A First-In-Human Study of CDK9 Inhibitor KB-0742 Demonstrates Evidence of Tolerability and Clinical Activity

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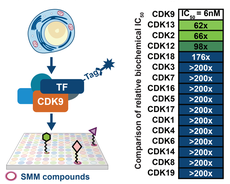
Background & rationale

- Transcription deregulation is a hallmark of cancer that often confers selective tumor dependence on components of the cellular transcriptional machinery. This "transcriptional addiction" can involve requirements for high transcription rates of oncogenes such as MYC or chimeric fusion transcription factors (TFs).
- Cyclin-dependent kinase 9 (CDK9) is a hub for transcriptional control that interacts with many oncogenic TFs, marking it a promising therapeutic target in transcriptionally addicted tumors.
- Using our small molecule microarray (SMM) platform, we identified and optimized KB-0742, a potent, selective, orally bioavailable CDK9 inhibitor. KB-0742 is currently being studied in a phase 1/2 dose escalation trial in solid tumors and NHL and cohort expansion for patients with transcription-dependent tumors (NCT04718675).

KB-0742: a highly selective orally bioavailable CDK9 inhibitor

KB-0742 emerged from a SMM screen against an oncogenic variant of the androgen receptor TF

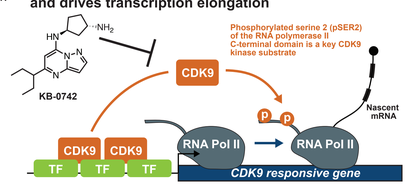


CDK	IC_{50} = 6nM
CDK13	62x
CDK2	66x
CDK12	133x
CDK18	176x
CDK3	>200x
CDK7	>200x
CDK16	>200x
CDK5	>200x
CDK17	>200x
CDK1	>200x
CDK4	>200x
CDK6	>200x
CDK14	>200x
CDK8	>200x
CDK19	>200x

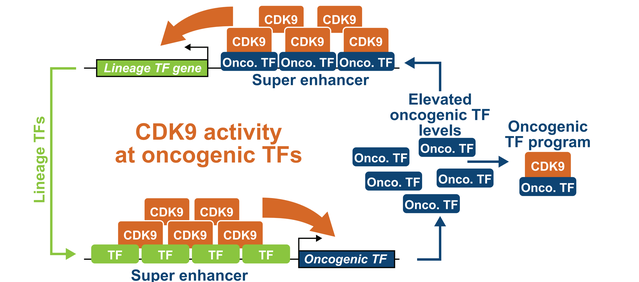
Comparison of relative biochemical IC_{50}

Richters et al., 2020 Cell Chemical Biology

CDK9 is a kinase that is recruited to DNA by TFs and drives transcription elongation



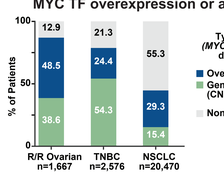
CDK9 drives multiple forms of transcriptional addiction



Two examples of CDK9 driven oncogenic TFs and tumors sensitive to KB-0742

1 Oncogenic TF = MYC

Tumors with high prevalence of MYC TF overexpression or amplification



2 Oncogenic TF = Fusion TF (TF #1 / TF #2)

Tumors with TF fusions

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

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Fig. 1: KB-0742 dose escalation trial design

This is a Phase 1, first-in-human, open-label dose escalation (N = 28) and expansion study of KB-0742 in patients with relapsed or refractory solid tumors or NHL

10 mg (n=3) → 20 mg (n=4) → 40 mg (n=7) → 60 mg (n=14) → Continued escalation / RP2D → Expansion cohorts

Oral administration 3d on / 4d off QW

Goals

To determine the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and evaluate the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of KB-0742 in patients with relapsed/refractory (R/R) solid tumors.

Eligibility

- Any R/R solid tumor
- Age > 18 years, acceptable organ function and ECOG PS < 2
- Tumor types of interest, including:
  - SCLC, epithelial ovarian cancer, TNBC, or NSCLC
  - DLBCL with documented MYC translocation or Burkitt's lymphoma
  - Sarcoma with documented TF fusion
  - Chordoma, NUT midline carcinoma, or adenoid cystic carcinoma

Endpoints

The primary endpoint was a descriptive safety analysis of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), and laboratory assessments.

The secondary endpoints included an evaluation of the pharmacokinetic profile, progression free survival (PFS), overall response rate (ORR) and duration of response (DOR).

