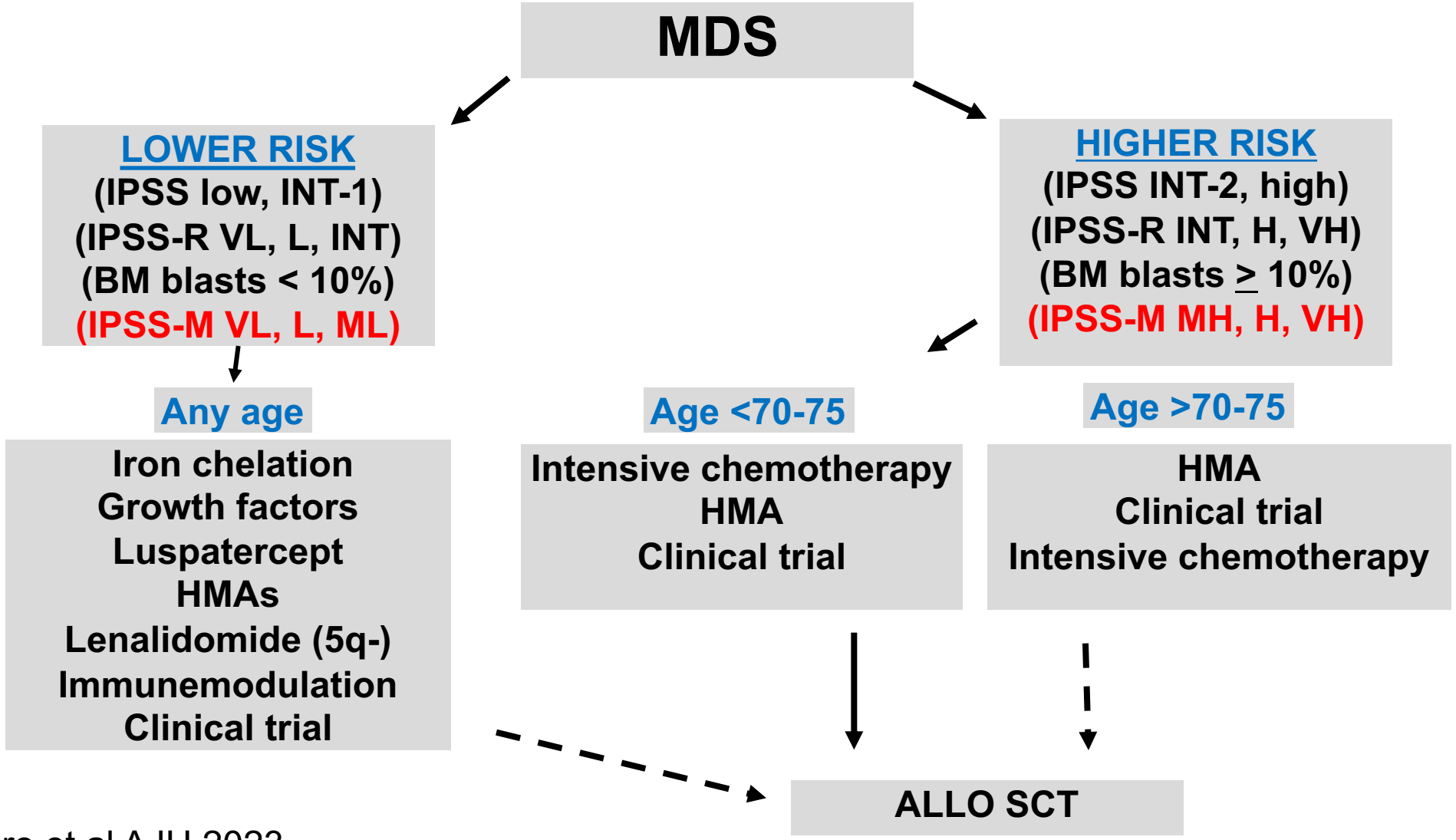
MDS update 2024

Guillermo Garcia-Manero
Department of Leukemia
MD Anderson Cancer Center

Tampa 2024

Proposed treatment algorithm for patients with MDS 2024



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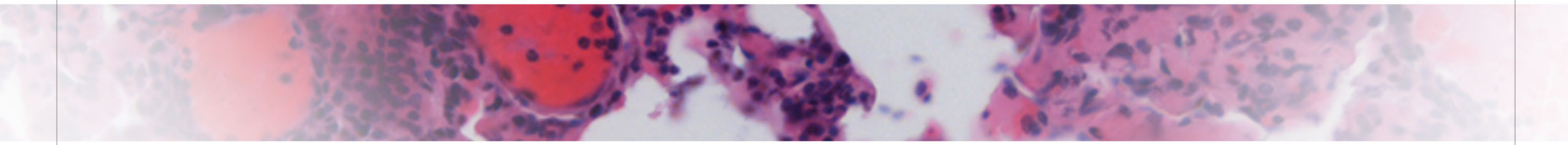

Data-Driven Harmonization of 2022 WHO and ICC Classifications of Myelodysplastic Syndromes/Neoplasms (MDS): A Study By the International Consortium for MDS (icMDS)

L Lanino*, S Ball*, JP Bewersdorf*, M Marchetti, G Maggioni, E Travaglino, NH Al Ali, P Fenaux, U Platzbecker, V Santini, M Diez-Campelo, AM Singh, AG Jain, LE Aguirre, SM Tinsley-Vance, ZI Schwabkey, O Chan, Z Xie, AM Brunner, AT Kuykendall, JM Bennett, R Buckstein, R Bejar, HE Carraway, AE DeZern, EA Griffiths, S Halene, R Hasserjian, J Lancet, AF List, S Loghavi, O Odenike, E Padron, MM Patnaik, GJ Roboz, M Stahl, MA Sekeres, DP Steensma, MR Savona, J Taylor,

ML Xu, K Sweet, DA Sallman, SD Nimer, CS Hourigan, AH Wei, E Sauta, S D'Amico, G Asti, G Castellani, UM Borate, G Sanz, F Efficace, SD Gore, TK Kim, N Daver, G Garcia-Manero, M Rozman, A Orfao, SA Wang, MK Foucar, U Germing, T Haferlach, P Scheinberg, Y Miyazaki, M Iastrebner, A Kulasekararaj, T Cluzeau, S Kordasti, AA van de Loosdrecht, L Ades, AM Zeidan#, RS Komrokji# and MG Della Porta#

*co-first authors
#co-senior authors

Proposal for a hierarchical harmonized MDS classification

2 or more ***TP53* mutations**, or 1 *TP53* mut with evidence of copy number loss or cnLOH
BM blasts < 20%

→ **MDS with biallelic inactivation of *TP53***

5q deletion alone, or with 1 other abnormality
Absence of -7 or complex karyotype
BM blasts < 5%

→ **MDS with del(5q)**

Mutated SF3B1, absence of del(7q), abn(3q), del (5q), *RUNX1*^{mut} or complex karyotype
BM blasts < 5%

→ **MDS with mutated *SF3B1***

MDS with defining genomic abnormalities

Blast count ≥5%

→ **MDS IB1 - MDS-EB**

→ **MDS IB2 - MDS/AML**

MDS with low blasts

MDS morphologically defined

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Reclassification according to this algorithm was concordant with ICC and WHO labels in 97.2% and 98.1%

Parallel Genomic Analysis from Paired Bone Marrow and Peripheral Blood Samples of 200 Cytopenic Patients

S. Huber, N. Wossidlo, T. Haferlach, M. Meggendorfer, S. Hutter, G. Hoermann, I. Summerer, H. Ruge, C. Baer, W. Kern, C. Haferlach

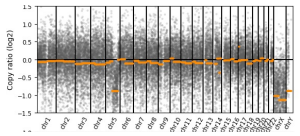
MLL Munich Leukemia Laboratory

Summary and Conclusion

SNV/ small indels

- 99.5% concordance regarding mutational clonality (199/200)
- BM VAF ≥13%: 100%; BM VAF <13%: 89%
- PPV: 100% (130/130)
- NPV: 98.6% (69/70)
  - n=1: *DNMT3A* 9% in BM only (BM morphology: no MDS)

Copy number variations



- 82% concordance regarding cytogenetic clonality (98/119)
- 80% identical IPSS-R cytogenetic risk group
- PPV: 98% (48/49)
- NPV: 78% (71/91)
  - n=20: 80% MUT in PB
    20% no MUT (BM: 2/4 MDS)

PB NGS

- High degree of overlap between PB and BM regarding clonality detection in patients with unclear cytopenia using next generation sequencing

Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive patients with transfusion-dependent lower-risk myelodysplastic syndromes: full analysis of the COMMANDS trial

