Resminostat, a new treatment option in cutaneous T cell lymphoma (CTCL)

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Resminostat and CTCL

Resminostat, an orally available inhibitor of HDAC class I, IIb, and IV, is in Phase II clinical development. It was tested in various cancer indications (HCC, CRC, HL, NSCLC, pancreatic and biliary tract cancer), demonstrated safety in over 300 patients, and showed a survival benefit in a subgroup of patients with advanced liver cancer.

Cutaneous T cell lymphoma (CTCL) is a non-Hodgkin lymphoma characterized by proliferation of skin-homing T cells. Advanced stage CTCL is characterized by a phenotypic plasticity with regard to T helper cell status, switching from Th1 to Th2 status at progression. This switch is associated with epigenetic induced changes in the expression of STAT4/STAT6 (Litvinov et al. 2014).

The purpose of this in vitro study is to investigate resminostat's anti-tumoral efficacy against CTCL-derived cell lines and its impact on STAT4/STAT6 expression to support resminostat's clinical development in CTCL.

Primary mode of action

Resminostat induces increase in protein acetylation in CTCL cell lines

Upon treating different CTCL cell lines (HH, HuT78, MyLa CD4+) with vehicle or 3 µM resminostat for 3 h, cells were fixed, stained with anti-acetylated lysine antibody and subsequently analyzed via flow cytometry. A. Representative histogram of HuT78 cells. B. Total acetylation in all three CTCL cell lines.

Resminostat affects growth of CTCL cell lines

Resminostat displays growth inhibitory potency in three CTCL cell lines, shows only moderate effect on cell cycle but increases fraction of apoptotic cells

A: In vitro potency (IC50) on CTCL cell lines assay after 72 h of treatment with resminostat. B. C. MyLa CD4+ cells were treated with vehicle or 4 µM resminostat for 72 h and cell cycle distribution (B) was determined by Propidium Iodide (PI) staining. Cell cycle phases are depicted in percentages. Apoptosis (C) was determined via Annexin V and PI staining using flow cytometry analysis. The different populations are represented as percentages.

Resminostat might affect differentiation in CTCL cells

Early stages of CTCL are associated with an overexpression of STAT4, which favors the T helper (Th1) 1 differentiation. Late disease stages are associated with a predominantly Th2 phenotype and loss of the STAT4 expression (Litvinov et al. 2014).

Conclusions

Resminostat displayed conclusive in vitro anti-tumor activities in all three tested CTCL cell lines. The regulation of the aberrant STAT signaling on transcription level suggests a stabilization of the less advanced CTCL stage (Th1) or even a reconversion of the advanced Th2 to the Th1 phenotype. Normalizing the epigenetic dysregulation which drives CTCL to progression provides a biological rationale for a maintenance therapy. A clinical Phase II trial to evaluate resminostat for maintenance treatment of patients with advanced stage (IIb-IV) mycosis fungoides or Sézary syndrome that have achieved disease control with systemic therapy is currently in preparation.

For more information on Resminostat, please also visit poster boards # P080, # P087 (Epigenetic modulators session) and # P111 (Immunotherapy session) on Wednesday, November 30

For more information on 4SC-202, please also visit poster board # P112 (Immunotherapy session) on Wednesday, November 30

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