Medizinische Klinik und Poliklinik I & DKMS
Johannes Schetelig

cGvHD Prophylaxe mit ATG vs PTCy vs Abatacept

12. Oktober 2024

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition

TU Dresden, Medizinische Klinik I und DKMS Group

2. Beratungs- bzw. Gutachtertätigkeit

Advisory Board Teilnahmen für Abbvie, AstraZeneca, BeiGene, BMS, Janssen, Sanofi und MSD

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

-

4. Patent, Urheberrecht, Verkaufslizenz

-

5. Honorare

Vortragshonorare: Astellas, AstraZeneca, BeiGene, BMS, Novartis, Eurocept, Medac und Janssen

6. Finanzierung wissenschaftlicher Untersuchungen

-

7. Andere finanzielle Beziehungen

-

8. Immaterielle Interessenkonflikte

-

Outline

- ATG
- PTCy
- Abatacept

GVHD prophylaxis: one piece of a puzzle

Choices prior to HCT: donor type (age, HLA-mm, female to male, pregnancies), graft type / manipulation, conditioning intensity

Prophylaxis

Assessments, Biomarkers, MRD

Treatment timely & stringent

ATG

rATG for GVHD prevention

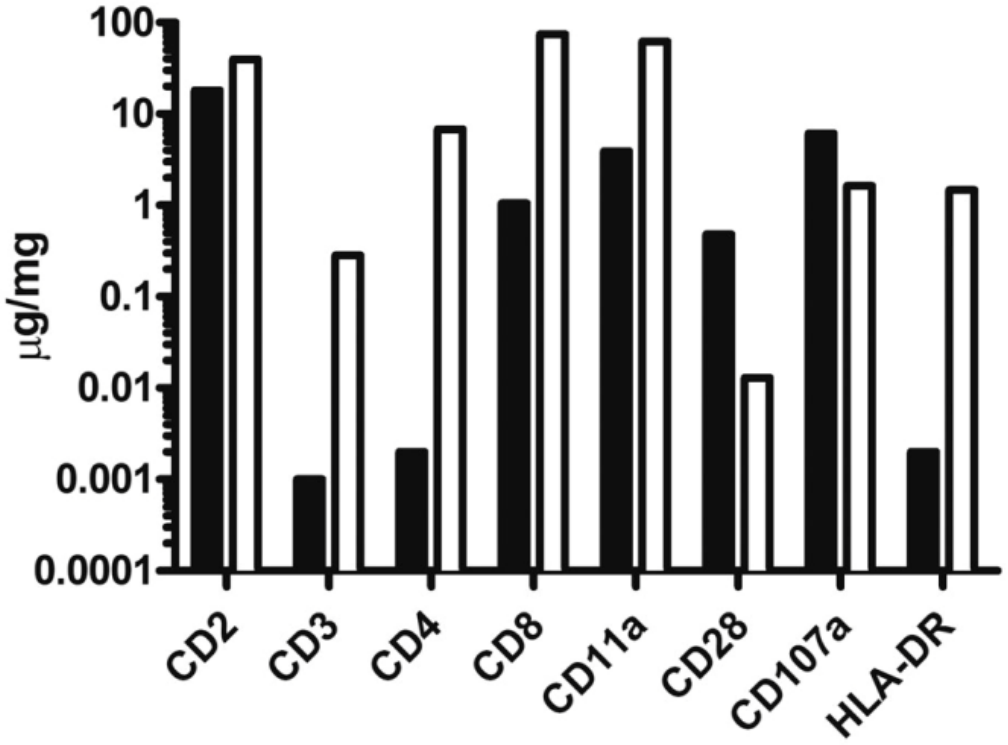


Figure 1. Quantification of ATG antibodies targeting specific human antigens. (adapted from Table 1 from Popow *et al.*[29]) Black bars represent ATG-F data and white bars ATG-T data.

- rATG: Grafalon, Thymoglobulin
- polyclonal rabbit antibodies against human T-cells (Grafalon® Jurkat T-cell line, Thymoglobulin ®, human thymocytes)
- T-cell killing complement-mediated, direct apoptosis, ADCC
- rATG delays recovery of B-cell, CD4- and CD8-cells; *in vito* rATG co-incubation induces regulatory T cell phenotype
- effects on regeneration of specific T-cell subsets incompletely understood
- few dosing/timing studies

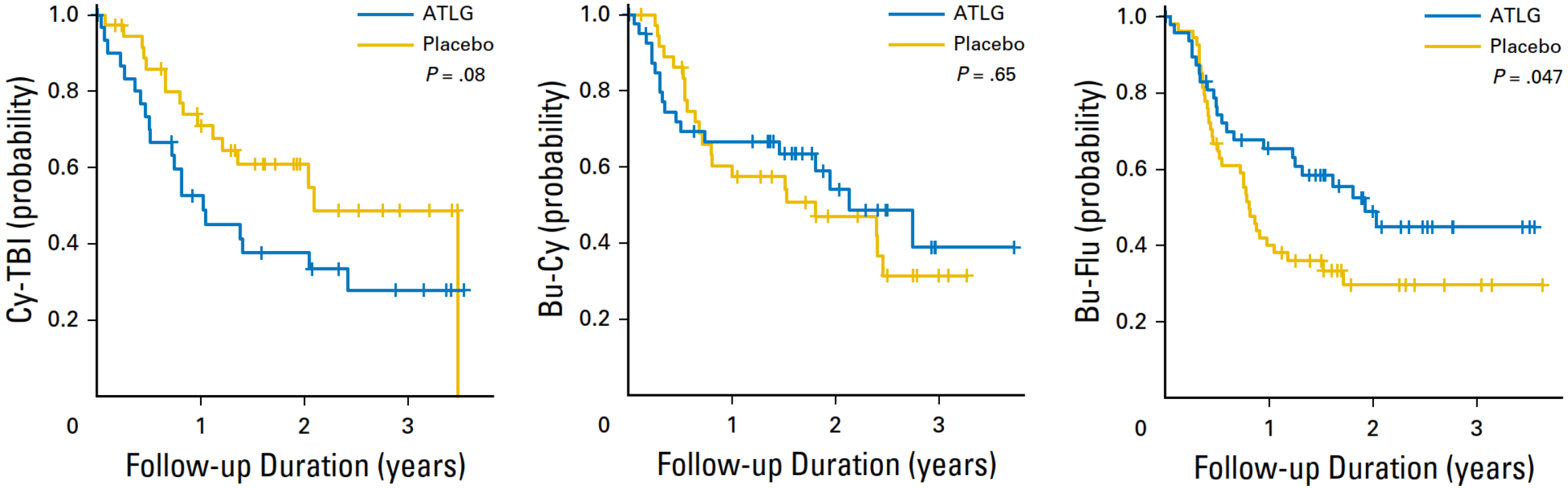
Baron, Haematologica 2017

Randomized controlled trials: ATG vs CNI/MTX

	Finke 2009	Kröger 2016	Soiffer 2017	Walker 2020
N	202	168	254	203
Study Drug	20 mg/kg ATG-F x 3 days	10 mg/kg ATG-F x 3 days	20 mg/kg ATG-F x 3 days	4.5 mg/kg Thymoglobulin
Conditioning + GVHD Prophylaxis	Myeloablative + CSA/MTX	Myeloablative + CSA/MTX	Myeloablative + Tacro/MTX	Any Conditioning + CNI/MTX or MMF
Donor (mismatch)	~60% 8/8 UD	HLA-identical Sibling	100% 8/8 UD	~80% 8/8 UD
Cell Source	82% PBSCs	100% PBSC	79% PBSC	88% PBSC
Acute GVHD °II-IV	**33% v 51% p=0.01**	11% v 18% p=0.1	**23% v 40% p=0.004**	**50% v 65% p=0.012**
mod/severe cGVHD	**12% v 43% p<0.001**	**11% v 47% p<0.001**	**12% v 33% p<0.001**	**26% v 41% p=0.03**
NRM	20% v 29% p=0.20	14% v 12% p=0.6	21% v 14% p=0.5	21% v 31% p=0.15
Relapse	29% v 24% p=0.6	32% v 25% p=0.2	32% v 21% p=0.1	16% v 18% p=0.7
EFS	52% v 48% p=0.7	59% v 65% p=0.2	**47% v 65% p=0.04**	
OS	59% v 52% p=0.5	74 % v 78% p=0.5	**59% v 74% p=0.03**	**71% v 53% p=0.017**

Dose of ATG too high for lymphopenic patients?

