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Tumor-selective delivery of a pan-RAS(ON) inhibitor by the novel CEACAM5-targeted ADC AN4035 expands the therapeutic window and enables potent, well-tolerated combination with EGFR blockade

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Adlai Nortye Group Ltd.

EORTC European Organisation for Research and Treatment of Cancer
NIH NATIONAL CANCER INSTITUTE
AACR American Association for Cancer Research

Disclosure Information

Archie Tse MD PhD

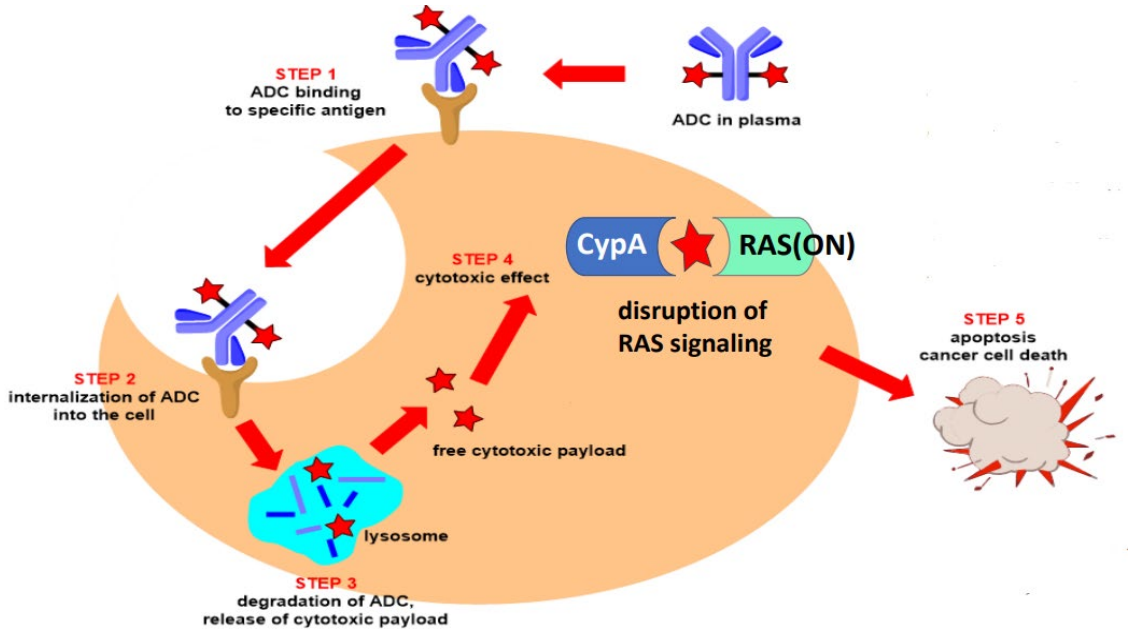
I have the following relevant financial relationships to disclose:

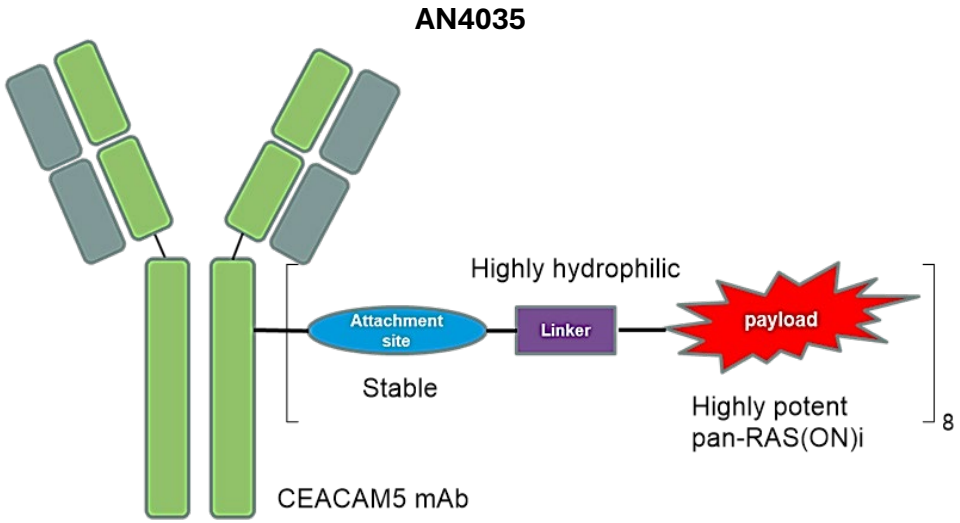
Employee and Stockholder of: Adlai Nortye Group Ltd. (Nasdaq: ANL)

AN4035: A first-in-class CEACAM5-targeting ADC armed with a pan-RAS(ON) inhibitor as payload

