

# AA&MDSIF **MDS Research Summary**

**From the 2014 American Society of Hematology Annual Meeting**

*A Summary of Selected Scientific Abstracts  
for Patients with Myelodysplastic  
Syndromes (MDS) and their Caregivers*

 **Aplastic Anemia & MDS**  
INTERNATIONAL FOUNDATION

The Aplastic Anemia & MDS International Foundation (AA&MDSIF) is an independent non-profit organization. Our mission is to support patients, families, and caregivers coping with:

- ◆ Aplastic anemia
- ◆ MDS (myelodysplastic syndromes)
- ◆ PNH (paroxysmal nocturnal hemoglobinuria)
- ◆ Related bone marrow failure diseases

This booklet offers summaries of selected abstracts presented at the 56<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH) in December 2014. It provides some of the most up-to-date information about new research into the biology and treatment of myelodysplastic syndromes (MDS).

Although the information in this booklet has undergone a thorough, independent medical review to insure its accuracy, this information is not intended to be a substitute for the advice of your doctor. You should always seek medical advice from a qualified physician. For more information, call us at (800) 747-2820, or visit us online at [www.AAMDS.org](http://www.AAMDS.org).

Aplastic Anemia & MDS International Foundation  
100 Park Avenue, Suite 108  
Rockville, MD 20850  
(301) 279-7202 or (800) 747-2820  
[info@aamds.org](mailto:info@aamds.org)  
[www.AAMDS.org](http://www.AAMDS.org)



*Copyright © 2015, Aplastic Anemia & MDS International Foundation*

*This publication is made possible through an unrestricted education grant from Celgene Corporation.*

Dear Patient or Caregiver,

The purpose of this booklet is to provide you with the most up-to-date information about new research into the biology and treatment of myelodysplastic syndromes (MDS), as presented at the 56<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH) Annual Meeting in December 2014.

The ASH Annual Meeting is the world's largest professional gathering of hematologists and hematological oncologists—i.e., doctors who care for patients with blood disorders or blood and bone marrow cancers. This conference is where many major findings in the field of blood and marrow disorders are first announced to attendees, the larger medical and scientific community, and the media.

New information that researchers hope is important enough to be presented at this meeting is submitted a few months ahead of the conference in the form of an “abstract”—a brief summary of the study and its results—and authors of the most interesting and noteworthy abstracts are asked by ASH to present their research in more detail, either in the format of a tacked-up printed poster or an oral (podium) presentation.

We selected the ASH abstracts in this summary because we feel they are the most relevant and important for patients who currently have MDS to know about. Please note that the research results discussed at the ASH Annual Meeting often involve experimental drugs that are not yet approved by the Food and Drug Administration (FDA) for general use or investigations of potential new uses of previously approved treatments. By providing summaries of the research presented, we do not intend to recommend or endorse any particular medication or treatment approach. Our goal is simply to inform you about current news and trends in research related to MDS.

If you are interested in participating in research studies such as those discussed in this booklet, we encourage you to speak with your doctor about clinical trials or to visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

As always, please contact AA&MDSIF if you have questions about these summaries or any aspect of managing your disease.

**Mikael Sekeres, MD, MS**

*The Cleveland Clinic Taussig Cancer Institute  
Member, AA&MDSIF Medical Advisory Board*

---

*The abstracts summarized in this booklet may be viewed on the American Society of Hematology web site at <https://ash.confex.com/ash/2014/webprogram/>. You may type in the abstract number or title in the search box. Any conflicts of interest or other relevant disclosures by the study authors are noted in each abstract.*

242

### ***Dnmt3a* and *Tet2* Genes Jointly Interfere with DNA Signaling in Stem Cells that Form Blood Cells**

Xiaotian Zhang, BS; Mira Jeong, PhD; Jianzhong Su; Myung Gon Ko, PhD; Yun Huang, PhD; Hyun Jung Park; Anjana Rao, PhD; Wei Li, PhD and Margaret A. Goodell, PhD

DNA methylation is a chemical process that helps control gene activity. When DNA methylation is abnormal, a person can develop MDS. The *Tet2* gene speeds up changes in DNA methylation. The *Tet2* gene is often mutated in various blood cancers. Patients with T cell lymphoma, for example, often have mutations in both *Tet2* and *DNMT3A* genes, which work in the same DNA methylation pathway.

The authors explored the cooperation between *Tet2* and *DNMT3A* to form cancerous blood cells. They transplanted bone marrow into a mouse breed (DKO mice) whose *Tet2* and *DNMT3A* genes weren't working, a breed without functioning *DNMT3A* (*Dnmt3a*KO mice), and one that without functioning *Tet2* (*Tet2*KO mice). The authors measured levels of engraftment, meaning that the transplanted cells reached the bone marrow and began making healthy blood cells.

### *Key Findings:*

- Engraftment was best in DKO mice, followed by *Tet2*KO mice.
- DKO mice had three times more Lin-Sca1+cKit+ (LSK) cells (stem cells in bone marrow that form blood cells) than *Tet2*KO mice 6 months after transplantation.
- Forty weeks after transplantation, DKO mice developed deadly B-cell acute myelogenous leukemia.
- *Tet2*KO mice had no signs of blood cancer 1 year after transplantation.
- Stem cells from DKO mice had a gene signature also found in people with acute myelogenous leukemia (AML) who have both *DNMT3A* and *TET2* mutations.

### *Conclusions:*

- Losing *DNMT3A* function increases the ability of cells with a *TET2* mutation to outgrow other cells.
- The mutation in DKO mice and patients with AML who have both *DNMT3A* and *TET2* mutations might drive leukemia development.
- In stem cells that form blood cells in bone marrow, both *Tet2* and *Dnmt3a* probably repress DNA signaling through methylation in parts of the genome that can change the activity levels of certain genes.

