CARE TEAM FORUM®

A Violent Graft in a Vulnerable Host:
THE FUTURE OF aGvHD MANAGEMENT

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Current and Emerging Therapies for aGvHD in the Post-HSCT Setting: Prevention and Initial Therapy

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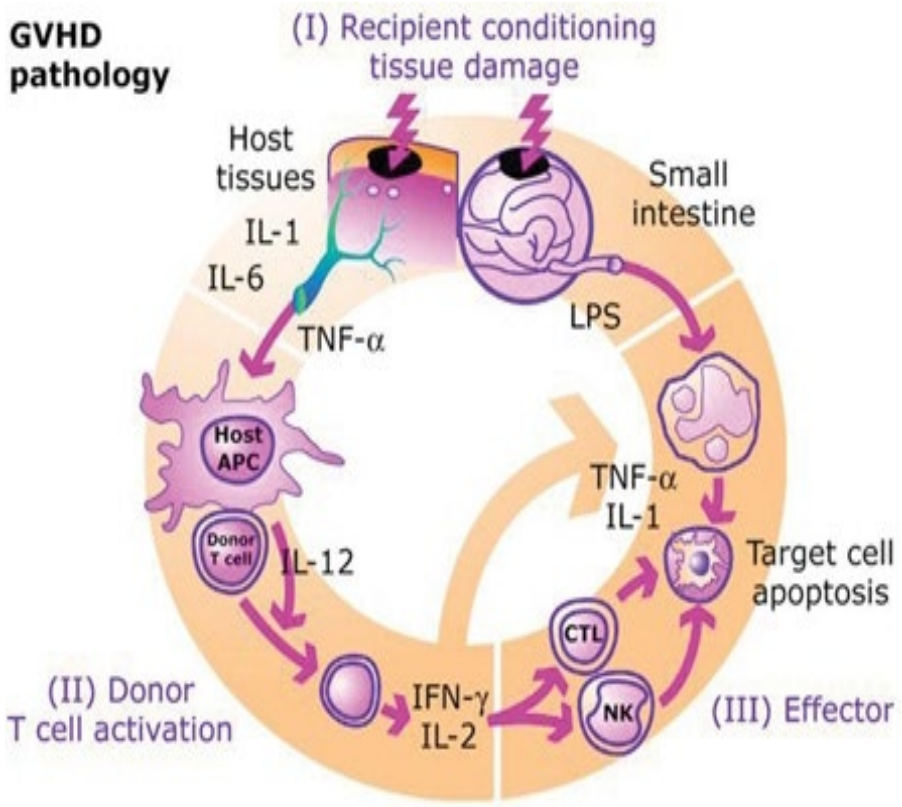
Foundations of Acute GvHD

Pathophysiology of Acute GvHD

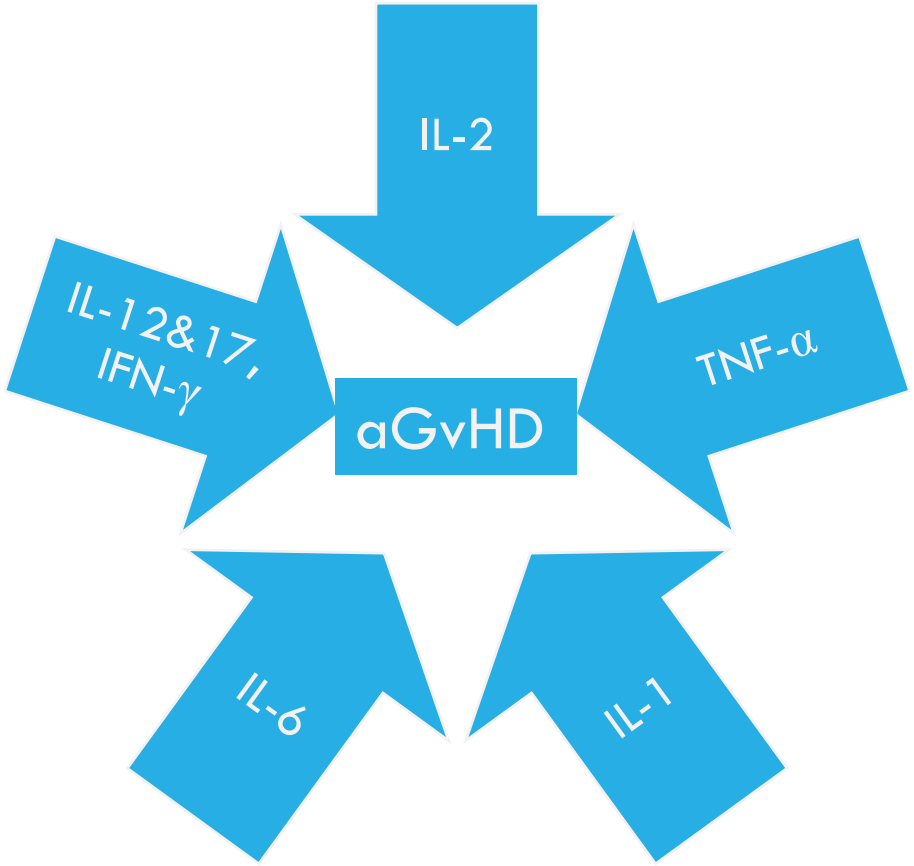
- Recognition and destruction of recipient tissues and organs by the donor immune effector cells
- Three Phases:
  - Phase 1 (Afferent): Damage to recipient tissue secondary to conditioning regimen; loss of microbiome
  - Phase 2 (Efferent): Donor T cells interact with recipient's APCs leading to proliferation and differentiation into activate T cells
  - Phase 3 (Effector): Cytotoxic T lymphocytes and natural killer cells target organs causing tissue damage



Malard F, et al. *Nat Rev Dis Primers.* 2023;9(1):27.
Martinez-Cibrian N, et al. *Blood Rev.* 2021;48:100792.

