EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Should We Transplant Relapsed AML/MDS Not in Remission?

Not usually!!!

Martha L. Arellano, MD

Professor and Director, Hematology & Medical Oncology Fellowship Program

Winship Cancer Institute of Emory University, Atlanta, GA

DDHO

July 22, 2022

Disclosures

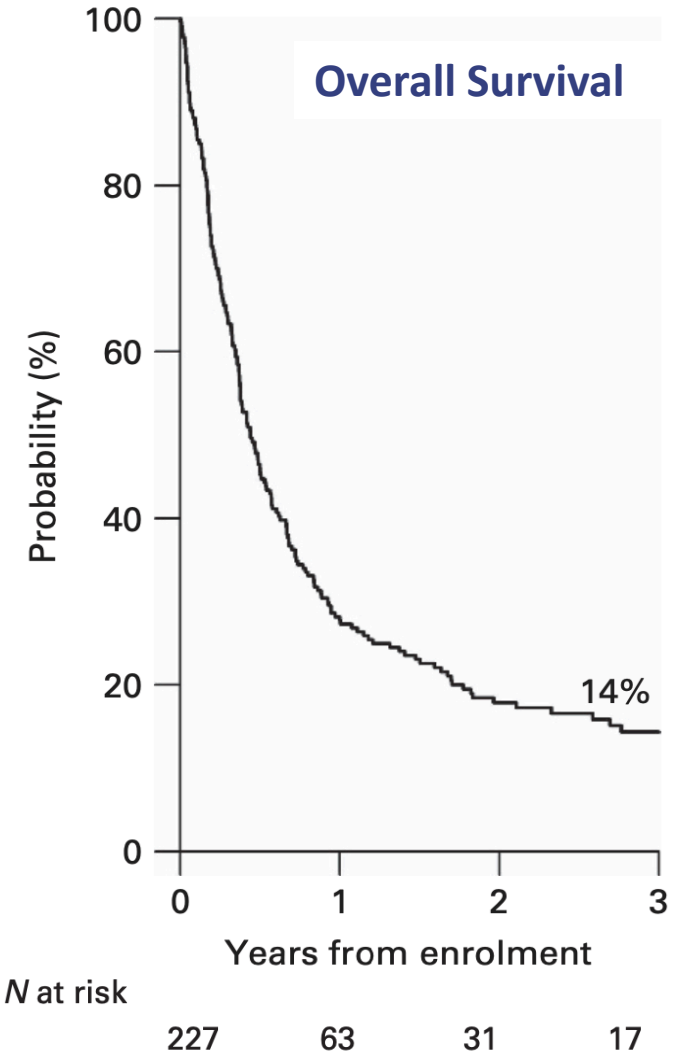
Company Name	Role
Gilead Sciences Inc	Advisory board, on management of ALL
Syndax Pharmaceutical	Advisory board, on management of AML and ALL

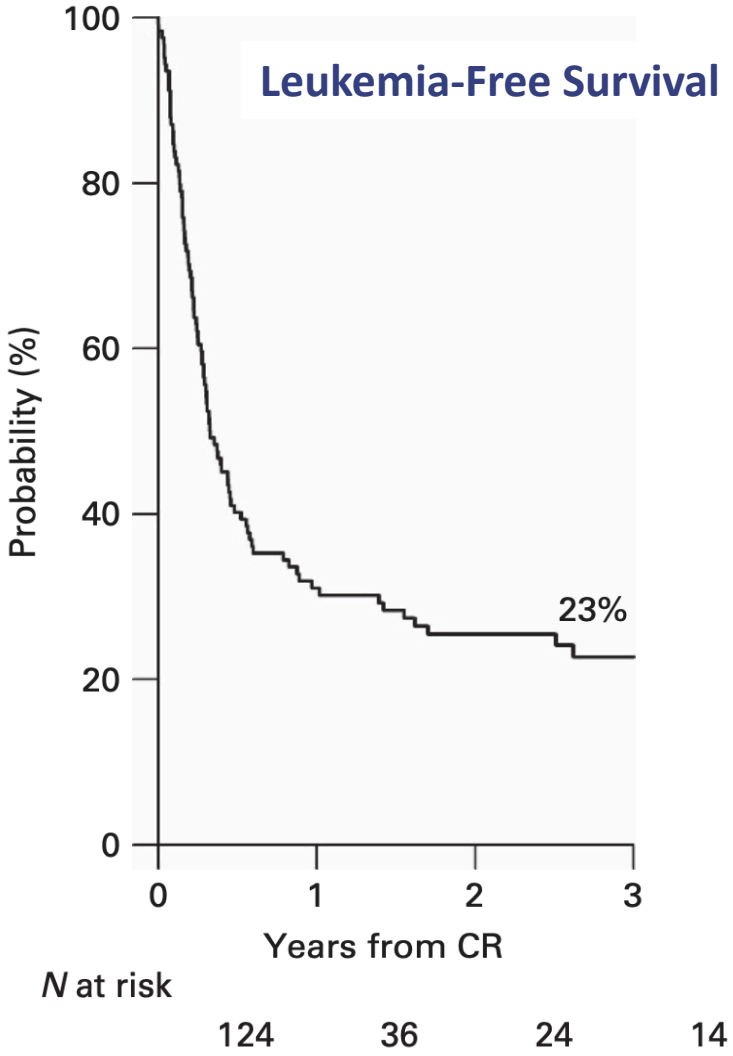
Objectives

- Convince you that there is little reason to transplant most patients with MDS or AML who have active leukemia at time of transplantation.

Outcomes of Patients with AML Transplanted with Primary Refractory Disease are Dismal!

This glass is not half full, Amy!





Todisco E, Ciceri F, Boschini C, et. Al. Bone Marrow Transplantation (2017) 52, 955–961
From Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

Case 1

- 43 year-old woman with normal karyotype, NPM1-mutated AML.
- Received 7+3 induction, did not achieve CR.
- Received MEC (mitoxantrone, etoposide, cytarabine).
- Continued to have circulating blasts.
- No response to azacytidine plus venetoclax.

