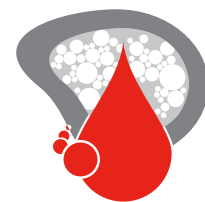AAMDSIF
MDS Research Summary *from the*
2017 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

A Summary of Selected Scientific Abstracts for Patients with
Myelodysplastic Syndromes (MDS) and their Caregivers

AA·MDS
INTERNATIONAL FOUNDATION

The Aplastic Anemia and MDS International Foundation (AAMDSIF) is an independent non-profit organization. Our mission is to support patients, families, and caregivers coping with:

- Aplastic anemia
- MDS (myelodysplastic syndromes)
- PNH (paroxysmal nocturnal hemoglobinuria)
- Related bone marrow failure diseases

This booklet offers summaries of selected abstracts presented at the 59th Annual Meeting of the American Society of Hematology (ASH) in December 2017. It provides some of the most up-to-date information about new research into the biology and treatment of myelodysplastic syndromes (MDS).

Although the information in this booklet has undergone a thorough, independent medical review to insure its accuracy, this information is not intended to be a substitute for the advice of your doctor. You should always seek medical advice from a qualified physician.

For more information, call us at (800) 747-2820, or visit us online at www.aamds.org.

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INTRODUCTION

Dear Patient or Caregiver,

The purpose of this guide is to provide you with the most up-to-date information about the latest new research into the biology and treatment of myelodysplastic syndromes (MDS), as presented at the 59th Annual Meeting of the American Society of Hematology (ASH) Annual Meeting in December 2017.

The ASH Annual Meeting is the world's largest professional gathering of hematologists and hematological oncologists–i.e., doctors who care for patients with blood disorders or blood and bone marrow cancers. This conference is where many major findings in the field of blood and marrow disorders are first announced to attendees –the larger medical and scientific community, and the media.

New information that researchers hope is important enough to be presented at this meeting is submitted a few months ahead of the conference in the form of an "abstract"– a brief summary of the study and its results –and authors of the most interesting and noteworthy abstracts are asked by ASH to present their research in more detail, either in the format of a tacked-up printed poster or an oral (podium) presentation.

We selected the ASH abstracts in this summary because we feel they are the most relevant and important for MDS patients to know about. Please note that the research results discussed at the ASH Annual Meeting often involve experimental drugs that are not yet approved by the Food and Drug Administration (FDA) for general use or investigations of potential new uses of previously approved treatments. By providing summaries of the research presented, we do not intend to recommend or endorse any particular medication or treatment approach. Our goal is simply to inform you about current news and trends in research related to MDS.

If you are interested in participating in research studies such as those discussed in this booklet, we encourage you to speak with your doctor about clinical trials or to visit www.clinicaltrials.gov.

As always, please contact AAMDSIF if you have questions about these summaries or any aspect of managing your disease.

Mikkael Sekeres, MD, MS
The Cleveland Clinic Taussig Cancer Institute
Member, AAMDSIF Medical Advisory Board

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KDM6B Overexpression and MDS Development

Yue Wei, PhD, Guillermo Garcia-Manero, MD, Hong Zheng, Yu Jia, Naran Bao, Shan Jiang, Joseph David Khoury, MD, Caleb Class, Simona Colla, PhD, Carlos E. Bueso-Ramos, MD, PhD

The *KDM6B* gene controls the development of bone marrow stem cells into different types of blood cells. This gene is overexpressed (uses more of its information to control protein formation) in bone marrow stem cells and immature blood cells in more than half of patients with MDS.

The goal of this study was to find out whether *KDM6B* overexpression plays an important role in the development of MDS. The researchers used a mouse breed that has overexpressed *KDM6B*.

Key findings:

- Overexpressed *KDM6B* led to low counts of white blood cells and immature blood-forming cells.

- Exposing the mice to Toll-like receptor ligand lipopolysaccharide (LPS), which elicits strong immune responses, activated more than 130 genes. A significant proportion of these genes are overexpressed in patients with MDS.

