Resminostat increases NK cell-mediated lysis of malignant cells beneficially affecting the function of opsonizing antibodies

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Illuminating the mode of action of HDAC inhibition

- Preclinical studies examining resminostat's mode of action in CTCL cells

**Debulking effects**

- Cell death / Apoptosis
- Cell Proliferation

**Modulation of cell phenotype**

- Immune Modulation
  - NK cell response
- Gene Regulation
  - Th1/Th2 Skin homing receptors
- IL-31 cytokine reduction

**Resminostat**

Hyperacetylation

of histone and non-histone proteins

**TUMOR CELL**

**RESMAIN**

Abstract 007
Session 4/Biologic Insights III, Friday 27th September 2019, at 09.00 – 10:30

Abstract 027
Session 4/Biologic Insights III, Friday 27th September 2019, at 09.00 – 10:30

Abstract 106
Session/Quality of life, Friday 27th September 2019, at 15.30 – 16:15

Abstract 088
Session/Treatment I, Friday 27th September 2019, at 16:45 – 18:00
NK cell response and HDAC inhibition

Increase expression of NKG2DL*
Decrease expression of CCR4§
(target of mogamulizumab)

HDAC inhibition

Reduce NK cell viability and function#

* Skov et al., Cancer Res. 2005; Armeanu et al., Cancer Res. 2005; Diermayr et al., Blood, 2007; Wu et al., Neoplasia 2012; Shi et al., BMC Cancr 2014; Zhu et al., Pharm. Res. 2015;
# Kitadate et al., Haematologica 2018
Effects of resminostat on the NK cell response

- Resminostat increases expression of NKG2D ligands on tumor cells of various origin.
- Resminostat dose-dependently increases sensitivity of target cells towards NK-cell lysis.
- Resminostat-mediated effect is dependent on NKG2DL upregulation.

→ Resminostat treatment increases tumor cell susceptibility towards NK cells.
HDAC inhibition and NK cell viability and function

- NK cell viability seems to be affected by HDAC inhibitors

- Upregulation of the activation marker on NK cells suggests rather an activation induced cell death than a cytotoxic effect on cell viability

- NK-cells pretreated with resminostat show increased cytolytic activity

→ Resminostat activates NK cells and thereby increases activity of NK cells towards tumor cells
Resminostat’s effect on NK cell response

Resminostat beneficially affects anti-tumoral NK cell response by increasing both, tumor cell susceptibility and NK cell activity.
How to translate this effects into clinic?

- Combination with opsonizing antibodies
Expression of CD20 is not affected by resminostat

Resminostat increases DLBC lymphoma’s sensitivity towards rituximab mediated cytolysis by NK cells
Resminostat in combination with mogamulizumab?

• Does resminostat affect the expression of CCR4?

• Treatment of CTCL cell lines with resminostat at non-toxic concentrations did not reduce CCR4 expression on Hut78 (SS), Myla (MF) or L428 (HL) cells

→ Resminostat does not reduce expression of CCR4 on CTCL cells
Resminostat in combination with mogamulizumab

- Resminostat increased the sensitivity of CTCL cells to mogamulizumab-mediated NK cell response

→ these preclinical data suggest the combination of resminostat with opsonizing antibodies like mogamulizumab as potential therapy option in CTCL
Summary

Increases expression of NKG2DL
No effect on CD20 and CCR4 expression

→ increased NK-cell mediated cytolysis in combination with opsonizing antibodies like rituximab and mogamulizumab
Mode of action of resminostat in CTCL cells

Resminostat’s mode of action in CTCL cells

Debulking effects ↔ Modulation of cell phenotype

- Cell death / Apoptosis
- Cell Proliferation
- TUMOR CELL
- Immune Modulation NK cell response
- Gene Regulation Th1/Th2 Skin homing receptors
- IL-31 cytokine reduction

Hyperacetylation of histone and non-histone proteins

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