

MDS NEWS HIGHLIGHTS

FROM THE GUEST EDITOR'S DESK

- **MicroRNA Signatures in Myelodysplastic Syndrome**
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PLAN TO ATTEND

14TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

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Guest Editorial: MicroRNA Signatures in Myelodysplastic Syndrome



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Myelodysplastic Syndrome – Incidence, Outcomes, Clinical Picture and Treatment

Myelodysplastic syndrome (MDS) represents the group of malignant hematologic disorders with dysplasia of one or more blood-forming cells in the bone marrow (Brunner et al., 2008). It is clinically reflected in one or several cytopenias and with the tendency of transformation into acute myeloid leukemia (AML). According to the American register SEER, incidence of MDS is 3.4 cases in 100,000 inhabitants with the increase of incidence depending on the age, with the aging median of 76 years during the diagnosis (Ma et al., 2007). It is expected that every year more than 10,000 cases of MDS are diagnosed, which makes it the most frequent hematologic neoplasm in elderly people. Prognosis of these patients is serious, i.e. the possibility that the patient can live up to three more years is only 35%. The most frequent cause of death in these patients is transformation into AML (46.6%), infections (27%) and bleeding (9.8%) (Nachtkamp et al., 2016).

Myelodysplastic syndrome (MDS) represents the group of malignant hematologic disorders with dysplasia of one or more blood-forming cells in the bone marrow.

Diagnosis of MDS is established on the basis of cytological puncture, i.e. the biopsy of bone marrow by defining the sub-type according to the World Health classification (Brunner et al., 2008). The key medical test is the karyogram due to the frequency of chromosome anomalies in MDS, and later on due to risk stratification. At the time of diagnosis, the patients are split into groups according to the risk for leukemic transformation. The oldest and the most frequent prognostic index is IPSS (Greenberg et al., 1997). The mentioned index uses the number of cytopenias, cytogenetic group and number of bone marrow blasts. It groups the patients in 4 special categories with regards to survival: “low” (survival median 5.7 years), “INT-1” (survival median 3.5 years), “INT-2” (1.2 years) and “high” (survival median 0.4 years). Further importance of this index is based on the fact that patients are treated differently according to the risk group. Recently, the mentioned index is revised in R-IPSS which uses the following variables: hemoglobin, number of neutrophils, number of thrombocytes, 5 cytogenetic groups, and number of bone marrow blasts (Greenberg et al., 2012). This index splits the patients in 5 different groups according to survival from the “very low” group with

a survival median of 8.8 years, to the “very high” group with a survival median of only 0.8 years. According to characteristics, this index is better than IPSS and it is expected that it will be introduced in standard clinical practice.

One curative option in these patients is the allogeneic transplantation of bone marrow. However, due to their age, the majority of the patients are not considered as candidates for this procedure due to the high mortality rate related to the transplantation procedure itself (Koencke et al., 2015). The patients are treated with regards to risk stratification. The treatment option for patients in the “high” and “INT-2” group is hypomethylating agent 5-azacytidine which showed better survival (with survival median of 24.5 months) when compared to the conventional therapy (with survival median of 15 months) (Fenaux et al., 2009).

On the basis of this study, 5-azacytidine has been approved by the European Medicines Agency (EMA). It also represents the gold standard in treating the high-risk patients in Croatia.

The low-risk patients are most frequently treated by compensations of blood derivatives. Anemia is the most frequent cytopenia and may be treated successfully with erythropoietic stimulating agents (ESAs). Decision about the group of patients who should respond to ESAs is made after analyzing the IPSS-R, endogenous erythropoietin levels, and transfusion independence. If ESA treatment fails, the available options may include lenalidomide, hypomethylating agents, and clinical trials.

Thrombocytopenia has been treated in experimental clinical trials with thrombomimetic agents that have shown good efficacy, but still not approved in clinical practice due to some safety

concern. Neutropenia in low-risk MDS is taken care of by growth factor support, while the immunosuppressive treatments are indicated mainly for pancytopenic, hypoplastic lower-risk MDS. The only curative option is stem cell transplant, and should be chosen for fit and younger MDS patients after detailed evaluation of possible risks and benefits (Santini, 2016).

(Epi)genetic pathogenesis of MDS

Two studies have tried to define molecular pathogenesis of MDS. The first study included 738 patients with MDS, sequencing 111 genes from peripheral blood or bone marrow (Papaemmanuil et al., 2013). 74% of patients have had at least one oncogenic mutation, 43% of patients have had two or more, while 10% of patients have had more than three oncogenic mutations. The frequency of certain mutations depended on the time function. SFRB1 mutation was an early event which preceded the occurrence of TET2 mutation (the most frequent mutation at MDS) with consequential occurrence of other specific mutations. This scientific discovery has led to hypothesis that clonal or consequential sub-clonal mutations influence the outcomes of MDS in the same manner. The second hypothesis was that the number of gained mutations itself during the disease influences the outcome. The patients with a larger number of gained “driver” mutations have had worse outcomes in the light of total survival or survival without leukemia transformation.

On the basis of this study, we may conclude that MDS by its very nature is a time function of the clonal or sub-clonal mutations, which reflects its dynamic pathogenic flow. The other study determined through the molecular proliferation of the frequency of 111 genes in 941 patients with MDS (Haferlach et al., 2014). After multi-variant analysis, 14

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genes are included in the model which could have anticipated the outcomes independently from the existing scores with genes, which vary from modification of chromatin to histonic modification. To conclude, the mutations of genes which take part in oncogenesis of MDS may be split into the following groups: RNA modification, DNA methylation, transcription, modification of chromatin, kinases, Cohesin route, RAS route and DNA recovery.

However, with regards to the partly disappointing scope of human genome, the focus of scientific circles has moved to epigenome. MDS is a disorder characterized by aberrant hypomethylation of CpG islands, which is connected to mutation of the TET2 gene responsible for regulation of methylation (Ko et al., 2010). Furthermore, aberrant mutilation differs with regards to the type of MDS, i.e. it is more expressed in high-risk forms (Jiang et al., 2009). Zhao et al. (2014) have identified the model of 6 aberrant mutilated genes linked to a worse outcome of the patients with MDS. The mentioned data indicate the rationale of the activity of 5-azacytidine in MDS. On the other hand, EZH2, the gene which encodes the histone methyltransferase, is often mutated in MDS and is connected to worse outcomes by implicating the alternated histonic

modification as one of the events in pathogenesis of MDS (Nikoloski et al., 2010). To conclude, in addition to genetic mutations, epigenetic mutations have a significant role in the appearance of malignant clone and transformation of MDS to AML. This makes it, according to certain authors and in our opinion, the prototype of epigenetic disorder (Issa et al., 2013, Milunović et al., 2016).

MicroRNA: History and Function

Pivotal study of microRNA (miRNA) comes from Lee et al. (1993) on the model of *C. elegans*. The authors have shown that lin14 of the gene does not encode protein, but two small molecules of RNA are made, of the size 22 and 61 bases. The smaller molecule links to 3'UTR region of mRNA lin14 gene and inhibits its translation. This finding has been welcomed with doubts from the scientists side, up to the isolation of miRNA gene let7, which linked to 3'UTR region of 4 different genes to *C. elegans* with consequential inhibition and influence on physiological development of this model (Reinhart et al., 2000). In human conditions, miRNA has firstly been analyzed in chronic lymphocytic leukemia (Calin et al., 2002). In patients with mutation 13q14, decreased levels of miRNA15 and 16 has been found. These studies brought miRNA in focus of epigenomics with rapid growth of discovering new miRNA in different diseases; so far, 3,786 miRNA are known with 22,563 targeted genes and 366,181 interactions (Lu et al., 2008, Chou et al., 2016).

The canonical linkage of miRNA linked to AGO proteins and Dicer within “RNA induced silencing” complex (RISC) for mRNA represents 3'UTR region mRNA (Ha et al. 2014, Milunović et al., 2016). Primary function is the inhibition of translation in its initiation during the recognition 5' CAP side of mRNA. RISC with the help of its numerous proteins also leads to inhibition of translation so that it

disables 60S ribosome unit in creating translation complex and inhibits 80S complex. The other way of inhibiting translation through miRNA is deadenylation with the help of RISC complex. The first phase is deadenylation, while the second phase is shortening of polyA tail mRNA. The stated mRNA is stored as inactive in cytoplasm, but its dissipation with intracellular exonucleases is also possible.

Circulating MicroRNA

Classic paradigm microRNA (miRNA) was that they are linked to a cell, i.e. the tissue by the occurrence of two pivotal theses in 2008 (Chim et al., 2008, Lawrie et al., 2008). In the first thesis of Chim et al. (2008), miRNA specific for placenta maternal plasma were found. In the second thesis it was shown that three miRNA are specific for diffusion B giant-cell lymphoma increased in the serum of the patients as opposed to healthy controls and their prognostic importance is also shown. The authors have claimed that the circulating miRNA could represent new non-invasive biomarker at diseases. These studies have posed questions on the origin and function of the circulating miRNA (Turchinovich et al., 2012).

In order to avoid degradation from serum RNA-s, the circulating miRNA in RISC complex may be exported from the cell in the form of micro-vesicles, exosomes and apoptotic bodies (Hunter et al., 2008, Valadi et al. 2007, Zernecke et al., 2009). Surprisingly, the fourth most frequent mechanism is independent of vesicles and is prevalent in circulating miRNA; it is also linked to AGO2 proteins (Turchinovich et al., 2011). It should be mentioned that for majority of these transports the mechanism of regulation is not known, while miRNA-AGO2 complex is most probably the consequence of cell death, i.e. they are spontaneously released in circulation. Circulating miRNA has more functions than inter-cellular communication, from immune-modulation

to proliferation and “knockout” cancer suppressor (Pegtel et al., 2010, Mittelbrunn et al., 2011, Skog et al., 2008, Oshima et al., 2010). Function of the largest part of circulating miRNA linked to AGO2 protein is not known. Certain authors make a hypothesis that it does not have physiologic function with regards to stable kinetics and detection throughout a longer period of time (Kosaka et al., 2010). This implicates that the majority of circulating miRNA actually reflects the tissue from which it was released, which makes it a potential candidate for non-invasive biomarker. We have chosen the circulating miRNA as a starting point for the proposed project.

MicroRNA in Oncogenesis

MiRNA in oncogenesis may be split into two groups: cancer suppressors and oncogenes (Berindan-Neagoe et al., 2014). One of most frequently studied miRNA, miRNA21, in the mouse model leads to pre-oncologic B cell phenotype which makes this miRNA to be oncogene (Medina et al., 2010). On the other side, deletion of 13q14 locus in chronic lymphocyte leukemia leads to deletion of LEU2/miR-15a/16-1 group and B clonal proliferation, which indicates miRNA may also be a cancer suppressor (Klein et al., 2010).

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It should be stressed here that miRNA takes part in almost all characteristics of the malignancy from replicative potential to angiogenesis (Berindan-Neagoe et al.,

2014). For example, as a reaction to hypoxia, the induction of transcription of the range of miRNA occurs, with consequential activation of angiogenesis (Kulshreshtha et al., 2008). In proliferation, miRNA 29 and 30 directly inhibit oncogene B myb leading to the senescence of the cell (Martinez et al., 2011). In invasion and metastatic potential on the model of lung cancer, miRNA 31 leads to migration, invasion and proliferation (Meng et al., 2013). However, several potential hypotheses on regulation and role of miRNA in oncogenesis should be mentioned (Milunović et al., 2016, Berindan-Neagoe et al., 2014). As opposed to normal tissues, miRNA is in malignant tissue suppressed, which is attributed to gene mutations which encode proteins in its biogenesis. This leads to loss of its inhibiting role to targeted genes and to oncogenes, facilitating thereby the malignant growth.

In spite of huge progress in the research of miRNA (number of articles at Medline database according to MESH abbreviations “microRNA“ and “cancer“ amounts to 15,121 including 2,649 of reviews), we are at the very beginning of understanding its real role in oncogenesis.

Micro-RNA in Myelodysplastic Syndrome

On the contrary to other malignant hematologic diseases, the research of miRNA in MDS is in its early phase.

