

MDS NEWS HIGHLIGHTS

FROM THE GUEST EDITOR'S DESK

■ THE 15TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES: AN OVERVIEW

Presented by: Drs. Lars Kjeldsen, Kirsten Grønbaek, Jakob Werner Hansen
Rigshospitalet National University Hospital, Copenhagen, Denmark



PLAN TO ATTEND



ASH 2019 MDS FOUNDATION BREAKFAST SYMPOSIUM

DECEMBER 6, 2019
Orlando, Florida



2ND REGIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

MARCH 5-6, 2020
Tel Aviv, Israel

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GUEST EDITORIAL

THE 15TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES: AN OVERVIEW



DRS. LARS KJELDEN, KIRSTEN GRØNBÆK and JAKOB WERNER HANSEN
The Symposium Chairs

The team behind the 15th International MDS Symposium had been preparing this meeting for almost two years, and were eager to kick off four scientific days focusing on MDS. The meeting started with three different well-attended workshops focused on nursing, basic science and clinical aspects of MDS, in order to reach out to the participants and give them an opportunity to stimulate their interest and to improve their knowledge in the field. The clinical management of MDS is an important topic, in a disease where the number of available drugs are few, but where numerous drug combinations and treatment strategies are possible; thus the clinical debates had a special focus at the symposium. Meanwhile, important advancements are currently emerging in preclinical models and complex data analyses with the use of whole genome sequencing and transcriptomics; all topics that were covered in the basic science workshop. Since MDS preclinical in vivo models are in high demand by the MDS scientific community, we included a special session on the development of patient derived xenografts (PDX) and their potential for improving our understanding of disease biology and treatment. The third workshop was for nurses, who play a pivotal role in the care of patients with MDS, many of whom are elderly and have comorbidities. This

workshop also gave the opportunity to establish an international community for nurses working with patients with MDS.

After the workshops, the opening ceremony took place with Dr. Stephen Nimer introducing the MDS Foundation and the invited speaker Benjamin Ebert, who gave a brilliant talk with the title "The Origins and Evolution of MDS". The entertainment was performed by the Danish magician Rune Klan, who took us on a trip back to the time of the Rubik's cube, even though his knowledge about MDS was – let us say – minimal. The day ended with a reception and a birthday song and cake for the MDS Foundation which has now existed for 25 years – CONGRATULATIONS!

Thursday and Friday were both scientific days, and in order to attract special attention to the submitted abstracts, the program consisted of both invited speakers and best oral presentation abstracts combined in the same sessions. We think this gave a synergistic effect and a lot of really interesting abstracts had been submitted. These contributions made the meeting varied and stimulating, with excellent presentations of the most recent and yet unpublished research in the field. Thus, we really appreciated that the delegates prioritized to submit and present their work at the international MDS Symposium – Thank you!

On Friday, a vivid panel debate with clinical cases took place, where the Chair, Dr. Moshe Mittleman, together with the panel did a great job making the session interactive and entertaining, and the audience – some more than others – also participated in the debate. Let's see if the clinical debate will reappear in Toronto in 2021! On Friday evening, we had the social event at Axelborg just next to Tivoli in central Copenhagen: The dinner was terrific, and we enjoyed the outstanding dancing skills of the MDS community – Just two minutes after the music started playing the dance floor was overcrowded.

Saturday started with a CMML session and then moved on to the Tito Bastianello Young Investigator Award, which was given to four promising researchers within the field of MDS. In addition, two young investigators awards were awarded to promising young researchers. It is important to encourage young investigators to continue their research within the field and bring the community forward, so we are delighted that these awards are possible, thanks to the MDS Foundation and the Bastianello family.

The last talk was given by Dr. David Steensma, who gave an impressive talk with the title "Bridging the canyon between discovery and therapy", where he summed up the improvements to date, but also pointed out some of the difficulties we face within the field of MDS. All of us are hoping for new treatments which will help our patients, as they are the reason why we were all together in Copenhagen in 2019.

Thank you all for coming to Copenhagen and especially thanks to the MDS Foundation for choosing Copenhagen and for the great effort you put into making the MDS Symposium 2019 a fantastic meeting! We are looking forward to the next meeting in Toronto in 2021. We are sure that Drs. Karen Yee and Rena Buckstein together with the MDS Foundation team will prepare an outstanding meeting.

MEETING HIGHLIGHTS AND ANNOUNCEMENTS

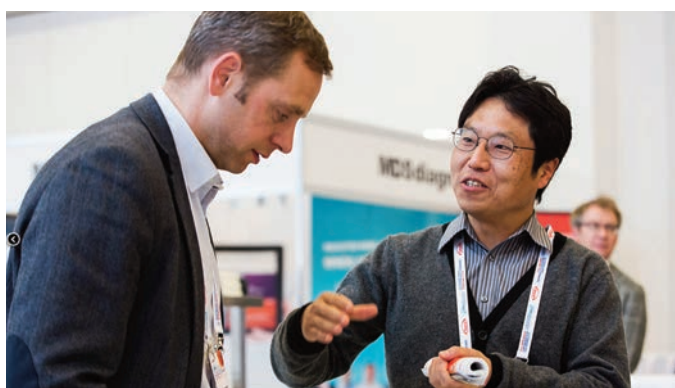
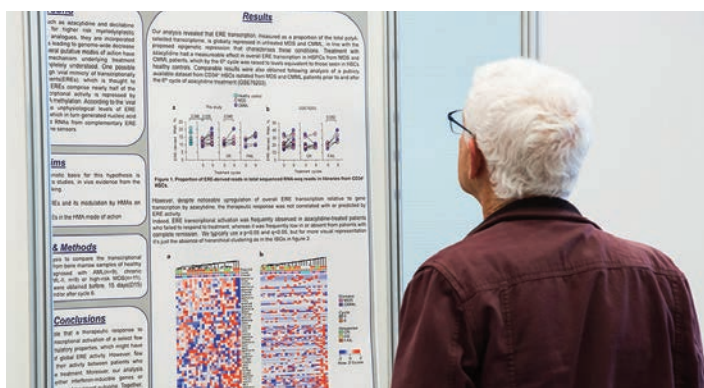
15TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES



**HIGHLIGHTS FROM THE
15TH INTERNATIONAL SYMPOSIUM
ON MYELODYSPLASTIC SYNDROMES**
May 8–11, 2019 • Copenhagen, Denmark



15TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES



VIEW SYMPOSIUM WEBCASTS HERE:
<https://www.mds-foundation.org/professional-learning-center/#Non-CME-CE-Programs>

THE CANYON BETWEEN DIAGNOSIS AND THERAPY IN MDS

BERGIT KORSCHAN-KUHLE

*LHRM-MDS-Pat-IG, Germany,
MDS-Alliance*

Having lived with Myelodysplastic Syndromes (MDS) for more than 13 years now, it seems unbelievable and fascinating to me how much progress has been made since 2005. In particular, the advances in the diagnosis of MDS achieved by the growing understanding of disease-related pathobiology, molecular genetics, and the processes of cell division and cell metabolism are very promising. Yet, MDS represent an extremely heterogeneous and dynamic group of diseases. This means there are many subgroups which may behave differently over time, some moving slowly, others behaving more aggressively. More and urgent research is needed to find targeted therapies. Lesson to learn: most probably there never will be the one and only cure for MDS, but personalized medicine with drugs dependent on the individually impaired genetic profiles. In Copenhagen, world renowned MDS scientists and clinicians from all over the world presented their highly acclaimed findings in these key areas.

I am not a physician, nor a geneticist or graduated biochemist. All those degrees would enable me to better understand the data presented at conferences about MDS than I currently do. In fact, I have been attending MDS congresses for many years, but still I need to google many acronyms, and after conferences I usually need to ask experts to translate relevant biochemical mechanisms, processes, and their interrelationships into more lay language. The more the researchers focus on the microcosm of the cell, including the world of proteins, the building blocks of the DNA and, into molecular signaling pathways, the more complex and complicated it becomes to understand my disease. Amateurish knowledge does not lead me



anywhere. I must abandon my inherent principle to base criticism and making demands on a full understanding of the disease. I am aware that I will rant without capturing the full disease landscape. On the other hand, I can rely on a sufficient overview of knowledge to assess the situation for MDS patients.

At the 15th International Symposium on MDS in Copenhagen in May 2019, slight optimism was spread by top-level speakers that the valuable insight into, and the increasing knowledge about the origin of the disease, will lead to targeted therapies soon. Speakers expressly emphasized the availability of top qualified young innovative researchers and the fruitful collaboration between researchers and clinicians across the globe. They confirmed there is funding for research and that new regulations for clinical trials will hopefully allow for inclusion of patients into these trials (e.g. inclusion criteria for patients' recruitment). Eight drugs have been approved for AML (Acute Myeloid Leukemia) in 2017-2018, which is seen as an encouragement for MDS research and potential drug development.

However, this optimism must be tempered by understanding the amount of time required to bring a new drug to market where patients not involved in clinical trials have access. We patients know it takes a long way from bench to bedside and most of the MDS patients have only little time to wait for another 10 years.

Physicians and patients are impatiently waiting for some major breakthrough, whereas researchers who work hard on different therapy approaches are still struggling with so many questions. Currently there is nothing more than hope. Hope is not a category that scientists report in their work. Rather, they report evidence-based data, response rates of drugs, percentage of overall survival, and patient-relevant endpoints. But there is no new MDS drug to report on.

The European Medicines Agency (EMA) has approved four drugs tackling MDS in one way or the other since 2006. Azacitidine (Aza) for high risk MDS-patients, was approved in 2008: 11 years ago! Besides Aza there is a similar compound called Decitabine, not yet approved by EMA, but by FDA and in EU countries administered in case Aza is failing. Azacitidine has a response rate of 40–47% and statistically an overall survival benefit of nine months. Revlimid (Lenalidomide) is a third option approved in some countries for MDS with del5q. Unfortunately, less than 15% of patients with MDS fit these criteria and if there are additional mutations, particularly TP53, this drug is of limited benefit.

Professor J.P Issa from the Coriell Institute for Medical Research in New Jersey called his talk "What's after AZA?" Most effectively, he presented a white, empty slide: "Nothing so far", he confirmed. In fact, he afterwards continued by enumerating several combination-therapies with Aza plus compound x being tested in Phase 1 or 2 clinical studies or located in the pipeline of the pharmaceutical industry. These combination drugs aim to reactivate or enhance Aza at the time of Aza failure. As it has turned out, many of the combination therapies in Phase 1 or 2 clinical trials have increased toxicities with low to moderate response rates. Among these approaches is a combination with AZA and Vitamin C which, in some cases, has shown an increase in effectiveness of Azacitidine.

Prof. David P. Steensma from the Dana-Farber Cancer Institute in Boston, MA, was one of the last speakers of the congress. He named his scientific talk "Bridging the Canyon between Discovery and Therapy", my column is referring to this title. As an introductory sentence, he asked himself, whether — after Copenhagen — he would treat MDS-patients differently as before? His answer was "No!" He topped that by describing MDS treating techniques and therapies as not having changed for many years. Although the molecular science of the disease has advanced significantly, this has not led to new drug approvals. In addition, he mentioned drowning in bureaucracy and red tape, it usually takes many months to open a full protocol so that patients can participate in a clinical trial. Yet, all currently available drugs are derived from clinical trials and continuing patient enrollment in these trials will be necessary to find new drugs.

I don't have to be a scientist to understand the extent of barriers to hope. One decisive improvement could be to involve patients/patient advocates into research and development. Patients are experts in patients' needs and could put pressure on drug development in the right and meaningful direction.

Apart from the disappointing outcomes concerning new treatments for MDS patients, it was a great congress. The organization of the MDS Foundation was brilliant and additionally a good platform for networking. I definitely expanded my horizon from the excellent talks of the speakers.

MUCH NEW KNOWLEDGE BUT NO NEW DRUGS

NIELS JENSEN
Slangerup

Every two years, the MDS Foundation holds an international symposium where doctors and researchers who work to improve the opportunities for patients with MDS meet for 2½ days to present the latest research results and discuss the diagnosis and treatment of the disease under the heading "Advancing Research and Patient Care". The symposium was announced with pictures of Copenhagen, but during the 2½ days there was not much time to see Copenhagen, despite the fact that one of the main forces of the Danish organization committee chief physician Kirsten Grønbaek from the Clinic for Blood Diseases at Rigshospitalet in the opening speech strongly urged the foreign guests to have a look at Copenhagen and North Zealand and pointing at a dozen places, which you definitely needed to see before traveling home.

The symposium was opened on Wednesday evening with a welcome speech by chief physician Kirsten Grønbaek and a keynote lecture entitled "The origins and evolution of MDS" by Dr. Benjamin Ebert, professor at Harvard Medical School. This lecture, together with all the other presentations at the symposium, is available as video on the MDS Foundation's website www.mds-foundation.org.

IMPORTANT NOTE: *The following is an MDS patient's reflections on participating in the symposium and may contain misunderstandings and expressions not medically correct. I am not a doctor, just a patient attempting to understand the disease better.*

The official program had lectures on Thursday from 8 am to 5 pm, Friday again from 8 am to 5:30 pm and Saturday from again from 8 am until noon. Every day was half an hour with the expert (Meet the Expert) within different specialties before



the official programme. Thursday morning, I heard Dr. Casey O'Connell talk about clinical experience with immune checkpoint inhibitors, and on Friday morning I heard Dr. Brigitte Schlegelberger talk about "Genetic counseling in MDS - What do I tell my patient?". Dr. Casey O'Connell gave an overview of which drugs were tested and examples of treatment with these drugs giving longer periods of stable disease yet failing to meet the criteria of the international working group. Dr. Brigitte Schlegelberger dealt with the dilemma of using the latest gene sequencing technology, where the result can tell about hereditary predisposition to various serious diseases, but not say anything about whether the patient will develop the disease in question at all.

A review of all twelve sessions will be long and probably boring for most readers, so I just want to tell you about lectures that I found particularly interesting, and otherwise refer to the videos on the MDS Foundation website.

BRIDGE BETWEEN DISCOVERY AND TREATMENT

As part of Saturday's program, Dr. David Steensma from Harvard Medical School, gave a keynote titled "Bridging the Canyon between Discovery and Therapy", in which he talked about the progress made in understanding the MDS disease, without any progress in the treatment of the disease. In fact, we need to go back to

2007 to find the latest approved treatment for MDS. Within the related disease AML, four new drugs were approved in 2018. However, there is some hope that the drug Luspatercept will be approved for the treatment of low risk MDS this year.

MDS Alliance had patient representatives from the United States, Denmark, France, Germany and Great Britain at MDS 2019, and MDS Alliance also had a booth there to inform participating doctors about our local organization in their countries.

EVEN THE MDS EXPERTS DISAGREE ON THE CHOICE OF TREATMENT

Friday afternoon, a panel of MDS experts was confronted with real-life patient cases from Aarhus University Hospital, Odense University Hospital and Rigshospitalet with information served as the treating doctors got them along the way during the course of the disease. The participating experts were Dr. Aristotle Giagounidis (Germany), Dr. David Bowen (UK), Dr. David Steensma (USA), Dr. Eva Hellström-Lindberg (Sweden), John Bennett (USA) and the moderator Dr. Moshe Mittelman (Israel). The individual patient cases were presented to the panel by doctors from the Danish hospital involved, and then the panel had to decide what the next step in the treatment of that patient should be.

It became an extremely instructive one and a half hour when, as a patient representative, my eyes were opened to see that the decision as to which treatment a given patient should have was not as black and white as one believed. There were many shades of gray. And often there was a great deal of disagreement among the members of the expert panel. It was really felt that the MDS experts dealt with the information as it was their own patients. And the conclusion was that MDS patients were not treated the same way in Boston, Leeds and Stockholm.

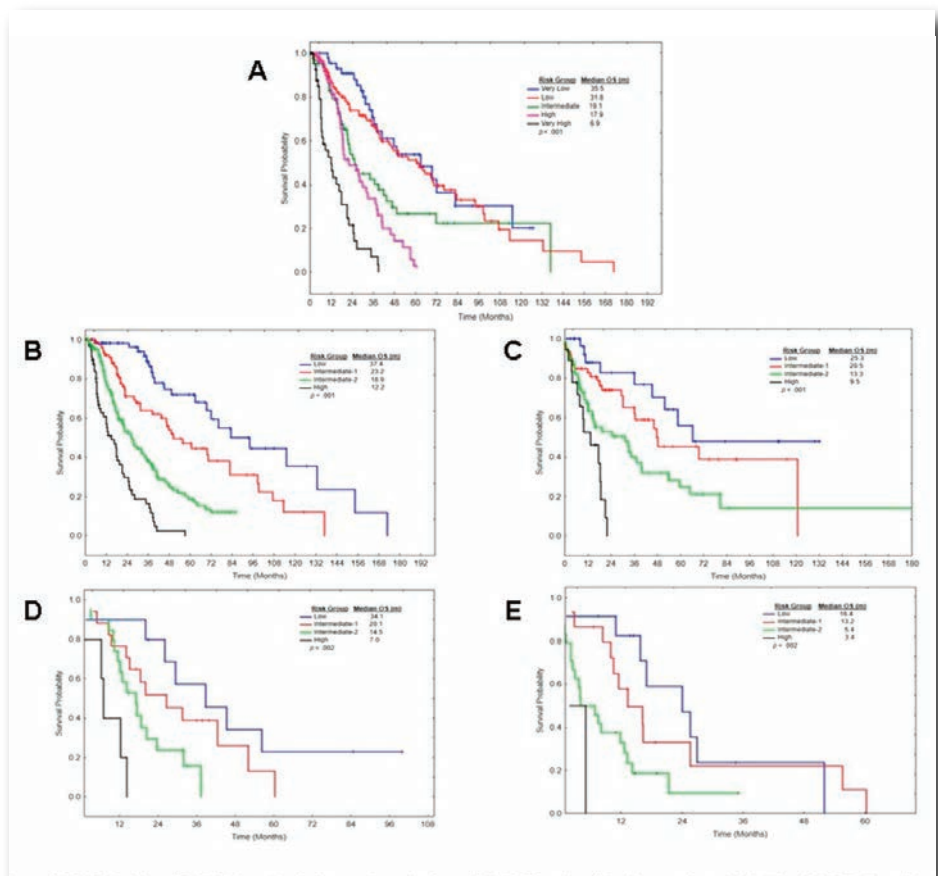
NEW PROGNOSTIC SCORING SYSTEM ON THE WAY

First, MDS doctors got IPSS – International Prognostic Scoring System. It was back in 1997. It contained four forecast levels: low, intermediate-1, intermediate-2 and high, and was used for more than ten years. Then in 2012 came IPSS-R. It contained five prognostic levels: very low, low, intermediate, high and very high, and was based on the cytogenetic category, percent blasts in the bone marrow, hemoglobin level, platelet level and neutrophil level. And at the 15th Int. Symposium on MDS in Copenhagen, Elli Papaemmanuil talked about the next

version of IPSS, which is expected to be completed by the end of this year or beginning of next, and which, in addition to the elements included in IPSS-R, will also rely on results from gene sequencing. **Figure 1** is from an article that actually discusses how molecular information can be used (*Blood*. 2015;126:607).

All of these prognostic systems are based on the patient's status at the time of diagnosis and cannot be used formally at a later time in the patient's course. Yet I noticed that this was exactly what the international experts did on Friday's panel discussion of various Danish patients. So practice takes a little light on the theoretical basis.

FIGURE 1.