Our RASiCA™ (RAS inhibitor Conjugated Antibody) platform was designed to overcome two major challenges in oncology therapeutics:

1. **ADC field:** limited diversity of payload classes leading to cross-resistance, which then limits treatment sequencing for ADCs
2. **RAS inhibitor field:** on-target, off-tumor toxicities associated with oral small molecule tri-complex pan-RAS(ON) inhibitors





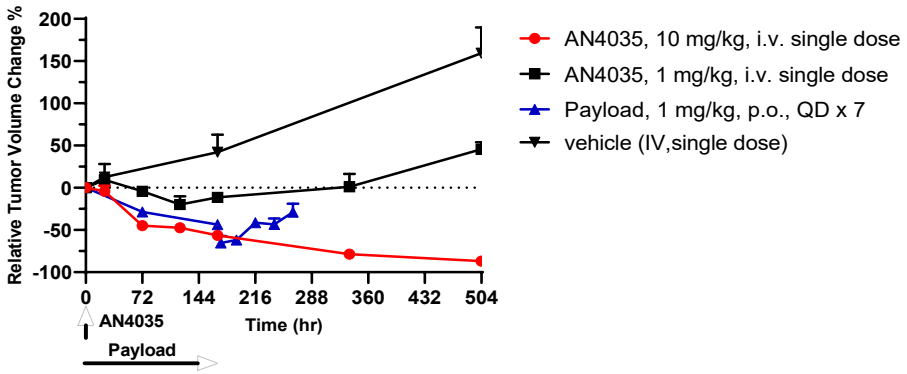
- ✓ First-in-class CEACAM5-targeted ADC delivering a potent pan-RAS(ON) inhibitor
- ✓ High conjugation and linker stability
- ✓ Potent direct cell-killing with strong intracellular payload retention and robust bystander effect
- ✓ Deep tumor regression in CEACAM5-positive/RAS-addicted CDX/PDX models
- ✓ Favorable PK and tolerability in cynomolgus monkeys

Source: AN4035 Late-Breaking Oral Presentation, 2025 AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics.

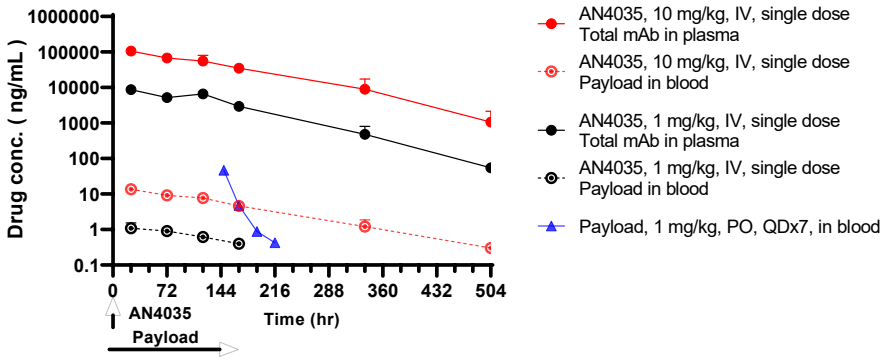
AN4035 exhibited dose-dependent anti-tumor and PK/PD effects in HPAC (KRAS ^{G12D}) CDX

PD biomarkers (p-ERK and Ki-67) were measured after a single dose of AN4035 (1 and 10 mg/kg) or 7-day continuous oral dosing of the payload (1 mg/kg, QD)

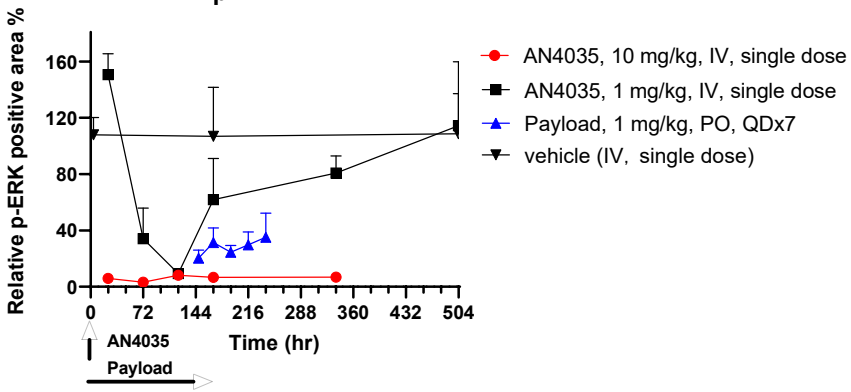
Tumor Volume



PK (total antibody in plasma or payload in blood)

