Exploring Current Considerations and Promising Investigational Approaches for Patients with Myelodysplastic Syndromes

A CME/MOC-Accredited Virtual Event

Thursday, September 8, 2022

5:00 PM – 6:00 PM ET

Faculty

Guillermo Garcia-Manero, MD
Gail J Roboz, MD
David Sallman, MD

Moderator

Neil Love, MD

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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

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

Gail J Roboz, MD
Director, Clinical and Translational Leukemia Programs
Professor of Medicine
Weill Cornell Medical College
NewYork-Presbyterian Hospital
New York, New York

MODERATOR
Neil Love, MD
Research To Practice

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This activity will also be featured as an "On Demand" session as part of the Society of Hematologic Oncology 2022 Annual Meeting.

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Management of MDS: Agenda
Where We Are, Where We're Headed

PROLOGUE: A Vision for the Future

MODULE 1: Classification and prognosis of MDS

MODULE 2: Current management of lower-risk MDS

MODULE 3: Current management of higher-risk MDS

MODULE 4: MDS-AML continuum and overlap – Venetoclax, other targeted therapy

MODULE 5: Immune checkpoint inhibitors – Magrolimab, sabatolimab

MODULE 6: Appendix

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Accreditation Information

Target Audience

This activity is intended for hematologists, hematology-oncology fellows, medical oncologists, radiation oncologists and other healthcare providers involved in the treatment of myelodysplastic syndromes.

Educational Objectives

Upon completion of this activity, participants should be able to

- Recognize the value of molecular testing for patients with myelodysplastic syndromes (MDS), and determine how various genetic alterations may affect MDS classification and risk assessment.
- Evaluate the importance of age, performance status, cytogenetic profile and other patient- and disease-related factors in the selection and sequencing of therapy for lower- and higher-risk MDS.
- Recognize the FDA-approved indication for oral hypomethylating agent therapy for intermediate- and high-risk MDS, and identify patients for whom this novel approach may be appropriate.
- Describe the biologic rationale for and available research findings with Bcl-2-targeted therapy for patients with high-risk MDS, and appraise the potential role of this strategy in current and future clinical care.
- Develop an understanding of the mechanisms of action of and available data with investigational therapeutic approaches for higher-risk MDS in order to prepare for their potential availability in routine practice.
- Implement a plan to manage the side effects associated with approved and investigational therapies for MDS to support quality of life and continuation of treatment.
- Recall the design of ongoing clinical trials for low- and high-risk MDS, and counsel appropriate patients about the potential benefits of participation.

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Accreditation Information

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute, Inc. and Research To Practice. Medical Learning Institute, Inc. is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

Medical Learning Institute, Inc. (MLI) designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Statement

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

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Support Statement

This program has been supported by an independent educational grant from Gilead Sciences, Inc.

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Dr Love — Disclosures

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Dr Garcia-Manero — Disclosures

No relevant conflicts of interest to disclose

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Dr Roboz — Disclosures

Consulting Agreements	AbbVie Inc, Agios Pharmaceuticals Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, bluebird bio, Blueprint Medicines, Bristol-Myers Squibb Company, Catamaran Bio, Celgene Corporation, GlaxoSmithKline, Helsinn Healthcare SA, Janssen Biotech Inc, Jasper Therapeutics Inc, Jazz Pharmaceuticals Inc, Mesoblast, Novartis, Pfizer Inc, Roche Laboratories Inc, Syndax Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc (IRC Chair)
Research Support	Janssen Biotech Inc

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Dr Sallman — Disclosures

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This educational activity may contain discussions of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this CE activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the CE activity are those of the presenters and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this CE activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this CE activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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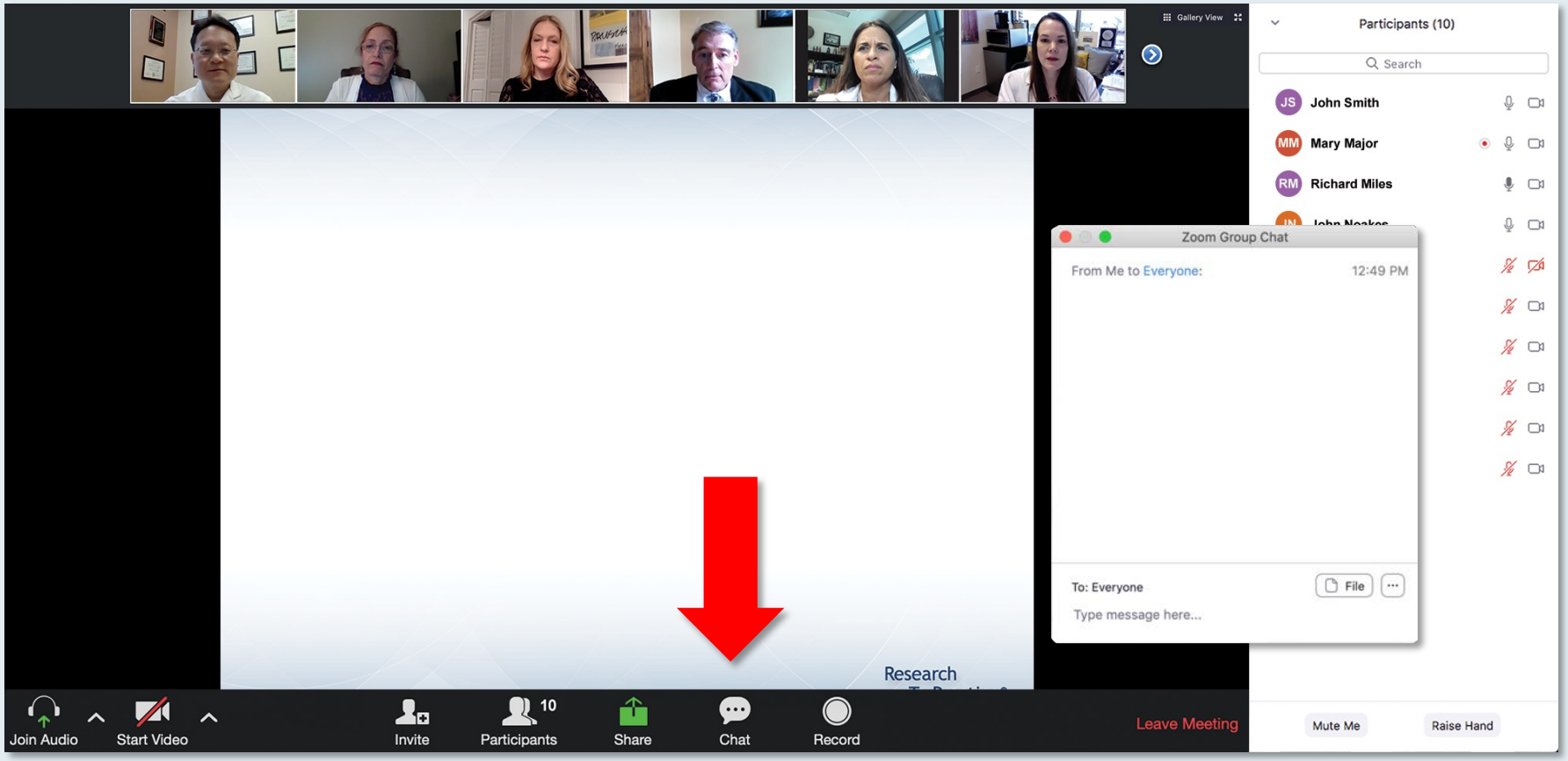

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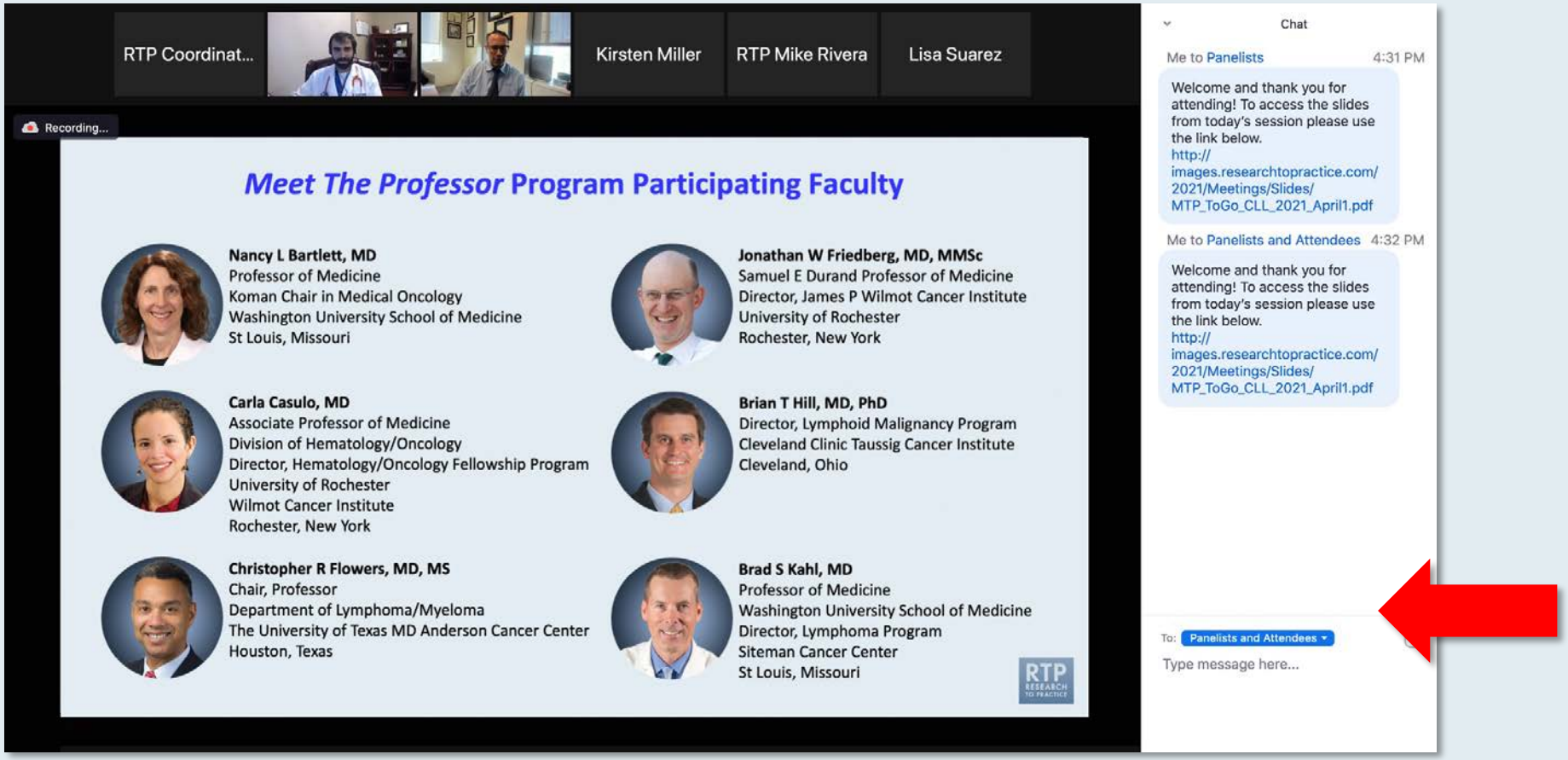

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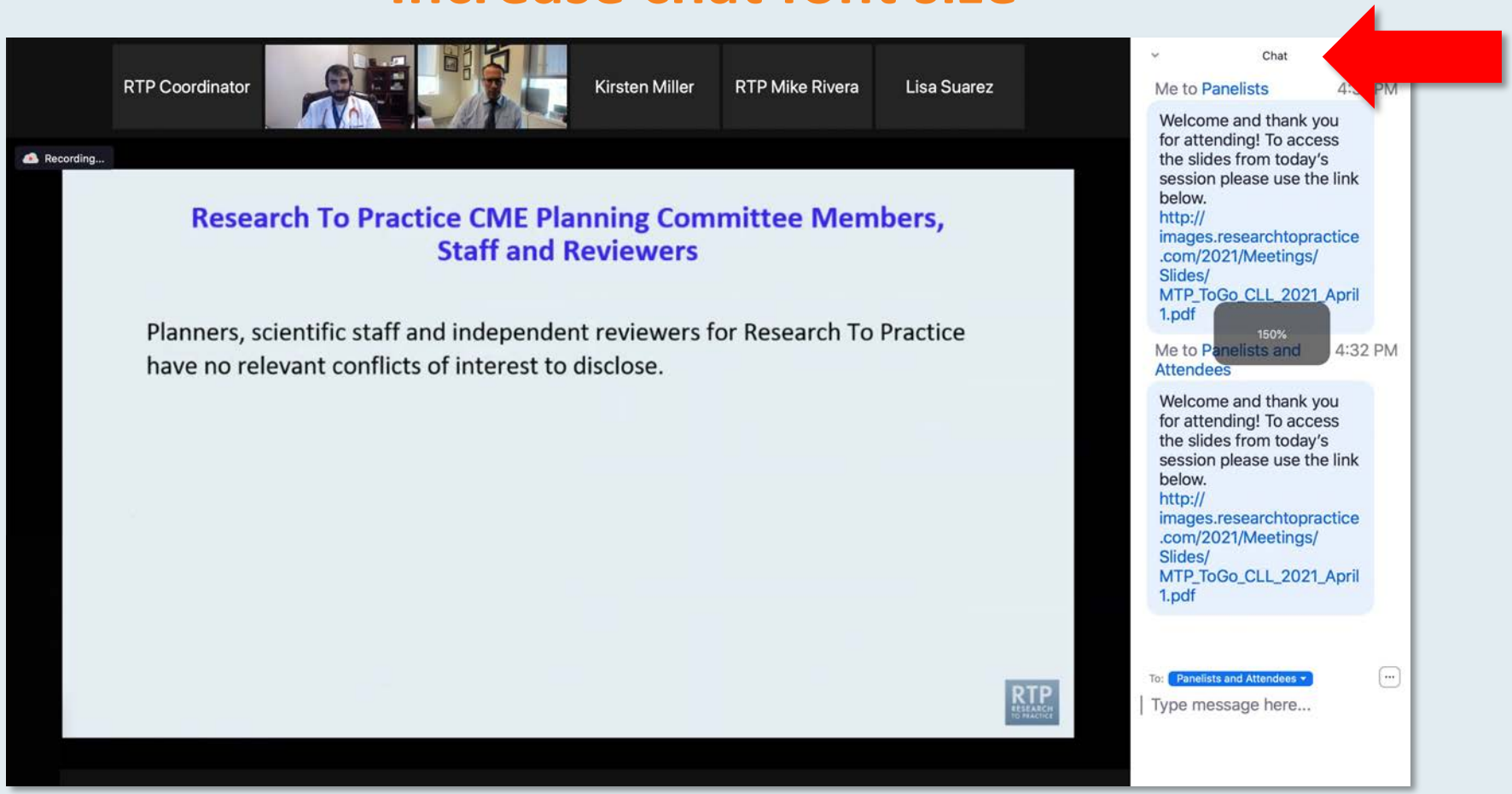

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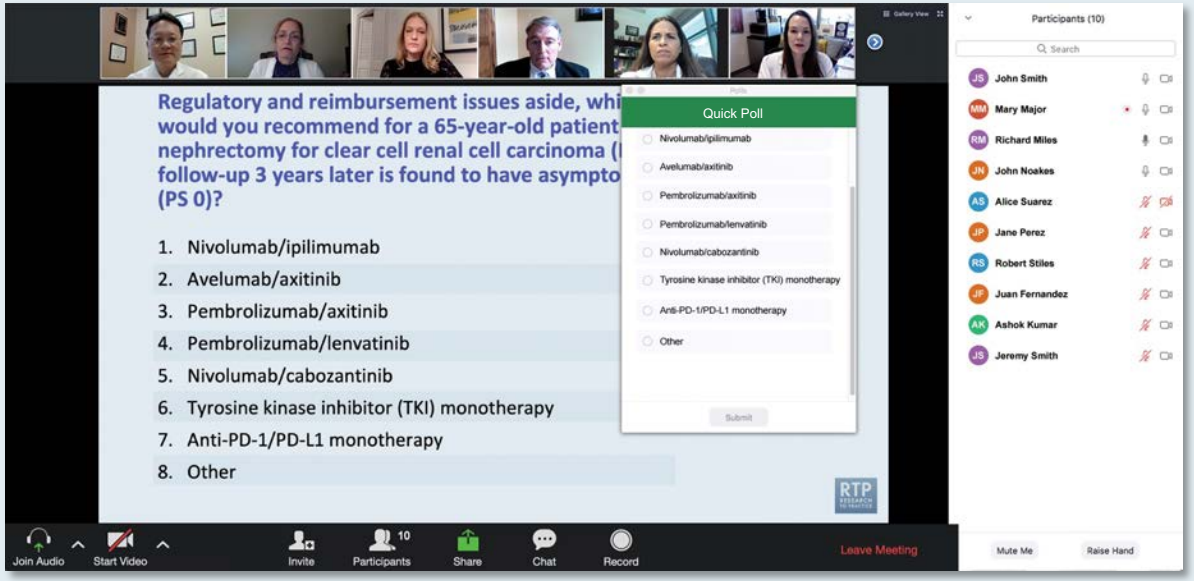

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Key Presentations on Acute Myeloid Leukemia and Myelodysplastic Syndromes from ASH 2021

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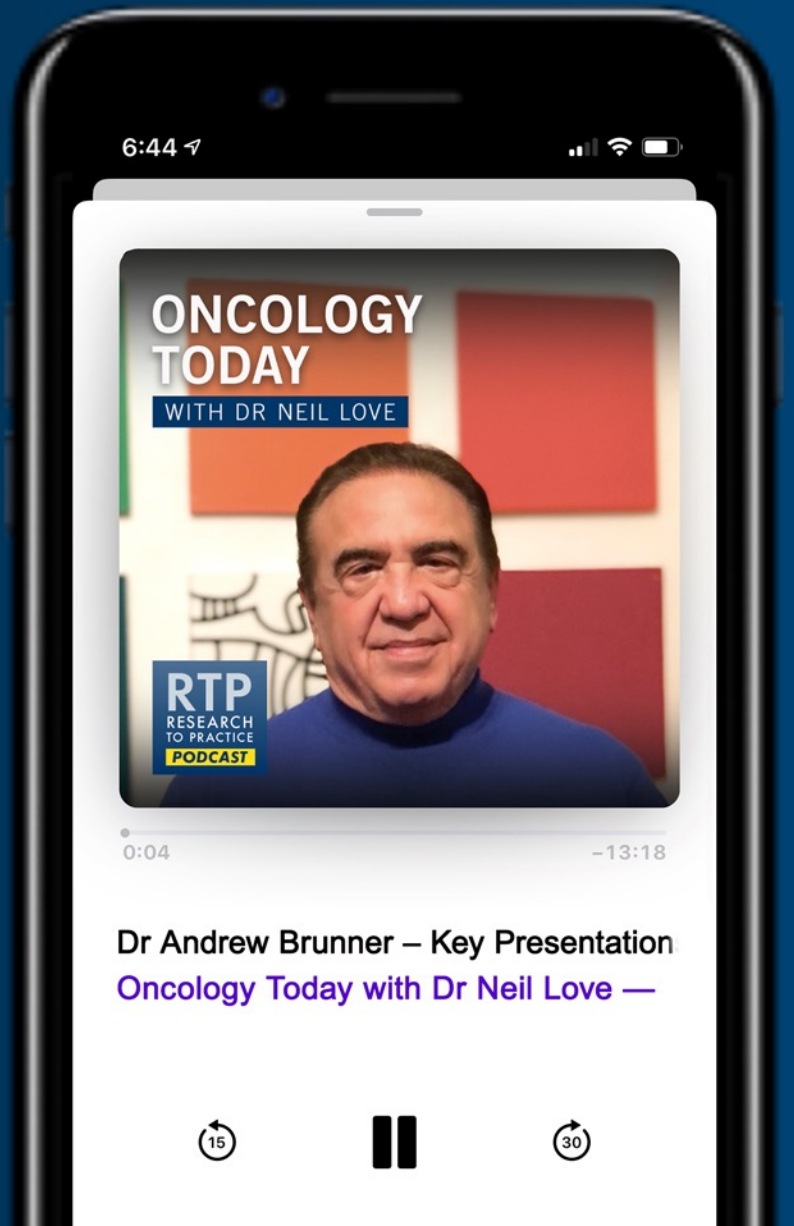

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Faculty

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Sonali M Smith, MD
Jason Westin, MD, MS

Moderator

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Oncology Today™ with Dr Neil Love — Management of Endometrial Cancer

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The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

Saturday, October 22, 2022

7:30 AM – 5:30 PM ET

JW Marriott Orlando| Orlando, Florida

Faculty

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Matthew P Goetz, MD
Ian E Krop, MD, PhD
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Prof Georgina Long, AO, BSc, PhD, MBBS
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Thank you for joining us!

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

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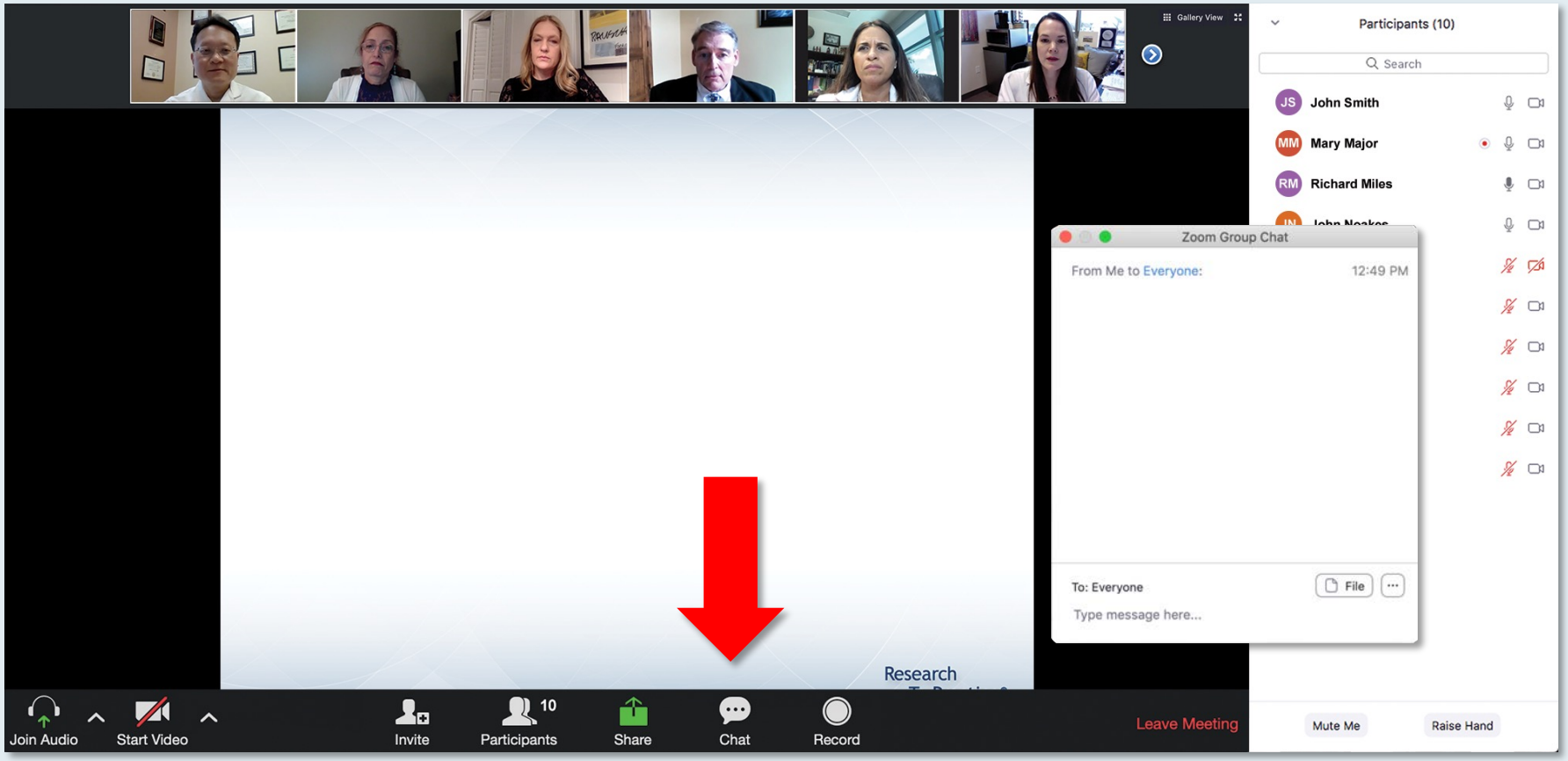

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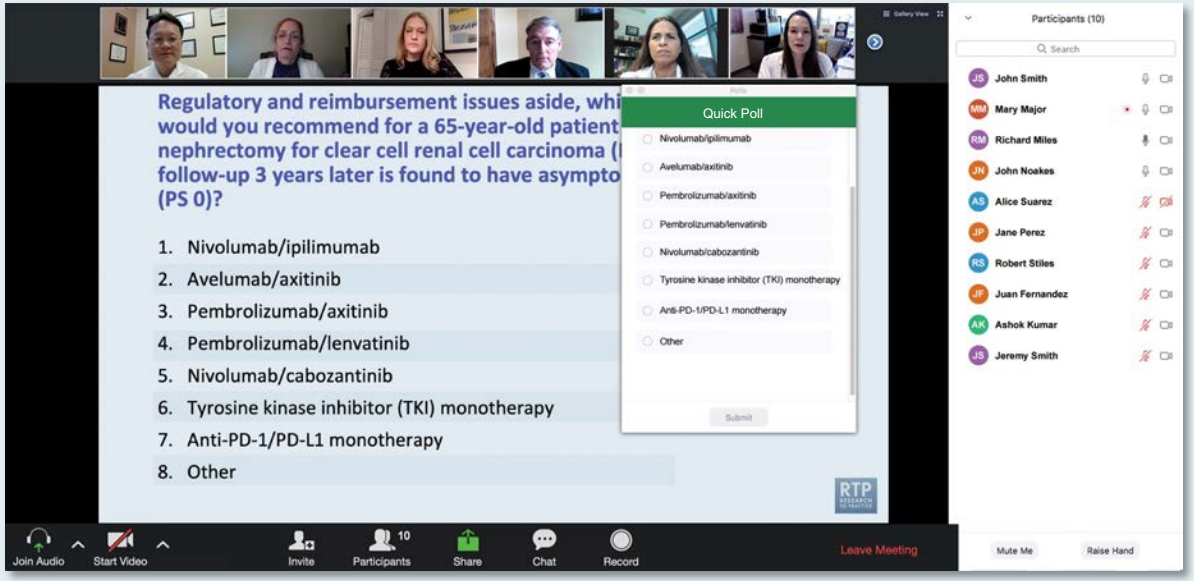

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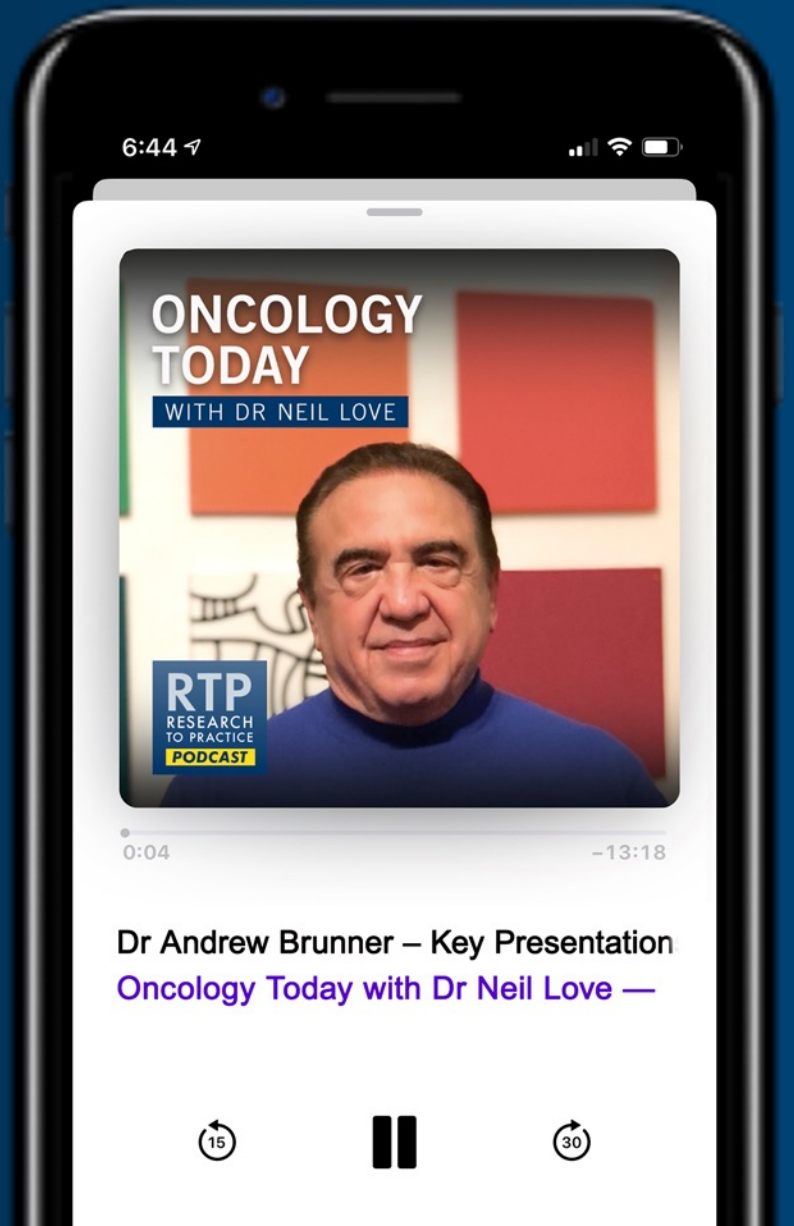

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Management of MDS: Agenda
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Clinical Cases

Dr Sallman: 60-year-old male with no PMH presents for evaluation of high-risk, complex-karyotype MDS

Dr Roboz: 55-year-old generally healthy man diagnosed with CMML in 2020

Dr Sallman: 68-year-old female with transfusion-dependent anemia with MDS-RS and an SF3B1 mutation

Dr Roboz: 73-year-old man initially diagnosed with MDS at age 60

Dr Garcia-Manero: 82-year-old woman diagnosed with RARS MDS and an SF3B1 mutation

Dr Garcia-Manero: 59-year-old woman with MDS and an NPM1 mutation

Dr Sallman: 78-year-old male with RAEB-2 MDS with trisomy 8 and ASXL1 and U2AF1 mutations

Dr Garcia-Manero: 79-year-old man with MDS with complex cytogenetics and TET2 and DNMT3A mutations

Dr Roboz: 74-year-woman with a history of breast cancer diagnosed with MDS with complex karyotype

Accreditation Information

Target Audience

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Participation information will be shared through the ACCME's Program and Activity Reporting System (PARS).

Support Statement

This program has been supported by an independent educational grant from Gilead Sciences, Inc.

Dr Garcia-Manero — Disclosures

No relevant conflicts of interest to disclose

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Dr Roboz — Disclosures

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Research Support	Janssen Biotech Inc

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Dr Sallman — Disclosures

Advisory Committee	AvenCell Therapeutics Inc, bluebird bio, Bristol-Myers Squibb Company, Intellia Therapeutics, Jasper Therapeutics Inc, Kite, A Gilead Company, Novartis, Servier Pharmaceuticals LLC, Shattuck Labs, Syndax Pharmaceuticals Inc
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Management of MDS: Agenda
Where We Are, Where We're Headed

PROLOGUE: A Vision for the Future

MODULE 1: Classification and prognosis of MDS

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MODULE 6: Appendix

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Dr Sallman
HR-MDS (hypothetical patient)

- 60 yo male with no PMH presents for evaluation of a very high risk, complex karyotype MDS with 12% blasts and pancytopenia. NGS shows *TP53* hot spot mutation with a VAF of 80%. The patient is highly interested in clinical trials.

- What options could be considered?

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Critical Importance in Evaluating HR-MDS Patients for Clinical Trial

- P3 VERONA Study (AZA+VEN), 500 pts, CR and OS
- P3 ENHANCE Study (AZA+MAGRO), 520 pts, CR and OS
- P3 STIMULUS-MDS2 Study (Aza+Saba), allows CMML-2, 500 pts, OS
- P3 SY-1425 + Aza for RARA-positive MDS patients, 190 pts, CR

- Additional Triplet Combinations on Top of Aza Backbone Are Planned

Our patient

- The patient was started on 7-day azacitidine + magrolimab. Patient was transfused to > 9gm/dL prior to day 1 of therapy, but had a 2gm/dL drop on day 1 and received an additional 2U of PRBC on day 1. The patient had no significant drop after day 4 of treatment.

- After 2 cycles BM blasts were down to 4% with a partial cytogenetic remission and repeat NGS showing TP53 VAF of 10%. Patient has an 8/8 MUD available

- Would you proceed with allo-HSCT vs continue on trial at this time?

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Our patient

- Patient was continued for 2 more cycles at which point patient had achieved CR, CCR, and serial NGS was negative. Patient was bridged to allo-HSCT and is currently in remission post-transplant.

Select Key Issues in the MDS Management Paradigm

- Doublet or triplet combinations using hypomethylating agent (HMA) backbones
- Selection of agents based on molecular profiling and definition of patient-centric goals of therapy
  - HMA/venetoclax doublet with or without magrolimab as pretransplant regimen
  - HMA combinations with limited additive toxicity for older or frail patients not fit for transplant (checkpoint inhibitors)
- Integration of molecular responses into the treatment paradigm; MRD status possibly determining timing of transplant
- MRD status as a basis for maintenance therapy after allogeneic stem cell transplant?