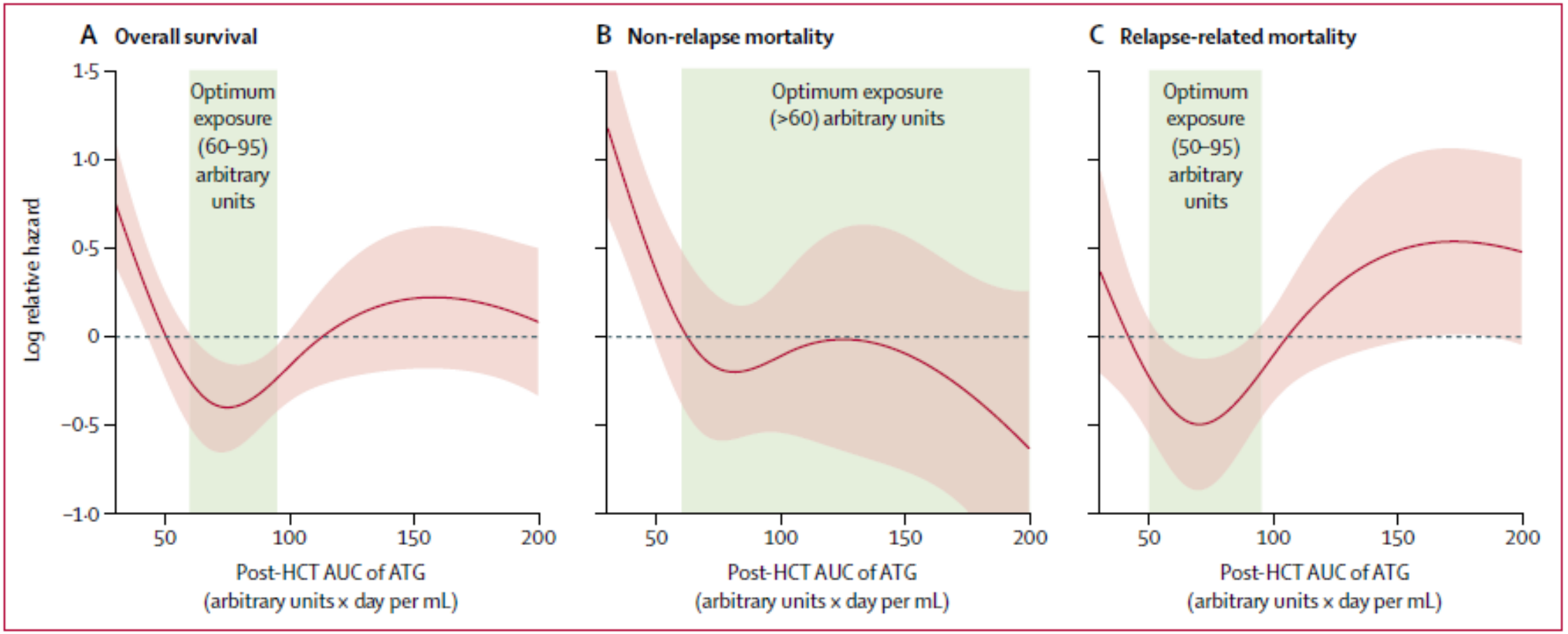
Interaction of conditioning (d-3 ALC) and outcome in US-trial



most TBI pts had day-3 ALC <0.1 GPt/L; most Flu/Bu or Bu/Cy pts had day-3 ALC >0.1 GPt/L

Soiffer, JCO 2017

Drug exposure of Thymoglobulin® determines success

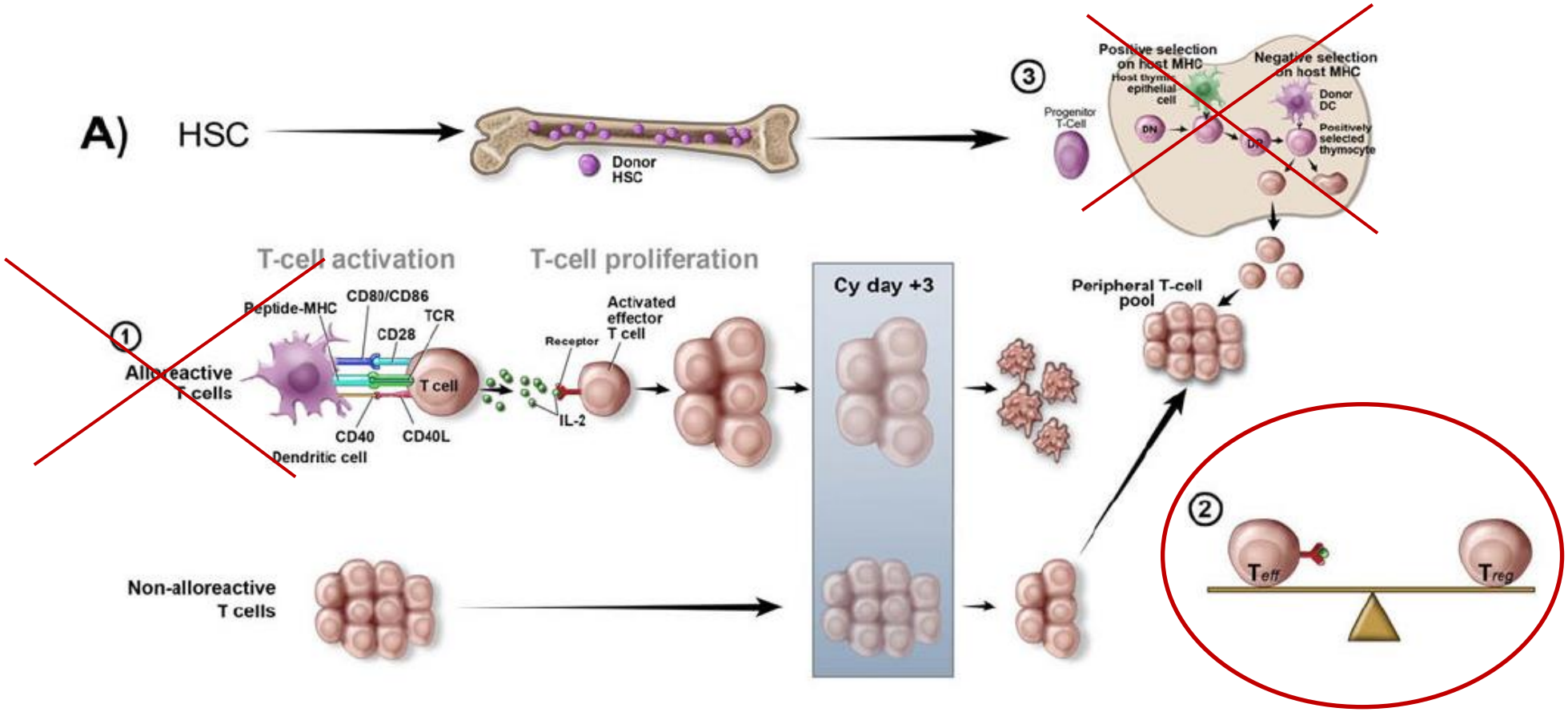


PK prediction based on pre-dose ALC

Admiraal … Boelens, Lancet Hematology 2017 & 2022

PTCy

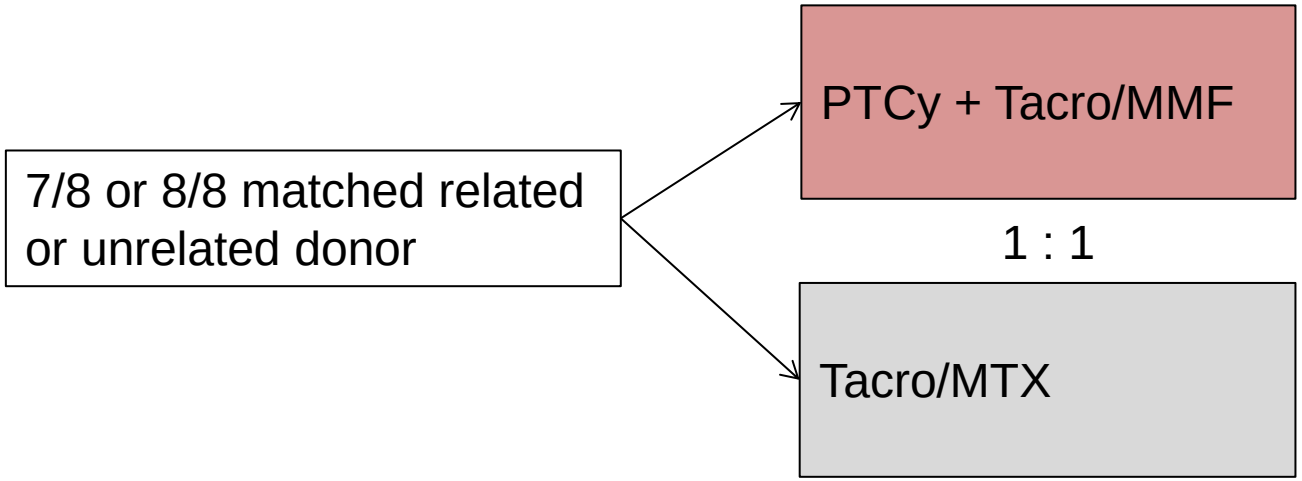
PTCy shifts the balance towards regulatory T-cells



Luznik et al. Semin Oncol 2013; Kanakry et al. Science Translational Med 2017 & Wachsmuth JCI 219

BMT-CTN-1703 – Progress III trial

PTCy Tacro/MMF vs Tacro/MTX



Actual Study Start Date : June 25, 2019

Primary Completion Date : February 2023

Estimated Study Completion Date : February 2024

Eligibility criteria

- AML, MDS, MDS/MPN, CMML, ALL, CML, CLL, FL, Hodgkin, DLBCL, MCL
- ≥ 7/8 matched donor referring to HLA-A, -B, C, and DRB1
- Fit for transplant

Conditioning:

- RIC: Flu/Bu2, Flu/Mel
- NMA: Flu/Cy, Flu/TBI-2, Flu/Cy/TBI

Endpoint: 1 year GVHD-free and relapse-free Survival

Statistics: 428 pts (214 pts per arm, test for superiority, accrual 36m, FU 12m)

Patient Characteristics

Older patients with comorbidity scheduled for RIC.

