Meet The Professor
Optimizing the Management of Myelodysplastic Syndromes

Rami Komrokji, MD
Senior Member and Section Head for Leukemia and MDS
Vice Chair, Department of Malignant Hematology
Moffitt Cancer Center
Professor of Oncologic Sciences
Morsani College of Medicine, University of South Florida
Tampa, Florida

Meet The Professor Program Participating Faculty

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Commercial Support

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Komrokji — Disclosures

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Piedmont Cancer Institute
Atlanta, Georgia

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
Lake Worth, Florida

John Yang, MD
Oncologist
Fall River, Massachusetts

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Agenda

Introduction: Myelodysplastic Syndromes (MDS) Treatment Paradigm

Module 1: Case Presentations

- Dr Brenner: An 81-year-old man with MDS and multilineage dysplasia
- Dr Chojecki: A 56-year-old man with high-risk MDS and a TP53 mutation
- Dr Sinha: A 74-year-old woman with chronic myelomonocytic leukemia
- Dr Friemel: A 78-year-old man with MDS and multifactorial anemia
- Dr Gupta: A 93-year-old woman with MDS and transfusion-dependent anemia
- Dr Rupard: A 97-year-old woman with transfusion-dependent anemia and concomitant multiple myeloma and MDS with del(5q)

Module 2: Key Recent Data Sets

Module 3: Journal Club with Dr Komrokji

Module 4: Appendix

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Leuk Lymphoma 2021;[Online ahead of print].

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.2018579

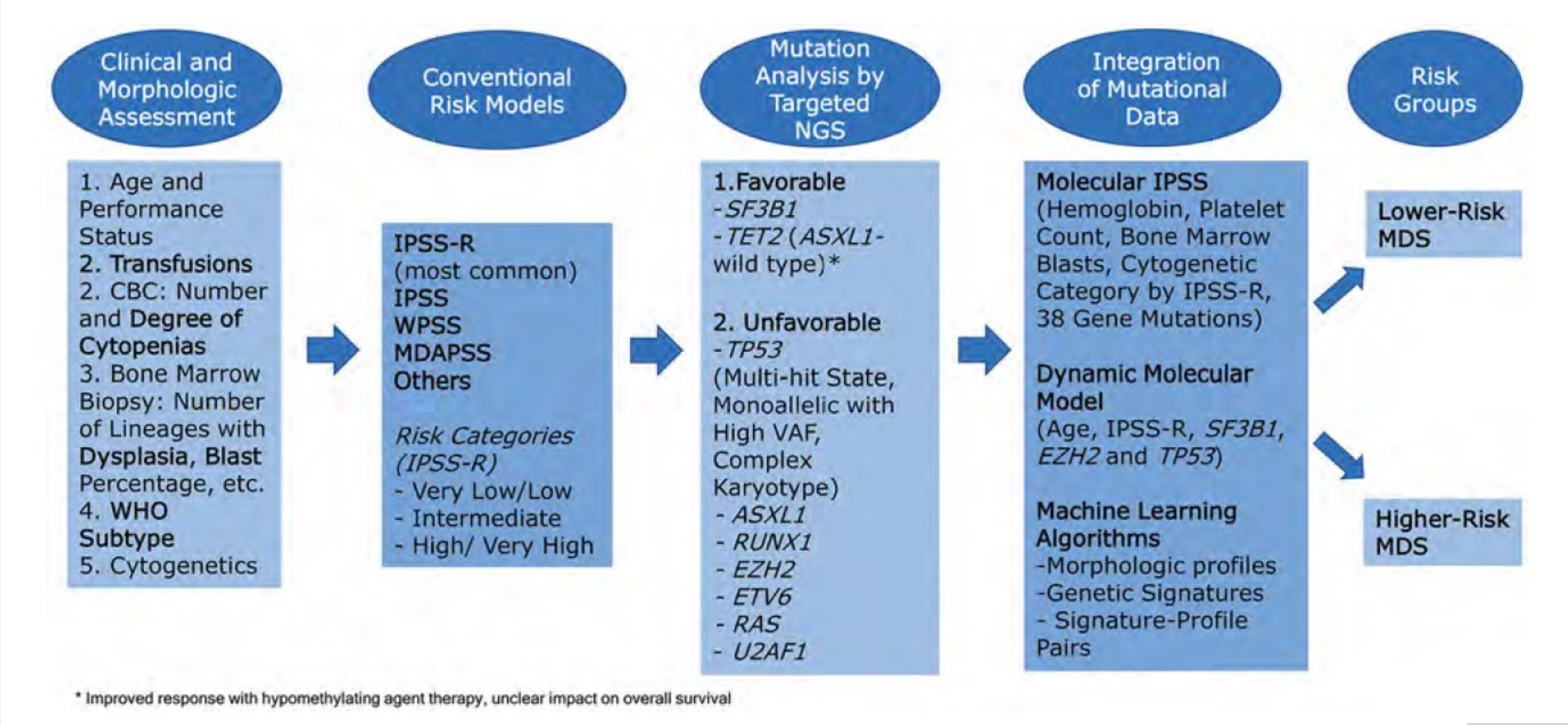
Taylor & Francis
Taylor & Francis Group

REVIEW

Prognostic scoring systems and risk stratification in myelodysplastic syndrome: focus on integration of molecular profile

Somedeb Ball, Rami S. Komrokji and David A. Sallman

Proposed Algorithm for Risk Stratification in Myelodysplastic Syndrome



Ball S et al. *Leuk Lymphoma* 2021;[Online ahead of print].

Ther Adv Hematol 2021;12:1-10.

Therapeutic Advances in Hematology

Treatment options for lower-risk myelodysplastic syndromes. Where are we now?

Virginia O. Volpe and Rami S. Komrokji

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/issn/15216926

It is time to shift the treatment paradigm in myelodysplastic syndromes: A focus on novel developments and current investigational approaches exploring combinatorial therapy in high-risk MDS

Luis E. Aguirre, Rami Komrokji, Eric Padron *

Best Pract Res Clin Haematol 2021;34(4):101325.

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Case Presentation: An 81-year-old man with MDS and multilineage dysplasia

Dr Warren Brenner (Boca Raton, Florida)

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Case Presentation: A 56-year-old man with high-risk MDS and a TP53 mutation

Dr Aleksander Chojecki (Charlotte, North Carolina)

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Case Presentation: A 74-year-old woman with chronic myelomonocytic leukemia

Dr Rajni Sinha (Atlanta, Georgia)

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Addition of venetoclax for patients not responding to a hypomethylating agent

Dr Prashant Sharma (Salt Lake City, Utah)

Dr John Yang (Fall River, Massachusetts)

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Case Presentation: A 78-year-old man with MDS and multifactorial anemia

Dr Susannah Friemel (Bettendorf, Iowa)

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Case Presentation: A 93-year-old woman with MDS and transfusion-dependent anemia

Dr Shaachi Gupta (Lake Worth, Florida)

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Case Presentation: A 97-year-old woman with transfusion-dependent anemia and concomitant multiple myeloma and MDS with del(5q)

Dr Erik Rupard (West Reading, Pennsylvania)

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Module 3: Journal Club with Dr Komrokji

Module 4: Appendix

ASH 2021;Abstract 66.

American Society *of* Hematology
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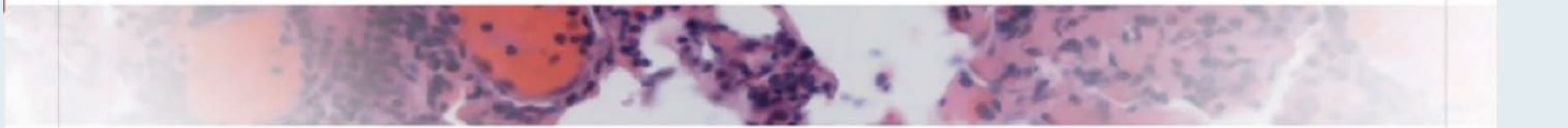

Oral Decitabine/Cedazuridine in Patients with Lower Risk Myelodysplastic Syndrome: a Longer-Term Follow-Up of from the ASCERTAIN Study

On behalf of the ASCERTAIN Investigators Team

Guillermo Garcia-Manero, MD[1], James K. McCloskey, MD[2], Elizabeth A. Griffiths, MD[3], Karen W.L. Yee, MD[4], Amer M. Zeidan, MBBS, MHS[5], Aref Al-Kali, MD[6], , H. Joachim Deeg, MD[7], Prapti A. Patel, MD[8], Mitchell Sabloff, MSc, MD, FRCPC[9], Mary-Margaret Keating, MD, FRCPC[10], Kim-Hien Dao, DO, PhD[11,26], Nancy Zhu, MD[12*], Nashat Gabrail, MD[13*], Salman Fazal, MD[14], Joseph Maly, MD[15], Olatoyosi Odenike, MD[16], Hagop M. Kantarjian, MD[17], Amy E. DeZern, MD[18], Casey L. O'Connell, MD[19], Gail J. Roboz, MD[20], Lambert Busque, MD[21], Richard A. Wells, MD, DPhil[22*], Harshad Amin, MD[23*], Jasleen K. Randhawa, MD[24], Brian Leber, MD[25], Yong Hao, MD, PhD[26*], Harold N. Keer, MD, PhD[26], Mohammad Azab, MD[26] and Michael R. Savona, MD[25]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Canada; [5]Yale University and Yale Cancer Center, New Haven, CT; [6]Mayo Clinic, Rochester, MN; [7]Fred Hutchinson Cancer Research Center, Seattle, WA; [8]University of Texas Southwestern Medical Center, Dallas, TX; [9]Division of Hematology, Department of Medicine, University of Ottawa and The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [10]Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [11]Astex Pharmaceuticals, Inc., Pleasanton, CA; [12]University of Alberta, Edmonton, AB, Canada; [13]Gabrail Cancer Center Research, Canton, OH; [14]West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; [15]Norton Cancer Institute, Louisville, KY; [16]University of Chicago, Chicago, IL; [17]Johns Hopkins University Hospital, Baltimore, MD; [18]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [19]Weill Cornell Medicine and The New York-Presbyterian Hospital, New York, NY; [20]Research Center, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada; [21]Sunnybrook Health Sciences Centre, Toronto, Canada; [22]Boca Raton Clinical Research, Boca Raton, FL; [23]Houston Methodist Cancer Center, Houston; [24]Department of Medicine, McMaster University, Hamilton, ON, Canada; [25]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

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Characteristics of Patients with Lower-Risk MDS in ASCERTAIN

Characteristics		Total Treated N=69[a]
Age in years (median, range)		70 (45-87)
Sex: Male/Female		45 (65%)/24 (35%)
Median weight, kg (range)/Median BSA, m^2 (range)		84 (50-127)/2.01 (1.4 - 2.6)
MDS, IPSS classification	Int-1 /Low-risk	64 (93%)/5 (7%)
Cytogenetics[b]	Intermediate-poor	28 (41%)
	Good	37 (54%)
Prior anticancer therapy		17 (24.6%)
Prior cycle of HMA		2 (2.8%)
Transfusion dependent	RBCs	27 (39%)
	Platelets	6 (9%)
ECOG PS	0/1	29 (42%)/40 (58%)

[a] 3 subjects received IV decitabine but did not receive ASTX727 and 1 subject received ASTX727 but not IV decitabine.
[b] Four (6%) were non-evaluable or missing.

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

ASCERTAIN: Grade ≥3 Treatment-Emergent Adverse Events (TEAEs) 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: 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

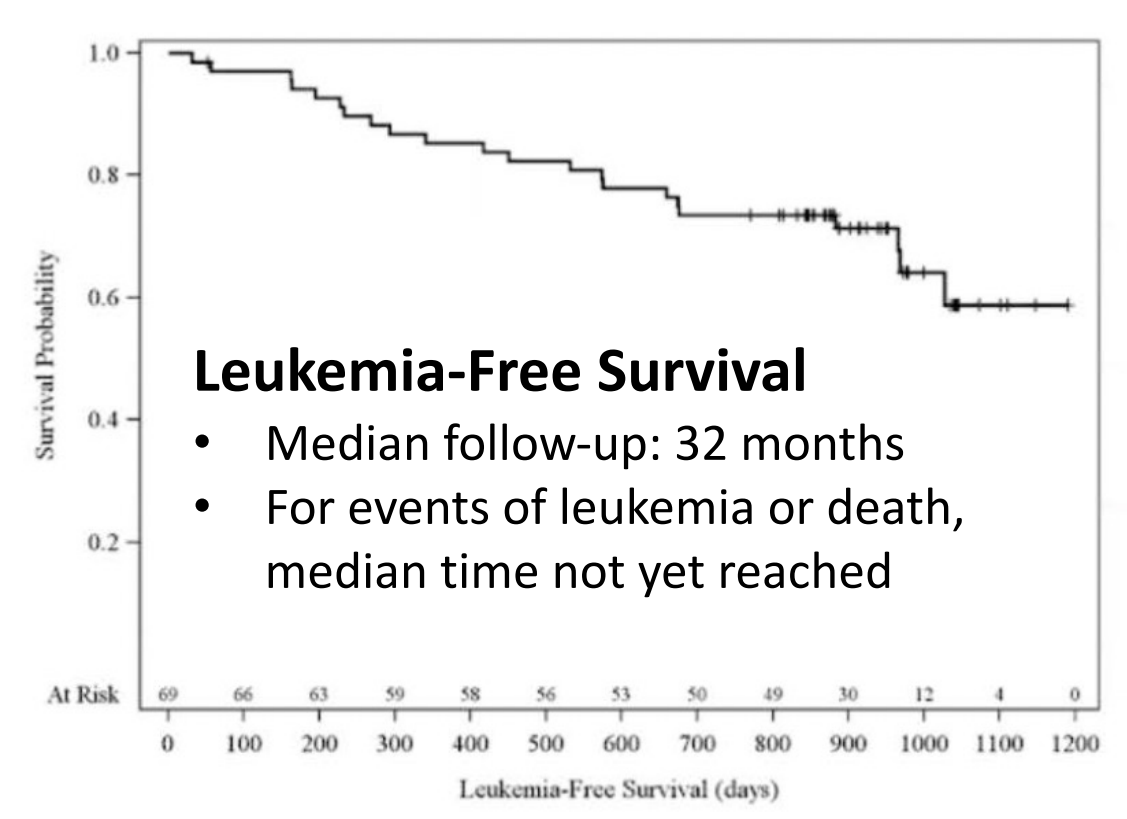
Garcia-Manero G et al. ASH 2021;Abstract 66.

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)

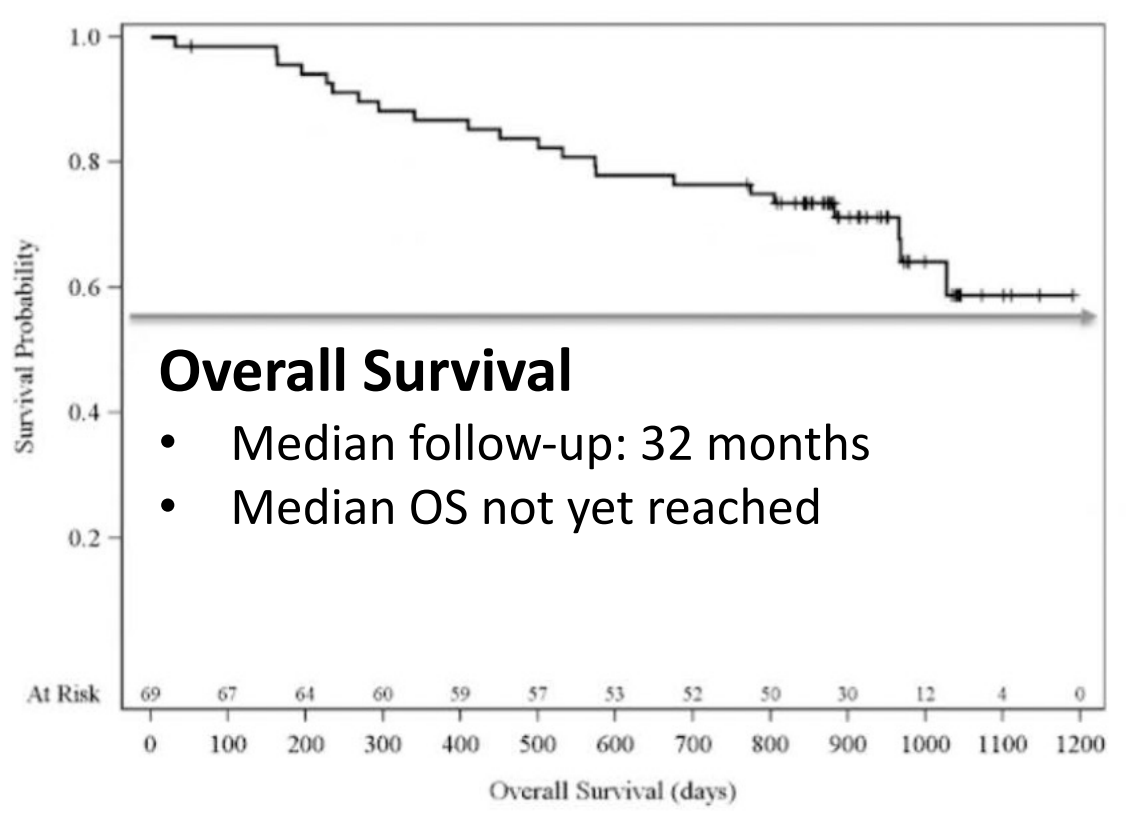
Garcia-Manero G et al. ASH 2021;Abstract 66.

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

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

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

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;39:1426-36.

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. Education Session. ASCO 2021.

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

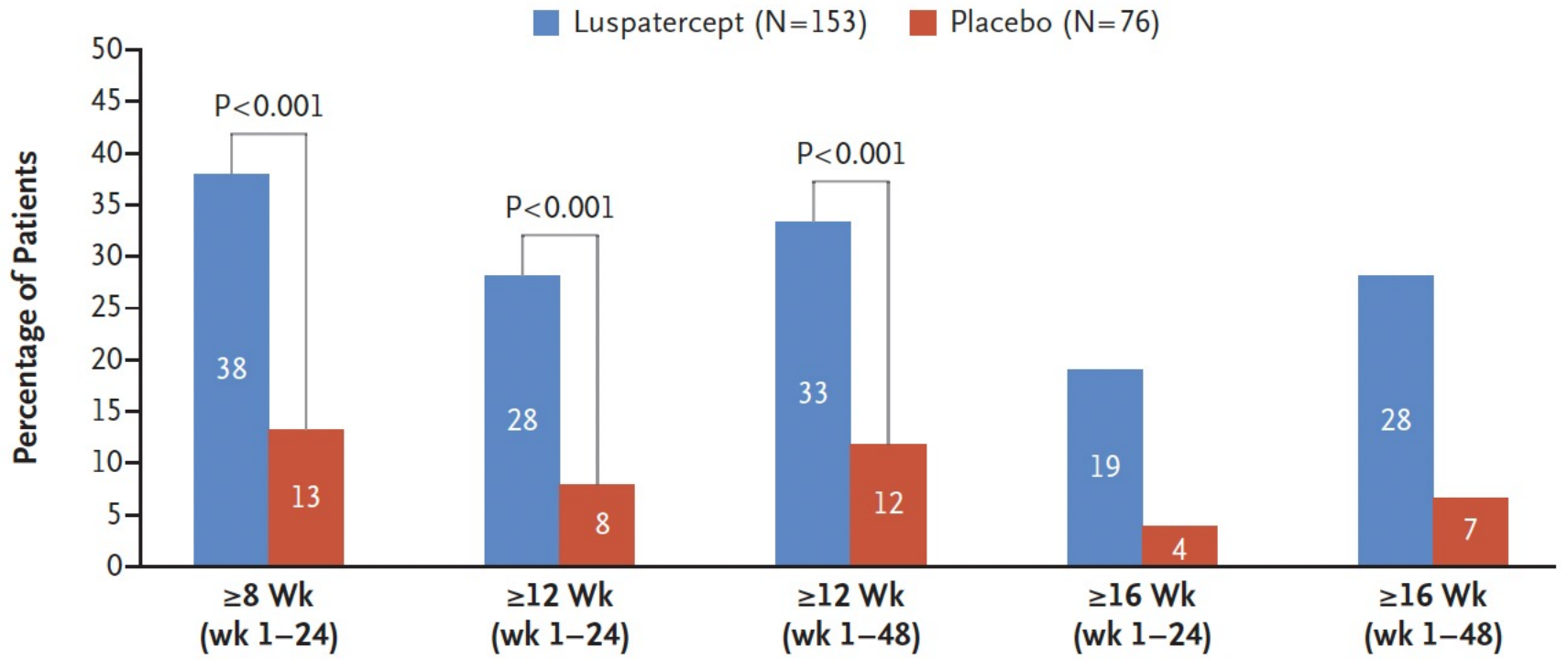
The NEW ENGLAND JOURNAL of MEDICINE

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;382:140-51.

Higher-Risk MDS: Improving Response and Duration of Response Is an Unmet Medical Need

AZACITIDINE (HMA) +

- Magrolimab
- APR246
- Pevonedistat
- Ivosidenib
- Gilteritininb
- Enasidenib
- Venetoclax
- Immune Checkpoint Inhibitors
  - MBG453
  - Ipilimumab
  - Nivolumab
  - Durvalumab
- Rigosertib
- Others……

Buckstein R. Education Session. ASCO 2021.

Venetoclax in Combination with Azacitidine Granted FDA Breakthrough Therapy Designation for Higher-Risk MDS

Press Release: July 21, 2021

"…the US Food and Drug Administration (FDA) granted a Breakthrough Therapy Designation (BTD) to venetoclax in combination with azacitidine for the potential treatment of adult patients with previously untreated intermediate-, high- and very high-risk myelodysplastic syndromes (MDS) based on revised International Prognostic Scoring System (IPSS-R).

