



mds news

newsletter of the myelodysplastic syndromes foundation

MDS NEWS HIGHLIGHTS

FROM THE GUEST EDITOR'S DESK

- **The 14th International Symposium on Myelodysplastic Syndromes: An Overview**
Presented by Symposium Chair: Guillermo F. Sanz, MD, PhD
May 3–6, 2017 • Valencia, Spain



PLAN TO ATTEND ASH 2017 MDS FOUNDATION BREAKFAST SYMPOSIUM

December 8, 2017 • Atlanta, Georgia

**PRESENTATIONS WILL BE AVAILABLE on the
MDS Foundation website www.mds-foundation.org**

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Guest Editorial – The 14th International Symposium on Myelodysplastic Syndromes: An Overview



Guillermo F. Sanz, MD, PhD
Head, Clinical Hematology
& Hematopoietic Cell
Transplantation Unit
Hospital Universitario y
Politécnico La Fe
Valencia, Spain

Valencia, Spain:

From May 3–6, 2017, the MDS Foundation and I, along with the members of the Scientific Subcommittee and the Local Organizing Committee of the Spanish Group on MDS (Grupo Español de Síndromes Mielodisplásicos, GESMD), welcomed 1,074 delegates coming from 65 countries to Valencia, Spain for the 14th International Symposium on Myelodysplastic Syndromes.

As Dr. Stephen Nimer, Chairman of the MDS Foundation, stressed at the Networking Event on the evening of May 5th, the meeting was a huge success and set a new standard for our upcoming bi-annual symposia. “This is the best MDS Foundation symposium we have ever had,” said Dr. Nimer. The scientific contents of the different sessions fully covered both the numerous established as well as the new breakthroughs in the field of MDS and allied hematological disorders. Session Chairs and invited speakers delivered sound, real and unbiased, scientific knowledge in the MDS arena, and all participants enjoyed an enthusiastic and positive atmosphere. The venue, the Valencia Congress Palace (Palacio de Congresos de Valencia), was the perfect

The scientific contents of the different sessions fully covered both the numerous established as well as the new breakthroughs in the field of MDS, and allied hematological disorders.

place for this meeting. The building, designed by Sir Norman Foster (also the architect of the new and magnificent Apple Park in Cupertino, CA), seemed to be specifically built for covering the needs of our Symposium. The light and warm environment, the latest up-to-date audio-visual technology, and the different polyvalent rooms and spaces of the Congress Center had a lot to do with the joyful, friendly, and interactive networking experienced by all delegates. Furthermore, the members of the symposium secretariat (KENES), the local organization (PALCONGRESS), and GESMD members did their best to succeed in easing and solving all the issues that really mattered at the event. The availability of several quite comfortable and well equipped hotels located within walking distance from the Congress Center was also an added value for attendees. And finally, the spring weather in Valencia was so splendid during the conference that it allowed all the different MDS stakeholders, including physicians, researchers, pharmacists, pharmaceutical company representatives, patient advocacy groups, and patients attending the Patient Forum meeting, to explore the diverse treasures that the city of Valencia holds.

The 14th Symposium came back to the original format of previous symposia with only one track running almost at all times. This ‘old’ format gave the delegates the opportunity to attend all relevant sessions, without losing any details of the relevant advances occurring in the biological knowledge of MDS, and in the current and future management of those patients. On May 3rd, and before the Opening Ceremony, there were 3 very well attended workshops on Flow Cytometry, Genetics, and Cytomorphology where both specialists in training and experienced physicians and biologists were able to freely interact with the most recognized international experts in those fields which is so essential for an accurate diagnosis and up-to-date management of MDS. At the Opening Ceremony, Dr. Nimer and I welcomed all attendees to the meeting and we had the pleasure of listening to the magisterial lecture on “Clonal diversity and clonal evolution in MDS progression” by Dr. Timothy Graubert, where he dissected the diverse genomic lesions that drive the appearance and progression of MDS. This was followed by the Welcome Reception that gave all of us the opportunity to enjoy the marvelous sound of the Orquesta Filarmónica Martín i Soler de Valencia and Orquesta Unión Musical Santa Cecilia de Onda, conducted by Mrs. Carmen Más Arocas. The audience shared the magic of those non-professional but exquisite musicians that amused us for more than one hour with a full repertoire of very-well known and admired songs coming from classic Spanish and other European country composers. After that remarkable performance, attendees were able to delight in some of the excellent typical dishes Valencia offers to those having the luck of visiting our city.

Other novelties of this 14th MDSF meeting were the 4 early morning Meet-the-Expert sessions where recognized experts in different areas of MDS diagnosis and management, offered their expertise and advice on particular clinical cases.

The 7 Plenary Sessions of the meeting fully covered all the relevant aspects regarding MDS, including Biology and Pathogenesis (2 sessions), Diagnosis and Prognosis, Chronic Myelomonocytic Leukemia – a borderline MDS disorder, Singular MDS Subtypes, such as 5q-syndrome and MDS in children, and Treatment (3 sessions), including current options, new therapies and allogeneic hematopoietic cell transplantation. Further, the 4 additional parallel sessions dealt with Health Economics and Research Outcomes, Predicting Response to Therapy, Controversial Issues, and Caring for the Patient with MDS, all of them underlying the pivotal and central role of MDS patients in our research and daily practice. All those sessions were featured by outstanding speakers who provided updated data, sometimes unpublished, of great valor for all delegates. It is almost impossible to highlight one lecture over the rest. True, the increasing impact on clinical practice of the massive developments on genetics and cell biology was recognized by attendees. Further, all this knowledge is translating into the discovery of new innovative drugs that are currently under evaluation in multiple clinical trials. The road to personalized medicine is already open and the preliminary results of targeted drugs, such as luspatercept for MDS patients with anemia and enasidenib for patients with IDH2 mutations are promising.

One fundamental aim of the Valencia meeting, stressed by the MDSF Board of Directors, was to rely on the local organizing committee for structuring the scientific program so that we were able to present new high quality data on MDS biology and treatment, and to give young

investigators, working in the field, the chance to present their research. Accordingly, the 14th MDSF meeting allocated sufficient time slots to feature 4 Oral Sessions, each with 6 oral abstracts, another 2 oral abstracts at every Plenary Session (overall, 16 abstracts) and the outstanding Tito Bastianello Young Investigator Session, with the 4 best abstracts coming from less than 35 year-old researchers and clinicians. All these oral, as well as the best quality abstracts selected for poster presentations, were chosen among the more than 380 submitted abstracts by a panel of more than 40 experts in the different areas of MDS research. I would like to thank all of the reviewers for their impressive commitment to that invaluable task.

Apart from the physicians main program, there were also three relevant sessions. The MDS Patient Forum, devoted to MDS patients and their caregivers, provided an excellent forum for vivid discussions and interactions with MDS physicians, and was a great success. Further, for the first time, the symposium hosted a Pharmacists Session that recognized the relevance of these professionals in the appropriate management of MDS patients.

The Valencia MDS Foundation meeting also brought new activities outside the

official program that were very well received. There were two Satellite Symposia, sponsored by the pharmaceutical companies Celgene and Novartis, respectively, and a Pipeline Session on MDS & Myeloid Malignancies, where six top representatives from different pharmaceutical companies presented first-hand to the audience their drug development in the field. That session was a big success, and we suggest this should be maintained in future MDSF meetings.

Finally, the Gala Networking Event, that was beautifully prepared by the LOC, took place at the Oceanographic Marine Park, one of the most beautiful aquariums in Europe. The delegates had the opportunity to explore that amazing animal habitat at their leisure, as well as viewing a wonderful dolphin show, followed by a delicious dinner in the best environment possible.

In conclusion, the Valencia MDS Foundation Symposium was a big success, not only from a scientific point of view, but for the unforgettable friendly atmosphere that allowed close, positive, and enthusiastic interaction between all delegates. In the end, MDS is like a great family and we did our best for everyone attending the meeting to feel at home — a really difficult task when you are abroad. We believe that in most cases we achieved that goal.



<http://www.tpi-webcast.com/MDS2017>

14TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES



14TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES



**HIGHLIGHTS FROM THE
14TH INTERNATIONAL SYMPOSIUM
ON MYELODYSPLASTIC SYNDROMES**

**May 3–6, 2017
Valencia, Spain**





14TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

MAY 3–6, 2017
VALENCIA, SPAIN

PATIENT SUMMARY

The purpose of this guide is to provide you with MDS related information recently presented at the MDS Foundation's **14th International Symposium on Myelodysplastic Syndromes** that took place in Valencia, Spain from May 3 – May 6, 2017. This guide includes material related to clinical aspects of MDS diagnosis, prognosis, and management as well as the newest data in MDS basic and translational research. The main lectures were delivered by recognized international leaders but also included high-level research talks selected from the abstracts submitted by attendees. New information that researchers hope is important enough to be presented at this meeting is submitted a few months ahead of the conference in the form of an abstract – a brief summary of the study and its results – and authors of the most interesting noteworthy abstracts are asked to present their research in more detail, either in the format of a printed poster or an oral presentation.

As the 14th meeting in our **biennial MDS international symposium program**, this meeting in Spain hosted nearly 1,100 delegates and included three workshops dedicated to specific MDS-related research developments. Also included were 10 plenary scientific sessions, roundtables and debates, and an abstract poster viewing. First the first time, we also offered a pharmacists session and medical pipeline sessions.

We selected the following discussions to summarize because we feel they are the most relevant and important for patients who are currently living with MDS. Please note that some of the research results discussed in this summary may include experimental drugs that are not yet approved for general use, or investigations of potential new uses of previously approved treatments. By providing summaries of these talks, we do not intend to recommend or endorse any particular medication or treatment approach. Our goal is to simply 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 guide, we encourage you to speak with your doctor about clinical trials, or call the MDSF Patient Liaison for assistance at 1-800-637-0839. Please feel free to also reach out to MDSF if you have any questions regarding these summaries or any aspect of managing your disease.

Rafael Bejar, MD

UC San Diego Moores Cancer Center
La Jolla, California, USA
MDSF Medical and Scientific
Advisory Board

Rena Buckstein, MD

Sunnybrook Health Sciences Centre
Toronto, Canada
MDSF Medical and Scientific
Advisory Board

Uwe Platzbecker, MD

University Hospital Carl Gustav Carus
Dresden, Germany
MDSF Medical and Scientific
Advisory Board



NEW CLASSIFICATION SYSTEMS

World Health Organization's 2016 Classification System for MDS

Dr. Ulrich Germing, M.D. (Heinrich Heine Universität Düsseldorf, Germany) gave an update on the World Health Organization (WHO) classification system for MDS. Doctors often use this system to assess MDS severity and predict a patient's outcomes. But this system, last updated in 2008, has some weaknesses. For example, up to 20% of patients with MDS have less severe **cytopenia*** than the WHO's cutoff level for an MDS diagnosis.

A panel of experts revised the WHO system in 2016 to improve its ability to predict the outcomes for individual patients. An independent analysis of data on 3,528 patients with MDS from the German MDS registry showed that the new WHO system categories work well. The main changes to the WHO 2008 classification system are described below.

1. Category names

The 2016 system has changed the names of several MDS subtypes by replacing "refractory anemia" with "MDS" wherever the term "refractory anemia" appeared. For example, refractory anemia with excess blasts I and II is now MDS with excess blasts 1 and 2, respectively.

2. New category for MDS with ring sideroblasts

The 2016 system redefined the old refractory anemia with **ring sideroblasts** and refractory cytopenia with **multilineage dysplasia** and ring sideroblasts subtype of MDS. The new category, MDS with ring sideroblasts, applies to patients who have single or multilineage dysplasia and one of the following (because these patients have the same favorable risk profile):

- A least 15% of ring sideroblasts
- OR
- At least 5% ring sideroblasts in patients with a mutation in the SF3B1 gene

3. New definition of MDS del(5q)

The 2016 system defines this MDS category as:

- Less than 5% **blasts** in the bone marrow

* Please see LIST OF ACRONYMS and GLOSSARY OF TERMS for all **highlighted** terms.

- Shortages of one or two types of blood cells
- **Del(5q)** with or without one additional cytogenetic abnormality, as long as this abnormality is not in chromosome 7

Also, the system is replacing the category of MDS del(5q) with pancytopenia. The new term is MDS, unclassifiable.

4. More precise definitions of MDS, unclassifiable

This category now includes:

- Less than 5% bone marrow blasts, no del(5q), and less than 1% blasts in peripheral blood
- Less than 5% bone marrow blasts, no del(5q), and 1% peripheral blood blasts at two or more times
- No clear dysplasia but abnormalities in chromosomes that are typically seen in MDS

5. New cutoffs for the proportion of blasts in bone marrow

The new cutoffs are:

- MDS with excess blasts 1: 5% to 9% blasts in bone marrow or 2% to 4% blasts in peripheral blood
- MDS with excess blasts 2: 10% to 19% blasts in bone marrow or 5% to 19% blasts in peripheral blood

MDS Risk Assessment Based on Other Diseases in Older Patients

Dr. Fernando Ramos (Hospital Universitario de León, Spain) explained that patients with MDS often have **comorbidities**. Patients are almost as likely to die of their comorbidities as of MDS.

Some comorbidity indexes can be used to assess patients. Most of these tools are generic, but the MDS-Specific Comorbidity Index is now available. More research is needed on its ability to accurately predict outcomes.

The Comprehensive Geriatric Assessment evaluates many factors in elderly patients, including comorbidities, physical and mental performance, nutritional status, muscle mass, and socioeconomic status. All of these factors should be taken into account, especially given the aging of the general population in North America and Europe. But this tool has some limitations. It is time consuming to use and needs to be completed by someone with geriatric expertise. Also, the screening tools used to identify patients who need the full assessment are far from perfect.

Some simplified geriatric assessment tools, including the Geriatric Assessment in Hematology scale, provide an alternative to the more comprehensive and generic tools. This tool measures the number of drugs the patient is taking, walking speed, mood, daily activities, perceived health status, nutrition, mental status, and comorbidities. It is currently being tested.

Another scale was developed to predict mortality at 4 years in adults older than 50 using just 12 questions. This questionnaire asks about comorbidities, behaviors, functional and physical performance, age, gender, and current smoking. Dr. Ramos tested this index in 200 patients with MDS. Use of this tool improved the ability of the [revised International Prognostic Scoring System \(IPSS-R\)](#) to predict patient survival. But the index didn't improve the

ability to predict risk of progression to acute myelogenous leukemia (AML).

Frailty can be defined as age-related loss of physiological capacity that can lead to loss of energy, motivation, illness, and disability. Frailty can be measured in different ways, but Dr. Ramos prefers the Clinical Frailty Scale. This scale has nine categories, ranging from very fit to terminally ill. The Clinical Frailty Scale was tested in more than 400 Canadian patients with MDS, and it did a good job of predicting overall survival independently of the IPSS-R.

Dr. Ramos believes that patients should receive the best available treatment for their MDS if their life expectancy would not otherwise be very short. He recommends taking into account IPSS-R score, age-adjusted frailty, and comorbidity for MDS prognosis.

CHROMOSOME AND GENETIC TESTING FOR MDS DIAGNOSIS AND PROGNOSIS

Uses of Chromosome Testing

Dr. Francisco Solé (Josep Carreras Leukaemia Research Institute, Barcelona, Spain) reported that new technologies, such as next-generation sequencing (NGS), can identify gene mutations indicating the presence of genetically abnormal cells and provide information about the likely prognosis. Some experts have therefore questioned whether doctors still need to evaluate [cytogenetic](#) abnormalities in patients with MDS. Dr. Solé argued that chromosome testing is still both useful and necessary and is likely to remain so in the coming years because it has value for prognosis, diagnosis, and treatment decisions.

Prognosis

The original [International Prognostic Scoring System \(IPSS\)](#) often failed to identify patients with apparently low-risk or intermediate-risk MDS who actually had a poor prognosis. The [IPSS-R](#) considers more abnormalities in certain chromosomes and takes the severity of [cytopenias](#) into account. Overall, the IPSS-R does a better job of categorizing risk in patients with MDS than the original IPSS.

Cytogenetic testing is also useful for monitoring a patient over time. If, for example, a change happens in a patient's chromosomes, this could affect his or her prognosis.

Diagnosis

Diagnosis of MDS requires laboratory testing and a bone marrow biopsy to assess the shape of blood cells, the presence of [blasts](#), and cytogenetic abnormalities. Doctors use this information to predict patient outcomes, choose the appropriate treatment, and monitor patients over time.

No more than half of patients with MDS have abnormalities in their chromosomes. Using a combination of genomic arrays, genetic sequencing, and cytogenetic testing can identify changes in genes or chromosomes in 90% of patients. No one technique is enough—they are all complementary.

Treatment Decisions

Certain treatment decisions for patients with MDS are based on cytogenetic information. Specifically, lenalidomide is the recommended treatment for patients with [del\(5q\)](#) MDS. Similarly, azacitidine is appropriate for patients with higher risk MDS who often have aberrations in chromosome 7 or a complex karyotype.

Use of Genetic Testing

Somatic Mutations in Prognosis

Dr. Rafael Bejar (Moore Cancer Center, UC San Diego, United States) reported that somatic mutations can give doctors more information than standard laboratory tests. Researchers have identified many somatic mutations in patients with MDS.

An analysis of data from more than 3,500 patients found that those who had a somatic mutation in the *SF3B1* gene alone tended to survive longer. But, several other mutated genes were associated with poorer outcomes. On average, prognosis worsened with every additional somatic mutation in genes other than *SF3B1*. Some of the mutations were associated with better or worse outcomes than the *IPSS-R* would predict.

Just looking at individual mutations in a patient doesn't give the whole picture—it's important to look at all mutations in each patient because this pattern can influence outcomes. For example, patients with *SF3B1* mutations tend to have very few other mutations that are associated with a poor prognosis. But patients without *SF3B1* mutations are likely to have mutations associated with a poor prognosis.

Somatic Mutations in Diagnosis

The expert panel that updated the WHO system didn't choose to include additional mutations to define MDS subtypes because some people can develop mutations associated with MDS as they age, even though they have no other signs of MDS. This condition is known as Clonal Hematopoiesis of Indeterminate Potential, or CHIP. If an older patient with low blood counts has one of these mutations, it might be hard to tell if the mutation is a marker of MDS or just part of the aging process.

However, some mutations might be useful for diagnosing MDS. For example, the WHO classification system uses *SF3B1* mutations to classify MDS with *ring sideroblasts*. Other mutations can predict progression to AML or another blood cancer in patients with unexplained *cytopenias*. Having no mutations in certain MDS genes means that the patient likely has a good prognosis. Mutations can also be useful for predicting prognosis once a patient's MDS has been diagnosed.

Example: Study of Changes in Genetic Mutations for Prognosis in MDS and Secondary AML

Dr. David Sallman (H. Lee Moffit Cancer Center & Research Institute, United States) described a study that used information on genetic mutations for prognosis. This study included 157 patients with MDS, chronic myelomonocytic leukemia (CMML), or *secondary AML*. All patients were assessed with NGS at least twice.

