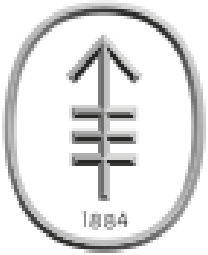

Memorial Sloan Kettering Cancer Center

Efforts to Increase Cord Blood Utilization

Juliet Barker, MBBS

Attending Physician & Director, CBT Program

Adult Bone Marrow Transplant Service, MSKCC

Professor of Medicine, Weill Cornell Medical College

Co-chair, ASTCT CB Special Interest Group

Acknowledgements

MSKCC Staff, NMDP, NYBC, HRSA.
Colleagues at the U of Minnesota
& many other national & international centers & CB banks.

Disclosures

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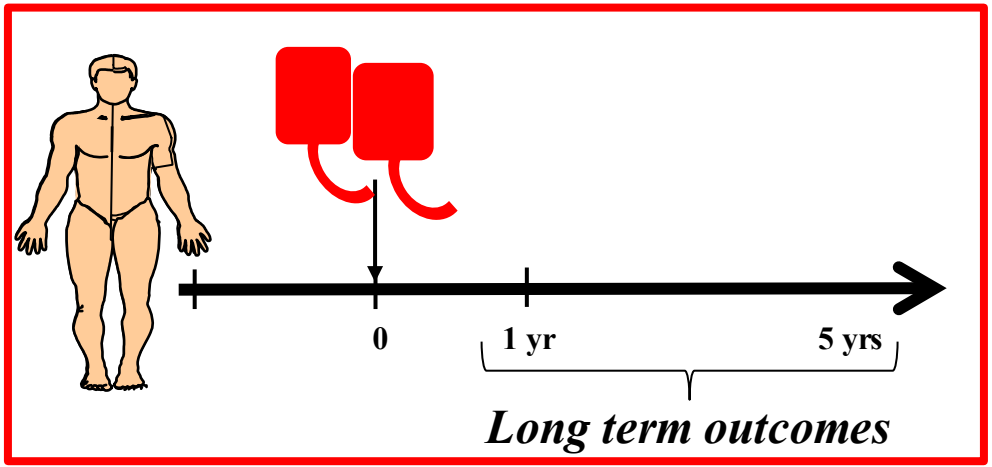
Gamida Cell & Merck.
Clinical trial funding:
Angiocrine Bioscience.

Major Benefits of CBT

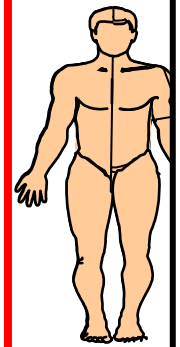
1) <u>Extending transplant access:</u>
- Rapid availability & easy scheduling.
- Many patients have good units.
- Reduced requirement for HLA-match.
- For some, CB is only available stem cell source.



2) <u>Long-term advantages</u>:
- Good immune recovery.
- Better GVHD treatment responses.
- Low rates chronic GVHD.
- Low relapse rates (no ATG).
- Advantages in GVL biology.
- Long-term cost benefits.

Supported by single center/ multi-center (eg U of MN, FHCRC, MSKCC, Duke, Colorado, Great Ormond St, Duke, Utrecht, Milan) & registry studies.

Major Benefits of CBT



However, not all of the transplant community rees.

Vastly opposing opinions re the value of CB.

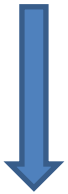
Supported by single center/ multi-center (eg U of MN, FHCRC, MSKCC, Duke, Colorado, Great Ormond St, Duke, Utrecht, Milan) & registry studies.

Utilization of CB has Declined: Reasons

- **Unit selection: more complicated than URD/ haplo.**
- **Cost of units/ longer early hospital stay.**
- **Complexity: early post-transplant.**
- **Selective focus: reduced relapse & cGVHD ignored.**
- **CBT as "last ditch" therapy.**
- **Expansion: adverse effect on CBT without expansion?**

Transplant Access

Q: Do you need CB? A: Yes

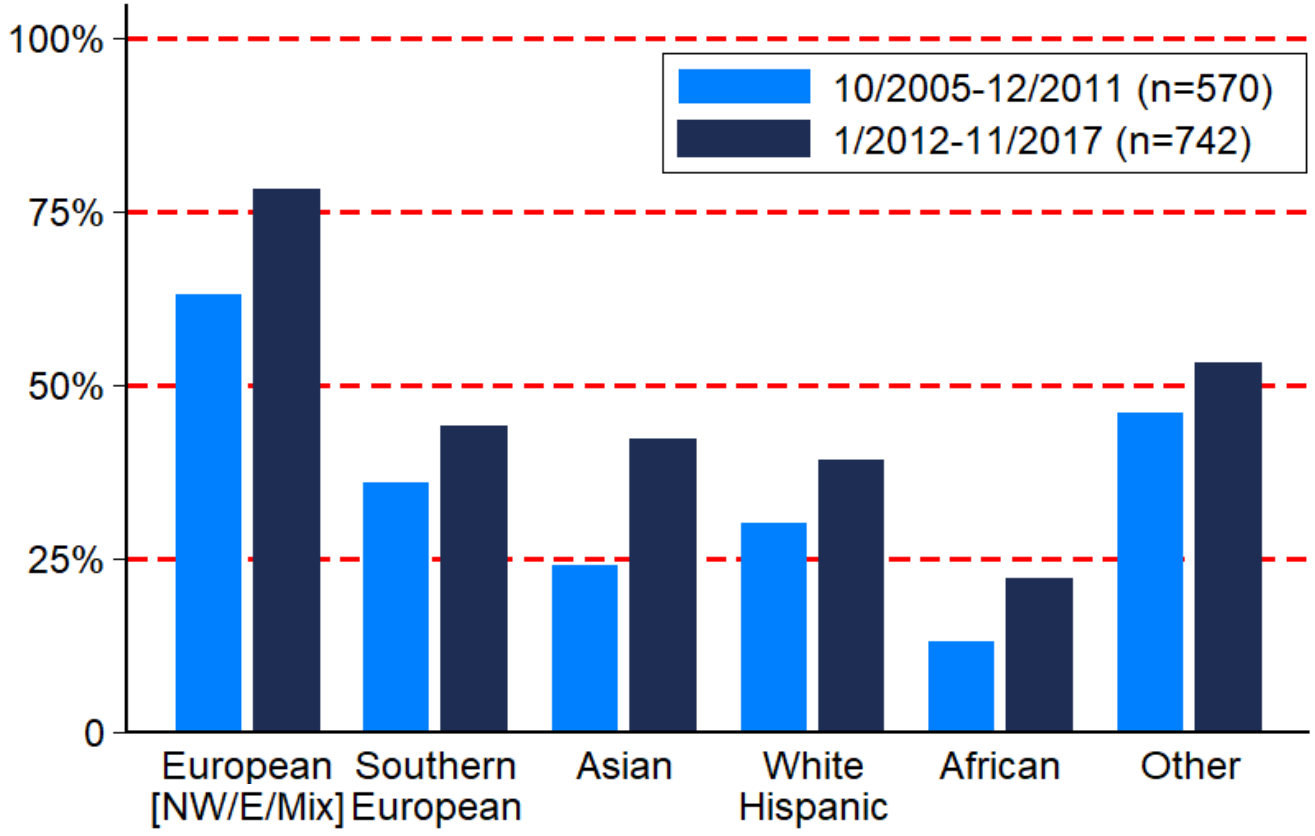


Why?

Q: Is there ongoing disparity in unrelated donor (URD) access according to patient race?

A: Yes.

Likelihood of Undergoing an 8/8 URD Transplant According to Patient Ancestry by Era (n = 1,312)



Major problems with adult volunteer donor access:
not appreciably improving for southern & non-European patients.

Barker et al, Blood Advances 2019

U.S. Population Becoming More Diverse

Young patients URD match rate getting worse:

- **Patient > 60 yrs: 54%**
- **Patient < 20 yrs: 34%.**

Young donors less likely to match patients of any age:

- **48% of new donors aged < 35 yrs have unique HLA.**
- **60% if Asian/ Hispanic.**
- **78% if Black.**

Thus, not going to get better.
This makes the CB inventory very important.