This designation is supported by data from the Phase 1b M15-531 study. In addition to the Phase Ib M15-531 study, venetoclax is being investigated in combination with azacitidine for the treatment of MDS in the Phase 1b M15-522 study in patients with relapsed or refractory disease, and the Phase 3 randomized VERONA study in patients with newly diagnosed higher-risk MDS."

https://www.prnewswire.com/news-releases/venetoclax-venclexta-granted-us-fda-breakthrough-therapy-designation-btd-in-higher-risk-myelodysplastic-syndrome-mds-301338030.html

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

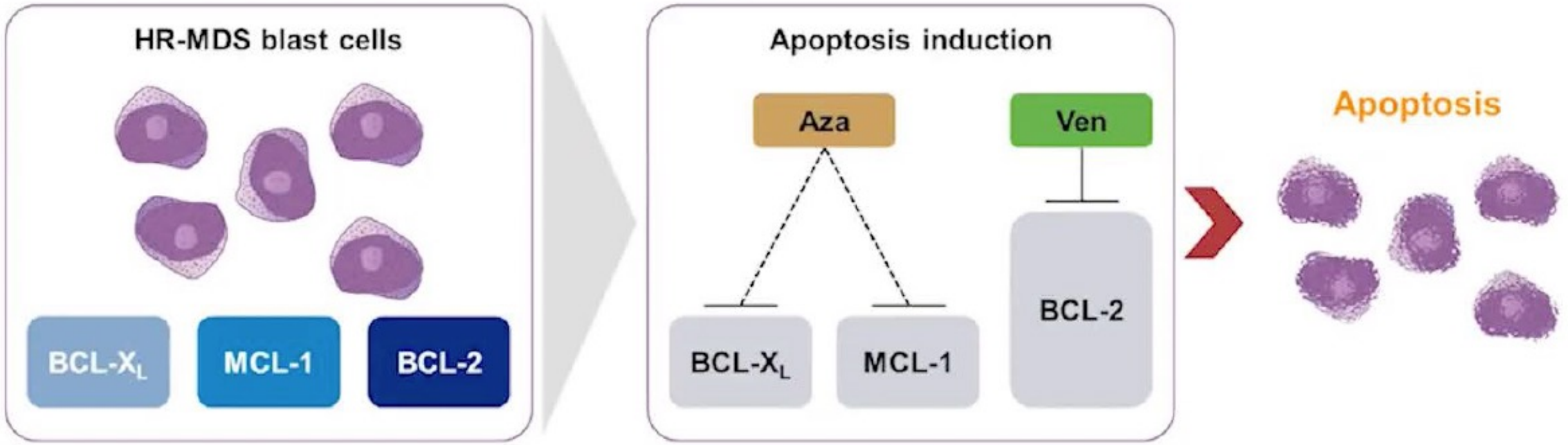
Jacqueline S. Garcia[1], Andrew H. Wei[2], Meagan A. Jacoby[3], Chun Yew Fong[4], Uma Borate[5], Maria R. Baer[6], Ilona Cunningham[7], Olatoyosi Odenike[8], Joseph G. Jurcic[9], Daniel Nowak[10], Pierre Peterlin[11], Uwe Platzbecker[12], Diana Dunshee[13], Ying Zhou[14], David Hoffman[14], Yan Sun[14],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

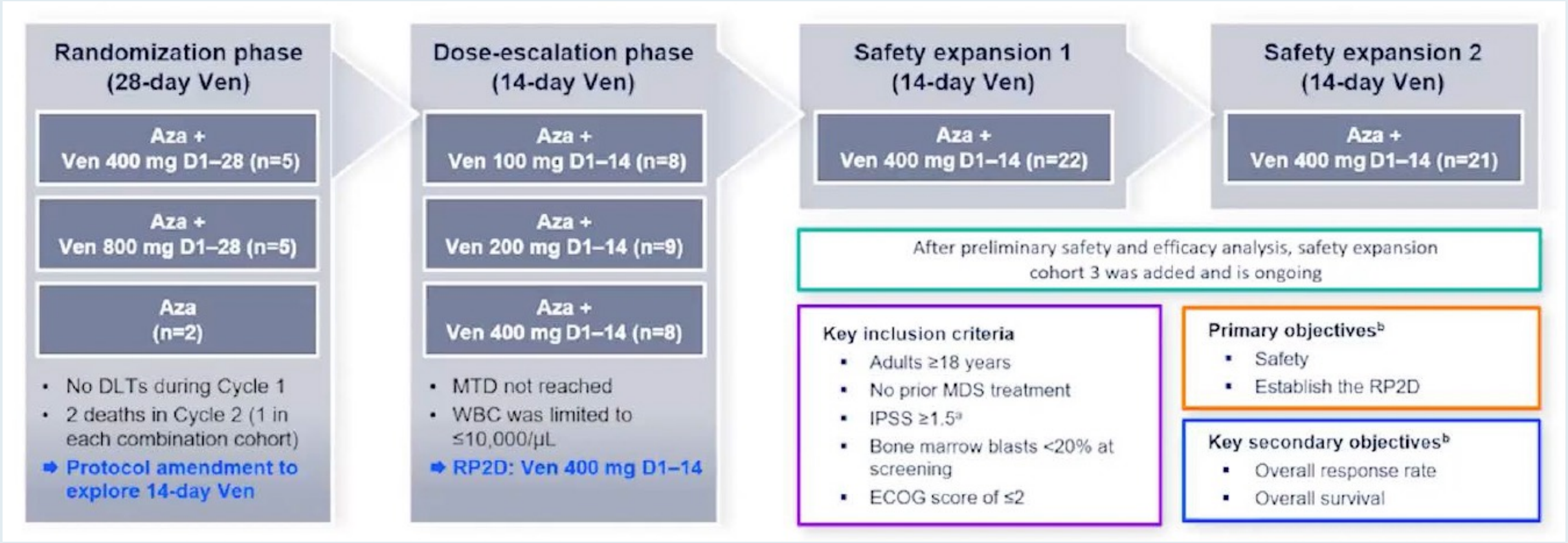
Venetoclax with Azacitidine Mechanism of Action



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.

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

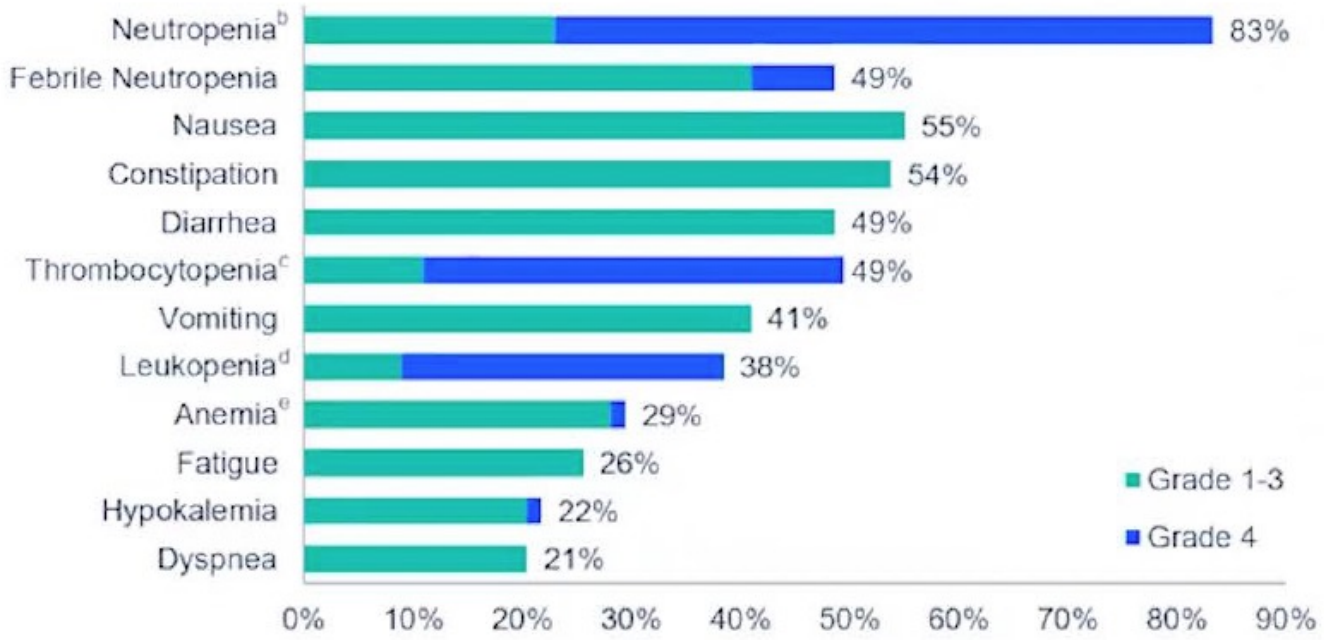


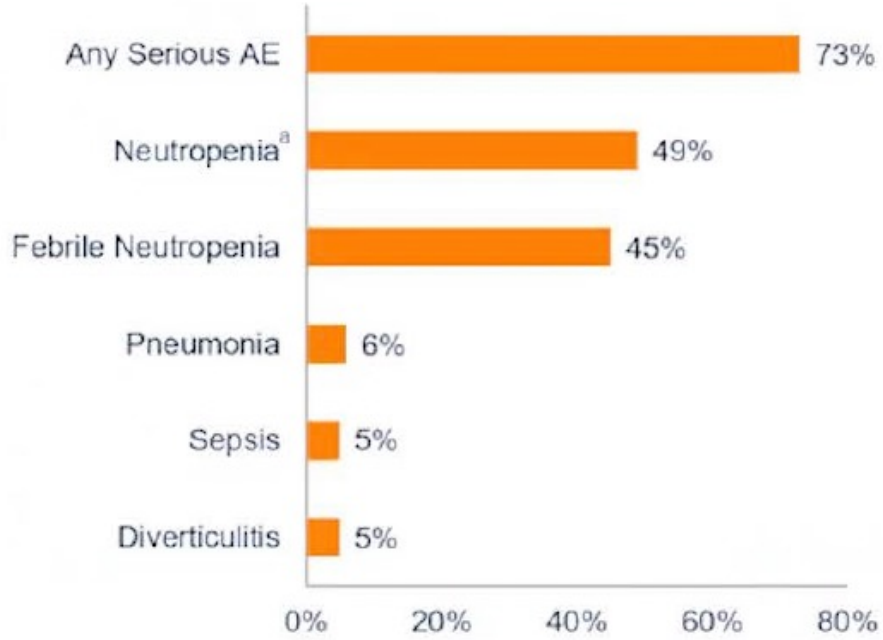
Garcia JS et al. ASH 2021;Abstract 241.

Safety of Venetoclax with 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]

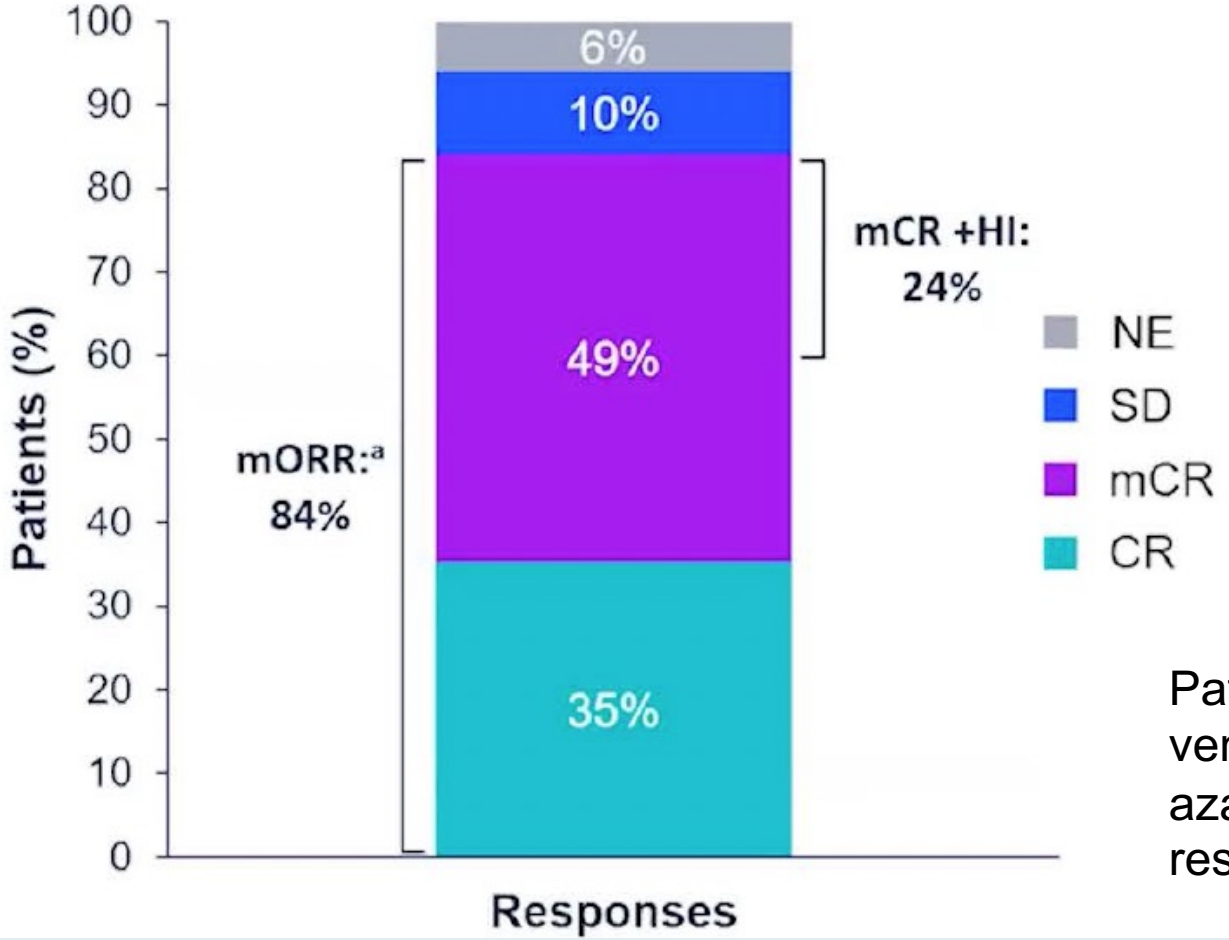




Garcia JS et al. ASH 2021;Abstract 241.

RTP RESEARCH TO PRACTICE

Response to Venetoclax with Azacitidine

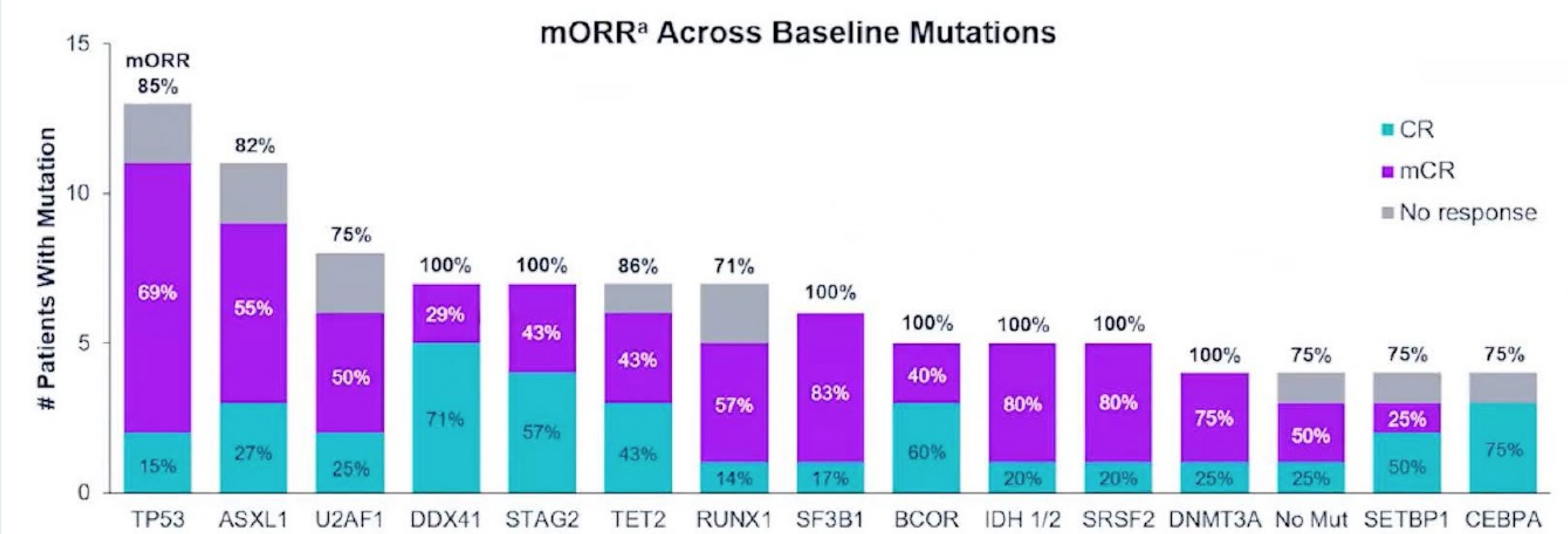


- Median time to response:
  0.9 months (95% CI, 0.7–5.8)
- Median duration of response:
  12.4 months (95% CI, 9.9–NR)

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 with Azacitidine Across the Mutational Spectrum

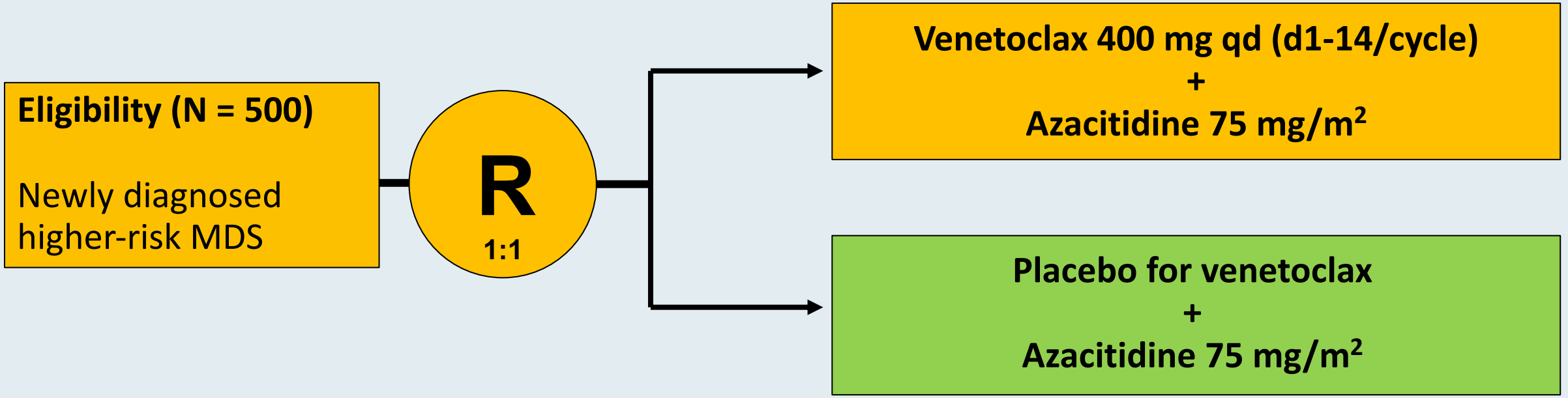


- 7 of 13 patients with *TP53* mutations had multi-hit/bi-allelic *TP53* mutations
- Responses of those with multi-hit/bi-allelic *TP53* were similar to responses in patients with any *TP53* mutation:
  - CR: 28.6% (2/7); mORR: 71.4% (5/7)

Data cutoff: Dec 15, 2

Garcia JS et al. ASH 2021;Abstract 241.

VERONA Phase III Study Design



Until relapse, progression or unacceptable toxicity

Dual primary endpoints: Complete remission and OS

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 and overall response

Zeidan AM et al. ASCO 2021;Abstract TPS7054.

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

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.

Phase I/II Study of Venetoclax with 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%)

Venugopal S et al. ASH 2021;Abstract 245.

Magrolimab, an Investigational Anti-CD47 Monoclonal Antibody, Receives FDA Breakthrough Therapy Designation for Treatment of Myelodysplastic Syndrome

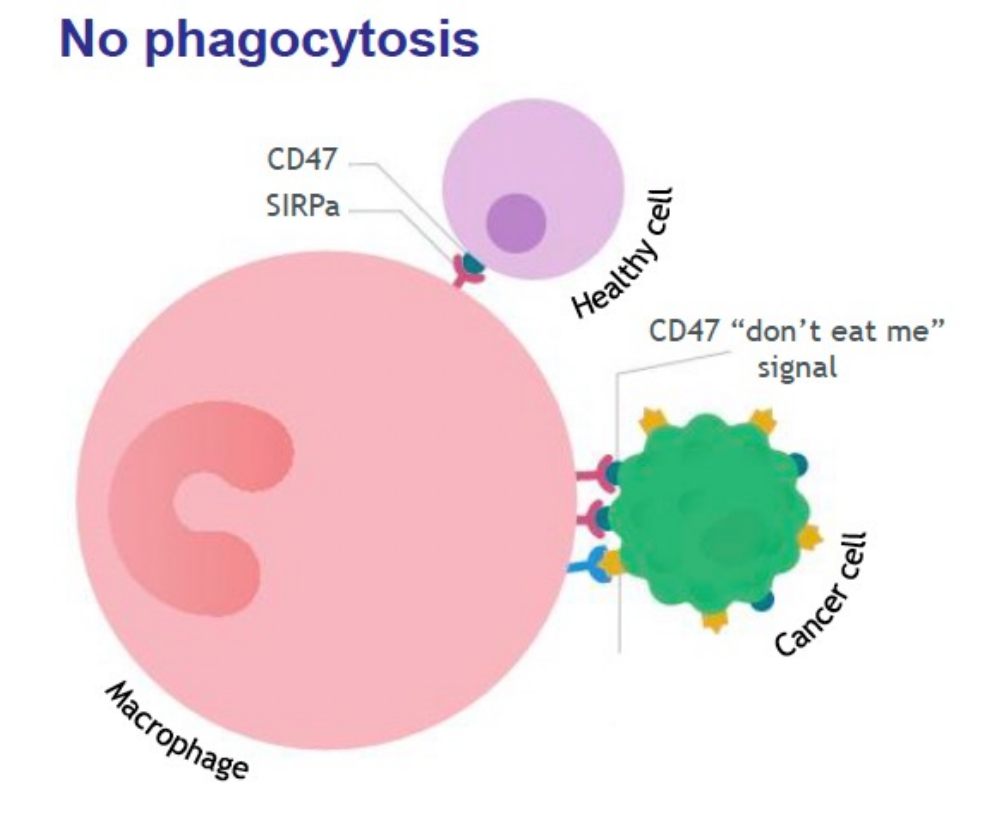
Press Release: September 15, 2020

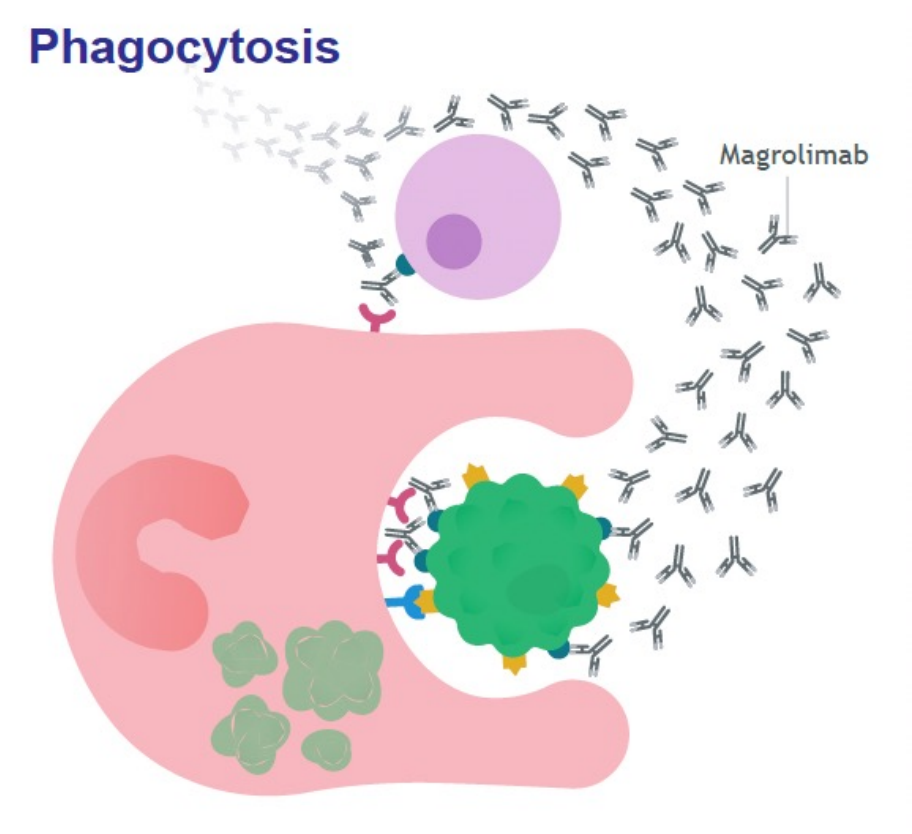
"The US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for magrolimab, a first-in-class, investigational anti-CD47 monoclonal antibody for the treatment of newly diagnosed myelodysplastic syndrome (MDS).

