GFH603: A molecular glue–like allosteric activator of the KEAP1-CUL3 E3 ligase complex for targeting NRF2-activated tumors

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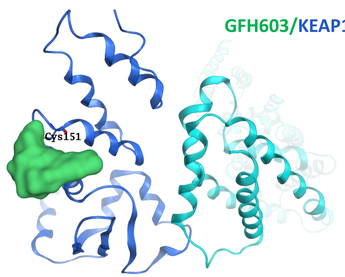
Abstract

Constitutive activation of the KEAP1–NRF2 pathway—driven by NFE2L2 gain-of-function mutations, KEAP1 loss-of-function alterations, or upstream oncogenic RAS signaling—leads to persistent NRF2 stabilization, metabolic reprogramming, and broad resistance to chemotherapy, immunotherapy, and targeted therapies. Such alterations are frequently observed in squamous cancers, including ESCC and LUSC, where hotspot NFE2L2 mutations disrupt KEAP1 binding; KEAP1 mutations also commonly co-occur with KRAS mutations in LUAD, and even in PDAC, elevated nuclear NRF2 is prevalent despite lower mutation rates. Although this pathway has strong clinical significance, no approved therapies directly target KEAP1/NRF2-mutant tumors. To address this unmet need, we developed GFH603, a molecular glue–like allosteric activator of KEAP1 designed to restore KEAP1-CUL3 E3 ligase function and promote NRF2 degradation. GFH603 enhances KEAP1-CUL3 complex formation, induces NRF2 degradation and suppresses proliferation in NRF2-activated cancer cells, and demonstrates strong antitumor activity in CDX and PDX models, accompanied by clear reductions in intratumoral NRF2 levels. GFH603 shows notable monotherapy activity in NRF2-driven squamous tumors and exhibits synergistic antitumor effects when combined with pan-RAS inhibitors in KRAS/KEAP1 co-mutant models. Collectively, these findings highlight GFH603 as a promising agent for targeting NRF2-activated tumors and overcoming therapy resistance across multiple cancer types.

Introduction



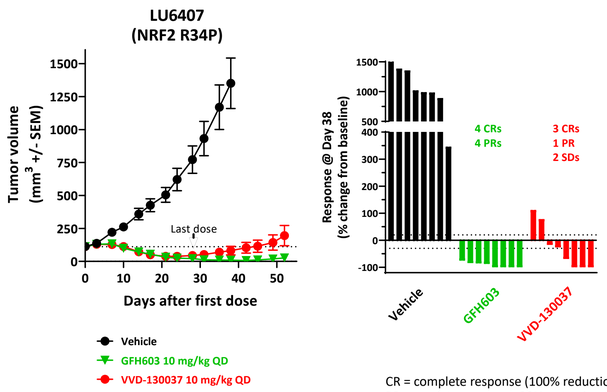
GFH603 covalently binds to the Cys151 of BTB domain of KEAP1, allosterically activates KEAP1 to promote the formation of an active KEAP1–CUL3 complex, and induces degradation of oncogenic NRF2, thereby suppresses tumor growth.

Results

GFH603 exhibits improved potency and ADME/PK properties over VVD-130037

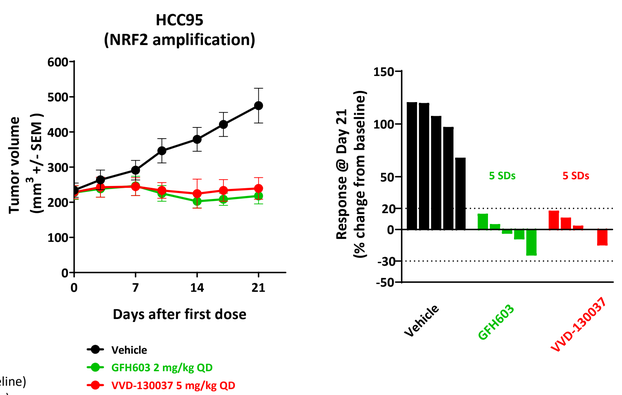
	GFH603	VVD-130037
Cellular NRF2 degradation (IC_{50}, nM)	1.7	3.1
HCC95 3D soft agar (IC_{50}, nM)	3.6	9.5
Caco-2 [P_{app} A-B(10^{-6} cm/s), efflux ratio]	18.62, 1.81	42.35, 0.69
Hepatocyte $T_{1/2}$ (min), human	>216.8	151.5
CL (mL/min/kg)/%F (m)	28/55.3	151/65.5
CL (mL/min/kg)/%F (r)	98/36.8	160/29.9
CL (mL/min/kg)/%F (d)	10/113	45/129

