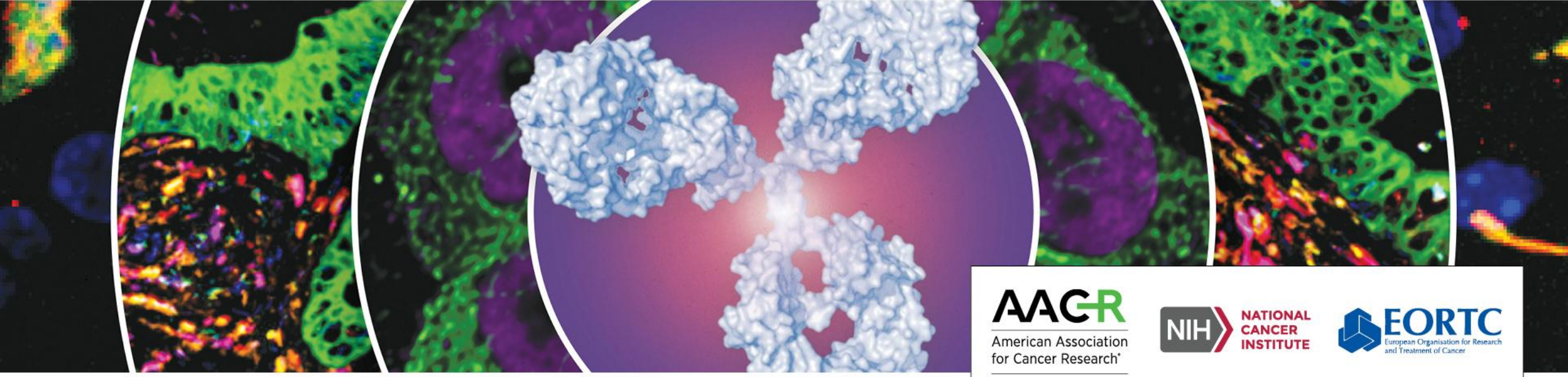

Discovery of AN4035: A Novel CEACAM5-Targeting Antibody Drug Conjugate (ADC) Armed with a Proprietary Pan-RAS(ON) Inhibitor Payload, Designed to Broaden the Therapeutic Window

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Adlai Nortye Ltd.

AACR-NCI-EORTC MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 22-26, 2025 | Hynes Convention Center | Boston, MA

Disclosure Information

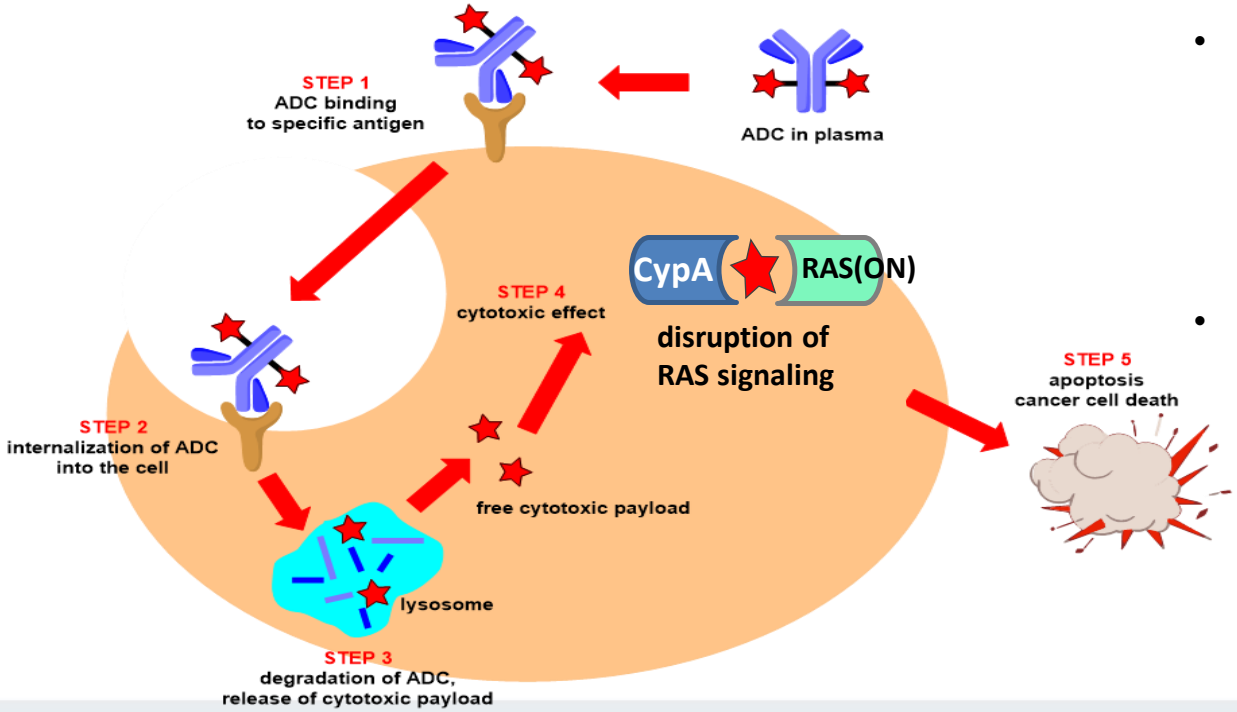
Archie Tse MD PhD

I have the following relevant financial relationships to disclose:

