Dose Escalation of the HDAC Inhibitor Resminostat in Combination Treatment with Sorafenib in Patients with Hepatocellular Carcinoma (HCC) - The Phase I-II SHELTER study

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Introduction

Resminostat
- Resminostat is a novel oral histone-deacetylase (HDAC)-inhibitor.
- Resminostat as single agent showed a convincing anti-tumor efficacy and a favorable safety profile in a completed Phase II study in Hodgkin's lymphoma.
- Resminostat as single agent showed a convincing anti-cancer properties in a completed Phase II study in Hodgkin's lymphoma.

Radiological staging according to AASLD criteria was performed at baseline, under sorafenib.

Patients with advanced stage HCC were enrolled after radiological progression and after sorafenib 1st line therapy.

Study Design

- Multi-center, international, open-label, two-arm design.
- Patients with advanced stage HCC were enrolled after radiological progression under sorafenib 1st line therapy was confirmed by central review.
- Patients had to be treated with at least 400 mg sorafenib for 8 weeks prior to study entry.
- Sorafenib intolerant patients were excluded.
- Study objective: to achieve a PFS rate (PFSR) of at least 20% after 6 cycles i.e. 12 weeks of treatment.
- Radiological staging according to AASLD criteria was performed at baseline, after Cycle 3 (6wk), and after Cycle 6 (12wk).
- In the phase I part of the study, a dose escalation of resminostat and sorafenib was performed to determine dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of the combination.

Pharmacokinetics

- Median plasma VEGF levels decreased under resminostat monotherapy.
- In the combination treatment VEGF levels displayed a slight increase.
- VEGF Plasma Levels

- Median plasma VEGF levels decreased under resminostat monotherapy.

Efficacy Assessment

- Combination treatment with 600 mg resminostat and 400 mg sorafenib (20/2) achieved a median PFS of 4.7 months (140.5 d).

Pharmacodynamics

- HDAC activity in leukocytes was effectively blocked already 3 hours after resminostat treatment with 400 mg or 800 mg of sorafenib had no influence on HDAC inhibition by resminostat.

Overall Survival (OS)
- Assessment of OS is ongoing in both study arms.
- Median OS values have not yet been reached in both study arms.

Conclusions

- Combination of resminostat with sorafenib yielded a median PFS value of 4.7 months in 2nd-line treatment of advanced stage HCC.
- Treatment duration in this 2nd-line setting was longer in a subset of patients in each study arm than their individual treatment duration with sorafenib in 1st-line.
- Combination of resminostat with sorafenib was safe and well tolerated. A formal MTD on the highest tested dose level of 600 mg resminostat in combination with 800 mg sorafenib TDD could not be established.
- Resminostat showed a dose-proportional PK profile when orally applied in combination with sorafenib.
- Effective modulation of pharmacodynamic biomarkers was observed.
- These data provide the basis for pivotal clinical development of the combination of resminostat and sorafenib as a new therapy option in 2nd-line advanced HCC, and also for further development in 1st-line treatment of HCC.

Acknowledgments

We would like to thank all participating patients and their families as well as investigators, site and operational staff of all protocol sites included in the conduct of the SHELTER trial.