A=IPSS-R, B=IPSS-Rm (training cohort), C=IPSS-Rm (validation cohort), D,E=IPSS-Rm (Paired)

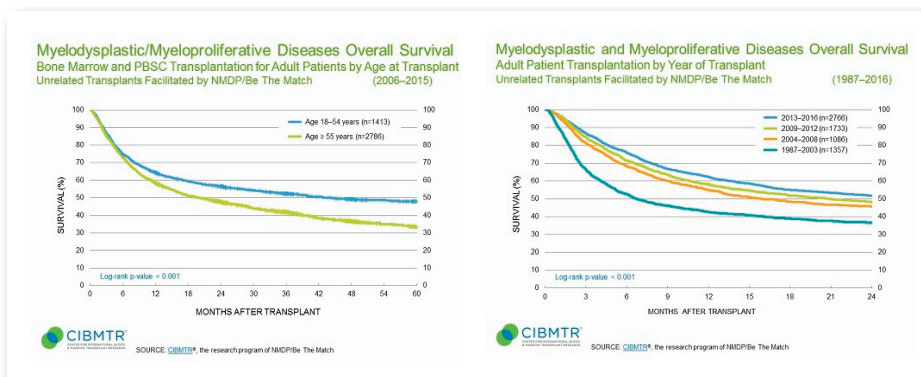
FANTASTIC TRANSPLANT RESULTS FROM RIGSHOSPITALET

It became very quiet in the big plenary hall when Dr. Lone Friis Thursday afternoon presented the results Rigshospitalet had achieved with a new combination cocktail of drugs for pretreatment of MDS patients who were to undergo an allogeneic hematopoietic stem cell transplant. She reported 1-year overall survival (OS) of 73% and 3 year OS of 65% in the MDS patients transplanted at her center over a three year period, despite the population being older and having more comorbidities than the patients in the previous years. Overall survival for the patients treated in the third year alone was 81% at 1 year and 71% at 3 years.

Figure 2 from *Be the Match* shows that the reported 5-year survival for patients with MDS or Myeloproliferative Neoplasms (MPNs) who had undergone a transplant was about 33%. The other figure also from *Be the Match*, however, shows that there has been an improvement in the 2-year survival from about 38% to about 53%. Although these figures combine MDS and MPNs, these outcomes are far from the results Dr. Lone Friis presented. The two figures are from the website *Be the Match* <https://bethematchclinical.org/transplant-indications-and-outcomes/disease-specific-indications-and-outcomes/mds/>.

MDS patients reported survival after allogeneic hematopoietic stem cell transplantation. The left figure compares the survival of patients who are either younger than 55 years or older. The right figure shows 2-year survival from four different time periods between 1987 and 2016. Source: *Be The Match*.

FIGURE 2.



THE REST OF THE SYMPOSIUM IN HEADLINES

MDS BIOLOGY

This session addressed questions such as: What is the role of the MDS stem cell in disease monitoring and therapeutic targeting? Is the stromal support of hematopoiesis in MDS improved by Luspatercept? What is the role of the stem cell in progression of MDS to AML? Is the so-called stem cell niche the chicken or the egg? How does S100A9 influence dysregulation of normal splicing patterns in MDS?

MDS EPIGENETICS

This session dealt with topics such as: What is the mechanism of TET2 epigenetics in myeloid cancers? How does TET2 loss reshape the binding regions of HMGA2 and promote the development of MDS? What is the relation between epigenetic therapy and the immune system? How does SRSF2 P95H initiate myeloid bias and myelodysplastic/myeloproliferative syndrome (MDS/MPN) from hematopoietic stem cells? What is the epigenetic regulation in MDS/AML?

MDS AND TARGETED MEDICINE

This session focused on issues such as: What is the origin of relapses in MDS/AML? What is the effect of clonal hematopoiesis in solid tumor patients on clonal evolution and risk of therapy related

leukemia? Is there a genetic algorithm for treatment of MDS? Can one develop a leukemic stem cell signature-based scoring system for predicting prognosis in Myelodysplastic Syndromes? (N. Jensen remark: That paper should properly have been rejected by the organizers) How does quality of life impact decision making in MDS?

The session ended with panel debate among the presenters Liran Shlush (Israel), Elli Papaemmanuil (USA) and Reinhard Stauder (Austria) and to other doctors Ghulam Mufti (Great Britain) and Jean-Pierre Issa (USA) on whether there is a role for personalized medicine in MDS.

DECISION MAKING IN ALLOGENEIC STEM CELL TRANSPLANT

As the headline suggests, the focus of this session was on allogeneic stem cell transplant with questions such as: What are the treatment options at relapse after allogeneic stem cell transplant? How can survival after allogeneic stem cell transplant be improved? Should one offer allogeneic stem cell transplant to CCUS patients with 3 or more mutations? And when? Should one transplant TP53 mutated MDS/AML patients?

IMMUNE ABERRANCIES IN MDS

In this session, issues related to the immune system were discussed. Such as: What is the role of myeloid suppressor cells in MDS? Can artificial intelligence for flow



cytometry data analysis in suspected MDS enable an accurate, objective and fast diagnosis? Is immune dysregulation in MDS an organized mess? (Is MDS a disease between autoimmunity and autoinflammation?) Does treatment of myelodysplastic mice with Luspatercept promote erythropoiesis and bone homeostasis?

MODULATING THE IMMUNE SYSTEM IN TREATMENT OF MDS

This session focused on treatments of MDS that affected the immune system, for example: Should one combine hypomethylating drugs and immune checkpoint inhibitors? What are the adherence to treatment recommendations according to Italian and European guidelines in MDS patients in Italy? Will oral vitamin C supplements for blood cancer patients treated with azacitidine normalize plasma vitamin C levels and cause epigenetic changes? What trials are underway on vaccination with MDS/AML? Is there a consensus core outcome set for treatment of myelodysplastic syndromes? Does CAR-T have a potential in myeloid cancers?

NEW DRUGS AND COMBINATIONS

In this session, the focus was on new treatments on the road ahead, such as: What's new for low-risk MDS patients? Is targeting splice factor mutations an option?

What is there after azacitidine for high risk MDS patients? Should azacitidine be given alone or in combination with lenalidomide (LEN), valproic acid (VPA) or idarubicin (IDA) to high risk MDS patients?

PREDISPOSITION SYNDROMES IN PEDIATRIC AND ADULT MDS PATIENTS

This session was about hereditary MDS and sought answers to questions such as: What gives genetic predisposition to MDS? What are the mechanisms of SAMD9 and SAMD9L mutations in myeloid malignancies? What is pediatric MDS? Ethical question: To do or not to do?

CMML

This session was about CMML, which is a blood cancer, but is not MDS: Can preclinical models of CMML (TET2/NRAS) tell about sensitivity to MAPK inhibitors? How are CMML including RAS mutated patients treated? What are the molecular characteristics and clonal architecture of MDS/MPN in adults? What are the long-term survival results and prognostic factors for high risk myelodysplastic syndrome/chronic myelomonocytic leukemia treated with guadecitabine?

4 Tito Bastianello awards were given to Francesca Vinchi (USA), Isabel Hofman (Sweden), Elli Papeemmanuil (USA) and Zuzana Tothova (USA).

Francesca Vinchi investigated iron as a risk factor for atherosclerosis in elderly transfusion dependent MDS patients. Isabel Hofman studied the frequency of wild hematopoietic cells and stem cells predicting treatment needs of MDS-RS patients. Elli Papeemmanuil studied a knowledge-based methodology for characterization and interpretation of molecular biomarkers in MDS. Zuzana Tothova investigated how cohesion mutations alter chromatin structure, DNA damage repair and splicing, and open new vulnerabilities in MDS and AML.

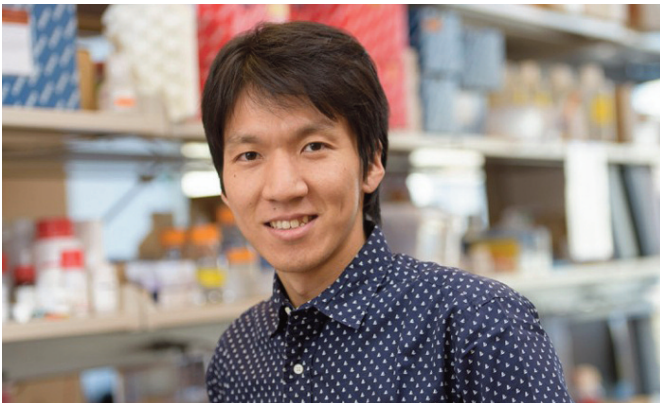
Tito Bastianello, whom this award is named after, received his MDS diagnosis in 2001, at a time when there were no treatment options other than blood transfusion and, in rare cases, a bone marrow transplant.

Participation in a symposium like the 15th International Symposium on Myelodysplastic Syndromes, in the Tivoli Hotel & Congress Center in Copenhagen over 3 days, is not cheap. The registration alone costs almost DKK 5.000, and it is not something you just pull out of your pocket. But in the Autumn of 2017, chief physician Kirsten Grønbæk asked in Lyles closed Facebook group for MDS patients who were interested in following her research on epigenetics and targeted treatment. Such persons are normally called "patient advocates" (we have yet to come up with a good Danish word). Three people signed up: Marika, Pauline and Niels. We were all offered participation in MDS 2019 in Copenhagen. But when you are on the labor market, it is difficult to tear 3-4 days out of the calendar to go to Copenhagen. So Pauline and I were the only two Danish MDS patients who participated in the symposium. It was a really good experience.

The 16th International Symposium on Myelodysplastic Syndromes is planned for Toronto, Canada in May 2021. Since my wife is from Canada, it is not unlikely that we choose to combine my participation in the symposium with a family visit in Ontario.

CONGRATULATIONS TO OUR 2019 YOUNG INVESTIGATOR GRANT WINNERS!

The MDS Foundation, Inc.'s Young Investigator Grant provides an investigator, aged 40 years or less, the opportunity to initiate, continue or complete a project that focuses on either basic or clinical management into the causation, epidemiology, molecular biology, cytogenetics, morphology, prognosis and treatment of the Myelodysplastic Syndromes.



DAICHI INOUE, MD, PHD

MDS Foundation Young Investigator Award Winner

FUNDED BY: MDS Foundation, Inc.

GRANT YEAR: 2019-2020

RESEARCH CENTER: Foundation for Biomedical Research and Innovation at Kobe, Hyogo, Japan

RESEARCH TITLE:

Understanding and Targeting ZRSR2-mutated MDS/AML

SUMMARY: Genes encoding RNA splicing factors are common mutational targets across myeloid neoplasms. This proposal will focus on a specific form of spliceosomal gene mutations which has received relatively little study and for which we have developed substantial novel reagents and preliminary data. Specifically, we aim to systematically determine the mechanistic, functional, and therapeutic consequences of ZRSR2 mutations in myeloid leukemias. As such, we expect our studies to provide novel insights into the biology of myeloid malignancies driven by spliceosomal gene mutations and uncover novel, mechanism-based therapeutic approaches for MDS and AML patients bearing ZRSR2 mutations.



SOO PARK, MD

MDS Foundation Young Investigator Award Winner

FUNDED BY: Gabrielle's Angel Foundation for Cancer Research

GRANT YEAR: 2019-2020

RESEARCH CENTER: University of California San Diego, La Jolla, California, United States

RESEARCH TITLE: *Use of Metformin for Prevention of Clonal Progression to Therapy-Related MDS/AML*

SUMMARY: Clonal hematopoiesis is a common and potentially targetable condition defined by the expansion of blood cells carrying mutations in leukemia-associated genes. This condition occurs more frequently with increasing age and after chemotherapy exposure where it is a strong risk factor for therapy-related myeloid neoplasms. Chemotherapy contributes to an inflammatory bone marrow microenvironment that selects for leukemogenic clones. Therapeutic targeting of the inflammatory microenvironment could reduce the risk of further clonal evolution to frank malignancy. We will investigate the effects of metformin on therapy-related clonal hematopoiesis and its impact on clinical outcomes in a high-risk group of breast cancer survivors.



ADVANCING RESEARCH & PATIENT CARE

**THE 16TH INTERNATIONAL CONGRESS ON
MYELODYSPLASTIC
SYNDROMES**

2021
5 - 8 MAY

TORONTO, CANADA



WWW.KENES.COM/MDS

MEETING HIGHLIGHTS AND ANNOUNCEMENTS

THE AMERICAN SOCIETY OF HEMATOLOGY 61ST ANNUAL MEETING & EXPOSITION • DECEMBER 2019

JOIN US FOR A BREAKFAST SYMPOSIUM

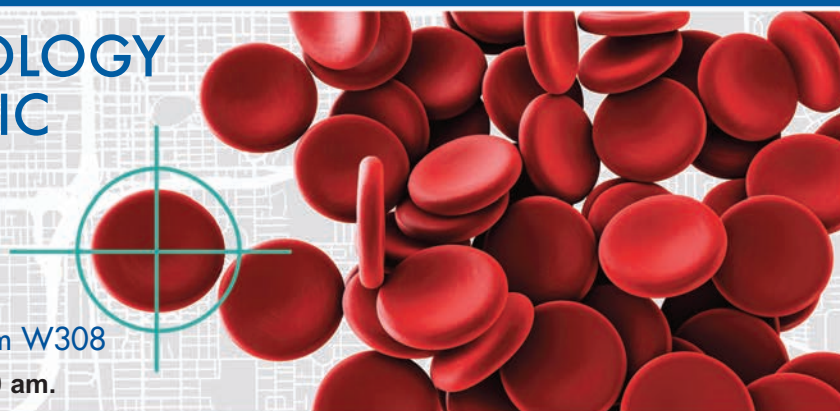
PRECISION HEMATOLOGY IN MYELODYSPLASTIC SYNDROMES

DECEMBER 6, 2019

7:00 – 11:00 am

Orange County Convention Center, Room W308

Breakfast will be served from 7:00 to 7:30 am.



ACTIVITY OVERVIEW

This symposium will describe recent advances in our understanding of the genetic basis of myelodysplastic syndromes and related myeloid neoplasms, and how these advances are being translated into precision medicine approaches to diagnosis, prognostication and treatment for patients with these hematologic malignancies.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

- Identify how to use molecular genetics in diagnostic and prognostic evaluation of MDS
- Discuss the fundamental concepts of inherited predisposition to myeloid neoplasms in general and myelodysplastic syndromes in particular
- Identify how to diagnose and treat patients with MDS under the age of 60
- Discuss how to diagnose CCUS
- Discuss how to diagnose clonal monocytosis of clinical significance
- Explain the molecular classification of MDS
- Describe the prognostic significance of germline and somatic mutations in MDS
- List current approaches to treatment of ineffective erythropoiesis in MDS
- List current approaches to personalized treatment in MDS.

ACCREDITATION

CME/CE provided by AKH Inc., Advancing Knowledge in Healthcare.

Physicians: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of AKH Inc., Advancing Knowledge in Healthcare and the Myelodysplastic Syndromes Foundation, Inc. (MDSF). AKH Inc., Advancing Knowledge in Healthcare is accredited by the ACCME to provide continuing medical education for physicians. AKH Inc., Advancing Knowledge in Healthcare designates this live activity for a maximum of 3.5 AMA PRA Category 1 Credit(s)[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistants: NCCPA accepts AMA PRA Category 1 Credit[™] from organizations accredited by ACCME.

Pharmacists: AKH, Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. AKH, Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 3.5 contact hour(s) (0.35 CEUs). UAN 0077-9999-19-045-104-P.

Nursing: AKH, Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 3.5 Contact Hours.

Activity is jointly-provided by AKH Inc., Advancing Knowledge in Healthcare and the Myelodysplastic Syndromes Foundation, Inc. (MDSF).

FACULTY

Mario Cazzola, MD
Symposium Co-Chair
Pavia, Italy

Stephen Nimer, MD
Symposium Co-Chair & MDSF Chairman
Miami, Florida

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DON'T FORGET TO VISIT OUR MDS FOUNDATION BOOTH #2219 IN THE NON-PROFIT EXHIBIT HALL

INTERNATIONAL WORKING GROUPS

MAKING CONNECTIONS AROUND THE WORLD

THE MDS/MPN INTERNATIONAL WORKING GROUP



MICHAEL SAVONA

*Vanderbilt University Medical Center
Nashville, Tennessee*

The first investigator driven, multi-national MDS/MPN-specific trial in the world is led by the MDS/MPN IWG and is set to commence! **ABNL MARRO – A Basket Trial of Novel therapy combinations in untreated MDS/MPN And Relapsed/Refractory Overlap Syndromes (ABNL-MARRO)** – is an international study designed to quickly test new compounds and combinations of therapy at referral centers within the MDS/MPN IWG which see MDS/MPN patients, study the biology and pathophysiology of the diseases, and have multilateral expertise in this area.

ABNL MARRO-001 is the first MDS/MPN IWG study and has been approved by the FDA awaiting enrollment by end of the year in the US, and then in EU countries shortly after. ABNL MARRO-001 uses an oral DNA methyltransferase inhibitor (DNMTi), ASTX727, as a backbone with combination therapies targeting JAK1, PIM kinase and LSD-1. DNMTi combinations have been evaluated in phase 1 safety studies, and will form 3 separate arms in ABNL MARRO-001. With ABNL MARRO-001, the MDS/MPN IWG aims to validate the proposed criteria for response in MDS/MPN, test QOL tools in patients

with MDS/MPN, develop new biomarkers for response to therapy, and augment efforts of large scale prospective genotyping efforts in MDS/MPN. This infrastructure will allow for ABNL-MARRO-002, -003, and so on, to quickly offer new therapies to patients with MDS/MPN.



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LATEST NEWS REGARDING THE MOLECULAR MUTATION PROJECT OF THE IWG-PM

In patients with MDS, *TP53* mutations associate with high-risk presentation, complex karyotype, acute myeloid leukemia (AML) progression and poor response to hematopoietic stem cell transplantation. These findings highlight the relevance of *TP53* as a prognostic and predictive biomarker. Despite the central role of *TP53* in MDS, the clinical implications of *TP53* mutations in the context of allelic state have not been extensively studied. Under the auspices of the International Working Group for Prognosis in MDS Molecular project (IWG-PM/Molecular) investigational efforts have generated data from which an abstract has been submitted to the ASH 2019 meeting describing results obtained from sequencing marrow or blood samples from a representative cohort of 3,324 peri-diagnosis MDS patients on a next generation sequencing (NGS) panel along with a validation cohort from a Japanese MDS sample compendium.¹

Data analysis of this study was able to segregate patients into two *TP53* states: a mono-allelic state where one wild type allele remained (33% of *TP53* mutated patients); and a multi-hit state where *TP53* was altered multiple times by either mutations, deletions or cnLOH. Data demonstrated that *TP53* state was associated with clinical presentation and outcomes. Mono-allelic *TP53* mutation patients presented with more favorable disease than multi-hit *TP53* mutated patients. Using multivariate models that considered age, peripheral blood counts, blasts and IPSS-R cytogenetic score, multi-hit *TP53* mutation state was an independent prognostic factor for overall survival and AML transformation, whilst mono-allelic *TP53* state was not. These findings indicated that *TP53* status is a critical candidate for incorporation into molecularly informed risk stratification schemas (molecular IPSS-R). Thus, *TP53*



mutation state is important for MDS risk estimation, disease monitoring and future correlative research.

The IWG-PM/Molecular group project is ongoing with plans for further development of a global classification schema for MDS (IPSS-R/molecular). This issue will be further discussed at the MDS Foundation Symposium at ASH 2019² and at the annual IWG-PM meeting at ASH.

