



# Results of the Phase II SAPHIRE Trial of Resminostat (4SC-201) in Patients with Relapsed/Refractory Hodgkin Lymphoma

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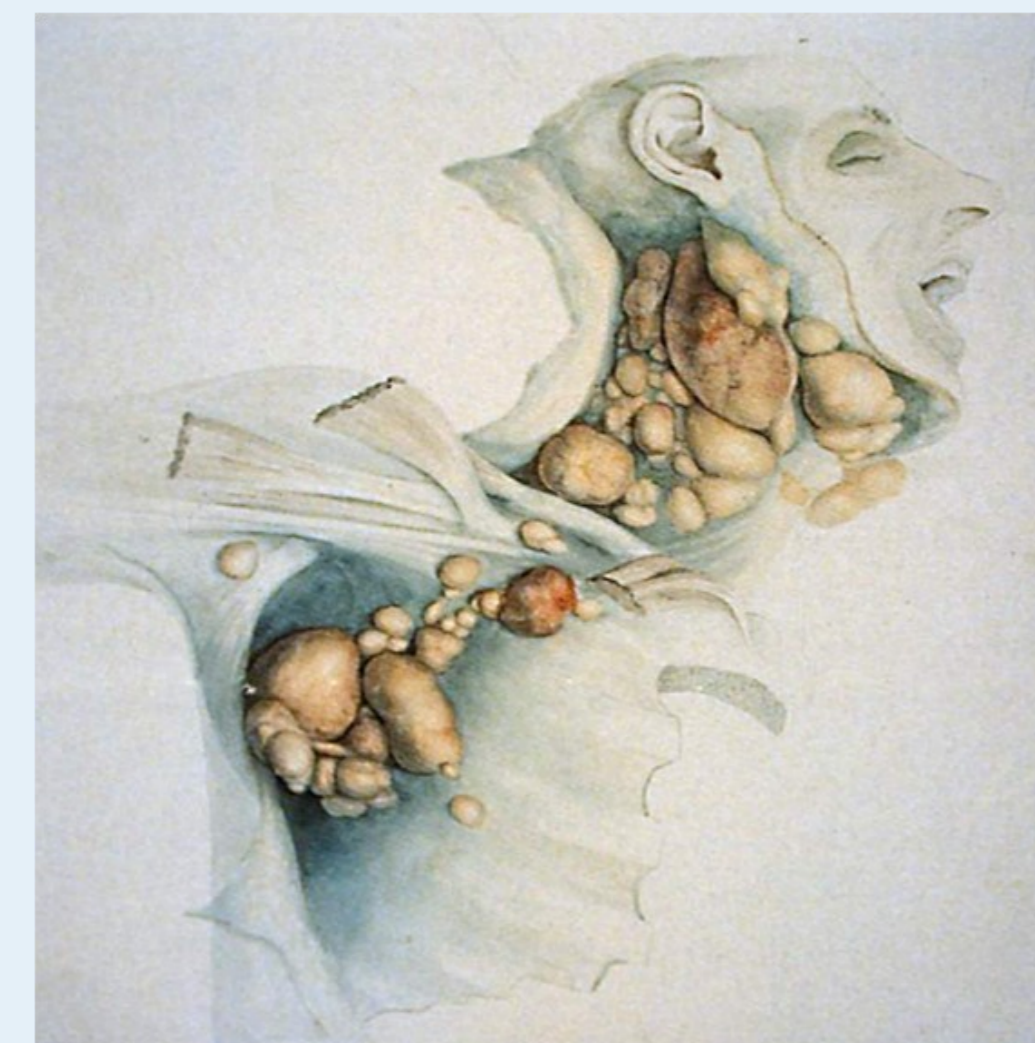
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## Background