Who would transplant this patient at this point?

Case 2

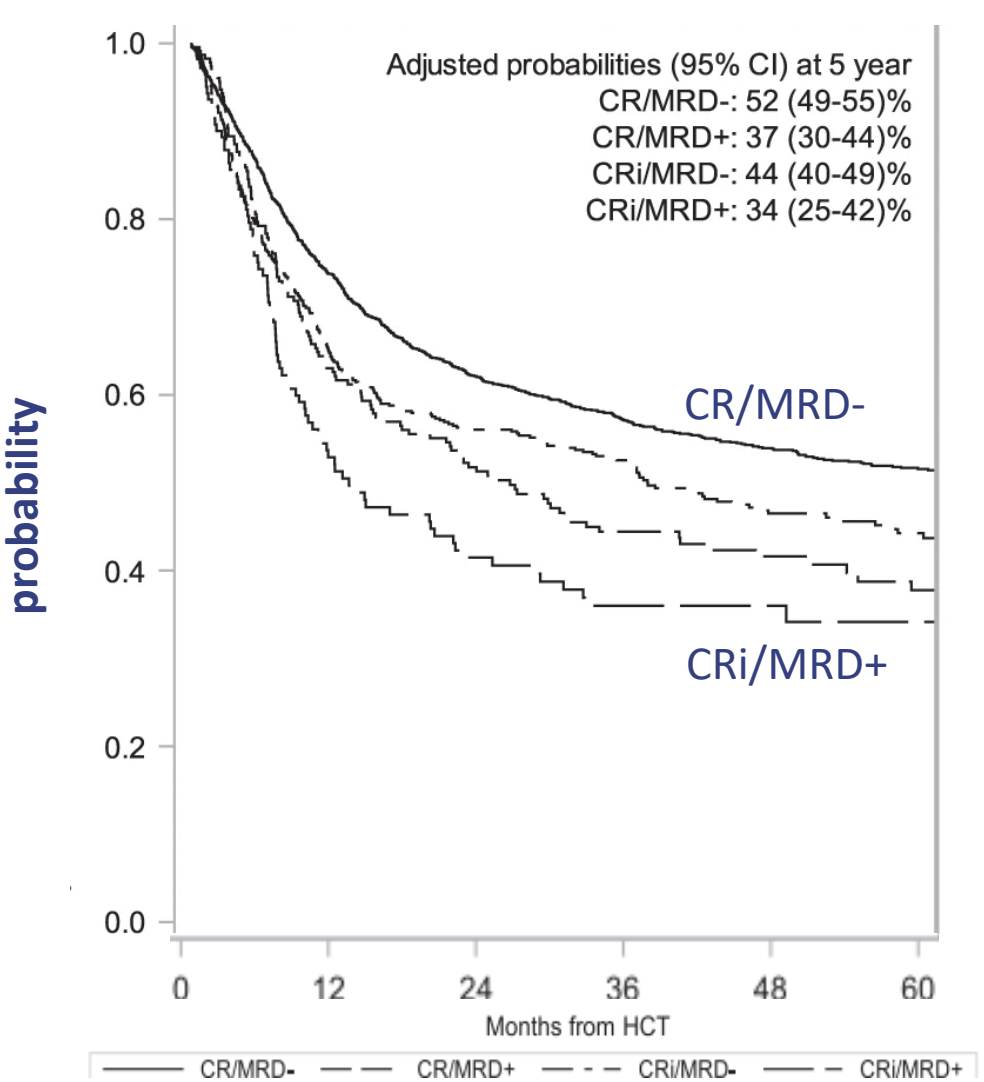
- 67 year-old woman with therapy-related MDS (multiple myeloma, 9 years ago, treated on Total Therapy II).
- She developed pancytopenia, ANC 700, Hemoglobin 10, plts 50k.
- Marrow was 70% cellular, with multi-lineage dysplasia, and 6% blasts.
- Karyotype: del(5q), der(3;7), -7, t(12;16), +21
- Mutations: TP53 (p.R337C) in 40% of alleles & TP 53 (p.P151A) in 45%.
- Started azacitidine.

Who would transplant this patient at this point?

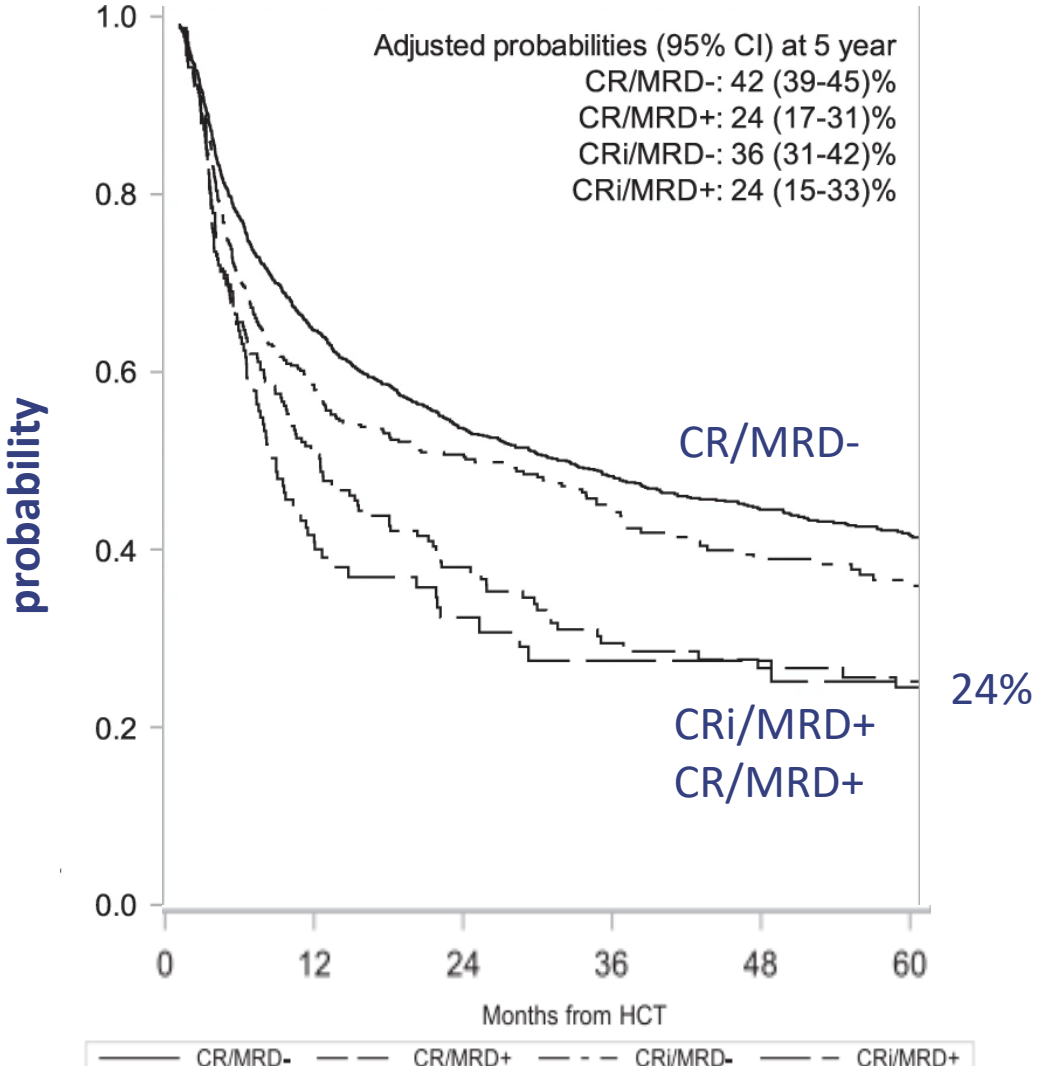
The Best of the Best, Depth of Response Prior to AlloHCT Matters

