VS-7375: An oral, selective KRAS G12D dual ON/OFF inhibitor with potent anti-tumor activity as a single agent and in combination with other agents

Silvia Coma[1], Brandon L. Mouery[2], Wen-Hsuan Chang[2], Ian Smith[3], Faiz Ahmad[3], Cristina Caffarra Malvezzi[4], Emilia Berardelli[4], Enrico Patrucco[4], Fusheng Zhou[5], Chiara Ambrogio[4], Clint A Stalnecker[2], David G DeNardo[3], Channing J Der[2], Jonathan A Pachter[1]

[1]Verastem Oncology, Needham, MA; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Department of Medicine, Washington University School of Medicine, St. Louis, MO; [4]Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; [5]Genfleet Therapeutics, Shanghai, China

#7100 (20)

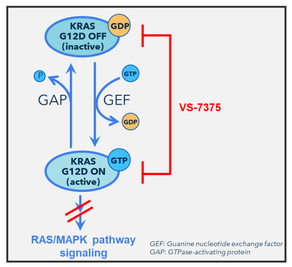
BACKGROUND

KRAS G12D is the most prevalent KRAS mutation in human cancers, present in 40%, 15%, and 5% of pancreatic, colorectal and lung cancers, respectively (Lee et al., 2022). Currently, there are no FDA-approved RAS inhibitors for patients with KRAS G12D-mutated cancers.

VS-7375 (GFH375) is an oral KRAS G12D-selective small molecule inhibitor that binds KRAS G12D in both the ON and OFF states. By blocking the activities of the ON and OFF states of KRAS G12D, VS-7375 has the potential to inhibit KRAS G12D signaling and tumor growth more completely than compounds that block KRAS G12D predominantly in the OFF state or only in the ON state. VS-7375 monotherapy and in combination with other agents is currently in clinical evaluation in the US (NCT07020221) and in China (NCT06500676; NCT07262567; NCT07259590).

RESULTS

VS-7375 is a potent KRAS G12D ON/OFF inhibitor with long residence time



B

Binding Affinity

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

C

Residence Time

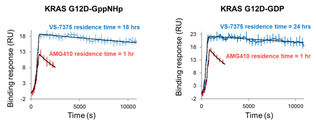


Figure 1. (A) Schematic showing that VS-7375 is a dual inhibitor of KRAS G12D ON (active; GTP-bound) and OFF (inactive; GDP-bound). **(B)** VS-7375 binds human KRAS G12D ON and OFF states with similar high affinity (K_D = 12-18 pM). **(C)** VS-7375 shows long residence time (18-24 hours) for the ON and OFF states of human KRAS G12D compared to short residence time (1 hour) with the pan-KRAS inhibitor AMG410.

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

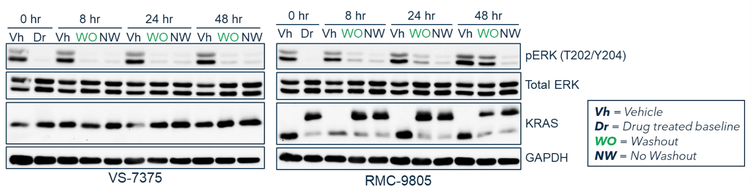


Figure 2. Pa14C KRAS G12D-mutated pancreatic cancer cells were treated with either VS-7375 (30 nM) or RMC-9805 (300 nM) for 24 hours (T = 0 hours in this figure) followed by drug washout for 8, 24, or 48 hours. Protein levels were analyzed by Western blot.

VS-7375 suppresses pERK, pAKT, pS6 and MYC levels more potently, rapidly, and durably than the KRAS G12D ON-only inhibitor zoldonrasib (RMC-9805)

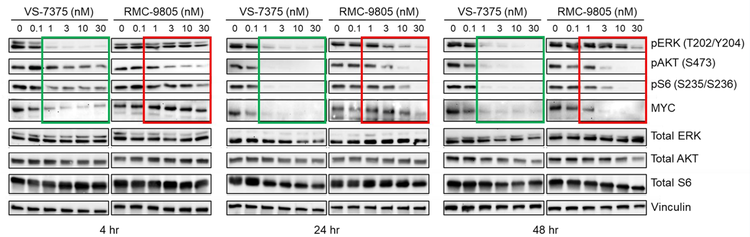


Figure 3. Pa14C KRAS G12D-mutated pancreatic cancer cells were treated with either VS-7375 or RMC-9805 for 4, 24 or 48 hours. Protein levels were analyzed by Western blot.