1896

### **Stem Cells that Promote Tumor Growth in Patients with CMML**

*Onima Chowdhury, MD, PhD; Petter S Woll, PhD; Una Kjällquist, PhD; Helen Doolittle, MD; Rikard Erlandsson, PhD; Kristina Anderson, MD, PhD; Ingunn Dybedal, MD, PhD; Adam Mead, MD PhD; Sally-Ann Clark, PhD; Mette S. Holm, MD, PhD; Peter Hokland, MD, DMSc; Lars Nilsson, MD, PhD; Sten Linnarsson, PhD; Eva Hellstrom-Lindberg, MD, PhD and Sten Eirik W Jacobsen, MD, PhD*

Identifying the stem cells that foster the spread of tumor cells in certain bone marrow cancers (tumor-propagating cells) could be useful for developing effective treatments for these cancers. But the conventional assays that researchers use to study stem cells might not be able to show the ability of different cell populations to help tumors grow.

The authors previously used two different techniques to show that Lin-CD34+CD38-CD90+ stem cells are the only tumor-propagating cells in low-risk and intermediate-risk MDS. The first technique, bone marrow cellular hierarchy analysis, identifies the cells that do and do not become cancerous. The second technique, in vivo genetic fate mapping, is used to study the development of mature cells from stem cells.

In this abstract, the authors reported on their use of these techniques to study tumor-propagating cells in samples from 10 patients with chronic myelomonocytic leukemia (CMML).

### *Key Findings:*

- Patients with CMML had similar compartments of stem cells and the somewhat more mature “progenitor” CMML cells compared to healthy people.
- Patients with CMML had many abnormal clones, or copies, of stem cells and progenitors of white blood cells.
- Patients with CMML often had mutations in genes that are involved in splicing messenger RNA (*SRSF2* and *ZRSR2*), regulating changes in gene function that don’t involve DNA changes (*TET2*, *ASXL1* and *EZH2*), transmitting instructions from DNA to RNA (*RUNX1* and *GATA2*), and allowing cells to send out signals (*CBL* and *NRAS*).
- All the mutations found in bone marrow tumor cells could be traced back to the CMML stem cells in 9 of 10 patients.

### *Conclusions:*

- This study provides compelling evidence that CD34+CD38-CD90+ stem cells are the tumor-propagating cells in most patients with CMML.

167

### **Improving Early Diagnosis of MDS by Deep DNA Sequencing and Array-Based Cytogenetics**

*Catherine Cargo, MB FRCPath; Nicola Rowbotham, PhD; Paul Evans, PhD; Sharon Barrans, PhD; Simon Crouch, PhD and Andrew Jack, PhD*

Identifying MDS by assessing the form and structure of patient cells is challenging, especially in patients who have fewer than 5% of blasts (abnormal, immature white blood cells) in their bone marrow. So far, cytogenetics (assessment of abnormalities in chromosomes) is the only way to identify clones, or abnormal copies of white blood cells, in MDS.

Researchers based in the United Kingdom compared arrays of single nucleotide polymorphisms (SNPs; a type of DNA building block) and deep DNA sequencing (method to determine a DNA molecule's sequence) for diagnosing MDS at an early stage. The investigators studied 26 of the most frequently mutated genes in 69 patients at the time of diagnosis diagnosis with MDS or acute myelogenous leukemia (AML; "diagnostic specimens") and 476 days earlier, on average, to investigate a low blood cell count ("non-diagnostic specimens").

### *Key Findings:*

- Ninety-one percent of non-diagnostic specimens and 94% of diagnostic specimens had a driver mutation, which helps cancerous cells grow.
- Most mutations in the non-diagnostic samples probably contributed to the development of tumor cells.
- The non-diagnostic samples had similar mutations to patients with MDS from earlier studies, except that *SF3B1* mutations were rare in the current study.
- Twenty six patients (38%) developed new mutations between the two specimens. This happened most often in patients who developed AML (15 of 21 patients, or 71%).
- Of the 21 patients who had AML, 20 had a mutation in the non-diagnostic sample.

### *Conclusions:*

- Patients who have MDS and unclear cell structure when they first come to a doctor's office for a low blood cell count tend to have mutations in genes that drive tumor growth.
- These mutations can be easily and cost-effectively identified by assessing a limited number of genes.
- Analysis of gene mutations may be an objective and reliable method of identifying patients with early-stage MDS.

409

### **Efficacy and Safety of Lenalidomide in Patients with Lower-Risk MDS: Randomized Phase III Clinical Trial**

*Valeria Santini, MD; Antonio Almeida, MD, PhD; Aristoteles Giagounidis, MD, PhD; Stephanie Gröpper, MD; Anna Jonasova, MD; Norbert Vey, MD, PhD; Ghulam J. Mufti, MD, PhD; Rena Buckstein, MD; Moshe Mittelman, MD; Uwe Platzbecker, MD; Ofer Shpilberg, MD; Ron Ram, MD; Consuelo del Canizo, MD, PhD; Norbert Gattermann, MD, PhD; Keiya Ozawa, MD, PhD; Jim Zhong, PhD; Francis Séguy; Albert Hoenekopp, MD; C.L. Beach, MD; and Pierre Fenaux, MD, PhD*

The main treatments for cancer-related anemia are transfusions with packed red blood cells and use of erythropoietin-stimulating agents (ESAs). The U.S. Food and Drug Administration has also approved the use of lenalidomide (Revlimid®), a biologic agent, to treat anemia in patients with del(5q) MDS, which means that they have a deletion in the long arm of chromosome 5.

This multicenter, randomized, double-blind, Phase III clinical trial compared the efficacy and safety of lenalidomide to placebo. The study included 229 patients with lower-risk MDS who did not respond to ESAs or had a relapse after ESA treatment. All patients needed transfusions of at least two red blood cell units every 28 days. On average, patients were 71 years old, 68% were male, and they had been diagnosed 2.6 years earlier. The study's main endpoint was red blood cell transfusion independence, defined as not needing red blood cell transfusions for at least 56 days in a row.

### *Key Findings:*

- Twenty-seven percent of patients treated with lenalidomide became transfusion independent, compared to just 3% of the placebo group.
- Those who became transfusion independent for at least 56 days did not need transfusions for 8.2 months.
- Patients treated with lenalidomide were most likely to become transfusion independent for 56 or more days if they:
  - Had been previously treated with ESAs
  - Had a level of erythropoietin (which helps the bone marrow form red blood cells) no higher than 500 mU/mL
  - Needed less than 4 units of red blood cell units every 28 days
  - Were female
- Almost two-thirds (62%) of patients treated with lenalidomide developed a white blood cell shortage compared to 11% of those in the placebo group. The rate of platelet shortages was 36% in the lenalidomide group and 4% in the placebo group.
- About a third (32%) of patients treated with lenalidomide stopped their treatment due to side effects, compared to 11% of those in the placebo group.

