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Preclinical investigation of ADCT-242, a novel exatecan-based antibody drug conjugate targeting Claudin-6, as single agent or in combination in ovarian and non-small cell lung cancer models

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ADC Therapeutics, London UK

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* Dr Tsang was an employee of ADCT when the study was conducted

Disclosure Information

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Chris Pickford PhD

I have the following relevant financial relationships to disclose:

Employee of ADC Therapeutics
Stockholder in ADC Therapeutics

Claudin-6: A Promising ADC Target

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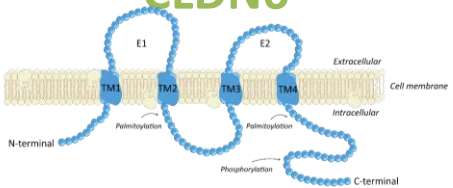
CLDN6



- Member of the CLDN family of proteins
- 23.3 kDa transmembrane protein with cytoplasmic C- and N-terminus
- Involved in tight junctions, regulating cell adhesion, maintaining tissue integrity
- Promotes cell proliferation, migration, invasion abilities and inhibits apoptosis
- Implicated in the initiation, progression and metastasis of some cancers
- Can be associated with poor prognosis in endometrial carcinoma
- Very restricted normal tissue expression

Clinical Rationale & Prevalence

Ovarian

25 – 75%
M+H – any

NSCLC

20 – 40%
M+H – any

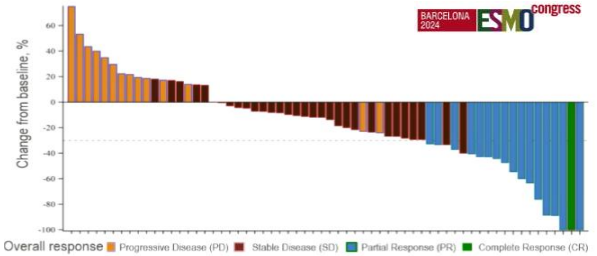
Endometrial

10 – 35%
M+H – any

Gastric

20 – 40%
M+H – any

- TORL-1-23/ixotatug vedotin (DAR 4 MMAE): 50%/42% ORR at 2.4/3.0 mg/kg in Pt-resistant ovarian cancer



M+H refers to percent of cases with H-score ≥100 Source: Kojima et al., *Cancer* (2020); Fierce Biotech; STAT news; Du et al., *Mol Med Rep* (2021); Cao et al., *Onco Targets Ther* (2018); ADC Therapeutics Internal Studies.

ADCT-242: A Claudin-6 targeting ADC delivering an exatecan payload with best-in-class potential

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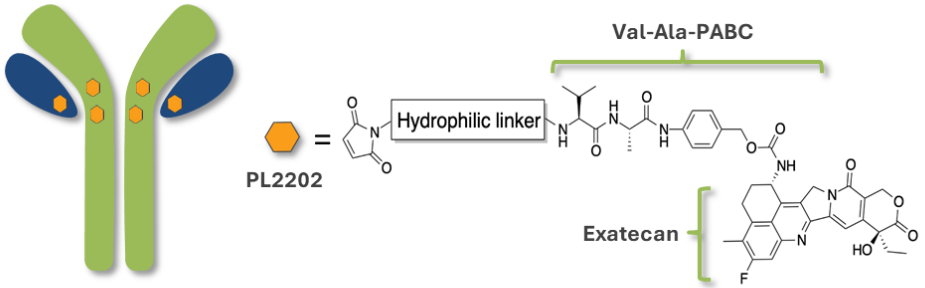
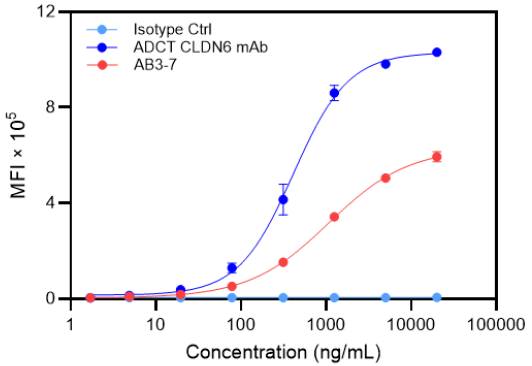
ADCT-242



