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SCT in Older Patients

Uday Popat MD MBA

Indus BMT Webinar

10/3/2020

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Key Points

Older patients are most in need and are increasingly undergoing SCT

- But Outcomes are inferior

Current standard of Care for Older Patients

- Flu/Mel compared to Flu/Bu
- Low relapse but high NRM with Flu/Mel

Prognostic Factors

- Comorbidity Index
- Geriatric assessment: IADL, Impaired cognition

How do you improve outcomes in older patients?

- **Better Conditioning regimen:**
- fractionated busulfan regimen
- **Better Supportive care:** Enhanced recovery in stem cell transplantation (ER-SCT)
- To maintain and improve physiological reserve
- To reduce non-relapse mortality

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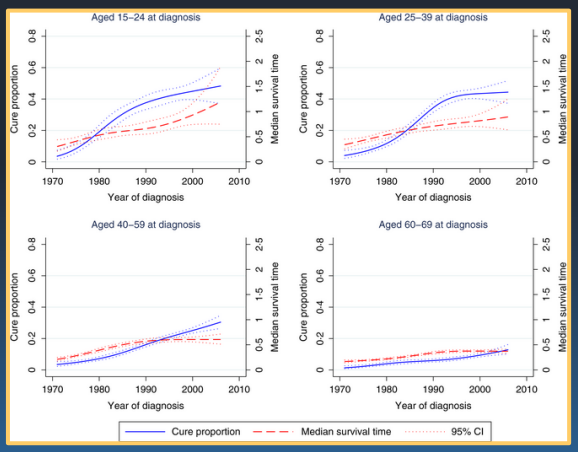
How old is old?

- It changes as I get older?
- ? >60
  - When prognosis is poor
  - When you use reduced intensity regimen
- ? >65
  - Medicare



Survival and cure of acute myeloid leukemia in England, 1971-2006: a population–based study Shah A et al Br J Haem 2013

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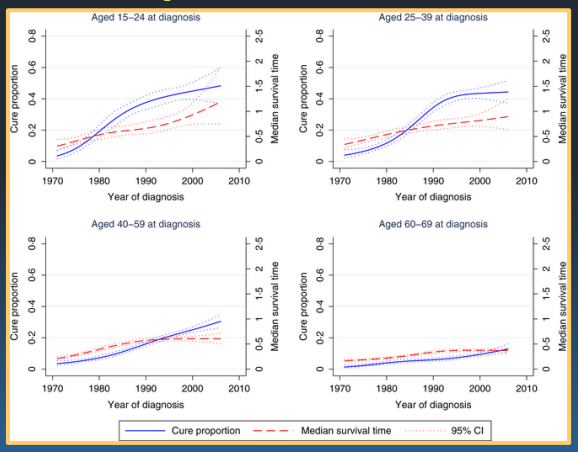
Why is SCT important in older patients?

- Median age of all heme malignancies except ALL is around 68-70
- It can be curative in substantial number of patients



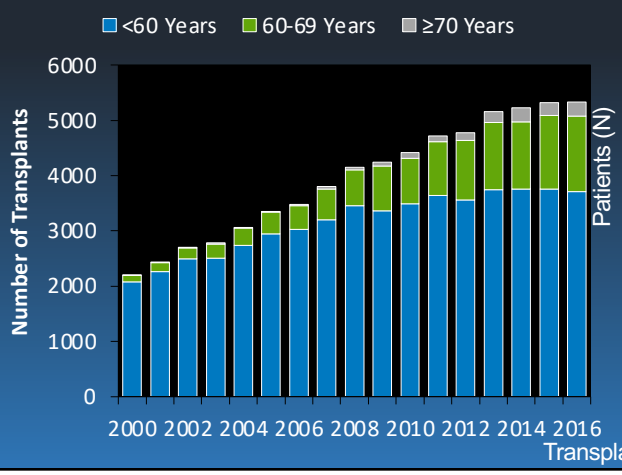
Survival and cure of acute myeloid leukemia in England, 1971-2006: a population–based study Shah A et al Br J Haem 2013

6

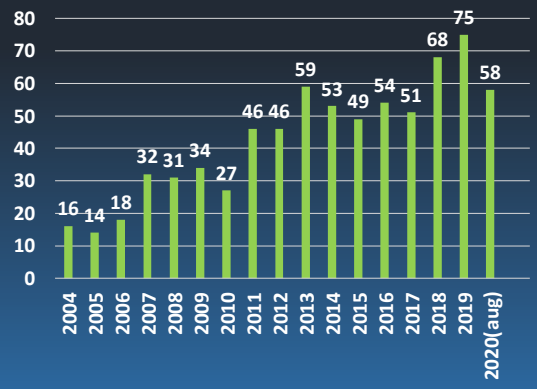
6

Trends in Allogeneic HCT by Recipient Age (Change)

CIBMTR Data



MD Anderson data ≥ 65 Years



Popat et al TCT20 abstract # 65

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Key Points

Older patients are most in need and are increasingly undergoing SCT

- **But Outcomes are inferior**

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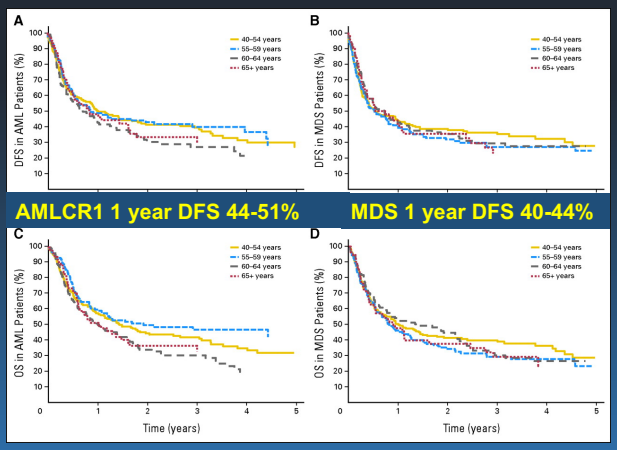
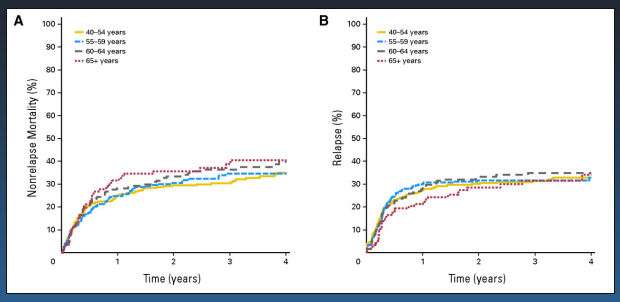
Reduced Intensity Transplantation In Patients with AML in CR1 or MDS



