MDS Research Review | 2013

A Summary of Selected Scientific Abstracts for Patients with Myelodysplastic Syndromes (MDS) and their Caregivers
The Aplastic Anemia & MDS International Foundation is an independent nonprofit 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 abstracts presented at major hematology/oncology scientific meetings in the past year and contains some of the most up-to-date information about new research into the biology and treatment of myelodysplastic syndromes (MDS).

- **American Society of Hematology (ASH), December 2012**
  The American Society of Hematology (ASH) is the world's largest professional society concerned with the causes and treatments of blood disorders.

- **American Society of Clinical Oncology (ASCO), June 2013**
  ASCO is a professional association of physicians in all oncology subspecialties who care for people with cancer.

- **European Hematology Association (EHA), June 2013**
  The European Hematology Association (EHA) promotes excellence in clinical practice, research, and education in European hematology.

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 only 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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Dear Patient or Caregiver,

The purpose of this abstract summary 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 major hematology and oncology scientific meetings in in the last year.

- American Society of Hematology (ASH), December 2012
- American Society of Clinical Oncology (ASCO), June 2013
- European Hematology Association (EHA), June 2013

These are the world's largest meetings of hematologists and hematological oncologists – i.e., doctors who care for patients with blood disorders or blood and bone marrow cancers and are 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” – i.e., a brief summary of the study and its results. Authors of the most interesting and noteworthy abstracts are asked by conference organizers to present their research in more detail, either in the format of a tacked-up poster with text and illustrations or an oral (podium) presentation.

We selected the abstracts in this summary because we feel they are the most relevant and important for MDS patients to know about. By reviewing the information presented in the booklet, we hope you will:

- Learn how ongoing research on MDS may affect the diagnosis, treatment, and prognosis of patients in the near term as well as the more distant future
- Understand how researchers are approaching the most promising areas of MDS therapy
- Learn about the importance of clinical trials in identifying novel therapies for MDS
- Know the most important issues about MDS which you may want or need to understand and to ask your health care providers about as part of your ongoing treatment

Please note that the research results discussed at these meetings often involve experimental drugs that are not yet approved for general use by the U.S. Food and Drug Administration (FDA) 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 to with your doctor about clinical trials or to visit www.clinicaltrials.gov.

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

David P. Steensma, MD, FACP
Dana-Farber Cancer Institute
Member, AA&MDSIF Medical Advisory Board
### Insights into Disease Biology

ASH 311: Detection of Recurrent Mutations by Pooled Targeted Next-Generation Sequencing in MDS Patients Prior to Treatment with Hypomethylating Agents or Stem Cell Transplantation

### Diagnosis and Classification

ASH 700: Prognostic Relevance of the Kinetics of Worsening of Cytopenias in Lower-Risk MDS: A Substudy from the European Leukemianet Low-Risk MDS (EUMDS) Registry

### Existing and Emerging Treatments

ASCO 7002: A Randomized Study of Lenalidomide (LEN) With or Without EPO in RBC Transfusion Dependent (TD) IPSS Low and Int-1 (Lower Risk) Myelodysplastic Syndromes (MDS) Without Del 5q Resistant to EPO

ASCO 7031: Phase II Study of Orally Administered Rigosertib (ON 01910.Na) in Transfusion-Dependent Lower-Risk Myelodysplastic Syndrome (MDS) Patients

ASCO 7116: A Phase II Study of Mocetinostat, an Oral Isotype-Selective Histone Deacetylase (HDAC) Inhibitor, in Combination with 5-Azacitidine in Patients with Myelodysplastic Syndrome (MDS)

ASH 421: Treatment with the Thrombopoietin (TPO)-Receptor Agonist Romiplostim in Thrombocytopenic Patients (Pts) with Low or Intermediate-1 (int-1) Risk Myelodysplastic Syndrome (MDS): Follow-up AML and Survival Results of a Randomized, Double-Blind, Placebo (PBO)-Controlled Study

ASH 424: Safety and Efficacy of Oral Azacitidine (CC-486) Administered in Extended Treatment Schedules to Patients with Lower-Risk Myelodysplastic Syndromes

ASH 425: Deferasirox Chelation Therapy in Transfusion Dependent MDS Patients. Final Report From the Gimena MDS0306 Prospective Trial

ASH 923: Efficacy and Safety of Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Interim Analysis of a Prospective, Randomized, Single-Blind, Placebo-Controlled Trial (EQoL-MDS)
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### Predicting Treatment Response

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### Patient Outcomes and Quality of Life (QoL)

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Detection of Recurrent Mutations by Pooled Targeted Next-Generation Sequencing in MDS Patients Prior to Treatment with Hypomethylating Agents or Stem Cell Transplantation

Rafael Bejar, Kristen E. Stevenson, Petar Stojanov, J. Eric Zaneveld, Michal Bar-Natan, Bennett Caughey, Hui Wang, Guillermo Garcia-Manero, Hagop M. Kantarjian, Corey Cutler, Jerome Ritz, Kristian Cibulskis, Gad Getz, David P. Steensma, Richard M. Stone, Rui Chen, Donna S. Neuberg and Benjamin L. Ebert

Myelodysplastic syndromes (MDS) affect different patients in different ways. Researchers are discovering some genetic mutations, or changes, that explain some of these differences. Researchers recently used next-generation sequencing to identify genetic mutations in DNA from two groups of MDS patients before their MDS treatment. The first group (Cohort 1) consisted of 200 patients who were treated with Vidaza® (azacitidine), Dacogen® (decitabine), or both azacitidine and decitabine. The 76 patients in Cohort 2 underwent a stem cell transplant. The researchers focused on 74 genes, including all genes known to be mutated in people with MDS. They excluded any genetic mutations found in at least 1% of the general population.

