# JAB-26766: a Small-molecule, Orally Bioavailable PARP7 Inhibitor with High Potency and Selectivity

**Abstract #4535**

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## Background

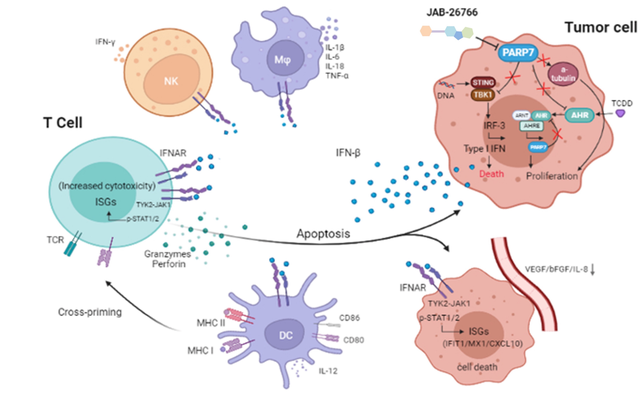
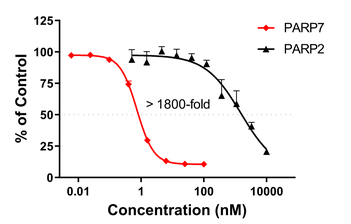



**Figure 1. Inhibition of PARP7 restores the type I IFN response in tumor cells and induces anti-tumor immunity.**

- PARP7 (also referred to as TIPARP or ARTD14) is a mono-ADP-ribosyltransferase that negatively regulates STING-Type I interferon pathway for immune evasion, as well as modulates autophagy to facilitate tumor progression.
- Jacobio has developed JAB-26766, a potent, selective PARP7 inhibitor.
- Pre-clinical data demonstrate that JAB-26766 can induce anti-tumor immunity through restoration of the type I interferon response in tumor cells, and combination of JAB-26766 with STING agonist JAB-27670 (Jacobio) or anti-PD-1 mAb showed enhanced anti-tumor effect.

## JAB-26766 is a potent and selective PARP7 inhibitor




| | JAB-26766 | RBN-2397 |
|---|---|---|
| PARP1 $IC_{50}$ (nM) | 2289 | 969 |
| PARP2 $IC_{50}$ (nM) | 1528 | 1227 |
| PARP7 $IC_{50}$ (nM) | 0.84 | 1.14 |
| PARP2/PARP7 ratio | 1819 | 1076 |

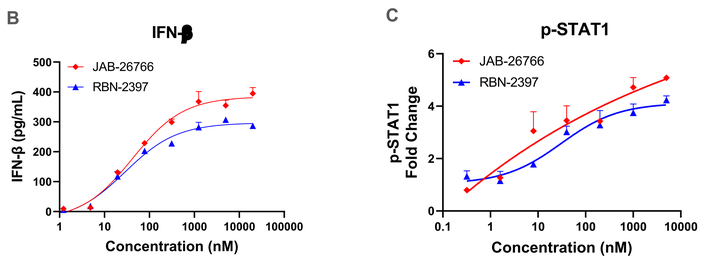


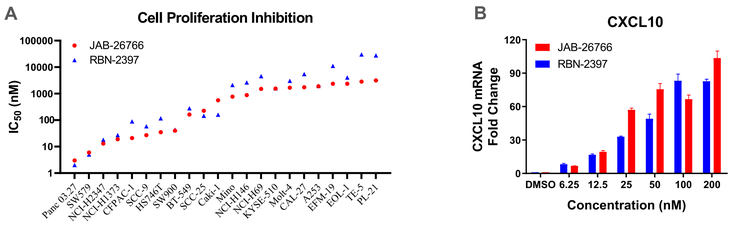

**Figure2. JAB-26766 is a potent PARP7 inhibitor that induces secretion of IFN-β and phosphorylation of STAT1.**

**A.** JAB-26766 showed >1800-fold selectivity on PARP7 over PARP2. Inhibition on the binding of PARP7 with biotinylated probes at the same binding site as $NAD^+$ by JAB-26766 was detected by Homogeneous Time-Resolved Fluorescence (HTRF).

**B.** IFN-β secretion by NCI-H1373 non-small cell lung cancer (NSCLC) cells was detected by HTRF after cells were treated with JAB-26766 or RBN-2397, each combined with 100 nM STING agonist JAB-27670 for 20 hours. PARP7 inhibitor RBN-2397 was synthesized in house.

**C.** Phosphorylation of STAT1 in NCI-H1373 cells was detected by HTRF after treatment with JAB-26766 or RBN-2397 for 24 hours.

