JAB-2485: a potent, highly selective small-molecule Aurora Kinase A inhibitor that targets cell division

Abstract #1645

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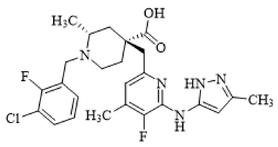
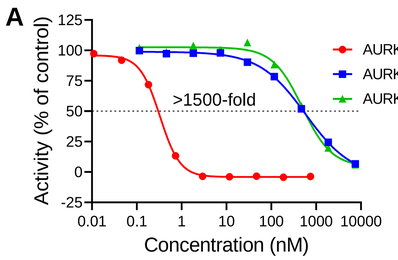
Background

- Aurora kinase A (AURKA) is frequently dysregulated in a wide range of cancers and contributes to clinical aggressiveness and poor patient survival, rendering it an attractive therapeutic target.
- We have developed JAB-2485, a potent, highly selective small-molecule AURKA inhibitor with 1500-fold selectivity over AURKB and AURKC.
- JAB-2485 exhibits favorable PK properties and robust antitumor effect in pre-clinical studies.
- A Phase 1/2a clinical trial evaluating JAB-2485 in adult patients with advanced solid tumors is ongoing in the US (NCT05490472).

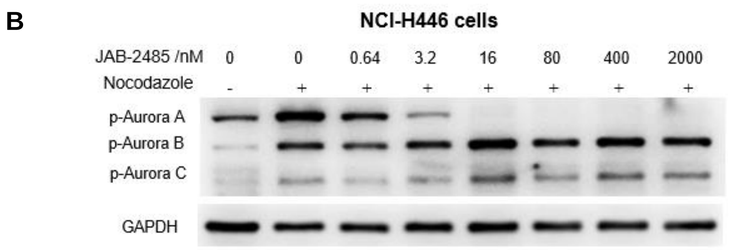


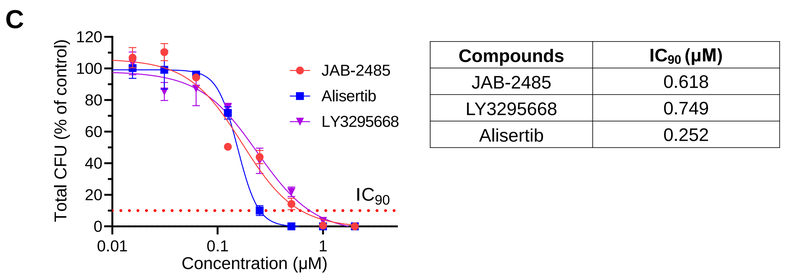
JAB-2485

JAB-2485 induces cell cycle arrest and apoptosis with minimal myelosuppression



Compounds	IC$_{50}$ (nM)		
	AURKA	AURKB	AURKC
JAB-2485	0.327	555	507
LY3295668	0.337	597	523





Compounds	IC$_{90}$ (μM)
JAB-2485	0.618
LY3295668	0.749
Alisertib	0.252

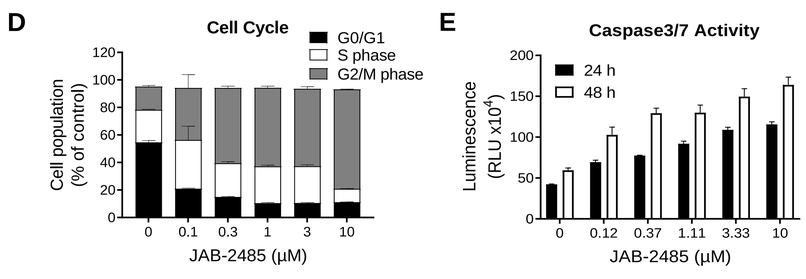


Figure 1. JAB-2485 is a potent, AURKA-selective inhibitor that induces cell cycle arrest and apoptosis with minimal myelosuppression.

A. Kinase assay shows subnanomolar potency of JAB-2485 on AURKA with >1500-fold selectivity over AURKB and AURKC.
B. Western blot shows nanomolar potency of JAB-2485 in inhibiting AURKA phosphorylation and high selectivity over p-AURKB and p-AURKC in NCI-H446 cells.
C. Colony-forming unit-granulocyte-macrophage (CFU-GM) assay shows minimal myelosuppression by JAB-2485 as measured by IC$_{90}$.
D. Flow cytometry assay shows that JAB-2485 induces G2/M phase cell cycle arrest in NCI-H446 cells.
E. Caspase 3/7 assay shows that JAB-2485 induces apoptosis in NCI-H446 cells.

