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Immune Recovery in Patients After Hematopoietic Stem Cell Treatment

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Memorial Sloan Kettering Cancer Center

The State of the Science of Hematopoietic Stem Cell Treatment and Disability: A Workshop



@DrMiguelPerales



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Miguel Perales MD Disclosures

- Member, Scientific Advisory Board:
 - NexImmune
- Ad hoc Advisory Board:
 - Abbvie, Astellas, Celgene, Bristol-Myers Squibb, Incyte, Karyopharm, Kite/Gilead, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Takeda, VectivBio AG, Vor Biopharma
- Consulting:
 - MSD, Omeros
- Member, DSMB:
 - Cidara Therapeutics, Medigene, Sellas Life Sciences, Servier
- Ownership:
 - NexImmune, Omeros
- Research Funding:
 - Incyte (clinical trial), Kite/Gilead (clinical trial), Miltenyi (clinical trial), Novartis (clinical trial)
- Academic/Not-for-Profit:
 - Board Member: Be The Match (NMDP)
 - CIBMTR Cellular Immunotherapy Data Resource (CIDR) Oversight Committee
 - Tufts Cancer Center DSMB, University of Barcelona CART T trial DSMB



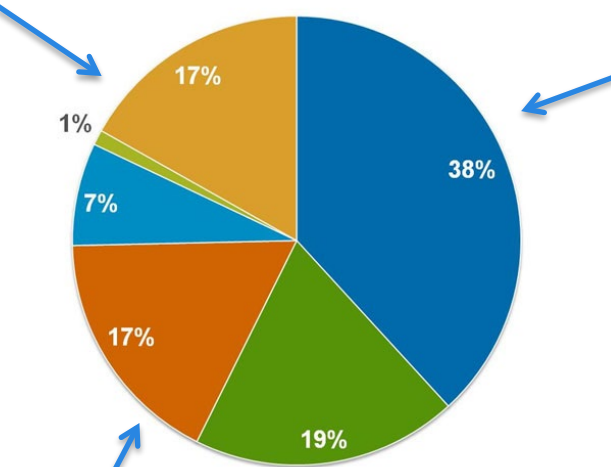
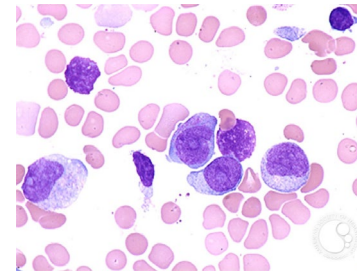
How can we improve outcomes after HCT?

Cause of Death after Unrelated Donor HCT

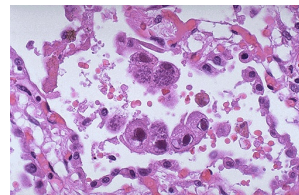
“Toxicity”



Relapse



Infection



GVHD



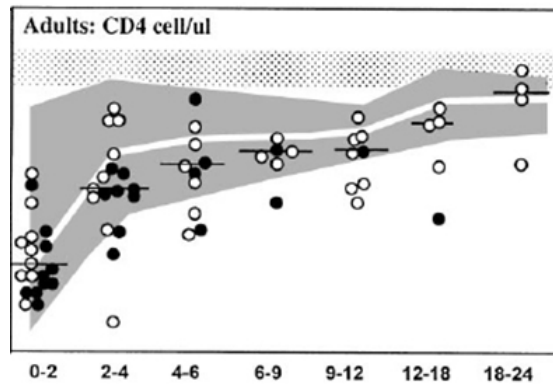
CIBMTR 2014



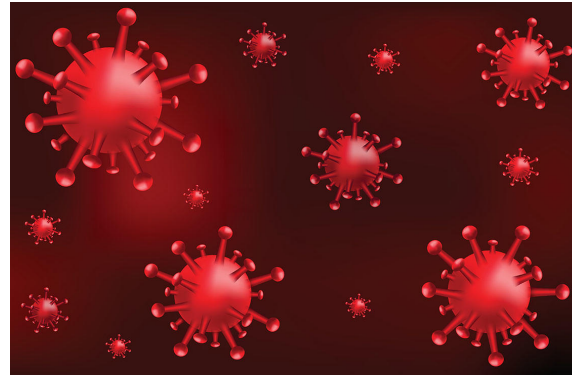
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Outline

Immune Reconstitution

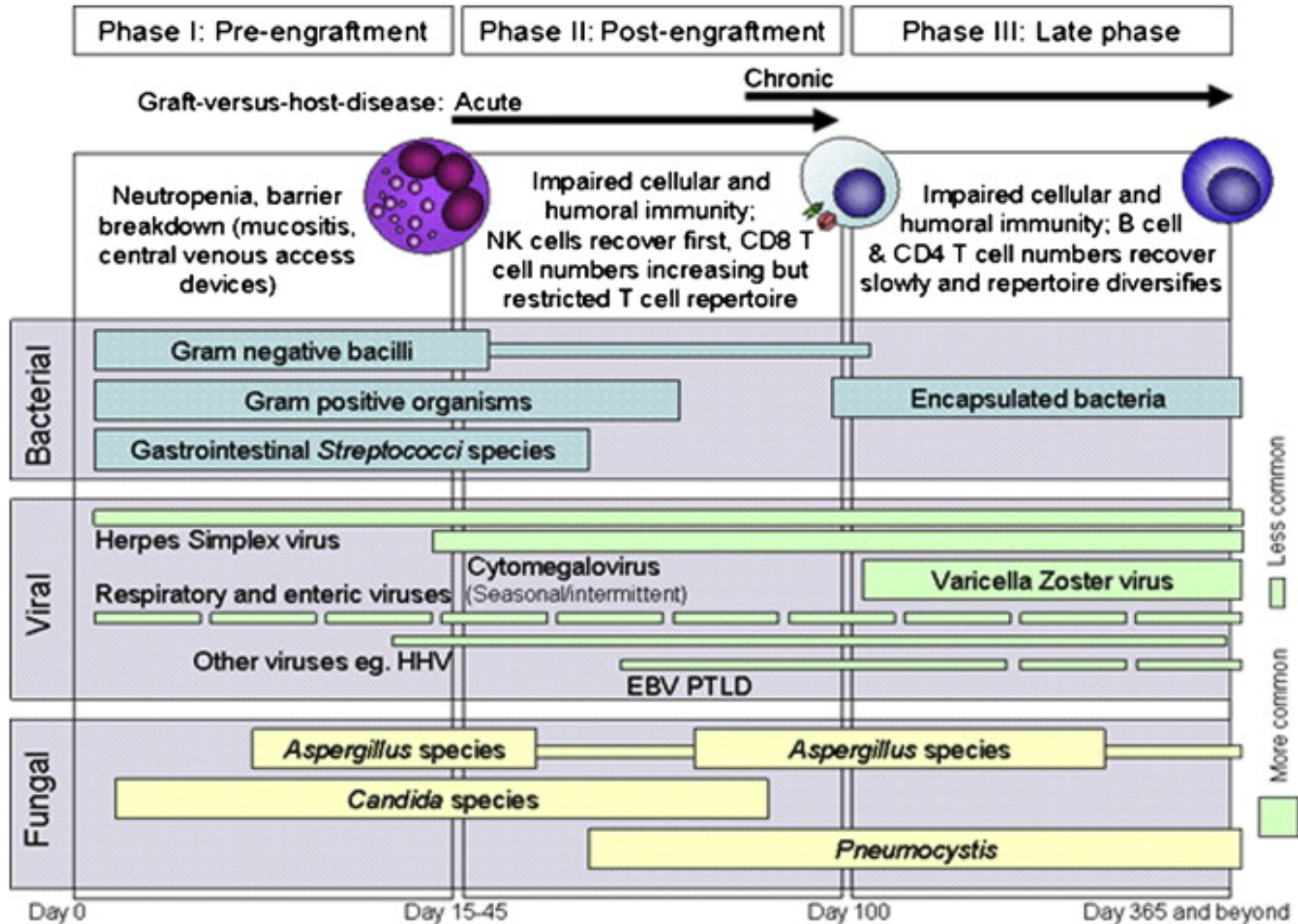


Covid in Transplant

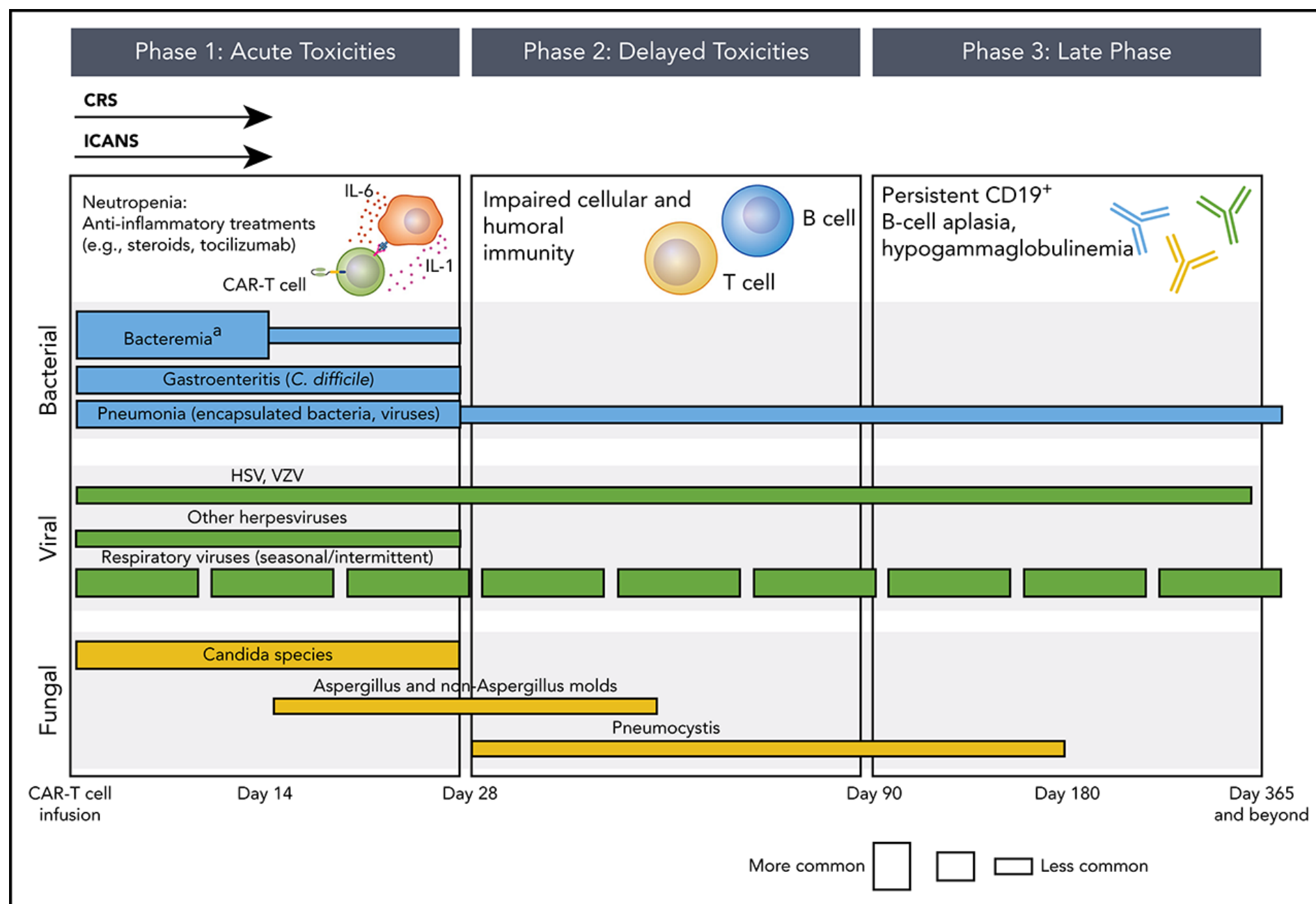


Vaccines





Source: Biology of Blood and Marrow Transplantation 2009; 15:1143-1238



Calcineurin Inhibitor-Free GVHD Prophylaxis in HCT with Myeloablative Conditioning Regimens and HLA-Matched Donors: Results of the BMT CTN 1301 Progress II Trial

