



# Initial Results from the SAPHIRE Study:

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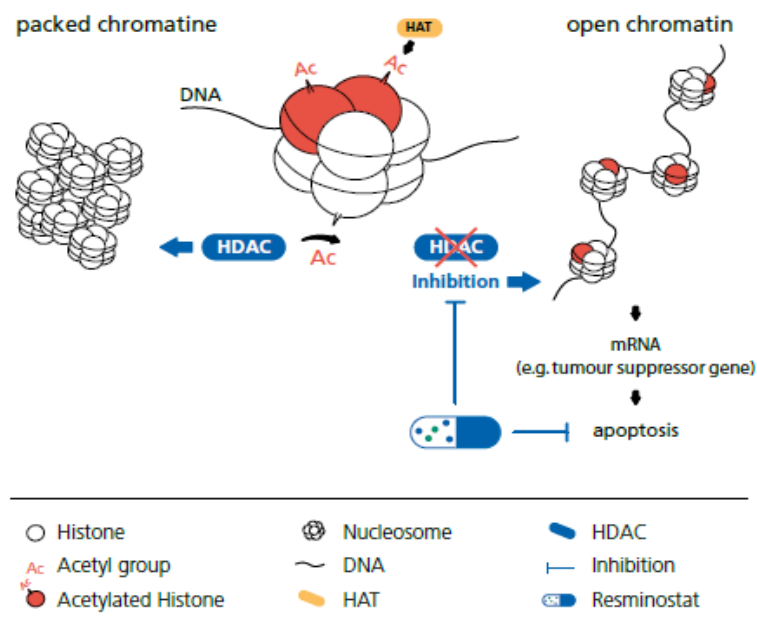
A Phase II Trial with the Novel Oral Histone  
Deacetylase (HDAC) Inhibitor Resminostat in Relapsed  
or Refractory Hodgkin Lymphoma Patients

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8th International Symposium on  
Hodgkin Lymphoma  
Cologne, Germany  
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# Background



- 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<sub>50</sub> values
- Animal xenograft studies showed a good tolerability and dose-dependent activity of **resminostat**

Cell Line	Tumor type	<b>Resminostat</b> IC <sub>50</sub> (μM)
L-540	Hodgkin Lymphoma	1.50
L-1236	Hodgkin Lymphoma	0.20



# Phase I Study (first-in-human)

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- 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 its good tolerability and positive PK/PD profile

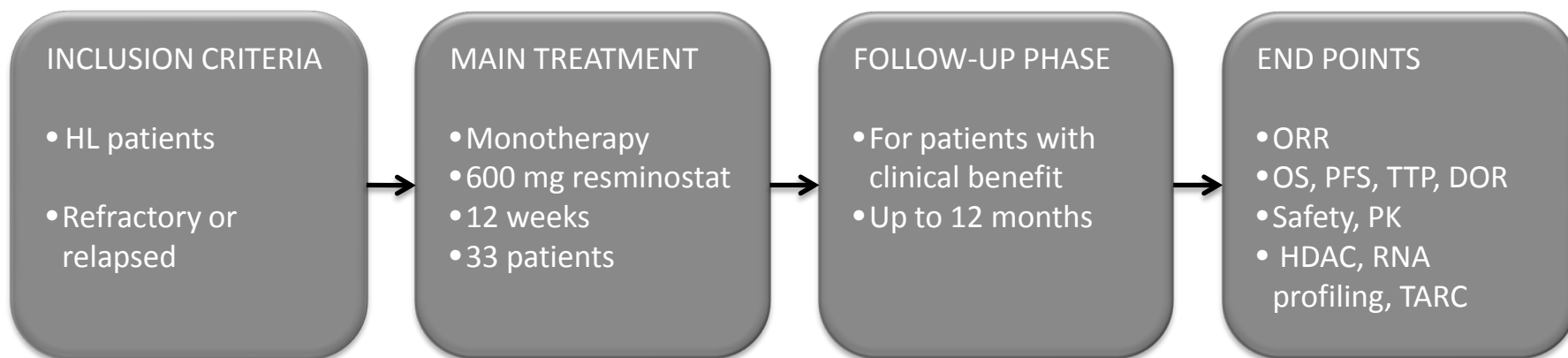
AT Brunetto et al. ASCO 2009; *J Clin Oncol* 27 (S15) Abstract No. 3530