Guillermo Garcia-Manero,[1] Uwe Platzbecker,[2] Valeria Santini,[3] Amer M. Zeidan,[4] Pierre Fenaux,[5] Rami S. Komrokji,[6] Jake Shortt,[7] David Valcarcel,[8] Anna Jonasova,[9] Sophie Dimicoli-Salazar,[10] Ing Soo Tiong,[11] Chien-Chin Lin,[12] Jiahui Li,[13] Jennie Zhang,[13] Ana Carolina Giuseppi,[13] Sandra Kreitz,[14] Veronika Pozharskaya,[13] Karen L. Keeperman,[13] Shelonitda Rose,[13] Thomas Prebet,[13] Andrius Degulys,[15,16] Stefania Paolini,[17] Thomas Cluzeau,[18] Matteo Giovanni Della Porta[19,20]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; [3]MDS Unit, Hematology, University of Florence, AOUC, Florence, Italy; [4]Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [5]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; [6]Moffitt Cancer Center, Tampa, FL, USA; [7]Monash University and Monash Health, Melbourne, VIC, Australia; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Medical Department Hematology, Charles University General University Hospital, Prague, Czech Republic; [10]Hôpital Haut-Lévêque, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [11]Malignant Haematology & Stem Cell Transplantation, The Alfred, Melbourne, VIC, Australia; [12]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [15]Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [16]Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [17]IRCCS Azienda Ospedaliero-Universitaria di Bologna - Istituto di Ematologia “Seràgnoli”, Bologna, Italy; [18]Département d'Hématologie Clinique, Université Cote d'Azur, CHU Nice, Nice, France; [19]Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; [20]Department of Biomedical Sciences, Humanitas University, Milan, Italy

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COMMANDS: study design

- COMMANDS is a global, phase 3, open-label, randomized controlled trial (NCT03682536)

Key patient eligibility criteria

- ≥ 18 years of age
- IPSS-R Very low-, Low-, or Intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2–6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status

R 1:1

Luspatercept (N = 182)
1.0 mg/kg s.c. Q3W
titration up to 1.75 mg/kg

Epoetin alfa (N = 181)[b]
450 IU/kg s.c. QW
titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

End treatment
Due to lack of clinical benefit[c] or disease progression per IWG 2006 criteria

Post-treatment safety follow-up

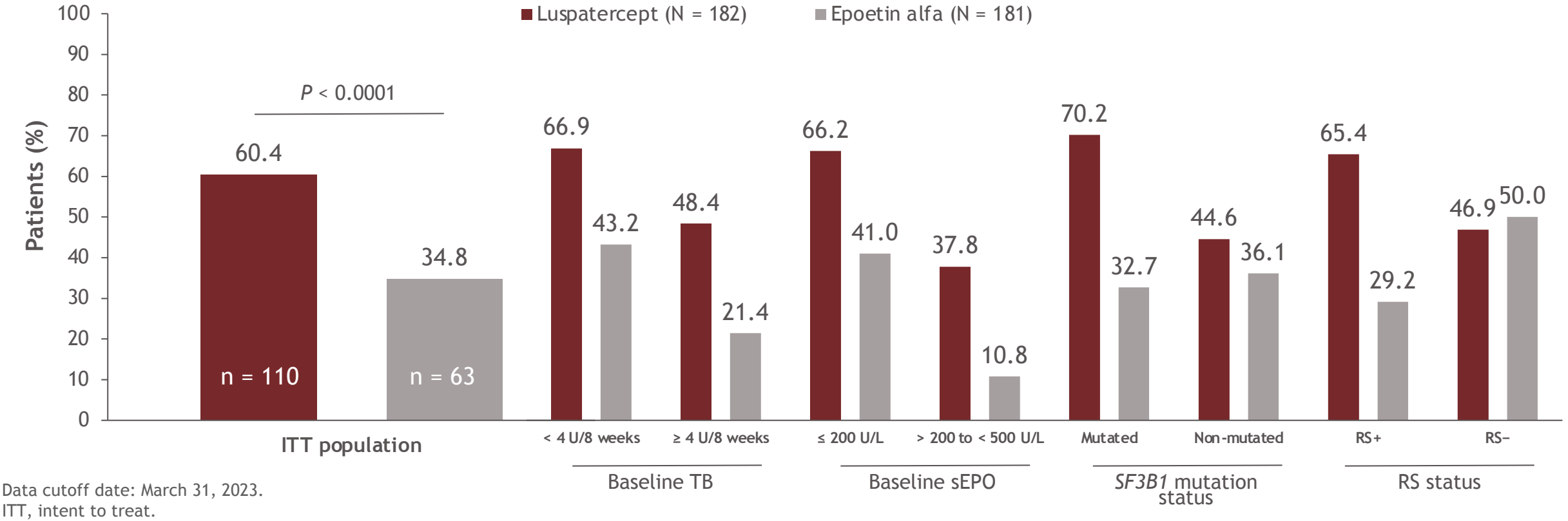
- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

[a]MDS patients with del(5q) were excluded; [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC units/8 weeks versus baseline.
AML, acute myeloid leukemia; HR-MDS, higher-risk MDS; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; pRBC, packed RBC; QW, once weekly; Q3W, every 3 weeks; R, randomized; RS, ring sideroblasts; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: achievement of primary endpoint in ITT population and subgroups

- The primary endpoint was achieved by 110 (60.4%) patients in the luspatercept arm versus 63 (34.8%) patients in the epoetin alfa arm ($P < 0.0001$)
  - Subgroup analysis of the primary endpoint showed greater response rates with luspatercept regardless of baseline TB, sEPO category, or *SF3B1* mutation status



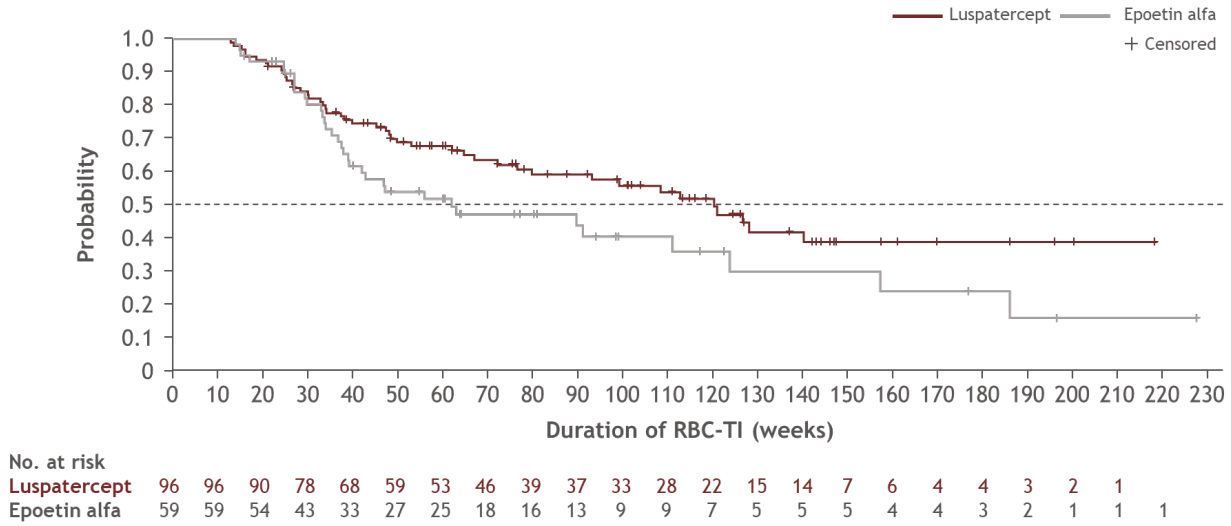
Data cutoff date: March 31, 2023.
ITT, intent to treat.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: duration of RBC-TI ≥ 12 weeks by RS subgroups (week 1–EOT)

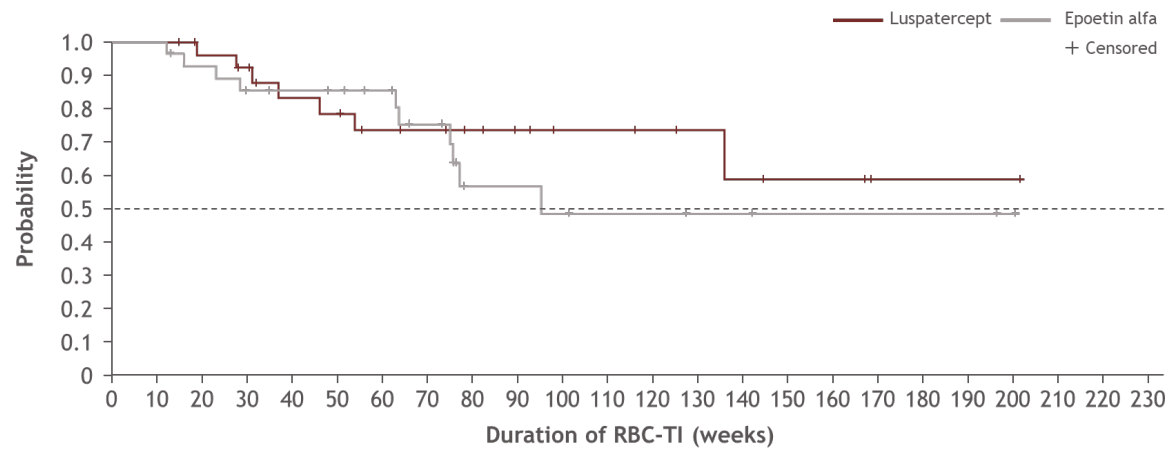
Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
RS+	120.1 (76.4-NE)	61.9 (38.9-123.9)	0.650 (0.415-1.018)
RS−	NE (135.9-NE)	95.1 (74.9-NE)	0.709 (0.269-1.866)

RS+



No. at risk																						
Luspatercept	96	96	90	78	68	59	53	46	39	37	33	28	22	15	14	7	6	4	4	3	2	1
Epoetin alfa	59	59	54	43	33	27	25	18	16	13	9	9	7	5	5	5	4	4	3	2	1	1	1

RS−



No. at risk																						
Luspatercept	28	28	25	22	18	17	14	13	11	9	7	7	6	5	4	3	3	1	1	1	1
Epoetin alfa	29	29	25	22	21	20	18	14	7	7	6	5	5	4	4	2	2	2	2	2	1

Data cutoff date: September 28, 2023.