Employee and Stockholder of: Adlai Nortye Ltd. (Nasdaq: ANL)

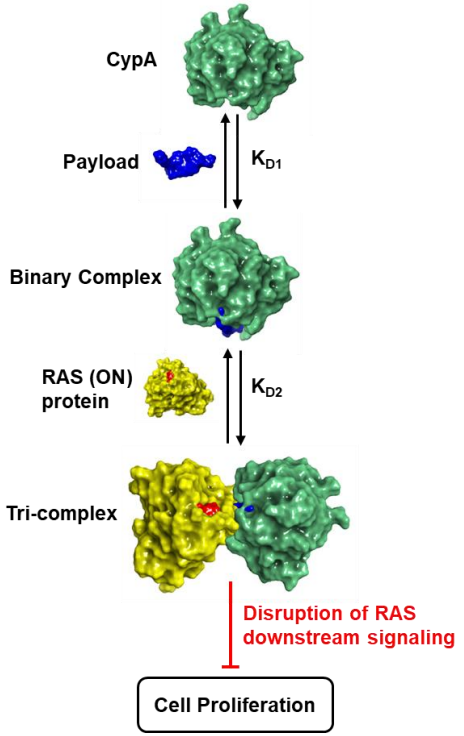
Pan-RAS(ON) inhibitor as a next-generation ADC payload

- **Background**: Tricomplex pan-RAS(ON) inhibitors (e.g. RMC-6236) are a promising class of therapeutics against RAS-driven cancers
- **Potential limitations**: on-target, off-tumor toxicities may restrict dose and limit safety in combinations
- **Our Hypothesis**: targeted delivery via an ADC could localize pan-RAS(ON) inhibitor activity to tumors while minimizing systemic RAS pathway inhibition
  - Widen therapeutic window
  - Enable rational combinations



- *Cyclophilin A, an abundant intracellular protein (μM levels), is the target engaged by pan-RAS(ON) inhibitors, much like MMAE targeting tubulin*
- *ADCs leveraging pan-RAS(ON) inhibitors could further enhance the therapeutic index*

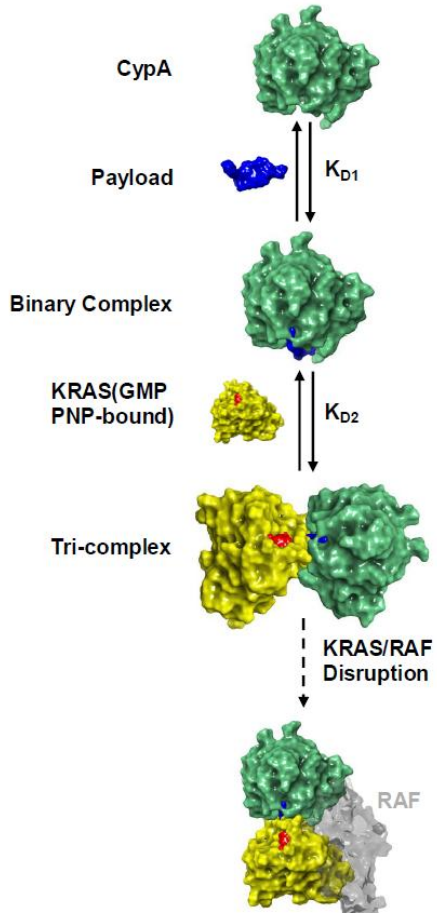
MOA of Pan-RAS(ON)i:



Payload is a proprietary highly potent pan-RAS(ON) inhibitor

MOA of Payload:

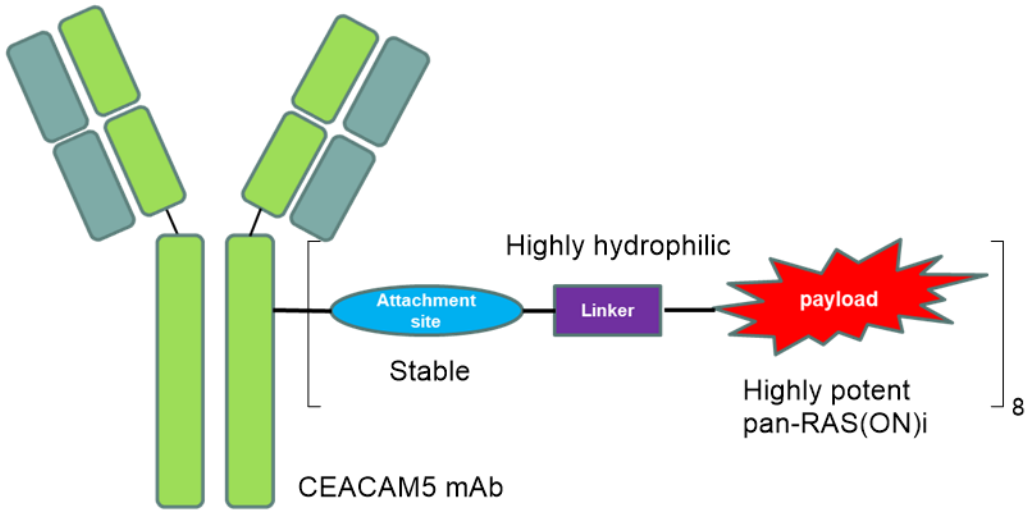
Pan-RAS(ON) molecular glue



Compound	Binary (CYPA) K_{D1} (nM)	Tri-complex (KRAS) K_{D2} (nM)			
		G12C	G12D	G12V	WT
Payload	14.9	4.7	30.5	14.0	18.6
RMC-6236	12.5	19.1	174	45.9	52.8

Cancer Cell Line	Indication	RAS Mutation Type	Payload 72h CTG	
			IC_{50} (nM)	I_{max} %
NCI-H2009	NSCLC	Kras G12A	0.02	65
NCI-H358		Kras G12C	0.06	93
NCI-H2030		Kras G12C	0.04	22
NCI-H2122		Kras G12C	0.01	93
NCI-H441		Kras G12V	<0.01	44
SW900		Kras G12V	0.12	80
ASPC1	PDAC	Kras G12D	0.06	63
HPAC		Kras G12D	0.07	63
KP4		Kras G12D	0.75	56
Capan1		Kras G12V	0.02	57
Capan2		Kras G12V	0.09	61
SW620	CRC	Kras G12V	0.01	80
HCT116		Kras G13D	0.41	93
LoVo		Kras G13D	0.34	67
T84		Kras G13D	2.59	74
LS1034		Kras A146T	1.0	80

AN4035 demonstrated favorable drug-like characteristics



CEACAM5: Overexpressed in CRC, PDAC, & NSCLC where RAS is frequently mutated

Conjugator: Homogenous DAR 8 with high stability; no retro-Michael reaction

Linker: Highly hydrophilic; excellent circulation stability and efficient payload release

Payload: Highly potent pan-RAS(ON) inhibitor

Stable Conjugator

Compound	Human Plasma Incubation Time	LC-MS DAR
AN4035	Day 0	8.04
	Day 7	7.85

Stable Linker-Payload

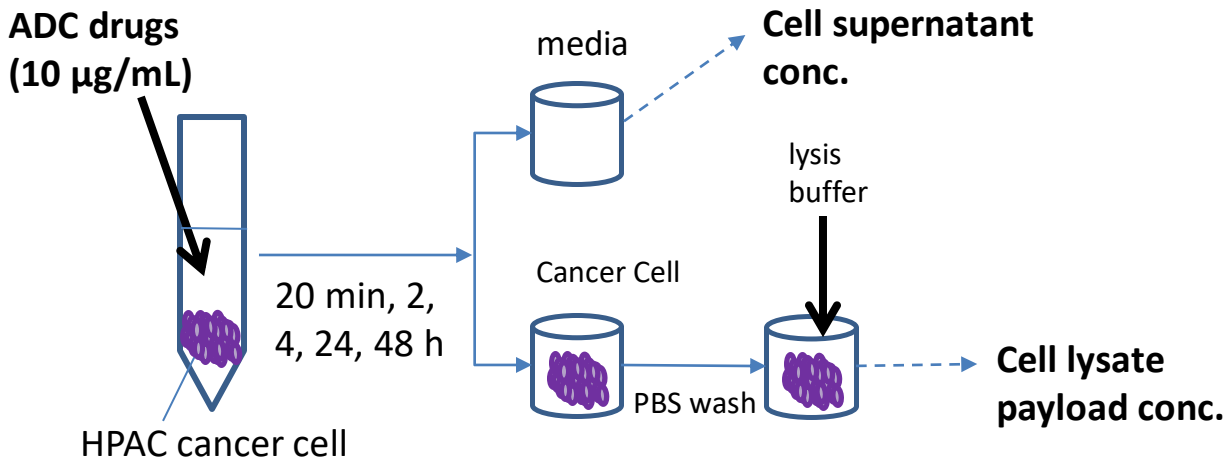
Compound	Plasma Incubation Time	Payload Released Rate %			
		Human	Mouse	Rat	Monkey
AN4035	Day 0	<0.05	<0.05	0.02	<0.05
	Day 7	<0.05	<0.05	0.01	<0.05
	Day 14	0.05	<0.05	0.01	0.06

