

Maximizing Success: Optimizing Prognostication and Timing of Allogeneic Stem Cell Transplant for MDS

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MDS Foundation Talk

DISCLOSURE

- I have the following financial relationships:
 - Advisory Board: Takeda Pharmaceuticals North America, Inc.
 - Consultant: Amgen
 - Research Committee: Millenium, Prometheus Labs

Case

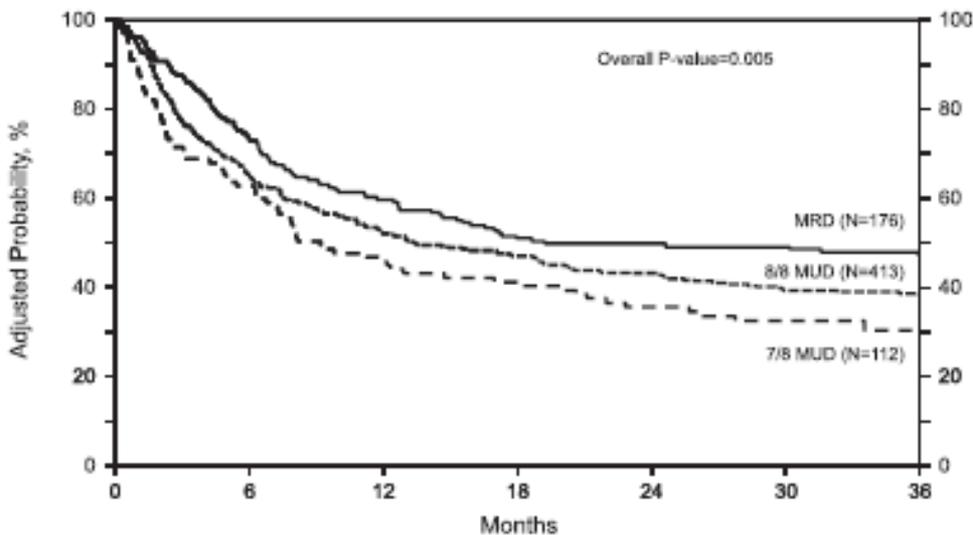
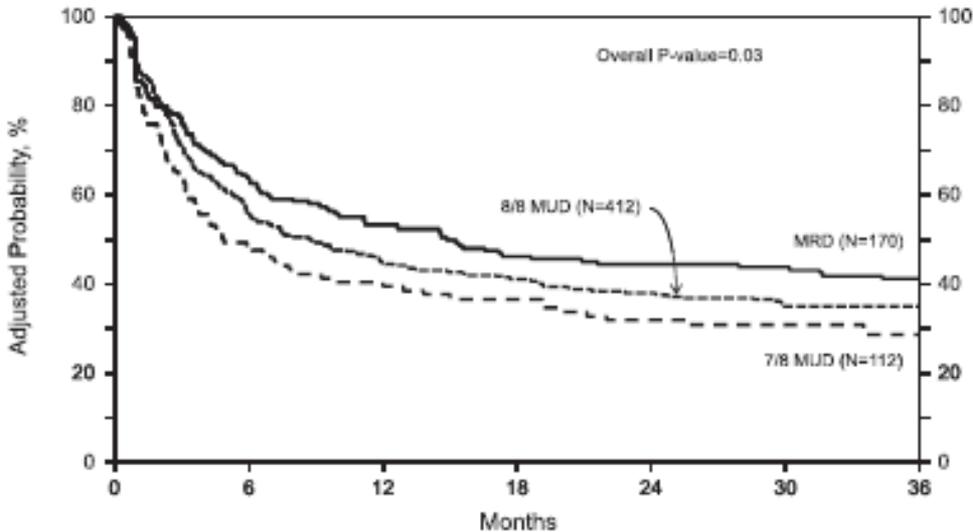
- 61 year old woman with no chronic illnesses
- Presents with new onset fatigue; physical examination unremarkable
 - WBCs 4.2 K/mm³ (normal diff)
 - Hb 8.9 gm/dL (MCV 102, low retic count)
 - Plts 130 K/mm³
 - Chemistries unremarkable
- Bone marrow examination:
 - 70% cellularity
 - Dysplastic erythrocytes and megakaryocytes
 - Normal iron stores
 - Diagnosis: Myelodysplastic Syndrome

Question 1

- What essential additional information is needed to stage the disease prior to treatment recommendations (including transplant)?
 - a. Blast count and cytogenetics
 - b. Flow cytometry
 - c. Mutational panel
 - d. All of the above

What's the evidence
transplant can help?

Impact of Transplantation in MDS

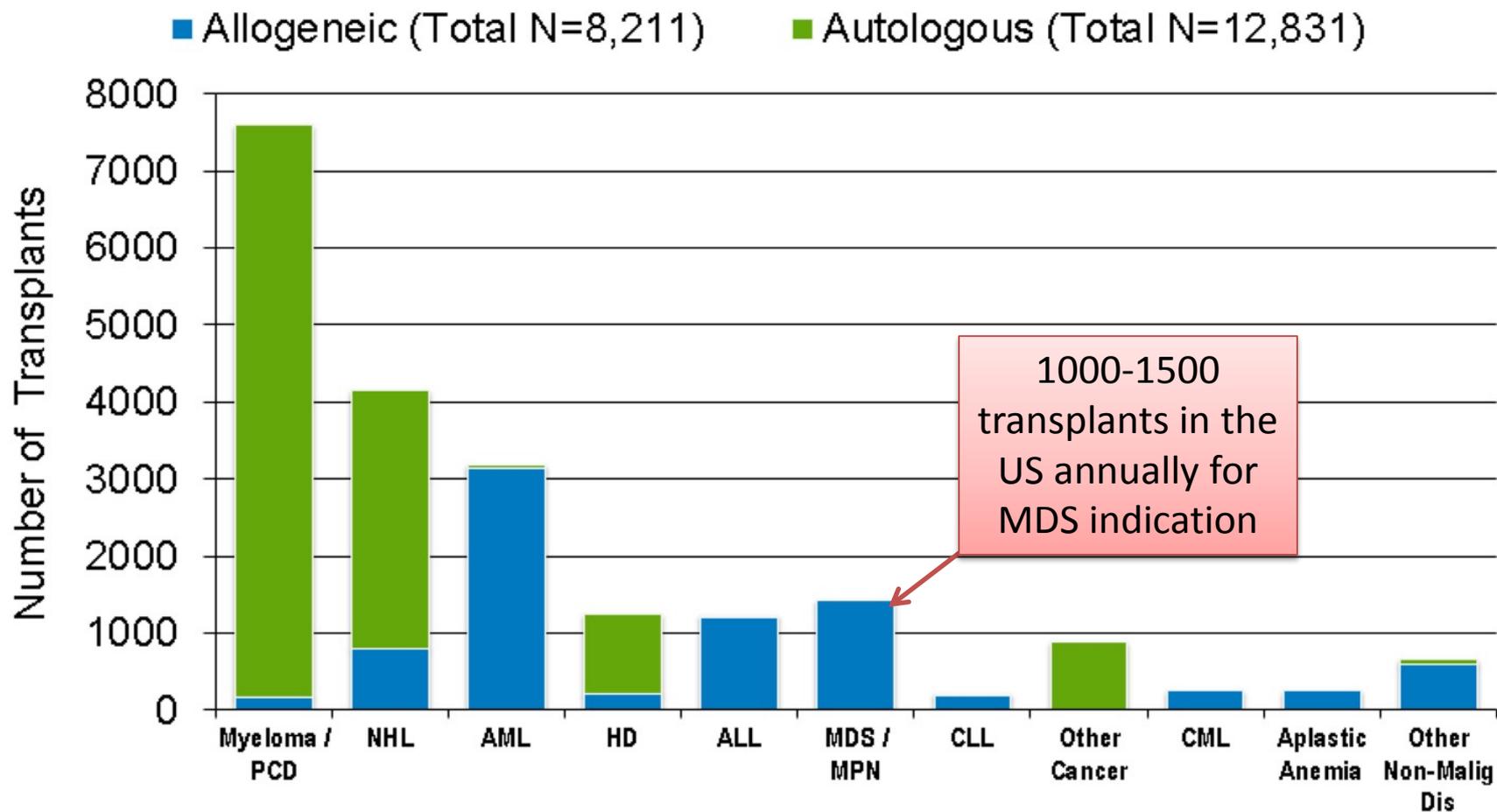


• Saber, et al reviewed outcomes for adult MDS patients (age ≥ 21 yrs) undergoing HSCT from 2002-2006 (n=701)

- ✓ Predominantly de-novo MDS
- ✓ 2/3rds had 'advanced MDS': RAEB/RAEB-T/CMML
- ✓ 60% received myeloablative conditioning (MAC) HSCT
- ✓ Conclusions:

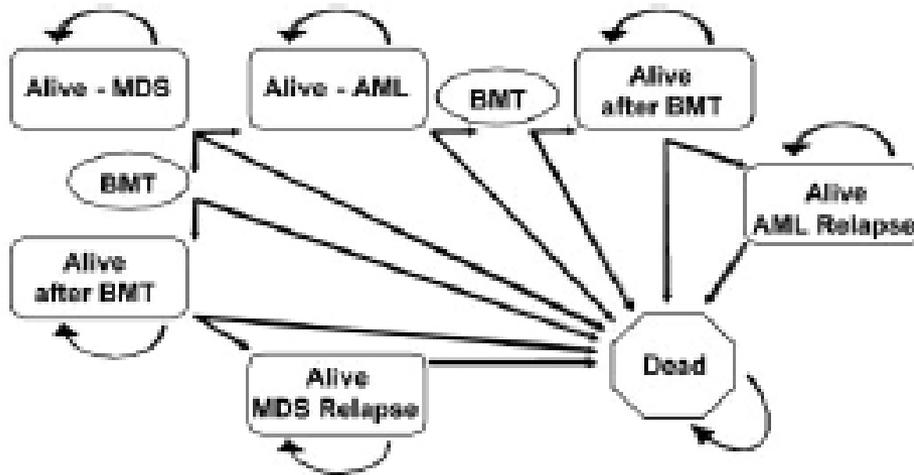
- Durable long-term DFS, OS is achievable, indicating cure of MDS is feasible
- 8/8 HLA-matched sibling and unrelated donors have comparable outcomes
- 7/8 HLA-matched unrelated donors have impaired outcomes

Indications for Hematopoietic Cell Transplant in the US, 2014



When to transplant MDS
patients?

