Background

Histone deacetylases (HDACs) are considered to be among the most promising targets in drug development for cancer therapy. Various HDAC inhibitors are currently under clinical investigation in a broad range of tumor entities including both histological subtypes and stages of disease.

In 2007, 4SC-201 (former code BYK408740) was developed, a specific, potent, orally administered HDAC inhibitor, which was developed by a collaboration between the pharmaceutical company Eisai and a German biotech startup.

Objectives

Study Design and Methods

Study design:

- Open label, inter-patient dose escalation, single-centre study
- Four treatment cycles each consisting of repeated oral doses for 5 consecutive days following a 8-9 day rest period
- Four sequential dose cohorts were planned, starting with doses of 50 mg orally administrated (QD) 50 or 100 mg, base line dose for the highest dose level of 400 mg.
- Tumor tissue samples were collected at each dose level depending on the evaluation of safety and tolerability.

Main eligibility criteria:

- Inclusion:
  - Male and/or female patients, age ≥ 18 years
  - Histological or cytological diagnosis of primary or metastatic solid tumors (except for melanoma or neuroendocrine disease)
  - ECOG Performance Status 0-1
- Exclusion:
  - Prior treatment with other HDAC inhibitors
  - Hematologic, hepatic or renal dysfunction
  - Active infection
  - History of severe drug allergies

Safety & Tolerability

- Grade 2-4 nonhematologic abnormalities were generally self-limiting.
- All grade 2 AD/4 abnormalities were generally self-limiting.
- No adverse events were severe enough to be life-threatening.
- All patients completed at least 3 cycle 4 treatment.
- Major surgery was performed within the last 6 weeks.
- DLT:
  - Grade 3-4 toxicity during cycle 4 dose escalation CTCE version 3.0.
  - Grade 3-4 hematologic toxicity except for neutropenia, thrombocytopenia, and bleeding (grade 4 maximum tolerated).

Study Results

First-in-human Phase I study of 4SC-201, an oral histone deacetylase (HDAC) inhibitor, in patients with solid tumors

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Pharmacodynamics

Determination of HDAC Enzyme Inhibition

- **Objective:** To determine the HDAC enzyme inhibition following administration of 4SC-201

Pharmacokinetics

- **Method and Analytic Principle:**
  - The HDAC inhibitors added to human whole blood and remove the cells. Deacetylation by HDAC inhibitors yields the deacetylated form of histone, which is then analyzed using a chromate quantification method.
- **Results:**
  - The percentage of deacetylated histones was measured in PBMCs to assess HDAC enzyme inhibition in vitro. The inhibitor showed a dose-dependent decrease in deacetylation, with higher inhibition observed at higher concentrations.

To assess pharmacokinetics of 4SC-201

- **Secondary objectives:**
  - To assess the pharmacokinetics of 4SC-201 in human whole blood.
- **Method and Analytic Principle:**
  - Plasma samples from study participants were analyzed using standard non-compartmental pharmacokinetic methods.
- **Results:**
  - The pharmacokinetic parameters were calculated using traditional non-compartmental methods. The inhibitor was found to be well-absorbed and rapidly distributed, with high inter-individual variability.

CT Scans of Patient 013 at Baseline (A) and after Cycle 24 (B)

Conclusions

- 4SC-201 was generally well tolerated.
- Major treatment-emergent adverse events were self-limiting.
- The maximum tolerated dose was determined to be 400 mg.
- The results of this study support further clinical evaluation of 4SC-201 as a potential novel anti-cancer agent.

References

2. J. Clin Oncol 2014, 32:2270-2277

**Insert Figure 1: Patients with Stable Disease per dose cohort**

**Insert Figure 2: HDAC Enzyme Inhibition in PBMC vs. dose groups (max. multiple of baseline value)**

**Insert Figure 3: Histone H4 Acetylation Status in PBMC vs. dose groups (max. multiples of baseline value)**

**Insert Table 1: Baseline patient and disease characteristics**

**Insert Table 2: 4SC-201 mean pharmacokinetic parameters, at dose levels, multiple, day 5**