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=1,167) 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 orally daily once 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 is a highly selective orally bioavailable CDK9 inhibitor with a 24 hour terminal half-life. KB-0742 is a critical cofactor of transcriptionally addicted tumors

CDK9 is a critical cofactor of transcriptionally addicted tumors

- CDK9 is a kinase that is recruited to the genome by transcription factors and drives transcription elongation at many oncogenes.
- Phosphorylated serine 2 (pS2E) of the RNA polymerase II C-terminal domain is a key CDK9 kinase substrate.

Cohorts with KB-0742-dependent transcriptional addiction

Tumors with high prevalence of MYC overexpression or amplification

<table>
<thead>
<tr>
<th>Example tumor type</th>
<th>Gene fusion</th>
<th>MYC overexpression or amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM</td>
<td>GNA16</td>
<td>86%</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>NUP98</td>
<td>80%</td>
</tr>
<tr>
<td>MLL/AF9</td>
<td>MYC</td>
<td>78%</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>MYC</td>
<td>76%</td>
</tr>
<tr>
<td>T-cell lymphoma</td>
<td>MYC</td>
<td>65%</td>
</tr>
</tbody>
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Study objectives

- Characterize the PK of KB-0742
- Characterize anti-tumor activity of KB-0742
- Characterize the PK of KB-0742
- Evaluate safety and tolerability of KB-0742 in defined patient cohorts
- Descriptive safety analysis of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), and laboratory assessments

Study endpoints

- Characterize the PK of KB-0742
- Characterize anti-tumor activity of KB-0742
- Safety and tolerability of KB-0742 in defined patient cohorts
- Preliminary data have been previously reported: Villalona-Calero et al., Abstract B159, AACR-NCI-EORTC, 2023.
- The ongoing trial (NCT04718675) will continue to enroll and examine additional dosage schedules (NCT04718675).

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