Meet The Professor

Optimizing the Management of HER2-Positive Breast Cancer

Thursday, September 1, 2022
5:00 PM – 6:00 PM ET

Mark D Pegram, MD
Susy Yuan-Huey Hung Endowed Professor of Oncology
Director, Clinical and Translational Research Unit
Associate Dean for Clinical Research Quality
Stanford University School of Medicine
Associate Director for Clinical Research
Stanford Comprehensive Cancer Institute
Stanford, California

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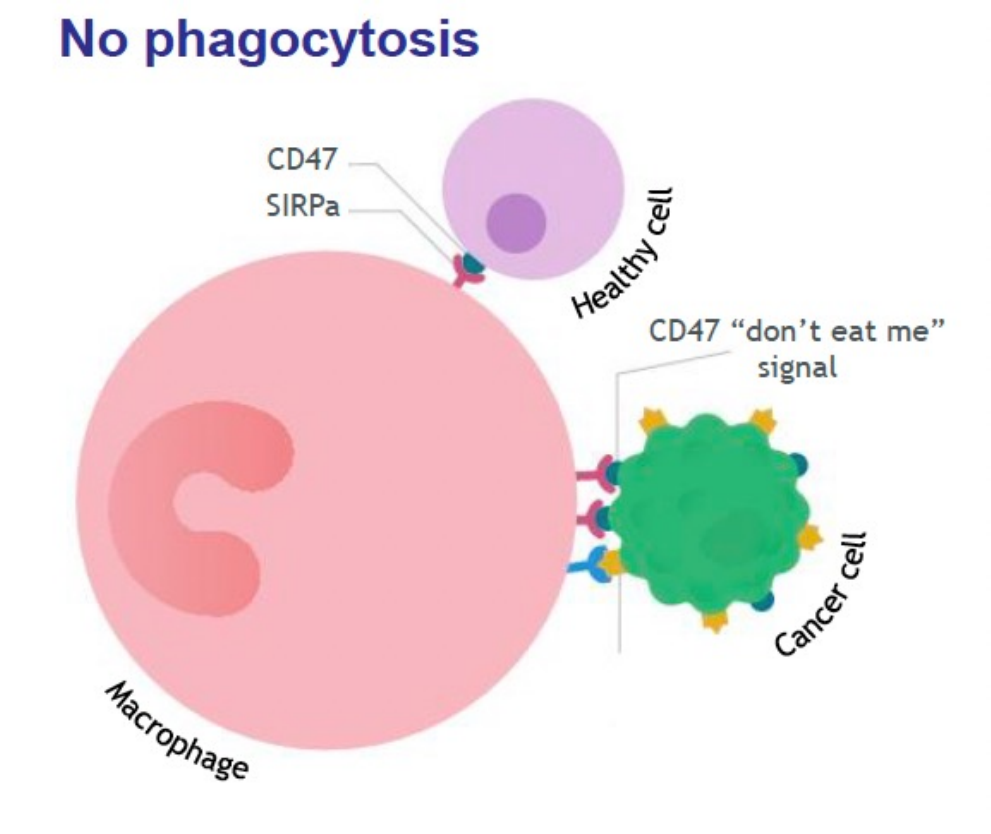
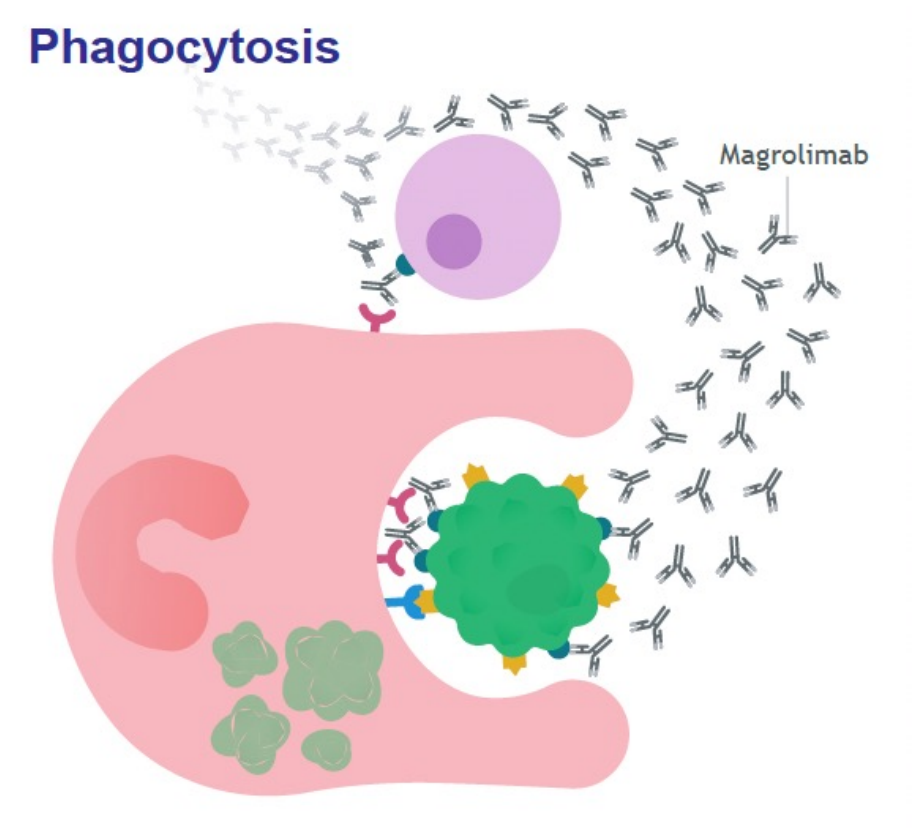
Proc Natl Acad Sci U S A 2021 July 20;118(29):e2026849118.

Combining CD47 blockade with trastuzumab eliminates HER2-positive breast cancer cells and overcomes trastuzumab tolerance

Rosalynd Upton[a], Allison Banuelos[a], Dongdong Feng[a], Tanuka Biswas[a], Kevin Kao[a], Kelly McKenna[a], Stephen Willingham[a], Po Yi Ho[a], Benyamin Rosental[b], Michal Caspi Tal[a], Tal Raveh[a], Jens-Peter Volkmer[a], Mark D. Pegram[c,1,2], and Irving L. Weissman[a,1,2]

Magrolimab/Azacitidine Mechanism of Action

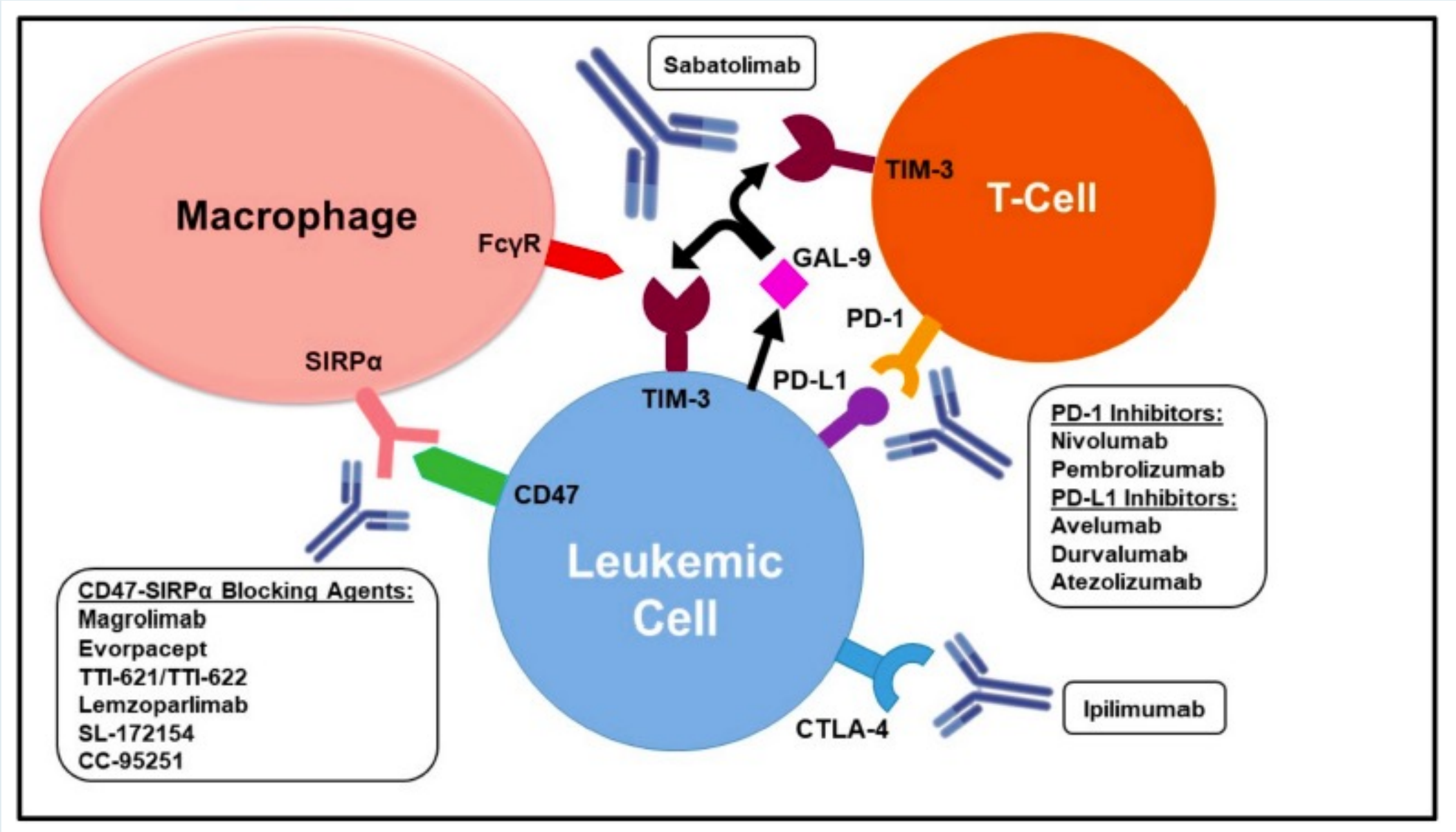




- Magrolimab is a first-in-class monoclonal antibody that blocks the macrophage inhibitory immune checkpoint cluster of differentiation CD47, a "do not eat me" signal overexpressed on tumor cells.
- Binding of magrolimab to CD47 leads to phagocytosis of tumor cells.
- Azacitidine increases expression of prophagocytic "eat me" signals, facilitating synergy with magrolimab.

Garcia-Manero G et al. ASCO 2021;Abstract TPS7055.

Mechanisms of Immune Evasion in MDS and AML



Abaza Y et al. *Cells* 2022;11:249.

Review Article

SOHO State of the Art & Next Questions: Myelodysplastic Syndromes: A New Decade

Virginia O. Volpe,[1] Guillermo Garcia-Manero,[2] Rami S. Komrokji[1]

Clinical Lymphoma, Myeloma and Leukemia 2021

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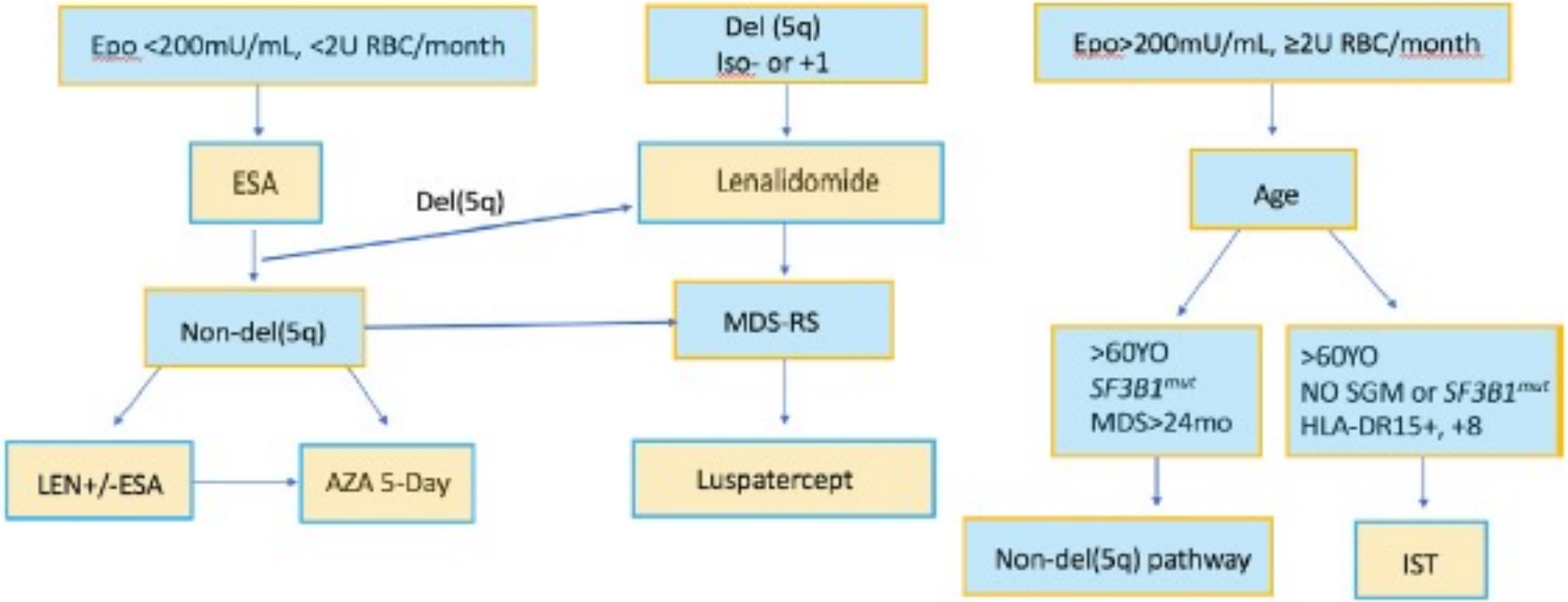
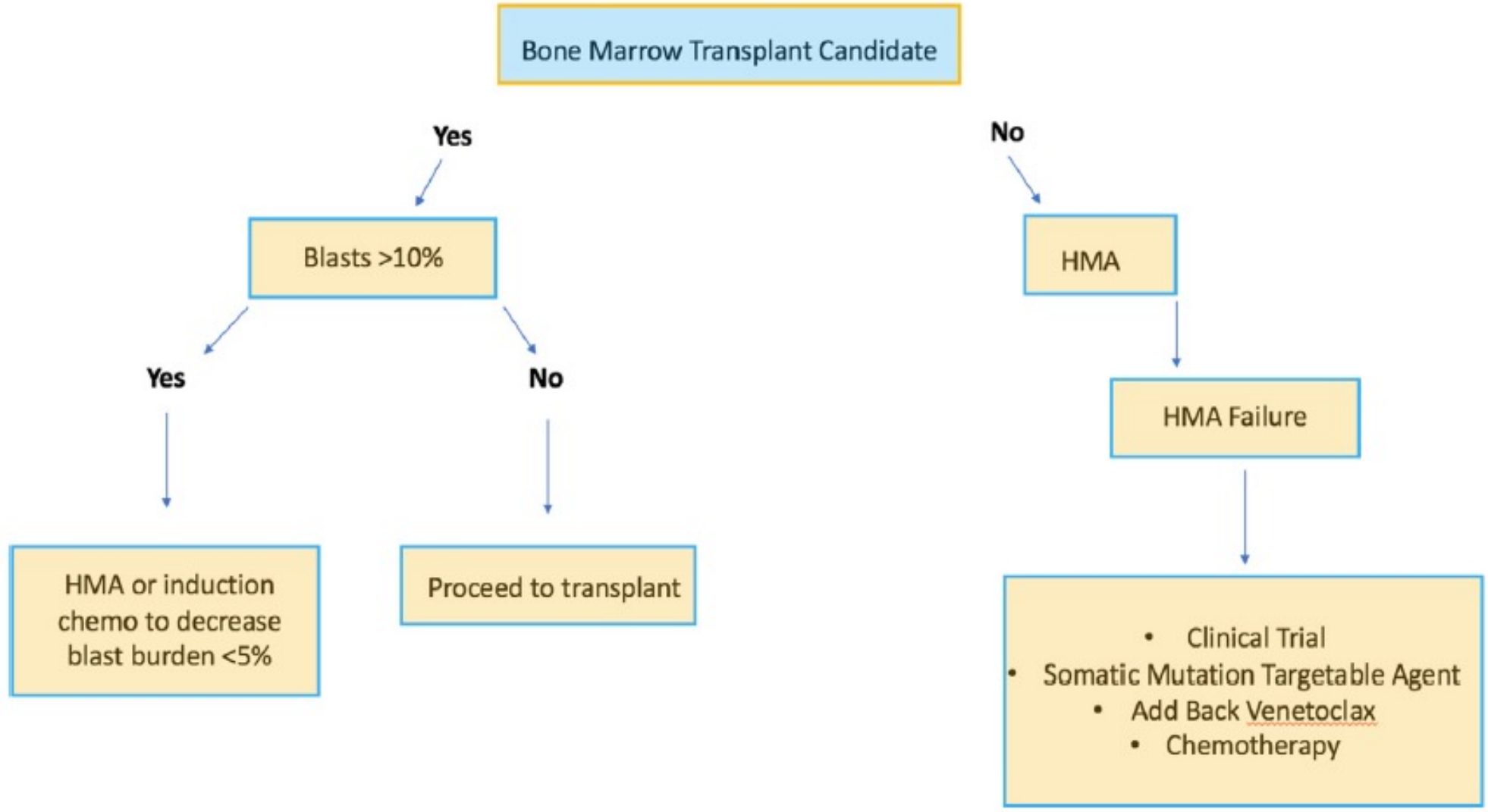
Management of Low-Risk MDS



EPO = erythropoietin; MDS-RS = myelodysplastic syndrome-ringed sideroblasts; IST = immunosuppressive therapy

Volpe VO et al. *Clin Lymphoma Myeloma Leuk* 2021;22:1-16.

Management of High-Risk MDS



Volpe VO et al. *Clin Lymphoma Myeloma Leuk* 2021;22:1-16.

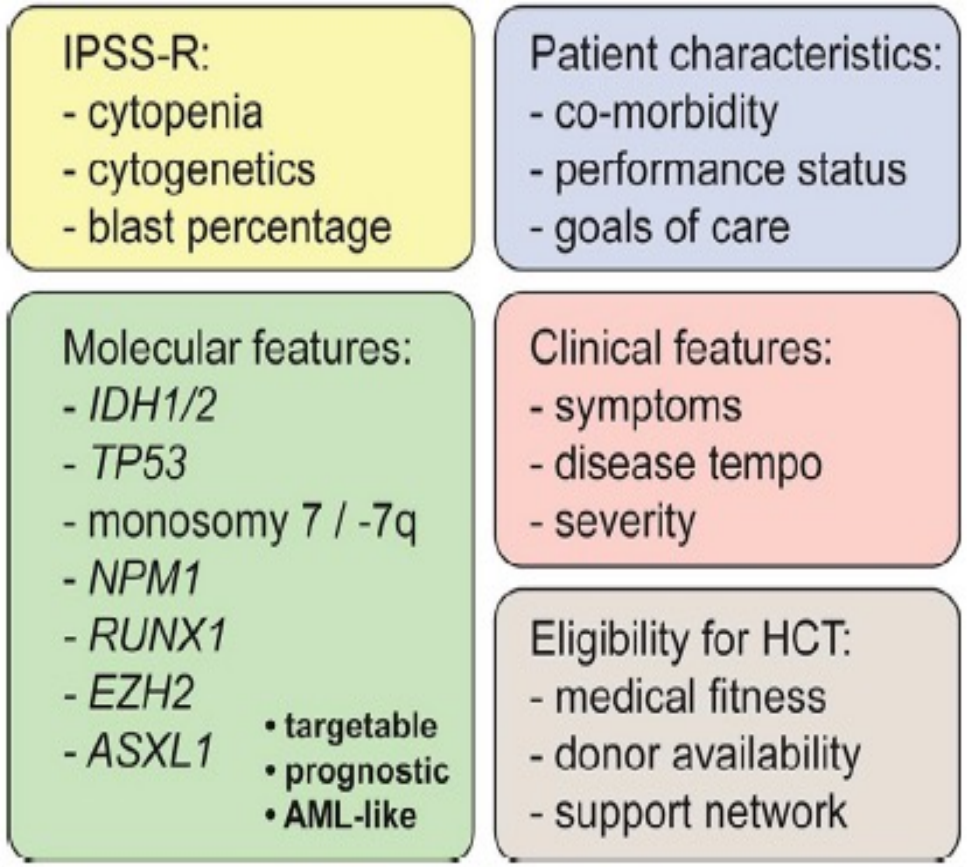
Review Article

SOHO State of the Art and Next Questions: Treatment of Higher-Risk Myelodysplastic Syndromes

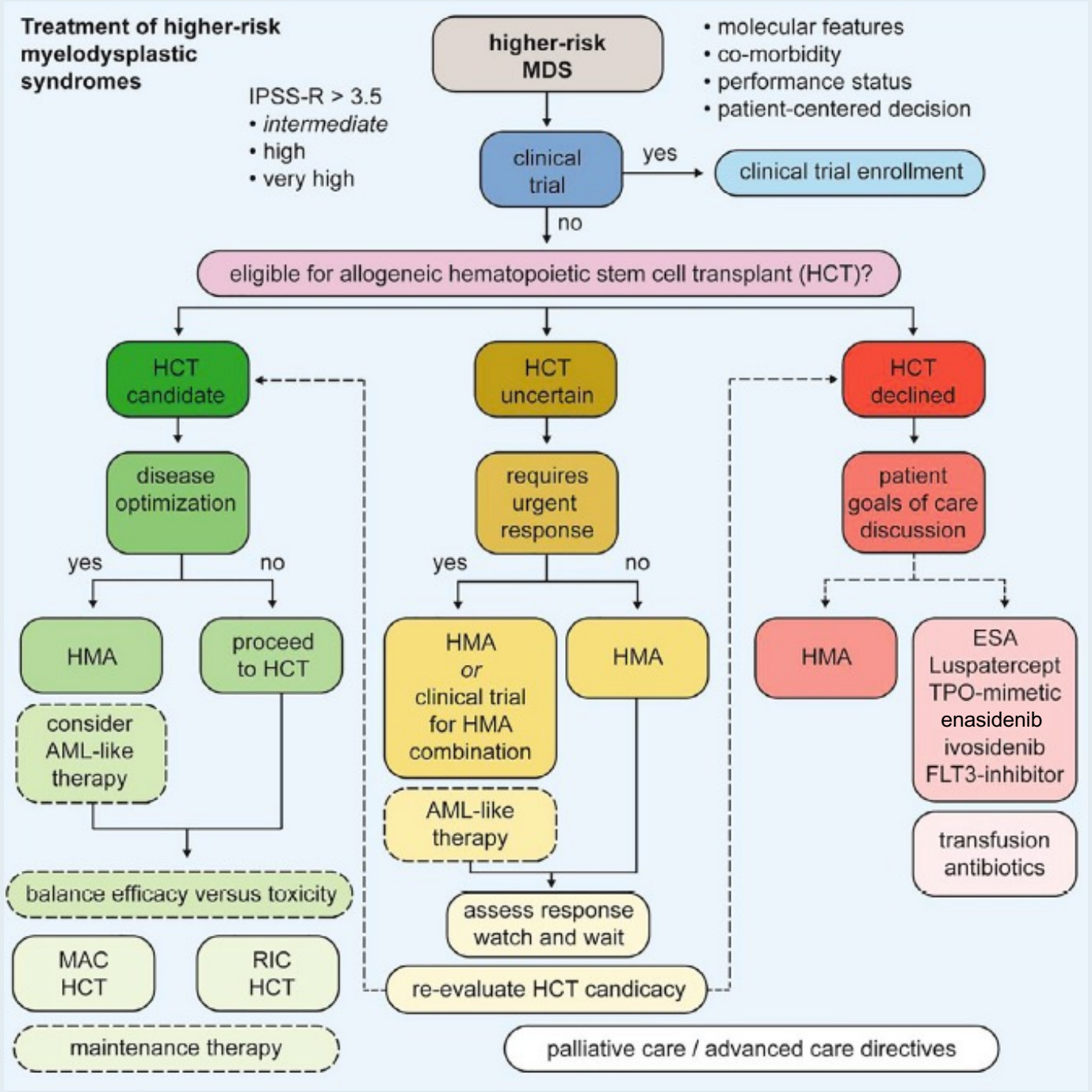
Brandon J. Aubrey, Andrew M. Brunner

Clinical Lymphoma, Myeloma and Leukemia 2022

Assessing Patient Risk and Goals of Care

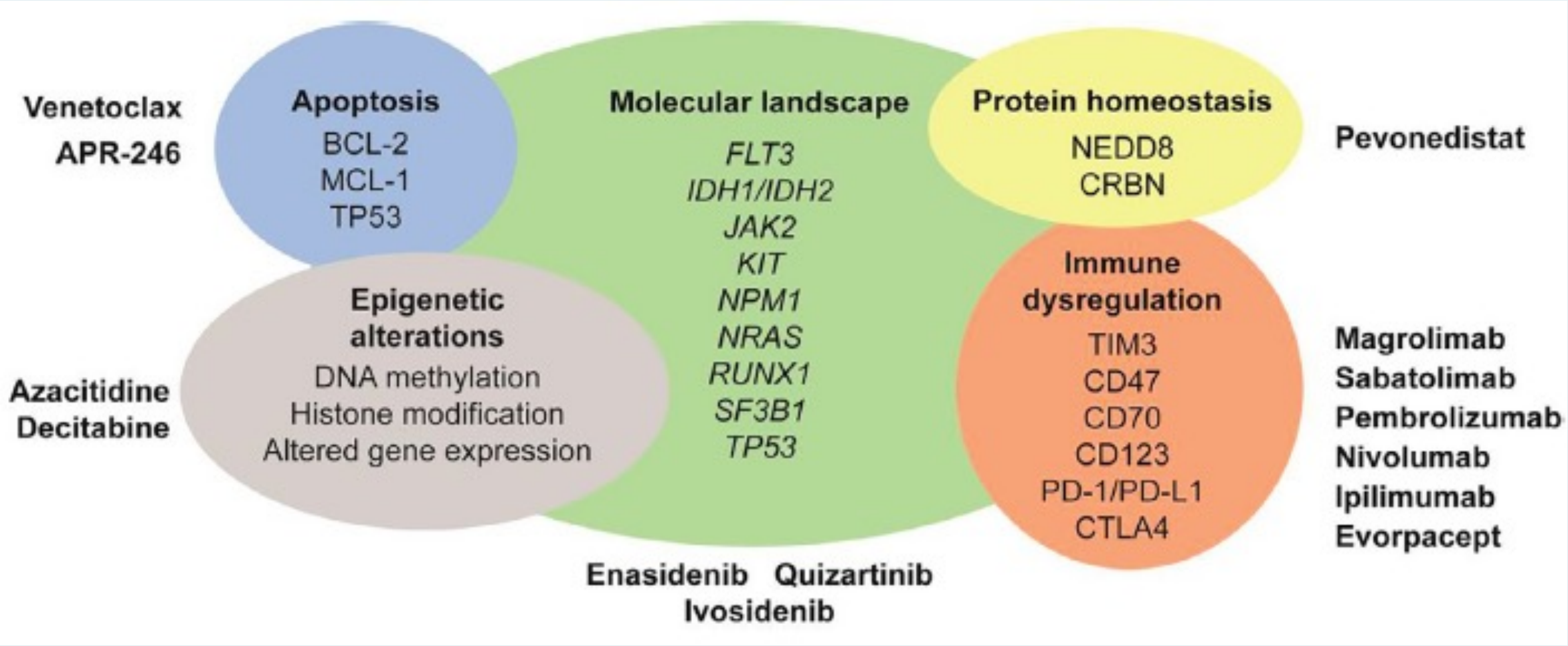


Aubrey BJ et al. *Clin Lymphoma Myeloma Leuk* 2022;[Online ahead of print].



Aubrey BJ et al. *Clin Lymphoma Myeloma Leuk* 2022;[Online ahead of print].

Future Directions for the Treatment of Higher-Risk MDS



Aubrey BJ et al. *Clin Lymphoma Myeloma Leuk* 2022;[Online ahead of print].

Dr Roboz – CMML Case

55 y/o generally healthy man diagnosed with CMML 2020 after presenting with anemia and leukocytosis, marrow with 14% blasts, normal cytogenetics, and TET2, U2AF1, DNMT3 mutations. Treated with oral decitabine/cedazuridine for 2 cycles with CR, taken to allogeneic stem cell transplant Haplocord SCT, conditioned with Fludarabine /Melphalan /TBI 400cGy. GVHD ppx: ATG, MMF, tacrolimus in Aug 2021 complicated by sepsis, neutropenic infections and grade 2 GI GVHD eventually with resolution and CR. Relapsed with AML in July 2022, now in CR after salvage with CLIA (cladribine, cytarabine, idarubicin) + venetoclax.

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NEJM Evidence

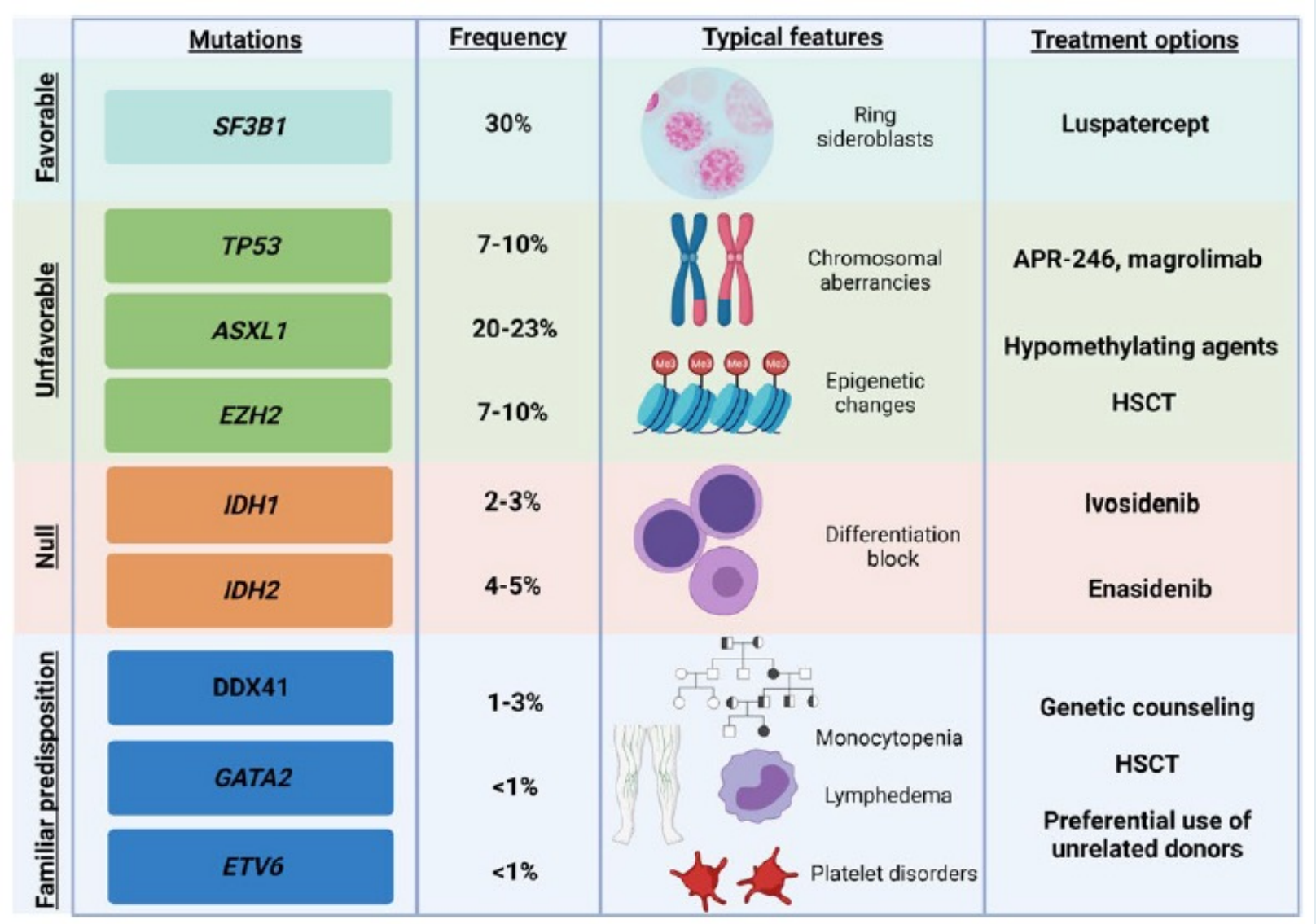
Published June 12, 2022
NEJM Evid 2022; 1 (7)
DOI: 10.1056/EVIDoa2200008

ORIGINAL ARTICLE

Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

Elsa Bernard, Ph.D.,[1] Heinz Tuechler, Peter L. Greenberg, M.D.,[2] Robert P. Hasserjian, M.D.,[3] Juan E. Arango Ossa, M.S.,[1] Yasuhito Nannya, M.D., Ph.D.,[4,5] Sean M. Devlin, Ph.D.,[1] Maria Creignou, M.D.,[6] Philippe Pinel, M.S.,[1] Lily Monnier, M.S.,[1] Gunes Gundem, Ph.D.,[1] Juan S. Medina-Martinez, M.S.,[1] Dylan Domenico, B.S.,[1] Martin Jädersten, M.D., Ph.D.,[6] Ulrich Germing, M.D.,[7] Guillermo Sanz, M.D., Ph.D.,[8,9,10] Arjan A. van de Loosdrecht, M.D., Ph.D.,[11] Olivier Kosmider, M.D., Ph.D.,[12] Matilde Y. Follo, Ph.D.,[13] Felicitas Thol, M.D.,[14] Lurdes Zamora, Ph.D.,[15] Ronald F. Pinheiro, Ph.D.,[16] Andrea Pellagatti, Ph.D.,[17] Harold K. Elias, M.D.,[18] Detlef Haase, M.D., Ph.D.,[19] Christina Ganster, Ph.D.,[19] Lionel Ades, M.D., Ph.D.,[20] Magnus Tobiasson, M.D., Ph.D.,[6] Laura Palomo, Ph.D.,[21] Matteo Giovanni Della Porta, M.D.,[22] Akifumi Takaori-Kondo, M.D., Ph.D.,[23] Takayuki Ishikawa, M.D., Ph.D.,[24] Shigeru Chiba, M.D., Ph.D.,[25] Senji Kasahara, M.D., Ph.D.,[26] Yasushi Miyazaki, M.D., Ph.D.,[27] Agnes Viale, Ph.D.,[28] Kety Huberman, B.S.,[28] Pierre Fenaux, M.D., Ph.D.,[20] Monika Belickova, Ph.D.,[29] Michael R. Savona, M.D.,[30] Virginia M. Klimek, M.D.,[18] Fabio P. S. Santos, M.D., Ph.D.,[31] Jacqueline Boultwood, Ph.D.,[17] Ioannis Kotsianidis, M.D., Ph.D.,[32] Valeria Santini, M.D.,[33] Francesc Solé, Ph.D.,[21] Uwe Platzbecker, M.D.,[34] Michael Heuser, M.D.,[14] Peter Valent, M.D.,[35,36] Kazuma Ohyashiki, M.D., Ph.D.,[37] Carlo Finelli, M.D.,[38] Maria Teresa Voso, M.D.,[39] Lee-Yung Shih, M.S.,[40] Michaela Fontenay, M.D., Ph.D.,[12] Joop H. Jansen, Ph.D.,[41] José Cervera, M.D., Ph.D.,[42] Norbert Gattermann, M.D.,[7] Benjamin L. Ebert, M.D., Ph.D.,[43] Rafael Bejar, M.D., Ph.D.,[44] Luca Malcovati, M.D.,[45] Mario Cazzola, M.D.,[45] Seishi Ogawa, M.D., Ph.D.,[4,46,47] Eva Hellström-Lindberg, M.D., Ph.D.,[6] and Elli Papaemmanuil, Ph.D.[1]

Exemplificative List of Genes Recurrently Mutated in MDS: Impact on Clinical Features and Treatment Options



Voso MT, Gurnari C. ASH 2021 Education Program.

