

MDS and AML Research Summaries for Patients

FROM THE
2020 EUROPEAN HEMATOLOGY ASSOCIATION
AND THE AMERICAN SOCIETY OF
CLINICAL ONCOLOGY MEETINGS



This publication offers summaries of selected abstracts presented at the 2020 Meetings of the European Hematology Association and the American Society of Clinical Oncology. It provides new and updated information about new research into the diagnosis, treatment and prognosis of Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) secondary to MDS. Abstracts were selected by Guillermo Garcia-Manero, MD with The University of Texas MD Anderson Cancer Center where he serves as Co-Leader of the MDS & AML Moon Shot initiative. Please see Dr. Garcia-Manero's recent webinar on this subject which can be found on the AAMDSIF website at <https://www.aamds.org/education/webinars> and is available for on-demand viewing.

Although the information in this booklet has undergone a thorough, independent medical review to ensure 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.

Additional resources for patients, families and caregivers living with MDS and/or AML secondary to MDS are invited to visit our website for the following free resources:

- MDS Toolkit: www.aamds.org/support/mds-toolkit
- MDS and AML Patient Guides: www.aamds.org/education/patient-guides-and-fact-sheets
- MDS and AML Webinars: <https://www.aamds.org/education/webinars>

For more information, call (800) 747-2820 x2, send an email to help@aamds.org, or visit us online at www.aamds.org.

Aplastic Anemia & MDS International Foundation
4330 East West Highway, Suite 230
Bethesda, MD 20814
Patient HelpLine: (301) 279-7202 x2 or (800) 747-2820 x2
Email: help@aamds.org
Website: www.aamds.org

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Venetoclax in Combination with Azacitidine for MDS Unresponsive to Previous Treatment or Relapsed

Amer M. Zeidan, Daniel A. Pollyea, Jacqueline S. Garcia, Andrew M. Brunner, Fernando Roncolato, Uma Borate, Olatoyosi Odenike, Ashish Bajel, Anne Marie Watson, Katharina Götze, Florian Nolte, Peter Tan, Haifa K. Al-Ali, Wan-Jen Hong, Ying Zhou, Lori Gressick, William Ainsworth, Jason Harb, Relja Popovic, Ahmed H. Salem, John Hayslip, Ronan Swords, Guillermo Garcia-Manero

Summary:

This Phase 1b clinical trial (NCT02966782) is evaluating the safety and efficacy of venetoclax alone or in combination with azacitidine (Vidaza) in adults who had not previously responded to standard treatment for High Risk MDS or who have relapsed MDS. Patients are treated with increasing doses of venetoclax every day for 14 days in 28 day cycles as well as azacitidine for the first 7 days of each cycle. As of the end of August 2019, 38 patients (84% male, average age 74) had been treated with both venetoclax and azacitidine for an average of 8 cycles.

Key findings:

- Common but serious side effects reported by at least 15% of patients include: low white blood cell counts (50%), low platelet counts (42%), low white blood cell counts with fever (29%), anemia (16%) and pneumonia (16%).
- 14 (37%) stopped treatment.
- Two patients died within the first month after their first venetoclax dose, and one patient died within the second month.
- Of the 37 patients whose responses could be evaluated, 15 (40%) had a complete remission or a complete remission in the bone marrow, and 9/13 (69%) who completed four cycles of treatment achieved a complete remission.
- Overall, patients survived for 9 months before their disease progressed and 65% survived for at least one year.
- 25% had increased blood cell counts and 35% stopped needing red blood cell or platelet transfusions for an average of four months.

Conclusions:

- Patients tolerated the combination of venetoclax and azacitidine well and the side effects were manageable.
- The efficacy results are encouraging.

CC-486 for Lower-Risk MDS

Guillermo Garcia-Manero, Valeria Santini, Antonio Almeida, Uwe Platzbecker, Anna Jonasova, Lewis Silverman, Jose Falantes, Gianluigi Reda, Francesco Buccisano, Pierre Fenaux, Rena Buckstein, María Díez Campelo, Stephen Larsen, David Valcarcel, Paresh Vyas, Valentina Giai, Esther Natalie Oliva, Jake Shortt, Dietger Niederwieser, Moshe Mittelman, Luana Fianchi, Jim Zhong, Eric Laille, Ignazia La Torre, Barry Skikne, CL Beach, Aristoteles Giagounidis

Summary:

CC-486 is a version of azacitidine (Vidaza) that patients take by mouth. QUAZAR AML-001 (NCT01757535) is a Phase III clinical trial of CC-486 in patients aged 55 or older with acute myelogenous leukemia (AML) who had not responded completely to previous treatment and were not eligible for stem cell transplantation. This analysis focused on the side effects of CC-486 in 469 patients (average 68 years).

