

AAMDSIF 2017

# MDS Research Summary

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)  
EUROPEAN HEMATOLOGY ASSOCIATION (EHA)

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



**AA·MDS**  
INTERNATIONAL FOUNDATION



The Aplastic Anemia and MDS International Foundation (AAMDSIF) 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 2017 Annual Meetings of The American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA). 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 material is not intended to be a substitute for the advice of your doctor. You should always seek medical advice from a qualified physician.

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**For more information, call us at (800) 747-2820, or visit us online at [www.aamds.org](http://www.aamds.org).**

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Dear Patient or Caregiver,

The purpose of this abstract summary 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 major hematology and oncology scientific meetings this year.

- American Society of Clinical Oncology (ASCO)
- European Hematology Association (EHA)

These are some of the world's largest meetings of hematologists and hematological oncologists—doctors who care for patients with blood disorders or blood and bone marrow cancers. This is where many major findings in the field of blood and marrow disorders are first announced to 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. Authors of the most interesting and noteworthy abstracts are asked by conference organizers to present their research in more detail, either in the format of a large displayed poster with text and illustrations, or an oral (podium) presentation.

We selected the abstracts in this summary because we feel they are the most relevant and important for MDS patients to know about. By reviewing the information presented in the booklet, we hope you will:

- Learn how ongoing research on MDS may affect the diagnosis, treatment, and prognosis of patients in the near term as well as the more distant future
- Understand how researchers are approaching the most promising areas of MDS therapy
- Learn about the importance of clinical trials in identifying novel therapies for MDS
- Know the most important issues about MDS which you may want or need to understand and to ask your health care providers about as part of your ongoing treatment

Please note that the research results discussed at these meetings often involve experimental drugs that are not yet approved for general use by the U.S. Food and Drug Administration (FDA) 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 AAMDSIF if you have questions about these summaries or any aspect of managing your disease.

**Mikkael Sekeres, MD, MS**

*Cleveland Clinic*

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# PROGNOSIS

## Chronic Hepatitis C and Risk of MDS

*Santiago Thibaud, Justin D. Kaner, Aditi Shastri, Anjali Budhathoki, Ashwin Sridharan, Swati Goel, Ioannis Mantzaris, Murali Janakiram, Noah Saul Kornblum, Ira Braunschweig, Amit Verma*

Chronic hepatitis C virus (HCV) infection has a known link to certain blood cancers, such as non-Hodgkin lymphoma. But very little is known about the relationship of HCV with MDS and AML.

The investigators studied the records of 478 patients with MDS, including some who MDS had progressed to AML. All patients were treated at a large urban hospital between 1997 and 2016. Thirteen of these patients had HCV.

## Key findings:

- Patients with both HCV and MDS survived just 16 months, on average, compared with 52 months for those without HCV.
- Those with HCV and MDS had lower red blood cell and platelet counts.
- Patients with HCV and MDS had a greater risk of MDS progression.
- Having HCV with cirrhosis or a higher HCV viral load (meaning more of the virus in the bloodstream) didn't reduce survival.

## Conclusions:

- Chronic HCV infection is closely associated with lower blood counts and higher-risk MDS at the time of MDS diagnosis.
- HCV might affect the biology of MDS.

## HFE Gene Mutations in Patients with Refractory Anemia with Ring Sideroblasts

*Rama Nanah, Mrinal Patnaik, Naseema Gangat, Darci Zblewski, Rong He, Phuong L. Nguyen, Michelle A. Elliott, William J. Hogan, Mark Robert Litzow, Aref Al-Kali*

Refractory anemia with ring sideroblasts (RARS) is a type of MDS. In patients with this disease, more than 15% of red blood cells in the bone marrow have ring-shaped iron deposits known as ring sideroblasts. These patients have a low red blood cell count that can't be treated with iron or vitamins. Patients with hereditary hemochromatosis have abnormal iron absorption and mutations of the HFE gene. Both RARS and hereditary hemochromatosis are associated with high levels of iron, suggesting that they might involve similar processes.

The researchers studied the records of 68 patients with RARS who visited the Mayo Clinic between 1994 and 2015. Of these patients, 17 were tested for HFE mutations.

### Key findings:

- Of the 17 patients tested, 16 (94%) had high levels of iron in the blood and 11 (65%) had an HFE mutation.
- Patients with RARS were almost twice as likely (65%) to have an HFE mutation than the general population (36%).
- Median survival was about 10 years for patients with HFE mutations and 6 years for those without the mutation.