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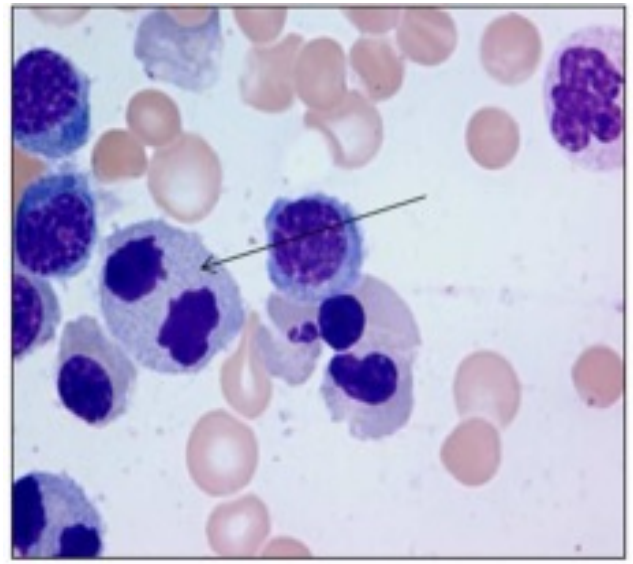
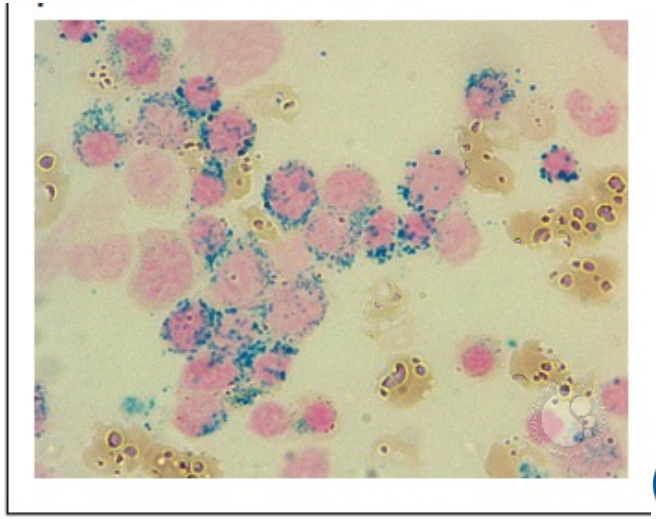
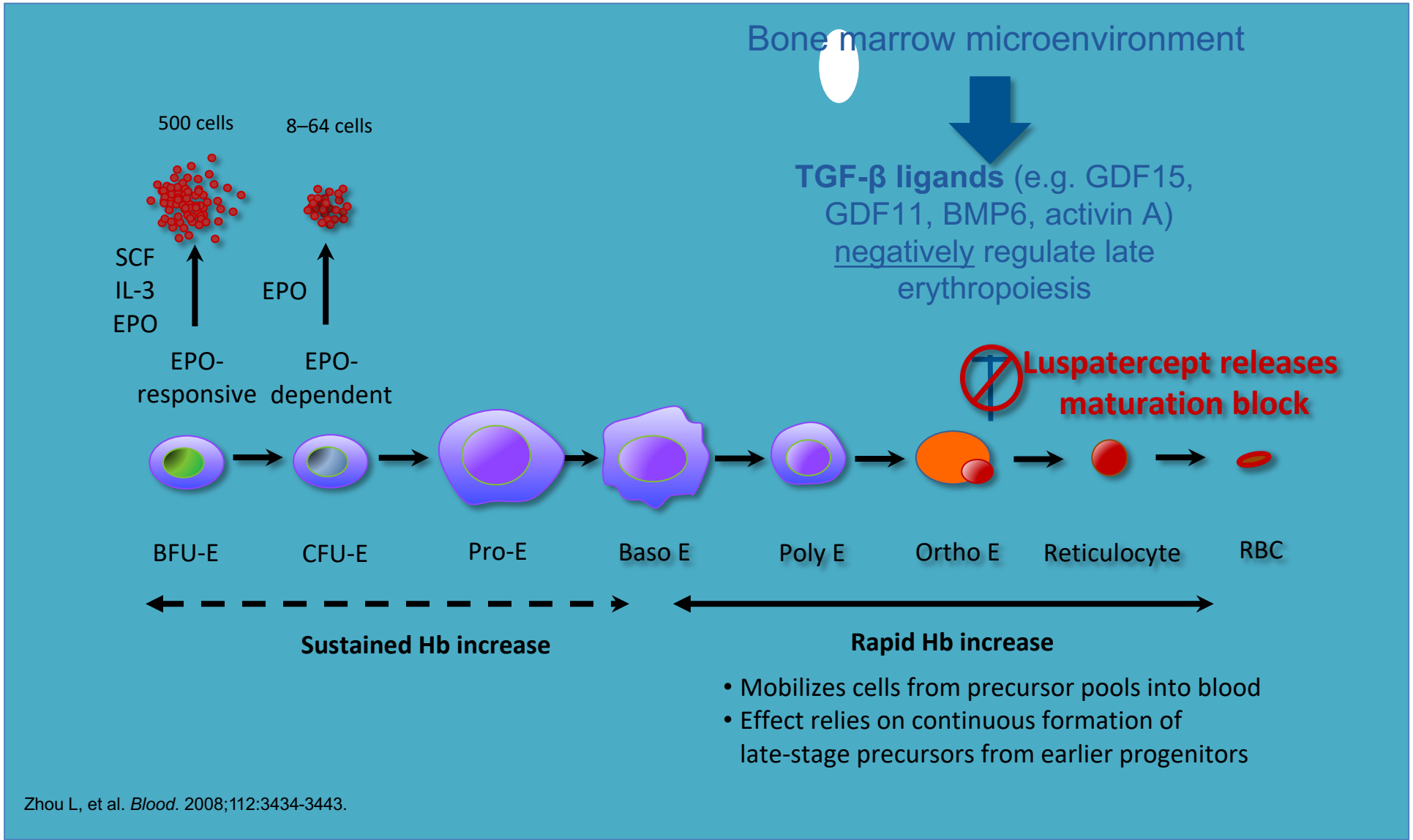
Dr Sallman
Clinical Presentation – Lower-Risk MDS

- 68 yo female with transfusion dependent anemia with MDS-RS with an isolated SF3B1 mutation and an IPSS-R of low presents for evaluation.
- CBC at baseline with hgb of 8gm/dL (2U PRBC 2 weeks prior) and nl ANC/platelets. BM biopsy showed 25% ringed sideroblasts with unilineage dysplasia and no increase in BM blasts.
- Patient had failed a 4-month trial of epoetin at 60,000U weekly.





Excess Smad2/3 Signaling Suppresses Late-Stage RBC Maturation in MDS



Zhou L, et al. *Blood.* 2008;112:3434-3443.

MOFFITT CANCER CENTER

Our Patient

- Patient was started on luspatercept 1 mg/kg every 3 weeks and patient had decreased transfusion requirement to 2 units monthly
- Patient increased up to 1.75 mg/kg and patient achieved transfusion independence that has been ongoing x 36 weeks to date

- What to do if no response despite maximum dose of luspatercept???

Dr Roboz – Lower-Risk MDS

73 y/o man diagnosed at age 60 with MDS when anemia (hgb 11.2 with elevated MCV) was identified on routine exam. Marrow 80% cellularity and 1% bone marrow myeloblasts. CEBPA, c-kit, FLT mutational analysis were all negative. Negative also for NPM1 mutation in exon 12, as was testing for k-ras and n-ras, normal cytogenetics. Note: the mutational testing reflected what was being done in 2010. Started on darbepoetin when hgb fell below 11 and remained on it, transfusion independent, until 2016 when hemoglobin drifted to 7-8 g/dL. Repeat bone marrow biopsy showed RCMD with 1% blasts and numerous ringed sideroblasts, myeloid mutation panel with SF3B1 mutation, started on combination with GCSF and darbepoetin, hgb increased to > 10 until 2020, when started drifting down, repeat marrow unchanged, started on luspatercept Dec 2020 with increased hemoglobin to >10, no transfusions, maintained to date.

Dr Garcia-Manero
Lower-risk case

An 82 year old woman is referred to you for symptomatic anemia. The patient has had an evaluation including a colonoscopy, iron studies, B12 and folate levels as well as rheumatological work up. All these studies were not significant. You performed a marrow exam that reveals a diagnosis of RARS. Eventually, NGS results indicate mutation on SF3B1 gene and cytogenetics were normal. In addition, you order an EPO level that comes back es elevated (over 300 mU/ML). Your recommendation is:

A. Start an ESA
B. Start luspatercept
C. Start lenalidomide
D. Start azacitidine
E. Refer to clinical trial

Dr Garcia-Manero
Lower-risk case (continued)

You decide to start the patient on an ESA. After 3 months of ESA use, the patient remains symptomatic and now is requiring blood transfusions monthly. Your next step is:

A. Continue ESA but optimize dosing
B. Start luspatercept
C. Start lenalidomide
D. Start azacitidine
E. Refer to clinical trial

You decide now to switch to luspatercept. You start at a dose 1 mg/kg every 3 weeks. After 3 injections, patient becomes transfusion independent but still is very symptomatic and with severe anemia. Your next step is:

A. Continue luspatercept at same dose
B. Increase luspatercept dose (i.e. 1.33 mg/kg)
C. Start lenalidomide
D. Start azacitidine
E. Refer to clinical trial

Dr Garcia-Manero
Lower-risk case (continued)

After B: the patient continues to be transfusion independent and hemoglobin increases

Teaching points: indication and dosing of luspatercept

N Engl J Med 2020;382(2):140-51.

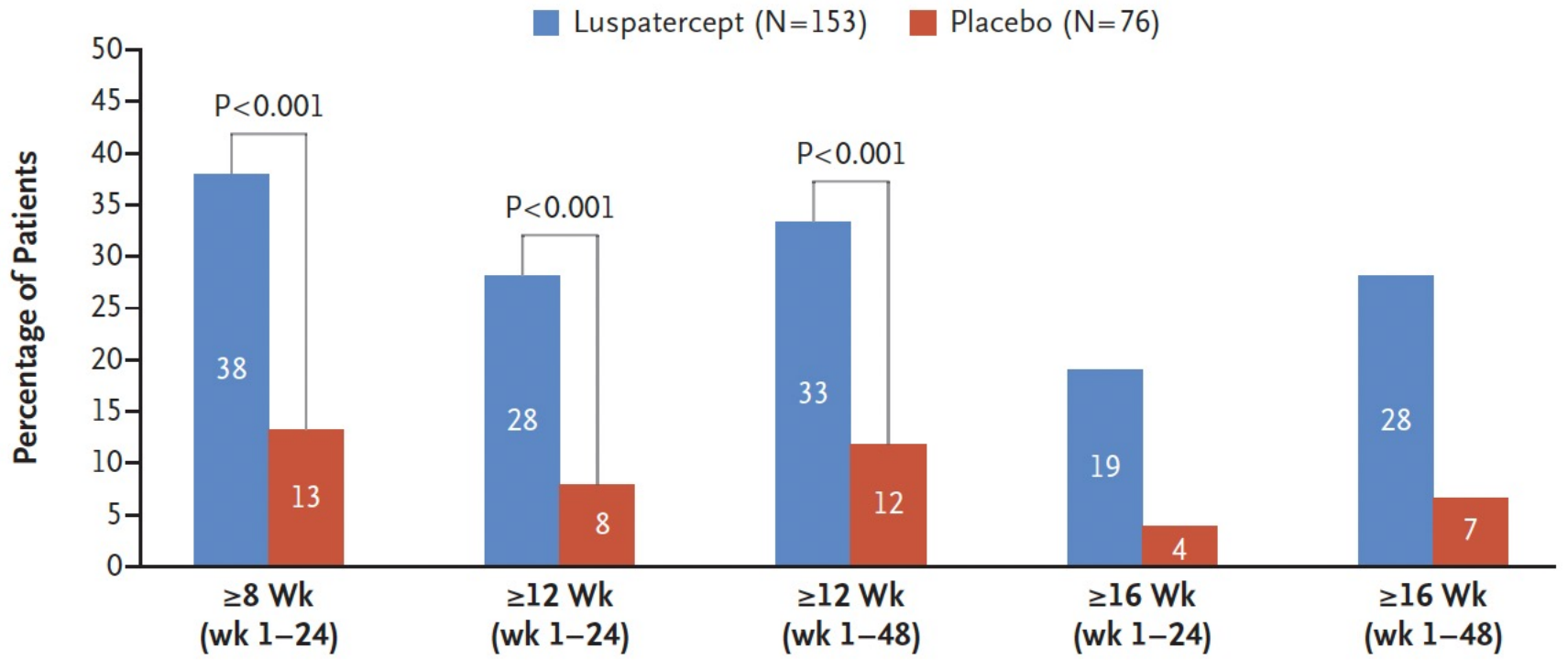
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

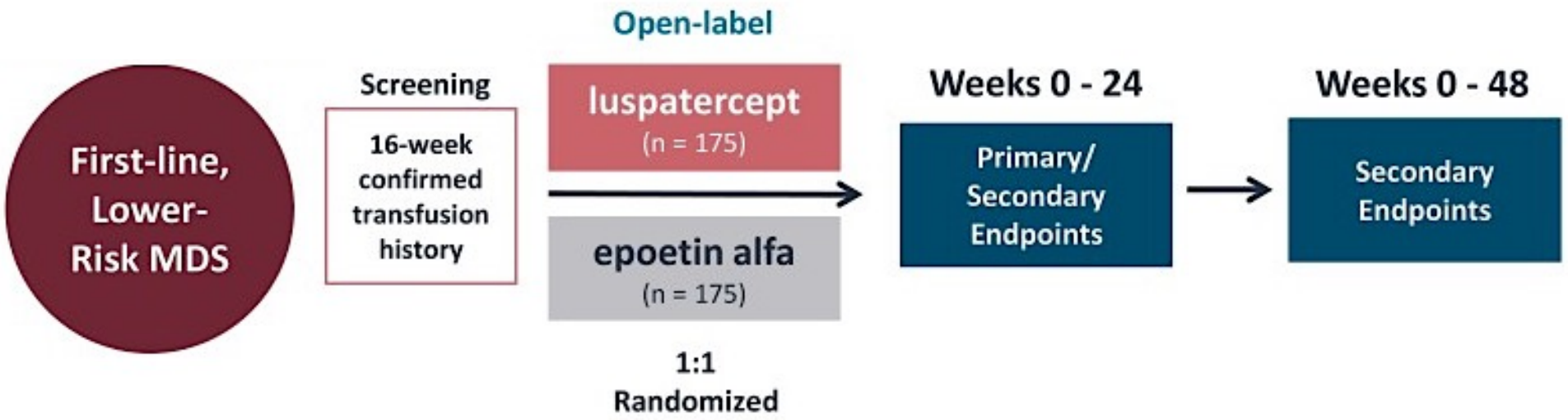
MEDALIST: Independence from Red Blood Cell Transfusion



No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux P et al. *N Engl J Med* 2020;382(2):140-51.

COMMANDS: Phase III Trial Design



- **Primary Endpoint**
  - RBC-transfusion independence (RBC-TI) over the first 24 weeks
- **Secondary Endpoints**
  - International Working Group hematologic improvement-erythroid (IWG HI-E)
  - ≥ 1.5 g/dL mean increase in hemoglobin over the first 24 weeks
  - Duration of RBC-TI and IWG HI-E

www.clinicaltrials.gov. NCT03682536. Accessed August 2022.

original reports

Phase III, Randomized, Placebo-Controlled Trial of CC-486 (Oral Azacitidine) in Patients With Lower-Risk Myelodysplastic Syndromes

Guillermo Garcia-Manero, MD[1]; Valeria Santini, MD[2]; Antonio Almeida, MD[3]; Uwe Platzbecker, MD[4]; Anna Jonasova, MD[5]; Lewis R. Silverman, MD[6]; Jose Falantes, MD[7]; Gianluigi Reda, MD[8]; Francesco Buccisano, MD[9]; Pierre Fenaux, MD[10]; Rena Buckstein, MD[11]; Maria Diez Campelo, MD[12]; Stephen Larsen, MBBS[13]; David Valcarcel, MD[14]; Paresh Vyas, MD[15]; Valentina Giai, MD[16]; Esther Natalie Olíva, MD[17]; Jake Shortt, PhD[18]; Dietger Niederwieser, MD[19]; Moshe Mittelman, MD[20,21]; Luana Fianchi, MD[22]; Ignazia La Torre, MD[23]; Jianhua Zhong, PhD[24]; Eric Laille, MS[24]; Daniel Lopes de Menezes, PhD[24]; Barry Skikne, MD[24,25]; C. L. Beach, PharmD[24]; and Aristoteles Giagounidis, MD[26]

J Clin Oncol 2021;39(13):1426-36.

ASH 2021;Abstract 66.

American Society of Hematology
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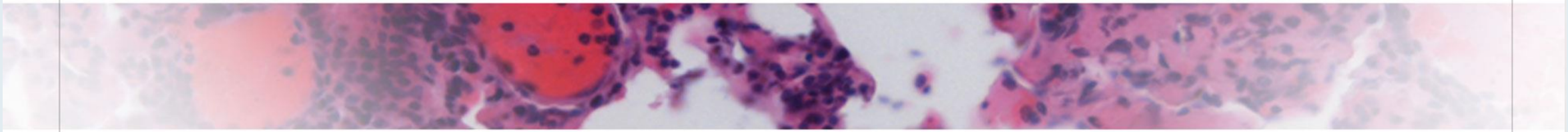

Oral Decitabine/Cedazuridine in Patients with Lower Risk Myelodysplastic Syndrome: a Longer-Term Follow-Up of the ASCERTAIN Study

On behalf of the ASCERTAIN Investigators Team

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ASCERTAIN: Efficacy in Patients with Lower-Risk MDS

Response Category	Treated Patients (N=69[a]), n (%)	95% CI
Complete response (CR)	16 (23.2%)	(13.9, 34.9)
Partial response (PR)	0	
Marrow CR (mCR)	18 (26.1%)	(16.3, 38.1)
mCR with hematologic improvement	9 (13.0%)	(6.1, 23.3)
Hematologic improvement (HI)	5 (7.2%)	(2.4, 16.1)
HI-erythroid[3]	1 (1.4%)	(0.0, 7.8)
HI-neutrophils[3]	0	
HI-platelet[3]	4 (5.8%)	(1.6, 14.2)
Overall response (CR + PR + mCR + HI)	39 (56.5)	(44.0, 68.4)

[1]Responses adjudicated by independent review committee per IWG 2006
[a] Includes 3 subjects who did not receive ASTX727 (received IV decitabine cycle 1 and did not continue)

For subjects with ≥ 5% bone marrow blasts (n=26):

- CR 7 (26.9%)
- mCR 11 (42.3%)

For the entire group (n=69):

- Median CR duration was 15.3 months
- Median duration of best response was 13.4 months
- Median time to first and best response were 3.0 months and 4.3 months, respectively
- 18 (26.0%) subjects proceeded to HCT

Garcia-Manero G et al. ASH 2021;Abstract 66.

ASCERTAIN: Transfusion Independence Among Patients with Lower-Risk MDS

	RBC Transfusion Dependent on Entry (N=27)	Platelet Transfusion Dependent on Entry (N=6)
Transfusion independent at 56 days	13 (48.1%) (28.7, 68.1)	4 (66.7%) (22.3, 95.7)
Transfusion independent at 84 days	11 (40.7%) (22.4, 61.2)	2 (33.3%) (4.3, 77.7)

Garcia-Manero G et al. ASH 2021;Abstract 66.

Oral HMAs for Lower-Risk MDS

	ORAL AZACITIDINE QUAZAR	ORAL DECITABINE-Cedazuridine ASCERTAIN
Dose	300 mg po daily x 21 days	35mg/100mg po x 5 days
Patient population	Low INT-1, TD, Plt < 75	Candidates for IV decitabine
Study design	Phase 3, placebo controlled	Phase 3 randomized cross-over
n	107	133 (69 lower risk)
CR	N/A	21%
TI; duration HI-E	31% ; 11 months 43%	52%
OS	17.3 months	Not reached after 24 months

Buckstein R. ASCO 2021 Education Session

Management of MDS: Agenda
Where We Are, Where We're Headed

PROLOGUE: A Vision for the Future

MODULE 1: Classification and prognosis of MDS

MODULE 2: Current management of lower-risk MDS

MODULE 3: Current management of higher-risk MDS

MODULE 4: MDS-AML continuum and overlap – Venetoclax, other targeted therapy

MODULE 5: Immune checkpoint inhibitors – Magrolimab, sabatolimab

MODULE 6: Appendix

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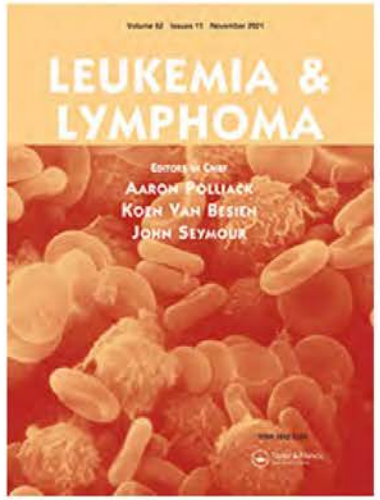
RESEARCH
TO PRACTICE



Taylor & Francis
Taylor & Francis Group

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

What is the optimal time to initiate hypomethylating agents (HMAs) in higher risk myelodysplastic syndromes (MDSs)?

Rami Komrokji, Najla Al Ali, Eric Padron, Jeffrey Lancet, Aziz Nazha, David Steensma, Amy DeZern, Gail Roboz, Guillermo Garcia-Manero, Mikkael A. Sekeres & David Sallman

2021; 62:11(2762-67).

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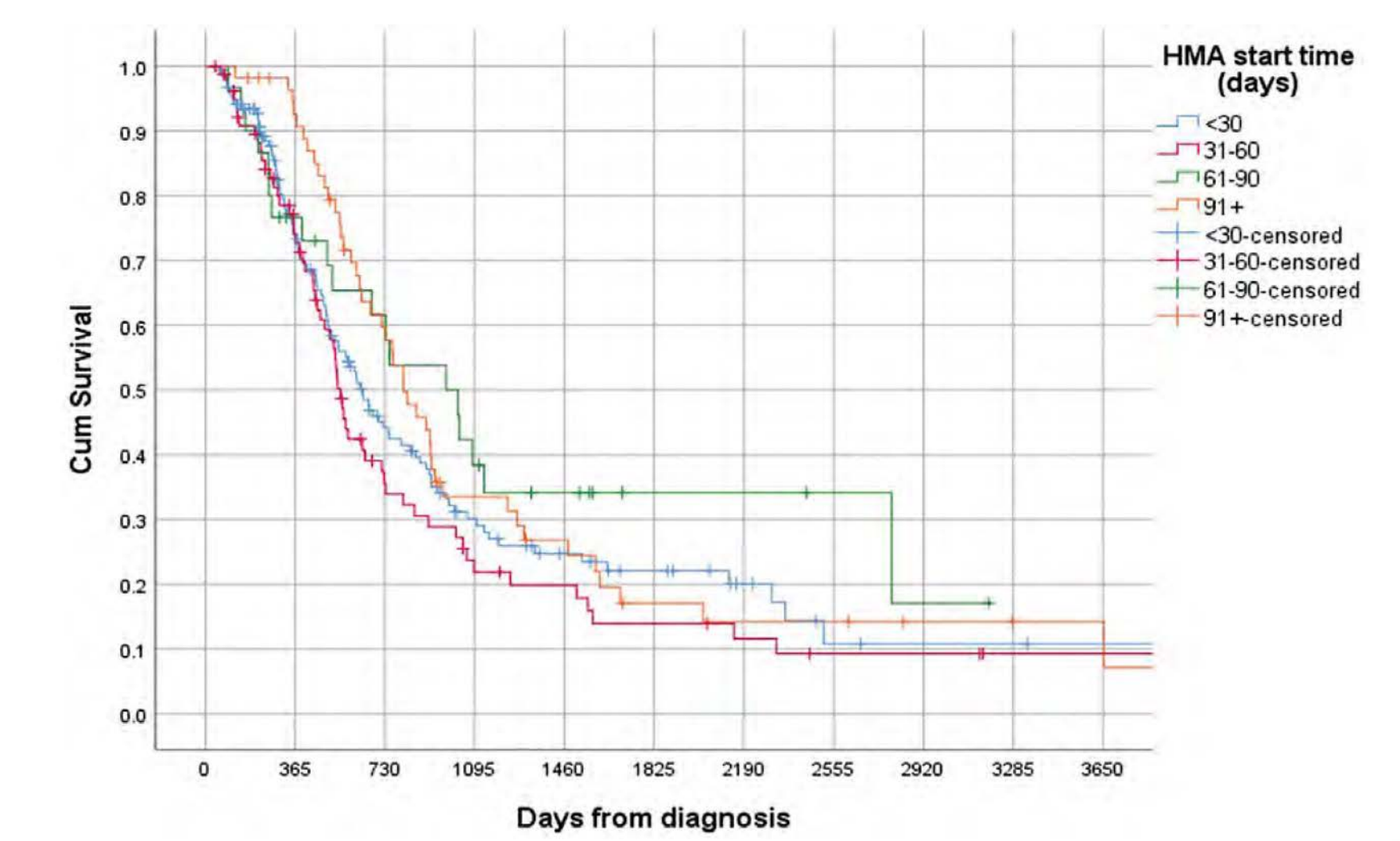
Overall Survival based on timing of HMA in higher-risk MDS



Komrokji R et al. *Leukemia & Lymphoma,* 2021;62:11(2762-67).

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Editorial

Time to blur the blast boundaries

Courtney D. DiNardo, MD, MSCE ; Guillermo Garcia-Manero, MD ; and Hagop M. Kantarjian, MD

Cancer 2022 April 15;128(8):1568-70.

"As prognostic classification systems for myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are further refined with the incorporation of cytogenetic and molecular data it is becoming increasingly challenging to submit to a 20% bone marrow blast cutoff to arbitrarily distinguish MDS from AML."

Courtney D DiNardo, Guillermo Garcia-Manero and Hagop M Kantarjian, *Cancer* 2022 April 15;128(8):1568-70.

Patient Case

- Healthy 57-year-old female patient with “MDS” who has 18% blasts, diploid cytogenetics and an NPM1 mutation

Courtney D DiNardo, Guillermo Garcia-Manero and Hagop M Kantarjian, *Cancer* 2022 April 15;128(8):1568-70.

Healthy 57-year-old women with “MDS” who has 18% blasts, diploid cytogenetics and an NPM1 mutation

- If this case were considered strictly as high-risk MDS, she would most likely be recommended to receive a hypomethylating agent alone instead of an intensive chemotherapy (IC) approach despite the known chemosensitivity of NPM1 mutations (even in the presence of underlying multilineage dysplasia) and her age and performance status, which would clearly advocate for IC had this been alternatively diagnosed as AML.

Courtney D DiNardo, Guillermo Garcia-Manero and Hagop M Kantarjian, *Cancer* 2022 April 15;128(8):1568-70.

Dr Garcia-Manero
HR MDS

You are referred a 59-year-old woman with 9% blasts and evidence of MDS. WBC is 2.5 and there is no evidence of proliferation. Your recommendation is:

A. Start induction therapy ASAP
B. Await for NGS and cytogenetic results

Because the patient is "clinically stable," you wait for the above results. Final report is MDS with excess blasts, diploid cytogenetics, NPM1 mutated but Flt-3 not mutated. Your plan is:

A. Start decitabine
B. Start azacitidine
C. Consider a clinical trial
D. Start an AML-like induction program containing high dose ara-C
E. Take the patient directly to stem cell transplantation

Dr Garcia-Manero
HR MDS (continued)

Your recommendation is D. You induce the patient with 7+3, followed by ara-C high dose consolidation. The patient achieves a complete remission including no evidence of minimal residual disease. At that point:

A. You recommend complete 4 cycles of HDAC and then observe
B. Complete HDAC x 4 and then continue oral azacitidine maintenance
C. Proceed to SCT at the time of best response
D. Stop therapy after 2 cycles of therapy
E. Consider clinical trial

Teaching point: treatment of rare cases of MDS/AML. Importance of NGS

Patient Case

- 68-year-old man with a history of prostate cancer previously treated with chemotherapy and ionizing radiation who has 24% blasts, marked trilineage dysplasia, complex cytogenetics and SRSF2 and ASXL1 mutations.

Courtney D DiNardo, Guillermo Garcia-Manero and Hagop M Kantarjian, *Cancer* 2022 April 15;128(8):1568-70.

68-year-old man with a history of prostate cancer, 24% blasts, marked trilineage dysplasia, complex cytogenetics and SRSF2 and ASXL1 mutations

- Should his disease be treated differently for AML (eg, with CPX-351 or an HMA and venetoclax) than if his blasts had alternatively been reported as 16% (oral decitabine/cedazuridine for MDS)?

- These 2 cases highlight some of the rather nonsensical yet clinically routine decisions generated by the excessive importance of the bone marrow blast percentage in myeloid cancer diagnoses.

- One paramount challenge due to this prominence of the bone marrow blast percentage is the lack of accuracy and reproducibility in the initial morphologic blast assessment.

Courtney D DiNardo, Guillermo Garcia-Manero and Hagop M Kantarjian, *Cancer* 2022 April 15;128(8):1568-70.

“Estey et al recently recommended defining patients with 10% to 30% blasts as ‘AML/MDS’ to ensure that they would be eligible for either MDS or AML therapies or novel clinical trials.”

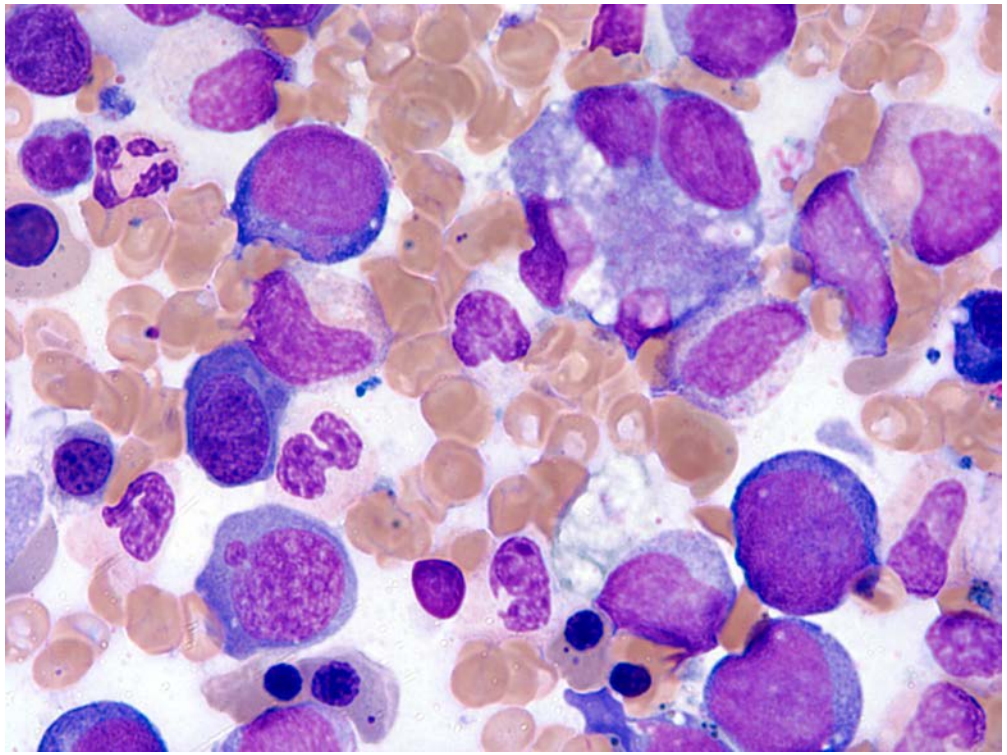
Courtney D DiNardo, Guillermo Garcia-Manero and Hagop M Kantarjian, *Cancer* 2022 April 15;128(8):1568-70.
Estey EH et al. *Blood,* 2021;139(3):323-32.

