Inside the Issue: Novel Agents, Approaches and Strategies in the Management of Higher-Risk Myelodysplastic Syndromes

A CME/MOC-Accredited Live Webinar

Tuesday, July 11, 2023 5:00 PM – 6:00 PM ET

Faculty Guillermo Garcia-Manero, MD David Sallman, MD



# Faculty



Guillermo Garcia-Manero, MD McCredie Professor of Medicine Chief, Section of MDS Vice Chair, Department of Leukemia The University of Texas MD Anderson Cancer Center Houston, Texas



Moderator

**Neil Love, MD** Research To Practice



**David Sallman, MD** Associate Member Malignant Hematology Moffitt Cancer Center Tampa, Florida



# **Commercial Support**

This activity is supported by an educational grant from Gilead Sciences Inc.



# **Dr Love — Disclosures**

**Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

# Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.



# **Dr Garcia-Manero — Disclosures**

No relevant conflicts of interest to disclose.



# **Dr Sallman — Disclosures**

Advisory Committee	AvenCell, bluebird bio, Bristol Myers Squibb, Intellia Therapeutics, Jasper Therapeutics Inc, Kite, A Gilead Company, Magenta Therapeutics, Nkarta Inc, Novartis, Servier Pharmaceuticals LLC, Shattuck Labs, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc
Consulting Agreements	AbbVie Inc, Affimed GmbH, Gilead Sciences Inc, Incyte Corporation, Molecular Partners, Precigen Inc, Takeda Pharmaceuticals USA Inc, Zentalis Pharmaceuticals
Contracted Research	Aprea Therapeutics, Jazz Pharmaceuticals Inc
Nonrelevant Financial Relationship	Intellisphere Oncology Specialty Group



# **We Encourage Clinicians in Practice to Submit Questions**



Feel free to submit questions now before the program begins and throughout the program.



### **Familiarizing Yourself with the Zoom Interface**

# **Expand chat submission box**



Drag the white line above the submission box up to create more space for your message.



# **Familiarizing Yourself with the Zoom Interface**

### **Increase chat font size**



Press Command (for Mac) or Control (for PC) and the + symbol. You may do this as many times as you need for readability.



# Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys





# **ONCOLOGY TODAY** WITH DR NEIL LOVE

Key Presentations in Acute Myeloid Leukemia and Myelodysplastic Syndromes from the 2022 ASH Annual Meeting



### DR RICHARD STONE DANA-FARBER CANCER INSTITUTE









Dr Richard Stone – Key Presentations Oncology Today with Dr Neil Love —

(30)

(15)

# Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology A Multitumor CME/MOC-Accredited Live Webinar Series

# Melanoma and Nonmelanoma Skin Cancers

Thursday, July 13, 2023 5:00 PM – 6:00 PM ET

> Faculty Omid Hamid, MD Evan J Lipson, MD



Inside the Issue: Integrating Bispecific Antibodies into the Management of Multiple Myeloma — Patient Selection and Toxicity Management

A CME/MOC-Accredited Live Webinar

Tuesday, July 18, 2023 5:00 PM – 6:00 PM ET

Faculty Hans Lee, MD Saad Zafar Usmani, MD, MBA



Inside the Issue: Current and Future Management of ER-Positive Metastatic Breast Cancer After Disease Progression on a CDK4/6 Inhibitor

A CME/MOC-Accredited Live Webinar

Thursday, July 20, 2023 5:00 PM – 6:00 PM ET

Faculty Aditya Bardia, MD, MPH Erika Hamilton, MD



Meet The Professor Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

> Tuesday, July 25, 2023 5:00 PM – 6:00 PM ET

Faculty Richard F Riedel, MD



Inside the Issue: Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

A CME/MOC-Accredited Live Webinar

Monday, July 31, 2023 5:00 PM – 6:00 PM ET

Faculty Neal D Shore, MD Mary-Ellen Taplin, MD



# Thank you for joining us!

# CME and MOC credit information will be emailed to each participant within 5 business days.



Inside the Issue: Novel Agents, Approaches and Strategies in the Management of Higher-Risk Myelodysplastic Syndromes

A CME/MOC-Accredited Live Webinar

Tuesday, July 11, 2023 5:00 PM – 6:00 PM ET

Faculty Guillermo Garcia-Manero, MD David Sallman, MD



# Faculty



Guillermo Garcia-Manero, MD McCredie Professor of Medicine Chief, Section of MDS Vice Chair, Department of Leukemia The University of Texas MD Anderson Cancer Center Houston, Texas



Moderator

**Neil Love, MD** Research To Practice



**David Sallman, MD** Associate Member Malignant Hematology Moffitt Cancer Center Tampa, Florida



# **Survey Participants**



Uma Borate, MD, MS

Associate Professor of Internal Medicine Division of Hematology The Ohio State University The James Cancer Center Columbus, Ohio



#### **Richard M Stone, MD**

Lunder Family Chair in Leukemia Chief of Staff Dana-Farber Cancer Institute Professor of Medicine Harvard Medical School Boston, Massachusetts



Andrew M Brunner, MD Assistant Professor, Harvard Medical School Leukemia Program Massachusetts General Hospital Cancer Center Boston, Massachusetts



Amy E DeZern, MD, MHS Professor of Oncology and Medicine Division of Hematologic Malignancies, Leukemia and Bone Marrow Transplant Program The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins The Johns Hopkins University School of Medicine Baltimore, Maryland



Eunice S Wang, MD Chief, Leukemia Service Professor of Oncology Roswell Park Comprehensive Cancer Center Buffalo, New York



# **We Encourage Clinicians in Practice to Submit Questions**



Feel free to submit questions now before the program begins and throughout the program.



# Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys





# Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology A Multitumor CME/MOC-Accredited Live Webinar Series

# Melanoma and Nonmelanoma Skin Cancers

Thursday, July 13, 2023 5:00 PM – 6:00 PM ET

> Faculty Omid Hamid, MD Evan J Lipson, MD



Inside the Issue: Integrating Bispecific Antibodies into the Management of Multiple Myeloma — Patient Selection and Toxicity Management

A CME/MOC-Accredited Live Webinar

Tuesday, July 18, 2023 5:00 PM – 6:00 PM ET

Faculty Hans Lee, MD Saad Zafar Usmani, MD, MBA



Inside the Issue: Current and Future Management of ER-Positive Metastatic Breast Cancer After Disease Progression on a CDK4/6 Inhibitor

A CME/MOC-Accredited Live Webinar

Thursday, July 20, 2023 5:00 PM – 6:00 PM ET

Faculty Aditya Bardia, MD, MPH Erika Hamilton, MD



Meet The Professor Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

> Tuesday, July 25, 2023 5:00 PM – 6:00 PM ET

Faculty Richard F Riedel, MD



Inside the Issue: Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

A CME/MOC-Accredited Live Webinar

Monday, July 31, 2023 5:00 PM – 6:00 PM ET

Faculty Neal D Shore, MD Mary-Ellen Taplin, MD



# **ONCOLOGY TODAY** WITH DR NEIL LOVE

Key Presentations in Acute Myeloid Leukemia and Myelodysplastic Syndromes from the 2022 ASH Annual Meeting



### DR RICHARD STONE DANA-FARBER CANCER INSTITUTE









Dr Richard Stone – Key Presentations Oncology Today with Dr Neil Love —

(30)

(15)

Inside the Issue: Novel Agents, Approaches and Strategies in the Management of Higher-Risk Myelodysplastic Syndromes

A CME/MOC-Accredited Live Webinar

Tuesday, July 11, 2023 5:00 PM – 6:00 PM ET

Faculty Guillermo Garcia-Manero, MD David Sallman, MD



# **Commercial Support**

This activity is supported by an educational grant from Gilead Sciences Inc.

# Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.



# **Dr Garcia-Manero — Disclosures**

No relevant conflicts of interest to disclose.



# **Dr Sallman — Disclosures**

Advisory Committee	AvenCell, bluebird bio, Bristol Myers Squibb, Intellia Therapeutics, Jasper Therapeutics Inc, Kite, A Gilead Company, Magenta Therapeutics, Nkarta Inc, Novartis, Servier Pharmaceuticals LLC, Shattuck Labs, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc
Consulting Agreements	AbbVie Inc, Affimed GmbH, Gilead Sciences Inc, Incyte Corporation, Molecular Partners, Precigen Inc, Takeda Pharmaceuticals USA Inc, Zentalis Pharmaceuticals
Contracted Research	Aprea Therapeutics, Jazz Pharmaceuticals Inc
Nonrelevant Financial Relationship	Intellisphere Oncology Specialty Group



### **Current Management of Higher Risk MDS**

Guillermo Garcia-Manero MD McCredie Professor Chief, Section of MDS Department of Leukemia MD Anderson Cancer Center Houston, TX 6/30/23

### Future Directions in the Management of Higher Risk MDS

David A. Sallman, MD Associate Member Myeloid Section Head david.sallman@moffitt.org

H. Lee Moffitt Cancer Center & Research Institute Tampa, FL





# **Key Data Sets**

### Guillermo Garcia-Manero, MD

- Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, riskstratification, and management. *Am J Hematol* 2023 June 8;[Online ahead of print].
- Bernard E et al. Molecular international prognostic scoring system for myelodysplastic syndromes. *NEJM Evid* 2022;1(7).
- Savona MR et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: A multicentre, open-label, dose-escalation, phase 1 study. *Lancet Haematol* 2019 April;6(4):e194-203.
- Savona MR et al. Prolonged survival observed in 133 MDS patients treated with oral decitabine/cedazuridine. International Congress on Myelodysplastic Syndromes 2021;Abstract P48.
- Savona MR et al. Prolonged survival in bi-allelic TP53-mutated (TP53mut) MDS subjects treated with oral decitabine/cedazuridine in the ASCERTAIN trial (ASTX727-02). ASH 2022;Abstract 854.



# **Key Data Sets**

### Guillermo Garcia-Manero, MD (Continued)

- Sekeres MA et al. Pevonedistat (PEV) + azacitidine (AZA) versus AZA alone as first-line treatment for patients with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML) or acute myeloid leukemia (AML) with 20-30% marrow blasts: The randomized Phase 3 PANTHER trial. *Blood* 2021;138(Suppl 1):242.
- Bazinet A et al. Azacitidine plus venetoclax in patients with high-risk myelodysplastic syndromes or chronic myelomonocytic leukaemia: Phase 1 results of a single-centre, dose-escalation, dose-expansion, phase 1-2 study. *Lancet Haematol* 2022 Oct;9(10):e756-65.
- Bataller A et al. Phase 1/2 study of oral decitabine/cedazuridine in combination with venetoclax in treatment-naïve higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia. EHA 2023;Abstract S172.
- Sallman DA et al. Long term follow-up and combined Phase 2 results of eprenetapopt (APR-246) and azacitidine (AZA) in patients with TP53 mutant myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia (AML). ASH 2021;Abstract 246.
- DiNardo CD et al. Targeted therapy with the mutant IDH2 inhibitor enasidenib for high-risk IDH2mutant myelodysplastic syndrome. *Blood Adv* 2023 June 13;7(11):2378-87.


## **Key Data Sets**

### David Sallman, MD

- Grob T et al. Molecular characterization of mutant TP53 acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood* 2022 April 14;139(15):2347-54.
- Tashakori M et al. TP53 copy number and protein expression inform mutation status across risk categories in acute myeloid leukemia. *Blood* 2022 July 7;140(1):58-72.
- Swoboda DM et al. Marrow ring sideroblasts are highly predictive for TP53 mutation in MDS with excess blasts. *Leukemia* 2022 April;36(4):1189-92.
- Sallman DA et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. ASCO 2020;Abstract 7507.
- Sallman DA et al. Magrolimab in combination with azacitidine in patients with higher-risk myelodysplastic syndromes: Final results of a phase Ib study. *J Clin Oncol* 2023 May 20;41(15):2815-26.
- Sallman DA et al. Magrolimab in combination with azacitidine for patients with untreated higher-risk myelodysplastic syndromes (HR MDS): 5F9005 phase 1b study results. EHA 2022;Abstract S166.



