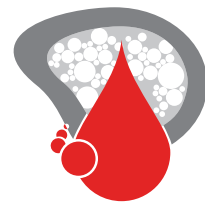


AA&MDSIF

**MDS Research Summary** *from the*  
2015 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

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



**AA·MDS**  
INTERNATIONAL FOUNDATION



The Aplastic Anemia & MDS International Foundation (AA&MDSIF) 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 57<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH) in December 2015. 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.

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**For more information, call us at (800) 747-2820, or visit us online at [www.AAMDS.org](http://www.AAMDS.org).**

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# INTRODUCTION

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Dear Patient or Caregiver,

The purpose of this booklet is to provide you with the most up-to-date information about new research into the biology and treatment of myelodysplastic syndromes (MDS), as presented at the 57<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH) Annual Meeting in December 2015.

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 patients who currently have MDS 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](http://www.clinicaltrials.gov).

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

## **Mikkael Sekeres, MD, MS**

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*The abstracts summarized in this booklet may be viewed on the American Society of Hematology web site at <https://ash.confex.com/ash/2015/webprogram/>. You may type in the abstract number or title in the search box. Any conflicts of interest or other relevant disclosures by the study authors are noted in each abstract.*

## 4 Therapies that Target Mutations in Spliceosomal Genes

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Spliceosomes are groups of proteins involved in splicing together certain sequences in RNA to form messenger RNA molecules. These molecules can then produce proteins that work properly. Patients with MDS and acute myeloid leukemia (AML) often have mutations in the SRSF2, U2AF1, and SF3B1 genes that control RNA splicing.

A previous study had tested the effects of a drug, E7107, that inhibits splicing in mice with SRSF2 mutations. To find out whether these findings can be translated to humans, the researchers compared the effects of E7107 treatment for 10 days in 10 mice that had been injected with cells from 5 patients with AML. Some patients had mutations in spliceosome genes, but others did not.

### Key findings:

- E7107 decreased the number of leukemia cells in all of the cells from the patients who had spliceosome mutations.
- The response of cells that did not have the spliceosome mutations was weaker.

### Conclusions:

- Leukemia cells with spliceosome mutations are more sensitive to drugs that inhibit splicing than cells that don't have these mutations.
- This finding could have important treatment implications for many patients with MDS and AML who have spliceosome mutations

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## Impact of Changes in Gene Mutations During the Course of MDS on Outcomes

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Many patients with MDS and related disorders have acquired mutations (mutations that they didn't inherit from their parents) in certain genes. This study identified genetic lesions and changes in clones (abnormal copies of immature white blood cells) in 718 patients with MDS. The authors studied 97 of these patients at several time points to explore the effects of changes in mutations on outcomes.

### Key findings:

- Clones were larger in patients whose MDS had progressed to acute myelogenous leukemia (AML) or chronic myelomonocytic leukemia than those with MDS.
- More than 80% of patients with low-risk MDS and all patients with AML had several mutations in their clones.
- In the 97 patients studied at different time points, the number of mutations in the PTPN11 gene increased most often, and these mutations were associated with progression to AML.
- Mutations in CBL, NRAS, STAG2, RUNX1, and IDH1 were associated with increasing clone size and evolution into high-risk MDS. Survival of patients with these mutations was much shorter than for the entire group.
- Significant expansions of JAK2, DNMT3A, SRSF2, TP53, U2AF1, and ASXL1 mutations resulted in progression of MDS to AML.
- EZH2, TET2, SF3B1 and PRPF8 mutations were associated with random changes in clone size but not with progression to AML.

### Conclusions:

- A detailed understanding of changes in clones allows new insights into the significance of non-inherited gene mutations.

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## Markers of Prognosis and Prognostic Scoring Systems in Therapy-Related MDS

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The data used to develop the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R) for MDS didn't include MDS cases caused by previous cancer treatments. The usefulness of these scoring systems for treatment-related MDS (tMDS) is therefore not fully understood.

The authors analyzed data on 1,511 patients (median age 68 years) with treatment-related MDS from Spain, Germany, Switzerland, Austria, the United States, Italy, and the Netherlands who had been diagnosed in 1975–2015. On average, 59 months of follow-up data were available on these patients. Some patients had had MDS treatment, but others had not.

### Key findings:

- Features that affected survival and time to progression to acute myelogenous leukemia included IPSS and IPSS-R score, chromosome abnormalities, hemoglobin and platelet counts, and treatment for the initial cancer with alkylating chemotherapy.
- Both the IPSS and IPSS-R did moderately well in treatment-related MDS, but not as well as in primary (not treatment-related) MDS.
- The usefulness of the IPSS and IPSS-R for treatment-related MDS varied by primary cancer and type of treatment for the primary cancer. For example, the IPSS-R did better in patients who had been treated with radiation therapy than those treated with chemotherapy.