PROGRESS II trial
Prevention and Reduction Of Gvhd and
Relapse and Enhancing Survival after
Stem cell transplantation



Progress

Prevention and Reduction Of Gvhd and Relapse
and Enhancing Survival after Stem cell transplantation

*Marcelo C. Pasquini, Leo Luznik, Brent Logan, Robert Soiffer, Juan (Maggie) Wu, Steven M. Devine, Nancy Geller, Sergio A Giral, Helen E. Heslop, Mary M. Horowitz, Mark R. Litzow, Adam Mendizabal, Lori Muffly, Eneida R. Nemecek, Lynn C. O'Donnell, Raquel Palencia, Johannes Schetelig, Leyla Shune, Scott R. Solomon, Sumithira Vasu, Vincent T. Ho and **Miguel-Angel Perales***



Transplantation &
Cellular Therapy Meetings™
of ASTCT* and CIBMTR*

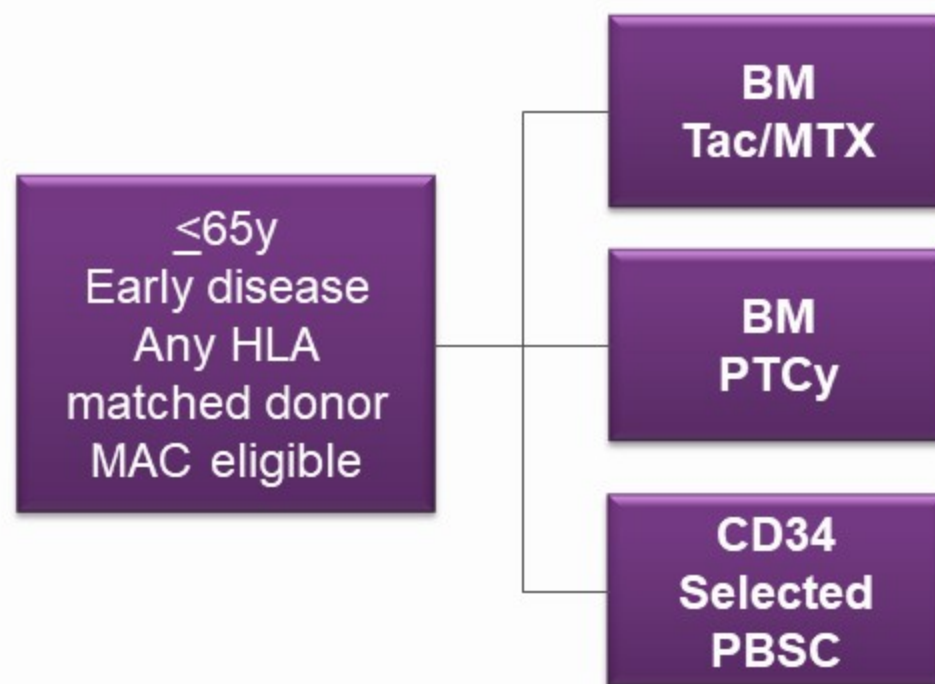
The 2021 TCT Meetings Digital Experience

February 8-12, 2021



BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

CNI free Trial: 3-arm Phase III



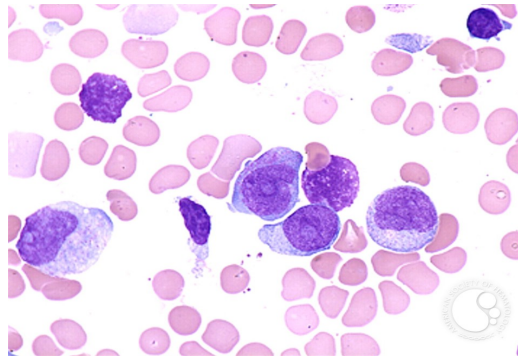
N=345 (115/arm)

cGVHD/Relapse-free Survival (CRFS) is a time-to-event composite endpoint

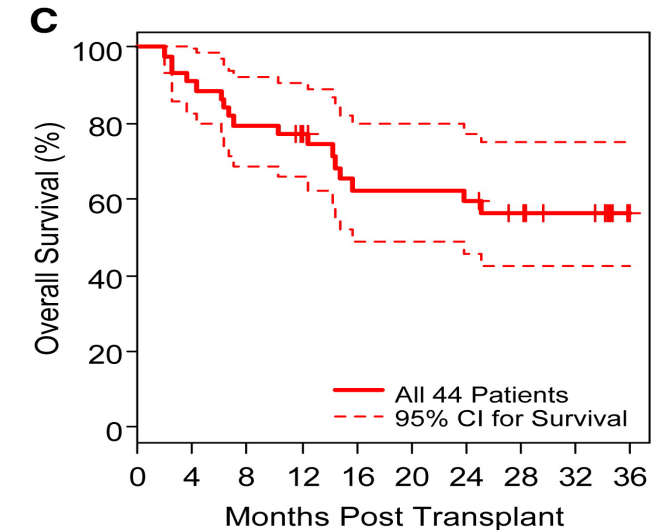
cGVHD



Relapse



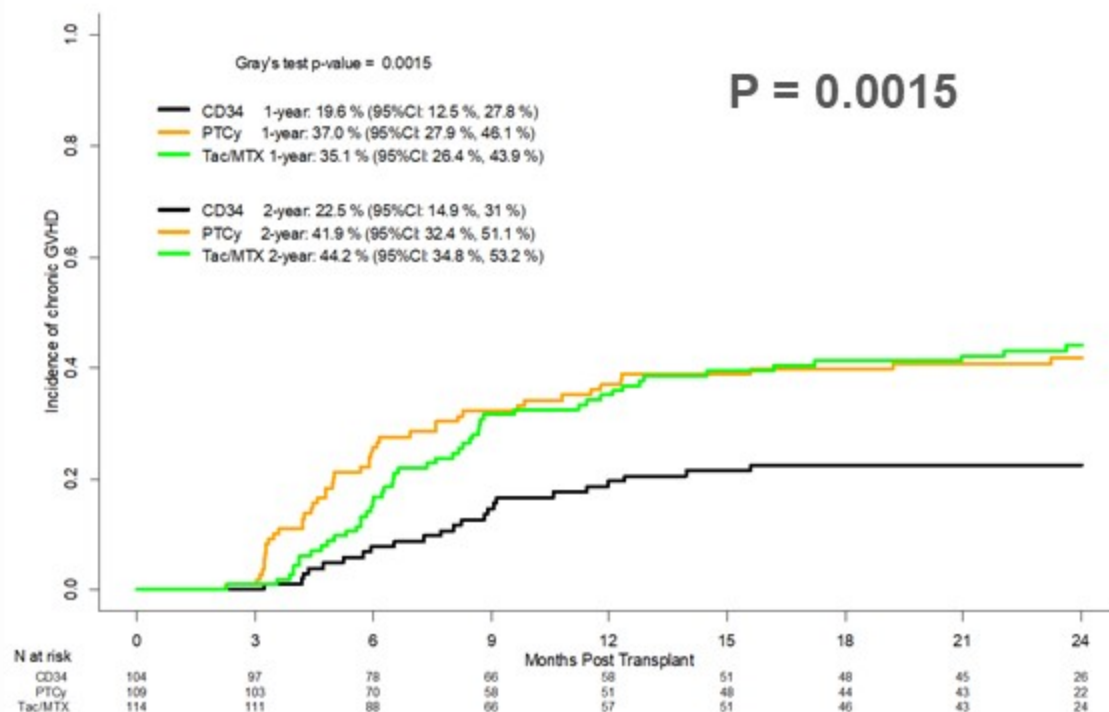
Survival



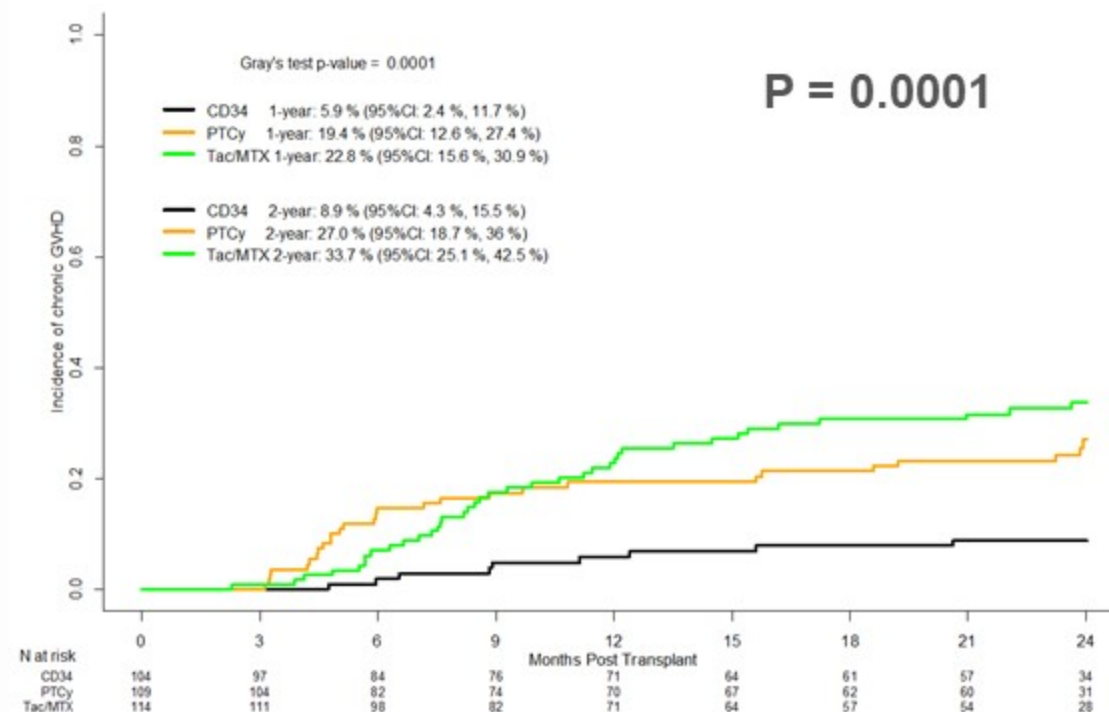
- Assumptions
 - aGVHD would have resolved by 1 year (either resulting in death, withdrawal of IS or progression to cGVHD)
 - Patients who developed cGVHD are still on IS at 1 year