The most common mutations at the first NGS test performed before treatment were in *ASXL1*, *TET2*, and *DNMT3A*. On average, patients had two mutations at this time. By the second assessment, conducted after patients were treated, 13% of patients had lost all their mutations, 27% had lost one mutation, and 37% had gained a mutation. Over half had increases in *variant allele frequency*.

Patients treated with azacitidine or decitabine who were in complete remission had decreases in variant allele frequency, although this change was not statistically significant. But patients who had the same treatments and were not in complete remission tended to have an increase in variant allele frequency. The results were similar for patients treated with chemotherapy. Most patients who had had a stem cell transplant and were in complete remission had no MDS mutations. But all those tested after a relapse had developed mutations.

Most patients who had no mutations detected by the first NGS were alive 18 months later, compared with only 34% of those with mutations at the first NGS. Those who lost their mutations at the second NGS survived much longer than those who continued to have mutations.

No particular type of mutation predicted whether a patient would have no mutations after treatment. However, most patients who had a mutation in the *TP53* gene lost this mutation after treatment with azacitidine or decitabine. Mutation gains and increases in variant allele frequency did not predict overall survival. Loss of mutations did predict better outcomes, but when patients who lost all mutations were excluded from the analysis, loss of mutations had no association with better outcomes.

The results from this study highlight the prognostic value of repeating NGS. They also show that negative NGS results after treatment indicate a good prognosis for patients with MDS.

Early Decreases in Platelet Counts for Prognosis of Lower-Risk MDS

Dr. Raphael Itzykson (Hôpital Saint-Louis, Université Paris Diderot, France) described the results of a study that assessed early declines in platelet counts for prognosis of lower-risk MDS using data from the European MDS Registry. The study included 807 patients from Europe and Israel who had been diagnosed within the previous 100 days. All patients had platelet count information when they joined the registry and again about 6 months later. About 60% were male, the median age was 73 years, and 70% had very low-risk or low-risk MDS according to the [IPSS-R](#).

During the first 6 months after diagnosis, platelet and neutrophil counts dropped by 5%, on average. Also, 27% of patients had rapid declines of at least 20% in platelet counts. The most striking difference between patients whose

platelet counts did and didn't drop by at least 20% was the frequency of red blood cell transfusions at inclusion in the registry and 6 months later.

Patients with a rapid platelet decline tended to survive for a median of 33 months, while those with slower declines survived a median of 57 months. This link between a rapid drop in platelet count and shorter survival held for patients in all IPSS-R categories, except for those with very low-risk MDS. In addition, needing blood transfusions at the 6-month assessment was independently tied to shorter survival.

Dr. Itzykson concluded that a 20% or greater drop in platelets over the first 6 months after diagnosis is associated with a poor prognosis in patients with "lower-risk" MDS. Evaluating changes in platelet counts and need for red blood cell transfusions at 6 months could be a free and reliable way to determine prognosis in MDS.

PREDICTING TREATMENT RESPONSE

Predicting Outcomes of Erythropoiesis-Stimulating Agents and Lenalidomide in Low-Risk MDS

Erythropoiesis-stimulating agents (ESAs) increase red blood cell counts in up to 70% of patients with low-risk MDS who have anemia. About 10% of patients with MDS have [del\(5q\)](#) MDS, and lenalidomide is the best treatment. Dr. María Díez Campelo (Universitario de Salamanca, Spain) described some of the factors that doctors can use to predict the effects of these treatments.

Erythropoiesis-Stimulating Agents

The factors that predict responses to ESAs include:

- Hemoglobin level higher than 10 g/dl
- No [blasts](#) in blood or bone marrow
- Few if any abnormalities in chromosomes
- Low-risk or very-low-risk MDS according to the [IPSS](#) or [IPSS-R](#)
- Higher ESA doses
- Need for few, if any, red blood cell transfusions
- [Erythropoietin](#) level lower than 200 U/L

Lenalidomide in Del(5q) MDS

Almost 65% of patients stop needing regular red blood cell transfusions with lenalidomide. Their hemoglobin levels rise, which is important for longer responses and better quality of life.

Perhaps the most important predictor of response to lenalidomide is a higher platelet count. Patients are also more likely to respond if they don't need many transfused red blood cell units, were diagnosed with MDS in the past 2 years, and don't have many [cytogenetic](#) abnormalities.

Patients with a mutation in the TP53 gene or strong [expression](#) of p53 are less likely to achieve [cytogenetic remission](#) after lenalidomide treatment. Mutations in U2AF1 and DDX41 genes and expression of CRBN and CSNK1A1 might also lower a patient's chances of responding to lenalidomide.

Lenalidomide in Non-Del(5q) MDS

Lenalidomide is only effective at durably eliminating the need for regular red blood cell transfusions in a small proportion of patients (17% according to one study) with non-del(5q) MDS. Response rates are highest in patients who

- Are female
- Need less than four units of transfused red blood cells/month
- Have had MDS for less time
- Have a platelet count higher than $150 \times 10^9/L$
- Have a favorable type of MDS according to the WHO classification system
- Have been treated with ESAs in the past
- Are treated with 10 mg/day of lenalidomide (as opposed to 5 mg/day)
- Have low-risk MDS
- Do not have many chromosome abnormalities or any linked with a poor prognosis

Predicting Outcomes of Azacitidine Treatment

Dr. Raphael Itzykson, (Université Paris Diderot, France) discussed markers of **hypomethylating agent (HMA)** response. Whether these drugs are equally effective in all types of higher-risk MDS is a tricky question to answer. They don't cure MDS, and response rates are not useful measures of their effectiveness.

One potential marker of HMA response and effects on survival is a doubling of the platelet count after one cycle of HMAs. But this happens in only a small proportion of patients. Also, patients with increased platelet counts don't necessarily do well over the long term.

The usual markers used to predict whether a given patient will respond to HMA treatment don't work well. For example, although some evidence shows that older patients and those with **comorbidities** don't do as well with HMAs, this evidence has some important weaknesses.

Abnormalities in chromosomes at the start of treatment also do a poor job of predicting responses to HMAs.

According to Dr. Pierre Fenaux (Hôpital St. Louis/Université Paris 7, France), the factors that seem to be most useful for predicting HMA outcomes include chromosome abnormalities, **IPSS-R score**, and mutations in certain genes.

Dr. Itzykson reported that experts have combined different types of markers into prognostic scoring systems. He worked on one of these systems, which categorizes MDS as low, intermediate, and high risk based on how long patients are likely to survive with azacitidine treatment. Researchers are also exploring whether genes involved in faulty **DNA methylation** might be useful for predicting HMA outcomes in patients with MDS.

Several ongoing efforts, including the HARMONY study, have a good chance of identifying the factors that predict HMA outcomes in MDS and other blood cancers and of predicting the effects of HMA treatment on quality of life, healthcare costs, and care strategies.

OPTIONS AFTER TREATMENT FAILURE

Treatment for Del(5q) MDS after Lenalidomide Failure

Dr. Aristoteles Giagounidis (Marien Hospital Düsseldorf, Germany), reported that some patients with [del\(5q\) MDS](#) who have a complete [cytogenetic remission](#) may enjoy long periods of transfusion independence after lenalidomide is discontinued. This is especially true if they were treated with lenalidomide for at least 6 months. But some have a relapse years later.

If MDS doesn't progress after a patient stops responding to lenalidomide, the patient might respond to lenalidomide again after a "drug holiday," at least for a while. But if MDS does progress during lenalidomide treatment, the prognosis is poor.

Patients who never respond to lenalidomide only survive for about 18 months, on average. The risk of progression to AML increases steadily over time after lenalidomide failure.

L-leucine, an amino acid, is effective for anemia in experimental mice with del(5q) MDS and in people with Diamond-Blackfan anemia. Clinical trials are testing L-leucine in patients with del(5q) MDS after lenalidomide failure.

Many patients do well with stem cell transplantation after lenalidomide failure. Even patients whose MDS progresses during lenalidomide treatment can benefit from this procedure. [HMAs](#) can prolong survival in patients who aren't eligible for stem cell transplantation.

The options after lenalidomide failure for patients with del(5q) MDS are to stop the lenalidomide temporarily and start it again, use HMAs if the MDS progresses, and offer stem cell transplantation to eligible patients (especially those who are younger). Two experimental treatments, L-leucine and cenersen, might become options after more research.

Enasidenib, an Inhibitor of the Mutant IDH2 Gene, in MDS after Treatment Failure

Dr. Eytan Stein (Memorial Sloan Kettering Cancer Center, New York) reported that about 5% of patients with MDS have a mutation in the *IDH2* gene. This mutation leads to the accumulation and release of R-2-hydroxyglutarate, a substance that affects [DNA methylation](#).

Enasidenib is a drug that inhibits mutant *IDH2*. A phase I/II clinical trial of enasidenib in 239 patients with AML included 17 patients with intermediate-1, intermediate-2, or high-risk MDS. All patients had an *IDH2* mutation and had experienced [treatment failure](#). The median age was 67 years, and 71% were male.

Ten of the 17 patients with MDS responded, including 1 with a complete remission, 1 with a partial remission, 1 with a complete response in the bone marrow, and 5 with higher blood cell counts. In addition, 7 of the 13 who had been treated with [HMAs](#) in the past responded. The most serious side effects included hyperbilirubinemia (jaundice), pneumonia, platelet shortages, and anemia. No patients died from the treatment.

Most patients who responded left the study because they had a stem cell transplant, their disease progressed, or they died. But a few patients stayed on the study for more than a year. The survival rate at 1 year was 58%.

Dr. Ades noted that the European IDEAL study will provide more information on enasidenib in patients with MDS who have an *IDH2* mutation and have not responded to HMAs.

NOVEL TREATMENTS AND COMBINATIONS OF TREATMENTS

The Best Partner for HMAs in Higher-Risk MDS

Dr. Mikkael Sekeres (Cleveland Clinic, Ohio) focused his presentation on combinations of HMAs and other drugs for higher-risk MDS.

A study compared azacitidine alone to the combination of azacitidine with the histone deacetylase (HDAC) inhibitor entinostat in patients with higher-risk MDS, CMML, or AML. Results were negative because the combination treatment group had higher rates of low platelet counts and fatigue. Results were also disappointing for the combination of azacitidine with the HDAC inhibitor pracinostat because patients in the placebo group did better than those in the treatment group.

But the combination of azacitidine and vorinostat seemed more promising. In a phase II clinical trial, about 70% of patients with untreated higher-risk MDS, CMML, or AML responded to the treatment, which was about double the expected rate for azacitidine alone. These responses lasted an average of 16 months. Similarly, response rates and duration of response were promising in a phase III clinical trial of the combination of lenalidomide and azacitidine for higher-risk MDS.

These findings led to a larger randomized phase II clinical trial in 282 patients with higher-risk MDS or CMML. The study treatments were azacitidine alone, azacitidine and lenalidomide, or azacitidine and vorinostat. The average age of study participants was 70 years. Unfortunately, response and survival rates were not significantly different between the three groups. Also, more patients in the two combination arms needed dose reductions or left the study because of complications than in the azacitidine-only arm.

Dr. Fenaux added that studies are also evaluating combinations of azacitidine with other treatments, such as valproic acid, venetoclax, immune checkpoint inhibitors, and idarubicin for higher-risk MDS or CMML. Other research is assessing more intensive HMA treatments or lower doses for longer use. Studies are testing different drugs, including venetoclax, cenersen, and a 10-day decitabine cycle, for MDS with TP53 mutations.

Dr. Sekeres concluded that azacitidine alone is still the standard treatment for higher-risk MDS. But some evidence hints at better and more long-lasting responses for

combination treatments if patients stay on them long enough. The HMA “partners” under investigation might become options for higher-risk MDS in some patients.

Combination of Eltrombopag and Azacitidine for MDS with Low Platelet Counts

Dr. Michael Dickinson (Peter MacCallum Cancer Centre, Melbourne, Australia) explained that low platelet counts are common in patients with MDS, especially if they have higher-risk MDS. HMA treatment can lower platelet counts even more, especially at first, so patients often need platelet transfusions and lower HMA doses. Effective treatment for low platelet counts can reduce the patient’s need for platelet transfusions and bleeding risk while allowing the patient to get the most effective HMA doses. But treatment options for severe platelet shortages in high-risk MDS are limited.

SUPPORT was a phase III clinical trial that compared eltrombopag plus azacitidine to placebo plus azacitidine in 356 patients with a low platelet count. The study measured the proportion of patients who did not receive platelet transfusions during the first four cycles of azacitidine. On average, patients were 68 years old, and 39% were female. Most patients had intermediate-2 or high-risk MDS according to the IPSS, and most did not need regular platelet transfusions.

An independent committee recommended ending the study early when the combination treatment arm had been treated for a median of 83 days and the placebo arm had been treated for 149 days. The reason was that only 16% of patients in the combination arm were platelet transfusion independent during the first four cycles of azacitidine, compared with 40% in the placebo arm. Also, the eltrombopag group had more side effects that led to treatment discontinuation.

At the final assessment of the 356 patients, only 16% of the combination treatment arm achieved transfusion independence, compared with 31% in the placebo arm. Rates of survival, side effects, and disease progression were the same in the two arms. But the rates of serious side effects and treatment discontinuation because of side effects were higher in the eltrombopag arm.

Guadecitabine for Untreated Higher-Risk MDS or CMML

Dr. Guillermo Montalbán-Bravo (M.D. Anderson Cancer Center, Houston, Texas) stated that, on average, patients with higher-risk MDS treated with **HMAs** survive, on average for only 4–6 months, so they need new treatments.

Previous research has shown that guadecitabine, a form of the HMA decitabine that resists metabolism, is safe and effective in MDS and CMML, even in patients who have been treated with other HMAs in the past.

A phase II clinical trial of guadecitabine in patients with untreated intermediate-2-risk MDS, high-risk MDS, or CMML is measuring overall response rates and survival. Patients are treated with guadecitabine over 5 consecutive days every 28 days. So far, the study has enrolled 61 patients, including 53 with MDS. Their median age is 69 years, and 64% are male.

About 85% of patients have had at least one side effect, usually fatigue, nausea, fever, or infections. Four patients have died of cardiac arrest, septic shock, or pneumonia.

A third of patients have needed their doses lowered because of low blood cell counts.

At this time, 64% of 56 patients who could be evaluated have responded, including 27% with a complete response. On average, responses last for six treatment cycles. Detected chromosome abnormalities disappeared in 24% of the 21 patients who had these abnormalities. Patients have survived a median of 14 months. The only factor found to be associated with worse survival is having several chromosome abnormalities.

Twenty-one patients are still enrolled in the study. Of these patients, seven still have a complete response, seven have a response in their bone marrow, five haven't yet responded, and two are finishing their first treatment cycle. Forty patients have been taken off the study because of disease progression, AML, lack of response, stem cell transplantation, or death.

A phase III clinical trial is evaluating guadecitabine for higher-risk MDS after HMA failure.

ONGOING CLINICAL TRIALS IN EUROPE AND THE UNITED STATES

Dr. Lionel Adès (Hôpital Saint Louis, Paris Diderot University) described recent and ongoing MDS clinical trials in Europe, and Dr. Guillermo Garcia-Manero (M.D. Anderson Cancer Center, Houston, Texas) discussed trials based in the United States. Because MDS has very different features in different patients, no one drug can cure most cases of MDS.

Low-Risk MDS

Phase II clinical trials in Europe have shown that two experimental drugs, sotatercept and luspatercept, might be effective for anemia for patients with low-risk MDS who don't respond to ESAs. They work at a later stage of red cell maturation than ESAs. In these studies, about half the patients responded to the drugs. But the response rate was higher, at around 60–70%, in those with a mutation in the SF3B1 gene or who had **ring sideroblasts**.

Lenalidomide has approval for **del(5q)** MDS in patients who need regular red blood cell transfusions. The ongoing SINTRA-REV study in Europe is investigating whether earlier use of lenalidomide might improve responses and prevent low-risk del(5q) MDS in patients who are transfusion independent from progressing. The MEDALIST trial is a large international phase III study comparing rates of transfusion independence (lasting at least 8 weeks) with luspatercept versus placebo in patients with low-risk MDS who are transfusion dependent, have not responded to ESAs, and have ring sideroblasts.

In the United States, studies are focusing on new **HMA** forms that patients can take by mouth as alternatives to current forms that are infused into the patient's vein or given under the skin. A challenge is that the cytidine deaminase enzyme rapidly clears these oral drugs from the bloodstream.

A recent U.S. phase I clinical trial assessed a combination of decitabine taken by mouth in combination with a new drug, E7727, that inhibits cytidine deaminase. The drug levels achieved with the oral formulation and degree of [DNA methylation](#) reduction were similar to those in previous studies with intravenous decitabine. A phase I/II study in the United States is now comparing an oral form of decitabine to intravenous decitabine.

Other U.S.-based research is evaluating lower doses of HMAs for low-risk MDS. A phase II clinical trial compared low doses of decitabine and azacitidine in 113 patients with low-risk or intermediate-1-risk MDS. More than a third of patients in each group had a complete response, although more patients in the decitabine group had some type of response. Both drugs were tolerable. Another U.S. study is assessing shorter azacitidine and decitabine dosing schedules for low-risk MDS.

Research is also seeking treatment options for patients who experience HMA treatment failure. They might benefit from early stem cell transplantation, and Dr. Garcia-Manero is designing a study to examine this possibility.

High-Risk MDS

HMAs are standard treatment for high-risk MDS. Several non-randomized phase II clinical trials have had promising results for combinations of HMAs with other drugs. However, randomized trials have found that adding vorinostat, lenalidomide, or pracinostat to HMAs does not increase survival. An ongoing trial in France is comparing combinations of azacitidine with valproic acid, lenalidomide, or idarubicin to azacitidine alone.

Many phase I and phase II clinical trials are evaluating a wide range of treatments, either alone or in combination with HMAs, for high-risk MDS. Even though non-randomized trials have shown what appear to be “better than expected” response rates, only randomized studies will truly determine whether these responses are reproducible and translate into longer survival. A randomized phase II clinical trial in Europe is using a “pick a winner” design to quickly evaluate different combinations of drugs with azacitidine for high-risk MDS.

U.S. trials are assessing the following treatments for high-risk MDS:

- Chemotherapy for some patients, such as those with certain gene or chromosome abnormalities
- Inhibitors of molecules attached to immune cells that tumor cells can use to protect themselves from the immune system
- Inhibitors of the FLT3 gene, which promotes cell growth

Options after HMA Failure

A major challenge in treating higher-risk MDS is that many patients eventually stop responding to HMAs. Many new drugs are being studied, alone or in combination with azacitidine, in the United States. Although a phase III clinical trial of rigosertib had negative results for higher-risk MDS after HMA failure, the drug lengthened survival in some patients. A study is evaluating this drug in the types of patients who benefited in the first trial, and research is also assessing different or more powerful HMAs for use after [treatment failure](#). Dr. Adès noted that the SAMBA trial in Europe is assessing talacotuzumab, a drug that attacks leukemia stem cells, in patients with MDS or AML who haven’t responded to HMAs.

IMPROVING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Transplantation Timing

Dr. Matteo G. Della Porta (Humanitas Research Hospital and Humanitas University, Milan, Italy) explained that stem cell transplantation is increasingly used to try to cure MDS. But it is important to offer this option only to patients who are likely to benefit from it at the time that will maximize the chances of success.