Expression of miRNA in MDS

One of the pivotal papers in this area included 25 samples of the bone marrow of patients with MDS (Pons et al., 2009). 12 enhanced expressed miRNA have been identified in bone marrow and 6 in peripheral blood. The majority of these miRNA belonged to the miRNA-17-92 group, the function of which is implicated by deregulation of proliferation and antiapoptotic mechanism, which may provide explanation for the disordered

proliferation of hematopoietic cells in MDS. In the further analysis, 6 miRNA were expressed and in the samples of peripheral blood implicating that peripheral blood may reflect the compartment of the bone marrow (Pons et al., 2009), 3 miRNA (miRNA 181a, 222 and 155) were intensively expressed in MDS of high risk as opposed to their low expression in MDS of low risk. In other research, as well as in other neoplasms, smaller expression of miRNA in MDS samples has been noticed, but the miRNA-1/miRNA-133a group was intensively expressed in all samples (Hussein et al., 2010). With regards to chromosome anomalies, only MDS del5q had a different miRNA profile; however, due to its specifics and different biology of MDS del5q, this is not an expected finding and we will not refer to this disorder any longer. Dostalova et al. (2011) have identified 13 intensively expressed miRNA and 9 decreasingly expressed miRNA. In the further analysis the patients were split into RAEB 1 (MDS of low risk), RAEB 2 (MDS of high risk) and AML. Profile of RAEB 1 was similar to healthy controls; RAEB 2 was similar to AML. The authors have separated two miRNA; miRNA 10-a and 34-a. MiRNA 10-a was linked to leukemia transformation in RAEB 2 subtype, while miRNA34-a was linked to alteration of hematopoiesis. This is also the first study which showed pathogenetic mechanism of miRNA in MDS. Erdogan et al. (2011) have analyzed 44,519 miRNA probes in low-risk MDS. 5 miRNA remained significantly in validation group with constructed algorithm of even 50 targeted genes which varied from transcription regulation to RNA translation, showing that a small number of miRNA may target multiple mRNA of targeted genes. Choi et al. (2015) conducted a research on the influence of trisomy 8 and 1q, of frequent chromosome abnormalities in MDS, to the expression of miRNA. Significant

elevation of miRNA-194-5p and miRNA-320a has been found in these patients with possible prognostic implication for miRNA-194-5p. In Pons et al., 25 patients with MDS identified the intensified expression of 12 miRNA in bone marrow⁵⁵. Furthermore, 6 of these miRNA were also expressed in peripheral blood.

miRNA-mRNA interactions in MDS

As it is presented, the expression of miRNA is aberrantly changed in MDS, but to understand the real pathogenesis miRNA-mRNA interaction should be understood. Only several studies assessed this role in MDS. Inefficient erythropoiesis is linked to miRNA21 in MDS through SMAD7 inhibition, i.e. activation of TGF-2 route (Bhagat et al., 2013). The other study tested the relation of miRNA22 and TET2 genes, frequently mutated in MDS on the mouse model (Song et al., 2013). In miRNA22 transgenic mice a low concentration of 5-hmC was recorded, implicating a disordered methylation and aberrant hematopoiesis (self-regeneration, displacement) developing into MDS or AML. As a targeted gene, TET2 cancer suppressor gene appeared, implicating that contrary to previous papers where its mutation was significant, the inhibition may be a lot more subtle at epigenetic level (Papaemmanuil et al., 2013, Haferlach et al., 2014). Arabanian et al. (2014) has shown that miRNA-23a is directly linked to 3'UTR region of CXCL12 mRNA, leading to inhibition of the activation of TGFBI route and proliferation of hematopoietic cells on the model of the cell cultures and human cells.

Prognostic Meaning of miRNA in MDS

So far in this bibliographical review, we have shown that miRNA and its role are disturbed in MDS; however, due to the small number of studies, the exact function of miRNA remains relatively unknown in

In this bibliographical review, we have shown that miRNA and its role are disturbed in MDS, However, due to the small number of studies the exact function of miRNA remains relatively unknown in its pathogenesis.

its pathogenesis. Furthermore, a question arises whether miRNA has any kind of clinical meaning in this context. Sokol et al. (2011) have managed in the sample of 44 MDS patients to find the miRNA profile, which included 10 different miRNA. This profile could have split the patients per IPSS scoring system to high-risk and low-risk patients. MicroRNA181B was more expressed in high-risk group; but the study was particularly interesting because its intensified expression in the low-risk group was linked to the worse survival (3.5 versus 9.3 years). Sokol et al suggested that analysis of the microRNA expression profile offers diagnostic utility, and provides pathogenetic and prognostic discrimination in MDS.

The previously described study by Song et al. (2013) on interaction of TET2 cancer suppressor and miRNA22 also included the group of 107 patients. MiRNA22 showed a strong correlation with decrease of expression of TET2 which indirectly had an influence on the total survival. The first study, which used the circulating miRNA (let 7a and miRNA 16) in the plasma of 50 MDS patients found the bi-modal distribution of expression of these biomarkers (Zuo et al., 2011). In the further

analysis, the authors have split the patients into two groups with regards to the level of expression. High levels of these biomarkers were linked to the worse outcome in the light of total survival and survival without leukemia transformation, while let 7a in multi-variant analysis was an independent factor. The largest study in this area used 800 probes of human circulating miRNA on 72 patients with MDS with normal karyogram (Zuo et al., 2015). The profile of 7 miRNA has been found (let 7a, miRNA 144, 16, 25, 451, 651 and 655) which could have split the patients with regards to the outcome into two groups with the risk to death totaling 6.54%. Furthermore, this profile could have anticipated the outcome with higher precision (75%) of the IPSS scoring system itself (50%). According to this bibliographical overview, we have found only one study which used miRNA as a prognostic factor for treatment with hypomethylating agents 5-azacytidine and decitabine. The study included 58 patients with primary outcome of the total response (Kim et al., 2014). The patients were stratified according to the expression of circulating miRNA21 into two groups. The group with high expression had a significantly lower rate of responses (41.2%) in comparison to the group with low expression (73.2%) with sensitivity of 83.3% and specificity of 45.8% for the stated biomarker. There is no significant difference in total survival, but the time

without leukemia transformation was significantly longer in the group with low expression of miRNA 21 (44.5 versus 14 months).

The field of microRNA research seems to be very complex, but may also open new horizons in pathophysiology, diagnostic and therapeutic options in MDS.

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MEETING HIGHLIGHTS AND ANNOUNCEMENTS

HIGHLIGHTS FROM THE AMERICAN SOCIETY OF HEMATOLOGY 58TH ANNUAL MEETING & EXPOSITION • DECEMBER 2016

BREAKFAST SYMPOSIUM



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We just can't stop reliving our amazing symposium turn out at the American Society of Hematology's 58th Annual Meeting! Crowd of 800+ hematologists participated in our sponsored satellite symposium.



It's so great to see such a full house when there is so much progress to be made in the field of MDS research!



A special THANK YOU to our Board of Directors for their continued support and excellent efforts in MDS!

PRESENTATIONS AVAILABLE

MDS Foundation Website: <http://www.mds-foundation.org/ash-breakfast-2016/>

INTERNATIONAL WORKING GROUPS

MDS FOUNDATION INTERNATIONAL WORKING GROUP FOR PROGNOSIS IN MDS

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

Mutations Predict Prognosis Independent of the IPSS-R: Overview

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

Prognostic Impact of TP53 Mutations

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

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

This work was presented by Dr. Rafael Bejar at the 2014 American Society of Hematology Meeting² with updating at the 2015 13th International MDS Foundation Symposium held in Washington, D.C.

Recent Molecular Results

Recently, molecular and clinical data on 3392 MDS patients gathered by members of the IWG-PM-Molecular Committee were combined and analysed and the abstract describing these findings was presented for oral presentation at the 2015 ASH Annual Meeting in Orlando.³ Survival data were available for 3200 patients. The 27 genes sequenced in at least half of the cohort and mutated in >1.5% of samples were included for analysis. Mutations in 12 genes were strongly associated with shorter overall survival in univariate analyses. The large size of the cohort allowed for more precise estimates of survival in the less frequently mutated genes. IPSS-R risk groups could be determined for 2173 patients and were strongly associated with survival. Adjusting the hazard ratio of death for IPSS-R risk groups identified several mutated genes with independent prognostic significance. Patients without mutations in any of the major adverse genes represented over half of the fully sequenced cohort and had a longer median survival than patients with adverse mutations even after correction for IPSS-R risk groups. A mutation score based on survival risk will be proposed and internally validated. The impact of somatic mutations in patients traditionally considered lower risk will also be explored.

Current Project Status, Plans for Sequencing of New Samples

In addition to the above assessment of previous samples, led by Dr Elli Papaemmanuil, the project is sequencing additional large numbers of MDS cases to further develop our database and mutational evaluations. An automated sample management system was recently implemented that links sample reception to library preparation and sequencing submission. The results of these analyses will serve as the template with which to build an integrated molecular risk model for MDS.



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References

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

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

The MDS/MPN International Working Group

Myelodysplastic syndromes represent a heterogeneous group of disease entities with diverse clinical features, genetic composition, natural history, and response to therapy. Mounting evidence has suggested that several MDS ‘subtypes’ are distinct enough that they should be considered unique disease entities. To this end, in 2008 the World Health Organization designated four clinical entities to be recognized as bona fide diseases with overlapping dysplastic and proliferative features. These include Chronic Myelomonocytic Leukemia (CMML), atypical CML (aCML), Juvenile Myelomonocytic Leukemia (JMML), and Myelodysplastic/Myeloproliferative Neoplasms Unclassifiable (MDS/MPN-U). Since this reclassification, many investigations have confirmed the unique molecular underpinnings and clinical trajectories of each of these diseases. However, this stratification has resulted in rare diseases that require collaborative efforts to make transformative changes in patient care.

The MDS/MPN International Working Group (MDS/MPN IWG) was originally developed in 2012. The work of this initial group resulted in the first two peer-reviewed publications. By the end of 2013, membership was expanded to include a CMML multi center project, and the group enlisted the support of the MDS Foundation. The overarching goal of this group is to identify key knowledge gaps in the area of MDS/MPNs and facilitate international, collaborative, translational science geared to rapidly improve our understanding of these fatal neoplasms. The current membership includes 32 investigators, from 20 centers, across 7 countries.

Work from collaborations within this group has resulted in several peer-reviewed publications:

- A consensus recommendation for response criteria that sets the foundation for a common endpoint across many MDS/MPN clinical trials.²
- A consensus review on the biology and clinical presentation of MDS/MPNs.²

- The development of an international CMML dataset that includes clinical and molecular data.³

Ongoing collaborations underway include:

- Expansion and prospective molecular sequencing of the international CMML data set.
- Exploring the consequence of an MDS/MPN diagnosis on quality of life.
- Identify/Generating a consensus CMML prognostic model.
- Exploring the role of transplant in molecularly defined CMML subtypes.
- Implementing international clinical trials on both sides of the Atlantic.

References:

1. Savona MR, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloprolif-



erative neoplasms (MDS/MPN) in adults. *Blood*. 2105;125:1857-1865, doi:10.1182/blood-2014-10-607341.

2. Mughal TI, et al. An International MDS/MPN Working Group's perspective and recommendations on molecular pathogenesis, diagnosis and clinical characterization of myelodysplastic/myeloproliferative neoplasms. *Haematologica*. 2105;100:1117-1130, doi:10.3324/haematol.2014.114660.
3. Padron E. et al. An international data set for CMML validates prognostic scoring systems and demonstrates a need for novel prognostication strategies. *Blood Cancer*. 2015;5, e333, doi:10.1038/bcj.2015.53.

LAUNCHING THE INITIAL GROUP CLINICAL STUDY IN 2018

MDS/MPN Committee Develops NL-MARRO: A Study of Novel Therapies in MDS/MPN

The MDS/MPN IWG, founded in 2012, is focused on understanding MDS/MPN and developing new therapy to improve the survival and reduce morbidity in these diseases. The MDS Foundation MDS/MPN Committee has supported the IWG's mission and after publishing proposed response criteria in the treatment of MDS/MPN in 2015 (Savona, et al. *Blood* 2015), now is poised to launch the initial group clinical study in 2018. Novel therapy combinations in untreated MDS/MPN And Relapsed/Refractory Overlap Syndromes (NL-MARRO) is a Phase II Basket Trial of Novel Combination Therapies in MDS/MPN patients naïve to therapy or who fail primary therapy with DNMTi (DNA methyltransferase inhibitors). This is first study testing the MDS/MPN IWG response criteria for all MDS/MPN, with goals:

1. To test new therapies in MDS/MPN
2. To validate/update the MDS/MPN Response Criteria
3. To develop biomarkers for response to therapy in MDS/MPN
4. To improve understanding of MDS/MPN

The MDSF MDS/MPN Subcommittee on Clinical Trials, led by Michael Savona, Vanderbilt University Medical Center, is building the infrastructure to conduct clinical trials in MDS/MPN at clinical sites that have developed local expertise diagnosing and treating MDS/MPN. This will allow MDSF clinical investigators in the US and Europe to cooperatively test promising therapies in a multi-institutional platform. Novel compounds which have completed safety assessment and dose finding experiments, typically with early efficacy signals in other myeloid disease, will be considered by the Subcommittee for NL-MARRO. Investigators are dedicated to data compliance for development of risk prognostication and stratification, enrollment of patients per WHO criteria, refine pathology/response criteria/treatment for MDS/MPN (eg central path), and refinement via regularly scheduled MDSF-sanctioned planning meetings. All interested investigators are welcome.

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. Bennett JM. Changes in the updated 2016: WHO classification of the myelodysplastic syndromes and related myeloid neoplasms. *Clin Lymphoma Myeloma Leuk*. 2016;16(11):607-609. (<https://www.ncbi.nlm.nih.gov/pubmed/27693133>)

This article highlights diagnostic dilemmas in the 2008 WHO classification and the changes made in 2016 update to resolve them. In MDS, dysplasias and cytopenias in individual lineages involved are not always concordant. The 2016 classification uses general term MDS with single or multiple lineage dysplasias to create diagnostic categories. In addition, for higher risk MDS, the disease with excess blasts is categorized as MDSEB 1 or MDSEB 2.