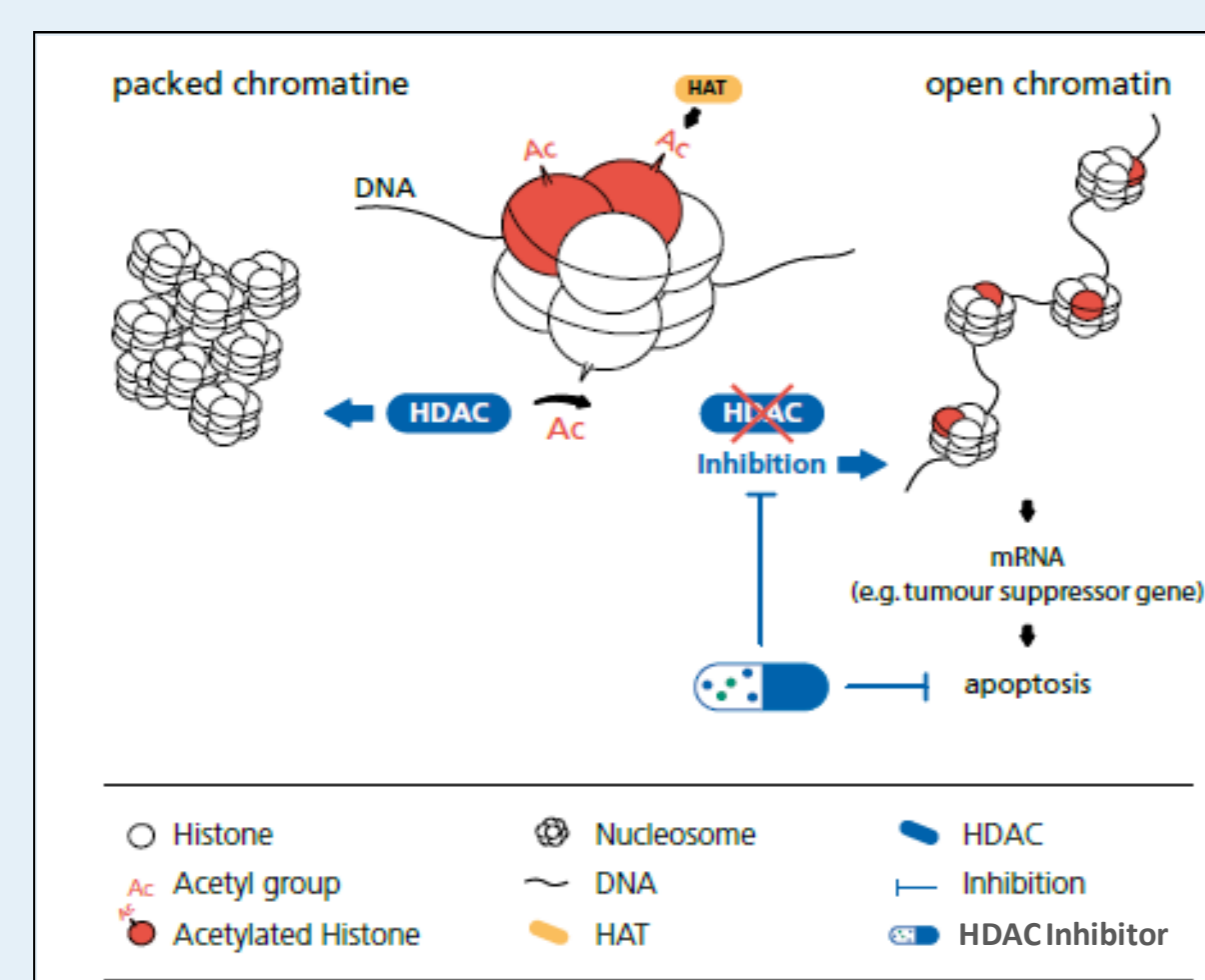
### Hodgkin Lymphoma

- 1<sup>st</sup> and 2<sup>nd</sup> line treatments in HL are efficacious (> 80% cure rate), but current therapies are associated with significant toxicities and the development of secondary malignancies
- Moreover, HL patients who are resistant to 2<sup>nd</sup> line treatments have a 5-year survival rate of only 17% (Sirohi et al., Ann Oncol 2008, 19: 1312-1319)
- There is thus a high medical need for new 3<sup>rd</sup> line options with less long-term toxicity and a potential for reduced chemotherapy use at earlier lines of treatment



