

## MDS NEWS HIGHLIGHTS

### FROM THE GUEST EDITOR'S DESK

#### ■ HIGH-RISK MDS AND AML: ONE OR TWO DISEASES?

Michael Heuser, MD, Hannover, Germany



### PLAN TO ATTEND OUR UPCOMING SYMPOSIA

#### 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

May 8–11, 2019  
Copenhagen, Denmark

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### GUEST EDITORIAL

#### HIGH-RISK MDS AND AML: ONE OR TWO DISEASES?



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Should high-risk MDS and *de novo* AML be considered and treated as one disease? Past modifications of the WHO classification and more recent decisions of several study groups suggested the answer to this question would be “yes”. The WHO classification incorporated the former MDS category RAEB-T into AML in 2001 and recent protocols for AML clinical trials allow inclusion of MDS patients starting from a blast count of 10% or higher. On the other hand, clinical data consistently show a poor prognosis of patients with AML and antecedent MDS when they were treated with an AML protocol, especially if patients were pre-treated with hypomethylating agents at the MDS stage.<sup>1,2</sup> Here, I will review characteristics, genetics, and prognosis of patients with high-risk MDS and low blast count AML and compare their response to established and novel treatments.

#### How are high-risk MDS and low blast count AML defined?

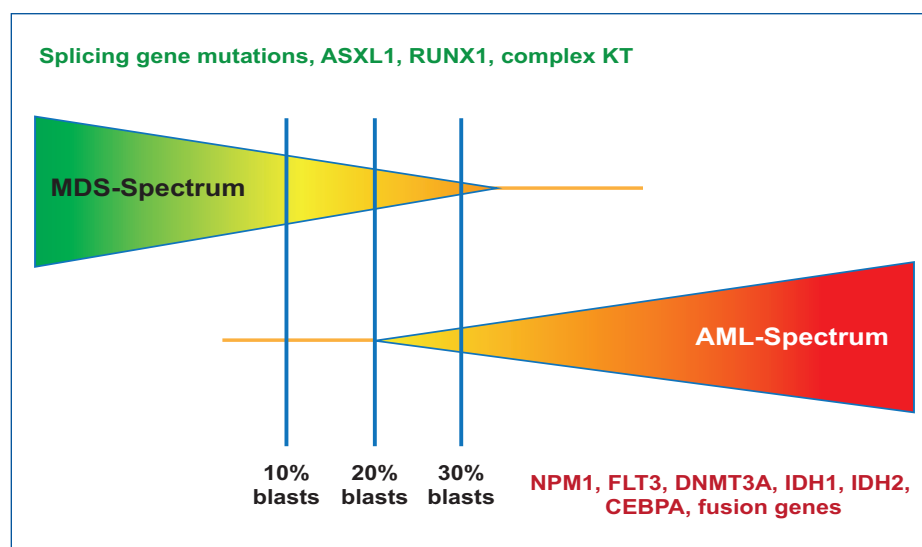
For the purpose of this review, high-risk MDS is defined as myelodysplasia with 10 to 19% blasts in the bone marrow, corresponding to MDS-EB-2 according to the 2016 WHO classification.<sup>3</sup> Based on the revised IPSS risk classification, patients with more than 10% blasts have the worst overall survival and the shortest freedom from AML progression, while patients with 5 to 10% blasts in the bone marrow have an intermediate risk.<sup>4</sup> Thus, the blast count is the second most important risk factor besides cytogenetics in the IPSS-R, which can switch a patient by one to two risk groups. In the original IPSS risk score, blast count was the most important risk factor, which may switch patients by two risk groups.<sup>5</sup> The blast count is also the most important risk factor in the WPSS score, and can switch patients by two to three risk groups.<sup>6</sup> In contrast to MDS, blast count is not a major risk factor in AML and is not included in the ELN classification nor does it play a role in most risks scores for adult AML patients.<sup>7</sup> Papaemmanuil and colleagues correlated mutations with the proportion of bone marrow blasts in MDS and found that mutations in *WT1*, *IDH2*, *STAG2*, *NRAS* and a complex karyotype were the factors most strongly contributing to a higher blast count, while *SF3B1* mutations were the most important factor that negatively correlated with blast count.<sup>8</sup> Here AML with 20 to 29% blasts in the bone marrow is considered as low blast count AML, corresponding to the former FAB criterion RAEB-T. AML with myelodysplasia related changes (MRC-AML) is an AML category defined by the 2016 WHO classification and includes AML with a history of MDS or at least 50% dysplastic cells in at least two lineages or MDS related cytogenetic aberrations.<sup>3</sup>

#### Comparison of patient characteristics, genetics and prognosis in high-risk MDS and low blast count AML

Ninety six high-risk MDS and 180 low blast count AML patients were compared in a study by Bacher and colleagues.<sup>9</sup> Age, patient sex, cytogenetic risk, blood counts and genetics were almost identical between these two groups. Surprisingly, the blast count had no effect on overall survival. Instead, cytogenetic and molecular aberrations were highly prognostic in these patients. An even larger study was published by DiNardo and colleagues in 2016.<sup>10</sup> 163 patients with high-risk MDS and 230 patients with low blast count AML and 1,159 patients with 30% blasts or more were compared for patient characteristics and outcome. Again, patient characteristics and overall survival were almost identical in high-risk MDS and low blast count AML, while patients with high blast count AML had a higher white blood cell count, higher LDH levels, less often a complex karyotype and were more often *NPM1* and *FLT3-ITD* mutated. Survival was worse for patients with high blast count AML, although the median overall survival differed only by 2.5 months. In multivariate analysis for overall survival marrow blasts were not prognostic between high-risk MDS and low blast count AML, while high blast count AML had a trend for shorter overall survival. Characteristics between 59 high-risk MDS and 160 MRC-AML patients who all underwent allogeneic transplantation are compared next.<sup>11</sup> Patient characteristics between these two groups were similar except a higher proportion of high-risk MDS patients who were untreated before allo-HCT, and therefore, bone marrow blasts before allo-HCT were also higher in the high-risk MDS group. The frequency of

cytogenetic aberrations and of molecular aberrations was similar between these two patient cohorts except a higher proportion of TET2 mutations in the MRC-AML cohort. Comparing this cohort of MRC-AML patients to 3,427 *de novo* AML patients from the AMLSG BiO-registry it becomes clear that these disease types have clear cytogenetic and molecular distinctions: monosomy 7 and 7q-, monosomy 5 and 5q- and *RUNX1* and *ASXL1* mutations were significantly more frequent in MRC-AML, while CBF leukemias, translocation t(15;17), *NPM1*, *DNMT3A*, *FLT3-ITD*, and *CEBPα* double mutations were significantly more frequent in *de novo* AML (AMLSG BiO-registry, unpublished).

In summary, marrow blasts are prognostic in MDS, while they are not prognostic when high-risk MDS is compared to low blast count AML. This already suggested that low blast count AML is more related to high-risk MDS than to *de novo* AML. In addition, high-risk MDS is genetically related to MRC-AML, while high-risk MDS/MRC-AML is genetically very distinct from *de novo* AML. MDS therefore seems to develop on a different trajectory than *de novo* AML. We can classify high-risk MDS and MRC-AML as diseases of the MDS spectrum, which is characterized by mutations in the splicing machinery, *ASXL1*, *RUNX1* and complex karyotype (and likely other mutations). On the other hand, we can classify *de novo* AML as a disease of the AML spectrum, which is characterized by mutations in *NPM1*, *FLT3*, *DNMT3A*, *IDH1*, *IDH2*, *CEBPα* and by the recurrent fusion genes (Figure 1). If patients are categorized into MDS and AML based on a blast cut-off of 20%, it is inevitable that patients with an AML spectrum disease will be found in the group of patients with 10 to 19% blasts, while patients with an MDS spectrum disease will be found in the patient cohort with 20 to 29% blasts. By estimate, the patient cohort with 10 to 19% blasts



**FIGURE 1.** MDS and *de novo* AML develop on different trajectories.

includes approximately 10% of *de novo* AML patients, while the comparisons of high-risk MDS and low blast count AML, described above, suggest that the patients with 20 to 29% blasts are enriched for high-risk MDS, similarly to the former RAEB-T risk group.

### How do patients with high-risk MDS, low blast count AML and high-blast count AML respond to established and novel treatments?

Patients with high-risk MDS (in this case 10 to 30% blasts) and patients in the subgroup with 20 to 30% blasts had very similar outcomes when they were treated with azacitidine: Seventeen and 18% of the patients achieved complete remission, respectively, and median overall survival was 24.5 months in both groups.<sup>12,13</sup> Azacitidine induced a similar CR rate (19.5%) in patients with high blast count AML, while the median overall survival was only 10.4 months.<sup>14</sup> Clearly, this cross study comparison has to be interpreted with caution and the high blast count AML cohort was clearly older than the high-risk MDS cohort.

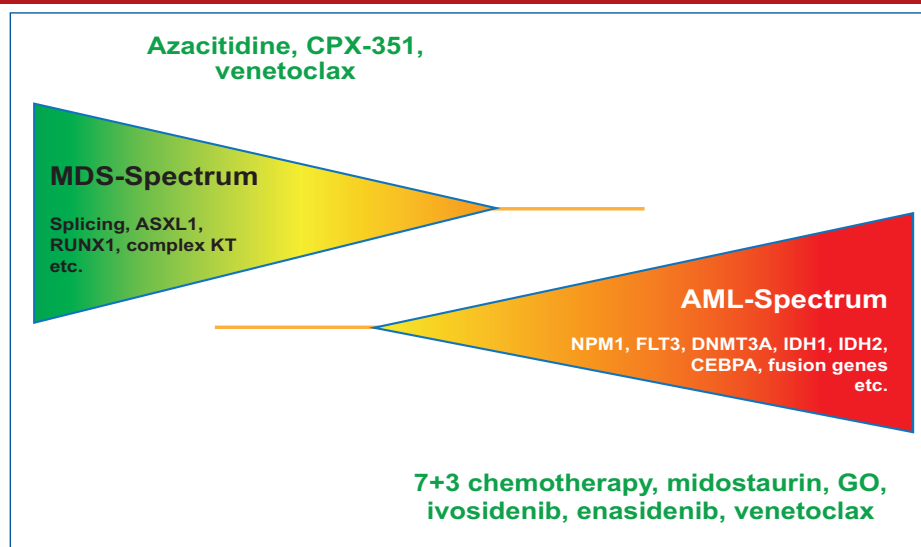
Intensive chemotherapy was given to a relatively small cohort of patients in

these studies and resulted in similar median survival for high-risk MDS (15.7 months), low blast count AML (14.2 months) and high blast count AML (12.2 months).<sup>12-14</sup> The newly approved drugs in AML have not been thoroughly evaluated in MDS patients. Therefore, their efficacy is compared between MRC-AML and *de novo* AML patients. In this regard, CPX-351 is beneficial in MRC-AML,<sup>1</sup> as is venetoclax combined with a hypomethylating agent<sup>15</sup> and enasidenib as monotherapy,<sup>16</sup> which has shown preliminary efficacy in *IDH2* mutated MDS patients at a similar rate as in AML patients. However, the *FLT3* inhibitors midostaurin and sorafenib did not synergize with azacitidine in MDS and secondary AML patients.<sup>17-19</sup> Similarly, gemtuzumab-ozogamicin combined with cytarabine and idarubicin did not improve the outcome in high-risk MDS and secondary AML patients.<sup>20,21</sup>

If we now compare again high-risk MDS patients with *de novo* AML patients, we recognize that these cohorts are different regarding patient characteristics, genetic characteristics, prognosis with azacitidine treatment and in the response to an *FLT3* inhibitor combined with a hypo-

methylating agent. In contrast, high-risk MDS and low blast count AML share many features regarding patient characteristics and genetic characteristics including prognosis under azacitidine treatment. Thus, high-risk MDS, low blast count AML and MRC-AML appear to be a common entity sharing genetic features and responsiveness to treatment. In contrast, high-risk MDS with 10 to 19% blasts does not appear to be an early stage of *de novo* AML.

We have progressed from a time where blast count was a major diagnostic tool to distinguish MDS from AML. We should now incorporate cytogenetic and molecular information in addition to patient history and morphology to distinguish an MDS spectrum disease (high-risk MDS and MRC-AML) from *de novo* AML. Thus, a genetic profile of MDS related cytogenetic aberrations and mutations in splicing factor genes, *ASXL1* and *RUNX1* may define a MDS spectrum disease independent of blast count, and a genetic profile of *NPM1*, *FLT3*, *DNMT3A*, *IDH1*, *IDH2*, *CEBP $\alpha$* , and the common AML fusion genes may define an AML spectrum disease independent of blast count. This proposal certainly needs to be refined and evaluated in large data sets, but could result in a more efficient drug development process. Currently, MRC-AML is again and again shown as a poor risk marker in clinical trials and confounds the efficacy of novel drug treatments that are less efficacious in MRC-AML than in *de novo* AML. A genetic separation of MDS and AML spectrum diseases may thus improve drug development by tailoring drugs to the right patients. That this approach can improve the outcome especially for MRC-AML patients has been shown by the approval of CPX-351, which was specifically developed in MRC-AML and tAML. Currently, CPX-351 and venetoclax appear as promising drugs besides the established hypomethylating agents in MDS spectrum diseases, while 7+3 based chemotherapy, midostaurin, gemtuzumab-ozogamicin,



**FIGURE 2.** Genetic classification of high-risk MDS/MRC-AML and *de novo* AML: implications for treatment.

ivosidenib, enasidenib and venetoclax are available as effective treatments in AML spectrum diseases (**Figure 2**). In conclusion, high-risk MDS and *de novo* AML should be treated as different diseases, while it is acknowledged that the therapeutic possibilities especially for the MDS spectrum diseases remain far behind our expectations.

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## MEETING HIGHLIGHTS AND ANNOUNCEMENTS

61ST ASH ANNUAL MEETING & EXPOSITION . DECEMBER 7-10, 2019 . ORANGE COUNTY CONVENTION CENTER ORLANDO, FL

BREAKFAST SYMPOSIUM • DECEMBER 6, 2019

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### PRECISION HEMATOLOGY IN MYELOYDYSPLASTIC SYNDROMES ORLANDO, FLORIDA



CONTINUING OUR MISSION OF INTERNATIONAL COLLABORATION IN THE FIELD OF MDS

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



*Thank you to all the doctors who presented at and attended our annual American Society of Hematology educational symposium! We reached approximately 350 physicians, researchers and nurses!*

BREAKFAST SYMPOSIUM • NOVEMBER 30, 2018



CONTINUING OUR MISSION OF INTERNATIONAL COLLABORATION IN THE FIELD OF MDS



THE PRESENTATIONS ARE NOW AVAILABLE ON OUR WEBSITE AT  
<https://www.mds-foundation.org/ash-2018-presentations/>

# Welcome to MDS 2019



On behalf of the Scientific and Local Organizing Committees and the MDS Foundation, it is our pleasure to invite you to the 15<sup>th</sup> International Symposium on Myelodysplastic Syndromes taking place at the Tivoli Hotel & Congress Center in Copenhagen, Denmark from May 8-11, 2019. As in previous years, the Symposium will cover the most recent discoveries in MDS basic and translational research as well as all relevant clinical aspects of MDS diagnosis, prognosis, and management. The main lectures will be delivered by recognized international leaders in the field, and we look forward to including high-level research presentations, selected from the abstracts submitted by colleagues.

Furthermore, we are very happy to offer you the opportunity to visit wonderful Copenhagen in the spring – and it does not get better than that!

Copenhagen is the lively capital of Denmark which features some of the happiest people in the world, the world's oldest monarchy and some of the world's best chefs. Enjoy everything from historic buildings, modern architecture and beautiful art to Tivoli gardens, harbor swims and alternative lifestyles in Christiania.

Join us for a vivid conference - and experience our special Danish way of life.

We look forward to seeing you all in Copenhagen!

