

VS-7375: A KRAS G12D ON/OFF KRAS inhibitor

*Preclinical rationale for combinations with pan-RAS,
EGFR, FAK or PRMT5 inhibitors*

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Disclosure/Disclaimer

- Jonathan Pachter is a paid employee and shareholder of Verastem, Inc.
- VS-7375 is a compound currently in development and is not approved for use anywhere in the world by any regulatory authority for any cancer types.

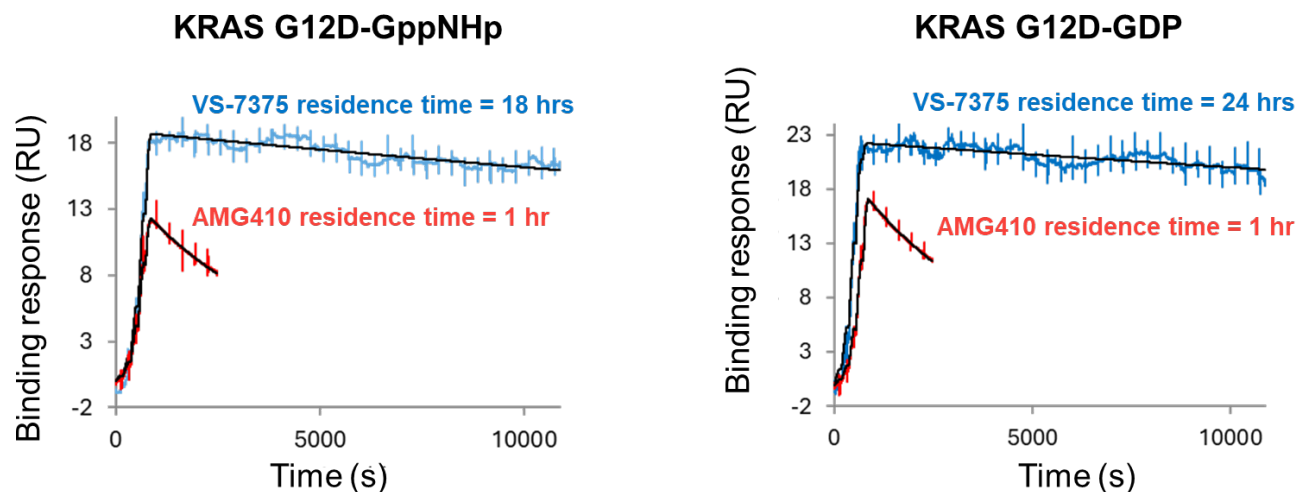
VS-7375 binds to KRAS G12D ON and OFF states with high affinity and long residence time

Affinity of various RAS inhibitors to human KRAS G12D ON and OFF states by SPR

	VS-7375 (G12D ON/OFF)	INCB161734 (Incyte; G12D ON/OFF) ¹	QTX3046 (Quanta; G12D OFF) ²	BBO-11818 (BridgeBio; pan-KRAS) ³
G12D ON (GTP) affinity	18 pM	320 pM	42100 pM	7400 pM
G12D OFF (GDP) affinity	12 pM	380 pM	13 pM	<3 pM
Preference for OFF state (G12D ON/OFF ratio)	1.5x	0.84x	3250x	>2450x

1. Incyte presentation at ESMO 2025; 2. Quanta presentation at AACR 2023; 3. Stahlhut et al., Cancer Discovery 2026

Residence time for KRAS G12D ON and OFF states by SPR



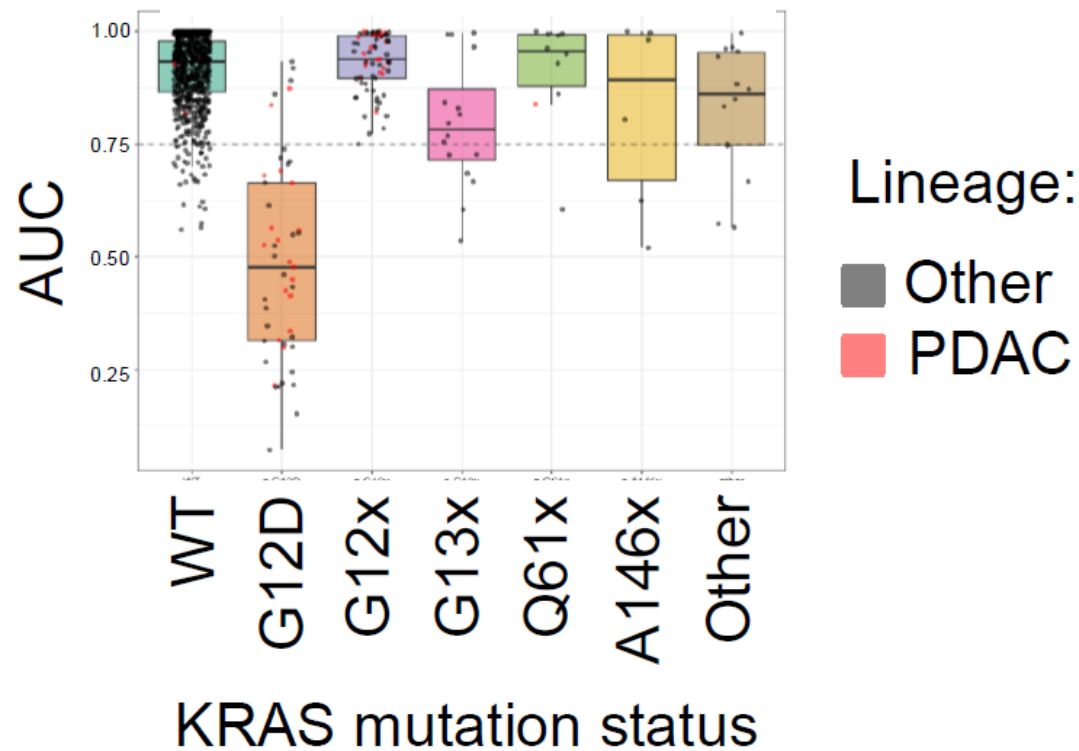
VS-7375 is a potent and selective KRAS G12D inhibitor among human tumor cell lines

VS-7375 3D proliferation

Cell Line	Indication	KRAS status	VS-7375 IC50 (nM)	Zoldonrasib 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

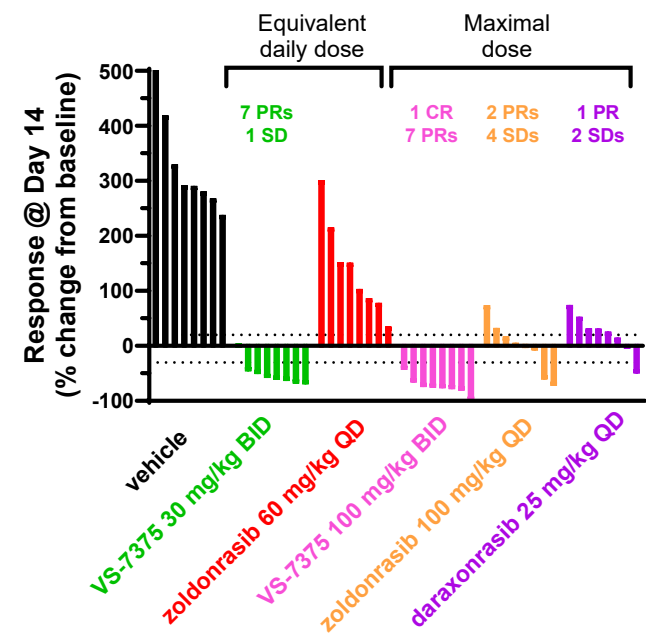
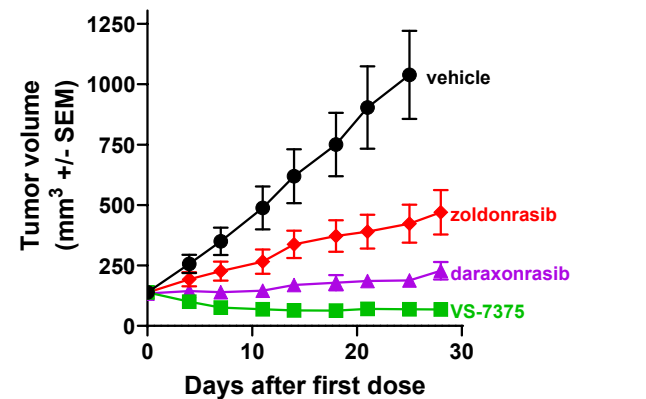
VS-7375 PRISM screening (~900 cell lines)



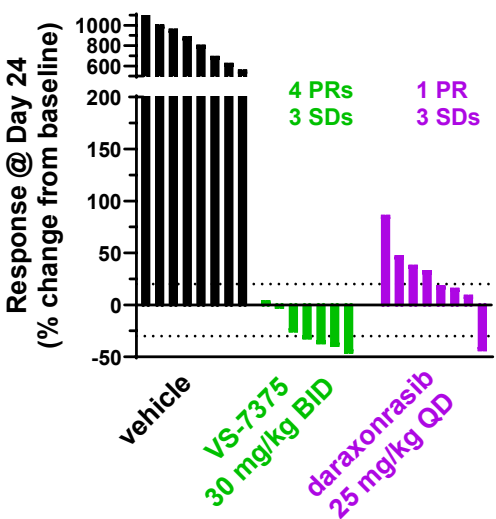
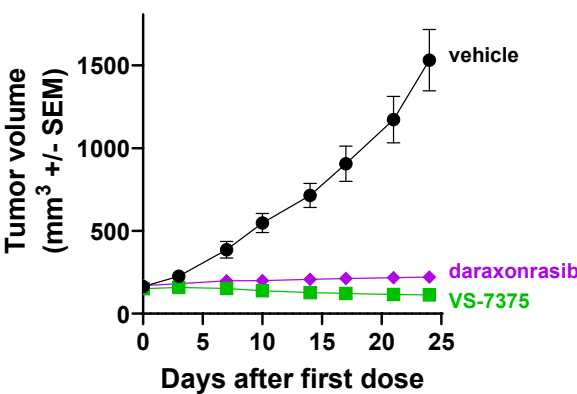
Poster #84 (Poster Session DAY 1): VS-7375, a non-covalent dual ON/OFF KRASG12D inhibitor, displays superior activity relative to ON-only RAS inhibitors in preclinical models of pancreatic cancer. *Brandon Mouery et al. (Channing Der & Clint Stalneck)*

