Efficient HDAC inhibition and TARC reduction in patients with refractory Hodgkin’s lymphoma treated with Resminostat PK/PD data from the Phase II SAPHIRE study

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Background

Hodgkin’s lymphoma (HL) is characterized by malignant Hodgkin/Reed-Sternberg cells surrounded by a complex inflammatory infiltrate including TH2 and Treg cells, dendritic cells and macrophages. Current first-line therapies in HL are highly efficacious (>80% cure rate) but are associated with significant toxicities and the development of secondary malignancies. HL patients who are resistant to 2nd line treatments have a 5-year survival rate of only 17% requiring the search for new 3rd line therapy options (Smith et al., Ann Oncol 2008, 19:1312).

Resminostat

• Hodgkin desacetylases (HDACs) control the deacetylation of nuclear histones and other proteins. They are involved in the remodeling of chromatin and play a key role in the epigenetic regulation of gene expression.
• Inhibition of HDACs has emerged as a promising strategy to reverse aberrant epigenetic changes associated with disease.
• The novel oral pan-HDAC inhibitor resminostat is currently evaluated in monotherapy or as a sensitizing agent in combination with established treatment regimens in solid tumors.

Study Design

Overview

Sampling Time Points

PET/CT

• Out of 34 patients centrally assessed by PET/CT for ORR, 19 patients (55.6%) obtained a clinical benefit (response or stabilization of disease) from resminostat treatment.
• 12 patients (35.5%) were assessed as complete or partial responders.
• 7 patients achieved stabilization of disease in response to resminostat treatment.
• In 65% of patients a reduction in size (CT) and in 71% a reduction in metabolic activity (PET) of target tumor lesions was achieved.

Response was assessed by central review of PET/CT images after three and six cycles of treatment and every fourth cycle thereafter.

PK/PD Data

HDAC Activity

• Inhibition of enzymatic HDAC activity was transient with a maximum median inhibition of up to 94% two hours post dose.
• Median HDAC enzyme inhibition compared to resminostat drug plasma concentrations for the 600 mg (n=10) and the 800 mg (n=9) dose cohort indicate a good correlation between resminostat pharmacokinetics and pharmacodynamic effects with maximum enzyme inhibition corresponding to median peak plasma levels of resminostat between 1 and 1.5 hours.

Chemokine Levels

TARC/CCL17

• Thymus and activation-regulated chemokine (TARC) is a small cytokine also known as CC chemokine ligand 17 (CCL17).
• All subtypes of Hodgkin/Reed-Sternberg cells and dendritic cells are responsible for the chemotactic attraction of T cells into the tumor microenvironment.
• The TARC plasma level is elevated in more than 90% of primary HL patients and has been described as a prognostic factor for poorer outcome (Weihrauch et al., Cancer Res. 2005, 65:5514).

Gene Expression

DEPDC7 and GTF3C6

• In order to identify characteristic changes of gene expression patterns in response to resminostat treatment, a preselected set of candidate genes was analyzed in peripheral leukocytes from SAPHIRE patients at different time points during treatment via quantitative real-time PCR.
• DEPDC7 and GTF3C6 serve as examples of two sets of genes whose expression levels are reproducibly either upregulated (DEPDC7) or downregulated (GTF3C6) in immediate response to resminostat dosing over the course of 5 hours and thus serve as additional pharmacodynamic markers for resminostat activity.

• Gene 1 is an example of a potential treatment stratification marker, as its baseline expression was higher (as indicated by decreased DCT values) in patients achieving a clinical benefit by resminostat treatment compared to patients who did not.
• Gene 2 exemplifies a potential predictive marker gene, as its expression decreases over the treatment period (as indicated by increased DCT values at Day 33 compared to Day 0) only in patients that obtained a clinical benefit from resminostat therapy.

Summary & Conclusion

Resminostat monotherapy delivered objective tumor responses in heavily pre-treated relapsed/refractory Hodgkin’s lymphoma patients.
• Inhibition of enzymatic HDAC activity was transient with a maximum median inhibition of up to 94% two hours post dose corresponding to median peak plasma levels of resminostat.
• Patients with lower baseline TARC/CCL17 plasma levels were more likely to benefit from resminostat treatment. TARC/CCL17 levels were reduced in the majority of patients over the course of the therapy with individual reductions of up to 95%.
• Reproducible up- or downregulated expression of a set of marker genes in response to treatment was observed in peripheral leukocytes of SAPHIRE patients, thus providing additional markers for the pharmacodynamic effect of resminostat. Furthermore, selected genes might also be suitable to serve as biomarkers for patient stratification or prediction of clinical response.
• Biomarkers determining functional inactivation of drug targets and changes in protein or gene expression levels of relevant marker proteins are valuable tools for an early determination of HDAC inhibitor activity and might provide means for patient stratification or prediction of clinical response to resminostat.

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