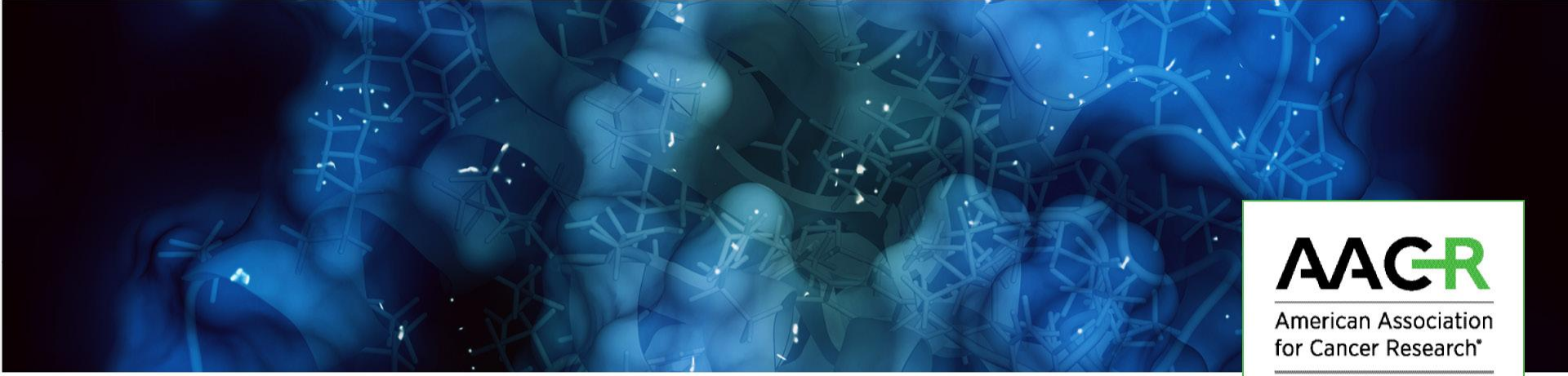


Anti-Tumor Efficacy of the Selective Oral KRAS G12D Dual ON/OFF Inhibitor VS-7375: Preclinical and Clinical Update

Jonathan A Pachter, PhD
Chief Scientific Officer
Verastem Oncology

RAS ONCOGENESIS AND THERAPEUTICS
March 5-8, 2026 | J.W. Marriott Los Angeles L.A. Live | Los Angeles, CA

Disclosure Information

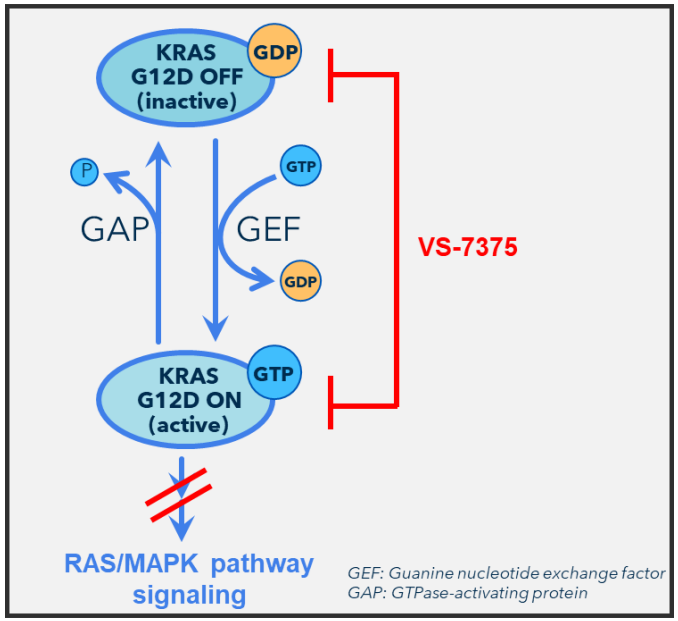
Jonathan A Pachter

I have the following relevant financial relationships to disclose:

Employee of: Verastem Oncology

Stockholder in: Verastem Oncology

VS-7375 is a potent KRAS G12D dual ON/OFF inhibitor



Binding Assays*

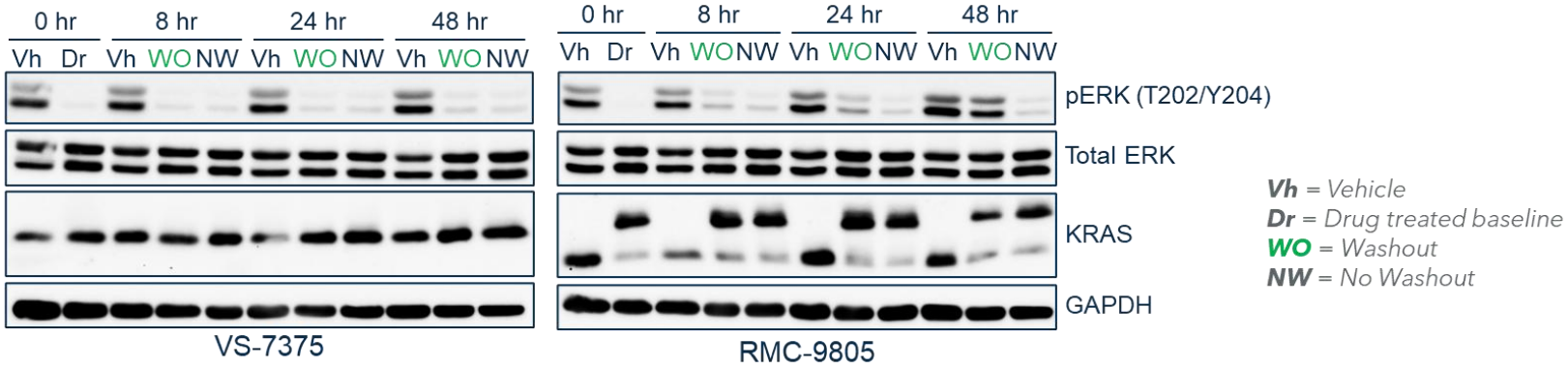
KRAS G12D State	VS-7375 K_D (pM)	Assay
GppNHp-bound (ON/active)	18	SPR affinity
GDP-bound (OFF/inactive)	12	SPR affinity

