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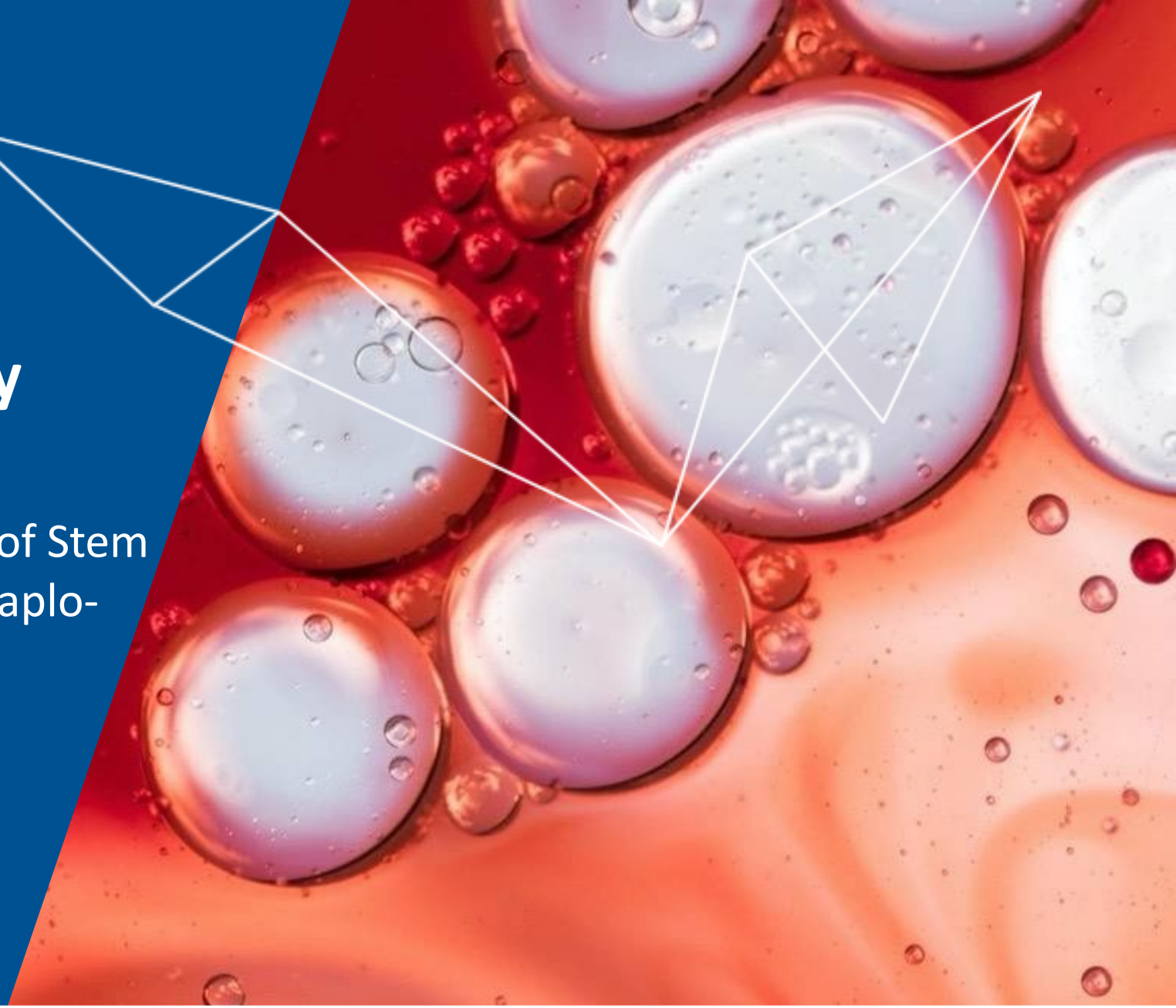
EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Clinical Case – Session Overview of Stem Cell Transplantation – Focus on Haplo-identical SCT

Speaker: Alexandros Spyridonidis

Hyderabad, India
March 1-3, 2024



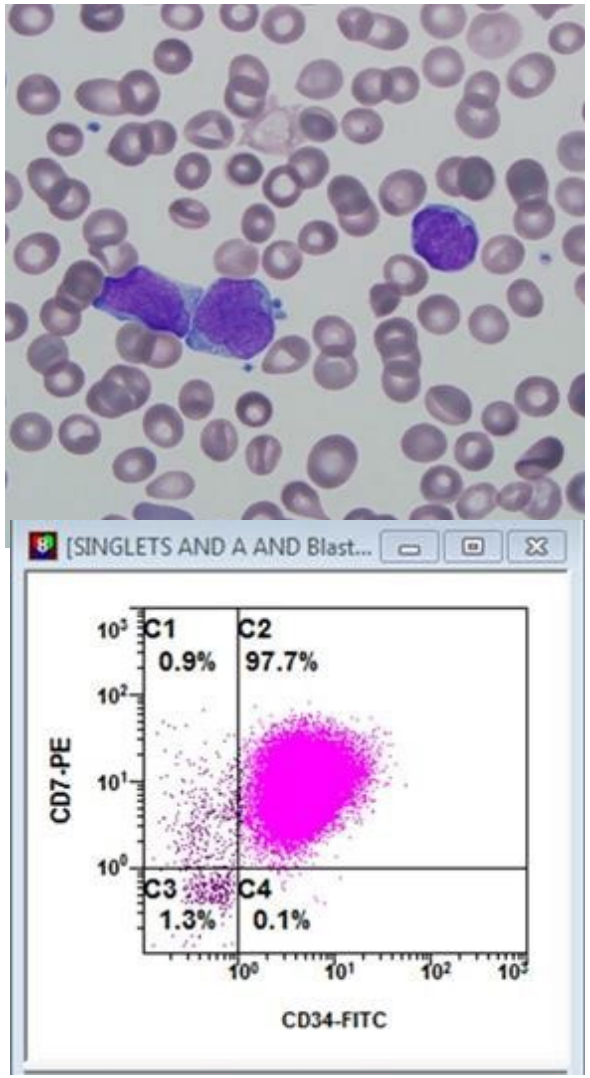
CLINICAL: Presentation

- A 32 year old male, computer scientist, presented to another hospital, with sore throat and fever for 3 days not responding to antibiotics
- Now he came to emergency room because of red spots on Legs
- History: β-thalassaemia trait, no medications
- Petechiae
- Lymphadenopathy (neck, axilla, inguinal)
- WBC: 140 × 10^9/l, Hb 97 g/l, PLTs 20 × 10^9/l
- LDH = 6803 IU/L, ALT and AST slightly elevated
- Mononucleosis spot test negative

CLINICAL: Diagnosis ETP

Early T-cell precursor ALL (ETP)

- PB smear: 80% agranular blasts
- BM smear: 95% agranular blasts
- BM FACS: 98% blasts CD3+, cytoplasmic CD3+, CD2+, CD7+, Tdt+, CD34+, HLA-DR+, CD1a- (non- thymic)
- Lumbar puncture: negative
- CT: LN enlargement max 4 cm
- NGS: ND
- Karyotype: failed, FISH BM: *KMT*2A rearrangement



CLINICAL: Therapy

- Hyper-CVAD with intrathecal prophylaxis
- No asparaginase
- No MRD studies
- Prophase + IA+IB → blasts BM 4% (FACS)
- IIA + IIB→ CR-1 blasts < 1% (FACS)
- HLA typing completed, referred to our BMT Unit

QUESTION: Should we transplant patients with T-ALL in CR-1?

| DISCUSSION: How do I decide to transplant?

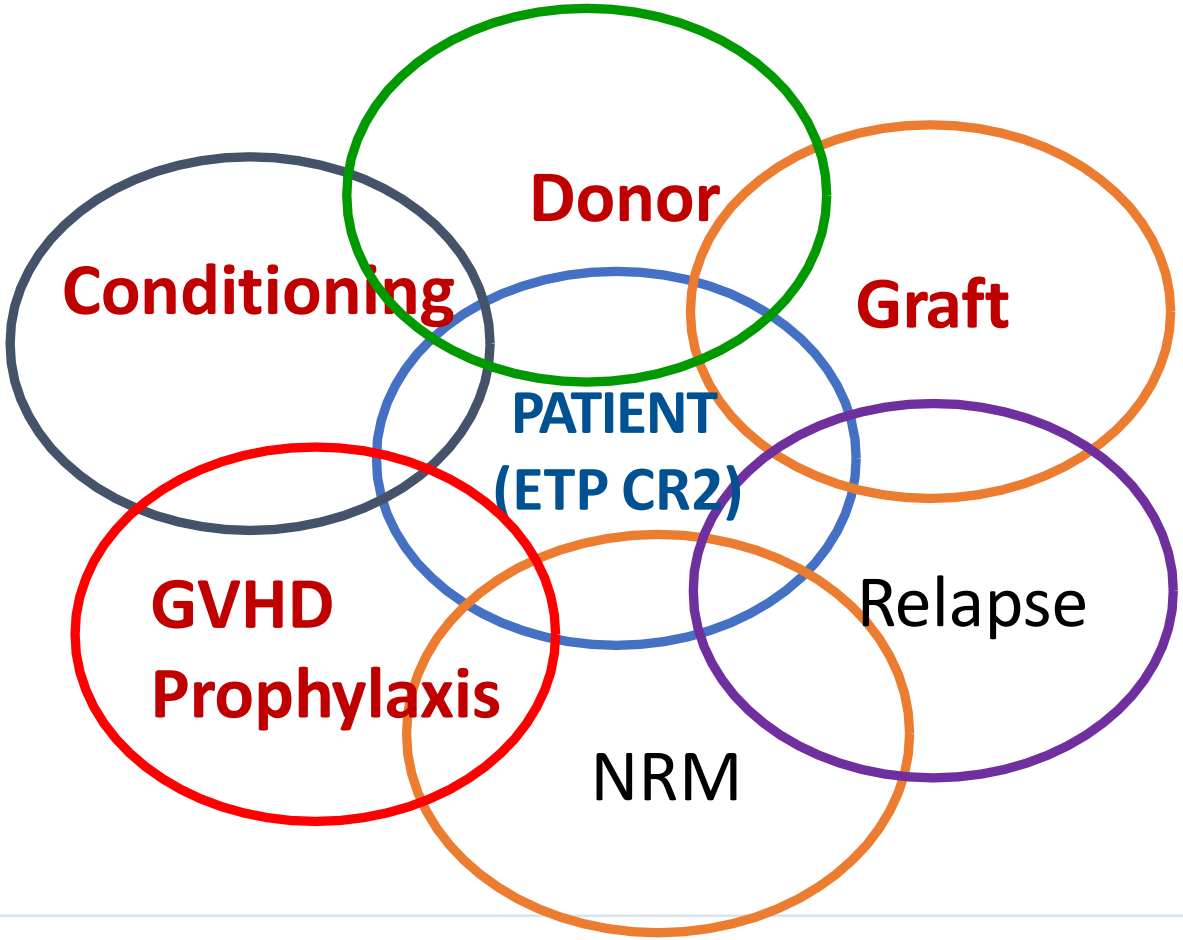
- High risk features
  - Immature, non thymic T-ALL
  - High WBC> 100 × 10^9/l
- Frontline therapy
  - Non-pediatric- inspired protocol
  - No asparaginase
- High risk genetics (*KMT2A*)
- No MRD data
- No good rescue therapies (e.g. CAR-T, bispecifics) if relapse

Nicola Gökbuget et al. Management of ALL in Adults: 2023 ELN Recommendations from a European Expert\ Panel. Blood 2024; February 2
https://doi.org/10.1182/blood.2023023568

CLINICAL: Relapse

- Consolidation I
- Diplopia, eyelid ptosis,
- RELAPSE with CNS, extramedullary (LN), BM, PET positive
- HD-methotrexate (MTX) 5g/m^2→ refractory
- Nelarabine + cyclophosphamide + asparaginase
- CR-2 (FACS, no MRD studies, CNS free)

CLINICAL: The transplant challenge; one size does not fit all



QUESTION: DONOR

QUESTION: What examination would you ask for?