Data courtesy of NMDP Be the Match, 2018

Haplo graft availability by patient ancestry if no 8/8 URD

(n = 81 patients evaluated)

Ancestry (N, % of total patients)	N (%) of Group with Suitable Haplo Graft	P Value
European (n = 37, 46%)	31/37 (84%)	*0.008*
African (n = 16, 20%)	7/16 (44%)	
Other Non-European (n = 28, 34%)	23/28 (82%)	

- **Racial differences in access to haplo-identical donors.**
- **Other limitations: delays with donor clearance or if must workup multiple donors or if use extended family.**

** donors targeted by recipient DSA allowed.*

Kosuri et al, BBMT 2017

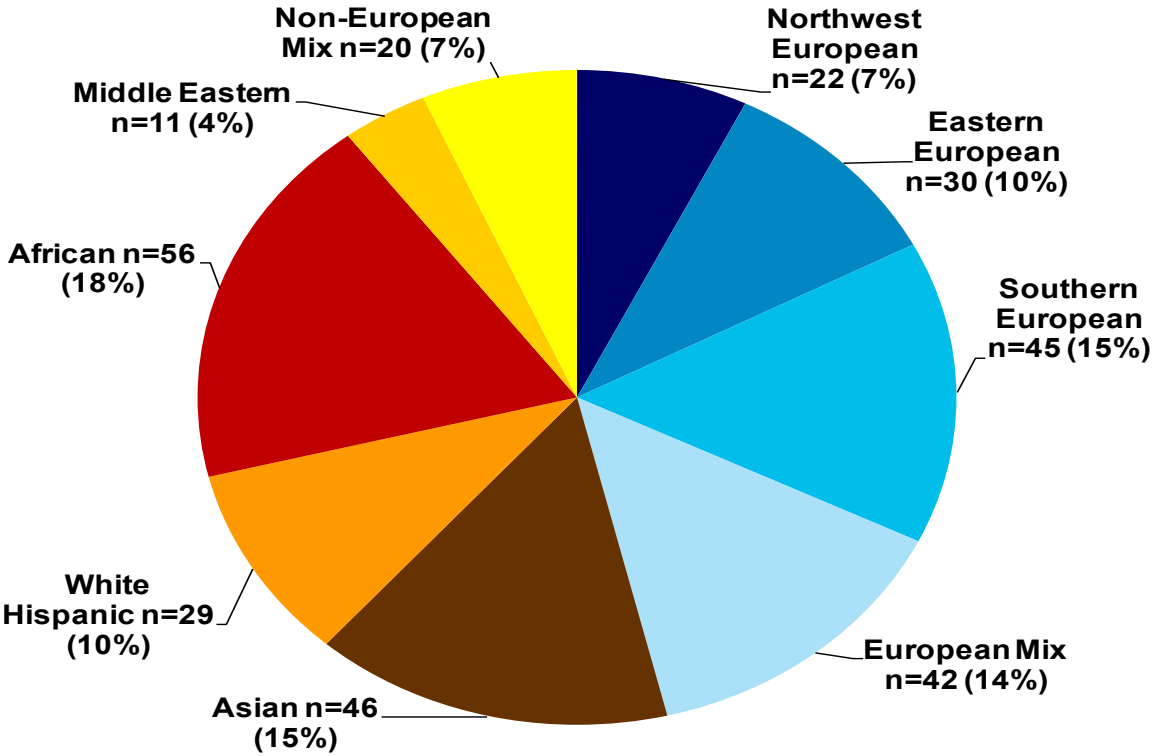
MSK CBT by Patient Ancestry 2005 - 2017 (n = 301)

Europeans: blues.
Non-Europeans: red-yellow-brown

Reduced requirement for HLA-match
(median HLA-match in adult CBTs 5/8)

⬇

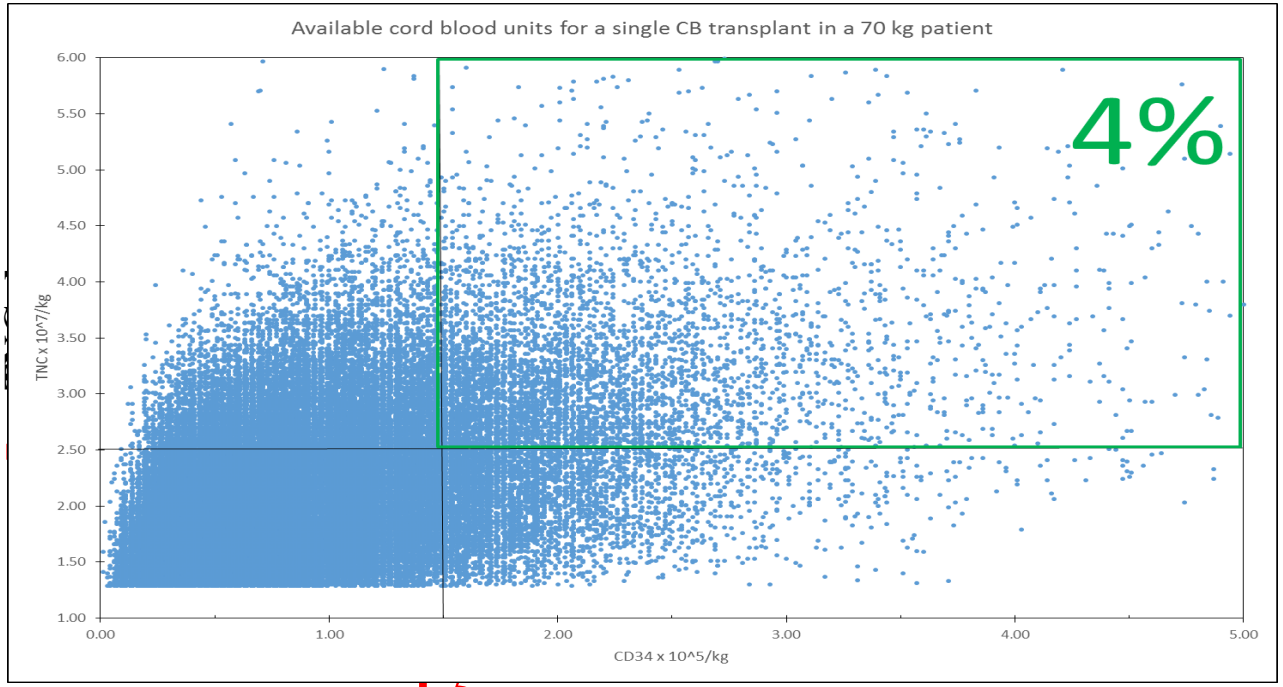
CB extends transplant access to all



Barker et al, Blood Advances 2019

TNC & CD34+ Cell Dose Distribution in NMDP U.S. Inventory for a 70 kg Patients (n = 126,000 Units)

1) Majority of units with adequate TNC do not have adequate CD34+ dose.
2) 4% adequate as single units.
3) With lower dose (TNC 1.5 & CD34+ 1.0) threshold, 22% of units had adequate dose for a double unit graft.

