# Preclinical Investigation of Orally Bioavailable, Potent Pan-KRAS (ON/OFF) Inhibitor JAB-23E73

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## Background

- Despite the recent success of mutant-specific KRAS$^{G12C}$ inhibitors, there are limited therapeutic options for patients carrying other *KRAS* driver mutations. Development of pan-KRAS inhibitors targeting a broad range of KRAS-driven cancers represents a promising strategy to address the unmet patient needs.
- JAB-23E73, a highly potent and orally bioavailable pan-KRAS (ON/OFF) inhibitor, has recently entered the clinical stage of development (NCT06959615, NCT06973564).

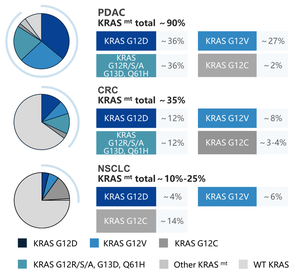


**Fig. 1 Epidemiology of *KRAS* Mutations**

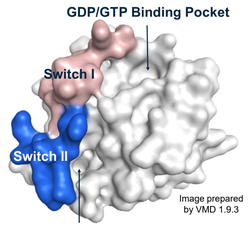


**Fig. 2 Surface Representation of the Binding Mode of JAB-23E73**

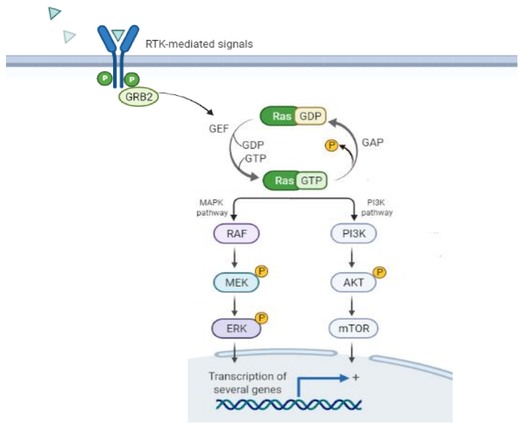


**Fig. 3 Overview of the RAS Signaling Pathway**

## *In Vitro* Potency and Selectivity

| RAS Protein | SPR, $K_D$ (nM) | |
|---|---|---|
| | GDP-loaded | GppNp-loaded |
| KRAS G12D | 0.112 | 35.7 |
| KRAS G12V | 0.172 | 28.2 |

**Table 1 Binding Affinity of JAB-23E73**
SPR assay was performed to determine the $K_D$ values for JAB-23E73 on both "ON" (GppNp-loaded) and "OFF" (GDP-loaded) forms of RAS protein. The GTP analogue GppNp was used in the assay.

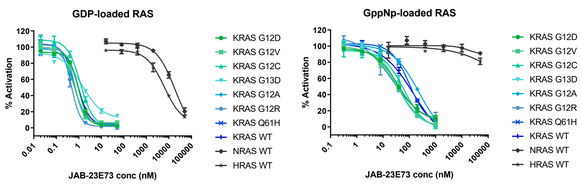


**Fig. 4 Biochemical Activities of JAB-23E73**
Nucleotide exchange assay and RAS::cRAF PPI assay were performed to determine the $IC_{50}$s for JAB-23E73 on GDP-to-GTP conversion on RAS protein (left panel) and the interaction between GTP-bound RAS and cRAF (right panel), respectively. The GTP analogue GppNp were used in the cRAF assays.

## Inhibition of Cellular ERK Phosphorylation

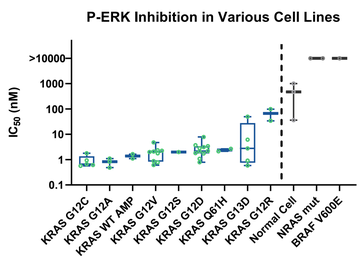


**Fig.5 Inhibition of Cellular ERK Phosphorylation by JAB-23E73**
The pERK$^{T202/Y204}$ HTRF assay was performed to determine the $IC_{50}$s for JAB-23E73 on ERK phosphorylation in various cell lines, including KRAS-dependent and -independent tumor cells and normal cells (HEK293, MRC5, HUVEC).