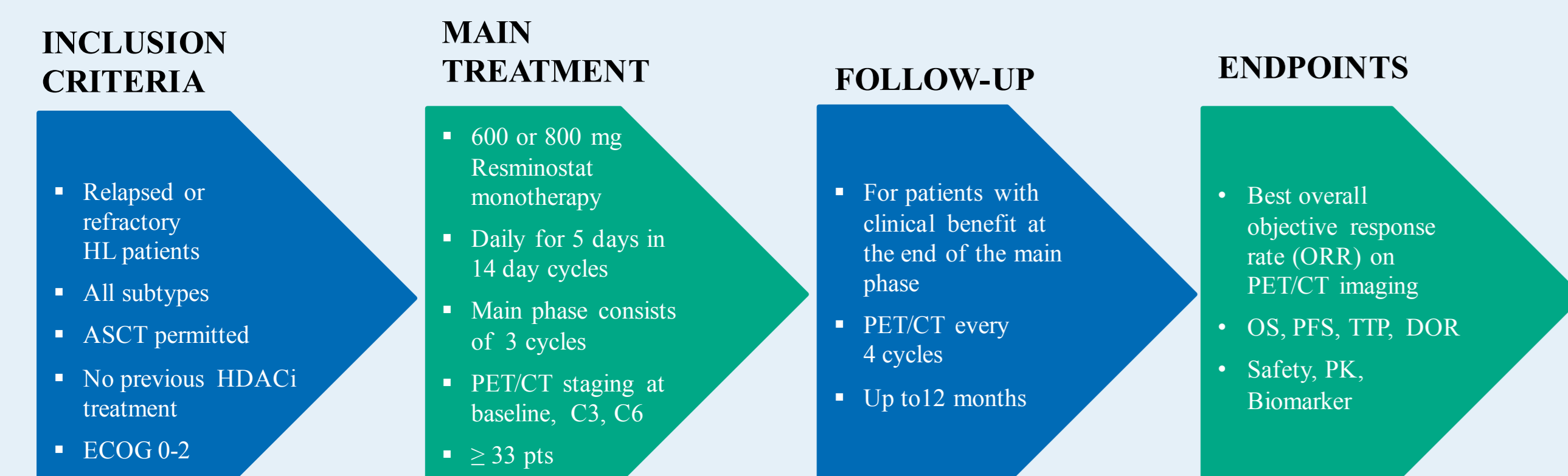
### Resminostat Mode-of action

- Histone deacetylases (HDAC) are 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 promising strategy to reverse aberrant epigenetic changes associated with cancer
- The novel orally available pan-HDAC inhibitor resminostat (4SC-201) is currently evaluated in monotherapy or as a re-sensitizing agent in combination with established treatment regimens in a number of tumor entities



## Study Design

### Overview



### Study Objectives and Endpoints

- Study Objective**
  - Determine the antitumor activity of resminostat monotherapy in relapsed/refractory HL
- Primary Endpoint**
  - Best overall objective response rate (ORR) based on PET/CT imaging assessed by an independent central review board according to Cheson/EORTC criteria
- Secondary Endpoints**
  - Progression free survival (PFS), Time to progression (TTP), Duration of response (DOR), Overall survival (OS)
  - Pharmacokinetics
  - Safety and Tolerability
  - Biomarker

