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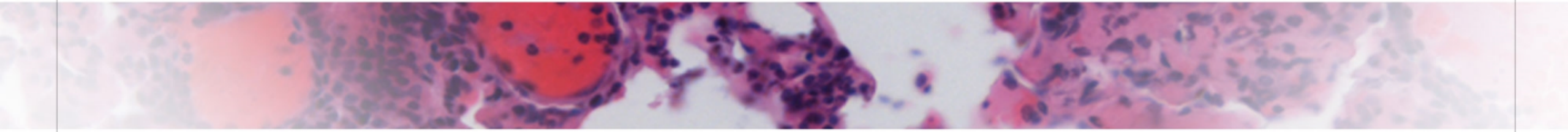

Hematopoietic Stem Cell Transplantation

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Speakers	Disclosures
Monzr Al Malki, MD	**Consultancy**: CareDx; NexImmune **Research Funding**: Gilead; Incyte; NexImmune **Speakers Bureau**: Sanofi **Membership on an entity's Board of Directors or advisory committees**: Hasna Biopharma, Stemline Therapeutics, CarDx, Incyte **Discussion of off-label drug use**: Not applicable

Learning Objectives

- Discuss the approach to transplant in relapsed/refractory acute myeloid leukemia
- Recognize associations between socioeconomic status, ancestry, and HLA-disparate grafts
- Summarize the impact of SARS-CoV-2 infection on mortality in the peri-transplant period
- Describe the impact of donor age during transplant donor selection
- Outline efforts to personalize conditioning regimen intensity
- Delineate novel methods for graft versus host disease (GVHD) prevention and treatment
- Discuss and describe emerging concepts for post-transplantation maintenance therapy

A 65-year-old female with adverse risk acute myeloid leukemia (AML) received standard induction therapy. Due to the adverse risk nature of her disease, allogeneic stem cell transplant was discussed as a potential curative modality. Unfortunately, she was found to be refractory to induction therapy.

What should be considered for salvage treatment?

Abstract 4: In Patients with Relapsed/Refractory AML Sequential Conditioning and Immediate Allogeneic Stem Cell Transplantation Results in Similar Overall and Leukemia-Free Survival Compared to Intensive Remission Induction Chemotherapy Followed By Allo-HCT: Results from the Randomized Phase III ASAP Trial

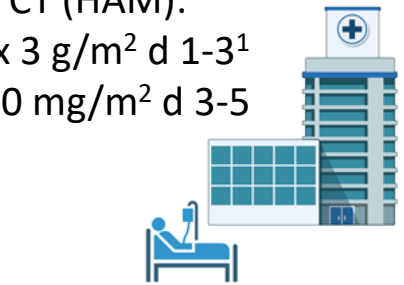
- Age 18 – 75 years
- poor response after first induction[2], non-favorable AML
- or first untreated relapse
- HLA compatible donor
- Fit for salvage CT and alloHCT [3]

R

1:1, stratified for disease status, AML biology and age

RIST

Salvage CT (HAM):
AraC 2 x 3 g/m² d 1-3[1]
Mitox 10 mg/m² d 3-5



Conditioning Intensity adapted to residual AML and patient condition

DisC

watchful waiting
or
low-dose AraC
or
Mitoxantron 10 mg/m²

Sequential Conditioning:
- FLAMSA-RIC
- HD-Melphalan +Flu/TBI

Primary Endpoint:
DFS@d56 after HCT
OS from Rando

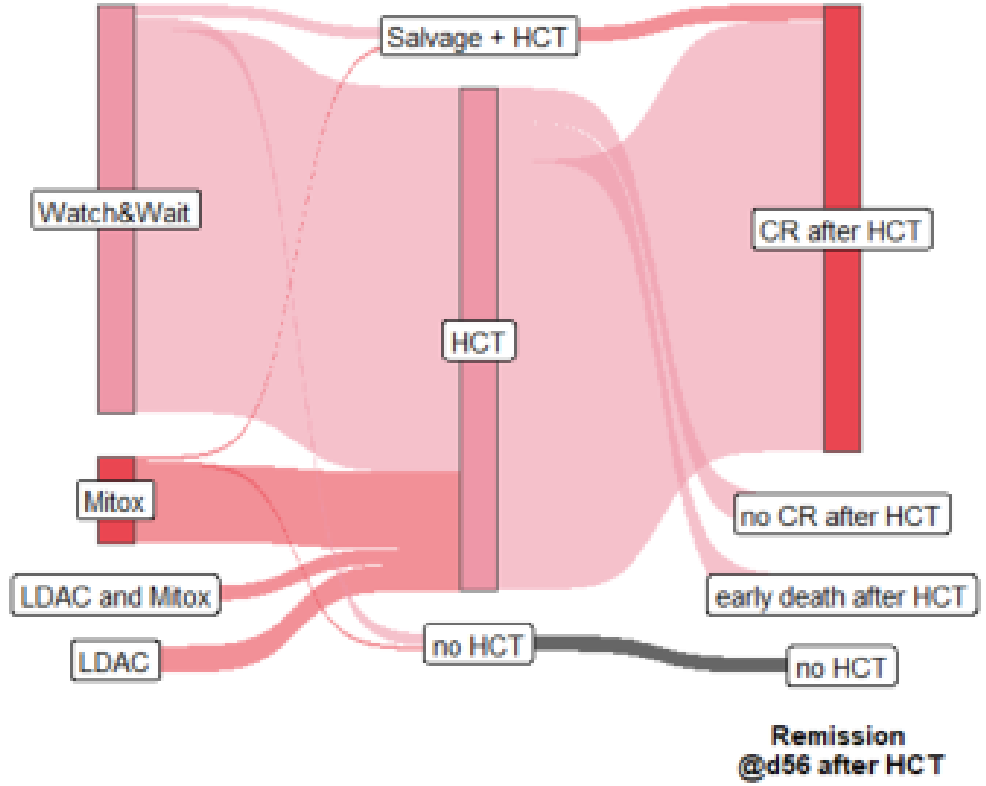
[1] Cytarabine 2 x 1 g/m² for patients >60 yrs; [2] poor response was defined as ≥5% marrow blasts after 1st induction, eventually within the SAL-Dauno-Double trial; C Röllig *et al*, abstract 217, ASH 2022;
[3] Patients with WBC≥50 GPT/L, CNS manifestations, prior alloHCT, LVEF <50%, O_2 supplementation., bilirubin >1.5xULN, GFR <50 ml/min were not eligible

Slide courtesy of: Dr. Johannes Schetelig

Disease Control arm

76% of patients bridged by watchful waiting

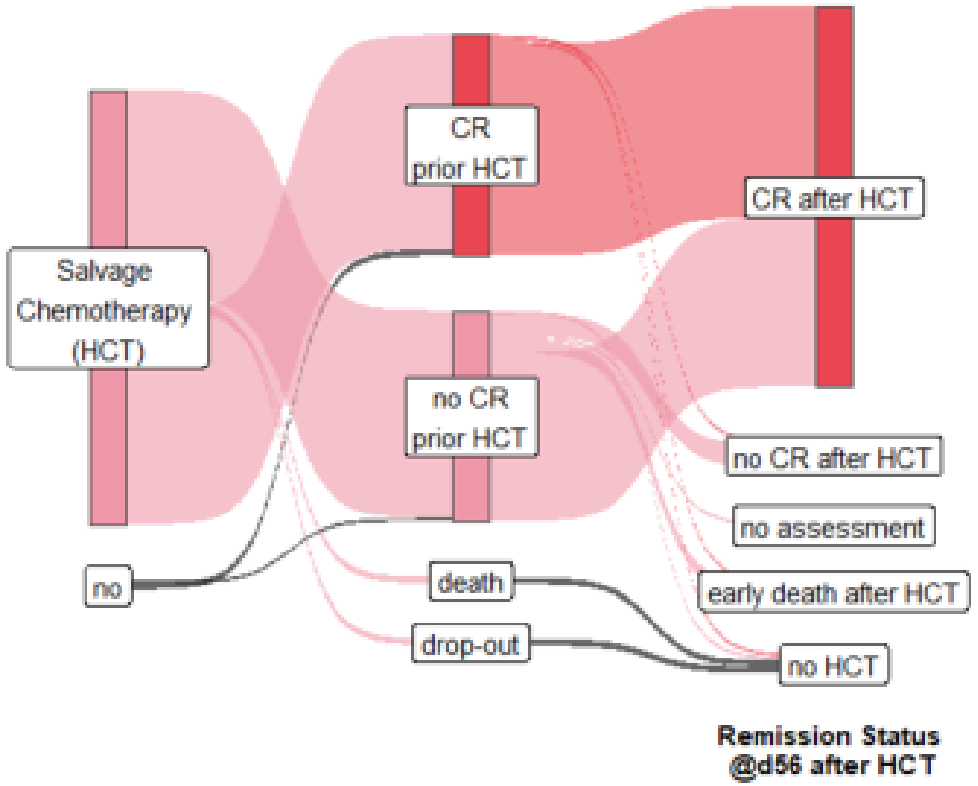
Median time to HCT 4 weeks, @24weeks 98% HCT



Remission Induction arm

Every second patient achieved a CR

Median time to HCT: 8 weeks, @24weeks 96% HCT



DKMS-14-01

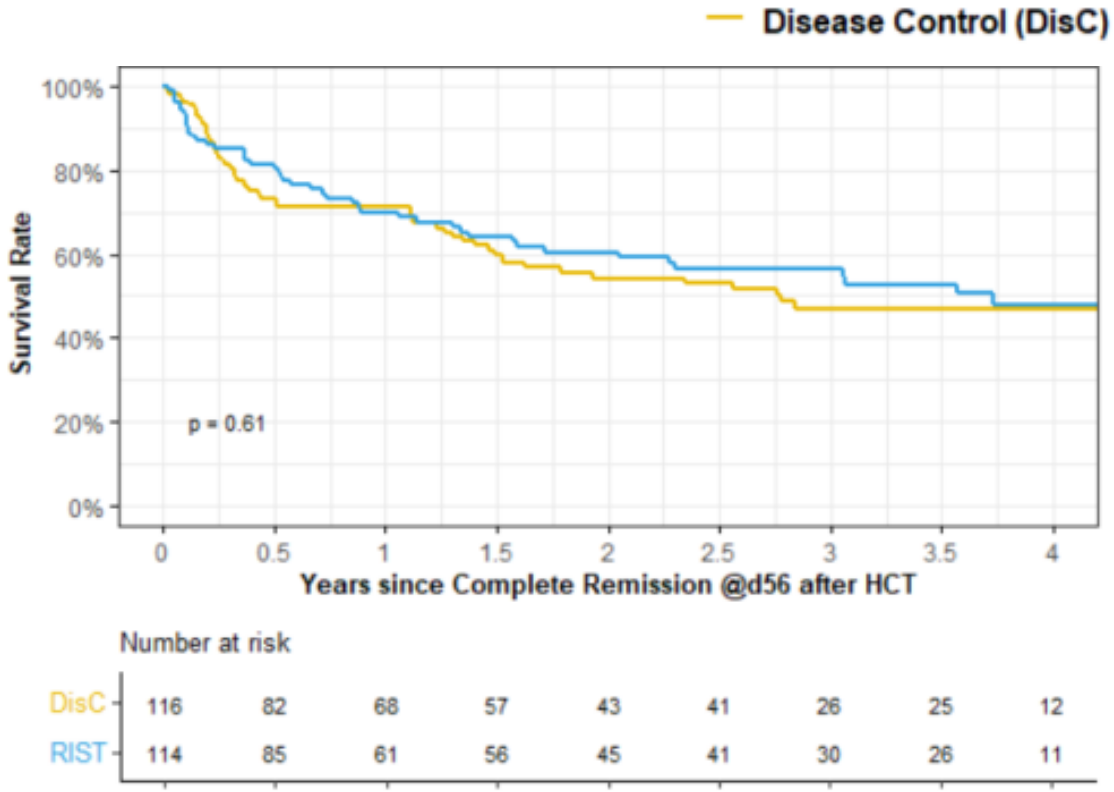
ITT populations, data lock 2022-07-19, analysis as of 2022-11-04

