

# Lay Summaries

ASH 2017

## **Purpose of Document:**

This document contains a collection of lay summaries of accepted ASH 2017 abstracts from the following investigators: MDS CRC Members/Affiliates, Fellows (past and present) and AAMDSIF Grant Recipients (past and present).

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## **MDS Clinical Research Consortium (MDS CRC) Abstract Summaries**

The MDS CRC is a six-institution consortium of leading academic institutions designed to undertake unique studies and trials to significantly advance treatments and improve outcomes for patients with myelodysplastic syndromes (MDS).

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### **Prediction of Clinically Relevant Mutations in MDS: A Report on Behalf of the MDS CRC**

*Sangmin Lee, MD*

Weill Cornell Medicine Leukemia Program

Mutation testing is commonly being done as part of the workup for MDS and other cancers. MDS patients often are told they have mutations in genes known to be associated with MDS. We examined if we can categorize the type of mutations that may impact outcomes in MDS. At this point, we conclude that clinical characteristics must be considered along with genetic mutations in predicting clinical outcomes.

### **Promising Results of a Phase I/II Clinical Trial of Ruxolitinib in Patients with CMML**

*Eric Padron, MD*

H. Lee Moffitt Cancer Center

Chronic myelomonocytic leukemia (CMML) is a lethal blood cancer for which no approved therapies exists. We have previously performed a Phase 1 clinical trial testing ruxolitinib, an FDA-approved treatment for myelofibrosis, that demonstrated it was safe for CMML patients. In Phase 2, we have demonstrated that ruxolitinib can decrease the size of enlarged spleens, improve disease-related symptoms and improve blood counts in some patients.

## Fellow Abstract Summaries

Known collectively as the “Edward P. Evans Fellows”, each fellow has the opportunity to work, learn and grow in a truly collaborative environment and will likely become the MDS clinical research leaders of the future.

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### Immune Checkpoint Profiling of TP53 Mutant Wild-Type Myeloid Malignancies: TP53 Mutations Direct Immune Tolerance via an Immunosuppressive Phenotype

David Sallman, MD

H. Lee Moffitt Cancer Center

Patients with myelodysplastic syndromes or acute myeloid leukemia with *TP53* mutations have poor outcomes with the lowest survival and decreased benefit from bone marrow transplantation. However, the reasons for the poor outcomes in this molecular subgroup are unclear. To find out why, we investigated how the immune microenvironment is different between patients with and without *TP53* mutations.

We identified the fact that leukemia cells of *TP53* mutant patients have increased PDL1 expression, which can turn off the immune system. We also found that there is a decrease in activated T-cells, i.e. cells that can eliminate cancer cells, as well as an increase in immunosuppressive immune cells, i.e. cells that can turn off the immune attack against the leukemia cells. Taken together, these studies indicate that inactivation of the immune system is a cardinal feature of *TP53* mutant patients and that re-activation through immune therapy may hold significant promise for the improvement of outcomes for these patients.

### Acute Myeloid Leukemia (AML) Patients Demonstrate Increased Prevalence of AML-Defining Mutations in Peripheral Blood Years Before the Development of Overt Leukemia

Pinkal Desai, MD

Weill Cornell Medicine Leukemia Program

**Background:** Clonal mutations can be detected in healthy people without evidence of hematological cancers, but the exact relationship of the presence of a specific mutation with risk of acute myeloid leukemia (AML) has not been clearly defined due to a lack of blood samples from patients in the years before their AML diagnosis.

**Methods:** The Women’s Health Initiative (WHI) cohort followed participants aged 50-79 for an average of 10.8 years to study the effect of hormone replacement on cardiovascular health. As part of the study blood samples were collected at baseline and participants were followed over time with some women being diagnosed with AML approximately 9.8 years after the blood draw. We analyzed these blood samples from the 212 women who developed AML and compared the results with 212 women who did not develop AML. We sequenced for the presence of AML-related mutations in both groups.

**Results:** Mutations in blood were detected an average of 9.8 years before the diagnosis of AML. Participants who eventually developed AML were four times more likely to have a mutation compared to participants who did not develop AML. Having a mutation at baseline increased the odds of

developing AML, but the risk was different based on the specific type of mutation. Moreover, certain mutations were associated with diagnosis of AML sooner than 5 years while with other mutations, the diagnosis of AML was many years later (average 9.8 years).

**Conclusions:** Mutations in the peripheral blood in individuals who are otherwise hematologically normal are associated with significantly increased odds of AML development. The data suggest the possibility of molecular monitoring and potentially early intervention in selected patients.

### **Factors Affecting Transfusion Utilization in Acute Myeloid Leukemia (AML) Patients Undergoing Initial Therapy**

*Sangmin Lee, MD*

Weill Cornell Medicine Leukemia Program

We examined blood and platelet utilization in AML patients undergoing induction chemotherapy. Certain factors, such as duration of hospitalization, having an infection, and being in the intensive care unit were associated with requiring more transfusions. Transfusions carry risks, and further studies are needed to determine a safe approach to decrease blood utilization during the treatment of AML patients.

