AA&MDSIF

# MDS Research Summary | 2015

**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*

Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION

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 this 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 Clinical Oncology (ASCO), June 2015**

  ASCO is a professional association of physicians in all oncology subspecialties who care for people with cancer.

- **European Hematology Association (EHA), June 2015**

  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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Aplastic Anemia & MDS INTERNATIONAL FOUNDATION

*This publication is made possible through an unrestricted education grant from Celgene Corporation.*

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 – 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 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 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.

**Mikkael Sekeres, MS, MD**
*Cleveland Clinic*
*Taussig Cancer Institute*

*Co-Chair*
*AA&MDSIF Medical Advisory Board*

# DIAGNOSIS

### EHA PB1824: Comparison Between Cytomorphology and Cytogenetic Analysis for the Diagnosis of Myelodysplastic Syndromes in Cohort of 374 Patients

*Elsa Lestang, Jacques Delaunay, Olivier Theisen, Yannick Le Bris, Marion Eveillard, Pierre Peterlin, Patrice Chevallier, Philippe Moreau, Catherine Godon, Marie C Béné, Soraya Wuilleme*

Analysis of abnormalities in chromosomes is essential to establish the prognosis in patients with MDS.

The aim of this research was to compare the efficiency of examination of blood and bone marrow specimens by a pathologist to chromosome analysis to diagnose MDS. The study include 374 patients (median age 66.8 years) who had shortages of at least one type of blood cell.

*Key findings:*

- Analysis of bone marrow specimens revealed no ineffective production (dysplasia) of blood cells in 53% of patients, dysplasia in one or more blood cell types in 42% of patients, and abnormal blood cells in 5% of patients.
- Analysis of chromosomes found that 84% of patients had normal chromosomes and 16% had at least one chromosome abnormality.
- 105 patients (29%) had MDS, and the blood cell shortages in 269 patients (71%) had other causes.
- The sensitivity (ability to identify which patients had MDS) of bone marrow examination was 59% for patients with MDS and 86.6% for patients without MDS. The specificity (ability to correctly rule out MDS) was 79.5% for patients with MDS and 68.7% for patients without MDS.
- The sensitivity of chromosome analysis ranged from 8.5% to 9.5% for patients with MDS and was 32.4% for those without MDS. The specificity was 92.5% to 100% for patients with MDS and 90.3% for patients without MDS.

*Conclusions:*

- Compared to analysis of abnormal chromosomes, examination of bone marrow specimens by a pathologist more accurately identifies patients with MDS but less accurately identifies those without MDS.
- For patients with a blood cell shortage but without many abnormal blasts (immature white blood cells) or cancerous cells, examination of blood and bone marrow specimens through the microscope could be the routine diagnostic procedure.
- Analysis of chromosomes could be delayed for one to three months after the confirmation of the diagnosis by examination of blood and bone marrow specimens.

# NOVEL THERAPIES

### ASCO E18079: Overall Survival (OS) and Baseline Disease Characteristics in MDS Patients With Primary HMA Failure in a Randomized, Controlled, Phase III Study of Rigosertib

*Pierre Fenaux, Aref Al-Kali, Maria R. Baer, Mikkael A. Sekeres, Gail J. Roboz, Gianluca Gaidano, Lewis R. Silverman, Bart L Scott, Peter Greenberg, Uwe Platzbecker, David P. Steensma, Karl A Kreuzer, Lucy A. Godley, Robert Collins, Ehab L. Atallah, Nozar Azarnia, Guillermo Garcia-Manero*

In patients with myelodysplastic syndromes (MDS), a chemical process known as "methylation" blocks DNA's ability to control cell growth. The hypomethylating agents (HMAs) azacitidine (Vidaza®) and decitabine

(Dacogen®) inhibit methylation so that DNA sequences can act normally. These drugs are the standard treatment for higher-risk MDS. The Food and Drug Administration has not approved any treatments for patients with MDS who do not benefit from HMA treatment.