- ADCT-242 is comprised of a CLDN6-specific, humanized and Fc-silenced IgG1 antibody to which 6 exatecan-containing PL2202 payloads have been conjugated (DAR 6)

Binding to NTERA-2 Cells



mAb	EC_{50} (pM)
ADCT CLDN6 mAb	412
AB3-7	1070
Isotype Control	No binding

ADCT-242 shows superior *in vitro* internalisation properties to AB3-7-MMAE and strong bystander activity

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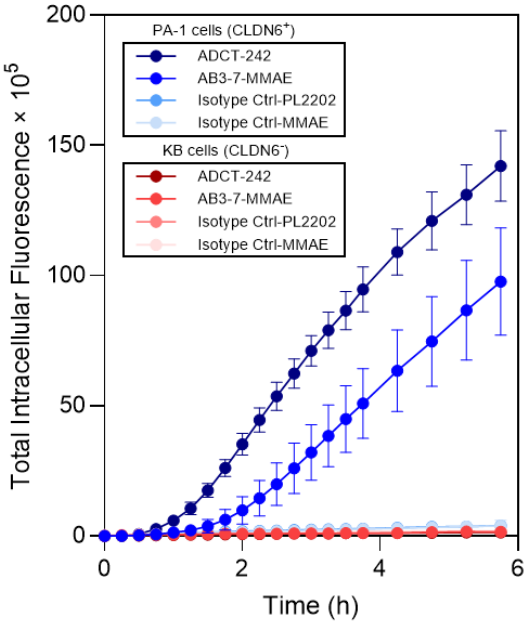
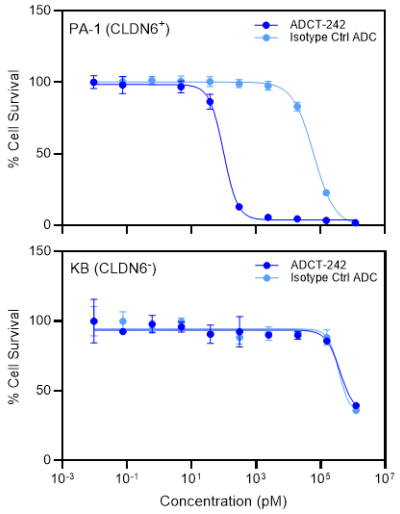
Internalisation

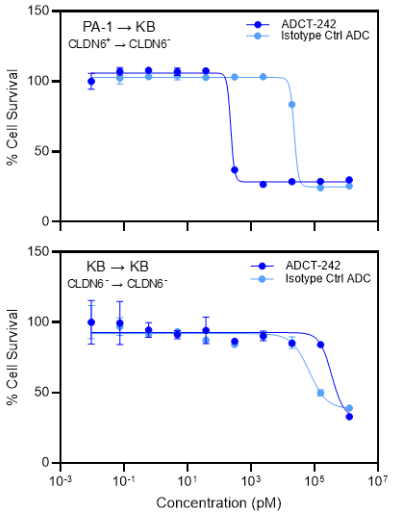


Primary Cytotoxicity



EC_{50} (pM)	PA-1	KB
ADCT-242	65	319,771
Isotype Ctrl ADC	70,318	518,196

Bystander Activity



ADC	EC_{50} (pM), from PA-1	EC_{50} (pM), from KB
ADCT-242	142	124,938
Isotype Ctrl ADC	25,337	38,699

ADCT-242 has potent anti-tumor activity *in vivo* in xenograft models of ovarian cancer with medium CLDN6 expression