Functional Assays

KRAS G12D State	VS-7375 IC_{50} (nM)	Assay
GppNHp-bound (ON/active)	2 ± 1	RAF1 binding
GDP-bound (OFF/inactive)	6 ± 1	Nucleotide exchange

** Residence time for VS-7375 is 18-24 hours compared to ~1 hour for AZD0022 (G12Di) or AMG410 (pan-KRASi)*

VS-7375 more potently and durably suppresses pERK levels than the KRAS G12D ON-only RMC-9805

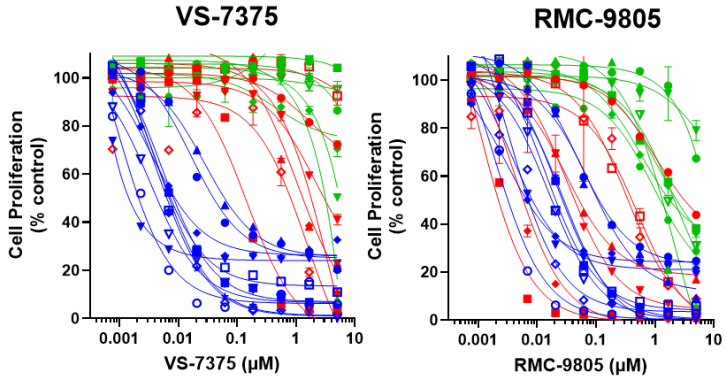


Pa14C cells treated with either VS-7375 (30 nM) or RMC-9805 (300 nM) for 24 hr (T = 0 hr in this figure) followed by drug washout for 8, 24, or 48 hr

VS-7375 suppressed pERK more durably than RMC-9805 over 48 hours despite the covalent interaction of RMC-9805 with KRAS

Collaboration with Channing Der (University North Carolina at Chapel Hill)

VS-7375 potently and selectively inhibits proliferation of KRAS G12D tumor cell lines



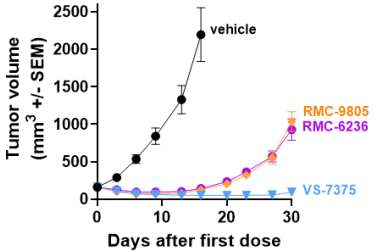
Cell Line	Indication	KRAS status	VS-7375 IC50 (nM)	RMC-9805 IC50 (nM)
SKLU1	NSCLC	G12D	8	7
KP4	PDAC	G12D	2	4
GP2D	CRC	G12D	2	8
HPAC	PDAC	G12D	7	9
HPAF-II	PDAC	G12D	5	18
AsPC1	PDAC	G12D	7	19
Panc08.13	PDAC	G12D	8	26
LS513	CRC	G12D	7	28
LS180	CRC	G12D	33	96
Panc04.03	PDAC	G12D	63	111
MiaPaca2	PDAC	G12C	133	3
H358	NSCLC	G12C	1471	6
H1373	NSCLC	G12C	3069	43
H2122	NSCLC	G12C	>5000	334
H441	NSCLC	G12V	828	51
A549	NSCLC	G12S	>5000	3337
HCT116	CRC	G13D	756	358
H1299	NSCLC	wild-type	>5000	1003
GAK	melanoma	wild-type	3287	1109
SKMEL2	melanoma	wild-type	>5000	1600
PC9	NSCLC	wild-type	>5000	1986
H1975	NSCLC	wild-type	>5000	2514
A375	melanoma	wild-type	>5000	>5000
HT29	CRC	wild-type	>5000	>5000

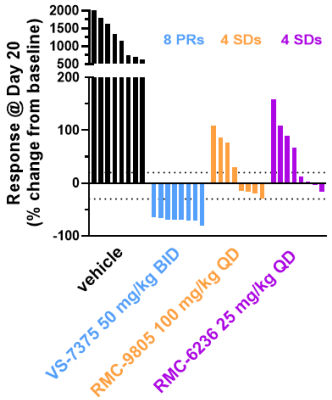
< 65 nM | 65-125 nM | > 125 nM

Oral dosing of VS-7375 is more efficacious than KRAS G12D ON and pan-RAS ON inhibitors in KRAS G12D tumor models in vivo

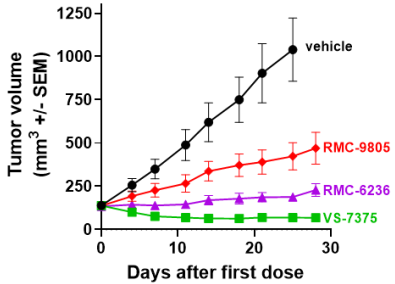
AACR American Association for Cancer Research