Key Findings:

- The rates of side effects with both CC-486 and placebo were similar in patients aged 55 to 64, 65 to 74, and 75 or older.
- The most common side effects were nausea, vomiting, diarrhea, and constipation.
- These side effects were more common in patients treated with CC-486 than those treated with placebo.
- Constipation was about 20% more common and low platelet counts were at least 20% less common in patients aged 75 years and older than in younger patients.
- Overall, 13% of patients in the CC-486 group and 4% in the placebo group stopped their treatment because of side effects.

Conclusions:

- Patients in all age groups, including those older than 74, in the QUAZAR study tolerated CC-486 well.

Disparities in Diagnostic Evaluations to Confirm MDS

Sudipto Mukherjee, Weichuan Dong, Abby Statler, Siran M. Koroukian

Summary:

A complete diagnostic evaluation to confirm MDS includes a bone marrow biopsy and testing for changes in genes and chromosomes. The purpose of this study was to identify factors that determined whether patients with MDS had a complete diagnostic evaluation.

The investigators analyzed data on 45,067 Medicare beneficiaries who had inpatient or outpatient visits for MDS within a 12-month period in 2012 and 2013.

Key Findings:

- Only 69% of patients received a complete diagnostic evaluation that included a bone marrow biopsy, chromosome testing, or both.
- There were some groups of patients who were less likely to receive a complete diagnostic evaluation including:
 - Patients over the age of 85 years (56% complete diagnostic evaluation)
 - Women of all ages (64% complete diagnostic evaluation)
 - Black patients (64% complete diagnostic evaluation)
 - Patients not requiring red blood cell transfusions (64% complete diagnostic evaluation)
- There were also some groups who were more likely to receive a complete diagnostic evaluation including:
 - MDS patients with excess blasts (89% complete diagnostic evaluation)
 - Patients with a shortage of all blood cell types (92% complete diagnostic evaluation)
 - Patients who required many red blood cell transfusions (80% complete diagnostic evaluation)

Conclusions:

- About 30% of patients with MDS in the Medicare database do not undergo a complete diagnostic evaluation, especially a bone marrow biopsy.

Impact of Treatment for Anemia on Quality of Life in People with Lower Risk MDS

Hege Garelius, Alex Smith, Simon Appleton, David Bowen, Pierre Fenaux, Argiris Symeonidis, Moshe Mittelman, Reinhard Stauder, Jaroslav Čermák, Guillermo Sanz, Saskia Langemeijer, Mette Skov Holm, Raphael Itzykson, Dominic Culligan, Sonja Heibl, Juliet Mills, Teresa Bernal, Ioannis Kotsianidis, Lionel Ades, Karin Koinig, Corine van Marrewijk, Simon Crouch, Theo de Witte, Eva Hellström-Lindberg

Summary:

The purpose of this study was to identify long-term changes in health-related quality of life (HRQOL) in 2,273 people with lower-risk MDS. Patients were treated for anemia with erythropoietin-stimulating agents (ESAs), red blood cell transfusions, both of these treatments, or neither of them.

Key Findings:

- Patients not treated with ESAs or red blood cell transfusions at any time had the highest HRQOL.
- Patients treated with ESAs but not blood transfusions had higher HRQOL at first, but their HRQOL dropped slightly later on.
- HRQOL declined gradually over time in patients who received red blood cell transfusions, ESAs, or both continuously throughout the study period.
- In patients who received ESAs but not red blood cell transfusions during their first three visits, HRQOL increased as hemoglobin levels rose.
- Those who received transfusions with or without ESAs did not have better HRQOL as their hemoglobin levels increased.

Conclusions:

- HRQOL was highest in patients with lower-risk MDS who did not need ESAs or red blood cell transfusions.
- HRQOL decreased over time in all patients, especially those receiving regular red blood cell transfusions.
- Based on their findings, the authors suggest that patient start ESA treatment before getting regular red blood cell transfusions.

Imetelstat for Anemia in Lower Risk Non-Del(5q) MDS

Uwe Platzbecker, Pierre Fenaux, David P. Steensma, Koen Van Eygen, Azra Raza, Ulrich Germing, Patricia Font, Maria Diez-Campelo, Sylvain Thepot, Edo Vellenga, Mrinal M. Patnaik, Jun Ho Jang, Helen Varsos, Esther Rose, Jacqueline Bussolari, Fei Huang, Laurie Sherman, Faye Feller, Souria Dougherty, Libo Sun, Ying Wan, Aleksandra Rizo, Valeria Santini

Summary:

Treatment options are limited for patients with lower-risk MDS who need regular red blood cell transfusions and do not respond to treatment with erythropoietin-stimulating agents (ESAs) as well as those who have a relapse after ESA treatment.

The Phase II/III IMerge clinical trial (NCT02598661) is evaluating imetelstat for these patients. The Phase II results show that imetelstat prevents the need for red blood cell transfusions over the long term.

