Volume 26 Issue 2

FALL/WINTER 2020

mds news
newsletter of the myelodysplastic syndromes foundation

26th Anniversary

MDS NEWS HIGHLIGHTS

FROM THE GUEST EDITOR'S DESK

- **UPDATES IN CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML): EVALUATION, CLASSIFICATION AND TREATMENT**

Presented by: *Eric Padron, MD*
Associate Member, Malignant Hematology, H. Lee Moffitt Cancer Center
Tampa, Florida

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GUEST EDITORIAL

UPDATES IN CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML): EVALUATION, CLASSIFICATION AND TREATMENT

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Since its initial description by Smith and Colleges in 1937 and its classification by the French American British group (FAB) in 1976, CMML has evolved from anecdote, to subtype of myelodysplasia, to bona fide disease entity recognized by the World Health Organization (WHO).[1-5] This evolution has resulted in a wide range of classification strategies and prognostic tools. Some of these classifications include the FAB system that bifurcates CMML into a dysplastic subtype (MDS-CMML) and a proliferative subtype (MPN-CMML) based on total leukocyte count as well as the WHO classification system that now trifurcates CMML into CMML-0, CMML-1, and CMML-2 based on bone marrow and peripheral blood myeloblast and promonocyte percentage.[2-5] There exist at least 10 prognostication systems that each incorporate a unique subset of clinical, cytogenetic, and/or genetic variables that have been demonstrated to have comparable, but modest, prognostic capacity.[6-15]

The incidence of CMML is estimated to be 0.4 per 100,000 which constitutes approximately 30,000 new diagnoses per year worldwide.[16] The rarity of CMML, its aforementioned historically abstruse classification, and the recent advances in management of this disease have made the clinical evaluation, classification, and treatment challenging for both patients, their physicians, and pharmaceutical industry partners. When evaluating a CMML patient in consultation I am often asked: (1) "Do I have two diseases? I was told that I have a myelodysplastic syndrome and a myeloproliferative neoplasm." or (2) "Thankfully, I was told that my disease was chronic and not acute. Does this mean that my disease is benign?" When discussing potential CMML clinical studies with pharmaceutical companies the disease is often characterized as: (1) "An ultra-rare disease with very few patients" and (2) "A disease that is difficult to identify and diagnose." In truth, several clinical and translational developments have been instrumental in fully characterizing CMML and beginning to unravel its therapeutic vulnerabilities. Below we will discuss these updates as it relates to diagnosis, prognostic classification, and treatment.

DIAGNOSING CMML

As has been the case since its initial classification by the WHO, the diagnosis of CMML requires the presence of peripheral monocytosis defined at a level of 1000 cells/dL that constitutes greater than 10 percent of the white blood cell count. Although bone marrow dysplasia is often seen during pathology review, it is not required for the diagnosis.[5] Because cytogenetic abnormalities are only identified in only 25% of cases, the diagnosis of CMML was historically delayed by the need to observe a consistent elevation in monocyte count and the exclusion of underlying reactive disorders. These challenges have all but disappeared as a result of two advances in the diagnosis of this disease. The first is the wide-spread adoption of next generation sequencing (NGS) at diagnosis. CMML is more genomically homogenous compared to MDS in that sequencing only seven genes can identify a clonal event in over 90% of CMML patients.[17] When a patient has a persistent monocytosis on multiple readings and the presence of a somatic mutation by NGS is identified, the diagnosis of CMML should be highly suspected. The second advance has been the observation that the monocytosis in CMML is restricted to classical monocytes. Classical monocytes are inflammatory monocytes characterized by the presence of CD14 and absence of CD16.[18] The presence of classical monocytes at diagnosis has been reported to be highly specific for the diagnosis of CMML.[19] With these two molecular tests, a conventional bone marrow aspirate and biopsy, and g-banding cytogenetics, the diagnosis of CMML has gone from challenging and prolonged to relatively straightforward. Of course, care should be taken to ensure that blasts and promonocytes are below 20% in the bone marrow as this would define acute monocytic leukemia. Additionally, the common association with CMML and other hematologic malignancies such as systemic mastocytosis, multiple myeloma, and chronic lymphocytic leukemia, should prompt additional diagnostic tests that may be warranted in some CMML patients.

These recently identified molecular diagnostic hallmarks of CMML have led some groups to re-evaluate the monocyte cut-off currently required for a WHO-defined diagnosis of CMML. The so-called 'oligomonocytic' subtype of CMML has been proposed and characterized by a monocyte count that constitute more than 10% of the differential but does not meet the 1000 cell cut off. Several groups have demonstrated that these patients have similar baseline clinical and genetic characteristics as WHO-defined CMML and often evolve to overt disease.[20] Whether this subclassification should be widely incorporated is unclear, but because of the emerging availability of these molecular diagnostics, the diagnosis of CMML has now become straight forward if considered in the differential diagnosis of unexplained monocytosis.

PROGNOSIS AND HOW TO USE IT IN YOUR PRACTICE

One of the most clinically challenging aspects of CMML management is prognostication. There exist several CMML specific prognostic models as well as several MDS models that incorporated subsets of CMML in their development.[8-14] Although there is no evidence that one model is superior to others, all CMML-specific models have modest predictive capacity that is enhanced with the incorporation of molecular data.[15] Which

molecular data to incorporate is still under investigation but all models agree that ASXL1 mutations appear to be the most reproducible prognostic genetic alteration in CMML. We and others have initiated an international collaboration, sponsored by the MDS Foundation, to tackle this important question. Over 20 institutions worldwide have collaborated with the goal of centrally sequencing 750 diagnostic CMML samples utilizing a 285 targeted gene panel. Once this genetic and clinical dataset is complete our goal will be to: (1) perform a comparative study of existing models in hopes of identifying a clearly superior prognostic model for CMML and (2) if no existing prognostic model is superior, we will utilize this dataset to establish and validate a novel prognostic for CMML. Therefore, at this time, we cannot recommend a specific CMML model to utilize. However, we routinely employ CMML-specific models that incorporate ASXL1 mutation such as the Mayo molecular and CPSS models in our practice.[12-14]

Ultimately, the most important question is how to utilize the prognostic information that these models provide. At present, there is no disease modifying CMML therapy and therefore treatment is generally symptom, and not risk, directed. The most widely used application for prognostic information is when considering allogeneic stem cell transplantation. The consensus among most experts is that patients with higher risk, by a CMML-specific model such as CPSS, should consider allogeneic transplant.[21] While the overall survival of CMML patients is estimated to be 32 months, there does exist a subgroup of lower risk patients that can be observed for a significant period of time.[15] This consensus is based on retrospective transplant studies and extrapolation of MDS statistical modeling that suggests that some higher risk patients undergoing this procedure may enjoy long durable remission with acceptable quality of life.[22] However, once a unified CMML model such as the R-IPSS for MDS is established, there will be a clear need for studies to definitively determine the subset of patients that will benefit from transplant.[23]

FUTURE TREATMENT OPTIONS

Because of its perceived rarity and diagnostic challenges, few CMML specific studies have been performed. In fact, only a single randomized phase 3 study has been completed which occurred over 20 years ago.[24] In the United States, the hypomethylating agents 5-azacitidine and decitabine are approved by the Food and Drug Administration (FDA) and clearly have objective response rates in CMML, their approval was based on pivotal studies that focused on Myelodysplastic Syndromes (MDS) rather than CMML.[25-28] In fact, only 12 CMML patients were included in the randomized clinical trial that led to the approval of 5-azacitidine across MDS and CMML subtypes.[29] Approval for the oral formulation of decitabine has also been granted by the FDA, in large part, due to bioequivalences studies that demonstrated similar activity to the intravenous formulation. Although these agents have demonstrated clear activity in single arm studies, there exists no prospective, randomized, evidence that establishes hypomethylating agents as disease modifying.[27]

Despite the historical paucity of studies, several ongoing studies and preclinical discoveries have led to an increase in clinical trials for CMML. For example, the second ever phase 3 clinical trial is currently ongoing testing the combination of decitabine and hydrea versus hydrea alone in myeloproliferative CMML. This is a critically important study as it may identify disease-modifying capacity for decitabine in this subgroup of patients that currently have a median survival of less than 2 years. It will also set the bar for response rates in a hydrea control arm, something that is currently unknown in the modern era. This data will enhance future proliferative CMML studies. Other clinical trials have leveraged therapeutic vulnerabilities that have been recently discovered in CMML. For example, our group has identified the GM-CSF signaling pathway as a therapeutic target in CMML.[30] This has led to two clinical trials testing ruxolitinib, a JAK1/2 inhibitor, and lenzulimab, a GM-CSF neutralizing antibody. Because JAK2 is required for GM-CSF signaling, we hypothesized that ruxolitinib may be a viable therapeutic in CMML. We have tested this in 50 patients in a phase 1 and 2 clinical study and presented the results in abstract form.[31] Although we believe that this therapy is most beneficial in patients with proliferative CMML, broad based activity was identified to include hematologic responses. A phase 1 study with lenzulimab has similarly identified modest activity, especially in RAS pathway mutated cases.[32] A second example is the recent observation that a subset of CMML patients have a bone marrow infiltration of clonal plasmacytoid dendritic cells that express CD123 at high levels.[33] This has led to an exploratory study in CMML which identified spleen responses in a subset of patients.[34] These and other studies suggest that an increase in the CMML armamentarium is on the horizon.

Our current algorithm for clinical management centers on symptom directed therapy. If our patients' predominant symptoms are proliferative in nature we prefer enrollment in our ruxolitinib clinical trial or cytoreduction with hydrea. This can often lead to dramatic improvements in quality of life that we now routinely measure utilizing the MPN symptom assessment form as recommended by the MDS/MPN International Working Group response criteria.[35] Proliferative symptoms in CMML are quite similar to that seen in classical myeloproliferative diseases to include B-symptoms, bone pain, and intractable pruritis. If patients are predominantly cytopenic we favor hypomethylating agents as single arm studies have demonstrating response rates that approach 40%.[27] If patients have both proliferative symptoms and clinically meaningful cytopenias, we favor decitabine as it is more cytoreductive in our hands. While there is some evidence that suggests that observation for some asymptomatic groups may promote disease progression and end organ damage, more evidence is needed before recommending treatment in this group. We anticipate that answers to this and other relevant questions in CMML will be further addressed in the near future.

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ACTIVITY OVERVIEW

Dr. Bejar will examine current challenges in MDS diagnosis, including the use of molecular profiling and the diagnosis of clonal cytopenia of undetermined significance (CCUS). Dr. DeZern will describe her recent experience in managing MDS in the wake of a global pandemic. Dr. Götze will explore the potential of venetoclax in the treatment of higher-risk MDS. Dr. Gill will discuss the role of CAR-T cells in myeloid malignancies, focusing on what we learned from their use in lymphoid malignancies. Finally, Dr. de Botton will illustrate current perspectives in the use of targeted therapies in MDS patients, focusing on drugs that have already been approved for treatment of AML (enasidenib, ivosidenib) or that are currently in clinical trials on MDS (APR-246).

LEARNING OBJECTIVES

- Describe molecular profiling in diagnostic and prognostic evaluation of MDS.
- Evaluate the impact of COVID-19 on management of MDS patients.
- Utilize venetoclax in higher-risk MDS patients.
- Identify the prospects of adoptive cellular immunotherapy modalities and novel transplant-related approaches in MDS.
- Describe targeted therapies in MDS.

AGENDA

7:00 – 7:05 am **Welcome – About the MDS Foundation, Inc.**
Stephen Nimer, MD (MDSF Chairman)
Miami, Florida, USA

7:05 – 7:15 am **Program Overview and Objectives**
Mario Cazzola, MD, *Pavia, Italy*

7:15 – 7:45 am **Challenges in MDS Diagnosis**
Rafael Bejar, MD, PhD
San Diego, California, USA

7:45 – 8:15 am **Managing MDS in the Wake of a Global Pandemic**
Amy DeZern, MD
Baltimore, Maryland, USA

8:15 – 8:45 am **Venetoclax in Higher-Risk MDS/AML**
Katharina S. Götze, MD
Munich, Germany

8:45 – 9:15 am **Role of CAR-T Cells in Myeloid Malignancies: Lessons Learned from Lymphoid Malignancies**
Saar Gill, MD, PhD
Philadelphia, Pennsylvania, USA

9:15 – 9:45 am **Targeted Therapies (enasidenib, ivosidenib, APR-246)**
Stéphane de Botton, MD, PhD
Villejuif Cedex, France

9:45 – 10:00 am **Conclusions & Perspectives**
Jane Churpek, MD
Madison, Wisconsin, USA

SAVE THE DATE AND VISIT THE MDS FOUNDATION VIRTUAL BOOTH DECEMBER 5-8, 2020.

PERSONAL HIGHLIGHTS FROM OUR RECENT 2ND REGIONAL SYMPOSIUM ON MDS HELD IN TEL AVIV, ISRAEL

DR. MOSHE MITTELMAN
Professor of Medicine and Hematology
Past Chairman, Dept. of Medicine
Tel Aviv Sourasky Medical Center
President,
Israel Society of Hematology

The second regional MDS symposium took part in Tel Aviv on March 5-6, 2020, in the Dan-Panorama hotel, on the beach. This initiative was a joint project organized by The MDS Foundation, Inc. (Mrs. Tracey Iraca, Ms. Lea Harrison), The Israel Society of Hematology and Transfusion Medicine, The Israel MDS Working Group (led by Dr. Drorit Merkel, also the co-chairman) and the Kenes Company (Mr. Perry Gil-Ran).

The COVID pandemic that reached Europe and the US in February significantly affected the preparations. We could not predict the events in the coming days, nor whether or not people, both attendees and faculty, would be able to attend. Somehow, we completed the preparations, and most speakers arrived, while others provided their talk by video.

Despite the corona pandemic, this happened to be a summit of world renowned experts. About 200 participants, local and several dozens of guests from many countries around the globe, attended the meeting. The scientific program combined educational sessions, updated and cutting-edge information from leading experts, and several stimulating discussions on real-world patients and the problems they presented.

According to the tradition, the MDS Foundation (Mrs. Audrey Hassan), together with the MDS Israel Alliance (Mrs. Iris Yahal), organized a separate session devoted to patients and families. Invited lectures on the disease were followed by open discussions on practical problems that patients and families face in daily life. More than 100 people attended that session and provided excellent feedback.

The scientific program covered the genetics, epidemiology, pathogenesis, and other biological aspects of the disease, while most of the second day focused on treatment strategies. Sessions of patient discussion were in between. Many of the presentations are available to view on the MDS Foundation website.

Dr. Stephen Nimer, Chair of the MDS Foundation, opened the meeting with greetings. He then described the activities of the foundation. I provided a short review of the history of myelodysplastic syndromes (MDS), going over the stages with development of the concept of the disease, the classifications and terminology.

Dr. Rafael Bejar from San Diego, CA reviewed the rapidly evolving field of molecular genetics in MDS, in which he is one of the pioneers. He described MDS as a clonal disease but explained why today clonality only is not enough to understand the disease biology. By giving credits to T. Haferlach, B. Ebert, E.Papaemmanuil, D.Steensma and others, in addition to his own work, Rafael summarized the long list of somatic mutations associated with MDS: TET2, SF3B1, ASXL1, SRSF2, DNMT3A, RUNX1, U2AF1, ZRSR2, STAG2, TP53, EZH2, CBL and others. The mutations can be classified according to the genetic function: Tyrosine kinase pathway, transcription factors, epigenetics, splicing factors, and others. None of these genetic signatures is MDS-specific, but some are more typical than in other myeloid disorders. Finally, Dr. Bejar described the recent reports on gene-gene interaction, correlating mutations with certain clinical phenotypes, and the international project IWG-PM correlating genetics with MDS prognosis and risk stratification. Dr. David Steensma from Boston, MA, went into details, describing the recently recognized biological discovery, age-related clonal hematopoiesis (ARCH), detected in "healthy" individuals, making the story more complex, as the boundaries between disease and normal state are not that clear.

Dr. Alan List from Tampa, FL has investigated MDS pathogenesis, focusing on the recently recognized inflammasome. In a very elegant lecture, he described the relations between inflammatory processes and MDS pathogenesis. He explained the role of the innate immunity, myeloid-derived suppressor cells, and S100A8/9-TLR signaling in the pathogenesis of MDS. He also described the pyroptosis process, a caspase-1 dependent inflammatory cell death. Some of the proteins involved can serve as therapeutic targets, and Alan provided several candidates and examples.

Dr. Drorit Merkel, one of the local experts, provided some insights into the etiology and epidemiology of MDS with some recent information. Dr. Inga Mandac Rogulj from Croatia presented her group's interesting approach using peripheral blood micro-RNA in the diagnosis, and predicting response to treatment. Micro-RNA 21, for instance, can help in the diagnosis of the disease. Dr.

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https://www.mds-foundation.org/professional-learning-center/#2ndregionalsymposium

Howard Oster from Tel Aviv presented a novel non-invasive diagnostic model. Together with the European MDS group, he and Dr. Mittelman compared data from 502 MDS patients to 502 controls. Using machine learning, with the assistance of the York team (Drs. Alex Smith and Simon Crouch), they developed a simple model and a web application. Introducing 10 simple clinical and lab parameters in the app, it enables inclusion or exclusion of an MDS diagnosis, skipping a bone marrow examination, with high accuracy. Dr. Yishai Ofran from Haifa talked about acute myeloid leukemia following MDS, focusing on the biological process.

Dr. Theo deWitte from the Netherlands, the founder of the European MDS group more than a decade ago, shared with the audience some lessons from the excellent pan-European LR-MDS registration. This real-world project started in 2008 and includes today about 3000 MDS registered patients from 18 countries. A double-digit number of first line journal papers have been published and several dozens of abstracts have been presented in international meetings, based on the data and conclusions from the registry. Among the interesting pieces of information, Theo described the role of erythroid stimulating agents (ESAs) in delaying the need for transfusions, with a tendency towards longer survival in treated patients; the documentation of impaired quality of life in MDS; the impact of RBC transfusion density on the course and prognosis of the disease; and some insights into iron chelating in MDS. The project is ongoing, with several ongoing substudies, for which we look forward.

Dr. Akiko Shimamura, from Boston MA, in an excellent review citing her and others findings, reminded that in some cases of MDS genetic predisposition is a key player. Moreover, such families and patients can open new horizons on the way to better understand the complicated biology of the disease.

Dr. Argiris Symeonidis, from Greece, talked about a relatively neglected topic so far, despite its importance — the impact of comorbidities in MDS. He provided some clues, in addition to the already known and studied

disease-related parameters, and how to incorporate patient-related factors into clinical practice. Argiris also summarized the role of infections on the course of MDS.

Dr. Peter Greenberg, from Stanford, CA, the leader of MDS prognostic classifications lectured by video. He described so nicely the considerations and the major points of both IPSS and IPSS-R, including some recent information that may lead to future modifications.

In the treatment session for low-risk MDS, Dr. Rena Buckstein from Canada, reviewed her experience as well as the currently available literature dealing with supportive treatment in lower-risk MDS, especially RBC and platelet transfusions. She also provided some recommendations on how to optimize the therapeutic approach. Prof. Uwe Platzbecker from Germany was asked to cover the treatment of anemia in Lower-risk MDS. In an excellent video talk, he reviewed the information on erythroid stimulating agents (ESAs), the new aranesp trial(s), and the recently published MEDALIST trial with encouraging data on the new activin (TGF-beta)-agent luspatercept. He also touched on the novel studied agents, such as roxadustat, imetelstsat and others. Uwe concluded his talk by describing the status of treatment of thrombocytopenia, with the current information on the two available agents, romiplostim and eltrombopag, and the associated delays in the development programs. Prof. Valeria Santini from Florence, Italy, another MDS pioneer, talked about additional therapeutic options in LR-MDS, especially lenalidomide (revlimid), in patients with del(5q), and patients with non-del(5q). Valeria was the leading author in the MDS-005 lenalidomide trial.

In the session of treatment for higher-risk MDS, Prof. Pierre Fenaux from Paris, France, the founder and leader of the very active GFM group, by video, elegantly described the role of hypomethylating agents (HMAs), in MDS, especially in the higher-risk groups. Pierre, the leading author in the pivotal AZA-001 trial, which made azacitidine the first line standard agent for HR-MDS, reviewed old and new data, focusing on practical aspects of both available HMAs, as well as potential solutions for the problems raised over a decade of use. Dr. Mikkael Sekeres from Cleveland Clinic, OH continued with the treatment of HR-MDS, describing HMA-based combinations with potential "pick the winner" agents. Summarizing his group's data, studies that he led and others, Mikkael gave some clues for possible future combination therapies. Dr. Lewis Silverman from Mt Sinai, NY gave a fantastic transatlantic review on the new agents that are currently studied. He provided data on novel agents, including Rigosertib (recently presented by his group at ASH), pevonedistat, glasdegib, venetoclax and others. Dr. Guillermo Garcia-Manero from Houston, TX completed that session by providing some encouraging "hot" data on current clinical trials, phase 1 and 2, conducted in his center, MD Anderson Cancer Center.

Prof. Theo de Witte reminded us that in 2020, stem cell transplant is still the only curative approach, although with a high price. Theo, one of the leaders in the field, reviewed the current open questions and provided data with possible answers. We can find his summary as a review with practical recommendations of the European group in *Blood* (2017).

Dr. Stephen Nimer from Miami, FL gave a stimulating talk, with a combination of currently available data, accumulating information, and potential future studies, especially from the genetic field, and how all can be introduced in tailoring an individualized therapeutic approach on the way to precision medicine.

During the 2-day conference, we had two high-level company-sponsored satellite symposia. In a Novartis-sponsored satellite symposium, Prof. Emanuelle Angelucci from Italy (by video) nicely covered the topic of iron chelation. After describing the role of iron toxicity, he focused on the recently published TELESTO trial, probably the only prospective randomized trial testing the effect of iron chelation. The iron chelation study indeed showed clinical benefit and prolonged event-free-survival. Prof. Uwe Platzbecker from Germany discussed potential targets for future treatments in MDS. The Bristol-Myers Squibb (Celgene)-sponsored symposium was devoted for erythropoiesis and treatment of anemia. I reviewed the process of normal bone marrow erythroid production, dyserythropoiesis in stem cell disorders, and finally our experience and data with ESAs. Prof. Valeria Santini from Italy superbly reviewed the TGF-beta pathway and described the MEDALIST luspatercept trial, in which she served as one of the leading investigators and was recently published in the NEJM.

In summary, we enjoyed two days of social and cultural events, together with an excellent scientific conference. Let's hope that soon we can reorganize such meetings again.

Note: The symposium became possible with the generous unrestricted assistance of several pharmaceutical companies to whom we are very grateful (Abbvie, Neopharm Israel, Novartis, Bristol-Myers Squibb, FibroGen, Acceleron, Gamida Cell, Takeda, Astex, and Onconova Therapeutics).

ADVANCING RESEARCH & PATIENT CARE
THE 16TH INTERNATIONAL CONGRESS ON
MYELODYSPLASTIC SYNDROMES
2021
23-26 SEPTEMBER
TORONTO, CANADA

WE LOOK FORWARD TO OUR 16TH INTERNATIONAL CONGRESS ON MDS IN TORONTO NEXT YEAR!