JAB-2485 inhibits the viability of cancer cells

A

Cell Lines	Cancer Type	RB1 Status	IC$_{50}$ (nM)
NCI-H69	SCLC	Nonsense	29.7
NCI-H2171	SCLC	Nonsense	46.1
NCI-H526	SCLC	Nonsense	55.6
NCI-H446	SCLC	Splice site	51.8
NCI-H82	SCLC	Splice site	249
NCI-H209	SCLC	Missense	406
NCI-H1975	NSCLC	WT	54.4
Calu-6	NSCLC	WT	64.9
SW1271	SCLC	WT	225
NCI-H1650	NSCLC	WT	365
DMS53	SCLC	WT	982

B

Cell Lines	Cancer Type	IC$_{50}$ (nM)
Hs578T	TNBC	30.6
BT20	TNBC	38.0
BT549	TNBC	61.6
HCC1806	TNBC	86.2
HCC1143	TNBC	95.2
CoC1	EOC	61.0
A2780	EOC	79.5
EFO-27	EOC	234
SH-SY5Y	NB	8.10
IMR-32	NB	11.3
SK-N-SH	NB	25.1

Table 1. JAB-2485 inhibits the viability of a broad panel of cancer cell lines in the CellTiter-Glo assay.
A. Small cell lung cancer (SCLC) cell lines with RB1 loss-of-function mutations tend to be more sensitive to JAB-2485 than the RB1 WT counterparts. NSCLC: non-small cell lung cancer.
B. Selected triple-negative breast cancer (TNBC), epithelial ovarian cancer (EOC) and neuroblastoma (NB) cell lines are sensitive to JAB-2485.

PK/PD study in NCI-H446 xenograft model

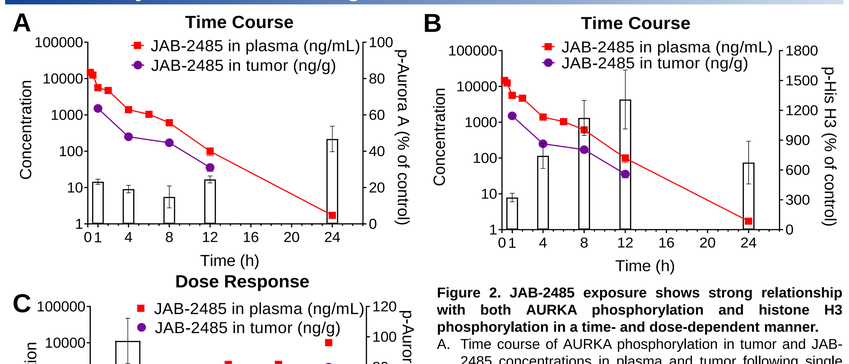


Figure 2. JAB-2485 exposure shows strong relationship with both AURKA phosphorylation and histone H3 phosphorylation in a time- and dose-dependent manner.
A. Time course of AURKA phosphorylation in tumor and JAB-2485 concentrations in plasma and tumor following single dose of JAB-2485 at 10 mg/kg in NCI-H446 xenograft.
B. Time course of histone H3 phosphorylation in tumor and JAB-2485 concentrations in plasma and tumor following single dose of JAB-2485 at 10 mg/kg in NCI-H446 xenograft.
C. Dose-dependent decrease of AURKA phosphorylation in tumor and increase of JAB-2485 concentrations in plasma and tumor at 1 h after single dose of JAB-2485 in NCI-H446 xenograft.
A-B: 3 mice/time point; C: 3 mice/dose.

JAB-2485 suppresses tumor growth as a monotherapy

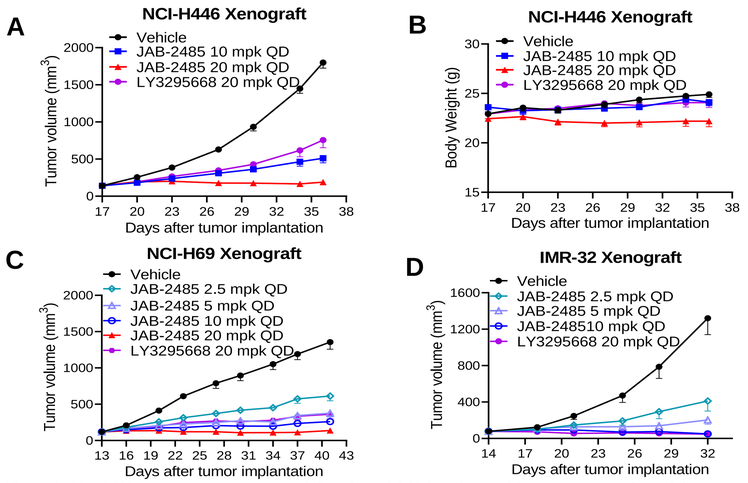


Figure 3. JAB-2485 suppresses tumor growth in selected SCLC and neuroblastoma xenograft models.
A-B. Tumor volume and body weight of NCI-H446 SCLC xenograft model after treatment of JAB-2485 (po. 10 mg/kg QD, 20 mg/kg QD, 5 mg/kg BID, 10 mg/kg BID) and LY3295668 (po. 20 mg/kg QD).
C. Tumor volume of NCI-H69 SCLC xenograft model after treatment of JAB-2485 (po. 2.5, 5, 10, 20 mg/kg QD) and LY3295668 (po. 20 mg/kg QD).
D. Tumor volume of IMR-32 neuroblastoma xenograft model after treatment of JAB-2485 (po. 2.5, 5, 10 and 20 mg/kg QD) and LY3295668 (po. 20 mg/kg QD).
A-D: 9 mice/group.