AMLCR1 1 year DFS 44-51%

MDS 1 year DFS 40-44%



Brian L. McClune et al. JCO 2010;28:1878-1887

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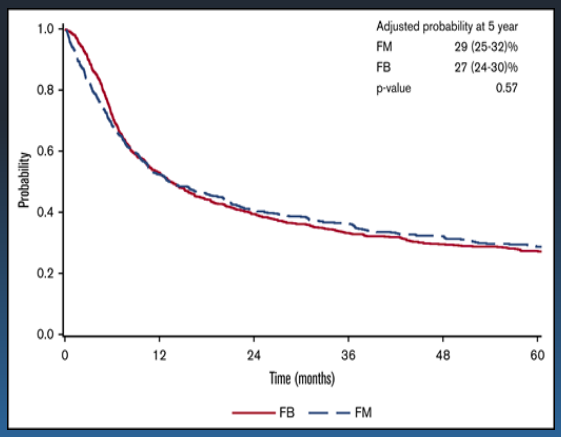
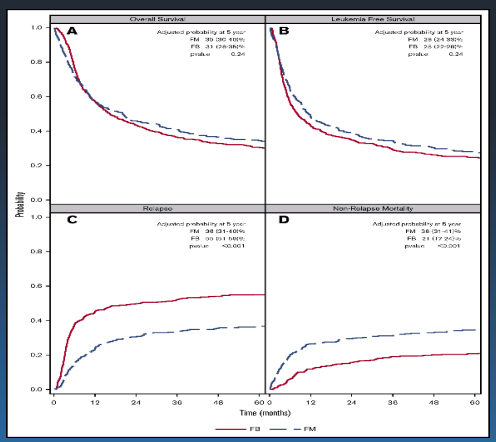
Reduced Intensity Transplantation In Patients with AML





Zhou et al. Blood Advances 2020;4 (13): 3180–90

10

Is there an optimal conditioning for older patients with AML receiving allogeneic hematopoietic cell transplantation?

- Analyzed 404 consecutive patients ≥60 years, with AML receiving 1st AHCT between 01/2005 – 08/2018
- Patients received one of the following conditioning regimens:
  1. **FM100**: fludarabine 160mg/m^2 + melphalan 100mg/m^2 (N=89)
  2. **FM140**: fludarabine 160 mg/m^2 + melphalan 140mg/m^2 (N=78)
  3. **Bu20000**: fludarabine (+/-clofarabine) 160mg/m^2 + IV busulfan x 4 days (AUC>/=5,000 µmol.min/day; equivalent dose 130mg/m^2/day) (N=131)
  4. **Bu16000**: fludarabine (+/-clofarabine) 160mg/m^2 + IV busulfan x 4 days (AUC 4,000 µmol.min/day; equivalent dose 110mg/m^2/day) (N=106)

Ciurea et at Blood (2020) 135 (6): 449–452

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Transplant Outcomes

	FM100	FM140	Bu20000	Bu16000	P value
3-year-NRM	19%	39%	35%	21%	0.06
3-year CI of relapse	32%	32%	30%	55%	0.003
5-year PFS	49%	30%	34%	23%	0.02
5-year GRFS	28%	20%	18%	9%	0.006
5-year PFS for patients with KPS< 90%	41%	27%	32%	22%	0.007
5-year PFS for patients >65 years	43%	28%	29%	16%	0.008

Ciurea et at Blood (2020) 135 (6): 449–452

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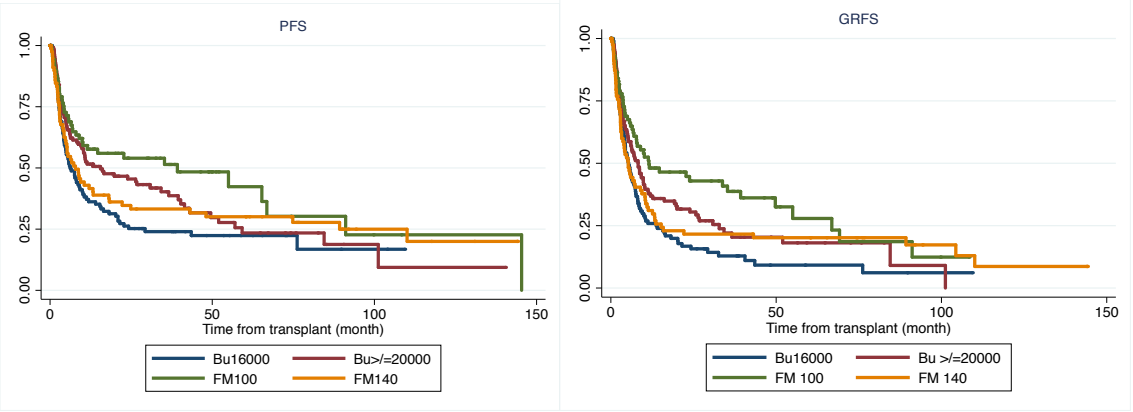
PFS and GRFS



Ciurea et at Blood (2020) 135 (6): 449–452

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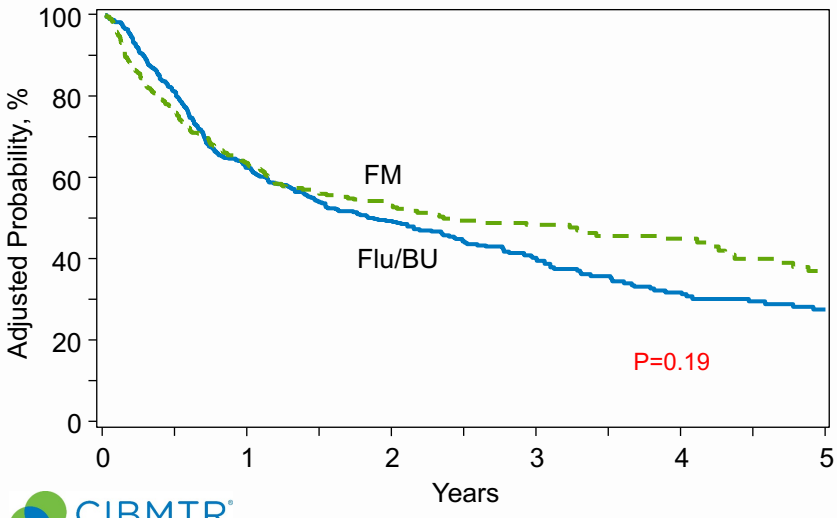
MDS: FM VS FB-Overall Survival



