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mds news
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MDS NEWS HIGHLIGHTS

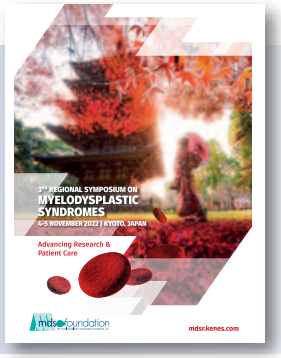
FROM THE GUEST EDITOR'S DESK

- **MANAGING MDS IN THE WAKE OF A GLOBAL PANDEMIC**

Presented by: *Amy Elizabeth DeZern, MD, MHS*
Director, Bone Marrow Failure and MDS Program, Associate Professor of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

PLAN TO ATTEND

ASH 2021: MDS FOUNDATION VIRTUAL SYMPOSIUM
December 10, 2021, Atlanta, Georgia



3RD REGIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES
4–5 November 2022
Kyoto, Japan

IN THIS ISSUE

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GUEST EDITORIAL

MANAGING MDS IN THE WAKE OF A GLOBAL PANDEMIC

AMY ELIZABETH DEZERN, MD, MHS
Director, Bone Marrow Failure and MDS Program
Associate Professor of Oncology
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

INTRODUCTION

Few people would dispute that 2020 into 2021 has been an unprecedented time throughout the world. Much of this is attributable to Coronavirus disease 2019 (COVID-19). Briefly, COVID-19 is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. The disruptions have ranged from modest to supreme and have affected all differently. However, patients suffering with myelodysplastic syndromes (MDS) have had unique and specific challenges.

RISK TO MDS PATIENTS DEFINED

Older and immunocompromised populations appear to be at a higher risk for severe, potentially life-threatening illness related to COVID-19 compared with the general population, with reported case fatality rates as high as 15% in patients aged 80 years or older in early series from China.[1] The initial study of COVID-19 and Cancer Consortium (CCC19) data found that 30-day all-cause mortality was 13% among patients with active or prior cancer and confirmed SARS-CoV-2 infection.[2] This presents a particular concern for patients with MDS.

More specific to MDS, a systematic review and meta-analysis quantified the outcomes (deaths, hospitalizations, and complications) of patients with hematologic malignancy and COVID-19.[3] This included MDS as an acquired bone marrow failure syndrome. This analysis of 14 studies and a total of 231 patients included showed a pooled risk of death of 53% (95% CI, 34-72; I2, 77%) for patients with MDS, the highest of all hematologic malignancy subtypes. These sobering data nearly a year into the pandemic required us to "double-down" on our efforts to protect our patients.

ISSUES SPECIFIC TO MDS PATIENTS

As we know, patients diagnosed with MDS may have various disease manifestations depending on their disease phenotype. Management can range from close observation of mild cytopenias to supportive treatments with transfusions all the way through active chemotherapy and even early allogeneic hematopoietic stem transplantation (BMT). Nonetheless, as the world was shutting down, all of these were impacted, disrupting the therapeutic pathway for patients with MDS. This interference with standard clinical care was compounded by the added fear that immunosuppressed MDS patients were at increased risk of morbidity and mortality from COVID-19. This led to many discussions (often via telemedicine) between patients, families, and providers. In the early days of the pandemic, there were few hard data to guide treatment or protective recommendations, and guidance was limited to expert opinion.[4,5]

For patients whose disease required close observation and monitoring, care interruptions may have manifested as limited access to laboratory appointments for blood work assessment. Patients who required transfusional support, especially those who lived in areas with few transfusion facilities, were markedly impacted by the nationwide shortage of blood supply. And patients undergoing chemotherapy were faced with decreased clinic/infusion center operating hours and inaccessible providers. Moreover, for patients in need of chemotherapy there was the ongoing concern that the ensuing immunosuppression after chemotherapy could further predispose them to COVID-19 infection and severe disease. In many cases, this may have altered the balance between risk and benefit of chemotherapy. Finally, there were simply the fear of unknown. How long could patients go without treatment? What risk does an active cancer, whether low- or high-grade, impart to an individual human being? And from a human perspective, how could patients weigh the risks of seeing family or friends, knowing both that social gatherings would increase the risk of infection and that their remaining time together may be shortened due to their diagnosis of MDS.

GENERAL RECOMMENDATIONS[5]

Expert consensus panels rapidly assembled to pool knowledge and provide guidance to patients and clinicians.[6] (https://www.hematology.org/covid-19/covid-19-and-myelodysplastic-syndromes) These panels emphasized that, as always, treatment decisions should be based on category in the revised international prognostic scoring system. Close observation without definitive treatment remained a reasonable strategy in patients with only modest cytopenias.[7] For higher risk disease, newly diagnosed patients requiring treatment with a hypomethylating agent should commence therapy (and patients already on a hypomethylating agent should continue therapy). It was thought reasonable to maintain normal treatment intervals until evidence of response is seen, but in order to balance risk of exposure with risk of disease progression, once a response is evident, lengthening the duration between treatment cycles and reducing dosing within each cycle is reasonable. Subcutaneous azacitidine is preferred over intravenous azacitidine to decrease the time spent at infusion centers

and in contact with potential COVID-19 exposures. For lower risk MDS, consensus agreement favored a longer watch-and-wait approach for most patients. Erythropoiesis-stimulating agents (for patients naive to these agents) and early luspatercept initiated may avoid or delay the need for red blood cell transfusions. Most experts agreed with deferral of lenalidomide in newly diagnosed patients with del(5q) disease given the risk for myelosuppression. Over the course of the pandemic, this guidance has migrated back to baseline practice patterns of more aggressive treatment. This is primarily due to increasing comfort and confidence in infection prevention practices.

Unfortunately, clinical trials, a long-time priority in MDS, were dramatically and negatively affected by the COVID-19 pandemic. Many studies were paused, and study participation was nearly non-existent.[8] For studies that continued, rates of study deviations increased, and the shortage of laboratory supplies was a significant barrier to continued sample collection.

BLOOD IS AN (EVEN MORE) LIMITED RESOURCE

MDS patients have always been counseled that blood is not an unlimited resource, but relatively few have truly not had potential access to transfusional support. However, during the first summer of the pandemic, the US national and even world-wide blood supply reached an all-time low.[9,10] This posed an even greater challenge for patients in whom supportive care with red cells or platelets represented a way of life. Certainly, anemia from MDS causes decreased quality of life, but there are relatively sparse data regarding the minimum hemoglobin values for which a MDS patient may safely forgo transfusions with no evidence of end-organ damage. The work of Dr. Abel and colleagues provided some guidance on this topic during COVID. The authors applied a modified Delphi method with 13 expert MDS clinicians to discussions of minimum safe hemoglobin for this population. There was a 100% consensus that it be no greater than 7.5 g/dL.[11] This was a comfort to patient and physicians alike as we were able to pull back on individual transfusions to lower levels as well as single unit (as opposed to two) transfusion episodes to ration the blood supply where feasible.

DRUGS APPROVED DURING THE PANDEMIC

Ironically, given that it had been over 15 years since the last regulatory approval for a drug for patients with myelodysplastic syndromes, two drugs were approved during the pandemic timeframe. Both actually have particular relevance in the setting of goals to decrease healthcare interactions and space out clinic visits. On April 3, 2020, the Food and Drug Administration approved luspatercept-aamt (REBLOZYL, Celgene Corporation) for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). It is a first-in-class erythroid maturation agent that binds to the select transforming growth factor-β superfamily ligands to reduce aberrant Smad2/3 signaling and enhance late-stage erythropoiesis. In the MEDALIST trial[12] randomized, multi-center, double-blind, placebo-controlled trial in 229 patients with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes who had ring sideroblasts and required RBC transfusions (2 or more RBC units over 8 weeks), patients were randomized 2:1 to luspatercept or placebo. All patients received best supportive care, which included RBC transfusions. The main efficacy endpoint in MDS-RS and MDS-RS-T was the proportion of patients who were RBC-transfusion independent (RBC-TI), defined as the absence of any RBC transfusion during any consecutive 8-week period between Weeks 1 and 24. Of the 153 patients who received luspatercept, 58 (37.9%, 95% CI: 30.2, 46.1) were RBC-TI for at least 8 weeks, compared to 10 patients (13.2%, 95% CI: 6.5, 22.9) who received placebo (treatment difference 24.6% (95% CI: 14.5, 34.6; p<0.0001.) The most common (>10%) adverse reactions to luspatercept are fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, and hypersensitivity. The recommended starting dose of luspatercept is 1 mg/kg once every 3 weeks by subcutaneous injection. This was adopted efficiently in eligible patients in hopes of augmenting hemoglobin enough to avoid transfusion during the pandemic and beyond.

Also approved during the pandemic (July 7, 2020) was Inqovi (decitabine and cedazuridine) for treatment of adult patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). The approval was based on two open-label, randomized, crossover clinical trials that showed similar drug concentrations between IV decitabine and oral decitabine/cedazuridine. Additionally, about half of the patients who were formerly dependent on transfusions no longer required transfusions during an eight-week period. Both trials provided comparisons of exposure and safety in the first two cycles between oral decitabine-cedazuridine and IV decitabine and a description of disease response to the new medication. Comparison of disease response between decitabine-cedazuridine and IV decitabine was not possible because all patients received decitabine-cedazuridine starting in cycle 3. The overall safety profile of oral decitabine-cedazuridine was similar to IV decitabine.

DATA ON ACTIVE COVID INFECTIONS IN MDS PATIENTS

For ASH 2020, Feld and colleagues[13] prospectively reviewed the records of all patients seen in the MDS clinic in New York City in the spring of 2020 to report on the effects of COVID specifically on MDS patients. Overall, 27.1% of the patient population was diagnosed with COVID-19 and 39.1% of these patients died, or 10.6% of the overall cohort. The mortality rate

reported here is higher than anticipated, but at the time of the abstract, the majority of patients recovered and have resumed MDS directed therapy. This has been my personal experience as well. Further results hinted at another problem others were seeing as well: persistently positive PCR tests up to 6 weeks post infection and COVID-19 antibodies were found in 85.7% of COVID-19 PCR+ patients tested. This suggested that MDS patients may have delayed viral clearance, but can mount a humoral response.[13] We encouraged our patients to limit exposures but get tested where feasible. There have been persistently positive patients by PCR who required longer term isolation. We look forward to MDS specific data on convalescent plasma to inpatients, and monoclonal antibody therapy for outpatients as we have gained knowledge and use.

VACCINATION

Based on randomized phase III clinical trials, several COVID-19 vaccines became available throughout the world in late 2020, early 2021, with the BNT162b2 (Pfizer/BioNTech), ChAdOx1 nCoV-19 (Oxford/AstraZeneca), mRNA-1273 (Moderna) vaccines and the Johnson & Johnson single-dose COVID-19 vaccine approved. [14-16]

Ten patients with MDS were evaluated in a larger cohort for data on immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies.[17] Through robust evaluation of immune response after 2 BNT162b2 inocula including functional seroneutralization assay and assessment of T-cell response, the authors concluded a second BNT162b2 inoculum translates into a significant increase in humoral response, allowing almost half of the patients to achieve immune protection against COVID-19. Given the increase in seroconversion rate between the first and second vaccine injections, the authors noted that evaluation of the effectiveness of such a third inoculum will be imperative.

As such, in the late summer 2021, the U.S. Food and Drug Administration (FDA) has recently authorized a booster shot of either the Moderna or Pfizer COVID-19 vaccine for certain immunocompromised people. Studies show that some people with weakened immune systems — those who have received solid organ transplants and people with conditions considered to have an equivalent level of immunocompromise — are less likely to create an antibody response from two doses of the Pfizer or Moderna COVID-19 vaccine, and these people could benefit from a third dose.

CHANGES HERE TO STAY AND FUTURE DIRECTIONS

MDS patients are special. No reader (provider or patient or family and beyond) of this editorial will disagree. We learned from our colleagues and listened to our patients as we tried to protect them and still carry on with appropriate treatment. One innovation quite helpful was the development of dedicated "biomode" treatment and infusion spaces (negative pressure) to allow for a person under investigation or diagnosed with COVID to receive treatments and transfusions in an ongoing fashion. Centers also pioneered the concept of drive-up phlebotomy and shot clinics to allow patients to avoid even exiting their car to obtain routine labs and quick injections. Perhaps the largest paradigm shift, however, was the rapid expansion of telemedicine. Not only does this allow infirm or driverless patients to see their provider, but also allowed a larger number of patients to consult both with their local hematologist as well as MDS experts. For their part, providers enjoyed seeing patients in their homes and perhaps with several generations of family members. Concerns about access to care and drug availability were mitigated through increased prescription allowances: for example, Celgene REMs allowed a 56-day supply during the pandemic. Many of these initiatives were mandated by the COVID times but are likely a permanent part of MDS care in many areas.

The NHLBI MDS Natural History Study (NCT02775383) is an ongoing prospective cohort study conducted across 144 sites in the U.S. and Israel intended to establish a data and biospecimen repository to advance the understanding of MDS. In response to the COVID-19 pandemic, the study also collected data on COVID-19 infection and management. We will look forward to summary of COVID-19 outcomes from participants in this study and the impact of the pandemic in this population of MDS patients.

Clinical trial opening and accrual are also recovering as the pandemic enters a new stage. Uniquely, in 2021, there are more phase III studies in higher risk MDS than ever before. This has produced an interesting dynamic in which agents (and their developers) are competing both for accrual and to become the new standard of care. The trials all share a similar design in their phase III registration studies with the novel product in combination compared to single-agent azacitidine. Each trial has reasonable earlier phase data, usually in both AML and/or higher risk MDS, upon which they have based their current clinical investigations. A trial of magrolimab (NCT04313881) will examine first-in-class macrophage immune checkpoint inhibitors that targets CD47, a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system. Venetoclax (NCT04401748) will be studied in higher risk MDS at a truncated dosing schema (14 days) relative to its AML trials. Dual targeting of immune effectors and leukemic cells by sabatolimab (NCT04266301) is also a trial enrolling the same higher risk patients. SY-1425, a selective RARα agonist called Tamibaterone (NCT04797780), is a biomarker driven study for those MDS patients who overexpress RARα. Having this plethora of options brings back hope to MDS patients for the future after the pandemic.

CONCLUSION

In conclusion, this has been a most unusual and unprecedented time throughout the world in 2020–21. We're learning to adapt to the "new normal" — just as all MDS patients bravely adapt to their own novel routines after their MDS diagnosis. The COVID-19 pandemic has affected patients with MDS in a

myriad of ways, including diagnostic and treatment delays, scarcity of blood products, higher risks of morbidity and mortality from the viral infection itself, as well as necessity of vaccinations and additional boosters. Nonetheless, we forge ahead to find novel approaches to improve the quantity and quality of life for all MDS patients.

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MEETING HIGHLIGHTS AND ANNOUNCEMENTS

THE 63RD AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING AND EXPOSITION 2021 (ASH 2021)

PLEASE MAKE SURE TO VISIT THE MDS FOUNDATION BOOTH #3247 IN THE EXHIBIT HALL!

ACTIVITY OVERVIEW

The 2021 symposium will describe recent advances in the classification and management of myelodysplastic syndromes.

AGENDA TOPICS

- While the WHO Classification of MDS has Helped our Patients, We Should Now Move to a Genetically-Inspired Classification
- When and How Genetic Predisposition to MDS Should be Taken into Account in Clinical Decision Making
- Can Transplantation Improve Survival Rates For Older Patients with Higher-Risk MDS
- An Elderly Patient With MDS, Thrombcytopenia, and a Cardiovascular Comorbidity that Requires Anticoagulation or Antiplatelet Therapy
- A Patient with a Myeloid Neoplasm and a TP53 Mutation
- An Anemic Patient with CCUS

TARGET AUDIENCE

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

LEARNING OBJECTIVES

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

- Discuss how to use molecular profiling for the classification and management of MDS
- Evaluate genetic predisposition in the management of MDS
- Assess the eligibility for allogeneic stem cell transplantation in older patients with MDS
- Discuss how to treat elderly patients with MDS, thrombocytopenia, and a cardiovascular comorbidity that requires anticoagulation or antiplatelet therapy
- Review to treat MDS patients with a TP53 mutation
- Discuss how to treat an anemic patient with CCUS

FACULTY

Mario Cazzola, MD – *Symposium Co-Chair*

Rena Buckstein, MD – *Symposium Co-Chair*

Stephen D. Nimer, MD – *MDSF Chairman*

Rafael Bejar, MD, PhD

Elsa Bernard, PhD

Luca Malcovati, MD

Moshe Mittelman, MD

Ghulam Mufti, OBE, DM, FRCP, FRCPath, CPath

David Sallman, MD

Zhuoer Xie, MD, MS

AGENDA

7:00 – 7:10 am
Welcome & Program Overview and Objectives

7:10 – 7:35 am
While the WHO Classification of MDS has Helped our Patients, We Should Now Move to a Genetically-Inspired Classification

7:35 – 8:00 am
When and How Genetic Predisposition to MDS Should be Taken into Account in Clinical Decision Making

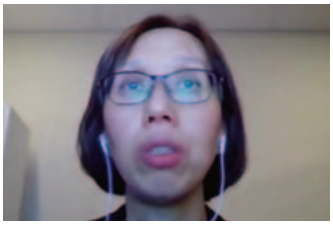
8:00 – 8:25 am
Can Transplantation Improve Survival Rates For Older Patients with Higher-Risk MDS

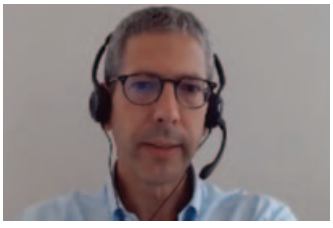
8:25 – 8:55 am
An Elderly Patient With MDS, Thrombocytopenia, and a Cardiovascular Comorbidity that Requires Anticoagulation or Antiplatelet Therapy

8:55 – 9:25 am
A Patient with a Myeloid Neoplasm and a TP53 Mutation

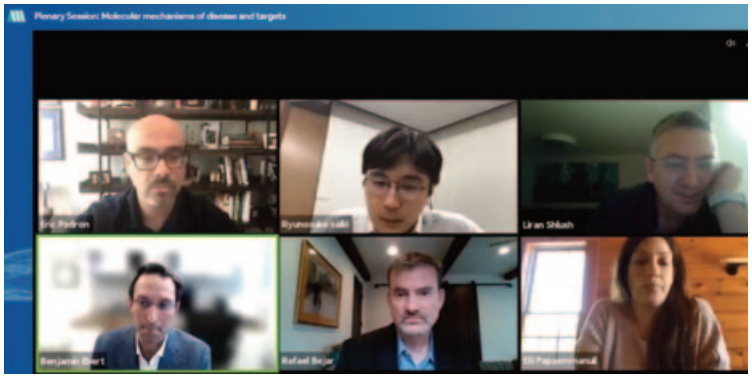
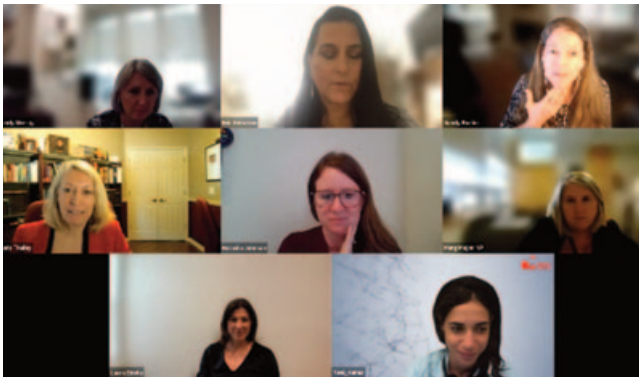
9:25 – 9:55 am
An Anemic Patient with CCUS

9:55 – 10:00 am
Closing Remarks



THANK YOU FOR ATTENDING OUR VIRTUAL TORONTO INTERNATIONAL CONGRESS ON MYELODYSPLASTIC SYNDROMES!

ADVANCING RESEARCH AND PATIENT CARE

The International Congress on Myelodysplastic Syndromes (MDS 2021) is the premier forum for presenting the latest advancements in myelodysplastic syndromes and offers the ultimate platform to enhance your scientific knowledge, establish new collaborations and bring together the MDS community. The MDS 2021 Congress took place online, from 23–26 September 2021, and covered the most recent discoveries in the field, basic and translational research as well as all relevant clinical aspects of MDS diagnosis, prognosis, and management.

LOOK FOR HIGHLIGHTS FROM OUR 16TH INTERNATIONAL CONGRESS ON MDS COMING IN OUR NEXT ISSUE!

Explore all Congress Science On-Demand: mds.kenes.com #MDS21
The Virtual Platform is available until 31 December 2021.

II LATIN-AMERICAN MDS FOUNDATION SYMPOSIUM

DR. MARCELO IASTREBNER
President
Latin-American MDS Group – GLAM

The VII Latin-American Myelodysplastic Syndrome Group Symposium and II Latin-American MDS Foundation Symposium was held virtually on April 23–24, 2021. It was co-organized by the Latin-American Myelodysplastic Syndrome Group (GLAM) and the MDS Foundation. Nineteen Ibero-american scientific societies were partners of the event (Mexico, Honduras, Guatemala, Costa Rica, Dominican Republic, Panamá, Colombia, Venezuela, Brazil, Ecuador, Bolivia, Perú, Paraguay, Chile, Uruguay, Argentina, GATLA and GESMD).

The purpose of this Symposium was to address the latest developments regarding Myelodysplastic Syndromes (MDS). High quality conferences were dictated by worldwide recognized experts in this field.

The Symposium had four major objectives: i. To share most recent advances in MDS biology, particularly the role of somatic mutations and bone marrow micro-environment. ii. To know how to incorporate genetic data in the diagnostic and prognostic evaluation of MDS in routine clinical practice. iii. To learn the differences in diagnosis and treatments between Aplastic Anemia and Hypoplastic MDS. iv. To review the current treatment approaches in low and high risk MDS patients and to learn how to manage MDS after hypomethylating agents failure.

1225 participants from 46 countries were registered: Argelia, Argentina, Australia, Belgium, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Croatia, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, France, Germany, Great Britain, Greece, Guatemala, Honduras, India, Indonesia, Iraq, Ireland, Israel, Italy, Japan, Kuwait, Mexico, Nepal, Pakistan, Panama, Paraguay, Peru, Poland, Portugal, Slovakia, Spain, Switzerland, Taiwan, Thailand, United States of America, Uruguay, and Venezuela.