## JAB-26766 exhibits potent anti-tumor activity *in vitro*



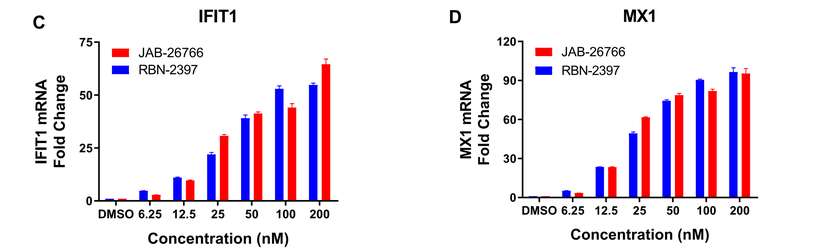
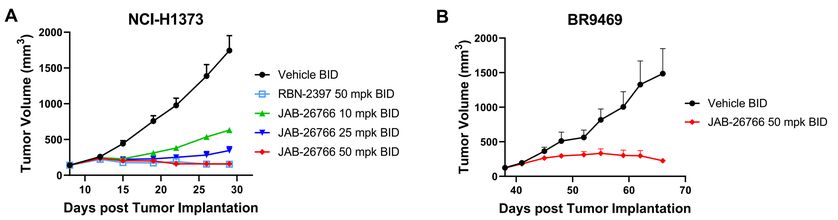




**Figure 3. JAB-26766 inhibits the proliferation of tumor cells and induces the expression of IFN-stimulated genes (ISGs).**

**A.** Cell proliferation inhibition of JAB-26766 was evaluated in multiple cancer cells by CTG viability assay (6 days of incubation).
**B-D.** CXCL10, IFIT1, MX1 mRNA of NCI-H1373 cells was detected by qPCR after treatment with JAB-26766 for 24 hours.

## JAB-26766 induces ISG expression and suppresses tumor growth *in vivo*



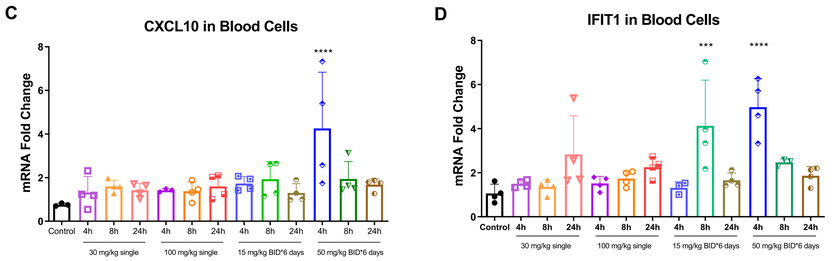




**Figure 4. JAB-26766 induces ISG expression and suppresses tumor growth *in vivo*.**

**A-B.** Tumor volume change during the treatment of JAB-26766 at indicated *p.o.* doses in NCI-H1373 NSCLC xenograft model and BR9469 breast cancer PDX model. 6 mice per group in NCI-H1373 model and 3 mice per group in BR9469 model.
**C-D.** Fold change of CXCL10 and IFIT1 mRNA in blood cells of mice bearing NCI-H1373 tumor by real-time PCR.

## PK/PD correlation of JAB-26766

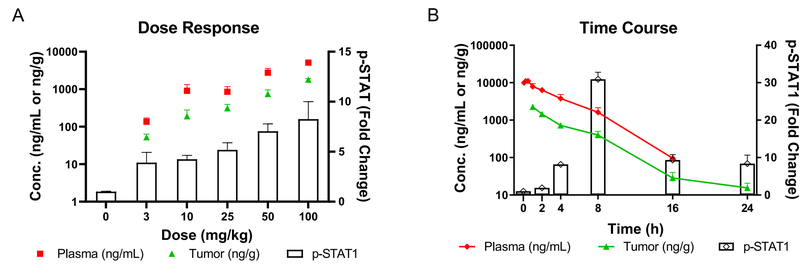



**Figure 5. PK/PD correlation of JAB-26766 in NCI-H1373 xenograft model.**

**A.** JAB-26766 was administrated at single doses, 3, 10, 25, 50 and 100 mg/kg, *p.o.* in NCI-H1373 model. Plasma and tumor tissue were collected 4 hours post-dose to assess PD ($pSTAT1^{Tyr701}$) and PK (drug concentration).
**B.** JAB-26766 was administrated at a single dose, 25 mg/kg, *p.o.* in NCI-H1373 model. Plasma and tumor tissue were collected at indicated time post-dose to assess PD ($pSTAT1^{Tyr701}$) and PK (drug concentration).

## Reference

1) Laura,M.P., et al., Nucleic Acids Res, 2013;41(3):1604-21.
2) Tim, J. W., et al., Cell Chem Biol, 2020;27(7):877-887.
3) Lavanya, P.P., et al., Elife, 2021;10:e60481.

