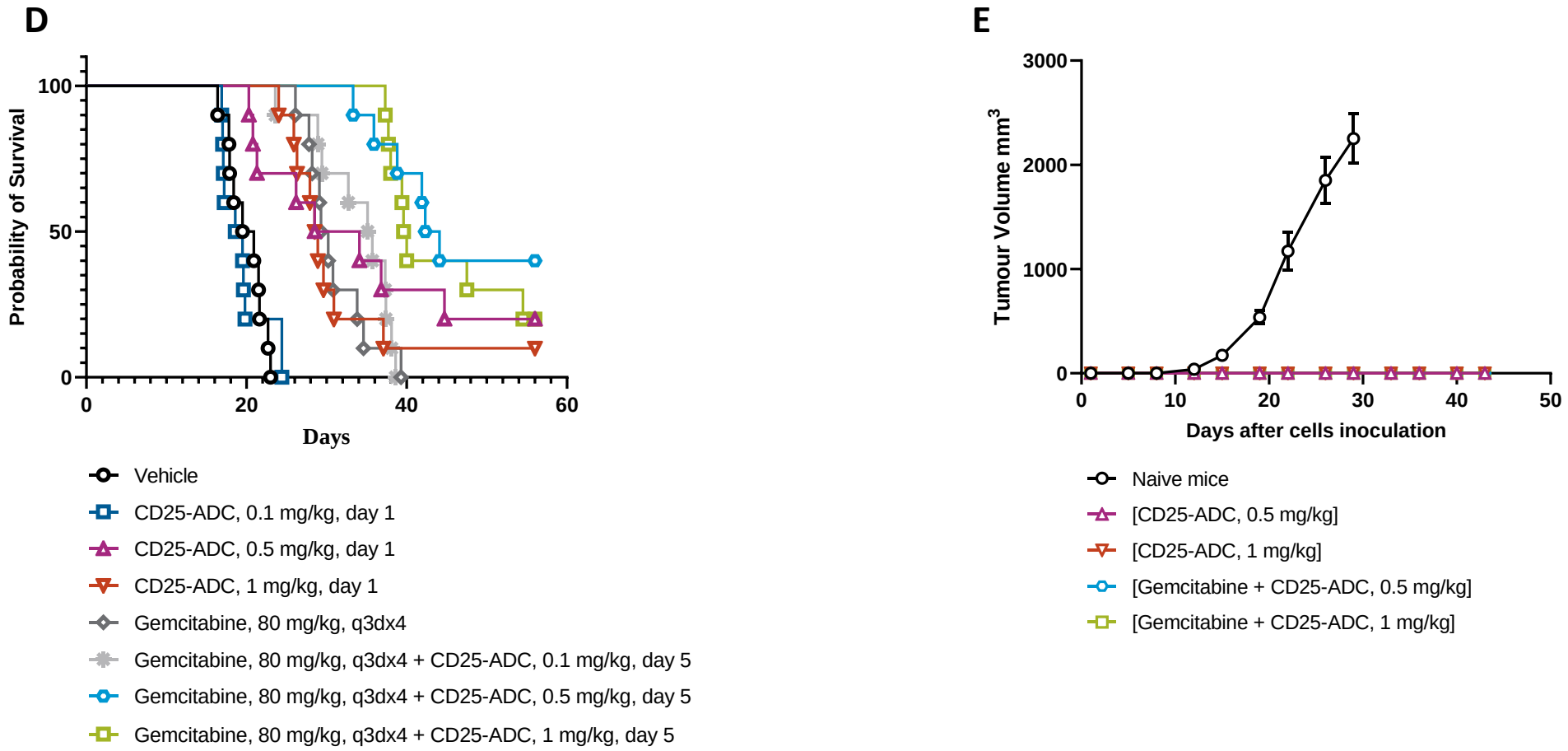


- CD25-ADC is an ADC composed of the mouse CD25 specific antibody PC61 conjugated to pyrrolobenzodiazepine dimer payload tesirine[3].
- CT26 is a CD25-negative syngeneic colorectal cancer model that exhibits tumor infiltration of CD25-expressing T regulatory cells (Tregs).
- Treatments started at mean TV of 104 mm^3. CD25-ADC was administered on day 1 as single dose (**A**, 0.1 mg/kg; **B**, 0.5 mg/kg; **C**, 1 mg/kg). Gemcitabine was administered from day 1, every 3 days, 4 times (at 80 mg/kg). In the combination group, CD25-ADC was administered as single dose on day 5 (24 hours after second dose of gemcitabine).
- Dotted line indicates day when the Coefficient of Drug Interaction (CDI) was calculated (last day at least half of the animals remain in the study).
- All treatments were well tolerated from the animals.

CD25-ADC anti-tumor activity synergizes with gemcitabine in the CT26 colorectal cancer model



D. Kaplan-Meier analysis of survival.

E. Re-challenge study: TFS mice from the main efficacy study were re-challenge with CT26 cells implanted on the opposite flank. A group of naïve mice served as control.

Conclusions

- The combination of camidanlumab tesirine (Cami) and gemcitabine was synergistic both *in vitro* and *in vivo* in CD25-expressing lymphoma preclinical models.

- CD25-ADC, a mouse-cross-reactive version of camidanlumab tesirine, demonstrated synergistic anti-tumor activity in combination with gemcitabine in the syngeneic CT26 model, a CD25-negative colorectal cancer model that exhibits tumor infiltration of CD25-expressing Tregs.

- Altogether, these novel pre-clinical data warrant translation of the combination between camidanlumab tesirine and gemcitabine into the clinic.

Conflict of Interest Disclosure

	Name of organization	Type of relationship
Asma Jabeen, PhD	ADC Therapeutics	Current Employment
Shiran Huang	N/A	No relevant financial relationship(s) to disclose
John A. Harley, PhD	ADC Therapeutics	Consultancy, Current equity holder in publicly-traded company and Research Funding
Patrick H. van Berkel, PhD	ADC Therapeutics	Current Employment and Current equity holder in publicly-traded company
Francesca Zammarchi, PhD	ADC Therapeutics	Current Employment and Current equity holder in publicly-traded company