Chronic GVHD was reduced in CD34+

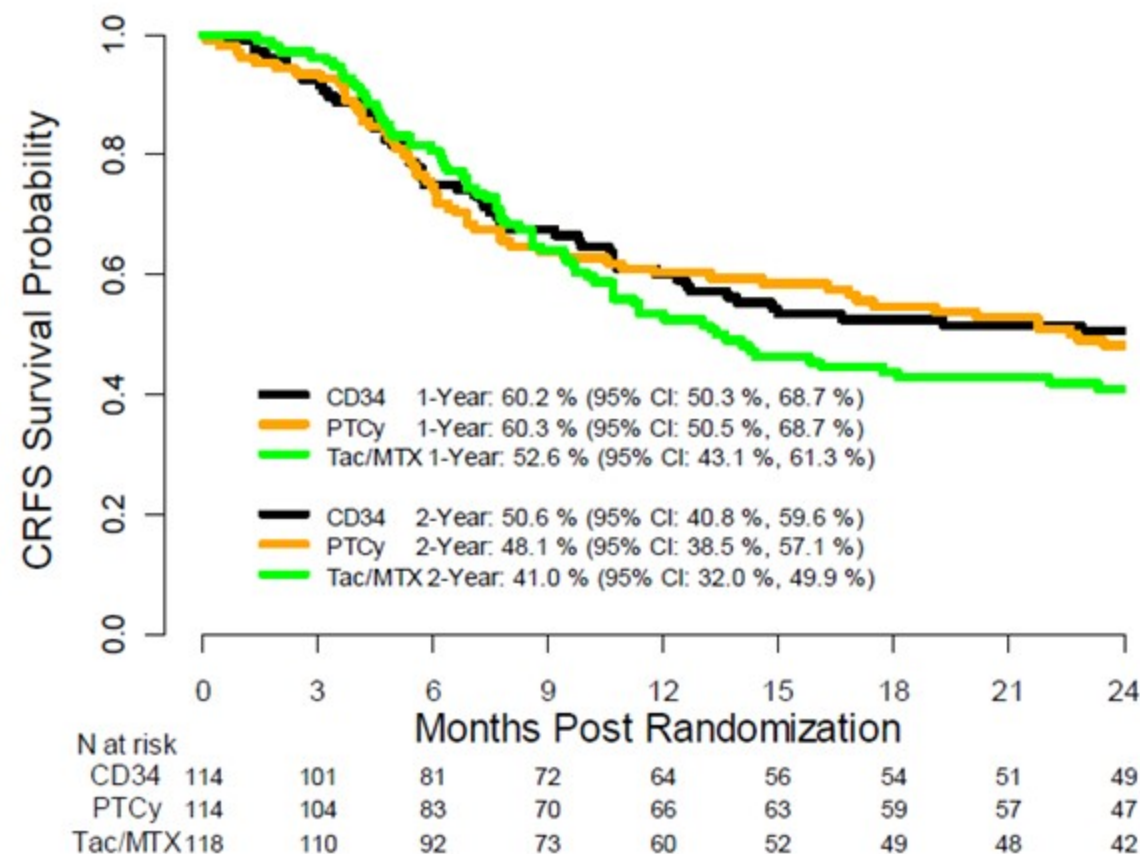
Chronic GVHD



Moderate to Severe Chronic GVHD



No Difference in Primary Endpoint: CRFS

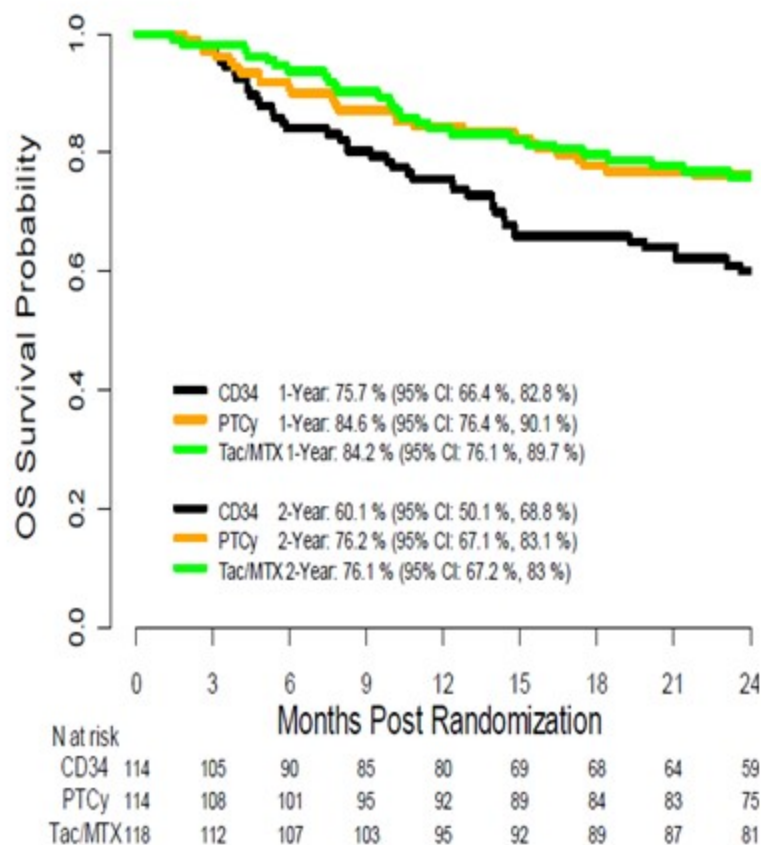


	Events for the Pair	HR	95% CI	P-value
CD34 Vs Tac/MTX	122 (232)	0.81	(0.56, 1.15)	0.27
PTCY vs Tac/MTX	127 (232)	0.86	(0.61, 1.23)	0.41
CD34 vs PTCY	111 (228)	0.93	(0.64, 1.36)	0.72