VS-7375 confers deeper tumor regression than KRAS G12D ON and pan-RAS ON inhibitors in KRAS G12D CRC and NSCLC models in vivo

LS513 Colorectal Cancer

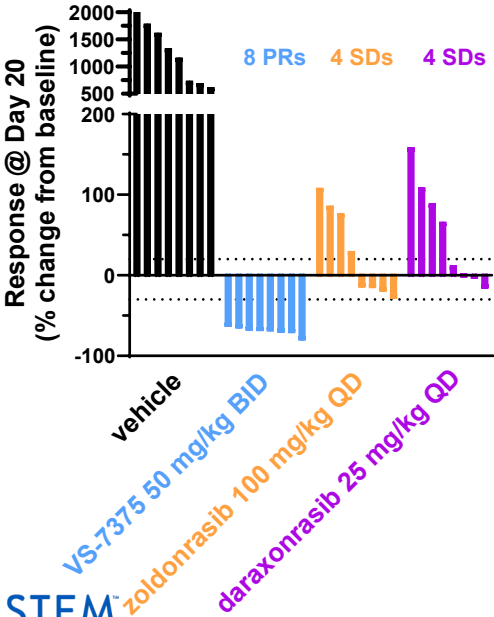
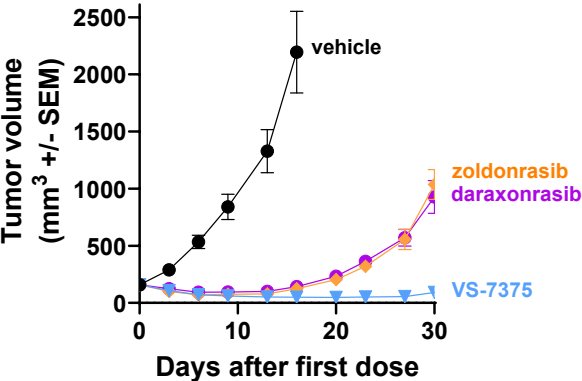


LU0876 NSCLC PDX

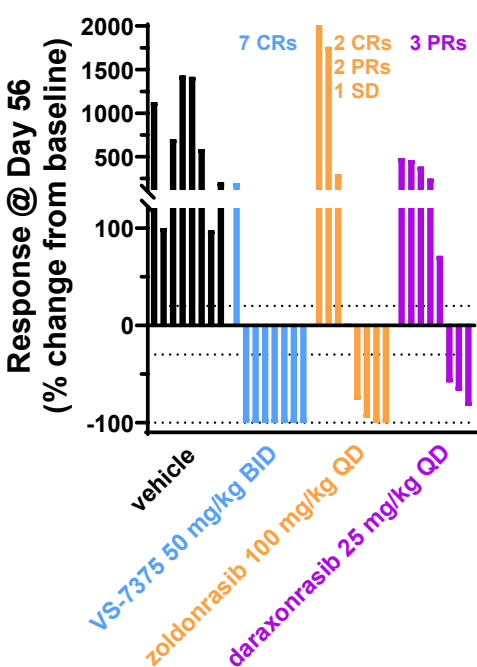
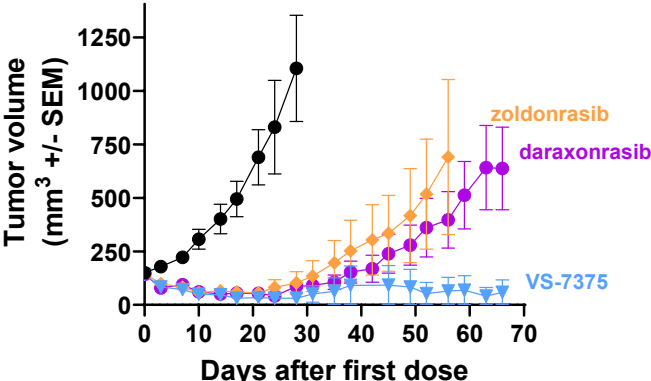


VS-7375 is more efficacious than KRAS G12D ON and pan-RAS ON inhibitors in KRAS G12D-mutated tumor models in vivo

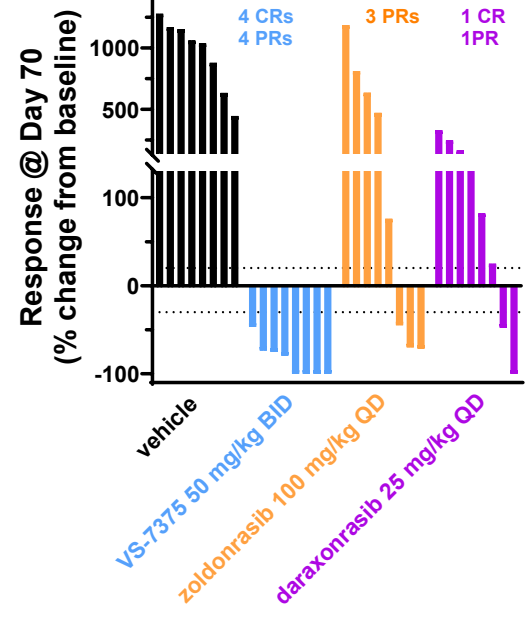
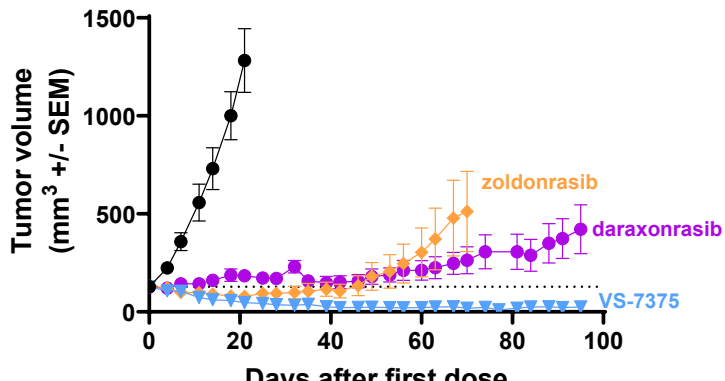
KP4 PDAC



PAXC020 PDAC

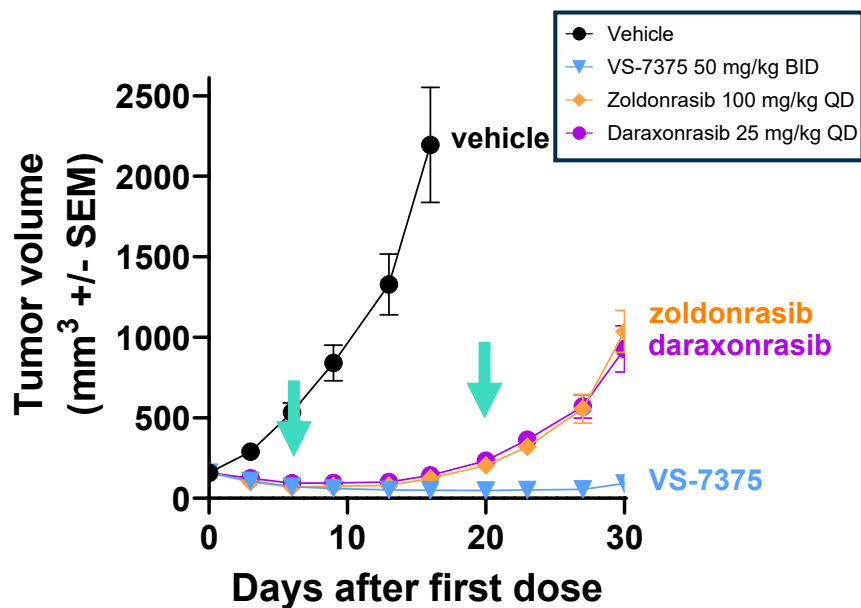


HPAF-II KRAS G12D amp PDAC



Mechanisms of resistance to the tricomplex inhibitors zoldonrasib and daraxonrasib do not limit the durability of VS-7375 efficacy

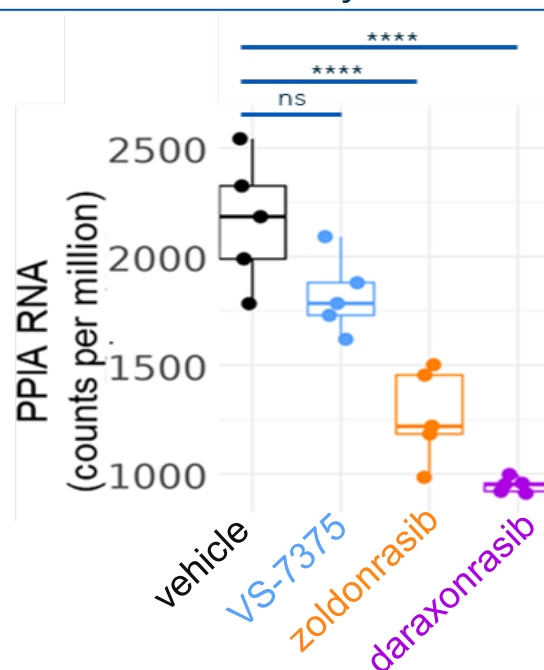
KP4 PDAC



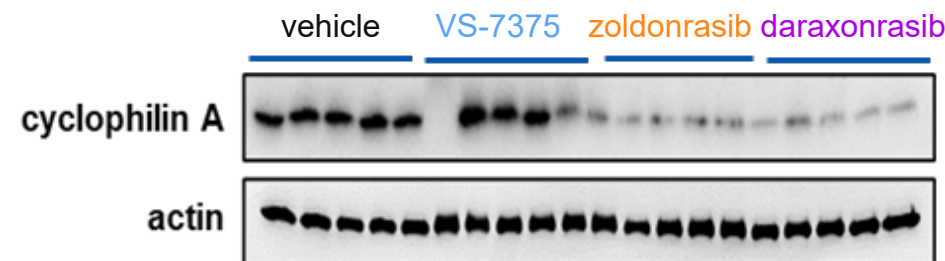
- Collect tumors 2 hours after the last dose on Day 6 or Day 20
- RNA and protein analysis