Clinical and prognostic differences between Japanese and Caucasian MDS patients in the IWG-PM

Clinical features of MDS could be influenced by many factors, such as disease-intrinsic factors (e.g., morphologic and cytogenetic subgroups, somatic mutations), management of patients, environmental features and ethnicity. Several previous studies described differences in MDS between Asian and European countries/USA but with a limited number of cases. In this study of the IWG-PM, to elucidate the differences in MDS between Japanese (JPN) and Caucasians (CAUC), patient data was analyzed from a large database. These data demonstrated that JPN MDS was significantly younger with more severe cytopenias and with difference in certain

cytogenetic subgroups. Patients with del(5q) were less frequent, and those including der(1;7) and del(20q) were more frequent among JPN MDS. Certain clinical factors demonstrated differences in their impact on survival but not time to transformation to leukemia between the two groups even after the adjustment for age and prognostic classification. Although confounding features such as diet, environmental factors and medical availability could not be excluded, to explain these clinical differences these results suggest that ethnic differences exist regarding prognostic factors in MDS.³

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3. Miyazaki Y, Tuechler H, Sanz G, Schanz J, Garcia-Manero G, Sole F, Bennett JM, Bowen D, Fenaux P, Dreyfus F, Kantarjian H, Kuendgen A, Malcovati L, Cazzola M, Cermak J, Fonatsch C, LeBeau MM, Slovak M, Santini V, Luebbert M, Maciejewski J, Machherndl-Spandl S, Magalhaes T, Pfeilstöcker M, Sekeres M, Sperr WR, Stauder R, Tauro S, Valent P, Teresa Vallespi T, van de Loosdrecht AA, Germing U, Haase D, Greenberg PL. Differing clinical features between Japanese and Caucasian patients with myelodysplastic syndromes: Analysis from the International Working Group for Prognosis of MDS. *Leukemia Research* 73:51-57, 2018.



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.

DO YOU KNOW YOUR MDS SUBTYPE AND IPSS-R SCORE?

We launched a recent survey which showed that only 50% of patients know their subtype and only about 30% know their IPSS-R Score. Your subtype and IPSS-R score determine your personalized treatment plan.

Knowing your subtype and IPSS-R score can help guide discussions with your doctor.

KNOWLEDGE IS POWER



www.mds-foundation.org

ASK YOUR HEALTHCARE TEAM...



Knowing your IPSS-R score and MDS subtype can guide discussions with your healthcare team about the best treatment options for you!

KNOW YOUR SCORE

The IPSS-R is a classification system used by doctors to help predict a person's risk of developing AML and overall survival without treatment.

CATEGORIES & SCORES

Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

KNOW YOUR SUBTYPE

MDS is classified into several different subtypes based on the following features:

- Blood cell counts
- Percentage of blasts in the bone marrow
- Cytogenetics

FAB SUBTYPES

Refractory Anemia (RA)
Refractory Anemia with Ringed Sideroblasts (RARS)
Refractory Anemia with Excess Blasts (RAEB)
Refractory Anemia with Excess Blasts in Transformation (RAEB-t)
Chronic Myelomonocytic Leukemia (CMML)
Acute Myeloid Leukemia (AML)

WHO SUBTYPES

MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity:
Refractory cytopenia of childhood

Calculate your IPSS-R Score and IPSS-R Category

Variables (units) [usage range]	Value
Hemoglobin 9g/dl0. [4–20] A possible conversion for Hb values: 10 g/dL=6.2 mmol/L, 8g/dL=5.0 mmol/L	<input type="text"/>
Absolute Neutrophil Count (x10 ⁹ /L). [0–15]	<input type="text"/>
Platelets (x10 ⁹ /L). [0–2000]	<input type="text"/>
Bone Marrow Blasts (percent). [0–30]	<input type="text"/>
Cytogenetic Category <input type="radio"/> Very Good <input type="radio"/> Good <input type="radio"/> Intermediate <input type="radio"/> Poor <input type="radio"/> Very Poor	
<input type="button" value="calculate >"/>	

More detailed information on IPSS-R scores and subtype can be found online in our Building Blocks of Hope resource.

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MDS AWARENESS



A heartfelt THANKS to all of our walkers, volunteers and sponsors for making our walks a huge success!



Check our website and facebook for updates on our 2020 events in Boston, Chicago, Nashville, and New Jersey/New York and save the date for the location nearest you!!

MDS FUNDRAISING EVENTS

WORKING TOGETHER FOR MDS

ATV 'TRASH THE DRESS FOR MDS' BENEFIT IN MEMORY OF TAYLOR MOEN

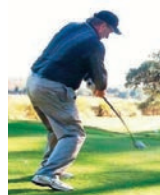
Shelly Guzek continues this ATV wheeler ride and mud run event as an annual tradition in honor of her son, Taylor Moen, who passed away on October 26, 2014. Taylor loved to ride 4-wheelers even during his struggle with MDS. Adding some humor and making this a unique ride she knows will give Taylor some good laughs up in heaven.



TOM 'SHU' SHUEY MEMORIAL GOLF TOURNAMENT

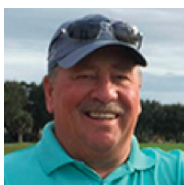


Since 2014, the annual Tom 'Shu' Shuey Memorial Golf Tournament has gathered members of the community to celebrate the life of this grandfather, father, and husband, who passed away in 2014 after battling MDS. Tom's son, Timothy Shuey, and his family held their fifth annual charity golf tournament on August 2nd. Shu was an avid golfer and one of Tim's biggest regrets was missing his last opportunity to golf with him. This inspired Tim and his family to organize an annual golf tourney in his memory. For years to come, they plan to keep Shu's memory in our hearts and minds by continuing to support the MDS Foundation. #HIGHFIVE2019



BILL SPRINGER MEMORIAL GOLF OUTING

In memory of Bill Springer, Paul Howlett and his family held their second annual charity golf tournament to help support the MDS Foundation on June 14, 2019 at the Williams Golf & Country Club in Weirton, WV. Their current target date for next year's event is Friday, June 19, 2020. We hope to see you there for another fun filled day for a good cause in memory of their loved one.



BILL OGLESBY MEMORIAL GOLF OUTING

Michael Bennert's good friend, Bob Oglesby, suffered from MDS and has sadly passed away. In his memory, Michael helped organize a charity golf tourney to help raise MDS awareness and to benefit the MDS Foundation and its work. The tournament was held at the Toiyabe Golf Club in Washoe Valley, Nevada on 27-28 August just outside of Carson City, NV with over 100 golfers attending. What a great tribute to his friend. We are sure he would have been VERY proud.

OTHER EVENTS

A special THANK YOU to those who created FUNDRAISERS FOR MDS FOUNDATION, INC. on our Facebook Page

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HIKING FOR MDS



Starting in April, JS Allen and Bonnie Getter began hiking the Pacific Crest Trail to raise money for MDS. The trail, known simply as the PCT, is a continuous 2650-mile wilderness trail stretching from Mexico to Canada through California, Oregon and Washington. Just hours east of the largest cities of the west coast, the trail crosses deserts, forests, rivers and the highest mountain range of the continental United States. The long-distance hikers that follow its spine race the seasons to hike as far as possible. The campaign was inspired by JS Allen's father, who was diagnosed with MDS.

Known by their trail names, Kosher Frank and Diamo, this hike is dedicated to Kosher Frank's father, who suffers from MDS, and will be fundraising for the MDS Foundation and its general mission to support research and patient support. Typically, they would be attempting a thruhike, that is hiking the entirety of the trail in one year and generally in one direction; however, the extensive snow pack across much of trail this year will persist far into summer, transforming a northbound thruhike from a test of endurance into a trial of patience and technical skill. In short, they will go as far north as they can, physically and logistically.

You can follow Diamo and Kosher Frank on their Facebook page (<https://www.facebook.com/HikingforMDS>) and on their Instagram feed (<https://www.instagram.com/brownsigntravels/>). You can also view their intro video at https://youtu.be/_doEktlW84.

There are two ways to give, and all monetary donations go to the MDS Foundation.

The MDS Foundation has set up a MobileCause site for direct donations via this link: <https://app.mobilecause.com/form/2vsnXg?vid=1exia>

MEASURING PATIENTS PERCEPTIONS WITH PATIENT REPORTED OUTCOMES

SARAH LIPTROTT, RN, PhD

Research Nurse/Infermiera di

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Traditionally, clinical measures such as risk scoring systems used in Myelodysplastic Syndromes (MDS) have been used to evaluate patient status and aid clinicians in the development of more personalized treatment strategies (Bejar, 2013), however, differences in patients' feelings, perceptions and experiences would suggest the need for greater understanding of meaning and impact for the individual. Patient Reported Outcomes (PRO's) are measurements based on reports coming directly from the patient about their status and the impact of disease and its treatment without any amendment or interpretation of the response by a healthcare professional or other person (EMA, 2016). They can provide insight into health-related quality of life (HRQOL), symptoms, function, satisfaction with care, treatment adherence, and perceived value of treatment (Calvert et al., 2013). Symptom evaluation using PRO's can provide clinically meaningful information which complements traditional clinical data, potentially identifying symptoms which have been undetected or underestimated by healthcare professionals (Basch, 10; Pakhomov et al., 08). Prompt signalling can permit rapid symptom management, avoiding troublesome problems that may impact on treatment adherence. PRO's can also provide information regarding physical and emotional wellbeing as well as role and social functioning, be they positive or negative experiences,



highlighting issues that are often overlooked during busy clinic appointments.

The inclusion of PRO's in cancer research is fully endorsed by funding agencies, research organizations and regulatory agencies, being cited as a source of evidence in pharmaceutical intervention evaluation and approval (US FDA, 09). Similarly, the development of the National Cancer Institute's PRO-Common Terminology Criteria for Adverse Events, highlights the key role of the patient's voice in health care management (Dueck et al., 2015). Research suggests several benefits to inclusion of PROs not only within clinical trials, but also in routine care, such as improved patient-physician communication, greater shared decision-making, improved symptom management, greater satisfaction with care as well with improved overall quality of life (Efficace & Cottone, 2019).

Care of patients with myelodysplastic syndromes (MDS) includes both supportive care and treatments such as hypomethylating agents, biological response modifiers or immunosuppressive therapy, low-dose or intensive chemotherapy, hematopoietic stem-cell transplantation (HSCT) or clinical trial participation (NCCN, 2019). While HSCT is potentially curative, not all patients are candidates for transplant. Other care options, however, permit many patients to live with the disease as a chronic illness, but effects are seen on HRQoL that there is risk of transformation to acute myeloid

leukaemia (AML) and reduced survival (Malcovati et al., 2013). A key feature of MDS tends to be chronic anemia, often complicated by infections or bleeding, with evidence suggesting fatigue is a major concern for patients, encompassing lethargy, reduced mental vigilance and physical weakness (Caocci et al., 2009; Meyers et al., 2005). The burden of disease can have both negative and positive impacts on QoL including diminished physical and mental capabilities, symptoms caused by MDS, toxicity of treatment, loss of independence, negative relationships with family and others, diminished role within the family, emotional burden, time spent on health-related care and employment and economic challenges, whilst positive impacts include reassessing life's priorities, improved relationships with family and friends, adopting positive health behaviors, a more positive outlook on life in general and a more meaningful spiritual life (Heptinstall, 2008). Improved communication with patients through the use of PRO's can facilitate greater understanding of the multidimensional impact of MDS and its treatment and assist in identifying patients' priorities so as to tailor interventions and management towards a truly patient centered approach.

Patient reported outcomes may be evaluated through patient interviews or more commonly through the use of standardized validated questionnaires, being self-administered in either paper based or in electronic formats. Many are available investigating a variety of concepts. PRO's are most commonly seen within the context of clinical trials and the influence of regulatory authorities on the selection of which PRO instrument has been used should not be ignored. Investigation by Myeloma UK (2018) highlighted how many studies used the EQ5D-5L generic PRO instrument in order to produce Quality Adjusted Life Years (QALYs) and therefore influence licensing and drug approval for Multiple Myeloma

therapy in the UK. Choice of PRO may also be influenced by what is available according to languages available for use, cost of using the instrument and software, potentially compromising use of what is truly relevant to patients' experiences.

The use of generic PRO's can facilitate comparison across treatments and diseases, and appears to be the most common approach within clinical trials however, they may not always capture what is of relevance to patients. In a recent systematic review of the use of PRO's in hematological malignancies, 50 symptoms were reported using 30 different instruments (Goswami et al., 2019). The most common being generic instruments – the European Organization for Research and Treatment of Cancer EORTC-QLQ-C30 and the Functional Assessment of Cancer Therapy FACT-G (General). Authors remind us that psychometric evaluation of these instruments has not been validated across all hematological malignancies and that consideration should also be given where validation is based on a US/European patient sample which may not be representative of all individuals with hematological malignancies.

PRO instruments with additional item banks are becoming more common. PROMIS — Patient-Reported Outcomes Measurement Information System (Shaw et al., 2017) and the National Cancer Institute's (NCI) PROM-CTCAE toolbox allow investigators to tailor generic instruments. Recent work by Bell et al., (2019) investigated the application of the EORTC item library to selected hematological malignancies (MDS/AML/Chronic Myelomonocytic Leukaemia CMML). Through revision of the literature along with patient and medical staff interviews, the generic QoL instrument (EORTC-QLQ-C30) was supplemented with 10 items felt to be relevant for this context (**Table 1**). This would suggest that generic measures are not completely capturing the issues and problems faced by individuals living with MDS.

- Bone aches or pains
- Arms or legs weak
- Slowed down
- Easily tired
- Lacked energy
- Bruising
- Dizziness
- Exertion shortness of breath
- Stop for breath when walking
- Stairs
- Getting up from chair
- Travel ability limitations
- Heavy housework
- Shopping exhausting

TABLE 1. *Supplementary items included in the evaluation of MDS/AML/CMML (Bell et al., 2019)*

Evaluating key symptoms however, can give greater insight - for example, patients self-reported fatigue provides independent prognostic information for overall survival in newly diagnosed patients with advanced MDS (Efficace et al., 2015). A more recent paper (Efficace et al., 2018) describes the development of the FA-ISS(h) index (h = high risk pts), a novel patient-centered prognostic index using the EORTC QLQ C30 Fatigue Scale for better stratification of patients and to improve patient management e.g. through timely palliative care referrals or identifying patients that may benefit from more aggressive therapies. Symptom specific measures however, may not capture unexpected events and may miss the synergistic and cumulative nature of the symptom experience (Lenz et al., 1997; Miaskowski, 2004), and it is suggested that they should be used in combination with a multidimensional HRQoL instrument in order to understand the global impact and ensure that the observed effect does not negatively impact on other areas (EMA, 2016).

Disease specific measures are one way of evaluating a specific population using an instrument that is more representative of

the constraints and symptoms experienced. Two instruments have been developed and validated specifically for the MDS population. Oliva et al., (2013) developed the first psychometric questionnaire assessing HRQoL in MDS patients (QOL-E©) using focus groups with patients to generate concepts important to MDS patients, in which 48 items were identified and then refined to a 29-item questionnaire containing a general well-being dimension, four general health dimensions (physical, functional, social, and sexual), and disease-related dimensions (fatigue and MDS-related disturbances). A study using this tool demonstrated safety and improved QoL for patients receiving lenalidomide (Oliva et al., 2013). Since this time Abel et al., (2016) have also developed and validated Quality of Life in MDS scale (QUALMS-1), developed through focus groups identifying relevant QoL domains, including physical, functional, social and sexual health, positivity, finances and information. Despite the availability of measures developed and validated within this patient group, there is limited evidence of their use.

In fact, despite the availability of a variety of PRO's, their use within clinical practice is much less common in hematological conditions compared with other cancers (Pereira-Salgado et al., 2017, Shaw et al., 2017). Less than 10% of NCI-sponsored clinical trials with leukaemia, lymphoma, and myeloma patients performed between 2004 and 2016, including PRO endpoints of health-related quality of life outcomes (Thanaranjasingam et al., 2018). Despite clinicians, and stakeholders championing the integration of assessment of HRQoL in care of patients with MDS (Malcovati et al., 2013, Cannella et al., 2015, Dueck et al., 2015), a recent systematic literature review identifying clinical trials of AML and MDS included PRO instruments between 1996–2017, evidenced only 16 manuscripts of which 5 studies focused on MDS (Bryant et al., 2018). Three studies evaluated drug efficacy +/- safety

(azacitadine, decitabine, lenalidomide) and two studies evaluating efficacy +/- safety of growth factors (erythropoietin / darbapoietin alfa +/- GCSF). Instruments measuring PRO's varied across studies, including generic (EORTC-QLQ-C30, Medical Outcomes Study – Short Form 36) and symptom specific (FACT-Anemia, FACT-Fatigue, Mental Health Inventory). In two of the studies, even though overall survival was not statistically significantly different in treatment groups, differences in physical, emotional wellbeing and fatigue were observed. A more recent study investigating HRQoL of patients with lower-risk MDS was assessed using generic instruments (EQ-5D index and EQ-VAS) showing lower HRQoL in patients of advanced age, marked comorbidities, low Hb-levels, transfusion dependence, and female sex (Stauder et al., 2018). Such results may aid in identification of subgroups where appropriate support can be directed.

It can be argued that knowledge from PRO's within the context of a clinical trial may not encompass all toxicities. Access to clinical trials is selective with homogenous groups of patients accessing treatment. In reality, populations are heterogenous with varying characteristics, comorbidities, and medications to name but a few. This is particularly true for an MDS population, where older patients tend to have comorbidities, polypharmacy and functioning and cognitive issues (EMA, 2016). Having information through PRO evaluation outside of the context of clinical trials can further enhance understanding of patients experience within the real world. Real World Data is described as data obtained by any non-interventional methodology that describe what is happening in normal clinical practice (ABPI, 2011). Technological advances can also facilitate PRO measurement providing a means for data collection through availability of mobile devices, such that obtaining data on a large scale would improve knowledge about real-world toxicity substantially (Thanarajasingam et al., 2018).

Whilst the value of PRO's appears clear, implementing this within clinical practice is not without challenges. For healthcare professionals this means evaluating the patient population and thinking of ways to support patients in completing PRO's. Data are only valid if respondents can understand what is asked of them and can provide a response that reflects their experiences or perspectives (Cella et al., 2012). Thanaranjasingam et al., (2018) highlight how misunderstanding of the goals of treatment can impact on subjective experience and acceptance of associated toxicities, emphasizing the need for data from patients who are realistic about the clinical benefit from a treatment. These observations point towards the need for high quality communication between patients and healthcare professionals providing explanations of the rationale and importance of PRO completion, and emphasizing the utility of identifying issues pertinent to the individual.

Healthcare professionals involved in collection and review of PRO data also need support in implementation. Inclusion of systematic PRO assessment might be perceived as time consuming and add an additional barrier to an already busy clinical practice (Efficace et al., 2019). Encouraging engagement of these stakeholders includes training to facilitate understanding of the instrument and its interpretation.

Evidence suggests that PRO collection may enhance physician satisfaction and prevent burnout after becoming more familiar with PRO use (Efficace et al., 2019) with enhanced efficiency and time saving during consultations (Rotenstein et al., 2017).

Implementation of PRO's be they within the clinical setting or within the context of a clinical trial surely requires a structured approach with buy-in from all parties. With regards to clinical trials, guidelines have recently been published highlighting items to be included in trials where PRO's are included as primary or secondary

outcomes (Calvert et al., 2019) in order to facilitate clear reporting and consideration of issues when planning and performing research in order to produce high quality data. In terms of clinical practice, documents such as the International Society for Quality of Life Research Users Guide for Implementation of PRO's in clinical practice, provides guidance and considerations in order to facilitate successful implementation (Chan et al., 2018).

CONCLUSION

The importance of PROs is recognized by patients and clinicians as well as finding encouragement from funding agencies, research organizations and regulatory agencies. Their implementation can facilitate patient evaluation and the identification of issues pertinent to the individual in order to tailor care and treatment accordingly. This is particularly relevant in the MDS setting where we see complex clinical situations impacting on patient's quality of life. Despite a wide range of PRO's being available including those specifically developed for MDS patients, their use remains limited. Patients and healthcare professionals should join together to encourage wider PRO's in care in order to promote a truly patient centered approach to care.