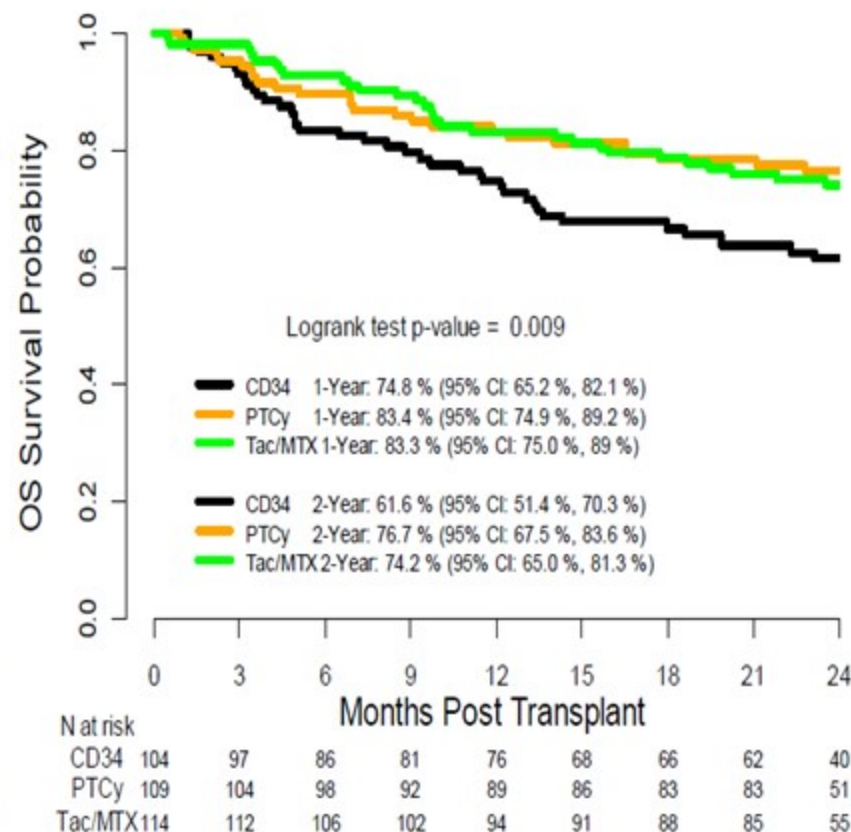
*Log-rank test

Overall Survival Decreased in CD34+

Post-Enrollment

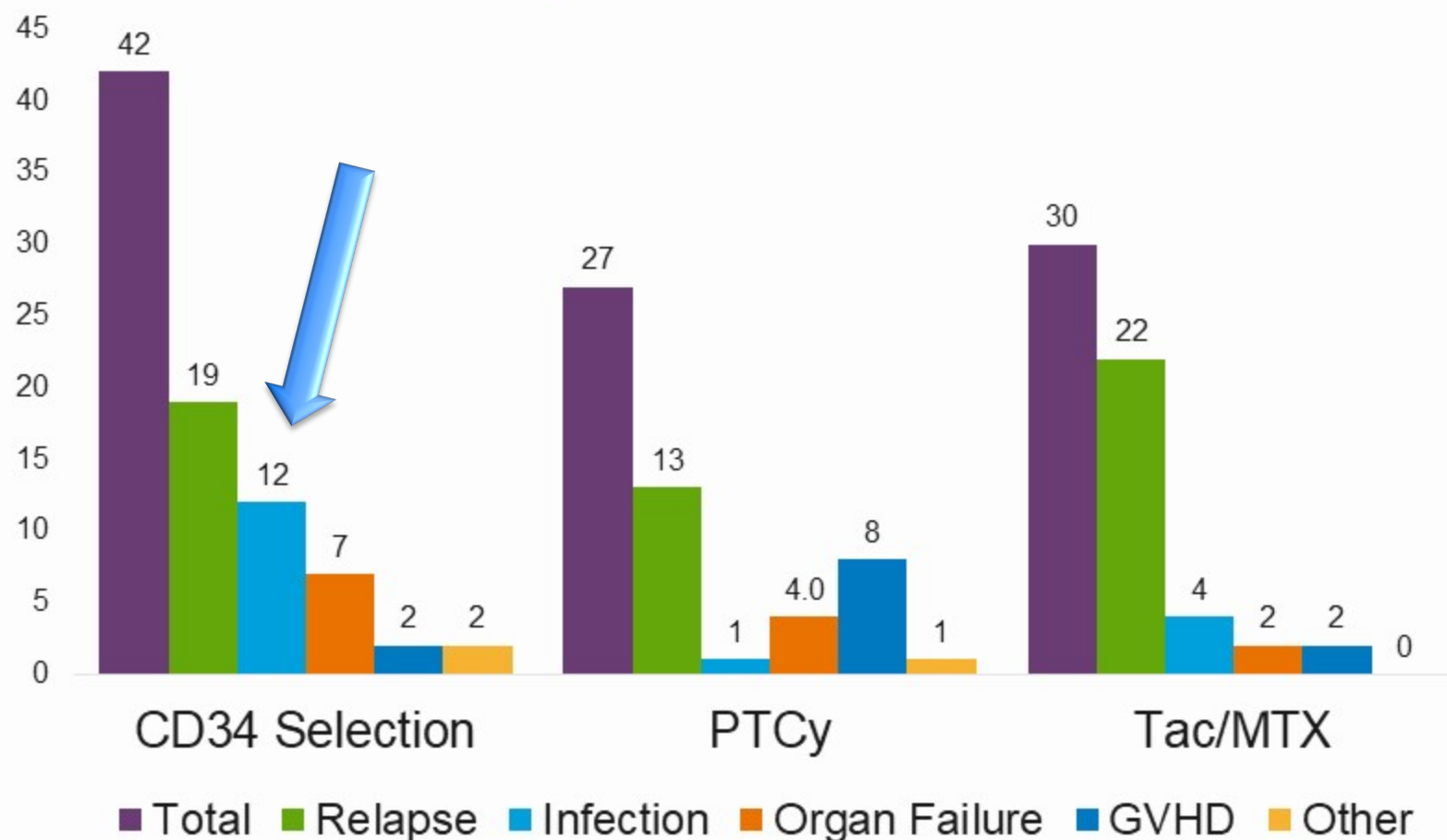


Post-Transplant

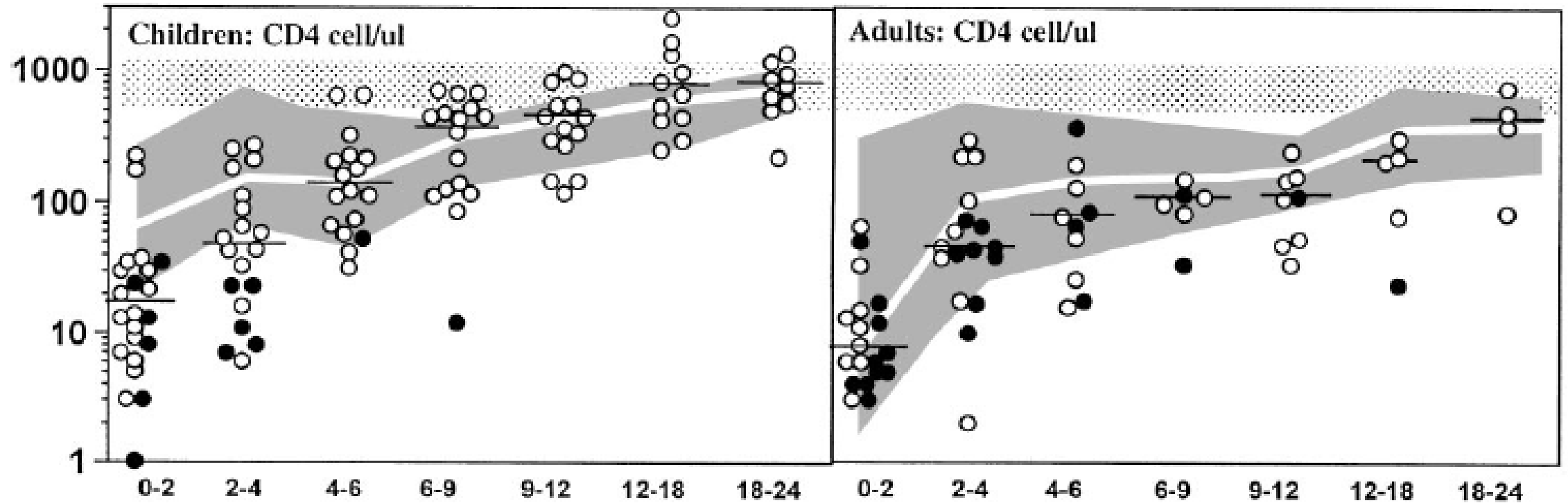


	Events for the Pair	HR	95% CI	P
CD34 Vs Tac/MTX	71 (232)	1.74	(1.09, 2.80)	0.02
PTCY vs Tac/MTX	56 (232)	1.02	(0.60, 1.72)	0.95
CD34 vs PTCY	69 (228)	1.78	(1.09, 2.89)	0.02

Causes of Death by Treatment Arm



Recovery of CD4⁺ T cells predicts risk of opportunistic infections in T-cell Depleted HCT

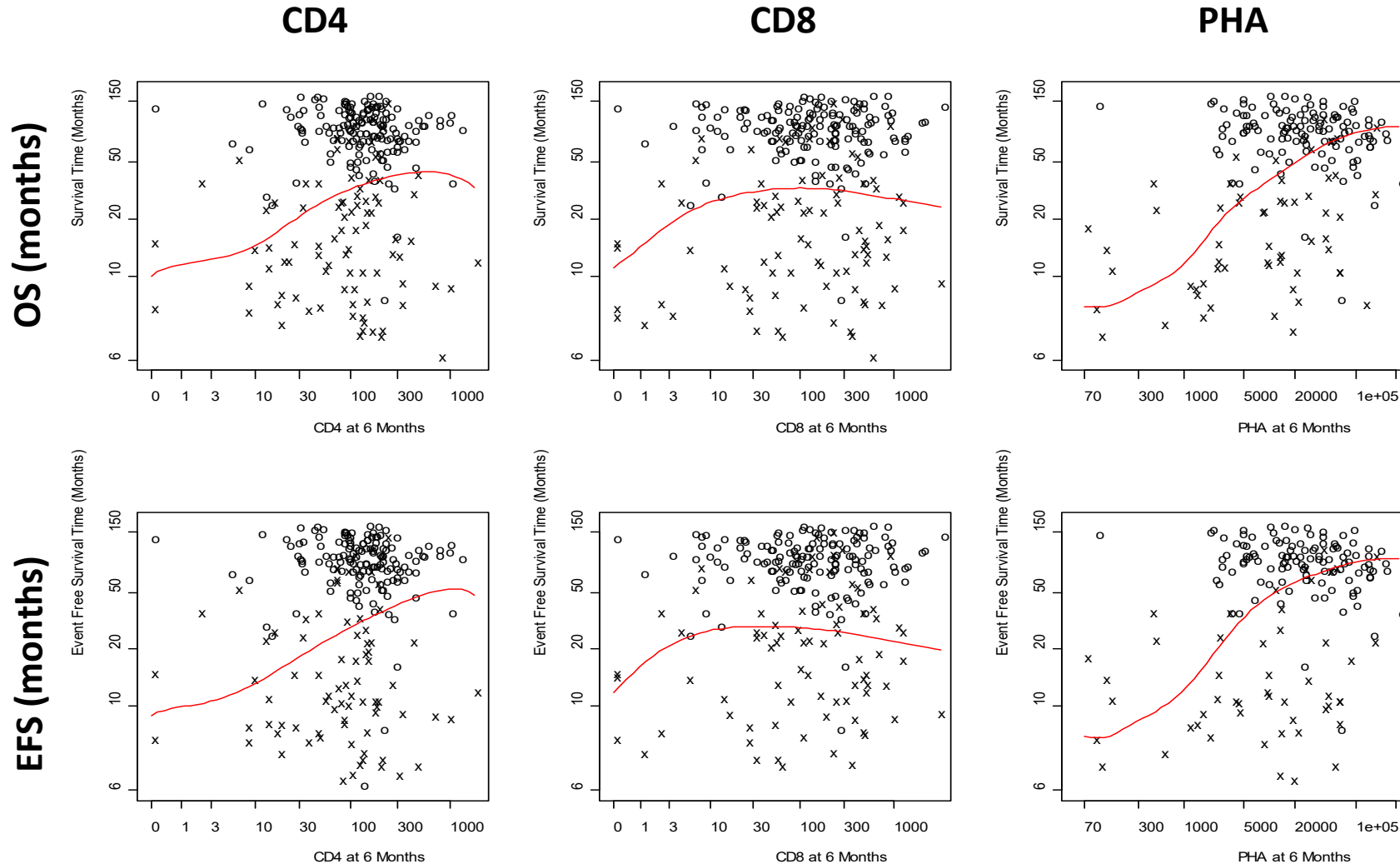


TN Small et al, Blood, 1999; 93:467-80.

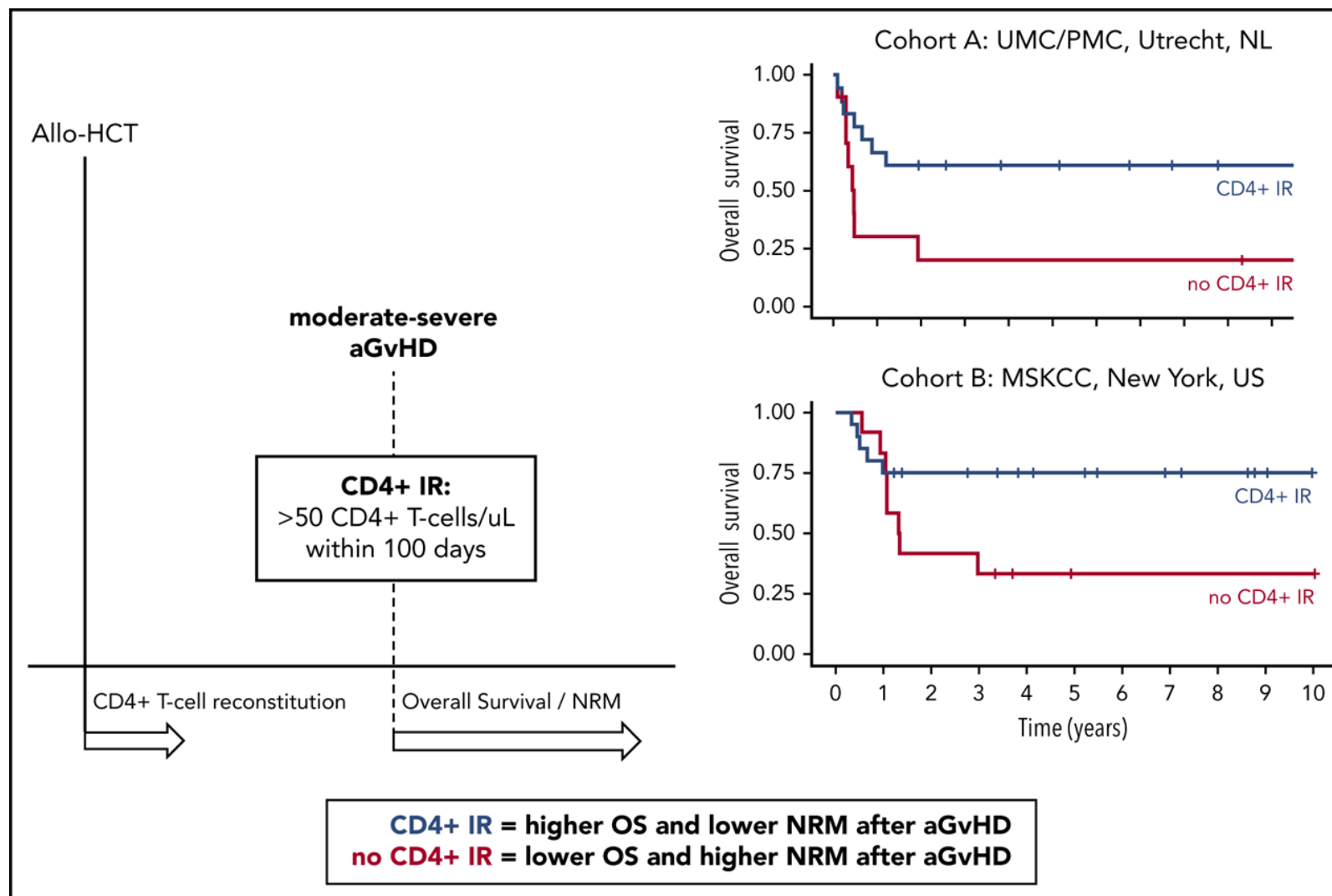


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Landmark analysis of immune reconstitution at 6 months on Overall Survival and Event-Free Survival



