Pharmacokinetic characteristics of the new treatment combination of sorafenib and resminostat, a novel histone deacetylase (HDAC) inhibitor, in patients with advanced hepatocellular carcinoma (HCC): the SHELTER study

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Background

- Resminostat (4SC-201) is a novel oral hydroxamate-type pan-HDAC inhibitor.
- Resminostat was investigated in a clinical Phase I/II study (SHELTER) aiming to evaluate safety, efficacy and pharmacokinetics (PK) in HCC patients exhibiting progressive disease under first-line treatment with sorafenib.1,2
- Convincing single agent anti-tumor efficacy and a favorable safety profile of resminostat have been shown in a completed Phase II study in relapsed/refractory Hodgkin’s lymphoma.3
- Current phase II studies in HCC and colorectal carcinoma evaluate resminostat as a combination partner for standard anti-cancer therapies.
- Clinical efficacy of resminostat was demonstrated in combination with sorafenib and in mono-therapy with median PFS of 5.4 and 3.2 months and median OS of 8.1 and 4.2 months, respectively.

Study Design

- Multi-center, international, open-label, two-arm design.
- Patients with advanced stage HCC were enrolled after radiological progression under sorafenib 1st-line treatment 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.
- 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.
- Resminostat was administered at oral doses of 200, 400 or 600 mg in combination with sorafenib or alone (600 mg) during 14-day cycles each consisting of a once-daily, repeated-dose schedule for 5 days followed by a 9-day drug-free period.
- Sorafenib was given twice-daily at total daily doses (TDD) of 400 or 800 mg continuously throughout the combination treatment.

Methods & Data Analyses

Formulations

- 4SC-201: hard gelatin capsule containing 255 mg of 4SC-201 mesylate salt, corresponding to 200 mg active ingredient (free base), along with 0.1% colloidal anhydrous silica.
- Sorafenib: Nexavar® film-coated tablets. Each film-coated tablet contains 200 mg of sorafenib active ingredient, formulated as tosylate salt.

Food status and intake specifications

- All patients were fasted until 1 hour after the administration on the PK-sampling days, i.e. Cycle 1 Day 1 (C1D1), C1D5 and C3D5.

Data Analyses

- Blood samples from 57 patients were analyzed to investigate PK parameters of resminostat and sorafenib on C1D1, C1D5 and C3D5. Evaluable patient numbers are provided in the tables / figures.
- Individual plasma concentration-time data and descriptive statistics of PK characteristics were evaluated by non-compartmental analysis using WinNonlin software.
- PK evaluation and individual graphing were performed using the actual sampling time when the actual sampling time deviated more than 20 minutes from the nominal time. All of the samples were obtained at the planned sampling times within the acceptable time deviation of 20 minutes, except for 4 samples which had a time deviation of approximately 0.5 hour.
- Nominal time was used for plotting multiple concentration-time curves, tabulating the concentrations and calculating the descriptive statistics.

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