### Conclusions:

- Future research on the value of testing for HFE mutations in patients with RARS might be useful.

# PROGNOSIS

## Hypomethylating Agent Treatment in Older Patients with Higher-Risk MDS

*Amer M. Zeidan, Xin Hu, Jessica B. Long, Rong Wang, Scott F. Huntington, Nikolai Alexandrovich Podoltsev, Smith Giri, Maximilian Stahl, Steven Gore, Xiaomei Ma, Amy J. Davidoff*

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Hypomethylating agents (HMAs), such as azacitidine (Vidaza®) and decitabine (Dacogen), are the standard treatment for higher-risk MDS. HMAs entered the U.S. market in the mid-2000s. In a clinical trial, azacitidine lengthened survival in patients with higher-risk MDS by a median of 9.5 months. But recent studies of patients in MDS registries didn't show much improvement in overall survival with HMA use.

This study assessed the effects of HMAs on overall survival using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results. The study focused on 2,581 patients aged 66 years or older at diagnosis who had refractory anemia with excess blasts (RAEB, a type of higher-risk MDS) and were diagnosed in 2001 and 2011. Of these patients, 36% were treated with HMAs.

### Key finding:

- HMA use was not associated with longer survival in these older adults with higher-risk MDS.

### Conclusions:

- The findings might have been due to improper use of HMAs (for example, patients might not have received the right doses or numbers of treatments) or use of decitabine (which didn't increase survival in randomized trials).
- Another possible explanation is that the patients in the current study might have had different characteristics from those in the clinical trial.

## Impact of Mutations in *PU.1* and *JDP2* on MDS Diagnosis and Prognosis

Rachael Simpson, Alan Goddard, James Lally, Matthew Simmonds, Ciro Roberto Rinaldi

The *PU.1* gene plays a key role in the formation of blood cells and is associated with various blood cancers. Previous studies have found that *PU.1* expression is downregulated (meaning that the gene loses some of its ability to produce its product) in MDS and AML.

The aim of this study was to clarify the function of *PU.1*. The study assessed the expression of *PU.1* and a related gene, *JDP2*, in bone marrow from 12 patients with MDS, 1 patient with AML, and 10 healthy volunteers. The MDS was low risk in 6 patients, intermediate risk in 3 patients, and high risk in 3 patients.

### Key findings:

- Both *PU.1* and *JDP2* are downregulated in MDS.
- The expression of these genes is higher in patients with lower-risk MDS and lower in patients with higher-risk MDS.
- The expression of *PU.1* correlates with the expression of *JDP2* in patients with MDS, showing that suppression of their expression could contribute to the development of AML.
- This correlation doesn't happen in healthy patients.
- Treatment with azacitidine (Vidaza®) improved *PU.1* and *JDP2* expression.

### Conclusions:

- *PU.1* and *JDP2* expression is associated with prognosis in MDS.
- These genes might be useful markers of diagnosis and prognosis in MDS.

# PROGNOSIS

## Relevance of Gene Mutations in Patients with MDS or Myelodysplastic/Myeloproliferative Neoplasms Whose Chromosomes Are Normal

*Guillermo Montalban-Bravo, Ana Alfonso Pierola, Koichi Takahashi, Marina Konopleva, Elias Jabbour, Gautam Borthakur, Naval Guastad Daver, Courtney Denton Dinardo, Zeev Estrov, Tapan M. Kadia, Naveen Pemmaraju, Farhad Ravandi, Carlos E. Bueso-Ramos, Hagop M. Kantarjian, Keyur Patel, Guillermo Garcia-Manero*

The outcomes of patients with MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) vary. In patients AML and no chromosome abnormalities, certain types of mutations and combinations are useful for prognosis. But whether this is true for MDS isn't known.

The investigators evaluated 225 patients with MDS and 100 with MDS/MPN. All patients had normal chromosomes and were seen between 2012 and 2016. None of the patients had been treated at the time of this assessment, and their median age was 69 years. The investigators analyzed bone marrow specimens to identify mutations in 28 genes or 53 genes at the time of diagnosis. They followed the patients for 12 months after the genetic analysis.

### Key findings:

- 202 (62%) patients had detectable mutations, and the median number of mutations per patient was 1.
- After their genes were analyzed, 111 (34%) patients—70 with MDS and 41 with MDS/MPN—were treated with hypomethylating agents, such as azacitidine (Vidaza) and decitabine (Dacogen).
- Patients who had MDS and mutations in TP53 tended not to survive as long as patients without these mutations.
- None of the mutations affected survival in patients with MDS/MPN.