The FDA granted Breakthrough Therapy designation for magrolimab based on positive results of an ongoing Phase 1b study, which evaluated magrolimab in combination with azacitidine in previously untreated intermediate, high and very high-risk MDS. In data presented at the 2020 European Hematology Society Congress, 91 percent of evaluable patients (n=33) treated with magrolimab plus azacitidine achieved an objective response, with 42 percent achieving a complete remission (CR). The combination of magrolimab plus azacitidine was generally well-tolerated. No maximum tolerated dose was reached and no MDS patients discontinued treatment due to a treatment-related adverse event."

https://www.gilead.com/news-and-press/press-room/press-releases/2020/9/gileads-magrolimab-an-investigational-anticd47-monoclonal-antibody-receives-fda-breakthrough-therapy-designation-for-treatment-of-myelodysplastic

Magrolimab/Azacitidine Mechanism of Action





- 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.
- 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 TPS 7055.

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]

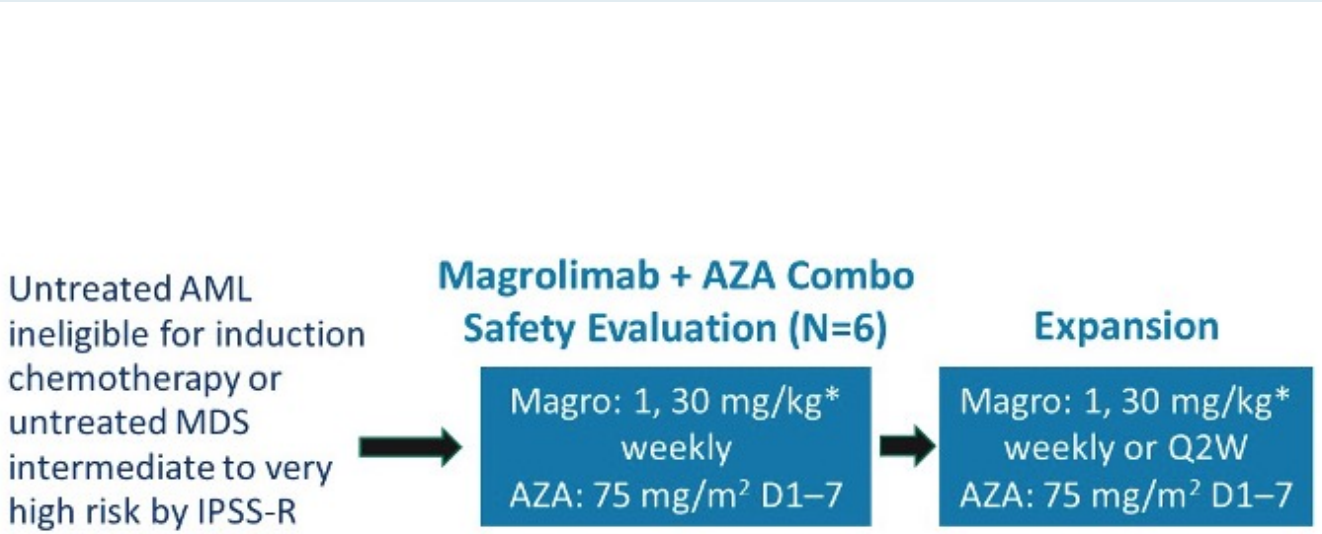
[1]Moffitt Cancer Center, Tampa, FL; [2]University of Oklahoma, Oklahoma City, OK; [3]City of Hope, Duarte, CA; [4]Columbia University, New York, NY; [5]MD Anderson Cancer Center, Houston, TX; [6]Sarah Cannon Research Institute, Nashville, TN; [7]University of Colorado, Denver, CO; [8]Healthcare Midwest, 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

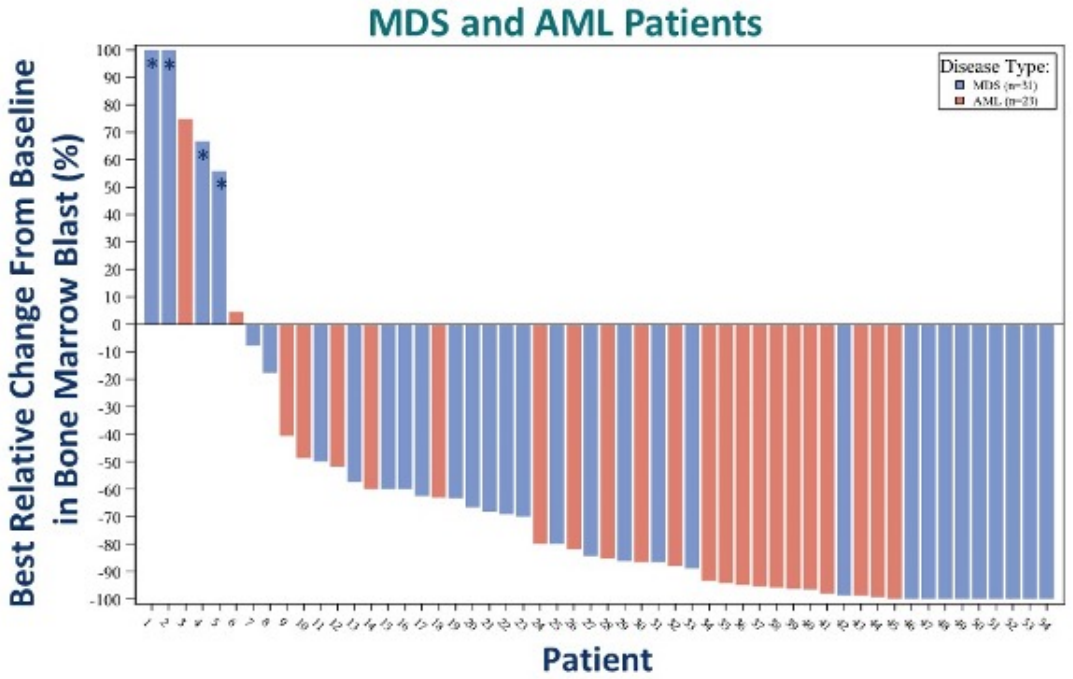
- A magrolimab priming dose (1 mg/kg) and dose ramp-up was utilized to mitigate on-target anemia

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])

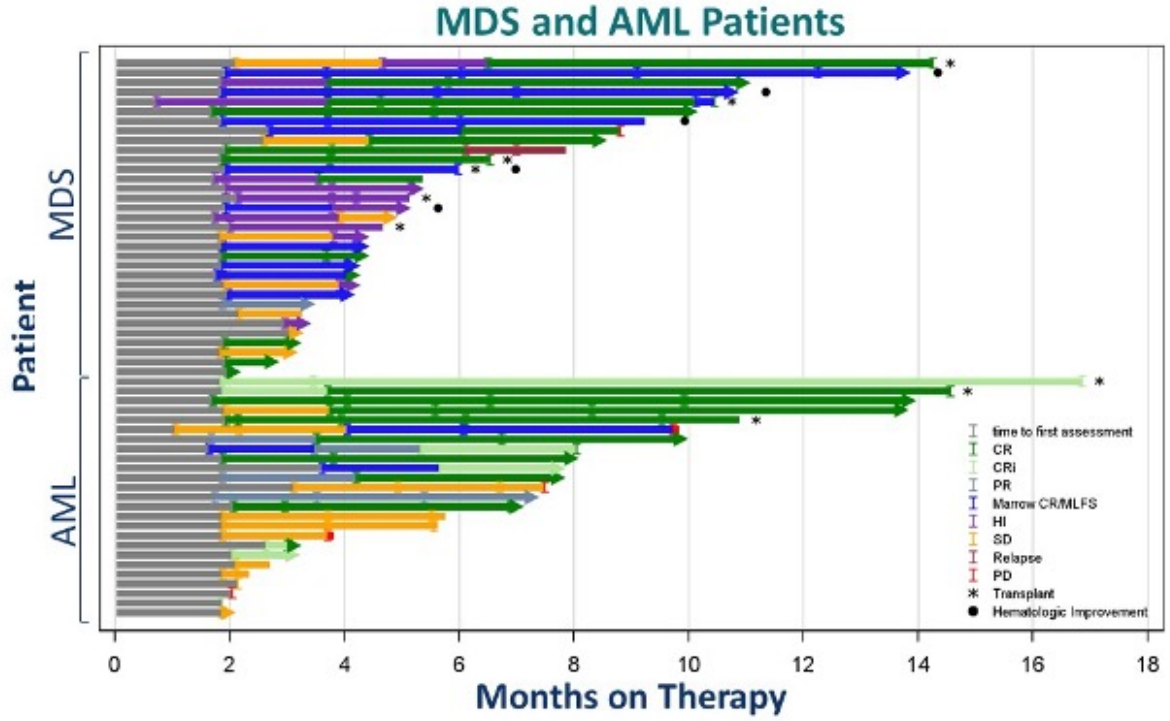
1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

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.

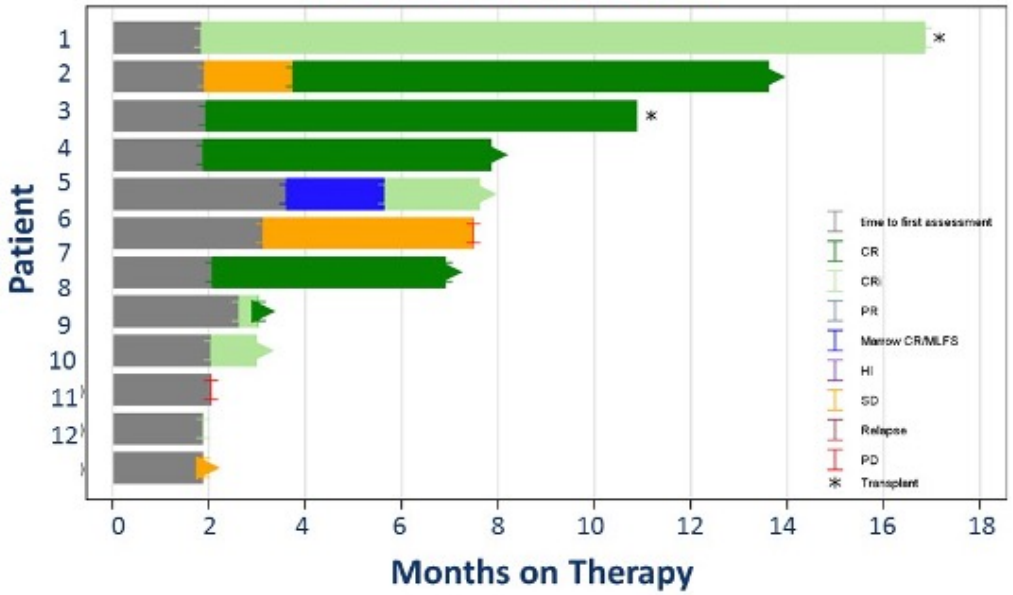
5F9005: Response to Magrolimab in Combination with Azacitidine for MDS and AML with TP53 Mutation

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.

***TP53*-Mutant AML Patients**

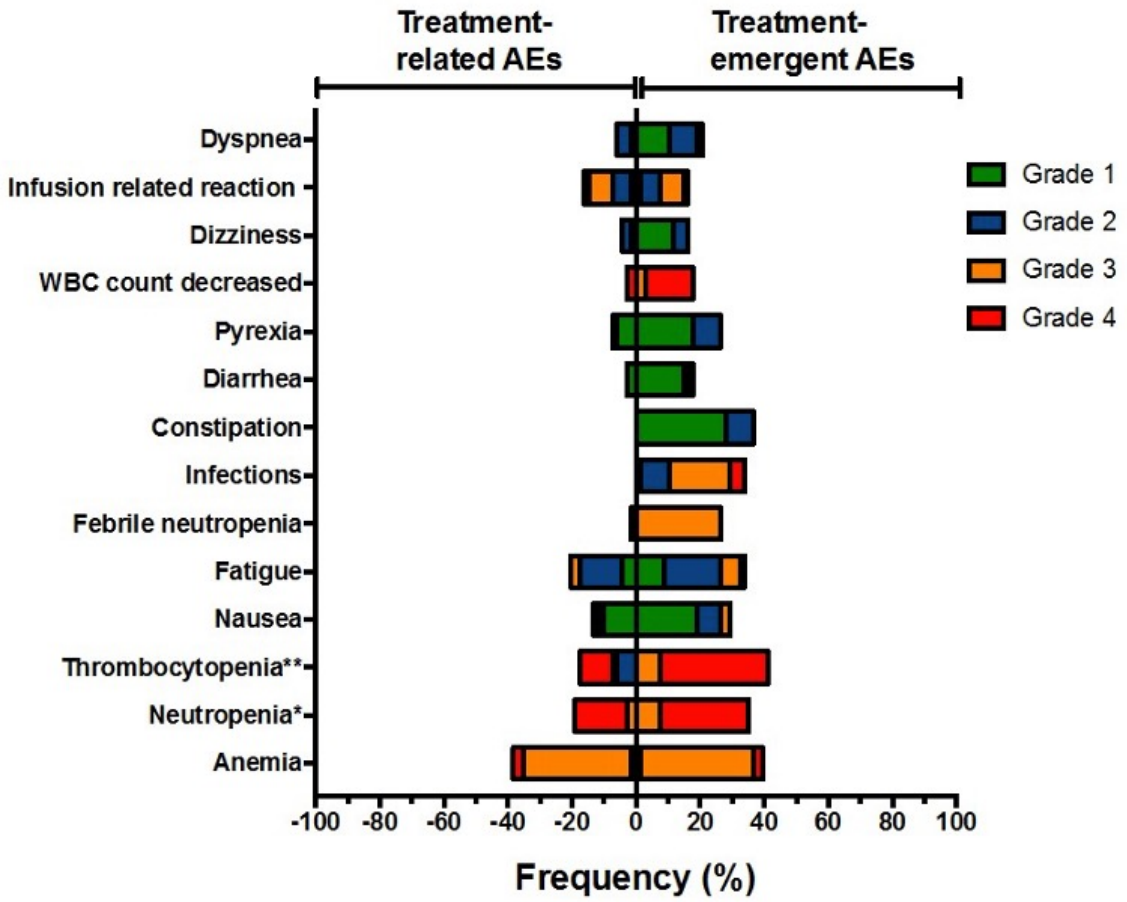


- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax + 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.

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

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		

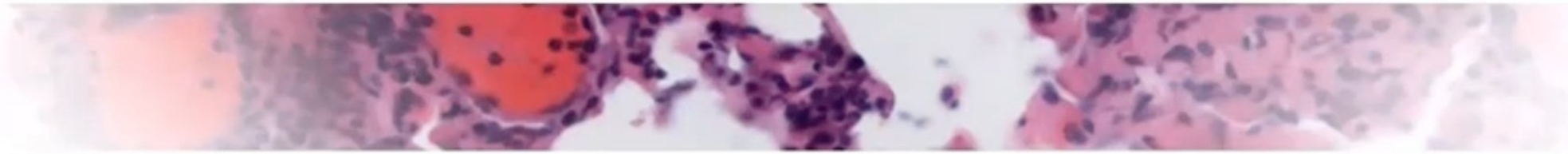
*Each cycle is 28 days.
IV, intravenous; SC, subcutaneous; Q2W, every 2 weeks.

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

Oral presentation #242

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



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

Sabatolimab Receives Fast Track Designation for MDS

Press Release: May 25, 2021

"The US Food and Drug Administration (FDA) has granted fast track designation for sabatolimab (MBG453) for the treatment of adult patients with myelodysplastic syndromes (MDS) defined with an IPSS-R risk category of high or very high risk in combination with hypomethylating agents. Fast track designation facilitates the development and expedites the review of drugs to treat serious conditions and fill unmet medical needs.

Sabatolimab is a first-in-class investigational immuno-myeloid therapy that binds to TIM-3, a novel target expressed on multiple immune cell types and leukemic cells and blasts, but not on the normal stem cells that induce blood formation; it is in development for HR-MDS and acute myeloid leukemia."

https://www.novartis.com/news/novartis-receives-fda-fast-track-designation-sabatolimab-mbg453-myelodysplastic-syndromes

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

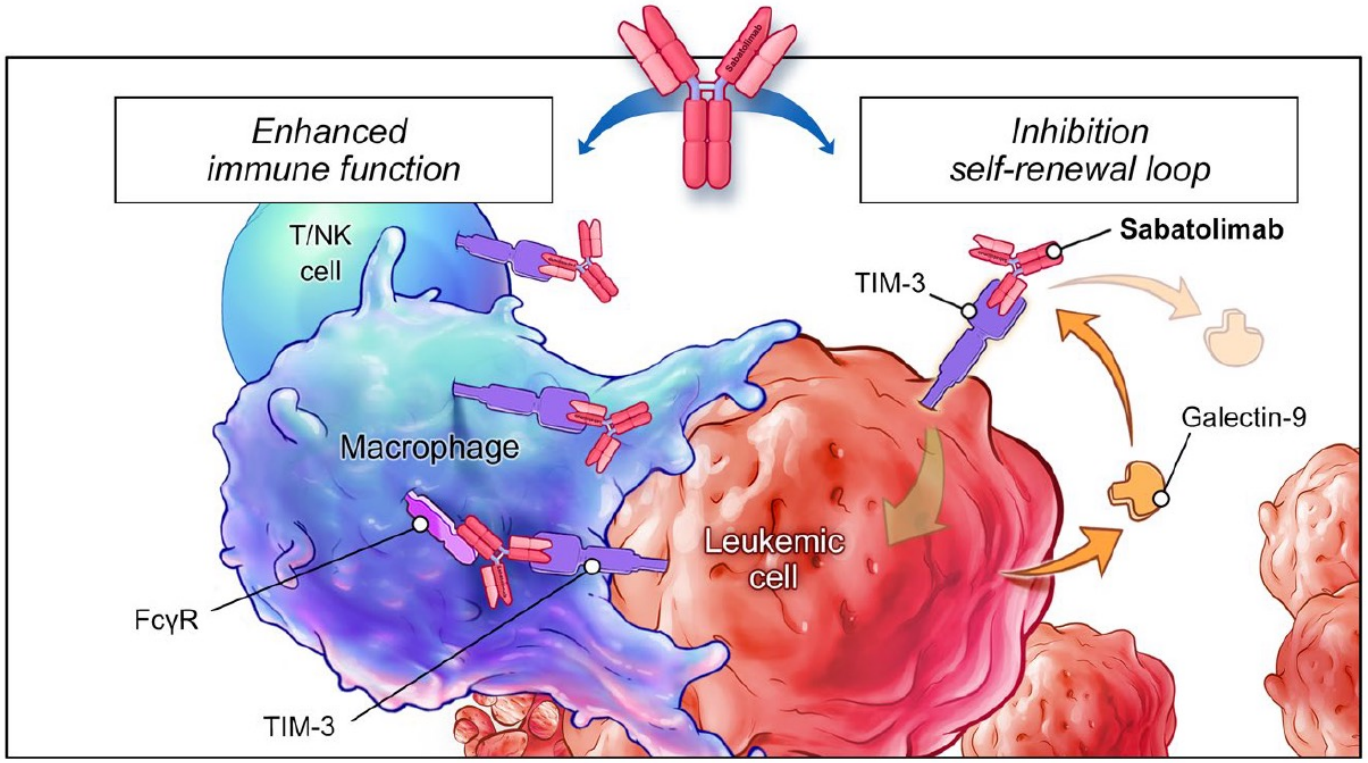
Andrew M. Brunner,[1] Jordi Esteve,[2] Kimmo Porkka,[3] Steve Knapper,[4] Elie Traer,[5] Sebastian Scholl,[6] Guillermo Garcia-Manero,[7] Norbert Vey,[8] Martin Wermke,[9] Jeroen Janssen,[10] Rupa Narayan,[1] Sun Loo,[11] Natalia Tovar,[2] Mika Kontro,[3] Oliver Ottmann,[4] Purushotham Naidu,[12] Marc 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.