# 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

- 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

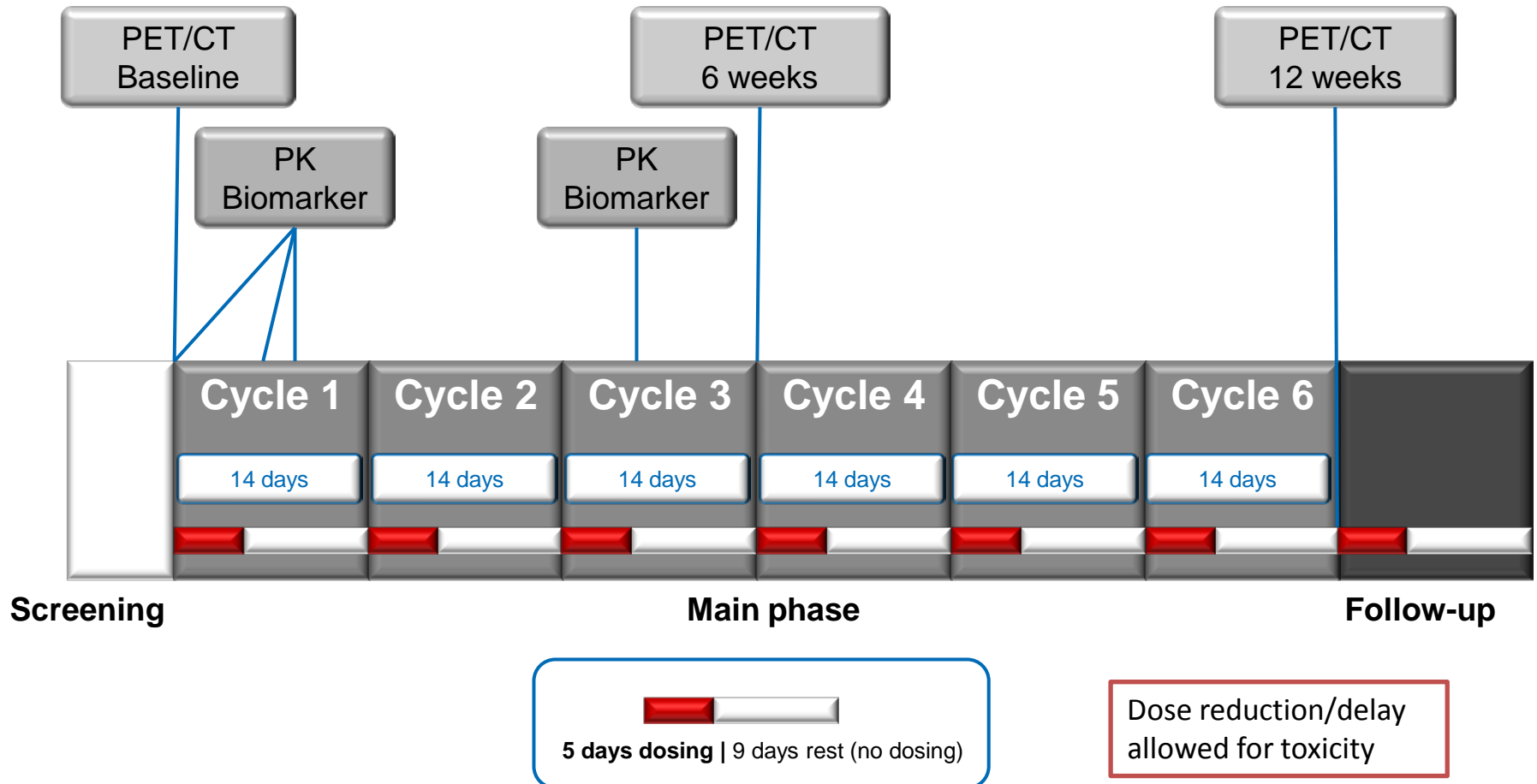
## ■ Exclusion Criteria

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

# SAPHIRE Study



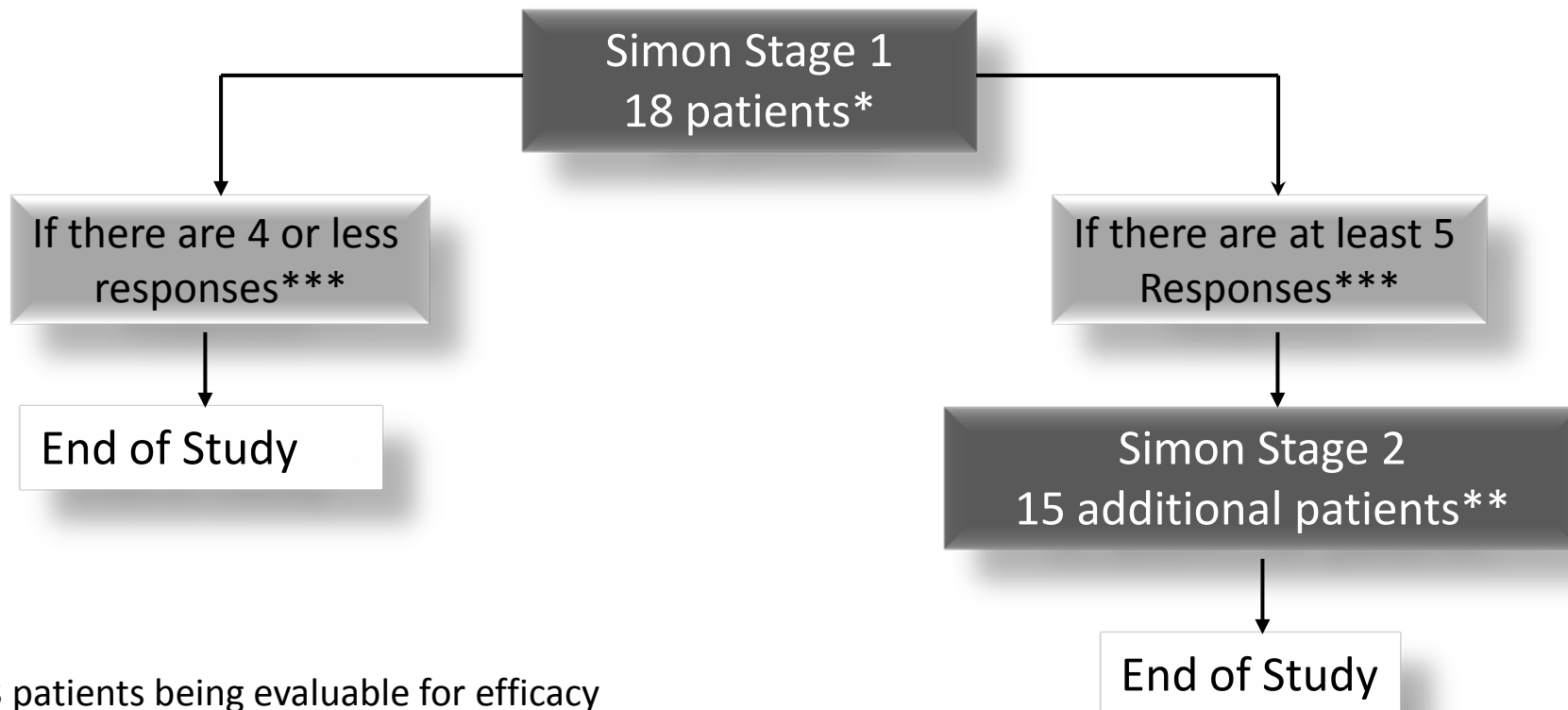