OS	RIC BuFlu	RIC FM
1-year	61 (57-65)%	63 (58-67)%
2-year	49 (44-53)%	51 (46-56)%
3-year	39 (35-44)%	45 (40-50)%

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Oran et al ASH 2019

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Key Points

Older patients are most in need and are increasingly undergoing SCT

- But Outcomes are inferior

Current standard of Care for Older Patients

- **Flu/Mel compared to Flu/Bu**
- **Low relapse but high NRM with Flu/Mel**

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How to predict NRM and OS:Comorbidity Index

- Score 1
  - Card: MI, CHF, CAD, A fib, EF≤ 50%
  - GI: IBD
  - Neuro: CVA, TIA
  - Hepatic: Chronic hepatitis, Bil ULN to X 1.5 ULN, AST/ALT ULN to X 2.5 ULN
  - Diabetes
  - Psych: Depression, Anxiety
  - Obesity: BMI >35
  - Infection:
- Score 2
  - Renal : Creat >2
  - Pulmonary: DLCO and/or FEV 1- 66-80% or dyspnea on slight activity
  - Peptic Ulcer
  - Rheum: SLE, RA,MCTD, Poly Rhem
- Score 3
  - Hepatic disease: Cirrhosis, Bil > 1.5 ULN, AST/ALT > 2.5 ULN
  - Previous solid tumor
  - Pulmonary: DLCO and/or FEV 1 ≤ 65%
  - Valvular heart disease

Sorror et al Blood. 2004; 104:961-968

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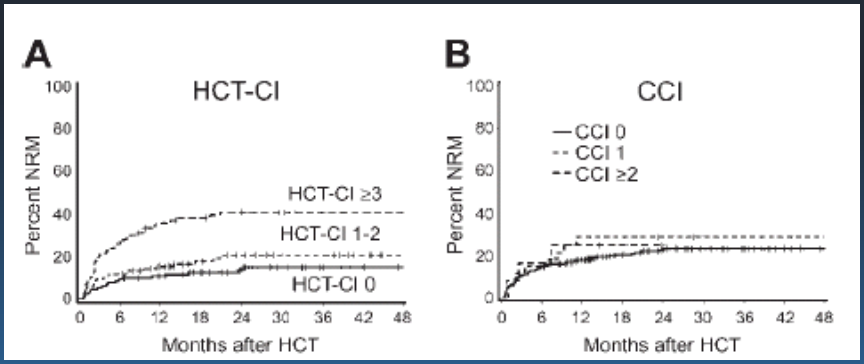
HCT-CI Comorbidity index: Results Comparison with CCI



Sorror et al Blood. 2004; 104:961-968

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Prognostic influence of GA in patients 50+ after Allograft (n=203)

All disease and all donor sources (matched related, unrelated, cord)

	Total Population			50-59 Years			60+ Years		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
GA Variables									
IADL Impairment	2.4	1.6-3.6	<.001	1.9	1.1-3.2	.03	3.3	1.8-6.1	<.001
Slow Walk Speed	1.8	1.1-2.8	.01	1.2	.6-2.3	.66	3.3	1.7-6.4	.001
Low Mental Health	1.7	1.1-2.5	.01	1.6	.9-2.6	.10	1.9	1.0-3.5	.04
Low Albumin	1.5	.9-2.5	.09	1.2	.6-2.6	.60	2.6	1.3-5.5	.01
High CRP	2.6	1.6-4.2	<.001	1.9	.9-3.8	.07	3.3	1.6-6.7	.001

Each GA variable adjusted for age, disease risk, conditioning regimen and HCT-CI

Muffly L,Haematologica, 2014

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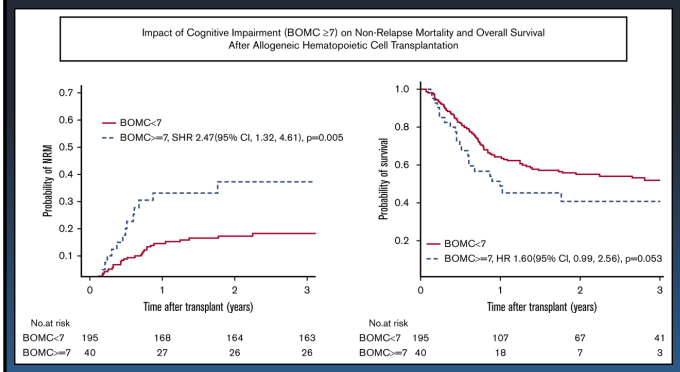
Geriatric assessment in older alloHCT recipients: association of functional and cognitive impairment with outcomes



Variable	Multivariate HR/SHR (95% CI, p value)
1-year NRM	
HCTCI score ≥3 (vs 0-2)	2.19 (1.22-3.94), p=0.009
Cognitive Impairment BOMC ≥7 (vs <7)	2.36 (1.21-4.60), p=0.01
1-year OS	
Cognitive Impairment BOMC ≥7 (vs <7)	1.94 (1.14-3.31), p=0.01

Rebecca L. et al Blood Adv, 2020,

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Key Points

Older patients are most in need and are increasingly undergoing SCT

- But Outcomes are inferior

Current standard of Care for Older Patients

- Flu/Mel compared to Flu/Bu
- Low relapse but high NRM with Flu/Mel

Prognostic Factors

- **Comorbidity Index**
- **Geriatric assessment: IADL, Impaired cognition**

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Main Idea

You can reduce toxicity and attendant mortality of Intense regimen by simply giving it over a longer period

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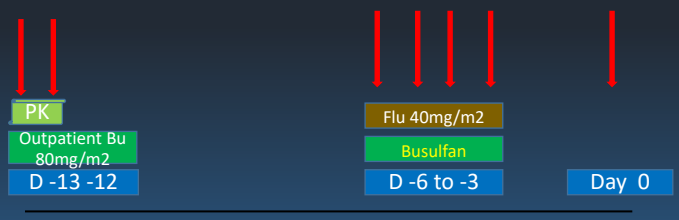
Fractionated Busulfan (f-Bu) Regimen (Timed Sequential Regimen):Lengthen Duration of Chemotherapy



- GVHD prophylaxis: Tacrolimus and mini Methotrexate
- Total Busulfan dose calculated to achieve AUC of 20,000. Equivalent to average AUC achieved with Myeloablative dose of IV busulfan 12.8mg/kg