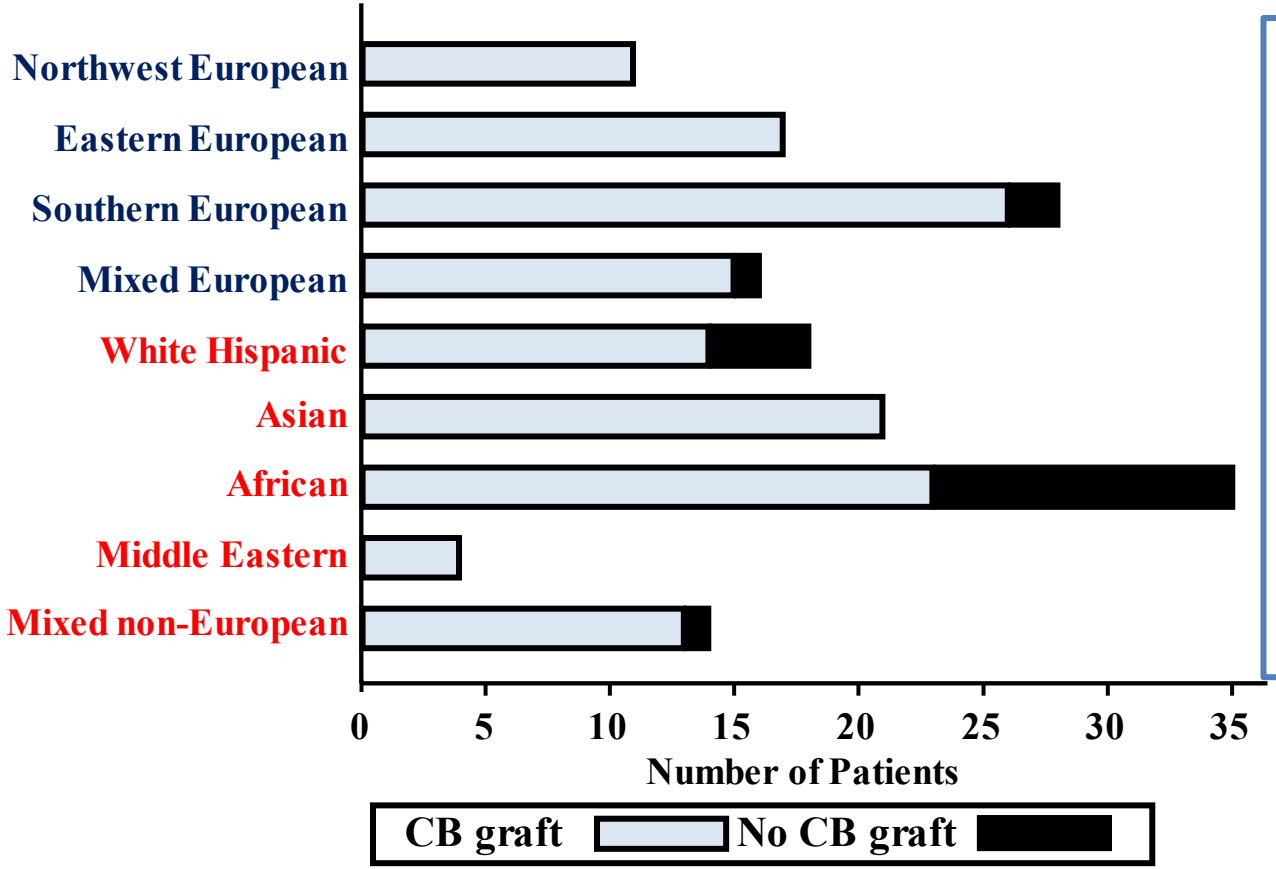


Barker et al, Blood Advances 2019

This data supports major focus should be on increasing inventory of high dose units *ie* increase lower limit of TNC for banking.

MSK: CB Graft Availability if No 8/8 URD (n = 164)

(adults, nearly all doubles, units 4-6/6 & ≥ 3/8 HLA-matched)



- Despite small inventory, adequate CB graft: 88%.
- Many have excellent grafts.
- Graft availability much better than URD eg more than triple for African ancestry pts.
- No CB graft: 12%. *(nearly all non-European. median weight 98 kg).*

Barker et al, 2019 (manuscript submitted)

“Nearly everyone has a CB graft & you don’t have to worry about donor availability”

"Nearly everyone has a CB graft & you don't have to worry about donor availability"

"Yes – but engraftment is slow & early TRM is high"

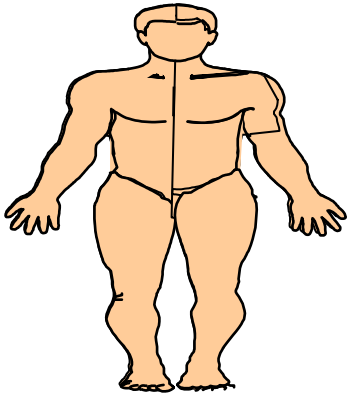
and

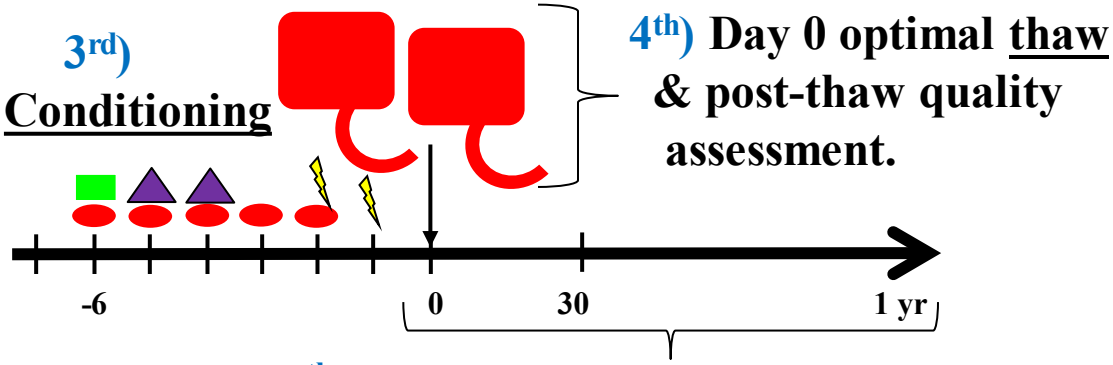
"You can only do CBT with expansion*"

***Limitations of expansion**: logistics, more complicated, possible compromise of T-cells with T-add back platforms?*

Can we make CBT easier?

Strategies to Reduce Mortality *without* Expansion





1st) Efficient URD/ CB searches (& haplo workups).

2nd) Unit selection:
- Quality, CD34+ dose & 8 allele HLA-match.
- Double unit grafts if needed.

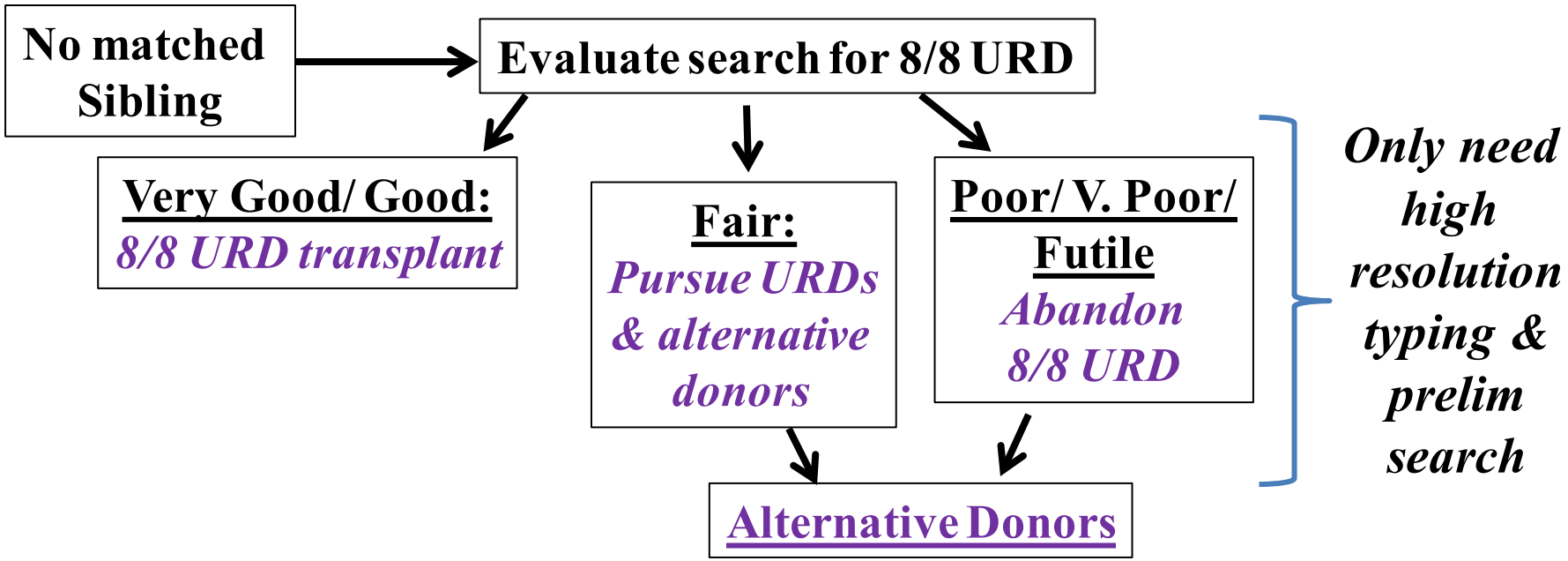
5th) Optimize immune suppression.

6th) Other:
- Management of slow engraftment.
- PES: prevention & therapy.
- aGVHD & CMV: prevention & therapy.
- other complications.