## **Key Data Sets**

### David Sallman, MD (Continued)

- Zeidan AM et al. Primary results of stimulus-MDS1: A randomized, double-blind, placebocontrolled phase II study of TIM-3 inhibition with sabatolimab added to hypomethylating agents (HMAs) in adult patients with higher-risk myelodysplastic syndromes (MDS). ASH 2022;Abstract 853.
- Zeidan AM et al. STIMULUS-MDS2 design and rationale: A phase III trial with the anti-TIM-3 sabatolimab (MBG453) + azacitidine in higher risk MDS and CMML-2. *Future Oncol* 2023 March;19(9):631-42.
- DiNardo CD et al. Targeted therapy with the mutant IDH2 inhibitor enasidenib for high-risk IDH2-mutant myelodysplastic syndrome. *Blood Adv* 2023 June 13;7(11):2378-87.



### Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

MODULE 5: Magrolimab/TP53

**MODULE 6: Targeted Treatment** 



## Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

MODULE 5: Magrolimab/TP53

**MODULE 6: Targeted Treatment** 



## **Overlap of MDS and AML**







Garcia-Manero et al AJH 2023

### Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

MODULE 5: Magrolimab/TP53

**MODULE 6: Targeted Treatment** 



### Molecular International Prognostic Scoring System for myelodysplastic syndromes

Elsa Bernard, PhD

**Research Associate** 

Computational Oncology | Papaemmanuil Lab | Memorial Sloan Kettering Cancer Center

🔰 @Elsa2Bernard



ASH 21, NEJM Evidence 2022

# Impact of number of mutations in survival in MDS

Adverse Factor		HR	P value	Assigned Score
IPSS-R	Intermediate	1.45	0.45	0.5
	High/Very high	4.66	<0.001	1.5
TP53 mutation		3.12	0.011	1
≥ 3 mutations		2.51	0.005	1

Montalban-Bravo et al. Oncotarget 2018

Which of the following genes do you consider essential to evaluate for alteration in a patient with newly diagnosed myelodysplastic syndromes (MDS)?

Dr Garcia- Manero	TP53, FLT3, NPM1, IDH2, ASXL1
Dr Sallman	IPSS-M main effect genes*
Dr Borate	IPSS-M main effect genes*
Dr Brunner	IPSS-M main effect genes*
Dr DeZern	IPSS-M main effect genes*
Dr Stone	IPSS-M main effect genes*
Dr Wang	IPSS-M main effect genes*

\* TP53, MLL/KMT2A, FLT3, SF3B1, NPM1, RUNX1, NRAS, ETV6, IDH2, CBL, EZH2, U2AF1, SRSF2, DNMT3A, ASXL1, KRAS



## In general, do you wait for next-generation sequencing (NGS) results before initiating treatment for your patients with MDS?

Dr Garcia- Manero	Yes
Dr Sallman	Yes
Dr Borate	Yes
Dr Brunner	Yes
Dr DeZern	Yes
Dr Stone	Yes
Dr Wang	Yes



A patient's MDS is designated as lower risk under the IPSS-R system but higher risk under the IPSS-M system. Would you generally treat this patient as having higher-risk MDS?

Dr Garcia- Manero	It depends
Dr Sallman	It depends
Dr Borate	It depends
Dr Brunner	It depends
Dr DeZern	Yes
Dr Stone	It depends
Dr Wang	Yes



### Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

MODULE 5: Magrolimab/TP53

**MODULE 6: Targeted Treatment** 



## **Oral HMAs in MDS: current status**

- ASTX727 (oral decitabine): approved US FDA
- CC-486: improves survival post-consolidation in AML
   Being re-studied in LR MDS
- ASTX030 (oral azacitidine): ongoing phase 1 trials

## **Ongoing studies oral decitabine cedazuridine**

- Lower risk MDS
- Multiple combinations
  - (IDH, venetoclax, Flt-3, Menin inhibitors, pediatrics)
- Post SCT: total therapy
- Oral azacitidine + cedazuridine (ASTX030)

# **Doublets in Higher Risk MDS**

- PANTHER (P-3001): azacitidine +/pevonedistat
- Azacitidine + APR-246 for p53 mutated MDS
- HMA + venetoclax
- HMA + sabatolimab
- HMA + anti CD47



#### Making Cancer History®

## Phase 1/2 study of oral decitabine/cedazuridine in combination with venetoclax in treatment-naïve higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia

<u>Alex Bataller</u>, Guillermo Montalban-Bravo, Alexandre Bazinet, Yesid Alvarado, Kelly Chien, Sangeetha Venugopal, Jo Ishizawa, Danielle Hammond, Mahesh Swaminathan, Koji Sasaki, Ghayas C. Issa, Nicholas J. Short, Lucia Masarova, Naval G. Daver, Tapan M. Kadia, Simona Colla, Wei Qiao, Xuelin Huang, Rashmi Kanagal-Shamanna, Stephany Hendrickson, Farhad Ravandi, Elias Jabbour, Hagop Kantarjian, Guillermo Garcia-Manero

Leukemia Department, The University of Texas MD Anderson Cancer Center, Houston (TX, USA)

June 10<sup>th</sup> 2023 s424 Clinical updates in MDS



## Efficacy

\*ĚHĂ

	Full cohort (n=39)	Phase 1 (n=9)	Phase 2 (n=30))
ORR, n (%, 95% CI) CR mCR mCR mCR + HI	37 (94.9, 82-99) 14 (35.9, 21-53) 23 (59, 42-74) 11 (28.2, 15-45) 12 (30.8, 17-48)	9 (100, 66-100) 6 (66.7, 30-93) 3 (33.3, 7-70) 2 (22.2, 3-60) 1 (11.1, 0-48)	28 (93.3, 78-99) 8 (26.7, 12-46) 20 (66.7, 47-83) 9 (30, 15-49) 11 (36.7, 20-56)
Cytogenetic response, n (%, 95% CI)	14/26 (53.8, 33-73)	4/5 (80, 28-99)	10/21 (47.6, 26-70)
Cycles to first response, n (range)	1 (1-2)	1 (1-1)	1 (1-2)
Cycles to best response, n (range)	1 (1-6)	1 (1-6)	1 (1-4)
Cycles received, n (range)	2 (1-13)	6 (2-13)	2 (1-8)
HSCT, n (%)	19 (48.7)	5 (55.6)	14 (46.7)



Survival



Median follow-up: 10.8m (6-16)

EHA2023



Survival



mOS: NR vs 8.3m (8.3-NR)

mOS: NR vs 9.6m (7-NR)

