

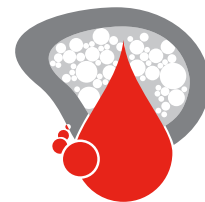
AA&MDSIF 2016

# MDS Research Summary


AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)  
EUROPEAN HEMATOLOGY ASSOCIATION (EHA)

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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 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 2016 Annual Meetings of The American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA). 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 material 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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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 this year.

- American Society of Clinical Oncology (ASCO)
- European Hematology Association (EHA)

These are some of the world's largest meetings of hematologists and hematological oncologists—doctors who care for patients with blood disorders or blood and bone marrow cancers. This is where many major findings in the field of blood and marrow disorders are first announced to 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. 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 large displayed 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 with your doctor about clinical trials or to visit [www.clinicaltrials.gov](http://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**

*Cleveland Clinic*

*Taussig Cancer Institute*

*Co-Chair*

*AAMDSIF Medical Advisory Board*

## EHA S446

### Genetic Mutations that Predict Therapy-Related Blood Cancers

*Koichi Takahashi, Feng Wang, Hagop Kantarjian, Doss Denaha, Kanhav Khanna, Erika Thompson, Keyur Patel, Sattva Neelapu, Curtis Gumbs, Carlos Bueso-Ramos, Courtney DiNardo, Simona Colla, Farhad Ravandi, Song Xingzhi, Jianhua Zhang, Xifeng Wu, Felipe Samaniego, Guillermo Garcia-Manero, Andrew Futreal*

Patients sometimes develop blood cancers after treatment with chemotherapy or radiation therapy for another cancer. Recent research suggests that patients might have mutations in the TP53 gene years before they develop one of these therapy-related cancers (known as secondary cancers). These secondary cancers can include MDS and acute myelogenous leukemia (AML). The TP53 mutations might drive the development of secondary cancers.

A research team decided to find out whether mutations that drive leukemia can be detected in patients who develop a therapy-related blood cancer at the time their first (primary) cancer is diagnosed. They sequenced 280 genes known to be associated with leukemia in specimens from 14 patients. Five of the patients (36%) developed treatment-related acute myelogenous leukemia (AML) and 9 (64%) developed treatment-related MDS.

#### Results:

- At the time they were diagnosed with a secondary blood cancer, the 14 patients had mutations in 21 genes known to drive leukemia.
- The most common mutations were in TP53 (29% of patients), DNMT3A (21%), TET2 (21%), and RUNX1 (20%).
- Ten (71%) of the patients had a leukemia driver mutation at the time their primary cancer was diagnosed—on average, 3 years before their secondary cancer diagnosis.

#### Conclusions:

- Leukemia driver mutations can be found in the genes of patients who later develop AML or MDS at the time their primary cancer is diagnosed.
- These data could be used to develop a model for assessing risk of treatment-related cancer at the time a primary cancer is diagnosed.

## EHA S129

### Effect of Low Platelet Count in MDS on Azacitidine Treatment Outcomes

*Guillermo Garcia-Manero, Steven D Gore, Bart L Scott, Michael R Savona, Christopher R Cogle, Thomas E Boyd, Suman Kambhampati, Joel Hetzer, Qian Dong, Keshava Kumar, Stacey M Ukrainskyj, Barry S Skikne*

About 40% to 65% of patients with MDS have a shortage of platelets in the bloodstream. Patients with low platelet counts have poorer outcomes than those with normal platelet counts. Some experts believe that patients who have severe platelet shortages and lower-risk MDS at diagnosis should be given the same treatments as patients with higher-risk MDS.

This study assessed the safety and efficacy of CC-486, the oral version of azacitidine (Vidaza®), in patients with MDS who do or do not have a low platelet count. The investigators analyzed data on 137 patients with MDS (median age 72 years) who had participated in one of three phase I/II clinical trials. Of these patients, 72 had a low platelet count.

#### Results:

- The CC-486 response rate was the same—42%—in patients with low platelet counts and those with high platelet counts.
- Two patients (14%) in the low-platelet group stopped needing platelet transfusions, and 17 (24%) developed high platelet counts.
- Serious bleeding events were rare. The low platelet group had no serious bleeding events, whereas these events occurred in 5 patients in the high platelet group.
- Rates of serious side effects were similar in the two groups.

#### Conclusions:

- Patients with lower-risk MDS, even those with low platelet counts, tolerate CC-486 well.
- Patients with low or high platelet counts were equally likely to respond to CC-486 treatment.