- GSK-J4, a compound that inhibits *KDM6B* activity, increased the number of bone marrow cells by 50% in mice treated with LPS.

- The same dose of GSK-J4 did not have this effect in cells from healthy donors.

Conclusions:

- *KDM6B* overexpression leads to hyperactivity in immune system cells and affects the cells in bone marrow that form blood cells.

- Therefore, *KDM6B* seems to play a role in the development of MDS.

- Inhibiting *KDM6B* activity could offer a way to treat MDS.

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CUX1 Mutations in Bone Marrow Failure

Mai Aly, MD, Zubaidah M. Ramdzan, PhD, Yasunobu Nagata, MD, PhD, Suresh K. Balasubramanian, M.D., Naoko Hosono, M.D., PhD, Hideki Makishima, M.D., PhD, Valeria Visconte, PhD, Bartlomiej P. Przychodzen, MSc, Cassandra M. Hirsch, Mikkael A. Sekeres, MD, MS, Alain Neveu, PhD, Jaroslaw Maciejewski, MD, PhD

The *CUX1* gene helps suppress tumors. Mutations in this gene are associated with certain bone marrow cancers.

The purpose of this study was to learn about the role of *CUX1* changes in bone marrow cancers. The study included 1,480 patients with lower-risk or higher-risk MDS, acute myelogenous leukemia (AML), MDS/myeloproliferative neoplasms (a blood and bone marrow disease), or myeloproliferative neoplasms.

Key findings:

- 4% to 6% of patients had one of two *CUX1* mutations, and both types of mutations were associated with shorter survival than in patients without the mutations.
- *CUX1* is underexpressed, meaning that it has abnormally low activity, in 60% of patients with -7/del(7q) MDS who had a mutation and 70% of those with -7/del(7q) AML.
- Patients with a *CUX1* mutation were more likely to also have mutations in *TET2*, *ASXL1*, and/or *BCOR*.
- The *CUX1* mutations delayed the repair of the DNA damage that is common in MDS.

Conclusions:

- Reduced *CUX1* expression is associated with reduced DNA repair efficacy.
- This alternation is also associated with a higher number of somatic mutations (which happen after conception in a patient's cells, are not inherited, and are not passed on to the patient's children).

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A Personalized and Risk-Based Prediction Model for MDS

Aziz Nazha, MD, Rami S. Komrokji, MD, John Barnard, PhD, Karam Al-Issa, MD, Eric Padron, MD, Yazan F. Madanat, MD, Teodora Kuzmanovic, Nour Abuhadra, MD, David P. Steensma, MD, Amy E. DeZern, MD, Gail J. Roboz, MD, Guillermo Garcia-Manero, MD, Alan F. List, MD, Jaroslaw P. Maciejewski, PhD, MD, Mikkael A. Sekeres, MD, MS

Experts have developed several prognostic scoring systems to categorize patients with MDS by risk of progression to acute myelogenous leukemia (AML) and death. But patients in the same category can have very different outcomes. As a result, many patients are undertreated or overtreated.

The purpose of this study was to use information on patient genomes (complete sets of DNA) to created a personalized computer model that predicts patient outcomes. The researchers used data from 975 patients with MDS, including information on 60 gene mutations that are common in MDS, to develop their model.

Key findings:

- According to the model, the factors that contributed most to patient survival included abnormalities in chromosomes, proportion of blasts (abnormal and immature white blood cells) in bone marrow, blood cell counts, and mutations in certain genes (*TP53, RUNX1, ANC, STAG2, SRSF2, NPM*1).

- Other factors that contributed to patient survival according to the model were whether the MDS was primary or secondary (meaning that it resulted from treatment for another cancer), patient age, and mutations in certain genes (*PHF6, IDH1, EZH2, SF3B1*).

- The new model was better at predicting survival than all commonly used prognostic scoring systems, including the original and revised International Prognostic Scoring system, World Health Organization system, and M.D. Anderson prognostic model.