Transplantation Timing

Dr. Della Porta and colleagues studied 1,800 patients who underwent transplantation at different stages of MDS. They found that delaying transplantation until patients have intermediate-risk MDS prolongs survival by about 5 years in those younger than 60 and about 3 years in older patients. But life expectancy drops when patients wait until they have higher-risk MDS.

Basing the timing of transplantation on **IPSS-R** score instead of **IPSS** score would change the timing of transplantation in 29% of patients with low-risk or intermediate-1-risk MDS according to the IPSS. These patients would gain an average 2 years of life.

Dr. Theo De Witte (Radboud Institute of Molecular Life Sciences, Nijmegen, The Netherlands) added that in a study on the timing of transplantation for patients with lower-risk MDS (who were identified as having a higher risk of disease progression based on other factors), those who had had MDS for less than 12 months tended to survive longer after transplantation. Therefore, Dr. de Witte recommended that when transplantation is a suitable option for a patient, it be considered as soon as the patient is identified.

Improving Outcomes for Patients with High-Risk MDS

Options for patients with a TP53 mutation can include scheduling the transplantation at an earlier disease stage, using different treatments to suppress the patient's immune system before transplantation, or using treatments that could prevent recurrence after transplantation.

According to Dr. David Valcarcel (Hospital Vall d'Hebron, Barcelona, Spain), about 70% of transplantation outcomes can be explained by patient age, overall health status, and ability

to perform routine tasks. Doctors need to look at these factors closely when choosing a conditioning treatment. The best approach might be to use standard **conditioning treatment** in patients with high-risk MDS who are fit enough, including patients with a TP53 mutation, and to use reduced-intensity conditioning in those older than 65 who have **comorbidities**.

Dr. Fenaux added that patients with high-risk MDS do best with transplantation if all 10 of their donor's blood markers match their own markers. Patients also have a better prognosis if they don't have many **cytogenetic** abnormalities or mutations in certain genes. Several teams of researchers are studying treatments to prevent relapse after transplantation in patients with a high risk of relapse.

Stem Cell Transplantation Candidates

Dr. De Witte explained that stem cell transplantation is appropriate for patients with higher-risk MDS who are in otherwise good health and have a suitable donor. Stem cell transplantation isn't a good option for patients with lower-risk MDS who have many chromosome abnormalities, persistent increases in **blasts**, or life-threatening blood cell shortages. Those who need at least two transfused red blood cell units a month for 6 months are also poor candidates.

The use of **haploidentical stem cell transplants** from family members is increasing in Europe. Most patients have acute leukemia, but 12% have MDS or myeloproliferative neoplasms. The average patient age, currently around 55 years, is rising.

Stem cell transplantation is the first choice for patients with intermediate-2-risk or high-risk MDS according to the IPSS, unless the patient has another disease or condition or the disease hasn't responded to other treatments. The procedure is also an option for patients with intermediate-1-risk MDS who are younger, have several chromosome abnormalities or life-threatening blood cell shortages, or have progressive MDS. For patients with low-risk MDS, stem cell transplantation is recommended if they have factors associated with a poor prognosis, such as lack of response to ESAs and/or lenalidomide.

Dr. De Witte demonstrated a new online tool in development for patients with MDS and their doctors. This tool helps users figure out whether a particular patient

is a good candidate for transplantation based on the [IPSS-R](#). If so, the tool helps doctors choose the conditioning treatment to prepare the patient for transplantation and the donor. The tool also offers recommendations for monitoring and treatment after the procedure.

Preventing Relapse After Transplantation

Dr. Charles Craddock (Queen Elizabeth Hospital and University of Birmingham, United Kingdom) stated that relapse, which is most common in the first year after transplantation, is the major cause of stem cell transplantation failure in patients with MDS or AML. Survival rates are low after relapse, so patients who have a relapse need new treatment options.

Minimal Residual Disease and Other Predictors of Relapse

[Minimal residual disease](#) status is an important predictor of relapse in patients who have had a stem cell transplant. A better understanding is needed of the association between minimal residual disease and relapse risk to help doctors figure out whether certain patients would benefit from more treatment before or after stem cell transplantation to prevent relapse.

The FIGARO clinical trial showed that treatment before transplantation with a combination of fludarabine, cytarabine, amsacrine, busulphan, and antithymocyte globulin prolonged survival in older patients with secondary AML. These patients had a high risk of relapse because of persistent or rising levels of minimal residual disease before transplantation.

Dr. Della Porta stated that [IPSS](#) category and disease status at the time of transplantation are the most important predictors of disease relapse after transplantation. But the IPSS and [IPSS-R](#) are less useful in the 60% of patients who have no chromosome abnormalities until later in the course of their disease. Furthermore, patients with [somatic mutations](#) in the TP53 gene are more likely to have a relapse after transplantation. Adding information on mutations to the IPSS-R could improve the ability to predict the procedure's outcomes.

Graft-versus-Leukemia Effect

Another important way to prevent relapse is to harness the [graft-versus-leukemia effect](#). It's possible that in some patients with MDS who have an early relapse, the donated T cells haven't had time to attack enough of the leukemia cells. Researchers are exploring ways to accelerate the graft-versus-leukemia effect or give it more time to work. For example, an infusion of immune cells from the original donor's blood can eliminate any remaining cancer cells. Donor lymphocyte infusions in patients with AML within the first 6 months after transplantation increase the risk of [graft-versus-host disease](#). But they are much safer when administered at a later stage.

Other Treatments

Other treatments being studied include the targeted chemotherapy drug sorafenib for patients with a mutation in the FLT3 gene. In a retrospective analysis of 81 patients, including 26 treated with sorafenib after stem cell transplantation, the relapse rate was 8% compared with 38% in patients not treated with sorafenib. This exciting result needs to be tested in prospective studies, and some are underway.

A maintenance approach after transplantation uses low doses of [HMAs](#). Of 37 patients treated with a low dose of azacitidine starting a median of 54 days after transplantation, 16 had a relapse at a median of 8 months after transplantation. However, patients who had a CD8+ T-cell response in their immune system had a lower rate of relapse. In another study, 53% of 30 patients treated with decitabine combined with fludarabine and radiation were still alive after 443 days of follow-up, and 27% had had a relapse. These studies show that HMAs might be useful after transplantation in some patients. However, the results from these small studies need to be confirmed in larger studies.

Dr. Valcarel pointed out that more intensive [conditioning treatments](#) can sometimes reduce the risk of relapse after transplantation. In addition, less intensive conditioning (also known as reduced-intensity conditioning) reduces the risk of death in patients with MDS after transplantation due to causes other than relapse, but the relapse rates are higher. Lower doses of conditioning treatment seem to benefit patients who are otherwise healthy or have few chromosome abnormalities.

New Sources of Stem Cells

Dr. Valcarcel explained that in recent years, the use of matched, unrelated donors for stem cell transplantation has increased. An analysis of data on 7,048 patients undergoing stem cell transplantation for MDS between 2004 and 2014 showed that the chance of surviving for at least 3 years was 53% in patients with early-stage MDS who had a matched related donor and 49% in those with a matched unrelated donor. Among patients with advanced MDS, the survival rates were 45% for matched related donors and 40% for matched unrelated donors. Based on these data, well-matched related and unrelated donors can be good options for patients with MDS needing stem cell transplantation.

Only a few studies have assessed umbilical cord blood as a source of stem cells in MDS. One study found that survival rates without relapse were good. However, these patients were much younger than most patients with MDS. In another study of cord blood transplantation in patients with MDS with a median age of 57 years, only 30% survived for at least 5 years, whereas survival rates were 43–50% in those with a peripheral blood transplant. The [conditioning treatments](#) were different in the two groups of patients, which might have influenced the outcomes.

Results of [haploidentical donor transplants](#) in leukemia are similar to those of transplants from related or unrelated donors. One of the few studies that included patients with MDS found poorer results with haploidentical transplantation, but another very small study found good survival rates.

Dr. Valcarcel recommended that doctors consider haploidentical unrelated donors, mismatched family or unrelated donors, or umbilical cord stem cell sources for patients who don't have a matched related donor. No one type of donor is best for all patients, but most patients have more than one potential donor.

Stem Cell Transplantation for Older Patients with MDS

Dr. Hidehiro Itonaga (Nagasaki University, Japan) explained that progress in transplantation approaches has increased opportunities for elderly patients to benefit from this treatment.

Dr. Itonaga reported the results of a retrospective Japanese study on a transplantation approach for older patients with MDS. This study used Japanese registry data on 651 patients with newly diagnosed MDS. Patients were 60–69 years old and had their first stem cell transplant between 2002 and 2013. Of these patients, 152 had early-stage MDS and 499 had late-stage MDS. The transplanted cells came from matched or unmatched related donors, unrelated donors, or cord blood from unrelated donors.

In the early-stage MDS group, 46% were still alive 3 years after transplantation. Rates of death due to MDS, death due to the transplant, and overall death were similar among patients aged 60–64 and those aged 65–69 years. The survival rate was lowest, at 36%, for those who received a cord blood donation. [Conditioning treatment](#) intensity didn't affect their likelihood of surviving for at least 3 years. But patients with a lower level of functioning tended not to survive as long as patients who were better able to perform routine tasks.

Of patients with advanced MDS, 37% were still alive 3 years later. As with the patients with early-stage MDS, rates of death due to MDS, due to the transplant, and overall were similar among patients aged 60–64 and those aged 65–69 years. Survival was best in patients with a matched related or matched unrelated donor and worst in those whose transplant came from cord blood or a mismatched donor. Again, conditioning treatment intensity didn't affect patients' likelihood of surviving for at least 3 years. Patients with more chromosome abnormalities had a lower risk of surviving for at least 3 years, as did those who had more difficulty with daily tasks.

Dr. Itonaga believes that stem cell transplantation is a promising option for long-term remissions in older patients with MDS. The ages of 60–69 don't seem to be a limiting factor for this procedure. But more careful management—such as choosing the right type of stem cell source and conditioning regimen for each patient as well as choosing patients with good performance status (level of functioning)—is necessary to improve outcomes after transplantation.

NEW TREATMENTS FOR LOW BLOOD CELL COUNTS IN MDS

Epoetin Alfa Treatment for Anemia in Lower-Risk MDS

Dr. Fenaux explained that although ESAs are commonly used to treat anemia in patients with lower-risk MDS, they have only recently been formally tested in patients with MDS in randomized, placebo controlled trials.

A phase III clinical trial compared the safety and efficacy of epoetin alfa, an ESA, to placebo in patients who had anemia and MDS. Epoetin alfa had not been approved for anemia in MDS in any country at the time of this study.

On average, the 130 participants were 74 years old. Slightly more than half were male, and all had low-risk or intermediate-1-risk MDS according to the [IPSS](#). The study's primary endpoint was [erythroid response](#).

During the first 24 weeks, 32% of patients treated with epoetin alfa in the study had an erythroid response, compared with 4% of those treated with placebo. Half of those who did not need transfusions at the start of the study responded, compared with 23% of those who did need transfusions. When only patients who were treated according to the study protocol were analyzed, 67% who were transfusion independent and 25% who were transfusion dependent responded.

But the study ran into some problems. The investigators had to interrupt treatment when the hemoglobin level reached 12 g/dL, so many patients could not be classified as responders because they did not reach the target by 8 weeks. Also, the evaluation of transfusion needs before treatment was based on only 8 weeks, so those who needed transfusions outside that period had to have an increase of 1.5 g/dL in their hemoglobin to be considered responders. If their baseline hemoglobin was high at the start of the study because of a recent transfusion, it was difficult to raise their hemoglobin level by 1.5 g/dL. Finally, hemoglobin levels were evaluated with different instruments that could have given different results.

The investigators therefore applied different criteria to the results, such as measuring baseline hemoglobin before transfusion and defining response as a 1.5 gram hemoglobin increase for less than 8 weeks if the drug was

stopped because the hemoglobin level was higher than the target level. Finally, the reviewers evaluated responses using centrally measured hemoglobin levels. Based on these revised criteria, 46% of all patients responded to the treatment. These observations led to an ongoing effort within the MDS research community to revise the MDS International Working Group's 2006 criterion for erythroid response.

The European Union's regulatory agency approved epoetin alfa for anemia in MDS based on this study. This was the first approval for an ESA for this purpose anywhere in the world.

Dr. Fenaux added in a separate presentation that early treatment with ESAs in patients with low-risk MDS might delay the need for red blood cell transfusions. A randomized clinical trial will compare the effects of early versus late ESA treatment in lower-risk MDS. Another trial is assessing the ability of lenalidomide to delay red blood cell transfusions for anemia in lower-risk [del\(5q\) MDS](#).

Modified Activin Receptors: A New Treatment for Anemia in MDS

Dr. Uwe Platzbecker (Medizinische Klinik und Poliklinik I Medizinische Fakultät Carl Gustav Carus, Dresden, Germany) described anemia as a hallmark of MDS, especially in patients who need red blood cell transfusions. Often, their immature red blood cells don't mature normally.

Luspatercept is an experimental drug that increases red blood cell counts and hemoglobin levels by blocking the activity of [cytokines](#) that play a role in red blood cell formation. The PACE-MDS study was a phase II study of luspatercept in Germany in patients with anemia and low-risk or intermediate-1-risk MDS according to the IPSS. These patients were given luspatercept by [subcutaneous](#) injection every 3 weeks for 3 months.

In the first 15 patients treated, the drug increased hemoglobin levels in those who were transfusion independent. In addition, the number of red blood cell units transfused dropped by at least 50% in 4 of 10 patients who had needed at least four units of transfused red blood cells in the 8 weeks before the study. None of the patients had any serious side effects related to the treatment. Responses were best in patients with [ring sideroblasts](#) and/or mutations in *SF3B1*.

The phase II PACE extension study is following 52 patients for 5 years and is enrolling new groups that have not been treated with ESAs in the past and do or do not have ring sideroblasts. About half the patients have responded to luspatercept. Again, response rates were highest (55–60%) in those with ring sideroblasts and/or mutations in the SF3B1 gene as well as patients with baseline erythropoietin levels that were lower than 500 IU/L. Encouragingly, even patients without ring sideroblasts responded to luspatercept, although the number of patients without ring sideroblasts in the study is still small.

The MEDALIST trial is comparing luspatercept with placebo in patients who have MDS with ring sideroblasts, are red blood cell transfusion dependent, and are no longer candidates for ESAs. The study has completed accrual ahead of schedule, and the investigators are analyzing the trial results.

Hopefully, in the near future, another drug will be available to treat lower-risk MDS in patients who have ring sideroblasts, are transfusion dependent, and have experienced ESA failure.

Treatment for Low Platelet Counts in MDS

Dr. Valeria Santini (Università di Firenze, Italy) reported that about a third of patients with MDS develop **thrombocytopenia**, which increases bleeding risk. This effect is more common in patients with higher-risk MDS. But the percentage of patients who die of thrombocytopenia doesn't differ by **IPSS-R** category. In low-risk MDS, in particular, platelet count is important for prognosis.

Patients with MDS who have mutations in the TP53 gene have lower platelet counts and worse outcomes. Dr. Santini recommended that doctors pay attention to platelet counts in these patients.

Low platelet counts sometimes respond to corticosteroids, high doses of androgens, or removal of the spleen. But these responses are often temporary and only partial. Treatment with interleukin-1 and interleukin-11 or with human thrombopoietin and a growth factor to stimulate platelet growth is either not effective or has major side effects. **HMAs** might be helpful, but they are not approved for this indication in Europe.

Thrombopoietin Mimetic Drugs

Thrombopoietin mimetic drugs increase platelet counts. The two available thrombopoietin mimetic drugs are eltrombopag and romiplostim. A clinical trial showed that eltrombopag increased platelet counts in patients with higher-risk MDS or AML. The treatment seemed to prolong survival, but the difference between the eltrombopag and placebo groups wasn't statistically significant. The SUPPORT trial, which assessed the combination of eltrombopag and azacitidine, was stopped early because of high rates of progression to AML in the treatment group and concerns about the drug's safety. In addition, more patients in the placebo group required fewer platelet transfusions. Further studies are aimed at understanding this unexpected result.

Furthermore, a study of romiplostim was stopped early because treated patients had higher numbers of blasts, or abnormal immature blood cells. But platelet counts did rise in treated patients, they needed fewer platelet transfusions, and they had less bleeding. Dr. Hagop Kantarjian (M.D. Anderson Cancer Center, Houston, Texas) presented updated long-term results from this trial at the meeting showing that the overall survival and risks of leukemia were not different between the placebo group or those treated with romiplostim. Results from an ongoing study will provide more information on this drug.

In 40 patients with low-risk or intermediate-risk MDS, the combination of romiplostim and azacitidine raised platelet counts. In a phase II clinical trial in 29 patients with intermediate-2 MDS according to the **IPSS**, this combination increased platelet counts and reduced platelet transfusions compared to placebo. Only two of these patients developed AML.

Dr. Santini concluded that both eltrombopag and romiplostim increase platelet counts in MDS with severe thrombocytopenia. These drugs can also have other beneficial effects, like raising counts of other blood cells in some patients. The increase in abnormal, immature blood cells with romiplostim in lower-risk MDS seems to be temporary and reversible when the drug is stopped.

OPTIONS FOR MDS TREATMENT COMPLICATIONS

Graft-versus-Host Disease and High-Risk Gene Mutations after Stem Cell Transplantation

According to Dr. Juan Carlos Caballero (Universidad de Salamanca, Spain), [somatic mutations](#) in certain genes affect survival, risk of relapse, and response to [HMA](#) treatment. They can also predict poorer outcomes after stem cell transplantation.

Patients sometimes develop chronic GVHD after stem cell transplantation. Chronic GVHD is associated with a lower risk of relapse, but patients sometimes develop serious health problems and can even die of this complication.

Dr. Caballero summarized the findings of a study on the impact of certain somatic mutations and [chronic GVHD](#) on outcomes after stem cell transplantation. This retrospective study included 115 patients with MDS treated at five hospitals in Spain between 1998 and 2015. The median age was 53 years, and 60% of patients were male. Half had high-risk or very-high-risk MDS according to the [IPSS-R](#). In addition, 38% had no mutations in the tested genes, one quarter had one mutated gene, another third had mutations in two or three genes, and the rest had mutations in four to six genes.

Altogether, 48% survived for at least 6 years. Patients with mutations in more genes tended to have worse outcomes, but this difference wasn't statistically significant. When the investigators divided the patients into two groups based on numbers of mutated genes, those with no more than two mutated genes had significantly longer survival and longer survival without a relapse.

Patients who developed GVHD survived longer, even if they had more than two mutated genes. Factors associated with shorter survival were having more chromosome abnormalities and mutations in TET2. Relapse rates in patients with the TET2 mutation who developed chronic GVHD were similar to relapse rates in patients without the mutation.

The results show that the number of mutations could be useful for the prognosis of MDS after stem cell transplantation. In addition, chronic GVHD may help overcome the negative impact of certain types and/or numbers of somatic mutations in patients with MDS after

transplantation. However, these findings need to be verified in studies with larger samples.