WMDA search		T-ALL, 32y, male								
	A*	B*	C*	DRB1*	DQB1*		ABO	CMV	Sex	
Pt	11:01	12:02	04:01	15:02	06:01		A+	+	M	
	68:01		03:01	16:01	05:02					
D1	11:01	12:02	04:01	15:02	06:01		0+	-	F	
	68:01	01:03	03:01	16:01	05:02					
D3	11:01	12:02	04:01	15:02	06:01		0+	+	F	
	68:01		03:02	16:01	05:02					

DISCUSSION: Check in the recipient for anti-HLA Donor Specific Antibodies (DSA)

- If you have to choose between mismatched(mm) donors in different loci than check for HLA DSA (especially multitranfused patients)
- Avoid mismatch to which the recipient is sensitized
- Graft failure/ late and partial engraftment is significantly increased when the recipient has DSA against the donor's HLA mismatch
- This is clear in haplo but also can be seen in unrelated donors

Gladstone DE, BBMT 2013; 19: 647-652

QUESTION: Which donor would you select?

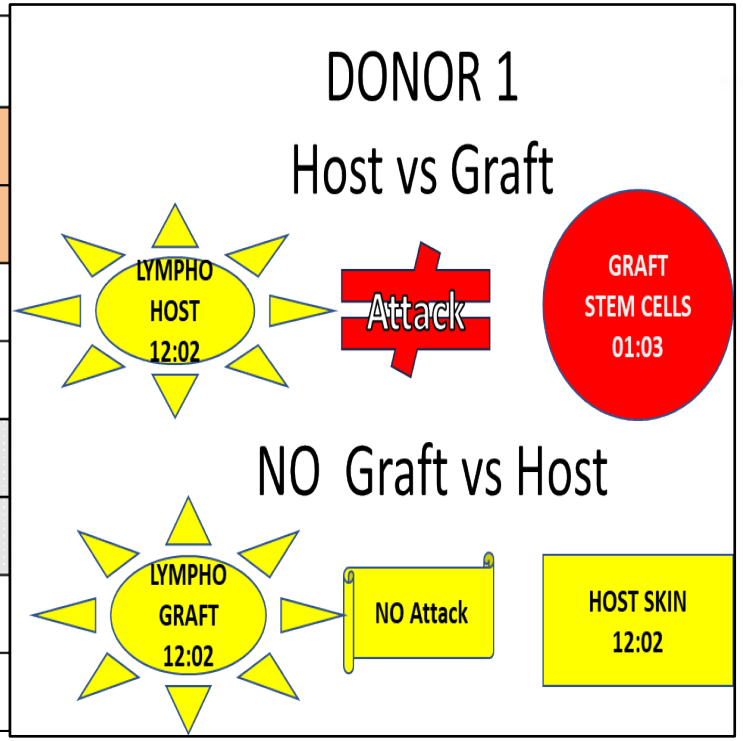
WMDA search		T-ALL, 32y, male								
	A*	B*	C*	DRB1*	DQB1*		ABO	CMV	Sex	
Pt	11:01	12:02	04:01	15:02	06:01	NO DSA	A+	+	M	
	68:01		03:01	16:01	05:02					
D1	11:01	12:02	04:01	15:02	06:01		0+	-	F	
	68:01	01:03	03:01	16:01	05:02					
D3	11:01	12:02	04:01	15:02	06:01		0+	+	F	
	68:01		03:02	16:01	05:02					

DISCUSSION: Algorithm for selecting a mm donor

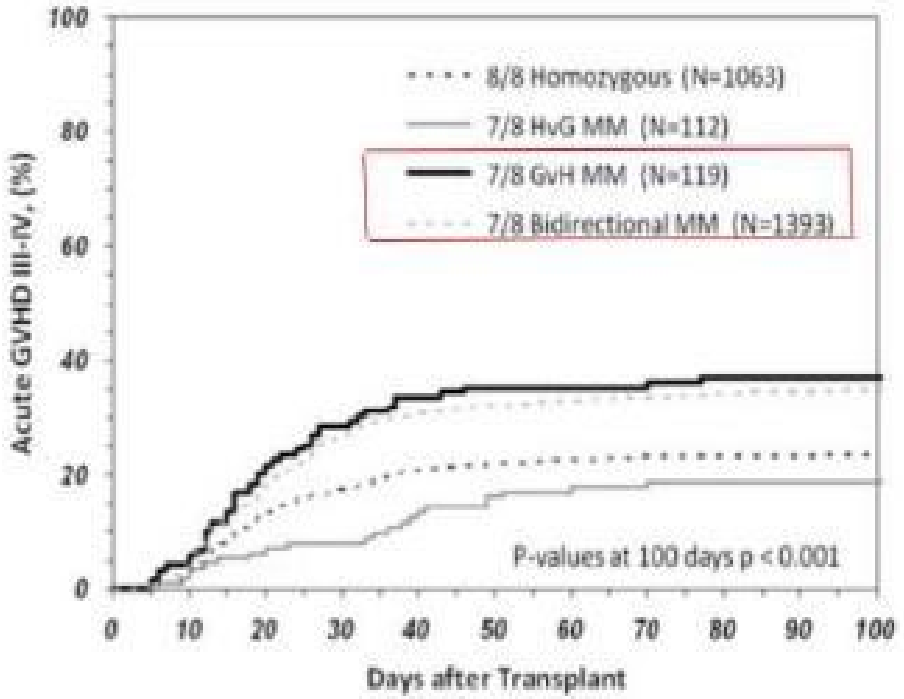
- HLA has the highest priority in selecting donor
- DSA
- max 7/8 mm (A, B, C, DRB1) though new studies with more mm and post-transplant cyclophosphamide (PTCY) are encouraging
- Ag = allele mm
  - DQB1 > C allele mm > C Ag mm >= B mm >= A mm
  - immune responses may be influenced by HLA expression levels and specific epitope amino acid variations

DISCUSSION: If D or R is homozygous at one locus, check mm vector (HvG mm is permitted)

	A*	B*	C*	DRB1*	DQB1*
Pt	11:01	12:02	04:01	15:02	06:01
	68:01		03:01	16:01	05:02
D1	11:01	12:02	04:01	15:02	06:01
	68:01	01:03	03:01	16:01	05:02
D2	11:01	12:02	04:01	15:02	06:01
	02:01		03:01	16:01	05:02
D3	11:01	12:02	04:01	15:02	06:01
	68:01		03:02	16:01	05:02



Unidirectional HvG mm does not affect GVHD and OS



DONOR 1 10/10 match in GvH direction, 9/10 match in HvG vector

DONOR 2 and 3 is 7/8 match in GvH direction

QUESTION: Is there a benefit in waiting for a completed UD vs proceeding directly with an haploidentical donor?

DISCUSSION: UD vs haploidentical donor

- **It is important to recognize the urgency of transplant, unrelated donor availability and registry metrics**
- Data are growing on the similarity in outcomes between haplo-SCT and MUD-SCT
- Search in parallel with other graft sources as donor risk index (DRI) is factored in
- **Are there contraindications for haplo family donor?**
  - Patient ALL (no familial genetic disorder)
  - Living relatives, willing to donate
  - Patient no anti-HLA DSA detected

QUESTION: Which Haplo-Donor would you select?

- Father 65 years, CMV pos, A+, CMV pos, cardiac problems,
- Mother 53 years, 1 child, no medical history, CMV pos
- No siblings
- 1 cousin 18 years, CMV negative, HLA not matched

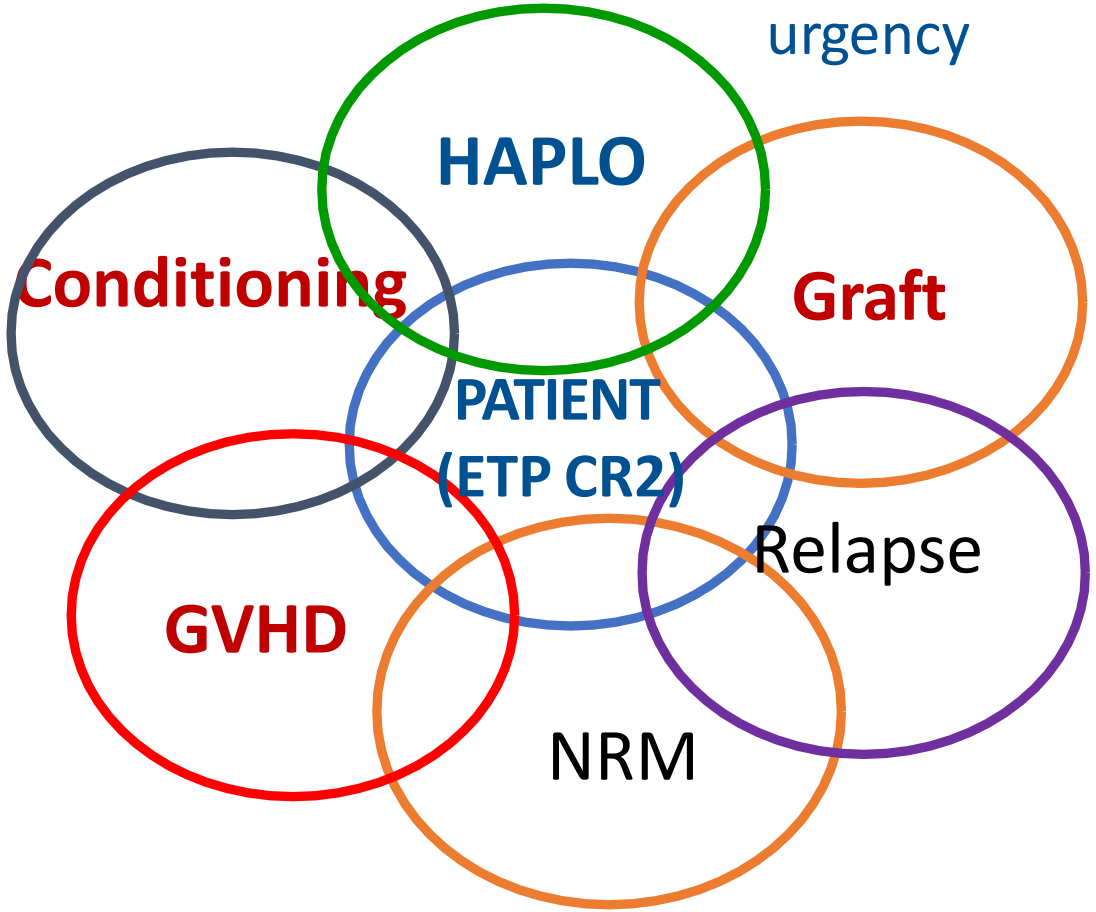
DISCUSSION: Donor

- Father 65 years, CMV pos, A+, CMV pos, cardiac problems,
- Mother 53 years, 1 child, no medical history, CMV pos
- No siblings
- 1 cousin 18 years, CMV negative, HLA not matched

CLINICAL: Haplo-SCT

- Immediate proceed to SCT
- No anti-HLA DSA detected
- We decided to proceed with Haplo
- Haplo-related Donor: mother (55 years)
- CMV serostatus: +/+, Blood group: A+/A+
- Graft: BM xxx TNC
- GvHD Prophylaxis: PTCY, TD 100 mg/kg (d+3,+5), CyA d+6, MMF D+6-D+28

QUESTION: Which graft would you prefer?