GFH603 drives tumor regression in the LU6407 (NRF2 R34P) squamous NSCLC PDX model

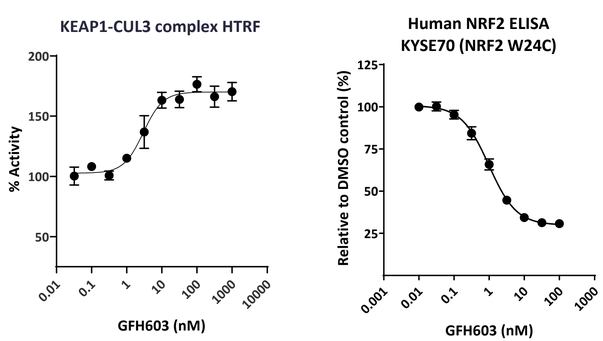


CR = complete response (100% reduction from baseline)
PR = partial response (≥30% reduction from baseline)
SD = stable disease (+20% to -30% relative to baseline)

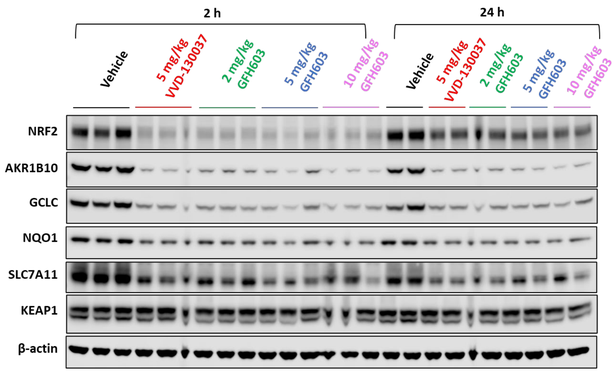
GFH603 exhibits potent anti-tumor activity in the HCC95 (NRF2 amplification) squamous NSCLC CDX model



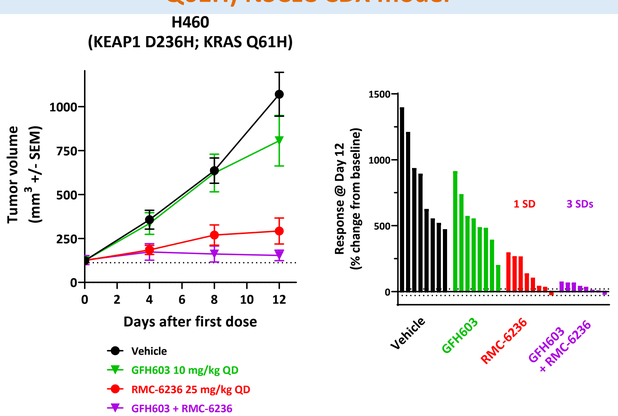
GFH603 enhances KEAP1-CUL3 E3 ligase assembly and drives NRF2 degradation



GFH603 suppresses NRF2-activated effector proteins in the HCC95 (NRF2 amplification) CDX model



GFH603 plus a pan-RAS inhibitor exhibits strong anti-tumor activity in the H460 (KEAP1 D236H; KRAS Q61H) NSCLC CDX model



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3. DeNicola GM et al. Nature. 2011 Jul 6;475(7354):106-9.
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5. Zhang DD. Nat Rev Drug Discov. 2025 Jun;24(6):421-444.

Conclusions

- GFH603 functions as a molecular glue–like allosteric activator of the KEAP1-CUL3 E3 ligase, restoring NRF2 ubiquitination and degradation.
- It demonstrates potent antitumor activity across NRF2-activated cancer models, showing low-nanomolar NRF2 degradation and proliferation inhibition *in vitro*, as well as significant tumor growth suppression in CDX and PDX models.
- GFH603 exhibits strong synergy with pan-RAS inhibitors in KRAS/KEAP1 co-mutant cell lines, highlighting its potential as part of combination strategies to overcome NRF2–driven therapeutic resistance.
- Its favorable ADMET properties, including low hERG liability, negative Ames test, and high oral bioavailability, support its suitability as a drug-like candidate.
- Overall, GFH603 represents a promising agent for targeting NRF2-activated tumors and addressing a major unmet need in oncology, warranting continued preclinical and clinical development.

