SP-2577 (Seclidemstat) for the Treatment of Relapsed or Refractory Ewing Sarcoma

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee

June 17, 2020
Introduction

David Arthur, CEO, Salarius
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td><strong>David Arthur, President and Chief Executive Officer, Salarius</strong></td>
</tr>
<tr>
<td>MoA, Design Rationale, Preclinical Data</td>
<td><strong>Bruce McCreedy, PhD, Chief Scientific Officer, Salarius</strong></td>
</tr>
<tr>
<td>Relapsed Ewing Sarcoma Lacks a Standard of Care</td>
<td><strong>Damon Reed, MD, Associate Professor, Moffitt Cancer Center, Primary Investigator</strong></td>
</tr>
<tr>
<td>Seclidemstat Clinical Trials</td>
<td><strong>Margaret Dugan, MD, Consulting Senior Medical Advisor, Salarius</strong></td>
</tr>
<tr>
<td>Summary and Conclusions</td>
<td><strong>Margaret Dugan, MD, Consulting Senior Medical Advisor, Salarius</strong></td>
</tr>
<tr>
<td>Question and Answer</td>
<td></td>
</tr>
</tbody>
</table>
Seclidemstat regulatory history

Proposed Indication: Seclidemstat as a single oral agent for the treatment of relapsed/refractory Ewing sarcoma patients

Abbreviations: IND, investigational new drug; FPI, first patient in; FTD, fast track designation.
Why we are here today

Salarius is seeking advice on future study patient populations and on the plan for a Proposed Pediatric Study Request (PPSR)

• Input at this moment will help define development plan and study population
  – Extensive preclinical data indicates Ewing sarcoma is a viable indication
  – Currently defining maximum tolerated dose (MTD)
  – Investigating exploratory biomarkers of target engagement and disease burden

• What are the efficacy outcomes needed to ensure we are capturing a signal in a heavily pretreated relapsed/refractory Ewing population?
  – Drugs targeting epigenetic reprogramming take time to demonstrate efficacy

• What innovative trials can we design to optimize development of seclidemstat for the pediatric population?
SP-2577 (Seclidemstat): MoA, Design Rationale, Preclinical Data

Bruce McCrreedy, PhD, Salarius
Epigenetic enzymes are attractive targets for cancer therapy

Epigenetic modifying enzymes affect gene expression by manipulating the chromatin structure\(^1\)

Overactive epigenetic enzymes can disrupt the transcriptional balance and lead to cancer development\(^2\)

Drugs that inhibit overactive epigenetic enzymes can help treat cancer by restoring a balanced transcriptional state

LSD1 (KDM1A): Epigenetic modifying demethylase that associates with multiple interacting protein partners

**Lysine Specific Demethylase 1**
- Demethylates mono- or di-methylated histone 3 lysine 4 (H3K4me1/2) & 9 (H3K9me1/2) in a context-dependent manner
- FAD-dependent enzymatic activity mediated through **Enzymatic domain**
- Interacts with numerous proteins and protein complexes through its **Tower domain**

**Normal development**
- Required for hematopoiesis
- Functions in stemness and differentiation
- Other functions – motility, EMT, autophagy

LSD1: A role in cancer and SP-2577 (seclidemstat) as a differentiated, reversible LSD1 inhibitor

LSD1 over-expression promotes tumor development

- LSD1 contributes to cancer cell proliferation via its:
  - Enzymatic activity (demethylase)
  - Scaffolding activity (protein-protein interactions)

• SP-2577 reversibly inhibits:
  - LSD1 demethylase activity
  - Scaffolding protein interactions

SP-2577
LSD1 IC$_{50}$ = 43 nM
Differentiated MOA of SP-2577 leads to differential activity

SP-2577 inhibits LSD1 enzyme activity

SP-2577 inhibits LSD1 associations (e.g., androgen receptor [AR])

SP-2577 treatment in cancer cell lines leads to increased methylation

AR Bound to LSD1 in LNCaP cells

AR immunoprecipitation, anti-LSD1 immunoblot

- UNRX
- SP-2577
- ORY-1001
- GSK-2879552
Targeting the root cause of Ewing sarcoma through LSD1 inhibition

Ewing sarcoma is driven by an oncogenic protein transcription factor, in 90% of cases EWS/FLI1, that results from a t(11;22) translocation that fuses the EWSR1 gene with the ETS transcription factor family gene FLI1.