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

IWG-PM/MOLECULAR PROJECT

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

Data analysis of this study segregated patients into two TP53 states: a mono-allelic state where one wild type allele remained (33% of TP53 mutated patients, n=126); and a multi-hit state where TP53 was altered multiple times by either mutations, deletions or cnLOH (67% of TP53 mutated patients, n=254). The findings demonstrated that TP53 allelic state was associated with clinical presentation and outcomes. Mono-allelic TP53 mutation patients presented with more favorable disease than multi-hit TP53 mutated patients. These findings indicated that TP53 status is a critical candidate for incorporation into molecularly informed risk stratification schemas (molecular IPSS-R). Thus, TP53 mutation state is important for MDS risk estimation, disease monitoring and future correlative research.

IWG-PM
INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

The IWG-PM/Molecular group project is ongoing with active plans for further development of a global classification and prognostic schema for MDS (IPSS-R/Molecular). This issue was discussed at the MDS Foundation Symposium at ASH 2019.[2]

SF3B1 MUTATED MDS AS A DISTINCT DISEASE SUBTYPE PROJECT

A large body of evidence indicates that in MDS, the SF3B1 mutation is closely associated with ring sideroblasts and ineffective erythropoiesis and is characterized by less aggressive clinical course. The available evidence supports recognition of SF3B1-mutant MDS as a distinct nosologic entity. To further validate this, Dr Malcovati and colleagues interrogated the dataset of the IWG-PM. Based on these findings, the following diagnostic criteria for the MDS with mutated SF3B1 was proposed as a distinct MDS subtype: (i) cytopenia defined by standard hematologic values; (ii) somatic SF3B1 mutation; (iii) isolated erythroid or multilineage dysplasia; (iv) the presence of any ring sideroblasts; (v) bone marrow blasts <5% and peripheral blood blasts <1%.[3]

IWG-PM: THERAPY-RELATED MDS PROJECT

In the current WHO classification, therapy-related Myelodysplastic Syndromes (t-MDS) are placed together with therapy-related Acute Myeloid Leukemia (t-AML) and Myeloproliferative Neoplasms (t-MPN) into one subgroup (t-MN) independent of morphological or prognostic features. Drs Kuendgen, Nomdedue, Tuechler and colleagues have assembled a database including 2087 t-MDS patients from different international MDS groups to evaluate current classification and prognostic tools.[4,5] They analyzed and compared 1245 t-MDS patients to 4593 primary MDS (p-MDS) patients represented in the IWG-PM database. These data demonstrated that the IPSS-R and WPSS-R separated t-MDS patients into differing risk groups effectively and indicated that all established prognostic risk factors for p-MDS maintained relevance for t-MDS, with cytogenetic features having enhanced predictive power. Poorer clinical outcomes occurred in each t-MDS compared to those from p-MDS subgroups. Despite t-MDS being considered as having a uniformly poor prognosis these data demonstrated differing outcomes for each t-MDS subgroup. Given these data, these findings suggest the ability and need for classifying t-MDS as a separate entity and distinct from the other WHO classified t-myeloid neoplasms (t-MNs). Application of this terminology would enable more reasonable treatment decisions and facilitate the inclusion of t-MDS patients into clinical studies.

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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 PROGNOSTIC SCORING

THE MDS/MPN INTERNATIONAL WORKING GROUP

MICHAEL SAVONA
Vanderbilt University Medical Center
Nashville, Tennessee

The first investigator driven, multi-national MDS/MPN-specific trial in the world is led by the MDS/MPN IWG and is set to commence! ***ABNL MARRO*** – **A B**asket Trial of **N**ove**L** therapy combinations in untreated **M**DS/MPN **A**nd **R**elapsed/**R**efractory **O**verlap Syndromes (***ABNL-MARRO***) – is an international study designed to quickly test new compounds and combinations of therapy at referral centers within the MDS/MPN IWG which see MDS/MPN patients, study the biology and pathophysiology of the diseases, and have multilateral expertise in this area.

ABNL MARRO-001 is the first MDS/ MPN IWG study and has been approved by the FDA awaiting enrollment by end of the year in the US, and then in EU countries shortly after. ABNL MARRO-001 uses an oral DNA methyltransferase inhibitor (DNMTi), ASTX727, as a backbone with combination therapy targeting JAK1. The JAK1/DNMTi combination has been evaluated in phase 1 safety studies, and will form the first arm in ABNL MARRO-001. With ABNL MARRO-001, the MDS/MPN IWG aims to validate the proposed criteria for response in MDS/MPN, test QOL tools in patients with MDS/MPN, develop new biomarkers for response to therapy, and augment efforts of large scale prospective genotyping efforts in MDS/MPN. This infrastructure will allow for ABNL-MARRO-002, -003, and so on, to quickly offer new therapies to patients with MDS/MPN. New proposals are currently under review.

MDS/MPN INTERNATIONAL WORKING GROUP

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PRESS RELEASE

LARGE INTERNATIONAL STUDY PINPOINTS IMPACT OF TP53 MUTATIONS ON BLOOD CANCER SEVERITY

YARDVILLE, NJ, AUGUST 25, 2020 (Newswire.com) — The MDS Foundation announces that a large international study led by researchers at Memorial Sloan Kettering finds that having two mutated copies of the TP53 gene, as opposed to a single mutated copy, is associated with worse outcomes in myelodysplastic syndrome and acute myeloid leukemia. The findings have immediate clinical relevance for risk assessment and treatment of people with myelodysplastic syndrome.

Considered the "guardian of the genome," TP53 is the most commonly mutated gene in cancer. TP53's normal function is to detect DNA damage and prevent cells from passing this damage on to daughter cells. When TP53 is mutated, the protein made from this gene (called p53) can no longer perform this protective function, which can result in cancer. Across many cancer types, mutations in TP53 are associated with much worse outcomes, like disease recurrence and shorter survival.

As with all genes, there are two copies of TP53 in our cells. One copy we get from our mothers, the other we get from our fathers. Until now, it was unclear whether a mutation in one copy of TP53 TP53 was enough to cause worse outcomes, or if mutations in both copies were necessary. A new study led by researchers at Memorial Sloan Kettering definitively answers this question for a blood cancer called myelodysplastic syndrome (MDS), a precursor to acute myeloid leukemia.

"Our study is the first to assess the impact of having one versus two dysfunctional copies of TP53 on cancer outcomes," says molecular geneticist Dr. Elli Papaemmanuil, a member of the Epidemiology and Biostatistics Department at MSK and the lead scientist on the study, whose results were published August 3 in the journal Nature Medicine. "From our results, it's clear that you need to lose function of both copies to see evidence of genome instability and a high-risk clinical phenotype in MDS."

"The consequences for cancer diagnosis and treatment are immediate and profound," she says.

A LARGE, MULTICENTER STUDY

The study analyzed genetic and clinical data from 4,444 patients with MDS who were being treated at hospitals all over the world. Researchers from 25 centers in 12 countries were involved in the study, which was conducted under the aegis in collaboration with investigators in the International Working Group for Prognosis in MDS (IWG-PM) whose goal is to develop new international guidelines for the treatment of this disease. Findings were independently validated using data from the Japanese MDS working group led by Dr. Seishi Ogawa's group at Kyoto University.

"Currently, the existing guidelines do not consider genomic data, like TP53 and other acquired mutations, when assessing a person's prognosis or determining appropriate treatment for this disease," says Dr. Peter Greenberg, Director of Stanford University's MDS Center, Chair of the National Comprehensive Cancer Network Practice Guidelines Panel for MDS, and a participant in the study. "Studies are ongoing reflecting this need for change."

Tracey Iraca, MDS Foundation Executive Director stated, "This study is important in updating the IPSS-R to include molecule information in light of the more personalized treatments now being explored for MDS patients."

Using new computational methods and the database and collaborative input of the IWG-PM, the investigators found that about one-third of MDS patients had only one mutated copy of TP53. These patients had similar outcomes as patients who did not have a TP53 mutation — that is, good response to treatment, low rates of disease progression, and better survival. Two-thirds of patients, on the other hand, had two mutated copies of TP53. These patients had much worse outcomes — including treatment-resistant disease, rapid disease progression, and low overall survival. In fact, the researchers found that TP53 mutation status — either 0/1 or 2 mutated copies of the gene — was the most important variable when predicting outcomes.

"Our findings are of immediate clinical relevance to MDS patients," Dr. Papaemmanuil says. "Going forward, all MDS patients should have their TP53 status assessed at diagnosis." – Dr. Elli Papaemmanuil Molecular Geneticist, Memorial Sloan Kettering

"Our findings are of immediate clinical relevance to MDS patients," Dr. Papaemmanuil says. "Going forward, all MDS patients should have their TP53 status assessed at diagnosis."

As for why it takes two "hits" to TP53 to see an effect on cancer outcomes, Dr. Elsa Bernard, a postdoctoral scientist in the Papaemmanuil lab and the study's first author, speculates that having one normal copy is enough to provide adequate protection against DNA damage. This would explain why having only one mutated copy was not associated with genome instability or any worse survival over having two normal copies.

Given the frequency of TP53 mutations in cancer, these results argue for examining the impact of one versus two mutations in other cancers as well. They also reveal the need for clinical trials designed specifically with these molecular differences in mind.

"With the increasing adoption of molecular profiling at the time of cancer diagnosis, we need large evidence-based studies to inform how to translate these molecular findings into optimal treatment strategies," Dr. Papaemmanuil says.

PARTICIPATING MDS FOUNDATION CENTERS OF EXCELLENCE:

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FUNDING:

This study was supported in part by the Celgene Corporation, the MDS Foundation, Inc., Bloodwise, Austrian Science Fund, Italian MIUR-PRIN grants, Associazione Italiana per la Ricerca sul Cancro, 5×1000 project, the Francois Wallace Monahan Fellowship, the Josie Robertson Foundation, the European Hematology Association, American Society of Hematology, Gabrielle's Angels Foundation, V Foundation, Damon Runyon-Rachleff, the Geoffrey Beene Foundation, the Japan Agency for Medical Research and Development, Japan Society for the Promotion of Science, and the Japanese Ministry of Education, Culture, Sports, Science and Technology. Dr. Papaemmanuil is a Josie Robertson-funded investigator at MSK. Drs. Papaemmanuil and Bernard have received research funding from Celgene.

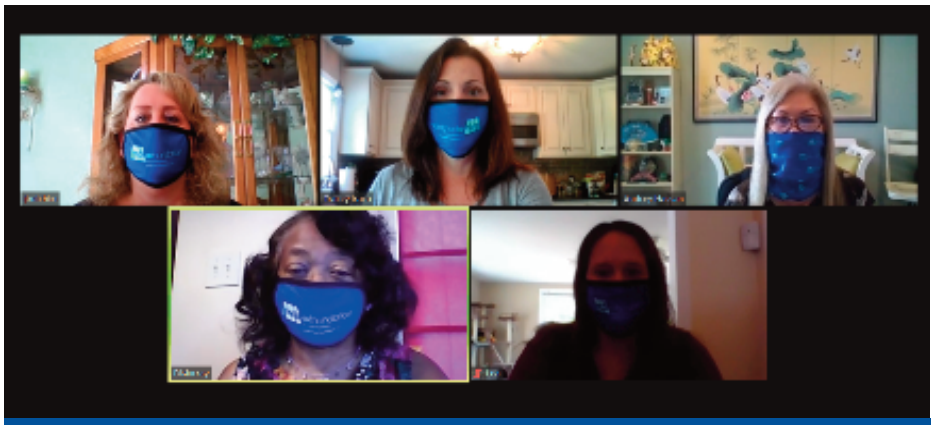
THE MDS FOUNDATION ALL **MASKED UP** AND WORKING HARD FOR YOU!

During these unprecedented times, while the MDS Foundation office remains closed, we have remained fully operational remotely from home. We know the spread of the coronavirus has created a very stressful environment for all of us, and especially for those living with MDS. During these difficult days, we want to assure you that we are active and working hard to help our MDS patients, their families, and the entire MDS community.

As we all strive together to weather the COVID-19 outbreak, the MDSF will continue to give you the latest news and tools keeping you connected.

The spread of the coronavirus has created a very stressful environment for all, and especially for those living with MDS.

Keeping yourself and others safe during the pandemic is especially important for those who already have compromised immune systems. The Centers for Disease Control and Prevention (CDC) says the virus is thought to be spread mainly from person to person between people who are in close contact with each other. Respiratory droplets from a person with COVID-19 can be spread through coughing, sneezing or talking. When out in public, people are encouraged to wear face masks or cloth masks.



IN THE FACE OF A CRISIS LIKE THIS, YOU CAN COUNT ON US!

DO YOU NEED A MASK OR BUFF?

Contact Dee via email at:
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WE ALL HAVE UNIQUE RELATIONSHIPS WITH MDS, BUT NO MATTER THE CIRCUMSTANCES OR STIPULATIONS, WE WILL ALWAYS BE HERE FOR YOU.

MDS AWARENESS

MDS AWARENESS WALK – A VIRTUAL EVENT WITH A PURPOSE

mds foundation
the myelodysplastic syndromes foundation, inc.

A HEARTFELT THANKS TO ALL OF OUR WALKERS, VOLUNTEERS AND SPONSORS FOR MAKING OUR WALKS A HUGE SUCCESS!

Dear Friends of the MDS Foundation,

The highest priority of the MDS Foundation, at this time, and always, is the health and safety of our community. With this in mind, we hosted five virtual MDS Awareness Walks in New York City, Chicago, Nashville, Boston, and Global. Although we couldn't come together as a community in person, that didn't mean we couldn't make a difference individually. It was so exciting to safely have our run/walks by going virtual!

Although great strides have been made, more work needs to be done in MDS and to better understand the needs of patients. Inspired by those impacted by MDS, our hope with our first-ever virtual run/walks is to start a movement with helping to further spread awareness and bring attention to this disease among the general public as well as the healthcare professional community.

Our mission was to:

- Elevate the conversation globally on the unmet needs of those living with MDS.
- Bring together the MDS and rare disease community and create new connections.
- Reinforce our commitment, along with our partner organizations, to help improve the lives of MDS patients and those who care for them.
- Establish the need and momentum for future MDS walks globally.

A heartfelt thanks to all of our walkers, and sponsors for making our virtual walks a huge success!
We appreciate your continued support!

Best wishes during this difficult time.

Tracey Iraca, Executive Director

WE THANK OUR **WALK TO SPREAD MDS AWARENESS** SPONSORS

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THANK YOU for making our virtual MDS Awareness Walk such an important part of our Foundation's history and future.

FACT #1

12-20K

new cases of MDS are reported every year in the U.S., with an average of **33-55** people diagnosed in the U.S. every day.[3,4,5]

FACT #2

60-170K people

are estimated to live with MDS in the U.S. with an estimated **87,000** new cases each year worldwide.[6,7]

FACT #3

YOUNGER — 60 — OLDER

75% of MDS patients are **60+** years of age, and the disease also can affect **children** and **young adults**.[8,9]

FACT #4

1 OUT OF 3

MDS patients (or 30%) progress to acute myeloid leukemia (AML).[1]

FACT #5

UP TO 6 YEARS

is the average survival rate for lower risk patients (who do not receive a bone marrow transplant) and approximately **5 months** for high-risk patients.[10,11]

HIGHLIGHTS OF LATEST LITERATURE IN MDS

SUNEEL D. MUNDLE, PHD
RHEA MUNDLE

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

EPIDEMIOLOGY, DIAGNOSIS AND PROGNOSIS:

1. Siddon AJ and Hasserjian RP. How I diagnose low-grade myelodysplastic syndromes. *Am J Clin Pathol.* 2020;154(1): 5-14. (10.1093/ajcp/aqaa046)

   This expert pathologist's perspective discusses diagnostic challenge for differential diagnosis of low grade MDS from other causes of peripheral blood cytopenia by integrating cytogenetics and next generation sequencing data along with morphologic dysplasia. The review also discusses how important it is to include the emerging knowledge of clonal hematopoiesis of indeterminate potential. The review provides a diagnostic algorithm and discusses illustrative cases.

2. Winter S, et al. Integrating the "Immunome" in the stratification of myelodysplastic syndromes and future clinical trial design. *J Clin Oncol.* 2020;38(15):1723-1735. (10.1200/JCO.19.01823)

   MDS risk stratification currently does not account for patient's immune status or molecular abnormalities. The review discusses immune monitoring strategies for refinement of patient stratification to enable predicting for response to treatment in MDS. The review also provides a proposal for a multicenter study to test their hypotheses.

Clinical Management During SARS-CoV-2 Pandemic:

1. Patnaik MM, et al. Special considerations in the management of patients with myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes during the SARS-CoV-2 Pandemic. *Am J Hematol.* 2020;95(8):E203-E208.(10.1002/ajh.25853)

   This letter to editor highlights the shared risks of the MDS/MPN overlap patients with SARS-CoV-2 infection, stemming from the increased proinflammatory milieu in these patients. The letter also provides a list of cytokine signaling directed ongoing clinical trials in SAR-CoV-2 patients. In addition, the authors share a best practice of forming a special emergency response expert panel at their institute to handle COVID-19 in MDS/MPN patients.

2. Raza A, et al. Rewriting the rules for care of MDS and AML patients in the time of COVID-19. *Leuk Res Rep.*2020;13: 100201. (10.1016/j.lrr.2020.100201)

   The report discusses the major changes occurring in the medical care of MDS and AML patients in the epicenter of pandemic with increasing remote management to save the patients from overly exposure to infection risk, and the unique challenges/management of transfusion and transplant. The report also throws light on challenges faced by the research laboratories working with precious patient specimens.

3. Paul S, et al. Targeting leukemia in the time of COVID-19. *Acta Haematol.* 2020: May 11 [Online ahead of print]. (10.1159/000508199)

   The report focuses on evaluating alternatives to reduce clinic visits and hospitalizations while enabling critical systemic therapies for leukemias to continue uninterrupted and makes recommendations on how to manage leukemia amidst the SARS-CoV-2 pandemic.

4. Boyd K, Parcell B and Tauro S. Immunosuppression in hematological cancer patients with Covid-19-uncomplicated infections but delayed viral clearance? *Leuk Res.* 2020;96:106407. (10.1016/j.leukres.2020.106407)

   This report discusses leukemia cases that tested positive for COVID-19. The report discusses their immune status and kinetics of viral clearance over a period of time.

5. Willan J, et al. Assessing the impact of lockdown: fresh challenges for the care of haematology patients in the COVID-19 pandemic. *Br J Haematol.* 2020;189(6): e224-e227. (10.1111/bjh.16782)

   The report provides a quantitative estimation of a reduction in the frequencies of routine hematology-oncology diagnoses, blood transfusions and a variety of other services during a transition period and while in the lockdown phase versus the time prior to COVID-19.

TREATMENT:

RBC Transfusion and Growth Factors:

1. Vicente A, et al. Eltrombopag monotherapy can improve hematopoiesis in patients with low to intermediate risk-1 myelodysplastic syndromes. *Haematologica.* 2020; May 21 [Online ahead of print]. (10.3324/haematol.2020.249995)

   A phase 2 dose escalation study in Low/int-1 risk MDS patients assessed eltrombopag (EPAG) at 50 mg/day to a maximum of

150mg/day over 16 weeks. Eleven of twenty five patients (44%) had hematologic response; 5 had uni-lineage and 6 bi-lineage. Presence of PNH clone, marrow hypocellularity, thrombocytopenia ± other cytopenia and elevated plasma thrombopoietin predicted response. The safety profile was consistent with previous experience of EPAG. Ten patients discontinued after med time on treatment of 16 months and having a response. Four of them restarted EPAG later and had a robust second response.

2. Duong Vu H, et al. A sequential two-stage dose escalation study of eltrombopag in patients with myelodysplastic syndrome and thrombocytopenia after hypomethylating agent failure. *Leuk Lymphoma.* 2020; 61(8):1901-1907.(10.1080/10428194.2020.1751841)

   Thrombocytopenia is seen often in MDS patients and this study conducted a trial of eltrombopag in MDS and MPN or AML patients after hypomethylating agent failure. They had a mean baseline platelet count <50 x 10^9 /L. The dose was upped from 50 mg to 200 mg daily. The maximally tolerated dose was determined with 37 patients, but it was not reached. In 9 patients (24%), 2 achieved marrow CR with hematologic improvement, 1 marrow CR without HI, and 6 HI. The median overall survival for these patients was 7.5 months and eltrombopag yielded modest results for mostly high-risk MDS patients post HMA failure.

Hypomethylating Agents:

1. Yalniz FF, et al. A phase II study of addition of pracinostat to a hypomethylating agent in patients with myelodysplastic syndromes who have not responded to previous hypomethylating agent therapy. *Br J Haematol.* 2020;188(3):404-412. (https://doi.org/10.1111/bjh.16173)

   This phase II study assessed the addition of pracinostat to hypomethylating agent (HMA) in MDS patients who showed primary or secondary failure on HMA or had stable disease without a clinical response. Forty five patients receiving a median 3 cycles showed one CR and 7 marrow CR with a median overall survival of 5.7 mo in previous HMA failure or 5.6 mo in previous stable disease on HMA. Grade ≥3 adverse events were seen in 84% patients with 33% discontinuing treatment. The study concluded with the need to optimize the dose of pracinostat.

2. Cai L, et al. Role of TP53 mutations in predicting the clinical efficacy of hypomethylating therapy in patients with myelodysplastic syndrome and related neoplasms: a systematic review and meta-analysis. *Clin Exp Med.* 2020;20(3):361-371 (10.1007/s10238-020-00641-4)

   This systematic review and meta-analysis report on 22 original studies demonstrates that while MDS patients with TP53 mutations respond to hypomethylating agents well, their overall survival may still be poor regardless of their response.

Immunosuppressive Therapies:

1. Stahl M, et al. Use of immunosuppressive therapy for management of myelodysplastic syndromes: a systematic review and meta-analysis. *Haematologica.* 2020;105(1): 102-111.(10.3324/haematol.2019.219345)

   A systematic literature review identified nine prospective cohort studies and 12 clinical trials using immunosuppressive therapy, mostly anti-thymocyte globulin ± cyclosporin A. The overall response rate was 42.5% with 12.5% CR and RBC transfusion independence rate of 33.4%. The leukemic transformation rate was 8.6% per patient year. The review highlights the immunosuppressive therapy as a therapeutic option to low-risk MDS patients.

Novel Therapies:

1. Fenaux P et al. Luspatercept in patients with lower risk myelodysplastic syndrome. *N Engl J Med.* 2020;382(2):140-151. (https://doi.org/10.1056/nejmoa1908892)

   This double blind placebo controlled ph 3 study assessed luspatercept (1 mg up to 1.75 mg per Kg body weight sc every 3 weeks) vs placebo in patients with very-low, low or intermediated risk MDS patients with ringed sideroblasts and who were transfusion dependent (N=229; 2:1: luspatercept: placebo).Primary end-point was transfusion independence for ≥8 weeks in first 24 weeks of treatment which was seen in 38% on luspatercept versus 13% with placebo (p<0.001). The most common adverse events were fatigue, diarrhea, asthenia, nausea, and dizziness.