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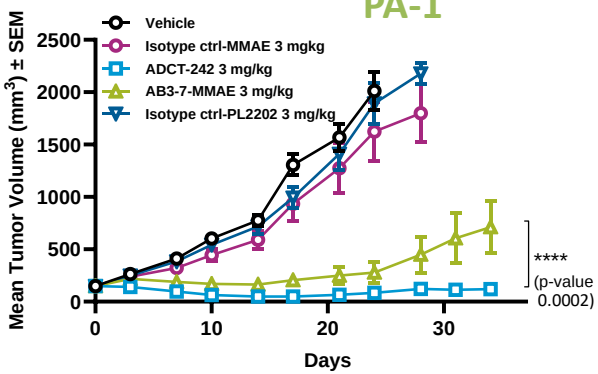
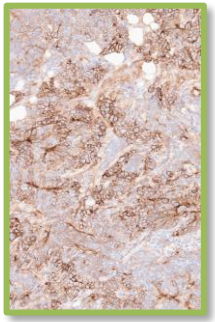
PA-1



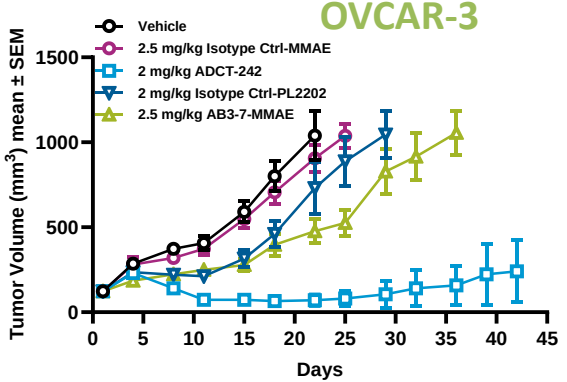


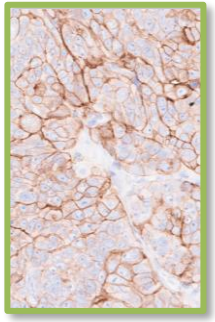
H-score = 162

Treatment	Regimen	PR	CR	TFS
3 mg/kg ADCT-242	QW×3	3/10	0/10	0/10
3 mg/kg Isotype Ctrl-PL2202	QW×3	0/10	0/10	0/10
3 mg/kg AB3-7-MMAE	QW×3	0/10	0/10	2/10
3 mg/kg Isotype Ctrl-MMAE	QW×3	0/10	0/10	1/10

PR=partial response; CR=complete response; TFS=tumor-free survivors

OVCAR-3





H-score = 164

Treatment	Regimen	PR	CR	TFS
2 mg/kg ADCT-242	QD×1	0/8	6/8	5/8
2 mg/kg Isotype Ctrl-PL2202	QD×1	0/8	0/8	0/8
2.5 mg/kg AB3-7-MMAE	QW×3	1/8	0/8	0/8
2.5 mg/kg Isotype Ctrl-MMAE	QW×3	0/8	0/8	0/8

PR=partial response; CR=complete response; TFS=tumor-free survivors

Claudin-6 dependent anti-tumour activity of ADCT-242 is observed in lung patient-derived xenograft models

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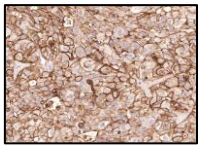
LU2049



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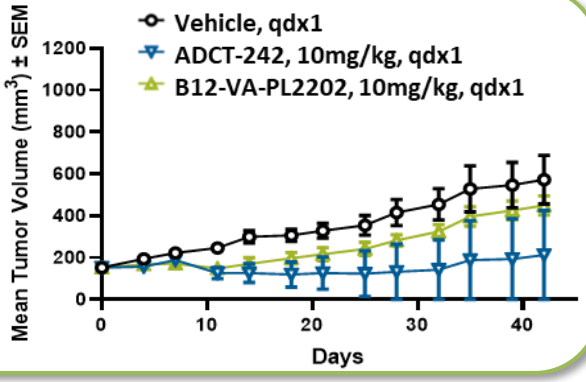

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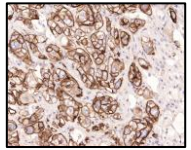