Key Findings:

• The most common mutations in Cohort 1 were in the ASXL1 (39% of patients), SF3B1 (24%), TET2 (23%), RUNX1 (19%), SRSF2 (18%), and DNMT3A (15%) genes.
• The most common mutations in Cohort 2 were in the ASXL1 (25% of patients), TP53 (22%), DNMT3A (17%), and RUNX1 (14%) genes.
• In Cohort 2, 37% of patients had a mutation in a splicing factor gene (SF3B1, U2AF1, SRSF2, or ZRSR2). These genes help cells splice together certain DNA sequences as part of the protein-formation process.

• A larger proportion of patients in Cohort 2 than Cohort 1 had a genetic mutation associated with a poor prognosis (especially TP53). Also, fewer Cohort 2 patients had a genetic mutation associated with a neutral or favorable prognosis (such as SF3B1 and TET2).

Conclusions:

• Next-generation sequencing can be used to identify genetic mutations associated with MDS in most MDS patients.
• Information on individual genetic mutations in patients with MDS might be useful for predicting which patients will respond to certain treatments.

What This Means For Patients

Our motivation was understanding MDS as a genetic disease. These are genetic mutations that patients are not born with, but are acquired and they generally change the way the cells behave. We’re getting more insight into what the potential spectrum of mutations could be for MDS, and we know that some mutations have different effects than others.

As we learn about the patterns of mutations in MDS and how they relate to different therapeutic options, we are going to learn more about genetic testing used to help us understand how to treat MDS, and what to tell our patients who have these disorders.

Rafael Bejar, MD, PhD
University of California, San Diego
Many doctors use the International Prognostic Scoring System (IPSS) to evaluate each patient’s myelodysplastic syndromes (MDS) and select appropriate therapy. But the prognosis of patients with a low or intermediate-1 IPSS score can vary widely. One reason might be that the IPSS and other MDS prognostic systems rely on patient information from only one point in time.

Researchers analyzed data on 530 patients with MDS from the European MDS Registry to find out whether changes in some of their blood test results could be useful for prognostic purposes. All of the patients had a low or intermediate-1 IPSS score, and blood test results were available from at least three visits over at least 12 months. None of the patients had been treated with a hypomethylating agent (such as Vidaza® [azacitidine] or Dacogen® [decitabine]), a granulocyte colony-stimulating factor, Hydrea®), (hydroxyurea) or Revlimid® (lenalidomide). Patients’ median age was 73 years, and 59% were male.

**Key Findings:**

- Patients with slower drops in absolute neutrophil counts (ANC) and platelet counts survived longer than patients with more rapid drops in these blood cell counts.
- Rates of overall survival did not differ in patients whose hemoglobin counts dropped more quickly or more slowly.
- The pace of change in ANC, platelet, and hemoglobin counts was not related to patient age, score on the IPSS or other MDS prognostic systems, or abnormal chromosomes.

**Conclusions:**

- Faster drops in ANC and, to a lesser extent, platelet counts, are associated with shorter survival regardless of the patient’s score on the IPSS, Revised IPSS, or World Health Organization classification-based prognostic scoring system.
- The rate of changes in hemoglobin counts is not related survival, possibly because patients with low hemoglobin counts are often treated with blood transfusions or erythropoiesis-stimulating agents.
- In patients with lower-risk MDS, doctors can use the rate of ANC and platelet count declines to predict the course of the disease.
EXISTING AND EMERGING TREATMENTS

ASCO 7002
A Randomized Study of Lenalidomide (LEN) With or Without EPO in RBC Transfusion Dependent (TD) IPSS Low and Int-1 (lower-risk) Myelodysplastic Syndromes (MDS) Without Del 5q Resistant to EPO

Andrea Toma, Sylvie Chevret, Olivier Kosmider, Jacques Delaunay, Aspasia Stamatoullas, Christian Rose, Odile Beyne-Rauzy, Anne Banos, Agnes Guercy-Bresler, Eric Jourdan, Veronique Sardnal, Denis Caillot, Kamel Laribi, Benoît De Renzis, Dominique Bordessoule, Borhane Slama, Laurence Sanhes, Michaela Fontenay, Pierre Fenaux, Francois Dreyfus

Erythropoiesis-stimulating agents (ESAs) are used as first-line treatment for anemia in patients with lower-risk myelodysplastic syndromes (MDS) who do not have 5q- syndromes. But only about 40–50% of these patients respond to ESAs. Lenalidomide (Revlimid®) can eliminate the need for red blood cell transfusions in about 25% of patients with lower-risk MDS who do not have 5q-syndrome, need regular transfusions, and do not respond to ESAs or start needing transfusions again after ESA treatment.

A group of researchers from France reported results from a multicenter, open-label, Phase II clinical trial that compared lenalidomide to lenalidomide plus erythropoietin, an ESA. The study included 132 patients with lower-risk MDS without 5q- syndrome who had needed at least four red blood cell units over the previous eight weeks. These patients had not responded to ESAs or had started needing transfusions again after ESA treatment. Their median age was 73, and about one third of patients were female.

Key Findings:

- Counts of erythrocytes (a type of red blood cell) improved in 15 patients (23%) in the lenalidomide group and 26 (40%) in the lenalidomide/erythropoietin group.
- In the 99 patients who finished four treatment cycles, 15 patients (31%) in the lenalidomide group had improved erythrocyte counts compared to 26 (52%) in the lenalidomide/erythropoietin group.
- In these 99 patients, nine patients (18%) in the lenalidomide group and 16 (32%) in the lenalidomide/erythropoietin group stopped needing regular red blood cell transfusions.
- Side effects were similar in the two groups.
- An expression profile of 29 genes and a polymorphism (variant) in the CRBN gene correlated with erythrocyte responses.

Conclusions:

- The combination of lenalidomide and erythropoietin had a better effect on erythrocyte counts than lenalidomide alone in people with lower-risk MDS who did not have 5q- syndrome and whose anemia did not respond to ESAs alone.