2. Stein EM et al. Enasidenib in patients with IDH2 myelodysplastic syndromes: a phase 1 subgroup analysis of the multicenter, AG221-C-001 trial. *Lancet Haematol.* 2020;7(4):e309-e319. (https://doi.org/10.1016/s2352-3026(19)30284-4)

   Seventeen previously treated patients with IDH2 mutation received a median 3 cycles of Enasidenib, an IDH2 inhibitor; 5 with ≥12 cycles (60-300 mg QD PO in 28 day cycle). After median follow up of 11mo no dose limiting toxicities were observed. The most common grade 3–4 treatment emergent adverse events were indirect hyperbilirubinaemia (35%), pneumonia (29%) and thrombocytopenia (24%), and no treatment related deaths. The overall response was seen in 9/17 (53%) patients with median duration of response of 9.2 mo and median overall survival was 16.9 mo.

3. Navada SC, et al. Rigosertib in combination with azacytidine in patients with myelodysplastic syndromes or acute myeloid leukemia: Results of a phase 1 study. *Leuk Res.* 2020;94:106369 (10.1016/j.leukres.2020.106369)

   The phase 1 part of this phase 1/2 study involved 9MDS, 1CMML and 8AML patients. An oral Ras-inhibitor, rigosertib was given twice daily at 140 mg or 280 mg or 560 mg morning + 280 mg evening doses for 3 weeks of the 4week cycle. A standard dose azacytidine was given in the second week of the cycle. No dose limiting toxicities were noted and hence no maximum tolerated dose could be determined. The most frequent adverse events were diarrhea, constipation, fatigue,

nausea, pneumonia and back pain. The majority of responses were in MDS/CMML patients (7/9) with only 2/7 responses in AML.

4. Taylor J, et al. Safety and activity of selinexor in patients with myelodysplastic syndromes or oligoblastic acute myeloid leukemia refractory to hypomethylating agents: a single-center, single arm, phase 2 trial. *Lancet Haematol.* 2020;7(8):e566-e574. (10.1016/S2352-3026(20)30209-X)

   There is no current therapy for MDS refractory to hypomethylating agents under 6 months. This study aimed safety and activity of selinexor in MDS patients or oligoblastic acute myeloid leukemia (OAML). A phase 2 trial (18 y/o or older up to 30% MDS/OAML) received a 3-week long cycle of selinexor (60mg twice/week for 2 weeks, 1 week off). From the 23 patients evaluated, overall response rate was 26% (95% CI 10–48) in 6 patients with marrow complete remission and 12 patients (52%, 95% CI 31–73) had stable disease.

5. Kubasch AS, et al. Single agent talacotuzumab demonstrates limited efficacy but considerable toxicity in elderly high-risk MDS or AML patients failing hypomethylating agents. *Leukemia.* 2020; 34(4):1182-1186. (10.1038/s41375-019-0645-z)

   SAMBA study assessing anti-CD123 therapeutic monoclonal called talacotuzumab in 19AML and 5 High-Risk MDS patients was terminated as a part of discontinuation of the drug development program by the manufacturer. 16/24 patients were resistant including 8/24 patients who relapsed after initial response to prior HMA therapy. The treatment related toxicity was significant including 2 deaths with pneumonia possibly related to treatment. The eight-week mortality was 25% and overall response rate was 8.3% including one complete remission. The benefit/risk ratio for talacotuzumab was determined to be unfavorable and hence the study was terminated.

PATIENT REPORTED OUTCOMES:

1. Stauder R, et al. Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: Literature review and landscape analysis. *Eur J Haematol.* 2020;104(5):476-487. (10.1111/ejh.13389)

   This extensive review noted that across studies in MDS and AML, the most frequently used patient reported outcome measures (PROMs) were generic like SF-36 or EQ-5D or cancer specific like EORTC QLQ-C30, and FACT-An. However, MDS specific PROMS like QUALMS or QOL-E and AML specific PROMS like FACT-Leu or EORTC QLQ-Leu were used only in a minority of studies. The review underscores the need to use MDS/AML specific PROMS in future studies.

PATHOBIOLOGY:

1. Van Zeventer IA, et al. Mutational spectrum and dynamics of clonal hematopoiesis in anemia of older individuals. *Blood.* 2020;135(14):1161-1170. (https://doi.org/10.1182/blood.2019004362)

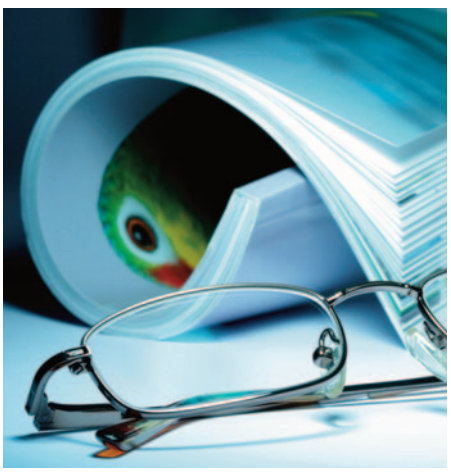
   From a population-based Lifeline cohort, a group of individuals ≥60 yr age with anemia (n=676) was selected with 1:1 matched control participants. Peripheral blood analysis at variant allele frequency (VAF) of 1% for 27 driver genes was undertaken to evaluate clonal hematopoiesis (CH). The results showed higher frequency of individuals with CH in the group with anemia versus the matched controls (46.6% vs 39.1% respectively, p<0.007). Subsequent analyses revealed waxing and waning of CH over a subsequent 44mo period regardless of anemia. Also, it was noted that while VAF <5% did not impact overall survival, that >5% showed increased risk of death.

2. Wouters HJCM, et al. Association of anemia with health-related quality of life and survival: a large population-based cohort study. *Haematologica.* 2019; 104(3): 468-476. (https://doi.org/10.3324/haematol.2018 .195552)

   The assessment of anemia and health related quality of life (HRQOL) measured by RAND-36 questionnaire in a population-based cohort demonstrated that anemia in individuals over 60 years of age has impact on their overall survival as well as HRQOL. While subjects younger that 60 years did not show similar correlation. Also, based on the impact on HRQOL and survival, the report identifies a need for considering the threshold of hemoglobin below 13g/dL in women 60 yrs or older as anemic.

3. Oh YJ, et al. Mutation of ten-eleven translocation-2 is associated with increased risk of autoimmune disease in patients with myelodysplastic syndrome. *Korean J Intern Med.* 2020;35(2):457-464. (10.3904/kjim.2018.247)

   This study explored if genetic mutations are linked with autoimmune disorders in MDS patients. Eighty-eight mutations were sequenced for 73 MDS patients (median age 70 y/o, 67.1% male). Autoimmune disorders (AID) were found in 16 (21.9%) patients and mutations were detected in 57 (78.1%) of patients. MDS patients with or without AID did not differ in percentage (68.8% vs. 80.7%) or mean number of mutations (1.8 ± 1.6 vs. 2.2 ± 1.8) with significance. Ten-eleven translocation-2 (TET2) mutation however was significantly higher in patients with AID vs without (31.3% vs. 5.3%). Thus, TET2 mutations in MDS patients may be linked to increased AID risk.



REVIEWS, PERSPECTIVES & GUIDELINES:

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

1. Garcia JS. Prospects for Venetoclax in myelodysplastic syndromes. *Hematol Oncol Clin North Am.* 2020; 34(2):441-448. (https://doi.org/10.1111/bjh.16206)
2. Hunter AM and Sallman DA. Targeting TP53 mutations in myelodysplastic syndromes. *Hematol Oncol Clin North Am.* 2020;34(2):421-440. (https://doi.org/10.1016/j.hoc.2019.11.004)
3. McCullough KB and Patnaik MM. Myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes-Advances in treatment. *Best Pract Res Clin Haematol.* 2020;33(2):101130. (https:// doi.org/10.1016/j.beha.2019.101130)
25. Hellström-Lindberg E, Tobiasson M and Greenberg P. Myelodysplastic syndromes: Moving towards personalized management. *Haematologica.* 2020;105(7): 1765-1779. (https://doi.org/10.3324/haematol.2020.248955)
26. Komrokji R. Luspatercept in myelodysplastic syndromes: Who and When? *Hematol Oncol Clin North Am.* 2020;34(2):393-400. (https://doi.org/10.1016/j.hoc.2019.10.004)
27. Park S et al., The prognostic value of serum erythropoietin in patients with lower-risk myelodysplastic syndromes: a review of the literature and expert opinion. *Ann Hematol.* 2020;9(1):7-19.(https://doi.org/10.1007/s00277-019-03799-4)
28. Bewersdorf JP and Zeidan AM. Following in the footsteps of acute myeloid leukemia: are we witnessing the start of a therapeutic revolution for higher risk myelodysplastic syndromes? *Leuk Lymphoma.* 2020;61 (10):2295-2312.(10.1080/10428194.2020.1761968)
29. Mittelman M. Balanced translocations in myelodysplastic syndromes (MDS) – an unrecognized MDS patient subgroup? *Br J Haematol.* 2020;190(2):141-142. (10.1111/bjh.16641)

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

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Our MDS Centers of Excellence are institutions that meet the highest standards for diagnosis, treatment and patient care. These centers help patients seeking first or second opinions and/or additional treatment options from experts in MDS. We currently have 76 Centers in the United States and 116 Centers in countries around the world. Our MDS Centers can be viewed here:

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Taipei, Taiwan
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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
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Manoj Raghavan, MD

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

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Bournemouth, United Kingdom
Sally Killick, MD

St. James's University Hospital St. James's Institute of Oncology
Leeds, United Kingdom
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Christopher Dalley, MD
Srinivasan Narayanan, MD

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Cardiff, Wales
Jonathan Kell, MD

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National Institute of Hematology and Blood Transfusion
Hanoi, Vietnam
Khanh Quoc Bach, MD, PhD

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

MDS treatment is individualized based on a patient's subtype and IPSS-R score. 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 infographics were designed to help you understand how your subtype and IPSS-R score are determined. This information will help facilitate discussions with your healthcare provider on what this information means for you personally.

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

KNOWLEDGE IS POWER

mds foundation
the myelodysplastic syndromes foundation, inc.

www.mds-foundation.org

ASK YOUR HEALTHCARE TEAM...

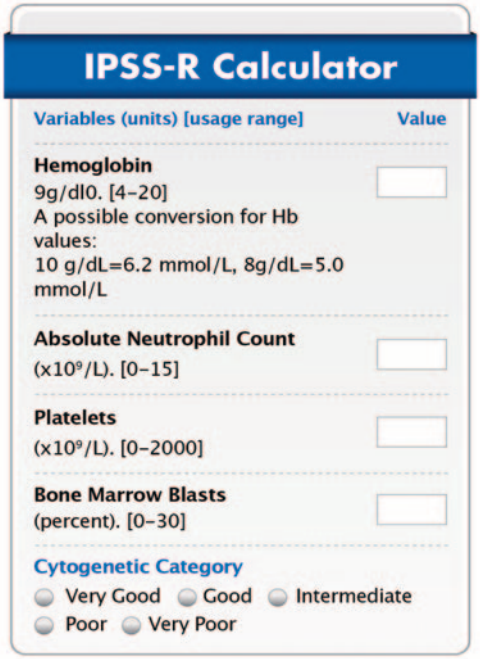
Knowing your IPSS-R score and MDS subtype can guide discussions with your healthcare team about the best treatment options for you!

KNOW YOUR SCORE

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

CATEGORIES & SCORES

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



KNOW YOUR SUBTYPE

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

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

WHO CLASSIFICATION SUBTYPES*

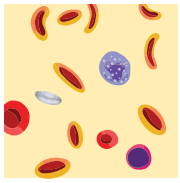
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity:
Refractory cytopenia of childhood

*The subtypes are based on the 2018 WHO Classification System. If you were classified under the 2008 WHO System (RA, RCUD, RARS, RCMD, RCMD-RS, RAEB-1, RAEB-2) your corresponding 2018 classification subtype is:

2008 Classification	2018 Classification
RA	MDS
RCUD	MDS-SLD
RARS	MDS-SLD with ring sideroblasts
RCMD	MDS-MLD
RCMD-RS	MDS-MLD with ring sideroblasts
RAEB-1	MDS-EB1
RAEB-2	MDS-EB2
5q- (5q minus) Syndrome	MDS with isolated del(5q)
Unclassified MDS	MDS-U (MDS, unclassifiable)

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

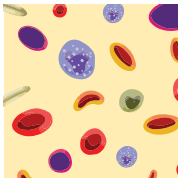
WHO MDS CLASSIFICATION SUBTYPES*



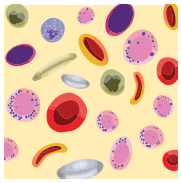
MDS WITH SINGLE LINEAGE DYSPLASIA (MDS-SLD)

Is a low number of one to two types of blood cells in the bloodstream and one type of blood cell looks abnormal (dysplasia) in the bone marrow. For the affected cell type, at least 10% of the cells look abnormal (dysplasia). Less than 5% of cells in the bone marrow are blast (immature) cells with no blasts in the bloodstream.

MDS WITH MULTILINEAGE DYSPLASIA (MDS-MLD)



Is a low number of one or more types of blood cells in the bloodstream and two or more types of blood cells look abnormal in the bone marrow. Of the affected cell types, at least 10% of the cells look abnormal. Less than 5% of cells in the bone marrow are blast cells with no blasts in the bloodstream.

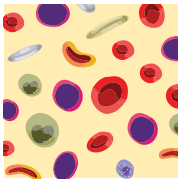


MDS WITH RING SIDEROBLASTS (MDS-RS)

Is a low number of one or more types of blood cells in the bloodstream and bone marrow. At least 15% of young red blood cells in the bone marrow show rings of iron called ring sideroblasts (or at least 5% of the cells also have a mutation in the SF3B1 gene). Less than 5% of cells in the bone marrow are blast cells. There are 2 types with:

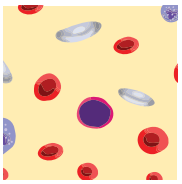
MDS-RS and Single Lineage Dysplasia (MDS-RS-SLD): same characteristics as MDS-SLD but with ring sideroblasts
MDS-RS and Multilineage Dysplasia (MDS-RS-MLD): same characteristics as MDS-MLD but with ring sideroblasts

MDS WITH EXCESS BLASTS (MDS-EB)



Is a low number of one or more types of blood cells in the bloodstream that also look abnormal in the bone marrow with an increased number of blast (immature) cells.

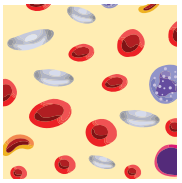
MDS-EB1: less than 5% of cells in the bloodstream are blasts. In the bone marrow, 5-9% of cells are blast cells.
MDS-EB2: 5-19% of cells in the bloodstream are blast cells and 10-19% of cells in the bone marrow are blast cells.



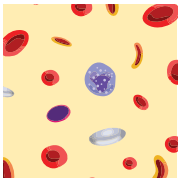
PROVISIONAL ENTITY: REFRACTORY CYTOPENIA OF CHILDHOOD (RCC)

Is characterized by persistent cytopenia with less than 5% blasts in bone marrow and less than 2% blasts in the bloodstream. It is the most common subtype of childhood MDS.

MDS WITH ISOLATED DEL(5Q)



Is identified when part of chromosome 5 is missing (deleted), this change is called del (5q). One additional chromosome abnormality is also permitted as long as it does not involve chromosome 7. There is a low number of red blood cells in the bloodstream and the number of platelets is normal or high. There is dysplasia in at least one cell type in the bone marrow and less than 5% of the cells are blast (immature) cells.



MDS UNCLASSIFIABLE (MDS-U)

Is when the features of the blood and bone marrow don't fit any of the other subtypes. One or more types of blood cells are low in the bloodstream, but less than 10% of that cell type may look abnormal in the bone marrow. Very few or no blast (immature) cells are found in the bloodstream on at least 2 occasions and less than 5% of the cells in the bone marrow are blasts. Sometimes the diagnosis is made solely based on the presence of a typical chromosome abnormality that is linked with MDS.

*The subtypes are based on the 2018 WHO Classification System. If you were classified under the 2008 WHO System (RA, RCUD, RARS, RCMD, RCMD-RS, RAEB-1, RAEB-2) your corresponding 2018 classification subtype is:

2008 Classification	2018 Classification
RA	MDS
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RAEB-2	MDS-EB2
5q- (5q minus) Syndrome	MDS with isolated del(5q)
Unclassified MDS	MDS-U (MDS, unclassifiable)

GENE MUTATION INFO TO FOLLOW

IPSS-R PROGNOSIS VALUES

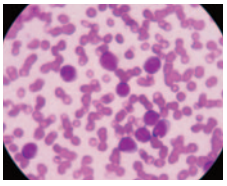
KNOWLEDGE IS POWER

The Revised International Prognostic Scoring System (IPSS-R) is used to estimate life expectancy for a patient newly diagnosed with MDS without treatment and to estimate the risk of developing acute myelogenous leukemia (AML).

A bone marrow biopsy and aspirate, cytogenetics and peripheral blood counts are used to determine your risk category (Very Low, Low, Intermediate, High, Very High).

CYTOGENETICS

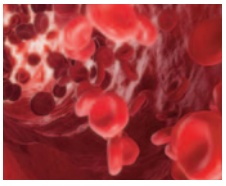
Cytogenetics is the study of the structure and function of the chromosomes. Long strings of DNA are coiled up with proteins to form the chromosomes. Cytogenetic testing is viewing chromosomes under a microscope to determine if there are any changes in the chromosomes (chromosomal abnormalities).



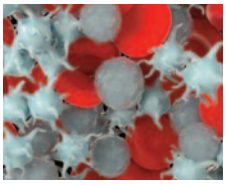
BONE MARROW BLASTS

Blasts are immature blood cells that do not function properly.

HEMOGLOBIN



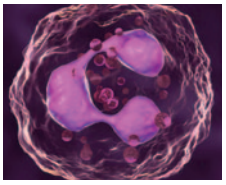
Hemoglobin (Hgb) is a large iron-containing protein in red blood cells that gives blood its red color and carries oxygen from the lungs to all body tissues.



PLATELETS

Platelets (Plts) are tiny blood cells that help your body form clots to stop bleeding.

ABSOLUTE NEUTROPHIL COUNT



Absolute Neutrophil Count (ANC) is a measure of the number of neutrophil granulocytes present in the blood. Neutrophils are a type of white blood cell that fights against infection.

WEBSITE COMING SOON!

You and MDS

An Animated Patient's Guide to Myelodysplastic Syndromes

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. You are invited to provide feedback to help direct future content as this site becomes part of your personal information resource on MDS. We welcome you to this online community resource to improve your quality of life and health outcomes.

Learn more at www.YouAndMDS.com.

COMING SOON!
SPANISH LANGUAGE
MDS PATIENT EDUCATION RESOURCE
"Guía animada para pacientes con síndromes mielodisplásicos" (*You and MDS: Animated Patient's Guide to Myelodysplastic Syndromes*)

WHY DONATE TO THE MDS FOUNDATION?

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

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

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

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

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

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

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

Rochelle Ostroff-Weinberg

SUPPORT YOUR LOVED ONE

BECOME A MEMBER

mds foundation
the myelodysplastic syndromes foundation, inc.

BECOME A MEMBER OF THE MDS FOUNDATION COMMUNITY

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
YOUR CARE

COMING TOGETHER
FOR A CURE

JOIN US TO PROMOTE
MDS AWARENESS & ADVOCACY

SUPPORT YOUR
LOVED ONES

BE A PART OF THE SOLUTION

BECOME A MEMBER

BENEFITS OF MEMBERSHIP

- 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.
- Opportunities to participate in or host support group events with your friends and community.
- Receive an MDSF Membership Packet including printed educational resources, MDSF masks and wristbands.

HOW DOES YOUR MEMBERSHIP HELP?

$35 ***Join The Community*** (includes benefits listed above)

$70 ***Share Hope***
Also includes a membership scholarship for a patient or caregiver in need.

$250 ***Change the Future of MDS***
Also includes member names listed on the MDSF website.

$500 ***Create the Path Towards a Cure***
In addition, 20% of your membership dues will be dedicated to MDS research.

Together we are a Community Resource of Hope for those LIVING with MDS.

Founded in 1994, the MDS Foundation is the only not-for-profit global organization dedicated solely to improving outcomes for patients with MDS.

Over the last 20 years, the treatment and understanding of MDS has evolved in many ways. Once referred to as pre-leukemia, MDS is now recognized worldwide as a blood cancer. Originally, there were no official treatments for MDS. Today, there are 5 approved treatment options with many more in the development phase.

OUR MISSION

The MDS Foundation, Inc. is an international non-profit advocacy organization whose mission is to support and educate patients and healthcare providers with innovative research into the fields of MDS, Acute Myeloid Leukemia (AML) and related myeloid neoplasms in order to accelerate progress leading to the diagnosis, control and cure of these diseases.

THE MDS FOUNDATION, INC.
4573 South Broad St., Suite 150, Yardville, NJ 08620
800-MDS-0839/609-298-1035
https://www.mds-foundation.org
The MDS Foundation, Inc. is a 501c3 tax exempt organization.

THINKING OF JOINING THE MDS FOUNDATION AS A PROFESSIONAL MEMBER OR CHANGE THE FUTURE OF MDS MEMBER?

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

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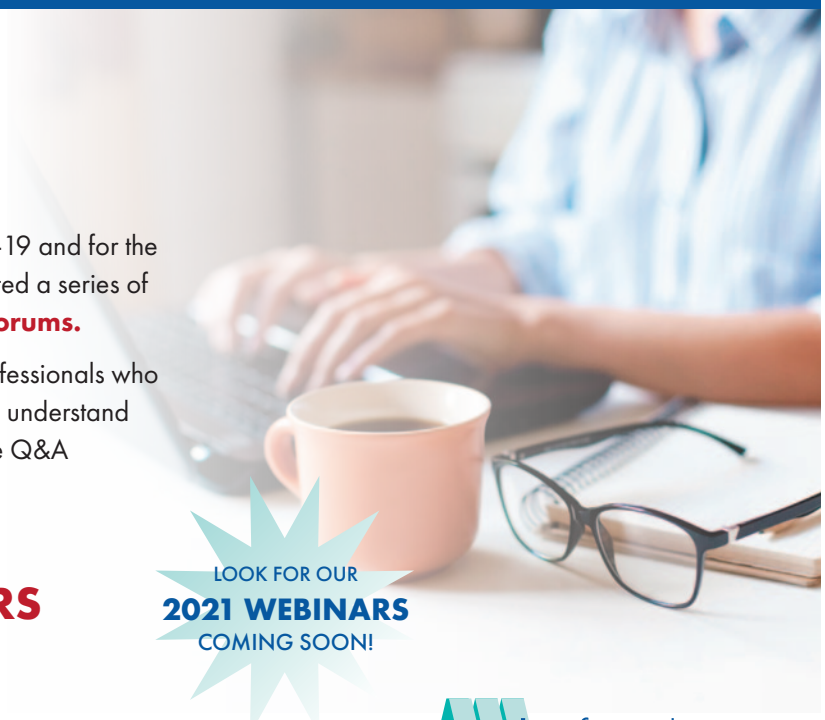
CREATE THE PATH TOWARDS A CURE MEMBERS: David Carden • Chris Holiday • Roy Rawlings

UPCOMING PATIENT WEBINARS

WE ARE VIRTUAL!