### *Conclusions:*

- The results suggest that lenalidomide can be used safely and effectively in patients with lower-risk MDS who need regular blood transfusions, do not respond to treatment with ESAs or respond and then have a relapse, and do not have del(5q) MDS.

409 (continued)

### What This Means For Patients

Lenalidomide is an oral drug that is very effective in improving anemia in a specific type of MDS patients carrying an abnormality of chromosome 5, del(5q).

The international MDS-005 study tested whether MDS patients without this anomaly could respond to lenalidomide, as no other active therapies are at present available. Out of 160 lower-risk MDS patients treated, 26.9% achieved transfusion independence lasting more than 8 weeks, while 17.5% stopped transfusions for as long as 24 weeks. As freedom from transfusions prolongs survival, and the drug was quite well tolerated, the challenge now is to identify clinical, chromosomal and molecular characteristics of the responding patients to allow in the future effective targeted treatment.



#### Valeria Santini, MD

Associate Professor of Hematology  
University of Florence Medical School  
Florence, Italy

Those with high EPO levels might not respond to treatment with erythropoiesis-stimulating agents (ESAs), or they might have a relapse after ESA treatment.

ACE-536 is being developed to treat anemias that result from ineffective formation by the bone marrow of red blood cells because, for example, they have MDS. ACE-536 increases the production of mature red blood cells in a different way from ESAs.

This ongoing, Phase II, multicenter study is evaluating the effects of ACE-536 on anemia in patients with lower-risk MDS who either do or don't need frequent red blood cell transfusions (at least four units of red blood cells in the 8 weeks before the study). Patients are adults with anemia and an erythropoietin level higher than 500 U/L. Participants have not responded to ESAs or had a relapse after ESA treatment.

The investigators are gradually increasing the doses of ACE-536 every 3 weeks in 7 groups of 3 to 6 patients each and following the patients for 3 months. The preliminary findings reported here are based on 26 patients with a median age of 71 years. Half were female, and 19 needed frequent red blood cell transfusions.

#### Key Findings:

- Hemoglobin levels increased in 2 of the 7 patients who did not need frequent transfusions. Six of these 7 patients stopped needing transfusions for at least 8 weeks during the study.
- Six of the 19 patients who needed frequent transfusions were transfused with at least 50% fewer red blood cell units over 8 weeks during the study. Five of these patients stopped needing regular transfusions for at least 8 weeks during the study.
- Patients had few side effects from ACE-536, and none of their side effects was serious.

411

### Treatment in Patients with Lower-Risk MDS: Preliminary Results from a Phase II Clinical Trial

Uwe Platzbecker, MD; Ulrich Germing, MD; Aristoteles Giagounidis, MD, PhD; Katharina Goetze, MD; Philipp Kiewe, MD; Karin Mayer, MD; Oliver Ottman, MD; Markus P. Radsak, MD; Thomas Wolff, MD; Detlef Haase, MD; Monty Hankin; Dawn M. Wilson; Adberrahmane Laadem, MD; Matthew L. Sherman, MD; and Kenneth M. Attie, MD

Patients with MDS often have high levels of erythropoietin (EPO), a hormone that helps the bone marrow form healthy red blood cells.

## NOVEL TREATMENTS: LOWER-RISK MDS

- The most common side effects were diarrhea (4 patients), bone pain (3 patients), and fatigue (3 patients).

### Conclusions:

- Based on preliminary data in patients with lower-risk MDS, up to 5 doses of ACE-536 administered under the skin every 3 weeks increased hemoglobin levels or decreased the number of red blood cell transfusions that patients needed.
- ACE-536 was safe in this group of patients.
- These data strongly support further evaluation of longer-term treatment with ACE-536 in patients with MDS.

---

### 3251

#### Phase II Clinical Trial of Sotatercept (ACE-011) in Patients with Lower-Risk MDS and Anemia

Rami S Komrokji, MD; Guillermo Garcia-Manero, MD; Lionel Ades, MD, PhD; Abderrahmane Laadem, MD; Bond Vo, PharmD; Thomas Prebet, MD, PhD; Aspasia Stamatoullas, MD; Thomas Boyd, MD; Jacques Delaunay, MD; David P. Steensma, MD; Mikkael A. Sekeres, MD, MS; Odile Beyne-Rauzy, MD, PhD; Jun Zou, MS; Kenneth Attie, MD; Matthew L. Sherman, MD; Pierre Fenaux, MD, PhD; and Alan F. List, MD

Anemia, a hallmark of MDS, is challenging to treat, particularly in patients who have a relapse after treatment with erythropoiesis-stimulating agents (ESAs). Sotatercept (ACE-011) is an artificial protein that promotes the formation of healthy mature red blood cells and their release into the bloodstream.

The main objective of this Phase II, open-label study was to find the safest and most effective dose of sotatercept in patients with anemia and lower-risk MDS or chronic myelomonocytic leukemia (CMML). Patients had not responded to ESAs or had had a relapse after ESA treatment.

The investigators tested four sotatercept doses injected under the skin every 3 weeks.

This report focused on 53 patients with MDS. Their median age was 71 years, and they had been diagnosed 4 years earlier, on average. Seventy percent of patients were male. Forty-five patients (83%) received 4 or more RBC units in the 8 weeks before starting treatment (high transfusion burden), and 9 pts (17%) received less than 4 units (low transfusion burden).

### Key Findings:

- Red blood cell counts improved in 21 patients (40%).
- Five patients with a high transfusion burden stopped needing transfusions for at least 8 weeks.
- Hemoglobin levels increased in 8 of 9 patients with a low transfusion burden. Six of these patients stopped needing transfusions for at least 8 weeks.
- Twenty patients (37%) had at least one side effect (such as fatigue or headache) that was probably related to sotatercept.

