Poster ID
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Phase I study of GFH018, a small molecular TGF-βRI inhibitor, in patients with advanced solid tumors

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Introduction

- TGF-β is a multifunctional polypeptide cytokine and the pathway is a classic membrane–to–nucleus signaling process involving direct receptor-mediated activation of SMAD transcription factors[1].
- TGF-β pathway activation promotes tumor metastasis and progression, mediates epithelial-mesenchymal transmission suppressing immunosurveillance in advanced tumors[2, 3]. High expression of TGF-β always correlates with poor disease prognosis[4, 5].
- Inhibition of TGF-β signaling pathway can inhibit tumor growth and progression through multiple ways, including inhibiting metastasis, enhancing anti-tumor immune responses within the tumor microenvironment, and inhibiting intra-tumor angiogenesis[6].
- Biological rationales have been provided for combining PD-1/L1 with TGF-β inhibitors. Inhibiting TGF-β pathway impacts regulatory T cell production and can potentially augment the effect of PD-1/L1 inhibitors leading to improved response[6].

Investigational treatment

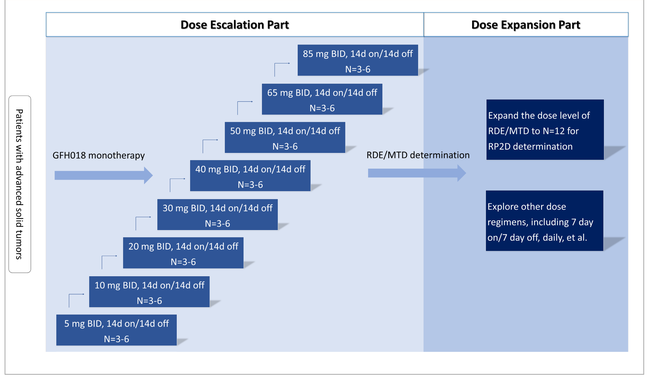
- GFH018, a novel small molecule that inhibits TGF-βRI kinase, blocks TGF-β signaling transduction thus inhibits tumor progression.
- GFH018 can inhibit kinase activity of TGF-βRI and inhibit Smad2/3 protein phosphorylation and gene expression induced by TGF-β-Smad signaling pathway *in vitro*.
- GFH018 showed significant anti-tumor activity in single agent as well as a synergistic effect with PD-1/L1 immune checkpoint inhibitors in low *dose in vivo*.

Methods

NCT05051241 is an ongoing, phase I, open-label, multicenter study.

- Comprising of a modified 3 + 3 dose escalation part followed by an expansion part. GFH018 doses of 5mg up to 85 mg twice daily were tested.
- Eligible patients with advanced solid tumors failed to standard therapies were administrated with GFH018 BID orally, 14-day on/14-day off.
- AEs were graded per NCI-CTCAE v5.0. PK analysis was performed using a non-compartmental method. Tumor response was evaluated per RECIST 1.1.

Figure 1. Study Design



Adverse events of special interest (AESI) was defined as below:

- Increased cardiac biomarkers with clinical significance, including N-terminal prohormone brain natriuretic peptide (NT-proBNP) and troponin.
- Abnormal echocardiography with clinical significance.

Key inclusion criteria

- Aged 18-75 years old.
- Previously treated, histologically or cytologically confirmed advanced solid tumors.
- At least one evaluable lesion per RECIST 1.1.
- ECOG performance status 0-1.
- Life expectancy ≥ 12w.

Key exclusion criteria

- With unstable CNS metastasis.
- With clinically significant cardiac diseases.
- Active infection.
- History of autoimmune disease.
- History of prior anti-tumor therapy within the protocol-specified timeframe.

Results

Baseline and disease characteristics

- As of Jan 25, 2022, 39 patients (5 mg [n=4]; 10 mg [n=3]; 20mg [n=4]; 30 mg [n=7]; 40, 50 mg [n=4 each]; 65 mg [n=6] and 85 mg [n=7]) were sequentially enrolled in the dose escalation part.
- 79.5% (n=31) of enrolled patients received ≥ 3 prior antitumor therapies.
- 56.4% (n=22) of patients received anti-PD-1 antitumor therapy previously.

Table 1. Baseline and disease characteristics

	Total (N=39)
Age (years), Median (range)	53.0 (27-68)
Sex, n (%)	
Male	17 (43.6%)
Weight (kg) , Median (range)	59.3 (34.5-83.1)
ECOG performance status, n (%)	
0/1	3 (7.7%)/36 (92.3%)
Lines of prior anti-tumor therapies, n (%)	
1	3 (7.7%)
2	5 (12.8%)
≥ 3	31 (79.5%)
Have ever received anti-PD-1 therapy, n (%)	
Yes	22 (56.4%)

Safety

- No dose limiting toxicity (DLT) was observed and the maximal tolerance dose (MTD) was not reached.
- No patients discontinued due to AEs.
- 35 patients (89.7%) had at least one treatment related AE and 2 (5.1%) experienced ≥ G3 treatment related AE.
- The most common treatment-related AEs (all Grade/≥G3) were proteinuria (20.5%/2.6%), AST increased (15.4%/0), ALT increased (12.8%/0), anemia (12.8%/0), lymphocyte count decreased (10.3%/2.6%), ALP increased (10.3%/0), and LDH increased (10.3%/0).