Dr Sallman
Clinical Presentation – HR MDS

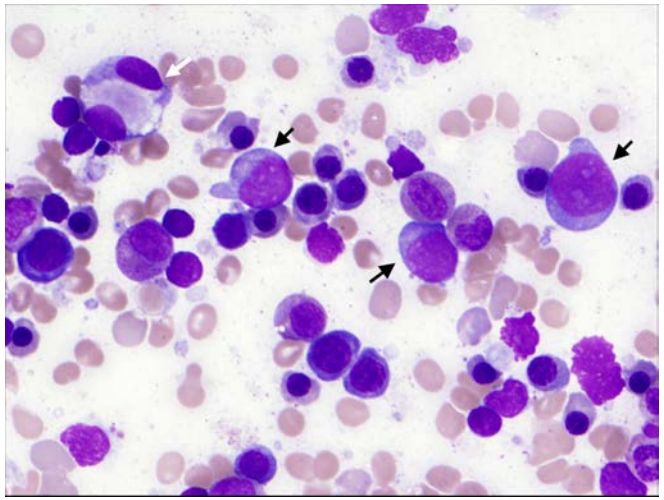
- 78 yo male with PMH of hypertension presents with severe fatigue, dyspnea on exertion and easy bruising.
- CBC shows ANC of 0.3 k/µl; Hgb 7 gm/dL; Platelets 45 k/µL.
- Patient has no history of gastrointestinal bleeding or other blood loss.
- BM Biopsy is performed and shows a hypercellular bone marrow (80%) with RAEB-2 MDS with 14% BM blasts, trilineage dysplasia and no increase in marrow fibrosis.
- Cytogenetics show Trisomy 8 and NGS myeloid panel shows an *ASXL1* and *U2AF1* mutation
- IPSS-R Classification is Very High

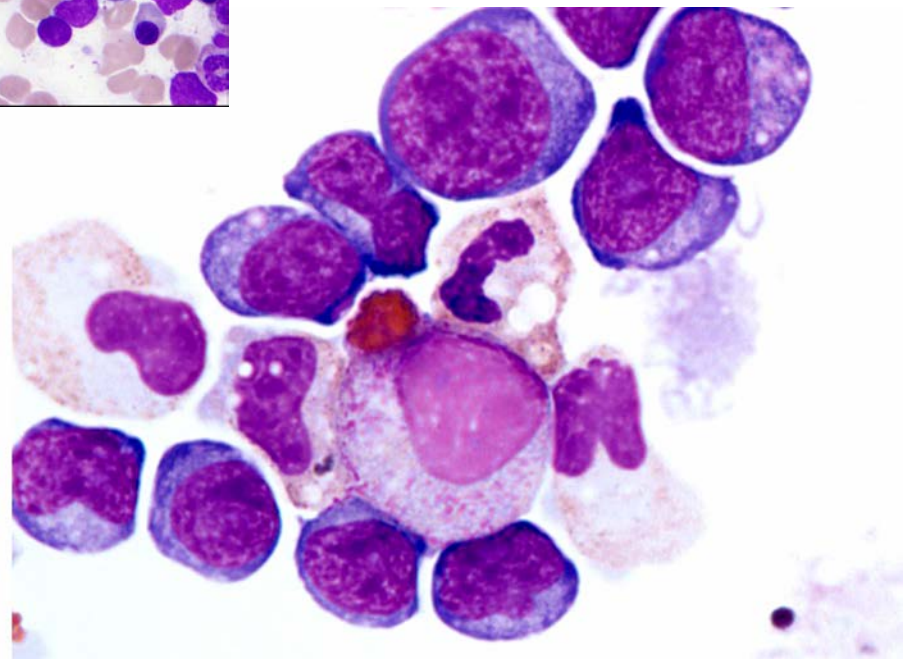
BM Pathology

Trilineage Dysplasia

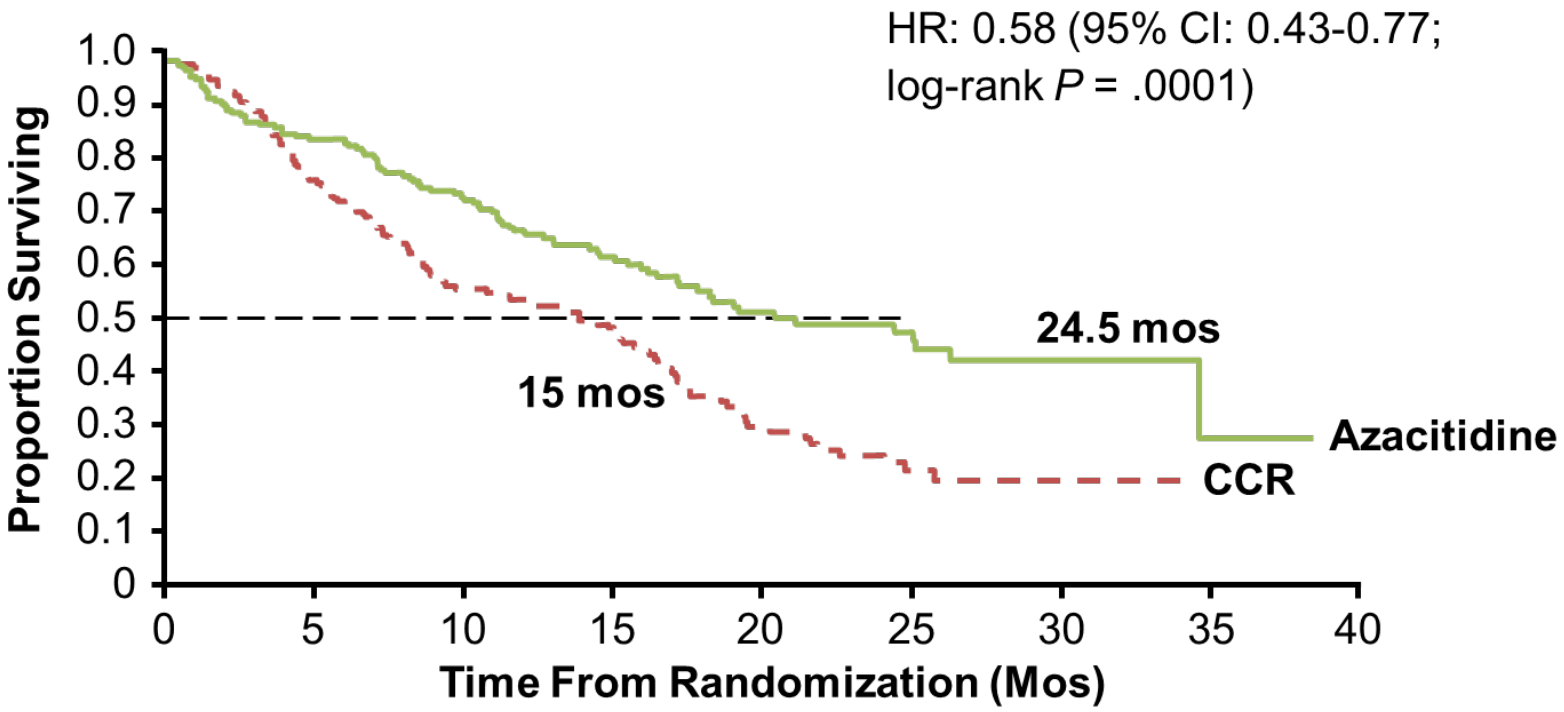


Increased BM Blasts





AZA-001 and OS



Real World OS has been 14-18 months; 40-50% ORR; 15-20% CR

Fenaux P, et al. Lancet Oncol. 2009;10:223-232; Zeidan A et al, Leukemia, 2016

MOFFITT CANCER CENTER

Our Patient

- Patient was treated with Azacitidine 7 day schedule + venetoclax 14 day schedule (antibacterial/antimicrobial/antiviral ppx were utilized)
  - Day +21 BM biopsy with < 5% blasts, therapy held until day 42 at which point ANC was 1.1, Hgb 10 gm/dL, Platelets 155; ppx d/c
  - Patient continued on same schedule C1, but ANC dropped to 0.4 mid-cycle
  - Patient dropped to 7 day schedule of venetoclax with 7 day azacitidine and CBC with ANC 1.6, Hgb 11.2 gm/dL, Platelets 160

Goals of Therapy for Our Patient

- What is/are the optimal goals for elderly HR-MDS patients?
  - Complete Remission
  - Transfusion Independence
  - QOL
  - Overall Survival
  - Duration of Response

Molecular Responses Are Observed Across Mutational Spectrum in Treatment-Naïve Higher-Risk Myelodysplastic Syndrome Patients Treated With Venetoclax Plus Azacitidine

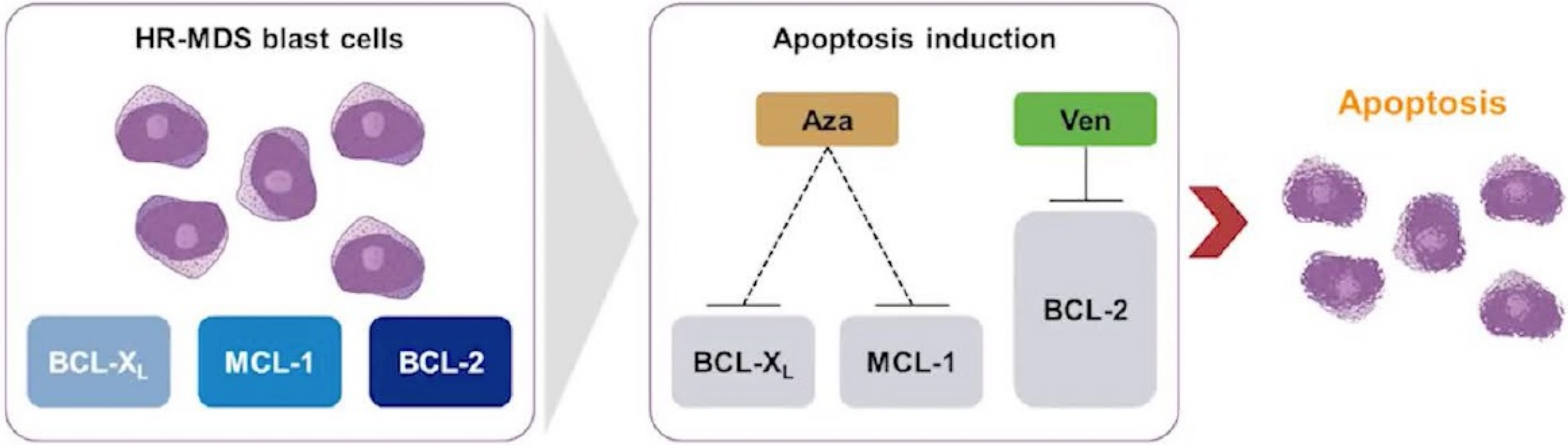
Jacqueline S. Garcia[1], Andrew H. Wei[2], Meagan A. Jacoby[3], Chun Yew Fong[4], Uma Borate[5], Maria R. Baer[6], Ilona Cunningham[7], Olatoyosi Odenike[8], Joseph G. Jurcic[9], Daniel Nowak[10], Pierre Peterlin[11], Uwe Platzbecker[12], Diana Dunshee[13], Ying Zhou[14], David Hoffman[14], Yan Sun[14], Relja Popovic[14], Barrett Ainsworth[14], Kiran Naqvi[13], Steve Kye[14], Leah Hogdal[14], Guillermo Garcia-Manero[15]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [3]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St Louis, MO, USA; [4]Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia; [5]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [6]Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [7]Concord Repatriation General Hospital, University of Sydney, Sydney, Australia; [8]University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, USA; [9]Herbert Irving Comprehensive Cancer Center, New York-Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY, USA; [10]Medical Faculty Mannheim of the Heidelberg University, Mannheim, Germany; [11]Nantes University Hospital, Nantes, France; [12]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Germany; [13]Genentech Inc., South San Francisco, CA, USA; [14]AbbVie Inc., North Chicago, IL, USA; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

American Society of Hematology Annual Meeting, December 11–14, 2021, Atlanta, Georgia

ASH 2021;Abstract 241.

Venetoclax + Azacitidine Mechanism of Action



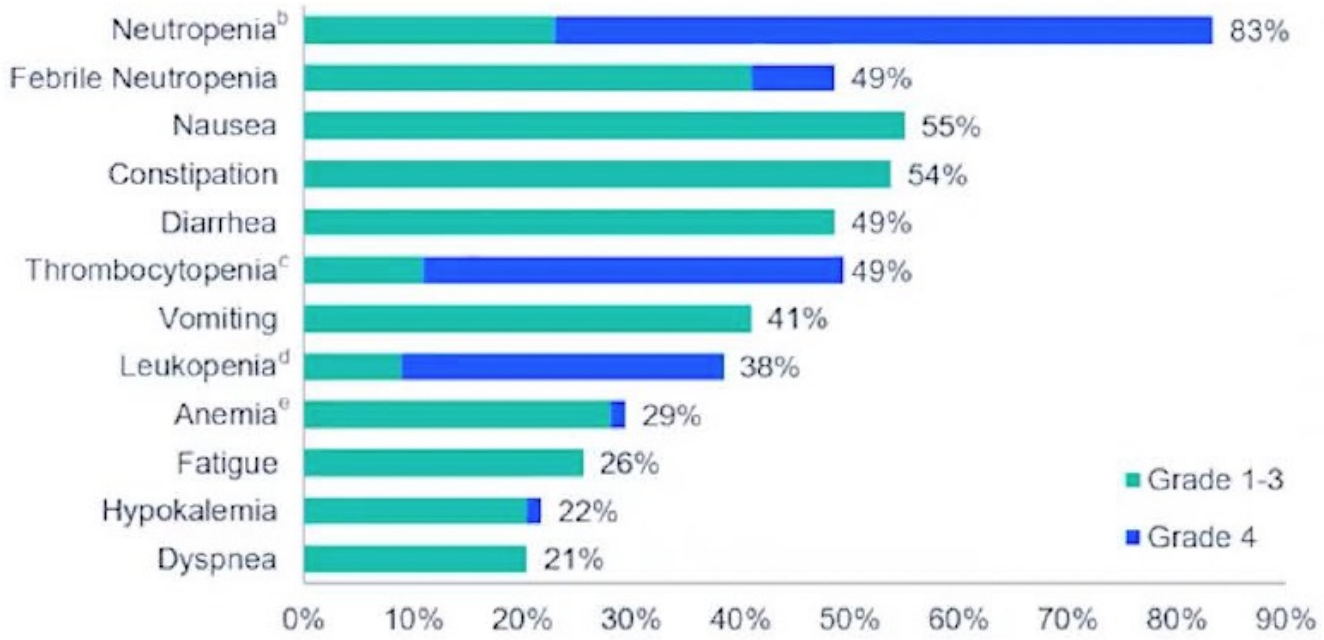
Size of rectangles indicates relative dependency on specific protein for survival.
Dotted lines indicate an indirect therapeutic effect on BCL-2 family member dependency

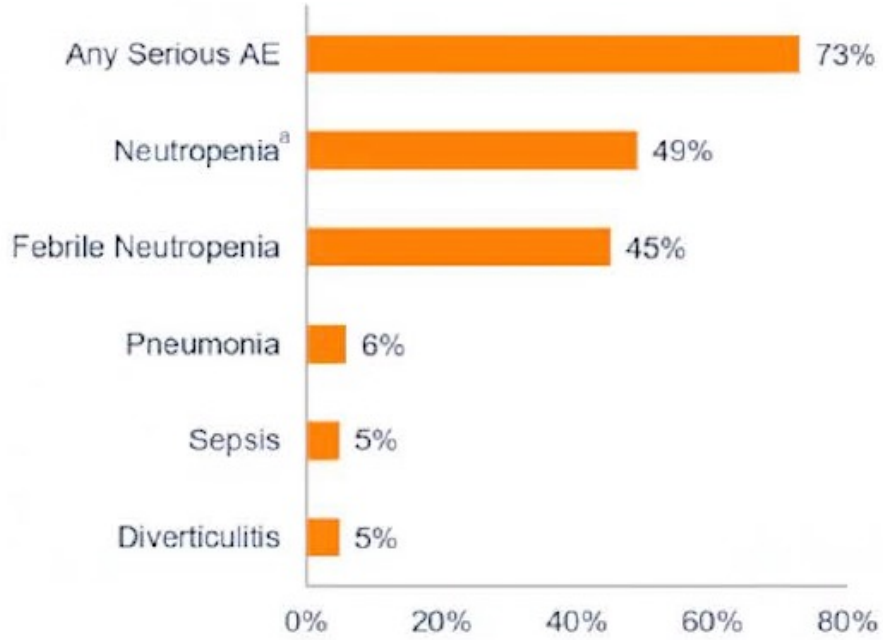
Garcia JS et al. ASH 2021;Abstract 241.

Safety of Venetoclax + Azacitidine

- Median **cycles of Aza received**: 4 (range 1-27); median **cycles of Ven received**: 4 (range 1-27)
- 30-day mortality after first dose was 1%; 7 patients (9%) experienced an AE leading to death[a]

Summary of Adverse Events in All Patients (N=78)[1]





Garcia JS et al. ASH 2021;Abstract 241.

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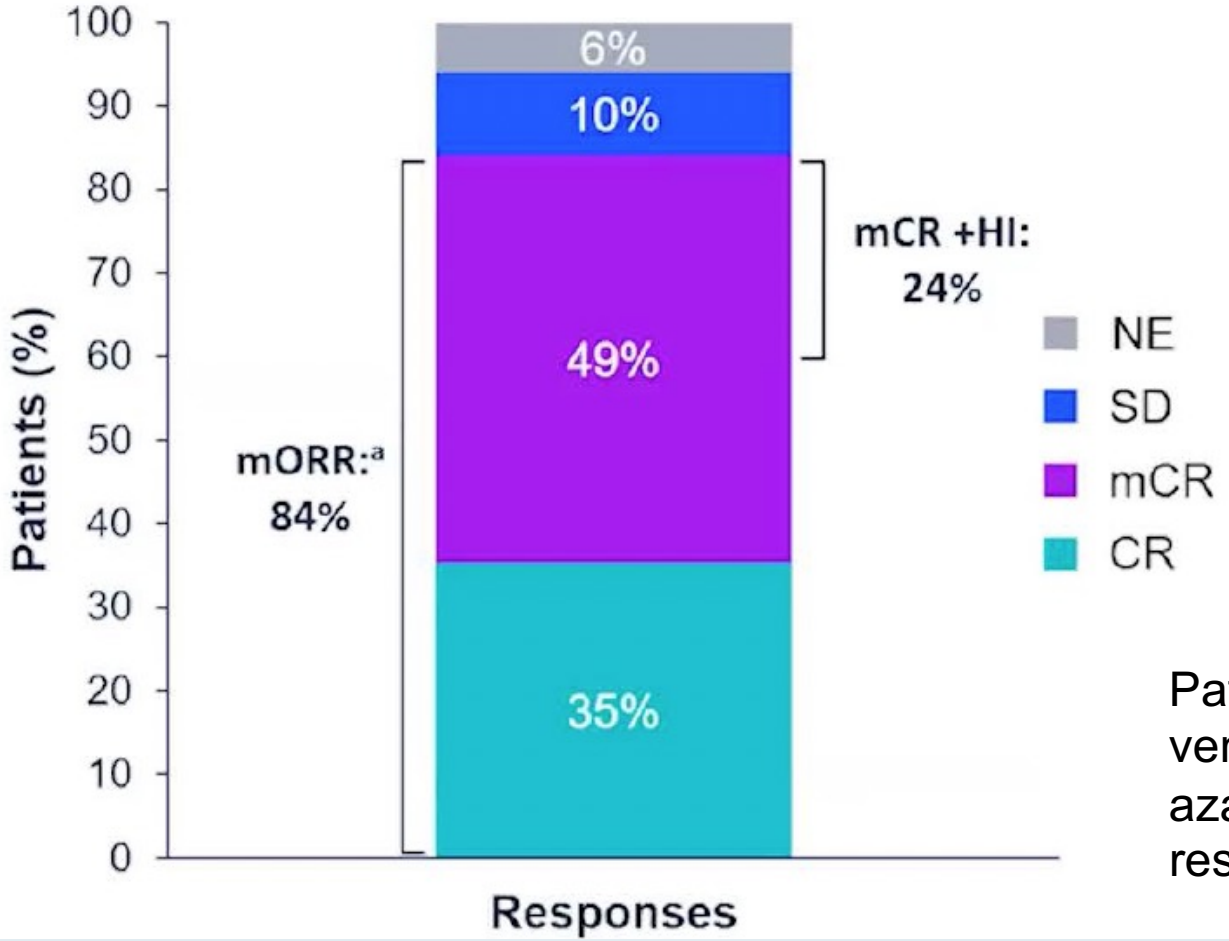
Response to Venetoclax + Azacitidine

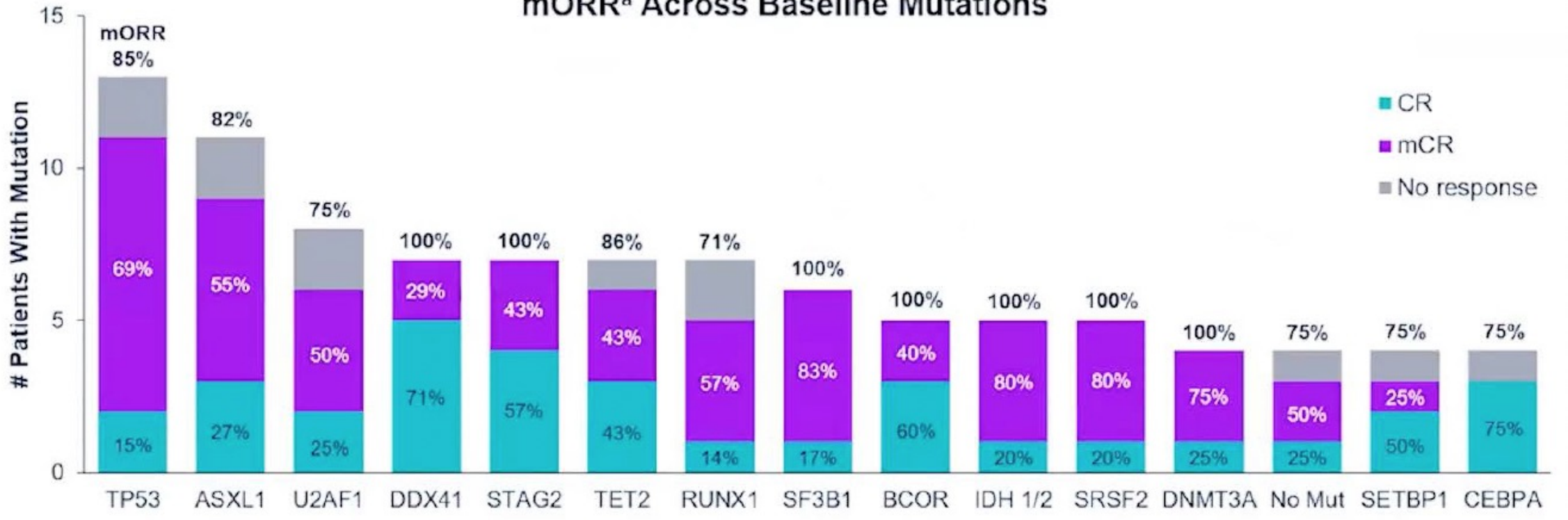


- Median time to response:
  0.9 months (95% CI, 0.7–5.8)
- Median duration of response:
  12.4 months (95% CI, 9.9–NR)

Patients with HR-MDS treated with venetoclax (400 mg D1-14) and azacitidine (75 mg/m^2) had rapid, durable responses with high remission rates

Garcia JS et al. ASH 2021;Abstract 241.

Response to Venetoclax + Azacitidine Across the Mutational Spectrum



- 7 of 13 patients with *TP53* mutations had multi-hit/bi-allelic *TP53* mutations
- Responses of those with multi-hit/bi-allelic *TP53* were similar to responses in patients with any *TP53* mutation:
  - CR: 28.6% (2/7); mORR: 71.4% (5/7)

Data cutoff: Dec 15,

Garcia JS et al. ASH 2021;Abstract 241.

ASH 2021;Abstract 537.

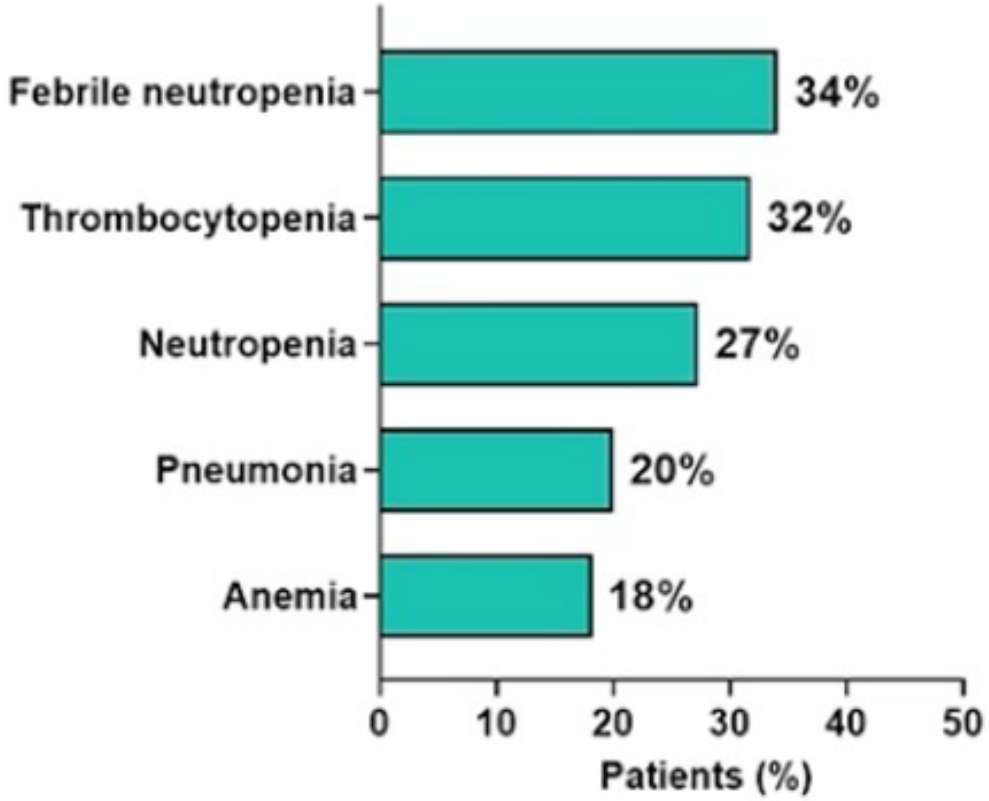
Venetoclax and Azacitidine in the Treatment of Patients with Relapsed/Refractory Myelodysplastic Syndrome

Amer M Zeidan[1], Uma Borate[2], Daniel A Pollyea[3], Andrew M Brunner[4], Fernando Roncolato[5], Jacqueline S Garcia[6], Robin J Filshie[7], Olatoyosi Odenike[8], Anne-Marie Watson[9], Ashish Bajel[10], Kiran Naqvi[11], Jiuhong Zha[12], Leah Hogdal[12], Ying Zhou[12], David Hoffman[12], Steve Kye[12], Guillermo Garcia-Manero[13]

[1] Section of Hematology, Department of Internal Medicine, Yale University and Yale Cancer Center, New Haven, CT, USA; [2] Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [3] Department of Hematology, University of Colorado, Aurora, CO, USA; [4] Center for Leukemia, Massachusetts General Hospital, Boston, MA, USA; [5] Department of Hematology, University of New South Wales, Sydney, Australia; [6] Department of Medicine, Dana-Farber Cancer Institute, Boston, MA, USA; [7] Department of Hematology, St Vincent's Hospital, Melbourne, AUS; [8] University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, USA; [9] Department of Haematology, Liverpool Hospital, Liverpool, AUS; [10] Department of Clinical Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, AUS; [11] Genentech, South San Francisco, CA, USA; [12] AbbVie Inc, North Chicago, IL, USA; [13] Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

American Society for Hematology 2021, December 11-14, Atlanta, GA, USA

Treatment-Emergent Adverse Events with Venetoclax/Azacitidine

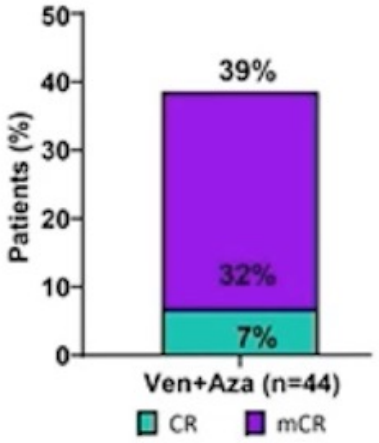


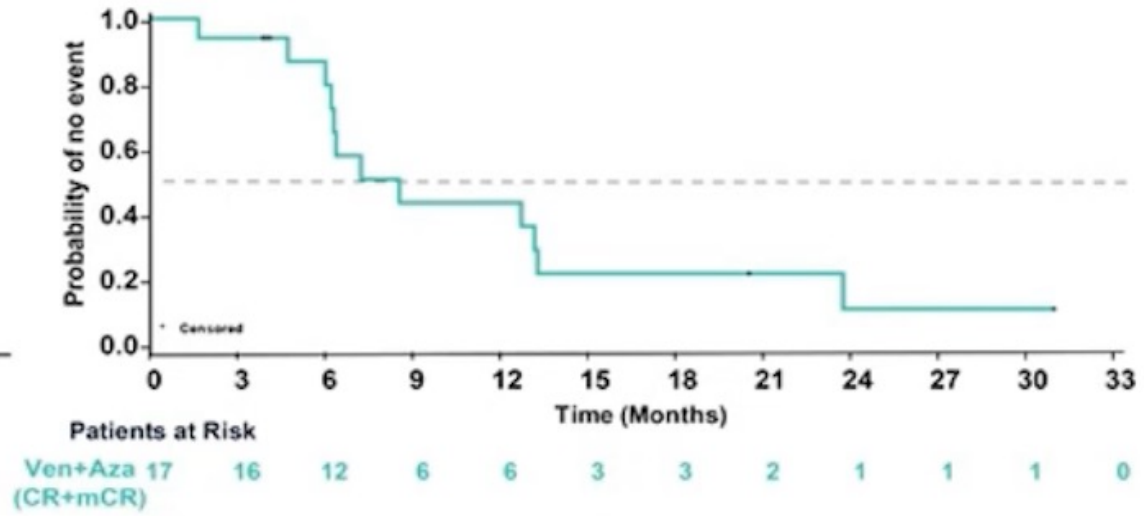
Treatment-emergent adverse events grade≥3[a]

- Patients received a median of 4 cycles (range 1 – 32) of venetoclax and 4 cycles (range 1 – 31) of azacitidine
- All 44 patients (100%) had at least one treatment-emergent adverse event (TEAE) of any grade and 42 (96%) had at least one grade ≥3 TEAE
- Predominant grade ≥ 3 AEs were hematological AEs and infections
- Grade ≥ 3 TEAE related to Ven was reported in 30 (68%) patients
- SAE related to Ven was reported in 10 (23%) patients
- No event of tumor lysis syndrome was reported without ramp up

Zeidan AM et al. ASH 2021;Abstract 537.

Response to Venetoclax/Azacitidine





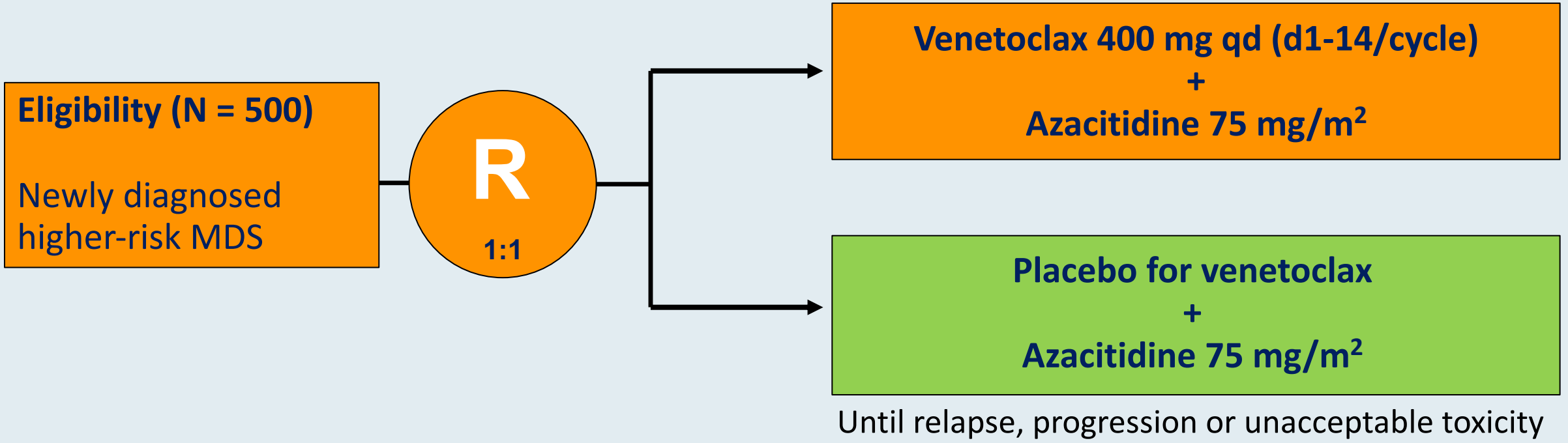
- The median duration of follow up was 21.2 months (range 0.4 – 37.5[a])
- The median DoR for CR+mCR was 8.6 months (95% CI 6.0 – 13.3)
- Median time to first response of CR or mCR was 1.2 months (range 0.7 – 6.3)
- Stable disease was observed in 18 (40.9%) patients and progressive disease in 2 (4.5%) patients [b]

DoR	# of events	12-month, % (95% CI)	24-month, % (95% CI)	Median DoR, months (95% CI)
Ven+Aza (CR+ mCR)	12	43.4 (18.1 – 66.6)	10.9 (0.8 – 35.8)	8.6 (6.0 – 13.3)

CR = complete remission; mCR = marrow CR; DoR = duration of response

Zeidan AM et al. ASH 2021;Abstract 537.

VERONA Phase III Study Design



Dual primary endpoints: Complete remission and overall survival
Secondary endpoints: RBC and platelet transfusion independence for patients who are transfusion dependent at baseline, change from baseline in fatigue, time to deterioration of physical functioning, overall response

Zeidan AM et al. ASCO 2021;Abstract TPS7054.

A Phase I/II Study of Venetoclax in Combination with ASTX727 (Cedazuridine/Decitabine) in Treatment-Naïve High-Risk Myelodysplastic Syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML)

Venugopal S et al.

ASH 2021;Abstract 245.

Ivosidenib in Patients with *IDH1*-Mutant Relapsed/Refractory Myelodysplastic Syndrome (R/R MDS): Updated Enrollment and Results of a Phase 1 Dose-Escalation and Expansion Substudy

Sallman DA et al.

ASCO 2022;Abstract 7053.

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Oral presentation #242

American Society *of* Hematology

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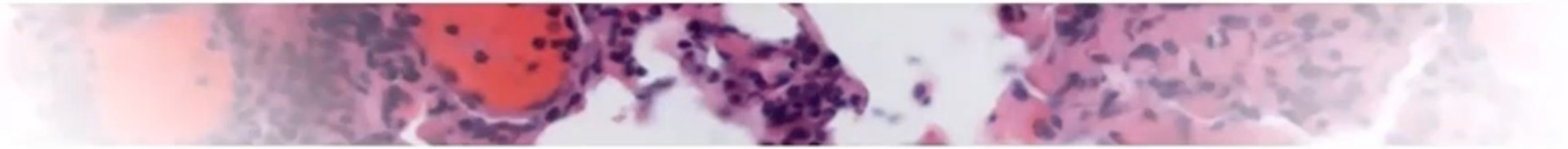


Pevonedistat + azacitidine versus azacitidine alone as first-line treatment for patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia or acute myeloid leukemia with 20–30% marrow blasts: The randomized phase 3 PANTHER trial (NCT03268954)

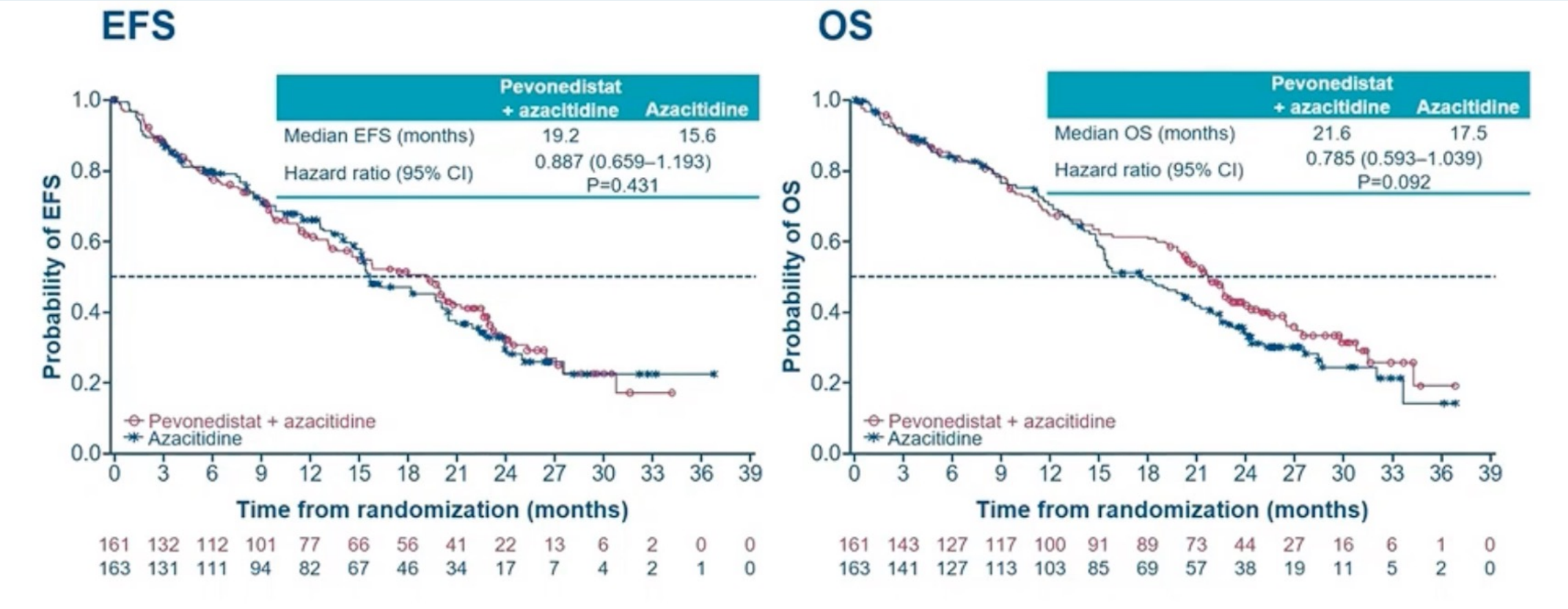
Mikkael A. Sekeres,[1] Larisa Girshova,[2] Vadim A. Doronin,[3] Maria Diez Campelo,[4] David Valcarcel,[5] Suman Kambhampati,[6] Nora-Athina Viniou,[7] Dariusz Woszczyk,[8] Raquel De Paz Arias,[9] Argiris Symeonidis,[10] Achilles Anagnostopoulos,[11] Eduardo Ciliao Munhoz,[12] Uwe Platzbecker,[13] Valeria Santini,[14] Robert J. Fram,[15] Ying Yuan,[15] Sharon Friedlander,[15] Douglas V. Faller,[15] Lionel Adès[16]

[1]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [2]Federal Almazov North-West Medical Research Centre, Saint-Petersburg, Russia; [3]City Clinical Hospital #40, Moscow, Russia; [4]University Hospital of Salamanca, IBSAL Institute for Biomedical Research of Salamanca, Salamanca, Spain; [5]Hematology Department, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [6]Sarah Cannon at Research Medical Center, Kansas City, MO, USA; [7]Hematology Unit, First Department of Internal Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece; [8]University of Opole, Provincial Hospital, Opole, Poland; [9]Hematology, Hospital Universitario La Paz–IDIPaz, Madrid, Spain; [10]Hematology Division, Dept of Internal Medicine, University Hospital Patras, Patras, Greece; [11]Hematology Department, General Hospital "George Papanikolaou", Thessaloniki, Greece; [12]Hospital Erasto Gaertner, Curitiba, Brazil; [13]Leipzig University Hospital, Leipzig, Germany; [14]MDS Unit, Hematology, AOU Careggi, University of Florence, Florence, Italy; [15]Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA; [16]AP-HP, Hôpital Saint Louis and University of Paris, and INSERM U944, Paris, France

ASH 2021;Abstract 242

RTP RESEARCH TO PRACTICE

PANTHER (Pevonedistat-3001): Event-Free Survival (EFS) and OS in the Higher-Risk MDS Cohort



- No statistically significant difference between the 2 study arms in EFS (p = 0.557) or OS (p = 0.181) in the ITT population

Sekeres MA et al. ASH 2021;Abstract 242.