ASCO 7031
Phase II Study of Orally Administered Rigosertib (ON 01910.Na) in Transfusion-Dependent Lower-Risk Myelodysplastic Syndrome (MDS) Patients

Azra Raza, Siddhartha Mukherjee, Andrew Eisenberger, J. Gregory Mears, Francois Wilhelm

Rigosertib (Estybon®) is a small-molecule inhibitor of pathways that plays important roles in the growth and proliferation of cancerous cells. An earlier clinical trial had shown that when the drug is taken by mouth, it is well absorbed and has activity in patients with myelodysplastic syndromes (MDS) who need regular blood transfusions.

Researchers reported preliminary data from an ongoing multicenter Phase II clinical trial of rigosertib. This study is enrolling adults with MDS that has relapsed or who are resistant.
EXISTING AND EMERGING TREATMENTS

to the hypomethylating agents azacitidine or decitabine. Patients are treated with oral rigosertib either intermittently (every day for two weeks, followed by a week off) or continuously. Patients who have had transfusions with at least four units of red blood cells in the past eight weeks can continue to have blood transfusions and be treated with erythocyte-stimulating agents (ESAs) while they are in the study. As of December 17, 2012, the study had recruited 29 patients with MDS. Of these patients, 25 had intermediate-1 and 4 had low-risk MDS according to the International Prognostic Scoring System.

Key Findings:
- In general, patients tolerated oral rigosertib well.
- Five of nine patients in the continuous dosing arm had moderate to severe urinary side effects (such as painful urination or bloody urine). So the investigators switched all of the patients to the intermittent dosing schedule, which sharply reduced urinary side effects.
- In the 15 patients who had intermittent treatment for at least eight weeks, 7 (47%) stopped needing red blood cell transfusions.
- Six of the patients who responded to intermittent treatment had not responded to earlier ESA treatment. Five of these patients were treated with ESAs while they were in the rigosertib study, suggesting that rigosertib might lower ESA resistance.

Conclusions:
- Intermittent dosing of rigosertib administered orally is well tolerated.
- The treatment produces transfusion independence in approximately 50% of patients with lower-risk MDS who need regular blood transfusions.

ASCO 7116
A Phase II Study Of Mocetinostat, an Oral Isotype-Selective Histone Deacetylase (HDAC) Inhibitor, in Combination With 5-Azacitidine In Patients with Myelodysplastic Syndrome (MDS)

Selina M. Luger, Casey Lee O’Connell, Virginia Klimek, Maureen A. Cooper, Emmanuel C. Besa, James M. Rossetti, Gregory K. Reid, Rachel Humphrey, Robert E. Martell, Guillermo Garcia-Manero

Mocetinostat (MGCD0103) is a histone deacetylase (HDAC) inhibitor that interferes with certain genetic changes involved in myelodysplastic syndromes (MDS). Preclinical studies have shown that mocetinostat has activity when used alone or in combination with hypomethylating agents (such as azacitidine [Vidaza®]) to treat blood-related cancers and solid tumors.

This open-label, Phase II clinical trial enrolled patients with MDS or acute myelogenous leukemia. Patients were treated with both mocetinostat, which they took by mouth, and azacitidine administered subcutaneously (under the skin). This report focuses on the patients with MDS. Of the 28 patients with MDS, 18 (64%) had intermediate- or high-risk MDS based on the International Prognostic Scoring System. Half had been treated for their MDS in the past, but none had been treated with azacitidine before. The patients’ median age was 72 years, and half were male.

Key Findings:
- Seventeen patients (61%) responded to the combination treatment: ten patients (50%) had a complete response and seven had improved blood cell counts.
- Of 22 patients who had needed regular red blood cell transfusions before the study, eight (36%) stopped needing transfusions.
- Median overall survival was 13 months.
• The most common severe side effects were fatigue, nausea, diarrhea, and vomiting.

Conclusions:
• The combination of mocetinostat and 5-azacitidine in patients with MDS had an acceptable safety profile.
• This study provides encouraging evidence that the combination treatment has clinical benefit in MDS.

What This Means For Patients
This intriguing study suggests activity of a combination of two drugs targeting pathways known to be involved in the development of myelodysplastic syndromes. The combination approach seems rational scientifically, given that these two pathways tend to recruit one another. This study provides some early clinical confirmation that our scientific understanding of these diseases can be translated into the clinical setting. Importantly, the combination of these two agents appears to be relatively safe and also potentially active even in patients who have received prior therapy. This trial will encourage further study of combined agents given the complex biology of MDS.

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Hagop M. Kantarjian, Ghulam J. Mufti, Pierre Fenaux, Mikkael A. Sekeres, Jeffrey Szer, Uwe Platzbecker, Andrea Kuendgen, Gianluca Gaidano, Wieslaw Witkor-Jedrzejczak, John M. Bennett, Anne Meibohm, Allen S. Yang, and Aristoteles Giagounidis

Patients with low-risk or intermediate 1-risk myelodysplastic syndromes (MDS), according to the International Prognostic Scoring System, sometimes have severe thrombocytopenia (platelet shortage). Romiplostim (Nplate®) is a protein used to treat low platelet counts. An international group of researchers completed a 58-week Phase 3 clinical trial of romiplostim in 250 patients with lower-risk MDS and thrombocytopenia. Two-thirds of the patients were treated with romiplostim and the other third with placebo. Patients were followed for 18 months, on average, after the treatment period ended.

Key Findings:
• At the end of the 58-week treatment period:
  • 18% of patients in the romiplostim group and 21% of those in the placebo group had died.
  • 20% of patients in the romiplostim group and 23% of those in the placebo group had survived without developing acute myelogenous leukemia (AML).
• Among patients followed beyond 58 weeks
  • 38% of those in the romiplostim group and 37% of those in the placebo group had died.
  • 40% of patients in the romiplostim group and 39% of those in the placebo group had survived without developing AML.
  • 31% of patients in the romiplostim group and 23% of those in the placebo group had been treated for MDS.
EXISTING AND EMERGING TREATMENTS

- 6% of patients in the romiplostim group and 7% of those in the placebo group had been treated for AML.