Patient characteristics, safety and tolerability

Table 1: Patient characteristics

Patient characteristic	10 mg (N=3)	20 mg (N=4)	40 mg (N=7)	60 mg (N=14)	Total (N=28)
Median age, years (range)	60.0 (51 - 60)	48.5 (29 - 70)	62.0 (34 - 83)	58.5 (41 - 84)	59.5 (29 - 84)
Female, N (%)	2 (67)	2 (50)	4 (57)	9 (64)	17 (61)
Ethnicity, N (%)					
Asian	0	1 (25)	1 (14)	0	2 (7)
Black or African American	1 (33)	0	1 (14)	0	2 (7)
White	2 (67)	3 (75)	5 (71)	14 (100)	24 (86)
Other	0	0	0	0	0
Median prior systemic anticancer regimens, N (range)	2.0 (0 - 3)	6.5 (5 - 11)	4.0 (0 - 8)	3.0 (0 - 6)	3.5 (0 - 11)

Table 2: Most common TEAEs (in ≥10% of total)

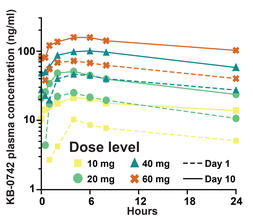
Dose level, N	10 mg (N=3)	20 mg (N=4)	40 mg (N=7)	60 mg (N=14)	Total (N=28)		
Events, N (%)	Any grade				Gr 1/2	Gr 3/4	Any
Any TEAE	3 (100)	4 (100)	7 (100)	14 (100)	17 (61)	11 (39)	28 (100)
Vomiting	1 (33)	2 (50)	6 (86)	10 (71)	19 (68)	0 (0)	19 (68)
Nausea	1 (33)	3 (75)	5 (71)	9 (64)	18 (64)	0 (0)	18 (64)
Fatigue	0	4 (100)	1 (14)	3 (21)	8 (29)	0 (0)	8 (29)
Peripheral edema	1 (33)	1 (25)	1 (14)	3 (21)	6 (21)	0 (0)	6 (21)
Cholesterol increase	0	0	1 (14)	4 (29)	5 (18)	0 (0)	5 (18)
Proteinuria	0	0	1 (14)	4 (29)	5 (18)	0 (0)	5 (18)
Cognitive disorder	0	0	3 (42)	1 (7)	4 (14)	0 (0)	4 (14)
Constipation	1 (33)	0	1 (14)	2 (14)	4 (14)	0 (0)	4 (14)
Diarrhea	0	0	2 (29)	2 (14)	4 (14)	0 (0)	4 (14)
Dizziness	0	0	2 (29)	2 (14)	4 (14)	0 (0)	4 (14)
Hypertriglyceridemia	0	0	1 (14)	3 (21)	4 (14)	0 (0)	4 (14)
Hypertension	0	1 (25)	2 (29)	1 (7)	2 (7)	2 (7)	4 (14)
Arthralgia	1 (33)	0	0	2 (14)	3 (11)	0 (0)	3 (11)
Confusional state	0	1 (25)	2 (29)	0	3 (11)	0 (0)	3 (11)
Hyperglycemia	0	0	1 (14)	2 (14)	3 (11)	0 (0)	3 (11)
Hypokalemia	0	0	1 (14)	2 (14)	3 (11)	0 (0)	3 (11)
Hyponatremia	0	0	1 (14)	2 (14)	3 (11)	0 (0)	3 (11)
Headache	0	0	1 (14)	2 (14)	3 (11)	0 (0)	3 (11)
Insomnia	1 (33)	0	1 (14)	1 (7)	3 (11)	0 (0)	3 (11)
LDH increase	0	0	0	3 (21)	3 (11)	0 (0)	3 (11)
Mental status changes	0	0	2 (29)	1 (7)	2 (7)	1 (4)	3 (11)
Muscular weakness	0	1 (25)	0	2 (14)	3 (11)	0 (0)	3 (11)
Urinary tract infection	0	0	1 (14)	2 (14)	3 (11)	0 (0)	3 (11)

Table 3: Hematologic laboratory abnormalities (based on NCI-CTCAE grading)

Dose level, N	10 mg (N=3)	20 mg (N=4)	40 mg (N=7)	60 mg (N=14)	Total (N=28)		
Events, N (%)	Any grade				Gr 1/2	Gr 3/4	Any
Anemia	2 (67)	2 (50)	5 (71)	12 (86)	21 (75)	0	21 (75)
Lymphopenia	1 (33)	2 (50)	4 (57)	11 (79)	9 (32)	9 (32)	18 (64)
Neutropenia	1 (33)	1 (25)	0	0	2 (7)	0	2 (7)
Thrombocytopenia	0	0	0	4 (29)	4 (14)	0	4 (14)

At the time of data cut-off (9/1/23), a total of 28 patients were enrolled in dose escalation 10 mg - 60 mg. The most common treatment-emergent AEs (TEAEs) were nausea (64.3%), vomiting (67.9%) and fatigue (28.6%), all of which were grade 1/2; Two patients experienced DLTs including altered mental status/seizure (at 40 mg) and encephalopathy (at 60 mg) (Table 2). No grade 3/4 neutropenia was observed (Table 3). No treatment-related deaths were observed; One grade 5 AE unrelated to study treatment was observed (due to staphylococcal sepsis).