N = 2,492 patients with AML

Overall Survival



Disease-free Survival

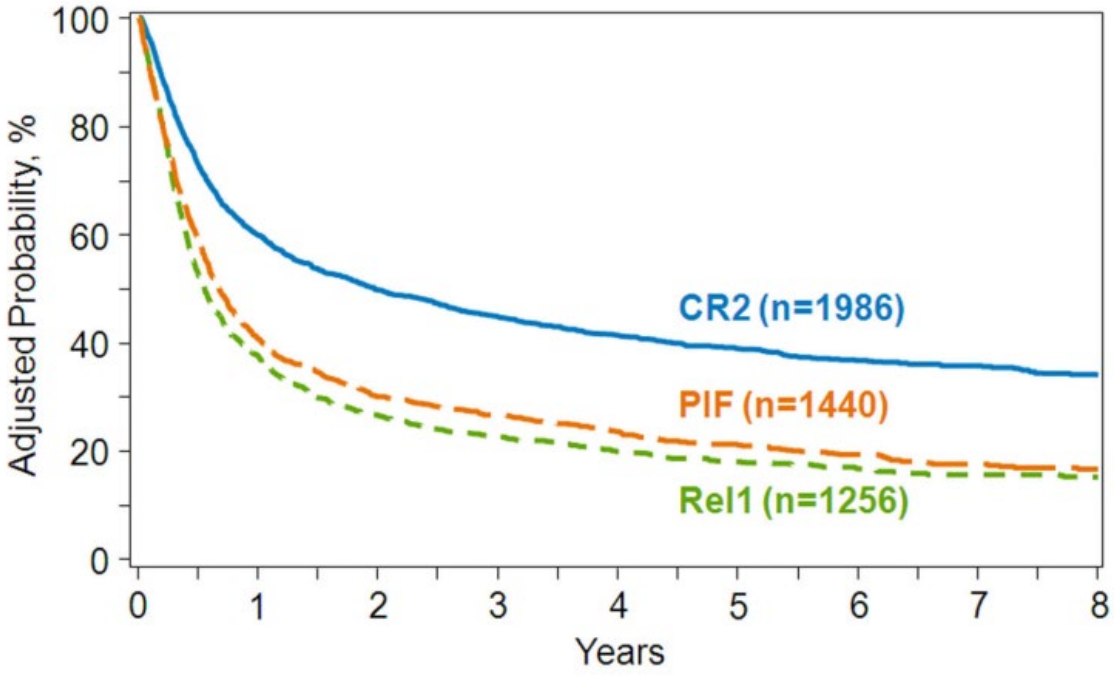


24%

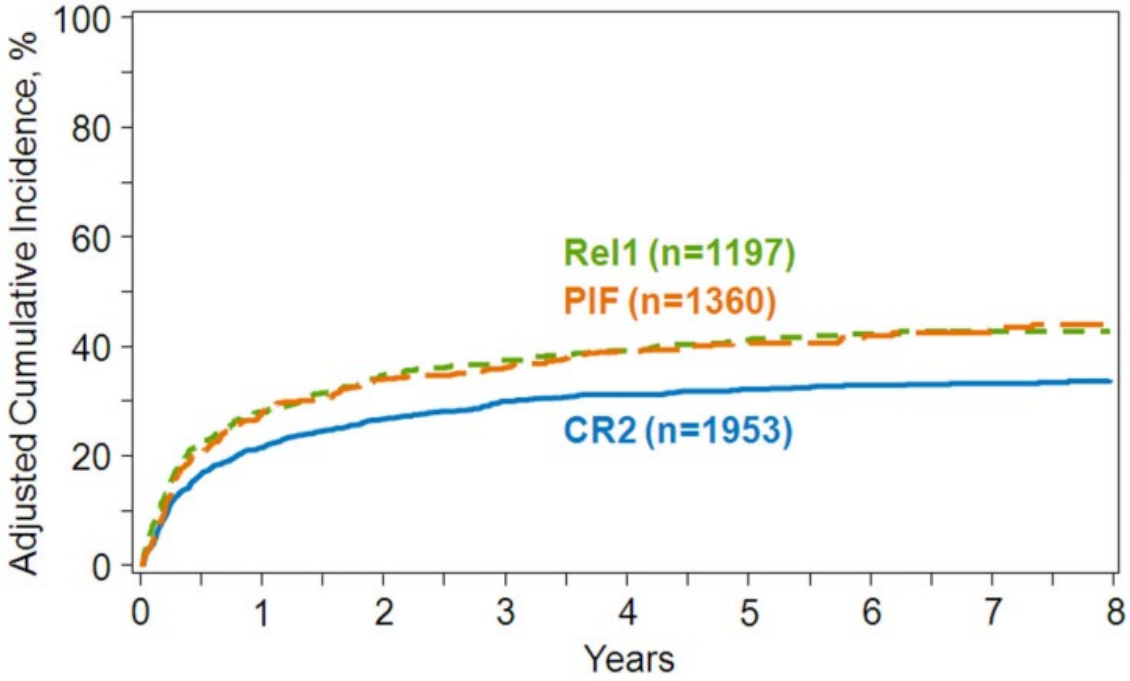
Not quite!

