

Glecirasib (KRAS G12C Inhibitor) in Combination with JAB-3312 (SHP2 Inhibitor) in Patients with KRAS p.G12C Mutated Solid Tumors

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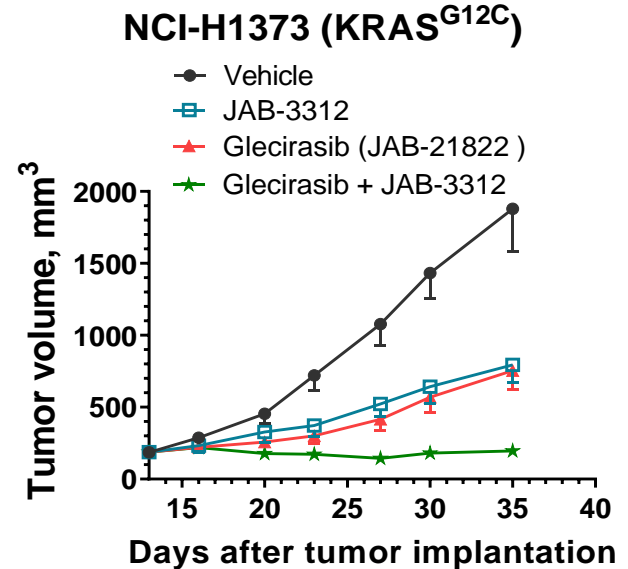
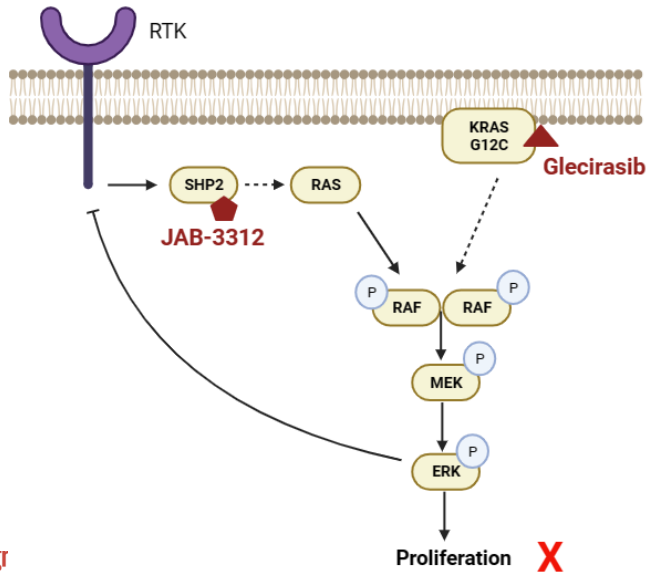
Declaration of Interests

Jie Wang

I confirm that I have no conflicts of interest to declare.

Background

- SHP2 lies downstream of receptor tyrosine kinase (RTK) and plays a positive regulatory role upstream of RAS, sustaining RAS/ERK pathway activity.
- Synergistic effects were observed when combining the KRAS G12C inhibitor (Glecirasib) and SHP2 inhibitor (JAB-3312) in preclinical xenograft models.



Background

- **Glecirasib** is a highly selective covalent oral KRAS G12C inhibitor.
 - Promising preliminary activity with a well tolerated safety profile was reported at the 2022 ASCO.
 - Recommended phase 2 dose was 800mg QD.
 - Pivotal trials for NSCLC and PDAC are ongoing in China.
 - Multiple glecirasib-based combinations are being explored in the clinical space.
- **JAB-3312** is a potent oral allosteric SHP2 inhibitor with best-in-class potential.
 - Safety and efficacy studies are ongoing in the US, Europe and China.
 - Recommended phase 2 dose was 4mg QD.
 - Common adverse events of JAB-3312 include CPK increased, PLT count decreased, AST/ALT increased, WBC/Neutrophil count decreased, anemia, edema, and rash.