Popat et al: The Lancet Haematology 2018 5, e532-e542

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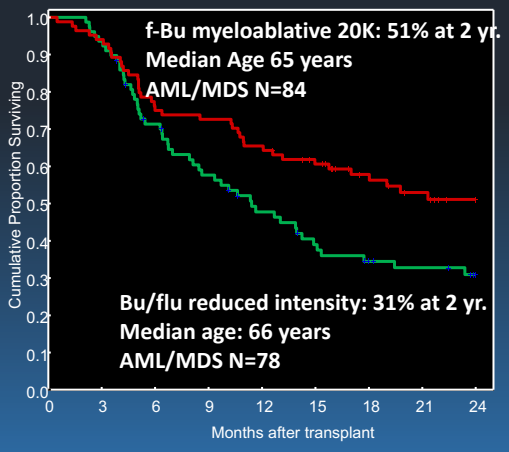
Myeloablative Fractionate busulfan(f-bu): Reduces Relapse and Improves Survival Compared to RIC regimen

- Safe
  - Non-relapse mortality was 6% at 100 days and 22% at 1 year in older patients
- Promising efficacy
  - When compared to reduced intensity Bu/Flu,
    - Reduced relapse rate 58% vs 34% (p=0.003)
    - Similar Non-relapse mortality
    - Better survival 31% VS 51%



Popat et al: The Lancet Haematology 2018 5, e532-e542

Popat et al ASCO 2017

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Hypothesis: Even longer administration of busulfan and post transplant cyclophosphamide will reduce GVHD, toxicity and non-relapse mortality

- GVHD prophylaxis: Cy on 3 and 4 and Tacrolimus +/- MMF starting day +5
- Busulfan AUC 20,000 equivalent to Bu 12.8mg/kg IV
- More intense than Bu/Flu or Bu/Cy

Popat et al TCT20 abstract# 6

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RESULTS: Patient Characteristics

	N=78	%
Age, median (range)	61	(39-70)
Diagnosis		
AML(CR/Cri/Not CR)	19(10/3/6)	24%
MDS(R-IPSS high/V.High)	21(14)	27%
MPD (DIPSS Plus Int 2/High)	31(14/11)	40%
Myeloma/CML/ALL	1/3/3	9%
Disease Risk Index		
High or Very high	18	23%
Low/Intermediate	60	77%

	N=78	Percentage
Donor		
Matched Related	29	37%
Matched Unrelated	49	63%
Comorbidity Score		
0	11	14%
1-2	34	44%
3 or more	33	42%
Cell source		
Peripheral blood	73	94%