Decrease of Cyclophilin A Expression by RAS ON Inhibitors

RNA on day 20

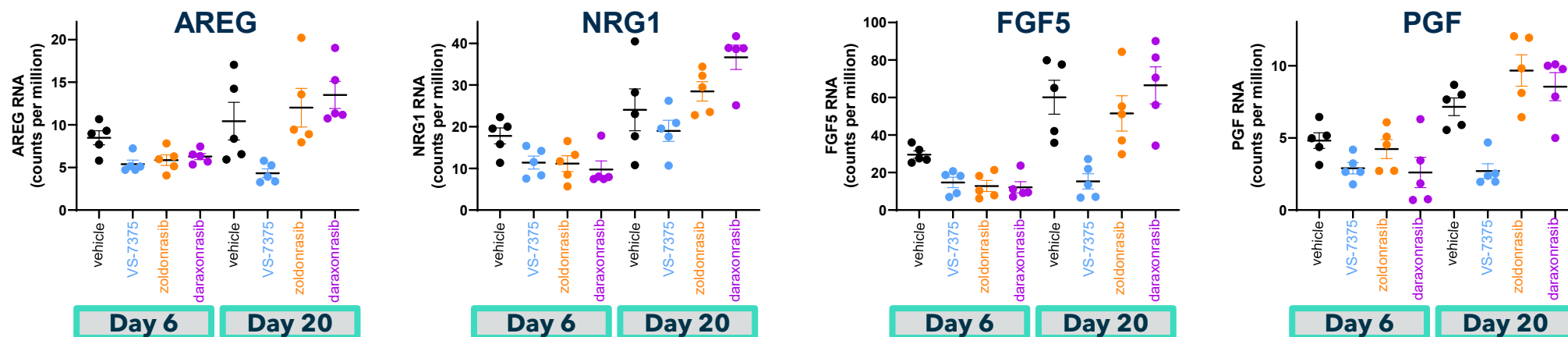


Protein on day 20

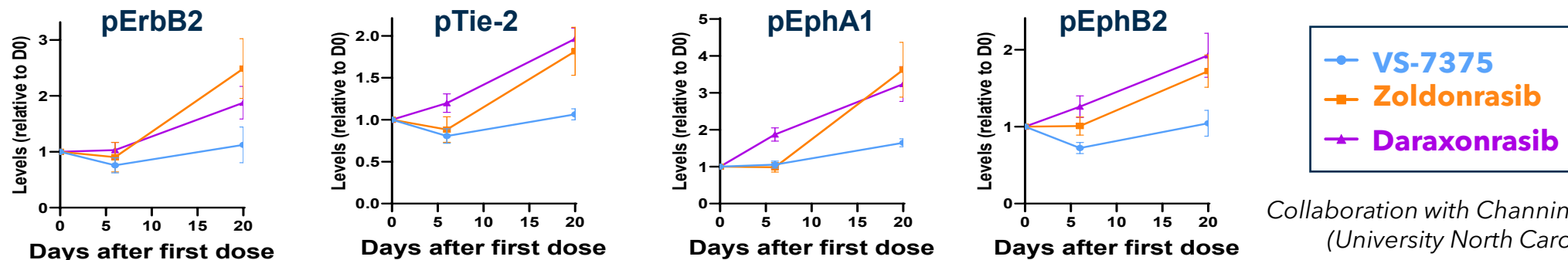


Mechanisms of resistance to the tricomplex inhibitors zoldonrasib and daraxonrasib do not limit the durability of VS-7375 efficacy

Increase of Receptor Tyrosine Kinase Ligands by RAS-Only Inhibitors



Increase of Receptor Tyrosine Kinase Activation by RAS-Only Inhibitors



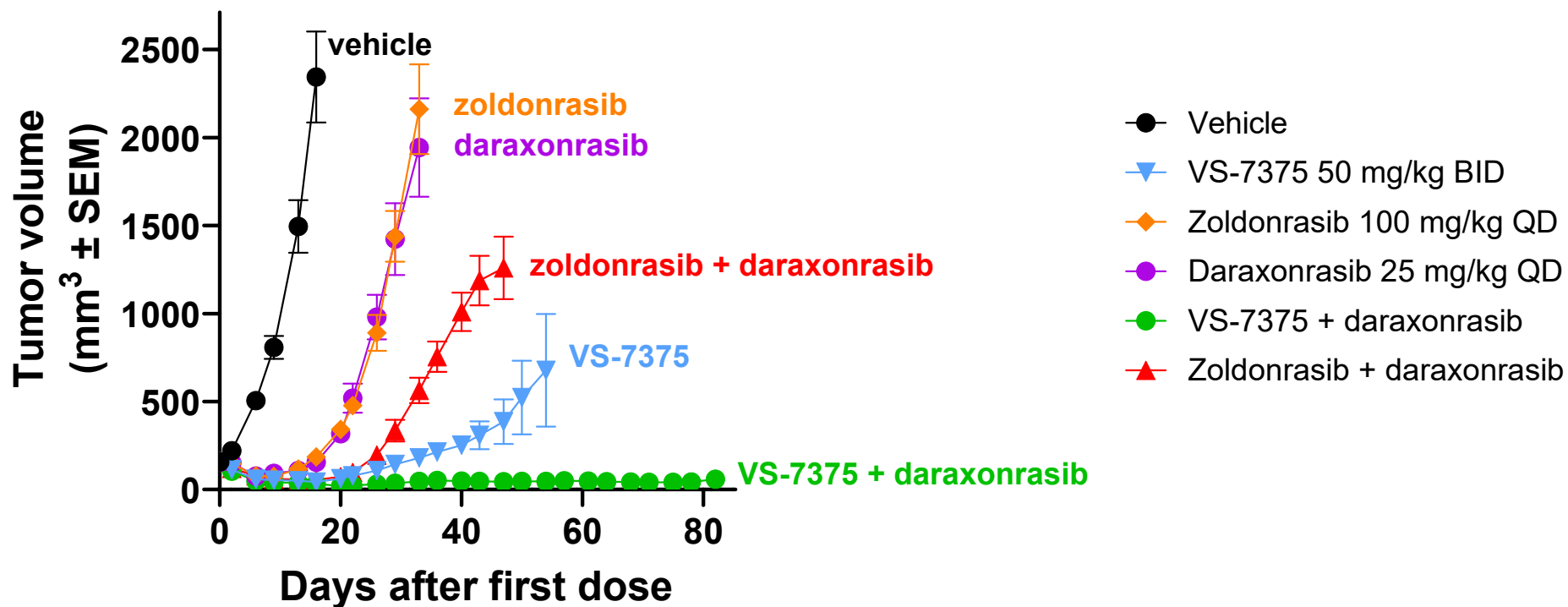
Collaboration with Channing Der & Clint Stalnecker
(University North Carolina at Chapel Hill)

Daraxonrasib has been shown to induce:

- Increased RTK (EGFR, HER2, HER3) expression in preclinical PDAC models (Zhuang et al., AACR RAS meeting 2026)
- Acquired RTK (HER2, FGFR1, MET) activating alterations in PDAC patients progressing on daraxonrasib (Aronchik et al., Nature Medicine 2026)

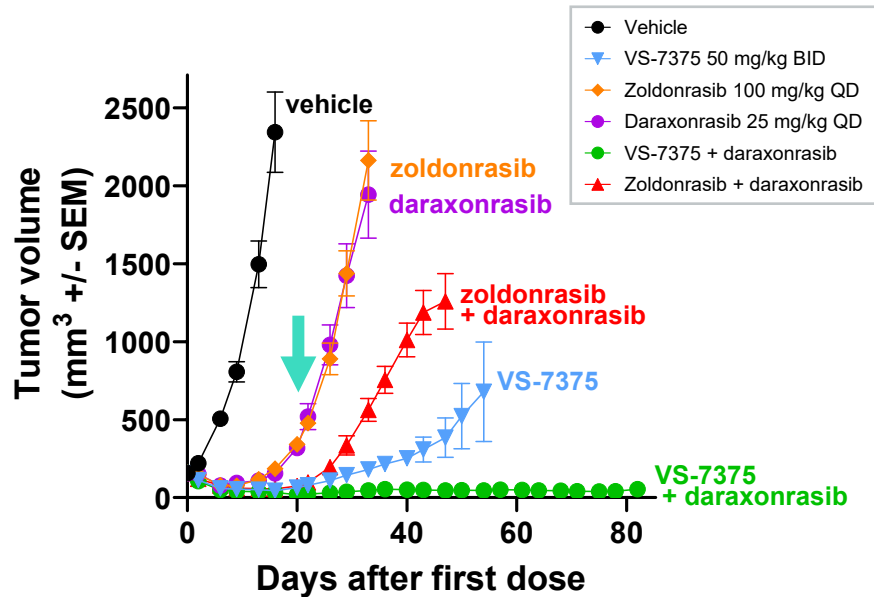
Combination of VS-7375 with daraxonrasib yields more sustained tumor regression than combination of zoldonrasib + daraxonrasib