Preclinical evaluation of GFH276 monotherapy and combination therapy for RAS-mutant tumors

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#4565

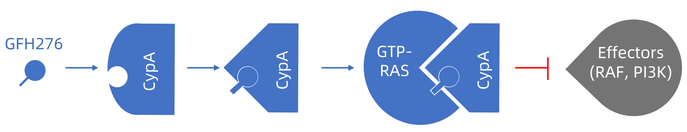
Introduction

- Members of the RAS gene family—*KRAS*, *HRAS*, and *NRAS*—are frequently mutated across human cancers, including ~33% of non-small cell lung cancers (NSCLC), ~50% of colorectal cancers (CRC), ~90% of pancreatic ductal adenocarcinomas (PDAC), ~26% of cholangiocarcinomas, ~20% of endometrial carcinomas (EC), and several other tumor types.
- RAS had been long considered 'undruggable' for decades until the approval of Sotorasib, the first KRAS G12C inhibitor in 2021. However, effective therapies targeting other RAS mutants remain urgently needed for patients.
- GFH276 is a molecular glue panRAS(ON) inhibitor developed by GenFleet Therapeutics and is currently being evaluated in a Phase 1 clinical trial.
- To explore the therapeutic potential of GFH276, we evaluated its target affinity, in vitro potency and in vivo efficacy of monotherapy and combination therapy in preclinical studies.

Results

GFH276 recruits CypA to target active GTP-bound RAS proteins.

MOA of GFH276



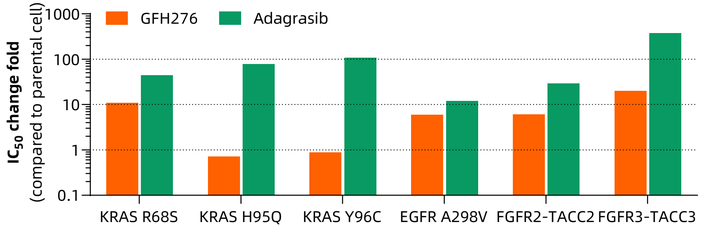
GFH276 effectively inhibits RAS signaling in RAS-dependent cells.

p-ERK IC_{50} in cell lines

No.	Cell	Mutation	GFH276	RMC-6236
1	NCI-H441	KRAS G12V	0.63 nM	0.79 nM
2	AsPC-1	KRAS G12D	0.57 nM	0.90 nM
3	MIA PaCa-2	KRAS G12C	0.42 nM	0.30 nM
4	A-375	BRAF V600E	> 10000 nM	>10000 nM

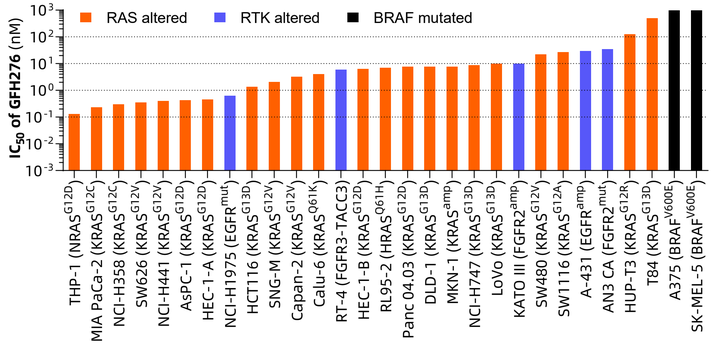
GFH276 remains active against KRAS G12Ci-resistant tumor cells.

Effect of KRAS G12Ci resistance drivers on anti-proliferative activity



GFH276 displays potent anti-proliferative activity in RAS-addicted tumor cells.

Anti-proliferative activity

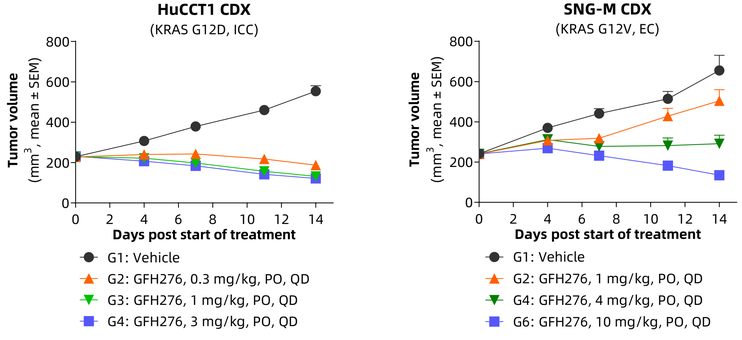


GFH276 demonstrates robust anti-tumor efficacy in KRAS-mutant CDX tumor models with a superior dose advantage over RMC-6236.