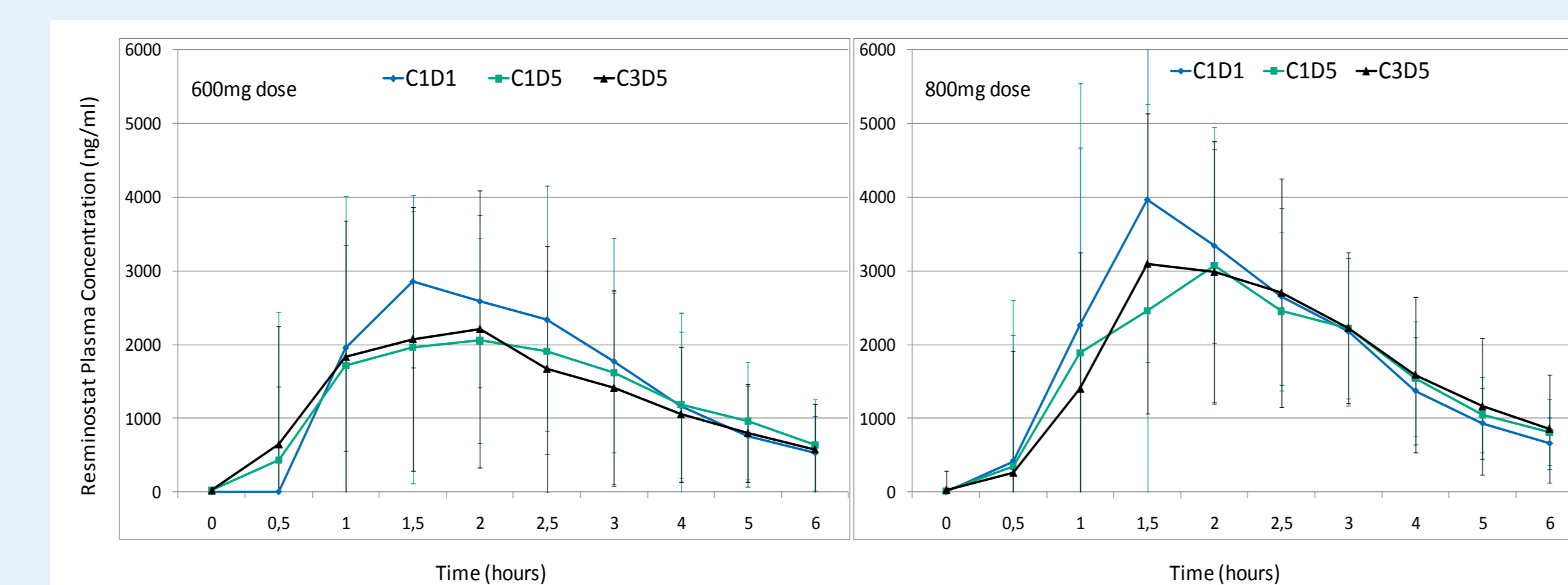
## Patients

### Demographics and Baseline Characteristics

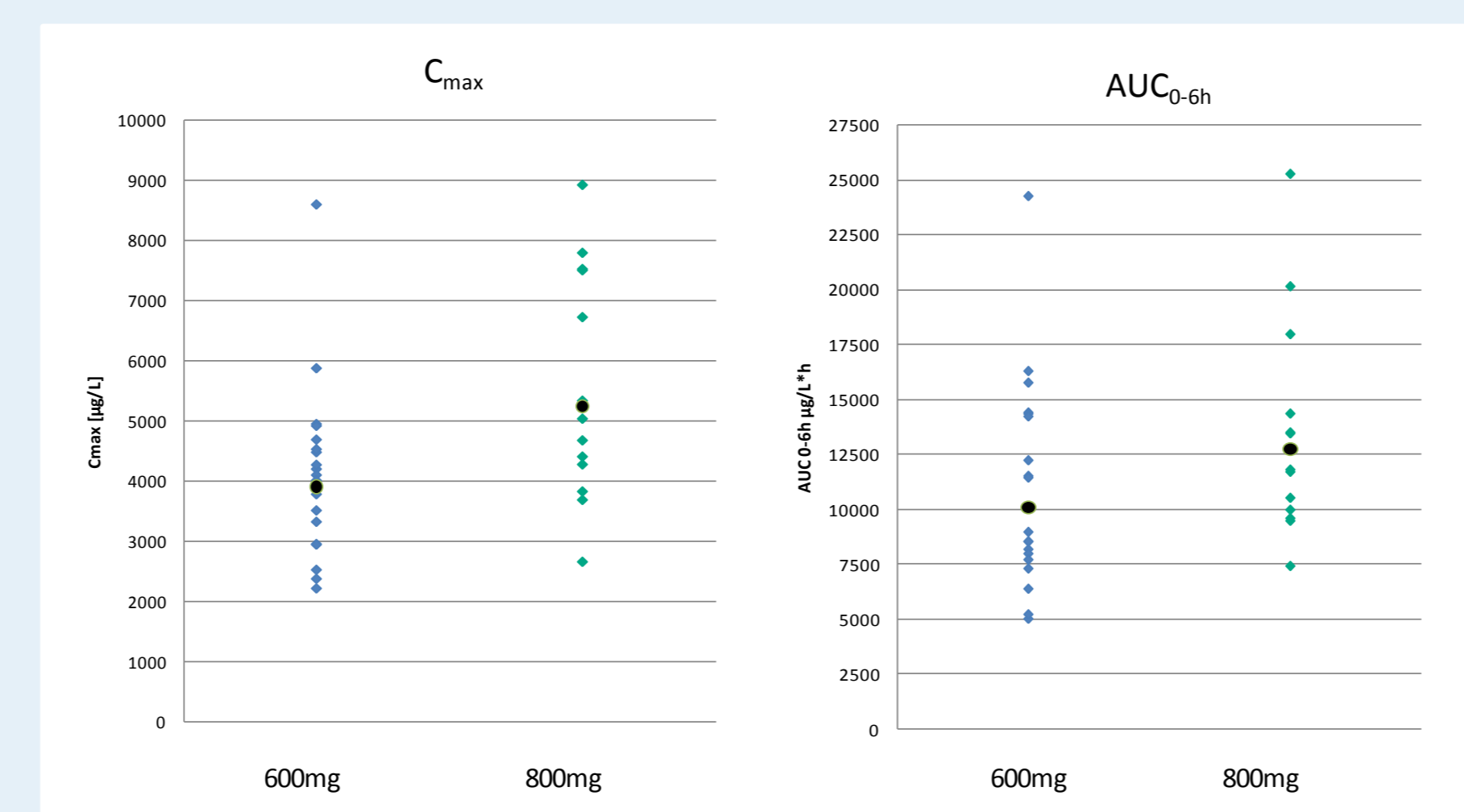
	N=37
Age (years) [median (range)]	34 (19-71)
Gender (M/F)	19/18
BMI [median (range)]	23.4 (15.1 – 31.3)
ECOG status at baseline (0/1/2)	19/15/3
Ann Arbor stage at baseline (2/3/4)	6/4/27
ASCT	21 (57%)
Relapse < 1 year post ASCT	14 out of 21 (67%)
Prior therapies* [median (range)]	6 (1-12)
Patients with > 5 prior therapies*	26 (70%)
B-symptoms at baseline	17 (46%)

