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Background

Disruption of transcriptional regulatory networks that drive normal cellular differentiation and development can result in oncogenic transformation and transcriptional addiction. Many pediatric sarcomas are defined by/harbor oncogenic fusion proteins, resulting from chromosomal translocations such as the *EWSR1* gene fused to an ETS family transcription factor (TF) gene (*FLI1* or *ERG*) in Ewing sarcoma, or *PAX3/PAX7* and *FOXO1* translocations in alveolar rhabdomyosarcoma. In neuroblastoma, MYCN, a member of the MYC family of TFs, is often amplified and localizes to super enhancer regions, where it rewires lineage-specific transcriptional programs driving oncogenesis.

Oncogenic TFs have proven difficult to target directly; we and others have proposed targeting associated transcriptional co-regulators to inhibit their activity. CDK9 interacts with many oncogenic TFs and is essential for TF-mediated transcription elongation through phosphorylation of the C-terminal domain of RNA pol II. KB-0742 is a potent, selective, and orally bioavailable inhibitor of CDK9 currently in clinical development that shows antitumor activity in preclinical models of sarcoma and neuroblastoma.

Materials and methods

Cell lines and low-passage patient-derived cells (PDCs) were tested for antiproliferative effects of KB-0742, using either Cell Titer Glo (Promega) or Alamar Blue cell viability reagent (Bio-Rad). Pharmacodynamic (PD) markers of KB-0742 treatment, including phospho-SER2 (pSER2) on RNA pol II, MYCN, MYC, and cleaved poly ADP ribose polymerase (PARP), were measured by Western blot. The antitumor activity of KB-0742 was evaluated using patient-derived xenograft (PDX) models of Ewing sarcoma and alveolar rhabdomyosarcoma *in vivo*. Tumor samples and plasma were collected to determine PD effects and drug concentrations, respectively. The transgenic TH-MYCN model of neuroblastoma was used to study antitumor effects of KB-0742. All *in vivo* models were performed according to IACUC guidelines.

Disrupted transcription regulatory networks in pediatric cancers