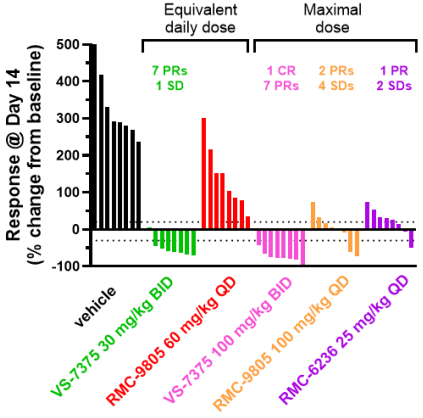
KP4 Pancreatic Cancer Model



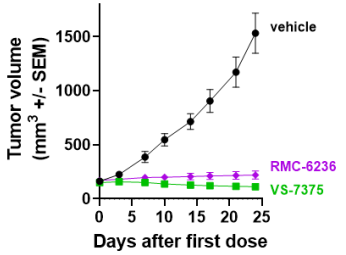


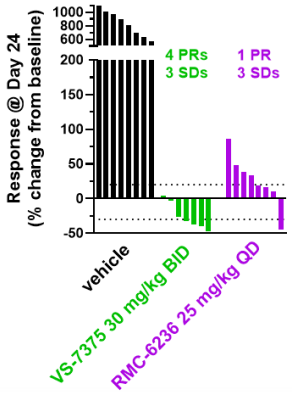
LS513 Colorectal Cancer Model





LU0876 NSCLC PDX Model



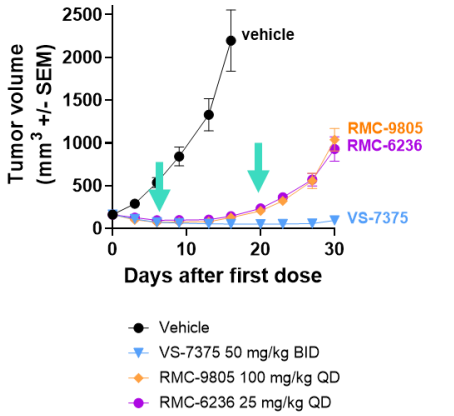


Pharmacodynamic analysis of VS-7375 vs ON-only inhibitors

VS-7375 confers more durable inhibition of MAPK, MYC and PI3K signaling than KRAS G12D ON and pan-RAS ON inhibitors

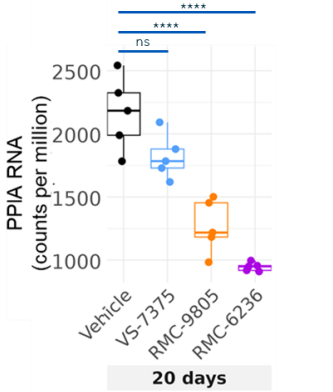
AACR American Association for Cancer Research

KP4 Pancreatic Cancer Model

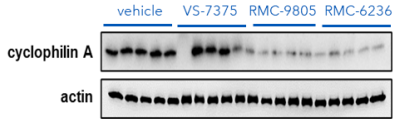


- Collect tumors 2 hours after the last dose on Day 6 or Day 20
- RNA and protein analysis

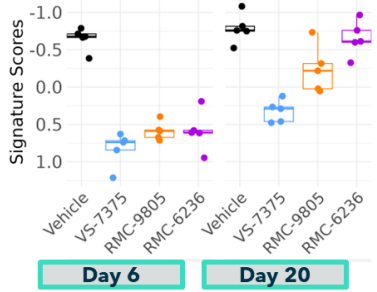
Cyclophilin A
(RNA and protein)



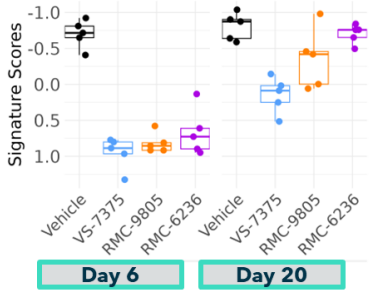
VS-7375 vs VH 20 days p-value: 0.18
RMC-9805 vs VH 20 days p-value: 2.5e-06
RMC-6236 vs VH 20 days p-value: 3.5e-09



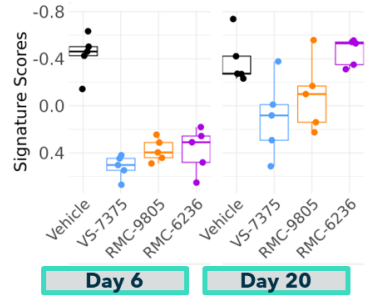
MAPK signaling
(RAS signature)



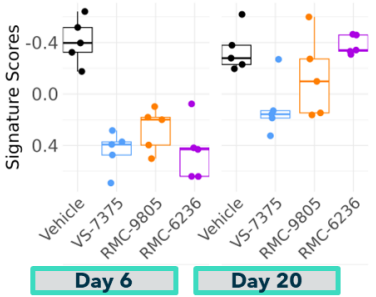
MAPK signaling
(ERK signature)



MYC signaling



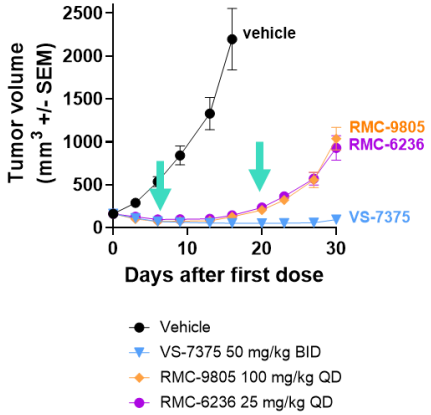
PI3K signaling



** RAS signature (RAS UP; Channing Der); ERK signature (ERK DOWN; Channing Der); MYC signature (MYC UP; Channing Der); PI3K signature (PI3K UP; Zhang et al., 2018). Y-axis has been inverted for visualization*

