Initial Results from the SAPHIRE Study:

A Phase II Trial with the Novel Oral Histone Deacetylase (HDAC) Inhibitor Resminostat in Relapsed or Refractory Hodgkin Lymphoma Patients

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8th International Symposium on Hodgkin Lymphoma
Cologne, Germany
October 23 – 26, 2010
Histone deacetylases (HDACs) are involved in the remodeling of chromatin and have a key role in the epigenetic regulation of gene expression (i.e. tumor suppressor genes).

Resminostat is a hydroxamate-type orally available small molecule inhibitor of class I and class II HDAC isoenzymes.

Resminostat has in-vitro activity against a range of cell lines including HL with low cellular IC$_{50}$ values.

Animal xenograft studies showed a good tolerability and dose-dependent activity of resminostat.
Phase I Study (first-in-human)

- Oral monotherapy with resminostat in 18 patients with progressive solid tumors
- Daily dose between 100 mg and 800 mg x 5 days x 4 cycles q. 14 d. - well tolerated
- Peak plasma levels after 2 hrs (T_{max}) indicate good bioavailability
- Dose dependent AE profile of nausea, vomiting and fatigue
- Dose dependent target modulation (HDAC activity, H4 histone hyperacetylation)
- Stable disease (SD) in more than 50% of patients achieved in this trial
- No MTD/DLT identified up to 800 mg dose
- The 600 mg dose was recommended for subsequent Phase II studies based on good tolerability and positive PK/PD profile

AT Brunetto et al. ASCO 2009; J Clin Oncol 27 (S15) Abstract No. 3530
SAPHIRE Study

Study outline
- Single-arm, open-label, Simon-two-stage design
- Phase II, multi-centre, international trial, target accrual: 33 patients
- Once-daily oral dosing of 600 mg resminostat
- 5+9 treatment schedule in 14 day cycles
- 6 cycles (12 weeks) treatment period in main study phase
- Optional extension of treatment upon clinical benefit at the end of main phase
- Study started in Jan 2010
- Enrolment of 18 Patients (1st Simon stage) completed

INCLUSION CRITERIA
- HL patients
- Refractory or relapsed

MAIN TREATMENT
- Monotherapy
- 600 mg resminostat
- 12 weeks
- 33 patients

FOLLOW-UP PHASE
- For patients with clinical benefit
- Up to 12 months

END POINTS
- ORR
- OS, PFS, TTP, DOR
- Safety, PK
- HDAC, RNA profiling, TARC
SAPHIRE Study

- **Inclusion Criteria**
  - Histological or cytological evidence of Hodgkin lymphoma (all subtypes)
  - Relapsed or refractory HL after second or higher line therapy
  - High-dose chemotherapy with autologous stem cell transplantation (ASCT) is permitted if at least 12 weeks prior to study entry
  - ECOG status of 2 or less

- **Exclusion Criteria**
  - Previous treatment with other HDAC inhibitor
  - Allogeneic stem cell transplantation
  - Treatment with QT prolonging agents or confirmed QTcF > 450 ms
SAPHIRE Study

Study Design

- **Screening**
  - PET/CT Baseline
  - PK Biomarker

- **Main phase**
  - Cycle 1: 14 days
  - Cycle 2: 14 days
  - Cycle 3: 14 days
  - Cycle 4: 14 days
  - Cycle 5: 14 days
  - Cycle 6: 14 days
  - 5 days dosing | 9 days rest (no dosing)
  - Dose reduction/delay allowed for toxicity

- **Follow-up**
  - PET/CT 6 weeks
  - PET/CT 12 weeks
**SAPHIRE Study**

**Simon Design**

![Diagram of Simon Design]

*18 patients being evaluable for efficacy  
**33 (18+15) patients being evaluable for efficacy  
*** Response = CR, PR or SD with PMR (Partial Metabolic Response - metabolic improvement, i.e. > 25% decrease of sum SUVmax as per EORTC PET SG
Patient characteristics

- 11 male and 7 female caucasian patients with a median age of 34.5 years (range 19 – 64 years) were available for efficacy analysis.

- ECOG status at screening:
  - 9 patients had a status of 0
  - 6 patients had a status of 1
  - 3 patients had a status of 2

- Mean number of previous HL treatments including radiotherapy and ASCT was 8 (range 3 -12)

- Average treatment duration with resminostat was approx. 9 weeks
Safety & Tolerability

- **Adverse Events (AEs)**
  - Majority of events were related to gastrointestinal toxicities: nausea, vomiting, and upper abdominal pain of mild to moderate grade
  - Hematological toxicity seen in some patients: anemia and thrombocytopenia

- **Serious Adverse Events (SAEs)**
  - 10 SAEs were reported in 6 patients of the 1st Simon Stage
  - 4 SAEs: non-hematological (respiratory symptoms and fever)
  - 6 SAEs: hematological (thrombocytopenia, anemia)
  - Anemia was judged as primarily related to the underlying disease
Pharmacokinetics

- Substantial inter-individual variability of plasma resminostat levels was observed.

- Oral dosing of 600 mg resminostat yielded plasma concentrations equivalent to appr. 10 fold IC_{50} levels.

- Similar C_{max} values observed after repeat dosing, indicate no accumulation of resminostat.

- Time of maximum plasma (t_{max}) concentration was appr. 2 hrs and thus consistent with observation in Phase I study.