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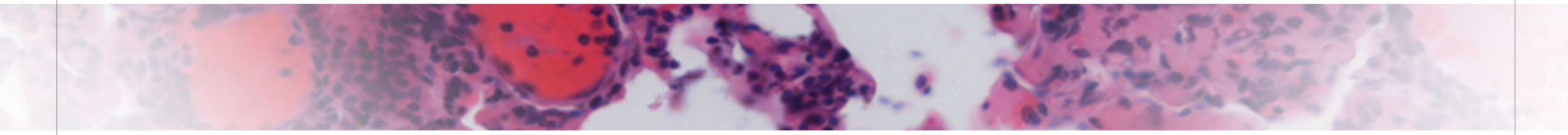
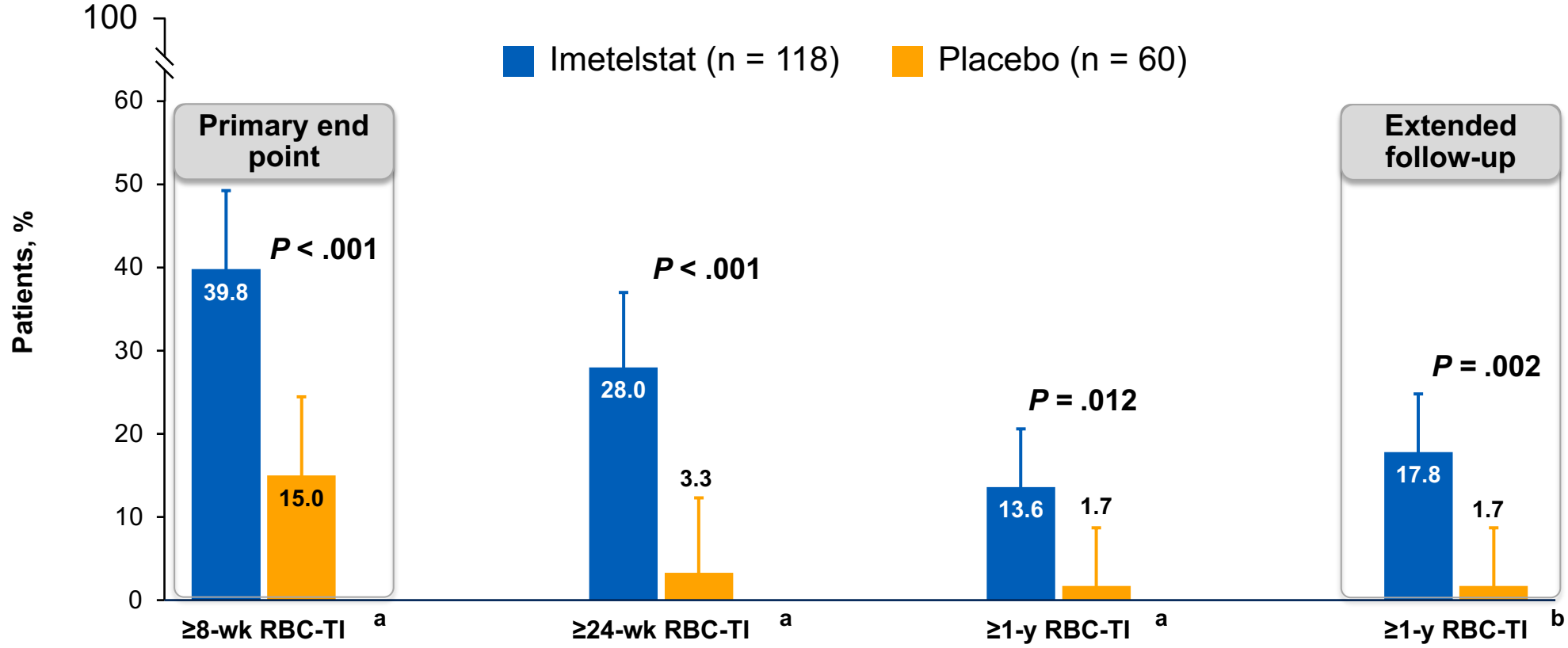


Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence Across Different Risk Subgroups in Patients With Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis-Stimulating Agents in IMerge Phase 3 Study

Rami Komrokji,[1] Valeria Santini,[2] Pierre Fenaux,[3] Michael R. Savona,[4] Yazan F. Madanat,[5] Tymara Berry,[6] Laurie Sherman,[7] Shyamala Navada,[6] Faye Feller,[6] Libo Sun,[6] Qi Xia,[6] Ying Wan,[6] Fei Huang,[6] Amer M. Zeidan,[8] and Uwe Platzbecker[9]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]MDS Unit, Hematology, AOUC, University of Florence, Florence, Italy; [3]Hôpital Saint-Louis, Université de Paris 7, Paris, France; [4]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; [5]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [6]Geron Corporation, Parsippany, NJ, USA; [7]Vividion Therapeutics, San Diego, CA, USA; [8]Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [9]Cellular Therapy and Hemostaseology, Leipzig University Hospital, Leipzig, Germany

Overall Population: Higher Rates of Longer-Term Duration of RBC-TI With Imetelstat vs Placebo[1,2]



[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.

The *P* value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1–risk) applied to randomization.

IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

1. Zeidan A, et al. ASCO 2023. Abstr 7004. 2. Platzbecker U, et al. *Lancet.* Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

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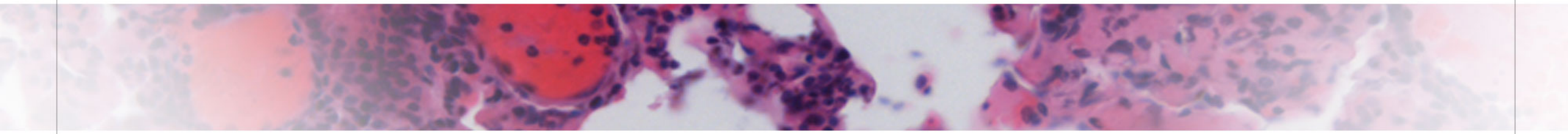


Durable Clinical Benefit with KER-050 (elritercept) Treatment: Findings from an Ongoing Phase 2 Study in Participants with Lower-Risk MDS

Maria Diez-Campelo, MD[1], David M. Ross[2], Aristoteles Giagounidis[3], Shuhying Tan[4], Thomas Cluzeau[5], Lynette C.Y. Chee[6], David Valcarcel[7], Montserrat Arnan[8], Christine Graham[9], Allie McGinty[9], Miranda Ross[9], Wei Feng[9], Ming Yang[9], Ying Jiang[9], Suresh Bobba[9], Noah Dcruz[9], Montagu Hankin[9], Christopher Rovaldi[9], Dena Grayson[9], Simon Cooper[9] and Jen L. Salstrom[9]

1. Universidad de Salamanca, Spain; 2. Department of Haematology, Flinders Medical Centre and University, Adelaide, Australia; 3. Dept. Oncology, Hematology and Palliative Care, Marienhospital Dusseldorf, Germany; 4. St. Vincent's Institute of Medical Research, East Melbourne, Australia; 5. Nice University Hospital, France; 6. Department of Clinical Haematology and Bone Marrow Transplant Service, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Parkville, Australia; 7. Department of Hematology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; 8. Institut Catala d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain; 9. Keros Therapeutics, Lexington, MA

Hematologic Responses

Responders/N (%)	$mITT_{24}$[a]	
	All (N=60)	HTB (N=33)
Overall Response[a,b]	**30/60 (50)**	**15/33 (45.5)**
Modified IWG 2006 HI-E[c]	**28/60 (47)**	**15/33 (45.5)**
RS+	23/40 (58)	12/23 (52.2)
non-RS	5/20 (25)	3/10 (30)
TI ≥8 weeks[d]	**18/46 (39.1)**	**11/33 (33.3)**
RS+	15/32 (46.9)	8/23 (34.8)
non-RS	3/14 (21.4)	3/10 (30)

HI-E and TI response rates in $mITT_{24}$ participants with HTB were similar to those observed in the overall $mITT_{24}$ population, supporting the potential for KER-050 (elritercept) to treat a broad array of patients with MDS including those with greater bone marrow dysfunction

HI-E = hematological improvement-erythroid; HTB = high transfusion burden IWG = international working group; LTB = low transfusion burden; $mITT_{24}$ = modified intent to treat 24-week population; NT = non-transfused; RBC = red blood cell; RS = ring sideroblasts; TI = transfusion independence

Development of oral decitabine/cedazuridine Primary Endpoint (5-day Decitabine AUC Equivalence)

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

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero et al Lancet Hematology 2023

Treatment algorithm 2024 LR MDS

Entity	First line	Second line
Del5q- MDS isolated anemia	lenalidomide	HMA, alloSCT
Isolated anemia, very low risk features	Growth factors Luspatercept	HMA, len, alloSCT Imetelstat?, KER-050?
RARS pre/post ESA	luspatercept	HMA, len, alloSCT
Other lower risk MDS (bilineal cytopenia)	HMA	alloSCT
IDH1, IDH2, p53, SF3B1	Consider targeted approach	

Questions in lower risk MDS

- Should we treat earlier presentations of MDS?
- Should we treat transfusion independent patients with lower risk MDS?
- Can we decide therapy based on molecular alterations?
  - Instead of transfusion burden
- Results of COMMANDS trial
- Therapy for thrombocytopenia
- Role of attenuated doses of HMA
- Role of SCT?

