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Efficacy and safety of GFH375 monotherapy in previously treated advanced KRAS G12D-mutant pancreatic ductal adenocarcinoma (PDAC)

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Background

Oncogenic KRAS mutations are most common in PDAC with G12D being most frequent (⊠40%) and predicting poorer prognosis. GFH375 is an oral, potent, highly selective inhibitor that binds to both GDP- and GTP-bound KRAS G12D. Here we report the data of GFH375 in patients (pts) with previously treated advanced KRAS G12D-mutant PDAC.

Methods

NCT06500676 is a phase I/II study to evaluate the safety, PK and efficacy of GFH375 in previously treated advanced solid tumors. Pts with previously treated KRAS G12D-mutant PDAC were enrolled and received GFH375 600mg QD. PDAC pts in phase I or the PDAC cohort of phase II were included in the analysis. The primary endpoint is objective response rate (ORR) per RECIST 1.1. Other endpoints include disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), safety and exploratory biomarkers.

Results

As of August 27, 2025, a total of 66 PDAC pts received GFH375 600mg QD with a median exposure duration of 117 days (d, range: 7, 336), 45 (68.2%) of whom had received at least two prior lines of anti-tumor treatment. The ORR was 41% (24/59, 90%CI: 30%, 52%) and DCR was 97% (57/59, 90%CI: 90%, 99%) among the pts who had at least one post-treatment assessment. The 3-month PFS rate was 83% (90%CI: 76%, 92%) with a median follow up of 141d. GFH375 presented a manageable safety profile. No grade (G) 5 TRAEs. G3 TRAEs occurred in 20 pts (30%) and a G4 TRAE occurred in 1 pt (2%). TRAEs resulted in a dose reduction in 4 pts (6%) and discontinuation in 2 pts (3%). The most common TRAEs (all G/≥G3) included diarrhea (56%/3%), neutrophil count decreased (49%/8%), vomiting (47%/1.5%), nausea (47%/0), anaemia (42%/8%), white blood cell count decreased (36%/2%), decreased appetite (33%/3%), hypoalbuminemia (33%/0), platelet count decreased (29%/2%) and asthenia (26%/0). Among pts with baseline ctDNA available (N=62), 44 (71%) tested positive for KRAS G12D mutation in plasma. The most frequent co-mutations were in TP53, CDKN2A, and SMAD4. Data with longer follow-up time and co-mutation results will be reported in the full presentation.

Conclusions

GFH375 monotherapy shows promising efficacy with a manageable safety profile in previously treated KRAS G12D-mutant PDAC. The trial is still ongoing.

Clinical trial identification

NCT06500676.

Legal entity responsible for the study

GenFleet Therapeutics (Shanghai) Inc.

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Disclosure

Y. Wang, H. Shen, H. Zhu, S. Zheng, S. Wang, Z. Cui: Financial Interests, Personal, Full or part-time Employment: GenFleet Therapeutics. All other authors have declared no conflicts of interest.