What's New in Iron Overload Treatment for MDS?

Dr. Norbert Gattermann (Heinrich-Heine-University, Düsseldorf, Germany) explained that the risk of death due to causes other than leukemia rises dramatically in patients who have MDS and low hemoglobin counts because of red blood cell shortages. So patients with MDS need regular red blood cell transfusions. However, frequent red blood cell transfusions cause [iron overload](#), which has a negative effect on survival.

Iron overload can affect the [endothelium](#). Endothelial dysfunction increases the risk of stroke and heart attacks. Iron overload might also aggravate bone marrow dysfunction in MDS and start a vicious cycle. Specifically, MDS causes anemia, which leads to the need for red blood cell transfusions, which cause iron overload. Experts hypothesize that the iron overload may cause heart problems and might contribute to the development of new genetic mutations in MDS.

Iron Chelation Treatment

Iron chelation treatment can improve endothelial function in patients with coronary artery disease. This beneficial effect might be important for elderly patients with MDS, who often have blood vessel disease as a part of aging.

Iron chelation can overcome the destructive effects of iron overload. For example, it can improve blood cell formation in a small subset of patients with MDS. The secret to success is maintaining the treatment over a very long time.

A recent study showed that low doses of the iron chelator deferasirox increase the growth of immature red blood cells. This finding led to a phase II clinical trial in France on the effects of early introduction of low doses of deferasirox in patients with low-risk MDS who don't respond to ESA treatment for anemia.

Another recent study that used data from the Canadian MDS registry showed an impressive difference in overall survival between patients treated with iron chelation and those not treated. An imbalance in some patient characteristics may also contribute to these findings, so the investigators are now doing a more sophisticated analysis of these data.

The best evidence so far comes from an analysis of data from the European LeukemiaNet MDS. The overall survival of 192 chelated patients was significantly better than that of a comparison group of 573 patients, even after the investigators took into account patient age, sex, other health conditions, ability to perform routine tasks, and number of transfused red blood cell units.

Low White Blood Cell Counts

Dr. Fenaux explained that HMAs, especially during the early cycles, can suppress the bone marrow's ability to form blood cells. The resulting low white blood cell counts can lead to infections, and the lower platelet counts can cause bleeding. Doctors sometimes use antibiotics or antifungal medicines, among other treatments, to prevent the infections.

LIST OF ACRONYMS

AML: acute myelogenous leukemia

CMML: chronic myelomonocytic leukemia

ESA: erythropoietin-stimulating agent

GVHD: graft-versus-host disease

HMA: hypomethylating agent

IPSS: International Prognostic Scoring System

IPSS-R: revised International Prognostic Scoring System

MDS: myelodysplastic syndromes

NGS: Next-generation sequencing

WHO: World Health Organization

GLOSSARY OF TERMS

Blasts: abnormal, immature blood cells

Comorbidities: additional diseases beyond MDS

Complex karyotype: three or more abnormalities in their chromosomes

Conditioning treatment: used to kill all remaining cancer cells before stem cell transplantation

Cytogenetic remission: no detectable chromosome abnormalities

Cytogenetics: study of chromosomes

Cytokines: proteins

Cytopenia: low blood cell count

del(5q): deletion in the long (q) arm of chromosome 5

DNA methylation: a process that helps control gene activity, resulting in blockage of cell growth.

Dysplasia: blood cells in bone marrow with an abnormal appearance

- Multilineage dysplasia: abnormalities in more than one type of blood cell
- Single lineage dysplasia: abnormalities in only one type of blood cell

Endothelium: layer of cells lining the heart and blood vessels

Erythroid response: According to the 2006 criteria developed by the International Working Group for the Prognosis of MDS:

- In patients who have not received red blood transfusions—hemoglobin increase of 1.5 g/dl
- In those who have had transfusions—reduction in transfusions by at least four units of packed red blood cells over 8 weeks compared with the 8 weeks before treatment

Erythropoietin: a hormone that promotes red blood cell formation

Gene expression: the process that genes use to make their products, such as proteins

Graft-versus-host disease (GVHD): Attack by transplanted cells on the recipient's body in which the transplanted cells cause inflammation of some normal tissues.

- Acute: within 3 months of transplantation
- Chronic: starting more than 3 months after transplantation

Graft-versus-leukemia effect: T cells (part of the immune system) in the donated stem cells can attack the remaining cancer cells

Haploidentical stem cell transplantation: the donor's blood markers match half the patient's markers

Histone deacetylase (HDAC) inhibitors: drugs that interfere with DNA's ability to control gene activity by inhibiting the histone deacetylase enzyme; can kill tumor cells by stopping them from dividing

Hypomethylating agents (HMAs): category of drugs—including azacytidine (Vidaza) and decitabine (Dacogen)—that block the methyl groups attached to genes needed for normal blood cell development, preventing the silencing of certain genes involved in controlling cancer and allowing normal functioning of the tumor suppressor genes

International Prognostic Scoring System (IPSS): often used by doctors to classify MDS severity

Iron chelation treatment: removes extra iron from the blood

Iron overload: too much iron in the blood

Minimal residual disease: small numbers of cancer cells that stay in the body after treatment

Revised IPSS (IPSS-R): takes more information into account than the IPSS and categorizes patients into five risk groups instead of four

Ring sideroblasts: abnormal red blood cells with ring-shaped iron deposits

Secondary AML: AML that developed after treatment for MDS or another cancer

Somatic mutation: change in a gene that happens after conception in a patient's cells, is not inherited, and is not passed on to the patient's children

Subcutaneous: under the skin

Thrombocytopenia: low platelet count

Treatment failure: occurs when a patient doesn't respond to the treatment, responds only temporarily, or has to stop the treatment because of side effects.

Variant allele frequency: frequency of the selected mutated genes

GENERIC AND BRAND NAMES OF DRUGS

GENERIC NAME	BRAND NAME
Amsacrine	Amsidine
Antithymocyte globulin	Thymoglobulin
Azacitidine	Vidaza
Busulphan	Busulfex
Cenersen	Aeza
Cytarabine	Cytosar-U
Decitabine	Dacogen
Deferasirox	Exjade, Jadenu
Eltrombopag	Promacta

GENERIC NAME	BRAND NAME
Epoetin alfa	Epogen, Procrit
Fludarabine	Fludara
Idarubicin	Idamycin
Lenalidomide	Revlimid
Romiplostim	Nplate
Sorafenib	NEXAVAR
Venetoclax	Venclexta
Vorinostat	Zolinza

MEETING HIGHLIGHTS AND ANNOUNCEMENTS

THE AMERICAN SOCIETY OF HEMATOLOGY 59TH ANNUAL MEETING & EXPOSITION • DECEMBER 2017

BREAKFAST SYMPOSIUM



ACTIVITY OVERVIEW

Recent developments in our knowledge of the immune system, the bone marrow micro-environment and the genetic evolution of MDS are optimizing prognostication and management strategies. Intrinsic and extrinsic factors contributing to disease pathogenesis and influencing therapeutic response will be discussed.

TARGET AUDIENCE

This activity is intended for physicians, oncology nurses, nurse practitioners, physician assistants, pharmacists and other health care professionals interested in the treatment and management of patients with Myelodysplastic Syndromes.

LEARNING OBJECTIVES

Upon completion of the educational activity, participants should be able to:

- Describe the various stages of clonal hematopoietic evolution in the elderly
- Identify the complex interplay between the MDS clone and its microenvironment
- Describe molecular background, which plays a role in the dysregulation of the innate and adaptive immune system in MDS
- Discuss both inherited and acquired genetic factors that contribute to MDS pathogenesis and influence prognosis
- Describe the various processes of inflammation and oxidative stress that are associated with the development and (vasculitic) symptoms of MDS

- Utilize objective response predictors and strategies to maximize the successful use of hypomethylating agents
- Apply the objective prognostic factors and measures to identify the patients most suitable for allogeneic stem cell transplant, which may lead to better outcomes

FACULTY

Stephen Nimer, MD
Miami, Florida

Rena Buckstein, MD, FRCPC
Toronto, Canada

Mario Cazzola, MD
Pavia, Italy

Jude Fitzgibbon, PhD
London, United Kingdom

Rami Komrokji, MD
Tampa, Florida

Shahram Kordasti, MD, PhD
London, United Kingdom

John Koreth, MD, PhD
Boston, Massachusetts

Luca Malcovati, MD
Pavia, Italy

**Don't forget to visit our
MDS Foundation Booth
#1640 in the Exhibit Hall**

AGENDA

7:00 – 7:30 am

Complimentary Breakfast

7:30 – 7:35 am

Welcome – About the MDS Foundation, Inc.
Stephen Nimer, MD

7:35 – 7:40 am

Program Overview and Objectives
Rena Buckstein, MD, FRCPC
Mario Cazzola, MD

7:40 – 8:15 am

Myeloid Neoplasms with
Germline Predisposition
Jude Fitzgibbon, PhD

8:15 – 8:50 am

Clonal Cytopenia and Myeloid Neoplasms
Luca Malcovati, MD

8:50 – 9:25 am

Abnormalities of the Immune System
and Inflammation in MDS Pathogenesis
Shahram Kordasti, MD, PhD

9:25 – 10:00 am

Therapies for Higher Risk MDS Patients:
Optimizing HMA Approaches and
Use of Novel Agents
Rami Komrokji, MD

10:00 – 10:35 am

Maximizing Success: Optimizing
Prognostication and Timing of Allogeneic
Stem Cell Transplant for MDS
John Koreth, MD, PhD

10:35 – 11:00 am

Questions/Answers/Discussion

INTERNATIONAL WORKING GROUPS

MDS FOUNDATION INTERNATIONAL WORKING GROUP FOR PROGNOSIS IN MDS

Latest News Regarding the Molecular Mutation Project of the IWG-PM

Mutations predict prognosis independent of the IPSS-R: Overview

The International Prognostic Scoring System (IPSS) and IPSS-R were developed by the International Working Group for Prognosis in MDS (IWG-PM) under the aegis of the MDS Foundation and have become the dominant clinical tools for predicting prognosis in patients with myelodysplastic syndromes (MDS)¹. A prognostic scoring system that integrates gene mutations into the known critical clinical features would have great additive utility for improved determination of prognosis in patients with MDS and has the potential for widespread clinical use. The ongoing project of the IWG-PM Molecular Committee (IWG-PM-M) has shown, with the IPSS-R and other scoring systems, using larger molecularly characterized datasets, that mutations are independent predictors of patients' overall survival. This finding justifies a prognostic scoring system that will integrate clinical and genetic features.

Prognostic Impact of TP53 mutations

A central aim of the IWG-PM Molecular project is to develop a large database of MDS patients with deep clinical annotation and genetic sequencing data for clinical, biologic and possibly therapeutic purposes. In addition to the analysis of previous samples, sequencing additional MDS cases will be performed to further develop the database.

As a first project for the IWG-PM molecular database, the impact of TP53 mutations in MDS demonstrated that this status divides MDS patients with complex karyotypes into distinct prognostic risk groups, with those carrying the mutation having poorer prognoses. Despite their strong associations with adverse clinical and cytogenetic abnormalities that are already incorporated into existing prognostic scoring systems, TP53 mutations carry significant independent prognostic value for decreased survival for patients with MDS. This work was presented at the 2016 American Society

of Hematology Meeting² with updating at the 2017 14th International MDS Foundation Symposium held in Valencia, Spain.

Recent Molecular Results

Molecular and clinical data on 3392 MDS patients gathered by members of the IWG-PM-Molecular Committee were combined and analysed and the abstract describing these findings was selected for an oral presentation at the ASH 2015 Annual Meeting in Orlando³. Survival data were available for 3200 patients. The 27 genes sequenced in at least half of the cohort and mutated in >1.5% of samples were included for analysis. Mutations in 12 genes were strongly associated with shorter overall survival in univariate analyses. The large size of the cohort allowed for more precise estimates of survival in the less frequently mutated genes. IPSS-R risk groups could be determined for 2173 patients and were strongly associated with survival. Adjusting the hazard ratio of death for IPSS-R risk groups identified several mutated genes with independent prognostic significance. Patients without mutations in any of the major adverse genes represented over half of the fully sequenced cohort and had a longer median survival than patients with adverse mutations even after correction for IPSS-R risk groups. A mutation score based on survival risk will be proposed and internally validated. The impact of somatic mutations in patients traditionally considered lower risk will also be explored.

Current Project Status, Plans for Sequencing of New Samples

In addition to the above assessment of previous samples, the project will sequence additional large numbers of MDS cases to further develop our database and mutational evaluations. An automated sample management system was recently implemented that links sample reception to library preparation and sequencing submission. The results of these analyses will serve as the template with which to build an integrated molecular risk model for MDS. Also presented at the meeting was the data aggregation update with integration of the data into cBioPortal. This is a mechanism for use of the data by all members of the group for their analyses for investigator-initiated projects.



DOWNLOAD OUR FREE APP
IPSS-R Calculators
(Basic and Advanced)
Available Online and at the App Store

References

1. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454-2465.
2. Bejar R, Papaemmanuil E, Haferlach T, Garcia-Manero G, Maciejewski JP, Sekeres MA, Walter MJ, Graubert TA, Cazzola M, Malcovati L, Campbell PJ, Ogawa S, Boultonwood J, Bowen D, Tauro S, Groves M, Fontenay M, Shih L-Y, Tuechler H, Stevenson D, Neuberg D, Greenberg PL, Ebert BL. TP53 Mutation Status Divides MDS Patients with Complex Karyotypes into Distinct Prognostic Risk Groups: Analysis of Combined Datasets from the IWG-PM-Molecular Prognosis Committee. *Proc Am Soc Hematology*, San Francisco, December, 2014, abstract, *Blood*. 2014; 124 (21): #532.
3. Bejar R, Papaemmanuil E, Haferlach T, Garcia-Manero G, Maciejewski JP, Sekeres MA, Walter MJ, Graubert TA, Cazzola M, Malcovati L, Campbell PJ, Ogawa S, Fenau P, Hellstrom-Lindberg, Kern W, Boultonwood J, Pellagatti A, Bowen D, Tauro S, Groves M, Vyas P, Quek L, Nazha A, Thol F, Heuser M, Shih L-Y, Padron E, Sallman D, Komrojki R, List A, Santini V, Fontenay M, Campbell P, Tuechler H, Stevenson D, Neuberg D, Greenberg P, Ebert BL. Somatic Mutations in MDS Patients Are Associated with Clinical Features and Predict Prognosis Independent of the IPSS-R: Analysis of Combined Datasets from the IWG-PM-Molecular Committee, ASH Orlando, December 2015, *Blood*. 126 (23); 2015 abstract #907.

This global project is being coordinated by Ben Ebert and Peter Greenberg (co-Chairs), Rafael Bejar and Ellie Papaemmanuil, with statistical support by Donna Neuberg, Kristin Stevenson and Heinz Tuechler.

The MDS/MPN International Working Group

The MDS/MPN IWG in 5 years has established a leadership role in research into the pathobiology and novel treatment for MDS/MPN. Since the publication of the Proposed MDS/MPN Response Criteria in 2015,¹ the clinical trial opportunities have dramatically increased. This led to explorations of MDS/MPN-specific trials led by MDS/MPN IWG members,² and most recently, the first MDS/MPN IWG study: **ABNL MARRO**. A Novel therapy combination in untreated MDS/MPN And Relapsed/Refractory Overlap Syndromes (**ABNL-MARRO** is a international basket study designed to allow new compounds and combinations of therapy to be introduced easily among MDS/MPN IWG clinical sites which see MDS/MPN patients, study the biology and pathophysiology of the diseases, and have multilateral expertise in this area. **ABNL MARRO-001** is the first MDS/MPN IWG study and is planned to begin in mid-2018. In addition to semi-annual meetings at ASH and EHA, the MDS/MPN IWG is conducting a biennial meeting in February 2018 in preparation for

the onset of this trial and to focus international efforts in MDS/MPN.

Additional efforts in the MDS/MPN IWG center around growing new models of disease. Recently, robust patient-derived xenografts transplant models for CMML were shown to be the first published reliable means to study specific genetic lesions in MDS/MPN in animals.³ Advances have also been made in molecular testing and diagnostics which allow tracking of specific mutations at diagnosis and with treatment.⁴ The means by which these mutational changes are able to define prognosis and effect treatment are the focus of the work of many MDS/MPN IWG members.

In 2018, in addition to beginning **ABNL MARRO-001**, the MDS/MPN IWG aims to update the proposed criteria for response in MDS/MPN, begin large scale prospective genotyping efforts in MDS/MPN, and leverage these data to enhance the many excellent prognostic models to develop genetic mutation-informed means of assessing risk in MDS/MPN.



References:

1. Savona MR, Malcovati L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood*. 2015;125:1857-65.
2. Padron E, Dezern A, Andrade-Campos M, et al. A Multi-Institution Phase I Trial of Ruxolitinib in Patients with Chronic Myelomonocytic Leukemia (CMML). *Clinical cancer research: an official journal of the American Association for Cancer Research* 2016;22:3746-54.
3. Yoshimi A, Balasis ME, Vedder A, et al. Robust patient-derived xenografts of MDS/MPN overlap syndromes capture the unique characteristics of CMML and JMML. *Blood*. 2017;130:397-407.
4. Merlevede J, Droin N, Qin T, et al. Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents. *Nature Communications*. 2016;7:10767.



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www.mds-foundation.org/membership

Together, we are community resource of Hope for those living with MDS.

Highlights of Latest Literature in MDS

Suneel D. Mundle, PhD
Rhea Mundle

Listed below are citations of some new publications relevant to MDS (pathogenesis, clinical characterization, management, etc.). To access the complete articles log on to www.pubmed.gov.

EPIDEMIOLOGY, DIAGNOSIS AND PROGNOSIS:

1. Kobayashi T et al. A nationwide survey of hypoplastic myelodysplastic syndromes (a multicenter retrospective study). *Am J Hematol.* 2017; Sept 11. [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28891083>)

A central review was conducted of 129 hypoplastic MDS cases from 20 institutions in Japan over a period of 10 years (Apr 2003–Mar 2012). A comparison was made to 115 non-hypoplastic MDS patients. This retrospective assessment showed that hypoplastic MDS group had a preponderance of RA subtype, and tended to have higher overall survival and leukemia-free survival.

TREATMENT:

1. Cogle CR et al. Early treatment initiation in lower-risk myelodysplastic syndromes produces an earlier and higher rate of transfusion independence. *Leuk Res.* 2017; 60:123–128. (<https://www.ncbi.nlm.nih.gov/pubmed/28818807>)

This American retrospective study based on SEER registry and Medicare claims database assessed the impact of a timing of initiating treatment with approved agents (azacytidine, decitabine or lenalidomide) since the date of transfusion dependence. Among the 508 transfusion dependent patients included in the study, 351 received approved therapies early at a median of 28 days

since transfusion dependence while 157 patients had delayed initiation of treatment (median 187 days from transfusion dependence). In a multivariate analysis, early treatment predicted transfusion independence and also showed higher rates of transfusion independence.

