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Efficacy and Safety of GFH375 in Advanced $KRAS^{G12D}$ Mutant Non-Small Cell Lung Cancer (NSCLC) Patients

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Disclosure

- Received speaker fees from AstraZeneca, Roche and Pfizer.

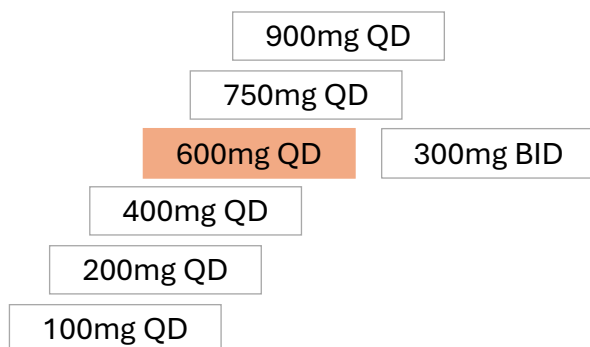
Background

- GFH375 is a potent, highly selective, orally administrated KRAS^{G12D} inhibitor that targets both the “ON” (GTP-bound) and “OFF” (GDP-bound) states.
- Preliminary clinical data of GFH375 had shown encouraging anti-tumor activity and good tolerability in NSCLC¹, PDAC², CRC and cholangiocarcinoma³ in the first-in-human study conducted in China (NCT06500676).
- Here we present the updated data of GFH375 monotherapy in KRAS^{G12D} mutant NSCLC.

Key eligibility criteria

- Advanced solid tumors with KRAS^{G12D} mutation
- Previously treated with standard therapies
NSCLC previously treated with ICI and/or platinum-based chemo therapies
- ECOG PS 0 - 1

Phase I: Dose escalation and expansion



Escalate with accelerated titration and BOIN design + backfilling

Phase II: Indication expansion

Cohort 1: NSCLC

Cohort 2: PDAC

Cohort 3: CRC

Cohort 4: Other solid tumors

Treatment until disease progression, intolerable toxicity or other reasons

Abbreviations: BID, twice daily; BOIN, Bayesian optimal interval; CRC, colorectal cancer; ECOG PS, eastern cooperative oncology group performance status; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; QD, once daily; RP2D, recommended phase 2 dose.

¹Lu S, et al. MA02.07. Journal of Thoracic Oncology, 20, S59-S60. ²Zhou A, et al. LBA84. Annals of Oncology, 36S1626. ³Zhu L, et al. J Clin Oncol 44, 3008-3008(2026).

Baseline Characteristics and Patient Disposition

- 75 patients with *KRAS*^{G12D} mutant NSCLC were treated with GFH375 600 mg once daily.
- The median prior lines of therapies was 1 (range: 1-4); all patients were pretreated with ICI and platinum; 38.7% (29/75) were pretreated with taxane.
- 29 (38.7%) patients were ongoing. The longest follow-up was 22.1 months.

	All NSCLC (n=75)
Discontinued n(%)	46 (61.3)
Disease progression	30 (40.0)
Adverse event	6 (8.0)
Death	2 (2.7)
Global deterioration of health	2 (2.7)
Physician's decision	3 (4.0)
Patient's decision	3 (4.0)

