

3rd edition

Unmet challenges in high risk hematological malignancies: from bedside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

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ROLE OF TRANSPLANTATION IN HIGH RISK MDS

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Disclosures of Giulia Rivoli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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NOTHING TO DISCLOSE

ROLE OF TRANSPLANTATION IN HIGH RISK MDS

TABLE 5 Summary of publications comparing outcomes of allo-HSCT versus other types of treatments

Reference	Method	Results
Platzbecker et al. ²⁹	Retrospective cohort study in high risk MDS age 60-70 years <ul style="list-style-type: none"> Allo-HSCT (n = 103) AZA (n = 75) 	2-year EFS 37% (95% CI 28-48) and 14% (95% CI 7-27), respectively; p = .04 2-year OS 39% (95% CI 30-50) and 23% (95% CI 14-40), respectively; p = .007
Robin et al. ³⁰	Prospective cohort study in high risk MDS age 50-70 years <ul style="list-style-type: none"> HLA match donor (n = 112) No donor (n = 50) 	4-year OS 37% (95% CI 28-48) and 15% (95% CI 6-39), respectively; p = .02
Nakamura et al. ³¹	Biologic assignment trial in intermediate-2 or high-risk MDS by IPSS age 50-75 years <ul style="list-style-type: none"> RIC allo-HSCT (n = 260) HMA/BSC (n = 124) 	3-year OS 47.9% (95% CI 41.3-54.1) and 26.6% (95% CI 18.4-35.6), respectively; p = .0001
Kröger et al. ³²	Prospective phase II study in intermediate-2 or high-risk MDS by IPSS or intermediate 1 with high-risk cytogenetics age 55-70 years <ul style="list-style-type: none"> RIC allo-HSCT (n = 81) AZA (n = 27) 	3-year EFS 34% (95% CI 22-47) and 0%, respectively; p < .001 3-year OS 50% (95% CI 39-61) and 32% (95% CI 14-52), respectively; p = .12

Current Treatment Algorithm in HR-MDS

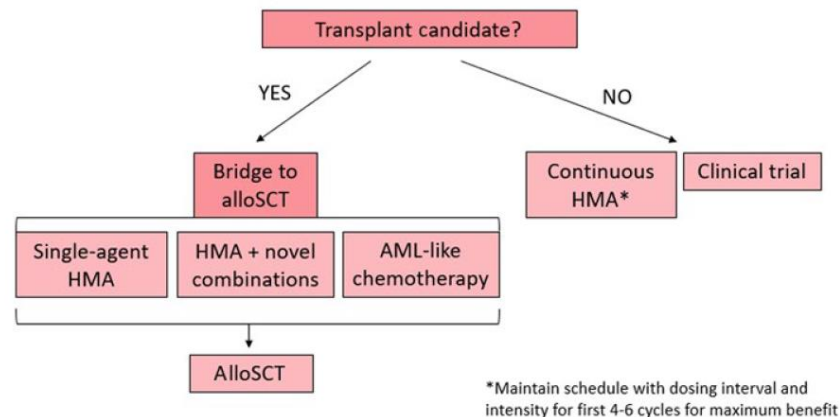


Figure 2. Treatment algorithm for HR-MDS based on current FDA-approved regimens.

HR currently defined according to R-IPSS in clinical practice (> 3.5 points)



Transplantation and
Cellular Therapy

journal homepage: www.tctjournal.org



Guideline

Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines



- ✓ What is the role of allogeneic HCT in MDS?
- ✓ How should chromosomal anomalies and somatic mutations be considered in the context of HCT?
- ✓ When should patients with MDS be referred for HCT evaluation?
- ✓ What is the role of pretransplant systemic therapy for MDS?
- ✓ Conditioning intensity, alternative donors and post-transplant issues

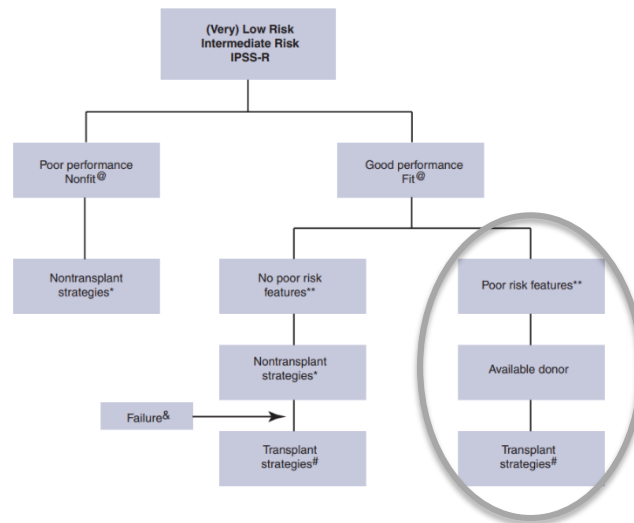
WHO TO TRANSPLANT?

- ✓ *What is the role of allogeneic HCT in MDS?*
- ✓ *How should chromosomal anomalies and somatic mutations be considered in the context of HCT?*

WHEN TO TRANSPLANT?