**Lars Kjeldsen, Jakob Werner Hansen  
and Kirsten Grønbæk**  
Symposium Chairs



# THE 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

COPENHAGEN, DENMARK | 8-11 MAY 2019



## LEGEND:

Plenary Session	Interactive Session	Meet the Expert	Nurses Program	Networking Event	Industry Sessions	Young Investigators Award
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## WEDNESDAY, MAY 8, 2019

	AUDITORIUM 2	AUDITORIUM 3	MEETING ROOM 1
13:00	<b>Workshop I: Basic Science</b>  <b>Welcome:</b> Bo Porse <b>PDX Mouse Models:</b> Dominique Bonnet, Christophe Come, Hind Medyouf	<b>Workshop II: Clinical Management</b>  <b>Welcome:</b> Jakob Werner Hansen <b>Epidemiology:</b> Jan Nørgaard, Lene Granfeldt, Martin Jädersten	<b>Patient and Caregiver Perspectives</b> <b>Narrative and Experience From a Patient:</b> Clement Harlang <b>Health-Related Quality of Life in Patients with MDS:</b> Helle Egeberg Hother <b>Patient Ambassador Support (PAS):</b> Kristina Nørskov <b>Family Caregiver Ambassador Support (FAMCARE):</b> Mary Jarden
14:05	<b>Dendritic Cells and Monocytes in Myelodysplastic Syndromes:</b> Sine Reker Hadrup, Arjen van de Loosdrecht, Johanna Olweus	<b>ICUS/CCUS - How to Handle:</b> Jakob Werner Hansen, Luca Malcovati	<b>Break</b>
14:15	<b>CRISPR/CAS Technology:</b> Rasmus Bak, Kristian Helin <b>Single Cell Sequencing:</b> Adam Mead	<b>Clinical Cases:</b> David Bowen, Eva Hellström-Lindberg, Magnus Tobiasson	<b>MDS Update and Novel Treatment</b> <b>MDS Update - Classification and Treatment:</b> Lars Kjeldsen <b>Future Treatment to MDS - Genetics:</b> Marie Bill <b>Symptom Management in Patients with MDS:</b> Anne Dunweber
15:15	<b>Bioinformatics and Management of Big Data:</b> Elli Papaemmanuil, Kyong Jae Won	<b>Clinical Management of Familial Diseases: Patient History and Cases:</b> Brigitte Schlegelberger, Mette Klarskov Andersen	<b>Break</b>
15:30	<b>Closing Remarks</b>	<b>Closing Remarks</b>	<b>Patient Involvement and Self-Management During and After Treatment</b> <b>Patient Involvement in Treatment - Home Based Treatment:</b> Katrine Fridthjof <b>Patient Activation Through Counseling and Exercise in Patients with Acute Leukemia (PACE-AL) - A Randomized Controlled Trial:</b> Mary Jarden
18:00	<b>Break</b>		
	<b>AUDITORIUM 1</b>		
18:30	<b>Opening Ceremony</b> <b>18:30</b> Introductory Welcome: Kirsten Grønbæk <b>18:40</b> Welcome from the MDS Foundation: Stephen Nimer <b>18:50</b> TBA: Benjamin Ebert <b>19:20</b> Tito Bastianello Young Investigator Awards: Stephen Nimer <b>19:30</b> Entertainment		
20:00	<b>Welcome Reception (Exhibition Area)</b>		



# THE 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

COPENHAGEN, DENMARK | 8-11 MAY 2019



## LEGEND:

Plenary Session	Interactive Session	Meet the Expert	Nurses Program	Networking Event	Industry Sessions	Young Investigators Award
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## THURSDAY, MAY 9, 2019

	AUDITORIUM 1	AUDITORIUM 2	AUDITORIUM 3	MEETING ROOM 1
07:00-08:00	Industry Supported Session Not Included in main event CME/CPD Credit			
07:30-08:00		Meet the Expert I Sideroblastic Anemia: Eva Hellström-Lindberg	Meet the Expert II Clinical Experience with Immune Check Point Inhibitors in MDS: Casey O’Connell	Meet the Expert III Iron Chelation: Norbert Gattermann
	AUDITORIUM 1			
08:00-09:30	MDS Biology   Chair: Bo Porse and Liran Shlush 8:00 MDS Stem Cell Surveillance and Therapeutic Targeting: Stein Eirik W. Jacobsen 8:20 Oral Presentation 8:35 Stem Cell Origins of MDS to AML Progression: Ulrich Steidl 8:55 Oral Presentation 9:10 The Niche: The Hen or the Egg: Marc Raijmakers			
09:30-10:00	Coffee Break, Poster Viewing, and Exhibition Visit			
10:00-11:30	MDS Epigenetic Deregulation   Chair: Kirsten Gronbaek and Jean Pierre Issa 10:00 Mechanisms of TET2 Epigenetics in Myeloid Cancers: Kristian Helin 10:20 Oral Presentation 10:35 Epigenetic Therapy and the Immune System: Peter A Jones 10:55 Oral Presentation 11:10 Epigenetic Regulation in MDS /AML: Maria Figueroa			
11:30-13:00	Industry Supported Session Not Included in main event CME/CPD Credit		Lunch Break, Poster Viewing, and Exhibition Visit	
13:00-15:00	Personalized Medicine in MDS   Chair: Mario Cazzola and Peter Woll 13:00 The Origin of Relapses MDS/AML: Liran Shlush 13:20 Oral Presentation 13:35 A Genetic Algorithm for Treatment: Elli Papaemmanuil 13:55 Oral Presentation 14:10 How Does Quality of Life Impact Descission Making in MDS: Reinhard Stauder 14:30 Panel Debate: Is There a Role for Personalized Medicine in MDS? Liran Shlush, Elli Papaemmanuil, Jean Pierre Issa, Reinhard Stauder			
15:00-15:30	Coffee Break, Poster Viewing, and Exhibition Visit			
15:30-17:00	Decision Making in Allogeneic SCT   Chair: Guillermo Sanz and Theo de Witte 15:30 Treatment After Relapse - Post Allo: Thomas Schrøder 15:50 Oral Presentation 16:05 Pro & Con Debate - Transplantation of CCUS with 3 Mutations or More? When and How: Eva Hellström-Lindberg, Pierre Fenaux 16:25 Pro & Con Debate - How to Handle TP53 Mutated MDS/tMDS: To Do or not to Do Transplantation - Eva Hellström-Lindberg, Pierre Fenaux 16:45 Discussion			
17:00-19:00	Poster Vewing (Exhibition Area)			
18:00-19:00	Industry Supported Session - Not Included in main event CME/CPD Credit			

# THE 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

COPENHAGEN, DENMARK | 8-11 MAY 2019



## LEGEND:

Plenary Session	Interactive Session	Meet the Expert	Nurses Program	Networking Event	Industry Sessions	Young Investigators Award
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## FRIDAY, MAY 10, 2019

	AUDITORIUM 1	AUDITORIUM 2	AUDITORIUM 3	MEETING ROOM 1
07:00-08:00				
07:30-08:00	<b>Industry Supported Session</b> Not Included in main event CME/CPD Credit	<b>Meet the Expert IV</b> Shared Decision Making in Allo SCT: Nicolaus Krøger	<b>Meet the Expert V</b> Aplastic Anemia/PNH and MDS: Austin Kulasekararaj	<b>Meet the Expert VI</b> Genetic Counselling in MDS - What Do I Tell my Patient? Brigitte Schlegelberger

	AUDITORIUM 1
08:00-09:15	<b>Immune Aberrancies in MDS   Chair: Sine Hadrup and Kulasekararaj</b> 8:00 Myeloid Suppressor Cells in MDS: Sheng Wei 8:20 Oral Presentation 8:35 Immune Pathogenesis in MDS: Shahram Kordasti 8:55 Oral Presentation
09:15-09:45	Coffee Break, Poster Viewing, and Exhibition Visit
09:45-11:45	<b>Therapy I: Modulating the Immune System in MDS Treatment   Chair: Ghulam Mufti and Andreas Due Ørskov</b> 09:45 Combining Hypemethylation Drugs and Immune Check Point Inhibitors: Guillermo Garcia-Manero 10:05 Oral Presentation 10:18 PD-L1+ Guadecitabine: Casey O'Connell 10:38 Oral Presentation 10:51 Vaccination Trials in MDS/AML: Arjan van de Loosdrecht 11:11 Oral Presentation 11:24 CAR-T - A Potential In Myeloid Cancers? Katherine Cummins
11:45-13:15	<b>Industry Supported Session</b> Not Included in main event CME/CPD Credit
	Lunch Break, Poster Viewing, and Exhibition Visit
13:15-14:30	<b>Therapy II: New Drugs and Combinations   Chair: Luca Malcovati and Ari Giagoundidis</b> 13:15 Low Risk Disease- What's New?: Uwe Platzbecker 13:40 Oral Presentation 13:55 Targeting Splice Factor Mutations: Seishi Ogawa 14:15 High Risk Disease: What's After Aza: Jean Pierre Issa
14:30-15:00	Coffee Break, Poster Viewing, and Exhibition Visit

Continued on next page

# THE 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES


COPENHAGEN, DENMARK | 8-11 MAY 2019



## LEGEND:

Plenary Session	Interactive Session	Meet the Expert	Nurses Program	Networking Event	Industry Sessions	Young Investigators Award
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## FRIDAY, MAY 10, 2019 (continued)

	AUDITORIUM 1
15:00-16:15	<b>Predisposition Syndromes in Pediatric &amp; Adult MDS Patients   Chair:</b> Mette Klarskov and Brigitte Schlegelberger 15:00 Genetic Predisposition to MDS: Jane Churpek 15:20 Oral Presentation 15:35 Pediatric MDS: Akiko Shimamura 15:55 To Do or not to Do - Ethical Debate: Jane Churpek and Akiko Shimamura
16:15-17:30	<b>Clinical Cases - Panel Debate   Chair:</b> Moshe Mittleman <b>Panel Experts:</b> Ghulam Mufti, Ari Giagounidis, David Bowen, David Steensma, Eva Hellström-Lindberg, John Bennet CCUS Low Risk with High Risk Genetic Profile Low Risk Severe Thrombocytopenia High Risk MDS
18:30	<b>Networking Dinner Event (Axelborg )</b> 

## SATURDAY, MAY 11, 2019

	AUDITORIUM 1
08:00-09:30	<b>CMML   Chair:</b> Johanna Ungerstedt and Guillermo Sanz 8:00 Preclinical Models of CMML (TET2/NRAS) and Sensitivity to MAPK Inhibitor: Alan Shih 8:30 Oral Presentation 8:45 Treatment of CMML Including RAS Mutated: Raphaël Itzykson 9:15 Oral Presentation
09:30-10:00	Coffee Break
10:00-10:45	<b>Keynote   Chair:</b> Jakob Werner Hansen TBA: David Steensma
10:45-11:45	<b>Awards and Best Talks   Chair:</b> Stephen Nimber
11:45-12:00	<b>Closing Ceremony</b>

# THE 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

COPENHAGEN, DENMARK | 8-11 MAY 2019



## REGISTRATION

	REGULAR FEE From March 13 until April 30, 2019	LATE/ONSITE FEE From May 1, 2019
MDSF member*	€ 700	€ 800
Non member	€ 800	€ 900
Hematologists in training **	€ 600	€ 700
Nurse**	€ 275	€ 325
Student**	€ 225	€ 250
Workshop 1: Basic Science***	€ 30	€ 50
Workshop 2: Clinical Management***	€ 30	€ 50
Networking Dinner	€ 100	€ 100

\* In order to become a member of the MDS Foundation and benefit from reduced fees, please visit the [MDSF Membership website](#).

\*\* In order to benefit from the special fee, a submission of your status confirmation (approval letter signed by the Head of Department or copy of your status ID) must be uploaded during online registration.

\*\*\* The Workshops have limited availability and registration is on a first-come first-serve basis.

### FEES FOR ALL MEETING PARTICIPANTS INCLUDE

- Entrance to all scientific sessions
- Access to the exhibition area
- Invitation to the Opening Ceremony & the Welcome Reception
- Coffee & lunch during breaks, as indicated in the program
- Printed material of the Symposium
- Certificate of attendance

### PAYMENT METHODS

Payment of registration fees (in Euro) can be made as follows:

**By Credit Card:** Visa, MasterCard or American Express

**By Bank Transfer:** (Additional 30 Euro handling fee is required)

#### Please make drafts payable in Euro only to:

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Bank Details: Credit Suisse Geneva, 1211 Geneva 70, Switzerland  
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Please ensure that the name of the meeting and of the participant is stated on the bank transfer.

Bank charges are the responsibility of the participant and should be paid at source in addition to the registration fees.

Registration will only be valid upon receipt of the full payment by

the registration department according to the deadline indicated. An email confirming registration will only be sent after receipt of the required fees.

Outstanding payments will be collected on-site and charged the on-site rate. A copy of the bank transfer (or other proof of payment) will be required in the event that registration fees were not credited to the meeting account on time.

### REGISTRATION CANCELLATION POLICY

All cancellations must be electronically mailed. Refund of registration fee will be as follows:

Note, in case of cancellation at any stage, the Bank transfer handling fee (30 Euro) will not be refunded - applicable to Bank Transfer payments only.

Cancellations received between March 7 to May 1, 2019 - 50% will be refunded

From May 2, 2019 - no refund will be made

### GROUP REGISTRATION

For group registration (10 participants and more) please contact the registration department at: [reg\\_mds19@kenes.com](mailto:reg_mds19@kenes.com)



# THE 15<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

COPENHAGEN, DENMARK | 8-11 MAY 2019



## ACCOMMODATION

MDS 2019 Symposium participants enjoy exclusive rates on their accommodation in Copenhagen. Choose from a wide selection of quality hotels – close to the venue and city center- catering to all budgets.

Browse hotels and book through our secure system on <https://hotel.kenes.com/en/congress/MDS19>

## PATIENT & FAMILY FORUM

**Save the Date for Saturday, May 11, 2019**

**Location:** IDA Mødecenter, Kalvebod Brygge 31-33, Copenhagen

FREE One-Day Conference for MDS Patients & Caregivers LIVING with MDS . Whether you are a newly diagnosed patient, a long-term survivor, or caregiver, this event will have something for you. Learn from experts about treatment therapies and strategies for Patients & Caregivers LIVING with MDS.

På [www.lyle.dk](http://www.lyle.dk) under arrangementer

Via email til [niels@lyle.dk](mailto:niels@lyle.dk)

## NETWORKING EVENT

Join us for an evening of networking and discussions with your international colleagues. Meet old friends and make new connections at the Networking Dinner which will take place at

**Axelborg on Friday 10 May at 18:30**



# INTERNATIONAL WORKING GROUPS

MAKING CONNECTIONS AROUND THE WORLD

## THE MDS/MPN INTERNATIONAL WORKING GROUP



**MICHAEL R. SAVONA, MD**  
Vanderbilt University Medical Center  
Nashville, Tennessee

The MDS/MPN IWG was established in 2012 and has established a leadership role in research into the pathobiology and novel treatment for MDS/MPN. Since the publication of the Proposed MDS/MPN Response Criteria in 2015,<sup>1</sup> the clinical trial opportunities have dramatically increased, including the first investigator-driven, multi-national MDS/MPN-specific trial led by MDS/MPN IWG members: **ABNL MARRO**. A Novel therapy combination in untreated MDS/MPN And Relapsed/Refractory Overlap Syndromes (**ABNL-MARRO**) is a inter-national basket study designed to allow new compounds and combinations of therapy to be introduced easily among MDS/MPN IWG clinical sites which see MDS/MPN patients, study the biology and pathophysiology of the diseases, and have multilateral expertise in this area. ABNL MARRO-001 is the first MDS/MPN IWG study and is opening spring 2019 in the US, and then in EU countries shortly after.

**ABNL MARRO-001** uses an oral DNA methyltransferase inhibitor (DNMTi), ASTX727, as a backbone with combination therapies targeting JAK1, PIM kinase and LSD-1. DNMTi combinations have been evaluated in phase 1 safety studies, and will form 3 separate arms in **ABNL MARRO-001**.

With **ABNL MARRO-001**, the MDS/MPN IWG aims to validate the proposed criteria for response in MDS/MPN, test QOL tools in patients with MDS/MPN, develop new biomarkers for response to therapy, and augment efforts of large scale prospective genotyping efforts in MDS/MPN.

### References:

1. Savona MR, Malcovati L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood*. 2015;125:1857-65.

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## 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)<sup>1</sup>. 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<sup>1</sup> 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 359 MDS patients from 19 collaborative IWG-PM centers 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.<sup>2</sup>

### Recent Molecular Results

Prospective molecular and clinical data on 4270 MDS patients gathered by members of the IWG-PM-Molecular Committee were combined and preliminary analysis was presented at the MDS Symposium of the MDS Foundation at the ASH 2018 meeting.<sup>3</sup> Members of the Coordinating, Oversight, Cytogenetic and Classification Committees along with sequencing performed at Memorial Sloan Kettering Cancer Center have contributed to this ongoing analysis. At least one driver mutation was present in 95% of the patients (median 4). 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 the patients and were strongly associated with survival. 27 genes were mutated in >1.5% of samples and were included for analysis. Mutations in 12 genes were strongly associated with shorter overall survival in univariate analyses. Adjusting the hazard ratio of death for IPSS-R risk groups identified several mutated genes with independent prognostic significance. Association of WHO morphologic MDS subtypes and mutational composition has been characterized. A clinical/mutation score based on survival and AML transformation risk is being developed and validated. Further plans include identifying genetic predictors of response to hypomethylating agents and sequential mutation analysis of disease progression.

### Current Project Status, Plans for Sequencing of New Samples

In addition to the above assessment of previous samples, the project will sequence additional large numbers of MDS cases to further develop our database and mutational evaluations. An automated sample management system



was recently implemented that links sample reception to library preparation and sequencing submission. The results of these analyses will serve as the template with which to build an integrated molecular risk model for MDS. Also presented at the meeting was the data aggregation update with integration of the data into cBioPortal. This is a mechanism for use of the data by all members of the group for their analyses for investigator-initiated projects.

### References

1. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012; 120:2454-2465.
2. Haase D, Stevenson KE, Neuberg D, Maciejewski JP, Nazha A, Sekeres MA, Ebert BL, Garcia-Manero G, Haferlach C, Haferlach T, Kern W, Ogawa S, Nagata Y, Yoshida K, Graubert TA, Walter MJ, List AF, Komrokji RS, Padron E, Sallman D, Papaemmanuil E, Campbell PJ, Savona MR, Seegmiller A, Adès L, Fenaux P, Shih LY, Bowen D, Groves MJ, Tauro S, Fontenay M, Kosmider O, Bar-Natan M, Steensma D, Stone R, Heuser M, Thol F, Cazzola M, Malcovati L, Karsan A, Ganster C, Hellström-Lindberg E, Boulwood J, Pellagatti A, Santini V, Quek L, Vyas P, Tüchler H, Greenberg PL, Bejar R; International Working Group for MDS Molecular Prognostic Committee. TP53 mutation status divides myelodysplastic syndromes with complex karyo-types into distinct prognostic subgroups. *Leukemia*. 2019 Jan 11. doi: 10.1038/s41375-018-0351-2. [Epub ahead of print]
3. Bernard E, Update of mutational impact on diagnostic and prognostic evaluation of MDS. MDS Symposium, MDS Foundation, ASH meeting, San Diego, November 2018.

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

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### 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](http://www.pubmed.gov).

