Combination of KRAS\textsuperscript{G12C} inhibitor JAB-21822 with SHP2 inhibitor JAB-3312 overcomes adaptive resistance to KRAS\textsuperscript{G12C} inhibition

Peng Wang\textsuperscript{1}, Qian Zheng\textsuperscript{1}, Di Kang\textsuperscript{1}, Xin Sun\textsuperscript{1}, Sha Zhu\textsuperscript{2}, Yanping Wang\textsuperscript{1}, Wei Long\textsuperscript{1}, Yiwei Lin\textsuperscript{2}
\textsuperscript{1}Jacobio Pharmaceuticals Co., Ltd., Beijing, China  \textsuperscript{2}Jacobio (US) Pharmaceuticals, Inc., Lexington, MA, USA

### Background
Mutant-selective KRAS\textsuperscript{G12C} inhibitors, such as MRTX349 (Adagrasib) and AMG510 (Sotorasib), have demonstrated efficacy in KRAS\textsuperscript{G12C}-mutant cancers including NSCLC. However, adaptive reactivation of MAPK pathway through multiple growth receptors (RTKs) occurs soon after treatment and is the major mechanism of bypass resistance to KRAS\textsuperscript{G12C} inhibitors. SHP2 is a key nodal phosphatase downstream of multiple RTKs and contributes to rebound activity of MAPK signaling during KRAS\textsuperscript{G12C} inhibitor treatment. Combinatorial inhibition of SHP2 along with KRAS\textsuperscript{G12C} may be an effective avenue to overcome adaptive resistance to KRAS\textsuperscript{G12C} inhibition.

Jacobio has developed JAB-21822, a potent, selective, and covalent KRAS\textsuperscript{G12C} inhibitor (under evaluation in clinical trials NCT05009329, as well as JAB-3312, a selective SHP2 allosteric inhibitor (under evaluation in clinical trials NCT04270976, NCT04121288, and NCT04045496). Pre-clinical data demonstrate that the combination of KRAS\textsuperscript{G12C} inhibitor JAB-21822 and SHP2 inhibitor JAB-3312 showed synergistic anti-tumor efficacy in KRAS\textsuperscript{G12C} inhibitor-resistant NSCLC, CRC, and PDAC models. These data support clinical combination of JAB-21822 with JAB-3312 in patients with adaptive resistance to KRAS\textsuperscript{G12C} inhibition.

### In vitro synergy of combined SHP2/KRAS\textsuperscript{G12C} inhibition in KRAS\textsuperscript{G12C}-resistant cell lines

- **A** Cysteine proteome analysis of NCI-H358 cell lysates after treatment with 1 μM JAB-21822 or DMSO
- **B** Cell growth inhibition (IC\textsubscript{50}) of JAB-21822 evaluated in different cell lines bearing G12C mutation. JAB-21822 at 10 mg/kg PO QD (CDX) or 100 mg/kg PO QD (D) Tumor growth inhibition of JAB-21822 evaluated in CDX or PDX mouse models.

### In vivo synergy of combined SHP2/KRAS\textsuperscript{G12C} inhibition in KRAS\textsuperscript{G12C} inhibitor-resistant mouse models

- **A** KRAS\textsuperscript{G12C} inhibitor MPA Ca2-2 Xenograft model. JAB-21822 or KRAS\textsuperscript{G12C} inhibitor at 30 mg/kg PO QD; JAB-3312 at 0.5 mg/kg PO QD. A, Tumor volume. B, Tumor weight at the end of the study (day 16)

### Efficacy and selectivity of JAB-2182 monotherapy

- **A** Cysteine proteome analysis of NCI-H358 cell lysates after treatment with 1 μM JAB-21822 or DMSO
- **B** Cell growth inhibition (IC\textsubscript{50}) of JAB-21822 evaluated in different cell lines bearing G12C mutation. JAB-21822 at 10 mg/kg PO QD (CDX) or 100 mg/kg PO QD (PDX)

### Acknowledgment and Disclosure

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### Table 1. Clinical trials on KRAS\textsuperscript{G12C} inhibitor and SHP2 inhibitor combination.

<table>
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<th>KRAS\textsuperscript{G12C} inhibitor</th>
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<th>Inclusion criteria</th>
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### Conclusions

- **JAB-21822** is a potent, selective, and covalent KRAS\textsuperscript{G12C} inhibitor currently under evaluation in clinical trials in patients with KRAS\textsuperscript{G12C}-mutant NSCLC, CRC and other tumor types.
- **JAB-3312** is a selective inhibitor of SHP2, which mediates key resistance to KRAS\textsuperscript{G12C} inhibitor.
- **JAB-21822 in combination with JAB-3312** can synergistically inhibit tumor growth in KRAS\textsuperscript{G12C} inhibitor-resistant models.
- **Combination of JAB-21822 and JAB-3312** may overcome adaptive resistance to KRAS\textsuperscript{G12C} inhibitor in clinical patients.