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Safety and Efficacy of GFH276 Monotherapy in Previously Treated RAS-mutated Advanced Solid Tumors

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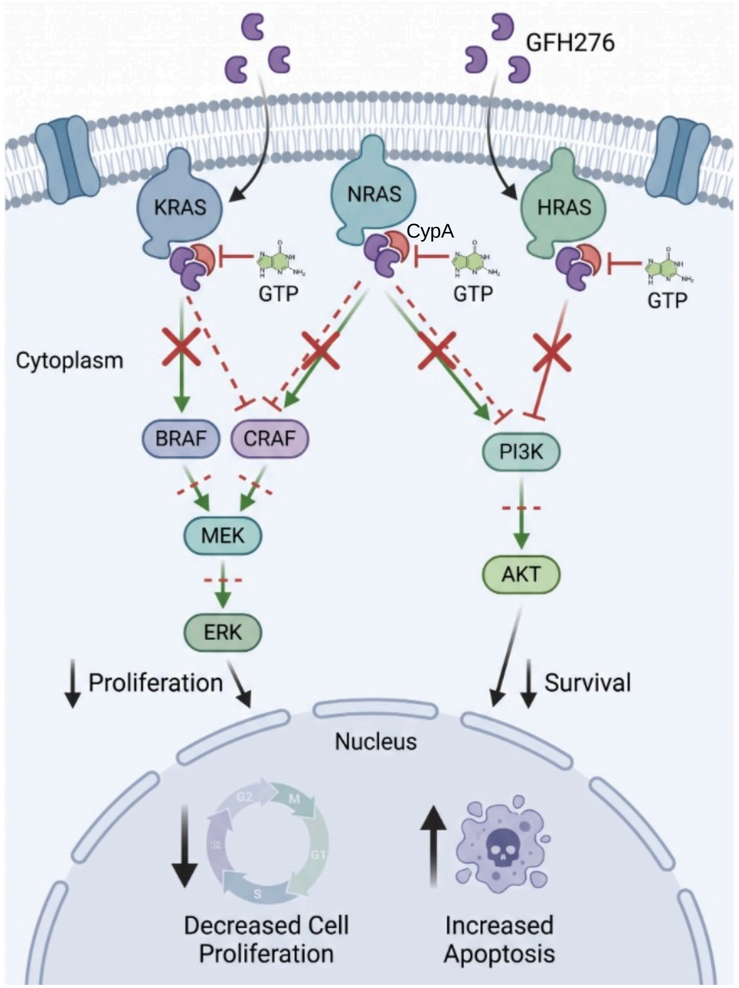
Declaration of Interests

Yuxiang Ma, MD

The presenter declares no conflict interest.

Background

- RAS mutations affect approximately 30% of solid tumors[1]. RAS(ON) multi-selective inhibition is now a validated class in previously treated metastatic pancreatic cancer[2]. However, significant unmet clinical needs remains.
- GFH276 is an oral molecular-glue pan-RAS(ON) inhibitor. It engages GTP-bound mutant and wild-type RAS and showed robust, dose-dependent antitumor activity across RAS-mutant tumor models with a superior dose advantage[3, 4].
- Here we report safety of GFH276 in previously treated RAS-mutated advanced solid tumors, and preliminary efficacy in pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC).