Other trials in LR MDS

- **IRAK4 inhibitors**
- **SF3B1 inhibitors**
- **Oral azacytidine (CC-486)**
- **Luspatercept**
- **Canakinumab**

Efficacy and Safety of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Treatment-Naive, Higher-risk Myelodysplastic Syndromes

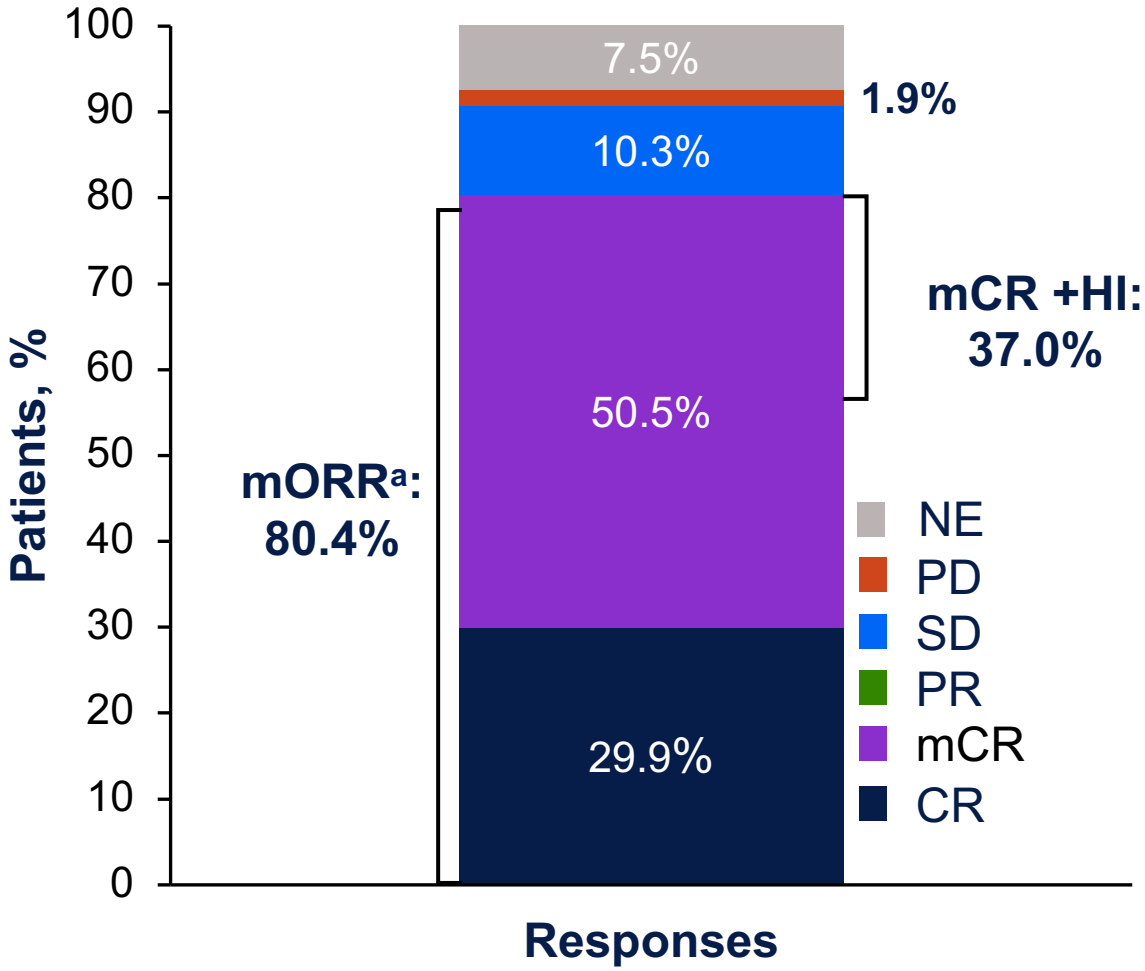
Jacqueline S. Garcia[1], Uwe Platzbecker [2], Olatoyosi Odenike[3], Shaun Fleming[4], Chun Yew Fong[5], Rachel Cook[6], Meagan Jacoby[7], Daniel Nowak[8], Brenda Chyla[9], Huipei Wang[9], Grace Ku[10], Jalaja Potluri[9], Guillermo Garcia-Manero[11]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Universitätsklinikum Leipzig, Saxony, Germany; [3]The University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, USA; [4]Alfred Health, Melbourne, Australia; [5]Austin Health, Heidelberg, Australia; [6]Oregon Health and Science University, Portland, OR, USA; [7]Washington University-School of Medicine, St. Louis, MO, USA; [8]Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [9]AbbVie Inc, North Chicago, IL, USA; [10]Genentech Inc., South San Francisco, CA, USA; [11]University of Texas MD Anderson Cancer Center, Houston, TX, USA

American Society of Hematology Annual Meeting, December 9-12, 2023, San Diego, California

Best Responses for Ven 400 mg + Aza

>80% of Patients Who Received Ven + Aza Responded



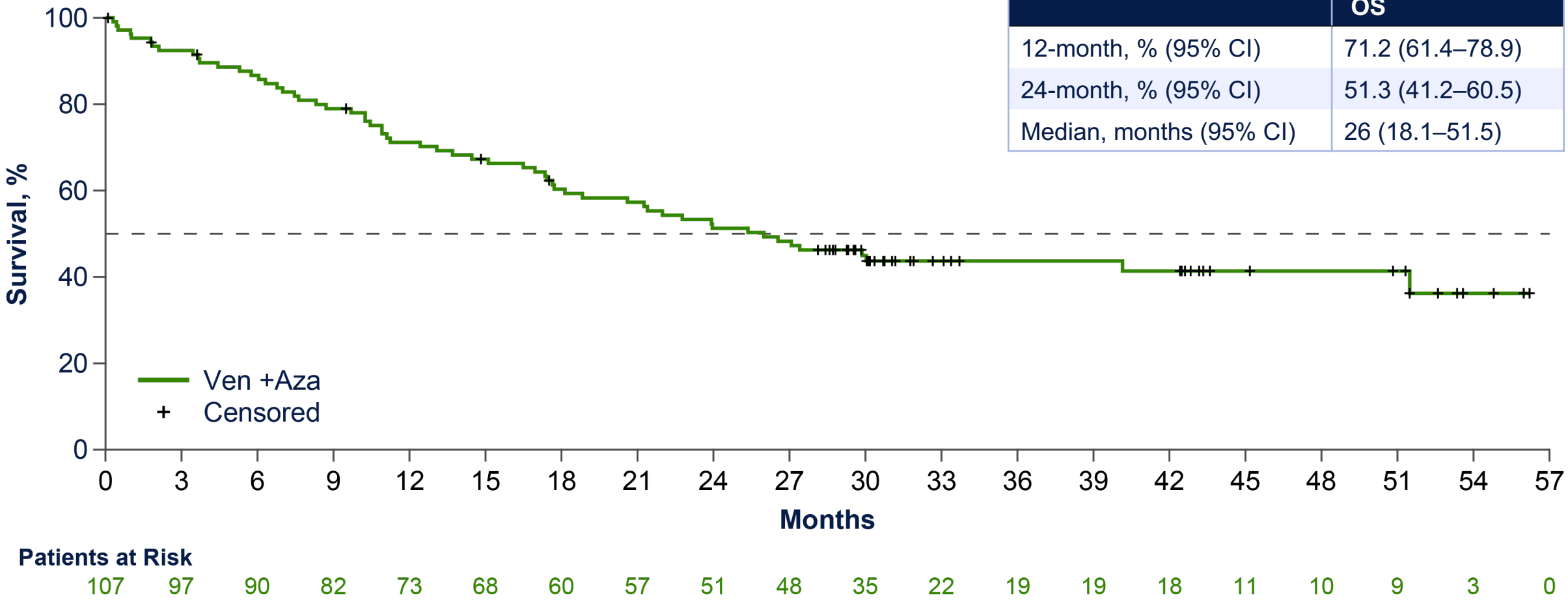
- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months (range, 0.72–29.31)

[a]mORR=CR+mCR+PR; PR, n=0; response rates based on International Working Group 2006 response criteria.

AML, acute myeloid leukemia; Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; MDS, myelodysplastic syndromes; mORR, modified overall response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax.

