Biomarker summary analysis for the histone deacetylase inhibitor resminostat – Review and conclusions based on three oncology Phase I and Phase II trials

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Introduction

Background: Following a successful first-in-man (FIM) trial [1] in 19 patients with advanced solid tumors, three Phase I or Phase II studies have been conducted in oncology indications in a total of 111 patients with the histone deacetylase (HDAC) inhibitor resminostat: The SHELTER [2] (hepatocellular carcinoma, NCT00943449), the SAPHIRE (Hodgkin lymphoma, NCT01037478), and the SHORE (colorectal cancer, NCT01277406) study. Blood-based biomarker assays were performed in all resminostat trials to monitor the pharmacodynamic (PD) on-target and target-downstream effects of resminostat in monotherapy as well as in combination therapy. The combination therapy used was sorafenib (400 mg and 800 mg BID) in SHELTER and the standard regimen of FOLFIRI in SHORE.

Material and methods: Enzymatic HDAC activity was measured in blood leucocytes with the fluorogenic HDAC substrate Boc-K(Ac)AMC, gene expression in peripheral blood cells by RT-qPCR, and plasma concentration of resminostat by LC-MS/MS. Biomarker data were correlated with efficacy parameters, e.g., overall survival (OS). Pharmacokinetic (PK) data were analyzed using non-compartmental analysis [3]. Statistical software R [4] was used for all other analyses.

Pharmacokinetic Analysis

The FIM trial had shown that exposure (AUC and Cmax) to resminostat increased dose-proportionally between 100 and 800 mg without drug accumulation observed. Peak plasma concentrations were reached after 2h (median value). Terminal plasma elimination half-life (T1/2) ranged from min. 2.4 to max. 4.4h across dose levels.

<table>
<thead>
<tr>
<th>Resminostat Dose</th>
<th>Concurrent Therapy</th>
<th>Cmax (geometric mean) [ng/mL]</th>
<th>tmax (median) [h]</th>
<th>AUC (geometric mean) [ng*h/mL]</th>
<th>CL/F (geometric mean) [ng*h/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>3</td>
<td>2,710</td>
<td>1</td>
<td>4,050</td>
<td>50,050</td>
</tr>
<tr>
<td>600 mg</td>
<td>Sorafenib 400 mg</td>
<td>3,680</td>
<td>1.5</td>
<td>8,420</td>
<td>58,360</td>
</tr>
<tr>
<td>800 mg</td>
<td>Sorafenib 400 mg</td>
<td>3,410</td>
<td>1.25</td>
<td>8,750</td>
<td>58,620</td>
</tr>
</tbody>
</table>

Pharmacodynamic Analysis

Strongest effects on transcriptional regulation were generally observed 5h post dose, as shown for zinc-finger protein 64 (ZFP64) mRNA in cycle 1 day 1 (C1D1) and cycle 3 day 5 (C3D5).

Changes in gene expression levels of ZFP64 correlated with plasma concentration of resminostat irrespective of combination treatment.

Meta-Analysis

In order to combine the three studies in terms of efficacy, two separate methodologies were applied:
- Standardizing and combining the data per study
- Performing a meta-analysis based on hazard ratios

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Proportion of patients</th>
<th>Follow-up time in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40%</td>
<td>10</td>
</tr>
<tr>
<td>0.5</td>
<td>40%</td>
<td>20</td>
</tr>
<tr>
<td>0.25</td>
<td>40%</td>
<td>30</td>
</tr>
</tbody>
</table>

Overall, patients with a termed “high” baseline ZFP64 gene expression showed a significant longer OS compared to those with termed “low” baseline ZFP64 gene expression.

Conclusions & Outlook

- Resminostat exhibits robust pharmacokinetic and pharmacodynamic behavior in the clinic and can be administered to patients with various oncology indications judged by the consistency of the results presented here.
- The epigenetic mode-of-action exhibited makes Resminostat a well-suited combination drug especially for, but not limited to, advanced cancer indications.
- Biomarker data analyses for the ZFP64 gene in correlation with OS give rise to the potential use in well-defined patient populations in order to enhance the probability for a clinically favorable outcome.
- Further experiments and analyses are currently being performed to investigate the potentially prognostic and/or predictive character of ZFP64.

Literature

3) Phoenix/WiinLinn 6.4, Certara (2016)