### Conclusions:

- Many of the patients had lower-risk disease and therefore were likely to survive longer. So a longer follow-up period would be needed to better determine the value of mutations for prognosis in these patients.

## **Interphase Fluorescence in Situ Hybridization Analysis Plus Standard Chromosome Analysis for MDS Diagnosis and Prognosis**

*Benjamin Joseph Lang, Carol Minyon, Neelam Dhiman, Saurabh Gupta, Stella Wenceslao, Milena Vuica-Ross, Robin Dobson*

Interphase fluorescence in situ hybridization (FISH) is a test that can detect abnormal chromosomes in cancer cells. The purpose of this study was to find out whether adding interphase FISH to standard chromosome analysis improves the detection of abnormal chromosomes in patients being evaluated for MDS, AML, or myelodysplastic/myeloproliferative disorders. If so, addition of interphase FISH to standard chromosome analysis could provide useful information for diagnosis and prognosis.

The researchers evaluated all orders related to MDS at Baylor University Medical Center between January and September 2015. They looked for discrepancies between standard chromosome analysis and FISH results. The analysis included 1,066 patient specimens.

### **Key findings:**

- Standard chromosome analysis alone was much better at detecting abnormal chromosomes than FISH alone.
- FISH detected only 7 samples with abnormal chromosomes that had been classified as normal by standard chromosome analysis. This means that standard chromosome analysis would have missed 0.66% of patients with abnormal chromosomes.

### **Conclusions:**

- Adding interphase FISH to standard chromosome analysis has limited value for samples that have undergone standard chromosome analysis.

## Phase I Clinical Trial of Ipilimumab

*Amer M Zeidan, Hanna Knaus, Tara M. Robinson, Joshua F. Zeidner, Amanda L. Blackford, David Rizzieri, Mark G. Frattini, Moshe Yair Levy, Mark A. Schroeder, Anna K. Ferguson, Katherine Sheldon, Amy Elizabeth Dezern, Ivana Gojo, Steven Gore, Howard Streicher, Leo Luznik, Amy Duffield, B. Douglas Smith*

Patients with high-risk MDS who don't respond or stop responding to the hypomethylating agents (HMAs) azacitidine (Vidaza<sup>®</sup>) and decitabine (Dacogen<sup>®</sup>) tend to survive for less than 6 months. One reason for resistance to HMAs in MDS is that the cancer cells suppress the immune system. Ipilimumab (Yervoy<sup>®</sup>) helps the immune system work properly, which could help these patients.

This Phase 1 clinical trial enrolled 29 patients (average age 67 years) who had not responded or had stopped responding to HMAs. Just under half the patients (45%) had intermediate-1-risk MDS; the rest had intermediate-2 or high-risk MDS. Patients were treated with four cycles of 3 mg/kg or 10 mg/kg of ipilimumab every 3 weeks, followed by a maintenance phase involving 4 doses every 3 months for those whose MDS didn't progress. The investigators then followed the patients for 12 months.

## Key findings:

- 9 patients had moderate to severe side effects. Stopping the ipilimumab or using steroids reversed these side effects.
- 15 (52%) underwent all four of the initial doses, and 7 (24%) received at least one maintenance dose.
- 15 patients died because of disease progression or other complications, but none of the deaths was a result of ipilimumab treatment.
- 2 patients (7%) had a complete response in the bone marrow.
- MDS was stable for at least 46 weeks in 6 patients (21%) and for at least 54 weeks in 3 patients (10%).
- 5 patients (17%) underwent stem cell transplantation after finishing their ipilimumab treatment.
- The median overall survival was 294 days for all patients and, for the 7 who received at least one maintenance dose, 400 days.

## Conclusions:

- Patients tolerate ipilimumab.
- This treatment can lead to prolonged stable disease or complete responses in bone marrow for some patients.
- However, ipilimumab's efficacy after HMA failure is limited, and studies should assess ipilimumab in combination with other drugs.

