Background

Hodgkin Lymphoma

- 1st and 2nd 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 2nd line treatments have a 5-year survival rate of only 17% (Gallamini et al., Ann Oncol 2008; 19: 1321-26).
- There is thus a high medical need for new 3rd line options with less long-term toxicity and a potential for reduced chemoresistance seen 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

- MAIN TREATMENT
- FOLLOW UP
- ENDPOINTS

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 Chicago/EORTC criteria.
- Secondary Endpoints
  - Progression-free survival (PFS); Time to progression (TTP).
  - Duration of response (DOR); Overall survival (OS).
  - Pharmacokinetics
  - Safety and tolerability.

Patients

Demographics and Baseline Characteristics

- Age (median [range]) 34 (19-71)
- Gender (M/F) 19/18
- BMI (median [range]) 23.4 (15.1 – 31.3)
- ECOG status 6 (1-12)
- B-symptoms at baseline 17 (46%)
- * Including radiotherapy

Dose Cohorts

- 600 mg resminostat (n=19)
- 800 mg resminostat (n=18)

Pharmacokinetics

- Peak plasma levels of resminostat were achieved at T_max = 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_max and AUC increased proportionally from 600 mg to 800 mg dose (shown are CI95 data).

Pharmacodynamics

- HDAC Inhibition
  - HDAC enzyme activity was assessed in leukocytes from 10 per dose group pre-dose as well as 2 h and 5 h post-dose on CD1, CD5, CD10 and CD20.
  - Inhibition of enzymatic activity was time-dependent and reversible and reached its maximum at 2 h, corresponding to peak plasma levels of resminostat.

Efficacy

- 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.

- Out of 34 patients assessed centrally by PET/CT for ORR as of Dec 2011, 19 patients (55.9 %) obtained a clinical benefit from resminostat treatment.
- 12 out of 34 patients (35.3 %) qualified as responders (Cheim/ EORTC criteria).
- 1 additional 17 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.

Safety

- 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%).

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 pretreated patient population.
- Further development of resminostat in Hodgkin Lymphoma is warranted.