Timing of Transplantation: Younger MDS



Cutler, et al sought to address timing of MAC HSCT for younger MDS patients (age <60 yrs)

- ✓ Multi-state Markov Model of life expectancy after MAC transplantation vs. Non-transplantation therapy, stratified by MDS risk (IPSS)
 - Low/Int-1 IPSS: MAC HSCT vs. BSC
 - Int-2/High: MAC HSCT vs. BSC
 - Survival adjusted for quality-of-life
 - Sensitivity analyses to confirm robustness of conclusions

Figure 1. Markov decision model. All patients began alive in the Alive-MDS state and were able to transition after each 6-month cycle to other health states. Patients could have remained in an alive state for any number of cycles without transitioning to another health state. The BMT state was transitory and all subjects entering the BMT state transitioned to another health state by the end of the cycle. MDS indicates myelodysplastic syndrome; AML, acute myelogenous leukemia; BMT, bone marrow transplantation.

Timing of Transplantation: Younger MDS

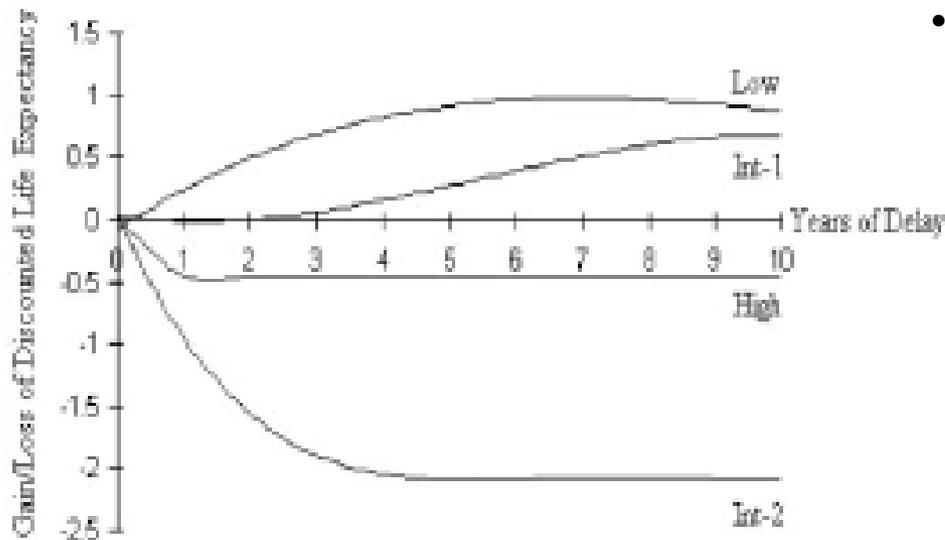


Figure 3. Net benefit or loss of overall discounted life expectancy for the 4 IPSS risk groups are shown above and below the x-axis. A net benefit for delaying transplantation is noted for low and Int-1 risk groups, whereas any delay in the time to transplantation is associated with a loss in survivorship in the higher risk groups.

- Cutler, et al sought to address timing of RIC HSCT for younger MDS patients (age <60 yrs) receiving MAC HSCT
 - ✓ Multi-state Markov Model of life expectancy after MAC transplantation vs. Non-transplantation therapy (BSC), stratified by MDS risk (IPSS)
 - Low/Int-1 IPSS: Life expectancy benefit with strategy of deferred HSCT (but prior to AML)
 - Int-2/High: Life expectancy benefit with strategy of upfront HSCT
 - Survival adjusted for quality-of-life
 - Sensitivity analyses to confirm robustness of conclusions

Timing of Transplantation: Younger MDS

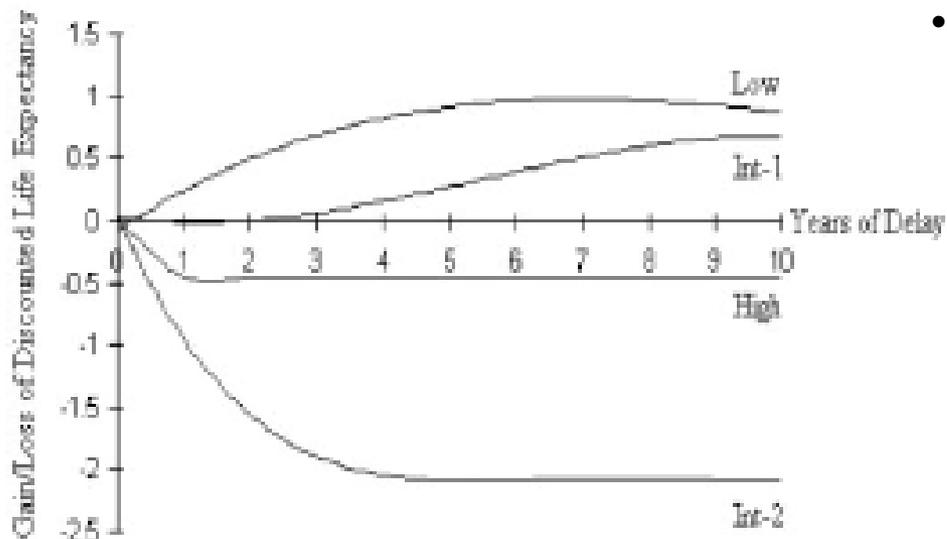
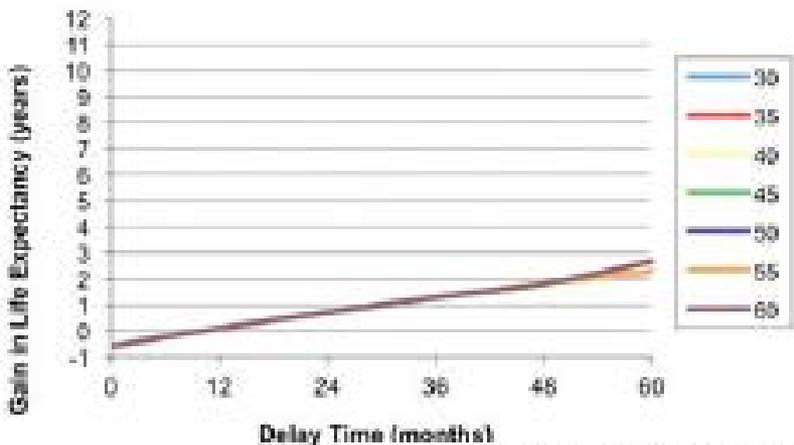


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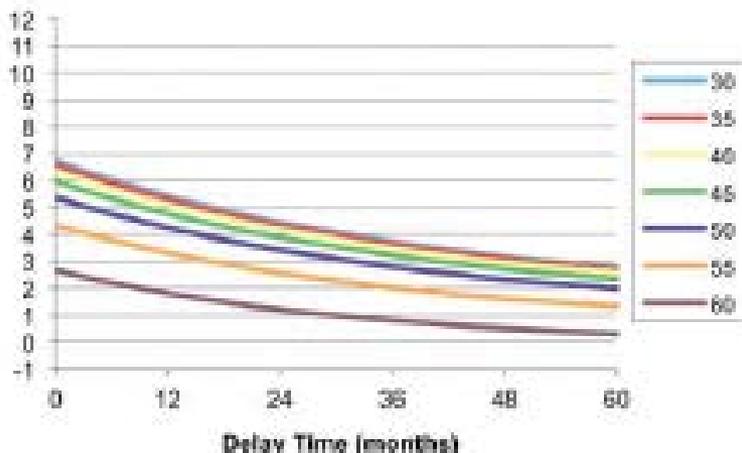
- Cutler, et al sought to address timing of RIC HSCT for younger MDS patients (age <60 yrs) receiving MAC HSCT
 - ✓ Multi-state Markov Model of life expectancy after MAC transplantation vs. Non-transplantation therapy (BSC), stratified by MDS risk (IPSS)
 - Caveats:
 - 1. Only IPSS at diagnosis considered, but what about MDS progression?
 - 2. Transplantation and non-transplantation datasets relatively outdated.

Timing of Transplantation: Younger MDS

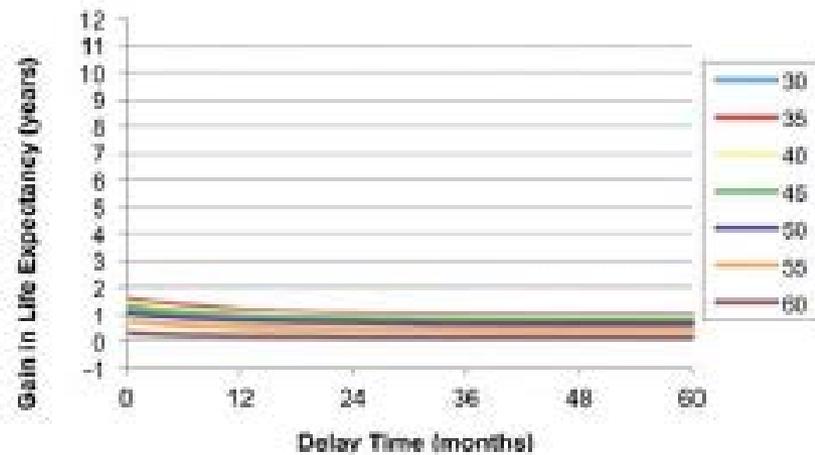
Policy 1: low IPSS



Policy 2: intermediate-1 IPSS



Policy 3: intermediate-2 IPSS



- Alessandrino, et al sought to readdress timing of MAC HSCT for younger MDS patients (age <65 yrs)
 - ✓ Multi-state Markov Model of life expectancy after MAC transplantation vs. Non-transplantation therapy (BSC) after MDS diagnosis.
 - Strategy 1: Transplant in low-risk MDS (varying time points after diagnosis) vs. BSC
 - Strategy 2: Transplant in Int-1 IPSS MDS (varying time points after progression) vs. BSC
 - Strategy 3: Transplant in Int-2 IPSS MDS (varying time points after progression) vs. BSC.

