Resminostat

- Resminostat is a novel oral HDAC inhibitor with broad anti-tumor activity in various cancer models.
- Resminostat as single agent showed promising anti-tumor efficacy and a favorable safety profile in a completed phase II Hodgkin's lymphoma (HL) trial.
- Results from a phase II trial in hepatocellular carcinoma (HCC) patients warrant further development of the combination of resminostat and the kinase inhibitor sorafenib as a new therapy option in advanced HCC.

Resminostat in preclinical CRC models

- Resminostat revealed synergistic effects with 5-FU and irinotecan/SN38, indicating its sensitization potential when applied in combination therapy.
- Resminostat down-regulates thymidylate synthase involved in drug resistance to 5-FU.
- Resminostat effectively inhibits HDAC2, one of the target enzymes described to be involved in CRC cell signalling.

Study Design

- Open-label, intra-patient, “3+3” dose escalation design with increasing doses of resminostat combined with standard FOLFIRI therapy.
- Inclusion of patients with advanced CRC having previously received 5-FU alone or in combination with other agents who were assigned for FOLFIRI in second or later treatment lines.
- Patients received resminostat on 5 consecutive days, followed by a 9-day drug free period (5/6 scheme, i.e. 14-day cycles). FOLFIRI was administered on Day 3 and Day 4 of each cycle.
- Study objectives were analysis of safety and tolerability, determination of the maximum tolerated dose (MTD) of resminostat when combined with FOLFIRI and pharmacokinetics of resminostat and the FOLFIRI components. Radiological staging according to RECIST criteria was performed at baseline, 8 weeks after study start and every 8 weeks thereafter.
- Resminostat dosing: 200, 400, 600 mg OD (3 patients each) and 400 mg BID (6 evaluable patients) plus FOLFIRI.
- FOLFIRI: irinotecan: 180 mg/m² i.v. over 90 minutes (Day 2)
  - Folinic acid: 400 mg/m² i.v. over 2h parallel to irinotecan (Day 3)
  - Followed by 5-FU 400 mg/m² i.v. bolus (Day 3)

Patient Enrollment

- Patient enrollment
  - Patients: 17
  - Dose escalation
    - 1st dose level: 200 mg OD
    - 2nd dose level: 400 mg OD
    - 3rd dose level: 600 mg OD

Pharmacokinetics

- PK profiles of resminostat upon different dosings in each combination with FOLFIRI:
  - On Cycle 1 Day 1:
    - Cmax values reached 3.51 mg/l for 400 mg and 4.48 mg/l for 600 mg.
    - Mean AUC values reached 6.94 mg*h/l for 400 mg and 13.8 mg*h/l for 600 mg.
    - Mean t1/2 was in the range of 1.6-2.2 hours.
  - Cmax and AUC of resminostat increased in a dose dependent manner.
  - The plasma concentrations of resminostat observed at 600 mg OD were comparable with those observed in previous resminostat studies at the same dose.
  - PK analyses revealed consistency with the described PK profiles of both resminostat and the FOLFIRI agents without indication of interaction of resminostat with any of the FOLFIRI components.

Efficacy / Treatment Duration

- Phase I dose escalation of the oral histone deacetylase inhibitor (HDACi) resminostat in combination with FOLFIRI in colorectal cancer (CRC) patients: the SHORE trial
- 200 mg resminostat OD 0201 mutated second 5 cycles
- 200 mg resminostat OD 0102 mutated second 4 cycles
- 400 mg resminostat OD 0201 mutated second 12 cycles
- 400 mg resminostat OD 0202 mutated second 15 cycles
- 400 mg resminostat OD 0105 mutated second 12 cycles
- 600 mg resminostat OD 0204 wild-type fourth 6 cycles
- 600 mg resminostat OD 0106 mutated third 11 cycles
- 600 mg resminostat OD 0107 wild-type third 3 cycles
- 600 mg resminostat BID 0206 wild-type second 4 cycles
- 600 mg resminostat BID 0105 wild-type second 4 cycles
- 600 mg resminostat BID 0205 wild-type second 4 cycles
- 400 mg resminostat BID 0209 wild-type second 7 cycles
- 400 mg resminostat BID 0210 mutated second 2 cycles
- 400 mg resminostat OD 0112 wild-type fourth 6 cycles

Safety

- CT Scans of Patient 0202 at Baseline (A) and after Cycle 10 (B)

Pharmacodynamics

- HDAC Target Enzyme Inhibition
  - HDAC target enzyme activity in leukocytes was effectively blocked starting already at a dose of 200 mg resminostat OD
  - BID administration showed prolonged inhibition of HDAC activity
  - Concomitant FOLFIRI treatment had no influence on HDAC inhibition by resminostat.

Conclusions

- Resminostat in combination with standard FOLFIRI was safe and well tolerated with resminostat doses up to 800 mg total daily dose. No DLT was observed and no formal MTD has been established.
- The pharmacokinetic profiles of resminostat and FOLFIRI components were within the expected ranges showing no interaction of the drugs.
- The successful combinability of resminostat with the FOLFIRI components 5-FU and irinotecan opens the opportunity for various chemotherapeutic combinations with resminostat in a broad range of cancers.

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