Overall Survival[a] for Patients Who Received Ven 400 mg + Aza

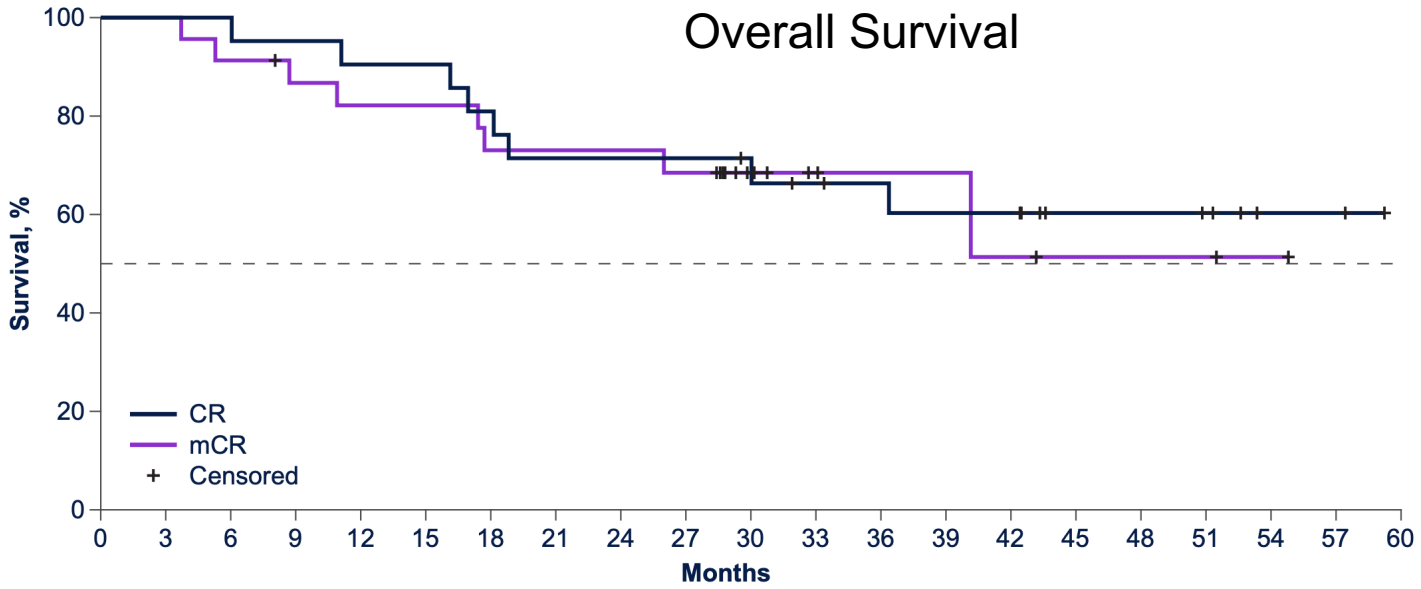
	OS
12-month, % (95% CI)	71.2 (61.4–78.9)
24-month, % (95% CI)	51.3 (41.2–60.5)
Median, months (95% CI)	26 (18.1–51.5)



[a]Overall survival was defined as the number of months from the date of the first dose of study drug to the date of death. The data were censored at the date the patient was last known to be alive on or before the cutoff date. Aza, azacitidine; OS, overall survival; Ven, venetoclax.

RESULTS: Survival by Response Prior to SCT

	Achieved CR n=21	Achieved mCR n=23
Median overall survival, months (95% CI)	NR (18.8-NR)	NR (17.7-NR)
Median follow up, months (95% CI)	43.6 (33.4-52.6)	30.2 (28.7-33.1)
12-month overall survival estimate, % (95% CI)	90.5 (67.0-97.5)	82.2 (59.2-92.9)
24-month overall survival estimate, % (95% CI)	71.4 (47.2-86.0)	73.0 (49.5-86.9)



- 33 patients remained alive post-SCT

Aza, azacitidine; CI, confidence interval; CR, complete response; mCR, marrow complete remission; NR, not reached; SCT, stem cell transplantation; Ven, venetoclax.

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

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

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

June 10th 2023
s424 Clinical updates in MDS

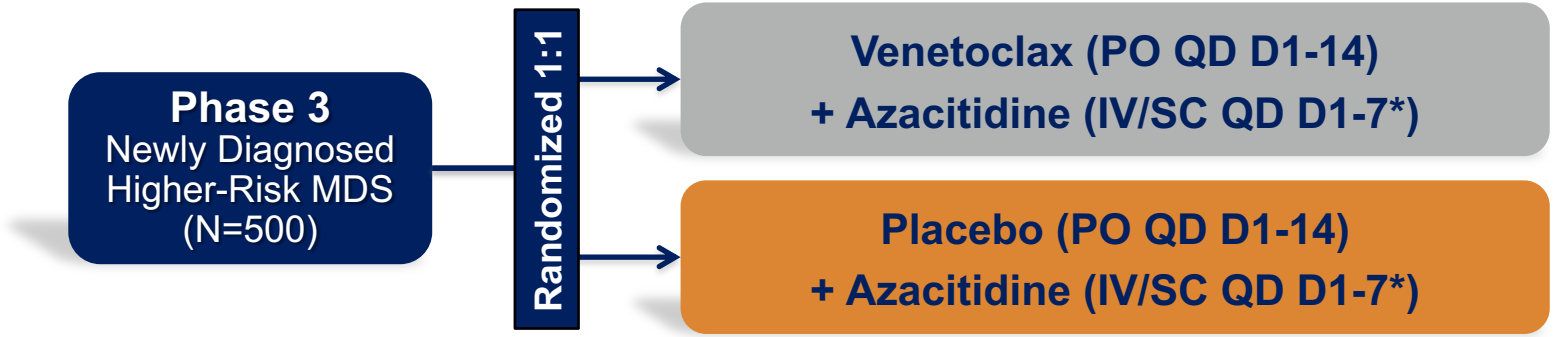
Efficacy

	Full cohort (n=39)	Phase 1 (n=9)	Phase 2 (n=30)
ORR, n (%) CR mCR mCR mCR + HI	37 (94.9) 14 (35.9) 23 (59) 11 (28.2) 12 (30.8)	9 (100) 6 (66.7) 3 (33.3) 2 (22.2) 1 (11.1)	28 (93.3) 8 (26.7) 20 (66.7) 9 (30) 11 (36.7)
Cytogenetic response, n (%)	14/26 (53.8)	4/5 (80)	10/21 (47.6)
Cycles to first response, n (range)	1 (1-2)	1 (1-1)	1 (1-2)
Cycles to best response, n (range)	1 (1-6)	1 (1-6)	1 (1-4)
Cycles received, n (range)	2 (1-13)	6 (2-13)	2 (1-8)
HSCT, n (%)	19 (48.7)	5 (55.6)	14 (46.7)

Phase 3 VERONA (NCT04401748)

Study Design and Endpoint

VERONA Study Design



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

Select Inclusion Criteria

+ ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
+ <20% BM blasts
+ ECOG PS 0-2
+ IPSS-R score of >3 (Intermediate, High, Very High)
+ No planned HSCT at the time of C1D1

Select Exclusion Criteria

– Prior therapy for MDS with HMA, chemotherapy, or allo-HSCT
– Prior diagnosis of therapy-related MDS, MDS evolved from MPN, MDS/MPN including CMML, aCML, JMML, and unclassifiable MDS/MPN

End Points

Primary: *CR, OS*

Secondary: *mOR, TI, ORR, fatigue score, physical functioning score, time to deterioration in physical functioning*

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

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Abstract # 1876

Results of a Phase II Study of Cladribine, Low Dose Cytarabine and Venetoclax, Alternating with Azacitidine and Venetoclax, in Patients with Higher Risk Chronic Myelomonocytic Leukemia and Myelodysplastic Syndromes

Guillermo Montalban-Bravo[1], Nicholas J. Short[1], Kelly S. Chien[1], Yesid Alvarado[1], Naval Daver[1], Gautam Borthakur[1], Mahesh Swaminathan[1], Abhishek Maiti[1], Danielle E. Hammond[1], Graciela Nogueras-Gonzalez[2], Xuelin Huang[2], Heather Schneider[1], Kristen Shelly[1], Tapan Kadia[1], Hagop Kantarjian[1], Guillermo Garcia-Manero[1]

Departments of Leukemia[1], Biostatistics[2] The University of Texas MD Anderson Cancer Center, Houston, TX