Ewing sarcoma cells highly express and depend on LSD1 for survival
- Elevated expression levels are associated with worse overall survival

LSD1 Gene Expression Across Cancer Type

Box plot based on data from the Cancer Cell Line Encyclopedia (CCLE), the Broad Institute.
LSD1 and EWS/FLI work in concert with interacting protein partners to promote the abnormal EWS/FLI transcriptional program

SP-2577 disrupts EWS/FLI1 activity via inhibition of LSD1 interaction with

Co-activators

Co-activator EWS FLI

Seclidemstat

Oncogenes (Tumor growth)

Co-repressors

Co-repressor EWS FLI

Seclidemstat

Tumor Suppressors

Salarius generation one compound (SP-2509) reverses EWS/FLI transcriptional profile and inhibits ES cell viability

Vehicle

Control sh-RNA

SP-2509

EWS-FLI sh-RNA

Upregulated

Downregulated

Control sh-RNA

EWS/FLI sh-RNA

EC50 = 113nM

EWS-FLI sh-RNA

EC50 = 1,825nM

Abbreviations: ES, Ewing sarcoma; sh-RNA, short hairpin RNA.
**SP-2577 activity in vitro and in vivo models of Ewing sarcoma**

**In vitro**
- SP-2577 shows anti-proliferative effect across six Ewing sarcoma cell lines (GI$_{50}$ values range from 185 nM to 1269 nM)

**In vivo**
- SP-2577 shows anti-tumor activity in a variety of Ewing sarcoma models
- In a SK-N-MC mouse xenograft model, SP-2577 treatment resulted in complete cures in 80% of animals treated, whereas controls all had to be sacrificed by week 3

---

**Tumor volume**

**Survival curves**

*Abbreviation: IP, intraperitoneal.
Data on file. Saliarius.*
Rationale for SP-2577 in treating other sarcomas

Given the proposed mechanism of action of SP-2577 in Ewing sarcoma, additional sarcomas are of interest for future clinical trials because they:

1. Contain a FET/TET gene family (e.g. EWS, FUS) fusion gene

   Ewing sarcoma

   Desmoplastic small round cell tumor

   Myxoid liposarcoma

2. Have elevated LSD1 expression and rely on LSD1 for proliferation/growth/colony formation

   LSD1 Gene Expression

   Rhabdomyosarcoma

   Osteosarcoma

   Ewing sarcoma

Relapsed Ewing Sarcoma Lacks a Standard of Care

Damon Reed, MD, Associate Professor, Moffitt Cancer Center, Primary Investigator
Ewing sarcoma
Epidemiology and standards of care at presentation

**Diagnosis**
- ~400 new patients each year
- Median age of diagnosis ~15 years
  - 75% localized
  - 25% with metastasis

**Standard of Care**
- 29 weeks of chemotherapy with at least 35 inpatient days
- Cardiotoxicity, secondary cancers and other morbidities
- Some improvement in outcome for localized patients but not for metastatic or relapsed patients

Surgery or
Chemo
Radiation
Ewing sarcoma
Outcome in first line

Improved Survival in New Localized\textsuperscript{1}

No Improvement in Metastatic Survival\textsuperscript{2}

Abbreviations: CAV, cyclophosphamide, doxorubicin, and vincristine; CAV-IE, CAV plus ifosfamide and etoposide.
\textsuperscript{1} Adapted from Gorlick R et al. \textit{J Clin Oncol}. 2018. \textsuperscript{2} Grier HE et al. \textit{NEJM}. 2003.
Relapsed Ewing sarcoma is an unmet need

- A third of Ewing patients relapse
- Very poor outcome
- No FDA-approved agent for relapsed Ewing sarcoma

- Unmet need: 3rd most common solid tumor on pedi-MATCH
  - Parsons DW, et al. ASCO 2019