Slide courtesy of: Dr. Johannes Schetelig

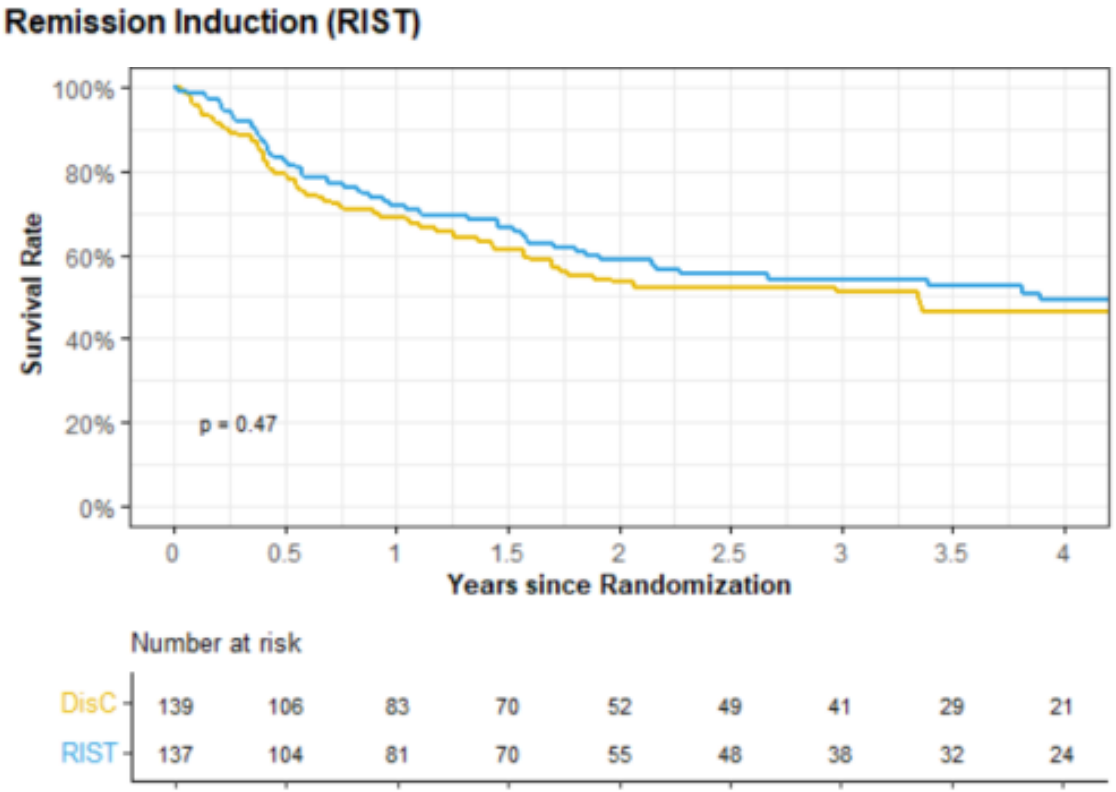
ASAP Trial: Survival Outcomes

Primary Endpoint DFS@d56: 84% vs 81.3% in DisC vs RIST arm, respectively

Leukemia-free Survival



Overall Survival



Median follow-up from Randomization: 37 months

ITT/PP population, data lock 2022-07-19, analysis as of 2022-11-04

Slide courtesy of: Dr. Johannes Schetelig

Allogeneic stem cell transplantation was recommended. The patient is noted to be a 65-year-old female with non-European ancestry and no other medical co-morbidities. A donor search was pursued. Her parents, siblings, and children were agreeable to HLA-typing.

What do we know about donor options for this patient?

Abstract 127: Adult Allograft Recipients Reveals Associations between Non-European Ancestry, Low Socioeconomic Status, and Receipt of HLA-Disparate Grafts

- **Racial/ ethnic[1-3] & socio-economic status (SES)[4-6] disparities both impact patient care in bone marrow transplant (BMT):**
  - **Access to BMT & to optimal donors.**
  - **Post-transplant outcomes.**
- **However, the relationship between ancestry & SES, & their interaction with donor type, are unknown.**

<u>Hypothesis for analysis</u>:
low SES disproportionately impacts non-European (non-EURO) recipients of HLA-mismatched transplants (ie cord blood, haploidentical, or mismatched unrelated donors).

[1]Fingrut & Barker, Blood Advances 2022a; [2]Fingrut & Barker, Blood Advances 2022b; [3]Kosuri et al., BBMT 2017; [4]Gutman et al., BMT 2022; [5]Bona et al., Blood 2021; [6]Paulson et al., BBMT 2019.

Slide courtesy of: Dr. Warren Fingrut

Donor distribution by pt ancestry

Donor type	EUROs (n = 292)		Non-EUROs (n = 133)	
HLA-Id SIB	14% (n = 42)		12% (n = 16)	
8/8 URD	61% (n = 179)		31% (n = 41)	
Cord Blood	7% (n = 19)		19% (n = 25)	
Haploidentical	8% (n = 22)	**25%**	22% (n = 30)	**57%**
5-7/8 URD	10% (n = 30)		16% (n = 21)	

Non-EURO pts receive >2x as many HLA-disparate grafts ($p < 0.001$).

African pts (n = 45):

- **least likely to receive HLA-id SIB or 8/8 URDs (9/45, 20%).**
- **18% received Cord Blood, 36% haploidentical, & 27% 5-7/8 URDs.**

HLA-matched grafts predominately serve EURO pts.
Non-EURO pts predominantly receive HLA-disparate grafts.

Slide courtesy of: Dr. Warren Fingrut

Intersection of ancestry & SES with donor type

Non-EURO HLA-disparate graft recipients (vs EUROs):

- **> 2x with at least 1 low SES surrogate (3x with at least 2).**
- **> 4x on Medicaid.**
- **> 2x financial support.**
- **Pts supported: 50% more funds.**

		EURO ancestry (n = 292)	Non-EURO ancestry	
			HLA-matched (n = 57)	HLA-disparate* (n = 76)
Surrogates of low SES	≥ 1	71 (24%)	24 (42%)	**43 (57%)**
	≥ 2	25 (9%)	9 (15%)	**21 (28%)**
Neighborhood poverty (ADI ≥60)		14 (5%)	2 (4%)	**5 (7%)**
Medicaid insurance		11 (4%)	8 (14%)	**13 (17%)**
Financial support *medical* expenses		29 (10%)	12 (21%)	**22 (29%)**
Financial support *cost-of-living*		47 (16%)	13 (23%)	**27 (36%)**
Mean fold difference in funds dispensed / pt receiving support		Ref.	117%	**150%**

African HLA-disparate graft recipients (n = 36): most low SES by ≥ 1 (64%) or ≥ 2 (31%) surrogates.

** 25 Cord Blood, 30 haplos, 21 mmURD.*
Red: p < 0.001

The most vulnerable patients (non-EUROs w/ low SES) received the most specialized transplants (ie HLA-mismatched) that require highest level of care.

Slide courtesy of: Dr. Warren Fingrut

Just prior to admitting for transplant, the patient was diagnosed with SARS-CoV-2. The team considered the potential implications for her upcoming transplant.

What do we know about the impact of SARS-CoV-2 on stem cell transplantation?

Abstract 387: BMT within Four Weeks of Sars-Cov-2 Infection Is Associated with Increased Risk of Mortality: A National COVID Cohort Collaborative Study

- **Dataset**: National COVID Cohort Collaborative (N3C) enclave

- **Inclusion Criteria:** Patients with a diagnosis of hematological malignancies who underwent BMT between January 1st,2020 and October 31st, 2022, were identified. Recipients of BMT after a documented SARS-CoV-2 infection were further stratified according to time from infection to BMT