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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. Palomo L et al. Spanish guidelines for the use of targeted deep sequencing in myelodysplastic syndromes and chronic myelomonocytic leukemia. *Br J Haematol*, 2019; Oct 16 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/31621063>)

The revised guidelines of the Spanish MDS Group (GESMD) have aimed at establishing quality standards for implementation and interpretation of next generation sequencing in myeloid malignancies.

2. Sekeres M et al. The national MDS natural history study: design of an integrated data and sample biorepository to promote research studies in myelodysplastic syndromes. *Leuk Lymphoma*, 2019;21:1–11. (<https://www.ncbi.nlm.nih.gov/pubmed/3111762>)

This NCI supported study facilitates availability of MDS biospecimens for scientific discovery. The study plans to recruit up to 2000 MDS/MPN patients and up to 500 cases of idiopathic cytopenia of undetermined significance (ICUS). The present report details study design and plans for specimens and data collection.

TREATMENT:

Iron Chelation:

1. Hoeks M et al. Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes



participating in the European MDS registry. *Haematologica*, 2019; Jul 5 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/31278207>) Low risk MDS patients with iron chelation therapy (224/2200 or approx. 10.2%) within European MDS registry were compared to contemporary non-chelated patients. After adjustment for demographic and disease characteristics the chelated patient showed 50% risk reduction in overall survival (HR=0.50), which improved further in propensity-score analysis of matched cases (HR=0.42). Approximately 39% chelated patients had erythroid response.

Transplantation:

1. Beelan DW et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic hematopoietic stem cell transplantation for older patients with acute myeloid leukemia or myelodysplastic syndromes (MC-FludT.14/L): a randomized, non-inferiority, phase 3 trial. *Lancet Haematol*, 2019;Oct 9 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/31606445>) This report is based on the final analysis of the study with a median f/u of 15.4 mo for treosulfan and 17.4 mo for busulfan. AML patients in first or consecutive complete remission (marrow blasts <5%) or MDS with marrow blasts <20% were randomized

in this open label study to receive Treosulfan (iv 10 g/m² daily x 3 d) or busulfan (0.8 mg/kg). Both groups received iv fludarabine 30 mg/m² daily x 5 d. The treosulfan arm had higher 2-year event-free survival rate (64%) compared to the busulfan arm (50.4%, HR=0.65, p=0.0051 for superiority). The safety profiles were similar in the two groups. Treosulfan-fludarabine may therefore hold the promise of standard preparative regimen for allogeneic HSCT in AML.

Hypomethylating Agents:

1. Qin Y et al. Hypomethylating agents for patients with myelodysplastic syndromes prior to hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Ann Hematol*, 2019; Oct 22 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/31637485>) A meta-analysis of 6 cohort studies with MDS patients demonstrated that overall survival and relapse free survival were comparable regardless of the use of hypomethylating agents compared to chemotherapy or best supportive care prior to HSCT (OS–HR=0.81, p=0.104 and RFS–HR=0.96, p=0.749).
2. Reilly B et al. DNA methylation identifies genetically and prognostically distinct subtypes of myelodysplastic syndromes. *Blood Adv*, 2019;3(19): 2845–2858. (<https://www.ncbi.nlm.nih.gov/pubmed/31582393>)

Bone marrow DNA samples from 141 MDS patients showed 5 distinct CG methylation clusters which demonstrated distinct subtypes of patients otherwise not distinguished by mutations or clinical features. Patients with diverse genetic lesions converge into single methylation group who may share pathogenic mechanisms and clinical outcomes.

3. Vij R et al. A phase II multicenter study of the addition of azacitidine to reduced-intensity conditioning allogeneic transplant for high-risk myelodysplasia (and older patients with acute myeloid leukemia): Results of CALGB 100801 (Alliance). *Biol Blood marrow Transplant*, 2019;25(10): 1984–1992. (<https://www.ncbi.nlm.nih.gov/pubmed/31212080>)

A total of 63 patients (40 unrelated and 23 matched related donors) received Fludarabine iv d -7 to d -3, busulfan daily to AUC 4000 $\mu\text{M}/\text{min}$ d -6 to d -3 (after a prior test dose) and ATG d -6 to d -4. All patients also received up to 6 cycles of Azacitidine starting between d +42 to d +90. In total 41 patients received AZA starting on median day 61 post-transplant of whom 17 completed 6 cycles. The 2-year cumulative rates of non-relapse mortality was 33.4%, and relapse of 25%. At med f/u of approx. 59 mo, the estimated PFS was approx. 41% at 2 year and 27% at 5 year. For the entire group of patients, the overall median PFS was 15.8 mo and median overall survival was 19.2 mo.

4. Garcia-Manero G et al. Guadecitabine (SGI-110) in patients with intermediate or high-risk myelodysplastic syndromes: phase 2 results from a multicenter, open-label, randomized phase 1/2 trial. *Lancet Haematol* 2019;6(6): e317–e327. (<https://www.ncbi.nlm.nih.gov/pubmed/31060979>)

Int-1, Int-2 or High risk MDS patients with or without prior exposure to

hypomethylating agents were randomized to sc guadecitabine 60 mg/m² (n=55) or 90 mg/m² (n=50) on d1–5 in 28 d cycle. With median 3.2 yr f/u, the overall response (a composite of CR, PR, Marrow CR and HI) did not differ between the two dose levels (40% vs 55% respectively). For patients who were treatment naïve and those who were relapsing after previous exposure to hypomethylating agents, the overall response rates were 51% vs 43% respectively. The grade ≥ 3 adverse events included thrombocytopenia, neutropenia, febrile neutropenia, anemia and infections. The deaths due to adverse event were 7%. The recommended dose for future studies thus is 60 mg/m².

5. Qin T et al. Risk of disease progression in low-risk MDS is linked to distinct epigenetic subtypes. *Leukemia*, 2019; Jul 22 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/?term=Qin+T+and+Nimer+SD>)

A set of paired diagnostic and f/u samples were assessed in a cohort of 20 patients (13 with stable MDS and 7 with progressive MDS). Targeted sequencing was carried out with a panel of 59 genes frequently mutated in myeloid malignancies. The progressive disease patients had higher frequency of mutations/patient (3.2) vs stable disease patients (1.2, $p=0.01$). Furthermore, the study identified 356 differentially methylated regions (DMRs) between progressive and stable low-risk MDS. Whereas the methylation pattern of stable disease patients was closer to normal, that for progressive disease patients was significantly divergent. Supervised analysis showed that the number of DMRs nearly doubled (681) with progressive disease.

Novel Therapies:

1. Faraoni I et al. Cytotoxicity and differentiating effect of the poly (ADP-Ribose) polymerase inhibitor Olaparib in myelodysplastic syndromes. *Cancer*, 2019;11(9):E1373. (<https://www.ncbi.nlm.nih.gov/pubmed/31527467>)

In primary cultures of bone marrow mononuclear cells from 28 MDS patients, olaparib showed cytotoxic effects with a median IC₅₀ of 5.4 μM , which is lower than the peak in vivo concentration reached with standard olaparib dose. Moreover, the cytotoxicity appeared specific to myeloid blasts and simultaneously an increase in metamyelocytes and mature granulocytes was noted while sparing the uninvolved lymphoid cells. These cytotoxic and differentiation effects were further augmented in combination with decitabine.

2. Santini V et al. Phase 2 study of the ALK5 inhibitor Galunisertib in very low, low- and intermediate-risk myelodysplastic syndromes. *Clin Cancer Res*, 2019; Sept 3 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/31481511>)

Galunisertib, an oral inhibitor of TGF beta receptor type I kinase (ALK5), was evaluated in a phase 3 study at twice daily 150 mg dose in 14 days on/14 days off schedule in VLR, LR and IR MDS patients (n=41). The hematologic improvement- erythroid was seen in 24.4% patients per IWG 2006. Among transfusion dependent patients Ht-E was seen in 32.1%. Overall median duration of response in all patients was 90 days. The adverse events were grade 1/2 in 49% patients (fatigue, diarrhea, pyrexia, and vomiting).

3. Sallman DA et al. A phase 2 trial of the oral smoothened inhibitor glasdegib in refractory myelodysplastic syndromes (MDS). *Leuk Res*, 2019;81:56–61 (<https://www.ncbi.nlm.nih.gov/pubmed/31030089>)

LITERATURE HIGHLIGHTS

Glasdegib was assessed in higher risk MDS patients (n=35) with hypomethylating agent. The overall response was seen in 2 patients (6%) with marrow CR with HI as the best response. The median overall survival was 10.4 mo. ≥ 3 infections occurred in 11% with non-hematologic toxicities generally being rare.

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. Spaulding TP et al. The evolving role of next generation sequencing in myelodysplastic syndromes. *Br J Haematol*, 2019; Oct 1 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/31571207>)
2. Kubasch AS and Platzbecker U. The

wolf of hypomethylating agent failure: what comes next? *Haematologica*, 2019;104(8):1505-1508. (<https://www.ncbi.nlm.nih.gov/pubmed/31366462>)

3. Germing U et al. Novel therapies in low- and high-risk myelodysplastic syndromes. *Expert Rev Hematol* 2019; 12(10):893-908. (<https://www.ncbi.nlm.nih.gov/pubmed/31353975>)
4. Loghavi S and Wang SA. Defining boundary between myelodysplastic syndromes and myeloproliferative neoplasms. *Surg Pathol Clin*, 2019; 12(3):651-669. (<https://www.ncbi.nlm.nih.gov/pubmed/31352979>)
5. Gil-Perez A and Montalban-Bravo G. Management of myelodysplastic syndromes after failure of response to hypomethylating agents. *Ther Adv Hematol*, 2019; 10 eCollection. (<https://www.ncbi.nlm.nih.gov/pubmed/31156799>)
6. Kaplan HG, Malmgren JA and Calip GS. Granulocyte colony-stimulating factors in therapy-related myelodysplastic syndromes and acute myeloid

leukemia. *JAMA Oncol*, 2019; 5(7): 1065-1066. (<https://www.ncbi.nlm.nih.gov/pubmed/31070689>)

7. Adès L, Serbet M, Fenaux P. Guadecitabine in myelodysplastic syndromes: promising but there is still progress to be made. *Lancet Haematol*, 2019;6(6):e290-e291. (<https://www.ncbi.nlm.nih.gov/pubmed/31060978>)
8. Valent P et al. Proposed diagnostic criteria for Classical chronic myelomonocytic leukemia (CMML), CMML Variants and Pre-CMML Conditions. *Haematologica*, 2019, 104(10): 1935-1949. (<https://www.ncbi.nlm.nih.gov/pubmed/31048353>)

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

Did You Know?

The Myelodysplastic Syndromes (MDS) Foundation, Inc. was established by an international group of physicians and researchers to provide an ongoing exchange of information relating to MDS.

Until the Foundation was set up, no formal working group had been devoted to MDS. Since its inception, we have conducted 15 international symposia in Austria, England, the United States (Chicago, Washington, DC), Spain (Barcelona, Valencia), Czech Republic, Sweden, France, Japan, Italy, Greece, Scotland, Germany, and Denmark. The 16th International Symposium will be held in Toronto, Canada on May 5-8, 2021.

A major **MDS Foundation** effort is our international information network. This network provides patients with referrals to Centers of Excellence, contact names for available clinical trials, sharing of new research and treatment options between physicians, and extension of educational support to physicians, nurses, pharmacists and patients.

In response to the needs expressed by patients, families, and healthcare professionals, we have established patient advocacy groups, research funding, and professional educational initiatives.

The MDS Foundation is a publicly supported organization, exempt from federal income tax under section 501(C)(3) of the IRS code.

Learn more about

The Myelodysplastic Syndromes Foundation, Inc.

and find additional resources here:

www.mds-foundation.org



MDS CENTERS OF EXCELLENCE

Our MDS Centers of Excellence are institutions that meet the highest standards for diagnosis, treatment and patient care. These centers help patients seeking first or second opinions and/or additional treatment options from experts in MDS. We currently have 72 Centers in the United States and 112 Centers in countries around the world. Our MDS Centers can be viewed here:

<https://www.mds-foundation.org/mds-centers-of-excellence>



BENEFITS OF MEMBERSHIP:

- MDSF CoEs form the referral base for the patients who contact the Foundation daily.
- MDSF CoEs are proudly recognized on the Foundation website, within our printed newsletters, and through our various social media platforms.
- MDSF CoEs are offered reduced registration rates at our Int'l Symposia and discounted subscription rates to *Leukemia Research*.
- MDSF CoEs have full access to MDSF educational resources for distribution to your patients.
- In addition, along with your \$500 CoE renewal payment, your annual MDSF Professional Membership dues are waived. MDSF Professional Members are also listed, by name, on our website and in our printed newsletters.
- The work of your institution can be shared with our patient and professional contacts via our website and/or our social media channels. We can spread the word of your clinical trials, research projects, etc.

Would you like your treatment center to become part of the referral system for MDS patients and be designated as a Center of Excellence?

To be recognized as a Center of Excellence, an institution must have the following:

- An established university (or equivalent) program
- Available cytogenetics and/or molecular genetics
- Documentation of peer-reviewed publications in the field
- Recognized morphologic expertise in MDS
- Ongoing research, including Institutional Review Board-approved clinical trials

Please contact the Foundation for further information and an application form for your center.

The following centers have qualified as MDS Centers of Excellence:

UNITED STATES

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Birmingham Comprehensive Cancer Center
Birmingham, Alabama
Kimo Bachiashvili, MD

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Mayo Clinic Hospital
Phoenix, Arizona
Lisa Sproat, MD

The University of Arizona Cancer Center
Tucson, Arizona
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UCLA School of Medicine
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City of Hope National Medical Center
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Stephen J. Forman, MD

Moores Cancer Center-UC San Diego Health
San Diego, California
Rafael Bejar, MD, PhD
Peter Curtin, MD

Stanford University Medical Center
Stanford, California
Peter L. Greenberg, MD

UCLA Health Hematologic Malignancies and Stem Cell Transplant Program
Los Angeles, California
Gary J. Schiller, MD

University of Southern California
Keck School of Medicine
Los Angeles, California
Casey L. O'Connell, MD

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University of Colorado Cancer Center
Aurora, Colorado
Daniel Aaron Pollyea, MD, MS

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Yale University School of Medicine
New Haven, Connecticut
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Rush University Medical Center
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IOWA

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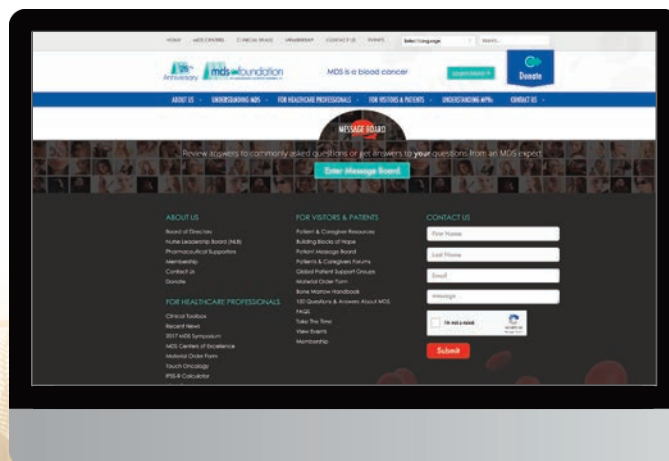
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GERON STARTS PHASE 3 CLINICAL TRIAL IN LOWER RISK MYELODYSPLASTIC SYNDROMES

MENLO PARK, CA, AUGUST 8, 2019 –

Geron Corporation (Nasdaq: GERN) today announced the opening of patient screening and enrollment for the Phase 3 portion of IMerge to evaluate imetelstat, a first-in-class telomerase inhibitor, in lower risk myelodysplastic syndromes (MDS).

"The start of the Phase 3 portion of IMerge is a significant milestone for Geron and imetelstat," said John A. Scarlett, M.D., Chairman and Chief Executive Officer. "We are hopeful that the Phase 3 will confirm the encouraging results from the Phase 2 portion, and that imetelstat could become a much-needed treatment alternative for patients with lower risk MDS."

IMerge is a two-part Phase 2/3 clinical trial of imetelstat in transfusion dependent

patients with lower risk MDS who are relapsed after or refractory to erythroid stimulating agents (ESAs). The Phase 3 portion is planned to enroll approximately 170 patients in a randomized, double-blind, placebo-controlled clinical trial to test the hypothesis that imetelstat improves the rate of red blood cell transfusion independence (TI). The trial is planned to be conducted at multiple medical centers globally, including North America, Europe, Middle East and Asia. The primary efficacy endpoint is 8-week TI rate, which is defined as the proportion of patients achieving transfusion independence during any consecutive eight weeks since entry into the trial. Key secondary endpoints include the rate of transfusion independence lasting at least 24 weeks, or 24-week TI rate, durability of transfusion independence and the amount and relative change in transfusions.

Many key aspects from the Phase 2 portion of IMerge remain the same for the Phase 3 portion. A target patient population

of non-del(5q) lower risk MDS patients who are naïve to treatment with hypomethylating agents

(HMAs) and lenalidomide was identified from the Phase 2 portion, and will be enrolled in the Phase 3. In addition, the primary and secondary endpoints, the dose and schedule of imetelstat administration and many of the clinical sites remain the same as in the Phase 2. Recently reported Phase 2 data highlighted the meaningful and durable transfusion independence, disease-modifying activity, and efficacy responses across MDS patient subgroups potentially achievable with imetelstat treatment.

Based upon current planning assumptions, Geron expects top-line results for the IMerge Phase 3 trial to be available by mid-year 2022.

To learn more about IMerge and whether the study is enrolling patients in your area, please visit www.clinicaltrials.gov.

MDS SUPPORT GROUP TOOLKIT

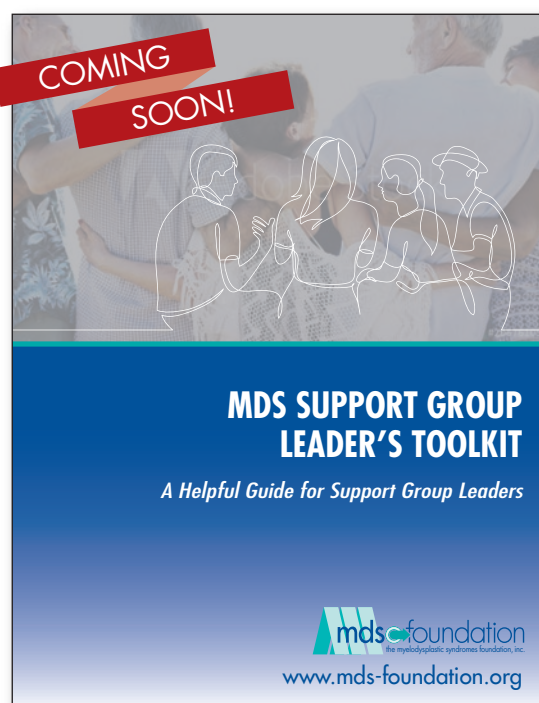
ONE OF MDSF'S GOALS IS TO EXPAND THE NUMBER OF SUPPORT GROUPS WORLDWIDE

We are always on the lookout for people who are willing to start a group, offer some support in their area, and widen our support services to include more individuals affected by MDS.

We want to make it as easy as possible for volunteers to create and run support groups to ensure they can provide continuous comfort to those utilizing them.

We have created a **Support Group Leader Toolkit** that will provide guidance on how to run the group, suggestions for discussion topics, useful tools like onsite attendance forms, and various other resources to help the meetings run smoothly.

If you are interested in starting a support group of your own, please contact Audrey Hassan at 1-800-MDS-0839 Ext. 210 or email ahassan@mds-foundation.org.



