**Preclinical investigation of orally bioavailable, potent KRAS\textsuperscript{G12C} inhibitor JAB-23425**

Peng Wang, Yanping Wang, Xin Sun, Dan Liu, Xiaoyu Liu, Wei Zhang, Xueling He, Rui Zhuo, Cunbo Ma, Amin Li, Yiwei Lin, Wei Long

Jaccobio Pharmaceuticals Co., Ltd., Beijing, China

Correspondence: peng.wang@jaccobiopharma.com

**Abstract #1660**

**Background**

- KRAS is the most frequently mutated oncoprotein and there has been an urgent and unmet need to target KRAS mutations in KRAS-driven cancer, such as KRAS\textsuperscript{G12C}, KRAS\textsuperscript{G12D} and KRAS\textsuperscript{G12S}.
- We have developed JAB-23425 as a highly potent and orally bioavailable KRAS\textsuperscript{G12C} inhibitor.
- JAB-23425 targets both "ON" and "OFF" states of KRAS, with good selectivity over HRAS and NRAS. JAB-23425 inhibits robust antitumor activities in preclinical models with multiple KRAS mutant lines, while sparing KRAS-independent cells.

**JAB-23425 is a potent and selective KRAS\textsuperscript{G12C} inhibitor**

- **Table 1.** JAB-23425 inhibits the growth of KRAS-mutant cancer cells.
  - A. JAB-23425 IC\textsubscript{50} data in KRAS-dependent cancer cell lines harboring multiple KRAS mutations. By exposing cell lines to multiple concentrations of JAB-23425, the IC\textsubscript{50} values were determined.
  - B. JAB-23425 IC\textsubscript{50} data in KRAS WT cell lines with or without KRAS amplification, by exposing cell lines to multiple concentrations of JAB-23425.
  - C. JAB-23425 IC\textsubscript{50} data in KRAS WT cell lines with or without HRAS/CRAK amplification, by exposing cell lines to multiple concentrations of JAB-23425.

**JAB-23425 inhibits ERK phosphorylation and growth of KRAS-mutant cell lines**

**Figure 1.** Binding surface of KRAS.

**Figure 2.** Western blot of NCI-H441 cell line, p\textsuperscript{ERK} was decreased by JAB-23425 treatment.

**Figure 3.** In vitro efficacy of JAB-23425 in combination with other therapeutic drugs.

**Figure 4.** PK/PD Correlation of JAB-23425.

**Figure 5.** Antitumor activities of JAB-23425 as monotherapy in vivo.

**Figure 6.** Antitumor activities of JAB-23425 in combination with cetuximab in vivo.

**Conclusions**

- JAB-23425 is a potent KRAS\textsuperscript{G12C} inhibitor targeting both "ON" and "OFF" forms of KRAS, with good selectivity over HRAS and NRAS.
- JAB-23425 significantly reduces p\textsuperscript{ERK} and inhibits growth of KRAS-dependent tumor, in pre-clinical models across different cancer types.
- JAB-23425 is orally bioavailable and shows good tolerability in mice.
- JAB-23425 has synergistic effects in combination with cetuximab.

**Reference**