POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

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VIFOR							DMC
Menarini			x		X		
GILEAD-KITE					X		
Novartis						X	
Regeneron						X	

Terapia delle sindromi mielodisplastiche ad alto rischio

Emanuele Angelucci
UO Ematologia e terapie cellulari
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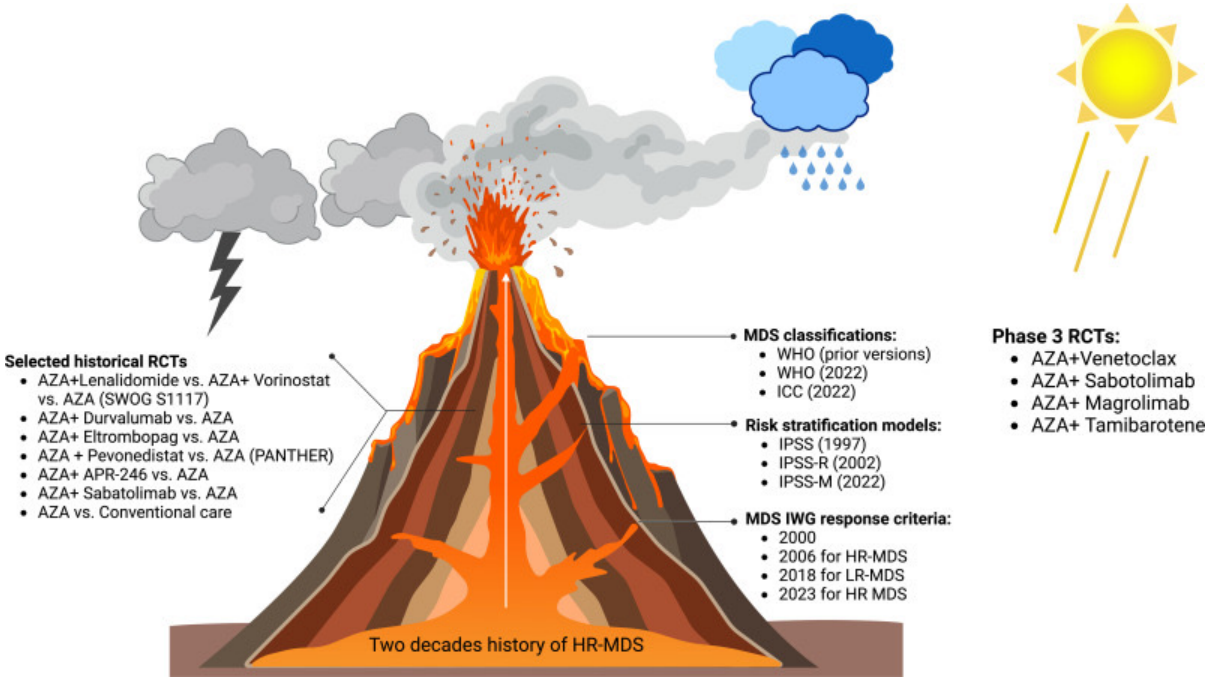
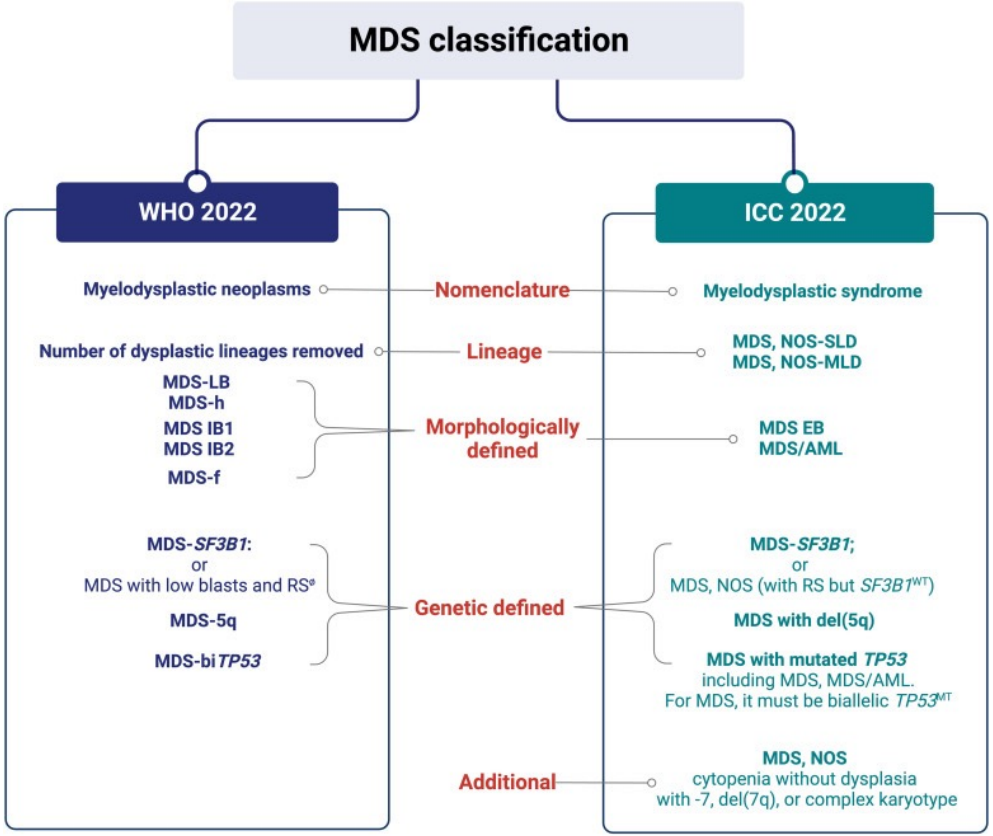
FRONTLINE TREATMENT OPTIONS FOR HIGHER-RISK MDS: CAN WE MOVE PAST AZACITIDINE?