Barker et al, BBMT Optimal Practices 2017

1st) CBT Recipients Benefit from Efficient URD Searches

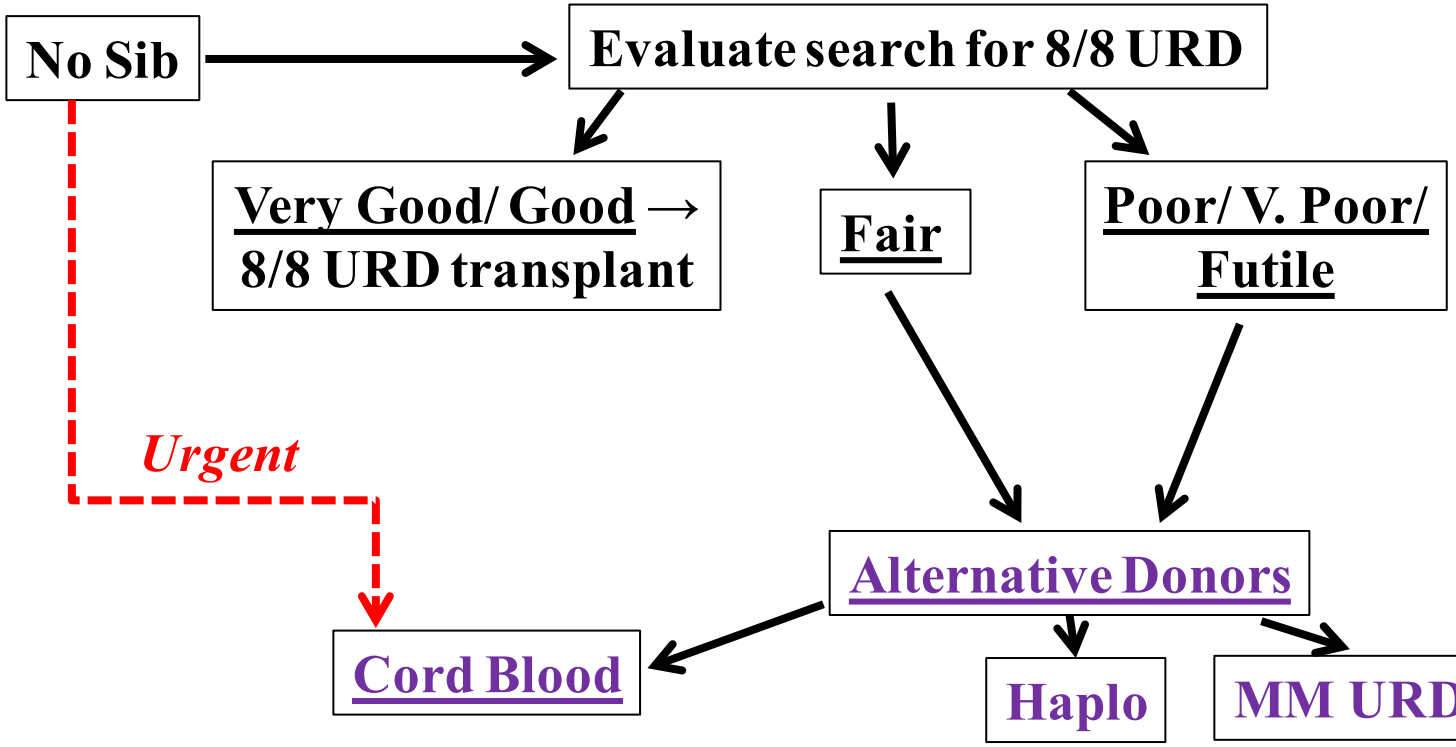
MSKCC 8/8 URD Search Prognosis using NMDP Haplologic Predictions



Can predict 8/8 URD likelihood at search initiation

Davis et al, BBMT 2018

MSK Algorithm: Efficient Donor Searches



Davis et al, BBMT 2018

Promptly permits pursuit of alternative donors if needed.

2nd) Optimal Unit Selection: Quality, Dose, HLA-match

ASTCT CB SIG & NMDP Unit Selection Guidelines

Unit quality
eg RBC depleted, standard cryoprocessing

↓

Cell Dose:
Single unit: TNC ≥ 2.5 & CD34+ ≥ 1.5
Double unit: TNC ≥ 1.5 & CD34+ ≥ 1.0

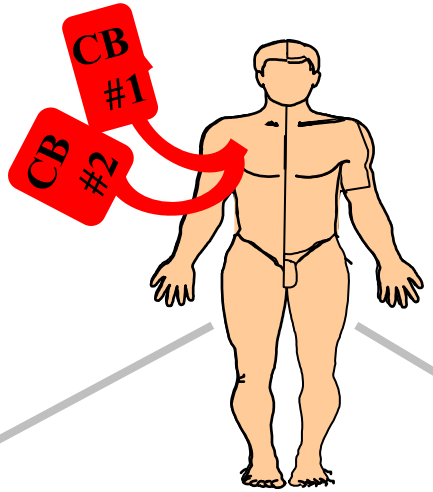
Higher doses ideal.

↓

8 allele HLA-match (HLA-A, -B, -C, -DRB1)
Guidelines ≥ 4/8 (MSKCC ≥ 3/8 to extend access)

Need to make a distinction between adults & pediatrics, & patient diagnosis.
How to trade off between dose (TNC/ CD34+) & allele HLA-match?: unknown.

3rd) Conditioning: Examples



High*
Cy 120
Flu 75
TBI 1375

Midi***:
Cy 50
Flu 150
Thio 10
TBI 400

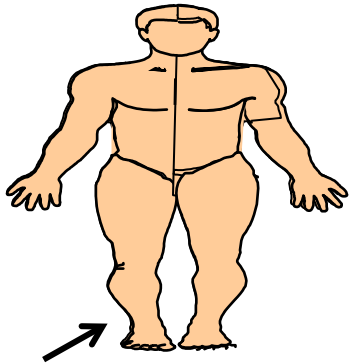
Mini**
Cy 50
Flu 150
TBI 200

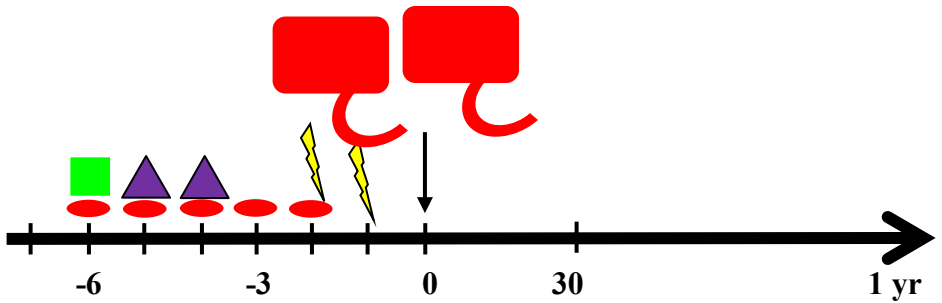
Tailor intensity to pt age & comorbidity status ("fitness": aaHCT-CI)

** Barker et al, Blood 2003, **Barker et al, Blood 2005 ***Ponce et al, BBMT 2013*

MSKCC Midi Prep for Adults

Cy 50/ Flu 150/ Thio 10/ TBI 400 + dCBT





CSA/ MMF (*no ATG**)

- Adults ≤ 65 yrs.
- High risk heme malignancies.

Ablative *but* intermediate intensity

Ponce et al, BBMT 2013

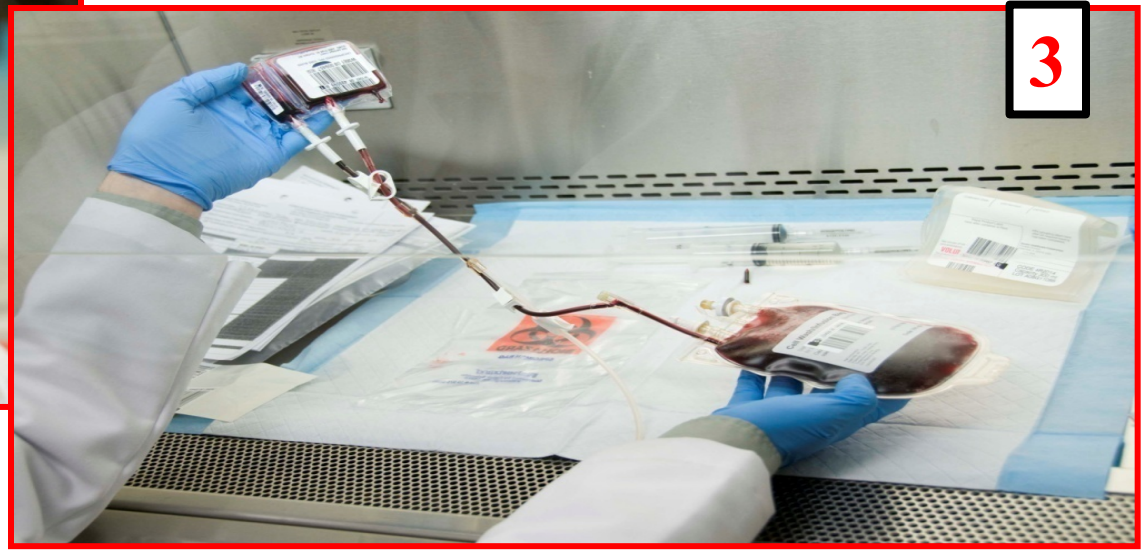
Politikos et al, TCT 2019 (manuscript in preparation)

** ATG abandoned in 2005*

4th) Optimize Thaw & Infusion

Rapid analysis of post-thaw CD34+ viability*.