Figure adapted from Stahl M et al. Pediatr Blood Cancer. 2011.
Relapse regimens but no standard for relapsed Ewing sarcoma

- Little prospective evidence
- No published randomized evidence

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Primary toxicities</th>
<th>Trials</th>
<th>N</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide / Topotecan</td>
<td>Myelosuppression, requires myeloid growth factor; alopecia</td>
<td>3</td>
<td>79</td>
<td>32%</td>
</tr>
<tr>
<td>Gemcitabine / Docetaxel</td>
<td>Myelosuppression, neuropathy, requires myeloid growth factor, alopecia</td>
<td>3</td>
<td>24</td>
<td>29%</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Myelosuppression, requires myeloid growth factor, alopecia</td>
<td>1</td>
<td>35</td>
<td>34%</td>
</tr>
<tr>
<td>Irinotecan / Temozolomide</td>
<td>Diarrhea, myelosuppression</td>
<td>7</td>
<td>166</td>
<td>47%</td>
</tr>
<tr>
<td>Etoposide with carbo- or cisplatin</td>
<td>Myelosuppression, requires myeloid growth factor, allergic reaction, hearing loss, alopecia</td>
<td>1</td>
<td>107</td>
<td>29%</td>
</tr>
<tr>
<td>Oral etoposide</td>
<td>Myelosuppression, secondary malignancy</td>
<td>1</td>
<td>58</td>
<td>19%</td>
</tr>
</tbody>
</table>

Translational path

- No clear track record of a path/bar of activity
- Our Phase 1 has correlates to advance the science in this disease
  - cell-free DNA
  - circulating tumor cells
  - lactate dehydrogenase, hemoglobin F and other potential pharmacodynamic biomarkers
  - for dose expansion: frozen, serial biopsies required at screening, Cycle 2 and end of treatment
- In this rare, relapsed population:
  - historical cohort should be considered with ongoing work to help with threshold setting
  - event-free survival
    - Collier et al. presented 12% point estimate at 6 months based on completed Children’s Oncology Group Phase 2 studies
    - rEECur study ongoing which will add prospective evidence
  - response rate could also be considered

Abbreviations: rEECur, International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma.
Seclidemstat Clinical Trials
Margaret Dugan, MD, Consulting Senior Medical Advisor, Salarius
Phase 1 first-in-human study of seclidemstat in Ewing sarcoma

Primary Objective

- Evaluate the safety and tolerability of single-agent seclidemstat across multiple escalating doses, administered orally twice-daily

Secondary Objectives

- Determine the maximum tolerated dose (MTD)
- Characterize the pharmacokinetics (PK)
- Evaluate the effect of food on the PK
- Evaluate preliminary anti-tumor activity
Ewing sarcoma – Exploratory objectives

Exploration of cfDNA, CTCs, tumor tissue as pharmacodynamic markers of disease burden, drug effect and tumor response

• cfDNA
  – Quantify the EWS/ETS translocation and correlate with disease outcome
  – Ultra-low passage whole genome sequencing, TranSS-Seq targeted sequencing and patient-specific droplet digital PCR

• CTCs
  – Quantify changes in CTC number and correlate with disease outcome
  – Assess gene expression profiles by single cell RNA-seq to assess biological changes due to LSD1 inhibition

• Tumor biopsies (dose expansion only)
  – Assess genome-wide expression patterns associated with response or resistance by RNA-seq molecular signatures
  – Assess mutational profile of tumors by whole-exome sequencing and LSD1 protein levels by immunohistochemistry

Abbreviations: cfDNA, cell-free DNA; CTCs, circulating tumor cells.
Ewing sarcoma – Key study eligibility

• Histologic diagnosis of Ewing sarcoma that is refractory* or recurrent and:
  – At least one prior course of therapy for Ewing sarcoma
  – Prior camptothecin-based regimen, contraindication or declined treatment with camptothecin-based regimen
• Age ≥ 12 years and weight ≥ 40 kg
• KPS ≥ 70% for ≥ 16 years old and Lansky ≥ 70% for < 16 years old
• Measurable disease by CT or MRI by RECIST v1.1 (dose expansion only)