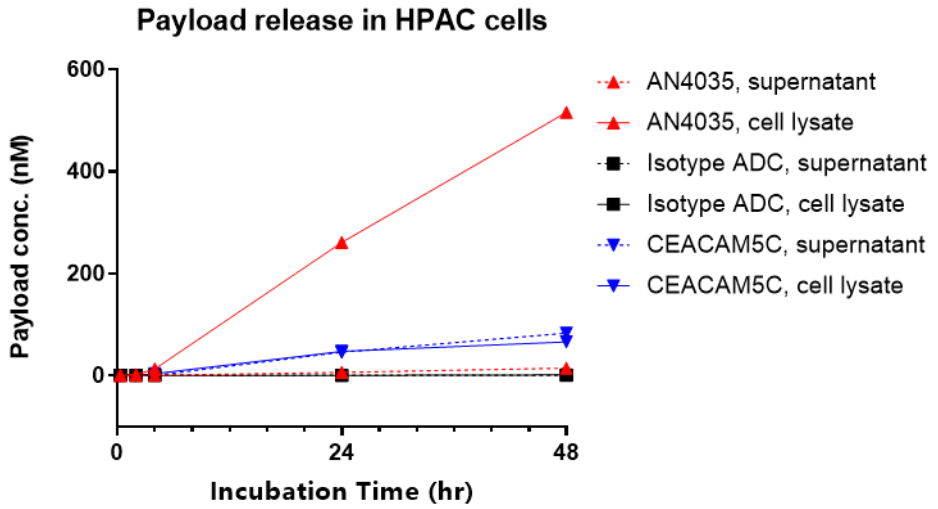
No aggregation after incubation for 72h at 40℃

Compound	Incubation Time	SEC-HPLC Aggregation %
AN4035	0 hr	0
	72 hr	0

Incubation buffer: 20 mM Histidine, 240 mM Sucrose, pH 5.5

AN4035 achieved superior target-mediated intracellular payload retention





Incubation Time	AN4035 RASi ADC (10 µg/mL)			Isotype-control ADC (10 µg/mL)		CEACAM5C Top1 ADC (10 µg/mL)		
	Cell supernatant payload conc. (nM)	Cell lysate payload conc. (nM)	**Cell lysate / supernatant payload ratio**	Cell supernatant payload conc. (nM)	Cell lysate payload conc. (nM)	Cell supernatant payload conc. (nM)	Cell lysate payload conc. (nM)	**Cell lysate / supernatant payload ratio**
20 min	BQL	BQL	-	BQL	BQL	BQL	BQL	-
2 hr	BQL	1.75	-	BQL	BQL	BQL	BQL	-
4 hr	BQL	12.9	-	BQL	BQL	BQL	3.58	-
24 hr	5.97	261	**44**	BQL	BQL	45.8	47.5	**1.0**
48 hr	14.4	516	**36**	BQL	1.41	83.1	66.0	**0.79**

BQL, below quantitation limit

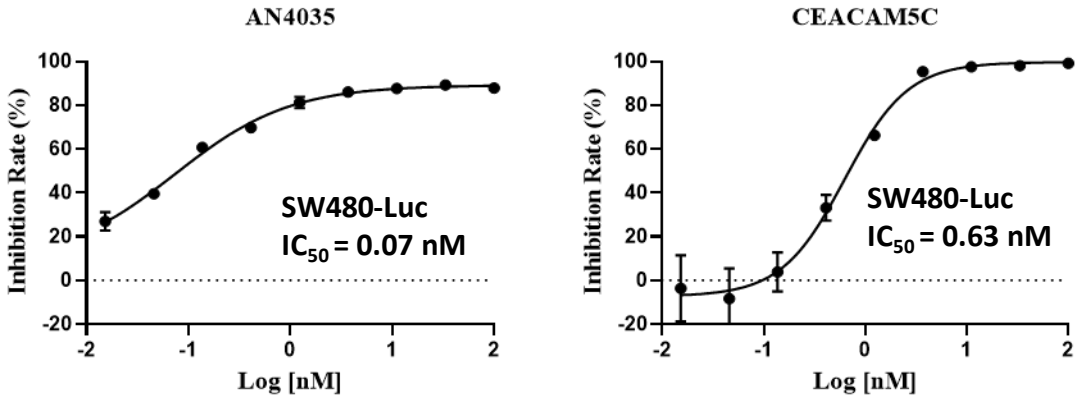
AN4035 demonstrated potent cytotoxicity and a robust bystander effect in CEACAM5-positive, RAS-addicted cancer cell models