Nursing guidelines for infusion.**

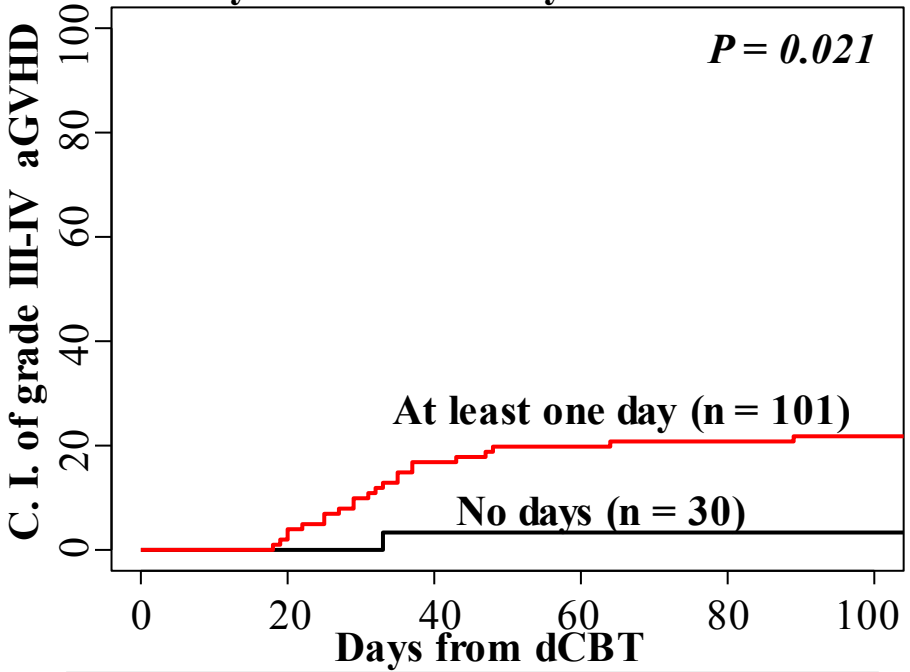


** Scaradavou et al, BBMT 2009*

***Dahi et al, BBMT 2014*

5th) Importance of Immune Suppression: eg CSA & MMF

Association between N of days sub-therapeutic CSA between days -1- to +7 & day 100 severe aGVHD.



Sub-therapeutic CSA days -1 - +7: increased risk of severe acute GVHD.

Bhatt et al, TCT 2018

Multivariate Analysis: is MMF Dose Associated with Day 100 Grade III-IV aGVHD Risk?

(Also included pt age, gender & CMV status).

Variable	HR (95% CI)	p
MMF Dose & Dominant Unit-Recipient HLA-Match		
Low Dose & Worse Match (n = 30)	Reference	0.05
High Dose & Worse Match (n = 18)	0.23 (0.03-1.84)	
Low Dose & Better Match (n = 71)	0.46 (0.20-1.07)	
High Dose & Better Match (n = 55)	0.26 (0.09-0.75)	

Total daily dose split at median.
Worse HLA-match: 1-3/6 alleles (vs 4-6/6).

Increased MMF dose: offset adverse impact of more HLA-mismatch.

Harnicar et al, BBMT 2015

Q: Can focusing on optimizing multiple components of the transplant improve post-transplant survival?

A: Yes.

MSKCC Adult Midi Prep dCBT (n = 102, 2014- 2017)

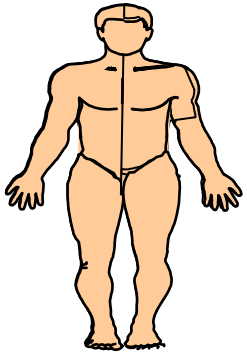
Median survivor follow-up: 40 months (range 20-67)

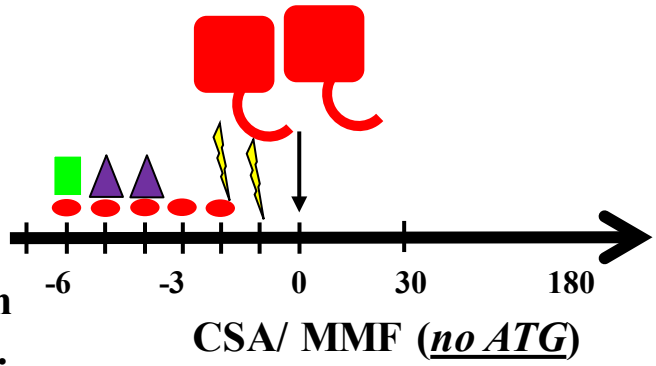
Characteristic	Value
Median Age	**50 yrs (range 21-65)**
Median Weight	**80 kg (range 36-137)**
N (%) Diagnosis	
Acute leukemia*	**71%**
MDS/ CML/ other MPD*	**17%**
NHL	**14%**
Median HLA-match units to patient	**5/8 (range 3-7)**
Median CD34+ cell dose *(infused 10^5/kg/unit)*	**1.3 (range 0.2-8.6)**

** Myeloids ≤ 10% & ALL < 5% blasts pre-CBT*

Politikos et al, TCT 2019

MSK Midi dCBT (n = 102 adults)



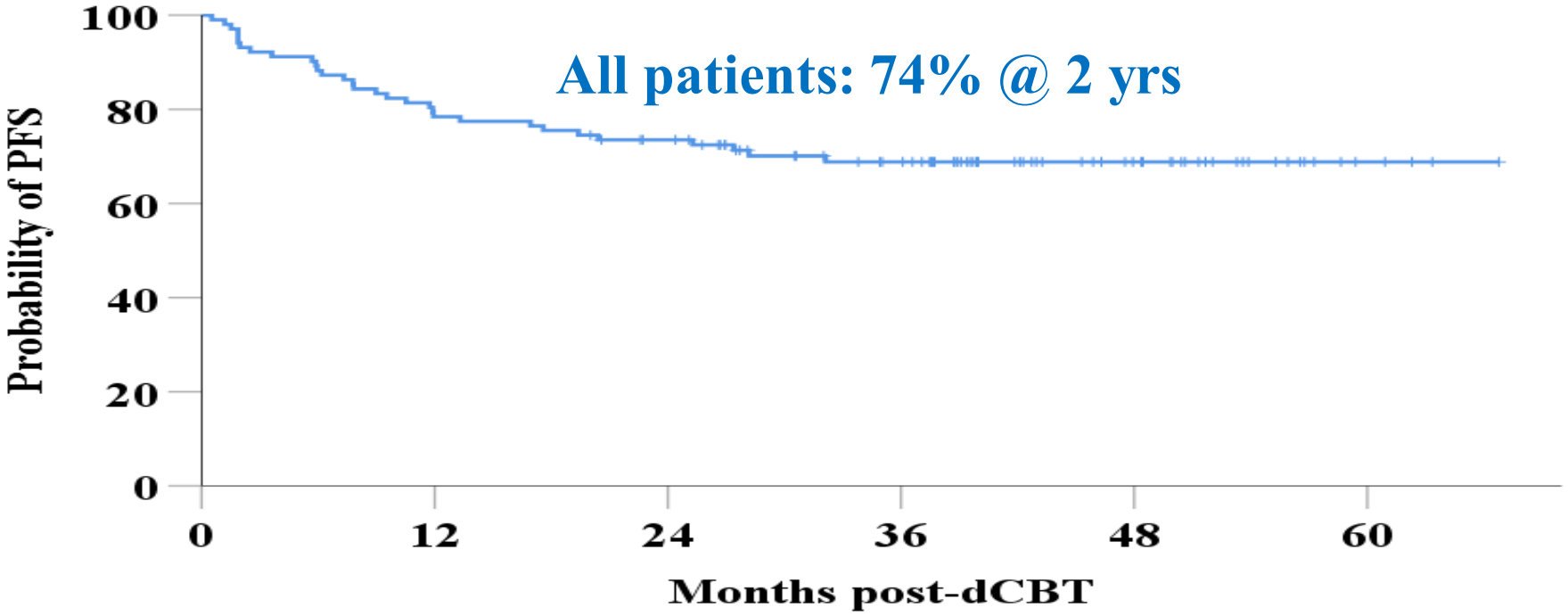


- Adults median 50 yrs (21-65).
- High risk heme malignancies.