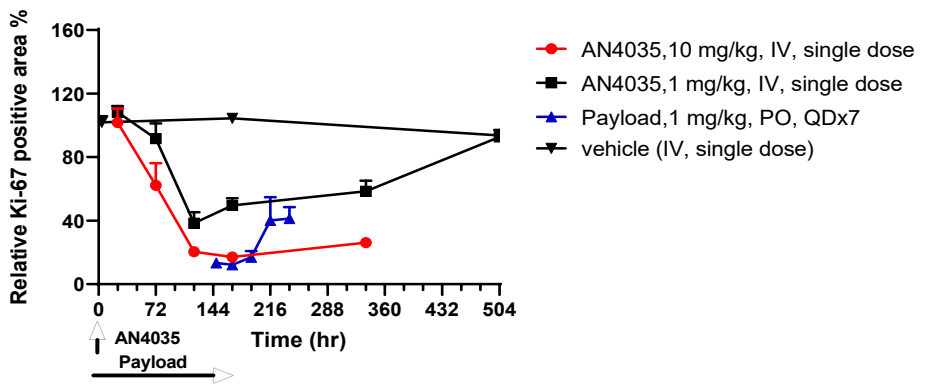


p-ERK IHC



The p-ERK data at 504 h (21 day) of AN4035 10 mg/kg group was unavailable due to the small tumor size

Ki-67 IHC

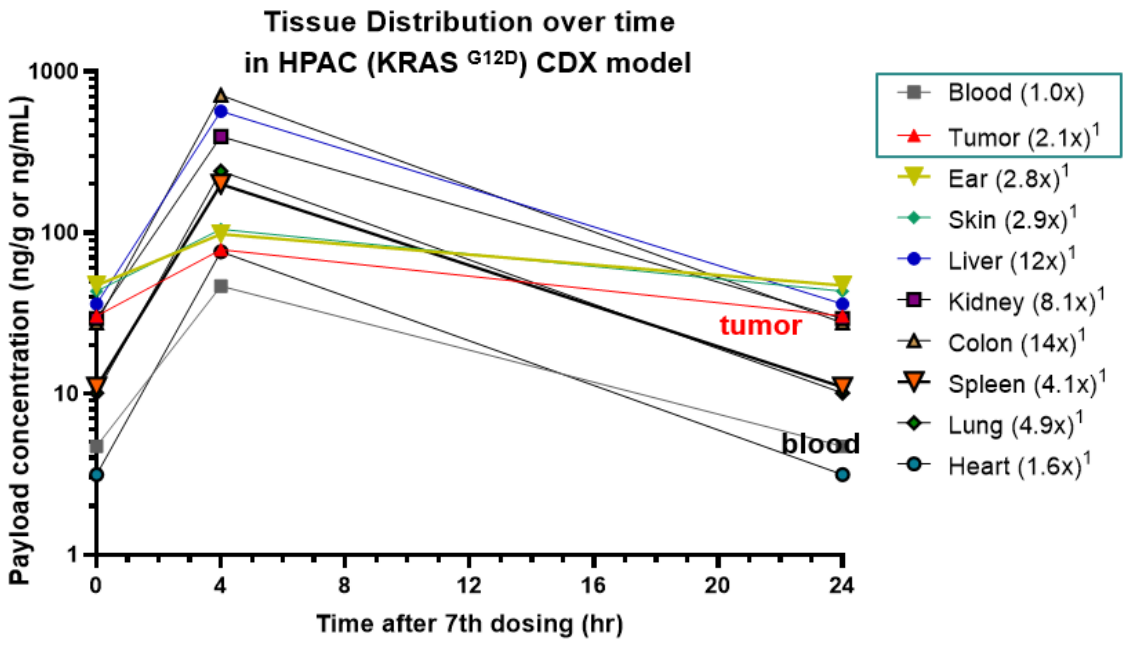


The Ki-67 data at 504 h of AN4035 10 mg/kg group was unavailable due to the small tumor size