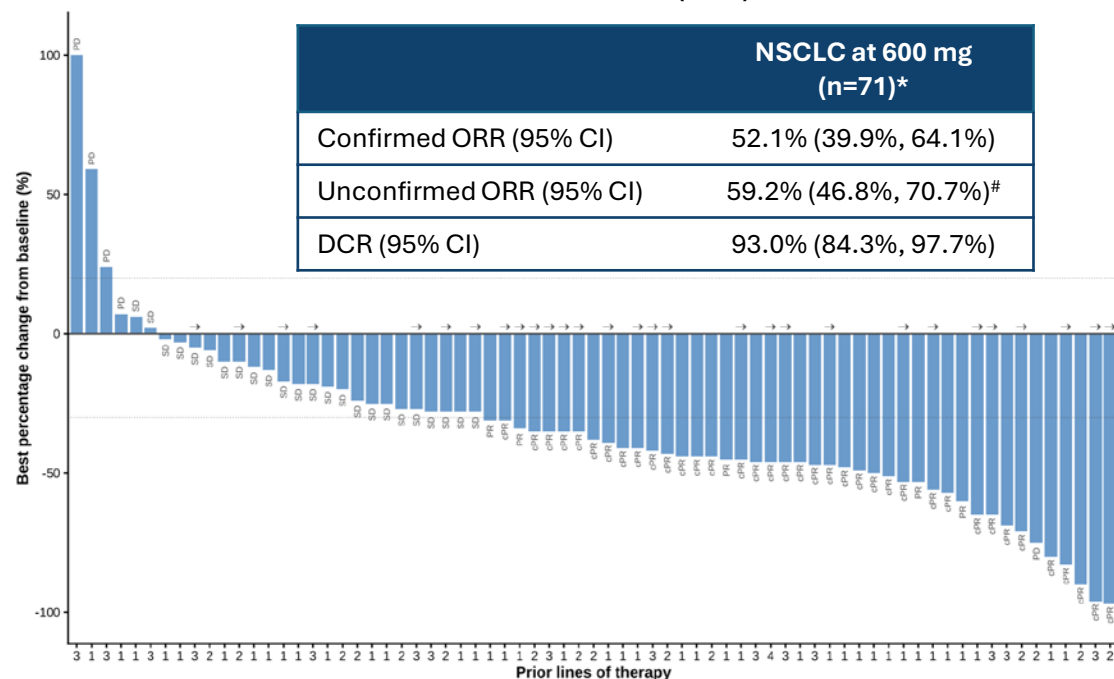
Data cut-off date: 04 Sep 2026.

Percentage denominator is 54. * A neoadjuvant and adjuvant therapy would be counted as a line of system therapy if patient relapsed or progressed during treatment or within 6 months of last dose.

	NSCLC at 600 mg (n=75)
Age, median (range), years	62 (21-74)
Female, n(%)	27 (36.0)
Smoking status, n(%)	
Current or former	36 (48.0)
Never	39 (52.0)
ECOG PS, n(%)	
1	66 (88.0)
Pathology, n(%)	
Adenocarcinoma	70 (93.3)
Squamous cell carcinoma	3 (4.0)
Adenosquamous carcinoma	2 (2.7)
Baseline metastasis, n(%)	74 (98.7)
Bone	28 (37.3)
Brain	12 (16.0)
Liver	10 (13.3)
PD-L1 TPS, n(%)	
Known	54 (72.0)
< 1%	27 (50.0) [#]
1-49%	19 (35.2) [#]
≥ 50%	8 (14.8) [#]
Prior lines of therapies, median (range)*	1 (1-4)
1	43 (57.3)
≥2	32 (42.7)
Prior ICI, n(%)	75 (100)
Prior platinum, n(%)	75 (100)
Prior ICI+platinum concurrent, n(%)	68 (90.7)
Prior taxane, n(%)	29 (38.7)

Objective Response

- Among the 71 patients with at least one post-treatment efficacy evaluation, ORR was 59.2% (42/71), confirmed ORR was 52.1% (37/71).
- Among the 9 patients with brain metastases and at least one post-treatment evaluation, ORR was 55.6% (5/9)[&].
- Median (range) time to response: 1.4 months (1.4-8.3 months)
- Median duration of response: 8.3 months (95% CI: 6.3, NA)