Implicated Cytokines

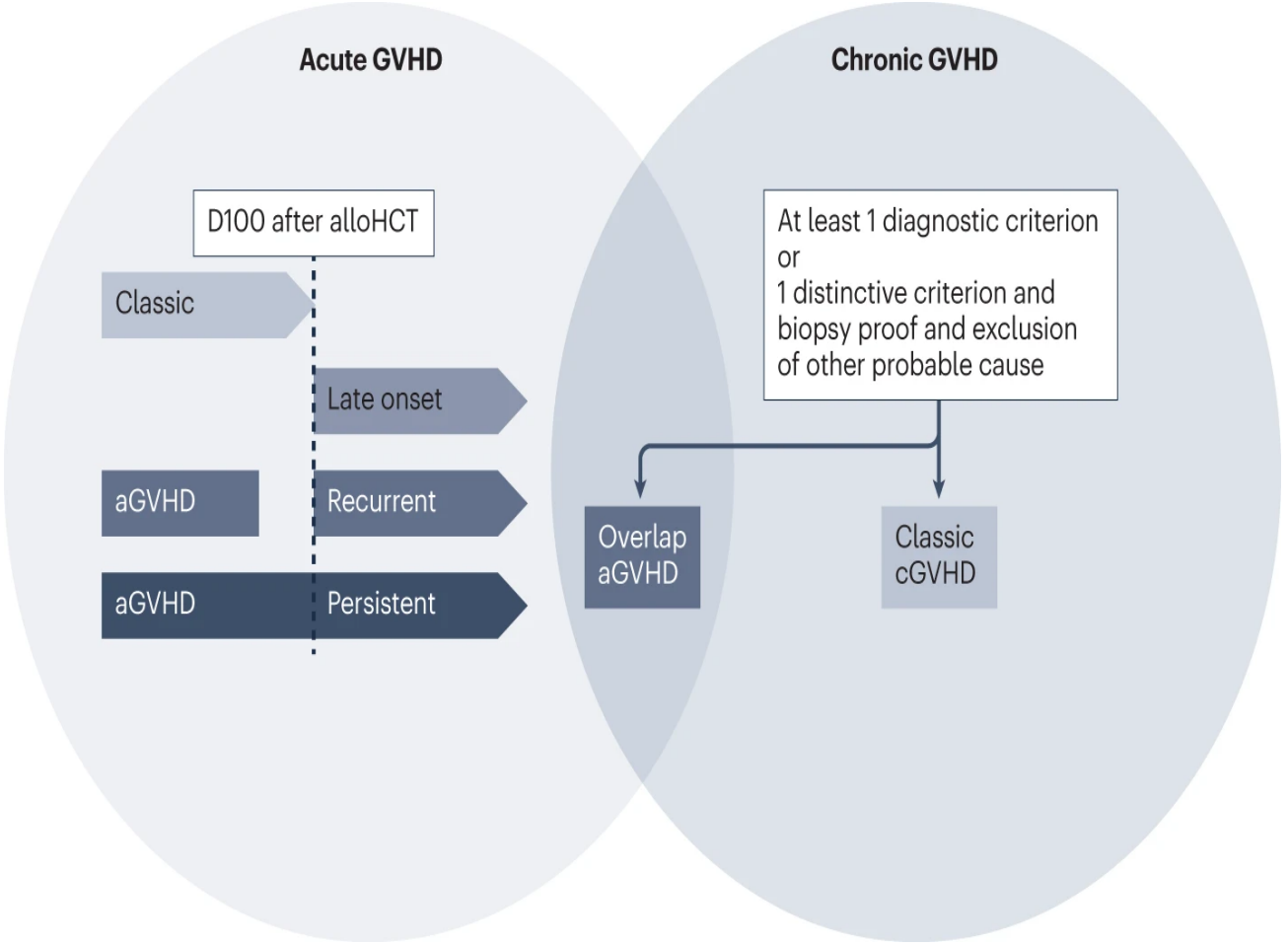
- Interleukin-2 (IL-2) activation and proliferation of T cells
- Tumor necrosis factor-alpha (TNF-α) promotes inflammation and tissue damage in GvHD
- Interleukin-1 (IL-1) contributes to tissue damage and inflammation
- Interleukin-6 (IL-6) proinflammatory cytokine involved in the pathogenesis of GvHD
- Others:
  - IL-12 stimulates the differentiation of naïve T cells that are involved in cell-mediated immune responses associated with GvHD
  - IL-17 promotes inflammation and tissue damage; particularly in the gut
  - Interferon-gamma (IFN-γ) involved in the inflammatory response and tissue damage characteristic of GvHD



Malard F, et al. *Nat Rev Dis Primers.* 2023;9(1):27.