\* including radiotherapy

## Pharmacokinetics



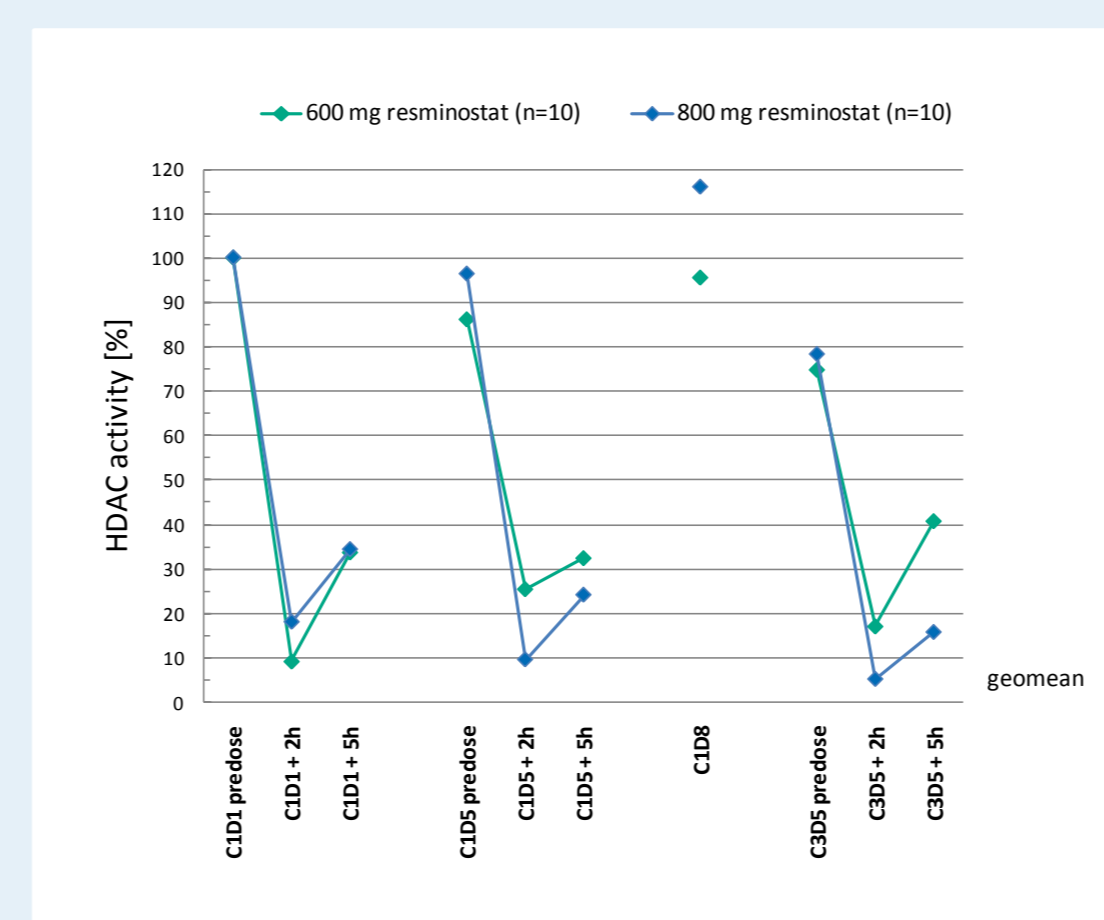
- Peak plasma levels of resminostat were achieved at T<sub>max</sub> = 2 h post application in both 600 mg (n=19) and 800 mg (n=18) dose cohorts
- PK profiles after first and consecutive administrations of resminostat were similar in both dose cohorts
- C<sub>max</sub> and AUC increased proportionally from 600 mg to 800 mg dose (shown are C1D1 data)