Efficacy Data

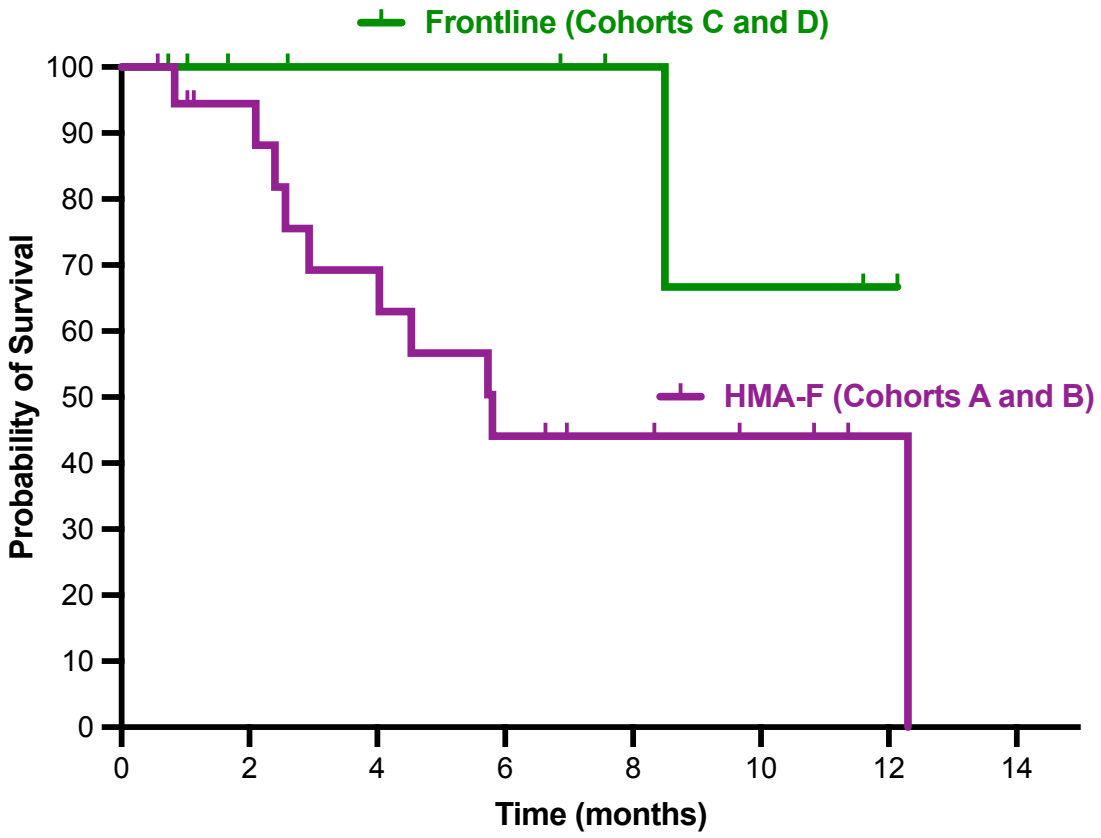
Response	Full cohort (n=26)	Cohort A (n=13)	Cohort B (n=5)	Cohort C (n=4)	Cohort D (n=4)
2006 IWG Response Criteria					
ORR	12 (46)	4 (31)	2 (40)	4 (100)	2 (25)
CR	5 (19)	1 (8)	1 (20)	3 (75)	0 (0)
mCR total	6 (23)	3 (25)	1 (20)	1 (25)	1 (25)
mCR+HI	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)
mCR alone	5 (19)	2 (15)	1 (20)	1 (25)	1 (25)
2023 IWG Response Criteria					
ORR	-	3 (25)	-	4 (100)	-
CR	-	1 (8)	-	3 (75)	-
CRbi	-	1 (8)	-	1 (25)	-
CRuni	-	1 (8)	-	0 (0)	-
Cycles to best response	1 [1-3]	1 [1-3]	1 [1-2]	1 [1-2]	2 [1-3]
Cycles given	2 [1-6]	1 [1-6]	2 [1-4]	4 [1-5]	2 [1-3]

ORR: Overall response rate; CR: complete response; mCR: marrow complete response; HI: hematological improvement.

Survival outcomes

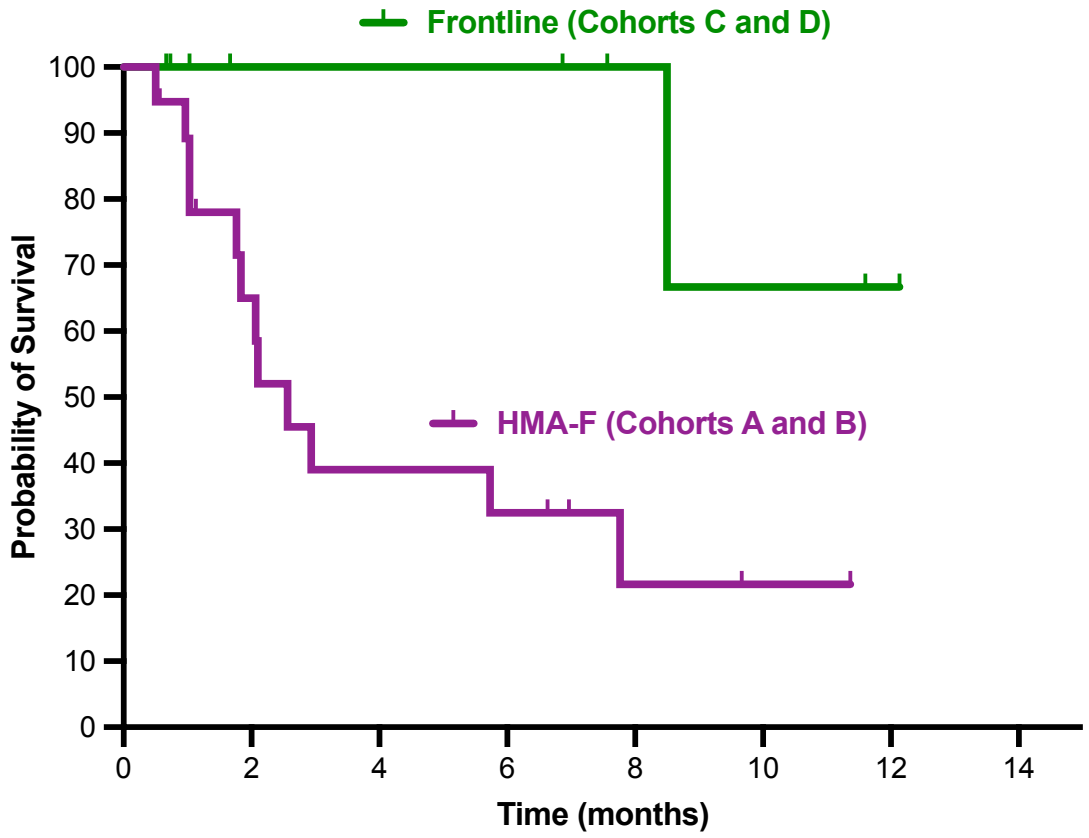
Median follow up 7.6 months (95% CI 3.4-8.2 months)

Overall survival



Relapsed cohorts (A + B): 5.8 months (95% CI 3.4-8.2 months)
Frontline cohorts (C+D): not reached (95% NC-NC)

Event-free survival



Relapsed cohorts (A + B): 2.6 months (95% CI 1.5-3.7 months)
Frontline cohorts (C+D): not reached (95% NC-NC)

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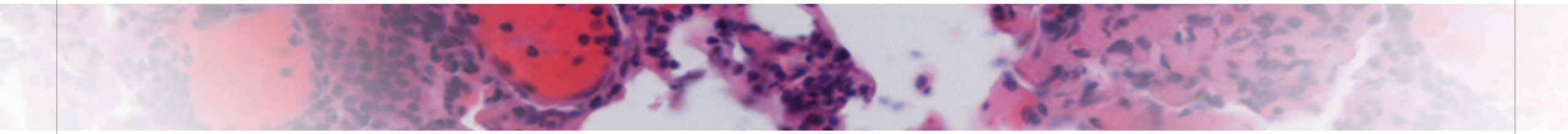

Development of Oral Azacitidine with Cedazuridine for Myelodysplastic Syndrome (MDS) and Myeloproliferative Neoplasms (MPN) including CMML (Chronic Myelomonocytic Leukemia) by Targeting Pharmacokinetic AUC Equivalence vs Subcutaneous Azacitidine

Guillermo Garcia-Manero[1], James McCloskey[2], Bart Scott[3], Elizabeth A. Griffiths[4], Bonnie Kiner-Strachan[5], Gail J. Roboz[6], Janelle Meyer[7], Winny Chan[8], Beloo Mirakhur[8], Yuri Sano[8], Aram Oganesian[8], Harold N. Keer[8], Michael R. Savona[9]

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ASTX030-01 Phase 1 Cohorts

Dose Combination of AZA and CED in Each Cohort

Cohort	AZA	CED	# Dosed subject
1 and 101	100 mg (IR tablets)	100 mg	14
2a	100 mg (IR tablets)	80 mg	7
2b and 102	80 mg (IR tablets)	100 mg	12
3	60 mg (capsules-DR1)	100 mg	7
4	60 mg (capsules-DR2)	60 mg	6
5	60 mg (capsules-DR2)	40 mg	7
6	100 mg (capsules-DR2)	20 mg	6
7	136 mg (capsules-DR2)	20 mg	7
103 (Phase 1B)	144 mg (capsules-DR2)	20 mg	13
		Total	79