Probability of Overall Survival in Patients with Advanced AML Undergoing Stem Cell Transplantation, by Disease Status at Time of Transplant

Probability of Overall Survival by Disease Status



Probability of Relapse by Disease Status



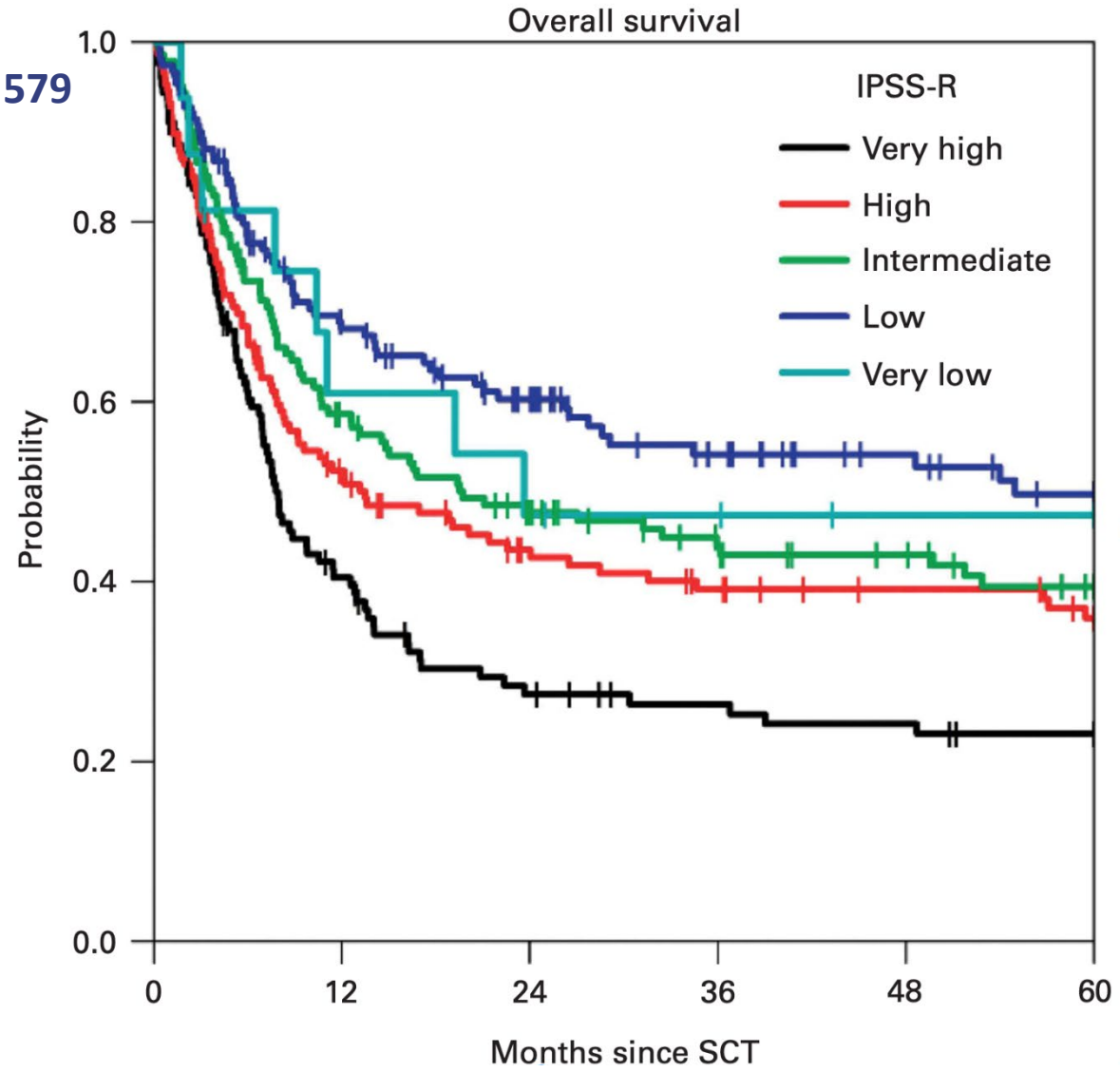
Glass is not half full!