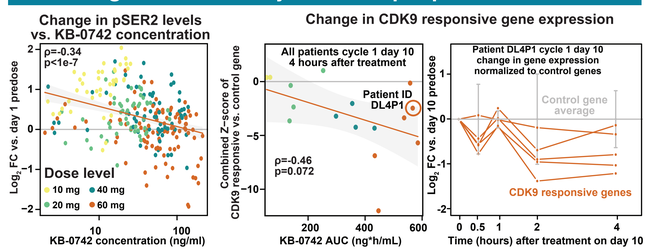
Fig. 2: Pharmacokinetics



KB-0742 plasma concentrations at day 1 and 10 of dosing across the 10 to 60 mg cohorts.

KB-0742 plasma half-life is approximately 24 hours, leading to accumulation ratios (AUC Day 10/AUC Day 1) of 2.1 to 2.5

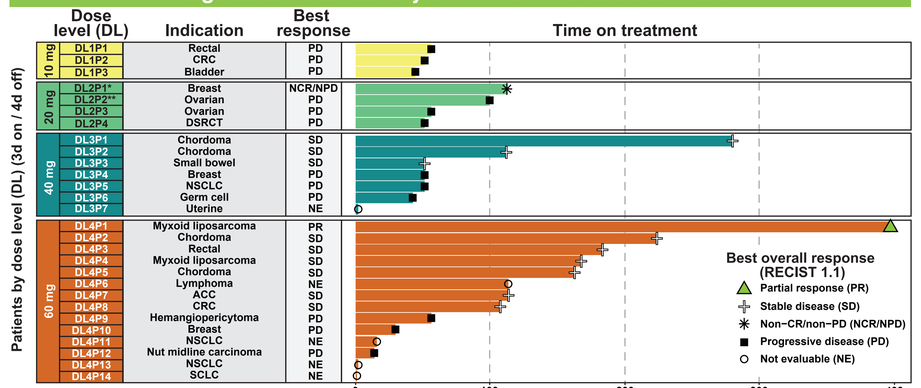
Fig. 3: Pharmacodynamics in peripheral blood



Target engagement assessed in peripheral blood day 1 and day 10 of treatment and assayed for changes in pSER2 or gene expression of CDK9 responsive genes.

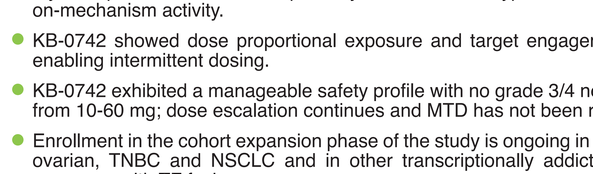
Left: Scatter plot of pSER2 change vs. KB-0742 plasma concentration. Measurements are colored by patient dose level. **Middle:** Scatter plot of CDK9 responsive gene expression change (cumulative Z-score) vs. KB-0742 cumulative exposure (AUC) is plotted. **Right:** Normalized CDK9 responsive gene expression changes on day 10 for patient DL4P1.

Fig. 4: KB-0742 efficacy across dose escalation cohort

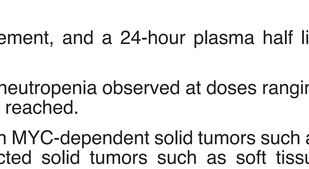


Duration of KB-0742 treatment and clinical outcome is plotted for all patients (N=28) in the part 1 dose escalation portion of the trial. Patients are organized and colored by dose level. Patient tumor indication, time on trial and best overall response (RECIST 1.1) are plotted. *Patient DL2P1 response NCR/NPD was due to the patient having evaluable but not measurable disease at baseline. **Patient DL2P2 progressed at an earlier date and stayed on treatment post-progression.

Maximum % change in tumor size



Myxoid liposarcoma patient DL4P1 scan



Waterfall plot showing patients ranked by maximum change in tumor size from baseline. Of the 21 patients with at least 1 overall response assessment, one partial response (per RECIST v1.1) was observed lasting 113 days in a 7th line myxoid liposarcoma patient (scan on the right). 9 (43%) patients had stable disease (SD) as the best response and the overall disease control rate was 48% (defined as a CR (Complete Response), Partial Response (PR), or Stable Disease (SD)).

Conclusions

- KB-0742, a selective CDK9 inhibitor, demonstrated objective single agent anti-tumor activity in heavily pre-treated patients with transcriptionally addicted tumor types.
- Tumor reduction (1 PR, 1 SD with 26% reduction in tumor diameter) was observed in two patients with myxoid liposarcoma, a transcriptionally addicted tumor type characterized by a fusion TF consistent with on-mechanism activity.
- KB-0742 showed dose proportional exposure and target engagement, and a 24-hour plasma half life enabling intermittent dosing.
- KB-0742 exhibited a manageable safety profile with no grade 3/4 neutropenia observed at doses ranging from 10-60 mg; dose escalation continues and MTD has not been reached.
- Enrollment in the cohort expansion phase of the study is ongoing in MYC-dependent solid tumors such as ovarian, TNBC and NSCLC and in other transcriptionally addicted solid tumors such as soft tissue sarcomas with TF fusions.

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