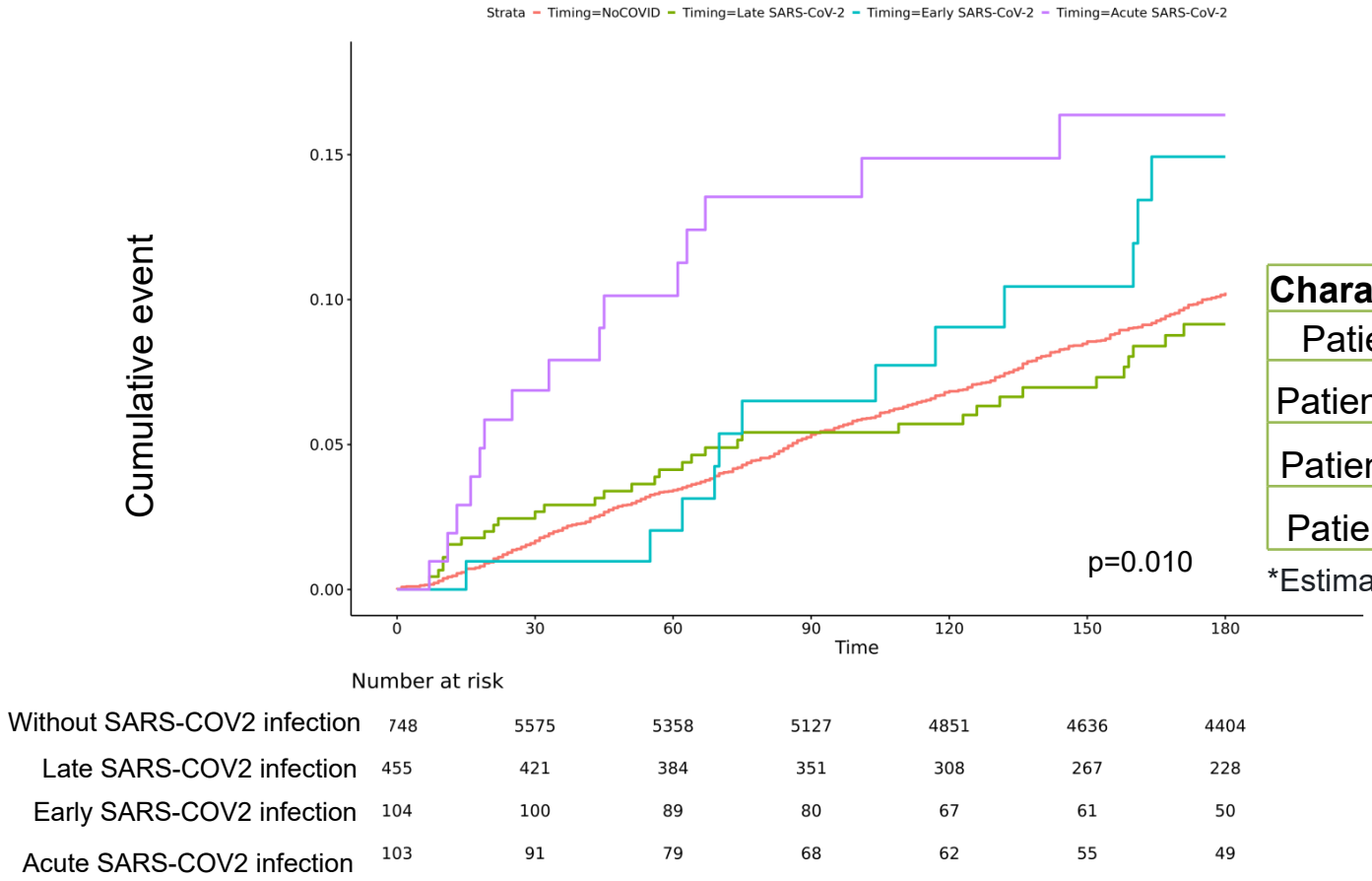
- Definition of timing of SARS-CoV-2 infection with respect to BMT
  Acute SARS-CoV-2 infection is < 4 weeks from SARS-CoV-2 diagnosis
  Early SARS-CoV-2 within 4-8 weeks from SARS-CoV-2 diagnosis
  Late SARS-CoV-2 >8 weeks after SARS-CoV-2 diagnosis
- Severity of SARS-CoV-2 infection was predefined by N3C according to WHO clinical progression scale*

- **Primary Objective:** Comparison of clinical outcome by timing and severity of SARS-CoV-2 infection preceding BMT

* WHO Clinical progression scale, ***Lancet Infect Dis*** **202**

Slide courtesy of: Dr. Meera Mohan

Acute SARS-CoV-2 Infection Increases Transplant Mortality

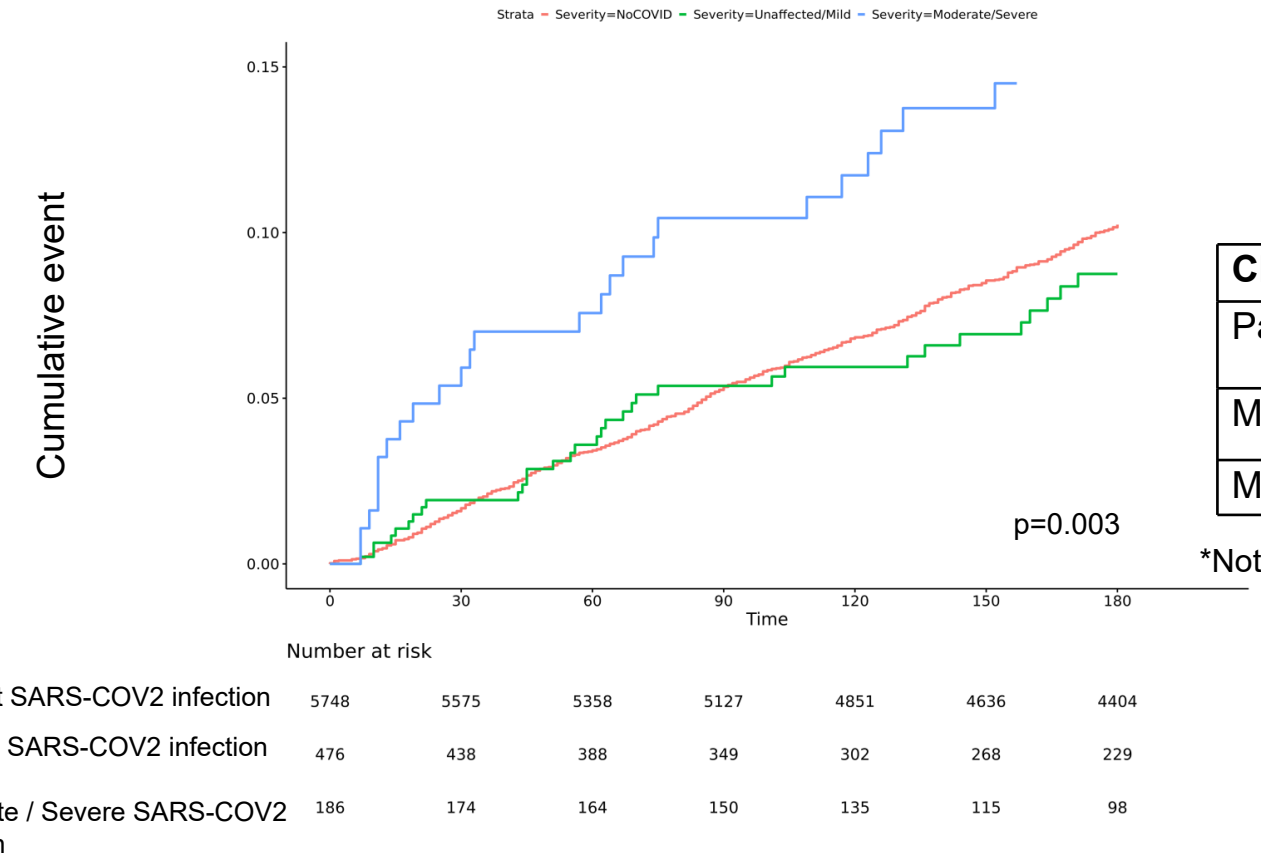


Characteristic	90 days*
Patients without SARS-CoV-2	5.7 (5.1, 6.2)
Patients with Acute SARS-CoV-2	14 (7.1, 20)
Patients with Early SARS-CoV-2	4.1 (<0.1, 7.9)
Patients with Late SARS-CoV-2	4.9 (2.9, 6.8)

*Estimated cumulative incidence of mortality by time

Slide courtesy of: Dr. Meera Mohan

Moderate To Severe SARS-CoV-2 Infection Increases Transplant Mortality



Characteristic	90 day*
Patients without SARS-CoV-2	5.3 (4.8, 5.9)
Mild SARS-CoV-2	5.4 (3.2, 7.5)
Moderate/Severe SARS-CoV-2	10 (5.9, 15)

*Note: Values are percentages with 95% confidence intervals

Slide courtesy of: Dr. Meera Mohan

During donor workup, several potential donors were identified. Her 62-year-old brother was identified as full match. Additionally, from the national donor registry, a fully matched unrelated 22-year-old male was identified.

Which donor would be preferred in this case?

Abstract 374: Comparison of Allogeneic HCT Outcomes from Younger Matched Unrelated Donor versus Older Sibling Donor for AML

- Allogeneic hematopoietic cell transplant (alloHCT) offers cure for adult patients with AML.
- With an ageing population, there is a need for improved access and outcomes of alloHCT for geriatric population.
- HLA-matched sibling donors (MSD) are considered the preferred donor type in clinical practice. However, MSDs for these patients are also likely to be older, often with higher comorbidities.
- Prior registry studies demonstrated that older donor age is associated with inferior survival. The impact of donor age is unknown in AML.

Slide courtesy of: Dr. Muhammad Bilal Abid

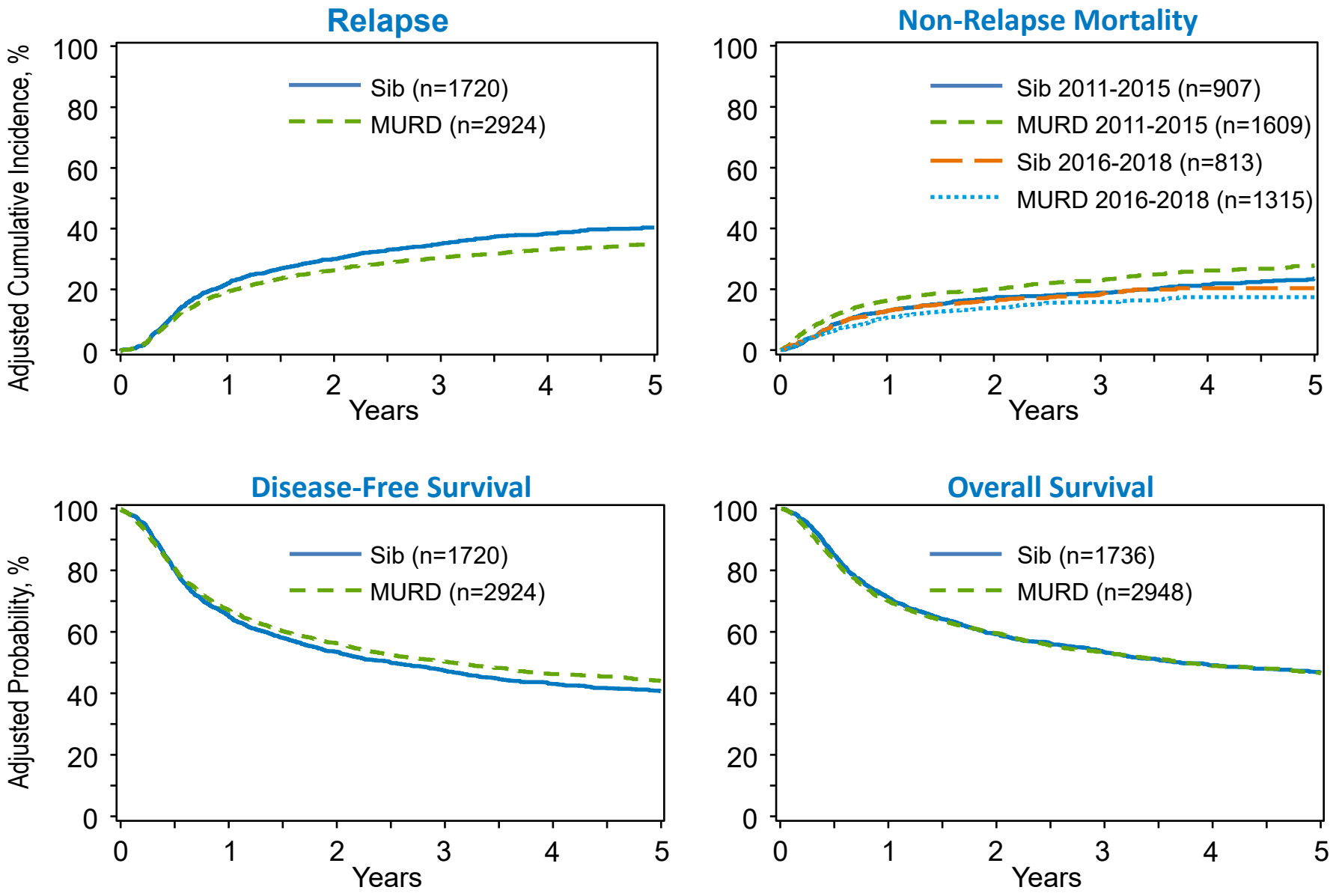
Multivariate Analysis

5-Year Adjusted CI of Relapse and NRM and Survival Probability

Outcome	No. of Patients	HR (95% CI)	P-value
Relapse			
MSD	327	41% (38%-43%)	***0.003***
MUD	557	35% (33%-37%)	
NRM 2011-2015			
MSD	304	24% (20%-27%)	***0.045***
MUD	530	28% (25%-30%)	
NRM 2016-2018			
MSD	23	20% (17%-24%)	0.147
MUD	27	17% (15%-20%)	
DFS			
MSD	327	41% (38%-43%)	***0.045***
MUD	557	44% (42%-46%)	
OS			
MSD	287	47% (44%-49%)	0.953
MUD	523	47% (45%-49%)	

Slide courtesy of: Dr. Muhammad Bilal Abid

AML 5-Year Survival



Slide courtesy of: Dr. Muhammad Bilal Abid

The patient recovered from SARS-CoV-2 and admission was planned for allogeneic stem cell transplant from a fully matched unrelated donor. The team discusses the conditioning regimen that will be pursued for the patient.