Cancer Cell Line	Indication	CEACAM5 mRNA nTPM	RAS Mutation Type	6-day CTG		
				AN4035		Isotype ADC
				IC_{50} (nM)	Imax %	IC_{50} (nM）
CL-40	CRC	1821	Kras G12D	0.77	98	
SK-CO-1		784	Kras G12V	0.02	99	
LS513		208	Kras G12D	0.15	100	
SW403		443	Kras G12V	2.8	95	
SW1463		198	Kras G12C	2.3	99	
LoVo		122	Kras G13D	4.4	48	
GP2D		42	Kras G12D	1.4	84	
QGP-1	PDAC	1360	Kras G12V	0.05	91	
HPAC		714	Kras G12D	0.10	73	>100
ASPC1		499	Kras G12D	0.31	88	
Capan1		97	Kras G12V	0.23	76	
NCI-H2122	NSCLC	616	Kras G12C	0.30	94	
NCI-H727		332	Kras G12V	0.09	93	
MKN45	Gastric Cancer	1087	Kras WT	0.13	95	>100

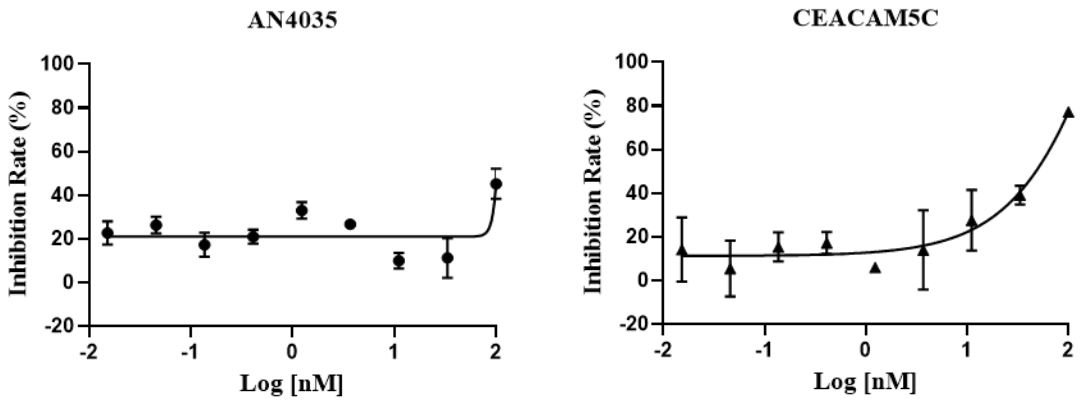
nTPM, normalized transcript per million

AN4035 showed a superior bystander killing effect compared to CEACAM5 Top1-based ADC

SK-CO-1 (CEACAM5+) : SW480-Luc (CEACAM5 neg) = 10:1

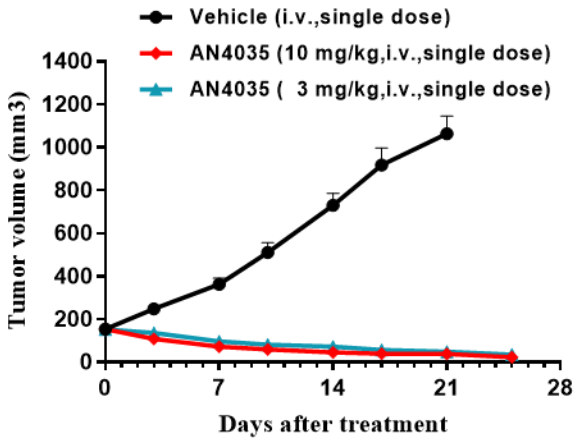


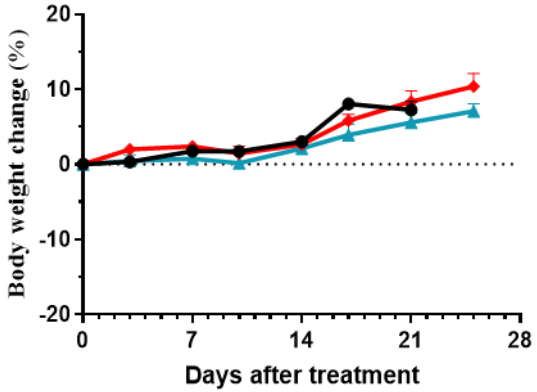
SW480-Luc (CEACAM5 neg) only



AN4035 demonstrated robust anti-tumor activity in CDX models

HPAC$^{KRAS\ G12D}$ model (PDAC, CEACAM5 mRNA 714):