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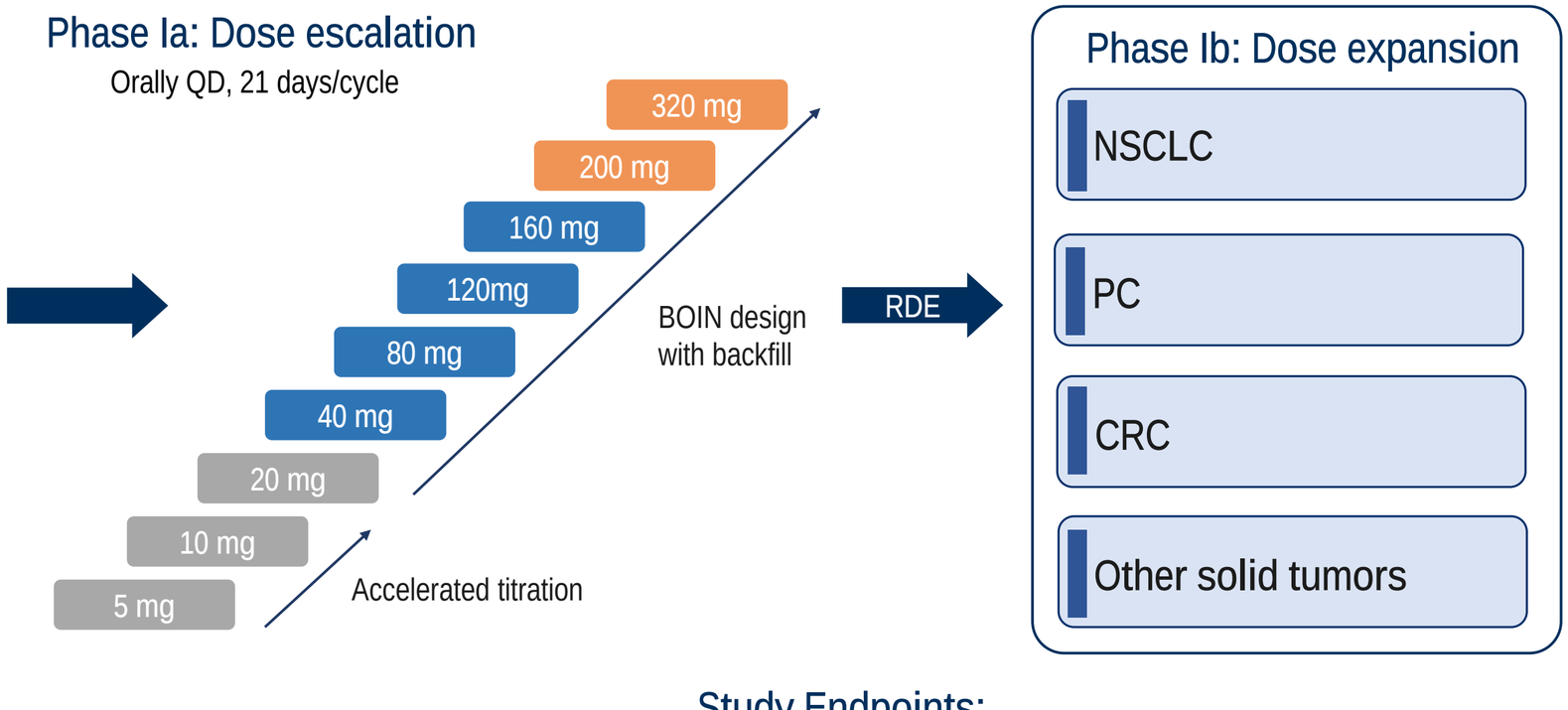
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FIH study of GFH276 (NCT07198321)

- As of 15 June 2026, a total of **98 patients** were enrolled in the **Phase Ia** study and treat with GFH276 5~320 mg QD, including 73 PDAC, 18 NSCLC, 5 CRC and 2 others.

Key eligibility criteria:

- Pathologically confirmed, **advanced solid tumors** harboring **RAS mutations** using local testing results
- **Previously treated** with standard therapies
- ECOG PS 0~1



Study Endpoints:

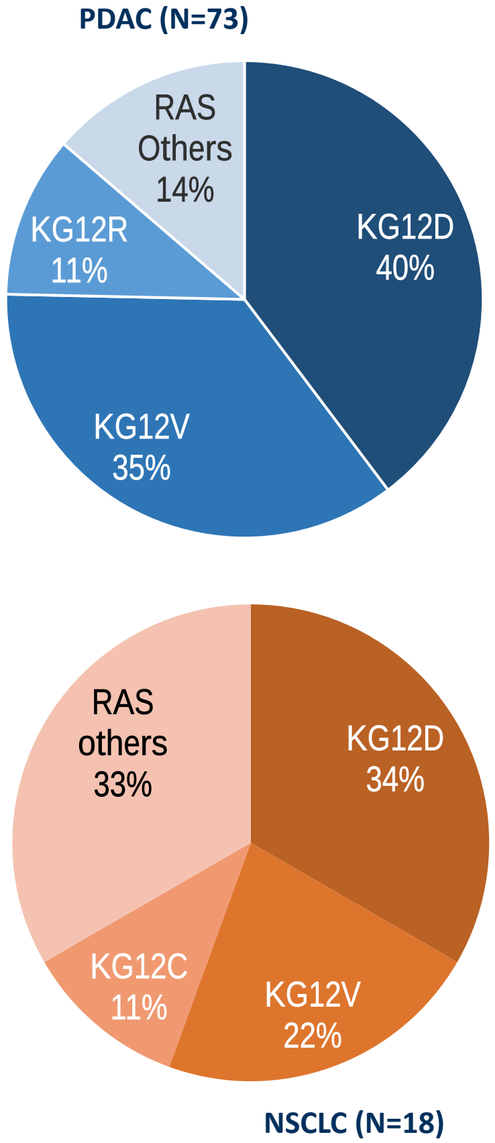
- Safety and tolerability
- Investigator-assessed ORR, DoR, DCR, PFS per RECIST v1.1
- Pharmacokinetics
- Exploratory biomarkers

Abbreviations: ECOG, Eastern Cooperative Oncology Group. PS, performance status. QD, once daily. BOIN, Bayesian optimal interval. RDE, recommended dose for expansion. NSCLC, non-small cell lung cancer. PC, pancreatic cancer. CRC, colorectal cancer. DCR, disease control rate. DoR, duration of response. NSCLC, non-small cell lung cancer. ORR, objective response rate. PFS, progression-free survival. PK, pharmacokinetics. RDE, recommended dose for expansion. RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1.

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Demographics and Disease Characteristics

