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GFH375 (VS-7375): An oral, selective KRAS G12D (ON/OFF) inhibitor with potent anti-tumor efficacy

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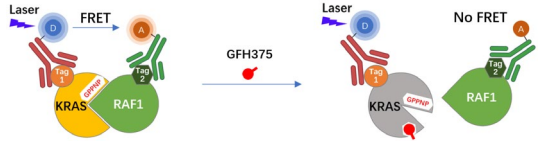
Introduction

- KRAS is one of the most frequently mutated oncogenes but had long been considered 'undruggable' until the approval of the first KRAS G12C inhibitor sotorasib in 2021. However, most current clinical-stage KRAS inhibitors target KRAS G12C mutant. Inhibitors for other KRAS mutants such as KRAS G12D identified in 37% PDAC, 12.5% CRC and 5% NSCLC are needed for patients.
- Unlike KRAS G12C, KRAS G12D is a slow-cycling KRAS protein. Therefore, targeting the 'ON' state (GTP-bound) of KRAS G12D is desirable for sufficient target inhibition and anti-tumor efficacy.
- Besides enhancing single-agent efficacy via patient selection biomarkers, combination strategies will likely be needed to antagonize the diverse adaptive resistance mechanisms in the MAPK pathway to maximize the clinical benefit of a KRAS inhibitor.
- We have developed GFH375 (VS-7375), an orally bioavailable, selective KRAS G12D inhibitor targeting both "ON" (GTP-bound) and "OFF" (GDP-bound) states. The in vitro potency and selectivity, oral bioavailability, and in vivo efficacy of monotherapy and combination therapy with avutometinib, a unique RAF/MEK clamp, were evaluated in preclinical studies.

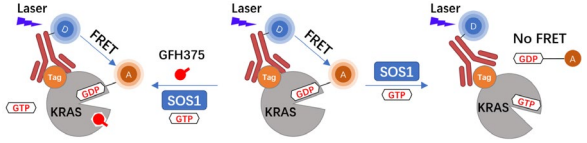
Results

GFH375 targets both active and inactive KRAS G12D

IC_{50} to active, GppNHp-bound KRAS G12D: 2 nM
(KRAS-RAF1 binding assay)

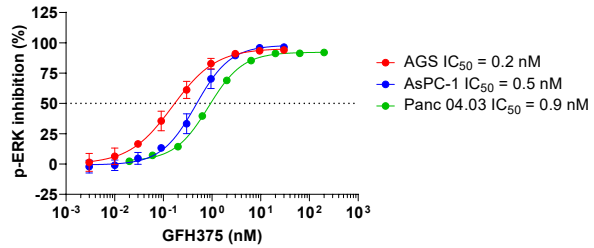


IC_{50} to inactive, GDP-bound KRAS G12D: 6 nM
(nucleotide exchange assay)

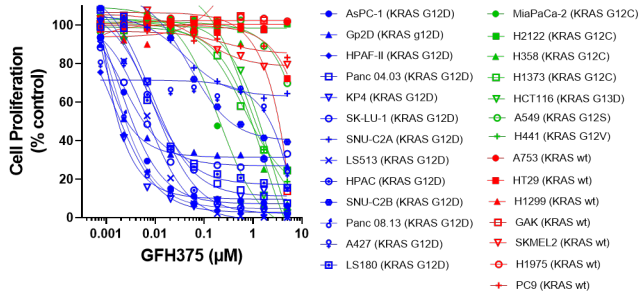


GFH375 potently and selectively inhibits p-ERK signaling and proliferation in KRAS G12D mutant tumor cells