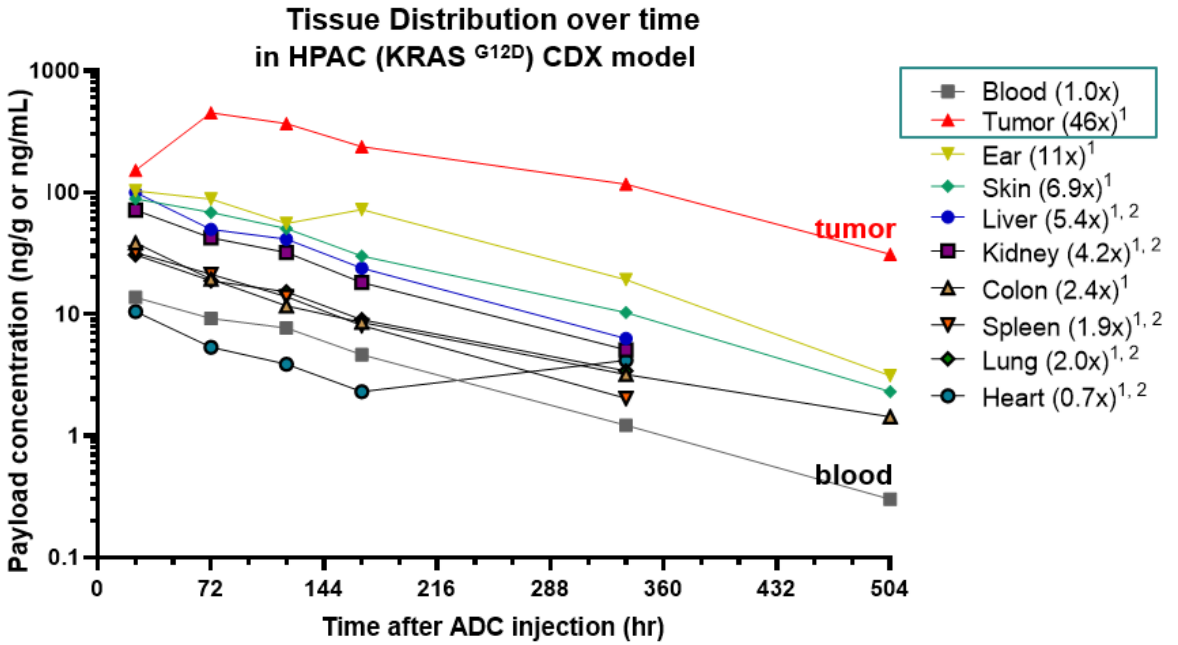
Deep and sustained p-ERK and Ki-67 suppression was observed with a single 10 mg/kg dose of AN4035.

Enhanced payload retention in tumor after AN4035 than after free-payload dosing

Free payload concentrations in tumor, normal tissues and blood after a 7-day continuous dosing of the **payload alone** at 1 mg/kg, PO



Free payload concentrations in tumor, normal tissues and blood after a single dose of **AN4035** at 10 mg/kg, IV

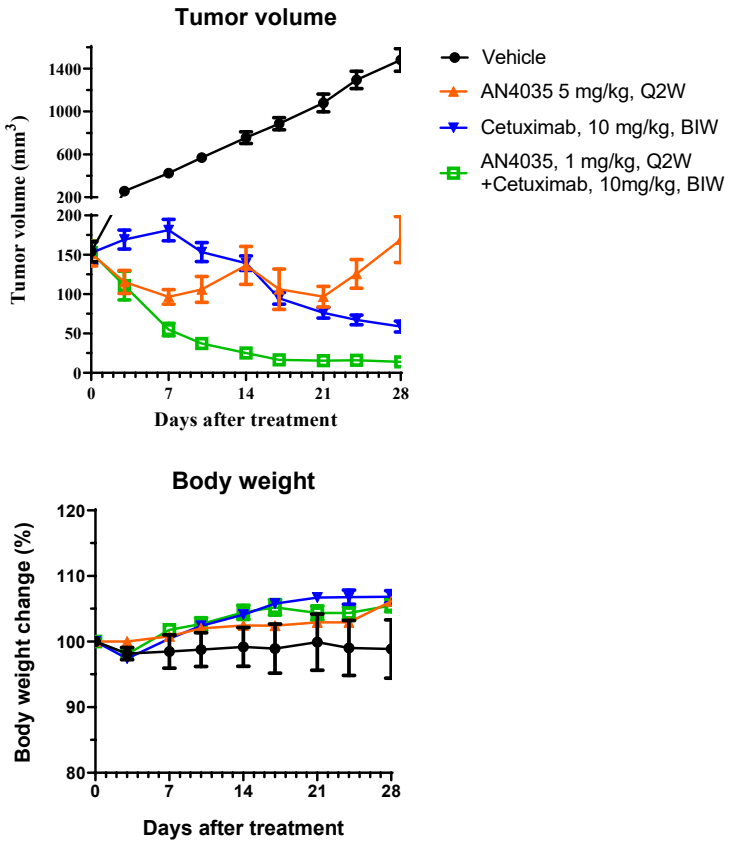


(1) Ratio of tumor/tissue concentration (or AUC exposure) over blood concentration.
(2) Concentrations in these tissues were below the limit of quantification (BQL) at 504 hr.
(3) Ratio of tumor/tissue payload exposure (AUC) normalized to blood exposure.