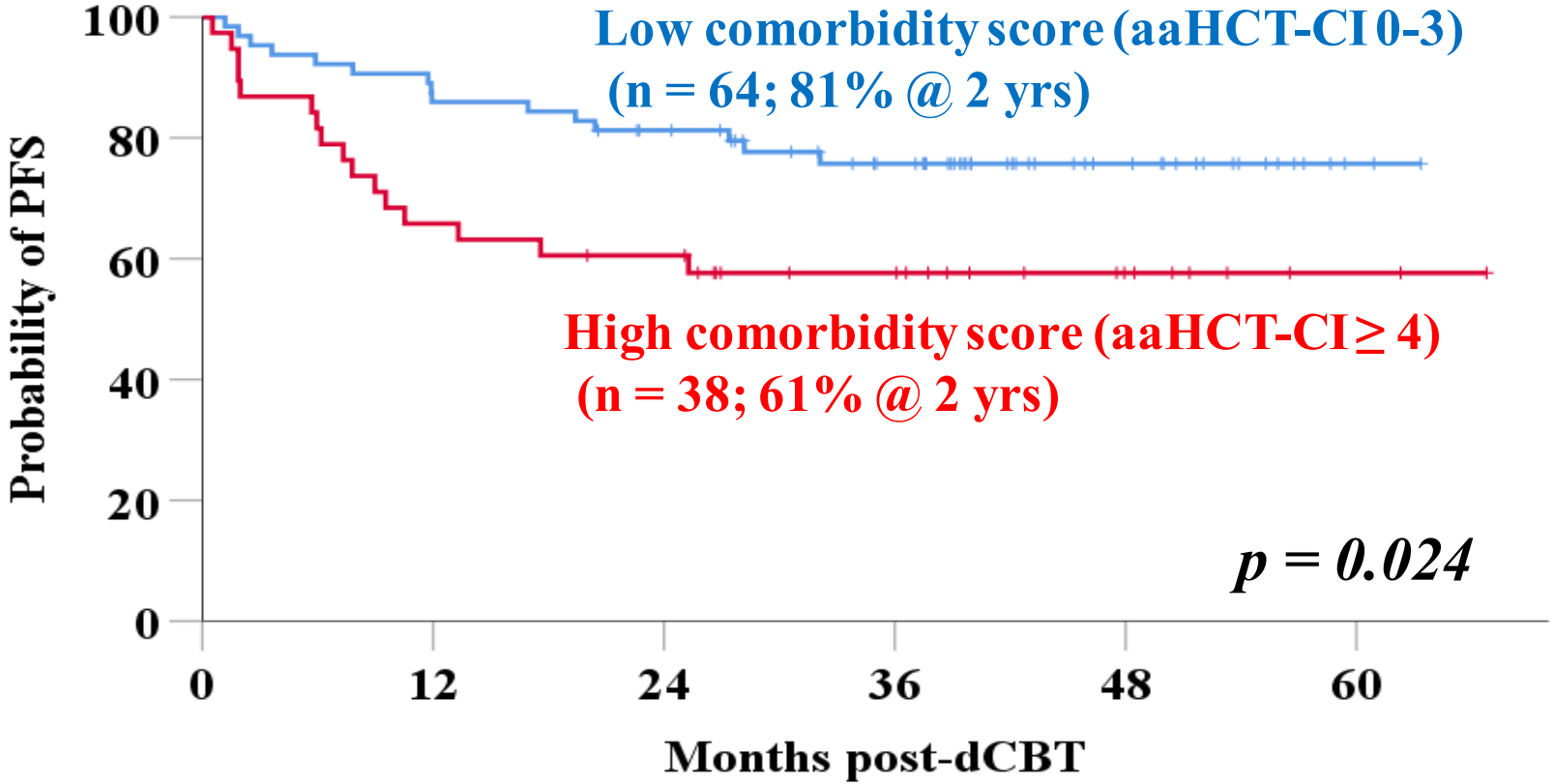
Outcome	Value
Day 45 engraftment	97% *(Median +25 days)*
Day 180 grade III-IV aGVHD	23% *(II-IV: 77%)*
1-yr cGVHD	4%

Politikos et al, TCT 2019

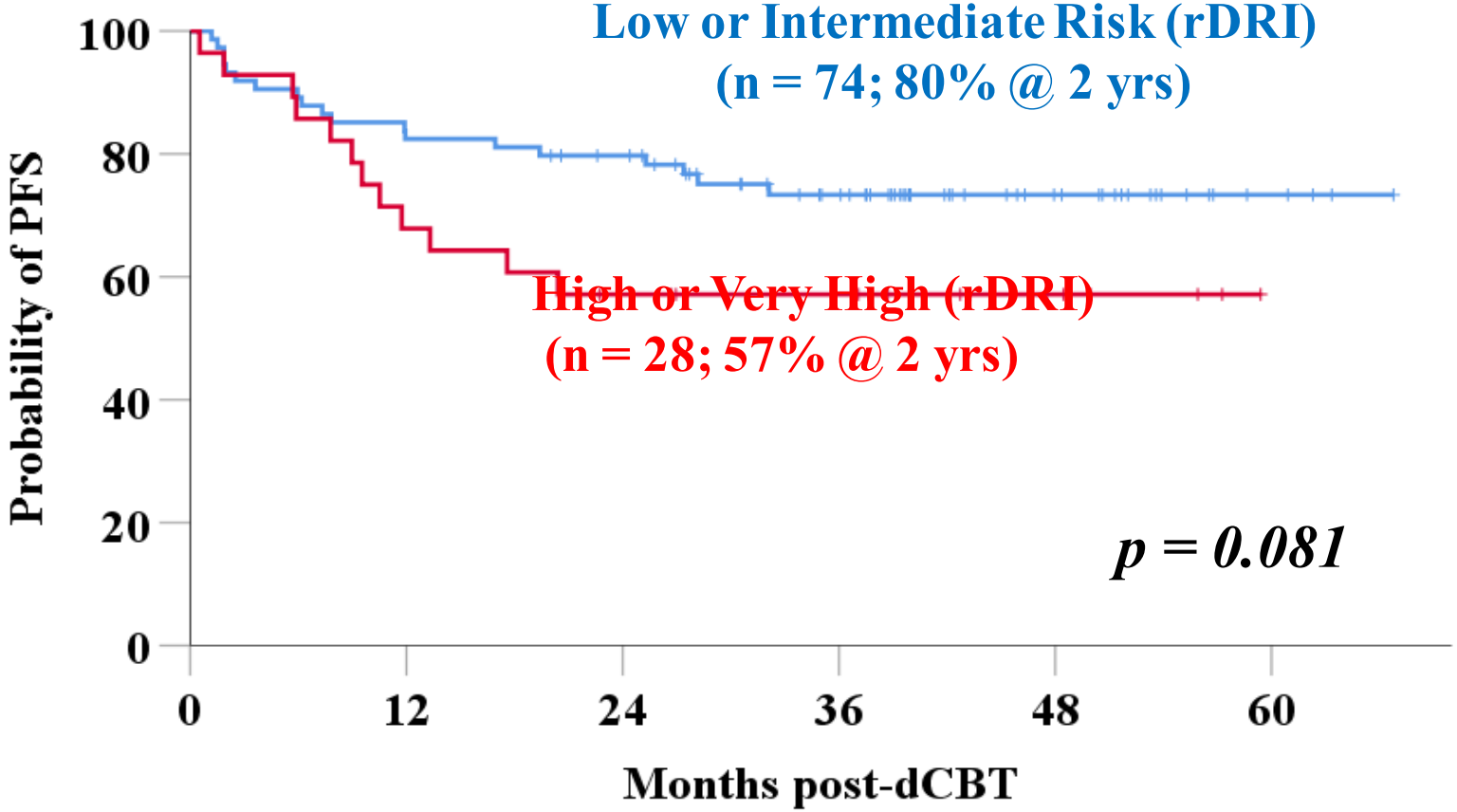
MSK Midi dCBT: Progression-Free Survival (n = 102)



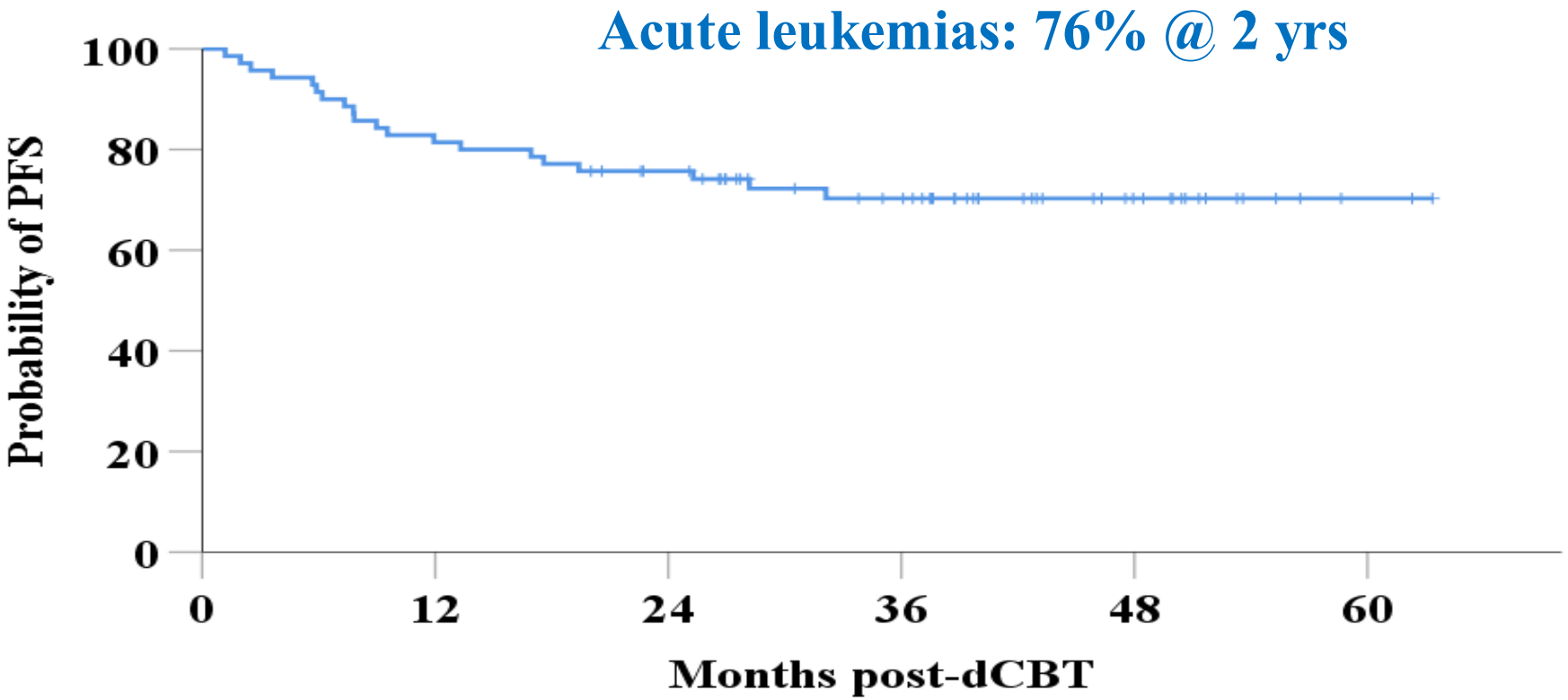
MSK Midi dCBT Progression-Free Survival (n = 102) by Patient Co-morbidities