The Symposium was structured in 8 sessions:

- **Session I.** Biology of MDS. This session included 3 conferences by Dr. Elvira Velloso (Brazil), Dr. Rafael Bejar (USA) and Dr. Carolina Belli (Argentina) with 314 attendees.
- **MDS Satellite Symposium organized by Novartis.** This session included 2 conferences by Dr. Matilde Boada (Uruguay) and Jorge Arbelbide (Argentina) with 362 attendees.
- **Session II.** Low Risk MDS. This session included 4 conferences by Dr. Pierre Fenaux (France), Dr. Silvia Magalhaes (Brazil), Gabriela Vidal (Peru) and Carlos Hernández (Mexico) with 433 attendees.
- **MDS Satellite Symposium organized by Bristol Myers Squibb Company.** This conference was held by Dr. Guillermo Garćia-Manero (USA) with 449 attendees.
- **E-Poster session.** Twelve abstracts were selected and presented in this session. There were 464 attendees.
- **Meeting with Experts.** 4 Simultaneous sessions. Genetic, Morphology, Flow Cytometry and Bone marrow Transplantation.
- **Session III.** High Risk MDS. This session included 4 conferences by Dr. Stephen D. Nimer (USA), Dr. Pierre Fenaux (France), Dr. Virginia Abello Polo (Colombia) and Dr. Ximena Valladares (Chile) with 208 attendees.
- **Satellite Symposium organized by Abbvie.** This session included 3 conferences by Dr. Maria Marta Rivas (Argentina), Dr. Andŕes Gomez (Mexico) and Dr. Nicolas Cazap (Argentina) with 238 attendees.
- **Session IV.** MDS progression and Chronic Myelomonocytic Leukemia (CMML). This session included 3 conferences by Dr. Valeria Santini (Italy), Rafael Bejar (USA) and Raphael Itzykson (France) with 262 attendees.

All sessions are available "on demand" at GLAM Website www.grupoglam.org. **A Latin-American MDS Patient Meeting** was successfully held online with 138 registered. Dr Pierre Fenaux received his recognition as a GLAM **"Honorary Member." Welcome words, conclusions and remarks were expressed by Dr Stephen Nimer and Marcelo Iastrebner**.

This event was jointly prepared between the MDS Foundation (Mrs. Tracey Iraca, Ms. Lea Harrison) and the Latin-American MDS Group – GLAM/LATAM.

The COVID pandemic that has caused thousands of deaths in Latin-America and all over the world, tremendously affected our organization but fortunately, the convening of the Symposium was a real success. It was challenging to actively keep the attention of the audience during 2 consecutive days (exactly, 14 hours).

The MDS Foundation (Mrs. Audrey Hassan), together with patients associations from Colombia (Fundación Leucemia Linfoma, led by Yolima Mendez) and Argentina (ACLA Group, led by Haydee Gonzalez) organized a separate session devoted to patients and families. People who attended that session provided excellent feedback.

During my welcome speech I provided a short review of Glam history and the Latin-America state of the art in myelodysplastic syndromes. We had a cultural event enjoying Uruguayan music and a friendly virtual time. We also announced the next Latin-American Symposium that will be held in Chile, 2023.

We are very grateful with several pharmaceutical companies like Abbvie, Novartis, Bristol-Myers Squibb and Megalab. Without their assistance, this high-quality meeting couldn't have been possible.

In short, we experienced two spectacular days with excellent scientific conferences in a friendly atmosphere.

3RD REGIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

4-5 NOVEMBER 2022 | KYOTO, JAPAN

Advancing Research & Patient Care

mds foundation
the myelodysplastic syndromes foundation, inc.

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INTERNATIONAL WORKING GROUPS

MDS FOUNDATION INTERNATIONAL WORKING GROUP FOR PROGNOSIS IN MDS

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

IWG-PM/MOLECULAR PROJECT

The Molecular Project of the International Working Group for Prognosis in MDS (IWG-PM) has been working to develop a clinical-molecular risk model (IPSS-Molecular or IPSS-M). To this end, mutations in diagnostic MDS samples from 2957 patients from 13 countries and 25 global centers were analyzed. These data were presented by Elli Papaemmanuil and Elsa Bernard at the Toronto MDS Symposium and the IWG-PM group meeting, and submitted as an abstract to the 2021 American Society of Hematology meeting.[1] Clinical, cytogenetic, and molecular variables were evaluated for associations with leukemic transformation and overall survival. At least one genetic driver alteration in 94% of patients. Multivariate analysis identified multi-hit TP53, FLT3 mutation, and *MLL* partial tandem duplication as top genetic predictors of adverse outcomes. SF3B1 mutation was associated with favorable outcomes, but this was modulated by co-mutation patterns. Using hematologic, cytogenetic and molecular data on 31 genes, the IPSS-M was developed as a continuous score. A discrete six-category risk schema was further derived. The IPSS-M re-stratified 46% of MDS patients compared to the IPSS-R, improving discrimination across clinical endpoints. A web calculator was built that, upon entering predictor variables, outputs a patient-tailored score, its corresponding risk category, and temporal estimates for clinical endpoints. The IPSS-M prognostic risk score is personalized, interpretable and reproducible. Combining conventional parameters with genomic profiling, the IPSS-M represents a valuable tool for clinical decision-making for MDS patients.

IWG-PM
INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

ONGOING AIMS FOR THE MOLECULAR PROJECT INCLUDE GENERATING DATA FOR AN MDS CLASSIFICATION MODEL, GENETIC PREDICTORS OF RESPONSE TO HMAS, AND ANALYSIS OF MECHANISMS OF DISEASE PROGRESSION OBTAINED FROM SEQUENTIAL PROFILING.

Other ongoing aims for the Molecular Project include generating data for an MDS Classification model, genetic predictors of response to HMAs, and analysis of mechanisms of disease progression obtained from sequential profiling.

At the Toronto IWG-PM group meeting, updates were also provided by Andrea Pellagatti regarding his project, Gene expression in MDS HSPCs using single cell analysis: Disease pathophysiology and outcome prediction, and by Andrea Kuendgen regarding cytogenetic features from the treatment-related MDS project.

Also reviewed were publications related to recent efforts by members of the group:

1. Bernard E, Tuechler H, Greenberg PL, et al. Ebert B, Bejar R, Malcovati L, Cazzola M, Ogawa S, Hellström-Lindberg E, Papaemmanuil E. A Clinical-Molecular and Personalized Risk Scoring System for Patients with MDS (IPSS-M), Proceedings ASH 2021, Atlanta, December.
2. Haase DT, Stevenson K, Neuberg D, Maciejewski J, et al, Bejar R. TP53 Mutation Status Divides MDS with Complex Karyotypes into Distinct Prognostic Risk Groups. *Leukemia*. 2019, 33:1747–1758.
3. Bernard E, Nannya Y, Hasserjian, et al, Papaemmanuil E. Implications of TP53 Allelic State for Genome Stability, Clinical Presentation and Outcomes in MDS. *Nature Medicine*. 2020, 26:2549–2556.
4 Papemmanuil E, Classification and personalized prognosis in MDS. MDS Foundation Symposium, ASH meeting, 2019 Orlando, December.

5. Malcovati L, Stevenson K, Papaemmanuil E, Neuberg D, Bejar R, et al, Cazzola M. SF3B1-mutant MDS as a distinct disease subtype — A Proposal IWG-PM. Blood 2020, 136:157–1704.
6. Kuendgen A, Tuechler T, Nomdedeu M, et al, Sanz G. Therapy-related MDS deserve specific diagnostic sub-classification and risk-stratification — An approach to classification of t-MDS. *Leukemia*. 2021, 35:835-849.
7. Nomdedeu M, Tuechler H, Kuendgen A, et al, Haase D. Cytogenetic findings in therapy-related MDS — relation with primary disease and therapy. Proc MDS Foundation Symposium, Copenhagen, May 2019, #127.

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.

INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS (IWG-PM)

IWG-PM
INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

The International Working Group for Prognosis in MDS (IWG-PM) consists of a group of international investigators aligned through the MDS Foundation whose focus is aimed at defining the clinical and biologic features of MDS thus providing the foundation for understanding the nature and potential for progression of this spectrum of disorders.

To this end, the group has generated programs leading to seminal projects and publications characterizing and classifying the disease.

Current group investigations include determining the impact of mutational features that further delineate disease status and potential therapeutic targets providing novel treatment approaches for MDS.

MDS RISK ASSESSMENT CALCULATOR

THE IWG-PM UNDER THE AEGIS OF THE MDS FOUNDATION, INC. DEVELOPED A PROGNOSTIC TOOL, THE IPSS-R CALCULATOR, TO DETERMINE A PATIENT'S RISK OF PROGRESSING TO ACUTE MYELOID LEUKEMIA (AML).

BASIC CALCULATOR:
https://www.mds-foundation.org/ipss-r-calculator/

ADVANCED CALCULATOR:
https://www.mds-foundation.org/advanced-calculator/

APPLE STORE:
https://apps.apple.com/app/id585168085

GOOGLE PLAY STORE:
https://play.google.com/store/apps/details?id=com.basiccalculator

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COLLOQUY

Share In Confidence

Colloquy provides the MDS community with the opportunity to share personal stories and hear real-life experiences; allowing patients, carers and loved ones to learn more about their condition and to help others.

In partnership with the MDS Foundation

LAUNCHING IN 2022

- Capturing diverse perspectives to uncover the true unmet needs in healthcare
- Colloquy will be available online (through any web browser) or via a mobile application

Supporting you to...

- Share experiences amongst your community within a safe and personal environment
- Hear real-world experiences from people like you
- Gain access to resources to learn about various aspects of MDS, gain confidence in your condition, and discover how to improve your care

Guided by our ambassadors

Colloquy is led by a team of ambassadors to ensure the patient perspective is brought to the forefront of everything we do. The team of ambassadors are made up of patients, loved ones, experts and nurses, who facilitate exchanges and direct you to resources and tools that support you along your journey.

The ambassadors are advocates for the patient community and work to ensure Colloquy provides support to the MDS community, and people like you.

Register your interest today

Want to gain immediate and personalized access to a safe and supportive community bringing those impacted by MDS together?

To register your interest, visit the website below or scan the QR code!
www.colloquy.health

SCAN ME

QUESTIONS ANSWERED

VISIT OUR NEW MICROSITE

DO YOU KNOW YOUR MDS SUBTYPE, IPSS-R SCORE & GENE MUTATION PROFILE?

MDS treatment is individualized based on a patient's subtype, IPSS-R score and, to some extent, genetic mutation. This knowledge will empower patients and their caregivers to take a more active role in decisions about their treatment and advocate for appropriate treatments that may prolong their life and improve their quality of life. The following information is designed to help you understand how your subtype and IPSS-R score are determined, as well as general information on genetic mutations commonly found in MDS and the importance of genetic testing for these mutations.

Knowing your subtype, IPSS-R score and gene mutation profile will help facilitate discussions with your healthcare provider on what this means for you personally and help select the best treatment options.

IPSS-R SCORE

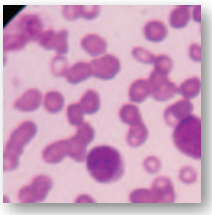
The IPSS-R is a classification system used by doctors to help predict a person's risk of developing AML and overall survival without treatment.

MDS SUBTYPE

MDS is classified into several different subtypes based on the following features: Blood cell counts, Percentage of blasts in the bone marrow, and Cytogenetics.

MUTATION PROFILE

Genetic mutations occur when a gene is damaged and alters the genetic message. Mutations can potentially identify effective therapies to treat your disease.



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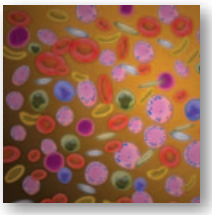
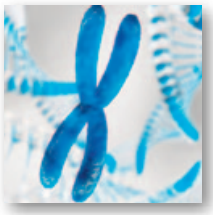


MDS-RS-MLD



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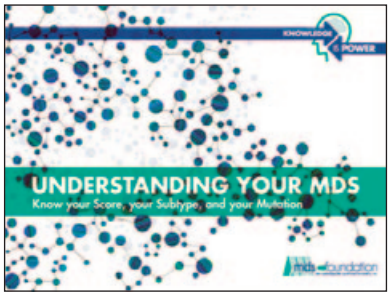

UNDERSTANDING YOUR MDS: KNOW YOUR SCORE, YOUR SUBTYPE, AND YOUR MUTATION

This brochure is intended to help you better understand the diagnosis of MDS. Created by the MDS Foundation staff, Board of Directors, and medical and scientific leaders, it will explain the various MDS subtypes; how a prognostic scoring system is designed and where you can place yourself with the help of your physician and other health professionals. You will learn about normal and abnormal blood cells; leukemic blasts; blood counts; chromosomes and molecular mutations that may assist your provider in further modifying your subtype and, possibly, selecting the type of therapy for you.

John M. Bennett, MD
First Chair and Founding Member of the MDS Foundation

To order your free copy of **UNDERSTANDING YOUR MDS: Know your Score, your Subtype, and your Mutation**, please call 1-609-298-1035 or order online at https://www.mdsknowledgeispower.com/order-a-brochure/.

To learn more, visit our website at https://www.mdsknowledgeispower.com/.

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WHAT, IN YOUR OPINION, MAKES THE MDS FOUNDATION/ MOVE FOR MDS COMMUNITY EVENTS SPECIAL? WHAT DO YOU THINK IT DOES FOR THE PEOPLE WE SERVE?

The MDS Foundation/Move for MDS event brings the MDS community together and provides a sense of hope and strength for patients. Events such as this, have never been more important than today as we continue to deal and cope with the COVID pandemic.

HOW IS COMMUNITY ENGAGEMENT INCORPORATED INTO YOUR COMPANY'S CULTURE? HOW DOES THE MDS FOUNDATION AID THAT EFFORT?

Like the MDS Foundation, Abbvie is also committed to advancing MDS research. We embrace the responsibility of making a remarkable impact on people's lives through the innovative medicines and solutions we create together. AbbVie is a patient-focused organization that partners with patients, patient organizations, caregivers, and their communities, to understand how MDS impacts their lives and how our innovative medicines can potentially advance patient health and well-being.

HOW LONG HAS YOUR COMPANY BEEN INVOLVED WITH THE MDS FOUNDATION? WHY PROMPTED THE PARTNERSHIP?

AbbVie has recently partnered with the MDS Foundation to join their efforts in supporting education of patients and their families as they face an MDS diagnosis and subsequent treatment. AbbVie and the MDS Foundation share a common goal of advancing MDS research to better diagnose, control and ultimately cure this disease.

"This is the fourth year we are partnering with our communities to Move for MDS. The MDS community continues to exceed our expectations. With 2020 and 2021 being such challenging years worldwide, it is motivating to know that nothing has stopped us from fighting this difficult to treat disease together. It is inspiring to see so many people planning to come together on a single day from across the globe.

From the US, to Germany, to Australia, we are seeing our worldwide community joining together to be a part of the Global Move for MDS Walk."

DR. STEPHEN NIMER, CHAIR, THE MDS FOUNDATION, INC.

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EDITORIAL

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR OLDER ADULTS WITH MDS

RYOTARO NAKAMURA, MD
Division of Leukemia
Department of Hematology &
Hematopoietic Cell Transplantation
Director, Center for
Stem Cell Transplantation
City of Hope National Medical Center,
Duarte, CA

1. INTRODUCTION

Myelodysplastic syndrome (MDS) refers to a heterogeneous group of hematologic disorders characterized by acquired and ineffective clonal hematopoiesis leading to various degrees of cytopenia, dysplastic morphology in the bone marrow, and a tendency to transform into acute myelogenous leukemia (AML).[1] MDS are typically diseases of older adults with a median age of 76 years at diagnosis.[2] Clinical presentation of MDS can range from mild/asymptomatic to severe/symptomatic with transfusion-dependent cytopenia, recurrent infections, and rapid progression to AML. Despite the better understanding of the molecular pathogenesis, advances in treatment options and supportive care in the past decades, and availability of therapeutic agents that has led to prolongation of life,[3] allogeneic hematopoietic cell transplantation (alloHCT) remains the only potentially curative therapy. However, alloHCT is associated with a significant risk of transplant-related mortality (TRM) due to infections, graft-versus-host disease (GVHD), regimen-related toxicities, and graft rejection. Moreover, disease relapse can still occur after HCT. Therefore, the decision-making process for alloHCT is complex and highly individualized, weighing the risks of "HCT-related complications" against those of "low survival rate without HCT", for patients with MDS due to disease heterogeneity in clinical presentations and progression pace.

While the therapeutic role of alloHCT is well-established in younger patients with MDS,[4-6] the relative benefits of HCT over non-HCT therapy in older adults with MDS is not well defined. In fact, in the United States, the Centers for Medicare and Medicaid Services (CMS) released their Decision Memo for alloHCT for MDS (CAG-00415N) in August 2010, stating: "The evidence does not demonstrate that the use of alloHCT improves health outcomes in Medicare beneficiaries with MDS. However, we believe the available evidence shows that alloHCT for MDS is reasonable and necessary under §1862(a)(1)(E) of the Act through Coverage with Evidence Development (CED)".

Although the number of HCTs performed for MDS is increasing according to the Center for International Blood and Marrow Transplant Research (CIBMTR);[7] HCT for MDS is likely remaining under-utilized. In a large trial for older patients with high-risk MDS, only 13% of patients proceeded to HCT,[8] and in a cross-sectional survey of 101 physicians treating 4,154 patients with MDS, fewer than 5% of patients were evaluated for HCT.[9]

In this article we will review accumulating data from studies aimed to address benefits of alloHCT in older MDS patients and discuss additional considerations with emerging data in both HCT and non-HCT therapies.

2. NON-TRANSPLANT THERAPIES AND SURVIVAL OUTCOMES

Current treatments for MDS include best available supportive care with transfusions, prophylactic/therapeutic antibiotics, and growth factor support as appropriate.[10] Additionally, in patients with lower-risk MDS, lenalidomide is used as an immuno-modulating agent.[11-13] Benefits of lenalidomide have been particularly evident for patients with the del(5q) chromosomal abnormality.[13] Comparative studies have not shown a benefit in any of the intensive chemotherapy regimens used for MDS treatment.[14,15] Azacitidine and decitabine are DNA-hypomethylating agents (HMAs) that are currently approved by the Food and Drug Administration (FDA) for treatment of MDS. The rationale for hypomethylation therapy was based on the observation that aberrant DNA methylation is a dominant process in MDS.[16-19] HMAs indirectly deplete methylcytosine, resulting in hypomethylation of target genes promoters involved in disease initiation/progression, making them appropriate targets for pharmacologic therapy. Administration of HMAs leads to a hematological response with steady improvement in cell counts in 40–50% of treated patients and delay in progression to AML in patients with higher-risk MDS.[20] The duration of response is, however, usually limited to less than two years with a median duration of 11–15 months.[21,22] Furthermore, the prognosis after azacitidine failure in patients with high-risk MDS is dismal with a median overall survival (OS) of 5.6 months, and 2-year survival probability of only 15%.[23] The overall survivals (OS) reported in large phase II/III trials using HMAs for MDS are summarized in **Table 1.**

3. SURVIVAL OUTCOMES AFTER ALLOHCT IN MDS

AlloHCT offers a potential cure of MDS through intensive conditioning chemo-radiotherapy and potent graft-versus-leukemia (GVL) effects. The introduction of reduced intensity conditioning (RIC) regimens over the last two decades has allowed expansion of the upper age limit for alloHCT, providing access to transplantation for older patients with MDS. Over the last several years, multiple groups have used alloHCT with RIC to treat MDS with 2–3-year OS rates, ranging from 27–70% depending on the cohort and regimen characteristics.[24-27] Lim and colleagues reported outcomes of 1333 patients with MDS/secondary AML aged ≥50 years using the European Society for Blood and Marrow Transplantation

Table 1 Overall Survival Data with Hypomethylating Agents

Design/Therapy	Total N	Median Age, years (range)	Overall Survival
Cohort: Outcome after AZA-failure[23]	435	69 (not available)	15% (2 year)
Cohort: Compassionate Use AZA[64]	282	71(20–89)	17.5% (3 year)
Phase III: Low-Dose Decitabine vs. BSC[65]	233	70 (60–90)	19% (2 year)
Phase III: European AZA-001: AZA vs. BSC[3]	358	69 (38–88)	50.8% (2 year), ~30% (3 year by survival curve)
Phase III: CALGB AZA vs. BSC[66]	191	69 (31–92)	~45% (2 year), ~25% at (3 year by survival curves)

AZA: azacytidine, BSC: best supportive care, CALGB: Cancer and Leukemia Group B

(EBMT) data;[28] and showed that disease stage at time of transplantation, but not recipient age or the intensity of the conditioning regimen, is the most important factor influencing outcomes. McClune *et al*, investigated the effect of age on RIC-HCT outcomes in older patients (age 40 years or above) with MDS (n=545) or AML (n=535); using the CIBMTR data, and reported that MDS patients age 40 to 54, 55 to 59, 60 to 64, and >65 years had 2-year survival rates of 42%, 35%, 45%, and 38%, respectively (*P*=.37).[29] As in the EBMT study, the CIBMTR data showed no significant impact of age on HCT outcomes. In another large CIBMTR study, Saber and colleagues evaluated outcomes of adult patients with MDS (n=701) at the median age of 53 years (range: 22–78) who underwent alloHCT between 2002 and 2006, in which 40% of patients received RIC regimens.[30] Focusing on the impact of donor source on HCT outcomes, they reported adjusted 3-year OS estimates of 47%, 38%, and 31% for matched-related donor (MRD), 8/8 HLA allele matched unrelated donor (MUD), and 7/8 MUD, respectively.