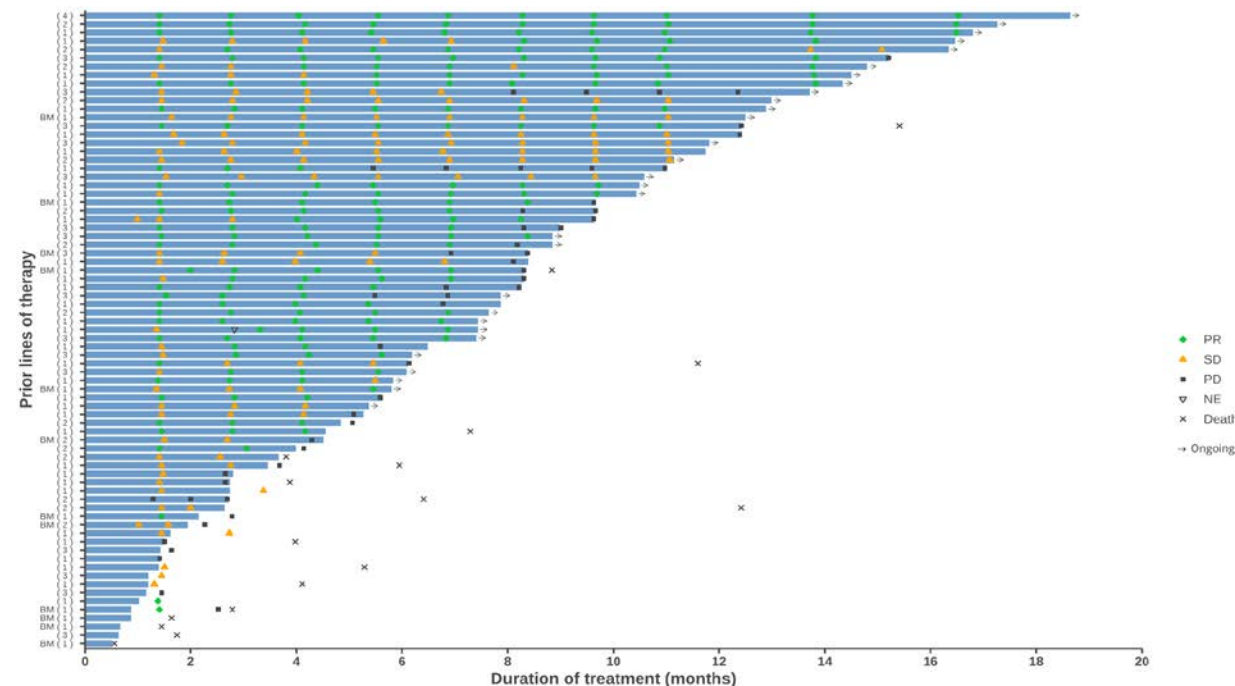
Data cut-off date: 04 Sep 2026.

* Four patient dropped out early without post-baseline tumor assessment (2 due to death, 1 due to patient's global deterioration of health, and 1 due to physician's decision), 3 among whom had baseline brain metastases.

[#] One was ongoing and pending for confirmed PR. Four patients achieved PR but discontinued before response confirmation: 1 dropped out due to AE (G4 hepatic function abnormal and recovered after discontinuation), 2 had disease progression at the second assessment, and 1 had stable disease at the later assessments.

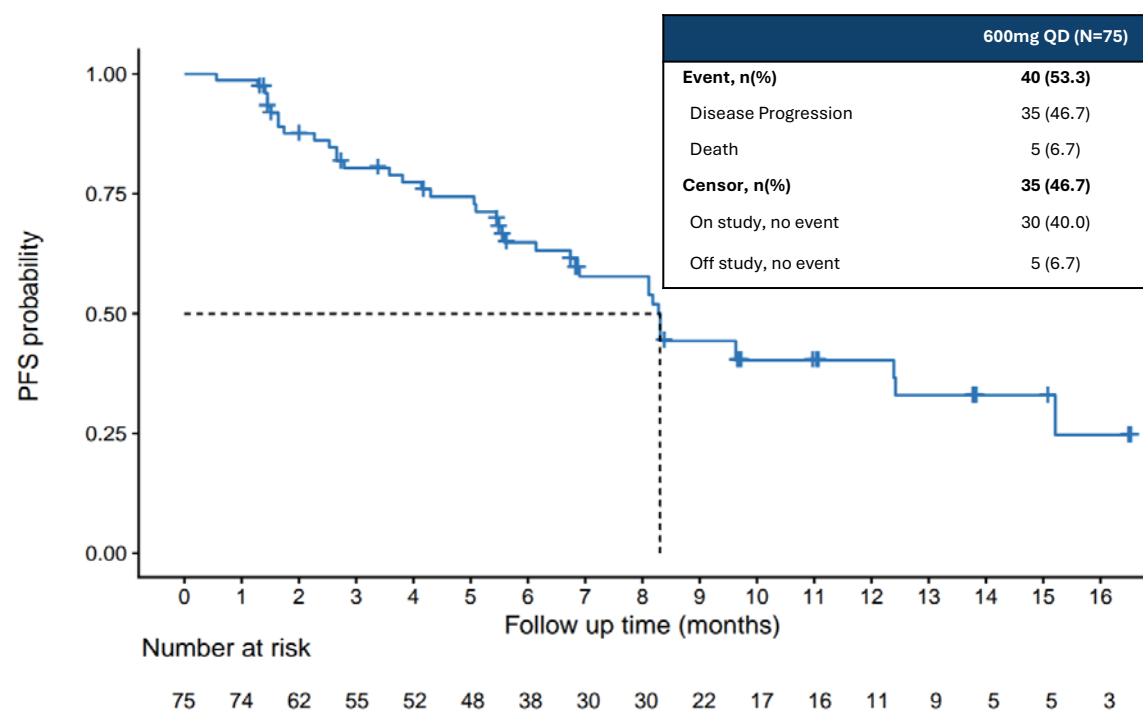
[&] No cerebral metastatic lesions were chosen as target lesions among the patients.