### Conclusions:

- The IPSS-R and IPSS can be used for prognosis in patients with treatment-related MDS, although the IPSS-R is a better choice.
- The prognostic power of both scores is lower for treatment-related MDS than for primary MDS.

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## Gene Mutations in Patients with MDS, Associated Disease Features, and Prognosis

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Doctors use the International Prognostic Scoring System (IPSS) and revised IPSS (IPSS-R) to determine the prognosis of patients with MDS. But these systems don't take into account patients' somatic (non-inherited) mutations in genes, even though some of these mutations are associated with specific disease features.

The International Working Group for Prognosis in MDS-Molecular Committee examined the relationship between mutations in genes associated with MDS and outcomes, including survival. The study analyzed samples from 3,392 patients from around the world using next-generation sequencing. The abstract focused on 3,200 patients followed for a median of 3.7 years, including 2,173 patients whose IPSS-R score could be calculated.

### Key findings:

- Mutations in 12 genes were strongly associated with shorter survival: ASXL1, CBL, EZH2, IDH2, NF1, NRAS, PTPN11, RUNX1, SRSF2, STAG2, TP53, and U2AF1.
- Mutations in SF3B1 were associated with longer survival.
- Mutations in U2AF1 and ASXL1 were associated with shorter survival.
- Mutations in TP53, CBL, EZH2, and RUNX1 were associated with a poorer prognosis, regardless of the patient's IPSS-R score.
- Patients who didn't have mutations in TP53, CBL, EZH2, RUNX1, U2AF1, or ASXL1 survived longer (median of 4.8 years) than patients with any of these mutations (1.6 years), even after IPSS-R scores were taken into account.

### Conclusions:

- Several MDS-associated genes are useful for prognosis, even after IPSS-R scores are taken into account.
- Certain mutations could be used to refine prognostic scoring systems.

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### Eltrombopag for Low-Risk and Intermediate-1-Risk MDS

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About 10% of patients with low-risk MDS have severe thrombocytopenia (platelet shortage). These patients sometimes have severe bleeding. Eltrombopag (Promacta®) stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow, which increases the number of platelets and decreases bleeding risk.

The authors present interim results of a Phase 2 clinical trial. This trial is comparing the efficacy and safety of eltrombopag to placebo in 70 patients (average age 68.3 years, 32 women) with low-risk or intermediate-1-risk MDS who have severe thrombocytopenia.

#### Key findings:

- 23 patients (50%) treated with eltrombopag had higher platelet counts compared to 2 (8%) of those treated with placebo.
- In the 33 patients who had completed at least 24 weeks of the study, median time to response was 14 days.
- Platelet count increased by an average of 53.2 Gi/L in patients in the treatment group and did not change significantly in the placebo group by week 24
- Patients who responded to treatment had less fatigue than before treatment.
- 10 patients treated with eltrombopag had severe or life-threatening adverse effects, including nausea, high levels of liver enzymes, and heart failure. Only 1 patient (4%) in the placebo group had a severe side effect, scarring in the bone marrow.
- MDS progressed to acute myelogenous leukemia (AML) in 5 patients (11%) in the treatment group and 2 (8%) in the placebo group.

#### Conclusions:

- Eltrombopag increases platelet counts and decreases fatigue in patients with lower-risk MDS who have severe thrombocytopenia.
- The drug appears to be well-tolerated and not associated with MDS progression to AML.



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## Luspatercept Treatment in Patients with Low or Intermediate-1 Risk MDS

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Luspatercept is an experimental treatment that increases red blood cell counts. Studies are assessing luspatercept in patients with anemia whose bone marrow doesn't form enough healthy red blood cells, including patients with MDS.

The authors report on an ongoing phase 2 clinical trial that is evaluating the long-term effects of luspatercept on anemia in patients with low-risk or intermediate-1-risk MDS. This analysis focused on 22 patients (median age 70.5 years) who had been treated once every three weeks for up to 24 months.

### Key findings:

- Treatment with luspatercept increased hemoglobin levels in 8 of 9 patients (89%) with a low transfusion burden (needing less than 4 red blood cell units every 8 weeks).
- Ten of 13 (77%) patients with a high transfusion burden (needing 4 or more red blood cell units every 8 weeks) needed fewer transfusions after they started luspatercept treatment.
- Of the 14 patients who were transfused with at least two red blood cell units over 8 weeks before starting treatment, 6 (43%) stopped needing transfusions for at least 8 weeks.
- The treatment didn't result in any major adverse effects.