2. Strupp C et al. New proposals of the WHO working group (2016) for the diagnosis of myelodysplastic syndromes (MDS): characteristics of refined MDS types. *Leuk Res*. 2017;57:78-84. (<https://www.ncbi.nlm.nih.gov/pubmed/28324772>)
A validation of the new 2016 WHO classification of MDS was conducted with centrally diagnosed 3528 patients in the Düsseldorf registry, showing MDS single lineage dysplasia (MDS SLD) in 7.3%, multilineage dysplasia (MDS MLD) in 27.7%, MDS RS SLD in 6.4%, MDS RS

MLD in 9.1%, Del(5q) in 4.5%, MDS with excess blasts 1 (MDSEB 1) in 13.6% and MDSEB 2 in 17.6% patients. The overall survival and AML transformation were also in line with the risk categorization. When compared to WHO 2008 classification, a major shift was observed in approx. 17% non-blastic patients from RCMD (2008) to MDS RS MLD or MDS Del(5q) (2016). Survival was higher in SLD and Del(5q) patients than MLD or EB1/2 patients. For AML progression rate, as compared to SLD, MLD and del(5q) categories, EB1 showed nearly 2x higher and EB2 had 3x higher rates.

3. Xavier AC et al. Incidence and outcomes of paediatric myelodysplastic syndrome in the United States. *Br J Haematol*. 2017; Feb 27 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28240841>)

The analysis of SEER database records between 2001 and 2011 revealed an incidence of pediatric MDS at 1.16 cases/million population/year. Furthermore, similar to adult MDS, the 5-year survival of therapy-related pediatric MDS (41.2%) was significantly poorer as compared to de novo pediatric MDS (71.3%, $p=0.004$).

TREATMENT:

Hypomethylating Agents:

1. Drusbosky L et al. Computational drug treatment simulations on projections of dysregulated protein networks derived from the myelodysplastic mutanome match clinical response in patients. *Leuk Res*. 2017;52:1-7. (<https://www.ncbi.nlm.nih.gov/pubmed/27855285>)
Drug response was simulated for lenalidomide or hypomethylating agents (HMA) or for HMA+Lenalidomide. Using computational biology of genomic abnormalities in each patient intracellular pathway map was computed for individual patients. The computational

model matched clinical responses in 80% MDS patients treated with lenalidomide (37/46) or HMAs (12/15) while the matching was 100% (10/10) in patients treated with HMA + Lenalidomide.

ESAs and Growth Factors

1. Park S et al. Outcome of lower-risk patients with myelodysplastic syndromes without 5q deletion after failure of erythropoiesis-stimulating agents. *J Clin Oncol*. 201, Mar 28 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28350519>)

Using an international retrospective cohort of 1698 patients with non-del(5q) lower risk MDS treated with ESA, the effect of second line treatment subsequent to ESAs was assessed. The HI-E in frontline with ESA treatment was 61.5% with a median response duration of 17 months. Patients without any response to ESAs had a higher rate of AML transformation than those who initially responded to ESA and then relapsed. Nearly 40% patients received second line therapy after ESA failure including Hypomethylating agents, and lenalidomide, while approx. 60% patients received RBC transfusion only. The HMA and Lenalidomide treated patients had higher propensity for AML transformation and lower 5year survival rates as compared to those receiving transfusions only or treatment with other agents.

2. Oliva EN et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single blind, randomized controlled phase 2 superiority trial. *Lancet Haematol*. 2017; 4(3):e127-e136. (<https://www.ncbi.nlm.nih.gov/pubmed/28162984>)
Eltrombopag (50mg to 300 mg) treatment for at least 24 weeks and until disease progression versus placebo, showed platelet response (HI-plt) in 47% (24/59) patients as compared to 3% of the total 31 patients on placebo arm. Nearly 42%

of the placebo patients had bleeding events versus 14% with eltrombopag treated patients ($p=0.0025$). The AML transformation and disease progression rates were comparable in the two groups.

3. Garelius HK et al. Erythropoiesis-stimulating agents significantly delay the onset of a regular transfusion need in non-transfused patients with lower-risk myelodysplastic syndrome. *J Intern Med*. 2017;28(3):284-299. (<https://www.ncbi.nlm.nih.gov/pubmed/27926979>)

The clinical impact of ESA use was evaluated among 1696 subjects registered in EUMDS registry between 2008 and 2014. Nearly 46% patients received ESAs for a median duration of 27.5 months. When compared with non-ESA patients, those treated with ESAs showed a trend of survival benefit ($HR=0.82$, $p=0.09$) with the best results in patients not needing transfusions prior to ESA treatment. Among the latter group of patients, post-ESA treatment, first transfusion was needed after a median of 23.3 months ($p<0.0001$), while in those with prior transfusions, the time to post-ESA first transfusion was significantly shorter (median 6.1 month). Additionally, the responding patients showed significantly lower risk of death ($HR=0.065$, $p=0.018$).

4. Deshet-Unger N et al. Erythropoietin administration is associated with improved T-cell properties in patients with myelodysplastic syndromes. *Leuk Res*. 2017;52:20-27 (<https://www.ncbi.nlm.nih.gov/pubmed/27870945>)

In this study, MDS patients treated with ESA were compared to non-ESA treated MDS patients or healthy donors. At baseline, all MDS patients showed reduced number and function of CD4⁺ T cells and elevated CD8⁺ T cell number/activity. Post ESA, the CD4⁺ CD25⁺ cell counts were normalized in the periphery. Also, in vitro activation of both T cell populations, CD4⁺ and

CD8⁺ with phytohemagglutinin as measured by CD69 expression, nearly doubled after ESA treatment compared to non-ESA treated patients.

Hypomethylating Agents:

1. Zhang Z et al. Decitabine treatment sensitizes tumor cells to T-cell mediated cytotoxicity in patients with myelodysplastic syndromes. *Am J Transl Res*. 2017;9(2):454-465. (<https://www.ncbi.nlm.nih.gov/pubmed/28337274>)

Decitabine treatment of MDS-derived cell lines significantly improved surface expression of cancer-testis antigens (CTAs) and also led to incremental recognition of CTA expressing MDS derived cells by cytotoxic T cells. There was increased HLA and ICAM-1 expression specific to cytotoxic T cells. These data may support a role of decitabine in active adaptive immunity in MDS.

2. Apuri S et al. Evidence for selective benefit of sequential treatment with hypomethylating agents in patients with myelodysplastic syndrome. *Clin Lymphoma Myeloma Leuk*. 2017 Jan 10 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28185797>)

A single institution study evaluated effectiveness of sequencing the two hypomethylating agents with each other. In the first line HI rates were comparable with both agents 63% with Azacitidine and 50% with decitabine. In the second line though, decitabine post azacitidine showed 19% HI as the best response compared to 40% with azacitidine post-decitabine. In line with these results, AML transformation was lower with the latter (29% vs 20% respectively). The median survival from the initiation of second line however was comparable (17.8 mo vs 22 mo).

3. Garcia-Manero G et al. Phase 2, randomized, double-blind study of pracinostat in combination with azacitidine in patients with untreated,

higher risk myelodysplastic syndromes. *Cancer*. 2017;123(6):994-1002. (<https://www.ncbi.nlm.nih.gov/pubmed/28094841>)

Int-2/high-risk MDS patients ($n=102$) were randomized 1:1 between azacitidine + pracinostat vs azacitidine + placebo. Respectively in the two groups, the CR rate by cycle 6 was 18% vs 33% ($p=0.07$), median overall survival of 16 and 19 months, and progression free survival of 11 and 9 months.

4. Welch JS et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;375(21):2023-2036. (<https://www.ncbi.nlm.nih.gov/pubmed/27959731>)

This single institution trial enrolled a total of 116 subjects with AML or MDS with 46% patients clearing marrow blasts to <5% level. The unfavorable cytogenetic profile patients had better response (67%) with 20 mg/m² x 10 days administration of decitabine than those with intermediate or favorable cytogenetics (34%, $p<0.001$). Moreover, specifically in patients with TP53 mutations the response was 100% (21/21 patients) vs. 41% in wild type TP53 patients ($p<0.001$).

5. Pappa V et al. A retrospective study of azacitidine treatment in patients with intermediate-2 or high risk myelodysplastic syndromes in a real-world clinical setting in Greece. *Int J Hematol*. 2017;105(2):184-195. (<https://www.ncbi.nlm.nih.gov/pubmed/27815858>)

A single country, multicenter, retrospective chart review study (RETRO-AZA-MDS-001) conducted between Feb–Nov 2012 assessed clinical benefit/risk profile of azacitidine in routine practice in int-2/high risk MDS. A total of 88 patients with a median of 6.6 month treatment duration showed ORR- approx. 38%, HI rate of 33%, AML transformation in 6.8%, transfusion independence in 7.3% among transfusion-dependent patients, and serious adverse events in

42%. Patients with no prior ESA were nearly 8 times more likely to achieve a clinical response with azacitidine ($p=0.012$).

IMiDs:

1. Prebet T et al. Outcome of patients treated for myelodysplastic syndromes without deletion 5q after failure of lenalidomide therapy. *Oncotarget*. 2017, Feb 8 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28184031>)
An international retrospective study assessed lenalidomide treated lower risk non-del(5q) MDS patients (n=384). Among these patients, 55% were treated with ESAs and 23% with hypomethylating agents (HMA) before lenalidomide treatment. The response to lenalidomide was seen in 17% patients with a median lenalidomide treatment duration of 15 mo. Conversely, for the 64% who did not respond to lenalidomide, the median duration of treatment was only 4 mo. When HMA were used after lenalidomide, the overall survival was 51 mo vs. 31 mo with the best supportive care after lenalidomide ($p=0.01$).

Allogeneic Bone Marrow Transplant:

1. Martino R et al. Long-term follow-up of a retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic transplantation from matched related donors in myelodysplastic syndromes. *Bone Marrow Transplant*. 2017; Mar 20 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28319072>)
A multicenter retrospective study involving 843 MDS patients received allogeneic marrow transplant from HLA-matched sibling donor. This study showed that a 13 year relapse rate was significantly higher after reduced conditioning regimen (48%) vs standard myeloablative regimen (31%, $p=0.04$), without any impact on overall survival. However, non-relapse mortality was higher in myeloablation group as

compared to reduced-intensity regimen (40% vs 31%, $p=0.1$).

RBC Transfusions:

1. Lin Y et al. Prophylactic RhCE and Kell antigen matching; impact on alloimmunization in transfusion-dependent patients with myelodysplastic syndromes. *Vox Sang*. 2017;112(1):79-86. (<https://www.ncbi.nlm.nih.gov/pubmed/28097704>)
A study of 176 transfusion dependent MDS patients reveals importance of an institutional policy for prophylactic antigen matching for RhCE and Kell antigens. Overall, 17% of the patients developed alloantibodies, with the majority showing at least one anti-RhCE or Kell antigens. When assessed for the prophylactic matching policy before transfusion, the rate was significantly lower (11%) vs. when no policy was applied (23%).

Novel Therapies:

1. Wermke M et al. Mammalian-target of rapamycin inhibition with temsirolimus in myelodysplastic syndromes (MDS) patients is associated with considerable toxicity: results of the temsirolimus pilot trial by the german MDS study group (D-MDS). *Br J Haematol*. 2016;175(5): 917-924. (<https://www.ncbi.nlm.nih.gov/pubmed/27714772>)
A prospective study enrolled lower risk MDS patients with transfusion dependent anemia and/or neutropenia and higher risk patients relapsed/refractory to 5-azacitidine. A total of 20 patients (9 lower- and 11 higher-risk) were treated with a weekly 25mg dose of Temsirolimus. Only four patients showed stable disease without HI after four months. The remaining patients discontinued early due to adverse events. A significant decline in marrow vascularization was seen with treatment without impact on the balance of peripheral blood T-cell populations.
2. Swords RT et al. KB004, a first-in-class monoclonal antibody targeting the receptor tyrosine kinase EphA3 in

patients with advanced hematologic malignancies: results from a phase 1 study. *Leuk Res*. 2016;50:123-131. (<https://www.ncbi.nlm.nih.gov/pubmed/?term=Sword+RT+and+EphA3>)

An anti-Ephrin receptor tyrosine kinase monoclonal antibody was tested in a phase 1 study with multiple hematologic malignancies including MDS and AML. The most common toxicities were grade 1/2 infusion reactions in approx. 80% treated patients becoming dose limiting beyond 250 mg. The weekly schedule of the drug was found to be well tolerated with clinical responses noted in all the hematologic conditions tested.

PATHOBIOLOGY:

1. Hlaváčková A et al. Enhanced plasma protein carbonylation in patients with myelodysplastic syndromes. *Free Radic Biol Med*. 2017 Mar 12 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28300669>)
A total of 32 patients with MDS (RARS, RCMD, RAEB 1, or RAEB 2) were examined for protein carbonylation, indicative of reactive oxygen radical activity. These MDS patients and, in particular, the RARS category, showed elevated protein carbonylation as compared to healthy controls. Additionally, using tandem mass spectrometry, 27 uniquely carbonylated proteins were identified in RARS patients, the pathobiologic significance of which needs further exploration.
2. Diamantopoulos P et al. Poly(ADP-ribose) polymerase-1 mRNA levels strongly correlate with the prognosis of myelodysplastic syndromes. *Blood Cancer J*. 2017;7(2):e533. (<https://www.ncbi.nlm.nih.gov/pubmed/28212373>)
The median PARP1 mRNA levels correlated with advanced disease among WHO 2008/2016 categories as well as among IPSS/IPSS-R categories. Moreover, the median overall survival and 5-yr survival

rates were worse in patients with high vs. low PARP1 mRNA levels (OS- 37.4 mo vs not reached, $p=0.0001$, and 29.8% vs 88.9% respectively).

