IMMUNOMODULATING PROPERTIES OF A NOVEL HDAC INHIBITOR RESMINOSTAT

MARCH 26TH 2014
DR. SVETLANA HAMM
Employee of 4SC Discovery GmbH, a subsidiary of 4SC AG that is developing Resminostat for anti-cancer therapy
RESMINOSTAT: CLINICAL DEVELOPMENT

ENTRY INTO HEMATOLOGICAL INDICATIONS

Hodgkin’s Lymphoma “SAPHIRE”
- Relapsed/refractory HL patients who are resistant to 2nd-line therapy have very low survival rate
- 3rd-line treatment
- Single-arm study
- Simon 2-stage design
- Resminostat monotherapy
- Aiming for short development timeline and fast market entry

FIRST ENTRY INTO SOLID TUMOR INDICATIONS

Hepatocellular Carcinoma “SHELTER”
- Only one therapy available in advanced HCC (sorafenib)
- Very high unmet need in Asia-Pacific region
- 2nd-line therapy
- 2-arm study
  - Resminostat monotherapy
  - Resminostat + sorafenib combination therapy

EXTENDED ENTRY INTO SOLID TUMOR INDICATIONS

Colorectal Cancer “SHORE” (ongoing)
- 3rd most frequent cancer
- Ph. I/II with patients w/ KRAS-mutated tumors
- 2nd-line therapy
- Randomized, 2-arm study
  - FOLFIRI (standard chemo regimen) +/- resminostat combination therapy

RESMINOSTAT HAS DEMONSTRATED CLINICAL EFFICACY AS SINGLE AGENT ANTI-CANCER DRUG AND IN COMBINATION WITH ESTABLISHED TUMOR THERAPIES.
Resminostat is an inhibitor of histone deacetylases (HDACs)

- HDACs deacetylate histones and various other proteins
- Inhibition of HDACs changes acetylation status of:
  - Histones → open chromatin structure
  - And more relevant of:
    - Specific promoter/enhancer and
    - Transcriptional machinery
  - Transcriptional profile: up and down

Resminostat changes tumor cells by modulation of gene expression
RESMINOSTAT: PLEIOTROPIC EFFECTS

- **TUMOR CELL PROLIFERATION BY INDUCTION OF CELL CYCLE ARREST AND APOPTOSIS:**
  - upregulation of tumor suppressors
  - balance of pro- and anti-apoptotic proteins

- **INHIBITION/REVERSION OF EMT (EPITHELIAL–MESENCHYMAL TRANSITION)**
  - Inhibition of WNT signaling
  - Increased E-Cadherin/N-Cadherin ratio
Resminostat induces transcriptional changes that can modulate anti-cancer immune response at different levels:

- Tumor associated antigens ➔ Immunogenicity
- Stress molecules ➔ NK cell mediated recognition and killing
- Catabolizing enzymes ➔ Immunosuppression in tumor microenvironment
RESMINOSTAT IS ABLE TO ENHANCE EXPRESSION OF TUMOR ASSOCIATED ANTIGENS AND MHC CLASS I MOLECULES IN VARIOUS TUMOR CELLS
RESMINOSTAT IS ABLE TO ENHANCE EXPRESSION OF MHC CLASS II AND CO-STIMULATORY MOLECULES POTENTIALLY CONVERTING TUMOR CELLS INTO “UNPROFESSIONAL” APC
NK CELL RECOGNITION

**RESMINOSTAT UPREGULATES EXPRESSION OF NKG2D LIGANDS ON VARIOUS CELL LINES AND STRONGLY BOOSTS NK CELL MEDIATED CELL CYTOTOXICITY**
IMMUNOSUPPRESSION

**RESMINOSTAT IS ABLE TO REDUCE ARGINASE1 AND INDUCIBLE AS WELL AS CONSTITUTIVE EXPRESSION OF IDO1 IN VARIOUS TUMOR CELL LINES**
SUMMARY: IMMUNOMODULATING EFFECTS OF RESMINOSTAT

[Diagram showing TUMOR CELL, IDO/ARG, NK cell, and T cell connected]
SUMMARY: IMMUNOMODULATING EFFECTS OF RESMINOSTAT

RESMINOSTAT

TUMOR CELL

IDO/ARG

TAA PRESENTATION

NKG2D LIGANDS

NK cell

T cell

3934 up

3273 down
CLINICAL RELEVANCE: COMBINATION THERAPY

RESMINOSTAT

- Enhance immunogenicity
- Potentiation of anti-tumoral T cell response

Reduce unspecific immunosuppression

- Enable attack on tumor by CTL and NK cells + remove additional brakes
- Enable attack on tumor by CTL and NK cells + remove additional brakes

Enhance NK cell function

- Enhance NK cell function
- Enhance and direct NK cell mediated toxicity

IMMUNOSTIMULATING AGENTS:
- cytokines (IFN-α, IL-12, IL-2, ect.)
- immunostimulating antibodies (CD40, CD137)
- TLR ligands
- Tumor vaccination

IMMUNE CHECKPOINT BLOCKERS:
- Anti-CTLA4
- Anti-PD1/PD-L1

OPSONIZING ANITBODIES:
- CD20
- CD30
- EGFR
THANK YOU VERY MUCH!