### Conclusions:

- Luspatercept treatment led to increased hemoglobin levels
- For most patients, the treatment decreased transfusion requirements or allowed them to stop needing transfusions.

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## Low-Dose Hypomethylating Agents in Patients with Low- or Intermediate-1-Risk MDS

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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®) remove the methyl groups that attach to DNA so that DNA sequences can act normally. HMAs improve survival of patients with higher-risk MDS, but their role is less clear in patients with lower-risk MDS.

This study tested the safety and efficacy of low doses of HMA therapy in 83 patients with low- or intermediate-1-risk MDS according to the International Prognostic Scoring System. Patients were treated with azacitidine or decitabine for 3 days per 28-day cycle.

### Key findings:

- The overall improvement rate for the entire group of patients was 61%.
- Of the 83 patients in the analysis, 32 (39%) achieved a complete remission, 11 (13%) achieved remission with insufficient recovery of blood cell counts, and 8 (10%) had increased blood cell counts.
- Of the 38 patients who needed regular red blood cell transfusions at the start of the study, 9 (24%) stopped needing transfusions.
- Patients tolerated the drugs well, and only 6 patients (7%) needed a lower dose and 19 (23%) needed to delay a dose.
- After 1 year, 86% of patients had survived. Four patients (5%) developed acute myelogenous leukemia, and 17 (20%) died.

### Conclusions:

- Patients with low- and intermediate-1-risk MDS tolerated low-dose HMA therapy well.

## 1665

### Outcomes of Patients with Lower-Risk MDS Who Don't Respond to Anemia Treatment

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The first treatment for patients with lower-risk MDS is often an erythropoietin-stimulating agent (ESA). ESAs can treat anemia and reduce the need for red blood cell transfusions. About half of these patients respond to ESA treatment. Other ("second-line") treatments are used in patients with ESA failure (meaning that they don't respond to ESAs or their disease progresses on ESA treatment). But the effects of these treatments on survival isn't known.

This study collected data on 1,611 patients from France, Italy, Spain, Greece, and Germany who had lower-risk MDS had been treated with ESAs. The researchers assessed outcomes in patients with ESA failure and the effects of second-line treatments on survival.

### Key findings:

- The 1,038 patients with ESA failure survived for a median of 4 years.
- Among the 336 (32%) patients who received a second-line treatment other than red blood cell transfusions, response rates were 46% for azacitidine (Vidaza®) or decitabine (Dacogen®), 39% for lenalidomide (Revlimid®), and 33% for other treatments (including chemotherapy and thalidomide).
- Median overall survival didn't differ significantly by type of second-line treatment.
- Median overall survival was 4.2 years in patients who had a relapse with ESA treatment and 3.7 years in patients who never responded to ESAs.

### Conclusions:

- Overall survival after ESA failure was similar in patients who never responded to ESAs and those who had a relapse after ESA treatment.
- None of the second-line treatments had a better effect on overall survival than best supportive care.

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## Pracinostat Combined with Azacitidine for Previously Untreated MDS

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Histone deacetylase (HDAC) inhibitors are a class of cancer drugs that interfere with DNA's ability to express and repress gene activity by inhibiting the enzyme HDAC. In this way, HDAC inhibitors stop tumor cells from dividing.

This study evaluated a combination of pracinostat, an HDAC inhibitor, and azacitidine (Vidaza®) in 102 patients (median age 69, 69% male) with intermediate-2-risk or high-risk MDS. Patients were randomly assigned to treatment with azacitidine (75 mg/m) for 7 days per 28-day cycle with or without pracinostat (60 mg 3 days per week for 3 weeks) or placebo. When the interim report was written, patients had completed six cycles of treatment.

### Key findings:

- 18% of patients treated with azacitidine plus pracinostat responded to treatment, compared with 31% of those treated with azacitidine plus placebo.
- Those treated with the combination therapy survived without disease progression for 10.7 months, on average, compared to 9.2 months for those treated with azacitidine alone.
- 26% of those treated with the combination stopped their treatment because of adverse effects, whereas only 10% of those treated with azacitidine alone did this.
- Severe side effects included lower platelet counts, low white blood cell counts with fever, and fatigue.

### Conclusions:

- Pracinostat didn't increase the effectiveness of azacitidine in patients with higher-risk MDS.
- The reason for this finding is probably that more patients in the combination group left the study.
- However, patients might benefit from pracinostat if they can tolerate it for at least four cycles.