Dr Garcia-Manero
HR MDS

You are referred a 79 year old man with 13% blasts. Marrow exam shows evidence of MDS, complex cytogenetics and NGS is positive for mutations on TET2 and DNMT3A. Your recommendation is:

A. Start azacitidine
B. Start decitabine
C. Start oral decitabine
D. Consider 7+3 induction
E. Consider a clinical trial of azacitidine + magrolimab. An antibody against CD47.

Because the standard of care is still suboptimal in HR-MDS, you opt for the clinical trial. The patient is transfusion dependent on red cells. Your advice to the patient is:

A. Admit to the hospital and perform preventive transfusions of red cells prior to starting magrolimab until you reach an acceptable hemoglobin level
B. Do not provide any other care that you do not provide when treating patients of this age with single agent azacitidine

Dr Garcia-Manero
HR MDS (continued)

Because severe anemia can be an early complication of the use of magrolimab, you opt for A. With the first cycle of therapy, the patient achieves a complete remission including a complete cytogenetic response and complete count recovery. For the next cycle of therapy, you recommend:

A. Admit to the hospital and perform preventive transfusions of red cells prior to starting magrolimab until you reach an acceptable hemoglobin level
B. Do not provide any other care that you do not provide when treating patients of this age with single agent azacitidine

Teaching points: discuss specific toxicities related to magrolimab

Dr Roboz – Higher-Risk MDS

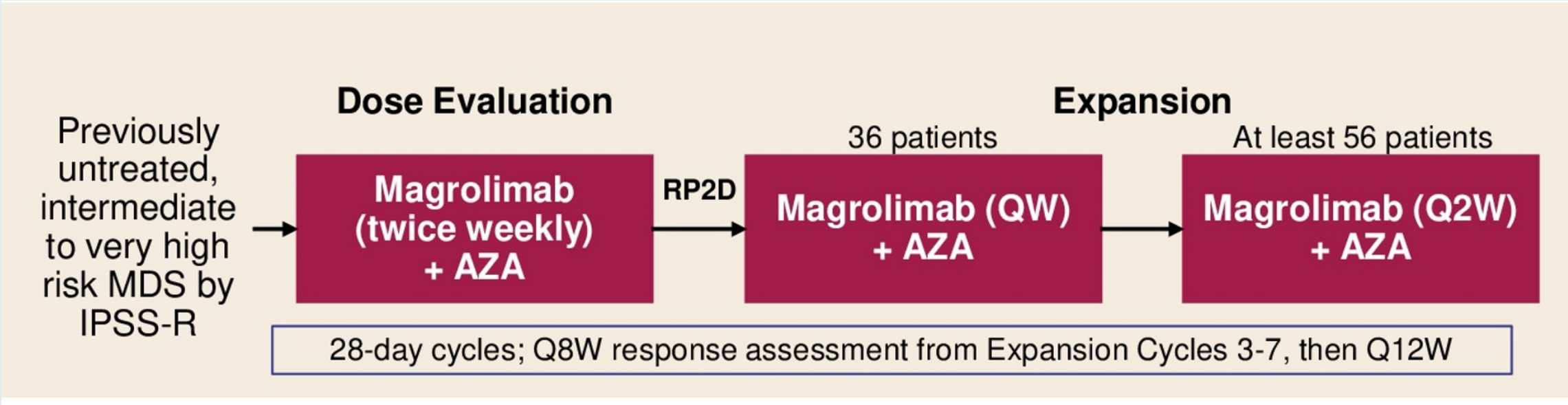
74 y/o with hx breast cancer diagnosed in 2000, treated with chemo/radiation, diagnosed with MDS in 2020, trilineage dysplasia, 5% blasts, complex karyotype, no TP53 mutation, treated initially with darbepoetin without improvement, then referred for participation in magrolimab/placebo + azacitidine randomized trial. Had transient improvements in transfusion requirements, reduction in blasts to 2% but no change in cytogenetics, declined stem cell transplantation, ultimately treated for 7 cycles complicated by ongoing transfusions and eventually taken off study for supportive care with transfusions.

Magrolimab in Combination with Azacitidine for Untreated Higher-Risk Myelodysplastic Syndromes (HR-MDS): 5F9005 Phase 1b Study Results

Sallman DA et al.

ASCO 2022;Abstract 7017.

5F9005 Study Design: Magrolimab in Combination with Azacitidine for Previously Untreated Intermediate to Very High-Risk MDS



Sallman DA et al. ASCO 2022;Abstract 7017.

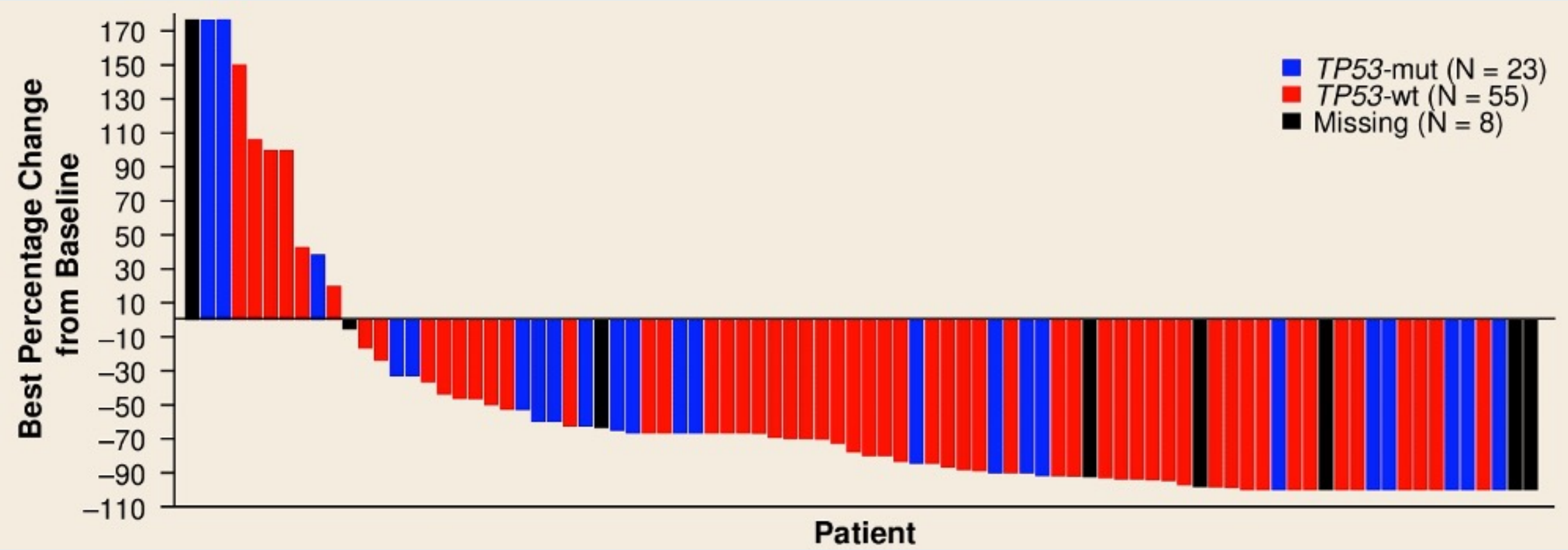
5F9005: Efficacy Outcomes with Magrolimab in Combination with Azacitidine for Untreated Higher-Risk MDS (HR MDS)

Outcome	All (N = 95)*	*TP53*-wt (N = 61)	*TP53*-mut (N = 25)
ORR, %†	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4, 43.0)	31.1 (19.9, 44.3)	40.0 (21.1, 61.3)
Marrow CR, %	31.6	37.7	20.0
Any HI, %	58.9	60.7	56.0
Marrow CR with HI, %	16.8	19.7	12.0
SD with HI, %	10.5	9.8	8.0
DCR, median (95% CI), mo	11.1 (7.6, 13.4)	12.9 (8.0, NR)	7.6 (3.1, 13.4)
Time to CR, median (range), mo	3.7 (1.7, 7.2)	4.6 (1.7, 7.2)	3.1 (1.9, 4.0)
DOR, median (95% CI), mo	9.8 (8.8, 12.9)	9.8 (8.5, 18.5)	9.2 (5.0, 12.2)
Time to OR, median (range), mo	1.9 (0.7, 10.9)	1.9 (0.7, 5.5)	1.9 (1.8, 10.3)
Conversion to RBC transfusion independence, n/N (%)‡	13/37 (35.1)	6/23 (26.1)	6/13 (46.2)
PFS, median (95% CI), mo	11.6 (9.0, 14.0)	11.8 (8.8, 16.6)	11 (6.3, 12.8)
OS, median (95% CI), mo	NR (16.3, NR)	NR (21.3, NR)	16.3 (10.8, NR)

ORR = objective response rate; CR = complete remission; HI = hematologic improvement; SD = stable disease; DCR = duration of complete remission; DOR = duration of response; OR = objective response; PFS = progression-free survival; OS = overall survival; NR = not reached

Sallman DA et al. ASCO 2022;Abstract 7017.

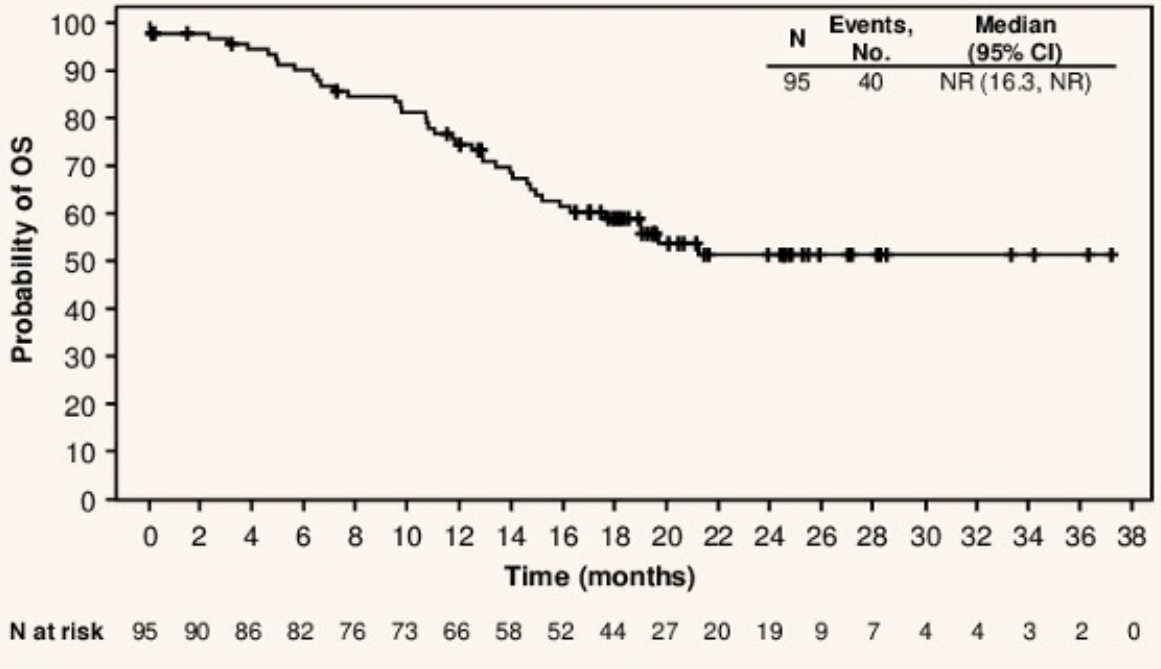
5F9005: Best Change from Baseline in Percent Bone Marrow Blasts with Magrolimab in Combination with Azacitidine for Untreated HR MDS



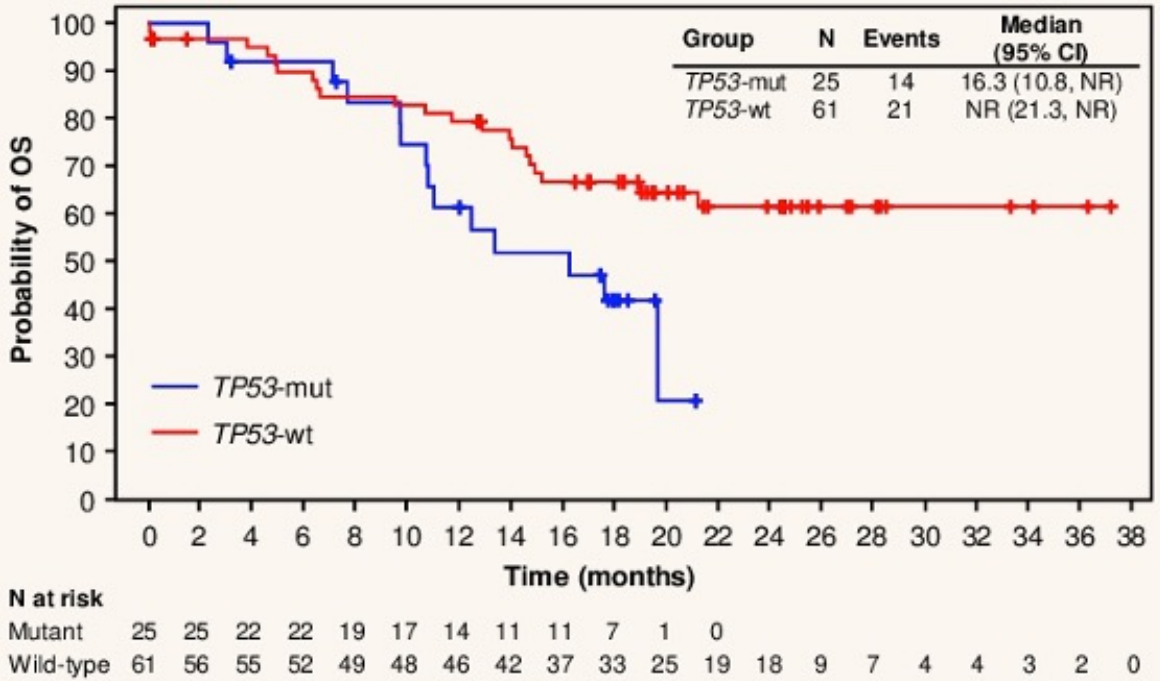
Sallman DA et al. ASCO 2022;Abstract 7017.

5F9005: Kaplan-Meier Overall Survival Curves for Magrolimab in Combination with Azacitidine for Untreated HR MDS

All Patients



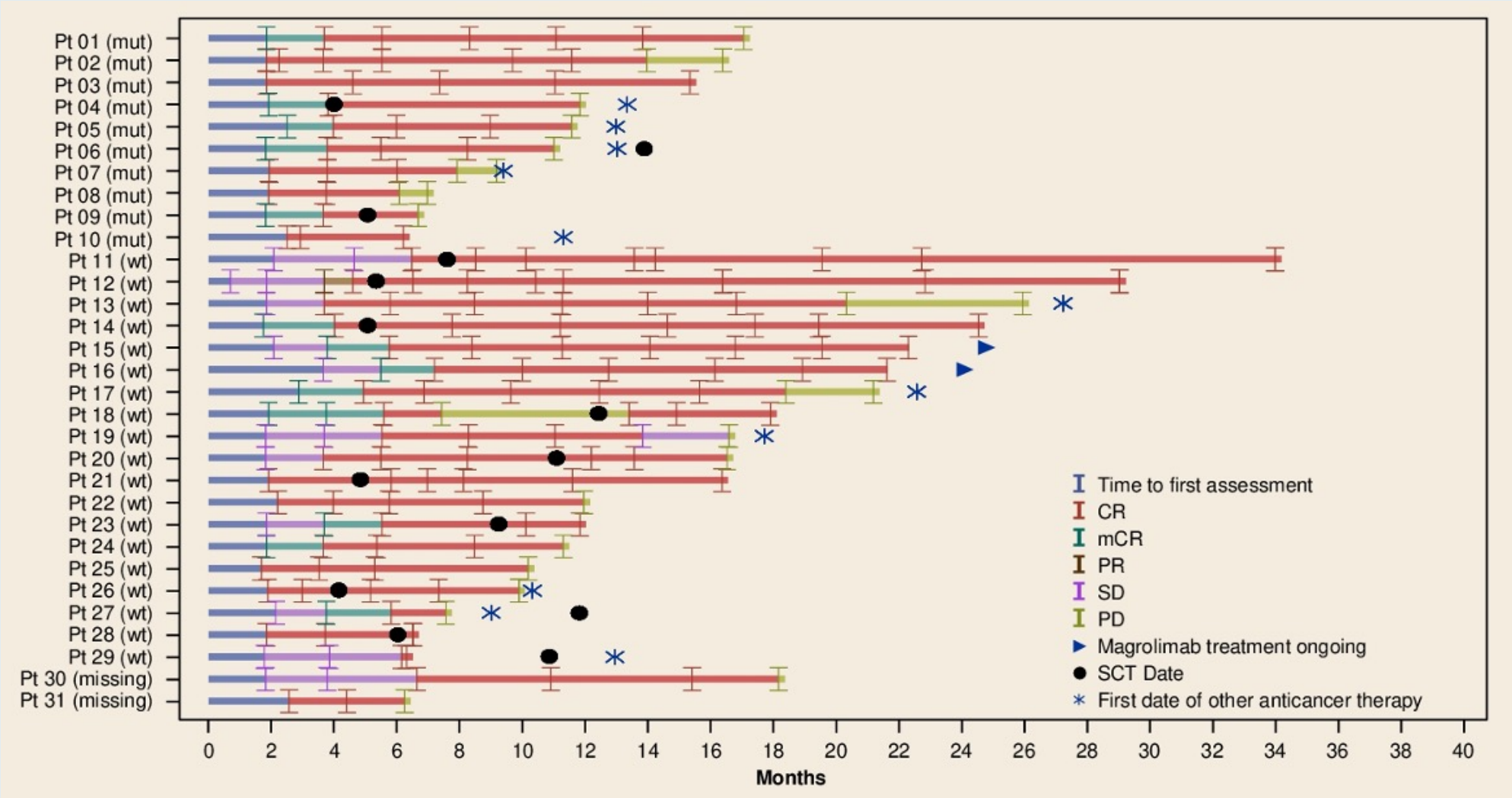
By *TP53* Mutation Status



Sallman DA et al. ASCO 2022;Abstract 7017.

RTP RESEARCH TO PRACTICE

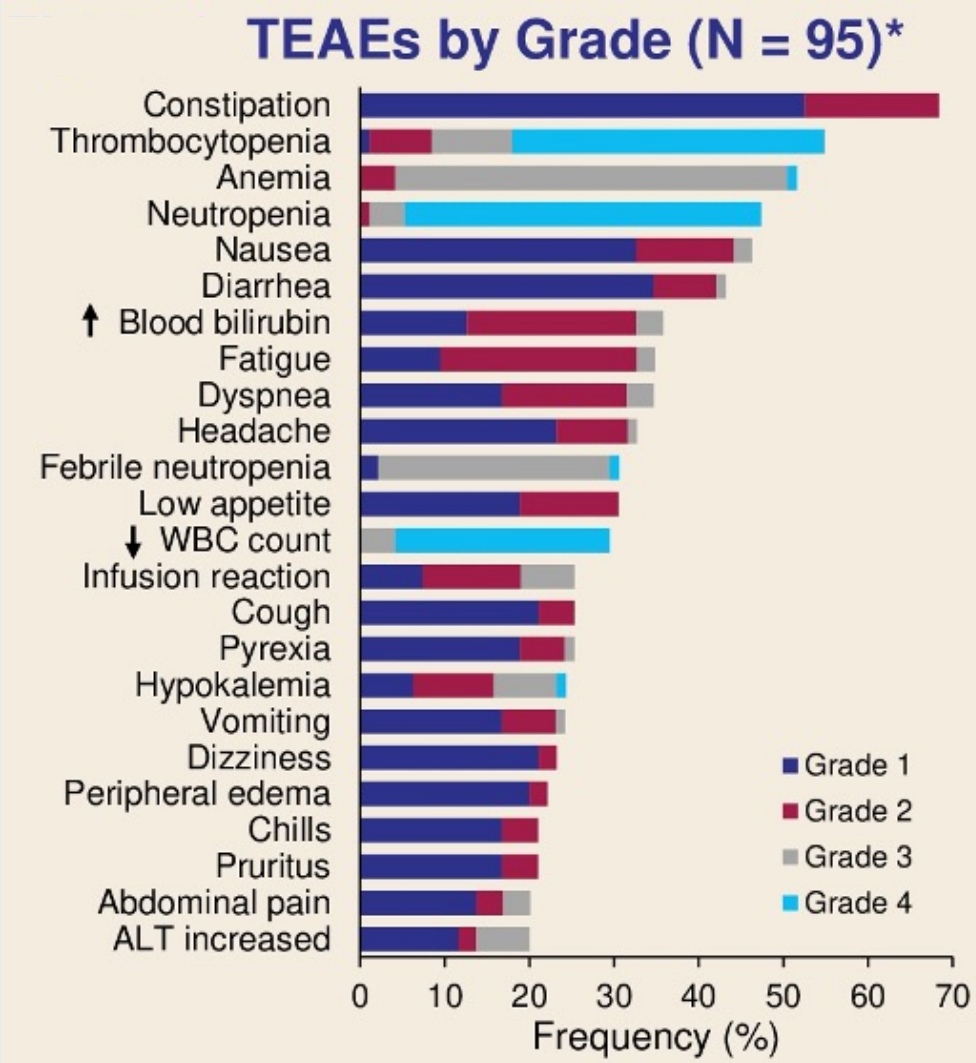
5F9005: Responses Over Time in Patients Achieving CR with Magrolimab in Combination with Azacitidine for Untreated HR MDS



CR = complete remission; mCR = morphologic CR; PR = partial remission; SD = stable disease; PD = progressive disease; SCT = stem cell transplantation

Sallman DA et al. ASCO 2022;Abstract 7017.

5F9005: TEAEs Reported in ≥20% of Patients Treated with Magrolimab in Combination with Azacitidine for Untreated HR MDS



- Grade ≥ 3 TEAEs occurred in 90.5% of patients (magrolimab related, 60.0%; AZA related, 69.5%).
- Serious AEs were reported in 63.2% of patients.
- TEAEs led to death in 8 patients: pneumonia in 2 patients†; COVID-19, intracranial hemorrhage, leukemia, myocardial ischemia, pulmonary embolism, and sepsis in 1 patient each.
- Grade 4 anemia was not magrolimab related.

TEAEs = treatment-emergent adverse events; AEs = adverse events

Sallman DA et al. ASCO 2022;Abstract 7017.

5F9005: Author Conclusions

- Magrolimab + AZA is well tolerated in patients with HR-MDS.
  - Low rates of discontinuation due to AEs were shown.
  - No significant immune-related reactions occurred.
  - Expected on-target anemia was manageable with priming dose mitigation.
- Promising efficacy was shown in both *TP53*-wt and *TP53*-mut patients.
- Magrolimab + AZA is being studied in patients with HR-MDS in the Phase 3 ENHANCE trial (currently recruiting; NCT04313881).

Sallman DA et al. ASCO 2022;Abstract 7017.

Poster TPS7055

Magrolimab + Azacitidine versus Azacitidine + Placebo in Untreated Higher Risk Myelodysplastic Syndrome: The Phase 3, Randomized, Double-Blind ENHANCE Study

Guillermo Garcia Manero[1], Naval G. Daver[1], Jin Xu[2], Mark Chao[2], Trisha Chung[2], Anderson Tan[2], Yan V. Wang[2], Andrew H. Wei[3], Paresh Vyas[4], and David A. Sallman[5]

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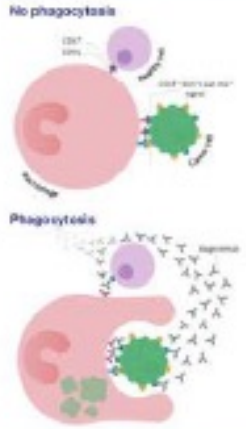
Background

- Myelodysplastic syndrome (MDS) is a clonal myeloid disorder characterized by cytopenia and ineffective hematopoiesis[1].
- MDS is a disease of the elderly, with a median age of 71-76 years at diagnosis[1,2]; prognosis and treatment are guided by the Revised International Prognostic Scoring System (IPSS-R) criteria[3].
- Patients with intermediate, high and very high risk MDS (HR-MDS) have a median overall survival (OS) of 0.8 to 3 years[4].
- Despite the high unmet need in this patient population, azacitidine and decitabine are the only approved therapies for HR-MDS to date[5].
- Magrolimab is a first-in-class monoclonal antibody that blocks the macrophage inhibitory immune checkpoint cluster of differentiation (CD)47, a "do not eat me" signal overexpressed on tumor cells[6].
- Binding of magrolimab to CD47 leads to phagocytosis of tumor cells[6].
- Azacitidine increases expression of prophagocytic "eat me" signals, facilitating synergy with magrolimab[7].
- In an ongoing Phase 1b study, the combination of magrolimab + azacitidine induces an overall response rate (ORR) of 91%, a complete response rate of 42% (with no duration of response [DOR] reached), and an acceptable safety profile without significant immune-related adverse events[8].
- ENHANCE (NCT04313881) is a Phase 3 trial comparing the efficacy and safety of magrolimab + azacitidine with that of azacitidine + placebo in previously untreated patients with HR-MDS[9].

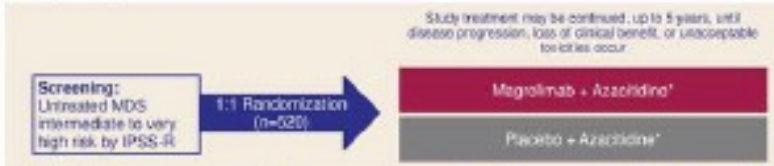
Magrolimab Mechanism of Action[6]



Objectives

- To evaluate the efficacy of magrolimab + azacitidine compared to that of azacitidine + placebo in previously untreated patients with HR-MDS by IPSS-R.
- To evaluate safety, pharmacokinetics, pharmacodynamics, and immunogenicity of magrolimab + azacitidine.

Study Design



Dosing	Cycle* 1	Cycle 2	Cycle 3 and Beyond
Magrolimab	Priming (1 mg/kg) on Days 1 and 4 15 mg/kg on Day 8 30 mg/kg on Days 11, 15, 22	30 mg/kg on Days 1, 8, 15, 22	30 mg/kg QDW on Days 1, 15
Placebo (saline)	Days 1, 4, 8, 11, 15, 22	Days 1, 8, 15, 22	Days 1, 15
Azacitidine	75 mg/m² IV or SC on Days 1-7 (or Days 1-5 and 8-9) every cycle		

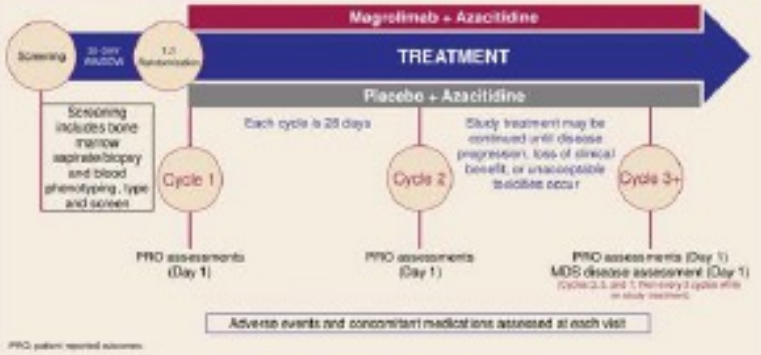
*Each cycle is 28 days.
IV, intravenous; SC, subcutaneous; QDW, every 2 weeks.

Endpoints

Primary Endpoints:	Secondary Endpoints:		
• CR rate*	• Duration of CR	• MRD-negative response rate	• Safety
• OS	• ORR and DOR	• Time to transformation to AML	• Anti-magrolimab antibody rate
Exploratory:	• RBC transfusion independence rate	• Serum concentration of magrolimab	• FACT-Anemia response rate
• Biomarkers	• PFS	• EFS	

*Based on investigator-assessed International Working Group 2006 MDS criteria[10]. AML, acute myeloid leukemia; CR, complete response; EFS, event free survival; FACT, Functional Assessment of Cancer Therapy; MRD, minimal residual disease; PFS, progression-free survival; RBC, red blood cell.

ENHANCE Key Assessments and Timing



PRO, patient reported outcomes

Patient Eligibility

ENHANCE Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Previously untreated individuals with intermediate to very high risk MDS by IPSS-R	• Prior treatment with CD47 or Signal-regulatory protein alpha (SIRPα)-targeting agents
• Adequate performance status and hematologic, liver, and kidney function	• Any prior antileukemic therapy for treatment of intermediate, high, very high risk MDS per IPSS-R
	• Contraindications to azacitidine
	• Clinical suspicion of active central nervous system involvement by MDS
	• Known active or chronic hepatitis B or C infection or human immunodeficiency virus
	• Pregnancy or active breastfeeding

Note: Other protocol defined inclusion/exclusion criteria may apply.

Enrollment

- The study opened to accrual in September 2020 and is currently recruiting participants at 37 study sites in the United States, and 16 study sites in Australia.

- **United States Sites:** Alabama, California, Florida, Georgia, Illinois, Kansas, Maryland, Michigan, Missouri, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Wisconsin
- **Australia Sites:** New South Wales, Queensland, South Australia, Tasmania, Victoria

- Additional information available at ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04313881

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2. Ma X, et al. *Cancer*. 2007;109(8):1536-1542.
3. Sperling AS, et al. *Nature Reviews Cancer*. 2017;17(1):5.
4. Greenberg PL, et al. *Blood*. 2012;120(12):2454-2465.
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6. Liu J, et al. *PLOS One*. 2015;10(9):e0137345.
7. Feng D, et al. Poster presented at: 60th ASH Annual Meeting and Exposition; 01-04 December 2018; San Diego, CA. Abstract 615.
8. Sallman D, et al. Presented at: 25th EHA Annual Congress; 11-21 June 2020; Virtual EHA 2020. Abstract #S187.
9. ENHANCE Protocol SF9009 Amendment 2. 09 October 2020.
10. Cheson BD, et al. *Blood*. 2006;108(2):419-425.

Acknowledgments

We extend our thanks to the patients, family, friends, and caregivers, as well as to the study staff. This study was funded by Gilead Sciences, Inc.

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Garcia-Manero G et al. ASCO 2021;Abstract TPS 7055.

RTP RESEARCH TO PRACTICE

ENHANCE Phase III Study Design

Study treatment may be continued, up to 5 years, until disease progression, loss of clinical benefit, or unacceptable toxicities occur

Screening:
Untreated MDS intermediate to very high risk by IPSS-R

1:1 Randomization (n=520)

- Magrolimab + Azacitidine*
- Placebo + Azacitidine*

Dosing	Cycle* 1	Cycle 2	Cycle 3 and Beyond
Magrolimab	Priming (1mg/kg) on Days 1 and 4 15 mg/kg on Day 8 30 mg/kg on Days 11, 15, 22	30 mg/kg on Days 1, 8, 15, 22	30 mg/kg Q2W on Days 1, 15
Placebo (saline)	Days 1, 4, 8, 11, 15, 22	Days 1, 8, 15, 22	Days 1, 15
Azacitidine	75 mg/m^2 IV or SC on Days 1-7 (or Days 1-5 and 8-9) every cycle		

*Each cycle is 28 days.
IV, intravenous; SC, subcutaneous; Q2W, every 2 weeks.

Garcia-Manero G et al. ASCO 2021;Abstract TPS 7055.

Partial Clinical Hold for Studies Evaluating Magrolimab in Combination with Azacitidine

Press Release: January 25, 2022

"The US Food and Drug Administration (FDA) has placed a partial clinical hold on studies evaluating the combination of magrolimab plus azacitidine due to an apparent imbalance in investigator-reported suspected unexpected serious adverse reactions (SUSARs) between study arms. While no clear trend in the adverse reactions or new safety signal has been identified at this time, the partial clinical hold is being implemented across all ongoing magrolimab and azacitidine combination studies worldwide in the best interests of patients as additional data is gathered and analyzed to address the concerns raised by FDA.