2. Ramos F et al. Multidimensional assessment of patient condition and mutational analysis in peripheral blood, as tools to improve outcome prediction in myelodysplastic syndromes: A prospective study of the Spanish MDS Group. *Am J Hematol.* 2017;92(9):E534-E541. (<https://www.ncbi.nlm.nih.gov/pubmed/28612357>)

This study evaluated the prospects of adding patient condition and peripheral blood mutational status to IPSS-R, in a ten-year prospective cohort of 200 consecutive MDS patients. Patients originally categorized per IPSS-R were stratified by patient condition (per Lee Index) and mutations detected in peripheral blood with next generation sequencing. The addition of patient condition significantly improved overall survival ($HR=3.02$, $p<0.001$), while mutational status improved prediction of leukemic transformation ($HR=2.71$, $p<0.001$).

ESAs and Growth Factors

1. Houston BL et al. A predictive model of response to erythropoiesis-stimulating agents in myelodysplastic syndromes: from the Canadian MDS patient registry. *Ann Hematol.* 2017, Oct 3 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28975386>)

Using WHO 2008 criteria, response was evaluated in a total of 208 ESA-treated patients from a prospective Canadian registry. The patients were primarily low/int-1 per IPSS or low/very low per IPSS-R. The erythroid response rate with Epoetin alfa was 50%, while darbepoietin was 39% ($p=0.2$). The multivariate analysis underscored independent predictive value of low-risk IPSS score ($p=0.0016$) and serum EPO

<100 mIU/mL ($p<0.0001$). Using a score of 1 for low risk and 2 for serum EPO<100mIU/mL, the authors suggest to have improved sensitivity with higher response rate seen in the best risk group as compared to the previously established Nordic score.

2. Fenaux P et al. Romiplostim monotherapy in thrombocytopenic patients with myelodysplastic syndromes: long-term safety and efficacy. *Br J Haematol.* 2017;178(6):906–913. (<https://www.ncbi.nlm.nih.gov/pubmed/28616874>)

This was an open label extension study in 60 patients with lower risk MDS and platelet counts $\leq 50 \times 10^6/L$. The median extension study treatment time was 25 weeks and subsequent observations for 57 weeks. Treatment related AEs were seen in 23% patients. Median duration of platelet response was 33 weeks with 82% patients showing continuous response. 15% (5/34) of the platelet responders had grade ≥ 3 bleeding events.

Hypomethylating Agents:

1. Kantarjian HM et al. Guadecitabine (SGI-110) in treatment-naïve patients with acute myeloid leukemia: phase 2 results from a multicenter, randomized, phase 1/2 study. *Lancet Oncol.* 2017; 18(10):1317–1326. (<https://www.ncbi.nlm.nih.gov/pubmed/28844816>)

This cohort report focuses on outcomes in treatment naïve AML patients from a large randomized phase 1/2 study with AML and MDS patients. The patients were ≥ 65 yrs old and were not eligible to receive intensive chemotherapy. A total of 107 patients received Guadecitabine in a 28-day cycle on three schedules; 60 mg/m² d1-5 (n=26), 90 mg/m² d1-5 (n=28), or 60 mg/m² d1-10 (n=53). Efficacy seemed comparable across the three schedules, with a composite complete response attained in approximately half the patients. The most frequent grade 3 AEs were febrile neutropenia, thrombocytopenia, neutropenia, pneumonia, anemia and sepsis. The 5-day vs 10-day

- schedule remained comparable. 22% deaths were related to AEs, were mainly due to sepsis. The recommended dose for future studies is 60 mg/m² d1-5 in a 28-day cycle.*
7. Sanchez-Garcia J et al. Prospective randomized trial of 5 days azacitidine versus supportive care in patients with lower risk myelodysplastic syndromes without 5q deletion and transfusion-dependent anemia. *Leuk Lymphoma*. 2017; Aug 24 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28836866>)
The efficacy of azacitidine was tested against the best supportive care in a prospective study with 36 lower-risk non-del (5q), transfusion dependent MDS patients subsequent to ESAs. The HI-E rate in azacitidine group after nine cycles was 44.4% vs 5.5% in the control group (p<0.01). Transfusion independence was noted with extended azacitidine treatment (median duration of 50 weeks).
 8. Jabbour E et al. Randomized phase 2 study of low-dose decitabine vs Low-dose azacitidine in lower-risk MDS and MDS/MPN. *Blood*. 2017;130(13): 1514–1522. (<https://www.ncbi.nlm.nih.gov/pubmed/28774880>)
Low/Int-1 risk MDS and MDS/MPN patients (n=113) were randomly assigned to receive decitabine 20 mg/m² IV daily (n=73) or azacitidine 75 mg/m² IV or SC daily (n=40) for 3 consecutive days in a 28-day cycle for a median of 9 cycles. When decitabine was compared with azacitidine, the ORR was 70% vs 49% (p=0.03), transfusion independence rates were 32% vs 16% (p=0.2), cytogenetic response was 61% vs 25% (p=0.02), overall event-free survival at a follow up of 20 months was 20 mo. vs 13 mo. (p=0.1), respectively. Both treatments were well tolerated.
 9. Daver N et al. Vosaroxin in combination with decitabine in newly diagnosed older patients with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Haematologica*. 2017;102(10):1709–1717. (<https://www.ncbi.nlm.nih.gov/pubmed/28729302>)
Vosaroxin and decitabine combination was tested in ≥60 yr. old patients with newly diagnosed AML (n=58) or high risk MDS (n=7). Decitabine was given at 20 mg/m² d1-5 every 4–6 weeks up to 7 cycles. In combination, the initial dose of Vosaroxin 90 mg/m² d1 and d4 in first 22 patients showed high incidence of Mucositis and was reduced in latter 43 patients to 70 mg/m² d1 and d4. The ORR with combination was 74% including CR in 48%, and CRi Platelet in 17%. The 70mg/m² dose of Vosaroxin showed comparable ORR (74% vs 73%), better CR (51% vs 41%), better survival (14.6 mo. vs 5.5 mo., p=0.007) and significantly reduced the incidence of Mucositis (30% vs 59%, p=0.02) as well as lowered 8 week-mortality (9% vs 23%, p=0.14) when compared to 90 mg/m² dose respectively. The multiparametric MRD negative status achieved in 54% subjects was correlated to improved survival (34 mo. in MRD neg. vs 8.3 mo. MRD pos., p=0.023).
- IMiDs:**
1. Talati C, Sallman D and List A. Lenalidomide: myelodysplastic syndromes with del (5q) and beyond. *Semin Hematol*. 2017;54(3):159-166. (<https://www.ncbi.nlm.nih.gov/pubmed/28958290>)
The article describes the differential mechanism of action for lenalidomide in del (5q) MDS vs non-del (5q) MDS. While lenalidomide may lead to elimination of the involved clone in patients with del (5q), it may enhance EPO receptor signaling in non-del(5q) patients. In the latter case, therefore, lenalidomide therapy may work better in combination with EPO-alfa.
- Allogeneic Bone Marrow Transplant:**
1. Aldoss I et al. Favorable impact of allogeneic stem cell transplantation in patients with therapy-related myelodysplasia regardless of TP53 mutational status. *Haematologica*. 2017; Sept 29 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28971906>)
The present report evaluates the impact of pre-transplant genetics and other clinical characteristics on allogeneic HSCT in 67 therapy-related MDS (t-MDS) patients compared to 199 patients with de novo MDS receiving allogeneic HSCT. Despite the higher proportion of Int-2/High risk disease and high-risk cytogenetics in t-MDS, the 5-yr overall survival was comparable in t-MDS and de novo MDS patients (49.9% vs 53.9% respectively, p=0.61). Moreover, neither the presence of TP53 mutation nor the mutations of other high-risk genes like EZH2, ASXL1 etc. showed any impact on overall or relapse-free survival.
 2. Ciurea SO et al. Haploidentical transplantation for older patients with acute myeloid leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2017; Sept 14. [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28918304>)
The report describes a single center experience with 43 AML/MDS patients (median age- 61 yr.) undergoing haploidentical SCT with fludarabine-melphalan based conditioning and post-transplant cyclophosphamide based GVHD prophylaxis. All but one patient engrafted donor cells very well. The rates of acute gr 2–4 GVHD at 6 months was 35% and of overall chronic GVHD at 2 yrs. was 9%. At a median 19 mo. follow up both OS and PFS rates were 42%.
 3. Scheid C et al. Validation of the revised IPSS at transplant in patients with myelodysplastic syndrome/transformed acute myelogenous leukemia receiving allogeneic stem cell transplantation: a retrospective analysis of the EBMT chronic malignancies working party. *Bone Marrow Transplant*, 2017; Sept 11. [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/28892084>)

A retrospective analysis of the EBMT database was conducted to understand the impact of the IPSS-R score immediately prior to a transplantation rather than abiding by the score assigned at diagnosis. The multivariate analysis highlighted IPSS-R, graft source, age, and prior treatment as prognostic factors. IPSS-R at transplant showed significant difference in OS and in relapse free survival (Low risk with 55 mo/24.8 mo as the highest and Very High risk with 7.8 mo./5.5 mo. as the lowest respectively, $p < 0.001$).

Novel Therapies:

1. Ueda Y et al. A phase 1/2 study of the WT1 peptide cancer vaccine WT4869 in patients with myelodysplastic syndrome. *Cancer Sci.* 2017; Sept 26 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/28949050>)

In a dose finding study transfusion dependent MDS patients were administered with a synthetic peptide vaccine WT4869 derived from WT1 gene at 5–1200 µg/dose intradermally every 2 weeks. Among the 25 enrolled patients, dose limiting toxicity was observed in one patient at 50 µg/dose level and in another patient at 400 µg/dose level. With overall response rate of approximately 18% and median survival of 65 weeks, the MTD remained undetermined. WT1-specific cytotoxic T cells were detectable in 11/25 evaluable patients.

2. Platzbecker U et al. Luspatercept for the treatment of anemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicenter, open-label phase 2 dose-finding study with long-term extension study. *Lancet Oncol.* 2017;18(10):1338-1347. (<https://www.ncbi.nlm.nih.gov/pubmed/28870615>)

Luspatercept is postulated to relieve the TGFβ protein superfamily imposed inhibition of erythropoiesis and hence may have a therapeutic role in treating MDS related anemia. PACE-MDS is a phase 2 study in low/int-1 MDS patients

or non-proliferative CMML who had persistent anemia with or without RBC transfusion support at the time of enrollment. In this dose-finding study, Luspatercept was administered subcutaneously every 3 weeks (dose range – 0.125 mg/kg to 1.75 mg/kg for first 5 doses and then in extension study starting at 1 mg/kg titrated up to 1.75 mg/kg). The base study with 27 patients receiving a range of doses, safety and responses were assessed at week 12. Further, 31 patients were enrolled in the extension study cohort. 32/51 (63%) total patients receiving higher doses (0.75–1.75 mg/kg) achieved HI-E per IWG criteria vs. only 2/9 responders among patients receiving lower doses. With three treatment-related Gr 3 AEs, the treatment was overall well-tolerated.

PATHOBIOLOGY:

1. Tefferi A et al. Targeted next-generation sequencing in myelodysplastic syndromes and prognostic interaction between mutations and IPSS-R. *Am J Hematol.* 2017; Sept 5 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28875545>)

Using a 27-gene next generation sequencing (NGS) panel in 179 cases of primary MDS, 82% patients were found to have at least one mutation/variant detectable with 23% harboring ≥3 mutations/variants. The top three frequent mutations/variants were ASXL1 (30%), TET2 (25%) and SF3B1 (20%). The three mutations that particularly showed impact on survival were ASXL1, SETBP1 and TP53 in the overall study population, however had no impact in IPSS-R low/very low subgroup. The report concludes that the number of mutations/variants did not add to conventional prognostication.

2. Neukirchen J et al. Cytogenetic clonal evolution in myelodysplastic syndromes is associated with inferior prognosis. *Cancer.* 2017;July 26. [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28746789>)

A longitudinal karyotype analysis of 549 patients from the Dusseldorf MDS registry demonstrated clonal evolution in 24% patients (18% among those treated with best supportive care). The clonal evolution was associated with an increased risk of leukemic transformation (HR=2.23, $p=0.036$) and poorer survival (HR=3.68, $p<0.001$). Similarly, detectability of cytogenetic subclones at diagnosis had a similar impact on survival and 5-year probability of leukemic transformation.

3. McGraw K and List A. Erythropoietin receptor signaling and lipid rafts. *Vitam Horm.* 2017;105:79–100. (<https://www.ncbi.nlm.nih.gov/pubmed/28629526>)

The intactness of lipid bilayer membrane may be quintessential for EPO receptor signaling. Lipid rafts composed of densely packed sphingolipids and cholesterol provide a membrane microdomain for understanding the mechanics of EPO signaling. Disruption of lipid rafts impair EPO signaling which may thus help in a therapeutic assessment of EPO signaling deficiencies.

REVIEWS, PERSPECTIVES & GUIDELINES

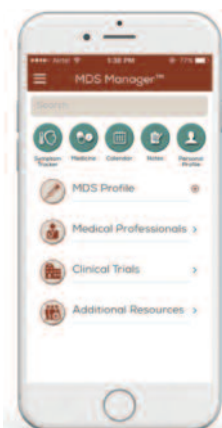
The following articles provide significant review of literature and/or innovative perspective on the state-of-the-art in MDS or discuss therapeutic management guidelines and identify need for additional prospective studies.

1. Galán-Díez, Cuesta-Domínguez Á, and Kousteni S. The bone marrow micro-environment in health and myeloid malignancy. *Cold Spring Harb Perspect Med.* 2017; Sept 29, [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28963115>)
2. Cargo C and Bowen D. Individual risk assessment in MDS in the era of genomic medicine. *Semin Hematol.* 2017;54(3): 133–140. (<https://www.ncbi.nlm.nih.gov/pubmed/28958286>)

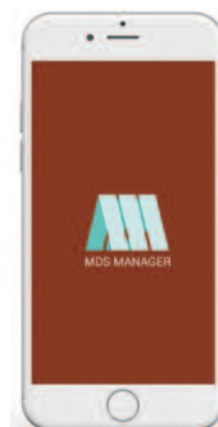
We would like to thank Suneel Mundle, a member of the MDS Foundation, and Rhea Mundle for their assistance in monitoring these important peer-review publications on MDS.

3. Miles A and Platzbecker U. Increasing effectiveness of hematopoiesis in myelodysplastic syndromes: erythropoiesis stimulating agents and transforming growth factor- β superfamily inhibitors. *Semin Hematol.* 2017;54(3):141–146. (<https://www.ncbi.nlm.nih.gov/pubmed/28958287>)
4. Madanat Y and Sekeres MA. Optimizing the use of hypomethylating agents in myelodysplastic syndromes: selecting the candidate, predicting the response and enhancing the activity. *Semin Hematol.* 2017;54(3):147–153. (<https://www.ncbi.nlm.nih.gov/pubmed/28958288>)
5. Pardo-Pastor J et al. Image gallery: Pyoderma gangrenosum in a patient with myelodysplastic syndromes treated with azacitidine. *Br J Dermatol.* 2017; 177(3):e68. (<https://www.ncbi.nlm.nih.gov/pubmed/28940271>)
6. Zeidan AM, Pullarkat VA and Komrokji RS. Overcoming barriers to treating iron overload in patients with lower risk myelodysplastic syndrome. *Crit Rev Oncol Hematol.* 2017;117:57–66. (<https://www.ncbi.nlm.nih.gov/pubmed/28807236>)
7. Santini V. First-line therapeutic strategies for myelodysplastic syndromes. *Clin Lymphoma Myeloma.* 2017;17S:S31–S36. (<https://www.ncbi.nlm.nih.gov/pubmed/28760300>)
8. Boddu P et al. The emerging role of immune checkpoint based approaches in AML and MDS. *Leuk Lymphoma.* 2017; Jul 6. [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28679300>)

Introducing... MDS MANAGER



MDS Manager™ is a newly developed mHealth application designed for smartphones and tablets that includes a variety of features to assist the patient and caregiver LIVING with MDS to more effectively manage their care, improve communication with and among providers, and track their response to treatment.



It represents a digital adaptation of book 5 of the Building Blocks of Hope®, My MDS Plan, which includes tools and strategies for staying well.

TO LEARN MORE, GO TO:

<https://www.mds-foundation.org/mdsmanager>

MDS CENTERS OF EXCELLENCE



Our MDS Centers of Excellence are comprised of the leading institutions and clinicians in the field of MDS that meet the highest standards of diagnosis, treatment and patient care. If you are a patient that would like a second opinion or if you are a physician that would like your treatment center to become part of the referral system for MDS patients, please contact our Patient Liaison, Audrey Hassan, at ahassan@mds-foundation.org.

TO VIEW THE COMPLETE INTERNATIONAL
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PATIENTS & CAREGIVERS LIVING WITH MDS

SPREADING THE NEWS WORLDWIDE

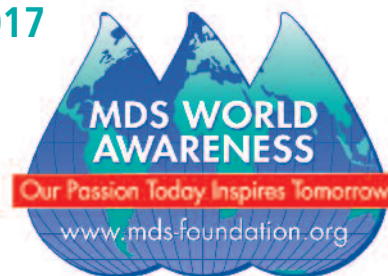
Celebrating MDS World Awareness Day – October 25, 2017 A Day to Celebrate Global Solidarity and Hope for MDS

October 25th was marked by a global community of patients, patient groups and professionals supporting people living with MDS. Events and campaigns took place throughout the month of October bringing the global MDS community together to share stories, raise awareness and campaign with and for everyone affected by myelodysplastic syndromes. In honor of MDS World Awareness Day, the MDS Foundation held two MDS Patient & Caregiver Forums, one in California and another in Georgia. We also spearheaded a social media campaign, throughout the month of October, focusing on the latest science of MDS from leading experts from our Board of Directors and Centers of Excellence. Our Executive



*MDS Awareness at the
YANKEE'S Playoff games!*

Director, Tracey Iraca, also participated in an #MDSAwarenessDay Facebook Live event with MDS patient, Jack Becker, hosted by MDS Matters.



*MDS Patient & Caregiver Forum in
Stanford, California*



MDS Patient & Caregiver Forum in Atlanta, Georgia

FREE One-Day Forums for MDS Patients and Their Families

Ongoing meetings in the US and Europe addressing quality of life issues for MDS patients are planned for 2018. Learn the latest on the diagnosis and treatment of MDS from leading experts in the field. These events will occur in eleven cities around the world in 2018. A global patient forum will be held alongside the 23rd European Hematology Association (EHA) Congress in Stockholm, Sweden.

CALENDAR OF EVENTS

FEBRUARY 3, 2018	San Diego, CA
MARCH 3, 2018	Albuquerque, NM
APRIL 28, 2018	Pittsburgh, PA
MAY 5, 2018	Salt Lake City, UT
JUNE 9, 2018	Hackensack, NJ
JUNE 13, 2018	Stockholm, Sweden
JULY 21, 2018	Baltimore, MD
AUGUST 18, 2018	Minneapolis, MN
SEPTEMBER 15, 2018	Charlottesville, VA
SEPTEMBER 29, 2018	Cincinnati, OH
NOVEMBER 10, 2018	Miami, FL

Register online at <https://www.mds-foundation.org/patient-and-family-forums> or contact Janice Butchko at 1-800-637-0839, Ext. 212, or email jbutchko@mds-foundation.org.