Should reduced intensity or myeloablative conditioning be pursued for this patient?

Abstract 876: The Novel Scoring System to Personalize the Conditioning Intensity in Elderly Patients

- The use of reduced-intensity conditioning (RIC) has dramatically increased worldwide over the past few decades
- RIC (vs. myeloablative conditioning): NRM ⬇ Relapse ⬆ OS ➡
- It is unclear how we should select the conditioning intensity for each individual Dr. Akahoshi et al proposed a novel scoring system that can guide the selection of conditioning intensity
- Patients with 1st allogeneic SCT aged 50-69 with acute leukemia in CR1 or CR2 or MDS, transplanted between 2008-2019 were included
- Patients who received haploidentical transplant with post-transplant Cytoxan or ATG/Campath were excluded
- Primary endpoint: Non-relapse mortality (NRM)

	Interaction *P* values
Age, category	
<60 vs. ≥60	**0.200**
Sex mismatch	
F to M vs. Others	0.300
Disease	
ALL vs. AML	0.580
MDS vs. AML	0.420
DRI	
Low/Int vs. High	0.240
KPS	
<80 vs. ≥80	0.240
HCT-CI	
<2 vs. ≥2	**0.077**
Donor type	
MUD vs. MRD	0.640
MMUD vs. MRD	0.660
UCB vs. MRD	**0.087**
GVHD prophylaxis	
CSA-based vs TAC-based	0.490
In-vivo T-cell depletion	
No vs. Yes	0.250

RICE score

Advanced age (≥ 60 y)

+

HCT-CI (≥ 2)

+

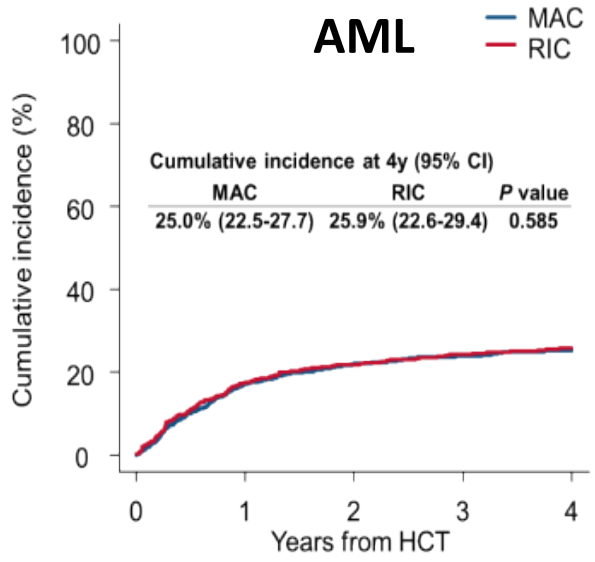
Umbilical cord blood

0/1 point: Low risk

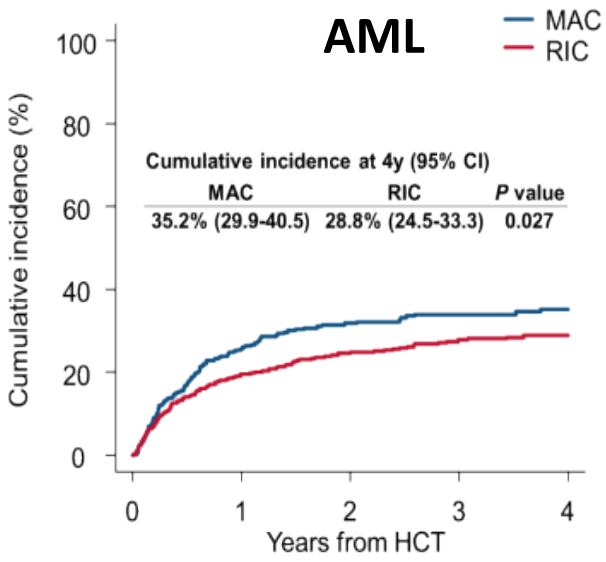
2/3 point: High risk

Slide courtesy of: Dr. Yu Akahoshi

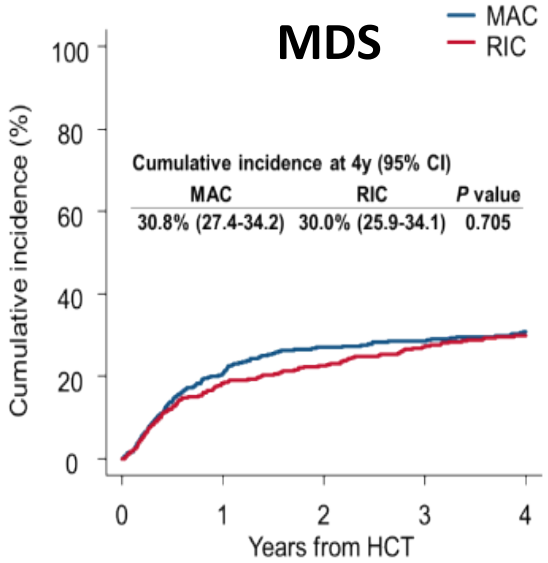
Low RICE score



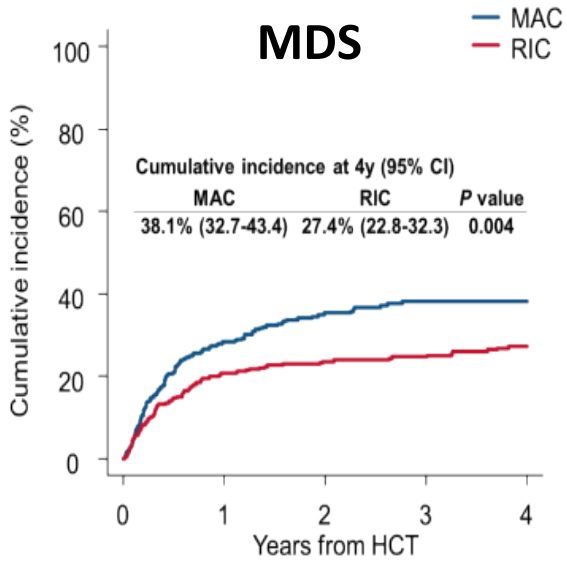
High RICE score

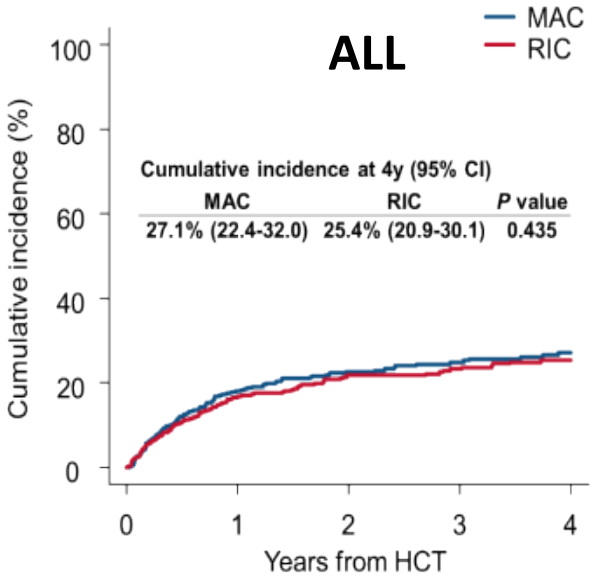


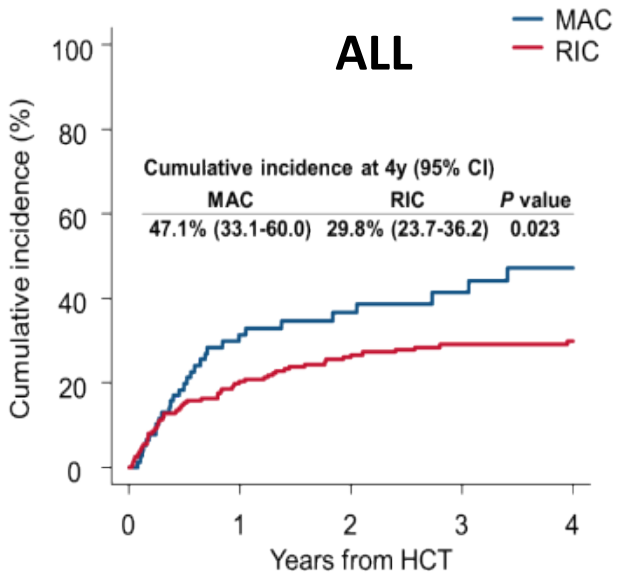
Low RICE score

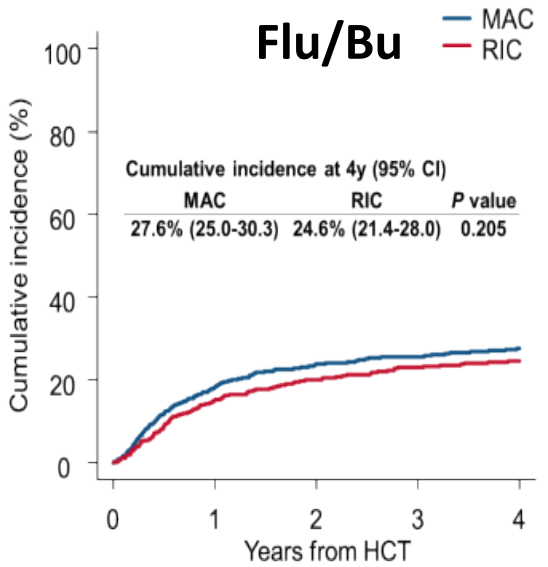


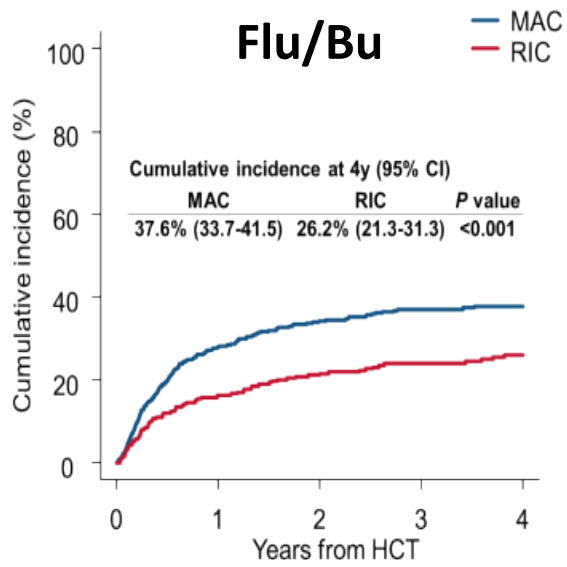
High RICE score











Slide courtesy of: Dr. Yu Akahoshi

The patient was admitted for allogeneic stem cell transplantation with a fully matched unrelated donor. Reduced intensity conditioning was recommended. The transplant team discussed options for GVHD prevention with the patient.