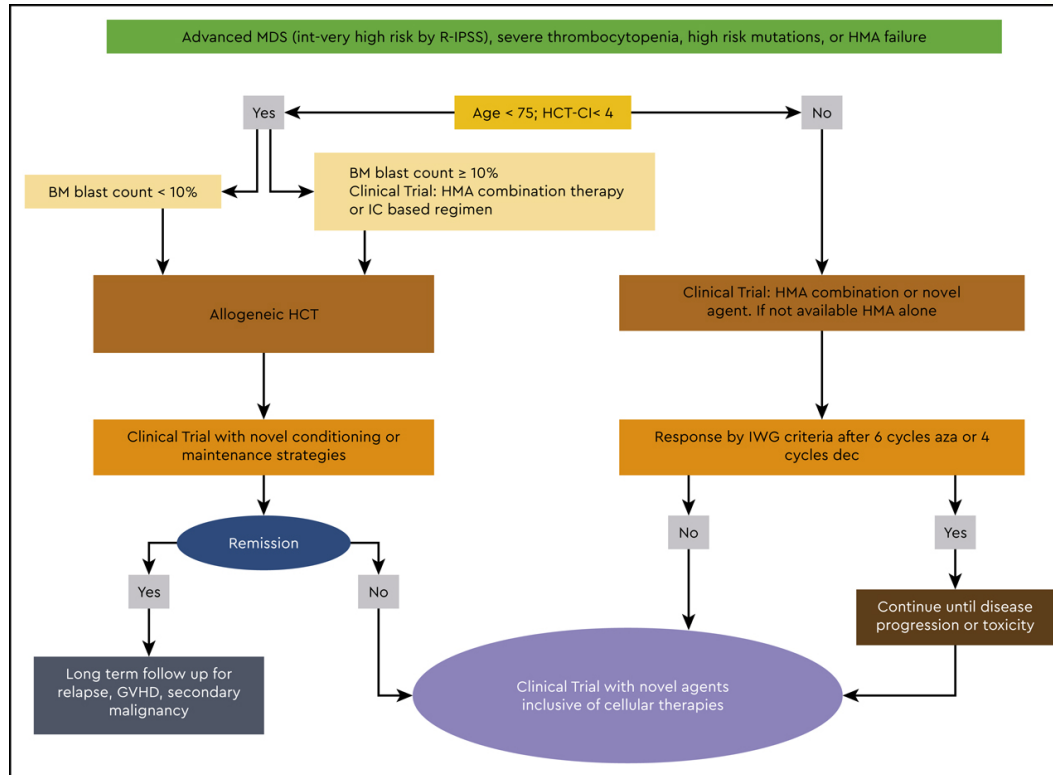
HOW TO TRANSPLANT?

PROGNOSTIC STRATIFICATION AND ALLO-SCT IN LOW-RISK MDS: IS LOW R-IPSS RISK ALWAYS LOW?



- Molecular assessment, M-IPSS
- Clinical evaluation: response/non-response to available therapies, transfusion requirements, kinetics and complications related to cytopenias, comorbidities, quality of life → dynamic outcome indicators ⁽²⁾

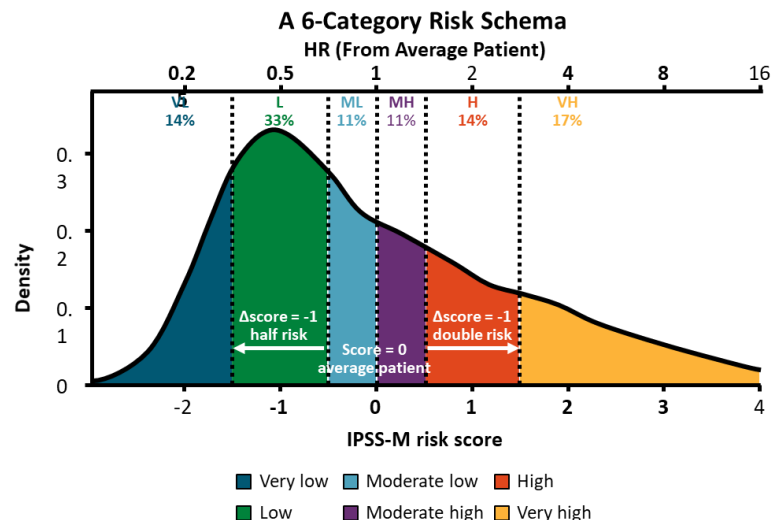
Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

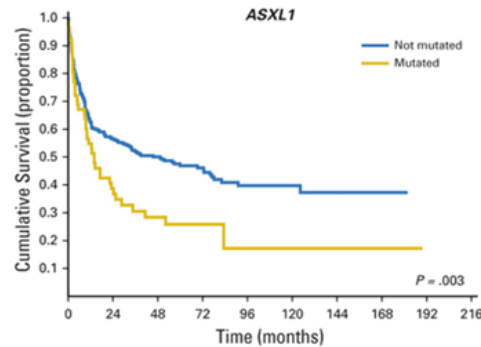
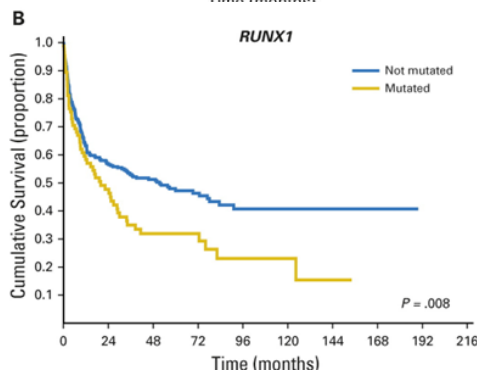
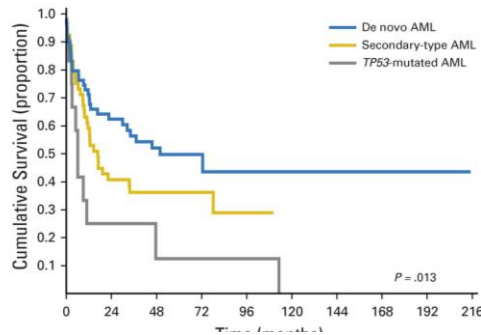
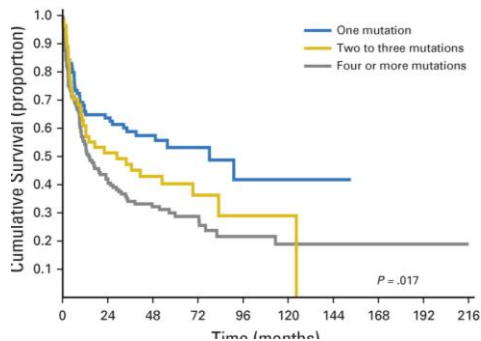