The authors report here on the long-term efficacy and safety of imetelstat in 38 patients with lower-risk non-del(5q) MDS. All of the patients needed transfusions of at least 8 units of blood every 16 weeks or at least 4 units every 8 weeks. They had either not responded to ESAs or had had a relapse after starting ESA treatment. None had been treated with lenalidomide (Revlimid), azacitidine (Vidaza), or decitabine (Dacogen) before.

Patients were treated with imetelstat every 4 weeks. They were then monitored for an average of 24 months.

Key Findings:

- Of the 38 patients, 16 (42%) stopped needing blood transfusions for at least 8 weeks.
- Hemoglobin levels in these 16 patients were at least 3.0 g/dL higher than before they started imetelstat treatment.
- Twelve patients (32%) stopped needing transfusions for at least 24 weeks, and 11 (29%) were transfusion free for at least a year.
- In addition, 26 patients (68%) had increases in healthy red blood cells.
- The most common side effects were low blood cell counts, but these effects were manageable.

Conclusions:

- Enrollment is ongoing in the Phase III portion of IMerge.

Genetic Testing Patterns in Patients with MDS and Acute Myelogenous Leukemia

Tracy George, Jay L. Patel, Mehrdad Abedi, Christopher R. Cogle, Harry Paul Erba, Guillermo Garcia-Manero, David L. Grinblatt, Pavel Kiselev, Rami S. Komrokji, Chrystal Ursula Louis, Jaroslaw P. Maciejewski, Melissa Nifenecker, Daniel Aaron Pollyea, Gail J. Roboz, Michael R. Savona, Bart L. Scott, Mikkael A. Sekeres, David P. Steensma, Michael A. Thompson, Kathryn Foucar

Summary:

The World Health Organization (WHO) updated its classification criteria for the diagnosis of MDS and acute myelogenous leukemia (AML) in 2016.

To understand whether the genetic testing recommendations based on the WHO criteria changed clinical practice, this study evaluated patterns of genetic testing for patients with MDS or AML in the periods before and after the WHO released its criteria.

The investigators used the Connect MDS/AML Registry (NCT01688011), which collects data on patients aged 18 years or older with MDS and patients aged 55 years or older with AML. This analysis used data from December 12, 2013, to December 13, 2019 on 800 patients with MDS (median age 74 years, 66% male) and 626 with AML (median age 71 years, 62% male).

Key Findings:

- The proportion of patients with MDS who had genetic testing was higher in those who enrolled in 2017 or later (40%) than in those who enrolled before 2017 (17%).
- For patients with AML, the testing rates were 85% for patients enrolled in the database in or after 2017 and 69% for those who enrolled before 2017.
- The average number of genetic mutations included in tests creased from 7 before 2017 to 13 in 2017 or after for MDS and from 6 to 10 for AML.
- The most common mutations included in tests were ASXL1 for MDS and FLT3-ITD for AML.

Conclusions:

- Genetic testing rates for patients with MDS and AML have increased since the publication of the WHO's 2016 criteria.
- Genetic testing rates for patients with MDS are lower than those for patients with AML in clinical practice.

Impact of DDX41 Mutations on MDS and Acute Myelogenous Leukemia (AML)

Hideki Makishima, Yasuhito Nannya, June Takeda, Yukihide Momozawa, Tetsuichi Yoshizato, Yoshiko Atsuta, Yusuke Shiozawa, Yuka Iijima-Yamashita, Ryunosuke Saiki, Kenichi Yoshida, Yuichi Shiraishi, Yasunobu Nagata, Nobuyuki Kakiuchi, Makoto Onizuka, Kenichi Chiba, Hiroko Tanaka, Ayana Kon, Yotaro Ochi, Hiroo Ueno, Masahiro Nakagawa, Hidehiro Itonaga, Yoshinobu Kanda, Yasushi Miyazaki, Keizo Horibe, Masashi Sanada, Hisashi Tsurumi, Senji Kasahara, Akifumi Kondo-Takaori, Kazuma Ohyashiki, Toru Kiguchi, Fumihiko Matsuda, Jaroslaw Maciejewski, Eva Hellström Lindberg, Chantana Polprasert, Mario Cazzola, Torsten Haferlach, Yoichiro Kamatani, Michiaki Kubo, Satoru Miyano, Seishi Ogawa

Summary:

Inherited mutations in the DDX41 gene can cause MDS and acute myelogenous leukemia (AML) in older adults. This study evaluated the featured of MDS and AML caused by DDX41 gene mutations.

The investigators analyzed the genes of 5,856 adults with different forms of MDS and AML. They then compared the frequency of mutations in DDX41 and other genes commonly associated with MDS and AML in these patients and in 13,962 healthy people.

Key Findings:

- A total of 208 (3.6%) patients had DDX41 mutations.
- Half of these patients had both inherited and acquired DDX41 mutations.
- The most common types of DDX41 varied by country (i.e. Japan, Germany, United States). The most common variant in Japan was A500fs and D140fs in the United States.
- People with a DDX41 mutation were older and three times more likely to be male.
- DDX41 mutations were more common in people with MDS (4.7%) and AML (2.9%) than in people with other bone marrow failure diseases.
- Length of survival was similar in patients with and without a DDX41 mutation.