RESULTS

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

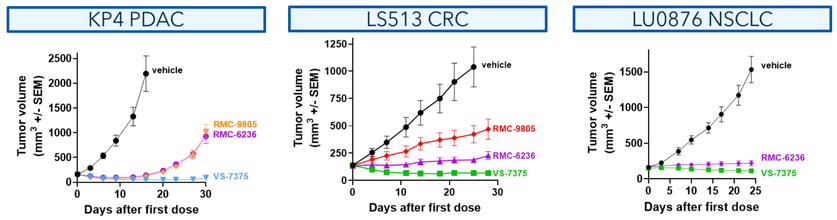
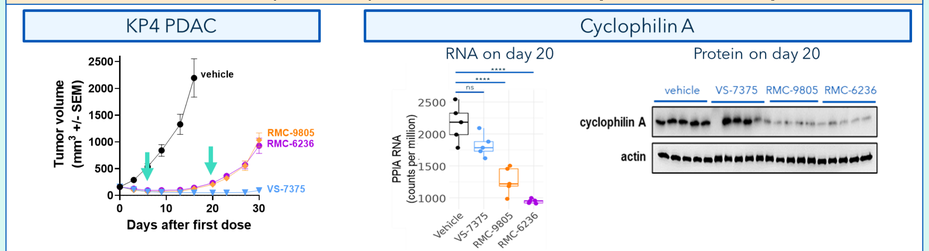
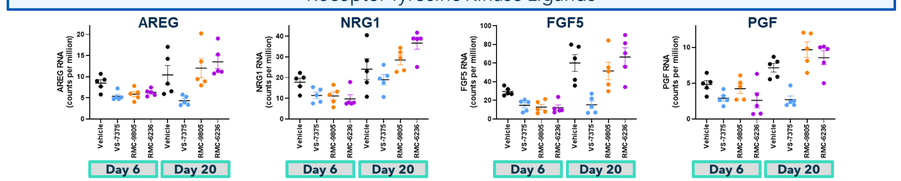


Figure 4. Mice bearing KRAS G12D-mutated tumors were treated with VS-7375 (KP4: 50 mg/kg orally twice daily; LS513 & LU0876: 30 mg/kg orally twice daily), RMC-9805 (KP4: 100 mg/kg orally once daily; LS513: 60 mg/kg orally once daily) or RMC-6236 (25 mg/kg orally once daily), N = 8 mice/group. Average tumor volumes over time are shown. PDAC = pancreatic cancer; CRC = colorectal cancer; NSLCL = non-small cell lung cancer.

Mechanisms of resistance observed with the tricomplex inhibitors zoldonrasib (RMC-9805) and daraxonrasib (RMC-6236) do not limit the durability of VS-7375 efficacy





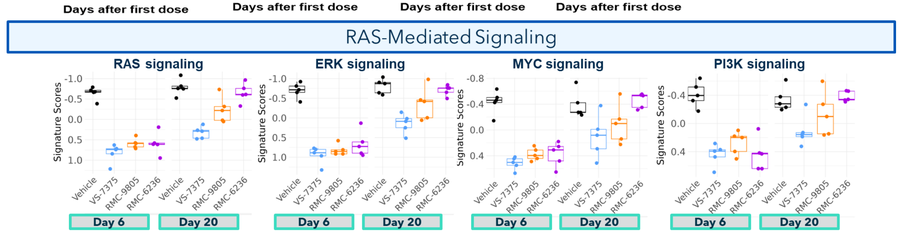


Figure 5. Mice bearing KP4 KRAS G12D-mutated pancreatic tumors were treated with VS-7375 (50 mg/kg twice daily), RMC-9805 (100 mg/kg once daily) or RMC-6236 (25 mg/kg once daily) for 6 or 20 days, N = 5 mice/group. Tumors were collected 2 hours after the last dose for RNAseq and protein analysis. Effects on cyclophilin A RNA and protein levels, receptor tyrosine kinase (RTK) ligand expression, RTK phosphorylation (pRTK), and RAS-mediated signaling (RAS UP and ERK down signatures), MYC signaling (MYC UP signature) and PI3K signaling (PI3K UP signature; Zhang et al., 2018) are shown. Y-axis has been flipped for visualization.

