Eltanexor (KPT-8602), a Second Generation Selective Inhibitor of Nuclear Export (SINE) Compound, in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC)

Jingsong Zhang¹, David Chism², Scot T. Tagawa³, Paul Monk⁴, Robert S. Alter⁵, William Reichmann⁶, William Senapedis⁶, Erkan Baloglu⁶, Jatin Shah⁶, Sharon Shacham⁶, Michael G. Kauffman⁶

(1) Moffitt Cancer Center, Tampa, FL 33612, USA (2) Vanderbilt–Ingram Cancer Center, Nashville, TN 37232, USA (3) Weill Cornell Medicine, New York, NY 10065, USA (4) Ohio State University, Columbus, OH 43210, USA (5) Hackensack University Medical Center, Hackensack, NJ, 07601, USA (6) Karyopharm Therapeutics Inc, 85 Wells Ave, Newton, MA 02459, USA

Contact Information: Jingsong Zhang, MD, PhD (Jingsong.Zhang@moffitt.org)
William Senapedis, PhD (wsenapedis@Karyopharm.com)
Background

- Overexpression of exportin 1 (XPO1) in malignant cells increases the nuclear export / inactivation of tumor suppressor proteins (e.g. p53, IκB), and promotes the translation of Eukaryotic translation initiation factor 4E (eIF4E)-bound messenger ribonucleic acids (mRNA) coding oncoproteins (e.g. c-MYC, BCL-2).

- XPO1 inhibition reduces total androgen receptor (AR) levels, including AR variant 7 (ARv7), via eIF4E inhibition and may re-sensitize prostate cancer cells to androgen deprivation therapy.

- Inhibition of XPO1 using selinexor, the first-in-class, orally bioavailable reversible covalent Selective Inhibitor of Nuclear Export (SINE) compound, showed anticancer activity in patients (pts) with solid tumors including Metastatic Castrate-Resistant Prostate Cancer (mCRPC), however, the adverse events profile limited further development in this patient population.

- Eltanexor (ELTA/KPT-8602), a second-generation, orally bioavailable reversible covalent SINE compound, showed promising anticancer activity in preclinical models of PC, including in abiraterone resistant cell lines.

- Therefore, eltanexor +/- abiraterone (+ Abi) was evaluated in mCRPC.

1 Senapedis, W. et al. Seminars in Cancer Biology, 2014, 27, 74
2 Razak, A.R. et al. Journal of Clinical Oncology, 2016, 34(34), 4142
3 Wei, X.X. et al. The Oncologist, 2018, 23, 1
Preclinical Rationale

**Abiraterone**
CYP17A1 inh. / blocks androgen synthesis

**Enzalutamide**
Competitive binder of AR
Blocks cyto. to nuclear translocation of the AR
Inhibits AR binding to DNA

Eltanexor kills **22RV1** AR H874Y
Abi/Enza refractory cells

XPO1 knockdown reduces AR mRNA levels

XPO1 inhibition results in an increase in nuclear ARv7 mRNA and a decrease in cytoplasmic ARv7 mRNA, likely due to nuclear sequestration of the XPO1 cargo eIF4E

22rv1 xenograft model in mice confirms eltanexor activity in combination with abiraterone in a difficult to treat mCRPC cell line
This is part of a phase 1/2 study (NCT02649790) to determine the safety, preliminary efficacy, and recommended phase 2 dose (RP2D) of eltanexor in patients with advanced cancers. In this dose expansion cohort, patients with mCRPC received once daily oral eltanexor +/- Abi for 5 days per week (qdx5) at Dose Limiting Toxicity (DLT) cleared dosed levels of 20 and 30 mg.

- **Objectives**
  - Determine RP2D, dosing schedule, and evaluate the safety and tolerability, including DLT in mCRPC
  - Assess the preliminary evidence of anti-tumor activity (response was evaluated by RECIST v1.1 criteria)

- **Key Inclusion Criteria**
  - Histological documentation of adenocarcinoma of the prostate cancer.
  - Surgically or medically castrated, with testosterone levels of < 50 ng/dL (< 2.0 nM)
  - Measurable and documented progressive disease by RECIST v1.1, bone metastasis, and/or prostate specific antigen (PSA) levels.
  - Initial response to 2nd generation anti-hormonal therapy (abiraterone, enzalutamide, or TAK-700) but later relapsed
  - 0-2 taxane based chemotherapy regimen
  - + Abi arm: currently on abiraterone and corticosteroid but progressing (stable dose for 30 days prior to C1D1)
  - Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 with life expectancy of ≥ 4 months