### EPIDEMIOLOGY, DIAGNOSIS AND PROGNOSIS:

1. Morton LM et al. Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. *JAMA Oncol.* 2018; Dec 20 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/30570657>)

*A total of 1619 cases were identified in SEER database with tMDS/AML among 700,612 adult cases that had a prior history of primary solid tumor malignancy during 2000–2013. The study found significantly elevated risk of tMDS/AML after chemotherapy for 22 of 23 solid tumor types documented. The majority (78%) died with a median survival of 7 mo. The study also estimated that of the total tMDS/AML cases seen in the next 5 years, approximately 3/4 will be post-chemotherapy.*

2. Neukirchen-Strapatsas J et al. Additional prognostic impact of the percentage of erythroid cells in the bone marrow of patients with myelodysplastic syndromes. *Leukemia Res.* 2019;77:8-13. (<https://www.ncbi.nlm.nih.gov/pubmed/?term=Neukirchen-Strapatsas>)

*In a retrospective multicenter analysis, bone marrow erythroid cell percentage (bmery) was determined in diagnostic bone marrow biopsies of 2453 MDS patients. Three distinct categories showed prognostic impact in terms of survival and leukemic transformation ( $p < 0.001$ ); Bmery  $\leq 10\%$  (poor), 11–25% or  $> 45\%$  (intermediate) and 26–*

*45% (good) with median overall survival of 23, 40 and 48 mo respectively ( $p < 0.001$ ). When added to IPSS-R, bmery was found to enhance the prognostic impact further for both survival and time to AML.*

### TREATMENT:

#### ESAs and Growth Factors

1. Park S et al. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1-risk myelodysplastic syndrome: a systematic literature review. *Br J Haematol.* 2019;184(2):134–160. (<https://www.ncbi.nlm.nih.gov/pubmed/30549002>)

*The review included 53 articles on 35 studies. A consistent erythroid improvement was seen in 45–73% in ESA-naïve patients, and with previous ESA exposure, the erythroid response rate was 25–75%. The review concludes that erythroid response is durable and also contributes to overall survival. The safety continues to be manageable.*

2. Fenaux P et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin- $\alpha$  in anemic patients with low-risk MDS. *Leukemia.* 2018;32(12):2648–2658. (<https://www.ncbi.nlm.nih.gov/pubmed/29895954>)

*A phase 3 double blind placebo controlled study assessed epoetin  $\alpha$  at 450 IU/Kg/week  $\times$  24 weeks with treatment extension in responders. The study randomized (2:1::epoetin  $\alpha$ : placebo) 130 low/int-1 MDS patients*

*with no or moderate pRBC transfusion dependence ( $\leq 4$  pRBC units/8 weeks) and  $\leq 10$  g/dL Hb. The erythroid response by IWG 2006 criteria was 31.8% with epoetin  $\alpha$  vs 4.4% on placebo ( $p < 0.001$ ). The treatment effect was also seen in the reduction in transfusion requirement and in delaying time to first transfusion.*

#### Hypomethylating Agents:

1. Savona MR et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicenter open-label, dose-escalation, phase 1 study. *Lancet Hematol.* 2019; 6(4):e194–e203. (<https://www.ncbi.nlm.nih.gov/pubmed/30926081>)

*Inhibition of cytidine deaminase (CDA) in gut and liver is necessary for bioavailability of oral decitabine, which is achieved with coadministration of cedazuridine. This phase 1 study showed that an oral combination of 100mg cedazuridine with 30 or 40 mg decitabine produced mean decitabine AUCs closest to the mean AUC of intravenous standard dose decitabine. The toxicity of combination remained consistent with known intravenous decitabine safety profile.*

2. Sébert M et al. A phase II study of guadecitabine in higher-risk myelodysplastic syndrome and low blast count acute myeloid leukemia after azacitidine failure. *Hematologica.* 2019; Feb 7 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/30733271>)



- The study included 56 patients with HR MDS and low blast count AML of which 55 received guadecitabine at 60 mg/m<sup>2</sup>/day SC x 5 days of 28 day cycle (med 3 cycles). The response rate was approximately 14% (8/56), which included 2 complete responses, med duration of response of 11.5 mo, and overall survival in responders was approximately 18 mo (Med survival in all patients was ~7 mo). No or least identified somatic mutations was the only predictive factor for response ( $p=0.035$ ). Additionally, as seen in a multivariate analysis, high rate of demethylation in blood in the first cycle was associated with response ( $p=0.03$ )
3. Wei AH et al. Venetoclax combined with low dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol*. 2019; Mar 20 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/30892988>) Previously untreated AML patients  $\geq 60$  yr that were ineligible for intensive chemotherapy ( $N=82$ ) were treated with a recommended phase 2 dose of venetoclax 600 mg PO daily x 28 day cycle along with low dose cytarabine (20 mg/m<sup>2</sup> per day). Common grade  $\geq 3$  adverse events included febrile neutropenia (42%), thrombocytopenia (38%), leukopenia (34%), with early (30-day) mortality rate of 6%. The CR/CRi was 54%, duration of response (DOR) was 8.1 mo and overall survival (OS) was 10.1 mo. Those without any prior exposure to hypomethylating agents (approx. 70%), had CR/CRi of 62%, DOR 14.8 mo and OS of 13.5mo.
  4. Platzbecker U et al. Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial. *Lancet Oncol*. 2018;19(12):1668-1679. (<https://www.ncbi.nlm.nih.gov/pubmed/?term=Platzbecker+U+and+RELAZA2>) A phase 2, open label, relapse prevention with azacitidine (RELAZA 2) study assessed treatment of MDS or AML patients demonstrating measurable residual disease (MRD) after conventional chemotherapy or allogeneic HSCT, with azacitidine 75 mg/m<sup>2</sup>/day sc on 1–7 day of 29 day cycle x 24 cycles. The baseline MRD status was assessed by either quantitative PCR for relevant gene mutations or in patients with HSCT, by donor chimerism in flow cytometry sorted CD34+ cells. The MRD was reassessed after six cycles of azacitidine. Of the 198 patients screened 60 (30%) had MRD of whom 53 were eligible for treatment. 31/53(58%) were relapse free and alive at 6 mo ( $p<0.0001$ ) and relapse free survival at 12 mo was 46%. The most common grade 3/4 toxicity was neutropenia.
  5. Dickinson M et al. Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia. *Blood*. 2018; 132(25):2629-2638. (<https://www.ncbi.nlm.nih.gov/pubmed/30305280>) A phase 3 randomized study tested a combination of platelet supporting eltrombopag (starting-max dose-200–300 mg/day; in East Asians 100–150 mg/day) with azacitidine (75 mg/m<sup>2</sup>/day sc on 1–7 day of 28 day cycle) versus placebo + azacitidine (1:1 randomization) in Int-1, Int-2 and High- risk MDS patients with baseline platelets  $<75 \times 10^9/L$ . The study was prematurely stopped on advice by IDMC. When stopped, the study showed 16% and 31% patients in eltrombopag vs placebo groups respectively being platelet transfusion free during cycles 1-4 of azacitidine. Overall response in the two groups were 20% and 35% respectively and the hematologic improvement was similar in the two groups. The prominent adverse events in eltrombopag + azacitidine were febrile neutropenia and diarrhea. Also compared to placebo+ azacitidine control, the eltrombopag combination worsened the platelet recovery, had lower response rate and showed a trend toward increased AML progression.
  6. Diamantopoulos PT et al. Bone marrow PARP1 mRNA levels predict response to treatment with 5-azacytidine in patients with myelodysplastic syndrome. *Ann Hematol*. 2019; Mar 15 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/30877373>) PARP1 mRNA levels were measured using quantitative RT PCR in bone marrow samples of 77 MDS patients treated with 5-azacytidine. Patients with higher PARP1 mRNA had better response by IWG criteria ( $p=0.006$ ) and longer survival ( $p=0.033$ ). A multivariate analysis validated the significance of this observation.

#### IMiDs:

1. Garcia-Manero G et al. Clinical benefit-risk profile of lenalidomide in patients with lower-risk myelodysplastic syndromes without del5(q): Results of a phase III trial. *Clin Lymphoma Myeloma Leuk*. 2018;Dec 21 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/30770308>) The phase III MDS-005 study previously demonstrated benefit of lenalidomide in lower risk non del5(q) MDS patients. In the present analysis, an attempt was made to determine a ratio of clinical benefit measured as a composite end point of transfusion independence/reduction by 4pRBC units, Hb increase of  $\geq 1.5$  g/dL or cytogenetic response to risk of hematologic adverse events (B/R: composite end point /AEs). The clinical benefit was seen in approximately 32% patients treated with lenalidomide versus approximately 4% on placebo. The clinical benefit was likely in patients who had  $\geq 1$  dose reduction due to toxicity than patients without any dose reductions.
2. Kenealy M et al. Azacitidine with or without lenalidomide in higher risk myelodysplastic syndrome and low blast acute myeloid leukemia. *Haematologica*, 2018; Dec 13 [Epub ahead of print] (<https://www.ncbi>.

nlm.nih.gov/pubmed/30545923)

A combination of azacitidine (75 mg/m<sup>2</sup>/day 1–5 of 28 day cycle) with lenalidomide (10 mg day 1–21 of 28 day cycle from cycle 3) vs standard azacitidine treatment were tested in a total of 160 MDS/AML/CMML patients (med f/u 33.1 mo). The overall response rates were 57% with azacitidine and 69% with lenalidomide + azacitidine combination. The combination was tolerable, but the efficacy was comparable to azacitidine alone.

### Novel Therapies:

1. Cortes JE et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019;33(2):379–389. (<https://www.ncbi.nlm.nih.gov/pubmed/30555165>)

A phase II randomized open label multicenter study evaluated a hedgehog pathway inhibitor glasdegib (100 mg PO QD x 28 day cycle) in combination with low dose ara-C (LDAC; 20 mg SC BID, 10 days in 28 day cycle, n=88) versus LDAC alone (n=44) in newly diagnosed AML or HR-MDS. Median overall survival was 8.8 mo with combination vs. 4.9 mo with LDAC (HR=0.51, p=0.0004) and complete responses were noted in 17% vs 2.3% in the two groups respectively (p<0.05). Among non-hematologic Grade 3/4 adverse events, while pneumonia was seen in both groups (~17% vs 15% respectively), fatigue was seen with the combination (14%).

2. Kubasch AS et al. Clinical, molecular, and immunological responses to pembrolizumab treatment of synchronous melanoma and acute myeloid leukemia. *Blood Adv*. 2018;2(11):1187–1190. (<https://www.ncbi.nlm.nih.gov/pubmed/29844203>)

A case report of concurrent melanoma and AML treated with pembrolizumab showed platelet response and clearance of IDH1 mutations. Additionally, response to pembrolizumab was

associated with PD-L1 expression on AML blasts and T cells.

### PATHOBIOLOGY:

1. Shiozawa Y, et al. Aberrant splicing and defective mRNA production induced by somatic spliceosome mutations in myelodysplasia. *Nat Commun*. 2018;9(1):3649 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6128865/>)

A transcriptomic analysis of 265 MDS bone marrows and validation with CRISPR/Cas-9 mediated gene editing showed that the SF3B1 intron retaining isoforms were the most frequently observed splicing alteration in SF3B1 mutated samples. Tumor suppressors and genes of mitochondrial iron metabolism or heme biosynthesis appear to be the target genes.

2. Haase D et al. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. *Leukemia*. 2019; Jan 11 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/30635634>)

This study by the International Working Group for MDS Molecular Prognostic Committee examined 359 complex karyotype MDS (CK MDS) cases. TP53 mutated patients showed fewer co-mutations, but were enriched for del(5q) (p<0.005), monosomal karyotype (p<0.001) and high complexity with >4 cytogenetic abnormalities (p<0.001). The monosomal karyotype, high complexity and TP53 mutations were individually associated with poorer overall survival. The poor prognosis of CK MDS thus seems to be related to its association with TP53 mutations.

3. Im H et al. Distinct Transcriptomic and Exomic Abnormalities Within Myelodysplastic Syndrome Marrow Cells. *Leuk Lymphoma*. 2018;59(12):3454–3464. (<https://www.ncbi.nlm.nih.gov/pubmed/29616851>)

Using RNA-Seq, CD34+ cell transcriptome was evaluated in MDS and two distinct expression profiles

differentiated the patients who remained stable versus who transformed into AML within 12 mo. When combined with exomic analysis, distinct gene isoforms emerged within MDS mutational subgroups correlating with characteristic functional impairments.

4. Zhang P, et al. Chromatin regulator Asxl1 loss and Nf1 haploinsufficiency cooperate to accelerate myeloid malignancy. *J Clin Invest*. 2018; 128(12):5383–5398 (<https://www.ncbi.nlm.nih.gov/pubmed/30226831>)

This study in mice demonstrated cooperation between epigenetic mechanism with proliferation signaling pathway in leukemogenesis. Concomitant mutational loss of ASXL1 and the haploinsufficiency in Nf1 (negative regulator of Ras signaling) was shown to cause transcriptional activation of critical pathways for myeloid proliferation.

### 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. Betaller A et al. The role of TGFβ in hematopoiesis and myeloid disorders. *Leukemia*. 2019; Feb 28 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/30816330>)
2. Florensa L et al. The importance of adequate recognition of normal and dysplastic myelopoiesis for the diagnosis of myelodysplastic syndromes. *Histol Histopathol*. 2019; Feb 19 [Epub ahead of print]. (<https://www.ncbi.nlm.nih.gov/pubmed/30779051>)
3. Sekeres M and Steensma D. Rethinking clinical trial endpoints in myelodysplastic syndromes. *Leukemia*. 2019;33(3):570–575. (<https://www.ncbi.nlm.nih.gov/pubmed/30700839>)
4. Sallman DA and List A. The central role of inflammatory signaling in the pathogenesis of myelodysplastic



## LITERATURE HIGHLIGHTS

- syndromes. *Blood*. 2019;133(10):1039–1048. (<https://www.ncbi.nlm.nih.gov/pubmed/30670444>)
5. Kennedy AL and Shimamura A. Genetic predisposition to MDS: clinical features and clonal evolution. *Blood*. 2019;133(10):1071–1085. (<https://www.ncbi.nlm.nih.gov/pubmed/30670445>)
  6. Tanaka TN and Bejar R. MDS overlap disorders and diagnostic boundaries. *Blood*. 2019;133(10):1086–1095. (<https://www.ncbi.nlm.nih.gov/pubmed/30670443>)
  7. Platzbecker U. Treatment of MDS. *Blood*. 2019;133(10):1096–1107. (<https://www.ncbi.nlm.nih.gov/pubmed/30670446>)
  8. Chandhok NS et al. What are the most promising new agents in myelodysplastic syndromes? *Curr Opin Hematol*. 2019;26(2):77–87. (<https://www.ncbi.nlm.nih.gov/pubmed/30632987>)
  9. Fenaux P, Kijadjan JJ and Platzbecker U. Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis. *Blood*. 2019;133(8):790–794. (<https://www.ncbi.nlm.nih.gov/pubmed/30602619>)
  10. Lee JH, List A and Sallman DA. Molecular pathogenesis of myelodysplastic syndromes with deletion 5q. *Eur J Haematol*. 2019;102(3):203–209. (<https://www.ncbi.nlm.nih.gov/pubmed/30578738>)
  11. Weinberg OK and Hasserjian RP. the current approach to the diagnosis of myelodysplastic syndromes. *Semin Hematol*. 2019;56(1):15–21. (<https://www.ncbi.nlm.nih.gov/pubmed/30573039>)
  12. Crisp R et al. Myelodysplastic syndromes in Latin America: state of the art. *Blood Adv*. 2018; 2 (Suppl 1): 60–62. (<https://www.ncbi.nlm.nih.gov/pubmed/30504205>)
  13. Aleshin A and Greenberg PL. Molecular Pathophysiology of MDS: Insights for Targeted Therapy. *Blood Advances*. 2018;2:2787–2797. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6199665/>)
  14. Sockel K and Platzbecker U. Current and Future Treatment Options for Myelodysplastic Syndromes: More Than Hypomethylating Agents and Lenalidomide? *Drugs*. 2018;78(18):1873–1885. (<https://www.ncbi.nlm.nih.gov/pubmed/30467725>)
  15. Platzbecker U et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2018 Nov 7 [Epub ahead of print] (<https://www.ncbi.nlm.nih.gov/pubmed/30404811>)
  16. Kubasch AS and Platzbecker U. Beyond the Edge of Hypomethylating Agents: Novel Combination Strategies for Older Adults with Advanced MDS and AML. *Cancers (Basel)*. 2018; 10(6). pii: E158. (<https://www.ncbi.nlm.nih.gov/pubmed/29795051>)

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peer-review publications.

## NEW ABSTRACT

Presented at: INTERNATIONAL CONFERENCE ERYTHROPOIESIS CONTROL AND INEFFECTIVE ERYTHROPOIESIS: FROM BENCH TO BEDSIDE.

### INFLAMMATION AS A DETERMINANT OF INEFFECTIVE ERYTHROPOIESIS IN MYELODYSPLASTIC SYNDROMES

ALAN F. LIST, MD, Moffitt Cancer Center, Tampa, FL

Ineffective erythropoiesis in patients with myelodysplastic syndromes (MDS) has long been regarded as arising from apoptosis provoked by inflammatory cytokines. We now recognize that aberrant innate immune activation within the malignant clone directs pro-inflammatory circuits that serve as key pathogenic drivers of the disease. In particular, S100A9-mediated NLRP3 inflammasome activation directs what is recognized as an inflammatory, lytic form of cell death termed pyroptosis that underlies many of the characteristic features of the disease. This circuit, which results in the release of other danger-associated molecular patterns (DAMPs), expands bone marrow myeloid derived suppressor cells (MDSC), creating a feed-forward process that reinforces inflammasome activation. Somatic gene mutations of a varied functional classes license the NLRP3 inflammasome to generate a common phenotype with excess reactive oxygen species generation, Wnt/ $\beta$ -catenin-induced proliferation, cation flux-induced cell swelling, caspase-1 activation and gasdermin-D cleavage to generate pyroptotic erythroid precursors and the variant allele frequency or number of somatic mutations. Importantly, knockdown of NLRP3 suppress pyroptosis, ROS generation, and nuclear  $\beta$ -catenin in MDS primary specimens and are intermediates in inflammasome signaling offer the potential for development of novel classes of anemia modifying agents for MDS.