Timing of Transplantation: Older MDS

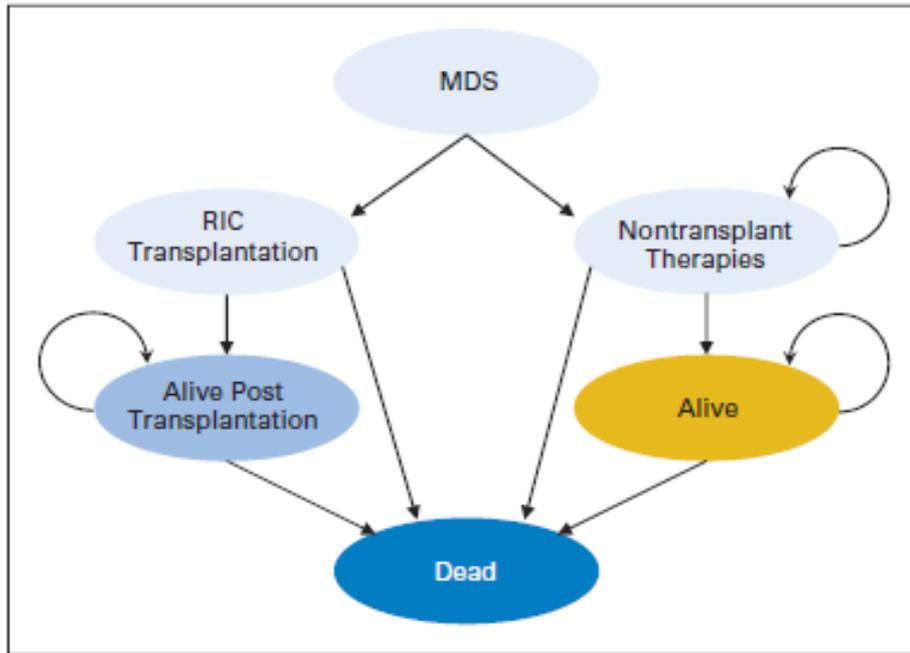
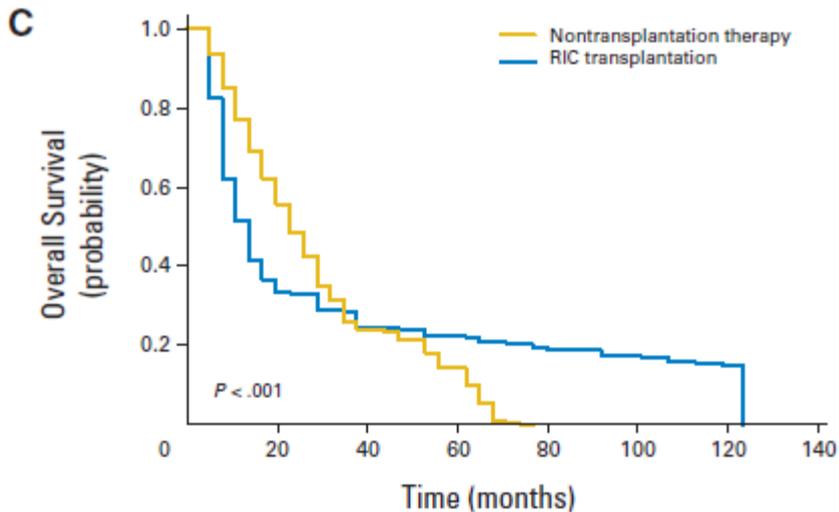
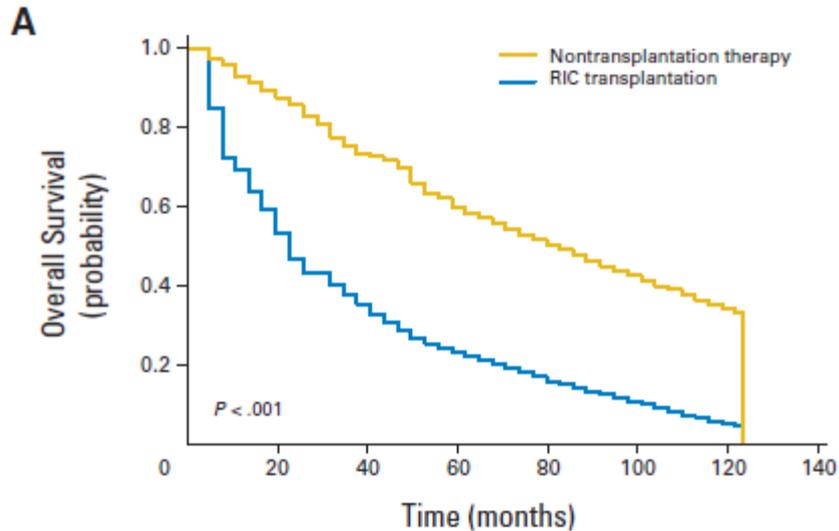


Fig 1. Markov decision model. All patients (stratified by risk state into low/intermediate-1 International Prognostic Scoring System [IPSS; model A] or intermediate-2/high IPSS [model B]) began in the “alive with MDS” state and were able to transition after each 3-month cycle to other health states as indicated. The reduced-intensity conditioning (RIC) transplantation state was transitory, and all patients entering the transplantation state transitioned to another health state by the end of the cycle. MDS, myelodysplastic syndromes.

- Koreth, et al sought to address timing of RIC HSCT for older MDS patients (age 60-70 yrs)
 - ✓ Multi-state Markov Model of life expectancy after RIC transplantation vs. Standard-of-care non-transplantation therapy, stratified by disease risk (IPSS)
 - Low/Int-1 IPSS: RIC HSCT vs. BSC, growth factors
 - Int-2/High: RIC HSCT vs. hypomethylating agents
 - Survival adjusted for quality-of-life
 - Sensitivity analyses to confirm robustness of conclusions

Timing of Transplantation: Older MDS

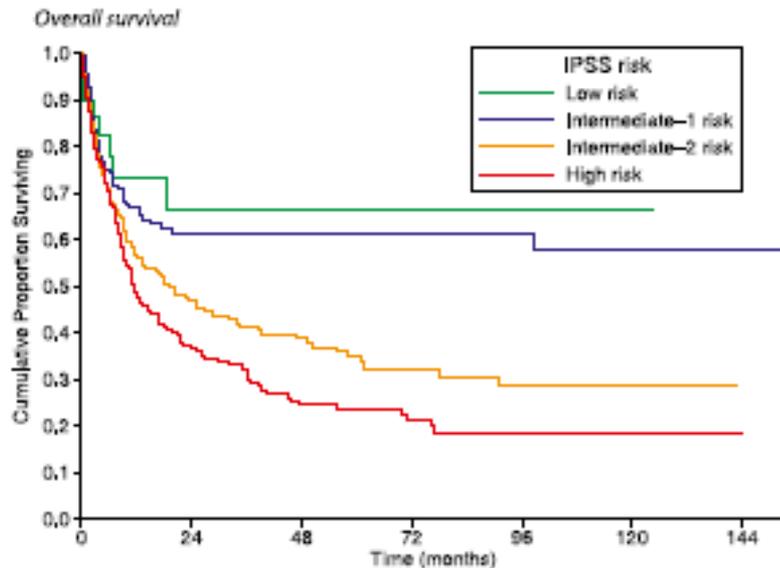
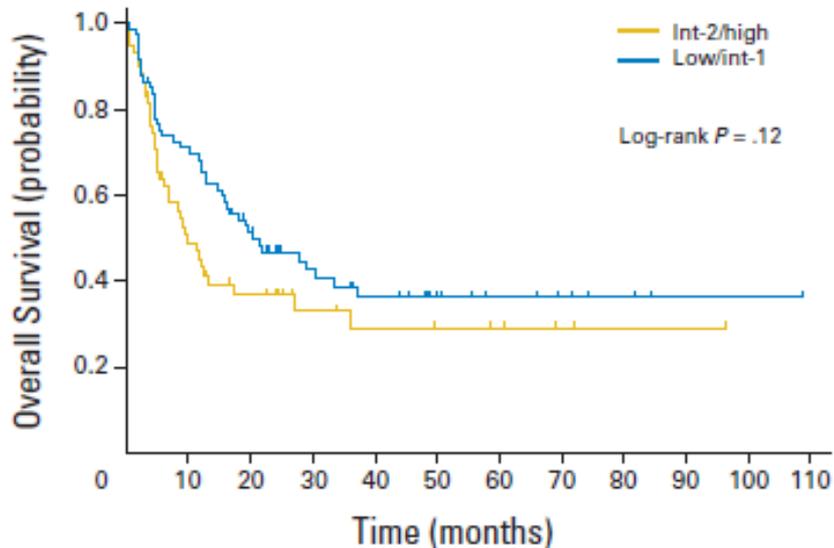


- Conclusions:

- ✓ Multi-state Markov Model of life expectancy after RIC transplantation vs. Standard-of-care non-transplantation therapy, stratified by disease risk (IPSS) in older MDS patients (60-70 yrs)

- Low/Int-1 IPSS: RIC HSCT offer no life expectancy benefit vs. BSC, growth factors
- Int-2/High: RIC HSCT offers life expectancy benefit vs. hypomethylating agents
- Survival adjusted for quality-of-life does not change the conclusions
- Sensitivity analyses confirm robustness of conclusions.

Timing of Transplantation: Older MDS



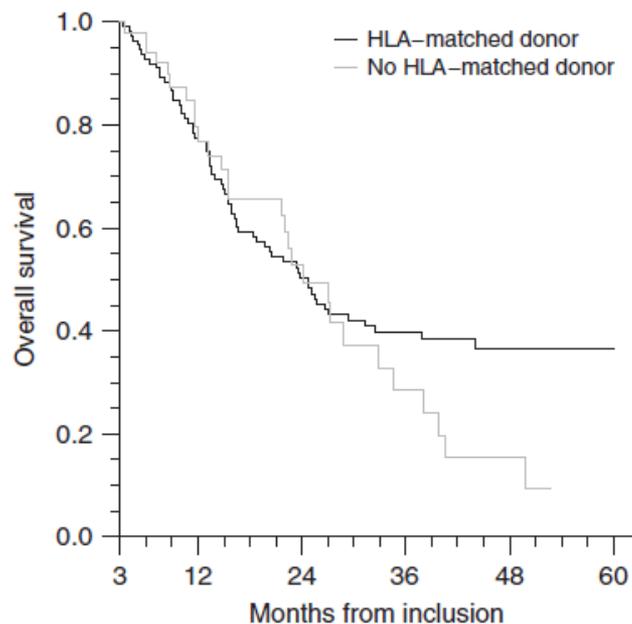
- Caveats:

- ✓ Multi-state Markov Model of life expectancy after RIC transplantation vs. Standard-of-care non-transplantation therapy, stratified by disease risk (IPSS)

- Retrospective analyses remain susceptible to bias and confounding
- Detailed information on MDS progression unavailable, analysis based on MDS IPSS risk pre-HSCT.
- Conclusions derived from cohort survival in the underlying datasets

Is there MDS transplant data
beyond decision models?

