Hepatocellular carcinoma
• The prognosis of patients with advanced HCC is poor; median survival is less than one year, about 700,000 deaths/year.
• Sorafenib (Nexavar®) is the only approved systemic therapy for advanced HCC; no second line therapy for sorafenib-refractory patients.
• There is urgent need for second line treatment.

Study Design
• Multi-center, open-label, randomized, two-arm design
• Eight study sites in Germany and seven study sites in Italy
• Resminostat dosing: 600 mg total daily dose, given once daily, repeated cycles of five consecutive days followed by nine days rest (5 + 9 scheme, 14 days per cycle)
• Sorafenib dosing (combination): 400 mg total daily dose, given twice daily continuously throughout the treatment
• Study objective: to achieve a PFS rate (PFSR) of at least 20% after 6 cycles (12 weeks) of study treatment

Resminostat
• Novel oral pan-HDAC inhibitor, hydroxamate-type
• Clinical development in various cancer indications (HCC, CRC, Hodgkin’s lymphoma)
• Completed phase II trial in Hodgkin’s lymphoma: promising anti-tumor efficacy and favorable safety profile in mono therapy

Tumor re-sensitization
• Growing evidence that resistance to cancer drugs involves a reversible “drug-tolerant” state. HDACs are supposed to be crucial in drug tolerance development (Sharma et al., Cell, 2010).
• HDAC inhibitors can potentially overcome drug tolerance. The SHELTER study in HCC patients investigates the re-sensitization of tumors to sorafenib by resminostat.

Pharmacokinetics

No PK interaction of resminostat with sorafenib was detected.

Safety
• No PK interaction of resminostat with sorafenib was detected.
• Plasma concentrations of sorafenib were in the expected range (data not shown).
• Plasma concentrations of resminostat in the dose escalation correlated with the dose administered (data not shown).

Drug-Related Adverse Events for Combination

Drug-Related Adverse Events for Mono Therapy

Conclusions
• Resminostat might offer a new therapeutic option for advanced HCC patients progressing under first line sorafenib treatment.
• In combination mono therapy and the combination of resminostat and sorafenib to date are safe and well tolerated.
• Resminostat appears to re-sensitize HCC to sorafenib treatment in a considerable number of patients.
• In particular, the final data of the combination therapy are expected to provide the basis for pivotal clinical studies in advanced HCC for both, second and first line therapy.

INCLUSION CRITERIA

CRITERIA

PFS  [d]
Progression Free Survival
Mono Therapy and Combination

Visit 1 Visit 2
Day C6 (Cycle 3)
Day C6 (Cycle 3)
Day C10 (Cycle 6)
Day C10 (Cycle 6)

Day C6 (Cycle 3)
Day C10 (Cycle 6)

Day C6 (Cycle 3)
Day C10 (Cycle 6)
Day C16 (Cycle 10)
Day C16 (Cycle 10)

No. of Patients
Disease Stabilization
Combination
Drop-Out
Progressive Disease
Stable Disease

Probability of PFS
(osm) 140d (4.6m)