Abbreviations: KPS, Karnofsky performance status; RECIST, Response Evaluation Criteria in Solid Tumors.
* Refractory disease is metastatic or unresectable disease that has either progressed or is stable at completion of planned therapy.
Ewing sarcoma – Study schema

**Study design:**
- Enroll up to 7 dose escalation steps ranging from 75 mg to 1500 mg PO BID
- Follow accelerated dose escalation (single-patient cohorts) for the initial dose steps
- At first occurrence of any drug-related ≥ Grade 2 adverse event in Cycle 1, start the conventional 3+3 dose escalation design
- Upon defining maximal tolerated or maximal acceptable dose, expand to a total of 20 patients for further safety and preliminary efficacy data

Abbreviations: BID, twice daily; MTD, maximum tolerated dose; PO, by mouth.
Ewing sarcoma – Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Patients N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment start, years</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>25.2 (15.2-67.6)</td>
</tr>
<tr>
<td>≤ 18</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 18 to ≤ 29</td>
<td>9</td>
</tr>
<tr>
<td>≥ 30</td>
<td>5</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Karnofsky score, n (%)</td>
<td>n=14</td>
</tr>
<tr>
<td>90 to 100</td>
<td>10 (71.4)</td>
</tr>
<tr>
<td>70 to 80</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Lansky score, n (%)</td>
<td>n=2</td>
</tr>
<tr>
<td>90 to 100</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>70 to 80</td>
<td>1 (50.0)</td>
</tr>
</tbody>
</table>

Note: All data as of December 31st, 2019.
## Ewing sarcoma – Prior disease history and disease characteristics

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>All Patients N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, n (%)</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>Radiation therapy, n (%)</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>Chemotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Camptothecin-containing regimen</td>
<td>13 (81.3)</td>
</tr>
<tr>
<td>Non-camptothecin-containing regimen</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Number of prior lines of chemotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (2-12)</td>
</tr>
<tr>
<td>2</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>3</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>4</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>

| Rearrangements of EWSR1, n (%)         | 16 (100)            |
| Measurable disease, n (%)              | 13 (81.3)           |
| Sites of metastatic disease, n (%)     |                     |
| Bone only                              | 5 (31.3)            |
| Pleuropulmonary only                   | 3 (18.8)            |
| Multiple sites                         | 8 (50.0)            |
| Time from initial diagnosis of ES to C1D1, n (%) |       |
| Median, years (range)                  | 4.2 (1.9-14.6)      |
| < 1 year                               | 0                   |
| 1 to < 2 years                         | 2 (12.5)            |
| 2 to < 5 years                         | 7 (43.8)            |
| ≥ 5 years                              | 7 (43.8)            |

Note: All data as of December 31st, 2019.
Ewing sarcoma – Single-dose Cycle 1 pharmacokinetics

- Time above expected efficacy concentration increasing (1000 ng/mL)

Data presented as median (IQR) values of all patients at each dose level

Abbreviation: IQR, interquartile range.
Ewing sarcoma – Conclusions

- Dose escalation continues at the highest doses to define the MTD/MAD
- Seclidemstat, at cleared dose levels, is safe and tolerable as a continuous dosing BID regimen
- PK demonstrates dose-proportionality with sustained exposure for up to 24 hours at the higher doses
- The study population represents an advanced, heavily pre-treated group of Ewing sarcoma patients with extensive disease involvement who define an unmet medical need

Abbreviations: BID, twice per day; MAD, maximum administered dose; MTD, maximum tolerated dose; PK, pharmacokinetics.
Summary and conclusions

• Seclidemstat is a novel, selective, reversible LSD1 inhibitor
  – Developed by Salarius to address this unmet medical need
  – Selectively targets underlying mechanism of disease to improve patient outcomes

• Ongoing phase 1 studies are in development with a commitment to the pediatric population

• Seeking guidance on the appropriate studies for a Proposed Pediatric Study Request
Thank you
Question and Answer Session
Backup Slides Shown
Enzymatic inhibition of LSD1 is insufficient to reduce cell viability in Ewing sarcoma and DSRCT