KP4 KRAS G12D PDAC



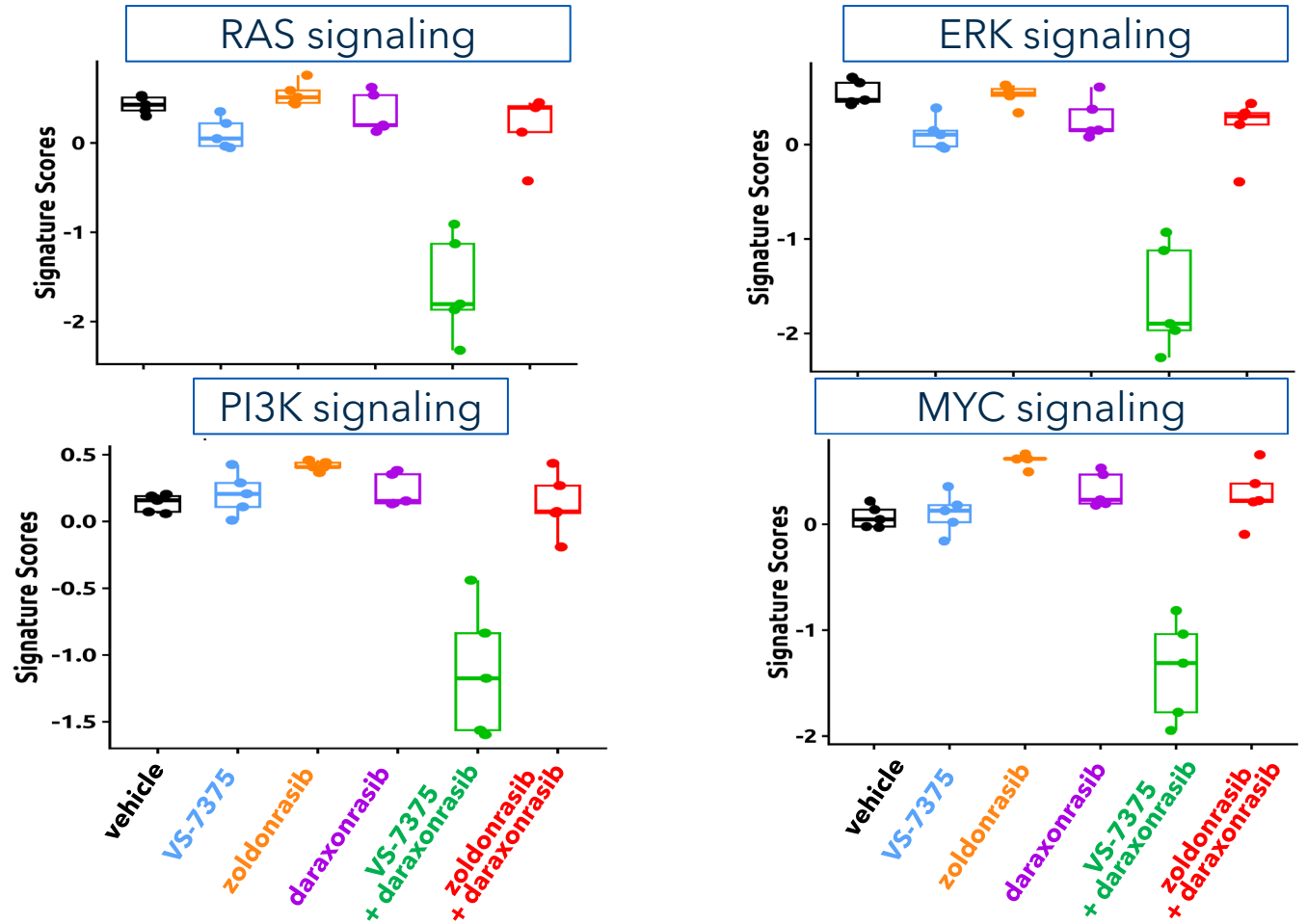
Combination of VS-7375 + pan-RAS inhibitor improves MAPK pathway inhibition and overcomes putative mechanisms of resistance including PI3K and MYC signaling pathways

KP4 KRAS G12D PDAC



- Collect tumors 2 hours after the last dose on Day 20
- RNA analysis

Deep and durable inhibition of MAPK, MYC and PI3K signaling with VS-7375 + pan-RASi

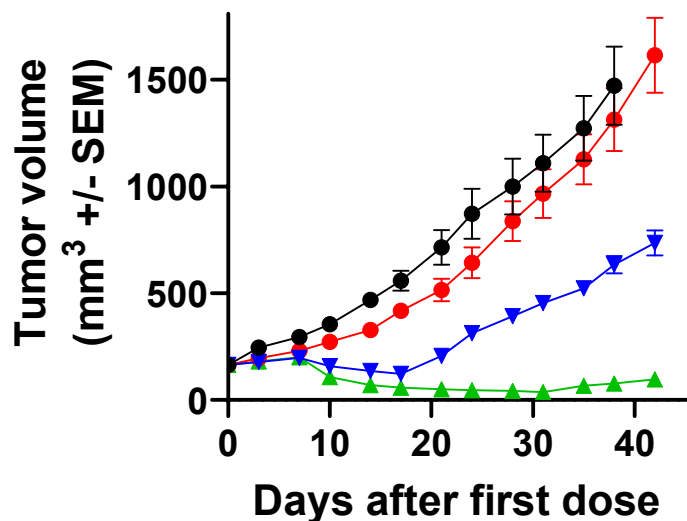


RAS signaling (RAS DOWN; Channing Der); ERK signaling (ERK UP; Channing Der); PI3K signaling (PI3K DOWN signature; Zhang et al., 2018); MYC signaling (MYC DOWN; Channing Der);

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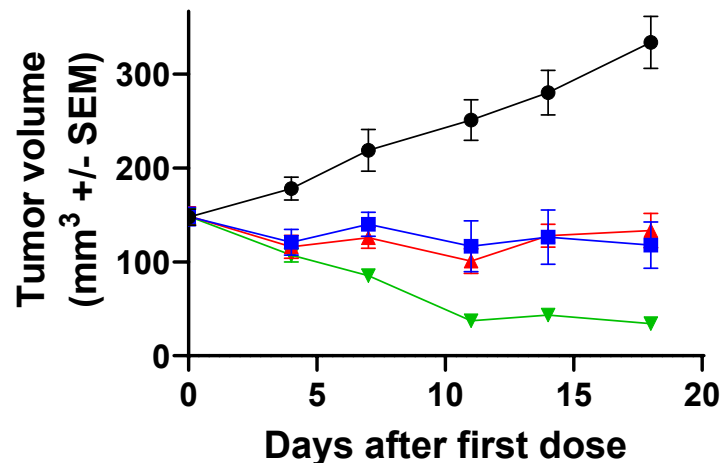
Combination of anti-EGFR Ab (cetuximab) with VS-7375 induces strong tumor growth inhibition in KRAS G12D-mutated cancer models

CR1245 CRC PDX



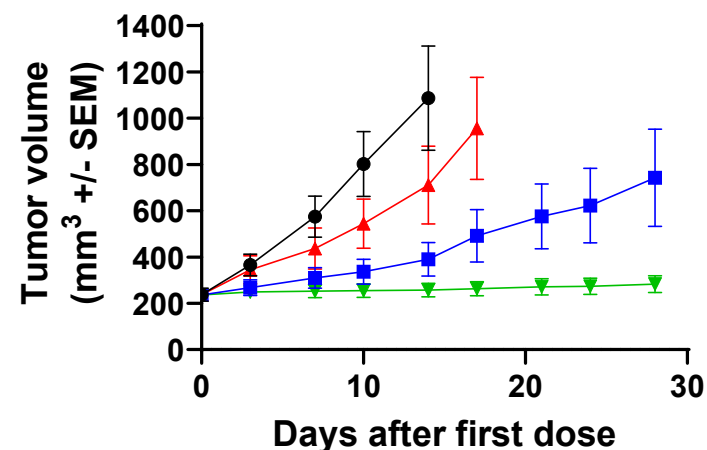
- Vehicle
- VS-7375 10 mg/kg PO BID
- ▲ Cetuximab 0.25 mg/mouse IP Q3D
- ▼ VS-7375 + cetuximab