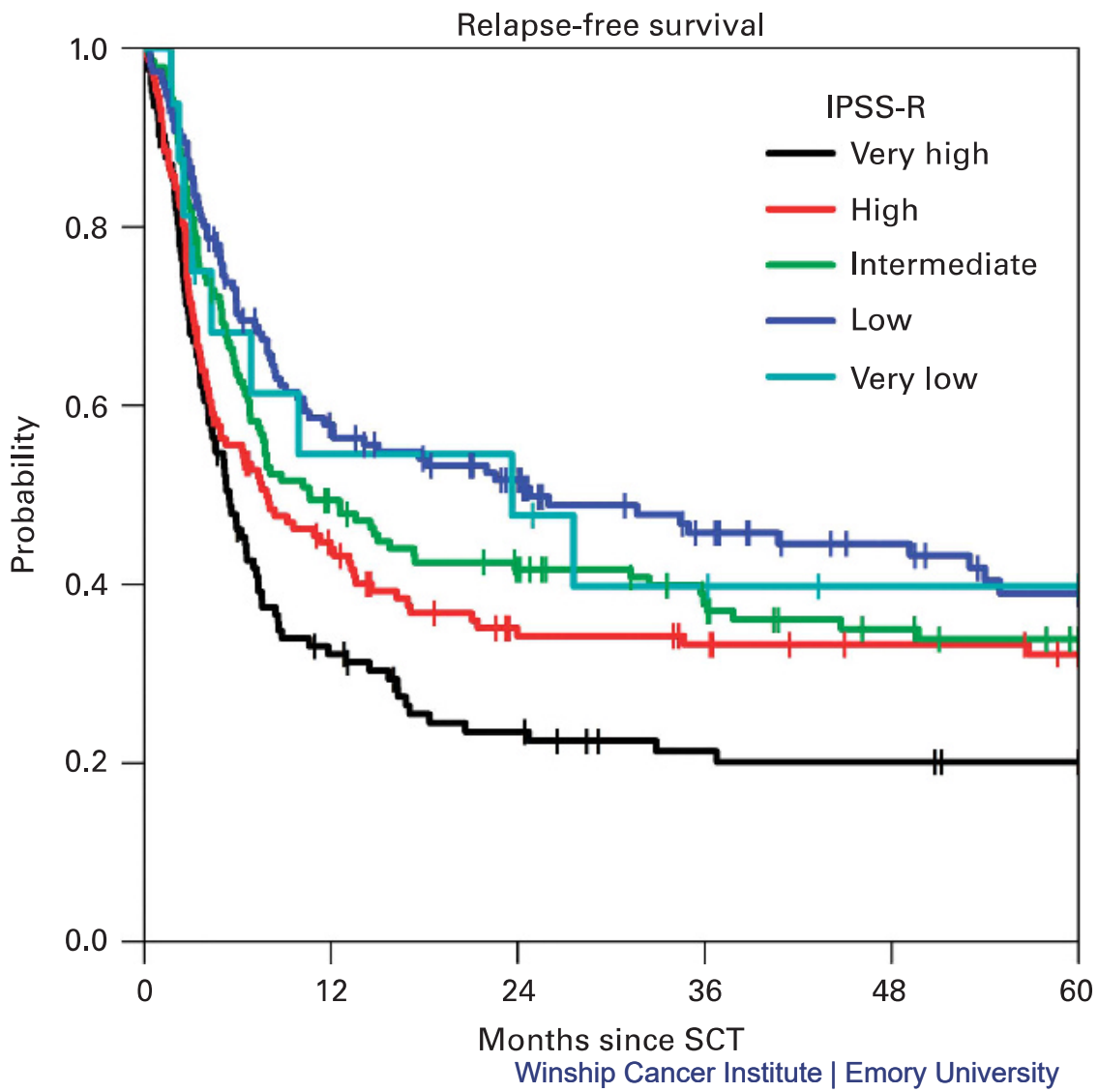
CR2= 2nd complete remission
PIF= primary induction failure (failed ≥ 2 re-inductions)
Rel1= First relapse after CR (failed ≥ 1 re-induction, or untreated).

D Weisdorf, Millard H, Horowitz M, et. Al. Cancer. 2017 June 01; 123(11): 2025–2034

IPSS-R at Time of Transplant Predicts Post-Transplant Outcomes for Patients with MDS

N= 579



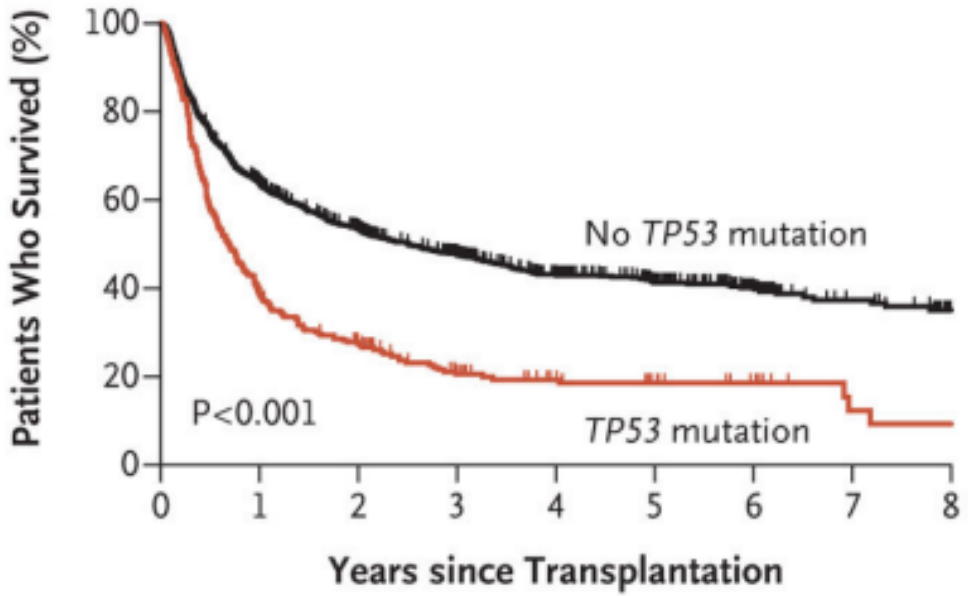


Scheid C, de Wreede L, van Biezen A, Koenecke C, Göhring G, Volin L, et al. Bone Marrow Transplant (2017) 52(11):1519–25. doi: 10.1038/bmt.2017.171

Role of TP53 mutations in Prognosis of Patients with Myelodysplastic Syndrome Undergoing Transplantation