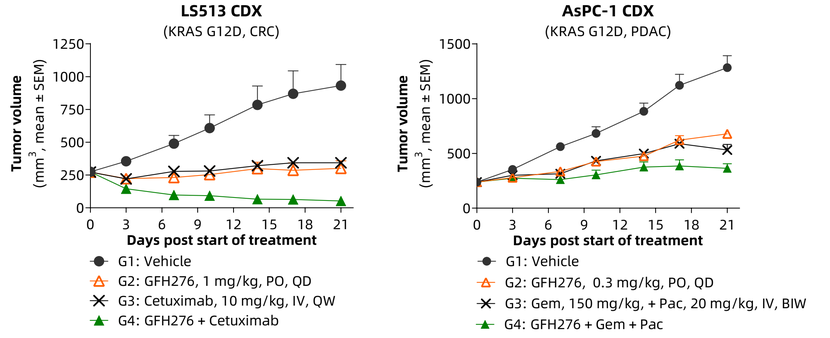
In vivo efficacy summary

No.	CDX	Mutation	Disease	TGI of GFH276 (3 mg/kg, PO, QD)	TGI of RMC-6236 (10 mg/kg, PO, QD)
1	NCI-H441	KRAS G12V	NSCLC	125%	120%
2	AsPC-1	KRAS G12D	PDAC	120%	81%
3	NCI-H1373	KRAS G12C	NSCLC	109%	103%
4	SW620	KRAS G12V	CRC	107%	98%
5	HCT116	KRAS G13D	CRC	96%	72%
6	SW480	KRAS G12V	CRC	96%	99%
7	NCI-H2122	KRAS G12C	NSCLC	99%	90%

GFH276 exhibits dose-dependent antitumor efficacy in cholangiocarcinoma and endometrial cancer CDX models.

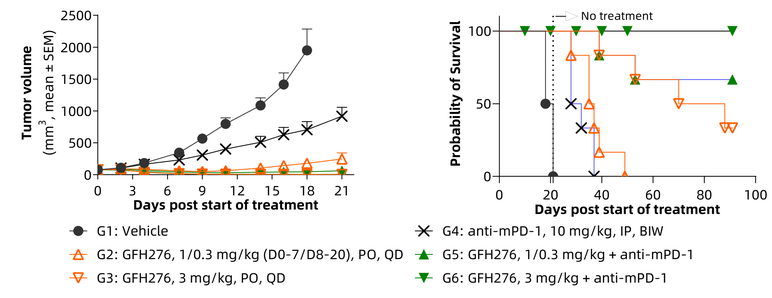


GFH276 demonstrates synergistic antitumor activity with standard-of-care (SOC) regimens in colorectal and pancreatic cancer CDX models.



PD-1 blockade potentiates the antitumor efficacy of GFH276 and sustains tumor-free survival following treatment cessation.

CT26 (KRAS G12C) CDX



Conclusions

- GFH276 recruits CypA to achieve panRAS(ON) inhibition with a potential of serving as a next-generation RAS inhibitor.
- GFH276 demonstrates robust antitumor activity in tumor models of various types, supporting its broad therapeutic potential for RAS-mutated tumors.
- GFH276 acts synergistically with SOC regimens for different type of cancers, highlighting its potential to improve clinical outcomes for both frontline and late-line patients.
- GFH276 cooperates with PD-1 blockage, underscoring the benefit of incorporating immune checkpoint inhibition in RAS-targeted therapies.
- Collectively, these findings strengthen the rationale for developing GFH276 in RAS-mutant cancers and provide mechanistic and translational insights to guide its future clinical development.

GFS784, a next-generation ADC with a novel panRAS(ON) inhibitor payload

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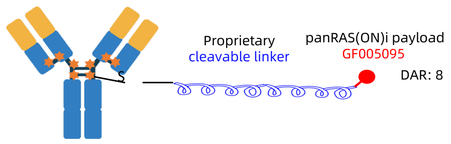
Introduction

- Antibody-drug conjugates (ADCs) have emerged as an effective therapeutic modality. However, the potential synergy and coordination between the antibody and payload components of an ADC are often overlooked.
- Upregulation of EGFR drives adaptive resistance to KRAS inhibitors, and combination of EGFR mAbs with KRAS G12C inhibitors have demonstrated synergistic effect in both preclinical and clinical studies.
- GFS784 is a novel EGFR-targeted ADC developed using GenFleet Therapeutics' proprietary Functional Antibody and Synergistic Conjugate (FAScon™) platform, a next-generation ADC technology. The therapeutic potential of GFS784 against RAS-addicted tumors was comprehensively assessed in preclinical studies.