- **Key Exclusion Criteria**
  - Patients who have been treated with their most recent chemotherapy or investigational drugs ≤ 21 days or 5 half-lives prior to the first dose of eltanexor, and/or have any acute toxicities due to prior chemo and/or radiotherapy that have not resolved to Grade 0 or 1.
  - Initiating bisphosphonate therapy or adjusting bisphosphonate dose/regimen within 30 days prior to C1D1. Patients on a stable bisphosphonate or denosumab regimen are eligible and may continue
Results

The dose escalation was completed in patients with Relapsed Refractory Multiple Myeloma (RRMM). The protocol defined Maximum Tolerated Dose (MTD) was not reached. The RP2D / schedule in RRMM was determined to be 20 mg of eltanexor + low dose dexamethasone / qdx5. The highest dose limiting toxicity (DLT) cleared dose / schedule in RRMM arm was 40 mg / qdx5 and 60 mg / qodx3.

Cycle 1 Day 1 PK Profile of Eltanexor in Pts with Multiple Myeloma from Escalation Cohorts

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>C_{max} (ng/mL)</th>
<th>T_{max} (h)</th>
<th>AUC_{0-inf} (ng*h/mL)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3</td>
<td>30.6</td>
<td>1.0</td>
<td>164</td>
<td>4.0</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>60.5</td>
<td>3.0</td>
<td>347</td>
<td>5.1</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>123</td>
<td>2.0</td>
<td>754</td>
<td>5.0</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>269</td>
<td>1.0</td>
<td>1,635</td>
<td>7.1</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>147</td>
<td>3.0</td>
<td>1,204</td>
<td>5.8</td>
</tr>
<tr>
<td>60</td>
<td>4</td>
<td>284</td>
<td>2.0</td>
<td>2,581</td>
<td>6.4</td>
</tr>
</tbody>
</table>

- Eltanexor was absorbed with a T_{max} of ~2 hours
- Plasma concentration (C_{max}) generally increased with dose
- Dose-proportional increased in exposure (AUC_{0-inf})
- The terminal elimination phase (t_{1/2}) was relatively short, independent of dose
- There is no clear evidence of accumulation across the dose range over the 28-day cycle
- Evaluation of ELTA in mCRPC pt samples +/- Abi is on-going.


Patient Demographics for mCRPC Cohort

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>ELTA QDx5 (N=13)</th>
<th>ELTA + Abi QDx5 (N=17)</th>
<th>All N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>72 (56-86)</td>
<td>70 (48-84)</td>
<td>71 (48-86)</td>
</tr>
<tr>
<td>Median Prior Treatments (range)</td>
<td>5 (1-12)</td>
<td>3 (1-8)</td>
<td>4 (1-12)</td>
</tr>
</tbody>
</table>
### Safety

**Treatment-Related Adverse Events (TRAEs) in mCRPC Patients**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>20 mg ELTA (N = 7)</th>
<th>30 mg ELTA (N = 6)</th>
<th>20 mg ELTA + Abi (N = 13)</th>
<th>30 mg ELTA + Abi (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr1/2</td>
<td>Gr 3+</td>
<td>Gr1/2</td>
<td>Gr 3+</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>4</td>
<td>12 (40.0)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Gr1/2</td>
<td>Gr 3+</td>
<td></td>
<td>Gr1/2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dypsnea</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**DLT Definition**
- Grade ≥3 nausea/vomiting while on optimal supportive medication or any other Grade ≥3 non-hematological toxicity except alopecia or electrolyte abnormalities correctable with supportive therapy
- Grade 4 neutropenia >5 days; febrile neutropenia; Grade 4 thrombocytopenia; Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
- >4 missed doses due to tolerability of eltanexor within cycle 1

**Noteworthy Events in Cycle 1 (C1)**
- 2 patients with G3 non-heme TRAE in C1: fatigue (20 mg ELTA) and vomiting (20 mg ELTA + Abi)
- 3 patients (1 at 20 mg ELTA, 1 at 30 mg ELTA, 1 at 30 mg ELTA + Abi) had >4 missed doses due to TRAE in C1
- 1 patient (30 mg ELTA + Abi) had a dose reduction due to TRAE in C1
- 2 patients (1 at 20 mg ELTA and 1 at 30 mg ELTA + Abi) discontinued treatment due to TRAEs in C1