Given the growing concerns surrounding COVID-19 and for the safety of our attendees, the MDS Foundation hosted a series of webinars **in place of our in-person patient forums.**

We collaborated with renowned hematology professionals who addressed key topics and questions using easy to understand language in a 90-minute format that included live Q&A opportunities for all participants.



ON DEMAND WEBINARS

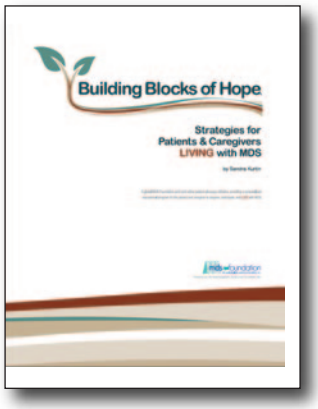
MDS WEBINARS ON DEMAND

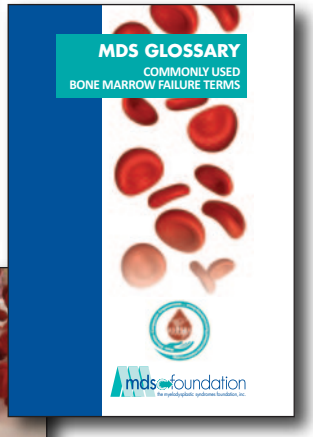
LOOK FOR OUR
2021 WEBINARS
COMING SOON!

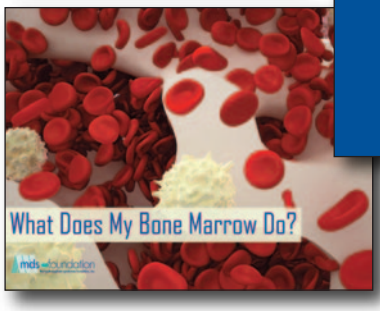
mds foundation
the myelodysplastic syndromes foundation, inc.

VIEW PREVIOUS LIVE WEBINARS AT A TIME THAT IS CONVENIENT FOR YOU!!

https://www.mds-foundation.org/upcoming-2020-webinars-for-mds-patients-caregivers







FIND THE TRUSTED RESOURCES YOU NEED...

You or someone you know has been diagnosed with MDS

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

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

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

PRESS RELEASES

APPROVAL

EUROPEAN COMMISSION APPROVES REBLOZYL (LUSPATERCEPT) FOR THE TREATMENT OF TRANSFUSION-DEPENDENT ANEMIA IN ADULT PATIENTS WITH MYELODYSPLASTIC SYNDROMES OR BETA THALASSEMIA

European Commission Approves Reblozyl (luspatercept) for the Treatment of Transfusion-Dependent Anemia in Adult Patients with Myelodysplastic Syndromes or Beta Thalassemia

Reblozyl regulates late-stage red blood cell (RBC) maturation to potentially reduce or eliminate the need for regular RBC transfusions

Reblozyl is the first and only erythroid maturation agent to be approved in the European Union, representing a new class of therapy

PRINCETON, N.J. AND CAMBRIDGE, MASS., JUNE 26, 2020 — Bristol Myers Squibb (NYSE: BMY) and Acceleron Pharma Inc. (NASDAQ: XLRN) today announced that the European Commission (EC) has approved Reblozyl (luspatercept) for the treatment of:

- Adult patients with transfusion-dependent anemia due to very low-, low- and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response or are ineligible for erythropoietin-based therapy.
- Adult patients with transfusion-dependent anemia associated with beta thalassemia.

"Dependence on blood transfusions caused by anemia in hematologic malignancies like MDS can often mean frequent and lengthy hospital visits, which can pose additional health risks and affect patients' quality of life," said Uwe Platzbecker, M.D., lead investigator of the MEDALIST study, Head of Clinic and Policlinic for Hematology and Cell Therapy, Leipzig University Hospital. "Today's approval of Reblozyl provides healthcare professionals with a new therapy that has been shown to significantly reduce the number of red blood cell transfusions needed by MDS patients and, in some cases, helped them to achieve transfusion independence."

"While beta thalassemia remains an orphan disease, the lifelong blood transfusions often needed by patients can have a significant impact on the limited blood supply in their communities, and there are few treatment alter¬¬natives," said Maria Domenica Cappellini, M.D., lead investigator of the BELIEVE study, Professor of Medicine, University of Milan, Fondazione IRCCS Ca Granda. "The European Commission's approval of Reblozyl provides eligible adult patients with beta thalassemia a new, much needed treatment option for their anemia, and with it, the possibility of becoming less dependent on red blood cell transfusions."

Reblozyl is the first and only erythroid maturation agent approved in the European Union, representing a new class of therapy for eligible patients. This approval is based on data from the pivotal Phase 3 MEDALIST and BELIEVE studies, evaluating the ability of Reblozyl to effectively address anemia associated with MDS and beta thalassemia, respectively.

"Across the EU, 25 million blood transfusions occur every year, some of which are needed by patients with anemia due to hematologic diseases like MDS and beta thalassemia," said Diane McDowell, M.D., vice president, Hematology Global Medical Affairs, Bristol Myers Squibb. "Reblozyl has the potential to address the ineffective erythropoiesis associated with MDS and beta thalassemia, decrease patients' dependence on red blood cell transfusions and impact the underlying consequences of the high burden of anemia for these patients. Alongside our partners at Acceleron, we recognize the continuing need in disease-related anemias and are committed to working collaboratively with European health authorities to make Reblozyl available to these patients as quickly as possible."

ABOUT BELIEVE

BELIEVE is a Phase 3, randomized, double-blind, placebo-controlled multi-center study comparing Reblozyl plus BSC versus placebo plus BSC in adults who require regular RBC transfusions (6-20 RBC units per 24 weeks with no transfusion-free period greater than 35 days during that period) due to beta thalassemia.

The trial showed a statistically significant improvement in RBC transfusion burden during weeks 13 to 24 compared to the baseline 12-week interval prior to randomization (21.4% Reblozyl versus 4.5% placebo), meeting the study's primary endpoint. The trial also met the secondary endpoint of transfusion burden reduction of at least 33% (with a reduction of at least two units) during weeks 37 to 48, which was achieved in a significantly greater proportion of patients receiving Reblozyl versus placebo. The trial also met an exploratory endpoint, with 70.5% of patients treated with Reblozyl achieving at least a 33% reduction in RBC transfusion burden of at least two units for any 12 consecutive weeks compared to the 12-week interval prior to treatment, compared to 29.5% of patients on placebo.

The majority of TEAEs were Grade 1-2. Discontinuation due to an adverse reaction (Grades 1-4) occurred in 5.4% of patients who received Reblozyl. The most common adverse reactions (>10%) were headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea and dizziness.

Results of the BELIEVE trial were first presented at the ASH Annual Meeting in December 2018 and selected for the Best of ASH. The New England Journal of Medicine published the BELIEVE trial results in March 2020.

ABOUT BETA THALASSEMIA

Beta thalassemia is an inherited blood disorder caused by a genetic defect in hemoglobin. The disease is associated with ineffective erythropoiesis, which results in the production of fewer and less healthy RBCs, often leading to severe anemia—a condition that can be debilitating and can lead to other complications for patients—as well as other serious health issues. Treatment options for anemia associated with beta thalassemia are limited, consisting mainly of frequent RBC transfusions that have the potential to contribute to iron overload, which can cause serious complications such as organ damage. Across the United States, Germany, France, Italy, Spain and the United Kingdom, there are approximately 17,000 patients with beta thalassemia.

ABOUT REBLOZYL®

Reblozyl (luspatercept-aamt), a first-in-class erythroid maturation agent, promotes late-stage red blood cell maturation in animal models. Bristol Myers Squibb and Acceleron are jointly developing Reblozyl as part of a global collaboration. Reblozyl is currently approved in the U.S. for the treatment of:

- anemia in adult patients with beta thalassemia who require regular red blood cell transfusions, and
- anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell 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).

Reblozyl is not indicated for use as a substitute for red blood cell transfusions in patients who require immediate correction of anemia.

ABOUT BRISTOL MYERS SQUIBB

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, Facebook and Instagram.

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol-Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

ABOUT ACCELERON

Acceleron is a biopharmaceutical company dedicated to the discovery, development, and commercialization of therapeutics to treat serious and rare diseases. Acceleron's leadership in the understanding of TGF-beta superfamily biology and protein engineering generates innovative compounds that engage the body's ability to regulate cellular growth and repair.

Acceleron focuses its commercialization, research, and development efforts in hematologic and pulmonary diseases. In hematology, Acceleron and its global collaboration partner, Bristol Myers Squibb, are co-promoting REBLOZYL® (luspatercept-aamt), the first and only approved erythroid maturation agent, in the United States for the treatment of anemia in certain blood disorders. The Companies are also developing luspatercept for the treatment of chronic anemia in patient populations of MDS, beta-thalassemia, and myelofibrosis. In pulmonary, Acceleron is developing sotatercept for the treatment of pulmonary arterial hypertension, having recently reported positive topline results of the Phase 2 PULSAR trial.

APPROVAL

ASTEX PHARMACEUTICALS, TAIHO ONCOLOGY, AND OTSUKA PHARMACEUTICAL ANNOUNCE FDA AND HEALTH CANADA APPROVAL OF INQOVI® (DECITABINE AND CEDAZURIDINE) TABLETS, ORAL HYPOMETHYLATING AGENT (HMA) THERAPY FOR INTERMEDIATE AND HIGH-RISK MDS AND CMML

NQOVI is the first orally administered hypomethylating agent approved by the FDA and Health Canada

INQOVI is a fixed-dose combination of the hypomethylating agent decitabine and the cytidine deaminase inhibitor cedazuridine, which prevents degradation of decitabine in the gastrointestinal tract and liver and enables its absorption via oral dosing

Approval is based on the ASCERTAIN phase 3 and other supporting studies that compared systemic exposure to decitabine from oral INQOVI with exposure from IV decitabine and assessed safety and efficacy of INQOVI

INQOVI delivers an option for intermediate and high-risk MDS and CMML patients to potentially reduce the number of office visits and to take their medication from the convenience and comfort of their homes

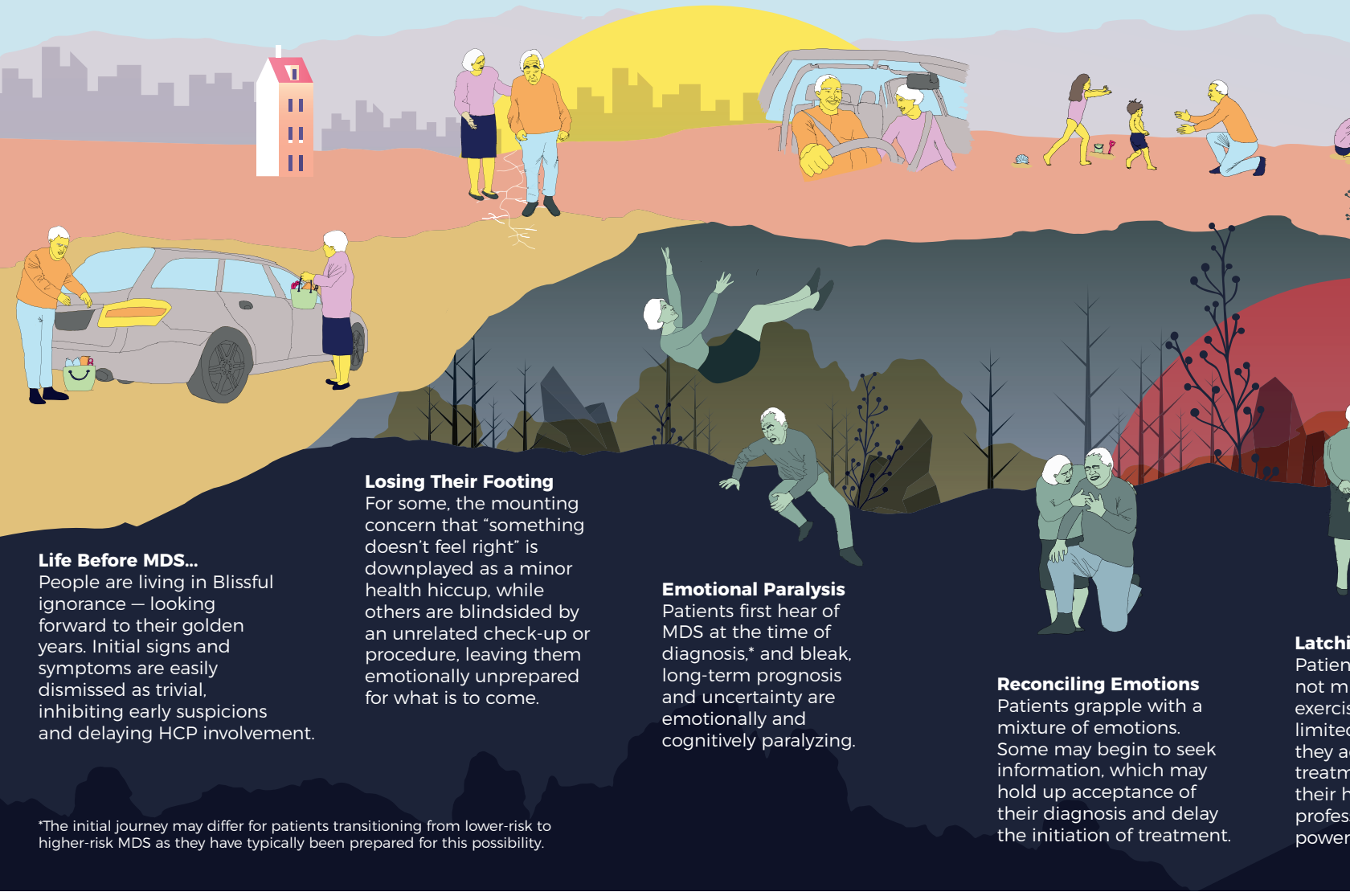
PLEASANTON, CA, PRINCETON, NJ, AND TOKYO, JULY 7, 2020 — Astex Pharmaceuticals, Inc.; Taiho Oncology, Inc.; and Otsuka Pharmaceutical Co., Ltd. today announce that the U.S. Food and Drug Administration (FDA) and Health Canada have approved INQOVI® (decitabine and cedazuridine) tablets. The three companies are all part of the Otsuka group of companies.

INQOVI is the first and only orally administered hypomethylating agent for the treatment for

continued on page 38

The Alternate World of Higher-Risk Myelodysplastic Syn

Higher-Risk Myelodysplastic Syndrome (HR MDS) can surface at a time when people are looking forward to their golden years. Whether hopes and dreams for this next stage of life are shattered by their HR MDS diagnosis. What you see below is the alternate world of HR M expected to live, while the lower portion captures the emotional highs and lows of what patients and caregivers experience while living is like walking in a fog, because what lies ahead is unseen, and it makes me feel like I have no control over my own fate." The alternate v



Life Before MDS...
People are living in Blissful ignorance — looking forward to their golden years. Initial signs and symptoms are easily dismissed as trivial, inhibiting early suspicions and delaying HCP involvement.

Losing Their Footing
For some, the mounting concern that "something doesn't feel right" is downplayed as a minor health hiccup, while others are blindsided by an unrelated check-up or procedure, leaving them emotionally unprepared for what is to come.

Emotional Paralysis
Patients first hear of MDS at the time of diagnosis,* and bleak, long-term prognosis and uncertainty are emotionally and cognitively paralyzing.

Reconciling Emotions
Patients grapple with a mixture of emotions. Some may begin to seek information, which may hold up acceptance of their diagnosis and delay the initiation of treatment.

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*The initial journey may differ for patients transitioning from lower-risk to higher-risk MDS as they have typically been prepared for this possibility.

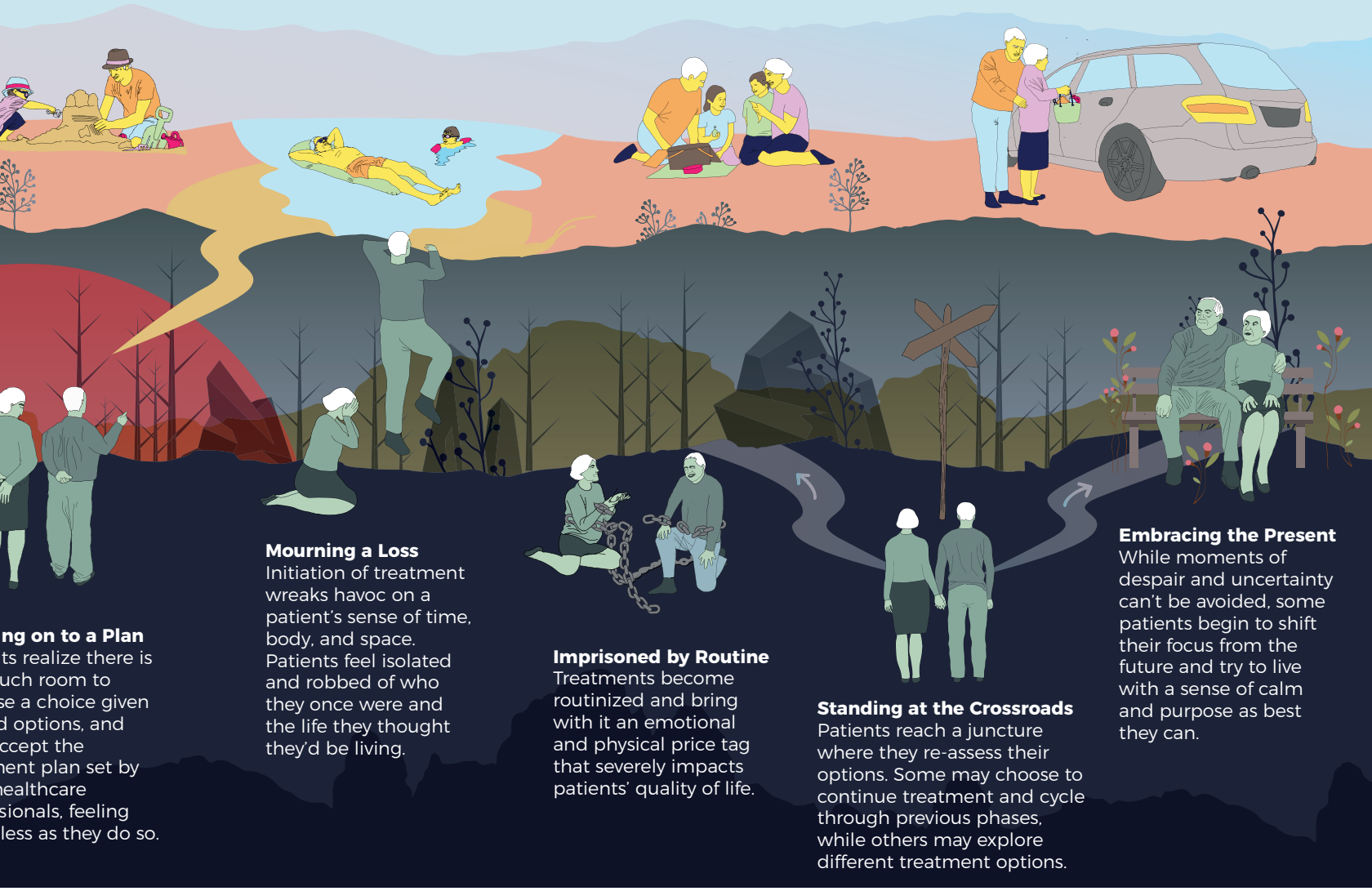
NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

7/20

drome

r it's retirement or the newfound freedom of more time to relax, their MDS. The upper part of the visual shows the life patients and caregivers with HR MDS. As one patient described, "living with Higher-Risk MDS world of Higher-Risk MDS may be a journey with many unknowns.



ng on to a Plan
ts realize there is uch room to se a choice given d options, and ccept the ent plan set by ealthcare sionals, feeling less as they do so.

Mourning a Loss
Initiation of treatment wreaks havoc on a patient's sense of time, body, and space. Patients feel isolated and robbed of who they once were and the life they thought they'd be living.

Imprisoned by Routine
Treatments become routinized and bring with it an emotional and physical price tag that severely impacts patients' quality of life.

Standing at the Crossroads
Patients reach a juncture where they re-assess their options. Some may choose to continue treatment and cycle through previous phases, while others may explore different treatment options.

Embracing the Present
While moments of despair and uncertainty can't be avoided, some patients begin to shift their focus from the future and try to live with a sense of calm and purpose as best they can.

G-MBG-1233692

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

adults with intermediate and high-risk myelodysplastic syndromes (MDS) including chronic myelomonocytic leukemia (CMML),1 two blood malignancies.

Approval was based on data from the ASCERTAIN phase 3 study and supporting phase 1 and 2 clinical studies. The ASCERTAIN phase 3 study evaluated the five-day, decitabine exposure equivalence between oral INQOVI and intravenous decitabine. The safety and efficacy of INQOVI was also assessed in the clinical studies.

The review and approval of INQOVI was conducted under the ORBIS initiative from the FDA Oncology Center of Excellence (OCE) with simultaneous submission and regulatory review in the U.S., Canada, and Australia. The FDA also reviewed the NDA under Priority Review status. INQOVI is not currently approved in Australia. INQOVI was formerly named ASTX727, its experimental compound code.

"Intravenous or subcutaneous administered hypomethylating agents have been the cornerstone for the treatment of patients with MDS and CMML since the mid-2000s," said Guillermo Garcia-Manero, MD, Professor and Chief of Section of Myelodysplastic Syndromes, Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston, Texas, and Principal Investigator of the ASCERTAIN clinical study. "The FDA's approval of INQOVI builds on the proven therapeutic utility of hypomethylating agents in these diseases and offers a new orally administered option that offers patients an alternative to five consecutive days of IV infusions every month during a treatment period that can extend to several months."

"Until now, patients with intermediate and high-risk MDS and CMML have not had an approved, orally administered hypomethylating agent option for treatment of their disease," said Mohammad Azab, MD, president and chief medical officer of Astex Pharmaceuticals, Inc. "The INQOVI clinical program was designed to deliver an oral alternative to IV decitabine based on comparative decitabine exposure data in the clinical trials, and to assess INQOVI's safety and efficacy profile. As part of the ORBIS project initiative of FDA and Health Canada we were able to share and address information requests simultaneously with both agencies resulting in a more efficient review and completion of assessment in a timely manner. The outcome is expedited availability of this important oral alternative to patients in both countries" added Dr. Azab. "We greatly appreciate the FDA's priority review and Health Canada's review of the INQOVI NDA/NDS under Project ORBIS and the approval of a new therapeutic option for patients with these diseases."