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

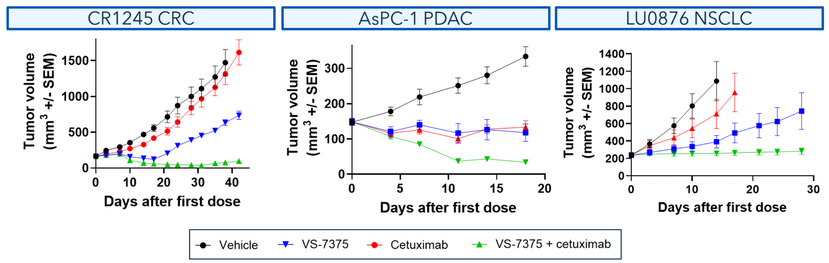


Figure 6. Mice bearing KRAS G12D-mutated tumors were treated with VS-7375 (CR1245: 30 mg/kg orally twice daily; AsPC1 & LU0876: 10 mg/kg orally twice daily), the anti-EGFR antibody cetuximab (10 mg/kg intraperitoneally twice weekly) or the combination. N = 8 mice/group. Average tumor volumes over time are shown. CRC = colorectal cancer; PDAC = pancreatic cancer; NSLCL = non-small cell lung cancer.

Combinations of a FAK inhibitor ± the RAF/MEK clamp avutometinib with VS-7375 induce deep tumor regressions in a KRAS G12D-mutated pancreatic cancer model

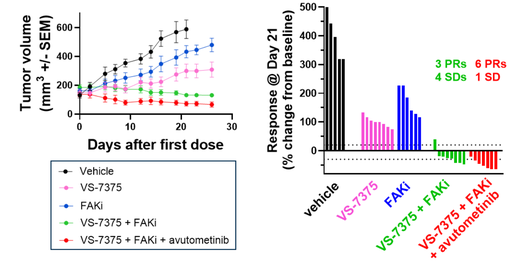


Figure 7. Mice bearing KP2 KRAS G12D-mutated pancreatic tumors were treated with VS-7375 (10 mg/kg orally twice daily), the RAF/MEK inhibitor avutometinib (0.1 mg/kg orally once daily), the FAK inhibitor VS-4718 (FAKi; 50 mg/kg orally twice daily) or the combination. N = 5-10 mice/group. (Left) Average tumor volumes over time are shown. (Right) Tumor responses at Day 21 are shown. PR = partial response (≥30% reduction from baseline); SD = stable disease (+20% to -30% relative to baseline).

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

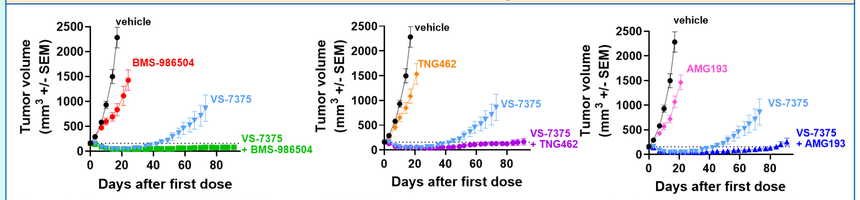


Figure 8. Mice bearing KP4 KRAS G12D-mutated/MTAP-deleted pancreatic tumors were treated with VS-7375 (50 mg/kg orally, twice daily), a PRMT5 inhibitor (BMS-986504 & AMG193: 100 mg/kg orally, once daily; TNG462: 30 mg/kg orally, twice daily) or the combination. N = 8 mice/group. Average tumor volumes over time are shown.

CONCLUSIONS

- VS-7375 is a potent KRAS G12D ON/OFF inhibitor with long residence time (18-24 hours) leading to more potent and durable suppression of pERK than the KRAS G12D ON-only inhibitor zoldonrasib (RMC-9805)
- Across KRAS G12D-mutated tumor models in vivo, oral dosing of VS-7375 is more efficacious than KRAS G12D and pan-RAS ON-only inhibitors
- In a KRAS G12D-mutated pancreatic cancer model, mechanisms of resistance observed with the tricomplex inhibitors zoldonrasib (RMC-9805) and daraxonrasib (RMC-6236) do not limit the durability of VS-7375 efficacy
- Combinations of VS-7375 with other targeted therapies (e.g. cetuximab, FAK inhibitor, avutometinib, PRMT5i) confer durable tumor regressions
- These results support the ongoing clinical evaluation of VS-7375 as monotherapy and in combinations for treatment of patients with KRAS G12D-mutated cancers (VS-7375-101; NCT06500676)