AsPC-1 PDAC

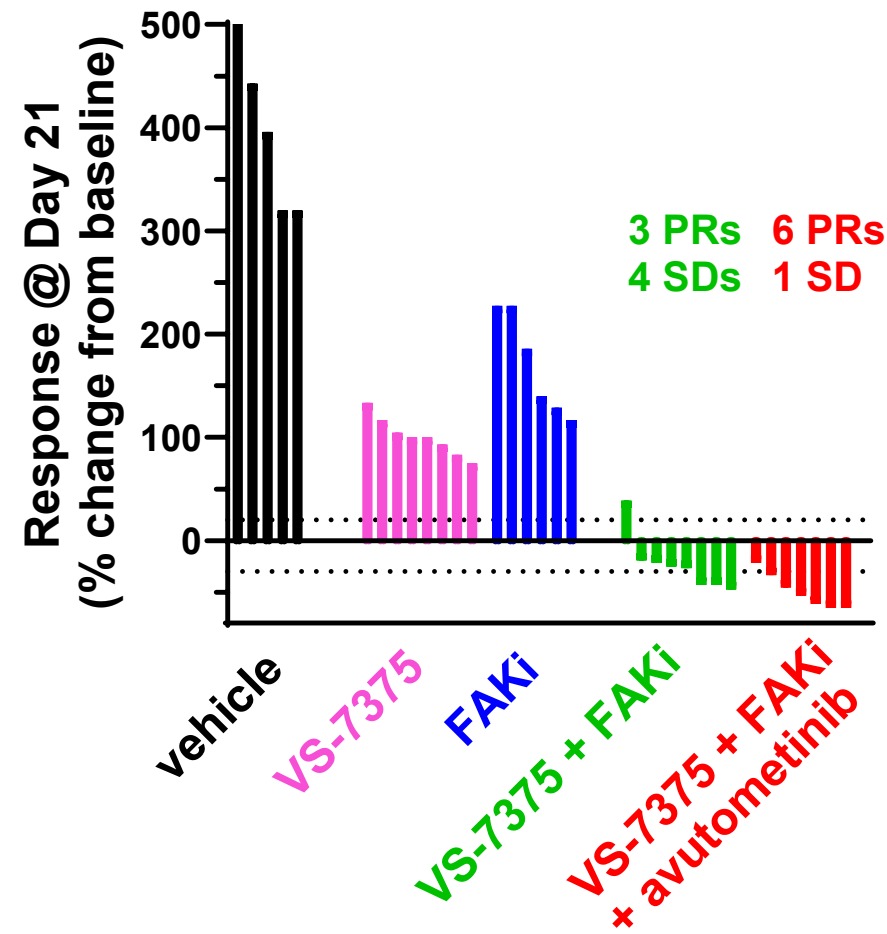
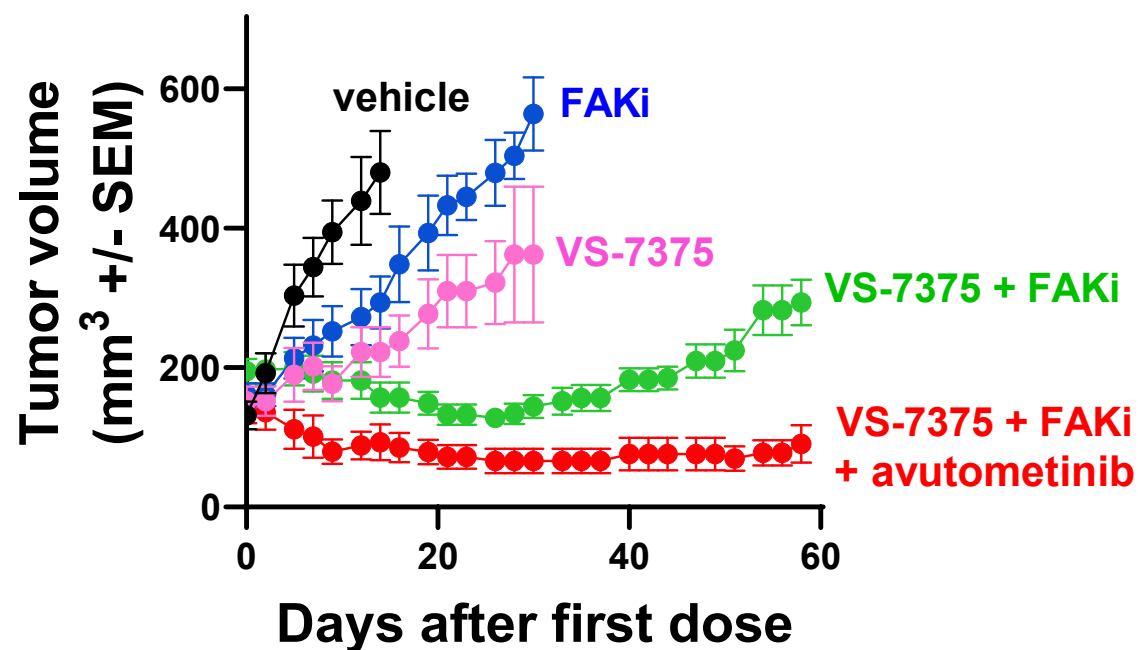


- Vehicle
- ▼ VS-7375 30 mg/kg BID
- ▲ Cetuximab 10 mg/kg BIW
- ▼ VS-7375 + cetuximab

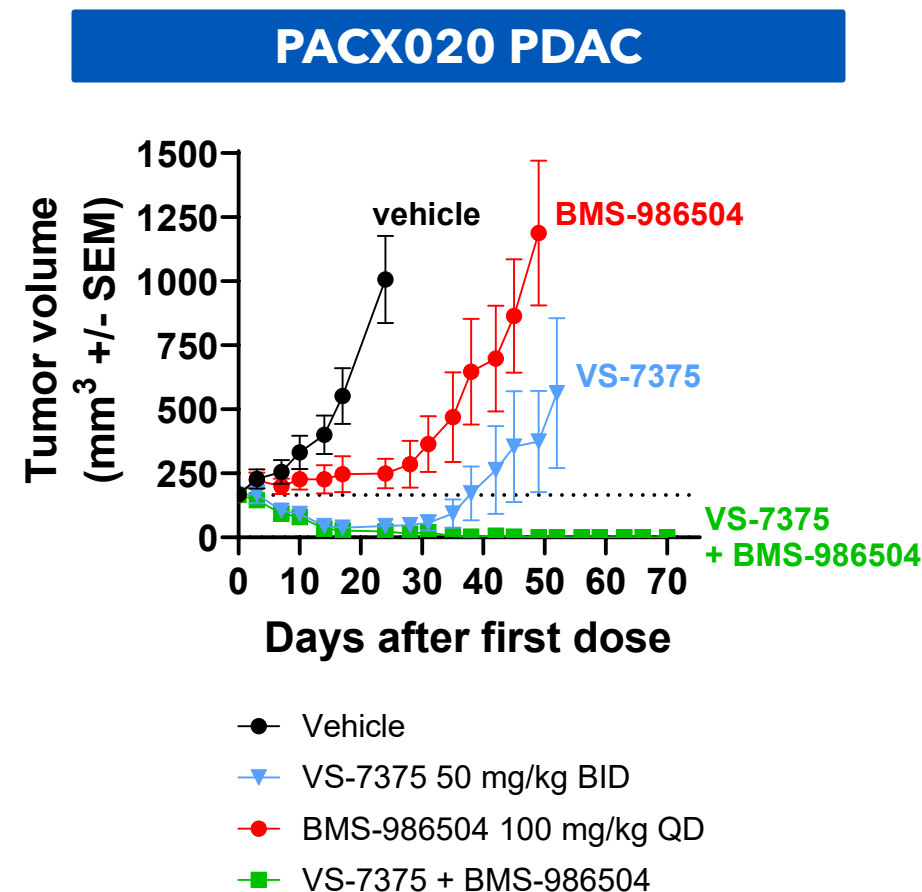
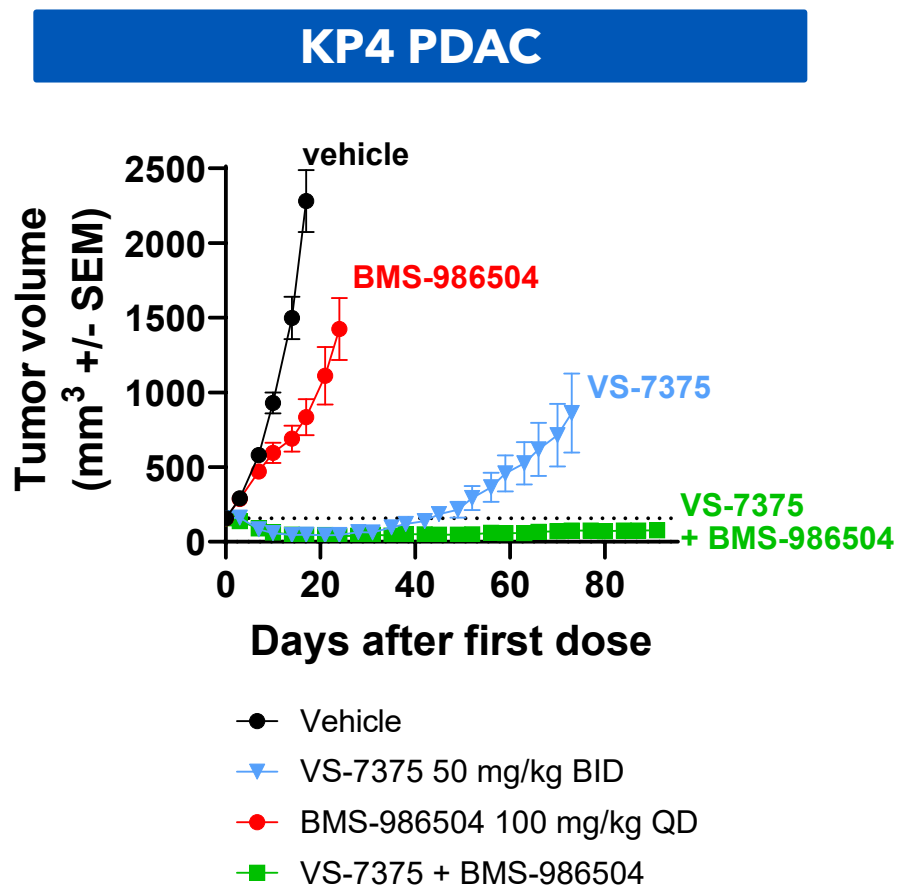
LU0876 NSCLC PDX



Combinations of a FAK inhibitor $\pm$ the RAF/MEK clamp avutometinib with VS-7375 induce deep tumor regressions in a syngeneic KRAS G12D pancreatic cancer model (KP2)