CD4⁺ T-cell reconstitution predicts survival outcomes after acute GVHD



Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study



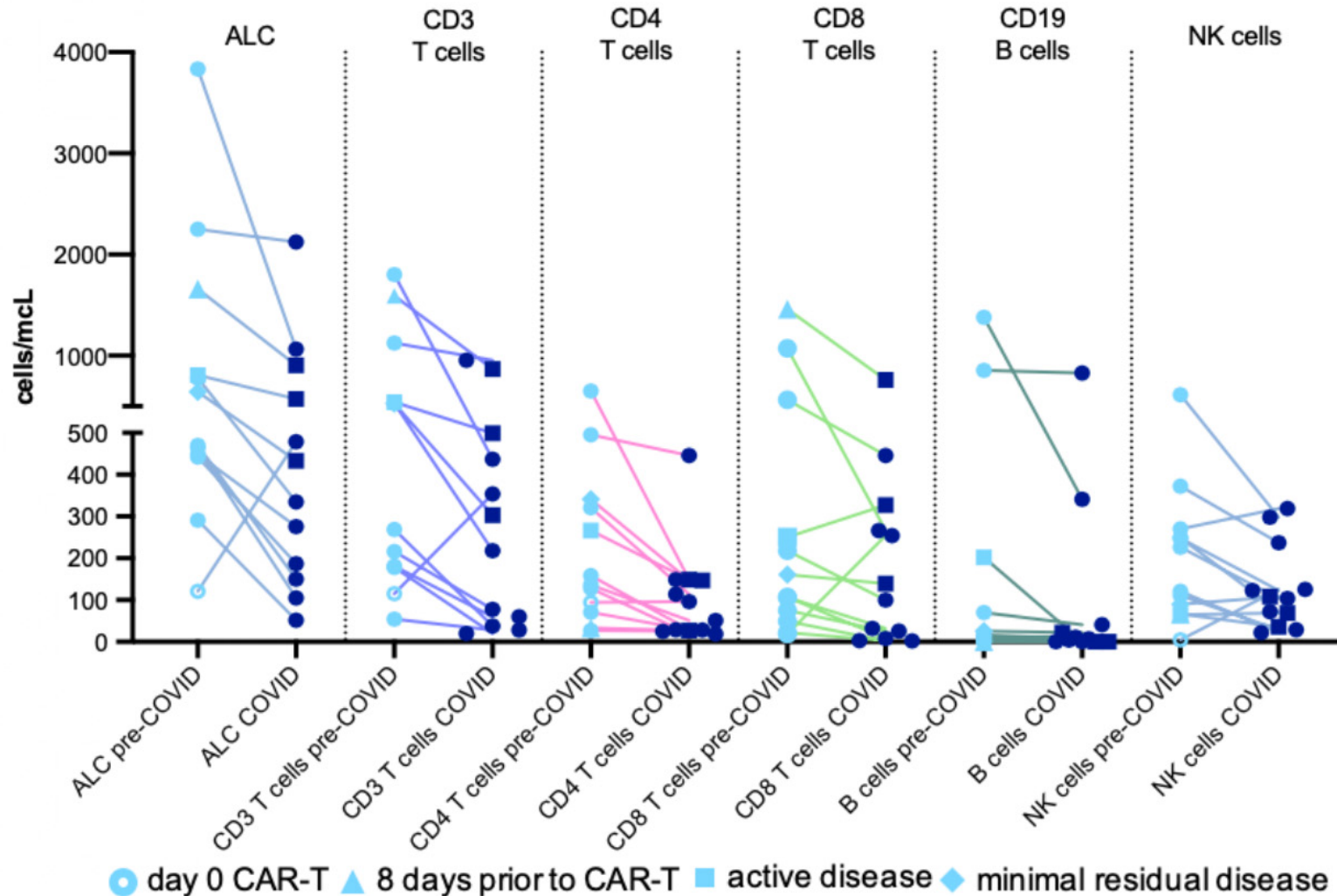
Akshay Sharma, Neel S Bhatt*, Andrew St Martin, Muhammad Bilal Abid, Jenni Bloomquist, Roy F Chemaly, Christopher Dandoy, Jordan Gauthier, Lohith Gowda, Miguel-Angel Perales, Stuart Seropian, Bronwen E Shaw, Eileen E Tuschl, Amer M Zeidan, Marcie L Riches†, Gunjan L Shah†*

Sharma et al, Lancet Haematology 2021

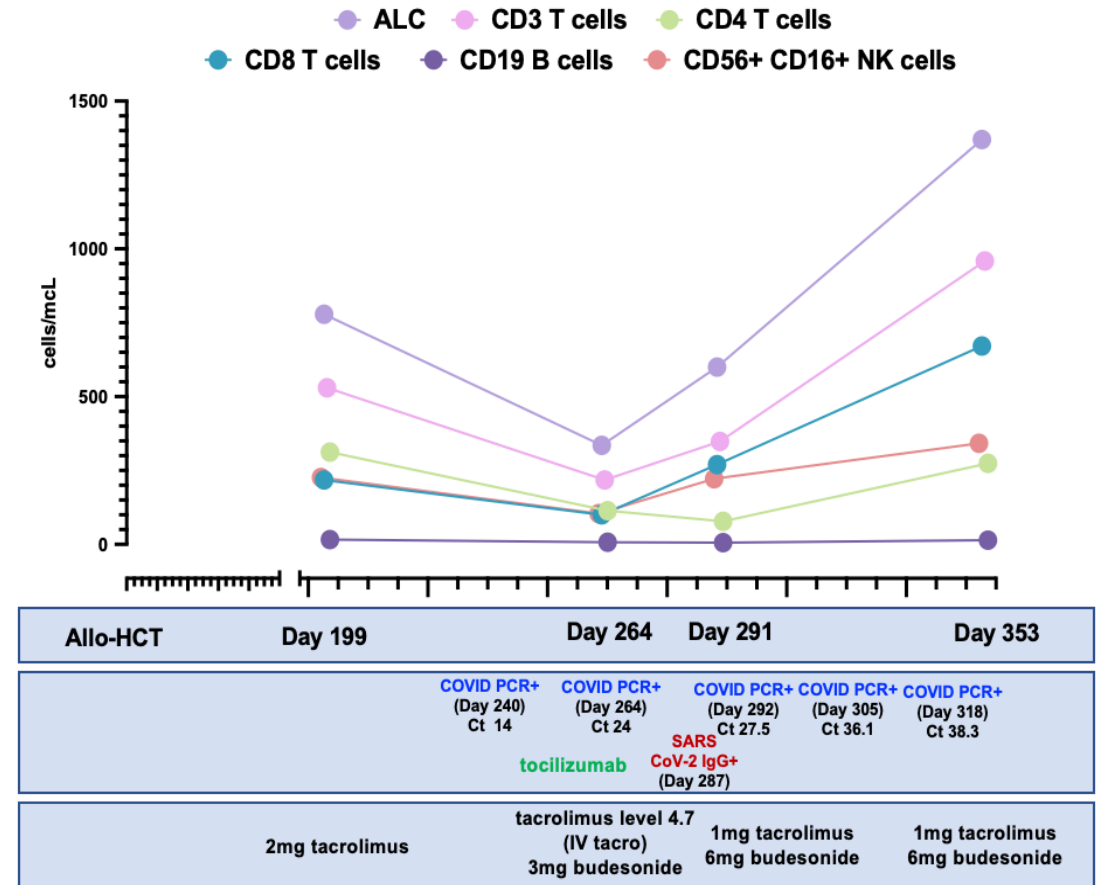
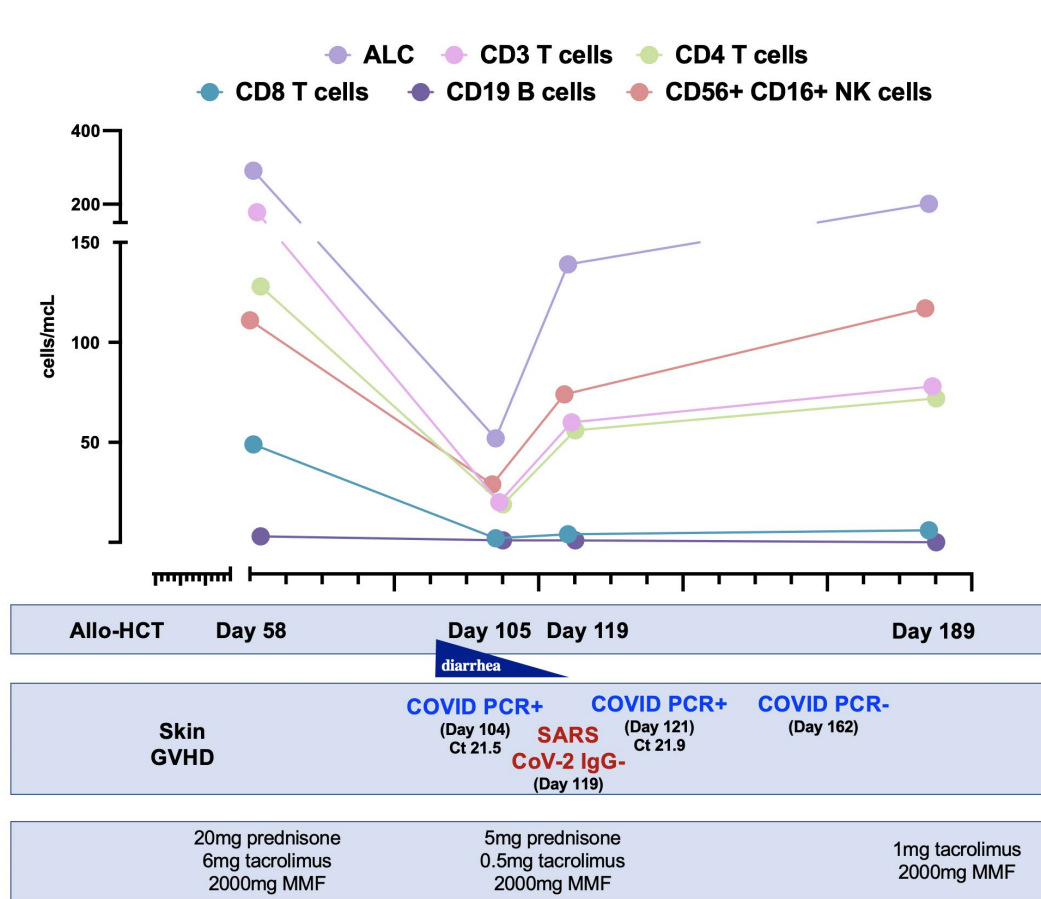


