Modulation of the tumor microenvironment by epigenetic intervention

12 October 2017
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
PD-1 vs. Dacarbazin in melanoma

Checkpoint inhibitors provide melanoma patients with a real alternative in tumor therapy.

NIVO: Nivolumab (anti-PD-1)
DTIC: Dacarbazin
Checkpoint inhibitors: a success story

- 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

AACR Cancer progress report 2017
Additional anti-cancer therapies in the immuno-oncology space required

• High unmet medical need demands alternative/additional treatment options
  o Low response rates in some cancers

• Possible approaches:
  o Novel checkpoint inhibitors
  o Combination therapies (chemotherapy, radiotherapy, other entities…)

Anti-PD-1/PD-L1 – Overall response rates

<table>
<thead>
<tr>
<th>Indication</th>
<th>Response Rate [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small cell lung cancer (NSCLC), squamous</td>
<td>15-20%</td>
</tr>
<tr>
<td>and non-squamous</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Melanoma</td>
<td>40%</td>
</tr>
</tbody>
</table>

Explosion in combinatorial therapies

Adapted from: Curie Institute; Bryan, Garnier & Co.
The Cancer-Immunity Cycle

- Complex relationship between tumor, tumor microenvironment and immune system
- Leaves multiple ways for pharmacological intervention

- Chemotherapy
- Radiotherapy
- Targeted Therapy

- Anti-CTLA4
- Anti-VEGF
- Vaccines
- CARs
- Anti-PD-1
- Anti-PD-L1

Chen&Mellman 2013
Why do some patients respond to CIs – and some not?

- Degree of inflammation plays a critical role in facilitating bodies own immune system to fight cancer

- Tumor microenvironment
  - Number, type and location of immune cells
  - Other immunological parameters (mutational load, cytokines)

Galon et al., Clin Cancer Res; 2014
Inflamed and noninflamed tumors respond differently to CIs

• Predisposition of tumor microenvironment rendering it more or less susceptible to CI treatment?

Conversion from noninflamed to inflamed tumor by epigenetic intervention?

Enter 4SC-202

- Small molecule HDAC class 1 inhibitor (HDAC 1, 2 and 3)
- Orally available
- Phase I data in 24 patients ‘TOPAS’
  - study in patients with hematological malignancies
  - completed 2015
  - safe, well tolerated with anti-cancer activity

Important: Checkpoint inhibitors still required
4SC-202 in preclinical mouse models

- Comparison of models with/without functional immune system

CT26 mouse model

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

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

- 4SC-202 stimulates infiltration of CD8⁺/ CD4⁺ immune cells into tumor
- This is not due to an increased proliferation of cells
Increased infiltration CD8$^+$ T-Cells

Enhanced expression of MHC

- 4SC-202 increases the expression of MHC molecules
Effect of HDAC inhibitors on T-Cell viability

### T-Cell viability [IC50; µM]

<table>
<thead>
<tr>
<th>HDAC inhibitor</th>
<th>CD4+ T cells*</th>
<th>CD8+ T cells*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>naive</td>
<td>memory</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Mocetinostat</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Entinostat</td>
<td>2.1</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>4SC-202</strong></td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

* T cells were stimulated with CD3/28 beads; different subpopulations were isolated using appropriate Miltenyi kits according to manufacturers instructions; cells were treated with indicated compounds for 48 h; viability was determined using Vialight Kit (Lonza); ** up to 10 µM

4SC-202 is less toxic to immune effector cells when compared to other HDAC inhibitors.
Immune modulatory effects of 4SC-202

• Epigenetic modulation changes the tumor microenvironment
  o Increased infiltration of immune cells into tumor
  o Enhanced expression of MHC molecules
  o Induction of tumor associated antigen expression
  o Increases expression of chemokines like IFN-γ in TME

• Some 'stand-alone' anti-tumor effects by 4SC-202
  o Less toxic to effector cells when compared to other HDACi

• Synergistic effects in combination with checkpoint inhibitors?
4SC-202 synergizes with PD-1 blockade in C38 tumor models

- Some single agent activity with PD-1 blockade and 4SC-202
- Combination of both results ins stronger anti-tumor activity
4SC-202 in combination with CIs

CT26 Model: Tumor burden

CT26 Model: Survival

C38 Model: Tumor burden

C38 Model: Survival

Combination of 4SC-202 and checkpoint inhibitor reduces tumor burden and increases survival in animal models.
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 anti-PD-1 monotherapy
- 3 dose cohorts [100, 200, 2 x 200 mg 4SC-202 + Pembrolizumab 2 mg/kg q3w]

Dose finding
N=10 per cohort

Expansion

<table>
<thead>
<tr>
<th>100 mg OD</th>
<th>200 mg OD</th>
<th>200 mg BID</th>
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<tr>
<td>+ Pembrolizumab</td>
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<table>
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<th>200 mg OD</th>
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Recommended Phase II dose

OD: once a day; BID: bis in die, twice a day
SENSITIZE dosing scheme and study objectives

• Primary Endpoint:
  o Safety and tolerability

• Secondary Endpoints:
  o PK/PD Analysis
  o Antitumor activity per irRECIST

Dosing scheme for dose finding part

4SC-202

Days 1-14

Treatment pause

Days 15-21

Days 1-14

Days 1-14

Days 1-14

Days 15-21

Days 15-21

Days 15-21

Days 15-21

Cycle 1

Cycle 2 and 3

Cycle 4

Cycle x

biopsy sample for biomarker analysis; administration of pembrolizumab

Important: translation of preclinical findings into the clinic
Biomarker Assessment

• 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 analysis planned for some of the patients
SENSITIZE is currently recruiting

- 6 cancer centers in Germany
- PI: Dirk Schadendorf, Essen
Thank you!
Contact

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