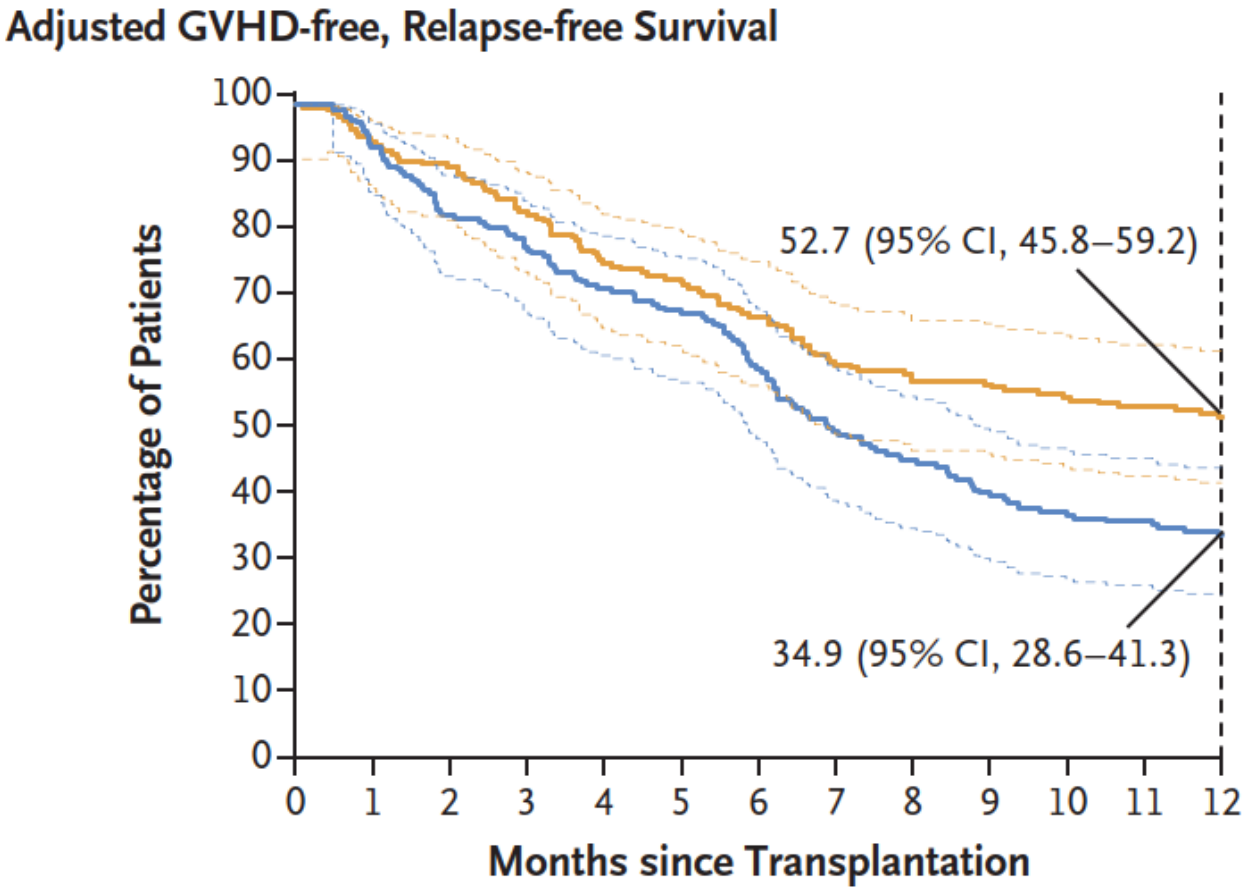
Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Experimental-Prophylaxis Group (N=214)	Standard-Prophylaxis Group (N=217)	All Patients (N=431)
Age			
Mean — yr	64.2±8.5	64.5±8.9	64.3±8.7
≥65 yr — no. (%)	120 (56.1)	125 (57.6)	245 (56.8)
Donor type and HLA matching — no. (%)			
Related donor 6/6	60 (28.0)	68 (31.3)	128 (29.7)
Unrelated donor 7/8	7 (3.3)	8 (3.7)	15 (3.5)
Unrelated donor 8/8	147 (68.7)	141 (65.0)	288 (66.8)

Bolanos-Meade, NEJM 2023

Superior GRFS with PTCy/Tac/MMF

Rates of infections differ in first two months before they level off.



1-year immunosuppression-free survival (alive, no relapse, no immunosuppression)

PTCY/Tac/MMF	50% (95%-CI, 43 - 57)
Tac/MTX	39.7% (95%-CI, 33 - 47)

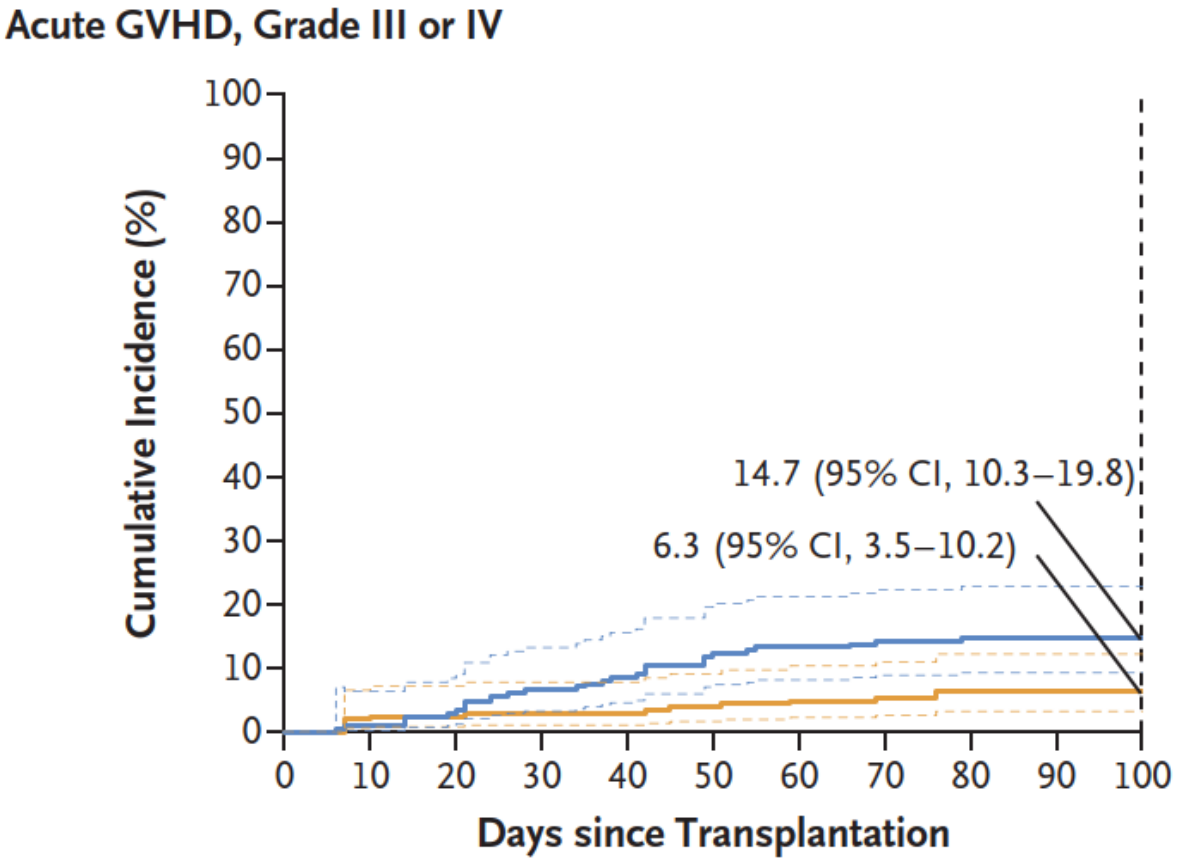
No significant differences in overall or DFS, relapse-incidence or NRM.

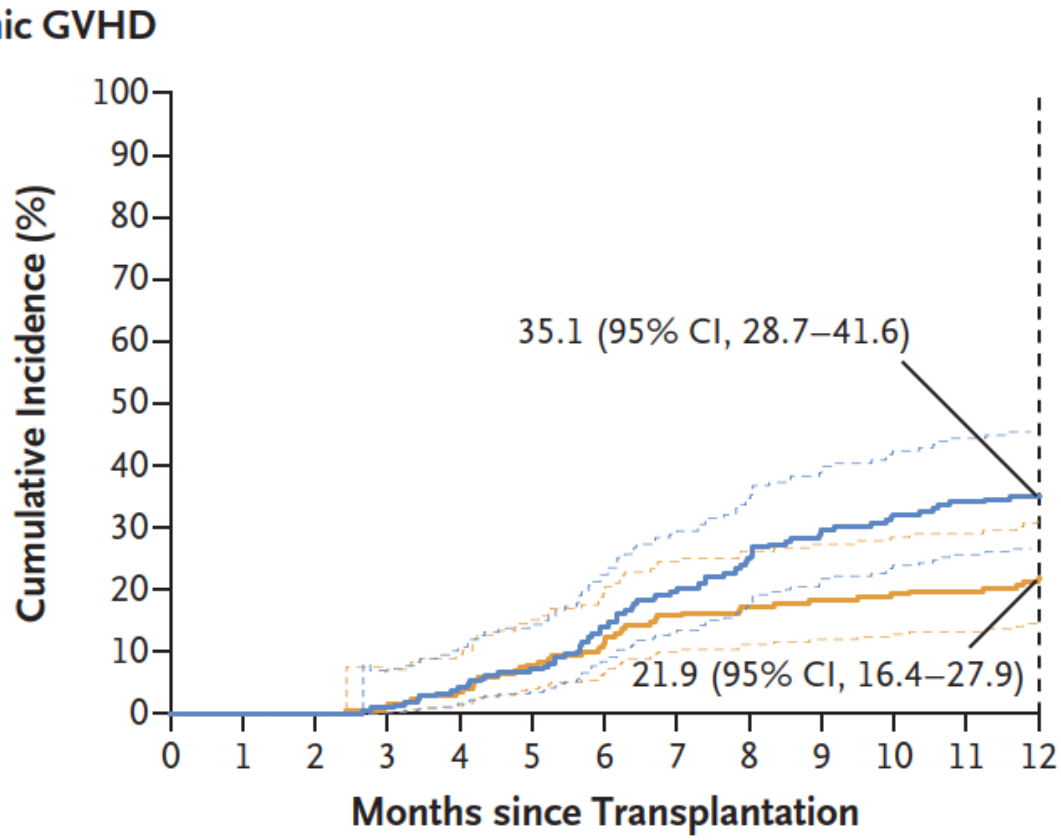
Bolanos-Meade, NEJM 2023

BMT-CTN-1703 – Progress III trial

Less cGVHD with PTCy

Lower rates of aGVHD III-IV (aGVHD II-IV 54% vs 52%!); lower incidence of cGVHD.