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Hospital Clínic, Barcelona, Spain; [3]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [4]Cardiff University, Cardiff, UK; [5]Oregon Health & Science University, Portland, OR, USA; [6]University Hospital Jena, Jena, Germany; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Institut Paoli-Calmettes, Marseille, France; [9]University Hospital Dresden, Dresden, Germany; [10]Amsterdam University Medical Centers, location VUmc, Amsterdam, The Netherlands; [11]The Alfred Hospital, Melbourne, Victoria, Australia; [12]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [13]Novartis Institutes for BioMedical Research, Cambridge, MA, USA; [14]The Alfred Hospital and Monash University, Melbourne, Australia

ASH 2021;Abstract 244.

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



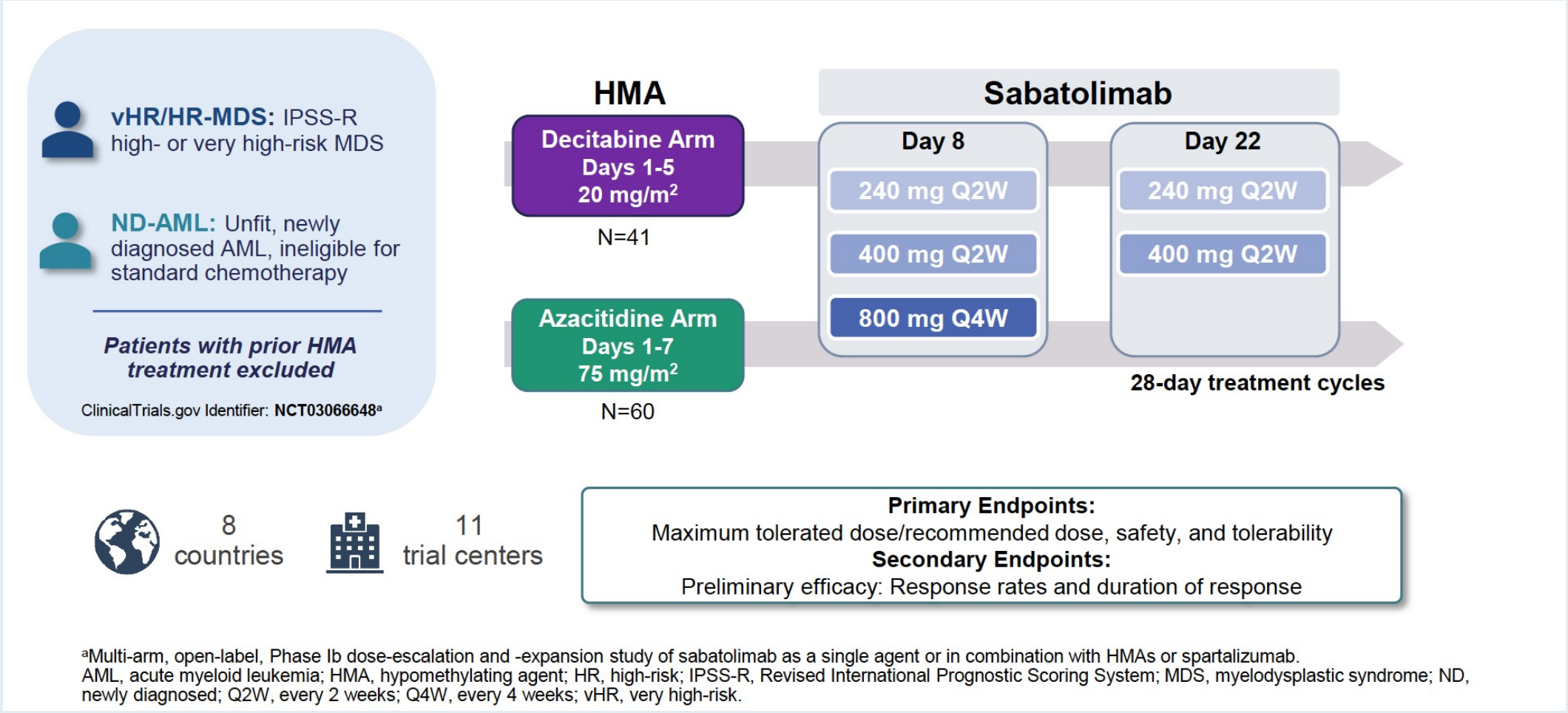
- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts[1-4]
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

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.

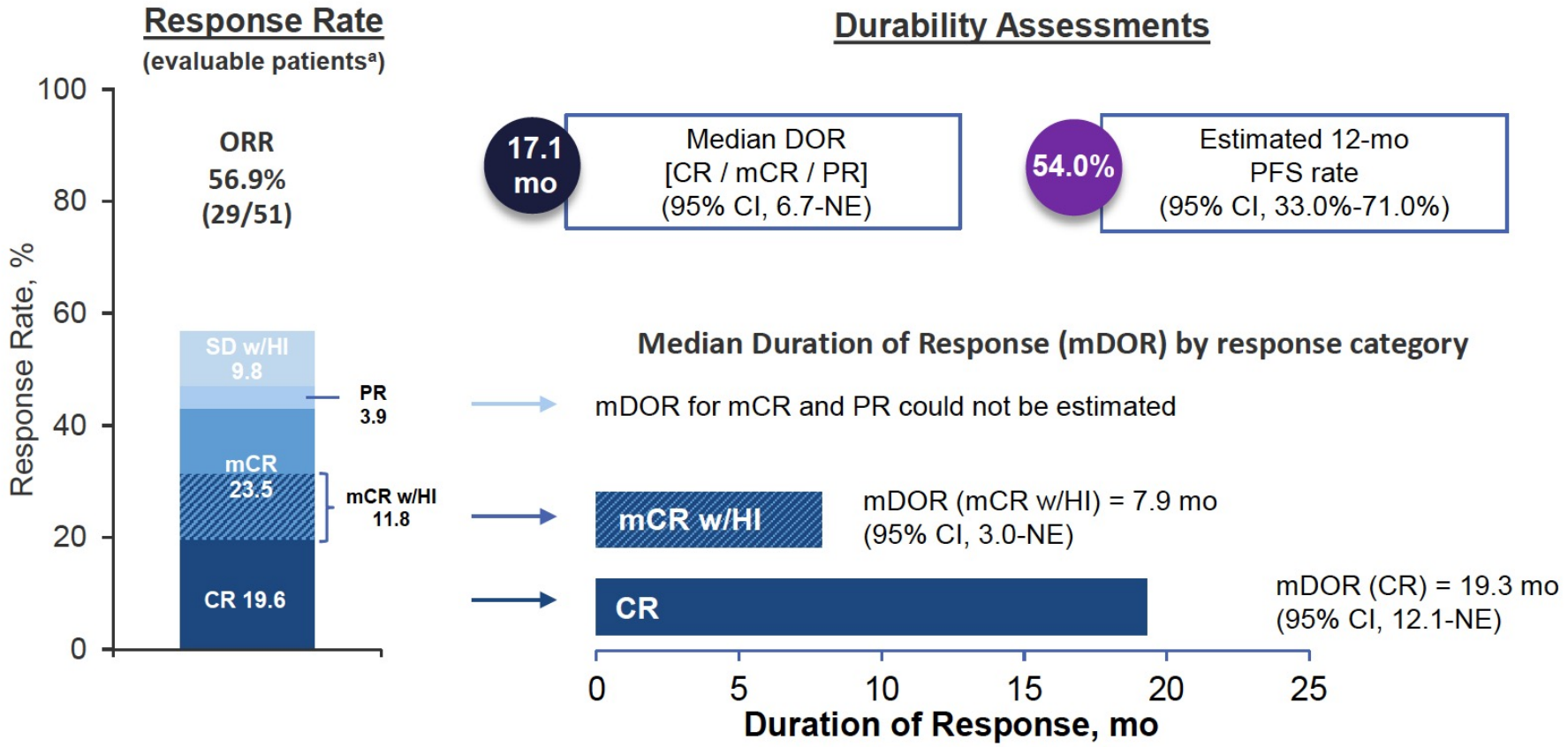
Phase IB Trial Design of Sabatolimab Combined with Hypomethylating Agents (HMA) in MDS and AML



[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.

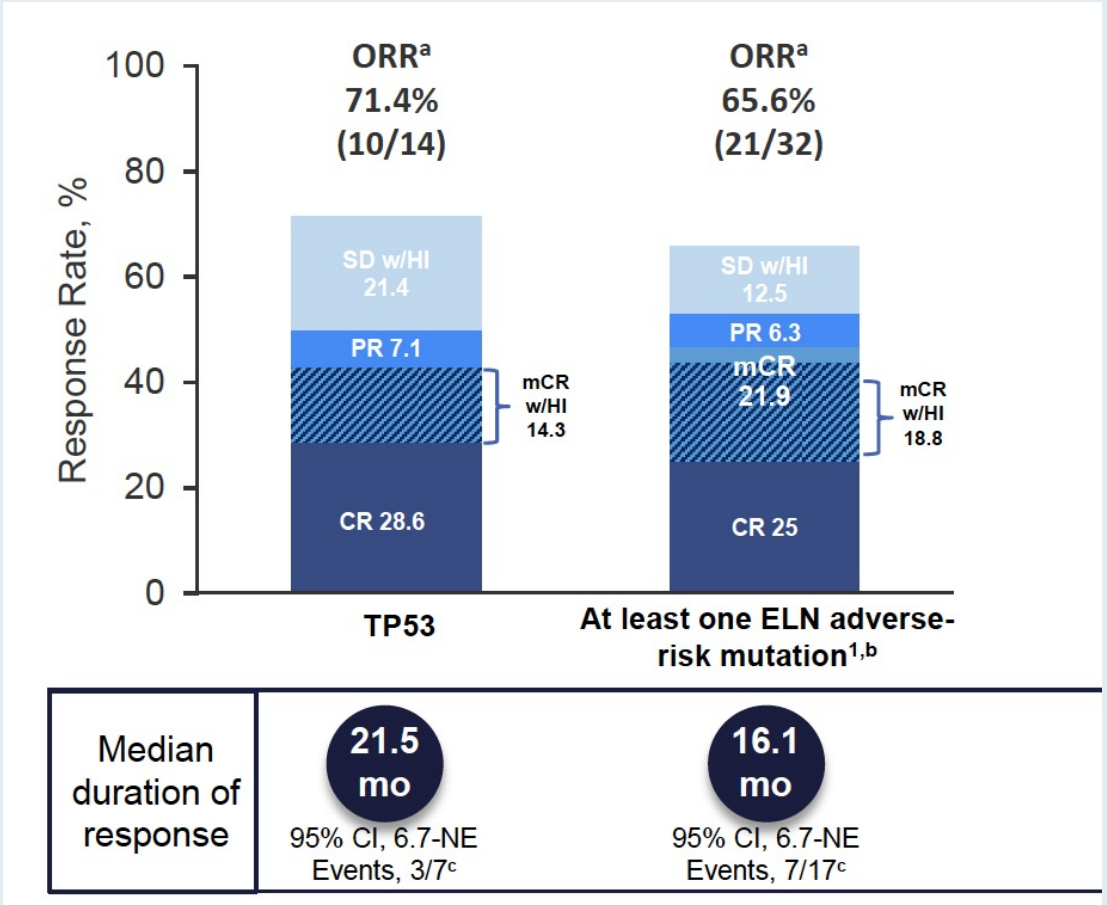
Clinical Responses Associated with Sabatolimab Combined with HMA in Very High-Risk/High-Risk MDS (vHR/HR-MDS)



[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.

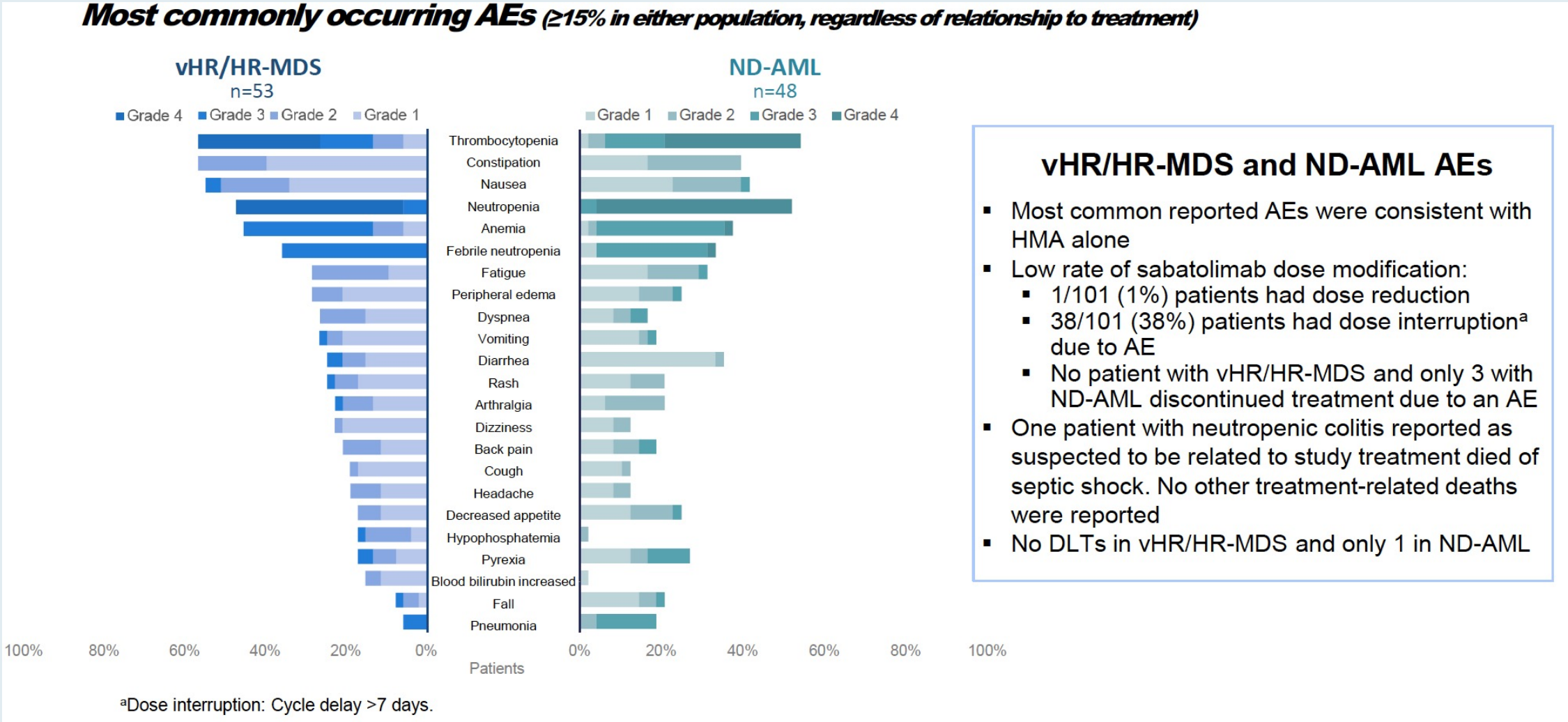
Durability of Responses Associated with Sabatolimab Combined with HMA for vHR/HR-MDS



[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



[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

Brunner AM et al. ASH 2021;Abstract 244.

RTP RESEARCH TO PRACTICE

STIMULUS: Clinical Trial Program for Sabatolimab in 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

RTP RESEARCH TO PRACTICE

Agenda

Introduction: Myelodysplastic Syndromes (MDS) Treatment Paradigm

Module 1: Case Presentations

- Dr Brenner: An 81-year-old man with MDS and multilineage dysplasia
- Dr Chojecki: A 56-year-old man with high-risk MDS and a TP53 mutation
- Dr Sinha: A 74-year-old woman with chronic myelomonocytic leukemia
- Dr Friemel: A 78-year-old man with MDS and multifactorial anemia
- Dr Gupta: A 93-year-old woman with MDS and transfusion-dependent anemia
- Dr Rupard: A 97-year-old woman with transfusion-dependent anemia and concomitant multiple myeloma and MDS with del(5q)

Module 2: Key Recent Data Sets

Module 3: Journal Club with Dr Komrokji

Module 4: Appendix

RTP
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Best Response Rates to first line therapy

	1L HMA VEN	1L HMA	
All cohort	n=35	n=1127	
ORR	77%	40%	<.005
CR	34%	13%	
mCR	37% (62% + HI)	11%	
PR	3%	1%	
HI	3%	15%	
***ASXL-1* MT**	n=16	n=106	
ORR	87%	32%	<.005
CR	44%	8%	
TP53 MT	n=12	n=137	
ORR	75%	44%	.038
CR	25%	17%	.47

* Among evaluable pts for response

American Society *of* Hematology

63rd ASH® Annual Meeting and Exposition

Komrokji RS et al. ASH 2021;Abstract 536.

Conclusions

- Among higher risk MDS patients, 1L HMA/Ven combination yields significantly higher complete response rates including *ASXL-1* mutant MDS compared to 1L HMA alone.
- Our data suggest early promising activity among those who received 1L HMA/Ven combination and proceeded to AHSCT (2-year OS probability of 91% compared to 51% with 1L HMA alone).
- Venetoclax add back strategy to HMA after 1L HMA failure has clinical activity and was associated with OS benefit.
- The OS survival benefit for 1L HMA/Ven in higher risk MDS pts can only be addressed and confirmed in context of randomized clinical trial.

American Society *of* Hematology

63rd ASH® Annual Meeting and Exposition

Komrokji RS et al. ASH 2021;Abstract 536.

Received: 20 January 2022 | Revised: 11 February 2022 | Accepted: 16 February 2022

DOI: 10.1002/ajh.26504

CORRESPONDENCE

Hypomethylating agent and venetoclax in patients with chronic myelomonocytic leukemia: Is the combination indeed better?

Ball S et al. *Am J Hematol* 2022;[Online ahead of print].

Clin Lymphoma Myeloma Leuk 2022;[Online ahead of print].

Therapeutic Outcomes and Prognostic Impact of Gene Mutations Including *TP53* and *SF3B1* in Patients with Del(5q) Myelodysplastic Syndromes (MDS)

Onyee Chan, Najla Al Ali, David Sallman, Eric Padron, Jeffrey Lancet, Rami Komrokji

Int J Mol Sci 2021;22(18):10105.

International Journal of
Molecular Sciences

MDPI

Review

Personalized Medicine for TP53 Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia

Thomas Cluzeau [1,2,3,*], Michael Loschi [1,2], Pierre Fenaux [3,4], Rami Komrokji [5] and David A. Sallman [5]

COVID-19 Outcomes Among Participants in the NHLBI Myelodysplastic Syndromes (MDS) Natural History Study

Padron E et al.

ASH 2021;Abstract 2611.

ASH 2021;Abstract 217.

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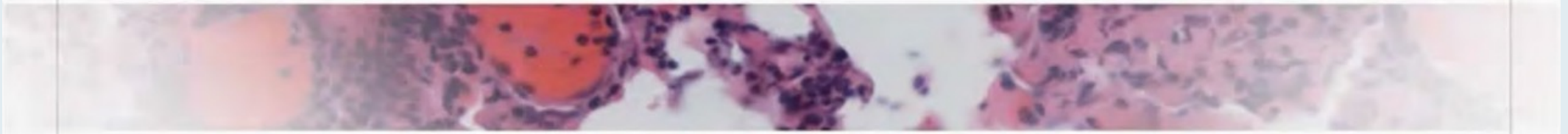


Responses to SARS-CoV-2 Vaccines in Patients with Myelodysplastic Syndrome and Acute Myeloid Leukemia

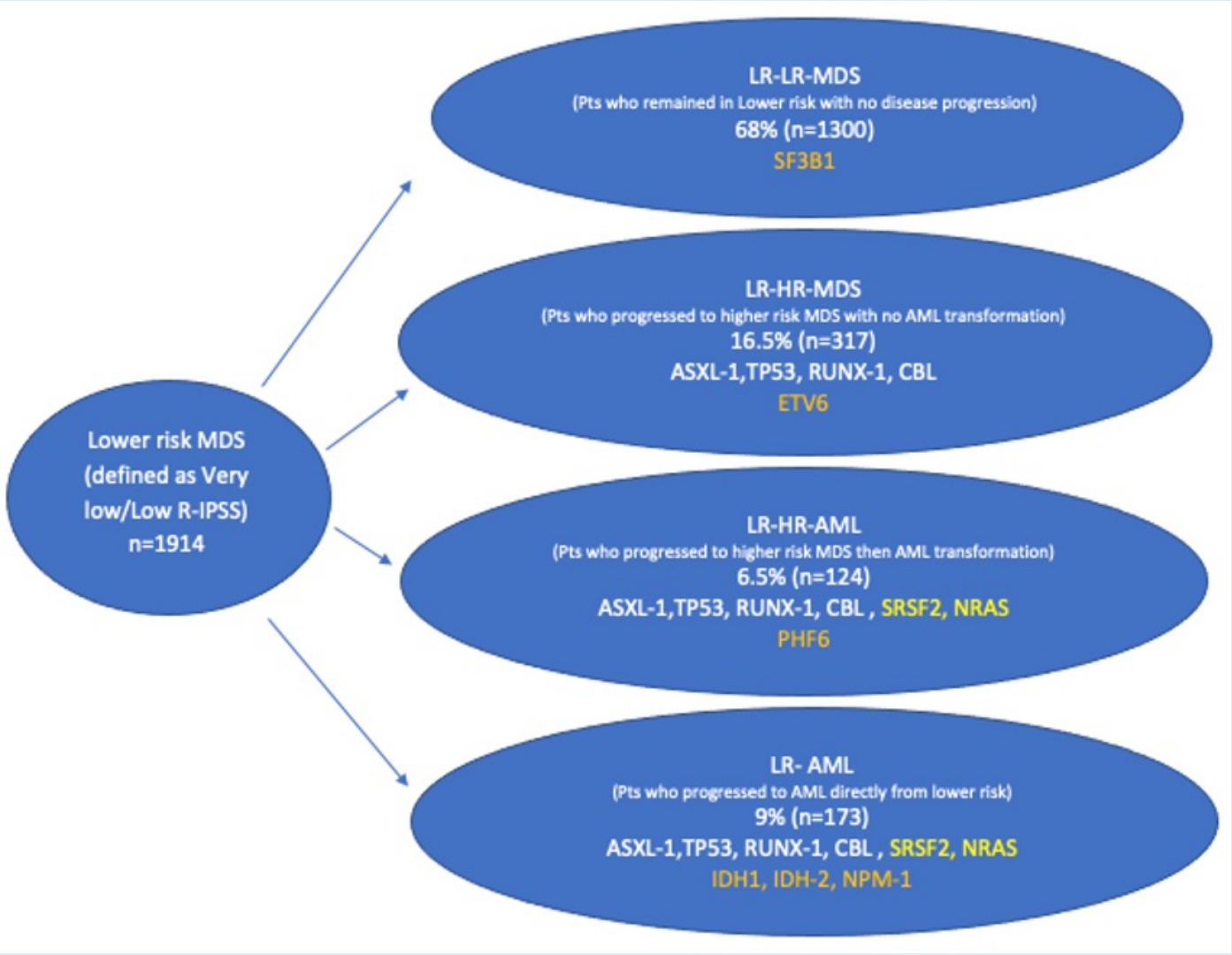
Akriti Jain, Ning Dong, Somedeb Ball, Elaine Tan, Junmin Whiting, Rami Komrokji, Kendra Sweet, Onyee Chan, David Sallman, Eric Padron, Andrew Kuykendall, Anna Giuliano, Jeffrey E. Lancet

The Natural History of Lower Risk MDS: Factors Predicting Progression to High-Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia in Patients with Very Low and Low Risk MDS According to the R-IPSS Criteria

Jain AG et al.

