Poster CT158

A dose escalation and cohort expansion study of the CDK9 inhibitor KB-0742 in relapsed, refractory and transcriptionally addicted solid tumors

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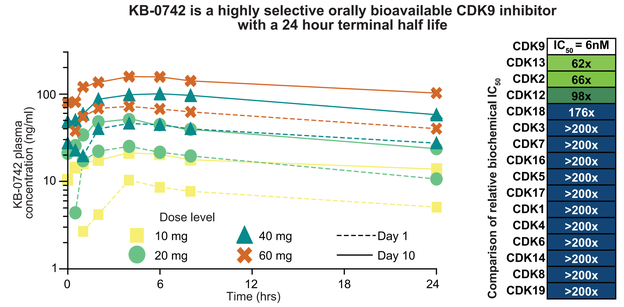
Background and rationale for targeting CDK9 in transcriptionally addicted tumors

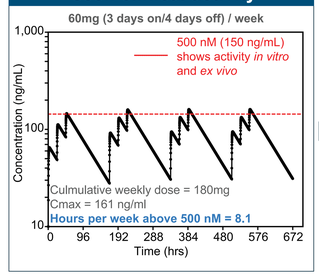
- Two categories of transcriptionally addicted tumors are sarcomas with transcription factor fusions and tumors with MYC deregulation.
- We have previously shown clinical benefit in myxoid liposarcomas with TF fusions (Villalona-Calero et al., abstract B159, AACR-NCI-EORTC, 2023).
- Analysis of a real-world solid tumor cohort including NSCLC (n= 20,470), SCLC (n=1,517), TNBC (n=2,576) and ovarian cancer (n=1,667) demonstrated MYC family overexpression and/or genomic amplification in 47% to 87% of patients.
- Both TF-fusion and MYC deregulated tumors exhibit high dependency on cyclin-dependent kinase 9 (CDK9) activity.
- KB-0742 is a potent, selective, and orally bioavailable inhibitor of CDK9 with a long plasma half-life. KB-0742 is being evaluated in an ongoing Phase 1 /2 study in advanced solid tumors (NCT04718675).
- KB-0742 is dosed orally once daily for three consecutive days followed by four days off in 28-day cycles until unacceptable toxicity or disease progression. Based on pharmacokinetic data, alternate dosing schedules are being explored with KB-0742 dosed four consecutive days on, followed by three days off treatment schedule.

KB-0742 plasma concentrations at day 10 of dosing across the 10mg to 60mg cohorts

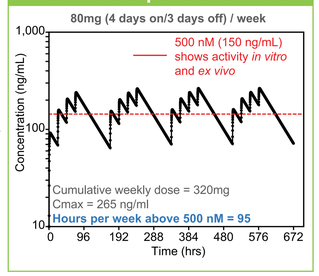


KB-0742 long half-life and kinase selectivity allows selective targeting of transcriptional addiction

Dose at which we have currently seen clinical activity



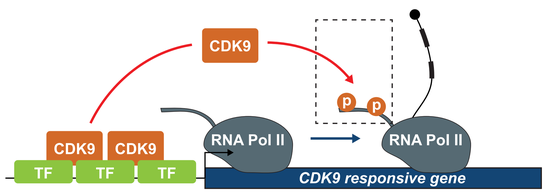
Dose at which we expect to enroll expansion cohort



CDK9 is a critical cofactor of transcriptionally addicted tumors

CDK9 — **CDK9 is a kinase that is recruited to the genome by transcription factors and drives transcription elongation at many oncogenes**

Phosphorylated serine 2 (pSER2) of the RNA polymerase II C-terminal domain is a key CDK9 kinase substrate

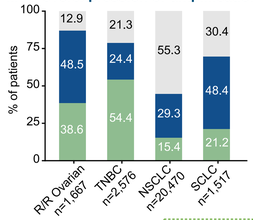


Cohorts with CDK9-dependent transcriptional addiction

Cohort A: Oncogenic TF = MYC

Cohort B: Oncogenic TF = Fusion Partner (TF#1, TF#2); Oncogenic TF = Lineage Specific

Tumors with high prevalence of MYC overexpression or amplification[1]



Example tumor type	TF#1	TF#2
Ewing sarcoma	EWSR1	FLI1
	FUS	ERG
Myxoid liposarcoma	DDIT3	FUS
Adenoid cystic carcinoma	MYB	NFIB
Alveolar rhabdomyosarcoma	PAX3	FOXO1
	PAX7	FOXO1

SCLC is also addicted to lineage specific TFs (Cohort B)

Example tumor type	Example lineage TF
Small Cell Lung Cancer*	NEURDO1
	ASCL1
	POU2F3
	YAP1

Est. Drug Treatable ≥2L U.S. Patients >100,000[1]

Est. Drug Treatable U.S. Patients >50,000[1,2,3,4]

KB-0742 – 1001 overall trial design (NCT04718675)

Phase 1/2, first-in-human, open-label dose escalation and expansion study of KB-0742 in patients with relapsed or refractory solid tumors or NHL

Oral administration 3 days on / 4 days off

10mg (n=3) → 20mg (n=4) → 40mg (n=7) → 60mg (n=14)

mCRM Design
Dose escalation enrolled "all-comer" solid tumors and NHL

Oral administration 4 days on/3 days off

80mg (n=3+3)