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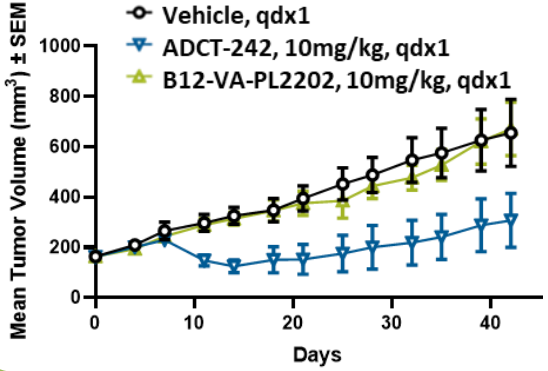

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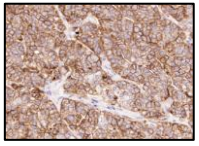

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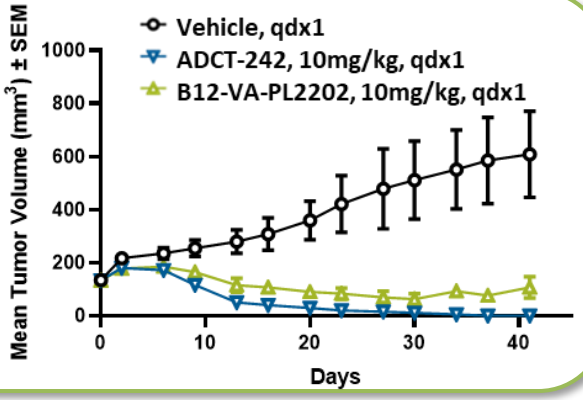

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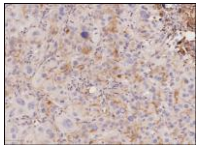

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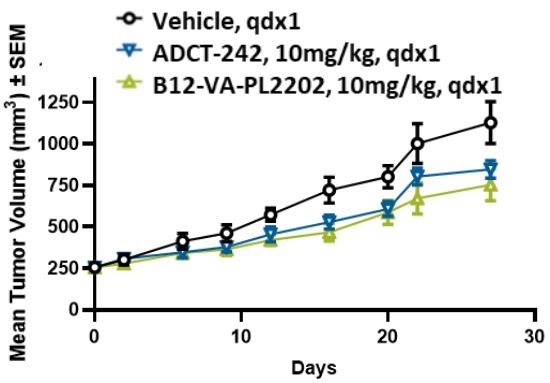

In vitro combination studies demonstrate synergy of ADCT-242 with Olaparib across multiple cancer cell lines

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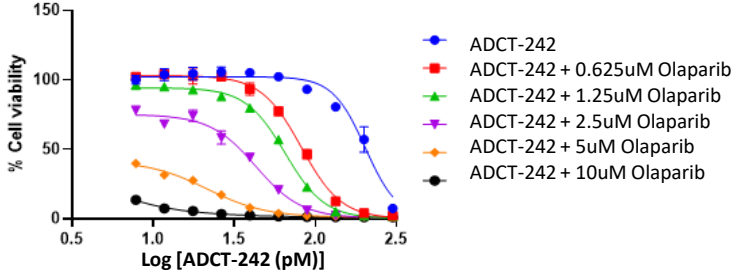
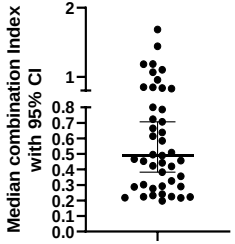
Drug combination of ADCT-242 and Olaparib in PA-1 cells



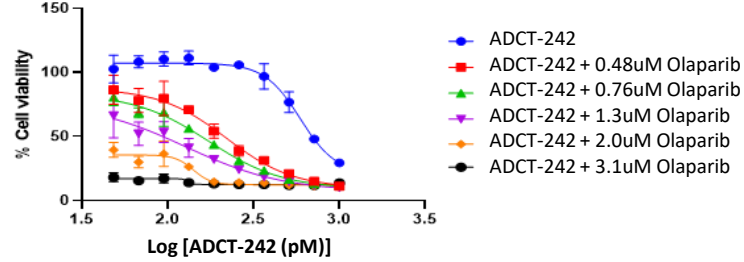
Combination Index (CI) of ADCT-242 and Olaparib combination in PA-1 cells