ASH 2021;Abstract 2600.

Major Mutations Found in Each Cohort and the Mutations that Predict Progression



Jain AG et al. ASH 2021;Abstract 2600.

Kanagal-Shamanna et al. *Blood Cancer Journal* (2021)11:52
https://doi.org/10.1038/s41408-021-00446-y

Blood Cancer Journal

CORRESPONDENCE Open Access

Evolutionary action score identifies a subset of *TP53* mutated myelodysplastic syndrome with favorable prognosis

Rashmi Kanagal-Shamanna[1], Guillermo Montalban-Bravo[2], Panagiotis Katsonis[3], Koji Sasaki[2], Caleb A. Class[4], Elias Jabbour[2], David Sallman[5], Anthony Michael Hunter[5], Christopher Benton[2], Kelly S. Chien[2], Rajyalakshmi Luthra[1], Carlos E. Bueso-Ramos[1], Tapan Kadia[2], Michael Andreeff[2], Rami S. Komrokji[5], Najla H Al Ali[5], Nicholas Short[2], Naval Daver[2], Mark J. Routbort[1], Joseph D. Khoury[1], Keyur Patel[1], Irene Ganan-Gomez[2], Yue Wei[2], Gautam Borthakur[2], Farhad Ravandi[2], Kim-Anh Do[2], Kelly A. Soltysiak[2], Olivier Lichtarge[3], L. Jeffrey Medeiros[1], Hagop Kantarjian[2] and Guillermo Garcia-Manero[2]

IDH Mutations Are Enriched in Myelodysplastic Syndromes Patients with Severe Neutropenia: A Potential Targeted Therapy

Komrokji RS et al.

ASH 2021;Abstract 1526.

Leukemia 2022;[Online ahead of print].

LETTER OPEN

Check for updates

MYELODYSPLASTIC SYNDROME

Luspatercept for myelodysplastic syndromes/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis

Rami S. Komrokji[1]✉, Uwe Platzbecker[2], Pierre Fenaux[3], Amer M. Zeidan[4], Guillermo Garcia-Manero[5], Ghulam J. Mufti[6], Valeria Santini[7], María Díez-Campelo[8], Carlo Finelli[9], Joseph G. Jurcic[10], Peter L. Greenberg[11], Mikkael A. Sekeres[12], Amy E. DeZern[13], Michael R. Savona[14], Jeevan K. Shetty[15], Rodrigo Ito[16], George Zhang[16], Xianwei Ha[16], Jay T. Backstrom[17] and Amit Verma[18]

LEUKEMIA & LYMPHOMA
2021, VOL. 62, NO. 11, 2762–2767
https://doi.org/10.1080/10428194.2021.1938028

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

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

Rami Komrokji[a], Najla Al Ali[a], Eric Padron[a], Jeffrey Lancet[a], Aziz Nazha[b], David Steensma[c], Amy DeZern[d], Gail Roboz[e], Guillermo Garcia-Manero[f], Mikkael A. Sekeres[b] and David Sallman[a]

Blood 2021;138(11):989-92.

Letters to *Blood*

TO THE EDITOR:

Validation of the international working group proposal for *SF3B1* mutant myelodysplastic syndromes

Rami Komrokji, Virginia Volpe, Onyee Chan, Najla Al Ali, David Swoboda, Andrew Kuykendall, Eric Padron, and David A. Sallman

A Focus on Phenotype and Genotype: Racial/Ethnic Disparities in Myelodysplastic Syndromes

Tinsley-Vance SM et al.

ASH 2021;Abstract 1985.

Clin Lymphoma Myeloma Leuk 2022;22(1):1-16.

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]

Haematologica 2022;107(3):737-9.

Dual pyroptotic biomarkers predict erythroid response in lower-risk non-del(5q) myelodysplastic syndromes treated with lenalidomide and recombinant erythropoietin

Chen Wang,[1,2] Kathy L. McGraw,[2] Amy F. McLemore,[2] Rami Komrokji,[2] Ashley A. Basiorka,[2] Najla Al Ali,[2] Jeffrey E. Lancet,[2] Eric Padron,[2] Olivier Kosmider,[3] Michaela Fontenay,[3] Pierre Fenaux,[4] Alan F. List[2#] and David A. Sallman[2#]

haematologica
Journal of The Ferrata Storti Foundation

SF3B1-mutant myelodysplastic syndrome/ myeloproliferative neoplasms: a unique molecular and prognostic entity

by Abhishek A. Mangaonkar, Terra L. Lasho, Christy Finke, Rhett P. Ketterling, Kaaren K. Reichard, Kristen McCullough, Naseema Gangat, Aref Al-Kali, Kebede H. Begna, William H. Hogan, Mark R. Litzow, Hassan Alkhateeb, Mithun Shah, Animesh Pardanani, Ayalew Tefferi, Najla H. Al Ali, Chetasi Talati, David Sallman, Eric Padron, Rami Komrokji, and Mrinal M. Patnaik

Haematologica **2022;[Online ahead of print].**

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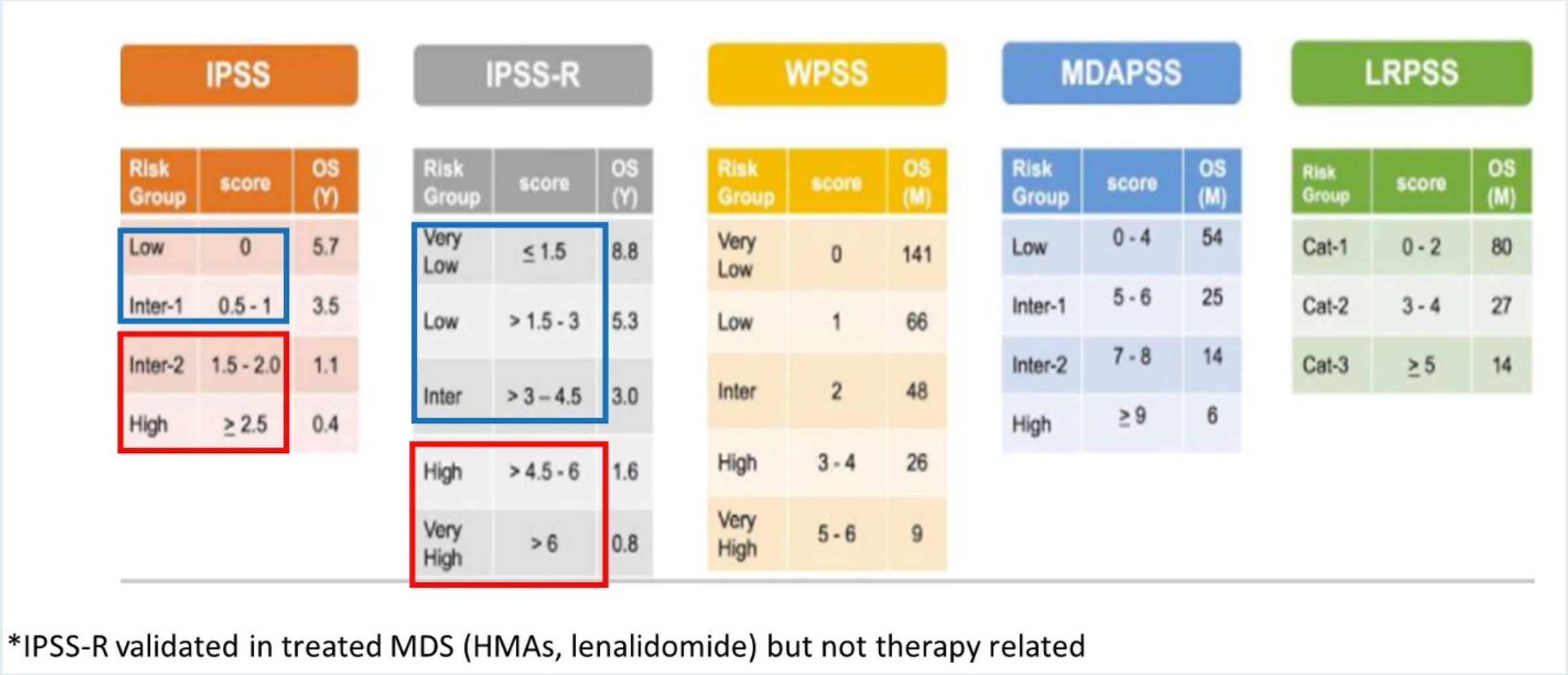
RTP RESEARCH TO PRACTICE

Lower-Risk MDS

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

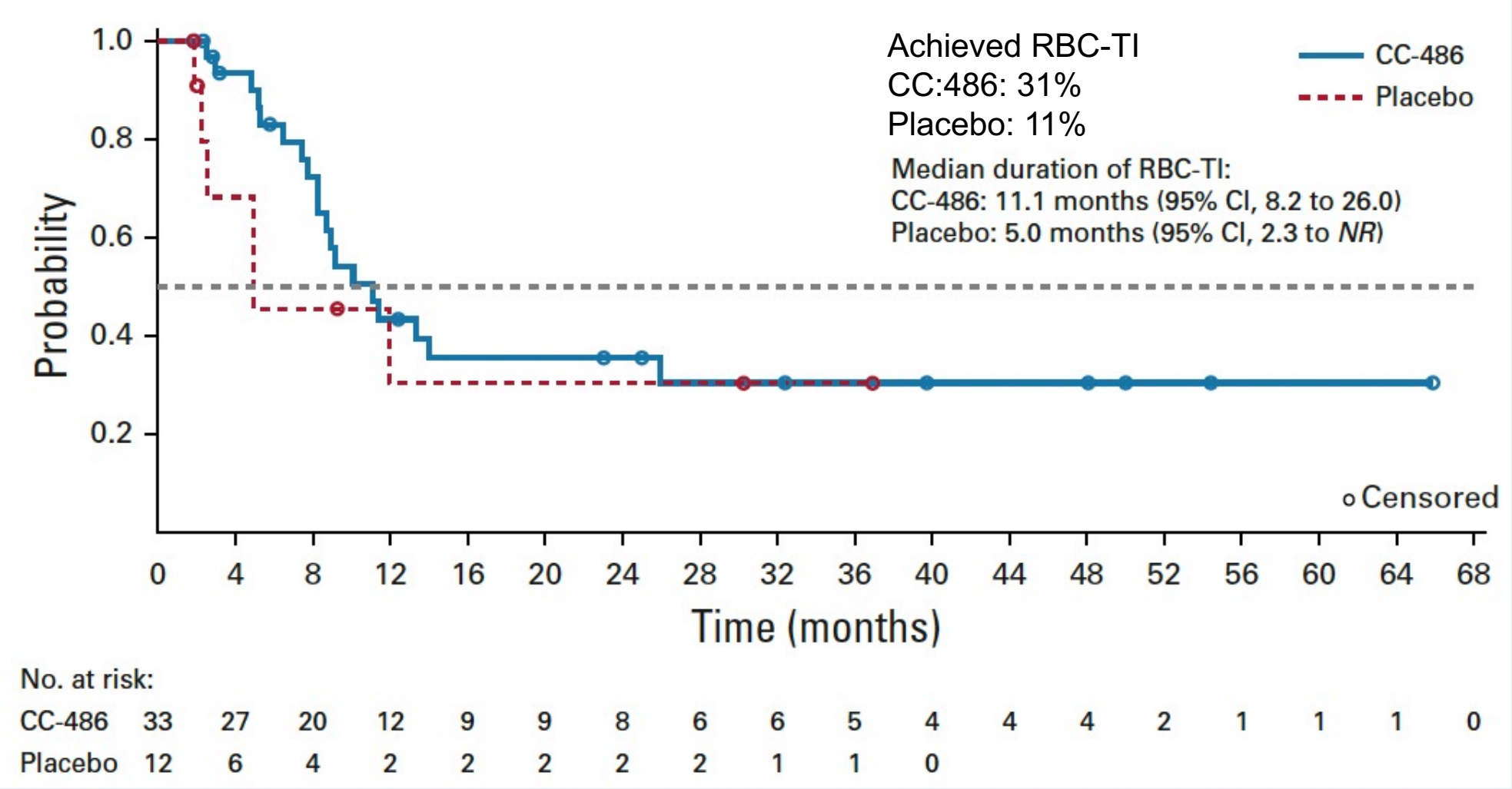
Buckstein R. Education Session. ASCO 2021.

AZA-MDS-003: Baseline Disease Characteristics

Characteristic	CC-486 (n = 107)	Placebo (n = 109)	Total (N = 216)
IPSS risk, n (%)			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate-1	106 (99.1)	109 (100)	215 (99.5)
Intermediate-2	1 (0.9)	0 (0.0)	1 (0.5)
High	0 (0.0)	0 (0.0)	0 (0.0)
IPSS-R risk, n (%)			
Very low (≤ 1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Low (> 1.5-3)	24 (22.4)	21 (19.3)	45 (20.8)
Intermediate (> 3-4.5)	51 (47.7)	48 (44.0)	99 (45.8)
High (> 4.5-6)	27 (25.2)	33 (30.3)	60 (27.8)
Very high (> 6)	1 (0.9)	0 (0.0)	1 (0.5)
Missing	4 (3.7)	7 (6.4)	11 (5.1)
Platelet transfusion–dependent,[d] n (%)	30 (28.0)	35 (32.1)	65 (30.1)
RBC transfusion requirement per 28 days,[e] units, median (range)	3.3 (1.3-10.0)	3.3 (1.3-9.5)	3.3 (1.3-10.0)
Hemoglobin, g/dL, median (range)	8.3 (5.4-10.9)	8.1 (5.7-10.1)	8.1 (5.4-10.9)

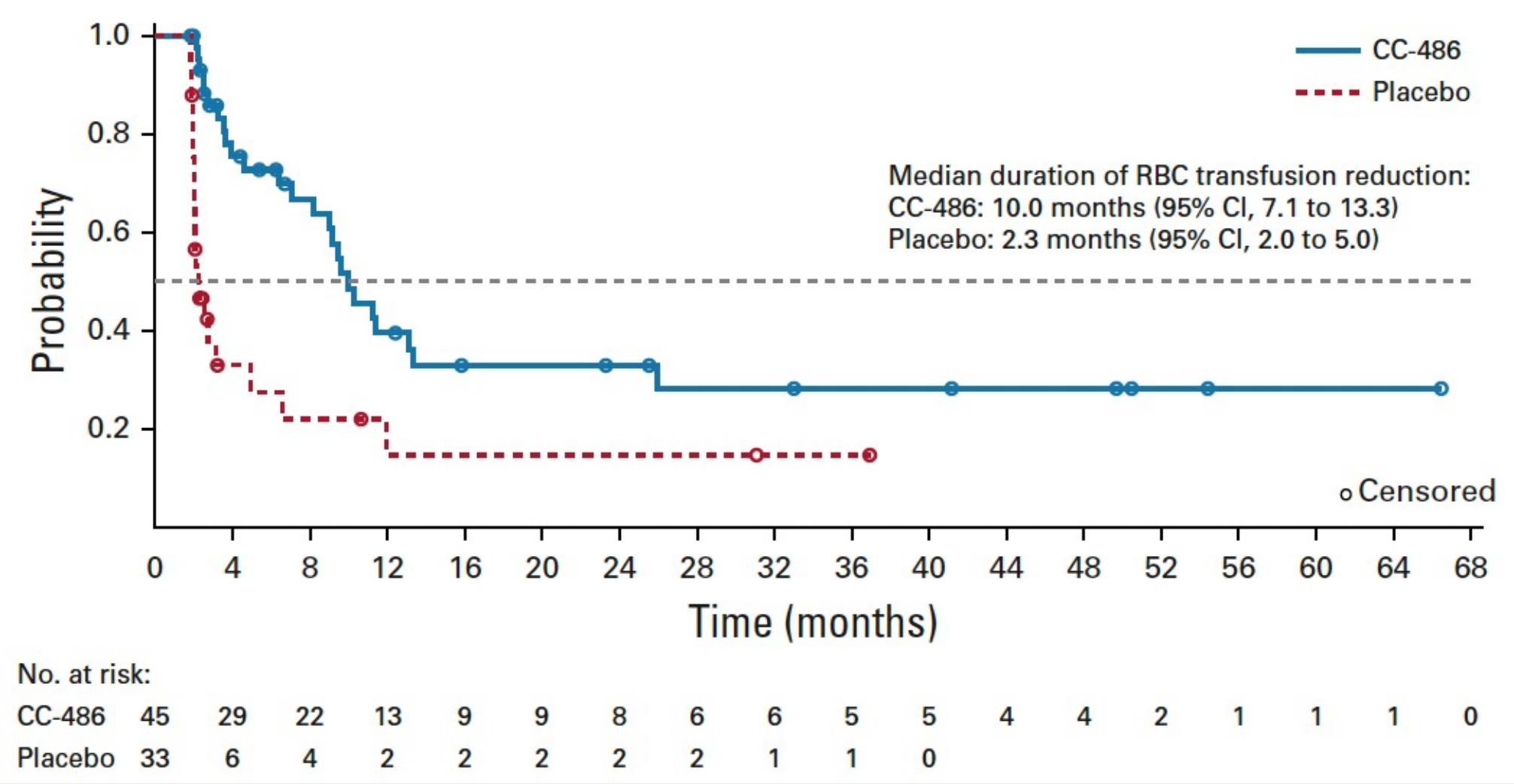
Garcia-Manero G et al. *J Clin Oncol* 2021;39:1426-36.

AZA-MDS-003: Achievement and Duration of Red Blood Cell Transfusion Independence



Garcia-Manero G et al. *J Clin Oncol* 2021;39:1426-36.

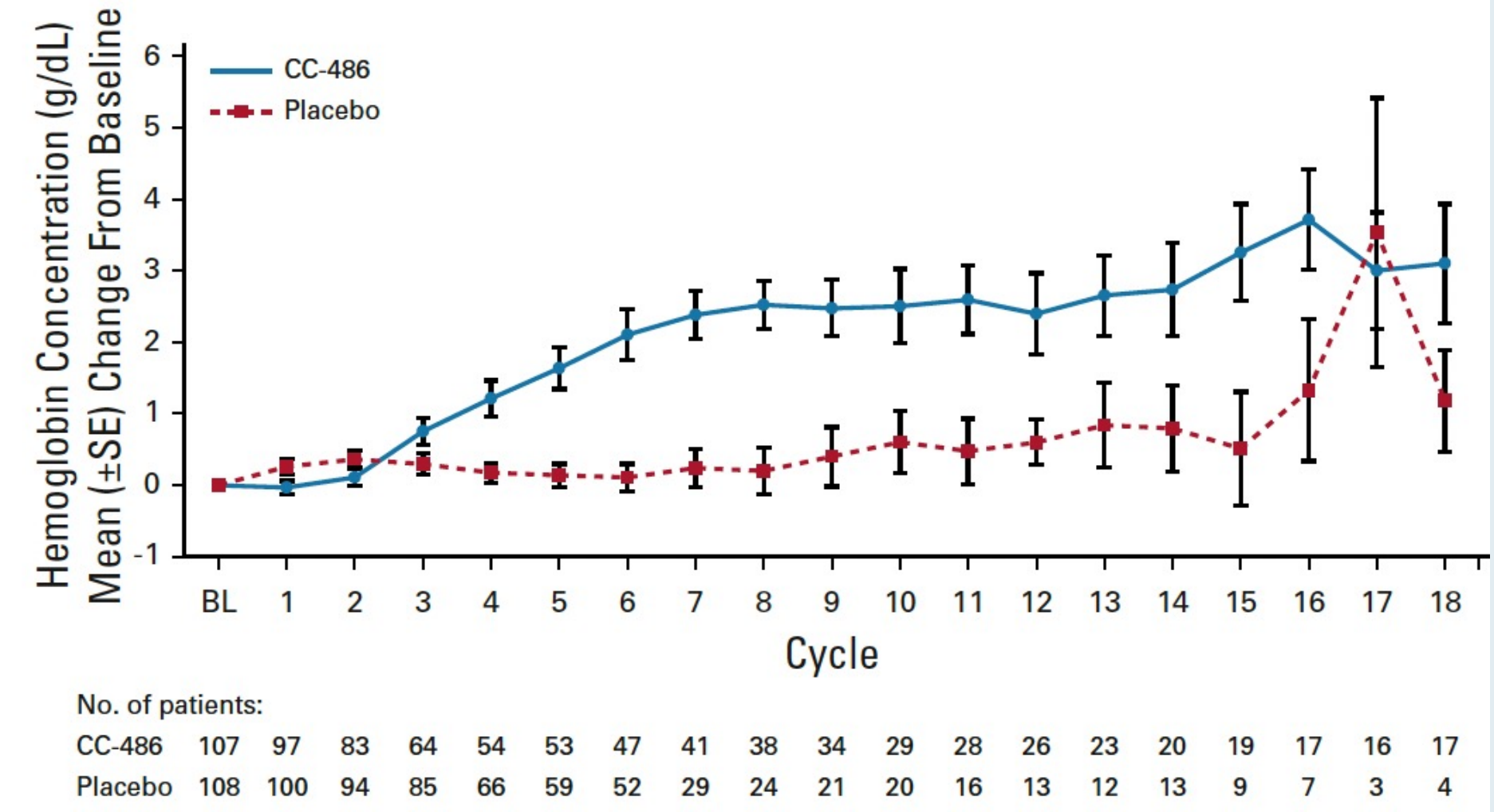
AZA-MDS-003: Duration of RBC Transfusion Reduction



Garcia-Manero G et al. *J Clin Oncol* 2021;39:1426-36.