Transplant vs. Non-transplant therapy in MDS: Prospective Data-I



No. at risk:

	3	12	24	36	48	60				
HLA-matched donor	112	85	63	50	39	33	23	14	8	5
No matched donor	50	29	21	15	8	6	3	2	0	0

Variable	HR (95% CI)	P
< 1 year after HSCT	1.07 (0.60–1.91)	0.82
1–2 year after HSCT	0.69 (0.28–1.69)	0.31
> 2 years after HSCT	0.024 (0.003–0.22)	0.0009

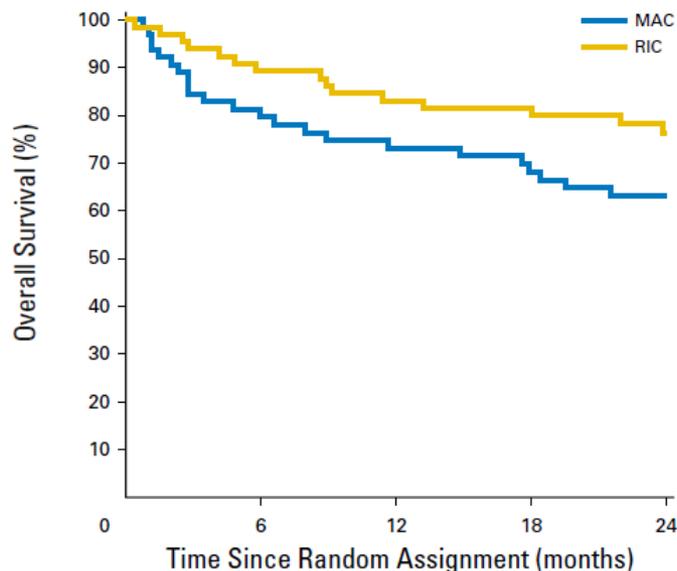
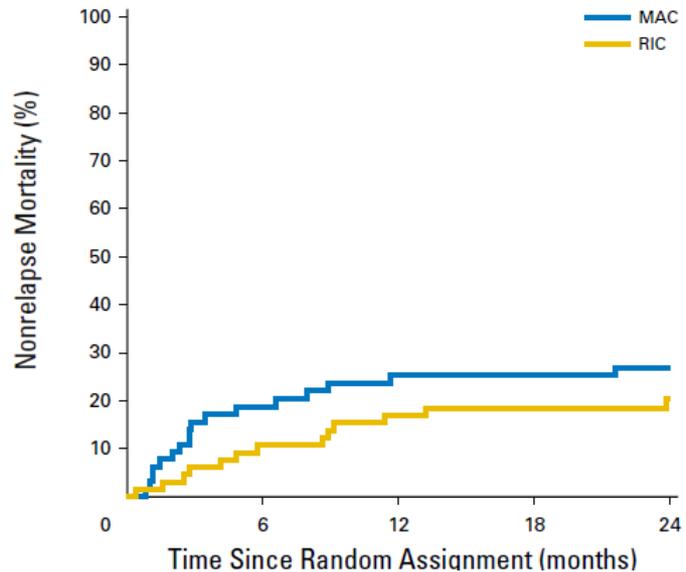
Abbreviations: CI, confidence interval; HR, hazards ratio; HSCT, hematopoietic stem cell transplantation.

- Robin, et al for the SFGM-TC and GFM, prospectively evaluated outcomes of older patients (age 50-70 yrs) with 'de-novo or t-MDS' with available HLA-matched donor (n=112) vs. no donor (n=50)
 - ✓ 'de-novo or t-MDS': int-2/high IPSS (or int-1 with higher-risk: poor-risk karyotype, platelet transfusion dependent), CMML (WBC>12k; Splenomegaly; Cytopenias) (~84% Int-2/High IPSS MDS)
 - ✓ Bu/Flu/ATG RIC HSCT with CyA/MMF GVHD PPx
 - ✓ Cohorts broadly comparable: HSCT group not significantly younger (60 vs. 61 yrs), with similar time since diagnosis, IPSS and IPSS-R risk, and % BM blasts.
- ✓ Conclusions:
 - No HSCT benefit in year 1, 2
 - Significant OS benefit after year 2 (p=0.0009)

Transplant vs. Non-transplant therapy in MDS: Prospective Data-II

- A German study is assigning newly diagnosed MDS patients to HSCT vs. non-HSCT therapy on the basis of donor availability
 - ✓ Accrual goal: 230 MDS patients aged 55-70 yrs
 - ✓ Higher-risk MDS: Int-1 with poor risk cytogenetics, Int-2, or High-risk IPSS
 - ✓ All subjects will initiate AZA therapy for 4-6 cycles
 - ✓ Biologic assignment to RIC HSCT based on donor availability: HLA-matched sibling, MUD; vs. continued AZA for no-donor subjects.
 - ✓ Powered to 3-year OS difference of 50% vs. 30%
 - ✓ NCT014044741
- A BMT-CTN study (1102) is enrolling diagnosed MDS patients to HSCT vs. non-HSCT therapy on the basis of donor availability
 - ✓ Accrual goal: 400 de-novo MDS patients aged 50-75 yrs
 - ✓ Higher-risk MDS: Int-2 or High-risk IPSS
 - ✓ Prior therapy optional
 - ✓ Biologic assignment to RIC HSCT based on donor availability: HLA-matched sibling or MUD; vs. HMA/BSC for no-donor subjects.
 - ✓ Primary endpoint: 3-year OS
 - ✓ NCT02016781

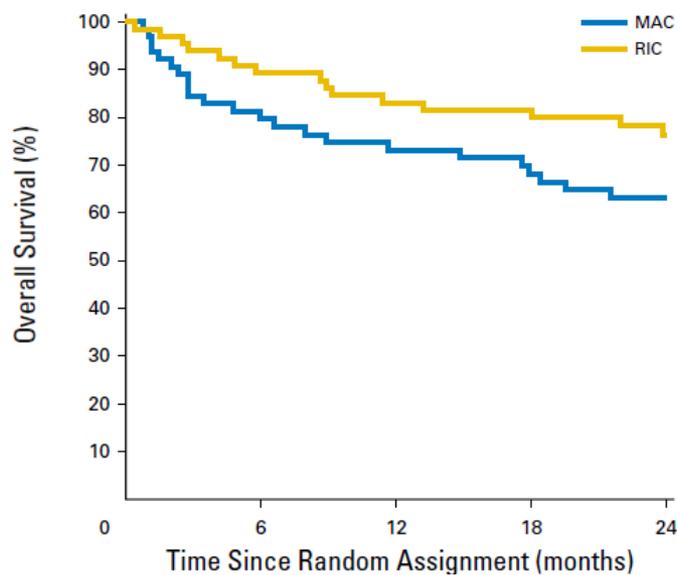
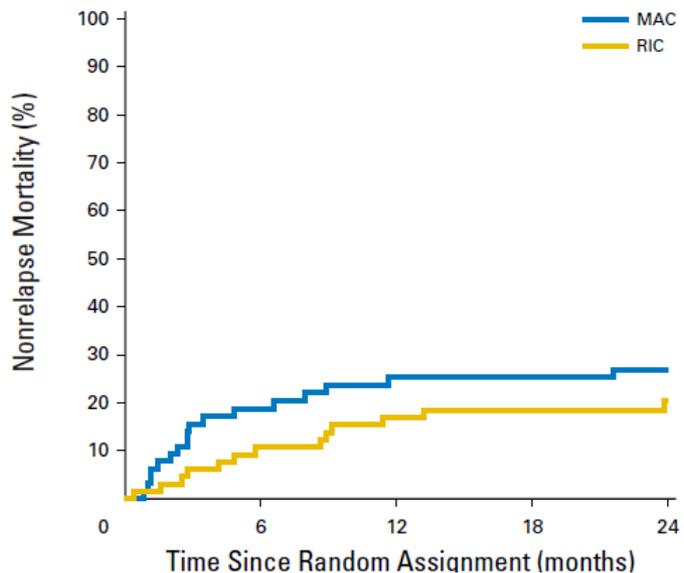
Transplant Intensity in MDS: RCT Data



- Kroger, et al randomized MDS and sAML patients to RIC vs. MAC HSCT
 - ✓ Ph III trial of 129 patients, median age 50 years (range 19-64), randomized to Bu/Flu RIC vs. Bu/Cy MAC HSCT with 7-8/8 HLA matched donors and CyA/Mtx GVHD prophylaxis
 - ✓ Primary endpoint: 1 year NRM
 - ✓ Secondary endpoints included 2-year EFS and OS
 - ✓ Conclusions:
 - NRM was not worse for MAC vs. RIC
 - Relapse was not increased for RIC vs. MAC.
 - OS was not different between RIC vs. MAC (p=0.08), though in MVA RIC associated with improved survival

Overall survival		
RIC	0.41 (0.19 to 0.87)	.02
Cytogenetics		< .001
Low risk	6.06 (1.69 to 21.80)	.005
High risk	4.51 (1.28 to 15.86)	.02
ECOG > 0	2.32 (0.99 to 5.43)	.05
Advanced disease	2.26 (0.95 to 5.39)	.06

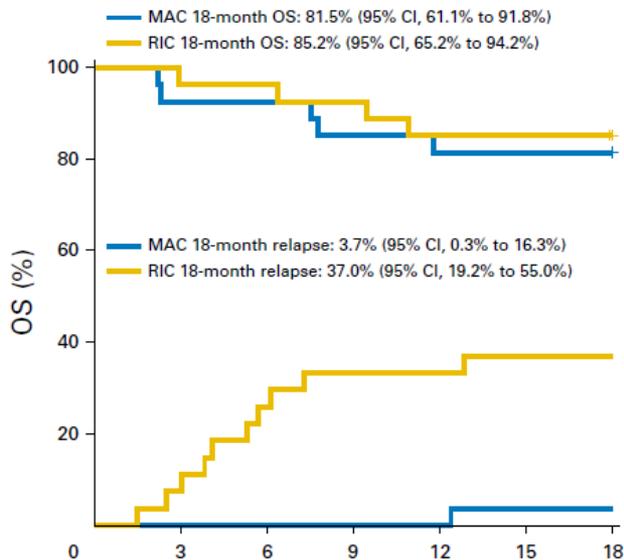
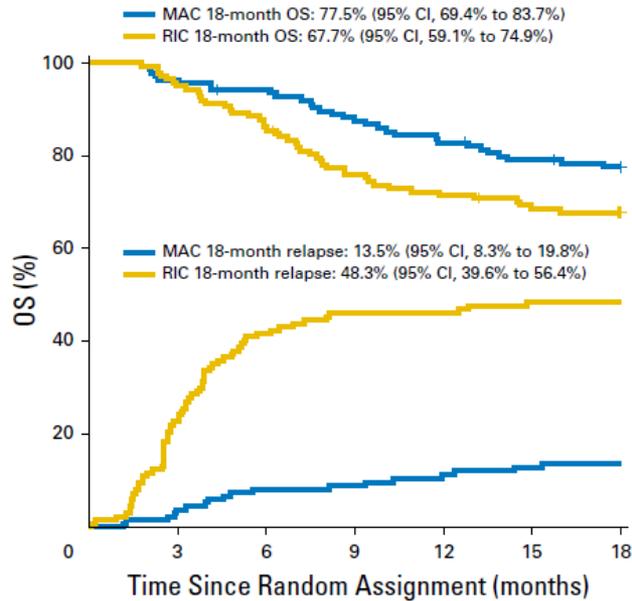
Transplant Flavor in MDS: RCT Data