Epidemiology

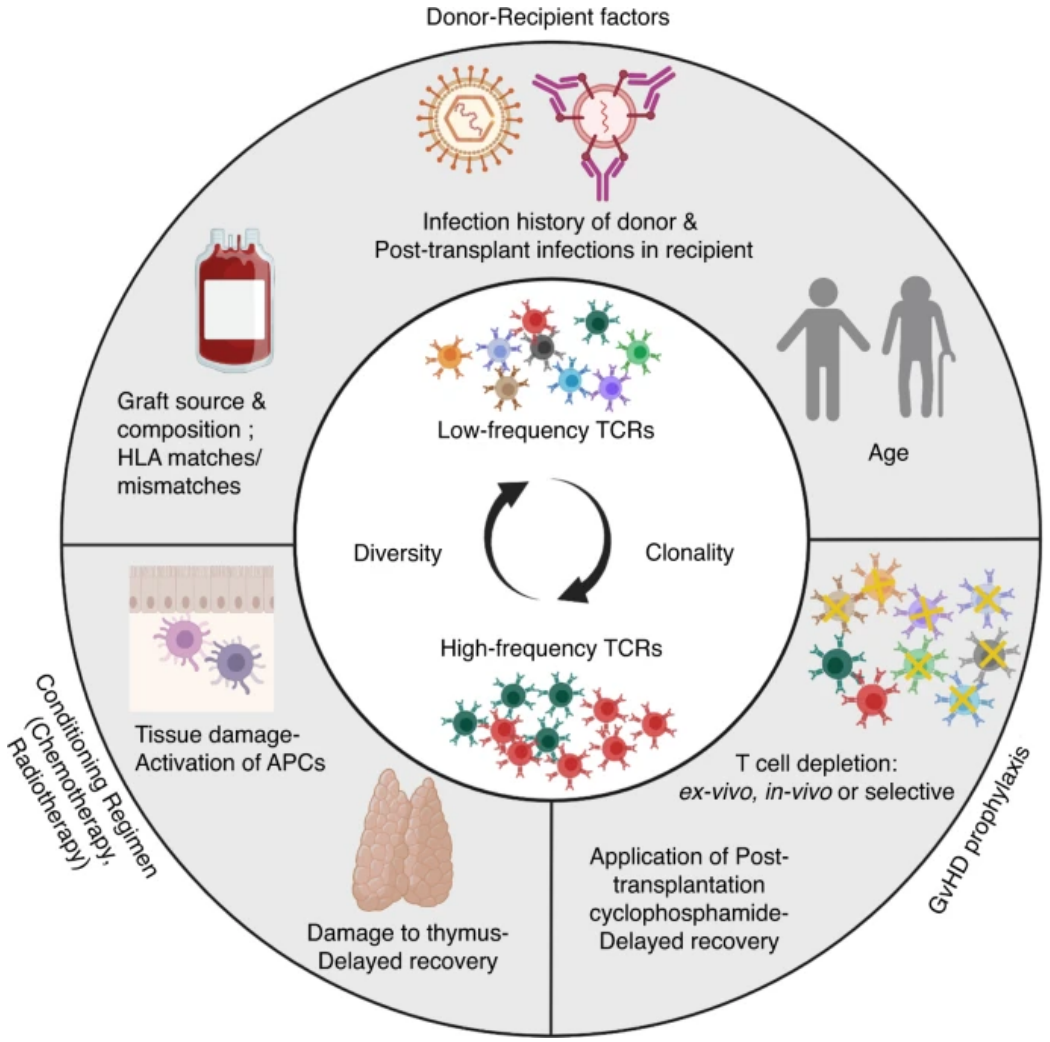
- aGvHD incidence remains high (30% to 62%)
  - Significant cause of NRM in adults/peds
  - Variance among HLA mismatch, patient ethnicity
- 1-year OS of 70% in patients with grade II acute GvHD and 40% in patients with grade III–IV acute GvHD



Malard F, et al. *Nat Rev Dis Primers.* 2023;9(1):27.
Zeiser R, et al. *N Engl J Med.* 2017;377(22):2167-2179.

Risk Factors for Acute GvHD

- HLA mismatch
  - Increasing risk with greater HLA disparity
- Donor factors
  - Older donor age
  - Gender mismatching
- Recipient factors
  - Older age
- Transplant related factors
  - Intensity of conditioning regimen
  - Stem cell source
- Ineffective prophylaxis



Goel, M, et al. *Bone Marrow Transplant*. 2023;58(3):239-246.