Sallman DA, Xie Z. Frontline treatment options for higher-risk MDS: can we move past azacitidine? Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):65-72. doi: 10.1182/hematology.2023000421. PMID: 38066872; PMCID: PMC10727006

DIAGNOSTIC CHANGES IN MDS

should patients with MDS and blast count 10-19% be treated as AML patients?



[a] RS≥15% and SF3B1 not available or wild type
MDS unclassifiable removed in both WHO 2022 and ICC 2022

- New entities: h-MDS, MDS f

Concerns:

- older age
- decreased reserve of funcional hematopoiesis
- increased toxicity (cytopenias)

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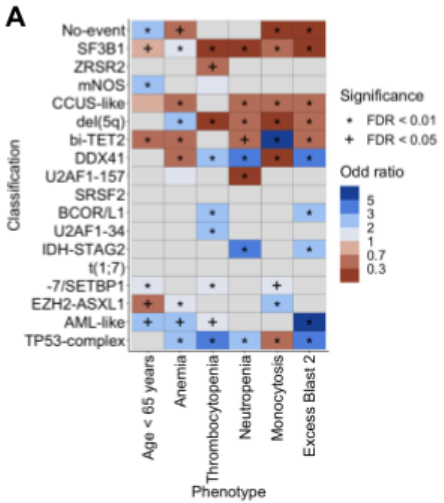
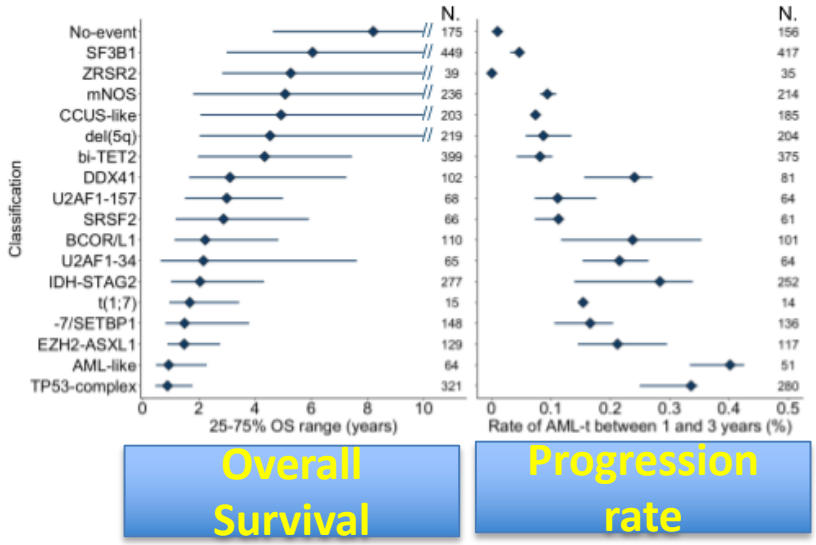
MOLECULAR TAXONOMY OF MYELODYSPLASTIC SYNDROMES AND ITS CLINICAL IMPLICATION

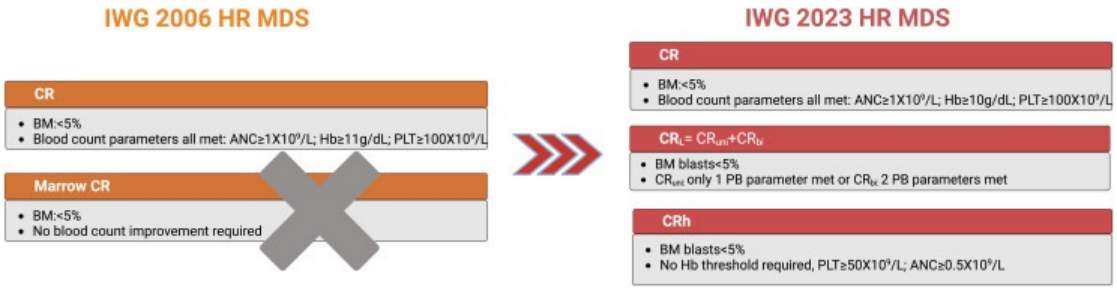
- 3233 patients
- 18 distinct MDS molecular subgroups
- **The prognostic influence of BM blasts varied in individual genetic subgroups: <u>clinical impact of increased blasts may depend on the genetic context</u>**





Elsa Bernard et al, Molecular Taxonomy of Myelodysplastic Syndromes and Its Clinical Implications, **Blood, Volume 142, Supplement 1, 2023, Page 997**, ISSN 0006-4971, https://doi.org/10.1182/blood-2023-186863.