# OUTCOME AND RESPONSE

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## Using Genomics to Explain Reasons for Resistance to Azacitidine Therapy in MDS and CMML

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Azacitidine (Vidaza®) is the main treatment for high-risk MDS and chronic myelomonocytic leukemia (CMML). Patients who respond to azacitidine survive longer than those who don't respond. But only half of patients respond to azacitidine, and few treatments are available for those who don't respond. Also, a large proportion of patients who do respond to azacitidine eventually have a relapse.

The authors explored these issues in bone marrow samples from 18 patients in Australia who had high-risk MDS or CMML. They collected the bone marrow at seven different times over up to two years after patients started azacitidine treatment.

### Key findings:

- Ten patients had a complete response to azacitidine treatment, and 8 did not respond well.
- Responders and non-responders had differences in the expression of 1,148 genes.
- Genes involved in cell division and responses to DNA damage had higher levels of expression (formation of messenger RNA to create proteins) in responders than in non-responders.
- Even responders to azacitidine continued to form abnormal clones, or copies of immature white blood cells. The cause was gene mutations in some immature blood cells that did not respond to azacitidine.

### Conclusions:

- The continuing formation of abnormal clones in patients who respond to azacitidine treatment might explain why these patients eventually have a relapse.
- The findings could be used to identify azacitidine non-responders early and to suggest combination treatments that might increase response rates.

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## Impact of Non-Inherited Mutations on MDS after Stem-Cell Transplantation

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Hematopoietic stem cell transplant (HSCT) is the only potential cure for MDS. However, the procedure is risky, and patients sometimes develop major adverse effects or even die. Several prognostic scoring systems are being used to choose the right patients for HSCT, but these systems are based on data from patients whose MDS had never been treated. So these prognostic scoring systems might not be useful for patients with MDS who undergo HSCT.

The authors analyzed data from 719 patients (median age 53 years) with MDS in Japan who were treated by HSCT from unrelated donors between 2006 and 2013. They assessed mutations in 68 genes.

### Key findings:

- Patients who had at least one genetic mutation or abnormal number of copies of at least one gene (especially TP53, NRAS, ETV6, CBL, EZH2, KRAS, U2AF2, JARID2, and RIT1) did not survive as long as those who didn't have these abnormalities.
- Patients with mutations in PRPF8 survived longer than those who didn't have this mutation.
- The factors most associated with poor survival were a combination of TP53 mutations, complex karyotype (abnormalities in several chromosomes), high-grade graft-versus-host disease, and number of red blood cell transfusions received before HSCT.
- Patients with mutations in one or more genes were more than twice as likely to have a relapse. However, those with mutations in TP53, NRAS, ETV6, PRPF8, and WT1 were less likely to have a relapse.
- The factors associated with relapse were mutations in ETV6 or WT1, complex karyotype, high-risk MDS, and high-grade graft-versus-host disease.

### Conclusions:

- Non-inherited mutations in several genes could be used to predict length of survival and likelihood of relapse.
- This information could be used to guide treatment decisions for people with MDS.

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## Validation of International Working Group Response Criteria in Higher-Risk MDS

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The main goal of treatment for higher-risk MDS is to increase survival and delay the progression of MDS to acute myeloid leukemia (AML).

Doctors and researchers use the International Working Group's (IWG's) 2006 response criteria to assess the efficacy of MDS therapies.

The aim of this study was to assess the IWG 2006 response criteria in 646 patients with higher-risk MDS who had been treated for their MDS, usually with azacitidine (Vidaza®) or decitabine (Dacogen®).

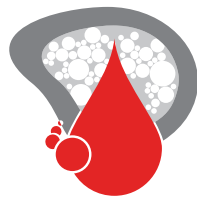
### Results

- The best responses among 597 patients whose data could be evaluated were complete response (disappearance of all signs of MDS) in 93 patients (16%), complete response in bone marrow in 10 patients (2%), partial response in 57 patients (10%), improved blood cell counts in 60 patients (10%), stable disease in 233 patients (39%), and disease progress in 144 patients (24%).

- Median survival was 41 months for patients with a complete response, 12 months for marrow complete response, 26 months for partial response, 13 months for improved blood cell counts, 14 months for stable disease, and 7 months for disease progression.
- Of patients treated with azacitidine or decitabine, 15% achieved a complete response, 2% had a marrow complete response, 10% had a partial response, 12% had improved blood cell counts, 40% had stable disease, and 21% had disease progression.
- The best response by IWG 2006 criteria predicted overall survival after the investigators took revised International Prognostic Scoring system scores into account.

### Conclusions:

- The best response by IWG 2006 criteria to initial therapy in higher-risk MDS correlates with overall survival.
- A complete response by IWG 2006 response criteria can be as a marker of overall survival in patients with higher-risk MDS in randomized Phase II clinical trials, can be used to create comparison arms of Phase III trials, and for regulatory purposes.



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