# MDS CENTERS OF EXCELLENCE

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

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



## BENEFITS OF MEMBERSHIP:

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

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

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

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

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

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St. James's University Hospital  
St. James's Institute of Oncology  
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# MDS FOUNDATION MEMBERSHIP

## BENEFITS OF MEMBERSHIP

- You are part of the solution to change MDS outcomes. Your membership fee helps support global physician and patient educational initiatives, and helps to empower patients with courage and hope.
- Updates on the status of our Global Centers of Excellence and their live patient and family forum events that allow for more rapid dissemination of new research and treatment developments.
- Information on the latest clinical trials to potentially share or participate in.
- Access to MDS awareness materials to share with family and friends.
- Opportunities to participate in or host support group events with your friends and community.
- Receive two printed issues of *The MDS News*, which includes the latest on MDS research as well as inspiring patient and caregiver stories.

## YOUR MEMBERSHIP MAKES A DIFFERENCE

**\$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**

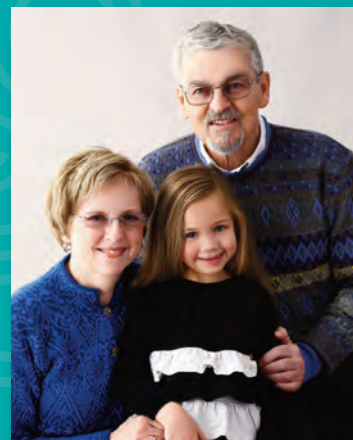
Membership (includes benefits listed above as well as additional support for the MDS Foundation as we work together to change the future of MDS). Member names are listed on the MDSF website.



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

The Fournier Family

Tim Fournier, MDS Patient, 79 years old,  
3 children, 8 grandchildren



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

The Cook Family

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

*"When I was diagnosed with MDS in 2008, the MDS Foundation became my primary source of accurate, comprehensive and understandable information about this complex and challenging bone marrow disease.*

*I donate to the MDS Foundation because it's an unparalleled resource for patients, caregivers, treatment providers and researchers. Additionally, I donate because of the wonderful, caring professional staff."*

MDS patient, 68 years old

**TO BECOME A MEMBER VISIT:**

**<https://www.mds-foundation.org/membership>**

## 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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**Clinical Studies – Research – Education**  
*Please help us continue to inspire and encourage more!*  
**Every membership counts!**

Please help the MDS Foundation share and promote these efforts!

*Please join today!*

[www.mds-foundation.org/membership](http://www.mds-foundation.org/membership)

**Together, we are community resource of Hope for those living with MDS.**

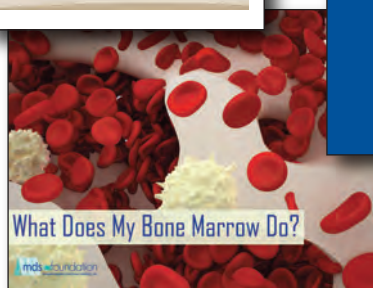
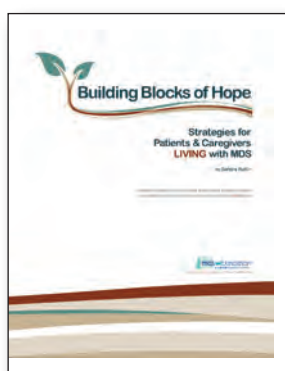
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To join the MDS Foundation and help us fulfill our mission of moving closer to a cure for MDS, please visit our website at <https://www.mds-foundation.org/changing-the-future-of-mds-membership>.

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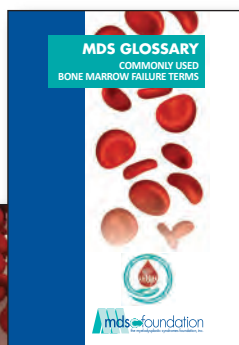
- You are part of the solution to change MDS outcomes. Your membership fee helps support global physician and patient educational initiatives, and helps to empower patients with courage and hope.
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## FIND THE TRUSTED RESOURCES YOU NEED...

*You or someone you know has been diagnosed with MDS*



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

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

To order your FREE copy of our resources available in multiple languages, please visit our website:

**<https://www.mds-foundation.org/material-order-form-4/>**



# 2019 PATIENT FORUMS

SPREADING THE NEWS WORLDWIDE

MARK YOUR CALENDAR FOR THE LOCATION NEAREST YOU!

📅 **FEBRUARY 2**  
Los Angeles, CA

📅 **MARCH 9**  
Phoenix, AZ

📅 **MARCH 30**  
Jacksonville, FL

📅 **APRIL 27**  
Pittsburgh, PA

📅 **MAY 11**  
Copenhagen, Denmark

📅 **JUNE 22**  
Baltimore, MD

📅 **JULY 20**  
Iowa City, IA

📅 **AUGUST 10**  
Seattle, WA

📅 **SEPTEMBER 19**  
Nashville, TN

📅 **OCTOBER 12**  
Westwood, KS

📅 **NOVEMBER 9**  
Dallas, TX



*Register Today*  
FOR OUR FREE EVENTS

LEARN MORE AT:

**[www.mds-foundation.org/patient-and-family-forums](http://www.mds-foundation.org/patient-and-family-forums)**

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

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



# PATIENT RESOURCES

## PATIENT RESOURCES

### YOU AND MDS

#### AN ANIMATED PATIENT'S GUIDE TO MYELOYDYSPLASTIC SYNDROMES

We are excited to announce the MDS Foundation's new online patient education resource, titled "You and MDS: An Animated Patient's Guide to Myelodysplastic Syndromes".

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

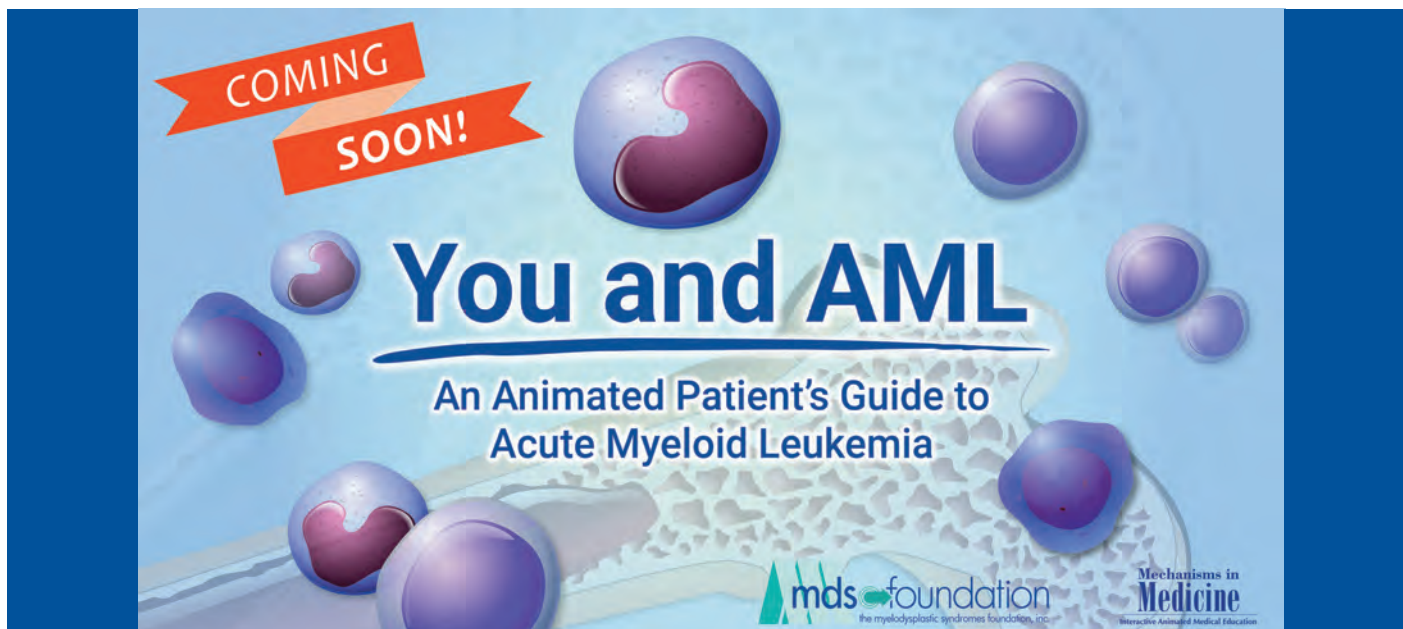
New educational content to be added to Animated Patient's Guide to MDS – [www.YouAndMDS.com](http://www.YouAndMDS.com). In partnership with Mechanisms in Medicine (MIM) we are creating additional educational content on MDS and erythropoiesis-stimulating agents to address needs related to better patient understanding on the importance of erythroid maturation defects, and therapeutic advances as this responds to the needs of a subgroup of MDS patients.



#### YOU AND ANEMIA:

An Animated Patient's Guide to Myelodysplastic Syndromes – RBC Mechanisms and Maturation in Erythropoiesis – Abbreviated Title: MDS and Anemia  
*Coming soon!*

Learn more at  
[www.YouAndMDS.com](http://www.YouAndMDS.com)



Animated Patient Education Resources to be hosted on  
[www.MDS-Foundation.org](http://www.MDS-Foundation.org)

### CELGENE CORPORATION AND ACCELERON PHARMA ANNOUNCE SUBMISSION OF LUSPATERCEPT BIOLOGICS LICENSE APPLICATION TO US FDA

SUMMIT, NJ & CAMBRIDGE, MASS.,  
APRIL 5, 2019 (BUSINESS WIRE) –

- *BLA submission includes both myelodysplastic syndromes and beta-thalassemia indications*
- *EMA marketing application for both indications planned for Q2:19*

Celgene Corporation (NASDAQ: CELG) and Acceleron Pharma Inc. (NASDAQ: XLRN) today announced that Celgene has submitted a Biologics License Application (BLA) for luspatercept, an erythroid maturation agent, for the treatment of adult patients with very low to intermediate risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions and for the treatment of adult patients with beta-thalassemia-associated anemia who require RBC transfusions.

The submission is based on the safety and efficacy results of the pivotal phase 3 studies MEDALIST and BELIEVE, both recently presented at the American Society of Hematology annual meeting, where MEDALIST was included in the plenary session.

“There remains a high unmet medical need for patients with MDS or beta-thalassemia who suffer from the effects of their disease-related anemia. The primary treatment option for these patients currently is chronic transfusion of red blood cells which can be associated with complications such as iron overload,” said Jay Backstrom, MD, Chief Medical Officer for Celgene. “New treatment options are urgently needed for these patients. With this submission, we look forward to

working with the Agency to deliver luspatercept to patients with these serious blood diseases.”

The companies also plan to submit a marketing application to the European Medicines Agency in the second quarter of 2019.

“The BLA submission is a key milestone for Acceleron and a credit to our longstanding collaboration with Celgene,” said Habib Dable, President and Chief Executive Officer of Acceleron. “We believe luspatercept’s positive clinical trial results demonstrate its potential as a novel treatment for patients with lower-risk MDS as well as in beta-thalassemia. All involved have worked diligently to develop luspatercept for patients with chronic anemias associated with these serious blood disorders.”

Luspatercept is an investigational therapy that is not approved for any use in any country for any indication.

#### About Luspatercept

Luspatercept is a first-in-class erythroid maturation agent (EMA) that regulates late-stage red blood cell maturation. Acceleron and Celgene are jointly developing luspatercept as part of a global collaboration. A phase 3 trial (COMMANDS) in ESA-naïve, lower-risk MDS patients, the BEYOND phase 2 trial in non-transfusion-dependent beta-thalassemia, and a phase 2 trial in myelofibrosis are ongoing. For more information, please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

#### About MEDALIST

MEDALIST is a phase 3, randomized, double blind, placebo-controlled, multicenter study evaluating the safety and efficacy of luspatercept in adults with very low-, low-, or intermediate-risk myelodysplastic syndromes (MDS). All patients were RBC transfusion dependent and were either refractory or intolerant to prior erythropoiesis-stimulating agent (ESA) therapy or were ESA naïve with

endogenous serum erythropoietin  $\geq 200$  U/L and had no prior treatment with disease modifying agents. The median age of the patients enrolled in the trial was 71 years in the luspatercept treatment group and 72 years in the placebo group. Median transfusion burden in both treatment arms was 5 RBC units/8 weeks. 229 patients were randomized to receive either luspatercept 1.0 mg/kg (153 patients) or placebo (76 patients) by subcutaneous injection once every 21 days. The study was conducted at 65 sites in 11 countries.

#### About BELIEVE

BELIEVE is a phase 3, randomized, double blind, placebo-controlled multicenter study comparing luspatercept + best supportive care (BSC) versus placebo + BSC in adults with beta-thalassemia patients who require regular RBC transfusions. The median age of the patients was 30 years in both treatment arms. 336 patients were randomized to receive either luspatercept 1.0 mg/kg (224 patients) or placebo (112 patients) by subcutaneous injection every 21 days for up to 48 weeks. Crossover to the luspatercept treatment groups was allowed after unblinding based on the recommendation of an independent Data Safety Monitoring Committee; patients treated with luspatercept will be followed for up to 3 years. The study was conducted at 65 sites in 15 countries.



## CELGENE CORPORATION ANNOUNCES KEY REGULATORY UPDATES FOR REVLIMID® IN LYMPHOMA AND LUSPATERCEPT IN MDS AND BETA-THALASSEMIA

- US FDA grants Priority Review for REVLIMID® (lenalidomide) in combination with rituximab (R<sup>2</sup>) for previously treated follicular and marginal zone lymphoma
- Prescription Drug User Fee Act action date set for June 27, 2019
- Luspatercept Biologics License Application (BLA) submission timing updated to April 2019

**SUMMIT, NJ (BUSINESS WIRE) (2/26/2019)** – Celgene Corporation today announced that the U.S. Food and Drug Administration (FDA) has granted Priority Review designation for the company's supplemental New Drug Application (sNDA) for REVLIMID® (lenalidomide) in combination with rituximab (R<sup>2</sup>) for the treatment of patients with previously treated follicular and marginal zone lymphoma. Under the Prescription Drug User Fee Act (PDUFA), the FDA has set its action date as June 27, 2019.

"R<sup>2</sup> has the potential to offer patients with previously treated follicular lymphoma and marginal zone lymphoma a chemotherapy free option" said Jay Backstrom, MD, Chief Medical Officer and Head of Global Regulatory Affairs for Celgene. "We look forward to working with the FDA to bring the R<sup>2</sup> regimen to patients as quickly as possible."

The sNDA is based on results from the randomized, double-blind, phase 3 AUGMENT study, which evaluated the efficacy and safety of the investigational R<sup>2</sup> combination versus rituximab plus placebo in patients with relapsed/refractory follicular and marginal zone lymphoma. Results from the study were presented at the 2018 American Society of Hematology (ASH) Annual Meeting and Exposition.

Earlier this year, Celgene submitted and had accepted a Marketing Authorization Application (MAA) for R<sup>2</sup> to the European Medicines Agency (EMA) for the treatment of relapsed/refractory follicular and marginal zone lymphoma.

REVLIMID alone or in combination with other agents is not approved for use in follicular lymphoma or marginal zone lymphoma in any geography.

Celgene also announced updated timing for the anticipated submission of a

Biologics License Application (BLA) with the U.S. FDA for luspatercept in adult patients with anemia related to very low to intermediate myelodysplastic syndromes (MDS) with ring sideroblasts who require red blood cell transfusions, and in adult patients with anemia related to beta-thalassemia who require regular red blood cell transfusions. The company expects to submit the BLA in April 2019.

### About Revlimid

REVLIMID® (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of patients with multiple myeloma (MM). It is indicated as maintenance therapy in patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT). REVLIMID® is indicated for the treatment of patients with transfusion-dependent anemia due to low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. It is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. REVLIMID® is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

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### MDS FOUNDATION



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### MDS MANAGER

**EFFECTIVELY MANAGE  
YOUR MDS CARE**

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

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



Available in the Google Play Store and iTunes



#### DAIICHI SANKYO INITIATES FIRST NOVEL COMBINATION STUDY OF TWO INVESTIGATIONAL AGENTS WITHIN ITS AML FRANCHISE IN PATIENTS WITH AML

TOKYO, MUNICH AND BASKING RIDGE,  
NJ (12/19/2018) –

- Phase 1 study initiated to evaluate the combination of a FLT3 inhibitor, quizartinib, and an MDM2 inhibitor, milademetan (DS-3032), in patients with relapsed/refractory FLT3-ITD AML or newly-diagnosed FLT3-ITD AML unfit for intensive chemotherapy
- Expansion of an ongoing phase 1 study to evaluate the combination of milademetan and 5-azacitidine, an inhibitor of DNA methylation, is also underway in AML and high-risk MDS
- The AML Franchise of Daiichi Sankyo is evaluating multiple investigational agents as single agents and in combination to further advance the treatment of patients with AML Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced that the first patient has been dosed in the first novel-combination study evaluating two investigational agents within its AML Franchise. The phase 1 study will evaluate the safety and activity of the combination of a FLT3 inhibitor, quizartinib, and an MDM2 inhibitor, milademetan (DS-3032), in patients with relapsed/refractory FLT3-ITD acute myeloid leukemia (AML) or newly-diagnosed FLT3-ITD AML unfit for intensive chemotherapy, a very aggressive form of the disease associated with poor prognosis.