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 (geometric mean ratio of the 5-day cumulative decitabine area-under-the-curve following 5 consecutive once daily doses of INQOVI compared to that of intravenous decitabine was 99% (90% CI: 93, 106). The phase 1 and phase 2 clinical study results have been published in Lancet Haematology4 and Blood, respectively. The phase 3 ASCERTAIN study data was presented at the American Society of Hematology (ASH) Meeting in Orlando, Florida, in December 2019 by Dr. Garcia-Manero.

Astex's parent company, Otsuka Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd. previously announced that, subject to regulatory approvals, commercialization of oral INQOVI in the U.S. and Canada will be conducted by Taiho Oncology, Inc. and Taiho Pharma Canada, Inc. respectively.

"Our partnership with Astex is a demonstration of the commitment that Taiho Oncology has to bringing new therapeutic options to patients with cancer," said Tim Whitten, president and chief executive officer of Taiho Oncology, Inc. "The approval of INQOVI makes the possibility of at-home hypomethylating agent treatment of intermediate and high-risk MDS and CMML a reality, enabling patients to take their medication from the convenience and comfort of their home. This is especially significant during the COVID-19 pandemic, allowing patients to potentially reduce the number of office visits needed for current IV treatment administration. We look forward to working with all healthcare professionals to help deliver the first new oral HMA treatment alternative for patients with intermediate and high-risk MDS and CMML in nearly fifteen years."

ABOUT INQOVI

INQOVI is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

ABOUT ASTEX, TAIHO, AND OTSUKA

Astex is a leader in innovative drug discovery and development, committed to the fight against cancer. Astex is developing a proprietary pipeline of novel therapies and has multiple partnered products in development under collaborations with leading pharmaceutical companies. Astex is a wholly owned subsidiary of Otsuka Pharmaceutical Co. Ltd., based in Tokyo, Japan.

Taiho Oncology, Inc., is a subsidiary of Taiho Pharmaceutical Co., Ltd. and an indirect subsidiary of Otsuka Holdings Co., Ltd. Taiho has established a world-class clinical development organization that works urgently to develop innovative cancer treatments and has built a commercial business in the U.S.

Taiho has an oral oncology pipeline consisting of both novel antimetabolic agents and selectively targeted agents.

Otsuka Pharmaceutical is a global healthcare company with the corporate philosophy: "Otsuka–people creating new products for better health worldwide." Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and nutraceutical products for the maintenance of everyday health.

GAMIDA CELL ANNOUNCES POSITIVE TOPLINE DATA ON SECONDARY ENDPOINTS FROM PHASE 3 CLINICAL STUDY OF OMIDUBICEL IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Study met secondary endpoints related to platelet engraftment, infections and hospitalizations, key clinical measures in bone marrow transplant

Omidubicel represents potential transformative treatment option for patients in need of a bone marrow transplant

Company anticipates initiating BLA submission in fourth quarter of 2020

BOSTON, MA, OCTOBER 6, 2020 (BUSINESS WIRE) — Gamida Cell Ltd. (Nasdaq: GMDA), an advanced cell therapy company committed to cures for blood cancers and serious blood diseases, today announced that the Phase 3 study of omidubicel, an investigational advanced cell therapy in development as a potential life-saving treatment option for patients in need of bone marrow transplant, met all three of its secondary endpoints. Omidubicel is the first bone marrow transplant product to receive Breakthrough Therapy Designation from the U.S. Food and Drug Administration and has the potential to be the first FDA-approved engineered bone marrow transplant graft.

The international, multi-center, randomized Phase 3 study was designed to evaluate the safety and efficacy of omidubicel in patients with hematologic malignancies undergoing a bone marrow transplant compared to a comparator group of patients who received a standard umbilical cord blood transplant. In May, Gamida Cell reported that omidubicel achieved its primary endpoint, demonstrating a highly statistically significant reduction in time to neutrophil engraftment, a key milestone in recovery from a bone marrow transplant. The prespecified secondary endpoints of the study, analyzed in all randomized patients (intent-to-treat), were the proportion of patients who achieved platelet engraftment by day 42, the proportion of patients with Grade 2 or Grade 3 bacterial or invasive fungal infections in the first 100 days following transplant, and the number of days alive and out of the hospital in the first 100 days following transplant. All three secondary endpoints demonstrated a statistically significant improvement among patients who received omidubicel compared to the comparator group. The company anticipates reporting the full data set at a medical meeting in the fourth quarter of 2020.

"These data, obtained in a global, randomized, multi-institutional setting could represent an important step forward in the field. In addition to more rapid platelet engraftment, a key step toward recovery, reducing infections and hospitalizations are considered meaningful patient outcomes and have the potential to provide substantial value for patients, their families and the healthcare system," said Mitchell Horwitz, M.D., principal investigator and professor of medicine at the Duke Cancer Institute. "The totality of these data strengthen my belief that omidubicel has the potential to be a graft source for any patient who does not have access to a matched related donor and could help make stem cell transplantation more accessible and more successful for patients with lethal blood cancers."

"These additional data reinforce the potential of omidubicel and move us another step closer toward bringing potentially curative therapies to patients. We look forward to presenting data at a future medical meeting, and we are continuing our work to enable the submission of our biologics license application for omidubicel to the FDA on a rolling basis, both expected in the fourth quarter," stated Julian Adams, Ph.D., chief executive officer of Gamida Cell. "We deeply appreciate the patients who participated in this study, the incredible encouragement from their caregivers and the support we have received from investigators and their teams."

Despite the curative potential of bone marrow transplant, it is estimated that more than 40 percent of eligible patients in the United States do not receive a transplant for various reasons, including the lack of a matched donor. Even for patients who do receive a transplant, treatment is not always effective and can lead to serious complications that can dramatically affect their quality of life. Omidubicel is intended to address the current limitations of bone marrow transplant by providing a therapeutic dose of stem cells while preserving the cells' functional therapeutic characteristics.

ABOUT OMIDUBICEL

Omidubicel is an advanced cell therapy under development as a potential life-saving allogeneic hematopoietic stem cell (bone marrow) transplant solution for patients with hematologic malignancies (blood cancers). In both Phase 1/2 and Phase 3 clinical studies (NCT01816230, NCT02730299), omidubicel demonstrated rapid and durable time to engraftment and was generally well tolerated. Omidubicel is also being evaluated in a Phase 1/2 clinical study in patients with severe aplastic anemia (NCT03173937). The aplastic anemia investigational new drug application is currently filed with the FDA under the brand name CordIn®, which is the same investigational development candidate as omidubicel. For more information on clinical trials of omidubicel, please visit www.clinicaltrials.gov.

Omidubicel is an investigational therapy, and its safety and efficacy have not been evaluated by the U.S. Food and Drug Administration or any other health authority.

ABOUT GAMIDA CELL

Gamida Cell is an advanced cell therapy company committed to cures for patients with blood cancers and serious blood diseases. We harness our cell expansion platform to create therapies with the potential to redefine standards of care in areas of serious medical need.

STANFORD STUDY FINDS THAT NOTABLE'S DRUG SENSITIVITY SCREENING PLATFORM CAN IDENTIFY POTENTIALLY USEFUL DRUGS FOR MDS PATIENTS REFRACTORY TO STANDARD THERAPIES

First peer-reviewed publication highlighting Notable's platform published today in Blood Advances

FOSTER CITY, CA, JUNE 23, 2020 – Notable, which is redefining cancer treatment by taking a functional approach to precision oncology in hematological cancers, announced today that the results of a Stanford study using its drug sensitivity screening platform have been published in Blood Advances (June 23, 2020; Volume 4, Issue 12).

This study was designed to evaluate Notable's drug sensitivity screening platform in patients with myelodysplastic syndrome (MDS) and related myeloid neoplasms. After piloting the platform in 33 patients, the authors conducted a prospective feasibility study, enrolling 21 MDS patients refractory to standard therapies: azacitidine (Vidaza) or decitabine (Dacogen). The primary endpoint of the study was to determine if the drug sensitivity results could be returned to a Tumor Board within a clinically actionable timeframe (<30 days) to inform personalized treatment recommendations. The study met its primary endpoint with drug sensitivity data provided to the Tumor Board at a median turnaround time of 15 days, and these data helped identify potentially useful drugs and drug combinations for MDS patients refractory to standard therapies. Among 21 patients who received a therapy that was tested in Notable's platform, the authors demonstrated a positive predictive value of 92%, negative predictive value of 82%, and overall accuracy of 85% of the platform in predicting clinical responses.

Additional key details of the study are listed below:

- 54 patients were enrolled at Stanford University Medical Center between September 2016 and March 2019 and had a diagnosis of MDS, MDS/myeloproliferative neoplasm (MPN), or acute myeloid leukemia (AML).
- Blood samples and bone marrow aspirate samples were provided to Notable Labs, and ex vivo drug sensitivity screening was performed using Notable's fully automated high-throughput platform, evaluating sensitivity to a panel of 74 individuals drugs and 36 drug combinations.
- Notable's platform identified three groups of patients with distinct drug sensitivity patterns.
- Correlations were observed between genotype and phenotype, with specific gene mutations associated with distinct drug sensitivity patterns.

Notable and Stanford are currently enrolling a second cohort of patients to validate the initial data set.

"We set out to explore whether this platform could produce accurate results in a timely manner, and the answer is yes," said Peter Greenberg, MD, Professor of Medicine (Hematology) and Director, Stanford MDS Center at Stanford University Cancer Center. "These data demonstrate the utility of this approach for identifying potentially useful and often novel therapeutic drugs for patients with myeloid neoplasms refractory to standard therapies."

"This peer-viewed research is a substantial clinical milestone for Notable and for precision medicine in oncology," said Laurie Heilmann, CEO of Notable. "One significant aspect of this research is the dataset Notable is amassing. Our bioinformatics and machine learning models are generating vast datasets that will help inform future drug development. These data are critical for biotech and pharma companies who want to accelerate their go-to-market. We look forward to working closely with Stanford to continue this important research."

In Jan. 2020, Notable announced the launch of its new observational clinical trial. The trial is being conducted at multiple sites across the country and will focus on hematologic malignancies (blood cancers). The primary objective is to establish a tumor registry with annotated clinical outcomes. Exploratory objectives will include correlation of ex vivo drug screening results with clinical outcomes as well as identification of potential biomarkers that correlate clinical responses with genotype and/or phenotype. More details on Notable's Institutional Review Board-approved clinical trial is available at https://clinicaltrials.gov/ct2/show/NCT04014764.

ABOUT NOTABLE

Notable is redefining cancer treatment with a clinically validated AI platform that rapidly advances cancer drug development at a fraction of traditional costs. Notable's approach combines AI with an automated lab to determine which drugs or combination of drugs will be most effective for specific types of cancers, enabling drug companies to recruit the right patients into clinical trials. The resulting high response rates in those trials can accelerate the process, eliminating much of the time and cost in later-stage trials, and helping to get drugs to market years faster at a lower cost to patients. Learn more at https://notablelabs.com/ or follow @notablelabs.

GERON REPORTS FOUR IMETELSTAT DATA PRESENTATIONS AT VIRTUAL EDITION OF THE EUROPEAN HEMATOLOGY ASSOCIATION (EHA) ANNUAL CONGRESS

MENLO PARK, CA, JUNE 12, 2020 (GLOBE NEWSWIRE) – Geron Corporation (Nasdaq: GERN), a late-stage clinical biopharmaceutical company, today announced that an oral presentation and three poster presentations of new clinical data and analyses related to imetelstat, the Company's first-in-class telomerase inhibitor, are now available on Geron's website as well as to participants of the Virtual Edition of the 25th Annual EHA Annual Congress.

UPDATED EFFICACY AND SAFETY DATA FROM THE IMERGE PHASE 2 CLINICAL TRIAL

"The EHA presentation reports encouraging continued durability data from the IMerge Phase 2 clinical trial, including a median duration of

8-week transfusion independence of 20 months, which is the longest duration we have reported to date in this trial, and that 29% of patients were transfusion free for more than one year," said Aleksandra Rizo, M.D., Ph.D., Geron's Chief Medical Officer. "We expect these data to drive further interest of investigators, which will promote enrollment for the ongoing IMerge Phase 3 clinical trial in lower risk MDS."

TITLE: ***Treatment with Imetelstat Provides Durable Transfusion Independence (TI) in Heavily Transfused Non-del(5q) Lower Risk MDS (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis Stimulating Agents (ESAs) (Abstract #S183)***

The oral presentation reports long-term efficacy and safety data from 38 patients in the IMerge Phase 2 clinical trial, based on a February 4, 2020 cut-off date and a median follow-up of 24 months. IMerge is a two-part Phase 2/3 clinical trial evaluating imetelstat in transfusion dependent patients with Low or Intermediate-1 risk myelodysplastic syndromes (lower risk MDS), who are relapsed after or refractory to prior treatment with ESAs. The first part of IMerge was designed as a Phase 2, open label, single arm study to assess the efficacy and safety of imetelstat. The primary efficacy endpoint is 8-week TI rate, which is defined as the proportion of patients achieving red blood cell transfusion independence during any consecutive eight weeks since entry into the trial. Secondary endpoints include rate of hematologic improvement-erythroid (HI-E) and duration of TI. Several patients remain on treatment in the IMerge Phase 2 clinical trial.

The conclusions of the oral presentation are as follows:

- Meaningful and durable transfusion independence (TI):
  - High rates of TI and HI-E: 42% 8-week TI rate and 68% HI-E rate
  - Durable TI and HI-E: Median duration of TI is 20 months and median duration of HI-E is 21 months
  - TI across multiple patient subtypes: ringed sideroblast positive (RS+) and RS-, high and very high transfusion burden
- Potential disease-modifying activity:
  - 29% of patients transfusion free for more than 1 year
  - 75% of 8-week TI responders had a hemoglobin rise of >3g/dL from pretreatment level
  - Reduction in variant allele frequency (VAF) of SF3B1 mutation correlated with shorter time to TI and duration of TI
- No new safety signal identified:
  - Reversible cytopenias, without significant clinical consequences were most frequent adverse events

The slide presentation is available on Geron's website at www.geron.com/r-d/publications.

Ongoing IMerge Phase 3 Clinical Trial

The IMerge Phase 3 clinical trial is a double-blind, randomized, placebo-controlled clinical trial with registration intent. The trial is designed to enroll approximately 170 patients with lower risk transfusion dependent MDS who are relapsed or refractory to an ESA, have not received prior treatment with either a hypomethylating agent (HMA) or lenalidomide and who are non-del(5q). The trial was opened for screening and enrollment in August 2019. As of the end of April 2020, approximately 68% of planned clinical sites for the IMerge Phase 3 trial were open for enrollment. Geron expects to complete patient enrollment by the end of the first quarter of 2021. Under current assumptions, the Company expects top-line results to be available in the second half of 2022.

NEW ANALYSES OF DATA FROM IMBARK PHASE 2 CLINICAL TRIAL IN INTERMEDIATE-2 OR HIGH-RISK MYELOFIBROSIS

"Taken together, we believe the three EHA poster presentations reporting new analyses of IMbark Phase 2 data substantiate the OS outcome observed in IMbark and indicate potential disease-modifying activity of imetelstat in yet another hematologic indication," said Aleksandra Rizo, M.D., Ph.D., Geron's Chief Medical Officer. "These analyses also provide further support for our planned Phase 3 clinical trial in refractory MF, which is expected to open for enrollment in the first quarter of 2021."

IMbark was designed as a Phase 2 clinical trial to evaluate two dosing regimens of imetelstat (either 4.7 mg/kg or 9.4 mg/kg administered by intravenous infusion every three weeks) in patients with Intermediate-2 or High-risk myelofibrosis (MF) who have relapsed after or are refractory to prior treatment with a janus kinase inhibitor (JAKi). The co-primary efficacy endpoints for IMbark were spleen response rate, defined as the proportion of patients who achieve a reduction of at least 35% in spleen volume as assessed by imaging, and symptom response rate, defined as the proportion of patients who achieve a reduction of at least 50% in Total Symptom Score (TSS), at 24 weeks. Key secondary endpoints were overall survival (OS) and safety.

TITLE: ***Telomerase Activity, Telomere Length and hTERT Expression Correlate with Clinical Outcomes in Higher-Risk Myelofibrosis (MF) Relapsed/Refractory (R/R) to Janus Kinase Inhibitor Treated with Imetelstat (Abstract #EP1098)***

The conclusions of the poster are as follows:

- Imetelstat achieved dose- and exposure-dependent reduction of telomerase activity and human reverse transcriptase (hTERT) expression level, demonstrating on-target mechanism of action.
- Achieving optimal pharmacodynamic (PD) effect in patients treated with imetelstat is correlated with longer OS, as well spleen and symptom response.
- Significant dose-dependent reduction in VAF of JAK2, CALR and MPL mutations were observed, indicating that imetelstat has disease-modifying activity by targeting the underlying MF malignant clones.
- Treatment with 9.4mg/kg of imetelstat improved clinical outcomes in patients with short telomeres or high hTERT expression level at baseline. The results are consistent with telomere biology in cancer cells and provide evidence for on-target mechanism of action of imetelstat through telomerase inhibition.
- This is the first clinical report to systematically evaluate the mechanism of action based PD effect of imetelstat, and its relationship to exposure and clinical benefits.

The poster presentation is available on Geron's website at www.geron.com/r-d/publications.

TITLE: ***Imetelstat Treatment Results in Clinical Benefits, Including Improved Overall Survival, in Patients with Higher-Risk Triple Negative Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitors (JAKI) (Abstract #1101)***

The overall conclusion of the poster is that triple negative (TN) patients who are relapsed/refractory to JAKi and treated with 9.4 mg/kg of imetelstat had better clinical outcomes and prolonged overall survival (OS) compared to non-TN patients, suggesting that imetelstat may improve the poor outcomes expected for TN patients. Additional highlights from the poster include:

- With 9.4 mg/kg of imetelstat treatment, clinical response rates were higher in TN vs non-TN pts: spleen response rate was 18.8% in TN vs 7.3% in non-TN; and symptom response was 50.0% in TN vs 24.4% in non-TN patients.
- Imetelstat treatment at 9.4 mg/kg resulted in significantly longer median OS of 35.9 months for TN patients compared to 24.6 months for non-TN patients.
- A majority (94%) of the TN patients enrolled on the study had grade three fibrosis. Higher rate of bone marrow fibrosis improvement was noted in the TN (50%) vs non-TN (39.1%) patients.
- TN patients enrolled on the study had short telomere length and high hTERT expression level at baseline, representing a suitable target population for imetelstat, a first-in-class telomerase inhibitor.

The poster presentation is available on Geron's website at www.geron.com/r-d/publications.

TITLE: ***Favorable Overall Survival with Imetelstat Treatment Correlates with Other Clinical Benefits in Intermediate-2 or High-Risk Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitor (Abstract #1107)***

The poster reports new analyses of data from all 107 patients in both arms (59 patients in the 9.4 mg/kg arm and 48 patients in the 4.7 mg/kg arm) of the IMbark Phase 2 clinical trial with a data cut-off date of February 19, 2020 and a median follow-up of 41.7 months. As of the data cut-off date, median OS was 28.1 months in the 9.4 mg/kg arm and 19.9 months in the 4.7 mg/kg arm.

The overall conclusion of the poster was that imetelstat showed dose-related improvement in OS in patients who are R/R to JAKi. The survival benefit observed with imetelstat was supported by the trend of correlation with other clinical benefits. Additional highlights from the poster include:

- Among 57 patients across both treatment arms that had matching bone marrow samples, 20 patients (35%) had ≥1 degree of bone marrow fibrosis improvement while on study and had a significantly longer OS than those who had worsening bone marrow fibrosis. A similar trend was seen in 29 patients (51%) with stable vs. worsening fibrosis.
- Patients who achieved symptom and spleen response at week 24 showed a trend of longer OS compared to patients who did not achieve response.
- Transfusion dependency, response to last JAKi, higher baseline neutrophils, lower baseline hemoglobin and platelet values correlated with increased risk of death.

The poster presentation is available on Geron's website at www.geron.com/r-d/publications.

Planned Phase 3 Clinical Trial in Refractory MF

The planned Phase 3 clinical trial in refractory MF is designed to be an open label 2:1 randomized, controlled trial with registration intent to evaluate imetelstat (9.4 mg/kg administered by intravenous infusion every three weeks) in approximately 320 patients with Intermediate-2 or High-risk MF. Patients eligible for the trial will be required to be refractory to a JAK inhibitor, an inclusion criterion that is planned to be defined as having an inadequate spleen response or symptom response after treatment with a JAK inhibitor for at least six months, including an optimal dose of a JAK inhibitor for at least two months. The control arm is planned to be best available therapy (BAT), excluding JAK inhibitors. The primary efficacy endpoint for the trial is planned to be overall survival (OS). Planned key secondary endpoints include symptom response, spleen response, progression free survival, complete response, partial response, clinical improvement, duration of response, safety, pharmacokinetics, and patient reported outcomes. Under current assumptions, the Company expects to complete patient enrollment in the second half of 2022, to conduct an interim analysis in the first half of 2023 and to conduct a final analysis in the first half of 2024. The final analysis for OS is planned to be conducted after more than 50% of the patients planned to be enrolled in the trial have died. An interim analysis of OS is planned to be conducted after approximately 70% of the total projected number of events for the final analysis have occurred. Both the planned interim and final analyses are event driven and could occur on different timelines than currently expected.

ABOUT IMETELSTAT

Imetelstat is a novel, first-in-class telomerase inhibitor exclusively owned by Geron and being developed in hematologic myeloid malignancies. Early clinical data suggest imetelstat may have disease-modifying activity through the apoptosis of malignant stem and progenitor cells, which allows potential recovery of normal hematopoiesis. Clinical studies of imetelstat sponsored by Geron include IMerge, a Phase 2/3 trial in lower risk myelodysplastic syndromes (MDS), and IMbark, a Phase 2 trial in Intermediate-2 or High-risk myelofibrosis (MF). 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 MF whose disease has relapsed after or is refractory to janus 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 hematologic myeloid malignancies. For more information about Geron, visit www.geron.com.

AGIOS RECEIVES FDA BREAKTHROUGH THERAPY DESIGNATION FOR TIBSOVO® (IVOSIDENIB) FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MYELODYSPLASTIC SYNDROME WITH AN IDH1 MUTATION

CAMBRIDGE, MA, DEC 16, 2019 – Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for TIBSOVO® (ivosidenib) for the treatment of adult patients with relapsed or refractory myelodysplastic syndrome (MDS) with a susceptible IDH1 mutation as detected by an FDA-approved test. MDS is a group of bone marrow disorders that can cause severe complications, such as infections and uncontrolled bleeding, and can lead to the development of acute myelogenous leukemia (AML).

"There is a significant need for new targeted therapeutic approaches for individuals with MDS whose disease continues to progress despite treatment with standard of care," said Chris Bowden, M.D., chief medical officer at Agios. "The Breakthrough Therapy designation is based on results from the initial 12 patients in the MDS arm of our Phase 1 study in advanced hematologic malignancies with an IDH1 mutation and recognizes the potential for single-agent treatment with TIBSOVO® to make an impact on these patients. We recently re-opened the MDS arm of this study with the goal of generating sufficient data to pursue a regulatory filing in this indication."

The FDA's Breakthrough Therapy designation is intended to expedite the development and review of a drug candidate that is under investigation to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.