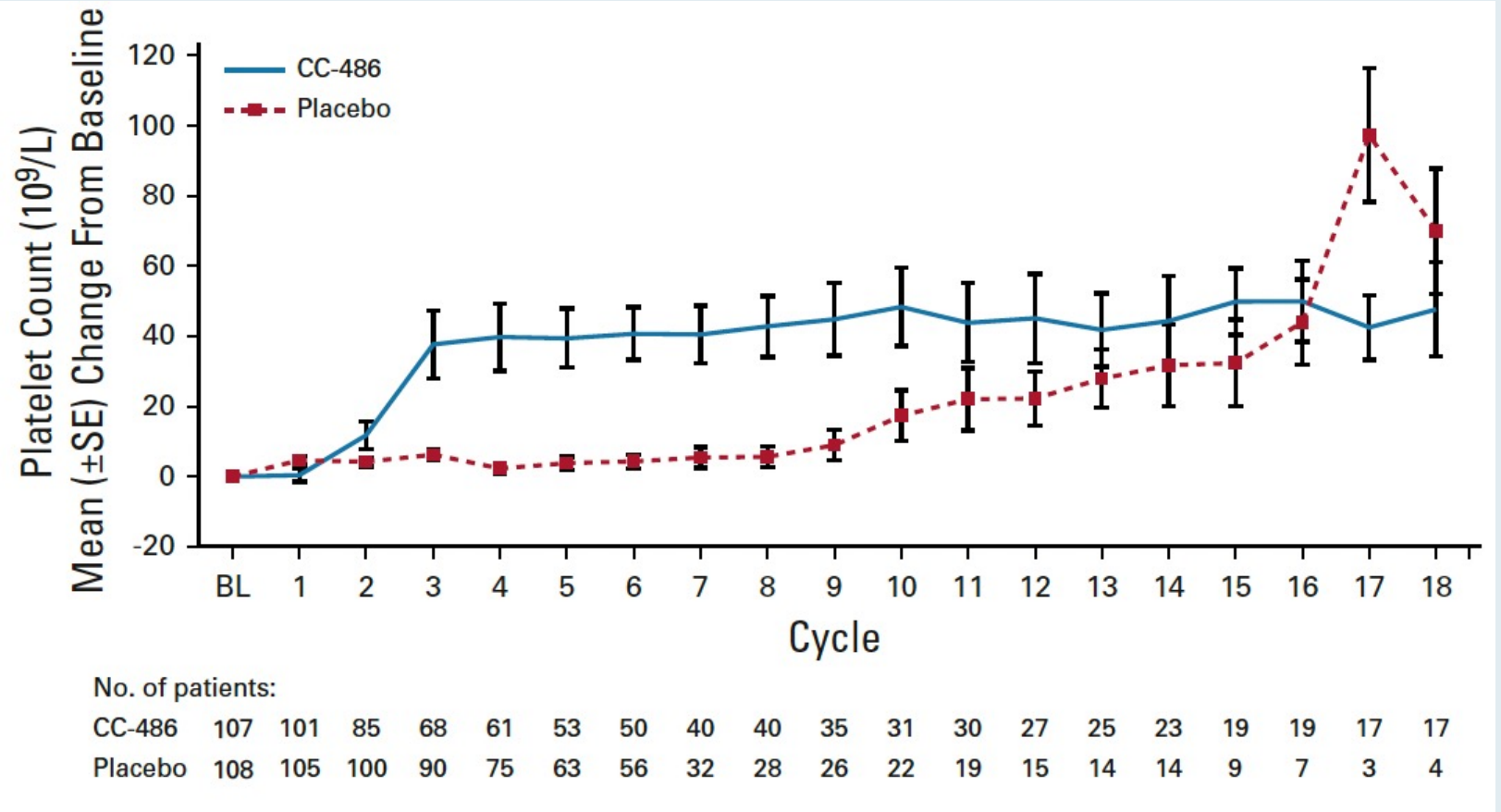
RTP RESEARCH TO PRACTICE

AZA-MDS-003: Change in Hemoglobin from Baseline



Garcia-Manero G et al. *J Clin Oncol* 2021;39:1426-36.

AZA-MDS-003: Platelet Count Change from Baseline



Platelet transfusion independence in 75 patients who were transfusion-dependent at baseline:

- CC-486: 16.7% (median duration 12.1 months)
- Placebo: 14.3% (median duration 4.4 months)

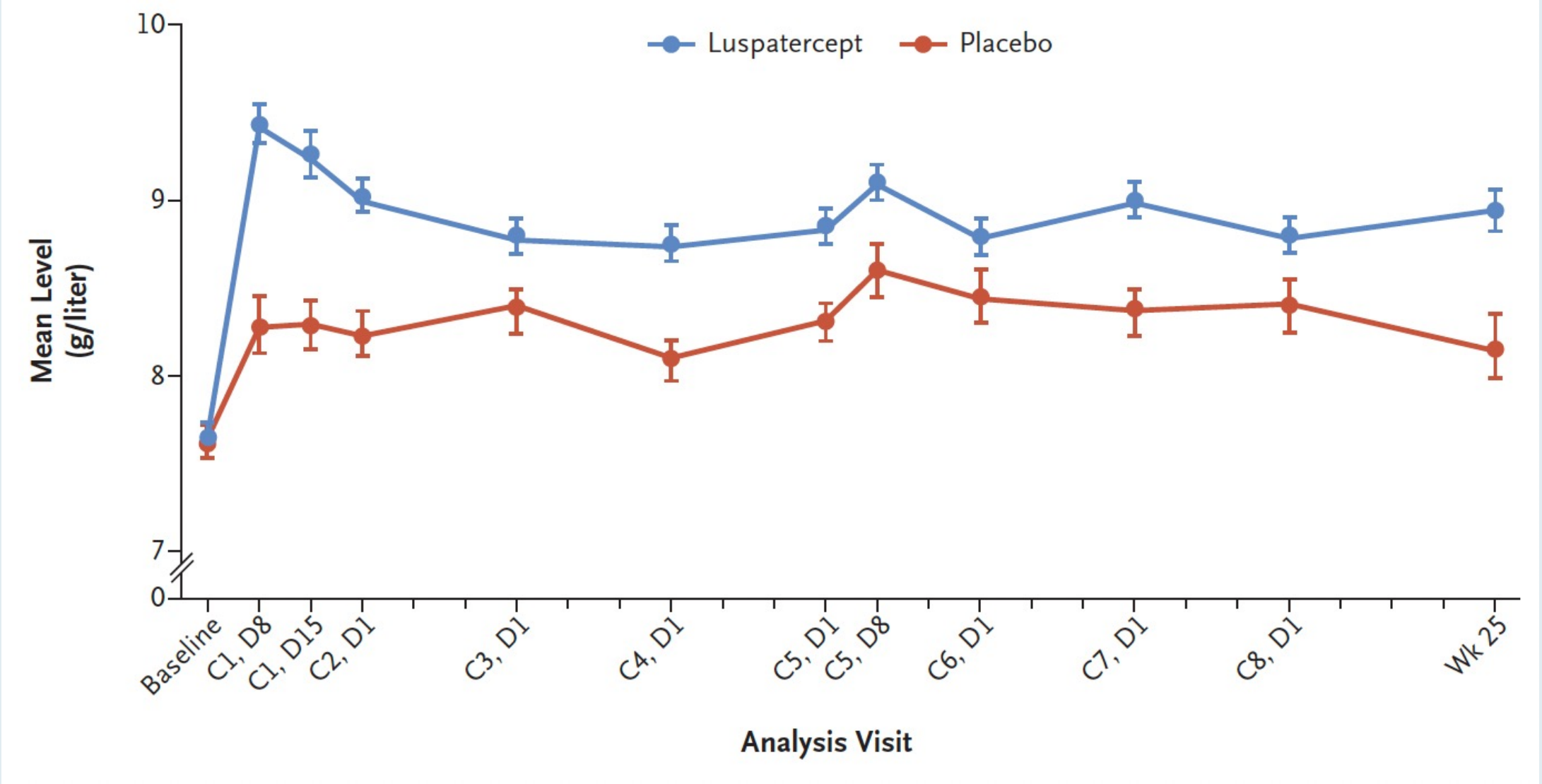
Garcia-Manero G et al. *J Clin Oncol* 2021;39:1426-36.

MEDALIST: Erythroid Response and Increase in Mean Hemoglobin Level

End Point	Luspatercept (N = 153)	Placebo (N = 76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

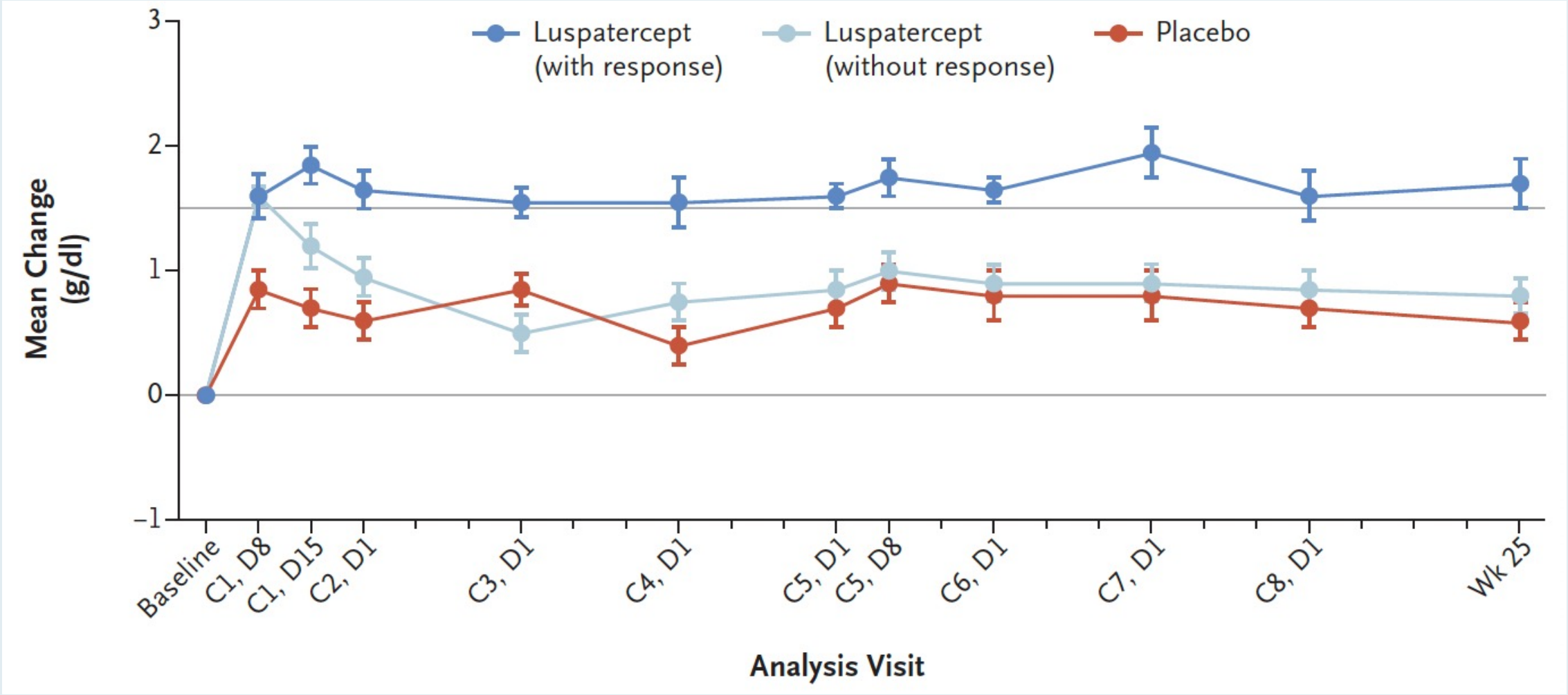
Fenaux P et al. *N Engl J Med* 2020;382:140-51.

MEDALIST: Change in Mean Observed Hemoglobin Level over Time



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

MEDALIST: Change from Baseline in Hemoglobin Level



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

MEDALIST: Adverse Events Occurring in at Least 10% of Patients

Event	Luspatercept (N=153)		Placebo (N=76)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
General disorder or administration-site condition				
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Asthenia	31 (20)	4 (3)	9 (12)	0
Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
Diarrhea	34 (22)	0	7 (9)	0
Nausea†	31 (20)	1 (1)	6 (8)	0
Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
Dizziness	30 (20)	0	4 (5)	0
Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal or connective-tissue disorder				
Back pain†	29 (19)	3 (2)	5 (7)	0
Arthralgia	8 (5)	1 (1)	9 (12)	2 (3)
Respiratory, thoracic, or mediastinal disorder				
Dyspnea†	23 (15)	1 (1)	5 (7)	0
Cough	27 (18)	0	10 (13)	0
Infection or infestation				
Bronchitis†	17 (11)	1 (1)	1 (1)	0
Urinary tract infection†	17 (11)	2 (1)	4 (5)	3 (4)

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

Higher-Risk MDS

FDA Approves Oral Combination of Decitabine and Cedazuridine for MDS

Press Release: July 7, 2020

"On July 7, 2020, the Food and Drug Administration approved an oral combination of decitabine and cedazuridine for adult patients with myelodysplastic syndromes (MDS) including the following:

- previously treated and untreated, *de novo* and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and
- intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

[The combination] was investigated in two open-label, randomized, crossover trials. Trial ASTX727-01-B (NCT02103478) included 80 adult patients with MDS (International Prognostic Scoring System [IPSS] Intermediate-1, Intermediate-2, or high-risk) or CMML and trial ASTX727-02 (NCT03306264) included 133 adult patients with MDS or CMML, including all French-American-British classification criteria and IPSS Intermediate-1, Intermediate-2, or high-risk prognostic scores.

In both trials, patients were randomized 1:1 to receive 35 mg decitabine and 100 mg cedazuridine orally in cycle 1 and decitabine 20 mg/m^2 intravenously in cycle 2 or the reverse sequence. Both [the oral combination] and intravenous decitabine were administered once daily on days 1 through 5 of a 28-day cycle. Starting with cycle 3, all patients received [the combination] orally once daily on days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-oral-combination-decitabine-and-cedazuridine-myelodysplastic-syndromes

RTP RESEARCH TO PRACTICE

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

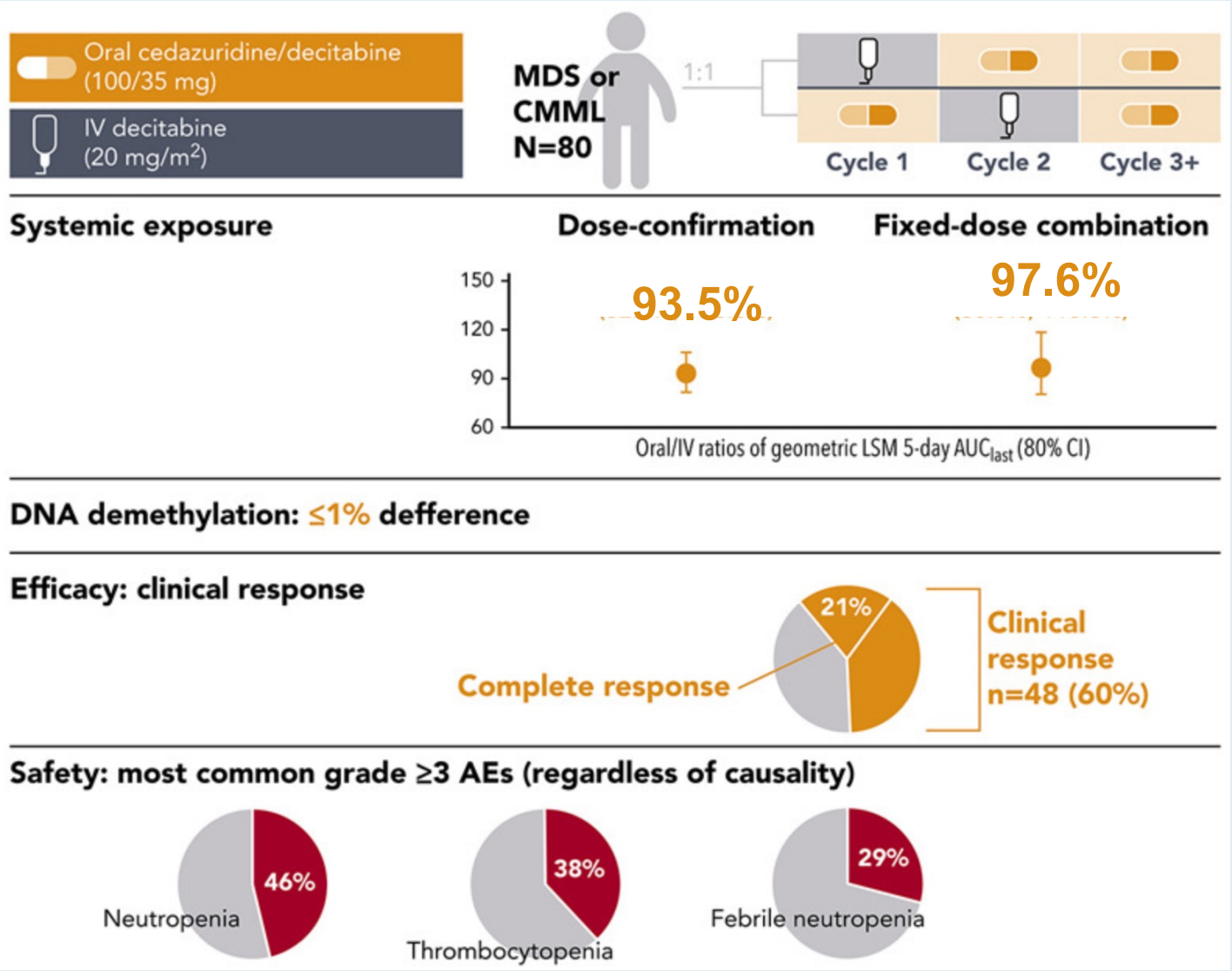
Regular Article

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

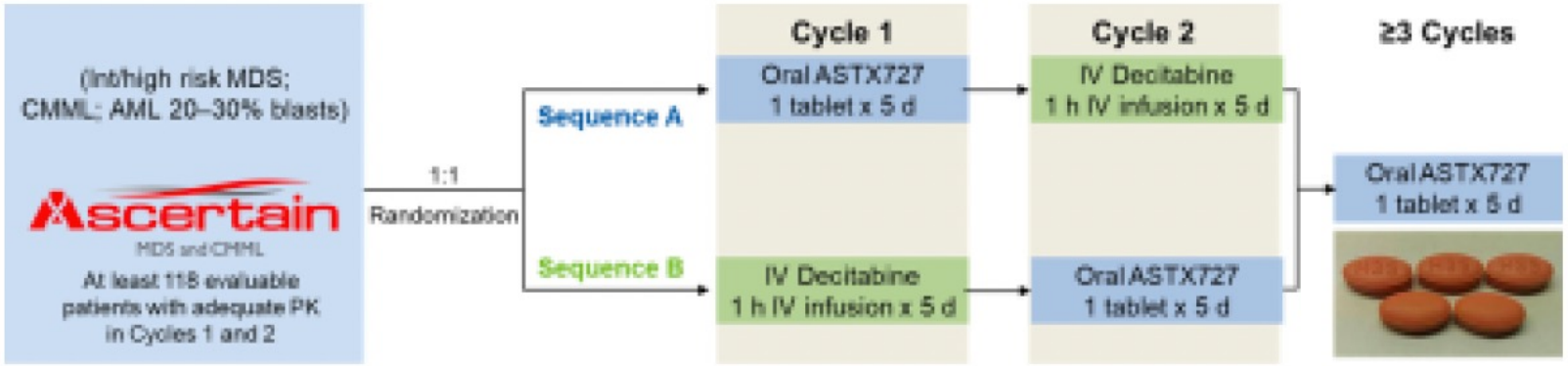


Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

Prolonged Survival Observed in 133 MDS Patients Treated with Oral Decitabine/Cedazuridine

Savona MR et al.
16th International Congress on Myelodysplastic Syndromes (MDS 2021);Abstract 48.

ASCERTAIN Phase III Study Design



Major entry criteria

- Candidates for IV decitabine
- ECOG PS 0 – 1
- Life expectancy of ≥3 months
- Adequate organ function

Primary endpoint

- Total 5-day decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints

- Efficacy: Response rate; transfusion independence; duration of response; leukemia-free and overall survival
- Safety of ASTX727
- Maximum LINE-1 demethylation

Savona MR et al. MDS 2021;Abstract 48.

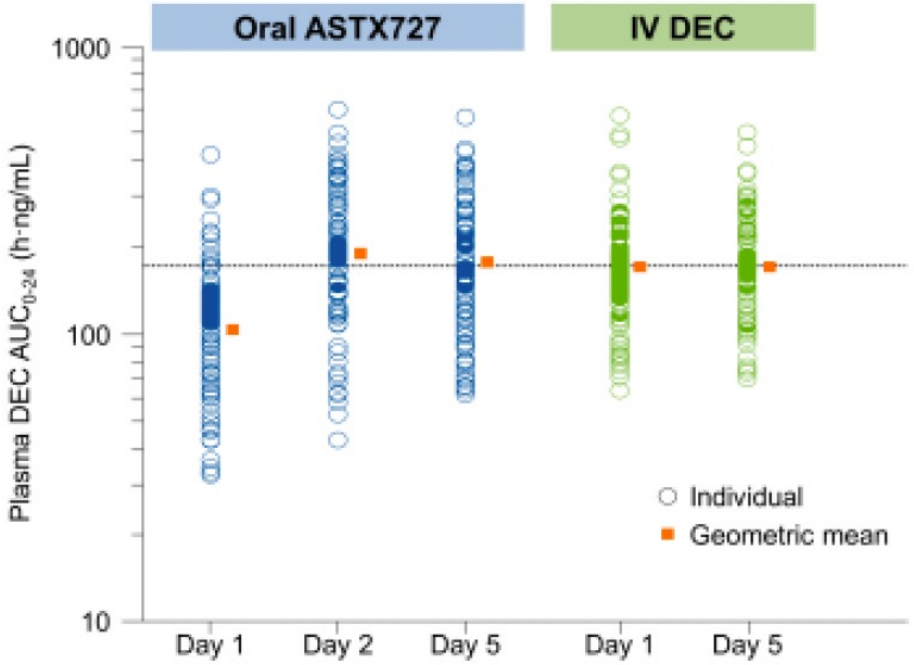
ASCERTAIN Study Population

Characteristics		Total Treated N=133
Median age, years (range)		71 (44–88)
Sex	Male	87 (65%)
	Female	46 (35%)
Median weight, kg (range)		83 (45 -158)
Median BSA, m^2 (range)		1.98 (1.4 - 2.9)
CMML		16 (12%)
MDS, IPSS classification	High risk	21 (16%)
	Int-1 and 2	90 (68%)
	Low risk	6 (5%)
Transfusion dependent	RBCs	53 (40%)
	Platelets	12 (9%)
ECOG PS	0	55 (41%)
	1	78 (59%)

Savona MR et al. MDS 2021;Abstract 48.