"We have initiated this combination study of quizartinib and milademetan in order to determine the safety and tolerability of the combination and if the addition of the MDM2 inhibitor milademetan may potentially further improve the outcomes of patients with relapsed/refractory FLT3-ITD AML beyond what has been previously reported with single agent quizartinib," said Arnaud Lesegretain, Vice President, Oncology R&D and Head, AML Franchise, Daiichi Sankyo. "In this study, we also are exploring the potential of the combination of quizartinib and milademetan in patients with newly-diagnosed FLT3-ITD AML who are unfit for intensive chemotherapy. This study is the first of several planned studies that will evaluate the potential of novel combinations within our investigational AML Franchise, as we are committed to continuously improving the standard of care for patients with AML."

Quizartinib is the first FLT3 inhibitor to demonstrate a survival benefit as an oral, single agent compared to chemotherapy in a randomized, phase 3 study (QuANTUM-R) in patients with FLT3-ITD AML, which was refractory or relapsed within six months of first remission, and single agent milademetan has demonstrated preliminary

The first of several  
planned studies that will  
evaluate the potential  
of novel combinations

clinical activity in AML and myelodysplastic syndrome (MDS) in a phase 1 study.<sup>1,2</sup> Additionally, preclinical research has shown that the combination of quizartinib and milademetan has greater activity in FLT3-ITD AML cells compared to the respective single agent treatments.<sup>3</sup>

In the QuANTUM-R study, the median treatment duration with quizartinib was 4 cycles of 28 days each versus 1 cycle in the salvage chemotherapy arm. Incidence of treatment-emergent adverse events was comparable between patients who received single agent quizartinib and those who received salvage chemotherapy. The most common adverse drug reactions (>30 percent, any Grade) in patients treated with quizartinib included infections, bleeding, nausea, asthenic conditions, pyrexia, febrile neutropenia and vomiting, and the most common Grade  $\geq 3$  adverse drug reactions (>20 percent) were

# KNOW AML

World Awareness Day  
**21st April**

**#knowAML**



infection and febrile neutropenia. The most common laboratory adverse reactions (incidence >50 percent) were decreased white blood cell count, decreased lymphocyte count, decreased hemoglobin, decreased neutrophil count and decreased platelet count. The safety profile observed in QuANTUM-R appears consistent with that observed at similar doses in the quizartinib clinical development program.

In addition to the quizartinib and milademetan combination study, an ongoing phase 1 study of milademetan has been expanded to include evaluation of milademetan in combination with the hypomethylating agent 5-azacitidine, an inhibitor of DNA methylation, in patients with newly-diagnosed AML unfit for intensive chemotherapy, relapsed/ refractory AML or high-risk MDS.

### About the Quizartinib/Milademetan Combination Study

The multi-center, non-randomized, phase 1, open-label, two-part study is investigating the safety and efficacy of the combination of quizartinib and milademetan in patients with relapsed/refractory *FLT3*-ITD AML or newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy. The first part of the study (dose escalation) will assess the safety and tolerability of the combination to determine the dosing schedule, maximum tolerated dose and recommended dose for expansion. The second part of the study (dose expansion) will confirm the safety and tolerability at the recommended dose for expansion of the combination and will identify a recommended phase 2 dose. The primary objective of the study is safety. Secondary objectives include evaluation of pharmacokinetics and preliminary efficacy. The study is expected to enroll approximately 110 patients in the US, EU and Japan. For more information about the study, visit [ClinicalTrials.gov](http://ClinicalTrials.gov).

### About the Milademetan/ 5-Azacitidine Combination Study

The multi-center, non-randomized, phase 1, open-label, two-part study is investigating the safety and efficacy of milademetan as a single agent and in combination with the hypomethylating agent 5-azacitidine. The first part of the study (dose escalation) will evaluate the safety and tolerability and identify the maximum tolerated dose and recommended dose for expansion of milademetan as a single agent and in combination with 5-azacitidine in patients with relapsed/ refractory AML or high-risk MDS. The second part of the study (dose expansion) will confirm the safety and tolerability at the recommended dose of milademetan in combination with 5-azacitidine and will identify a recommended phase 2 dose in patients with relapsed/refractory AML, newly-diagnosed AML unfit for intensive chemotherapy or high-risk MDS. The primary objectives of the study are safety and tolerability, maximum tolerated dose, recommended dose for expansion and response to treatment. Key secondary objectives include evaluation of pharmacokinetics and pharmacodynamic effects. The study is expected to enroll up to 200 patients in the U.S. For more information about the study, visit [ClinicalTrials.gov](http://ClinicalTrials.gov).

### About Quizartinib

Quizartinib, the lead investigational agent in the AML Franchise of the Daiichi Sankyo Cancer Enterprise, is an oral selective type II *FLT3* inhibitor currently in phase 3 development for relapsed/refractory *FLT3*-ITD AML (QuANTUM-R) in the U.S. and EU; phase 3 development for newly-diagnosed *FLT3*-ITD AML (QuANTUM-First) in the US, EU and Japan; phase 2 development for relapsed refractory *FLT3*-ITD AML in Japan; and phase 1 development in combination with an investigational agent, milademetan, for relapsed/refractory *FLT3*-ITD AML and newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy in the US, EU and Japan.

Quizartinib has been granted Priority Review and Breakthrough Therapy designation for the treatment of adult patients with relapsed/refractory *FLT3*-ITD AML, and Fast Track designation for the treatment of relapsed/refractory AML by the US Food and Drug Administration (FDA). Quizartinib also has been granted accelerated assessment by the European Medicines Agency (EMA) for the treatment of adults with relapsed or refractory AML, which is *FLT3*-ITD positive, and granted Orphan Drug designation by both the FDA and the European Commission (EC) for the treatment of AML and by the Japan Ministry of Health, Labour and Welfare (MHLW) for the treatment of *FLT3*-mutated AML.

### About Milademetan

Milademetan (DS-3032) is an oral selective MDM2 inhibitor currently in phase 1 clinical development for solid and hematologic malignancies, including a combination study with quizartinib in relapsed/refractory *FLT3*-ITD AML or newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy in the US, EU and Japan; a single agent and combination study with 5-azacitidine in newly-diagnosed AML unfit for intensive chemotherapy, relapsed/refractory AML or high-risk MDS in the US; and two single agent studies in lymphomas and solid tumors in the U.S. and Japan.

Quizartinib and milademetan are investigational agents that have not been approved for any indication in any country. Safety and efficacy of these investigational agents have not been established.

### References

1. Cortes J, et al. 2018 EHA Annual Congress Oral Presentation. Abstract #LB2600.
2. DiNardo C, et al. 2016 ASH Annual Meeting Oral Presentation. Abstract #593.
3. Andreeff M, et al. 2018 EHA Annual Congress Poster Presentation. Abstract #PF219.

# **AGIOS RECEIVES FDA BREAKTHROUGH THERAPY DESIGNATION FOR TIBSOVO® (IVOSIDENIB) IN COMBINATION WITH AZACITIDINE FOR THE TREATMENT OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (AML) WITH AN IDH1 MUTATION IN ADULT PATIENTS INELIGIBLE FOR INTENSIVE CHEMOTHERAPY**

CAMBRIDGE, MASS., MARCH 26, 2019  
(GLOBE NEWSWIRE) –

Agiros Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for TIBSOVO® (ivosidenib) in combination with azacitidine for the treatment of newly diagnosed acute myeloid leukemia (AML) with an IDH1 mutation in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

“Outcomes for newly diagnosed AML patients ineligible for intensive chemotherapy are still poor, and there are no approved options specifically for patients with an IDH1 mutation,” said Chris Bowden, MD, chief medical officer at Agios. “The Breakthrough Therapy designation provides further support that combining azacitidine and ivosidenib for these patients has the potential to be a compelling treatment option.”

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

Results from the Phase 1/2 study of ivosidenib in combination with azacitidine were last presented at the 17th International Symposium on Acute Leukemias in Munich. In the ivosidenib arm of the Phase 1b portion of the study, 23 patients received 500 mg of ivosidenib daily plus azacitidine. The median age was 76 years old, and 52% of patients were age 75 or older. The safety profile of combination therapy remains consistent with the safety profile of ivosidenib and azacitidine alone in this patient population. As of the August 1, 2018 data cutoff, mean neutrophil and platelet counts were maintained near or above thresholds for complete response (CR) with partial hematologic recovery (CRh) while on study treatment with ivosidenib and azacitidine. Overall, 78% (18/23) of patients had a response and 57% (13/23) of patients had a CR. The median duration of CR had not been reached (95% CI 7.7, NE). In addition, the 12-month survival rate was 82%.

Ivosidenib is not approved in any country for the treatment of patients with newly diagnosed AML or approved in combination with azacitidine.

## **About TIBSOVO® (ivosidenib)**

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

## **IMPORTANT SAFETY INFORMATION**

### **WARNING: DIFFERENTIATION SYNDROME**

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

### **WARNINGS AND PRECAUTIONS**

**Differentiation Syndrome:** See Boxed WARNING. In the clinical trial, 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation

and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased. Of the 34 patients who experienced differentiation syndrome, 27 (79%) recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

**QTc Interval Prolongation:** Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. One patient developed ventricular fibrillation attributed to TIBSOVO. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT<sub>3</sub> receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

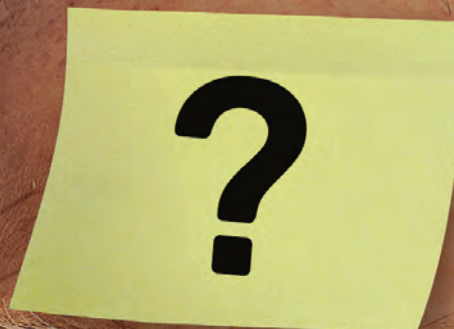
**Guillain-Barré Syndrome:** Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with TIBSOVO in the clinical study. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

Please see full Prescribing Information, including Boxed WARNING.



# KNOW AML

World Awareness Day 21st April



## What is acute myeloid leukemia?

Acute myeloid leukemia (AML) is a kind of cancer that affects the blood and bone marrow. It is the most common form of acute leukemia in adults. AML is characterized by the rapid production and growth of abnormal blood cells, which can build up in the bone marrow and prevent the production of normal blood cells. The most common signs and symptoms of AML include shortness of breath, bruising, fever, weakness, and infection.

[know-aml.com](http://know-aml.com)

#knowAML

## Daiichi Sankyo Cancer Enterprise

The mission of Daiichi Sankyo Cancer Enterprise is to leverage our world-class, innovative science and push beyond traditional thinking to create meaningful treatments for patients with cancer. We are dedicated to transforming science into value for patients, and this sense of obligation informs everything we do. Anchored by three pillars we aim to deliver seven distinct new molecular entities over eight years during 2018 to 2025:

- Antibody Drug Conjugate Franchise
- Acute Myeloid Leukemia Franchise
- Breakthrough Science

*Our powerful research engines include:*

- Two laboratories for biologic/immuno-oncology and small molecules in Japan
- Plexxikon Inc., our small molecule structure-guided R&D center in Berkeley, CA

For more information, please visit: [www.DSCancerEnterprise.com](http://www.DSCancerEnterprise.com).

### The Acute Myeloid Leukemia (AML) Franchise of the Daiichi Sankyo Cancer Enterprise

The AML Franchise is pushing the boundaries of science aiming to define a new standard of care for patients with AML, a fast-growing form of leukemia that has the lowest five-year survival rate of all leukemias. Advancements in the understanding of the molecular biology of AML are creating opportunities for our researchers to discover and develop therapies that target the underlying drivers of the disease.

For more than 30 years, the standard of care for the treatment of AML went unchanged in part due to the complex biology of AML. While a few new treatments have been approved recently, there is still significant unmet need and much work to be done to continue to expand the treatment options available for patients with AML. Our investigational AML Franchise is evaluating a portfolio of therapies that leverage three distinct strategies for the treatment of AML. Our investigational AML Franchise will evaluate combination regimens including these and other compounds for their potential to change the standard of care for patients with AML.

### Daiichi Sankyo's Obligation & Commitment

We are dedicated to transforming science into value for patients, and this sense of obligation informs everything we do. As an anchor in the Daiichi Sankyo Cancer Enterprise, significant investment and resources have been committed to the investigational AML Franchise. The formation of the investigational AML Franchise underscores our commitment to understanding AML tumor biology and developing therapies that improve the depth and quality of responses by targeting AML on multiple fronts. Combination regimens, which may address the heterogeneity and polyclonality of the disease, may be key to changing the standard of care for AML. With a portfolio of compounds that target different AML drivers, our investigational AML Franchise is an ideal platform in which to study various combination therapies.

### Daiichi Sankyo's Partnerships & Collaborations

Daiichi Sankyo Cancer Enterprise is actively pursuing partnerships and collaborations with experts and academic centers worldwide to help advance the science of AML. A collaboration with MD Anderson Cancer Center, one of the largest integrated leukemia centers worldwide, is focused on accelerating the development of novel therapies for AML. Multiple phase 1 and 2 clinical trials, led by MD Anderson, will be launched to evaluate our investigational compounds and multiple agents in combination regimens.

Incorporation of translational work, including exploration of novel biomarkers, as well as preclinical studies of new agents, is aimed at improving our understanding of mechanisms of resistance to existing and emerging treatments.

### Daiichi Sankyo's Relentless Focus on Transforming Science

Molecular subtyping (classifying tumors into distinct categories based on molecular features) is creating new scientific opportunities to better understand the science behind AML and improve on current treatment options. Our investigational AML Franchise is currently developing a portfolio of therapies that leverage three distinct strategies. Pursuing multiple pathways and studying these investigational compounds in combination with other therapies may potentially enable us to deliver more effective treatment options and expedite development to reach patients sooner.

Our investigational AML Franchise is currently developing a portfolio of therapies that leverage three distinct strategies:

- Growth Factor Receptor Inhibition (FLT3 inhibitor)
- Tumor Suppressor p53 Reactivation (MDM2 inhibitor)
- Targeting Epigenetic Regulation (dual EZH1/EZH2 inhibitor, BRD4 inhibitor and IDH1 inhibitor)



## Connect<sup>®</sup> MDS and AML: The Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) Disease Registry

**Celgene is researching the following objectives in patients with MDS, Idiopathic Cytopenias of Undetermined Significance (ICUS) and AML:**

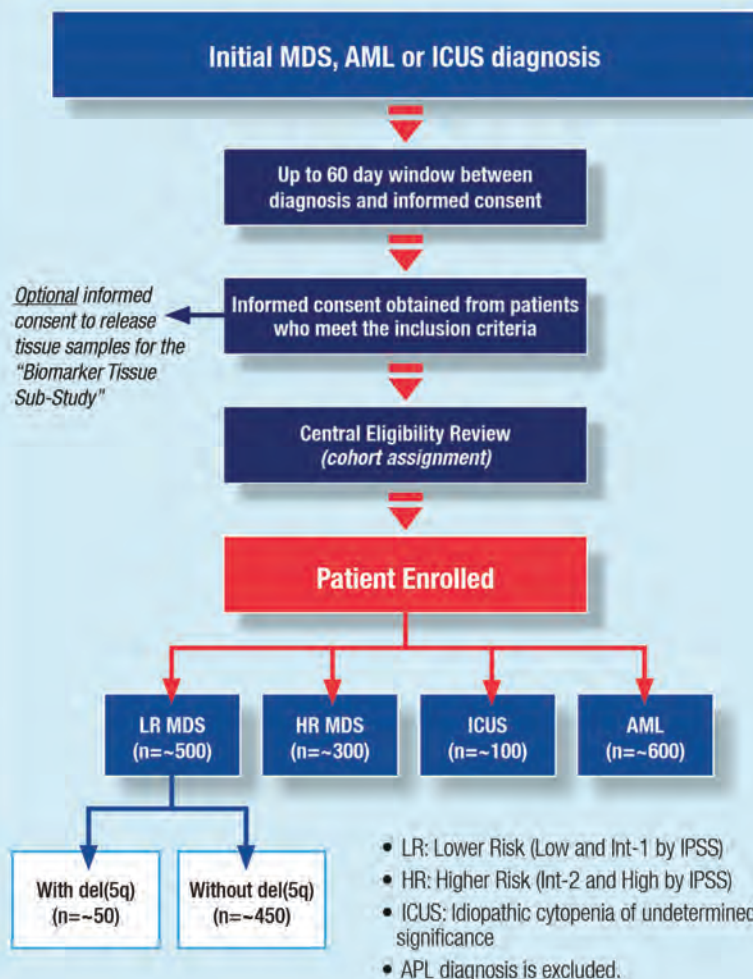
- 🔬 Current and evolving patterns for diagnosing, treating, and monitoring patients
- 🔬 Outcome measures
- 🔬 How routine practice compares to national treatment guidelines
- 🔬 Treatment patterns and outcomes in patients with del(5q), with or without additional cytogenetic abnormalities
- 🔬 Association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

### Select eligibility criteria:

- 🔬 Newly diagnosed,\* primary or secondary MDS, ICUS or AML
- 🔬 MDS/ICUS 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; and therefore proficient in either English or Spanish

\*To be considered "newly diagnosed," the diagnosis must have been confirmed no more than 60 days prior to the date the patient signs the informed consent (ICF) documents.

*Note: Concomitant patient enrollment in other studies is permitted.*



**To learn more about this  
MDS/AML Disease Registry Study,  
Visit <https://celgeneregistry.com/public/home>  
contact: [connectmdsaml-registry@celgene.com](mailto:connectmdsaml-registry@celgene.com)  
(ClinicalTrials.gov Identifier: NCT01688011)**

MDS FOUNDATION, INC.

# MDS AWARENESS WALK

**CHICAGO**  
JUNE 22, 2019  
&  
**BOSTON**  
SEPT. 14, 2019

## JOIN US AND WALK WITH PURPOSE!

### MYELODYSPLASTIC SYNDROMES (MDS) BY THE NUMBERS

Myelodysplastic syndromes (MDS) are an often unrecognized, underdiagnosed rare group of bone marrow failure disorders, where the body no longer makes enough healthy, normal blood cells in the bone marrow. The disease is also known as a form of blood cancer.