REVISED INTERNATIONAL WORING GROUP 2023 RESPONSE CRITERIA FOR HIGHER RISK MDS



2023 consensus for revised IWG response crieteria

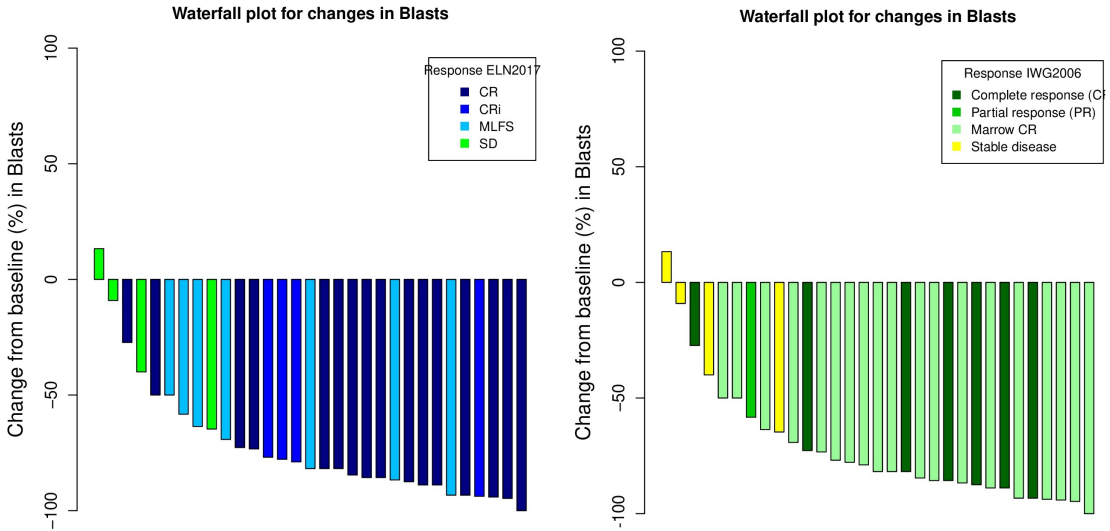
Complete remission:

- Hb threshold decreased to ≥ 10 g/dl
- Removal of marrow CR (caveat for patients bridged to alloSCT)
- Provisional entities:
  - CR_L: CR **with limited count recovery (QoL ?)**
  - CRh: **complete remission with hematologic recovery**

Sallman DA, Xie Z. Frontline treatment options for higher-risk MDS: can we move past azacitidine? **Hematology Am Soc Hematol Educ Program. 2023** Dec 8;2023(1):65-72. doi: 10.1182/hematology.2023000421. PMID: 38066872; PMCID: PMC10727006

Amer M. Zeidan, Uwe Platzbeckeret al Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes. Blood 2023; 141 (17): 2047–2061. doi: https://doi.org/10.1182/blood.2022018604

CPX-351 IN HR-MDS



- 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.**

Pierre Peterlin,Pascal Turlure,Patrice Chevallier,Marie-Pierre Gourin,Pierre-Yves Dumas,Sylvain Thepot,Anna Berceanu,Sophie Park,Marie Anne Hospital,Thomas Cluzeau,Jose Miguel Torregrosa Diaz,Louis Devron,Sylvie Chevret,Marie C Bene,Yannick Le Bris,Rosa Sapena,Fatiha Chermat,Sophie Dimicoli-Salazar,Pierre Fenaux, CPX 351 As First Line Treatment in Higher Risk MDS. a Phase II Trial By the GFM, Blood, 2021, Figure 1

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 • 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 • 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 • 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 I with high-risk cytogenetics age 55–70 years • 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; $p = .12$

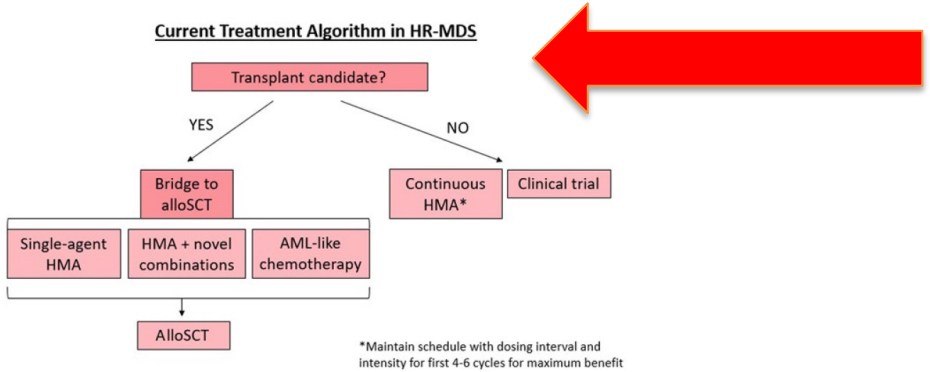


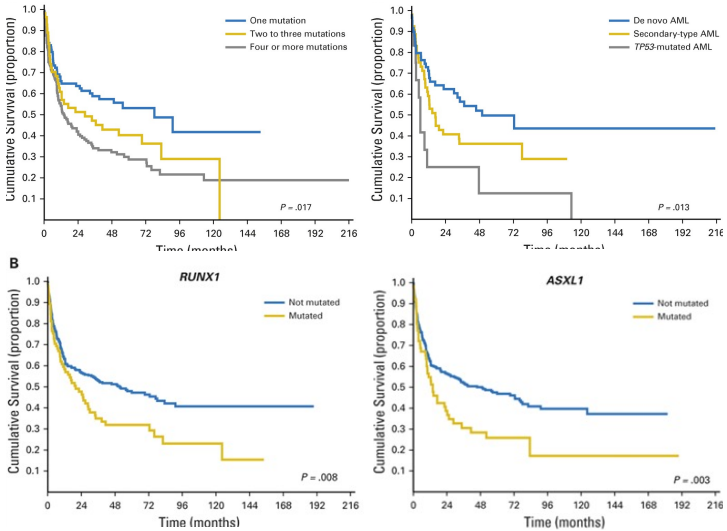
Figure 2. Treatment algorithm for HR-MDS based on current FDA-approved regimens.