What regimen should be considered for GVHD prevention in this case?

Abstract LBA-4: Post-Transplant Cyclophosphamide, Tacrolimus, and Mycophenolate Mofetil As the New Standard for GVHD Prophylaxis in Reduced Intensity Conditioning: Results from Phase III BMT CTN 1703

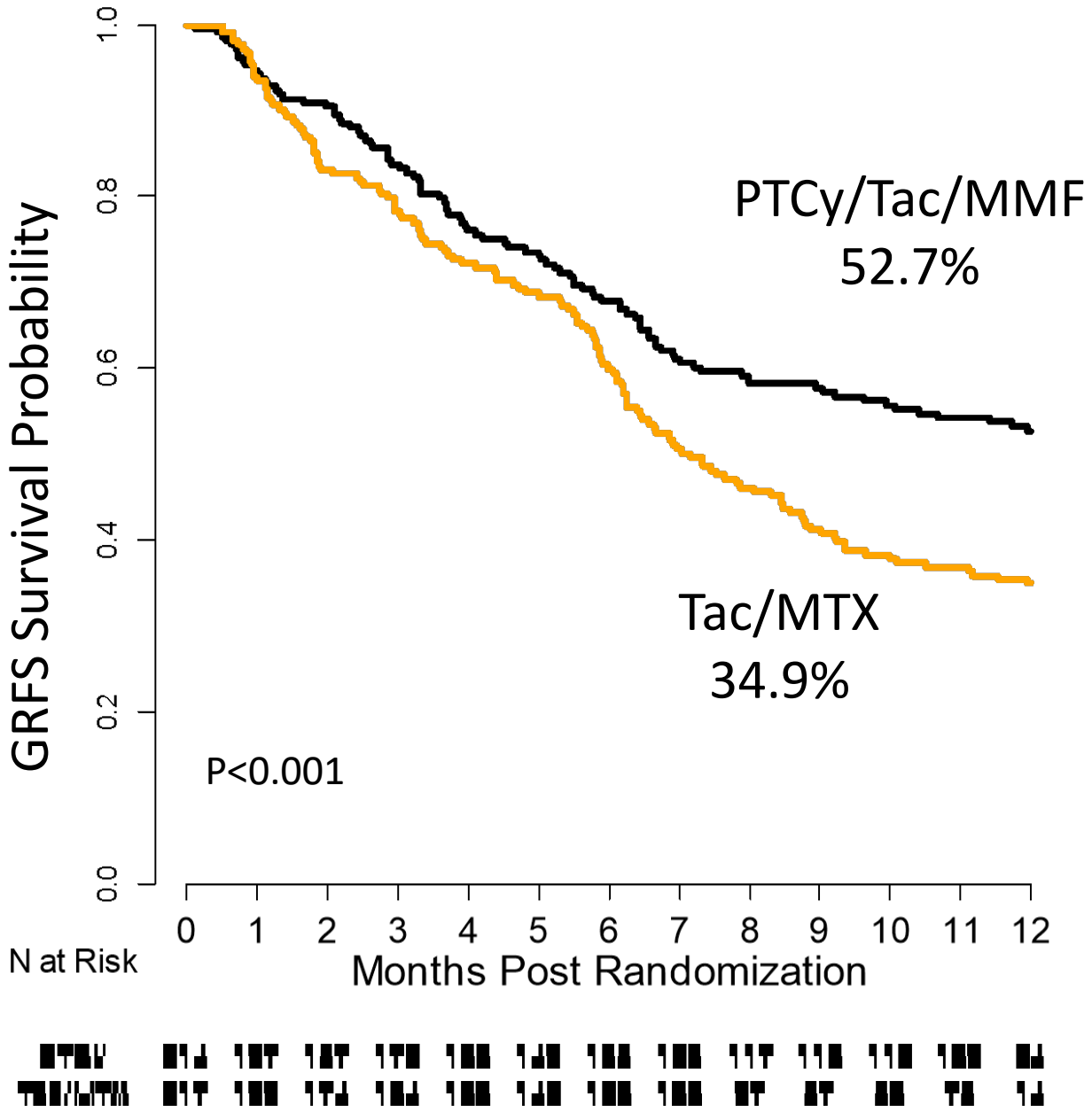
- Adults, reduced intensity conditioning, peripheral blood stem cell grafts
- 6/6 HLA-matched related donors or 7-8/8 HLA-matched unrelated donors
- Randomized 1:1 to PTCy/Tac/MMF vs Tac/MTX
- **Primary endpoint: 1-year GRFS** (time-to-event)
  - Event defined as grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppression, relapse/progression, or death
- **Secondary endpoints:** acute/chronic GVHD, systemic immunosuppression-free survival, hematologic recovery, engraftment, relapse/progression, transplant-related mortality (TRM), overall survival, infections, patient-reported outcomes.

Slide courtesy of: Dr. Shernan Holtan

BMT CTN 1703 PRIMARY ENDPOINT:

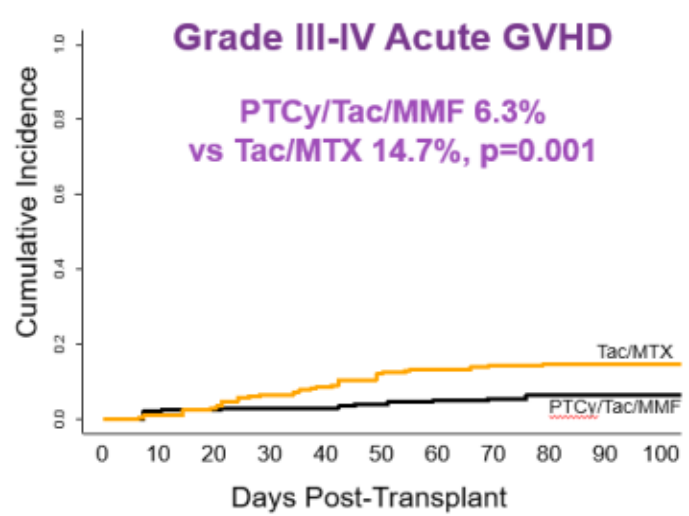
1-year GRFS superior with PTCy/Tac/MMF

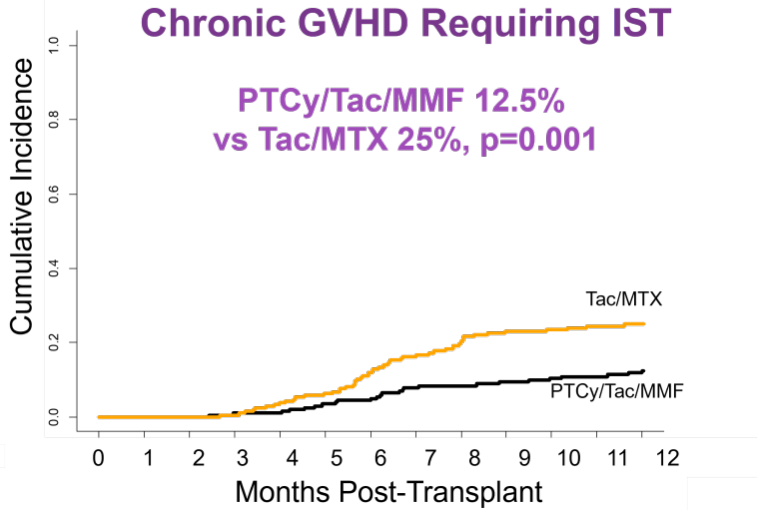
Hazard ratio 0.641
p<0.001

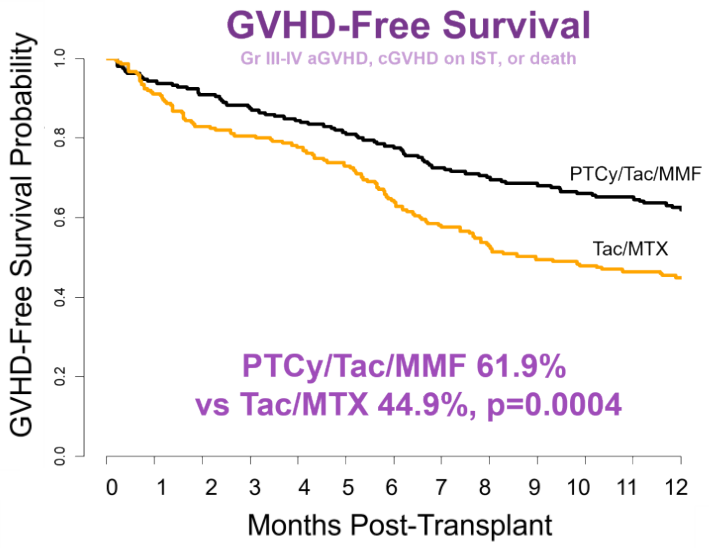


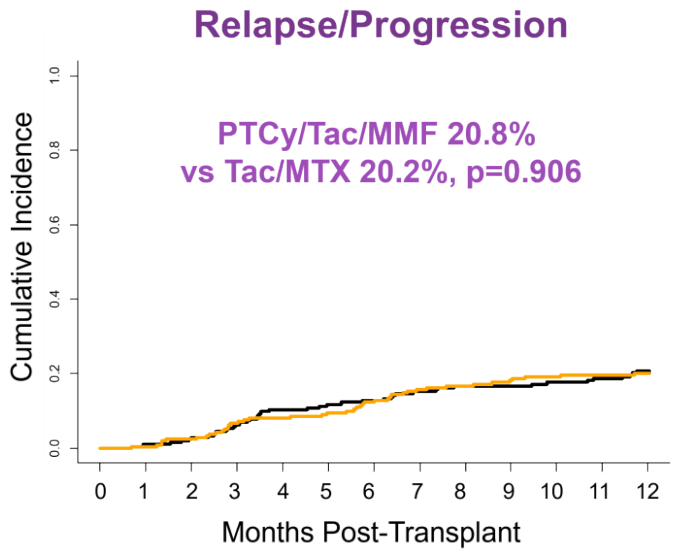
Slide courtesy of: Dr. Shernan Holtan

Improved GVHD outcomes not at expense of relapse.