Study Design

Phase 1/2a [NCT05288205]

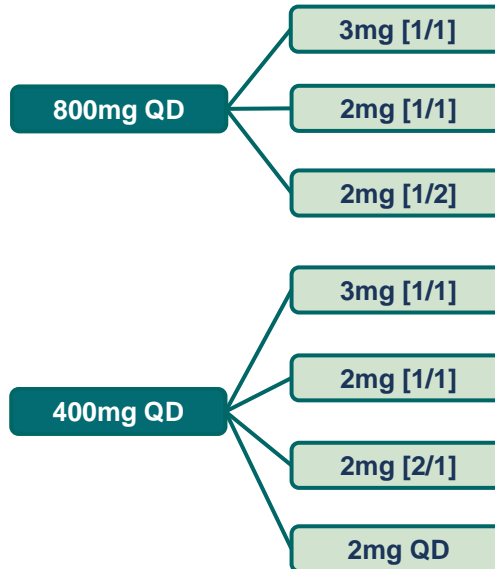
Key eligibility criteria

- Locally advanced or metastatic advanced solid tumors harboring KRAS p.G12C mutation who have failed or lack SOC or are unwilling to undergo or intolerant to SOC
- At least one measurable lesion as defined by RECIST v1.1
- ECOG 0-1
- No active brain metastases

Dose exploration/optimization

- Primary objective: Safety and tolerability
- Secondary objective: Efficacy, PK

Glecirasib + JAB-3312



Dose expansion

- Primary objective: Efficacy
- Secondary objective: Safety and tolerability

Cohort 1-NSCLC

- Previously untreated with KRAS G12C inhibitor
- Previously received ≤ 2 lines of systemic therapy

Cohort 2-NSCLC

- Previously treated with KRAS G12C inhibitor
- Previously received ≤ 3 lines of systemic therapy

Cohort 3-Other solid tumors

- No previous use of KRAS G12C inhibitor

Patient Baseline Characteristics

	All tumors (N=144)
Median age, years (range)	64 (28-84)
Male, n (%)	107 (74.3%)
Race	
Asian	144 (100%)
ECOG PS, n (%)	
0	35 (24.3%)
1	109 (75.7%)
Tumor type, n(%)	
NSCLC	129 (89.6%)
Naïve to KRAS G12C inhibitor	103 (71.5%)
0 line of prior systemic therapy	69 (47.9%)
≥ 1 line of prior systemic therapy	34 (23.6%)
Prior treated with KRAS G12C inhibitor	26 (18.1%)
CRC	14 (9.7%)
PDAC	1 (0.7%)
Stage at study entry, n (%)	
III	8 (5.6%)
IV	136 (94.4%)
Median lines of prior therapy, n (range)	1 (0-8)

- Data cut-off : August 4, 2023. Median follow-up: 3.3 months (range, 0.1-14.9). 106 (73.6%) patients remained on treatment.

Safety Overview

- Across all dosage groups, 92.4% (133/144) of patients experienced at least one treatment-related adverse event (TRAE*), and 39.6% (57/144) of patients experienced at least one TRAE of grade 3 or grade 4. No grade 5 (fatal) TRAE occurred.
- TRAEs (>20%) included hypertriglyceridemia, anemia, ALT/AST increased, bilirubin increased, CPK increased, neutropenia/leukopenia, edema, and weight increased. One dose-limiting toxicity (grade 3 pneumonitis) was observed at the highest dose level of glecirasib 800mg QD +JAB-3312 3mg [1/1].
- To better optimize dose/schedule and explore efficacy, additional patients were enrolled in the three groups below.

Glecirasib JAB-3312	400mg QD		800mg QD
	2mg [1/1]	3mg [1/1]	2mg [1/1]
Patients enrolled**	(N=35)	(N=30)	(N=49)
TRAE	34 (97.1%)	28 (93.3%)	45 (91.8%)
Grade 3 or 4 TRAE	17 (48.6%)	10 (33.3%)	18 (36.7%)
SAE (related to treatment)	4 (11.4%)	1 (3.3%)	3 (6.1%)
TRAE leading to glecirasib discontinuation	0	0	1 (2.0%)
TRAE leading to JAB-3312 discontinuation	4 (11.4%)	1 (3.3%)	1 (2.0%)

*related to either or both drugs. **Including all tumor types.

Treatment-related Adverse Events (incidence ≥10%)