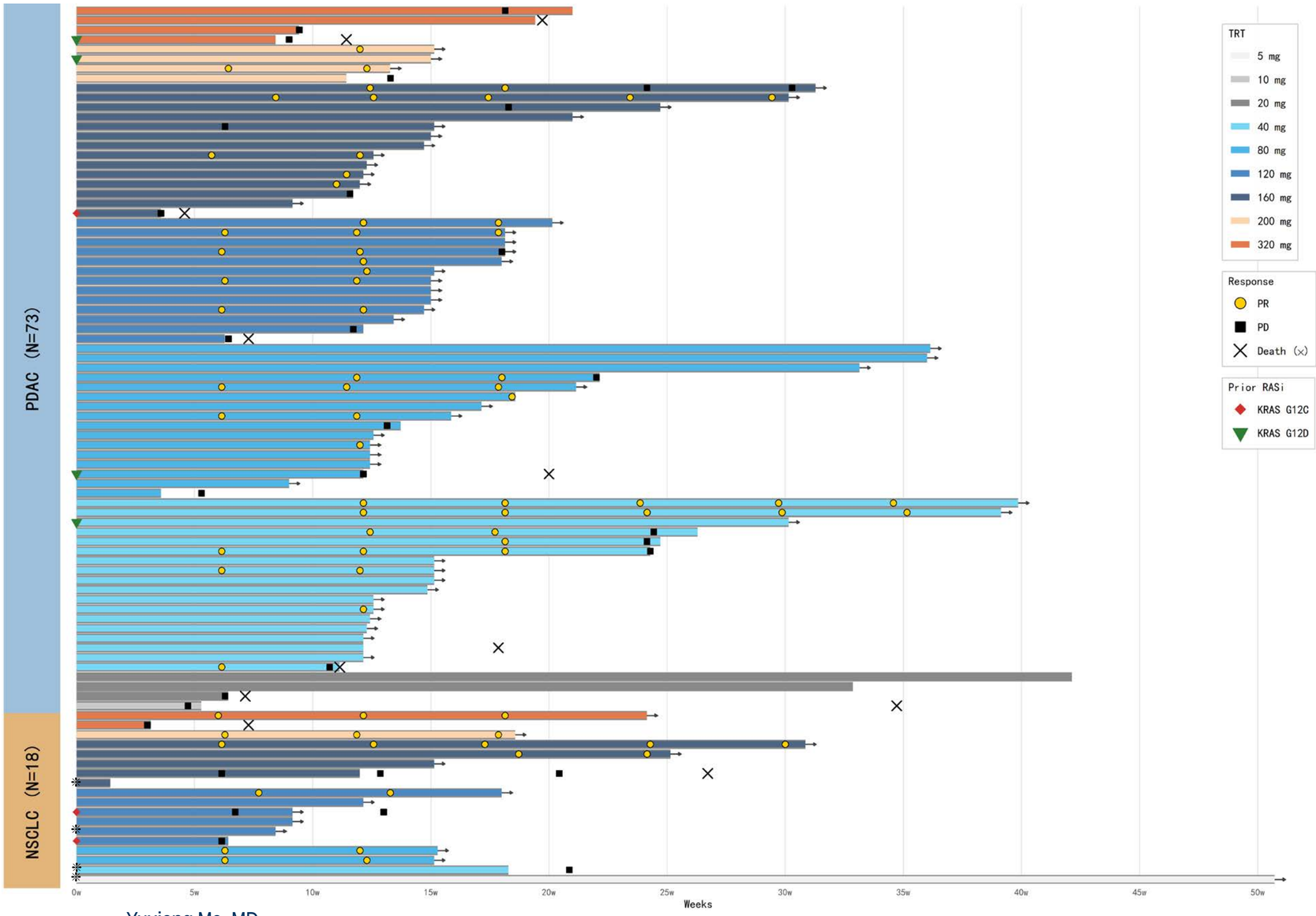
	PDAC (N=73)
Age, median (range), years	61.0 (20.0, 74.0)
≥60, n (%)	43 (58.9)
Male, n (%)	36 (49.3)
ECOG PS 0/1, n (%)	24 (32.9) / 49 (67.1)
Stage IV at study entry, n (%)	71 (97.3)
Baseline metastasis, n (%)	
Liver	57 (78.1)
Peritoneum	23 (31.5)
Lung	12 (16.4)
Bone	6 (8.2)
Number of prior lines of antitumor therapy, median (range)	2 (0, 6+)
0/1/≥2, n (%)	1 (1.4) / 19 (26.0) / 53 (72.6)
Prior antitumor therapy, n (%)	
Chemotherapy	72 (98.6)
Gemcitabine-containing	66 (90.4)
Taxane-containing	63 (78.8)
Fluorouracil-containing	57 (78.1)
Irinotecan-containing	52 (71.2)
Platinum-containing	41 (56.2)
Immune checkpoint inhibitor	24 (32.9)
RAS inhibitor	5 (6.8)



	NSCLC (N=18)
Age, median (range), years	61.5 (53.0, 72.0)
≥60, n (%)	12 (66.7)
Male, n (%)	12 (66.7)
ECOG PS 0/1, n (%)	5 (27.8)/ 13 (72.2)
Stage IV at study entry, n (%)	18 (100)
Pathological type	
Adenocarcinoma/squamous carcinoma/other	16 (88.9)/ 1 (5.6)/1 (5.6)
PD-L1 (TPS) High/intermediate/ negative/missing	4 (22.2) / 2 (11.1) / 1 (5.6) / 11 (61.1)
Baseline metastasis, n (%)	
Lung	14 (77.8)
Bone	13 (72.2)
Brain	7 (38.9)
Liver	4 (22.2)
Number of prior lines of antitumor therapy, median (range)	2 (0, 6+)
0/1/≥2, n (%)	1 (5.6) / 6 (33.3) / 11 (61.1)
Prior antitumor therapy, n (%)	
Chemotherapy	17 (94.4)
Immune checkpoint inhibitor	15 (83.3)
RAS inhibitor	2 (11.1))

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Duration of Treatment



- Median follow-up time : 18.0 weeks (range: 4.6, 50.7)
- Median duration of treatment : 15.0 weeks (range: 1.4, 50.7) .
- 63 out of 91 were still on treatment.