Content courtesy of: Dr. Shernan Holtan

Eight weeks following allogeneic stem cell transplant, the patient developed GVHD of the skin. She was found to have Minnesota Grade 1 and Ann Arbor Score 1 (AA1) GVHD.

What treatment should be considered for her GVHD diagnosis?

JAK INHIBITORS: NON-STEROID GVHD TREATMENT

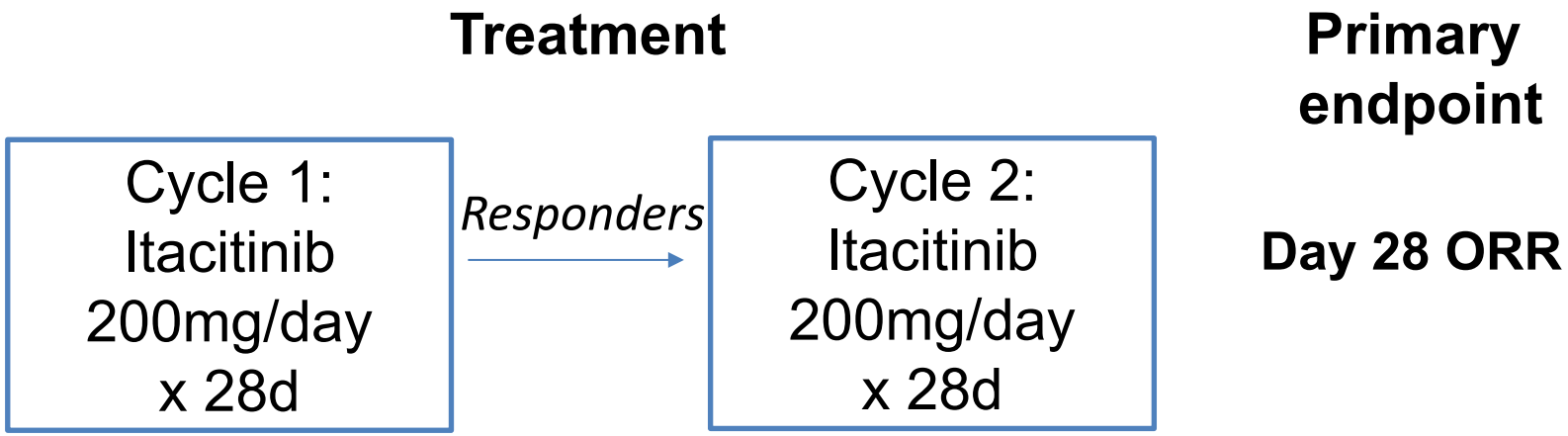
- Ruxolitinib (JAK1/2 inhibitor) is approved for steroid refractory GVHD (SR-GVHD)
  - Key side effect is cytopenia

- In a recent phase III clinical trial for initial GVHD treatment, itacitinib (selective JAK1 inhibitor) in combination with systemic corticosteroids was well tolerated

- The authors hypothesized that **itacitinib monotherapy** would effectively treat low risk GVHD with less infectious morbidity than SCS and little hematologic toxicity

Zeiser, NEJM, 2020 |Zeiser, Lancet Haematology, 2022
Slide courtesy of: Dr. Aaron Etra

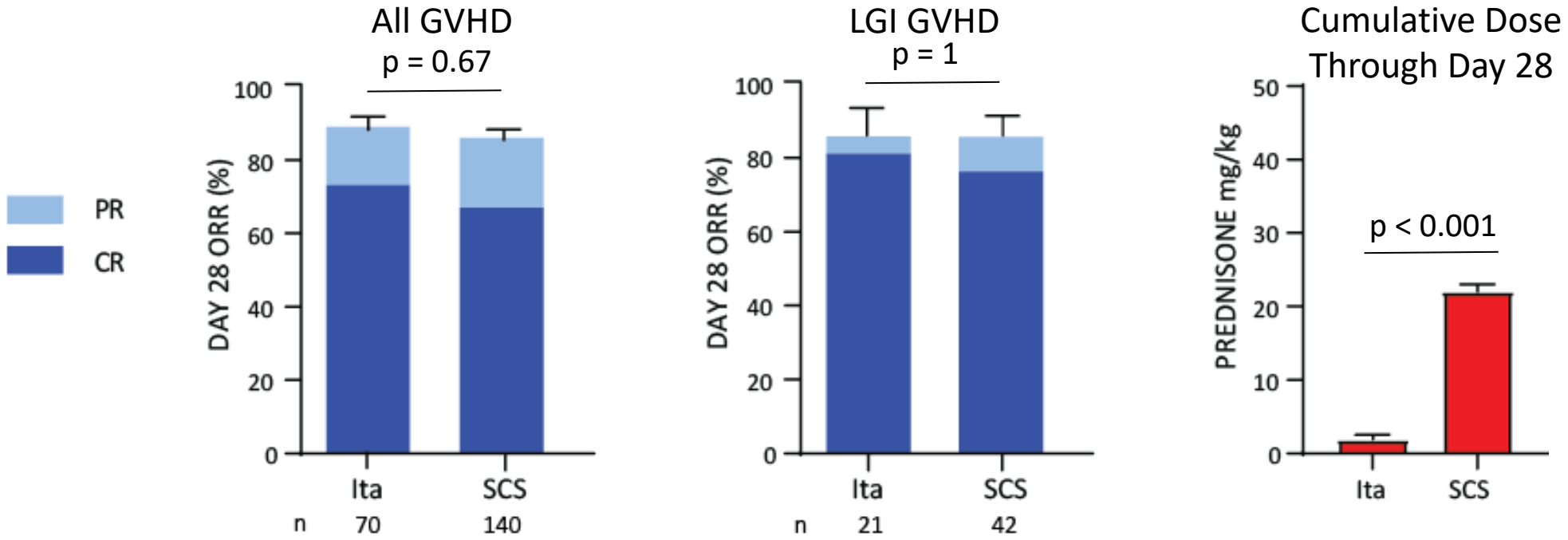
STUDY DESIGN: TREATMENT AND ENDPOINTS



Secondary endpoints:
NRM, relapse, cGVHD, and OS
Rates of serious infections, grade ≥3 cytopenias and non-infectious/non-hematologic TEAEs (up to 90 days post start of treatment)

Slide courtesy of: Dr. Aaron Etra

PRIMARY ENDPOINT: ITACITINIB AS EFFECTIVE AS SCS



- Itacitinib treated pts were more likely to respond by day 7 (81% vs 66%, p=0.02)
- Itacitinib treatment failures were salvaged with steroids (7/8)
- No difference in flares through day 90 (11% vs. 12%, p=0.88)
- No significant difference regardless of target organ, patient, transplant, or donor characteristics
- Itacitinib treated patients received 90% less systemic corticosteroids within the first month

Slide courtesy of: Dr. Aaron Etra

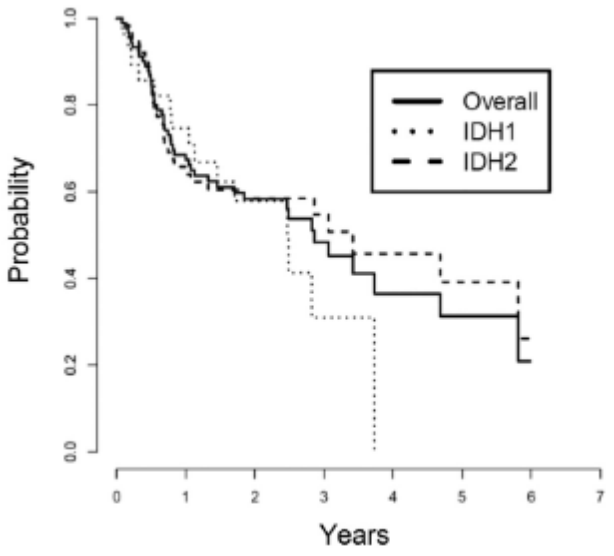
The patient's low risk acute skin GVHD resolved. The patient was known to have a mutation in IDH2 at diagnosis. She is curious if there is anything that will further increase her chances of remaining in remission following transplantation.

Is there a role for maintenance therapy following allogeneic stem cell transplant?

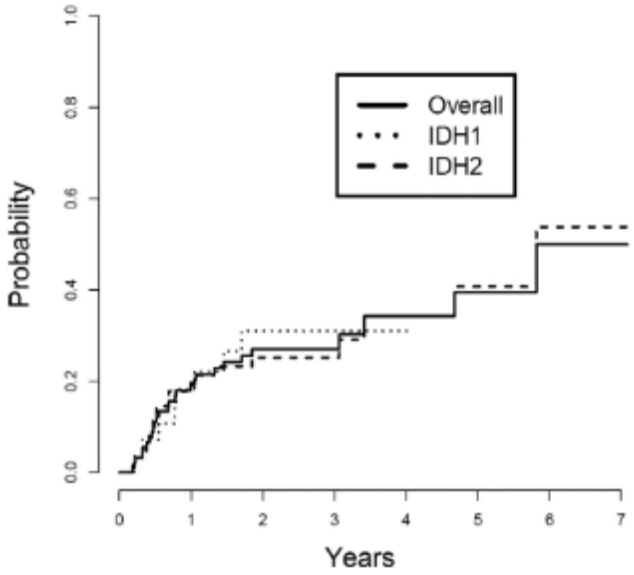
mIDH and Allo-HCT Outcomes

- Patients carrying *mIDH1/2* (n=112) underwent allo-HCT (MGH/DFCI/OSU)
- Median age: 64.1 years
- Median FU: 27.5 months
- ELN int/adverse risk: 78.5%
- HCT in CR1: 82%
- MAC regimen: 34%
- **2-year CIR: 28%**