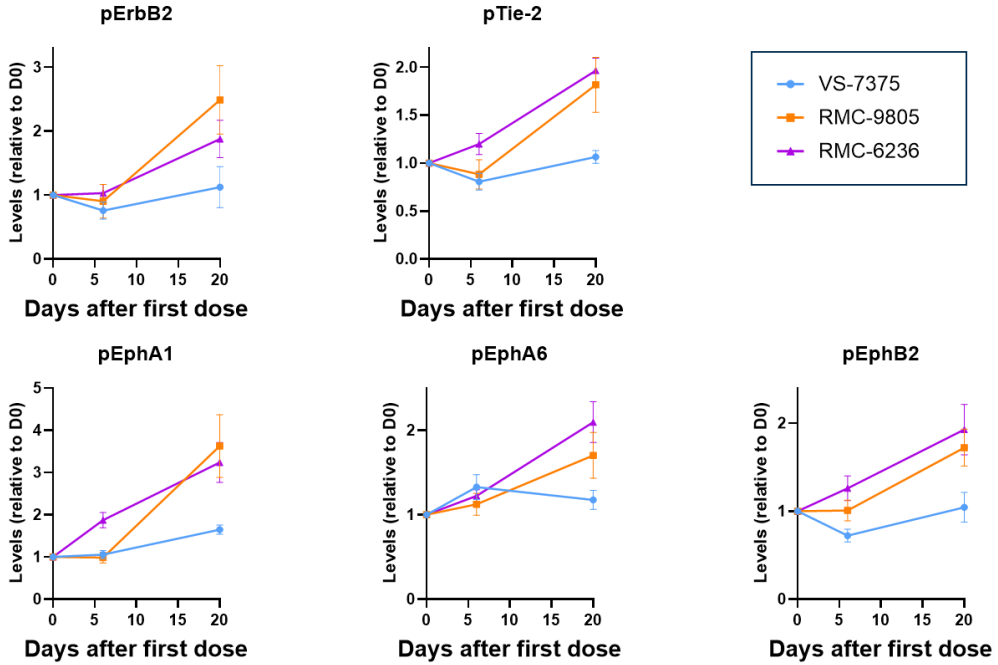
Loss of efficacy with the RAS ON inhibitors also correlates with increased RTK signaling in the KP4 PDAC model

KP4 Pancreatic Cancer Model

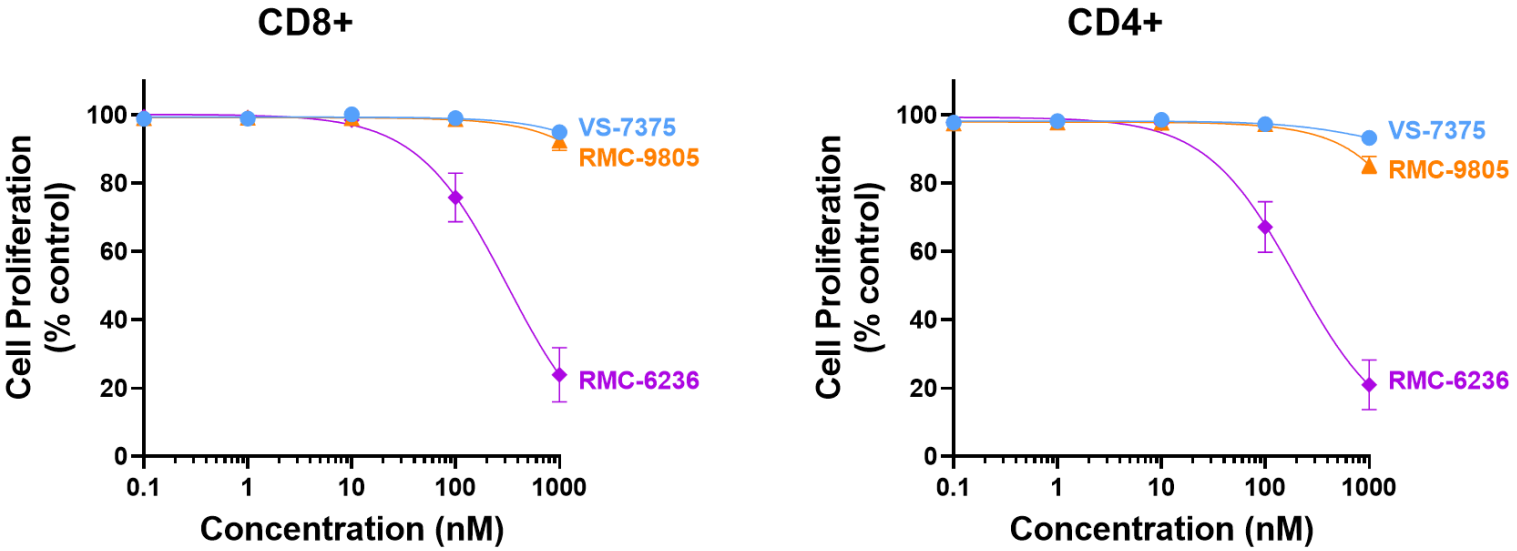


- Collect tumors 2 hours after the last dose on Day 6 or Day 20
- RNA and protein analysis

Receptor Tyrosine Kinase Activation



Variant-selective KRAS inhibitors spare T cell proliferation in contrast to pan-RAS ON inhibitor

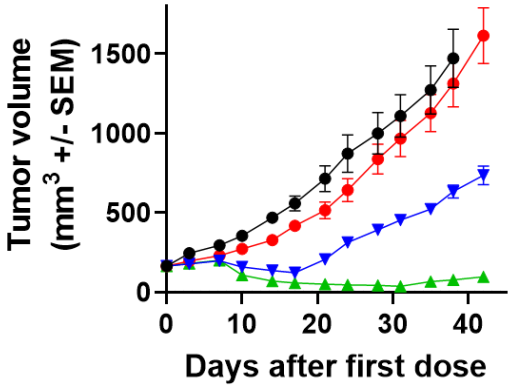


Isolated CD3+ T cells from PBMCs from triplicate human donors were cultured with anti-human CD3/CD28 beads and treated for 3 days

Addition of cetuximab with VS-7375 induces strong tumor growth inhibition in KRAS G12D cancer models in vivo

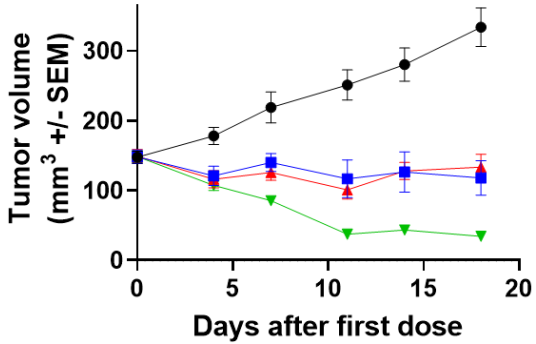
AACR American Association for Cancer Research