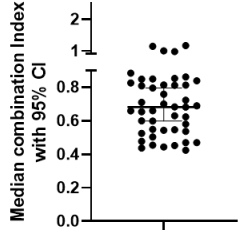
Statistics	
Median	**0.489**
Upper confidence limit	0.707
Lower confidence limit	0.382

(0.3-0.8 represents synergy)

Drug combination of ADCT-242 and Olaparib in OVCAR-3 cells



Combination Index (CI) of ADCT-242 and Olaparib combination in OVCAR-3 cells



Statistics	
Median	**0.681**
Upper confidence limit	0.795
Lower confidence limit	0.598

(0.3-0.8 represents synergy)

Suboptimal doses of ADCT-242 and Cisplatin combine to drive complete tumour regression in the OVCAR-3 xenograft model

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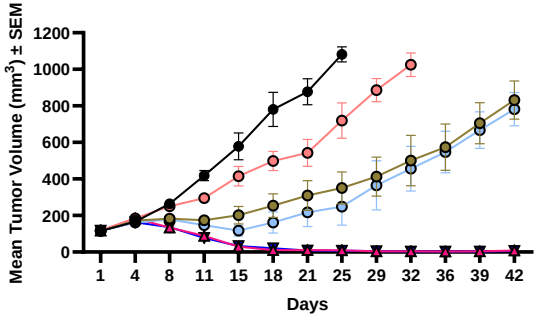
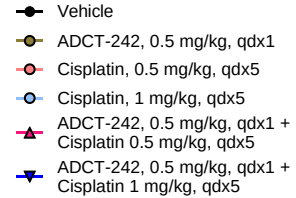
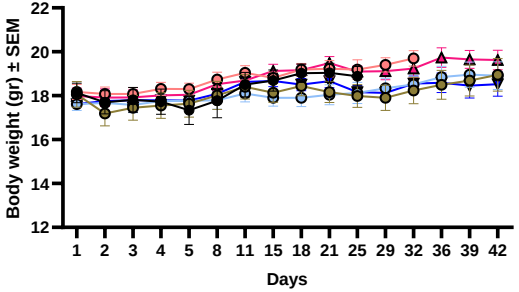
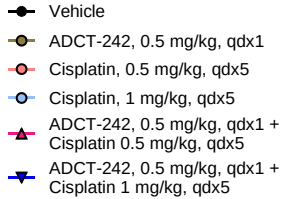


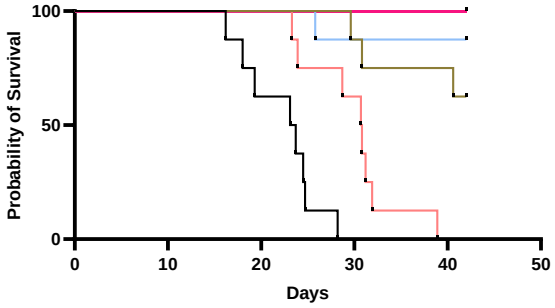


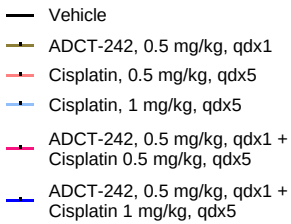
Treatment	PR	CR	TFS
Vehicle	0	0	0
0.5 mg/kg ADCT-242	1	0	0
0.5 mg/kg Cisplatin	0	0	0
1 mg/kg Cisplatin	1	0	0
0.5 mg/kg ADCT-242 + 0.5 mg/kg Cisplatin	0	8	7
0.5 mg/kg ADCT-242 + 1 mg/kg Cisplatin	0	8	7