Popat et al TCT20 abstract# 6

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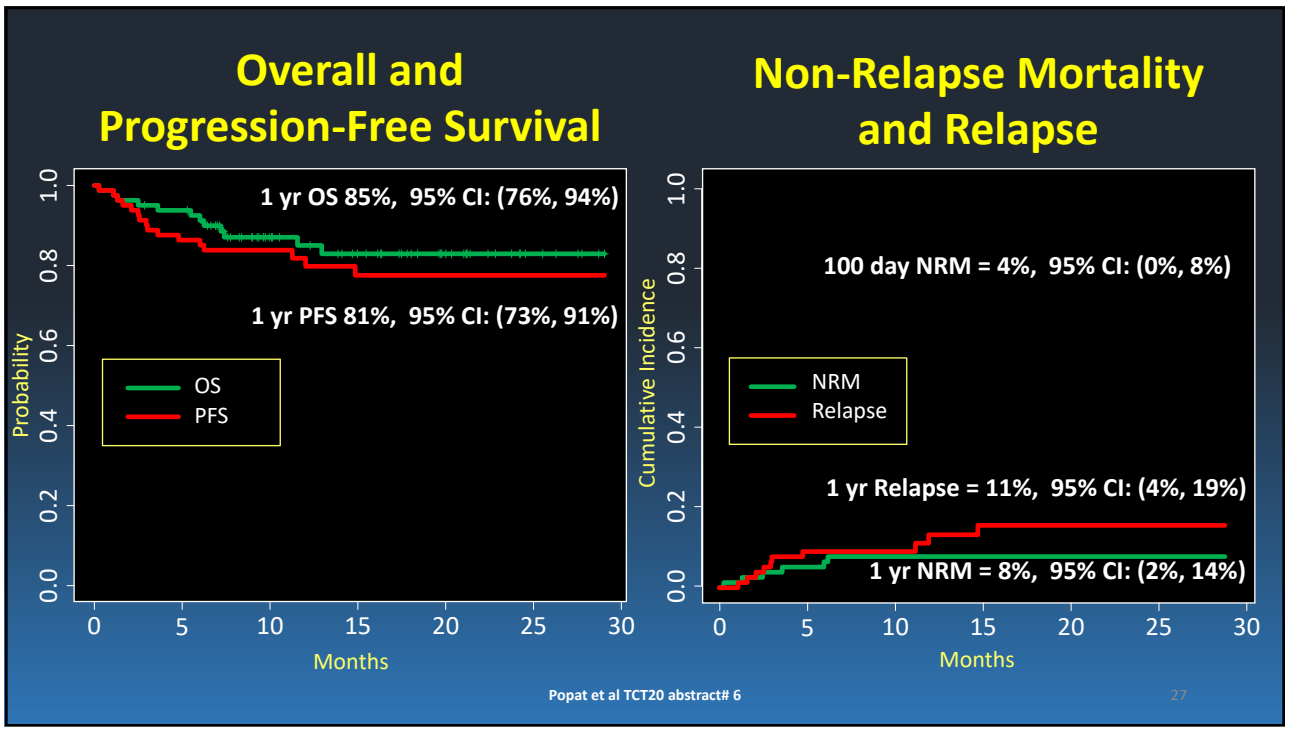
Overall and Progression-Free Survival
1 yr OS 85%, 95% CI: (76%, 94%)
1 yr PFS 81%, 95% CI: (73%, 91%)
OS
PFS
Probability
Months
Non-Relapse Mortality and Relapse
100 day NRM = 4%, 95% CI: (0%, 8%)
NRM
Relapse
1 yr Relapse = 11%, 95% CI: (4%, 19%)
1 yr NRM = 8%, 95% CI: (2%, 14%)
Cumulative Incidence
Months
Popat et al TCT20 abstract# 6
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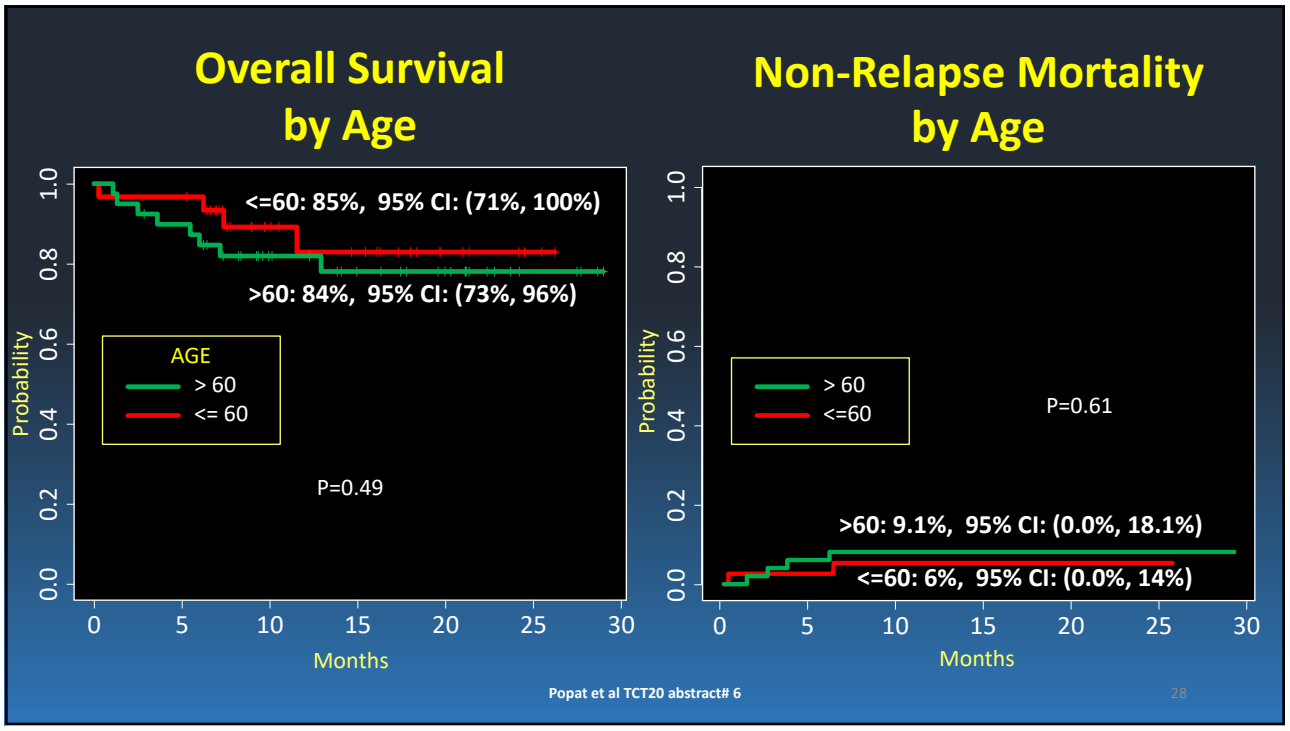
Overall Survival by Age
<=60: 85%, 95% CI: (71%, 100%)
>60: 84%, 95% CI: (73%, 96%)
AGE
> 60
<= 60
P=0.49
Probability
Months
Non-Relapse Mortality by Age
> 60
<=60
P=0.61
>60: 9.1%, 95% CI: (0.0%, 18.1%)
<=60: 6%, 95% CI: (0.0%, 14%)
Probability
Months
Popat et al TCT20 abstract# 6
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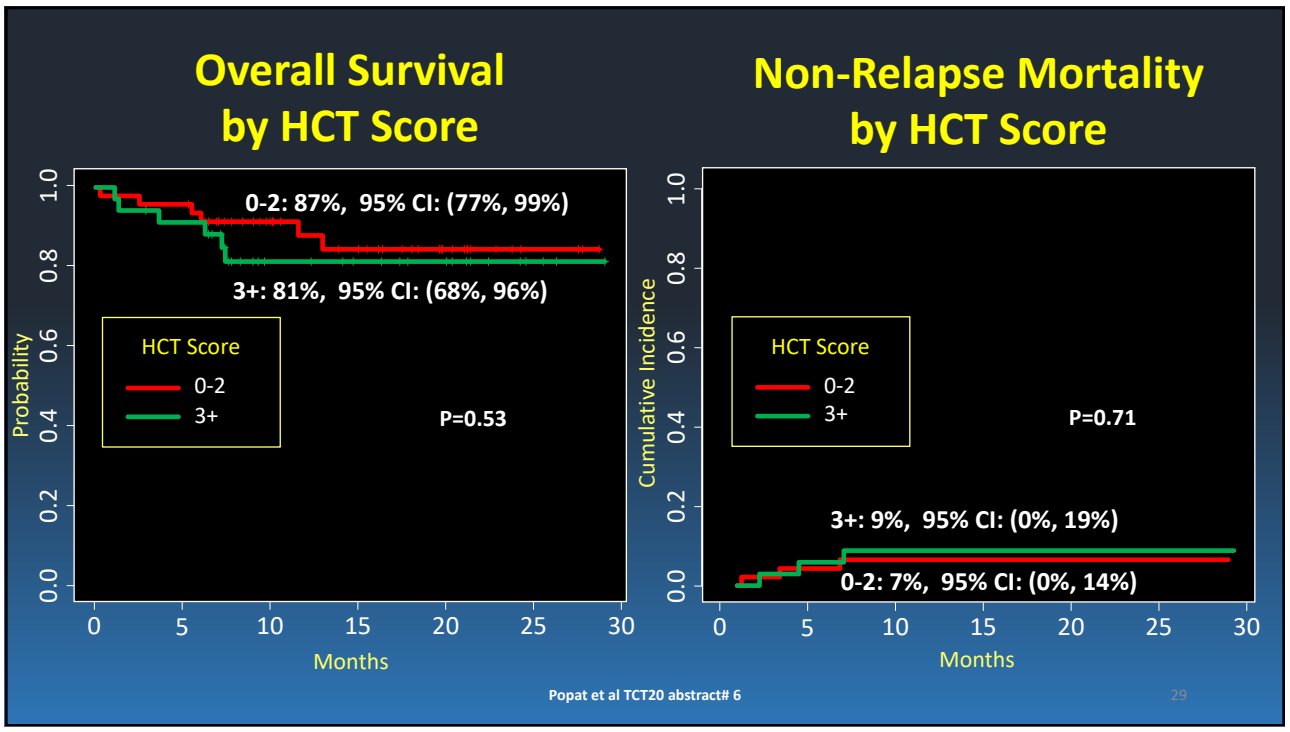
Overall Survival by HCT Score
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0-2: 87%, 95% CI: (77%, 99%)
3+: 81%, 95% CI: (68%, 96%)
HCT Score
0-2
3+
P=0.53
0
5
10
15
20
25
30
Months
Non-Relapse Mortality by HCT Score
Cumulative Incidence
HCT Score
0-2
3+
P=0.71
3+: 9%, 95% CI: (0%, 19%)
0-2: 7%, 95% CI: (0%, 14%)
Months
Popat et al TCT20 abstract# 6
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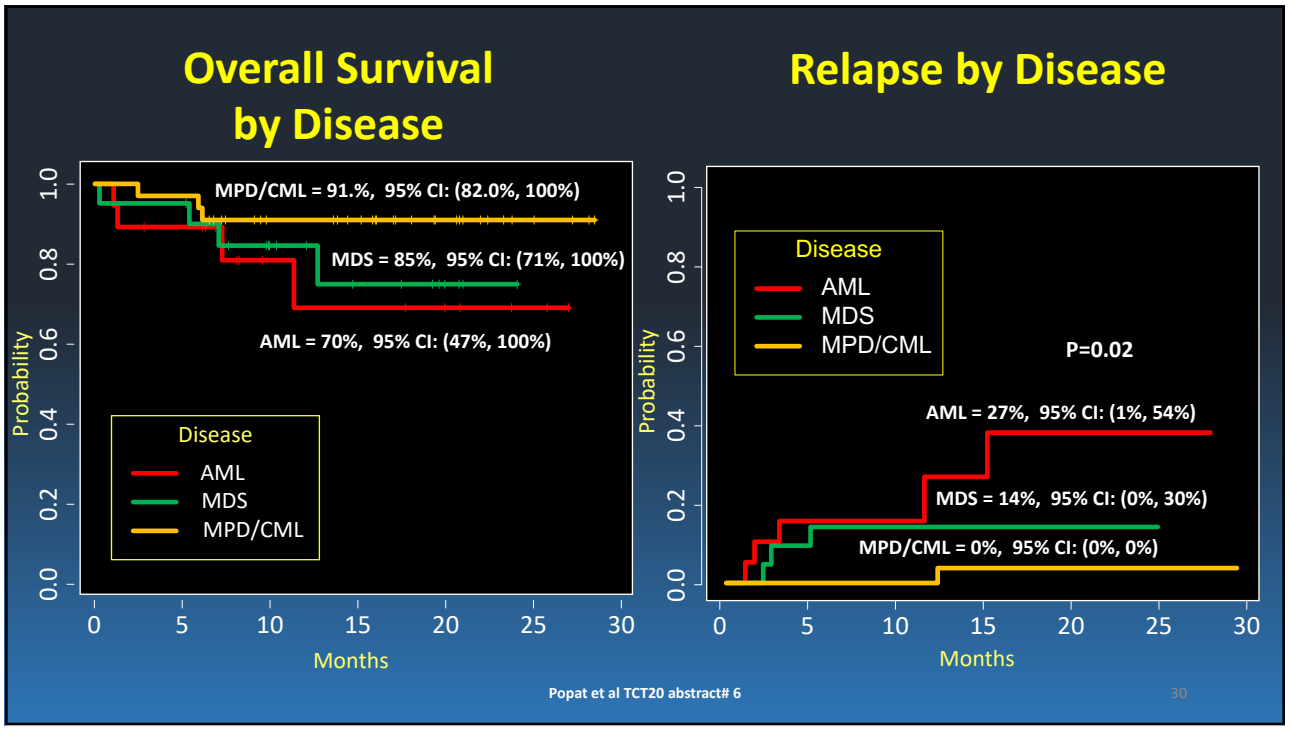
Overall Survival by Disease
Probability
0.0
0.2
0.4
0.6
0.8
1.0
MPD/CML = 91.%, 95% CI: (82.0%, 100%)
MDS = 85%, 95% CI: (71%, 100%)
AML = 70%, 95% CI: (47%, 100%)
Disease
AML
MDS
MPD/CML
0
5
10
15
20
25
30
Months
Relapse by Disease
Probability
Disease
AML
MDS
MPD/CML
P=0.02
AML = 27%, 95% CI: (1%, 54%)
MDS = 14%, 95% CI: (0%, 30%)
MPD/CML = 0%, 95% CI: (0%, 0%)
Months
Popat et al TCT20 abstract# 6
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Key Points

