Resminostat in HCC

Resminostat In Advanced Hepatocellular Carcinoma (HCC): Overall Survival Subgroup Analysis Of Prognostic Factors In The SHELTER Trial

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No conflicts to disclose.
RESMINOSTAT: A NEW EPIGENETIC OPTION FOR THE THERAPY OF ADVANCED HCC

EPIGENETIC REPROGRAMMING

Aberrant epigenetic modifications play a role in HCC development

HDAC-INHIBITOR

CANCER INTRACELLULAR SIGNALING

Inhibition of WNT-TGF-β pathways crosstalk in HCC

THE HDAC INHIBITOR RESMINOSTAT TARGETS HCC DEVELOPMENT AND PROGRESSION FROM MULTIPLE ANGLES

1 Liu et al., 2012; 2 Yuzugullu et al., 2009; 3 McDonald et al., 2009; 4 Lachenmayer et al., 2012; 5 Sharma et al., 2010; 6 van Zijl et al., 2009; 7 van Malenstein et al., 2012

HDAC-INHIBITOR

Inhibition of HDAC-driven development of drug tolerance: “(re)-sensitization” of tumors

Inhibition of “Epithelial-Mesenchymal Transition” (EMT)

TUMOR PROGRESSION, METASTASIS, STEMNESS

DRUG TOLERANCE DEVELOPMENT

HCC
RESMINOSTAT: Phase II SHELTER Trial in HCC

- Phase II open-label, non-randomized, two-arm parallel group trial in 8 German and 6 Italian centers.¹
- Resminostat: 14-day treatment cycles (“5+9”, i.e., 5 days on, 9 days off).
- Sorafenib (combination arm): continuous administration.

**INCLUSION CRITERIA**
- Documented progression under 1st line Sorafenib
- BCLC B and C
- Child-Pugh A or B (max 7 pts)
- ECOG 0, 1 or 2

**COMBINATION**
- 600 mg Resminostat + 400 mg Sorafenib

**END POINTS**
- Primary: PFS Rate week 12
- Secondary: PFS, PFS Rate week 6, TTP, RR, OS, Biomarkers, Safety, PK

**MONOTHERAPY**
- 600 mg Resminostat

¹ www.clinicaltrials.gov: NCT00943449
SHELTER STUDY IN 2ND-LINE ADVANCED HCC: OVERALL SURVIVAL (OS)\(^1\)

- Open-label, uncontrolled, non-randomized, two-arm parallel group clinical trial
- ITT analysis set; Combination Therapy (n=26) and Monotherapy (n=19)
- Cutoff value is 10.8 months for Combination Therapy and 7.0 months for Monotherapy

**THE RESMINOSTAT/SORAFENIB COMBINATION THERAPY ACHIEVED A MEDIAN OVERALL SURVIVAL OF 8.1 MONTHS**

\(^1\) Bitzer et al., ILCA 2012; Bitzer et al., ASCO 2012
CORRELATION OF BASELINE CHARACTERISTICS WITH OS IN THE SHELTER MONOTHERAPY ARM

Patients subgroups analyzed in the monotherapy arm

- **BCLC B (n=3) vs. C (n=16)**
- **Child-Pugh A (n=14) vs. B (n=5)**
- **ECOG 0 (n=11) vs. 1 (n=6)**
- **Etiology HBV (n=3) vs. Alcohol (n=3)**
- **Interval after 1st-line Short (n=10) vs. Long (n=9)**
- **TACE YES (n=8) vs. NO (n=11)**
- **Extrahepatic Spread YES (n=16) vs. NO (n=3)**
- **Vascular Invasion NO (n=8) vs. YES (n=10)**

* Statistically significant

HR < 1 indicate less risk to observe an event of OS in the patients presenting the specified baseline characteristic

- **ECOG 0 (n=11) vs. 1 (n=6)**
  - HR 0.25, 95% CI 0.07-0.9
- **TACE YES (n=8) vs. NO (n=11)**
  - HR 0.28, 95% CI 0.08-1.0

IN THE MONOTHERAPY ARM, ECOG STATUS AND PRETREATMENT WITH TACE HAVE A SIGNIFICANT INFLUENCE ON OVERALL SURVIVAL
CORRELATION OF BASELINE CHARACTERISTICS WITH OS IN THE SHELTER COMBINATION ARM

Patients subgroups analyzed in the combination therapy arm

- **BCLC B (n=5) vs. C (n=21)**
- **Child-Pugh A (n=20) vs. B (n=6)**
- **ECOG 0 (n=15) vs. 1 (n=11)**
- **Etiology HBV (n=8) vs. Alcohol (n=8)**
- **Interval after 1st-line Short (n=15) vs. Long (n=11)**
- **TACE YES (n=14) vs. NO (n=12)**
- **Extrahepatic Spread YES (n=16) vs. NO (n=10)**
- **Vascular Invasion NO (n=16) vs. YES (n=10)**

HR < 1 indicate less risk to observe an event of OS in the patients presenting the specified baseline characteristic

- **HR 0.19, 95% CI 0.06-0.55**
- **HR 0.15, 95% CI 0.05-0.44**
- **HR 0.37, 95% CI 0.15-0.93**

*Statistically significant

IN THE COMBINATION THERAPY ARM, CHILD-PUGH, ECOG AND VASCULAR INVASION HAVE A SIGNIFICANT INFLUENCE ON OVERALL SURVIVAL
ZINC FINGER PROTEIN 64 (ZFP64) WAS IDENTIFIED AS AN IMPORTANT PHARMACODYNAMIC MARKER IN THE SHELTER (HCC) AND SAPHIRE (HODGKIN’S LYMPHOMA, HL) PHASE II TRIALS
ZFP64 AS A PHARMACODYNAMIC MARKER FOR RESMINOSTAT