## Study Design



# SAPHIRE Study



## 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 -

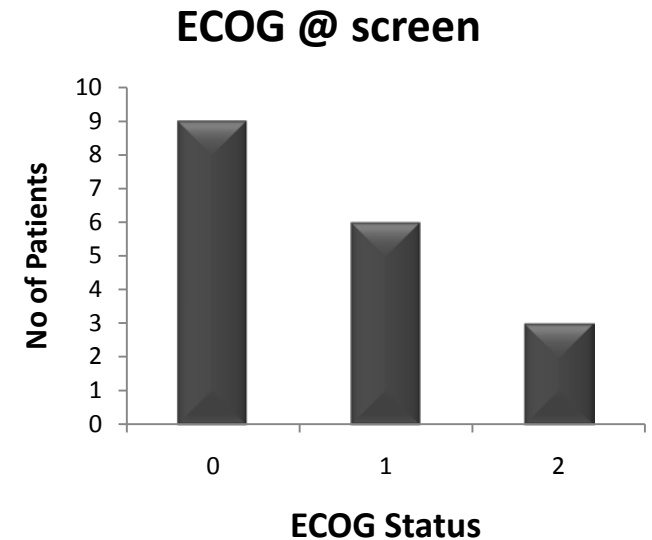
metabolic improvement , i.e. > 25% decrease of sum SUVmax as per EORTC PET SG

# SAPHIRE Study – 1<sup>st</sup> Simon Stage



## 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

