Lead Principal Investigator Rebekka Schneider-Kramann presents the clinical plan and positioning of tasquinimod in myelofibrosis

Dec 1st 2023, Audiocast summary

Dr. Erik Vahtola, MD, PhD
Chief Medical Officer, Active Biotech

Univ.-Prof. Dr. med. Rebekka Schneider-Kramann, PhD
Director, Institute of Cell and Tumor Biology at the University Hospital in Aachen, Germany
Oncode Principal Investigator, Oncode Institute and Associate Professor, Cancer Center Erasmus MC , Rotterdam, The Netherlands

Professor Schneider-Kramann shares her preclinical research results with tasquinimod in animal models of myelofibrosis. The results provide a strong rationale to initiate a phase II clinical trial in patients with myelofibrosis who are ineligible to JAK inhibitor therapy.

Before starting her own research group at the Erasmus MC, Rebekka worked between 2012 and 2015 as a post-doc researcher in Benjamin Ebert's lab at Harvard Medical School. Her research is focused on the role of the microenvironment in the bone marrow in myeloid malignancies and she has 93 publications in peer reviewed journals.

Tasquinimod is a novel small molecule immunomodulator which has previously been in phase III clinical development for prostate cancer and is now running in a phase I/II clinical trial in multiple myeloma. Two clinical studies in myelofibrosis are planned to start in 2024, the first one in Europe and the second in the US.

Myelofibrosis – a rare disease with unmet need for new treatments

Myelofibrosis is a rare blood cancer which belongs to a class of myeloproliferative neoplasms (MPNs), where a blood-forming stem cell is mutated and starts to proliferate uncontrollably resulting in bone marrow fibrosis replacing blood-forming cells.

MPNs can be classified depending on the dominant cell type involved: polycythemia vera (PV) if excess red blood cells dominate or essential thrombocythemia (ET) with an excess of platelets. Primary myelofibrosis (PMF) or secondary myelofibrosis (post-PV MF or post-ET MF) are rare forms of MPNs with prevalence ranging from 2 / 100 000 to 100 / 100 000 depending on the source of information.

In patients with myelofibrosis the inability of the fibrotic bone marrow to form adequate blood cells leads to a compensatory enlargement of the spleen. Anemia, changes in white blood cell counts and constitutional symptoms are common, and myelofibrosis is associated with premature risk of death due to bone marrow failure and transformation to leukemia.

There is an **unmet clinical need for effective therapies** that would have an effect on the underlying disease and inhibit bone marrow fibrosis and for a biomarker that could predict treatment effectiveness. Currently there are no anti-fibrotic therapies available and the only

curative treatment option, allogeneic stem cell transplantation is a high-risk procedure and available only for a select few patients. JAK inhibitors including ruxolitinib have been in use for over 10 years for patients with myelofibrosis. They are effective as symptom-directed treatments but lack effect on fibrosis. Furthermore, there is a high degree of drug discontinuation and developing dose-limiting changes in blood counts including anemia and thrombocytopenia.

Tasquinimod in myelofibrosis

The **tumor microenvironment** is a key driver of bone marrow fibrosis in myelofibrosis and at present no approved therapies that target the tumor microenvironment exist. A preclinical animal model carrying the same MPN-mutations as in humans was developed to identify fibrosis driving cells in the tumor microenvironment and to test the effect of tasquinimod on disease characteristics. The animals develop the basic characteristics of myelofibrosis including spleen enlargement, changes in blood cell counts and bone marrow fibrosis. Mesenchymal stromal cells 1 and 2 were identified as fibrosis-driving cells in the tumor microenvironment. Treating the animals with tasquinimod resulted in normalization of spleen size and white blood cell counts and inhibition of bone marrow fibrosis. Furthermore, blood samples from patients with myelofibrosis showed that certain markers of inflammation named alarmins (S100A8/A9) are increased. Alarmin concentration in the blood correlated with grade of disease, with higher degree of alarmins in patients with more fibrotic bone marrow. Importantly, these alarmins were not increased in non-diseased i.e. normal bone marrows.

Alarmins present a promising novel target in myelofibrosis. Tasquinimod blocks alarmin signaling and may therefore have potential as a disease modifying treatment in patients.

A **clinical phase II trial, TasqForce,** will start recruiting patients in 2024 to evaluate tasquinimod as a new treatment option in patients who are ineligible for JAK inhibitor therapy. The study will investigate the effect of tasquinimod on spleen volume and bone marrow fibrosis in patients with primary or secondary myelofibrosis. Further, the study will test the possibility to use alarmins as an actionable biomarker to predict treatment response to tasquinimod.