## Updated Results from a Phase II Study of Guadecitabine for Higher-Risk MDS or Chronic Myelomonocytic Leukemia

*Guillermo Montalban-Bravo, Prithviraj Bose, Yesid Alvarado, Naval Guastad Daver, Farhad Ravandi, Gautam Borthakur, Koichi Takahashi, Michael Andreeff, Jorge E. Cortes, Courtney Denton Dinardo, Elias Jabbour, Tapan M. Kadia, Steven Kornblau, Maro Ohanian, Xuelin Huang, Graciela M. Nogueras-Gonzalez, Kristy Bodden, Sherry Pierce, Hagop M. Kantarjian, Guillermo Garcia-Manero*

The current treatment response rates and outcomes of patients with higher-risk MDS and chronic myelomonocytic leukemia (CMML) aren't high enough. Guadecitabine is a new type of hypomethylating agent (HMA) that can reverse abnormal DNA methylation, a chemical process that stops genes in patients with MDS from carrying out their normal activities.

This Phase II clinical trial evaluated guadecitabine in 53 patients (median age 67 years) with newly diagnosed higher-risk MDS (43 patients) or CMML (7 patients). Of these patients, 50 could be evaluated for side effects and 44 for response.

### Key findings:

- After a median of six treatment cycles, the response rate was 71%.
- Ten patients (20%) underwent allogeneic stem cell transplantation.
- Patients survived a median of 14 months.
- 45 (90%) patients had at least one side effect during therapy. The most common mild side effects were fatigue (66% of patients), nausea (38%), and breathing problems (26%).
- 3 (6%) patients died within 8 weeks of starting the treatment.

### Conclusions:

- Patients tolerate guadecitabine well, and it is active in patients with higher-risk MDS or CMML.

# NOVEL TREATMENTS

## Phase II Clinical Trial of OPN-305 in Patients with Lower Risk MDS

*Guillermo Garcia-Manero, Guillermo Montalban-Bravo, Hui Yang, Yue Wei, Yesid Alvarado, Courtney DiNardo, Naval Daver, Marina Konopleva, Katherine Hearn, Robert Miller, Sarah Arbe-Barnes, Peter McGuirk, Tara Kearney, Brian Keogh, Hagop Kantarjian, Mary Reilly*

Toll-like receptor 2 (TLR2) is involved in immune system signaling. It is often overactive in the bone marrow of patients with MDS, especially after treatment with azacitidine (Vidaza®) or decitabine (Dacogen®). OPN-305 is an antibody that inhibits the activity of TLR2.

This Phase II clinical trial evaluated the potential therapeutic value of OPN-305 in 21 patients (median age 72 years) with low-risk or intermediate-1-risk MDS who had not responded or stopped responding to azacitidine or decitabine. All patients needed transfusions of at least 2 units of red blood cells in 8 weeks.

### Key findings:

- 5 patients (29%) had mild side effects related to OPN-305.
- The most common side effects were stomach problems.
- Blood cell counts increased in 8 patients (38%).
- Of these patients, 3 (20%) stopped needing red blood cell transfusions.
- The likelihood of responding didn't depend on the patients' gene mutations or abnormal chromosomes.
- Patients with higher levels of TLR2 seemed to be more likely to respond, but this difference wasn't statistically significant.

### Conclusions:

- Patients with previously treated lower-risk MDS tolerated OPN-305 well.
- The results indicated a possible link between TLR2 levels and chances of response.

## Long-Term Results from the Phase II PACE-MDS Study of Luspatercept for Lower-Risk MDS

*Aristoteles Giagounidis, Ulrich Germing, Katharina Götze, Philipp Kiewe, Thomas Wolff, Karin Mayer, Joerg Chromik, Markus Radsak, Dawn Wilson, Xiaosha Zhang, Abderrahmane Laadem, Matthew L. Sherman, Kenneth M. Attie, Peter G. Linde, Uwe Platzbecker*

Anemia is common in patients with MDS, especially those who need red blood cell transfusions, because their immature red blood cells often don't develop normally. Treating anemia in patients with MDS can be challenging.

Luspatercept (also known as ACE-536) is an experimental drug that might be able to treat anemia in patients with lower-risk MDS. This ongoing Phase II clinical trial is assessing the effects of luspatercept in patients with low-risk or intermediate-1-risk MDS who haven't been treated with azacitidine (Vidaza) or decitabine (Dacogen®) in the past. This analysis includes 115 patients.

