ZFP64 – a predictive RNA biomarker for cancer treatment with the HDAC-inhibitor Resminostat

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Biomarker Discovery at IMGM

IMGM offers a plethora of genomic services for identification and validation of biomarkers in clinical as well as research studies. The long-standing experience and the fleet of both well-established and latest technology platforms together with bioinformatics expertise and a professional quality management system assure excellent support for all customers in their biomarker studies.

Identification of a Pharmacodynamic Biomarker Panel

A microarray experiment was conducted to identify mRNA biomarkers for monitoring Resminostat’s inhibitory effects on transcription of cells and human blood. Biomarker selection criteria were robust up- and down-regulation of the genes of interest with high amplitude and stable expression signals. After thorough analysis, the identified pharmacodynamic marker genes demonstrated solid regulation of gene expression in e.g. HT29 and HepG2 cells as well as in samples from healthy donors.

ZFP64 was identified among a set of the pharmacodynamic marker genes and showed a robust down-regulation in various cancer cell lines, peripheral blood cells, and whole blood samples from healthy donors as well as in patients from three different clinical trials. The regulation is dose-dependent and reaches the maximum change about 5 hours post-dose in human blood samples, very well correlating with Resminostat’s pharmacokinetic profile.

Analysis of differential gene expression
- Screening for biomarkers
  - Microarray analysis
  - RNA-seq
- Analysis of biomarker gene panels
  - TaQMan® arrays
  - Drug response
- Disease state
- Development of custom microarrays
- Single cell analysis using qPCR

4SC Clinical Studies & Concept of Resminostat

Resminostat is a novel oral pan-HDAC inhibitor with an attractive safety profile as revealed by a phase I FIM study in patients with solid tumors [1]. Subsequently, the compound was evaluated in clinical studies for various cancer indications. It has shown promising results in patients with advanced hepatocellular carcinoma (HCC, SHELTER trial), advanced Hodgkin’s lymphoma (HL, SAPHIRE trial), and colorectal carcinoma (CRC, SHORE).

Based on its epigenetic mode of action and supported by pre-clinical data, Resminostat is an ideal candidate for development in combination therapy with classical cancer drugs in a broad variety of potential cancer indications.

ZFP64 regulation in cells and whole blood

Biological Aspects & Summary

ZFP64 expression is observed in liver cancer, lymphoma, pancreatic cancer and thyroid cancer [2]. In the literature ZFP64 is described as a co-stimulatory molecule for NFκB signaling [3]. Other publications hint at a role in the Notch signaling pathway. ZFP64 is described to be involved in the differentiation of myogenic progenitor cells by co-activation of Notch [4]. ZFP64 gene expression at baseline (Cycle 1 Day 1 Hour 0) in clinical trials was investigated for a potential use in patient stratification retrospectively. Baseline ZFP64 expression levels allow for separating patients with radiologically confirmed progression (PD) from those with stable disease (SD). In order to gain deeper insight and to correlate ZFP64 with accepted clinical endpoints (PFS, OS), time-to-event analysis was performed. Intriguingly, the analysis of the SHELTER data revealed a statistically significant correlation of baseline mRNA levels of ZFP64 with overall survival. High baseline ZFP64 expression, as observed in about 75% of the patients, correlated with an extended medium OS value in comparison to patients with low baseline ZFP64 expression. Importantly, this correlation was observed in the SAPHIRE trial as well, indicating a predictive character of this biomarker for response to Resminostat treatment. Given the fact that the third clinical trial with Resminostat also gave hints of a comparable correlation, although based only on a small number of patients, this is a strong indication of ZFP64’s marker potential and a promising signal for a personalized medicine approach with Resminostat. Further clinical development of Resminostat will incorporate the focus to confirm ZFP64’s role to serve as a prognostic or predictive biomarker.

References