3. Makishima H et al. Dynamics of clonal evolution in myelodysplastic syndromes. *Nat Genet.* 2017;49(2):204-212. (<https://www.ncbi.nlm.nih.gov/pubmed/27992414>)

Clonal dynamics were studied using whole exome and/or targeted sequencing of 699 patients (122/699 studied longi-tudinally). The number of mutations, their diversity and clone size increased at progression. A set of mutations including FLT3, PTPN11, WT1, IDH1/2, NPM1 and N-RAS grouped as Type 1, were found to be newly acquired at AML transformation, related to faster progression and poorer survival. On the other hand, another set of mutations enriched in higher risk MDS like TP53, GATA2, KRAS, RUNX1, ASXL1, ZRSF2, STAG2, and TET2 (Type2) did not correlate with AML progression or survival.

4. Westers TM et al. Immunophenotypic analysis of erythroid dysplasia in myelodysplastic syndromes. A report from the IMDS Flow working group. *Haematologica.* 2017;102(2):308-319. (<https://www.ncbi.nlm.nih.gov/pubmed/27758818>)

This multicenter study of the IMDS Flow working group attempted to define flow parameters to distinguish MDS associated dyserythropoiesis from non-clonal cytopenias. In a multivariate analysis, expression of CD36 and CD71, intensity of CD71, and % CD117+ erythroid progenitors best discriminated MDS from non-clonal cytopenias. The high specificity (92%) of this marker set was verified in a validation cohort.

5. Cremers EM et al. Implementation of erythroid lineage analysis by flow cytometry in diagnostic models for myelodysplastic syndromes. *Haematologica.* 2017;102(2):320-326. (<https://www.ncbi.nlm.nih.gov/pubmed/27658438>)

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

The study analyzed 167 bone marrow aspirates (106 MDS and 61 cytopenic controls). The results showed a correlation of the presence of erythroid aberrancies with MDS diagnosis and the addition of erythroid aberrancies to two different flow cytometric models increased sensitivity of detecting MDS.

QUALITY OF LIFE

1. Luskin MR et al. Self-reported sleep disturbance and survival in myelodysplastic syndromes. *Br J Haematol.* 2017 Mar 8 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/28272741>)

In a single institution study with MDS patients, using the "European organization for research and treatment of cancer quality of life questionnaire," multivariable models showed that anemia and sleep disturbance were both associated with fatigue ($p<0.001$). Additionally, sleep disturbance ($p=0.002$) and fatigue ($p=0.04$) were individual predictors of overall survival.

REVIEWS, PERSPECTIVES & GUIDELINES

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

1. Stahl M and Zeidan AM. Management of lower-risk myelodysplastic syndromes without del 5q; current approach and future trends. *Exp Rev Hematol.* 2017; 10(4):345-364. (<https://www.ncbi.nlm.nih.gov/pubmed/2827785>)
2. Greenberg PL et al. Myelodysplastic syndromes, version 2.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2017;15(1):60-87. (<https://www.ncbi.nlm.nih.gov/pubmed/28040720>)
3. Almeida A et al. Recent advances in the treatment of lower-risk non del(5q) myelodysplastic syndromes (MDS). *Leuk Res.* 2017;52:50-57. (<https://www.ncbi.nlm.nih.gov/pubmed/27883945>)
4. Bejar R and Greenberg PL. The impact of somatic and germline mutations in myelodysplastic syndromes and related disorders. *J Natl Compr Canc Netw.* 2017; 15(1):131-135. (<https://www.ncbi.nlm.nih.gov/pubmed/28040723>)
5. Bejar R. Implications of molecular genetic diversity in myelodysplastic syndromes. *Curr Opin Hematol.* 2017; 24(2):73-78. (<https://www.ncbi.nlm.nih.gov/pubmed/27875374>)
6. Wlodarski MW et al. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. *Blood.* 2016; 127(11):1387-1397. (<https://www.ncbi.nlm.nih.gov/pubmed/26702063>)

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PhotoVoice for Patients with Myelodysplastic Syndromes – Understanding the Patients' Stories

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Learning from patients' experiences in order to improve care services is a core feature of the quality strategy at our clinic. MDS is a malignant disease that is associated with anemia, increased risk of infections and bleeding tendency. Approximately 30% of the patients develop acute myeloid leukemia. Getting a malignant diagnosis is always life changing and living with a serious illness can lead to increased anxiety and decreased quality of life for the individual. Most studies focus on medical aspects of the disease. However, few qualitative studies explore patients' experiences of living with MDS. The aim of the study was to learn how MDS impacts patients' daily lives, bringing their lived experiences in focus using 'Photovoice' — a participatory research approach. The second aim was to explore if the study could increase the patient's sense of empowerment.

Fourteen patients on active treatment for MDS at the hematology clinic at the Sahlgrenska University Hospital, Goteborg, Sweden, were invited to participate in the study. Four patients (two women and two men) consented to participate, age 65–79 years. The patients had had the diagnosis for more than 3 months. The research team consisted of a senior consultant in hematology, two registered nurses specializing in hematology nursing working in the

outpatient clinic, one representative from the Regional Cancer Centre specializing in health care improvement, and the research leader working at the Centre for Health Care Improvement (CHI) at Chalmers. The study was approved by the Regional Ethical Board in Goteborg.



The research group

A Photovoice approach was used — the patients used cameras to capture images of events and experiences from their everyday life that illustrated various perspectives on living with the disease. Each patient contributed approximately 25 pictures. The patients then told their stories associated with each picture in individual interviews. The interviews were tape recorded and transcribed verbatim. Compiled narratives for each photo were then created by the researchers and sent to the patients for validation.

All pictures, together with the narratives, were categorized in groups and subgroups by the patients together with the researchers in two consecutive half-day dialogue sessions to jointly identify common themes and sub-themes that illustrated aspects of living with the disease. Various strategies to cope with the disease in everyday life were identified. The photographs and narratives were categorized into six groups:

1. Being an individual person — more than a diagnosis.

2. Experiences of living with the disease, e.g. anxiety, physical limitations and the necessity of medications.



*Life goes on out there anyway.
It is a sign of loneliness which has been forced upon you.*

3. Experiences of meeting the healthcare system. The healthcare system is necessary for coping with the disease while, at the same time, it disempowers patients.

4. Different strategies for coping with the disease, e.g. finding comfort in faith, obtaining knowledge about the disease, creating structures for reflection.



Music is positive, so of course, everything that is positive keeps one happy and cheerful and able to enjoy life.

5. Strategies for wellbeing despite the disease, e.g. being in nature, physical exercise.

6. Living here and now, accepting the disease.



They are a part of the good things in life, so I think that I will show a picture of this, it means so much, for the wellbeing.

During dialogue sessions, as well as in the follow up interviews, the patients expressed feeling empowered by this method of processing the diagnosis of MDS together with other patients.

The patients also expressed that sharing experiences with others is a powerful way to encourage empowerment – it expands ones own repertoire to handle everyday aspects of living with a malignant disease.

The combination of the patients' narratives and photos provides a rich understanding of the patients' experiences living with MDS. These narratives emphasize the importance of having health care professionals taking the time to listen to patient stories to learn about individual patient experiences and perceptions relative to living with MDS. This study was a participatory process in which patients and researchers worked side by side during the entire project. Our experience is that PhotoVoice is a valuable participative approach to capture patient experiences. It might also be used with other patient groups, e.g. patients with impaired cognitive function. The pictures and narratives are currently being used as a vehicle to inspire improvement efforts from a patient's perspective. The study has been presented as a poster at the International Forum on Quality and Safety in Health Care in Singapore 2016 and will be presented at the Quality Fair in Health Care in Goteborg 2017.

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FROM THE FOUNDATION

NEWS FROM AROUND THE WORLD

GLAM ASH 2016

The Latin-American Group for Myelodysplastic Syndromes (GLAM) meeting was held on the 4th of December at the Manchester Hyatt Hotel in San Diego. Authorities from Latin-American Hematology Societies, American Society of Hematology, AA&MDS International Foundation, the MDS International Foundation and colleagues from Argentina, Brazil, Bolivia, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Peru, Paraguay, Uruguay and Venezuela attended this meeting.

Main topics discussed:

MDS Survey

This survey aims to collect epidemiological and state-of-the-art diagnostic and therapeutic tools in the region. This data will be updated and published every two years. Results might be ready for the MDS Foundation's International Symposium in Valencia, May 2017.



Training and Teaching

One of the most important projects of GLAM is to organize scientific MDS meetings, workshops, symposiums, etc. in different Latin American countries. Colleagues from Mexico have shown a trailer from Chiapas City, a beautiful place where the 6th Latin American MDS Symposium is going to be celebrated in 2018.

MDS Latin-American Common Registry

It is extremely necessary to develop a Latin American online common MDS Registry. All the attendants agreed to share



a database with similar variables and a centralized coordination. An Argentinean platform has been chosen.

Investigation and Clinical Trials

We reconfirmed that GLAM is determined to encourage investigation and help to promote clinical trials in MDS throughout Latin America.

Patients, Relatives and Healthcaregivers Information and Support

GLAM's web page is under construction and will be a useful tool to

help Latin American groups of MDS patients, relatives and healthcaregivers.

LATIN-AMERICAN GROUP FOR MYELODYSPLASTIC SYNDROMES

The Latin-American Group for Myelodysplastic Syndromes (GLAM) is a multi-disciplinary group integrated by health professionals from Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, Uruguay and Venezuela, with a common aim: study MDS from pathogenesis through clinical and therapeutic approaches.



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In honor of
MDS WORLD
AWARENESS DAY,
our Center of Excellence
in Shanghai, China,
The Sixth Hospital Affiliated
to Shanghai Jiaotong
University, held lectures
for both healthcare
professionals and
patients with
their families.



MDS IN FOCUS

MDS Remains an Incurable Disease For the Majority of Patients

Myelodysplastic Syndromes in Focus on World MDS Awareness Day

Sandra Kurtin, RN, MS, AOCN, ANP-C, PhDc
Nurse Practitioner
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Tracey Iraca
MDS Foundation, Inc.

Myelodysplastic syndromes (MDS) represent a group of rare bone marrow failure cancers most common in the older adult population, with a median age of onset of 73 years. Healthy bone marrow produces immature blood cells — called stem cells, progenitor cells or blasts — that normally develop into mature, fully functional red blood cells, white blood cells and platelets. In MDS, these stem cells may not mature and may accumulate in the bone marrow or they may have a shortened lifespan, resulting in fewer than normal mature blood cells in the circulation. Low blood cell counts are a hallmark feature of MDS and are responsible for some of the symptoms that MDS patients experience — infection, anemia, spontaneous bleeding or easy bruising.

MDS remains an incurable disease in the absence of an allogeneic bone marrow transplant, which is not an option for the majority of MDS patients due to their age, having other illnesses and/or not having a caregiver that is able to provide complex care daily for several months following the transplant. There are only three FDA-approved disease-modifying agents for the treatment of these diseases, all of these being developed through clinical trials. Unfortunately, the estimated clinical trials enrollment in the United States for cancer



patients is approximately 4 percent of the total cancer patient population. When considering the older adult and rare diseases such as MDS, this number is estimated to drop below 2.5 percent.

In addition, the majority of health care is provided in the outpatient setting with only brief episodes of health care provider interaction. Caregivers, including partners/spouses, other family members and friends, are expected to assume a primary role in

providing medical and personal care and support of the patient with little or no formal training. Many patients and caregivers may be overwhelmed and are at increased risk for anxiety, depression, fatigue and other physical and psychological distress. The MDS Foundation, Inc. works to provide hope with innovation in science, advocacy and most importantly support of patients and caregivers living with MDS.

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**.

Qualifying for a Compassionate Allowance with MDS

Thankfully, for those diagnosed with MDS, Social Security disability benefits are an option. Both Social Security Disability Insurance (SSDI) and Supplemental Security Income (SSI) were created to help people in need and can provide financial assistance to those with disabling conditions. In some severe cases, MDS can even qualify for a Compassionate Allowance, meaning your claim could be approved in as little as 10 days.

Qualifying for Disability

First, it is important to understand what qualifies for disability benefits. When reviewing applications, the first thing a Social Security agent looks to is your diagnosis. Diagnoses are evaluated using the “Blue Book” — a list of all disabilities approved by the Social Security Administration (SSA). Those with MDS qualify under Section 7.10 of the Blue Book: “Disorders of bone marrow failure.” If you can show evidence of their MDS diagnosis as well as records of three hospital visits within a year due to your illness, or blood transfusions every 6 weeks or more, then the SSA will consider you “disabled” and medically eligible for benefits.