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

1. Vittayawacharin P, Kongtim P, Ciurea SO. Allogeneic stem cell transplantation for patients with myelodysplastic syndromes. **Am J Hematol. 2023 Feb;**98(2):322-337. doi: 10.1002/ajh.26763. Epub 2022 Oct 28. PMID: 3625134

2. New investigational combinations for higher- risk MDS Kristin L. Koenig and Uma Borate, http://**ashpublications.org/hematology/article- pdf/2022**/1/368/2021729/368

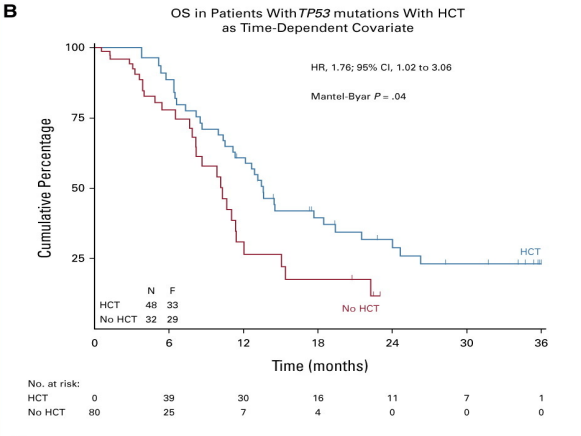
MDS TREATED WITH HSCT: IMPACT OF DRIVER SOMATIC MUTATIONS ON SURVIVAL OUTCOMES



- **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

Published in: **Matteo G. Della Porta**; et al; Journal of Clinical Oncology 2016 343627-3637.
DOI: 10.1200/JCO.2016.67.3616

GENETIC ANALYSIS OF THE BMT CTN 1102 STUDY (TP53)



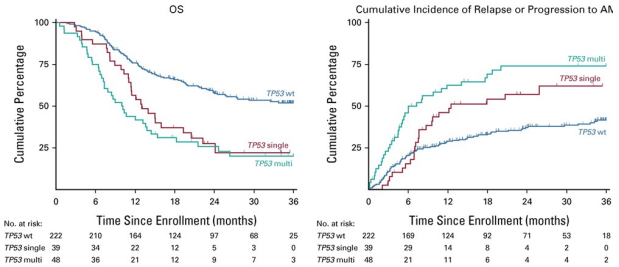
TP53 mut patients undergoing HCT had improved OS compared with non-HCT treatment

(OS at 3 years: 23% ± 7% v 11% ± 7%; P = .04)

HR of 3.89; 95% CI, 1.87 to 8.12; P < .001

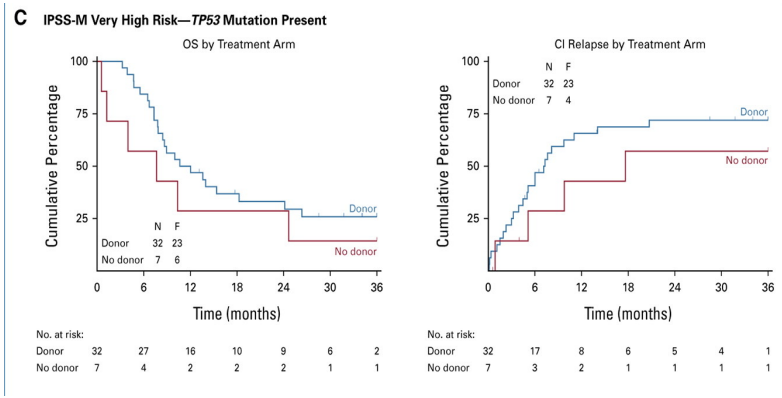
OS in TP53 mut patients was worse compared with TP53 wt patients (21% ± 5% [SE] v 52% ± 4% at 3 years; P < .001).

No significant OS difference between TP53single versus TP53multihit (22% ± 8% v 20% ± 6% at 3 years; P = .31).



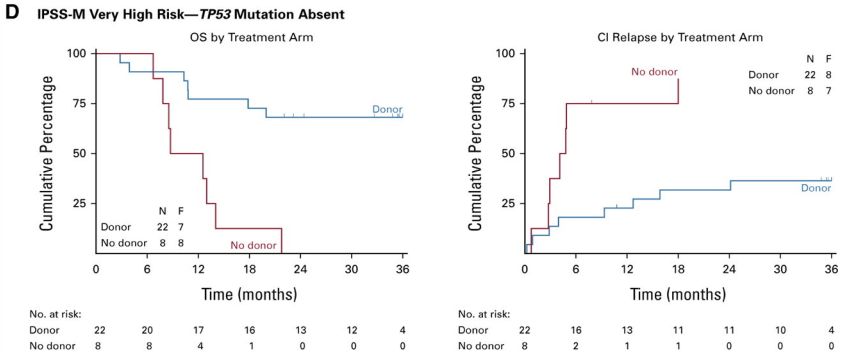
Jurjen Versluis; et al; Journal of Clinical Oncology Ahead of Print DOI: 10.1200/JCO.23.00866

GENETIC ANALYSIS OF THE BMT CTN 1102 STUDY IN VERY HIGH RISK IPSS_M (ASH2021)