4. HCT VS NO-HCT – RETROSPECTIVE STATISTICAL MODELING STUDIES

Previous statistical modeling analyses demonstrated the potential benefits of early HCT in older populations. Koreth and colleagues evaluated RIC-HCT vs non-HCT therapies in older adults with MDS using a Markov decision model with quality-of-life (QOL) utility estimates for different MDS/transplant states.[31] The key outcomes were life expectancy (LE) and QOL-adjusted LE. The study included 513 patients with *de novo* MDS aged 60–70 years, and compared RIC-HCT (n=132) stratified by International Prognostic Scoring System (IPSS) risk with best supportive care for those with IPSS intermediate-1 disease without anemia (n=123), growth factors for patients with anemia and IPSS-low/intermediate-1 (n=94), and HMAs for patients with intermediate-2/high IPSS. Their analyses showed that for patients with low/intermediate-1 IPSS, nontransplantation approaches should be preferred whereas for intermediate-2/high IPSS patients, RIC-HCT offers overall and quality-adjusted survival benefit.

Platzbecker and colleagues also reported their analyses on the outcomes of two well-balanced cohorts of patients with high-risk MDS defined by age (60–70 years), performance status (Eastern Cooperative Oncology Group score ≤2), and donor availability (yes/no).[32] The study included 103 patients undergoing HCT and 75 patients without the HCT option who received azacitidine. The estimated 2-year OS after the start of treatment was 39% for HCT patients and 23% for the patients receiving azacitidine. A multivariate analysis showed an advantage for HCT over azacitidine (HR=0.3; *P*=0.007) for OS.

5. IMPACT OF HCT/DONOR AVAILABILITY IN MDS – PROSPECTIVE STUDIES

Prospective trials to evaluate the benefit of HCT in older MDS patients are summarized in **Table 2**. Although a randomized study comparing transplantation to nontransplant therapies would be optimal, this design has been considered impractical.[33-35] A biologic assignment design based on the availability of a matched donor can allow for unbiased identification of patients who are HCT eligible and equally fit, yet, not proceeding with HCT, creating a clinically comparable cohort against HCT cohort.

Robin et al, conducted a study on behalf of the SFGM-TC (Société Francophone de Greffe de Moelle et de Thérapie Cellulaire) and GFM (Groupe Francophone des Myélodysplasies) to compare OS in MDS patients who are considered as candidates for HCT according to donor availability.[36] The study accrued 162 patients (50 without and 112 with an available donor) and demonstrated that 4-year OS is significantly better in patients with an HLA matched donor (37%) undergoing HCT compared to patients who did not receive HCT (15%).

More recently, Kroger and colleagues reported a protective trial of 190 patients (median age: 63) who received 4–6 cycles of azacitidine followed by HLA-compatible RIC-HCT or continuous azacitidine if no donor was identified.[37] In this study, 28 patients did not meet the inclusion criteria and of the remaining 162 patients who received azacitidine, 108 (67%) were eligible for subsequent allocation to HCT (n=81) or continuous azacitidine (n=27). Reasons for premature study termination of 54 patients (33%) within the first four 5-aza cycles were disease progression (n=26), death (n=12), or other reasons (n=16). The 3-year OS after azacitidine pretreatment and treatment allocation was reported at 50% with HCT and 32% with continuous azacitidine (*P*=0.12). The event-free survival (EFS) was 34% with HCT and 0% with continuous azacitidine (*P*<0.0001). Patients progressing after continuous azacitidine (n=14) received a salvage allograft from an alternative donor, and 43% were alive at last follow-up. The authors concluded that in older patients with MDS, RIC-HCT results in a significantly improved EFS compared to continuous azacitidine therapy. Bridging with azacitidine to HCT is associated with a considerable rate

Table 2. Protective Trials Examining the Role of HCT in Older Adults with MDS

Study	N	Age Median (range)	MDS Eligibility	Study Design	Outcomes
SFGM-TC and GFM[36]	Total: 162 - Donor: 112 - No Donor: 50	60 (50-70)	- *de novo* or therapy-related MDS - int-2 or high IPSS, or - int-1 IPSS with poor risk cytogenetics or - platelet transfusion-dependent thrombocytopenia, or - low or int-1 IPSS MDS that progressed to higher risk MDS or AML - CMML	Landmark: 3 months from registration Conditioning: RIC	Four-year survival was 37% in the Donor group compared with 15% in the No Donor group (P=0.02).
VidazaAllo[37]	Total: 190 -Received AZA: 162 -Eligible for assignment: 108 - HCT: n=81 - AZA: n=27	63 (55-72)	- *de novo* or therapy-related MDS or CMML - IPSS: int-2-risk or high-risk/int-1 with high-risk cytogenetics, or secondary acute myelomonocytic leukemia and blasts ≤ 30% (RAEB-T according to French-American-British classification)	biologic allocation after 4 cycles of AZA pretreatment and achievement of at least stable disease Conditioning: RIC	The event-free survival and OS after AZA pretreatment and treatment allocation at 3 years were 34% (95% CI, 22 to 47) and 50% (95% CI, 39 to 61) after HCT and 0% and 32% (95% CI, 14 to 52) after continuous AZA treatment (P < .0001 and P = .12), respectively.
BMT CTN 1102[40]	Total: 384 - Donor arm: 260 - No-Donor arm: 124	66.7 (50-75)	- *de novo* MDS - IPSS int-2 or high - therapy-related MDS or transformed AML excluded	- at registration - assignment at 90 days from registration Conditioning: RIC	Adjusted OS at 3 years was significantly higher in the Donor arm when compared with the No-Donor arm: 47.9% (95% CI, 41.3 to 54.1) versus 26.6% (95% CI, 18.4 to 35.6, absolute improvement 21.3% [95% CI, 10.2 to 31.8], P = .0001)
DFCI study[37]	Total: 290 - HCT: 113 - No HCT: 177	69 (60-75)	MDS, MDS/MPN-U, or CMML, with disease sufficiently advanced to warrant consideration of RIC HCT	- single cohort - HCT was treated as a time-dependent variable Conditioning: RIC	In multivariable analyses controlling for age, gender, ECOG performance status, cytogenetic risk, and IPSS risk group, HR for death was 0.75 (p=0.13) for HCT compared to no HCT, 0.57 (p=0.01) for adverse MDS risk and 1.33 (p=0.36) for standard risk with severe cytopenia.
CIBMTR study[38]	Total: 1280 (all HCT) ≥ 65yo: 688 55-64yo: 592	NA	Any MDS	Comparisons between the two age groups Conditioning: MAC or RIC	The 3-year OS was 37% vs 42% for the 65 years or older group vs the 55 to 64 years age group, respectively. On multivariable analysis after adjusting for excess risk of mortality in the older group, age group had no significant association with OS (HR, 1.09; 95% CI, 0.94-1.27; P = .23) or NRM (HR, 1.19; 95% CI, 0.93-1.52; P = .16).

of dropouts because of progression, mortality, and adverse events.

Another prospective longitudinal observational study recently conducted at the Dana-Farber/Harvard Cancer Center was designed to examine survival, QOL, and other outcomes for RIC-HCT vs non-HCT approaches for HCT-eligible patients aged 60–75 years with adverse MDS risk (intermediate-2/high-risk IPSS, low/intermediate-1 IPSS with poor-risk cytogenetics, or therapy-related MDS) or standard risk with severe cytopenia.[38] A total of 290 patients were enrolled and 113 underwent HCT after a median of 5 months. In multivariable analyses controlling for age, gender, ECOG performance status, cytogenetic risk, and IPSS risk group, HR for death was 0.75 (P=0.13) for HCT vs no-HCT, 0.57 (P=0.01) for adverse MDS risk and 1.33 (P=0.36) for standard risk with severe cytopenia.

A recently reported prospective CIBMTR study (NCT01166009) was one of the two CMS-approved trials under the CED program. The study compared transplant outcomes in MDS patients aged ≥65 years (n=688) with those at 55-64 years of age (n=592).[39] The 3-year OS was 37% vs 42% for the ≥65 years vs the 55–64 years age group, respectively. On multivariable analysis after adjusting for excess risk of mortality in the older group, age group had no significant association with OS (P=0.23) or NRM (P=0.16).

Lastly, the Blood and Marrow Transplantation Clinical Trial Network (BMT CTN) initiated a large prospective multicenter biologic assignment trial comparing outcomes of patients with de novo MDS (IPSS intermeiate-2/high), aged 50–75 years, based on donor availability.[40] This trial was in accordance with suggestions from a review article by Giralt et al. regarding clinical trials to provide evidence for Medicare coverage of HCT for MDS,[41] and was the second study approved by the CMS as meeting their criteria for CED. Between January 2014 and November 2018, a total of 384 patients (median age: 67 years) were enrolled and 260 (67.7%) were biologically assigned to the Donor arm and 124 (32.3%) assigned to the No-Donor arm. OS at 3 years (adjusted for prespecified variables: age, race or ethnicity, performance status, disease status, comorbidity index, IPSS score, MDS disease duration, and response to HMA therapy) was significantly higher in the Donor arm when compared with the No-Donor arm: 47.9% vs 26.6%, with an absolute improvement of 21.3% (95% CI: 10.2–31.8, P=0.0001). The survival benefit was seen across all subgroups examined including age over 65 years. The as-treated analysis, accounting for cases of non-compliance to the biologic assignment, demonstrated a significant advantage in 3-year OS (47.4% vs 16.4%, P<.0001) for HCT subjects. Importantly, the preliminary data showed that the QOL measures between the two groups in this trial were similar, indicating that the observed survival benefit with RIC-HCT was achieved without an early decrement in QOL.

6. ADDITIONAL CONSIDERATIONS IN HCT VS. NO-HCT

Patient-specific factors – age/comorbidity

With advances in supportive care and the use of RIC, HCTs are increasingly feasible in even 'older' patients.[28,30] In fact, HCTs for patients >70 years old are increasingly used with promising results.[42] In HCT, the comorbidity index (HCT-CI) developed by Sorror et al. has shown prognostic significance in clinical studies and is being widely used to predict transplant outcomes and risk of mortality.[43] A MDS-specific comorbidity index (MDS-CI) may also inform patients and physicians about more refined prognostic predictions incorporating patient-related factors with disease-related prognostic factors.[44] Lastly, geriatric assessments for functional reserve and resiliency are increasingly incorporated into HCT practice, and likely provide insight and guidance towards personalized decisions for HCT in elderly MDS patients.[45,46]

Disease-specific factors — somatic mutations

As discussed above IPSS/IPSS-R have been used as the standard prognostic scoring system for MDS, and the available data support that patients with intermediate-2/high-risk by IPSS would benefit from an early HCT. There is accumulating evidence that somatic mutations in MDS are highly prognostic and can impact transplant outcomes. Mutations in *ASXL1*, *SRSF2*, *RUNX1*, *U2AF1*, and *TP53* genes are associated with poor prognosis.[47] A combination of TP53 mutation with complex karyotype is associated with inferior prognosis especially in the post-HCT setting.[48] A large CIBMTR cohort analysis of somatic mutations showed a negative impact for *TP53* mutation on survival, and indicated that presence of RAS pathway mutations was associated with shorter survival due to relapse while JAK2 mutations were associated with shorter survival due to NRM.[49] On the contrary, Aldoss et al, reported that the survival outcome of therapy-related MDS was not different between *TP53* mutated and unmutated cases.[50] Future studies are warranted to better define the benefit of HCT according to molecularly informed prognosis toward personalized medicine.

Transplant-related factors — alternative donors, conditioning intensity

Potential donors for alloHCT include MRD, MUD from the donor registry, and alternative donors, including haploidentical donors, mismatched unrelated donors (MMUD) and cord blood units. While a matched young sibling donor is preferred as the first donor choice, as most patients with MDS are older, a MUD is more commonly available. Studies, including the above mentioned CIBMTR study,[30] have shown comparable results with MRD and MUD transplants, and were the basis of biologic assignment trials. Recent data from transplant studies using alternative donors are also encouraging. HLA-haploidentical donor (haplo) HCT using post-transplantation cyclophosphamide (PTCY) for GVHD prophylaxis is increasingly offered for hematologic malignancies, including MDS. In a recent CIBMTR analysis comparing haplo and MUD-HCT, multivariate analysis revealed higher relapse (HR=1.56; *P*=0.0055; 2-year relapse rate, 48% vs. 33%) and lower disease-free survival rates after haploidentical HCT (HR=1.29; *P*=.042; 2-year disease free survival [DFS], 29% vs 36%).[51] However, OS rates did not differ between donor types due to mortality associated with chronic GVHD. Regarding conditioning intensity, a multi-center randomized trial by the BMT CTN (0901) compared MAC and RIC in patients with AML or MDS, demonstrating a significant advantage with MAC in relapse-free survival, primarily due to reduced relapse rate despite of the reduced TRM.[52] However, since MDS represented only ~20% of the entire cohort, specific conclusion on MDS could not be made. In general, more fit, and younger patients with no significant comorbidities are considered for MAC, while relatively frail patients with comorbidities would likely benefit from RIC-HCT. Additionally, the CIBMTR examined fludarabine/melphalan-based vs. fludarabine/busulfan-based RIC in MDS and found that fludarabine-melphalan-based regimens are associated with superior DFS and OS compared with fludarabine/busulfan due to reduced relapse incidence despite higher TRM.[53]

Advances in non-HCT therapy

As both HCT and non-HCT therapies are constantly evolving and improving, relative benefits and risks of HCT against non-HCT therapy would be changing overtime. Combination therapy of HMA with lenalidomie[54] or vorinostat[55] have been explored with promising results in early phase trials. However, a three-arm randomized phase II study by the Southwest Oncology Group (SWOG) evaluating azacitidine alone or in combination with lenalidomide or with vorinostat for higher risk MDS failed to show clinical advantage of the combination therapy over azacitidine alone.[8] More recently, HMA in combination with venetoclax showed favorable results in AML,[56] and this promising combination is now being explored in high-risk MDS. PRIMA-1Met (APR-246) is a methylated derivative of PRIMA-1, which induces apoptosis in human tumor cells through restoration of the transcriptional transactivation function of mutant *TP53*. APR-246, has demonstrated reactivation of mutant TP53 in clinical trials, currently being tested in a phase III trial with HMAs (NCT03745716).[57] Magrlimab, which targets CD47, a macrophage immune checkpoint, has been combined with azacitidine with promising response rates.[58] These novel therapeutic options might change the expected clinical course of MDS, which in turn, can impact the decision process for HCT. Effective non-HCT therapies may increase the number of transplant candidates due to a better disease control.

Cost of Care

While alloHCT is an expensive treatment modality,[59-61] non-HCT care for MDS can also be costly. A study using the Optum database, conducted before the FDA approval of 2 new agents (luspatercept and decitabine-cedazuridine) in 2020 for MDS, demonstrated that the average monthly cost of care per patient was $17,361 following diagnosis.[62] Another study showed similarly high total health care costs after HMA failure (~$77,000 during the first 6 months) primarily driven by nonpharmacy costs (i.e. blood transfusions, clinic/infusion visits).[63] A detailed prospective cost-effectiveness analysis is currently underway using the BMT CTN1102 trial.[40]

7. SUMMARY

The decision-making process to proceed or not proceed to HCT for patients with MDS is complex and requires considerations for both the disease-related and patient-related factors in a dynamic/longitudinal fashion (**Figure 1**). The accumulating evidence including prospective biologic assignment trials supports early referral for HCT consultation so that HCT is included as an integral part of MDS management plans in fit older adults with higher-risk MDS.

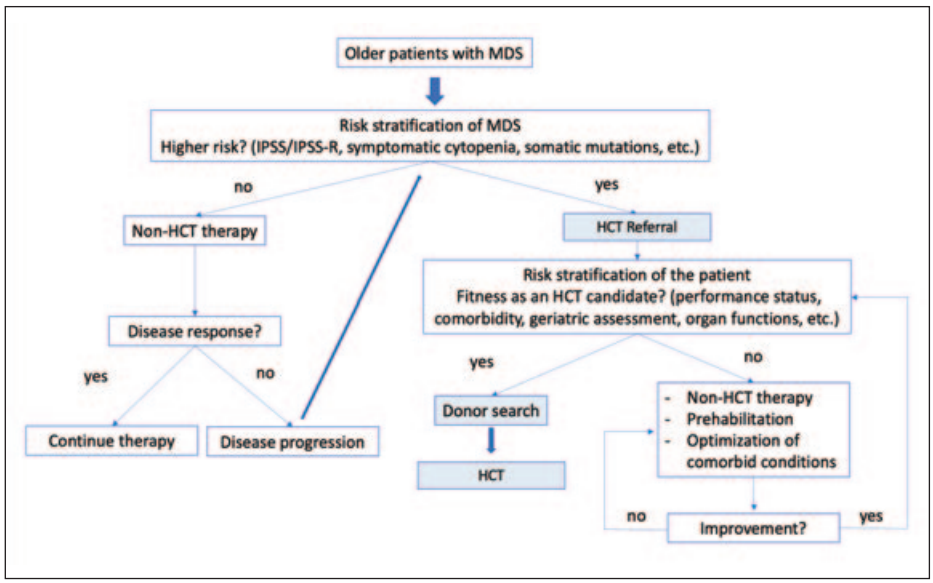

Figure 1. Proposed flow diagram of transplant referral and pre-transplant evaluations for older adults with MDS based on disease-related factors and patient-related factors.

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Blood and marrow transplants (BMT) help people with advanced myelodysplastic syndromes (MDS)

Not enough people have access to life-saving transplant

Although BMT is the only known cure for MDS, many people aren't aware of BMT or think that they're too old to have one because of its side effects.

Using smaller doses of therapy with BMT have made it safer. Now a new study of 400 older adults, aged 50 to 75, suggests that this type of BMT, along with a matched donor, helps people with advanced MDS live longer with a similar quality of life.

If a donor was found within 90 days, then patients got BMT. Otherwise, patients got other types of therapies. After 3 years:

- About half the people who got BMT were alive;
- Only about a quarter of the people who did not get BMT were alive;
- Quality of life after BMT was similar whether patients got BMT or not.

Experts say community doctors and transplant doctors should team up to care for people with MDS. They should work with insurance companies and patient advocacy groups to:

- Spread the news about BMT for older patients;
- Help patients visit a transplant center to find a donor for BMT early;
- Make health care affordable;
- Provide emotional support for patients and families;
- Help patients and families to get transportation and housing if they need to travel for transplant;
- Listen to and collaborate with communities of color.

Ask your doctor

Is transplant a treatment option for me? What are the possible benefits and harms?

Sources

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Learn more about

- MDS at BeTheMatch.org, NCCN.org, and MDS-foundation.org
- Clinical trials for MDS at CTsearchsupport.org
- More study summaries at CIBMTR.org

About this research summary

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) is a collaboration of The Center for International Blood and Marrow Transplant Research® (CIBMTR®); The Medical College of Wisconsin; The National Marrow Donor Program® / Be The Match®; and The Emmes Company®.

Clinical Trial ID

NCT02016781, BMT CTN 1102

BMT CTN Data Coordinating Center

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HIGHLIGHTS OF LATEST LITERATURE IN MDS

SUNEEL D. MUNDLE, PHD
RAMA BHAGWAT

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. Schwabkey Z, et al. Impact of obesity on survival of patients with myelodysplastic syndromes. *Hematol.* 2021;26(1):393-397 (DOI: 10.1080/16078454.2021. 1929692)

   In a retrospective single institution database analysis (Moffitt, USA) of 3089 men with known body mass index (BMI), 31% (n=963) were regarded as obese. While no significant difference was noted in baseline characteristics between groups of BMI < or ≥30, the median overall survival (OS) was better for those with BMI <30 (37 mo vs 34 mo, p=0.04), particularly in lower risk patients (57 mo vs 52 mo, p=0.08) or those with age <45yrs (116 mo vs 25 mo, p=0.034). BMI retained association with OS in a multivariate analysis as well. Also, for patients with BMI <30 the rate of AML trans-formation was lower (32% vs 36%, p=0.009).

2. Baba Y, et al. Increased serum C-reactive protein is an adverse prognostic factor in low-risk myelodysplastic syndromes. *Int J Hematol.* 2021;114(4):441-448. (DOI: 10.1007/s12185-021-03187-7)

   The study investigated the significance of inflammation in MDS by utilizing serum CRP levels as an indication of the degree of systemic inflammation. Traditionally, inflammatory cytokines are correlated with low survival in MDS patients. A retrospective analysis was conducted on 90 IPSS classified low-risk MDS patients. After examining CRP in the context of other known prognostic factors at diagnosis, it was concluded that serum CRP ≥0.58 mg/dL was associated with poor survival – both in the overall study as well as particularly in the 73 low-risk MDS patients defined by the revised IPSS. The study concluded that increased CRP may be a predictor of poor prognosis, and serum CRP levels can indicate clonal hematopoiesis and non-hematological comorbidity in low-risk MDS patients.

3. Kanagal-Shamanna R, et al. Only SF3B1 mutation involving K700E independently predicts overall survival in myelodysplastic syndromes. *Cancer.* 2021;127(19):3552-3565. (DOI: 10.1002/cncr.33745)

   A multivariate analysis including 55 MDS patients demonstrated that the previously known good prognosis with SF3B1mut may be limited to SF3B1mut K700E as the non-K700E variants showed comparatively lower survival similar to SF3B1wt. This was especially the case with lower risk MDS patients and those with ringed sideroblasts.

4. Natchkamp K, et al. Eligibility for clinical trials is unsatisfactory for patients with myelodysplastic syndromes, even at a tertiary referral center. *Leuk Res.* 2021, May 11 [Online ahead of print] (DOI: 10.1016/j.leukres.2021.106611)

   A simulation exercise from Düsseldorf MDS registry with historical 1809 patients and 47 clinical trials logged into the database, reevaluated eligibility of patients if all trials were to take place in 2016 with all patients as potential candidates for eligibility. On an average for any trial in general only 18% patients would be eligible, while 34% patients would be eligible for at least 1 of 9 trials from 2016. Further, the eligibility rates for pharma led studies were half of those for investigator led studies (10% vs 21%). The main reasons for exclusion were karyotype (58%), comorbidities (40%) and prior therapies (55%). Authors concluded that pharma study eligibility appeared to be more restrictive and not reflective of the real-life patients.

5. Kuendgen A, et al. Therapy-related Myelodysplastic Syndromes deserve specific diagnostic sub-classification and risk-stratification — An approach to classification of patients with t-MDS. *Leukemia.* 2021; 35(3):835–849. (DOI: 10.1038/s41375-020-0917-7)

   An analysis of 2087 patients with therapy related MDS (t-MDS) from different international groups evaluating classification and prognostication tools, it was found that application of WHO classification for primary MDS (pMDS) could successfully predict time to leukemic transformation and survival both (p<0.001). t-MDS were found to be equally heterogeneous as p-MDS in terms of cytogenetics and prognostic score distribution. Clinical outcomes however were less favorable in each t-MDS group as compared to p-MDS (IWG p-MDS data were used for comparison). These observations strongly suggest that t-MDS should be classified as a distinct group in WHO-classification of therapy related myeloid neoplasms.