Conclusions:

- A personalized, precision medicine model for predicting survival outcomes in patients with MDS based on clinical and genomic information outperformed all commonly used prognostic models.

- The authors are developing an online application to make the model easy for clinicians to use.

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Genomic Markers That Predict Responses to MDS Treatment

Aziz Nazha, MD, Mikkael A. Sekeres, MD, MS, Rafael Bejar, MD, PhD, Rami S. Komrokji, MD, John Barnard, PhD, Karam Al-Issa, MD, Bartlomiej P. Przychodzen, MSc, Cassandra M. Hirsch, David P. Steensma, MD, Amy E. DeZern, MD, Gail J. Roboz, MD, Guillermo Garcia-Manero, MD, Benjamin L. Ebert, MD, PhD, Jaroslaw P. Maciejewski, PhD, MD

Treatment with the hypomethylating agents (HMAs) azacitidine (Vidaza) and decitabine (Dacogen) reduces blood cell shortages and prolongs survival in patients with MDS. But not all patients respond. Identifying patients who won't respond to these treatments could prevent the associated side effects and decrease unnecessary costs.

The authors studied the usefulness of several gene mutations for predicting response to HMAs using data on 636 patients with MDS (median age 70 years; 28% female). They hoped to find mutations that increase a patient's likelihood of having a certain other mutation.

Key findings:

- No single mutation was more common in patients who responded to HMAs than those who didn't, except that NF1 mutations were more common in nonresponders.

- Several combinations were strongly associated with no response:
  - *ASXL1* and *NF1*
  - *ASXL1, EZH2,* and *TET2*
  - *ASXL1, EZH2,* and *RUNX1*
  - *EZH2, SRSF2,* and *TET2*
  - *ASXL1, EZH2,* and *SRSF2*
  - *ASXL1, RUNX1,* and *SRSF2*
  - *ASXL1, TET2,* and *SRSF2*
  - *ASXL1, BCOR,* and *RUNX1*
  - *SRSF2, RUNX1,* and *BCOR*

- Patients with mutations in *TET2, RUNX1*, and *SRSF2* were more likely to respond to HMA treatment.

Conclusions:

- Genetic markers can accurately identify about a third of patients with MDS who won't respond to HMAs.

- This information can be used to tailor treatments for these patients.

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Clinically Relevant Genetic Mutations in MDS

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Somatic mutations are changes in genes that happen after conception in a patient's cells. These mutations are not inherited or passed on to the patient's children. They are common in patients with MDS. Identifying a patient's somatic mutations is becoming a common part of the diagnostic process for MDS.

This research team used the Ensembl Variant Effector Predictor tool to identify somatic mutations that correlate with outcomes in patients with MDS. The study included data on 963 patients with MDS and another 270 patients treated with azacitidine (Vidaza) or decitabine (Dacogen). The focus was on somatic mutations that patients had when they were diagnosed with MDS in the following genes: *ASXL1, DNMT3A, EZH2, RUNX1, TET2*, and *TP53*.

Key findings:

- The only mutations that correlated with poorer overall survival were in *DNMT3A* and *TP53*.
- All of the mutations had a moderate or high impact on the behavior of proteins produced by the genes.
- High-impact mutations in *DNMT3A*, but not moderate-impact mutations, were associated with poorer overall survival and poorer azacitidine or decitabine treatment outcomes.
- High-impact and moderate-impact mutations in *TP53* were associated with poor overall survival, but only moderate-impact *TP53* mutations were associated with poorer azacitidine or decitabine treatment outcomes.

Conclusions:

- An abnormal mutation on its own is not enough to predict a patient's outcomes.
- Both the mutation's predicted impact (high, moderate, or low) and the patient's symptoms affect the mutation's effects on outcomes.

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Prognostic Scoring System for Intermediate-Risk MDS

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Doctors use the International Prognostic Scoring System (IPSS) to predict outcomes and choose therapies for patients with MDS. But patients with the same type of MDS according to the revised IPSS (IPSS-R) can have very different outcomes, which makes it hard for doctors to choose the right treatments.

