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mds news

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MDS NEWS HIGHLIGHTS

FROM THE GUEST EDITOR'S DESK

- **MDS: Regulatory Aspect, Cost Effectiveness and Costs of Care**

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PLAN TO ATTEND

2018 LATIN AMERICAN MDS FOUNDATION SYMPOSIUM

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IN THIS ISSUE

GUEST EDITORIAL

Guest Editorial – Regulatory Aspect, Cost Effectiveness and Costs of Care

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The licensing and market entry of active drugs to treat MDS patients (azacitidine, decitabine, lenalidomide) during the 2000s represented important progress in improving outcomes for those patients who achieve a clinically meaningful response. These agents have different licensed indications and price points between the US and European countries. These differences are good examples of the different ways the US Federal Drug Administration (FDA) and the European Medicines Agency (EMA) interpret efficacy and safety data, and the consequent benefit:risk ratio assessment that determines final market authorisation and indication.

MDS is an expensive condition to manage. Average 5-year per patient treatment costs for MDS are higher than any of the 18 most prevalent cancers in the US.[1,2] These costs are driven not only by the expensive drugs mentioned above, but also by costly supportive care (e.g., transfusions, growth factors, iron chelators) and high use for other health care services (e.g., inpatient admissions and emergency department visits).

What interests the authors is how healthcare systems could assess the 'value' of a given treatment, and consequently how to use that assessment to decide whether the intervention (drug) is affordable within the given healthcare system.

The focus of our Editorial will be the cost of care for MDS and the analyses and processes that inform and optimise market access. In Europe these analyses, collectively called health technology assessment (HTA), are typically comparative effectiveness (CE) or cost effectiveness analysis (CEA). The US has a much different process wherein the FDA first decides whether a new drug can be marketed and then the federal health insurance program, Medicare, decides whether it will pay for the drug, with Medicare ultimately covering most drugs approved by the FDA. In stark contrast to European countries, Medicare is forbidden by law to directly negotiate price with drug makers, although private payers can do so. What interests the authors is how healthcare systems could assess the 'value' of a given treatment, and consequently how to use that assessment to decide whether the intervention (drug) is affordable within the given healthcare system. We present perspectives from the European (predominantly UK) and from the US healthcare systems.

Where We Have Come From, Where We Are

European Perspective (with focus on UK)

In the UK, there is a semi-transparent process for cost effectiveness analysis, with only the details of the company Patient Access Scheme (typically a simple discounted price) always marked 'commercial in confidence'. An objective analysis of clinical efficacy, survival benefit and quality of life benefit creates an Incremental Cost Effectiveness Ratio (ICER) and a cost per Quality-Adjusted Life Year (QALY) which must be below agreed thresholds for affordability by the NHS to permit market access into the NHS. Because the NHS has a fixed annual budget, any new expenditure within this budget inevitably displaces other NHS activity. Other countries also conduct CEA and an example of variation from country to country for CEA analyses, in this case for azacitidine, can be seen in the Table.

Countries that have no formal process for cost effectiveness analysis will negotiate price directly with the company based either on a formal comparative effectiveness analysis and a framework for the pricing negotiation that follows this analysis (e.g. France/Germany), or if no CEA process operates in that country, based on other discount models, some of which involve comprehensive registry data collection as a mandatory commitment, such as Italy.

For many years, NICE has been considered the 'bad guy', reviewing new drugs too slowly and then declining market access because the drugs are not considered a cost effective use of NHS resources by the defined, and still widely approved, criteria. NICE has recently created a CEA process contemporaneous with EMA's market authorisation delib-

	Cost per QALY	Managed access in model	Analysis
NICE (UK)[3]	€55,945	Yes; simple discount	Weighted average for CCR based on 'real world' data for BSC vs LDAC vs IC
Spain[4]	€34,673	No	Cost effectiveness
Canada[5]	€58,074	No	'Cost utility'

eration. There is now also an emerging public understanding that much of the responsibility for facilitating market access in the UK (and elsewhere) rests with realistic pricing from the pharmaceutical industry. One example is a small, recently established pressure group, JustTreatment, that claims some success in lobbying Pfizer to reduce the cost to the UK NHS for palbociclib as treatment of adjuvant breast cancer therapy, such that NICE was then able to approve market access.

US Perspective

Much ink has been spilt by others detailing the unique challenges and opportunities in the US market, where comparative effectiveness and cost effectiveness analyses play a less influential role in establishing the price and accessibility of new drugs. Because of the lower cost-effectiveness bar, more therapies are generally available to US patients more rapidly, but usually at a much higher cost.

However, the US marketplace is gradually taking a harder look at the cost-effectiveness and ultimate value of health care good and services in oncology. For example, Medicare now publishes a dashboard highlighting the drugs that account for the highest total Medicare spending and per user spending. Lenalidomide is featured prominently in the top 10 of both spending areas (7th in total spending and 9th in per user spending), including applications in both MDS and multiple myeloma. These high cost drugs are the most likely to receive greater initial scrutiny regarding cost-effectiveness.

Interestingly, unwarranted clinical variation in MDS care, more so than the price of any specific drug, may be one of the biggest drivers of high costs. In the US, 2-year MDS related costs vary significantly by geographic region, from $40,793 per patient in New Mexico to $78,156 in Detroit, Michigan.[6] Even though some areas spent nearly twice as much on care, this spending was not correlated with different patient populations or better survival. There is a huge opportunity to better understand what drives value and cost-effectiveness in MDS across the continuum of care for the disease. Published cost-effectiveness research in MDS remains low. A search of the Pubmed database reveals nearly 4,000 journal articles published in 2016 on 'cost-effectiveness', but only 15 papers that included MDS in the analysis.

This cost variation data suggests that there may be a significant opportunity to increase the overall value and cost-effectiveness of care by standardizing care around the best available evidence-based practices, and integrating new therapies into those treatment pathways as they become available. In the US, both Medicare and commercial insurers are launching new programs to encourage and reward more efficient, standardized care. Medicare, for example, has launched the Oncology Care Model which bundles payment for the first six months after initiation of chemotherapy and provides specific payments of care coordination. This program includes MDS patients and seeks to incentivize providers and health systems to deliver the most cost-effective care, contingent on achieving specific quality measures. This can certainly include drug selection, but also efforts to reduce complications and costly hospitalizations.

Initiatives aimed at measuring 'value' are far from perfect, but these value frameworks are increasingly used in oncology. One such framework is a (somewhat arbitrary) points-based system combining efficacy and toxicity assessment with simple cost, exemplified by the ESMO and ASCO models. Value frameworks have strikingly been used to call into question the true value of many of the oncology drugs licensed by FDA between 2000–2015[7], and will likely intensify scrutiny on new drugs coming to market.

Where We Are Going?

The future is bright in oncology therapy, but not without costs. A tranche of remarkably effective oncology therapies is now reaching the market, but these therapies continue to test the upper thresholds for cost around the world.

Comparative/cost-effectiveness analyses in oncology can be challenging for a number of reasons, including:

1. Early licensing of promising new agents based on non-randomised trials in small sub-populations with no direct trial comparator and short term follow up only. This produces little data for cost-effectiveness analyses.

2. Novel mechanisms of action, for example, immune checkpoint inhibitors produce a durable benefit (so called 'long tail' of survival), but only in a small proportion of patients. The pharmacodynamics of response is highly challenging for traditional cost effectiveness analysis models
3. One-hit therapies, such as CAR-T cell therapy, gene therapy, gene editing, are clinically exciting, but the personalized nature of the treatment makes large scale cost-effectiveness analyses difficult or impossible.

MDS is a high-cost, heterogeneous disease. Ultimately, patients, providers and payers will be best served by approaching questions of value and cost-effectiveness across the care continuum. To do this successfully, we need better information and studies on cost-effectiveness opportunities for MDS, better diagnostic tools to identify the best candidate for existing and emerging therapies, and new treatment tools to address the clinical needs of different patient populations.

It is encouraging that the pharmaceutical industry is engaging actively with patients, HTAs, and with payers for early dialogue about timely market access. This strong collaboration between multiple stakeholders will help MDS patients to access new drugs globally at the earliest opportunity possible.

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BREAKFAST SYMPOSIUM

On behalf of the MDS Foundation and our Board of Directors,
THANK YOU for joining our Breakfast Satellite Symposium!

Great turnout at our educational symposium

THANK YOU to all the attendees for braving the snow and visiting the MDS Foundation Booth!

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Inherited Risk of MDS and AML

Dr. Jude Fitzgibbon (Barts Cancer Institute, London, UK) explained that more than 95% of cases of MDS and acute myelogenous leukemia (AML) do not seem to be inherited. In less than 5% of cases, though, two or more members of a family have AML, MDS, or other bone marrow failure syndromes. The genes associated with inherited MDS/AML have variable penetrance. As a result, some people who carry these genetic variants have symptoms of the diseases, and others do not.

Single Inherited Mutation

In 2004, Dr. Fitzgibbon and colleagues reported on a father and two daughters who had AML and the same mutation in the *CEBPA* gene. Family members who did not have AML also did not have the mutation. All three patients were treated and went into remission for 10 to 30 years.

Since then, Dr. Fitzgibbon has worked with colleagues all over the world to identify 25 additional patients with AML from 11 families with the *CEBPA* mutation. Remission after the initial treatment is typically quite long in these patients. But because they still have the inherited mutation, they can develop a new leukemia after the first case is cured. Fortunately, these new leukemias can be treated successfully.

Combinations of Inherited Mutations

The situation is more complicated when patients with a genetic predisposition acquire another mutation that is not inherited. For example, two first cousins with an inherited *GATA2* mutation developed high-risk MDS with monosomy 7. Both had acquired *ASXL1* mutations that were not inherited. Although the two cousins underwent hematopoietic stem cell transplantation (HSCT), both died. The inherited *GATA2* mutations predisposed these cousins to develop MDS or AML, and they acquired monosomy 7 and *ASXL1* mutations that triggered their MDS.

Identifying Inherited Mutations Associated with MDS and AML

Dr. Fitzgibbon has collected data on 82 families with inherited MDS and AML. Of these families, 41 have known genetic variants, but the genes involved in the other 41 have not been identified. Genome sequencing of a few individuals from each family could show dozens of genes that are not known to be associated with MDS or AML but might drive the disease in that family. Figuring out which gene is actually the culprit is tricky. But if other families have the same variant, that gene might be worth studying further.

In summary, the challenges for inherited MDS and AML are:

- It can be hard to identify patients with inherited forms of the disease.
- Clinical guidelines do not say much about how to treat inherited MDS and AML.
- Only three or four inherited genetic mutations have been identified in more than a few families with inherited MDS or AML.
- Several other mutations have been found in some families with inherited MDS or AML, but the link between these mutations and the inherited diseases still needs to be established.
- Sibling stem cell donors for patients with inherited MDS or AML need to be carefully screened to make sure that they do not carry the genetic variants that caused the inherited disease.

Abnormal Bone Marrow Cells, Genetics, and MDS Diagnosis

Dr. Luca Malcovati (University of Pavia, Pavia, Italy) explained that MDS occurs when a patient develops one or more somatic mutations in hematopoietic stem cells. These stem cells proliferate more successfully than healthy stem cells, and abnormal clones of bone marrow cells take over the bone marrow. MDS becomes evident when these immature blood-forming cells do not mature properly and do not turn into healthy blood cells.

Clonal Cytopenia of Undetermined Significance

People with clonal cytopenia of undetermined significance (CCUS) have persistently low counts of at least one type of blood cell that are not explained by any other disease. Dr. Malcovati and colleagues have identified a set of genes that are often mutated in MDS. Patients with CCUS often have at least one of these mutations. Those with two or more of these mutations are likely to develop MDS or another bone marrow failure syndrome within the next 4 years.

Persistent Anemia in Older Adults

When an older patient has anemia or a low count of white blood cells or platelets, doctors rarely investigate further. Up to 20% of adults aged 70 or older have anemia. In about a third of cases, conventional blood tests do not explain the cause of their anemia, and this condition is usually known as unexplained anemia. Older adults with unexplained anemia tend to have higher levels of abnormal clones and mutation patterns that are closely associated with MDS. At least some of these older adults might have very early MDS based on their genetic profiles.

Clonal Hematopoiesis of Indeterminate Potential

Three large studies have now shown that the formation of abnormal bone marrow clones driven by somatic mutations becomes much more common with age. These mutations are very rare in adults in their 30 and 40s, but up to 20% of older adults might have them. Somatic mutations in *DNMT3A* and *TET2*, in particular, might drive the expansion of abnormal clones during aging.

People with age-related abnormal clones have a significantly higher risk of developing a blood cancer in the next year. In addition, older adults with abnormal clones have an increased risk of dying from any cause, and this increased risk is not completely explained by their higher risk of cancer. In fact, some of the mutations are associated with a higher risk of heart-related complications, for example.

Clonal hematopoiesis of indeterminate potential (CHIP) means that the patient has a somatic mutation associated with MDS or another bone marrow failure syndrome but no other signs or symptoms of MDS, or any other bone marrow failure syndrome.

The available scientific data suggest that CHIP develops when a mutation occurs in a hematopoietic stem cell, most commonly in an epigenetic regulator or a splicing factor gene. Early on, the variant allele frequency (VAF) of the mutation is low, and the abnormal bone marrow clones expand without any signs of MDS. When a second mutation happens, the clones grow, the VAF rises, and the patient develops mild, unexplained blood cell shortages and CCUS. The larger the abnormal clone, the more severe the blood cell shortage. Finally, the VAF rises enough and the clones get large enough to result in MDS. The specific VAF associated with each stage in MDS development probably varies by gene mutation.

In conclusion, analysis of genetic mutations might be useful for:

- Diagnosing patients suspected of having MDS or at higher risk of developing MDS.
- Providing useful information for classification, prognosis, and decisions about treatment.
- Identifying patients with CHIP.
- Diagnosing older patients with unexplained anemia that needs further investigation.

Role of the Immune System and Inflammation in MDS

Dr. Shahram Kordasti (King's College Hospital, London, UK) discussed the role of the immune system in MDS. Normally, the immune system fights off antigens associated with infections or malignant cells. An impaired immune system is believed to play an important role in the development of MDS. The MDS interferes with the proper functioning of the immune system, and, in turn, the impaired immune system helps the disease progress.

T Regulatory Cells

Patients with MDS have a higher proportion of immune suppressor cells known as T regulatory (Treg) cells. These proportions are highest in those with high-risk MDS. Patients who have low-risk MDS but a high percentage of Tregs also have a higher risk of progression to AML and a poorer prognosis.

Dr. Kordasti has used a new technology, mass cytometry, to identify two different types of Tregs in patients with aplastic anemia, another bone marrow failure syndrome, and MDS. His study showed that the frequency of these types of Tregs can be used to predict responses to immunosuppressive therapies in patients with aplastic anemia. These Tregs might also be useful for predicting disease progression in MDS.

Inflammation and Immune Cell Death

The body uses inflammation to protect itself and its cells from injuries and irritants by rapidly neutralizing the proportion of myeloid-derived suppressor cells (MDSCs), which play a key role in inflammatory responses, rises in the

bone marrow of some people with MDS. This seems to interfere with the formation of healthy blood cells and a functioning immune system. Furthermore, patients with high-risk MDS have more MDSCs than those with low-risk MDS.

The death of bone marrow cells, that can produce an immune response, occurs in the development of all types of cancer. When these cells die, proteins that are not usually exposed become available. These proteins present antigens to the immune system, leading to the expansion of T cells. In addition, somatic mutations in certain genes lead to abnormal immune responses.

The combination of the death of bone marrow cells with mutations in some genes leads to low levels of persistent inflammation (also known as "smoldering" inflammation). This inflammation can lead to more alterations in genes and turn cells into cancer cells. As a result, the MDS progresses toward AML.

It is important to develop innovative tests to detect smoldering inflammation at an early stage and potentially prevent disease progression by controlling the harmful inflammation while sparing the healthy immune response. This is the current focus of many cancer immunology research teams around the word.

Treatments for Higher-Risk MDS

Dr. Rami Komrokji (H. Lee Moffit Cancer Center & Research Institute, Tampa, Florida) defined higher-risk MDS as intermediate-2 or high-risk MDS according to the International Prognostic Scoring System. Based on this definition, one third of patients with MDS have higher-risk disease. Dr. Komrokji also reviewed the new definition of higher-risk MDS based on new clinical risk models and somatic gene mutations.

Current Hypomethylating Agents

Treatment for higher-risk MDS typically starts with a hypomethylating agent (HMA). If the patient seems to be eligible for HSCT, the next steps are to find a well-matched donor and assess whether the patient is well enough for the procedure. If so, the transplant takes place. But if not, that patient will probably continue HMA treatment. Patients on HMAs usually take them until they stop working. At that point, only experimental therapies are available.

Azacitidine (Vidaza), an HMA, has been the standard treatment for higher-risk MDS for the last decade based on a clinical trial, published in 2009, showing that this drug increases survival. Patients whose counts of at least one type of blood cell increases with HMAs tend to survive longer. Patients whose disease is stable for several months with azacitidine treatment have a lower risk of death than patients with progressive disease.

The original clinical trials of decitabine (Dacogen), another HMA, did not show that the drug increased survival in higher-risk MDS. But those studies used a different dose than the one doctors use now. More recent data show that median survival with decitabine treatment is close to that with azacitidine in real-world experience. No studies have compared the effects of azacitidine to those of decitabine on survival in patients with higher-risk MDS. Recent research suggests that decitabine can clear P53 mutated clones and might be used as a treatment for patients who have these clones and are waiting for transplant.

Given the large proportions of patients who do not respond or stop responding to HMAs, the field needs to do a better job of identifying patients who will benefit from HMAs. Other important priorities are expanding rates and durations of responses, as well as finding new drugs, including new HMAs.