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 - Caveat, BMTCTN 0902

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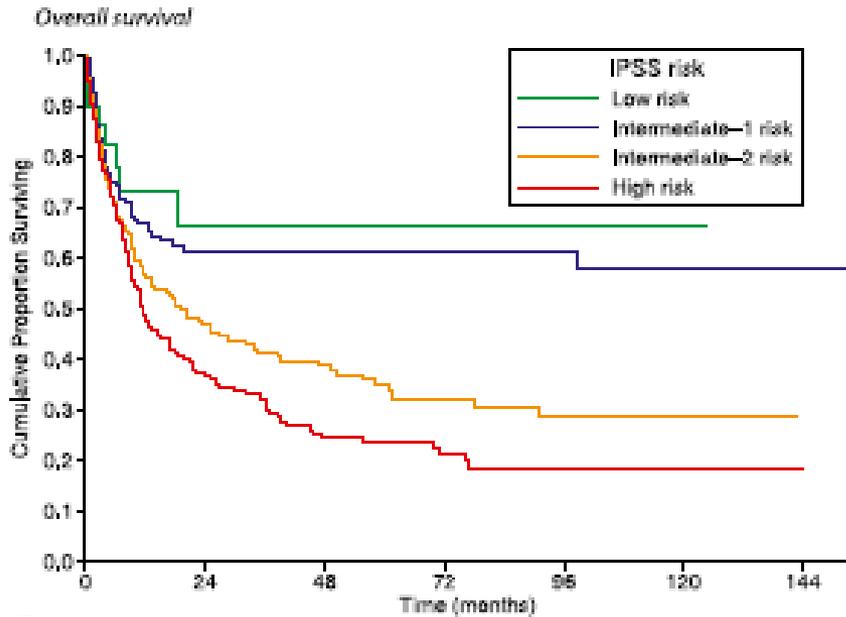
Transplant Flavor in MDS: RCT Data



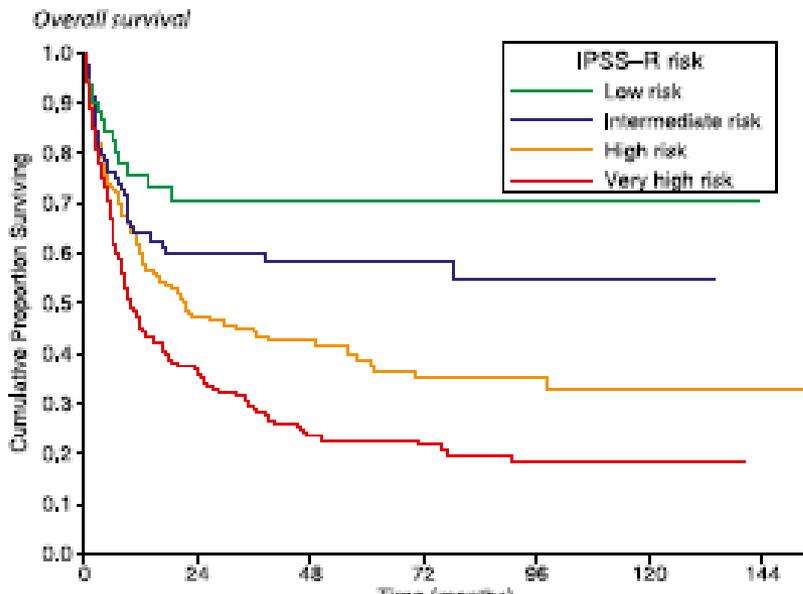
- Scott, et al randomized AML and MDS patients with <5% BM blasts to RIC vs. MAC HSCT (BMTCTN 0902)
 - ✓ Phase III trial of 272 patients, median age 55 years (range 22-66), randomized to Bu/Flu or Flu/Mel RIC vs. Bu/Flu or Bu/Cy or Cy/TBI MAC HSCT with 7-8/8 HLA matched donors and CNI/Mtx or CNI/Sir or CNI/MMF GVHD prophylaxis
 - ✓ Primary endpoint: 18 month OS
 - ✓ Secondary endpoints included RFS, TRM and relapse
 - ✓ Conclusions:
 - Relapse risk increased for RIC vs. MAC overall, and for the MDS subgroup (~20%)
 - OS was not different for RIC vs. MAC
 - MAC may be preferred for younger fitter patients where feasible

Novel MDS predictors
relevant to transplant?

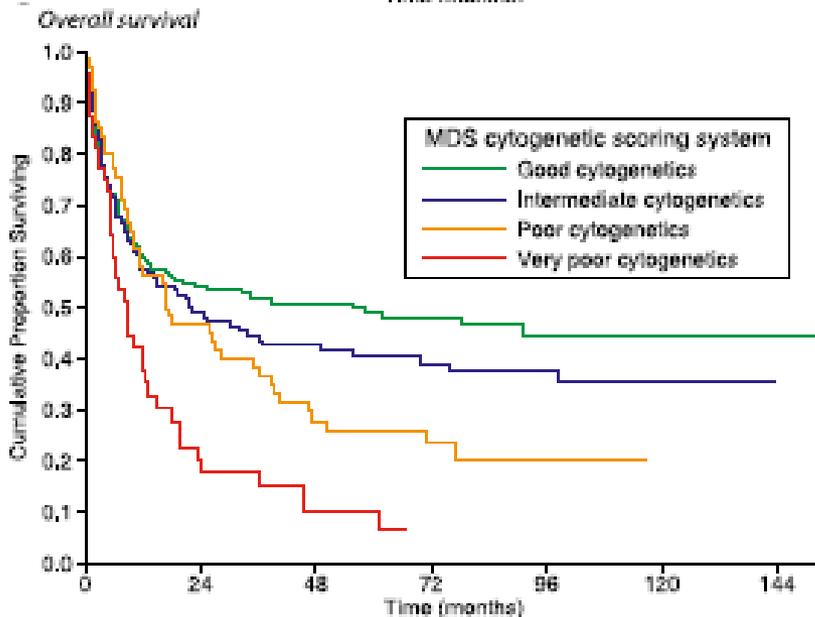
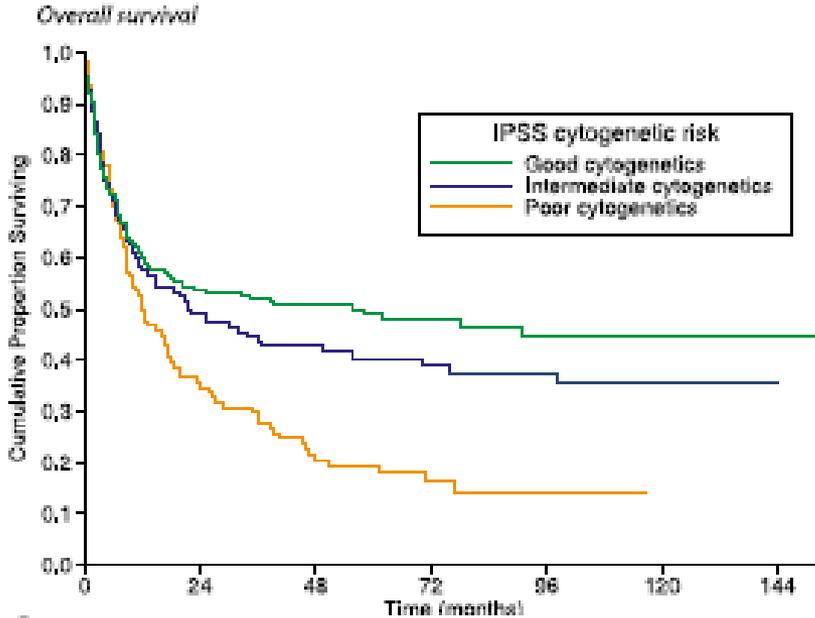
Transplant in MDS: IPSS-R



- Della Porta, et al reviewed HSCT outcomes for IPSS vs. revised IPSS-R risk groups
 - ✓ Cohort of MDS (n=374) and 'oligoblastic AML' (n=145) staged per IPSS and IPSS-R at time of upfront HSCT or pre-HSCT therapy
 - ✓ 2/3rd received myeloablative conditioning (MAC) HSCT
 - ✓ Conclusions:
 - Both IPSS and IPSS-R predicted survival and relapse post-HSCT



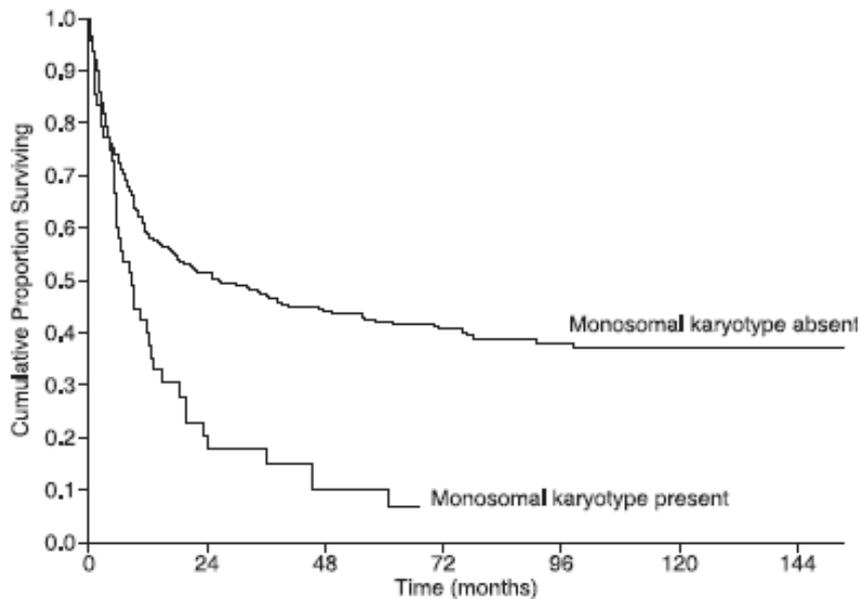
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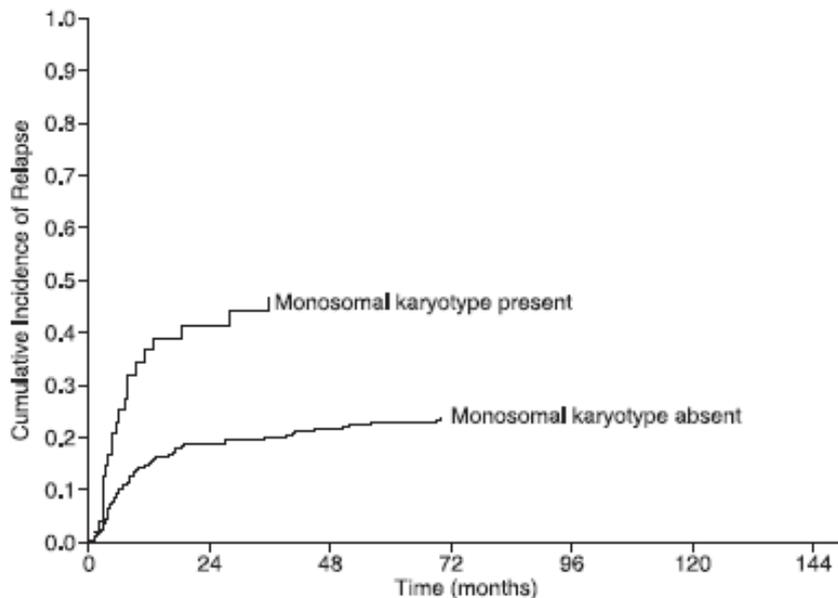
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 - ✓ 2/3rd received myeloablative conditioning (MAC) HSCT
 - ✓ Conclusions:
 - Both IPSS and IPSS-R predicted survival and relapse post-HSCT
 - Cytogenetic risk via IPSS and IPSS-R also predicted survival and relapse post-HSCT