PR=partial response; CR=complete response; TFS=tumor-free survivors









- Sub-optimal doses of ADCT-242 and Cisplatin combine to show strong synergy *in vivo*
- Single dose combination leads to 8/10 CR and 7/10 TFS in the OVCAR-3 xenograft model

ADCT-242 drives strong tumour growth inhibition of the OVCAR-3 xenograft *in vivo* model following treatment with a Claudin-6 targeting MMAE-based ADC (AB3-7-MMAE)

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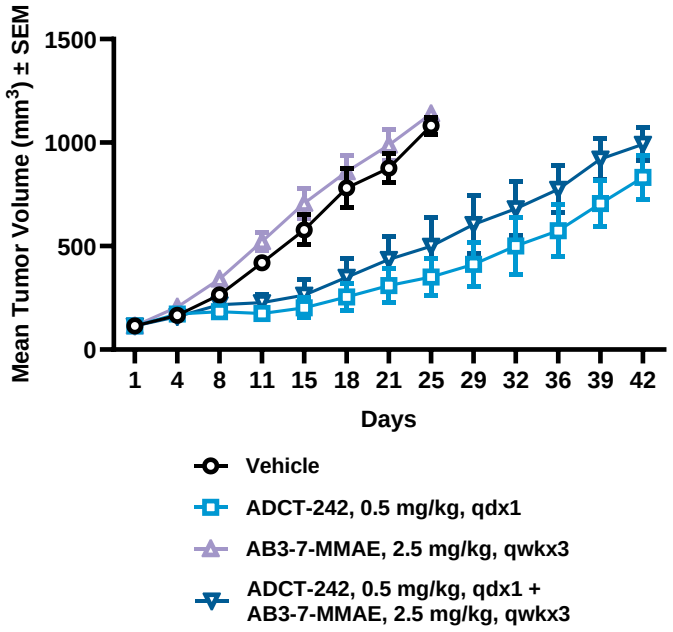

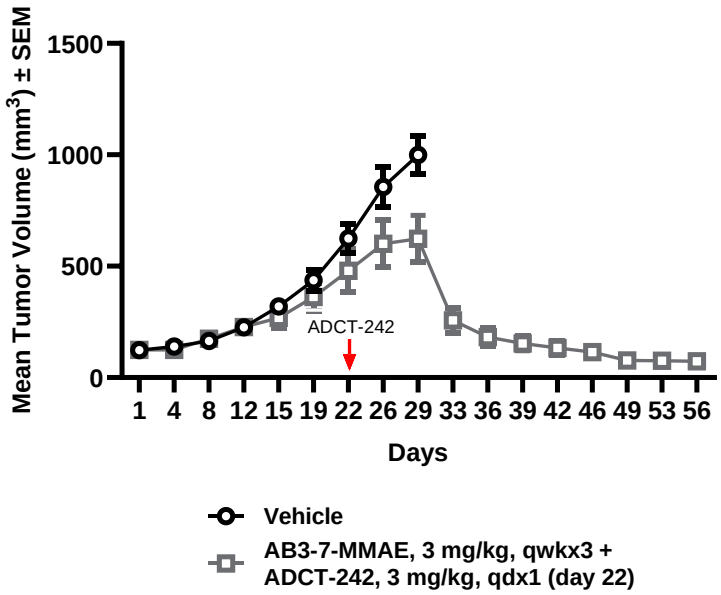

- ADCT-242 and AB3-7-MMAE dosed in combination show antagonistic activity in vivo
- Sequential treatment of AB3-7-MMAE followed by ADCT-242 shows strong tumour growth reduction

ADCT-242 was tolerated at doses up to 150 mg/kg in mice or 40 mg/kg in cynomolgus monkeys, indicative of a good therapeutic index