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Infection with SARS-CoV-2 results in a drop in lymphocyte populations

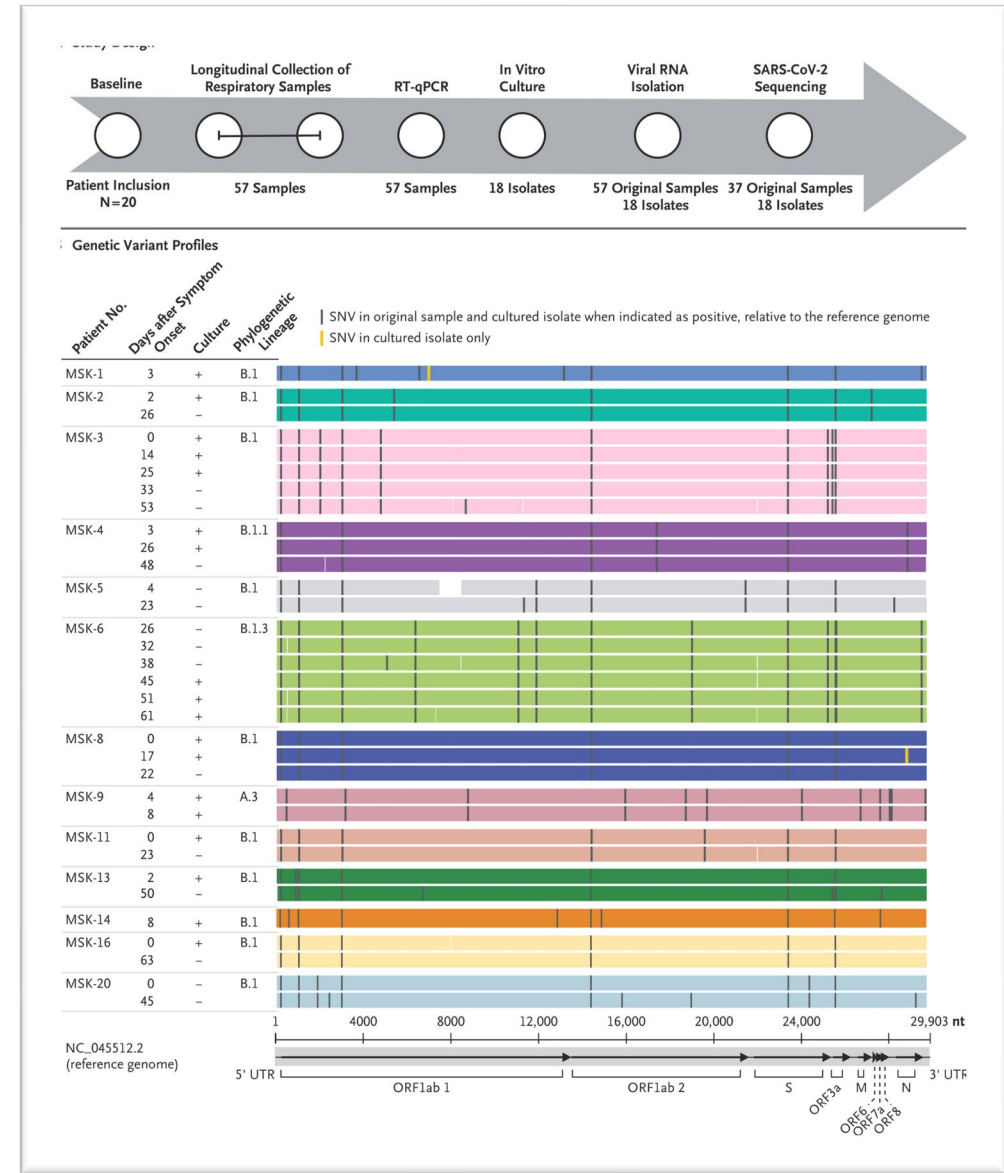


Lymphopenia with COVID-19 does not impair long-term immune reconstitution in BMT patients



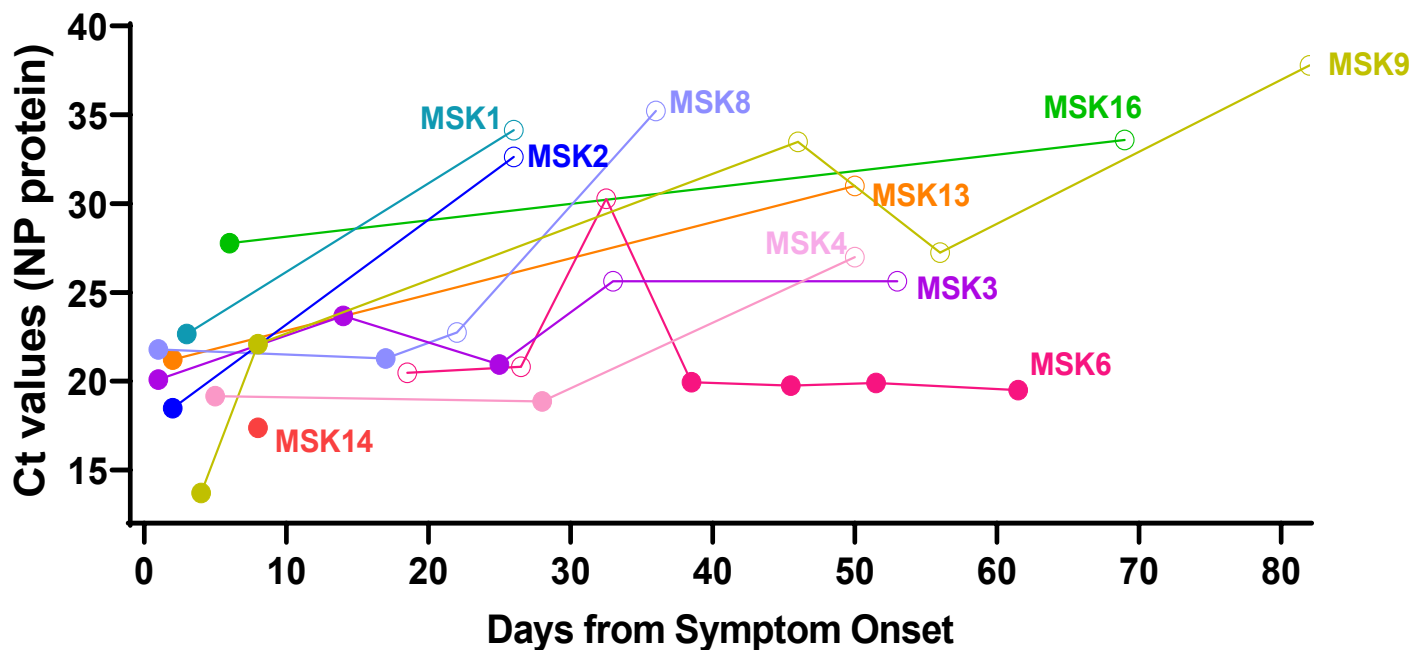
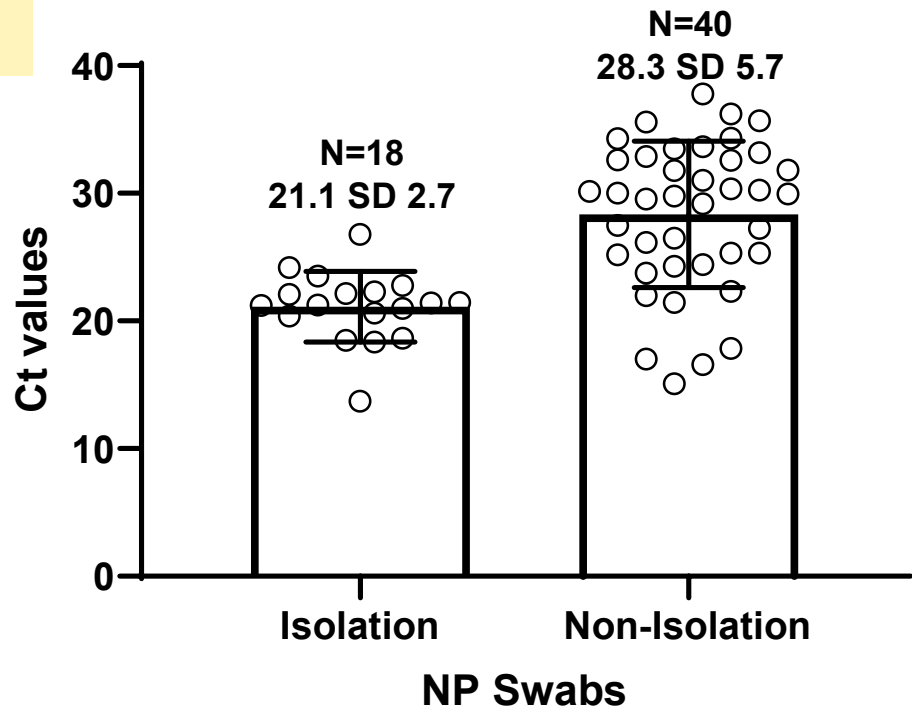
Prolonged shedding of viable SARS Cov-2 can be seen post HCT

- > 20 days in three patients
- Longest up to day 61
- Early post HCT/CAR-T (<6 mo)
- No evidence of reinfection
- Secondary cases not assessed