Predicting Response

No existing clinical tools predict which patients will respond to HMA treatment or the outcomes when HMAs do not work. Patients with a mutation in the *TP53* gene are more likely to respond to HMAs than patients without this mutation, and outcomes are similar or better than with intensive chemotherapy. Unfortunately, outcomes are still poor in patients with a *TP53* mutation. Some studies have found that response rates to HMAs are somewhat higher in patients with a *TET2* mutation and wild-type *ASXL-1*.

Once disease progresses during HMA treatment for higher-risk MDS, the outcomes are typically poor. Patients who never respond to HMAs tend to survive only 5 or 6 months. Those who respond at first but then stop responding survive about 7 months. Their outcomes might be better if they have HSCT or enroll in a clinical trial.

New HMAs, Combination Treatments, and Novel Treatments

Studies are testing new forms of HMAs (including oral azacitidine, oral decitabine, and SGI-110). Several studies have added different therapies to HMAs but have not found these combinations to be beneficial. More studies of promising combinations with azacitidine are ongoing, including combinations with checkpoint inhibitors and antiapoptotic agents (such as venetoclax [VENCLEXTA]). Studies are also using new types of treatments, such as splicing inhibitors, p53 modulators, and IDH-1/2 inhibitors, in certain groups of patients who have the genetic mutations that these treatments target. Finally, the U.S. Food and Drug Administration has recently approved CPX-351 (Vyxeos), a new formulation of two traditional chemotherapy drugs, daunorubicin and cytarabine, for secondary and treatment-related AML.

How to Improve the Timing of Stem Cell Transplantation for MDS

Dr. John Koreth (Dana-Farber Cancer Institute, Boston, Massachusetts) explained that HSCT is the only curative treatment for MDS. Even in patients with high-risk MDS, this procedure can lengthen survival. About 1,000 to 1,500 patients with MDS undergo HSCT in the United States every year.

HSCT Timing

The timing of HSCT is a complicated issue. For patients who are younger than 60 or 65, studies that used mathematical modeling found that the best timing depends on the International Prognostic Scoring System (IPSS) category. For patients with intermediate-2 risk or high-risk MDS, HSCT soon after diagnosis maximizes life expectancy. But for those with low-risk or intermediate-1 risk, delaying HSCT for a few years lengthens survival, as long as the HSCT is done before the MDS progresses to AML.

For patients aged 60–70 years, some mathematical modeling evidence shows that HSCT with reduced-intensity conditioning does not extend life expectancy in patients with low-risk or intermediate-1 risk MDS. But for patients with intermediate-2 or high-risk MDS, survival is longer with HSCT than with HMA treatment.

Data from a recent study that evaluated outcomes in patients aged 50–70 years with MDS found that about twice as many patients who underwent HSCT survived for at least 4 years as those who had other treatments. Ongoing clinical trials are comparing the outcomes of HSCT with reduced-intensity conditioning to other treatments in patients with MDS.

Conditioning Treatments

Studies are also assessing different types of conditioning treatment for HSCT. A 2017 phase III clinical trial in 129 patients with MDS or AML found that relapse risk and survival were similar in patients treated with standard conditioning and those with reduced-intensity conditioning. But another phase III trial in 272 patients with MDS or AML found that patients with MDS who were treated with reduced-intensity conditioning had a higher risk of relapse, although overall survival was similar for both conditioning regimens. The authors concluded that standard-intensity conditioning might be the best option for younger, healthier patients.

Predicting Outcomes

Researchers have studied the ability of different MDS classification systems to predict outcomes after HSCT. Both the IPSS and revised IPSS (IPSS-R) predicted survival and relapse after HSCT in a study of 374 patients with MDS and 145 with AML. Whether patients had certain abnormalities in their chromosomes also, and independently, predicted their likelihood of surviving and having a relapse.

Mutations in certain genes can also be used to predict outcomes. For example, patients with mutations in *TP53*, *RAS* pathway mutations, or a combination of these mutations do not seem to survive as long after HSCT as patients without these mutations.

Dr. Koreth concluded that HSCT is an underused curative therapy for MDS. He suggested basing decisions about HSCT on patient characteristics, disease severity, and gene mutations. Finally, he recommended considering patient fitness and disease characteristics in decisions about conditioning intensity.

List of Acronyms

AML: acute myelogenous leukemia

HMA: hypomethylating agent

HSCT: hematopoietic stem cell transplant

IPSS: International Prognostic Scoring System

Glossary of Terms

Acute myelogenous leukemia *(AML, also known as acute myeloid leukemia)***:** A rapidly growing disease in which the bone marrow and blood have too many myeloblasts (immature white blood cells)

Anemia: Low levels of red blood cells or hemoglobin, a protein in red blood cells that transports oxygen

Antibody: Protein made by the immune system that defends the body from a specific type of antigen

Antigen: Substance (e.g., chemical, bacteria, pollen, or virus) that the body's immune system does not recognize

Aplastic anemia: Failure of bone marrow to make enough blood cells

Bone marrow failure: Failure of bone marrow to produce blood cells

Clones: Abnormal copies of immature blood cells

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

Epigenetic: Change in the chemical structure of DNA that does not change the DNA coding sequence

Hematopoietic stem cells: Stem cells in the bone marrow that form blood cells

Hematopoietic stem cell transplant (HSCT): Infusion of healthy hematopoietic stem cells from a healthy donor with the same HLA (immune system) markers as the patient. The donor's stem cells (known as a graft) enter the bone marrow, where they form healthy blood cells.

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 tumor-suppressor genes

Immune system: Enables the body to defend itself from foreign substances (such as viruses and bacteria).

Immunosuppressive therapy: Drugs to weaken the patient's immune system, stop it from attacking the bone marrow, and help the bone marrow make more healthy blood cells.

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

Monosomy 7: Only one copy, not the usual two copies, of chromosome 7

Penetrance: Proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder

Reduced-intensity conditioning: Use of lower doses than typical conditioning treatments to potentially make HSCT safer

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

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

Splicing factor: Gene that controls the splicing together of certain sequences in RNA to form messenger RNA molecules. Messenger RNA contains the genetic coding information needed to make proteins.

T regulatory (Treg) cells: Control the activity of other T cells, which are a type of white blood cell that helps protect the body from infection

Variant allele frequency: Frequency of selected mutated genes

Wild-type gene: natural, nonmutated (unchanged) form of a gene

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The MDS/MPN International Working Group

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The 2018 MDS/MPN IWG Biennial Meeting in Charlotte, NC, was a great opportunity to meet with IWG members and discuss plans for the group. The first day of the meeting was dedicated to a series of excellent talks on the state of the science in MDS/MPN. Special guests "Ken" Figueroa, Jason Gotlib, Amy Dezern, Courtney DiNardo and Virginia Klimek joined the working group, speaking on epigenetic signatures in CMML, and novel approaches in the treatment of MDS/MPN and CNL. Several members discussed mutational burden and clonal evolution in MDS/MPN, as well as ongoing approaches to tackle classification conundrums, response criteria, and risk stratification in MDS/MPN. The second day was completely dedicated to our group's clinical trial ambitions and plans to study novel therapies simultaneously in the US and Europe, and potentially, ultimately, globally. ***ABNL MARRO*** (A Basket study of Novel therapy for untreated MDS/MPN and Relapsed/Refractory Overlap Syndromes) is the infrastructure for our first studies in MDS/MPN. ABNL MARRO 001 (AM001) is the first fully funded study to be conducted by the IWG, and was reviewed at the meeting. AM001 will include 6 sites in the US, as well as sites in France, Spain, Italy and Germany. Subsequent concepts for AM002, AM003, and so forth, will be discussed by the IWG, and interested sites that may not have participated in AM001 will have priority options to participate in later trials.

During the meeting, we proposed the development of protocol specific committees to facilitate meeting our ambitious goals and timelines for first patient enrolled (January 1, 2019). To this end, members volunteered to serve on committees. If there are additional members of the MDS/MPN IWG with interest in serving on specific committees in ABNL MARRO 001 according to their individual expertise, please contact abnlmarro001@vumc.org. There is not a particular limit to the membership of the committees, but they should be "workable" numbers of colleagues (<10) willing to meet quarterly, at least, by TC. I very much appreciate and welcome your willingness and thoughtful contributions, and enthusiasm for the trial. We will discuss ***ABNL MARRO*** again in Stockholm at EHA. Please stay tuned for this!

EXECUTIVE COMMITTEE:
Michael Savona, Pierre Fenaux, Eric Padron, Mrinal Patniak, Uwe Platzberger, Valeria Santini, Guillermo Sanz
****Recommended size of each committee is 5-8 members***

PROTOCOL WRITING COMMITTEE
- Tamara Moyo
- Courtney DiNardo
- Jason Mendler
- Raphael Itzykson
- Dan Ayers (Statistician)
- *TBD (US/EU)*

PRO/SYMPTOM ASSESSMENT COMMITTEE
- Aaron Gerds
- Ruben Mesa
- Francesco Onida
- *TBD (US/EU)*

CORRELATIVE SCIENCE AND BIOSPECIMEN COMMITTEE
- Eric Padron
- Eric Solary
- Virginia Klimek
- Jarek Maciejewski
- Adam Seegmiller
- TBD (US/EU)

OPERATIONS COMMITTEE
- Tamara Moyo
- Jason Gotlib
- VCC/Theradex Representatives
- *TBD (US/EU)*

RISK ASSESSMENT AND CONSENSUS CRITERIA VALIDATION COMMITTEE
- Aziz Nazha
- Mrinal Patniak
- Rahael Itzykson
- TBD (US/EU)

DSMB *(not including enrolling PIs)*
- Amy DeZern
- Courtney DiNardo
- *TBD (US/EU)*

MDS/MPN IWG meeting, Charlotte, NC

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 Meeting[2] 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 Orlando[3]. 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.

IWG-PM meeting during the 2017 ASH Congress

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, Boultwood 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, Fenaux P, Hellstrom-Lindberg, Kern W, Boultwood 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 Myeloid Continuum of Diseases

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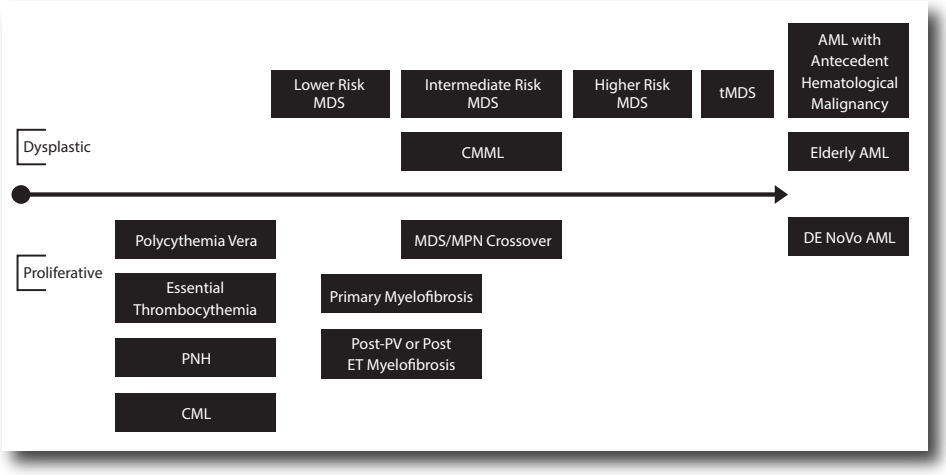
Breakthroughs in scientific discovery for cancer are emerging at a pace never experienced before. These breakthroughs have been largely due to continued investigation of the genome as it relates to diseases, including MDS. The MDS Foundation continues to work with and support international experts in myeloid diseases to continue this work. As we come to identify and refine the defining features of MDS, it has become clear that MDS, along with other myeloid diseases occur on a continuum. There are several International Working Groups focused on mapping the characteristics of the myeloid diseases including MDS, Myelo-proliferative Neoplasms (MPNs), MDS/MPN crossover disease, and Acute Myeloid Leukemia (AML). This myeloid family of diseases share several traits, but, we are learning more about features that make them distinctly different. Many of these features are the focus of clinical trials aimed at the development of new treatments. With this evolution of the science, the MDS Foundation has broadened its focus to continue support for not only the science and scientists and other health care professionals that are studying these diseases, but the patients LIVING with these myeloid diseases.

Understanding this science and how it applies to you can be challenging. There are several new projects underway at the MDS Foundation to help you learn about these exciting new discoveries.

MDS Building Blocks of Hope® and NEW MPN Building Blocks of Hope® *(coming soon)*

The Building Blocks of Hope® MDS Patient and Caregiver Resource is a print and online patient advocacy initiative that provides personalized education for the patient and caregiver to prepare, participate and LIVE with MDS. It has been provided to more than 25,000 individuals worldwide and is translated in to 12 languages. With the many changes in the science of MDS and the anticipated changes in available treatment options, this resource will be released in an updated and more digital friendly format later this summer. To meet the needs of patients who are LIVING with MPNs and/or MDS/MPN crossover disease, we will be releasing a new patient and caregiver resource this summer, the MPN Building Blocks of Hope®. This tool will be developed in collaboration with the MPN Advocacy and Education International. Both versions of Building Blocks of Hope® will move toward a more interactive digital format that will allow the users to access resources on your smartphone, tablet or desktop computer. We will continue to provide the in-print format at our patient and caregiver forums or by request at the MDS Foundation.



MDS MANAGER™

MDS Manager™ is a newly developed mobile health (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. MDS Manager™ will allow you to track information related to your health, and quickly link you to tailored resources. 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.

Embracing the Digital Age: The MDS Manager Study™

We are currently conducting a clinical trial aimed at understanding the use of digital technology by MDS patients and their caregivers. The results of this trial will guide the refinement of digital tools to assist the user in managing their health. This will allow The MDS Foundation to notify the user when new treatments or other resources are available, including clinical trials. If you have a smartphone or tablet (ipad, Samsung etc.), consider participation in the trial.

Participation in the MDS Manager™ study will require:

1. Downloading the MDS Manager application to your smartphone and/or tablet.
2. Register for the study. The registration process will take approximately 15 minutes. You can access a registration guide on the MDS Foundation website. https://www.mds-foundation.org/mdsmanager/.
3. Complete two questionnaires over the 4-week study period, each one taking approximately 25–30 minutes.
4. Entering data into the MDS Manager to allow for tailoring of resources.
5. Response to push-notification sent to your device with study updates.
6. You can get started now by going to the MDS Foundation website, through your MDS Manager™, or by contacting:

The MDS Foundation patient liaison:
Phone within the US: 1-800-MDS-0839
Fax: 1-609-298-0590
E-mail: patientliaison@mds-foundation.org

Information obtained from the MDS Manager™ Study will also be used to guide the development of MPN Manager™, a companion tool to the MPN Building Blocks of Hope®. We will kick off a clinical trial using MPN Manager™ later this year.

Managing your health is critical to staying well. We hope these new tools will provide you with resources to navigate the exciting scientific discoveries in the myeloid diseases. We believe these tools can help you to stay well, improve your awareness of and access to clinical trials and new treatments, and gain new knowledge and resources to manage your health.

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Highlights of Latest Literature in MDS

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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. Valent P et al. Proposed minimal diagnostic criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions. *Oncotarget*. 2017;8(43): 7348373500 (https://www.ncbi.nlm.nih.gov/pubmed/29088721)

   The detection of MDS-related molecular abnormalities or incidence of peripheral blood cytopenias in individuals without any pathological diagnosis yet, and with a possibility of developing bone marrow conditions other than MDS in some of such individuals, have posed new challenges to MDS diagnosis. The 2016 working conference of the international consensus group discussed such challenges and developed a proposal for classification of pre-MDS conditions and also updated the minimal diagnostic criteria for MDS. In addition, the report defines diagnostic standards for differentiating normal, pre-MDS and MDS conditions.

2. Duong VH et al. The prognostic value of circulating myeloblasts in patients with myelodysplastic syndromes. *Ann Hematol.* 2018;97(2):247–254. (https://www.ncbi.nlm.nih.gov/pubmed/29167940)

   An institutional database review identified 223 patients with a primary diagnosis of MDS and ≥1% bone marrow blasts in peripheral blood, while 1535 MDS patients did not have blasts in blood. When compared, the patients with blasts in blood tended to be younger with frequent trilineage cytopenia, complex karyotype, higher IPSS score, transfusion dependence and therapy related MDS. Moreover, the rates of leukemic transformation were significantly higher and overall survival significantly shorter in those with blasts in blood than those without (AML-49% vs 26%, p<0.005; med OS- 16.5 mo vs 45.8 mo, p<0.005, respectively). The Cox regression analysis identified presence of blasts in blood as independent prognostic factor.

3. Borges DP et al. Prognostic importance of aurora kinases and mitotic spindle gene transcript levels in myelodysplastic syndrome. *Leuk Res*. 2018;64:61–70. (https://www.ncbi.nlm.nih.gov/pubmed/29220700)

   Proteins related to the mitotic spindle (AURKA, AURKB, TPX2), to the mitotic checkpoint (MAD2, CDC20) and the regulation of the cell cycle (p21) are directly related to chromosomal stability and tumor development. CDC20 expression were significantly increased in patients with dysmegakaryopoiesis, thrombocytopenia and high-risk patients. MAD2 expression were decreased in patients with 2 or 3 cytopenias and neutrophil below 800/mm^3. TPX2 was over-expressed in patients presenting dysmegakaryopoiesis. A decrease in AURKA and AURKB expression was observed in patients with altered karyotype, who presented dysplasia in 3 lineages and hemoglobin below 8 g/dL (p=0.024). The expression of AURKA, AURKB and MAD2 were decreased in patients with hypoplastic MDS, associated with high frequency of chromosomal alterations and high mortality rate. This study confirmed the importance of aurora kinases and mitotic spindle genes in the pathogenesis and clinical evolution of MDS.