Conclusions:
- The researchers are continuing to analyze follow-up data from this study.
- The team is still studying the risk of progression to AML among study participants.

What This Means For Patients

This study randomized patients with lower-risk MDS and a low platelet count to receive the drug romiplostim, a growth factor that stimulates platelet production, or a placebo. The study was stopped early due to concerns that there may be a higher rate of leukemia in patients receiving romiplostim compared to patients receiving placebo. In this updated analysis, investigators found that, with longer follow-up, the rate of patients who developed leukemia was similar, and low, in both treatment groups. Survival was also similar in both groups. The authors concluded that romiplostim appears safe in lower-risk MDS patients who do not have excess blasts in their bone marrow, but should not be administered to patients with excess blasts.

Mikkael Sekeres, MD, MS
Cleveland Clinic Taussig Cancer Institute Member, AA&MDSIF Medical Advisory Board

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Treatment for myelodysplastic syndromes (MDS) often involves the use of hypomethylating agents that kills unhealthy cells in bone marrow. Vidaza® (azacitidine), a hypomethylating agent, is the current standard treatment for high-risk MDS. Azacitidine is typically injected under the skin (subcutaneously) or into a vein (intravenously) once a day for seven days, and the cycle is repeated every four weeks.

Researchers are studying a new, oral version of azacitidine in a multicenter, Phase 1 clinical trial. This trial is enrolling patients with lower-risk MDS who need regular red blood cell transfusions, have thrombocytopenia (low platelet count), or both. At the time this report was written, 53 patients had been treated with 1 to 12 oral azacitidine cycles. The 26 patients in Group 1 (average age 73 years) were treated with 300 mg oral azacitidine once a day for 14 days in repeated 28-day cycles. Group 2 (average age 70 years) was treated with the same dose every day for 21 days in repeated 28-day cycles.

Key Findings:
- 39% of Group 1 and 30% of Group 2 responded to the treatment.
- 47% of Group 1 and 33% of Group 2 did not need red blood cell transfusions for 56 days.
- Six patients (three in each group) dropped out of the study because of side effects that might have been related to the treatment.
- Response rates among the 33 patients treated with at least four cycles of oral azacitidine were 47% in Group 1 and 50% in Group 2.

Conclusions:
- Oral azacitidine in 300 mg daily doses over 14 or 21 days of repeated 28-day cycles was effective and well tolerated in patients with lower-risk MDS in this study.
- Outcomes were similar in patients treated over 14 or 21 days of repeated 28-day cycles.

ASH 424
Safety and Efficacy of Oral Azacitidine (CC-486) Administered in Extended Treatment Schedules to Patients with Lower-Risk Myelodysplastic Syndromes

Guillermo Garcia-Manero, Steven D. Gore, Suman Kambhampati, Bart L Scott, Ayalew Tefferi, Christopher R Cogle, William Edenfield, Joel Hetzer, Keshava Kumar, and Barry S. Skikne
• The most common side effects were gastrointestinal and were manageable.
• Oral azacitidine should be studied further in randomized clinical trials.

What This Means For Patients

This study continues the development of an oral formulation of azacitidine. Patients with lower risk MDS, but who were transfusion dependent and had low platelets received a variety of schedules of oral azacitidine. Azacitidine may exert its activity through reversal of a chemical modification of DNA known as methylation. In order to reverse DNA methylation, administration of lower doses of azacitidine for prolonged periods of time may be more effective. This study examined such schedules of oral azacitidine and appeared to have significant activity. This study has led to the development of a Phase III trial in similar patients randomizing between oral azacitidine and placebo. If the oral azacitidine has significant activity in the Phase III trial, this will likely lead to application to the FDA for the approval of oral azacitidine.

Steven Gore, MD
Sidney Kimmel Comprehensive Cancer Center Member, AA&MDSIF Medical Advisory Board

Patients with myelodysplastic syndromes (MDS) who have had many red blood cell transfusions often develop high levels of iron, known as iron overload, because red blood cells carry iron. Iron overload can damage the body’s tissues and organs. The U.S. Food and Drug Administration has approved deferasirox (Exjade®) to treat iron overload in patients with MDS who need regular blood transfusions. But the approval was based on limited data from patients with MDS. A research team from Italy completed a 12-month clinical trial of deferasirox in 152 patients (96 men and 56 women, average age 72 years) with lower-risk MDS. These patients had been undergoing regular blood transfusions for 21 months, on average.

Key Findings:

• 68 patients (45%) completed the 12 months of treatment.
• Average blood iron levels decreased significantly during the study, from 1,966 ng/ml to 1,475 ng/ml.
• The average number of blood transfusions dropped from three per month at the start of the study to one per month after a year.
• 22 patients stopped needing regular blood transfusions.
• At 12 months, MDS progressed in 13% of patients, and 25% had died.
• 66 patients (43%) had a side effect that might have been or was definitely related to the deferasirox treatment. These side effects were severe in 11 patients (7%).

Conclusions:

• Deferasirox was effective in lowering blood iron levels and reducing the need for regular blood transfusions in a substantial proportion of patients.
EXISTING AND EMERGING TREATMENTS

ASH 923
Efficacy and Safety of Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Interim Analysis of a Prospective, Randomized, Single-Blind, Placebo-Controlled Trial (EQoL-MDS)

Esther Natalie Oliva, Valeria Santini, Gina Zini, Giuseppe A Palumbo, Antonella Poloni, Agostino Cortelezzi, Maria Teresa Voso, Alfredo Molteni, Grazia SanpaoLo, Antonio Marino, Filippo Rodà, Caterina Alati, Francesca Ronco, Francesco Di Raimondo, Pietro Leoní, Giuliana Alimena, Silvia Finotto, Roberto Latagliata, and Francesco Nobile

Patients with low-risk or intermediate 1-risk myelodysplastic syndromes (MDS), according to the International Prognostic Scoring System, sometimes have severe thrombocytopenia (platelet shortage). Platelet transfusions can help, but their effects aren’t long lasting and some patients stop responding to them. Eltrombopag (Promacta®) is an alternative to platelet transfusions. This drug stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow. A team of researchers from Italy is conducting a Phase 2 clinical trial of eltrombopag in patients with low-risk MDS. They reported on the results in the first 17 patients (average age 64 years). Of these patients, ten were treated with eltrombopag and seven with placebo.