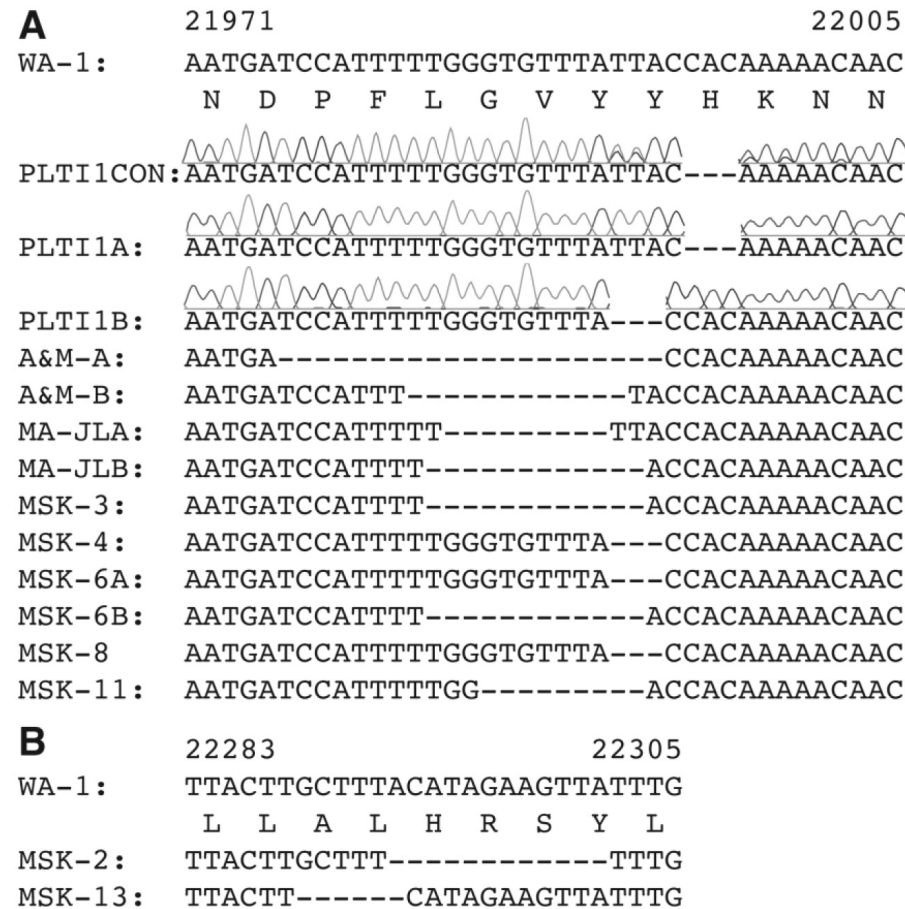


Aydillo, Kamboj, NEJM 2020

Infectious samples have lower Cycle Threshold values



Deletions in SARS-CoV-2 spike arise during long-term persistent infections in immunosuppressed patients



BACK 2
SCHOOL



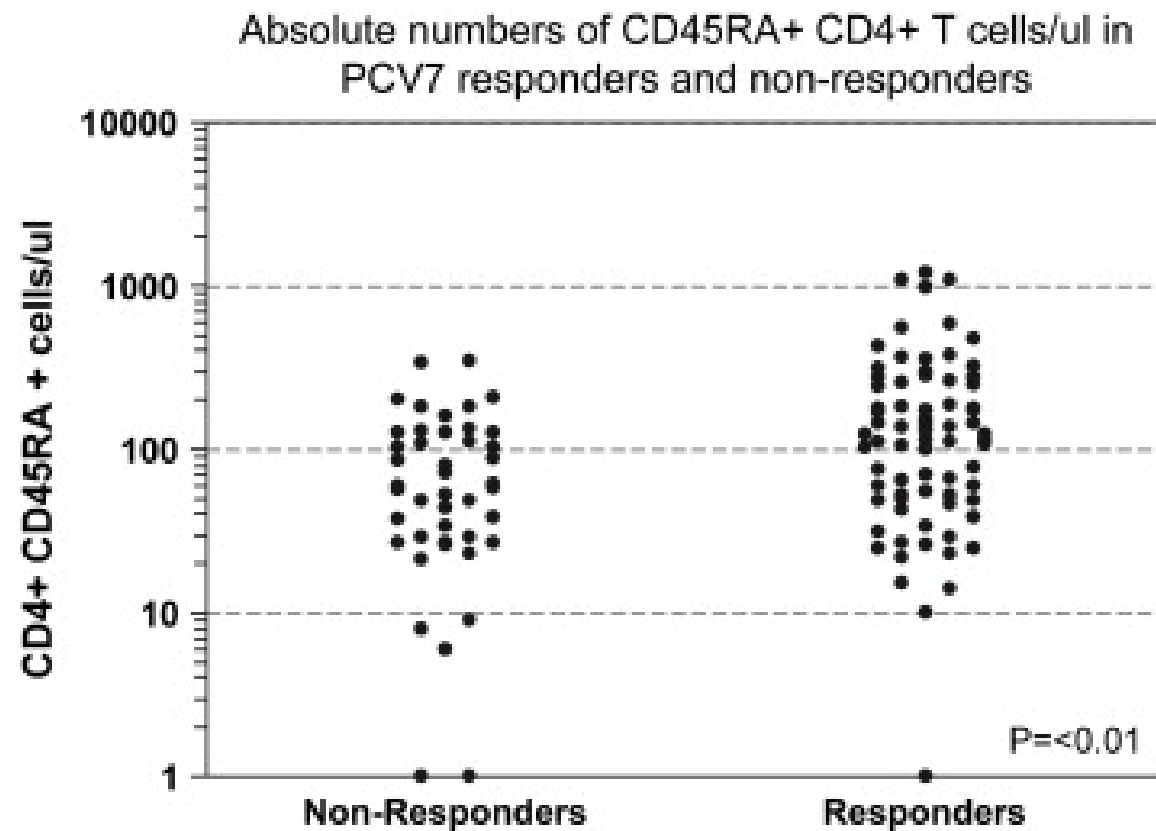
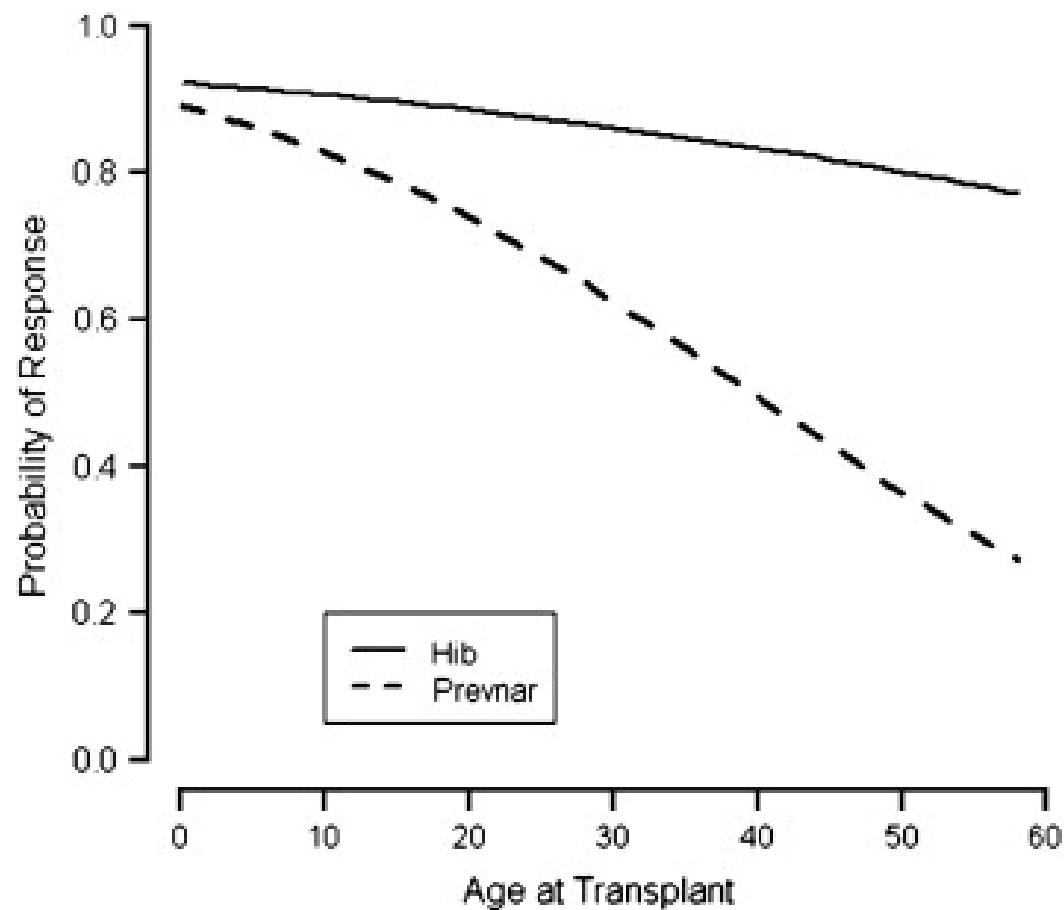
Patient: 55 year old NYC Public school teacher

- Diagnosis: acute myelogenous leukemia
- Transplant: T-cell depleted transplant from HLA-matched sister
- Post-transplant course: routine, no GVHD, delayed immune recovery (expected)
- Return to work:
 - Delay due to vaccine requirement
 - Delay extended because of medical clearance in March & decision of school principal to delay return to new academic year

Patient: 50 year old ER physician

- Diagnosis: T-cell acute lymphoblastic leukemia
- Transplant: T-cell depleted transplant from HLA-matched unrelated donor
- Post-transplant course: routine, no GVHD, delayed immune recovery (expected)
- Return to work:
 - Delay due to vaccine requirement including demonstration of response to MMR
 - Confirmation of MMR response required sending samples to CDC

Response to Vaccines in Allogeneic HCT Recipients Decreases with Age



Pao et al, BBMT, 2008; 14:1022-30.



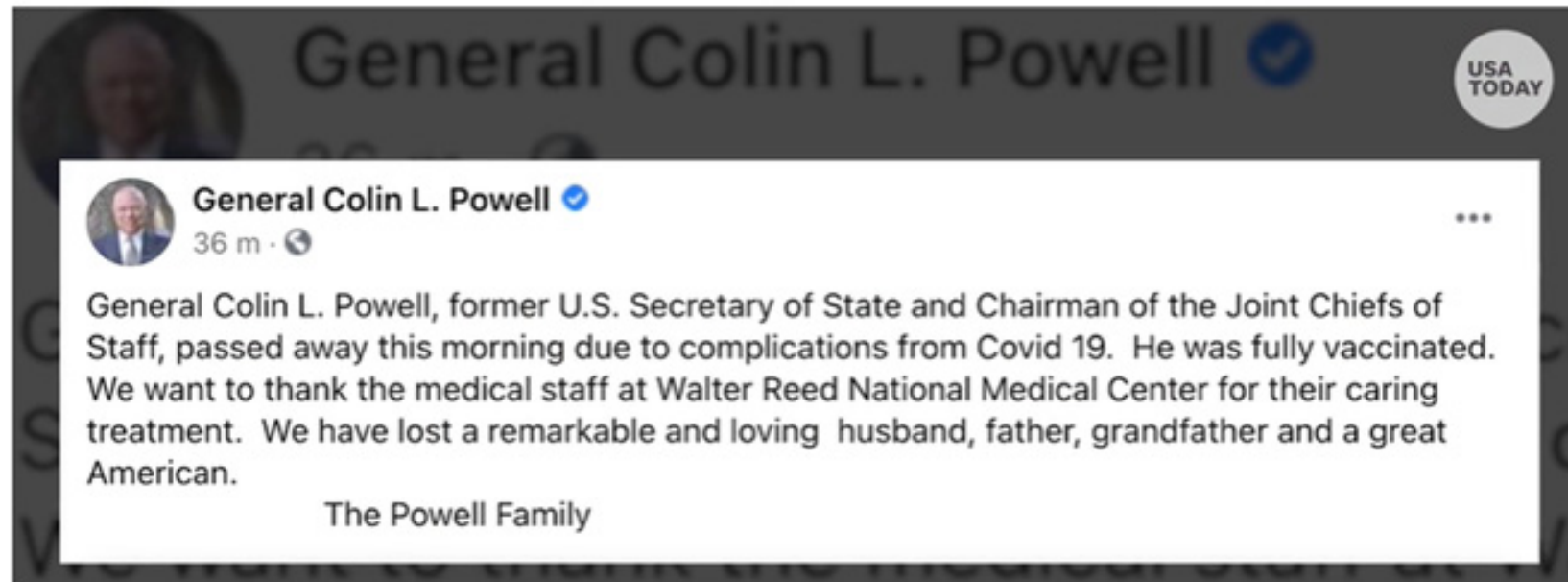
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Colin Powell was vaccinated against COVID but still died of complications. Here's what you need to know