TREATMENT:

Patient-Reported Outcomes:

1. Troy JD et al. Patient-reported distress in myelodysplastic syndromes and its association with clinical outcomes: A retrospective cohort study. *J Natl Compr Cancer Netw*. 2018;16(3):267–273. (https://www.ncbi.nlm.nih.gov/pubmed/29523665)

   NCCN defines distress as a multi-functional unpleasant emotional experience of a psychologic nature that may interfere with patient's ability to cope with cancer symptoms and treatment. A single center retrospective 2-yr study on patient-reported distress demonstrated increased risk for death with even a single point increase on the distress scale used (HR=1.18) suggesting a need for further exploration of this topic.

2. Santini V et al. The effect of lenalidomide on health-related quality of life in patients with lower-risk non-del (5q) myelodysplastic syndromes: results from the MDS-005 Study. *Clin Lymphoma Myeloma Leuk*. 2018;18(2):136–144. (https://www.ncbi.nlm.nih.gov/pubmed/29429612)

   MDS-005 study in RBC-transfusion dependent low risk non-del(5q) MDS had previously shown effectiveness of lenalidomide in achieving RBC-transfusion independence (TI ≥8 wks) in approx. 27% patients (p<0.001) vs placebo (2.5%). EORTC QOL questionnaire-core 30 tool was used in the current investigation to assess HRQOL. At week 24, after adjusting for baseline score, emotional functioning showed benefit with lenalidomide treatment. Also, a positive correlation with all 5 preselected scales (fatigue, dyspnea, global QOL, physical functioning and emotional functioning) was observed with achieving TI ≥8 wks (p<0.01) and with all except emotional functioning in case of increased Hb (p<0.05).

3. Efficace F et al. Patient-reported outcomes enhance the survival prediction of traditional disease risk classifications: An international study in patients with myelodysplastic syndromes. *Cancer*. 2018;124(6):1251–1259. (https://www.ncbi.nlm.nih.gov/pubmed/29231969)

   A new prognostic index adding patient-reported fatigue severity to IPSS [FA-IPSS(h)- Fatigue-IPSS (high risk)] was developed based on previously untreated MDS patients who completed EORTC QOL questionnaire-core 30 at baseline. The index estimated median overall survival in FA-IPSS-risk-1 or -2 or -3 as 23,16, and 10 months respectively. The predictive accuracy of this new index was higher than conventional IPSS alone in development cohort as well as in a subsequent validation cohort that in addition included previously treated patients.

ESAs and Growth Factors

1. Platzbecker U et al. A phase 3 randomized placebo-controlled trial of darbepoietin alfa in patients with anemia and lower-risk myelodysplastic syndromes. *Leukemia*. 2017;31(9):1944–1950. (https://www.ncbi.nlm.nih.gov/pubmed/?term=Platzbecker+and+Darbepoietin)

   Low/Int-1 risk MDS patients with Hb ≤10 g/dL, sEPO ≤500 mU/mL and low transfusion burden (N=147) were randomized 2:1 to receive 500 µg darbepoietin alfa sc q3w or placebo for 24 weeks, followed by 48 week of open label darbepoietin alfa. Between week 5 and 24,

darbepoietin alfa treated patients had lower transfusion incidence (36.1% vs 59.2%, p=0.008) and higher erythroid response (14.7% vs 0%, p=0.016). In the open label 48 weeks phase, darbepoietin dosing increased from q3w to q2w with a corresponding higher erythroid response rate of 34.7%. Safety of darbepoietin was consistent with previous reports.

2. Kantarjian HM et al. Long-term follow up for up to 5 years on the risk of leukemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim vs placebo in randomized double-blind trial. *Lancet Haematol*. 2018;5(3):e117–e126. (https://www.ncbi.nlm.nih.gov/pubmed/29396092)

   A ph 2 study with 58 wk romiplostim treatment in low/int-1 risk MDS with thrombocytopenia (n=250) demonstrated clinical benefits in reducing platelet transfusions and with respect to HI-platelet response rate. However, based on the potential risk of progression to AML noted in initial analysis treatment was discontinued and patients were followed for long term outcomes. Among 210/250 patients (84%) who entered a 5-yr follow up phase (139 treated with romiplostim and 83 with placebo), AML progression occurred in 12% patients from romiplostim arm vs 11% from the placebo arm (HR=1.06, p=0.88), while 56% vs 54% patients died respectively on the two arms (HR=1.03, p=0.89). These long-term data may thus warrant an in-depth reassessment of benefit/risk profile of romiplostim.

Hypomethylating Agents:

1. Sekeres MA et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. *J Clin Oncol*. 2017; 35(24):2745–2753. (https://www.ncbi.nlm.nih.gov/pubmed/28486043)

   In the phase II part of this phase II/III study, 277 high risk MDS/CMML patients were randomized to receive azacitidine alone (75 mg/m^2/d 1–7 of 28 d cycle, n=92), or in combination with lenalidomide (10 mg/d1–21, n=93) or with vorinostat (300 mg bid d3–9, n=92). At a median follow up of 23 months, the ORR was 38% with azacitidine alone as compared to 49% with azacitidine+lenalidomide (p=0.14) and 27% with azacitidine+ vorinostat (p=0.16). CMML patients showed higher ORR with lenalidomide combination than azacitidine alone (68% vs 28%, p=0.02).

2. Shapiro RM and Lazo-Langner A. Systematic review of azacitidine regimens in myelodysplastic syndrome and acute myeloid leukemia. *BMC Hematol*. 2018; Jan 31 [Epub ahead of print]. (https://www.ncbi.nlm.nih.gov/pubmed/29435331)

   A metaanalysis of RCTs showed higher pooled proportion of overall response rate (ORR) with two 7-day schedules, 44.8% for 7-0-0 and 45.8% for 5-2-2, as compared to 41.2% on 5-day schedule (5-0-0).

3. Sohn SK et al. No benefit of hypo-methylating agents compared to supportive care for higher risk myelo-dysplastic syndrome. *Korean J Intern Med*. 2017; Dec 15 [Epub ahead of print] (https://www.ncbi.nlm.nih.gov/pubmed/29232940)

   A retrospective analysis of 279 high/very high MDS patients from the Korean MDS working party database estimated 3-yr survival rate of 53.1% with allogeneic HCT + HMA, 75% with allogeneic HCT without HMA, 17.3% with HMA alone and 20.8% with best supportive care. The multivariate analysis demonstrated association of OS with only allogeneic HCT alone (HR=0.36, p=0.002).

4. Komrokji R et al. Azacitidine in lower-risk myelodysplastic syndromes: a meta-analysis of data from prospective studies. *Oncologist*. 2018;23(2):159–170. (https://www.ncbi.nlm.nih.gov/pubmed/29118268)

   A 15-yr retrospective search for ph 2/3 studies with azacitidine and patient level data from identified relevant studies led to analysis of 233 selected patients; approx. 90% non-del(5q) low risk MDS. The pooled estimates of RBC-transfusion independence and overall clinical benefit were approx. 39% and 42% respectively. Also, in a multivariate analysis, a planned use of ≥6 cycles was predictive of a response.

5. Medeiros BC et al. Randomized study of continuous high dose lenalidomide, sequential azacytidine and lenalidomide, or azacitidine in persons 65 years and over with newly diagnosed acute myeloid leukemia. *Haematologica*. 2018;103(1): 101–106. (https://www. ncbi.nlm.nih.gov/pubmed/29097499)

   A randomized open-label ph 2 study compared three therapeutic strategies in patients newly diagnosed with AML and ≥65 yrs of age; continuous high dose lenalidomide (n=15), sequential azacytidine and lenalidomide (n=39), or azacitidine (n=34) and demonstrated 1-yr survival rates of 21%, 44% and 52% respectively. Also, the hazard of death was greatest with continuous high dose lenalidomide.

IMiDs:

1. Almeida A et al. Safety profile of lenalidomide in patients with lower-risk myelodysplastic syndromes without del (5q): results of a phase 3 trial. *Leuk Lymphoma*. 2018; Jan 11, [Epub ahead of print]. (https://www.ncbi.nlm.nih.gov/pubmed/29322849)

   This report presents the safety profile of lenalidomide treatment of low risk non-del(5q) ESA refractory/ineligible MDS patients (n=239) from a phase 3 study. Compared to the placebo, lenalidomide had higher incidence of grade 3/4 treatment emergent AEs (TEAE-44% vs 86% respectively). The risk of infection or hemorrhagic events, however, were not increased. Grade 3/4 non-hematologic events were rare. The report also provides guidance on managing lenalidomide related TEAEs.

Allogeneic Bone Marrow Transplant:

1. Deeg HJ et al. Transplant conditioning with Treosulfan/fludarabine with or without total body irradiation: a randomized phase II trial in patients with myelodysplastic syndrome and acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2017;Dec 20 [Epub ahead of print] (https://www.ncbi.nlm.nih.gov/pubmed/29274396)

   In a prospective randomized ph 2 study assessing transplant conditioning with treosulfan (iv 14 g/m^2/day days –6 to –4) + fludarabine(iv 30 mg/m^2/day days –6 to –2) with or without 2Gy total body irradiation (TBI) in reducing post-transplant relapse in MDS, CMML and AML patients (N=100; med age- 57 yr). Donors were related in 43 patients and unrelated in 57 patients. With a median follow up of 20 months, the rate of 1-yr survival was 80% in the TBI arm vs 69% for non-TBI conditioning. The 1-yr relapse

rates for MDS and AML with TBI vs non-TBI regimens were 27% vs 33% and 16% vs 35% respectively. The report concluded that treosulfan/ fludarabine/low-dose TBI provides effective conditioning for allogeneic hematopoietic cell transplantation.

2. Schmid C et al. Outcome after relapse of myelodysplastic syndrome and secondary acute myeloid leukemia following allogeneic stem cell transplantation: a retrospective registry analysis of 698 patients by the chronic malignancies working party of the European society of blood and marrow transplantation. *Haematologica*. 2018;103(2):237–245. (https://www.ncbi.nlm.nih.gov/pubmed/29101205)

   This retrospective registry analysis explored post relapse therapeutic practices used for MDS patients who had allogeneic HSCT. Generally, the overall survival from relapse was short (median-4.7 months, 2-yr OS-17.7%). Shorter remission post-transplant (p<0.001), advanced disease (p=0.001), older age (p=0.007), unrelated donor (p=0.008), GVHD prior to relapse (p<0.001) were adversely related to OS. Among the three major practices noted at 6 mo post-relapse, the OS (median and 2-yr % OS) rates were as follows- palliative chemotherapy and/or supportive care (n=375, med OS 8.9 mo and 2-yr OS-29.7%), Donor lymphocyte infusion (n=213, med OS-6.0 mo and 2-yr OS 27.6%) or second transplant (n=110, med OS-4.2 mo and 2-yr OS-17%). For second transplant, longer remission after the first transplant, complete remission after second transplant and change to a new donor were of prognostic value.

Novel Therapies:

1. Savona MR et al. Phase 1b study of Glasdegib, a hedgehog pathway inhibitor, in combination with standard chemotherapy in patients with AML or high risk MDS. *Clin Cancer Res*. 2018; Feb 20, [Epub ahead of print]. (https://www.ncbi.nlm.nih.gov/pubmed/29463550)

   An open label dose finding phase 1b study in newly diagnosed high risk MDS/AML (N=52) assessed Glasdegib at 100 or 200 mg daily po in 28-day cycle in combination with low-dose cytarabine or decitabine in patients not suitable for induction chemotherapy or in combination with cytarabine/ daunorubicin in fit patients. Whereas no dose limiting toxicities (DLT) were observed with combination treatments in unfit patients, there was one DLT of grade 4 neuropathy noted for combination in fit patients. Overall 16/52 (31%) patients achieved CR/CR-with incomplete hematopoietic recovery. The RP2D of 100 mg was selected for combination with standard chemotherapy.

2. Komrokji R et al. Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial. *Lancet Haematol*. 2018;5(2):e63–e72. (https://www.ncbi.nlm.nih.gov/pubmed/29331635)

   RBC-transfusion dependent low/int-1 risk MDS patients refractory or ineligible to ESAs who were either non-del(5q) or were del(5q) but refractory to lenalidomide, were randomly assigned to receive sotatercept subcutaneously at 0.1 mg/kg (n=7) or 0.3 mg/kg (n=6) or non-randomly assigned to 0.5 mg/kg (n=21), 1 mg/kg (n=35) or 2 mg/kg (n=5). HI-E, the primary endpoint was achieved in 29/62 patients (47%) with high baseline transfusion burden and 7/12 (58%) patients with low transfusion burden. The most commonly reported AEs were fatigue (26%) and peripheral edema (24%). Among the grade 3/4 treatment emergent AEs reported (5%), most common were lipase increase and anemia. One death was noted due to treatment emergent hematoma and fall.

PATHOBIOLOGY:

1. Lin P et al. Isocitrate dehydrogenase 2 mutations correlate with leukemic transformation and are predicted by 2-hydroxyglutarate in myelodysplastic syndromes. *J Cancer Res Clin Oncol*. 2018; Mar 16 [Epub ahead of print](https://www.ncbi.nlm.nih.gov/pubmed/29549529)

   In a genetic profiling study of 281 MDS patients, elevated levels of an oncogenic protein, 2-hydroxyglutarate (2HG) were found to correlate with inferior overall and leukemia-free survival as well as with the presence of IDH mutations. IDH2 mutations in particular, demonstrated a link with additional simultaneous mutations in DNMT3A and SRSF2 genes and showed higher rates of leukemic transformation. Lastly, IDH2 mutations were prognostic in low-risk MDS.

2. Montalban-Bravo G et al. Impact of the number of mutations in survival and response outcomes to hypomethylating agents in patients with myelodysplastic syndromes or myelodysplastic/ myeloproliferative neoplasms. *Oncotarget*. 2018;9(11):9714–9727 (https://www.ncbi.nlm.nih.gov/pubmed/29515765)

   The present report on whole exome sequencing of bone marrow samples from 83 MDS and 31 MDS/MPN patients detected mutations cumulatively in 31 genes in 86% patients. The multivariate analysis showed the impact of TP53 mutations (HR=3.1, p=0.011) and ≥3 concurrent mutations (HR=2.5, p=0.005) in predicting a shorter survival.

3. Schwartz JR et al. The genomic landscape of pediatric myelodysplastic syndromes. *Nat Commun*. 2017;8(1):1557. (https://www.ncbi.nlm.nih.gov/pubmed/29146900)

   A genomic sequencing of 77 pediatric bone marrow samples with diagnosis of primary MDS, MDS/MPN or AML with MDS related changes revealed preponderance of RAS/MAPK pathway mutations (45% of Primary MDS), while mutations in RNA splicing genes were rare (2% of primary MDS). Newly in pediatric samples, germline variants were detected in SAMD9 and SAMD9L genes in 17% of primary MDS.

4. Balaian E et al. Erythropoietin inhibits osteoblast function in myelodysplastic syndromes via the canonical Wnt pathway. *Haematologica*. 2018;103(1):61–68 (https://www.ncbi.nlm.nih.gov/pubmed/29079596)

   Upon in vitro erythropoietin (EPO) treatment, the expression of osteoblast specific genes and subsequent osteoblast mineralization increased in mesenchymal stromal cells from young healthy donors, while in the cells from old healthy donors and MDS patients, EPO did not have the same increase, rather inhibited cell differentiation and inhibited canonical Wnt pathway gene expression. Activation of Wnt pathway with lithium chloride or parathyroid hormone could rescue EPO inhibition of differentiation. EPO thus seems to uniquely modulate the osteo-hematopoietic niche in young age, vs old age donors and MDS patients.

5. Cull AH et al. Overexpression of arginase 1 is linked to DNMT3A and TET2 mutations in lower-grade myelodysplastic syndromes and chronic myelomonocytic

leukemia. *Leuk Res*. 2018;65:5–13 (https://www.ncbi.nlm.nih.gov/pubmed/29227812)

The report found elevated relative arginase-1 activity in marrow mononuclear cells from patients with CMML (n=15), low grade MDS (n=12) and high grade MDS (n=12) compared to controls (n=8). This corresponded to the overexpression of arginase-1 protein in patients' cells. Furthermore, immunohistochemistry showed higher protein expression in CMML and low grade MDS than the high grade MDS marrow biopsies. Lastly, DNMT3A and/or TET2 mutations were significantly enriched in patients with elevated arginase-1 activity (p=0.0386).

6. Ribeiro HL Jr et al. DNA repair gene expressions are related to bone marrow cellularity in myelodysplastic syndrome. *J Clin Pathol*. 2017;70:970-980 (https://www.ncbi.nlm.nih.gov/pubmed/28554891)

The expression of genes related to nuclear excision (ERCC8, XPA and XPC), homologous recombination and non-homologous end-joining (ATM, BRCA1, BRCA2 and LIG4) repair mechanisms was evaluated in 51 MDS cases. Patients with hypocellular marrows showed decreased expression of ATM, BRCA1, BRCA2 and LIG4 (DNA double stranded repair genes), and increased expression of XPA and XPC (DNA single stranded repair genes). In hypoplastic marrows lower expression of the ATM, LIG4 and ERCC8 was associated with higher preponderance of chromosomal abnormalities as well.

