JAB-3312, a Potent Allosteric SHP2 Inhibitor that Enhances the Efficacy of KRAS^{G12C} Inhibitor Glecirasib

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Background

- While the class of direct KRAS^{G12C} inhibitors have shown promising efficacy, acquired resistance inevitably occurred in patients following initial therapies.
- The nonreceptor protein tyrosine phosphatase SHP2 functions as a critical node on which diverse receptor tyrosine kinase pathways converge to relay downstream RAS signaling cascade. Blocking SHP2 represents a rational strategy to overcome KRAS^{G12C} inhibitor resistance.
- We have previously developed glecirasib, a selective covalent KRAS^{G12C} inhibitor and JAB-3312, a selective allosteric SHP2 inhibitor, both of which have entered multiple clinical trials. The combination therapy of JAB-3312 and glecirasib is currently being explored.

Glecirasib shows potent anti-tumor effect both *in vitro* and *in vivo*

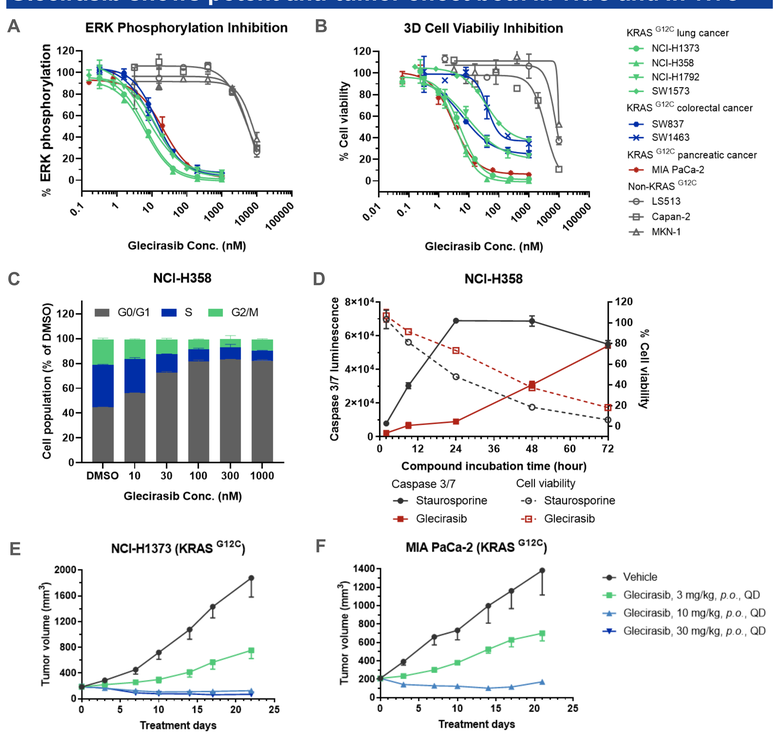
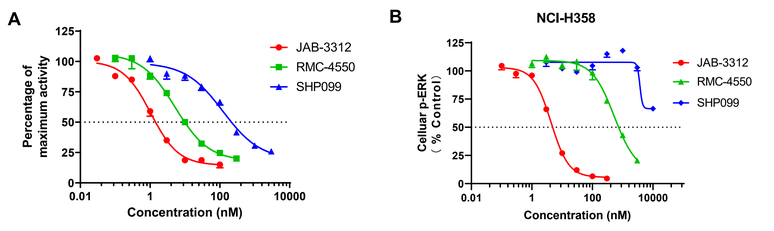


Figure 1 A. pERK inhibition in multiple cancer cell lines by treatment of glecirasib for 2 hours. **B.** Inhibition of 3D cell viability by treatment of glecirasib for 6 days. **C.** Cell cycle arrest in NCI-H358 cells by treatment of glecirasib for 24 hours, examined by flow cytometry. **D.** Time course of caspase 3/7 activity and cell viability following treatment of glecirasib (1μM) in NCI-H358 cells. **E-F.** Inhibition of tumor growth by glecirasib in NCI-H1373 and MIA PaCa-2 xenografts. 6 mice per group. All data was represented in mean ± SEM.