**12-20K**

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

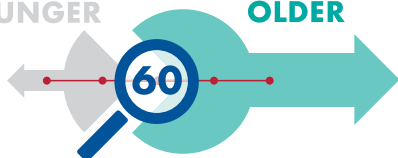
**60-170K**  
people



are estimated to live with MDS in the U.S. with an estimated **87,000** new cases each year worldwide.<sup>6,7</sup>

YOUNGER

OLDER



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

**1 OUT OF 3**



**MDS patients (or 30%)** progress to acute myeloid leukemia (AML).<sup>1</sup>

UP TO



**YEARS**

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

## Learn more about the MDS Awareness Walks and additional information about MDS.

[www.mds-foundation.org](http://www.mds-foundation.org)



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## PATIENT STORIES

### OUR PATIENT STORIES

#### MY DIAGNOSIS...

**SHERRY PRATT**

*Ridgeland, Mississippi*

Someone once said, "Life is what happens to you when you make other plans". I have learned that statement is so very true.

I NEVER thought I would ever get a cancer diagnosis. I taught exercise classes, walked every day, ate a Mediterranean diet, paid attention to the products I used, and the food I ate. I even became a certified Health Coach and taught healthy living classes.

But I did get a cancer diagnosis; a rare blood cancer called Myelodysplastic Syndromes (MDS). My specific subtype is Refractory Anemia with Ringed Sideroblasts (RARS). This affects the red blood cells and has no cure, except for a stem cell transplant (also called a bone marrow transplant).

At first, I was scared, mad, confused, and in denial. Then I decided that if David faced a giant called Goliath and was not defeated, I could too. God is still in the miracle business, and I began to strengthen my faith by staying in the Word. You know you cannot learn a foreign language well by practicing and listening to your studies only on Sunday morning. You must stay in the Word of God daily. It is His medicine.

Every day, all day, I would say a silent prayer, "Thank you Jesus for my healing." I read Bible verses every day that were about healing. My friend Millie put a small booklet of those verses together for me on a flipchart. I still read those verses every day. My husband framed them and we placed them all over my home, so I would see them all the time. I put pictures of healthy red blood cells all over my home too, so I could visualize them – I even have that picture as my background wallpaper on my phone. I submersed myself in God's word. I purchased a new Bible that had weekly devotions in it for the year of 2016 — the Year of Jubilee (Rod Parsley Jubilee Bible).



When I was first diagnosed on August 19, 2014, my hemoglobin was in the 9's (normal is 12–18). I was told I would be given various therapies to help raise my red blood cell count, so I could function properly. I sought a second opinion in New Orleans at Ocshners. They told me I could get a stem cell transplant eventually, but that my disease is one that would be treated with differing therapies and drugs. Several of those were used to no avail, and by the time September 2016 rolled around, my hemoglobin had dropped into the 7's.

I took a drug called lenalidomide (Revlimid®), which was very expensive and did not work. The epoetin alfa (Procrit®) shots I got every Tuesday would raise my red blood cells for a couple of days, but

not continually. By the time the next Tuesday rolled around, my labs would show that my counts were about the same or sometimes even lower.

I had reluctantly agreed to a drug therapy called azacitidine (Vidaza®). It is a hypomethylating agent that helps to increase your red blood cell counts. I was to take a 1-hour drip of this 5 days a month, for 5 years. It was not a cure, just a crutch. I was 62 when this would begin and in five years, I would be 67 — older and probably much sicker. I asked my doctor what happens at the end of five years and he said, "You will have to go somewhere to get a stem cell transplant."

I was scheduled to begin the azacitidine (Vidaza®) infusions on August 29, 2016. The Wednesday before, my dear friend Susan asked me if I had ever thought about the Cancer Treatment Centers of America (CTCA)? Frustrated at the whole situation I just told her no. I start azacitidine (Vidaza®) the next week and left it at that. On the Friday before the 29th of August, I was taking a nap on the couch and woke up to a Cancer Treatment Center of America commercial on TV. Something just tugged at my heart and I called the number. It was the first of many miracles that God would bestow on me in the next 12 months.



*Day Zero – Sherry with her donor, her sister Sonya, and sister Sheila.*

## OUR PATIENT STORIES

The first miracle happened the next morning when I called my siblings and asked their opinion on what I should do. My younger sister Sonya said to cancel the Vidaza and go to Chicago (Zion, Illinois) for a third opinion. God knew all along that Sonya would be a KEY player in my recovery.

On September 12, Wally and I were in Zion at the CTCA for the first time. When we walked into the foyer of the hospital, there were people everywhere asking if you needed help. There was a lady on the second floor of the foyer playing "Amazing Grace" on a grand piano. I was touched by this place. It did not resemble a hospital at all. I could feel the love and peace in the atmosphere. I had read my devotion that morning and it said "Today you are marked for a miracle."

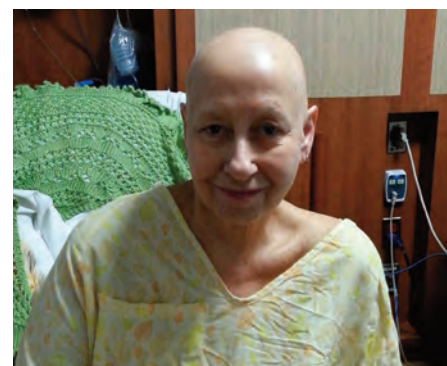
All during the week, God was literally walking the halls with us. We met so many people who had been told by their local physicians to go home and get their affairs in order – they wouldn't live over 6 months. Some of those people were there for their annual checkups after 12 years.

When I first met with my doctor, he explained my disease in great length and he looked at me and paused... I was going to ask him what he would recommend if I were

his mother, but he beat me to it. He told me "If you were my mother, I would do a stem cell transplant so you can have many more years of quality life." Cold chills ran down my spine. Little did I know at that point the standard of care used at CTCA is coined the Mother Standard of Care. Everyone from the doctors, to nurses, to janitors and food service workers treat you as if you were their mother. They also include a naturopathic doctor and nutritionist to minister to your care while you are there. They know that your attitude during a cancer diagnosis is key to your healing.

Once we decided to treat there, I had my blood tested daily. My doctors at CTCA wanted to try a medication called Decitabine (Dacogen®). It was a drug much like azacitidine (Vidaza®), and it too increased red blood cells in some patients. I took 5 days of that drug and flew home on the 20th of September with lots of instruction on what to do if I started a fever or if my numbers began to drop.

They did drop drastically within the next week. I was hospitalized twice with fever and had blood cultures done. I took lots of antibiotics and had platelet and blood transfusions. The hospitals in my hometown were not equipped for a neutropenic patient, and I begged my



doctors at CTCA to allow me to return. I returned to CTCA on October 8, 2016 and never left there until my transplant and 100 days were over.

We discussed possible donors for me. They began looking for donors on the worldwide registry. They inquired about my siblings, but decided they may have been too old to donate.

The second week at CTCA my devotion was from 1 Cor 2:12 — *Now we have received not the spirit of the world, but the spirit which is of God, so that we might know the things that are freely given to us by God.* I wasn't meant to wonder where my help would come from, I took hold of what God had to offer... healing...

My devotions continued to lift me each week. Isaiah 41:10 *Do not fear for I am with you; do not be dismayed for I am your God, I will strengthen you, I will help you, yes I will uphold you with my righteous right hand.*

My fourth week at CTCA my devotion was entitled "The Cure". *He knows how to treat the broken-hearted patient, the anxious patient. He knows how to treat the scared patient. He is the cure. He cures physical illness and disease.* Your Bible is full of examples. Jesus' cures are real today.

By that time, I had met with the head of the stem cell unit and he said he wanted to test my younger sister Sonya to see if she might be a match. She was 55, just 6 years younger than I. I was elated that they wanted to do this, but anxious for her. She agreed wholeheartedly, and they sent her a blood testing kit.



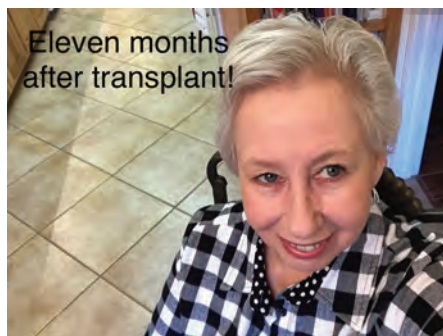


## OUR PATIENT STORIES

On November 3rd, my devotion was entitled "Anointed Vessels". I learned an example of the tangible transfer of God's anointing is found in Acts 5. *There the lame and sick were placed in the street so that the shadow of Peter would fall on them as he passed. Just his shadow transferred the anointing of God.* These things did not just happen in Jesus' day. They happen today. On November 3rd we were told my younger sister Sonya was a 100% match for my stem cells. (There is only a 25% chance a sibling will be a 100% match). Her stem cells would physically make me whole again, and they would be transferred to me. God knew when he knit her in my mother's womb 55 years ago, as He would be using her stem cells to sustain my life.

What is even more amazing is that Sonya was our family's accident baby. There are no coincidences with God. No accidents. He is always working behind the scenes.

On December 27th, my devotion was about how God delights in blessing you with miracles. That week I entered the hospital for the transplant. I was in for conditioning chemo, where they would give me 3 kinds of chemo to kill my diseased stem cells — at least most of them — to make way for my donor cells. A week after the chemo infusions, I got very ill. It was also the time I would get my new donor stem cells. Through the sickness, I



continued to pray the Lord's prayer, read my healing verses, and say thank you to Jesus for my healing. I had that peace that passes all understanding. God was in control, not me.

On January 3, 2017, I received 7.69 million stem cells from my little sister Sonya. I had received my miracle.

We are now actually twins but not identical... 6 years apart!!!

The next 28 days were not so easy. I got Cdiff from all the antibiotics I had taken, I was very weak some days, and in general felt bad. But I tried my best to persevere through the bad feelings. I walked the halls every day, because I knew I had to keep my strength up. There were even some days I don't remember. I got fevers a couple of times, and some mouth sores. Luckily, my caregivers kept a meticulous journal about my condition each day. This helped me tremendously to recount what I went through. I repeated "Thank you Jesus for my healing" every day all day, and I recited the Lord's prayer.

The anointing of God's Holy Spirit can cool the fevered brow of an infant child, cause blindness to disappear, cancer to cease its destruction, finances to increase and favor to become your constant companion... My hope for each of you today is that through prayer you have had a personal conversation with God confessing your sins, and asking Him to come into your heart and life. You can do that at any time, but it is so important to know him as your savior and follow His word daily — so you too can face your adversity with God in your favor.

You will face battles in your lifetime. Walking in a deeper relationship with God will develop stronger courage. It builds strong faith and patience to wait on Him to lead you to your miracle.

Joshua 1:9 says, "Have not I commanded you? Be strong and courageous. Do not be afraid or dismayed, for the Lord your God is with you wherever you go."

Don't forget Him in your busy day. Take Him with you daily.

Don't wait for your difficult seasons in life to become strong in your faith. Just being in God's word daily will strengthen you to trust totally in Him for whatever you face. Just read His word. He tells you all over the Bible that He will protect you, and heal you, and help you.

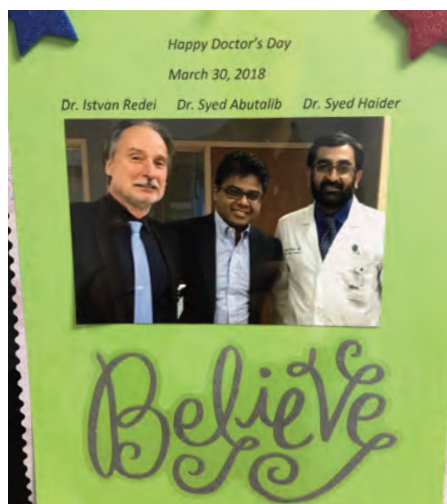
I firmly believe that God placed me at CTCA to strengthen my faith and to anoint me to share my story with others.

I want to thank my sister Shelia and my husband Wally for their unwavering and outstanding caregiving. They helped me heal and stay focused on resting. I want to thank Sonya for giving me the ultimate gift of life, and for God who saved me by dying on the cross. Without Him, we all would be nothing.

I have learned that God did not choose to anoint me with healing to showcase my strength, but to reveal HIS strength.

My message to others is that you can get through a big deep valley. You must mind your thought process and let God handle the rest. He surely has for me.

And at 19 months post-transplant, I am still "Thanking Jesus for my healing".



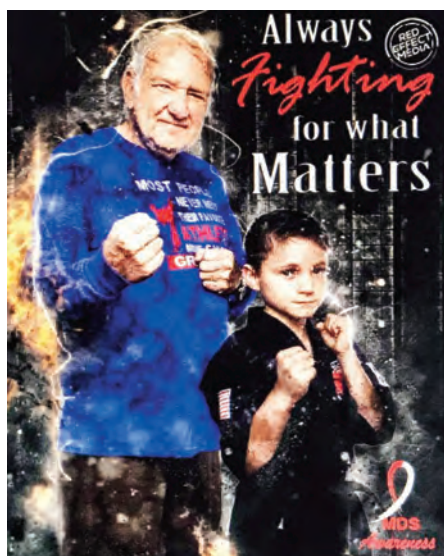
## ALL FIGHTING FOR WHAT MATTERS!

**JOHN KENISON**

*Hannibal, Missouri*

I spent a couple of years watching my blood counts go up and down and my platelet count decreasing. It was June 2017 when I was diagnosed with MDS by Dr. Ali at the James Carey Cancer Center in Hannibal, MO. We made a trip to MD Anderson Medical Center in Houston, TX for a second opinion. They agreed on the diagnosis, and the treatment. My wife and I discussed the options we had, and I decided one good year was better than 2 or maybe 3 years with the treatment. I discussed this with each of my five children and received mixed reactions. I asked them to prepare the grandchildren in their own way, when they thought the timing was right. My three older boys were ok with my decision. My youngest daughter was upset and called to talk to me. She had cried all week and thought I needed to do whatever was needed even if it was only 2-3 years. My older daughter became very angry and told me in no uncertain terms that I would not let any of them get by with that decision. She also felt I needed to do all I could to fight the disease.

Jeanne, my 4th child, has a 9 year-old son, Chase, who is in karate. He wrote the letter here, and gave it to me. I also received a letter from another grandson who said he was thinking about me and hoped I do not die. With all the objections from my kids and grandkids, I changed my mind and started treatment for MDS in July 2017 in Hannibal, Missouri. My 9 year-old grandson, Chase, has progressed in his karate training, and I have shared in his accomplishments. He had a karate belt made with his name on one side and MDS Awareness on the other side; and a key chain made for me that has the MDS logo. He told me to carry it with me at all times. He told me he was fighting for me and wanted me to fight for him. I know he supports me, and I support him. Together, we have both done quite well, in spite of hurdles that we faced.



I have gotten good reports on my progress. The Dacogen treatments are working well for me so far. I have to take the drip for five consecutive days each month. The week of the treatment, and the next week, I feel very tired and not very energetic. There is also pain in my legs, an upset stomach, and I walk slowly as the platelets and blood counts go down. However, this all improves over the following two weeks, as counts go up and I have some quality time. After a couple treatments, we found I did not need transfusions. I am now able to go an extra week before the next treatment as the counts continue to increase. This gives me an extra week of feeling better before it is

Dear Grandpa,

I know that you have been sick, and doing treatments, and to help you get better. You have been trying to fight it for a few months now, and I know that you are a fighter, and so am I. You are trying to fight it because, you want to stay alive. You want to stay alive for us, and everyone else you love. I will be competing in NASKA next year, in the black belt division. This year's fight will be for you. I have a new belt coming with the MDS ribbon on it, just like yours. This will be worn at every tournament I go to. I feel like if we fight together, we will both win. Every time I feel like giving up, I will look at my belt, and that will help me push through it. I hope you can do the same. If you don't give up, I won't give up. I love you, we will fight this together!

xoxo  
Chase Youngmiller

time to start over. I continue to go to MD Anderson for check-ups every 6 months. They agree the treatment, and the extra week, is working well for me.

Chase has also progressed very well in his karate. He won 3 national titles at the end of 2017, and has done quite well in many tournaments. Additionally, he was recruited by a travel team out of St. Louis. His photo has been used on several promotional magazine covers — some of which have allowed him a platform to encourage donations to the MDS Foundation. Chase also tried out for the USA team at the age of 10, and qualified to compete in 6 events in Athens, Greece, at the end of October. While in Athens, he heard on the news that it was MDS Awareness Day, and chose to wear a shirt they had made that says "Fight for what Matters" with the MDS ribbon. He wears this quite often. Chase made finalist in all of his weapons and forms events, and came home with Bronze Medals in all of them.

His brother, Jacob (age 5), told me at Christmas that he is going to fight for me as well when he goes to his karate tournaments. He also wears the "Fight for What Matters" shirt.





## OUR PATIENT STORIES

The love and support of my whole family has meant so much to me, and has brought me this far. My kids, grandkids, and I can talk about my disease as well as about their shortcomings, disappointments, and accomplishments. We are all fighting very hard to work together to improve and better ourselves in all areas. I have an 80 year-old sister who also calls me after treatments to keep updated on my test results. My wife is the one who is with me at each appointment, keeping the records, and making sure we have the information we need. She encourages me daily. The week of the drip I am not very alert, and she drives me around. The weeks to follow, as I feel the side effects and discomforts, she is there for me. I love her very much and I am thankful to have her help. I was amazed to find this year that I could still get on the dance floor with her. In the picture of us dancing, you can see the MDS keychain my grandson gave me, hanging out of my pocket.