Glecirasib JAB-3312	400mg QD				800mg QD	
	2mg [1/1]		3mg [1/1]		2mg [1/1]	
	(N=35)		(N=30)		(N=49)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypertriglyceridemia	19 (54.3%)	6 (17.1%)	13 (43.3%)	3 (10.0%) ^[a]	34 (69.4%)	10 (20.4%) ^[a]
Anemia	14 (40.0%)	0	15 (50.0%)	1 (3.3%)	24 (49.0%)	2 (4.1%)
Blood bilirubin increased	11 (31.4%)	0	9 (30.0%)	0	19 (38.8%)	1 (2.0%) ^[c]
AST increased	19 (54.3%)	2 (5.7%)	16 (53.3%)	0	18 (36.7%)	0
Blood CPK increased	9 (25.7%)	2 (5.7%)	7 (23.3%)	2 (6.7%)	17 (34.7%)	0
ALT increased	16 (45.7%)	3 (8.6%) ^[b]	13 (43.3%)	0	16 (32.7%)	1 (2.0%)
Neutropenia	11 (31.4%)	1 (2.9%)	9 (30.0%)	0	15 (30.6%)	3 (6.1%) ^[d]
WBC decreased	10 (28.6%)	1 (2.9%)	4 (13.3%)	0	12 (24.5%)	2 (4.1%)
Edema	11 (31.4%)	1 (2.9%)	11 (36.7%)	1 (3.3%)	11 (22.4%)	0
Weight increased	10 (28.6%)	0	6 (20.0%)	0	11 (22.4%)	0
Bilirubin conjugated increased	3 (8.6%)	0	3 (10.0%)	0	8 (16.3%)	0
Thrombocytopenia	2 (5.7%)	0	7 (23.3%)	0	6 (12.2%)	1 (2.0%)
Diarrhea	5 (14.3%)	2 (5.7%)	3 (10.0%)	1 (3.3%)	5 (10.2%)	1 (2.0%)
Blood creatinine increased	5 (14.3%)	0	2 (6.7%)	0	4 (8.2%)	0

[a] One patient with grade 4 hypertriglyceridemia in each group. [b] One patient with grade 4 ALT increased. [c] One patient with grade 4 blood bilirubin increased. [d] Two patients with grade 4 neutropenia.

Efficacy in NSCLC

- Out of 129 NSCLC patients, 107* had at least one assessment scan. ORR was 51.4% (55/107) and DCR was 91.6% (98/107).
 - Out of 20 evaluable NSCLC patients received prior KRAS G12Ci, one PR and 10 SD were observed.
 - In KRAS G12Ci naïve NSCLC patients, ORR was 62.1% (54/87) and DCR was 100%.

KRAS G12Ci naïve NSCLC	All dosage groups	In the frontline setting	In the second and later setting
	(N=87)	(N=58)	(N=29)
Objective response rate ^[a] , n (%)	62.1%	65.5%	55.2%
95% CI ^[b]	(51.0, 72.3)	(51.9, 77.5)	(35.7, 73.6)
Disease control rate, n (%)	100%	100%	100%
95% CI	(95.8, 100.0)	(93.8, 100.0)	(88.1, 100.0)

[a] Assessed by investigator per RECIST v1.1; [b] Exact 95% CI is calculated using the Clopper Pearson method

- ORR includes both confirmed and unconfirmed PRs, as the follow-up period was short that most patients were still receiving treatment at the time of data cut-off date.
- *Twenty-two patients have no efficacy results, including 18 who have not yet reached the first scan, two who died before the first scan, one withdrew consent, and one withdrew due to COVID-19.

Efficacy in NSCLC in the Frontline Setting

Glecirasib (800mg QD) + JAB-3312 2mg [1/1] resulted in the ORR of 86.7% in the frontline setting.

Glecirasib	400mg QD		800mg QD
	2mg [1/1]	3mg [1/1]	2mg [1/1]
In the frontline setting	(N=18)	(N=16)	(N=15)
Best overall response, n (%) ^[a]			
Complete Response (CR)	0	0	0
Partial Response (PR)	10 (55.6%)	8 (50.0%)	13 (86.7%)
Stable Disease (SD)	8 (44.4%)	8 (50.0%)	2 (13.3%)
Progressive Disease (PD)	0	0	0
Objective response rate, n (%)	10 (55.6%)	8 (50.0%)	13 (86.7%)
95% CI ^[b]	(30.8, 78.5)	(24.7, 75.3)	(59.5, 98.3)
Disease control rate, n (%)	18 (100%)	16 (100%)	15 (100%)
95% CI ^[b]	(81.5, 100.0)	(79.4, 100.0)	(78.2, 100.0)

[a] Assessed by investigator per RECIST v1.1; [b] Exact 95% CI is calculated using the Clopper Pearson method

- ORR includes both confirmed and unconfirmed PRs, as the follow-up period was short that most patients were still receiving treatment at the time of data cut-off date.