Key Findings:

- After six months, on average, five patients in the eltrombopag group had achieved a complete remission, meaning that their platelet counts had returned to normal.
- Platelet counts did not change in the placebo group.
- After two months, none of the patients in the eltrombopag group had any serious bleeding, but three patients in the placebo group had bleeding.
- None of the patients in the eltrombopag group and three patients in the placebo needed platelet transfusions.
- Quality of life improved significantly in the eltrombopag group, but not in the placebo group.
- None of the patients in the eltrombopag group had any serious treatment-related side effects.

Conclusions:

- Preliminary results suggest that eltrombopag raises platelet counts, reduces the risk of bleeding, and improves quality of life in patients with low-risk and intermediate-1 risk MDS.
- Eltrombopag seems to be safe in patients with lower-risk MDS.

EHA 3339
Outcomes of Intermediate or High Risk Myelodysplastic Syndromes (MDS) Patients Post Azacitidine and/or Decitabine Treatment Failures with SGI-110, a Novel Second Generation Hypomethylating Agent (HMA)

Casey O’Connell, Raoul Tibes, Katherine Walsh, David Rizzieri, Karen Yee, Wendy Stock, Hagop Kantarjian, Michael Savona, Elizabeth Griffiths, Patricia Kropf, Jean Pierre Issa, Sue Naim, Yong Hao, Lynne Buí, Gavin Choy, Mohammad Azab, Gail Roboz

SGI-110, an investigational drug, is an inactive version of decitabine (Dacogen®) that the body converts to decitabine. The decitabine that SGI-110 releases stays in the body longer than standard decitabine. This study was designed to find the right dose of SG-110 for treating MDS and to evaluate the drug’s safety.

The study included 15 patients with intermediate-risk or high-risk MDS and one patient with chronic myelomonocytic leukemia.
Patients' median age was 74 years. On average, patients had been treated with two different therapies, and all of the patients had been treated with decitabine and/or azacitidine in the past. Patients were treated with 3 to 125 mg/m² of SGI-110 by injection once daily for five consecutive days or once a week for three weeks.

**Key Findings:**
- Five patients (33%) responded to the treatment, and their responses lasted for up to 224 days.
- The most effective dose was 60 mg/m² once daily for five consecutive days.
- Patients tolerated the SGI-110 treatment well.

**Conclusions:**
- A substantial proportion of patients who had been treated with many therapies (including azacitidine and/or decitabine) for their MDS, including patients with high-risk MDS, responded to SGI-110 treatment.
- Injections of SGI-110 were well tolerated.
- The trial is continuing to enroll patients with untreated MDS in the Phase 2 dose-expansion phase. These patients will be randomly assigned to treatment with 60 or 90 mg/m² SGI-110 once daily for five consecutive days.

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EHA 3621

**p53 Protein Expression Predicts Outcome and Cytogenetic Response in Patients with Low-/Int-1 Risk Myelodysplastic Syndromes Treated with Lenalidomide: Results from the MDS004 Clinical Trial**

Leonie Saft, Mohsen Karimi Mehran Ghaderi, Andras Matolscy, Pierre Fenaux, Ghulam Mufti, Aristoteles Giagounidis, Dominik Selleslag, Petra Muus, Guillermo Sanz, Moshe Mittelman, David Bowen, Anna Porwit, Tommy Fu, Jay Backstrom, Kyle J. MacBeth, Eva Hellström-Lindberg

Patients with 5q- syndrome, a type of myelodysplastic syndromes (MDS), have a deletion (loss) of the long (q) arm of chromosome 5. Experts generally believe that 5q- syndrome progresses slowly. But some recent research shows that 5q- disease can be more aggressive, leading to shorter survival times, in certain patients. Of these patients, 18% have a mutation in the TP53 gene at diagnosis, which increases the risk that their MDS will progress to acute myelogenous leukemia (AML). Studies have shown that people who have a TP53 genetic mutation also tend to have strong expression of the p53 protein.

The purpose of this international study was to evaluate the association between p53 protein expression and responses to treatment with lenalidomide (Revlimid®), treatment outcomes, and TP53 gene mutations. The study used immunohistochemistry (an assay technique) to assess bone marrow biopsy specimens from 85 patients with 5q- syndrome who had been treated with lenalidomide.

**Key Findings:**
- p53 expression was strong in more than 1% of bone marrow cells of 30 patients (35%).
- Having more than 1% of bone marrow cells with strong p53 expression was associated with shorter overall survival and higher risk of progression to AML.
- p53 status was not associated with duration of response to lenalidomide or the likelihood that a patient would stop needing regular red blood cell transfusions.
- Eighteen of 35 patients (51%) without strong p53 expression had a cytogenetic response to lenalidomide treatment, meaning that their bone marrow cells were normal. In comparison, three of 21 patients (14%) with strong p53 expression had a cytogenetic response.
**EXISTING AND EMERGING TREATMENTS**

**Conclusions:**

- p53 status measured by immunohistochemistry can be used to predict responses to lenalidomide in patients with 5q- syndrome.
- Strong p53 expression is a marker for underlying mutations in the TP53 gene.
- Risk-assessment systems for 5q- syndrome should take TP53 mutation status into account.

