**A phase 1, dose-escalation, safety, pharmacokinetic, pharmacodynamic study of thioureidobutyronitrile, a novel p53 targeted therapy, in patients with advanced solid tumors**


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### INTRODUCTION

**Thioureidobutyronitrile, Kevetrin™,** has demonstrated anti-tumor activity in several wild type and mutant p53 xenografts without evidence of genotoxicity. Kevetrin induces cell cycle arrest and apoptosis through activation and stabilization of wild type p53 via a novel mechanism that targets the MDM2-p53 interaction. Kevetrin also alters proteasomal turnover of MDM2, and induces monoubiquitination of wild type p53, enhancing its stability (Kumar et al, 2011).

Activation of wild type p53 by Kevetrin in non-genotoxic and induces apoptosis in tumors. p53 function is lost or inactive in about 90% of human cancers. Various stresses induce mutations and decrease the fitness, turning through a p53-MDM2 pair in the apoptotic pathway. This node is very important for preventing cancers. p53 is a tumor-suppressor protein that induces cell cycle arrest and apoptosis in response to genotoxic stress. p53 is regulated primarily by the ubiquitin ligase MDM2, which binds to p53 and leads to its degradation in the proteasome.

Mutant p53 is an array of mutant proteins with oncogenic properties varying among patients. Mutant p53 proteins increase proliferation and chemoresistance in cancer cells. Depletion of mutant p53 in tumors decreases the proliferation of cancer cells. Activation of wild type p53 is critical for the treatment of tumors, which are caused by mutations in p53. Kevetrin induces cell cycle arrest and apoptosis through activation and stabilization of wild type p53 and induces apoptosis in vivo (Kumar et al, 2011). Kevetrin therefore has the unique ability to target tumors with both wild-type and mutant p53.

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### METHODS

- Evaluate preliminary evidence of anti-tumor activity
- Evaluate the safety, tolerability, maximum tolerated dose (MTD) and determine recommended Phase 2 dose

### Mutant p53 is an array of mutant proteins with oncogenic properties varying among patients. Mutant p53 proteins increase proliferation and chemoresistance in cancer cells. Depletion of mutant p53 in tumors decreases the proliferation of cancer cells. Activation of wild type p53 is critical for the treatment of tumors, which are caused by mutations in p53. Kevetrin induces cell cycle arrest and apoptosis through activation and stabilization of wild type p53 and induces apoptosis in vivo (Kumar et al, 2011). Kevetrin therefore has the unique ability to target tumors with both wild-type and mutant p53.

**Expression levels of p21 in lymphocytes is a biomarker for Kevetrin.**

**Population of wild type p53 in A549 (wt p53)**

**Background**

**Kevetrin induced apoptosis and cell cycle arrest in MDA-MB-231 (wt p53).**

**Kevetrin inhibited phosphorylation of HDAC (216).**

**Kevetrin inhibit p53 signal transduction pathways for increasing apoptosis in A549, MDA-MB-231 and K-562 cell lines.**

**Kevetrin has potent anti-tumor activity in xenograft models with varied p53 status.**

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**PHASE 1 STUDY**

**Harvard Cancer Centers**

Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Massachusetts General Hospital

### Objectives:

- Evaluate the safety, tolerability, maximum tolerated dose (MTD) and determine recommended Phase 2 dose
- Characterize pharmacokinetics (PK) profiles
- Evaluate preliminary evidence of anti-tumor activity
- Explore potential biomarkers of tumor response

### Methods:

- Mean intravenous infusion once weekly for 3 weeks in 28-day cycle
- Starting dose = 10 mg/kg
- Dose escalation in a 3+3 design; groups of 2-6 patients evaluated for toxicity at each dose level.
- Dose escalation is based upon the number and intensity of adverse events in cycle 1.
- The number of subjects per cohort is up to 40.
- Once the MTD is established, up to 12 additional subjects may be enrolled at the MTD dose level.
- PK is characterized for the first and last dose given in cycle 1.
- An adverse event (AE) of grade 1 or 2 will be assessed as an AE.
- Dose limitation of treatment of patients is monitored.

### PB Biomarker:

- p73 expression in peripheral blood mononuclear cells.

**Key Eligibility Criteria:**

- Adults with refractory locally advanced/metastatic solid tumors; acceptable liver, kidney function, and hematologic status.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eligibility</th>
</tr>
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<tbody>
<tr>
<td>Metastatic cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Yes</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>No</td>
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<tr>
<td>Renal impairment</td>
<td>No</td>
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<tr>
<td>Liver impairment</td>
<td>No</td>
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<tr>
<td>Bone marrow depression</td>
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</tbody>
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### Results:

- **Phase 1 Completed September 7, 2012**
- A total of 10 patients have been enrolled to date.
- Cohorts 1, 2, and 3 have been completed without DLT.
- The MTD has not yet been reached; the trial is ongoing.

**Expression levels of p21 is a biomarker for Kevetrin.**

**Kevetrin did not induce the phosphorylation of HDAC (216) indicating that Kevetrin is genotoxic.**

**Kevetrin doxil induced the phosphorylation of HDAC indicating that Kevetrin is genotoxic.**

**Kevetrin has potent anti-tumor activity in xenograft models with varied p53 status.**

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**CONCLUSIONS**

- p53 induction by Kevetrin is non-genotoxic.
- Tumors harboring both mutant and wild type p53 can be treated with Kevetrin.
- Kevetrin induced apoptotic cell death in wild type p53 and mutant p53 cells through p53 apoptotic pathways.
- Kevetrin stabilized p53 and induced transcriptional targets in wild type p53.
- Inhibition of MDM2 by Kevetrin induces transcriptional independent apoptosis.
- Kevetrin induced degradation of mutant p53 mediated by reactivation of MDM2 E2 ligase.
- Kevetrin is a potent anti-tumor agent.
- Expression of p21 in lymphocytes is a biomarker for Kevetrin.
- Kevetrin is in a Phase 1 clinical trial; 3 cohorts have been completed without DLT.

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**For further information please contact Cellectix Corporation at 781-234-6717 info@cellectix.com**

More information on this and related projects can be obtained at www.cellectix.com.