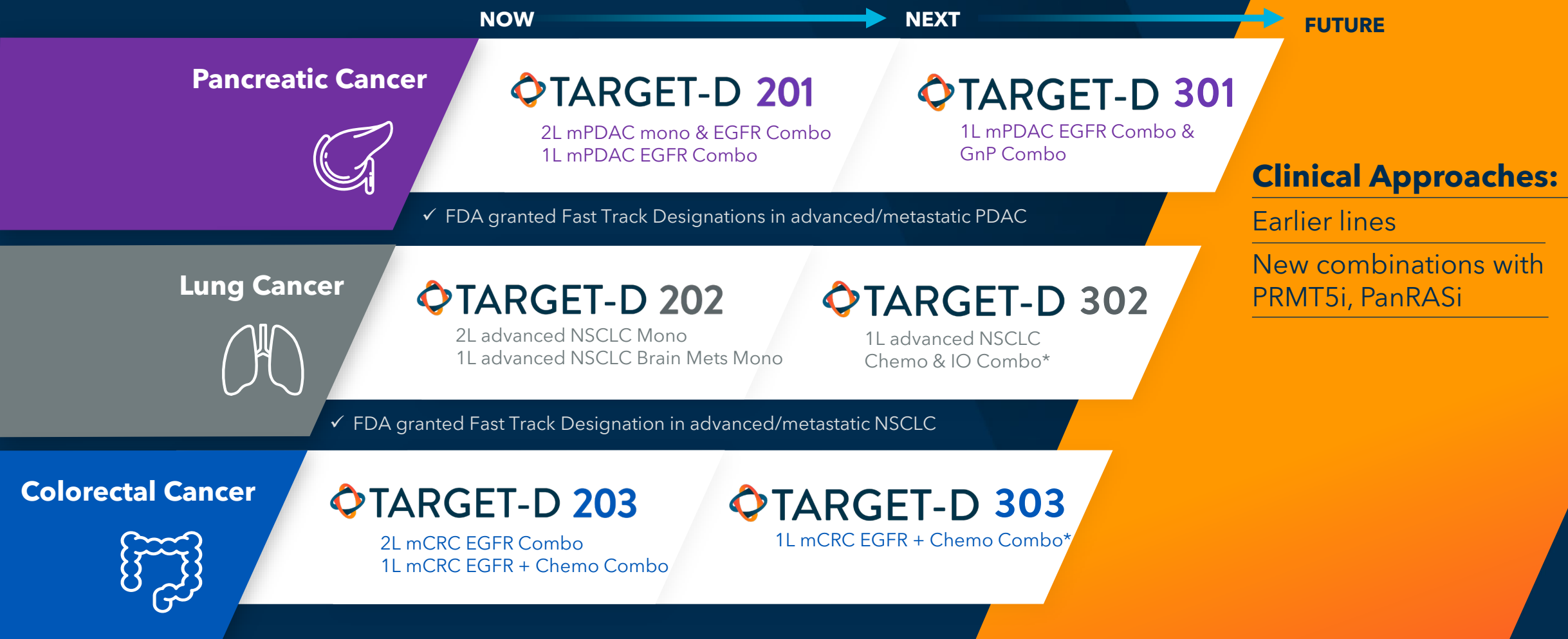


Combination of a PRMT5 inhibitor with VS-7375 induces durable tumor regressions in KRAS G12D-mutated;MTAP-deleted pancreatic cancer models

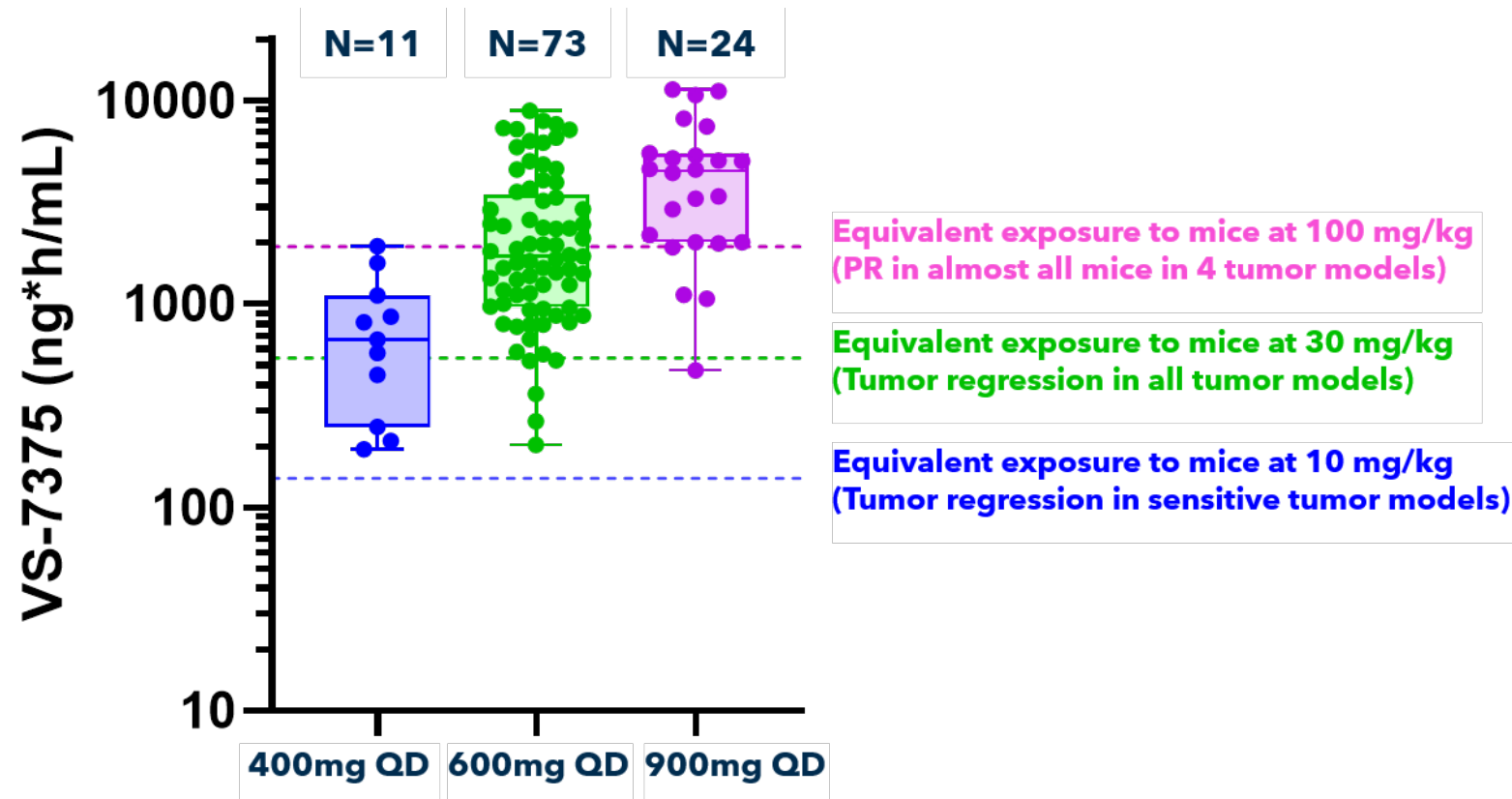


Poster #88 (Poster Session DAY 1): Strong durable tumor regressions with the KRASG12D ON/OFF inhibitor VS-7375 in combination with PRMT5 inhibition in MTAP-deleted/KRASG12D-mutant pancreatic cancer. *Ryan Mouery et al.*
(Channing Der & Clint Stalnecker)

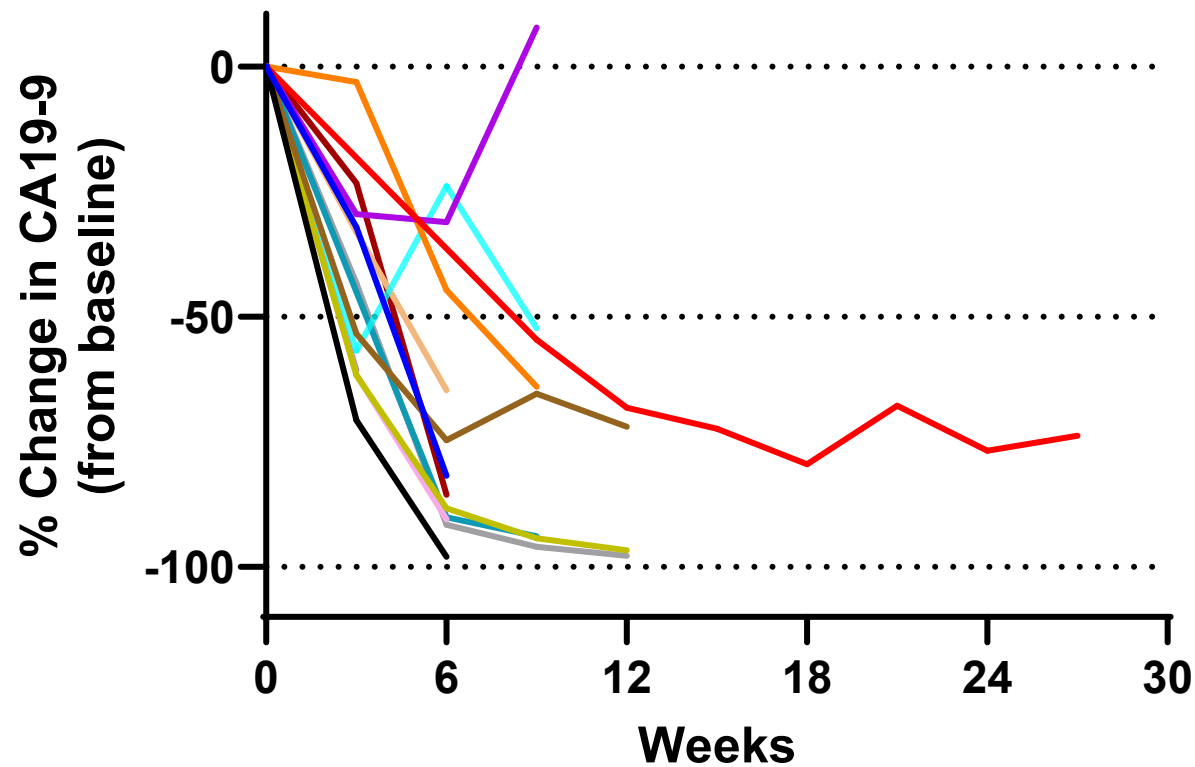
Positioning VS-7375 for broad registrational development across multiple cancer indications



900 mg QD of VS-7375 achieves the targeted human AUC_{ss} in the majority of patients corresponding to maximal tumor regression across mouse models



93% of mPDAC Patients Treated with VS-7375 900 mg QD Achieved >50% Reduction in CA19-9



14 patients dosed at 900 mg QD had elevated levels of CA19-9 at baseline (>37 U/mL) and at least one scheduled on-treatment measurement