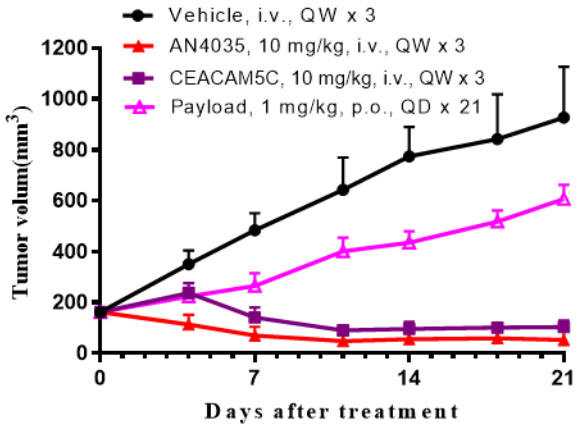


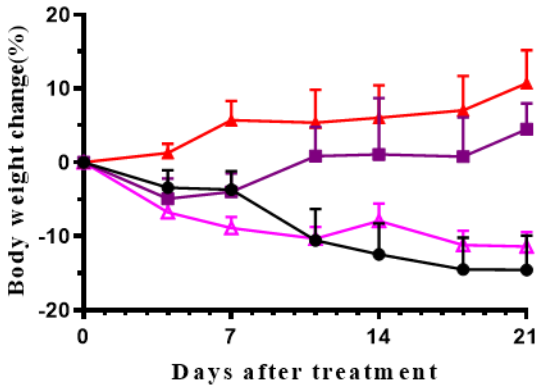
Compound	CTG[1] (IC_{50}, nM)	Dose (mg/kg)	ΔRTV[1] (%) on Day 25
AN4035	0.10	3, single dose	-78%
		10, single dose	-85%

(1) CTG = cell-titer glow *in vitro* assay (2). ΔRTV = relative tumor volume; relative to the tumor volume at the start of treatment, ΔRTV = (Vt-V0) / V0 × 100

- Durable tumor regression with single-dose of 3 mg/kg

CL40$^{KRAS\ G12D}$ model (CRC, CEACAM5 mRNA 1821):



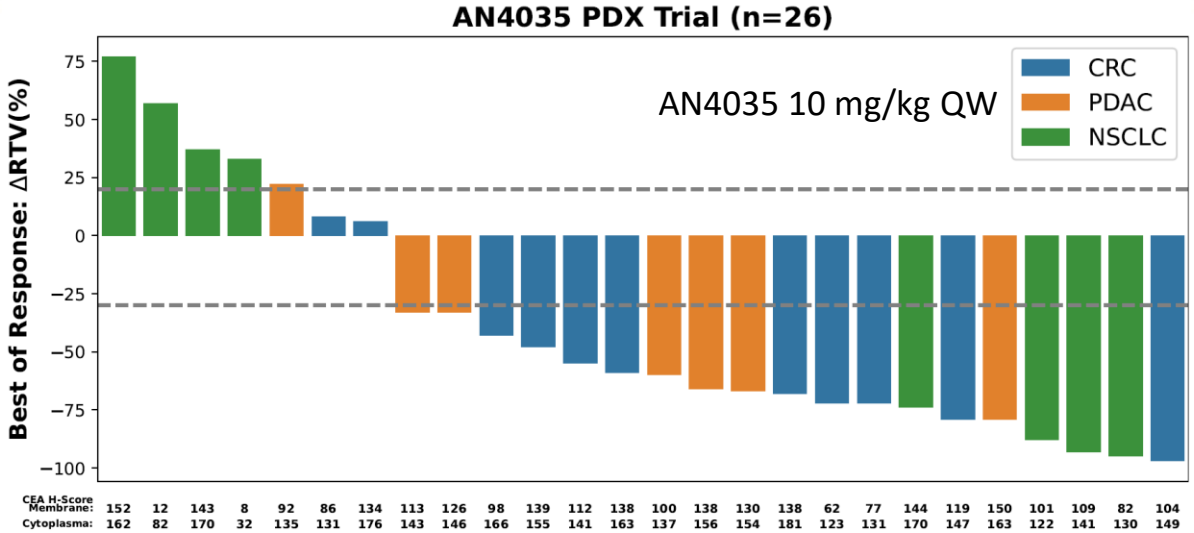


CDX, cell line-derived xenograft

Compound	CTG (IC_{50}, nM)	Dose (mg/kg)	ΔRTV[1] (%) on Day 21
AN4035	0.38	10, QW	-89%
CEACAM5C	1.2	10, QW	-36%
payload	0.08	1, QD	276%