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. Daver N et al. Hypomethylating agents in combination with immune checkpoint inhibitors in acute myeloid leukemia and myelodysplastic syndromes. *Leukemia*. 2018; Feb 22, [Epub ahead of print] (https://www.ncbi.nlm.nih.gov/pubmed/29487386)
2. Steensma DP. Prognosis in myelodysplastic syndromes: The attractions and limitations of simplicity. *Am J Hematol*. 2018; Feb 16, [Epub ahead of print] (https://www.ncbi.nlm.nih.gov/pubmed/29451319)
3. List A, Ebert BL and Fenaux P. A decade of progress in myelodysplastic syndrome with chromosome 5q deletion. *Leukemia*. 2018; Jan 30, [Epub ahead of print]. (https://www.ncbi.nlm.nih.gov/pubmed/29445113)
4. Shallis RM and Zeidan AM. Lenalidomide in non-deletion 5q lower-risk myelodysplastic syndromes: a glass quarter full or three quarters empty? *Leuk Lymphoma*. 2018; Feb 7, [Epub ahead of print]. (https://www.ncbi.nlm.nih.gov/pubmed/29411698)
5. Montalban-Bravo G and Garcia-Manero G. Myelodysplastic syndromes: 2018 update on diagnosis, risk stratification and management. *Am J Hematol*. 2018; 93(1):129–147. (https://www.ncbi.nlm.nih.gov/pubmed/29214694)
6. Steensma DP. The evolving role of genomic testing in assessing prognosis of patients with myelodysplastic syndromes. *Best Pract Res Clin Haematol*. 2017; 30(4):295–300. (https://www.ncbi.nlm.nih.gov/pubmed/29156198)
7. Sallman DA, Tanaka TN, List A and Bejar R. SOHO state of the art update and next questions: Biology and treatment of myelodysplastic syndromes. *Clin Lymphoma Myeloma Leuk*. 2017;17(10):613–620. (https://www.ncbi.nlm.nih.gov/pubmed/29025689)
8. Furutani E and Shimamura A. Germline genetic predisposition to hematologic malignancy. *J Clin Oncol*. 2017:35(9): 1018–1028 (https://www.ncbi.nlm.nih.gov/pubmed/28297620)

A special thanks to Suneel and Rhea Mundle for their great efforts in monitoring these important MDS peer-review publications.

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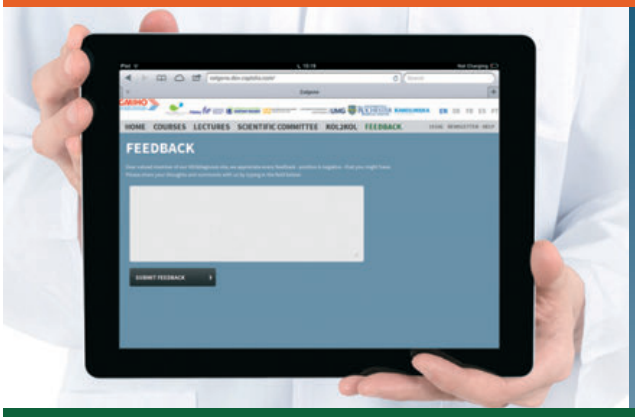

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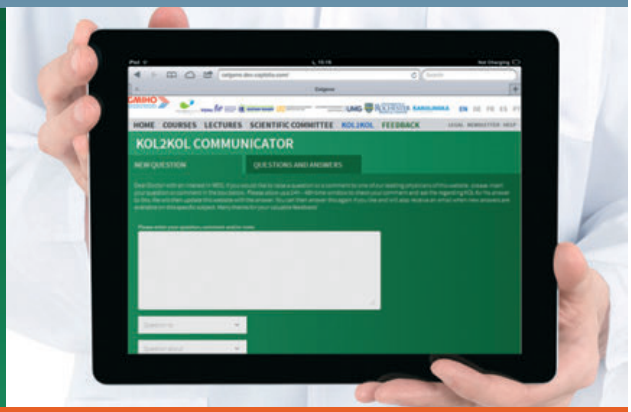

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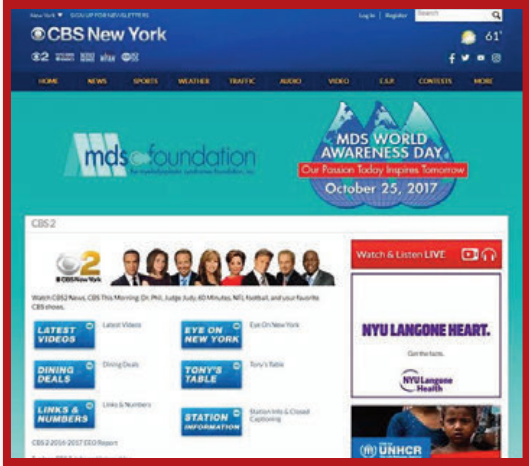
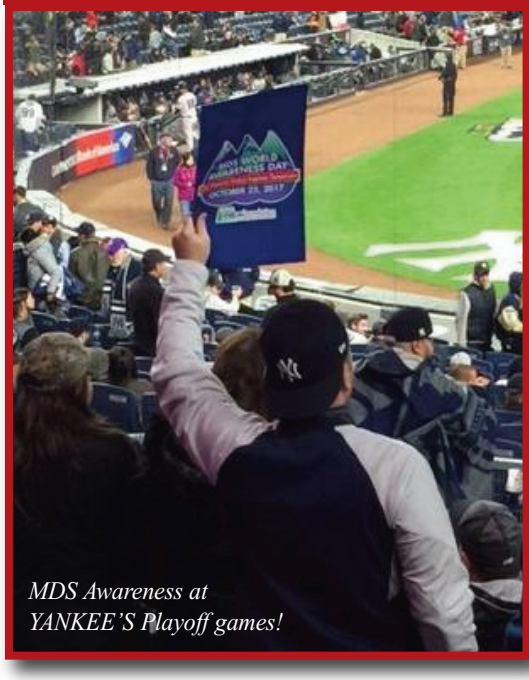


Thank you CBS New York!



MDS Awareness at YANKEE'S Playoff games!

BUENOS AIRES, ARGENTINA

Sanatorio Sagrado del Corazón

VALENCIA, SPAIN

Hospital Universitario La Fe

ATLANTA, GEORGIA

Emory Winship

Texas Oncology

SAN ANTONIO, TEXAS

STANFORD, CALIFORNIA

Stanford University Cancer Center

CANADA

ALBUQUERQUE, NEW MEXICO

University of New Mexico Comprehensive Cancer Center

THANK YOU TO ALL OF THE AMAZING PEOPLE WHO SUPPORT OUR MISSION TO HELP AND EMPOWER MDS PATIENTS WORLDWIDE!

Sixth Hospital Affiliated to Shanghai Jiaotong University

CHINA

International collaboration at its finest...Janssen China sponsored 10 Chinese physicians to attend a 3-day MDS training event at MD Anderson that included educational sessions, case discussions, and inpatient rounds.

GERMANY

BUFFALO, NEW YORK

Roswell Park Cancer Center

SEATTLE, WASHINGTON

Fred Hutchinson Cancer Center

UNITED KINGDOM

BRONX, NEW YORK

Albert Einstein Cancer Center

TOKYO, JAPAN

Metropolitan Research and Treatment Center for Blood Disorders

LA JOLLA, CALIFORNIA

Moores Cancer Center

New Jersey Rare Disease Alliance Commemorates Global Rare Disease Day 2018

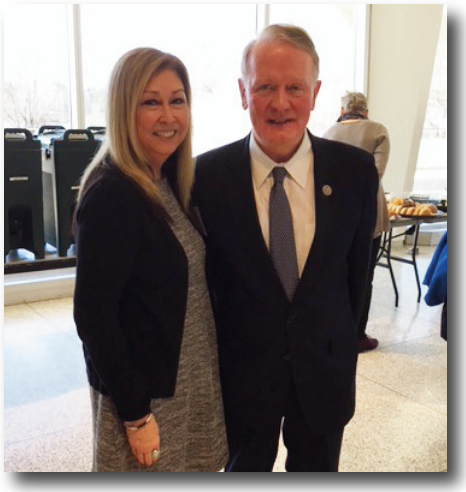
The New Jersey Rare Disease Alliance, dedicated to improving the lives of the more than 800,000 rare disease patients in New Jersey, held its annual Rare Disease Day commemoration on Monday, March 5th in honor of Rare Disease Day, at the New Jersey State Museum, 205 W. State Street, Riverview Court (1st floor), Trenton, from 8:30 am–12:30 pm. Entitled "A Better World for People Living with Rare Diseases: State, National and Global Action", this year's event featured Congressman Leonard Lance, Co-Chair of the Rare Disease Caucus of the United States Congress, as the keynote speaker.

Co-sponsored by the National Organization for Rare Diseases (NORD), BioNJ, and the HealthCare Institute of New Jersey (HINJ), the event began with networking and a continental breakfast followed by soeakers from the rare disease community including patients, patient advocates, biomedical healthcare professionals, and industry leaders. Topics included "Effective Advocacy—Real World Advice" and "A Collaborative Approach to Rare Disease Treatment Development". Attendees also heard from members of the New Jersey legislature. Following lunch, all in attendance walked to the State House to engage with legislators and staff about issues of concern to the rare disease community.

The NJ Rare Disease Alliance, is a state-based coalition of different rare disease groups, of which the MDS Foundation is a member, hoping to find strength in numbers-hoping their combined lobbying will help spread awareness of issues that are important to the rare disease community. Together we are stronger than any of us are alone.

Record turnout of 130 advocates making the voice of rare diseases heard!

Meeting with Assemblyman Gary S. Schaer to voice the needs of the MDS community.



Audrey Hassan of The MDS Foundation with Leonard Lance, Co-Chair of the Rare Disease Caucus of the US Congress

PATIENT FORUMS

SPREADING THE NEWS WORLDWIDE

MARK YOUR CALENDAR FOR THE LOCATION NEAREST YOU!

- **FEBRUARY 3, 2018**
  La Jolla, CA
- **MARCH 3, 2018**
  Albuquerque, NM
- **APRIL 28, 2018**
  Pittsburgh, PA
- **MAY 5, 2018**
  Salt Lake City, UT
- **JUNE 9, 2018**
  Short Hills, NJ
- **JUNE 13, 2018**
  Stockholm, Sweden
- **JULY 21, 2018**
  Boston, MA
- **AUGUST 11, 2018**
  Minneapolis, MN
- **SEPTEMBER 15**
  Charlottesville, VA
- **SEPTEMBER 29, 2018**
  Cincinnati, OH
- **NOVEMBER 10, 2018**
  Miami, FL

Register Today
FOR OUR FREE EVENTS

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.

LEARN MORE AT:

www.mds-foundation.org/patient-and-family-forums

Many patients and caregivers have never met another person diagnosed with MDS until they connected with them at one of our forums. If you've never attended one, you won't want to miss this opportunity to meet others and to learn more about MDS, current treatments, and emerging therapies from leading experts. Not only will you find answers, support and hope for MDS but you will learn tips and strategies for patients and caregivers **LIVING** with MDS.

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

mds foundation
the myelodysplastic syndromes foundation, inc.

Become a Member of the MDS Foundation

Get access to patient advocacy services and support the mission of improving the lives of patients with myelodysplastic syndromes.

This year nearly 90,000 people will be told they have MDS worldwide – 12,000 to 18,000 newly diagnosed MDS patients in the United States alone. The MDS Foundation, Inc. is working hard to support these patients and the loved ones who care for them. We are asking for your membership support in our global efforts to change the outcomes of MDS.

We are here for you...

AT YOUR TIME OF DIAGNOSIS

"It took a long time to wrap our heads around a disease without a cure when my husband felt just fine – The MDS Foundation gave me the information I so badly needed to be a good caregiver. The MDS Foundation was there when we needed it desperately."

The Cook Family
MDS Caregiver, 70 years old, 2 children, 1 grandchild ("Grandpa's best medicine")

FOR REFERRALS TO A SPECIALIST

"She asked if I would like for her to make an appointment. We had an appointment WITHIN A WEEK and were treated royally. That is some seriously appreciated clout. Now anyone out there experiencing MDS in your family or with friends I tell from experience there is ONLY ONE KIND of doctor you should be seeing: A DOCTOR RECOMMENDED BY THE MDS FOUNDATION"

The Fournier Family
MDS Patient, 79 years old, 3 children, 8 grandchildren

ALWAYS

"When I was diagnosed with MDS in 2008, the MDS Foundation became my primary source of accurate, comprehensive and understandable information about this complex and challenging bone marrow disease. I donate to the MDS Foundation because it's an unparalleled resource for patients, caregivers, treatment providers and researchers. Additionally, I donate because of the wonderful, caring professional staff."

MDS patient, 68 years old

MDS PATIENT AND PROFESSIONAL MEMBERSHIP

MEMBERSHIP OPPORTUNITY

MDS FOUNDATION MEMBERSHIP

WHAT ARE MDS MEMBERSHIP BENEFITS?

- You are part of the solution to change MDS outcomes. Your membership fee helps support global physician and patient educational initiatives, and helps to empower patients with courage and hope.
- Updates on the status of our Global Centers of Excellence and their live patient and family forum events that allow for more rapid dissemination of new research and treatment developments.
- 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 & community.
- Receive two printed issues of *The MDS News*, which includes the latest on MDS research as well as inspiring patient and caregiver stories.

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.

CURRENT PROFESSIONAL MEMBERS:

Calum Adams, ANP
Aref Al-Kali, MD
Steven L. Allen, MD,
Hanan Alwazzan, MD
Sergio Amadori, MD
Martha Arellano, MD
Christopher Arthur, MD
Anita Atema, MSc
Maria R. Baer, MD
Gabriela Baerlocher, MD
Asad Bashey, MD
Marielle Beckers, MD
Rafael Bejar, MD, PhD
John M. Bennett, MD
Harriet A. Bering, MD
Massimo Bernardi, MD
Emmanuel C. Besa, MD
James S. Blachly, MD
Leigh-Anne Blair
Nicolas Bonadies, MD
Dominique Bordessoule, MD
Adam Boruchov, MD
Michael Boxer, MD
Raul C. Braylan, MD
Andrew M. Brunner, MD
Rena Buckstein, MD, FRCPC
Gesine Bug, MD
Thomas W. Butler, MD
Jheremy Enrique Reyes Castellanos, MD
Mario Cazzola, MD
Jaroslav Čermák, MD, PhD
Victor Chang, MD, FACP
Lynette Chee, MD
Suning Chen, MD, PhD
Jason X. Cheng, MD, PhD
June-Won Cheong, MD
Alden Chesney, MD
Laura Yolanda Chialanza Garcia, MD
Shigeru Chiba, MD
Jonathan K. Cho, MD
Grace Christou, MD
Stephen Chung, MD
Christopher R. Cogle, MD
Robert H. Collins, Jr., MD, FACP
Seth J. Corey, MD
Larry Cripe, MD
Gerard Crotty, MD
Guiyun Cui, MD
Peter T. Curtin, MD
Lucy Cussans
Magdalena Czader, MD, PhD
Christopher Dalley, MD
Carlos M. de Castro, MD
Theo J.M. de Witte, MD, PhD
H. Joachim Deeg, MD
Michel Delforge, MD, PhD
Matteo G. Della Porta, MD
Mike Dennis, MD
Amy E. DeZern, MD, MHS
Bruce Dezube, MD
Maria Diez-Campelo, MD, PhD
John F. DiPersio, MD, PhD
Xin Du, MD
M. Tarek Elghetany, MD
Douglas V. Faller, MD, PhD
Salman Fazal, MD
Lenn Fechter, RN, BSN
Kalman Filanovsky, MD
Chun Yew Fong, MD
James M. Foran, MD, FRCP
Stephen Forman, MD
Heiner Frost, MD
Steven Fruchtman, MD
Arnold Ganser, MD
Alejandro Garcia-Hernandez, MD
Guillermo Garcia-Manero, MD
Michelle Geddes, MD
Ulrich Germing, MD
Gudrun Goehring, MD
Stuart L. Goldberg, MD
Carlos Vigil Gonzales, MD
Steven D. Gore, MD
Katharina Götze, MD
Marie Pierre Gourin, MD
Timothy Graubert, MD
Uri Greenbaum, MD
Peter L. Greenberg, MD
Stephanie Gregory, MD
Elizabeth A. Griffiths, MD
George Grigoriadis, MD
Kirsten Grønbaek, MD
Emmanuel Gyan, MD, PhD
Detlef Haase, MD, PhD
Torsten Haferlach, MD
Gregory Hale, MD
Amr Hanbali, MD
Curtis A. Hanson, MD
Robert P. Hasserjian, MD
Guangsheng He, MD
Stefan Heinrichs, PhD
Eva Hellström-Lindberg, MD, PhD
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Andreas Himmelmann, MD
Michel Hoessly, MD
Inga Hofmann, MD,
Gang Huang, PhD
Sang Mee Hwang, PHD
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Ishmael Jaiyesimi, DO
Peng Ji, MD
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Mark Juckett, MD
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Jonathan Kell, MD
Melita Kenealy, MD
Michael Kenneth Keng, MD
Wolfgang Kern, MD