Clinical Presentation of Acute GvHD

SKIN

- Maculopapular, erythematous rash
- Bullae
- Desquamation

LIVER

- Transaminitis (Bilirubin, ALK)
- Coagulopathy
- Hyperammonemia

GI

Upper

- Early satiety
- Anorexia
- Persistent nausea

Lower

- Secretory diarrhea
- Cramping abdominal pain

Zeiser R, et al. *N Engl J Med.* 2017;377(22):2167-2179.

aGvHD Organ Staging

Stage	Skin	Liver	Gastrointestinal (Upper)	Gastrointestinal (Lower)
0	No active GvHD Rash	<2 mg/dL	No or intermittent nausea, vomiting or anorexia	Child: <10 mL/kg/day or <4 ep/day Adult: <500 mL/day or <3 ep/day
1	Maculopapular Rash <25% BSA	2 to 3 mg/dL	Persistent nausea, vomiting or anorexia	Child: 10 to 19.9 mL/kg/day or 4 to 6 ep/day Adult: 500 to 999 mL/day or 3 to 4 ep/day
2	Maculopapular Rash <50% BSA	3.1 to 6.0 mg/dL	–	Child: 20 to 30 mL/kg/day or 7 to 10 ep/day Adult: 1000 to 1500 mL/day or 5 to 7 ep/day
3	Maculopapular Rash >50% BSA	6.1 to 15 mg/dL	–	Child: >30 mL/kg/day or >10 ep/day Adult: >1500 mL/day or >7 ep/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL	–	Severe abdominal pain with or without ileus or grossly blood stool (regardless of volume)

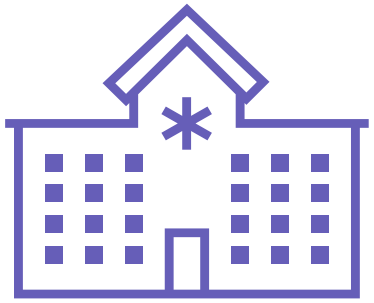
Overall aGvHD Grading

Grade	MAGIC
Grade I	Stage 1-2 skin; no liver or GI involvement
Grade II	Stage 3 skin or Stage 1 liver or Stage 1 GI
Grade III	Stage 0-3 skin with Stage 2-3 liver or Stage 2-3 GI
Grade IV	Stage 4 skin, liver, or GI involvement

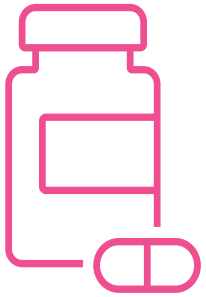
Harris AC, et al. *Biol Blood Marrow Transplant*. 2016;22(1):4-10.

GvHD Prophylaxis

Acute GvHD Prophylaxis

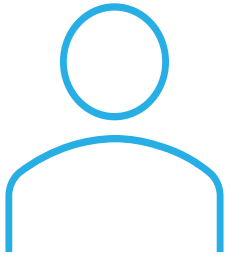


Institution Dependent



Regimens

- Calcineurin inhibitors
- Methotrexate
- Mycophenolate mofetil
- Sirolimus
- Post-transplant cyclophosphamide
- T cell Depletion (*ex vivo* or *in vivo*)
  - Rabbit anti-thymocyte globulin



Donor Selection

Penack O, et al. *Lancet Haematol*. 2024;11(2):e147-e159. 2024

Current Studies

CARE TEAM FORUM®

- Abatacept
- Alpha-1 Antitrypsin
- Post-transplant Cyclophosphamide
- Vedolizumab
- Vorinostat
- Starch

Martinez-Cibrian N, et al. *Blood Rev.* 2021;48:100792.

Abatacept

- Abatacept 2 (ABA2) trial
  - Multicenter Phase 2 trial
  - Abatacept plus CNI/MTX for GvHD prevention in 8/8 HLA MUD and 7/8 MMUD HCT
  - MMUD cohort demonstrated a significant reduction in grade 3 to 4 aGvHD
  - Significant improvements in TRM and overall survival (OS) at 2 years for patients receiving abatacept
- Multicenter retrospective analysis
  - 26 pediatric patients, 24 adult patients
  - 7/8 MMUD HCT with BM or PBSC for hematologic malignancy
  - Abatacept (Day –1, +5, +14, +28) plus CNI/MTX
  - Results supportive of ABA2
    - Low incidences of grade 3 to 4 aGvHD and TRM and encouraging DFS
    - Results assessed by age group unlike ABA2

CNI, calcineurin inhibitor; MTX, methotrexate; MUD, matched unrelated donor; MMUD, mismatched unrelated donor

Watkins B, et al. *J Clin Oncol.* 2021;39(17):1865-1877.
Raghunandan S, et al. *Blood Adv.* 2023;7(16):4395-4399.

