A new Epigenetic Treatment Option for HCC

- Resminostat is a novel oral HDAC inhibitor with broad anti-tumor activity in various cancer indications.
- Resminostat has yielded remarkable clinical results in a recent Phase II study in advanced hepatocellular carcinoma (HCC) (the SHELTER study) either alone (arm A) or in combination with the standard treatment sorafenib (arm B).
- Epigenetic modulation of resminostat suggests a possible targeting of HCC from multiple angles.

Overall Survival in the SHELTER Study

- Resminostat in combination with sorafenib achieved a median overall survival (OS) of 8.1 months in 2nd line treatment of patients with advanced HCC.
- Expected median OS after tumor progression on 1st line sorafenib is 5.2 months.
- The resminostat/sorafenib combination thus gains almost 3 months additional survival for patients who experienced tumor progression under sorafenib 1st line treatment.

Correlation of Patient Baseline Characteristics with Overall Survival

- In the monotherapy arm, an overall good performance status of the patient (ECOG 0) and treatment with a local ablative therapy (TACE, transarterial chemoembolization) correlated with a longer survival outcome.
- In the combination therapy arm, in addition to ECOG 0 also the absence of liver cirrhosis (Child-Pugh A) and end of vascular invasion of the liver tumor was identified to correlate with a prolonged survival.
- Notably, in both treatment arms the time interval between the end of 1st line sorafenib therapy and the treatment start in the SHELTER trial (‘drug holidays’) had no influence on the median OS of SHELTER patients.

Selection of Gene Markers regulated by Resminostat

- Based on Affymetrix analysis and qPCR validation 10 genes were identified from human PBMCs to be robustly and reproducibly regulated by resminostat.
- Pharmacodynamic regulation of these genes by resminostat was confirmed in various cancer cell lines and in peripheral blood from patients treated with resminostat in Phase I and Phase II studies (HCC, HL, CRC).

ZFP64 in Cancer Biology

- ZFP64 (zinc-finger protein) is a member of the C2H2-type zinc-finger type DNA-binding transcription factors, the largest family of transcription factors in the mammalian genome - with a largely unknown function.
- In comparison to the primary tumor, ZFP64 is upregulated in liver metastases of CRC patients.
- ZFP64 is involved in the differentiation of mesenchymal cells by co-activation of Notch/β.
- ZFP64 interacts with the intracellular domain of Notch1 (MCTD), inducing transactivation and upregulation of Notch target genes Hes1 and Hey.
- ZFP64 is a positive regulator of TLR signaling in innate immune reactions, with NF-κB activation and subsequent inflammatory responses to invading pathogens linking ZFP64 to liver inflammation and HCC progression.

ZFP64 is a Pharmacodynamic Marker for Resminostat

- Resminostat treatment leads to down-regulation of ZFP64 expression levels in peripheral blood of patients treated with either resminostat alone (in HCC and HL study) or in combination with sorafenib (in HCC study).
- High ZFP64 expression levels at baseline, i.e. prior to treatment with resminostat, is indicative of achieving a longer overall survival (OS) in HCC and HL (Hodgkin’s lymphoma) patients when treated with resminostat.

ZFP64 Gene Expression in Cancer Cell Lines

- Treatment with resminostat (10µM) leads to time-dependent (0 - 24hrs) down-regulation of ZFP64 expression levels in several cancer cell lines.

Summary & Conclusions

- Epigenetic down-regulation of ZFP64 expression by resminostat in ZFP64-dependent tumor types.
- Reduced pro-tumorigenic Notch and pro-inflammatory TLR/NF-κB signaling due to the resminostat induced down-regulation of the co-activator ZFP64.
- Cancer patients with high ZFP64 baseline levels might therefore specifically benefit from resminostat treatment.

References

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