During the partial clinical hold, screening and enrollment of new study participants will be paused in any study investigating the combination of magrolimab with azacitidine. Patients already enrolled in these clinical studies may continue to receive magrolimab and azacitidine, or placebo, and continue to be closely monitored according to the current study protocol... Other magrolimab studies, or cohorts, that are not studying the combination of magrolimab plus azacitidine, will continue without any impact by the partial clinical hold."

https://finance.yahoo.com/news/gilead-announces-partial-clinical-hold-235200540.html

RTP RESEARCH TO PRACTICE

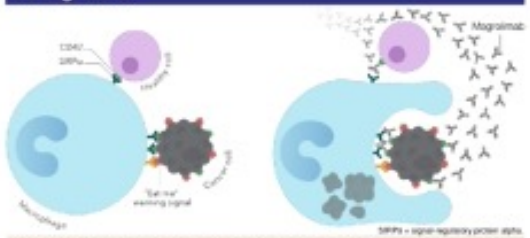
Poster 7054

Impact of Magrolimab Treatment in Combination with Azacitidine on Red Blood Cells in Higher-Risk Myelodysplastic Syndrome (HR-MDS) Patients

James Y. Chen[1], Lisa Johnson[2], Kelly M. McKenna[2], Timothy S. Choi[2], Jiaqi Duan[2], Dongdong Feng[2], Jonathan M. Tsai[3], Natalia Garcia-Martin[4], Kavitha Sompalli[2], Roy Maute[2], Paresh Vyas[4], Ravindra Majeti[5], Chris H.M. Takimoto[2], Jie Liu[1], Giridharan Ramsingh[2], Mark P. Chao[2], Jens-Peter Volkmer[2*], Irving L. Weissman[6*]

[1]Stanford University School of Medicine, Stanford, CA, USA; [2]Gilead Sciences, Inc., Foster City, CA, USA; [3]Brigham and Women's Hospital, Boston, MA, USA; [4]Weatherall Institute for Molecular Medicine, University of Oxford, Oxford, UK; [5]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, CA, USA; [6]Ludwig Center for Cancer Stem Cell Research, Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, CA, USA; *contributed equally

Background



Magrolimab is a monoclonal immunoglobulin (Ig)G4 antibody (Ab) that blocks CD47, a "don't eat me" signal expressed on cancer cells to escape immune surveillance and macrophage-mediated clearance. Prior preclinical studies have shown that CD47 is critical to red blood cell (RBC) homeostasis, with CD47 deficiency decreasing RBC half-life.[1] Fc-mediated opsonization also depletes RBCs, raising concerns for potential on-target anemia from anti-CD47 agents via multiple mechanisms. Notwithstanding, several clinical trials have demonstrated that magrolimab can be safely administered as a monotherapy with an initial lower "priming" dose, yielding transient anemia with compensatory reticulocytosis, with anemia not observed at subsequent higher maintenance doses.[2,3] However, the mechanism underlying this observed protection has not been fully defined. Here we describe manageable anemia in patients with treatment-naive/unfit (TN/U) HR-MDS and acute myeloid leukemia (AML) treated with magrolimab in combination with azacitidine (AZA) and further investigate these underlying mechanisms in preclinical models.

Methods

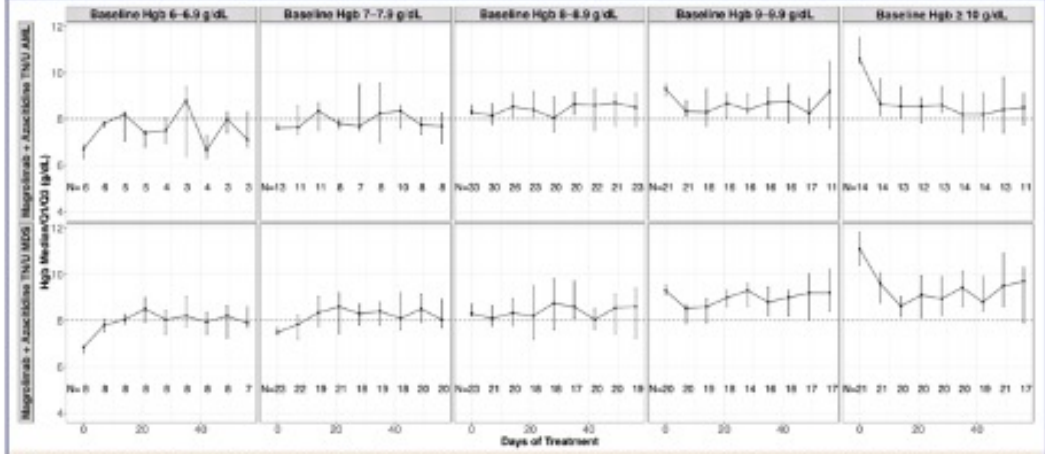
In a multicenter, prospective study (NCT03248479), patients with TN/U HR-MDS (n = 95) or AML (n = 87) were treated with magrolimab in combination with AZA. Magrolimab was administered intravenously as a 1 mg/kg priming dose on Days 1 and 4, then ramp-up to 30 mg/kg weekly or every 2 weeks maintenance dosing. AZA 75 mg/m^2 was administered on Days 1-7 of each 28-day cycle. Complete blood counts, peripheral blood, and bone marrow were collected at prespecified time points to analyze hemoglobin (Hgb) levels and CD47 expression. Flow cytometry analysis for CD47 expression and magrolimab binding was conducted with anti-IgG4 and anti-CD45. RBCs were defined as CD45 negative and white blood cells (WBCs) as CD45 positive.

Preclinical modeling studies were conducted to further investigate the underlying mechanism of CD47 loss from RBCs, using the following mouse models and reagents:

- Mouse models: C57BL/6J, FcG1,3 knockout (KO; Fcer1g KO, B6.129P2-Fcer1gtm1Rav N12), FcG2 KO (Fcgr2b KO, B6.129S4-Fcgr2btm1T9K N12), C57BL/6J B-hSIRPA/hCD47.
- Antibodies: anti-CD47 (MIAP410), anti-CD47 (magrolimab), anti-IgG4 (G17-4), CD45 (2D1), anti-IgG1 (RMG1-1); anti-CD47 Fab and F(ab')2 fragments were generated from intact anti-CD47 Ab (MIAP410) by digestion using immobilized ficin and purified over protein A resin. Purity was assessed by SDS-PAGE.

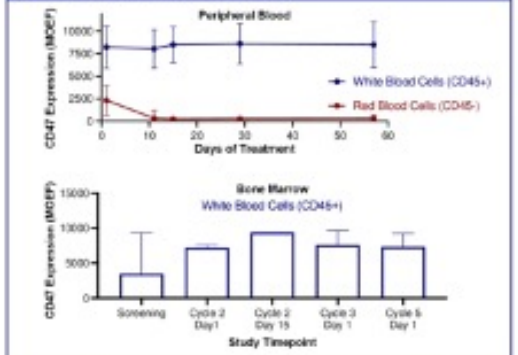
Results

Therapeutic Prime–Maintenance Dosing Regimen Enables Manageable Anemia in Patients with HR-MDS and AML



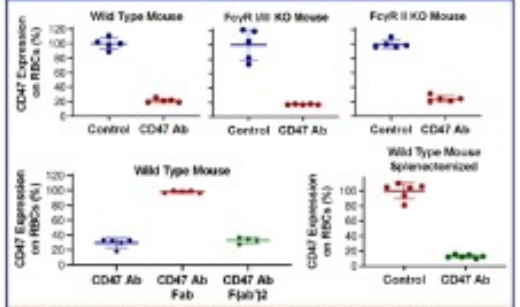
- Hgb trends over time of TN/U HR-MDS and AML patients treated with magrolimab at 1 mg/kg priming dose followed by 30 mg/kg maintenance dose in combination with AZA (NCT03248479)
- Patients are grouped based on baseline Hgb levels, as indicated.

CD47 Loss Is Limited to RBCs



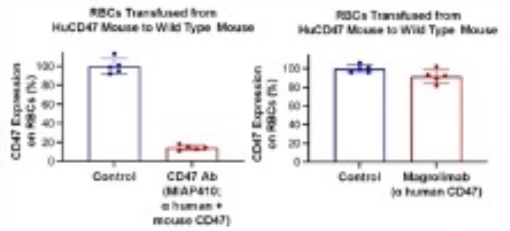
- CD47 expression over time analyzed in peripheral blood and bone marrow of TN/U MDS patients dosed with magrolimab in combination with AZA (NCT03248479).

CD47 Loss Is Not Mediated by Fc or Splenic Function



- CD47 expression on RBCs in splenectomized vs sham surgery mice
- RBC CD47 expression in wild-type mice (left) vs Fc gamma receptor (FcγR) I/III KO mice (middle) and FcγR II KO mice (right) treated with phosphate-buffered saline (blue) or anti-CD47 (red)
- RBC CD47 expression in mice treated with intact anti-CD47 (blue), CD47 Fab (red), and anti-CD47 F(ab')2 (green)

CD47 Loss Is Mediated by CD47 Cross-linking of RBCs with Non-RBCs



- Donor mouse RBCs that exclusively expressed human CD47 were transfused into wild-type recipients that exclusively expressed mouse CD47.
- CD47 expression was measured post treatment with either an anti-mouse–human cross-reactive CD47 Ab (MIAP410) or anti-human specific CD47 Ab (magrolimab).

Results

Combination treatment of magrolimab with AZA resulted in manageable anemia that correlated with a rapid, near-complete loss of CD47 from RBCs, but not WBCs. The initial 1 mg/kg priming dose was sufficient for this CD47 loss, which persisted under subsequent 30 mg/kg maintenance doses. Both findings are consistent with prior clinical observations in solid-tumor patients with magrolimab monotherapy and lymphoma patients in combination with rituximab.[2,3] Our preclinical studies with mouse models revealed that the CD47 removal is mechanistically independent of previously described RBC antigen modulation mechanisms and cellular compartments. Instead, this CD47 loss requires anti-CD47 cross-linking between RBCs and non-RBCs.

Conclusions

Overall, these results support that on-target magrolimab-mediated anemia is manageable in patients with HR-MDS and AML who are treated with magrolimab in combination with AZA.

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1. Oldenborg PA, et al. *Science*. 2000;288:2051-2054.
2. Advani R, et al. *N Engl J Med*. 2018;379(18):1711-1721.
3. Sikic BI, et al. *J Clin Oncol*. 2019;37(12):946-953.

Acknowledgments

We thank the late Dr. Stanley Schrier, former Chief of Stanford Hematology, for his scientific guidance. This study was funded by Gilead Sciences, Inc.

Correspondence: chenjyt@gmail.com

Presented at American Society of Clinical Oncology 2022 Annual Meeting; June 3-7, 2022; Chicago, IL.

Chen JY et al. ASCO 2022;Abstract 7054.

Efficacy and Safety of Sabatolimab in Combination with Hypomethylating Agents in Patients with Very High/High-Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia: Final Analysis from a Phase Ib Study

Andrew M. Brunner,[1] Jordi Esteve,[2] Kimmo Porkka,[3] Steve Knapper,[4] Elie Traer,[5] Sebastian Scholl,[6] Guillermo Garcia-Manero,[7] Norbert Vey,[8] Martin Wermke,[9] Jeroen Janssen,[10] Rupa Narayan,[1] Sun Loo,[11] Natalia Tovar,[2] Mika Kontro,[3] Oliver Ottmann,[4] Purushotham Naidu,[12] Marc Pelletier,[13] Andrew Lewandowski,[13] Na Zhang,[13] Anisa Mohammed,[12] Mikael L. Rinne,[13] Uma Borate,[5*] Andrew H. Wei[14*]

*Co-senior authors Uma Borate and Andrew H. Wei contributed equally to this work.

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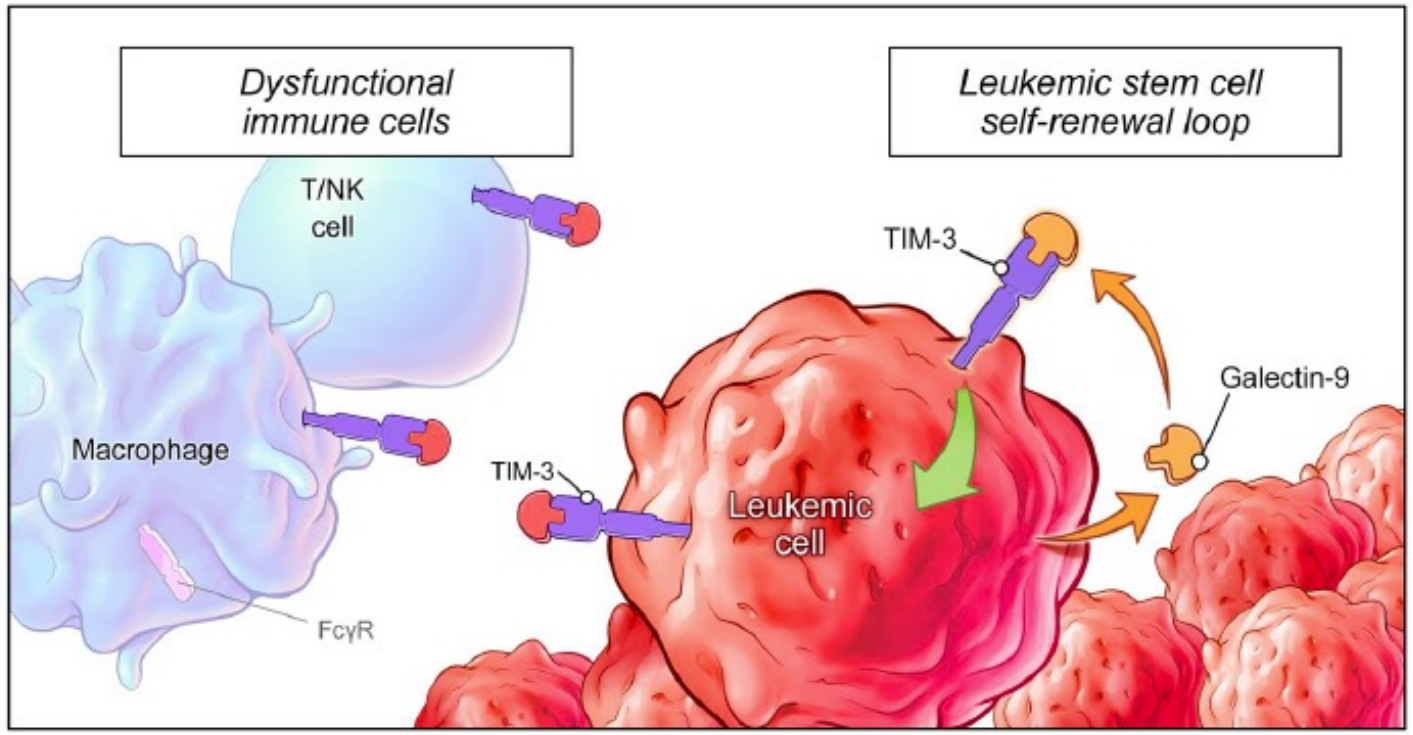
ASH 2021;Abstract 244.

TIM-3 is an immuno-myeloid regulator expressed on immune and leukemic cells



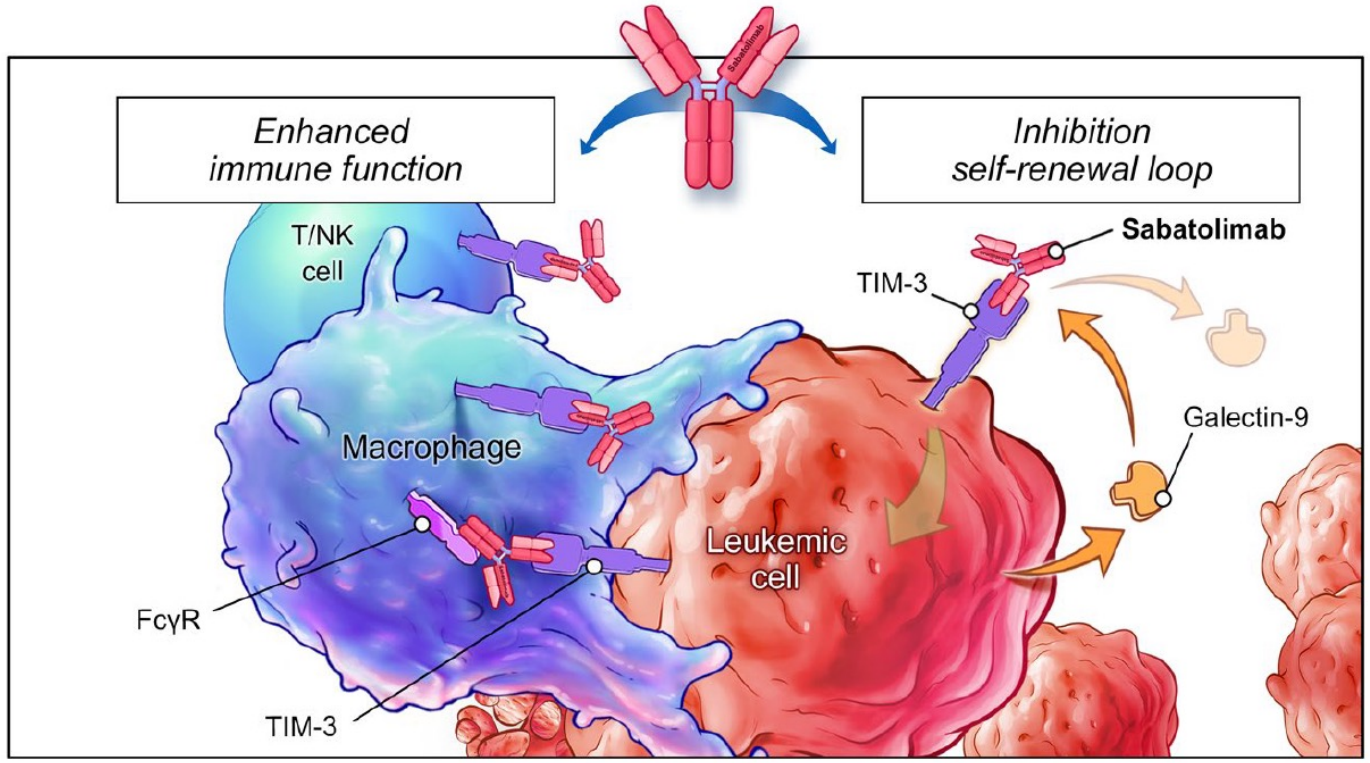
- TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- TIM-3 is aberrantly expressed on LSCs and blasts, but not on normal HSCs,[1-5] which makes it a promising target in treatment for MDS and AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which promotes LSC self-renewal[2,7,8]

FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; LSC, leukemic stem cell; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264; 2. Das M, et al. *Immunol Rev*. 2017;276(1):97-111; 3. Kikushige Y, Miyamoto T. *Int J Hematol*. 2013;98(6):627-633; 4. Kikushige Y, et al. *Cell Stem Cell*. 2010;7(6):708-717; 5. Ngiow SF. *Cancer Res*. 2011;71(10):3540-3551; 6. Sakuishi K, et al. *Trends Immunol*. 2011;32(8):345-349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

Brunner AM et al. ASH 2021;Abstract 244.

Sabatolimab targets TIM-3 on immune and leukemic cells: A novel immuno-myeloid therapy



- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts[1-4]
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

LSC = leukemic stem cell

Brunner AM et al. ASH 2021;Abstract 244.

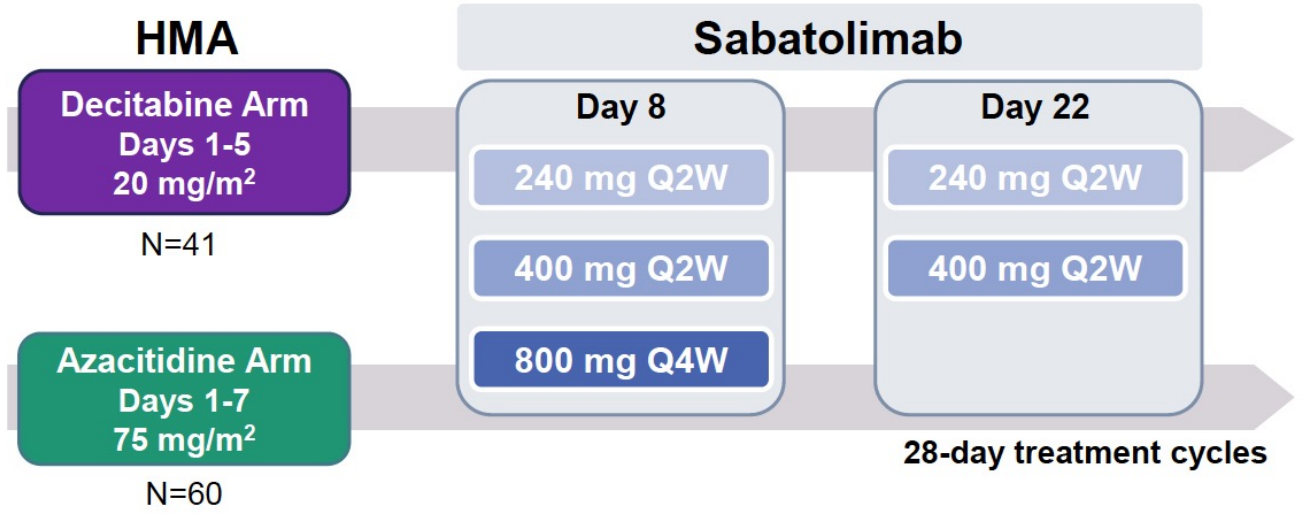
Phase Ib Trial Design of Sabatolimab Combined with HMA for MDS and AML

vHR/HR-MDS: IPSS-R high- or very high-risk MDS

ND-AML: Unfit, newly diagnosed AML, ineligible for standard chemotherapy

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: **NCT03066648**[a]



8 countries

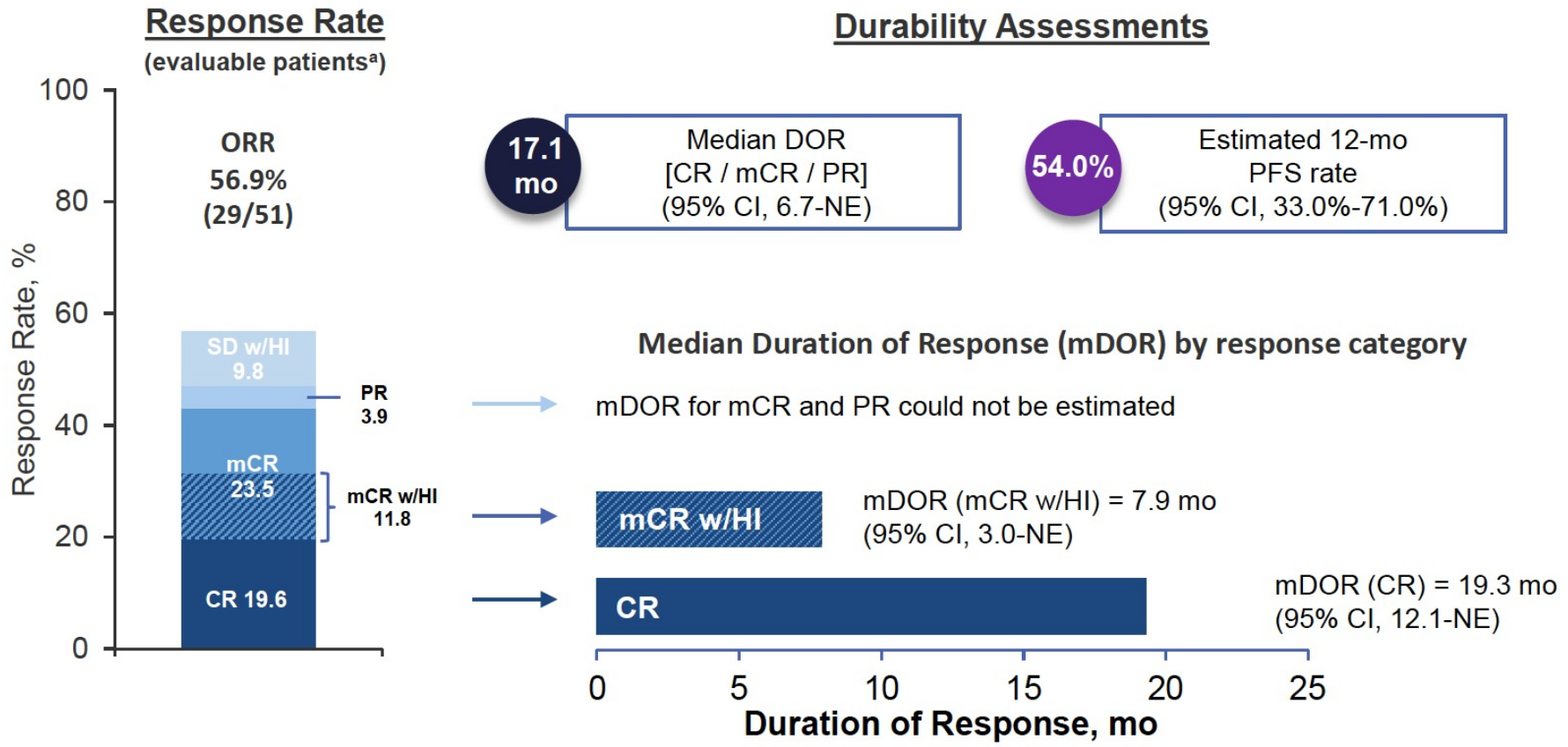
11 trial centers

Primary Endpoints:
Maximum tolerated dose/recommended dose, safety, and tolerability
Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

[a]Multi-arm, open-label, Phase Ib dose-escalation and -expansion study of sabatolimab as a single agent or in combination with HMAs or spartalizumab.
AML, acute myeloid leukemia; HMA, hypomethylating agent; HR, high-risk; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; ND, newly diagnosed; Q2W, every 2 weeks; Q4W, every 4 weeks; vHR, very high-risk.

Brunner AM et al. ASH 2021;Abstract 244.

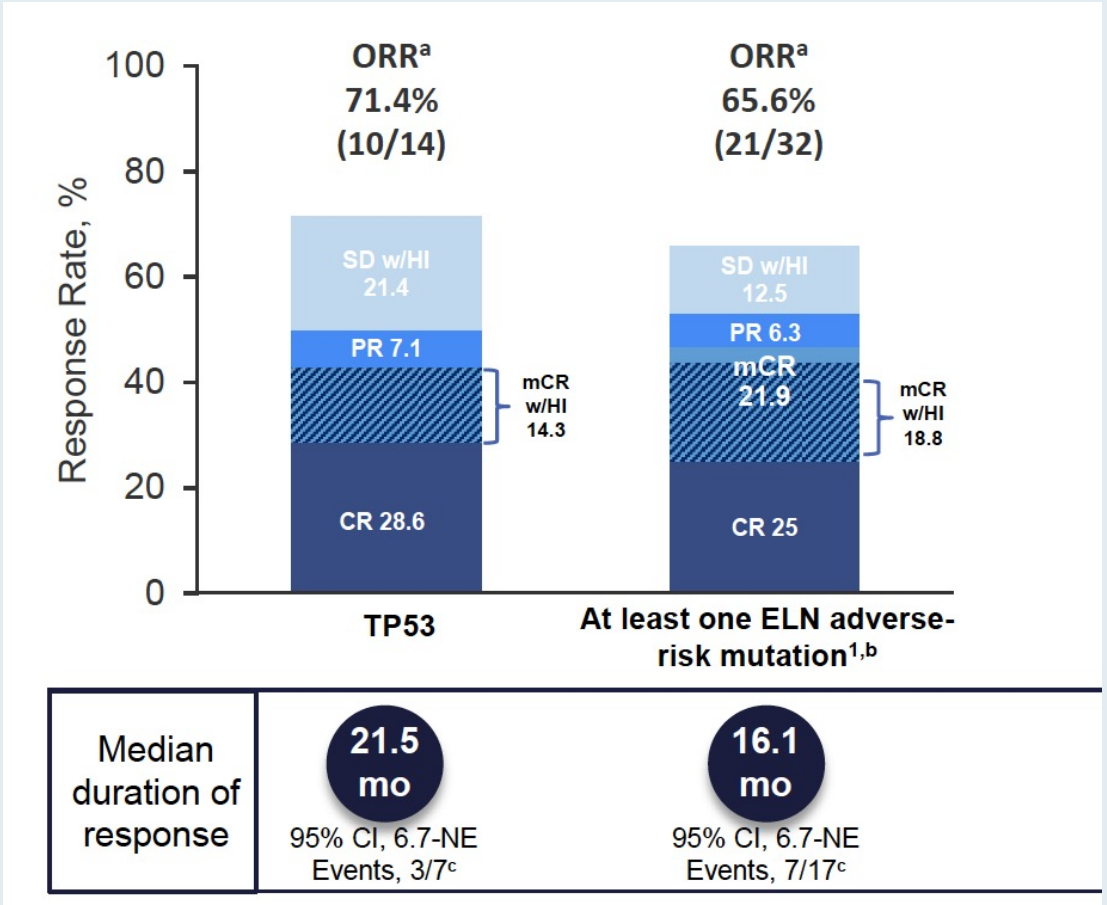
Clinical Responses Associated with Sabatolimab Combined with HMA for Very High-Risk or High-Risk MDS



[a]Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.
CR, complete remission; DOR, duration of response; HI, hematologic improvement; mCR, bone marrow CR; mDOR, median duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Brunner AM et al. ASH 2021;Abstract 244.

Durability of Responses Associated with Sabatolimab Combined with HMA for Very High-Risk or High-Risk MDS

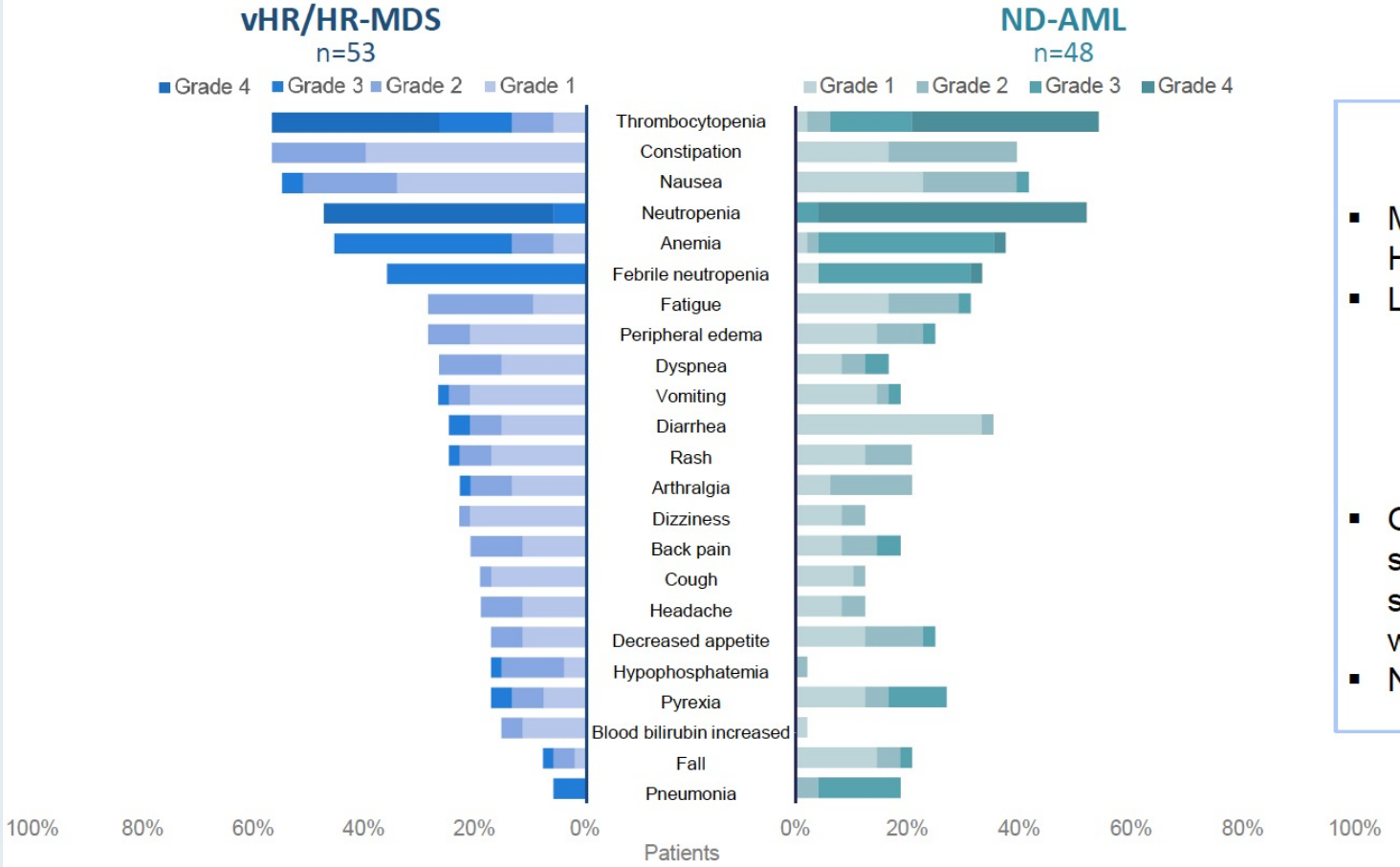


[a]ORR for patients with MDS was defined as CR + mCR + PR + SD with HI; [b]ELN adverse-risk mutations: TP53, ASXL1, and RUNX1; [c]DOR events (including progression/relapse and death) reported out of the number of patients with a BOR of CR, mCR, or PR (forMDS). 1.Döhner H, et al. Blood.2017;129(4):424-447.

Brunner AM et al. ASH 2021;Abstract 244.

Adverse Events Associated with Sabatolimab Combined with HMA for MDS and AML

Most commonly occurring AEs ***(≥15% in either population, regardless of relationship to treatment)***



[a]Dose interruption: Cycle delay >7 days.

vHR/HR-MDS and ND-AML AEs

- Most common reported AEs were consistent with HMA alone
- Low rate of sabatolimab dose modification:
  - 1/101 (1%) patients had dose reduction
  - 38/101 (38%) patients had dose interruption[a] due to AE
  - No patient with vHR/HR-MDS and only 3 with ND-AML discontinued treatment due to an AE
- One patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other treatment-related deaths were reported
- No DLTs in vHR/HR-MDS and only 1 in ND-AML

ND-AML = newly diagnosed AML; AEs = adverse events; DLTs = dose-limiting toxicities

Brunner AM et al. ASH 2021;Abstract 244.

STIMULUS: Clinical Trial Program for Sabatolimab for MDS

Trial identifier	Phase	Setting	Study arms
STIMULUS-MDS1 (NCT03946670)	II	IPSS-R Intermediate-, High- or Very High-risk MDS	• Sabatolimab + HMA • Placebo + HMA
STIMULUS-MDS2 (NCT04266301)	III	High- or Very High-risk MDS	• Sabatolimab + azacitidine • Placebo + azacitidine
STIMULUS-MDS3 (NCT04812548)	II	High- or Very High-risk MDS	• Sabatolimab + azacitidine + venetoclax

www.clinicaltrials.gov. Accessed March 8, 2022.