TREATMENT:

RBC Transfusion and Growth Factors:

1. Rozema J, et al. Patterns of transfusion burden in an unselected population of patients with myelodysplastic syndromes: A population-based study. *Transfusion.* 2021; Sept 3 [Online ahead of print] (DOI: 10.1111/trf.16631)

   An observational, retrospective, population-based study of MDS patients (n=292) from the HemoBase registry in a Friesland province of the Netherlands (2005-2017), showed high RBC transfusion burden (HTB >8units/16wk) in 46.6% patients and low transfusion burden (LTB) in 5.8% patients. Once univariate and multivariable regression analyses were performed, the odds ratio for HTB was particularly high in

patients aged 75-84 years, or those with high risk MDS or MDS-EB-2.

7. Komrokji R, et al. Treatment outcomes for patients with myelodysplastic syndrome/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis. *Leuk Lymphoma.* 2021; Aug 27 [Online ahead of print] (DOI: 10.1080/10428194.2021.1971217)

   MDS/MPN-RS-T is characterized by anemia, ring sideroblasts, and persistent thrombocytosis. 167 MDS/MPN-RS-T patients at a single institute (Moffitt, USA) were evaluated to compare the hematological improvement (HI) response rates among different therapies, including lenalidomide. 84% patients had SF3B1 mutations and 43% had JAK2 V617F mutations. Overall, 46% patients received erythropoiesis stimulating agents (ESA), 28% had lenalidomide and 27% got hypomethylating agents (HMA). The HI rate with the three treatments were 58%, 53% and 24% respectively. The median duration of treatment was 11 months for lenalidomide compared to 6 months for HMA.

Hematopoietic Stem Cell Transplant:

1. Shimoni A, et al. Allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome using treosulfan based compared to other reduced-intensity or myeloablative conditioning regimens. A report of the chronic malignancies working party of the EBMT. *Br J Haematology.* 2021; Sept 12 [Online ahead of print] (DOI: 10.1111/bjh.17817)

   Reduced intensity conditioning (RIC) is known for lower non-relapse mortality and higher relapse rates as compared to myeloablative conditioning (MAC). The assessment of post-allogeneic transplant outcomes, compared a type of RIC with Fludarabine/treosulfan (FT, n=367), with traditional RIC (n=687) and MAC (n=668). Besides the older age in FT and RIC compared to MAC, there were no other differences in baseline characteristics among the three groups. After a median f/u of over 5 years (64mo), FT matched RIC in lower NRM (30% and 27% respectively) vs MAC (34%, p=0.008), while it showed lower 5-year relapse comparable to MAC (25% for both) vs RIC (38%). In a multivariate analysis, FT was associated with lower risk of relapse (HR=0.55, p<0.001) and better OS (HR=0.72, p<0.01). Authors concluded that FT may a preferred regimen for allogeneic-hematopoietic cell transplant in MDS.

2. Kurosawa S et al, Fludarabine/busulfan versus busulfan/cyclophosphamide as myeloablative conditioning for myelodysplastic syndrome: a propensity score-matched analysis. *Bone Marrow Transplant.* 2021; Sept 7 [Online ahead of print] (DOI: 10.1038/s41409-021-01447-y)

   While Fludarabine/busulfan (Flu/Bu4) is effective in myeloablation prior to allo-HSCT in AML, it is not established in MDS. The nationwide registry data from Japan between 2006 and 2018 was reviewed (N=2482) for comparison of allo-HSCT outcomes with Flu/Bu4 (n=153) versus Busulfan/Cyclophosphamide (Bu4/Cy, n=153) conditioning in MDS patients. The cumulative non-relapse mortality, cumulative incidence of relapse, the 3-year progression free survival or the 3-year OS were not significantly different with the two conditioning regimens.

3. Wei Y, et al. Low-dose decitabine plus venetoclax is safe and effective as post-transplant maintenance therapy for high-risk acute myeloid leukemia and myelodysplastic syndrome. *Cancer Sci.* 2021; 112(9):3636-3644.(DOI:10.1111/cas.15048)

   A combination of Low dose decitabine (LDEC, 15 mg/m^2 day 1-3) with venetoclax (VEN, 200 mg day 1-21) in a 2 mo cycle x 10 cycles, was tested in a prospective study of 20 AML/high-risk MDS patients starting approximately on day 100 post-transplantation. The median follow up was approximately 20 mo. For primary end points, the median 2-year event-free survival (EFS) was 17.5 mo (525 days) with 17 patients event free. The most common adverse events (AEs) were neutropenia, anemia, thrombocytopenia, neutropenic fever and fatigue. No >3 grade AEs were observed. GVHD of any grade was observed in 55% patients.

4. Modi D, et al. Post-transplant cyclophosphamide versus thymoglobulin in HLA-mismatched unrelated donor transplant for acute myelogenous leukemia and myelodysplastic syndrome. *Transplant Cell Ther.* 2021;27(9):760-767. (DOI: 10.1016/j.jtct.2021.06.018)

   This retrospective study of 76 patients with AML or MDS assessed (2006-2019) the efficacy and safety of two GVHD prophylaxis regimens post-transplant with HLA mismatched unrelated donor. Cyclophosphamide (50 mg/kg on day 3 and 4) treatment was compared with thymoglobulin (total dose 4.5 mg/kg). Although, the grade 3-4 acute GVHD at day 100 did not show significant difference (12% vs 19.6%, p=0.38), chronic GVHD at 1 year was significantly lower with cyclophosphamide (16% vs 49%, p=0.006). Also with cyclophosphamide, the median time to engraftment was shorter for both neutrophils (15 vs 11days, p<0.001) and platelets (21 vs 15 days, p=0.002). No difference in OS, relapse rate, relapse free survival or GVHD-free relapse-free survival were noted with the two agents tested. In a propensity-score-based multi-variate analysis, besides higher acute and chronic GVHD incidence, higher non-relapse mortality was demonstrated with thymoglobulin compared to cyclophosphamide.

Hypomethylating Agents:

1. Kantarjian H, et al. Results of a randomized phase 3 study of oral sapacitabine in elderly patients with newly diagnosed acute myeloid leukemia (SEAMLESS). *Cancer.* 2021; Aug 23 [Online ahead of print] (DOI: 10.1002/cncr.33828)

   An oral nucleoside analogue, Sapacitabine was tested in an alternating cycles with decitabine. In a phase 3 randomized multicenter international study, elderly patients of ≥70 years age who were not candidates for standard induction chemotherapy were randomized 1:1 to receive decitabine (20 mg/m^2 1-hr iv qd x 5d every 8wk) in alternating cycles with sapacitabine in the test arm or decitabine alone in the control arm with same dosing in a every 4 week cycle. Patients with prior hypomethylating agent exposure were excluded. The primary endpoint was OS. A total of 482 patients were randomized to decitabine-sapacitabine vs decitabine monotherapy (n=241 each). The OS and CR rates were comparable between arms (OS: 5.9 mo vs 5.7 mo respectively, p=0.8902; CR: 16.6% vs 10.8% respectively, p=0.1468). However, in patients with low baseline WBC <10x10^9/L, OS and CR were higher with sequential therapy than control mono-therapy (n=321) (OS: 8.0 mo vs 5.8 mo respectively, p=0.145 and CR: 21.5% vs 8.6% respectively, p=0.0017).

2. Swaminathan M, et al. A phase I/II study of the combination of quizartinib with azacytidine or low-dose cytarabine for the treatment of patients with acute myeloid leukemia and myelodysplastic syndrome.

Haematologica. 2021;106(8):2121-2130. (DOI: 10.3324/haematol.2020. 263392)

AML patients FLT3-like tyrosine kinase-3-internal tandem duplication (FLT3-ITD) mutations receiving first salvage therapy (n=39) or previously untreated MDS/AML patients with >60 years age (n=34) were treated with quizartinib plus azacytidine (AZA) or low dose cytarabine (LDAC). The composite response rate among previously untreated patients was 87% (13/15; CR-8) with quizartinib+AZA and 74% (14/19; CR=1) in quizartinib+LDAC with median OS/relapse free survival (RFS) of 19.2/10.5 mo and 8.5/6.4 mo respectively. Among previously treated patients the composite response rate and median OS with two treatments were, 64%/12.8 mo vs 29%/4 mo respectively.

Targeted Therapies:

1. Bewersdorf JP, et al. Venetoclax-based combination in AML and high-risk MDS prior to and following allogeneic hematopoietic cell transplant. Leuk *Lymphoma.* 2021; Sept 3 [Online ahead of print] (DOI: 10.1080/10428194.2021. 1966788)

   A retrospective study of AML/High-risk MDS patients from Memorial Sloan Kettering Cancer Center and Yale University, who received venetoclax either prior to or after allo-HCT between 2016 and 2020 showed 1-year OS rate of 79% in those receiving venetoclax before and 43.4% in those receiving after allo-HCT. These results demonstrate the feasibility of venetoclax therapy as a salvage regimen.

Novel Therapies:

1. Uckun FM, et al. A clinical phase 1B study of the CD3xCD123 bispecific antibody APVO436 in patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome. *Cancers (Basel).* 2021;13(16):4113. (DOI: 10.3390/cancers13164113)

   A total of 46 RR AML/MDS patients who had failed multiple lines of prior therapy received APVO436 weekly as iv infusion at 10 dose levels between 0.3 mcg to 60 mcg. Maximum tolerable dose (MTD) was not reached at 60 mcg weekly. Infusion related reaction was the most common AE seen in 28.3% patients, along with cytokine release syndrome (CRS) in 21.7% patients. The recommended phase 2 dose was determined at 0.2 mcg/kg which showed appreciable clinical response including a CR.

Patient Reported Outcomes:

1. Stojikov I, et al. Core set of patient-reported outcomes for myelodysplastic syndromes – EUMDS Delphi study in patients and hematologists. *Blood Adv.* 2021; Sept 7 [Online ahead of print] (DOI:10.1182/bloodadvances. 2021004568)

   As a part of the prospective European LeukemiaNet MDS (EUMDS) registry, a 2-round survey was conducted with MDS patients and hematologists for the selection of preferred PRO measures out of 40 well selected instruments based on a systematic MDS literature search. Per the agreement between patients and hematologists, and based on predefined inclusion criteria, "general quality of life" was chosen by both patients and hematologists. Whereas, hematologists also selected two additional measures, "transfusion-dependency burden" and "ability to work/activities of daily living."

2. Abel GA, et al. Peri-transfusion quality of life assessment for patients with myelodysplastic syndromes. *Transfusion.* 2021; July 12 [Online ahead of print] (DOI: 10.1111/trf.16584)

   A total of 62 MDS patients were enrolled in the study, of which 37 completed 1-day-pre- and 7-day-post- RBC transfusion questionnaires (QOL in myelodysplasia scale (QUALMS)). Among these 37 patients, 35% reported increased QUALMS score, 46% had no change and 19% reported a decrease post transfusion. Also, 23% reported that their physician discussed the results before next transfusion.

3. Amitai I, et al. Patient-reported fatigue refines prognosis in higher-risk myelodysplastic syndromes (MDS): a MDS-CAN study. *Br J Haemaol.* 2021;194(2):319-324. (DOI: 10.1111/ bjh.17537)
4. Parker WB and Thottassery JV. 5-Aza-4'-thio-2'-deoxycytidine, a new orally bioavailable non-toxic "best-in-class" DNMT1 depleting agent in clinical development. *J Pharmacol Exp Ther.* 2021; Sept 9 [Online ahead of print]. (DOI: 10.1124/jpet.121.000758)
5. Santini V. Advances in myelodysplastic syndrome. *Curr Opin Oncol.* 2021; Sept 1 [Online ahead of print] (DOI: 10.1097/CCO.0000000000000790)
6. Hecker JS, Paschzelt L, and Götze KS. Are myelodysplastic syndromes ready for venetoclax? Exploring future potential and considerations. *Expert Rev Hematol.* 2021;14(9):789-793. (DOI: 10.1080/17474086.2021.1968822)
7. Patel SS. Pediatric myelodysplastic syndromes. *Clin Lab Med.* 2021;41(3): 517-528. (DOI: 10.1016/j.cll.2021. 03.015)
8. Schiffer M, et al. The development and clinical use of oral hypomethylating agents in acute myeloid leukemia and myelodysplastic syndromes: Dawn of the total oral therapy era. *Expert Rev Anticancer Ther.* 2021;21(9):989-1002. (DOI: 10.1080/14737140.2021.1918002)
9. Platzbecker U, Kubasch AS, Bouthiette CH, and Prebet T. Current challenges and unmet medical needs in myelodysplastic syndromes. *Leukemia.* 2021;35(8):2182-2198. (DOI: 10.1038/s41375-021-01265-7)
10. Kasprzak A, et al. Guidelines for myelodysplastic syndromes: converting evidence into action? *Int J Environ Res Public Health.* 2021;18(14):7629. (DOI: 10.3390/ijerph18147629)
10. Ferrara F and Bernardi M. 2021 BSH guidelines for the management of adult myelodysplastic syndromes: a practical approach to a challenging disease. *Br J Haematol.* 2021;194(2):235-237. (DOI: 10.1111/bjh.17640)
11. Killick SB, et al. British society for haematology guidelines for the management of adult myelodysplastic syndromes. *Br J Haematol.* 2021;194(2): 267-281. (DOI: 10.1111/bjh.17612)
12. Killick SB, et al. British society for haematology guidelines for the diagnosis and evaluation of prognosis of adult myelodysplastic syndromes. *Br J Haematol.* 2021;194(2):282-293. (DOI: 10.1111/bjh.17621)
13. Hellstrom-Lindberg E, Tobiasson M, Greenberg PL. Centenary Review: Myelodysplastic Syndromes: Moving towards personalized management. *Haematologica.* 2020;105:1765-1769. (DOI: 10.3324/haematol.2020.248955)
14. Greenberg PL. Metchnikoff's Inflamed Legacy: The Dysplastic Nature of Myelodysplastic Syndrome's Innate Immunity (Editorial). *Haematologica.* 2021; Aug 5 [Online ahead of print] (DOI: 10.3324/haematol.2021.279419)

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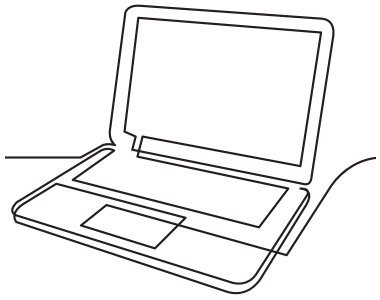

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The North Carolina Cancer Hospital University of North Carolina Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina
Matthew Foster, MD/Brandi Reeves, MD

Novant Health Cancer Institute
Charlotte, North Carolina
Patricia Kropf, MD

Wake Forest University School of Medicine Comprehensive Cancer Center
Winston-Salem, North Carolina
Bayard L. Powell, MD

OHIO

Cleveland Clinic Foundation, Taussig Cancer Center
Cleveland, Ohio
Jaroslaw Maciejewski, MD, PhD

Hoxworth Blood Center, George L. Strike Bone Marrow Transplant Program University of Cincinnati – UC Health
Cincinnati, Ohio
Emily Curran, MD

The Ohio State Comprehensive Cancer Center, James Cancer Hospital and Solove Research Institute
Columbus, Ohio
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Fox Chase-Temple University Hospital Bone Marrow Transplant Program
Philadelphia, Pennsylvania
Henry Fung, MD, FACP, FRCPE/Rashmi Khanal, MD,
Michael Styler, MD/Asya Varshavsky-Yanovsky, MD, PhD

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Pittsburgh, Pennsylvania
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University of Texas, MD Anderson Cancer Center
Houston, Texas
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Hagop Kantarjian, MD

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Dallas, Texas
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Salt Lake City, Utah
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Lombardi Comprehensive Cancer Center
Washington, D.C.
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George Washington University, VA Medical Center
Washington, D.C.
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University of Wisconsin Health
Madison, Wisconsin
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Medical College of Wisconsin
Hematologic Malignancies Program
Milwaukee, Wisconsin
Ehab Atallah, MD

University of Wisconsin, Madison Medical School
Madison, Wisconsin
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Hematology Center after R.Yeolyan
Yerevan, Armenia
Anna Sevoyan, MD

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Melbourne, Australia
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Clayton, Victoria, Australia
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University of Melbourne
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The Royal Melbourne Hospital
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Vienna, Austria
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Medical University of Vienna
Vienna, Austria
Peter Valent, MD

University Hospital of Innsbruck
Innsbruck, Austria
Reinhard Stauder, MD

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Brugge, Belgium
Dominik Selleslag, MD

University Hospital Leuven
Leuven, Belgium
Marielle Beckers, MD, PhD
Michel Delforge, MD, PhD

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AC Camargo Hospital–Cancer Center
São Paulo, Brazil
Luiz Fernando Lopes, MD, PhD

Hospital das clínicas da Faculdade de Medicina da Universidade de São Paulo
São Paulo, Brazil
Elvira D. Rodrigues Pereira Velloso, MD, PhD

Universidade Federal de Ceará
Ceará, Brazil
Silvia Maria M. Magalhães, MD, PhD

Universidade Federal de São Paulo
São Paulo, Brazil
Maria de Lourdes Chauffaille, MD, PhD

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Princess Margaret Hospital
Toronto, Ontario, Canada
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Odette Cancer Centre
Sunnybrook Health Sciences Center
Toronto, Ontario, Canada
Rena Buckstein, MD, FRCPC/Richard A. Wells, MD

St. Paul's Hospital
Vancouver, British Columbia, Canada
Heather Leitch, MD, PhD

University of Toronto Hospital for Sick Children
Toronto, Ontario, Canada
Yigal Dror, MD

CHINA

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Guangdong Academy of Medical Sciences
Guangzhou, China
Xin Du, MD, PhD

Institute of Hematology and Blood Diseases Hospital
Chinese Academy of Medical Sciences
Tianjin, China
Zhijian Xiao, MD

The First Affiliated Hospital of Soochow University,
Jiangsu Institute of Hematology
Jiangsu Province, China
Suning Chen, MD, PhD

The First Affiliated Hospital of Zhejiang University
Zhejiang Province, China
Hongyan Tong, MD, PhD

The Sixth Hospital Affliated to
Shanghai Jiaotong University
Shanghai, China
Xiao Li, MD, PhD

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Clinical Hospital Merkur
Zagreb, Croatia
Inga Mandac Ragulj, MD

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Prague, Czech Republic
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The University of Southern Denmark
Odense, Denmark
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Rigshospitalet National University Hospital
Copenhagen, Denmark
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Rouen, France
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Grenoble, France
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Dominique Bordessoule, MD

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Nancy, France
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Bobigny, France
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Hôpital Cochin/University Paris V
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Paris, France
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Hôpital Saint-Vincent de Paul (Lille)
Lille, France
Christian Rose, MD

Institut Paoli-Calmettes
Marseille, France
Norbert Vey, MD

Service des Maladies du Sang
Hôpital Claude Huriez
Lille, France
Bruno Quesnel, MD

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Göttingen, Germany
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Hannover Medical School
Medizinische Hochschule Hannover
Hannover, Germany
Arnold Ganser, MD

Heinrich-Heine Universität Düsseldorf
University Hospital
Düsseldorf, Germany
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Johannes Gutenberg University
Medical Center Mainz
Mainz, Germany
Markus Radsak, MD, PhD

Johann Wolfgang Goethe Universität
Frankfurt Main, Germany
Gesine Bug, MD

Klinikum Rechts der Isar
Technical University of Munich
Munich, Germany
Katharina Götze, MD

MLL Münchner Leukämielabor
Munich, Germany
Torsten Haferlach, MD/Wolfgang Kern, MD

Rems-Murr-Klinik Winnenden
Winnenden, Germany
Prof. Dr. med Markus Schaich, MD

St. Johannes Hospital
Heinrich-Heine Universität
Duisburg, Germany
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University of Heidelberg Medical Center
St. Lukas Klinik Solingen
Solingen, Germany
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Freiburg, Germany
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Hamburg, Germany
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Universitätsklinikum Carl Gustav Carus
Dresden, Germany
Katja Sockel, MD

University Children's Hospital
Freiburg, Germany
Charlotte Niemeyer, MD

University of Cologne
Cologne, Germany
Karl-Anton Kreuzer, MD

University Hospital Essen
Dept. for Hematology and Stem Cell Transplantation
Essen, Germany
Thomas Schroeder, MD

University Hospital Leipzig
Leipzig, Germany
Uwe Platzbecker, MD

University Hospital Mannheim
Mannheim, Germany
Wolf-Karsten Hofmann, MD

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Patras University Hospital
Patras, Greece
Argiris Symeonidis, MD

University of Athens Laikon Hospital
Athens, Greece
Nora Viniou, MD

University General Hospital Attikon
Athens, Greece
Vassiliki Pappa, MD

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Semmelweis University School of Medicine
Budapest, Hungary
Judit Várkonyi, MD, PhD

INDIA

Tata Medical Centre
Kolkata, India
Col (Dr.) Deepak Kumar Mishra, MD

Tata Memorial Hospital
Mumbai, India
Manju Sengar, MD

IRELAND

Adelaide and Meath Hospital
Dublin, Ireland
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ISRAEL

Tel-Aviv Sourasky Medical Center
Tel-Aviv, Israel
Moshe Mittelman, MD

Chaim Sheba Medical Center
Tel Hashomer, Israel
Drorit Grizim Merkel, MD

ITALY

Cancer Center – IRCCS Humanitas Research Hospital
Milan, Italy
Matteo G. Della Porta, MD

Centro di Riferimento Oncologico di Basilicata (CROB)
Rionero in Vulture (PZ), Italy
Pellegrino Musto, MD

Istituto di Ematologia
Universita' Cattolica Sacro Cuore
Rome, Italy
Giuseppe Leone, MD

Policlinico Universitario di Roma Tor Vergata
Rome, Italy
Sergio Amadori, MD/Maria Teresa Voso, MD