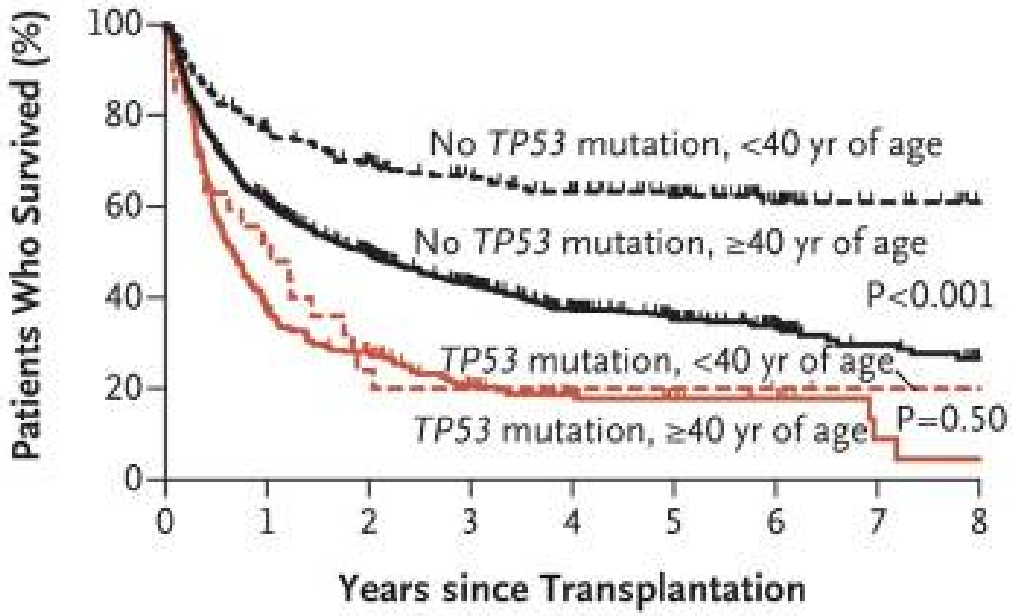
Overall Survival according to TP53 Mutation Status

N= 1514



No. at Risk									
No *TP53* mutation	1224	757	529	370	261	183	109	53	32
TP53 mutation	289	109	66	39	26	20	14	6	5

Overall Survival according to TP53 Mutation Status and Age



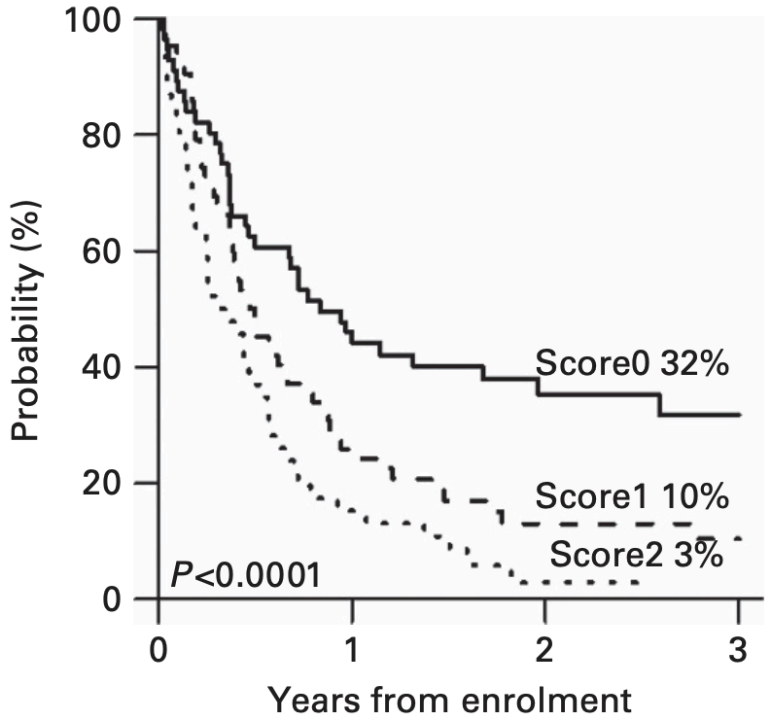
No. at Risk									
No *TP53* mutation									
<40 yr of age	214	159	133	115	100	78	42	23	13
≥40 yr of age	1010	598	396	255	161	105	67	30	19
TP53 mutation									
<40 yr of age	27	14	7	5	5	5	4	4	3
≥40 yr of age	262	95	59	34	21	15	10	3	2

Lindsley RC, Saber,W, Redd MR, et. Al. N Engl J Med. 2017 February 09; 376(6): 536–547. doi:10.1056/NEJMoa1611604.

Can We Identify which Patients with Refractory AML May Benefit from Allogeneic Transplantation?

N = 227

Score variables	Score	Data available	*N* (%)	P-value
Chemotherapy cycles		220		
≤2	0		122 (55)	0.0028
>2	1		98 (45)	
Blast infiltration		197		
BM<25% or no PB	0		78 (40)	0.0078
BM≥25% or any PB	1		119 (60)	
Age		227		
≤60	0		187 (82)	0.0223
>60	1		40 (18)	
Cytogenetics/ Molecular biology		191		
Favorable/Intermediate I	0		81 (42)	0.0508
Intermediate II /Adverse	1		110 (58)	



Score	Risk factor	*N*=165	HR (95% CI)	*P*	OS at 3 years
0	0-1	56 (34)			32%
1	2	63 (38)	1.73 (1.13-2.63)	0.0112	10%
2	3-4	46 (28)	2.62 (1.68-4.10)	<0.0001	3% 2 Yrs

Not exactly!