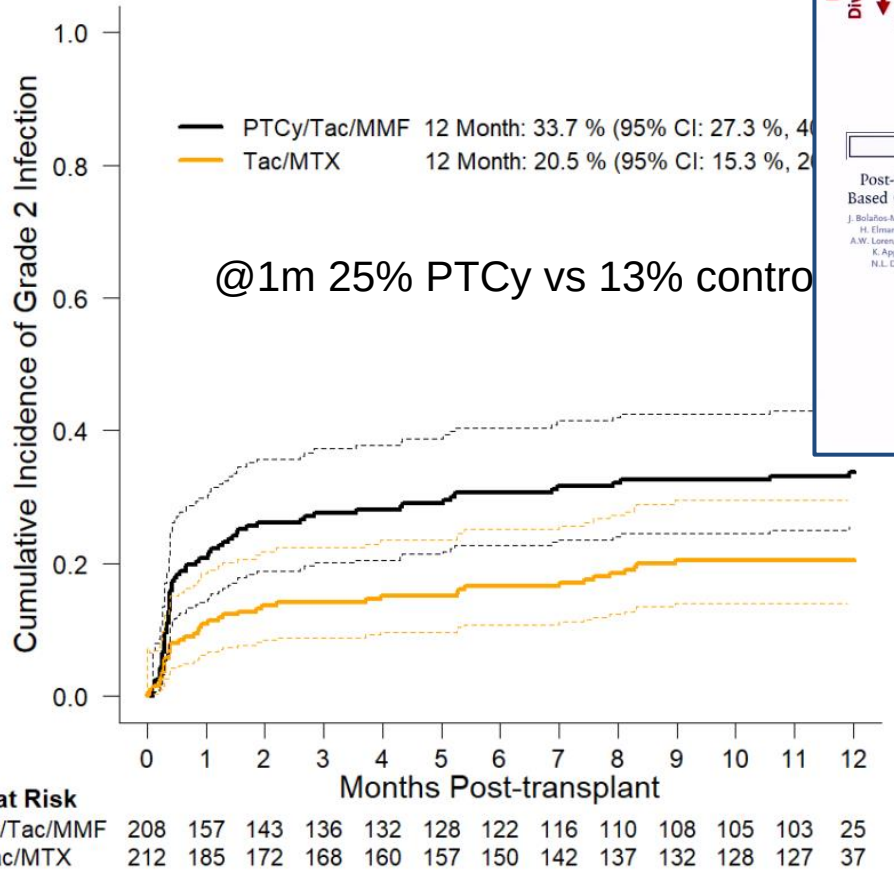


Bolanos-Meade, NEJM 2023

BMT-CTN-1703 – Progress III trial

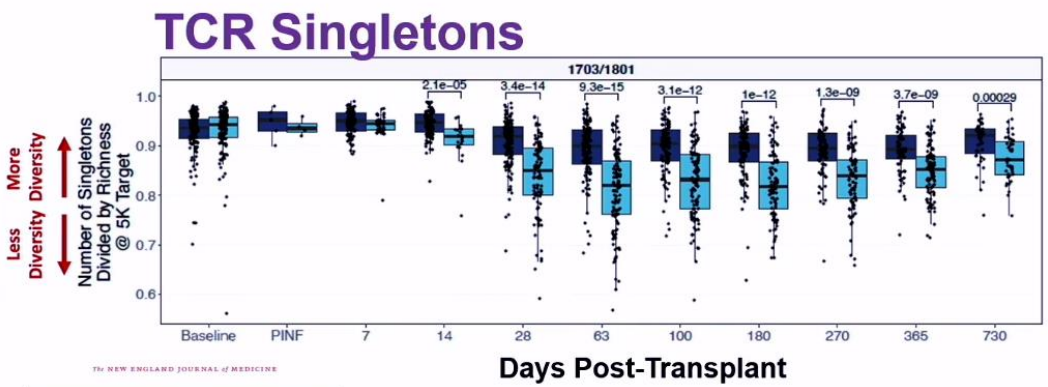
More early infections

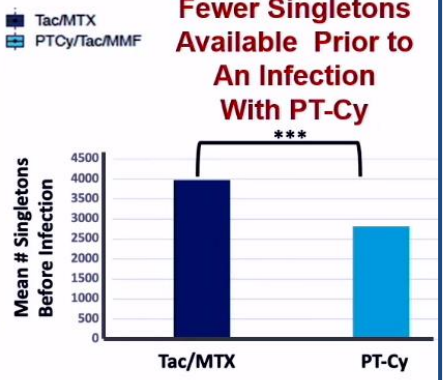
Rates of infections differ in first two m



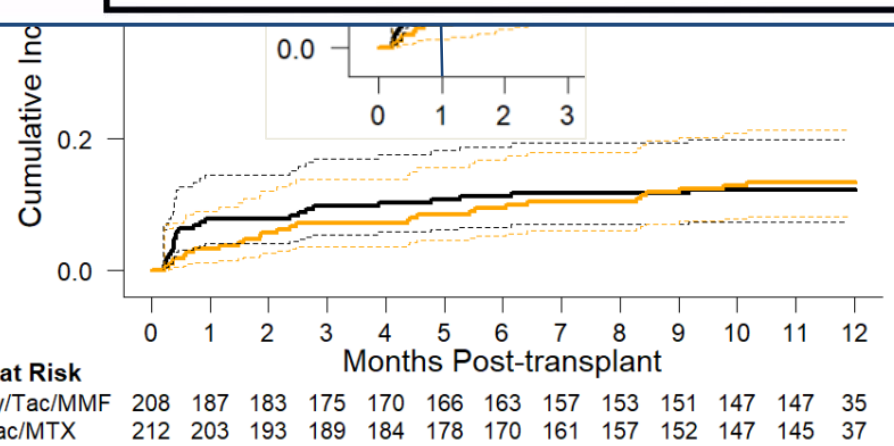
@1m 25% PTCy vs 13% contro

Significantly Decreased Singletons with PT-Cy Correlates with Increased Risk of Infection





Cumulative incidence of infections at 1 yr	PT-Cy	Tac/MTX
Grade 2 or 3	40.0 (33.2–46.7)	30.4 (24.3–36.7)
Grade 2	33.7 (27.3–40.2)	20.5 (15.3–26.2)



Bolanos-Meade, NEJM 2023; see also: Kean EBMT 2024

PTCy – immune reconstitution

More early infections after PTCy

Retrospective Studies:

- **Mehta** (JTCT 2022): more bacterial infections (54% vs 40%, p=.005), more hemorrhagic cystitis (42% vs 18%, p<.001) with PTCy (N=140) versus controls (N=272).
- **Massoud** (Haematologica 2022): more infections with PTCy (N=123) vs ATG (476) but more EBV infections with ATG
- **Ustun** (BMT 2023): more bacterial infections (48% vs 35%, p<.001) after SIB alloHCT with PTCy (N=403) versus CNI (N=1605);
- **Oshima** (BloodAdv 2023) and **Khimani** (JTCT 2021) also report higher incidences of viral infections (CMV, BK, …).

Prospective Trials

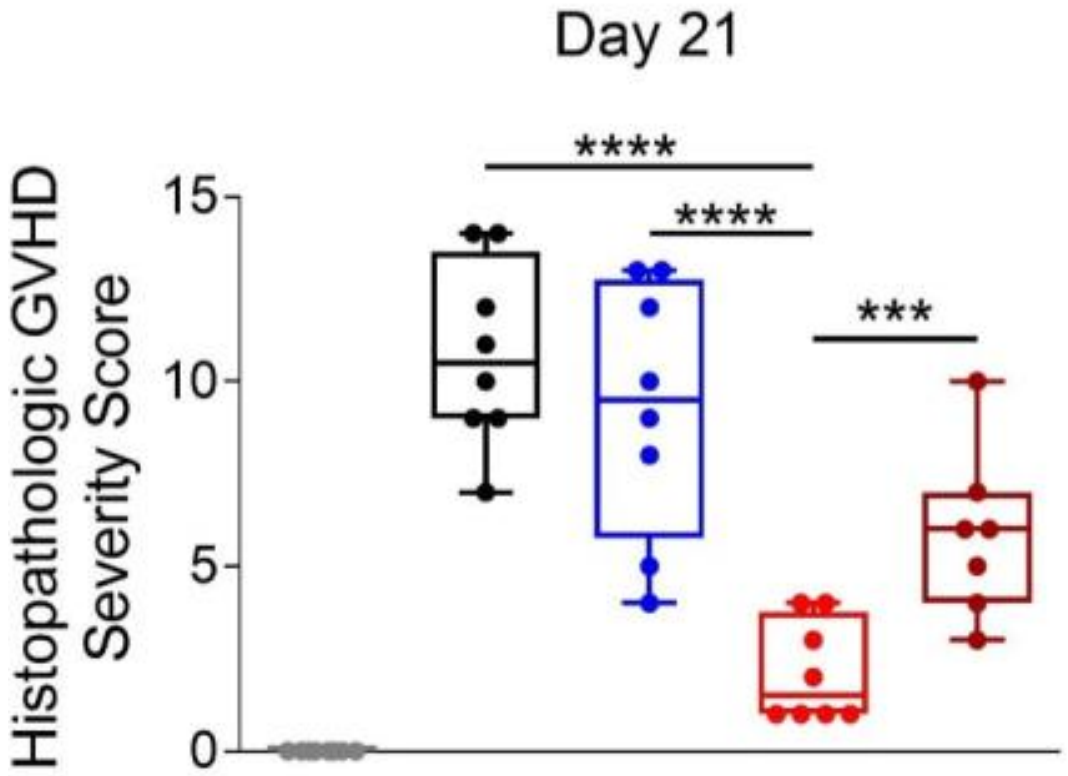
- **Broers** (BloodAdv 2022) infections grade ≥3 41% vs 21%, febrile neutropenia 25% vs 15% with PTCY/CSA vs CSA/MMF, CMV infections not different
- **Brissot** (BloodCancerJ 2023), infections in 1st month post HCT 73% vs 60% (ns), febrile neutropenia 78% vs 64% with PTCY vs ATG.