Results

GFS784 is a novel EGFR-targeted ADC equipped with a panRAS(ON) inhibitor payload.

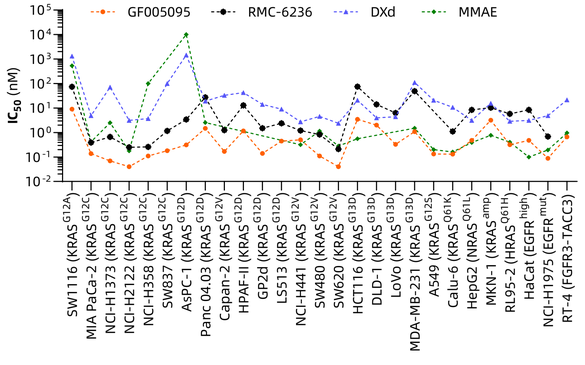
Structure of GFS784



GF005095 is a highly potent molecular glue panRAS (ON) inhibitor.

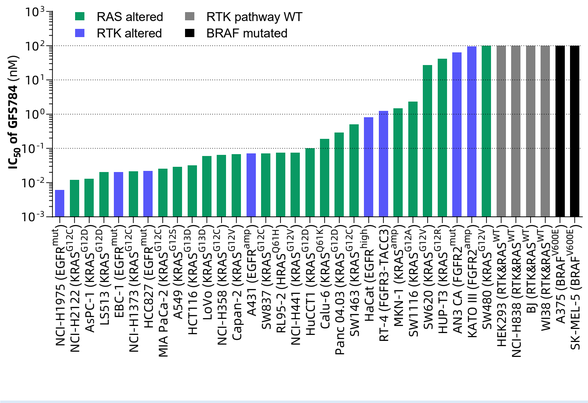
MOA of GF005095

Anti-proliferative activity of GF005095



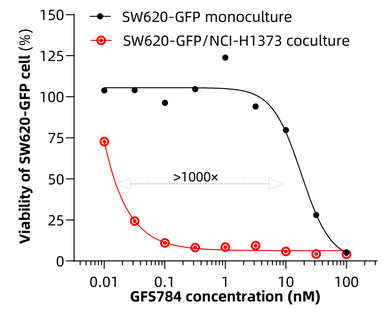
GFS784 exhibits potent anti-proliferative activity in RAS-addicted tumor cell lines.

Anti-proliferative activity of GFS784



GFS784 elicits a significant bystander effect.

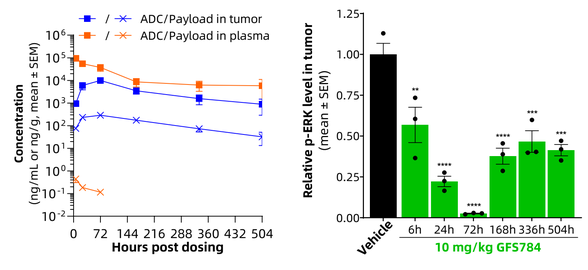
In vitro bystander effect assay



Cell line	EGFR copy/cell
SW620-GFP	17
NCI-H1373	116846

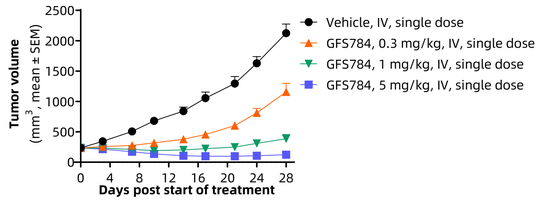
GFS784 selectively and efficiently delivers its payload to achieve profound target inhibition in CDX tumors.

PK/PD in HCT116 CDX (single dose via IV)

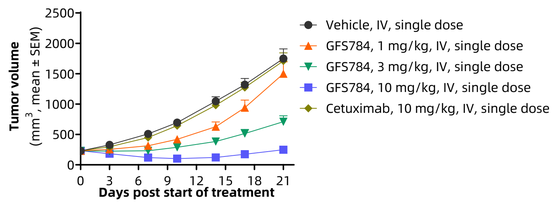


A single dose of GFS784 achieves robust antitumor efficacy in KRAS-mutant tumor models.