Management of MDS: Agenda
Where We Are, Where We're Headed

PROLOGUE: A Vision for the Future

MODULE 1: Classification and prognosis of MDS

MODULE 2: Current management of lower-risk MDS

MODULE 3: Current management of higher-risk MDS

MODULE 4: MDS-AML continuum and overlap – Venetoclax, other targeted therapy

MODULE 5: Immune checkpoint inhibitors – Magrolimab, sabatolimab

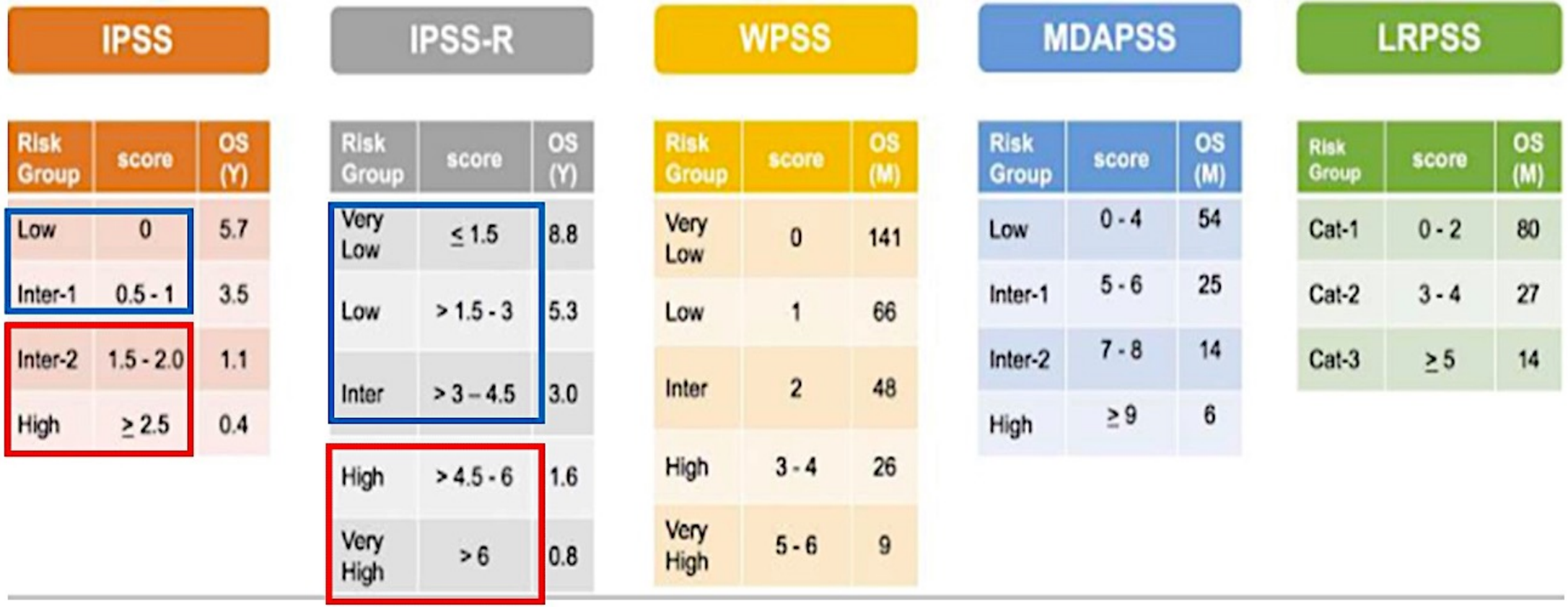
MODULE 6: Appendix

RTP
RESEARCH
TO PRACTICE

Clinical Prognostic Scoring

RTP
RESEARCH
TO PRACTICE

Clinical Prognostic Scores in MDS



IPSS

Risk Group	score	OS (Y)
Low	0	5.7
Inter-1	0.5 - 1	3.5
Inter-2	1.5 - 2.0	1.1
High	≥ 2.5	0.4

IPSS-R

Risk Group	score	OS (Y)
Very Low	≤ 1.5	8.8
Low	> 1.5 - 3	5.3
Inter	> 3 – 4.5	3.0
High	> 4.5 - 6	1.6
Very High	> 6	0.8

WPSS

Risk Group	score	OS (M)
Very Low	0	141
Low	1	66
Inter	2	48
High	3 - 4	26
Very High	5 - 6	9

MDAPSS

Risk Group	score	OS (M)
Low	0 - 4	54
Inter-1	5 - 6	25
Inter-2	7 - 8	14
High	≥ 9	6

LRPSS

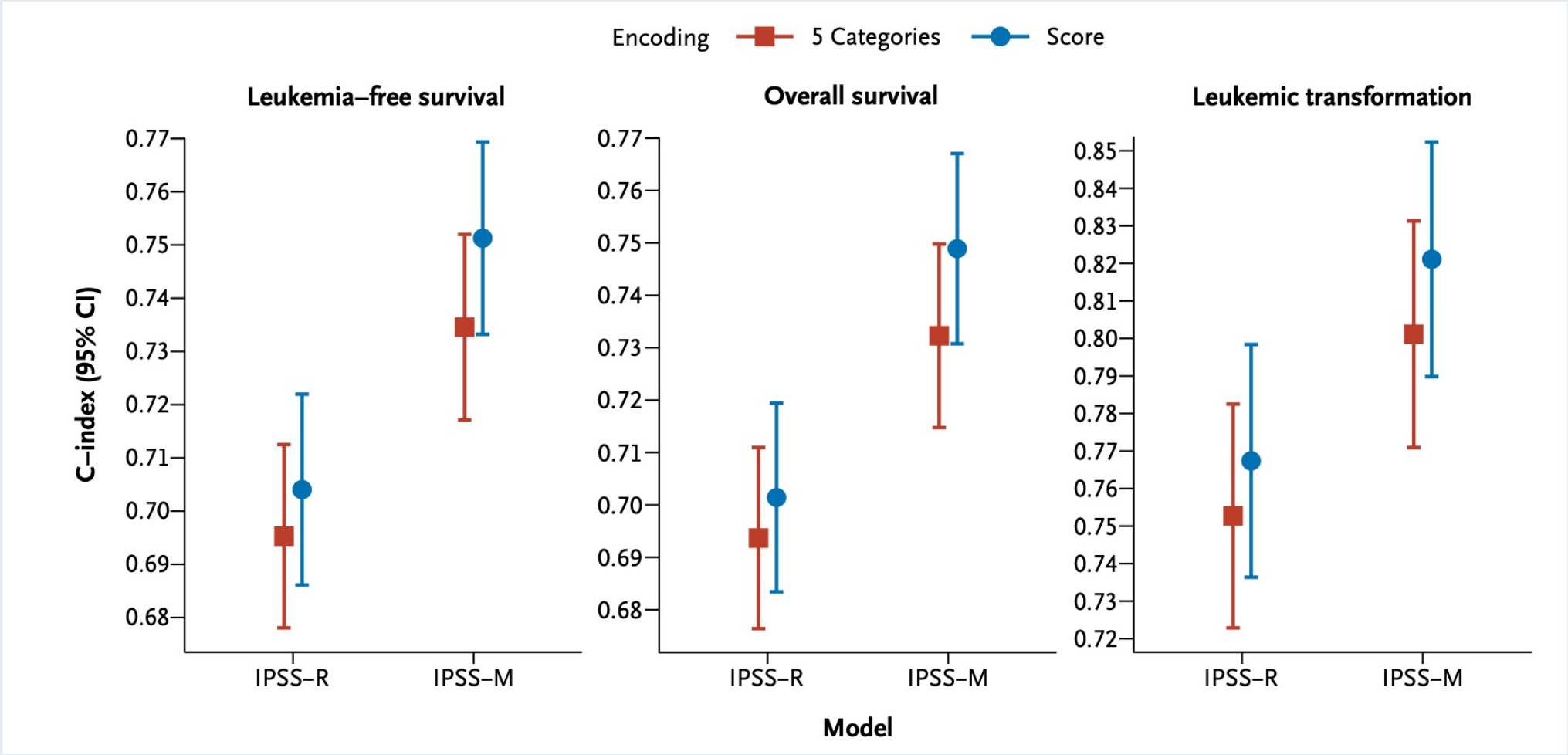
Risk Group	score	OS (M)
Cat-1	0 - 2	80
Cat-2	3 - 4	27
Cat-3	≥ 5	14

*IPSS-R validated in treated MDS (HMAs, lenalidomide) but not therapy related

Buckstein R. ASCO 2021 Education Session.

RTP RESEARCH TO PRACTICE

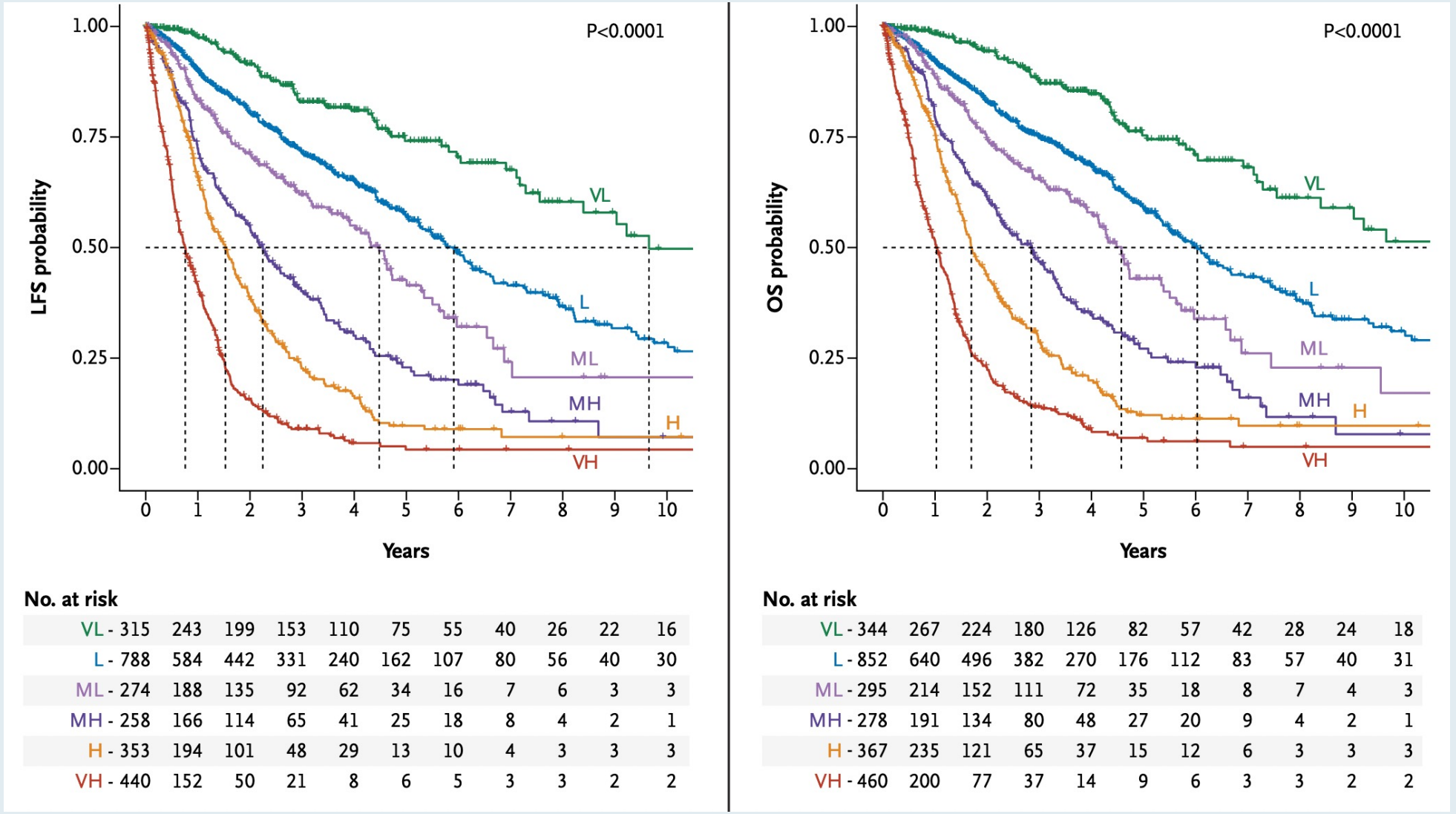
Comparison of the International Prognostic Scoring System – Revised and the International Prognostic Scoring System – Molecular



Bernard E et al. *NEJM Evidence* 2022;1(7).

RTP RESEARCH TO PRACTICE

IPSS-M Risk Score and Risk Categories



Bernard E et al. *NEJM Evidence* 2022;1(7).

RTP RESEARCH TO PRACTICE

Lower-Risk MDS

ASCERTAIN: Grade ≥3 Treatment-Emergent Adverse Events in Patients with Lower-Risk MDS

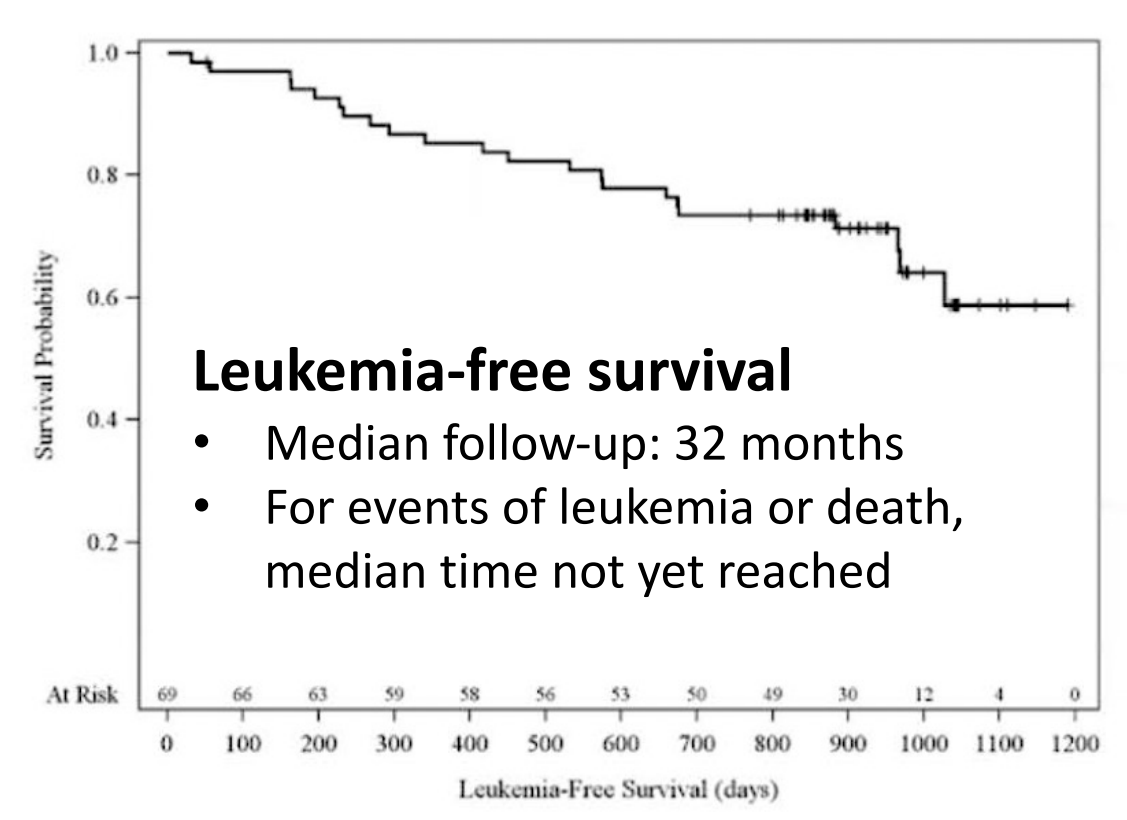
Preferred Term	Total in Cycles 1- 2 (N=66)	Total for Treatment Duration (N=66)
Neutropenia	30 (45.5%)	38 (57.6%)
Thrombocytopenia	26 (39.4%)	36 (54.5%)
Anemia	16 (24.2%)	27 (40.9%)
Leukopenia	13 (19.7%)	15 (22.7%)
Febrile Neutropenia	9 (13.6%)	19 (28.8%)
Pneumonia	3 (4.5%)	10 (15.2%)

- Safety profile consistent with that of decitabine
- Most grade 3 or higher events related to myelosuppression
- Febrile neutropenia and pneumonia increased with duration of treatment often reflecting progressive disease

There were no deaths in the first 56 days in patients receiving ASTX727.
A single subject died on study day 28 but had received IV decitabine cycle 1 and did not receive ASTX727
Total of subjects treated excludes 3 subjects who received IV decitabine cycle 1 but did not receive ASTX727

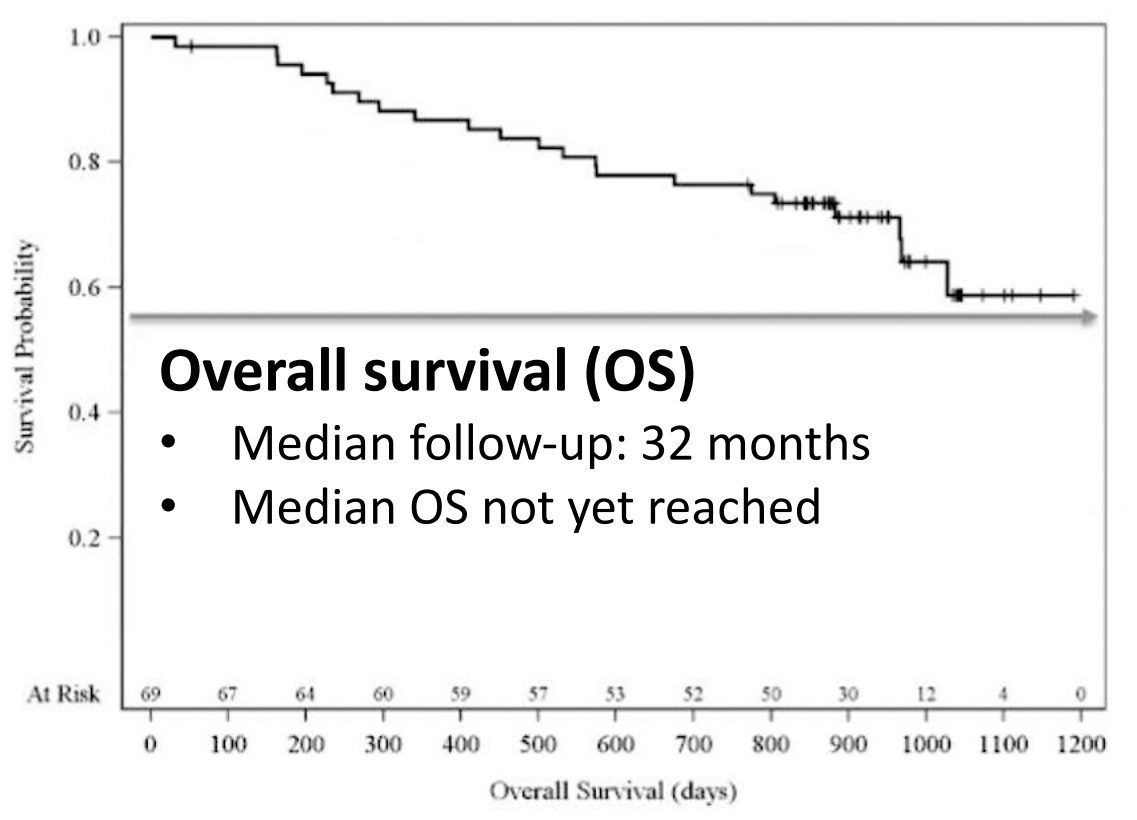
Garcia-Manero G et al. ASH 2021;Abstract 66.

ASCERTAIN: Survival Analyses of Patients with Lower-Risk MDS



Leukemia-free survival

- Median follow-up: 32 months
- For events of leukemia or death, median time not yet reached



Overall survival (OS)

- Median follow-up: 32 months
- Median OS not yet reached

Garcia-Manero G et al. ASH 2021;Abstract 66.

RTP RESEARCH TO PRACTICE

Blood 2020;136(6):674-83.

blood

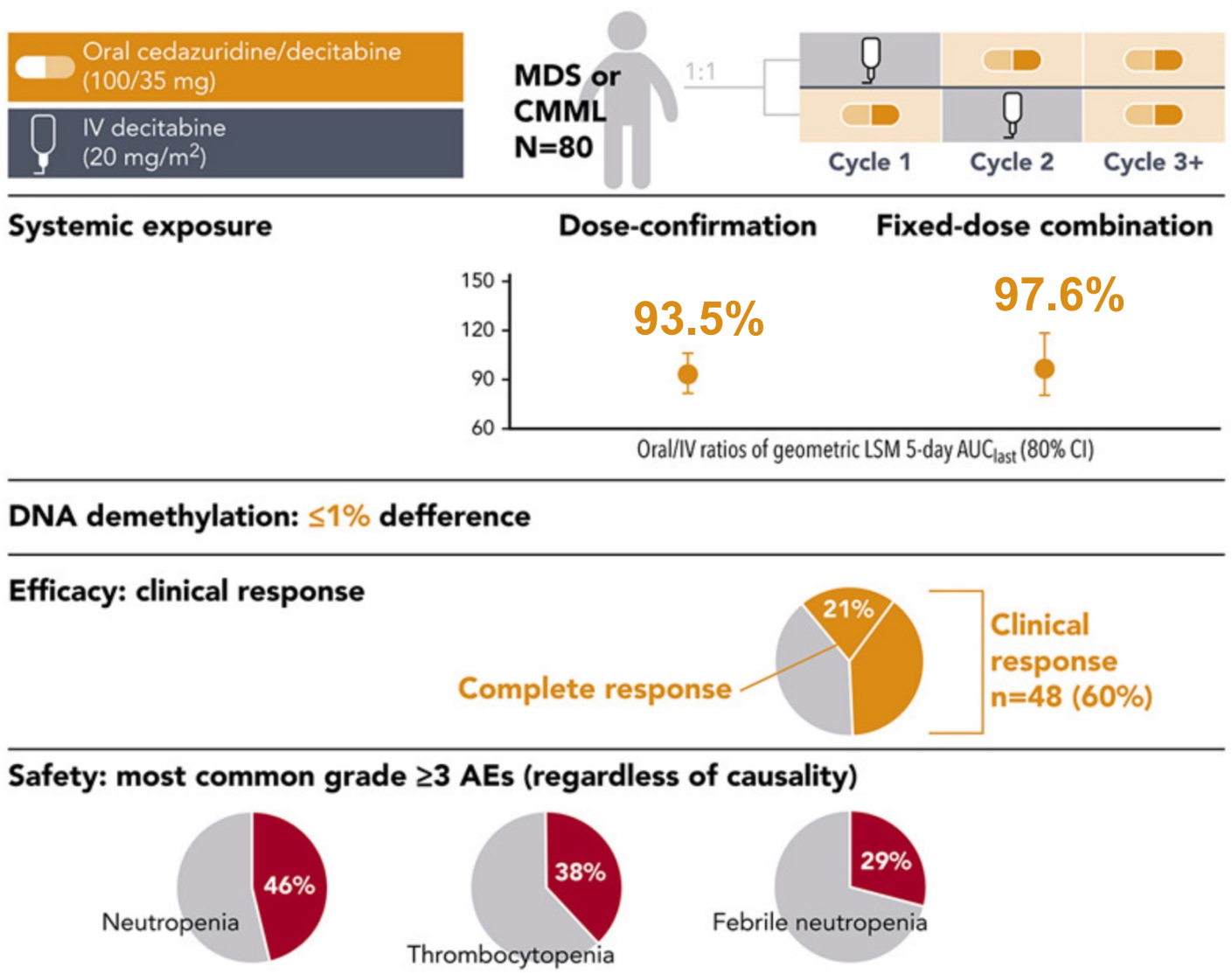
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study

Guillermo Garcia-Manero,[1] Elizabeth A. Griffiths,[2] David P. Steensma,[3] Gail J. Roboz,[4] Richard Wells,[5] James McCloskey II,[6] Olatoyosi Odenike,[7] Amy E. DeZern,[8] Karen Yee,[9] Lambert Busque,[10] Casey O'Connell,[11] Laura C. Michaelis,[12] Joseph Brandwein,[13] Hagop Kantarjian,[1] Aram Oganesian,[14] Mohammad Azab,[14] and Michael R. Savona[15]

ASTX727-01: Schema and Summary of Endpoints



Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

Pharmacokinetic Characteristics of Hypomethylating Agents

Agent	Bioavailability of single oral dose (% of parenteral)	$T_{1/2}$	T_{max} (range)	C_{max} in ng/mL (% coefficient of variation)
Azacitidine IV[34,40]	100%	4h	0.5h	Similar to SQ
Azacitidine SQ[34,40]	89%	4h	0.5h (0.2–1.1)	750 (54%)
CC-486[40,52]	11%	0.5h	1h (0.47–2)	145 (64%)
Decitabine IV[35]	100%	0.5h	1h	147 (49%)
Decitabine PO[41]	3.9%-14.1%	0.36–0.93h	0.5h	—
C-DEC[43]	60% (55–65) D1; 106% (98–114) D5	1.5h	1h (0.3–3.0)	145 (55%)

C-DEC = decitabine-cedazuridine

Griffiths EA. ASH 2021 Education Program.

Features in Lower-Risk MDS that Suggest Higher-Risk Behavior

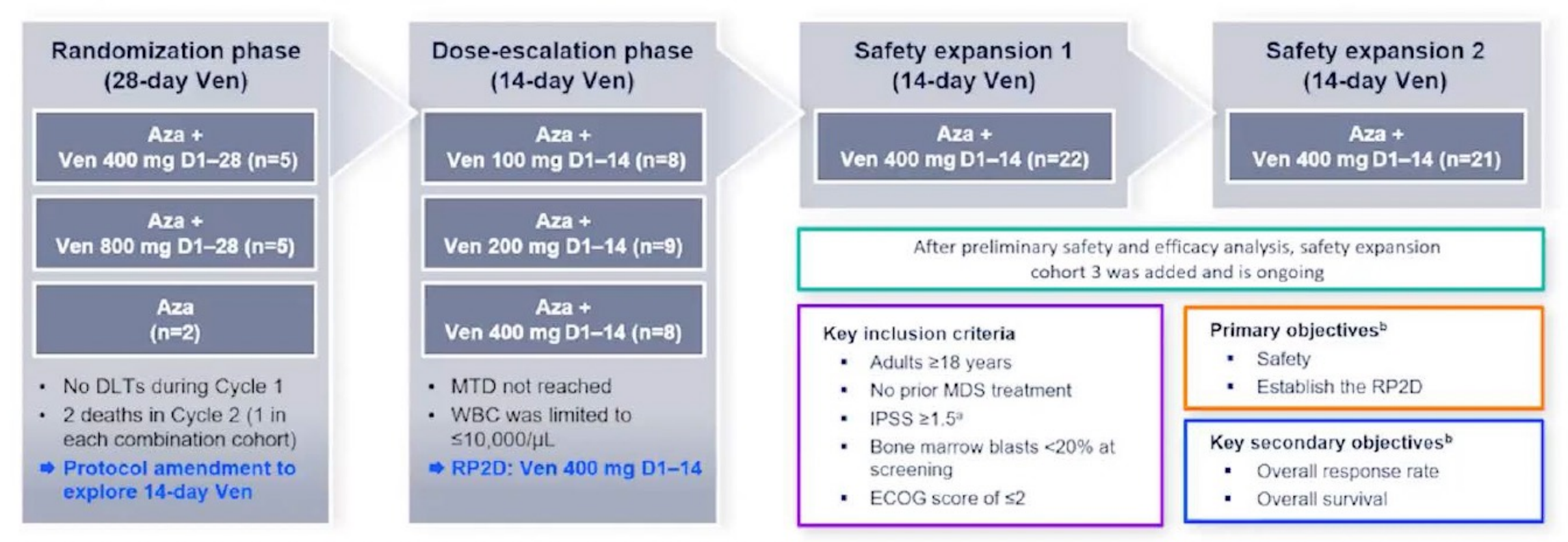
MDS characteristic	Feature associated with lesser prognosis
Etiology of MDS	Treatment related, can behave in a heterogenous fashion
Fibrosis in core biopsy	Grade 2 or higher
Cytopenia	Symptomatic neutropenia
	Decrease in PLTs >25%
	Ongoing RBC transfusion dependence
	Anemia or thrombocytopenia refractory to transfusions
Karyotype	Clonal emergence of unfavorable karyotype
Somatic mutations	Multiple mutations (≥3 somatic mutations)
	T53, *RUNX1*, *ASXL1* mutations
	Absence of *SF3B1* mutation (especially in MDS with ring sideroblasts)
	Multiple somatic mutations
Inherited predisposition	Patients with known germline variant in their disease may be less likely to respond to traditional therapies and require stem cell therapy sooner
Treatment response	Primary treatment failure vs secondary failure

DeZern AE. ASH 2021 Education Program.

RTP RESEARCH TO PRACTICE

Higher-Risk MDS

Phase Ib Study of Venetoclax + Azacitidine for Treatment-Naïve High-Risk MDS



Garcia JS et al. ASH 2021;Abstract 241.

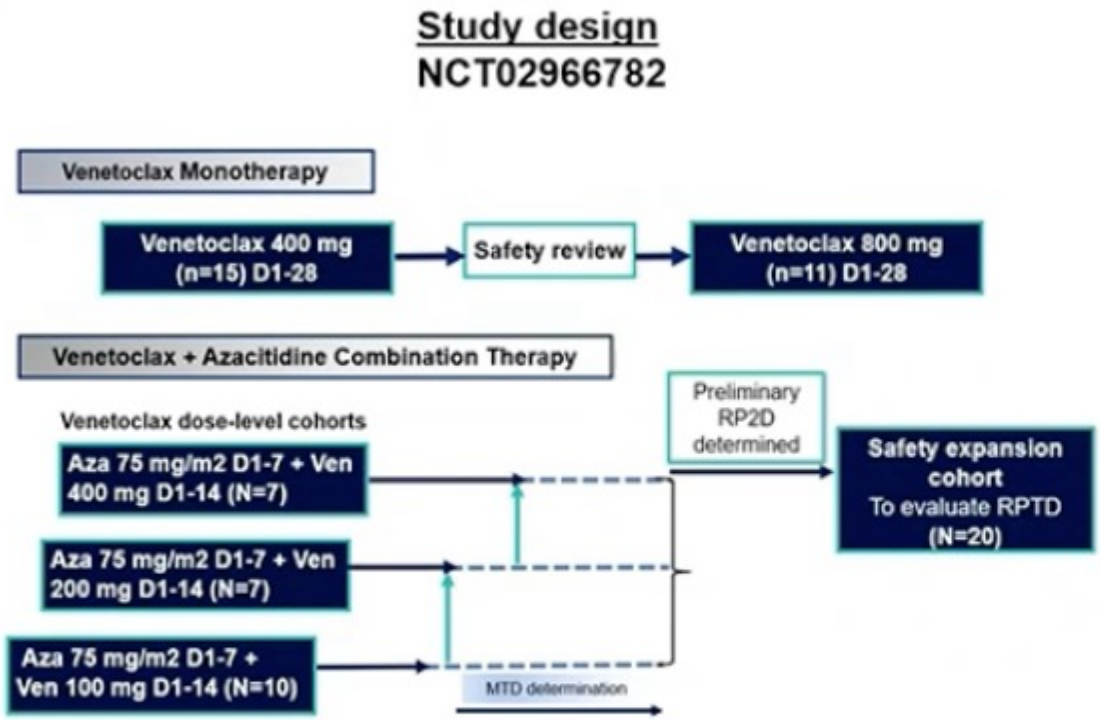
Phase I/II Study of Venetoclax + ASTX727 for Treatment-Naïve High-Risk MDS and CMML

Characteristics	Total (N = 7)
Median age	72 years
Disease subtype Higher-risk MDS CMML	 5 2
Hematology parameters ANC (x 10^9/L) Hb (g/dL) Platelets (x 10^9/L)	 1.7 8.9 33
Median bone marrow blasts	33%
Cytogenetics Good Intermediate Poor	 2 4 1
Response ORR CR mCR	 7 (100%) 3 (43%) 4 (57%)

MDS = myelodysplastic syndromes; CMML = chronic myelomonocytic leukemia; ORR = overall response rate; CR = complete remission; mCR = marrow/morphologic CR

Venugopal S et al. ASH 2021;Abstract 245.

Study Design



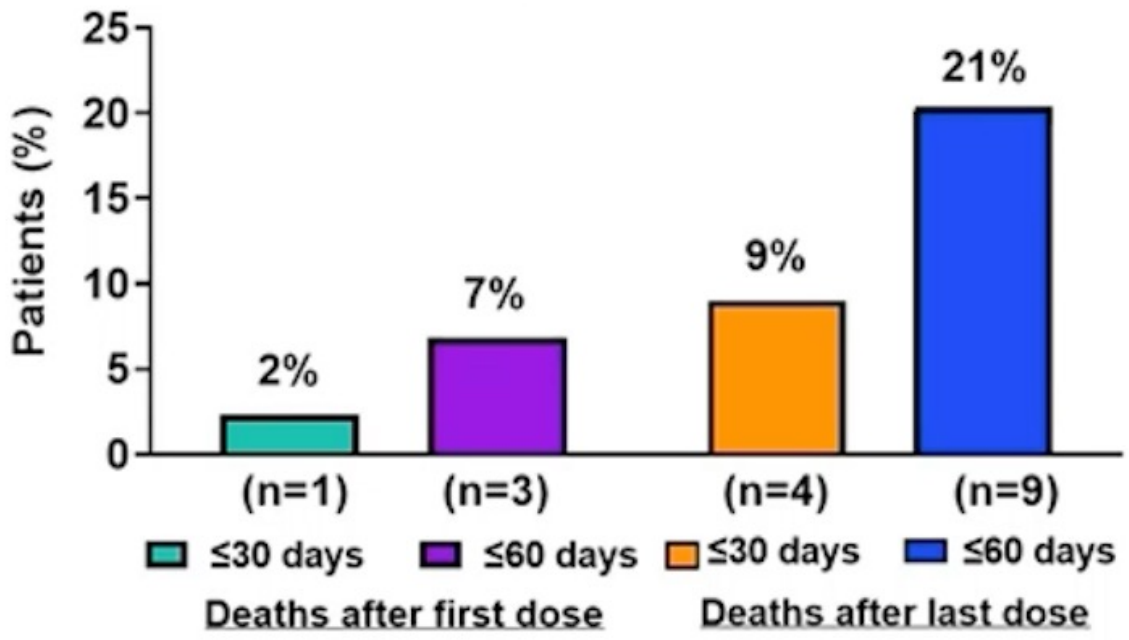
Key endpoints

Safety, objective response rate, hematological improvement and transfusion independence, overall survival, molecular mutation, and patient-reported outcomes

- Ongoing Phase 1b study in patients with R/R MDS treated with escalating doses Ven+Aza
- Responses were assessed per modified International Working Group 2006 criteria[1]
- Mutation status was determined in bone marrow mononuclear cells with Archer's VariantPlex Myeloid/Core Myeloid Next-generation sequencing panel and in the peripheral blood with Illumina's TruSight Myeloid panel. The limit of detection for these panels was 1-5%
- Baseline %BCL-2+/%BCL-xL blast ratio was determined by flow cytometry[2]
- The RPTD of Ven is 400 mg for 14 days for the treatment of R/R MDS

Zeidan AM et al. ASH 2021;Abstract 537.