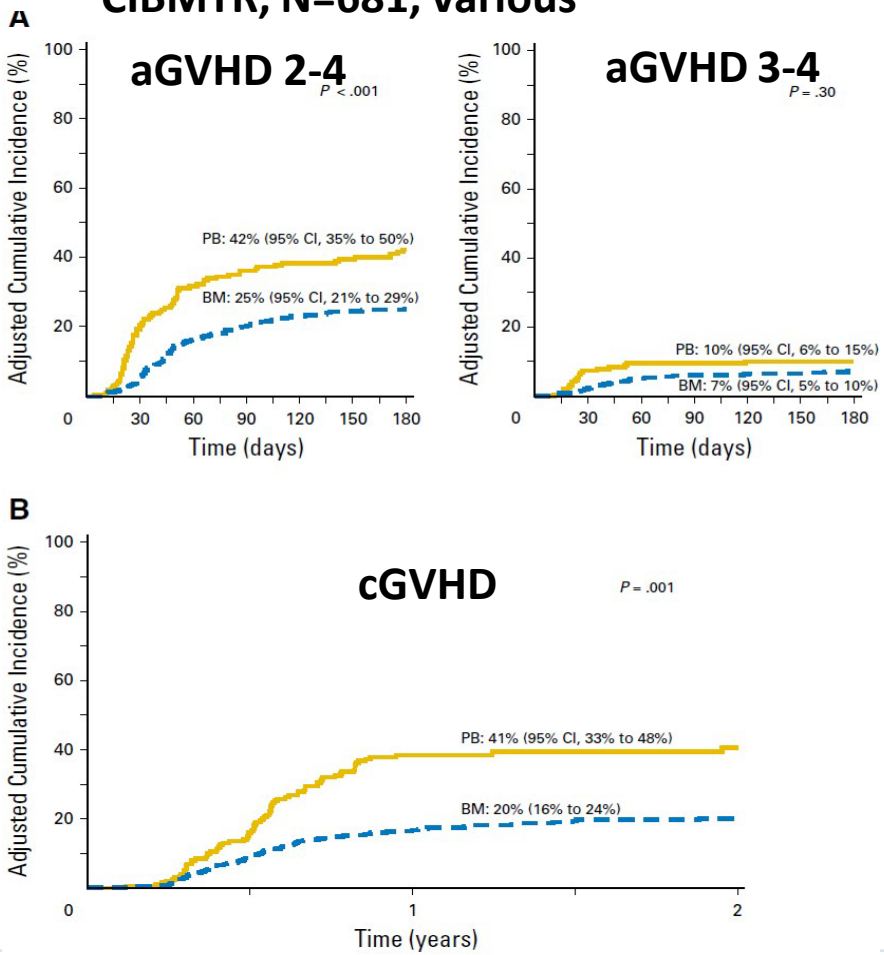
- BM
- PBSC

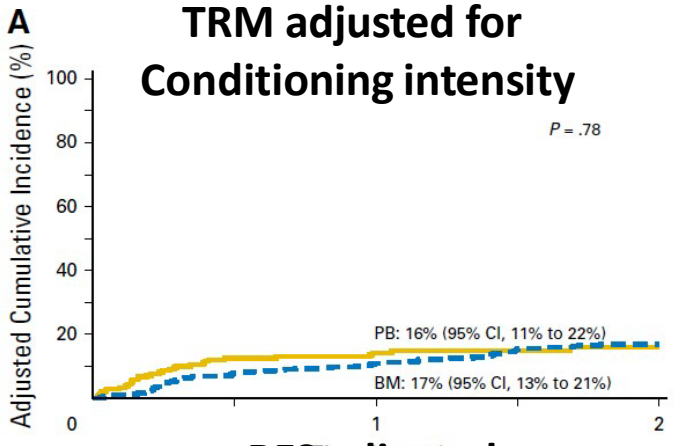
DISCUSSION: Haplo BM vs PBSC?

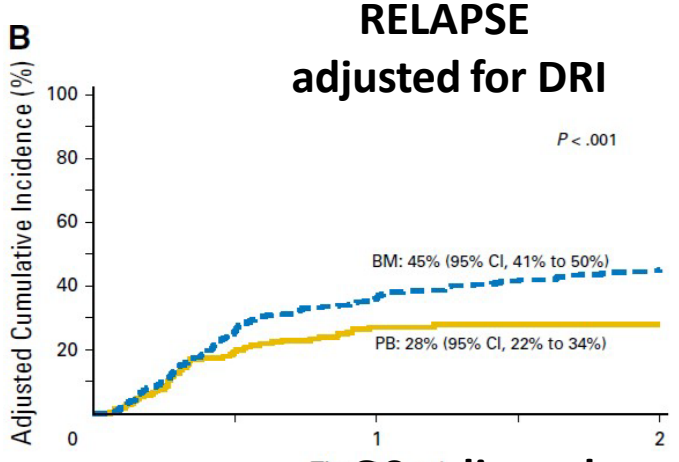
- PBSCT: no anesthesia, less logistics,
- BM, experienced harvesters to get high mononuclear cell count (MNC) (better PFS)
- Engraftment: PBSCT vs BM 1-2 days earlier
- aGVHD: PBSCT > BM in some studies
- cGVHD: PBSCT > BM in some studies
- OS: most studies no difference (especially in CR-1 pts)

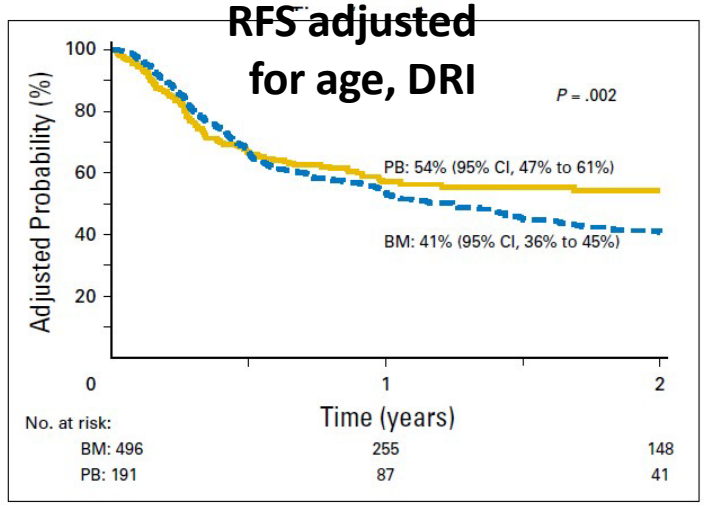
DISCUSSION: Haplo-PBSC may be associated with reduced relapse

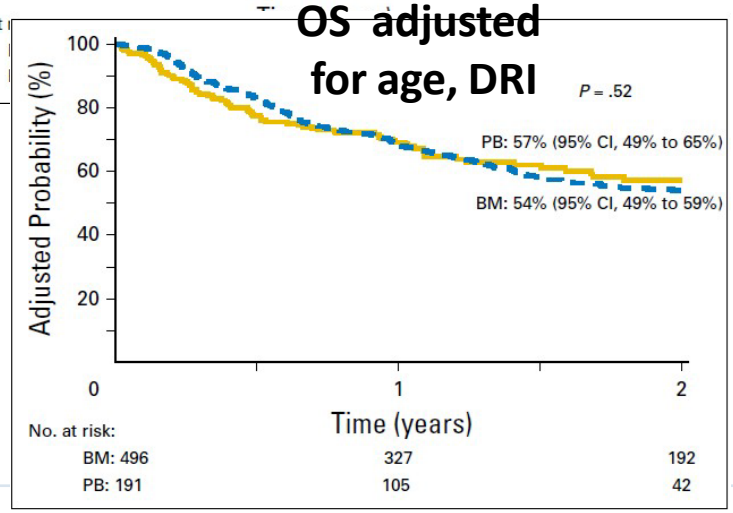
CIBMTR, N=681, various











Bashey et al. JCO 2017; 35: 2002-3009

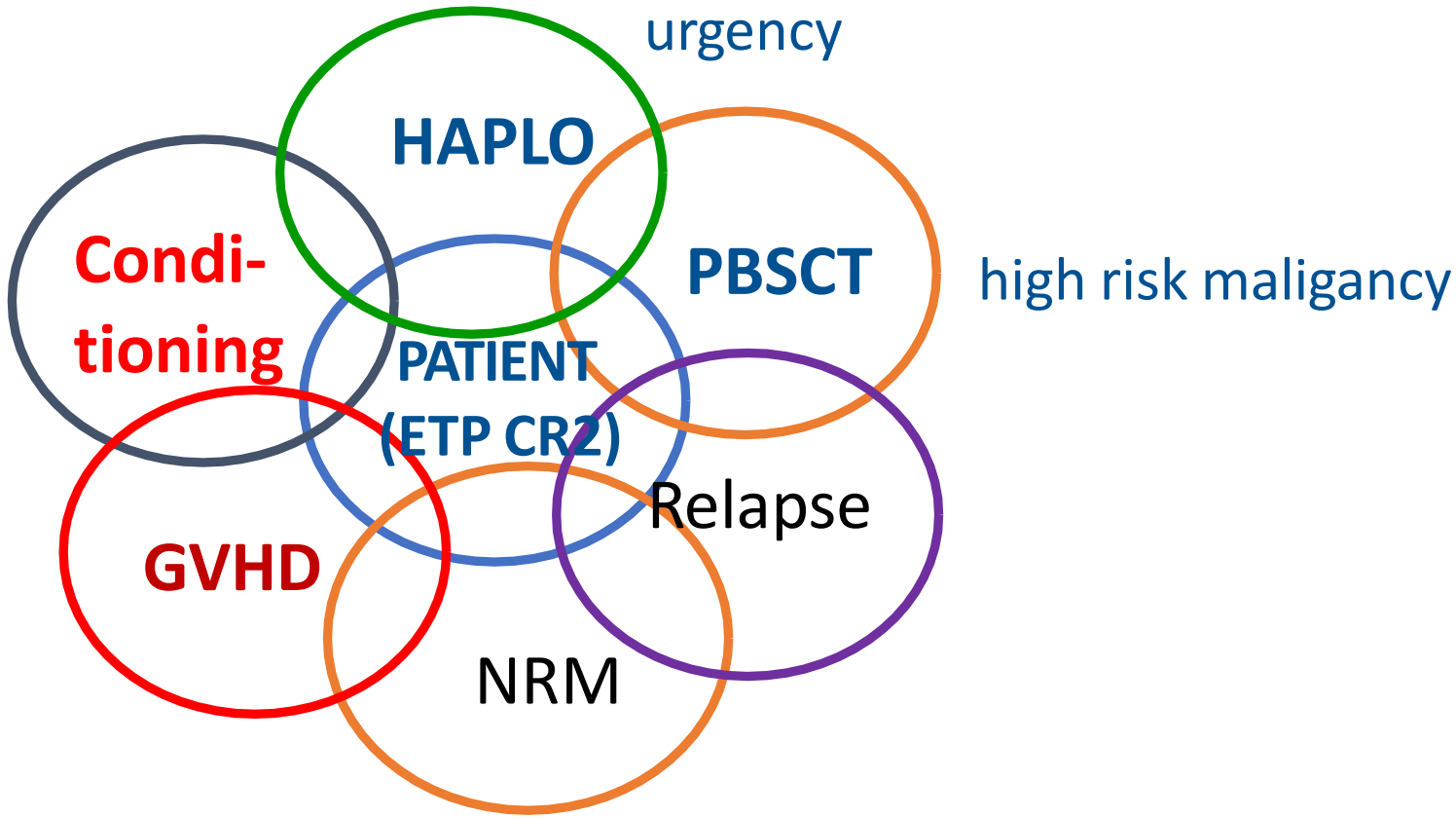
CLINICAL: Haplo- PBSCT (Mother)

- We decided on PBSCT as patient had a high risk malignancy and was in good functionl status
- CD34+:

Bashey et al. JCO 2017; 35: 2002-3009

QUESTION: Which conditioning would you use?