JAB-3312 shows potent anti-tumor effect both *in vitro* and *in vivo*



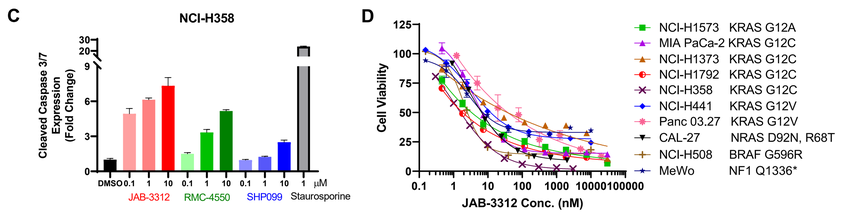


Figure 2 A. The inhibitory effect of JAB-3312, RMC-4550, and SHP099 on the enzymatic activity of full length SHP2, determined using the surrogate substrate DiFMUP in a prompt fluorescence assay format. **B.** p-ERK inhibition in NCI-H358 cells by treatment of JAB-3312, RMC-4550, and SHP099 for 2 hours. **C.** Apoptosis of NCI-H358 cells induced by JAB-3312, RMC-4550, and SHP099. **D.** Inhibition of cell viability by treatment of JAB-3312 for 6 days.

JAB-3312 enhances the anti-tumor effect of glecirasib

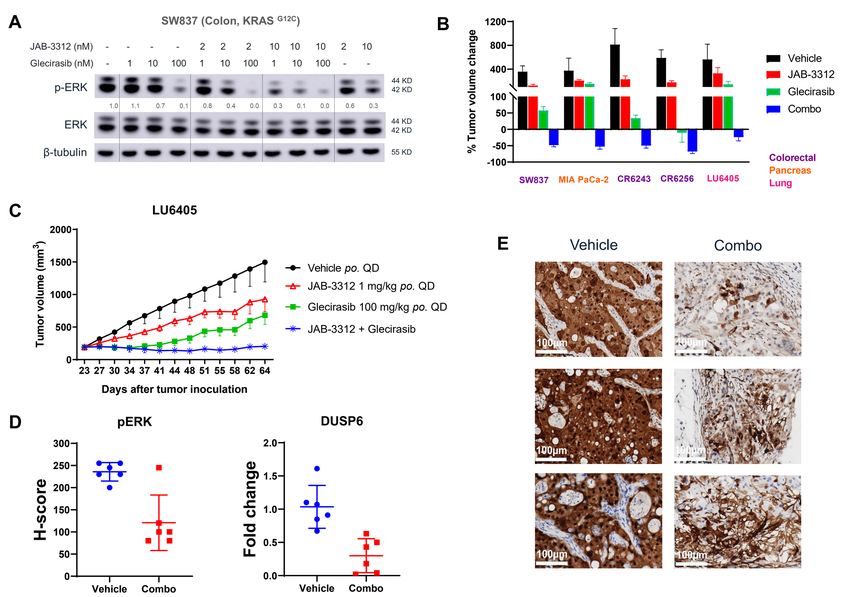
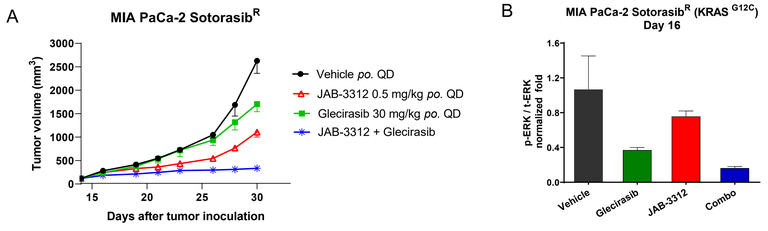


Figure 3 A. Western blot of p-ERK in SW837 cells treated with glecirasib, JAB-3312, or their combination for 2 hours. **B.** *In vivo* efficacy of glecirasib in combination with JAB-3312 in a panel of CDX and PDX models harboring KRAS G12C mutation. JAB-3312: 0.5 mg/kg in SW837 and MIA PaCa-2; 1 mg/kg in CR6243, CR6256, and LU6405. Glecirasib: 3 mg/kg in MIA PaCa-2; 10 mg/kg in SW837; and 100 mg/kg in CR6243, CR6256, and LU6405. For combination, JAB-3312 was administered at 0.5 mg/kg, and glecirasib at the same dose as single agent. **C.** In LU6405 xenograft, tumor growth over time of treatment was plotted. **D.** In LU6405 xenograft, p-ERK level and DUSP6 mRNA expression from FFPE tissues after 41-day combination treatment were evaluated by IHC and qPCR, respectively. **E.** Representative IHC images were shown (200x magnification). Mean tumor volumes ±SEM were shown.