CR1245 CRC PDX Model

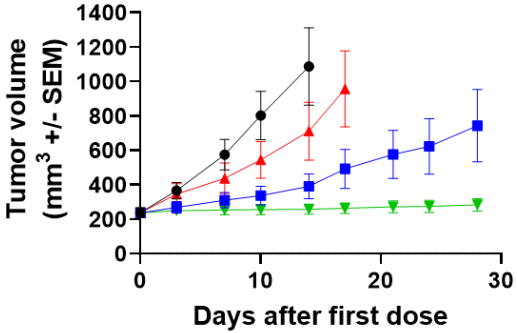


- Vehicle
- VS-7375 30 mg/kg BID
- Cetuximab 10 mg/kg BIW
- VS-7375 + cetuximab

AsPC-1 PDAC Model



LU0876 NSCLC PDX Model



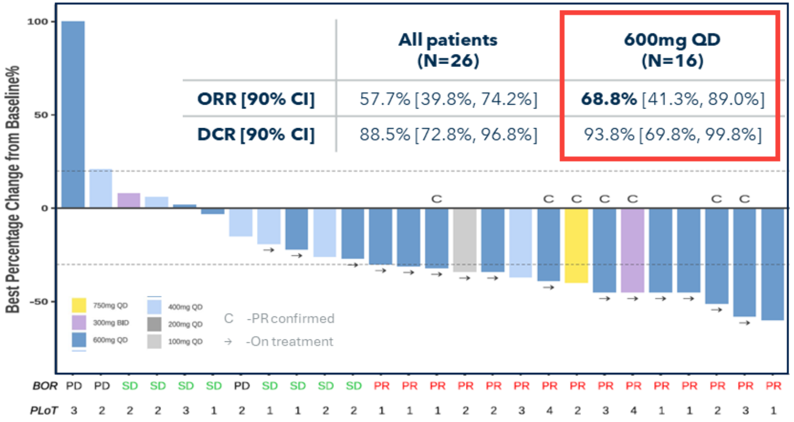
- Vehicle
- VS-7375 10 mg/kg PO BID
- Cetuximab 0.25 mg/mouse IP Q3D
- VS-7375 + cetuximab

GFH375/VS-7375 confers single agent anti-tumor activity in patients with previously treated NSCLC and PDAC (GenFleet study in China)

American Association for Cancer Research

NSCLC

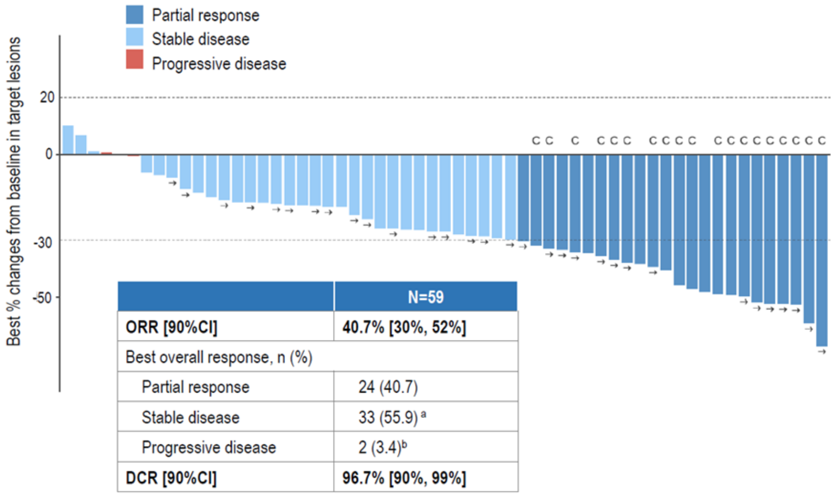
- **68.8% ORR (n=16) at 600 mg QD**; 57.7% ORR (n=26) evaluable pts*
- Among the 5 pts with baseline brain metastases, 2 achieved PR



	All patients (N=26)	600mg QD (N=16)
ORR [90% CI]	57.7% [39.8%, 74.2%]	**68.8%** [41.3%, 89.0%]
DCR [90% CI]	88.5% [72.8%, 96.8%]	93.8% [69.8%, 99.8%]