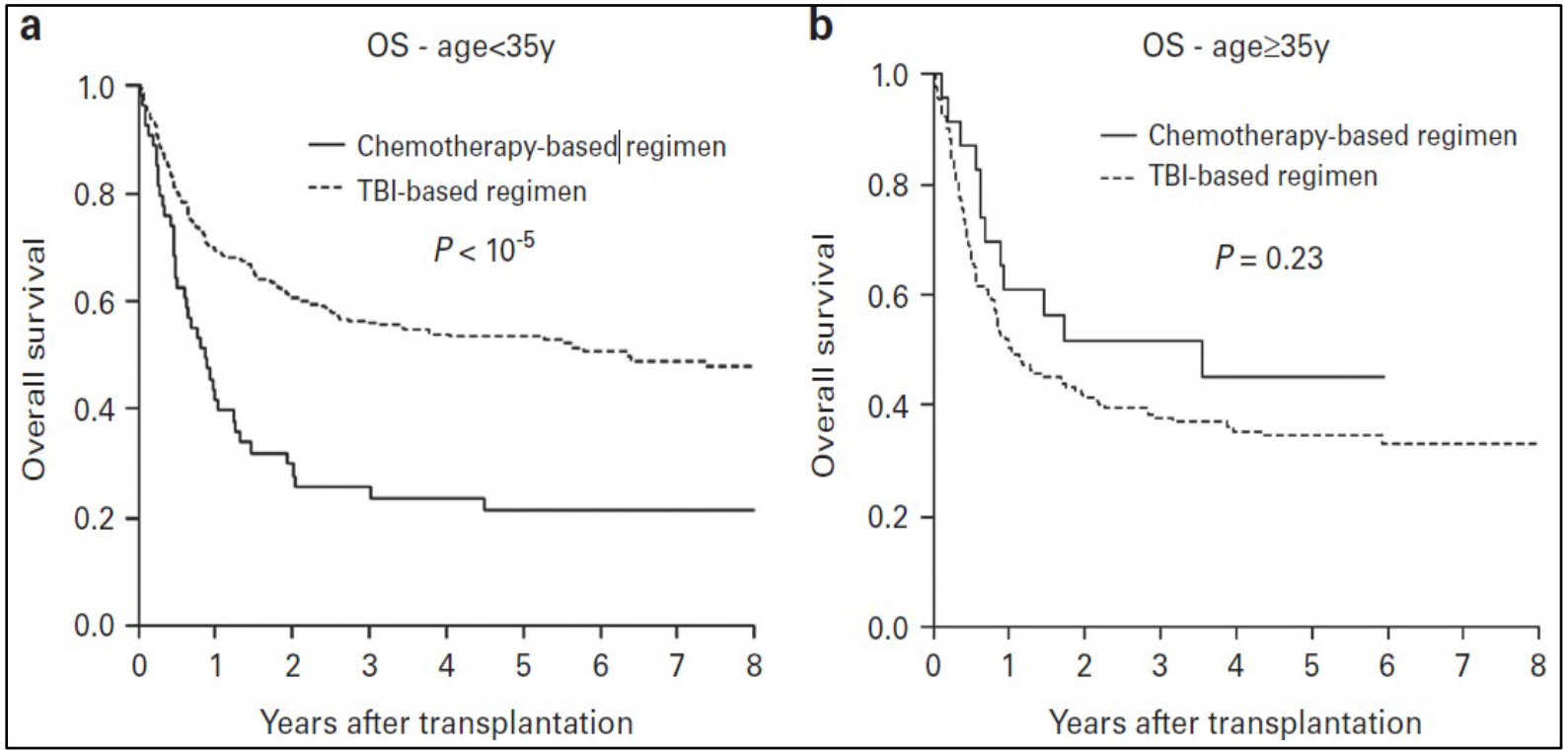
- TBI OR CHEMO
- IF TBI WITH WHICH CHEMO?
- IF ONLY CHEMO WHICH?
- WHICH INTENSITY?

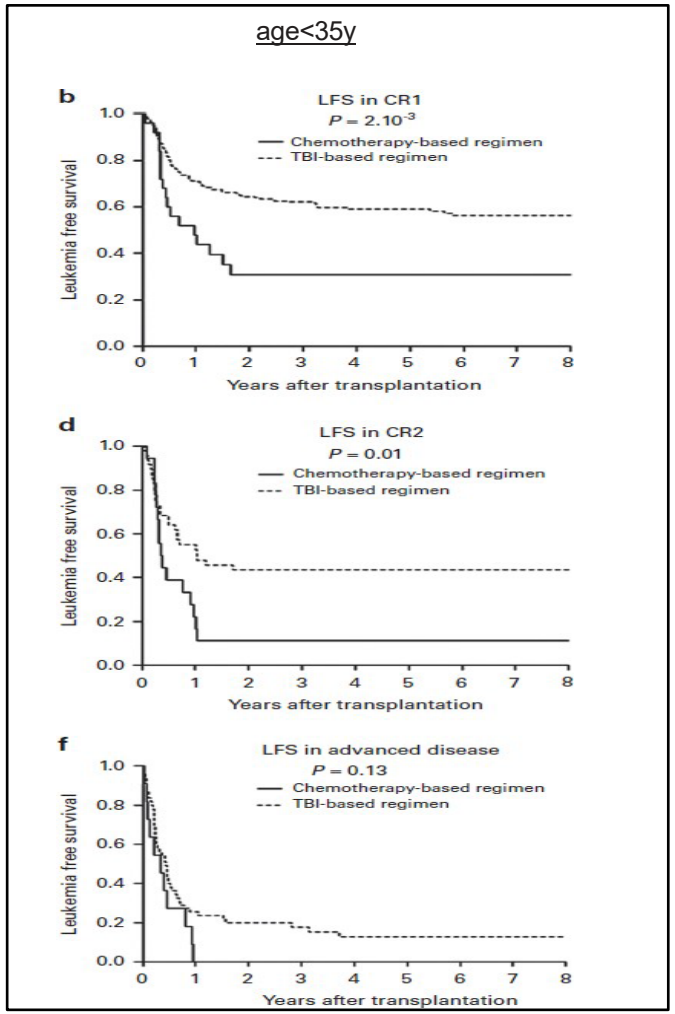


DISCUSSION: Lower relapse: TBI vs BU in T-ALL

EBMT, Retrospective, 601 pts

- Same TRM in younger but higher TRM in older pts
- Lower RR with TBI

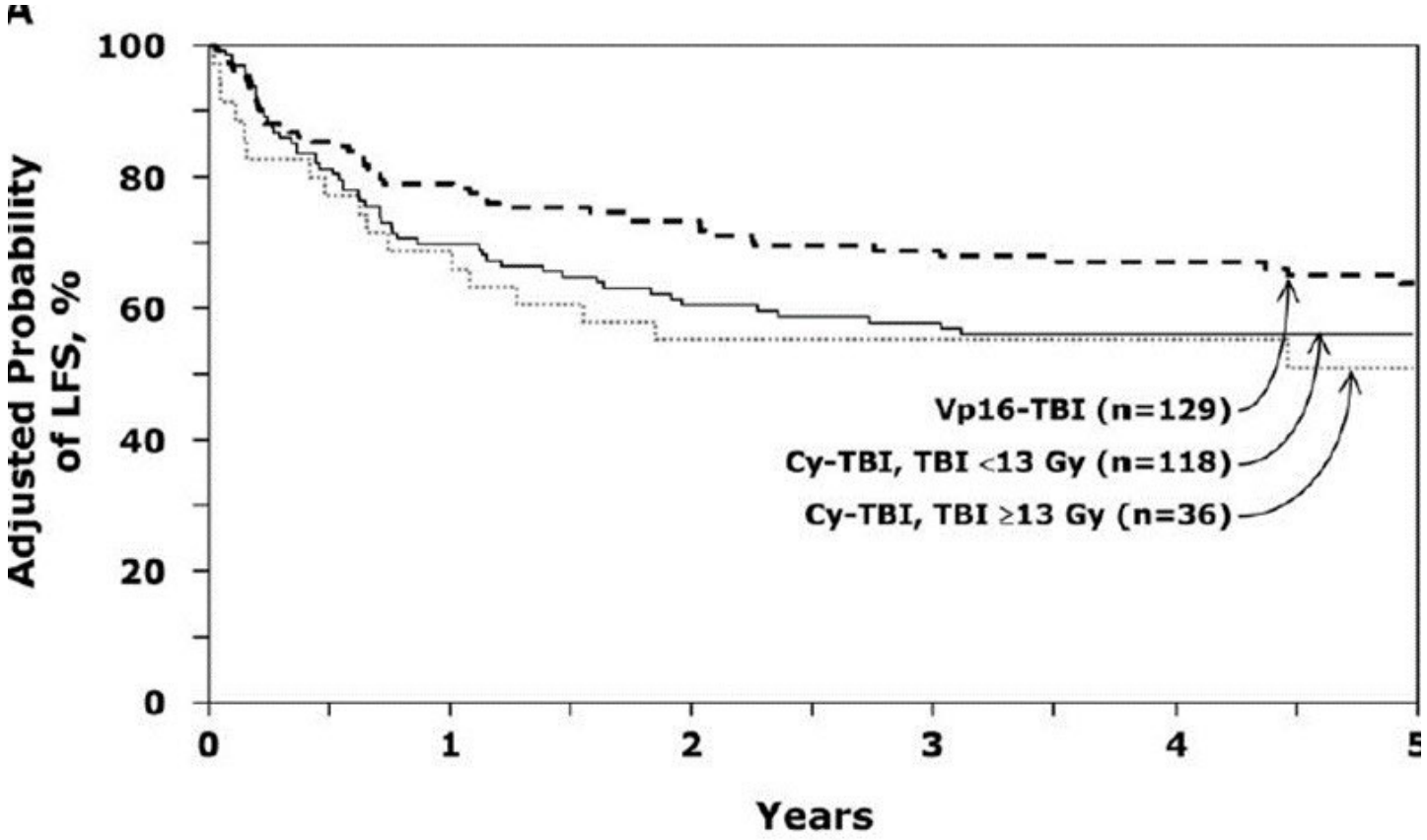




Bone marrow transplantation. 2016 ;51(3):351-7

DISCUSSION: potential benefit with VP16 in CR-2

CIBMTR, adult and pediatric ALL, TBI/Cy vs TBI/VP16



Biol Blood Marrow Transplant 12:438-453 (2006

DISCUSSION: Thiotepa in ALL shows anti-leukemic activity

- Penetrates CNS
- Part of the TBF regimen
- TBF: Thiotepa, Busulphan, Fludara

EBMT matched paired ALL
TBI-CY vs Thiotepa based: non inferiority

TBF : intensity variation

Donor	SIB		WMUD		MMUD		HAPLO	
Patient	Regimen	CRT-I	Regimen	CRT-I	Regimen	CRT-I	Regimen	CRT-I
young, high risk	TB4F90	4	TB4F120	4.5	TB4F150	5	TB4F150-PTCY	6
young	TB3F90	3	TB3F120	3.5	TB3F150	4	TB4F150-PTCY	5
old/reduced PS	TB2F90	2	TB2F90	2.5	TB2F150	3	TB2F150-PTCY	4
active disease	+ precon	+0.5	+ precon	+0.5	+ precon	+0.5	+ precon	+0.5

