Efficacy, safety, tolerability and PK of the HDAC inhibitor resminostat in sorafenib-refractory hepatocellular carcinoma (HCC): Phase II SHELTER study

SHELTER Study Group

Introduction

Resminostat
- Resminostat is a novel oral histone deacetylase-type pan-HDAC inhibitor.
- Resminostat as single agent showed promising anti-tumor efficacy and a favorable safety profile in a completed phase II Hodgkin’s lymphoma trial.
- Current phase II studies in HCC and colorectal carcinoma evaluate resminostat as combination partner for anti-cancer therapies.

Tumor sensitization
- There is growing evidence that resistance to cancer drugs involves a reversible “drug-resistant” state. HDAC enzymes are supposed to be crucial in this 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.

Study Design

- Multi-center, international, open-label, two-arm design.
- Patients with advanced stage HCC exhibiting progressive disease under sorafenib treatment (radiological progression proven by central review) were enrolled. Patients had to be treated with at least 400 mg sorafenib for 8 weeks in first line. Sorafenib intolerant patients were excluded.
- Study objective: to achieve a PFS rate (PFSR) of at least 20% after 6 cycles i.e. 12 weeks (12w) of study treatment.
- Radiological staging according to AASLD criteria was performed at baseline, after cycle 3 (w), after cycle 8 (12w) and every 4 weeks thereafter.
- Resminostat dosing: 600 mg total daily dose, given once daily, repeated cycles each consisting of five consecutive treatment days followed by nine days rest (5 + 9 scheme, 14 days per cycle).
- Sorafenib dosing: 400 mg total daily dose, given as 200 mg twice daily continuously throughout the combination treatment.

Patient Enrollment

Patient Characteristics

- ECOG performance status
- Albumin
- Child-Pugh score
- Race
- Sex

Combination treatment VEGF levels displayed a slight increase.

Pharmacodynamics

HDAC Activity
- HDAC activity in leukocytes was effectively blocked already 2 hours after resminostat dosing.
- Concomitant sorafenib treatment had no influence on HDAC inhibition by resminostat.

Pharmacokinetics

- Cmax and AUC of resminostat increased in a dose dependent manner in the dose escalation phase of the study.
- PK analyses revealed consistency with the described PK profiles of both substances without indication of interaction of resminostat with sorafenib or an influence of pre-existing liver disease such as cirrhosis.

Patient Enrollment

- Enrolled
- Dose escalation
- Dose level 1
- Dose level 2
- Dose level 3
- Dose level 4
- Study arms
- Monotherapy

Patient Characteristics

- Race
- Sex
- ECOG performance status
- Child-Pugh score
- Albumin

Pharmacokinetics

- Cmax
- AUC
- Tmax

PK analyses revealed consistency with the described PK profiles of both substances without indication of interaction of resminostat with sorafenib or an influence of pre-existing liver disease such as cirrhosis.

Study arms
- Combination
- Monotherapy

Enrolled
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Study arms
- Combination
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Efficacy Assessment

- Overall Survival
- For monotherapy (n=18) the median PFS has not yet been reached.
- For combination (n=20) the median PFS is 4.7 months in 2nd line advanced HCC therapy.
- Effective modulation of pharmacodynamic biomarkers was observed in both study arms.
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- Combination of resminostat with sorafenib yielded a median PFS value of 4.7 months in 2nd line advanced HCC therapy.
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- Combination of resminostat with sorafenib yielded a median PFS value of 4.7 months in 2nd line advanced HCC therapy.
- These data provide the basis for pivotal clinical development of the combination of resminostat + sorafenib as a new therapy option in both 2nd as well as 1st line advanced HCC.

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