Older patients are most in need and are increasingly undergoing SCT
- But Outcomes are inferior

Current standard of Care for Older Patients
- Flu/Mel compared to Flu/Bu
- Low relapse but high NRM with Flu/Mel

Prognostic Factors
- Comorbidity Index
- Geriatric assessment: IADL, Impaired cognition

How do you improve outcomes in older patients?
- **Better conditioning regimen:**
  - **? fractionated busulfan regimen**

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How do we further improve outcomes?
Can we redesign transplant program for older patients rather than modify what we do for younger patients?

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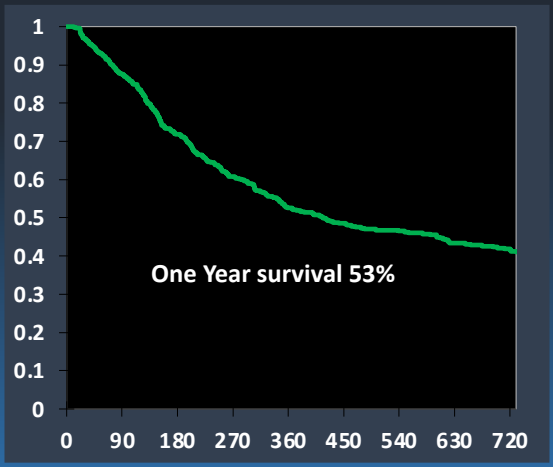
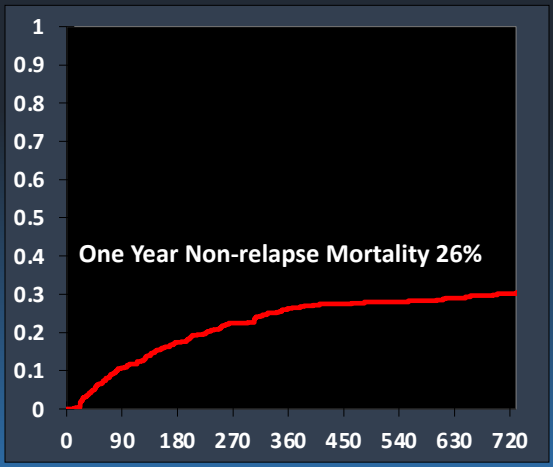
Outcomes Patients≥65 (n=500): MDACC





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Should We Consider Problems Of Aging?