DEVELOPMENT OF IPSS-M

After adjusting for age, sex, MDS type (primary vs therapy related), and IPSS-R raw score, multiple genes were associated with adverse outcomes including LFS (14 genes), OS (16 genes), and AML transformation (15 genes)¹

46% of patients were re-stratified from IPSS-R: 74% upstaged / 26% down-staged



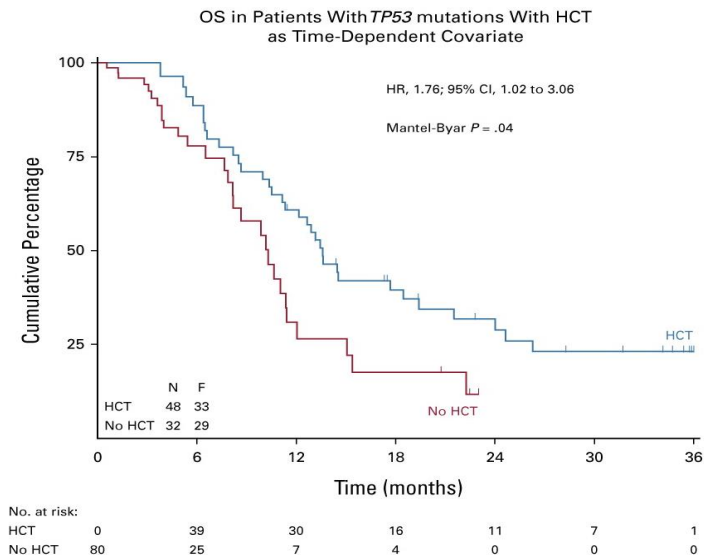


MDS TREATED WITH HSCT: IMPACT OF DRIVER SOMATIC MUTATIONS ON SURVIVAL OUTCOMES

- **ASXL1 // RUNX1 // TP53**: independent predictors of OS and relapse after HSCT in MDS and AML post-MDS
- The **number of somatic mutations** is associated with survival outcome

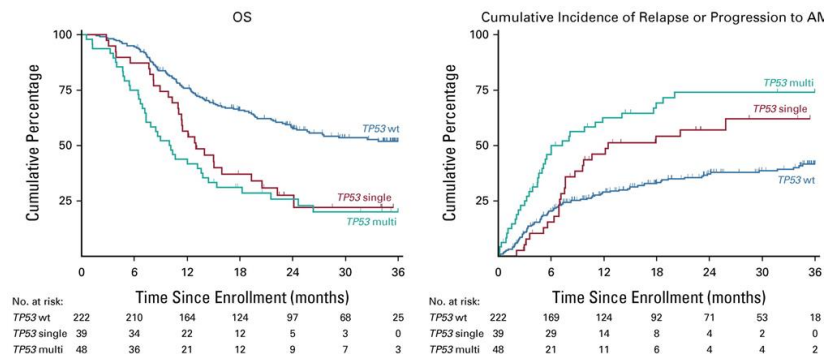
GENETIC ANALYSIS OF THE BMT CTN 1102 STUDY

B



OS in *TP53* mut patients was worse compared with *TP53* wt patients ($21\% \pm 5\%$ [SE] v $52\% \pm 4\%$ at 3 years; $P < .001$).

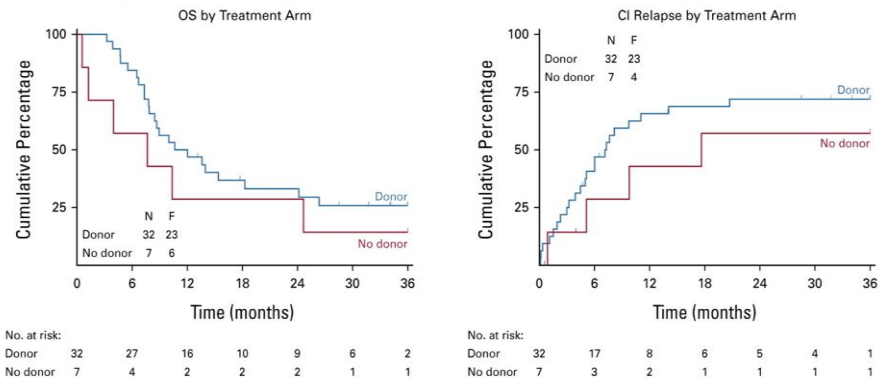
No significant OS difference between *TP53*single versus *TP53*multihit ($22\% \pm 8\%$ v $20\% \pm 6\%$ at 3 years; $P = .31$).