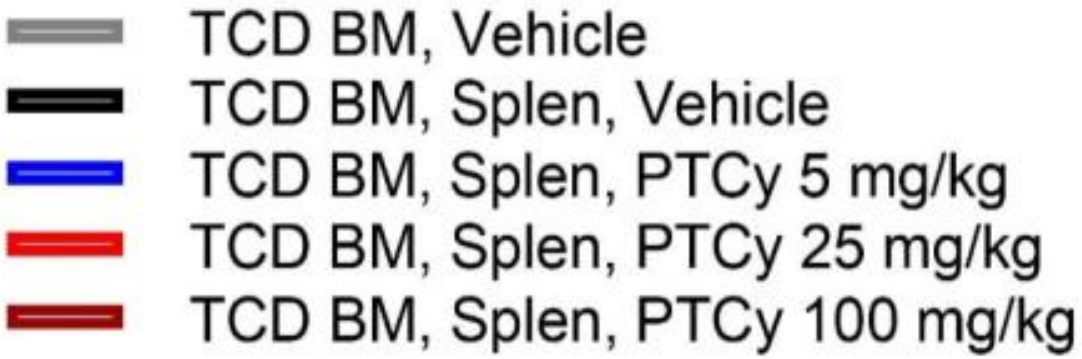
PTCy with 3-4 days longer neutropenia than ATG

BMT-CTN 1703 and 2 large retrospective EBMT studies show later engraftment (3-4 days later) with PTCy vs ATG (**Chalandon,** BloodAdv 2024; **Nagler**, AmJHematol 2024). Chalandon reported higher rate of primary graft failure with PTCy vs ATG (6% vs 3%, p=.025).

No simple dose-response relationship for PTCy

Murine haplo MHC models indicate: Cy 25 mg/kg optimal to prevent GVHD



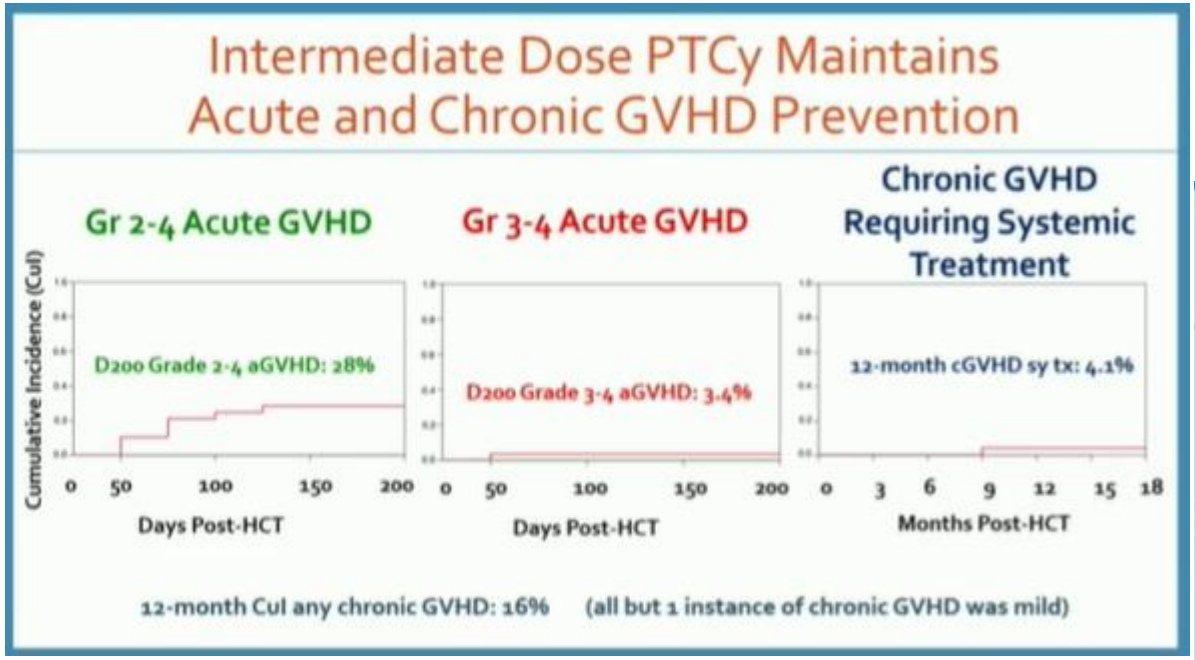


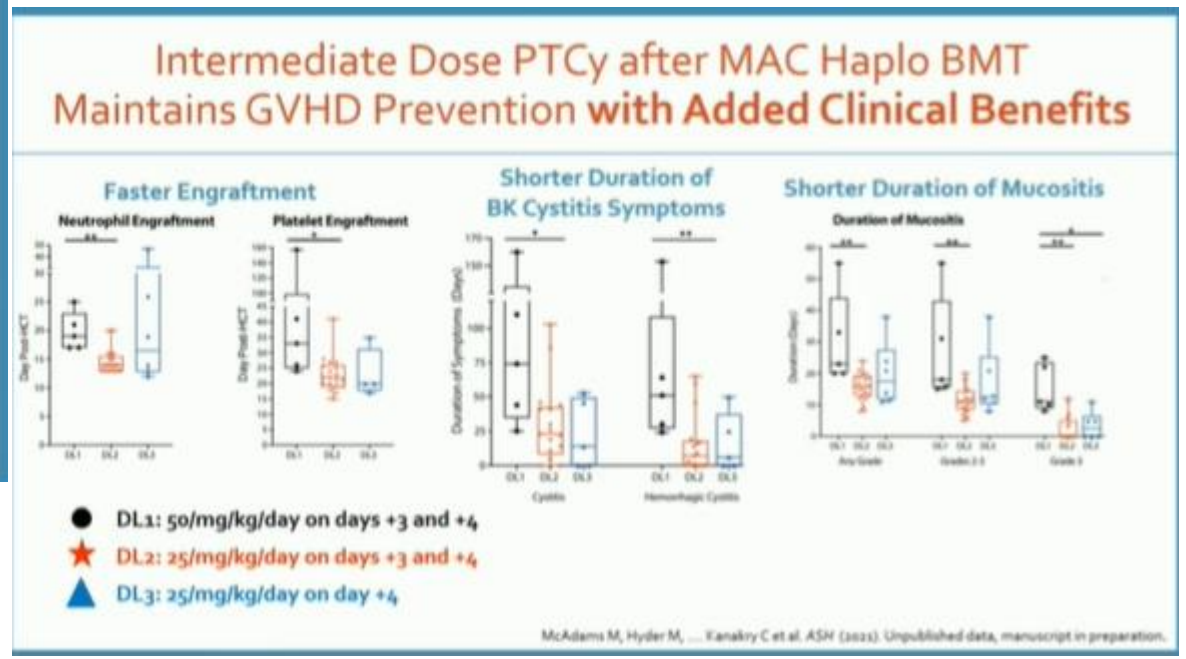
- Optimal constraint of alloreactive T-cell reconstitution
- Highest percentages of Treg

Wachsmuth … Kanakry, JCI 2019

Deescalation of PTCy for HLA-mm related/unrelated BMT

Older or comorbid patients; Flu/Cy/TBI-4 conditioning; PTCy 25 mg/kg d 3+4, Sirolimus + MMF;



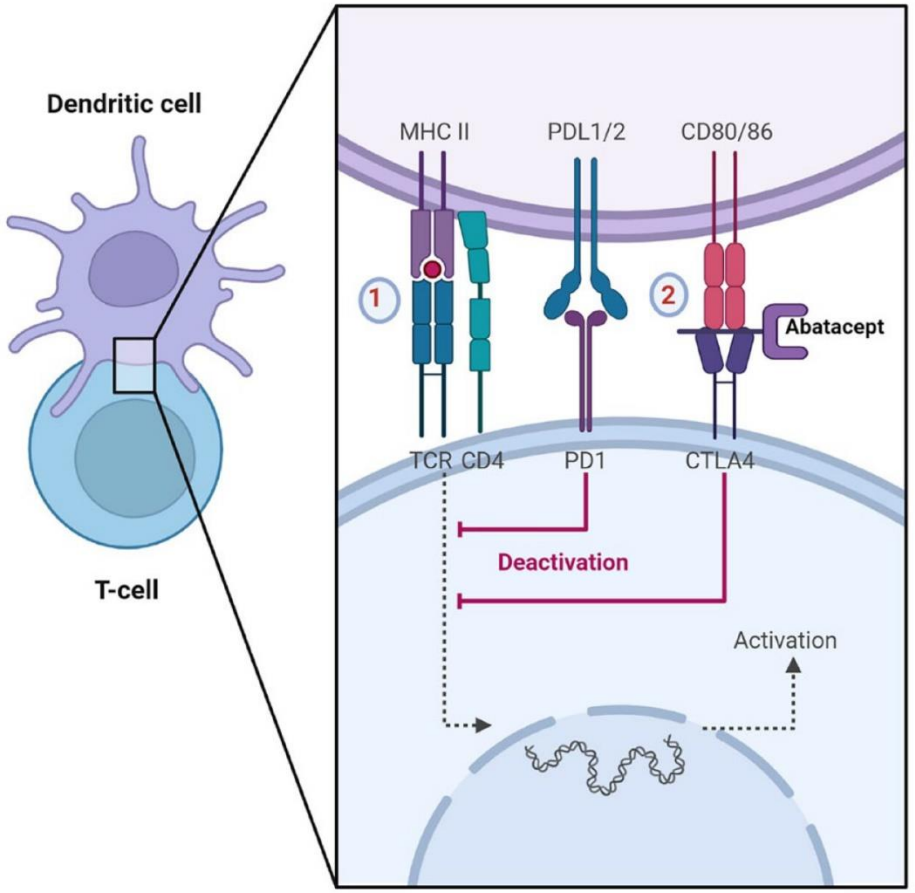


- OPTIMIZE (CIBMTR) MMUD PBSCT ~ 190 pts
- NIH: PTCy + MMF reduction for haplo BM ~ 400 pts

McCurdy TCT 2024; McAdams ASH 2021; see also: Zhang ASH 2023

Abatacept

Abatacept for GVHD prevention



Approved for prevention of GVHD by FDA and for treatment of rheumatoid& Psoriasis arthritis by FDA & EMA; Abatacept was first drug approved for GVHD prevention in US.