AML CORNER

AML PRESS RELEASES

CELGENE ANNOUNCES PHASE 3 QUAZAR® AML-001 STUDY OF CC-486 AS MAINTENANCE THERAPY IN PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA MET PRIMARY AND KEY SECONDARY ENDPOINTS

*Celgene Announces Phase 3
QUAZAR® AML-001 Study of CC-486 as
Maintenance Therapy in Patients With
Newly Diagnosed Acute Myeloid Leukemia
Met Primary and Key Secondary Endpoints*

SUMMIT, NJ, SEPTEMBER 12, 2019 –

Celgene Corporation (NASDAQ: CELG) today announced top-line results from the international phase 3, randomized, double-blind, placebo-controlled study, QUAZAR AML-001. The study evaluated the efficacy and safety of investigational therapy CC-486 as maintenance therapy in patients with newly diagnosed acute myeloid leukemia (AML) who achieved first complete response (CR) or complete response with incomplete blood count recovery (CRi) with induction chemotherapy (with or without consolidation). The study demonstrated

that maintenance treatment with CC-486 resulted in a highly statistically significant and clinically meaningful improvement in overall survival compared to placebo. The key secondary endpoint of relapse-free survival (RFS) also showed a statistically significant improvement.

CC-486 was well-tolerated and there were no unexpected safety events in QUAZAR AML-001. This phase 3 study enrolled 472 patients, randomized 1:1 to receive either oral CC-486 300mg or placebo once daily for 14 days of a 28-day cycle plus best supportive care until disease relapse.

"AML remains a deadly blood cancer where most patients are not curable and less than 30% of patients survive five years¹," said Jay Backstrom, MD, MPH, Chief Medical Officer for Celgene. "The CC-486 QUAZAR AML-001 study is the first phase 3 trial to demonstrate that the addition of maintenance therapy has the potential to extend overall survival in a broad population of patients with newly diagnosed AML who have achieved remission with induction chemotherapy."

Data from QUAZAR AML-001 will be submitted to a future medical meeting. Celgene also plans regulatory submissions for CC-486 beginning in the first half of 2020.

CC-486 is an investigational compound and not approved for any use in any geography.

About QUAZAR AML-001

Phase 3, randomized, double-blind, placebo-controlled study of CC-486 as AML maintenance therapy in patients who achieved first CR or complete response with incomplete blood count recovery (CRi) with induction chemotherapy (with or without consolidation). The primary endpoint of the study was overall survival. Key secondary endpoints included relapse-free survival (RFS), safety and tolerability, healthcare resource utilization and patient-reported outcomes per the FACIT-Fatigue Scale and EQ-5D questionnaire. The study enrolled 472 patients, randomized 1:1 to receive either oral CC-486 300mg or placebo once daily for 14 days of a 28-day cycle plus best supportive care until disease progression.

About QUAZAR CC-486

CC-486 is a cytidine nucleoside analogue and incorporates into DNA and RNA. The main mechanism of action is thought to cause DNA hypomethylation and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The antineoplastic effect of CC-486 is hypothesized to cause death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanism.

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MDS FOUNDATION



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MDS MANAGER

**EFFECTIVELY MANAGE
YOUR MDS CARE**

**MDS Manager™ is a newly developed
mobile app for smartphones and tablets!**

This app includes a variety of features to assist patients and their caregivers LIVING with MDS to more effectively manage their care, improve communication with providers, and track their response to treatment.



Available in the Google Play Store and iTunes



SYROS ANNOUNCES NEW DATA FROM PHASE 2 TRIAL OF SY-1425 IN COMBINATION WITH AZACITIDINE DEMONSTRATING HIGH RESPONSE RATES, RAPID ONSET OF ACTION AND FAVORABLE TOLERABILITY PROFILE IN RARA-POSITIVE NEWLY DIAGNOSED UNFIT

62% Composite Complete Response Rate, with 82% of Patients Achieving or Maintaining Transfusion Independence

Data Support RARA as the Optimal Predictive Biomarker for Patient Selection

CAMBRIDGE, MASS, OCTOBER 24, 2019

Syros Pharmaceuticals (NASDAQ: SYRS), a leader in the development of medicines that control the expression of genes, today announced that updated clinical data from its ongoing Phase 2 trial evaluating SY-1425, its first-in-class selective retinoic acid receptor alpha (RAR α) agonist, in combination with azacitidine, continue to demonstrate high complete response rates, rapid onset of action and a favorable tolerability profile in a genomically defined subset of newly diagnosed acute myeloid leukemia (AML) patients who are not suitable candidates for standard intensive chemotherapy. These data are being presented at the European School of Haematology (ESH) 5th International Conference Acute Myeloid Leukemia "Molecular and Translational": Advances in Biology and Treatment in Estoril, Portugal.

"I am very encouraged by these data. AML patients continue to need new treatment options, despite recent advances in the field, that are well-tolerated and can be used in combination to extend survival and improve quality of life," said Stéphane de Botton, M.D., Head of Acute Myeloid Malignancies at Institut Gustave Roussy and a clinical investigator in the Phase 2 trial of SY-1425. "These data show that SY-1425, a targeted therapy, in combination

with azacitidine is highly active in a subset of patients that can be readily identified and that the combination is generally well-tolerated even in very sick AML patients. I believe SY-1425 is a promising combination agent with the potential to provide a meaningful benefit for a subset of AML patients, and I look forward to its continued development."

"These data mark an important milestone in the development of SY-1425," said David A. Roth, MD, Chief Medical Officer of Syros. "SY-1425 in combination with azacitidine continues to demonstrate high complete response rates, rapid onset of action and a favorable tolerability profile in RARA-positive AML patients. As we study the combination in more patients, we are also seeing a high rate of transfusion independence and early evidence of durable responses. We are gratified to see our discovery of this novel patient subset, as defined by our RARA biomarker, translating into clinical benefit. These results demonstrate the power of our gene control platform to identify which genes to modulate in which patients to maximize the chances of providing them with a profound benefit. We look forward to continuing to evaluate SY-1425 in our ongoing study and to reporting potential proof-of-concept data next year in RARA-positive relapsed or refractory AML patients."

Updated Clinical Data on SY-1425 in Combination with Azacitidine in Newly Diagnosed, Unfit AML Patients

Syros presented updated data from its Phase 2 trial of SY-1425 in combination with azacitidine, a standard-of-care hypomethylating agent, in newly diagnosed unfit AML patients. The trial evaluated the safety and efficacy of the combination in patients with either the RARA or IRF8 biomarker, as well as in patients without the biomarkers. All patients were treated with azacitidine administered at standard daily doses of 75 mg/m² intravenously or subcutaneously for seven days, followed by SY-1425

administered at 6 mg/m²/day orally, divided in two doses, for the remainder of each 28-day cycle.

As of Aug. 22, 2019, 40 newly diagnosed unfit AML patients had been enrolled in the trial and were eligible for the safety analysis. The median age of patients enrolled in the study was 76. Of the 17 biomarker-positive patients evaluable for response, 13 were RARA-positive and four were IRF8-positive. Enrollment in the newly diagnosed unfit cohorts of the ongoing Phase 2 trial is nearly complete. Syros will continue to follow patients enrolled in the trial to further characterize the overall profile of the combination, including safety, efficacy and durability of response.

Clinical Activity Data

- 62% complete response (CR) and complete response with incomplete blood count recovery (CRi) rate, as defined by Revised International Working Group, IWG, criteria), in RARA-positive patients.
- 54% CR rate in RARA-positive patients, consisting of seven CRs, including three molecular CRs and three cytogenetic CRs.
- Most initial responses were seen at the first response assessment.
- Duration of these responses in RARA-positive patients was up to 344 days, with three of the eight responding patients having responses lasting beyond seven months at the time of the data cutoff.
- 82% of RARA-positive patients achieved or maintained transfusion independence.
- Responses were seen in RARA-positive patients across AML risk groups, including patients with mutations that are typically associated with poor outcomes.
- In patients with only the IRF8-biomarker, the CR/CRi rate was 0%, supporting Syros' decision to use RARA as the sole biomarker for patient selection in SY-1425 clinical trials going forward. Based on data from 112 newly

diagnosed patients screened for its clinical trial, Syros believes that approximately 30% of newly diagnosed AML patients are RARA-positive.

- In the 22 response-evaluable RARA-negative patients, the CR/CRi rate was 27%, which is consistent with the published response rates of 18–29% observed in newly diagnosed unfit AML patients treated with single-agent azacitidine.

Safety Data

- SY-1425 in combination with azacitidine was generally well-tolerated with no evidence of increased toxicities beyond what is seen with either SY-1425 or azacitidine alone.
- Rates of myelosuppression, including neutropenia, were comparable to reports of single-agent azacitidine in this AML population.
- The majority of non-hematologic AEs were low grade.

- Across all grades and of all causalities, the most commonly reported AEs were nausea (38%), decreased appetite (38%), constipation (33%), fatigue (33%) and peripheral edema (30%).

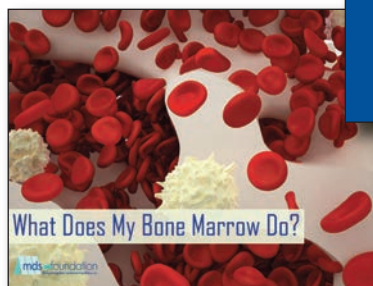
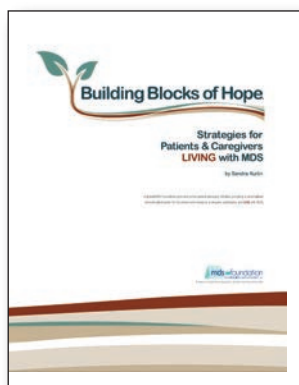
The most commonly reported Grade 3 or higher AEs (all causality) were thrombocytopenia (25%), anemia (23%), and febrile neutropenia (23%).

The poster presented at ESH is now available on the Publications and Abstracts section of the Syros website at www.syros.com.

The ongoing Phase 2 trial is actively enrolling patients with relapsed or refractory AML patients who are positive for the RARA biomarker. Syros expects to report potential proof-of-concept from the cohort in relapsed or refractory AML patients in 2020. Additional details about the Phase 2 trial of SY-1425 can be found using the identifier NCT02807558 at www.clinicaltrials.gov.

About Syros Pharmaceuticals

Syros is redefining the power of small molecules to control the expression of genes. Based on its unique ability to elucidate regulatory regions of the genome, Syros aims to develop medicines that provide a profound benefit for patients with diseases that have eluded other genomics-based approaches. Currently focused on cancer and monogenic diseases, Syros is advancing a robust pipeline of development candidates, including SY-1425, a first-in-class oral selective RARα agonist in a Phase 2 trial in a genomically defined subset of acute myeloid leukemia patients, and SY-5609, a highly selective and potent oral CDK7 inhibitor in investigational new drug application-enabling studies in cancer. Syros also has multiple preclinical and discovery programs in oncology and sickle cell disease. For more information, visit www.syros.com and follow us on Twitter (@SyrosPharma) and LinkedIn.



FIND THE TRUSTED RESOURCES YOU NEED...

You or someone you know has been diagnosed with MDS



Hearing the words Myelodysplastic Syndromes or MDS can be frightening. The diagnosis of MDS is often unexpected and filled with both immediate and long-term challenges. You probably have many questions. Have you accessed your complete set of tools to prepare, participate, and **LIVE** with MDS?

Dealing with MDS can be very difficult, but it helps to have helpful resources that are reliable and that you can trust.

To order your FREE copy of our resources available in multiple languages, please visit our website:
<https://www.mds-foundation.org/material-order-form-4/>

Do you...

KNOW AML

ACUTE MYELOID LEUKEMIA

also called AML, is a type of cancer that affects the stem cells in the bone marrow. It is one of the most common types of leukemia in adults, but can develop in children too.



@KNOW_AML



#KnowAML



KNOW AML

Know AML is the first global AML awareness and education initiative. Our goal is to facilitate and improve AML knowledge worldwide and develop community-based initiatives to overcome current and future challenges.

For more information, visit:

www.know-aml.com

SIGNS & SYMPTOMS

AML develops quickly, which is why it is termed “acute”, and is often diagnosed at an advanced stage. It is important for everyone to fully understand the signs and symptoms to ensure a diagnosis is made as early as possible.

Here are some of the general signs and symptoms of AML to look out for:

- ✓ **WEIGHT LOSS**
- ✓ **TIREDNESS OR FATIGUE**
- ✓ **FEVER**
- ✓ **LOSS OF APPETITE**
- ✓ **NIGHT SWEATS**
- ✓ **BLEEDING/BRUISING MORE EASILY**



PATIENT STORIES

OUR PATIENT STORIES

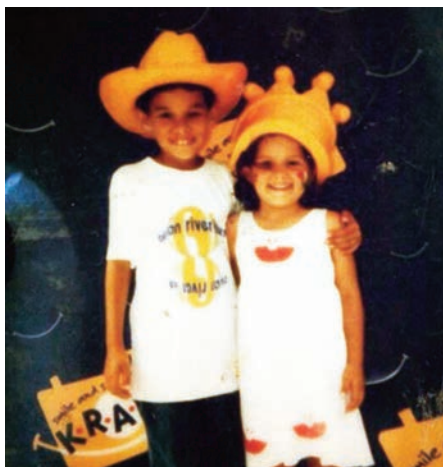
ONE LIFE FOR THE TWO OF US

ASHLEY CÁMARA
Skokie, Illinois

My story begins a few years back in Mérida, Yucatán, México, where my brother and I were born and raised. My brother and I were the type of kids that would rarely get sick, maybe once or twice a year, from a simple cold or runny nose. We also had the brother-sister relationship of fights and good times too. Who doesn't right?

The both of us were raised to be very independent, responsible, caring, hard-working and had always been the type of kids that loved spending time with friends and family. While we had different personality traits, deep down we were one and the same. We both shared the same passion for helping others whether giving someone a laugh after having a bad day or lending an ear when in distress.

My brother studied to be a graphic designer, recently graduated college, and was starting his life, when in November of 2013 he wasn't feeling well. I remember it was a weekend and he just stayed in his room the whole time, didn't go out with friends or anything, he just wanted to sleep. We would check on him regularly but he didn't express anything other than "I don't feel good". As the days passed by, his skin started to turn yellow, he still didn't feel well and we thought it was hepatitis so he went to get a blood test. A few hours after the test, I received a phone call from one of his friends who went to check on him. The laboratory where he was tested advised he go to the emergency room ASAP. I remember I was in college at that time; I left my class to answer the phone call and my heart stopped for a second when I heard the news. All of the endless possibilities of what could be and bad thoughts came into play. I honestly don't remember what day of the week but I sure do remember the date when everything started. November 26th of 2013. That day is when we found out he had MDS. Myelodysplastic Syndromes.



When I found out about his diagnosis I was freaking out because I was scared. I was hoping that he would be okay and that it was just a quick antibiotic solution so he could come home. It wasn't. When we heard his diagnosis, all we could think was, "OK, MDS, what is that?" We had no idea about myelodysplastic syndromes. It was very difficult to understand the whole situation. First of all, I've never heard anything about this disease, I've heard about cancer but just not this type of blood cancer. Second of all, he was just 23 years old, why did this happen to him? My family and I began researching this disease. We found out that MDS is often referred to as a "bone marrow failure disorder", which can develop into a type of Leukemia. It is



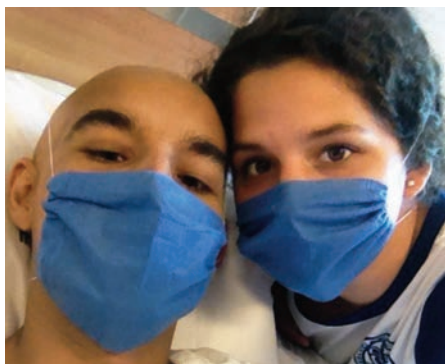
usually a disease of the elderly and this is why we couldn't understand why my brother developed it at such a young age.

Next, was the treatment plan. What was needed to cure him? The end game was that he needed a Stem Cell Transplant. A Stem Cell Transplant is a procedure that replaces defective or damaged cells in patients whose bone marrow is damaged. I was tested to see if I would be a match and could donate stem cells. Unfortunately, I wasn't. This is another thing we couldn't understand, coming from the same parents and not being a match but I guess this is how genetics work. During testing, it was noticed he had chromosome mutations and was put on medicine to help with the symptoms. Meanwhile, the doctors were trying to find a donor but according to his genetic "make up" it was going to be difficult to find an exact match. So the doctors decided on a half match donation. My mother was to be that donor.

Now, remembering that we were in Mérida, Yucatán, México, they didn't have a hospital equipped for doing a Stem Cell Transplant. So we had to travel to the north of Mexico, Monterrey, a very long way from home. This in itself was another problem as now we had to find housing close to the hospital. It also meant we did not have our support group with us, which was very important not only for us, but for my brother. Before we left Mérida, my brother had been battling with a fungus in one of his lungs. This situation supposedly was under control before the transplant started. He also developed AML (Acute Myeloid Leukemia).

So we traveled to Monterrey for the transplant. Luckily, we were able to find a place walking distance from the hospital. My brother had to stay in the hospital in a closed room, and the only way of communication was through a phone that was connected to the inside of his room. We couldn't be in the room with him, which was very, very hard. But we knew him, and we could tell when he wasn't feeling good, or if there was a change.

OUR PATIENT STORIES



He was treated and underwent a Stem Cell Transplant but because of his low immune system, the fungus activated in his lungs, and the doctors could not control it. My brother died in January of 2015 at the age of 24. When he passed away, I wondered if I needed to start getting tested more frequently as a preventive measure. I remember the doctor telling me that it is rare that siblings could have the same disease...but guess what – August of 2016, I woke up with my feet hurting and not being able to walk. My mother took me to the emergency room, where doctors realized something was not right. After being in the hospital for three and a half weeks, getting test after test, they finally decided to do a bone marrow biopsy and aspiration. On September 1, 2016, at the age of 22, I was diagnosed with Myelodysplastic Syndromes; same disease as my brother. Additionally, I developed an Autoimmune disease called Vasculitis. This was a shock to me and my family. Before I even knew I had the disease, I was hoping that everything was going to be okay.

So we were back to the beginning but this time I was the patient. My only chance of survival was a Stem Cell Transplant. When I got sick we wanted to do things differently so we told our doctor in Merida, Dr. Adrian Ceballos, that we wanted to go to Chicago for treatment. My mom's family lives in the Chicago area and would be a great support system. Thankfully, we found Dr. Lucy Godley and Dr. Satyajit Kosuri at the University of Chicago Medicine, where I ended up receiving treatment. While testing at the University of Chicago

Medicine with Dr. Godley, results showed that I had a mutation in the GATA-2 gene. She went on to explain that this was a common factor they had recently discovered a few years back and the reason why some young adults were developing MDS. In my case, I was fortunate enough to have several unknown, unrelated perfect matches. The doctors picked one, and I received my Stem Cell Transplant June 27, 2017. I remember that day like it was yesterday. It was a very important day and I'm not going to lie, it was a scary one too. It was already hard enough for me knowing that my brother died from this procedure, but now I was going to experience it first-hand. I was scared that I would die too.

There were many aspects that came into play after transplant: not being able to eat, throwing up frequently, and physical and emotional changes. I wasn't able to do much, I couldn't have many visitors and all of this was just scary. It took me a long time to actually feel "normal" and heal.

When you go through something like this for the first time with someone you love, it can be very hard. But when you have to go through it again, this time as the patient, it's even harder. There are no words that can make you feel better; you just have to get through it.

The recovery process wasn't easy and I honestly don't know the exact reason that kept me going. I believe unconsciously I decided to live for my brother and for myself. He didn't have the chance to live the full life he deserved, so I was determined to live it for him, and for me.

