Preclinical Activity of KB-0742, An Oral, Highly Selective, CDK9 Inhibitor, in Cell Lines and in MYC-High Expressing, Patient-Derived Models of Multiple Breast Cancer Subtypes

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Introduction

• Phosphorylation of the C-terminal domain of RNA polymerase II (RNPAP) at serine 2 (pS2) by cyclin-dependent kinase 9 (CDK9) is a necessary step to proceed from transcription initiation to elongation.

• The oncogenic transcription factor MYC requires high levels of transcription and is therefore critically dependent on CDK9 for the expression and function as a cancer driver.

• Thus, inhibition of CDK9 could have anti-tumor effects in tumors that express high levels of MYC, including triple-negative breast cancer (TNBC).

• KB-0742 is an orally available, clinical stage CDK9 inhibitor that is potent and highly selective for CDK9 over cyclin-dependent kinases 2 and 4.

• KB-0742 treatment decreased viability of primary, metastatic, and TNBC cell lines and patient-derived tumors treated with KB-0742 sensitized across models, with an emphasis on genes that increased the magnitude fold-change between 2 and 8 hours.

Figure 1. CDK9 is a key dependency in tumor transcriptional reprogramming.

A. CDK9 expression is reduced in primary breast tumors compared to immortalized cell lines. B. CDK9 transcriptional reprogramming in immortalized breast cancer cell lines.

Figure 2. MYC expression across breast cancer subtypes.

A. A representative western blot is shown for the basal subtype. The reduced expression of MYC in basal subtype compared to ER+/HER2- cancers has been previously reported. B. A box plot of MYC mRNA in the basal subtype shows that MYC has significantly higher expression of MYC than either ER+/HER2- or ER-/HER2+ subtypes. C. A box plot of MYC copy number, log transformed, shows that MYC has a significantly higher myeloid MYC copy number than either ER+/HER2- or ER-/HER2+ subtypes.

Figure 3. KB-0742 is a potent and selective CDK9 inhibitor.

KB-0742 inhibits growth in patient-derived cell lines (PDC) and immortalized breast cancer cell lines.

PDC Models

Immunized Cells

KB-0742 inhibits growth of TNBC patient-derived organoid cultures (PDO) that are resistant to treatment with standard of care (SOC) agents.

Figure 4. TNBC cells are preferentially sensitive to KB-0742. Ten patient PDO models representing different breast cancer subtypes were treated with a single-dose of KB-0742 at 60 mg/kg. Each model was treated with a single-dose of KB-0742 at 60 mg/kg and analyzed for cell death. The C50 values for the KB-0742/HER2+ subtypes were lower than for the ER+/PR- subtypes.

Figure 5. KB-0742 shows greater activity than SCD3 compounds in 2 PDO models of TNBC. Two TNBC PDO models with different treatment responses were used to compare the activity of KB-0742 to SCD3 compounds. KB-0742 showed greater activity in both models than all 4 SCD compounds.

Figure 6. KB-0742 inhibits tumor growth in 3 MYC-amplified TNBC models of breast cancer. Animals bearing established subcutaneous TNBC PDO models were treated with either vehicle (saline), KB-0742, MYC siRNA, or MYC shRNA. MYC knockdown was determined by western blot analysis. KB-0742 treated PDO models showed a significant increase in tumor volume control and MYC siRNA-treated PDO models had a significant increase in tumor volume compared to saline treated PDO models. The median survival time of mice treated with KB-0742 was 40 days versus 30 days for mice treated with saline. The median survival time of mice treated with MYC siRNA was 40 days versus 30 days for mice treated with saline.

Figure 7. KB-0742 modulates expression of genes in tumors and PBMCs from treated mice. Tumors and PBMCs from CTG-0886 tumor-bearing animals were analyzed 2 and 8 hours post-dose for expression of either KB-0742 or MYC. Changes in expression of both KB-0742 and MYC were determined using the respective HT-1080 assay. The plasma concentration of KB-0742 was 702 ng/ml (2.5 µM) and 170 ng/ml (0.5 µM) at 2 and 8 hours post-dose, respectively.

Figure 8. Treatment with KB-0742 abrogates gene expression in tumors and PBMCs from treated mice.

A. Western blot analysis of protein expression in tumors from patients treated with vehicle or KB-0742 60 mg/kg. B. Gene expression profiling of TNBC PDO models after treatment with KB-0742.

TNBC expresses significantly higher levels of MYC than either HER2+ or ER-/PR- breast cancers.

A. Whole genome screening using TCGA data shows that MYC is consistently highly expressed across all subsets of TNBC patients. B. A box plot of MYC expression across breast cancer subtypes shows that MYC has significantly higher expression of MYC than either ER+/HER2- or ER-/HER2+ subtypes. C. A box plot of MYC copy number, log transformed, shows that MYC has a significantly higher myeloid MYC copy number than either ER+/HER2- or ER-/HER2+ subtypes.

Figure 9. KB-0742 is a highly selective and orally bioavailable CDK9 inhibitor.

A. Treatment of a panel of breast cancer cell models with KB-0742, including HER2+, ER+, HER2+/ER+, and TNBC subtypes, resulted in cell death viability.

References


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