Results from the MDS arm of the ongoing TIBSOVO® Phase 1 dose-escalation and expansion study in hematologic malignancies were presented at the 7th Society of Hematologic Oncology Annual Meeting, held September 11-14, 2019, in Houston, Texas. These demonstrate that TIBSOVO® administered as a monotherapy was well tolerated and associated with durable remissions as well as the achievement and maintenance of transfusion independence in patients with relapsed or refractory MDS with an IDH1 mutation. Among the 12 patients who received 500 mg of oral TIBSOVO® daily, the median treatment duration was 11.4 months. The median age was 72.5 years, and 42% of patients were age 75 or older. As of the November 2, 2018 data cut-off, 75% (9/12) of patients had a response and 42% (5/12) had a complete response (CR). The median duration of CR had not been reached (95% CI, 2.8 months, NE). Of the patients who had a CR, 60% remained relapse-free at 12 months. In addition, 9 (75%) patients were transfusion-independent for 56 days or longer during study treatment. The most common adverse events (AEs) of any grade were back pain, diarrhea, fatigue and rash. Grade 2 IDH differentiation syndrome was observed in 1 of 12 patients. No AEs resulted in permanent discontinuation of treatment.

TIBSOVO® CLINICAL DEVELOPMENT IN MDS

The MDS arm of the Phase 1 dose-escalation and expansion study evaluating TIBSOVO® (ivosidenib) in adults with advanced hematologic malignancies with IDH1 mutations is assessing the clinical activity, safety, tolerability, pharmacokinetics and pharmaco-dynamics of TIBSOVO® in adult patients with relapsed or refractory MDS with a susceptible IDH1 mutation. The arm was re-opened in October 2019 and will enroll up to 25 total patients with the goal of generating sufficient data to pursue a potential regulatory filing in this indication. Study recruitment is ongoing across 22 sites in the U.S. and France.

TIBSOVO® is not approved in any country for the treatment of patients with MDS.

ABOUT TIBSOVO® (IVOSIDENIB)

TIBSOVO® (ivosidenib) is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test. For more information, visit TIBSOVO.com.

A PHASE 3 RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY INVESTIGATING THE EFFICACY AND SAFETY OF ROXADUSTAT (FG-4592) FOR TREATMENT OF ANEMIA IN PATIENTS WITH LOWER RISK MYELODYSPLASTIC SYNDROME (MDS) WITH LOW RED BLOOD CELL (RBC) TRANSFUSION BURDEN (LTB)

FibroGen has been conducting together with Astra Zeneca and Astellas a global Phase-3 study to assess the efficacy and safety of Roxadustat for treatment of anemia in patients with lower risk Myelodysplastic Syndrome (MDS) with low red blood cell (RBC) transfusion burden (LTB). The study has been enrolling patients at approximately 70 global sites (Australia, Belgium, Germany, Israel, Italy, Russia, Korea, Spain, UK and USA). The first patient was randomized in April 2019. We hope that upon study completion we will be able to provide MDS patients with Roxadustat, an effective and safe, oral drug to treat anemia. Since this is a double-blind study, we do not know what the efficacy of Roxadustat is until all the data has been collected, and analyzed in an unblinded fashion.

Our drug, Roxadustat is a potent and reversible orally bioavailable small-molecule inhibitor of HIF-PH enzymes. By inhibiting HIF-PH, roxadustat stimulates erythropoiesis via the HIF pathway in a manner consistent with the physiologic response to hypoxia. Its ability to stimulate erythropoiesis makes it a candidate for the treatment of anemia associated with many diseases such as MDS, chronic kidney disease (CKD) in nondialysis dependent chronic kidney disease (NDD-CKD) and dialysis-dependent chronic kidney disease (DD CKD) patients, as well as non-myeloid malignancies under chemotherapy. We are also testing Roxadustat to treat anemia in patients who undergo chemotherapy due to different malignancies, such as lung-, pancreatic- and ovarian cancers. As of 07 September 2019, 13132 subjects (943 healthy subjects, 12120 CKD patients, 68

MDS patients, and 1 CIA patient) have received study drug in the roxadustat clinical program, of which an estimated >7,000 subjects have received roxadustat.

The pharmacodynamics and efficacy of roxadustat can be summarized by the following:

- Roxadustat produces more than dose proportional increases in endogenous plasma EPO levels, with peak increases at 8 to 12 hours post-dose.
- Roxadustat increases hemoglobin (Hb) in a dose-dependent manner, regardless of baseline iron status or dependence on IV iron supplementation during treatment.
- Roxadustat increases reticulocytes in healthy subjects and subjects with CKD.
- Decreases in cholesterol were observed in healthy subjects and in subjects with NDD CKD and DD-CKD treated with roxadustat.
- No differences in pharmacology and efficacy were observed across different ethnicities.

Anemia is the most common clinical presentation in lower risk MDS, which results in prolonged transfusion requirements and risks related to RBC transfusion itself (Gupta, 1999), iron overload (Jabbour, 2008; Rose, 2001), and significant impairment of the quality of life (QoL) (Pinchon, 2009) in affected patients. The pathophysiology of anemia in MDS is complex, and involves ineffective erythropoiesis, dysregulated cytokine signaling, dysplastic features of hematopoietic progenitors and increased apoptosis of erythroid precursors, among other factors (Sekeres, 2007). The erythroid dysfunction in MDS often presents with fatigue and low Hb level. Anemia in MDS becomes more symptomatic with poorer clinical outcomes at lower Hb level (i.e., below 9 g/L) (Malcovati, 2011). As erythroid function continues to decline, RBC transfusion may become necessary as supportive treatment. Dependency on RBC transfusion has been associated with shorter life expectancy in patients with MDS (Malcovati, 2005).

The disease burden of anemia in MDS is high. Severe anemia interferes with patients' QoL and ability to work, and it negatively impacts the function other organ systems due to insufficient oxygen delivery (Cogle, 2015). When RBC transfusions become necessary to sustain bodily functions, not only are the frequent trips to the hospital burdensome to the patient, but the risk of transfusion-related infections can further threaten MDS patients. A fraction of MDS patients may also have a primary neutropenia due to bone marrow dysfunction or secondary neutropenia associated with medications for the treatment of MDS. Thus infection is the number one cause of death in MDS patients (Dayyani, 2010). Additional risks of transfusion include transfusion reactions (risk accumulates with exposure to more antigens through transfusions) and the iron overload from cumulative transfusions may lead to additional organ complications, particularly in heart, liver and endocrine organs (Dasararaju, 2015).

There is no FDA or EMA approved effective and safe pharmacologic treatment to treat anemia in lower risk MDS patients who are not suitable for lenalidomide or hypomethylating agents. ESAs are at times used off-label despite these agents not being approved by global health authorities for the treatment of MDS. With the recent addition of some new international sites in (Canada, France, Netherlands, Sweden, Denmark, Norway, Turkey, Poland, Serbia and India), we hope that we will be able to show the efficacy and safety of Roxadustat to treat anemia in MDS patients upon completion of this study. Please contact us, if you are interested in more details on the study itself or our published findings on Roxadustat in anemia patients. You can find the general information about this study on https://clinicaltrials.gov. You can also contact the Sponsor's medical study lead directly at kmodelska@fibrogen.com

MY 20 YEAR JOURNEY...

FRAN BOYLE
Glen Mills, Pennsylvania

My MDS Journey started in 2000, when my family doctor noticed that my Hgb was going down slightly during my yearly physical. After this occurred three years in a row, he referred me to a local hematologist in 2003 who told me he didn't know what to make of it, so I would return to him yearly until he decided to do a bone marrow biopsy. That was in 2006. I was 56.

Results showed that I had RARS. Refractory anemia with ringed sideroblasts. At that time, my Hgb was around 10-11.

The hematologist didn't give me any information, he just told me not to look it up on the internet as I could have this for years without needing any treatment. It was only after surfing the web that I found out that what I had was considered a blood cancer. Apparently, some hematologists don't know much about the disease! I eventually found the MDS Foundation while searching the web and realized that I needed to go to an MDS Center of Excellence.

I consulted with Dr. Porter at the University of Pennsylvania where I had my second bone marrow biopsy with pretty much the same result – RARS. It was suggested that two of my four brothers (two of them were over 70 and were considered too old) get tested to see if either of them might be a match for a bone marrow transplant. Up until then I was reluctant to tell my daughter, family members, and friends about my diagnosis because I didn't have any idea what direction my MDS would take.

I WISH SOMEONE HAD TOLD ME THAT BLOOD TRANSFUSIONS ARE NO BIG DEAL. THEY HAVE KEPT ME GOING NOW FOR OVER 10 YEARS.

Neither of my brothers was a match but I was put in the bone marrow database, just in case my MDS got worse. It was suggested that I was not a good candidate for a bone marrow transplant at the time, since my MDS was in the low risk range.

I then saw a specialist at Thomas Jefferson, Dr. Emanuel Besa, whom I had met at an MDS Foundation seminar. Dr. Besa was conducting his own trial with a drug called Accutane which is basically high doses of Vitamin E. He had achieved some positive results that showed that Accutane could delay the need for transfusions. And so, I started Accutane, which I had to buy from Canada since it was not approved for the treatment of MDS in the US. I took that for about a year, but then began to need regular transfusions in September 2009. Dr. Besa then referred me to Dr. Erev Tubb at Crozer Hospital.

Under Dr. Tubb, I was tried on Procrit, then Aranesp then both together, which did not work.

I was then started on Revlimid. As part of the protocol, it was required that I have bone marrow biopsies before treatment began and after it failed. (I've had 6 biopsies and found that some doctors are much better at performing them than others)!

Revlimid — 3/25/2010 – 9/12/2010 – Was transfusion independent for 143 days, then stopped working.

Tried again 10/25/2010 – 12/14/2010 – No response.

Vidaza — 2/14/2011 – 7/19/2011 – Was transfusion independent 33 days and 42 days, then no response.

And so, after Vidaza failed, I thought for sure that I was a goner!

I wish someone had told me that blood transfusions are no big deal. They have kept me going now for over 10 years. I've never had a bad reaction. I have been able to work full time and most of the time I feel almost normal. The nurses at Crozer were terrific.

My biggest issue with transfusions is that some Doctors don't want to transfuse until the Hgb iis under 8.

This was the policy at Crozer. On my last visit there in 2011, my Hgb was 8 but was told to come back in 3 days.

I argued that my Hgb would most suredly go down in one day, but they would not order the blood. When I returned 3 days later, they agreed to order a transfusion but discovered I had developed an antibody. It then took 3 more days to get the blood and by the time I was transfused, my Hgb was below 7.

As you can imagine, I decided that practice was not for me and consulted the Message Board on the MDS Foundation website and through that met Bob Weinberg. Bob also had

MDS, diagnosed in his late 40's. He was on the Board of Directors of the MDS Foundation and was very helpful and changed my life by recommending I go to Lankenau to see Dr. Cliff Pemberton.

On my first appointment with Dr. Pemberton, my Hgb was mid 6's and I was not doing well at all. He immediately ordered 2 units and another a few days later and then I finally felt alive again.

Eight years later, I have many antibodies but the blood bank always comes through! Exjade (Now Jadenu or Desferasirox) since 8/13/2011 keeps my Ferritin in the low 3,000 range. I am fortunate that side effects are minimal — diarrhea, some dry skin issues.

I continue to consult with the hematologists at the University of Pennsylvania as they are listed as a Center of Excellence by the MDS Foundation. They clearly know a lot more about MDS than local hematologists. I guess because it is considered a rare disease.

Through them, I found out about Luspatercept or Reblozyl as it is now marketed. After waiting for two years, I finally got my first shot in late April of this year. I was considered a good candidate as I have RARS along with the mutated gene SF3B1.

IF LUSPATERCEPT (REBLOZYL) DOESN'T WORK FOR ME, I WILL BE DISAPPOINTED BUT WON'T HESITATE TO GET INVOLVED IN THE NEXT CLINICAL TRIAL. AS LONG AS I HAVE THE HELP AND SUPPORT OF MY FAMILY, DOCTOR AND NURSES, I'M GOOD!

Since then, I have had 7 injections. My white count which was always a little low has returned to normal. My platelets also went up.

Still waiting on the red count to change.

Side effects for me are stomachache, fatigue, dizziness when standing, diarrhea, some occasional pains in my arms and legs but nothing I haven't been able to handle. Side effects seem to diminish over time.

My current doctor at Main Line Oncology is Zonera Ali as Dr. Pemberton has retired. They have an excellent practice, nurses are great, hardly ever have to wait and they do their best to accommodate my needs.

I am encouraged by the new drugs coming out and the ongoing research being done. Newly diagnosed patients now have a better chance of having treatments designed for their specific MDS diagnosis rather than guessing what might work.

At present, I am 70 years old. Although being transfusion dependent for the past 11 years has been inconvenient, I am thankful that the blood has been available. At the beginning of Covid, when there was a blood shortage, I sometimes could only get one unit. That was kind of scary for me — at times, my Hgb went down to below 7 and when that happens, my quality of life suffers. I need my husband to drive me to the hospital and it becomes difficult for me to walk the distance to the infusion room.

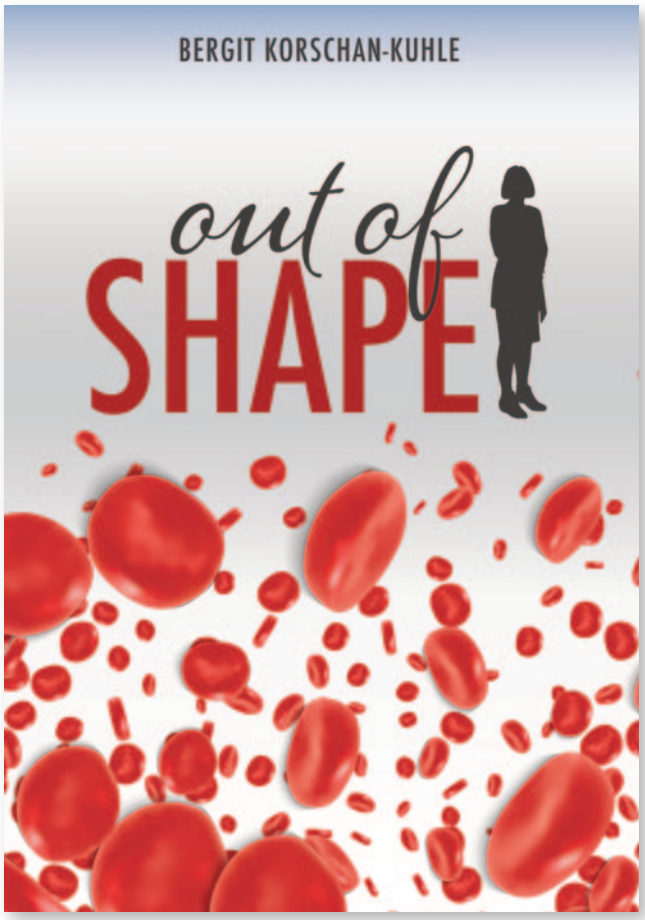
Things are a little better now with the blood shortage and as long as my Hgb stays in the 8's, I can take care of myself, although I do sleep a lot and nap a lot also.

I was laid off from my full-time job in April so it's been less stressful for me to manage all the doctor's visits. I can relax now and get to know my neighbors and see my friends more, although Covid has limited that to some extent.

One of my biggest concerns about retiring was insurance. I had a great plan where I worked and rarely had to pay anything other than my deductible and co-insurance. When I was laid off, I contacted a Medicare Advisor who got me set up on Medicare in two days. Fortunately, Medicare and the supplemental insurance have paid for the Luspatercept shots with my only out of pocket expense being the annual deductible. That was a big relief since each shot costs around $15,000!

So, today I'm in a good place, even after having MDS for 14 years! The hardest thing about MDS is the fear of the unknown and the worry that it causes my husband and daughter. I worry it will get worse but try not to dwell on that.

If Luspatercept (Reblozyl) doesn't work for me, I will be disappointed but won't hesitate to get involved in the next clinical trial. As long as I have the help and support of my family, doctor and nurses, I'm good!



OUT OF SHAPE
A PATIENT STORY

NOW AVAILABLE!

Bergit speaks very openly about her fears, the chaos of emotions that the illness caused in her and the uncertainty about what is to come... She lets MDS patients and their relatives share her knowledge about the disease and her perception of MDS. In my opinion, this is a very valuable addition to the medical perspective, which can help patients to better cope with the disease.

Prof. Dr. Detlef Haase
Clinics for Hematology and Medical Oncology
University Medical Center, Göttingen, Germany

MEET BERGIT KORSCHAN-KUHLE

MDS Patient. MDS Advocate... and now the author of a new book outlining her life since 2006 when she was first diagnosed.

Bergit Korschan-Kuhle was born in 1957, and is the mother of two sons. She studied Geosciences, History, German Language and Literature in Darmstadt and Braunschweig, graduating with a Master's degree in Geosciences and passing the 1st and 2nd state examinations for grammar schools. Her career has led her into several professions, all of which were related to education, training, communication and editing. For the last 15 years of her active professional life, she worked as a coordinator at management level at a grammar school in Lower Saxony/Germany. At the age of 49, Bergit fell ill with the still incurable malignant blood disease, myelodysplastic syndromes (MDS). She had to take early retirement in 2011 because of this disease. In 2007, Bergit started to contact other patients and patient organisations via the Internet. Over the years, her growing number of contacts, her German, European and international networking, as well as her attendance at patient events and specialist congresses, have increased her desire and opportunities to become more professionally involved in patient representation. Today, Bergit is on the Board of Directors of the LHRM, a patient organisation for leukaemic patients and their carers (the German Leukämiehilfe Rhein-Main e.V.), and is the contact person of the German MDS-PAT-IG (www.mds-patienten-ig.org). Bergit is a blogger, article writer and guest speaker on topics such as blood cancer diseases from the patient perspective and patient participation. She is a Steering Committee and Founding Member of the MDS-Alliance, the global network of MDS patient organizations. The EUPATI (European Patients' Academy of Therapeutic Innovations) training course 2015/16 turned her perspective on drug research and development from head to toe and broadened her horizons, particularly with regard to the circumstances of rare and chronic diseases. This enabled her to systematically organize the experience and knowledge she had accumulated over the years from her own involvement and from her grassroots work with patients. In 2017, a well-connected MDS Facebook group was created from her commitment, which successfully promotes the exchange between patients and relatives, and passes on serious information about the disease

For your copy, email dmurray@mds-foundation.org or call the office at 1-800-637-0839.

The German translated version can be ordered from LHRM-MDS Patienten-Interessen Gemeinschaft by emailing buero@LHRM.de.

WATCH, WAIT AND PRAY

CONNIE E. CONNELY
Tulsa, Oklahoma

"Your doctor thinks you have cancer!" my mother exclaimed. "I have some of the signs of multiple myeloma, so we are ruling out the possibility", I explained. "The office will call to set up the bone marrow biopsy". They x-rayed my full body. I can now tell people that I've had my head x-rayed! I also had to collect my urine for a full day. Yes, we were able to rule out multiple myeloma. It turns out that I had something else.

I had my bone marrow biopsy on May 17, 2017. Waiting for test results is always hard. June 2, 2017, my oncologist pulled up her chair next to my mother and me and said, "I was surprised by the results." Oh, no! What's wrong? I thought. I learned a new word, myelodysplastic syndromes. Doesn't that sound like something written for a Star Trek episode, maybe something Mr. Spock would acquire? I had to learn how to pronounce it, spell it, and explain it.

"It's a good thing you retired from teaching," my mother said. I had planned to teach for forty years. I made it thirty-nine years, so that's still an accomplishment. Fall 2016, I felt like fatigue hit me like a ton of bricks. I would wake up tired in the mornings. The stress of state-mandated achievement testing for my third graders with learning disabilities affected my health, so I knew it was time to leave the profession.

June 2017, started a new chapter of my life. My oncologist gave me a list of trusted websites about MDS, so I immediately contacted the MDS Foundation. They sent a packet of information within a few days, and I even received a phone call from them! Learning makes you hopeful.

I feel like I have been studying all my life. I did a ton of homework from elementary school through college. As a teacher, I was always learning about my students' medical conditions or learning styles. Now, I feel like I"m studying to save my life.

Fall 2017, I made a trip to MD Anderson in Houston, Texas, for a second bone marrow biopsy. Not awful, but not a walk in the park either. Luckily, my MDS is considered low risk. I learned about blasts in my bloodstream. These are immature cells causing my blood counts to be lower than preferred. I have 5q deletion MDS. I am glad that I obtained a second opinion because I would be in denial if I hadn't. If the percentage of these blasts gets too high, I will begin a cycle of Revlimid. Presently, I am on Watch and Wait. Come on, all you brilliant people! We don't need any more apps for our phones. What we need is a cure for cancer or at least some new treatment options. Invent that!

Shortly after my trip to MD Anderson, my cousin Scott called and said, "I've been reading about what you have. If I'm a match, I will donate bone marrow for you." Tears came to my eyes. The same cousin that I gave a black eye to when I was eight years old had just offered me bone marrow as nonchalantly as if he were letting me borrow his lawn chairs for the weekend. I knew our grandparents would have been proud of him.

Scott's older brother, Richard, has also been sweet to me. Despite his health issues, he has been kind to visit my mother and me when he is in the Tulsa area. I lost contact with these cousins after my father passed away in 1983. We reconnected through their mother in 2010. I think God had a plan for us to get back together.

Most days, I feel fine, but I have to pace myself and get plenty of sleep. When I retired from teaching, my friend Linda said, "People think a retired teacher is capable and has a lot of time on her hands, so you will have to learn to say no when asked to do too much." Linda was right. I have to advocate for myself. I can help with Meals on Wheels, but don't expect me to come running when someone cancels at the last minute. The low red blood counts cause dizziness when I try to hurry.

I like to keep busy. I have traced my ancestry back to the Revolutionary War, so I am a member of the Daughters of the American Revolution (DAR). My state of Oklahoma honors those citizens who reach the age of 100, Centenarians of Oklahoma. They put me in charge of mailing out birthday and Christmas cards. I like to help with Meals on Wheels when it's my turn, but I remind them that I can't hurry.

My favorite volunteer job is reading aloud to second graders in Catoosa, Oklahoma.

As a teacher, I submitted articles to teacher magazines and had a few things published. I also took some writing classes during the summers. In 2019, I contributed two stories to the website Blood-Cancer. I received lovely comments about both pieces. January 2020, I started writing for them monthly. They say when life gives you lemons, make lemonade. I say, when life gives you blood cancer, start writing.

PERSEVERANCE IS A GREAT WORD TO USE. I WILL BE PROACTIVE, NOT OBSESSIVE ABOUT MY HEALTH. I WILL READ A LOT, BUT I WON'T TRUST DR. GOOGLE.

I have always believed that a positive attitude helps us achieve. In the classroom, I saw students who grew up in challenging homes still thrive. Perseverance is a great word to use. I will be proactive, not obsessive about my health. I will read a lot, but I won't trust Dr. Google. Someday, I will throw darts at those life-expectancy charts. I plan to live for many more years. MDS is along for the ride.