Transplant in MDS: IPSS-R

A Overall survival



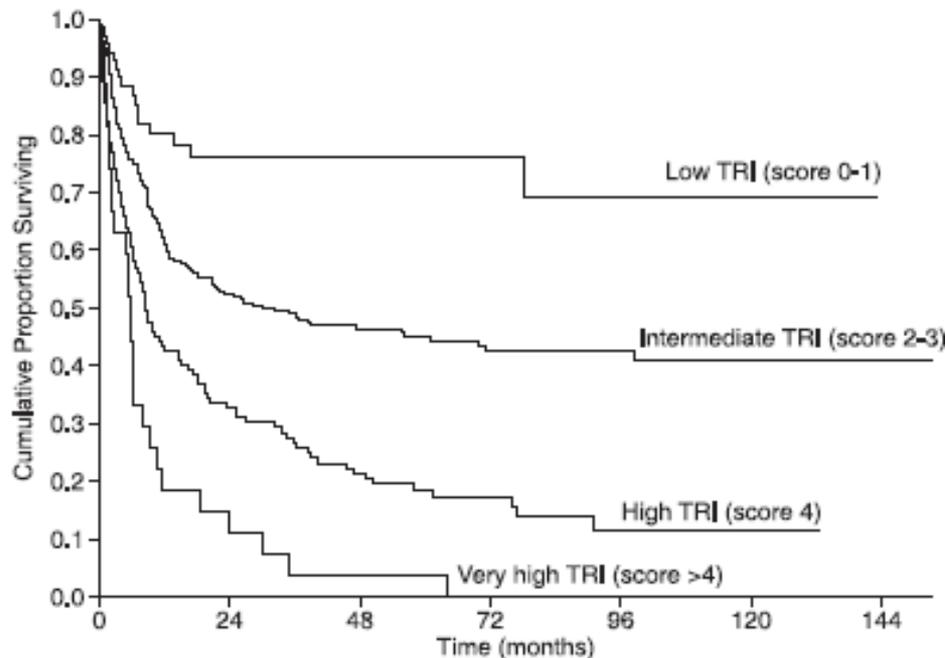
B Cumulative incidence of relapse



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 - Cytogenetic risk via IPSS and IPSS-R predicted survival and relapse post-HSCT
 - Monosomal Karyotype independently predicted survival and relapse post-HSCT

Transplant in MDS: IPSS-R

B Posttransplantation outcome according to TRI



- Della Porta, et al reviewed HSCT outcomes for IPSS vs. revised IPSS-R risk groups

- ✓ Cohort of MDS (n=374) and 'oligoblastic AML' (n=145) staged per IPSS and IPSS-R at time of upfront HSCT or pre-HSCT therapy

- ✓ 2/3rd received myeloablative conditioning (MAC) HSCT

- ✓ Conclusions:

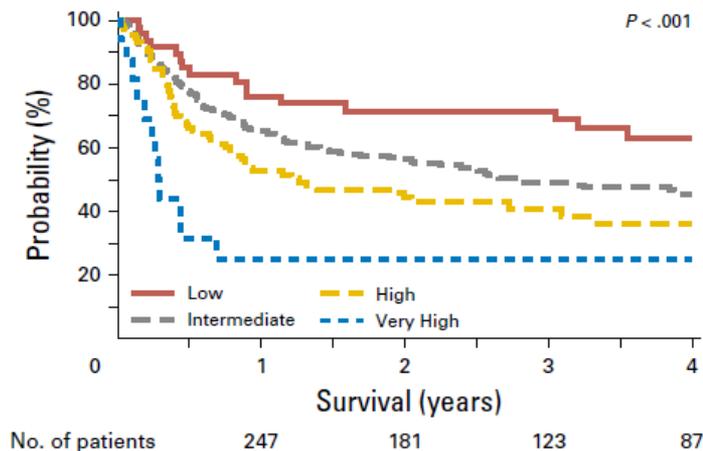
- Both IPSS and IPSS-R predicted survival and relapse post-HSCT
- Cytogenetic risk via IPSS and IPSS-R predicted survival and relapse post-HSCT
- Monosomal Karyotype independently predicted survival and relapse post-HSCT
- MDS transplantation risk Index was derived

Prognostic variable	Score values			
	0	1	2	3
Age, yr	<50	≥50	-	-
IPSS-R	low	intermediate	high	very high
Monosomal karyotype	no	yes	-	-
HCT-CI	low/intermediate	high	-	-
Refractoriness to induction chemotherapy	no	yes	-	-

Transplant in MDS: CIBMTR Risk Index

Factor	No. of Patients	HR for Death (95% CI)	P
Patient age, years			.003
18-29	77	1 (reference)	
30-49	289	1.60 (1.09 to 2.35)	
≥ 50	785	1.93 (1.36 to 2.83)	
KPS, %			.014
90-100	702	1 (reference)	
< 90	386	1.25 (1.06 to 1.28)	
Cytogenetics			< .001
Very good, good, or intermediate	720	1 (reference)	
Poor or very poor	149	1.43 (1.14 to 1.80)	
MK	195	2.01 (1.65 to 2.45)	
Blood blast before HCT, %			.005
≤ 3	877	1 (reference)	
> 3	89	1.41 (1.08-1.85)	
Platelet count before HCT, × 10 ⁹ /L			< .001
> 50	658	1 (reference)	
≤ 50	489	1.37 (1.18 to 1.61)	

- Shaffer, et al reviewed CIBMTR HSCT outcomes to derive novel HSCT-specific risk groups
 - ✓ Training cohort of MDS (n=1,151) and Validation cohort (n=580) staged per IPSS at dx, karyotype, pre-transplant therapy (HMA, IC, BSC), labs (CBC, BMBx, LDH), PS, HSCT variables (Conditioning intensity, Graft type (PB, BM), ATG, Donor type, KPS etc)
 - ✓ 58% received myeloablative conditioning (MAC) HSCT
 - ✓ Conclusions:
 - Prior MDS therapy was not a significant variable in the model
 - HSCT Conditioning intensity was not a significant variable in the model
 - MK was an independent high risk variable
 - IPSS, IPSS-R, and CIBMTR Risk Index predicted survival, NRM and relapse post-HSCT



Risk Group	Validation Cohort		
	No. of Patients	HR (95% CI)	P
Low (0-1)	47	1.00	
Intermediate (2-3)	258	1.66 (1.01 to 2.71)	.045
High (4-5)	104	2.29 (1.35 to 3.87)	.002
Very high (≥ 6)	18	5.02 (2.48 to 10.15)	< .001
Overall <i>P</i> *			< .001

Transplant in MDS: Genomic Mutations

- Bejar, et al reviewed outcomes of MDS mutation analysis in an HSCT cohort

- ✓ Cohort of MDS patients (n=87) pre-HSCT BM/PB for mutations in 40 MDS-associated genes

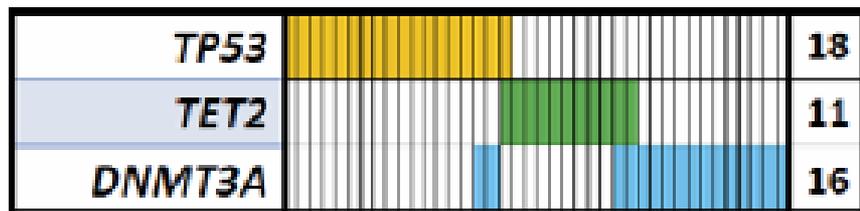
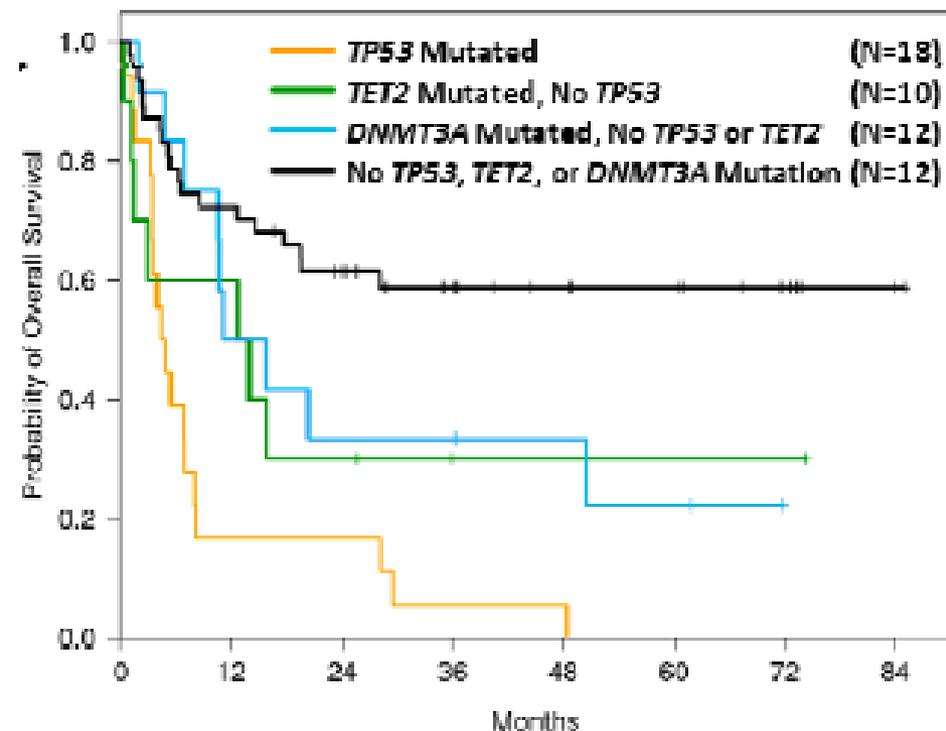
- ✓ 71% received RIC HSCT