ONTIME was a randomized clinical trial that compared rigosertib with best supportive care in patients with higher-risk MDS. All patients had had had a relapse after treatment with HMAs, had not responded to HMA treatment, or their disease had progressed during HMA treatment.

An international team of researchers studied the relationship between disease characteristics before treatment and overall survival in 299 ONTIME patients who had higher-risk MDS and HMA failure. Most (69%) were male, their median age was 73, and 80% had high-risk or very-high-risk MDS according to the International Prognostic Scoring System.

*Key findings:*

- Median overall survival was better in the rigosertib group compared to the best supportive care group.
- Median overall survival was also better than with best supportive care in patients treated with rigosertib who:
    - Had high-risk or very-high-risk MDS
    - Had 5–19% bone marrow blasts
    - Had been treated previously with HMAs for less than nine months
- 99% of patients in the rigosertib group and 88% of those in the best supportive care group reported adverse effects.
- The most serious adverse effects were anemia, thrombocytopenia (shortage of platelets in the bloodstream), neutropenia (white blood cell shortage) with or without fever, and pneumonia.

*Conclusions:*

- Patients with HMA treatment failure who were treated with rigosertib had better overall survival than those treated with best supportive care.
- The same conclusion pertains to certain subgroups that can be identified using disease characteristics before treatment.
- These characteristics should be considered in the design of future trials of second-line rigosertib therapy in patients with HMA failure.

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**ASCO 7021: A Multi-Institution Phase I Trial of Ruxolitinib in Chronic Myelomonocytic Leukemia (CMML)**

*Eric Padron, Amy Elizabeth Dezern, Kris Vaddi, Peggy A Scherle, Qing Zhang, Yan Ma, Maria Balasis, Sara Tinsley, Hanadi Ramadan, Casandra Zimmerman, David P. Steensma, Gail J. Roboz, Jeffrey E. Lancet, Alan F. List, Mikkael A. Sekeres, Rami S. Komrokji*

Chronic myelomonocytic leukemia (CMML) is a type of cancer that starts in the bone marrow cells that form new blood cells. Abnormal blood cells known as myeloblasts and myelocytes accumulate in the bone marrow and other organs, and they interfere with the production of healthy blood cells. Treatments for this deadly disease are limited.

A research team completed the first Phase I clinical trial of the safety and efficacy of ruxolitinib in CMML. This drug has Food and Drug Administration approval for treatment of polycythemia vera, a bone marrow disorder that causes production of too many red blood cells.

The study enrolled four groups of patients who were treated with doses of ruxolitinib ranging from 5 mg to 20 mg twice daily. Of the 19 patients in the study (median age 71 years), 11 had undergone other treatments before.

*Key findings:*

- None of the side effects was serious enough to stop patients from getting a higher dose of ruxolitinib.
- The only side effect associated with ruxolitinib was thrombocytopenia, platelet shortage, in one patient.
- In the 15 patients whose responses could be evaluated, three had higher blood counts and one had a partial response to treatment.
- The spleen shrunk by more than 50% in six of nine patients with an enlarged spleen at the start of the study.
- B symptoms (fever, night sweats, and weight loss) stopped or declined sharply in 14 patients.

*Conclusions:*

- Ruxolitinib has promising activity in CMML.
- Ruxolitinib is particularly beneficial in patients with B symptoms due to CMML.
- A Phase II clinical trial will further test the efficacy of ruxolitinib in CMML.

## What this Means For Patients

This abstract reported the results of a clinical trial testing the safety and potential efficacy of ruxolitinib, an FDA approved orally administered tablet for the treatment of myelofibrosis, in chronic myelomonocytic leukemia (CMML). The study treated 20 CMML patients with increasing doses of ruxoltinib and found that this drug did not cause serious side effects.

Further, some patients on this study achieved improvements in blood counts, reduction in spleen size, and improvement in disease related symptoms. A phase 2 study further testing the efficacy of ruxolitinib in CMML is ongoing.