Samer Khaled, MD
Sally Killick, MD
Lars Kjeldsen, MD, PhD
Jeffery Klco, MD
Virginia M. Klimek, MD
H. Phillip Koeffler, MD
Rami Komrokji, MD
Janusz Krawczyk, MD
Ravi Krishnadasan, MD, FACP
Nicolaus Kröger, MD, PhD
Patricia Kropf, MD
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Amelia Langston, MD
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Xiao Li, MD, PhD
Jane L. Liesveld, MD
Alan F. List, MD
Mark R. Litzow, MD
Johannes Loferer, MD
Selina Luger, MD
Roger M. Lyons, MD
Rochelle Mackey, APRN, AHN, QTTT, CCAP
Alan MacWhannell, MD
Ulrich Mahlknecht, MD, PhD
Inga Mandac Rogulj, MD
Lori Maness, MD
Markus G. Manz, MD
Maria Teresa Massaro, MD
Akira Matsuda, MD
Philip L. McCarthy, MD
Zoe McQuilten, MD
Stephen Medlin, MD
Kenneth R. Meehan, MD
Raul R. Mena, MD
Wolfgang Meyer, MD
Ken Mills, MD
Moshe Mittelman, MD
Yasushi Miyazaki, MD
Sanjay Mohan, MD
Joseph O. Moore, MD
Alvaro Moreno-Aspitia, MD
Lynn Moscinski, MD
Suneel D. Mundle, PhD
Srinivasan Narayanan, MD
Abdulqadir Nashwan
Shyamala Navada, MD
Phuong L. Nguyen, MD
Charlotte Niemeyer, MD
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Benet Nomdedeu, MD
Nicolas Novitzky, MD
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Margaret O'Donnell, MD
Kiyoyuki Ogata, MD, FACP
Kazuma Ohyashiki, MD, PhD
Stephen Opat, MD
Rose Ann Padua, PhD
Elli Papaemmanuil, PhD
Vassiliki Pappa, MD
Stefani Parmentier, MD
Jakob R. Passweg, MD
Michael Pfeilstöcker, MD
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Jun Qian, MD
Bruno Quesnel, MD
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Fernando Ramos, MD, PhD, MPH
Michael Rauh, MD
Azra Raza, MD
Elvira Rodrigues Pereira Velloso, MD, PhD
Christian Rose, MD
Alicia Rovo, MD
Nitzan Sagy
Grazia Sanpaolo, MD
Michael R. Savona, MD, FACP
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Paul Shami, MD
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Akiko Shimamura, MD, PhD
Jake Shortt, MD
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Michail Spanoudakis, MD, PhD
Kellie Sprague, MD
Lisa Sproat, MD
Aspasia Stamatoullas, MD
Harry Staszewski, MD
Reinhard Stauder, MD
David P. Steensma, MD
Galia Stemer, MD
John Storring, MD
Argiris S. Symeonidis, MD
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Gevorg Tamamyan, MD
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Hwei-Fiang Tien, MD
Masao Tomonaga, MD
Hongyan Tong, MD
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Athina Nora Viniou, MD
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John P. Whitecar, Jr., MD
Stefan Wirths, MD
Dan Wiseman, MD
Zhijian Xiao, MD
Yumi Yamamoto, BA
Karen Yee, MD
Cecilia Arana Yi, MD
Yataro Yoshida, MD
Jacqueline Emilie Vizhnay Zambrano, MD
Ling Zhang, MD

PRESS RELEASE

Onconova Moving Forward With Phase 3 INSPIRE Pivotal Trial With Increased Sample Size Following Promising Interim Analysis

- *Independent Data Monitoring Committee (DMC) recommends continuation of INSPIRE trial with trial expansion per adaptive design based on interim analysis results for overall survival*
- *Trial Executive Committee unanimously agreed to continue the Intent To Treat (ITT) study population and increase clinical trial enrollment by adding 135 patients to the original target of 225 patients, based upon the DMC's recommendations*
- *In the INSPIRE trial enrollment so far, the predefined subgroup of Very High Risk (VHR) patients constitutes greater than 70% of patients enrolled to date*

NEWTOWN, Pa., January 17, 2018 (GLOBE NEWSWIRE) – Onconova Therapeutics, Inc. (Nasdaq:ONTX), a Phase 3-stage biopharmaceutical company focused on discovering and developing small molecule drug candidates to treat cancer, today announced that it is moving forward with its Phase 3 INSPIRE pivotal trial following the interim analysis, consistent with the DMC's recommendation. The DMC recommended continuation of the trial with a one-time expansion in enrollment, using a pre-planned sample size re-estimation, consistent with the Statistical Analysis Plan (SAP). The INSPIRE pivotal trial is studying intravenously-administered (IV) rigosertib in patients with higher-risk myelodysplastic syndromes (MDS) who have progressed on, failed to respond to, or relapsed after prior hypomethylating agent (HMA) therapy. The Company remains blinded to the interim analysis results.

> ***Choices are very limited for higher risk MDS patients after failure of HMA therapy and no second-line therapy has ever been approved by the Health Authorities for these patients. These patients have a very short life-span and there is a tremendous unmet medical need. We remain highly supportive of Onconova's efforts. After the interim analysis, continuation of the INSPIRE study is encouraging for patients.***
>
> **Guillermo Garcia-Maner, MD**

Guillermo Garcia-Manero, M.D, Professor and Chief of the MDS Section at the MD Anderson Cancer Center, a lead investigator on the INSPIRE study, commented, "Choices are very limited for higher risk MDS patients after failure of HMA therapy and no second-line therapy has ever been approved by the Health Authorities for these patients. These patients have a very short life-span and there is a tremendous unmet medical need. We remain highly supportive of Onconova's efforts. After the interim analysis, continuation of the INSPIRE study is encouraging for patients."

The SAP for the INSPIRE trial featured an adaptive trial design, permitting several options following the interim analysis, which included continuation of the trial as planned, discontinuation of the trial for futility, trial expansion using pre-planned sample size re-estimation, and trial continuation for only the pre-defined treatment subgroup of patients classified as VHR based on the Revised International Prognostic Scoring System (IPSS-R).

The expanded INSPIRE study will continue to enroll eligible patients based on the current trial design of the overall ITT population and will increase enrollment by adding 135 patients to the original target to reach a total enrollment of 360 patients, with the aim of increasing the power of the trial. Due to the adaptive trial design and the DMC's assessment, the INSPIRE trial will continue to analyze both the ITT and the VHR population for the primary endpoint of overall survival. The design of the trial with the expanded study enrollment will be identical to the current study design and will include the analysis of the overall survival endpoint in the ITT and the pre-specified VHR subgroup.

Steve Fruchtman, M.D., Chief Medical Officer of Onconova, added, "With no FDA approved therapies for many patients with higher-risk MDS who are refractory to HMAs, we are encouraged by these results and pleased to be at the forefront of advances in this treatment landscape. The DMC's recommendation based on the pre-planned interim analysis includes the expansion of the INSPIRE trial and retains the analysis of survival in both the ITT and the VHR pre-defined subgroups. Patients with MDS who are refractory to HMAs have the highest unmet medical need due to an extremely poor prognosis following failure of HMA therapy. We look forward to completing enrollment and for the opportunity to analyze overall survival in the higher-risk MDS patients who have failed prior HMA therapy."

Currently, the INSPIRE study is active at approximately 175 trial sites in 22 countries across four continents, and has enrolled more than 170 patients. In Japan, patients have been enrolled to this study by SymBio Pharmaceuticals, our collaboration partner for Japan and Korea. Onconova believes that this trial is the most advanced study for a new therapeutic agent in this indication, and there are no FDA approved therapies specifically for MDS patients after failure of front-line HMAs.

National Comprehensive Cancer Network® adds Jazz Pharmaceuticals' Vyxeos™ (daunorubicin and cytarabine) Liposome for Injection to Clinical Practice Guidelines in Oncology

DUBLIN, February 8, 2018 – Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the National Comprehensive Cancer Network® (NCCN®) added Vyxeos™ (daunorubicin and cytarabine) liposome for injection to the Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia (AML).

The United States Food and Drug Administration (FDA) approved *Vyxeos* on August 3, 2017 for the treatment of adults with two types of AML, a rapidly progressing and life-threatening blood cancer. *Vyxeos* is the first FDA-approved treatment specifically for adults with newly-diagnosed Therapy-Related AML (t-AML) or AML with Myelodysplasia-Related Changes (AML-MRC). Based on the data from the pivotal Phase 3 randomized trial of *Vyxeos* versus the standard of care, the NCCN Guidelines now include a Category 1 recommendation for use of *Vyxeos* for adult patients 60 years of age or greater with newly-diagnosed t-AML or AML-MRC. The Category 1 recommendation indicates that based upon high-level evidence, there is uniform NCCN consensus that *Vyxeos* is appropriate for these patients.

"We appreciate the decision by the NCCN to incorporate *Vyxeos* into the Clinical Practice Guidelines in Oncology as it supports our commitment to ensuring that patients, through their health care professionals, are able to access this important new treatment option," said Karen Smith, M.D., Ph.D., executive vice president of research and development and chief medical officer of Jazz Pharmaceuticals. "*Vyxeos* is the first chemotherapy advance for adults with newly-diagnosed t-AML or AML-MRC in more than 40 years."

The NCCN, a not-for-profit alliance of 27 leading U.S. cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care. The intent of the NCCN Guidelines is to assist in the decision-making process of individuals involved in cancer care—including physicians, nurses, pharmacists, payers, patients and their families—with the ultimate goal of improving patient care and outcomes.

About Vyxeos™

Vyxeos™ (daunorubicin and cytarabine) liposome for injection 44mg/100mg is a liposome formulation of a fixed combination of daunorubicin and cytarabine for intravenous infusion.[1] *Vyxeos* is indicated for the treatment of adults with newly-diagnosed t-AML or AML-MRC. For more information about *Vyxeos* in the United States, please visit https://vyxeos.com.

Important Safety Information

Vyxeos has different dosage recommendations from other medications that contain daunorubicin and/or cytarabine. Do not substitute Vyxeos for other daunorubicin- and/or cytarabine- containing products.

Vyxeos should not be given to patients who have a history of serious allergic reaction to daunorubicin, cytarabine or any of its ingredients.

AML PRESS RELEASE

Syros Announces Clinical Supply Agreement with Janssen to Evaluate SY-1425, Its First-in-Class Selective RARα Agonist, in Combination with Daratumumab in Genomically Defined AML and MDS Patients

Cohort Added to Ongoing Phase 2 Trial of SY-1425 to Evaluate Safety and Efficacy of the Combination in Biomarker-Selected Relapsed or Refractory AML or Higher-Risk MDS Patients

CAMBRIDGE, Massachusetts
January 2, 2018 (BUSINESS WIRE) – Syros Pharmaceuticals (NASDAQ:SYRS), a biopharmaceutical company pioneering the development of medicines to control the expression of disease-driving genes, today announced that it has entered into a clinical supply agreement with Janssen Research and Development, LLC. Under the agreement, Janssen will supply daratumumab for a recently added combination dosing cohort in Syros' ongoing Phase 2 clinical trial of SY-1425, a first-in-class selective retinoic acid receptor alpha (RARα) agonist, in genomically defined subsets of patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Daratumumab (DARZALEX®) is an anti-CD38 antibody approved for use in various multiple myeloma populations.

"We are delighted to work with Janssen to investigate the potential of SY-1425 in combination with daratumumab to benefit AML and MDS patients with the RARA or IRF8 biomarkers," said Nancy Simonian, MD, Chief Executive Officer of Syros. "By inducing expression of CD38 in these patients' tumors, we believe SY-1425 may sensitize them to treatment with daratumumab, which is believed to induce tumor cell death in CD38-positive cells through multiple immune-mediated mechanisms. Based on preclinical data supporting this hypothesis as well as CD38 induction seen in the bone marrow of AML and MDS patients treated with SY-1425, we added a cohort to our ongoing Phase 2 clinical trial of SY-1425 and look forward to starting to enroll patients early this year."

In exchange for providing daratumumab, Janssen will receive access to data from the cohort evaluating the safety and efficacy of SY-1425 in combination with daratumumab for its research and development programs related to daratumumab. The study will continue to be sponsored solely by Syros.

Syros is assessing the safety and efficacy of SY-1425 in combination with azacitidine in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy, and in combination with daratumumab in patients with relapsed or refractory AML or higher-risk MDS, in an ongoing Phase 2 clinical trial. All patients enrolled or to be enrolled in this clinical trial are prospectively selected using the Company's proprietary RARA and IRF8 biomarkers. Enrollment in the combination cohort with azacitidine began last year and is ongoing. Syros expects to begin enrolling patients in the combination cohort with daratumumab in early 2018. Syros expects to present initial clinical data on both combinations in 2018.

Syros is assessing the safety and efficacy of SY-1425 in combination with azacitidine in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy

Analysis of bone marrow biopsies from relapsed or refractory AML and higher-risk MDS patients enrolled in the ongoing clinical trial showed increased CD38 expression in 11 out of 13 (85 percent) of evaluable patients. Preclinical studies showed that SY-1425 induced CD38 in RARA biomarker-positive AML cells comparable to levels of CD38 seen in multiple myeloma cells that are known to be responsive to daratumumab, as well as in an in vivo model of biomarker-positive AML. Notably, AML cells do not normally express high levels of CD38. Preclinical studies also showed that SY-1425 in combination with daratumumab triggered robust activation of natural killer cells and immune-cell mediated tumor cell death in biomarker-positive AML cells.

DARZALEX is the first CD38-directed monoclonal antibody approved to treat patients with multiple myeloma. It was first approved by the U.S. Food and Drug Administration (FDA) in November 2015 for patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent. DARZALEX is also approved in Europe, Canada and several other countries for a similar patient population. DARZALEX was more recently approved by the FDA in November 2016 for use in combination with lenalidomide (an immunomodulatory agent) and dexamethasone, or bortezomib (a PI) and dexamethasone, for multiple myeloma patients who have received at least one prior therapy. Daratumumab received Breakthrough Therapy Designation from the FDA for this indication in July 2016. In June 2017, the FDA approved a supplement for DARZALEX use in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. Janssen licensed daratumumab from Genmab A/S in August 2012 and is responsible for all global development, marketing and manufacturing.

"InDACtion" vs "3+7" Induction in AML

Brief Summary: Older patients with acute myeloid leukemia (AML) have a small (< 10%) chance of long-term survival. Despite the treatment of elderly AML patients with intensive chemotherapy, the survival has not been improved during the last decades.

The purpose of this study is to determine whether frontline therapy with a 10-day decitabine schedule provides a better survival than standard intensive combination chemotherapy in elderly AML patients (≥ 60 years).

Condition: Acute Myeloid Leukemia

Drug: Standard combination chemotherapy

Drug: Decitabine, Phase 3

Detailed Description:

The overall survival (OS) of older AML patients has not been improved during the last decades with intensive chemotherapy based on cytarabine combined with an anthracycline ("3+7").

Next generation sequencing technology reveals that mutations in genes involved in epigenetics are frequently mutated in AML (e.g. DNMT3a), suggesting an important role of epigenetics in the pathophysiology of AML. Decitabine (given in a 5-day schedule) has been shown to be superior to low-dose Ara-C.

A retrospective analysis revealed that epigenetic therapy (either azacitidine or decitabine) is associated with similar survival rates as intensive chemotherapy in older patients (n=671) with newly diagnosed AML.

The recently published encouraging phase 2 data with the 10-day decitabine schedule suggests that decitabine results in similar CR rates compared with intensive chemotherapy. Allogeneic transplantation (alloHCT) also offers the opportunity for cure among older AML patients, therefore treatment strategies should aim to allograft older AML patients.

Decitabine treatment can lead to very interesting cure rates when used as "bridging" to allografting.

Based on the data summarized above, we hypothesize that decitabine at a daily dose of 20 mg/m² starting with the 10-day schedule followed by an alloHCT or by continuation of 5-days decitabine cycles is superior to conventional intensive chemotherapy in older AML patients.

Study Design

Study Type: Interventional (Clinical Trial)

Estimated Enrollment: 600 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: None (Open Label)

Primary Purpose: Treatment

Official Title: *10-day Decitabine Versus Conventional Chemotherapy ("3+7") Followed by Allografting in AML Patients ≥60 Years: a Randomized Phase III Study of the EORTC Leukemia Group, CELG, GIMEMA and German MDS Study Group*

Study Start Date: November 2014

Estimated Primary Completion Date: December 2019

Estimated Study Completion Date: December 2019

FDA Accepts New Drug Application and Grants Priority Review for Ivosidenib in Relapsed or Refractory AML with an IDH1 Mutation

CAMBRIDGE, Massachusetts

Feb. 15, 2018 (GLOBE NEWSWIRE) – Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced that the U.S. Food and Drug Administration (FDA) has accepted the company's New Drug Application (NDA) for ivosidenib (AG-120) for the treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase 1 (IDH1) mutation. The NDA was granted Priority Review and has been given a Prescription Drug User Fee Act (PDUFA) action date of August 21, 2018. The FDA's Priority Review status accelerates the review time from 10 months to a goal of six months from the day of filing acceptance and is given to drugs that may offer major advances in treatment or may provide a treatment where no adequate therapy exists. Agios completed the NDA submission in late December 2017.

"After decades of little change, treatment of AML has begun to shift dramatically as result of new therapies, and IDHm inhibitors will play an important role in how we treat this terrible disease," said David Schenkein, M.D., chief executive officer of Agios. "Today marks an important milestone in our efforts to rapidly advance what could be the first targeted treatment for R/R AML patients with an IDH1 mutation. We appreciate the FDA's collaboration during the application process, and we look forward to continuing our productive dialogue."

Ivosidenib is a first-in-class, oral, targeted inhibitor of mutant IDH1. The NDA submission is based on results from AG120-C-001, a Phase 1 dose-escalation and expansion study of ivosidenib in patients with advanced hematologic malignancies and an IDH1 mutation. Data from the R/R AML patients in this study were presented at the 2017 American Society of Hematology (ASH) Annual Meeting.

Additionally, Abbott has submitted a Premarket Approval (PMA) application for the FDA review of an IDH1 assay on the Abbott m2000 RealTime System, an automated sample preparation and batch analyzer system for nucleic acid amplification and detection. In 2014, Abbott and Agios entered into an exclusive agreement under which Abbott is responsible for development and commercialization of a RealTime PCR assay for detection of the IDH1 mutation in bone marrow and blood. The Abbott assay will serve as a companion diagnostic for ivosidenib.

IDH1 mutations occur in about 6 to 10 percent of AML patients. Recent publications have highlighted the advances in the understanding of the genetics underlying AML and the need for routine mutational analysis at diagnosis and relapse.