NCI-H441 CDX ($KRAS^{G12V}$, NSCLC)

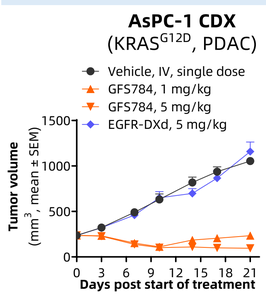


HCT116 CDX ($KRAS^{G13D}$, CRC)

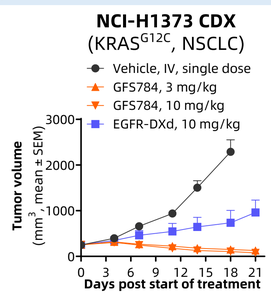


GFS784 remains effective against DXd-resistant tumors.

AsPC-1 CDX ($KRAS^{G12D}$, PDAC)

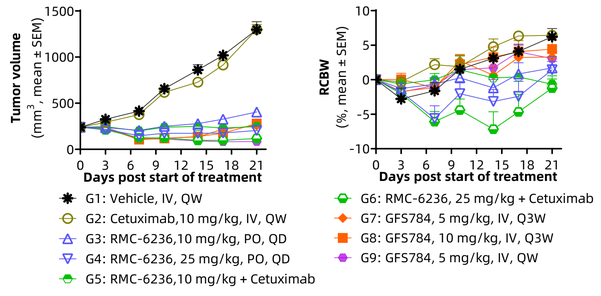


NCI-H1373 CDX ($KRAS^{G12C}$, NSCLC)



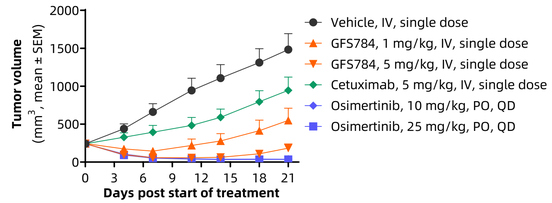
GFS784 exhibits equivalent efficacy yet superior safety compared with EGFR mAb + panRAS(ON)i combination.

AsPC-1 CDX ($KRAS^{G12D}$, PDAC)

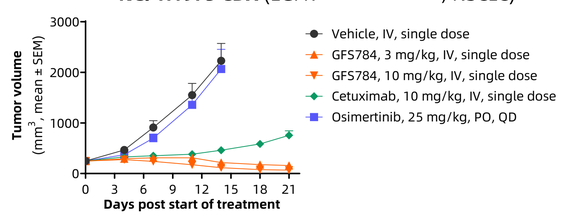


GFS784 is effective against both Osimertinib-sensitive and -resistant EGFR-mutant tumors.

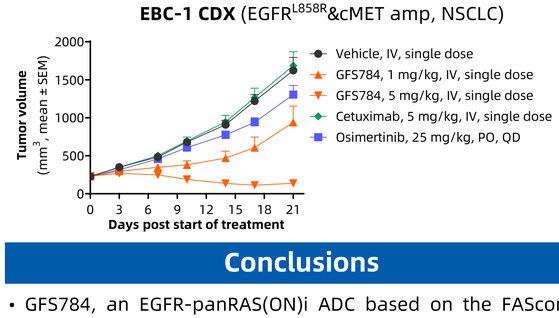
NCI-H1975 CDX ($EGFR^{L858R\&T790M}$, NSCLC)



NCI-H1975 CDX ($EGFR^{L858R\&T790M\&C797S}$, NSCLC)



EBC-1 CDX ($EGFR^{L858R}$&cMET amp, NSCLC)



Conclusions

- GFS784, an EGFR-panRAS(ON)i ADC based on the FAScon™ platform, was successfully constructed and comprehensively characterized.
- GFS784 demonstrates promising therapeutic potential for RAS-addicted tumors, which include 80% of NSCLC (EGFR- or RAS-mutant), 50% of CRC (RAS-mutant), 90% of PDAC (RAS-mutant), and other RAS-mutant malignancies.
- The unique MOA of its panRAS(ON)i payload GF005095 also endows GFS784 with the potential to treat tumors resistant to conventional ADCs or EGFR inhibitors.
- The development of GFS784 represents an innovative way of broadening payload diversity, expanding RAS-targeting strategies and unlocking the full potential of the ADC modality by leveraging antibody-payload coordination.
- The FAScon™ platform has been validated as feasible across 10+ antibodies targeting different antigens in preclinical evaluations.
- IND application for GFS784 was filed in H1 2026.