**Eric Padron, MD**

### EHA P241: Randomized, Placebo (PBO)-Controlled, Phase I/II Trial of the Thrombopoietin Receptor Agonist Eltrombopag (EPAG) in Thrombocytopenic Patients with Advanced Myelodysplastic Syndromes (MDS)

*Uwe Platzbecker, Raymond S.M. Wong, Sergio Araujo, John Feigert, John Bennett, Conrad Messam, Frank Mannino,Yasser Mostafa Kamel, Souria Dougherty, Geoffrey Chan, Aristoteles Giagounidis*

Eltrombopag (Promacta®) increases platelet counts and has the potential to prevent relapses and increase survival in patients with bone marrow failure diseases.

This study explored the safety, tolerability, and efficacy of eltrombopag in 32 patients with advanced-stage MDS. All patients had either not responded to previous MDS treatment or had had a relapse after their previous treatment. Their platelet counts were lower than 30×109/L, and 10–19% of their bone marrow blasts (young white blood cells) were abnormal. Patients were randomly assigned to treatment with placebo (14 patients) or with 50 mg eltrombopag once a day (18 patients). The investigators increased doses every two weeks up to 300 mg in patients whose platelet counts didn't rise.

*Key findings:*

- Of 14 patients with bone marrow examination results after baseline, abnormal bone marrow blast counts increased to at least 20% in eight treated with eltrombopag (56%) and three in the placebo group (60%).

- Five patients (28%) in the eltrombopag group and three patients (21%) in the placebo group stopped needing platelet transfusions for at least eight weeks.
- The median overall survival in patients on eltrombopag was 16.1 weeks, compared to 7.7 weeks for those taking a placebo.
- Thirteen patients (72%) in the eltrombopag group and eight (57%) in the placebo group had a serious side effect.
- The most common side effects of eltrombopag were diarrhea (six patients, 33%), constipation (five patients, 28%), and fever (six patients, 33%).
- Five patients (28%) in the eltrombopag group and six (43%) in the placebo group died while on treatment or within 30 days of the last dose.

*Conclusions:*

- Patients with advanced-stage MDS tolerated eltrombopag well.
- Changes in blast counts were similar in patients treated with eltrombopag or placebo.
- The different survival rates in the eltrombopag and placebo groups might be partly due to the direct effects of eltrombopag, MDS treatments, or differences between the groups in the number of patients with features associated with a poor prognosis.

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**EHA S509: Luspatercept Increases Hemoglobin and Reduces Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from the Phase 2 PACE-MDS Study**

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

Luspatercept is a fusion protein made by joining parts of two different genes, Investigators are studying luspatercept to treat anemia in patients whose bone marrow forms red blood cells inefficiently. In a study in healthy volunteers, luspatercept increased hemoglobin levels.

This ongoing, phase 2, multicenter study is assessing the effects of different doses of luspatercept on anemia in patients with low-risk or intermediate-1 risk MDS according to the International Prognostic Scoring System. The doses ranged from 0.125 to 1.75 mg/kg, and patients received luspatercept up to five times. In particular, the researchers measured changes in the numbers of red blood cell units that patients needed for transfusion and the treatment's safety. So far, the authors have results for 44 patients whose average age is 68 years.

*Key findings:*

- Hemoglobin levels increased in 77% of the 13 patients treated with 0.75 to 1.75 mg/kg luspatercept, and 69% had higher red blood cell counts.
- On average, hemoglobin levels increased by 2.7 g/dL in the higher-dose groups and by 0.9 g/dL in the lower-dose groups.
- Of the 28 patients who had had red blood cell transfusions in the eight weeks before the study, 10 (36%) did not need transfusions for at least eight weeks during treatment.
- Patients tolerated luspatercept well, and side effects were mostly mild to moderate.
- The most common side effects were bone pain, headache, diarrhea, muscle pain, and pain in the arms and legs.