### Key findings:

- 37 of 52 patients (71%) who have MDS with ring sideroblasts and levels of erythropoietin (a hormone that helps form red blood cells) lower than 200 units per liter have responded to luspatercept.
- 12 of 19 patients (63%) with ring sideroblasts and erythropoietin levels of 200 to 500 units per liter have responded.
- 23 of 33 patients (70%) with ring sideroblasts and lower levels of erythropoietin as well as 6 of 14 (43%) with higher levels of erythropoietin didn't need red blood cell transfusions while on luspatercept.
- 3 patients had serious side effects: increased counts of blasts (abnormal and immature white blood cells), muscle pain, and general worsening.

### Conclusions:

- Many patients with lower-risk MDS treated over the long term with luspatercept had robust and long-lasting increases in hemoglobin and stopped needing red blood cell transfusions.
- A Phase III clinical trial of luspatercept in patients with lower-risk MDS and ring sideroblasts (MEDALIST) is underway.

### **Phase II Clinical Trial of Guadecitabine for Patients with Untreated MDS or Chronic Myelomonocytic Leukemia**

*Guillermo Montalban-Bravo, Prithviraj Bose, Yesid Alvarado, Naval Daver, Farhad Ravandi, Gautam Borthakur, Koichi Takahashi, Michael Andreeff, Jorge Cortes, Courtney DiNardo, Elias J. Jabbour, Tapan Kadia, Steven Kornblau, Maro Ohanian, Ana Alfonso, Xuelin Huang, Graciela Noguera Gonzalez, Kristy Bodden, Sherry Pierce, Carlos Bueso-Ramos, Hagop Kantarjian, Guillermo Garcia-Manero*

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The current treatment response rates and outcomes of patients with higher-risk MDS and chronic myelomonocytic leukemia (CMML) aren't high enough. Guadecitabine is a new type of hypomethylating agent (HMA) that can reverse abnormal DNA methylation, a chemical process that stops genes in patients with MDS from carrying out their normal activities.

This Phase II clinical trial evaluated guadecitabine in 53 patients (median age 67 years) with newly diagnosed higher-risk MDS (43 patients) or CMML (7 patients). Of these patients, 50 could be evaluated for side effects and 44 for response.

#### **Key findings:**

- After a median of six treatment cycles, the response rate was 71%.
- Ten patients (20%) underwent allogeneic stem cell transplantation.
- Patients survived a median of 14 months.
- 45 (90%) patients had at least one side effect during therapy. The most common mild side effects were fatigue (66% of patients), nausea (38%), and breathing problems (26%).
- 3 (6%) patients died within 8 weeks of starting the treatment.

#### **Conclusions:**

- Patients tolerate guadecitabine well, and it is active in patients with higher-risk MDS or CMML.

# COMBINATIONS OF NEW TREATMENTS WITH AZACITIDINE

## Clinical Trial of Atezolizumab With or Without Azacitidine

*Aaron T. Gerds, Bart L. Scott, Peter Greenberg, Amit Verma, Patrick Phuong, Mark Yan, Monique Dail, Cherie Green, Chunze Li, Kartik Krishnan, William Donnellan*

Hypomethylating agents (HMAs), such as azacitidine (Vidaza®) and decitabine (Dacogen®), are the standard treatment for MDS. But up to 60% of patients don't respond to these drugs, and those who do respond usually stop responding after about a year. The treatment options are very limited for patients who didn't respond or stop responding to HMAs.

Atezolizumab (Tecentriq®) is a medicine that binds to programmed death-ligand 1 (PD-L1), a protein that might play a role in MDS resistance to HMA treatment. Atezolizumab might benefit patients treated previously with HMAs.

The goal of this open-label Phase I clinical trial was to assess the safety and effects of atezolizumab alone in 10 patients or in combination with azacitidine in 6 patients. Patients' median age was 76 years, and all had been treated with azacitidine in the past. Some had also been treated with decitabine or another treatment.

## Key findings:

- Every patient had at least one treatment-related side effect.
- The most common serious side effects were fever and low neutrophil (a type of white blood cell) count in 25% of patients and a lower neutrophil count in 25% of patients.
- One patient died of an unknown cause.
- After an average of 101 days of treatment with atezolizumab alone or 93 days with the combination treatment, 60% of patients in each group had stable disease.
- Patients treated with atezolizumab alone needed fewer red blood cell transfusions than before treatment, but this change wasn't statistically significant.

## Conclusions:

- The safety of atezolizumab in this study was as expected for these patients.
- The fact that patients could continue atezolizumab treatment for at least 3 months, on average, was encouraging for these individuals who have no standard treatment options.