Abbreviation: BM, brain metastases; CI, confidence interval; cPR, confirmed partial response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

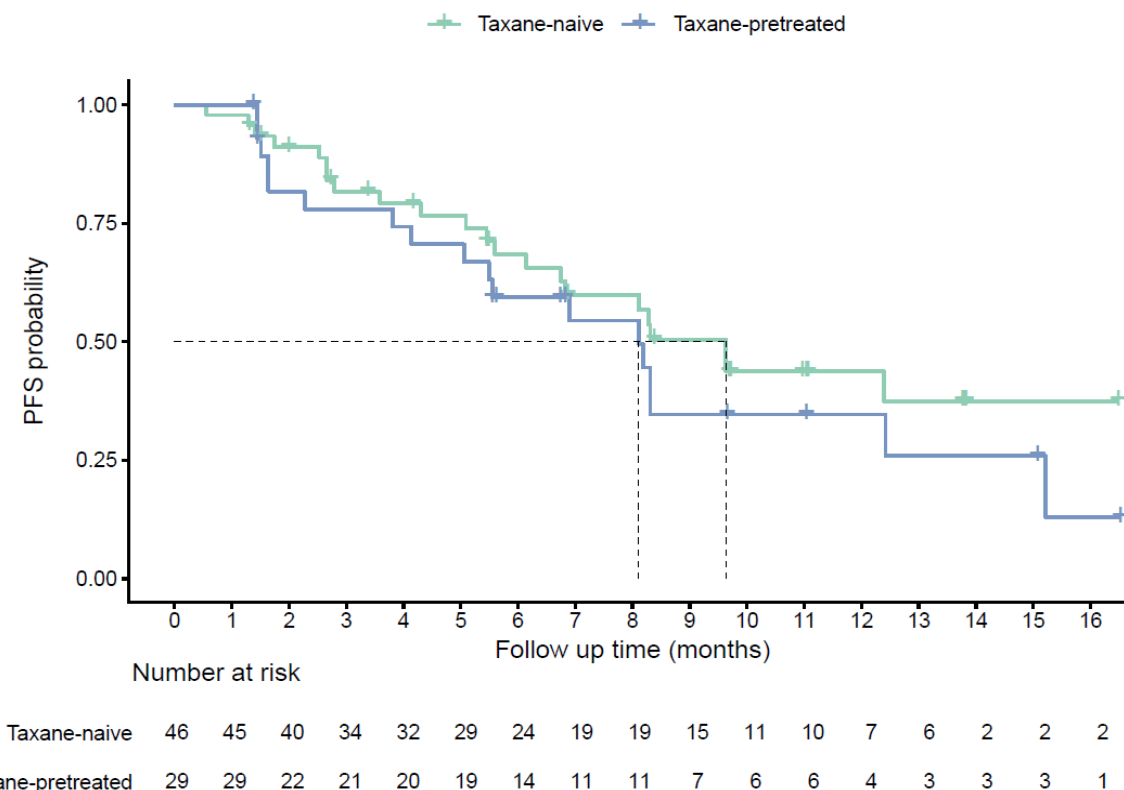


PFS and OS

- Median PFS was 8.3 months (95% CI: 6.8, NA) with median follow-up time 11.0 months.
 - Among taxane-naïve patients, median PFS was 9.6 months (95% CI: 6.7, NA)
 - Among taxane-pretreated patients, median PFS was 8.1 months (95% CI: 5.5, NA)
- Median OS was not reached (95% CI: 15.4 m, NA) with median follow-up time 11.2 months. 12-months OS rate was 77.0% (95% CI: 66.9%, 88.7%).