## Inhibition of Tumor Cell Growth

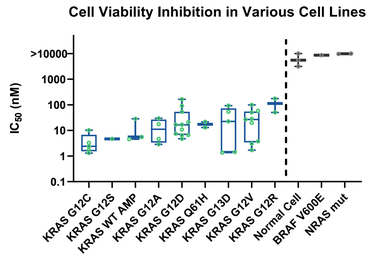


**Fig.6 Inhibition of Cell Viability by JAB-23E73**
The CTG viability assay was performed to determine the $IC_{50}$s for JAB-23E73 on the growth of various cell lines, including KRAS-dependent and -independent tumor cells and normal cells (HEK293, MRC5, HUVEC).

## Efficacy in KRAS G12V Mutant Xenograft

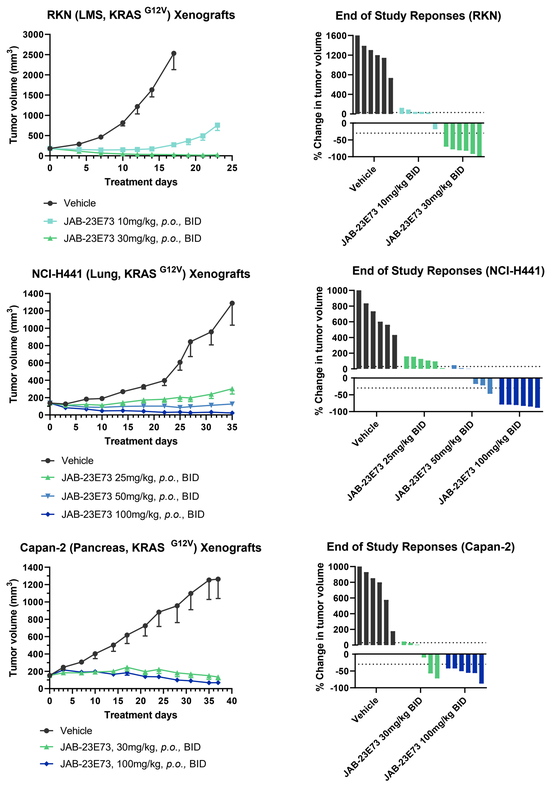


**Fig. 7 *In Vivo* Efficacy of JAB-23E73 in Xenografts Harboring *KRAS* G12V Mutation**
Xenografts of different indications were treated with JAB-23E73 at indicated doses, and tumor volume along treatment time (left panels) and change of tumor volume (in percentage) at end of study (right panels) were plotted. LMS: leiomyosarcoma.

## Efficacy in KRAS G12A Mutant Xenograft

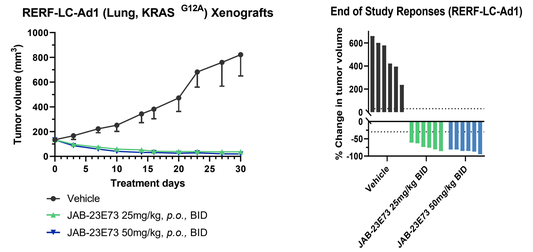


**Fig. 8 *In Vivo* Efficacy of JAB-23E73 in Xenograft Harboring *KRAS* G12A Mutation**
The RERF-LC-Ad1 lung xenograft was treated with JAB-23E73 at indicated doses, and tumor volume along treatment time (left panel) and change of tumor volume (in percentage) at end of study (right panel) were plotted.