S. Eugenio Hospital Tor Vergata University
Rome, Italy
Paolo de Fabritiis, MD/Pasquale Niscola, MD

University of Florence Azienda OSP Careggi
Florence, Italy
Valeria Santini, MD

University of Pavia School of Medicine Fondazione IRCCS Policlinico San Matteo
Pavia, Italy
Mario Cazzola, MD

JAPAN

Kyoto University Hospital
Kyoto, Japan
Akifumi Takaori, MD

Metropolitan Research and Treatment Center for Blood Disorders (MRTC Japan)
Tokyo, Japan
Kiyoyuki Ogata, MD, FACP

Nagasaki University Hospital School of Medicine, Atomic Bomb Disease Institute
Nagasaki City, Japan
Yasushi Miyazaki, MD

Saitama Medical University International Medical Center
Hidaka, Saitama, Japan
Tomoya Maeda, MD, PhD

Tokyo Medical College
Tokyo, Japan
Kazuma Ohyashiki, MD, PhD

MEXICO

Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran American-British-Cowdray Cancer Center
Mexico City, Mexico
Alvaro Aguayo, MD

THE NETHERLANDS

Radboud University Nijmegen Medical Center
Nijmegen, The Netherlands
Saskia M.C. Langemeijer, MD

Vrije Universiteit Medical Center
Amsterdam, The Netherlands
Arjan A. van de Loosdrecht, MD, PhD

POLAND

Jagiellonian University Collegium Medicum
Kraków, Poland
Aleksander Skotnicki, MD, PhD

Medical University of Warsaw
Warsaw, Poland
Krzysztof Madry, MD

PORTUGAL

Hospital de Santa Maria
Lisbon, Portugal
Joao F. Lacerda, MD

SAUDI ARABIA

King Faisal Specialist Hospital & Research Centre
Riyadh, Saudi Arabia
Amr Hanbali, MD

King Khaled University Hospital King Saud University
Riyadh, Saudi Arabia
Ak Almomen, MD

SINGAPORE

Singapore General Hospital
Aloysius Ho, MD

SOUTH AFRICA

University of Cape Town Groote Schuur Hospital
Cape Town, South Africa
Nicolas Novitzky, MD, PhD

SOUTH KOREA

Catholic Blood and Marrow Transplantation Center The Catholic University of Korea
Seoul, Korea
Yoo-Jin Kim, MD

Seoul National University Hospital Seoul National University College of Medicine
Seoul, Korea
Dong Soon Lee, MD, PhD

Yonsei Cancer Centre, Severance Hospital Yonsei University College of Medicine
Seoul, Korea
June-Won Cheong, MD, PhD

SPAIN

Hospital Universitario de Salamanca
Salamanca, Spain
Maria Diez-Campelo, MD, PhD

Hospital Universitario La Fe
Valencia, Spain
Guillermo F. Sanz, MD, PhD

Vall d'Hebron Institute of Oncology Universitary Hospital Vall d´Hebron
Barcelona, Spain
David Valcárcel, MD, PhD

SWEDEN

Karolinska Institute at Karolinska University Hospital Huddinge
Stockholm, Sweden
Eva Hellström-Lindberg, MD, PhD

SWITZERLAND

Basel University Hospital
Basel, Switzerland
Jakob R. Passweg, MD, MS

Bern University Hospital and University of Bern
Bern, Switzerland
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University Hospital Zurich
Zurich, Switzerland
Markus G. Manz, MD/Stefan Balabanov, MD

TAIWAN

Chang Gung Memorial Hospital Chang Gung University
Taoyuan, Taiwan
Lee-Yung Shih, MD

National Taiwan University Hospital
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THAILAND

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TUNISIA

Hospital Aziza Othmana
Tunis, Tunisia
Balkis Meddeb, MD

TURKEY

Ankara University School of Medicine Hospital
Ankara, Turkey
Osman Ilhan, MD

UKRAINE

Research Center for Radiation Medicine
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Dimitry Bazyka, MD

UNITED KINGDOM

Aberdeen Royal Infirmary Aberdeen University School of Medicine
Foresterhill, Aberdeen, Scotland
Dominic Culligan, MD

Cambridge University Hospitals
Cambridge, United Kingdom
Alan J. Warren, MD, PhD

Christie NHS Foundation Trust
Manchester, United Kingdom
Mike Dennis, MD/Dan Wiseman, MD

King's College London & King's College Hospital
London, United Kingdom
Ghulam J. Mufti, DM, FRCP, FRCPath

Queen Elizabeth Hospital University Hospital Birmingham NHS Trust
Birmingham, United Kingdom
Manoj Raghavan, MD

Radcliffe Hospitals & University of Oxford
Oxford, United Kingdom
Paresh Vyas, MD

Royal Bournemouth Hospital
Bournemouth, United Kingdom
Sally Killick, MD

St. James's University Hospital St. James's Institute of Oncology
Leeds, United Kingdom
David T. Bowen, MD

University Hospital Southampton (NHS Foundation Trust)
Southampton, Hampshire, UK
Christopher Dalley, MD
Srinivasan Narayanan, MD

University Hospital of Wales
Cardiff, Wales
Jonathan Kell, MD

VIETNAM

National Institute of Hematology and Blood Transfusion
Hanoi, Vietnam
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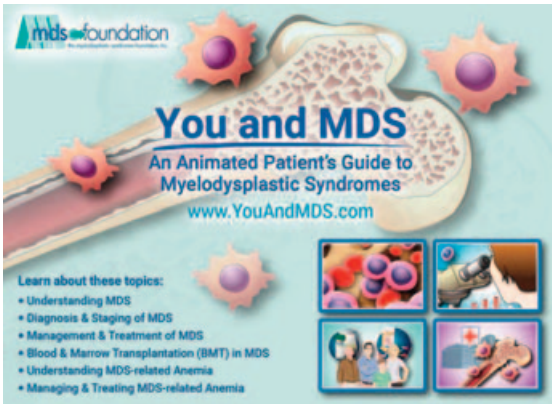
PATIENT RESOURCES

You and MDS

An Animated Patient's Guide to Myelodysplastic Syndromes

NOW AVAILABLE IN SPANISH

This resource is intended for patients with MDS, as well as family members and caregivers. You will find expert advice about MDS to help you discuss key issues with your health care provider and make important decisions related to management and treatment. **Easy-to-understand animations** with **audio narration, expert video explanations, patient interviews, illustrated slide shows**, and **educational downloads** are available to you. We welcome you to this online community resource to improve your quality of life and health outcomes.



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SPANISH LANGUAGE MDS PATIENT EDUCATION RESOURCE

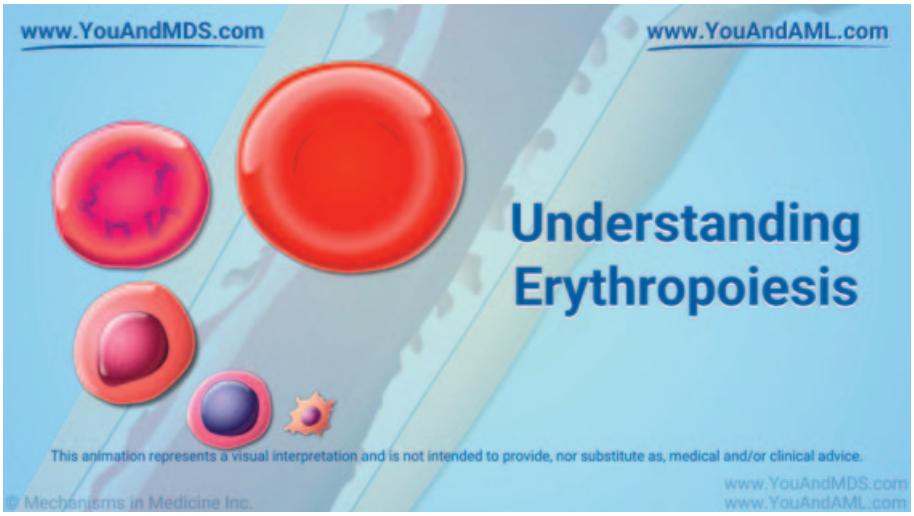
"Una guía animada para pacientes con síndromes mielodisplásicos"

(You and MDS: Animated Patient's Guide to Myelodysplastic Syndromes)

Have you checked out our latest module for our "You and MDS" Animated Video series, Understanding Erythropoiesis, yet?

UNDERSTANDING ERYTHROPOIESIS

This animation explains erythropoiesis, which is the term for the production of red blood cells. Red blood cells, called erythrocytes, carry oxygen around your body. This animation explains the erythrocyte life cycle and describes how a low red blood cell count causes anemia. Anemia typically results from bleeding, red blood cell destruction, or decreased red blood cell production in the bone marrow, as seen in disorders such as myelodysplastic syndromes (MDS). The animation describes treatments for a low red blood cell count, including medications, blood transfusions, and stem cell transplant.



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mds foundation
the myelodysplastic syndromes foundation, inc.

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GET ACCESS TO PATIENT ADVOCACY SERVICES AND SUPPORT THE MISSION OF IMPROVING THE LIVES OF PATIENTS WITH MYELODYSPLASTIC SYNDROMES.

This year nearly 90,000 people will be told they have MDS worldwide – 12,000 to 18,000 newly diagnosed MDS patients in the United States alone. The MDS Foundation, Inc. is working hard to support these patients and the loved ones who care for them.

We are asking for your membership support in our global efforts to change the outcomes of MDS.

WE ARE HERE FOR YOU...

AT YOUR TIME OF
DIAGNOSIS

WITH SPECIALIST
REFERRALS

THROUGHOUT
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JOIN US TO PROMOTE
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SUPPORT YOUR
LOVED ONES

BE A PART OF THE SOLUTION

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- You are part of the solution to change MDS outcomes. Your membership fee helps support global physician and patient educational initiatives, drive research, and helps to empower patients with courage and hope.
- Updates on the status of our Global Centers of Excellence and their live patient and family forum events that allow for more rapid dissemination of new research and treatment developments.
- Information on the latest clinical trials to potentially share or participate in.
- Access to MDS awareness materials to share with family, friends and your primary care physician.
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- Receive an MDSF Membership Packet including printed educational resources, MDSF masks and wristbands.

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

THE MDS FOUNDATION, INC.
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Phone within the US: 1-(800)-637-0839, Outside the US only: 1-609-298-1035
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2022 WEBINAR CALENDAR COMING SOON

WE ARE VIRTUAL!

We are planning a comprehensive series of webinars for 2022 bringing experts and the MDS community together to provide educational information, best practices, tools, and resources.

Whether you are a newly diagnosed patient, a long-term survivor, or caregiver, our webinar series will have something for you.

We have collaborated with renowned hematology professionals who will address key topics and questions using easy to understand language in a 90-minute format that includes a live Q&A opportunity for all participants.

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MDS FOUNDATION PODCASTS – NOW AVAILABLE!

MDS PROFESSIONAL REPORT

THIS PODCAST SERIES PROVIDES IMPORTANT UP-TO-THE-MINUTE INFORMATION ON MDS INCLUDING DIAGNOSIS, TREATMENT AND CLINICAL RESEARCH.

The explosion of information on MDS forces us to seek novel, alternative ways to distribute it. Podcasts gives us an easy and popular way to communicate this information in a short time.

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The **MDS PROFESSIONAL REPORT** will cover international meetings as well as recently published articles on MDS, combining educational materials with cutting-edge information. The format will include a description of studies by the editors, interviews with experts, conversations, round table discussions as well as other relevant formats. We are planning to include several episodes per year lasting 20–25 minutes covering a range of topics.

SEASON 1: EPISODE 4: ***Do Immune Check Inhibitors have a Role in the Treatment of Higher-Risk MDS?***

Our host, Howard S. Oster, MD, PhD, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, will discuss the combination of azacitidine and pembrolizumab in patients with higher-risk MDS, a personalized prediction model based on clinical and genomic data, the classification of therapy-related MDS as well as the importance of platelet counts as a prognostic factor.

Visit our website to listen to previous episodes:

SEASON 1: EPISODE 1: *TP53 Mutations: Were They Born Equal?*

SEASON 1: EPISODE 2: *Don't Withhold Anti-Neoplastic Treatment from your Hematological Patients Infected by COVID*

SEASON 1: EPISODE 3: *Will Venetoclax Become The New Standard?*

WE HOPE YOU FIND THE MDS PROFESSIONAL REPORT INFORMATIVE, INTERESTING, AND USEFUL.

PRESS RELEASES

GERON ANNOUNCES COMPLETION OF PATIENT ENROLLMENT IN IMERGE PHASE 3 CLINICAL TRIAL IN LOWER RISK MYELODYSPLASTIC SYNDROMES

Top-Line Results Expected at the Beginning of January 2023

FOSTER CITY, CALIFORNIA – October 18, 2021. Geron Corporation (Nasdaq: GERN), a late-stage biopharmaceutical company focused on the development and commercialization of treatments for hematologic malignancies, today announced the completion of patient enrollment in the IMerge Phase 3 clinical trial to evaluate imetelstat, a first-in-class telomerase inhibitor, in lower risk myelodysplastic syndromes (MDS). Based upon current planning assumptions, Geron expects top-line results for IMerge Phase 3 to be available at the beginning of January 2023.

"Completing patient enrollment in IMerge Phase 3 brings us one step closer to delivering imetelstat as a potential treatment alternative for patients with lower risk MDS who are relapsed or refractory to ESAs. Achieving durable transfusion independence remains a significant medical need for these patients," said Aleksandra Rizo, M.D., Ph.D., Geron's Chief Medical Officer. "I would like to thank all of the patients and their families, the investigators, clinical site staff, as well as our employees for supporting the achievement of this important milestone."

Patients from the IMerge Phase 2 clinical trial achieved durable transfusion independence with imetelstat treatment, including transfusion-free periods greater than one year, irrespective of the disease subgroup, such as ringed sideroblast positive or ringed sideroblast negative. Such durability provides significant and meaningful clinical benefit to lower risk MDS patients given their chronic anemia and the debilitating impact of serial blood transfusions. In addition, depletion of cytogenetic abnormalities and reductions in key driver mutations associated with lower risk MDS were observed, and these results were also correlated with transfusion independence. Based on the IMerge Phase 2 data, taken together, the durability, molecular and cytogenetic data provide strong evidence for disease-modifying activity of imetelstat, which has the potential to differentiate it from other currently approved and investigational treatments in lower risk MDS today.

ABOUT IMERGE PHASE 3

IMerge Phase 3 is a double-blind, randomized, placebo-controlled Phase 3 clinical trial with registrational intent. The trial is designed to enroll approximately 170 transfusion dependent patients with Low or Intermediate-1 risk myelodysplastic syndromes (MDS), also referred to as lower risk MDS, who have relapsed after or are refractory to prior treatment with an erythropoiesis stimulating agent (ESA). The primary endpoint is the rate of red blood cell (RBC) transfusion independence (TI) for any consecutive period of eight weeks or longer, or 8-week RBC-TI rate. Key secondary endpoints include the rate of RBC-TI lasting at least 24 weeks, or 24-week RBC-TI rate, and the rate of hematologic improvement-erythroid (HI-E), defined as a reduction of at least four units of RBC transfusions over eight weeks compared with the prior RBC transfusion burden.

For further information about IMerge Phase 3, visit ClinicalTrials.gov/NCT02598661.

ABOUT IMETELSTAT

Imetelstat is a novel, first-in-class telomerase inhibitor exclusively owned by Geron and being developed in myeloid hematologic malignancies. Data from Phase 2 clinical trials provide strong evidence that imetelstat targets

telomerase to inhibit the uncontrolled proliferation of malignant stem and progenitor cells in myeloid hematologic malignancies resulting in malignant cell apoptosis and potential disease-modifying activity. Imetelstat has been granted Fast Track designation by the United States Food and Drug Administration for both the treatment of patients with non-del(5q) lower risk MDS who are refractory or resistant to an erythropoiesis-stimulating agent and for patients with Intermediate-2 or High-risk myelofibrosis whose disease has relapsed after or is refractory to janus associated kinase (JAK) inhibitor treatment..

ABOUT GERON

Geron is a late-stage clinical biopharmaceutical company focused on the development and potential commercialization of a first-in-class telomerase inhibitor, imetelstat, in myeloid hematologic malignancies. The Company currently is conducting two Phase 3 clinical trials: IMerge in lower risk myelodysplastic syndromes and IMpactMF in refractory myelofibrosis. For more information about Geron, visit www.geron.com.

VENETOCLAX (VENCLEXTA®) GRANTED US FDA BREAKTHROUGH THERAPY DESIGNATION (BTD) IN HIGHER RISK MYELODYSPLASTIC SYNDROME (MDS)

NORTH CHICAGO, ILLINOIS – JULY 21, 2021. AbbVie (NYSE: ABBV) announced today that the U.S. Food and Drug Administration (FDA) granted a Breakthrough Therapy Designation (BTD) to venetoclax (VENCLEXTA®) in combination with azacitidine for the potential treatment of adult patients with previously untreated intermediate-, high- and very high-risk myelodysplastic syndromes (MDS) based on revised International Prognostic Scoring System (IPSS-R). A BTD is intended to expedite the development and review of medications to treat a serious medical condition and is granted when preliminary clinical evidence indicates the investigational

therapy may demonstrate substantial improvement over existing therapies. This marks the sixth BTD granted to venetoclax.

MDS are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. Patients living with MDS may experience symptoms such as infection, anemia, spontaneous bleeding, and easy bruising. Roughly 10,000 patients in the US are diagnosed with MDS each year and around 30 percent of those patients will progress to acute myeloid leukemia (AML). Although MDS can occur at any age, it is most commonly found in patients aged 60 and older.

"MDS is a devastating diagnosis – not only does it have the potential to greatly impact patients' quality of life, but 30 percent of patients will also progress to AML," said Jalaja Potluri, executive medical director, oncology, AbbVie. "This Breakthrough Therapy Designation underscores the need for more treatment options for these patients and the utility of venetoclax to potentially treat different forms of blood cancer."

This designation is supported by data from the Phase 1b M15-531 study. In addition to the Phase Ib M15-531 study, venetoclax is being investigated in combination with azacitidine for the treatment of MDS in the Phase Ib M15-522 study in patients with relapsed or refractory disease, and the Phase 3 randomized VERONA study in patients with newly diagnosed higher-risk MDS.

VENCLEXTA is being developed by AbbVie and Roche. It is jointly commercialized by AbbVie and Genentech, a member of the Roche Group, in the U.S. and by AbbVie outside of the U.S.

ABOUT VENCLEXTA® (VENETOCLAX)

VENCLEXTA®/VENCLYXTO® (venetoclax) is a first-in-class medicine that selectively binds and inhibits the B-cell lymphoma-2 (BCL-2) protein. In some blood cancers, BCL-2 prevents cancer cells from undergoing their natural death or self-destruction process, called apoptosis. VENCLEXTA/VENCLYXTO targets the BCL-2 protein and works to help restore the process of apoptosis.

VENCLEXTA/VENCLYXTO is being developed by AbbVie and Roche. It is jointly commercialized by AbbVie and Genentech, a member of the Roche Group, in the U.S. and by AbbVie outside of the U.S. Together, the companies are committed to BCL-2 research and to studying venetoclax in clinical trials across several blood cancers. Venetoclax is approved in more than 80 countries, including the U.S.

USES OF VENCLEXTA® (VENETOCLAX) IN US

VENCLEXTA is a prescription medicine used:

- to treat adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- in combination with azacitidine, or decitabine, or low-dose cytarabine to treat adults with newly diagnosed acute myeloid leukemia (AML) who:
- are 75 years of age or older, or
- have other medical conditions that prevent the use of standard chemotherapy.

It is not known if VENCLEXTA is safe and effective in children.

ABOUT ABBVIE IN ONCOLOGY

At AbbVie, we are committed to transforming standards of care for multiple blood cancers while advancing a dynamic pipeline of investigational therapies across a range of cancer types. Our dedicated and experienced team joins forces with innovative partners to accelerate the delivery of potentially breakthrough medicines. We are evaluating more than 20 investigational medicines in over 300 clinical trials across some of the world's most widespread and debilitating cancers. As we work to have a remarkable impact on people's lives, we are committed to exploring solutions to help patients obtain access to our cancer medicines. For more information, please visit http://www.abbvie.com/oncology.

ABOUT ABBVIE

AbbVie's mission is to discover and deliver innovative medicines that solve serious health issues today and address the medical challenges of tomorrow. We strive to have a remarkable impact on people's lives across several key therapeutic areas: immunology, oncology, neuroscience, eye care, virology, women's health and gastroenterology, in addition to products and services across its Allergan Aesthetics portfolio. For more information about AbbVie, please visit us at www.abbvie.com. Follow @abbvie on Twitter, Facebook, Instagram, YouTube and LinkedIn.

SYROS ANNOUNCES FIRST PATIENT DOSED IN SELECT-AML-1 TRIAL OF TAMIBAROTENE IN COMBINATION WITH VENETOCLAX AND AZACITIDINE IN NEWLY DIAGNOSED UNFIT AML

CAMBRIDGE, MASS – SEPT. 9, 2021. Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today announced that the first patient has been dosed in the SELECT-AML-1 clinical trial of tamibarotene, its first-in-class selective retinoic acid receptor alpha (RARα) agonist, in combination with venetoclax and azacitidine. The randomized Phase 2 trial is enrolling RARA-positive newly diagnosed unfit patients with acute myeloid leukemia (AML).

"Despite recent advances, one third of newly diagnosed unfit AML patients still don't respond to front-line treatment and many more relapse," said Eytan M. Stein, M.D., Assistant Professor of Medicine and Director of the Program for Drug Development in Leukemia at Memorial Sloan Kettering Cancer Center. "These patients need new therapies that can deliver durable remissions with minimal or manageable toxicities. I am encouraged by tamibarotene's distinct safety profile, as well as the compelling clinical and translational data that has emerged, suggesting it may benefit patients in the greatest need of new treatment options. I look forward to further exploring its potential in this clinical trial as part of a triplet regimen with venetoclax and azacitidine."

Tamibarotene has demonstrated promising results in combination with azacitidine in RARA-positive newly diagnosed AML patients who are not suitable candidates for standard chemotherapy. At the 62nd American Society of Hematology (ASH) Annual Meeting in December 2020, Syros presented data from a Phase 2 clinical trial, demonstrating a 67% overall response rate and a 61% composite complete response (CR/CRi) rate. The data also showed that tamibarotene in combination with azacitidine was generally well-tolerated, with no evidence of increased myelosuppression compared to single-agent azacitidine.