ASCERTAIN: Pharmacokinetics and Pharmacodynamics

- The change in LINE-1 demethylation between oral vs. IV decitabine was less than 1% for both cycles 1 and 2 with overlapping 95% confidence intervals suggesting similar biologic effect.



Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

Savona MR et al. MDS 2021;Abstract 48.

ASCERTAIN: Response Rates

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22%)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)
Hematologic improvement (HI)	10 (7.5%)	(3.7,13.4)
HI-erythroid	2 (1.5%)	(0.2,5.3)
HI-neutrophils	1 (0.8%)	(0.0,4.1)
HI-platelet	7 (5.3%)	(2.1,10.5)
Overall response (CR + PR + mCR + HI)	82 (61.7%)	(52.8,69.9)
Progressive Disease	6 (4.5%)	(1.7,9.6)
No Response	28 (21.1%)	(14.5, 29.0)
Non-evaluable	17 (12.8%)	(7.6, 19.7)

- Median CR duration was 14.0 months. (range 2-29 months)
- Median duration of best response was 12.7 months. (range 1-33 months)
- 34 (26%) of subjects proceeded to HCT.
- No survival difference was seen between subjects proceeding to HCT vs. others.
- Subjects received median 9 cycles of treatment

Savona MR et al. MDS 2021;Abstract 48.

ASCERTAIN Safety Results: TEAEs in >10% of Patients*

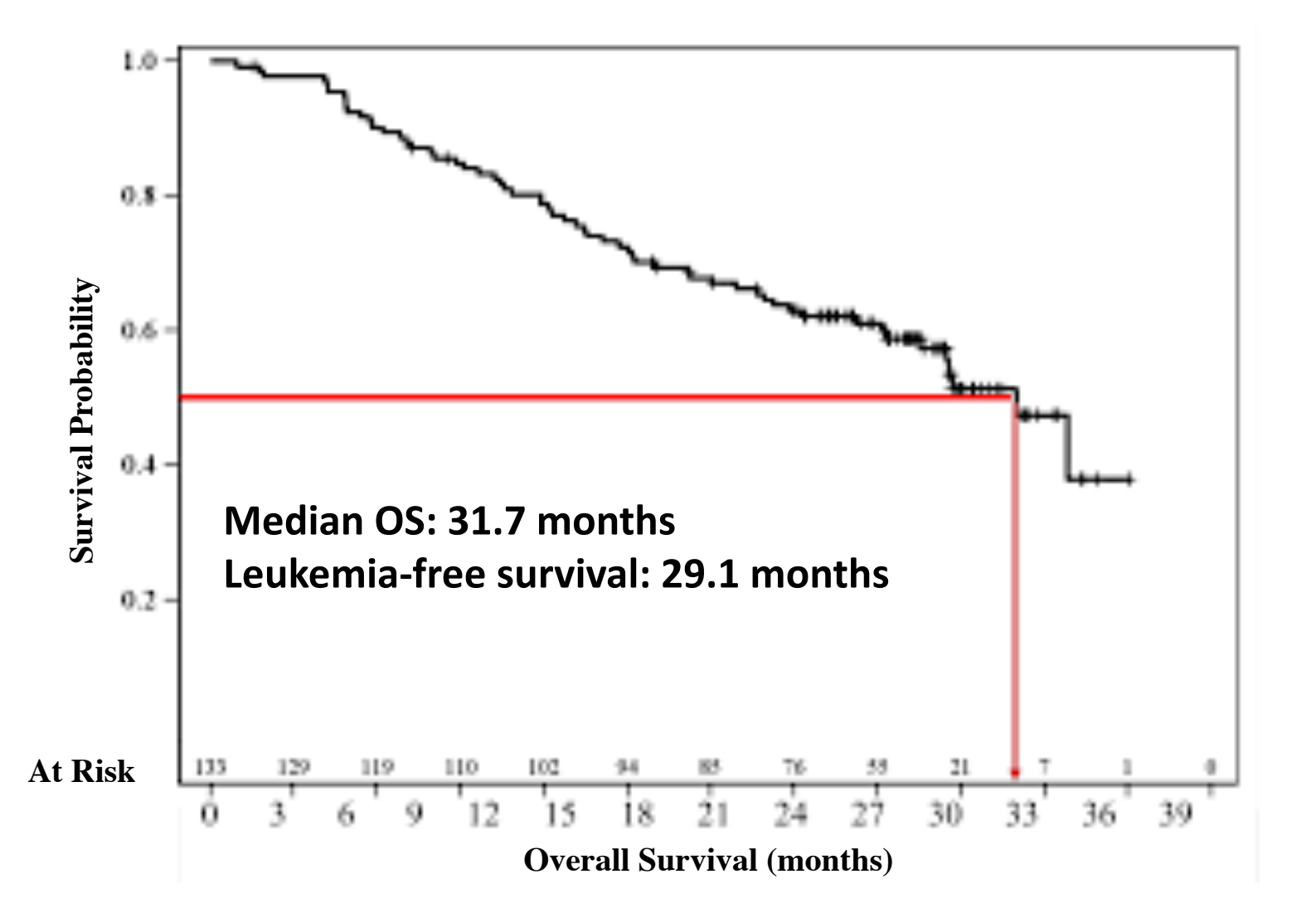
Preferred Term	Phase 3 Total (N=133, n [%])	Phase 3 Total Grade 3 or higher
Neutropenia	68 (51%)	65 (49%)
Thrombocytopenia	71 (53%)	62 (47%)
Anaemia	55 (41%)	47 (35%)
Leukopenia	33 (25%)	29 (22%)
Febrile Neutropenia	18 (14%)	17 (13%)
Fatigue	32 (24%)	3 (2%)
Diarrhea	22 (17%)	2 (2%)
Nausea	33 (25%)	0 (0%)
Decreased Appetite	19 (14%)	0 (0%)
Constipation	18 (14%)	0 (0%)

*Events attributable to oral decitabine/cedazuridine

- Safety profile consistent with that of IV decitabine.
- No new safety concerns with longer follow up.

Savona MR et al. MDS 2021;Abstract 48.

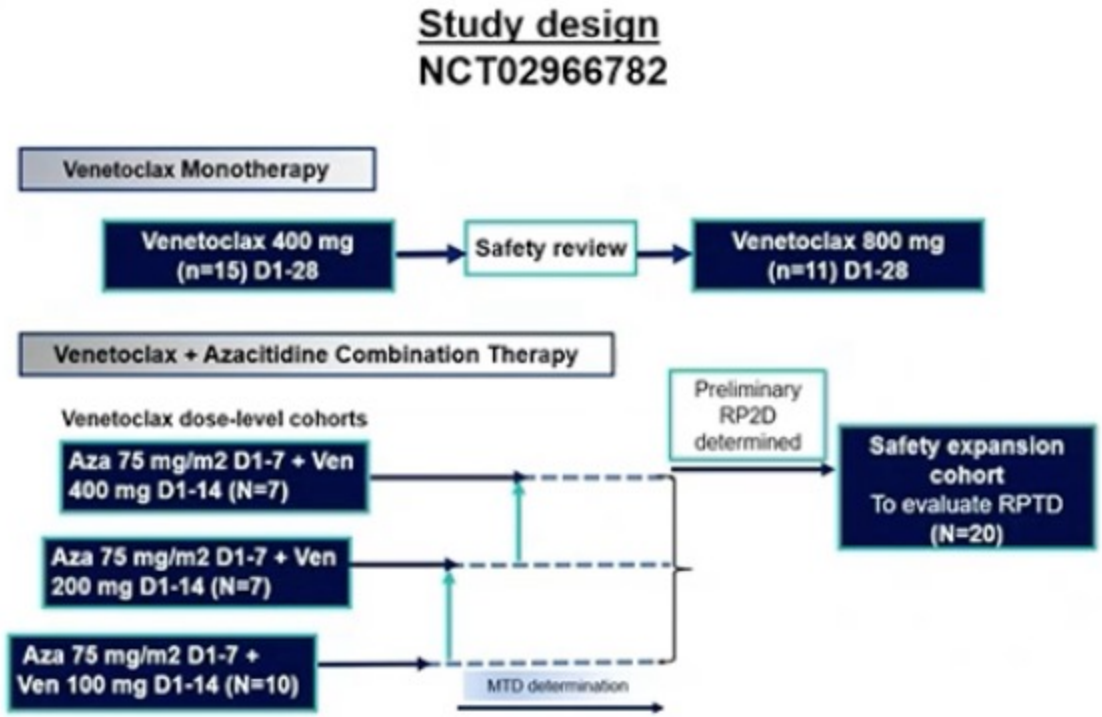
ASCERTAIN: Updated Overall Survival (OS) with 32-Month Follow-Up



Savona MR et al. MDS 2021;Abstract 48.

RTP RESEARCH TO PRACTICE

Study Design



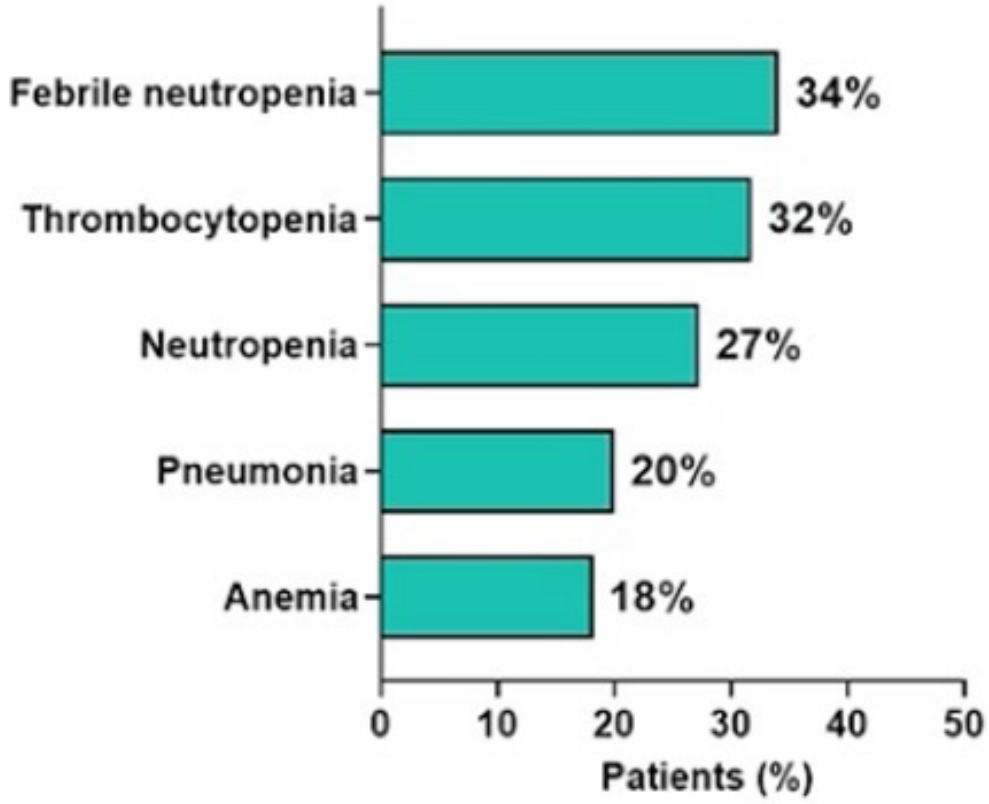
Key endpoints

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.

TEAEs 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

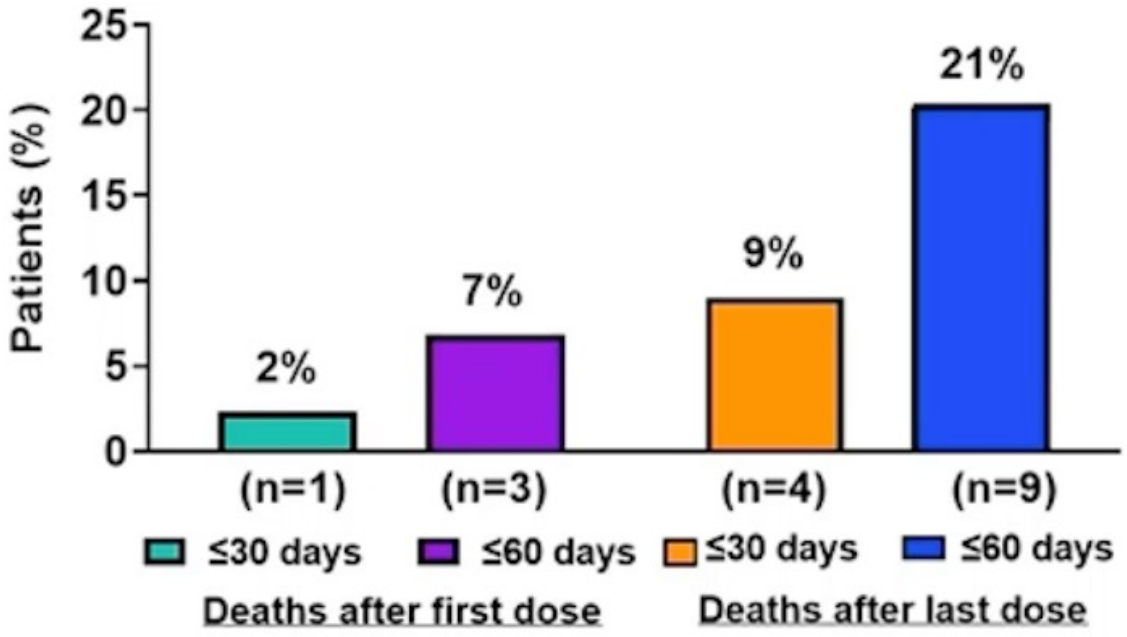
Zeidan AM et al. ASH 2021;Abstract 537.

Study Drug Discontinuation and Dose Modifications Due to TEAEs

	Ven n (%)	Aza n (%)
Study drug discontinuation[a]	9 (20.5)	7 (15.9)
Dose interruption[b]	21 (47.7)	18 (40.9)
Febrile neutropenia	7 (15.9)	7 (15.9)
Neutropenia	4 (9.1)	3 (6.8)
Pneumonia	3 (6.8)	1 (10)
Pneumonia fungal	2 (4.5)	1 (10)
Oral infection	1 (2.3)	1 (10)

Zeidan AM et al. ASH 2021;Abstract 537.

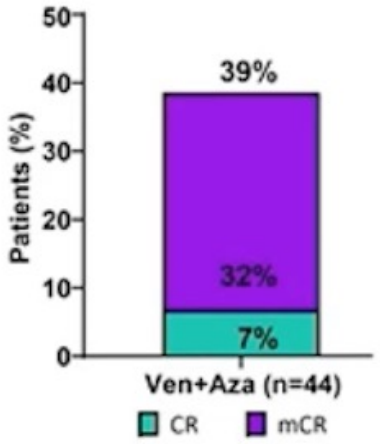
Deaths Among Patients Who Received Venetoclax/Azacitidine

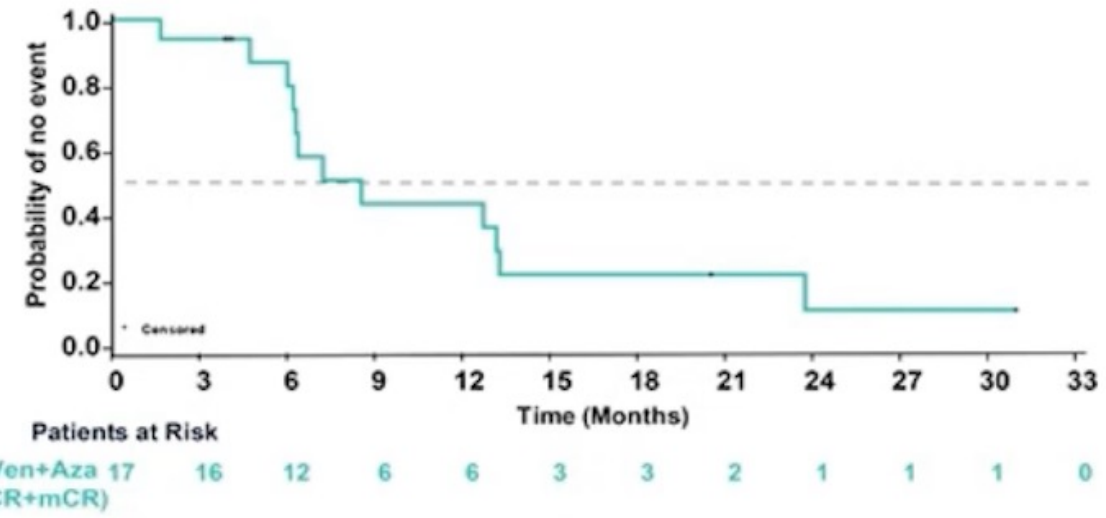


- There were 29 (66%) deaths among patients[b]
  - — 9 due to disease progression
  - — 4 due to TEAE[c]
  - — 16 due to other causes
- 1 (2%) patient died of pneumonia related to Ven treatment

Zeidan AM et al. ASH 2021;Abstract 537.

Response to Venetoclax/Azacitidine



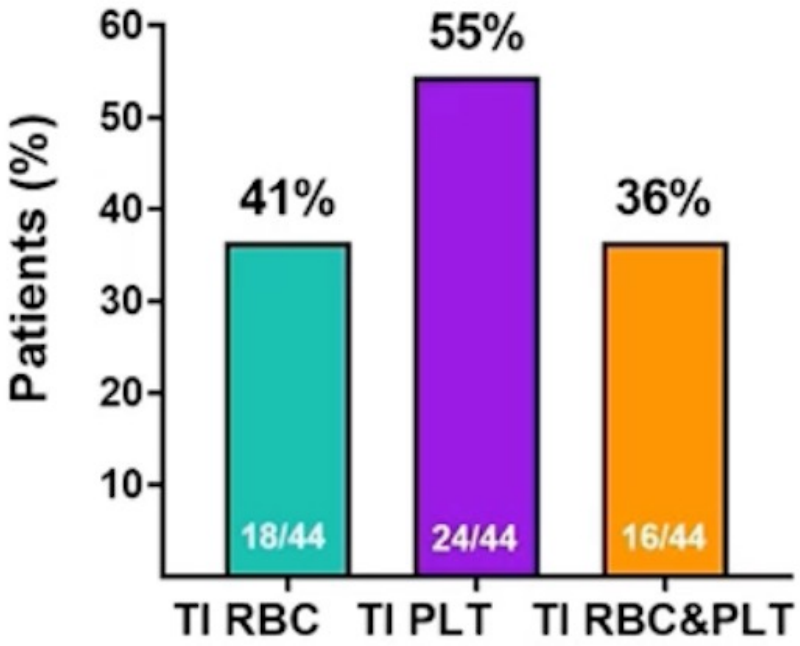


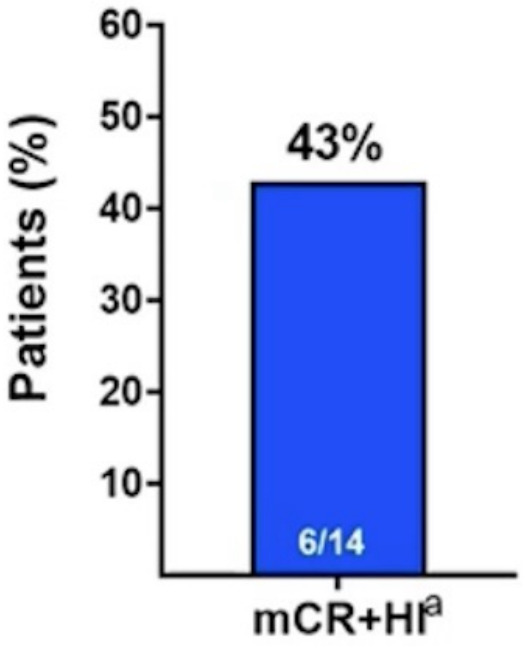
DoR	# of events	12-month, % (95% CI)	24-month, % (95% CI)	Median DoR, months (95% CI)
Ven+Aza (CR+ mCR)	12	43.4 (18.1 – 66.6)	10.9 (0.8 – 35.8)	8.6 (6.0 – 13.3)

- 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]

Zeidan AM et al. ASH 2021;Abstract 537.