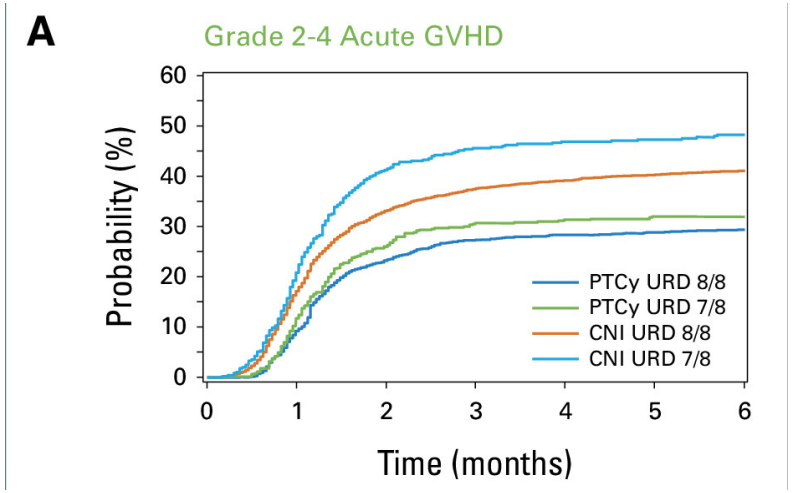
Post-Transplant Cyclophosphamide

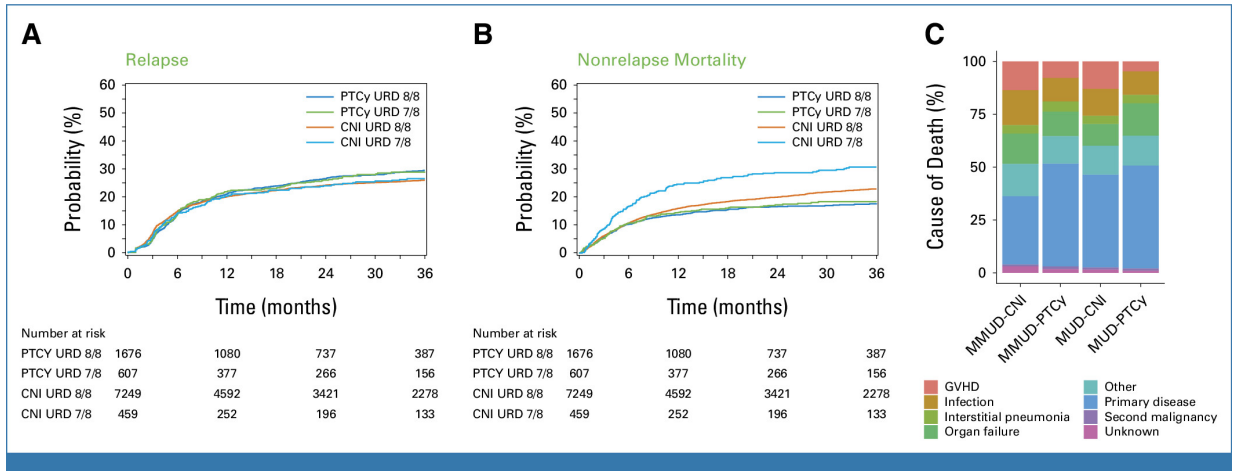
- Retrospective single-institution cohort
- N=196 (peds & adults)
- PTCy on Day +3 & +4 plus tacrolimus & MMF
- Myeloablative & RIC conditioning
- BM & PBSC grafts (MRD & MUD)
- 28% developed aGvHD
- 16% developed Grade II-III requiring systemic steroids; 0 Grade IV
- Incidence of SR aGvHD 4.6%

Herzog S, et al. *Transplant Cell Ther*. 2024;30(7):688.

Post-Transplant Cyclophosphamide

- Retrospective study CIBMTR database
- 10,025 adult patients from 153 centers with leukemia & MDS
- MUD (8/8) versus MMUD
- CNI with MTX or MMF with or without ATG & PTCy regimens included a CNI or sirolimus with or without MMF and ATG
- Improved OS for MUD with PTCy compared to MUD HCT with CNI (*P*=.004)
- GRFS improved with PTCy after MUD (*P*<.0001) & MMUD (*P*<.0001)
- Increased donor access





Shaffer BC, et al. *J Clin Oncol.* 2024;42(28);3277-3286.

Vorinostat

- Histone deacetylase inhibitor (HDACi)
  - Downregulates expression of pro-inflammatory cytokines
  - Reduces activation of donor T Cells
- Vorinostat + Standard prophylaxis
- Phase I/II trial
  - Reduction in grade II-IV aGvHD
  - Well tolerated
    - Cytopenias, electrolyte imbalance, GI symptoms

The Microbiome

Microbiome

- Mucosal damage & alteration of the gut microbiota contribute to aGvHD
- GI GvHD severity associated with:
  - Shift toward *enterococcus* in the gut
  - Reduction in specific microbial metabolites, such as butyrate
- Studies looking at:
  - Fecal microbiome transplant (treatment)
  - Pro & prebiotics (prophylaxis and treatment)

Yoshifuji K, et al. *Blood Adv.* 2020;4(19):4607-4617.

Resistant Potato Starch (RPS)

- Mucosal damage and alteration of the gut microbiota increase risk of GI GvHD
- Modify the intestinal microbiome
  - Increase intestinal butyrate (short chain fatty acid)

