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

Feng Yan, Jichen Zhao, Jingyang Zhang, Siyuan Le, Fusheng Zhou, Jiong Lan, Qiang Lu

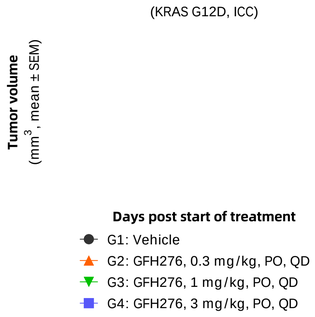
GenFleet Therapeutics, Shanghai, China

Introduction

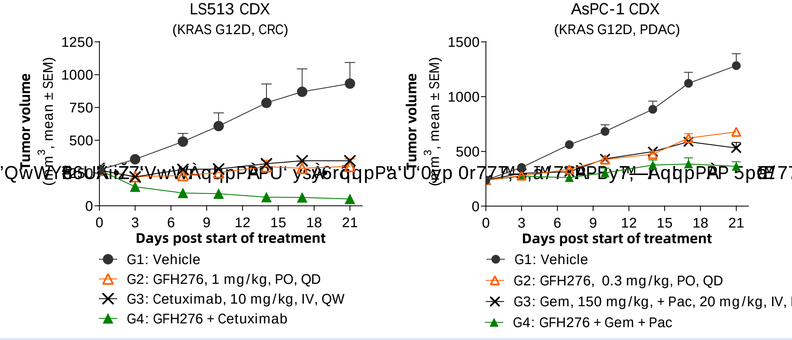
- Members of the RAS gene family—*KRAS*, *HRAS*, and *NRAS*—are frequently mutated across human cancers, including ~33% of non-small cell lung cancers (NSCLC), ~50% of colorectal cancers (CRC), ~90% of pancreatic ductal adenocarcinomas (PDAC), ~26% of cholangiocarcinomas, ~20% of endometrial carcinomas (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.

Results

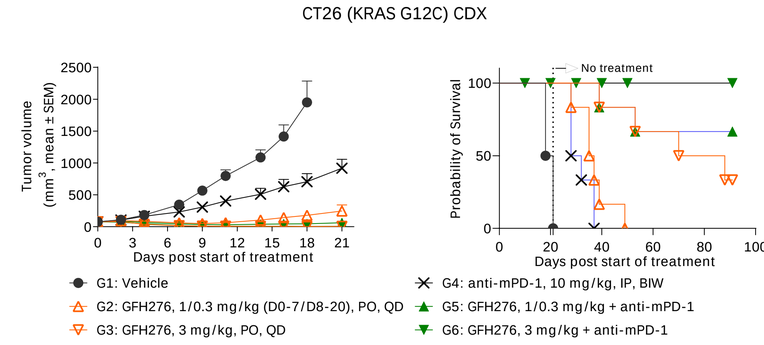
GFH276 demonstrates robust anti -tumor efficacy in KRAS -mutant CDX tumor models with a superior dose advantage over RMC -6236.



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.



Conclusions

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

Feng Yan, Jichen Zhao, Jingyang Zhang, Li Wang, Yumei Li, Siyuan Le, Fusheng Zhou, Jiong Lan, Qiang Lu

GenFleet Therapeutics, Shanghai, China

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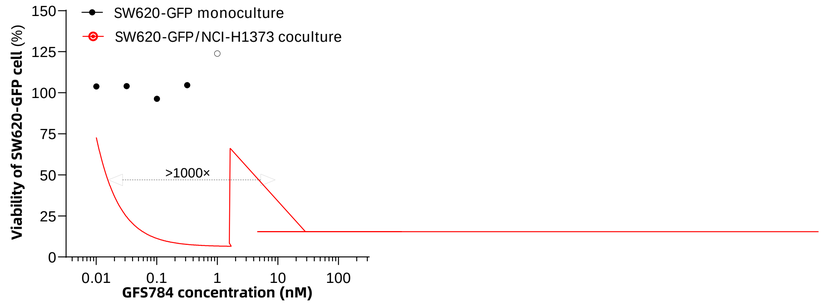
Introduction

- 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.

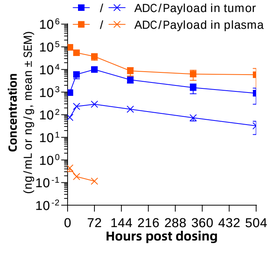
Results

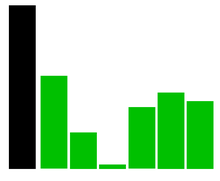
GFS784 is a novel EGFR-targeted ADC equipped with a panRAS(ON) inhibitor payload.

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



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





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

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.