Also at ASH, Syros presented translational data demonstrating that most RARA-positive newly diagnosed unfit AML patients in the Phase 2 trial of tamibarotene had a monocytic disease phenotype associated with resistance to venetoclax, which, in combination with azacitidine, is the standard of care for newly diagnosed unfit patients. These data suggest that the RARA biomarker selects for patients who are more likely to benefit from tamibarotene and who may be less likely to benefit from venetoclax.

"AML is a complex, heterogenous disease, and many patients may present upfront with both monocytic and non-monocytic leukemia cells," said David A. Roth, M.D., Chief Medical Officer at Syros. "By employing a triplet strategy that combines tamibarotene with venetoclax and azacitidine, we believe we can simultaneously target both cell types, reducing the emergence of resistant disease and increasing the likelihood of deeper and more durable responses. We are excited to be actively enrolling patients in this study, as we advance our portfolio of targeted hematology therapies with the aim of setting new standards of care for people with acute leukemias and myelodysplastic syndrome."

The SELECT-AML-1 trial is designed with a single-arm safety lead-in, followed by the randomized portion of the trial, which will evaluate the safety and efficacy of tamibarotene in combination with venetoclax and azacitidine compared to venetoclax and azacitidine in approximately 80 patients randomized 1:1. The trial will also evaluate the triplet regimen as a salvage strategy in patients in the control arm who do not respond to venetoclax and azacitidine. The primary endpoint of the trial will be composite CR rate.

Syros is also evaluating tamibarotene in combination with azacitidine in the SELECT-MDS-1 Phase 3 clinical trial in RARA-positive patients with newly diagnosed higher-risk myelodysplastic syndrome.

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. Syros is advancing a robust clinical-stage pipeline, including: tamibarotene, a first-in-class oral selective RARα agonist in RARA-positive patients with higher-risk myelodysplastic syndrome and acute myeloid leukemia; SY-2101, a novel oral form of arsenic trioxide in patients with acute promyelocytic leukemia; and SY-5609, a highly selective and potent oral CDK7 inhibitor in patients with select solid tumors. Syros also has multiple preclinical and discovery programs in oncology and monogenic diseases. For more information, visit www.syros.com and follow us on Twitter (@SyrosPharma) and LinkedIn.

ASTEX PHARMACEUTICALS PRESENTS OVERALL SURVIVAL DATA FROM ASCERTAIN PHASE 3 STUDY OF ORAL HYPOMETHYLATING AGENT INQOVI® (DECITABINE AND CEDAZURIDINE) IN MDS AND CMML AT INTERNATIONAL CONGRESS ON MDS

- ***Study achieved median overall survival of 31.7 months***
- ***Updated efficacy data demonstrated an overall response rate of 62%, with 22% of patients achieving a complete response***
- ***INQOVI is the only oral hypomethylating agent with equivalent exposure to its intravenous (IV) form***

PLEASANTON, CA – SEPT. 23, 2021. Astex Pharmaceuticals, Inc., a wholly owned subsidiary of Otsuka Pharmaceutical Co. Ltd., based in Tokyo, Japan, today announced updated clinical data, including median overall survival (mOS), from the ASCERTAIN phase 3 trial of INQOVI®, the company's orally administered fixed-dose combination of decitabine and cedazuridine (ASTX727 or DEC-C) in adults with intermediate and high-risk myelodysplastic syndromes (MDS) including chronic myelomonocytic leukemia (CMML). mOS was 31.7 months.

The data were featured in a presentation given today at the 16th International Congress on Myelodysplastic Syndromes in Toronto, Canada, by Michael Savona, MD, Professor of Medicine and Cancer Biology, Department of Internal Medicine at Vanderbilt University School of Medicine, Tenn., on behalf of the study investigators.

The ASCERTAIN clinical trial was designed as a randomized crossover study comparing oral decitabine (35mg) and cedazuridine (100mg) fixed-dose combination tablet given once daily for 5 days on a 28-day cycle to IV decitabine (20mg/m2) administered as a daily 1-hour IV infusion for 5 days on a 28-day cycle, in the first 2 cycles. Patients continued to receive oral decitabine and cedazuridine from Cycle 3 onwards. The primary endpoint data for the study of total 5-day decitabine area-under-the-curve (AUC) equivalence of oral decitabine and cedazuridine and IV decitabine was previously presented at the American Society of Hematology Annual Meeting in December 2019. The oral/IV decitabine 5-day AUC was 98.9% with a 90% Confidence Interval between 92.7% and 105.6%.

Safety findings from the study were similar to those anticipated with IV decitabine, with incidence of cytopenias slightly higher with INQOVI during Cycle 1 compared to IV decitabine. The most common adverse events (AEs) of thrombocytopenia, neutropenia, and anemia were consistent with expected AEs with parenteral hypomethylating agent treatment.

In the more mature data set used to evaluate overall survival, the complete response (CR) rate for evaluable patients was 22%, with an overall response rate (CR + Partial Response + Marrow CR + Hematological Improvement) of 62%.

"Taken together, the ASCERTAIN phase 3 study data support considerable therapeutic utility of oral decitabine and cedazuridine in the treatment of patients with MDS and CMML," said Co-Principal Investigator of the ASCERTAIN phase 3 study, Michael Savona, MD. "The fixed-dose combination of decitabine and cedazuridine is the only available oral DNA methyltransferase inhibitor/hypomethylating agent that has demonstrated equivalent exposure to an IV form. The median overall survival data from this study makes oral decitabine and cedazuridine an alternative option to parenteral administration of decitabine for patients with these diseases."

Added Timothy Whitten, president and CEO of Taiho Oncology, Inc., Astex's commercialization partner for INQOVI in the United States: "We are encouraged by data from the ASCERTAIN trial that continue to show oral decitabine and cedazuridine is a promising treatment option for patients living with MDS and CMML. Importantly, patients can benefit from the convenience of an at-home hypomethylating agent treatment and potentially reduce the number of office visits and associated travel."

Based on the data from the ASCERTAIN clinical program, INQOVI is being investigated in combination with other agents in hematological malignancies, according to Harold Keer, MD, PhD, chief medical officer of Astex Pharmaceuticals, Inc. "The first of these studies is investigating the all-oral combination of decitabine and cedazuridine with venetoclax for the treatment of AML. We are extremely grateful to all the patients, caregivers, partner research and manufacturing organizations, as well as the healthcare professionals who have contributed to the clinical development program of oral decitabine and cedazuridine."

INQOVI is an orally administered, fixed-dose combination of the approved anti-cancer DNA hypomethylating agent, decitabine, together with cedazuridine, an inhibitor of cytidine deaminase. By inhibiting cytidine deaminase in the gut and the liver, INQOVI is designed to allow for oral delivery of decitabine over five days in a given cycle to achieve comparable systemic exposure to IV decitabine. The phase 1 and phase 2 clinical study results have been published in *Lancet Haematology* and *Blood*, respectively.

INQOVI was approved in July 2020 by the U.S. Food and Drug Administration (FDA) and by Health Canada. INQOVI is the first and only oral hypomethylating agent approved by the FDA and by Health Canada for the treatment of adults with intermediate and high-risk MDS including CMML.

A TRIBUTE TO MY DONOR: SERVING AS A VOICE

NATHANIEL MONTGOMERY
New York, New York

I am a cancer survivor and a fan of the people who dedicate their lives to fighting cancer. It took a great deal of time before I got comfortable with the idea of sharing my journey with the broader public. On my journey, I was exposed to some wonderful people who shared in my experiences. It is the charitable spirit of one particular person and the unfortunate loss of two very special friends that motivated me to write this article. I was diagnosed with Myelodysplastic Syndromes (MDS) in January of 2017. I was in disbelief when I received the initial diagnosis from my doctor. As a healthy and active African-American man who never smoked or drank alcohol I was stunned to learn that I had MDS. My wife and I immediately sought second and third opinions from other MDS specialists. My wife and I traveled from coast-to-coast in search of an answer that would assure us of a positive outcome. Because of the uncertainties associated with cancer in general there were no reassuring answers. Each specialist that I spoke with confirmed my initial diagnosis and politely proceeded to explain all of the treatment options available to me. The most comforting aspect of my consultations with each specialist was their acknowledgement of the medical advancements that had been made in the area of MDS. It was clear to me that I needed to identify a viable donor so that I could undergo a bone marrow transplant. My wife and I agreed that I would begin treatment at Memorial Sloan Kettering Cancer Center (MSKCC).

Initially, I worked with the wonderful team at MSKCC. Once the coronavirus spread throughout New York City, my wife and I decided that it would be in my best interest to transfer to the Vanderbilt University Medical Center (VUMC) in Nashville, Tennessee. The transplant team at

IT IS MY INTENTION TO USE THIS ARTICLE AS A PLEA TO ENCOURAGE INDIVIDUALS OF COLOR TO CONSIDER BECOMING DONORS.

VUMC welcomed me with open arms. The doctors, nurses, and administrative staff provided me with the information and support that I needed in order to navigate the transplant process. The transplant team at VUMC notified me that a donor had been identified. The time had come to move forward with the bone marrow transplant. I do not know if I was more nervous about the bone marrow transplant or relocating halfway across the country. Nevertheless, my wife and I made the move to Nashville and I immediately started chemotherapy. After undergoing chemotherapy, the donor's stem cells had arrived and the bone marrow transplant was performed.

Now that I am more than one year removed from my transplant the motivation for this article is the selflessness of my donor and the unfortunate loss of two special friends who were battling cancer, too. As a father and a grandfather, it was difficult to talk to my family about me not possibly being around in the future. The actions of one human being not only changed my outlook on life, but changed the future outlook for those who depend on me. It is because of the actions of someone who recognized the importance of being a donor that I am in a position to share my story. The actions of my donor serve as a highlight in my story, but not everyone on my journey fared as well as I did. In the past year, I lost two very special friends who passed away during their battles with cancer. The loss of these two very special friends is a stark reminder that there is more work to be done in the fight against cancer. It is my pledge to serve as a voice in the African-American community for those who are currently battling cancer, as well as for those who might be faced with this terrible disease in the future. It is my intention to use this article as a plea to encourage individuals of color to consider becoming donors. I dedicate this article to my donor, my colleague's wife, and my former mentor and friend.

TAYLOR'S JOURNEY

JEFF BROWN
Tempe, Arizona

We intended to share our story sooner, but as we all are aware 2020 changed everyone's plans, including a delay to the next phase of Taylor's journey. It felt incomplete to share without some positive long-term outcome.

Back to the beginning, Taylor always excelled at school and was a self-motivated hard worker. Achievement came naturally to her and she had big plans for the future. We are not sure when her major medical issues first arose, but we suspect she was dealing with some level of it for quite a long time before the obvious signs appeared.

Taylor left high school and went on to study engineering at Arizona State University pulling the typical college student burn-the-candle-at-both-ends lifestyle. In her junior year (2016–2017), our first overt signs of trouble appeared. We noticed she would be sleeping in the afternoon each day and was having a lot of nausea. For a while we chalked the tiredness up to crazy college hours, trying to get all her work in, and contribute to the research lab where she worked. In retrospect, we have realized Taylor would frequently get very tired and sleep after high school too, we just never connected the dots or acted on it.

A trip to her primary care physician for some routine blood tests proved to be much more confusing than we could have anticipated. Taylor had hemoglobin around 8 mg/dL, platelet count ~30K and neutrophils (what were those???) at 800. We quickly learned how out of range these were and anxiously awaited some follow up testing which only confirmed something serious was wrong.

We were referred over to a local cancer center with that set of information in hand. None of it was real to us at the time but after the oncologist ordered the first bone marrow biopsy, the scope of what was in front of us

changed quickly. BMB results were not very conclusive, but that information, along with the ongoing issues in the CBC, escalated our concern. The doctor was pointing to bone marrow failure and sketching out a venn diagram of aplastic anemia/MDS/PNH on a post-it-note. It was shocking and surreal to be at a cancer center and hear those words spoken about our 21-year-old daughter. We heard things like "cytopenia", "immense amount of therapy and pharmaceuticals...", "more testing", "very rare, a couple cases per million" ...

> IMMEDIATELY, THE TEAM AT MAYO TOOK OWNERSHIP OF TAYLOR'S CASE, AND WE GAINED CONFIDENCE IN THE PATH THEY LAID OUT FOR HER.

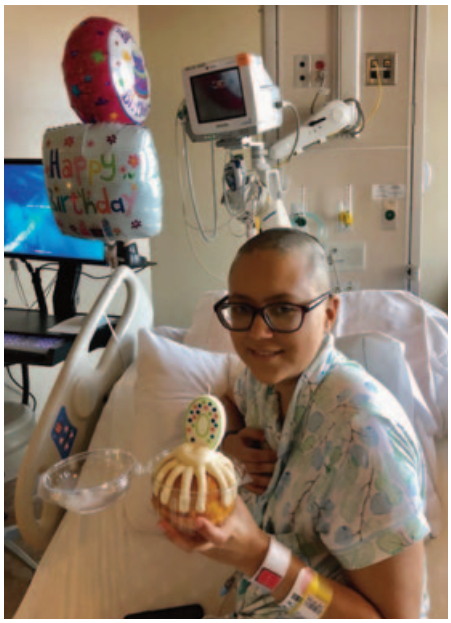
All the while, Taylor completed her junior year of engineering school under these circumstances (maintained Dean's List!!) and was weeks away from departing for a summer engineering internship.

Another biopsy was called for, this time an in-office procedure at the oncologist's office. So much information was passed around, we missed the detail about how that procedure would go. The initial BMB was done in an outpatient surgical center under moderate sedation. Taylor was not a fan of the sedation; she was so tiny and anemic that the sedation affected her significantly. For the in-office procedure, we expected the same approach. We prepared by asking the staff for minimal sedation, but learned the plan was to use only local anesthesia with a light oral antianxiety medication if desired. Taylor toughed it through that procedure and the results confirmed an empty marrow (<10% cellularity) to go along with the tri-lineal cytopenia. The oncologist thought Taylor had Aplastic Anemia and said only 600–1000 cases were diagnosed in the US each year. He also indicated that he might see one AA patient every 5–10 years and was recommending we seek out specialists in the field to best handle Taylor at that point. The oncologists had colleagues from earlier in his career with more relevant experience, and took the lead on finding the right path forward for Taylor. At the same time, we went to work trying to learn all we could about bone marrow failure and aplastic anemia. Scared the crap out of us. The oncologist connected us with the team at the Mayo Clinic in Phoenix. Fortunately, we live only 30 minutes from there. We have seen so many other patients and caregivers that must travel longer or temporarily relocate for treatment.

Immediately, the team at Mayo took ownership of Taylor's case, and we gained confidence in the path they laid out for her. For AA, the first protocol is a matched sibling donor for stem cell transplant (this was not available for Taylor), second was to follow an immunosuppressive routine (ATG/cyclo-

sporine), and third was an unrelated matched donor for HCST. Mayo identified a 10/10 matched donor in the worldwide database and placed a "hold" on that donor for Taylor while trying the IST routine. There were so many trying moments along the way, like reading 100.4˚F temp at an office visit and being checked into Mayo immediately for 36 hours of IV antibiotics, or being in the room while a PICC line is inserted into your daughter's heart.

While getting settled with Mayo, we consulted with NIH about the IST/Eltrombopag clinical trial that showed promise for AA patients. The IST routine alone historically had limited short/mid-term success along with common relapse or clonal evolution problems. Eltrombopag had shown to improve the first responses in many patients. The NIH had recently published the Eltrombopag study in NEJM which allowed us to get the protocol at Mayo too. So that was our course of action. The weeks and months that followed were a blur of 3 to 5 days per week in the infusion clinic for blood testing, and red blood and platelet transfusions when called for (hemoglobin at 6 is tough to live with as all the readers of our story will know), all the while watching any blip or jump in numbers with excitement. This went on for 5–6 months until we realized there was no response to IST at for Taylor. This was not the 2017 holiday



season our family hoped for. Another biopsy confirmed Taylor's marrow was still empty and along with the tri-lineal cytopenia confirmed the situation was still dire and maybe progressing. This biopsy also revealed some cytogenic anomalies for the first time (del 7q). It was stem cell transplant time for Taylor. The diagnosis for Taylor was ultimately hypoplastic MDS, which apparently is a derivative, hidden or related outcome for a small portion of young aplastic anemia patients.

After a few weeks of mental prep and thorough health checks, we brought Taylor into the Mayo Clinic Phoenix transplant wing in mid-January 2018. The calendar-based transplant schedule provided was so basic yet communicated so effectively the day by day activity ahead, surreal to say the least. Day –7, –6, –5...counting down on the white board. Check the box for a shower, check the box for a walk around the pod, check the box for oral care...simple tasks in a normal life, but this was far from normal. We witnessed every minute of the process never leaving Taylor alone. Taylor says it was all a blur and fortunately for her not a lot of clear memories of the treatment duration. Nothing emotionally prepares parents for shaving your 21-year old daughters head because long hair and multiple IV tubes are just not compatible. It was a relief to let go of the hair, and she looked great that way too! Chemo finished on Day –2, then a day of rest while Taylor's anonymous donor was in their preparation routine halfway around the world and a *Be the Match* courier volunteer escorted the donation all the way to Phoenix. Those lifesaving stem cells arrived promptly on Day 0, January 25, 2018 and with a little ceremony the IV transfusion began. It was a very apprehensive day—would there be a reaction? Fortunately, uneventful, a mini-Bundt cake to celebrate her second additional birthday, and the healing process began! Taylor passed through the trough/nadir from the chemo and then a little blip in her numbers. Her white cell count went from zero to 0.1 overnight on about day 6 or 7 and steadily climbed thereafter. A few bouts of fevers and just general crappy feeling for Taylor. She was physically hanging in there, but the cabin fever was ramping up hard. By about day 10 Taylor pretty much had it with the whole process (can't blame her), as her parents we wanted to ensure it would be a complication and stress-free transition home. We would have kept her in the pod until day 100 if we could, but Taylor was having none of that. We heard that most people get discharged at day 16–20. Taylor was discharged at day 13. Home we went. It was

way more nerve wracking than when we took her home after her actual birth. This was adrenaline on adrenaline 24/7. Routine follow-ups were 3 to 4 days a week back the Ambulatory Infusion Clinic at Mayo for blood work and medication adjustments. We basically knew all the nurses, physician assistants and physicians so well at that point. Taylors numbers climbed steadily; blood product transfusions were a thing of the past. Now we were on to figuring out a way to nourish and hydrate Taylor when there really was no desire to take anything in. These times were tough. We are a fairly tech savvy family, but a reactivation of CMV virus lead us to have to give her "Party Ball" antiviral infusions at home 4 times a day for a month. A trainer came to the house and laid out the process we should follow by the supplies used at each step. Thorough hand wash, alcohol wipe, the flush syringes, clean the port, connect the IV, wait an hour, clean the port, clean the flush syringe, new port caps....daunting for sure, but routine in a few days. It was surreal to explain what we had to do to my co-workers. Fascinating and scary. We plugged along after the CMV was dealt with. Day 100 for Taylor was on Cinco De Mayo, but there were no margaritas for any of us yet. Appetite and gastric issues continued; it was determined there was a bit of gastric aGVHD which introduced a new medication to the equation. All the while blood numbers showed Taylor to be a "normal" person at this point. A few months of the aGVHD treatment and gradually Taylor began to eat and drink at enough of a level to see her physically perk up and even put some weight back on. It was amazing to see her be able to get up a couple flights of stairs when only months earlier she would do it while seated on each step the whole way, one step at a time. Now she was bounding up the stairs. We took Taylor to Boston in July 2018 to visit family, see the Foo Fighters at Fenway Park, and attend the MDS Foundation Patient and Family Seminar. Taylor is unique at these conferences since she is so young in the MDS world. Later that summer, Taylor re-enrolled at ASU to complete her senior year of biomedical engineering. It was not always easy, always a small issue here or there that we completely lost our s**t over. Eventually, it was graduation day. Taylors's life has been disrupted but she still has managed to achieve many personal goals.

WE TOOK TAYLOR TO BOSTON IN JULY 2018 TO VISIT FAMILY, SEE THE FOO FIGHTERS AT FENWAY PARK, AND ATTEND THE MDS FOUNDATION PATIENT AND FAMILY SEMINAR. TAYLOR IS UNIQUE AT THESE CONFERENCES SINCE SHE IS SO YOUNG IN THE MDS WORLD.

In early 2020 at the 2-year mark, we were introduced to Taylor's selfless donor Andrezj from Poland. We have been able to communicate regularly with him using translate apps. We can't thank Andrezj, his wife, and his children enough for completing the donation process on Taylor's behalf. COVID and 2020 put further barriers in Taylors's life. 2020 was another on-hold year, but onward and upward in 2021! Since transplant Taylor has been volunteering regularly with the Phoenix based Be the Match team and now will be joining National Marrow Donor Program (NMDP) and working with donors who have matched with patients from all over the world, preparing them to save more lives like her own. As parents we are so happy to see her get back to full life!

We were very fortunate in many ways that my employer provided great insurance coverage for all procedures to this point and for what is still ahead of us. We realize not everyone is so fortunate to have access to great care networks, a matched donor, or the insurance to make it all possible. We are very grateful for all of that, to the scientists and pioneers in this field, and the current practitioners and support teams of this miracle cure.

I WRITE THIS TO ENCOURAGE YOU...

KES BUCKLEY
London, UK

I was diagnosed with a rare blood cancer called Myelodysplastic Syndromes. I'd been having symptoms for a while but was officially diagnosed and confirmed in 2000. I had my first strange blood tests in the 80's when I was in my early 20s. My GP discovered I had very large red cells and was a bit anaemic. She asked me if I was drinking too much and gave me some iron and left it at that. This continued to come up as an issue every now and again for the next few years. One day my GP phoned me at work and asked me if I was lactating. I started to laugh and said had she rung the right patient? She said that my prolactin was sky high. She repeated the test a couple of times and got the same high reading. Also, my cortisol was high too. On top of this some of my thyroid tests were a bit off as was my calcium but not all of them were off. She eventually referred me to a specialist. I was given a brain scan as they thought I might have a pituitary tumour. This was negative. I was prodded and poked many times and by a variety of specialists. Lots of things were just slightly off but nothing conclusive was discovered. After a couple of years, I was sent to a local haematologist as the one consistent was the large red cells and the low-grade anaemia. They did some tests and said that it could possibly be MDS. So my diagnosis became MDS. Eventually in 2000 I was sent to Kings who did a bone marrow biopsy. This was when I got to meet the amazing Professor Mufti. He told me it was definitely MDS and put me on what was called "watch and wait" It's a horrible term because it's like you are waiting for something to happen. It's like the sword of Damocles hanging over your head and it can fall at any time. Active monitoring is a much more positive way of putting it.