Blockade of co-stimulatory receptor CTLA4

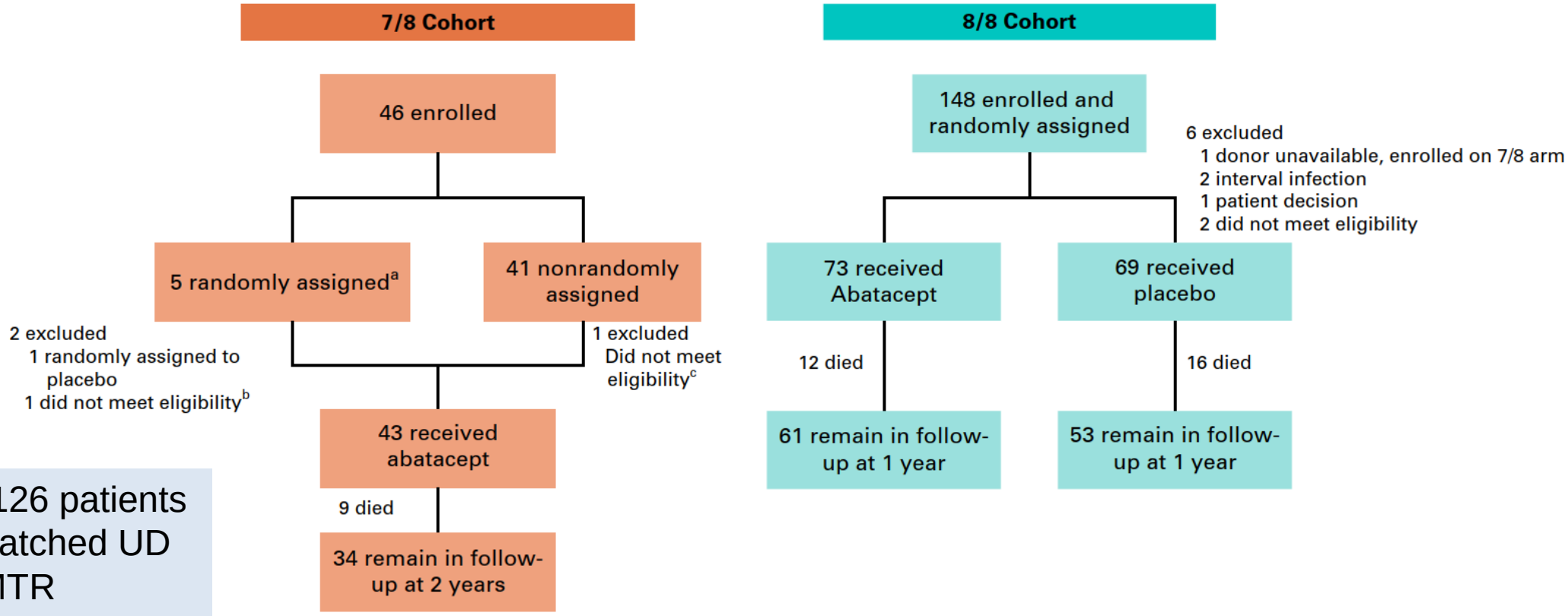
Abatacept administered at dose of 10 mg/kg on days -1, +5, +14, and +28 for GVHD-prophylaxis

Ngwube, TherAdvHematol 2023

ABA2 – randomized phase II trial

CNI+MTX +/- Abatacept for GVHD prevention

Patients: any hematologic malignancy, any conditioning, children & adults (median <40yrs)



Controls: 126 patients with 7/8 matched UD from CIBMTR

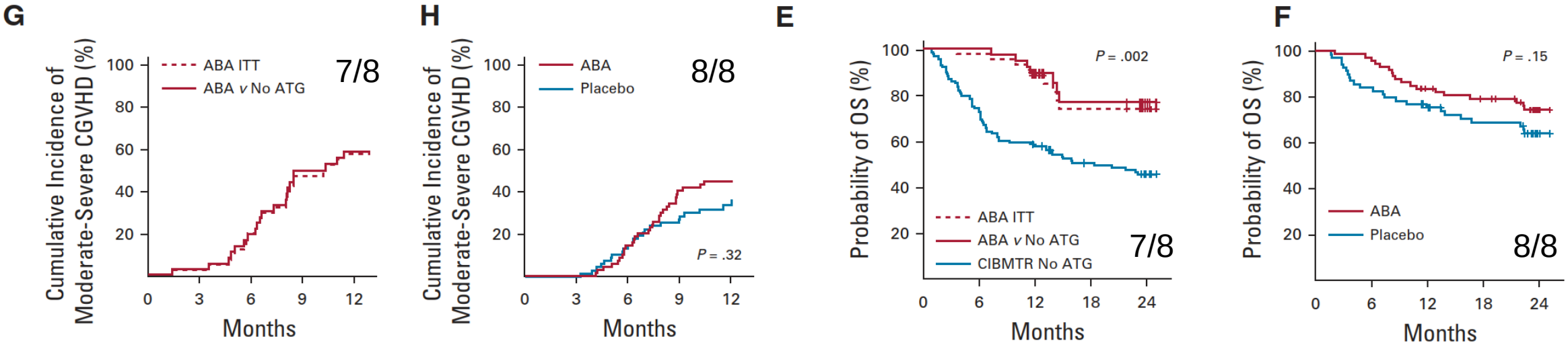
Watkins, JCO 2021

ABA2 – randomized phase II trial

Low risk of severe aGVHD, low NRM with Abatacept

No significant advantage of abatacept for patients with 8/8 matched unrelated donors

Chronic GVHD **Overall Survival**



EBMT recommendations 2024: „The panel did not judge the direct evidence for abatacept versus standard of care sufficient to support a formal recommendation for standard of care in Europe “

Watkins, JCO 2021; Penack, Lancet Hematol 2024

What have we learned?

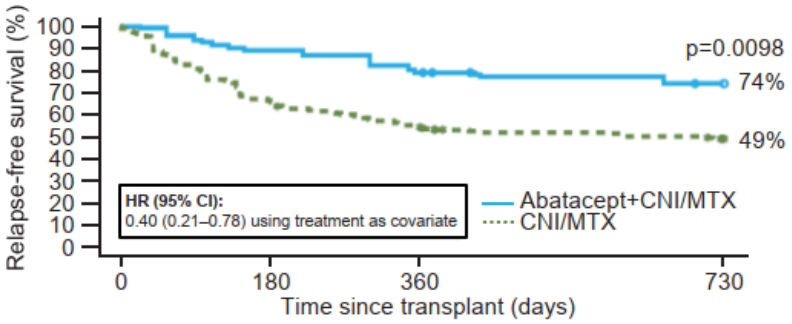
CNI + MTX alone is dead.

Comparisons
PTCy vs ATG vs Aba

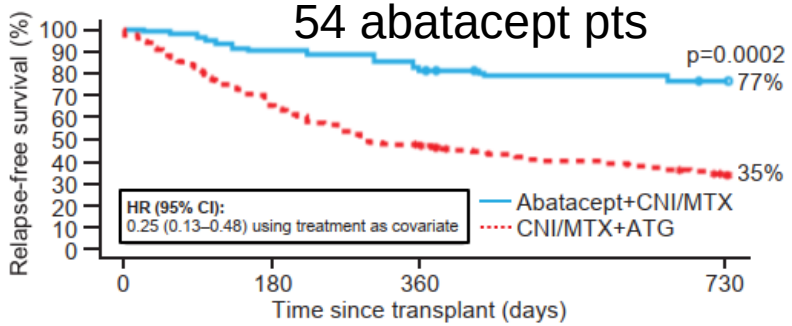
Retrospective comparisons with registry data

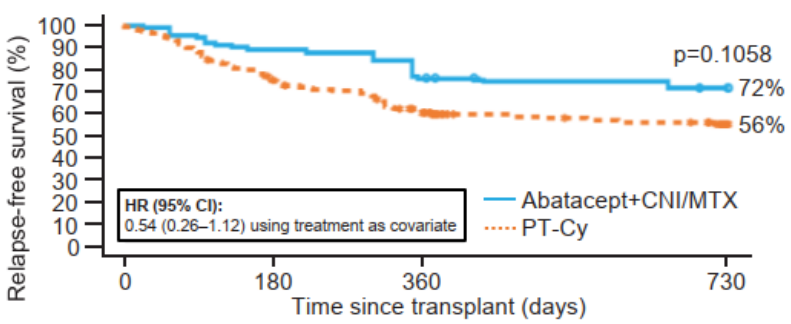
CIBMTR registry data (mainly ABA2 pts): ABA vs ATG vs PTCy