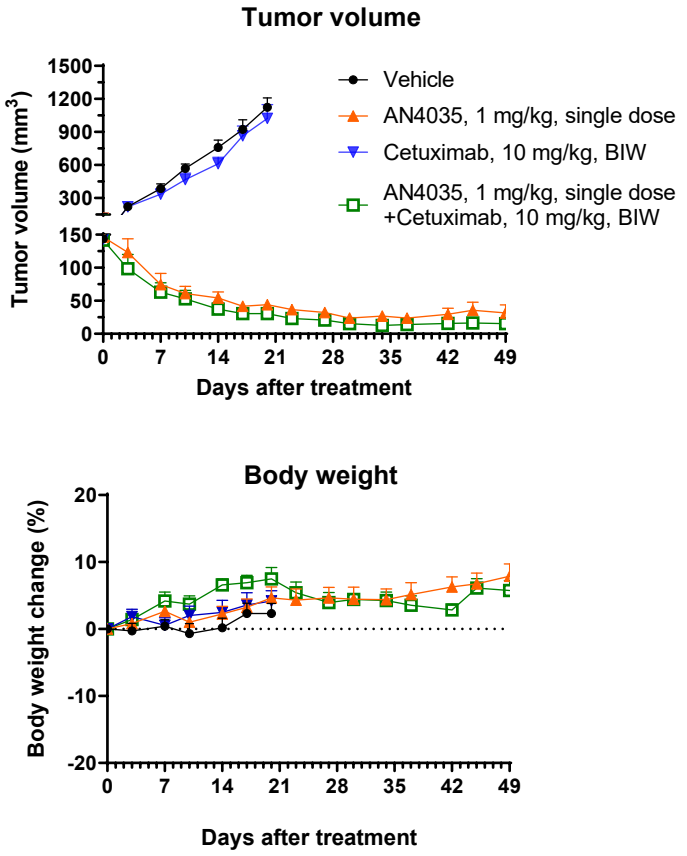
AN4035 demonstrated >20-fold greater target-mediated tumor retention than the unconjugated payload, resulting in markedly improved tumor selectivity over normal tissues.

AN4035 plus EGFR blockade produced deep and durable tumor regression across CDX models