Conclusions:

- Most DDX41 mutations were inherited.
- Types of DDX41 mutations varied by ethnicity.

Glasdegib for Untreated Acute Myelogenous Leukemia or High Risk MDS

Michael Heuser, Tadeusz Robak, Pau Montesinos, Brian Leber, Walter M. Fiedler, Daniel Aaron Pollyea, Andrew Brown, Ashleigh O'Connell, Wendy Ma, Geoffrey Chan, Jorge E. Cortes

Summary:

Glasdegib (Daurismo) is a chemotherapy drug with U.S. Food and Drug Administration (FDA) approval for use in combination with cytarabine to treat newly diagnosed acute myelogenous leukemia (AML).

BRIGHT AML 1003 (NCT-01546038) is a Phase II trial that evaluated the efficacy of glasdegib in combination with cytarabine to treat AML or High Risk MDS. The investigators monitored 132 patients for 4 years. Participating patients were newly diagnosed with AML or High Risk MDS and they were not eligible for intensive chemotherapy because of other health conditions or they were unresponsive to the intensive chemotherapy. Two thirds of participants were treated with glasdegib and low-dose cytarabine and one third were treated with low-dose cytarabine alone. At the time of the analysis, participants had been treated with the combination therapy for an average of 83 days or with cytarabine alone for 47 days.

Key findings:

- Survival rates after one year were 40% for the combination therapy group and 10% for cytarabine group. Survival rates after two years were 18% for the combination therapy group and 2% for the cytarabine group.
- 18% of the combination therapy group achieved a complete remission. 2% of the cytarabine group did.
- 38% of the combination therapy group stopped treatment due to the side effects vs. 46% with cytarabine group.
- The most common side effect for the combination group was a change in sense of taste (25%), muscle spasms (23%) and hair loss (11%).

Conclusions:

- The combination of glasdegib and low dose cytarabine is acceptably safe.
- Overall survival rates are higher with combination therapy than with cytarabine alone.

Glasdegib + Azacitidine for Untreated Acute Myelogenous Leukemia (AML), High Risk MDS or Chronic Myelomonocytic Leukemia (CMML)

Amer Methqal Zeidan, Michael Schuster, Magalie Joris, Jurgen Krauter, Johan Maertens, Emmanuel Gyan, Tibor Kovacsovics, Amit Verma, Paresh Vyas, Eunice S. Wang, Wendy Ma, Mirjana Zeremski, Art Kudla, Geoffrey Chan, Mikkael A. Sekeres.

Summary:

Glasdegib (Daurismo) is a chemotherapy drug with U.S. Food and Drug Administration (FDA) approval for use in combination with cytarabine to treat newly diagnosed acute myelogenous leukemia (AML).

BRIGHT 1012 trial (NCT02367456) is evaluating the safety and efficacy of the combination of glasdegib with azacitidine (Vidaza) in patients with untreated High Risk MDS, AML, or CMML. Participants were not eligible for intensive chemotherapy or they were over the age of 74. This analysis focused on the effect of the combination of drugs on the recovery of healthy blood cell production in the bone marrow and the need for red blood cell transfusions. The study looked at 30 MDS patients treated over approximately 5 months.

Key findings:

- Patients began recovery of white blood cells, red blood cells, and platelets during the first cycle of treatment with the combination.
- Patients who recovered platelet counts early were more like to achieve a complete or partial remission. 54% of patients who had at least 100,000 platelets per microliter during cycle 2 achieved partial or complete remission.
- Two patients (out of 26) had to delay a second cycle due to side effects.
- 54% of transfusion-dependent patients (13/26) were able to discontinue transfusions.

Conclusions:

- Patients with MDS, AML, or CMML who are not eligible for intensive chemotherapy show promising rates of early bone marrow recovery using the combination of glasdegib and azacitidine.
- More research is needed on the link between early recover of blood cell counts in the bone marrow and the efficacy of the combination of glasdegib and azacitidine in MDS patients.

Treatment-Related MDS and Acute Myeloid Leukemia after Modern Cancer Therapies

Abhay Singh, MD, MPH, Chebli Mrad, MD, Mark G. Faber, DO, Theresa Hahn, PhD, Megan Herr, PhD, Swapna Thota, MD

Summary:

Certain types of cancer treatment can cause MDS or AML, including targeted cancer treatments which attack cancer cells and spare health cells and immunotherapies which help the patient's immune system fight the cancer cells.

This study reviewed data on 565,149 patients who survived for at least one year after a diagnosis of melanoma, kidney cancer, non-small-cell lung cancer, or multiple myeloma between 2000 and 2015. The investigators calculated the risk of secondary MDS or AML in three periods of 2000—2005, 2006—2010 and 2011—2015 (referred to as P1, P2 and P3).