- ✓ Evaluated for association of mutations with clinical variables including OS

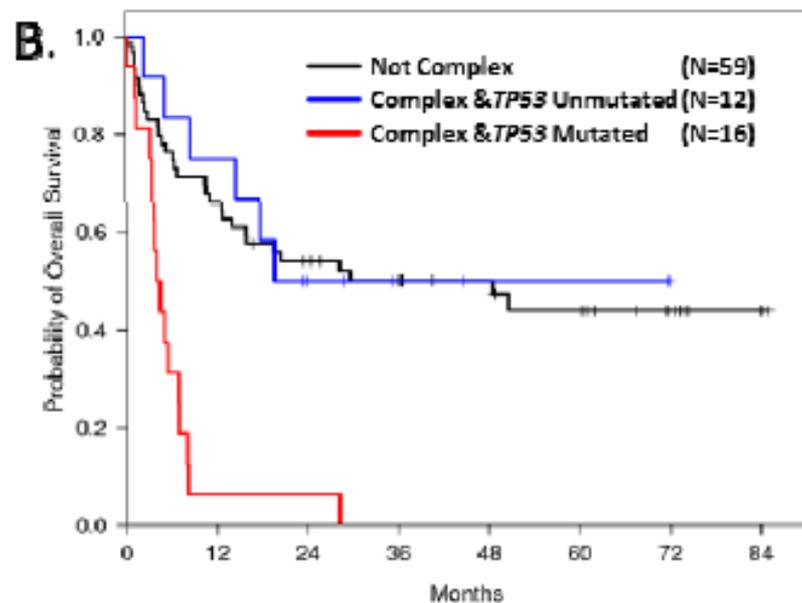
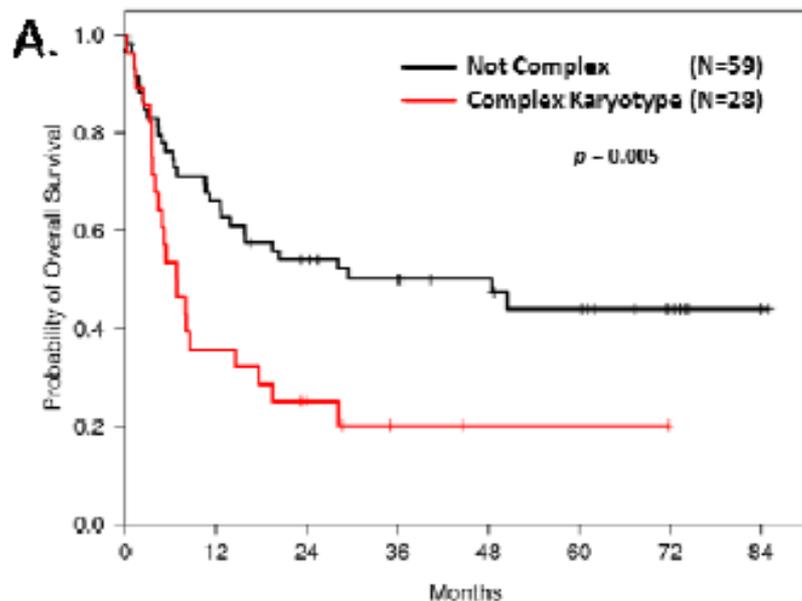
- ✓ Conclusions:

- 92% of patients had ≥ 1 mutations (ASXL1 29%, TP53 21%, DNMT3A 18%, RUNXI 16%)

- Mutations in TP53, TET2, and/or DNMT3A involved 47% of patients, were largely non-overlapping, and associated with impaired survival

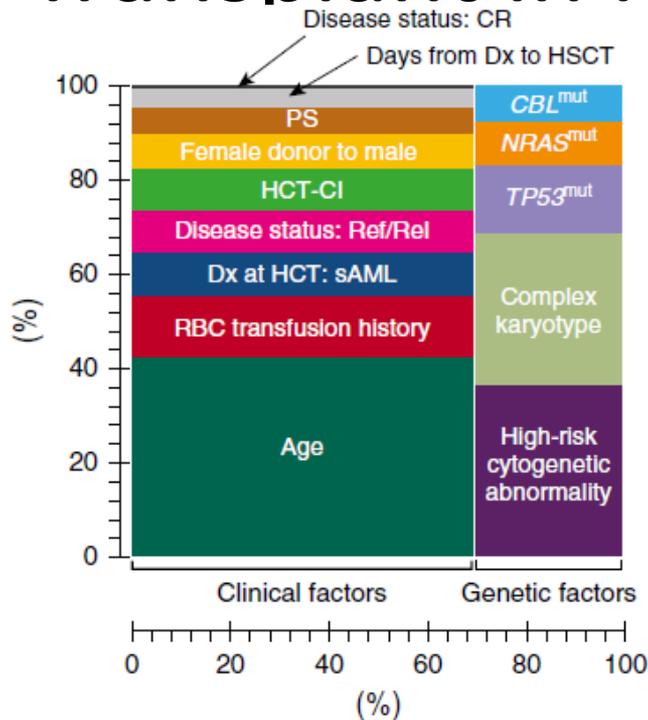


Transplant in MDS: Genomic Mutations



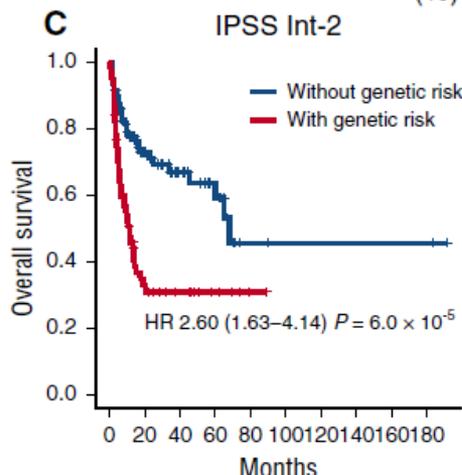
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 - ✓ Cohort of MDS patients (n=87) pre-HSCT BM/PB for mutations in 40 MDS-associated genes
 - ✓ 71% received RIC HSCT
 - ✓ Evaluated for association of mutations with clinical variables including OS
 - ✓ Conclusions:
 - 92% of patients had ≥ 1 mutations (ASXL1 29%, TP53 21%, DNMT3A 18%, RUNX1 16%)
 - Mutations in TP53, TET2, and/or DNMT3A involved 47% of patients, were largely non-overlapping, and associated with impaired survival
 - TP53 mutations strongly associated with complex karyotype MDS
 - Impaired survival of complex karyotype MDS appeared TP53 driven

Transplant in MDS: Genomic Mutations

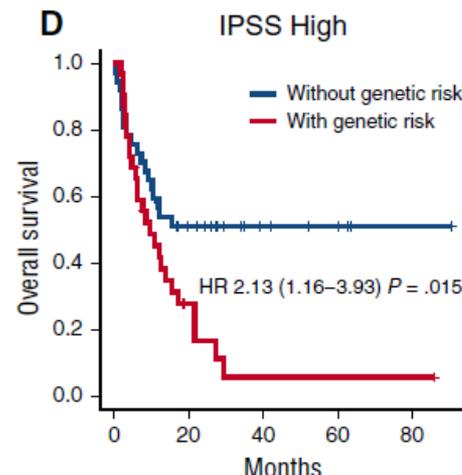


- Multiple groups have now reviewed outcomes of MDS mutation analysis in larger HSCT cohorts
 - ✓ Della Porta, et al evaluated 401 patients with MDS or MDS/AML (GITMO) for 34 recurrently mutated genes
 - ✓ Yoshizato, et al evaluated 797 patients with MDS (JHSCT) for 69 recurrently mutated genes
 - ✓ Lindsley, et al evaluated 1514 patients with MDS (CIBMTR) for 129 recurrently mutated genes
 - ✓ Conclusions:

- TP53, complex karyotype (CK) and RAS pathway mutations were independent negative predictors of HSCT outcome beyond IPSS-R
- RAS pathway mutation prognosis may be subtype dependent (MDS/MPN), and may be overridden with increased conditioning intensity (MAC) HSCT



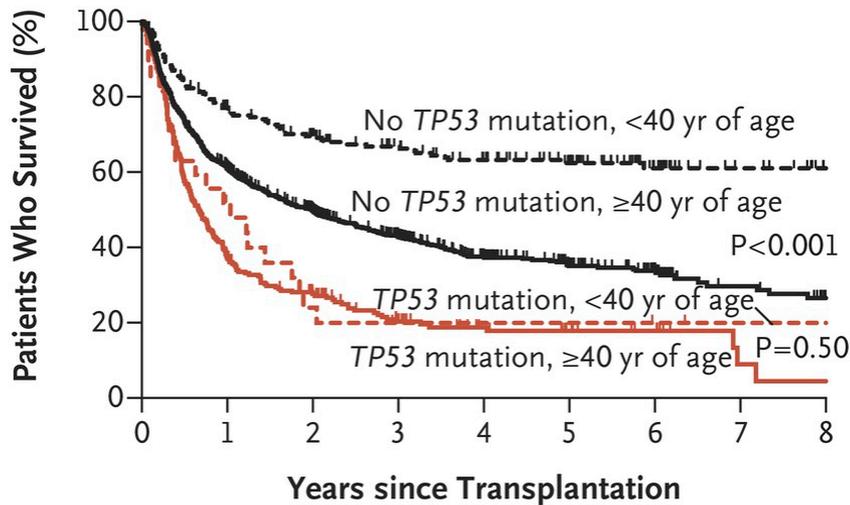
94	41	24	14	3	2	2	2	2
69	17	11	6	1				



37	15	6	4	1
32	5	1	1	1

Source Della Porta et al, *JCO* 2016.
 Yoshizato et al, *Blood* 2017
 Lindsley et al, *NEJM* 2017

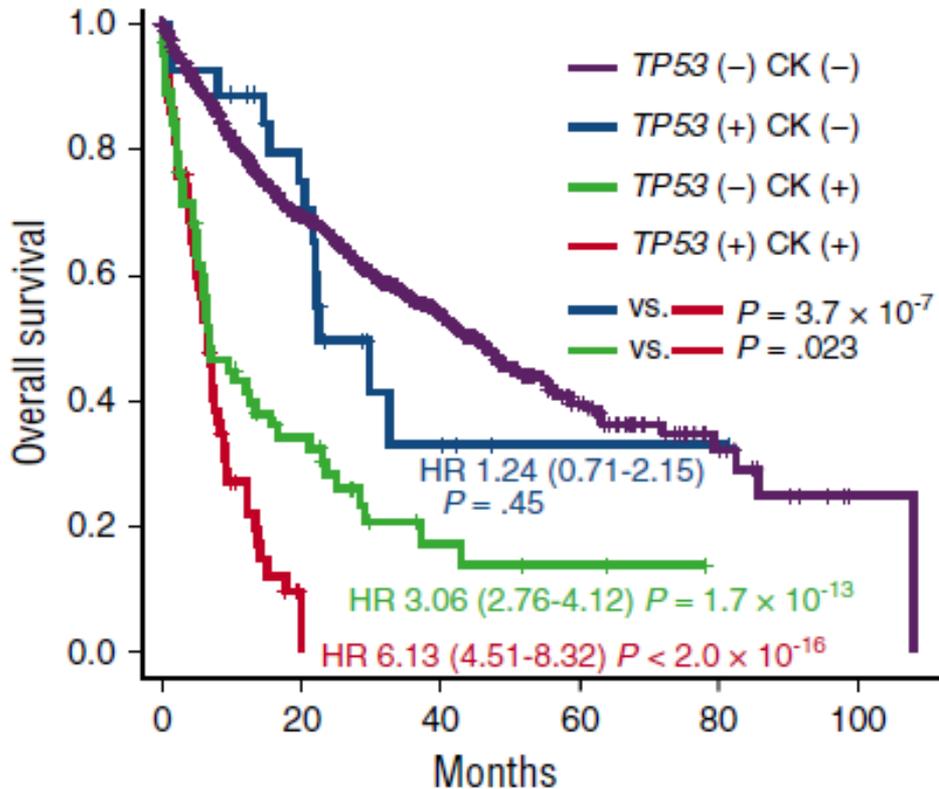
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Transplant in MDS: Genomic Mutations

