AN9025, an orally bioavailable pan-RAS(ON) inhibitor with potent, broad-spectrum anti-tumor activity

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Background

- RAS mutations drive approximately 30% of human cancers, especially in pancreatic, lung, and colorectal cancers, representing a critical unmet clinical need.
- Pan-RAS(ON) inhibitors such as RMC-6236, bind to cyclophilin A (CypA) to form a binary complex which then engages the RAS (ON) protein to create a tri-complex that effectively inhibits downstream signaling pathways. RMC-6236 has shown encouraging clinical efficacy in Ras-mutated cancers.
- Here we report the preclinical characterization of a novel pan-RAS(ON) inhibitor, AN9025, with improved potency and a favorable PK/PD profile.

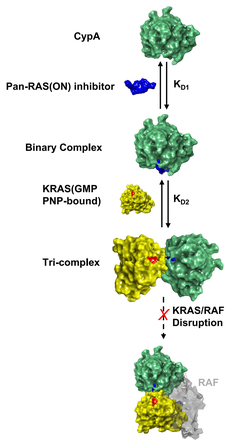

Figure 1. MOA of pan-RAS(ON)i

AN9025 forms a tri-complex with high affinity

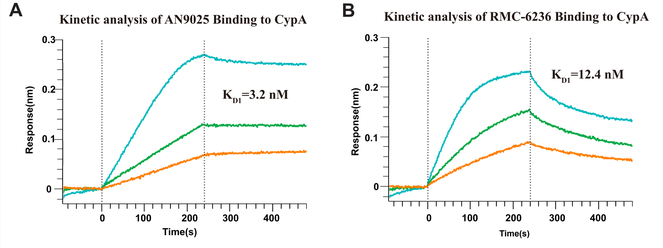

Figure 2. Binding kinetics of AN9025 and RMC-6236 to CypA. His-tagged CypA was immobilized on an NTA sensor and then incubated with AN9025 (A) or RMC-6236 (B) to monitor BLI signal changes associated with binary complex formation.

- AN9025 exhibits a 4-fold stronger binding affinity to CypA compared to RMC-6236, driven by its slower dissociation rate.

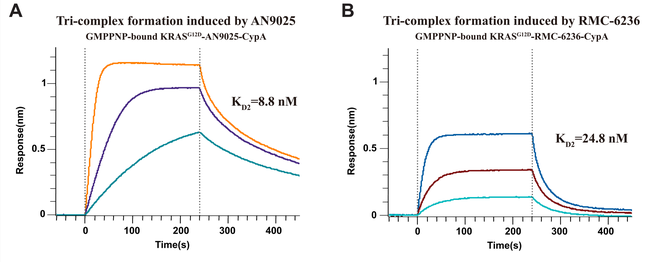

Figure 3. Kinetic of tri-complex formation induced by AN9025 and RMC-6236. His-tag KRAS^{G12D} protein in the GMPPNP-bound state was first immobilized on a NTA sensor, followed by incubation with with AN9025 (A) or RMC-6236 (B) and CypA to monitor the BLI signal changes indicative of tri-complex formation.

Mutant RAS(ON) Protein	AN9025		RMC-6236	
	K_{D2} (nM)	Max response (nm)	K_{D2} (nM)	Max response (nm)
KRAS^{G12D}	8.8	1.2	24.8	0.7
KRAS^{G12C}	4.5	1.1	17.8	0.9
KRAS^{G12V}	8.3	2.4	68.4	1.5
KRAS^{G12R}	15.5	2.6	80.5	1.1
KRAS^{G13D}	15.5	2.5	69.7	1.1
KRAS^{Q61H}	11.0	2.5	45.4	1.6
KRAS^{WT}	10.0	2.3	52.8	1.3
NRAS^{WT}	6.6	1.8	33.9	1.3
HRAS^{WT}	4.0	1.6	20.2	1.3
KRAS^{G12D}(OFF)	Little binding		No binding	

Table 1. Tri-complex binding affinity of AN9025 and RMC-6236 with various RAS mutant proteins

- AN9025 exhibits a 3- to 8-fold higher binding affinity for tri-complex formation and 1.5- to 2- fold greater maximum response compared to RMC-6236, suggesting enhanced formation of tri-complex by AN9025.

