Resminostat affects transcriptional regulation of disease-related processes in CTCL
## Conflicts of interest

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>–</td>
</tr>
<tr>
<td>Employee</td>
<td>– 4SC AG</td>
</tr>
<tr>
<td>Consultant</td>
<td>–</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>–</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>–</td>
</tr>
<tr>
<td>Honoraria</td>
<td>–</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>–</td>
</tr>
</tbody>
</table>
Resminostat – at a Glance

• Orally available HDAC-Inhibitor (class I, IIB, IV)
  o Small molecule inhibitor (MW = 349 g/mol)
  o Established compound class: hydroxamic acid

• Clinical development status:
  o To date more than 300 patients treated with resminostat
  o Most frequent AEs:
    o GI disorders, thrombocytopenia, fatigue
    o No significant effect on cardiovascular system observed
  o Majority of AEs were mild to moderate, manageable and reversible
  o Clinical efficacy observed in rel/refr Hodgkin’s Lymphoma¹ and HCC patients²
  o Pivotal phase II study in CTCL: RESMAIN – currently recruiting

¹ Walewski et al. 2018., Leuk Lymphoma. 2018 Aug 30:
Pleiotropic Action of HDAC Inhibitors

Resminostat

Cell growth
Apoptosis
Cell differentiation
Immune modulation

Gene regulation

TUMOR CELL

Change in gene regulation is the major impact of resminostat
Gene expression analysis of CTCL cell lines by RNA-seq

**Genome wide Approach: Resminostat’s Action in CTCL**

- Gene expression analysis of CTCL cell lines by RNA-seq

### Gene expression analysis by RNA-seq (24h treatment, 4 µM resminostat vs DMSO), Differential gene expression (DGE) analysis by DESeq2 (DEGs: log2 FC > |1|, p adj < 0.05); EC50: Cell viability assay (CellTiterBlue) after 72h treatment

<table>
<thead>
<tr>
<th>DEGs</th>
<th>MyLa CD4+</th>
<th>HH</th>
<th>HuT78</th>
</tr>
</thead>
<tbody>
<tr>
<td>up</td>
<td>1622 (83%)</td>
<td>2659 (63.3%)</td>
<td>2592 (85.5%)</td>
</tr>
<tr>
<td>down</td>
<td>332 (17%)</td>
<td>1544 (36.7%)</td>
<td>475 (15.5%)</td>
</tr>
<tr>
<td>total</td>
<td>1954</td>
<td>4203</td>
<td>3067</td>
</tr>
<tr>
<td>EC50 [µM]</td>
<td>0.94 (+/- 0.17)</td>
<td>0.74 (+/- 0.06)</td>
<td>1.24 (+/- 0.33)</td>
</tr>
</tbody>
</table>

**Resminostat primarily modulates gene expression in CTCL cell lines**
CTCL Pathogenesis: Skin Homing of Malignant T Cells

Skin homing receptor gene expression from RNA-seq data:

- Heatmap of selected integrins & chemokine receptors

<table>
<thead>
<tr>
<th></th>
<th>My-La CD4+</th>
<th>HH</th>
<th>HuT78</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ctrl</td>
<td>res</td>
<td>ctrl</td>
</tr>
<tr>
<td>Integrins / chemokine receptors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ctrl = DMSO control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>res = Resminostat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA expression level</td>
<td>row max</td>
<td></td>
<td></td>
</tr>
<tr>
<td>row min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not expressed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Resminostat reduces gene expression of skin-homing T cell receptors

Heatmap of mean-centered gene expression [TPM] per cell line, hierarchical clustering of genes (https://software.broadinstitute.org/morpheus/)
Th Cell Subtype Population Changes in CTCL Patients

- Th1 / Th2 imbalance in CTCL: Phenotypic Th1 to Th2 shift
- Th1 / Th2 differentiation driven by STAT4 (Th1) and STAT6 (Th2)

Resminostat affects STAT4 / STAT6 expression in CTCL

- **STAT4 (Th1)**
  - Early stages CTCL
  - Loss prognostic for CTCL progression

- **STAT6 (Th2)**
  - Late stage, aggressive disease
  - Inversely regulated to STAT4

**RNA expression analysis by qPCR; 24h treatment**

Resminostat induces STAT4 and reduces STAT6 expression in a dose-dependent manner
Resminostat switches gene expression from Th2 to Th1

- Heatmap of Th1 / Th2 gene expression from RNA-seq data:

Heatmap of mean-centered gene expression [TPM] per cell line, hierarchical clustering of genes (https://software.broadinstitute.org/morpheus/)

Resminostat may favor the Th1 phenotype
Resminostat modulates CTCL progression genes

- CTCL progression associated gene signature (Litvinov et al. 2017):
  - Up-regulated in advanced (≥IIB) stage versus early (≤IIA) stage CTCL

Heatmap of mean-centered gene expression [TPM] per cell line, hierarchical clustering of genes (https://software.broadinstitute.org/morpheus/)

Resminostat reduces IL31, a pruritus marker in CTCL

Pruritus affects HrQoL in CTCL patients

- IL31 (Interleukin 31)
  - Th2 cytokine
  - Histamine-independent pruritus mediator
  - Produced by malignant T cells in CTCL
  - IL31 receptor expressed on sensory neurons mediates T helper cell-dependent itch
  - Levels correlate with pruritus

Resminostat may have a beneficial effect on pruritus

Summary / Conclusion

• RNAseq gene expression data suggest, resminostat
  o Affects aberrant skin homing of T-cells in CTCL
  o Affects the Th1/Th2 imbalance favoring the Th1 phenotype
  o may prevent disease progression
  o may reduce pruritus

• Preclinical data set supporting the clinical development of resminostat in CTCL:

  RESMAIN

• Associated translational research program investigates the suggested modes of action of resminostat in patients

• Correlation with the clinical outcome of the RESMAIN study
Many Thanks to the 4SC Team

• Translational Pharmacology
  o Anne Catherine Bretz
  o Ulrike Parnitzke
  o Tanja Wulff
  o Gundula Streubel
  o Kerstin Kronthaler
  o Svetlana Hamm
Thank you!
Disclaimer

The information contained in this presentation is for background purposes only and is subject to amendment, revision and updating. Certain statements and information contained in this presentation may relate to future expectations and other forward-looking statements that are based on management’s current views and assumptions and involve known and unknown risks and uncertainties. In addition to statements which are forward-looking by reason of context, including without limitation, statements referring to risk limitations, operational profitability, financial strength, performance targets, profitable growth opportunities, and risk adequate pricing, other words such as "may, will, should, expects, plans, intends, anticipates, believes, estimates, predicts, or continue", "potential, future, or further", and similar expressions identify forward-looking statements. By their nature, forward-looking statements involve a number of risks, uncertainties and assumptions which could cause actual results or events to differ materially from those expressed or implied by the forward-looking statements. These include, among other factors, changing business or other market conditions and the prospects for growth anticipated by 4SC's management. These and other factors could adversely affect the outcome and financial effects of the plans and events described herein. Statements contained in this presentation regarding past trends or activities should not be taken as a representation that such trends or activities will continue in the future. 4SC does not undertake any obligation to update or revise any statements contained in this presentation, whether as a result of new information, future events or otherwise. In particular, you should not place undue reliance on forward-looking statements, which speak only as of the date of this presentation.
Contact

Matthias Borgmann, Ph.D.
Sr Manager Development Products
matthias.borgmann@4sc.com

RESMAIN
resmain@4sc.com

4SC AG
Fraunhoferstr. 22
82152 Planegg-Martinsried
Germany

+49 89 700763-0
public@4sc.com

www.4sc.com