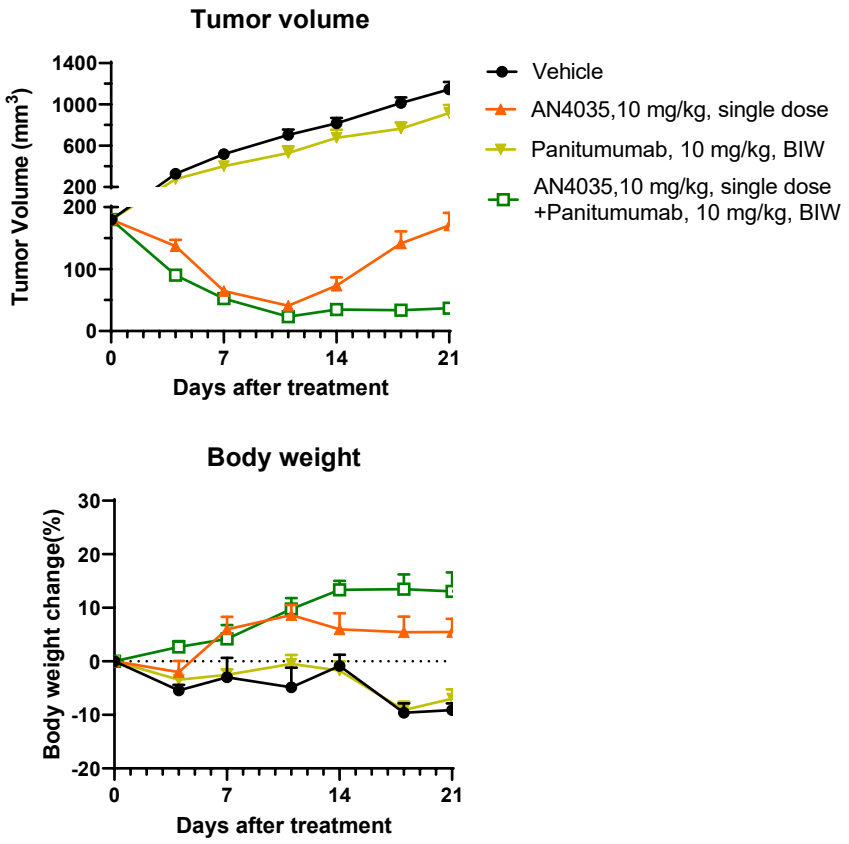
NCI-H2122
KRAS G12C, NSCLC



HPAC
KRAS G12D, PDAC



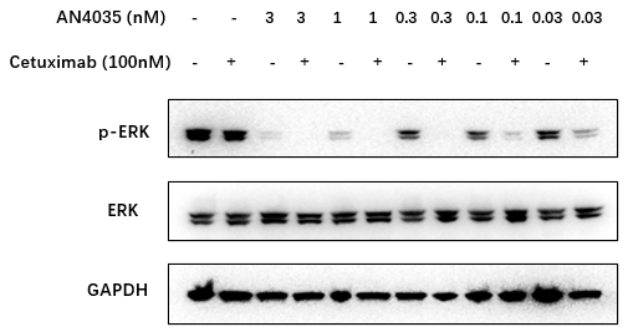
CL-40
KRAS G12D, CRC

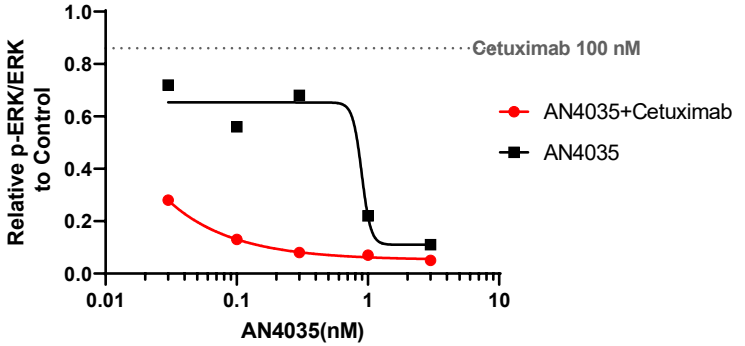


AN4035 plus EGFR antibodies resulted in deeper and more durable tumor regressions than either agent alone across CRC, PDAC, and NSCLC CDX models.

AN4035 plus cetuximab achieved more profound PD effects in CL40 model *in vitro* and *in vivo*

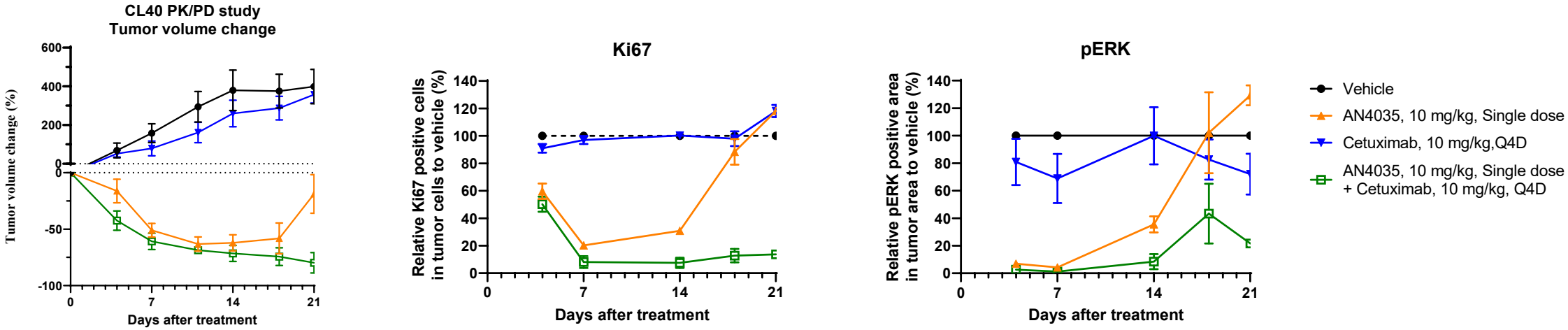
In vitro: Cetuximab enhanced dose-dependent pERK inhibition by AN4035 in CL40 cells (KRAS G12D)[1]





[1] ERK phosphorylation levels were assessed 24 h after treatment.

In vivo: AN4035 in combination with cetuximab suppressed tumor pERK and Ki-67 more than either agent alone and produced greater tumor regression [2]



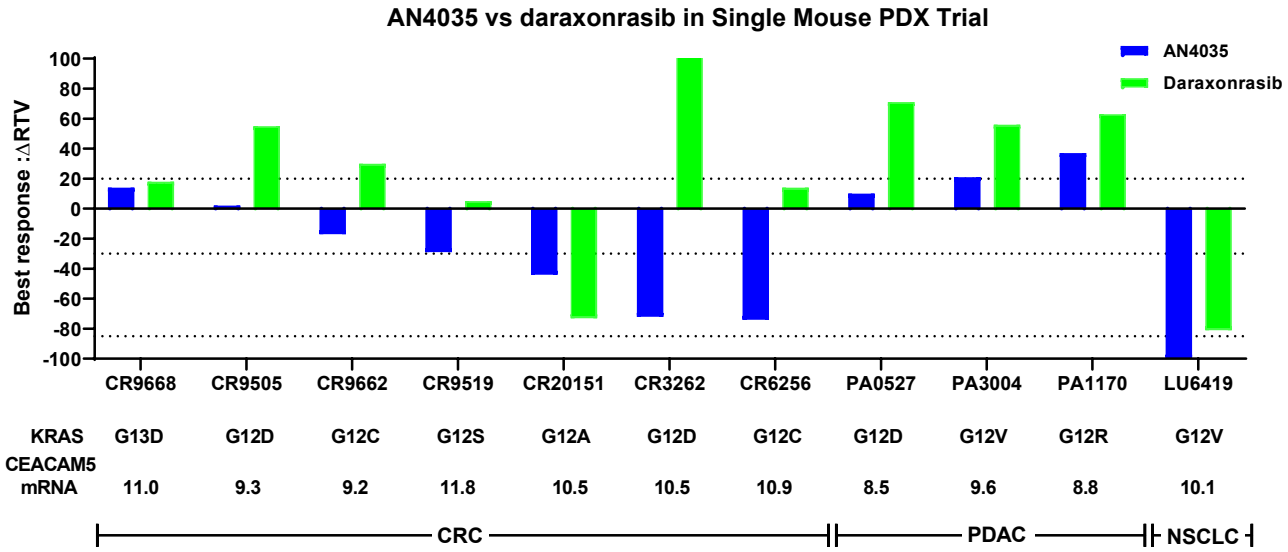
[2] PD biomarkers (pERK and Ki67) were measured at multiple time points after a single dose of AN4035 (10 mg/kg) with/without cetuximab (10 mg/kg, Q4D) in the CL40 CDX model