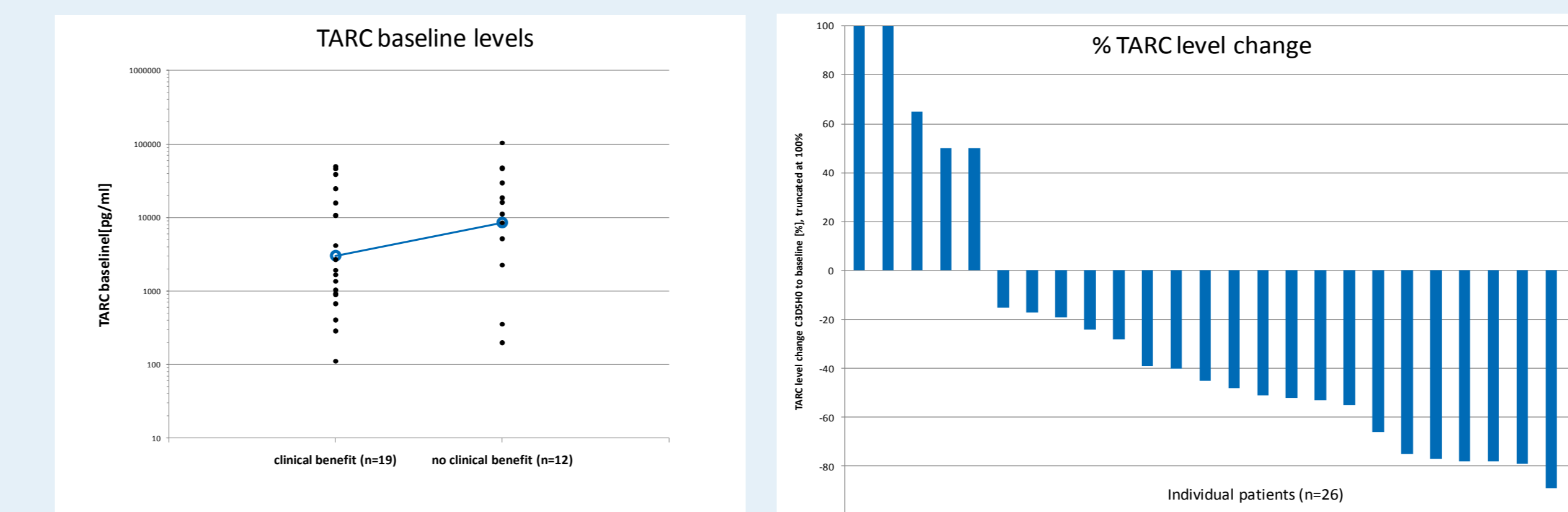
## Pharmacodynamics

### HDAC inhibition

- HDAC enzyme activity was assessed in leukocytes from 10 pts per dose group pre-dose as well as 2 h and 5 h post-dose on C1D1, C1D5, C1D8 and C3D5
- Inhibition of enzymatic activity was time-dependent and reversible and reached its maximum at 2 h, corresponding to peak plasma levels of resminostat