**EHA 3848**  
**Multicenter Study Evaluating the Impact of Hypomethylating Agents as Bridging Therapy to Hematopoietic Stem Cell Transplantation in Myelodysplastic Syndromes**

Yundeok Kim, Jieun Jang, Je Hwang Lee, In-Ho Kim, Joon Ho Jang, Hyeong Joon Kim, Soo Jeong Kim, Yoo Hong Min

Hematopoietic stem cell transplantation (HSCT), the infusion of stem cells from a healthy donor into a patient, is the only cure for MDS. The hypomethylating agents (HMAs) azacitidine (Vidaza®) and decitabine (Dacogen®) are sometimes used to control MDS before HSCT. This multicenter study examined the effects of HMAs used before HSCT on HSCT outcomes. A team of researchers reviewed the medical records of 113 patients (of which 44 were female) who had undergone HSCT in five South Korean centers between 2007 and 2010. Of these patients, 85 (median age 47) had been treated before HSCT with azacitidine, decitabine, or both. The median age of patients not treated with an HMA before HSCT was 42 years.

**Key Findings:**

- In general, whether patients were treated with an HMA before HSCT or not didn’t affect their survival.

- But survival after HSCT was one year longer in patients who had a high count of abnormal blasts (young white blood cells) at diagnosis and were treated with an HMA before HSCT.
- Median time to neutrophil engraftment, when the patient’s bone marrow began producing healthy white blood cells, was 28 days in patients with and 12 days in patients without HMA pretreatment.
- Median time to platelet engraftment was 35 days and 19 days without HMA pretreatment.
- The effects of HMA pretreatment on graft failure or graft-versus-host disease weren’t clear.

**Conclusions:**

- This study didn’t show that HMA treatment before HSCT benefits most patients with MDS. However, for patients with a large proportion of abnormal blasts, HMA pretreatment might increase survival after HSCT.
- Engraftment took longer in patients who underwent HMA pretreatment than those who didn’t.
- HMA treatment to stabilize MDS prior to HSCT might not be appropriate for all patients with MDS.

**EHA 4449**  
**Benefits of the Use of Azacitidine in Patients with Acute Myeloid Leukemia (AML) Refractory or Relapsed After Intensive Chemotherapy**

Giovania Giagnuolo, Claudio Cerchione, Piera Angelillo, Orsola Vitagliano, Novella Pugliese, Luana Marano, Giorgia Battipaglia, Simona Avilia, Fiorella Alfinito, Giuseppe Cerciello, Fabrizio Pane

Treatment with azacitidine (Vidaza®) prolongs survival, delays progression to acute myelogenous leukemia (AML), and reduces the need for blood transfusions in patients with intermediate-2- or high-risk myelodysplastic
EXISTING AND EMERGING TREATMENTS

syndromes (MDS) according to the International Prognostic Scoring System. The purpose of this study was to find out whether azacitidine treatment could prolong survival, reduce the number of side effects, and improve quality of life in patients with MDS or AML that had not responded to intensive chemotherapy or had relapsed after chemotherapy.

A team from Naples, Italy, reported on their experience with azacitidine therapy in eight patients with intermediate-2- or high-risk MDS and nine with AML. Five of the patients with AML had been treated with intensive chemotherapy and either had not responded or their disease had relapsed. Patients’ median age was 77 years, and all of them needed regular red blood cell transfusions. The patients were treated with azacitidine injections on seven days of every month until their disease progressed.

Key Findings:
- On average, patients with MDS survived for 16 months.
- Platelet counts improved in all patients.
- After three cycles of treatment, all five patients with relapsed or resistant AML had higher hemoglobin concentrations and two stopped needing blood transfusions.
- None of the patients had any treatment-related infections or needed to be hospitalized.

Conclusions:
- Azacitidine appears to be an effective and safe treatment for patients with AML who are not eligible for intensive chemotherapy because their disease has not responded to chemotherapy in the past or the disease relapsed after treatment.
- In these patients, azacitidine reduces dependence on blood transfusions, improves quality of life, and prolongs survival.
- Patients treated with azacitidine have fewer infections and are less likely to be hospitalized than those treated with conventional therapy.

EHA 4522
Impact of 5q Breakpoints on Clinical Outcomes in Patients with IPSS Low-/Int-1-Risk Myelodysplastic Syndromes (MDS) and Isolated Del(5q) Treated with Lenalidomide in the MDS-004 Study

Patients with 5q- syndromes, a type of myelodysplastic syndrome (MDS), have a deletion (loss) of the long (q) arm of chromosome 5. Proximal breakpoints are damaged locations on chromosomes that are near the centrosome (center of the x-shaped chromosome). Distal breakpoints are further away from the centrosome. Whether the breakpoints on 5q are proximal or distal can affect how quickly 5q- syndrome progresses. The goal of this study, led by an international research team, was to find out whether the location of chromosomal breakpoints affects overall survival, progression to acute myelogenous leukemia (AML), and need for regular red blood cell transfusions. The study included 137 patients with 5q- syndrome who had been treated with lenalidomide (Revlimid®) for at least 26 weeks.

Key Findings:
- Sixty-four percent of patients had a proximal breakpoint at location q14q34.
EXISTING AND EMERGING TREATMENTS

- On average, patients with breakpoints at q14q34 survived for 3.8 years, compared to 4.4 years in patients with breakpoints at other locations.
- MDS progressed to AML within five years in 37% of patients with a breakpoint at q14q34 and 35% in patients with breakpoints at other locations.
- Similar proportions of patients with breakpoints at q14q34 and other locations stopped needing regular red blood cell transfusions.

Conclusions:

- The breakpoint at q14q34, which was the most common location, was not associated with different probabilities of progression to AML, survival times, or rates of independence from red blood cell transfusions compared to breakpoints at more distal locations.
- Genes involved in the very proximal portions of the 5q chromosome are unlikely to influence response to treatment, survival, or progression to AML in patients with 5q-syndrome.

EHA 4985
High Doses of Eltrombopag Are Well-Tolerated in Conjunction with Azacitidine and the Combination Demonstrates Encouraging Activity in Patients with MDS and AML.

