A FIRST-IN-HUMAN STUDY OF CDK9 INHIBITOR KB-0742 DEMONSTRATES PRELIMINARY EVIDENCE OF CLINICAL ACTIVITY IN TRANSCRIPTIONALLY ADDICTED SARCOMAS

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KB-0742 is a highly selective, orally bioavailable inhibitor of CDK9, a critical regulator of oncogene transcription.

KB-0742 emerged from a small molecule microarray (SMM) screen against an oncogenic variant of the androgen receptor TF.

Reference: Richters et al., 2020, Cell Chemical Biology
KB-0742 modulates CDK9, a kinase that is recruited to DNA by TFs (Transcription Factors) and drives transcription elongation.

Reference: Richters et al., 2020, Cell Chemical Biology
KB-0742 reduces the expression of key oncogenic TFs in sarcoma models*

Presented by:
Brian Van Tine, M.D., Ph.D.

*With Berkley Gryder, CWRU

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

KB-0742 Phase I Dose Escalation Trial Design

- Relapsed/refractory solid tumors and NHL (no enrichment for transcriptionally addicted tumors)
- MTD not yet defined; continuing to dose escalate in parallel with expansions at 60 mg

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## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>10 mg (N=3)</th>
<th>20 mg (N=4)</th>
<th>40 mg (N=7)</th>
<th>60 mg (N=14)</th>
<th>Total (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60.0 (51 - 60)</td>
<td>48.5 (29 - 70)</td>
<td>62.0 (34 - 83)</td>
<td>58.5 (41 - 84)</td>
<td>59.5 (29 - 84)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>4 (57)</td>
<td>9 (64)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (25)</td>
<td>1 (14)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (14)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>White</td>
<td>2 (67)</td>
<td>3 (75)</td>
<td>5 (71)</td>
<td>14 (100)</td>
<td>24 (86)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median prior systemic anticancer regimens, N (range)</td>
<td>2.0 (0 - 3)</td>
<td>6.5 (5 - 11)</td>
<td>4.0 (0 - 8)</td>
<td>3.0 (0 - 6)</td>
<td>3.5 (0 - 11)</td>
</tr>
</tbody>
</table>
Safety & tolerability: most common TEAEs (in ≥ 10% of patients)

- All 28 patients experienced at least one TEAE, with more than half (61%) of these events being grade 1 or 2*

Grade Distribution, Total Population (n=28)

*AEs occurring in < 10% of patients include two patients who experienced a single episode of seizures. While there is no known mechanistic link between CDK9 inhibition and CNS toxicity, these events are being closely monitored.

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Safety & tolerability: hematologic laboratory abnormalities (based on NCI-CTCAE grading)

- No grade 3/4 neutropenia was observed with KB-0742 treatment
KB-0742 anti-tumor activity: objective regressions in 2 TF fusion-driven tumor patients

- One partial response lasting 113 days in a 7th line myxoid liposarcoma patient who was on treatment for 398 days. Second patient achieved 26% reduction in tumor diameters
- 9 (43%) patients had stable disease (SD) as the best response
- Overall disease control rate was 47.8% - defined as a CR (Complete Response), Partial Response (PR), or Stable Disease (SD)
At the 60 mg dose, median time on treatment was:

- Total population (n=14): 111 days
- Sarcoma subjects (n=3): 168 days
  - Myxoid liposarcoma subjects (n=2): 282.5 days
- Chordoma subjects (n=2): 193.5 days

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Case report: Patient DLP41 with Myxoid Liposarcoma

Patient characteristics and treatment history

- 50-year-old female
- Diagnosed with myxoid liposarcoma in MAY 2009
- Stage 4 at enrollment
- Six prior lines of therapy included:
  - Doxorubicin/Ifosfamide: APR-SEP 2015
  - Atezolizumab: JUL-SEP 2016
  - Trabectedin: DEC 2016-JAN 2017
  - NY-ESO-1<sup>C259</sup> T: SEP 2017-JUN 2018
  - Atezolizumab: NOV 2018-JUN 2019
  - Ifosfamide: DEC 2021-JAN 2022

KB-0742 treatment course

- KB-0742 treatment initiated in JUL 2022
- 60 mg for 398 days on treatment
- PR achieved at cycle 10 lasting 113 days

KB-0742 PK/PD profile is suitable for achieving sustained partial inhibition of CDK9 and measurable target engagement

- 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

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

- Dose dependent CDK9 inhibition measured in peripheral blood
- Sustained, measurable reduction of RNA Pol II pSER2 observed at the 60 mg dose level

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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 expansion phase of the study is ongoing in MYC-dependent solid tumors such as ovarian cancer, TNBC and NSCLC and in other transcriptionally addicted solid tumors such as soft tissue sarcomas with TF fusions