Transfusion Independence and Hematologic Improvement with Venetoclax/Azacitidine

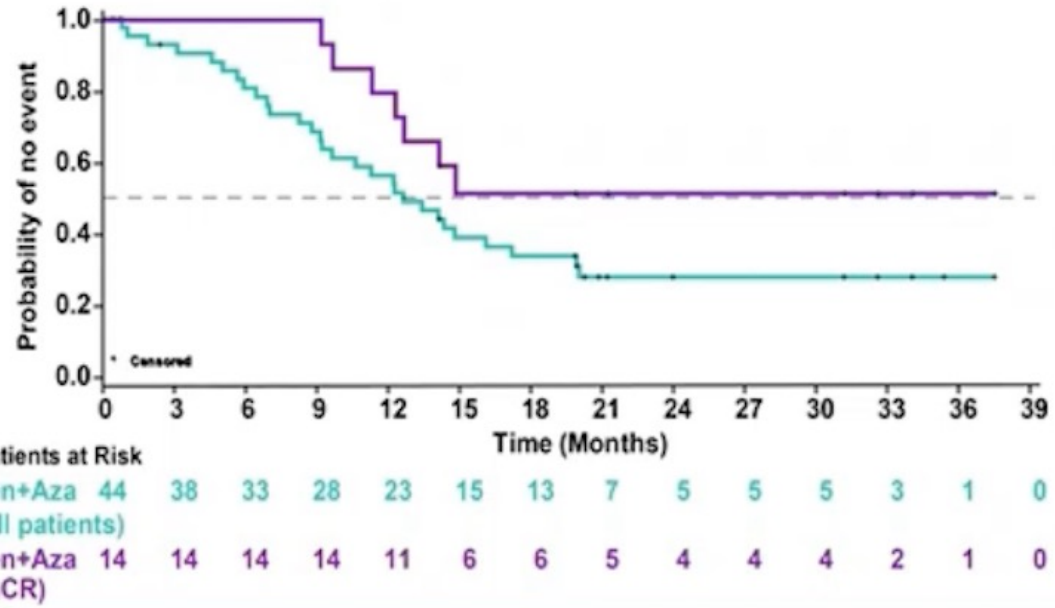


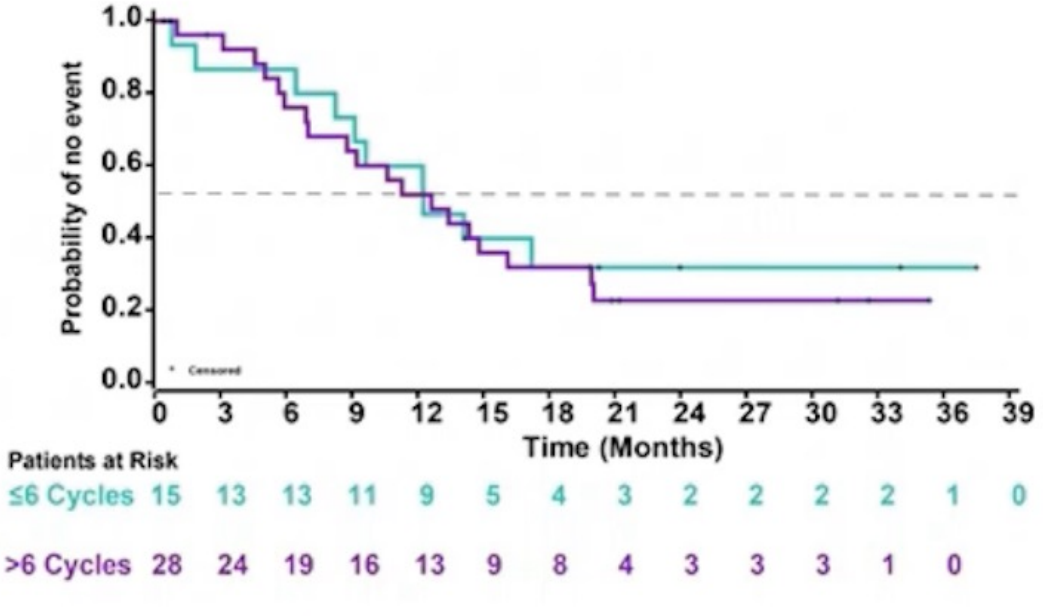


- Post-baseline TI (RBC or PLT) was achieved by 10/32 (31%) patients who were transfusion dependent at baseline
- Median time to next treatment[b] was 5.7 months (95% CI 4.8 – 8.8)
- 9 (21%) patients transformed to AML
- 9 (21%) patients received post-study transplant of which 3 (7%) had bone marrow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

Zeidan AM et al. ASH 2021;Abstract 537.

OS 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)

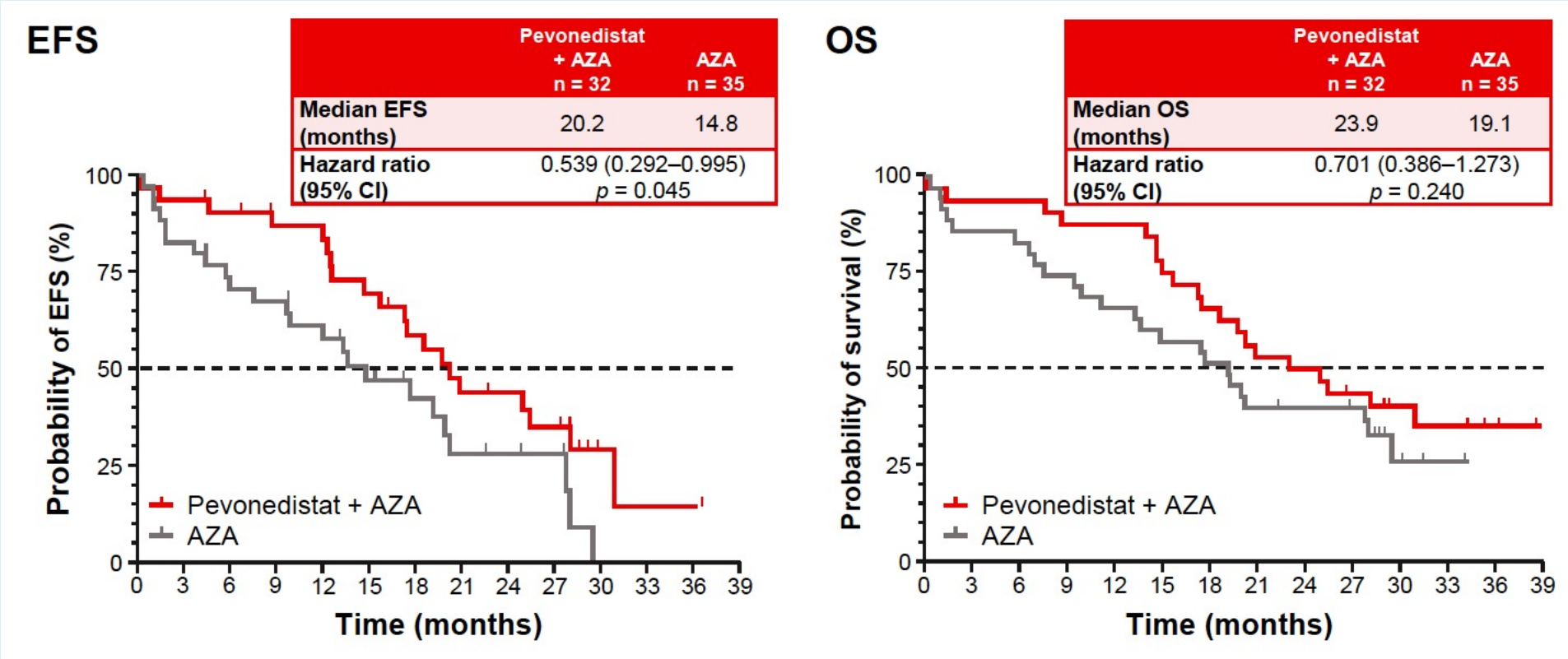
Zeidan AM et al. ASH 2021;Abstract 537.

Pevonedistat plus Azacitidine vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS): Efficacy and Safety Results from Study P-2001 (NCT02610777)

Watts J et al.

SOHO 2021;Abstract MDS-344.

P-2001: Phase II Study of Pevonedistat with Azacitidine for Higher-Risk MDS



Watts J et al. SOHO 2021;Abstract MDS-344.

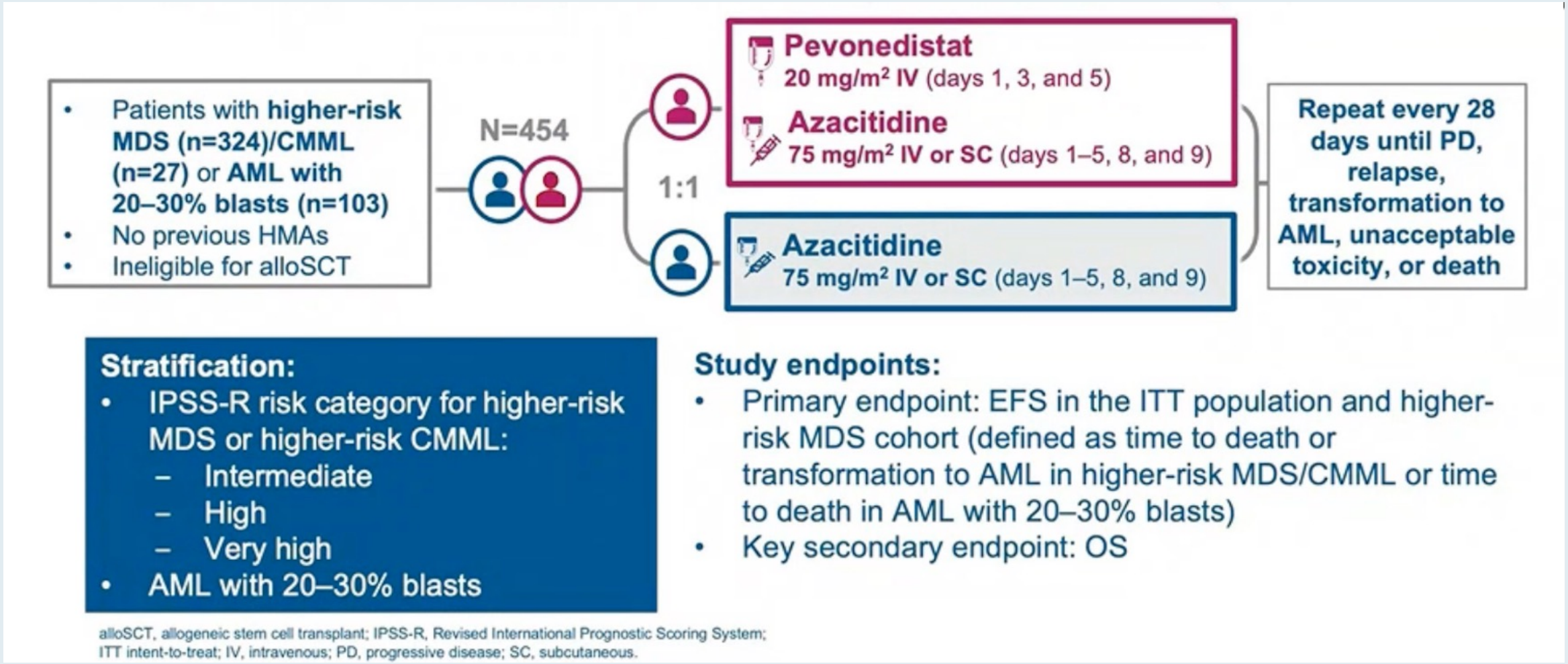
P-2001: Exposure-Adjusted Adverse Event Rates Among Patients with Higher-Risk MDS

	Pevonedistat + AZA (n = 32)	AZA alone (n = 35)
Any AE, n (normalized n)	32 (1.96)	35 (3.27)
Treatment-related AE, n (normalized n)	22 (1.35)	27 (2.52)
SAE, n (normalized n)	24 (1.47)	20 (1.87)
Treatment-related SAE, n (normalized n)	4 (0.25)	3 (0.28)
Grade ≥ 3 AE, n (normalized n)	30 (1.84)	29 (2.71)

Normalized n = n/mean number of cycled dosed.
AE, adverse event; AZA, azacitidine; MDS, myelodysplastic syndromes; SAE, serious adverse event.

Watts J et al. SOHO 2021;Abstract MDS-344.

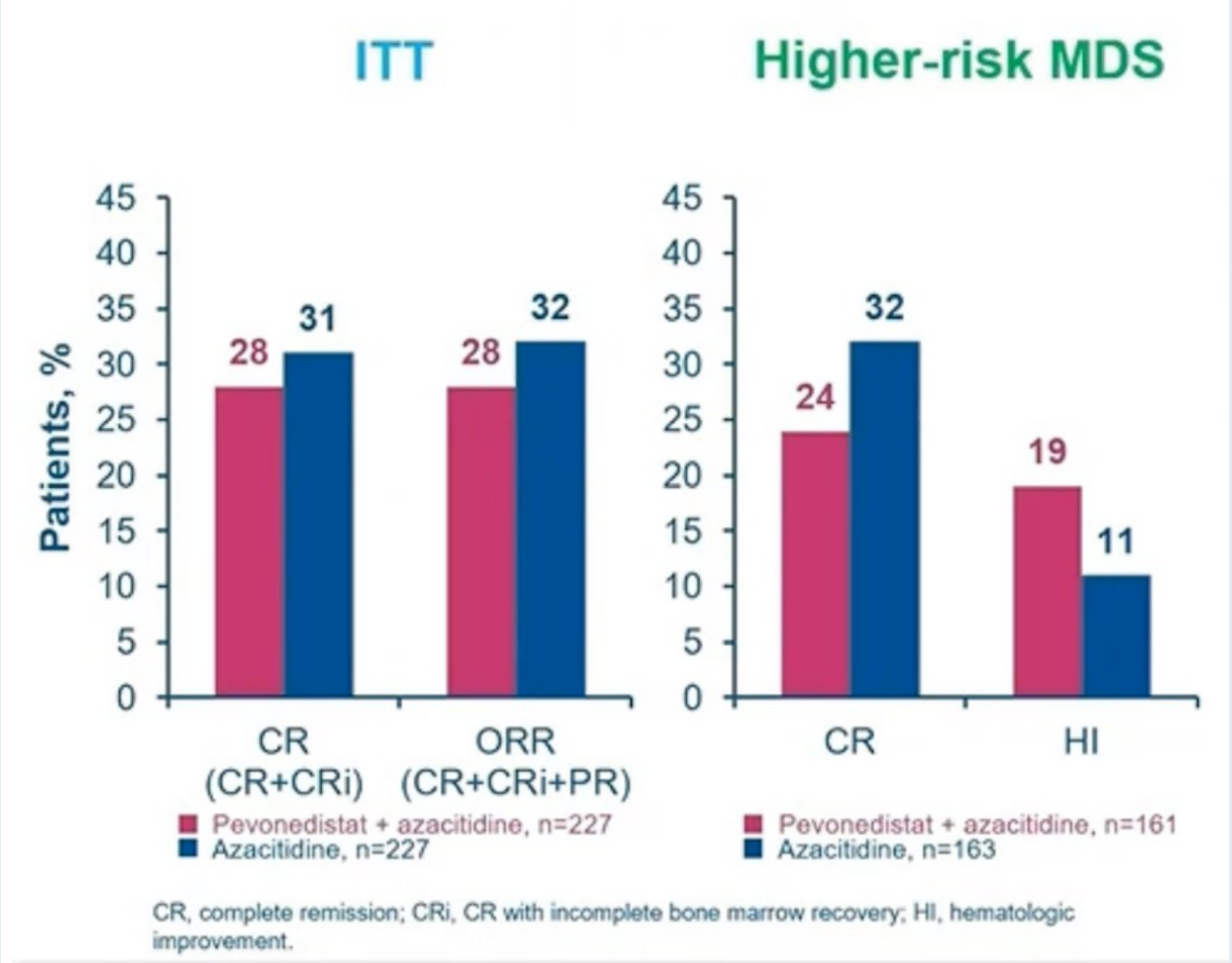
PANTHER (P-3001): Phase III Trial Schema



alloSCT, allogeneic stem cell transplant; IPSS-R, Revised International Prognostic Scoring System; ITT intent-to-treat; IV, intravenous; PD, progressive disease; SC, subcutaneous.

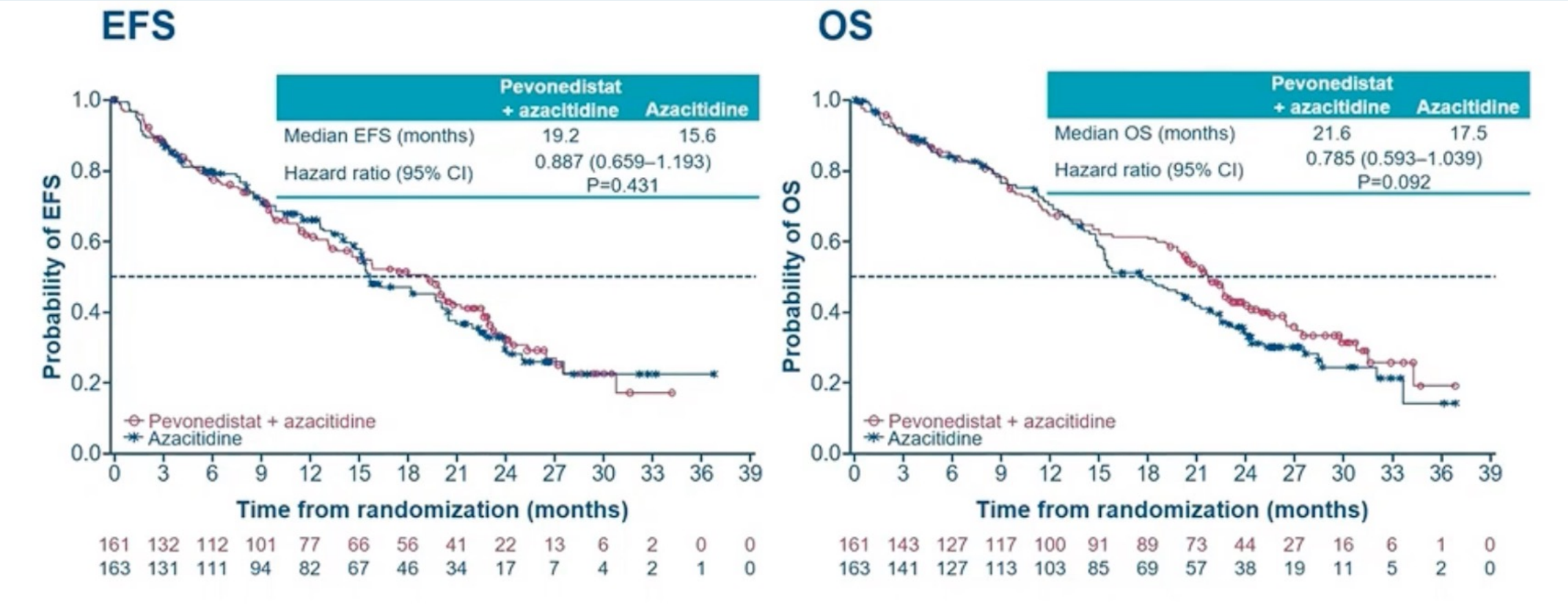
Sekeres MA et al. ASH 2021;Abstract 242.

PANTHER (P-3001): Overall Response Rate in the Intent-to-Treat (ITT) Population and in the Higher-Risk MDS Cohort



Sekeres MA et al. ASH 2021;Abstract 242.

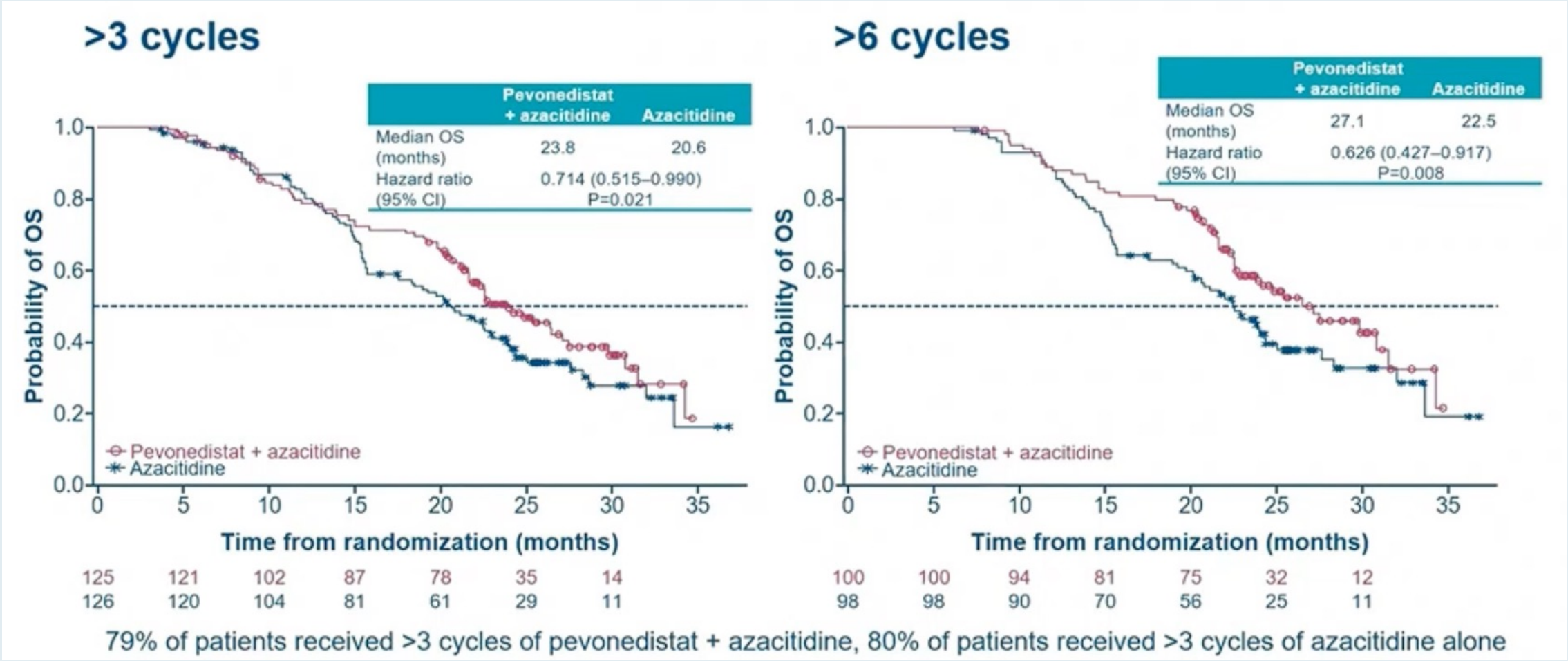
PANTHER (P-3001): Event-Free Survival (EFS) and OS in the Higher-Risk MDS Cohort



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

Sekeres MA et al. ASH 2021;Abstract 242.

PANTHER (P-3001): OS for Patients with Higher-Risk MDS by Number of Cycles Received



Sekeres MA et al. ASH 2021;Abstract 242.

PANTHER (P-3001): Treatment Discontinuation

n, (%)	AE	Progression to AML	PD	Withdrawal by patient	Other	Total
Pevonedistat + azacitidine n=161	22 (13.7)	4 (2.5)	5 (3.1)	2 (1.2)	3 (1.9)	36 (22.4)
Azacitidine n=163	15 (9.2)	5 (3.1)	3 (1.8)	8 (4.9)	6 (3.7)	37 (22.7)
Total n=324	37 (11.4)	9 (2.8)	8 (2.5)	10 (3.1)	9 (2.8)	73 (22.5)

Rate of early discontinuation of pevonedistat almost double that in P-2001 study[1]

1. Sekeres MA, et al. Leukemia 2021;35:2119–24.

- No new safety signals were identified

Sekeres MA et al. ASH 2021;Abstract 242.