Efficacy of Glecirasib in Combination with JAB-3312 as a Front-line Treatment for Patients with KRAS p.G12C mutated NSCLC with PD-L1 Expression Levels or Co-mutations.

FPN: 1261P

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Background

- The combination of glecirasib (KRAS G12C inhibitor) and JAB-3312 (SHP2 inhibitor) demonstrated a favorable safety profile and promising efficacy as a front-line treatment for non-small cell lung cancer (NSCLC) patients with KRAS G12C mutations.
- As presented at ASCO 2024[1], 102 front-line NSCLC patients were enrolled by April 7, 2024.
  - The incidence of grade 3 or 4 Treatment-related adverse events (TRAE) is 43.8% in the front-line NSCLC. No grade 5 TRAE was seen.
  - Confirmed objective response rate (ORR) was 64.7% and the preliminary median progression-free survival (mPFS) was 12.2 months (95% CI: 7.4, NE) in 102 front-line NSCLC patients.
- Currently, the standard of care of front-line treatment for NSCLC harboring KRAS G12C mutation is chemo-immunotherapy, which is the same as for NSCLC without driver mutations.

Table 1 Efficacy data from KEYNOTE-189 study[2]

Study	N	PD-L1 TPS	ORR	mPFS (months) 95% CI	12m-PFS rate
KEYNOTE-189 study[2] Pembrolizumab + pemetrexed + platinum in non-squamous NSCLC	410	All	48.3%	9 (8.1,10.4)	39.4%
	132	≥ 50%	62.1%	11.1 (9.2,16.5)	48.8%
	128	1-49%	50.0%	9.4 (8.1,13.8)	43.8%
	127	< 1%	33.1%	6.2 (4.9,8.1)	26.0%

Table 2 Efficacy data for first-line treatment of NSCLC in a real-world study[3]

Study	N	PD-L1 TPS	mPFS (months) 95% CI
Platinum-doublet chemotherapy and anti-PD(L)-1 blockade in KRAS G12C NSCLC	125	All	6.8 (5.5,10)
	24	≥ 50%	6.9 (3.1, NR)
	37	1-49%	6.0 (5.3, 20)
	53	< 1%	6.2 (4.0,11)

ORR and PFS rate were not reported in this study[3].

Methods

- Efficacy endpoints included ORR and progression-free survival (PFS) by investigator per RECIST 1.1.
- Tumor cell proportion score (TPS) data of PD-L1 were collected either from local laboratory results or tested in a central lab using baseline tumor samples.
- Co-mutations were also explored in this study.

Reference

[1] Jun Zhao, et al. *JCO* 42, 3008-3008(2024).
[2] Rodríguez-Abreu D, et al. *Ann Oncol*. 2021;32:881-895.
[3] Elkrief A, et al. *Oncologist*. 2024 Jan 5;29(1):e166.

Results

Table 3 Baseline characteristics

PD-L1 TPS	≥50%	1-49%	< 1%	Unknown	Total
N	N=14	N=34	N=41	N=13	N=102
Age, years					
Median (range)	67.5 (58, 84)	65.5 (47, 77)	67.0 (46, 80)	67.0 (50, 81)	67.0 (46, 84)
Male, n (%)	10 (71.4%)	29 (85.3%)	30 (73.2%)	11 (84.6%)	80 (78.4%)
Race					
Asian	14 (100%)	34 (100%)	41 (100%)	13 (100%)	102 (100%)
ECOG PS, n (%)					
0	2 (14.3%)	8 (23.5%)	12 (29.3%)	3 (23.1%)	25 (24.5%)
1	12 (85.7%)	26 (76.5%)	29 (70.7%)	10 (76.9%)	77 (75.5%)
Histology, n (%)					
Adenocarcinoma	13 (92.9%)	32 (94.1%)	40 (97.6%)	11 (84.6%)	96 (94.1%)
Other	1 (7.1%)	2 (5.9%)	1 (2.4%)	2 (15.4%)	6 (5.9%)
Bone metastasis, n (%)	6 (42.9%)	17 (50.0%)	18 (43.9%)	6 (46.2%)	47 (46.1%)
Brain metastasis, n (%)	5 (35.7%)	14 (41.2%)	12 (29.3%)	2 (15.4%)	33 (32.4%)
Liver metastasis, n (%)	1 (7.1%)	0	2 (4.9%)	1 (7.7%)	4 (3.9%)
Stage at study entry, n (%)					
IV	12 (85.7%)	33 (97.1%)	36 (87.8%)	12 (92.3%)	93 (91.2%)
Follow-up duration, months					
median (range)	14.6 (7.8, 23.0)	14.3 (5.1, 19.7)	12.8 (1.2, 25.4)	18.2 (3.2, 19.4)	14.4 (1.2, 25.4)

As of August 20, 2024, 102 patients with NSCLC received the combination therapy as a front-line treatment and were enrolled.