Michael Dickinson, Kirsten Herbert, Caroline Sardjono, Thao Le, Emma Link, Diana Zannino, Sam Ruell, John Seymour, Melita Kenealy, H. Prince

When a patient with myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML) has thrombocytopenia, the first cycles of treatment with azacitidine (Vidaza®) can exacerbate this platelet shortage. Platelet shortages can increase the risk of bleeding and require platelet transfusions. The purpose of this Phase 2 clinical trial was to find out whether combining eltrombopag (Promacta®) with azacitidine can treat thrombocytopenia and prevent the progression of MDS to AML.

The investigators plan to recruit 25 patients with newly diagnosed or relapsed MDS, AML, or chronic myelomonocytic leukemia (CMML) to the trial. Patients with particularly low platelet counts (less than 100,000 per microliter) started eltrombopag treatment 14 days before their azacitidine cycle. The other patients started eltrombopag treatment on the same day that their 28-day azacitidine treatment cycle began. The results presented at the EHA meeting were based on the first 17 patients recruited to the study.

Key Findings:

- About three-quarters of patients responded to the combination treatment. Of these, four patients had a complete response, meaning that they had no evidence of MDS, CMML, or AML.
- Platelet counts improved in nine of the 15 patients whose original platelet count was less than 100,000 per microliter by 63 days, on average, after starting combination treatment or, for one patient, after treatment with eltrombopag only.
- Four patients developed severe thrombocytosis, or the production of too many platelets. These patients had to stop the eltrombopag treatment.
- One patient had a liver problem related to the eltrombopag that was successfully treated.
EXISTING AND EMERGING TREATMENTS

Conclusions:

- The combination of eltrombopag treatment with azacitidine had promising response rates.
- The combination therapy was well tolerated.
- The 14 days of pretreatment with eltrombopag in patients with platelet counts less than 100,000 per microliter wasn’t enough to consistently improve their platelet counts.

Key Findings:

- Nineteen patients (73%) responded to the azacitidine treatment. Of these, 19% had a complete remission, meaning that they had no evidence of MDS. Another 14 (54%) had higher blood counts.
- Among the seven patients (27%) whose condition didn’t improve after azacitidine treatment, MDS remained stable in four patients and progressed in three.
- Median overall survival from the start of azacitidine treatment was 16 months.
- Thirteen patients (45%) had a moderately severe side effect.

EHA 5200
Prolonged Low-Dose Azacitidine Schedule in High-Risk MDS Patients: Long Term Efficacy and Relationship with Molecular Response

Cristina Clissa, Carlo Finelli, Matilde Follo, Marta Stanzani, Cristina Papayannidis, Antonio Curti, Stefania Paolini, Sara Mongiorgi, Lucia Manzoli, Giovanni Martinelli, Lucio Cocco, Michele Cavo

Azacitidine (Vidaza®), the first drug approved by the U.S. Food and Drug Administration to treat myelodysplastic syndromes (MDS), is usually given on seven consecutive days of each 28-day cycle. The typical dose is 75 mg per square meter each day. Some research has shown that different azacitidine dosing schedules that avoid treatments on weekends might increase the response rate.

Researchers from the University of Bologna, Italy, studied the effects of administering azacitidine on five consecutive days, followed by two days off, and then another five days of treatment over a 28-day cycle. The dose was 50 mg per square meter per day. The study included 26 patients (average age 70 years) with high-risk or intermediate-2-risk MDS according to the International Prognostic Scoring System. The patients were treated with at least six cycles of azacitidine.

EHA 5412
Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Results of a Prospective, Randomized, Trial

Esther Oliva, Valeria Santini, Gina Zini, Giuseppe Palumbo, Antonella Poloni, Agostino Cortelezzi, Francesco Rodeghiero, Maria Teresa Voso, Alfredo Molteni, Grazia Sanpaolo, Anna Marina Liberati, Fortunato Morabito, Enrico Ballestri, Stefana Imperia, Flavia Salvi, Maria Antonietta Aloe Spiri, Antonio Marino, Filippo Rodà, Caterina Alati, Francesca Ronco, Francesco Di Raimondo, Pietro Leoni, Giuliana Alimena, Giuseppe Fioritoni, Roberto Latagliata, Francesco Nobile
Patients with low-risk or intermediate-1-risk myelodysplastic syndromes (MDS), according to the International Prognostic Scoring System, sometimes have severe thrombocytopenia (platelet shortage). Eltrombopag (Promacta®) stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow.

The purpose of this Phase 2, multicenter clinical trial led by an Italian research team is to evaluate eltrombopag’s ability to increase platelet counts in 171 patients with lower-risk MDS and thrombocytopenia. Twice as many patients will be randomly assigned to daily treatments with eltrombopag as placebo.

The researchers reported on the results in the first 31 patients (average age 66 years), of which 13 were female. Of these patients, 21 have been treated with eltrombopag and 10 with placebo.

**Key Findings:**

- Platelet counts increased in 12 of 15 patients who were treated with eltrombopag for at least 12 weeks. The higher platelet counts stopped their abnormal bleeding and their need for platelet transfusions.
- Platelet counts didn’t change in the patients on placebo.
- On average, platelet counts in the eltrombopag group rose by 64,000 per microliter.
- The eltrombopag group had less fatigue and better quality of life after 12 weeks of treatment.
- The number of abnormal bone marrow blasts (immature white blood cells) went down in four patients in the eltrombopag group, but they went up in two patients in the placebo group.

**Conclusions:**

- Preliminary results suggest that eltrombopag is safe and effective in patients with low-risk and intermediate-1-risk MDS who have thrombocytopenia.

**What This Means For Patients**

Eltrombopag is an oral drug normally used with success for treatment of immune thrombocytopenia (lowering of platelet count due to autodisturbance). In this study, this drug was employed in lower-risk MDS patients who have a good prognosis, but have extremely low platelet counts, resulting in bruises and serious bleeding. Platelet transfusions are only used in emergency situations and their beneficial effects are short term. It is thus very significant that the preliminary finding is this oral drug, with no major side effects, induces increase of platelets and reduces bleeding in lower-risk MDS patients. Its use could avoid serious complications and improve quality of life of these patients.