AN9025 inhibits the viability of RAS-addicted cancer cell lines

Cell Line	Tissue of Origin	Cell Viability, IC_{50} (nM)	RAS Status
MIAPACA2	Pancreas	0.004	KRAS:p.G12C
ASPC1		0.0063	KRAS:p.G12D
HPAC		0.043	KRAS:p.G12D
CAPAN2		0.01	KRAS:p.G12V
CAPAN1		0.02	KRAS:p.G12V
PSN1		0.0149	KRAS:p.G12R
NCIH2122	Lung	0.0009	KRAS:p.G12C
NCIH441		0.0054	KRAS:p.G12V
NCIH727		0.0017	KRAS:p.G12V
NCIH2009		0.01	KRAS:p.G12A
A549		0.02	KRAS:p.G12S
NCIH1355		0.1	KRAS:p.G13C
SW1271		0.022	NRAS:p.Q61R
NCIH2087		0.003	NRAS:p.Q61K
NCIH1915		0.377	HRAS:p.Q61L
NCIH322		0.3632	WT
LS513	Colon	0.003	KRAS:p.G12D
SW480		0.0581	KRAS:p.G12V
SKCO1		0.02	KRAS:p.G12V
HCT116		0.03	KRAS:p.G13D
KYSE30	Esophagus	0.365	HRAS:p.Q61L
MKN45	Stomach	0.01	WT
HEPG2	Liver	0.0152	NRAS:p.Q61L
OCIM2	Hematopoietic and lymphoid tissue	0.033	NRAS:p.Q61K
OCIAML3		0.034	NRAS:p.Q61L
AML193		0.0353	NRAS:p.G13V

Table 2. Viability inhibition of RAS-addicted cancer cell lines by AN9025. IC_{50} values of AN9025 in RAS-addicted cancer cell lines harboring multiple RAS mutations or RAS WT were determined using the CellTiter-Glo (CTG) assay. Cells were treated with varying concentrations of the compounds for 72 hours.

- AN9025 demonstrates potent inhibition of cell viability in RAS-addicted cancer cell lines at picomolar level.

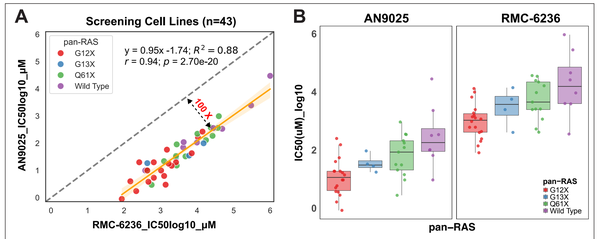

Figure 3. Cancer cell line panel screening. A. Correlation of IC_{50} values between AN9025 and RMC-6236. IC_{50} values of RMC-6236 (x-axis) and A9025 (y-axis) were compared across 43 cell lines with different RAS mutations. B. IC_{50} values of AN9025 and RMC-6236 stratified by RAS genotype.

- AN9025 exhibits approximately 100-fold greater potency in inhibiting cell viability across RAS-mutant cell lines compared to RMC-6236.
- AN9025 displays a similar RAS-mutant sensitivity pattern to RMC-6236, with the hierarchy G12X>G13X≈Q61X>Wild Type.

