4SC-202 plus Anti-PD1: Breaking PD1-refractoriness to increase efficacy of checkpoint inhibition in patients with advanced melanoma

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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.
Checkpoint Inhibitors have revolutionized Cancer Therapy

- Checkpoint inhibitors (CIs) are the new paradigm for the treatment of cancer patients in many indications
- CIs overcome tumor-specific immune escape mechanisms

**Immune escape**
Evasion strategies by tumor cells; expression of cell surface PD-L1 molecules

**Checkpoint blockade**
Pharmacological intervention of PD-1/PD-L1 binding

**Tumor Elimination**
Inhibition of T-lymphocytes is abrogated; elimination of tumor cells
Despite successes: additional anti-cancer therapies in the immuno-oncology space required

- First approved in 2011 (ipilimumab; CTLA-4) in melanoma
  - Since then: mostly PD-1/ PD-L1 antibodies
- Quite dramatic responses in some patients
  - Increasing number of indications; some even as First-Line-Treatment
- High unmet medical need demands alternative/ additional treatment options
  - Low response rates in some cancers

<table>
<thead>
<tr>
<th>Indication</th>
<th>Response Rate [%]</th>
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<tbody>
<tr>
<td>Non-small cell lung cancer (NSCLC), squamous and non-squamous</td>
<td>15-20%</td>
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<tr>
<td>Small cell lung cancer (SCLC)</td>
<td>15%</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>15-20%</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>25%</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>20%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>15%</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>20%</td>
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<tr>
<td>Melanoma</td>
<td>40%</td>
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Adapted from: Curie Institute; Bryan, Carrier & Co.
Combining therapies to address the needs adequately

• Possible approaches:
  o Novel immuno-oncology targets
  o Combination therapies (chemotherapy, radiotherapy, other entities…)
  • Modulation of multiple pathways
  • Variable targeting (e.g. tumor microenvironment/ tumor/ immune cells)
  • Sequence of existing therapies

Explosion in combinatorial therapies
Why do some patients respond to CIs – and some not?

- Multiple factors have been shown to influence the likelihood of response to immune therapies:
  - Location, type and quantity of immune effector cells
  - Mutational burden
  - Neoantigen load and clonality
  - Expression of antigen presenting molecules and immune checkpoints
  - Composition of tumor microenvironment: 'Hot' vs. 'Cold' Tumors

Conversion from noninflamed to inflamed tumor by epigenetic intervention?

Rationale for Epigenetic Modulation

• Current evidence suggests that epigenetic mechanisms play an important part in immune evasion of tumor cells

• Changes in expression with immunological relevance
  o Neoantigen expression (e.g. ‘TINATS’)
  o MHC presentation machinery
  o Rejuvenating exhausted effector cells
  o Release of proinflammatory chemokines

• Clinical evaluation with Entinostat class I HDACi (ENCORE 601); combination with pembrolizumab
  o ORR 24% anti-PD(L)-1-naïve; 10% in patients that progressed under PD(L)-1

Can 4SC-202 induce epigenetic effects leading to modulation of immune parameters in tumors?
Enter 4SC-202

- Small molecule HDAC class I inhibitor (HDAC 1, 2 and 3)
- Orally available
- Phase I data in 24 patients ‘TOPAS’
  - study in patients with hematological malignancies
  - safe, well tolerated with anti-cancer activity
    - 20/24 [83.3%] 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]
4SC-202 in preclinical mouse models

• Comparison of models with/ without functional immune system

CT26 mouse model

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

Anti-tumor activity observed with 4SC-202 only in syngenic mouse tumor model (murine colon carcinoma).