Riwes, MM, et al. *Nat Med.* 2023;29:2805-2813

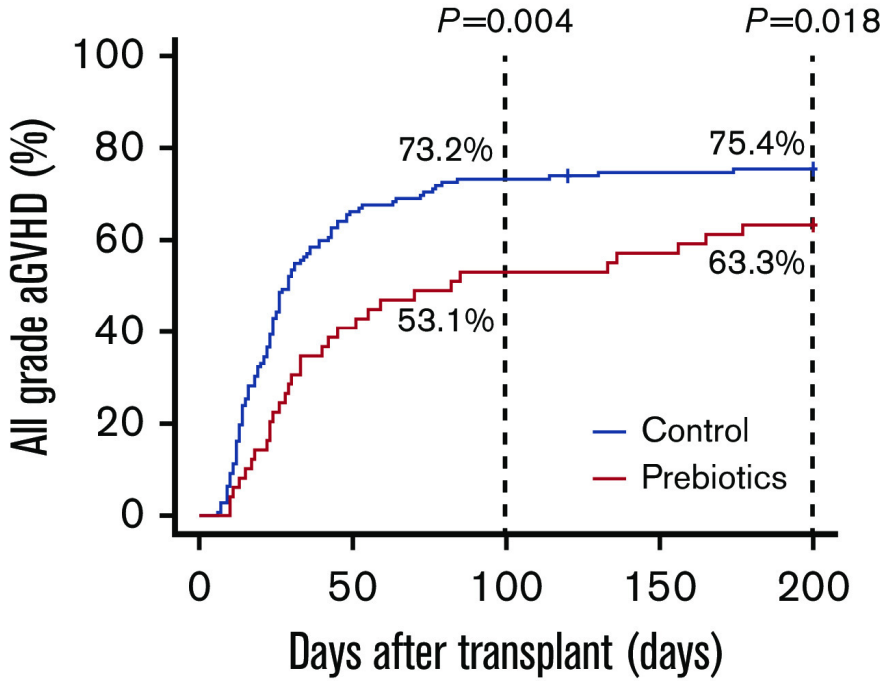
Resistant Potato Starch (RPS)

- Single-center prospective, single-arm, longitudinal study
  - Bob's Red Mill Starch
    - 20 g daily x 3 days
    - 20 g BID
    - Day –7 to Day 100
    - N=10
  - Stool samples: Day –7, nadir, engraftment, Day 100
  - Increase in intestinal SCFA butyrate levels
  - Well tolerated; No adverse effects

Riwes, MM, et al. *Nat Med.* 2023;29:2805-2813

Resistant Potato Starch (RPS)

- Prospective study
  - Resistant starch (RS) and oligosaccharide (GFO)
    - GFO with breakfast, RS with lunch and dinner
    - Start of conditioning to Day 28
    - N=49; Control group 72 patients
  - Stool samples: Pre-transplant, Day 28.
  - Primary outcome: mucositis and diarrhea
    - No change in severity of mucositis or diarrhea
    - Significantly shorter duration of mucositis in study group
    - Shorter duration of diarrhea study
  - Secondary: GvHD
    - Day 100 significant reduction all grade aGvHD
    - Late aGvHD incidence high in study group
  - Secondary: TPN requirement
    - No change
  - Well tolerated; No adverse effects



Yoshifuji K, et al. *Blood Adv.* 2020;4(19):4607-4617.

Recent Failures in Prophylaxis

- Inhibition of cytokines
  - Tocilizumab
  - Etanercept
  - Infliximab
- Defibrotide
- Mesenchymal stem cells

EBMT Recommendations

- **2024 Update Summary**
  - Rabbit anti-T-cell (thymocyte) globulin or post-transplantation cyclophosphamide as standard GvHD prophylaxis in peripheral blood stem-cell transplantations for unrelated donors
  - Methotrexate is the recommended antimetabolite for patients receiving MAC; MMF use only if MTX is contraindicated

Penack O, et al. *The Lancet Haematology*, 2024;11(2):e85.

Acute GvHD
Initial Therapy

Biomarkers to Predict Outcomes

- MAGIC Algorithm Probability
  - Reg3α & ST2
  - 6-month NRM of 28% in the high-risk group and 7% in the low-risk group
- MAGIC Algorithm Probability
  - Pretreatment and 4 weeks
- Elafin (Skin GvHD)
- Hepatocyte growth factor and cytokeratin 18 (CK18) fragment levels (GI GvHD)

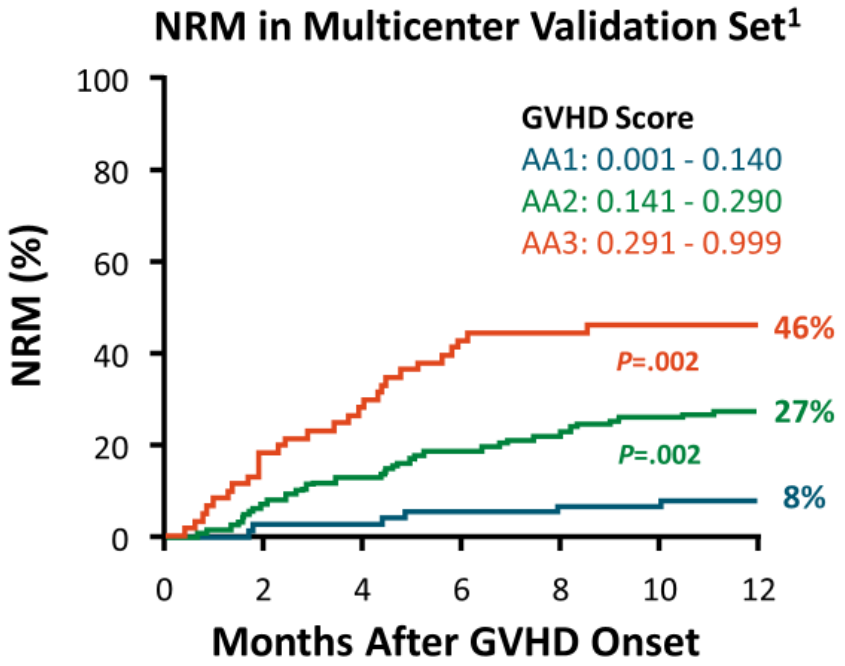
NRM, non-relapse mortality; REG3α, regenerating islet-derived 3; ST2, suppression of tumorigenicity 2