*Conclusions*

- These data strongly support further studies of luspatercept in patients with low-risk or intermediate-risk MDS.

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**EHA S510: A Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients with Lower-Risk Myelodysplastic Syndromes (MDS) and Anemia Requiring Transfusion**

*Rami Komrokji, Guillermo Garcia-Manero, Lionel Ades, Abderrahmane Laadem, Bond Vo, Thomas Prebet,Aspasia Stamatoullas, Thomas Boyd, Jacques Delaunay, David P. Steensma, Mikkael A. Sekeres, Odile Beyne-Rauzy, Jun Zou,Kenneth M. Attie, Matthew L. Sherman, Pierre Fenaux, Alan F. List*

Patients with MDS often develop anemia, meaning that they have low levels of red blood cells or hemoglobin. Hemoglobin is a protein in red blood cells that transports oxygen. Anemia is hard to treat, especially if patients don't respond to standard treatment with erythropoiesis-stimulating agents (ESAs).

This phase 2 clinical trial is testing the safety and effectiveness of sotatercept in patients with lower-risk MDS who have anemia. Sotatercept is an experimental protein that increases red blood cell counts.

As of February 4, 2015, the study had enrolled 59 patients (median age 71 years, 66% male). Patients were treated with sotatercept doses ranging from 0.1 to 2. mg/kg. Patients had received a median of six red blood cell units in the eight weeks before sotatercept treatment, and 95% had been treated with ESAs before. This report is based on data from 53 patients.

*Key findings:*

- 23 patients (43%) had higher red blood cell counts after treatment.
- None of the patients in the 0.1 mg/kg group had higher red blood cell counts, compared with four of six patients (67%) of those treated with 0.3 mg/kg.
- Of 45 patients who had needed transfusions of at least eight red blood cell units in the eight weeks before the study, six (13%) did not need red blood cell transfusions for at least eight weeks. Patients in the 1.0 mg/kg group did not need transfusions for a median of up to 123 days.
- Of eight patients who had needed transfusions of at least four red blood cell units in the eight weeks before the study, five (63%) did not need transfusions for up to 472 days.
- Patients tolerated sotatercept well. The most common side effects were fatigue, swollen legs, and diarrhea.

*Conclusions:*

- This study provides promising evidence of sotatercept's clinical activity in patients with anemia and lower-risk MDS who had not responded to ESAs or whose anemia came back after ESA treatment.

## What this Means For Patients

Sotatercept (ACE-011) is a promising investigational treatment that aims to promote red blood cell (RBC) growth. This drug is an injectable activin receptor fusion protein that acts on late-stage erythropoiesis to increase mature erythrocyte release into circulation via a mechanism distinct from erythropoietin. This drug and its class of agents show promise treating anemia and reducing the burden of regular blood transfusions or eliminate this need among lower-risk MDS patients especially those with low

transfusion burden or sideroblastic anemia. A large, randomized study is planned to confirm these promising results with this class of investigational agents.

**Rami Komrokji, MD**

# PREDICTING RESPONSE TO TREATMENT

**EHA S507: Clinical and Molecular Predictors of Response to Erythropoiesis Stimulating Agents (ESA) in Lower Risk MDS Patients**

*Olivier Kosmider, Marie Passet, Valeria Santini, Uwe Platzbecker, Valerie Andrieu, Gina Zini, Odile Beyne-Rauzy,Pierre Fenaux, Francois Dreyfus, Michaela Fontenay, Sophie Park*

Up to half of patients with lower-risk MDS respond to treatment with erythropoietin-stimulating agents (ESAs), which can reduce anemia and delay the need for red blood cell transfusions. One way to predict which patients will respond is to measure levels of erythropoietin in the blood. This hormone helps the bone marrow form red blood cells. But researchers don't know if it's possible to use information on gene mutations to predict response to ESAs.

