Phase Ib cohort 1 data of class I HDAC inhibitor 4SC-202 (domatinostat) in combination with pembrolizumab in advanced cutaneous melanoma patients refractory or non-responding to prior anti-PD1 therapy.
Conflict of interest statement

With reference to this presentation, I hereby declare that I do not conduct activities that would involve a conflict of interest with CME-accreditable training, but that in the past 2 (two) years I have been a paid employee of 4SC AG.
Objectives

• Provide preclinical rationale for combination of selective class I HDAC inhibitor domatinostat with immune checkpoint inhibitors in advanced cutaneous melanoma patients and other skin cancers
• Current status clinical trials
  o SENSITIZE
• Planned studies and outlook
The problem…

- Multiple factors have been shown to influence the likelihood of response to immune therapies:
  - Mutational burden
  - Neoantigen load and clonality
  - Expression of antigen presenting molecules and immune checkpoints
  - Composition of tumor microenvironment: inflamed vs. non-inflamed tumors
Conversion from non-inflamed to inflamed tumor by epigenetic intervention?

• Domatinostat (4SC-202); small molecule HDAC class 1 inhibitor (HDAC 1,2 and 3)

• Phase I data in 24 patients ‘TOPAS’*
  o Hematological malignancies; heavily pretreated
  o safe, well tolerated with anti-cancer activity [monotherapy]
  o 20/24 of patients demonstrated an ORR, 18 patients a SD, 1 patient a PR, 1 patient experienced a CR [angioimmunoblastic T-cell lymphoma, 200 mg BID]

• HDAC inhibitors show pleiotropic effects
  o Modulation of tumor cells
  o Modulation of immune cells
    • Modulation of tumor microenvironment

*Von Tresckow et al., 2018

Domatinostat – versatile immune modulation capabilities

Domatinostat is expected to critically contribute to an effective and/or deeper response in Immuno-Oncology combination approaches on multiple levels.
Domatinostat in preclinical mouse models leads to changes in the tumor microenvironment

- Comparison of models with/without functional immune system

**CT26 mouse model**

<table>
<thead>
<tr>
<th>Immune competent</th>
<th>Immune compromised</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td>vehicle</td>
</tr>
<tr>
<td>4SC-202</td>
<td>4SC-202</td>
</tr>
</tbody>
</table>

Estimated tumor volume [mm$^3$] vs. Time [days]

- Anti-tumor activity observed with 4SC-202 only in syngenic mouse tumor model (murine colon carcinoma)
Domatinostat induced immune-modulation in tumors

- Changes on cellular and protein level
  - Increased infiltration of CD8+ T-Cells
  - Upregulation of MHC I molecules

CT26 cell line, MHC I

CT26 tumor, IHC: CD3/CD8+

- vehicle
- domatinostat

CT26 tumor, CD8+ T cells

% of tumor

% in blood

Vehicle
Domatinostat

Isotype ctrl.
Domatinostat induces genes of PD-1 response signature

Does Domatinostat regulate genes involved in PD-1 blockade response?

➔ Analyze immune-related gene expression signature (Ayers M et al JCI 2017)
  - Baseline tumor samples ➔ signature correlates with clinical benefit of PD-1 blockade (Pembrolizumab)


![Heatmap of gene expression](image)

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ccl5</td>
<td>chemokine (C-C motif) ligand 5</td>
</tr>
<tr>
<td>Cd2</td>
<td>CD2 antigen</td>
</tr>
<tr>
<td>Cd3d</td>
<td>CD3 antigen, delta polypeptide</td>
</tr>
<tr>
<td>Cd3e</td>
<td>CD3 antigen, epsilon polypeptide</td>
</tr>
<tr>
<td>Cita</td>
<td>class II transactivator</td>
</tr>
<tr>
<td>Cxcl10</td>
<td>chemokine (C-X-C motif) ligand 10</td>
</tr>
<tr>
<td>Cxcl13</td>
<td>chemokine (C-X-C motif) ligand 13</td>
</tr>
<tr>
<td>Cxcl9</td>
<td>chemokine (C-X-C motif) ligand 9</td>
</tr>
<tr>
<td>Cxcr6</td>
<td>chemokine (C-X-C motif) receptor 6</td>
</tr>
<tr>
<td>Gzmc</td>
<td>granzyme C</td>
</tr>
<tr>
<td>Gzmk</td>
<td>granzyme K</td>
</tr>
<tr>
<td>H2-Ea-ps</td>
<td>histocompatibility 2, class II antigen E alpha, pseudogene</td>
</tr>
<tr>
<td>H2-T23</td>
<td>histocompatibility 2, T region locus 23</td>
</tr>
<tr>
<td>Ido1</td>
<td>indoleamine 2,3-dioxygenase 1</td>
</tr>
<tr>
<td>Ifng</td>
<td>interferon gamma</td>
</tr>
<tr>
<td>Ii2rg</td>
<td>interleukin 2 receptor, gamma chain</td>
</tr>
<tr>
<td>Lag3</td>
<td>lymphocyte-activation gene 3</td>
</tr>
<tr>
<td>Nkg7</td>
<td>natural killer cell group 7 sequence</td>
</tr>
<tr>
<td>Stat1</td>
<td>signal transducer and activator of transcription 1</td>
</tr>
<tr>
<td>Tgap</td>
<td>T cell activation Rho GTPase activating protein</td>
</tr>
</tbody>
</table>