How does the tumor microenvironment compare +/- 4SC-202 treatment?
Increased influx of immune cells

- 4SC-202 stimulates infiltration of CD8\(^+\)/CD4\(^+\) effector cells into tumor
- Not due to increased proliferation of cells
4SC-202 changes expression of cytokines in tumor

- 4SC-202-mediated changes in gene expression
  - Increases expression of chemokines in TME
  - Decreases expression of pro-inflammatory cytokines in TME
  - Increases IFN-γ in TME

CT26 tumor: inflammatory genes

Ccl8: Chemokine (C-C motif) ligand 8
Ccl5: Chemokine (C-C motif) ligand 5
Cxcr6: C-X-C chemokine receptor type 6
Cxcr8: C-X-C chemokine receptor type 8
Irf4: Interferon regulatory factor 4
Stat4: Signal transducer and activator of transcription 4
Ifng: Interferon gamma
Enhanced expression of MHC

- 4SC-202 increases the expression of MHC molecules

4SC-202 mediates changes in tumor/ tumor microenvironment; does this result in a benefit when combined with checkpoint inhibitors?
4SC-202 synergizes with anti-PD-1 blockade

C38 model

Anti-tumor activity observed with 4SC-202 alone; synergistic effects in combination with anti-PD-1.

PD-1 blockade alone: 2 responding, 18 non-responding

C38: murine colon carcinoma (syngenic)
4SC-202 synergizes with anti-PD-1 blockade

Tumor growth control with 4SC-202 alone; combination of 4SC-202 with anti-PD-1 results in tumor regression.
Combination leads to increased median and overall survival

- In the C38 tumors combination of 4SC-202 and anti-PD-1 antibody resulted in up to 55% tumor-free animals

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<thead>
<tr>
<th>Treatment</th>
<th>Median (d)</th>
<th>OS (%)</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>4SC-202, 60 mg/kg</td>
<td>58</td>
<td>10</td>
</tr>
<tr>
<td>Combo with 60 BID</td>
<td>&gt;70</td>
<td>55</td>
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Combination of 4SC-202 with PD-1 blockade results in sustained responses

Anti-tumor effects of combination treatment are long-lasting even upon drug removal.
4SC-202 as combination partner for other CIs

- Epigenetic modulation changes the tumor microenvironment
  - Increased infiltration of immune cells into tumor
  - Enhanced expression of MHC molecules
  - Induction of tumor associated antigen expression
  - Increases expression of chemokines like IFN-γ in TME
- Some 'stand-alone' anti-tumor effects by 4SC-202
- Pleiotropic immune-modulatory features; 4SC-202 as backbone combination partner for different checkpoint inhibitors

Combination of 4SC-202 and checkpoint inhibitor reduces tumor burden and increases survival in animal models. Can we translate the findings into the clinic?
Translation 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 prior anti-PD-1 monotherapy
- 3 dose cohorts [100, 200, 2 x 200 mg 4SC-202 + Pembrolizumab 2 mg/kg q3w]

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<thead>
<tr>
<th>Dose finding</th>
<th>Expansion</th>
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<tr>
<td>N=6-10 per cohort</td>
<td>4SC-202</td>
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- **4SC-202**
  - 100 mg OD
  - 200 mg OD
  - 200 mg BID

- **Pembrolizumab**

- **Recommended Phase II dose**

OD: once a day; BID: bis in die, twice a day
SENSITIZE Study Objectives

• Primary
  o The primary objective of the study is to determine safety and tolerability of combination treatment with 4SC-202 and Pembrolizumab
  o AEs, lab tests, vital signs, ECG, ECOG PS, physical examination, concomitant medication

• Secondary
  o Examine preliminary efficacy of combination treatment with 4SC-202 and Pembrolizumab
  o Determine
    • Non-tolerated dose (NTD)
    • Maximum tolerated dose (MTD)
    • Recommended phase 2 dose (RPTD)
  o Characterize pharmacokinetics (PK) of 4SC-202
SENSITIZE dosing scheme and exploratory objectives

• Exploratory Endpoint Biomarker assessment
  o Gene expression tumor and blood
  o IHC Analysis (tumor; skin biopsies)
  o Exosome collection and analysis

• PK/ PD sampling
  o PK/PD relationship analysis planned for some of the patients
SENSITIZE is currently recruiting

- 6 cancer centers in Germany
- PI: Dirk Schadendorf, Essen
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