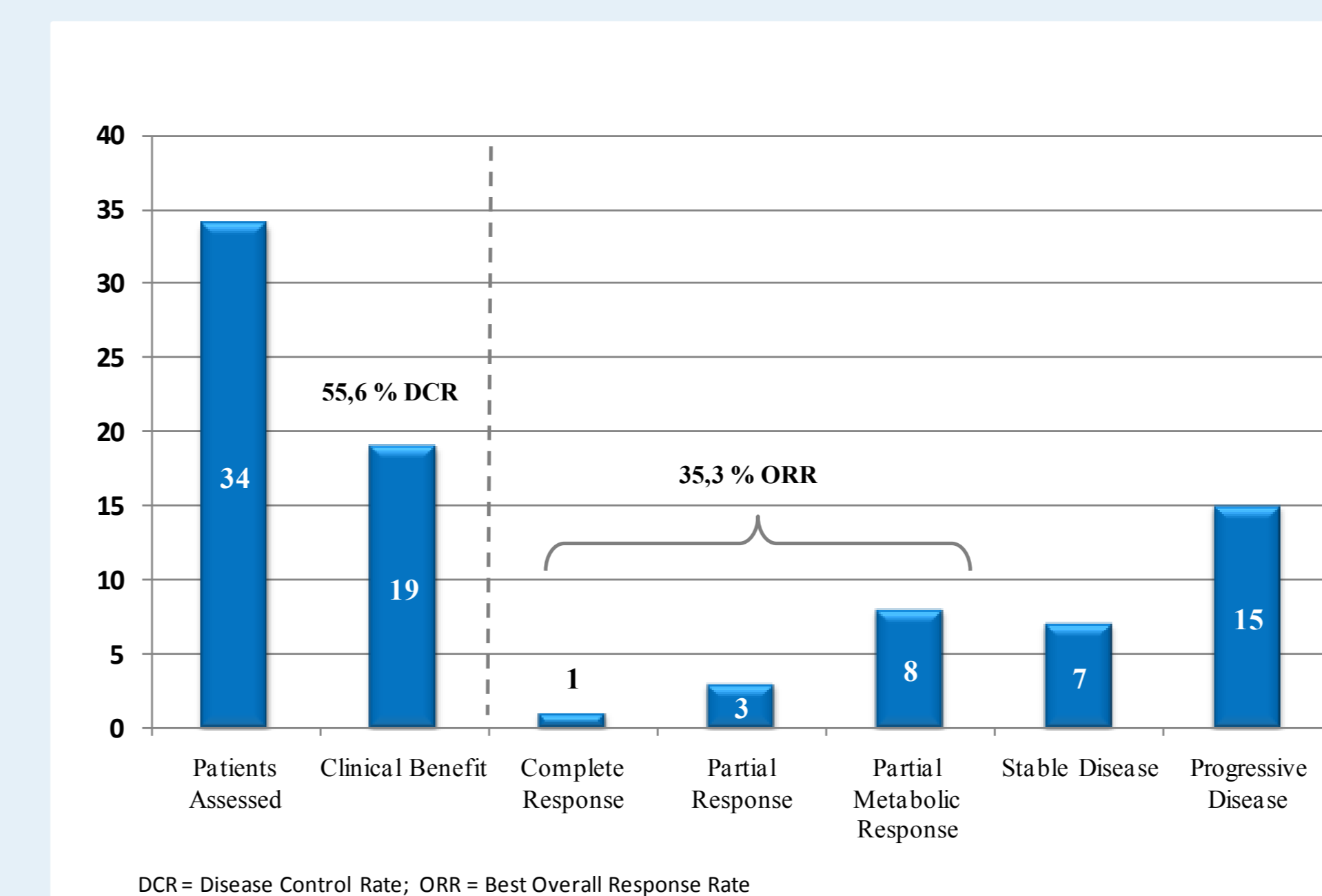


## TARC



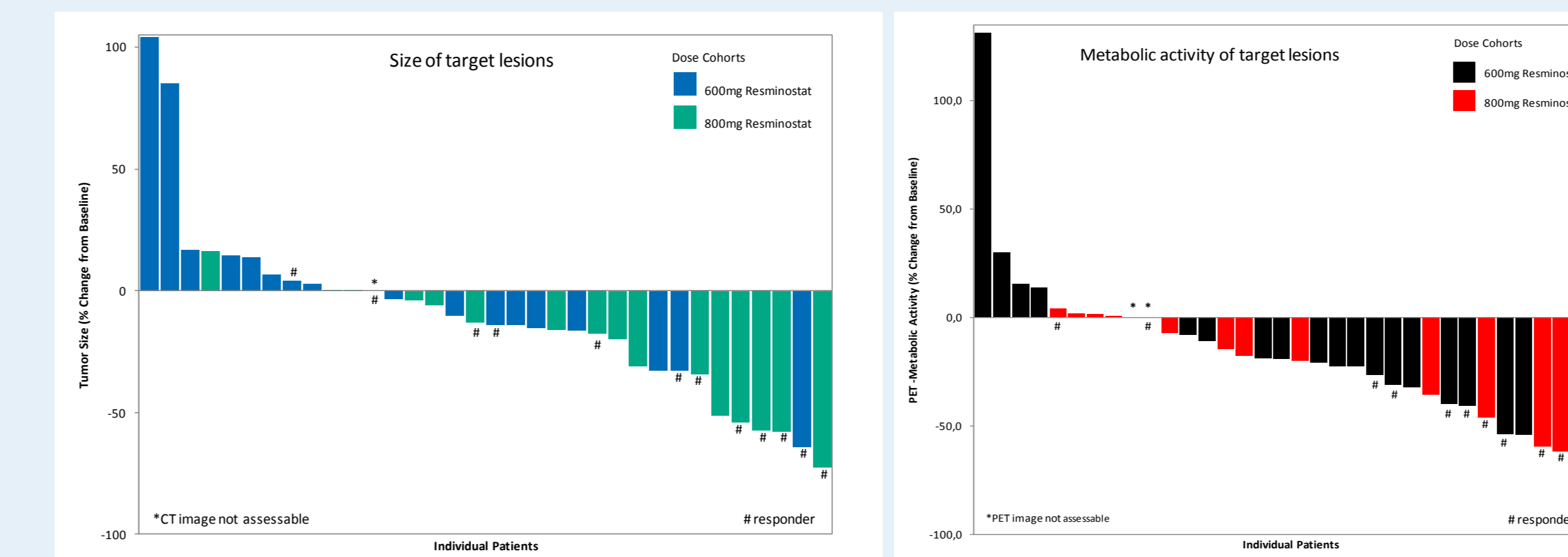
- Lower baseline plasma levels of TARC (CCL-17) were associated with clinical benefit
- TARC levels at the end of the main treatment phase were reduced compared to baseline levels