TP53 mut patients undergoing HCT had improved OS compared with non-HCT treatment (OS at 3 years: $23\% \pm 7\%$ v $11\% \pm 7\%$; $P = .04$)
HR of 3.89; 95% CI, 1.87 to 8.12; $P < .001$

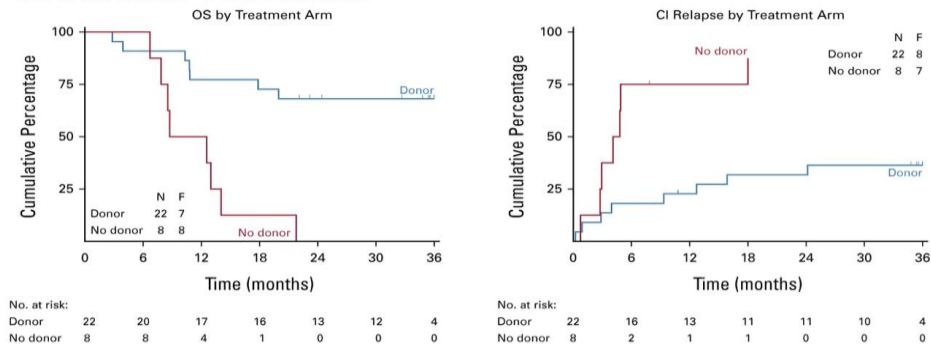
GENETIC ANALYSIS OF THE BMT CTN 1102 STUDY

C IPSS-M Very High Risk—TP53 Mutation Present

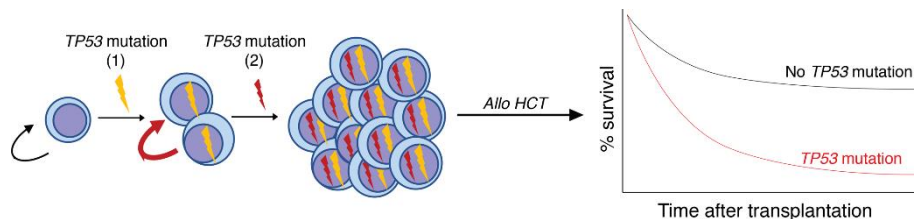


OS among patients with molecular IPSS (IPSS-M) very high risk without a TP53 mutation was significantly improved if they had a donor ($68\% \pm 10\% v 0\% \pm 12\%$ at 3 years; $P = .001$).

D IPSS-M Very High Risk—TP53 Mutation Absent



TRANSPLANT FOR TP53-MUTATED MDS AND AML: BECAUSE WE CAN OR BECAUSE WE SHOULD?



Disease subtype

- TP53 allelic state
- Co-occurring mutations
- Immunophenotype

Treatment

Response

- Depth of remission
- Molecular MRD status
- Extent of prior therapy

Conditioning

- Modify intensity
- Novel drug combinations

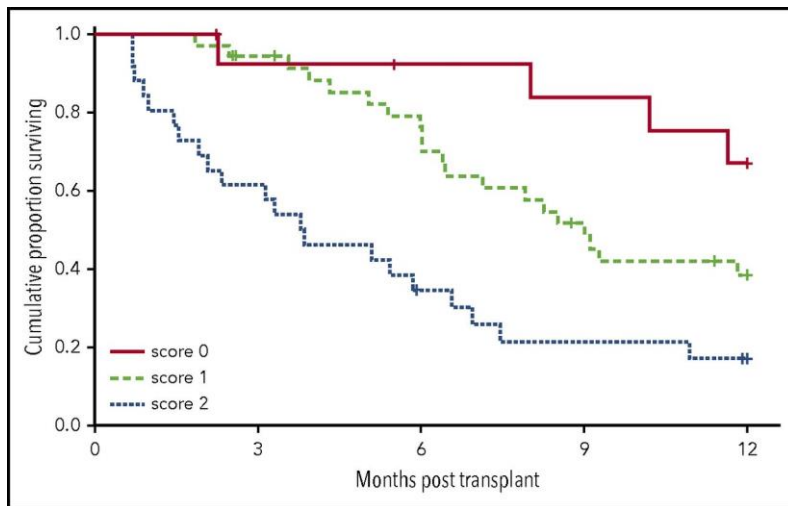
Allogeneic HCT

- Donor selection: HLA disparity vs. early availability

Post-HCT phase

- Maintenance treatment
- Early tapering of immunosuppression
- Prophylactic or preemptive DLI

TRANSPLANT FOR TP53-MUTATED MDS



Retrospective series of 84 TP53 mut patients (55 SCT)

3 independent factors associated with worse OS: HCT-CI > 4 // KPS ≤ 80% // disease not in CR1/2

1 year OS according to risk score (0, 1 and ≥ 2). 67% - 39% - 17%

WHO TO TRANSPLANT?

WHEN TO TRANSPLANT?

- ✓ ***When should patients with MDS be referred for HSCT evaluation?***

Should allogeneic HCT routinely be offered early for advanced (int-2/high) de novo MDS?	Yes	A	1++
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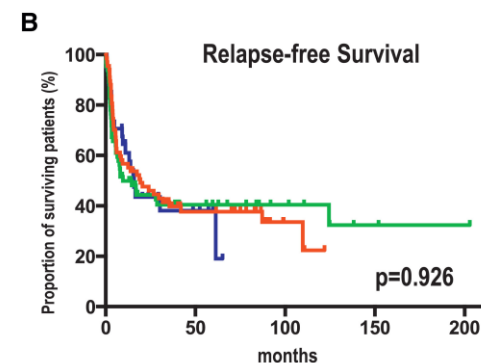
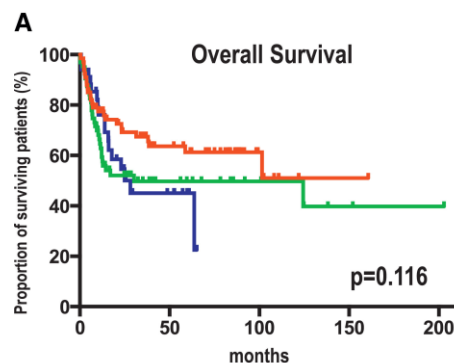
- ✓ ***What is the role of pretransplant systemic therapy for MDS?***

