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KB-0742 Is Active in Preclinical *MYC*-High Models of TNBC, Ovarian, and DLBCL Cancers

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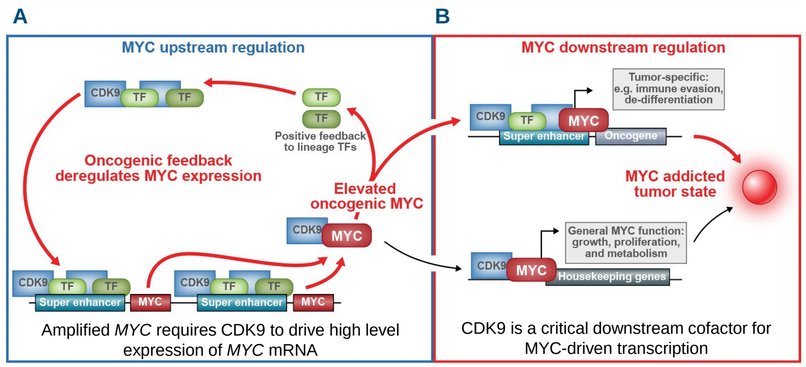
Abstract

- Previously, we profiled pan-cancer sensitivity to KB-0742, a potent, selective, and orally bioavailable small-molecule inhibitor of cyclin-dependent kinase 9 (CDK9), and identified *MYC*-amplified cancers as being especially sensitive to KB-0742. We are currently in dose escalation with KB-0742 in a phase 1/2 clinical trial (NCT04718675). Once a recommended phase 2 dose is determined, we plan to move into expansion cohorts, including one cohort for *MYC*-amplified/dependent tumors. To prioritize the tumor types for the *MYC*-amplified expansion cohort, we evaluated 11 different tumor types using immortalized cell lines, patient-derived cell lines (PDCs), patient-derived organoids (PDOs), and patient-derived xenografts (PDXs). Of the 11 cancer types, triple-negative breast cancer (TNBC), ovarian cancer, and lymphoma showed good responses to KB-0742 treatment. For TNBC and ovarian cancer, immortalized cell lines and PDCs indicated lower half maximal inhibitory concentration (IC_{50}) values with increased *MYC* amplification or expression, and in vivo assessments using 15 PDX models showed good correlation of tumor growth inhibition (TGI) and *MYC* amplification/expression. Two PDO models of TNBC with different treatment histories were also treated with KB-0742 and compared to 4 standard-of-care (SOC) compounds; KB-0742 showed much greater activity in the models, with maximal inhibition rates of 100% and 89%.
- Cell-line screens of blood cancer-derived cell lines showed that lymphocyte-derived cell lines were the most sensitive to KB-0742 when compared with all other cancer types. We tested several PDX models for response to our compound. Treatment with KB-0742 resulted in TGIs of over 50% in several lymphoma models, including a TGI of 56% in 1 model of double-hit diffuse large B-cell lymphoma (DLBCL).
- These data support the selection of TNBC, ovarian cancer, and lymphoma for the *MYC*-amplified expansion cohort in the KB-0742 phase 1/2 clinical trial (NCT04718675).

CDK9 Is Both an Upstream and Downstream Cofactor of MYC in *MYC*-Amplified Tumors



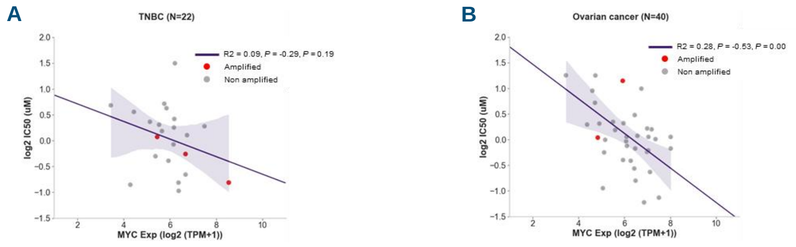
(A) Lineage-specific transcription factors recruit CDK9 to the *MYC* super enhancer, driving high levels of *MYC* expression. Center: Elevated oncogenic MYC activates lineage-specific transcription factors, creating a positive feedback loop. **(B)** CDK9 is an essential cofactor of MYC and allows MYC to drive both tumor-specific and normal gene expression programs.