## **EHA Education Session: Myelodysplastic Syndromes— Effects of Gene Mutations in MDS**

*Rafael Bejar*

More than 90% of patients with MDS have a mutation in at least one gene known to be associated with MDS. Testing for these genes can sometimes help doctors choose the best treatment for a patient.

Doctors use the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R) to classify patients into different risk categories. But some somatic (not inherited) mutations in MDS genes offer predictive information beyond the IPSS and other scoring tools. For example, having a mutation in certain genes (such as TP53, EZH2, ASXL1, CBL, and U2AF1) increases the risk that MDS will progress in patients with lower-risk IPSS-R categories. But mutations in SF3B1 mean that a patient is likely to survive longer than their IPSS-R category says.

Some somatic mutations are also useful for predicting how a patient will respond to a given treatment. For example, patients with a mutation in TET2 are more likely to respond to treatment with azacitidine (Vidaza®) or decitabine (Dacogen®). Those with a TP53 mutation aren't likely to respond well to azacitidine, decitabine, lenalidomide (Revlimid®), or stem cell transplantation.

Doctors don't consider gene mutations when they diagnose MDS. But mutations might be helpful for diagnosing unexplained blood cell shortages.

## EHA P257

### Gene Mutations and Risk of Progression to MDS

*Jakob Werner Hansen, Maj Karoline Westman, Lene Dissing Sjö, Leonie Saft, Lasse Sommer Kristensen, Andreas Due Ørskov, Marianne Treppendahl, Mette Klarskov Andersen, Kirsten Grønbæk*

Low blood cell counts are common in elderly patients. Doctors often use several tests to try to find the cause.

The purpose of this study was to measure the frequency of gene mutations known to be associated with MDS in patients with long-lasting low blood cell counts with an unknown cause after routine testing. The study included 60 patients (median age 70 years) who had had low blood cell counts for at least 6 months.

### Findings:

- 37 patients (62%) had a mutation in at least 1 of 20 genes assessed in the study.
- The most common mutation—found in 26 patients (43%)—was in TET2.
- Six patients (10%) developed MDS or chronic myelomonocytic leukemia (CMML) over the next 1 to 8 years.
  - Five of these patients had 1 of the 20 mutations when they joined the study.
  - At the time they developed MDS or CMML, 4 patients had a new mutation in NRAS, TP53, GATA2 or ASXL1.

### Conclusions:

- Patients with persistent low blood cell counts and no clear diagnosis often have mutations in genes associated with blood cancers.
- Next-generation sequencing (a new technique to study genomes) might be useful for diagnosing low blood cell counts with an unknown cause.

## EHA S442 Changes in Genes and Clones in MDS Progression

*Hideki Makishima, Tetsuichi Yoshizato, Kenichi Yoshida, Thomas LaFramboise, Matthew Ruffalo, Mikkael Sekeres, Hiromichi Suzuki, Bartłomiej Przychodzen, Yasunobu Nagata, Manja Meggendorfer, Masashi Sanada, Yusuke Okuno, Yusuke Sato, Aiko Sato-Otsubo, Tomas Radivoyevitch, Naoko Hosono, Yuichi Shiraishi, Kenichi Chiba, Claudia Haferlach, Wolfgang Kern, Hiroko Tanaka, Yusuke Shiozawa, Inés Gómez-Seguí, Holleh Husseinzadeh, Swapna Thota, Kathryn Guinta, Brittney Dienes, Tsuyoshi Nakamaki, Shuichi Miyawaki, Yogen Saunthararajah, Shigeru Chiba, Satoru Miyano, Lee-Yung Shih, Torsten Haferlach, Seishi Ogawa, Jaroslaw Maciejewski*

Clones in MDS are immature white blood cells. A bone marrow failure disease like MDS starts when a clone becomes abnormal. This abnormal clone makes clones of itself. These cells might not be able to make normal blood cells or they might not make as many blood cells as the body needs.

This research team studied the relationships between gene mutations and clones in 779 patients with MDS or secondary acute myelogenous leukemia (AML).

### Findings:

- Patients with higher-risk MDS had more mutations, more mutations in different genes, and larger clones.
- Many more patients with AML had large numbers of mutations in many different genes than patients with lower-risk MDS.
- New mutations often developed before the disease progressed.
- Patients with AML were more likely than those with higher-risk MDS to have mutations in FLT3, PTPN11, IDH1, CBL, or NRAS.
  - In patients with these mutations, MDS progressed more quickly to AML than in patients without these mutations.
  - Patients with mutations in TP53, GATA2, RUNX1, IDH2, STAG2, ASXL1, and NPM1 had a higher risk of dying before their MDS progressed to AML than patients with other mutations.