- All patients remain on treatment
- Includes 2-4L patients

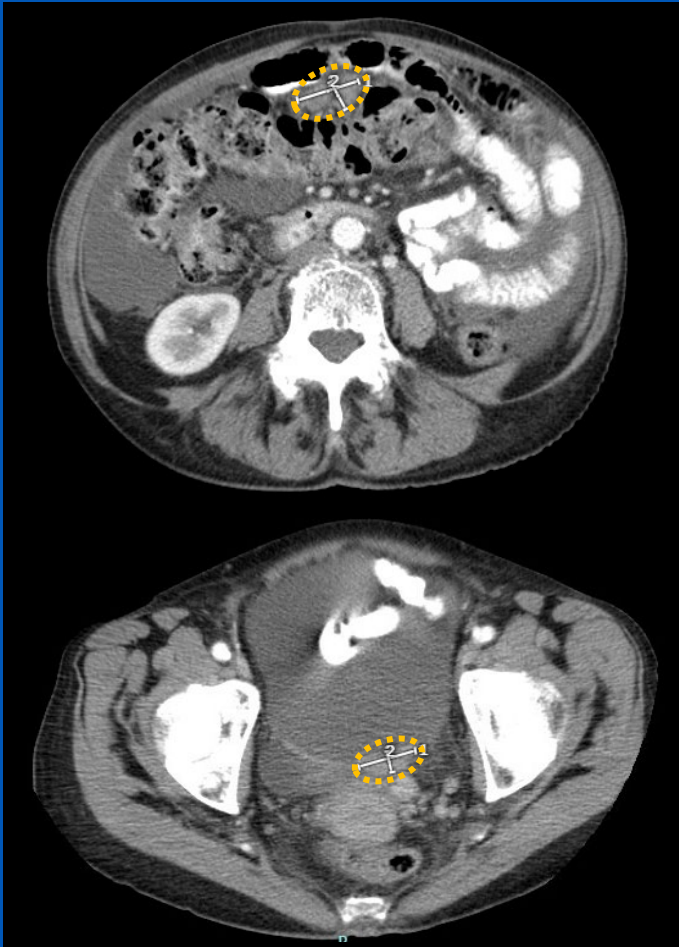
93% (13/14) of patients showed >50% reduction in CA19-9

≥50% reduction in CA19-9 has been correlated with improved PFS and OS for patients with PDAC^{1,2}

Complete resolution of target lesion at week 6 with VS-7375 900 mg QD monotherapy in 79 y/o female with metastatic PDAC

Baseline Lesion:

Mesentery, peritoneum
(SLD: 64mm)



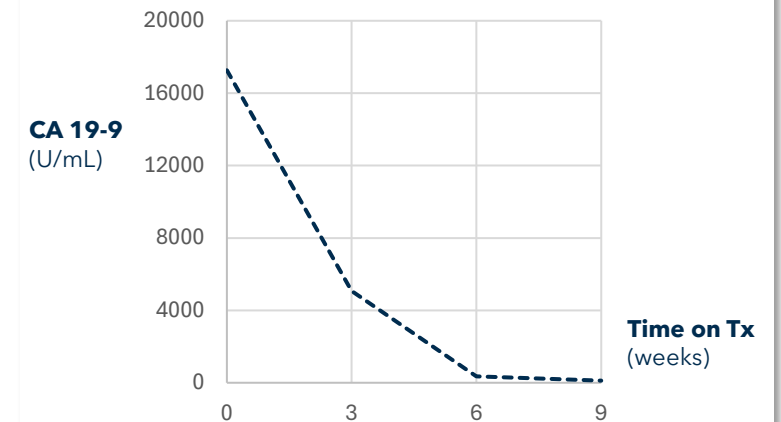
Week 6:

uPR (-100%) (SLD: 0mm)
Response ongoing



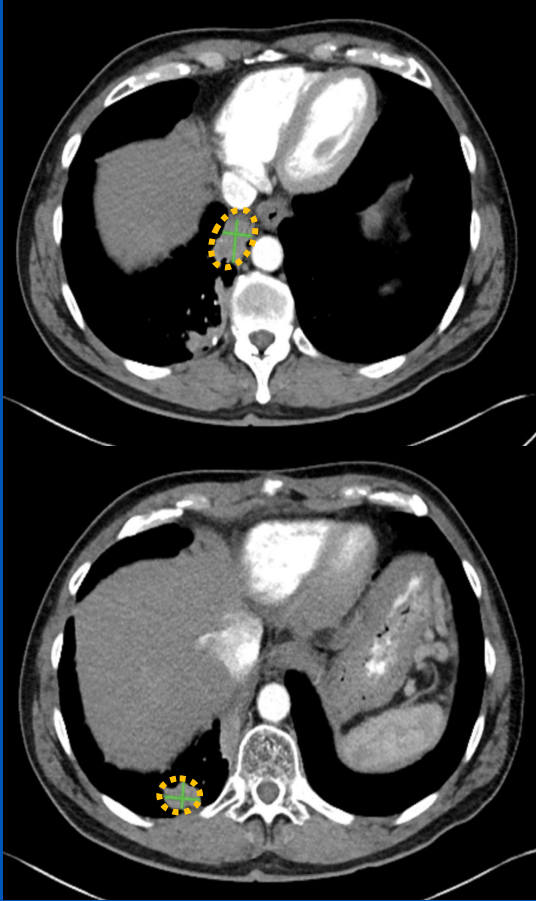
- Prior Gem/NabP (6 mos of Tx) , NALIRI (11 mos of Tx), and FOLFOX (3 mos of Tx)
- Investigator-reported abdominal pain and distention (caused by ascites) resolved in 2 weeks
- Selected AE: G2 diarrhea (resolved), G2 fatigue, G2 anorexia
- Highly elevated CA-19-9 levels at baseline with >60% reduction in 3 weeks and >99% reduction in 6-9 weeks

>99% reduction of CA 19-9

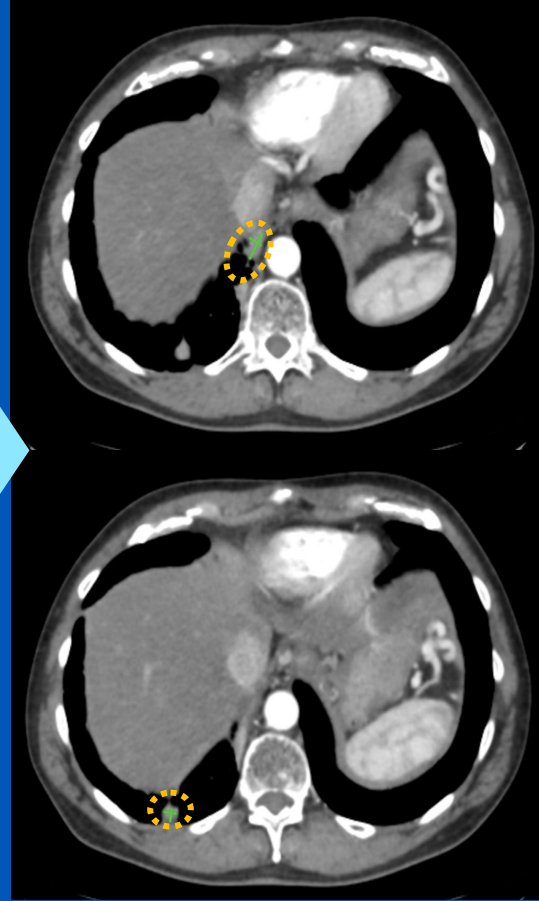


Deep and rapid response achieved at subtherapeutic dose with VS-7375 400 mg QD + anti-EGFR in 64 y/o male with metastatic PDAC

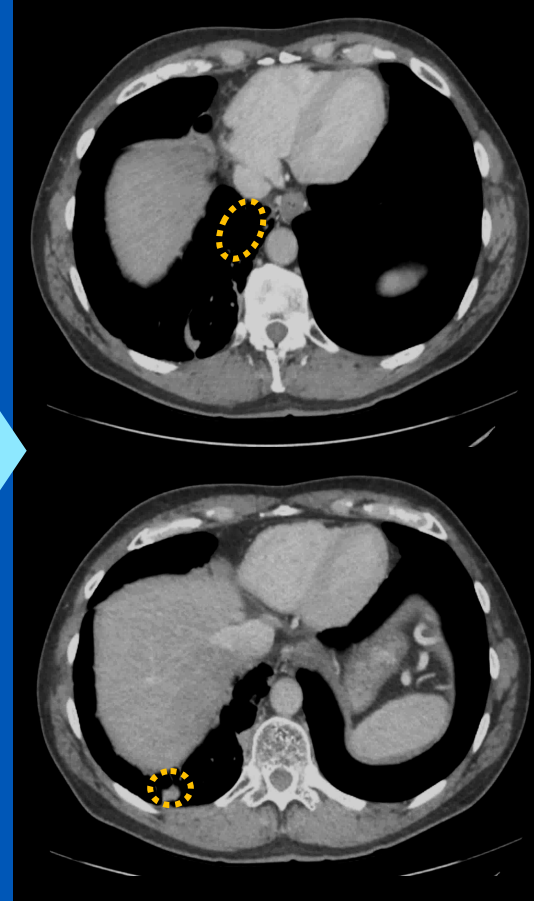
Baseline Lesion: Pleura, lung, mediastinum lymph node (52mm)



Week 6:
cPR (-46%) (28mm)

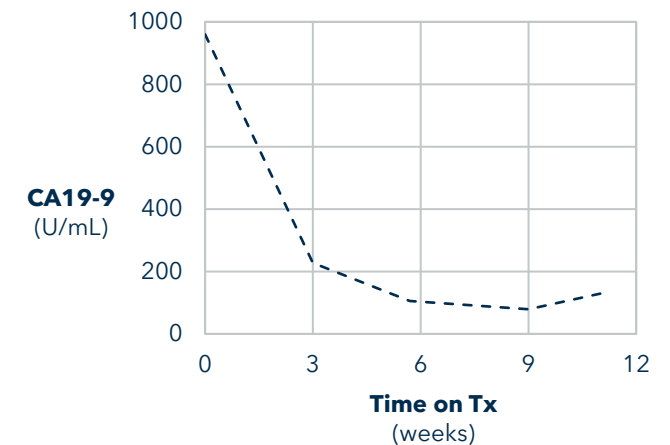


Week 12:
cPR: (-70%) (16mm)



