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

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

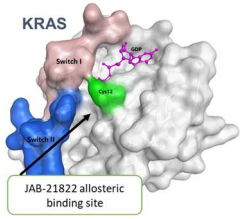
Background

Mutant-selective KRAS^{G12C} inhibitors, such as MRTX849 (Adagrasib) and AMG510 (Sotorasib), have demonstrated efficacy in KRAS^{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^{G12C} inhibitors.

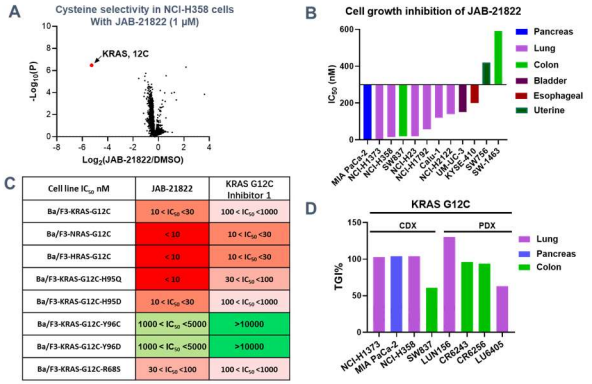
SHP2 is a key nodal phosphatase downstream of multiple RTKs and contributes to rebound activity of MAPK signaling during KRAS^{G12C} inhibitor treatment. Combinational inhibition of SHP2 along with KRAS^{G12C} may be an effective avenue to overcome adaptive resistance to KRAS^{G12C} inhibition.

Jacobio has developed JAB-21822, a potent, selective and covalent KRAS^{G12C} inhibitor (under evaluation in clinical trials NCT05276726 and NCT05009329), as well as JAB-3312, a selective SHP2 allosteric inhibitor (under evaluation in clinical trials NCT04720976, NCT04121286, and NCT04045496).

Pre-clinical data demonstrate that the combination of KRAS^{G12C} inhibitor JAB-21822 and SHP2 inhibitor JAB-3312 showed synergistic anti-tumor efficacy in KRAS^{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^{G12C} inhibition.



Efficacy and selectivity of JAB-21822 monotherapy



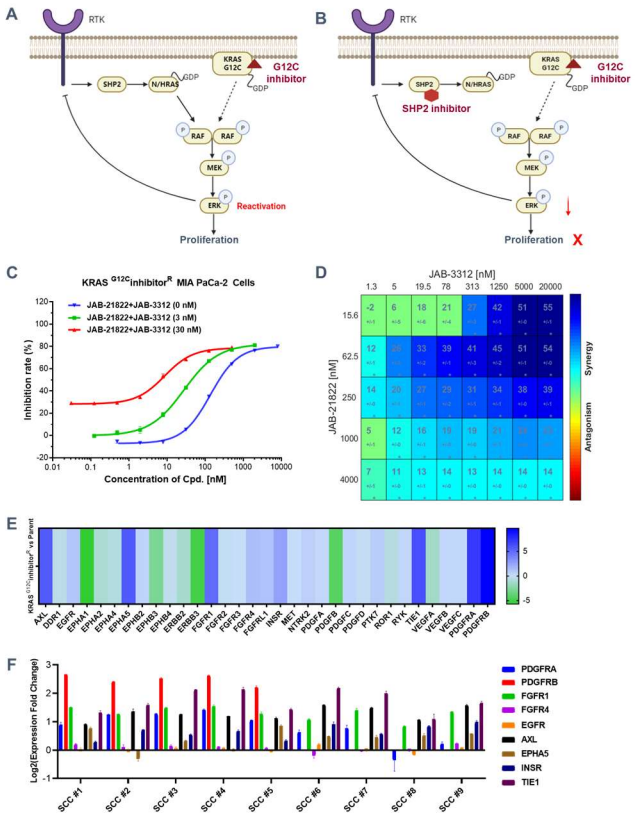
Cell line IC_{50} nM	JAB-21822	KRAS G12C Inhibitor 1
Ba/F3-KRAS-G12C	10 < IC_{50} <30	100 < IC_{50} <1000
Ba/F3-NRAS-G12C	< 10	10 < IC_{50} <30
Ba/F3-HRAS-G12C	< 10	10 < IC_{50} <30
Ba/F3-KRAS-G12C-H95Q	< 10	30 < IC_{50} <100
Ba/F3-KRAS-G12C-H95D	10 < IC_{50} <30	100 < IC_{50} <1000
Ba/F3-KRAS-G12C-Y96C	1000 < IC_{50} <5000	>10000
Ba/F3-KRAS-G12C-Y96D	1000 < IC_{50} <5000	>10000
Ba/F3-KRAS-G12C-R68S	30 < IC_{50} <100	100 < IC_{50} <1000