Deaths Among Patients Who Received Venetoclax/Azacitidine

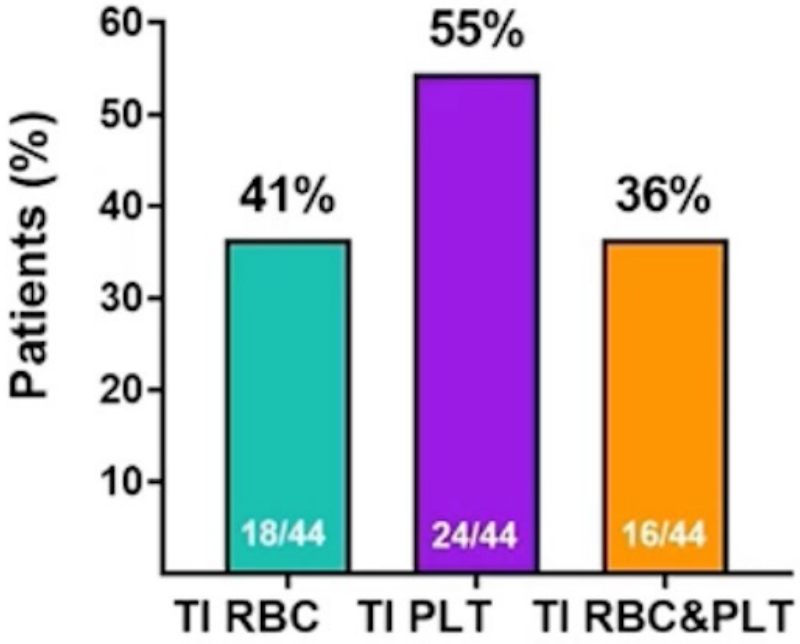


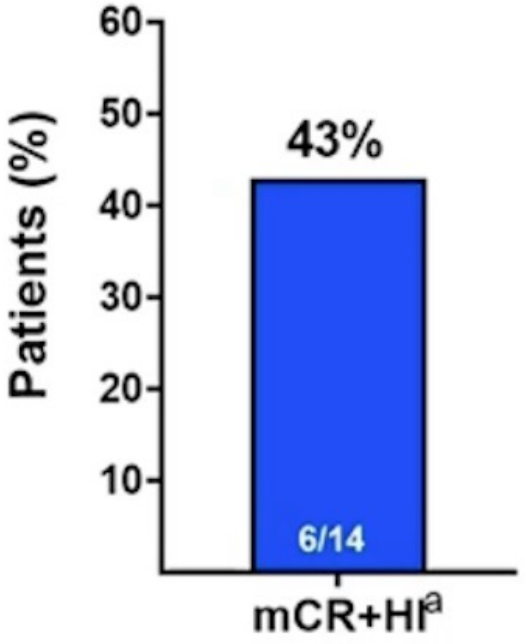
- There were 29 (66%) deaths among patients
  - 9 due to disease progression
  - 4 due to TEAE
  - 16 due to other causes
- 1 (2%) patient died of pneumonia related to Ven treatment

TEAE = treatment-emergent adverse event

Zeidan AM et al. ASH 2021;Abstract 537.

Transfusion Independence (TI) and Hematologic Improvement (HI) with Venetoclax/Azacitidine



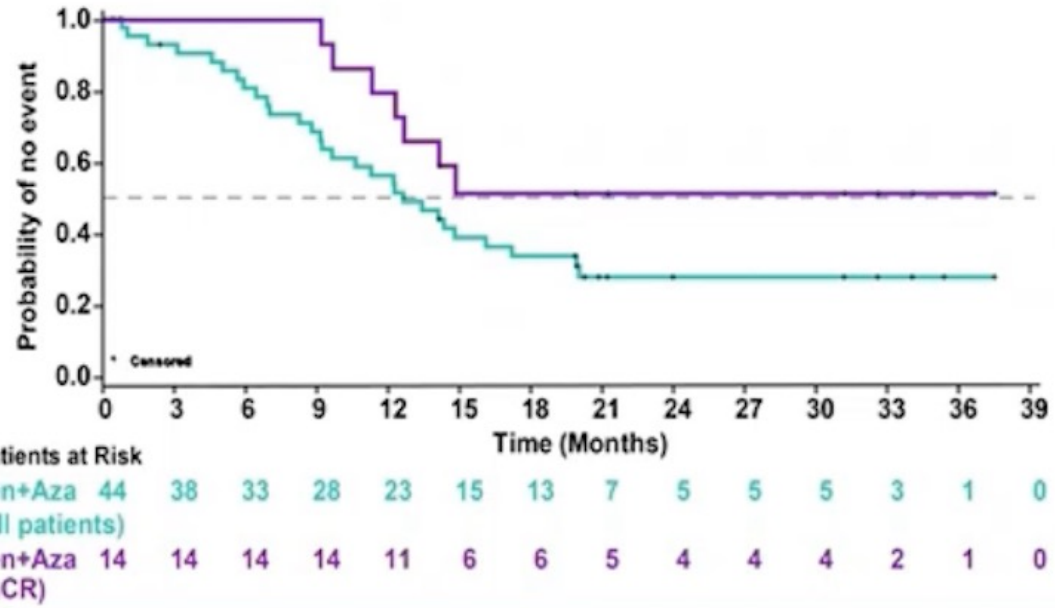


- Post-baseline TI (RBC or PLT) was achieved by 10/32 (31%) patients who were transfusion dependent at baseline
- Median time to next treatment[b] was 5.7 months (95% CI 4.8 – 8.8)
- 9 (21%) patients transformed to AML
- 9 (21%) patients received post-study transplant of which 3 (7%) had bone marrow transplant and 6 (14%) had peripheral blood stem cell transplant

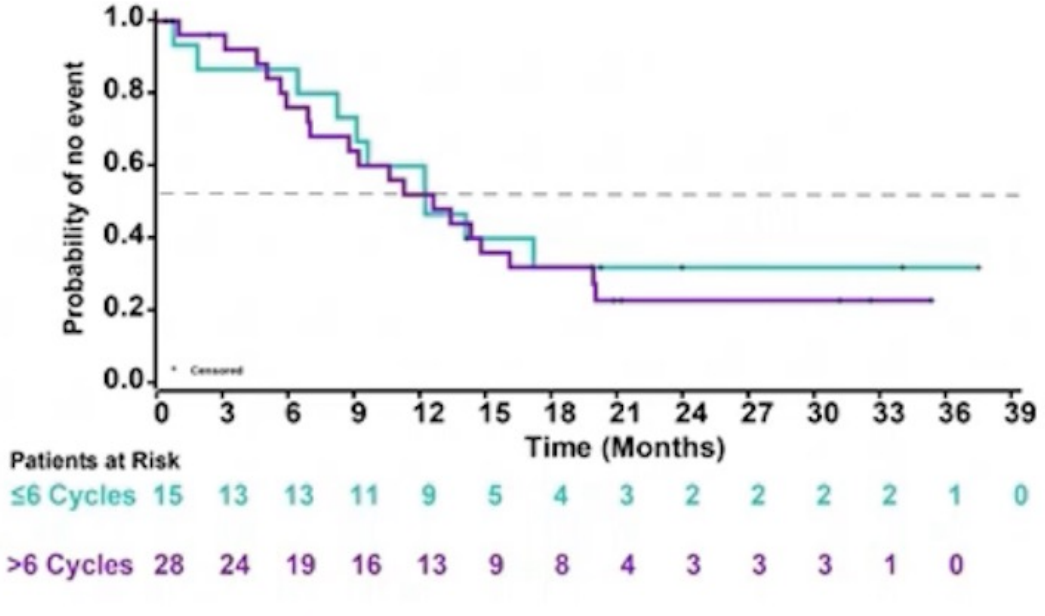
mCR = marrow complete remission; AML = acute myeloid leukemia

Zeidan AM et al. ASH 2021;Abstract 537.

Overall Survival with Venetoclax/Azacitidine



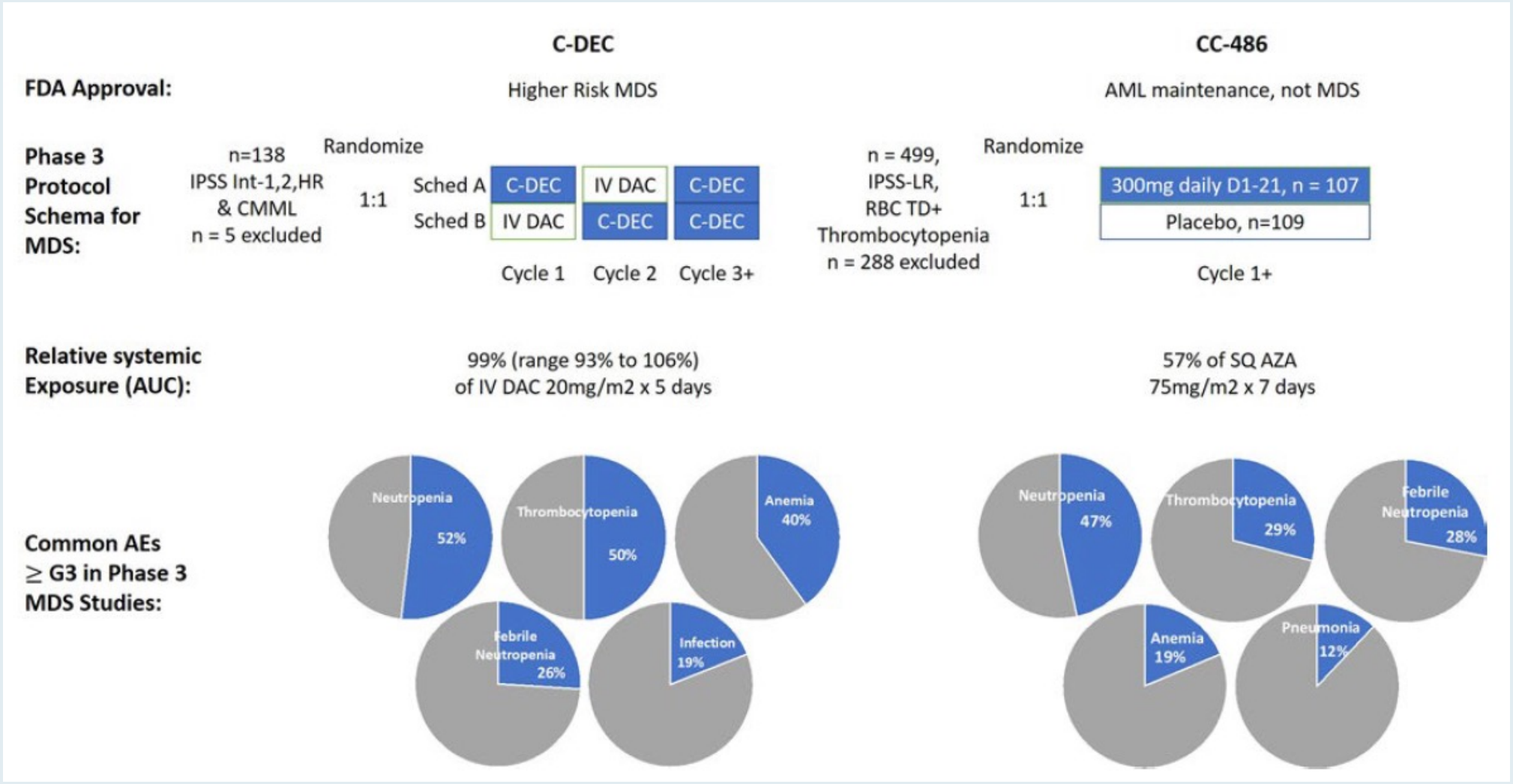
OS	# of events	12-month, % (95% CI)	24-month % (95% CI)	Median OS, months (95% CI)
Ven+Aza (All patients)	29	56.2 (39.8 – 69.7)	27.7 (14.8 – 42.3)	12.6 (9.1 – 17.2)
Ven+Aza (mCR)	7	78.6 (47.2 – 92.5)	49.0 (21.6 – 71.7)	14.8 (11.3 – NE)



OS	# of events	12-month, % (95% CI)	24-month % (95% CI)	Median OS, months (95% CI)
≤ 6 cycles of prior HMA	10	60.0 (31.8 – 79.7)	32.0 (10.9 – 55.7)	12.3 (6.4 – NE)
> 6 cycles of prior HMA	19	52.1 (31.3 – 69.3)	22.9 (8.8 – 40.9)	12.6 (7.0 – 19.9)

Zeidan AM et al. ASH 2021;Abstract 537.

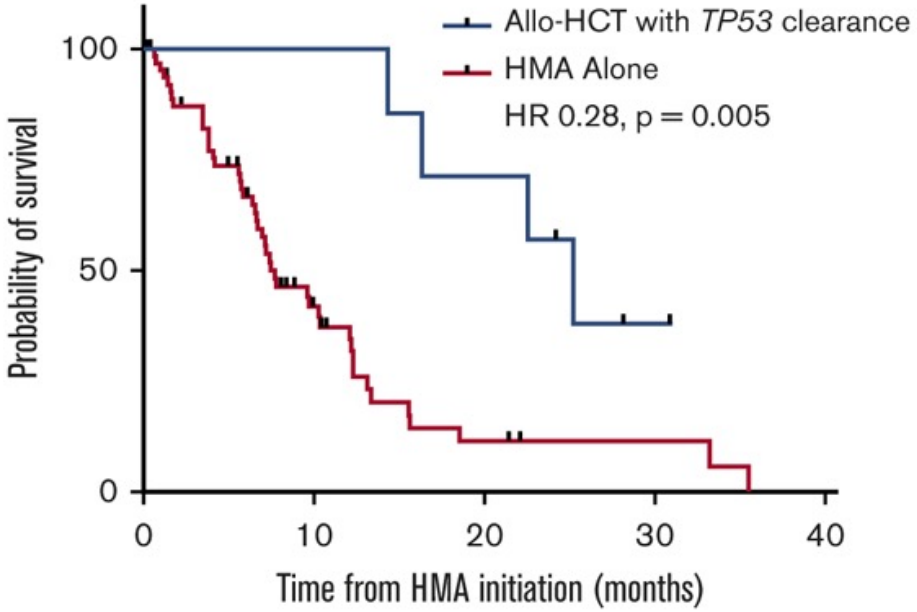
Summary of the 2 Completed Phase III Studies of C-DEC and CC-486 for MDS

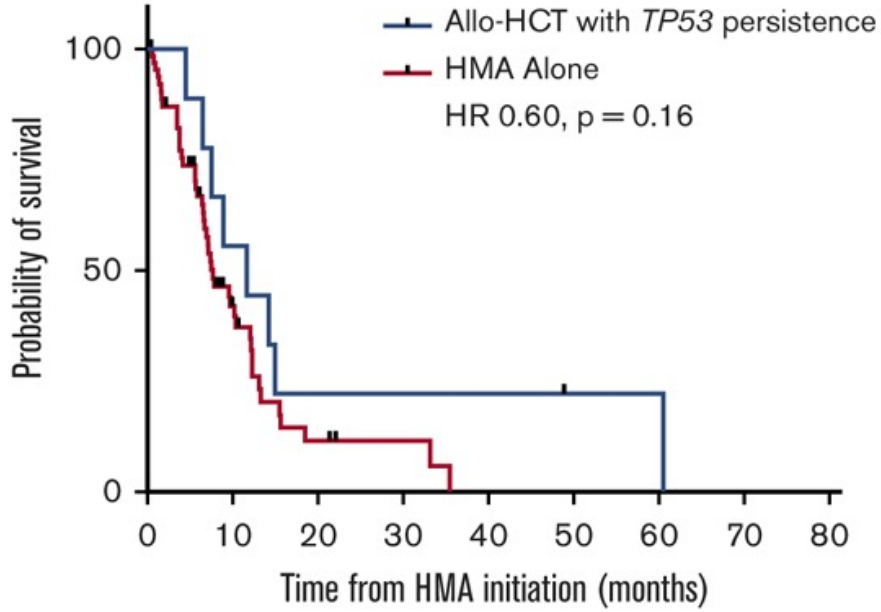


C-DEC = decitabine-cedazuridine

Griffiths EA. ASH 2021 Education Program.

Impact of *TP53* clonal clearance on overall survival with HMA therapy and allo-HCT





Proposed treatment algorithm for *TP53* mutated MDS:

TP53 mutated, higher-risk MDS → Frontline therapy with a hypomethylating agent → Serial next generation sequencing to assess molecular response

- Clearance of *TP53* mutation → Proceed to allogeneic transplant (if candidate)
- Persistent *TP53* mutation detected → Clinical trial evaluating novel therapy

Hunter et al., *Blood Advances* 2021

Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine in MDS and AML Patients: Phase 1b Results

David A Sallman[1], Adam Asch[2], Monzr Al-Malki[3], Daniel Lee[4], Guillermo Garcia-Manero[5], William Donnellan[6], Daniel Pollyea[7], Suman Kambhampati[8], Eunice Wang[9], Deepa Jeyakumar[10], Gabe Mannis[11], Terrence Bradley[12], Richard Larson[13], Tiffany Tanaka[14], Wanxing Chai-Ho[15], Josh Zeidner[16], Guido Marcucci[3], Rami Komrokji[1], Joanna Van Elk[17], Ming Lin[17], Jens-Peter Volkmer[17], Roy Maute[17], Chris Takimoto[17], Mark Chao[17], Paresh Vyas[18], Naval Daver[5]

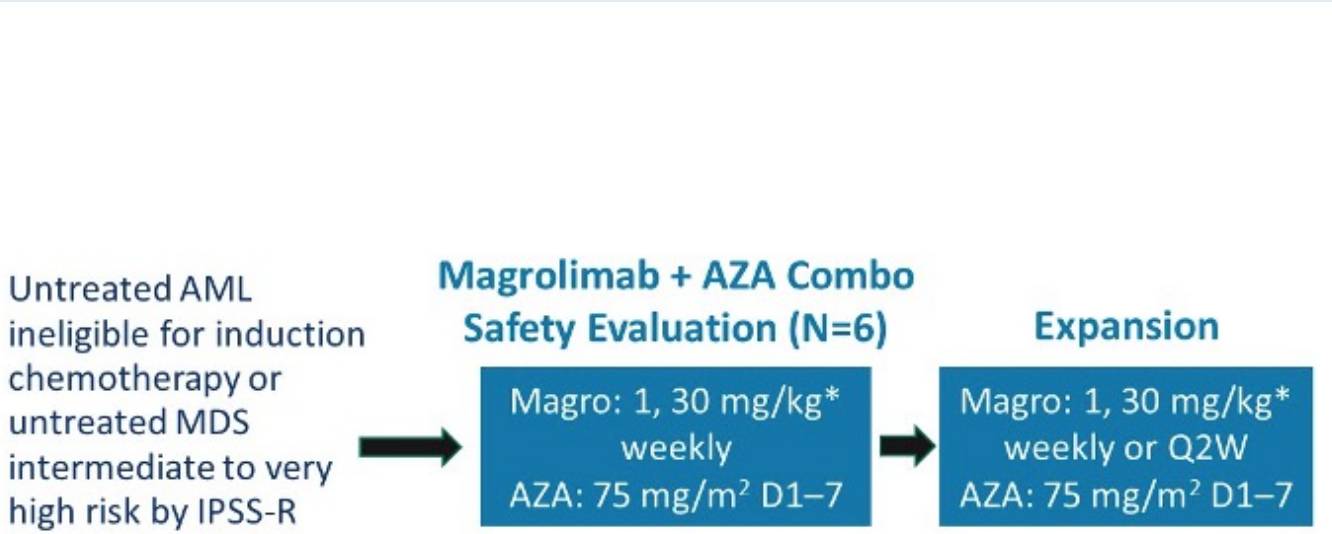
[1]Moffitt Cancer Center, Tampa, FL; [2]University of Oklahoma, Oklahoma City, OK; [3]City of Hope, Duarte, CA; [4]Columbia University, New York, NY; [5]MD Anderson Cancer Center, Houston, TX; [6]Sarah Cannon Research Institute, Nashville, TN; [7]University of Colorado, Denver, CO; [8]Healthcare Midwest, Kansas City, MO; [9]Roswell Park Cancer Center, Buffalo, NY; [10]University of California Irvine, Irvine, CA; [11]Stanford University, Stanford, CA; [12]University of Miami, Miami, FL; [13]University of Chicago, Chicago, IL; [14]University of California San Diego, San Diego, CA; [15]University of California Los Angeles, Los Angeles, CA; [16]University of North Carolina, Chapel Hill, NC; [17]Forty Seven, Inc., Menlo Park, CA; [18]University of Oxford, Oxford, UK

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: DAVID A. SALLMAN, MD

ASCO 2020;Abstract 7507.

5F9005 Study Design: Magrolimab in Combination with Azacitidine for MDS and Acute Myeloid Leukemia (AML)



Primary objectives

1. Safety of magrolimab alone or with AZA
2. Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary objectives

1. Pharmacokinetics, pharmacodynamics, and immunogenicity of 5F9
2. Additional measures of efficacy (DOR, PFS, OS)

Exploratory objective

To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

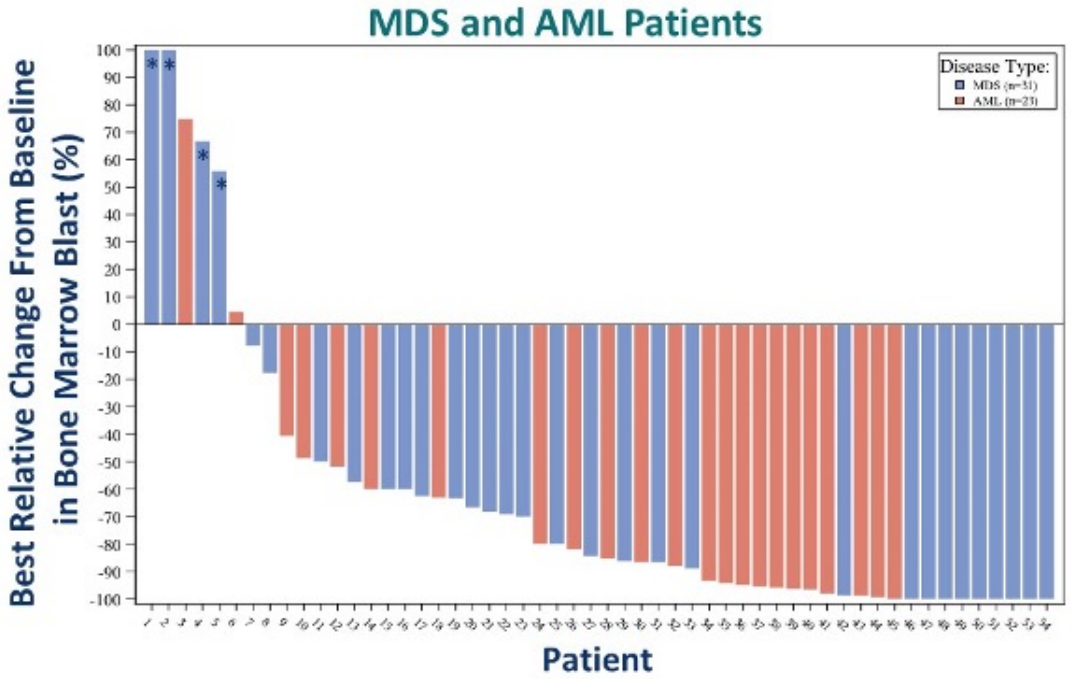
- A magrolimab priming dose (1 mg/kg) and dose ramp-up was utilized to mitigate on-target anemia

Sallman DA et al. ASCO 2020;Abstract 7507.

5F9005: Response to Magrolimab in Combination with Azacitidine for MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

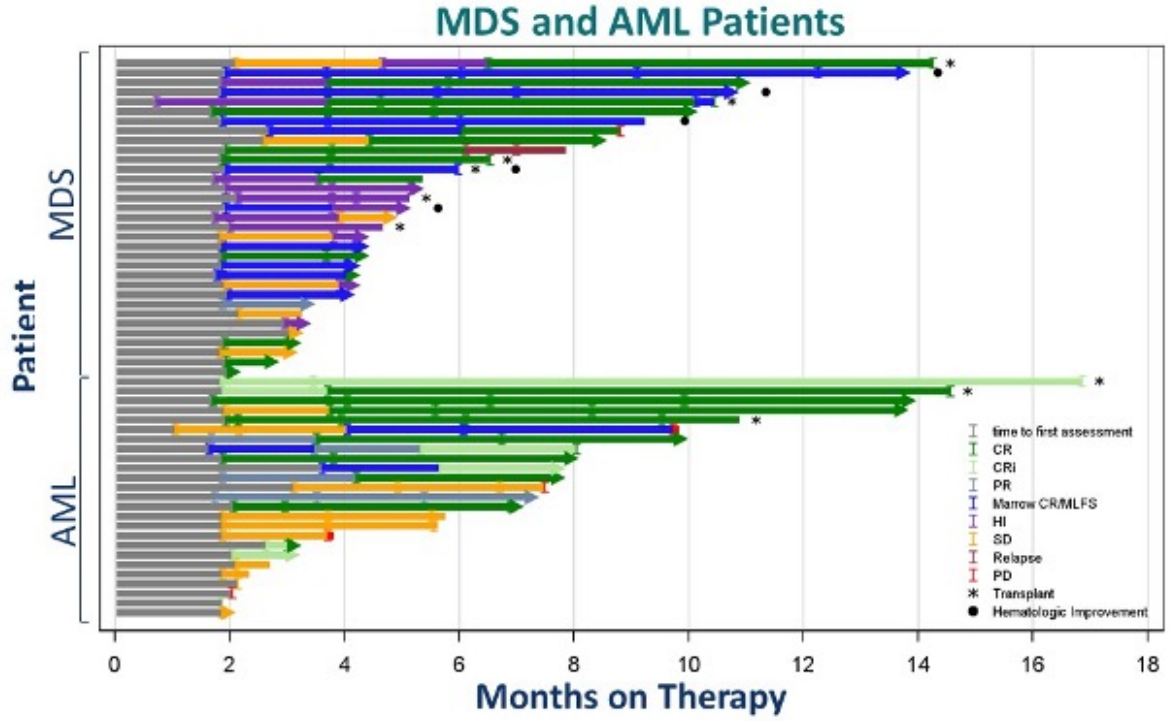
1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman DA et al. ASCO 2020;Abstract 7507.

5F9005: Durability of Response to Magrolimab in Combination with Azacitidine for MDS and AML

Parameter	1L MDS N=33	1L AML N=25
RBC transfusion independence*	11/19 (58%)	9/14 (64%)
Complete cytogenetic response†	9/26 (35%)	6/12 (50%)
MRD negativity in responders	6/30 (20%)	8/16 (50%)
Median duration of response (months)	Not reached (0.03+ – 10.4+)	Not reached (0.03+ – 15.1+)
Median follow-up (range) (months)	5.8 (2.0–15.0)	9.4 (1.9–16.9)

MRD was evaluated by multiparameter flow cytometry; cytogenetic response defined per 2003 and 2006 IWG criteria.
*Patients shown for those who were RBC transfusion dependent at baseline and achieved RBC transfusion independence at any time on study.
†Responses shown for all responding patients with abnormal cytogenetics at baseline.



- Complete cytogenetic responses and MRD negativity is observed in MDS and AML patients
- No median duration of response has been reached for MDS or AML
- 16% of patients (9/58) received an allogeneic stem cell transplant
- Median OS has not been reached in either MDS or AML patients

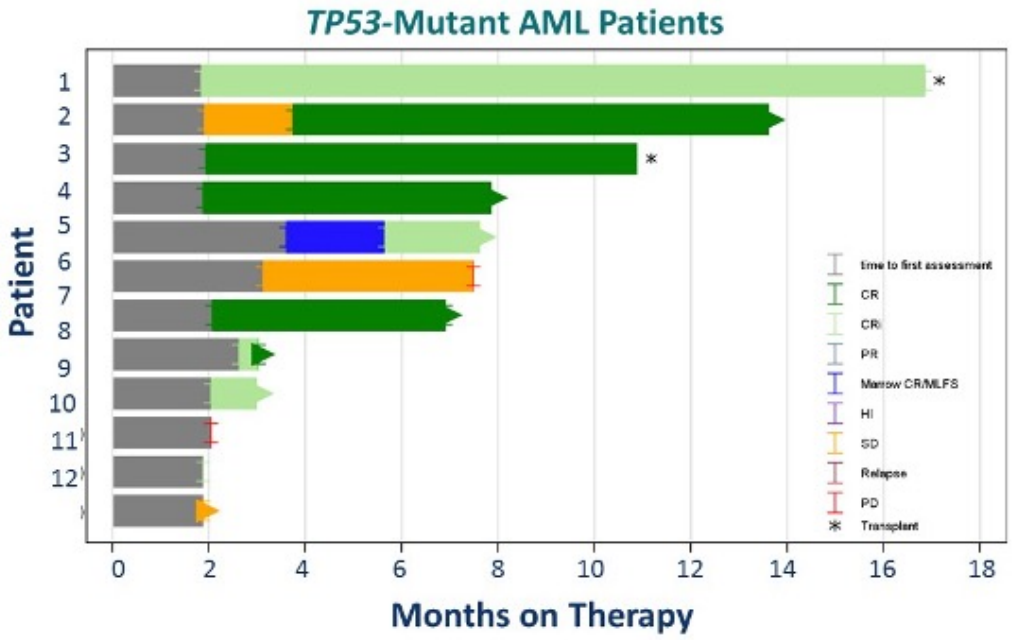
Sallman DA et al. ASCO 2020;Abstract 7507.

5F9005: Response to Magrolimab in Combination with Azacitidine for MDS and AML with TP53 Mutation

Efficacy in *TP53*-Mutant Patients

Best Overall Response	AML *TP53* Mutant (N=12)	MDS *TP53* Mutant (N=4)
ORR	9 (75%)	3 (75%)
CR	5 (42%)	2 (50%)
CRi/marrow CR	4 (33%)	1 (25%)
Complete cytogenetic response *	4/8 (50%)	3/3 (100%)
MRD negative of responders	4/9 (44%)	0
Median duration of response (months)	Not reached (0.03+ – 15.1+)	Not reached (0.03+ – 5.2+)
Survival probability at 6 months	91%	100%
Median follow-up (range) (months)	8.8 (1.9 – 16.9)	7 (4.2 – 12.2)

*Responding patients with abnormal cytogenetics at baseline.

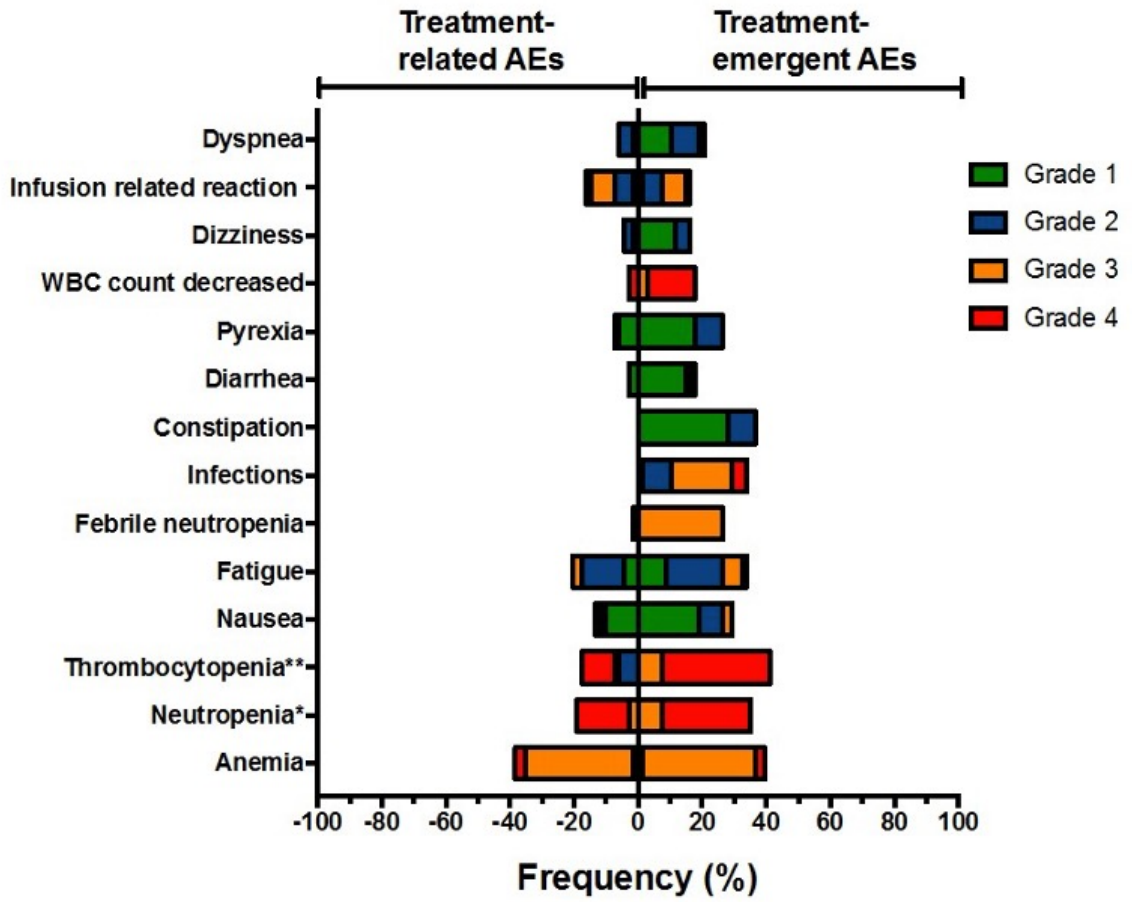


- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax + AZA in AML: ORR 47%, DOR 5.6 mo, OS 7.2 mo[1]

1. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

Sallman DA et al. ASCO 2020;Abstract 7507.

5F9005: Safety of Magrolimab in Combination with Azacitidine for MDS and AML with TP53 Mutation



- No maximum tolerated dose was reached; magrolimab + AZA profile consistent with AZA monotherapy
- No significant cytopenias, infections, or immune-related AEs were observed (most patients were cytopenic at baseline)
- Anemia and transfusion frequency improved over time
- No deaths occurred during the first 60 days on study for either AML or MDS patients
- Treatment discontinuation due to drug-related AE occurred in only 1 of 68 (1.5%) of all patients treated with magrolimab + AZA

Sallman DA et al. ASCO 2020;Abstract 7507.

Challenging Cases from the Community: Investigators Provide Perspectives on the Optimal Management of Diffuse Large B-Cell Lymphoma

A CME/MOC-Accredited Virtual Event

Tuesday, September 13, 2022

5:00 PM – 6:00 PM ET

Faculty

Jeremy Abramson, MD
Sonali M Smith, MD
Jason Westin, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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

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