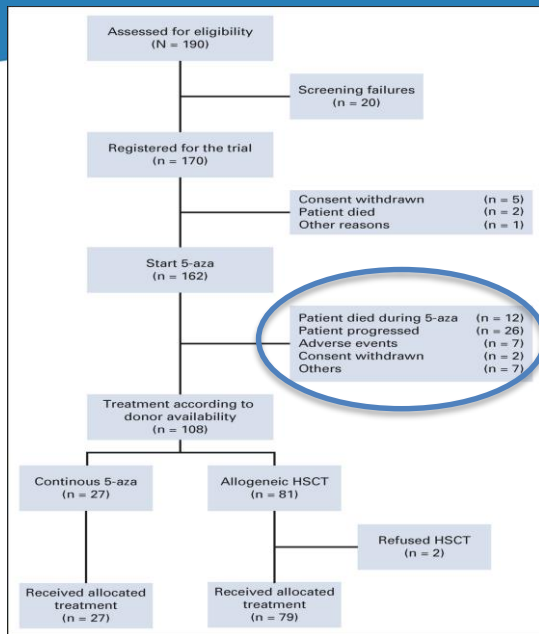
Should patients with MDS receive disease-directed therapy prior to HCT?	Unclear	C	2++
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HOW TO TRANSPLANT?

COMPARISON BETWEEN UPFRONT SCT AND DIFFERENT PRETRANSPLANT CYTOREDUCTIVE TREATMENT APPROACHES IN PATIENTS WITH HR-MDS AND S-AML

- 126 pts with excess blast MDS // retrospective analysis
 - 77 (41%) upfront SCT
- 98 (59%) received preSCT cytoreductive treatment (IC, n = 64; HMAs, n = 34)
- An upfront transplant strategy is at least not inferior to pretransplant cytoreduction



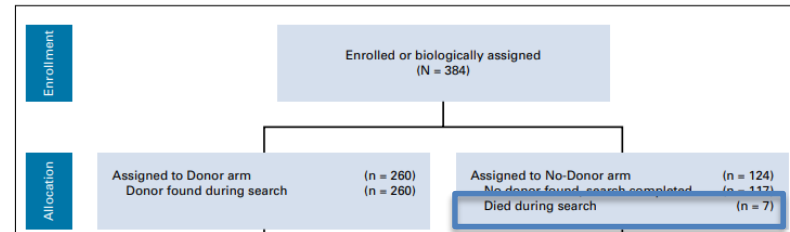


Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study)

Nicolaus Kröger, MD¹; Katja Sockel, MD¹; Christine Wolchke, MD¹; Wolfgang Bethge, MD¹; Richard F. Schlenk, MD^{2,3}; Dominik Wolf, MD^{2,3}; Michael Stadler, MD³; Guido Kobbe, MD³; Gerald Wulf, MD³; Gesine Bug, MD³; Kerstin Schäfer-Eckart, MD³; Christof Scheid, MD³; Florian Nolte, MD³; Jan Krönke, MD³; Matthias Steljes, MD³; Dietrich Beelen, MD³; Marion Heinemann³; Detlef Haase, MD³; Hannes Bucher, PhD³; Gabriele Bleckner, PhD³; Aristoteles Giagounidis, MD³; Uwe Platzbecker, MD³; on behalf of the German MDS Study Group and the German Cooperative Transplant Study Group

original reports Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome

Ryotaro Nakamura, MD¹; Wael Saber, MD, MS¹; Michael J. Martens, PhD²; Alyssa Ramirez, BS¹; Bart Scott, MD¹; Betul Oran, MD³; Eric Leifer, PhD⁴; Roni Tamari, MD⁵; Asmita Mishra, MD⁶; Richard T. Maziarz, MD⁷; Joseph McGuirk, DO⁸; Peter Westervelt, MD, PhD¹¹; Sumithra Vasu, MBBS¹²; Mrinal Patnaik, MBBS¹³; Ramnurti Kamble, MD¹⁴; Stephen J. Forman, MD¹; Mikkael A. Sekeres, MD, MS¹⁵; Frederick Appelbaum, MD¹; Adam Mendizabal, PhD¹; Brent Logan, PhD¹; Mary Horowitz, MD, MS¹; and Corey Cutler, MD, MPH¹; on behalf of the Blood and Marrow Transplant Clinical Trials Network



44 patients in the donor group (16.7%) did not undergo HSCT:

- Disease progression
- Comorbidities
- Subject preference
- Donor or insurance issues
- death



ORIGINAL ARTICLE

HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM

M Robin^{1,2,3}, R Porcher^{4,5}, L Adès⁶, E Raffoux⁷, M Michallet⁸, S François⁹, J-Y Cahn¹⁰, A Delmer¹¹, E Wattel¹², S Vigouroux¹², J-O Bay¹³, J Cornillon¹⁴, A Huynh¹⁵, S Nguyen¹⁶, M-T Rubio¹⁷, L Vincent¹⁸, N Maillard¹⁹, A Charbonnier²⁰, RP de Latour^{1,2,3}, O Reman²¹, H Dombret^{2,6}, P Fenaux^{2,6} and G Socié^{1,2,3}

31 patients in the donor group (31/112, 28%) did not receive HSCT because of:

