A Phase I/II Study of Resminostat, an Oral Histone Deacetylase Inhibitor (HDACi), in Combination with FOLFIRI as Second-Line Treatment in KRAS Mutated Colorectal Cancer (CRC) patients - the SHORE Study

S. Bauer1, H. Schulte-Bergkamen1, D. Jäger1, F. Mayer2, B. Bitzer2, B. Hauns3, K. Resemann3, R. Jankowsky4, A. Mais5, H. Kohlhub3, B. Hentsch2

1National Centre for Tumor Diseases (NCT), Heidelberg, Germany, 2University of Tübingen Medical Center, Tübingen, Germany, 3ISC AG, Flensberg-Martinsried, Germany

Background

Resminostat

- Novel oral pan-HDAC inhibitor.
- In clinical development for several cancer indications: hepatocellular carcinoma, Hodgkin’s lymphoma and colorectal carcinoma.
- Inhibition of HDAC enzymes at sub-micromolar concentrations.
- IC50 values in cellular cancer models in the low micro-molar range.
- Anti-tumour activity in various in vivo cancer models, covering a broad range of oncological indications.
- Considerable additive or synergistic effects in combination with other chemotherapeutics in vitro and in vivo.

Resminostat in CRC

- Overexpression of class I HDAC enzymes is common in patients with colorectal cancer (CRC), this overexpression is linked to poor prognosis of such patients.
- Resminostat effectively inhibits class 1 HDACs, among them the cancer cell survival factor HDAC-2.
- About 40% of all CRC patients bear KRAS-mutated tumours, these patients are excluded from EGFR inhibitor therapy. Thus, the need for new treatment has arisen for CRC patients carrying mutated KRAS genes.
- The SHORE study addresses this medical need for patients with KRAS mutated CRC.

Study Design

The SHORE study evaluates resminostat in combination with FOLFIRI in patients with KRAS mutated CRC in the second therapy line with regard to safety, tolerability and efficacy.

- Eligible patients: KRAS mutated CRC having failed a prior first-line therapy with 5-FU alone or in combination, no previous irinotecan therapy.
- Resminostat is given once daily for 5 consecutive days, followed by 9 days rest ("5+9" scheme), resulting in treatment cycles of 14 days. On days 3 and 4 of each cycle, standard FOLFIRI regimen is administered:

  - Staging according to RECIST criteria is performed every eight weeks. Patients who benefit from the treatment can stay on treatment for an unlimited period.
  - The SHORE study comprises two parts:
    1. Phase I part for the determination of the maximum tolerated dose (MTD) of the resminostat/FOLFIRI combination
    2. Phase II part (subsequent to phase I part)

Phase I part

- 3+3 dose escalation
- 200 - 800 mg resminostat (O.D. administration) + FOLFIRI
- Option: B.I.D. administration for resminostat

Phase II part

- 2-arm, randomised
- Arm A: MTD Resminostat + FOLFIRI, 25 patients
- Arm B: FOLFIRI alone (control arm), 25 patients

Study Status

- The phase I part (dose escalation) is currently in progress:
  - 200 mg Resminostat (O.D.) + FOLFIRI Finalised (3 patients enrolled)
  - 400 mg Resminostat (O.D.) + FOLFIRI In progress
  - 600 mg Resminostat (O.D.) + FOLFIRI Pending
  - 800 mg Resminostat (O.D.) + FOLFIRI Pending
- The combination of 200 mg Resminostat and FOLFIRI was well tolerated. No dose-limiting toxicity (DLT) was observed.
- Side effects on the first dose level were in line with expectations, including mainly gastrointestinal events. According to preliminary analysis, these effects can be attributed to the FOLFIRI regimen. A detailed analysis of the side effects is in progress.

Summary and Outlook

- Resminostat has the potential to considerably improve the treatment options for CRC patients, due to the novel and innovative epigenetic mode of action (HDAC inhibition).
- Due to its HDAC-inhibitory properties, resminostat is in particular promising as a combination partner for other chemotherapeutics. This combination approach is pursued in the SHORE study, using the combination with the established FOLFIRI regimen.
- The SHORE study addresses a high medical need in CRC, namely for patients with KRAS mutated tumours.
- The SHORE study is currently in the phase I part, the dose escalation is ongoing. The phase II part is in preparation, study sites are currently under evaluation.