Data cut-off date: 04 Sep 2026.

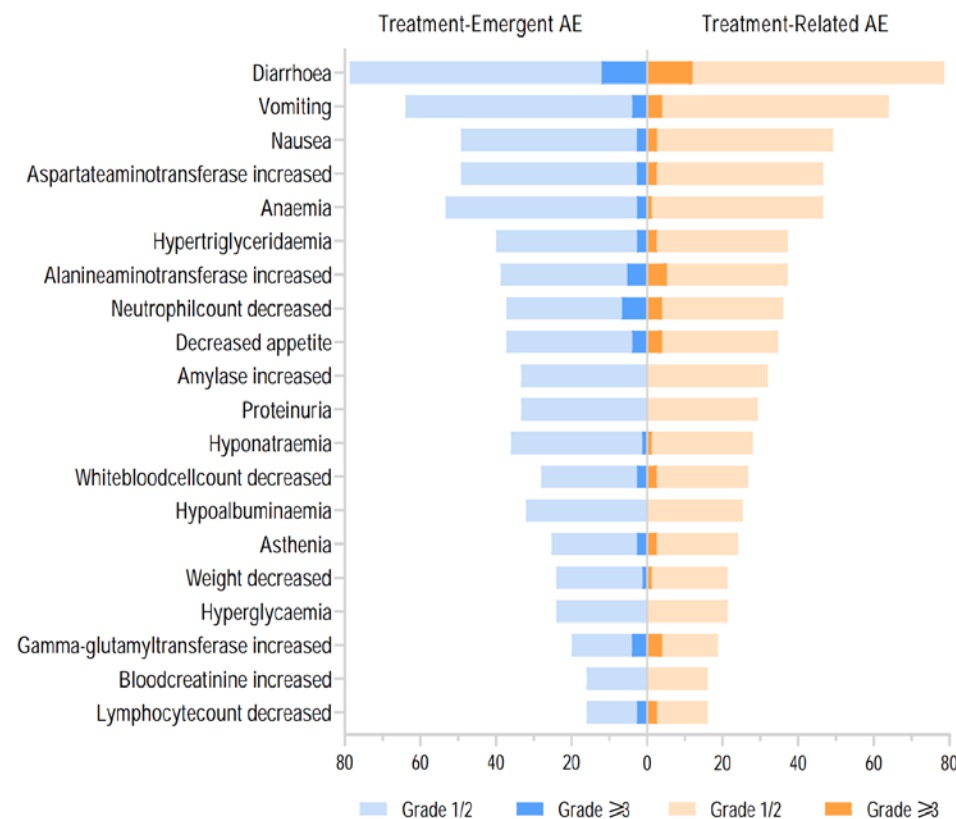


Safety in Patients with NSCLC

- GFH375 presented a manageable safety profile in pretreated NSCLC patients.
- The safety profile was consistent with prior reports¹⁻³, without new safety signals.
- Common TRAEs were gastrointestinal, hematological AEs and transaminitis; most were grade 1 or 2 and recovered with supportive treatment.

Adverse events, n(%)	600 mg QD (N=75)
TEAEs	
All grades	75 (100)
Grade ≥3	42 (56.0)
Leading to discontinuation	6 (8.0)
Leading to reduction	19 (25.3)
Leading to interruption	33 (44.0)
SAE	27 (36.0)
Leading to death	5 (6.7)
TRAEs	
All grades	75 (100)
Grade ≥3	31 (41.3)
Leading to discontinuation	3 (4.0)
Leading to reduction	19 (25.3)
Leading to interruption	28 (37.3)
SAE	16 (21.3)
Leading to death	0

Data cut-off date: 17 June 2026.



TEAEs and TRAEs occurred in ≥15% of patients

The median exposure time to GFH375 in all NSCLC patients at 600 mg was 5.3 months (range: 0.5-16.1) by the cut-off date. The mean relative dose intensity was 89.8%.

Abbreviations: SAE, serious adverse event; TEAE, treatment emergent adverse event; TRAE, treatment related adverse event.

¹Lu S, et al. MA02.07. Journal of Thoracic Oncology, 20, S59-S60. ²Zhou A, et al. LBA84. Annals of Oncology, 36S1626. ³Zhu L, et al. J Clin Oncol 44, 3008-3008(2026).