- progressive disease with BM blasts > 10% despite treatment (n=16)
 - acquisition of a comorbidity contraindicating HSCT (n=9)
- death during IC or HMA in responders or before assessment (n=4)
 - patient refusal/social reasons (n=2)

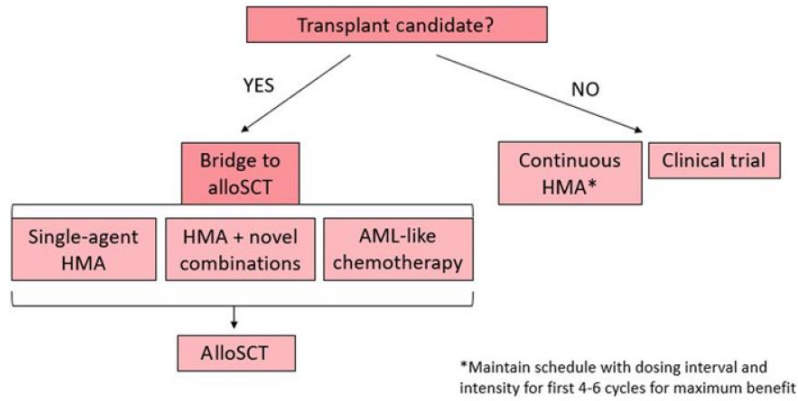
Current Treatment Algorithm in HR-MDS

Figure 2. Treatment algorithm for HR-MDS based on current FDA-approved regimens.

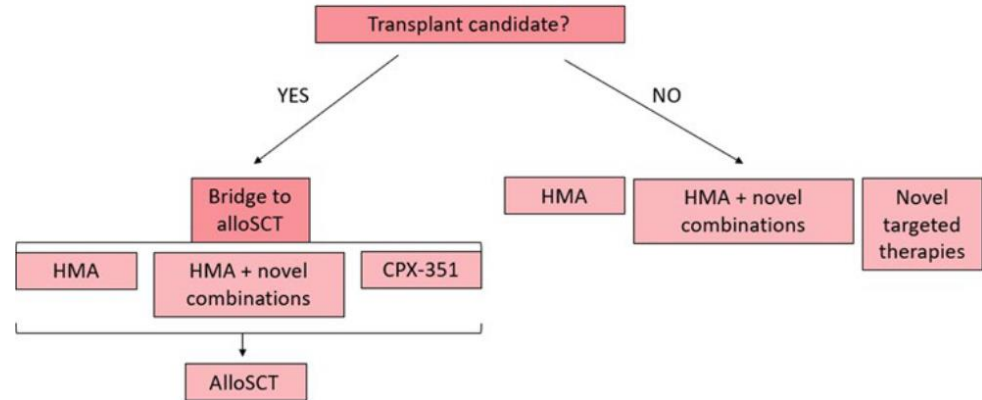
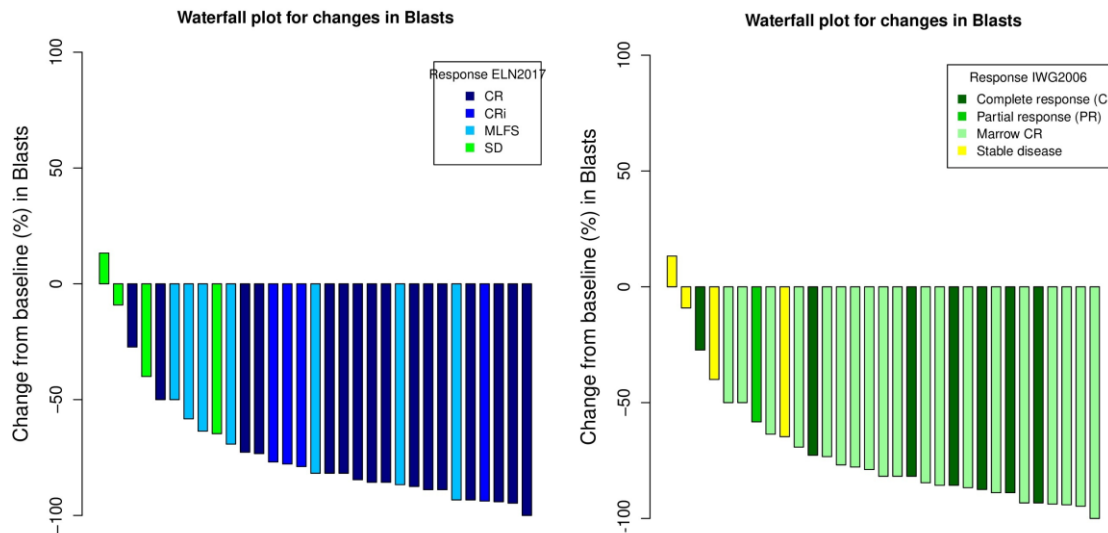
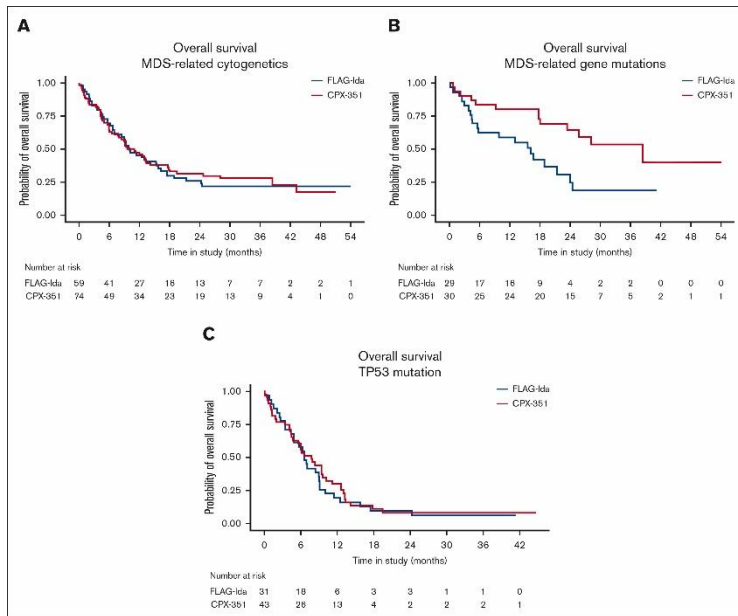
Potential Treatment Algorithm in HR-MDS