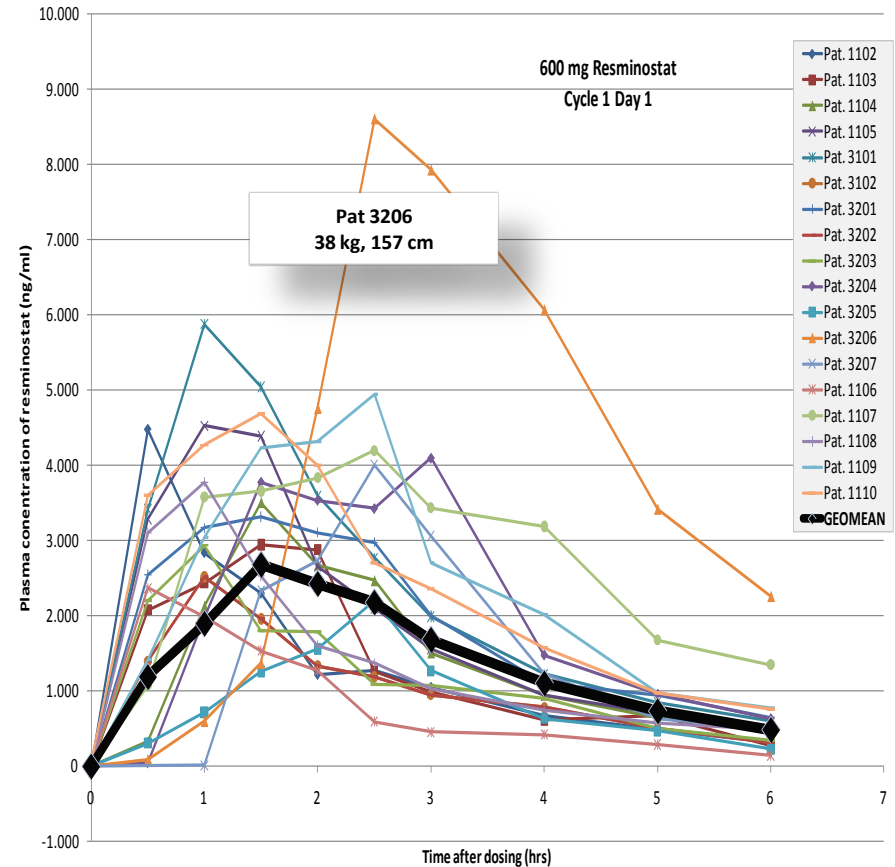
- Adverse Events (AEs)
  - Majority of events were related to gastrointestinal toxicities: nausea, vomiting, and upper abdominal pain of mild to moderate grade
  - Hematological toxicity seen in some patients: anemia and thrombocytopenia
  