FOLLOW YOUR HEART

SUE NICKERSON
Ocala, Florida

Back in 2003, the singer Jewel released a song titled "Intuition". Catchy tune, easy to sing and one of those choruses that gets stuck in your head. At least for awhile. Then one day - poof - it's replaced by the next toe-tapper.

Fast forward 17 years and that chorus and those lyrics have come back to swirl around in my head. They have never been more true.

Follow your heart.

Your intuition.

It will lead you in the right direction.

After living a somewhat symptom-free life with a Myeloproliferative Neoplasm called Essential Thrombocythemia JAK2+ for 18 years, there was a change in my normal labs. Blasts showed up and a bone marrow biopsy was done to check for Leukemia. I was relieved to find out that Leukemia had been ruled out but there were some questionable results that I did not understand. But I'm not a Dr. so I accepted

the advice that was given. Watch and wait. What was I waiting for? As it turned out, if my blasts continued to go higher, my disease would likely turn into Leukemia, AML to be exact.

I've always had higher than normal platelets. At diagnosis, in the year 2000, my platelets were nearing a million. I was put on Hydroxyurea for 13 years. Because I was stable and there had been no major changes or issues, my Hematologist and I decided to see how I would do without Hydroxyurea, and for five years, things were good. Then out of the clear blue, came the blasts.

Having access to my 1st bone marrow biopsy report was very helpful but also very confusing. I Googled a lot of different letters and numbers to try and find out what was going on and when I asked questions, I was still being told I had a Myeloproliferative Neoplasm with a complex karyotype and we had to wait and see what the disease decided to do. I was also told the medication regularly used to treat my issues would not help me because of two Tp53 mutations. That made me nervous but these were cancer specialists (I had seen three different Hem/Oncs) so I tried to have faith. With my white count and blasts on the rise, there was one sequence that I couldn't stop thinking about; del (5q).

Everything I read about it pointed to Myelodysplasia Syndrome. My oncologist mentioned MDS along with AML and MF, as possible outcomes of my progressing disease but no one could explain why I had del (5q) with "just" a Myeloproliferative Neoplasm. I have since learned that it is absolutely possible!

My intuition pushed me and I decided it was time to look for a specialist in myeloid disorders. I was fortunate to find a doctor at Moffitt Cancer Center in Tampa, FL who was interested in exactly what was happening to me. He firmly believes he can help me.

The second bone marrow biopsy seemed more extensive although they were almost exact — except for the first time — myelodysplastic syndrome was thrown into the vocabulary mix. Literally.

FINAL SYNOPTIC DIAGNOSIS:

Mixed MDS/MPN features following a known chronic myeloproliferative neoplasm, (progressive/transformed disease).

My intuition had known I had MDS, even before the doctor told me. I was well versed on the subject by the time I met with the specialist. I am now considered high risk and was put on 400 mgs of Venclexta a day (since February) and Vidaza infusions since January. The hope was to knock my counts down into remission and I just received the results of my biopsy. I have responded very well to treatment and I will go forward with a transplant on August 1st. My testing started on the 22nd of June and will continue until July 31st. I'll continue on Venclexta until 1 week before I am hospitalized. Vidaza treatment stopped on July 3rd. As I write this, we are seeking shelter for the 90 days post-transplant housing that the hospital requires from us and I am officially two weeks from my transplant. As scary as all of this is, I am so very grateful for my unknown 22-year-old donor and that I got that second opinion!

REMEMBER . . . FOLLOW YOUR HEART. YOUR INTUITION. IT WILL LEAD YOU IN THE RIGHT DIRECTION – *JEWEL*

IN DEFIANCE OF MYELODYSPLASTIC SYNDROME

DALE R. SKOGMAN
Michigan

In September of 2004 I was diagnosed with MDS and it was indicated that I might live two to five years with the disease. Sixteen years later I'm still alive! I will be 81 in October.

At the onset of the disease I had a very thorough family doctor who was suspicious of my low red & white blood counts. He referred me to the Mayo Clinic in Rochester, MN where a world famous physician confirmed that I had MDS. He also indicated that the onset was caught early and that I might anticipate living two to five years. The diagnosis was a shock and with trepidation my wife and I shared the news with family and friends. We also proceeded to get our worldly affairs in order.

We live in rural northern Michigan which has a lack of doctors, with frequent turnover and during the past sixteen years I have been exposed to a revolving door of hematologist/oncologists. This resulted in a lack of continuity in my care. My great blessing is that my wife, Josephine (Jo), is a retired geriatric nurse who kept meticulous records of my treatment. On many occasions, she would correct a doctor's

DEFY AND GIVE MDS A FIGHT FOR WELLNESS!

assumptions and provide continuity to my treatment protocol.

Starting in October 2016 as my red blood counts were monitored, I would be administered the drug Procrit if my red count would go below 10. At the time of this writing I haven't had a Procrit shot for the last nine months as my red counts have remained above 10. On seven occasions when my red count went low, I have received a blood transfusion.

Since I am a retired bishop who has served congregations in Northern Michigan and Wisconsin I have had contact with numerous people. As I have been open about my MDS, I have had many other MDS patients contact me to discuss our illness. The mutual support and analysis of our illness has proved to be helpful. I regret that all but one of the other MDS patients have died of the disease.

In addition to MDS, I struggle with numerous other health issues, seventeen in number! I have had surgery for: Kidney stones, prostate cancer, appendicitis, knee replacement and esophageal strictures. I also struggle with ankylosing spondylitis, arthritis, sinusitis, allergies, colitis, gout, ring worm, gingivitis, high blood pressure, macular degeneration, diverticulosis and hemorrhoids!

Recently, I had surgery for squamous cell skin cancer on my head followed by thirty-three grueling and excruciating radiation treatments. I have been declared cancer free except for my MDS!

A realist, I have no desire to prolong my life when its quality makes living no longer enjoyable and have been open in discussing end of life wishes with my doctors!

THE FINAL WORD: A diagnosis of MDS is not necessarily an immediate death sentence! Keep the faith! Reach out to others! Keep meticulous records and partner with your medical providers! Defy and give MDS a fight for wellness!

WILLIAM "BILL" STEWART: DEVOTED TO ALL. PARAGON OF GOODNESS

ROCHELLE OSTROFF-WEINBERG
Wynnewood, Pennsylvania

This tribute to Bill holds up his memory as an exemplar of devotion and kindheartedness. Devoted to his son, Edward, and family, devoted to his companion, Juanita, devoted to his friends. A role model as a good person who conveyed optimism in spite of living with and under the dark cloud of MDS.

Bill became my friend through my *MDS Family: Coping and Caring Program*. He and Juanita first came to the July 2014 gathering and returned to future events regularly, either at the White Dog Café where he always sat at the end of the table; it became his place, or at the Baltimore event in 2017. Loquacious, informed and upbeat, Bill brought a special presence to each gathering.

He charmed everyone!

I am fortunate to have spent a lovely afternoon with Bill and Juanita at a French bistro in Philly this January. We shared lunch, chatted, laughed. We simply enjoyed being alive, being together. I will treasure the memory of that afternoon, happy to have a photo of a great moment with a beautiful human being.

THE DAUGHTER OF A CHERISHED MOTHER

DEBORAH PEIRCE
Concord, Massachusetts

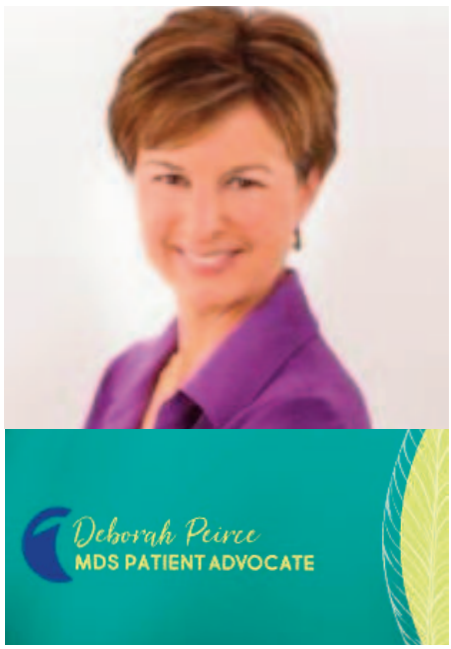
One of the first signs we noticed something was not right with my mother, Patricia Ewing Jackson (1935-2007), came 10 years before her passing during a trip she and my father took to the Galapagos Islands where she was biking around the Island with a travel group. She fell off her bike, unfortunately,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

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

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

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

While living in China, my mother first was diagnosed with pancytopenia with bruising (1997-98), even though her blast cells already were high (20-25%). The first mention of MDS came to us in 1999, when she had her first bone marrow aspirate and she was diagnosed with Refractory Anemia with Excess Blasts (RAEB, a subtype of MDS). She just had become a grandmother with the birth of our firstborn daughter, Morgan. My mother's MDS started to accelerate in 2000-02 when several referring hematologist saw "features of AML" when her ANC went to 200/mm3; in fact, she was diagnosed with hypocellular AML. During this time, she consulted with four University Hospitals in Chicago whom all advised induction chemotherapy with possible allogeneic bone marrow transplantation once in remission. She was 67 years old and grandmother to four children by 2002.



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

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

The crisis moment in 2003 was not the end of my mother's life, fortunately; even though her platelet count was at 28K. She went on Azacitidine (FDA approved in 2004), but was in-and-out of the hospital constantly to treat low-grade fevers, ear infections, and pneumonia. In 2005, she was diagnosed with AML and neutropenia after a "5-year history of MDS". Her fourth bone marrow aspirate revealed 31% blasts. And, ANC of 200 and platelets of 26,000. She was receiving monthly blood transfusions. She was living on nothing except her faith, her spirit, and...waiting for my return home to Chicago.

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

MY MOTHER GAVE ME THE GIFT OF LIFE AS HER OWN WAS COMING TO AN END. SHE CONTINUED TO SUPPORT AND BE GENEROUS, ACTUALLY GENERATIVE, TO MY DAUGHTERS AND ME UNTIL THE VERY END.

My mother gave me the gift of life as her own was coming to an end. She continued to support and be generous, actually generative, to my daughters and me until the very end. Her generativity fueled a desire in me to be an advocate for all patients, and a supporter of MDS patients specifically. Soon after my expatriate assignment in Beijing ended, I left the high-tech industry after 12 years and applied my expertise in Human Resources to the healthcare industry. I eventually took on a new role in the area of advocacy for a biotech company focused on rare diseases. This new role brought me to Cambridge, MA in 2016 where I worked directly with oncology-focused patient organizations. Today, I am privileged to sit on the Development Board for the MDS Foundation where we are focused on fundraising to support the MDSF mission.

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

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

AML RESOURCES

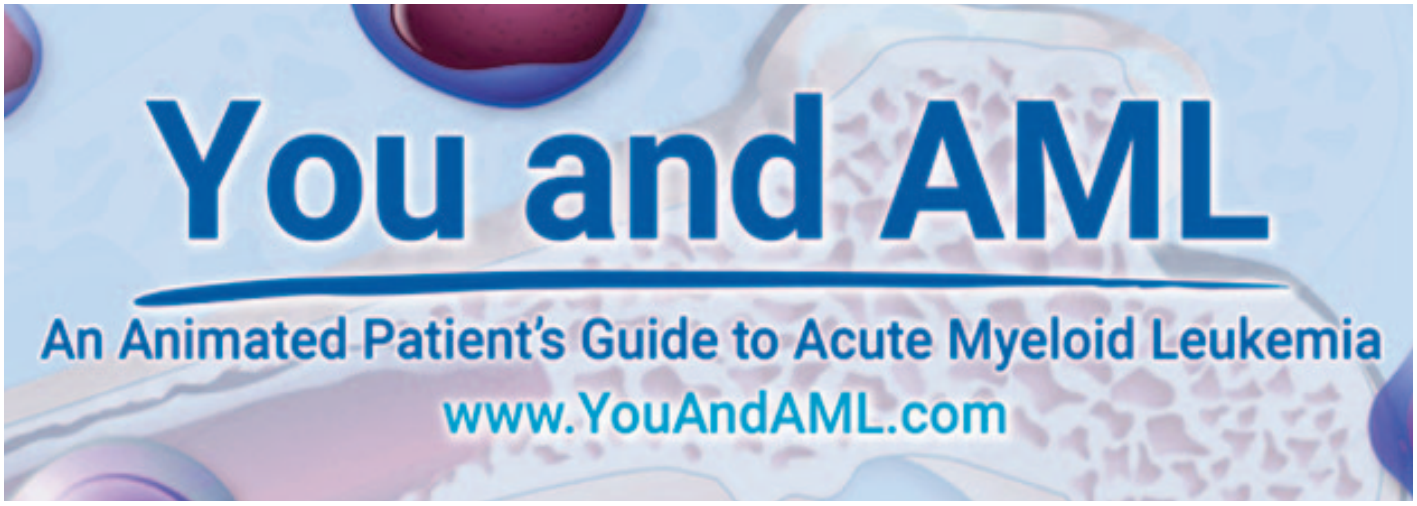
YOU AND AML: AN ANIMATED PATIENT'S GUIDE TO ACUTE MYELOID LEUKEMIA

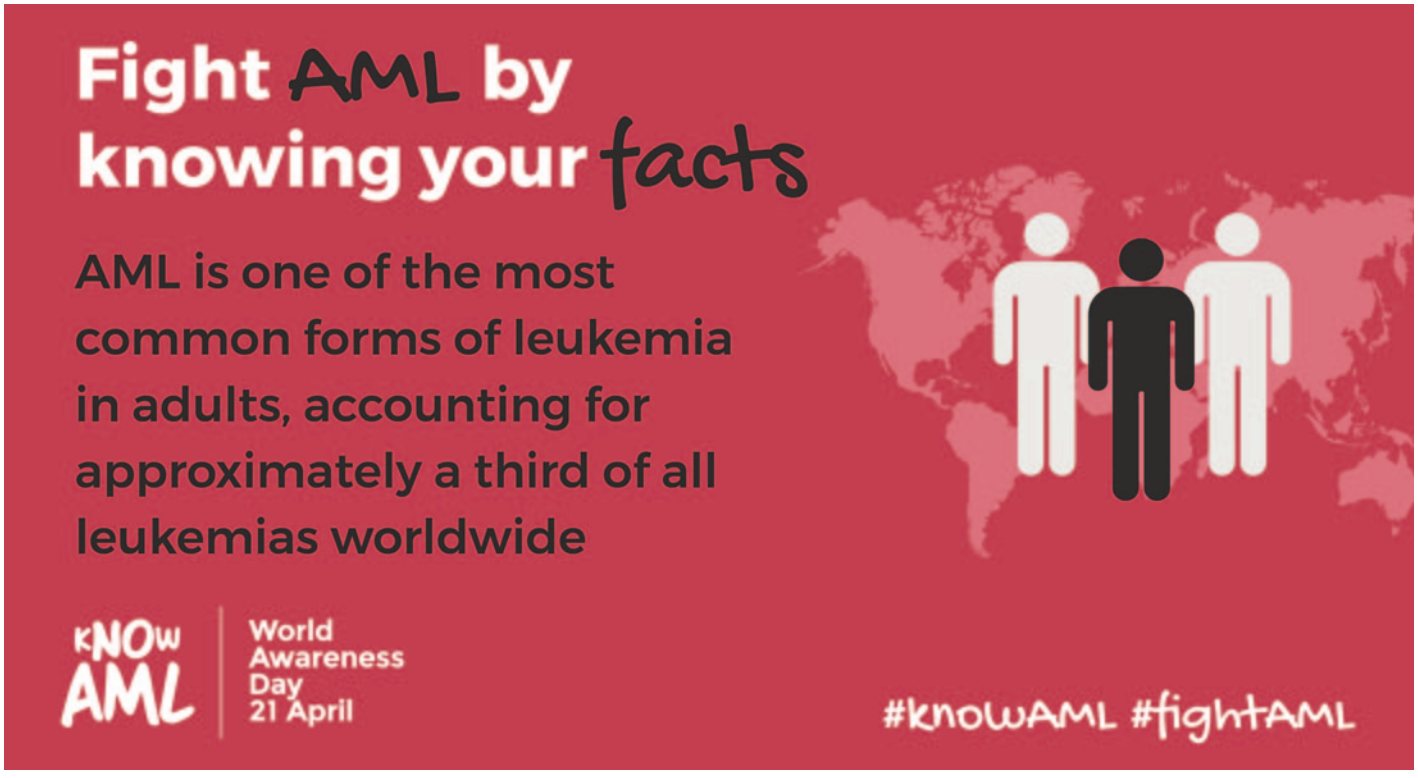
This resource is intended for patients with acute myeloid leukemia (AML). You will find expert advice about AML, AML with myelodysplasia-related changes (AML-MRC) and treatment-related AML (tAML) to help you discuss key issues with your healthcare provider and make important decisions related to management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

"YOU AND AML" CONTAINS 4 LEARNING MODULES:

- Understanding AML
- Understanding AML-MRC and tAML
- Diagnosing AML, AML-MRC and tAML
- Treatment of AML

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





U.S. FOOD AND DRUG ADMINISTRATION APPROVES ONUREG® (AZACITIDINE TABLETS), A NEW ORAL THERAPY, AS CONTINUED TREATMENT FOR ADULTS IN FIRST REMISSION WITH ACUTE MYELOID LEUKEMIA

In the QUAZAR® AML-001 study, Onureg significantly improved overall survival by nearly 10 months compared to placebo (24.7 months [95% CI: 18.7 to 30.5] vs. 14.8 months [95% CI: 11.7 to 17.6]) in patients with acute myeloid leukemia in first remission

PRINCETON, N.J., SEPTEMBER 1, 2020 – Bristol Myers Squibb (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved Onureg® (azacitidine 300 mg tablets, CC-486) for the continued treatment of adult patients with acute myeloid leukemia (AML) who achieved first complete remission (CR) or CR with incomplete blood count recovery (CRi) following intensive induction chemotherapy and who are not able to complete intensive curative therapy. AML is one of the most common acute leukemias in adults.

The approval is based on results from the pivotal Phase 3 QUAZAR® AML-001 study in which treatment with Onureg resulted in a statistically significant and clinically meaningful improvement in overall survival (OS), the study's primary endpoint, of nearly 10 months compared to placebo. Median OS from time of randomization was greater than two years (24.7 months; 95% Confidence Interval [CI]: 18.7 to 30.5) among patients who received Onureg compared to 14.8 months (95% CI: 11.7 to 17.6) among patients receiving placebo (Hazard Ratio [HR]: 0.69, 95% CI: 0.55 to 0.86; p=0.0009). Onureg was continued until disease progression or unacceptable toxicity. Onureg has warnings and precautions for risks of substitution with other azacitidine products, myelosuppression, increased early mortality in patients with myelodysplastic syndromes (MDS) and embryo-fetal toxicity. Due to substantial differences in the pharmacokinetic parameters, Onureg should not be substituted for intravenous or subcutaneous azacitidine as it may result in a fatal adverse reaction. New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received Onureg, respectively. Febrile neutropenia occurred in 12% of patients. Complete blood counts should be monitored, dosing should be modified as recommended and standard supportive care should be provided if myelosuppression occurs. Enrollment was discontinued early in the study AZA-MDS-003 due to a higher incidence of early fatal and/or serious adverse reactions in the Onureg arm compared with the placebo arm. Treatment of MDS with Onureg is not recommended outside of controlled trials. Onureg can cause fetal harm when administered to a pregnant woman.

"Continued treatment with Onureg demonstrated an overall survival benefit in adults with AML who had achieved first complete remission in the QUAZAR® AML-001 study and, notably, it has the potential to do this in a convenient manner, given its once daily oral formulation,"1 said Andrew Wei, MBBS, Ph.D., QUAZAR® AML-001 lead investigator, Alfred Hospital and Monash University, Melbourne, Australia. "This approval should help establish continued treatment with Onureg as a standard component of AML therapy for adults who achieved first complete remission following chemotherapy and who cannot proceed to intensive curative therapy, like hematopoietic stem cell transplant."

"The FDA approval of Onureg is the culmination of over a decade of research and 13 pre-clinical and clinical trials. We are grateful to the patients, families and caregivers who participated in and supported these trials, and who ultimately made today's advancement possible," said Giovanni Caforio, M.D., chairman and chief executive officer, Bristol Myers Squibb. "This milestone is representative of our commitment to helping patients with hard-to-treat cancers live longer, and the approval of Onureg as an oral therapy option for patients is more relevant now than ever as the world continues to navigate the COVID-19 pandemic."

The New Drug Application was granted Priority Review Designation by the FDA, and a Marketing Authorization Application (MAA) for this indication was validated by the European Medicines Agency in May 2020.

QUAZAR® AML-001 PIVOTAL TRIAL RESULTS

The FDA approval of Onureg is based on data from QUAZAR® AML-001, a Phase 3, international, randomized, double-blind study.1 Eligible patients were ages 55 years or older, had AML, were within four months of achieving first CR or CRi following intensive induction chemotherapy with or without consolidation treatment (per investigator preference prior to study entry), and were not candidates for hematopoietic stem cell transplant (HSCT) at the time of screening. The study enrolled 472 patients, randomized 1:1 to receive either Onureg 300 mg (n=238) or placebo (n=234) orally, once daily, for 14 days of a 28-day cycle, plus best supportive care.

Results showed continued treatment with Onureg significantly improved OS in patients with AML in remission compared to placebo, establishing Onureg as a new continued therapy option for patients who are not able to complete intensive curative therapy, including HSCT. Median OS, the primary endpoint, from time of randomization was greater than two years (24.7 months; 95% CI: 18.7 to 30.5) in the Onureg arm compared to 14.8 months for placebo (HR: 0.69, 95% CI: 0.55 to 0.86; p=0.0009). A subgroup analysis showed consistency in the OS benefit for patients in either CR or CRi. The median duration of treatment was 12 cycles (1 to 82) for Onureg and 6 cycles with placebo (1 to 76).

Serious adverse reactions occurred in 15% of patients who received Onureg. Serious adverse reactions in ≥2% of patients who received Onureg included pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received Onureg. The most common adverse reactions with Onureg versus placebo were nausea (65%, 24%), vomiting (60%, 10%), diarrhea (50%, 21%), fatigue/asthenia (44%, 25%), constipation (39%, 24%), pneumonia (27%, 17%), abdominal pain (22%, 13%) arthralgia (14%, 10%), decreased appetite (13%, 6%), febrile neutropenia (12%, 8%), dizziness (11%, 9%) and pain in extremity (11%, 5%). Of patients who received Onureg, permanent discontinuation due to an adverse reaction occurred in 8% of patients.

Results from the QUAZAR® AML-001 trial were first presented at the American Society of Hematology (ASH) Annual Meeting in December 2019.

ABOUT ONUREG®

Onureg, the first and only FDA-approved continued AML therapy for patients in remission, is an oral hypomethylating agent that incorporates into DNA and RNA. The main mechanism of action is thought to be hypomethylation of DNA, as well as direct cytotoxicity to abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for cell differentiation and proliferation.

