Clinical Update of the SHELTER Study: A Phase I/II Trial of HDAC Inhibitor Resminostat in Patients with Sorafenib-Resistant Hepatocellular Carcinoma (HCC)


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Background

- Resminostat (4SC-201) is a novel oral pan-HDAC inhibitor in clinical development for several cancer indications.
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- IC50 values in cellular cancer models are in the low micro-molar range.
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- There is broad anti-tumour activity in preclinical cancer models.
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- Additive or synergistic activity in combination with established chemotherapeutic agents was proven in cancer models.
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- Resminostat has a direct effect on the regulation of genes relevant to cancer therapy, e.g. thymidylate synthase (TYMS).
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- A phase I study in cancer patients revealed a favourable safety profile. A remarkable number of patients could be stabilised under resminostat treatment.
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- The SHELTER study evaluates safety, tolerability and efficacy in HCC patients exhibiting progressive disease under sorafenib first-line therapy.

Methods

- Radiological imaging is performed after 6 and 12 weeks treatment, using dynamic contrast-enhanced magnetic resonance tomography (DCE-MRT). Analysis of the DCE-MRT images is performed according to AASLD/EASL criteria for the differentiation of vital and total lesion size.
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- Primary endpoint: progression-free survival rate at 12 weeks.
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- Secondary endpoints: PFSR at 6 weeks, DFS, safety, tolerability, overall response rate, time to progression, overall survival, assessment of pharmacokinetics and biomarkers.
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- Study sites: 8 sites in Germany and 7 sites in Italy.

Patients Treated

- To date, 25 patients have been treated.
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- On average, the patients were treated for about 12 weeks.
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- Due to medical benefit, several patients have been treated for 20 weeks and more. Two patients were under treatment for at least 36 weeks.
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- Dose levels 1, 2 and 3 of the combination treatment (200-600 mg resminostat plus 400 mg sorafenib) were successfully administered, and these levels were well tolerated. Dose level 4 (600 mg resminostat plus 800 mg sorafenib) is currently in progress.

Initial Pharmacokinetics Data

- The systemic resminostat exposure was in good correlation with the dose administered.
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- The AUC (0-6 h) values increased dose-dependently, with values of 10.5 h*mg/l (for 600 mg resminostat mono) and 9.0 h*mg/l (for 600 mg resminostat plus 400 mg sorafenib combo).
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- No PK interference of resminostat with sorafenib was detected.
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- Resminostat plasma exposure (preliminary data):

- Initial Safety Data

- The majority of adverse events included gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhea), rash, vertigo and fever, all of those were of mild to moderate intensity (*).
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- Most of the SAEs were singular and included transient troponin I elevation, incarcerated hernia, QT prolongation in association with T wave abnormality, insulin, anemia, detachment of retina, thrombosis, bleeding, kidney failure and cholangitis (**);
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- these events occurred only once in single patients and were at least partly attributable to the underlying disease. Asacites occurred several times, supposed to be caused by the underlying disease.
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- (*) The data on adverse events are preliminary and are currently being analysed, also with respect to their relationship to the study medication.

Conclusions

- The preliminary clinical data show the favourable PK and safety profile of resminostat.
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- The initial data on the clinical activity of resminostat are promising with regard to a new second line treatment option in HCC, potentially overcoming resistance to sorafenib.