The other factor when determining eligibility is income and past work history. These will determine if you technically qualify for benefits, as well as what type of benefits you qualify for. To receive SSDI, an applicant must have contributed a certain amount of money (called “work credits”) to the Social Security system in their working years. The older an applicant is, the more credits they must have contributed in order to qualify. The good news is that the vast majority of applicants who had just part-time jobs will qualify for SSDI benefits.

Thankfully, for those diagnosed with MDS, Social Security disability benefits are an option.

If an applicant has not contributed enough credits or is unemployed (a stay-at-home mom, for example), he or she may qualify for SSI instead. Qualification for SSI is based strictly on income — if you are deemed disabled and do not earn more than the monthly cut-off, then you are eligible for SSI benefits. Because SSI is needs based, you will not be approved if you have a spouse who’s earning a decent wage.

Qualifying for a Compassionate Allowance

MDS can be an incredibly limiting disorder, causing extreme physical, mental, and financial strain for those affected. Because of its severity, people can occasionally qualify for a Compassionate Allowance during their disability application.

Compassionate Allowances are expedited processes that provide financial benefits to applicants far sooner than other normal disability applicants. Terminal cancers and severe genetic disorders often qualify because of the time constraints their severe impairments present. MDS is considered a type of severe bone and blood cancer, so applicants in late stages of the disorder are often candidates for the program. While payments still take anywhere from a few weeks to a few months to be dispersed, the approval is much quicker than the traditional 6–12+ month decision period.

To qualify for the Compassionate Allowance, your MDS must be severe enough to require a bone marrow transplant. After the transplant, you will automatically medically qualify for Social Security benefits for 12 months. After 12

months, the SSA will reevaluate your claim to determine if you are still medically eligible for benefits.

It is important to note that Compassionate Allowance recipients do not receive Medicare faster than normal. Just as with other disability applicants, Medicare is usually awarded 24 months after the disability onset date. If Compassionate Allowance financial benefits are still not enough to cover the medical/financial strain of MDS, it is important to seek other insurance options during this waiting period.

Applying for Benefits

Applications for SSDI can be found on the SSA’s main website. FAQs and other important information can also be found here if you have any questions about the application or the process. Applications can also be filed in person at your local Social Security office.

Applications for SSI are currently unavailable online. However, it is recommended that the Online Application for Disability Benefits be filled out prior to applying for benefits. While this isn’t the official application, the information provided can be transferred to your application and helps to start the disability process. An appointment can then be made to fill out an application by calling your Social Security office.

When applying, be sure to submit as much information as possible: How your MDS keeps you from working, the names and locations of every doctor who has treated you, and your response to any treatment. The more medical evidence you have on your side, the more likely you are to be approved for disability benefits with MDS.


This article was provided by Disability Benefits Help, an independent organization dedicated to helping people receive the Social Security disability benefits they need. If you would like to know more about qualifying for disability benefits with MDS, email help@disability-benefits-help.org.

PATIENTS & CAREGIVERS **LIVING** WITH MDS FORUMS

SPREADING THE NEWS WORLDWIDE

MARK YOUR CALENDAR FOR THE LOCATION NEAREST YOU! PLANNED FUTURE MDS FORUM EVENTS FOR 2017

*Don't miss out on these informative, **FREE** events.*



Register Today
FOR OUR FREE EVENTS


MIDWEST/WEST
May 20
Seattle, WA
October 28
in honor of MDS World Awareness Day
San Francisco, CA
November 18
Iowa City, IA

MIDATLANTIC
June 17
Middletown, NJ
September 9
Buffalo, NY

MIDWEST
May 20
Chicago, IL

INTERNATIONAL
May 5
Valencia, Spain

SOUTH
October 28
in honor of MDS World Awareness Day
Atlanta, GA
November 18
San Antonio, TX



LEARN MORE AT:

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

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

MDS PATIENT AND PROFESSIONAL MEMBERSHIP

MEMBERSHIP OPPORTUNITY

Today, 238 people were told that they have MDS-worldwide. The MDS Foundation, Inc. is working hard to change this reality and we ask for your membership support in our global efforts to change the outcomes of MDS.

"When the MDS diagnosis first came, I had nothing. I had no information and no support. Once I connected with MDSF, I soon had lots of knowledge, understanding, and caring support."



WHAT ARE YOUR 2017 MDS MEMBERSHIP BENEFITS?

- You are part of the solution to change MDS outcomes. Your membership fee helps support global physician and patient educational initiatives, and helps to empower patients with courage and hope.
- You will receive two printed issues of The MDS-News, which includes the latest on MDS as well as exceptional patient and caregiver stories.
- You are updated regularly on the status of our Global Centers of Excellence and their patient events that encourage collaboration.
- You are provided information on the latest clinical trials to potentially share or participate in.
- You gain access to MDS awareness materials to share with family and friends.
- You are given the opportunity to participate in or host support group events with your friends & community.

HOW DOES YOUR MEMBERSHIP HELP?

- Your membership supports over 1,000 educational packets to families and caregivers free of charge annually, to help navigate through their MDS diagnosis.
- Your membership helps our Patient Liaison respond to over 1,300 on-line requests annually.
- Your membership supports over 170 Centers of Excellence worldwide. We believe this is imperative as these centers serve as our patient referral base, and this partnership helps the MDS community collaborate and engage in innovative practices in the diagnosis and care of MDS patients.
- Your membership helps to distribute over 8,000 translated pieces of MDS materials annually.
- Your membership enables MDSF to support approximately 250 professionals collaborating through International Working Groups – with researchers in 37 countries, and on 6 of the 7 continents.
- Your membership helps to educate patients, caregivers and professionals at live events. This year MDSF will host our International Symposia in Valencia, Spain. We anticipate 1,500 professionals in attendance. We will also host 11 live patient events.
- Your support in 2017 will help the MDS Foundation develop the growth of our Pediatric Centers of Excellence program to support children and their families who are living with MDS.



Although most cases of MDS are found after the age of 50, MDS can occur at any age.

In children, about 30 percent of MDS progresses to acute myeloid leukemia (AML). We believe that through greater collaboration, science will change these outcomes.

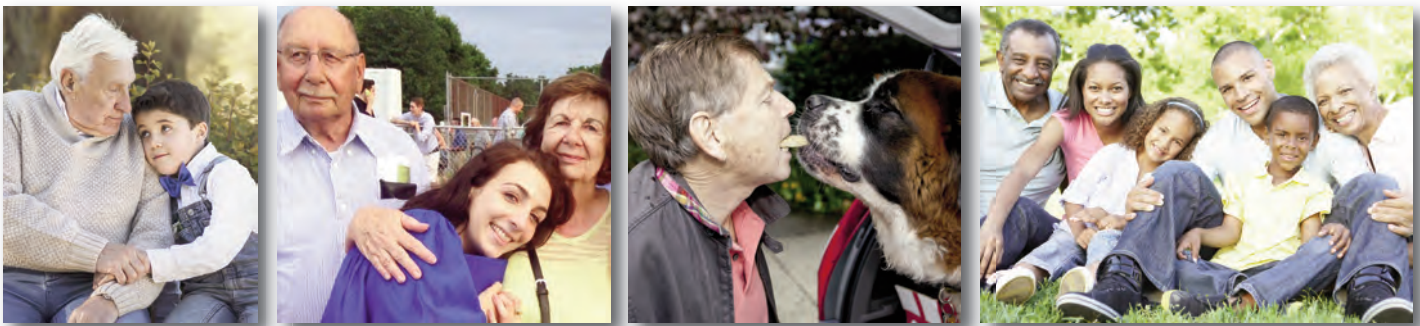
MEMBERSHIP OPPORTUNITY

2017 MDS PATIENT MEMBERSHIP OPTIONS

- \$35** *Community* Membership (includes benefits listed above)
- \$70** *Sharing Hope* Membership
(includes benefits listed above as well as a membership scholarship for a patient or caregiver in need)
- \$250** *Changing the Future of MDS* Membership (includes benefits listed above as well as additional support for the MDS Foundation as we work together to change the future of MDS) Member names are listed on the MDSF website.

2017 MDS PROFESSIONAL MEMBERSHIP OPTIONS

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



TOGETHER WE ARE A COMMUNITY RESOURCE OF HOPE FOR THOSE **LIVING WITH MDS**

Founded in 1994, the US-based MDS Foundation is the only not-for-profit international organization dedicated solely to MDS. Worldwide, 87,000 cases are diagnosed each year and our mission is to serve MDS patients to ease the burden of this terrible disease and ultimately change MDS outcomes. 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 3 approved treatment options with many more in the development phase.

OUR MISSION: The MDS Foundation, Inc., is an international organization devoted to the support and education of patients and healthcare providers with innovative research into the fields of MDS and related myeloid neoplasms in order to accelerate progress leading to the control and cure of the myelodysplastic syndromes.

OUR VISION: By building an international community of physicians, researchers, and patients, we will make potential curative therapies accessible to all patients with MDS.

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

The MDS Foundation, Inc.

4573 South Broad Street, Suite 150, Yardville, NJ 08620

800-637-0839/609-298-1600

The MDS Foundation, Inc. is a 501c3 tax exempt organization.

Thinking of joining the MDS Foundation as a Professional Member?

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

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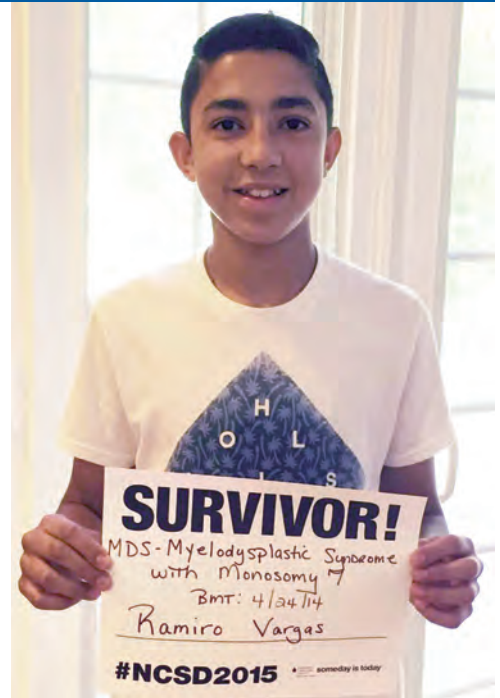
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the myelodysplastic syndromes foundation

statement of purpose

The Myelodysplastic Syndromes Foundation, established by an international group of physicians and researchers, is a nonprofit health organization devoted to serving those patients afflicted with MDS. Until the Foundation was set up, no formal organization had been devoted to MDS.

the foundation's mission

The MDS Foundation, Inc. (MDSF) is an international organization devoted to the support and education of patients and healthcare providers with innovative research in the fields of MDS and related myeloid neoplasms in order to accelerate progress leading to the control and cure of these diseases. By building an international community of physicians, researchers, and patients, we will make potentially curative therapies available for all patients with MDS.

contact us

Phone within in the US: 1-800-MDS-0839

Outside the US only: 1-609-298-1035

Fax: 1-609-298-0590

E-mail: patientliaison@mds-foundation.org



The MDS Foundation, Inc.
4573 South Broad Street
Suite 150
Yardville, NJ 08620

To learn about MDS visit us at
www.mds-foundation.org

TESTIMONIALS

"My father was diagnosed with MDS in Oct 2016 and this is the best site I have found online"

I would love to provide him with these books of information about MDS. Thank you.

Rebecca V.

"My parents being technologically challenged, these books would be a great resource in this, the beginning of our education. Thank you for aiding us in this time of need. Let the battle begin!"

Tracey A.

"Thank you for providing a booklet that addresses many of my questions and provides resources to seek answers to other questions."

Lindsay G.

"This information was very helpful to help me understand all about MDS. I want to share a copy with a friend."

Anna A.

"The online book is very helpful. Would be very happy to have the hardcopy for my family."

Debbie L.

"Great association!"

Selemon G.

"Thank you for making these books available. They're the most accessible I've found so far."

Maya T.



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

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Jane Massey, far left, with her family

JANE MASSEY, MDS PATIENT, SPEAKS:

**Not too many people can say this,
but breast cancer saved my life.**

It came as a shock. After a few months of being cancer free, I was devastated when I was diagnosed with Myelodysplastic Syndromes (MDS) in December 2016. As a 50 year old wife, mother of three, and someone who just beat breast cancer, I was looking forward to returning to my work as a pharmacist and spending more time with family and friends. This new diagnosis put everything on hold; never did I think I would have blood cancer.

I would have to fight for my life one more time.

My doctors told me that a transplant is the only course of treatment for MDS. What's more, I would need one as soon as possible. It was difficult to accept what would happen to me if I didn't find a match.

We learned that the first step, though rare, is to test my siblings to see if they are compatible before turning to the potential donor database. Sara, my daughter and a pharmacy student at University of Missouri-Kansas City, couldn't wait to see if my siblings were a donor match and quickly started the process to set up a donor drive with DKMS, the nonprofit leading the fight against blood cancer. As fate would have it, two of my siblings turned out to be perfect matches, and I'll receive my bone marrow transplant in the next few months.

However, not everyone is as lucky as me.