As the years rolled by the appointments got closer together as my illness progressed. I've had sepsis around 14 times. I've had serious line infections from having a hickman line inserted into my chest which would sit just above my heart. Last year I had 2 types of flu and have had flu every year since I had my transplant as well as a few times before. I've had NG and NJ tubes and still have a PEG J inserted in my tummy due to long periods of not being able to eat.

When all this started, I was a young fit football player. I never walked anywhere, instead I used to run. I rode a big motorbike. I worked full time, sang in a choir, volunteered with St. John Ambulance, was a Venture Scout Leader as well as playing and training hard with my football. I played for Millwall Lionesses and went on to play for Charlton Ladies.

After all these years of cancer being my constant companion officially for just over 20 years, there were early tell-tale signs 30 years ago, and I now live a very different life.

I had a stem cell transplant in Oct 2016. My younger sister was my donor and my life was saved by the amazing team of haematologists and allied health care professionals at Kings many times over. My life has definitely been saved but at what cost. My quality of life is much less than what it was. I now walk very short distances with a stick or use a mobility scooter. I have serious hearing loss and wear bilateral hearing aids. This is due to damage from the high dose chemo and antibiotics. I have myopathy, which is muscle weakness from all the steroids I've needed. My lung function is not what it used to be, and I get breathless very easily on exertion or when singing. My skin feels like it constantly has ants crawling all over it. I have awful reflux and wake up choking in the night. I can't lie down at night because of this and that has an impact in my neck and shoulders. I get ulcers and lesions in my mouth and several of my teeth have cracked and snapped off. My muscles and joints throb, burn and ache. I haven't been able to work since my transplant and this has been a big blow. The list feels endless and there's often a new issue to add.

CANCER HAS TAUGHT ME TO LIVE DEEP WITHIN MY SOUL. IT'S TAUGHT ME WHAT'S IMPORTANT IN LIFE AND NOT TO SWEAT THE SMALL STUFF. IT'S MADE ME EVEN MORE RESILIENT THAN MY UNUSUAL CHILDHOOD HAD ALREADY MADE ME.

Abseiling to show my adventurous spirit. I did this for charity off Guys Hospital Tower, and it was an amazing experience.

Despite all of that, I'm glad I'm still here. I've seen my daughter grow up into a wonderful woman and capable mother. I've loved and nurtured my 4 beautiful grandchildren and miss hugging them terribly during this awful pandemic. I'm still here and in love with my long-suffering partner. When someone in the family has cancer, the whole family has cancer.

Cancer has taught me to live deep within my soul. It's taught me what's important in life and not to sweat the small stuff. It's made me even more resilient than my unusual childhood

had already made me. It's introduced me to some fantastic people among the patients, doctors, scientists, advocates, allied professionals, admin teams, cleaners, patient support groups personnel and charity workers.

I've also met two amazing sisters and a brother and their wonderful families who I had never met before. We share the same dad. My cancer diagnosis spurred me on to keep looking for them. I'm so glad I did.

I am also blessed to live in a country with a first-rate health service. I have the most supportive and loving family around me. Not everyone is so fortunate. I also have some very clever and creative consultants and medics who I trust and who always have my best interests at heart even in these strange COVID times we are living through.

My job is to keep on top of it all and not curse the darkness but just keep lighting candles.

TO ALL OF YOU AT DIFFERENT STAGES OF YOUR OWN STORY, I WRITE THIS TO ENCOURAGE YOU. SOMETIMES THE ONLY THING YOU CAN DO IS GRIT YOUR TEETH AND BREATHE THROUGH IT. THERE WILL BE DAYS THOUGH WHEN THE SMILE OF A GRANDCHILD LIFTS YOUR DAY OR A CUPPA WITH A FRIEND EASES THE BURDENS OR A HUG FROM THE PARTNER REMINDS YOU THERE'S MORE TO YOU THAN CANCER.

I saw Victoria, my dedicated consultant on Tuesday. I have IVIG once a month. This is a drip and stands for Intra Venous Immuno Globulin. It gives me some antibodies to try and help me to have an immune response.

With my youngest sister Gail who is my life saver. She donated to me.

Victoria told me one of the things to be looked at in clinical trials is adding COVID antibodies into the mix to see if that helps people like me who probably won't respond fully to the vaccine. Scientists and doctors and Pharma companies are so clever. Let's hope they find a way for it to work.

Victoria also said that she would look into a new drug that may help me. She was going to discuss it with her colleagues and then see if I would be appropriate for funding. It's so good that the team behind me are still committed to making me as well as possible. They haven't given up on me once. I'm touched by their commitment and faith in me. I'm also willing to give anything a go that may help. Advances are being made all the time.

When I get to the end of my rope, what I need to do is tie a knot in it and hang on.

I've had both my COVID vaccinations but no guarantee it will work. Even if it gives me a tiny bit of immunity it's worth it. I've been told very clearly; I need to continue shielding for the foreseeable future. Regular readers of mine will know this was hard news to swallow and made me feel down for a few days. I've bounced back as I usually do because I have to choose to live in hope.

To all of you at different stages of your own story, I write this to encourage you. Sometimes the only thing you can do is grit your teeth and breathe through it. There will be days though when the smile of a grandchild lifts your day or a cuppa with a friend eases the burdens or a hug from the partner reminds you there's more to you than cancer. I try not to be defined solely by my illness. There is so much more to me than cancer, hospitals, and medication.

I'm a partner, mother, grandmother, auntie, sister, cousin, niece, priest, friend, and neighbour. Cancer can't rob me of that, and I choose to keep moving forward and step out in the hope and light of each new day.

"Act as if what you do makes a difference. It does!"

I let my grandkids draw on my head so they wouldn't be so upset or scared about my bald head.

MY MDS STEM CELL TRANSPLANT EXPERIENCE

MICHAEL GERAGHTY
County Mayo, Ireland

NOVEMBER 2018

I had a biannual blood test to monitor my cholesterol as I had a heart stent fitted 17 yrs previously. My platelet count was observed to be 100, down from usual 150/200.

I was referred to a nearby haematologist in Galway who did various tests over the next year to conclude in January 2020 that I had MDS. He advised that a stem cell transplant was my only solution and referred me to Dr. Conneally at St. James Hospital in Dublin. This is the only one in Ireland to do SCT. My diagnosis is that the TP53 gene has mutated and gone rogue making a chromosome complex problem. It attacks the maintenance of correct levels. Therefore the levels may drop soon again or after a while of treatment with Vidaza. They need stable levels to create a window of opportunity in which to do a marrow transplant. But it is possible that the activity of the TP53 may destroy new marrow, making it pointless doing the transplant. They will figure this out from the next marrow of 23 June with results in late July leading to a transplant in or after September, if it's deemed suitable.

I started on monthly Vidaza injections in March, which I received over 7 cycles. I didn't encounter any issues with Vidaza when given anti nausea meds at the same time. It worked to excite the marrow into improving my blood numbers so I was suitable to have the SCT. Platelets increased from 48 in Jan to 129. Early on my brother was tested to be a likely donor but found unsuitable. One from abroad was found on the database.

I was admitted to Galway Hospital on 15th September for a week of tests and prepping for the SCT. I also had a Hickman line/port inserted in my chest. This was my first taste of the confinement I will have to endure.

I arrive to Denis Burkitt Ward St. James Hospital before 6 pm. Entry is via a double door system. Outer door has to close before opening the inner one. Sink, shower and toilet are activated by non touch sensors which gives an inkling as to the attention to cleanliness. All walls are covered with hard plastic sheeting for ease of cleaning. Day –12 the 23rd, I was given many examinations and visited by the consultant who gave clearance to go ahead with the chemo which started about 2:30. The first treatment took half an hour, straight after that, the second one was an hour, and the third was two and a half hours later and lasted for 4 hours. That was the routine for the next 3 days (day –11, 10, 9) for 4 days total.

THEY NEED STABLE LEVELS TO CREATE A WINDOW OF OPPORTUNITY IN WHICH TO DO A MARROW TRANSPLANT.

During my free time I wanted to be active while I felt up to it. I briefly walked the corridor for exercise.

The next 2 days after that period were free of chemo treatment, that is Sunday and Monday (–8,7). Sunday night I slept and Monday I woke up quite a new man and had a good day.

My next chemo was Tuesday at 4 a.m. for two hours and that chemo will be given every 6 hours until Friday morning.

I experienced very slight side effects, i.e. on the Sunday a bit of vomiting and diarrhoea with some light-headedness, on other days it was an easy time.

On Friday it changes to a different chemo for 12 hours and the same drug on Saturday and Sunday for 10 hours each day. I was forewarned that these last days can be a bit rough. The prediction was correct as the chemo caused nausea, irritability, lack of sleep. This brings me to the goal of day 0 transplant day on Monday, I didn't feel the best in the morning but hoped being finished with chemo that I would recover quickly. I was told mid-morning that the transplant plasma wouldn't be arriving until the following day, so this gave me more time to recover. My platelets were down at 10 and needed to be at 50 so I was given a transfusion. I was well improved by day 0, 6/10/20. I received preparation drugs by IV drip with the donor stem cell plasma bag arriving around 12:30 pm. I was expertly set up by nurse Margarita assisted by nurse Hindu. As with all IV work, there is constant sterilising wiping of the parts they are using. The drip of salvation started at 12:49 pm. My BP, temp, oxygen level, and heart rate were taken every 5 minutes to check in case I had a reaction. Everything went well and the last drop passed into me at 1:40, 50 minutes in total.

I was left to rest for a few hours before getting more IV meds. These finished up around 9 and I looked forward to an IV chemo free sleep for a change.

ONTO DAY +1, 2, 3

These days establish a routine of IV anti rejection drugs which give me a headache if given too quickly. Also each day I get a transfusion of platelets and possibly blood. This pattern will be in place for about three weeks until my new system is producing enough on its own. On day two, a sore mouth and throat set in. I struggle with even soft food. Food tastes very bland and I become super sensitive to sugary tastes and don't want them. A special mouthwash is tried with a very short-term effect.

This day I'm recommended to shave my hair which is falling out. On day three the consultant specifies connection of a morphine pump to deal with it. She also recommends from day 4 being fed through my line. This will give adequate calories and vitamins and I will feel full.

DAY 4: OCT 10 SATURDAY

I had a great rest when I felt the energy drain from my body and got restful sleep for the first time in a while. At the end of the day I was well rested.

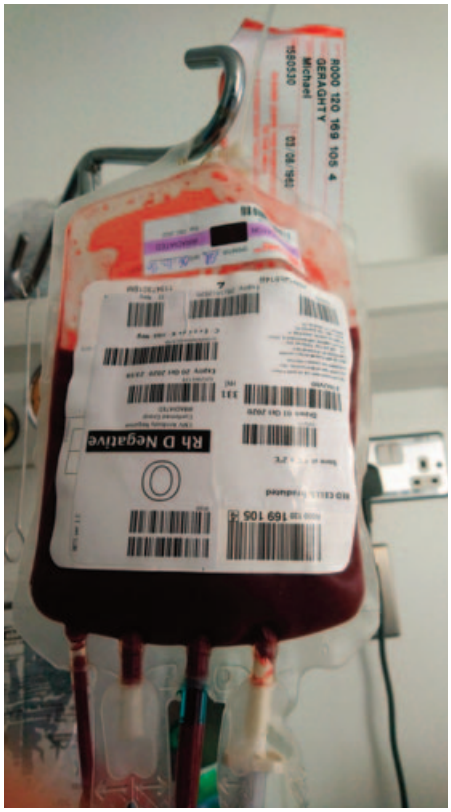
DAY 5

I had woken a few times during the night but still was very well rested in the morning. However, by about 10.30, I was experiencing the wriggers as I had the day previous. These severe shakes were cured within half an hour. I spent the rest of the day as weak as a kitten and slept a lot.

Day 6 was very similar!

DAY 7 TO DAY 14

I began to feel progressively better each day and ate at each mealtime as the effect of the morphine eased the pain. Therefore, the line feeding only lasted 5 nights, reduced to half ration for the last two nights. I established a daily routine based around daily drips which would finish or be stopped around 2 to allow me to shower, exercise, and walk the corridor for 20 mins. Some days I felt tired and slept thus delaying my routine until evening.



I was released from hospital eventually on November 1st on a Sunday in the afternoon. It was a long awaited event, to breathe fresh air and embrace my partner Trish. She had come with lots of luggage, driven by my sister-in-law Joanie with the assistance of my brother John who would bring Joanie home. We found our nearby apartment which was arranged by the hospital in a complex where the Irish Bone Marrow Trust owns apartments for this purpose. This was to be home for us for probably six weeks. I was feeling weak and not very able to do any of the lugging, but my helpers sorted that out. Later Trish served up some Irish stew which went down very well.

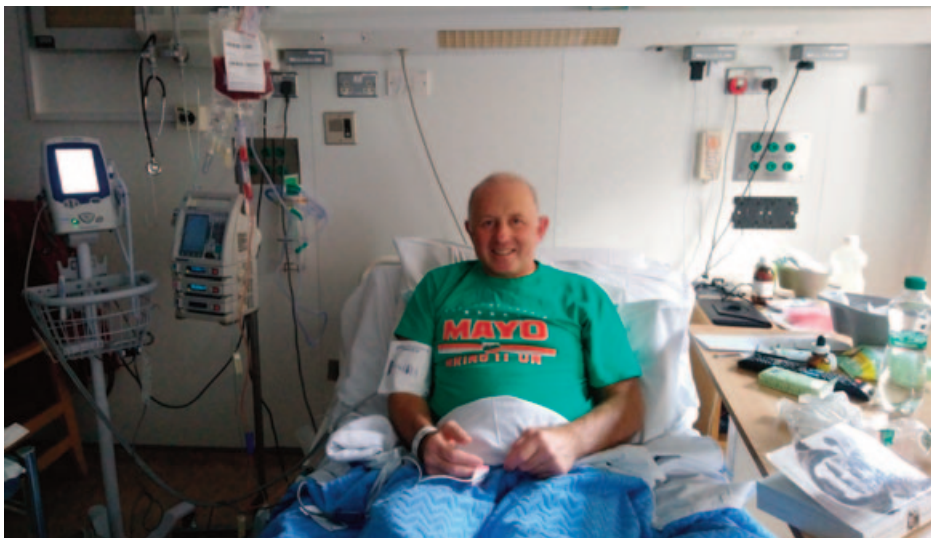
I had to attend the hospital two or three days a week for checkups. Meanwhile we made efforts to get out for at least an hour a day to walk. I steadily improved in strength over two weeks. Having the car with us gave the chance to do some trips, however due to the COVID pandemic restrictions, we were limited in how far we could go. Over the period of two weeks, however, other than being lethargic, having a GVHD skin rash and GVHD mouth sores, I had discomfort at night. Initially the main one was a dry mouth which would cause me to awaken 5-6 times to take a drink. This was increasingly accompanied by the need to urinate which became increasingly painful in my urinary tract. Clots and blood also became obvious. The hospital team gave me various remedies without improvement. Eventually, after two weeks of freedom, they decided I would need to come back into the hospital for investigation. This necessitated me attending the emergency room on Saturday 15th to be admitted to an isolation ward where I had a COVID test. On the following day I was moved to the Burkitt ward as being COVID negative. They quickly determined I had an infection by the BK virus. They explained that while the chemo clears out most viruses the BK one is a very old one which is present in everybody but is kept dormant by a normal immunity system. They also detected activity of a glandular fever causing virus. They started me on treatment for both. At this stage urinating had become so painful that they fitted a catheter with a urine bag. This mostly confined me to bed for three weeks. When I was released I felt much weaker than at the initial release. I was released by the hospital clinic to go home to Mayo on December 15th, just in time to get settled for the Christmas season. However, I would return to the clinic at least every two weeks for the foreseeable future. It took me probably six weeks to get to a comfortable level of strength and lose most of the lethargy. However, bouts of lethargy are ever present after mild exertion, such as gardening and wheel barrowing. Most of my active time, other than walking or cycling, is spent gardening with Trish. In Summer of 2020, we spent a lot of time transforming our surroundings, by planting flower beds and developing a greenhouse, which was all new work to us.

The urinary tract pain receded but the dry mouth was still uncomfortable. Various remedies didn't work. In early February, I began to experience the urinary tract pain again. My oncologist prescribed Betmiga, which did not improve it after a month. I was

sent to a urologist who recommended Vesomni, which again did not have an effect after a month. More tests were done and it was found that it was the BK virus again. This time I was given IV treatment similar to that as an inpatient. This happened weekly over four weeks. However, it did not improve and it was concluded that it was also decreasing my blood quality. My oncologist decided to stop it as well as the Betmiga and Vesomni, and work on increasing my immunity instead. The severity of the pain has eased, but the 4-6 nightly urinations still persist. While for the first few months I would be very awake for each event and return to sleep quickly, I am now a bit drowsier doing it but still get back to sleep quickly. Each bout of sleep is accompanied by a separate distinct dream. Some of which I am happy to waken from!

Throughout my recovery I found myself evolving through it. My taste buds sensitivity to salt, spice and sweetness eased, but not fully. I perceived my surroundings differently over time, not realising that my early perceptions were off.

This remains the situation as of mid-July 2021.



THROUGHOUT MY RECOVERY I FOUND MYSELF EVOLVING THROUGH IT.

OUR CAREGIVER VILLAGE: OUR DEVOTION TO OUR FATHER, OUR FORCE AND OUR STRENGTH.

MARITZA FORERO SANCHEZ
Boston, Massachusetts

Over the last three years, our family has come together to help with the care of our wonderful father, Luis. He is our 89 years "young" gentleman whom we refer to as "Papi" and who has been living with MDS.

Our father arrived in the US almost 54 years ago from Bogota, Colombia to pursue a better life for his family as an electrician. Two years later in 1969, he brought over his wife and family of 6 children to begin their new life together in Boston, Massachusetts.

Through my childhood I cannot remember my father being sick. He was so dedicated, providing for his family, always making sure that we had all that we needed. He was a pillar of a man, filled with life and heath and he lived like this for 85 years. In April 2018, he came down with a high fever, and was hospitalized with a blood clot. It was during this hospital stay that the doctors discovered that his blood platelets were extremely low and of great concern. He was immediately assigned to a hematologist who ordered a battery of tests, and a bone marrow biopsy. After a few weeks of thorough testing and evaluations, the tests revealed that he had a blood disorder and was referred to a medical oncologist who confirmed that he had MDS. "What the heck is MDS", we thought. We never heard of such an illness – we originally thought he had said MS.

To our devastation, the doctor thoroughly explained what MDS was. Our minds were running away with us, so many questions, such a horrifying feeling in the pit in my stomach. Was our Papi going to die, was this a terminal cancer, how many months will he be on this earth with us? I went home with my father in a state of shock and immediately called my siblings to let them know. I went on

line and googled MDS and the first information I came upon was The MDS Foundation. I contacted them via telephone as I wanted to speak to a live person, someone who could hear the concern in my voice. I particularly wanted information in Spanish so that my father would fully understand what he was reading and not what I would otherwise be translating in my non-medical terminology and knowledge of this disease. The agent on the phone proved to be a great resource to us as we received a plethora of information in both Spanish and English. It was the beginning of our "educational journey of MDS".

My siblings and I arranged for a family meeting to plan our Papi's medical course of action. We understood the commitment to our father and decided that we would all be involved in his caregiving, and the responsibility would be shared by all of us. It was all a learning curve as we accompanied him on his first bone marrow infusion. We felt so anxious for him, praying that his body would tolerate it and that he wouldn't suffer a negative reaction to someone else's blood. It was difficult to watch, but yet it was a lifesaving procedure that kept him healthy for a few months. This process left such an impact on one of my brothers that he now donates blood and platelets monthly, and is a vibrant advocate of blood donations.

Eventually the visits to the infusion center became less and less frequent as his platelets count continued to drop and it was no longer a benefit for him. His doctor searched for other treatments and stumbled upon what we call a "miracle drug". He started our father on this drug therapy and to our pleasant surprise his blood platelets began to rise and have been at over 170,000 for over two years.

We are in the middle of our father's MDS journey and we know that things may not always be this easy. We are a very fortunate family as the caregiving experience has been a positive one. It is not a typical experience

because we have the blessing of sharing it with each other. Our father's therapy has been successful thus far. This is largely attributed to the fact that he has outstanding medical care. His nurses, and doctors go above and beyond in communicating with us about his care. At the same time, our father is a great patient, exercises, eats healthy, and takes all his medications. Thanks as well to the dedication of our mother, also 89, who makes sure he stays on course.

We will always remain involved and dedicated to our Papi's care. We will continue to participate in the MDS walks, the educational seminars, and virtual events. We will be there every step of the way, as it really does take a village.

BECAUSE OF POP-POP: HIS INFLUENCE CONTINUES

ELIZABETH DELANEY
Wilmington, Delaware

It is because of my grandfather—Frank A. Maviglia—that I have dedicated my career and my volunteer efforts to raising awareness about rare hematologic malignancies, like myelodysplastic syndrome (MDS).

My grandfather was your typical, strong-headed Italian man. Born in 1925 in Jersey City, he was the oldest male in his family. As one of five children, he experienced first-hand the hardness of the Great Depression. When he turned 18, he was drafted for World War II and spent 2.5 years fighting in what we now know to be the Middle East. He received multiple honors, including the World War II Victory Metal.

After the war ended, Pop met my grandmother, and together they had five children. He had an entrepreneurial spirit and opened Frank's Quality Cleaners in North Arlington, New Jersey. Although the cleaners was eventually sold and has since closed, the secrets of getting any stain out of a piece of clothing has not been lost (Ever heard of Lestoil? It's a miracle serum).

Growing up, my grandparents had a constant presence in my life. They were there for all my dance recitals and band concerts. During the summers, my sister and I would relish the weeks we would spend at their lake house, spending countless hours sliding down a metal slide that would burn your legs as you slid into the sea-weedy lake. My grandfather was a self-taught woodcraftsman. He would surprise us with handmade beds for our dolls or shelves for our rooms. When we were finally old enough to be in his woodshop, he would help us make projects of our own. For me, my fondest memory was building a bridge for my Girl Scout Council to use for bridging ceremonies.