EHA2023



## Survival after HSCT

EHP



- Median n of cycles: 2 (2-11)
- Median time to HSCT: 3.7m (2.3-15)

- 4 patients died (2 TRM, 2 disease progression)
- 3 patients relapsed after HSCT



## Case Presentation – Dr Garcia-Manero

A 78-year-old man presents to your clinic with a history of cytopenia. Bone marrow exam reveals 15% blasts, cytogenetic analysis trisomy 8 and results of NGS reveal TET2 and DNMT3A mutations. Patient is not a candidate for alloSCT. You offer an HMA: azacitidine, decitabine or oral decitabine/cedazuridine. A 78-year-old man presents with a history of cytopenia. Bone marrow exam reveals 15% blasts, cytogenetic analysis shows trisomy 8 and NGS indicates TET2 and DNMT3A mutations. The patient is not a candidate for allogeneic HSCT. Which front-line treatment would you recommend?

Dr Garcia- Manero	Oral decitabine and cedazuridine +/- venetoclax
Dr Sallman	Azacitidine/venetoclax
Dr Borate	HMA
Dr Brunner	Oral decitabine and cedazuridine
Dr DeZern	Azacitidine/venetoclax
Dr Stone	Azacitidine
Dr Wang	Oral decitabine and cedazuridine

NGS = next-generation sequencing; HSCT = hematopoietic stem cell transplant; HMA = hypomethylating agent



### Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

MODULE 5: Magrolimab/TP53

**MODULE 6: Targeted Treatment** 



## Phase 3 VERONA (NCT04401748)

### Study Design and Endpoints

#### **VERONA Study Design**



\*7 days within the first 9 calendar days/28 day cycle

Select Inclusion Criteria	Select Exclusion Criteria	
≥18 years old with newly diagnosed MDS according	<ul> <li>Prior therapy for MDS with HMA,</li> <li>characterizer and USCT</li> </ul>	End Points
to 2016 WHO classification	<ul> <li>Prior diagnosis of therapy-related MDS,</li> </ul>	Primary: CR, OS
ECOG PS 0-2	MDS evolved from MPN, MDS/MPN including CMML, aCML, JMML, and	Secondary: mOR, TI, ORR, fatigue score,
IPSS-R score of >3 (Intermediate, High, Very High) No planned HSCT at the time of C1D1	unclassifiable MDS/MPN	deterioration in physical functioning

aCML=Atypical Chronic Myeloid Leukemia. allo-HSCT=Allogeneic Hematopoietic Stem Cell Transplant. AML=Acute Myeloid Leukemia. BM=Bone Marrow. C=Cycle. CMML=Chronic Myelomonocytic Leukemia. CR=Complete Remission. D=Day. ECOG PS=Eastern Cooperative Oncology Group Performance Status. HMA=Hypomethylating Agent. HSCT=Hematopoietic Stem Cell Transplantation. IPSS-R=Revised International Prognostic Scoring System. IV=Intravenous. JMML=Juvenile Myelomonocytic Leukemia. MDS=Myelodysplastic Syndrome. mOR=Modified Overall Response. MPN=Myeloproliferative Neoplasm. ORR=Overall Response Rate. OS=Overall Survival. PO=Oral. QD=Daily. SC=Subcutaneous. TI=Transfusion Independence. WHO=World Health Organization. 1. ClinicalTrials.gov. NCT04401748. <u>https://clinicaltrials.gov/ct2/show/NCT04401748</u>. Accessed July 2021

## **Targeting TIM-3 and Sabatolimab**

- TIM-3 promotes autocrine LSC self-renewal
- Blocking TIM-3 inhibits downstream signaling that promotes selfrenewal
- TIM-3 ligation on T-Cells leads to apoptosis of the effector cell
- May also promote phagocytosis by myeloid cells, macrophages



Acharya N, et al. J Immunother Cancer. 2020;8:e000911. Kikushige et al., Cell Stem Cell 2015

Courtesy of David A Sallman, MD

# Sabatolimab + HMA did not result in a statistically significant improvement in CR or PFS



	Sabatolimab + HMA n=65	Placebo + HMA n=62
Primary CR rate (95% Cl), %	21.5 (12.3-33.5)	17.7 (9.2-29.5)
P value <sup>a</sup>	0.769, ns	
PFS, median <sup>b</sup> (95% Cl), mo	11.1 (7.6-17.6)	8.5 (6.9-11.3)
P value <sup>c</sup>	0.102, ns	
Hazard ratio <sup>d</sup>	0.749 (0.479, 1.173)	

 CR was evaluated earlier (March 10, 2021) by an independent data monitoring committee based on data up to 7 months after the last patient was randomized

### Sabatolimab + HMA may have a delayed-onset benefit in terms of PFS

Lower Burden of Disease (<10% blasts, IPSS-R and IPSS-M int/high risks) with improved outcomes



## STIMULUS-MDS2 Phase 3 Study

#### Primary objective:

Evaluate overall survival of patients with intermediate-, high-, or very high-risk MDS or CMML-2 treated with sabatolimab + azacitidine or placebo + azacitidine alone as a first-line therapy



#### Secondary endpoints:

FACIT-fatigue and EORTC QLQ-C30 (emotional and physical functioning), RBC transfusion-free intervals, RBC/platelet transfusion independence, CR/mCR/PR/HI, PFS, LFS, safety, PK, immunogenicity, EQ-5D-5L

Zeidan A et al., Future Medicine, 2023

#### Courtesy of David A Sallman, MD



What would you predict to be the outcome of a Phase III randomized trial evaluating <u>sabatolimab/HMA versus HMA alone</u> as first-line treatment for higher-risk MDS?

Dr Garcia- Manero	Efficacy is about the same with both regimens
Dr Sallman	Efficacy is about the same with both regimens
Dr Borate	Efficacy is about the same with both regimens
Dr Brunner	Efficacy is about the same with both regimens
Dr DeZern	Efficacy is about the same with both regimens
Dr Stone	Efficacy is about the same with both regimens
Dr Wang	Efficacy is about the same with both regimens

HMA = hypomethylating agent



## Case Presentation – Dr Garcia-Manero

A 70-year-old man presents to your clinic with a history of cytopenia. Bone marrow exam reveals 15% blasts, cytogenetic analysis trisomy 8 and results of NGS reveal an ASXL1 mutation. Patient is a candidate for alloSCT. You offer an HMA: azacitidine, decitabine or oral decitabine/cedazuridine and discuss potential clinical trial in combination with venetoclax. A 70-year-old man presents with a history of cytopenia. Bone marrow exam reveals 15% blasts, cytogenetic analysis shows trisomy 8 and NGS indicates an ASXL1 mutation. Which front-line treatment would you recommend? Would you recommend allogeneic HSCT? If you were able to access magrolimab, would you recommend it?