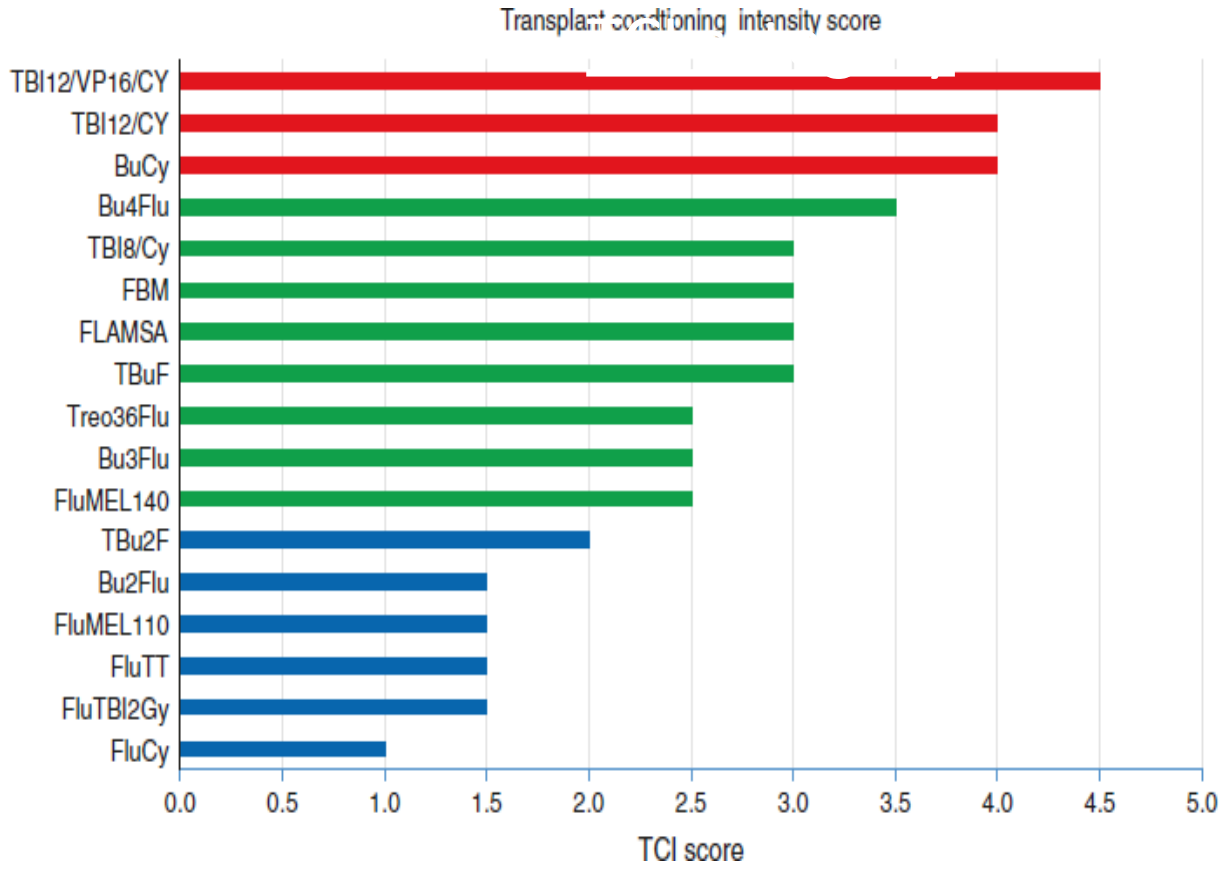
Am J Hematol. 2017;92:997–1003., Biol Blood Marrow Transplant 22 (2016) 1449-1454, American Journal of Hematology, Vol. 92, No. 1, January 2017

Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients

TCI score: Sum of the weights for each component

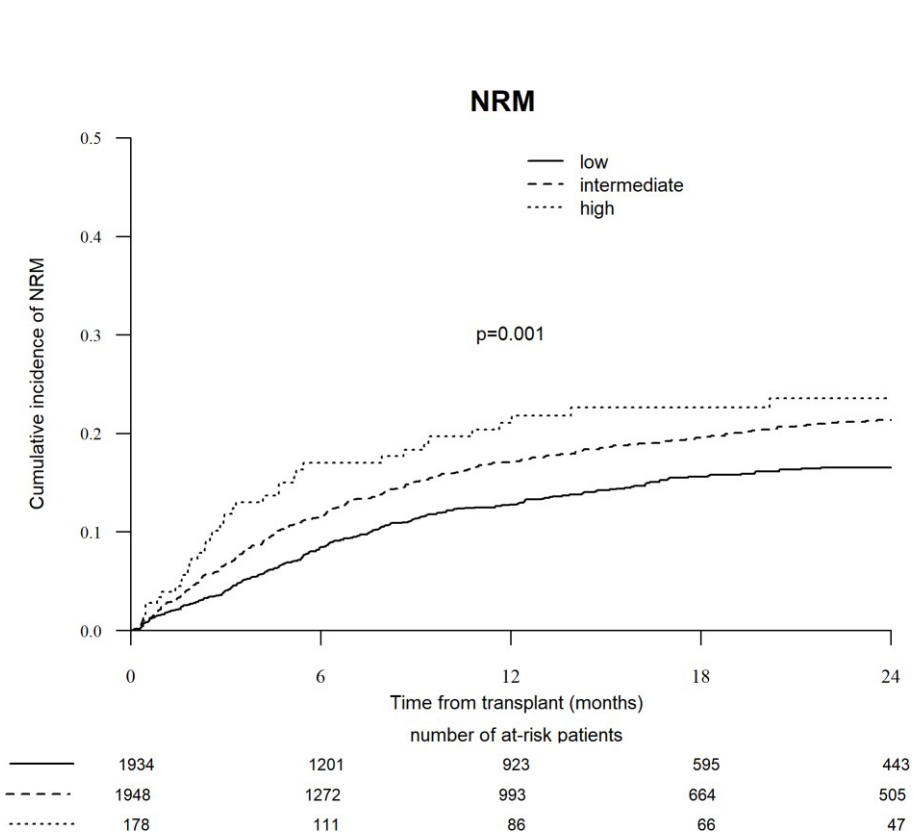
Component	Dose level			Added points for each dose level
	Low	Intermediate	High	
TBI fractionated (Gray)	≤5	6–8	≥9	1
Busulphan (mg/kg)	≤6.4 iv & ≤8 po	9.6 iv & 12 po	12.8 iv & 16 po	1
Treosulfan (g/m2)	30	36	42	1
Melphalan (mg/m2)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m2)	≤160	>160		0.5
Clofarabine (mg/m2)	≤150	>150		0.5
Cyclophosphamide (mg/kg)	<90	≥90		0.5
Carmustine (mg/m2)	≤250	280–310	≥350	0.5
Cytarabine (g/m2)	<6	≥6		0.5
Etoposide (mg/kg)	<50	≥50		0.5

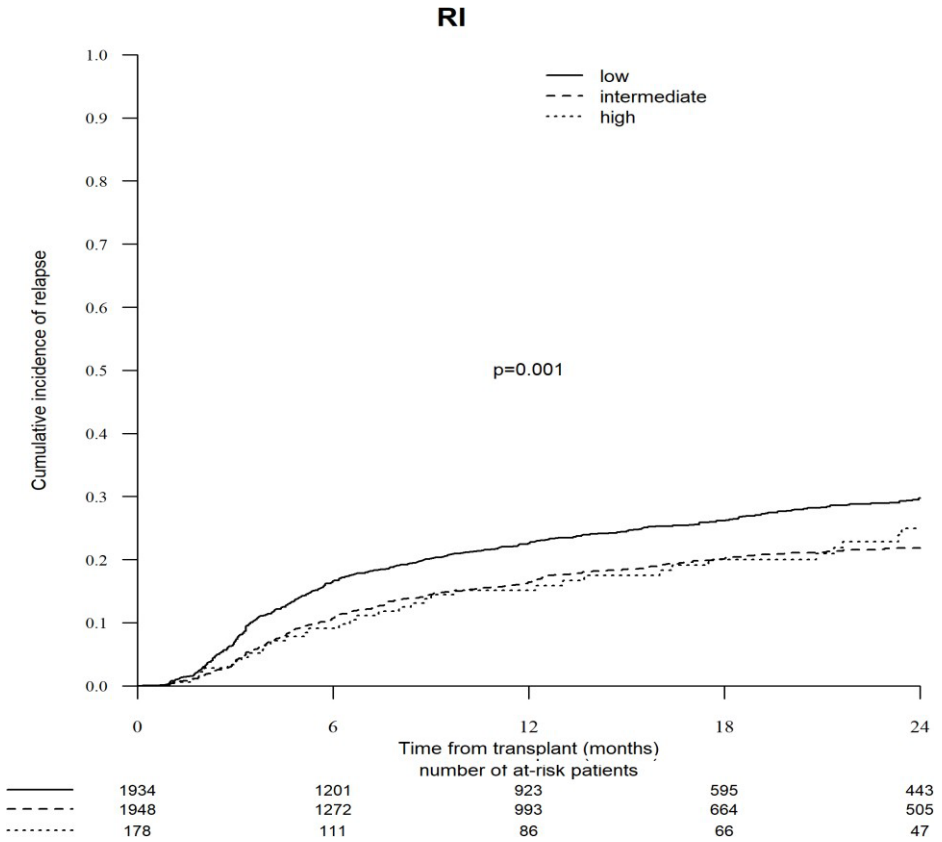
iv intravenously, *po* per os, *TBI* total body irradiation.



Spyridonidis et al, Bone Marrow Transplantation (2020) 55:1114–1125

Validation Transplant Conditioning Intensity Score(TCI)

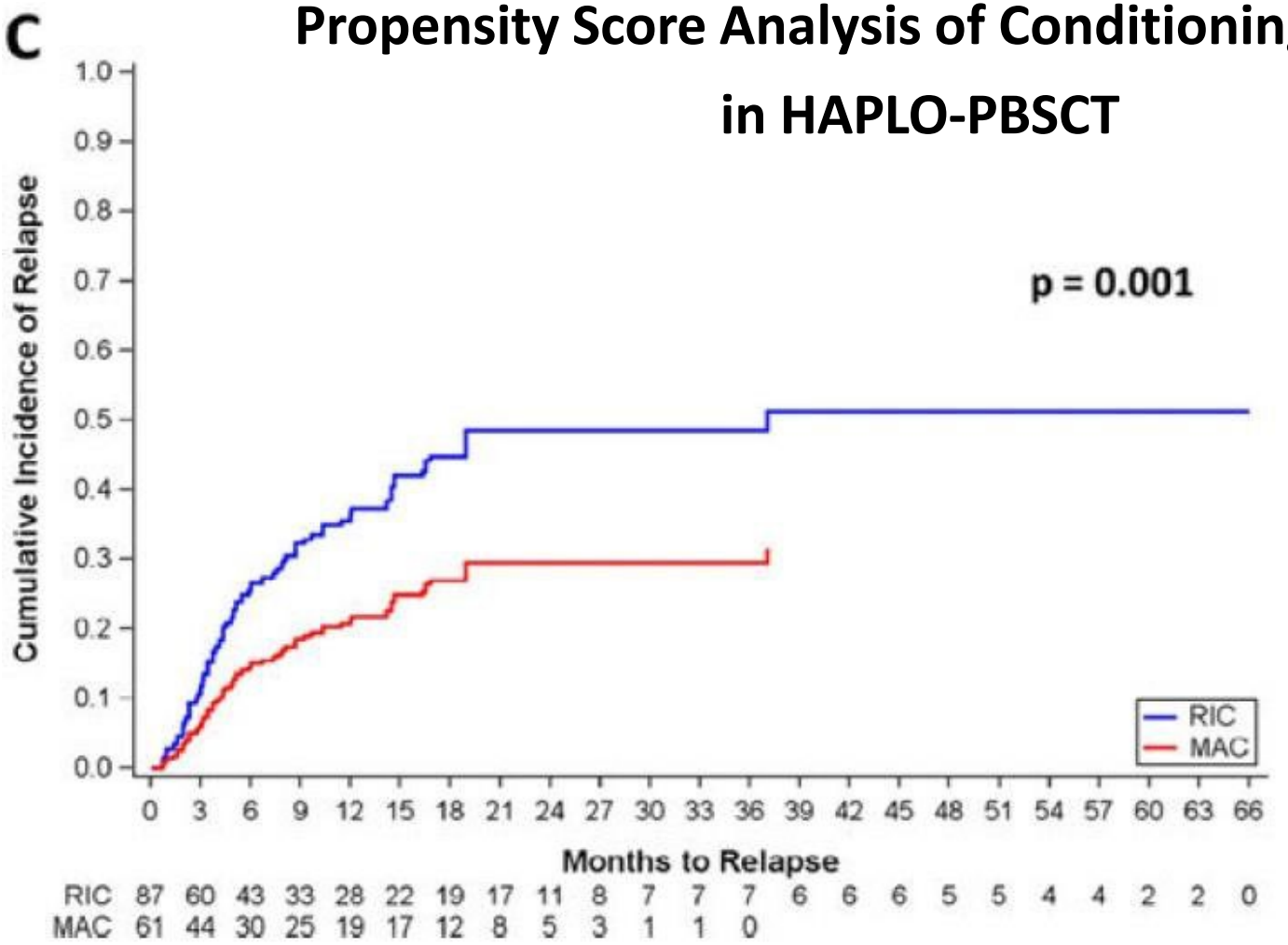




https://qxmd.com/calculate/calculator_871/transplant-conditioning-intensity-tci-score

