Recent advancements in understanding the pathology of the disease has shown that small-cell lung cancer (SCLC) tumorigenesis and evolution are governed by increased expression of neuroendocrine-associated and other proto-oncogenic transcription factors. Thus, targeting transcription may be an effective therapeutic strategy. Cyclin-dependent kinase 9 (CDK9) is a serine-threonine kinase involved in transcriptional elongation through the phosphorylation of the RNA polymerase II (RNAPII), and it interacts with transcription factors to promote the activation of target genes. We developed KB-0742, a highly selective and orally bioavailable inhibitor of CDK9.

Evaluation of KB-0742 activity in cell lines showed a correlation between MYC copy-number amplification (CNA) and sensitivity, with amplified lines having smaller area under the curve (AUC) values than nonamplified lines. In a panel of 6 patient-derived organoid (PDO) SCLC models with different treatment histories, KB-0742 was more active than the standard-of-care (SOC) compounds. In a separate study of 4 treatment-naive PDO models, KB-0742 was active in 3 different transcription factor-driven subtypes of SCLC, and the response correlated significantly with e-MYC and MYCL expression. Lastly, we used 4 patient-derived xenograft (PDX) models to evaluate KB-0742 activity in vivo. The tumor growth inhibition (TGI) rate ranged from 54% to 92%, with tumor regressions observed in 2 of the 4 models, and 1 model showed greater TGI with KB-0742 when compared with SOC.

These data support the evaluation of KB-0742 as a potential treatment for SCLC. Patients with relapsed or refractory solid tumors or non-Hodgkin lymphoma are currently being enrolled in a phase 1/2 clinical trial of KB-0742 (NCT04718676) with an expansion arm for SCLC being planned after the recommended phase 2 dose is identified.

Conclusions

- Sensitivity to CDK9 inhibitor KB-0742 is associated with MYC expression/amplification in SCLC cells.
- MYC and MYCL expression correlates with KB-0742 activity in PDO models.
- SCLC PDO models showed sensitivity to KB-0742 regardless of the treatment history.
- KB-0742 showed antitumor activity in multiple PDO models of SCLC, representing different tumor subtypes with tumor regressions observed in half of the models.
- KB-0742 activity in SCLC PDO models correlated with MYC protein family expression. (A) Four PDO models with different transcription-factor drivers were treated with a range of KB-0742 concentrations and cell viability measured using CellTiter-Glo® (Promega). (B) Dose-response curves of the 4 models treated with KB-0742. (C) Sensitivity to KB-0742 correlated with increased expression of MYC and MYCL.

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Target Engagement Observed in SCLC PDO Tumors

KB-0742 treatment reduced phosphorylation of RNAPII (pS2E) levels and altered RNA expression profiles in PDO tumors. (A) pS2E protein levels were measured using a Meso Scale Discovery assay. KB-0742 60 mg/kg treatment resulted in a 50% or greater reduction after 3 days of dosing. (B) RNA sequencing of the LU11953 PDO tumors showed altered gene expression in key genes, including a reduction in MYC expression.

CDK9 Inhibitor KB-0742 Is Active In Preclinical Models of Small-Cell Lung Cancer

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Abstract

SCLC comprises multiple molecular subtypes defined by the expression of specific transcription factors: ASCL1, NEUROD1, POU2F3, and YAP1. Evolution between subtypes is amplified/highly expressed in the other subtypes.

SBDD, 2-bromodeoxyuridine 4’, 6-cyclit 7’, 5-D, 2-Dihydro-1-bromo2-dideoxyadenosine-sensitivity inducing factor; NSIL = negative elongation factor; P = phosphate; TF = transcription factor

As a transcriptional regulator, CDK9 is a key dependency in transcriptionally addicted tumors. KB-0742 helps promote the tumor-associated transcriptional landscape through 2 mechanisms:

1. (A) Supporting expression of key oncogenes, and
2. (B) Working as a cofactor to oncogenic transcription factors, such as MYC, to promote high rates of transcription

CDK9 is a Key Dependency in Tumor Transcriptional Reprogramming

SCLC is Governed by Proto-oncogenic Transcription Factors

Conclusions

• Sensitivity to CDK9 inhibitor KB-0742 is associated with MYC expression/amplification in SCLC cells.
• MYC and MYCL expression correlates with KB-0742 activity in PDO models.
• SCLC PDO models showed sensitivity to KB-0742 regardless of the treatment history.
• KB-0742 showed antitumor activity in multiple PDO models of SCLC, representing different tumor subtypes with tumor regressions observed in half of the models.
• KB-0742 activity in SCLC models correlated with transcription-factor activity, whether it was MYC or MYCL.
• Together, these data support the development of KB-0742 as a potential treatment for SCLC.