## Acknowledgment

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## Combinational study of JAB-26766 *in vitro*

**A**

| Cell Line | Cancer Type | JAB-26766 $IC_{50}$ (nM) | JAB-27670 $IC_{50}$ (nM) | Combo |
|---|---|---|---|---|
| MDA-MB-468 | TNBC | 5649 | 135 | 16.8 |
| SW403 | CRC | > 10000 | 9435 | -8.09 |
| SW620 | CRC | > 2000 | > 2000 | 2.07 |
| LS174T | CRC | 2594 | 285 | 9.73 |
| LS513 | CRC | 5560 | 102 | 13.7 |
| CAL27 | H&N | 2026 | >10000 | 8.30 |
| FaDu | H&N | > 2000 | > 2000 | 26.9 |
| SCC-25 | H&N | 4761 | 358 | 16.3 |
| EBC-1 | NSCLC | 5281 | 849 | 11.4 |
| NCI-H1975 | NSCLC | >40000 | 25 | 12.0 |
| NCI-H441 | NSCLC | 6814 | 17.3 | 14.6 |
| T3M4 | PDAC | 4696 | 552 | 9.85 |
| YAPC | PDAC | 8895 | > 10000 | 12.3 |

| ZIP score | > 5 | -5 to 5 | < -5 |
|---|---|---|---|
| | synergy | additivity | antagonism |

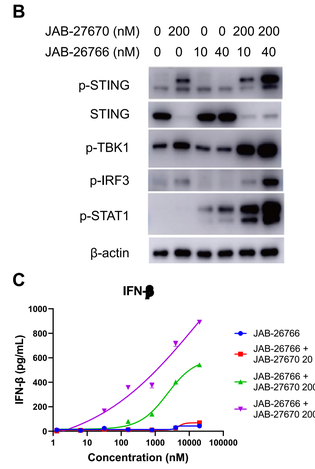


**Figure 6. *In vitro* efficacy of JAB-26766 in combination with STING agonist JAB-27670.**

**A.** Synergistic score of JAB-26766 and JAB-27670 combination in multiple cancer cell lines. TNBC: triple-negative breast cancer; CRC, colorectal cancer; H&N, head and neck cancer; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.
**B.** Activation of STING pathway by JAB-26766 and JAB-27670 combination.
**C.** Increased IFN-β secretion of NCI-H1373 cells induced by JAB-26766 and JAB-27670 combination detected by HTRF.

## JAB-26766 in combination with JAB-27670 or anti-PD-1 mAb results in enhanced *in vivo* anti-tumor effects

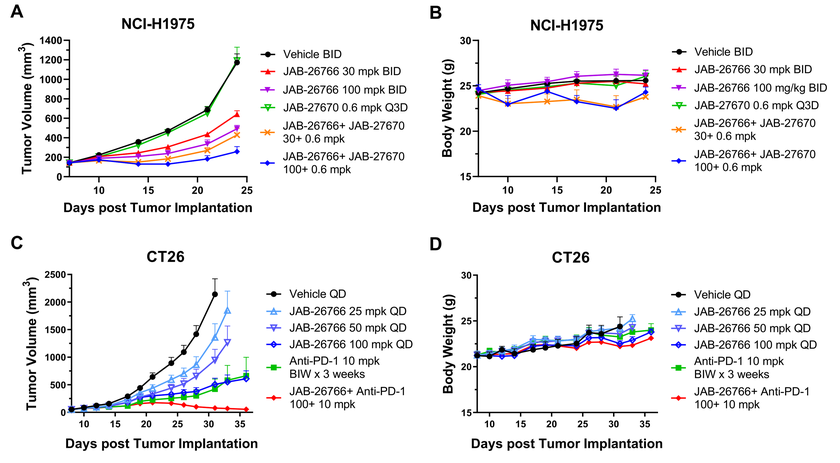


**Figure 7. *In vivo* anti-tumor activities of JAB-26766 in combination with STING agonist JAB-27670 or anti-PD-1 mAb.**

**A-B.** Tumor volume (A) and body weight (B) during the treatment of JAB-26766 in combination with JAB-27670 in NCI-H1975 xenograft model. JAB-26766 at 30, 100 mg/kg, *p.o.*, BID and JAB-27670 at 0.6 mg/kg, *p.o.*, Q3D. 6 mice per group.
**C-D.** Tumor volume (C) and body weight (D) during the treatment of JAB-26766 in combination with anti-PD-1 mAb in CT26 syngeneic model. JAB-26766 at 25, 50, 100 mg/kg, *p.o.*, QD and anti-PD-1 mAb at 10 mg/kg, *i.p.*, BIW. All groups were co-dosed with 1-ABT (1-aminobenzotriazole), a cytochrome P450 inhibitor, to increase mouse exposure to drugs. 9 mice per group.

## Conclusions

- JAB-26766 is a potent, orally bioavailable PARP7 inhibitor with >1800-fold selectivity on PARP7 over PARP2.
- JAB-26766 efficiently induces IFN-β secretion and STAT1 phosphorylation, and enhances the expression of IFN-stimulated genes (ISGs) in tumor cells and blood cells.
- JAB-26766 exposure shows strong relationship with STAT1 phosphorylation in both time- and dose-dependent manners.
- JAB-26766 as a single agent shows potent *in vivo* anti-tumor activities, which can be further enhanced through combination with STING agonist JAB-26766 or anti-PD-1 mAb.