According to DKMS, only 30% of patients are able to find a matching donor within their family. The other 70% will rely on an unrelated donor to save their life. The humbling realization that most MDS patients are not as fortunate as I am to find a match in their family has inspired my family to team up with DKMS to take action and help other patients by registering new donors; a need that is critical.

Every three minutes someone in the U.S. is diagnosed with a blood cancer and over 170,000 Americans are diagnosed with a blood cancer each year.

 **EVERY THREE MINUTES**
someone in the U.S is diagnosed with a blood cancer

 **170,000 AMERICANS**
diagnosed with a blood cancer each year

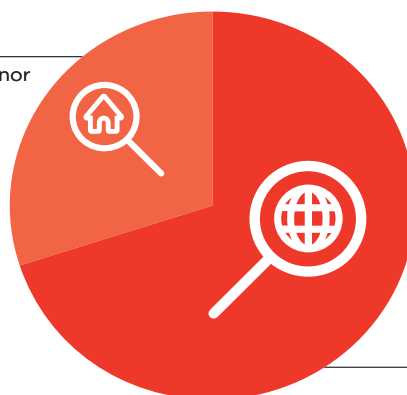
After seeing first-hand the difficulty faced by blood cancer patients, Sara was determined to take action. She brought together pharmacy students from the UMKC Schools of Pharmacy in Kansas City, Springfield, and Columbia, MO, to help register potentially lifesaving bone marrow donors with DKMS. As president of her student pharmacy group, APhA-ASP, Sara worked directly with DKMS to organize a series of bone marrow registration drives to raise awareness about MDS and bone marrow transplants in general.

Since my diagnosis, my life has changed. Knowing that the cure for my type of MDS is only by **transplant has been a little overwhelming**. Knowing that to sustain my life, I am dependent upon someone else to give me a part of them is humbling. My diagnosis has motivated my family to take action and pay it forward. Helping others find a potential donor is getting us through this tough time and serves as a constant reminder of how lucky we are to have found my match in my siblings.

In the end, my breast cancer may have very well saved my life. If it wasn't for the **routine bloodwork** that I received during my treatment, I may still not know that I have MDS.

30%

able to find donor within family



rely on unrelated donor

70%



Jane with daughter, Sara

I encourage everyone who can to take time to become a part of the bone marrow registry. It's a simple process and your blood could bring new life to someone who will die without it. The donor journey begins with a swab of the cheek that takes less than 60 seconds and can be the action that leads to a lifesaving transplant.

My family's goal is to reach as many people as we can throughout the state of Missouri and the rest of the United States. My hope is our story can help inspire thousands of people around the world. If you're interested in helping to raise awareness, holding a drive, registering yourself or your family and friends, please visit DKMS.org to learn more.

DKMS
WE DELETE BLOOD CANCER

SPREAD THE WORD



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Syros Announces Approval of Investigational Device Exemption (IDE) for Blood Test to Identify Cancer Patients with Proprietary Biomarkers

IDE Allows Syros to Expand Ongoing Phase 2 Clinical Trial of SY-1425 into Newly Diagnosed Acute Myeloid Leukemia and Low-Risk Myelodysplastic Syndrome Patients

CAMBRIDGE, Massachusetts

October 11, 2016 – Syros Pharmaceuticals (NASDAQ: SYRS) today announced that the U.S. Food and Drug Administration (FDA) has approved an investigational device exemption (IDE) for a laboratory-based blood test to detect proprietary biomarkers discovered using the Company's gene control platform to select patients for enrollment in the ongoing Phase 2 clinical trial of Syros' lead drug candidate, SY-1425, a selective retinoic acid receptor alpha (RAR α) agonist.

The approval of the IDE allows Syros to expand its Phase 2 clinical trial to include newly diagnosed acute myeloid leukemia (AML) patients 60 years of age or older who are not suitable candidates for standard chemotherapy and low-risk transfusion-dependent myelodysplastic syndrome (MDS) patients who test positive for the biomarkers. The trial is currently enrolling genomically defined patients with relapsed or refractory AML or high-risk MDS identified using the biomarker test.

"The approval of the IDE is an important milestone in the development of SY-1425 because it allows us to expand into a broader set of AML and MDS patients and potentially benefit four patient populations with high unmet medical need," said Nancy Simonian, MD, Syros'

Chief Executive Officer. "This achievement is a testament to our ability to discover genomically defined subsets of patients who are most likely to respond to our gene control therapies and collaborate with partners to develop biomarker tests to identify these patient subsets, which is a key part of our strategy to advance a new wave of gene control medicines."

Using its gene control platform, Syros discovered subsets of AML and MDS patients whose tumors have a highly specialized regulatory region of non-coding DNA, known as a super-enhancer, that is associated with the RARA gene, which codes for the RAR α transcription factor. The super-enhancer is believed to lead to over-production of the RAR α transcription factor, locking cells in an immature, undifferentiated and proliferative state. Syros further investigated this biology directly in patient tissues and conducted preclinical studies showing that the RARA super-enhancer is predictive of response to treatment with SY-1425 in models of AML. Based on those data, Syros developed a biomarker strategy for its Phase 2 trial to identify these subsets of AML and MDS patients it believes are most likely to respond to treatment with SY-1425. Syros estimates that approxi-

mately 25 percent of AML and MDS patients have the RARA super-enhancer.

The proprietary biomarkers were developed into a validated laboratory test in collaboration with a diagnostics company under Clinical Laboratory Improvement Amendment, or CLIA, guidelines using a well-established diagnostic platform. The test is currently being used to select relapsed or refractory AML or high-risk MDS patients in the ongoing Phase 2 trial of SY-1425. The diagnostics company submitted the IDE to the FDA, which was required for prospective selection of patients with newly diagnosed AML and low-risk transfusion-dependent MDS for the trial.

The Phase 2 clinical trial of SY-1425 is a multi-center, open-label trial exploring safety and efficacy. The primary endpoint is overall response rate for AML and high-risk MDS patients and red blood cell transfusion-independence rate for low-risk MDS patients. Other endpoints include assessment of pharmacodynamic biomarkers, duration of response, safety and tolerability, and overall and progression-free survival.

Additional details about the trial can be found using the identifier NCT02807558 at www.clinicaltrials.gov.

Fight AML by knowing your facts

AML is one of the most common forms of leukemia in adults, accounting for approximately a third of all leukemias worldwide

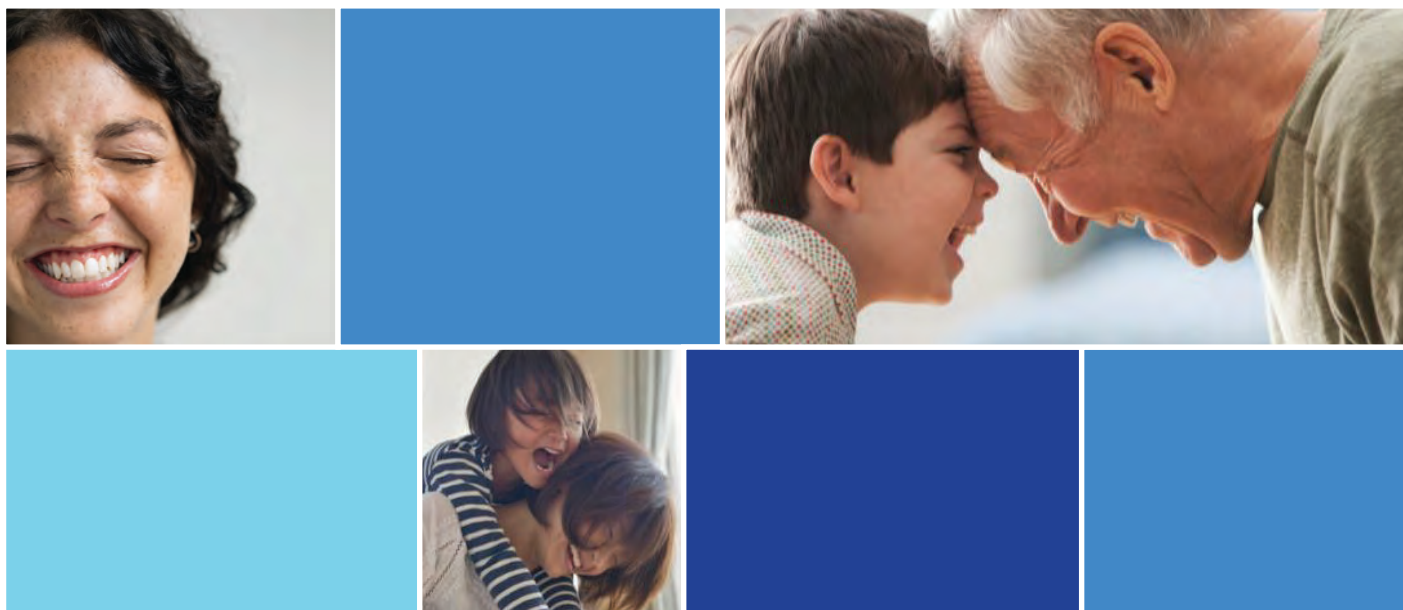
KNOW
AML

World
Awareness
Day
21 April

#KNOWAML #fightAML



An expression makes a world of difference



To all the patients participating in clinical trials and to the families, nurses and physicians who support them, we thank you.

For you and with you, we are committed to improving the lives of people with MDS, AML and other serious diseases by developing medicines that control the expression of disease-driving genes.

To learn more about our Phase 2 clinical trial in MDS, please visit clinicaltrials.gov and search by the trial identification number NCT02807558.

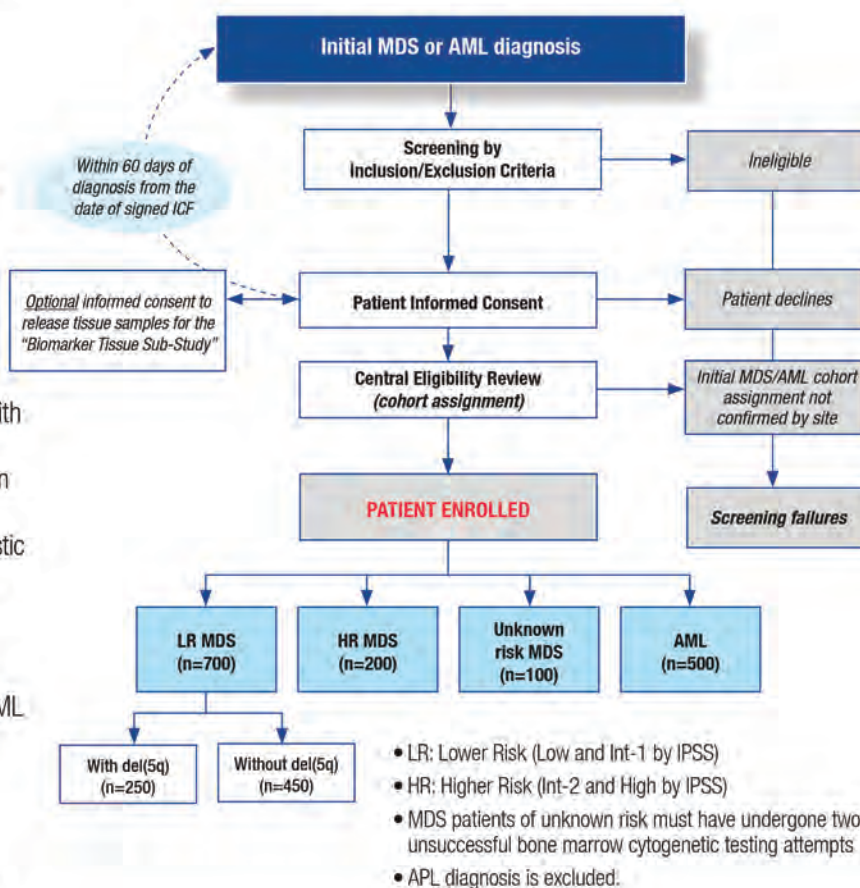
Celgene is researching the following objectives in MDS and AML patient populations:

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

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

Note: Concomitant patient enrollment in other studies is permitted.

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



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



MDS CENTERS OF EXCELLENCE



Our MDS Centers of Excellence are institutions that meet the highest standards for diagnosis, treatment and patient care. Your Center helps form the referral base for patients seeking first or second opinions and/or additional treatment options from experts in MDS. We currently have 67 Centers in the United States and 107 Centers in countries around the world. Our MDS Centers can be viewed here:

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

Benefits of membership include recognition as an MDS Center of Excellence by the MDS Foundation. Our MDS Centers of Excellence are recorded in our published newsletters and on the Foundation's website.

For many centers, the acknowledgement attracts patients who are seeking high-quality, MDS specific care, allowing these patients access to the latest programs and leading-edge thinking and treatment of the disease. Patient referrals through our Patient Liaison to the Center are a direct result of this recognition. The membership dues support the Foundation's mission and provide physicians with discounted registration rates for our biennial International MDS Symposium, as well as a reduced rate for subscription to *Leukemia Research*.