### Conclusions:

- Patients with lower-risk MDS tolerated sotatercept well at the doses tested.
- This study provided promising evidence that sotatercept might be effective in this group of patients.
- The investigators will explore higher doses of sotatercept over longer periods.

163

### **Phase III Clinical Trial of Rigosertib Versus Best Supportive Care in Patients with Higher-Risk MDS after Failure of Hypomethylating Agents**

*Guillermo Garcia-Manero, MD; Pierre Fenaux, MD, PhD; Aref Al-Kali, MD; Maria R. Baer, MD; Mikkael A. Sekeres, MD, MS; Gail J. Roboz, MD; Gianluca Gaidano, MD, PhD; Bart L. Scott, MD; Peter L. Greenberg, MD, PhD; Uwe Platzbecker, MD; David P. Steensma, MD; Suman Kambhampati, MD; Karl-Anton Kreuzer, MD; Lucy A Godley, MD, PhD; Robert Collins, Ehab Atallah, MD; Francois Wilhelm, MD, PhD; Isabelle E. Wilhelm, MD; Nozar Azarnia, PhD; Manoj Maniar, PhD; and Lewis R. Silverman, MD*

The U.S. Food and Drug Administration hasn't approved any treatments for patients with higher-risk MDS who don't respond to the standard treatment or have a relapse after treatment. This treatment consists of a hypomethylating agent (HMA), such as azacitidine (Vidaza®) or decitabine (Dacogen®).

This Phase III, randomized, controlled clinical trial evaluated the efficacy and safety of rigosertib (Estybon®), which kills cancer cells and immature stem cells (known as "blasts"). The study included 299 patients with higher-risk MDS. Of these patients, 25% had not responded to HMA treatment in the past, 37% had disease progression during HMA treatment, and 38% had a relapse after HMA treatment.

The results are based on 242 patients who died—161 treated with rigosertib and 81 treated with best supportive care to manage their symptoms. Two thirds of participants were male, and the average age was 74 years.

#### *Key Findings:*

- Patients in the rigosertib group survived for 2.3 months longer than patients in the supportive care group.
- The 184 patients who didn't respond to HMA treatment survived for 8.6 months if they were treated with rigosertib and 5.3 months if they were treated with supportive care.
- Patients survived longer if they had not responded to HMA treatment, had disease progression during HMA treatment, were treated with HMAs for no more than 9 months, were younger than 75, or had very high-risk disease.
- Patients tolerated rigosertib well. Only 5% needed a lower dose because of side effects.
- Rates of serious side effects were similar in the rigosertib and supportive-care groups.
- The most common side effects of rigosertib were nausea, diarrhea, constipation, and fatigue.

#### *Conclusions:*

- The differences in overall survival rates between patients treated with rigosertib and those treated with supportive care weren't statistically significant.
- However, rigosertib improved survival compared to supportive care in certain groups of patients, including those who didn't respond to HMAs or had very high-risk MDS.
- Rigosertib treatment was safe in this group of elderly patients with MDS.

164

### Phase I/II Clinical Trial of Azacitidine and Lenalidomide in Patients with Higher-Risk MDS and Acute Myeloid Leukemia

*Courtney D. DiNardo, MD; Naval Daver, MD; Elias Jabbour, MD; Tapan Kadia, MD; Gautam Borthakur, MD; Marina Konopleva, MD, PhD; Naveen Pemmaraju, MD; Hui Yang, MD, PhD; Yue Wei, William G. Wierda, MD, PhD; Carlos E. Bueso-Ramos, MD, PhD; Keyur P. Patel, MD, PhD; Jorge E. Cortes; Farhad Ravandi, MD; Hagop M. Kantarjian, MD; and Guillermo Garcia-Manero, MD*

The hypomethylating agents (HMAs) azacitidine (Vidaza®) and decitabine (Dacogen®) are the main treatments for higher-risk MDS. These drugs are also used to treat acute myelogenous leukemia (AML) in patients who aren't eligible for standard AML treatment, such as patients who are older.

Studies are assessing combinations of HMAs with several other drugs to improve HMA response rates. Some studies have shown that the combination of azacitidine with lenalidomide (Revlimid®) is effective in patients with higher-risk MDS and certain patients with AML. But the best dose of this combination or how it should be scheduled isn't known.

A Phase I/II clinical trial of azacitidine followed by lenalidomide included 88 patients with high-risk MDS or with AML and at least 30% blasts (abnormal immature white blood cells) in their bone marrow. Their average age was 67 years. Each patient was treated with 75mg/m<sup>2</sup> per day of azacitidine on days 1–5 of each 28-day cycle. They then took lenalidomide by mouth for 5 or 10 days, starting on day 6 of each cycle.

The Phase I part of the study evaluated different doses and schedules of lenalidomide. The Phase II component started with a lenalidomide dose of 50 mg per day for 10 days. But the first 20 patients had serious side effects with that dose. So the lenalidomide dose changed to 25 mg per day for 5 days.

### Key Findings:

- On average, 35% of all patients responded to the treatment.
- Patients survived for 33 weeks.
- Of the 40 patients treated with 25 mg per day of lenalidomide for 5 days each cycle, 22 (55%) had a response and survived about 18 months.
- The response of the 31 patients who responded to the 25 mg per day dose lasted 7 months.
- Thirteen of the patients who responded to the 25 mg per day dose later had a stem cell transplant, and 10 patients are still in remission.

### Conclusions:

- Treatment with 75mg/m<sup>2</sup> per day of azacitidine on days 1-5 followed by 25 mg per day of lenalidomide on days 6-10 over a 28-day cycle appears to be effective for high-risk MDS and AML with at least 30% blasts.
- Responses are rapid (taking just 2 cycles) and long-lasting.
- Patients tolerated this dosing schedule well.