Key findings:

- The risk of secondary MDS or AML was much higher in patients with kidney cancer in P1, possibly because they had been treated with chemotherapy.
- The risk dropped between P1 and P2 for patients with multiple myeloma but it was not considered statistically significant.
- The risk of secondary MDS or AML in patients with non-small-cell lung cancer rose between P1 and P2 but dropped between P2 and P3.

Conclusions:

- Possible explanations for this surprising finding that the risk of secondary MDS or AML increased in patients with multiple myeloma might be that patients with this type of cancer are not living longer, so they have more time to develop secondary MDS or AML.
- In addition to being more effective, easier to tolerate or both, modern cancer therapies have a lower risk of secondary MDS or AML.

CPX-351 vs 7+3 for Newly Diagnosed High Risk MDS or Treatment Related AML

Jeffrey E. Lancet, MD, Geoffrey L. Uy, MD, Laura Newell, MD, Tara Lin, MD, Ellen K. Ritchie, MD, Robert K. Stuart, MD, Stephen A. Strickland, MD, MSCI, MS, Donna E. Hogge, MD, Scott Solomon, MD, Dale Bixby, MD, Jonathan E. Kolitz, MD, Gary J. Schiller, MD, Matthew J. Wieduwilt, MD, Daniel H. Ryan, MD, Stefan Faderl, MD, Yu-Lin Chang, Jorge Cortes, MD

Summary:

Daunorubicin and cytarabine liposome (Vyxeos), a combination known as CPX-351, has approval from the FDA for the treatment of newly diagnosed, treatment-related AML or AML with myelodysplasia-related changes. In a Phase 3 trial (NCT011696084), CPX-351 led to longer overall survival in patients ages 60—75 years than conventional treatment (known as 7+3) consisting of continuous cytarabine for 7 days and short infusions of an anthracycline drug (such as daunorubicin) on each of the first 3 days. These results are based on a 5 year follow up from the trial. A total of 209 patients were randomly assigned to CPX-351 and were followed for up to 5 years after they entered the study.

Key findings:

- The survival rate at 5 years was 18% with CPX-351 and 8% with 7+3.
- The most common cause of death in both treatment groups was leukemia progression.
- Patients in the CPX-351 group survived an average of 9.3 months; patients in the 7+3 group survived an average of 6 months.
- In patients who had stem cell transplantation, the survival rate at 5 years was 52% for CPX-351 and 23% for 7+3.

Conclusions:

- CPX-351 appears to lead or contribute to long-term remission and survival in older patients with newly diagnosed High Risk MDS or secondary AML.

Venetoclax with Decitabine or Azacitidine

Abhishek Matti, Courtney Denton Dinardo, Naveen Pemmaraju, Tapan M. Kadia, Caitlin R. Rausch, Kiran Naqvi, Naval G. Daver, Gautam Borthakur, Maro Ohanian, Ghayas C. Issa, Yesid Alvarado, Nicholas James Short, Michael Andreeff, Elias Jabbour, Sherry A. Pierce, Farhad Ravandi, Guillermo Garcia-Manero, John Sutton Welch, Hagop M. Kantarjian, Marina Konopleva

Summary:

Venetoclax (VENCLEXTA) is a medicine combining azacitidine (Vidaza) and decitabine (Dacogen) to treat newly diagnosed AML. This treatment is for patients who are not eligible for standard chemotherapy because they are older than 74 or they have other medical conditions. The purpose of this clinical trial (NCT03404193) is to determine if adding Venetoclax to decitabine could improve outcomes in AML and High Risk MDS. The study enrolled 184 patients with newly diagnosed AML, treated or untreated secondary AML, relapsed AML, AML unresponsive to previous treatments and High Risk MDS. 58% of the participating patients were 70 years or older.

Key findings:

- 92% of patients were alive after 60 days of treatment.
- Patients experienced infections, infections with fever and low white blood cell counts as the most common side effects of treatment.
- 25 patients (14%) had a stem cell transplant and all were still alive 100 days after transplantation.
- 25% of patients remained on treatment after 15 months.

Conclusions:

- The combination of Venetoclax and decitabine is safe and very effective in newly diagnosed AML.
- This treatment can help control abnormal cells enough to prepare previously treated patients for stem cell transplantation.

Pevonedistat and Azacitidine to Treat AML

Lionel Ades, Justin M. Watts, Atanas Radinoff, Montserrat Arnan, Marco Cerrano, Patricia Font Lopez, Joshua F. Zeidner, Maria Diez-Campelo, Carlos Graux, Jane Liesveld, Dominik Selleslag, Nikolay Tzvetkov, Robert J. Fram, Dan Zhao, Douglas V. Faller, Mikkael A. Sekeres

Summary:

Pevonedistat is an experimental treatment that is being studied in combination with azacitidine (Vidaza) to treat acute myelogenous leukemia (AML). A clinical trial (NCT02610777) of this combination included 120 patients with higher-risk MDS, chronic myelomonocytic leukemia (CMML), and low-blast AML. None of these patients had been treated with azacitidine or decitabine (Dacogen) before.