(As of 19-Nov-2018)
Efficacy

Time on Treatment (ToT) for Evaluable Patients

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median ToT (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable pts</td>
<td>145 (40–368)</td>
</tr>
<tr>
<td>ELTA all doses (20 and 30 mg)</td>
<td>96</td>
</tr>
<tr>
<td>ELTA 20 mg</td>
<td>96</td>
</tr>
<tr>
<td>ELTA 30 mg</td>
<td>134</td>
</tr>
<tr>
<td>ETLA (20 and 30 mg) + Abi</td>
<td>155</td>
</tr>
<tr>
<td>ELTA 20 mg + Abi</td>
<td>164</td>
</tr>
<tr>
<td>ELTA 30 mg + Abi</td>
<td>145</td>
</tr>
</tbody>
</table>

Discontinuation
- RECIST v1.1 PD
- Clinical PD
- Withdrawal by pt
- AE
- On Study

Dose
- 20
- 30
- RECIST v1.1 Best Response
- PR
- SD
- PD

(As of 19-Nov-2018)
# Efficacy

## Summary of Responses and Clinical Benefit

<table>
<thead>
<tr>
<th>Cohort</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>DCR (PR+SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥8 weeks</td>
</tr>
<tr>
<td>ELTA (N=11)</td>
<td>1</td>
<td>8 (72%)</td>
<td>5 (45%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>ELTA + Abi (N=12)</td>
<td>1</td>
<td>9 (75%)</td>
<td>6 (50%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Total (N=23)</td>
<td>2</td>
<td>17 (74%)</td>
<td>11 (48%)</td>
<td>4 (17%)</td>
</tr>
</tbody>
</table>

Responses based on interim unaudited data (as of 19-Nov-2018) were assessed using RECIST v1.1 criterion.

**PR**: Partial Response, **SD**: Stable Disease, **PD**: Progressive Disease, **DCR**: Disease Control Rate.

*NE*: 7 Non-Evaluable patients: 2 AE, 2 pt decision, 2 physician decision, 1 pt non-compliant.
Radiographic Progression Free Survival (rPFS) via RECIST v1.1 after at least 8 weeks

Note: PSA progression not used in this assessment

- Using Kaplan-Meier analysis, the median rPFS was 6.1 months (95% CI: 4.8, 8.4) among evaluable patients
- Among 11 evaluable patients treated with single agent ELTA, median rPFS was 5.9 months (95% CI: 1.9, 11.2)
- Among 12 patients treated with ELTA + Abi combination, median rPFS was 6.1 months (95% CI: 1.9, NE)
In this dose expansion cohort, patients with mCRPC received once daily oral eltanexor +/- abiraterone for 5 days per week (qdx5) at DLT cleared dose levels of 20 and 30 mg of eltanexor.

- Heavily pre-treated patients (median of 4 prior treatment regimens) with mCRPC whose disease had progressed on most available therapies

The most frequent TRAEs at all doses levels are fatigue, nausea, decreased appetite, diarrhea, decreased weight, vomiting, cytopenias and dysgeusia.

The most common Grade 3 TRAEs were neutropenia and anemia. Grade 3 fatigue was observed mostly at eltanexor 30 mg dose. Two Grade 4 TRAE were neutropenia and AST increase both in 20 mg ELTA + Abi patients.

Corticosteroids may help alleviate the constitutional AEs in the ELTA + Abi cohorts when compared to the single agent ELTA.

Patients time on treatment was longer in the ELTA + Abi cohorts (median: 155 days [40-277]) compared to ELTA alone (96 days)

RECIST v1.1: 9% PR with an 83% DCR including SD at ≥8 weeks and 57% DCR including SD at ≥16 weeks on ELTA +/- Abi.

Median rPFS of 6.1 months was observed in all patients with evaluable response and no difference in median rPFS was observed between patients treated with ELTA vs. ELTA + Abi (Note: current 2nd line plus rPFS for abiraterone or enzalutamide is ~3 months)

Based on preliminary efficacy, safety and tolerability data, the RP2D / schedule of eltanexor in mCRPC is determined to be 30 mg qdx5 single agent ELTA.

These results warrant further investigation of single agent eltanexor therapy as well as in combination in mCRPC patients.