Cardiovascular toxicity

- No ≥ G2 AESIs were reported. Only G1 Troponin T from 10mg BID cohort or G1 NT-proBNP from 30mg BID cohort increased was reported respectively in two patients without symptoms or signs.

Bleeding events

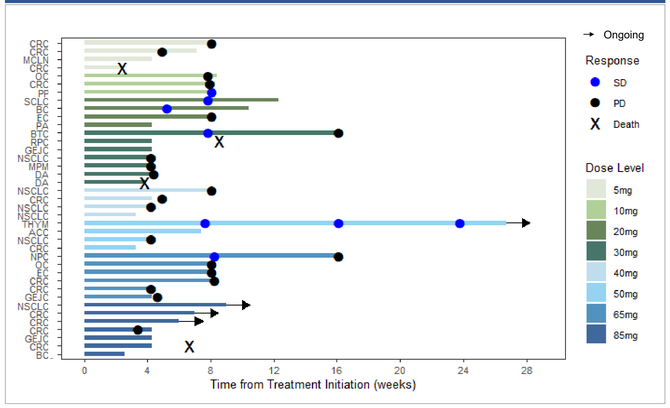
- No bleeding events were reported.

Table 2. TEAEs or TRAEs occur in ≥ 5 patients

	Treatment-Emergent AEs		Treatment-Related AEs	
	Any grades n (%)	≥ G3 n (%)	Any grades n (%)	≥ G3 n (%)
Proteinuria#	17 (44.7%)	2 (5.1%)	8 (20.5%)	1 (2.6%)
Anemia*	17 (44.7%)	2 (5.1%)	5 (12.8%)	0
Lymphocyte count decreased	8 (20.5%)	2 (5.1%)	4 (10.3%)	1 (2.6%)
AST increased	7 (17.9%)	0	6 (15.4%)	0
ALK increased	7 (17.9%)	0	4 (10.3%)	0
LDH increased	7 (17.9%)	0	4 (10.3%)	0
Sinus tachycardia	7 (17.9%)	0	3 (7.7%)	0
DBIL increased	6 (15.4%)	1 (2.6%)	1 (2.6%)	0
ALT increased	6 (15.4%)	0	5 (12.8%)	0
GGT increased	6 (15.4%)	0	3 (7.7%)	0
Asthenia	6 (15.4%)	0	1 (2.6%)	0
Constipation	6 (15.4%)	0	1 (2.6%)	0
Abdominal pain	5 (12.8%)	0	2 (5.1%)	0

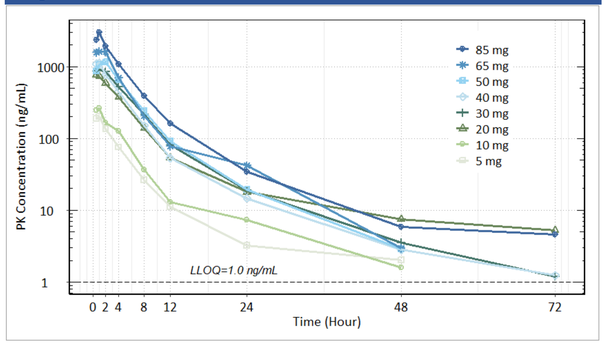
#The term proteinuria includes both proteinuria and protein urine present. *The term anemia includes both anemia and hemoglobin decreased.
Abbreviations: TEAE, treatment-emergent adverse event. **TRAE**, treatment-related adverse event.

Figure 2. Efficacy data of GFH018 monotherapy (Swimmer plot)



Abbreviations:
SD, stable disease. **PD**, progressive disease.
ACC, adenoid cystic carcinoma. **BC**, breast cancer. **BTC**, biliary tract cancer. **CRC**, colorectal cancer. **DA**, duodenal adenocarcinoma. **EC**, endometrial carcinoma. **GEJC**, gastroesophageal junction carcinoma. **MCLN**, metastatic carcinoma of lymph nodes. **MPM**, malignant pleural mesothelioma. **NSCLC**, non small cell lung cancer. **NPC**, nasopharyngeal carcinoma. **OC**, ovarian cancer. **PA**, pancreatic adenocarcinoma. **PP**, pelvic paraganglioma. **RPC**, renal pelvis carcinoma. **SCLC**, small cell lung cancer. **THYM**, thymic carcinoma.

Figure 3. GFH018 Mean Plasma Concentration - Time Curves Post Single Oral Dose



PK, pharmacokinetics.

Efficacy

- Five patients achieved stable disease (SD) out of 24 evaluable patients.
- One patient with thymic carcinoma receiving GFH018 at 50 mg achieved a durable SD with tumor shrinkage (maximum lesion decreased by 18.4%) and has stayed on treatment for 185 days as of the cut-off date.

Pharmacokinetics (PK)

- PK of GFH018 was linear and dose-independent with geometric mean half-life in the range of 3.11 h- 8.30 h.
- Accumulation in PK exposure was limited post multiple dosing.

Conclusions

- GFH018 in the current dosing regimen presented a favorable safety profile without cardiovascular toxicity and hemorrhage risk.
- Preliminary efficacy of GFH018 as monotherapy was observed in treating among patients with advanced solid tumors.
- Two clinical studies of GFH018 in combination with Toripalimab (NCT04914286) and with Toripalimab+ concurrent chemoradiotherapy (NCT05386888) are ongoing.

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The presenter states no conflict-of-interest on the poster. **Contact:** Y. Guo[1], pattrickguo@gmail.com