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

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

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

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

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COPING AND CARING

OUR CAREGIVER STORIES



The MDS Family: Coping and Caring Events

Rochelle Ostroff-Weinberg
Wynnewood, Pennsylvania

Coping and Caring Luncheon
November 5, 2016

MDS patients and their families gathered at the Craftbar Restaurant in New York City for a wonderful luncheon on November 5th, 2016. Guest speaker was Sarah Kelly, MSW, LCSW (Oncology Social Worker). Ms. Kelly's specialty is on cancer quality of life and psychosocial wellbeing issues.

We hope you will join us at our next gathering on Saturday, April 29, 2017, 1-4 pm at the White Dog Café in Philadelphia.

Kindly register by April 21st by calling 1-800-637-0839 or email ahassan@mds-foundation.org.



The Importance of Research and Clinical Trials

Page L. Wingfield
Durham, North Carolina

I'm sure that if you are reading this publication, you are aware of the importance of research and clinical trials. By sharing our story, my hope is you can see their value from a real life perspective.

In 1970 my husband Neal and I had been married for six short months when he was diagnosed with Stage IIIB Hodgkins Disease. At that time the expected survival rate was only two years, and radiation was the sole treatment available. However, there were promising clinical trials being held at the National Institutes of Health in Bethesda, Maryland. Neal was fortunate to be the last subject enrolled in a study testing the efficacy of a four drug treatment referred to as MOPP. It was a most difficult chemotherapy treatment, but he was one of those who reacted favorably to the drugs and his Hodgkin's Disease was brought into remission. As years passed and his remission held steady, we were able to build a life for ourselves.



We were given the precious gift of time... to have a family, raise our children and enjoy a full life together. He worked for NIH for twenty-three years, and then he followed the true calling of his life and



became a United Methodist pastor, serving for 18 years. As far as I am aware, Neal may have been one of the longest post-MOPP therapy survivors, living forty two years past his treatment.

The need for research and clinical trials is never ending. Today's cutting edge treatments depend in part on your willingness to take that leap of faith and participate in clinical trials you are eligible for.

In 2009, after more than a year spent seeking medical help for extreme fatigue and shortness of breath, a diagnosis of low-risk MDS was made. His MDS involved the red blood cells only, so for a while he received occasional transfusions and erythropoietin shots to stimulate red blood cell production. At first the doctors considered his MDS to be de novo (no known cause) because of his long remission from Hodgkins Disease. However, they later determined that it was indeed secondary to his previous chemotherapy.

Because of his age and medical history, he was not considered a good candidate for a bone marrow or stem cell transplant. Instead, he was treated first with Vidaza and then Revlimid. Revlimid worked for over one year, making him transfusion independent. When Revlimid stopped working our last hope was to once again enter a clinical trial. We traveled to Duke University Hospital and met with the principal investigator of the study. However, a second miracle was not to be. In January 2012, shortly after our trip to Duke, MDS claimed his life.

I am so grateful for all the years we had together and the research and clinical trials that made it possible. All those who work tirelessly in research labs, and those who conduct and participate in clinical trials are true heroes. Their efforts and God's grace gave us a wonderful life together.



The need for research and clinical trials is never ending. Today's cutting edge treatments depend in part on your willingness to take that leap of faith and participate in clinical trials you are eligible for. Increasing the body of knowledge will take us to a cure for MDS....and all cancers!



PATIENT STORIES

OUR PATIENT STORIES

My Journey With MDS

Rose Zumbiel
Edgewood, Kentucky

My MDS Journey began in 1997 on a beautiful summer afternoon while sitting on my porch in my northern Kentucky home enjoying my day. I noticed that I had several large bruises on my legs and became concerned so I decided to see my family practice doctor. I wasn't very worried since I felt fine.

My doctor ordered a CBC test and the results came back showing a low platelet count. I had a cold just prior to the test and my doctor attributed the cold to my low platelets. However, he asked that I repeat the CBC test in six months. So, in 1998, I had another CBC test but this time the platelet count came back even lower at 150,000, the low end of the normal range. My doctor then told me I should see a hematologist oncologist but even after being told that, I didn't realize how serious this condition could be.

In 1999 I went through my first bone marrow procedure. I was quite nervous, even scared, and it turned out to be as unpleasant as I feared. But the results were even more unnerving....being told I had a rare blood disease. I was told they didn't have a name for it and the disease mostly impacted the elderly. I was just 48 at the time and I worried about the impact on my husband, Bill, our three adult children and,



at that time, three grandchildren. I just couldn't imagine what would happen next.

Sometime over the next few years, I learned the name of my disease was myelodysplastic syndrome or MDS for short. Looking into it more deeply, I found out it was caused by benzene poisoning. But I didn't understand. I had never, to my knowledge, been exposed to benzene in my life. Yes, my parents were both heavy smokers and it crossed my mind that perhaps that brought it on. But my siblings didn't have MDS and neither did my parents. This didn't make sense.

Several more years passed and I was bruising like crazy! Other than being tired and feeling run-down throughout the day, bruising was my only noticeable symptom, again, being caused by my low platelets. My doctor just seemed to have a "wait and see" attitude and approach to my condition. I did not! I couldn't understand that if my platelets were dropping, why couldn't something be done to bring them back up.

So, I decided in 2004 to find a new doctor and that's when Bill and I met Dr. Manish Bhandari. I knew right away that Dr. Bhandari would help me. He was kind and compassionate and I really felt he had my interests at heart. He is just a wonderful doctor. He performed my second bone marrow procedure to determine where I

was in the progression of the disease. My platelets came back at 87,000 which was very scary. But Dr. Bhandari also had a "wait and see" approach but I now understood this is how you initially deal with this disease. So, I tried to get as mentally comfortable as I could in dealing with my MDS. I learned to make and sell jewelry and stay busy with our boat storage business. And, with three married children and now five grandchildren, all living within ten miles of us, it was getting easier in not thinking about my disease all the time. Nevertheless, I prayed daily that this disease with its bruising and fatigue side effects would go away. But, overall, life was good.

In 2005 Bill retired and I lost my medical insurance due to my pre-existing condition (MDS) and was not able to get new insurance right away. This was a major worry which proved warranted. During a normal check-up with Dr. Bhandari, he noticed new spots on my legs. I didn't think much of them but he did and ordered an immediate bone marrow procedure. Results showed my platelets dropped down to 30,000. Now this was bad! He first ordered platelets for me to see if that would help. But after just one week, all of these new platelets were gone and I was back to 30,000. Now, fortunately, with new insurance from our State's high risk Plan, the next step was my going to our local hospital's cancer care center. There, I had an infusion of a drug, whose name I can't recall. Anyway, I was allergic to the drug so the procedure was halted.



OUR PATIENT STORIES

It was now 2007 and Dr. Bhandari ordered an infusion of a new chemo drug, Vidaza. However, we were getting ready to open a beauty salon with our daughter so I didn't really want to start taking the chemo at that time. Therefore, I held off in taking Vidaza and we opened the salon where I could place my jewelry and help run the business. I loved it!

But the next year I felt I couldn't hold off from taking the Vidaza any longer so I began treatment. It involved taking 21 shots one week each month for six months. After six months, my platelets had increased to 57,000 so Dr. Bhandari stopped the Vidaza treatments to see what would happen. Over the next six months, my platelet levels moved around but generally increased so that by 2009 they were up to 86,000. This was great and I felt good. Over the next 2 years I continued to worry and also prayed a lot that the levels would continue to increase. They seemed to bounce around so much so that Dr. Bhandari dubbed me "The Bouncer". But their range stayed around 56,000 – 87,000.

My bruising, however, was getting worse. Therefore, I decided to call the MDS Foundation to seek out their advice and determine if my bruising was common among others with MDS. I spoke with Audrey Hassan who suggested I go to one of their Centers of Excellence in the United States. We learned one was within two hours in Indianapolis at the IU Cancer Center so I made an appointment with Dr. Larry Cripe. I had previously discussed with Dr. Bhandari my interest in this second opinion and Dr. Bhandari said that if he had the condition I have, he'd want to get a second opinion also. Dr. Bhandari sent all my bone marrow reports and information to Dr. Cripe. Bill and I saw Dr. Cripe in August 2011. Dr. Cripe was very thorough and professional, reviewed all the material sent to him and gave me an examination. While waiting to hear Dr. Cripe's analysis I prayed that he would have an answer about my bruising and



when he came back to see me he did! He said he could understand why Dr. Bhandari called my condition MDS when looking at my bone marrow but he believed I had an auto immune disease mimicking MDS! Well, when he said that, I felt I had a huge weight lifted off my shoulders. This was great! I just couldn't believe it and asked him to send his findings to Dr. Bhandari.

On the drive back home Bill and I talked and were stunned that I didn't have MDS. When I saw Dr. Bhandari a couple weeks later I asked him what he thought. He said he and Dr. Cripe were both correct...I have both MDS and an auto immune disease. I was confused and looked at him and said "Really?" He said Yes and I said "While I love you for all you have done for me, I am going to believe Dr. Cripe!" Dr. Bhandari laughed and said "Believe whatever helps you best." The fact that my condition could be an auto immune disease is not good. An auto immune disease can be very serious but not as bad, at least in my mind, as MDS.

However, a short time later my excitement faded. Dr. Bhandari told me that, after speaking with and reviewing my bone marrow biopsies with Dr. Cripe, they were in agreement that my 8th chromosome showed I definitely had MDS. Although this news was now definitive and I was quite troubled by it, I accepted it. What choice did I have?

At that time in 2011, my platelet count was 75,000. Over the next several years, my platelet count continued to bounce up and down but it began trending higher. One

month it might be 90,000, the next month, 80,000, the next month 110,000. But in 2016 the range increased even more to 110,000–150,000. During these years, I continued to go about my life, living it to the best of my ability. By 2016 my grandchildren count is up to nine and my family and jewelry business are keeping me busy and sane.

I've continued to pray for my bruising, fatigue and disease to leave me. But in November last year, just by happenstance, I became familiar with and started praying to a modern-day saint, St. Padre Pio, who has performed many miracles. I would pray to him off and on throughout the week whenever I would think of him. About a month after I started praying to him I received unsolicited in the mail a prayer card and chaplet from The St. Padre Pio Foundation. I was shocked! It was like St. Padre Pio himself was asking me to use the prayer card and chaplet to pray to him. So, I began praying to him every night for healing from this disease. In late December I saw Dr. Bhandari for my normal checkup where he again did a CBC and platelet check. When I learned that my platelet count was an all-time high of 182,000, I sought out Dr. Bhandari. I was so excited! When I saw him he sat me down and said, "Rose, I believe there has been a miracle!" I was stunned. I couldn't believe it. He said "I don't know how but you are cured." I sat there in shock. I was cured. It was a miracle! He shook my hand and said he'd see me in six months just to touch base. Now, I do believe in miracles. I prayed hard and often over the years and believe Padre Pio had a hand in my healing along with Dr. Bhandari.

Today I feel great. I am still tired and the bruising continues. Dr. Bhandari said it would because the bone marrow is damaged. But I look at the bruising and fatigue as my cross to bear. I still pray every day. I hope everyone reading this feels hope on their journey and I will be praying for all of you.

From Nothing About MDS in Danish – To Being Part of the Growing Danish Patient Society Lyle

Niels Jensen

Slangerup, Denmark

More than ten years ago when I was diagnosed with MDS—Myelodysplastic Syndromes—there was no information in Danish about MDS on the Internet. However, luckily, I managed to find several websites about MDS in English. Having lived and worked in Canada and with my wife, Anna, being Canadian we read those websites with great interest the day after having celebrated our 23rd year wedding anniversary. The English language websites were plenty for me, but Anna yearned to talk with others during the beginning stages of great uncertainty in my MDS diagnosis.

Here is the story of the journey from (almost) nothing about MDS in Danish to MDS now being an active and visible part of the growing Danish patient association Lyle.

Already in the summer of 2008, the MDS Foundation hosted a morning meeting for MDS patients and relatives at the Copenhagen Marriott Hotel with the opportunity to meet other MDS patients and their families. My doctor at Rigshospitalet made me aware of the meeting, and it was my first contact with the MDS Foundation. The Keynote speaker was Dr. Lars Kjeldsen of the Hematology



Clinic at Rigshospitalet, and I also remember the president of Lyle, Jytte Gamby, being there to invite those present to join the then less than a year old association for lymphoma and leukemia patients. I did not entertain the idea of joining at that time. I did not have such a dangerous disease, so I thought: I don't belong there!

Building an International Network via the MDS Foundation

Two years later, I contacted the MDS Foundation and with my input we worked together to update the MDS Foundation's website. Many email exchanges later and discussions via Skype across the Atlantic with Bob Weinberg, a member of the MDS Foundation's Board of Directors, resulted in a more user-friendly modern version of their previous website. During this time, I also acquired the domain mdsandyou.info.

Another result of the contact with the MDS Foundation in 2010 was that the following year I was invited to two meetings. The first was a family day for MDS patients and relatives during their 11th International Symposium on Myelodysplastic Syndromes in Edinburgh. The day ended with a 2-hour meeting regarding the need to establish MDS-specific patient groups worldwide. During that meeting, I learned about patients' associations in England and in France. The second meeting was a two-day Celgene event in Munich under the heading "Partners for Progress" (see participants in the photo above), which was about the rare

cancers. During that event, I learned about difficulty getting newer drugs to Eastern European countries and the initiative MDS Life Beyond Limits, which was largely funded by Celgene. On the return from these meetings, I started the website DK MDS Patient Support Group in the fall of 2011. The logo of my group was inspired by the MDS Foundation's logo. And with Celgene Denmark's help, we created postcards for potential new members to contact the group. These postcards were then distributed to the hematological centers around the country.