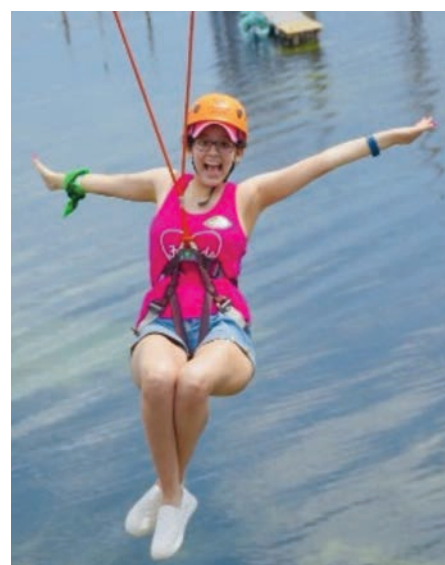
I am currently two years' post-transplant and enjoying every single day. I work two jobs, workout, travel, I'm independent from my family and I have been advocating for MDS awareness, AML (Acute Myeloid Leukemia) and I continue to learn more and more about these diseases. One of the events I recently participated in was the first ever MDS walk/run in Chicago. I ran a 5k. I was very proud of myself and I felt my brother running beside me the whole way.



If you are going through this illness as a patient keep pushing forward. It is hard, painful and it can be a long recovery like mine. But you will get there. If you are caring for someone, be patient, as us patients tend to take out our frustrations on you, the caregivers. If you know someone with this disease, be there for them, they need you, even if they don't ask for help. Just sitting in a room is a comfort as they know you are there for them.

My motto after all of this is, "live and love life". I got a second chance and I am doing this not just for myself but for the both of us.

With love, Ashley



A GENEROUS DONOR SAVED MY LIFE

STEPHEN WEBER

Ashburn, Virginia

I have kept physically active all my life, playing tennis in high school in the Washington DC area and handball in college in Minnesota. When I was twenty-eight, my econometrics professor in graduate school at the University of Wisconsin (Madison) introduced me to the wonderful game of squash racquets. And I have played ever since, even competing in the national age-bracket tournament every year since I turned 70.

Until four years ago. On July 9, 2015 my oncologist gave me the devastating results of my bone marrow biopsy conducted three weeks earlier. I was diagnosed with a serious and usually fatal blood cancer, Myelodysplastic Syndromes (MDS), with a specific type called RAEB-2 (High Risk). This disease strikes about 10,000 mostly elderly persons each year in the U.S. It often progresses to Acute Myeloid Leukemia (AML). My only symptom was a recent history of low white blood cell counts, which motivated my internist to send me to a hematological oncologist for a bone marrow biopsy to determine the cause.

The biopsy involved inserting a long needle into the top of my ilium (back hip bone) and extracting a bone chip and about an ounce of my bone marrow fluid. The cells were examined to determine the percentage of blasts. Blasts are stem cells that are not maturing to fully functioning blood cells: red cells to carry oxygen, white cells to fight infection, or platelets to arrest bleeding. A normal blast count is less than 5 percent; between 5 and 20 percent is diagnosed as MDS; while more than that is called AML. Unfortunately, my count was 17 percent, precariously close to leukemia.

Initially, my oncologist said that there were only two treatments. One was a chemical therapy (Vidaza) that might allow me to live about eighteen months. The other was a bone marrow transplant,



which could offer some chance of a permanent cure. He told me that, unfortunately, I was an unlikely candidate for a transplant because I was seventy-four. My wife, Mary Ellen, and I decided to begin the chemical treatments as soon as possible and to research the possibility of qualifying for a transplant. The Vidaza treatments were not too arduous and after five months of treatments—all the while continuing to play squash with an access port implanted in my chest—a second bone marrow biopsy at Johns Hopkins revealed that I was in remission. They reminded us, however, that the effectiveness of Vidaza was only temporary, so we decided, despite my age, to pursue seriously a bone marrow transplant.

Our research revealed that qualifying for a transplant was based on the physical condition of the patient, not just age alone. A common metric used is called the Clinical Frailty Scale, according to which thankfully I scored at the top of the charts as “Very Fit” because of my lifetime of physical activity. Survival statistics are also much more favorable for patients rated as “Very Fit.” We discovered from the website of the National Marrow Donor Program (Be The Match) that the MD Anderson Cancer Center in Houston performed among the most bone marrow transplants a year and annually treated over 300 MDS patients.

Mary Ellen, my caregiver and loving wife, took the lead and called the transplant center at MD Anderson. She persevered and obtained an evaluation

with the chief of bone marrow transplants at MD Anderson, Dr. Richard E. Champlin and his Physician’s Assistant, Toby Fisher, in December 2015. At the interview, we showed him photos of me in action on the squash court and after a battery of qualifying tests, he eagerly accepted me to be a transplant recipient.

MD Anderson completed a world-wide search in the transplant registry for a perfect match and found none in the twelve million donors registered in the U.S. at that time, but there was one perfect donor match in Europe out of the total of 20 million potential donors on the world registry. Now there are over 30 million world-wide. We returned to Houston January 31, 2016 to begin a ten-day chemotherapy conditioning protocol to kill all my stem cells to make room for those of the donor. In Europe they extracted about two liters of bone marrow fluid from my generous, anonymous donor and flew it by courier to Houston where it was processed and dripped into me on February 12, 2016. The medical staff refer to that day as my new birthday, since my blood type gradually changed from AB positive to O positive (same as the donor). I was like a newborn baby, without vaccinations and virtually no immune system.

After about two weeks of intensive care and observation on the transplant ward, I was released to out-patient status. For several more months, I had to report daily to the out-patient clinic for intravenous administration of tacrolimus, an anti-rejection drug, and various antibiotic and blood balancing fluids. I did have a few setbacks and twice endured multi-day in-patient hospital emergency stays at MD Anderson.

When we were finally allowed to return home to Virginia on May 19, I was on about fifteen different pills and ointments. I was weak and had lost most of my muscle. But I was determined to return to my active life and the game of squash. Luckily, most of my regular squash partners at the Potomac Squash Club were willing to just hit with me. Initially, I had to rest after

OUR PATIENT STORIES

every five minutes of play, but gradually my timing and stamina returned and I resumed weekly squash lessons. Already by January 2017, after an intensive round of prescribed physical therapy, I was playing at a higher level than before I was diagnosed, so I decided to enter the 75+ draw for the National Singles Tournament at the Philadelphia Cricket Club in March. Though I lost in the first round, I won my next two matches to win the consolation title. I came home with my first US Squash plaque, which we still prominently display for all to see when they enter our home.

In February 2019 we returned to MD Anderson for my third-year checkup and more rounds of vaccinations. I am thankful to report that all the test results were very encouraging with no sign of relapse and that my next checkup is not until the four-year anniversary of my transplant in February 2020.

I have since been in contact with my generous donor, Alexander Gaubatz. [See his story below.] I can never thank him and

his lovely family enough for saving my life. For those of you stricken with this disease and seeking a full cure, please explore the possibility of a matched unrelated



donor (MUD) transplant. For friends and family of MDS patients, spread the word and register with Be the Match (www.bethematch.org) to increase the likelihood that your loved one will find that life-saving match. Registration only takes a swab of your cheek.

An earlier version of this article appeared in the October 2017 issue of Squash Magazine. All photos are by Chris McClintick of US Squash.

Spread the word and register with *Be the Match* to increase the likelihood that your loved one will find that life-saving match.

HOW I BECAME A STEM CELL DONOR

ALEXANDER GAUBATZ

By 2010 I had reached a point in my professional and personal life where things could not have been better. That June we became parents for the second time, when our little daughter, Amelie, came into this world healthy and well. After a short stay my wife was able to leave the hospital and everything was perfect. The entire world seemed safe and I felt as though negative events and calamities were happening only to others.

Then in mid-2010, we received word that my uncle was terminally ill with cancer and had only a few months to live. My uncle had spent a lot of time with me during my childhood as I lived with him for half a year. He drove me to many soccer games on Sundays and gave me all kinds of advice and set a good example. When I was a teenager he often showed me my

proper place and always gave me his honest opinion about important things in life. He was for sure a person whom I looked up to as I aspired to be half as successful in life as he someday.



Sadly, he died at the end of 2011, after a brief, quite difficult illness. He had no chance. It suddenly became clear to me that nobody is safe from a stroke of fate and that life has its ups and downs. You have to be more appreciative of what you have and be grateful for the time you have with your family and friends. My uncle's sudden, though expected death affected me a lot. It made me think more about my fellow human beings.

In 2014 my sister called and told me that the son of a friend had become sick with a blood cancer. He was a two-year old boy with his whole life in front of him, who had never done anything wrong and yet was to meet this fate. I only saw from afar the difficult time he and his family were facing. At any rate I was so touched by this experience that I absolutely wanted

OUR PATIENT STORIES

to help. In December 2014 the DKMS (German Bone Marrow Donor Registry) conducted a special genetic typing campaign for little Henry Müller, the son of my sister's friend.

It turned out that I could not donate my own bone marrow to Henry. Shortly after the typing campaign had taken place, however, DKMS informed me that I could be the perfect donor for another person. By then Henry had also found a fitting donor and it is going really well with him now. In August 2019 he started first grade in school.

To some extent it can be said that Henry is responsible for Steve's finding a suitable donor. Meanwhile 40 people have donated bone marrow due to Henry's typing campaign and so, for me, Henry actually is the little hero of this story.

When the DKMS informed me that I could be the right donor for another human being, it was immediately clear to me, that there is no question whether or not I really want to donate. I was aware how horrible this disease is and how much people I know suffer from it. I was also aware of the difficult times, the fear, the sorrow, and the uncertainty these people live with day after day. I gladly accepted the invitation to undergo the various evaluations and tests, which confirmed that I, indeed, was the right donor for Steve. The tests also found,

I want to appeal to you... to register in your own country to become a donor, in order to make it possible for others to continue enjoying their lives.

however, that I have an autoimmune disease, requiring surgery to extract my bone marrow, rather than the relatively easier method (apheresis) of extracting it directly from my blood.

Now I was faced with deciding whether I would want to undergo an operation to benefit a complete stranger. Whether I would take a risk for someone I did not know or might never get to meet. I also had my doubts about whether my bone marrow could really help this stranger. Because I am a little fearful of surgery, the decision was not easy. Nevertheless, thinking of Henry and the suffering his family had to endure, I knew I had to donate.

After my decision the process went very quickly. On relatively short notice, I

received a date for the surgery. Of course, I went into the hospital with a great deal of awe and some fear. Because I was donating to an adult man and not to a child, quite a bit of bone marrow was removed from me. I was able to leave the hospital the very next day. At first I felt very good, although I had some pain in my back after the operation. Initially, I thought that was normal and that the pain would soon go away. That was unfortunately not true, however, as the pain continued to cause me some difficulty playing sports. Though the pain was there, I was able to continue living a normal life.

Now, however, everything is just fine again. I can romp with my kids and play and run with them. I can again play any sport I like and perform very well. I love to play soccer and lately ride a racing bike.

Recently I have been in touch with Steve, which makes me incredibly happy. Because of the donation, Steve can again lead a normal life and hopefully will have a long time with his family and friends.

In conclusion, I can say that the decision to be a donor was correct and that I want to appeal to you fellow human beings to register in your own country to become a donor, in order to make it possible for others to continue enjoying their lives.

THANK YOU TO OUR INDUSTRY PARTNERS FOR THEIR SUPPORT



**A SPECIAL
THANK YOU TO**

**GABRIELLE'S
ANGEL FOUNDATION
FOR CANCER RESEARCH**



for their very generous grant
in support of MDS research

MY MDS JOURNEY... AND LESSONS LEARNED

JANE M. BIEHL, PHD
North Canton, Ohio

I am not one of those people who can say I was in perfect health, and then one day was diagnosed with cancer. I have never been healthy. My mother and sister remember terrible sinus infections as a child when I struggled to breathe, and I recall hanging over the bed getting smelly nose drops leaving a terrible taste in my throat. I was fairly healthy in middle and high school and even had perfect attendance records. I was active in sports and did well.

I was born with a severe hearing loss, which was diagnosed when I started school. I wore a body aid all through until college, then I received behind the ear aids. My mother had the flu when pregnant with me, which doctors later conjectured caused Cytomegalovirus or CMV. There was no history of hearing loss in my family.

When I started college, all hell broke loose. I lost over 30 pounds my freshman year and then experienced nosebleeds. I went to the health services and then home. I was diagnosed with a kidney infection. I spent 21 days in the health center bed taking medications, getting notes from my friends and professors and finally finishing my freshman year. That summer I was referred to a urologist and admitted to the hospital for tests. I failed to respond to antibiotics and was sick all through college including 10 days in the hospital my sophomore year, and having to drop a semester of college. My junior year I trudged daily to the health center for 61 days getting shots of Loridine. I was on antibiotics for six years. I then left to go south to Atlanta for my master's degree and felt better in a temperate climate.

When I returned to Ohio for a job, the kidney problems disappeared, but I started constant bronchitis and upper respiratory problems. I was continuously on anti-



biotics. My family doctor referred me to Ohio State Medical Center where I was diagnosed with a rare IGA immune deficiency by an excellent infectious disease specialist. Later an immunologist from the Cleveland area diagnosed this as an insufficiency, since I have some immunity. It means one layer of immunity is gone, but the next layer is there, which keeps me from becoming fatally ill. The only treatment was symptomatic, but it explained why I was sick all the time.

I worked for the library profession and had several different jobs ranging from children's work to director. I decided I wanted to do something different and work with people with disabilities. In spite of all my health problems, I was very driven and went on to obtain another masters and a doctorate in counseling. I often worked two jobs and long days were the norm for me. Doctors would tell me to slow down, but I continued to work very hard. I did counseling for another 17 years and taught off and on for over 25 years at three different colleges.

Fast forward to 2010 and life was good. I was collecting a pension, and working two jobs I really enjoyed. One was as a part time counselor in a private

practice working with abused children, and the other was as an adjunct faculty member in a community college. My mother had died at the end of 2008 and since I lived close by and saw her every day, I really missed her. 2009 was stressful for me settling her estate and adjusting to not having her around. By 2010 life had settled down. I had received a gorgeous yellow lab hearing ear service dog. We had wonderful times together after work walking in the fields near my home. I had many close friends and my family would visit from out of state often.

One thing that was really striking was the need for 5 root canals in 2009. I suffer from Temporomandibular Joint Syndrome and Bruxism, but this was over the top. After my diagnosis, dental experts explained that those of us with cancer often suffer from dry mouth and changes in our body. I think the cancer was already rearing its ugly head, but cannot prove this.

I was exceptionally tired, but thought nothing about it. I was on constant antibiotics for various infections, but this was normal for me. I went to the family doctor for a routine physical, and he noted my blood counts were low. He put me on iron and did some follow up blood work a few months later. His office called me and said my blood counts were going the wrong way, referring me to a hematologist/oncologist.

Now you would think this set up red flags for me, but I was so convinced it was a blood infection from the IGA deficiency that I was not overly concerned. I figured they would find some infection and treat it.

This was one of the first times I did not follow my gut. I called the office for an appointment, and the receptionist told me the doctor to whom I was referred was very busy and could keep me waiting for appointments. I should see the other doctor. I should have been wary when an office does this, and found out later that patients loved the first doctor much more than the second one. I suspect the office was attempting to divert patients. I figured

one or two visits would be fine, so I agreed to see the second doctor. She took eight vials of blood, and when she could not find anything suggested a bone marrow biopsy. I still didn't understand what was happening, so when she asked if I had any questions I said no. Cancer never occurred to me and I was in denial. After the bone marrow biopsy, she told me I had Myelodysplastic Syndrome. I couldn't pronounce it much less spell it! Then it hit me like a ton of bricks – I really did have cancer!

I went home and started researching a little bit. There were confusing results on the Internet because some people lived 18 months and others 9 years. Some experts called it a cancer and others did not. I returned with a friend with me to see what the follow up plan would be from my doctor. I was having some trouble hearing the doctor and knew my friend would help me.

The doctor acted as if she was asking me for a cup of coffee when she stated "The average life span for this was 104 months." The world spun as my friend grabbed my hand, and told the doctor this is a lot to take in. She droned on that there might be new drugs down the road, but I was in shock and not absorbing anything. I was furious because as a counselor I was used to giving bad news and thought this was psychologically reprehensible. "But you caught this early," I stammered.

"Oh this is not like other cancers with stages 1–5," she answered, but never said anything more. She did not take the time to explain this was a blood cancer or outline a treatment plan except to put me on Procrit shots and Revlimid. She did not ask if I had any questions. I tried to ask questions about the Procrit shots I was getting and the Revlimid I was prescribed, but she simply left the room in a hurry. When I tried to question the nurse, he was worse. I told my friend I would find an oncologist who would fight with me to the end and be with me. She said I would not be able to find one. I thought to myself – watch me!

I used my contacts and went to another wonderful, warm and caring oncologist at the Aultman Cancer Center, Dr. Shruti Trehan. She is one of the brightest people I know and extremely compassionate. She lets me be involved in my health, answers all my questions, and researches night and day to find new treatments for her patients. I am convinced I would not be alive without her.

I looked up the MDS, which was deletion 5q with the prognosis of being the type where patients typically live longer. I later found out that MDS was not called a cancer until 2008, thus the confusion over the name. Originally it was looked on as a bone marrow failure, and then scientists confirmed there had to be a bad cell to start the problem, so it is classified as a cancer. I finally stopped reading about it and started living.

I began on the Revlimid, and found how naïve I really was. I made the mistake of thinking because it was oral; it would not have the side effects an IV medicine would. This might be true, but there were still many problems. The first to hit me was the extreme fatigue. The second was the constant diarrhea.

The worst was my hearing loss. I had heard about ototoxic medications and taught about them in college. But Revlimid wasn't on the list. When I visited my audiologist, I realized why the world was fading away. My audiogram was much worse and had gone from severe to profound. I mentioned this to her, but she thought it was Presbycusis due to aging. I disagreed and realized I had switched to her recently and she did not have all my records. I brought in my earlier audiogram, and she was shocked too. I had lost about 25 decibels. We decided since I still had about 10–15 decibels left that we could try to preserve that. I have hearing tests every few months and if it worsens, she will contact my oncologist. I also dug deeper and found out that Revlimid is a derivative of Thalidomide, which is an ototoxic drug. The oncologists tell me they have not heard

of hearing loss due to Revlimid. However, I had a previous hearing loss and was on the Revlimid a longer time - 6 years. So I was the perfect storm. I became an advocate and wrote to the Food and Drug administration to place warnings on the labels. I wrote an article on ototoxic medications for the national Hearing Loss Association of American magazine. I even presented on this topic at a national conference in Salt Lake City. As the Revlimid made me more and more tired, I was forced to quit my counseling job, but continued to teach part time.

I also began experiencing terrible stomach pains. Dr. Trehan referred me to a gastroenterologist and I had esophagitis with multiple ulcerations. I looked it up and yep — a potential side effect from chemo! One magic pill helped this problem so I was lucky!

When first diagnosed, I went to Case Western Reserve University Hospital in Cleveland. The first doctor was great but left, and the second one retired. Before he left, he told me I was in good hands with my local oncologist and I already knew that! I then went to the James Center in Columbus. I really liked the doctor there, but she didn't communicate with my local oncologist and I couldn't drive 2 ½ hours away if I became really sick. So that option didn't work either.

After 6 years of twice yearly bone marrow biopsies, the numbers of my deletion 5q compromised cells kept increasing. Dr. Trehan and I decided together to put me on Vidaza shots. Meanwhile, she told me that I should leave teaching because of the risk of infection. I sobbed and sobbed because teaching was my passion.

However, we cancer survivors learn how to make lemonade out of lemons. I began writing articles for *Cure Today* magazine and in two years have written over 80 articles.