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Biomarker HDAC Activity

- HDAC enzyme inhibition by resminostat was determined in peripheral blood mononuclear cells (PBMC) from 9 patients ex-vivo by a cell permeable HDAC substrate.
- Enzyme activity was assessed pre-dose as well as 2 hrs and 5 hrs post-dose on Day 1 and Day 5 of Cycle 1 and on Day 5 of Cycle 3.
- Inhibition of enzymatic activity was time-dependent and reversible within the observation period and ranged from 50% to 100%.
### PET/CT Response Criteria

<table>
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<tr>
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<th><strong>CHESON (CT+PET)</strong></th>
<th><strong>EORTC (PET)</strong></th>
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<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>PET negative</td>
<td>Complete Metabolic Response (CMR)</td>
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<td>Mass of any size permitted if PET negative</td>
<td>Complete resolution of FDG uptake within tumor volume</td>
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<td><strong>Partial Response (PR)</strong></td>
<td>≥50% decrease in SPD of up to 6 largest dominant masses One or more PET positive lesion</td>
<td>Partial Metabolic Response (PMR) Reduction of minimum of 15% of tumor SUV after 1 cycle and minimum 25% after more than 1 cycle</td>
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<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>PET positive at prior sites of disease No new sites on CT or PET</td>
<td>Stable Metabolic Disease (SMD) Increase in tumor FDG SUV &lt;25% or decrease &lt;15%</td>
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<tr>
<td><strong>Relapsed or Progression Disease (PD)</strong></td>
<td>Appearance of new lesions ≥50% increase in SPD PET positive</td>
<td>Progression Metabolic Disease (PMD) Increase in tumor FDG SUV &gt;25% or appearance of new FDG uptake</td>
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SPD: Sum of Product of Diameters


Response Assessment*

- 18 patients were assessed on the basis of combined Cheson and EORTC Response Criteria

- 10 of 18 patients showed reduced metabolic activity of target lesions
  - 5 patients showed partial metabolic response (>25% reduction) (PMR)
  - further 5 patients showed minor metabolic response (<25% reduction) and were classified with stable metabolic disease (SMD)
  - 2 of 5 PMR patients qualified as partial responders (PR) with target lesion size reduction of >50%

* Best response over treatment time
Case Study [pt # 11-10]

- Male, 47 year old
- Dx : cHL
- Previous treatments
  - 2000: CHOP: CR [initially misdiagnosed as TCRBCL]
  - Subsequent years: ICE, splenectomy, CNOP–dc’ed due to toxicity (septic shock)
  - 2009: PD – ESHAP x 6: SD (CT scan)
  - 2010: PD
- SAPHIRE study scans
  - Screening PET/CT scan: March 2010
  - 1st PET/CT scan after Cycle 3: May 2010
  - 2nd PET/CT scan after Cycle 6: June 2010
  - 3rd PET/CT scan after Cycle 10: September 2010
SAPHIRE Study – 1st Simon Stage

Case Study – PET Overview

Baseline  Cycle 3  Cycle 6  Cycle 10
SAPHIRE Study – 1\textsuperscript{st} Simon Stage

Case Study – PET/CT Images

Baseline

Min: 0.4 SUV
Max: 14.9 SUV
Mean: 3.6 SUV
StdDev: 3.4 SUV

Cycle 3

Min: 0.2 SUV
Max: 11.6 SUV
Mean: 4.5 SUV
StdDev: 2.7 SUV

Cycle 6

Min: 0.4 SUV
Max: 7.6 SUV
Mean: 2.9 SUV
StdDev: 1.9 SUV

Cycle 10

Min: 0.2 SUV
Max: 7.7 SUV
Mean: 1.8 SUV
StdDev: 1.4 SUV

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### Case Study – Response Assessment

<table>
<thead>
<tr>
<th>Measure \ % Change</th>
<th>Cycle 3</th>
<th>Cycle 6</th>
<th>Cycle 10</th>
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<tr>
<td>SUM PD (CT)</td>
<td>-31%</td>
<td>-54%</td>
<td>-65%</td>
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<tr>
<td>Response according to CHESON</td>
<td>SD</td>
<td>PR</td>
<td>PR</td>
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<tr>
<td>SUM SUV (PET)</td>
<td>-27%</td>
<td>-47%</td>
<td>-44%</td>
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<tr>
<td>Response according to EORTC</td>
<td>PMR</td>
<td>PMR</td>
<td>PMR</td>
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SAPHIRE Study – 1st Simon Stage

Conclusions

- Oral monotherapy with daily 600 mg resminostat is well tolerated with mild to moderate gastrointestinal and hematological side effects
- PK data indicate good bioavailability of resminostat with peak plasma levels well above average $IC_{50}$ values
- Time dependent HDAC enzyme inhibition after dosing confirms pharmacodynamic activity
- PET/CT assessment of relapsed /refractory HL patients indicate significant anti-tumor activity resulting in clinical benefit /metabolic response in 10 of 18 patients treated in the 1st Simon 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 Simon stage of the study
# SAPHIRE Study

## Acknowledgements

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<th>Study Sponsor</th>
<th>Investigators</th>
<th>Central Response Assessment Board</th>
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Maria Skłodowska-Curie Memorial Institute, Warsaw, Poland  
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Gabriela Borsaru  
Coltea Clinical Hospital, Bucharest, Romania | Agnieszka Warszewska  
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