Inhibition of phospho-ERK1/2 in KRAS G12D cells

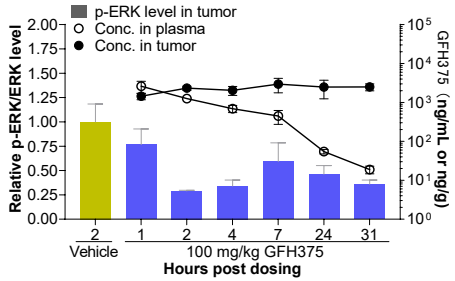


Anti-proliferative potency in tumor cell lines

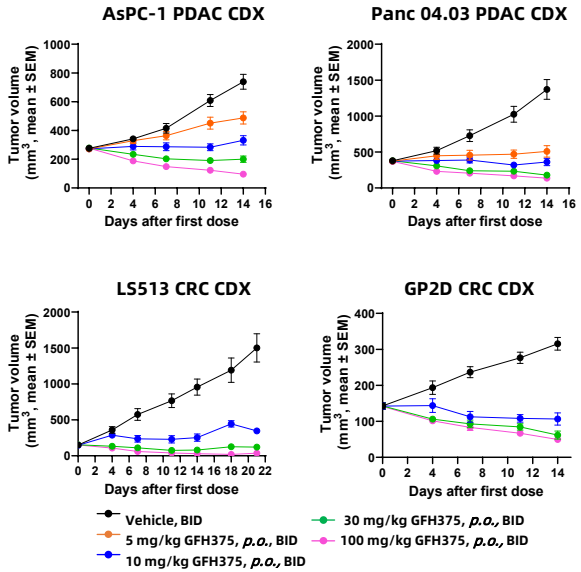


GFH375 accumulates in tumor tissue and elicits sustained inhibition of p-ERK signaling following a single oral administration

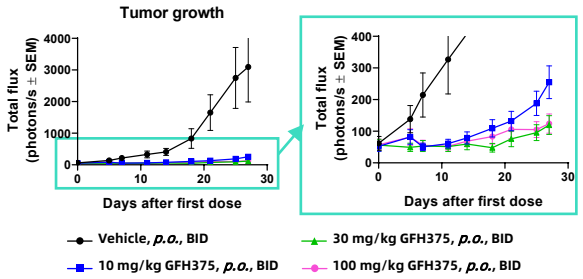
PK/PD study in Panc04.03 PDAC CDX mice



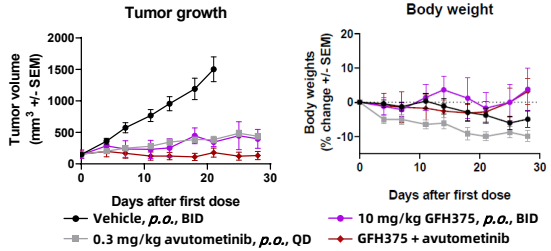
GFH375 induces tumor regression in multiple KRAS G12D subcutaneous CDX tumor models via oral administration



GFH375 demonstrates significant anti-tumor activity in intracranial GP2D CDX tumor model



RAF/MEK clamp avutometinib enhances anti-tumor efficacy of GFH375 in LS513 CDX tumor model



GFH375 shows favorable oral bioavailability across preclinical species and no liability vs safety-related targets

Evaluation	Results
Bioavailability (F%, Mouse/Rat/Dog)	41%/9.3~18.6%/13.2~42.5
hERG inhibition	9.65 μM
Kinase selectivity	≤25% inhibition across 72 representative human kinases at 10 μM
SafetyScreen44 panel	No significant inhibition of 44 safety-related targets

Conclusions

- GFH375 (VS-7375) is a highly potent and selective inhibitor of KRAS G12D (ON/OFF).
- GFH375 is orally bioavailable across preclinical species and holds promising therapeutic potential for treatment of KRAS G12D solid tumors according to its performance in multiple CDX tumor models.
- GFH375 may also be useful for treating KRAS G12D cancers with brain metastases.
- Combining GFH375 and avutometinib may bring further benefit for treating KRAS G12D cancers based on the observation that avutometinib enhances the anti-tumor efficacy of GFH375 in vivo.
- IND application was submitted in Q1 2024.

References

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2. John C Hunter 2015, Mol Cancer Res 13, 1325
3. Alessandro Di Federico 2023, Curr Oncol Rep 25, 1017
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