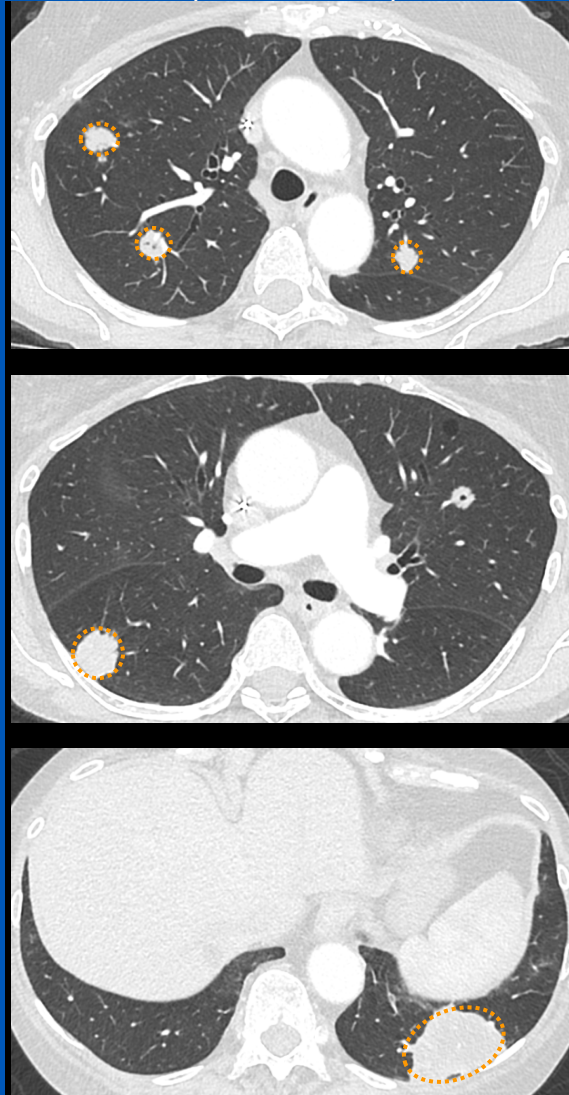
- Prior FOLFIRINOX + RT (PR) and FOLFIRINOX (SD for 3 mos)
- Investigator-reported cough had resolved within 1 week of treatment
- Selected TEAEs included upper GI hemorrhage*, anemia*, gastritis* and rash maculopapular**

Significant drop in CA19-9 Levels by Week 3

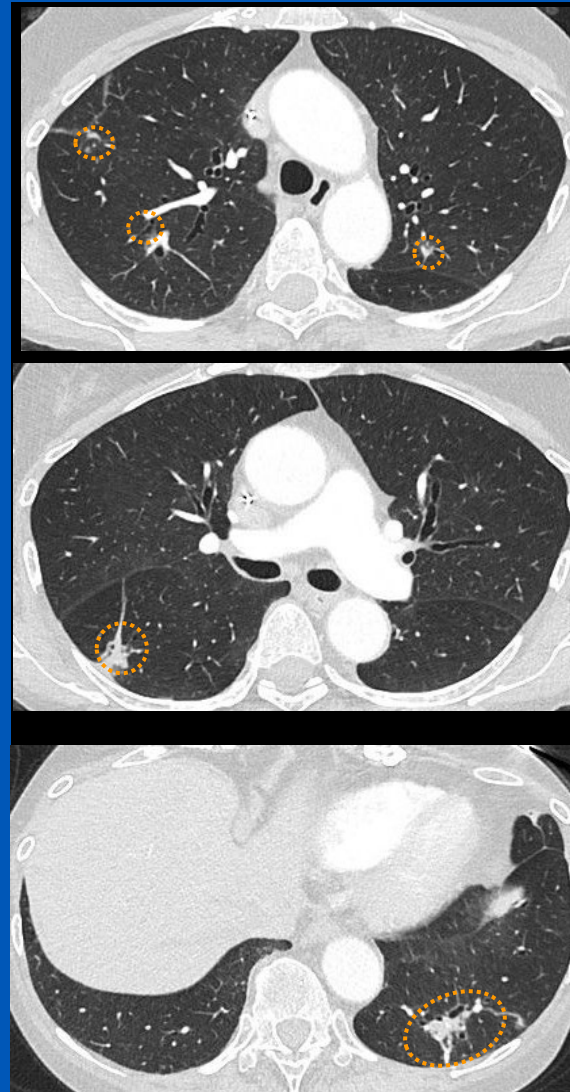


Confirmed partial response at week 6 with deepening of response through week 12 at VS-7375 600 mg QD in 77 y/o female with advanced NSCLC

Baseline Lesion:
(SLD 69mm)



Week 12:
cPR (-49%) (SLD: 35mm)



- Prior therapy of Pemetrexed-Carbo-Pembro (SD 4 mos)
- Patient had an unconfirmed partial response at week 6 (-34%) that was confirmed at week 12 (-49%)
- Investigator-reported shortness-of-breath and tumor pain improved within 2 weeks of dosing
- TEAE: diarrhea G3, dose reduced in cycle 3 to 400 mg for 4 weeks and re-escalated to 600 mg after in cycle 4

VS-7375 well-tolerated up to 900 mg; Low-grade GI AEs most common

TRAEs reported in >1 patient

System Organ Class / Preferred Term	600 mg (N=57)					900 mg (N=25)				
	Gr. 1 n(%)	Gr. 2 n(%)	Gr. 3 n(%)	Gr. ≥4 n(%)	All Gr. n(%)	Gr. 1 n(%)	Gr. 2 n(%)	Gr. 3 n(%)	Gr. ≥4 n(%)	All Gr. n(%)
Gastrointestinal disorders										
Diarrhoea	22 (39)	7 (12)	2 (4)	0	31 (54)	9 (36)	3 (12)	0	0	12 (48)
Nausea	20 (35)	8 (14)	1 (2)	0	29 (51)	9 (36)	3 (12)	1 (4)	0	13 (52)
Vomiting	16 (28)	4 (7)	1 (2)	0	21 (37)	5 (20)	1 (4)	0	0	6 (24)
Constipation	5 (9)	0	0	0	5 (9)	0	0	0	0	0
Dyspepsia	4 (7)	0	0	0	4 (7)	1 (4)	0	0	0	1 (4)
Abdominal distension	1 (2)	0	0	0	1 (2)	2 (8)	1 (4)	0	0	3 (12)
Abdominal pain	1 (2)	0	1 (2)	0	2 (4)	1 (4)	0	0	0	1 (4)
Flatulence	1 (2)	0	0	0	1 (2)	2 (8)	0	0	0	2 (8)
General disorders										
Fatigue	14 (25)	3 (5)	0	0	17 (30)	5 (20)	3 (12)	0	0	8 (32)
Oedema peripheral	2 (4)	0	0	0	2 (4)	0	0	0	0	0
Investigations										
Lipase increased	4 (7)	2 (4)	0	0	6 (11)	0	1 (4)	0	0	1 (4)
Amylase increased	3 (5)	1 (2)	0	0	4 (7)	1 (4)	0	0	0	1 (4)
Alanine aminotransferase increased	2 (4)	0	0	0	2 (4)	1 (4)	0	0	0	1 (4)
Blood and lymphatic system disorders										
Neutropenia	2 (4)	3 (5)	1 (2)	0	6 (11)	0	2 (8)	0	0	2 (8)
Anaemia	0	4 (7)	0	0	4 (7)	0	2 (8)	0	0	2 (8)
Leukopenia	2 (4)	0	0	0	2 (4)	0	0	0	0	0
Thrombocytopenia	1 (2)	0	0	0	1 (2)	1 (4)	0	0	0	1 (4)
White blood cell count decreased	1 (2)	1 (2)	0	0	2 (4)	0	0	0	0	0
Metabolism and nutrition disorders										
Decreased appetite	0	2 (4)	0	0	2 (4)	4 (16)	1 (4)	0	0	5 (20)
Hypomagnesaemia	2 (4)	0	0	0	2 (4)	0	0	0	0	0
Nervous system disorders										
Dysgeusia	3 (5)	0	0	0	3 (5)	2 (8)	0	0	0	2 (8)
Dizziness	1 (2)	0	1 (2)	0	2 (4)	0	0	0	0	0
Skin and subcutaneous tissue disorders										
Pruritus	3 (5)	0	0	0	3 (5)	0	0	0	0	0
Rash	3 (5)	0	0	0	3 (5)	0	0	0	0	0
Urticaria	0	0	1 (2)	0	1 (2)	1 (4)	0	0	0	1 (4)
Renal and Urinary disorders										
Acute kidney injury	0	0	1 (2)	0	1 (2)	0	1 (4)	0	0	1 (4)

Conclusions

- **VS-7375 is a potent, selective, orally administrated KRAS G12D inhibitor that targets both the ON (GTP-bound) and OFF (GDP-bound) states**
 - In KRAS G12D mutant preclinical tumor models, VS-7375 is more efficacious than G12D ON and pan-RAS ON inhibitors and is not subject to some mechanisms of resistance observed with tricomplex inhibitors
 - Oral dosing of VS-7375 gives dose proportional exposure in patients with 900 mg QD (RP2D) achieving drug levels corresponding to maximal tumor regression across mouse models in the majority of patients
 - VS-7375 shows deep and durable tumor regressions in combinations with inhibitors of pan-RAS, EGFR, FAK ($\pm$ RAF/MEK inhibitor) or PRMT5 across KRAS G12D preclinical tumor models
- **In patients with previously treated KRAS G12D-mutated cancers**
 - VS-7375 has shown promising clinical activity as monotherapy and in combination with cetuximab, and shows a manageable tolerability profile
 - Phase 2 trials are enrolling in PDAC, NSCLC and CRC, and front-line Phase 3 trials will be initiated by 1H 2027

Acknowledgments

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