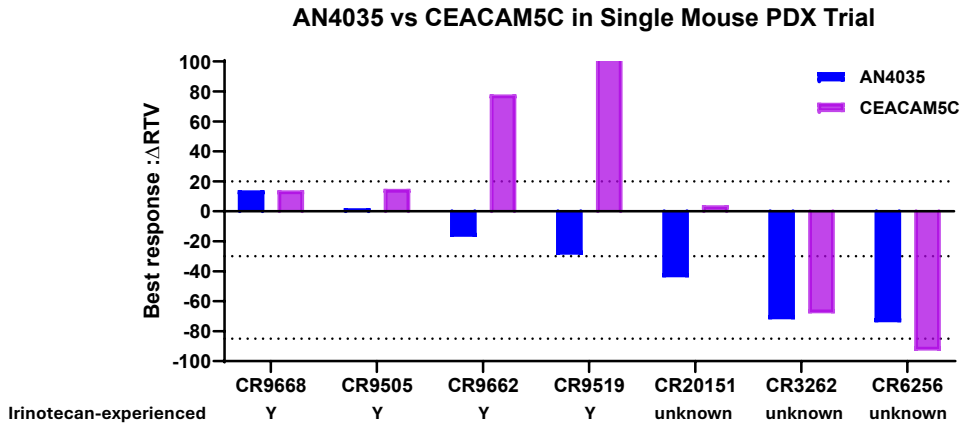
AN4035 showed superior antitumor activity to daraxonrasib and CEACAM5C in selected less-sensitive PDX models harboring various KRAS mutations

Efficacy in PDX Models[1]

	Selected less-sensitive models		Historical
Drug	**AN4035**	Daraxonrasib	AN4035
CR	1	0	4
PR	3	2	15
SD	5	3	2
PD	2	6	5
ORR (%)	36 (4/11)	18 (2/11)	73 (19/26)
DCR (%)	82 (9/11)	45 (5/11)	81 (21/26)

Drug	**AN4035**	CEACAM5C
CR	0	1
PR	3	1
SD	4	3
PD	0	2
ORR (%)	43 (3/7)	29 (2/7)
DCR (%)	100 (7/7)	71 (5/7)





Dose Regimens:

CR9668, CR6256, CR9505: AN4035 / CEACAM5C, Single dose, 10 mg/kg

CR9662, CR20151, CR3262, CR9519, PA1170, PA0527, PA3004: AN4035 / CEACAM5C, Q2W, 10 mg/kg

LU6419: AN4035, Q3W, 10 mg/kg

CR9505: CEACAM5C group mouse was dead at day17 (body weight loss >20%)

PA3004: daraxonrasib group dosed daraxonrasib 25 mg/kg + RMC5127 100 mg/kg, PO, QD