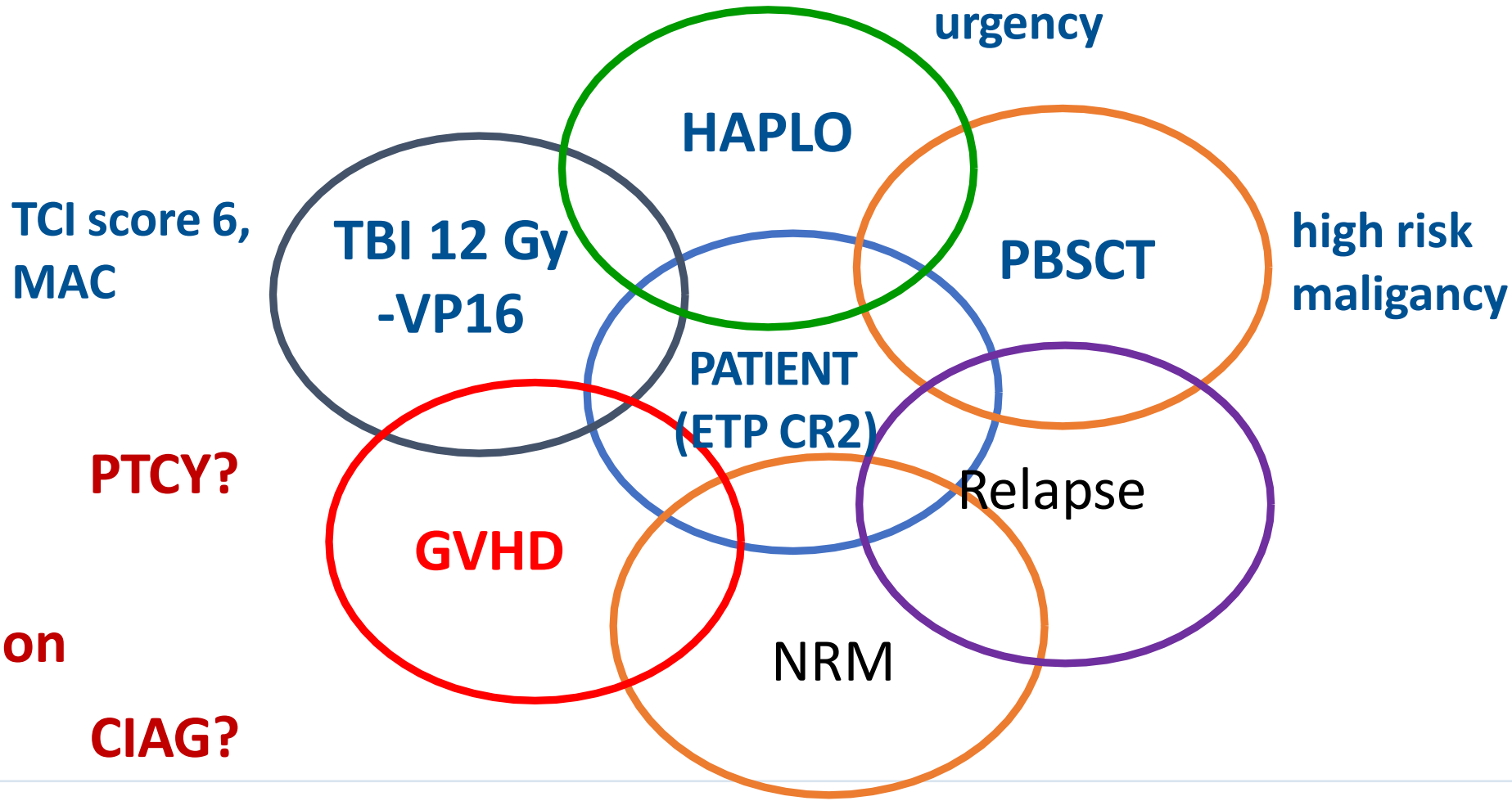
Spyridonidis et al. Bone Marrow Transplant. 2024 Feb;59(2):217-223.

DISCUSSION: Conditioning intensity does matter also in Haplo



Huselton et al. BBMT 2018; 24: 2047-2055

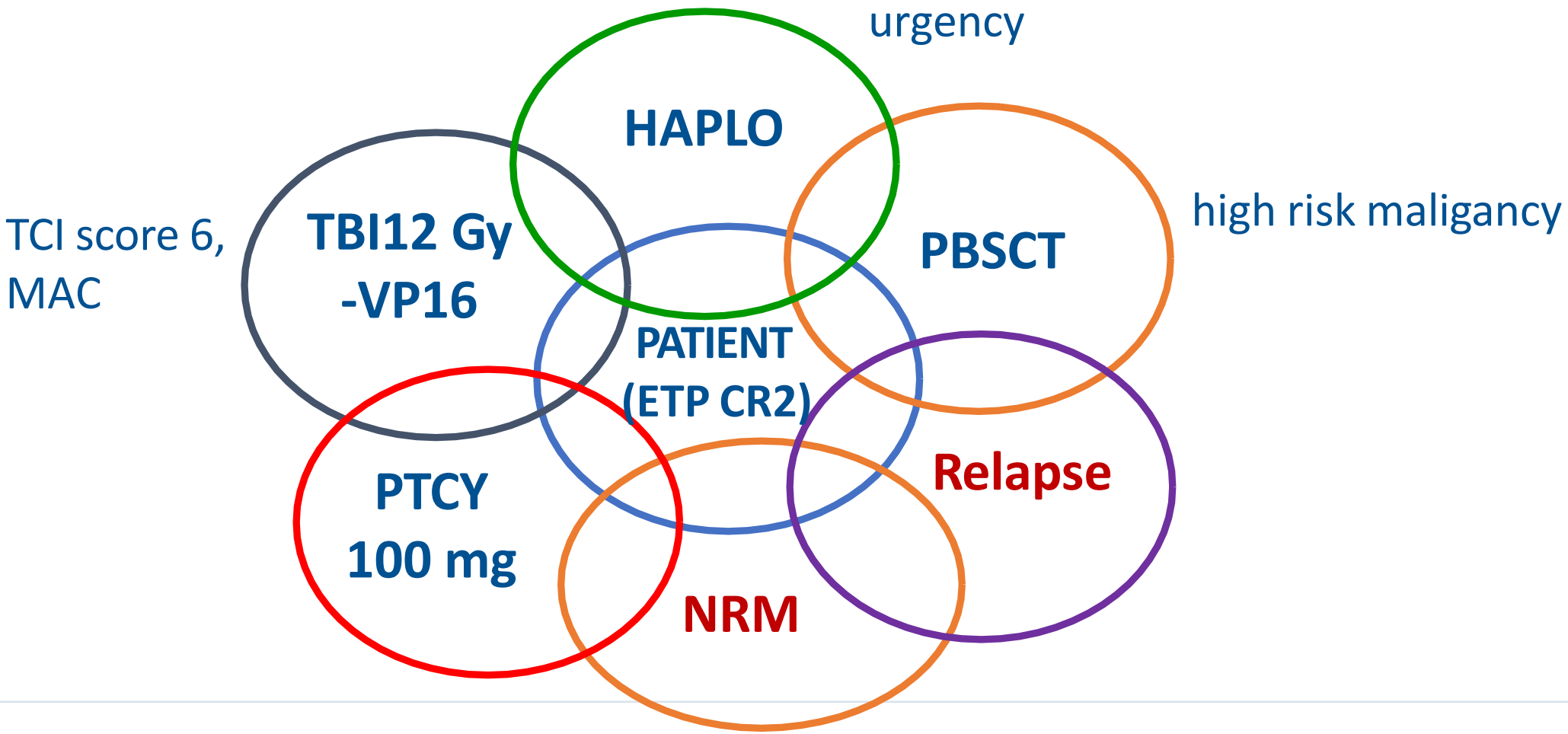
QUESTION: Which GVHD Prophylaxis?



DISCUSSION: PTCY is the winner

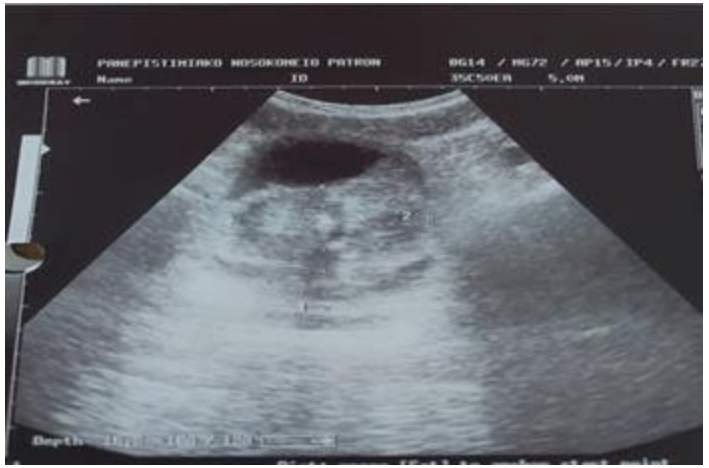
Am J Hematol.

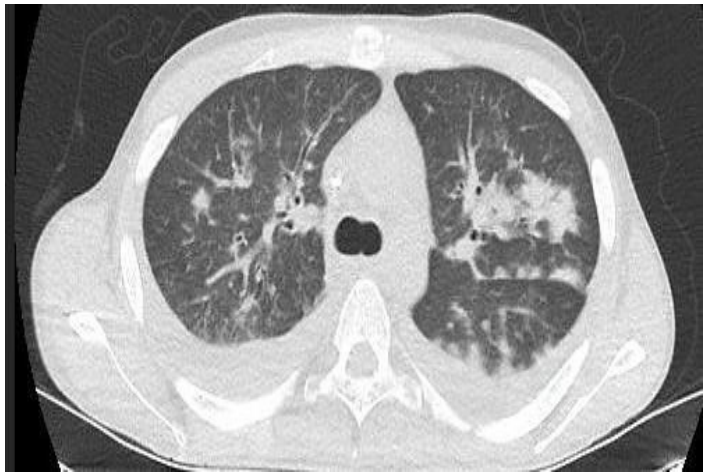
QUESTION: What specific side effects of PTCY do you expect?



CLINICAL: CRS, Severe haemorrhagic cystitis (HC)

- Haplo-PBSCT, TBI 12 Gy-VP16, PTCY 50mg/kg d+4, d+5, start CsA/MMF d0
- **D+2 non-infectious fever 39 C (CRS grade I)** -> antipyretics, antibiotics, resolved d+6
- MESNA (2-mercaptoethanesulfonate), prophylactic continuous bladder irrigation (CBI)
- **Start d+25 Hemorrhagic Cystitis**, BKV-DNA urine > $5x10^9$ copies/ml, Hematocyst
- MMF discontinued d+26
- **D+48 pneumonia**



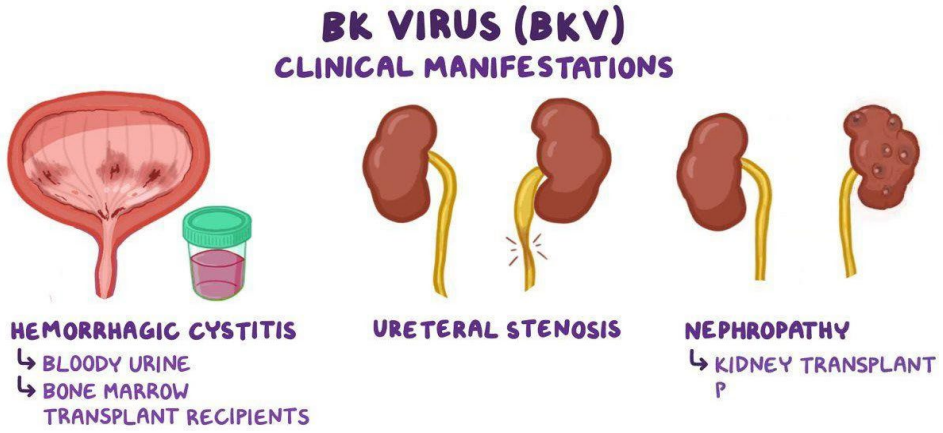


Vose JM, Reed EC, Pippert GC, et al. Mesna compared with continuous bladder irrigation as uroprotection during high-dose chemotherapy and transplantation: a randomized trial. J Clin Oncol. 1993;11:1306–1310.