Patients were randomly assigned to the combination of pevonedistat with azacitidine or to azacitidine alone. They continued 28-day cycles of their treatment until they developed unacceptable side effects, had a relapse, or their disease progressed. The study was designed to assess overall survival.

Key Findings:

- Patients received an average of 13 cycles of the pevonedistat and azacitidine combination or 9 cycles of azacitidine alone.
- On average, those in the combination group survived for 22 months, whereas those in the azacitidine group survived 19 months.
- Among the 67 patients with MDS, those treated with the combination survived for an average of 24 months, and those treated with azacitidine alone survived for 19 months.
- Of patients whose responses could be evaluated, 71% responded to the combination treatment and 60% to azacitidine alone.
- In patients with higher-risk MDS, 52% of those treated with the combination achieved complete remission, as did 27% with azacitidine alone.
- Rates of serious side effects, at around 90%, were similar in both groups and the most common serious side effects were low white blood cell counts with or without fever, anemia, and low platelet count.

Conclusions:

- The safety of pevonedistat and azacitidine was similar to that of azacitidine alone.
- The effects of the combination of pevonedistat and azacitidine were not significantly different from those of azacitidine alone on overall survival or response rates.

Combination of MBG453 with Decitabine or Azacitidine Before Stem Cell Transplantation in Patients with Higher-Risk MDS or Acute Myelogenous Leukemia

Andrew Brunner, Rupa Narayan, Jordi Esteve, Kimmo Porkka, Steve Knapper, Norbert Vey, Sebastian Scholl, Guillermo Garcia-Manero, Martin Wermke, Jaroen Janssen, Chong Chyn Chua, Natalia Tovar, Mika Kontro, Oliver Ottmann, Andrew Wei, Elie Traer, Uma Borate

Summary:

For most patients with MDS or acute myelogenous leukemia (AML), the only cure is stem cell transplantation. But some patients have a relapse after this procedure, often because of the failure to eliminate all of the leukemia stem cells as well as rejection of the donated cells.

MBG453 is an experimental immunotherapy, which means that it uses the body's own immune system to fight cancer cells. This study's purpose was to use patient records to understand the outcomes of MBG452 in combination with decitabine (Dacogen) or Azacitidine (Vidaza) before stem cell transplantation.

The study included 15 patients (average age 66 years, 7 female) who had higher-risk MDS or AML. None of the patients had been treated with decitabine or azacitidine before.

Key Findings:

- On average, the interval between the last MBG453 dose and transplantation was 29 days.
- Six patients developed graft-versus-host disease within the first 3 months after transplantation, but cases were not serious.
- Three patients developed graft-versus-host disease after the first 3 months.
- One patient had a relapse on day 134 after transplant and died.

Conclusions:

- After treatment with MBG453 and decitabine or azacitidine for MDS or AML, patients can successfully undergo stem cell transplantation.
- Side effects associated with graft-versus-host disease with this treatment are limited.

Combination Pracinostat and Azacitidine for High Risk or Very High Risk MDS

Ehab L. Attalah, Samer K. Khaled, Brenda W. Cooper, Erica D. Warlick, David A. Ramies, Joanne Li, Riccardo Spezia, Silvia Mappa, Michael Kenneth Keng

Summary:

Pracinostat is an experimental treatment that can change genes whose abnormal activity plays an important role in MDS. A study of pracinostat plus azacitidine (Vidaza) in patients with untreated higher risk MDS had to end early because of serious side effects. This follow-up Phase 2 clinical trial (NCT03151304) is evaluating a lower dose of pracinostat in combination with azacitidine to reduce side effects and rates of leaving the study early and to improve outcomes. At the time of this analysis, the study had enrolled 64 patients (67% male, average age 68 years) whose higher risk MDS had not been treated with azacitidine or decitabine (Dacogen). Patients are treated with 45mg pracinostat 3 days a week for 3 weeks as well as a standard dose of azacitidine for 7 days of each 28 day cycle.

Key findings:

- After an average of 18 months, 31% of patients were still on the treatment.
- A total of 69% of patients stopped the combination, citing as reasons such as going to stem cell transplant (25%), disease progression (17%) or side effects (11%).
- The most common side effects not involving blood counts were constipations (55%) nausea (52%), fatigue (45%), decreased appetite (39%), swelling (36%), diarrhea (31%) and shortness of breath (31%).
- One third of patients achieved complete remission.
- At one year, 77% of patients were still alive.

Conclusions:

- Patients with higher risk MDS tolerated a lower dose of pracinostat in combination with azacitidine and the treatment's efficacy is promising.