TP53 mutation present

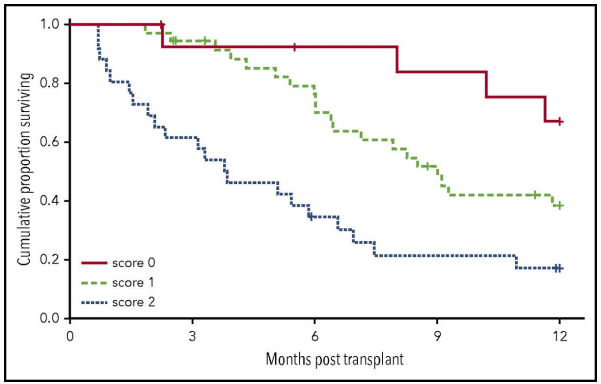
TP53 mutation absent



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

Jurjen Versluis; et al; Journal of Clinical Oncology Ahead of Print DOI: 10.1200/JCO.23.00866

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%

Stefan O. Ciurea et al. , Prognostic factors influencing survival after allogeneic transplantation for AML/MDS patients with TP53 mutations, Blood, 2018, Figure 1

CLINICAL AND GENOMIC BASED DECISION SUPPORT SYSTEM TO DEFINE THE OPTIMAL TIMING OF HSCT IN PATIENTS WITH MYELODSYSPLASTIC SYNDROMES

- Aims: to develop and validate a Decision Support System to define the optimal timing of HSCT in MDS patients based on clinical and genomic information provided by **IPSS-M vs conventional IPSS-R**
  - Retrospective cohort of **8326** patients
- **Patients with either low or moderate-low IPSS-M risk benefit from a delayed transplant policy**
- **In patients with moderate high, high and very high risk disease immediate transplantation was associated with prolonged life expectancy**

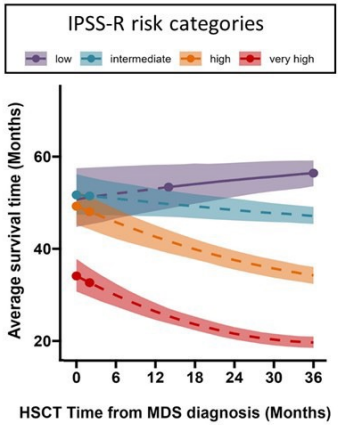


Figure 1. Optimal timing of transplantation in the learning cohort, according to a IPSS-R based-policy. The decision model based on microsimulation simulated a hypothetical randomized clinical trial where subjects are randomized to receive HSCT at different time points upon disease diagnosis. Results were used to estimate the average survival time over an 8-year time horizon (Restricted Mean Survival Time, RMST), for each combination of covariates. RMST estimates were compared among different transplantation policies thus determining the optimal transplantation policy.

Cristina Astrid Tentori, Matteo Giovanni Della Porta et al
Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndromes (MDS), Blood, Volume 142, Supplement 1, 2023, Page 197, ISSN 0006-4971, https://doi.org/10.1182/blood-2023-182194.

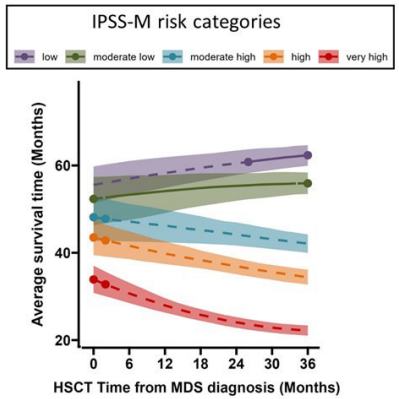
CLINICAL AND GENOMIC BASED DECISION SUPPORT SYSTEM TO DEFINE THE OPTIMAL TIMING OF HSCT IN PATIENTS WITH MYELODSYSPLASTIC SYNDROMES

Modelling decisions on IPSS-M vs IPSS-R changed transplantation policy in a signficant proportion of patients:

***19% candidated to immediate HSCT under R IPSS would benefit from a delayed strategy underIPSS M**

***21% candidates to delayed HSCT under R IPSS would benefit from an immediate strategy under IPSS M**

Figure 2. Optimal timing of transplantation in the learning cohort, according to a IPSS-M based-policy.



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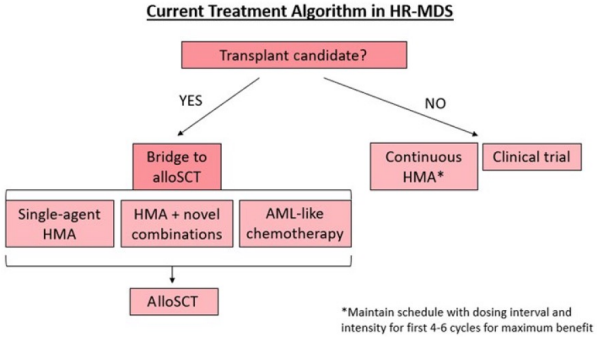
TREATMENT ALGORYTHM IN HIGH RISK MDS BASED ON THERAPIES UNDER DEVELOPMENT



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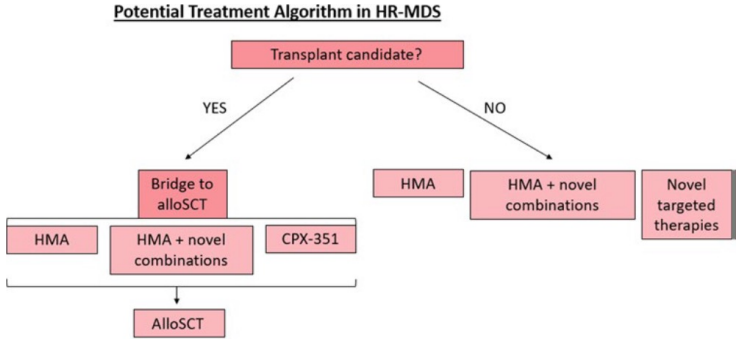

Figure 3. Treatment algorithm for HR-MDS based on therapies under development.