	Preferred treatment	Allogeneic HSCT	Magrolimab
Dr Garcia- Manero	Oral decitabine/ cedazuridine and venetoclax	Yes	Νο
Dr Sallman	Azacitidine/venetoclax	Yes	Yes
Dr Borate	HMA +/- venetoclax	Yes	Yes
Dr Brunner	Oral decitabine/ cedazuridine	Yes	Yes
Dr DeZern	Azacitidine/venetoclax	Yes	Νο
Dr Stone	Azacitidine	Yes	Yes
Dr Wang	Azacitidine	Yes	Yes

NGS = next-generation sequencing; HSCT = hematopoietic stem cell transplant; HMA = hypomethylating agent

Please describe the last patient with MDS to whom you administered a hypomethylating agent with venetoclax either on or off protocol.

	<b>Clinical characteristics</b>	Treatment	Outcome
Dr Garcia- Manero	67 y/o M; 15% blasts, diploid cytogenetics, ASXL1	Oral decitabine/ cedazuridine and venetoclax	CR
Dr Sallman	80 y/o M; 15% blasts, RUNX1, ASXL1	Azacitidine/venetoclax	mCR
Dr Borate	67 y/o F; 15% blasts, complex cytogenetics, RUNX1, DNMT3A	Decitabine/venetoclax	MLFS
Dr Brunner	74 y/o M; 15% blasts, t(3;21), PPM1D, TET2, DNMT3A, prior MM	Decitabine/venetoclax	mCR
Dr DeZern	73 y/o F; 14% blasts, RUNX1, SRSF2, ASXL1fs, TET2, DNMT3A	Azacitidine/venetoclax	CRi
Dr Stone	68 y/o M; 10% blasts, NK, ASXL1; RUNX1	Azacitidine/venetoclax	CR
Dr Wang	78 y/o M; PD after multiple cycles of azacitidine	Azacitidine/venetoclax	Brief response

mCR = morphologic complete remission; CRi = complete remission with incomplete count recovery; MLFS = morphological leukemia-free state; PD = progressive disease

In general, when administering HMA/venetoclax to a patient with MDS, for how many days do you administer the venetoclax during the first cycle?

For how many days do you typically administer the venetoclax during subsequent cycles?

	Venetoclax cycle 1	Venetoclax subsequent cycles
Dr Garcia- Manero	14 days	7 days
Dr Sallman	14 days	7 days
Dr Borate	14 days	7-10 days
Dr Brunner	14 days	7-14 days
Dr DeZern	14-21 days	7-14 days
Dr Stone	14 days	7 days
Dr Wang	14 days	7 days

HMA = hypomethylating agent

## In general, when administering HMA/venetoclax to a patient with MDS, when do you order the first bone marrow biopsy?

Dr Garcia- Manero	After 21-28 days
Dr Sallman	After 21 days
Dr Borate	After 21-28 days
Dr Brunner	After 21 days
Dr DeZern	After 21 days
Dr Stone	After 24 days
Dr Wang	After 21 days

HMA = hypomethylating agent



### Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

**MODULE 5: Magrolimab/TP53** 

**MODULE 6: Targeted Treatment** 



## **Case Presentation – Dr Sallman**

67 yo male presents with severe pancytopenia, 12% myeloblasts, trilineage dysplasia and molecular results show a *TP53* mutation with a VAF of 55% and complex karyotype. The patient has minimal co-moribidities and is still able to walk 1 mile/day. Based on the poor standard of care in *TP53* mutant patients, the patient was enrolled in a clinical trial of azacitidine + magrolimab. The patient had a 2gm/dl drop in hemoglobin on day 1 after infusion of magrolimab without other magrolimab related adverse events. The patient achieved mCR + HI after 2 cycles of therapy and subsequently full CR after 4 cycles and was bridged to allogeneic stem cell transplant.


A 67-year-old man with minimal comorbidities presents with severe pancytopenia and 12% myeloblasts. Molecular testing reveals a TP53 mutation with a <u>variant allele frequency (VAF) of 55% and complex karyotype</u>. What is your usual front-line systemic treatment? Would you recommend allogeneic HSCT? If you were able to access magrolimab, would you recommend it?

	Preferred treatment	Allogeneic HSCT	Magrolimab				
Dr Garcia- Manero	Oral decitabine/ cedazuridine	Yes	Yes				
Dr Sallman	Decitabine	Yes	Yes				
Dr Borate	HMA +/- venetoclax	Yes	Yes				
Dr Brunner	Oral decitabine/ cedazuridine	Yes	Yes				
Dr DeZern	Decitabine	Yes	Yes				
Dr Stone	Azacitidine	Yes	Yes				
Dr Wang	Azacitidine	Yes	Yes				

HSCT = hematopoietic stem cell transplant; HMA = hypomethylating agent

A 67-year-old man with minimal comorbidities presents with severe pancytopenia and 12% myeloblasts. Molecular testing reveals a TP53 mutation with a <u>VAF of 10% and no complex karyotype</u>. What is your usual front-line systemic treatment? Would you recommend allogeneic HSCT? If you were able to access magrolimab, would you recommend it?