This study analyzed data on 298 patients with intermediate-risk MDS according to the IPSS-R. The goal was to improve the classification of these patients and the ability to choose the right treatments. The investigators assigned 2 points for age 66 or higher, 1 point for at least 2% blasts (abnormal young white blood cells) in blood, and 1 point for a history of red blood cell transfusions. Patients with a score of 0–1 were classified as int-favorable, and those with a score of 2–4 were classified as int-adverse.

Key Findings:

- Patients in the int-favorable group survived for about 6 years after diagnosis, on average, whereas those in the int-adverse group survived just 2 years.

- An analysis of 111 other patients with intermediate-risk MDS according to the IPSS-R found that overall survival was 4 years for those in the int-favorable group and 2 years for the int-adverse group.

Conclusions:

- The prognostic information considered in this study can help clinicians choose the most appropriate treatments for patients with intermediate-risk MDS.

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Artery Disease in Patients with MDS or Chronic Myelomonocytic Leukemia and TET2 Mutations

Remco J. Molenaar, Tomas Radivoyevitch, PhD, Mikkael A. Sekeres, MD, MS, Sudipto Mukherjee, MD, PhD, MPH, Jaroslaw P. Maciejewski, PhD, MD

This research team from the Cleveland Clinic investigated deaths due to heart disease and diseases of the arteries and other blood vessels in MDS and chronic myelomonocytic leukemia (CMML). *TET2* mutations are common in patients with these diseases. The study included data on 4,699 patients with CMML and 38,304 with MDS. The investigators also included data on 1,053,780 patients with breast cancer and 1,082,390 with prostate cancer as comparison groups because these types of cancer aren't associated with *TET2* mutations or other risk factors for heart disease.

Key findings:

- Death rates from heart disease and blood vessel disease were as follows:

Patient Disease	Rate of Death from Heart Disease	Rate of Death from Blood Vessel Disease
CMML	8.6%	1.4%
MDS	10.7%	1.5%
Breast Cancer	6.4%	1.7%
Prostate Cancer	9.9%	2.0%

- Compared with the U.S. general population, the risk of death due to heart disease or blood vessel disease was higher in patients with CMML or MDS.

- The risk of death due to blood vessel disease was higher in the first year after diagnosis with CMML or MDS.

- Although this risk decreased after that first year, it was still two or three times as high as in the overall population for the first 10 years after diagnosis.

Conclusions:

- The high risk of death due to heart or blood vessel disease in the year after CMML or MDS diagnosis suggests that these patients already had heart disease when their bone marrow failure disease was diagnosed.

- The authors recommend that clinicians manage risk factors for cardiovascular disease in these patients.

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Long-Term Survival of Older Patients with MDS Treated with Hypomethylating Agents

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In patients with MDS, a chemical process known as methylation blocks DNA's ability to control cell growth. The hypomethylating agents (HMAs) azacitidine (Vidaza) and decitabine (Dacogen) inhibit methylation so that DNA sequences can act normally. Clinical trials have shown that about half of patients with MDS survive for at least two years with azacitidine treatment. But the long-term survival rates of patients treated with HMAs haven't been formally assessed.

This study evaluated data on 1,187 patients with MDS (median age at diagnosis 77 years; 64% male) who were treated with azacitidine or decitabine. The study included at least 4 years of follow-up data on these patients.

Key findings:

- On average, patients survived for 14 months, and only 12% survived for at least 5 years.
- Patients with refractory anemia with excess blasts, a high-risk type of MDS, survived just 11 months after starting HMA treatment, and only 4% survived for at least 5 years.
- Survival rates were similar for azacitidine and decitabine.
- Patients who needed a red blood cell transfusion during the 8 weeks before starting HMA treatment had a higher risk of death.

Conclusions:

- HMAs are less than ideal for treating MDS in real-world patients.
- The authors recommend that clinicians consider other treatment options, including clinical trials, for patients with MDS.