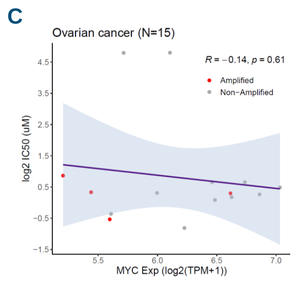
Evaluation of MYC and KB-0742 Activity Across a Variety of Models Representing 11 Cancer Types Identified TNBC, Ovarian, and Lymphoma as Prioritized Indications

Indication	Immortalized Cell Lines	PDCs	PDOs	PDXs	Overall Assessment
TNBC	🔵	🔵	🔵	🟢	🟢
Ovarian	🔵	🔵	⚪	🟢	🟢
Lymphoma	🔵	⚪	⚪	🟢	🟢

Correlation between *MYC* amplification/high expression and KB-0742 activity was assessed in 11 different indications using 4 model platforms (cell lines, PDCs, PDOs, and PDXs). *Green dots* (🟢) indicate statistically significant correlation between *MYC* expression and sensitivity to KB-0742; *blue dots* (🔵) indicate trends; and *gray dots* (⚪) indicate no available data. From this analysis, we identified TNBC, ovarian cancer, and lymphoma as potential expansion cohorts.

KB-0742 Sensitivity Trends With *MYC* Expression Levels in TNBC and Ovarian Cell Models





KB-0742 shows greater activity in *MYC*-elevated cell line models. **(A)** Twenty-two TNBC cell lines were evaluated using the Broad PRISM platform. Cell lines that had *MYC* copy number amplifications (*red dots* indicate 3 or more) trended with lower IC_{50} values than nonamplified cell lines, and IC_{50} values trended with *MYC* RNA expression. **(B)** Forty ovarian cell lines were evaluated using the Broad PRISM platform. Cell lines with higher RNA expression of *MYC* trended with lower IC_{50} values. **(C)** Fifteen PDC models of ovarian cancer were treated with increasing doses of KB-0742. Consistent with the PRISM screen, PDCs with higher expression of *MYC* trended with lower IC_{50} values.

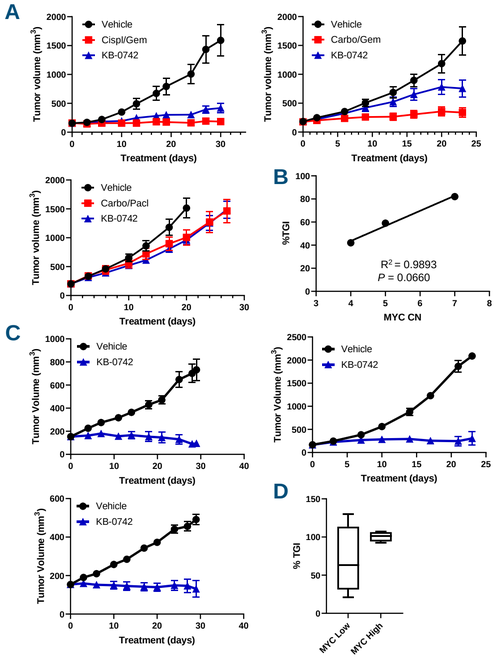
KB-0742 Is Active Against Chemotherapy-Resistant TNBC PDOs

Model Number	Treatment History	Cisplatin		Pemetrexed		Paclitaxel		Gemcitabine		KB-0742	
		IC_{50}	Inh%	IC_{50}	Inh%	IC_{50}	Inh%	IC_{50}	Inh%	IC_{50}	Inh%
KOBR-011	EPI + Pacl 6 cycles	No effect				~0.005	31.56	25.67	59.99	3.49	100
KOBR-472	Pacl + Carbo 4 cycles					>5	14.16	~21.56	15.06	3.42	89

Carbo = carboplatin; EPI = epirubicin; Inh% = percent inhibition; Pacl = paclitaxel.

KB-0742 shows greater activity in 2 PDO models of TNBC compared with 4 SOC compounds. KB-0742 gave significantly higher maximum inhibition rates in both models than all the SOC compounds tested.

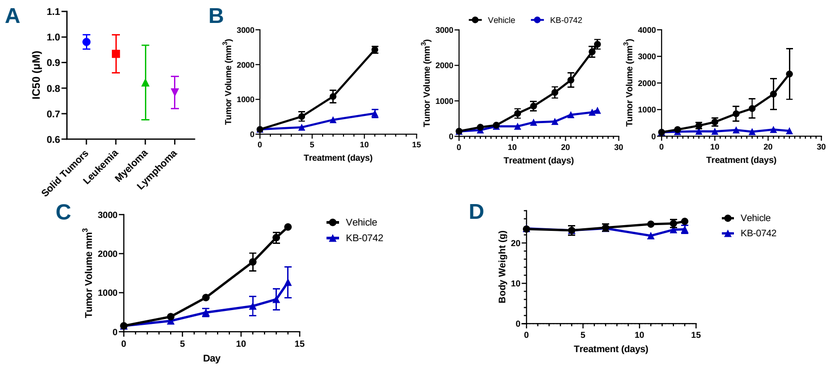
Antitumor Activity Observed With KB-0742 in In Vivo Models of TNBC and Ovarian Cancer