	PDAC	NSCLC
All	N=73	N=18
Discontinued n(%)	23 (31.5)	5 (27.8)
Disease progression	15 (20.5)	4 (22.2)
Adverse event	-	1 (5.6)
Death	5 (6.8)	-
Physician's decision	1 (1.4)	-
Patient's decision	1 (1.4)	-
Other#	1 (1.4)	-
40-160 mg	N=61	N=14
Discontinued n(%)	14 (23.0)	4 (28.6)
Disease progression	9 (14.8)	3 (21.4)
Adverse event	-	1 (7.1)
Death	4 (6.6)	-
Physician's decision	1 (1.6)	-

Data cutoff date: 15 September 2026
❊ Represents patients not evaluable for anti-tumor activity: 2 had no target lesions at baseline; 1 discontinued without post-dose tumor assessment due to an AE; 1 had no evaluable post-dose tumor assessment and was remained on treatment.
One patient in the 200 mg cohort discontinued study treatment because of fever and cholecystitis, which resulted in a treatment interruption of more than 28 days; both unrelated to GFH276.
Abbreviations: TRT, treatment. RASi, selective RAS inhibitor

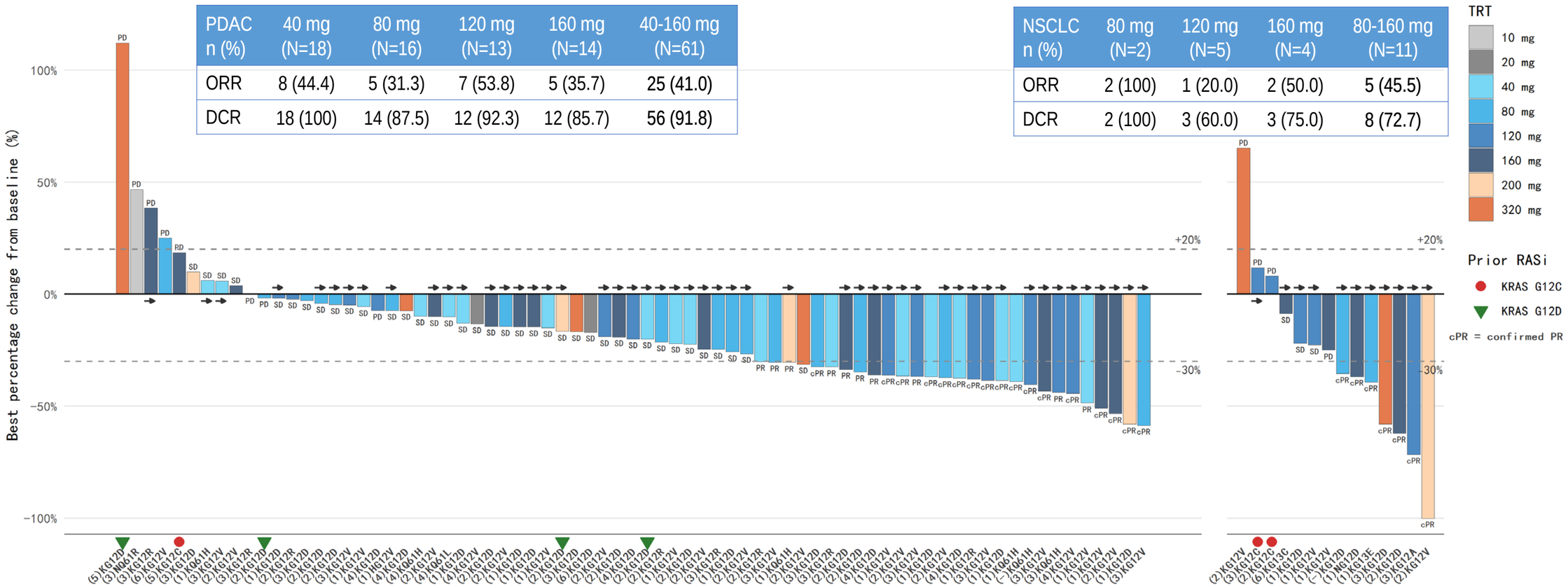
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Objective Response