PDAC

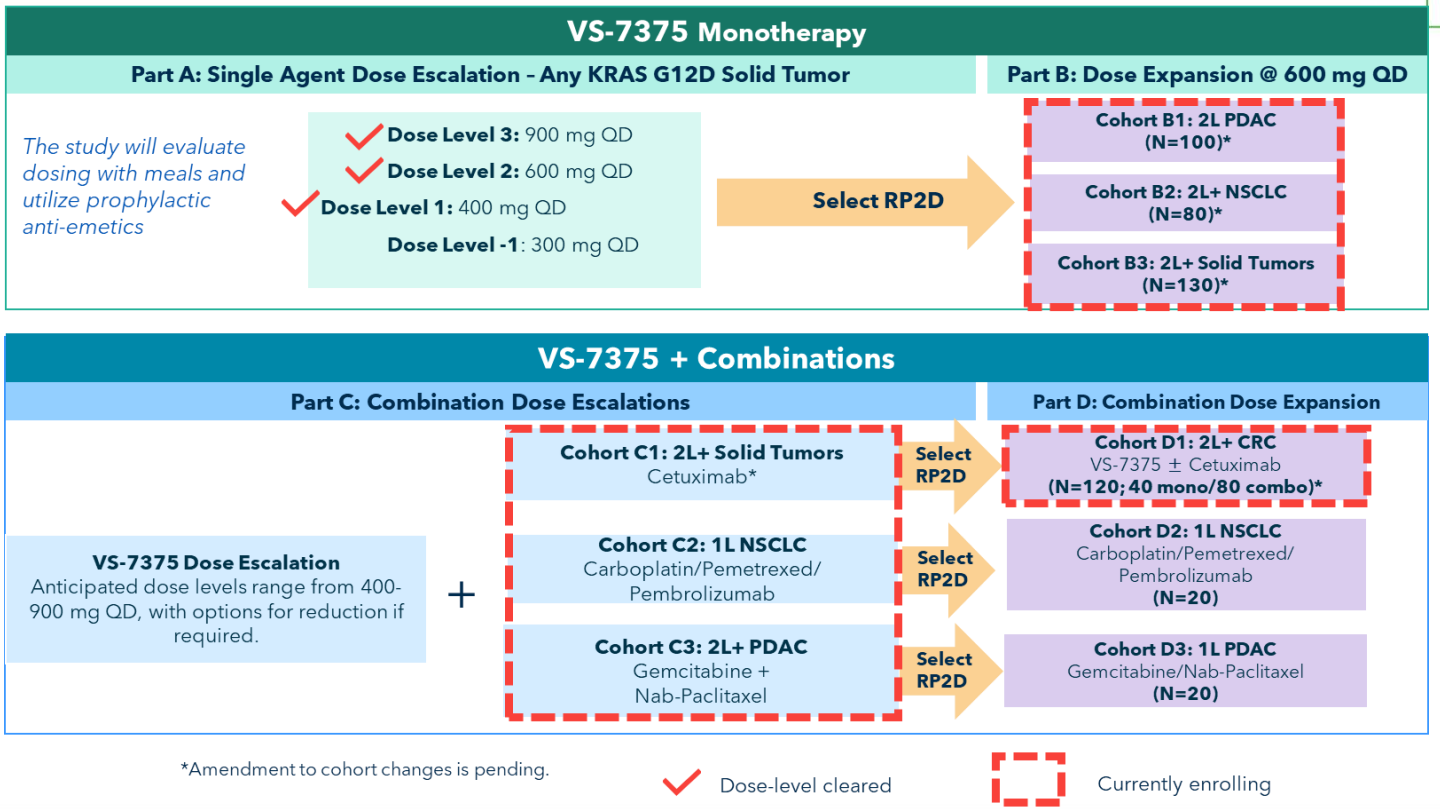
- **ORR = 40.7% (24/59) at 600 mg QD in heavily pretreated patients**
  - o 68% of patients were 3L or later



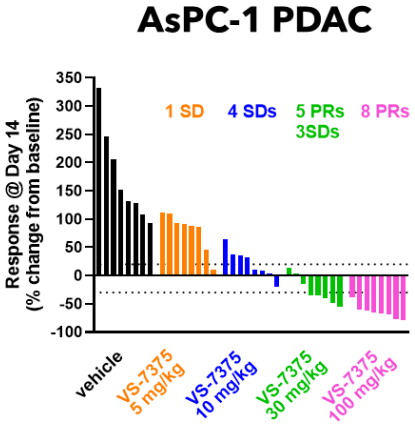
	N=59
ORR [90%CI]	40.7% [30%, 52%]
Best overall response, n (%)	
Partial response	24 (40.7)
Stable disease	33 (55.9) [a]
Progressive disease	2 (3.4)[b]
DCR [90%CI]	96.7% [90%, 99%]

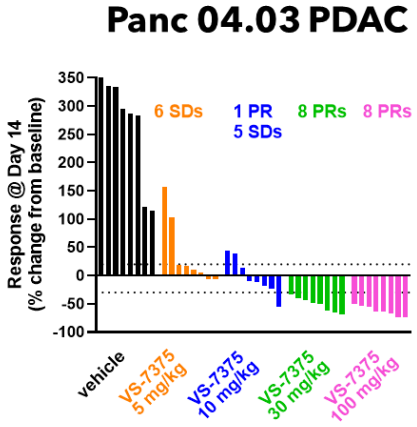
GFH375 is being developed by GenFleet Therapeutics in China. Source of data: GenFleet presentation at WCLC, ESMO 2025. QD: once daily; PR: partial response; TRAE: treatment related adverse events; 2L: second line

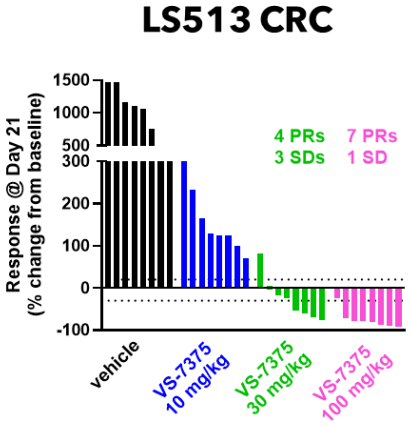
VS-7375-101 study: Efficiently testing VS-7375 monotherapy and SOC combinations across KRAS G12D indications

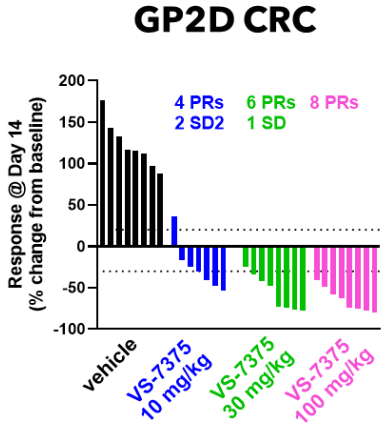


Oral administration of VS-7375 inhibits tumor growth in a dose-dependent manner in KRAS G12D models