Later in 2012, I attended a Lyle hosted event in Copenhagen and announced the idea of creating a Danish association for MDS patients and relatives. I still remember one patient's gripping tale during the meeting about her bone marrow transplant at Rigshospitalet, and her remark after having attended the first minutes of my little after meeting: "Good luck with the project. I am cured, so I'm not interested in an association of MDS patients". There were maybe about 25–30 participants at the small after meeting and my contacts in Celgene Denmark had told me that around 200 to 300 patients a year were confronted with the diagnosis of MDS in Denmark. Based on this and the survival curves, which I had seen in various medical articles, I then estimated that there were around 800–1000 people living with MDS in Denmark. I was somewhat optimistic and thought at that time that the new association could easily get 200 to 300 members to join.

The First Meetings for MDS Patients and Relatives Were Successes

In the Spring of 2013, the first meeting for MDS patients and relatives was held in conjunction with the Novartis Iron Summit at the Bella Center that year. There were three speakers: Dr. Lars Kjeldsen from Rigshospitalet in Copenhagen, Dr. Norbert Gateman from HeinrichHeine University Hospital in Germany and Dr. Richard Wells from Sunnybrook Health Sciences Centre in Canada. About 60 people registered for the event of which about 45 showed up. In the picture above Dr. Richard Wells speaks about the myths of MDS.

The next meeting, which was held at Roskilde Hospital in January 2014, was an even bigger success with over 70 people registering for the event and about 60 of them finding the way to the hospital auditorium. Guest speakers were consultant Klas Raaschou Jensen from the local hospital and Dr. Theo de Witte from the Netherlands, who was in Roskilde to attend a meeting of Danish hematologists. Dr. Theo de Witte's presentations were given in English, but translated into Danish by interpreter.

The image below shows a loved one supporting a MDS patient during the meeting in Roskilde.



Then interest seemed to evaporate. At a meeting in Stakladen in Aarhus with Dr. Eva HellströmLindberg from Karolinska in Sweden as keynote speaker and a whisper interpreter who translated from Swedish to Danish only 25 of the 45 registered participants showed up. Attendance at the next meeting in Odense with consultant



Claus Werenberg Marcher from University Hospital and Professor Detlef Haase from GeorgAugust University of Göttingen as keynote speakers was even less. What I most remember from that meeting was the very inspirational nurse, Winnie Krejsing, which Dr. Marcher had brought along, as well as the subsequent conversation with Dr. Haase about the importance of research for the future treatment of MDS patients. A planned meeting in Aalborg had to be canceled due to little interest.

Our finances were rather limited. We had received a startup grant from the MDS Foundation and had entered into a few collaboration agreements with Novartis. These agreements allowed us to use the communications company Geelmuyden. Kiese to perform all the practical work in connection with our meetings, such as contacting speakers to arrange dates and travel, finding a venue, drafting an invitation and getting printed and distributed, registering people wanting to come to the meeting, and arranging translation of foreign speakers to Danish.

Time to Find Partners Nationally

Based on these developments, the MDS DK Patient Support Group Board decided to explore cooperation opportunities in Denmark. In spring 2015, the board held a meeting with the Danish Cancer Society, who told us that we could well achieve the status of a network under them, but they would recommend a look at other opportunities for cooperation. This resulted in a meeting between board members from

MDS DK Patient Support Group and board members from Lyle in late summer 2015. The participating board members from MDS DK Patient Support Group were very happy with the meeting, and the board decided to seek our activities continued under the auspices of the patient society Lyle and thus discontinue MDS DK Patient Support Group as an independent association. Subsequently, I attended a board meeting in Lyle, which was a very good experience. The board decision was endorsed at our annual general meeting in the autumn, and then the way was open for a binding cooperation.

At the same time international cooperation was intensified. MDS DK Patient Support Group became an associate member of the MDS Alliance and participated in a Novartis Iron Overload Patient Advisory Board meeting in Berlin.

At Lyle's general meeting on April 1, 2016, I was elected to Lyles board. Then MDS DK Patientsupport group held as our statutes prescribe an extraordinary general meeting on 13 April at Karens Minde Culture House, where the autumn decision on the association's abandonment was confirmed. So now, the activities of MDS DK Patient Support Group is part of something bigger, namely the growing patient association Lyle fully in line with what Celgene CEO recommended at Partners for Progress in Barcelona in 2012: Go together across diseases and borders, and stand stronger against politicians and companies both nationally and internationally.

What Has MDS DK Patient Support Accomplished?

In its few years of existence, MDS DK Patient Support has created a website, which provides information about MDS in Danish both for the newly diagnosed and for those who have been living with MDS for some time. This will continue under the patient association Lyle.

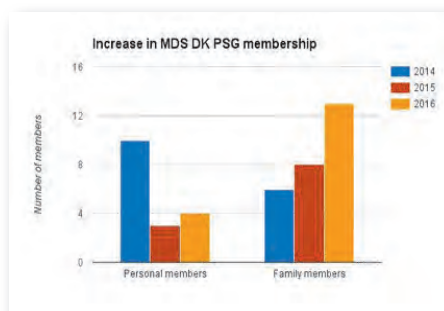
Month after month, we have attempted to bring information about the latest research development around MDS mainly based on the periodical Leukemia Research and the Google+ group Advances in Medicine and Biology. This will continue under the patient association Lyle and expand to other information sources.

We took initiative through Celgene to having the website MDS Life Beyond Limits available in Danish and other Scandinavian languages. After publication of the MDS Foundation's patient booklet in Danish on our website, Celgene took the initiative to create the website blodceller.dk specifically aimed at the newly diagnosed MDS patients and their relatives also in all Scandinavian languages. The information on this website is also available in printed form through the patient society Lyle. Our latest finished project is the Danish translation of the MDS Foundation's booklet "What Does My Bone Marrow Do?", and it is available for distribution to patients and their caregivers in Denmark, and will in the near future also be available as a downloadable PDFfile on the website dkpsg.mdsandyou.info.

In 2015, in a last minute membership drive we also created a postcard to advertise our website which was distributed to Danish hematological centers in a holder. Some people on the picture are MDS patients and some are not. This postcard was financed by the startup grant from the MDS Foundation.

What I Bring to the Patient Society Lyle

What am I bringing to Lyle? I have an interest in delving into the latest scientific



breakthroughs in medical research. My background as a chemical engineer makes this possible. Until the middle of 2015, my focus was only on articles that specifically mentioned MDS, but recently interest has spread to other abbreviations such as AML, ALL, CLL, CMML abbreviations, which I hope to get a little more knowledge of during the coming months. In addition, I am interested in photography and for what is happening in Danish politics. Those interested can read more about that on my Google+ pages and see some of my photo

on 500px. Besides the website www.mds-andyou.info with links to MDS groups worldwide and a world map of MDS Centers of Excellence and the website dkpsk.mdsandyou.info, I am also webmaster of a few other websites so IT takes up a little in my everyday life. In everyday life, I use mainly computers with the operating system openSUSE, which is based on the same core code as most of the world's supercomputers. Over the past years, I find that I am increasingly using browser based tools, which also works on my smartphone or tablet.

I share the hope of the Chairman of Lyle that this patient support group eventually will develop into a support organisation for all blood cancer patients in Denmark. Including adding MDS to diseases such as AML, ALL, CMML is a step in that direction. As is the structure, which the board of Lyle have created to deal with many diseases.

DANISH MDS AWARENESS POSTCARDS

The idea behind the picture is that one cannot identify who has MDS. Three people in this picture have been diagnosed with MDS. Patients are sometimes hurt by comments along the lines of "but you don't look sick."





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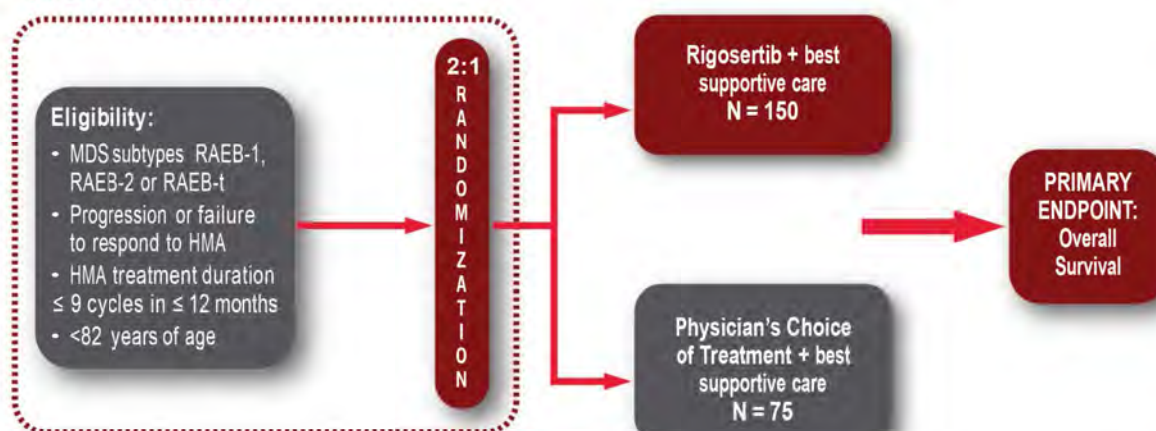
The Pivotal MDS Trial **INSPIRE** is Now Recruiting Patients

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

STUDY DESCRIPTION

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

STUDY SCHEMA



PRIMARY ENDPOINTS

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

INTERNATIONAL TRIAL

More than 150 trial sites.

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

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



A clinical trial is NOW ENROLLING

MEDALIST is an international clinical trial for people who have myelodysplastic syndrome (MDS). MEDALIST will determine whether an investigational drug called luspatercept* can help

- reduce the number of red blood cell transfusions
- improve the symptoms of anemia associated with MDS



IF YOU HAVE MDS

of very low-, low-, or intermediate risk and require regular blood transfusions, you may be eligible to take part in an international clinical trial called the MEDALIST Trial.

**Ask your doctor about the MEDALIST Trial.
Together you can decide if this clinical trial
is right for you.**



MEDALIST

Learn more about the MEDALIST Trial at
www.clinicaltrials.gov by searching for NCT02631070.
Or request information by e-mail at
clinicaltrialdisclosure@celgene.com or call 1-888-260-1599.



*The safety and efficacy of luspatercept has not been established. There is no guarantee that luspatercept will become commercially available.



NEW CLINICAL STUDY IN MDS

PEVONEDISTAT-2001

A Phase 2, Randomized, Controlled, Open-Label, Clinical Study of the Efficacy and Safety of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine in Patients with Higher-Risk Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML), and Low-Blast Acute Myelogenous Leukemia (AML).

Takeda Pharmaceuticals International Co. is currently enrolling patients for a Phase 2 clinical trial of the study drug pevonedistat. The purpose of this study is to evaluate the efficacy and safety of pevonedistat plus azacitidine versus single-agent azacitidine in participants with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia and low-blast acute myelogenous leukemia.

This study will look at the overall survival, event-free survival and response to treatment in people who take pevonedistat and azacitidine when compared to people who take single-agent azacitidine.

The study will enroll approximately 117 participants. Once enrolled, participants will be randomly assigned (by chance, like flipping a coin) to one of the two treatment groups in a 28 day treatment cycle:

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

All participants will receive azacitidine via the intravenous or subcutaneous route. Participants randomized to the combination arm will also receive pevonedistat intravenous infusion. This multi-center trial will be conducted worldwide. Patients may qualify for this study if:

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

In order to refer a patient with MDS, CMML, or low-blast AML for enrollment to this study and review eligibility criteria, physicians/health care providers should visit www.clinicaltrials.gov (NCT02610777)

Contact: 1-877-674-3784; globaloncologymedinfo@takeda.com

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

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NEW CLINICAL STUDY: IMerge Lower-Risk MDS

Current Status: Part 1 recruitment complete; Part 2 is not yet open for recruitment. For additional details, refer to the Geron press release (12Sep2016) at

<http://ir.geron.com/phoenix.zhtml?c=67323&p=irol-newsArticle&ID=2201055>.

Janssen Research & Development, LLC is conducting a Phase 2/3 clinical study referred to as "IMerge", with the study drug Imetelstat, which is a first-in-class telomerase inhibitor. With its novel mechanism of action, Imetelstat may provide clinical benefit to MDS patients. In this study, Imetelstat is administered as a 2-hour intravenous infusion every 28 days.

IMerge is a study for people with MDS who need blood transfusions due to anemia (low red blood cell counts). People with low or intermediate-1 risk MDS that has relapsed or is refractory to Erythropoiesis-Stimulating Agents (ESAs) treatment are enrolled in the study. This study is being conducted at multiple hospitals and institutions around the world, in approximately 80 sites globally.

For more information about this clinical study, please visit

www.clinicaltrials.gov (NCT02598661)



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