VENCLEXTA® (VENETOCLAX) RECEIVES FDA FULL APPROVAL FOR ACUTE MYELOID LEUKEMIA (AML)

The FDA approval of VENCLEXTA for newly-diagnosed AML patients who are ineligible for intensive chemotherapy is supported by data from a series of trials including two Phase 3 trials – VIALE-A (M15-656) and VIALE-C (M16-043)

The Phase 3 VIALE-A trial showed that significantly more patients treated with VENCLEXTA in combination with azacitidine achieved complete remission and lived longer versus patients treated with azacitidine alone

AML is one of the most aggressive and difficult-to-treat blood cancers with a very low survival rate

The National Comprehensive Cancer Network (NCCN) guidelines recommend the VENCLEXTA and azacitidine combination as a Category 1 Preferred AML treatment regimen for patients ineligible for intensive chemotherapy

NORTH CHICAGO, Ill., OCT 16, 2020 /PRNewswire/ — AbbVie (NYSE: ABBV) today announced that the U.S. Food and Drug Administration (FDA) has provided full approval to VENCLEXTA® (venetoclax) in combination with azacitidine, or decitabine, or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. The approval is supported by data from the Phase 3 VIALE-A (M15-656) and VIALE-C (M16-043) studies and updated data from the Phase 1b M14-358 and the Phase 1/2 M14-387 studies. The FDA previously granted accelerated approval to VENCLEXTA for this indication in 2018.

"AML is a complex and challenging disease with generally low survival rates. This approval is significant because data from our VIALE-A trial has shown that newly-diagnosed patients, who cannot undergo intensive chemotherapy, lived longer when treated with VENCLEXTA plus azacitidine than those treated with azacitidine alone," said Mohamed Zaki, M.D., Ph.D., vice president and global head of oncology development, AbbVie. "This trial also provides physicians more information for managing patients – from treatment initiation, to assessing response and management post disease remission."

Positive overall survival (OS) data seen at an interim analysis of the VIALE-A trial led to an early submission supporting the FDA approval of VENCLEXTA in AML. The trial showed patients on the active regimen of VENCLEXTA plus azacitidine achieved a 34% reduction in the risk of death compared to azacitidine in combination with placebo (Hazard Ratio [HR]=0.66 [95% CI: 0.52-0.85], p<0.001). The median OS for patients in the VENCLEXTA arm was 14.7 months (95% CI: 11.9, 18.7) versus 9.6 months in the placebo arm (95% CI: 7.4, 12.7). Additionally, patients in the VENCLEXTA plus azacitidine arm achieved a complete remission (CR) rate of 37% (95% CI: 31%, 43%) with a median duration of CR of 18.0 months (95% CI: 15.3, -) compared with patients in the placebo plus azacitidine arm with a CR rate of 18% (95% CI: 12%, 25%) with a median duration of CR of 13.4 months (95% CI: 8.7, 17.6). The observed safety profile was generally consistent with the known safety profile of VENCLEXTA in combination with azacitidine. For patients taking VENCLEXTA in combination with azacitidine, the most frequent serious adverse reactions (ARs; ≥5%) at first use were febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%) and hemorrhage (6%).

Data from VIALE-A was presented for the first time as a late-breaking abstract at the 25th European Hematology Association (EHA) Annual Congress in June 2020 and recently published in the *New England Journal of Medicine*.

"For far too long, people with AML had very few treatment options, aside from very intense chemotherapy. Today's news continues the progress of bringing more treatment options to patients with this devastating disease," said Lee Greenberger, Ph.D., chief scientific officer of The Leukemia & Lymphoma Society.

Data from the VIALE-C trial was presented at both the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting and the EHA Annual Congress and previously published in *Blood*. The median OS for VENCLEXTA in combination with LDAC was 7.2 months (95% CI: 5.6, 10.1) and 4.1 months for LDAC in combination with placebo (95% CI: 3.1, 8.8). The HR for the primary endpoint of OS was 0.75 (95% CI: 0.52-1.07; p=0.114). The trial did not meet its primary endpoint of statistically significant improvement of OS for patients with AML who are ineligible for intensive chemotherapy at the time of the planned analysis. Efficacy was based on the rate of CR and duration of CR with supportive evidence of rate of CR + complete remission with partial hematologic recovery (CR+CRh), duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. In the VENCLEXTA arm, the most frequent serious ARs were (≥10%) pneumonia (17%), febrile neutropenia (16%) and sepsis (excluding fungal; 12%).

AML is an aggressive and difficult-to-treat blood cancer with a low survival rate. Despite recent advances in available therapies, the five-year survival rate for patients diagnosed with AML remains approximately 29%. AML typically worsens quickly, and due to age or comorbidities, not all patients are eligible to receive intensive chemotherapy.

The FDA reviewed the clinical data under the FDA's Real-Time Oncology Review (RTOR) pilot program and Project Orbis initiative, which led to approval in the U.S. in October 2020. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. The U.S. FDA, the Australian Therapeutic Goods Administration, Swissmedic, Health Canada and ANVISA (Agência Nacional de Vigilância Sanitária) collaborated on this review based on the marketing applications submitted in their respective countries.

Venetoclax 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 THE VIALE-A AND VIALE-C CLINICAL TRIALS VIALE-A (M15-656) PHASE 3 TRIAL[1,7]

A total of 431 patients were randomized in the double-blind, placebo-controlled, multicenter, Phase 3 VIALE-A trial, which evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine (n=286) in patients with AML who are ineligible for standard induction therapy versus azacitidine in combination with placebo (n=145). The primary endpoint was OS.

The VENCLEXTA plus azacitidine combination showed a median OS of 14.7 months (95% CI: 11.9, 18.7) versus 9.6 months (95% CI: 7.4, 12.7) with azacitidine in combination with placebo. The study also met its secondary endpoints, with the VENCLEXTA combination arm resulting in a CR rate of 37% (95% CI: 31, 43) and a CR+CRh rate of 65% (95% CI: 59, 70) compared to a CR rate of 18% (95% CI: 12, 25) and a CR+CRh rate of 23% (95% CI: 16, 30) in the placebo arm. The median time to first response of CR or CRh was 1.0 months (range: 0.6 to 14.3 months) with VENCLEXTA in combination with azacitidine. The median duration of treatment was 7.6 months (range: <0.1 to 30.7 months) in the VENCLEXTA arm.

The most frequent ARs (≥30% with a difference between arms of ≥5%) for patients taking VENCLEXTA in combination with azacitidine were mostly hematologic and gastrointestinal in nature and consisted of, nausea (44%), diarrhea (43%), febrile neutropenia (42%), musculoskeletal pain (36%), fatigue (31%), and vomiting (30%). Serious adverse reactions were reported in 83% of patients in the VENCLEXTA arm, with the most frequent serious ARs (≥5%) being febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%) and hemorrhage (6%).

VIALE-C (M16-043) PHASE 3 TRIAL

A total of 211 patients were enrolled and treated in the randomized, double-blind, placebo-controlled, multicenter, Phase 3 VIALE-C trial, which evaluated the efficacy and safety of VENCLEXTA in combination with LDAC (n=143) versus placebo with LDAC (n=68). The primary endpoint was OS.

VENCLEXTA in combination with LDAC did not significantly improve OS versus placebo in combination with LDAC. The HR for OS was 0.75 (95% CI: 0.52, 1.07); p-value 0.114. The median OS for VENCLEXTA in combination with LDAC arm was 7.2 months (95% CI: 5.6, 10.1) and for PBO+LDAC arm was 4.1 months (95% CI: 3.1, 8.8).

Efficacy was based on the rate of CR and duration of CR with supportive evidence of rate of CR+CRh, duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The CR rate in the VENCLEXTA in combination with LDAC arm was 27% (95% CI: 20%, 35%) with a median duration of CR of 11.1 months (95% CI: 6.1, -), and the CR rate in the placebo arm was 7.4% (95% CI: 2.4%, 16%) with a median duration of CR of 8.3 months (95% CI: 3.1, -). The CR+CRh rate in the VENCLEXTA in combination with LDAC arm was 47% (95% CI: 39%, 55%) and in the placebo arm was 15% (95% CI: 7.3%, 25%) with a median duration of CR+CRh of 11.1 months with VENCLEXTA in combination with LDAC and 6.2 months with LDAC in combination with placebo. The median time to first response of CR or CRh was 1.0 month (range: 0.7 to 5.8 months) with VENCLEXTA in combination with LDAC.

The most frequent AR (≥30% with a difference between arms of ≥5%) for patients taking VENCLEXTA in combination with LDAC was nausea (42%). Serious ARs were reported in 65% of patients in the VENCLEXTA arm, with the most frequent (≥10%) being pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%).

ABOUT VENCLEXTA® (venetoclax)

VENCLEXTA® (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 targets the BCL-2 protein and works to help restore the process of apoptosis.

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. Together, the companies are committed to BCL-2 research and to studying venetoclax in clinical trials across several blood and other cancers. VENCLEXTA is approved in more than 50 countries, including the U.S.

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.

JAZZ PHARMACEUTICALS LAUNCHES INITIATIVE TO HELP EDUCATE PEOPLE LIVING WITH RARE FORM OF LEUKEMIA

Program aims to empower patients and their loved ones living with secondary acute myeloid leukemia or myelodysplastic syndromes through powerful tools and real stories

DUBLIN, SEPTEMBER 17, 2020 — Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced the launch of Find the Right Fit (FindTheRightFit-sAML.com), a U.S. patient education program developed in consultation with the Myelodysplastic Syndromes (MDS) Foundation, Inc. and the Cancer Support Community focused on empowering people affected by secondary acute myeloid leukemia (sAML) and MDS.

Within the hematology oncology community, certain patient groups face especially difficult odds. In particular, patients newly diagnosed with sAML and related blood disorders have few resources focused on disease education and managing daily life that are dedicated to this community. As a subtype of AML, which has the lowest survival rate of all leukemias, sAML has a particularly poor prognosis.

"During Blood Cancer Awareness Month, we reflect on the unwavering strength of patients, caregivers, families and healthcare providers battling or impacted by blood cancer," said Kim Sablich, executive vice president and general manager of North America at Jazz Pharmaceuticals. "Find the Right Fit was created with the understanding that an sAML diagnosis can be overwhelming, but that education can help inform optimal treatment plans that work best for each individual patient."

Find the Right Fit—Nagivating sAML offers patients and their caregivers a powerful collection of tools, including articles, videos, and patient stories, intended to educate on the science behind sAML, provide information on which subtypes patients should be tested for, and offer resources regarding treatment options and coping strategies. The program also shares the stories of patients, which are featured to help those impacted by sAML relate to the various experiences and perspectives that exist within the community.

"In addition to the support available through the Cancer Support Community and the Myelodysplastic Syndrome Foundation, Inc., we are pleased that Find the Right Fit adds resources and information to help inform and inspire people during this critical point in time," said Linda Bohannon, MSM, BSN, RN, president of the Cancer Support Community.

Making up approximately 30 percent of AML cases, sAML can spread quickly and requires a specialized treatment approach, which is why it is important that patients know what to discuss with their doctors in order to pursue the route best suited for their unique needs. By listening to advocacy groups, patients and their care teams, Jazz hopes to continue evolving the Find the Right Fit program to better serve those living with an sAML or MDS diagnosis.

"With 16 years of experience at the MDS Foundation, I understand how overwhelming a cancer diagnosis can be for a family," said Tracey Iraca, executive director of the MDS Foundation, Inc. "The foundation is proud to partner with Jazz on the launch of Find the Right Fit – Navigating sAML, to help provide patients with vital information to navigate a rare disease diagnosis."

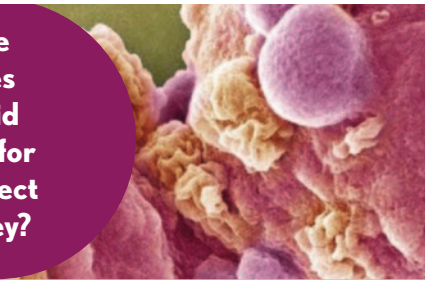
ABOUT JAZZ PHARMACEUTICALS

Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharmaceutical company dedicated to developing and commercializing life-changing medicines that transform the lives of patients with serious diseases – often with limited or no options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in key therapeutic areas. Our focus is in neuroscience, including sleep and movement disorders, and in oncology, including hematologic malignancies and solid tumors. We actively explore new options for patients including novel compounds, small molecule advancements, biologics and innovative delivery technologies. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in more than 90 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

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

CONTRIBUTIONS TO THE MDS FOUNDATION

THANK YOU

The MDS Foundation relies on gifts to further its work. We would like to acknowledge the generosity of the following individuals and organizations that have recently provided gifts to the Foundation:

Sara Maureen Abbott
Ingeborg Ellen Adams
Emily Adney
Mefi Alapat
Henry Albert
Lenore Alexander
Jeanne Allen
Maria Allen
Meredith Alvarez
Nicole Amar
Mimi Andersen
Kate Anderson
Michelle Anderson
Kim Anic
Lisa Anzisi
Alison Armstrong
Keith Arnold
Karen Ash
Margaret Ault
Patty Aversa
Sivani Babu
Emily Backels
Ara and Leslie Bagdasarian
George and Pamela Baker
Elissa Baldwin
Susan Balezentis
Margaret Ballinger
Amanda Bappert
Ann Barabush
Kevin Barenblat
Suzanne Barker
Pam Barrows
Edward R. Baureis
CL Beach
Michelle Beccio
Myra Becker
Art and Nicole Bedard
Elitza Belcheva
Stephanie Bell
Virginia Belling
Soraya Benitez
John and Carol Bennett
Arnold & Barbara Bennigson
Susanne Bentley
Ruth and Howard Berkowitz
Marvin Berlin
Marc Bernanke
John and Karen Berner
John Berry
Laura Biel
Nancy and George Bierer
Eleanor Bird
Lawrence Bitter
Bob and Liz Bitterman
Mark Blackmon
Danielle Blair
Dawna Blake
Elizabeth Blasko
Kari Bliss
Bob and Roberta Bloch
Andrew and Yvette Block
Amber Bloomer
Kenneth Boardman
Hedda Boege
Peter and BJ Boland
Mary Bonen
Jennifer Bonura
Christine Booher
Sieg and Edith Borck
Marjorie Borden
Michelle Borza
Silviu Borza
Viorel Borza
Sabina Borza-Flynn
Barbara Bosse
Sheri-Ann Boudreau
Glen and Lequita Bowen
Claudia Bowes
Walt and Jane Brandt
Gretchen Breau
Cindy Breese
David Bremm
Katherine Brenton
Jerri Bresnahan
Stephen Brill
Patricia Brilliant
David and Nancy Bristol
Jaclyn Brletic
Rhonda Broadbent
Eva Brodkin
Kate & Alexander Brodsky
Louise Brooks
Priscilla Brostek
Nicole Brown
Melissa Brumback
Dennis and Barbara Bruns
Jason Bryant
Pamela and Gary Buccafurri
Donna Buckley
Eugene Buckley
Valerie Budziak
Jennifer Bugara
Kayleigh Bull
Tamara Bullard
Daryl Burd
Thea Burgess
Alan and Gayle Burgess
Ruth Burgess
Richard and Ann Burgy
Fred Burke
Nicholas Burke
Robert Burke
Thomas Burke
Janet Burleson
Ken and Sandi Burrows
Michael R. & Carolyn Buxton
Chelsey Byrne
Marie Byrne
Amanda Cadle
Helen Calvi
Ashley Cámara
Malvina Camhi
Susan Campbell
Tom and Dorel Canty
Faruk Capan
Lori Cappello
Lisa Careccia
Nicole Carlson
Antonia Carroll
David, Betty & Tom Carroll
Thomas Carroll
Janet and Locke Carter
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Linda Case
Carlos Castillo
Rachel Castor
Marla Catron
Meghan Chambers
Nancy Ann Charest
Cheryl & Jordan Cheifetz
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Lori Childs
Zachary Chippin
Joseph & Micheline Chisholm
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Yuki Chorney
Cindy Ciccarelli
Teru Clavel
Diane Clifford
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Paul Cohen
Thelma Cohen
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Valerie and Jack Coleman
BD and Patti Colen
Christine Condino-Mecklenburg
Nora Conlin
Deeann Connor
Michaelina Considine
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Barbara Costigan
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Maida Crocicchia
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Alia Dixon
Evan Dixon
Pamela M. Doane
Amy Dolhay
Thomas Dollinger
Tanya Dominguez
Matthew Donohoe
The Dooley Family
Jerry and Harriet Dorf
Julie Dorf
Stan Dorf
Sarah Dougherty
Patricia Dow
Donald & Antje Draganski
Barbara Drago
David and Millie Dubrow
Edward Duffy
Bonnie Dunham

CONTRIBUTIONS TO THE MDS FOUNDATION

Judith Dunham
Pamela Dunhom
Karen Dupree
Patrick Dwyer
Tyler Dycus
John Dyson
Henry Earl
Denise Mirena Eaton
Louisa Eberle
Kathy Ecklund
Doris Edwards
Robyn Eiseman
John Ellicott
Patrick Ellicott
Tara Ellicott
Charles Emala, Jr.
Lauri Emerton
Cathy Eng
Amanda English
Nancy English
Catherine Erdelyi
Pat Erikstrup
Ron and Janet Ernst
Greg Eskinazi
Stephen Fabina
Lawrence & Roberta Fachler
Judith Fahy
Sharon Fair
Joe Famiglietti
Sharla Farley
John and Alyssa Fasano
Shazma Fazal
Loretta Feldman
J. Fell
Carol and Arnie Feltoon
Daniel Fernandez
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Agnieszka Gorska
Paul and Eleanor Gorski
Ana Grandinetti
Linda Grandolfo
Rachi Grant
Terry and Suzy Gray
Steven Greenberg
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HOW TO FIND OPEN MDS CLINICAL TRIALS

SEARCH OPEN STUDIES AT THE MDS FOUNDATION

Clinical trials are a final and crucial step on the path to developing better treatments for patients… and we now have the opportunity to participate in more clinical trials than ever, specifically for MDS.

Historically, 85% of all clinical trials face delays and 30% never get off the ground because of lack of volunteers.

The good news is that you now have the power to propel clinical research towards breakthroughs that MDS patients can feel in their everyday lives.

Learn which studies are currently seeking participants at www.mds-foundation.org/clinical-trial-announcements.

SEARCH A NATIONAL REGISTRY OF CLINICAL TRIALS

Search the NIH registry of MDS clinical trials underway in the United States and beyond at ***www.clinicaltrials.gov.***

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IVOSIDENIB (AG-120)
NEW CLINICAL TRIAL NOW ENROLLING

Do You Have MDS with an IDH1 Mutation?

If you have **relapsed/refractory MDS** with an **isocitrate dehydrogenase-1 (IDH1) mutation**, you may be eligible for this trial.

For more information regarding this study, please visit www.clinicaltrials.gov (NCT03503409).

FOR ADDITIONAL INFORMATION ON THE TRIAL OR FOR SITES:

Please contact Agios Medical Information:
E-mail: medinfo@agios.com
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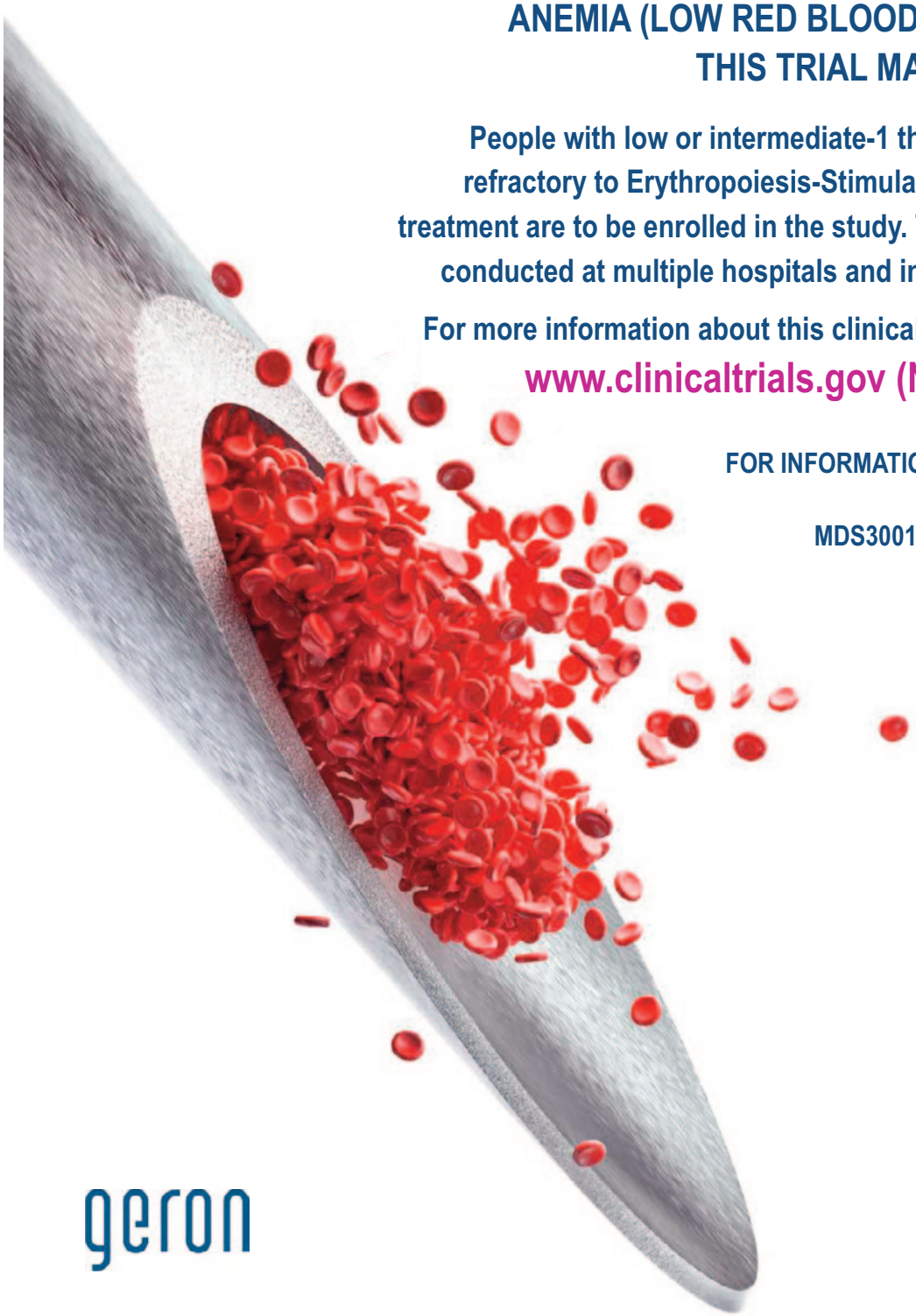
LOWER-RISK MDS CLINICAL STUDY NOW ENROLLING

IF YOU NEED BLOOD TRANSFUSIONS DUE TO ANEMIA (LOW RED BLOOD CELL COUNTS), THIS TRIAL MAY BENEFIT YOU.



People with low or intermediate-1 that is relapsed or is refractory to Erythropoiesis-Stimulating Agents (ESAs) treatment are to be enrolled in the study. This study is being conducted at multiple hospitals and institutions globally.

For more information about this clinical study, please visit www.clinicaltrials.gov (NCT02598661).

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