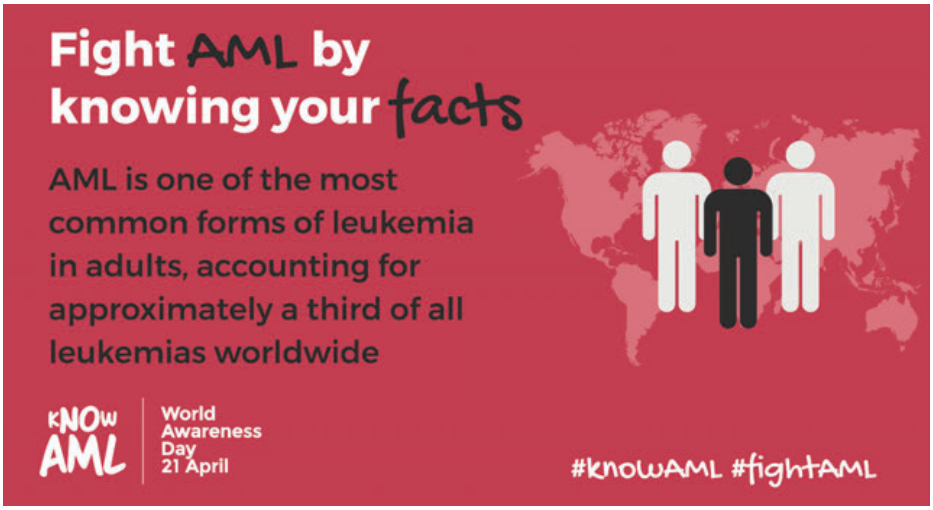
Ivosidenib is an investigational drug that has not been approved for any use in any country.

About Acute Myelogenous Leukemia (AML)

AML, a cancer of blood and bone marrow characterized by rapid disease progression, is the most common acute leukemia affecting adults. Undifferentiated blast cells proliferate in the bone marrow rather than mature into normal blood cells. AML incidence significantly increases with age, and the median age at diagnosis is 68. The vast majority of patients do not respond to chemotherapy and progress to relapsed/refractory AML. The five-year survival rate for AML is approximately 20 to 25 percent. IDH1 mutations are present in about 6 to 10 percent of AML cases.

About Agios

Agios is focused on discovering and developing novel investigational medicines to treat cancer and rare genetic diseases through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has an approved oncology precision medicine and multiple first-in-class investigational therapies in clinical and/or preclinical development. All Agios programs focus on genetically identified patient populations, leveraging our knowledge of metabolism, biology and genomics. For more information, please visit the company's website at www.agios.com.



Connect® MDS|AML Disease Registry

An MDS/AML Prospective Observational Study

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:

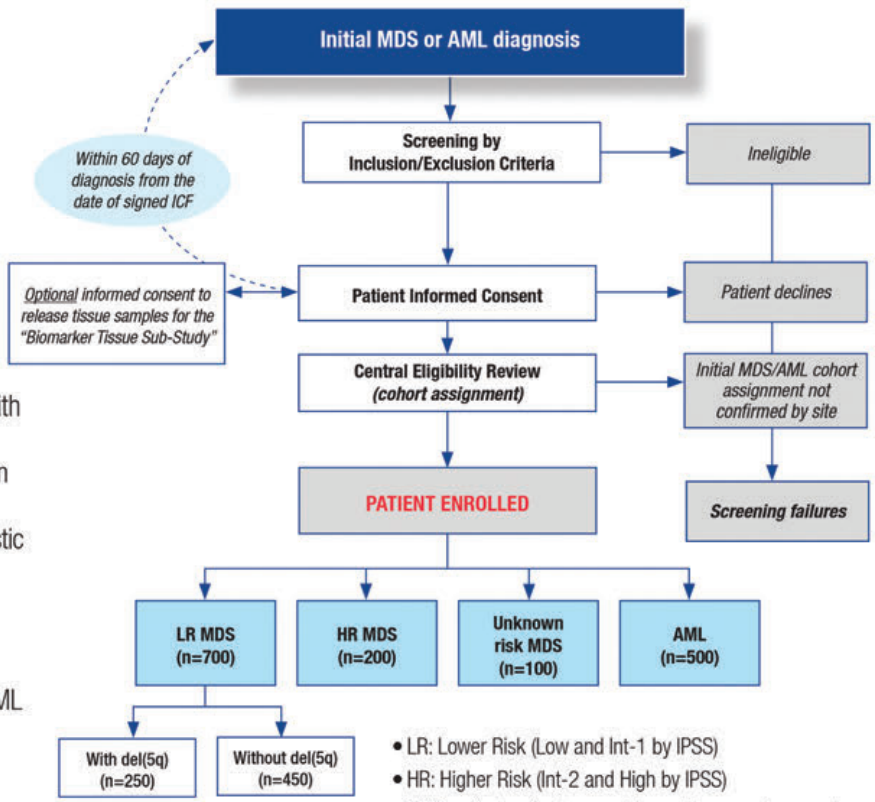
- Newly diagnosed,* primary or secondary MDS or AML
- MDS patients must be at least 18 years
- AML patients must be at least 55 years of age
- Patients must be willing and able to complete enrollment and follow-up HRQoL instruments, for which patients must be proficient in either English or Spanish

*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:

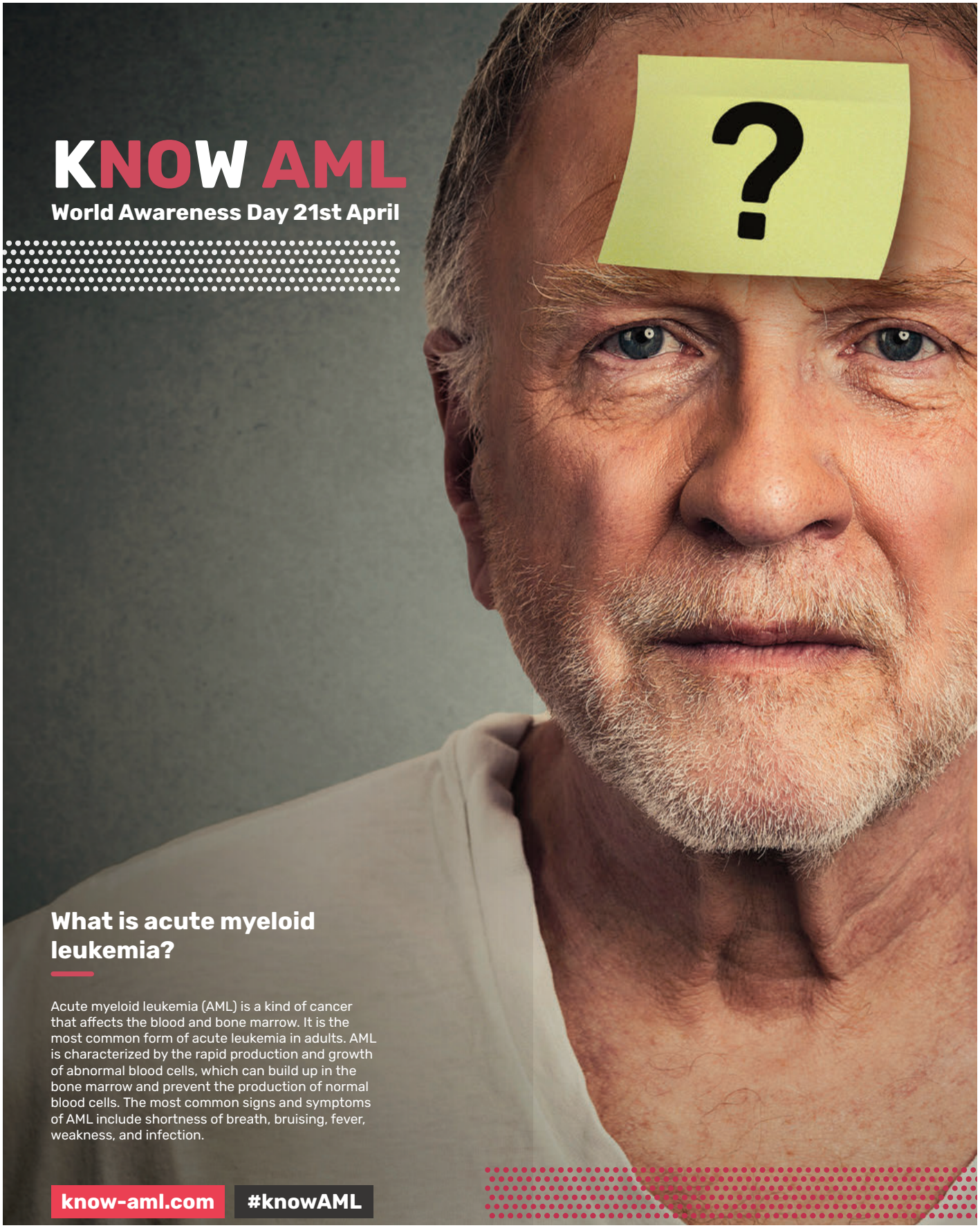
- Your site supports clinical trials
- Your site sees at least 2 suspected MDS or AML patients per quarter



- 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)

Celgene


KNOW AML
World Awareness Day 21st April
What is acute myeloid leukemia?
Acute myeloid leukemia (AML) is a kind of cancer that affects the blood and bone marrow. It is the most common form of acute leukemia in adults. AML is characterized by the rapid production and growth of abnormal blood cells, which can build up in the bone marrow and prevent the production of normal blood cells. The most common signs and symptoms of AML include shortness of breath, bruising, fever, weakness, and infection.
know-aml.com
#knowAML

MDS Update

Ron Cook
Worthington, Ohio

My battle with MDS began when I was diagnosed in the summer of 2011. In January 2012, I began to receive infusions of Vidaza seven times each month. In August of 2015, I wrote an article about my experience with the disease and its treatment. The article was published by the MDS Foundation in the Fall 2015 issue of The MDS News. This is a brief update on my fight against the disease.

My treatments with Vidaza continued until August 2016, when they were no longer effective. I received 414 infusions over the course of those treatments. The treatments had permitted me to continue most of my usual activities. In late 2015, I had cataract surgery on both eyes and, in May of 2016, a successful hip replacement. These surgeries were routine, except that I was required to undergo platelet transfusions before each surgery.

In August of 2016, I met with a bone marrow transplant surgeon at The James Cancer Hospital at The Ohio State University to whom I had been referred in the course of my treatments. We had previously discussed the possibility of receiving a stem cell transplant. Dr. Blum found three perfect matches for me and arranged for me to undergo an extensive battery of screening tests. He advised me that the success rate of transplants was about 35–40%.

I was admitted to the hospital on November 3, 2016, and began receiving chemotherapy. I knew only that my donor was a young German man, and I received the transplant on November 10.

I was in the hospital for a total of about thirty days. The hospital experience was less arduous than I expected. I was surprised to learn prior to entering the hospital that the actual transplant involved nothing more than a transfusion of stem cells. Nonetheless, the entire stay involved enduring a steady stream of

inconveniences and some periods of boredom, especially in the first two weeks. It also involved a restricted diet, developing unsteady hands (I was unable to write my name legibly), some degree of mental confusion and forgetfulness, and the loss of thirty-five pounds, more than one-sixth of my body weight. It also resulted in the loss of all my hair except, for unknown reasons, my mustache and eyebrows.

Now, almost 15 months after my transplant, I seem to be experiencing some acceleration in my recovery process.

My more substantial aggravations during the hospital stay included occasional nausea, complete loss of taste, loss of appetite, constant fatigue, and sleep difficulties. Among the revelations during my stay was that only one food always tasted exactly like it should: a fresh orange, which I therefore enjoyed daily. The staff gave me excellent attention and treatment throughout my stay and provided daily reports on my progress toward discharge. We live close to The James, and my wife was able to visit me twice each day. I also had as many visits as I felt strong enough to schedule with family and friends.

Upon my release from the hospital, I began the long recovery process (still not complete as of today). I began with twice weekly visits to the transplant clinic, with the interval between visits gradually increasing to weekly, then monthly, then approximately every three months. I was unprepared for the substantial fatigue I would experience and the extent to which I would be unable to resume many regular activities, often because of risk of infection. Gardening and working with my bonsai plants were the things I missed most. I was fortunate to experience very little graft versus host disease (some skin rash and upper GI tract problems), and I was able to avoid infections.

Now, almost fifteen months after my transplant, I seem to be experiencing some acceleration in my recovery process. I have a bit more energy every day. One result of the long period of little activity has been the development of a lack of flexibilty in my joints. I have now resumed daily stretching exercises and am playing tennis (although still at a slower pace) once a week. The slight depression and more pronounced attacks of anxiousness that I had been experiencing have ceased. I now look forward to gardening and tending my bonsai plants in the spring. At 73 years of

age, I have no idea how much of my prior strength, energy and flexibility will return to the levels I enjoyed before my transplant. I am hopeful, however.

Throughout this entire process, I had excellent help from my caregiver, my wife, Janice. She also kept family and friends well-informed as to my progress by frequent e-mails and postings on Facebook. She was aided to a significant extent by contacts she developed with other care-givers and caregiver groups. She was also able to share helpful advice with others.

About a year after the transplant, I was given another bone marrow biopsy and was delighted to learn that no trace of MDS could be found in my bone marrow. I am still described as "in remission," but another favorable report a year from now would provide an even higher comfort level that I have received something close to a cure. During the first few years after my diagnosis, I never dreamed that this was possible. Clearly my transplant and the necessary recovery period since then have been worthwhile.

Why Blood Counts Matter in Myelodysplastic Syndrome

This article was reprinted with the permission of Cure® magazine and Curetoday.com

by Leah Lawrence

When Rose Zumbiel was diagnosed with myelodysplastic syndrome at age 48, she was far from the average patient. Myelodysplastic syndrome, or MDS, tends to affect older individuals — average age at diagnosis: 71 — and occurs more often in men than women.

The condition can occur when stem cells in the bone marrow are damaged and may not properly mature into red blood cells that carry oxygen, white blood cells that fight infection or platelets that help blood to clot. In fact, until recently, MDS was sometimes called "preleukemia" because the disease can progress into acute leukemia.

Approximately 13,000 people in the United States are diagnosed with the disease each year.

"When I was diagnosed, they told me they did not even really have a name for what I had," Zumbiel, now 69, recalls. "It was known as a rare blood disease."

After beginning a regimen of low-dose aspirin to stave off heart disease, Zumbiel began to notice large bruises on her legs and thought the aspirin might be thinning her blood too much. Her family doctor ordered blood work, which came back normal. However, a second blood test several months later revealed a platelet count of 150,000 per microliter of blood, at the bottom of the accepted normal range of 150,000 to 400,000 per microliter. Eventually diagnosed with MDS by a hematologist, Zumbiel was left wondering how this happened to her.

EXAMINING LOW BLOOD COUNTS

"MDS is a result of damage to the DNA of the cells in the bone marrow. Those injuries accumulate during life," says David P. Steensma, M.D., an associate professor of medicine at Harvard Medical School in Boston. "A 70-year-old person has more DNA changes than a 40-year-old, and a 40-year-old has more than a teenager. They occur randomly whenever a cell divides and DNA is copied, just as randomly as when medieval scribes used to transcribe manuscripts and accidently put the wrong letter in the wrong place. Most of the time, those mistakes have no major consquence, but, if by random chance the DNA is written in the wrong place on the wrong day, it can cause quite a dramatic change in bone marrow behavior — just like certain letter changes may change the meaning of a word."

There are few clear risk factors for developing MDS, Steensma said. In addition to older age and male gender, prior treatment with chemotherapy or combination chemotherapy and radiation therapy may increase the likelihood of developing MDS, known as treatment-related MDS. Some evidence also indicates that genetic syndromes, smoking or environmental exposures, such as to the chemical benzene, can also increase risk.

Patients with low platelet counts (thrombocytopenia) might experience bruising, like Zumbiel did, or bleeding in the nose, gums or stool. According to Steensma, a low platelet count occurs in about one of every three cases of MDS and is the only dominant feature of the disease in 5 percent or fewer cases. "Low platelet counts are not a big problem until they get much lower, around 30,000 per microliter or below," Steensma says.

The most common symptom of MDS is a reduced level of red blood cells, or anemia, seen in 70 to 75 percent of cases, says Thomas Prebet, M.D., Ph.D., an associate professor of hematology at Yale Cancer Center in New Haven, Connecticut. Symptoms of anemia include shortness of breath, unusual paleness and fatigue.

"Low red blood cell counts with larger-than-average red cells, called macrocytic anemia, is one of the hallmarks of MDS," Prebet says. "More than two-thirds of patients with MDS will at one point of their disease require some transfusion of red blood cells."

Joan Powell, 64, has become familiar with fatigue and transfusions since her diagnosis of MDS in 2014. Always a go-getter, Powell started consistently experiencing extreme fatigue and weakness. Her sister urged her to visit a doctor and get blood work done. The results revealed anemia, and the physician told her to go to the emergency department right away because she required a transfusion.

Normal hemoglobin levels are above 12 grams per deciliter for women and 13.5 grams for men. "My count was five," Powell recalls. "I was in crisis mode. I was given three packs of blood, connected to a heart monitor and oxygen, and given a variety of tests. I was in the hospital for three days."

"In these cases, having anemia is like living with a backpack of 50 pounds on your shoulders each minute of life," Prebet says.

Powell's physicians ran a battery of tests in search of an explanation for her symptoms until they finally diagnosed her with MDS. "It was a shock to my world," Powell says. "They told me it was not curable — treatable but not curable."

Often, people with MDS have no symptoms and are diagnosed only after undergoing routine lab work. Sometimes diagnosis follows an infection in people found to have a low number of white blood cells called neutrophils, a condition called neutropenia, which increases risk of infection.

People with MDS may have issues with any one — or all three — of these types of blood counts.

TREATMENT FOR MDS

The only potential cure for MDS is stem cell transplantation. However, this often requires a high-intensity preparative conditioning regimen, which limits the number of people healthy enough to undergo the procedure. Transplantation can be done for patients who are under age 75, are otherwise healthy and have a matched donor.