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Impact of Donor Age on Outcomes of Stem Cell Transplantation

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Nonmyeloablative conditioning is a less intensive chemotherapy treatment, with fewer side effects, to prepare patients with MDS or acute myelogenous leukemia (AML) for stem cell transplantation. Because this conditioning regimen is safe in older patients, more and more stem cell transplants are performed in patients older than 60 years. As a result, the average age of potential donors is also increasing.

This study assessed whether the age of the stem cell donor and the donor's relationship to the patient affects outcomes of nonmyeloablative stem cell transplants in patients treated with cyclophosphamide after transplantation. The study included data on 586 adults and children with AML (28% of patients), MDS (6%), or another form of leukemia or lymphoma.

Key findings:

- Patients who received transplants from younger donors tended to survive longer without a relapse.

- The likelihood of surviving at least 3 years without disease progression was 45% for patients with donors younger than 30 and 37% for patients with donors aged 30 or older.

- The relationship between stem cell donors and patients did not affect rates of survival after 3 years without disease progression: survival rates were 40% for stem cells from parents, 39% for stem cells from siblings, and 39% for stem cells from the patient's children.

Conclusions:

- Transplantation of stem cells from donors younger than 30 with nonmyeloablative conditioning and cyclophosphamide treatment afterward is beneficial.

- The donor's relationship with the patient (sibling, child, or parent) does not affect the patient's survival.

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Immunosuppressive Therapy (IST) for MDS

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Not all patients with lower-risk MDS respond to standard treatments. Even when patients do respond, these treatments often stop working. Therefore, new treatments are needed.

This study assessed the outcomes and predictors of response of immunosuppressive therapy (IST) in 198 patients (median age 65, 63% male) with MDS. These drugs weaken the patient's immune system and stop it from attacking the bone marrow. Most patients (91%) had low-risk or intermediate-1 risk MDS according to the International Prognostic Scoring System.

Key findings:

- In 114 patients with enough data, the overall response rate was 45%.

- Specifically, 13.2 % had a complete remission, 5.3% had a partial response, and 31.6% had improved blood cell counts.

- Another 38.6% of patients had stable disease, and 11.4% had disease progression.

- On average, patients survived about 4 years after starting IST.

- Patients who had a complete response or did not need regular red blood cell transfusions were still alive after 4 years, when the study ended.

Conclusions:

- This study confirmed that about 45% of patients with MDS respond to IST.

- However, this study did not find any markers that seem to have a positive or negative impact on likelihood of responding to IST.

How AAMDSIF Can Help You ...

Many FREE services and programs are available to anyone impacted by, or just interested in, bone marrow failure diseases:

- **Personalized Support** from Information Specialists at (800) 747-2820 or help@aamds.org

- **Educational Materials** on diseases and treatments at www.aamds.org/materials

- **Global Educational Materials** in Spanish, French, German and Portuguese at www.aamds.org/global-education

- **The Online Academy** with 90+ live and recorded educational classes and much more at www.aamds.org/learn

- **Patient and Family Conferences** connecting patients with professionals and building community with each other at www.aamds.org/conferences

- **Print and Electronic Newsletters** with the latest news in treatment and research

- **Clinical Trials Information** at www.aamds.org/clinicaltrials

- **Peer Support Network** staffed by specially-trained volunteers who listen and offer guidance at www.aamds.org/support-networks

- **Community Connections** support groups run by volunteers for fellowship and support

Looking for a way to help?
Volunteer and help raise awareness for bone marrow failure diseases! Your work can directly help newly diagnosed patients and their families. Call 301-279-7202 or email fitzgerald@aamds.org to learn how you can get involved.

- **Online Supporters** who hold digital fundraisers in their community or workplace

- **Event Organizers** who plan "March for Marrow" fundraising walks or other events

- **Awareness Campaigners** who teach their community about bone marrow failure

- **Community Connections** leaders who coordinate local patient support groups

Learn more about volunteering at ambassadors@aamds.org or (301) 279-7202 x122.

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