- Serious Adverse Events (SAEs)
  - 10 SAEs were reported in 6 patients of the 1<sup>st</sup> 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

# SAPHIRE Study – 1<sup>st</sup> Simon Stage



## 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<sub>50</sub> levels
- Similar C<sub>max</sub> values observed after repeat dosing, indicate no accumulation of resminostat
- Time of maximum plasma (t<sub>max</sub>) concentration was app. 2 hrs and thus consistent with observation in Phase I study

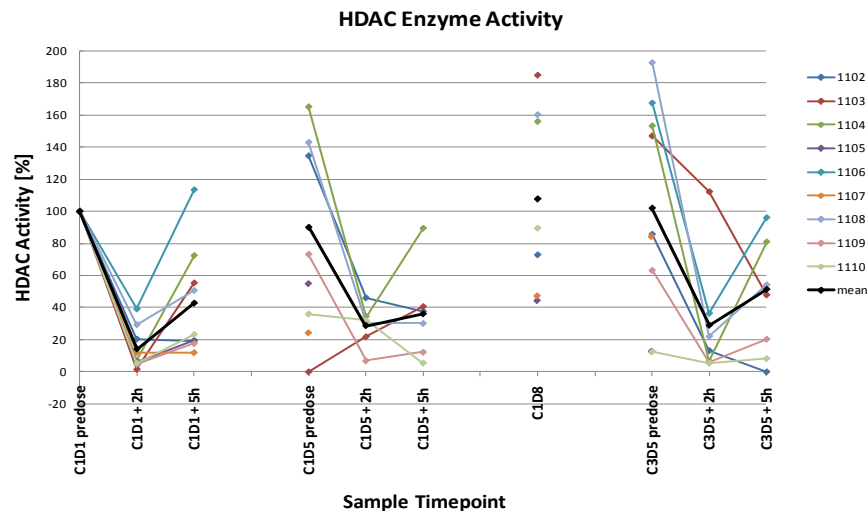


# SAPHIRE Study – 1<sup>st</sup> Simon Stage



## 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%



# SAPHIRE Study – 1<sup>st</sup> Simon Stage



## PET/CT Response Criteria

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

SPD: Sum of Product of Diameters

BD Cheson et al. *J Clin Oncol* 2007; 25: 579

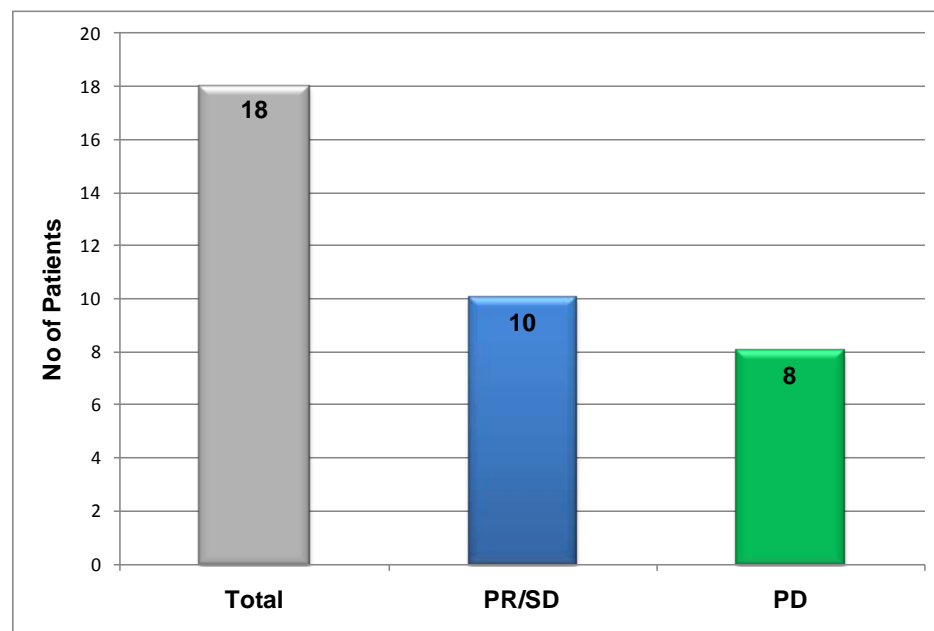
H Young et al. *Eur J Cancer* 1999; 35: 1773

# SAPHIRE Study – 1<sup>st</sup> Simon Stage



## 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

# SAPHIRE Study – 1<sup>st</sup> Simon Stage

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## Case Study [pt # 11-10]

- Male, 47 year old
- Dx : cHL
- Previous treatments
  - 2000: CHOP: CR [initially misdiagnosed as TCRBCL]
  - 2003/2004: PD - ABVD, auto-HCT
  - 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 – 1<sup>st</sup> Simon Stage