Figure 3. Treatment algorithm for HR-MDS based on therapies under development.



- 31 treatment-naive adult patients with HR-MDS >70 years old.
 - CR 23%, marrow CR (mCR) 45%, HI 6%
- 89% of patients with BM blasts >10% achieved <5% after induction.
- 22 patients went on to receive an alloSCT, with 5 allo-SCTs still planned.

A RANDOMIZED COMPARISON OF CPX-351 AND FLAG-IDA IN ADVERSE KARYOTYPE AML AND HIGH-RISK MDS: THE UK NCRI AML19 TRIAL



- ✓ 189 patients: 30% high-risk MDS.
- ✓ No difference in OS (13.3 months vs 11.4 months) or EFS in multivariable analysis.
- ✓ In high-risk AML and MDS, CPX-351 did not improve response or survival compared with FLAG-Ida but produced better relapse-free survival.
- ✓ In the exploratory subgroup of patients defined by the presence of mutations in MDS-related genes, CPX-351 improved OS.

AZACITIDINE PLUS VENETOCLAX IN PATIENTS WITH HIGH-RISK MDS: PHASE 1-2 STUDY

Phase I/II study

23 patients enrolled in phase I (74% HMAs naïve, 26% post-HMAs failure)

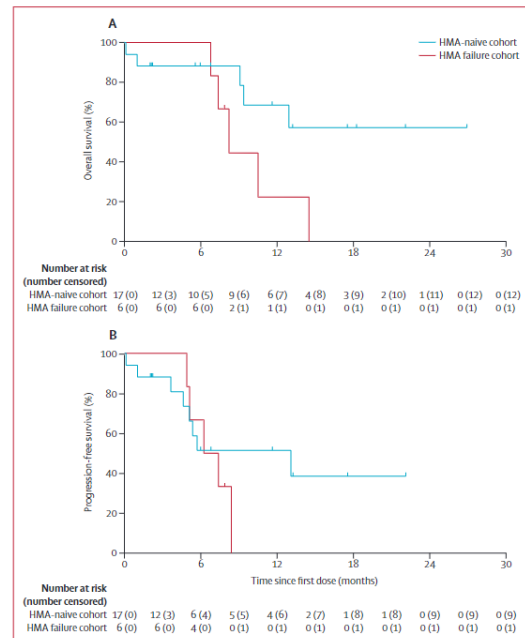
Median FU 13.2 months

Dose/duration reduction in azacytidine and venetoclax administration

ORR 87%; median TTR 1 cycle

Median OS not reached in HMAs-naïve cohort vs 8.3 months in HMAs failure

Median PFS 13.1 mo vs 6.2 mo



WHO TO TRANSPLANT?

WHEN TO TRANSPLANT?

HOW TO TRANSPLANT?

- ✓ ***Conditioning intensity, alternative donors and post-transplant issues***

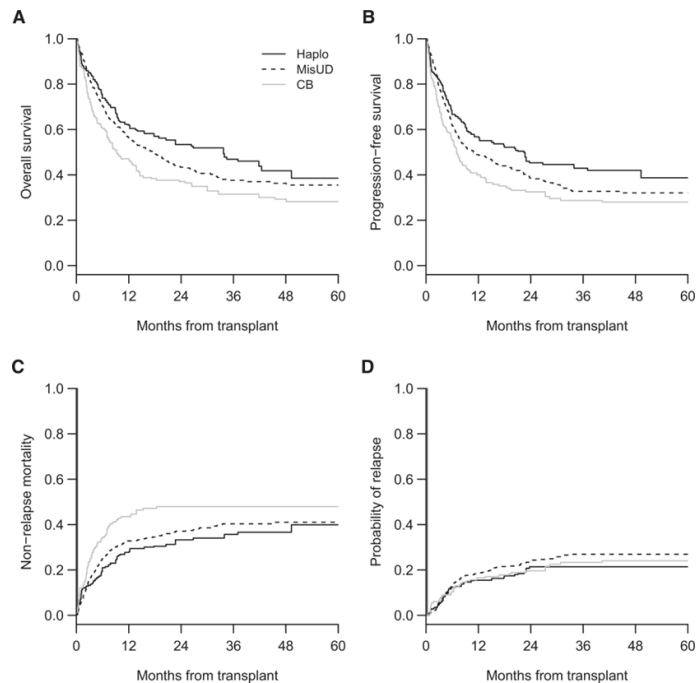
Conditioning regimen			
Are RIC regimens an acceptable alternative for adults considered unfit for MAC regimens?	Yes	A	1++
Should MAC be the preferred conditioning intensity in fit patients?	Unclear	A	1++
Alternative donors			
Can haploidentical relatives, MMUDs, and umbilical cord blood be considered as alternative donor options?	Yes	C	2+