(A) Cysteine proteome analysis of NCI-H358 cell lysates after treatment with 1 μM JAB-21822 or DMSO
(B) Cell growth inhibition (IC_{50}) of JAB-21822 evaluated in different cell lines bearing G12C mutation
(C) Cell growth inhibition (IC_{50}) of JAB-21822/KRAS G12C inhibitor 1 evaluated in Ba/F3 cell lines bearing G12C mutation or secondary mutations
(D) Tumor growth inhibition of JAB-21822 evaluated in CDX or PDX mouse models bearing G12C mutation. JAB-21822 at 10 mg/kg PO QD (CDX) or 100 mg/kg PO QD (PDX)

Reference and Correspondence

Reference: 1) Yaeger, R., et al., Clin Cancer Res, 2020;26(7):1538-40.; 2) Ruess, D.A., et al., Nat Med, 2018;24(7):954-60.; 3) Ryan, M.B., et al., Clin Cancer Res, 2020;26(7):1633-43.
Correspondence: Peng Wang, peng.wang@jacobiopharma.com

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



(A-B) Schematic diagram showing that RTK/SHP2-mediated MAPK pathway reactivation is the key mechanism underlying KRAS^{G12C} inhibitor resistance. Combining SHP2 inhibitor with KRAS^{G12C} inhibitor leads in maximal down-regulation of MAPK pathway activity
(C) KRAS^{G12C} inhibitor^R MIA PaCa-2 cell line treated with combination of JAB-21822 and JAB-3312 under different concentrations for evaluation of inhibitory activity on cell proliferation
(D) Synergistic score of JAB-21822 and JAB-3312 combination in the KRAS^{G12C} inhibitor^R NCI-H358 cell line
(E) Log_2 Fold change of gene expression in NCI-H358 cells with acquired resistance against KRAS^{G12C} inhibitor by RNAseq
(F) The gene expression level in single clones of NCI-H358 cells with acquired resistance against KRAS^{G12C} inhibitor by real-time PCR

Acknowledgment and Disclosure

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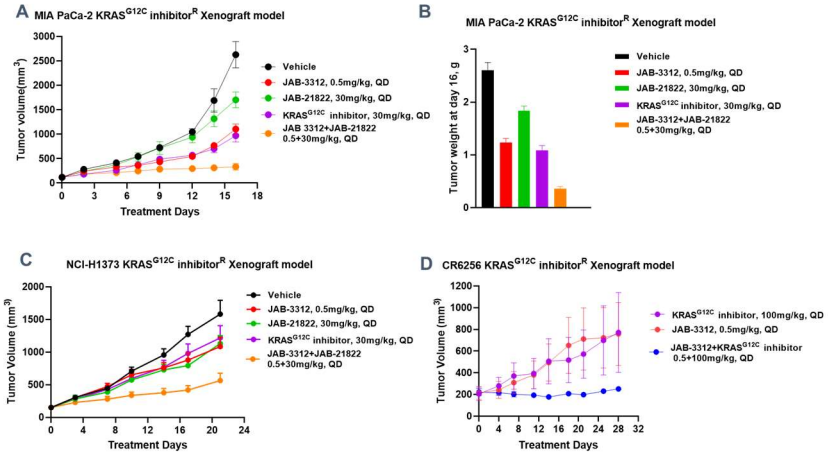
The authors are employees of Jacobio Pharmaceuticals. There are no further conflicts of interest to disclose.

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



(A-B) KRAS^{G12C} inhibitor^R MIA PaCa-2 Xenograft model. JAB-21822 or KRAS^{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)
(C) KRAS^{G12C} inhibitor^R NCI-H1373 Xenograft model. JAB-21822 or KRAS^{G12C} inhibitor at 30 mg/kg PO QD; JAB-3312 at 0.5 mg/kg PO QD
(D) KRAS^{G12C} inhibitor^R CR6256 PDX model. KRAS^{G12C} inhibitor 100 mg/kg treated for 63 days until tumor rebound growth, KRAS^{G12C} inhibitor at 100 mg/kg PO QD; JAB-3312 at 0.5 mg/kg PO QD

Table 1. Clinical trials on KRAS^{G12C} inhibitor and SHP2 inhibitor combination.

KRAS^{G12C} inhibitor	SHP2 inhibitor	Clinical trial	Indication	Inclusion criteria	Region
AMG510 (Sotorasib)	JAB-3312	NCT04720976*	NSCLC	G12Ci Naïve	United States
JAB-21822	JAB-3312	NCT05288205*	NSCLC	G12Ci Naïve or Resistant	China
AMG510 (Sotorasib)	RMC-4630	NCT05054725	NSCLC	G12Ci Naïve	United States
AMG510 (Sotorasib)	BBP-398	/	/	/	/
MRTX 849	TNO-155	NCT04330664	NSCLC and CRC	/	United States
JDQ-443 (+ anti PD-1)	TNO-155	NCT04699188	NSCLC and CRC	G12Ci Naïve	Global

* Sponsored by Jacobio

Conclusions

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