Usually, people with MDS undergo treatments to reduce or manage symptoms, known as palliative or supportive treatments. The use of specific therapies often depends on whether the disease is classified as lower or higher risk. This is based on several characteristics found in the blood and bone marrow, including the number of immature cells (called blasts) and blood counts, as well as the results of studies looking for chromosomal and genetic abnormalities.

Usually, people with MDS undergo treatments to reduce or manage symptoms, known as palliative or supportive treatments. The use of specific therapies often depends on whether the disease is classified as lower or higher risk.

"If a patient has lower-risk MDS with a low risk to progression of leukemia, we think the disease will potentially have a long duration and evolution, and we try to focus on the management of the cytopenias (a reduction in the number of blood cells) and delay more aggressive treatments," Prebet says. "In higher-risk cases with a higher risk to progression of leukemia, we have to use active treatment more systematically and more quickly."

Although Zumbiel's platelet counts remained manageable for many years after her diagnosis, they eventually dropped below 30,000 per microliter, and her hematologist recommended a platelet transfusion.

"Unfortunately, the half-life of platelets is very short," explains Kebede H. Begna, M.D., an assistant professor of medicine at Mayo Clinic in Rochester, Minnesota. "Even newly synthesized platelets only usually survive about 14 days, meaning that individuals may require multiple transfusions."

Transfusions are often required in patients with low red blood cell counts, too. Powell calls the red blood cell transfusions she undergoes every 4 to 6 weeks her new normal. "My life has begun centering around MDS," she says.

For each transfusion, she travels to the hospital for an 8- to 9-hour outpatient procedure. The frequent visits have made her close with the staff and nurses and opened her eyes to the generosity of people who donated the blood that flows into her veins with each transfusion, she says.

Frequent transfusion carries several risks, however. "Platelet transfusions can cause allergic reactions, fever or hives," Steensma said. "Over time, recurrent platelet transfusion exposes the body again and again to foreign platelets and the body may start to form antibodies — that is

called being platelet refractory or alloimmunized." Alloimmunization can also occur in patients undergoing transfusions for red blood cells.

Patients who undergo multiple red blood cell transfusions per month also run the risk of developing iron overload, Prebet said. Excess iron can be stored in important organs such as the heart and liver and, down the road, impair function. Treatment for iron overload may depend on a person's life expectancy. In people with lower-risk disease, iron overload can be treated with removal of the blood, or phlebotomy.

This cannot be done in patients who are anemic. In addition, two FDA-approved iron chelators are commonly used for anemia related to MDS. Intravenous Desferal (deferoxamine) is given via a pump, often during nighttime rest. The second iron chelator Deferasirox comes in two tablet forms: Exjade, dissolved in juice or water once daily, or Jadenu, taken once daily on an empty stomach or with a light meal.

White blood cells cannot be transfused, though. "White blood cells' job is to recognize what is you and what is foreign, so if we put your white cells into me, they would be very confused and vice versa," Steensma says.

For low white blood cell counts, recombinant human granulocyte colony-stimulating factor or recombinant human granulocyte–macrophage colony-stimulating factor can be used to stimulate production of a patient's own white blood cells.

Low-intensity chemotherapy may also be given to patients with MDS in an attempt to change bone marrow cells so they produce normal red blood cells, white blood cells and platelets.

After undergoing a platelet transfusion, Zumbiel began receiving Vidaza (azacitidine), a low-intensity chemotherapy shown to increase survival and improve quality of life in patients with MDS. Six months of treatment brought her platelet count back up to about 57,000 per microliter. The two other FDA-approved chemotherapies used for MDS are Dacogen (decitabine) and Revlimid (lenalidomide).

In between transfusions, Powell takes a hematopoietic growth factor called Procrit. Hematopoietic growth factors promote growth and development of blood cells but are not always effective in people with MDS.

HOPEFUL FOR THE FUTURE

Despite the promising treatments being explored in oncology, it is difficult to know what the future holds for patients with MDS. "There have been some exciting new drugs in solid tumors, like immune checkpoint inhibitors, but those tend not to be as effective in MDS or leukemia, especially as single agents," Steensma says.

More work also needs to be done toward understanding the disease and identifying genetic mutations that might provide a target for treatment. "In MDS, there are more than 40 different genes that have been found to be mutated in the bone marrow, and no single gene is mutated in more than 20 percent of patients," Steensma says. "That is a real problem for designing targeted therapies, since no single drug is likely to work for a large proportion of patients."

Begna hopes to begin to more effectively harness next-generation sequencing — now used to classify patients and provide prognosis — to understand the characteristics of the different forms of leukemia cells associated with MDS.

Two drugs under study, sotatercept and luspatercept, trigger a hematologic response, improving red cell counts in about 60 percent of patients with mutations in the transforming growth factor–beta signaling pathway, according to Prebet. "It will not be used for all patients, but in patients with MDS harboring ring sideroblasts and/or an SF3B1 mutation, there is some real hope that this medication will have some efficacy," he says.

Like MDS treatments, Powell and Zumbiel both face uncertain futures.

Powell's disease is currently considered lower risk, and her experience has inspired her to become more active in the MDS community. She is involved with the Aplastic Anemia and MDS International Foundation's Patient Advisory Committee on Clinical Trials (PAACT+), which was designed to bring a patient voice to the industry and academic researchers focusing on rare bone marrow disorders.

"In this group, we are able to have well-rounded conversations with patients, caregivers, doctors, nurses and researchers to let people know that this disease exists [and] what it is like and to find out more about what they are doing to help us," Powell says.

After living for two decades with MDS, Zumbiel has begun to consider herself cured. Shortly after receiving definitive confirmation of her MDS diagnosis with chromosomal tests, her platelet counts began to recover, with her most recent counts upward of 180,000 per microliter.

She credits her physician and her prayers to Saint Padre Pio for her recovery. "I am always a mess when I go for my blood counts, but you have to just trust your doctors and pray that you are strong enough to get through it," Zumbiel said. "Whatever happens, you can take it!"

Out of the Blue

Suzanne Bloom
Palm Harbor, Florida

Officially diagnosed with Myelodysplastic Syndromes (MDS) in October 2011, I had never heard of it, couldn't spell it, and certainly didn't know what it was! Wow, things have changed since then.

First a little background: in 2008, my mammogram showed an area of concern. After biopsies and an MRI, I was diagnosed with simultaneous bilateral breast cancer, not a very common occurrence. After surgery, pathology results showed it was not in my lymph nodes so no radiation was needed. I had four rounds of chemo and reconstruction surgeries planned. I started the anti-estrogen drug Tamoxifen and struggled with the side effects while working. After chemo, my blood numbers struggled to reach normal. My breast cancer doctor, Dr. Jennifer Ball, who practices with Florida Cancer Specialists, found a cycling pattern in my platelets and white cells. There were peaks near normal and valleys well below normal. She cautioned a bone marrow biopsy may be needed one day.

I've been through breast cancer, chemo, multiple surgeries, and I'm still on the anti-estrogen drug Tamoxifen. I went through all this to save and continue my life! I was distraught, those pesky low white cells and low platelets are another cancer called MDS!

Three years later I complained often about tiredness and frequent illness. Having worked in the aerospace industry for 29 years, I had a high stress job as a manufacturing engineer. I worked on fun stuff: navigation and guidance systems for the Space Shuttle as well as various rockets and satellites. Often, I worked long hours plus I was overseeing my disabled mother's care until she passed in 2010. I thought, "Who wouldn't be tired?" By mid-2011 my numbers had been in a valley for 6 months. Dr. Ball said it was time for a bone marrow biopsy.

Dr. Ball carefully explained the report to my husband and me and said that I might have a bone marrow cancer called MDS. She explained about MDS and that its only cure was a bone marrow transplant (BMT). I was only in my middle 50s and remembered thinking, "I've been through breast cancer, chemo, multiple surgeries, and I'm still on the anti-estrogen drug Tamoxifen. I went through all this to save and continue my life!" I was distraught, those pesky low white cells and low platelets are another cancer called MDS! As a typical engineer, I went into full data collection mode. Within 24 hours I found the MDS Foundation in New Jersey and found much of the data I needed.

I was extremely lucky to find an MDS Center of Excellence only an hour from my home. After some additional research, I chose Dr. Alan List at Moffitt Cancer Center in Tampa. During my initial visit, he thought I had secondary MDS due to the timing following my breast cancer treatment. To be certain, he ordered more blood work and another bone marrow biopsy. A few weeks later, Dr. List confirmed that I had MDS but he determined that it was primary MDS, not secondary, and if I ever needed a BMT I would need a donor. Dr. List said I was in a "watch and wait mode" with no treatment required at that time.

Now, I had two oncologists. My white cells and platelets continued to decline and I was always tired. Also, I was constantly ill and out of work for weeks at a time. In 2012, I had another issue thought to be caused by the Tamoxifen. I had been warned that there was a 2% chance of this happening before I started this drug, but I didn't feel that I really had a choice. Surgery was required and this one scared me because of my low white cells and low platelets. My platelets were now down to 54K (normal is 140K–400K) and the surgeon warned me that I may need a transfusion during surgery; he didn't want me frightened if I saw a bag of blood when I woke up.

As it turned out, I was very lucky. I didn't need blood and, one week later, I learned the tumor and several cysts were all benign. By 2013, I was constantly seeing my primary physician, Dr. Robert Shobe, who encouraged me to think about early retirement. I hadn't planned on that. I liked my work and felt I was still too young. But my illnesses and fatigue continued, so I adjusted my schedule as much as possible to try to accommodate my situation.

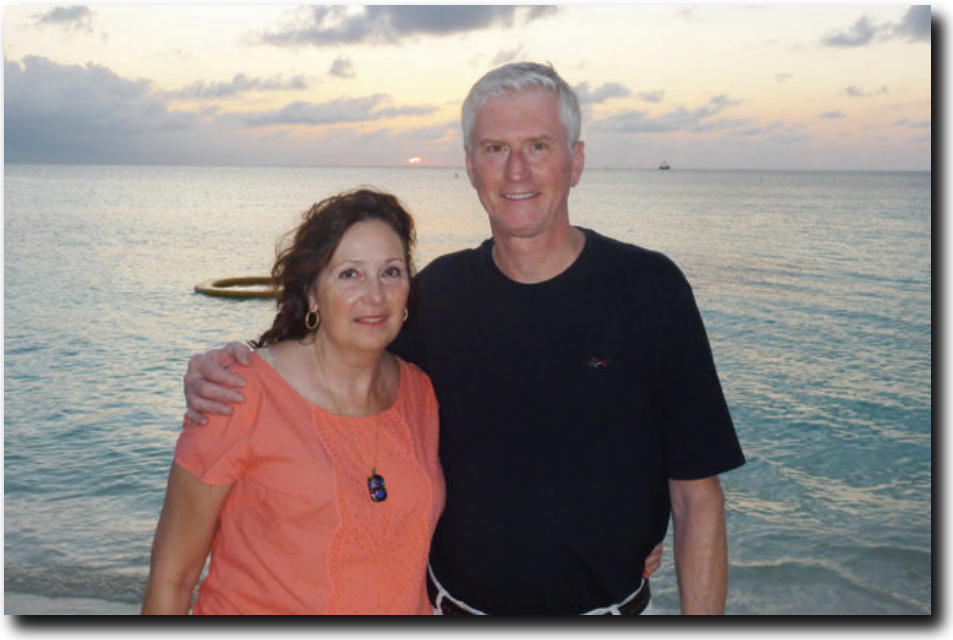
In May 2014, we were on vacation in Grand Cayman and I got really ill and required medical help. Thankfully, I got very good care. When I got home I saw Dr.

Shobe and Dr. Ball who ordered blood work and Neupogen shots that, unfortunately, failed to boost my white blood cell count. I returned to Dr. List earlier than originally scheduled. My blood numbers were again sliding and I really felt lousy. The time to leave work had arrived and the whole team was in agreement. I really did love my aerospace work, but I knew it was time to take care of me first.

Leaving work was the right decision. I can plan my activities to reduce my fatigue and try to limit my exposure to germy situations. My blood numbers since 2014 have continued to decline, but I am still in watch and wait mode. I have not yet needed a transfusion for low platelets (now in the 20K range), but even a potential tooth extraction puts me in jeopardy for a transfusion.

I am ever so grateful to my doctors and their staff for being part of my life:

- My internist, Dr. Robert Shobe and his staff at Diagnostic Clinic; he has been my excellent primary physician for about 28 years. He always has the right diagnosis and has been so caring. I had many emergency visits when I was ill. He completed all my absentee work forms for each illness episode those last few years in/out of work. He's still my first contact when I'm not feeling well.
- My local oncologist and hematologist Dr. Jennifer Ball at Florida Cancer Specialists and her staff treated and cured my breast cancer. She recognized the unusual cycling blood pattern after chemo and followed me extra closely. I always knew she had my back, and I was right. She still monitors me and does my monthly blood checks.
- My MDS specialist Dr. Alan List at Moffitt Cancer Center is a leading MDS researcher. He's an extra busy doctor having become President and CEO of Moffitt Cancer Center. I am very lucky to have his expert care and to have found a BMT center so close to my home. Every visit when I leave, he tells me "You know where I am if you need me."



I can't even begin to express my love and thankfulness to my wonderful husband Richard, who, after 35 years of marriage, has always been there for me, especially through the past several difficult years and as we are facing an uncertain future. We have no other family in Florida, but my younger sister Audrey, who lives in northern California, is ready and willing to be tested for a BMT match when the time is right.

Thank you to all my family, friends and neighbors who have been so very supportive along the way.

I encourage each cancer patient to make choices and decisions that are best for you and to be respectful of each individual's choices, as what is best for you may not be the best for another.

I'm a Stem Cell Transplant Survivor

MJ West
Santa Clarita, California

My name is MJ West and I want to share my story. First of all, I am a Stem Cell Transplant Survivor! Although my doctors think more time is needed, I know in my heart I am cured.

My journey started in 1998 when my General Practitioner (GP) noticed a trend in my blood work and referred me to a hematologist. After a bone marrow biopsy, it was determined that I had Myelodysplastic Syndromes (MDS) – Refractory Anemia. The hematologist checked up on me every few months, but we were in a 'watch and wait' period.

In 2003, 5 years later, I had to come home early from a camping trip because I was exhausted to the point I couldn't lift my arms and move my legs. I began Procrit shots to boost my RBC production. The doctor added Neupogen shots three times a week as a way to boost the effectiveness of the Procrit injections. When it was decided this treatment of Procrit and Neupogen wasn't working, I was changed to a treatment regimen of a 3-week dose of Aranesp every week. Through the years, I was put on Thalidomide (May 2005 through February 2007) and then Revlimid, beginning March 2007. The Revlimid did not help at all. My counts dropped every week in August so the doctor stopped Revlimid in September 2007 after 6 months. Thalidomide had worked so I didn't need the transfusions but left me with neuropathy. My only treatment option was the transfusions, which over the years became more and more frequent.

In 2005, my family suggested a second opinion, so I began seeing a doctor at the City of Hope. After several years of the same supportive treatments, in 2008, my City of Hope doctor began consideration for a transplant. They tested my five natural siblings and the tests showed I had

My 60th Birthday

2 perfect donors – my brothers. In the end, the City of Hope committee decided I should stay on the supportive treatments and not have the transplant.

The only supportive care I had since 2008 was blood transfusions. I was also taking Exjade to try to bring my ferritin levels down from the transfusions. The frequency of the transfusions was increasing to bi-weekly. In November 2016, I had a post-transplant reaction to a transfusion, which sent me to the hospital; my hemoglobin was down to 4. After hospitalization and several units of RBCs, my local doctor sent me to a transplant specialist at UCLA and after a bone marrow biopsy, I was told I needed a stem cell transplant. Because I had 2 possible donors, UCLA was able to expedite my transplant. Beginning in February 2017 and ending in March, I had Vidaza treatments to prepare for the transplant. The doctors were also concerned about my high ferritin levels because of the many transfusions I had.

Pre-transplant in hospital

I received my stem cell transplant from my brother on April 14, 2017. I had 10 days of low density chemotherapy prior to the transplant. I was not feeling well after the transplant, so we didn't celebrate. I expected that it would be anticlimactic, but I didn't think I would be sick. Four days after the transplant, I developed flash pulmonary edema and was placed in ICU. I literally could not breathe. My husband and daughter were there, and they were petrified. The nurses in the transplant ward helped them pack up my belongings and gave emotional support.

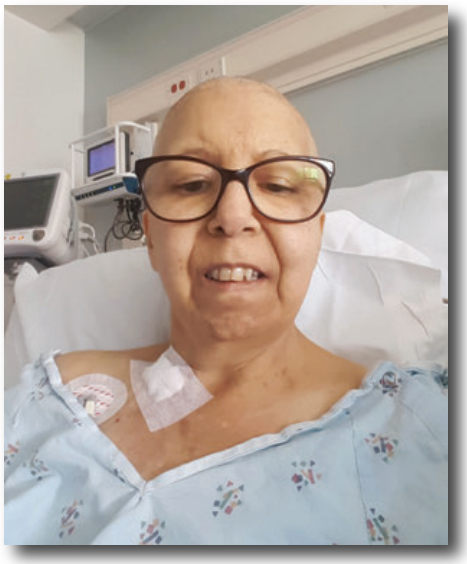
I was able to come back to the transplant ward after one night and a day in ICU. The transplant ward felt like home and the nurses and staff are so wonderful in their care. I continued to watch my counts go up and down until I could be released. In the end, I spent 43 days in the hospital, which was disappointing to me. I had my goal set for 30 days. I was released to a facility near UCLA called Tiverton House where my husband/caregiver and I stayed for 28 days. The joy I felt when I was able to feel the sun, take a walk in the neighborhood, and eat something I wanted was invigorating. I still relish those freedoms.

