Resminostat
An Epigenetic Approach for
CTCL Maintenance Treatment

Matthias Borgmann, 3rd WCCL New York, 28 October 2016
Disclosure

I am an employee and shareholder of 4SC AG
Resminostat at a Glance

• Orally available HDAC-Inhibitor (class I, IIB, IV)
  o Small molecule compound
  o Established compound class: hydroxamic acid

• Clinical development status: Phase II
  o About 300 patients treated with resminostat, to date
  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 Lymphoma and HCC patients

Phase II maintenance trial in CTCL in preparation
Primary Mode of Action – HDAC Inhibition

- Flow cytometry analysis of acetylated proteins in CTCL cell lines

**Resminostat treatment results in a ~ 2-fold increase in acetylated proteins**
Pleiotropic Action of HDACi

Changes in gene regulation are the major impact of resminostat
Growth Inhibition in CTCL Cell Lines

<table>
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<tr>
<th>Cell lines</th>
<th>HH</th>
<th>HuT78</th>
<th>MyLa CD4+</th>
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<tr>
<td>Resminostat IC₅₀ [µM]</td>
<td>0.58 (+/- 0.18)</td>
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Cell Cycle Analysis

Resminostat: Growth inhibitory potency without significant impact on cell cycle distribution
Growth Inhibition in CTCL Cell Lines

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Analysis of Apoptotic Processes

Resminostat treatment results in an increased fraction of apoptotic cells
Does Resminostat Affect Cell Differentiation in CTCL?
e.g.: STAT4 / STAT 6 Regulation

- STAT4 overexpression is associated with early stages of CTCL
- STAT4 expression favors the Th1 phenotype differentiation
- Loss of STAT4 expression is a prognostic marker for CTCL progression
- STAT6 expression correlates with Th2 phenotype
- STAT6 expression is associated with late stage, more aggressive disease

adapted from Kudo et al 2013

Litvinov et al 2014
Resminostat Affects STAT4/6 Expression

- qPCR analysis of STAT4 and STAT6 expression

Resminostat induces STAT4 expression (STAT4 high correlates with Th1 phenotype)
Resminostat reduces STAT6 expression (STAT6 high correlates with Th2 phenotype)
Impact on STAT4 Promoter Status

- Chromatin Immune-Precipitation with anti-H3K9ac and anti-H3K27ac ABs
- STAT4 promoter quantification by qPCR

Resminostat enhances histone acetylation at the STAT4 promoter
Hypothesis

Resminostat might affect the Th1/Th2 imbalance in CTCL

Resminostat might stabilize early disease stages of Th1 phenotype
Resminostat might be able to redirect the more aggressive Th2 phenotype
Phase II Maintenance Trial

Patients

- Mycosis fungoides (Stage IIB – IV) or Sézary Syndrome
- Disease control after prior systemic therapy (CR, PR, SD)

Design

Primary endpoint: PFS
Key secondary endpoint: TTSW (Pruritus)

Secondary endpoints: ORR, PFS2, Safety, etc.

Resminostat
N=75

Placebo
N=75

1:1 Randomization

Follow up

Follow up

CTCL: cutaneous T-cell lymphoma; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease;
PFS: progression free survival; TTSW: time to symptom worsening; ORR: overall response rate

28.10.2016
Acknowledgement to the 4SC Team

- Translational Pharmacology
  - Tanja Wulff
  - Anne Catherine Bretz
  - Sabine Schrepfer
  - Kerstin Kronthaler
  - Svetlana Hamm
  - Roland Baumgartner

- Clinical Team
  - Susanne Danhauser-Riedl
  - Martin Orlovius
  - Babett Krauss
  - Eunice Braz

…thank you for your attention!
Contact

Dr. Matthias Borgmann
Manager Development Products
matthias.borgmann@4sc.com

4SC AG
Am Klopferspitz 19a
82152 Planegg-Martinsried
Germany

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

www.4sc.com