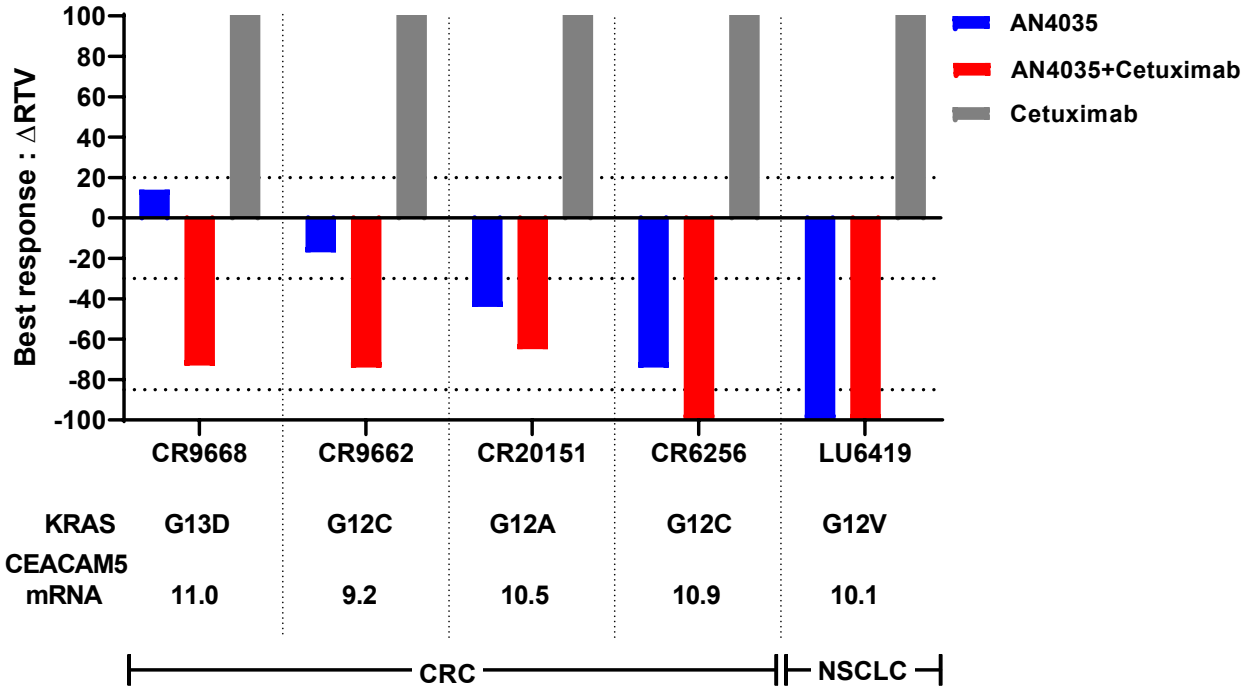
Daraxonrasib : 25 mg/kg, PO, QD

Across most PDX models, AN4035 monotherapy demonstrated greater antitumor activity than daraxonrasib or CEACAM5C, a Top1i-based ADC

(1) 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 an 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);

AN4035 plus EGFR blockade demonstrated enhanced efficacy in PDX models

AN4035 and EGFR blockade in single mouse PDX trial



Efficacy in PDX Models[1]

Drug	AN4035	AN4035 +Cetuximab	Cetuximab
CR	1	**2**	0
PR	2	**3**	0
SD	2	**0**	0
PD	0	**0**	5
ORR (%)	60 (3/5)	**100 (5/5)**	0 (0/5)
DCR (%)	100 (5/5)	**100 (5/5)**	0 (0/5)

Dose Regimens:
CR9668, CR6256: AN4035, Single dose, 10 mg/kg
CR9662, CR20151: AN4035, Q2W, 10 mg/kg
LU6419: AN4035, Q3W, 10 mg/kg
Cetuximab: BIW, 10 mg/kg

When combined with Cetuximab, AN4035 produced deeper and more durable tumor regressions than either agent alone in CRC PDX models.

(1) 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 an 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);

AN4035 in combination with cetuximab was generally well tolerated in cynomolgus monkeys with no evidence of additive toxicity

STUDY DESIGN

Exploratory non-GLP | AN4035 and cetuximab: IV, Q2W × 3 doses | 1Male + 1Female/group

Dose (mg/kg/dose)	AN4035	Cetuximab
Cetuximab alone	0	14
Combination 1	7.5	14
Combination 2	20	7
Highest combination	**20**	**14**

HISTORICAL REFERENCE — SEPARATE GLP STUDY

AN4035 monotherapy: 20 mg/kg/dose, Q2W × 3
Moderate skin ulceration considered adverse (below HNSTD)

HIGHEST TESTED COMBINATION

AN4035 20 mpk + cetuximab 14 mpk
Generally well tolerated

KEY SAFETY FINDINGS

1. **Consistent skin toxicity profile**
   Moderate skin ulceration was adverse at AN4035 20 mg/kg/dose in both monotherapy GLP and combination studies.
2. **No clear exacerbation**
   No consistent dose-dependent worsening of skin findings across combination groups.
3. **Overall tolerability**
   All animals survived; no notable GI clinical signs or treatment-related changes in body weight or food intake.

HNSTD, highest non-severely toxic dose

Summary

- **AN4035 is a first-in-class CEACAM5-targeted ADC armed with a proprietary pan-RAS(ON) inhibitor payload**
  - **Demonstrated compelling single-agent antitumor efficacy and favorable tolerability in preclinical studies**
  - **Showed tumor-enriched payload distribution, and enhanced PD effect and antitumor activity with EGFR blockade**
  - **Combination with cetuximab showed no clear evidence of additive toxicity relative to AN4035 monotherapy in monkeys**
- **These results support the ongoing Phase I study of AN4035 as monotherapy and in combination with cetuximab in patients with advanced solid tumors harboring RAS mutations and enriched for CEACAM5 expression (NCT07686445)**