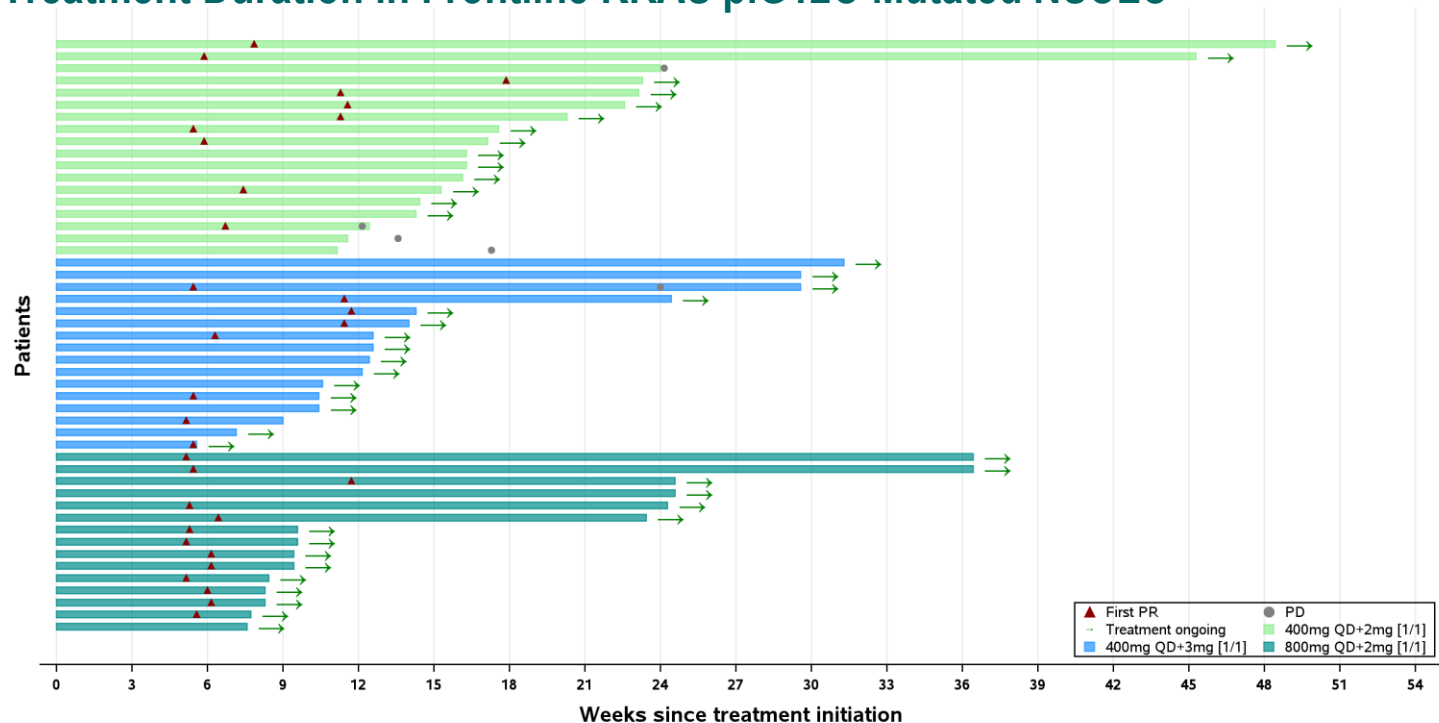
Best Tumor Change from Baseline in Frontline KRAS p.G12C Mutated NSCLC



PR*: confirmed PR

- Tumor shrinkage was observed in 96% (47/49) of patients across these three dosage groups.
- ORR was 55.6%, 50%, and 86.7% for the 400mg QD +2mg [1/1], 400mg QD +3mg [1/1], and 800mg QD +2mg [1/1] dose groups, respectively.

Treatment Duration in Frontline KRAS p.G12C Mutated NSCLC



- As of the data cut-off, 90% (44/49) of patients in these three dosage groups were still on treatment.
- The median time-to-response across these three dosage groups was 1.4 (1.2-4.1) months.