529

### First Results of a Randomized Phase II Clinical Trial of SGI-110 in Patients with Higher-Risk MDS or Chronic Myelomonocytic Leukemia

Guillermo Garcia-Manero, MD; Ellen K. Ritchie, MD; Katherine Walsh, MD; Michael Savona, MD; Patricia Kropf, MD; Casey O'Connell, MD; Raoul Tibes, MD; Naval G. Daver, MD; Elias Jabbour, MD; Scott Lunin, MD; Todd L. Rosenblat, MD; Karen Yee, MD; Wendy Stock, MD; Elizabeth A. Griffiths, MD; Joseph R Mace, MD; Nikolai A. Podoltsev, MD, PhD; Jesus G. Berdeja, MD; Jean-Pierre Issa, MD; Woonbok Chung, PhD; Sue Naim, Pietro Taverna, PhD; Yong Hao, PhD; Mohammad Azab, MD; Hagop M. Kantarjian, MD; and Gail J. Roboz, MD

The only treatments with approval from the U.S. Food and Drug Administration for higher-risk MDS are azacitidine (Vidaza®) and decitabine (Dacogen®). Both of these drugs are hypomethylating agents, which help DNA act normally. SGI-110 is a new type of hypomethylating agent that stays in the body longer than Dacogen.

The purpose of this Phase II clinical trial was to compare responses at different SGI-110 doses in 102 patients with higher-risk MDS or chronic myelomonocytic leukemia (CMML). Of these patients, 49 had not been treated for MDS or CMML in the past, and 53 had either not responded to treatment or had had a relapse after treatment. Patients were randomly assigned to a dose of either 60 mg/m<sup>2</sup> or 90 mg/m<sup>2</sup> daily for 5 days every 28 days. Average patient age was about 72 years, and 60 to 70% of patients in each treatment group were male.

#### Key Findings:

- Ten of the 53 patients (19%) in the 60 mg/m<sup>2</sup> group and 11 of 49 (22%) in the 90 mg/m<sup>2</sup> group had a complete response, meaning that they had no signs of MDS or CMML.
- Seven of 49 patients (14%) who had not been treated before and 11 of 53 previously treated patients (23%) had a complete response.

- More patients who had not been treated before stopped needing transfusions than previously treated patients.
- Eighty-one percent of patients in the 60 mg/m<sup>2</sup> group and 88% in the 90 mg/m<sup>2</sup> group had a serious side effect.

#### Conclusions:

- SGI-110 changed bone marrow biology and reduced symptoms in patients with higher-risk MDS or CMML.
- This new hypomethylating agent is especially promising in patients previously treated with azacitidine or decitabine.
- Patient responses and rates of side effects did not differ by SGI-110 dose.

#### LBA-5

### A Randomized Phase II Study of Azacitidine, Lenalidomide, and Vorinostat in Patients with Higher-Risk MDS and Chronic Myelomonocytic Leukemia

Mikael A. Sekeres, MD, MS; Megan Othus, PhD; Alan F. List, MD; Olatoyosi Odenike, MD; Richard M. Stone, MD; Steven D. Gore, MD; Mark R. Litzow, MD; Rena Buckstein, MD; Mario R. Velasco, Jr., MD; Rakesh Gaur, MD; Ehab Atallah, MD; Eyal Attar, MD; Frederick R. Appelbaum, MD; and Harry P. Erba, MD, PhD

The standard treatment for higher-risk MDS and chronic myelomonocytic leukemia (CMML) is the use of hypomethylating agents, such as azacitidine (Vidaza®). Another treatment used in some forms of MDS is lenalidomide (Revlimid®), which slows down the growth of blood vessels that feed abnormal MDS cells. The histone deacetylase inhibitor vorinostat (Zolinza®) works with azacitidine to reactivate genes that are no longer active as a result of the disease. Whether combinations of azacitidine with lenalidomide or vorinostat have higher response rates than azacitidine alone is unknown.

## NOVEL TREATMENTS: HIGHER-RISK MDS

This Phase II clinical trial randomly assigned patients with higher-risk MDS or CMML to treatment with azacitidine alone, azacitidine and lenalidomide, or azacitidine and vorinostat. The patients continued their treatment until their disease progressed or relapsed, they had an unacceptable side effect, or their disease did not respond. The study was designed to measure improvements in overall response rates of one of the combination groups compared to the azacitidine-only group.

The results presented here are based on 260 patients. Patients were treated for 23 weeks, on average, and were followed for 9 months.

### *Key Findings:*

- On average, patients in the azacitidine-only group took 15 weeks to achieve their best response, compared to 16 weeks for azacitidine and lenalidomide and 16 weeks for azacitidine and vorinostat.
- Overall response rates were similar in the three groups: 36% for azacitidine only, 37% for azacitidine and lenalidomide, and 22% for azacitidine and vorinostat.
- Rates of serious side effects were as follows:
  - Azacitidine only: 10% for low white blood count with a fever, 4% for stomach and intestinal problems, 2% for infection, and 2% for rash
  - Azacitidine and lenalidomide: 13% for low white blood count with a fever, 11% for stomach and intestinal problems, 3% for infection, and 12% for rash
  - Azacitidine and vorinostat: 13% for low white blood count with a fever, 23% for stomach and intestinal problems, 3% for infection, and 1% for rash

### *Conclusions:*

- In patients with higher-risk MDS, overall response rates were similar for azacitidine alone compared to azacitidine plus lenalidomide or vorinostat.
- Certain patients within each group might have benefitted more from combination therapy than from azacitidine alone.
- The investigators are analyzing data on longer-term outcomes.

### **What This Means For Patients**

The standard therapy for MDS patients with higher-risk disease is either azacitidine or decitabine. This trial tried to improve on the efficacy of single-drug azacitidine by adding other drugs – either lenalidomide or vorinostat – that have worked well in MDS patients in the past. The overall response rate – the number of patients who had a remission or improvement in blood counts – was no different whether they had azacitidine or azacitidine combined with one of the other drugs. However, it appeared that patients who went into a remission or who had improved blood counts to azacitidine combined with vorinostat remained better for longer than those treated with azacitidine. We are still awaiting data on whether subgroups of patients did better when they received combinations of drugs, and whether patients receiving combinations of drugs lived longer than those who received the azacitidine alone.