The authors studied factors that can predict responses to ESAs in 90 patients with lower-risk MDS. Patients' median age was 74 years, and 56% were male.

*Key findings:*

- Patients who were male, had an abnormally high erythropoietin level, or had intermediate-risk MDS had poorer red blood cell responses to ESAs.
- Factors that had no effect on red blood cell responses to ESAs included the most common gene mutations (in the SF3B1, ASXL1, TET2, or DNMT3A genes), age, abnormal chromosomes, or extent of abnormal bone marrow cells.

*Conclusions*

- The gene mutations studied had no effect on whether patients responded to ESAs.

## What this Means For Patients

The majority of MDS patients with lower-risk MDS have anemia, and this problem can often be solved by treatment with erythropoietic agents. Mutations in the genes of patients with MDS have shown prognostic significance, and therefore could have importance in understanding who will respond to ESAs. The number of gene mutations found in patient is important for predicting this response. A patients carrying more than two mutations in different genes had lower probability of having an increased hemoglobin after receiving ESAs.

**Valeria Santini, MD**

### ASCO 7091: Influence of Variant Allele Frequency (VAF) on the Phenotypic Penetrance of TP53 Mutations in Myeloid Malignancies

*David Andrew Sallman, Rami S. Komrokji, Christine Vaupel, Najla Al Ali, Jeffrey E. Lancet, Alan F. List, Jeff Hall, Eric Padron*

Next-generation genomic sequencing is a new technique that can detect the order of nucleotides (building blocks) in large amounts of DNA. This technique has allowed researchers to detect important genetic mutations in people with myeloid cancers. These mutations affect white blood cells that normally become different types of blood cells. But the relevance of the variant allele frequency (VAF) of these mutations is not known. VAF refers to how common a gene variant is in a group of people.

A research team from the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida assessed the VAF of mutations in the TP53 gene. The study included next-generation sequencing data on 43 patients with the TP53 mutation who had MDS. Patients with this mutation have a poorer prognosis than those without the mutation.

*Key findings:*

- The average VAF was 39.8%.
- 80% of patients with the TP53 mutation had a complex karyotype, meaning that they had at least three abnormalities in their chromosomes.
- All patients with a TP53 mutation and a VAF higher than 40% had a complex karyotype compared to 50% of those with a VAF lower than 20%.
- MDS patients with a TP53 VAF higher than 40% survived a median of 102 days.
- Patients with RUNX1 gene mutations or a higher VAF were more likely to have thrombocytopenia (shortage of platelets).

*Conclusions:*

- Determining the TP53 VAF makes prognosis more precise than simply determining whether the mutation is present or not.

## What this Means For Patients

TP53 mutations have been reported in 5-10% of MDS patients, although enriched in patients with complex cytogenetics (three or more chromosome abnormalities). TP53 mutations portend an independent, inferior overall survival. In this study we examined the impact of TP53 mutation variant allele frequency (VAF), which reflects the size of the clone carrying the mutation (percent of MDS cells carrying the mutation). The study confirmed the observation of poor outcome associated with p53 mutation. MDS patients with TP53 mutation particularly those with VAF >40% are strongly encouraged to consider clinical trials examining novel agents.

**Rami Komrokji, MD**

### ASCO 7001: Association Between KIR Genes and Risk of MDS

*May Daher, Catherine Sobieski, David Marin, Takuya Sekine, Elizabeth J. Shpall, Richard E. Champlin, Hagop M. Kantarjian, Guillermo Garcia-Manero, Katayoun Rezvani*

Natural killer (NK) cells are a type of white blood cell that destroys infectious or cancerous cells. The surfaces of NK cells have activating killer-cell immunoglobulin-like receptors (KIRs). These proteins regulate the activities of NK cells.

Different people inherit different numbers of the six activating KIR genes. Little is known about how these genetic differences affect people's susceptibility or resistance to developing MDS.