AN9025 shows potent anti-tumor activity in vivo

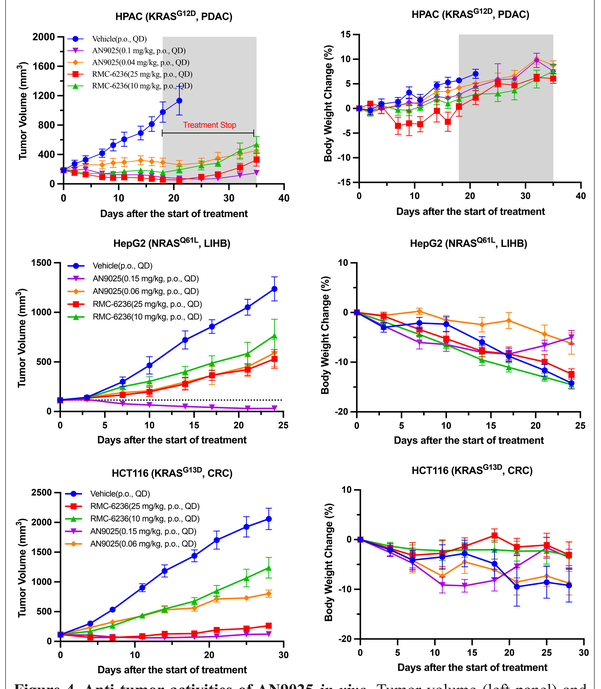

Figure 4. Anti-tumor activities of AN9025 *in vivo*. Tumor volume (left panel) and body weight change (right panel) during treatment with AN9025 at the indicated doses (*p.o.*, QD) in HPAC, HepG2 and HCT116 xenograft models. The gray shading denotes the drug withdrawal period. Data represent mean±SEM; n=7-8 mice per group.

- AN9025 achieved tumor regression in multiple CDX models harboring RAS mutation and demonstrated more sustained tumor suppression after drug withdrawal.

PK/PD correlation of AN9025

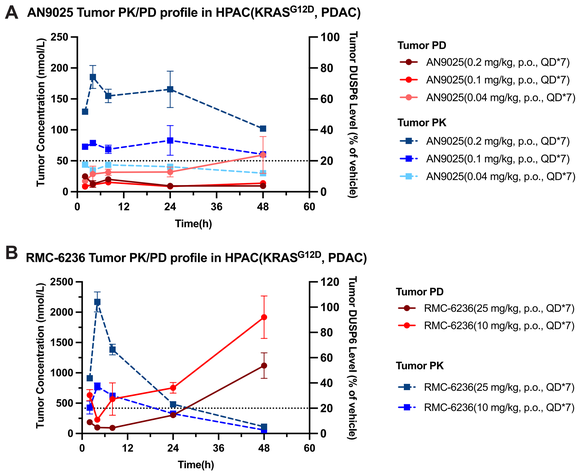

Figure 5. Pharmacokinetic (PK) and Pharmacodynamic (PD) profiles of AN9025 and RMC-6236 in HPAC xenograft models. AN9025 (A) and RMC-6236 (B) was administrated at indicated doses (*p.o.*, QD*7). Tumor tissue and blood were collected 2, 4, 8, 24 and 48 hours post-dose to assess PD (DUSP6) and PK (blood concentration).

- AN9025 exhibits more sustained DUSP6 inhibition compared to RMC-6236 across all tested doses.
- The prolonged tumor DUSP6 suppression following AN9025 administration suggests the potential for an intermittent dosing regimen to optimize tolerability and efficacy.

Conclusions

AN9025 is a novel pan-RAS(ON) inhibitor developed by Adlai Nortye:

- Strongly binds cyclophilin A (CypA) with a slow dissociation rate, enabling tight tri-complex formation and potent RAS inhibition.
- Shows potent anti-proliferative activity in RAS-addicted cancer cell lines (picomolar IC_{50} values).
- Demonstrates a favorable PK/PD and tolerability profile in vivo.
- Induces deep tumor regression, with efficacy comparable to or exceeding RMC-6236 in mouse CDX models.
- Is advancing through the IND-enabling stage.

- We are actively seeking strategic partnerships with leading pharmaceutical and biotechnology companies to advance the development of AN9025 and facilitate its availability to patients in need.
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