I had a picture book self published on my beloved hearing ear dog in 2012 called *Here to Bump and Bump to Hear*. I published two more books in 2018. One was titled *Paw Prints on my soul: Lessons of a service dog* and is a devotional on what my dog has taught me about love and caring. The second book is a compilation of several of my articles about my cancer journey, and is titled *Life is Short – Eat the Donut!* The articles are all on my website www.janeandsita.com. The books are available on Amazon.com. I am presently working on another book about growing up with hearing loss. This has turned out to be a perfect occupation for me, because I can write from home on my good days, and am not sick nearly as much as I was when teaching and working with kids.

The Vidaza shots were painful and I started with 7 days, and then cut back to 5 days every month with 2 shots in the stomach. I learned to cherish the oncology nurses who took such good care of me.

For vacation plans, I decided to take cruises. I would suggest this for anyone who is ill. I can stay on the ship if I am having a bad day, or go off and enjoy the excursion on a good day. I meet fascinating people and eat great food! I like being waited on and spoiled! I began traveling all over with family and friends.

After two years of having the shots, I went for a bone marrow biopsy and told Dr. Trehan that my stomach was really sore. She took one look at the red and swollen area and put me on antibiotics, salve and took me off the shots. I found out later this was a rebound effect from the chemo.

I was suffering even more side effects, including loss of balance, shortness of breath and peripheral neuropathy. I have been working with a personal trainer at the Livestrong program at the local YMCA and she has helped immensely with balance. I also attend nutrition classes there. One of the best suggestions the nutritionist had given me was to drink Kefir which is full of probiotics to help me with the intense diarrhea. However, I went back on the



Revlimid for a couple more years after the Vidaza rebound, and the diarrhea became worse. Dr. Trehan decided since the bone marrows were unchanged, I should go off the Revlimid for awhile. I think all cancer survivors can identify when I say that I thought diarrhea was normal after 8 years until it stopped! It is amazing how our bodies learn to adjust.

But I could feel the cancer progressing. I went on a cruise to Quebec, and took a side trip. I didn't know that it would be pouring down rain, uphill on cobbled streets and no place to sit. I could barely put one foot in front of the other and walked, slower and slower. I barely made it to the ship in time for the gangplank to go up. Later, Dr. Trehan explained to me the oxygen was not getting to the red blood cells. My muscle aches are always there and she also gave me a prescription cream to help.

During the cold months, I noticed my extremities were bothered by the weather and tingling. I knew then I had peripheral

neuropathy. I did not realize how dangerous this can be until I clipped my toenails one evening. I looked down a few minutes later and was bleeding where I had accidentally cut my toe. The scary part was I never felt it! As I stanced the bleeding, I realized how careful I needed to be.

I contacted Dr. Trehan a few weeks later, and said I was exceptionally tired. Through all these years, by some miracle, my hemoglobin had stayed above 10. She said when it went below I would need Procrit shots. At first my blood work was stable, but two weeks later my hemoglobin had dropped from 10.4 to 9.4. The bone marrow showed all the cells were compromised. She immediately referred me to the Cleveland Clinic and I was nervous.

I had made three previous trips to the Cleveland clinic over the past 50 years. The first trip was to an urologist, who barely talked to me and told me I had a routine bladder infection, go home and take antibiotics. My urologist at home was furious and said he would have thrown up his hands if he saw how sick I was. I was on the antibiotics for 6 years, which is hardly routine!

Twenty years later, I went back to the Cleveland Clinic ENT department because of ear pain, and that doctor also spent no time with me. He reported to my local doctor that it was nerves. A friend told me to look up Temporimandibular Joint Syndrome with deferred pain to the ears. I had a terrible case of TMJ and spent two years with the dentist and orthodontist wearing braces to correct it. I still wear a mouth guard at night. Fifteen years after that I visited an infectious disease specialist after having fever and swollen glands for months. They couldn't find my records; the doctor forgot the appointment, and came in late. He told me I did not have leprosy and sent me home. After several months the symptoms finally went away on their own. I think it ended up to be inflammation all through my body because of the IGA deficiency. But wouldn't he know that? I was tired of diagnosing myself.

My next step just proves to me that we need to be persistent. The Cleveland Clinic today has a stellar reputation for cancer treatment. Dr. Trehan called and made a referral to an oncologist she felt would be a match. This fourth time was the charm. The oncologist there, Mikkael Sekeres, was fantastic. He has a worldwide reputation with working with MDS patients. He is a rare combination of being both compassionate and knowledgeable.

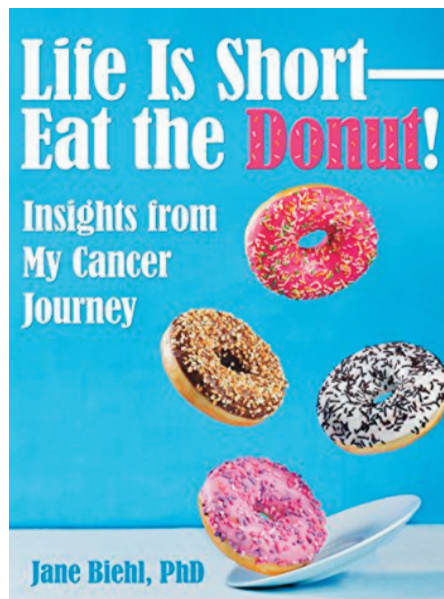
Best of all he gave me hope. Dr. Trehan had prescribed Procrit shots two days previously and already had my hemoglobin back up to 10 again. This usually doesn't happen so quickly, but I was very lucky! Dr. Sekeres told me not to worry about the compromised cells, since they were not malformed. I could be on the Procrit shots for a year.

Then Dr. Sekeres told me that two new possible drugs would be out by the end of the year, and one just for MDS. I had been so discouraged thinking that I was running out of time and options. I was nearing the end of the anticipated life expectancy for my type of cancer. However, the great thing about having cancer today is that research can come up with new possibilities all the time. For 9 years Revlimid and Vidaza were the two main chemo's you heard about, but now there are more!

I have been so fortunate to have my loyal service dog, who is now 14, by my side teaching me how to take every single day and enjoy it. She makes me laugh every morning and shows me the love of life. My 12 year old kitty is always in my lap.

I have a wonderful family, many great friends and a fantastic loving church. I am surrounded by love and prayer.

My journey is certainly not over, but constantly evolving. And that is part of life itself!



WHAT HAVE I LEARNED AND WHAT DO I WANT TO SHARE?

REACH OUT FOR HELP

I have lived independently alone for over 50 years. At first, it was hard for me to reach out and accept help. I asked a very close friend to go on doctor visits with me especially to new doctors when I am not sure I can hear them. She has been to every single appointment at the large clinics to be both my ears and support. She takes me to all my biopsies and I am so lucky. Other friends have brought food. I pay someone to clean and help me around the house more often.

DO WHAT YOU CAN FOR OTHERS

If you have always been busy and doing for others, you can find another way. I used to volunteer at churches, group homes and other places, but with my fatigue level and compromised immune system this is not feasible. One of the best things I can do is send cards to people at my church and in my community. It means a lot to them and can be done on cancer time!

ALWAYS SET UP A SMALL GOAL FOR YOURSELF

My goal is my next book. Sometimes a chapter a day is about all I can handle. Whether it is tending to a garden, cooking a small dish, engaging in a hobby, or doing scrapbooking for your grandchildren — set up something to keep you going every day.

DO THINGS JUST FOR FUN

It doesn't have to be a big fancy cruise. Going out to dinner, visiting with friends and family or just sitting in a park can help. And remember to laugh, because this is truly medicine for the body and soul!

KEEP YOUR FRIENDS AND FAMILY CLOSE

If some of them are negative, you may not want to be around them for long periods of time. But if they are positive and you remain connected, it will do you all the good in the world. It is so easy to just concentrate on your cancer. But other people have their problems too and it helps to talk to them about their situation. After hearing other people's problems, I often feel lucky!

TAKE NAPS

Enough said — it does wonders for you! Your body needs sleep and when it tells you — listen!

DON'T BE AFRAID OF SOCIAL MEDIA

If you are involved in social media, it can help. I was so afraid to show how discouraged and vulnerable I was when I was on the Vidaza, had a bad sinus infection and facing a gray Ohio winter. One day I got on Facebook simply asking for positive thoughts and prayers. The responses just blew me away. People I knew from all over the world gave me encouragement and support and thanked me for being "real." You do not have to tell people every detail of a problem, but they are usually there when you need them. Just remember that most people are good.

REACH OUT TO PLACES LIKE CURE TODAY, THE MDS FOUNDATION, AND SIMILAR GROUPS

These employees are fantastic and want to help. They would not be doing work with cancer survivors if they did not. They can give you invaluable information on the new drugs, good doctors and hospitals to go to and where support groups are.

JOIN A FAITH COMMUNITY

If you are inclined this is so important. My faith community has been there every step of the way.

LET YOUR FRIENDS AND FAMILY MEMBERS SURROUND YOU WITH LOVE AND HELP

They do want to help, but sometimes you just have to tell them how. Tell them you want to just cry. Or talk about your cancer. Or not talk about your cancer. If you need someone to visit and bring food speak up. They do not know how to help you if you do not ask.

IF THE FIRST DOCTOR OR CANCER CENTER DOES NOT WORK WELL WITH YOU – FIND ANOTHER ONE

As I explained, I went to three well known cancer centers before I found the right one. I switched local doctors and now have Dr. Trehan, who has kept me alive for nearly nine years and done it with love and grace. Keep looking until you find the right persons and places!

RESEARCHING IS GOOD THEN STOP!!! AND KNOW WHEN!!!

Every patient is different. If you begin to read all the bad things every single person suffered from side effects from chemo, you will drive yourself crazy. Be sure you are getting reliable sources like American Cancer Center, Cancer Treatment for America, Mayo Clinic, MD Anderson, Cleveland Clinic etc. The Internet will print anything and you need to be discriminating where the information is coming from. A patient is not always a reliable source, but a medical center of good reputation usually is.

Here is an example. I looked up Procrit shots after they were prescribed for me. To my surprise, the most dangerous side effect

is the possibility of blood clots. Instead of ruminating over 15 or 20 other possibilities, I figured that was the most important, and if I turned red go to the Emergency Room! I got off the computer and read a book!

ATTEND CLASSES IN NUTRITION, REIKI, EXERCISE, BALANCE, AND YOGA

I am so lucky that these are offered for free by Aultman Cancer Center and my local North Canton YMCA Livestrong program. These are invaluable programs.

ASK YOUR DOCTOR

There have been times I have looked up research and realized I just need to ask Dr. Trehan. She knows me better than anyone. And I need to be honest with her. I have talked to her about a number of problems like insomnia, which I never had before. She told me this is absolutely normal for cancer survivors and prescribed a non habit forming medicine to help me sleep.

ONE STEP AT A TIME – AND DON'T GIVE UP HOPE!

The last piece of advice seems so simple but it is not. The author Robert Updegraff said it all when he reminded us "Happiness is to be found along the way, not at the end of the road, for then the journey is over and it is too late." I do believe in miracles like newborn babies, and blooming flowers and gorgeous sunsets. Another miracle is that just as my anticipated life expectancy is reached, new drugs are being developed. Just take the cancer journey one step at a time. That is all you can do — and never give up hope! Sometimes this is all we have and it has to be enough.



MY SECOND BIRTHDAY

JIM ENGELMAN

Soquel, California

The day I received my brother's stem cells, also known among transplant recipients as our "second birthday", was July 6, 2012. 2 days earlier, July 4th, I vividly remember looking out my 6th floor hospital window at the City of Hope in Southern California watching the fireworks and thinking the real fireworks are yet to come. Being a medical doctor, internist, I was well aware or at least I thought I was of what was coming down the pike. My mind was racing with existential thoughts. It's an understatement to say this experience was life changing, a second chance, a lesson in patience, and the realization "I was NOT in control of my life". Just to list a couple other cliché's, man makes plans and God laughs, the only thing constant is change, and of course, what's the purpose of life.

My story begins in March of 2006. I was practicing medicine, delivering health care, minding my own business when I was blindsided. I noticed over 2 to 3 days I was short of breath doing things I had done daily without any effort. So I went and got a blood count that revealed an anemia, low red cell count. I knew this was an ominous sign so I saw one of my colleagues in Santa Cruz California, a hematologist/oncologist. He did further blood testing and soon thereafter, had the first of many bone marrow biopsies. I remember performing this procedure during my medical training. Let's just say it's better to give than to receive. The results were consistent with ineffective erythropoiesis, MDS ringed sideroblasts subtype. I was 56 years old.

I'd spent over 20 years telling people on occasions that their lives were forever changed due to some diagnosis but to be on the receiving side of that discussion was beyond words. My wife was with me and she held my hand. Inside I was scared and it was really the first time that I felt I was not



invincible, that I wouldn't live forever. Pretty ridiculous because I'm a doctor and I know first hand that "no one gets out of this alive". That was the beginning of many lessons yet to come. It took a bit of processing but I soon came to terms with my health status. Initially, it was a fairly benign course receiving sporadic blood transfusions when I became symptomatically anemic. As I recall, I just went on with life, only acknowledging my illness when it rudely intruded with symptoms of shortness of breath or fatigue.

Over the next year, we mostly monitored the progression of the disease. I had looked at the medical literature on MDS and knew it was usually a slow progressive disease occurring mostly in the later part of life, 70's plus. I was 56, which is a bit on the earlier side, but based on my personal experience with MDS patients,



most people died of something else and not directly from complications of MDS. That gave me some comfort. I was hoping that the field of medicine would make a breakthrough in the near future and provide a simple easy cure. Sort of like the calvary arriving in the nick of time.

I talked to my doctor who had trained at Stanford and was a good friend of Dr. Peter Greenberg MD, an international giant in the field of MDS. I saw Dr. Greenberg as a patient and we made a plan. I loved being a doctor and I was not going to cave-in, even if it was to the failing of my own body. The good news was that I had a favorable prognosis with a low risk IPSS, international prognostic scoring system. But the anemia progressed and in October of 2007, my hemoglobin dropped to 8.9 and we decided it was time to be a bit more proactive.

We started with occasional shots of Aranesp, a drug to stimulate the bone marrow to make more red blood cells. Initially that seemed to do the trick. But as expected, the MDS progressed, so we added Neupogen, another drug to stimulate the bone marrow in the hope of making more red blood cells. In spite of being a bit more therapeutically aggressive, the frequency of receiving these injections increased. Our next therapeutic intervention was to try a trial of Antithymocyte Globulin (ATG) and cyclosporine (immunosuppressant). That required a 5-day stay at Stanford Hospital. It made no difference and in fact, I had an episode of serum sickness, which is like an extremely intense flu syndrome. That was an eye opener for me. It was the first time I'd spent time in the hospital as a patient. It was definitely an odd feeling, being on the receiving end of health care. That experience had a profound impact on how I thereafter approached patients. I think I developed a greater understanding and empathy for being a patient. Another life changing experience and lesson.

In retrospect, that experience really brought home the old adage that many bad situations have a silver lining. Of course

OUR PATIENT STORIES

those “silver linings” may take some effort and time to recognize and appreciate. Many of my important life lessons are born from adversity. A seemingly bad situation like being hospitalized and developing serum sickness which, initially had no redeemable factors, resulted in something positive.

Then we tried a trial of Revlimid in the hope of slowing down the process. It seemed that no matter what we threw at the MDS, it had a mind of it's own and kept progressing. I developed mild neutropenia, low white blood cells and my IPSS progressed to intermediate. By the way, I knew that none of these interventions were a cure for MDS. At best, they merely postponed the inevitable. A common scenario is for MDS to eventually progress to acute myeloid leukemia. The only potential cure is a stem cell transplant, which is not a benign procedure.

As I mentioned, for quite a while MDS was more of an annoyance than anything else. I still continued working in my busy medical setting. Fortunately, my colleagues were very supportive and covered my medical practice at night for emergencies. I did not want to stop working and over the next year, received transfusions about every 4 weeks as needed. My fatigue and shortness of breath responded nicely to the bolus of red blood cells. I'd go to the infusion center at my hospital and rest as I received my IV “red bull”. In a way, as I recall, it was a break from my busy life. My wife and I viewed this as the new normal.

At this stage of my disease, which was not life threatening, I saw no reason to tell my 3 children, age 15 to 21. They had enough challenges on their plate to deal with and I didn't want to add one more thing to stress them out. We just went on with life. My fluctuating energy levels were the new normal.

It was about 2010 that I started exploring the option of a stem cell transplant. I first went to Stanford, which was where I had met Dr. Greenberg and had the failed ATG infusion. I approached it as a fact-finding mission. I wanted to educate myself so I could make a rational



informed decision about how to proceed. From my medical practice I knew how very important it is that the patient be involved with the decision making process. I had a couple of follow up visits and I was getting comfortable with having the transplant at Stanford until another “lesson” presented itself. My wife was with me for one of the appointments and as we're driving home, she says to me “wasn't that interesting what the doctor said”. I had no idea what she was talking about. When I questioned her, she said the doctor was surprised I wasn't looking at other transplant centers. First, I still don't recall him saying that to me and second, I said OMG of course I should look at another center. For me, the take home lesson was always having another set of ears present when having important medical conversations.

I was now getting transfusions about 2 times a month but my energy level wasn't balancing back like it used to. I made peace with the decision that I was probably on course to get a BMT in the not so distant future. I was aware of the risk but I also knew I didn't want to live like this and that my chance of survival was better if I did a transplant before my MDS progressed to AML. I decided to go to the Seattle Cancer Center, or “the Hutch” as it is known. Fred Hutchinson was a pioneer in the early years, 1950s, of bone marrow transplant development and it is one the most highly regarded transplant centers in the country. I met a doctor on the transplant team and had an informative consultation.

Afterwards, they showed me the transplant ward at the hospital and then the facility where I'd stay for 100 days after the transplant. I was very impressed. These international tertiary centers all operate smoothly and effortlessly.

In mid 2011, I told my family about my health situation. I looked good so telling them that I was thinking about having a transplant wasn't as overwhelming as it could have been. I had rehearsed how I'd present this to my kids. “It's not a big deal,” I said, we will still go on vacations together, etc.... But when I told my Jewish mother, that was another story. She insisted that I come to Los Angeles, where I grew up, to see the City of Hope. Let me say that it's much easier just to do it than to argue with my mother. So I hopped on a plane and went for an intake interview. I must admit I was totally blown away by City of Hope, it was a perfect fit.

I started the process of closing my practice in the fall of 2011 and my wife and I decided we'd take one last trip prior to the transplant and went to Israel. The trip was great but I developed a pulmonary nodule/infection that took about 6 months to fully resolve. This was a great lesson in patience and not getting too attached to my agenda.

My retirement from medicine was premature and bitter sweet. It was born out of my medical illness and not because I wanted to retire. I wasn't ready to retire but it did open up doors to follow interests that I had but never had the time to pursue. I also helped start a BMT support group in my community.

I had my transplant and wrote extensively of that experience and its many challenges, lessons, and miracles in a blog. Since then, every morning when I wake up, I say my mantra, “Thank you God for returning my soul to me”.

I chronologically blogged extensively about my transplant experience. If you're interested go to: jimengelman.wordpress.com using Chrome.

A DAY IN MY SHOES

BETH LEONARD

Lake Havasu City, Arizona

On September 13, 2017 at 9:00 pm, we received a phone call from our primary care doctor telling me I needed to send my husband to the hospital immediately! I asked why, and he said his blood counts were very low, and he mentioned words like white blood cells, red cells, hemoglobin, platelets and neutrophils. I had no idea what he was saying or what it all meant. I informed the doctor that Nathan felt fine and we were getting ready to go to bed, can't he just go in the morning. The doctor said, "NO! He needs to go now because I don't know if he will make it through the night."

There's nothing like receiving a call like that and thinking the worst. We got dressed and headed to the hospital. I had already been at the hospital all day with my mother-in-law who had shoulder surgery. Going back to the hospital was the last thing I wanted to do.