	Preferred treatment	Allogeneic HSCT	Magrolimab
Dr Garcia- Manero	Cladribine/low-dose ara-C/venetoclax	Yes	Yes
Dr Sallman	Azacitidine/venetoclax	Yes	Yes
Dr Borate	HMA/venetoclax	Yes	Yes
Dr Brunner	Oral decitabine/ cedazuridine	Yes	Yes
Dr DeZern	Azacitidine/venetoclax	Yes	Yes
Dr Stone	Azacitidine	Yes	Yes
Dr Wang	Azacitidine	Yes	Yes

VAF = variant allele frequency; HSCT = hematopoietic stem cell transplant

## **TP53 Mutant MDS and AML, One Disease?**



в





### **Can We Predict Patients for TP53 Mutation?**



В



Kulasekararaj A et al. BJH 2013; 160, 660–672; McGraw K et al., Haematologica 2016; Sallman D et al., JCO 2021; Tashakori et al., Blood 2022

## **TP53-mt MDS with Ring Sideroblasts**





Swoboda D... Sallman D et al. Leukemia 2021

### Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



**Macrophages Cancer cells** 

• Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers

# 5F9005 Study Design: Magrolimab in Combination with AZA in HR-MDS



Patients received magrolimab IV as a 1 mg/kg priming dose on Days 1 and 4, then ramp-up to 30 mg/kg QW or Q2W maintenance; AZA dose was SC or IV 75 mg/m<sup>2</sup> on Days 1-7 of each cycle.

Primary objectives	Secondary objectives	Exploratory objectives
Safety, tolerability and efficacy (CR rate) of magrolimab + azacitidine in HR-MDS	Efficacy of magrolimab + azacitidine; PK profile; Immunogenicity; MRD negativity	CD47 RO, Biomarkers, Efficacy in molecular subtypes of MDS

CR = complete remission; IPSS-R = Revised International Prognostic Scoring System; IV = intravenous; MRD = minimal residual disease; RO = receptor occupancy; RP2D = recommended Phase 2 dose; SC = subcutaneous; Q1W = weekly; Q2W = every two weeks.



#### Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

## Magrolimab Q2W Dosing Results in Similar CD47 Receptor **Occupancy as Q1W Dosing**



RO: receptor occupancy. Black line: linear regression best fit. Red lines: 95% confidence intervals.

- Patients were dosed with magrolimab Q1W throughout or Q2W dosing starting Cycle 3 and beyond
- Similar CD47 RO was observed in the peripheral blood and bone marrow after Q2W dosing change in Cycle 3+
- A magrolimab Q2W dose regimen has been selected based on PK/PD results and patient convenience

Sallman D..... Daver N et al., 2020 ASCO

\*Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing or 30 mg/kg Q2W starting Cycle 3+. IPSS-R: Revised International Prognostic Scoring System.

# Magrolimab in Combination with AZA Is Well Tolerated in HR-MDS

#### TEAEs by Grade Regardless of Causality in ≥ 25%

		(1) = :	, j					
Constipation								
Thrombocytopenia								
Anemia								
Neutropenia								
Nausea								
Diarrhea								
Increased blood bilirubin								
Fatigue								
Dyspnea								
Headache								
Febrile neutropenia								
Low appetite								
Decreased WBC count					G	rade 1		
Infusion reaction					G	rade 2		
Cough					G	rade 3		
Pyrexia					G	rade 4		
	0	10	20	30	40	50	60	7(
	reque	ncy (9	6)					

AE = adverse event; TEAE = treatment-emergent adverse event; WBC = white blood cell

- 30-day mortality was 2.1%, no additional deaths at 60 days.
- TEAEs led to magrolimab dose delays in 52.6% (no dose reductions), and to AZA dose delays in 49.5% (17.9% had dose reductions).
- One Grade 4 anemia occurred in Cycle 4.
- Infusion-related reaction in 25.3%, Grade 3 in 6.3%.
- Magrolimab discontinuation due to AEs in 6.3% and AZA discontinuation due to AEs in 7.4% of patients.



## On-Target Anemia Is a Pharmacodynamic Effect and Mitigated with a Magrolimab Priming and Maintenance Dosing Regimen



- An initial priming dose mitigated on-target anemia by CD47 blockade, resulting in a transient hemoglobin drop.
- Median hemoglobin change from baseline was -0.7 g/dL (range -3.1 to +2.4) at first post-treatment visit.
- 37 (38.9%) patients were transfusion dependent at baseline; 13 (35.1%) of these converted to RBC transfusion independence.



Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

## Magrolimab + AZA Induces High Response Rates in HR-MDS

#### TABLE 3. Efficacy Outcomes

Outcome	All (N = $95^{\circ}$ )	TP53-wt MDS (N = 61)	TP53-mut MDS (N = $25$ )	_	
OR rate, % <sup>b</sup>	74.7	78.7	68.0	170 -	
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)	-	Mutant (N = 23)
mCR, %	31.6	37.7	20.0	- 130 - - 110 -	Wild-type (N = 8 Missing (N = 8)
PR, %	0	0	0	- 0e Seli-	
SD with HI, %	10.5	9.8	8.0		
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 to NR)	7.6 (3.1 to 13.4)	- UL 30 -	
Time to CR, months, median (range)	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)	0 <sup>10</sup> –	
Duration of OR, months, median (95% CI)	9.8 (8.8 to 12.9)	9.8 (8.5 to 18.5)	9.2 (5.0 to 12.2)	- <sub>06</sub> - Jar	
Time to OR, months, median (range)	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)	- 00 -50 - -70 -	
mCR with HI/Any HI, %	16.8/58.9	19.7/60.7	12.0/56.0	<u> </u>	
Converted to RBC transfusion independence, % <sup>c</sup>	35.1	26.1	46.2		
PFS, months, median (95% CI)	11.6 (9.0 to 14.0)	11.8 (8.8 to 16.6)	11.0 (6.3 to 12.8)	-	
OS, months, median (95% CI)	NR (16.3 to NR)	NR (21.3 to NR)	16.3 (10.8 to NR)		



Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

## Durable Responses Are Seen in Patients Treated with Magrolimab + AZA and Deepen over Time





Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

## Median OS Is Encouraging in Both TP53-Wild Type and Mutant HR-MDS Patients

- With a median follow-up of 17.1 months, median OS was not reached and was 16.3 months in TP53-mut MDS.



Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

## Stem Cell Transplant Outcomes Are Encouraging in HR-MDS Patients Treated with Magrolimab + AZA



#### Time (months)

No. at risk:

Allo-HSCT	34	34	34	34	32	31	31	30	29	24	15	13	13	6	5	2	2	2	1	0
No allo-HSCT	61	56	52	48	44	42	35	28	23	20	12	7	6	3	2	2	2	1	1	0

#### **Kaplan–Meier Survival Estimates**

All Patients	SCT (N = 35)	No SCT (N = 60)
Median follow-up, months	19.6	12.9
Median OS (95% CI)	NR (NR, NR)	14.8 (11.9, 21.3)
1-year OS, % (95% CI)	91.4 (75.7, 97.2)	64.0 (49.9, 75.1)
2-year OS, % (95% CI)	77.3 (57.3, 88.8)	33.9 (20.0, 48.3)



Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

## OS and PFS in TP53 mutant MDS pts with Aza+Magro







Sallman D et al., JCO 2023



# Magrolimab in Combination with AZA Demonstrated Encouraging Response Rates in *TP53*-mut AML

#### **Efficacy Endpoints (Intent-to-Treat Analysis)**

Outcome	N = 72
ORR, % (95% CI)	48.6 (36.7, 60.7)
CR, % (95% CI)	<b>33.3 (22.7, 45.4)</b> (n = $24/72$ )
CB:/CBb = (%)	50.0 (29.1, 70.9) (II = 12/24)
CRI/CRI, II (%)	0 (8.3)
PR, n (%)	4 (5.6)
MLFS, n (%)	1 (1.4)
DOR, median (95% CI), mo	8.7 (6.5, 10.4)
DCR, median (95% Cl), mo	7.7 (4.7, 10.9)
$CCyR, n/N^{\dagger}(\%)$	10/31 (32.3)
PFS, median (95% Cl), mo	7.3 (3.7, 9.7)





- CR was achieved by 33.3% of patients with half of CR patients being MRD-.
- 30 (41.7%) patients achieved CR/CRi.
- 29.7% and 45.8% of baseline transfusion-dependent patients converted to RBC and platelet transfusion independence,<sup>‡</sup> respectively.

### **Overall Survival Is Encouraging in TP53-mut AML**



#### **Overall Survival with and Without SCT**

Daver N ..... Sallman D et al., EHA 2022; manuscript under review

Courtesy of David A Sallman, MD

## **Triplet Azacitidine + Venetoclax + Magrolimab**

Parameters		Full Frontline
		N=43
Overall response	CR	21 (49)
	CRI	10 (23)
	CR + CRI	31 (72)
	MLFS	4 (9)
MRD-ve best responses <sup>#</sup>	FCM-CR/CRi	16/28 (67)#
Cytogenetic responses*	CCyR	11/21 (52)*
Time to response	First response	23 [19-105]
(days)	Best response	51 [20-130]
Counts recovery	ANC ≥ 500/cu mm	36 [16-88]
(days)	Platelet ≥ 100 x 10 <sup>9</sup> /L	32 [0-74]
Cycles on therapy		3 [1-17]
Mortality:		
- 4 week		0 (0)
- 8 week		0 (0)
# Amongst CR/CRi patient	s with longitudinally MRD evaluat	le samples * Amo

Adjusted HR for AVM arm for death= 0.41, 95% CI=0.18-0.88

#### Comparison of overall survival (unmatched groups)





Courtesy of David A Sallman, MD

## **ENHANCE Randomized Phase 3 MDS Study**

Figure 4. Study 5F90

Study 5F9009 Schematic



Magrolimab (or saline placebo) dosing:

Cycle 1:

Priming (1 mg/kg) on Days 1 and 4 15 mg/kg on Day 8 30 mg/kg Days 11, 15, 22 Cycle 2: 30 mg/kg Days 1, 8, 15, 22 Cycle 3 and onward: 30 mg/kg Q2W

Azacitidine dosing: 75 mg/m<sup>2</sup> IV or SC Days 1-7 (or Days 1-5 and 8-9) every cycle

Cycles are 28 days long



## **Ongoing Phase 3 Studies with Magro in FL AML**

#### Phase III AZA+Magro vs Investigator Choice in TP53 AML (ENHANCE-2)



#### Phase III AZA+VEN+Magro vs AZA+VEN in older/unfit AML (ENHANCE-3)

### ENHANCE-3: Phase 3 study of 1L unfit All Comer AML with magrolimab +venetoclax+ azacitidine



#### Stratification:

- 1) Appropriateness for non-intensive therapy vs. intensive therapy
- 2) Age <75 vs. ≥75
- 3) Geographic region: US vs. outside the US

#### Endpoints:

- Primary endpoint: OS in TP53 mut AML population appropriate for non-intensive treatment
- First secondary endpoint (alpha controlled): OS in all TP53 mut AML population
- Other key secondary endpoints (alpha controlled): EFS, Transfusion independence, CR/CR<sub>MRD-</sub>, PRO in all TP53 mut AML population

#### Endpoints:

#### Primary endpoints: CR, Overall survival

Secondary endpoints: 1. MRD-ve CR 2.CR+CRh, 3. Duration of CR, 4. Duration of CR+CRh 5. Transfusion independence 6. EFS 6. QOL/PRO



Confidential 1

A 67-year-old man presents with 4% myeloblasts, mild pancytopenia and normal cytogenetics. NGS reveals ASXL1 and RUNX1 mutations. What is your usual front-line systemic treatment? Would you recommend allogeneic HSCT? If you were able to access magrolimab, would you recommend it?

	Preferred treatment	Allogeneic HSCT	Magrolimab				
Dr Garcia- Manero	Observation	Νο	Νο				
Dr Sallman	Azacitidine or observation	Yes	Yes				
Dr Borate	НМА	Yes	Yes				
Dr Brunner	Observation or ESA	Yes	Νο				
Dr DeZern	Azacitidine	Yes	Νο				
Dr Stone	Observation or ESA	Νο	Νο				
Dr Wang	Azacitidine	Yes	Yes				

NGS = next-generation sequencing; HSCT = hematopoietic stem cell transplant; HMA = hypomethylating agent; ESA = erythropoiesis-stimulating agent

## If magrolimab receives FDA approval, do you expect that it will be administered by general medical oncologists in an outpatient setting?

Dr Garcia- Manero	Νο
Dr Sallman	l'm not sure
Dr Borate	l'm not sure
Dr Brunner	l'm not sure
Dr DeZern	No
Dr Stone	Yes
Dr Wang	Yes



Based on available data and your clinical experience, how frequently should hemoglobin level be measured during the first week of treatment with magrolimab/azacitidine?