# COMBINATIONS OF NEW TREATMENTS WITH AZACITIDINE

EHA

## Phase II Clinical Trial of Nivolumab or Ipilimumab with Azacitidine for MDS

*Guillermo Garcia-Manero, Naval Daver,  
Guillermo Montalban-Bravo, Elias Jabbour,  
Courtney DiNardo, Steven Kornblau, Prithviraj Bose,  
Yesid Alvarado, Maro Ohanian, Gautham Borthakur,  
Jorge Cortes, Kiran Naqvi, Naveen Pemmaraju,  
Xuelin Huang, Graciela Nogueras-Gonzalez,  
Carlos Bueso-Ramos, Yvonne Gasior, Virginia Bayer,  
Sherry Pierce, Hui Yang, Simona Colla,  
Hagop Kantarjian*

The outcomes of patients with MDS who don't respond or stop responding to the hypomethylating agents (HMAs) azacitidine (Vidaza®) and decitabine (Dacogen®) are poor. Nivolumab (Opdivo®) and ipilimumab (Yervoy®) help the immune system work properly, which could help these patients.

This clinical trial evaluated the activity of nivolumab and ipilimumab alone or in combination with azacitidine in patients with MDS. Patients who had been treated with HMAs in the past were treated with one of three doses of nivolumab. The investigators could add azacitidine after 6 cycles for patients who hadn't responded or whose MDS had progressed. Patients with previously untreated MDS were treated with one of two different doses of nivolumab or with ipilimumab. At the time of this analysis, 54 patients could be evaluated.

### Key findings:

- Three (27%) patients treated with nivolumab and azacitidine, 6 (40%) with nivolumab, and 3 (33%) with ipilimumab had serious side effects.
- 9 patients had to delay their next treatment because of a rash; adrenal insufficiency (adrenal glands don't produce enough steroid hormones); or inflammation in the colon, thyroid, lungs, or kidneys.
- One patient died within 8 weeks because of bleeding inside the skull that wasn't related to the study treatment.
- 5 of 18 (30%) treated with ipilimumab responded, but none of the patients treated with nivolumab had a response.

### Conclusions:

- Nivolumab in combination with azacitidine in untreated patients with higher-risk MDS seems to have tolerable safety and some effectiveness.
- Treatment with nivolumab alone doesn't work in MDS.
- Ipilimumab can produce responses in patients with previously treated MDS.

# COMBINATIONS OF NEW TREATMENTS WITH AZACITIDINE

## Combination of Rigosertib with Azacitidine for AML and MDS

*Shyamala Navada, Guillermo Garcia-Manero,  
Katherine Hearn, Rosalie Odchimar-Reissig,  
Erin Demakos, Pierre Fenaux, Michael Petrone,  
Patrick Zbyszewski, Steven Fruchtman, Lewis Silverman*

Azacitidine (Vidaza®) is typically the first treatment for higher-risk MDS, and it's effective for AML in older patients. Studies in cells have shown that a combination of azacitidine with the experimental treatment rigosertib stops leukemia cells from growing and can even kill these cells.

A Phase I/II clinical trial assessed the effects of a combination of azacitidine with rigosertib. The study included 54 patients with MDS, AML, or chronic myelomonocytic leukemia (CMML). Some of the patients had never been treated with HMAs. The others had not responded or had stopped responding to HMAs.

### Key findings:

- Of 33 patients with MDS whose responses could be evaluated, 76% responded to the treatment.
- Response rates were 85% in patients with MDS who had never been treated with HMAs and 62% in those who hadn't responded to HMAs in the past.
- Of the 8 patients with AML whose responses could be evaluated, 3 (37.5%) responded to the combination treatment. Two other patients had stable disease.
- The most common side effects were diarrhea (70% of patients), nausea (50%), back pain (40%), constipation (40%), fatigue (40%), and swelling in the arms and legs (40%).

### Conclusions:

- Patients tolerated the combination treatment well.
- A Phase III clinical trial of rigosertib and azacitidine is being planned for patients whose MDS has never been treated.

# COMBINATIONS OF NEW TREATMENTS WITH AZACITIDINE

EHA

## Vosaroxin Plus Azacitidine for MDS

*Meagan A. Jacoby, Matthew J. Walter, John F. DiPersio, Camille N. Abboud, Peter Westervelt, Amanda F. Cashen, Keith Stockerl-Goldstein, Theresa Fletcher, Geoffrey L. Uy*

Hypomethylating agents (HMAs), such as azacitidine (Vidaza®) and decitabine (Dacogen®), are the mainstay of treatment for MDS. But HMAs lead to remission in only a small proportion of patients, and they can't cure MDS. Vosaroxin (Qinprezo®) is a derivative of quinolone, an antibiotic. Studies in cells show that the combination of vosaroxin and azacitidine is more effective than either treatment alone.