### **Mikkael Sekeres, MD, MS**

*Professor of Medicine*

*Director, Leukemia Program*

*Cleveland Clinic Taussig Cancer Institute*

## EXPLAINING LENALIDOMIDE'S EFFECTIVENESS

### 4

#### **Why Lenalidomide Is an Effective Treatment for Del(5q) MDS**

*Emma C. Fink, Jan Krönke, MD; Slater N. Hurst, Namrata D. Udeshi, PhD; Tanya Svinkina, Rebekka K. Schneider, MD; Marie E. McConkey, PhD; Marcus Järås, PhD; Lars Bullinger, MD, PhD; Steven A. Carr, PhD and Benjamin L. Ebert, MD, DPhil*

Lenalidomide (Revlimid®) is a very effective treatment for del(5q) MDS. People with del(5q) MDS have a deletion (loss) of the long (q) arm of chromosome 5.

Ubiquitin is a protein in most cells of the body that has several functions, including tagging proteins that the body doesn't need any more. Lenalidomide leads the CRBN-CRL4 E3 ubiquitin ligase, an enzyme, to ubiquitinate (mark for breakdown or transportation) the IKZF1 and IKZF3 proteins. Breaking down IKZF1 and IKZF3 probably doesn't explain lenalidomide's activity in del(5q) MDS.

This study's goal was to learn whether ubiquitination of a molecule bound by the CRBN ubiquitin ligase in human bone marrow cells explains lenalidomide's effectiveness for del(5q) MDS. Casein kinase 1A1 (CSNK1A1), an enzyme that increases ubiquitination and decreases the number of proteins after lenalidomide treatment, is in the del(5q) region of chromosome 5. So lenalidomide might attack this enzyme in del(5q) MDS.

#### *Key Findings:*

- Lenalidomide treatment decreased CSNK1A1 protein levels in several human cell lines without changing CSNK1A1 mRNA levels.
- Lenalidomide treatment increased ubiquitination of the CSNK1A1 enzyme.
- Inactivating the CRBN gene stopped the breakdown of CSNK1A1 by lenalidomide.
- Cells from mice without a functioning CSNK1A1 gene whose CRBN gene produced too much protein broke down the human CSNK1A1 protein after lenalidomide treatment.

#### *Conclusions:*

- Lenalidomide leads to the ubiquitination and breakdown of CSNK1A1 by the CRBN-CRL4 E3 ubiquitin ligase.
- del(5q) cells have only one copy of CSNK1A1, so their numbers drop sharply compared to cells without the abnormal chromosome.
- This result explains why lenalidomide is an effective treatment for del(5q) MDS.

166

### Similarities in Gene Mutations between Idiopathic Cytopenia of Undetermined Significance and Lower-Risk MDS

*Brian Kwok, MD; Prashanti Reddy, MD; Keming Lin, MD; Rachel Flamholz, MD; Aine Yung, MD; Bashir Dabbas, MD; Matthew McGinniss, PhD; Shareef Nahas, PhD; Julie Kines and Yin Xu, MD, PhD*

Idiopathic cytopenia of undetermined significance (ICUS) is a long-lasting, unexplained shortage of one or more types of blood cells that does not meet the criteria for MDS. ICUS sometimes progresses to MDS or acute myeloid leukemia. Most patients with MDS have at least one somatic (not inherited) mutation in driver genes that help MDS cells grow.

A research team from Genoptix Medical Laboratory in Carlsbad, California, used next-generation sequencing to explore the genomics of ICUS and its relationship to lower-risk MDS. They compared gene mutations in bone marrow specimens from 250 patients with ICUS and 90 patients with lower-risk MDS.

#### Key Findings:

- Thirty-three percent of patients with ICUS had at least one somatic mutation.
- The most common mutation, present in 38% of patients, was in the TET2 gene. This mutation seems to occur early in the development of bone marrow cancers.
- Most of the mutated genes in patients with ICUS were epigenetic (meaning that they didn't involve changes in DNA sequences) or were involved in splicing RNA to transmit genetic coding information.
- Patients with ICUS who had gene mutations were significantly older (average age 78 years) and more likely to be male than those without mutations (69 years).

- Eighty-three percent of patients with MDS had at least one somatic mutation.
- Almost half (47%) of patients with MDS had an SF3B1 mutation.
- As with ICUS, most of the gene mutations in patients with MDS were epigenetic or involved in RNA splicing.
- Among patients with mutations, those with lower-risk MDS were significantly more likely to have anemia than those with ICUS.

#### Conclusions:

- Patients who had ICUS and gene mutations had observable and genomic characteristics and that were more similar to patients with lower-risk MDS than patients with ICUS and no mutations.
- Next-generation sequencing might help identify patients with ICUS who are likely to develop MDS.

168

### A New Model to Predict Outcomes in Heavily Treated Patients with MDS

*Aziz Nazha, MD; David J. Seastone, DO, PhD; Tomas Radivoyevitch, PhD; Aaron T. Gerds, MD, MS; Sudipto Mukherjee, MD, MPH; Hetty E. Carraway, MD; Anjali S. Advani, MD; Matt E. Kalaycio, MD; Gina Rupp; Kristin Colaluka; Sean Hobson, MA; Jaroslaw P. Maciejewski, MD, PhD; and Mikkael A. Sekeres, MD, MS*

The Revised International Prognostic Scoring System (IPSS-R) categorizes the risk of certain outcomes in patients with MDS. Research has shown that the IPSS-R is valid in patients treated with one type of drug. But this research doesn't reflect typical patients with MDS who undergo different types of treatments in different orders.

## PREDICTING MDS OUTCOMES

### 168 (continued)

Researchers from the Cleveland Clinic developed a model to predict outcomes in patients with MDS regardless of what treatments they've had. This model includes data on gene mutations. The model is based on data from 333 patients with newly diagnosed MDS who were treated at the Cleveland Clinic between 2000 and 2012. On average, patients were 68 years old. Fifteen percent of patients had not been treated before. The other patients had been treated with up to seven different therapies.