**PLEASE MAKE SURE TO REGULARLY
CHECK OUR WEBSITE FOR MEETINGS
TAKING PLACE IN A CITY NEAR YOU!**

MDS ON YOUTUBE

MDS WORLD AWARENESS

Our Passion Today Inspires Tomorrow

www.mds-foundation.org

Current Science
in MDS at our
CENTERS OF EXCELLENCE

https://www.youtube.com/user/seomds

MDS at Rush University
Medical Center

MDS at Washington
University in St. Louis

MDS at MD Anderson Cancer
Center

MDS at Mass General Cancer
Center

MDS at Dana-Farber Cancer
Institute

MDS at Moffitt Cancer Center

MDS PATIENT AND PROFESSIONAL MEMBERSHIP

MEMBERSHIP OPPORTUNITY

MDS FOUNDATION MEMBERSHIP

WHAT ARE MDS MEMBERSHIP BENEFITS?

- Being part of the solution to change MDS outcomes. Membership fees help support global physician and patient educational initiatives, and help to empower patients with courage and hope.
- Two printed issues of *The MDS News*, which includes the latest on MDS as well as exceptional patient and caregiver stories.
- Regular updates on the status of our Global Centers of Excellence and their patient events that encourage collaboration.
- Information on the latest clinical trials to potentially share or participate in.
- Access to MDS awareness materials to share with family and friends.
- Opportunities to participate in or host support group events with your friends and community.

MDS PATIENT MEMBERSHIP OPTIONS

\$35 *Community Membership* (includes benefits listed above)

\$70 *Sharing Hope Membership* (includes benefits listed above as well as a membership scholarship for a patient or caregiver in need)

\$250 *Changing the Future of MDS Membership* (includes benefits listed above as well as additional support for the MDS Foundation as we work together to change the future of MDS) Member names are listed on the MDSF website.

MDS PROFESSIONAL MEMBERSHIP OPTIONS

\$35 *Community Professional Membership* (includes discounted registration rates at MDSF meetings, discounted subscription rates to Leukemia Research, as well as access to MDSF resources for distribution to your patients)

\$250 *Changing the Future of MDS Professional Membership* (includes discounted registration rates at MDSF meetings, discounted subscription rates to Leukemia Research, access to MDSF resources for distribution to your patients, as well as the opportunity to present at MDSF patient events in your region. In addition, \$50 of your membership will help support a Professional outside of the United States that represents a CoE in financial need. Member names are listed on the MDSF website.



TO BECOME A MEMBER VISIT:
<https://www.mds-foundation.org/membership>

HOW DOES MEMBERSHIP HELP?

- Supports over 1,000 educational packets to families and caregivers free of charge annually, to help navigate through their MDS diagnosis.
- Helps our Patient Liaison respond to over 1,300 on-line requests annually.
- Supports over 170 Centers of Excellence worldwide. We believe this is imperative as these centers serve as our patient referral base, and this partnership helps the MDS community collaborate and engage in innovative practices in the diagnosis and care of MDS patients.
- Helps to distribute over 8,000 translated pieces of MDS materials annually.
- Enables MDSF to support approximately 250 professionals collaborating through International Working Groups — with researchers in 37 countries, and on 6 of the 7 continents.
- Helps to educate patients, caregivers and professionals at live events. This year MDSF hosted its International Symposia in Valencia, Spain with over 1,000 professionals in attendance. We also host 11 live patient events every year.
- Helps the MDS Foundation develop the growth of our *Pediatric Centers of Excellence* program to support children and their families who are living with MDS.

Thinking of joining the MDS Foundation as a Professional Member?

To join the MDS Foundation and help us fulfill our mission of moving closer to a cure for MDS, please visit our website at <http://www.mds-foundation.org/professional-annual-membership-application>.

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TESTIMONIALS

"I am writing to say a huge THANK YOU for the above booklet received in the post this morning. From a quick glance at the contents, I can see that it is just what I needed, very upbeat and a welcome answer to my many questions."

We also prefer the title of Caregiver, rather than Carer which is what is used in the UK. So once again, many thanks!

Jan S.

**"God Bless you all.
Unreal what you all do for us!"**

Scott R.

"I just wanted to thank you for all the good you do. I won't claim to understand the things you sacrifice, but you are truly wonderful for doing so."

Not that a 2 line email is as much as you deserve – but not being able to give enough seems a poor excuse for not giving anything. For what it is worth, thank you!

Leah J.

"Encouraged to come across your website. I am feeling overwhelmed by all the technical, medical sites I have been researching on. Your introduction video is a comfort for 'regular' people, who have limited knowledge of this syndrome."

Rebecca M.

"My husband was very recently diagnosed with MDS. I am both impressed and appreciative of the format and information you have put together on this website."

I'm looking forward to receiving the books so I can share them with him.

Belinda L.

"I really appreciate this site and your handbook. I've got lots to learn."

Judy M

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"Your website is very helpful, looking forward to reading the Building Blocks of Hope resource."

James S.

"Your Building Blocks of Hope is going to be a wonderful resource for my family."

Phyllis A.

"Recently diagnosed with sideroblastic anemia and myelodysplastic syndromes. Thank you for making this book available."

Phyllis A.

"This book is filled with great information. I have been researching MDS for a few months. Thank you so much!"

Tracy K.



The Building Blocks of Hope Handbook provides strategies for patients and caregivers living with MDS. This program is designed to give patients and caregivers the in-depth information that they are looking for and to allow them to take an active part in their MDS journey. The BBoH is available in several languages. Call 1-800-MDS-0839 for your FREE copy today.

Celgene and Acceleron Complete Target Enrollment in the MEDALIST and BELIEVE Phase 3 Studies of Luspatercept in Myelodysplastic Syndromes and Beta-Thalassemia

SUMMIT, N.J. & CAMBRIDGE, MA. Celgene Corporation (NASDAQ: CELG) and Acceleron Pharma Inc. (NASDAQ: XLRN) today announced that they have completed target enrollment in the MEDALIST and BELIEVE Phase 3 studies of luspatercept in patients with myelodysplastic syndromes (MDS) and beta-thalassemia. The Companies expect to report top-line results from the clinical trials in the middle of 2018. Luspatercept is being developed to treat a range of hematologic diseases including MDS, beta-thalassemia, and myelofibrosis as part of a global collaboration between Acceleron and Celgene.

“We are excited to have completed target enrollment in our MEDALIST and BELIEVE Phase 3 studies of luspatercept, ahead of schedule, and look forward to reporting top-line results in the middle of next year,” said Michael Pehl, President, Hematology and Oncology for Celgene. “Patients suffering from both diseases have limited treatment options to improve their underlying anemia. We believe that luspatercept may be a potentially paradigm-changing treatment option for patients and physicians alike.”

“The rapid pace of patient recruitment in our global Phase 3 trials reflects the clear need for new MDS and beta-thalassemia therapies that can significantly reduce or eliminate dependence on red blood cell transfusions,” said Habib Dable, President and Chief Executive Officer of Acceleron. “We are grateful for the support and dedication of the MEDALIST and BELIEVE study investigators, our patient advocacy partners, and most importantly

the more than 500 patients and their families who are participating in our studies. I would also like to acknowledge the strong collaborative effort of the Celgene and Acceleron teams that led to this important achievement.”

The MEDALIST Phase 3 trial has enrolled 210 patients with lower-risk MDS. The BELIEVE Phase 3 trial has enrolled 300 patients with transfusion dependent beta-thalassemia. Patients who are currently in screening remain eligible for randomization into both Phase 3 studies. The trials will remain blinded for both the primary and secondary endpoints until the end of the 48-week treatment period for all randomized patients.

About the MEDALIST Study

The MEDALIST Phase 3 trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of luspatercept in patients with ring sideroblasts (RS+), lower-risk MDS with a baseline RBC transfusion burden of at least 2 units per 8 weeks over the 16-week period prior to treatment. The primary endpoint of the study is the proportion of patients who are red blood cell (RBC) transfusion independent over any consecutive 8-week period through week 24. Secondary endpoints include duration of RBC transfusion independence and proportion of patients achieving a modified hematologic improvement - erythroid (HI-E) per the International Working Group over any consecutive 8-week period during treatment. Patients were randomized 2:1, luspatercept to placebo treatment, administered subcutaneously every 3 weeks for 48 weeks. The MEDALIST study is being conducted at 74 investigational sites in 11 countries.

About the BELIEVE Study

The BELIEVE Phase 3 trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of luspatercept in patients with transfusion

dependent beta-thalassemia. The primary endpoint of the study is the proportion of patients achieving a $\geq 33\%$ reduction in red blood cell (RBC) transfusion burden from Week 13 to Week 24 compared to the baseline 12-week period prior to treatment. Secondary endpoints include reductions in RBC transfusion burden from Week 37 to Week 48 compared to baseline. Beta-thalassemia patients in the trial had a baseline RBC transfusion burden of 6 to 20 units over the 24-week period prior to treatment. Patients were randomized 2:1, luspatercept to placebo treatment, administered subcutaneously every 3 weeks for 48 weeks. The BELIEVE study is being conducted at 73 investigational sites in 15 countries.

About Luspatercept

Luspatercept is a modified activin receptor type IIB fusion protein that acts as a ligand trap for members in the transforming growth factor-beta superfamily involved in the late stages of erythropoiesis (red blood cell production). Luspatercept regulates late-stage erythrocyte (red blood cell) precursor cell differentiation and maturation. This mechanism of action is distinct from that of erythropoiesis-stimulating agents (ESAs), which stimulate the proliferation of early-stage erythrocyte progenitor cells. Acceleron and Celgene are jointly developing luspatercept as part of a global collaboration. Acceleron and Celgene are conducting two Phase 3 clinical trials that are designed to evaluate the safety and efficacy of luspatercept in patients with myelodysplastic syndromes (the “MEDALIST” study) and in patients with beta-thalassemia (the “BELIEVE” study). For more information, please visit www.clinicaltrials.gov.

Luspatercept is an investigational compound that is not approved for use in any country.

Source: Acceleron Pharma and Celgene Corporation.

FDA Grants Approval of IDHIFA®, the First Oral Targeted Therapy for Adult Patients with Relapsed/Refractory Acute Myeloid Leukemia and an IDH2 Mutation

SUMMIT, N.J. & CAMBRIDGE, MA. Celgene Corporation (NASDAQ:CELG) and Agios Pharmaceuticals, Inc. (NASDAQ:AGIO) today announced that IDHIFA® (enasidenib) was granted approval from the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory AML (R/R AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA approved test.¹ IDHIFA, an oral targeted inhibitor of the IDH2 enzyme, is the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation, which represents between 8 and 19 percent of AML patients.³

“The FDA approval of IDHIFA provides the first-ever treatment option for patients living with relapsed or refractory AML and an IDH2 mutation. We appreciate the FDA’s efforts to expedite the availability of IDHIFA for patients with this devastating disease weeks ahead of the PDUFA date,” said Mark Alles, Chief Executive Officer of Celgene. “This milestone further illustrates the value of Celgene’s unique distributed research model. Our partnership with Agios is an exceptional example of how Celgene and its collaborators can positively impact the lives of patients with high unmet needs.”

AML is a cancer of the blood and bone marrow marked by rapid disease progression and is the most common acute leukemia affecting adults with more than 21,000 new cases estimated in the U.S. each year.^{4,5,6} The majority of patients with AML eventually experience relapse. Relapsed or refractory AML has a poor prognosis.⁶ For 8 to 19 percent of AML patients, the mutated IDH2 enzyme

blocks normal blood cell development and results in an overabundance of immature blood cells.³

“The FDA approval of IDHIFA just four years after entering the clinic is the first of what we expect to be multiple first-in-class precision medicines for patients with cancer and rare genetic diseases from our productive discovery engine,” said David Schenkein, M.D., Chief Executive Officer of Agios. “We look forward to working closely with Celgene to co-commercialize IDHIFA and provide access for patients in the U.S. with this devastating disease.”

“AML is a complex, heterogeneous disease, which is particularly difficult to treat in the relapsed or refractory setting,” said Martin Tallman, M.D., Hematologic Oncologist and Chief, Leukemia Service at Memorial Sloan Kettering Cancer Center. “IDH2 mutations inhibit the normal maturation of myeloid cells, so having a treatment that targets this mechanism is promising for patients and encouraging to us as physicians who have it as our goal to provide options for every patient.”

Demonstrating Clinical Benefit & Safety with IDHIFA1

The FDA approval was based on the clinical data from an open-label, single-arm, multicenter, two-cohort clinical trial of adult patients with R/R AML and an IDH2 mutation (Study AG221-C-001, NCT01915498). IDHIFA was approved concurrently with the Abbott RealTime™ IDH2 companion diagnostic test, which is FDA-approved as an aid in identifying AML patients for treatment with IDHIFA.

The efficacy of IDHIFA was evaluated in 199 adult patients with R/R AML and an IDH2 mutation. IDH2 mutations were identified or confirmed by the Abbott RealTime™ IDH2 test. IDHIFA was given orally at a starting dose of 100 mg daily until disease progression or unacceptable toxicity. Dose reductions were allowed to manage side effects. Patients had a median age of 68 years (range of 19 to 100) and received a median of two prior anticancer regimens (ranging from one to six). More than half (52%) were refractory to previous therapy.

In this trial, IDHIFA demonstrated a combined complete response or complete response with partial hematologic improvement (CR/CRh) rate of 23% (n=46) (95% CI: 18%, 30%). Median duration of CR/CRh was 8.2 months (95% CI: range 4.3, 19.4). For patients who achieved a CR/CRh, the median time to first response was 1.9 months (range, 0.5 to 7.5 months) and the median time to best response of CR/CRh was 3.7 months (range, 0.6 to 11.2 months). Of patients achieving a CR/CRh, 85% (39 of 46 patients) did so within six months of initiating IDHIFA.

Among the 157 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 53 (34%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 42 patients who were independent of both RBC and platelet transfusions at baseline, 32 (76%) remained transfusion independent during any 56-day post-baseline period.

The safety of IDHIFA was evaluated in 214 patients with R/R AML and an IDH2 mutation. The median duration of exposure to IDHIFA was 4.3 months (range 0.3 to 23.6). The 30-day and 60-day mortality rates observed with IDHIFA were 4.2% (9/214) and 11.7% (25/214), respectively.

In the clinical trial, 14% of patients treated with IDHIFA experienced differentiation syndrome, which can be fatal if not treated. IDHIFA can cause fetal harm if administered to pregnant women. The most common adverse reactions ($\geq 20\%$) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite. Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were leukocytosis, diarrhea, nausea, vomiting, decreased appetite, tumor lysis syndrome, and differentiation syndrome.

About IDHIFA

IDHIFA (enasidenib) is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.

**Jazz Pharmaceuticals
Announces FDA Approval
of Vyxeos™ (daunorubicin
and cytarabine) Liposome
for Injection for the
Treatment of Adults with
Newly-Diagnosed Therapy-
Related Acute Myeloid
Leukemia (t-AML) or AML
with Myelodysplasia-
Related Changes (AML-MRC)**

**Vyxeos represents the first new
chemotherapy advance in more
than 40 years for these adults
with AML**

**Vyxeos improved overall survival
compared to standard of care
7+3 (cytarabine and daunorubicin)
regimen (9.6 months vs. 5.9
months, respectively)**

DUBLIN, August 3, 2017/PRNewswire
Jazz Pharmaceuticals plc (Nasdaq: JAZZ)
today announced that the U.S. Food and
Drug Administration (FDA) has approved
Vyxeos™ (daunorubicin and cytarabine)
liposome for injection for the treatment of
adults with two types of Acute Myeloid
Leukemia (AML), a rapidly progressing
and life-threatening blood cancer. Vyxeos
is indicated for the treatment of adults with
newly-diagnosed t-AML or AML-MRC.

“Vyxeos is the first new chemotherapy
advance in more than 40 years for adults
with newly-diagnosed therapy-related
AML or AML with myelodysplasia-related
changes,” said Bruce Cozadd, chairman
and chief executive officer of Jazz
Pharmaceuticals. “The FDA approval of
Vyxeos reflects our commitment to
addressing unmet needs within the
hematology oncology community.”



Designed with Jazz’s CombiPlex® proprietary technology, Vyxeos is a unique liposomal formulation that delivers a fixed-ratio of daunorubicin and cytarabine to the bone marrow that has been shown to have synergistic effects at killing leukemia cells in vitro and in animal models. Vyxeos is the first product developed with the company’s proprietary CombiPlex platform, which enables the design and rapid evaluation of various combinations of therapies.

“Vyxeos is the first chemotherapy to demonstrate an overall survival advantage over the standard of care in a Phase 3 randomized study of older adults with newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes,” said Jeffrey E. Lancet, MD, Chair of the Department of Malignant Hematology at Moffitt Cancer Center. “The prognosis for these patients is poor, so the FDA approval of this new drug provides a welcome therapeutic advance.”

**For more information about Vyxeos in the United States, please visit
<http://www.Vyxeos.com>.**

Connect[®] MDS and AML: The Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) Disease Registry

Celgene is researching the following objectives in MDS and AML patient populations:

- Current and evolving patterns for diagnosing, treating, and monitoring patients
- Outcome measures
- How routine practice compares to national treatment guidelines
- Treatment patterns and outcomes in patients with del(5q), with or without additional cytogenetic abnormalities
- Association of patient characteristics, treatment regimens and clinical outcomes with patient-reported Health Related Quality of Life (HRQoL) and economic outcomes
- Clinical outcomes based on treatment in patients with or without mutations
- Correlation between mutation detection/allele burden in bone marrow and peripheral blood samples
- Molecular and/or cellular marker's relation to prognostic classification, drug mechanism of action and clinical and treatment outcomes

Select eligibility criteria:

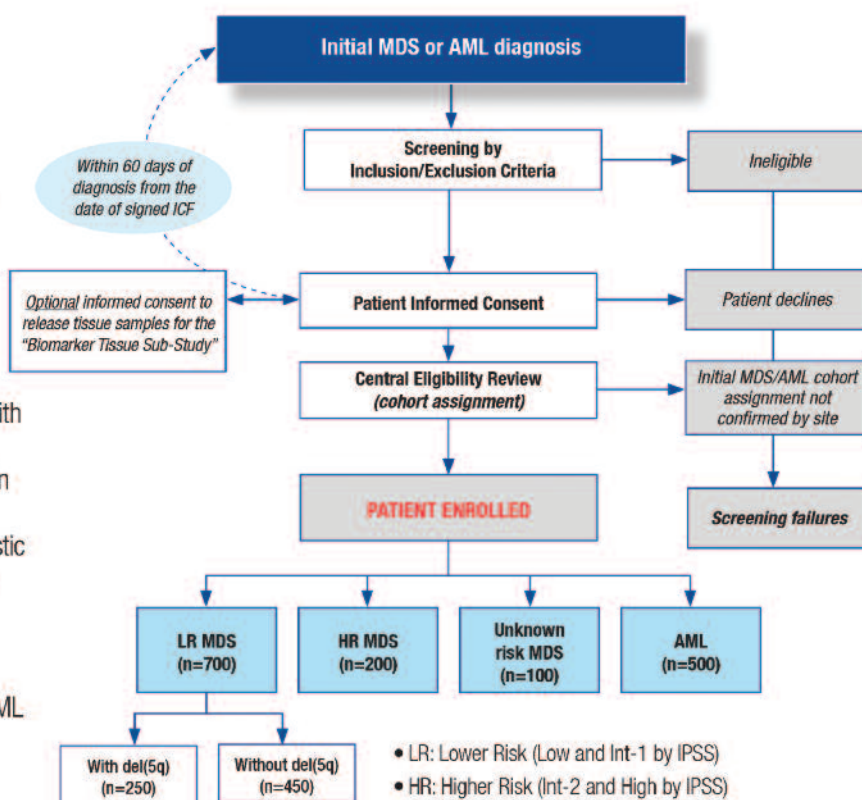
- Newly diagnosed,* primary or secondary MDS or AML
- MDS patients must be at least 18 years
- AML patients must be at least 55 years of age
- Patients must be willing and able to complete enrollment and follow-up HRQoL instruments, for which patients must be proficient in either English or Spanish

*To be considered "newly diagnosed," a patient's confirmed diagnosis must be made up to 60 days prior to the date of ICF signature.