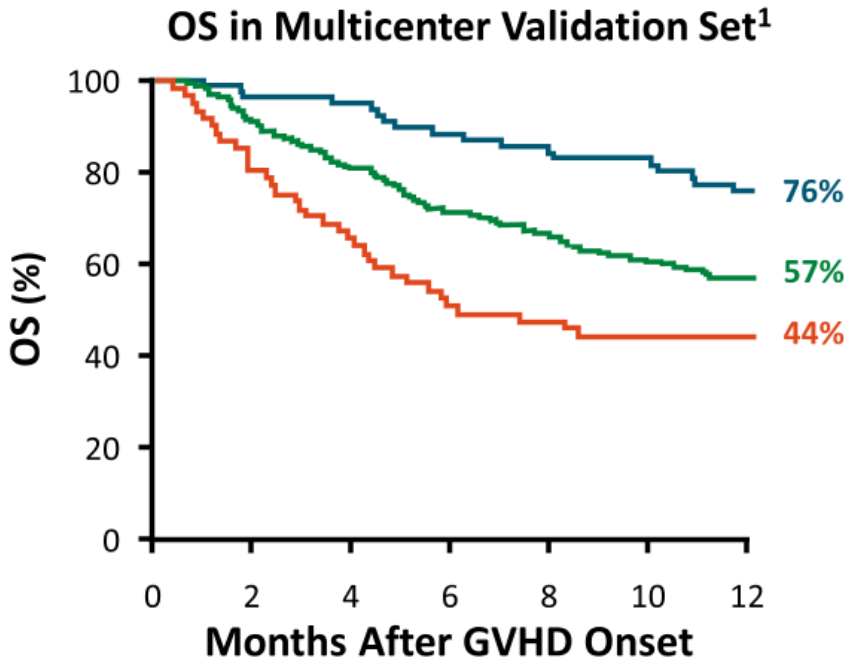
Levine JE, et al. *Lancet Haematol.* 2015:2(1):e21-29.
Srinagesh HK, et al. *Blood Adv.* 2019;3(23);4034-4042
Zeiser R, et al. *N Engl J Med.* 2017;377(22):2167-2179.

Risk Stratification

The MAGIC algorithm generates a single predicted probability (MAP) of 6-month NRM for each patient

– TNFRI + Reg3 + ST2 algorithm[1]; Reg3 + ST2 algorithm[2]





1. Levine JE, et al. *Lancet Haematol.* 2015;2(1):e21-29.
2. Hartwell MJ, et al. *JCI Insight*. 2017;2(3):e89798.

Risk Score

GvHD Risk Score	1 Organ (n)	2 Organs (n)	3 Organs (n)
Standard Risk (N=1, 454, 84%)	Stages 1-3 Skin (901)	Stages 1-3 Skin + Stage 1 GI (223)	
	Stages 1-2 GI (279)	Stages 1-3 Skin + Stages 1-4 Liver (51)	
High Risk (N=269, 16%)	Stage 4 Skin (13)	Stages 1-3 Skin + Stage 2 GI (54)	Stages 1-3 Skin + Stages 1-2 GI + Stages 1-3 Liver (23)
	Stage 3-4 GI (74)	Stages 1-2 Lower GI + Stages 1-3 Liver (12)	
	Stages 1-4 Liver (25)	Stages 3-4 GI + Stages 1-3 Skin (45)	Stages 1-3 Skin + Stages 3-4 GI+ Stages 1-4 Liver (13)
		Stages 3-4 GI + Stages 1-4 Liver (10)	

MacMillan ML, et al. *Biol Blood Marrow Transplant.* 2015;21(4):761-767.

Initial Treatment for aGvHD: NCCN

Acute GvHD Grade II - IV

Continue or consider restarting original immunosuppressive agent

(or escalate dose to achieve therapeutic blood level if GvHD developed during tapering of immunosuppressive therapy)

First-line Therapy

Clinical Trial

or

Systemic corticosteroids ± topical steroids

Upper GI Only

0.5 to 1 mg/kg/day methylprednisolone* + topical steroids

Skin/lower GI/Liver

1 to 2 mg/kg/day methylprednisolone* ± topical steroids†

or

Consider sirolimus for standard-risk acute GvHD

Taper steroids as clinically feasible

Response

No response

(steroid-refractory disease)

Additional Therapy

Clinical Trial

or

Addition of systemic agents to corticosteroids with steroid taper as clinically feasible.

**Or prednisone dose equivalent*

†Consider 1 mg/kg for Grade II

Loren AW, et al. NCCN Guidelines. Hematopoietic Cell Transplantation. Version 2.2024; 30 August 2024.