**The love and support of my whole family has meant so much to me and has brought me this far.**

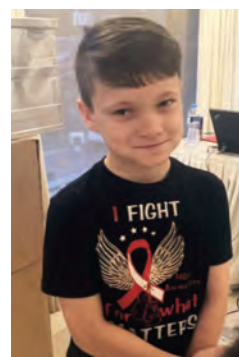
I would like to encourage everyone to do as my family wanted me to, and give treatment a chance. One of the doctors at the clinic, Dr. Buckstein, told me prior to starting the treatments that even though the success rate of the treatment for a man my age may be low, I may be the one in that percentage — but would not know without trying.

With other health problems as well, I was amazed to find it IS working well for me. I met a woman at my last visit at MD Anderson who told me she has been using this same treatment for 12 years. My wife

asked her if she also felt tired and had no energy while taking the treatment. She replied she used to, but as her hemoglobin and other counts went up things improved.

I am glad I was encouraged by my family to do the treatments and feel I have made progress. I realize the treatments will

continue the rest of my life. I have also been comforted and encouraged in watching and communicating with others dealing with the same disease. For those with MDS, please do not feel defeated and give up. There can be hope and improvements as time goes on.



## WATCH AND WAIT – MDS DOESN'T HOLD ME BACK

**BRIAN ANDERSON**  
Woodbridge, Virginia

### Discovery

My story begins in November of 2013 after a routine annual check-up with my doctor. I was 49 years young. Overall, my exam was uneventful, but a few days after my examination I received a call from the doctor's office asking me to return for a second blood draw.

I really wasn't concerned until my doctor said he couldn't explain why my counts, particularly for my platelets and white blood cells, were so low. The anxiety began to climb when he referred me to a hematologist/oncologist. Healthy people don't need to go there, do they?

### Search for Answers

During that first trip to the hematologist/oncologist in December of 2013, a bone marrow biopsy was performed and was found to be normal. Unfortunately, it did not shed any additional light on my condition and my doctor was unable to pin down a diagnosis. I went through a battery of tests. I tried a few different local doctors and spent those years receiving generic diagnoses of pancytopenia, thrombocytopenia, neutropenia, anemia and even copper deficiency. The cause for my lowered blood counts eluded my doctors and frustrated me.

Although I was frustrated, I didn't let my condition slow me down. I still ran 6-8 half marathons and 10K running events per year, joined a kickboxing gym, started biking and generally became more active than before. This wasn't particularly easy. I was slow and never in contention to win a race, but always had just enough energy to finish. I still didn't know what was wrong with my blood, but at this point in my life I felt relatively healthy and was in the best shape of my life.



### Diagnosis

*Fast Forward:* In the fall of 2016, my neutrophil counts really started to decline and my hematologist wanted to start me on the steroid prednisone. He was worried that my counts (ANC  $0.2 \times 10^3$ ) were so low that I was at serious risk of getting potentially life-threatening infections. As much as I was concerned about infections, I was less interested in being on a steroid just to see if it worked. Consequently, my wife and I packed up and flew to Moffitt Cancer Center in Tampa, Florida to get a second opinion.

A few blood tests and another bone marrow biopsy later, my new doctor called with the results and a new diagnosis — *de novo*, hypocellular myelodysplastic syndrome (MDS). The subtype is refractory anemia with excess blasts, also known as RAEB. He then told me my Revised International Prognostic Scoring System (IPSS-R) risk classification was Intermediate. This risk is associated with the chance of MDS progressing to acute myeloid leukemia (AML).

The hypocellular variant of my disease mimics aspects often associated with another disease affecting bone marrow, aplastic anemia. This similarity is rare but happens in 5–10 % of MDS patients. The difference in my case was the presence of 5% abnormal blast cells in my bone marrow and dysplasia (the abnormal shape and size of my blood cells).

### Initial Treatment

My doctor chose to initially treat my MDS using an immunosuppressive therapy

of horse anti-thymocyte globulin (h-ATG) as would be done if I had aplastic anemia. He saw a 30% chance that using h-ATG might “reset” my marrow and hopefully see my blood counts return to normal — at least for a while. We thought 30% was good enough and decided to initiate treatment.

In December of 2016, just over one month since diagnosis, I became an inpatient at Moffitt Cancer Center and received the h-ATG treatment. Except for a few incidents of unnerving fever/chills and the necessity for a few platelet infusions, the treatment went well. Fortunately, my wife could stay in the room and was able to sleep on a large chair that converted to a flat bed. Having the support of family is as important to the healing process as the knowledge and skill of my doctors and nurses.

I was discharged with a list of prescriptions that included antibiotics, antiviral and anti-fungal drugs, steroids and the immunosuppressive drug, cyclosporine. Over time, I tapered off the steroids, followed later by the anti-bacterial, viral and fungal medications. Eventually, the only drug that remained was the cyclosporine. My blood was monitored weekly and adjustments were frequently made to the amount of cyclosporine I needed.

After 5 months, it was clear that the treatment did not have the effect on my bone marrow that we hoped for. My white blood cell and neutrophil counts fell to levels that I had before the h-ATG was administered. Additionally, my anemia worsened. As my hemoglobin dropped, so did my energy. Before the treatment I had completed some challenging half marathons, I now found myself getting winded walking up one flight of stairs.

In May of 2017, I had a conversation with my doctor — it was clear the treatment was ineffective and we decided that I should stop taking the cyclosporine.

### Watch and Wait

As many struggling with this disease know, “watch and wait” is the treatment plan for many low to intermediate risk patients. I am now in that watch and wait category.



## OUR PATIENT STORIES

What does watch and wait mean for me? Right now, it calls for semi-annual trips to Moffitt to see my doctor and bi-monthly blood draws for routine CBC w/diff and a metabolic panel. No medications, over-the-counter or otherwise are required, and azacitidine (Vidaza®) is not yet needed. There aren't any currently recruiting clinical trials that apply to my situation.

My Moffitt transplant doctor agrees with my current treatment plan. Although he and his expert transplantation team stand ready to perform an allogeneic stem cell transplant, the only known treatment to cure MDS, he does not think now is the right time. He worries that despite my excellent health and the advantage of my relatively young age, the risks associated with stem cell transplantation outweigh the benefits. The game now is to simply monitor my consistently substandard blood test results and live my life.

### Life Moves Ahead

My watch and wait status let me continue to do things like participate in MDS Walks in Boston and 5K March for Marrow runs in Washington DC. It lets me continue to work, travel and more fully participate in the lives of my family.

But watch and wait is frustrating because I'd like this to be... done. I'd prefer not to be anemic and have more energy. I'd like to not worry about excessive bleeding or bruising. I also don't want to worry about contracting a potentially deadly virus, fungus or bacteria



whenever I leave my home as even shaking hands with a friend can have devastating consequences.

In time I know that a stem cell transplant might cure my MDS and return my life to a relative normality but it can potentially introduce new equally life-threatening medical issues, like graft versus host disease where my donor transplant's immune cells attack my own organs and tissues.

I also decided to get another opinion from the team at Dana Farber Cancer Institute in Boston, MA. There, my doctor did even more genetic testing and looked at the length of my chromosomes for something called short telomeres. Having shorter telomeres at the end of chromosomes is not a good thing from a prognosis perspective. After the tests came back, I was fortunate to discover that my telomer length was normal. With no additional discovery of genetic or chromosomal abnormalities, I was returned to my Watch and Wait status.

Deciding to take more control of my future, I decided to start up a support group for patients with MDS in the Washington DC area. It has been a wonderful experience to both share my story and listen to those of the participants. I also journal my thoughts to keep my mind focused and sharp. I have learned to lean on the support of family and friends and do so without reservation or hesitation. *This is too big for one person to handle alone.*

For now, learning to live with the uncertainty that things can get worse at any time is hard, but with the proper support from family and medical professionals, it can be done. I keep a cautious eye on my labs, continue to work with my support group and keep a positive attitude. Before I learned of the significant risks, a transplant was what I wanted. Now, I simply hope to live as long as I can in this watch and wait state with a good quality of life before a transplant becomes necessary. It's the best plan that I could have and I'm happy to have it!



## THANK YOU TO OUR INDUSTRY PARTNERS FOR THEIR SUPPORT



### A SPECIAL THANK YOU TO

GABRIELLE'S  
ANGEL FOUNDATION  
FOR CANCER RESEARCH



for their very generous grant  
in support of MDS research

### OUR FAMILY'S JOURNEY, TOGETHER

**CHRIS BARRETT**

*Worcester, Massachusetts*

On a warm October afternoon, my cell phone rang displaying a call from the hematologist at UMass Medical Center who had been treating our 16 year-old son, Matthew, for six months. I put it on speaker so my wife Marybeth and I could both hear. "The last of the tests came back," Dr. Newburger said. "Matthew has Myelodysplastic Syndromes." The details that followed are vague now, but he explained that Matthew's bone marrow was failing to produce healthy blood cells and that given Matt's condition he would need a bone marrow transplant. He emphasized that if the bone marrow transplant were successful it would be a cure, and told us that he was referring us to Boston Children's and Dana-Farber. Our minds were swimming.

Six months earlier, Matt was admitted to UMass with high fevers and such low blood numbers that doctors thought he might have leukemia. However, his bone marrow biopsy revealed no leukemia. His fevers persisted for thirty-six days, waking each night in drenched sheets. He lost weight, was fatigued, and missed much of the final quarter of his sophomore year. But by June Matt was slowly improving. His blood numbers were modestly better, and he had the endurance to return to school part-time. Marybeth and I felt the worst was behind us. Occasionally, his doctor would call letting us know that he was still pursuing Matthew's mysterious illness and troubling lab results, and consulting with doctors in Boston, Philadelphia, at the NIH, and in Cincinnati. I appreciated his diligence, but privately felt it seemed superfluous since Matt was looking so much better. How wrong I would be.

At the end of August, the day before Matt was to start his junior year, Matthew and Marybeth arrived at Dr. Newburger's office for follow-up lab work. A half hour later the tests showed Matt's numbers were alarmingly low. The results were so unexpected given that Matt was feeling



*Our son, Matthew*

better, that Marybeth asked him if he was certain that he was looking at that day's labs, and not the April reports when Matt was sick. He assured her that he was. Another bone marrow biopsy was ordered, as well as DNA testing. Seven weeks later, Dr. Newburger called us on an October afternoon with the results. "It's a very rare condition," he said, "only recently described in the last few years in the medical community." "How rare?" we asked. "Less than sixty cases." We sat quietly digesting the news. We hung up the phone wondering how we were going to tell Matt and his older brother Dan, and his two older sisters, Kate and Sarah. Later we would come to feel deep gratitude for Dr. Newburger's quiet dogged pursuit to get to the bottom of Matt's poor blood numbers.

At the end of October, during our initial meeting, we met with MDS specialist Dr. Inga Hofmann of Boston Children's Dana-Farber. The bone marrow transplant, she told us, would be scheduled for the beginning of December, and Matt would be admitted to Boston Children's.

It was at this first day of meetings that we and Matthew got to fully hear his diagnosis, the treatment plan, the challenges of going through a bone marrow transplant, but also the promise. It was a lot to take in. Marybeth and I wondered how all this sounded to him. We'd furtively look at him as the doctors talked to see if we could detect his reaction. On the drive home, Marybeth asked him, "So what do you think about

everything you heard today, Matt?" He paused and said from the back seat, "I won't be needing a haircut for awhile." Matt's sense of humor would be consistent throughout the experience. For the next year he'd joke with us, his nurses and CNAs, post comical pictures of his hospital room and his balding head. He found continual humor joking about his bodily fluids. His sisters rolled their eyes. His sense of humor would help him, and us, through the demanding physical struggles and complications he endured, and the emotional strain it put on all of us.

We felt reassured that we were in the most capable of hands. But still, there were the questions, the uncertainty, the risks, the what-ifs. We had many late night conversations. Matt's health and the approaching BMT pre-occupied our thoughts day and night. We worked hard at keeping a sense of a normal routine and of being attentive to our other children – but underlying all of this was deep concern. Many nights I'd hear Marybeth awake at 3:00 AM tossing and turning. At times there were no words that would ease the stress, so pulling her close seemed to slowly calm both of us. We prayed a lot. We prayed for healing and a successful transplant, we prayed for wise doctors, we prayed to be good parents, and we prayed for God's presence – to not leave us alone, to always be with us, to help our family grow closer because of this. We vowed not to let the beauty of each day be swallowed by the legitimate concerns we had. We would remain grateful and find the daily blessings given to us.

During our second visit to Dana-Farber, we coincidentally received a phone call from Dr. Newburger who told us that both Sarah and Kate were perfect bone marrow matches for Matt. Relief! Matt called Sarah on the way home. I could hear her scream of joy from Matt's cell phone. Sarah was the one closest in age to Matt – only a year and a half older, and the two played together growing up. Sarah mothered him, smothering him with attention when he was an infant and toddler and dressing him up in whatever costume she thought appropriate

## OUR CAREGIVER STORIES

for the imaginary game she was playing that day. It seemed remarkable that nestled in Sarah's bones, like a gift she had been quietly nurturing for eighteen years, was the cure for Matt's MDS.

Thanksgiving was nearly the height of our pre-BMT stress. Traditionally we head to New York to visit for a few days with Marybeth's family. We both come from large families. Our children have 43 first cousins! Our Thanksgiving visit would be the last time Matt could see everyone for months, so of course we wanted to be there. But with the bone marrow transplant only two weeks away, we worried how to keep him healthy around so many cousins. Any sign of illness and Matt's BMT would be pushed back until he was healthy and a bed became available – perhaps months away. The visit was marvelous for him, but by the time we left, the worry felt like a weight in my head. One look at Marybeth told me she felt the same way. Thanksgiving was over. We were now in countdown to his admission date.

Arrival at Boston Children's 6 West strangely felt like a relief. We were here. The pre-conditioning done, the wait over, the logistics largely worked out. I took a leave of absence from my middle school teaching job. A generous friend arranged for a hotel room nearby. I would sleep on the cot in Matt's room. Marybeth would catch a few hours of sleep every night at the hotel. Sarah, who was a freshman in college, would come to Boston Children's to donate her bone marrow on December 10th, just after classes were done and before exams began. We were amazed at her poise.

We hung a world map on the wall. In our earlier meetings at Dana-Farber we were struck by how many doctors, nurses, and staff were from around the world. It felt to us as if the world was coming together to save Matt. We wrote each name of every person who attended to Matt next to the country they were from. Doctors, nurses, custodial staff, recreation therapists, and nurse assistants from Germany, Russia, Italy, England, Canada, Nigeria, Pakistan, the Dominican Republic, and the United States. The map became a



*Matt asleep and surrounded by his siblings*

bit of a celebrity in its own right. By the end nearly 50 names dotted the map. Two and a half years later, when Matthew went off to college, he would hang the map in his college dorm room.

Over the next few days mail arrived from his cousins – letters of encouragement and posters with photos of all of them swimming at the lake, celebrating holidays, and on family outings. They were immediately hung on the walls of his room. The chemotherapy was fatiguing him. He slept more and his appetite dwindled. By the afternoon of his fourth day of treatment doctors were concerned with the electrolyte imbalance in his system. He slept around the clock. Doctors were concerned. They explained that they would try another course of action to improve the saline concentration in his system, that he would be closely monitored, and at his next lab draw at 2:00 AM, they were hoping to see an improvement. If not, Matt would need to be transferred to ICU. Marybeth stayed that night. We fitfully fell asleep around midnight. At just after 2:00 AM the attending doctor gently touched my shoulder to wake me. When I saw him leaning over me my stomach sank. "This can't be good," I said. "Matt needs to go to ICU," he told us. "They are waiting for him." Marybeth leaned over Matt's bed and hugged him and quietly cried. As I left to talk to the doctor in the hallway, I heard Matt whisper,

"It's going to be okay, mom."

The first few hours in ICU were nerve-racking. Doctors increased the concentration of saline to help get his body back in balance. Our nurse, who must have seen the worry on our faces, was reassuring. The chemotherapy, which was to destroy his ill bone marrow, was now wreaking havoc on his whole body. At early morning rounds, the ICU team and the bone marrow team gathered outside his door. A young ICU attending physician was clearly in charge. She explained the protocol, told the results she expected to see, and exuded such a confidence that we started to feel a small amount of relief. The BMT team then explained that the next chemo dose would be administered here in ICU later that day. At the end of the conference, I turned to the attending BMT doctor and asked, "So if the ICU doctors have a hard time getting his system back in balance can we stop the chemotherapy for a few days?" She looked somberly at me and shook her head. "No, we can only keep going now."

Matthew responded well to the increased concentration of saline. He became more alert and interacted with us. Matt remained in ICU for the remaining four days of his chemotherapy treatments. He returned to the BMT floor ready for his transplant.

Sarah arrived in Boston the night before and stayed over at the hotel with Marybeth. In the morning, she was



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wheeled into the procedure room to have her healthy bone marrow aspirated. Matt waited in his room for the miracle to arrive. Remarkably, the nurses were able to reserve the room right next to Matthew's for Sarah's recovery that afternoon. While Sarah slept off the effects of the anesthesia, the lab technician prepared her bone marrow to be dripped into Matthew later that evening. At just after midnight on December 11th, Matt's nurse carried Sarah's bone marrow into his room. It looked just like a regular bag of blood, but in it were the stem cells that would come to repopulate Matthew's now nearly eliminated bone marrow, and create a whole new healthy blood system for him. Matthew lay in bed sleepy from the Benadryl dose he had taken earlier to prepare for the transplant. The nurse asked Sarah, who was sitting in a wheelchair in a hospital johnny next to Matt's bed, if she would like to turn on the drip. She gladly reached over and pushed the button. Her bone marrow slowly dripped into the port in Matt's chest. We cheered. Matthew raised one arm high in the air eyes still closed. Sarah reached out and gently rubbed his head. It was the beginning of a new life.