Nathan was admitted for testing and observation. His counts were: WBC 1.2, RBC 2.19, hemoglobin 6.7, platelets 144, and neutrophils .6. At this time, we had no idea what was going on, but the word cancer was mentioned several times. This is how our journey began.

My name is Beth Leonard, wife of Nathan Leonard. We've been married for 35 years and we have 3 boys aged: 30, 25 and 21. We have a beautiful daughter-in-law, and we've been blessed with a grandson.

THIS IS MY STORY AS A CAREGIVER

We all have different kinds of shoes. We've heard there are glass slippers in Cinderella. There are the magical red slippers in the Wizard of Oz. Nike tells us to "just do it." But, do what? Elvis Presley sang about blue suede shoes. Forrest Gump said, "Mamma always said you can tell an awful lot about a person by the kind



Beth and her husband, MDS patient, Nathan

of shoes they wear." There are two things in life you can never have too many of; good friends and good shoes.

We all have different roles in our lives, we wear different shoes, and here are the shoes I wear:



I have church shoes...

These are my dress shoes. They're pretty and stylish. This is what most people see me in.



I have my "Mom" shoes...

They are New Balance shoes. As a Mom, you're always trying to balance everything.



I have my caregiver shoes...

a pair of old Sketchers. These are the shoes I wear the most. I've walked many miles in these shoes.



Then, there are my "Me" shoes...

A pair of new Sketchers. They're not worn as much as the others. I don't get to wear them as often as I would like.



And last, my slippers.

These shoes give me comfort, warmth and rest to my tired body.

My story begins with a day in my shoes. My mom shoes: As a mother of 3 boys, there was always baseball games, basketball games and volleyball games to attend. Taking the boys to and from school. And, the late night school projects one of them always forgot to tell me about. And, don't forget the housework and meal making. Then, there was the horses. They needed to be taken care of also.

MY CHURCH SHOES

We're very active in our church. We attend weekly and I was the secretary to the women's organization, with the responsibility of making phone calls, assignments and paperwork.

My "me" shoes the new Sketchers. Now, these shoes I don't get to wear as often as I'd like. But, when I do, I quilt, read a good book, paint and repurpose vintage jewelry.

MY CAREGIVER SHOES – OLD SKETCHERS

This is the shoe I wore the most and I'll tell you why.

I've always been some type of caregiver. My earliest memory is being a caregiver to my dog. Then, as a babysitter, which I happened to be very good at and was always in demand. Then I was a caregiver to my dad after my mom passed away at the age of 44. I help take care of my elderly in-laws. In addition, we have an adult autistic son that I care for.

But my story really begins as a caregiver to my husband, Nathan.

Nathan was diagnosed with myelodysplastic syndromes del 5q with 4% blasts. I attended all of Nathan's doctor appointments with him. I had to learn what the blood does and what it means to make sure Nathan stayed healthy. I needed to keep myself healthy and keep my chronic asthma under control.

Nathan's quality of life wasn't great, but it was durable at this time. We made it work. Nathan was on Revlimid, Granix shots and Procrit shots. Everything seemed to be working good and Nathan was feeling somewhat better. In June of 2018 Nathan took a turn for the worse, the medication had stopped working and it was time to consider a stem cell transplant.

We live in a very small town in Arizona. There is no facility capable of performing a transplant. We were required to travel to Phoenix to the Mayo Hospital, 4 hours away from our home.

At this time I had to change shoes and wear my "Mom shoes." Our youngest son was coming home from his 2 year church mission. He needed his Mom, as all boys do.

Not only was he needing me, our middle son also needed me. He has high function autism and he was going through a lot of emotions he didn't know how to deal with. He needed comfort and understanding of what was happening with his Dad. During this time our first grandchild a boy was born. He is now over a year old. He was a real comfort to me.

It was time to put on my church shoes. These shoes I needed the most. Without these shoes I think I would have been lost. I needed the blessings, guidance and comfort from my Heavenly Father to know that all will be well.

There definitely wasn't time for my "me" shoes. Maybe later.

Back to the caregiver shoes. Nathan has 2 brothers and a sister. They needed to be tested to see if one of them would be a match for the stem cell transplant.

His sister was a perfect match! She scored 10 out of 10. This was a miracle because we were told many times siblings don't match and the donor bank may have to be used. We were blessed with this perfect match!

We moved into our 27 foot 5th wheel RV in October of 2018. We were required to be less than an hour away from the Mayo hospital in Phoenix. I was able to locate a RV resort about 15 minutes from the hospital. We knew we would be living in the RV for at least 6 months.

I also had to make arrangements for a caregiver to be with our adult autistic son. He still needed assistance with basic living and needs care.

Nathan had many appointments before he was admitted to the hospital. Then, it was discovered he also had the beginning of prostate cancer, just a small spot. But, it was there!

Around Thanksgiving, Nathan's Sister was able to donate her stem cells. She had

a 5 day process to go through which wasn't easy for her. But, she said she would do whatever it took to save her brother's life. Her cells were frozen until Nathan was ready for them.

On November 28, Nathan was admitted to Mayo Hospital in Phoenix. The first day was very hard on him and me. Nathan had his central line put in. This procedure was delayed by 4 hours. At 9 pm, he was finally returned to his room. When Nathan got to his room he was exhausted and he still needed to receive his first dose of chemo. At 10 pm he was given his chemo. Our hospital experience was just beginning.

Later that evening, Nathan wanted no part of being in the hospital and wanted OUT! Nathan was having an anxiety attack!! Nurses helped calm him down and administered some medication to help him cope with the situation. By this time it was close to midnight and I had been at the hospital since 7 am Nathan begged me to stay until he fell asleep.

Once he was asleep, I was finally able to leave and go back to our RV. I walked into the trailer and I started bawling. I felt alone, scared and helpless. I screamed, I cried and I prayed. During this whole ordeal I received an impression in my mind saying, "all is well" My first thought was I wasn't well, he's not well, all is NOT well! How could this be?

Nathan was in a semi-isolation room. I didn't have to wear a gown or a mask unless I was coughing. I was required to wash my hands every time I left and entered his room. I wasn't allowed to bring any food in, I couldn't use his bathroom. Basically, I had a little area in his room that I had to stay in. The room had a special filtering system for whatever pollens or whatever else was on my clothes and in the air. Nathan wasn't allowed to leave the "pod" as it was called. And I wasn't allowed to touch him. That was very hard for me not able to hug, hold his hand or kiss him.

OUR CAREGIVER STORIES

Touch, how important can a touch be? I desperately wanted to hug my husband to comfort me and tell me everything would be alright. If I could have just touched his arm, his hand or leg how comforting it would be. If I could just touch him I knew I would make it. Then I would know all would be well, but I felt I had no one.

This made me think of when the Savior's garment was touched by a woman in a crowd of people who desperately needed to touch the Savior.

Luke 8:45-48

"And Jesus said who touched me? When all denied, Peter and they that were with him said, Master, the multitude throng thee and press thee, and sayest thou, who touched me?

"And Jesus said somebody hath touched me: for I perceive that virtue is gone out of me.

"And when the woman saw that she was not hid, she came trembling, and falling down before him, she declared unto him before all the people for what cause she had touched him, and how she was healed immediately.

"And he said unto her, Daughter, be of good comfort: thy faith hath made thee whole, go in peace."

At this time, it was extremely hard on Nathan. He had to have 10 days of the strongest chemo. The purpose of this is to kill all the good and the bad cells he had, so the donor's cell could grow in their place. Without white cells, he couldn't fight off any germs or bacteria. Everything had to be sanitized. Nathan got sick from the chemo. He lost his hair and to me that made it real!

My thought was "time to fight!"

Dec 7th was transplant day. His new "rebirth" as it's called.

3 days after the transplant, Nathan took a turn for the worse. Early that morning he started to run a temperature. It reached 105.6, he had the riggers and was in and out of consciousness. He had no white blood cells and wasn't able to fight off his

own germs. He had 3 different bacterial infections and E-coli, his central line was also infected. Nurses were frantically putting ice on him and giving him medication to get his temperature down. It is extremely frightening seeing your husband not responding and shaking uncontrollably and you can't do anything but speak calmly and pray.

Our oldest son was able to come to the hospital accompanied by his father-in-law to administer a blessing. This helped Nathan and he was able to sleep. He still had a temperature but it had dropped to 103.

Nathan's nurse came up to me later and said, "I don't know how you stayed so calm." I told her I may have seemed calm on the outside, but on the inside I was scared to death!

Our son had me go back to our RV to get some rest. I had been at the hospital for over 12 hours. He promised to call me in 2 hours to wake me so I could go back to the hospital and relieve him. An hour later our son called to tell me Nathan's fever had broke and his Dad was resting peacefully. I suggested he go home. The nurses promised me to call if there was any changes. I received no calls. We just received another one of many miracles.

I still needed Nathan's touch. Every night I prayed, for strength, support, guidance and to feel the Savior's love. I wanted to know why we had to go through this. One evening I received an answer from a dear friend. She said, "People who suffer with an illness are going through trials or tests. These tests, if accepted without anger or bitterness, serve to bring us closer to Christ, to rely on Him and recognize we must descend, before we ascend. This puts us in fellowship with fellow sufferers whose mission, like our Savior's, will be to lift others. These tests help us to ascend to higher planes. We rely on Him through them and glorify Him after them."

After receiving this message, I knew I needed to trust our Savior. I needed to rely on Him no matter what the outcome was.

Another thought was brought to my attention, this is why the Lord tells us to build our foundations on the rock of Jesus Christ in the scriptures – BEFORE the trials come. In this life, pretty much anything can be taken from us in a blink of an eye. It can literally be a matter of seconds and our lives are altered drastically. Our faith in Jesus Christ is the one thing that cannot be taken from us. That is willfully surrendered or neglected. I am thankful for my faith in Jesus Christ. I am clinging to it and it is giving me strength that I would never have on my own.

Then came the day Nathan's blood counts were high enough that I was able to touch him! I could finally touch him! How beautiful a touch could be! I held his hand, and cried for I knew now all would be well. I never wanted to let go!

The blessings and miracles have seemed endless. We have felt so loved by our friends, family and from those we don't even know through all of this. Hundreds of people have been praying for us and it has sustained us through our darkest hours. We have prayed many times to thank our Heavenly Father for the kindness of others. Most of all, we have felt the love of God through our trials. His hands have been evident at every turn, and we will forever praise His name.

I think the greatest miracle I received was peace. I was able to truly come to a point where I was willing to accept the Lord's will no matter what it was. There was no more turmoil, just calm assurance that God knows all and that He was going to take care of me and my family. Even if Nathan had passed away, I knew that our family would be together again and that God had a plan for us. That peace that I felt in the midst of a stormy sea was a beautiful and sacred miracle. Something that can only come from Jesus Christ. I know that this miracle was the results of thousands of prayers from countless individuals across the country, including my prayers. It was something so powerful and tangible that I will never ever forget.

OUR CAREGIVER STORIES

During this time I was wearing 3 different shoes.

My caregiver shoes, well worn.

My church shoes – without having faith and believing in prayers and many miracles we received I don't think I could have done what I had to do.

My mom shoes – Christmas still had to be planned and how to have it and where. Then getting all 3 of our sons together for the holiday. Now, I know most people would say don't worry about Christmas, celebrate it another time. To me it was important. I needed my family around me. We needed to make the best of it and we did. When Nathan was first admitted to the hospital, we were told to not plan on having him home for Christmas. As a family we decided to have a small family dinner and take our gifts to Nathan's room to open.

2 days before Christmas, Nathan was able to come home. Another miracle!

Nathan was weak, lost a lot of weight but he was on the road to recovery.

Since his central line had to be removed due to infection, Nathan was released with an IV in his arm. He needed antibiotics for the next 10 days. This required me to take him to the hospital daily for his medication and to have blood work done.

As a transplant patient, many medications have to be taken daily and at several times a day. My new job was to make sure he was taking his medication and to monitor for any signs of rejection.

Graft Verses Host Disease, transplant patients will always have to deal with this.

GVHD is when your own tissues are fighting the new cells or organs and a war is going on. GVHD can come as a rash, anywhere on your body and it can be very uncomfortable.

Nathan got a rash, he looked like a ripe tomato. This required covering his skin with a cream several times a day. Every day for the next 6 weeks I had to drive him to the Mayo hospital to have his blood drawn and see the Doctor. He was watched very closely.

Nathan started to gain weight. He was eating well, taking walks and starting to enjoy his new life. Eventually, Nathan only had to go to Mayo 3 times a week then eventually once a week.

I was able to start wearing my "me" shoes! I was able to start quilting again. I had my sewing machine and I would set up outside on nice days under our awning or go to the clubhouse at the RV park. This gave me stress relief that I dearly needed. But, I still couldn't leave Nathan for very long. I was only able to go to the clubhouse when he was napping.

We were required to stay near Mayo Hospital for 100 days after the transplant. On March 17th, we made it!! We could go HOME!! I so missed my home, my bed, my washing machine and dryer, no more saving quarters for the laundromat!

At this point, Nathan was doing extremely well. He was so far ahead of the recovery schedule that the Doctors didn't know how to act. Nathan was telling the Doctors he felt fabulous! That was a word

the Doctors didn't hear much from transplant patients. Nathan was able to go back to work while we were in our RV. He worked from home. He was walking 30 minutes a day, and he was able to go on some outings as long as he wore his mask. We called him the black bandit.

Nathan was now taking his own medication and I didn't have to monitor him 24 hours a day. I was able to leave him for an hour or so.

I could now wear my slippers, I could get some rest from my labors for a while.

Another miracle received was Nathan's cells are now 100% his sister's cells and he has no signs of the MDS. Nathan is in REMISSION!!! He feels better and stronger than ever. We knew this wouldn't be possible, if not for all the prayers we received from everyone. We felt every one of them and they gave us strength and support. We thank everyone for that with all our hearts.

A hug, what does a hug mean to you? Hugging is good medicine. It transfers energy and gives the person hugged an emotional lift. You need 4 hugs a day for survival, 8 for maintenance, and 12 for growth. Scientists say that hugging is a form of communication because it says things you don't have words for. And, the nicest thing about a hug is that you usually can't give one without getting one.

If you had to step into my shoes and walk the life I'm living, and if you get as far as I am, just maybe you will see how strong faith has made me.

Never take a touch for granted.



Coping and Caring Summer Dinner, Wynnewood, PA, August 24, 2019

THE MDS FAMILY: COPING & CARING EVENT

ROCHELLE OSTROFF-WEINBERG
Wynnewood, Pennsylvania

On a glorious summer afternoon on August 24 2019, veteran MDS Family Coping and Caring members gathered with first timers to share, learn, empathize, understand and network. Paul and Eileen Rothstein who attended the very first event in July 2013 returned, bringing added depth and, as always, delicious humor to the moment. How can I even come close to expressing in words the joy I felt to have them at this most recent event! Barbara Earl, who is recovering beautifully from a stem cell transplant, and her husband Jack, shared about their experience and the intense happiness to have reached this stage of successful recovery. Thrilled to have them with us a few weeks ago skims the surface of the emotional gladness to have them return once again, this time bringing such amazingly positive news.

Dr. Makiko Suzuki Fliss, our guest presenter, joined our Coping and Caring community, leading the group through mindfulness exercises, bringing calm, joyfulness and peace to all in attendance.

SAVE THE DATE

Save the date for my 2020 events on April 25th at the White Dog Café, Philadelphia, PA; July 25th at my home in Wynnewood, PA; and October 24th in Washington DC, venue TBD. Check the MDSF website and FB for updates and plan to attend the one nearest to you!



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THANK YOU

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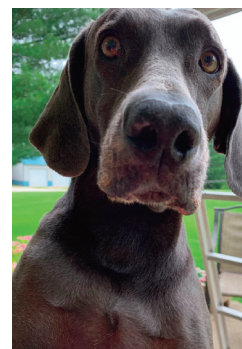
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ARE BLOOD TRANSFUSIONS HOLDING YOU BACK?

If you've been diagnosed with myelodysplastic syndromes (MDS) with anemia, the phase 3 COMMANDS Trial is a clinical research study investigating a potential treatment option that may help reduce the number of blood cell transfusions you need. To learn more, talk to your doctor and visit [ClinicalTrialCOMMANDS.com](https://ClinicalTrials.gov/study/COMMANDS).



ACE-536-MDS-002_COMMANDS_V1_26FEB2019_US_ENG



The Pivotal MDS Trial **INSPIRE** is Now Recruiting Patients

International **S**tudy of **P**hase III **I**ntravenous **R**igos**E**rtib

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).

Eligibility:

- MDS subtypes RAEB-1, RAEB-2, or RAEB-t
- Progression or failure to respond to HMA
- HMA treatment duration \leq 9 cycles in \leq 12 months
- < 82 years of age

2:1
R
A
N
D
O
M
I
Z
A
T
I
O
N

**Rigosertib + best
supportive care**
N = 240

**Physician's Choice of
Treatment + best
supportive care**
N = 120

**Primary
Endpoint:
Overall
Survival**

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, identifier: NCT02562443.

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

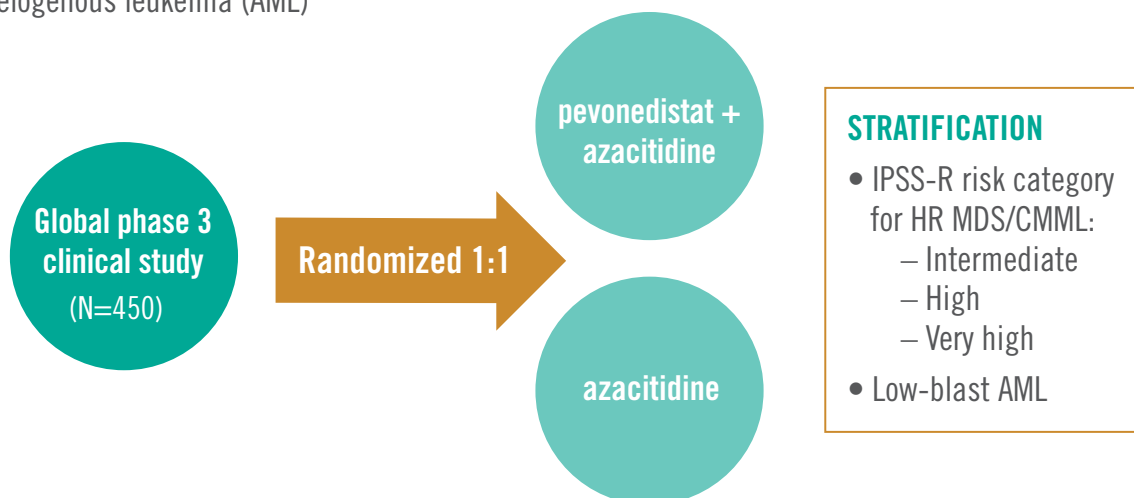


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NOW ENROLLING

PANTHER TRIAL

PEVONEDISTAT-3001 (NCT 03268954): Designed to evaluate the safety and efficacy of pevonedistat plus azacitidine versus single-agent azacitidine as a first-line treatment for patients with higher-risk myelodysplastic syndromes (HR MDS), chronic myelomonocytic leukemia (CMML), or low-blast acute myelogenous leukemia (AML)



Primary endpoint: Event-free survival (EFS)

Key secondary endpoint: Overall survival (OS)

Not a complete list of endpoints.

Enrolling countries

Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Russian Federation, South Korea, Spain, Turkey, UK, USA

For more information, including all inclusion and exclusion criteria

1-844-ONC-TKDA (1-844-662-8532) (US callers)

+1-510-740-1273 (ex-US callers)

www.clinicaltrials.gov or www.takedaoncology.com

For information on enrolling a patient, please contact GlobalOncologyMedInfo@takeda.com.

Pevonedistat is an investigational drug. Efficacy and safety have not been established.



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