### Conclusions:

- Changes in clones are closely associated with mutations in different genes.
- These changes are also associated with the likelihood that MDS will progress to AML or that the patient will die before developing AML.
- Screening for these mutations might help doctors predict outcomes in MDS.



## **EHA S128 Clinical Trial of Darbepoetin Alfa for Anemia in Patients with Lower-Risk MDS**

*Uwe Platzbecker, Argiris Symeonidis, Esther Oliva,  
Jeroen S Goede, Michel Delforge, Jiri Mayer, Sejal Badre,  
Eduard Gasal, Bhakti Mehta, Janet Franklin*

Treatment guidelines for health-care practitioners often recommend erythropoiesis-stimulating agents (ESAs) to treat anemia in patients with lower-risk MDS. However, regulatory agencies in some countries haven't approved ESAs for this use.

This phase III clinical trial evaluated the outcomes of darbepoetin alfa (Aranesp®), an ESA, in 147 patients with low-risk or intermediate-1-risk MDS in nine European countries. Patients were treated with darbepoetin alfa injection or placebo for 24 weeks.

### **Results:**

- The darbepoetin alfa reduced the number of transfusions that patients needed significantly compared with placebo.
- Eleven patients (14.7%) treated with darbepoetin had an erythroid response, meaning that their red blood cell counts returned to normal. None of the patients in the placebo group had an erythroid response.
- Negative side effects that were more common in the darbepoetin group were fatigue, fever, headache, and muscle pain.

### **Conclusions:**

- Darbepoetin alfa treatment for 24 weeks significantly reduced transfusions in patients with low-risk and intermediate-1-risk MDS and increased rates of red blood cell response.
- Darbepoetin alfa had no safety concerns.

## **EHA P248** **Clinical Trial of Epoetin Alfa** **for Anemia in Patients with** **Lower-Risk MDS**

*Pierre Fenaux, Valeria Santini, Maria Antonietta Aloe Spiriti, Aristoteles Giagounidis, Rudolf Schlag, Atanas Radinoff, Liana Gercheva-Kyuchukova, Achilles Anagnostopoulos, Esther Oliva, Argiris Symeonidis, Anna Potamianou, Hari Haralampiev, Robert Wapenaar, Iordanis Milionis, Uwe Platzbecker*

Treatment guidelines for health-care practitioners often recommend erythropoiesis-stimulating agents (ESAs) for anemia in patients with lower-risk MDS. However, regulatory agencies in some countries haven't approved ESAs for this use.

This international Phase III clinical trial compared the efficacy and safety of epoetin alfa, an ESA, to placebo in patients with anemia low-risk or intermediate-1-risk MDS. The 130 participants in the study (median age 75 years) were randomly assigned to treatment with epoetin alfa or placebo for 24 weeks.

### **Results:**

- Red blood cell counts returned to normal in 32% of the epoetin alfa group and 4% of the placebo group.
- In patients who responded, red blood cell counts stayed in the target range for a median of 197 days.
- The proportion of patients needing red blood cell transfusions dropped from 52% before the study to 25% by week 24 in the epoetin alfa group. This proportion didn't change in the placebo group.
- Quality of life improved in the epoetin alfa group compared with the placebo group.
- Treatment safety was similar in the epoetin alfa and placebo groups.

### **Conclusions:**

- Epoetin alfa reduced anemia by increasing hemoglobin counts in patients with low-risk or intermediate-1-risk MDS.
- Epoetin alfa also reduced the amount of red blood cell transfusions that patients needed.

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## **ASCO 7076 Luspatercept for Lower-Risk MDS with Ring Sideroblasts: the MEDALIST Trial**

*Uwe Platzbecker, Rami S. Komrokji, Pierre Fenaux, Guillermo Garcia-Manero, Ghulam J. Mufti, Mikkael A. Sekeres, Jennie Zhang, Aziz Benzohra, Abderrahmane Laadem, Bond Vo, Kenneth M. Attie, Alan F. List*

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About a third of patients with MDS have ring sideroblasts (ring-shaped iron deposits) in their bone marrow. As a result, their bone marrow can't form healthy red blood cells, which leads to anemia. Anemia in patients with MDS can be hard to treat successfully.