#### *Key Findings:*

- The researchers detected 25 of the gene mutations they studied in at least 10% of patients.
- A statistical model that included age, IPSS-R score, and these 25 mutations found that the following factors could predict patient outcomes:
  - Age
  - IPSS-R score
  - Mutations in ASXL1, BCOR, BCORL1, EZH2, IDH2, SF3B1, or TP53
- The investigators' model has four categories of disease with different outcomes:
  - Low (score 0 to 3.4, median survival 47.3 months)
  - Intermediate-1 (score of 3.5 to 4, median survival of 30.2 months)
  - Intermediate-2 (score of 4.1 to 5.4, median survival of 19.9 months)
  - High (score of 5.5 or higher, median survival of 12.2 months)

#### *Conclusions:*

- The authors developed a new mathematical model that can accurately predict how long patients with MDS or chronic myelomonocytic leukemia will survive regardless of the treatments they've had.
- This model shows the importance of using data on gene mutations along with observable patient characteristics to predict outcomes in patients with MDS.

### 532

#### **Effect of TP53 Mutations on Prognosis of Patients with MDS Who Have Many Chromosome Abnormalities**

*Rafael Bejar, MD, PhD; Elli Papaemmanuil, PhD; Torsten Haferlach, MD; Guillermo Garcia-Manero, MD; Jaroslaw P. Maciejewski, MD, PhD; Mikkael A. Sekeres, MD, MS; Matthew J. Walter, MD; Timothy A. Graubert, MD; Mario Cazzola, MD; Luca Malcovati, MD; Peter J Campbell, PhD; Seishi Ogawa, MD, PhD; Jacqueline Boulton, PhD; David Bowen, MD, PhD; Sudhir Tauro, PhD; Michael J Groves, PhD; Michaela Fontenay, MD, PhD; Lee-Yung Shih, MD; Heinz Tüchler; Kristen E. Stevenson; MS, Donna Neuberg, Sc.D.; Peter L. Greenberg, MD, PhD; and Benjamin L. Ebert, MD, PhD*

A karyotype (number and appearance of chromosomes) is complex when a patient has at least three abnormalities in their chromosomes. All of the systems used to predict outcomes in patients with MDS are based on the idea that patients with a complex karyotype have a poor prognosis.

Members of the International Working Group for Prognosis in MDS-Molecular Committee studied the relationship between TP53 mutations, number and type of chromosomal abnormalities, and patient outcomes. The study included 258 patients who had MDS and a complex karyotype from the United States and several European countries.

## PREDICTING MDS OUTCOMES

### *Key Findings:*

- Sixty percent (223) of the 258 patients had a *TP53* mutation.
- Patients with the *TP53* mutation survived for 7.7 months, on average, compared to 23.4 months without the mutation.
- Whether a patient had a *TP53* mutation had a higher impact on survival than other possibilities. These other possibilities included having only one copy and not the usual two copies of a chromosome, number of abnormalities in chromosomes, or platelet count.
- Patients with only three or four abnormalities in chromosomes survived longer than those with five or more abnormalities.

### *Conclusions:*

- *TP53* mutations are common in patients with MDS who have a complex karyotype.
- *TP53* mutations affect the prognosis of patients with MDS regardless of the other features of their disease, including other abnormalities in chromosomes.
- Knowing whether patients with a complex karyotype have a *TP53* mutation could help doctors make more accurate prognoses.

### **What This Means For Patients**

In MDS, the presence of three or more chromosomal abnormalities (called a complex karyotype) is considered a marker of poor prognosis. However, this is a diverse group and we need better tools to predict an individual's actual risk.

Our study found that in patients with complex karyotype MDS, the presence of *TP53* gene mutations was associated with a poor prognosis as were having five or more chromosomal abnormalities or loss of chromosome 7. Patients without these features had a much better prognosis than predicted. Our study makes the case that genetic testing for mutations of *TP53* helps improve our ability to predict outcomes in patients with complex karyotype MDS.



#### **Rafael Bejar, MD, PhD**

*Assistant Professor of Medicine  
Division of Hematology-Oncology  
University of California, San Diego*

823

### Classification of MDS by Early Acquired Gene Mutations

Hideki Makishima, MD, PhD; Kenichi Yoshida, MD, PhD; Thomas LaFramboise, PhD; Bartłomiej P. Przychodzen; Matthew Ruffalo; Inés Gómez-Seguí, MD, Yuichi Shiraishi, PhD; Masashi Sanada, MD, PhD; Yasunobu Nagata, MD, PhD; Yusuke Sato, MD; Aiko Sato-Otsubo, PhD; Kenichi Chiba, PhD; Hiroko Tanaka; Tsuyoshi Nakamaki, MD; Wolf-Karsten Hofmann, MD; Shuichi Miyawaki, MD, PhD; Shigeru Chiba, MD, PhD; Satoru Miyano, PhD; Holleh Husseinzadeh, MD; Naoko Hosono, MD, PhD; Chantana Polprasert, MD; Bhumika J Patel, MD; Swapna Thota, MD; Brittney Dienes; Kathryn M Guinta; Lee-Yung Shih, MD; Yogen Saunthararajah, MD; Yusuke Okuno, MD, PhD; Mikkael A. Sekeres, MD, MS; Seishi Ogawa, MD, PhD; and Jaroslaw P. Maciejewski, MD, PhD

Gene mutations that people acquire after birth (somatic mutations) play a key role in the development of MDS. These mutations are very diverse and are combined in many different ways in different patients. In addition, different patients with the same type of MDS can have very different somatic mutations or combinations of mutations. Studies in acute myelogenous leukemia (AML) have shown that the earliest (“ancestral”) mutations seem to have a greater effect on outcomes than mutations that happen later.

The authors studied ancestral mutations in samples from 100 patients with MDS.

#### Key Findings:

- Samples with earlier mutations tended to have more mutations, whereas samples with later mutations had fewer mutations.
  - About 80% of patients had ancestral mutations in TET2, DNMT3A, SF3B1, ASXL1, TP53, U2AF1, RUNX1, or SRSF2.
  - Many of these mutations could be used to predict patient outcomes alone (without any other information) only for patients whose disease was affected by ancestral mutations.
- Patients with TET2 mutations had more mutations than those without the mutation.
  - Mutations in SF3B1 and ASXL1 were not associated with more mutations in other genes.