IR: Immediate Release, DR1: Delay Release 1, DR2: Delay Release 2

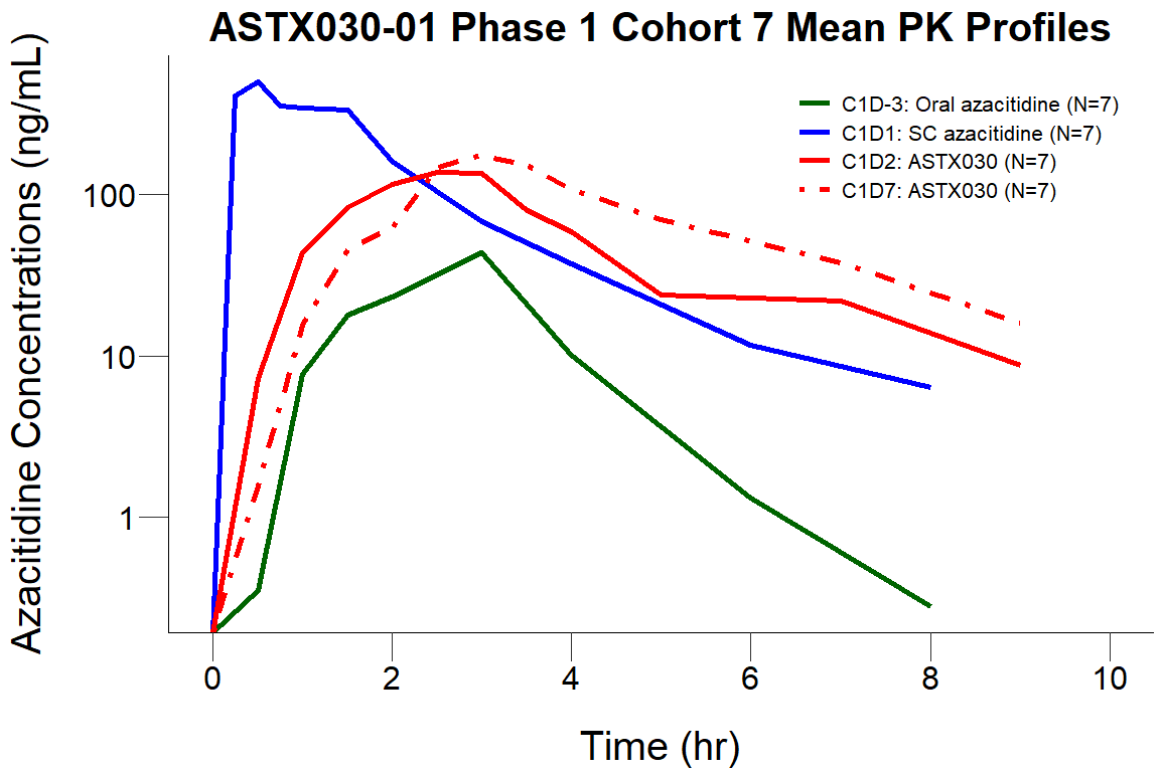
Treatment Exposure

	AZA (IR) (N=33)	AZA (DR1) (N=7)	AZA (DR2) (N=39)	All Subjects (N=79)
Range (Cycle)	1 - 32	1 - 16	1 - 10	1 - 32
Median (Cycle)	7	7	2	4

ASTX030-01 Results: PK

AUC Exposure Curves for Cohort 7

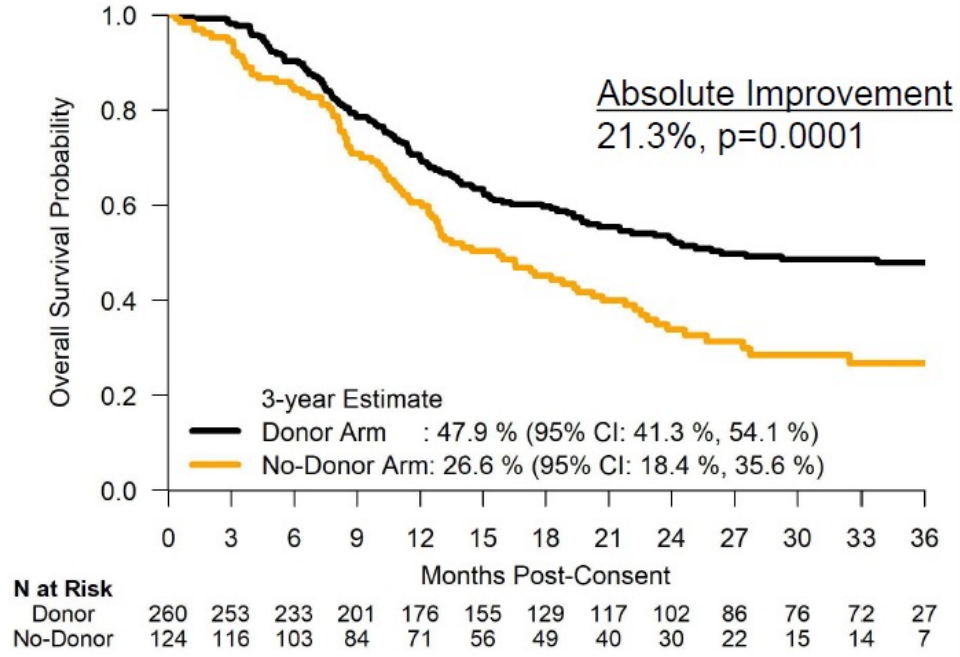
Semilog scale

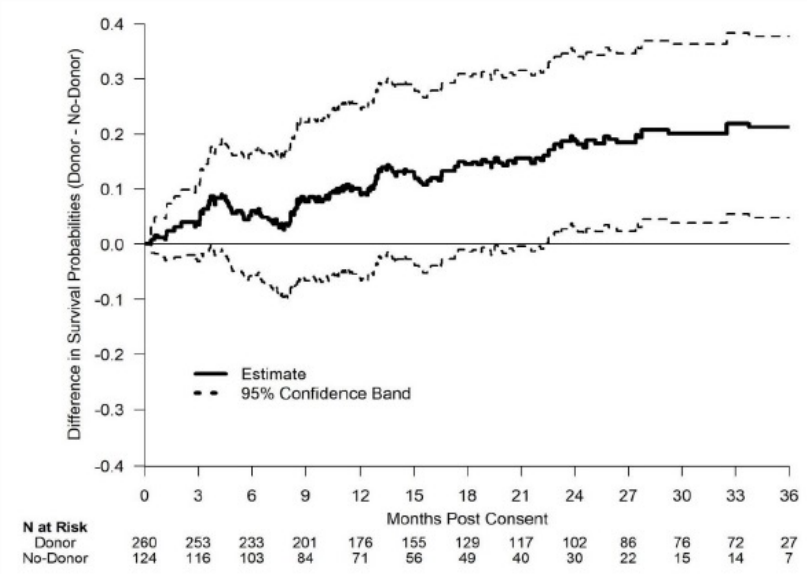


- Representative PK conc-time profiles on different occasions of treatment (Cohort 7, 20mg cedazuridine with 136mg azacitidine)

SCT in MDS

Primary Endpoint: 3 Year Overall Survival





BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Nakamura et al. JCO 2021

Sensitivity Analysis: Adjusted OS: 48.0% vs. 28.1%, p=0.0004

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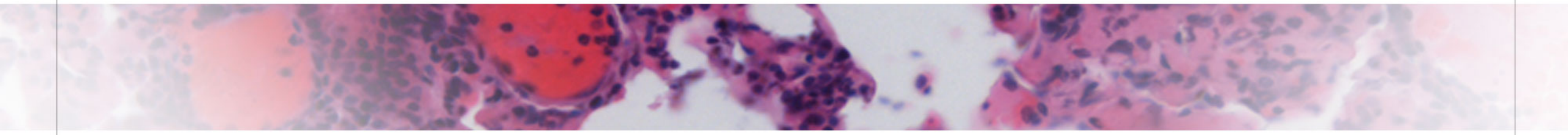


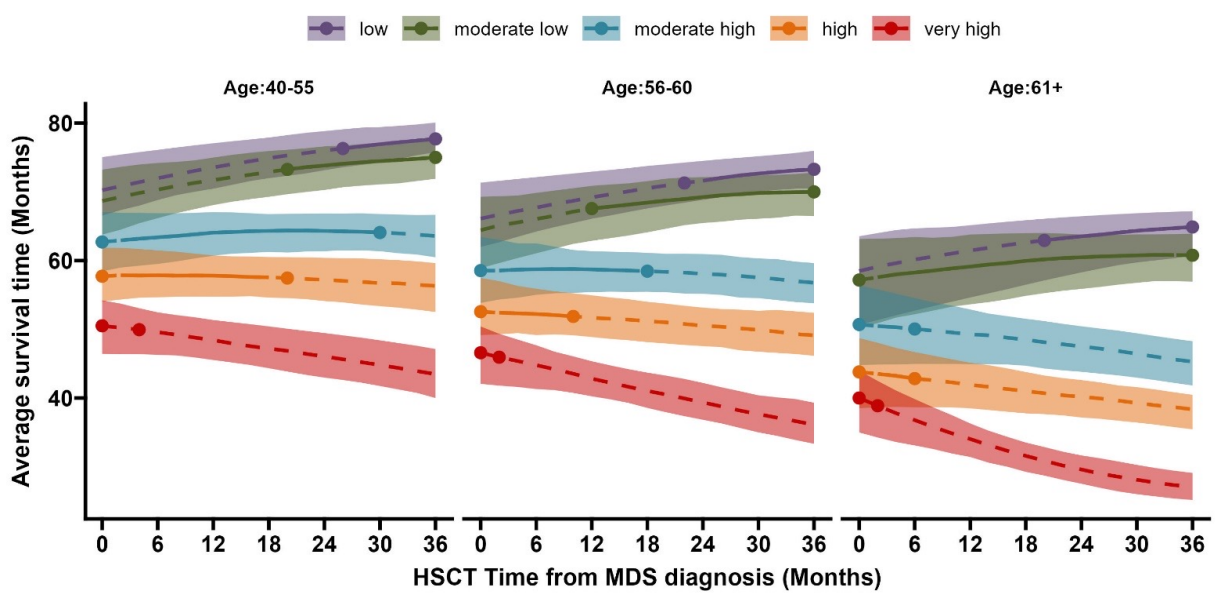
Clinical and genomic-based Decision Support System to define the optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic neoplasms