Note: Concomitant patient enrollment in other studies is permitted.

Physicians – you could be an Investigator if:

- Your site supports clinical trials
- Your site sees at least 2 suspected MDS or AML patients per quarter



- LR: Lower Risk (Low and Int-1 by IPSS)
- HR: Higher Risk (Int-2 and High by IPSS)
- MDS patients of unknown risk must have undergone two unsuccessful bone marrow cytogenetic testing attempts
- APL diagnosis is excluded.

To learn more about this MDS/AML
Disease Registry Study, contact:
connectmdsaml-registry@celgene.com
(ClinicalTrials.gov Identifier: NCT01688011)



Our Journey with Blood Cancers Continues

Michelle Fantaske
Laguna Hills, California

I arrived to the Bone Marrow Transplant Donation Room nearly 30 minutes before my appointment time. It was just after 7:30 a.m. and Jessica, the nurse who would be attending to my donation, greeted me cheerfully. “You’re early!” she exclaimed. “That’s good! I’m almost finished setting up.” I recognized Jessica’s melodic voice from our phone briefing the day before. She had called me to check-in and make sure that I was feeling fine for the “harvest”. I always thought that harvest made it seem like I was walking into a procedure that would leave me missing a kidney in a bathtub full of ice.

Jessica motioned me to make myself comfortable on the neatly made hospital bed where I would spend the next six to eight hours. I awkwardly positioned myself in a half-lean half-sit on the bed with my shoes still on. My husband, Nick, wedged himself into the small space with a chair next to the bed, being careful not to entangle himself in the waterfall of cables cascading from the appliances surrounding the bed, like a sea of expensive medical equipment. Nick and I came prepared for the long day. We had brought plenty of snacks, extra clothes, and a laptop on which to re-watch season six of *Game of Thrones*.

Jessica buzzed around the room — a very basic-looking, unadorned room tucked away on the sixth floor in the “old part” of UC Davis Medical Center — collecting tubes, syringes, and flipping switches on sophisticated looking machines. Watching Jessica prep for my donation made my head spin. I was already uncomfortable from the prep I had to give myself. For five days prior, I was instructed to give myself daily injections of Neupogen, a drug that stimulated the



creation of stem cells inside my bone marrow and mobilizes the stem cells into my bloodstream. Fortunately, like most donors, the only side effects I experienced were body aches due to the expanding of my bones from the increase production of stem cells. The level of soreness was comparable to how I felt the day after my first snowboarding trip. I felt stiff, it was hard to move quickly, and I couldn’t do a proper squat if you paid me. I imagined that as soon as catheters are placed in my veins to suck out the stem cells, my body would return to its normal level of tension and alleviate the soreness, like deflating an overinflated tire back to its recommended pressure.



I was nervous. Despite reading all the bone marrow transplant donor pamphlets, online donor forums and blogs, and reassurances from the oncology staff, my head filled with worry. I didn’t worry about the pain of having steel needles inserted in my veins, embolisms, or the having to use a portable commode. I worried about the chances of successfully fulfilling the reason that brought me here — saving my sister’s life.

A little over a year before all this, our dad passed away from complications due to myelodysplastic syndrome (MDS). He underwent a succession of medications and treatments before succumbing to a subdural hematoma he suffered after a fall and hitting his head. Before he passed, I could see what the MDS was doing to him — slowly draining his energy, thinning his blood, and bruising his skin. Regardless, he never spoke of his distress. He continued to be the positive and brilliant person he was until his last day.

To honor our dad’s memory, my sister, Lisa, went to a blood drive to donate blood. Our dad received several blood transfusions as part of his treatment and we became aware of how valuable blood products are and grateful for the volunteers that donate them. Unfortunately, Lisa was not able to donate. A preliminary screening revealed she had low hemoglobin. Eventually, a bone marrow biopsy would expose even more irregularities with her blood and bone marrow. After four months of hematological appointments, tests, and uncertainty, we received devastating news — Lisa has a rare form of leukemia, Chronic Myelomonocytic Leukemia (CMML).

The diagnosis, as shocking as it was, felt unfounded. By all outward appearances, Lisa looked fine. She wasn’t weak, she didn’t bruise, bleed, or fatigue easily. Just earlier that year she and I were celebrating her thirtieth birthday with a couple of friends on Austin’s infamous 6th street. And now at 30 years old, she was

OUR PATIENT STORIES

one of the rare four in every million¹ people in the United States each year diagnosed with CMML—a disease whose patients have a median age of 71–74 at diagnosis². Our doubts about Lisa having a blood cancer would soon be extinguished as her now routine tests showed progressively decreasing blood counts and increasing signs of pathology. More complex genetic testing indicated that Lisa's rare leukemia was due to an even rarer, inherited genetic condition known as familial platelet disorder with associated myeloid malignancy. Our dad had a 50% chance of passing the mutation associated with hematological malignancy onto his children. Lisa was the 50% that received the mutation and I was 50% that did not.

Lisa's doctors concluded a bone marrow transplant as soon as possible is her best shot at long-term survival. While Lisa's disease was progressing, she was still young and healthy enough to sustain the debilitating chemotherapy and promote successful engraftment. She needed a transplant as soon as possible and she needed a bone marrow transplant match—ideally a full-matched donor. Relatives and I were tested to be matches for Lisa, however we were all considered to be half-matched.

The news of Lisa's diagnosis reverberated throughout our social circles quickly. Family and friends held bone marrow donation drives and set up fundraisers, organizations supporting leukemia and bone marrow transplant awareness reached out to Lisa and spread her story through social media, and people my sister didn't even know—blood cancer survivors and those close to them—connected with my sister and shared their stories and support.

Five months after Lisa's diagnosis and no full matches on the donor registry, Lisa's oncologist recommended moving forward with a transplant — a haplo-identical transplant — with me as her



donor. With a game plan in place, events moved at light speed. Lisa moved into a private hospital room in the Bone Marrow Transplant Unit at UC Davis where she would stay for the next 25 days. In preparation for the transplant, she underwent multiple chemotherapy treatments and total body irradiation. I underwent evaluations and physical tests to clear me as a donor. I started to believe that every choice I made, no matter how small, would affect the outcome of the transplant somehow. The responsibility began to motivate me because I was no longer just looking after myself — I was looking after Lisa, too. I thought running one more mile when my legs were already sore could boost the number of stem cells I produce. Choosing a salad over a burger could prevent adverse side effects from the Neupogen injections. One more push-up could mean that my cells would engraft quickly. Whether this attitude had medical merit or was simply superstition didn't make a difference. I was changing.

There was another nurse in the room now, Alicia. The room was getting smaller with the two of them rapidly orbiting the room, bringing out new

equipment, unpacking more tubes and syringes, and handing me paperwork to sign. I had completely retreated to Hospital Bed Island, where I was now under the covers, restricted by the cuffs of blood pressure and heart beat monitors. Jessica and Alicia prepped my arms to receive the steel needles that would draw and return my blood.

It was 9:00 am by the time I was fully hooked up to the apheresis machine, a noisy, mechanical-looking device with spinning knobs. A long, thin tube filled with my blood wrapped around a heated metal core that warmed my blood before returning it back to my body. My stem cells, extracted via a separate tube, collected in a bag that hung above my head. Jessica sat next to me for the entire duration on my right, and Nick presented the day's entertainment by way of some Game of Thrones battle action on his laptop to my left. This is where the three of us would stay for the next few hours. Compared to the flurry of preparation activity earlier, the actual harvesting was uneventful. Aside from occasional beeps from the machines and outbursts of clashing swords from combat scenes on the laptop, the next few hours were quiet.

The presiding doctor came in a quarter to noon to inform me they'll be disconnecting me from the apheresis machine in a couple of hours. By their calculations, they will harvest more than the 6.6 million stem cells Lisa needs for her transplant. I would be unhooked from all the machines, free to leave Hospital Bed Island to visit my sister in the next building for her transplant.

Lisa was in high spirits. She sat upright in her hospital bed, our mom sitting in a chair next to her. One of her favorite nurses, Allie, was taking Lisa's vitals and administering her preparatory medications before transplant. For someone about to undergo a transplant, Lisa was remarkably upbeat.

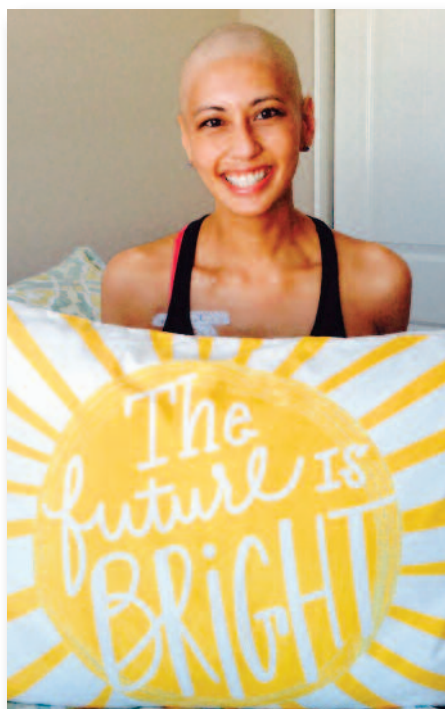
OUR PATIENT STORIES

The idea behind a successful stem cell transplant is that the donor stem cells will engraft into the recipients bone marrow and begin to produce healthy cells to fight off the cancer. The doctor overseeing Lisa's transplant explained that since Lisa will essentially be inheriting my immune system, her tastes in foods will start to resemble with mine, my allergies will become her allergies and conversely, allergies she has that I don't will go away. When her hair grows back, it will be my hair. To me, replacing someone's immune system entirely sounded like a procedure straight from science fiction.

The transplant doctor hung the bag that contained my 6.6 million stem cells on a hook that dangled above my sister. The stem cells transfused via a tube connected to a port implanted into my sister's chest. There were no scalpels, needles, or surgical instruments to hack into her bones, scrape out her marrow and replace it with mine—just a tiny bag barely the size of a sandwich baggie, dripping life-saving stem cells into Lisa. I remember looking at that tiny bag—that's all it could take to cure my sister's leukemia. Imagine if everyone who was capable could give their own tiny bag. It could provide the 20,000 patients needing a bone marrow transplant each year³ greater hope for a second chance at life.

It took two hours for the sandwich baggie to fully empty itself into Lisa. She was asleep for most of it, thanks to a hearty cocktail of Benadryl and Ativan. The transplant itself was just as how other patients described it—anticlimactic. The real action happens in the weeks and months following transplant.

A couple days after transplant, Lisa got violently sick and endured what is called a cytokine storm in response to the foreign cells. She lost her appetite, she lost physical strength, and she lost her hair. But just like our dad at his weakest, she didn't lose her spirit. Five days after transplant,



Lisa was feeling better and after 12 days, she was exhibiting signs of engraftment. Eighteen days after transplant, Lisa walked out of the Bone Marrow Transplant Unit, free to continue her recovery at home.

We were warned that the days after transplant would be the most turbulent. It's true. But those days turned to weeks. And those weeks turned to months. She is now over two months post-transplant and making incredible progress.



I was asked to share my experience donating bone marrow—but it's difficult to reduce it all to a single incident. The whole experience can't be defined by a few hours in a hospital room. It's defined by the rush of indescribable emotion I felt when I was told I'd be my sister's donor. It's defined by the people I've met — doctors and nurses at the hospital and the survivors and donors from the bone marrow donation drives. It's defined by people I've reconnected with — family and friends who have come out to show their support. It's defined by my sister's resilience and our mom's faith. It's defined by our dad's memory, and how the only reason she detected her leukemia was because she was trying to honor that memory.

Everyone that has connected to me in this experience and all the emotions will forever affect the choices I make and the way I see the world. I'm a different person now—for the better—because of this experience. Hopefully my sister will be, too. *Names have been changed to maintain anonymity.*

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Our Journey with Blood Cancers Continues

Donna Mitcham
Locust Grove, Georgia

I'd like to introduce my sons, Matt age 13 and Travis age 12, and tell you their MDS story. They were both diagnosed with MDS in the spring of 2016, but their story started way before they were even born.



First, I would have to start by telling you about their maternal grandfather Steve Purvine. Around the age of 36, he started feeling bad and showing

symptoms that the doctors just couldn't diagnose. For the next few years he continued to get sick, and at one point the doctors had decided he had Aplastic Anemia. That turned out to be the wrong diagnosis. After nearly three years of testing and finding no answers, a doctor straight out of medical school remembered studying about a rare disease called Myelodysplastic Syndromes or MDS. That was something the doctors had never thought of because young people didn't get this disease. Unfortunately, that new doctor was correct and Steve did have MDS. They immediately tested his siblings, and his brother was a perfect match for a bone marrow transplant. If only it hadn't come too late. At that point Steve was too sick to receive the transplant. In 2009, and at the age of 39, he passed away from this horrific disease.

When Steve passed away he left behind a wife and two young daughters, Natalie and Shannon. Growing up the younger daughter, Natalie, got sick a little more often than her sister and it always took her a little longer



to get over an illness. No one really thought much about it. She and her sister grew up and both had beautiful families of their own.

Fast forward to the year 2005. Natalie had 3 boys ages 8, 2 and 1. I distinctly remember around Thanksgiving seeing an awful bruise on her leg and questioning it. She laughed and said you know I'm clumsy and I have no idea where it came from. Slowly other symptoms started popping up, such as severe fatigue and more bruising. She eventually went to the doctor and was taken immediately to the hospital because her platelets were so low. She was so sick by the time she was admitted. It was what we had all feared. She had somehow inherited the disease that her dad had. She also had MDS. We couldn't understand how a disease that was supposed to be a disease of older people had now affected 2 generations of our family. We were told that they carried some kind of familial gene, and that it was very rare.



We couldn't understand how a disease that was supposed to be a disease of older people had now affected 2 generations of our family. We were told that they carried some kind of familial gene and that it was very rare.

Thankfully, Natalie's sister, Shannon, was a perfect match for her and a bone marrow transplant was performed in April of 2006.

She did very well at first. In March of 2007, while in Disney World with her boys, a tumor started growing in her cheek. It was right after that when the doctors discovered that she had relapsed and she had tumors all around her heart. She fought so hard to stay with her boys, but passed away on June 7, 2007.

When Natalie passed away her boys were 10, 2 and 3. Her oldest son, Marcus, went to live with his grandparents. Matt and Travis were my brother's boys and unfortunately he couldn't take care of them. That is when my husband and I

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received our unexpected blessings. It rocked our world as we already had 3 kids. We went from a family of 5 to a family of 7. It was crazy and chaotic, but we loved it. We love those boys just like our first three.

Our lives finally settled into a normal routine of school, football, friends and church. We are a busy family.

All of that changed on March 1, 2016 when Travis got a weird rash on his back and chest. Out of concern that it might be something contagious, I took him to a pediatric urgent care. The doctor looked at it and suggested that it looked like a petechiae rash. This is a rash caused by low platelets. At the mention of low platelets my heart sank, and I followed the doctor out the door to tell her of Travis' medical history. She did some blood work, and he did indeed have a low platelet count. She then told us to follow up the next day with our pediatrician.

The follow up with our pediatrician didn't go as smoothly as it should have. He disagreed with the urgent care doctor's diagnosis of petechiae and did blood work simply to appease me. I explained Travis' medical history, and my concerns, and he didn't seem to share those concerns at all.

When we got our blood work back his diagnosis was that Travis was anemic and that I should give him an iron pill. I said ok



and stewed on it for a couple of days. But my gut told me that something was just not right. At that point I called them back and told them I wanted a referral to the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta. They reluctantly agreed, and I got our appointment.

Two weeks later we were walking into the Aflac Clinic for our first appointment. My husband and I had asked Natalie's sister, Shannon, to come with us and help us with questions we needed to ask. We were lost in this world. Incredibly, the moment we met with our doctors I felt better. They took us seriously and were concerned from the very beginning. After looking at his labs they told us a bone marrow biopsy would be necessary to find out exactly what was going on. I have to say that I expected to leave that appointment feeling foolish, so I was completely blindsided by the request to do a biopsy.

The following week, Travis was so brave and did great during his biopsy. It was going to take a couple of days to get the results so we went back to work and school. I won't ever forget getting the call from the doctor at my work. She said it looks like Travis has MDS, and will need a transplant. Devastated doesn't begin to cover how we felt. I was not going to lose my baby to that monster too. Next came all the appointments to explain what a BMT is and how we would find a donor.

The first choice for Travis' donor was Matthew. We brought him to Aflac and they ran a complete blood panel on him before testing him as a match. His first set of blood work was a little suspicious, but he had a cold so we weren't worried. They had us bring him back once he was well to do another blood test. That was May 2. The doctor called me that afternoon, and said "I don't really know how to tell you this, but Matt's blood work looks a lot like Travis'. We need to do a biopsy on him." They told me that day they would be very surprised if he didn't have MDS as well.

Devastated doesn't begin to cover how we felt. I was not going to lose my baby to that monster too.



That night we sat the boys down and told them that they both had the same disease their mom had. I can't imagine hearing that. We all cried, hugged, laughed and put on our gloves to get ready for our fight. We were going to beat this stupid disease.

So back we went for Matt's biopsy. He was just as brave as Travis. A few days later on a rainy Friday, I got the call at work that Matt indeed did have MDS. I didn't even know how to feel. Travis had taken the news pretty well, but Matt understood more about the disease. I knew it was going to be harder for him.

That night we sat the boys down and told them that they both had the same disease their mom had. I can't imagine hearing that. Matt's only question was "Can I still play football?" We all cried, hugged, laughed and put on our gloves to get ready for our fight. We were going to beat this stupid disease. So it started.

Travis was admitted to Egelston on August 22, 2016 to start preparing for his transplant. His rebirth-day is August 29. He did so well. We had a few bumps in the road with fevers, but after 4 weeks in the hospital we were released to the Ronald McDonald House. We lived there for about 5 more weeks and then home! Travis has only had one hospital inpatient stay since he was released. It just happened to be when his brother was also in-patient. It was very interesting having two kids on the transplant floor at the same time. He continues to do



well, though his counts have stayed low and the doctors keep monitoring them.