Luspatercept is an investigational drug that increases red blood cell counts in patients who have anemia due to MDS or other rare blood disorders. MEDALIST is a phase III randomized controlled trial to study the efficacy and safety of luspatercept for lower-risk MDS with ring sideroblasts in patients needing regular red blood cell transfusions (at least 2 units of packed red blood cells every 8 weeks). These patients don't respond to erythropoiesis-stimulating agents (an anemia treatment), or they can't tolerate these drugs.

The investigators are randomly assigning adult patients to treatment with luspatercept every 3 weeks for 24 weeks or placebo. The primary endpoint is the rate of red blood cell transfusion independence for at least 8 weeks during the first 24 weeks of treatment. Secondary endpoints include transfusion independence for at least 12 weeks, safety, quality of life, duration of transfusion independence, progression to acute myelogenous leukemia, overall survival, and changes in hemoglobin counts.

The investigators hope to enroll 210 patients, and they opened the study to enrollment in December 2015.

## EHA S131

### Luspatercept for Anemia in MDS

*Uwe Platzbecker, Aristoteles Giagounidis, Ulrich Germing, Katharina Götze, Philipp Kiewe, Karin Mayer, Joerg Chromik, Markus Radsak, Thomas Wolff, Detlef Haase, Monty Hankin, Dawn Wilson, Xiaosha Zhang, Abderrahmane Laadem, Matthew L. Sherman, Kenneth M. Attie*

Luspatercept is an experimental drug used to increase red blood cell counts in patients with anemia. In laboratory mice with MDS, an analog to luspatercept improved the ability to form healthy red blood cells and increased hemoglobin counts.

This study assessed the outcomes of luspatercept treatment in patients with lower-risk MDS and anemia who had finished 3 months of luspatercept treatment in an earlier phase II clinical trial. Of the 58 patients in the original study, 32 (median age 72, 69% male) agreed to continue taking luspatercept for another 24 months.

#### Results:

- In 13 patients whose hemoglobin counts had increased in the original study, 11 (85%) continued to have hemoglobin count increases in the follow-on study.
- Half the 22 patients who had needed red blood cell transfusions before the study stopped needing transfusions after 8 or more weeks in the follow-on study.
- Most side effects were mild.

#### Conclusions:

- Red blood cell counts increased with luspatercept treatment in patients with lower-risk MDS.
- Hemoglobin counts increased, and patients were able to stop needing red blood cell transfusions for a substantial amount of time.
- Patients tolerated luspatercept well in both the original and follow-on studies.

## EHA S130

### Phase II Clinical Trial of Eltrombopag for Advanced MDS in Patients with a Low Platelet Count

*Moshe Mittelman, Uwe Platzbecker, Boris Afanasyev, Sebastian Grosicki, Raymond SM Wong, Achilles Anagnostopoulos, Benjamin Brenner, Claudio Denzlinger, Giuseppe Rossi, Arnon Nagler, Regina Garcia Delgado, Nicole Stone, Zewen Zhu, Stacey Kalambakas, Dominik Selleslag*

Severe shortages of platelets can be life threatening in patients with MDS or acute myelogenous leukemia (AML). Eltrombopag (Promacta®) is a drug that stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow. This process increases the number of platelets and decreases bleeding risk.

The purpose of this phase II clinical trial was to assess the effects of eltrombopag on platelet shortages in 145 patients with MDS or AML who had very low platelet counts. Patients were treated with eltrombopag or placebo for 12 weeks.

#### Results:

- Eltrombopag reduced the proportion of patients with severe platelet shortages.
- Fewer patients (42%) treated with eltrombopag had disease progression, compared with 60% of those treated with placebo.
- Side effects that were more common in the eltrombopag group included small red spots on skin caused by bleeding, nosebleeds, and fatigue.
- Almost 32% of patients in the eltrombopag group and 15% in the placebo group left the study because of side effects.

#### Conclusions:

- Eltrombopag treatment did not promote disease progression.
- Rates of serious bleeding were lower with eltrombopag.

## ASCO 7014 Lenalidomide for Low-Risk MDS without 5q Deletion

*Guillermo Garcia-Manero, Antonio Medina Almeida, Pierre Fenaux, Norbert Gattermann, Aristoteles Giagounidis, Stuart Goldberg, Keiya Ozawa, Jerry Weaver, Mary M. Sugrue, Valeria Santini*

Lenalidomide (Revlimid®), a biologic agent, slows down the growth of blood vessels that feed abnormal cells. Lenalidomide can eliminate the need for red blood cell transfusions in patients with 5q-deletion MDS.