Discussion: Treating HC is a challenge

Table 3 Clinical grading of haemorrhagic cystitis

Grade	*Severity*
I	Microscopic haematuria
II	Macroscopic haematuria
III	II + presence of blood clots
IV	III + renal impairment due to urinary obstruction



- ❑ Bladder irrigation (washout of blood)
- ❑ Endoscopically removal of clots/ Cystectomy
- ❑ OFTEN CHECK FOR OBSTRUCTION DUE TO URETERETIS (failure of peristaltic)→ Nephrostomies
- ❑ Cidofovir (cytosine analog that inhibits viral DNA synthesis) → intravesical, intravenous)
- ❑ BK specific T cells
- ❑ **Immunosuppression reduction**

Olson A et al. JCO 20;39(24):2710-2719., Ngo D, et al Transplant Cell Ther 2022; 28 (7): 349 354, Copelan OR, BBMT 2019; 25: 785,

CLINICAL: HAEMORHAGIC CYSTITIS

- 5 × surgery
- Cidofovir i.vesical, i.venous
- D+50 reduce calcineurin inhibitor (CNI)

QUESTION: When can we stop post-grafting CNI after PTCY?

TRANSPLANTATION

Comment on Kanakry et al, page 1389

How much immunosuppression do we need?

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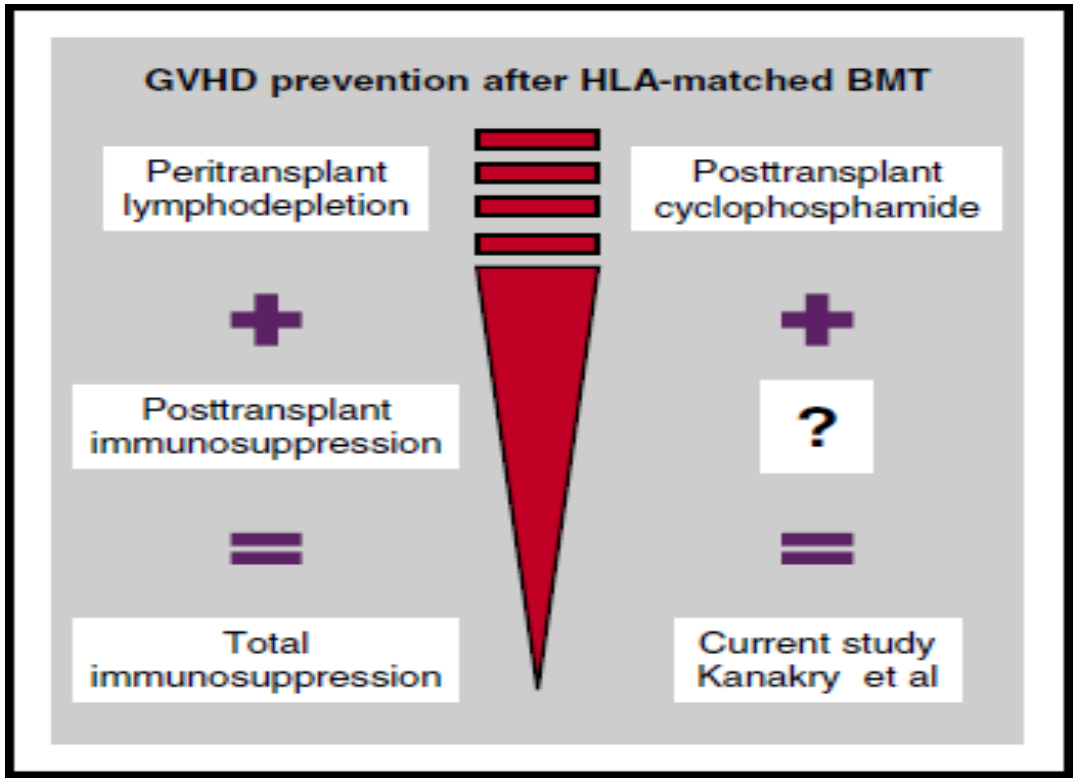


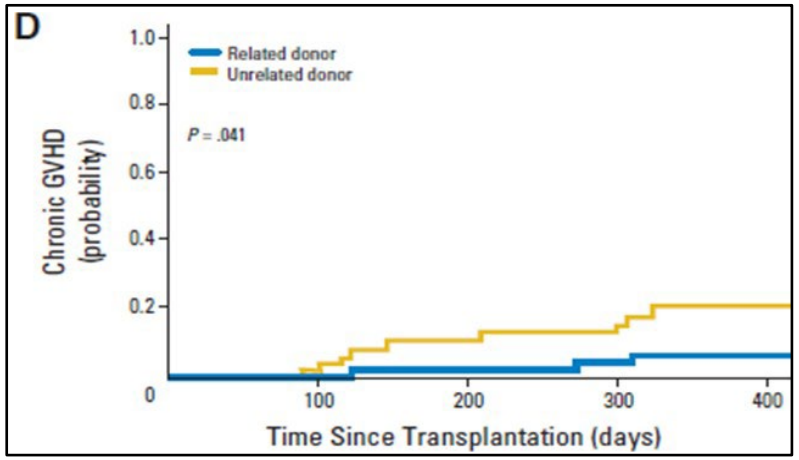
Spyridonidis A. Blood. 2017 Mar 9;129(10):1241-1243.

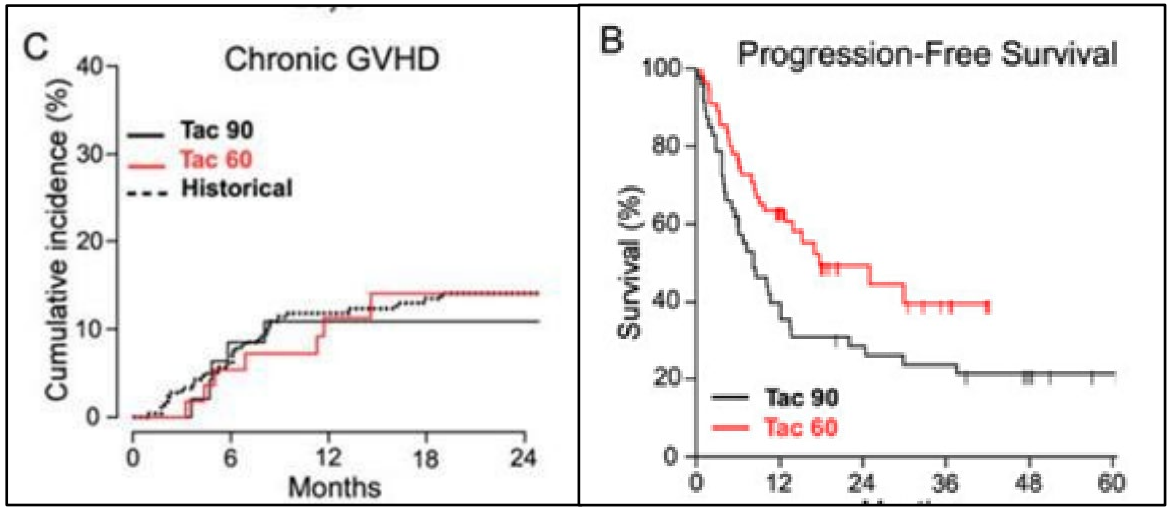
DISCUSSION: Immunosuppression (IMS) after PTCY can be stopped early

- ❑ PTCY-Matched SCT (MRD/MUD)
  - BMT: no post-grafting IMS
  - PBSCT: IMS needed, can be stopped before d+90

- ❑ PTCy-Haplo BMT: stopping IMS day +60 is feasible

- ❑ PTCY- Haplo PBSCT: stop at day +90 (?)



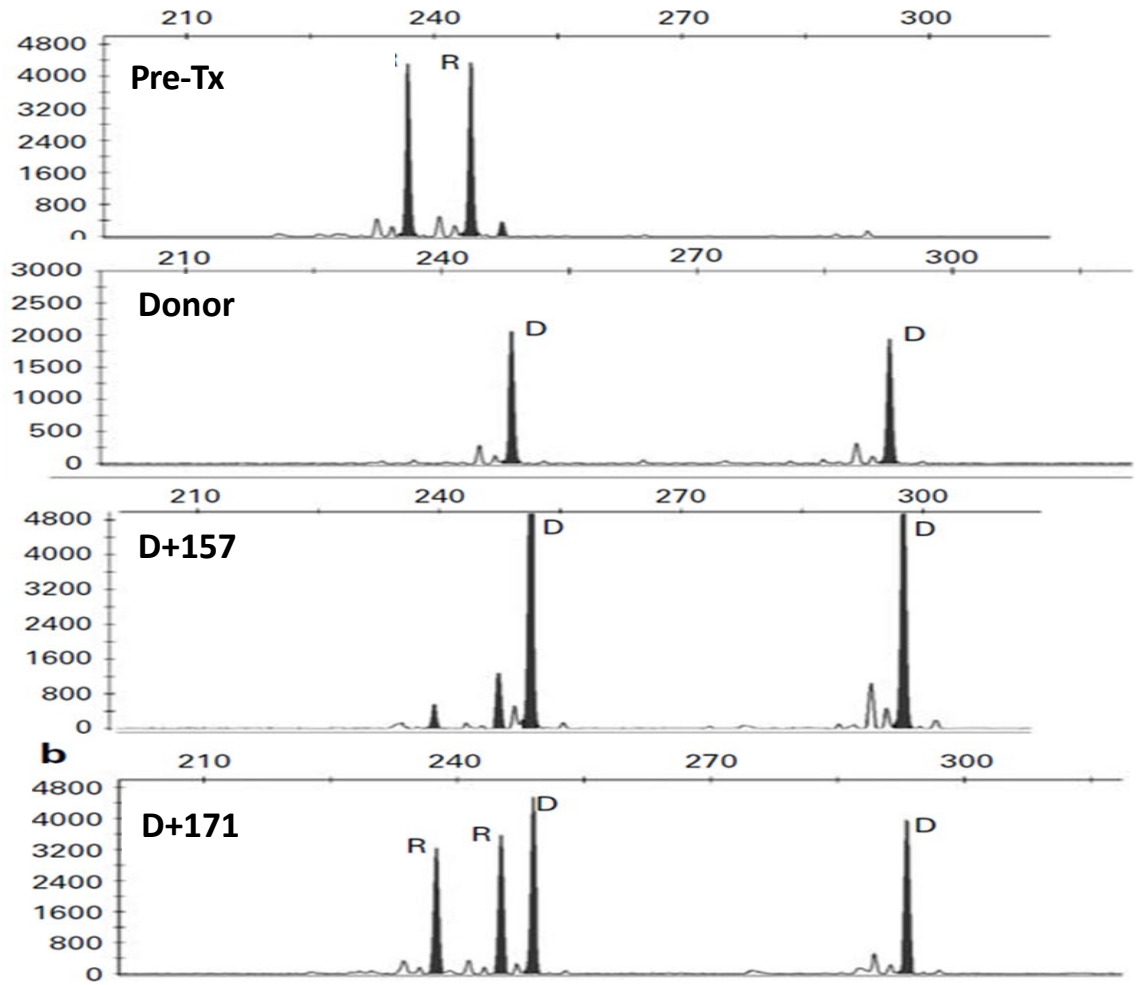


Kanakry C Blood. 2017;129(10):1389-1393, 5. Shannon R McCurdy BBMT 2019 Jun;25(6):1128-1135. Kasamon YL, BBMT 2018; 24:1022

CLINICAL: STOP CNI

- D+25 HC
- 5x surgery, pneumonia (CPAP)
- Cidofovir i.vesical, i.venous
- D+50 reduce CNI
- **D+70 stop CNI**
- D+ 112 exit from BMT Unit
- CR (FACS), Complete Chimerism

CLINICAL: conversion to increasing mixed chimerism



DISCUSSION: How I treat MRD after allo-HCT?

