Domatinostat (4SC-202) as a core immune-modulatory combination partner for immunotherapy

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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.
Domatinostat (4SC-202)

• Small molecule histone deacetylase (HDAC) inhibitor
  o Orally available, selective HDAC class I inhibitor
  o Direct anti-tumor activity and ability to modulate the tumor microenvironment

• Phase I study (TOPAS) in monotherapy
  o 24 patients with advanced hematological malignancies
  o Safe, well tolerated with anti-cancer activity
    • Mainly grade 1-2 gastrointestinal, laboratory [e.g. liver enzyme elevation] and hematologic treatment-related adverse events (reversible)
    • Grade 3 events included neutropenia/thrombopenia and increased liver enzymes [only in 200 mg BID repeated dosing]
    • No treatment related deaths
    • 20/24 [83.3%] at least stable disease, 1 partial response, 1 complete response (see B/U for additional details)
Efficacy in syngeneic murine CT26 colon carcinoma model

Anti-tumor activity of domatinostat requires a functional immune system
Domatinostat induces changes in the tumor microenvironment making it more susceptible for the treatment of checkpoint inhibitors → focus on combination therapy

- Conversion from a ‘immune-deserted‘ to ‘inflamed‘ tumor; higher susceptibility to combination treatment
- Preliminary results from combining entinostat [HDACi class I] with pembrolizumab (ENCORE 601; NCT02437136) → Proof of class combination concept

CT26 tumor model: treatment start at 150 mm³, 20 mg/kg BID domatinostat for ~14 days (~HED of 200 mg daily), analysis of intratumoral immune cells at day 20
Domatinostat in the cancer immunity cycle

Domatinostat may contribute to a more effective response in Immuno-Oncology combination approaches
Domatinostat in combination with PD-1 in syngeneic murine colon carcinoma model

Domatinostat displays anti-tumor activity in monotherapy; synergistic effects in combination with anti-PD-1
Domatinostat + anti-PD-1 increases survival rate

Prolonged survival for animals treated with domatinostat/ PD-1 combination; up to 55% of them are tumor free
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
Domatinostat in combination with PD-L1 in syngeneic mouse model

Synergistic benefit for combination of domatinostat with anti-PD-L1: reduced tumor burden and increased survival
Domatinostat in combination with 4-1BB (CD137) agonist

Combination results in regression in majority of animals
Domatinostat is a suitable partner for triple combinations: LAG3 and PD-1

No activity for LAG3 alone; some effects for domatinostat and PD-1 alone
Domatinostat is a suitable partner for triple combinations: LAG3 and PD-1

Synergistic effects in combination with most pronounced anti-tumor activity in triple combination setting
Combination of domatinostat with anti-PD1 and anti-LAG3 antibodies, triple combination

C38 triple combination

More regressions compared to domatinostat and anti-PD-1 monotherapies

Nearly all tumors regress
Immune modulatory effects of 4SC-202

• HDAC class I as the most promising immune-modulation HDACis
• 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
• HDAC class I as the most promising immune-modulation HDACs
  o pleiotropic immune-modulatory features > unique pattern potentially as backbone combination partner
Clinical development strategy domatinostat

- Translation of findings into the clinic:
  - Exploration of domatinostat in clinical setting
  - Combination with checkpoint inhibitors (PD-1/ PD-L1) in different indications
  - Domatinostat as potential combination partner with different checkpoint inhibitors in multiple indications
  - Goal for 2019: Initiation of single-arm Phase II Merkel Cell Carcinoma study

### Clinical development strategy domatinostat

**Phase Ib/II SENSITIZE study (4SC-sponsored)**
- domatinostat + pembrolizumab (anti-PD-1)
- 30-40 anti-PD-1 refractory/ non responding melanoma patients
- Cohort 1 completed in June 2018
- Top line data H2/2018

**Phase Ib/II EMERGE study (IST)**
- domatinostat + avelumab (anti-PD-L1)
- ~70 microsatellite-stable gastrointestinal cancer patients
- Study start: July 2018
- RP2D: Q4/2018

**Phase II MCC study**
- Domatinostat + anti-PD(L)-1 antibody
- advanced MCC patients
- Europe/ USA/ Australia
- FPI: H2/2019

**Phase II/III Combination Concepts**
- Domatinostat + anti-PD(L)-1 (+ alternative/ additional combo partner)
- Anti-PD(L)-1 naive and –experienced
- Advanced solid tumor patients
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