Relapse-free survival in 7/8 HLA MMUD HCT recipients:

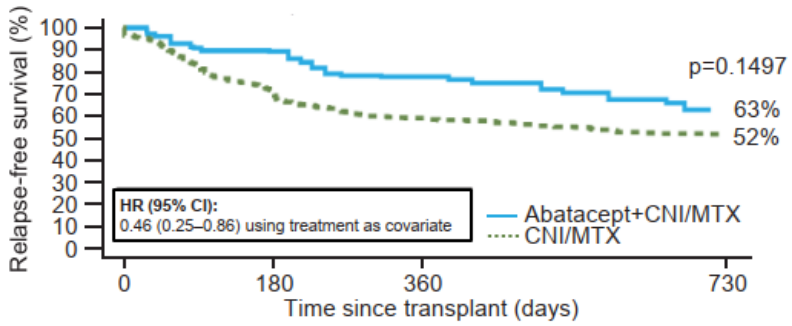


54 abatacept pts

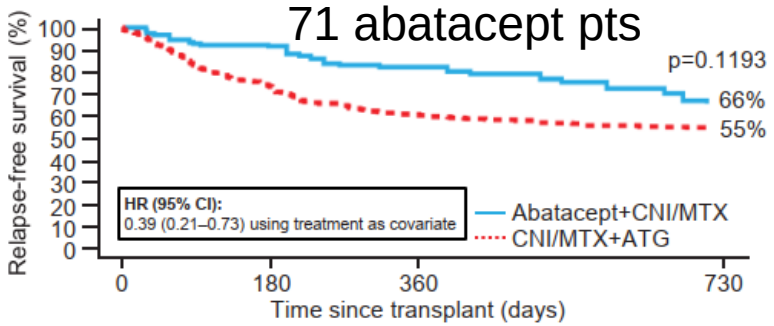


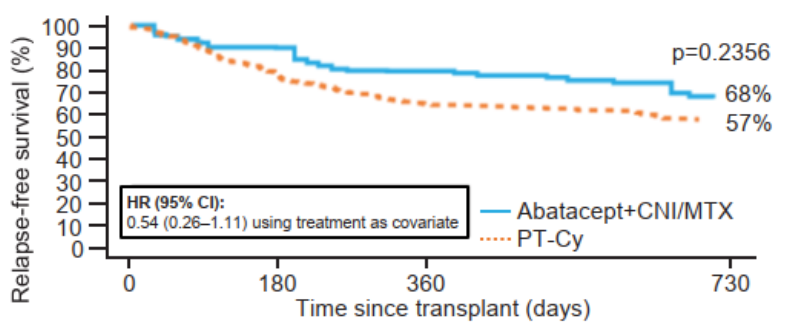


Relapse-free survival in 8/8 HLA MUD HCT recipients:



71 abatacept pts





- **Abatacept not recommended by EBMT (not approved for GVHD prophylaxis by EMA)**

Kean, Blood 2024

Retrospective comparisons based on registry data

Comparisons for UD HCT show advantage for PTCy vs ATG

10/10 matched UD: PTCY (N=1039) vs ATG (N=7725)

	HR (95% CI)	p-value
Non-relapse mortality	0.72 (0.55 to 0.94)	0.016
Relapse incidence	0.87 (0.75 to 1.00)	0.046
Overall survival	0.82 (0.72 to 0.92)	0.001
Progression-free survival	0.83 (0.74 to 0.93)	<0.001
GVHD-free and Relapse-free survival	0.80 (0.68 to 0.94)	0.006
Acute GVHD-II/IV	0.85 (0.69 to 1.04)	0.11
Acute GVHD-III/IV	0.76 (0.55 to 1.05)	0.091
Chronic GVHD	0.77 (0.63 to 0.95)	0.012
Extensive chronic GVHD	0.75 (0.62 to 0.91)	0.004

9/10 mismatched UD: PTCY (N=583) vs ATG (N=1540)

Outcome	HR (95% CI)	p-value
Non-relapse mortality	0.74 (0.56 - 0.97)	0.028
Relapse incidence	0.82 (0.67 - 1.01)	0.068
Overall survival	0.77 (0.65 - 0.90)	<0.001
Progression-free survival	0.78 (0.67 - 0.91)	0.001
GVHD-free and Relapse-free survival	0.80 (0.68 - 0.94)	0.006
Acute GVHD-II/IV	0.83 (0.66 - 1.04)	0.11
Acute GVHD-III/IV	0.78 (0.59 - 1.05)	0.10
Chronic GVHD	0.95 (0.74 - 1.22)	0.67
Extensive chronic GVHD	0.83 (0.63 - 1.10)	0.2

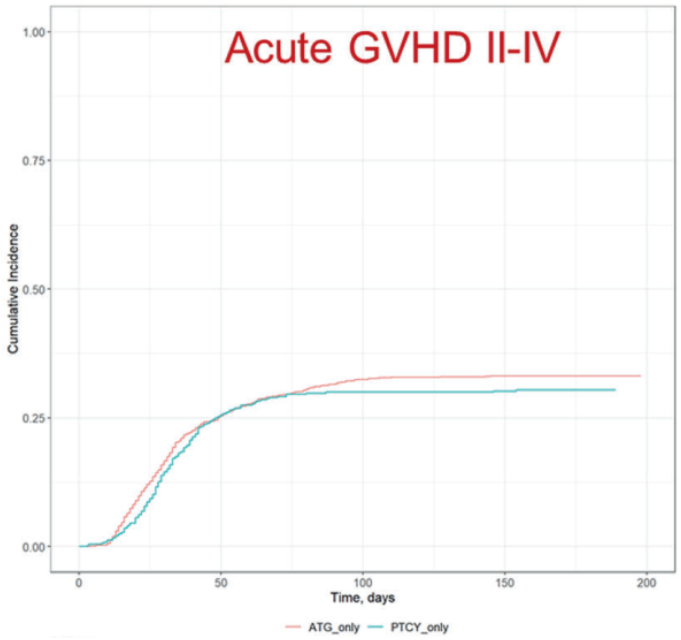
Penack, BloodCancerJ 2024 & Leukemia 2024; also: Chalandon, BloodAdv 2024 & Nagler AmJHematol 2024
results from CIBMTR-data comparing PTCy vs ATG: Shaffer JCO 2024

Retrospective comparisons with registry data

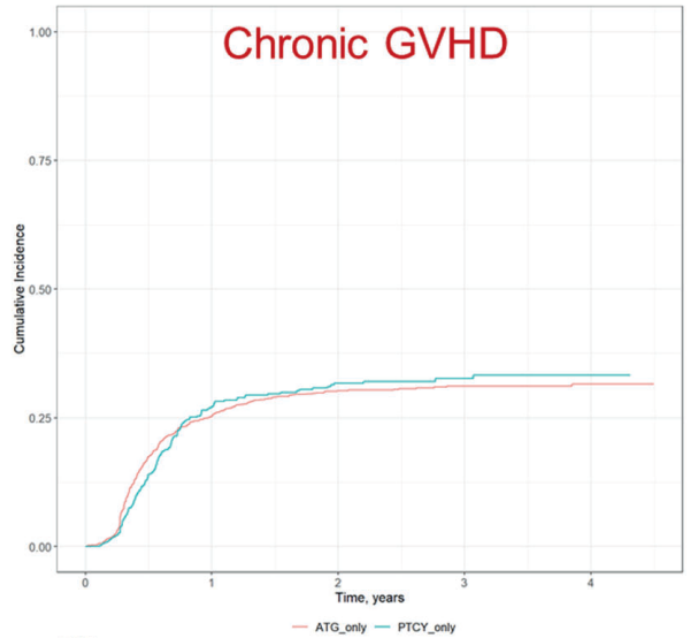
EBMT registry study for 9/10 matched UD

ATG patients
- 5 years older at HCT
- transplanted in earlier years (2018-2021)
- more often received TBI
- more with Hodgkins and NHL