Prior Exposure to ICIs Affected Safety and Tolerability

Patients receiving anti-PD1/PD-L1 therapy within 90 days before first dosing of GFH375 showed poorer safety and tolerability:

- Higher rates of hepatotoxicity
- Higher rates of grade ≥ 3 hepatotoxicity and diarrhea

Adverse events, n(%)	ICIs 28~90 days* (n=48)	ICIs >90 days (n=27)
TRAEs		
All grades	48 (100)	27 (100)
Grade ≥ 3	25 (52.1)	6 (22.2)
Leading to discontinuation	3 (6.3)	0
Leading to reduction	15 (31.3)	4 (14.8)
Leading to interruption	21 (43.8)	7 (25.9)
SAE	12 (25)	4 (14.8)
Hepatotoxicity (all grades/$\geq G3$)[#]	30 (62.5)/8 (16.7)	12 (44.4)/0
AST increased	26 (54.2)/2 (4.2)	9 (33.3)/0
ALT increased	23 (47.9)/4 (8.3)	5 (18.5)/0
Blood bilirubin increased	5 (10.4)/0	1 (3.7)/0
Diarrhea (all grades/$\geq G3$)	37 (77.1)/7 (14.6)	22 (81.5)/2 (7.4)

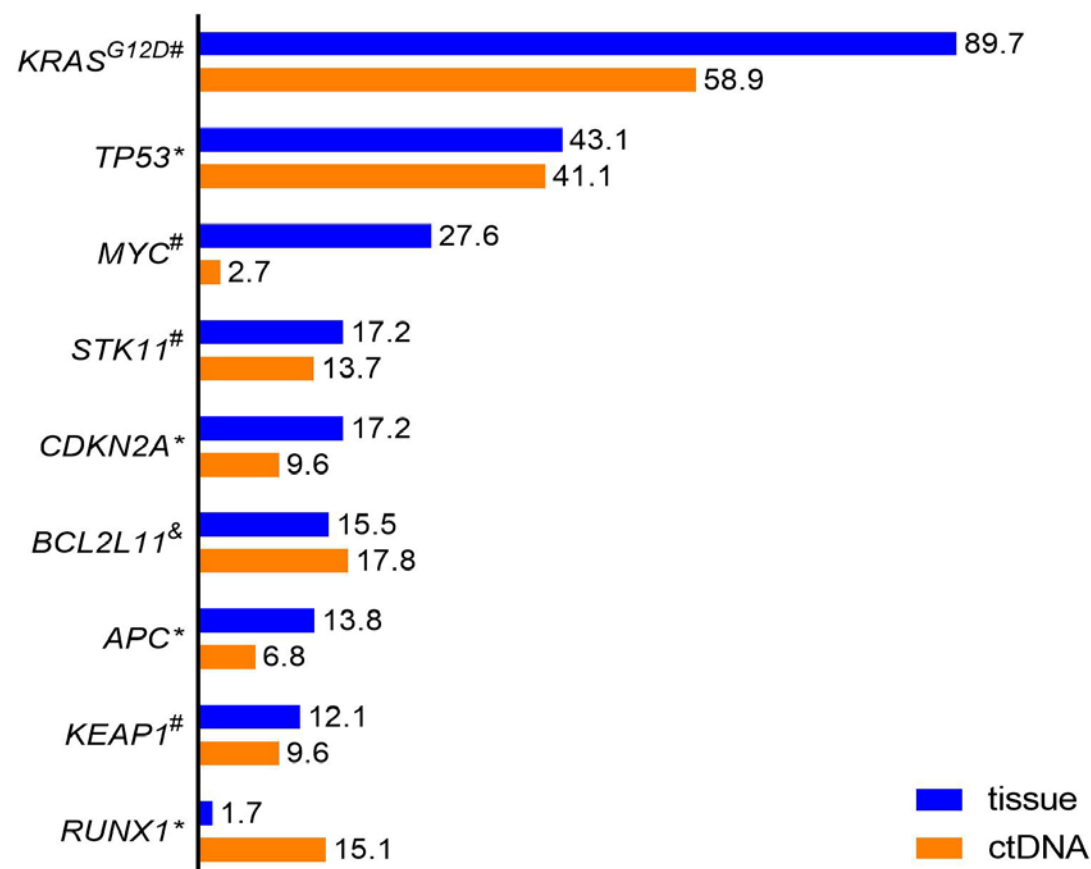
* Patients shall not receive PD-1 or PD-L1 antibodies within at least 28 days prior to the first dose administration per protocol.