Relative ZFP64 expression at **Day 1 dosing**

- Resminostat 600 mg (n=14 HCC + 16 HL)
- Resminostat 600 mg + Sorafenib 400 mg (n= 19 HCC)
- Resminostat 800 mg (n=15 HL)

Relative ZFP64 expression at **Day 5 dosing**

- Resminostat 600 mg (n=12 HCC + 14 HL)
- Resminostat 600 mg + Sorafenib 400 mg (n=18 HCC)
- Resminostat 800 mg (n=14 HL)

**RESMINOSTAT DOWN-REGULATES ZFP64 EXPRESSION WHEN APPLIED ALONE OR IN COMBINATION WITH SORAFENIB IN HCC PATIENTS (SHELTER TRIAL) AND IN HL PATIENTS (SAPHIRE TRIAL)**
THE ROLE OF ZFP64 IN CANCER BIOLOGY

- **ZFP64** is a member of the C2H2-type zinc-finger family, the largest kind of DNA binding transcription factors in the mammalian genome.
- The biological function remains largely unknown.
- Positive regulator in TLR signaling with NF-κB activation and subsequent inflammatory response to invading pathogens\(^1\).
- ZFP64 is **up-regulated in liver metastases** compared to the primary tumor in CRC patients\(^2\).
- Involved in the differentiation of **mesenchymal cells** by co-activation of **Notch1**\(^3\).
- Interaction with the intracellular domain of **Notch1 (NICD)**, followed by a transactivation and upregulation of Notch target genes Hes1 & Hey1\(^3\).

ZFP64 IS INVOLVED IN INFLAMMATORY RESPONSES, IS UPREGULATED IN METASTASIS OF THE LIVER AND INCREASES THE TRANSCRIPTIONAL ACTIVITY IN NOTCH SIGNALING

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GEF4 = Guanine Nucleotide Exchange Factor
GSTA3 = Glutathione-S-transferase A3
ZFP64 BASELINE EXPRESSION VS. OS IN WHOLE BLOOD SAMPLES OF HCC AND HL PATIENTS

- Baseline ZFP64 gene expression split – HIGH vs. LOW expression

SHELTER HCC Study (n=31)

- Split: 60% high / 40% low

SAPPHIRE HL Study (n=30)

- Split: 65% high / 35% low

High baseline ZFP64 expression is indicative of achieving longer overall survival in HCC and HL patients upon treatment with Resminostat.
Lower ZFP64 mRNA expression (= higher dCt baseline value) correlates with progressive disease (PD) in HCC patients upon resminostat treatment.

Higher ZFP64 mRNA expression (= lower dCt baseline value) correlates with stable disease (SD) as best response upon resminostat treatment.

NOTE: higher dCT value means lower gene expression, i.e. more rounds of PCR amplification required for detection vs housekeeping gene controls
ZFP64 IN HCC PATIENTS: BASELINE EXPRESSION VS. OS IN THE TWO ARMS OF SHELTER STUDY

IN THE SHELTER STUDY LONGER OVERALL SURVIVAL APPEARS TO CORRELATE WITH HIGH BASELINE ZFP64 LEVELS
ZFP64 GENE EXPRESSION BIOMARKER DATA IN DIVERSE CANCER CELL LINES

- The cancer cells were treated with 10 µM of Resminostat for 0 h, 2 h, 5 h, 24 h

ZFP64 TRANSCRIPTS ARE DOWNREGULATED IN SEVERAL CANCER CELL LINES UPON TREATMENT WITH 10 µM RESMINOSTAT
A POSSIBLE LINK OF ZFP64 TO HDAC ACTIVITY AND CANCER CELL SIGNALING

Presuming ZFP64 as a predictive biomarker for response to resminostat, the following mode of action can be hypothesized:

• Epigenetic down-regulation of ZFP64 expression by resminostat in ZFP64-dependent tumor types

• Downregulation of pro-tumorigenic Notch1 signaling pathway due to the lack of ZFP 64 as a co-activator

• Thus, cancer patients with high baseline ZFP64 levels might specifically benefit from resminostat treatment

"ZFP64-dependent" tumor cell with high baseline ZFP64 expression levels

IN THIS MODEL, ZFP64 BASELINE EXPRESSION IS ASSUMED TO BE A PREDICTIVE BIOMARKER FOR RESPONSE TO RESMINOSTAT TREATMENT
Summary

- In both study arms of the SHELTER study, ECOG status (0 vs 1) was a prognostic factor for overall survival in advanced HCC patients.
- Furthermore, Child-Pugh index and vascular invasion were prognostic factors for overall survival in the combination arm, whereas pretreatment with TACE was a prognostic factor in the monotherapy arm.
- Time interval after first-line sorafenib treatment (= potential “drug holiday”) is apparently not relevant.
- A novel gene expression marker ZFP64 appears to be indicative of overall survival.

Conclusions

- Recommendations for pivotal resminostat trials: inclusion of BCLC-C and Child-Pugh A patients only; stratified randomization with ECOG and vascular invasion.
- ZFP64 will be further evaluated as a predictive biomarker for resminostat response in the pivotal clinical development.
- ZFP64 offers the opportunity for the development of a companion diagnostic for patient stratification.
Thank you!

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

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Study sponsor:
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