New investigational combinations for higher- risk MDS
Kristin L. Koenig and Uma Borate, http://ashpublications.org/hematology/article-pdf/2022/1/368/2021729/368koenig.pdf by guest on 18 December 2022

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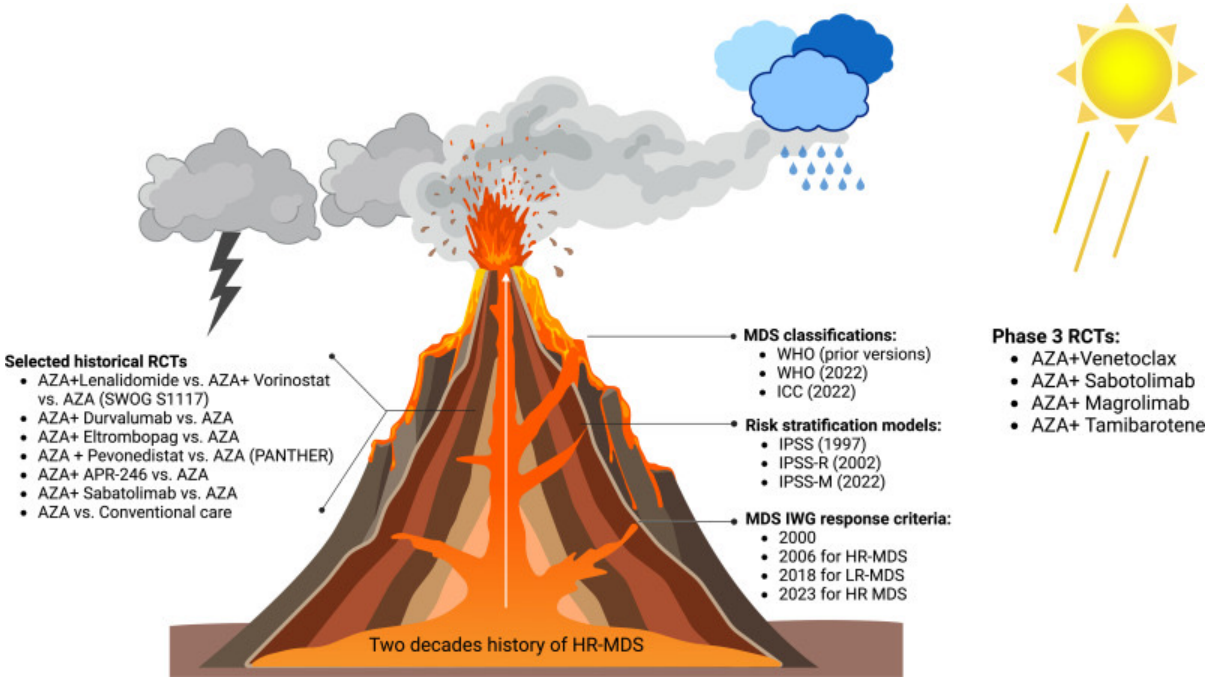

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Potential problems in MDS trials

- Heterogeneous population
- Response assessment (timing, criteria)
- Dose adjustments
- Lack of pre clinical rationale for the combination
- Endpoint definition

- Ongoing phase III trials with
  - sabatolimab,
  - magrolimab,
  - venetoclax,
  - tamibarotene

Trial name	Phase	Investigational arm	Control arm*	Patient population	Eligibility	Primary endpoint	Results of primary endpoint	Secondary endpoint	Reference #
SWOG S1117	2	azacitidine + lenalidomide (10 mg/day days 1–21)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	49% vs 38% ($P = 0.16$)	No improvement in OS	27
SWOG S1117	2	azacitidine + vorinostat (300 mg twice daily on days 3–9)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	27% vs 38%; ($P = 0.16$)	11.6 versus 16.7 months (p=0.74)	27
E1905 Study	2	azacitidine + entinostat (4 mg/m²/day on days 3 and 10)	azacitidine	Therapy-related MDS/AML	Any IPSS	CR, PR, or trilineage HI	17% vs 46%	OS versus 13 months	28
FUSION-AML-001 (MDS Cohort)	2	azacitidine + durvalumab (1500 mg IV q 4 weeks)	azacitidine	Int to very high MDS	IPSS-R int to very high	ORR (CR, mCR, HI)	61.9% vs 47.6% ($P = 0.18$)	No Increase PDL1 on BM Blasts	29
SUPPORT	3	azacitidine + eltrombopag (200 mg/day, up to 300 mg/day)	azacitidine	Int to HR-MDS	int-1, int-2, high IPSS	Platelet transfusion-free interval	16% vs 31% ($P = 0.001$)	ORR 20% vs 35%	25
NCT02610777	2	azacitidine + pevonedistat (20 mg/m² IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	OS	21.8 vs 19.0 months ($P = 0.334$)	EFS 20.2 vs 14.8 months ($p = 0.045$) for HR-MDS	34
NCT03745716	3	azacitidine + eprenetapopt (4.5 g IV days 1–4)	azacitidine	*TP53* mutant HR-MDS	IPSS-R int to very high	CR	34.6% vs 22.4%; $P = 0.13$	NA	NA
PANTHER	3	azacitidine + pevonedistat (20 mg/m² IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	EFS	17.7 months vs 15.7 months ($P = 0.447$)	OS 21.6 vs17.5 (0.293) in HR-MDS	26
STIMULUS-MDS1	2	azacitidine/decitabine + sabatolimab (400 mg day 8 and 22)	azacitidine/ decitabine	Int to very high MDS	IPSS-R int to very high	CR and PFS	PFS 11.1 vs 8.5 months ($P = 0.102$); CR 2[illegible]% vs 17.7% ($P = 0.769$)	Lower risk and <10% blasts with improved PFS	30
STIMULUS-MDS2	3	azacitidine + sabatolimab (800 mg day 8)	azacitidine	Int to very high MDS/CMML-2	IPSS-R int to very high	OS			
ENHANCE	3	azacitidine + magrolimab (priming/loading over C1–2; C3+30 mg/kg days 1 and 15)	azacitidine	Int to very high MDS	IPSS-R int to very high	CR and OS			
VERONA	3	azacitidine + venetoclax (400 mg days 1–14)	azacitidine	Int to very high MDS; excludes t-MDS	IPSS-R int to very high	OS			