Impact of Luspatercept on Red Blood Cell Transfusions (a summary of two studies presented at ASCO and EHA)

Study 1: Rami S. Komrokji, Mikkael A. Sekeres, Amer Methqal Zeidan, Pierre Fenaux, Alan F. List, Amy Elizabeth DeZern, Peter L. Greenberg, Michael R. Savona, Joseph G. Jurcic, Amit Verma, Ghulam J. Mufti, Rena Buckstein, Valeria Santini, Abderrahmane Laadem, Rodrigo Ito, Jennie Zhang, Chrystal Ursula Louis, Peter G. Linde, Guillermo Garcia-Manero

Study 2: Amer Mathqal Zeidan, Guillermo Garcia-Manero, Amy Elizabeth DeZern, Pierre Fenaux, Peter L. Greenberg, Michael Savona, Joseph G. Juric, Amit Verma, Ghulam J. Mufti, Rena Buckstein, Valeria Santini, Abderrahmane Laadem, Jennie Zhang, Anita Ramptersad, Daniel Sinsimer, Chrystal Ursula Louis, Peter G. Lind, Alan F. List, Mikkael A. Sekeres.

Summary:

Luspatercept (Reblozyl) is a drug that helps immature red blood cells in the bone marrow form healthy, mature red blood cells. MEDALIST was a Phase 3 clinical trial (NCT02631070) that evaluated the safety and efficacy of luspatercept in 229 adults (median age 71, 63% male) with low risk or intermediate risk MDS with ring sideroblasts who also had anemia. Two thirds of the patients were randomly assigned to luspatercept, the rest received a placebo. All patients received treatment every three weeks over the course of at least 24 weeks. Two abstracts were presented at ASCO 2020 and two at EHA 2020.

Key findings:

- The number of units of red blood cells needed for transfusion dropped by 50% in the luspatercept group and 15% of the placebo group.
- Six patients (9.1%) treated with luspatercept and one patient (3%) treated with placebo stopped needing transfusions during the 24 week study period.
- Healthy red blood cells in the bone marrow increased in 30% of the luspatercept group and 8% in the placebo group.
- 99% of the luspatercept group and 88% of the placebo group reported at least one side effect during the study period.
- 13% of the luspatercept group and 19.5% of the placebo group reported side effects related to transfusion.
- 24% of the luspatercept group and 46% of the placebo group stopped treatment due to the side effects.

Conclusions:

- Luspatercept was effective in patients with low risk MDS with ring sideroblasts.
- Luspatercept reduced the number of red blood cell units transfused and the number of transfusion side effects.

Pevonedistat and Azacitidine

Lionel Ades, Justin M. Watts, Atanas Radinoff, Montserrat Arnan, Marco Cerrano, Patricia Font Lopez, Joshua F. Zeidner, Maria Diez-Campelo, Carlos Graux, Jane Liesveld, Dominik Selleslag, Nikolay Tzyetkov, Robert J. Fram, Dan Zhao, Douglas V. Faller, Mikkael A. Sekeres

Summary:

Pevonedistat is an experimental treatment that is being studied in combination with azacitidine (Vidaza) to treat AML. A clinical trial (NCT02610777) of this combination included 120 patients with higher risk MDS, chronic myelomonocytic leukemia (CMML) and low blast AML. No patients had been previously treated with azacitidine or decitabine (Dacogen) previously.

Patients were randomly assigned to the combination of pevonedistat with azacitidine or to azacitidine alone. They continued 28 day cycles of their treatment until they developed unacceptable side effects, had a relapse or their disease progressed. The study was designed to assess overall survival.

Key findings:

- Patients received an average of 13 cycles of the pevonedistat and azacitidine combination or 9 cycles of azacitidine alone.
- On average, those in the combination group survived for 22 months, while those in the azacitidine group survived 19 months.
- Among the 67 patients with MDS, those treated with the combination survived for an average of 24 months and those treated with azacitidine alone survived for 19 months.
- Of the patients for whom responses could be evaluated, 71% responded to the combination therapy and 60% responded to the azacitidine alone.
- In patients with high risk MDS, 52% of those treated with the combination therapy achieved complete remission as did 27% with azacitidine alone.
- Rates of serious side effects were around 90% for both groups and included low white blood cell counts with or without fever, anemia and low platelet count.

Conclusions:

- The safety of pevonedistat and azacitidine was similar to that of azacitidine alone.
- The effects of the combination of pevonedistat and azacitidine were not significantly different from those of azacitidine alone on overall survival or response rates.

CC-486 for Maintenance Therapy in Older Adults with Acute Myeloid Leukemia in Remission After Chemotherapy

Farhad Ravandi, Andrew Wei, Hartmut Dohner, Hervé Dombret, Gert J. Ossenkoppele, Michael Pfeilstöcker, Felicitas Thol, Georg Feldman, Maria Teresa Voso, Paula Marlton, Michael Harvey, Valeria Santini, Luana Fianchi, Anna Candoni, Ignazia La Torre, Barry Skikne, Keshava Kumar, Qian Dong, C. L. Beach, Gail J. Roboz

Summary:

CC-486 is a version of azacitidine (Vidaza) that patients take by mouth. This trial, called QUAZAR AML-001 (NCT01757535), is a Phase III clinical trial of CC-486 in 486 patients aged 55 or older with acute myelogenous leukemia (AML) who had not responded completely to previous treatment and were not eligible for stem cell transplantation. This analysis focused on the side effects of CC-486 in 469 patients (average 68 years).