Dr Garcia- Manero	At least 3 times if not daily
Dr Sallman	2 times day 1 and 4 and day 2 check, minimum 5 times/first week
Dr Borate	Every other day
Dr Brunner	At least once daily
Dr DeZern	Daily
Dr Stone	Daily
Dr Wang	Immediately prior to first and second doses and then immediately following each dose to transfuse to baseline Hgb 9



Based on available data and your clinical experience, how problematic is the acute drop in hemoglobin associated with the administration of magrolimab/azacitidine?

Dr Garcia- Manero	Somewhat problematic	
Dr Sallman	Somewhat problematic	
Dr Borate	Very problematic	
Dr Brunner	Somewhat problematic	
Dr DeZern	Somewhat problematic	
Dr Stone	Somewhat problematic	
Dr Wang	Somewhat problematic	



To approximately how many patients have you administered magrolimab on a clinical trial?



## What has been your global experience with <u>anemia and the need for transfusions</u> in your patients who have received magrolimab?

Dr Garcia- Manero	If one follows mitigating approaches, the drug is safe
Dr Sallman	No issues with transfusion, just more aggressive monitoring/transfusion in first week, subsequent management similar to aza monotherapy
Dr Borate	Patients need frequent transfusions for prolonged periods of time especially if they don't respond
Dr Brunner	It can be a pretty significant issue for some patients, but only in the first week of treatment
Dr DeZern	Need is high after initial dosing, but wanes as older cells are cleared
Dr Stone	Most patients do okay
Dr Wang	Initially first 2 doses there is risk of acute hemolysis but otherwise there is overall much less anemia than venetoclax/azacitidine





## What has been your global experience with <u>neutropenia and thrombocytopenia</u> in your patients who have received magrolimab?

Dr Garcia- Manero	No different than with other HMA-based doublets
Dr Sallman	Overall mild increase in neutropenia, some patients with recurrent cytopenias on chronic therapy will need dose adjustment
Dr Borate	Some patients appear to have persistent thrombocytopenia
Dr Brunner	It does not seem to be an issue compared to HMA alone
Dr DeZern	No different than with other HMA-based doublets
Dr Stone	No different than with other HMA-based doublets
Dr Wang	No different than with other HMA-based doublets

HMA = hypomethylating agent



## What other toxicities or tolerability issues have you observed in your patients who have received magrolimab?

Dr Garcia- Manero	None	
Dr Sallman	Infusion reactions	
Dr Borate	Infusion reactions; LFT abnormalities	
Dr Brunner	Infusion reactions	
Dr DeZern	Fevers, feeling fluish	
Dr Stone	Infusion reactions	
Dr Wang	None	

LFT = liver function test



What would you predict to be the outcome of a Phase III randomized trial evaluating <u>magrolimab/azacitidine versus azacitidine alone</u> as first-line treatment for higher-risk MDS?

Would your response change if the trial participants all had TP53 mutations?

	Trial outcome	TP53
Dr Garcia- Manero	Magrolimab/azacitidine is more efficacious	Νο
Dr Sallman	Magrolimab/azacitidine is more efficacious	Νο
Dr Borate	Efficacy is about the same with both regimens	Yes
Dr Brunner	Magrolimab/azacitidine is more efficacious	Νο
Dr DeZern	Efficacy is about the same with both regimens	Νο
Dr Stone	Magrolimab/azacitidine is more efficacious	Yes
Dr Wang	Magrolimab/azacitidine is more efficacious	Yes

### Agenda

**MODULE 1: Biology of Acute Myeloid Leukemia/Myelodysplastic Syndromes** 

**MODULE 2: Assessment of Risk Status** 

**MODULE 3: Oral Hypomethylating Agents (HMAs)** 

**MODULE 4: HMA/Venetoclax; Other Combinations** 

MODULE 5: Magrolimab/TP53

**MODULE 6: Targeted Treatment** 



## **Targeted options in MDS**

- IDH-2 (5-10%): enasidenib, venetoclax
- IDH-1 (5%): ivosidenib, venetoclax
- Flt-3 (15%): multiple agents
- TP53 (10%): anti-CD47 ?
- NPM1 (1%): ara-C based
- Splicing: IRAK4, H3BIO, Clk

## Case Presentation – Dr Garcia-Manero

A 78-year-old man presents with a history of cytopenia. Bone marrow exam reveals 15% blasts, cytogenetic analysis shows trisomy 8 and NGS indicates TET2 and DNMT3A mutations.

The patient receives 16 cycles of oral decitabine/cedazuridine and becomes cytopenic after achieving CR. Repeat marrow exam still shows 15% blasts, trisomy 8 but NGS results now reveal a new IDH2 mutation. You discuss treatment with IDH2 inhibitor in a clinical trial for HMA failure.

## **Case Presentation – Dr Sallman**

84 yo male with PMH of RAEB-2 MDS presents for relapsed disease after 12 cycles of single agent azacitidine for which he obtained a CR. The patient is currently RBC transfusion dependent with ANC of 300 and platelets of 35,000 and a blast count of 12%. Although NGS was not obtained at baseline, NGS was performed at time of relapse and showed an *IDH2* mutation. The patient was treated with off-label enasidenib.



## **Practice Changing Potential**

Multiple HMA-based doublets currently in phase 3 clinical trials

- VERONA: AZA +/- VEN in ND HR-MDS (excludes therapy related)
- ENHANCE: AZA +/- Magrolimab in HR-MDS
- STIMULUS-MDS1: HMA +/- sabatolimab in HR-MDS
- SELECT MDS-1: AZA +/- tamibarotene in RARA-positive MDS
- Targeted Interventions for molecular subsets
  - IDH1/IDH2inh similar (if not more) activity than AML; TP53? Splicing?
- Improving Outcomes with HSCT: total therapy
- Further evaluation of mechanisms of synergy and resistance with combination therapies and other novel strategies
- Evaluation of MRD by serial high sensitivity NGS or duplex sequencing
- What to do for HMA failure and how will frontline landscape impact the R/R setting?

## Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology A Multitumor CME/MOC-Accredited Live Webinar Series

## Melanoma and Nonmelanoma Skin Cancers

Thursday, July 13, 2023 5:00 PM – 6:00 PM ET

> Faculty Omid Hamid, MD Evan J Lipson, MD

Moderator Neil Love, MD


## Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