*Azacitidine 75 mg/m² in all studies with exception of E19905 study, which used 50mg/m²×10 days).

BM, bone marrow; CMML, chronic myelomonocytic leukemia; HI, hematologic improvement; Int, intermediate; IPSS-R, revised International Prognostic Scoring System; mCR, marrow CR; PR, partial remission.

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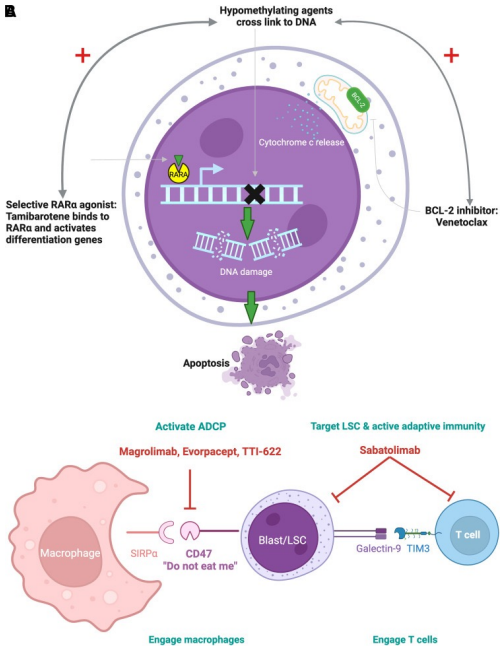
NCT02610777	2	azacitidine + pevonedistat (20 mg/m² IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	OS	21.8 vs 19.0 months ($P = 0.334$)	EFS 20.2 vs 14.8 months ($p = 0.045$) for HR-MDS	34
NCT03745716	3	azacitidine + eprenetapopt (4.5 g IV days 1–4)	azacitidine	*TP53* mutant HR-MDS	IPSS-R int to very high	CR	34.6% vs 22.4%; $P = 0.13$	NA	NA
PANTHER	3	azacitidine + pevonedistat (20 mg/m² IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	EFS	17.7 months vs 15.7 months ($P = 0.447$)	OS 21.6 vs17.5 (0.293) in HR-MDS	26
STIMULUS-MDS1	2	azacitidine/decitabine + sabatolimab (400 mg day 8 and 22)	azacitidine/ decitabine	Int to very high MDS	IPSS-R int to very high	CR and PFS	PFS 11.1 vs 8.5 months ($P = 0.102$); CR 2[illegible]% vs 17.7% ($P = 0.769$)	Lower risk and <10% blasts with improved PFS	30
STIMULUS-MDS2	3	azacitidine + sabatolimab (800 mg day 8)	azacitidine	Int to very high MDS/CMML-2	IPSS-R int to very high	OS			
ENHANCE	3	azacitidine + magrolimab (priming/loading over C1–2; C3+30 mg/kg days 1 and 15)	azacitidine	Int to very high MDS	IPSS-R int to very high	CR and OS			
VERONA	3	azacitidine + venetoclax (400 mg days 1–14)	azacitidine	Int to very high MDS; excludes t-MDS	IPSS-R int to very high	OS			

*Azacitidine 75 mg/m² in all studies with exception of E19905 study, which used 50mg/m²×10 days).

BM, bone marrow; CMML, chronic myelomonocytic leukemia; HI, hematologic improvement; Int, intermediate; IPSS-R, revised International Prognostic Scoring System; mCR, marrow CR; PR, partial remission.

Sallman DA, Xie Z. Frontline treatment options for higher-risk MDS: can we move past azacitidine? **Hematology Am Soc Hematol Educ Program. 2023** Dec 8;2023(1):65-72. doi: 10.1182/hematology.2023000421. PMID: 38066872; PMCID: PMC10727006

FRONTLINE TREATMENT OPTIONS FOR HIGHER-RISK MDS: CAN WE MOVE PAST AZACITIDINE?



3 ongoing studies with sole or co primary endpoint of OS

- STIMULUS-MDS2: phase 3 RCT double blind, comparing aza + **sabatolimab** vs aza + placebo.