My grandfather had had some health hardships. He battled and overcame prostate cancer, sustained a bad fall, and had an abdominal aneurism. Decades of smoking caused COPD and eventually he would need full-time oxygen. Little did we know that his biggest battle would be with MDS.

My mom assumed the position of medical caretaker for my grandparents. Since Pop-pop was a veteran, my mom would bring him to the Hackensack New Jersey VA Hospital for his routine care appointments. Pop-pop was always up before the sun, so he liked going for the first appointment of the day. Regardless of how early that meant mom needed to get up, she never complained. During routine blood work, his doctor noticed his red blood counts were low. At first, they decided to monitor for a few months, but after being consistently anemic, further tests were run.

In 2008, he has diagnosed with MDS-single lineage dysplasia, confirmed by a bone biopsy. My aunt was a registered nurse and would administer PROCRIT® injections. For a few days, the shots were successful in stabilizing his counts. When the shots were becoming less and less beneficial, his doctor recommended blood infusions. Every few months, my mom would bring him to the VA for his infusion.

In 2010, he started needing infusions more frequently. It was heart-breaking to see how lethargic and confused he would become every time his counts dropped low. Eventually, he switched to an amazing, local care team at St. Luke's in Easton, PA, where my grandparents lived.

On April 13, 2014, my grandfather lost his battle with MDS. Leaving behind 5 children and 9 grandchildren, Pop-pop left his mark on each of us.

I inherited his incredible work ethic and perseverance. When my family was grappling with Pop-pop's MDS diagnosis, we were told that there was no cure and MDS was a rare blood cancer; but I wish someone had told us about organizations like the MDS Foundation. I chose to pursue a career focused on raising education and awareness to help families like mine learn about the network of support available to them for rare hematologic malignancies, like MDS. I've dedicated countless hours supporting, fundraising, and volunteering with The Leukemia and Lymphoma Society in honor of my grandfather. I've only recently learned about the amazing support that the MDS Foundation offers people like my grandfather and believe their efforts are moving us closer to the cure that will save someone's 'Pop-pop'.

AML RESOURCES

YOU AND AML:
AN ANIMATED PATIENT'S GUIDE TO ACUTE MYELOID LEUKEMIA

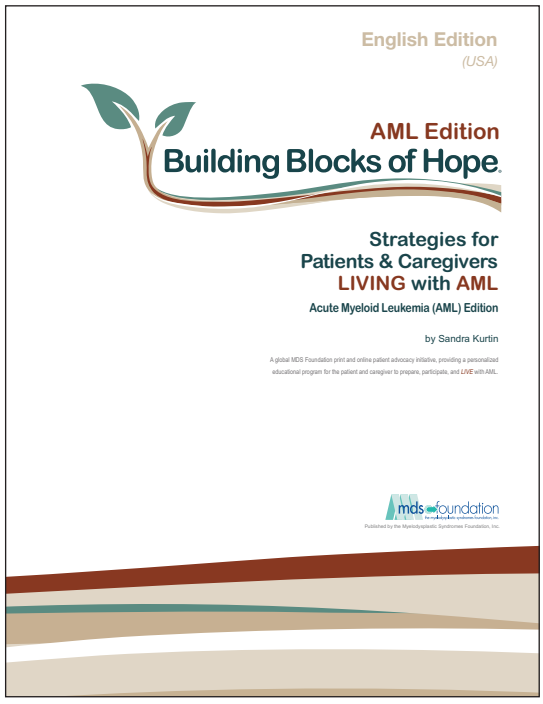
This resource is intended for patients with acute myeloid leukemia (AML). You will find expert advice about AML, AML with myelodysplasia-related changes (AML-MRC) and treatment-related AML (tAML) to help you discuss key issues with your healthcare provider and make important decisions related to management and treatment.

"YOU AND AML" CONTAINS 4 LEARNING MODULES:

- Understanding AML
- Understanding AML-MRC and tAML

Each module contains easy-to-understand animations with audio narration, video explanations by AML experts, patient interviews, and illustrated slide shows.

COMING SOON
A new module
Maintenance and Continuous Treatment in AML



BUILDING BLOCKS OF HOPE

You or someone you know has been diagnosed with AML.

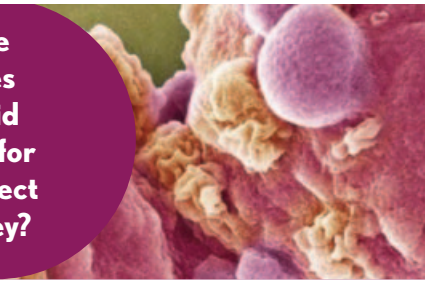
Hearing the words Acute Myeloid Leukemia or AML can be frightening. The diagnosis of AML is often unexpected and filled with both immediate and long-term challenges. You probably have many questions. Allow yourself time to adjust to the diagnosis of AML. Take time to explore the Building Blocks of Hope®, it is designed to help get you the information that you are looking for and take an active part in your AML journey. This is a great way to share this information with family and friends. The AML BBoH contains four chapters and a glossary of terms:

Chapter 1: Understanding Acute Myeloid Leukemia
Chapter 2: Seeking Treatment
Chapter 3: General Resources for Living with AML
Chapter 4: The MDS Foundation

FIND THE RIGHT FIT

Navigating Secondary Acute Myeloid Leukemia

Do you or a loved one have myelodysplastic syndromes or secondary acute myeloid leukemia and are looking for resources or ways to connect with others on your journey?



People affected by myelodysplastic syndromes (MDS) or secondary acute myeloid leukemia (sAML) often face many uncertainties on how these diseases develop and progress, what available treatment options there are and the impact they may have on everyday life.

For those in search of answers, Find the Right Fit can provide information and educational resources for people living with MDS or sAML, as well as their loved ones who often take on the role of caregiver.

A cancer diagnosis can be overwhelming, but **knowledge is power**. To help navigate each person's individual journey, Find the Right Fit **provides a collection of tools** including articles, videos, patient stories and more that:

Educate on the science behind MDS and sAML

Offer information regarding treatment options and coping strategies

Connect patients and their loved ones with the appropriate resources to manage an MDS or sAML diagnosis with confidence

Visit FindTheRightFit-sAML.com.

About AML

- AML is an aggressive (fast-growing) disease in which too many myeloblasts (immature white blood cells) are found in the bone marrow and blood.[1,2] sAML is one type of AML that may be linked to specific preexisting conditions, like MDS, or to prior treatment for a malignant or non-malignant disease.[3]

Visit FindTheRightFit-sAML.com to learn more about sAML subtypes and treatment options.

About MDS

- MDS, a form of blood cancer, are an often unrecognized, under-diagnosed, rare group of bone marrow failure disorders where the body can no longer make enough healthy, normal blood cells in the bone marrow.[4]

- The cause of MDS is unknown, but potential triggers include radiation and chemotherapy for cancer, as well as long-term exposure to certain environmental or industrial chemicals, such as benzene.[4]

Visit FindTheRightFit-sAML.com to learn how MDS can progress to sAML.

Find the Right Fit is a program from **Jazz Pharmaceuticals,** developed with consultation from the **Myelodysplastic Syndromes Foundation, Inc.** and the **Cancer Support Community.**

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Jazz Pharmaceuticals

CANCER MEANS LIFE IS HAPPENING

EDMUND OASA
Oakland, California

In fond memory of the passing of Edmund Oasa on October 26, 2021, diagnosed with MDS in 2016 and AML last year.

Ed and Shellye

This story begins with an MDS diagnosis in October 2016 and ends with an AML diagnosis in June 2020. While it covers cancer and illness, it is more about change and coming to terms with it.

I was born and raised in 1950s Hawaii as the oldest of three in a Japanese family. Owing to Hawaii's history and demographics, the Japanese as one of the many ethnicities there did quite well economically. They pursued the so-called American dream and many did well. My family was not privileged, but I'd say we lived comfortably.

I attended private school. My parents saved enough for me to attend a college on the U.S. mainland. I returned home for graduate studies at the University of Hawaii (UH) where I received a doctorate in political science in 1981. After that, I tried to make it in the academic world. I worked at the UH, the Institute for Environment and Society in West Berlin, Germany (before the wall fell), and the University of Kentucky. This effort ended in the mid-1980s when I was unable to find academic employment. After floundering for a bit, I became a self-employed California-licensed private investigator and specialized in criminal defense for over twenty years.

I offer this history to say that I really had no hardships to speak of. Sure, there were family pressures of growing up as the eldest child, a son no less, in a Japanese family. Unemployed in the middle of Kentucky was challenging at times, but I had good friends and a supportive family to turn to if I got into a pinch. I always felt that things would work out somehow. I don't remember feeling pessimistic or a loss of control about the future.

My MDS diagnosis brought the life just described to a halt. The first biopsy at a cancer clinic in Berkeley, CA read 13 percent excess blasts "with features concerning for evolving acute myeloid leukemia." I was referred to the Stanford University Cancer Clinic in Palo Alto, CA, where my hematologist informed me of a three-year prognosis without treatment. "But," he added, "my job is to cure you" by way of a bone marrow/stem-cell transplant "and that's what I'm going to do."

I crumbled and wept upon hearing his words. Though I was relieved, I was also aware of a statistic that has not changed much over the years; that is, less than 40 percent of transplant patients survived another five years.

Thoughts and emotions were mired in chaos and utter disbelief. Cancer was not supposed to happen. I told my sister, Suzanne, that for the first time in my life, I felt something was not going to work out.

I thought about death, so I read Sherwin Nuland's 1993 classic, "How We Die." I thought about things like whether I've had a good life, accomplishments, my legacy, a bucket list, etc. I didn't settle into any one of them, hence the notion of chaos. I now regard these questions as useless because ultimately, they are ego-based and self-centered.

Chaos ended abruptly when I learned of a conversation between my wife, Shellye, and Suzanne. Shellye related that Suzanne did not want to talk with me at the moment because, in Suzanne's words, "I'm too sad." I did not hear these words firsthand. In many Japanese families, words of sentiment are not expressed directly and often conveyed through another source.

My sister's words were comforting and assuring. The self-centered mental chaos ended because I realized how critical our connections and relationships are to life. Nothing else matters or should matter. Of course, the self-based thoughts come and go, but the frustration and anxiety of the mental chaos were gone.

After Nuland's book, I read Siddhartha Mukherjee's "The Emperor of All Maladies: A Biography of Cancer," and Susan Gubar's "Reading and Writing Cancer: How Words Heal." I am grateful for reading Gubar's book because it introduced me to a world of cancer memoirs and essays that I read during the pre-transplant period. I mention these readings because they relieved the anxiety of having cancer and made me feel that I am not alone.

Against this background, I was able to focus on pre-transplant treatment. I received azacitidine chemotherapy one week a month for six months before I underwent a stem-cell transplant in May 2017. My brother, Wesley, was my donor.

Before transplant, friends told me to "fight" and "stay positive." I never once felt I had to "beat" cancer. I can't say I appreciated such words of positivity and pugilism despite their

good intentions. One friend bought me a pair of professional boxing gloves. At times, those words actually felt like "punches to the gut."

The fact is I can't beat cancer. The doctors will. My job was to stay out of their way, trust them, and follow the program. I am grateful to Stanford doctors and nurses at its Cancer and Chest clinics. They are living proof that Stanford is a center of excellence.

Pre-transplant chemotherapy and the transplant itself went smoothly. I was spared the intolerable side effects described in many patient stories. I apologized to the nurses at Stanford's Infusion Treatment Area (ITA) for being a boring and unchallenging patient. They replied, "No worries. We like boring."

Shellye and I attended Stanford's MDS support group gatherings. Of the many handouts we received, one from the palliative care unit struck a nerve. It mentioned a saying translated from Sanskrit that read, "Suffering is holding on to something that has already changed." As the reader will see, these words both dogged and helped me throughout this four to five year period.

A biopsy in late August 2017 showed no sign of blasts. By then, I had started supplemental azacitidine chemotherapy in July to prevent a relapse that often occurs soon after a transplant. When this preventative measure ended in December 2017, things were looking up and I felt good about resuming life not as it was before cancer but may be close to it. After all, "something changed." By then, I was walking throughout my neighborhood and strengthening at home with bands and weights.

In December, my primary care physician questioned me about a cough that I dismissed as a mere reflex cough. The cough worsened during a trip to the Big Island of Hawaii in January 2018. Doctors arranged for two appointments in February and March at Stanford Hospital's Chest Clinic for a pulmonary work up. Doctors found nothing problematic.

In early April 2018, I was hit with viral pneumonia caused by the adenovirus, a common cold virus that morphed into pneumonia owing largely to GVHD. I remember being in the hospital for a couple days, wondering about a release date and experiencing mostly pleasant hallucinations possibly due to the infection and/or the medications I was on.

The next thing I knew, I woke up with a ventilator in my mouth and Suzanne at bedside telling me to rest and, "A lot of people are rooting for you." Either my family or a nurse, I don't remember, told me I had been in an induced coma in Stanford's intensive care unit. I learned that while comatose for about a week, the doctors advised Shellye, Suzanne, and Wesley that I was declining and they did not understand why.

I don't know what awoke me. All I remember of the next few days is a nurse getting excited to see my "blood oxygen" rise high enough to have the ventilator removed.

"Why did this happen?," I asked a hematologist familiar with my transplant history. I told her I followed the program and stuck to the rules, and this was the outcome? Was this supposed to make up for how easy the transplant was?

She answered in frustration, "I know, I know. This isn't fair." At the time, she was the only provider who gave me an assessment of what was happening; that is, I was still teetering, things could backslide, and she'll see to it that I remain comfortable.

I don't remember how much oxygen I was on but it was a lot. It might have been another week before I reached the oxygen saturation rate of 15 litres/minute, which is the minimum requirement for transfer out of ICU to Stanford's E Unit to recover.

While in E Unit, teams of providers visited daily – pulmonologists, hematologists, infectious disease specialists, and physical therapists. No one could tell me the extent of recovery or whether reliance on oxygen was permanent. One pulmonologist guessed maybe six months of oxygen. Well, she was wrong. A hematology medical fellow opined that if it weren't for the post-transplant exercising and strengthening, I would not have survived.

All I saw of myself was an atrophied tube-fed body, unable to sit up and dangle my feet off the bed for more than a minute without gasping for oxygen and feeling dizzy and even after a few weeks still unable to walk five feet with assistance. I was lifted in a motorized hammock-like contraption to get me from bed to chair so I could build stamina to sit. This was shocking.

I had just been out of ICU, so I probably wasn't thinking clearly in early May when a medical fellow said the team was considering a return to ICU "for just a little while" for observation. No way, I told him and added pejoratively, "You had a week. How much more are you going to learn?" I eventually learned that the pneumonia damaged my lungs permanently.

Shellye, Ed, Suzanne, and Wesley

I wasn't having any of this, meaning a future that depended on oxygen and others for daily living. I asked a social worker to call hospice because I wasn't about to embark on a life of dependency with no idea of the extent of recovery. All the doctors had to do was to cut the oxygen and turn on the morphine.

Obviously I was talked out of this. Shellye asked me to give it a chance. I also asked her to get me out of the hospital and care for me at home. She calmly responded in no uncertain terms that there was no way she could provide the level of care this setback required. I had no clue as to how sick I was.

I felt humiliated. I remember telling Shellye, "Enough of this already," and enough for her, too. She had retired in July 2016, a mere three months before the MDS diagnosis. Her life of retirement turned into a life of caregiving. It was not just the humiliating illness but the guilt I felt, and still do, about her sacrifice. Friends advised me not to feel guilty and reminded me that I'd do the same for her. Their words have done little to relieve this suffering.

Yet, I welcomed physical therapists who essentially taught me how to sit, stand, and walk. They propped me up in bed, helped me sit at the edge to dangle my feet, and braced me while I struggled to stand and take a step or two with a walker. Nurses used a Sharpie on a laminated sheet to note the number of steps I took each day.

One day in May, a physical therapist told me my oxygen flow was at eight liters/minute. I cried openly at this news because I was closing in on the "get-to-go-home" mark, which was four liters/minute.

I was hospitalized for two months. I returned home in June 2018 to begin three months of in-home caregiving and physical therapy. I strengthened enough to begin exercising on my own at home and was closely monitored by a Stanford pulmonologist for the next two years. I didn't know whether to laugh or cry when on my first visit to the Chest Clinic, a nurse greeted me with open arms, "Our miracle!" I was to hear these words again from a social worker at the ITA a week later. I am not supposed to be here.

Other than two brief hospitalizations in early 2019, I spent the year strengthening and taking slow walks up and down my street. By the end of the year, I went from depending on oxygen 24/7 to using it only when I sleep.

So, where did cancer go? Cancer? What cancer? Blood counts were robust. There were no signs to indicate a need for a biopsy. My hematologist and I were hopeful that the MDS was something I would not have to worry about again.

Life changed — no more long walks, hiking, gardening, bike riding, and occasional travel, all the things Shellye and I liked to do. My lungs wouldn't allow it. A flight home to Hawai'i in September 2019 was not fun. I struggled to maintain a desirable oxygen level, even with a portable oxygen concentrator, at an altitude of 35,000 feet for five and a half hours. I've decided on not flying again, which means I won't see my home and extended family again. This is why the Sanskrit saying mentioned above dogged me.

I knew offhand that Sanskrit was the early language of Buddhism, so I started studying the religion and enrolled in an introductory class. Reading, studying and listening to teachers continue to this day.

Buddhism has many lessons but the one that resonated deeply was that I really wasn't humiliated. I was humbled by life and the universal truth of life's impermanence. Hearing the difference between humiliation and humility was profound. One way of expressing this truth is, "Life lives me. I don't live life." Life happens. Cancer happens due to myriad causes and conditions that one does not control.

Realizing impermanence as truth about the flow of life is difficult and remains ongoing. Over time, gratitude and acceptance evolve out of the sadness and disbelief that illness causes. My teacher in Berkeley, CA said, "Illness teaches." Another Buddhist scholar wrote, "Illness, too, is a good friend."

In June 2020, Shellye and I experienced the wave of disbelief and sadness when I was diagnosed with AML with 43 percent excess blasts. The finding came out of nowhere as counts were robust just five months prior. The first suspicious blood test happened a few days shy of the third anniversary of the transplant. When told of AML, I remained silent and Shellye gasped.

A new hematologist was assigned to me for treatment. She did not have to tell me this is incurable and I am ineligible for a second transplant due to my age and pulmonary condition. If left untreated, the prognosis was four to six months. With treatment, three years of life is "rare." I flashed on the three years. It was the same prognosis for MDS if left untreated.

I started azacitidine chemotherapy right away. A biopsy in late August showed a meager drop in blast count to 38 percent. I started a daily dose of Venetoclax in August with no breaks through December. A biopsy on December 7, 2020 showed a blast count of less than five percent. Life is happening.

Gratitude brings comfort. I am grateful for my sister's words following the MDS diagnosis. They taught me to go beyond the entitled sense of self. I am grateful to her and Wesley. Though they don't live nearby, I have felt their constant presence which has reminded me that life is precious.

It's a cliché to say "there are no words to say thank you" to Shellye. The depth of gratitude really is beyond words. Just her presence mitigates the fear and vulnerability this cancer patient feels.

After twelve cycles of chemotherapy, my counts have been slow to rebound after treatment. I was told it is normal for my body to tire. A biopsy on July 1, 2021 revealed an AML comeback at a blast count of 15 percent. Life still happens.

AML, for me, means a lost hope for longevity and good health. Having no hope is not a bad thing because it also means no fear of illness. The duality between hope and fear disappears. With this loss comes the freedom to appreciate what life brings.

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MEMORY WALL

We are offering an opportunity to memorialize your loved one (at no cost) on the MDS Foundation website.

If this is something you may wish to consider, please visit our Memory Wall.

www.mds-foundation.org/memory-wall

Do you or someone you know have newly diagnosed Higher-Risk Myelodysplastic Syndrome (MDS)?

verona

Consider enrolling in the VERONA study—a clinical research study evaluating venetoclax in combination with azacitidine, versus azacitidine alone. The study is evaluating the effect of these treatments on Higher-Risk Myelodysplastic Syndrome (MDS).

Participants must meet the following criteria:

- 18 years of age or older
- Newly diagnosed with Intermediate, High-Risk or Very High-Risk (Higher-Risk) MDS
- Have not received prior treatment for MDS
- Are ineligible for a stem cell transplant OR are eligible for a stem cell transplant, but have not yet identified a donor or arranged for the transplant

If you meet these criteria and are interested in participating, please contact your doctor to discuss the VERONA study and your eligibility.

For more information, visit ClinicalTrials.gov and search NCT04401748.

Venetoclax is an investigational drug that is not approved by the FDA or other global health authorities in MDS. Safety and efficacy have not been established in MDS.

SYROS

An expression makes a world of difference

To all the patients participating in clinical trials and those who support them, we thank you.

We are committed to improving the lives of people with MDS and AML by developing medicines that control the expression of disease-driving genes. To learn more about SELECT-MDS, our Phase 3 clinical trial in higher-risk MDS, visit ClinicalTrials.gov and search NCT04797780.

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Looking back on our #MonthToMove

Throughout the month of June, Silence Therapeutics took the opportunity to 'move the needle' on public awareness of MDS, while moving its feet to raise funds for patients worldwide. For every kilometer collectively covered by our activities, we raised £1 for our patient group partners in MDS and our other focus disease areas.

Inspired by the MDS Foundation Awareness Walks, we relished the opportunity to dance, walk and move our way through June. The team covered a collective distance of 8,677 kilometers and raised additional sponsorship via a JustGiving page. Our efforts resulted in a donation raised of approximately £1,300 or $1,800 for each of our seven patient group partners.

We want to thank the MDS Foundation for everything it does to improve the lives of people and families affected by MDS. We hope that we can continue to spread the word through more activities like this and our participation in the MDS Foundation Global Walk in October.

#MonthToMove

SILENCE THERAPEUTICS

Silence Therapeutics is a leader in the discovery, development and delivery of novel short interfering ribonucleic acid (siRNA) therapeutics for the treatment of diseases with significant unmet medical need. Learn more at **www.silence-therapeutics.com**

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