Table 4 Efficacy summary by PD-L1 (TPS)

PD-L1 TPS	≥50%	1-49%	< 1%	Unknown	Total
N	N=14	N=34	N=41	N=13	N=102
Best overall response (BOR) (%) [a]					
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	12 (85.7%)	30 (88.2%)	28 (68.3%)	8 (61.5%)	78 (76.5%)
Stable Disease (SD)	1 (7.1%)	3 (8.8%)	10 (24.4%)	3 (23.1%)	17 (16.7%)
Progressive Disease (PD)	0 (0.0%)	1 (2.9%)	2 (4.9%)	0	3 (2.9%)
Not Evaluable (NE)	1 (7.1%)	0	1 (2.4%)	2 (15.4%)	4 (3.9%) [c]
ORR	12 (85.7%)	30 (88.2%)	28 (68.3%)	8 (61.5%)	78 (76.5%) [d]
Confirmed ORR	11 (78.6%)	28 (82.4%)	27 (65.9%)	6 (46.2%)	72 (70.6%)
95% CI [b]	49.2, 95.3	65.5, 93.2	49.4, 79.9	19.2, 74.9	60.7, 79.2
DCR	13 (92.9%)	33 (97.1%)	38 (92.7%)	11 (84.6%)	95 (93.1%)
95% CI [b]	66.1, 99.8	84.7, 99.9	80.1, 98.5	54.6, 98.1	86.4, 97.2
PFS[a]					
Median, months	11.0	15.0	12.4	8.1	12.2
95% CI	(4.3, NE)	(7.4, NE)	(6.9, NE)	(2.8, NE)	(8.3, 17.7)
6 months rate	61.5 (30.8, 81.8)	79.4 (61.6, 89.6)	67.6 (50.9, 79.8)	60.0 (25.3, 82.7)	70.2 (60.0, 78.2)
12 months rate	44.0 (16.8, 68.4)	52.5 (33.4, 68.5)	58.6 (41.2, 72.5)	24.0 (3.8, 53.7)	50.5 (39.4, 60.5)

[a] Assessed by investigator per RECIST v1.1. [b] Exact 95% CI is calculated using the Clopper Pearson method. [c] One SD was assessed less than 5 weeks after start of study treatment. Three patients discontinued treatment without efficacy results. [d] Six patients had a single PR and discontinued treatment.

Figure 1 Swimmer Plot by PD-L1 (TPS)

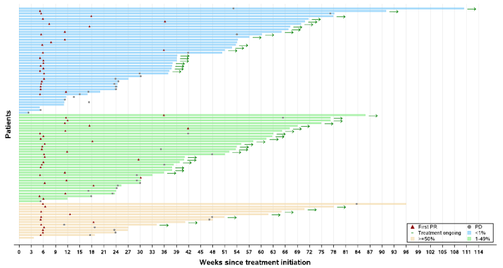


Figure 2 PFS Kaplan-Meier plot by PD-L1 (TPS)

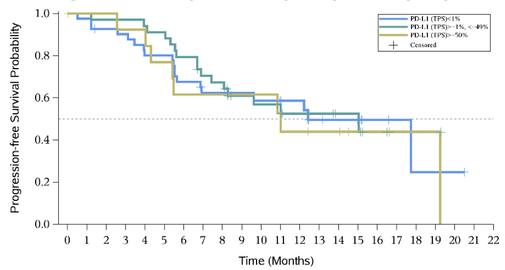
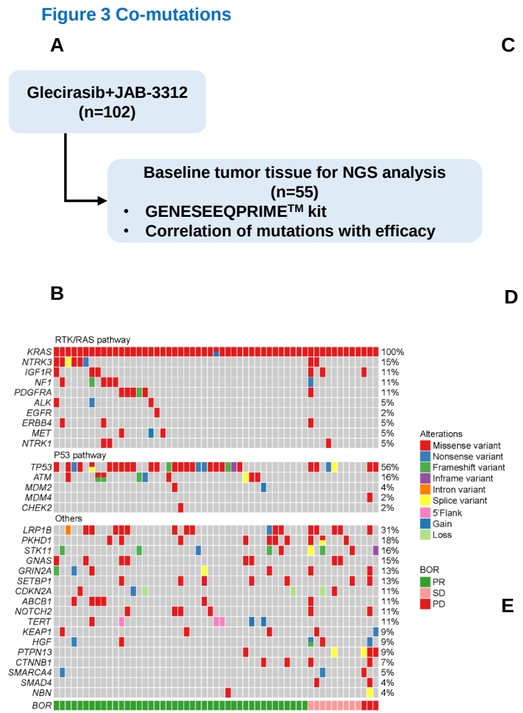
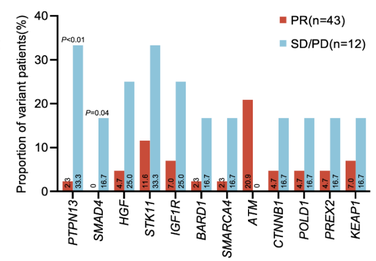
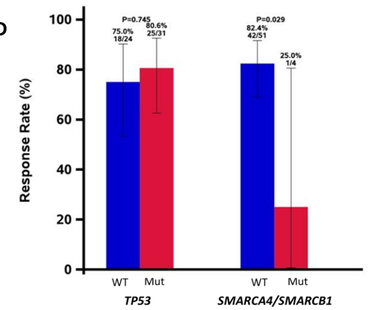
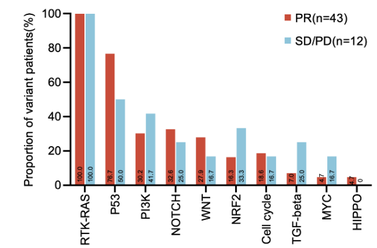


Figure 3 Co-mutations









A) The schematic description of NGS assay on baseline tumor tissue.
B) The heatmap of alterations with BOR.
C) The proportion of gene mutation in PR and SD/PD groups.
D) Comparison of ORRs between *TP53* WT vs Mutation, or *SMARCA4/SMARCB1* WT vs Mutation.
E) The proportion of pathway mutation in PR and SD/PD groups.

Conclusion

- Glecirasib plus JAB-3312 demonstrated a favorable ORR as a front-line treatment in KRAS p.G12C mutated NSCLC, regardless of PD-L1 expression.
- Co-mutations in *SMARC* family members may predict poor prognosis in this study population.

Acknowledgement

We would like to thank all the subjects, their families, the investigators, site staff, and the team members for their contributions.

Disclosure

The first author has no disclosures.