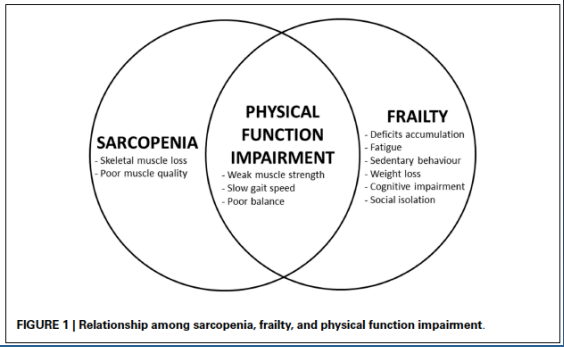
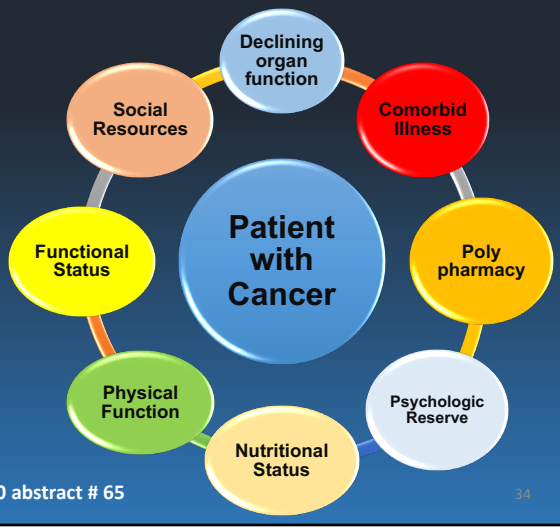


FIGURE 1 | Relationship among sarcopenia, frailty, and physical function impairment.



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- **Hypothesis: Multidisciplinary Supportive care program- Enhanced recovery in stem cell transplantation (ER-SCT) will**
  - Maintain and augment physiological reserve and
  - Reduce non-relapse mortality thereby improving survival

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Enhanced Recovery Stem Cell Transplant (ER-SCT)

- Objective/Goals for ER-SCT:
  - Initiate supportive care early in Allogeneic SCT recipients age 65 and older
  - Preserve and improve physiological reserve
  - Assess and manage conditions leading to worse QOL, morbidity and mortality
- Program roll out October 1 2017 after an year of planning
- Multidisciplinary Effort
  - PM&R Physicians, PT, OT
  - Dietician
  - Clinical Pharmacists
  - SCT APPs
  - SCT Registered Nurses
  - Geriatrician

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Enhanced Recovery-Stem Cell Transplantation (ER-SCT)

Geriatric Evaluation

Prehab	Pharmacy : Meds	Nutrition
• OT, PT, PMR team • Assess needs • Exercise program • Fatigue, cognition, ADL management • Sleep Hygiene	• Pre: Optimize HT, DM • Fluids, sedatives and supportive care appropriate for age during Hospitalization	• Assess needs • Counselling • Prevent and treat malnutrition • Supplements, Enternal, and TPN

Pre, during, and post hospitalization

PA/APRN/Pharm D

Nursing

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Inpatient Management

- Initiative to prevent fall and monitor for delirium
- Constant motivation for exercise and activities ADL/IADL during hospital stay
- Body image and coping strategies
- Normalizing their routine in the hospital
- Reduce default fluid rate
- No premeds for blood products
- Curtail opioid use
- Separate order sets for elderly with age appropriate meds and dose

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Enhanced Recovery (ER-SCT) First Year Experience

Enhanced Recovery Group

- Between 10/1/2017 – 9/30/2018
- 64 patients were eligible
- Age ≥ 65 years
- 57 patients (89%) enrolled into ER-SCT
- All 64 included in this analysis

Control Group

- Between 1/1/15-9/30/17
- 140 patients were eligible
- Age ≥ 65 years
- All 140 included

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Results: Patient Characteristics

	ER-SCT N=64	Controls N=140	P
SEX			0.7
F	26 (41)	53 (38)	
M	38 (59)	87 (62)	
Age, median	68 (65-74)	67 (65-79)	0.03
>70	12 (19)	24 (17)	0.8
Diagnosis			0.5
AML / MDS	45 (70)	108 (77)	
ALL	3 (5)	5 (4)	
CML / MPD	10 (16)	16 (11)	
CLL	4 (6)	3 (2)	
Lymphoma	2 (3)	4 (3)	
Myeloma	0	2 (1)	
Aplastic Anemia	0	2 (1)	

	ER-SCT N=64	Controls N=140	P
Prep & GVH proph*			
Post Cy			0.001
Fractionated-Busulfan+Flu	17 (27)	18 (13)	
Melphalan+Flu	28 (44)	17 (12)	
Tacro/Methotrexate			
Melphalan + Flu	9 (14)	24 (17)	
Busulfan 4 or Other + Flu	9 (14)	80 (57)	

*Conditioning Regimen and GVHD prophylaxis
1 additional pt had PCy and 4 days bu in each group

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Results: Patient Characteristics

	ER-SCT N=64	Controls	P
DRI	25 (39)	78 (56)	
High / v high	39 (61)	62 (44)	0.03
HCT-CI, median	2 (0-9)	3 (0-10)	0.1
>3	21 (33)	59 (41)	0.2
Donor type			
MUD	40 (62)	87 (62)	
MRD	15 (23)	42 (30)	
Haplo	9 (14)	11 (8)	0.3

	ER-SCT N=64	Controls	P
Cell source			
PB	48 (75)	86 (61)	0.06
BM	16 (25)	54 (39)	
Median follow up (range) months	16 (5-22)	28 (3-52)	N/A