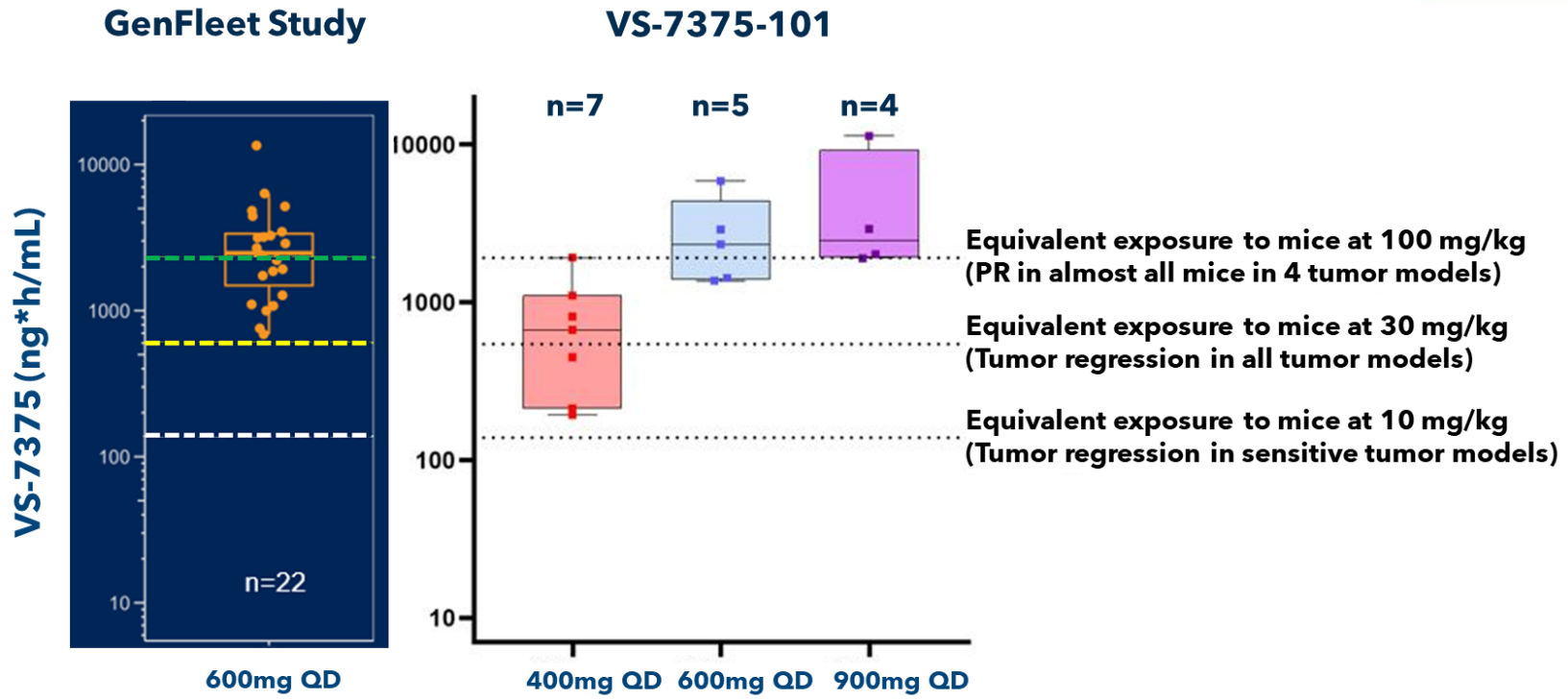






- 10 mg/kg conferred strong tumor regressions in the most sensitive model (GP2D)
- 30 mg/kg conferred strong tumor regressions across all models
- 100 mg/kg conferred partial responses (>30% reduction) in >95% of all mice

600 mg VS-7375 QD PO in clinical studies achieves the targeted human AUC_{ss} for maximal tumor regression across mouse models



ASCO 2025

VS-7375 Safety/Tolerability Profile

- No dose-limiting toxicities at 400, 600 or 900 mg QD
- No drug-related liver function abnormalities were reported in any patient across any of the dose levels evaluated
- No neutropenia >Grade 2 was reported
- Rates of nausea, vomiting and diarrhea are lower than those reported by our partner in China through dosing with food, use of standard prophylactic anti-nausea agents, and rapid institution of over-the-counter anti-diarrheals

	Monotherapy Dose Escalation Cohorts (All dose levels) N=23[1]; mDoT, median (range): 1.6 (0.7-5.6) months				
System Organ Class Preferred Term	**Gr. 1, n (%)**	**Gr. 2, n (%)**	**Gr. 3, n (%)**	**Gr. ≥4, n (%)**	**All Gr., n (%)**
Nausea	**11 (48)**	**1 (4)**	0 (0)	0 (0)	**12 (52)**
Diarrhea	**7 (30)**	**1 (4)**	**1 (4)**	0 (0)	**9 (39)**
Vomiting	**6 (26)**	0 (0)	0 (0)	0 (0)	**6 (26)**
Abdominal pain	0 (0)	**1 (4)**	0 (0)	0 (0)	**1 (4)**
Abdominal distention	**2 (9)**	0 (0)	0 (0)	0 (0)	**2 (9)**
Flatulence	**2 (9)**	0 (0)	0 (0)	0 (0)	**2 (9)**
General					
Fatigue	**6 (26)**	**1 (4)**	0 (0)	0 (0)	**7 (30)**
Edema peripheral	**1 (4)**	0 (0)	0 (0)	0 (0)	**1 (4)**
Investigations					
AST increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALT increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blood bilirubin increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GGT increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALP increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Amylase increased	**1 (4)**	**1 (4)**	**1 (4)**	0 (0)	**3 (13)**
Lipase increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blood & lymphatic/ investigations					
Anemia	**1 (4)**	**1 (4)**	0 (0)	0 (0)	**2 (9)**
Neutropenia[2]	**1 (4)**	**1 (4)**	0 (0)	0 (0)	**2 (9)**
WBC decreased	0 (0)	**1 (4)**	0 (0)	0 (0)	**1 (4)**
Platelet decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition					
Decreased appetite	**2 (9)**	**1 (4)**	0 (0)	0 (0)	**3 (13)**
Nervous system					
Dizziness	**1 (4)**	0 (0)	0 (0)	0 (0)	**1 (4)**
Headache	**1 (4)**	0 (0)	0 (0)	0 (0)	**1 (4)**
Skin & subcutaneous tissue					
Rash maculo-papular	**1 (4)**	0 (0)	0 (0)	0 (0)	**1 (4)**