A research team from the University of Texas MD Anderson Cancer Center compared DNA and activing KIR genes in specimens from 180 patients with MDS and 117 healthy people. Of these patients, 120 had high-risk MDS and 60 had low-risk MDS according to the International Prognostic Scoring System.

*Key findings:*

- Patients with high-risk MDS had many fewer activating KIR genes than patients with low-risk MDS or healthy people.
- Patients with low-risk MDS had fewer activating KIR genes than healthy people.
- Every additional activating KIR gene that a person inherited protected that person from developing high-risk MDS.

*Conclusions:*

- Inheriting more activating KIR genes protects people from developing MDS.
- People with MDS who have fewer activating KIR genes tend to have higher-risk disease.

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**ASCO 7017: Correlation of Overall Survival (OS) with Bone Marrow Blast (BMBL) Response in Patients with Myelodysplastic Syndromes**

*Lewis R. Silverman, Pierre Fenaux, Peter Greenberg, Erin P Demakos, Valeria Santini, John Francis Seymour, Shyamala Chendal Navada, Michael E. Petrone, Barbara R Snyder, Nozar Azarnia, Guillermo Garcia-Manero*

Patients with MDS have blasts, or immature white blood cells, in their bone marrow. The proportion of bone marrow blasts (BMBLs) of all cells in the bone marrow can be used to predict outcomes of MDS. However, only limited research has assessed use of BMBLs to predict responses of patients with MDS to treatment.

An international team of researchers studied the relationship before survival and BMBLs in 887 patients with higher-risk MDS. The data on these patients came from seven clinical trials.

*Key findings:*

- In ONTIME, a Phase III clinical trial in 299 patients, BMBL response or stabilization correlated with overall survival after four weeks of treatment and after 12 weeks of treatment.
- In four Phase I and Phase II studies, partial or complete BMBL response correlated with survival after four and eight weeks that was four times longer than in people with no BMBL response.
- In Study AZA-001, BMBL response or stabilization correlated with a lower risk of death.
- In Study 9221, overall survival was six times longer in patients with BMBL response or stabilization.

*Conclusions:*

- Studies conducted over a decade on different treatments show that BMBL response or stabilization in response to treatment correlates consistently with overall survival in patients with high-risk MDS.
- Reduction or stabilization of BMBLs could be a new indicator of early response to treatment, an intermediate endpoint to evaluate new treatments, and a marker of disease progression in high-risk MDS.

### EHA 5131: Clonal Architecture and Evolution in Myelodysplastic Syndromes

*Pedro da Silva-Coelho, Leonie I. Kroeze, Kenichi Yoshida, Theresia N. Koorenhof-Scheele, Louis T. van de Locht, Aniek O. de Graaf, Marion Massop, Marian J. Stevens-Kroef, Petra Muus, Gerwin Huls, Bert A. van der Reijden, Seishi Ogawa, Joop H. Jansen*

Patients with MDS sometimes have several clones (abnormal copies of immature white blood cells) in the bone marrow with different gene mutations. As the disease progresses, the composition of the clones can change, and the patient can acquire other genetic defects. The architecture of clones in each patient might help explain why the course of MDS and responses to treatment are so different in different patients.

The authors studied the composition of clones in 12 patients with low-risk to intermediate-risk MDS using profiles of non-inherited gene mutations throughout the course of the disease. They also evaluated correlations between architecture and evolution of clones, patient symptoms, and treatment responses.

#### *Key findings*

- Patients had a median of 14 gene mutations known to be associated with the development of MDS.
- Clones evolved in different ways in different patients. Some patients had just one main clone that remained stable for many years. Other patients had many changes in clones.
- In one of the patients who had a complete response to treatment with lenalidomide (Revlimid), the patient's gene mutations went away. But this patient had a relapse after acquiring mutations in the TP53 and RELN genes in the original clone.