Todisco E, Ciceri F, Boschini C, et. Al. Bone Marrow Transplantation (2017) 52, 955–961

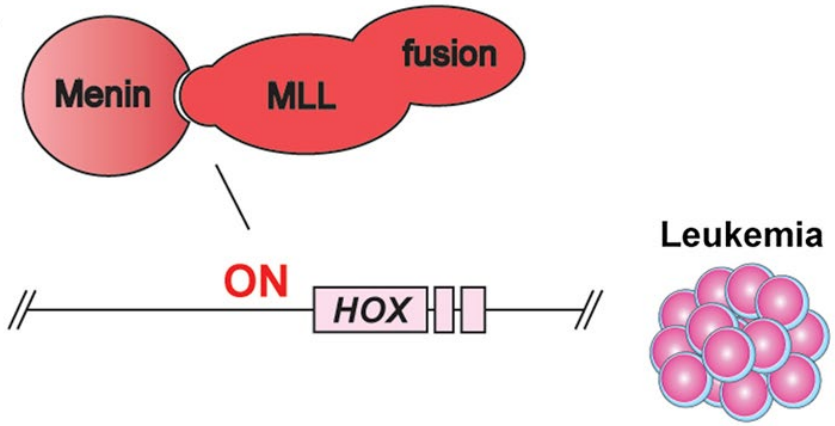
Back to our case 1…

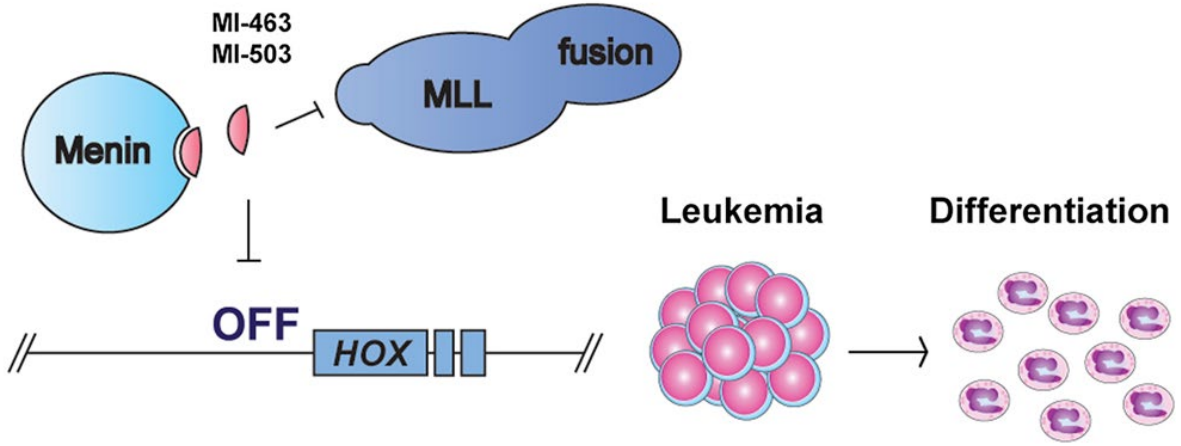
43 year-old woman with Normal Karyotype, NPM1-mutated AML.

- Did not achieve CR after 7+3 induction.
- Circulating blasts after 2 salvage chemo regimens.
- GITMO score = 1 (> 2 inductions, circulating blasts, predicted 3-year survival = 10%)
- **Would you transplant this patient now?**
- **Would you agree to be transplanted?**

- Enrolled on clinical trial of SNDX-5613
- Achieved MRD-negative CR, followed by allogeneic HCT in CR2

Augment-101: Phase 1/2 Trial of SNDX-5613 in Patients with R/R AML and ALL (with NPM1 mutation or MLL rearrangement)





- N= 54 (AML 44, ALL 9, MPAL 1)
- CR/CRh rates, 23% and 24% in mNPM1 and MLLr patients, respectively, with 92% being MRD-negative.
- Responses were durable; median not reached.
- No discontinuations due to treatment-related adverse events
- Coming up: combinations, post-HCT maintenance

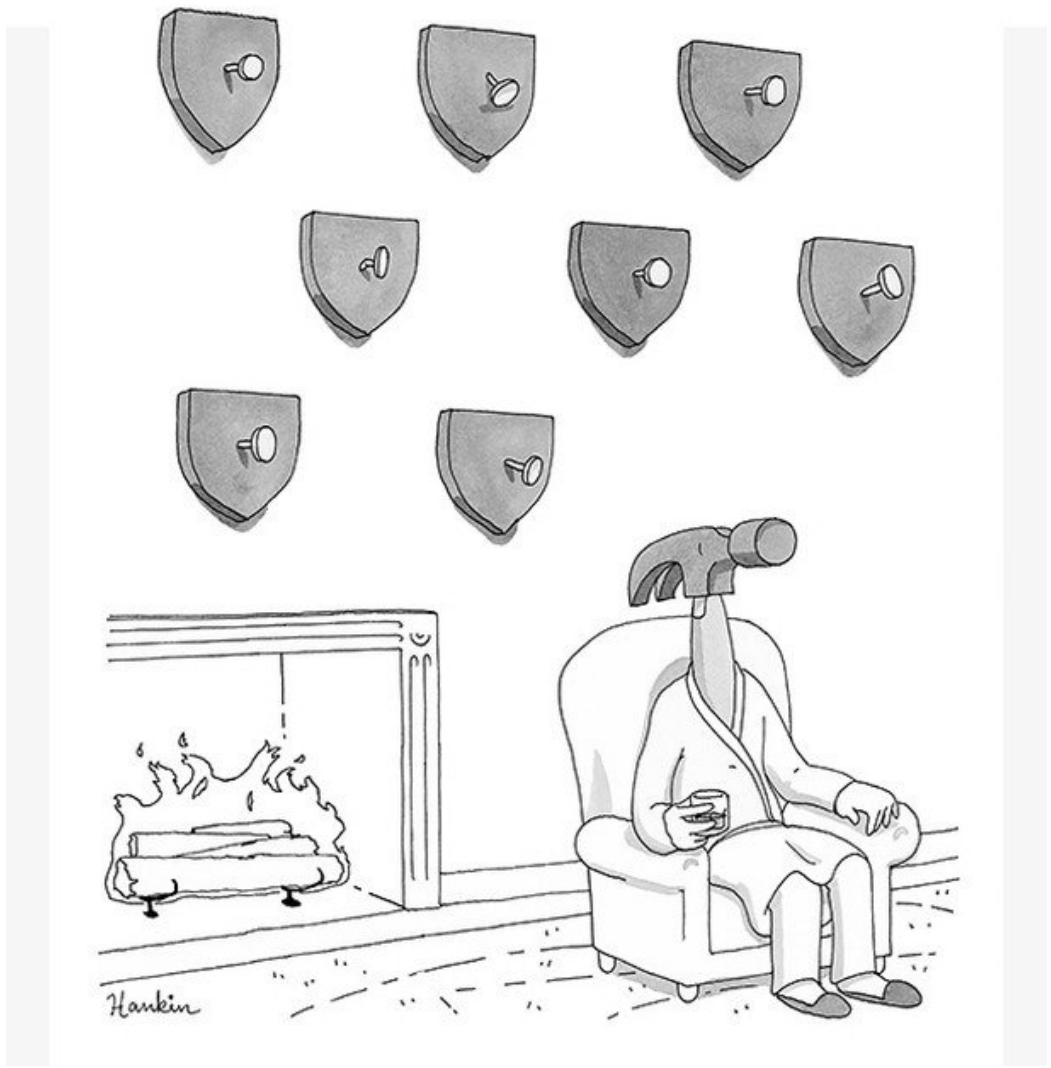
Michael W.M. Kühn, Scott A. Armstrong. Cancer Cell 2015 27431-433DOI: (10.1016/j.ccell.2015.03.012)