This Phase I clinical trial first identified the maximum dose that 13 patients could tolerate of vosaroxin when given in combination with azacitidine. The study then assessed the efficacy and safety of the combination treatment in another 22 patients. All patients were adults (median age 66 years) with intermediate-1-risk or more severe MDS and low blood cell counts who needed blood transfusions.

## Key findings:

- The study's first phase found that the maximum tolerated dose of vosaroxin was 34 mg/m<sup>2</sup>/day, and the researchers used this dose in the second phase.
- Serious side effects that might have been or were related to the drug included fever with or without low white blood cell counts, bleeding, and gastrointestinal problems.
- Two deaths might have been related to the treatment.
- Of 32 patients who completed at least one cycle of treatment, 25 (78%) had a response.

## Conclusions:

- The combination of vosaroxin and azacitidine showed promising activity with response rates that similar to or better than those that are typical with azacitidine alone.

## Survival in Patients with Persistent Cytopenia But Not MDS

*Jakob Werner Hansen, Maj Westman, Andreas Due Ørskov, Lene Sjö, Leonie Saft, Mette Skov Holm, Claus Marcher, Mohsen Karimi, Eva Hellstrom-Lindberg, Mette Klarskov Andersen, Kirsten Grønbaek*

Cytopenia, or a low blood cell count, is a hallmark of MDS. But many patients with long-term cytopenia don't meet the criteria for MDS. These patients have idiopathic cytopenia of undetermined significance (ICUS). Little is known about the prognosis of patients with ICUS.

The authors compared the outcomes and gene mutations of patients with ICUS to those of low-risk or very-low-risk MDS. The study had enrolled 157 patients (122 with ICUS, median age 65 years; 35 with MDS, median age 68 years) at the time of this analysis.

### Key findings:

- 53% of patients with ICUS and 73% of those with MDS had at least one gene mutation.
- The most common mutations—in *TET2* in 31% of patients, *SRSF2* in 13%, *DNMT3A* in 8%, and *ASXL1* in 8%—were the same in patients with ICUS and those with MDS.
- Overall survival was similar in patients with ICUS and those with MDS.
- Eight patients with ICUS developed a blood cancer during the follow-up period.

### Conclusions:

- Survival seems to be similar in patients with low-risk MDS and those with ICUS.
- Screening patients for mutations might help detect those at risk of progression.

# PROGNOSIS

## Genetic Counseling About Hereditary Blood Cancers

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Scientists have identified mutations in at least 12 genes associated with inherited blood cancers. Procedures for genetic counseling, testing, and monitoring for these families aren't well established.

The goal of this study was to identify individuals with inherited susceptibility to blood cancer at the University of Texas M. D. Anderson Cancer Center and analyze their genetic mutations.

### Key findings:

- 23 (24%) of 97 patients studied had an inherited susceptibility to a blood cancer.
- Seven (7%) had a *RUNX1* mutation associated with familial platelet disorder with predisposition to MDS.
- 6 (6%) had dyskeratosis congenita, and 3 (3%) had Li-Fraumeni syndrome caused by inherited *TP53* mutations.
- 2 (2%) had Diamond-Blackfan anemia; both developed MDS as adults after their Diamond-Blackfan anemia had gone into remission.

### Conclusions:

- People with hereditary susceptibilities to blood cancers are not as rare as previously thought.
- Genetic counseling and testing can identify several patients with a blood cancer in high-risk families.

## Predictors of Response to Azacitidine: Results of the UK Trials Acceleration Programme Study

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Azacitidine (Vidaza®) is an important treatment for AML and high-risk MDS in patients who aren't eligible for intensive chemotherapy. But the AML or MDS almost always progresses in spite of this treatment.

Vorinostat (Zolinza®) is a histone deacetylase inhibitor. It interferes with DNA's ability to control gene activity by inhibiting the histone deacetylase enzyme. This type of drug can kill tumor cells by stopping them from dividing.