- Partial responses were observed starting from the 40 mg dose cohort.
- 61 PDAC and 14 NSCLC received 40~160 mg:
  - ORR was 41.0% (25/61, 90% CI: 30.3-52.3) in PDAC, and 45.5% (5/11, 90%CI: 20.0-72.9) in NSCLC.
  - In RAS inhibitor naïve patients, ORR was 43.1% (25/58) in PDAC, and 55.6% (5/9) in NSCLC.

PDAC n (%)	40 mg (N=18)	80 mg (N=16)	120 mg (N=13)	160 mg (N=14)	40-160 mg (N=61)
ORR	8 (44.4)	5 (31.3)	7 (53.8)	5 (35.7)	25 (41.0)
DCR	18 (100)	14 (87.5)	12 (92.3)	12 (85.7)	56 (91.8)

NSCLC n (%)	80 mg (N=2)	120 mg (N=5)	160 mg (N=4)	80-160 mg (N=11)
ORR	2 (100)	1 (20.0)	2 (50.0)	5 (45.5)
DCR	2 (100)	3 (60.0)	3 (75.0)	8 (72.7)



Data cutoff date: 15 September 2026

ORR and DCR were calculated in the evaluable population, defined as patients with target lesions at baseline and at least one post-dose evaluable tumor assessment. Among the 14 NSCLC, 3 were not evaluable: 1 at 40 mg had no baseline target lesions; 1 at 120 mg had no evaluable post-dose tumor assessment but was still on treatment; 1 at 160 mg dropped out without post-dose tumor assessment due to G3 stomatitis.

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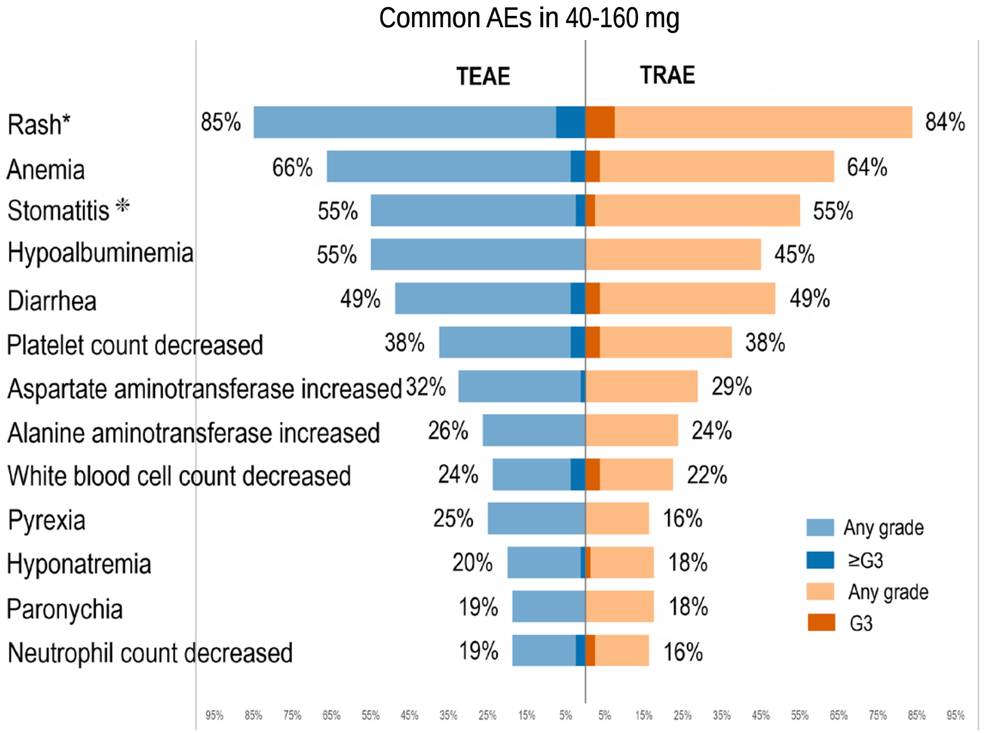
Safety Profile