MSK Midi dCBT Progression-Free Survival (n = 102) by Patient Disease Risk

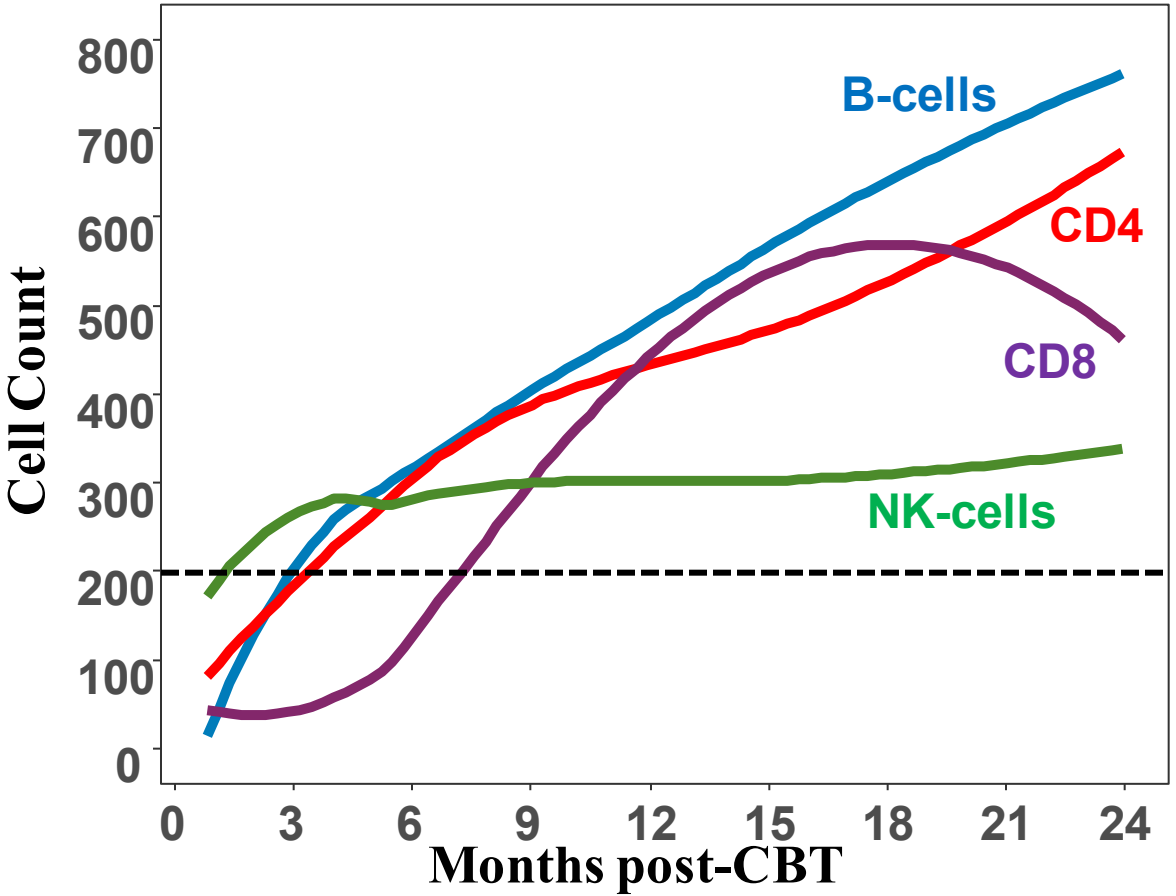


MSK Midi dCBT Progression-Free Survival: Acute Leukemia (n = 70)



Midi Adult dCBT Immune Recovery

(Median age 50 years, no ATG)



- **Patients do recover – including if prior aGVHD.**
- **Median day 120 CD4+ count: 204.**

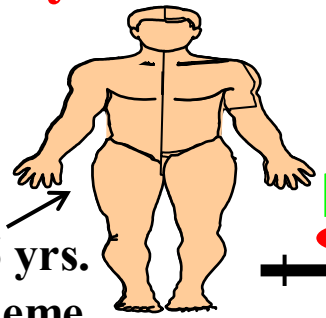
Politikos et al, 2019 (manuscript submitted)

MSKCC: Major Problems in Adult CBT

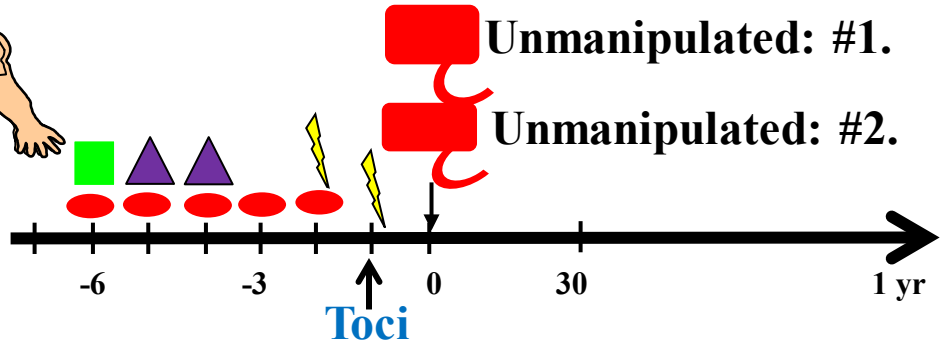
- **Acute GVHD - esp. GI tract.**
  (~20% grade III-IV aGVHD).

- **Early CMV infection.**
  (~ 60% seropositive & > 80% CMV+ will reactivate).

Midi Cy/ Flu/ Thio/ TBI dCBT + Day -1 Tocilizumab (n = 26)



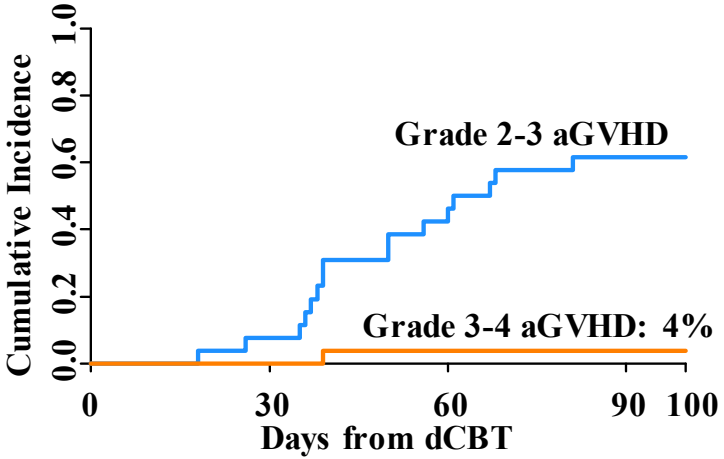
- Adults ≤ 65 yrs.
- High risk heme malignancies.



As per G. Hill group. Toci 8 mg/kg.