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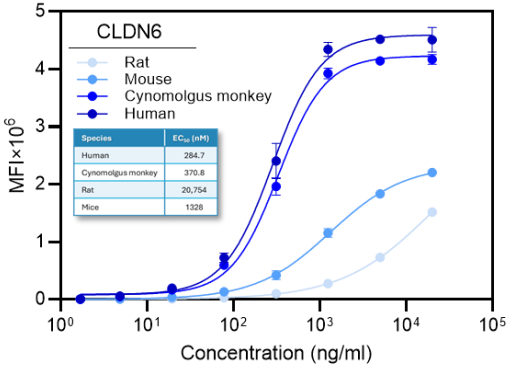
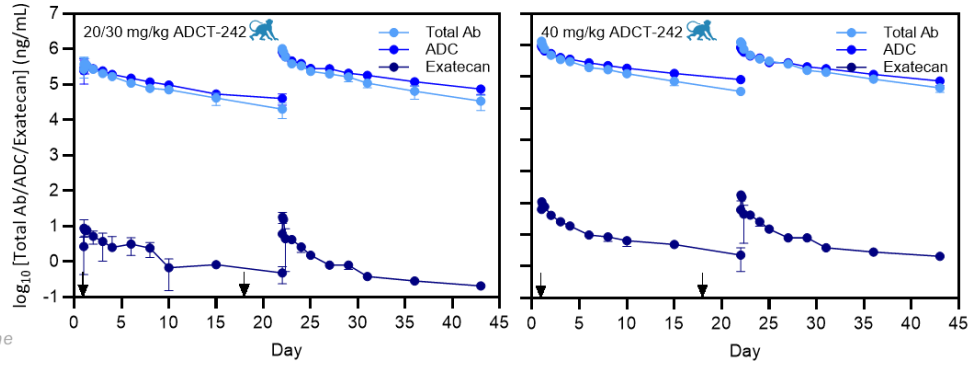


- Mice & cynomolgus monkeys were considered pharmacologically relevant species based on CLDN6 binding
- ADCT-242 Q3W×2 was well tolerated at doses up to 150 and 40 mg/kg, resp.
- Favourable PK profile with $t_{½}$ of 9.7-12.6 and 8.5-10 days in mice and monkeys, resp.

Tolerability of ADCT-242 in mice and cynomolgus monkeys

Species	Dose Q3W×2	Tolerated	Clinical Pathology & Histopathology
	75 mg/kg 150 mg/kg	Yes Yes	**Clinical pathology:** increases in RDW, RET and PLT; increases in ALP **Histopathology:** germ cell degeneration & tubular atrophy in the testes, increased spleen cellularity
	20/30 mg/kg 40 mg/kg 60 mg/kg	Yes Yes No	**Clinical Pathology:** reductions in red cell parameters; reversible reductions in RET, WBC & subpopulations **Histopathology:** no findings up to 40 mg/kg; GI tract lesions dose limiting at 60 mg/kg

ADCT-242 exhibits favourable exposure profile in cynomolgus monkeys



RDW = red cell distribution width; RET = reticulocytes; PLT = platelets; ALP = alkaline phosphatase; WBC = white blood cells

Conclusions

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- ADCT-242 is a Claudin-6 targeting ADC delivering an exatecan payload with best-in-class potential.
- ADCT-242 has potent anti-tumor activity i*n vivo* in PA-1 and OVCAR-3 xenograft models of ovarian cancer with medium CLDN6 expression levels.
- Claudin-6 dependent anti-tumour activity of ADCT-242 is observed in lung patient-derived tumour models.
- *In vitro* combination studies demonstrate synergy of ADCT-242 with Olaparib across multiple cancer cell lines.
- Suboptimal doses of ADCT-242 and Cisplatin combine to drive complete tumour regression in the OVCAR-3 xenograft model demonstrating strong synergy *in vivo*.
- ADCT-242 drives strong tumour growth inhibition of the OVCAR-3 xenograft *in vivo* model following treatment with a Claudin-6 targeted MMAE-based ADC.
- ADCT-242 was tolerated at doses up to 150 mg/kg in mice or 40 mg/kg in cynomolgus monkeys, indicative of a good therapeutic index.

Acknowledgements

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Lolke de Haan
Lina Baxter
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