**Valeria Santini, MD**  
University of Florence  
Member, AA&MDSIF Medical Advisory Board
EHA 5436

Improved Predictive Prognostic Power of Revised-IPSS (IPSS-R) in a Series of 301 Patients with Myelodysplastic Syndrome from a Single Center

Helena Pomares, Montse Arnan, Esther Alonso, Javier Grau, Valentin Navarro-Perez, Lina Abenoza, Isabel Sánchez-Ortega, Alberto Fernández de Sevilla, Rafael F Duarte

Doctors often use the International Prognostic Scoring System (IPSS) to choose treatments for their patients, but its predictions aren’t always precise enough. The revised IPSS (IPSS-R) is based on the same factors as the IPSS. But the IPSS-R takes more information into account than the IPSS and categorizes patients into five groups instead of four.

This study compared the predictive abilities of the IPSS and IPSS-R in 682 patients with MDS who were treated at a single center in Spain. Patients’ median age was 71 years, and 69% were male. A median of 47 months of follow-up data was available on these patients.

Key Findings:

• All patients with low-risk MDS according to the IPSS were in the very-low-risk or low-risk IPSS-R categories. Similarly, all patients with high-risk MDS based on the IPSS had high- or very-high-risk MDS based on the IPSS-R.
• But patients with intermediate-1 or intermediate-2 risk MDS according to the IPSS were spread out among all five IPSS-R categories.
• Of the seven patients with intermediate-1 MDS by the IPSS who were reclassified as having high-risk MDS based on the IPSS-R, five survived for 30 months or less, three developed acute leukemia, and six needed regular blood transfusions.
• Overall survival was about 60 months for two of three patients with intermediate-2 MDS who were reclassified as having low-risk MDS on the IPSS-R; the third patient died from a cause that was not related to MDS.

Conclusions:

• The IPSS-R score predicted overall survival and survival without leukemia more accurately than the IPSS.
• The more accurate classification of patients into risk categories by the IPSS-R could affect the therapies used to treat MDS because these choices are typically based on the initial risk assessment.
PATIENT OUTCOMES AND QUALITY OF LIFE (QOL)

ASCO 7033
Survival and Cause of Death in Patients with Refractory Anemias.
Yue Zhang, Bonnie Gould Rothberg, Daniel Morgensztern

A team of researchers from Yale University evaluated the outcomes of two types of low-risk MDS—refractory anemia (RA) and RA with ringed sideroblasts (RARS). Using data from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute, the investigators identified 6,505 patients diagnosed with RA or RARS between 2001 and 2009. Of these patients, 3,866 (59%) had RA and 2,639 (41%) had RARS.

Key Findings:
• Median overall survival was 39 months for people with RA and 48 months for those with RARS.
• 41% of patients with RA survived for at least five years compared to 38% of those with RARS.
• The rates of disease-specific survival, or the proportions that did not die of their MDS, were the same in the two groups—about 75%.
• About 25% of deaths in both groups were due to heart disease.
• About 23% of deaths in patients with RA and 20% in those with RARS were due to MDS. Another 9% of deaths in patients with RA and 11% of deaths in those with RARS were due to acute myelogenous leukemia (AML).

Conclusions:
• Both RA and RARS have a high five-year disease-specific survival rate.
• Most deaths in people with RA and RARS are due to causes other than MDS or AML, most commonly heart disease.

ASH 699
The Independent Effects of Frailty and Comorbidity On the Quality of Life in MDS Patients
Rena Buckstein, Shabbir M.H. Alibhai, Dina Khalaf, Adam Lam, Alex Mamedov, Lisa Chodirker, Liying Zhang, Martha Lenis, Matthew Cheung, Jeannie Callum, Janey Hsiao, Yulia Lin, Kenneth Rockwood, and Richard A. Wells, D.Phil.

The comorbidities, or diseases or conditions in addition to myelodysplastic syndromes (MDS), of patients with MDS have a major impact on their outcomes and quality of life. In addition to having comorbidities, many patients with MDS are elderly and frail. But experts did not know how frailty affects people with MDS.

Researchers from Canada measured comorbidities, frailty, and quality of life in 263 patients (63% were male) with MDS. The average age of patients at their first quality-of-life assessment was 72 years. Of 208 patients whose International Prognostic Scoring System (IPSS) score could be measured, 83% had low-risk or intermediate 1-risk MDS.

Key Findings:
• 46% of patients had a low comorbidity score, 41% had an intermediate score, and 12% had a high score.
• The average frailty score was three on a nine-point scale, meaning that the patients were managing well, and their medical problems were well controlled.
• In general, quality of life did not change over time.
• Patients with a lower frailty scores tended to have better quality of life, whereas patients with higher frailty scores had much worse fatigue.
• Patients with lower comorbidity scores had lower levels of fatigue and shortness of breath.
Conclusions:

- Health-related quality of life remains surprisingly stable over time in people with MDS.
- Frailty and comorbidities have independent effects on patients with MDS.
- Clinicians should consider monitoring both frailty and comorbidities in patients with MDS to determine their effects on quality of life, treatment side effects, and survival.

Key Findings:

- On average, scores on the EQ-5D dropped by 0.2 units a month.
- Scores were lower in older patients, but scores were similar in men and women.
- Scores and the rates at which scores dropped over time were different in different countries.
- In patients whose hemoglobin levels went up, scores also went up.
- Scores varied by type of MDS according to the World Health Organization categorization system. Patients having refractory anemia with excess blasts-2 had the lowest scores and those with 5q-syndrome had the highest scores.
- Patients undergoing blood transfusions had scores that were three units lower than those not having transfusions. Transfused patients’ scores dropped by 0.3 units a month, but this didn’t happen in patients who didn’t have transfusions.

Conclusions:

- Health status in patients with MDS depends on the type of MDS, hemoglobin level, and whether they need regular blood transfusions.
- Health status drops more quickly in patients who need regular blood transfusions than those who don’t. So preventing patients from needing transfusions might improve their health status.
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