[#] Included prefer terms: AST increased, ALT increased, blood bilirubin increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, hepatic function abnormal and liver injury.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; G3, grade 3.

Cooccurring Genetic Alterations in Tissue and ctDNA

- Eligibility based on local tissue/ctDNA results; centrally tested tissue (archival or screening biopsy) and ctDNA samples (blood collected at screening or C1D1).
- Central testing of baseline tissue samples were available for 58 patients and ctDNA samples for 73 patients.
- *KRAS*^{G12D} was detectable in 89.7% (52/58) of tissue and 58.9% (43/73) of ctDNA.
- The common cooccurring genetic alterations in both tissue and ctDNA were *TP53*, *STK11*, *CDKN2A*, *BCL2L11*, and *KEAP1*.

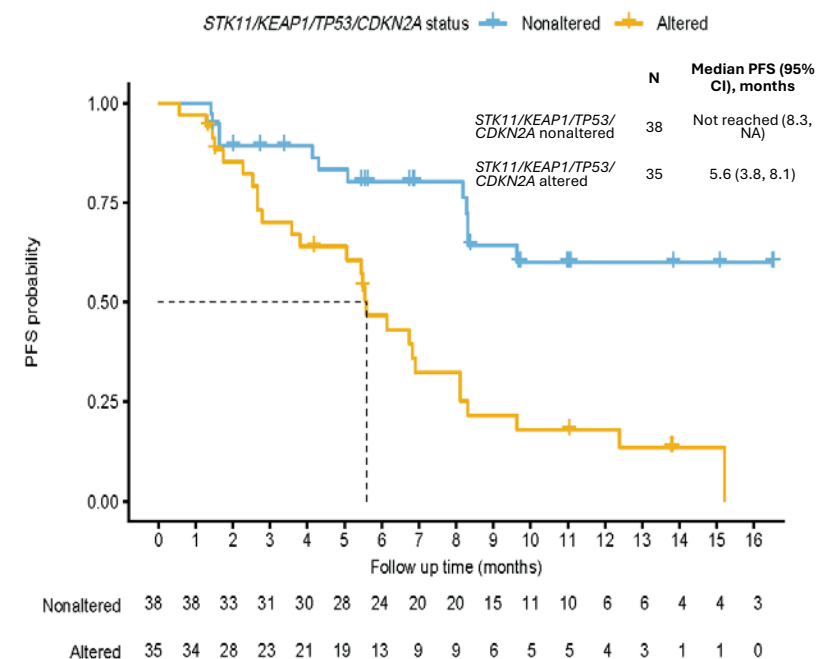
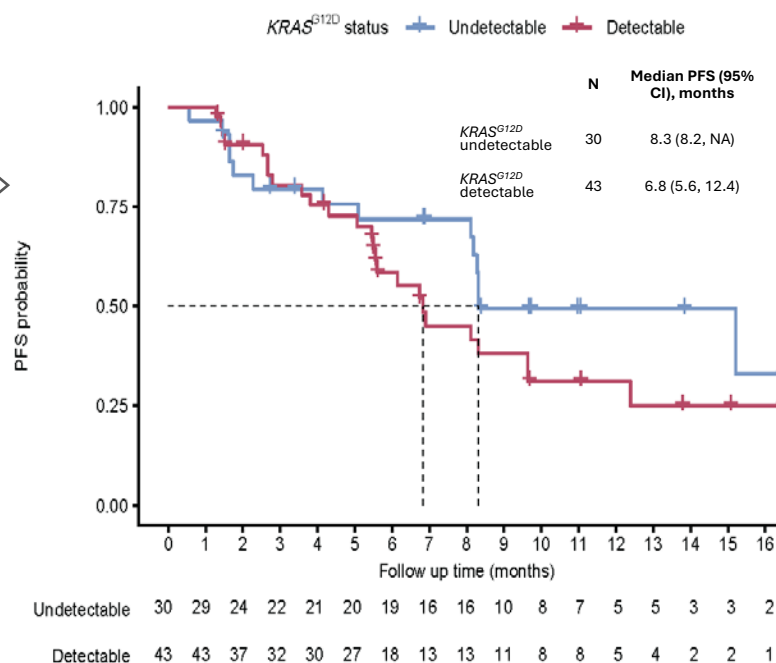
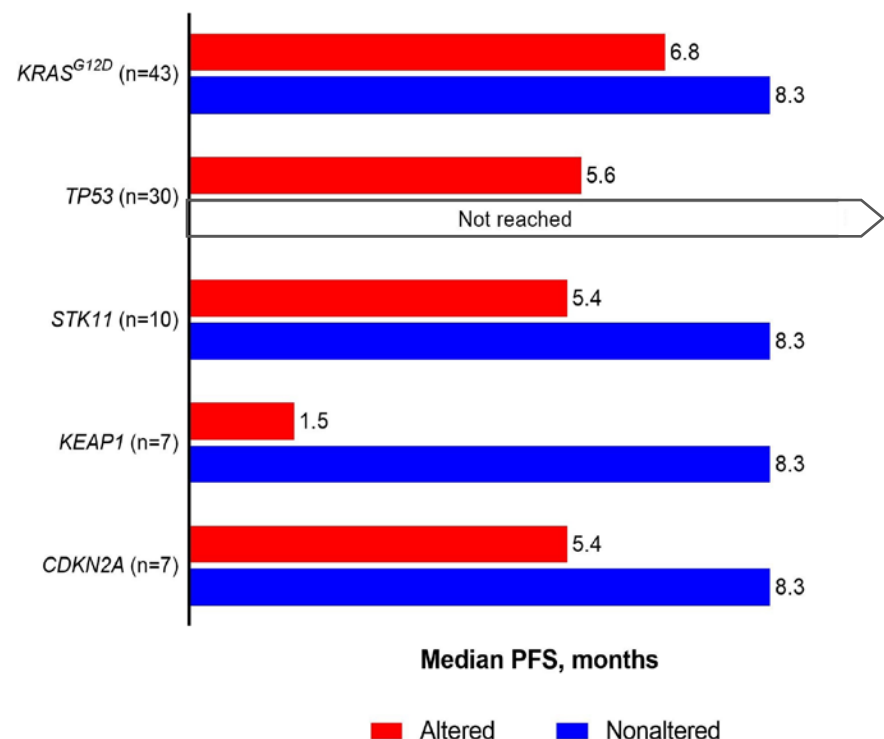