- No prophylactic medications were used in the Phase Ia part.
- GFH276 is well tolerated in dose range 40-160mg QD without DLTs observed.
- The most common TRAEs were cutaneous, hematological, mucosal, and gastrointestinal, most being grade 1 or 2.
- G3 TRAEs occurred in 27.5%, most commonly rash (7.5%), followed by anemia, diarrhea, platelet count decreased, and WBC count decreased (3.8% each).
- No G4 or G5 TRAEs were observed.

n (%)	40-160 mg (N=80)*	
	Any	G3
TRAE	79 (98.8)	22 (27.5)
TRSAE	9 (11.3)	8 (10.0)
TRAE leading to death	0	0
TRAE leading to dose modifications		
Leading to interruption	18 (22.5)	11 (13.8)
Leading to dose reduction	14 (17.5)	7 (11.3)
Leading to discontinuation	1 (1.3)	1 (1.3)

Data cutoff date: 15 July 2026.
* Including 61 PDAC, 14 NSCLC, 3 CRC, and 2 others.
Median follow-up time (range) was 8.7 (4.4, 31.1) weeks. Median duration of exposure (range) was 8.4 (1.4, 31.0) weeks.

Abbreviations: TRAE, treatment-related adverse event. TRSAE, treatment-related serious adverse event. WBC, white blood cell.