Key Findings:

- The rates of side effects with both CC-486 and placebo were similar in patients aged 55 to 64, 65 to 74, and 75 or older.
- The most common side effects were nausea, vomiting, diarrhea, and constipation.
- These side effects were more common in patients treated with CC-486 than those treated with placebo.
- Constipation was about 20% more common and low platelet counts were at least 20% less common in patients aged 75 years and older than in younger patients.
- Overall, 13% of patients in the CC-486 group and 4% in the placebo group stopped their treatment because of side effects.

Conclusions:

- Patients in all age groups, including those older than 74, in the QUAZAR study tolerated CC-486 well.

Decitabine as Maintenance Therapy in Core Binding Factor Acute Myeloid Leukemia

Mahran Shoukier, Hagop M. Kantarjian, Guillermo Garcia-Manero, Keyur P. Patel, Tapan M. Kadia, Farhad Rayandi, Maro Ohanian, Naval Gujastad Daver, Ghayas C. Issa, Jeffrey Aldrich, Gautam Borthakur

Summary:

The purpose of this study is to evaluate the effects of decitabine (Dacogen) as maintenance therapy for core binding factor AML. People with this type of AML have a shortage of mature white blood cells, red blood cells, and platelets. Unlike other forms of AML, core binding factor AML often begins during young adulthood.

Reverse transcription polymerase chain reaction (RT-PCR) tests were conducted every 2 or 3 months to determine whether patients still had cancer cells. These tests are used to evaluate abnormalities in patients' genes.

The study enrolled 34 patients, including 18 (Group 1) who had completed a full course of the FLAG (fludarabine, cytarabine and filgrastim) chemotherapy regime before being treated with decitabine because the RT-PCR tests continued to show that they had cancer cells. Another 16 (Group 2) were switched to decitabine when they did not complete consolidation treatment to prevent the leukemia cells from coming back.

In Group 2, 9 patients (56%) had negative RT-PCR results (meaning no sign of cancer cells) and 7 (46%) had positive RT-PCR results before starting decitabine. Group 1 patients were monitored for an average of 5 years and those in Group 2 were followed for about 2.5 years.

Key Findings:

- Only 1 patient in Group 1 and 1 patient in Group 2 (who had negative RT-PCR results before starting decitabine) had a relapse.
- 5 patients in Group 2 whose RT-PCR results were positive before starting decitabine had a relapse.

Conclusions:

- Decitabine seems to be an effective maintenance treatment for people with core binding factor AML whose RT-PCR results are positive after FLAG chemotherapy and those who cannot tolerate a full course of chemotherapy but have negative RT-PCR results.
- Stem cell transplantation may be a better option for patients whose RT-PCR tests continue to show cancer cells.

Long-Term Survivorship with Gilteritinib for Acute Myeloid Leukemia in Patients with a *FLT3* Mutation

Alexander E. Perl, Giovanni Martinelli, Andreas Neubauer, Ellin Berman, Maria R. Baer, Richard A. Larson, Amir Tahmash Fathi, Hisayuki Yokoyama, Naoko Hosono, Nahla Hasabou, Oiaoyang Lu, Erkut Bahceci

Summary:

Gilteritinib (Xospata) is used to treat AML in patients who have had a relapse or whose AML has not responded to treatment. The treatment only works in patients who have a mutation in the *FLT3* gene in their blood or bone marrow.

The Phase 3 ADMIRAL trial (NCT02421939) randomly assigned 247 adults with relapsed AML or AML that did not respond to previous treatment and who had a *FLT3* mutation to gilteritinib and 124 to chemotherapy.

The investigators continued to analyze the long-term effects of gilteritinib in patients for at least 18 months after the initial analysis as well as the long-term side effects of the treatment.

Key findings:

- Patients treated with gilteritinib survived longer (9 months) than those treated with chemotherapy (6 months).
- Rates of survival for at least 18 months were 27% with gilteritinib and 15% with chemotherapy.
- Of 62 patients treated with gilteritinib who survived for at least 18 months, 20 (32%) achieved complete remission before undergoing stem cell transplantation.
- The most common serious side effects after the first year were low white blood cell counts with fever (8%, down from 45% in the first year) and anemia (10%, down from 40% in the first year).

Conclusions:

- Long-term survival in patients treated with gilteritinib appears to depend on whether they stay in remission, undergo stem cell transplantation after starting gilteritinib and are treated with gilteritinib after stem cell transplantation.
- Rates of side effects dropped significantly after the first year.



4330 East West Highway, Suite 230

Bethesda, MD 20814

(800) 747-2820 | (301) 279-7902

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