Cumulative weekly dose of 240mg: 80mg (n=14) → 60mg (n=3+3)

3+3 Design
Dose escalation will enrolled "all-comer" solid tumors

80mg 4 days on/3 days off expansion cohort
Expected enrollment Q3 2024

Cohort A:
MYC-dependent solid tumors
(Ovarian, TNBC, NSCLC, SCLC)

60mg 3 days on/4 days off expansion cohort
Clinical update mid-2024

Cohort A: MYC-dependent solid tumors *(Ovarian, TNBC, NSCLC)*

Cohort B: Other transcriptionally addicted tumors *(SCLC*, TF fusion driven cancers (e.g., sarcomas, ACC))*

Ongoing Enrollment
Future Enrollment

ACC: adenoid cystic carcinoma. mCRM: modified continual reassessment method; NHL: Non-Hodgkin lymphoma; NSCLC: non-small cell lung cancer. SCLC: small cell lung cancer. TF: transcription factor. TNBC: triple negative breast cancer.

*SCLC is also MYC-dependent

Eligibility criteria

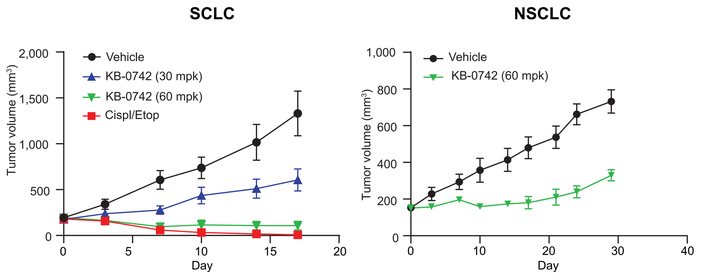
- Any R/R solid tumor with readily accesible biopsy sites and consenting to 1 baseline and 1 on-treatment biopsy
- Age ≥ 18, acceptable organ function and ECOG PS < 2
- Tumor types of interest include:
  - Small cell lung cancer
  - Ovarian, TNBC, or NSCLC
  - Diffuse large B-cell lymphoma or Burkitt's lymphoma with MYC translocation
  - Sarcoma of histologic subtype known to be associated with TF Fusion
  - Chordoma, nut midline carcinoma, adenoid cystic carcinoma

Eligibility criteria

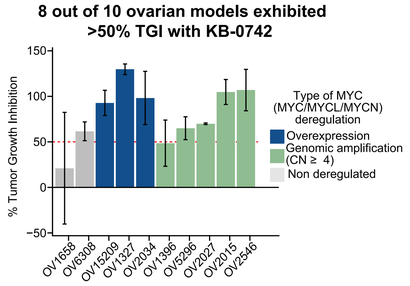
- Solid tumors that have failed, are intolerant to, or are ineligible for standard of care anticancer treatments
- **Cohort A:** Tumor types with high prevalence of MYC deregulation: ovarian, triple negative breast cancer, non small cell lung cancer
- **Cohort B:** Small cell lung cancer and transcriptionally addicted tumor types including sarcomas of histologic subtypes associated with TF fusion, chordoma, ACC and nut midline carcinoma

KB-0742 drives tumor growth inhibition in MYC deregulated *in vivo* tumor models

KB-0742 shows monotherapy anti-tumor activity in lung patient-derived xenografts



KB-0742 activity in ovarian cancer patient-derived xenograft (PDX) models



Left: KB-0742 showed antitumor activity in PDX models of SCLC and NSCLC. PDX models were treated with KB0742 at either 30 and 60mg/kg on a dosing schedule of 3 days on/4 days off. KB-0742 showed antitumor activity in a dose-dependent manner with 92% and 57% TGI in SCLC and NSCLC at 60mg/kg, respectively.[5] **Right**: Ovarian cancer mouse clinical trial results demonstrating broad single agent activity in MYC family amplified or overexpressed subtypes. Three animals per model were enrolled in the study.[6]

Study objectives

Primary

- Evaluate safety and tolerability of KB-0742 in defined patient cohorts

Secondary

- Characterize the PK of KB-0742
- Characterize anti-tumor activity of KB-0742

Study endpoints

Primary

- Descriptive safety analysis of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), and laboratory assessments

Secondary

- Evaluation of the pharmacokinetic profile, progression free survival (PFS), overall response rate (ORR) and duration of response (DOR)

Summary

- KB-0742 is an oral highly selective CDK9 inhibitor with an attractive profile including a long half-life.
- Preliminary data have been previously reported; Villalona-Calero et al., Abstract B159, AACR-NCI-EORTC, 2023.
- The ongoing trial KB-0742-1001 will continue to enroll and examine additional dosage/schedules (NCT04718675).

References: 1. Decision Resources Group 2022; 2. Huang et al. Scientific Reports 2023; 3. Gage et al. Oncotarget (2019); 4. Togashi et al. Modern Pathology (2018); 5. Day et. al., Presentation ID 2565, American Association for Cancer Research Annual Meeting, April 8-13, 2022, New Orleans, LA; 6. Kronos Bio Inc., Data on file, 2023

Presented at the 2024 American Association of Cancer Research Annual Meeting, April 5-10, 2024, San Diego, California.