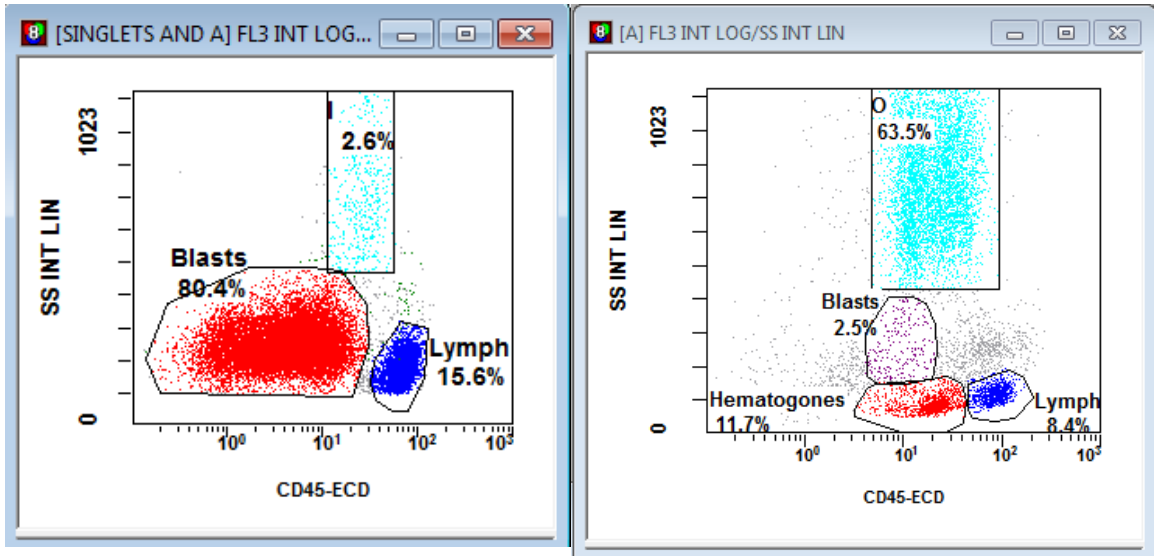
blood® How I Treat

How I treat measurable (minimal) residual disease in acute leukemia after allogeneic hematopoietic cell transplantation

Alexandros Spyridonidis
Department of Internal Medicine, Bone Marrow Transplantation Unit, University Hospital of Patras, Patras, Greece

MRD monitoring	Confounding variables after allo-HCT
Donor chimerism	Residual host signals, loss of heterozygosity in the HLA locus
FC	Regenerating hematogones
Leukemia-specific markers	Clearance depends on GVL dynamics, high clonal evolution rate
DNMT3	Donor-derived clonal hematopoiesis
Ig/TCR	Comparable sequences in regenerating T and B cells
WT1	Overexpression in regenerating marrow

Regeneration Post-HCT



Spyridonidis A. Blood. 2020 May 7;135(19):1639-1649.

Clinical applications of donor lymphocyte infusion from an HLA-haploidentical donor: consensus recommendations from the Acute Leukemia Working Party of the EBMT

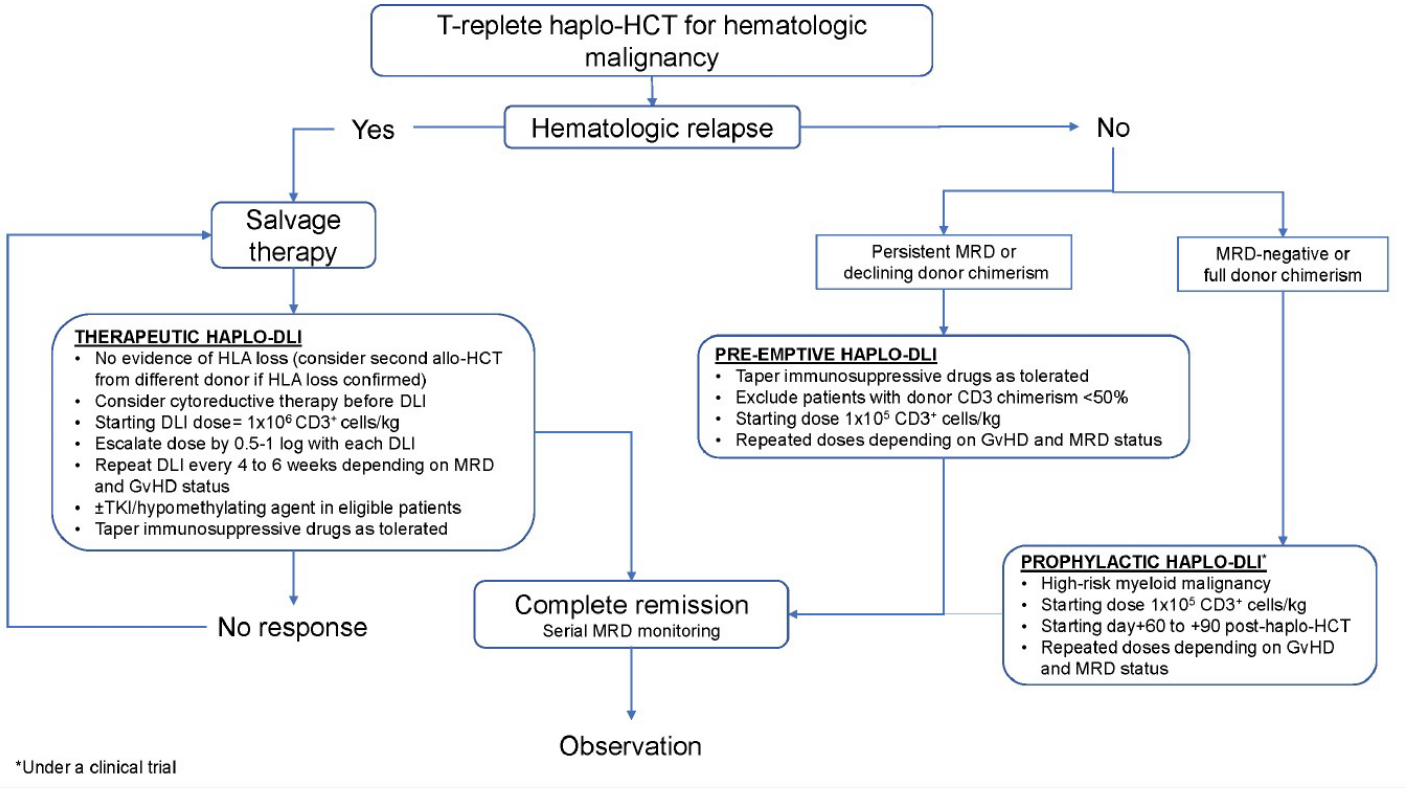


Figure 1. Proposed treatment algorithm of therapeutic, pre-emptive and prophylactic donor-lymphocyte infusion (DLI) following T-cell replete haploidentical hematopoietic cell transplantation (HCT). HLA: human leukocyte antigen; MRD: minimal residual disease; GvHD: graft-*versus*-host disease; TKI: tyrosine kinase

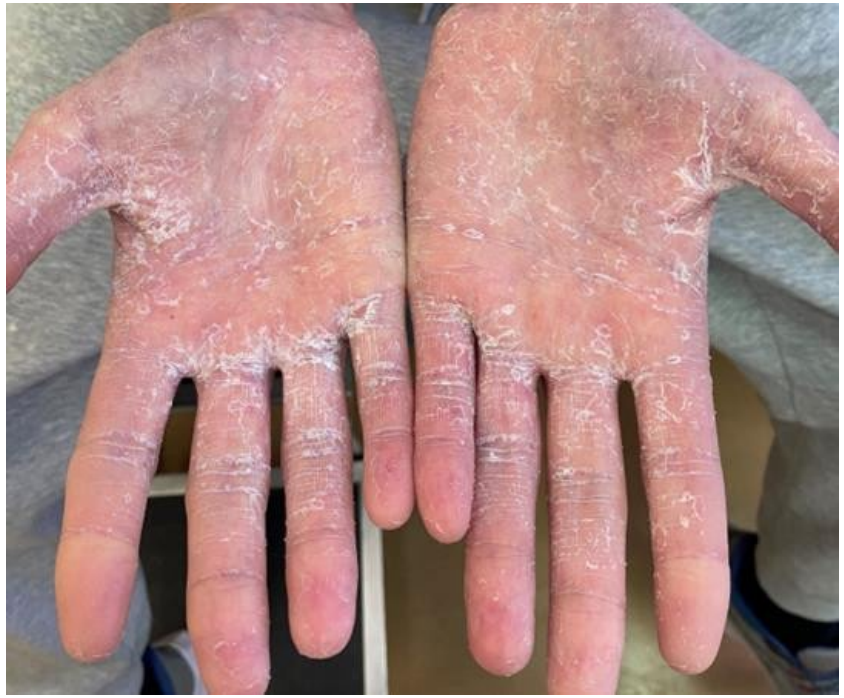
Series showing that Haplo DLI can induce sustained remissions

Bhagirathbhai Dholaria et al. Haematologica 2020 105(1):47-58, Zeidan AM et al. BBMT 2014; 20: 314-318

CLINICAL: chronic GVHD

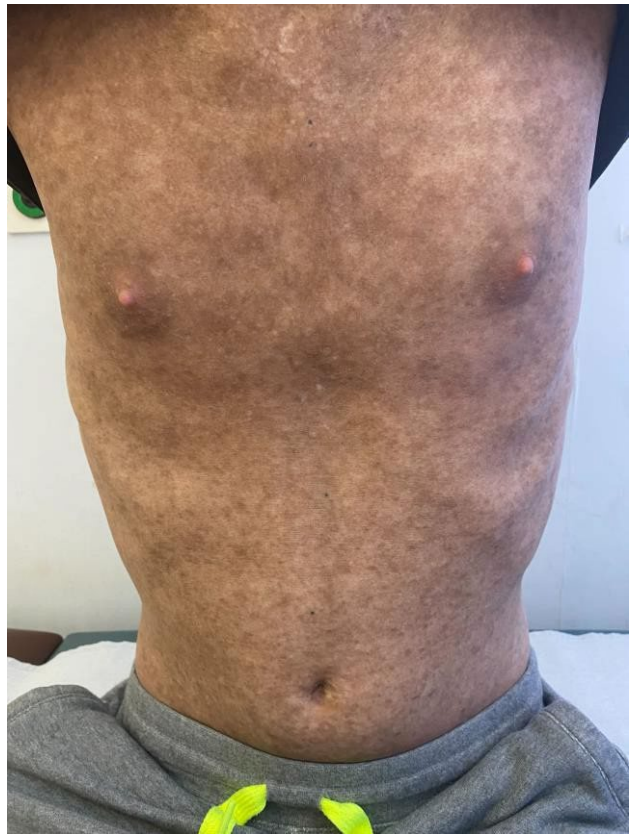
- D+175 Haplo DLI 3 × 10^5 T cells/ kg bw
- D+210 Haplo DLI 5 × 10^5 T cells/ kg bw

- Conversion to CC
- Moderate/ severe skin-liver GvHD
- ALT 161 IU/L, AST 157 IU/L, gGT 1431 IU/L, ALP 470 IU/L
- CYA → Ruxolitinib for 13 months



CLINICAL: current status

- D+3.5 years
- WBC: 4 × 10^9/l, Hb 123 g/l,
  PLT: 120 × 10^9/l
- CR, CC
- No active GVHD
- No IMS
- good performance, at work



QUESTION: Was the bad Haemorrhagic Cystitis and DLI the lifesaver?

- High risk disease →
- HC →
- Early cessation of IMS →
- Haplo- DLI for MC
- cGVHD
- NO RELAPSE!!