TK216 PHASE 1/2 STUDY IN METASTATIC, RELAPSED/REFRACTORY EWING SARCOMA

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DISCLOSURE INFORMATION

• Dr. Ludwig has no conflicts of interest to disclose

• This Ewing sarcoma study is sponsored by Oncternal Therapeutics, Inc., San Diego CA
• Major unmet medical need for relapsed or recurrent Ewing sarcoma
• Almost all Ewing sarcomas driven by ETS-family fusion protein (EWS-FLI1, EWS-ERG…)
• TK216 is the first clinical candidate targeting the oncogenic ES fusion protein
• TK216 is believed to disrupt transcriptome formation mediating:
  − Decreased oncogene and increased tumor suppressor transcription
  − Decreased tumor growth and apoptotic cell death
Preclinical Activity of ETS inhibitors

TK216 Inhibits Oncogenic Transcription and Cell Proliferation

- ↑ G2-M arrest
- ↑ cyclin B1
- ↓ microtubule-associated proteins
- ↑ microtubule depolymerization
- Enhanced apoptosis

TK216 Analogue YK-4-279 is Synergistic with Vincristine

- In Vitro
- In Vivo (A4573 xenograft)

Zoliner et al., 2017 Science Signaling

TK216 Analogue YK-4-279 Inhibited ES Tumor Growth, Induced Apoptotic Death

Control animals: Black
YK-4-279 treated: Red
Blue: catheter malfunction

Preclinical data strongly suggested that prolonged continuous infusion provided optimal antitumor activity
TK216 Phase 1/2 Study Design

- **Indication:** Recurrent or refractory Ewing sarcoma
- **Phase 1/2 clinical trial in 3 Parts:**
  - **Dose Escalation cohorts:**
    - Objectives: PK, DLT, MTD
    - 7 day infusions 18-288 mg/m²/day
  - **Schedule Escalation cohorts:**
    - Objectives: PK, Selection of Phase 2 dose
    - 10-14 day infusions 200-220 mg/m²/day
  - **Phase 2 Expansion cohort:**
    - Objectives: Tumor responses, PFS
    - RP2D: TK216 200 mg/m²/day for 14 days
      Vincristine (VCR) 0.75 mg/m² day 1

DLT = Dose Limiting Toxicity
MTD = Maximum Tolerated Dose
RP2D = Recommended Phase 2 Dosing regimen
# Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>N= 56</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Includes patients that have not reached their first evaluation timepoint)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean (Median)</td>
<td>30.9 (29.5)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>11 to 77</td>
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<tr>
<td>Gender</td>
<td>Female</td>
<td>22 (39.3%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>34 (60.7%)</td>
</tr>
<tr>
<td>Race</td>
<td>Asian:</td>
<td>7 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>Other:</td>
<td>5 (8.9%)</td>
</tr>
<tr>
<td></td>
<td>White:</td>
<td>44 (78.6%)</td>
</tr>
<tr>
<td>Time from Diagnosis to Enrollment (Years)</td>
<td>Median (Range)</td>
<td>3.4 (0.45 to 18)</td>
</tr>
<tr>
<td># Lines of Prior Systemic Therapy*</td>
<td>Median (Range)</td>
<td>3 (1 to 8)</td>
</tr>
<tr>
<td>Stage at Enrollment</td>
<td>Stage IV</td>
<td>56 (100%)</td>
</tr>
</tbody>
</table>

*includes all reported systemic therapy patient received for localized and metastatic disease
TK216: Dose and Schedule Escalation Results

**DOSE ESCALATION**

7-day TK216 infusions (mg/m²/day)

- Cohort 1 (N=3): 18 mg/m²/day
- Cohort 2 (N=3): 36 mg/m²/day
- Cohort 3 (N=3): 72 mg/m²/day
- Cohort 4 (N=3): 144 mg/m²/day
- Cohort 5 (N=7): 288 mg/m²/day

MTD for 7-day infusion: 220 mg/m²/day

- Cohort 5: DLT of Neutropenia / Neutropenic fever
- Variable and manageable myelosuppression
- Early signs of activity with stabilization of disease

**SCHEDULE ESCALATION**

10 to 14-day TK216 infusions (mg/m²/day)

- Cohort 7 (N=3): 220 x 2 weeks
- Cohort 8 (N=4): 200 x 10 days
- Cohort 9 (N=4): 200 x 14 days

RP2D for 14-day infusion: 200 mg/m²/day

- Cohort 7: DLT of Neutropenia
- Cohort 9: 200mg/m²/day CIV for 14 days has been well-tolerated.
- Vincristine (VCR) allowed starting in cycle 3

**EXPANSION**

Expansion Cohort: 200 mg/m²/day CIV for 14 days has been well-tolerated. VCR starts in Cycle 1
### Frequent (>7%) Adverse Events Considered Related to TK216