Progression-Free Survival



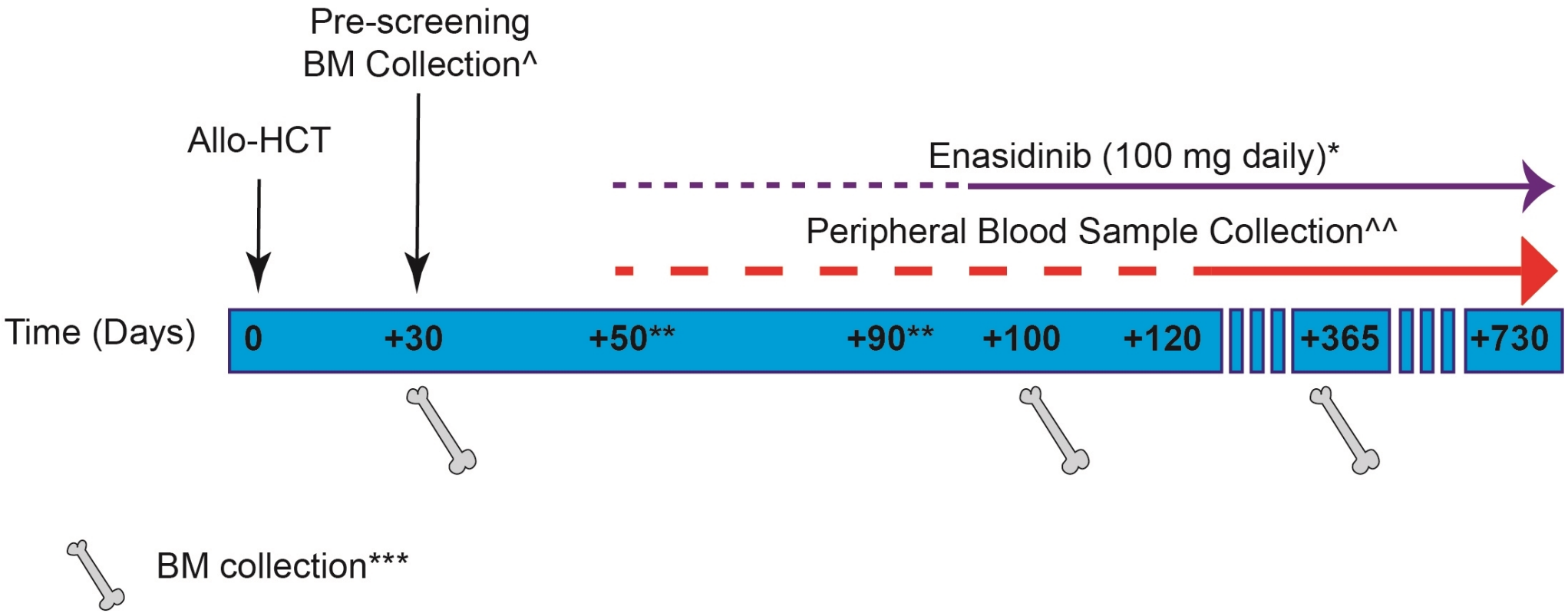
Cumulative Incidence of Relapse



Chen et al, Transplant Cell Ther, 2021

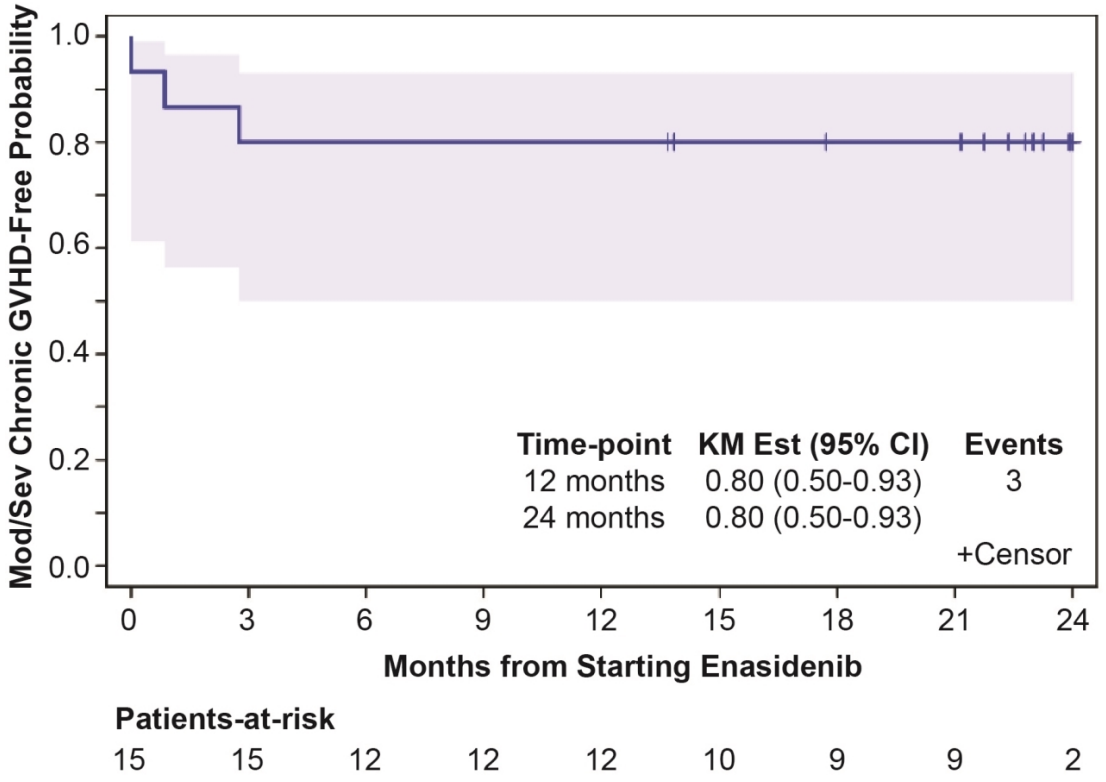
Slide courtesy of: Dr. Amandeep Salhotra

Study Schema

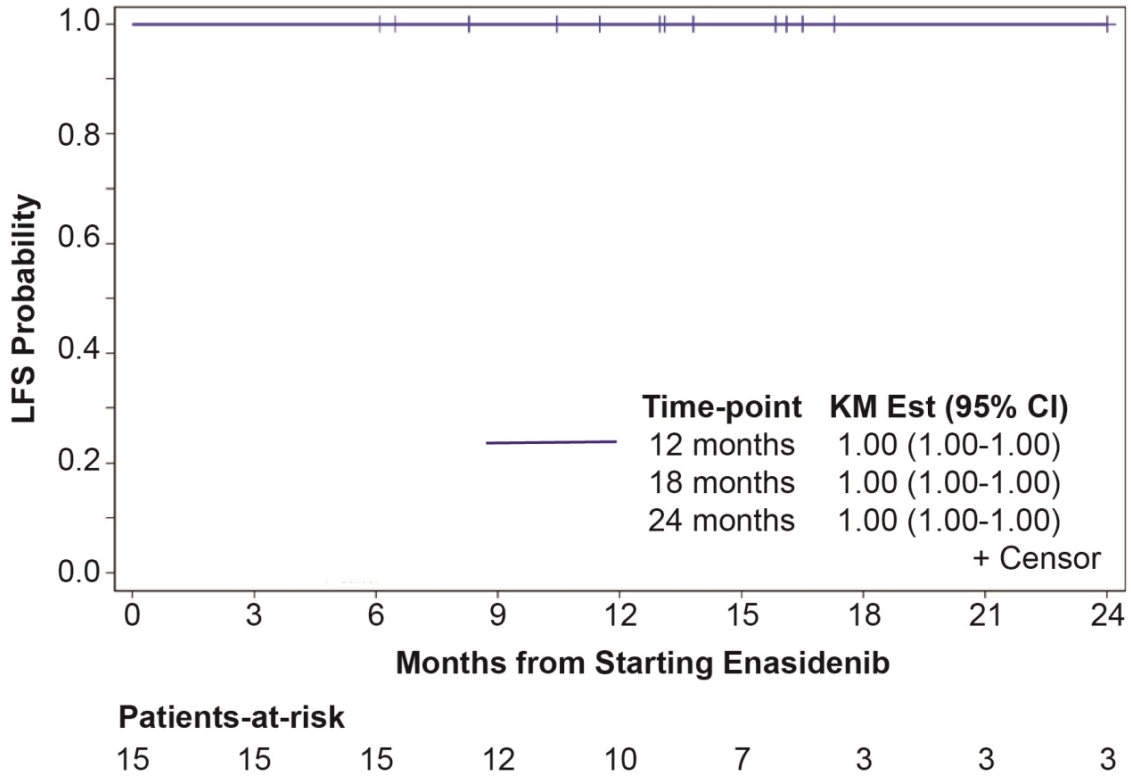


Slide courtesy of: Dr. Amandeep Salhotra

Chronic GVHD-Free Relapse-Free Survival



Leukemia Free Survival

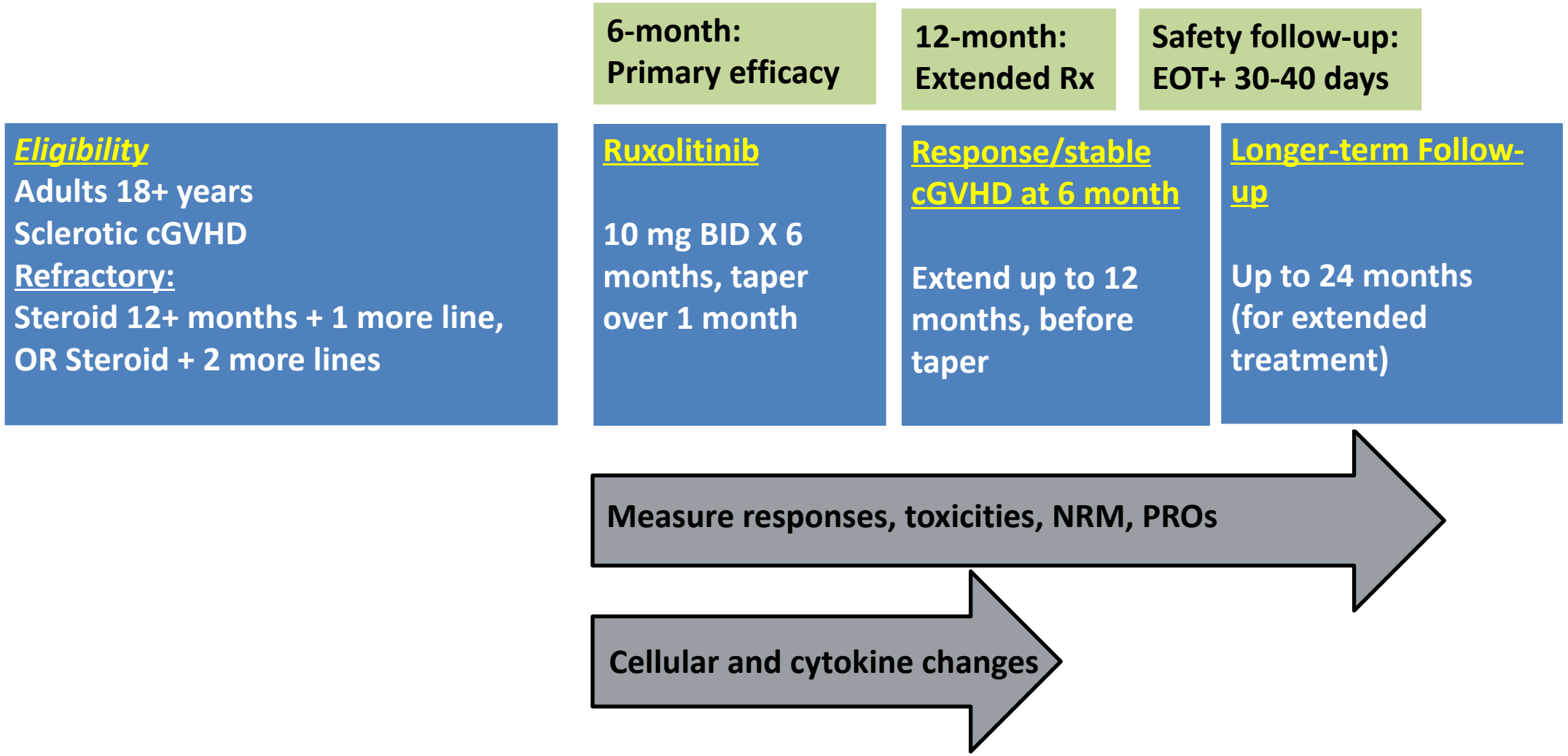


Slide courtesy of: Dr. Amandeep Salhotra

One year following transplant, the patient was diagnosed with chronic sclerotic GVHD of the skin. Unfortunately, she did not respond to steroid therapy.

