Background

Domatinostat is a clinical stage, orally available, class I specific inhibitor of histone deacetylases (HDACs) with favorable immune-modulatory capabilities in combination with anti-PD-(L)1 antibodies. Anti-PD-(L)1 therapy has recently become standard of care for advanced MCC patients with remarkable clinical effect. However, many patients show either primary or secondary resistance to this treatment due to known immune escape mechanisms:

- MHC class I and II downregulation
- Insufficient influx of immune effector cells (e.g., CD8+ T cells)
- Epigenetic silencing of antigen processing and presentation

Treatment with epigenetic modulators like domatinostat may overcome these escape mechanisms.

Figure 1: Domatinostat, a class I selective HDAC inhibitor and it’s immune-modulating capabilities

Domatinostat beneficially affects the tumor microenvironment:

- Upregulates the expression of tumor-associated antigens
- Enhances the infiltration of cytotoxic T cells into tumors
- Increases expression of cells key antigen presentation machinery (MHC I & II molecules and antigen processing machinery)

Important: no toxicity on immune effector cells by domatinostat in preclinical experiments

Figure 2: Domatinostat-induced upregulation of genes of the antigen processing machinery in MCC cell lines

Figure 3: Domatinostat-induced upregulation of APM and MHC proteins

Figure 4: Real-time PCR analysis of selected genes of the antigen processing machinery (APM) in MCC cell lines upon domatinostat combination.

Left 1 panels: Dose-dependent mRNA expression of TAP2 (Transporter 2, ATP Binding Cassette Subfamily B Member) and LMP2 (pre-treatment 2.5µM). Right 1 panels: Domatinostat combination. Left 2 panels: Dose-dependent mRNA expression of HLA-ABC (MHC class I) and HLA-A (HLA-A) in MCC cell lines upon domatinostat treatment. Right 2 panels: Protein expression of indicated proteins determined by immunostain in whole cell lysates. Data generated by J. Becker (University of Essen) and presented during AACR 2019.

Figure 5: Study Design MERKLIN 2

**Study Objectives**

- Primary Objective: Objective Response Rate (ORR) per RECIST v1.1
- Secondary Objectives:
  - Additional Efficacy Parameters
  - Safety and Tolerability
  - Pharmacokinetics
  - Health related Quality of Life (HRQoL)

**Key inclusion criteria**

- Histologically confirmed metastatic MCC
- Patients ≥ 18 years of age; ECOG ≤1

**Key exclusion criteria**

- Progression must be confirmed to be eligible

**Study Design MERKLIN 1**

Phase II, multi-center, single arm study; planned recruitment in USA/ Europe/ Australia

**Study Design MERKLIN 2**

Phase II, multi-center, single arm study; planned recruitment in USA/ Europe

**Conclusions**

The class I HDAC inhibitor domatinostat is able to favorably alter the tumor microenvironment, and -on a cellular level- may overcome possible escape and resistance mechanisms that are characteristic for MCC patients that fail PD-(L)1 therapy. Preclinical experiments with domatinostat have demonstrated that epigenetic intervention might be beneficial and therefore providing a rationale for the outlined complementary study concepts to test the combination of domatinostat and avelumab in clinical settings:

- **MERKLIN 1**: domatinostat in combination with avelumab (anti-PD-L1) in patients that are treatment-naive to checkpoint inhibitors to increase the number of durable responses, duration of response and potentially also the depth of responses; [study in preparation]

- **MERKLIN 2**: domatinostat in combination with avelumab in patients that are progressing on previous anti-PD-(L)1 therapy to enable or restore responsiveness [anticipated study start Q1/2020]

**Comments and Acknowledgements**

We thank Jürgen C. Becker (University of Essen) for performing preclinical experiments and providing data on domatinostat in MCC cell lines. Data has been presented during AACR 2019 (poster presentation). R.B., T.B., P.R. and FH are full-time employees of 4SC AG.

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\* MERKLIN 1 and MERKLIN 2 studies**