Stein EM, Aldoss I, DiPersio JF, et. Al. ASH 2021. 699

Case 2

- 67 year-old woman treated for multiple myeloma, on Total Therapy II.
- Diagnosed with MDS, with 6% blasts, complex karyotype, and TP53 mutations.
- IPSS-R = 7 (very high risk)
- Received 3 cycles of azacitidine.
- Persistent blasts and pancytopenia
- Underwent allogenic transplantation from 9/10 matched unrelated donor.
- Complicated by multi-organ failure, leading to death.

Just Because You Can, Does NOT Mean You Should!



All Patients with Relapsed/Refractory AML/MDS Should Be Referred for Clinical Trials

	Targets
Protein Kinase Inhibitors	**FLT3**, KIT PI3K/AKT/mTOR Aurora kinase, **Polo-like kinase**
Epigenetic modulators	DNA methyl-transferase Histone deacetylase (HDAC) **IDH1, IDH2, BET-bromodomain**
Mitochondrial inhibitors	**BCL-2**, BCL-XL, **Mcl-1**
Targeting oncogenic proteins	**NPM1, KMT2A** Hedgehog EVI1, **TP53**
Immunotherapy Antibodies, BiTEs, **DARTs,** CAR T cells, **Vaccines**	**CD33**, CD44, **CD47**, CD123, **KIR**, WT1, PD-1/PDL-1/CTLA-4

Highlighted targets = clinical trials available at Winship

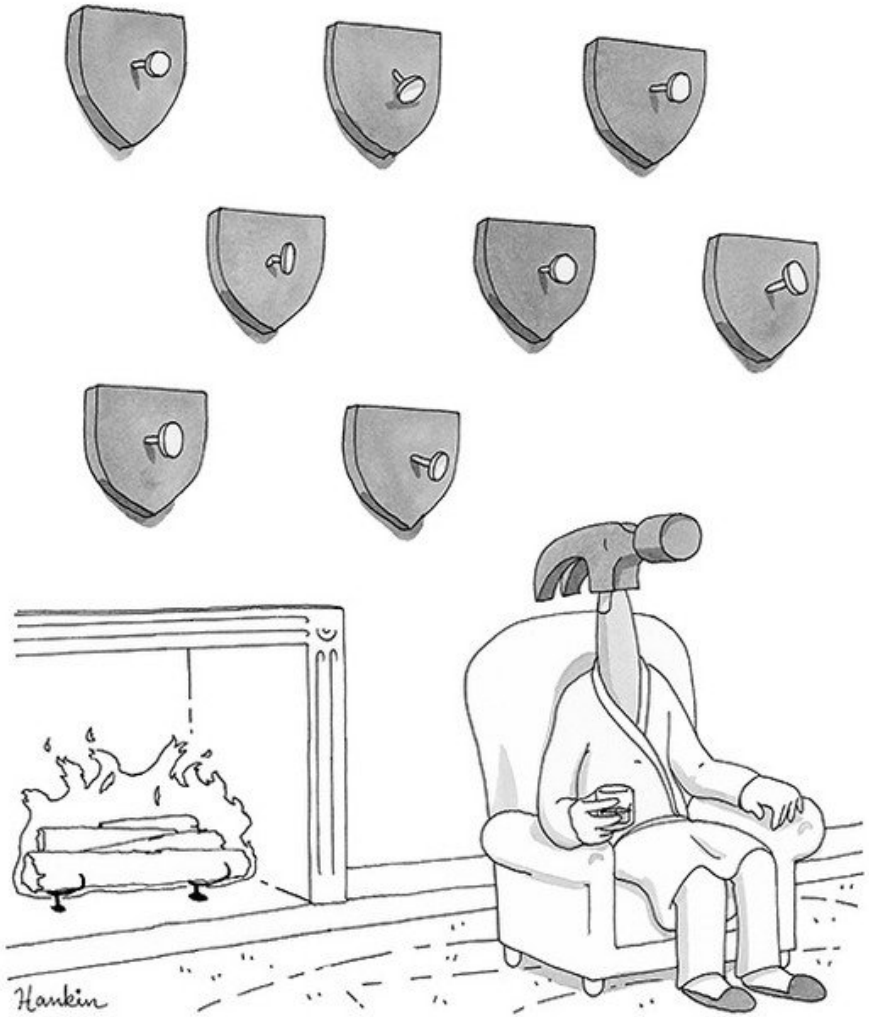
Summary

- Outcomes of patients with AML/MDS with active disease at time of transplantation are dismal.

- Factors associated with better outcomes:
  - Younger age (eligible for myeloablative conditioning)
  - Chemo-sensitive disease
  - Low disease burden
  - Favorable genetics/cytogenetics

- Clinical trial should be pursued for all patients with relapsed/refractory disease prior to transplantation.

My opponent, the hammer, the optimist…



"Look over there - summer!"

@nycartoons (New Yorker Cartoons)

Questions?

marella@emory.edu

678-886-0009