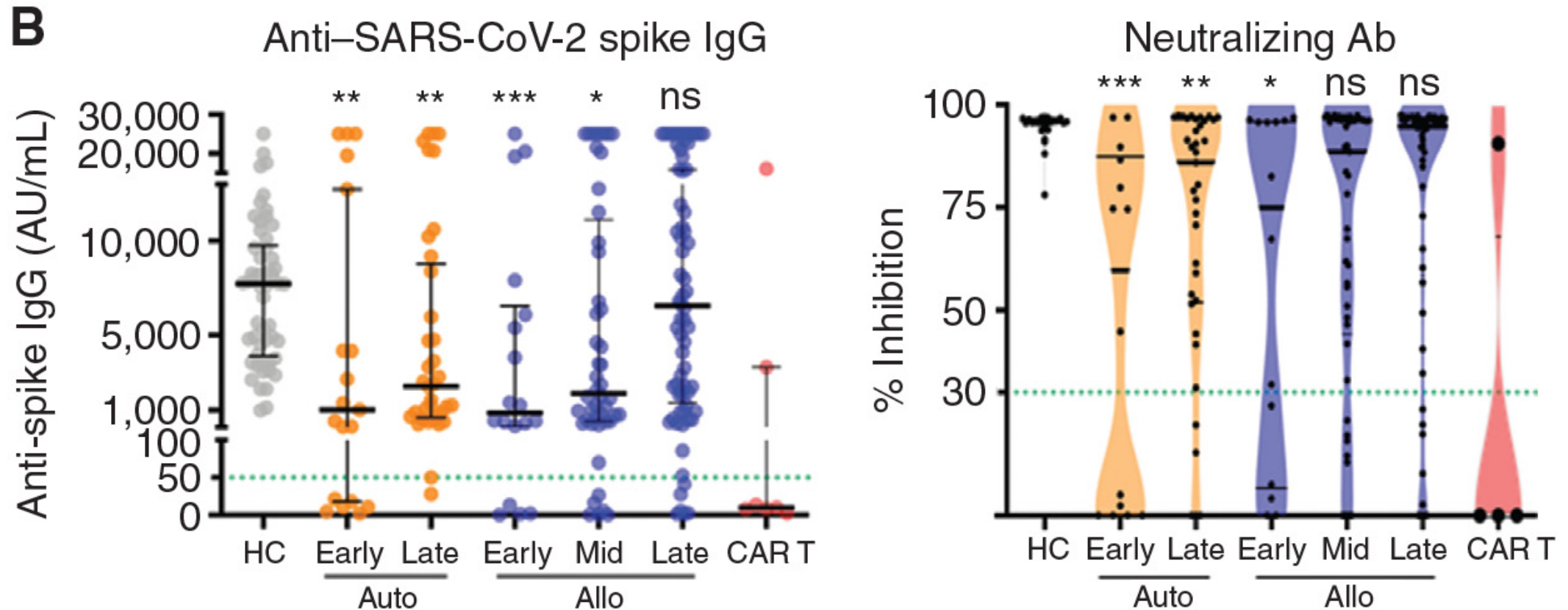
Max Filby The Columbus Dispatch

Published 10:00 p.m. ET Oct. 18, 2021 | Updated 1:22 p.m. ET Oct. 20, 2021

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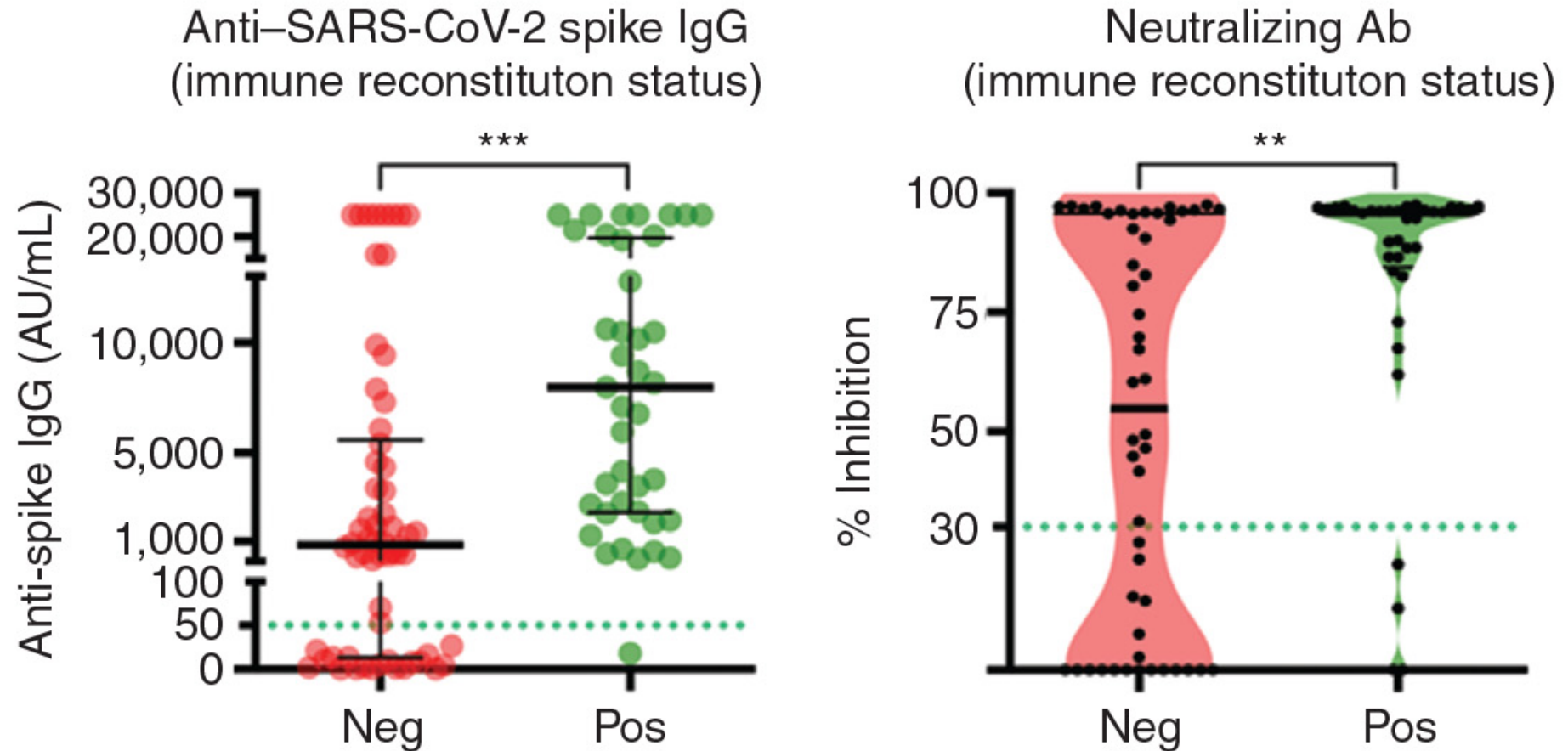
Antibody responses to COVID-19 vaccines vary according to type of cellular therapy and timing post treatment



Early allo, 1st year; mid-allo, 1 to 3 years; late allo, >3 years
Early auto, 1st year; late auto, >1 year.

Antibody responses to COVID-19 vaccines vary according to immune recovery

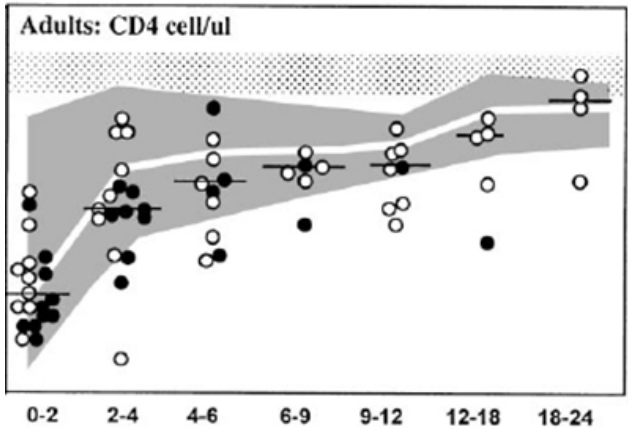
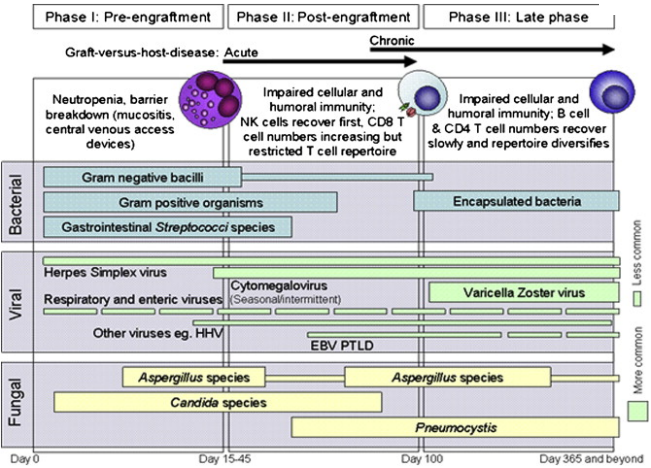
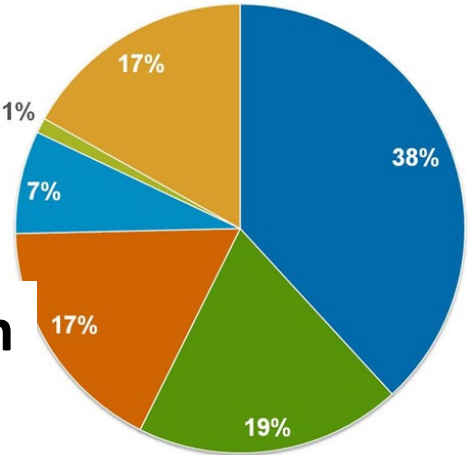
C



Pos, meeting all criteria: CD4+ >200 cells/ μ L, CD19+ >50 cells/ μ L, IgG >500 mg/dL, PHA >40%

Infections are common
Cause of death post HCT

Infection



Time post infusion
& risk factors

Immune
Reconstitution



Vaccines



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