**Safety population, N=57**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Occurrence</th>
<th>N=57</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>4</th>
<th>4</th>
<th>3</th>
<th>7</th>
<th>24</th>
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<tbody>
<tr>
<td>Anaemia</td>
<td>20 (35.1%)</td>
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<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
<td>2 (50.0%)</td>
<td>0</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (28.1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>2 (50.0%)</td>
<td>2 (50.0%)</td>
<td>0</td>
<td>0</td>
<td>3 (100.0%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>16 (28.1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75.0%)</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>1 (14.3%)</td>
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<tr>
<td>White blood cell count decreased</td>
<td>15 (26.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75.0%)</td>
<td>3 (75.0%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>2 (28.6%)</td>
<td></td>
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<tr>
<td>Alopecia</td>
<td>14 (24.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0%)</td>
<td>3 (75.0%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>2 (28.6%)</td>
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<tr>
<td>Nausea</td>
<td>11 (19.3%)</td>
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<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
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<td>1 (25.0%)</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>1 (14.3%)</td>
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<tr>
<td>Neutropenia</td>
<td>9 (15.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0%)</td>
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<td>2 (66.7%)</td>
<td>3 (42.9%)</td>
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<tr>
<td>Febrile neutropenia</td>
<td>8 (14.0%)</td>
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<td>0</td>
<td>0</td>
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<td>1 (25.0%)</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>3 (42.9%)</td>
<td>2 (8.3%)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>8 (14.0%)</td>
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<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>3 (42.9%)</td>
<td>2 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (14.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>2 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>7 (12.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75.0%)</td>
<td>2 (50.0%)</td>
<td>0</td>
<td>1 (14.3%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (12.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>2 (28.6%)</td>
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<tr>
<td>Platelet count decreased</td>
<td>5 (8.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (50.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
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<tr>
<td>Leukopenia</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>3 (42.9%)</td>
<td>0</td>
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<tr>
<td>Diarrhoea</td>
<td>5 (8.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>2 (28.6%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (8.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>4 (7.0%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (14.3%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>4 (7.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (50.0%)</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>4 (7.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (50.0%)</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Reported treatment-emergent adverse events. Myelosuppression is an expected, on target effect.
TK216 Elimination Pharmacokinetics

- Time = 0 values reflect steady state at the end of the TK216 infusion
- Half-life is relatively long (8-12 h) with dose proportional increase in concentrations
- Preclinical data suggest that TK216 levels in the 75 to 188 ng/mL range were effective at tumor killing in vitro, and plasma levels in the 265 to ~1500 ng/mL were associated with efficacy in animal tumor model.
Patients were considered evaluable for efficacy if they completed 2 planned cycles of treatment and follow-up tumor assessment studies or had documented or clinical PD following a complete first cycle of therapy.

<table>
<thead>
<tr>
<th></th>
<th>Evaluable Patients N= 50</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>Disease Control Rate CR+PR+SD</th>
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</thead>
<tbody>
<tr>
<td><strong>Dose Escalation Cohorts 1-6</strong></td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td><strong>Schedule Escalation Cohorts 7-8</strong></td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>RP2D Cohort 9 &amp; Expansion</strong></td>
<td>23</td>
<td>2 (9%)</td>
<td>2 (9%)</td>
<td>0</td>
<td>8 (35%)</td>
<td>43%</td>
</tr>
</tbody>
</table>

Interim efficacy analysis, 16 Oct 2020
Sustained Complete Response with TK216 in Patient with Extensively Treated Metastatic Relapsed / Refractory Ewing Sarcoma

- **Patient:** 19 y.o. male presented with Ewing sarcoma of his clavicle with multiple pulmonary metastases

- **Treatment History:**
  - Tumor genetics: EWSR1-FLI1 fusion
  - Initial Therapy: VDC/IE, surgical resection, RT 50.4 Gy
  - Relapsed 1.5 years after initial diagnosis
  - Multiple recurrences treated with: Whole lung RT, irinotecan/temozolomide, bevacizumab, pazopanib
  - Multiple growing lung nodules at study entry

- **TK216 Treatment:** TK216 200 mg/m²/day CIV for 14-28 days
  - Remains on treatment >1.5 y since enrollment with no evidence of disease (surgical CR)
Second Complete Response with TK216  
Patient with Heavily Treated Metastatic R/R Ewing Sarcoma

- **Patient:** 51-year-old with Ewing sarcoma  
  - Chest CT: 10-cm tumor near the right kidney and multiple lung metastases  
  - Tumor Genetics: EWSR1 translocation

- **Extensive Initial Treatment:**  
  - Chemo: Vincristine/doxorubicin and ifosfamide (VAI) x10, high-dose ifosfamide x1  
  - Surgery: Right nephrectomy and vascular reconstruction

- **Recurrence:** Multiple (>10) new & enlarging lung lesions  
  - RECIST 1.1: 20mm  
  - Relapsed 1.6 years after initial diagnosis

- **TK216 Treatment:**  
  - TK216 200 mg/m²/day for 14 days + vincristine 0.75 mg/m² day 1  
  - Treatment ongoing

- **Tumor Response:** Complete Response (CR)  
  - After 2 cycles, 90% reduction of all lesions  
  - After 6 cycles, CR with resolution of all lesions → ongoing
PFS of Evaluable Patients Treated at RP2D in Cohort 9 & Expansion

In a recently reported phase II, double-blind, placebo-controlled trial in previously treated Ewing sarcoma patients, the median PFS of the placebo control group (n= 13) was 3.9 weeks (CI 95%= 3.3-7.3). (REGOBONE, French Sarcoma Group and UNICANCER, ESMO 2020)
Summary

- **First in human study of TK216**: A novel agent directed against the ETS family of oncoproteins, whose members are highly expressed in Ewing sarcoma as well as other malignancies.

- **Safety**: Well-tolerated and manageable safety profile consisting of transient marrow suppression at the current TK216 schedule of 200 mg/m²/day for up to 14 days +/- VCR.

- **Efficacy**: Phase 2 dose demonstrated early evidence of activity.
  - 2 Complete responses and 8 SD
  - Disease control rate (CR+PR+SD) = 43% (10/23 evaluable patients)
  - The CRs have been durable.

- **Study Status**: These objective responses indicate clinical activity of TK216 in R/R, poor risk, heavily pretreated patients with Ewing sarcoma and warrant further investigation. Enrollment of the Expansion Cohort has been expanded and work on potentially predictive biomarkers is underway.