Consideration	Recommendation	Grade of Recommendation	Highest Level of Evidence
Should patients with MDS receive maintenance therapy after HCT??	Unclear	B	1+
Is there a preferred treatment for relapsed disease after HCT?	No	D	2-

HLA-MISMATCHED DONORS IN PATIENTS WITH MDS: AN EBMT REGISTRY ANALYSIS

- ✓ PFS better after haplo (versus mismatched unrelated, $P = .056$; vs CB, $P = .003$)
- ✓ OS tended to be superior after haplo (vs mismatched unrelated, $P = .082$; versus CB, $P = .002$)
- ✓ NRM not significantly different between haplo and mismatched unrelated donors
 - ✓ Relapse risk not influenced by the type of donor

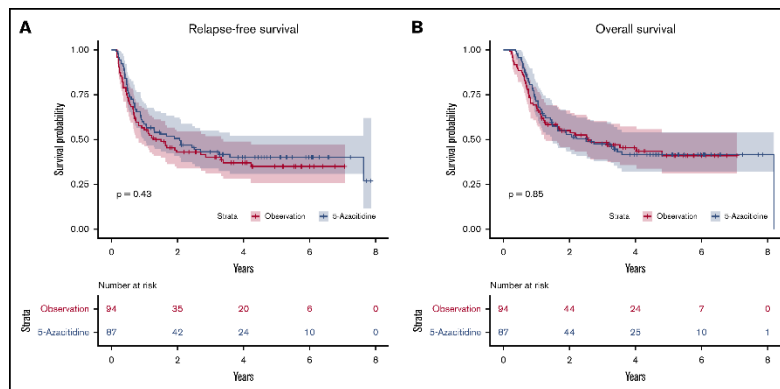
...patients with MDS from the EBMT registry receiving hematopoietic stem cell transplantation from a haplo donor have significantly better outcome than those receiving hematopoietic stem cell transplantation from a CB donor and at least similar or better outcome than with a mismatched unrelated donor....



A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients

Betül Oran,¹ Marcos de Lima,² Guillermo Garcia-Manero,³ Peter F. Thall,⁴ Ruitao Lin,⁴ Uday Popat,¹ Amin M. Alousi,¹ Chitra Hosing,¹ Sergio Giralt,⁵ Gabriela Rondon,¹ Glenda Woodworth,¹ and Richard E. Champlin¹

¹Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; ²University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH; ³Department of Leukemia and ⁴Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; and ⁵Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY



The use of subcutaneous 5-azacitidine as posttransplant maintenance strategy was not associated with improved RFS (A) and OS (B) compared with observation arm.

POST-HSCT MAINTENANCE NEW PERSPECTIVES

Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial

Uwe Platzbecker,¹ Jan Moritz Middelke,² Katja Sockel,³ Regina Herbst,⁴ Dominik Wolf,⁵ Claudia D Baldus,⁶ Uta Oelschlägel,⁷ Anke Mütterich,⁸ Lars Fransesky,⁹ Richard Noppeney,¹⁰ Gesine Bug,¹¹ Katharina S Götzke,¹² Alwin Krämer,¹³ Tilmann Bochtler,¹⁴ Matthias Stelljes,¹⁵ Christoph Groth,¹⁶ Antje Schubert,¹⁷ Marika Mende,¹⁸ Friedrich Stölzel,¹⁹ Christin Borkmann,²⁰ Anne Sophie Kubasch,²¹ Malte von Bonin,²² Hubert Serve,²³ Mathias Hänel,²⁴ Ulrich Dührsen,²⁵ Johannes Schetelig,²⁶ Christoph Röllig,²⁷ Michael Kramer,²⁸ Gerhard Ehninger,²⁹ Martin Bornhäuser,³⁰ Christian Thiede³¹

original reports

Eprenetapopt Plus Azacitidine After Allogeneic Hematopoietic Stem-Cell Transplantation for *TP53*-Mutant Acute Myeloid Leukemia and Myelodysplastic Syndromes

Asmita Mishra, MD¹; Roni Tamari, MD²; Amy E. DeZern, MD³; Michael T. Byrne, DO⁴; Mahasweta Gooptu, MD⁵; Yi-Bin Chen, MD⁶; H. Joachim Deeg, MD⁷; David Sallman, MD⁸; Phillip Gallacher, BSc⁹; Anders Wennborg, MD, PhD¹⁰; Denice K. Hickman, BSN, RN¹¹; Eyal C. Attar, MD¹²; and Hugo F. Fernandez, MD¹³

REGULAR ARTICLE

 blood advances

Enasidenib as maintenance following allogeneic hematopoietic cell transplantation for *IDH2*-mutated myeloid malignancies

Amir T. Fathi,¹ Haesook T. Kim,² Robert J. Soiffer,³ Mark J. Levis,⁴ Shuli Li,⁵ Annette S. Kim,⁶ Alice S. Mirra,⁷ Zachariah DeFilipp,⁸ Areej El-Jawahri,⁹ Steven L. McAfee,¹⁰ Andrew M. Brunner,¹¹ Rupa Narayan,¹² Laura W. Knight,¹³ Devon Kelley,¹⁴ AJ S. Bottoms,¹⁵ Lindsey H. Perry,¹⁶ Jonathan L. Wahl,¹⁷ Jennifer Brock,¹⁸ Elayne Breton,¹⁹ Vincent T. Ho,²⁰ and Yi-Bin Chen²¹

¹Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; ²Department of Data Science, Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, MA; ³Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; ⁴Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; ⁵Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and ⁶⁻²¹The Ohio State University Comprehensive Cancer Center, Columbus, OH

3rd edition

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