Since the transplant and being released from the hospital in May, I have had to be readmitted to the UCLA hospital 6 times.

- The first trip was an overnight stay at the end of May to treat my high potassium level.
- In July, I was suffering from headaches and my doctor had ordered a CAT scan, which showed a subdermal hematoma and I had also developed C DIFF (Clostridium Difficile), which is a bacterial infection. I fell my first day at Tiverton House, but I didn't tell my doctor until the headaches began in July.

- In September, I developed sepsis and was hospitalized for 5 days for antibiotic treatment. I was readmitted within 4 days for another round of antibiotics specifically targeted to the bacteria type. The doctors had found the infection started at my PICC line, which was removed. Thank goodness, I had a power port catheter that is now accessed for treatments and blood draws. My husband learned how to give me the Bactrim infusions, which I endured twice a day for over a month.
- In early October, I was still complaining of headaches, so the doctors admitted me for 2 days for treatment for hyponatremia (low sodium) for observation and another CAT scan.
- I was readmitted the first week of December for suspected graft vs. host disease (GVHD) because of abdominal pain and diarrhea. This was emotional for me because I had read that approximately 50% of transplant patients don't get GVHD and I wanted to be in the 'other 50%'. They were not able to have an endoscopy or colonoscopy at the time because my platelets were too low. I just was able to have the scopes completed in early February and I found out it was not GVHD. This is fabulous news because I want to wean off the steroids and stop being insulin-dependent.

Thanksgiving with my 2 brothers and my daughter



April 23, 2017 post transplant day 9 no hair

I include these re-admissions in my story because you can't let the setbacks get you down. You will eventually get to your goal of being a survivor, but your body has its own timeframe for recovery.

1. Since the transplant, I have received numerous transfusions of red blood cells and platelets until my body began producing its own. Although you may think you will not need any more transfusions, it takes a while, especially getting the platelets up to where they need to be.
2. Don't compare yourself to a standard. I had it in my head that I would be out of the hospital in 30 days. I did everything the doctors said to do. I walked around the ward and kept track of my laps. I continued to walk at Tiverton House and around our neighborhood once I got home. I rode an emotional roller coaster after Day 30 as my husband and I watched the counts every day. That's 13 days of stress I shouldn't have put on myself.
3. One of my goals was to get my weight up to 100. There were times I did not feel like eating but I tried to eat 4-6 small meals a day. My husband has been wonderful satisfying my food cravings. My lowest weight was 83 lbs. and I am now in the low 90 range.
4. My goal had been to go back to work full-time from home on January 3, 2018. When I was in the hospital in early December, I was sure I wouldn't make my goal. However, something changed around the end of 2017 and I began feeling stronger and more like my former self. I couldn't wait to go back to work. My husband said at this time I started looking and acting as a survivor, not like a patient. I had my old confidence and I was walking more confidently. Our friends and the medical staff, remarked similarly. The biggest accomplishment for me was meeting this goal. I have a sense of normalcy and purpose.
5. It takes a team to care for a stem cell transplant patient/survivor. My team includes a heart doctor, an infectious disease specialist, a liver specialist, neurologists, a GI doctor and an endocrinologist. It helps that they are at UCLA and the other specialists work with the transplant doctor and her team for the best patient care.

I was asked to write a story in 2009 for a friend's daughter for one of her classes. What I wrote about was the feeling of guilt that our life had become a 'new normal' that solely revolved around me and how I physically felt that day. I felt guilty for the roller coaster emotional state that may have put fear in my daughter and causing her to grow up too quickly. I began to see a psychologist who specialized in treating people with long-term illness. In 2017, because of the transplant, I learned many lessons, for example, to be patient, be a good patient to your caregivers, be grateful, appreciate the little things and find joy every day. I have always believed there are always others who are not doing as well as you are and give back to others. That is why I want to help other patients who have MDS, patients who are contemplating a stem cell transplant, or others in the watch and wait phase. I am looking forward to creating my 'new normal' as it evolves. Now is my time to give back for the gifts that I received.

My Mother's MDS... A Daughter's Perspective

Deborah Peirce
Concord, MA

Jackson Family Photo

One of the first signs we noticed something was not right with my mother, Patrica Ewing Jackson (1935–2007), came 10 years before her passing during a trip she and my father took to the Galapagos Islands where she was biking around the Island with a travel group. She fell off her bike unfortunately, and soon after, her body was covered in bruises. Enormously large and ghastly bruises, ones which I've never seen the likes of...

I'm the daughter of a MDS patient, and my story is about the transformative influence my mother's MDS continues to have on me.

You'll perhaps need to re-adjust your expectations of "how to take care" of a deeply cherished mother who was diagnosed with an unknown, life-threatening, rare blood disease — which MDS was to my family and me at the time of her diagnosis. You see, my mother married an adventurer — my father, already a licensed pilot, became a sailor after deciding to build a 41-foot sail boat with three other men and sail it from Hong Kong to Miami, FL (26,000 mile journey of high seas). As captured in the book, the Voyage of the Suzy Wong, the crew moored at many foreign ports during their two year adventure (1960–62), including a very important stop near the end of their trip in Barbados, where my father met my mother who was on the beach in a yellow swim suit, one of the few colors my father could see given his color blindness. Their wedding day occurred one year later, and I was born two years after that.

My parents volunteered together during their retirement years in Nanjing, China (1994–1999). My mother taught English, and my father taught business at Nanjing, University. My mother, a poly-sci graduate from Northwestern University, became an ESL teacher in the public schools in the Chicago area after raising me and my brother.

While living in China, my mother first was diagnosed with pancytopenia with bruising (1997–98), even though her blast cells already were high (20–25%). The first mention of MDS came to us in 1999, when she had her first bone marrow extract, and she was diagnosed with Refractory Anemia Excess Blasts (MDS RAEB). She just had become a grandmother with the birth of our first born daughter, Morgan. My mother's MDS started to accelerate in 2000–02 when several referring hematologist saw "features of AML" when her ANC went to 0.2; in fact, she was diagnosed with hypocellular AML. During this time, she consulted with four University Hospitals in Chicago who all advised induction chemotherapy with possible allogenic bone marrow transplant once in remission. She was 67 years old, and grandmother to four children by 2002.

In 2003, she began to rapidly decline with progressive thrombocytopenia. Her platelets dropped lower every month that passed (173K, 89K, 59K, 38K). She was on Aranesp to increase her red blood cell production. She had frequent fevers and was diagnosed with a serious fungal lung infection, blastomycosis. The doctors warned us that unless she responded to the antibiotics, her life would end. It's during this diagnosis period when events took on a transformative quality in my life. I was offered a three-year expatriate assignment to work in Beijing, China thus putting me in a position to make a decision to move from Chicago with our two daughters. How could I leave my mother at the time she needed me the most, and take far away her two granddaughters who were the lights of her life?

We think patients have nothing to give as they struggle to hold onto their own life as we care and support them. My mother told me to go to China; and I did, not knowing what would happen to her, and fearing the worst with her blastomycosis.

My mother, Patricia Ewing Jackson

The crisis moment in 2003 was not the end of my mother's life, fortunately; even though her platelet count was at 28K. She went on Azacitidine (FDA approved in 2004), but was in-and-out of the hospital constantly to treat low-grade fevers, ear infections, and pneumonia. In 2005, she was diagnosed with AML and neutropenia after a "5 year history of MDS". Her fourth bone marrow extract revealed her ANC level 0.2, 31% blasts, and 26K platelets. She was receiving monthly blood transfusions. She was living on nothing except her faith, her spirit, and…waiting for my return home to Chicago.

My mother managed to overcome her fevers and infections each time; but, she lived life in much isolation for fear of catching a cold, or other infections. She fought hard to stay alive until I returned home from my assignment abroad.

My mother gave me the gift of life as her own was coming to an end. She continued to support and be generous, actually generative, to my daughters and me until the very end. Her generativity

My daughters and me today.

fueled a desire in me to be an advocate for all patients, and a supporter of MDS patients specifically. Soon after my expatriate assignment in Beijing ended, I left the high-tech industry after 12 years, and applied my expertise in Human Resources to the healthcare industry. I eventually took on a new role in area of advocacy for a biotech company focused on rare diseases. This new role brought me to Cambridge, MA in 2016 where I worked directly with oncology focused patient organizations. Today, I am privileged to sit on the Development Board for the MDS Foundation where we are focused on fundraising to support the MDSF mission.

Despite my departure to China in 2003, my daughter and I were remarkably at my mother's bedside when she passed away in May 2007. We had almost a full year together in Chicago, and I was able to support her during the last months of her life sitting by her side during her monthly (and then, bi-weekly) blood transfusions; taking her to her doctor appointments, accompanying her for the bone marrow extractions.

During the heightened moments before her passing, the words that sprung from my lips were, "Thank you Mom. You have given me all that I need to stand on my own." After I whispered these words, she took her last breathe.

WHY DONATE TO THE MDS FOUNDATION?

Why do I donate? To be inspired… To Inspire…To encourage… To be encouraged… To help… Get help… Give help

These are the automatic thoughts that flowed through my mind as I reflected on the query why I donate to the MDS Foundation.

The French verb donner means to give which is an act of openness, an act from the heart. "Give and get back", the saying goes. What motivates me to give to the MDS Foundation? And what do I get back from giving?

Giving to the MDS Foundation is a 360° act. By giving, I inspire, my gift nudges others to do so too. By giving, I inspire those who are connected to the MDS Foundation to pursue their goals, to discover the cure, to continue their outreach efforts. By giving, I personally feel inspired.

By giving, I am encouraging those connected to the MDS Foundation to go forth with courage, to go in strength, to persist. For the MDS patient, my donation encourages her to persist in living a full life, knowing that there is hope for a future cure. For those responsible for the Foundation, my gift encourages them to further develop their programming, to extend their outreach network, to persist in their belief that what they do every day is worthy and valuable and needed. For the medical component of the Foundation, my gift encourages their work, their research, their pursuit of a deeper understanding of the disease.

By giving, I am providing help for those who need help, the MDS patients and their families, the Foundation itself. By giving, I am asking for help; I am asking the MDS Foundation to help find a cure, to help the MDS patients find the strength to go another day, to help the scientists, doctors, nurse practitioners do more to discover and create medical interventions.

I give to the MDS Foundation with openness, I give from the heart. In my heart, I know that I give because the MDS Foundation inspires me to help and to encourage MDS patients and their families. By giving, I am saying thank you for all that you do.

Rochelle Ostroff-Weinberg

Celebrating the Program's 5th Year Milestone: Honoring Bob Weinberg's Legacy

The MDS Family: Coping and Caring Event

Rochelle Ostroff-Weinberg
Wynnewood, Pennsylvania

Coping and Caring Luncheon October 28, 2017

MDS patients and their families gathered at Roy's Restaurant in Baltimore, Maryland for a wonderful luncheon on October 28th, 2017.

Thank you to Rochelle Weinberg for hosting a lovely Coping & Caring Luncheon for MDS patients and families!

We hope you will join us at our next gathering on Saturday, April 28th, 2018, 1–4 pm at the White Dog Café in Philadelphia.

Kindly register by April 20th by calling 1-800-637-0839 Ext. 210 or email ahassan@mds-foundation.org.

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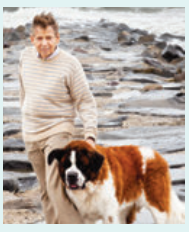

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Honor or memorialize your loved one at: www.mds.foundation.org/donate or contact us at 800-MDS-0839 (within US), 609-298-1035 (Outside US).

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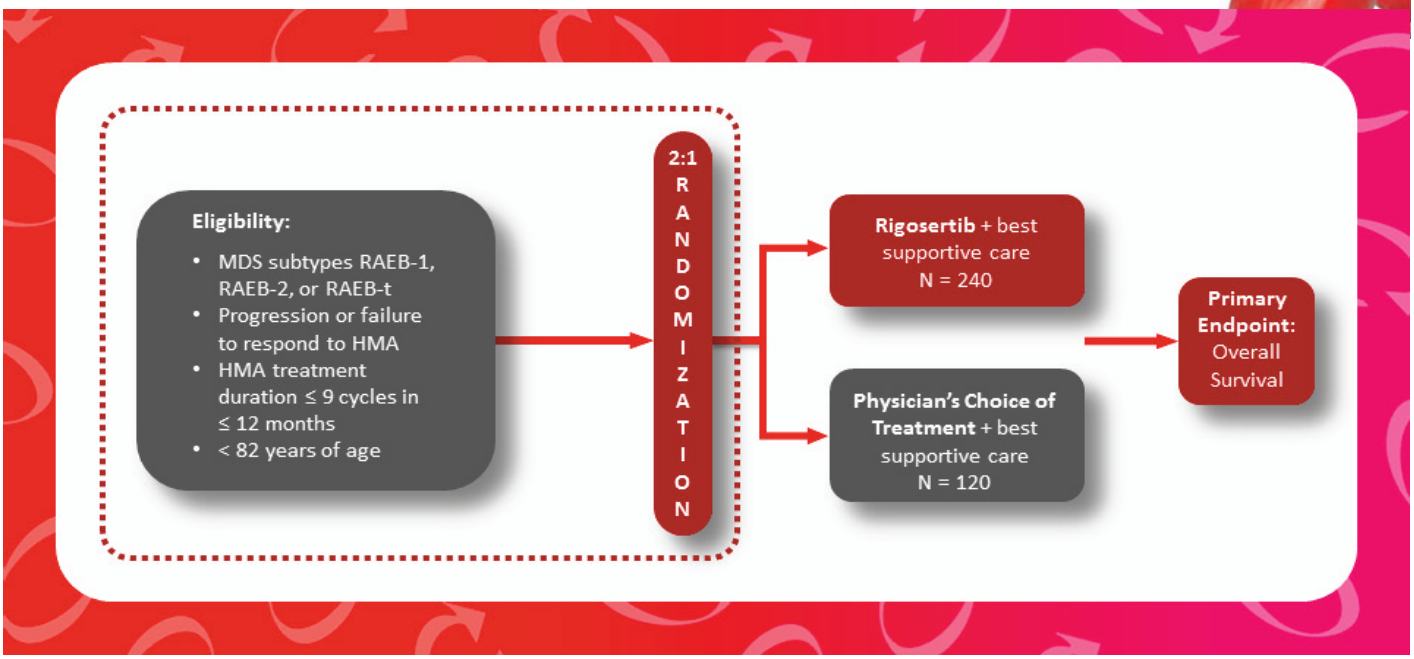
The Pivotal MDS Trial INSPIRE is Now Recruiting Patients

INternational Study of Phase III Intravenous RigosErtib

STUDY DESCRIPTION

A Phase 3, 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).



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 170 trial sites

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

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

ONCONOVA THERAPEUTICS

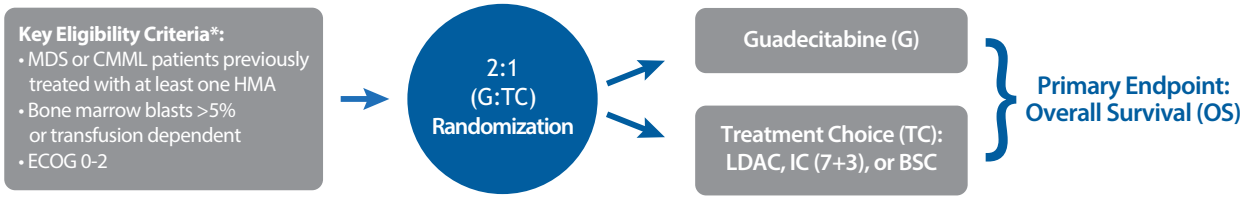
www.onconova.com

Phase 3 Clinical Trials **NOW ENROLLING**

Guadecitabine (SGI-110) in MDS or CMML

ASTRAL-3
Relapsed/Refractory MDS or CMML

408-Patient Multicenter, Randomized, Open-Label Study in Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) After Failure of Prior Azacitidine, Decitabine, or both

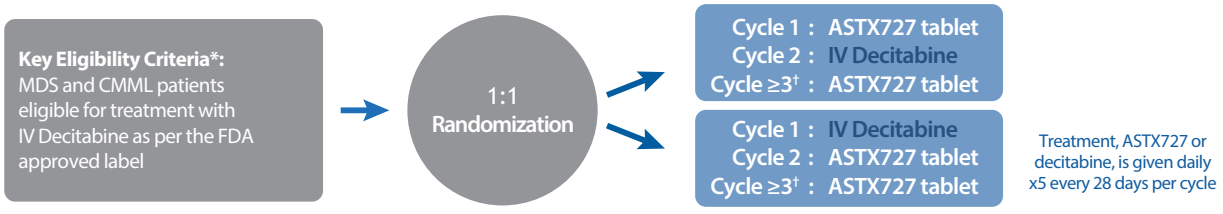


For more information: www.clinicaltrials.gov identifier: NCT02907359 or email: ASTRAL-3@astx.com

Oral ASTX727 in MDS and CMML (US and Canada)

Ascertain
MDS and CMML

A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)



For more information: www.clinicaltrials.gov identifier: NCT03306264 or email: Ascertain-1@astx.com

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A member of the Otsuka group

*For a full list of eligibility requirements go to clinicaltrials.gov
LDAC - low-dose cytarabine; BSC - best supportive care;
IC (7+3) - intensive chemotherapy (cytarabine/anthracycline)
† Continued dosing with ASTX727 until disease progression, unacceptable toxicity, subject discontinues treatment, or subject withdraws from study

www.astx.com March 2018 18ASTX-AD18(104)

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 myelogeneous 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 azacitidne 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

Takeda ONCOLOGY

PANTHER

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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MYELODYSPLASTIC SYNDROMES

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8-11 MAY 2019

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