## Efficacy



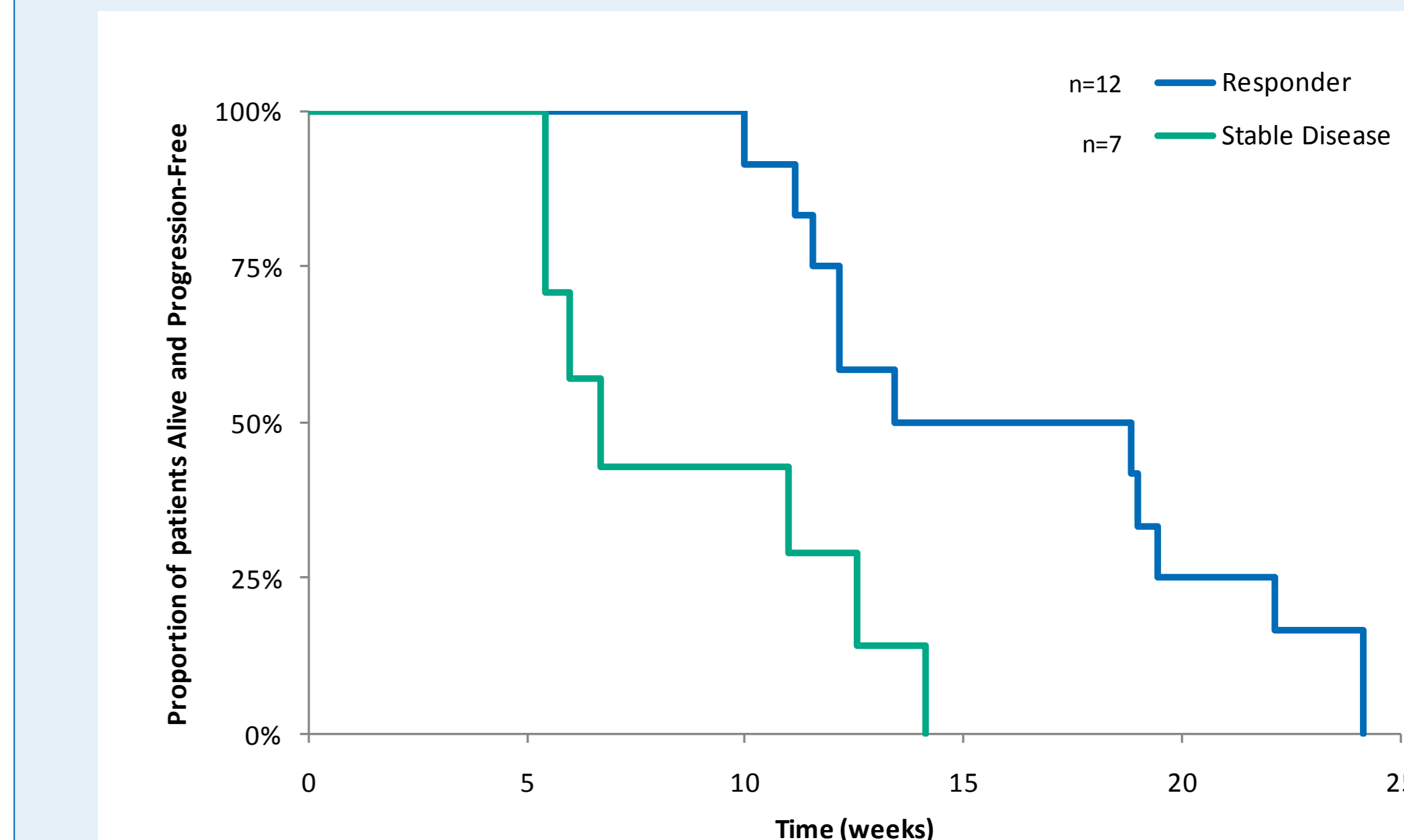
- Out of 34 patients assessed centrally by PET/CT for ORR as of Dec 2011, 19 patients (55,6 %) obtained a clinical benefit from resminostat treatment
- 12 out of 34 patients (35,3 %) qualified as responders (Cheson/EORTC criteria) and additional 7 patients achieved stabilization of disease
- 1 further patient is still under treatment, with stable disease for 30 weeks

## Size and metabolic activity of target tumor lesions



- In 22 out of 34 patients (65%) a reduction of target tumor lesion size was achieved
- In 24 out of 34 patients (71%) a reduction of metabolic activity of target tumor lesions was observed
- Almost all responders achieved a reduction in target tumor lesion size and metabolic activity
- Higher changes in size and metabolic activity of target tumor lesions were achieved by treatment with 800 mg resminostat

## Progression-free survival (PFS)



- Median progression-free survival (PFS) was 13.4 weeks for responder (n=12) and 6.7 weeks for patients with stable disease (n=7)
- In the responder group time to response (TTR) was 6 weeks (3 cycles) for 8 patients (67%) and 12 weeks (6 cycles) for the remaining 4 patients (33%)

## Safety

Term*	Grade	600 mg (N=19)	800 mg (N=18)	Overall (N=37)	No. of related Events
Thrombocytopenia / Platelet count decreased	2-4	8 (4)	13 (7)	21 (11)	20
Anemia	2-3	14 (7)	15 (6)	29 (13)	23
Diarrhea	2-3	0	4 (3)	4 (3)	4
Nausea	2-3	4 (2)	7 (5)	11 (7)	9
Vomiting	2-3	3 (2)	6 (4)	9 (6)	7
Fatigue	2-3	0	9 (4)	9 (4)	9
Fever	2	4 (3)	5 (4)	9 (7)	1
Respiratory Tract Infection	2-3	0	5 (5)	5 (5)	2
Pneumonia	2-3	3 (2)	0	3 (2)	0
Increased liver enzymes (ALT, AST)	2-3	4 (2)	1 (1)	5 (3)	5
Decrease of Appetite	2	0	4 (3)	4 (3)	4
Dysgeusia	2	0	3 (2)	3 (2)	3
Tachycardia	2	2 (2)	0	2 (2)	1

\*includes only AEs which occurred in more than one patient and with CTCAE grade >1; preliminary data (based on CRF pages)

## Conclusions

- Resminostat monotherapy achieved clear objective responses in relapsed or refractory HL patients
- Resminostat treatment led to target lesion size reductions of > 50% and frequent decreases in metabolic tumor activity
- Resminostat showed an excellent safety profile in this heavily pre-treated patient population
- Further development of resminostat in Hodgkin Lymphoma is warranted