- Superior or comparable efficacy to CEACAM5C, a CEACAM5 Topo I-based ADC or naked payload at tolerable doses

AN4035 exhibited compelling activity in single-mouse PDX trials

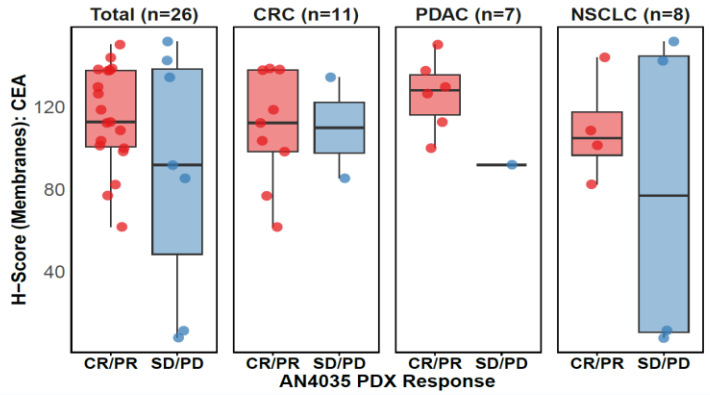


Indication	CR	PR	SD	PD	ORR	DCR
CRC	1	8	2	0	**82%**	**100%**
PDAC	0	6	0	1	**86%**	**86%**
NSCLC	3	1	0	4	**50%**	**50%**
Total	4	15	2	5	**73%**	**81%**

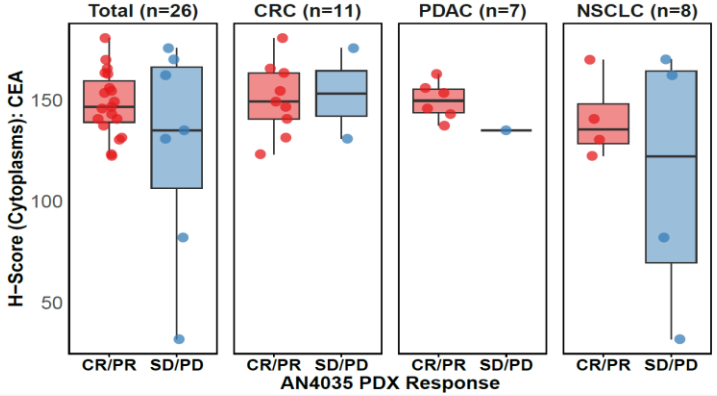
PDX, patient-derived xenograft

The response was determined by comparing tumor volume change at time t to its baseline with ΔRTV = (Vt-V0) / V0 × 100; Criteria for response were adapted from RECIST clinical criteria; Complete Response (**CR**): at least a 85% decrease in the tumor volume compared to baseline; Partial Response (**PR**):At least a 30% decrease in the tumor volume compared to baseline; Progressive Disease (**PD**):At least a 20% increase in the tumor volume compared to baseline; Stable Disease (**SD**):Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; **ORR,** overall response rate (CR+PR); **DCR,** disease control rate (CR+PR+SD).

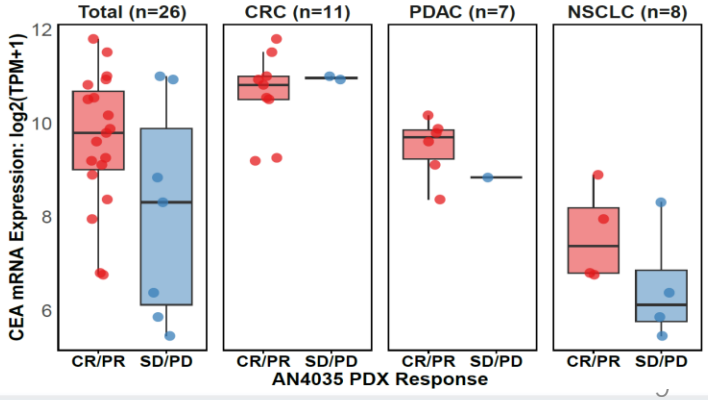
H-score (membrane)



H-score (cytoplasma)