#### *Conclusions:*

- The reason why MDS results in different symptoms and different responses to treatment in different patients seems to be the major differences in the composition of clones and how they evolve in different patients.
- The findings show the importance of monitoring the genetics of the disease and developing treatment strategies that can eradicate several different clones.

### EHA S508: Analysis of Prognostic Markers in 615 Patients with Therapy-Related Myelodysplastic Syndromes - Are Currently Available Scoring Systems Suitable in This Patient Group?

*Andrea Kuendgen, Heinz Tuchler, Meritxell Nomdedeu, Richard F Schlenk, Xavier Calvo, Sabine Blum, Arturo Pereira,Peter Valent, Dolors Costa, Aristoteles Giagounidis, Luis Benlloch, Uwe Platzbecker, Carmen Pedro, Michael Libbert,Maria Teresa Cedena, Sigrid Machherndl-Spandl, Maria Lopez-Pava, Detlef Haase, Ana Afrika Martin, Claudia D. Baldus,Montserrat Martinez de Sola, Reinhard Stauder, Brayan Marcel Merchan, Claudia Mende, Maria Teresa Ardanaz, Christina Ganster,Francesc Cobo, Thomas Schroeder, Jordi Esteve, Rainer Haas, Benet Nomdedeu, Ulrich Germing, Guillermo F. Sanz*

Doctors often use the International Prognostic Scoring System (IPSS) to evaluate each patient's MDS and choose appropriate treatments. The recently revised IPSS (known as the IPSS-R) takes more information into account than the IPSS. The IPSS-R improves the ability of physicians to predict the course of disease in each patient. But like the IPSS, the IPSS-R was developed using data from untreated patients only. Data on the usefulness of the IPSS-R for prognosis in treated patients is limited.

The authors analyzed data on 446 patients (average age 67 years) diagnosed between 1975 and 2015 at medical centers in Spain, Germany, Switzerland, and Austria.

*Key findings:*

- Factors that affected survival and when MDS progressed to acute myelogenous leukemia (AML) included age, IPSS score, IPSS-R score, platelet count, abnormal blasts (immature white blood cells) in marrow and blood, and year of diagnosis.
- Both the IPSS and IPSS-R performed moderately well in patients who been treated for MDS, but not as well as in untreated patients.

*Conclusions:*

- Scoring systems that include blasts in the peripheral blood that circulates throughout the body did slightly better than the IPSS or IPSS-R.
- Scoring systems that predict survival separately from time to development of AML would give different weights to most factors. Scoring systems for survival would give more weight to hemoglobin levels in blood and abnormal chromosomes. Scoring systems to predict progression to AML would emphasize bone marrow blasts.

# QUALITY OF LIFE

**EHA P242: The Effect of Lenalidomide on Health-Related Quality of Life in Patients with Myelodysplastic Syndromes: Results from the MDS-005 Trial**

*Valeria Santini, Antonio Almeida, Aristoteles Giagounidis, Chris Bartiromo, Albert Hoenekopp, Shien Guo, C.L. Beach,Arman Altincatal, Chengqing Wu, Barry Skikne, Jim Zhong, Henry Hu, Pierre Fenaux*

Patients with MDS who need regular blood transfusions to treat anemia often have poor health-related quality of life.

A team of researchers evaluated the effects of lenalidomide treatment on health-related quality of life in 178 patients with MDS who were part of a Phase 3 clinical trial. All patients had low-risk or intermediate-risk MDS according to the International Prognostic Scoring System. Patients had not responded to treatments intended to increase their red blood cell counts, or they had had a relapse of their anemia after these treatments. In the study, significantly more patients treated with lenalidomide stopped needing regular blood transfusions than those in the placebo group.

*Key findings:*

- After 12 weeks of treatment, average changes in scores on a health-related quality-of-life questionnaire since the start of the study were similar in both treatment groups.
- After 24 weeks, patients in the lenalidomide group had a better score for emotional functioning than the placebo group, but scores in both groups were the same for fatigue, breathing problems, physical functioning, and global quality of life.
- For patients in the lenalidomide group who stopped needing red blood cell transfusions, fatigue, breathing problems, emotional functioning, physical functioning, and global quality of life were significantly better than in the placebo group.