JAB-3312-glecirasib combination overcomes KRAS^{G12C} inhibitor resistance



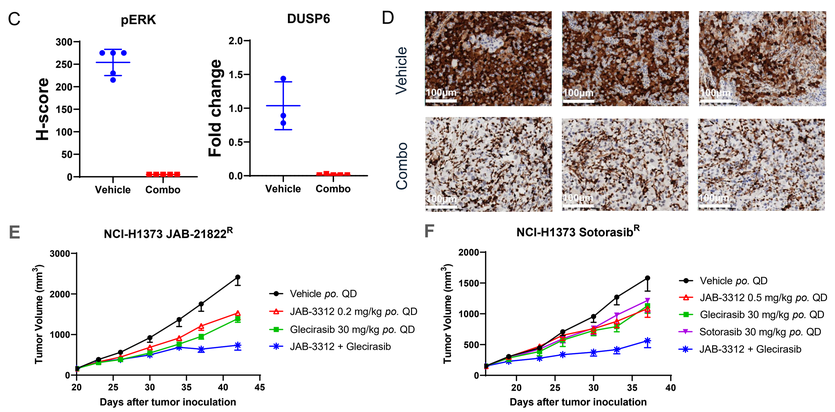
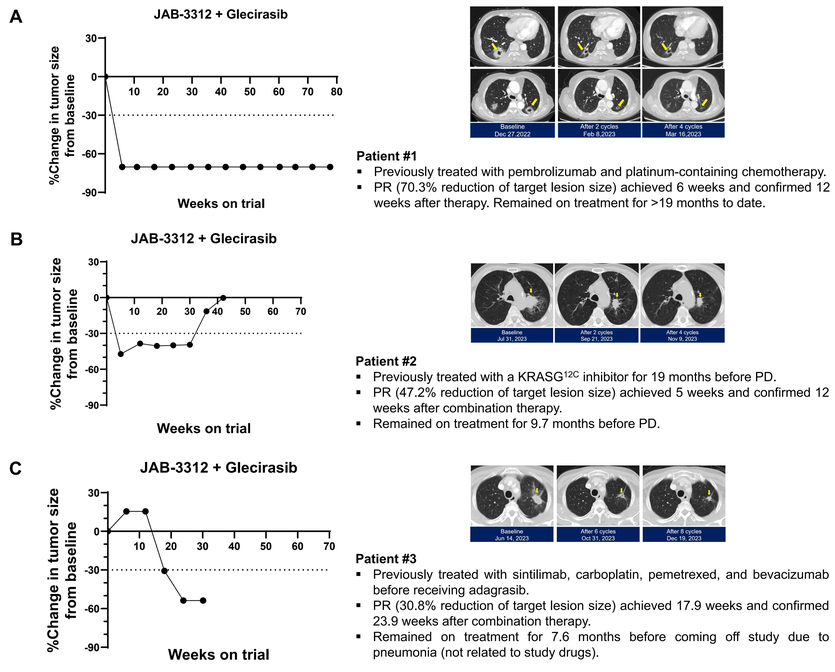


Figure 4 A-B. JAB-3312-glecirasib combination enhances inhibition of tumor growth and pERK in MIA PaCa-2 Sotorasib^{R} xenograft. **C.** In the same xenograft, pERK and DUSP6 mRNA from FFPE tissues after 16-day combination treatment were evaluated by IHC and qPCR, respectively. **D.** Representative IHC images were shown (200x). **E-F.** Tumor growth inhibition by JAB-3312-glesirasib combination in NCI-H1373 JAB-3312^{R} and Sotorasib^{R} xenografts. Mean tumor volumes ±SEM were shown.

JAB-3312-glecirasib combination shows clinical promise



Patient #1
- Previously treated with pembrolizumab and platinum-containing chemotherapy.
- PR (70.3% reduction of target lesion size) achieved 6 weeks and confirmed 12 weeks after therapy. Remained on treatment for >19 months to date.

Patient #2
- Previously treated with a KRASG^{12C} inhibitor for 19 months before PD.
- PR (47.2% reduction of target lesion size) achieved 5 weeks and confirmed 12 weeks after combination therapy.
- Remained on treatment for 9.7 months before PD.

Patient #3
- Previously treated with sintilimab, carboplatin, pemetrexed, and bevacizumab before receiving adagrasib.
- PR (30.8% reduction of target lesion size) achieved 17.9 weeks and confirmed 23.9 weeks after combination therapy.
- Remained on treatment for 7.6 months before coming off study due to pneumonia (not related to study drugs).

Figure 5 Changes in size of target lesion over time in three non-small cell lung cancer patients who received JAB-3312-glecirasib therapy. Imaging of target lesion mass during treatment were shown.

Conclusions

- Glecirasib is a promising KRAS^{G12C}-targeting drug with potent antitumor activity.
- JAB-3312, a potent SHP2 inhibitor, can enhance the efficacy of glecirasib in both KRAS^{G12C} inhibitor treatment-naïve and -resistant preclinical models.
- The preliminary data provide strong rationale for an ongoing clinical trial featuring the two-drug combination in treating KRAS^{G12C} mutant cancer patients (NCT05288205).