A



C



aGVHD and cGVHD incidences not different

… but main driver for better OS/PFS/GRFS with PTCY was lower NRM

Penack, Blood Cancer J 2024; Penack, Leukemia 2024

Retrospective comparisons with registry data

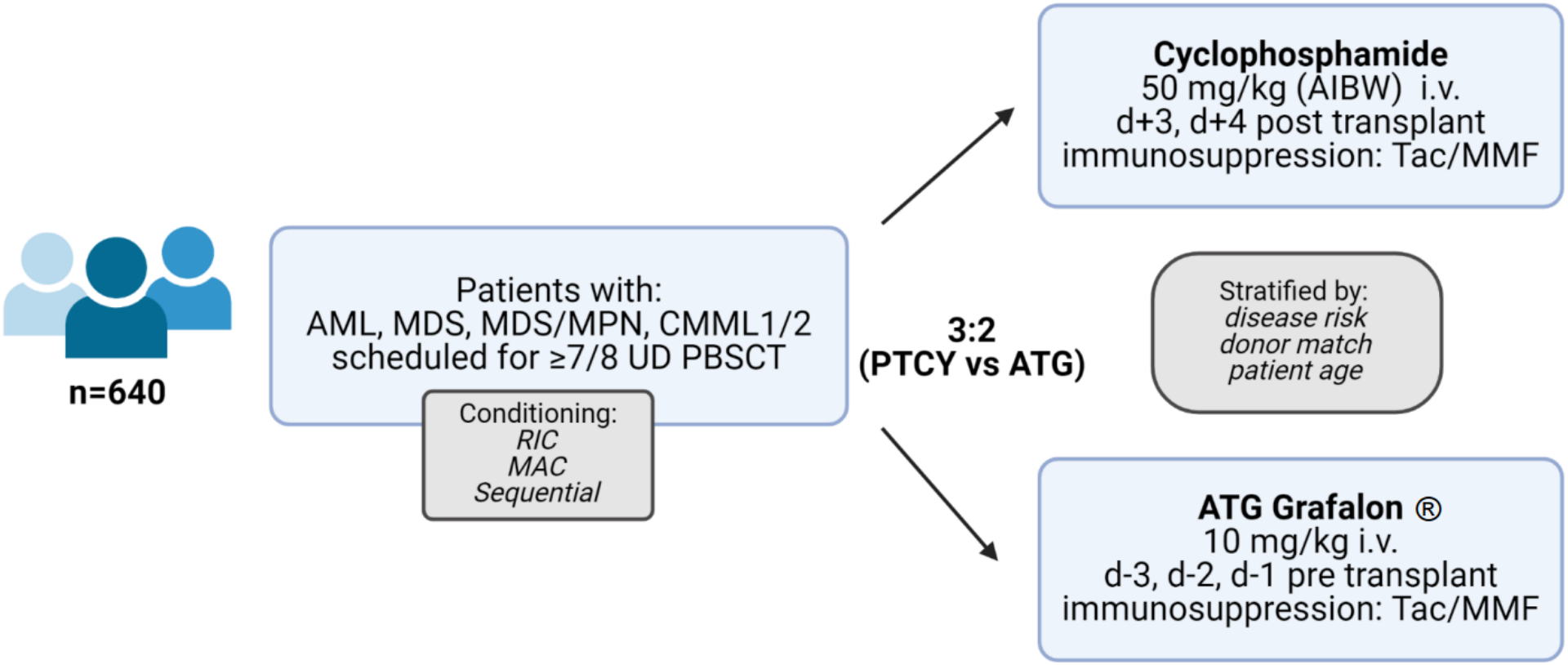
Which PTCy was “better” than which “ATG”?

GVHD Prevention Regimen		
CSA+MTX based	881 (57.2%)	3 (0.5%)
CSA+MMF based	446 (29.0%)	313 (53.7%)
MMF+TACRO/SIRO based	95 (6.2%)	174 (29.8%)
CSA based	47 (3.1%)	15 (2.6%)
TACRO/SIRO based	4 (0.3%)	54 (9.3%)
MTX+TACRO based	54 (3.5%)	0 (0.0%)
Other	13 (0.8%)	24 (4.1%)

Which regimen should be build on?

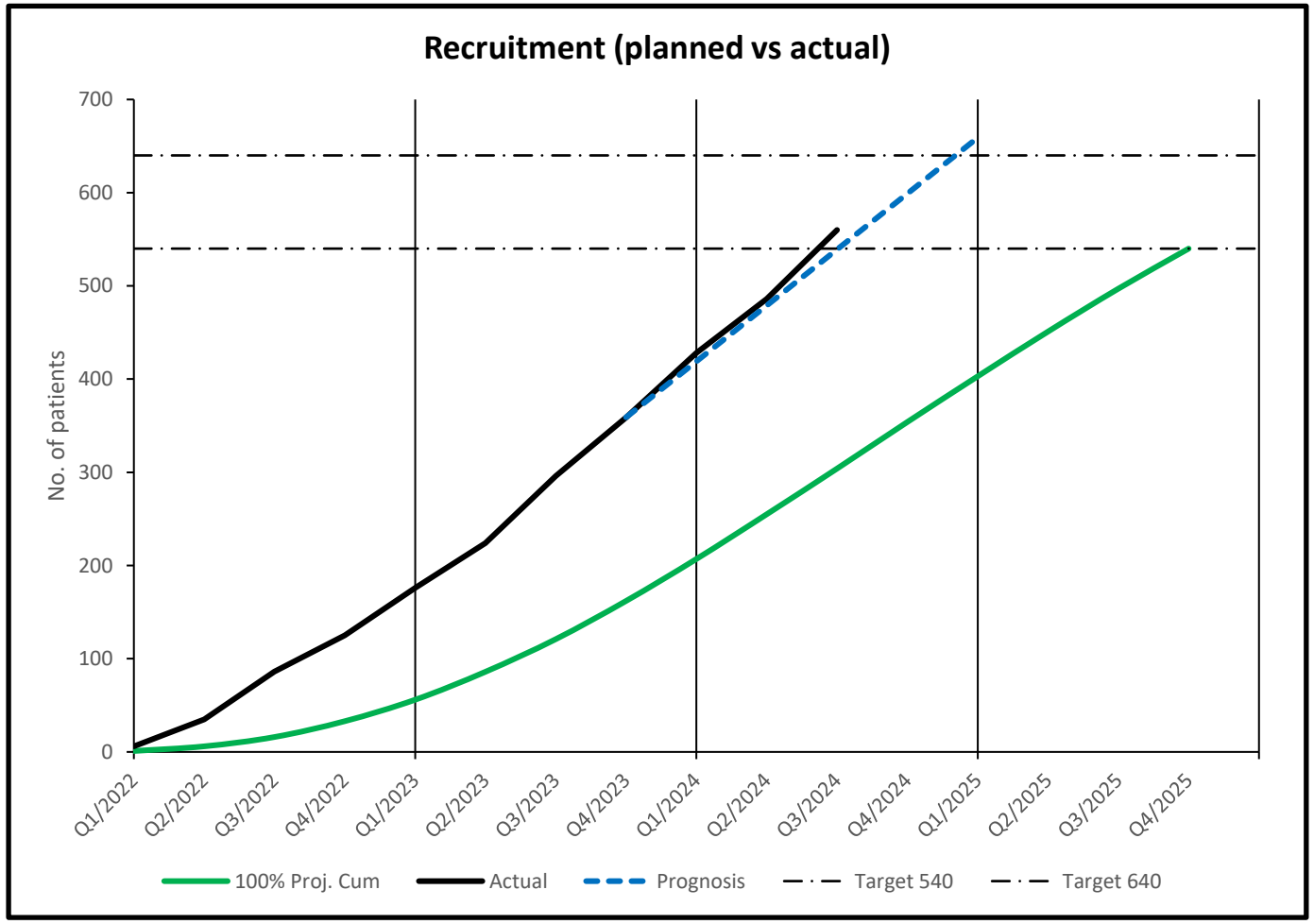
Penack, Blood Cancer J 2024; Penack, Leukemia 2024

Study Scheme: RCT comparing PTCy to ATG



Objective: To show non-inferiority of PTCy with respect to OS with a 5% non-inferiority margin.

573 patients randomized as of October 11, 2024 (target:640)



First patient in March 2022

Original sample size of 540 patients was reached September 2024

Sample size was increased to 640 with last amendment to increase chances to report at ASH 25

Average enrollment of 19 pts/month

With continued effort, last patient will be randomized this December.2024

Annual safety analysis 2023: @d28 more SAEs with PTCY!

System Organ Class	PTCy (n=220)	ATG (n=144)	Total (n=364)
Blood and lymphatic system disorders	1 (0.5%)	0	1 (0.3%)
Cardiac disorders	2 (0.9%)	1 (0.7%)	3 (0.8%)
Gastrointestinal disorders	2 (0.9%)	3 (2.1%)	5 (1.4%)
General disorders and administration site conditions	3 (1.36%)	0	3 (0.8%)
Hepatobiliary disorders	0	1 (0.7%)	1 (0.3%)
Immune system disorders	2 (0.9%)	0	2 (0.6%)
Infections and infestations	25 (11.4%)	7 (4.9%)	32 (8.8%)
Neoplasms benign, malignant and unspecified	1 (0.5%)	0	1 (0.3%)
Nervous system disorders	1 (0.5%)	2 (1.4%)	3 (0.8%)
Renal and urinary disorders	2 (0.9%)	3 (2.1%)	5 (1.4%)
Respiratory, thoracic and mediastinal disorders	4 (1.8%)	0	4 (1.1%)
TOTAL	43	17	60
N of SAEs/Patients	**43/220 (20%)**	**17/144 (12%)**	**60/364 (17%)**
N of patients with SAE/Patients per arm	**39/220 (18%)**	**16/144 (11%)**	**55/364 (15%)**

Summary

- Chronic GVHD possibly not the appropriate endpoint for making choices as long as survival differences cannot be „ruled out“.
- CNI + MTX alone is dead.
- Abatacept not recommended by EBMT (not approved by EMA).
- As of now, ATG and PTCy should both be considered standard for GVHD-prophylaxis for matched related and unrelated donor HCT.
- Further improvement is necessary! Which platform/dose/schedule to build on?

Thank you for your attention!

Thank you to investigators & patients!

Matthias Stelljes (Münster), Desirée Kunadt (Dresden), Thomas Schröder (Essen), Lutz P. Müller (Halle), Friedrich Stölzel (Kiel), Gesine Bug (Frankfurt), Anke Morgner (Chemnitz), Christian Junghanss (Rostock), Lorenz Thurner (Homburg), Edgar Jost (Aachen), Andreas Burchert (Marburg), Stefan Klein (Mannheim), Kerstin Schäfer-Eckart (Nürnberg), Martin Kaufmann (Stuttgart), Wolfgang Bethge (Tübingen), Christoph Schmid (Augsburg), Inken Hilgendorf (Jena), Ralf Meyer (Dortmund), Friederike Wortmann (Lübeck), Udo Holtick (Köln), Eva-Maria Wagner-Drouet (Mainz), Würzburg, Karsruhe, Guido Kobbe (Düsseldorf), Martin Bornhäuser (Dresden)

Trial Management Team & Biostatistics
Sarah Trost, Petrina Delivani, Cathleen Petzold & Henning Baldauf (DKMS)