#### Conclusions:

- Ancestral mutations might determine the observable features, genetic characteristics, and outcomes of MDS.
- When mutations in TET2 happen early in MDS development, they are associated with myelodysplastic/myeloproliferative neoplasms (MDS/MPN). MDS/MPN is a blood disease with features of both MDS and myeloproliferative diseases. But mutations at a later stage are associated with MDS.
- Earlier changes in genes are less diverse and more common in certain types of MDS than later changes.

#### What This Means For Patients

This study has two significant messages: 1) Ancestral mutations are acquired in the early status of MDS. 2) Secondary acquired subclonal mutations are associated with progression of disease. It is extremely important because MDS cells are usually affected by multiple mutations, which are various according to when and which order these mutations happened or will happen. All these findings might be partially predictable based on the preferable or exclusive relation between each mutated genes. Also, these combinations of mutations create very specific phenotype of diseases, which suggest that the variety of genetic events count on the clinical course in each patient.



#### Hideki Makishima, MD, PhD

Project Staff, Department of Translational Hematology and Oncology Research  
Cleveland Clinic Taussig Cancer Institute

840

### **Clones with Non-inherited Gene Mutations in Older People Who Develop Blood Cancers**

*Siddhartha Jaiswal, MD, PhD; Pierre Fontanillas, Jason Flannick; Alisa Manning; Peter Grauman; Brenton G. Mar, MD, PhD; R. Coleman Lindsley, MD, PhD; Craig Mermel; Noel Burtt; Alejandro Chavez; John M. Higgins, MD; Vladislav Moltchanov; Leena Kinnunen; Heikki Koistinen; Claes Ladenvall; Gad Getz, PhD; Adolfo Correa; Stacey Gabriel, PhD; Sekar Kathiresan; Heather Stringham; Michael Boehnke on behalf of GoT2D; Brian Henderson on behalf of SIGMA T2D; Mark McCarthy on behalf of T2D-GENES; Jaako Tuomilehto; Christopher A. Haiman; ScD; Leif Groop; Gil Atzmon; James Wilson; Donna S. Neuberg, ScD; David Altshuler and Benjamin L Ebert, MD, PhD*

The authors tested the hypothesis that patients who develop MDS or certain blood cancers often go through a premalignant state (before their MDS or cancer develops). In this premalignant state, cells with some of these mutations form growing numbers of clones, or abnormal copies of immature white blood cells. According to the hypothesis, these clones should be detectable in the blood of elderly individuals not known to have a blood disease.

The authors analyzed genomic data from blood cells of 17,182 people. They looked for mutations in 160 genes that are often mutated in blood cancers.

### *Key Findings:*

- The results showed 805 somatic (non-inherited) mutations in 73 genes from 746 individuals.
- The mutations became more common with age, rising from about 10% of people in their 70s to 18% of those 90 or older.
- Most mutations were in the *DNMT3A*, *TET2*, and *ASXL1* genes.
- People with one of the mutations had a higher risk of developing a blood cancer and of dying. But the higher death rate was due to more factors than just increased risk of blood cancer.

### *Conclusions:*

- The formation of clones associated with somatic mutations in a gene known to cause cancer is common in older people who later develop a blood cancer.
- These clones are associated with a higher risk of blood cancer and death from all causes.

# 2015 Patient and Family Conferences

Meeting You Where You Are



## Aplastic Anemia, MDS, PNH, and Bone Marrow Transplant

BALTIMORE, MD	<b>MARCH 28</b>
CLEVELAND, OH	<b>MAY 2</b>
SAN FRANCISCO, CA	<b>JULY 18</b>
BOSTON, MA	<b>SEPTEMBER 19</b>
CHICAGO, IL	<b>OCTOBER 24</b>
TAMPA, FL	<b>NOVEMBER 14</b>

Connect with patients and families  
Get answers from leading medical experts

### In the morning:

- Follow your disease track (aplastic anemia, MDS, PNH, or bone marrow transplant) and learn from experts in the field. Topics include the latest research in the treatment and diagnosis phase of your disease.

### In the afternoon:

- Follow your interests and learn how to manage your new normal by attending a session of interest which focuses on living well with a bone marrow failure disease or bone marrow transplant.
- Connect with other patients and families during our peer support forums. Relax and relate with others, and share your journey from both a caregiver and patient perspective

## Free Registration

LEARN MORE AT  
[WWW.AAMDS.ORG/CONFERENCES](http://WWW.AAMDS.ORG/CONFERENCES)

 **Aplastic Anemia & MDS**  
INTERNATIONAL FOUNDATION

## AA&MDSIF - Your best resource for medical and personal perspectives on myelodysplastic syndromes (MDS)

### IN PRINT

#### Fact Sheets

- AA&MDSIF Social Media
- Bone Marrow and Stem Cell Transplantation\*\*
- Clinical Trials\*\*
- Communities of Hope
- Financial Resources
- How to Evaluate Health Information on the Internet
- Iron Overload
- Online Learning Center

#### Patient Guides

- Your Guide to Understanding MDS\*
- Understanding MDS Drug Therapies
- Living Well With Bone Marrow Failure Disease\*\*

\* Available in French, German, Italian, Portuguese, and Spanish  
\*\* Available in Spanish

To order a patient packet, call (301) 279-7202 x116, or order online at [www.AAMDS.org/Info](http://www.AAMDS.org/Info).

### ONLINE

Online Learning Center  
[www.AAMDS.org/Learn](http://www.AAMDS.org/Learn)

Learn at your own pace and in the style that suits you best!

#### Explore

- Live and Archived Webinars
- Video Interviews with Experts
- Prerecorded Webcasts
- Interactive Learning Modules

### IN PERSON

#### Phone Support for Personal Attention

Contact our patient educator at (800) 747-2820, **option 1**, or by email at [info@aamds.org](mailto:info@aamds.org), for answers on a wide range of questions, including information on treatment options, clinical trials, financial resources, and more.

#### Support Connection

Our one-to-one Support Connection is a national network of trained volunteers, including patients, caregivers, and family members who offer information, personal experience, coping strategies, problem solving skills, and informational resources. To connect with a Support Connection volunteer, call (800) 747-2820, **option 1** and speak with our patient educator, who will match you with one of our volunteers. You can also email [info@aamds.org](mailto:info@aamds.org).