## Efficacy in KRAS G12D Mutant Xenograft

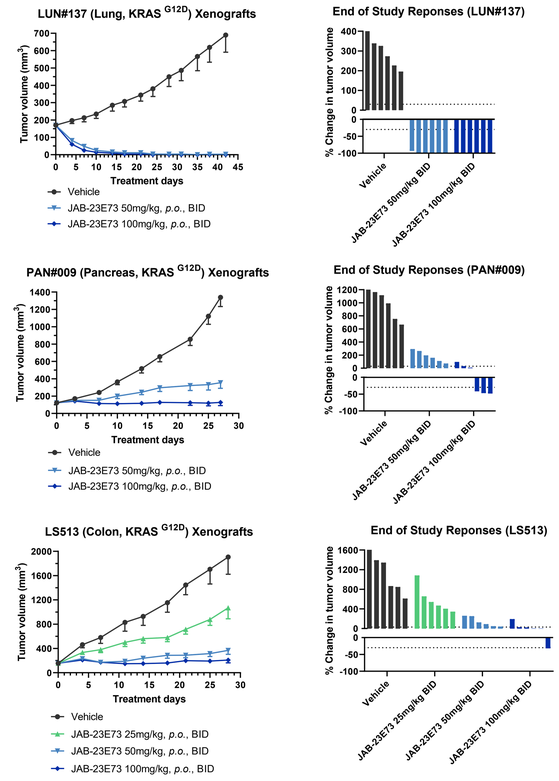


**Fig. 9 *In Vivo* Efficacy of JAB-23E73 in Xenografts Harboring *KRAS* G12D Mutation**
Xenografts of different indications were treated with JAB-23E73 at indicated doses, and tumor volume along treatment time (left panels) and change of tumor volume (in percentage) at end of study (right panels) were plotted.

## Reference


- Lee *et al.* Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. NPJ Precis Oncol. 2022 Dec 9;6(1):91.
- The cases of *KRAS* mutations are estimates in 2020 by the International Agency for Research on Cancer (IARC) and World Health Organization (WHO).
- For more information about Jacobio Pharmaceuticals and our KRAS programs: https://www.jacobiopharma.com/en/pipeline


## Efficacy in KRAS G13D Mutant Xenograft

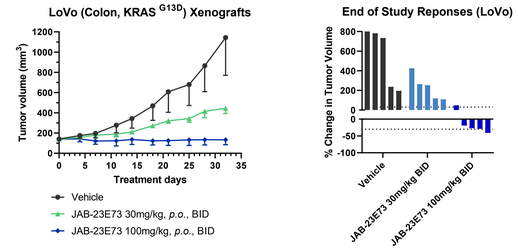


**Fig. 10 *In Vivo* Efficacy of JAB-23E73 in Xenograft Harboring *KRAS* G13D Mutation**
The LoVo colon xenograft was treated with JAB-23E73 at indicated doses, and tumor volume along treatment time (left panel) and change of tumor volume (in percentage) at end of study (right panel) were plotted.

## *In Vivo* PK/PD Correlation

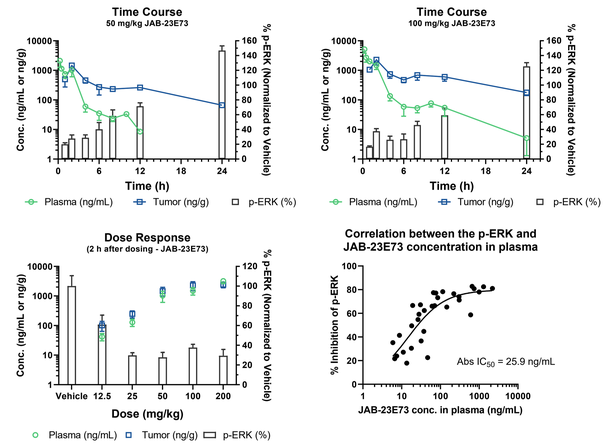


**Fig. 11 *In Vivo* PK/PD Correlation of JAB-23E73**
Top panels: JAB-23E73 was administered at single dose of 50 mg/kg (left panel) and 100 mg/kg (right panel) in the LS513 xenograft model. Plasma and tumor tissue samples were collected at indicated time post-dose for assessment of PD (pERK$^{T202/Y204}$) and PK (drug concentration). Bottom panels: JAB-23E73 was administered at different doses in the LS513 xenograft model. Plasma and tumor tissue samples were collected 2 hours post-dose for assessment of PD and PK (left panel); the correlation between p-ERK inhibition and JAB-23E73 concentration in plasma was plotted (right panel).

## Conclusion

- JAB-23E73 is a highly potent, pan-KRAS (ON/OFF) inhibitor with strong selectivity to spare HRAS and NRAS inhibition.
- JAB-23E73 exhibits superior antitumor activity across multiple cancer types harboring different *KRAS* driver mutations or amplification.
- JAB-23E73 induces tumor regression without causing significant body weight change in KRAS-driven mouse tumor models, indicating good tolerability and wide therapeutic window.
- JAB-23E73 has a favorable PK profile for oral administration, exhibiting plasma concentration-dependent intratumoral p-ERK inhibition.
- Phase I clinical trials of JAB-23E73 are currently ongoing in both China and the US for patients with advanced solid tumors harboring *KRAS* gene alterations (NCT06959615, NCT06973564).

## Acknowledgement


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