Matt was admitted for his transplant on November 21, 2016 and his rebirth day is November 29. It was hard to be in the hospital during the holidays, but we made the best of it by decorating and making it like home. Matt did pretty well, but got a lot sicker than Travis did. He developed GVHD of the gut, and it really made everything harder for him. We were so happy to get released to the Ronald McDonald house on December 23, so that our family could celebrate with us. We finally got to go home the second week in February for good. Matt's biggest struggle

has been GVHD. He has been diagnosed with chronic GVHD. He has it on his skin now. His counts are great, and he is back in school and loving it.

So that is, believe it or not, the short version of our journey. We have learned so much this past year. We've learned that people are so kind and generous. We've learned that MDS can take a lot of things from you, but it can't take your courage, faith or the love of your family. I have personally learned that my boys are the bravest two kids I have ever known, and I'm lucky that they call me Mom. MDS will not beat us, destroy us or break us. It has only made our family stronger and better than ever before!

PATIENT STORIES

OUR PATIENT STORIES

My New Normal...

Bambie Fontana

Everett, Washington

I don't feel my story is any different from anyone else's except for the fact that I was diagnosed at a much younger age. It all started during my honeymoon...

I got married in 2014, and my husband and I went on a wonderful two-week honeymoon vacation in Belize. We planned the trip to fit our lifestyle: active, adventurous and daring, with some relaxation at the end. We stayed in the jungle and explored Mayan ruins, caves, and trekked throughout the country. I noticed feeling out of breath and thought to myself how out of shape I'd gotten since completing a half-marathon just two months prior, and a Tough Mudder race the fall before. I remember telling myself that I would get back to my exercise regimen as soon as I returned home from our dream vacation – and brushed it off. Our last day in the jungle during a midday jungle hike, I fell far behind my husband, and when we caught up to each other he looked alarmed when he saw me. He said I looked white and pasty and that my lips turned blue. I was gasping for air and trying so hard to catch up. My heart was pounding and I felt uncomfortable palpitations in my chest.



I'm a Registered Nurse and I knew something was wrong. I think without having my training and experience, I still would have known something wasn't right. I was fairly young — only 36 with no health concerns, ever. My husband (a Canadian who grew up just north of Seattle) made the remark that maybe it was just the heat of Central America getting to me. I'm a Louisiana native, born and raised on the bayou in Monroe, Louisiana. I am

I'm a Registered Nurse and I knew something was wrong. I think without having my training and experience, I still would have known something wasn't right... I knew something sinister was going on and I immediately booked a checkup with my provider.

no stranger to extreme heat and humidity. I served in combat support zones during Operation Iraqi Freedom and spent two summers in the Middle East in confined spaces with temperatures above 120 degrees Fahrenheit. My point here being that I knew the heat was not a factor for me — perhaps it was for my Canadian born husband, but not for this Southern girl. I know what a hot summer can do to a body and I was taking precautions not to become dehydrated. I knew something sinister was going on, and I immediately booked a checkup with my provider when I got back to the states — which happened to have fallen on my 37th birthday.

When the lab results came back, my provider was puzzled. She and I poured over the CBC and iron test results and looked at each other quizzically. My H/H was low in the 9/27 range but my iron levels were through the roof. B₁₂, all B vitamins good. She looked at me and quickly grabbed her office phone to call a hematologist nearby. I had to wait an excruciating 6 weeks to get in to see the hematologist/oncologist who uttered the scary word: cancer. He ordered a bone marrow biopsy and what seemed like a million other tests to hopefully rule out a cancer diagnosis.

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It took months of bone marrow biopsy testing, months of back and forth, and a referral to the prestigious Seattle Cancer Care Alliance, in partnership with the Fred Hutch research facility and the University of Washington to be diagnosed with MDS. I'm low-risk and feel lucky to be able to manage my symptoms with blood transfusions. I've tried growth factors with no results, and have recently decided to not undergo any sort of treatment other than scheduled blood transfusions. I feel that I have so much life to live but I struggle to overcome feeling trapped by my medical needs and the limitations on my energy. I have always been very outdoorsy and active, and felt like I had more energy than I knew what to do with, but that has changed significantly over the last 2 years. My family life has been severely affected by my diagnosis and loss of energy. Just before I was diagnosed, my husband and I bought and started remodeling from top to bottom, our 1976 original owner home. My energy level somewhat halted my contributions to our project, and I'm sure I left my husband feeling totally responsible for our remodel. My 10-year-old daughter goes with me frequently to appointments and worries about our future. I try my best



to explain to her that I've won the "lottery" of cancer diagnoses, but she is not comforted by my tactics. She pressures me to tell her how I'm feeling every single day, while I wish it wasn't a thought in her head.

I went from working two jobs on the hospital floor, 60 hours a week, to working from home for an online university because of my energy level. I'm finally getting back on my feet with a regimented blood transfusion schedule, and feeling a bit of energy coming back now that I'm out of the lower hemoglobin and hematocrit levels. I also see a therapist to deal with my completely different lifestyle.

I've resolved to seek out the best quality of life I can have while being forgiving of myself and my new life changes. I rest when I'm tired and let the laundry pile up if it must.

I wish I could write this with a happy, thoughtful ending but I'm just not there yet. I have struggled with this diagnosis and the side effects of treatments and the meaning this has for my family. I have sought out counseling and others with MDS, but I feel so alone in my diagnosis. My healthcare team is amazing and I couldn't ask for more complete care. I know that I must come to terms with MDS and what it means for me. I've resolved to seek out the best quality of life I can have while being forgiving of myself and my new life changes. I rest when I'm tired, and let the laundry pile up if it must. I ask my family for understanding, and am vocal in my community about the effects of cancer — not only on patients but for our families as well. My children are old enough to know the word "cancer" is scary, and my husband (I'm sure) was not prepared to be pulling the weight of his relatively young wife. The stress has changed us all, and I worked to rid myself of resentment as quickly as I could and just get on with the business of living. But I can't help but consistently hear the sound of treatments, transfusions, insurance co-pays, claim denials, clinical trials, blood counts and time ticking away. I know this will become my new normal, and I look forward to the day when I can take each day as a blessing and never take one moment for granted.



The stress has changed us all, and I worked to rid myself of resentment as quickly as I could and just get on with the business of living.

Being Engaged With The MDS Foundation

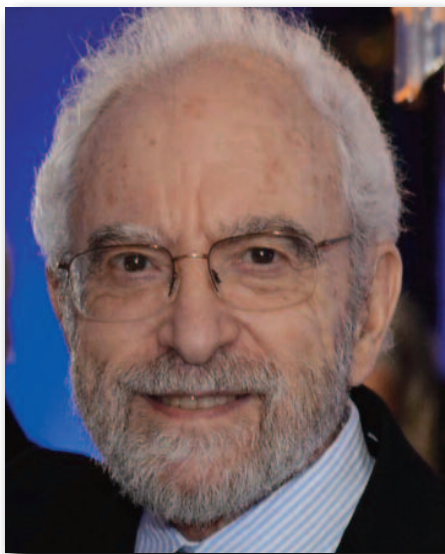
Jack Becker

Bedminster, New Jersey

My name is Jack Becker. This is my account of how I became an MDS patient, and how I am becoming actively engaged in working with the MDS Foundation.

I'm 81 years old, a retired engineer and physically quite active. I live in New Jersey with my wife of fifty-seven years, Gina. Our daughter, son-in-law, three grandchildren and one grand dog live on Long Island. Our son and his wife, and their pride of eight cats live in Florida.

In March of 2004, a routine medical examination revealed that I had developed type 2 diabetes. Always up for a challenge I was determined to control it with diet and exercise alone, and no medication. My wife was diagnosed six years later and claims she caught it from me. She, too, is able to control this disease by lifestyle changes alone. Together, we attend several support groups. These meetings provide camaraderie, understanding and education in a self-help and confidential environment. We both know how vital this type of



support is to people with any serious medical issue.

Over time, my primary care physician noticed an emerging pattern in my CBCs. My RBC, WBC and hemoglobin began to have lower than normal readings. They fell below the acceptable limits, whereas my monocytes were above the upper limit.

Subsequent CBC tests showed varying and out of range patterns. My doctor recommended that I consult a hematologist for further evaluation, even though I felt fine. My first visit to this specialist revealed that everything was in order. I was told to be rechecked every six months, then every four months. I had a bone marrow biopsy which didn't show anything. I had my blood checked again to determine if I lacked any nutrients that might be responsible for my anemia. The lab results were all in range. I was asymptomatic. The hematologist I was seeing at the time was not very forthcoming and I grew frustrated. My platelets fell to 50,000, where the lower limit was 150,000. In July 2015, I decided to get a second opinion. Using the "Health Grades" website I selected a different hematologist and had my records forwarded to this new doctor.

In October 2015, I met with my new doctor. After I was examined and tested he

said "You're not going to want to hear this, but you've got cancer." The doctor then sketched what resembled a tree lying on its side. It had branches labeled with names that I had never come across before. The tutorial sketch showed how red and white blood cells were generated in my bone marrow. I was told that I had MDS, with a CMML subclass and that I would not be a candidate for a stem cell bone marrow transplant because of my age. I had a malfunctioning blood cell generating factory that left me with blood cell mutations. My red blood cells appeared to be misshapen under the microscope. This dysplasia, coupled with my CBC results, was characteristic of low grade MDS. In time, MDS could develop into CMML. No treatment was warranted unless I began to show signs and symptoms of the disease progressing. My doctor will "watch and wait." I return at intervals to check my CBC and general health. Gina and I feel that I'm in good hands. This second opinion was up front and clear. There was a lot to absorb. I was plunged into the perplexing world of MDS, its language alien to me. Meanwhile, my routine diabetes labs are recorded concurrently and independently, by my primary care physician.

During this period, with no warning, I had low platelet symptoms on several independent occasions. It became difficult to stop minor bleeding after pricking my finger to check my blood glucose. There were also random symptoms of anemia. I felt chilled. My hands, feet, and sometimes my entire body, felt cold. Despite hot drinks and warm clothing, the chills continued. Then, both the bleeding and chills abruptly vanished and so far haven't returned. About a year ago, my diabetic CBC showed that my platelets fell to 37,000.

My primary care doctor put me on a four day course of low dose Prednisone. If that didn't help, I would have to be hospitalized to bring my platelets up. But it worked.

My wife and I attend several support groups. These meetings provide camaraderie, understanding and education in a self-help and confidential environment. We both know how vital this type of support is to people with any serious medical issue.

OUR PATIENT STORIES

Without warning, during the winter of 2016, I found myself with a lack of appetite, which still remains with me.

I still maintain my regular visits to my hematologist. For almost two years my CBCs have been monitored, showing nothing unusual. During my latest visit in July, 2017 the doctor said, "I don't know what you're doing, but keep it up. Everything looks great." I had the first improvement in almost two years. My RBC and WBC were both within acceptable ranges. My monocytes hit a new high. I've been trying to follow a predominantly plant based diet, coupled with regular physical exercise to maintain control over my diabetes. Could this lifestyle change have affected my CBC and the progression of MDS?

My focus now is to learn as much as possible about MDS. The materials provided by the MDS Foundation are invaluable to me. I've also gotten more information posted on reputable websites. As a barrage of information became overwhelming, I decided to give it a rest until the spring of 2017. At that time, I reached out to the MDS Foundation to ask if there were any support groups in New Jersey. I had the good fortune to speak with Audrey Hassan, Patient Liaison. She informed me of a group that met in Margate, New Jersey and a Patient Forum at the Memorial Sloan Kettering Cancer Center in Middletown, New Jersey. My wife and I attended both venues. The forum was an eye-opener. We have a much better understanding of how MDS patients,



families and caregivers deal with this rare disease; how it affects all involved.

The support group in Margate was hosted by Rochelle Ostroff-Weinberg in memory of her late husband, Robert. She provided us with a lovely gourmet dinner and a secure and confidential environment in which to share our stories and concerns. Also in attendance was her beautiful St. Bernard, Cognac. What a wonderful therapy dog.

In speaking with Audrey, I mentioned that it would be very helpful to start a support group closer to home in northern New Jersey. I had been a facilitator of an Alzheimer's disease caregivers support group at Overlook Hospital for 14 years and volunteered to facilitate an MDS group. Audrey said that if we could find an appropriate place to meet, the Foundation would sponsor it. Thanks to Patti Halicki, Administrative Assistant at the Robert Wood Johnson Steeplechase Cancer Center

in Somerville, New Jersey, we have that meeting place. Audrey also asked if I could reach out to a homebound MDS patient who lives alone and can no longer receive transfusions. All that's available now are hospice visits. I called and we spoke for over a half hour. It was an interactive support group of two. It was very gratifying to help. Even homebound MDS patients need not make their journey alone. I look forward to learning even more, and sharing information and being there for one another.

Our new support group held its first meeting on Wednesday evening, September 20th, 2017, at the RWJ Steeplechase Cancer Center, 30 Rehill Avenue, lobby level conference room, Somerville, NJ. Meetings are held the third Wednesday of every month from 7:00–8:30 pm. To register and for more information call me, Jack Becker, at 908-719-2276 or email me at thinkjk1@icloud.com.

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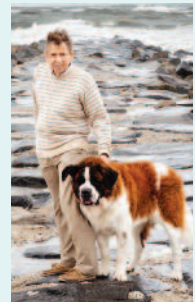
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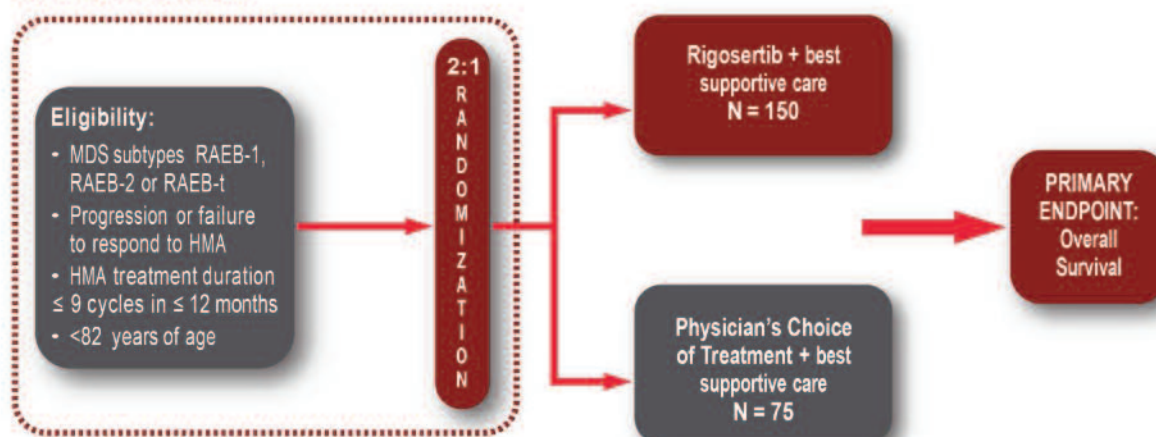
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STUDY DESCRIPTION

A Phase III, international, randomized, controlled study of Rigosertib + best supportive care versus physician's choice of treatment + best supportive care in patients with myelodysplastic syndrome (MDS) after failure of a hypomethylating agent (HMA).

STUDY SCHEMA



PRIMARY ENDPOINTS

Overall survival in the intention-to-treat population and in patients with very high risk per the Revised International Prognostic Scoring System (Greenberg et al, *Blood* 2012).

INTERNATIONAL TRIAL

More than 150 trial sites.

For additional information on this study, please call the INSPIRE help line at 1-267-759-3676 or visit www.clinicaltrials.gov, identifier: NCT02562443.

Rigosertib is an investigational agent and is not approved by the FDA or other regulatory agencies worldwide as a treatment for any indication.



PEVONEDISTAT-3001

TAKEDA'S PANTHER: A NEW CLINICAL STUDY

A Phase 3, Randomized, Controlled, Open-label, Clinical Study of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients with Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia.

Takeda Pharmaceuticals International Inc. is initiating a Phase 3 clinical study with the study drug Pevonedistat. The purpose of this study is to evaluate the efficacy and safety of pevonedistat plus azacitidine versus single agent azacitidine in participants with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia and low blast acute myelogenous leukemia. This study will look at the overall response, event free survival, and overall survival in people who take pevonedistat and azacitidine when compared to people who take single agent azacitidine.

The study will enroll approximately 450 participants. Once enrolled, participants will be randomly assigned (by chance, like flipping a coin) to one of the two treatment groups in a 28 day treatment cycles:

- Pevonedistat 20 mg/m² and azacitidine 75 mg/m² combination.
- Single agent azacitidine 75 mg/m².

All participants will receive azacitidine via the intravenous or subcutaneous route. Participants randomized to the combination arm also will receive pevonedistat intravenous infusion).

This multi-center trial will be conducted worldwide. Patients may qualify for this study if:

- 18 years of age or older.
- Patients have intermediate, high, or very high risk MDS or CMML, based on the Revised International Prognostic Scoring System (IPSS-R), a standard prognostic tool.
- Patients have low-blast AML defined as 20% to 30% myeloblasts in the bone marrow (Low-Blast AML) and ≤30% myeloblasts in the peripheral blood and considered appropriate for azacitidine based therapy.

In order to refer a patient with MDS, CMML, or low blast AML for enrollment to this study and review eligibility criteria, physicians/health care providers should visit: www.clinicaltrials.gov (NCT03268954)

Contact: Takeda Study Registration Call Center +1-877-825-3327; medicalinformation@tpna.com



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Journey PRO Research Study

Do you have chronic anemia?

The MDS Foundation wants you to know about the Journey PRO Research Study. Life with chronic anemia is a journey. Some days the path might feel easy. Other days, it might as well be quick sand. On top of it, managing your health – medications, appointments – can feel a heavy pack you have to carry. With your help, we hope to smooth the road and lighten the load for people with chronic anemia. If you have chronic anemia as a result of myelodysplastic syndromes (MDS) or you just want to help people who do, we would love for you to participate in this study.

Journey PRO is a study about chronic anemia and quality of life. In the study we will measure health and well-being using the Journey PRO app. We will track things like fatigue, memory, and fitness. You will help us learn about the range of experience for people with and without chronic anemia. You will help us find out how mobile devices can help measure what life is like with chronic anemia.

So long as you are 18 years old or older and have an iPhone model 5 or newer with iOS 8 or later, you can join Journey PRO. We specifically encourage people who have myelodysplastic syndromes (MDS) to join.

**To learn more about the Journey PRO study and
get the link to the Apple App Store to download the app,
please visit study website:**

www.journeypro.org

*Help make a difference in the journey.
Join Journey PRO today!*



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COPENHAGEN

THE 15TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

**COPENHAGEN, DENMARK
8-11 MAY 2019**

SAVE THE DATE

MDS 2019 Symposium Secretariat:
c/o Kenes International
Email: mds@kenes.com

For MDS Foundation Contact:
US number: 1-800-MDS-0839
Outside the US: 1-609-298-1035