Score (median log2 TPM)

unpaired t-test, two-tailed
P value = 0.0002
Combination therapies with ICI results in increased survival (in mouse models)

- Some single agent activity with domatinostat; enhanced in combination
- Key characteristics of CT26 and C38 tumor models
  - Immunologically competent and therefore serve as regular tumor models in I-O
  - PD(L)-1 monotherapy show modest anti-tumor activity (C38 > CT26)
    → best reflect non-responsive clinical situation
Translation of findings into the clinic: SENSITIZE

- Phase Ib single arm study in patients with unresectable stage III or stage IV cutaneous melanoma
- Patients must be primary refractory or non-responding to anti-PD-1 monotherapy
- Primary objective: safety and tolerability
  - 6 cancer centers in Germany
  - 1 center in Naples
  - PI: Dirk Schadendorf, Essen

Dosing scheme for dose finding part

- domatinostat
  - Days 1-14
  - Treatment pause
  - Days 15-21
  - Cycle 1
  - Cycle 2 and 3
  - Days 1-14
  - Days 15-21
  - Cycle 4
  - Days 1-14
  - Days 15-21
  - Cycle x

- biopsy sample for biomarker analysis
- administration of pembrolizumab

Extensive biomarker program associated with the study
Current status SENSITIZE

• Cohort 1 (100 mg) completed (10 patients)
  o No safety concerns; safety review committee cleared for cohort 2 [200 mg]
  o Patients for cohort 2 now enrolled
    • DLT observation period
  o Anticipated opening of cohort 3 early next year

• Exploratory biomarker analysis
  o PK/PD analysis
  o IHC Analysis tumor
    • Immune cell markers
    • PD assessment
  o Gene expression blood and tumor
Current Clinical Development Strategy Domatinostat

- Combination with checkpoint inhibitors (PD-1/ PD-L1) in different indications
- Domatinostat as potential combination partner with different checkpoint inhibitors in multiple indications

- **Phase Ib/II SENSITIZE study (4SC-sponsored)**
  - domatinostat + pembrolizumab (anti-PD-1)
  - 30-40 anti-PD-1 refractory/ non responding melanoma patients
  - Expansion cohort other melanoma/ skin cancer

- **Phase Ib/II EMERGE study (IST, RMH)**
  - domatinostat + avelumab (anti-PD-L1)
  - ~70 microsatellite-stable gastrointestinal cancer patients
  - Study start: December 2018
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- Combination with checkpoint inhibitors (PD-1/ PD-L1) in different indications
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- Goal for 2019: Initiation of single-arm Phase II Merkel Cell Carcinoma study

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**Phase II MCC study**
- Domatinostat + anti-PD(L)-1 antibody
- advanced MCC patients
- Europe/ USA/ Australia
- FPI: H2/2019
Rationale for use of domatinostat in Merkel Cell Carcinoma

• Merkel Cell Carcinoma
  o Rare but highly aggressive form of skin cancer
  o Response rates ~ 60% after PD-1/ PD-L1 therapy
  o Patients who fail therapy do not have many treatment options left -> combination with domatinostat

• Synergistic approach derived from current clinical studies
  o Proof of concept data in skin cancer, combination of check point inhibitor and domatinostat (SENSITIZE)
  o Safety data combination avelumab and domatinostat (EMERGE)

Becker et al., 2017
The future: potential triple combination approaches

- A triple combination of domatinostat with anti-PD1 and anti-LAG3 antibody could increase the patient benefit by supporting T cell activation and function
  - Only triple combination shows additional effects
- Clinical translation in patients who do not respond to PD-1 is currently under discussion

### Table: Mel Prior 10 (n = 48)

<table>
<thead>
<tr>
<th>LAG-3 expression</th>
<th>n</th>
<th>n (%)</th>
<th>ORR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1%</td>
<td>25</td>
<td>5 (20)</td>
<td>6.9</td>
<td>1.8 - 24.6</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>14</td>
<td>1 (7.1)</td>
<td>0.2</td>
<td>0.01 - 5.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>n</th>
<th>n (%)</th>
<th>ORR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1%</td>
<td>16</td>
<td>2 (13)</td>
<td>1.6</td>
<td>0.4 - 7.1</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>19</td>
<td>4 (21)</td>
<td>0.4</td>
<td>0.1 - 2.6</td>
</tr>
</tbody>
</table>

### Graph: C38 triple combination (mouse model)

- Vehicle
- anti-LAG3
- domatinostat
- anti-PD-1
- anti-PD-1 + anti-LAG3
- domatinostat + anti-LAG3
- domatinostat + anti-PD-1
- domatinostat + anti-PD-1 + anti-LAG3

Ascierto et al., 2017, ASCO
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**Phase II/III Combination Concepts**
- Domatinostat + anti-PD(L)-1 (+ alternative/ additional combo partner)
- Anti-PD(L)-1 naïve and –experienced
- Advanced solid tumor patients
Conclusions/ outlook

• Good preclinical rationale for class I specific HDACi domatinostat as combination partner with I/O approaches
  o Activity in preclinical animal models; single agent and in combination

• Versatile approach by modulating multiple aspects within cancer/ immunity cycle
  o Modulation of tumor cells (e.g. MHC upregulation; neoantigen presentation)
  o Modulation of immune cells and tumor microenvironment

• Current focus in clinical development melanoma

• Rationale for Merkel Cell Carcinoma

• Combination partner for other (immune modulatory) agents
  o TLRs, vaccines etc.
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