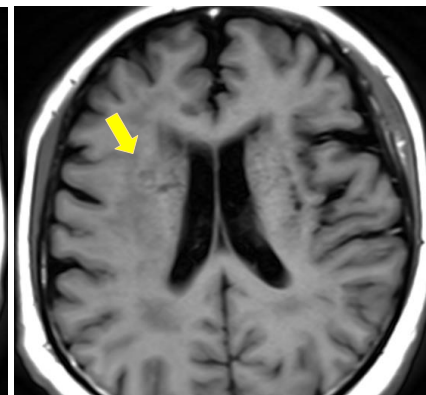
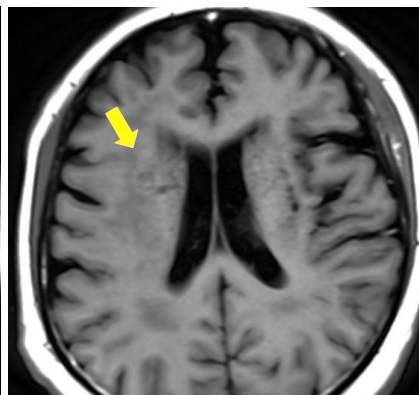
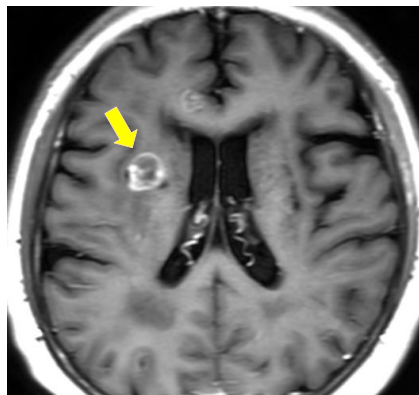
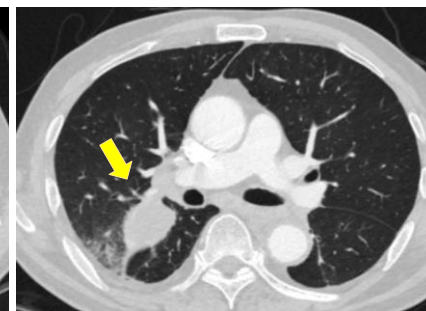
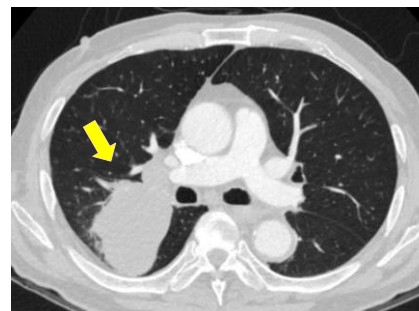
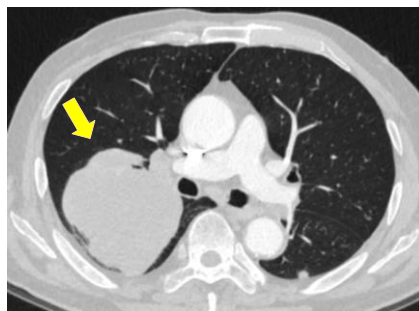
Patient Case

Medical history:

- In Feb of 2023, a 77-year-old male was diagnosed with NSCLC with KRAS G12C mutation with metastases in both lungs, mediastinal lymph nodes, brain, and bone.
- He declined standard frontline treatment and requested to participate clinical trial.

Gleceirasib + JAB-3312 study

- On Apr 4, 2023, C1D1 Gleceirasib (400mg QD) + JAB-3312 (2mg [1/1]) was initiated.
- Images after 2 cycles showed PR (-42.7%) per RECIST, and his brain metastases also shrank significantly.
- The patient has tolerated the treatment well while maintaining PR.
- Currently the patient is in cycle 6.
- No \geq Grade 3 TRAEs or dose modification were observed.



Baseline
Mar 31, 2023

After 2 cycles
May 11, 2023

After 4 cycles
Jun 27, 2023

Summary

- Glecirasib plus JAB-3312 has a manageable safety profile.
 - ◆ The incidence of grade 3 or 4 TRAEs is 39.6% of all dose levels and 36.7% for glecirasib (800mg QD) + JAB-3312 2mg [1/1], respectively.
 - ◆ No grade 5 TRAE was seen.
 - ◆ No new safety signals were identified compared to glecirasib and JAB-3312 as monotherapy.
- Glecirasib plus JAB-3312 has demonstrated promising efficacy in KRAS p.G12C NSCLC.
 - ◆ In frontline NSCLC, the ORR of all dose cohorts was 65.5% and DCR was 100%.
 - ◆ Glecirasib (800mg QD) + JAB-3312 2mg [1/1] dosage yielded ORR of **86.7%** (13/15) and DCR of 100%.
 - ◆ Biomarkers exploration are ongoing.
 - ◆ Median PFS and DOR have not been reached.

Acknowledgements

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