Genes frequency in tissue and ctDNA

* Somatic alterations or germline alterations; # Somatic alterations solely; & Germline alterations solely.

Genetic Alterations in ctDNA vs. PFS

- Patients with detectable *KRAS*^{G12D}, *TP53*, *STK11*, *KEAP1* or *CDKN2A* alterations presented shorter PFS.

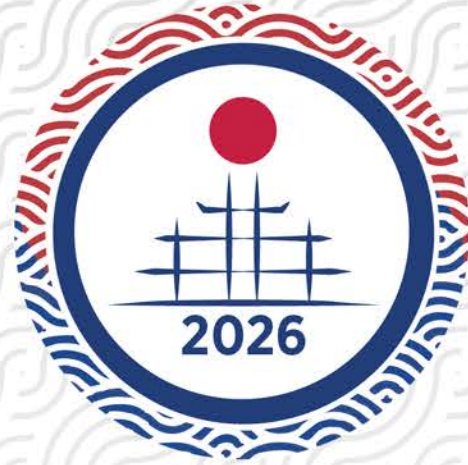


Conclusion

- GFH375 monotherapy presented encouraging anti-tumor activity in previously treated *KRAS*^{G12D} mutant NSCLC:
 - **52.1% confirmed ORR** in NSCLC patients treated at 600 mg QD
 - **8.3 months of median PFS** among all patients and **9.6 months among taxane-naïve patients**
 - **Median OS not reached** with 77.0% of 12-months OS rate
- GFH375 was well tolerated in previously treated patients with NSCLC; no new safety signals were identified.
- The data support further development of GFH375 as monotherapy for previously treated patients with *KRAS*^{G12D} mutant NSCLC.
- Phase III trial of GFH375 monotherapy vs. Docetaxel for pretreated NSCLC (NCT07668752) and phase II trial of combination therapies for treatment-naïve NSCLC patients (NCT07554859) are currently recruiting.

Acknowledgements

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Thank You.●