CA Tentori, C Gregorio, M Robin, N Gagelmann, C Gurnari, S Ball, JC Caballero Berrocal, L Lanino, S D'Amico, M Spreafico, G Maggioni, E Travaglino, E Sauta, M Meggendorfer, LP Zhao, M Bernardi, C Di Grazia, L Vago, G Rivoli, L Borin, P Chiusolo, L Giaccone, MT Voso, JP Bewersdorf, O Nibourel, M Díaz Beyá, A Jerez, F Hernández, K Velázquez Kennedy, B Xicoy, M Ubezio, A Campagna, A Russo, G Todisco, D Mannina, S Bramanti, M Zampini, E Riva, M Bicchieri, G Asti, F Viviani, A Buizza, B Tinterri, AS Kubasch, A Bacigalupo, E Angelucci, A Rambaldi, F Passamonti, F Ciceri, V Savevski, A Santoro, N Al Ali, D Sallman, F Sole, G Garcia-Manero, U Germing, S Kordasti, V Santini, G Sanz, W Kern, U Platzbecker, M Diez-Campelo, JP Maciejewski, L Ades, P Fenaux, T Haferlach, AM Zeidan, G Castellani, R Komrokji, F Ieva, and MG Della Porta

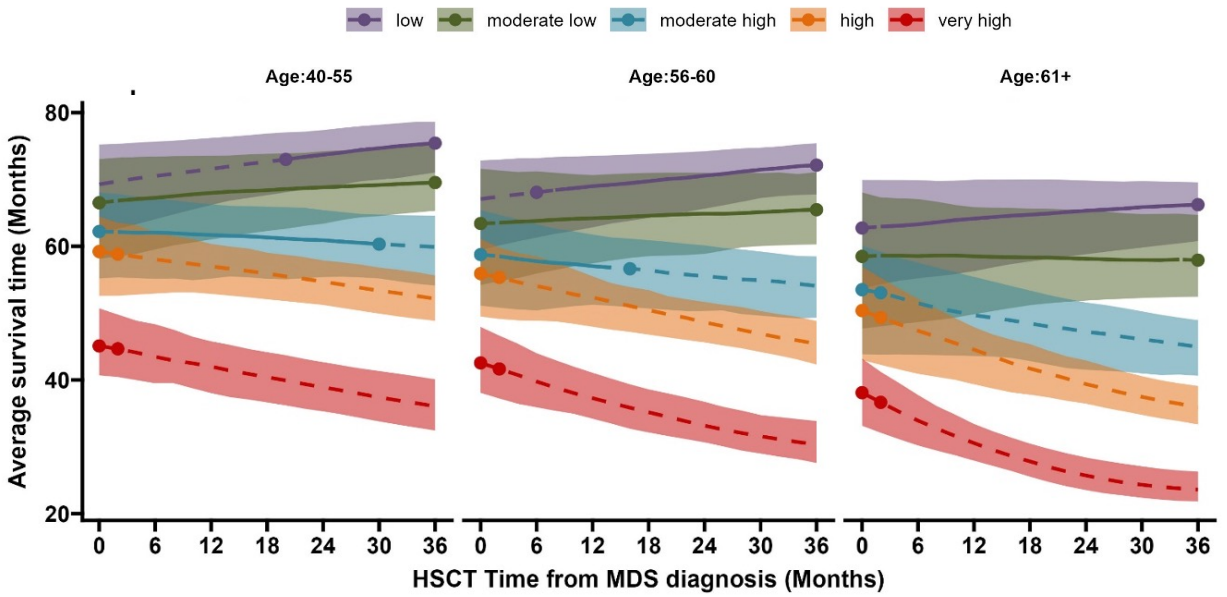
With the support of GenoMed4All, Synthema, EuroBloodNET, icMDS

IPSS-M based transplantation policy

A – TRAINING COHORT



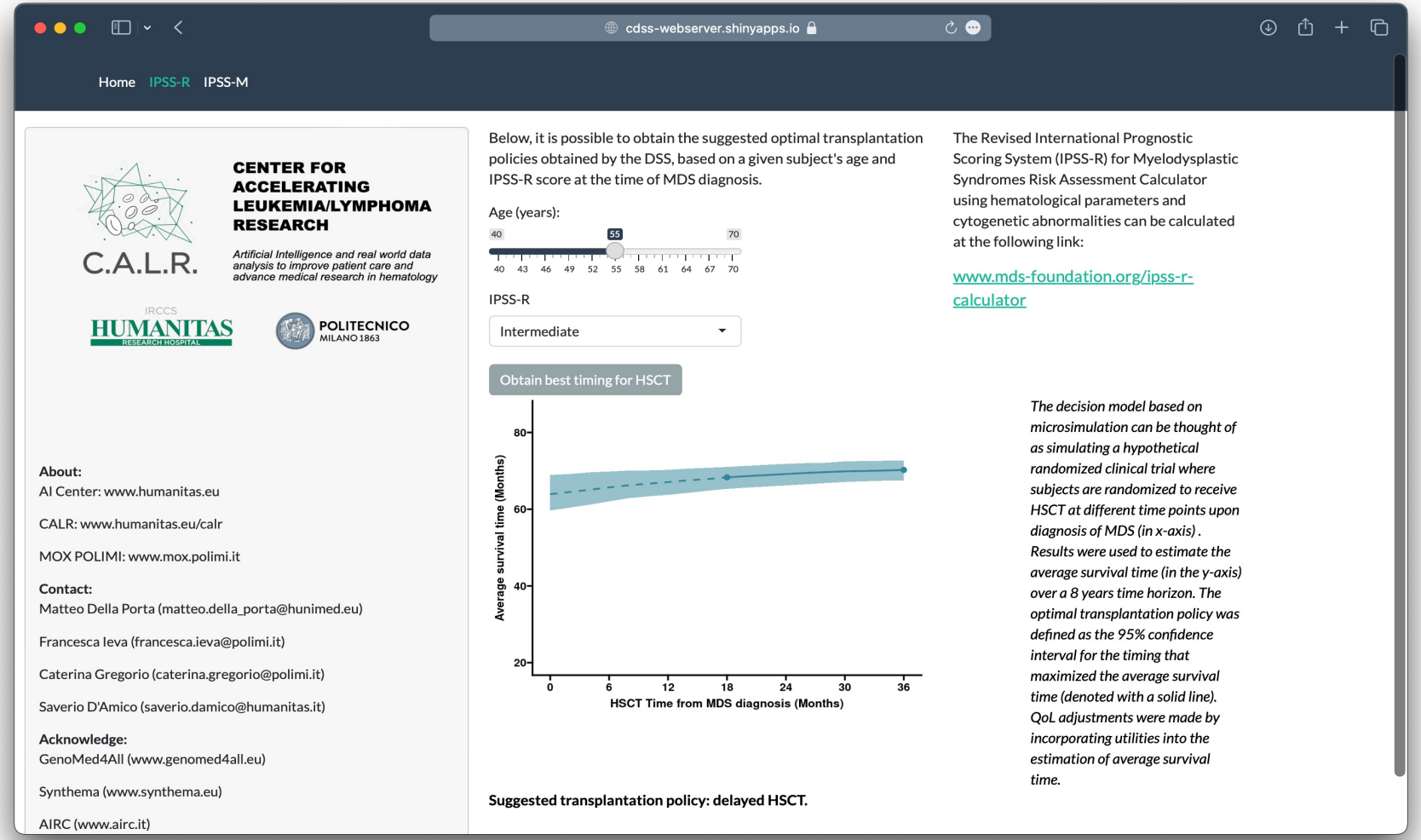
B – VALIDATION COHORT



- Under an IPSS-M based policy, in the training cohort, patients with either low- and moderate-low risk benefited from a delayed transplantation policy, while in those belonging to moderate-high, high- and very-high risk categories immediate transplantation was associated with a prolonged RMST

- All these results were confirmed in the validation cohort

Clinical Decision Support System for Transplantation in MDS WEB TOOL



HR-MDS conclusion

- Awaiting results of VERONA
- New oral azacitidine/cedazuridine formulation: ASTX-030
- IPSS-M impact on transplant decision

Targeted options in MDS

- **IDH-2 (5-10%): enasidenib, venetoclax**
- **IDH-1 (5%): ivosidenib, venetoclax**
- **Flt-3 (15%): multiple agents**
- **TP53 (10%): oral decitabine/cedazuridine**
- **NPM1 (1%): ara-C based**
- **ASXL1: HMA+venetoclax**

Other questions

- **Delay transition from CCUS to MDS**
- **Understand cross talk between comorbidities and MDS**
- **Develop therapies in LR-MDS that improve survival**
  - **Role of alloSCT**
- **Develop new combinations in HR-MDS**
- **Develop treatment strategies for p53 MDS**
- **Develop additional targeted approaches for MDS**
  - **IDH1, IDH2, SF3B1, IRAK4, Flt-3, CBL other**
- **Develop second line therapies for HMA failure MDS**
- **Integrate alloSCT: total therapy**

Thank you

Guillermo Garcia-Manero

Section of MDS

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