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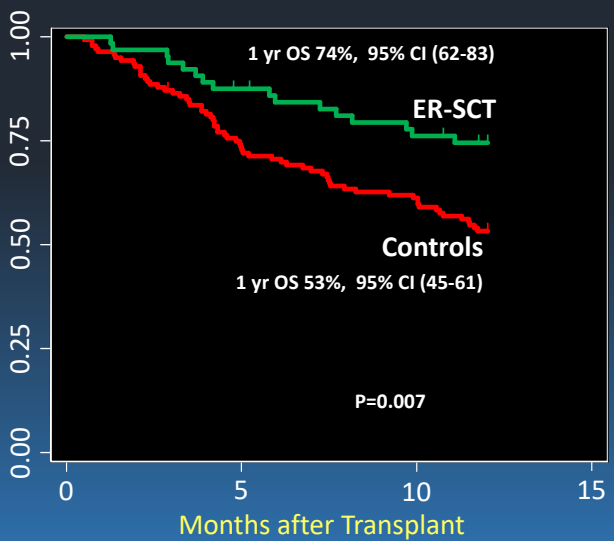
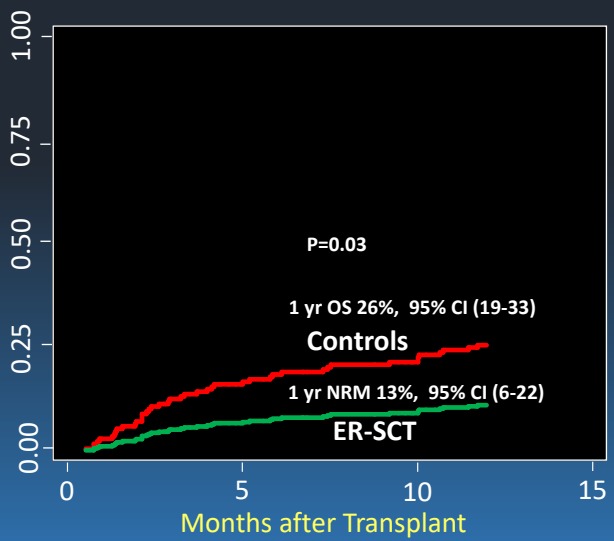
Overall Survival



Non-Relapse Mortality



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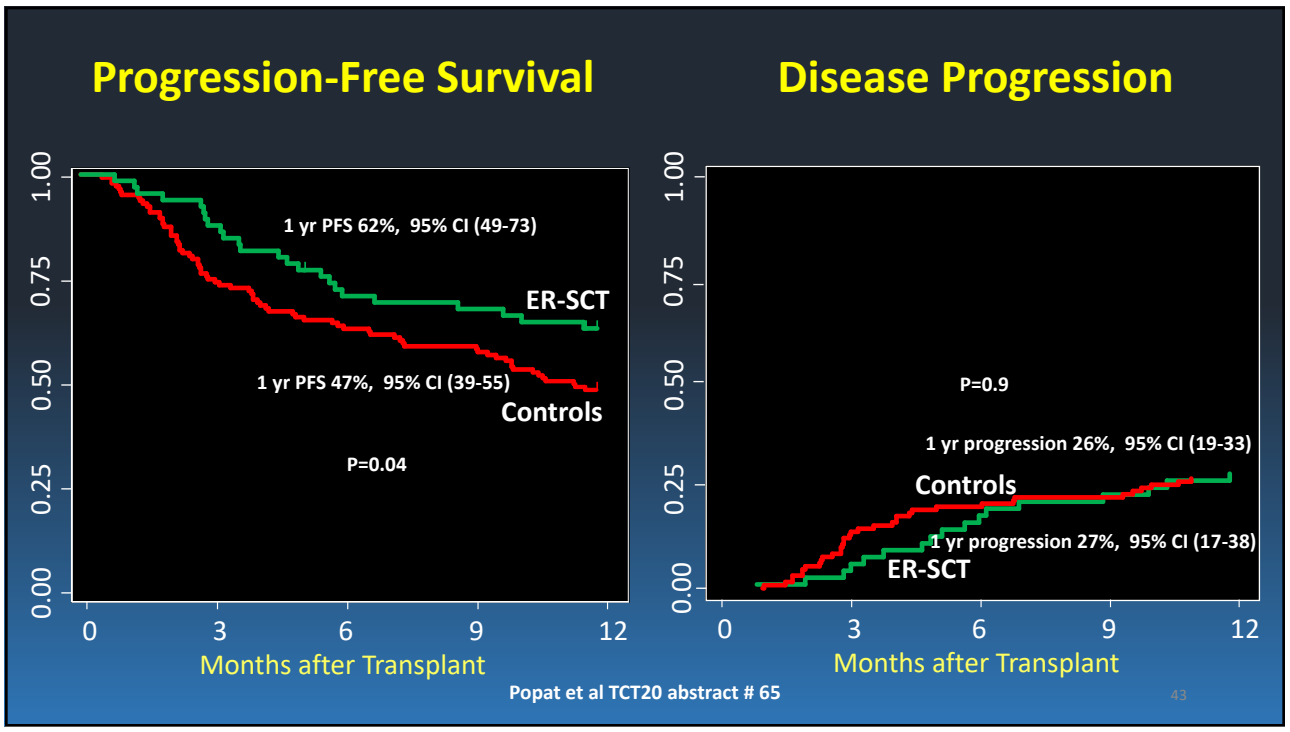

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NRM at 1 year: Multivariate Analysis

	HR (95% CI)	P
ER-SCT	0.4 (0.2-0.9)	0.02
HCT >3	2.0 (1.1-3.7)	0.02
Donor MRD	0.2 (0.1-0.7)	0.008

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Key Points

Older patients are most in need and are increasingly undergoing SCT
- But Outcomes are inferior

Current standard of Care for Older Patients
- Flu/Mel compared to Flu/Bu
- Low relapse but high NRM with Flu/Mel

Prognostic Factors
- Comorbidity Index
- Geriatric assessment: IADL, Impaired cognition

How do you improve outcomes in older patients?
- Better conditioning regimen:
  - ? fractionated busulfan regimen
- Better supportive care: Enhanced recovery in stem cell transplantation (ER-SCT)
  - To maintain and improve physiological reserve
  - To reduce non-relapse mortality

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Key Points

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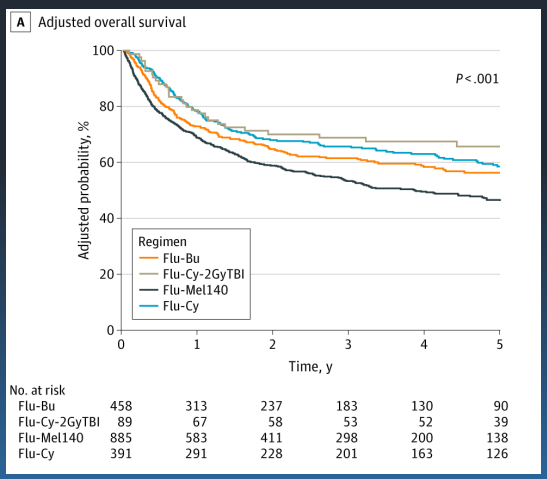
Lymphoma



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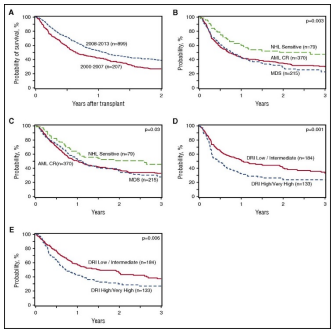
Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States



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