### **Phase II Clinical Study of the Clinical Efficacy and Safety of Tosedostat in Patients with MDS after Failure of HMA-Based Therapy**

*Sangmin Lee, MD*

Weill Cornell Medicine Leukemia Program

We studied a drug called tosedostat in patients with refractory MDS. It was studied in patients who previously were treated with azacitidine or decitabine. Tosedostat was well tolerated, and one patient had a long duration of remission with tosedostat. It is a drug that should be further explored in future clinical trials.

### **Germline Tissues and DNA Sequencing Analysis Methods for Optimal Somatic Variant Detection in MDS**

*Eric Padron, MD*

H. Lee Moffitt Cancer Center

Genetic studies have vastly advanced our understanding of blood cancer. However, the genetic mutations of most interest are those that are acquired in the leukemia and not in all other cells. To accurately detect these, a “normal” tissue sample needs to be sequenced in every patient so that researchers can “subtract” genetic mutations seen in both leukemia and normal samples, leaving only the acquired cancer-causing mutations to be identified. For this investigation, we performed the first systematic study to identify the best “normal” tissue sample for genetic studies in MDS and leukemias.

## AAMDSIF Grant Recipients (Past & Present) Abstract Summaries

AAMDSIF Grant Recipients are investigators who were awarded research grant by the Foundation to help advance the understanding and treatment of aplastic anemia (AA), myelodysplastic syndromes (MDS) and paroxysmal nocturnal hemoglobinuria (PNH). The ASH abstract summaries that are listed below are an extension of that research which was initially funded with AAMDSIF grant money.

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### **The Spliceosomal Component of SF3B1 is Essential for Hematopoietic Stem Cell Formation through the Regulating of the JAK/STAT Signaling Pathway**

*Rosannah Cameron, PhD*

Albert Einstein College of Medicine

In the Bowman Laboratory, we use zebrafish to understand how normal blood cells function and how alterations to this function contribute to myelodysplastic syndromes (MDS). Through our studies of a zebrafish mutant for one of the most commonly mutated genes in MDS patient blood cells (SF3B1; Splicing Factor 3B, subunit 1), we established that SF3B1 regulates the JAK/STAT signaling pathway. This pathway is important in many key cellular processes and signaling through this pathway is altered in blood cells from MDS patients. We are now utilizing our zebrafish model to help explain how SF3B1 dysfunction alters JAK/STAT signaling and its importance in MDS, which will give us a better idea of how to treat the disease.

### **Two Distinct but Functionally Related Autoreactive T-Cell Populations in PNH and Idiopathic Aplastic Anemia: Glycosylphosphatidylinositol-Specific and IFN $\gamma$ -Producing T-Cells**

*Rosario Notaro, MD*

Istituto Toscano Tumori, Florence, Italy

Paroxysmal nocturnal hemoglobinuria (PNH) and aplastic anemia (AA) are two blood disorders that share one important feature called bone marrow failure: The bone marrow cannot produce all the blood cells needed by the body. It means that there may be anemia, risk of infection (because of low white cells) and risk of bleeding (because of low platelets).

Recently, we have studied a type of lymphocytes called T-cells, and we have found that almost all PNH patients and a large fraction of AA patients have an excess of a very rare subset of T-cells that are able to recognize a specific glycolipid molecule (a molecule that contains both a sugar moiety and a fat moiety) called GPI. These T-cells could be responsible for the bone marrow failure because, upon GPI recognition, they produce interferon gamma – a substance that is toxic for the hematopoietic stem cells, the cells that generate all blood cells.

In the study we have presented to the 59<sup>th</sup> ASH, we found that the T-cells that recognize the GPI and those that produce interferon gamma are two distinct subsets of T-cells. We also found that these two subsets are strictly dependent. In fact, only when the T-cells that recognize the GPI are present is the second T-cell subset induced to produce the toxic interferon gamma. Our finding validates the notion that these cells are primarily responsible for the bone marrow failure typical of these diseases. The still

unknown mechanisms of this functional dependence need to be investigated because their targeting may make it possible to develop new and likely more effective therapies that are less toxic.

### **Quercetin: A Novel Targeted Chemoprevention for Patients with Fanconi Anemia (FA)**

*Parinda Mehta, MD*

Cincinnati Children's Hospital

Currently the only potentially curative option for patients with Fanconi Anemia (FA) is bone marrow transplant that can be associated with significant toxicity. There is clearly a need for a new approach both for prevention and/or treatment of progressive marrow failure associated with FA that has fewer and less severe side effects.

Reactive Oxygen Species (ROS) plays an important role in causing marrow failure in FA. Our study showed that a naturally occurring antioxidant, Quercetin, was safe and well tolerated in patients with FA. Quercetin achieved expected blood levels and decreased reactive oxygen species as we had predicted. We saw stable to slightly improved numbers and function of bone marrow stem cells after four months of treatment with Quercetin (One year follow-up data will be ready soon).

Patients are currently being enrolled in the Expansion Cohort, and we hope to confirm that a simple approach of treatment with oral Quercetin will maintain stem cell pool and, in turn, likely prevent progressive marrow failure in patients with FA.