VSTM: DOF, Jan. 30. 2026 cutoff; mDOT: median Duration of Treatment; AST: AspartateAminotransferase; ALT: Alanine Aminotransferase;GGT: Gammaglutamyl transferase; ALP: AlkalinePhosphatase; WBC: White Blood Count; Gr: Grade

1. 9 patients at 400mg, 9 patients at 600mg, 5 patients at 900mg
2. Included neutropenia and neutrophil count decreased

Case Study: 72 y/o Male with NSCLC

Stage	Baseline Tumor Burden
Initial: IVA Current: metastatic	TL: R't Lung, LN: R't hilar NTL: LN: mediastinum, Pleura

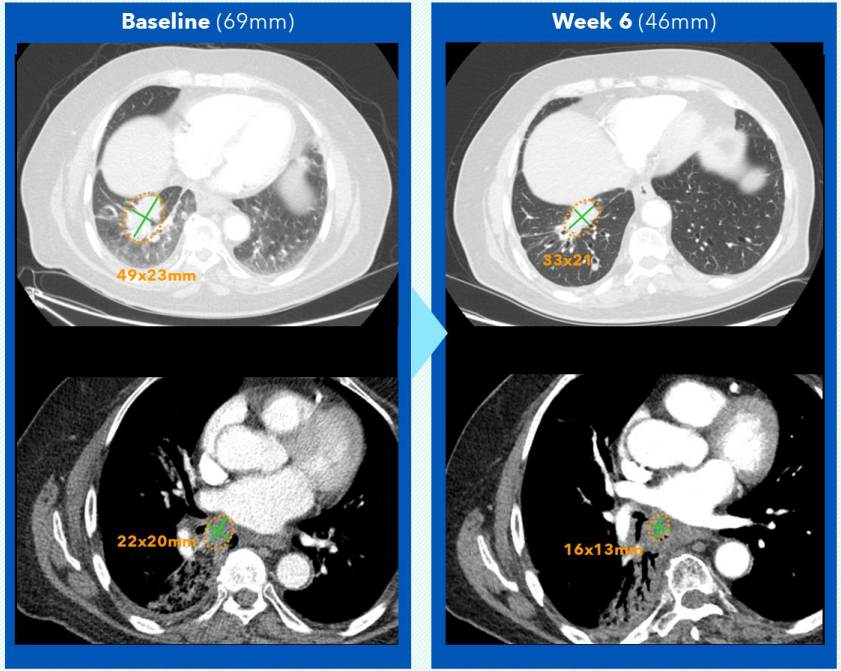
# Prior Tx	Setting	Prior Therapy/Best Response/Duration
1	M	Pembro-Pemetrexed/Carbo (PR, 10mo)

Treatment History with VS-7375

- **600 mg VS-7375 monotherapy**, C1D1=25 SEP 25
- **PR -33% SLD change from baseline at week 6**

Selected TEAEs	Max Gr.	Dose action
Nausea	1	None
Diarrhea	1	None
Fatigue	1	None
Anorexia	2	Dose reduced; late re-escalated
Lipase increase	2	None

Image Assessments



Abbreviations: M=Male, PMH: Past Medical History, NSCLC=Non-Small Cell Lung Cancer, TL=Target Lesion, NTL=Non-Target Lesion, N=Neoadjuvant, M=Metastatic, NR=Not Recorded, ABD=Abdominal, PS=performance status, uPR=unconfirmed partial response, SLD=Sum of longest diameter, SOB=shortness of breath, AE=Adverse Event, Gr=Grade. GI=gastrointestinal

Conclusions

- VS-7375 is a potent, selective, orally administrated KRAS G12D inhibitor that targets both the ON (GTP-bound) and OFF (GDP-bound) states of KRAS
  - VS-7375 is more efficacious than G12D ON and pan-RAS ON inhibitors in KRAS G12D mutant preclinical tumor models
  - VS-7375 shows longer duration of target coverage than zoldonrasib (RMC-9805), and is not limited by cyclophilin loss or RTK activation in preclinical models
- In GenFleet study, VS-7375 (GFH375) monotherapy has shown ORR of 41% and 69% in KRAS G12D heavily pretreated PDAC and advanced metastatic NSCLC, respectively
- In US study (VS-7375-101), VS-7375 has shown oral PK in patients which is comparable to the GenFleet study and covers exposures necessary for deep regressions in preclinical models
  - Well tolerated in US study @ 400 - 900 mg QD with very few Grade 3 AEs, and no Grade 4 AEs
  - Early scans showing responses within 6 weeks with VS-7375 monotherapy
- Further clinical evaluation is ongoing in the US assessing VS-7375 as monotherapy and in various combinations for patients with KRAS G12D mutant cancers (NCT07020221)

Acknowledgments

- Patients and their Caregivers
- Phase I Investigators
- GenFleet Therapeutics Team
- Verastem Oncology Team

- U North Carolina
  - Channing Der
  - Adrienne Cox
  - Clint Stalnecker
- U Turin (Italy)
  - Chiara Ambrogio
  - Cristina Caffarra
- Washington U/St Louis
  - David DeNardo
  - Xiuting Liu

- MSKCC
  - Neal Rosen
  - Dinesh Kuman
- DFCI
  - Ursula Matulonis
  - Joyce Liu
  - Praful Gokhale