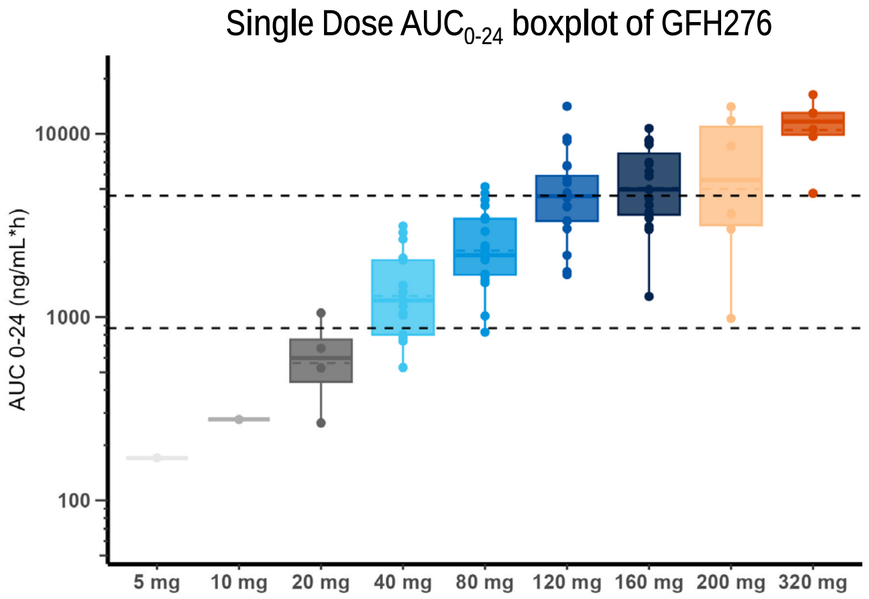


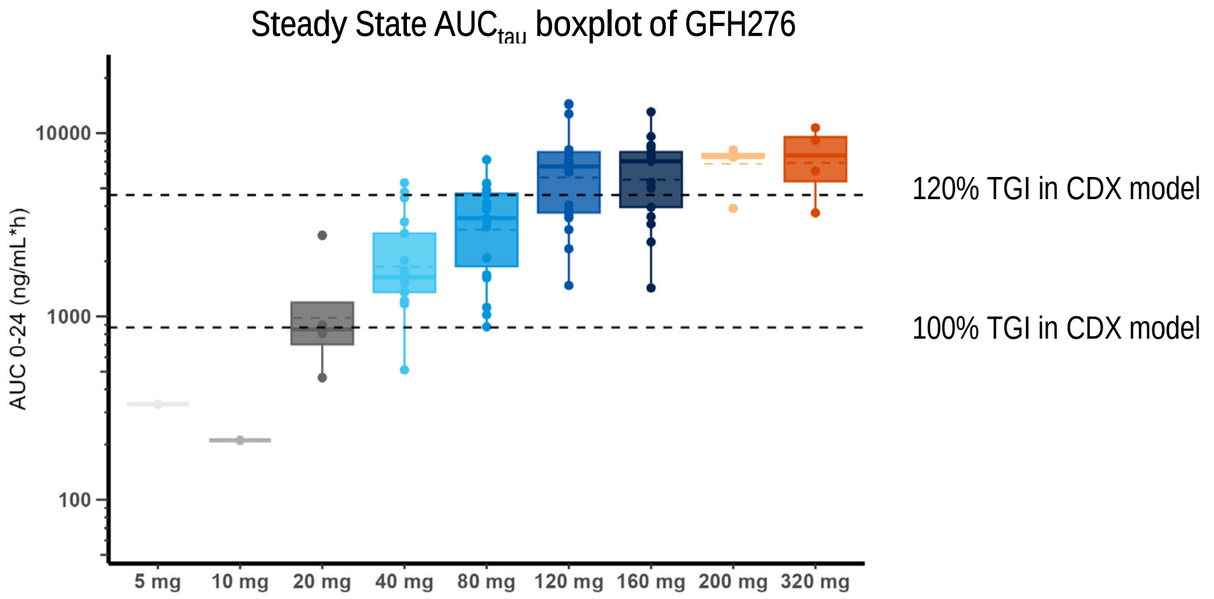
Common AEs were presented by TRAE ≥15%. No G4 or G5 TRAEs were observed.
* Pooled PTs: Rash, dermatitis acneiform, rash maculopapular, erythema nodosum, dermatitis exfoliative generalized, rash pustular, drug eruption, genital rash. Multiple types of rash may have occurred in the same patient.
* Pooled PT: Stomatitis, and mouth ulceration.

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PK Characteristics

- Approximately linear PK exposure with half-life 10.3-19.1 hours.
- No exposure plateau or significant accumulation observed.
- Exposure of 40 mg and 120 mg achieved target levels of 100% and 120% TGI in mice AsPC-1 CDX model, respectively.





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Conclusions

- GFH276 demonstrated:
  - ✓ **Favorable PK with wide therapeutic window:** PK exposure increased with tested doses of 5-320 mg.
  - ✓ **Good safety profile:** Common TRAEs were cutaneous, hematological, mucosal and gastrointestinal, most being grade 1 or 2, supporting potential combination with EGFR antibody, chemotherapy, and anti-PD-1 agents.
  - ✓ **Encouraging antitumor activity in previously treated advanced tumors across RAS mutational subtypes:**
    - ORR overall: *41.0%* in PDAC; *45.5%* in NSCLC.
    - ORR in RAS inhibitor naïve patients: *43.1%* (25/58) in PDAC; *55.6%* (5/9) in NSCLC.
- The efficacy and safety data support further clinical development as monotherapy.
- Clinical studies of combination therapies are ongoing.

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