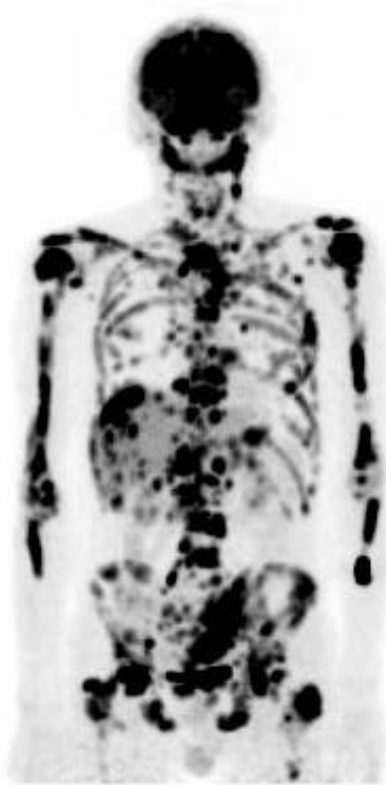
## Case Study – PET Overview

**Baseline**

**Cycle 3**

**Cycle 6**

**Cycle 10**



# SAPHIRE Study – 1<sup>st</sup> Simon Stage



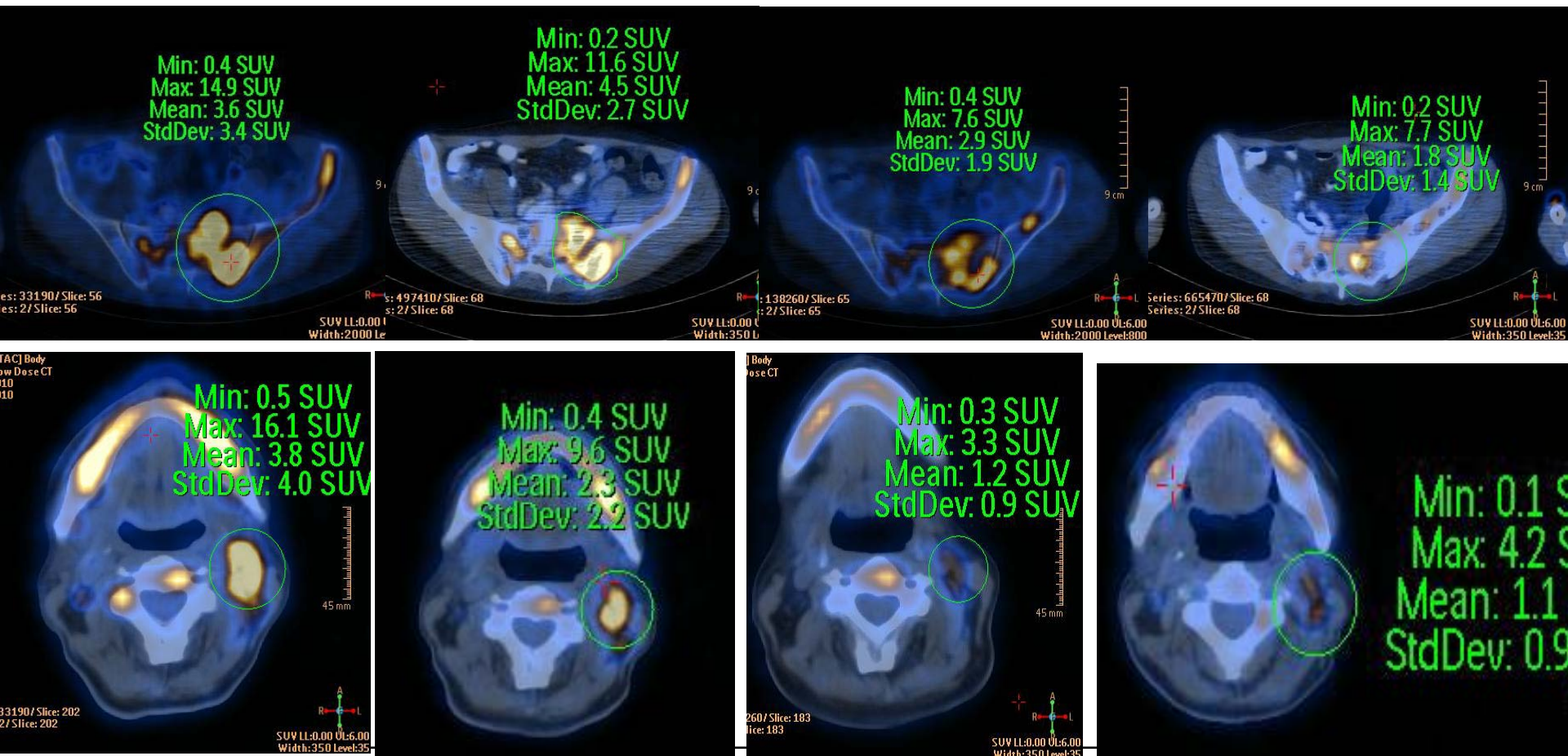
## Case Study – PET/CT Images

Baseline

Cycle 3

Cycle 6

Cycle 10



# SAPHIRE Study – 1<sup>st</sup> Simon Stage



## Case Study – Response Assessment

Measure \ % Change	Cycle 3	Cycle 6	Cycle 10
SUM PD (CT)	-31%	-54%	-65%
Response according to CHESON	SD	PR	PR
SUM SUV (PET)	-27%	-47%	-44%
Response according to EORTC	PMR	PMR	PMR

# SAPHIRE Study – 1st Simon Stage

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## 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 1<sup>st</sup> 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 2<sup>nd</sup> Simon stage of the study

## Acknowledgements

Study Sponsor	Investigators	Central Response Assessment Board
Anna Mais, Bernhard Hauns, Stefan Henning, Bernd Hentsch 4SC AG, Martinsried, Germany	Ewa Paszkiewicz-Kozik Maria Skłodowska-Curie Memorial Institute, Warsaw, Poland  Andreea Delia Moicean Fundeni Clinical Institute, Bucharest, Romania	Agnieszka Warszewska Maria Skłodowska-Curie Memorial Institute, Warsaw, Poland  Klaus Strobel Luzerner Kantonspital, Luzern, Switzerland
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