TP53 mutation/Complex Karyotype (CK)

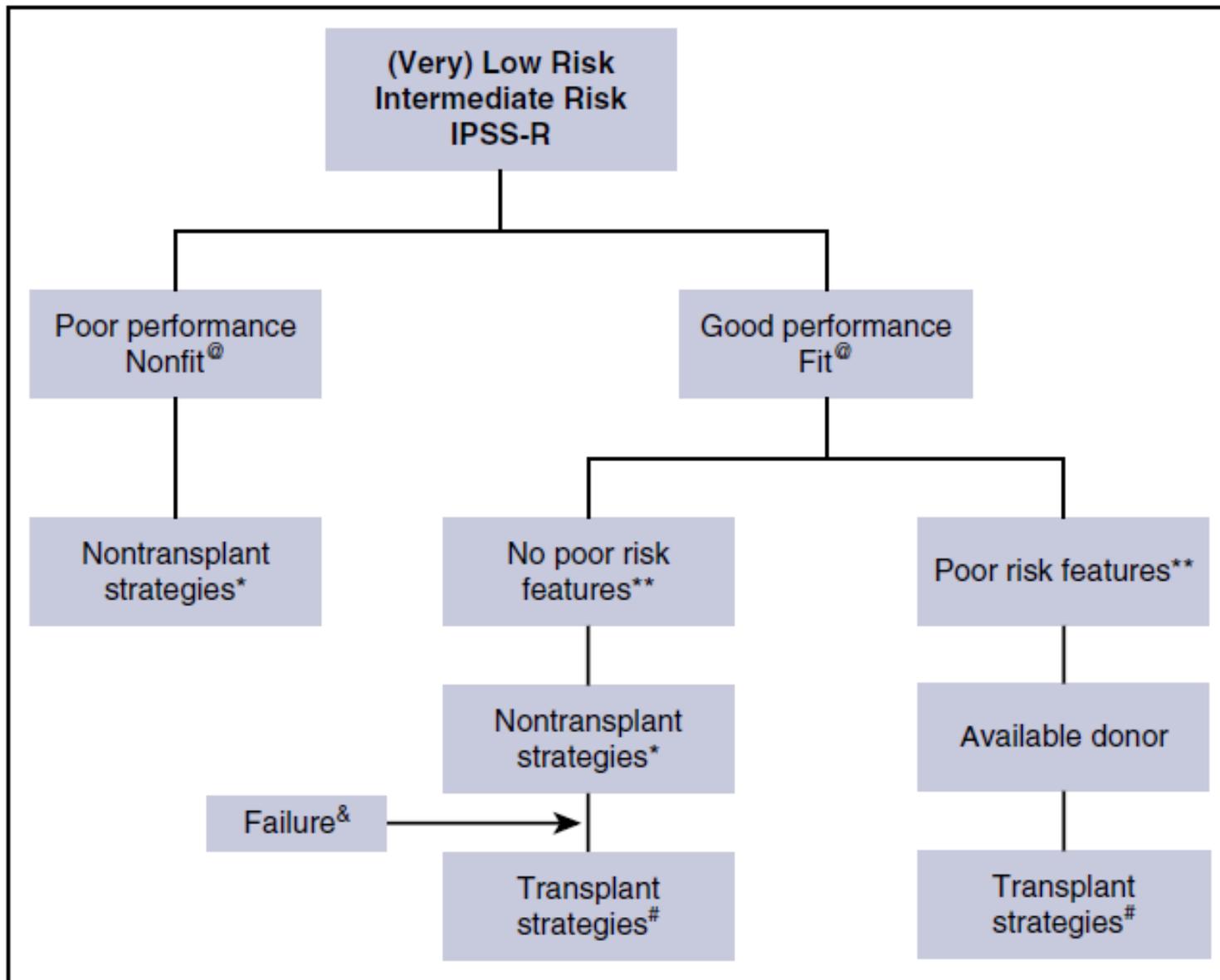


—	58				
—	27	16	4	1	1
—	67	18	5	3	
—	1201	585	235	55	13
					1

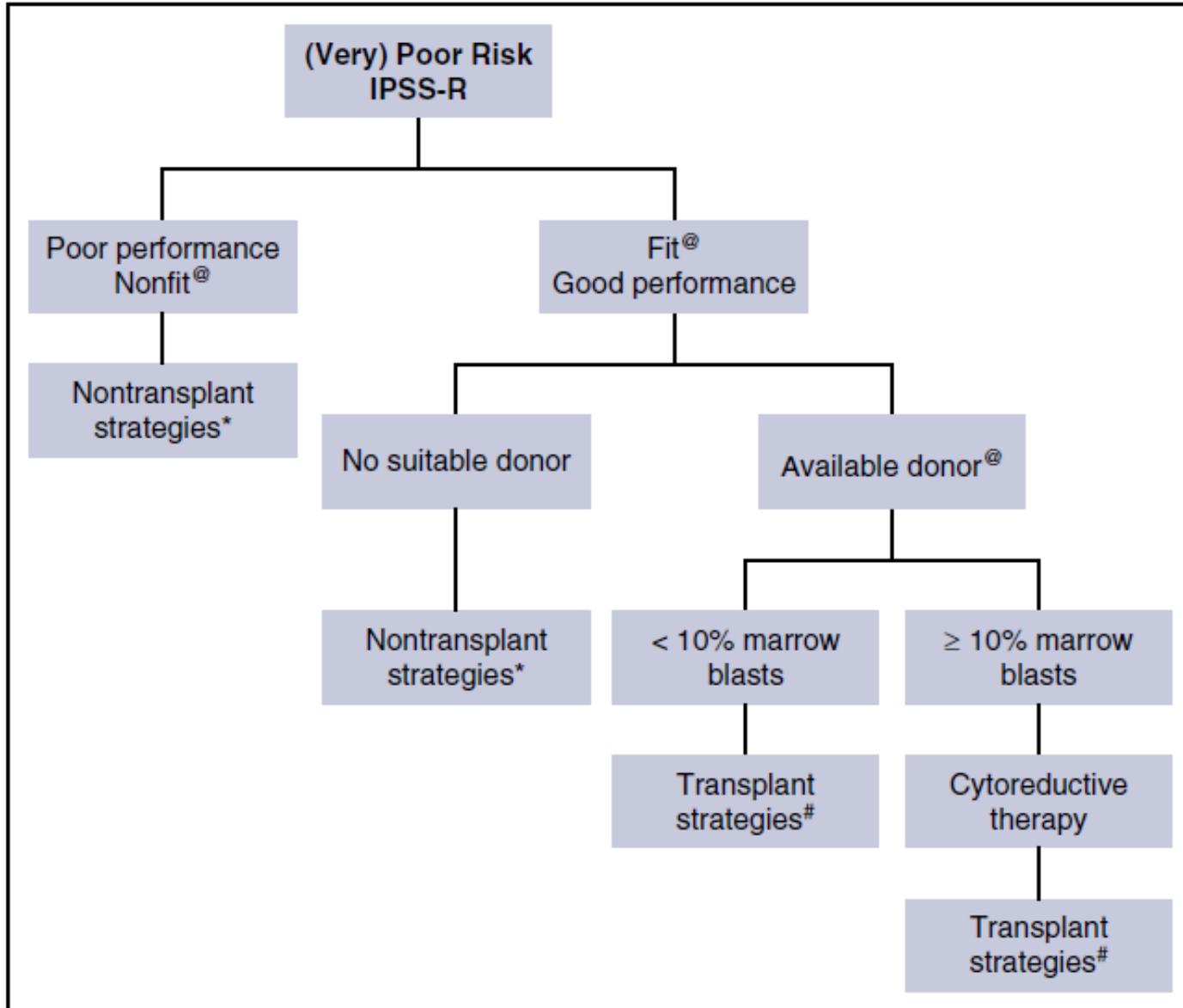
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 - RAS pathway mutation prognosis may be subtype dependent (MDS/MPN), and may be overridden with increased conditioning intensity (MAC) HSCT
 - *TP53* MDS had a poor prognosis with ‘usual’ HSCT
 - *TP53* plus CK mutations had a particularly poor prognosis with ‘usual’ HSCT

Source Della Porta et al, *JCO* 2016.
 Yoshizato et al, *Blood* 2017
 Lindsley et al, *NEJM* 2017

Transplant in MDS: Recommendations



Transplant in MDS: Recommendations



Conclusions: MDS and HSCT

- HSCT is an underutilized curative therapy in MDS
- HSCT deployment can be based on patient, disease (higher-risk IPSS/IPSS-R) and genetic features (higher-risk mutations)
- HSCT-specific MDS risk models may better prognosticate transplant outcomes
- RCTs support both RIC and MAC HSCT in MDS. Transplant intensity may be based on patient fitness and disease characteristics (e.g. RAS pathway and MAC)
- 'Usual' HSCT regimens appear insufficient for very high-risk disease (e.g. TP53+CK)

Case

- 61 year old woman with no chronic illnesses
- Presents with new onset fatigue; physical examination unremarkable
 - WBCs 4.2 K/mm³ (normal diff)
 - Hb 8.9 gm/dL (MCV 102, low retic count)
 - Plts 130 K/mm³
 - Chemistries unremarkable
- Bone marrow examination:
 - 70% cellularity
 - Dysplastic erythrocytes and megakaryocytes
 - Normal iron stores
 - Diagnosis: Myelodysplastic Syndrome

Question 1

- What essential additional information is needed to stage the disease prior to treatment recommendations (including transplant)?
 1. Blast count and cytogenetics
 2. Flow cytometry
 3. Mutational panel
 4. All of the above

Acknowledgements

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