Negative readout of phase 2 → focus on LR MDS

- ENHANCE phase 3, double blind, placebo controlled study comparing aza **+ magrolimab** vs aza + placebo → **magrolimab discontinued for MDS patients based on futility**

- VERONA **ongoing** phase 3 double blind placebo controlled RCT comparing **aza + ven vs aza** (ven 400 mg d 1-14)

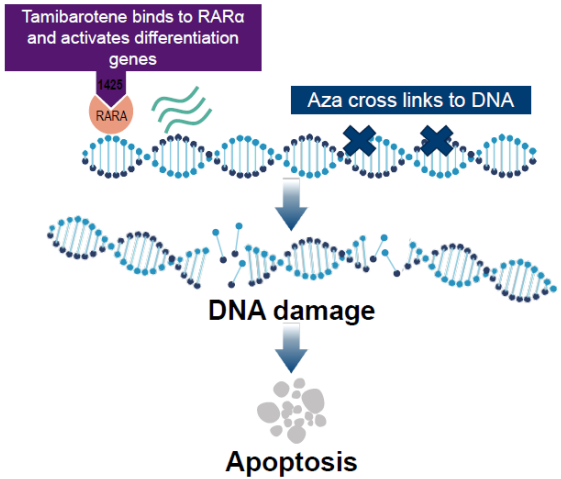
- SYROS ongoing phase 3 double blind placebo controlled RCT **comparing aza vs aza + tamibarotene**

TAMIBAROTENE IN COMBINATION WITH AZACITIDINE

RARA-positive HR-MDS is a novel patient subset with an actionable for treatment with Tamibarotene, an oral, selective RARα agonist

PRECI
for m

- Subset of HR-MDS patients characterized by overexpression of the *RARA* gene[1]
  - Novel blood-based biomarker test identifies patients for treatment with Tamibarotene, with typical 2 to 3-day turnaround time[2]
  - Approximately 30% of HR-MDS patients are RARA-positive[2]
- Single-agent activity of Tamibarotene in R/R HR-MDS[3]
- Preclinical synergy of Tamibarotene with azacitidine (Aza) supported development of the combination in RARA-positive myeloid malignancies[4]
- Tamibarotene/Aza demonstrates high CR rate and rapid onset of responses in RARA-positive newly diagnosed (ND) unfit AML[5]
- Unmet need for new active and well-tolerated therapies in HR-MDS



[1]McKeown, Cancer Discovery 2017; [2]Vigil, ESH 2017; [3]Jurcic, ASH 2017, [4]McKeown, Haematologica 2018; [5]de Botton, ASH 2020

EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH AZACITIDINE FOR THE TREATMENT OF PATIENTS WITH TREATMENT-NAIVE, HIGHER-RISK MYELODYSPLASTIC SYNDROMES –

A phase 1b Study,

- 107 patients with *de novo* treatment-naive HR MDS defined by IPSS-R score of >3, ECOG PS ≤2, BM blasts <20% at baseline
- Ven 400 mg orally daily on Days 1–14 and Aza 75 mg/m^2 intravenously or subcutaneously on Days 1–7 or on Days 1–5, 8, and 9
- Primary objective: CR rate
- Key secondary objectives: marrow CR (mCR), ORR, HI, postbaseline transfusion independence (TI), OS, duration of CR, TTNT, transformation AML and time to AML transformation

Table 1. (A) Baseline Characteristics and (B) Efficacy

(A) Baseline Characteristics	N=107
Median age (range), years	68 (26–87)
Male sex, n (%)	74 (69.2)
ECOG PS, n (%)[a]	
0	56 (52.8)
1	43 (40.6)
2	7 (6.6)
Baseline BM blast category, n (%)	
<5%	11 (10.3)
5–10%	32 (29.9)
>10%	64 (59.8)
Median baseline BM blast count, median % (SD)	11.0 (1.0–19.5)
IPSS-R prognostic score, n (%)	
Low	1 (0.9)
Intermediate	14 (13.1)
High	40 (37.4)
Very high	52 (48.6)
Baseline mutations, n/N (%)	
ASXL1	29/84 (34.5)
TP53	20/84 (23.8)

(B) Efficacy	N=107
Best response, n (%) [95% CI]	
CR	32 (29.9) [21.4–39.5]
mCR	54 (50.5) [40.6–60.3]
ORR (CR + PR)	32 (29.9) [21.4–39.5]
mORR (CR + PR + mCR)	86 (80.4) [71.6–87.4]
HI in patients with mCR, n/N (%) [95% CI]	20/54 (37.0) [24.3–51.3]
Postbaseline transfusion independence, n (%) [95% CI]	
RBC	66 (61.7) [51.8–70.9]
Platelets	77 (72.0) [62.5–80.2]
RBC and platelets	61 (57.0) [47.1– 66.5]
Median OS (95% CI), months	26.0 (18.1–51.5)
Median time to CR (range), months	2.8 (1.0 –16.1)
Median duration of CR (95% CI), months	16.6 (10.0–NR)
MDS to AML transformation, n/N (%) [95% CI]	13/106 (12.3) [6.7–20.1]
Median time to AML transformation (range), months	5.95 (0.72-29.31)
Median TTNT[b] (95% CI), months	6.8 (5.6–8.3)

[a]ECOG PS for 1 patient is missing. [b]TTNT defined as time from first dose of study drug to start of post-study systemic cancer therapy or post-study transplantation.

AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; HI, hematologic improvement; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; mCR, marrow complete remission; mORR, modified overall response rate; NR, not reached; ORR, overall response rate; OS, overall survival; PR, partial remission; RBC, red blood cell; SD, standard deviation; TTNT, time to next treatment.

CR 30%
mCR 50%

Jacqueline S. Garcia,, Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study, Blood, Volume 136, Supplement 1, 2020, Pages 55-57, ISSN 0006-4971, https://doi.org/10.1182/blood-2020-139492.

TAKE HOME MESSAGES AND KEY POINTS

- Clinical and therapeutical implications of molecular and genomic data

- Better (molecular) stratification → improvement of choice and timing for allo-HSCT

- Disappointing results for aza combination therapies, still pending results for venetoclax (VERONA trial) and tamibarotene

Thank you for your kind attention