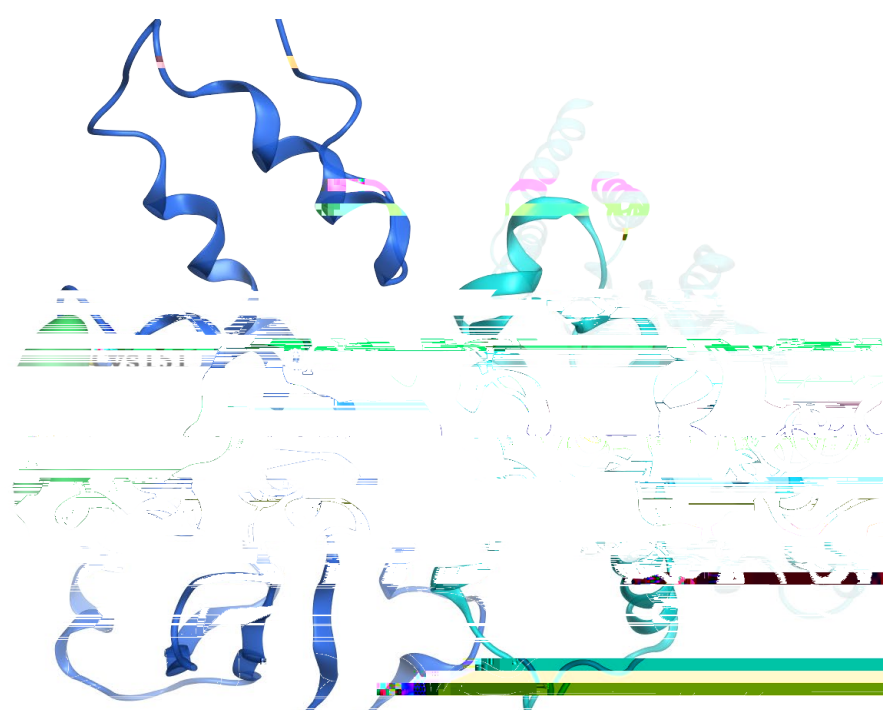


GFH603: A molecular glue–like allosteric activator of the KEAP1-CUL3 E3 ligase complex for targeting NRF2-activated tumors



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

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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 novel KRAS G12D inhibitor.

TumT2 (t)Teatnfe(57(s)2 ((A)2)-2mm40 Td(I))T6 0D)-16(D)270 c10 23 (K83.7m(3008w 0 1236 -14.9.7056 0 99024 224.7131 40.520 24y)2324)TatmT.7546 -1113.7546 1052.405 35800.79581 1295309

(KRAS G12D, ICC)

Days post start of treatment

Conclusions

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, so EGFR F o R B ds B21 inhibites

A d i n a

Results

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