Over the next month, Sarah's bone marrow slowly found a home in Matt. We waited each day for the news of his blood numbers and saw them climb ever so slowly. Matt's 24 year-old brother, Daniel, and his soon-to-be fiancée Meghan, and his 23 year-old sister Kate would come by after work. After Sarah's exams were done, she was with us too. They brought conversation, news, distraction, and joy with them. We'd have dinner together in Matt's room and we played many games of Scattergories, Password, Uno, card games, and Backgammon. Matt's walls were now covered with beautiful, intricate paper snowflakes that Dan made. Christmas ornaments, brought by a friend, now hung from the ceiling. Matt became an expert shot with his Nerf gun using the ornaments as his targets. Marybeth amazingly showed up Christmas morning with a waffle maker and made homemade waffles for our family and the nurses and



doctors. We celebrated New Year's Eve with an aunt and three cousins who were allowed to see Matt. Inspired by another family on the floor we had grown close to, we decorated the bedpans with streamers and sparkles to use as party hats!

In the first week of January, Matt's blood numbers finally hit the threshold to be discharged. We were delighted. The nurses gathered in the hallway and applauded and cheered as he walked off the unit. By now they were friends who seemed to care as much about Matt as we did.

It was a relief to be home. Before discharge we reviewed countless times how to clean his port and administer his IV medicine. I hoped I was up for the task. When Matthew awoke on the first morning home, his face was alarmingly swollen and his body covered in a rash. Less than 24 hours being home, we found ourselves back at Boston Children's with the BMT team examining him trying to determine the source of his reaction. Although we were warned that it is not uncommon to need to be readmitted during recovery, it was disheartening being back in the hospital so quickly. Matt was quite uncomfortable.

After a week, Matt was finally released and although he would be readmitted one more time for a few days in February, we settled into a routine at home. My day was focused on Matt. Making sure he took his numerous medications, disinfected counters, bathrooms, tables everyday, talking with doctors, and we driving with him once a week for his follow-up appointments. With

no school schedule to keep his sleep regulated he started staying up late playing on-line video games with a group of guys who would become his on-line friends during his isolation. We cooked him any food he wanted trying to entice him to eat. When he left the hospital he was but 119 lbs. on a 6' 1" frame. Through the months he would deal with nausea, loss of appetite, dry mouth and red, dry eyes. Doctors monitored for GVHD. He battled some opportunistic infections — the worst being a urinary tract infection that was quite painful. Later at his one-year check-up, his doctor would tell him his transplant looked great, but also acknowledged, "You endured your fair share of complications, Matt."

Social media seemed to be blessing and curse. It was a way for Matt to stay in touch with the outside world, but it also was the place to view the curated lives of his peers and remind him of what he was missing. Winter gave way to spring and then summer and Matt could get out more in the fresh air and see friends in our backyard. Doctors gave him clearance to return to school in September, nine months after his transplant. Matt returned to school as a junior — having missed nearly all of his junior year. His first few days were joy for him. He was out of the house. He could be with his classmates. "I just looked out the window of class at the trees," he told us one evening with appreciation in his voice. Yes, there were still some precautions, but generally he was to be treated like a normal high school boy we were told.

Except that things weren't all that normal. He was still drained and easily tired. He found focusing in class nearly impossible. He called it chemo fog. We suspected that he might also have ADD, which would take another two years to have properly diagnosed. He went to school late on many mornings or would need to come home early. He was in effect a part-time student for most of his junior year. But worse, underneath the physical effects and unbeknownst to us, was all of the mental wear and tear he had endured in isolation and the effort at trying to reintegrate to school. People treated him like



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everything was great now, or did not even acknowledge what had happened, but Matt was changed and he felt that his peers could not see nor understand what he had been through. He had been forced to journey to another land – one of mortality, doctors, uncertainty, stress, fear, and complications. It was a part of him now but he seemed alone in it. A piece of artwork he made later that spring captured his emotional and mental isolation – it is of two silhouetted figures. The one on the left is labeled “Cancer”; the one on the right “PTSD”. Over the cancer figure are the icons found on social media “likes,” “comments,” and “shares.” The cancer figure has hundreds of likes, comments, and shares. The PTSD figure has zero next to each icon.

Now more than one year after his transplant we noticed he seemed angry and belligerent often. He was struggling desperately to connect with his peers and to find friends. He confessed he was eating lunch alone in the bathroom at school. One night he sat on the landing of our staircase head bowed between his bent knees sobbing that he did not have any friends. As hard as the transplant was, this seemed even harder — to watch a our seventeen year old son sob as Marybeth wrapped her arms around him. It was almost too much to bear. He saw us as often suffocating him and could be very explosive toward us. We were deeply concerned, but figured with our love and support he would get through it. What we should have seen was that he was presenting symptoms of depression and anxiety. It was only after he was up late one night, which continued to be his pattern even after he returned to school much to our chagrin, that he told us he had been trying to get in touch with the psychologist at Boston Children’s he occasionally saw when he was an in-patient. He was crying for help, but we missed it. We hugged him and told him that we would call her immediately. She told us to bring him in that afternoon. I felt that I was coming up short. My entire focus was on Matt and his well-being for a year and a half, and yet while his physical health was improving, his mental health was deteriorating. And I failed to see it.



For the next couple of months we would drive into Boston once a week to see his psychologist. He enjoyed talking with her. She gave him strategies to deal with his depression. He was more open in talking with us. We discovered a teen group at the Jimmy Fund clinic and he immediately joined. They would help open up a path of healing. Over the next year Matt went on many outings with the group, including a spring training trip to Florida to see the Boston Red Sox. He loved the other teenagers. “We all get each other,” he said after one trip.

In retrospect, I now wish that part of Matt’s regular check-ups at the Jimmy Fund included a check-in with a counselor. Mental health counseling was readily available when he was an in-patient, but not as an outpatient. So much of our time and the medical professionals time was spent on Matt’s physical health, and indeed, it needed to be. But I realize now how beneficial, indeed essential, it would be if equal attention were paid to his mental health post-transplant. The toll of such prolonged isolation and the challenge of re-integration, I have come to realize, is an enormous struggle, especially for teenagers. Of course, this will require additional human resources, and perhaps changes to insurance companies’ coverage. But from our experience, if we truly want to give comprehensive care to those people who have been through such trauma, especially children and young adults, then attention to mental health must be equal to physical health.

It would still take many months for Matt to negotiate his relationships and the world

post-transplant. A chance meeting with a childhood friend he had not seen in years in a local frozen yogurt shop became the unexpected bridge to a group of high school kids who finally accepted him. Another miracle, we thought. I think he is still working out his new post-transplant reality. He is hypervigilant about his health. When he came down with pneumonia this past February while away at college, he feared he was actually suffering from a serious condition he once heard his doctor mention at one of his check-ups a year earlier. Marybeth had to reassure him at midnight that it was not that. He spent the better part of February at home recuperating.

Matt is now three and a half years post-transplant. Doctors are exceptionally pleased at the transplant. His good health is a testament to its success. We all feel grateful for how well he has done and the new life that his transplant has given him. Yes, I still look for signs of any trouble in his mental health. I think that will last for awhile. And there are mornings Marybeth and I awake and feel slightly unnerved. We can read it in each other without having to say anything. We have endured the unexpected hardship that life can hand out. It has left its mark on us too. But when we are able to step back and see the whole picture, we feel immense gratitude for the doctors, nurses, psychologists, his siblings, our daughter-in-law, and our large extended families who walked with us every step of the way.

Last week we were at the lake in Vermont at a small house my in-laws have. Marybeth and I were up early sitting in Adirondack chairs looking out at the still lake. The sun was just up and the air had a morning coolness to it. Matt sat in an old canoe fishing only twenty feet from the shore. His siblings were still asleep. He cast his line and slowly reeled it back in. He looked like the little boy who had done this so many summers before his illness. But here he was, twenty years old now, having endured his transplant and the many challenges. He was healthy. As I watched him, a wave of gratitude washed over me. I reached over to touch Marybeth’s hand and I softly cried.

## IN LOVING MEMORY...

## GREGG OSHITA

Cincinnati, Ohio

Unlike other stories you have read in the newsletter, our story is written in loving memory of **Robyn Anne Oshita** who passed away in October 2017 after losing her valiant battle with a rare form of AML where she required HLA transfusions twice a week, after it converted from MDS. Prior to her diagnosis, Robyn had been healthy all her life. It is our hope that by telling our story, it will help other families avoid the pain and sorrow our family experienced.

Robyn graduated from University of Illinois nursing school in 1974 and we were married the following year. Over the course of the next 42 years of our marriage, we were blessed with 2 beautiful children, Michael and Kimberly who grew up loving, kind and responsible adults. Nursing was the perfect career for Robyn because she befriended everyone she met which allowed her to quickly gain the trust of patients she treated.

Robyn retired in October 2016 and we were looking forward to traveling and spending more time with our kids. Life was good and the world was our oyster... or so we thought.

In July 2017, Robyn was experiencing shortness of breath and bruised easily. A blood test revealed Robyn's platelet count was extremely low, 10,000 versus a range of 150,000–450,000 in a healthy person. As a result, Robyn required a minimum of 2 matching platelet transfusions a week to prevent her from hemorrhaging. Since Robyn required special type of platelets (HLA), which were rare, our family stressed and worried, daily, for 2 1/2 months if matching HLA platelets would be available when Robyn needed them.

Two weeks later, in August 2017, Robyn was diagnosed after a bone marrow biopsy with Myelodysplastic Syndromes (MDS). Although her prognosis was not good, we were hopeful because her number of blasts was less than 5%. Her doctors told us that Robyn needed a bone marrow transplant within 7 months, before her MDS converted

to AML, to survive. Luckily we were able to find 2 matching donors over the next month who said they would donate. Unfortunately, Robyn's MDS converted to a rare form of Acute Myeloid Leukemia (AML) in 2 months versus the projected 7 months, and Robyn passed away in October 2017, 2 1/2 months after her initial diagnosis.

Robyn's closest childhood friend said this at her memorial service last year... *"In reflecting on all our shared childhood and adult experiences, the words that surface are compassionate, kind, giving... but most of all humble. Robyn always stepped away from the limelight; she was really good at deflecting attention from her accomplishments to others. Robyn you will see from your perch above how deeply you have touched our lives and left a loving legacy."*

Our family never expected to lose Robyn at such a young age **especially since she was healthy all of her life** prior to her diagnosis in July 2017. My children and I created a nonprofit 501(c)(3) foundation in loving memory of her called **The Gregg and Robyn Oshita (GRO) Foundation** ([www.thegrofoundation.org](http://www.thegrofoundation.org)) in January 2018. Our foundations mission is to inspire individuals to donate blood, plasma or platelets and register for the National Bone Marrow Registry, **"BE THE MATCH"** to help save the lives of loved ones battling serious illnesses. Whether it is the 2-year-old girl battling leukemia in Georgia or the new mother in Chicago battling cancer, please join us in helping



My wife, Robyn

[thegrofoundation.org](http://thegrofoundation.org)

save the lives of loved ones battling serious illnesses by donating at your local blood center. Although an estimated 38 percent of the U.S. population is eligible to donate blood at any given time, less than 10 percent of that eligible population actually donates blood each year. According to "Be the Match", a national bone marrow registry, even with a registry of millions, many patients who need donors who are a genetic match cannot find one.

The link below is another example of why our foundation exists. Thanks to people who donated to our foundation, we donated to Phoenix's GoFundMe page.

*Surprise daddy-daughter dance goes viral.*  
<https://www.cnn.com/videos/health/2018/08/21/daddy-daughter-dance-hospital-prince-charming-orig.cnn>

**Please join us in giving the most precious gift of all...the gift of life.**



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## IN YOUR OWN WORDS

### TESTIMONIALS

"I have just recently discovered your website, and I am **VERY IMPRESSED** with the resources you have available. I will be sharing with our patients and staff here at MGH." – Maxine C.

"Read the online version of your Building Blocks of Hope and was very impressed. **A LOT OF INFORMATION IN A SINGLE SOURCE.** I believe the hard copy would be a valuable information source that will be of great use for me as well as other members of my family. I also think the handbook will be a very useful tool during treatment." – Andrew M.

"Thank you so much for getting back to me so quickly and for all of the critical resources you offer through the foundation. You guys are the **SOLE OASIS OF HOPE** in an overwhelming sea of negative online search results and we are very grateful." – Katherine M.

"The 14th International Symposium on MDS Patient Summary, May 2017 in Valencia, Spain, is **ONE OF THE BEST** I have ever read on MDS to date!" – Patrick C.

"Thank you for the Building Blocks of Hope! This is the **BEST RESOURCE I HAVE FOUND** on the internet!" – Janet P.

"Thank you for the treasure trove of information that just showed up in my mailbox. I will be devouring it page by page, with highlighter in hand. I will also be signing up for the community membership to help support your good efforts to educate people like me who need more information on this diagnosis. **KNOWLEDGE IS POWER!**" – Elizabeth S.

"I cannot even begin to tell you how much I **APPRECIATE THE RESOURCES** that you provided. This is a very useful source of information to help get my mom on the right track. We are just beginning our journey and understanding MDS and I want to do everything I can to help her. Thank you so much for all that you do! With gratitude..." – Molly M.

"This is a belated Thank You for the telephone conversation we had a few weeks ago and the trove of printed information that you sent me. In particular, I found much valuable detail in the Building Blocks of Hope. **THE MDS FOUNDATION IS A GREAT AND VALUABLE RESOURCE** and I have contributed to the Foundation and will continue to do so." – Lewis G.

"Your **MOBILE APP** has been **EXTREMELY HELPFUL TO ME** and makes it so much easier than having to cart around all that paper." – Nancy R.

"I have registered as a member of your foundation because I have **VALUED YOUR WORK** very positively. Thank you very much for helping people from all over the world to know more about this disease, congratulations." – Roman S.G.

"**WE ARE GRATEFUL HOW THE MDS FOUNDATION GIVES SUPPORT** to all the patients and families like us. May God bless all of you and continue the great work." – Angelica R.

"Last week we talked and you told me all about the MDS Foundation. Then you sent some **WONDERFUL PUBLICATIONS** that gave me a lot of insight about MDS. Thank you very much for your help. Today I mailed my MDS Foundation membership application." – Bob B.

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

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

### STUDY DESCRIPTION

A Phase 3, international, randomized, controlled study of Rigosertib + best supportive care versus physician's choice of treatment + best supportive care in patients with myelodysplastic syndrome (MDS) after failure of a hypomethylating agent (HMA).

#### Eligibility:

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

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

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

**Primary  
Endpoint:  
Overall  
Survival**

### PRIMARY ENDPOINTS

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

### INTERNATIONAL TRIAL

More than 170 trial sites

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

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

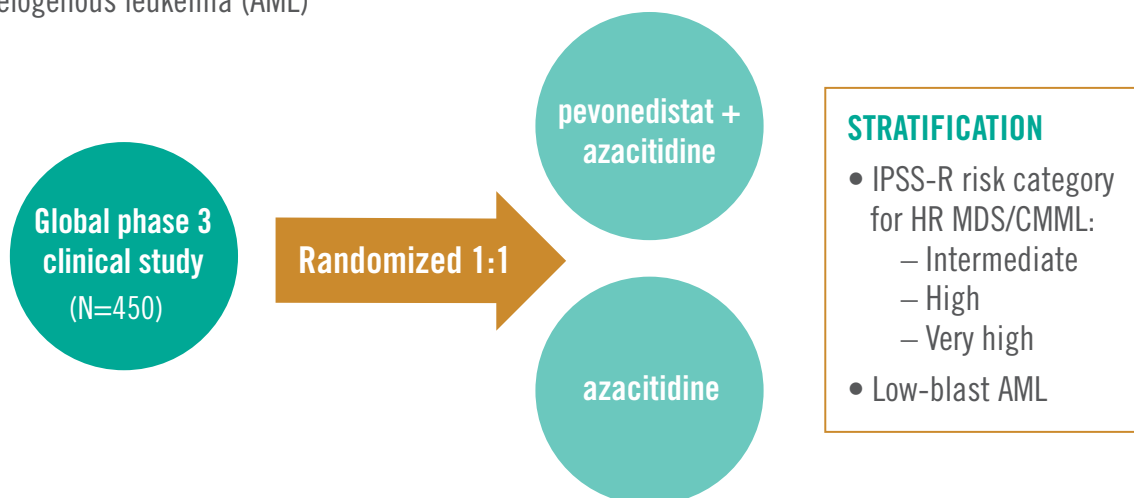


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**NOW ENROLLING**

# PANTHER TRIAL

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



**Primary endpoint:** Event-free survival (EFS)

**Key secondary endpoint:** Overall survival (OS)

Not a complete list of endpoints.

## Enrolling countries

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

## For more information, including all inclusion and exclusion criteria

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

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

[www.clinicaltrials.gov](http://www.clinicaltrials.gov) or [www.takedaoncology.com](http://www.takedaoncology.com)

For information on enrolling a patient, please contact [GlobalOncologyMedInfo@takeda.com](mailto:GlobalOncologyMedInfo@takeda.com).

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



ONCOLOGY



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## Phase 3 Clinical Trials NOW ENROLLING



### Guadecitabine (SGI-110) in MDS or CMML

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

For more information: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
Identifier: NCT02907359 or  
Email: ASTRAL-3@astx.com

### Oral ASTX727 LD in Lower Risk MDS

A Randomized, Open-Label, Phase 1-2 Study of ASTX727 Low Dose (ASTX727 LD) Extended Schedule in Subjects With Lower Risk (IPSS Low or Intermediate-1) Myelodysplastic Syndromes (MDS)

For more information: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
Identifier: NCT03502668 or  
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For a full list of eligibility requirements go to [clinicaltrials.gov](http://clinicaltrials.gov)



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8-11 MAY 2019**

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