JAB-2485 enhances anti-tumor efficacy in combination therapies

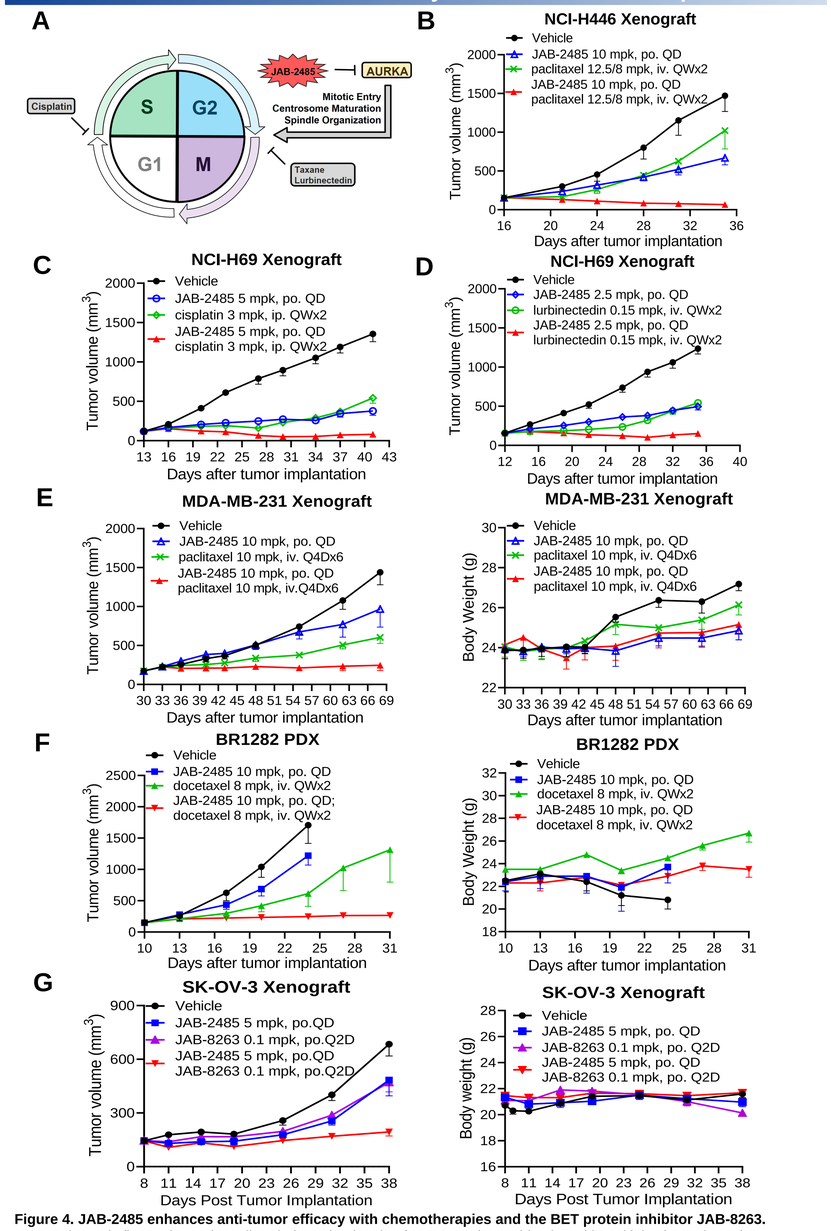


Figure 4. JAB-2485 enhances anti-tumor efficacy with chemotherapies and the BET protein inhibitor JAB-8263.
A. Schematic figure shows the cell cycle-based rationale of JAB-2485 in combination with multiple chemotherapies.
B-G. Anti-tumor activity of JAB-2485 in combination with Paclitaxel in NCI-H446 SCLC xenograft (B); with Cisplatin in NCI-H69 SCLC xenograft (C); with Lurbinectedin in NCI-H69 xenograft (D); with Paclitaxel in MDA-MB-231 TNBC xenograft (E); with Docetaxel in TNBC BR1282 PDX (F); and with BET inhibitor JAB-8263 (Jacobio, Beijing, China) in SK-OV-3 ovarian cancer xenograft (G).
B-E and G: 9 mice/group; F: 3 mice/group. Representative body weights are shown (E-G).

Conclusions

- JAB-2485 is a highly potent AURKA inhibitor, with 1500-fold selectivity over AURKB and AURKC.
- JAB-2485 has minimal pre-clinical myelosuppression owing to its high selectivity over AURKB and AURKC.
- JAB-2485 significantly induces decrease of AURKA phosphorylation and increase of histone H3 phosphorylation in tumor, which may serve as PD markers.
- JAB-2485 shows strong anti-tumor activity and good tolerability both as monotherapy and in combination with chemotherapies and the BET protein inhibitor JAB-8263 (NCT04587479 and NCT04686682) in small cell lung cancer, triple-negative breast cancer, epithelial ovarian cancer and neuroblastoma mouse models.

Reference

- Du *et al*., 2021 *Mol Cancer* 20(1):15.
- Mou *et al*., 2021 *Exp Mol Med* 53(5):835-847.
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Acknowledgment

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