Resminostat in Relapsed or Refractory Hodgkin Lymphoma: Initial Results of the SAPHIRE Phase II Trial with a Novel Oral Histone Deacetylase (HDAC) inhibitor

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Background

- Histone deacetylases (HDACs) are Zn2+ containing enzymes that control the deacetylation of nuclear histones and other proteins. They are involved in the remodelling of chromatin and have a key role in the epigenetic regulation of gene expression
- Inhibition of HDACs has emerged as a potential strategy to reverse aberrant epigenetic reprogramming of chromatin and have a key role in the epigenetic regulation of gene expression

The SAPHIRE Study

- Phase I Data
  - First oral administration of resminostat in 18 patients with various progressive solid tumours with daily doses between 100 mg and 800 mg for 5 days in 14 day cycles was well tolerated
  - High plasma levels were obtained after T_max=2 hr, indicating good bioavailability
  - Dose dependent AE profile of nausea, vomiting and fatigue was observed
  - Stabilisation of disease (SD) was achieved in more than 50% of patients
  - The 600 mg dose was recommended for subsequent Phase II studies based on the good tolerability and positive PK/PD profile

- Summary
  - Oral monotherapy with daily 600 mg resminostat is well tolerated with mild to moderate gastrointestinal and hematological side effect
  - PK data indicate good bioavailability of resminostat with peak plasma levels well above average IC50 values
  - Time dependent HDAC enzyme inhibition after dosing confirms pharmacodynamic activity
  - PET/CT assessments of relapsed refractory HL patients indicate significant anti-tumour activity resulting in clinical benefit metabolic response in 10 of 18 patients treated in the 1st Stage of the study
  - Due to the observed good tolerance a dose increase to a daily dose of 800 mg will be allowed in the 2nd Stage of the study

Study Layout

- Main Inclusion & Exclusion Criteria
  - Patients must have histological or cytological evidence of Hodgkin Lymphoma (HL, all subtypes) and must suffer from relapsed or refractory HL after second or higher line therapy with an ECOG status of 2 or less
  - High-dose chemotherapy with autologous stem cell transplantation (ASCT) is permitted if at least 12 weeks prior to study entry
  - Patients must not have had previous treatment with another HDAC inhibitor
  - Patients must not take QT prolonging agents or have confirmed QTcF > 450 ms

- Simon Two-Stage Design
  - At the end of the first Simon stage 18 patients are evaluated for efficacy. If at least 5 responders are identified, enrolment of additional 15 patients into the second Simon stage can commence
  - Response is defined as complete response (CR), partial response (PR) or stable disease (SD) acc. to Cheson criteria
  - Complete resolution of FDG uptake within tumor volume
  - Reduction of minimum of 15% increase in tumour FDG SUV greater than 1 cycle
  - Appearance of new lesions

- Study Overview
  - 600 mg dose was recommended for subsequent Phase II studies based on
  - Resminostat demonstrated pronounced dose-dependent activity of resminostat
  - Stabilization of disease (SD) was achieved in more than 50% of patients
  - Time of maximum plasma concentration was T_max = 2 hr and thus consistent with previous Phase I observations
  - Xenograft animal studies with resminostat were performed for various cancer indications with cellular IC50 values in the low to submicromolar range

- Results from 1st Simon Stage
  - 11 male and 7 female caucasian patients with a median age of 34.5 years (range=19 – 64 years) were available for efficacy analysis
  - Mean number of previous HL treatments including radiotherapy and ASCT was 8 (range = 3 – 12) and average treatment duration with resminostat was app. 9 weeks

- Characteristic
  - Majority of events were of mild to moderate grade and mainly related to gastrointestinal toxicities such as nausea, vomiting and upper abdominal pain
  - Haematological toxicities such as anaemia and thrombocytopenia were seen in some patients, with the anaemia cases being judged as primarily related to the underlying HL disease

Case Study

- 47 year old male patient diagnosed with classical HL in 2000
- Previous treatments with CHOP-IR (2002), progrem and treatment with ABVD and ASCT (2003/2004), ICE, splenectomy due to hazardous side effects incl. septic shock
- Recurrence in 2009, 6xESHAP resulted in SD based on CT scan; recurrence in 2010 and subsequent enrolment in SAPHIRE Study in March 2012

Pharmacokinetics

- A substantial inter-individual variability of resminostat plasma levels was observed in the first 18 patients of the study
- Oral dosing of 600 mg resminostat resulted in plasma concentrations of ~10μM, equivalent to about 10-fold IC50 levels
- Similar IC50 values were observed after repeated dosing of resminostat, indicating no accumulation of resminostat in the blood

- HDAC Enzyme Inhibition
  - HDAC enzyme inhibition by resminostat was determined in peripheral blood mononuclear cells (PBMC) from 9 patients or vivo by a cellular fluorescence-based enzyme activity assay
  - Enzyme activity was assessed pre-dose as well as 2 hr and 5 hr post-dose on C1/D1, C1/D5 and C3/D5
  - Inhibition of enzymatic activity was time-dependent and reversible within the observation period and ranged from 50% to 100%