KB-0742 shows antitumor activity in vivo, and response correlates with MYC levels. **(A)** Three PDX models of TNBC were treated with either vehicle, SOC, or KB-0742 at 60 mg/kg orally (PO), 3 days on/4 days off. **(B)** TGI rates correlated with *MYC* copy number. **(C)** Eight ovarian cancer PDX models were treated with either vehicle or KB-0742 at 60 mg/kg PO (3 days on/4 days off), and tumor growth stasis and regression were observed in 3/8 models. **(D)** The TGI rates in the models correlated with the expression of MYC family proteins (cMYC, MYCL, MYCN), with higher expression resulting in greater TGI rates. KB-0742 was well tolerated in all models with no body weight loss of over 15% observed.

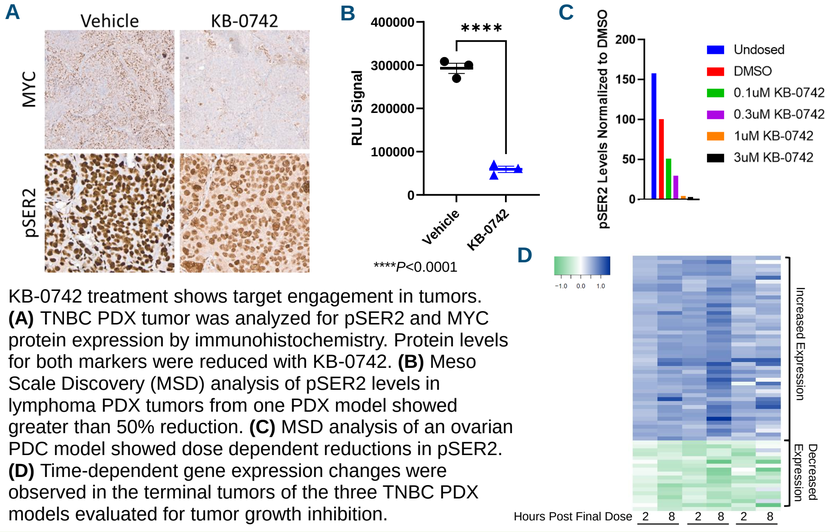
Cispl = cisplatin; Gem = gemcitabine.

KB-0742 Is Active in Models of Lymphoma



KB-0742 shows antitumor activity in models of lymphoma. **(A)** In a 300 cell-line screen, lymphocyte-derived cell lines were more sensitive to KB-0742 than other hematopoietic and solid tumor cell lines, observed by a lower mean IC_{50}. *Error bars* represent standard error of the mean. **(B)** Three PDX models of lymphoma were treated with either vehicle or KB-0742 at 60 mg/kg PO, 3 days on/4 days off. KB-0742 treatment resulted in TGI rates of 68%, 80%, and 98% (left to right). **(C)** A PDX model of double-hit lymphoma was treated with either vehicle or KB-0742 at 60 mg/kg PO, 3 days on/4 days off. KB-0742 treatment resulted in a TGI rate of 56%. **(D)** Similar to all of the models, KB-0742 was well tolerated in the double-hit lymphoma PDX with little variation in body weight.

KB-0742 Treatment Reduces pSER2 Levels and Alters Gene Expression



KB-0742 treatment shows target engagement in tumors. **(A)** TNBC PDX tumor was analyzed for pSER2 and MYC protein expression by immunohistochemistry. Protein levels for both markers were reduced with KB-0742. **(B)** Meso Scale Discovery (MSD) analysis of pSER2 levels in lymphoma PDX tumors from one PDX model showed greater than 50% reduction. **(C)** MSD analysis of an ovarian PDC model showed dose dependent reductions in pSER2. **(D)** Time-dependent gene expression changes were observed in the terminal tumors of the three TNBC PDX models evaluated for tumor growth inhibition.

Conclusions

- Of the 11 cancer types screened for MYC-dependent sensitivity to KB-0742, TNBC and ovarian cancer were identified as showing the strongest correlation between sensitivity and *MYC* expression.
- Several ovarian cancer PDX models showed tumor stasis and/or regression.
- Lymphoma was enriched for sensitivity to KB-0742 compared with other cancer types, but it was not clearly dependent upon *MYC* expression levels. There is ongoing work to better assess the relationship between *MYC* expression and response to KB-0742.
- KB-0742 showed antitumor activity of greater than 50% TGI in several PDX models of lymphoma, including 1 double-hit model.
- KB-0742 treatment showed target engagement in pan-tumor PDX models observed by the reduction of pSER2 levels and changes in gene expression.

A phase 1/2 clinical trial of KB-0742 (NCT04718675) is currently recruiting patients with relapsed or refractory solid tumors or non-Hodgkin lymphoma.

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