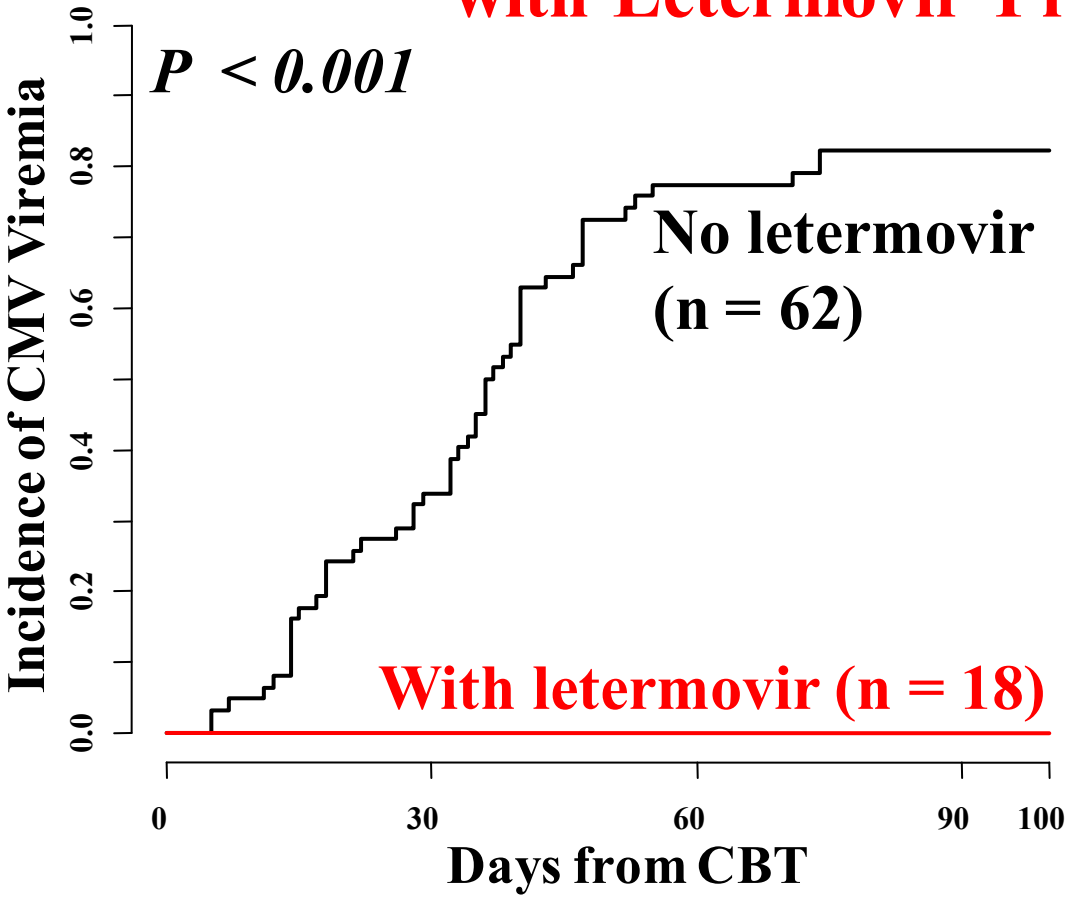
CSA/ MMF →
+7: Letermovir if CMV+.

Preliminary data (2018-2019):
- decreased grade 3-4 aGVHD: 4%. (1 pt with grade 3, no grade 4).



Updated from Politikos et al, TCT 2019

CMV Infections in Adult CMV+ CBT Recipients with Letermovir Prophylaxis



- Start letermovir day +7.
- Very effective (0%).
- No toxicity.
- Cost effective.
- New standard of care.
- Do not know when can safely stop.

Lau, C. et al, manuscript in preparation, 2019

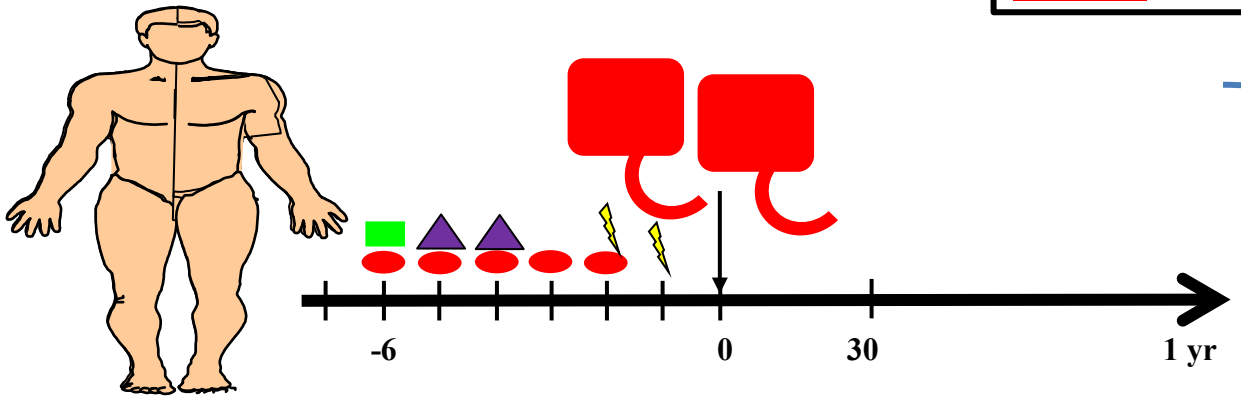
Despite multiple centers & trials showing outstanding results, CBT has declined in U.S. & Europe.

How to Fix?

<u>Note</u>: increased utilization of CB units will help patients & save the banks.

How to Correct CBT Decline?: Increase Interest/ Need/ Ease

BLACK: not working to date.
BLUE: will not be enough.
RED: will help.



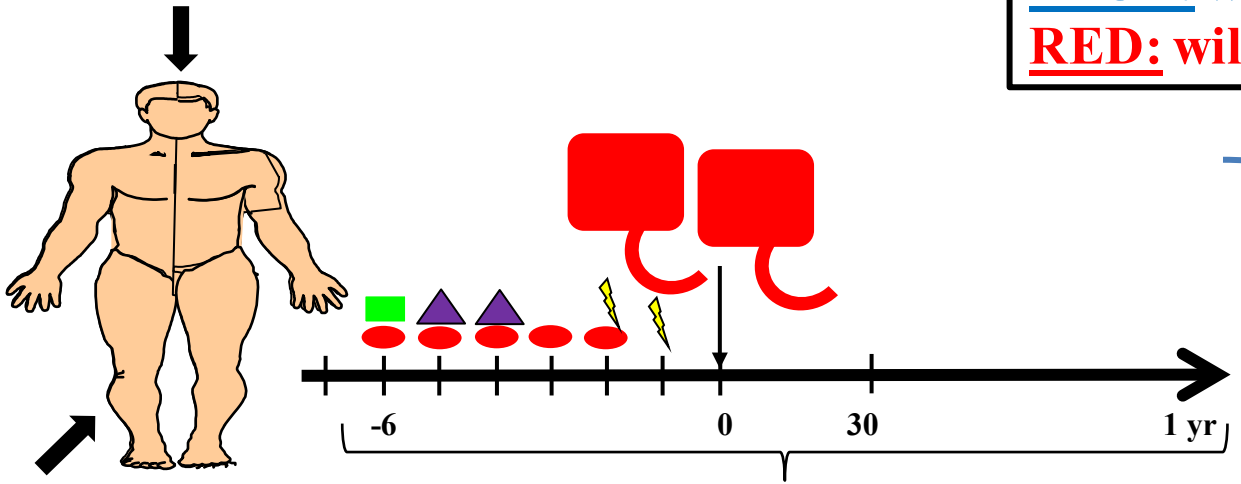
Field:

- Emphasize major advantages & good outcomes with CBT (especially in experienced centers).
- Offer advice to MDs who ask.

How to Correct CBT Decline?: Increase Interest/ Need/ Ease

- Ensure timely referral for transplant eligible pts.

BLACK: not working to date.
BLUE: will not be enough.
RED: will help.



- Efficient URD/ CB searches (& haplo workups). Stop futile URD searches.
- CB unit selection: make it much easier. Ensure optimal units selected.
- Optimal practice guidelines.

Field:
- Emphasize major advantages & good outcomes with CBT (especially in experienced centers).
- Offer advice to MDs who ask.

Proposal: Create a U.S. CBT Network

Aim is to facilitate:

- **Rapid collaborations & information exchange.**
- **Create/ share practice guidelines & protocols & share nationally.**
- **Speed publications.**
- **Perform clinical trials.**
- **Train junior MDs/ other transplant staff.**

Likely only approach that will effectively reverse decline in CBT.

Further Benefits of CBT Network

- Create momentum & increase perception in the field.
- Increase enthusiasm → recruit & train more staff in CBT.
- Support CBT centers so they do not abandon CBT.
- Rapidly share knowledge with centers not part of Network.
- Support the CB Banks (including staff morale).
- Provide improved mechanism to lobby insurance companies to pay for CB transplants.

Suggest these efforts be promoted by ASTCT & NMDP: to increase CBT visibility & make CBT more mainstream. Initiative is ambitious & will require funding.