The authors assessed the impact of azacitidine alone or with vorinostat on leukemic stem/progenitor cells (LSCs) in a randomized Phase II clinical trial, the RAVVA study. The study included 259 adults with AML or MDS. The researchers assessed mutations in 42 genes that are common in patients with AML or MDS. They also assessed LSC counts in 44 patients.

### Key findings:

- The survival rate was 43% for azacitidine alone and 41% for the combination treatment.
- On average, patients had 3.4 mutations in the 42 tested genes.
- Patients with mutations in *CDKN2A*, *IDH1*, and *TP53* tended not to survive as long as those without these mutations.
- Patients who had a complete response had lower LSC counts, but they still had some LSCs. LSC counts rose when patients had a relapse.
- The treatments had no significant impact on LSC numbers in patients who didn't have a full response.

### Conclusions:

- The association between the mutations and overall survival found in patients treated with azacitidine can help doctors determine a patient's risk of progression.
- The results of this study are also valuable for understanding how azacitidine works.
- LSC counts could be useful markers of response to azacitidine treatment, particularly in studies of combinations of azacitidine with other drugs.

### Impact of Gene Mutations at Diagnosis on Treatment Response in MDS and Chronic Myelomonocytic Leukemia

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Hypomethylating agents (HMAs), such as such as azacitidine (Vidaza®) and decitabine (Dacogen®), are the standard treatment for MDS. But patients who stop responding often do poorly. Several studies have tried to identify markers of response, but the impact of gene mutations at the time of progression on response isn't clear.

This study evaluated the impact of 28 gene mutations at the time of diagnosis on HMA treatment outcomes. The study included 222 patients with previously untreated MDS or chronic myelomonocytic leukemia (CMML) who were treated with azacitidine, decitabine, guadecitabine (a new HMA), or a combination at the University of Texas MD Anderson Cancer Center.

#### Key findings:

- 135 patients (61%) responded to the HMA treatment, and 161 (73%) had at least one mutation.
- Patients with mutations in *ASXL1*, *RUNX1*, or both *TP53* and high variant allele frequency were less likely to respond to treatment.
- Similarly, patients with mutations in chromatin or signaling genes were less likely to respond.
- Patients were less likely to have a complete response if they had any of the following:
  - *ASXL1* mutations, particularly if they didn't have a *TET2* mutation
  - More than 3 mutations
  - Signaling gene mutations
- Patients with *DNMT3A* mutations and high variant allele frequency took longer to respond.
- Patients who responded to treatment and had at least 3 mutations or *TP53* mutations with a high variant allele frequency tended to stop responding sooner than patients without these mutations.

#### Conclusions:

- The types and numbers of mutations at diagnosis might predict response to HMA treatment in patients with MDS or CMML.

# How AAMDSIF Can Help You ...

Many **FREE** services and programs are available to anyone impacted by, or just interested in, bone marrow failure diseases:

- **Personalized Support** from Information Specialists at (800) 747-2820 or [help@aamds.org](mailto:help@aamds.org)
- **Educational Materials** on diseases and treatments at [www.aamds.org/materials](http://www.aamds.org/materials)
- **Global Educational Materials** in Spanish, French, German, Italian, and Portuguese at [www.aamds.org/global-education](http://www.aamds.org/global-education)
- **The Online Academy** with 90+ live and recorded educational classes and much more at [www.aamds.org/learn](http://www.aamds.org/learn)
- **Patient and Family Conferences** connecting patients with professionals and building community with each other at [www.aamds.org/conferences](http://www.aamds.org/conferences)
- **Print and Electronic Newsletters** with the latest news in treatment and research
- **Clinical Trials Information** at [www.aamds.org/clinicaltrials](http://www.aamds.org/clinicaltrials)
- **Peer Support Network** staffed by specially-trained volunteers who listen and offer guidance at [www.aamds.org/support-networks](http://www.aamds.org/support-networks)
- **Community Connections** support groups run by volunteers for fellowship and support

AAMDSIF relies on its growing team of local Ambassadors – volunteers who contribute their time and talent in many ways, such as becoming:

- **Online Supporters** who hold digital fundraisers in their community or workplace
- **Event Organizers** who plan “March for Marrow” fundraising walks or other events
- **Awareness Campaigners** who teach their community about bone marrow failure
- **Community Connections** leaders who coordinate local patient support groups

Learn more about  
volunteering at  
[ambassadors@aamds.org](mailto:ambassadors@aamds.org)  
or (301) 279-7202 x122.



[www.aamds.org](http://www.aamds.org)



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