*Conclusions:*

- These findings demonstrate the beneficial effects of lenalidomide on health-related quality of life in patients with low-risk or intermediate-risk MDS who need regular blood transfusions to treat anemia.

## What this Means For Patients

Patients with MDS refractory anemia who no longer respond to erythropoietic stimulating factors or who have never responded to them, do not have many therapeutic options, apart from red blood cell transfusions. Lenalidomide has shown a striking efficacy in reducing transfusions and in normalizing hemoglobin levels in the majority of MDS patients carrying del5q cytogenetic anomaly. When patients treated with lenalidomide had their quality of life (QoL) indexes analyzed, it is clear that the achievement of sustained transfusion independence was accompanied by a significant improvement of QoL parameters. This is very important because it means that, despite some side effects, lenalidomide can ameliorate the general conditions of certain patients.

**Valeria Santini, MD**

### EHA S147: Accuracy of Physician Assessment of Treatment Preferences and Health Status in Patients with Higher-Risk Myelodysplastic Syndromes

*Giovanni Caocci, Maria Teresa Voso, Emanuele Angelucci, Reinhard Stauder, Francesco Cottone, Gregory Abel,Khanh Thi-Thuy Nguyen, Uwe Platzbecker, Odile Beyne-Rauzy, Gianluca Gaidano, Rosangela Invernizzi, Stefano Molica,Marianna Criscuolo, Massimo Breccia, Michael Lübbert, Grazia Sanpaolo, Francesco Buccisano, Alessandra Ricco,Giuseppe Palumbo, Pasquale Niscola, Huiyong Zhang, Susanna Fenu, Giorgio La Nasa, Franco Mandelli, Fabio Efficace*

This study evaluated the accuracy of physicians' perceptions of patients' health status and patients' preferences about being involved in treatment decisions. The study also examined physicians' attitudes toward patient involvement in treatment decisions and factors that influence physicians to involve or not involve patients in making treatment decisions. The study included 280 patients with high-risk MDS and 68 physicians.

*Key findings:*

- 49% of physicians correctly judged patients' preferences for involvement in treatment decisions.
- Among the 51% of physicians who misjudged patients' preferences, the differences were major in 15% of cases.
- In 45% of patients who preferred a passive role in treatment decisions, physicians thought that these patients preferred an active or collaborative role.
- Physicians only believed that their patients wanted no involvement in treatment decisions when patients didn't ask about their prognosis or the physicians thought that the patient's health was poor.
- Physicians and patients agreed on how healthy the patient was in 28% of cases.
- Physicians tended to overestimate the health status of patients who thought that their health was poor.

*Conclusions:*

- Physicians treating patients with MDS often have trouble understanding their patients' preferences.
- Some physicians don't think that their patients' preferences are important.
- Physicians need to better understand how healthy their patients are so that they can more accurately judge whether these patients are eligible to participate in clinical trials.

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- Your Guide to Understanding MDS*
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- Living Well With Bone Marrow Failure Disease**
- Standing Up for Your Health**
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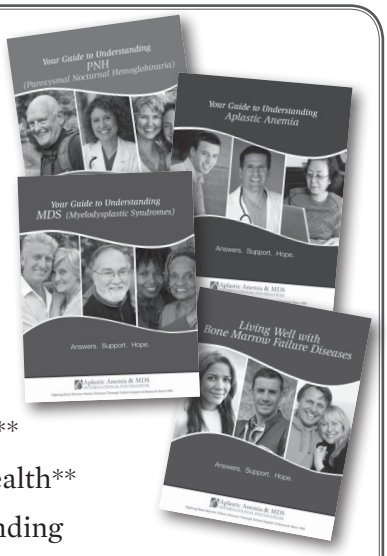


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