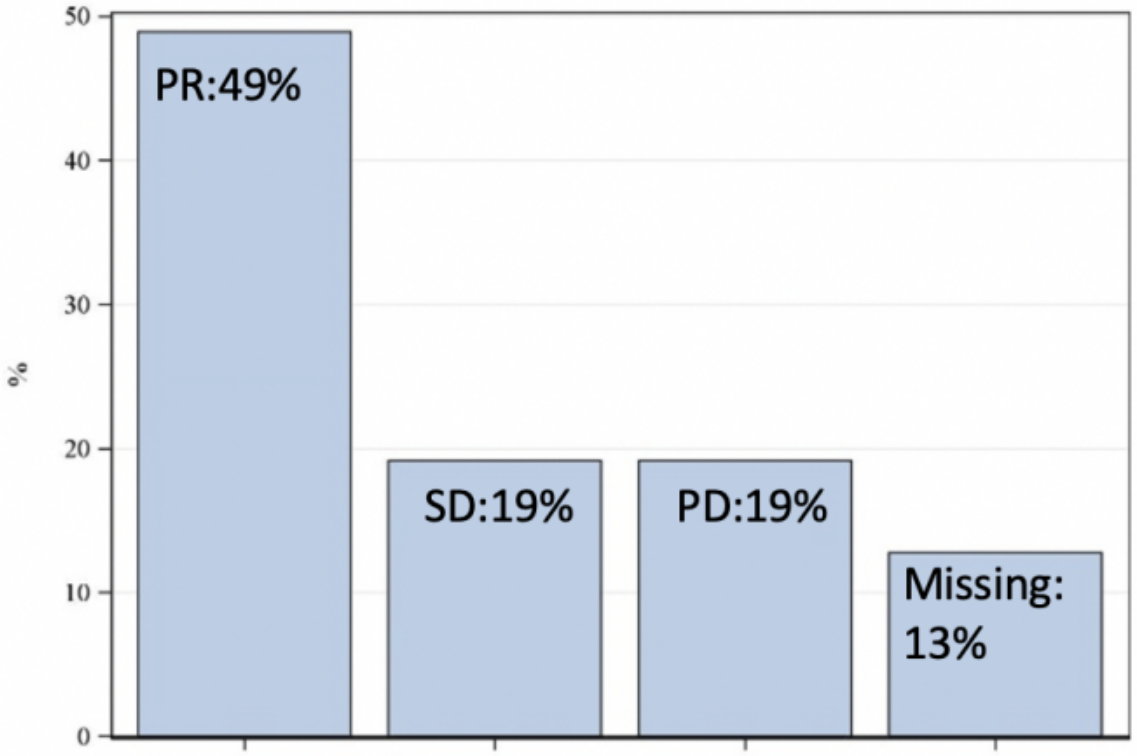
What treatment should be considered for her steroid-refractory chronic sclerotic GVHD diagnosis?

Schema: Multicenter Phase II Trial



Slide courtesy of: Dr. Vijaya Raj Bhatt

Skin/Joint Responses at 6 months



PR: 45% Joint; 19% Skin

Missing data: lack of follow-up, COVID-19 related, missing survey

Organ responses at 6 months

Eye 37%

Mouth 53%

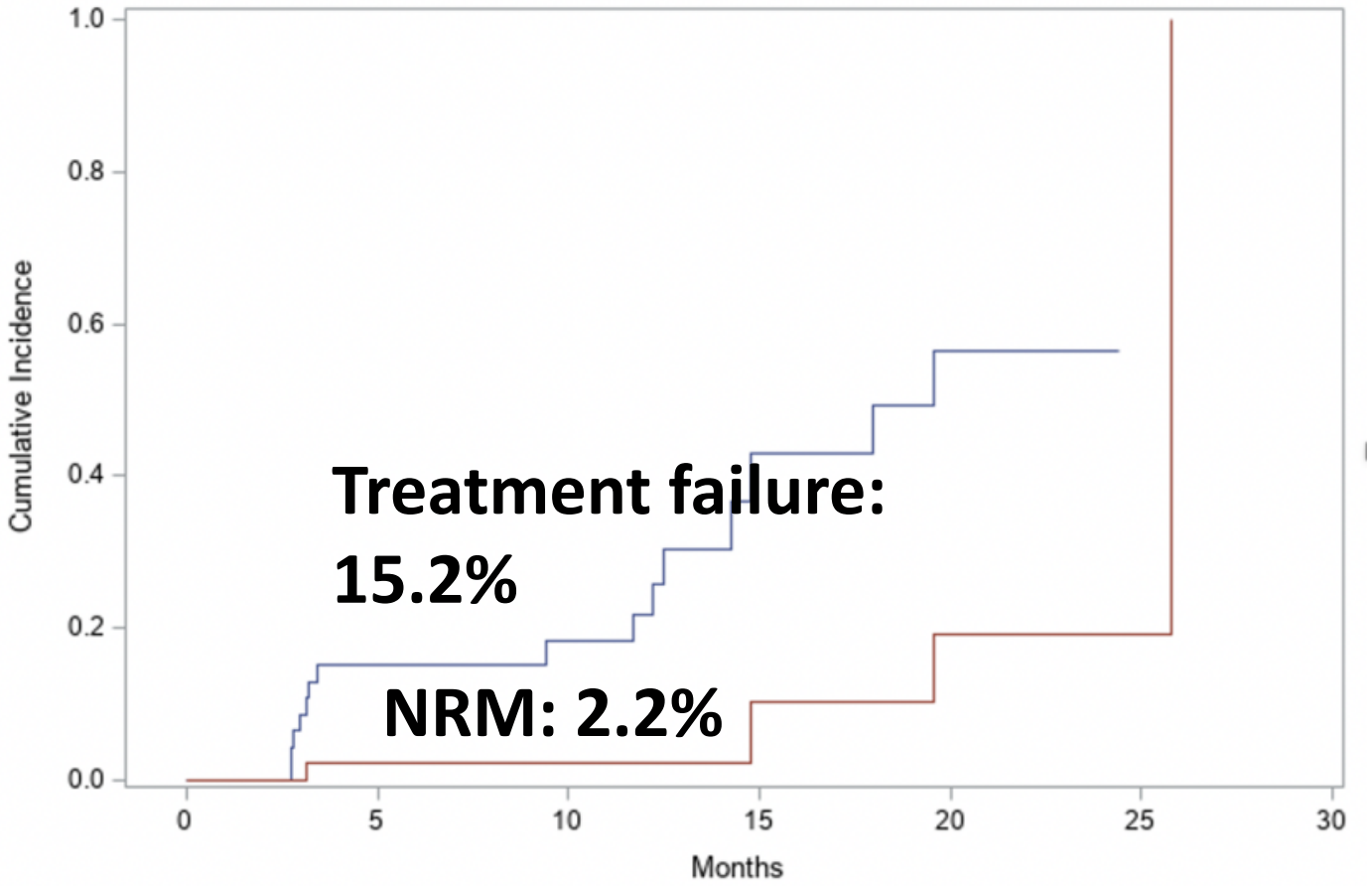
Esophagus 55%

Liver 36%

Small N: upper GI 67%, lower GI 67%, lung 11%, and liver 36%.

Content courtesy of: Dr. Vijaya Raj Bhatt

Treatment Failure and Non-Relapse Mortality at 6 Months



No malignancy relapse

Slide courtesy of: Dr. Vijaya Raj Bhatt

Conclusions

Discuss the approach to transplant in relapsed/refractory acute myeloid leukemia

- Watchful waiting and sequential conditioning prior to alloHCT results in comparable CR rates and overall survival and may be the preferred option whenever a stem cell donor is readily available.

Recognize associations between socioeconomic status, ancestry, and HLA-disparate grafts

- The most vulnerable patients (non-EUROs w/ low SES) received the most specialized transplants (ie HLA-mismatched) that require highest level of care.

Summarize the impact of SARS-CoV-2 infection on mortality in the peri-transplant period

- BMT within 4 weeks of SARS-CoV-2 infection was associated with a higher mortality.

Describe the impact of donor age during transplant donor selection

- Significant relapse reduction in AML pts undergoing alloHCT achieved with younger MUDs versus older MSDs.

Outline efforts to personalize conditioning regimen intensity

- The RICE score could identify patients with significant benefits regarding NRM if they underwent HCT with RIC

Delineate novel methods for graft versus host disease (GVHD) prevention and treatment

- PTCy/Tac/MMF should be standard GVHD prophylaxis in well-matched adult RIC PBSCT.
- A short course of itacitinib monotherapy was as effective as SCS in the treatment of low risk acute GVHD patients.
- Ruxolitinib was an effective treatment for steroid-refractory chronic sclerotic GVHD.

Discuss and describe emerging concepts for post-transplantation maintenance therapy

- Enasidenib maintenance post-HCT in pts with mIDH2 was safe and well tolerated and successfully prevented relapse.

Question 1

From the phase III ASAP Trial, for patients with relapsed or refractory AML between 18 and 75 years of age, proceeding to allogeneic transplant prior to salvage chemotherapy resulted in:

A) Lower complete remission rates

B) Higher rates of minimal residual disease negativity

C) Less time in the hospital

D) No beneficial effect of transplant prior to remission induction

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Question 2

Based on BMT CTN 1703, for patients proceeding to reduced intensity conditioning allogeneic stem cell transplant from a matched related or unrelated donor for AML, the following should be considered for graft versus host disease prevention:

A) Continuing tacrolimus for 1 year following transplantation

B) Provide cyclophosphamide on days 3 and 4 with tacrolimus and MMF

C) Reducing the dose of cells infused

D) Provide methotrexate and MMF for 6 months following transplant

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