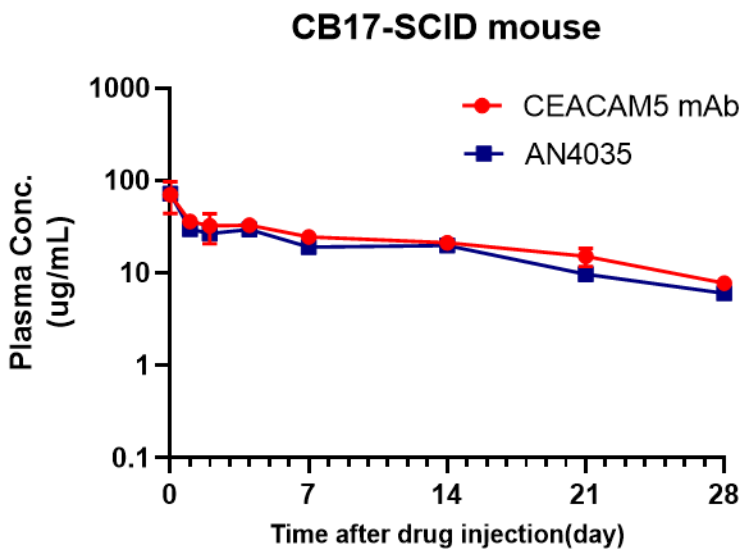


mRNA



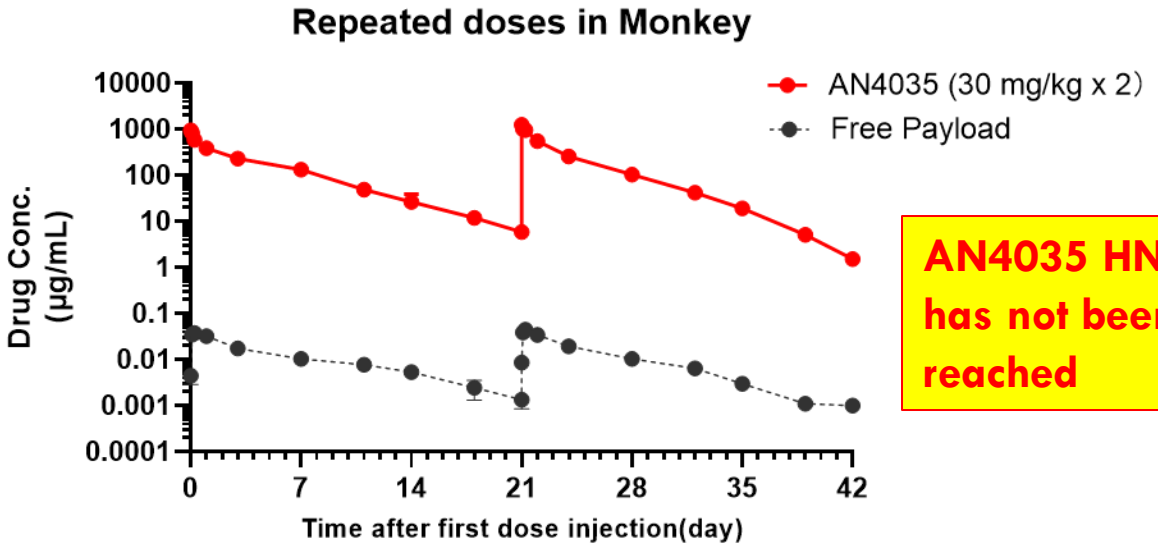
AN4035 demonstrated favorable PK and tolerability in monkeys

AN4035 showed an antibody-like PK profile, comparable to CEACAM5 mAB in mice[1]



Compound	Dose	C_0 (μg/mL)	AUC (h*μg/mL)	T1/2 (day)
AN4035	3 mg/kg, IV	72	13832	8.2
CEACAM5 mAb	3 mg/kg, IV	71	17218	9.7

AN4035 achieved high exposure with good tolerability (no skin or GI toxicities) in monkey[1, 2]



AN4035 HNSTD has not been reached

Compound	Dose	C_0 (μg/mL)	AUC (h*μg/mL)	T1/2 (day)
AN4035	30 mg/kg, IV	942	60377	3.3
Payload		0.038	5.40	4.3

1) total antibody in plasma; total antibody and payload concentration was measured in plasma and whole blood, respectively; 2) PK data from one monkey after the second AN4035 administration were excluded due to ADA development

Preclinical Summary of AN4035

- First-in-class CEACAM5-targeting ADC armed with a highly potent pan-RAS(ON) inhibitor payload
- Favorable thermal and plasma stability with desirable pharmacokinetic properties
- Strong intracellular payload retention, driving nanomolar to picomolar cytotoxicity in CEACAM5-positive/RAS-addicted cancer cell lines, along with a potent bystander-killing effect
- Robust anti-tumor activity with deep regression in CEACAM5-positive/RAS-addicted CDX and PDX models
- Favorable preliminary toxicology profile in cynomolgus monkeys
- IND-enabling studies ongoing

Please visit our poster in Poster Session C on Saturday, October 25, 12:30-4:00 pm
For BD inquiries, please contact Alex Ye at alex.ye@adlainortye.com