A phase III clinical trial recently showed that patients with lower-risk MDS but not 5q-deletion can also benefit from lenalidomide. Before enrolling the trial, these patients needed regular red blood cell transfusions to treat their anemia. In addition, they were not good candidates for erythroid stimulating agents or they did not respond to this treatment. In this clinical trial, more patients treated with lenalidomide stopped needing regular blood transfusions than those treated with a placebo.

The investigators analyzed data from the clinical trial to learn more about patient responses to lenalidomide. Patients in the study were randomly assigned to treatment with lenalidomide 10 mg a day (160 patients) or placebo (79 patients) once a day.

### Results:

- Among of the 43 patients whose results could be evaluated, 9 achieved a cytogenetic response, meaning that they had fewer abnormal Philadelphia chromosomes in their bone marrow.
- Of the 9 patients with a cytogenetic response, 5 also stopped needing red blood cell transfusions for more than 8 weeks.
- None of the patients in the placebo group had a cytogenetic response.
- Hemoglobin counts increased by at least 1.5 g/dL in 31 patients (19%) in the lenalidomide group, compared to 2 in the placebo group (3%).

### Conclusions:

- Compared to placebo, lenalidomide was associated with significantly greater clinical benefit than placebo in patients with lower-risk, non-5q-deletion MDS.
- The results show that measures other than transfusion independence might be useful for managing lower-risk, non-5q-deletion MDS.

## ASCO 7077

### INSPIRE: A Randomized Phase III Clinical Trial of Rigosertib in Higher-Risk MDS after Failure of Azacytidine or Decitabine

*Guillermo Garcia-Manero, Aref Al-Kali, Maria R. Baer, Gail J. Roboz, Uwe Platzbecker, Suman Kambhampati, Lucy A. Godley, Robert Collins, Jamile M. Shammo, Valeria Santini, Dr. Azra Raza, Lewis R. Silverman, Nozar Azarnia, Steven M. Fruchtman, Barbara R Snyder, Pierre Fenaux*

Rigosertib (Estybon®) is an investigational drug that selectively kills cancer cells and blasts (abnormal, immature white blood cells).

The investigators describe a Phase III, randomized clinical trial that has started enrolling patients with higher risk MDS who have not responded to azacitidine (Vidaza®) or decitabine (Dacogen®) after at least 9 months of treatment. Patients are randomly assigned to treatment with rigosertib or the physician's choice of treatment. In the treatment group, patients are treated with rigosertib (1,800 mg every 24 hours) for 72 hours every 2 weeks for 16 weeks and then every 4 weeks.

The primary endpoint is overall survival. Secondary endpoints include overall survival in patients with monosomy 7 or trisomy 8 (two types of abnormal chromosomes), overall response, bone marrow response, quality of life, and blood cell counts.

The study began enrolling patients in December 2015, and the investigators plan to enroll about 150 patients in the rigosertib group and 75 in the comparison group.

## ASCO 7078

### Combination of Oral Azacitidine and Durvalumab in MDS

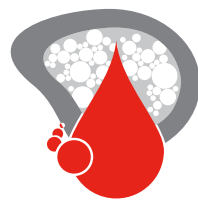
*Pierre Fenaux, Lewis R. Silverman, Ghulam J. Mufti, John Francis Seymour, Rami S. Komrokji, Stefan Faderl, Du Hung Lam, Michele Sharr-McMahon, C L. Beach, Guillermo Garcia-Manero*

About half of patients with higher-risk MDS respond to injected azacitidine (Vidaza®) or decitabine (Dacogen®). But treatment options for those who don't respond are very limited. These patients have a high risk of progression to acute myelogenous leukemia (AML) and death.

In an earlier study, about a third of patients (29%) responded to oral azacitidine, even though they hadn't responded to injected azacitidine or decitabine in the past. Durvalumab, an experimental drug, has produced long-lasting responses in patients with solid tumors.

This randomized Phase II clinical trial is evaluating the efficacy and safety of the combination of oral azacitidine and durvalumab in patients who didn't respond to injected azacitidine or decitabine in the past.

The primary endpoint is the proportion of patients with an objective response. The investigators define an objective response as improved blood cell counts, a partial response, complete remission, or complete remission in the bone marrow. Secondary endpoints include overall survival, time to response, duration of response, duration of survival without progression to AML, progression to AML, and safety. The investigators plan to enroll 194 patients to this study.



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