Management of Acute GvHD: First-line

Optimize Primary Immunosuppression

Corticosteroids

Supportive Care

- Nutritional support
- Infection prophylaxis
- Prevention of secondary complications

Emerging Therapies for aGvHD Prevention, Treatment, and Refractoriness

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Adult/Pediatric BMT and Cellular Therapies
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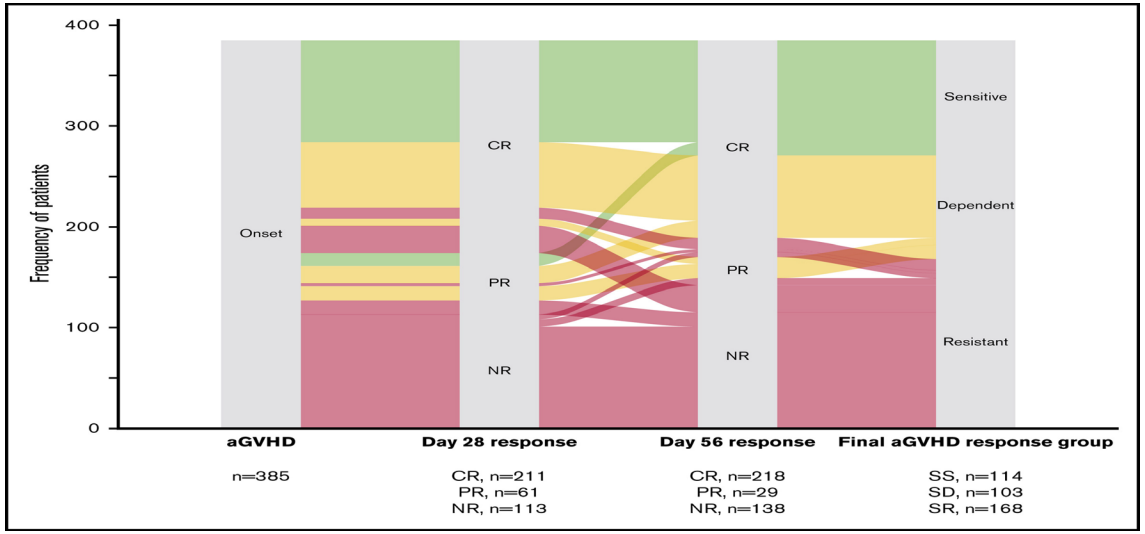
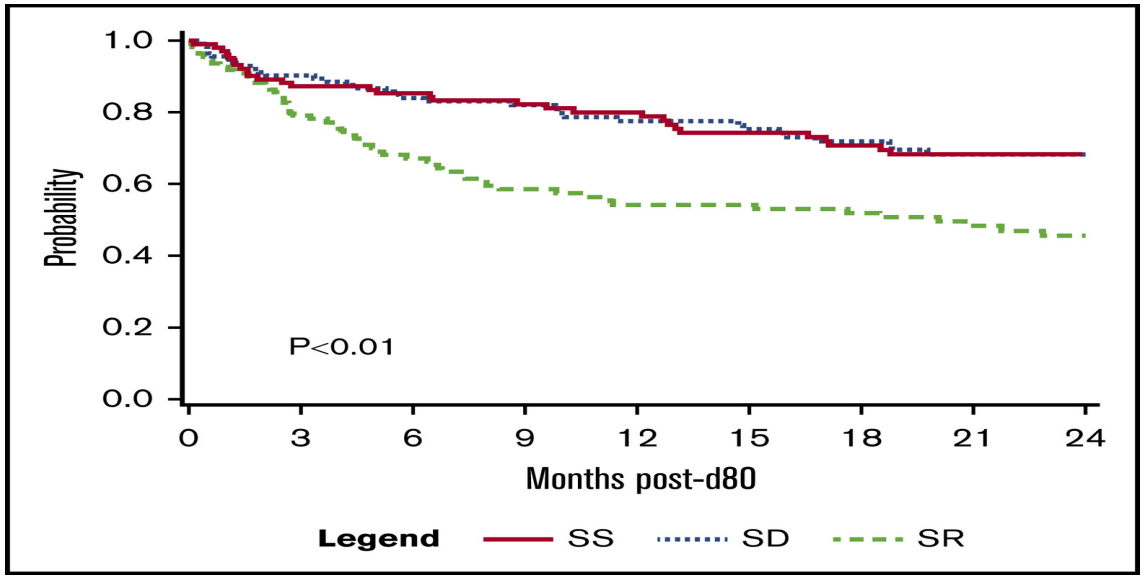
Steroid Refractory aGvHD

- Corticosteroids remain first-line therapy
  - ORR 40% to 60%
- Steroid refractory aGvHD → dismal prognosis
  - OS 5% to 30%





aGvHD, acute graft-versus-host disease; NRM, non-relapse mortality; ORR, overall response rate; OS, overall survival

MacMillan ML, et al. *Bone Marrow Transplant* 2020;55(1):165-171.
Zeiser R, et al. *N Engl J Med.* 2017;377(22):2167-2179.
El Jurdi N, et al. *Blood Adv.* 2021;5(5):1352-1359.

Management of SR aGvHD (NCCN)

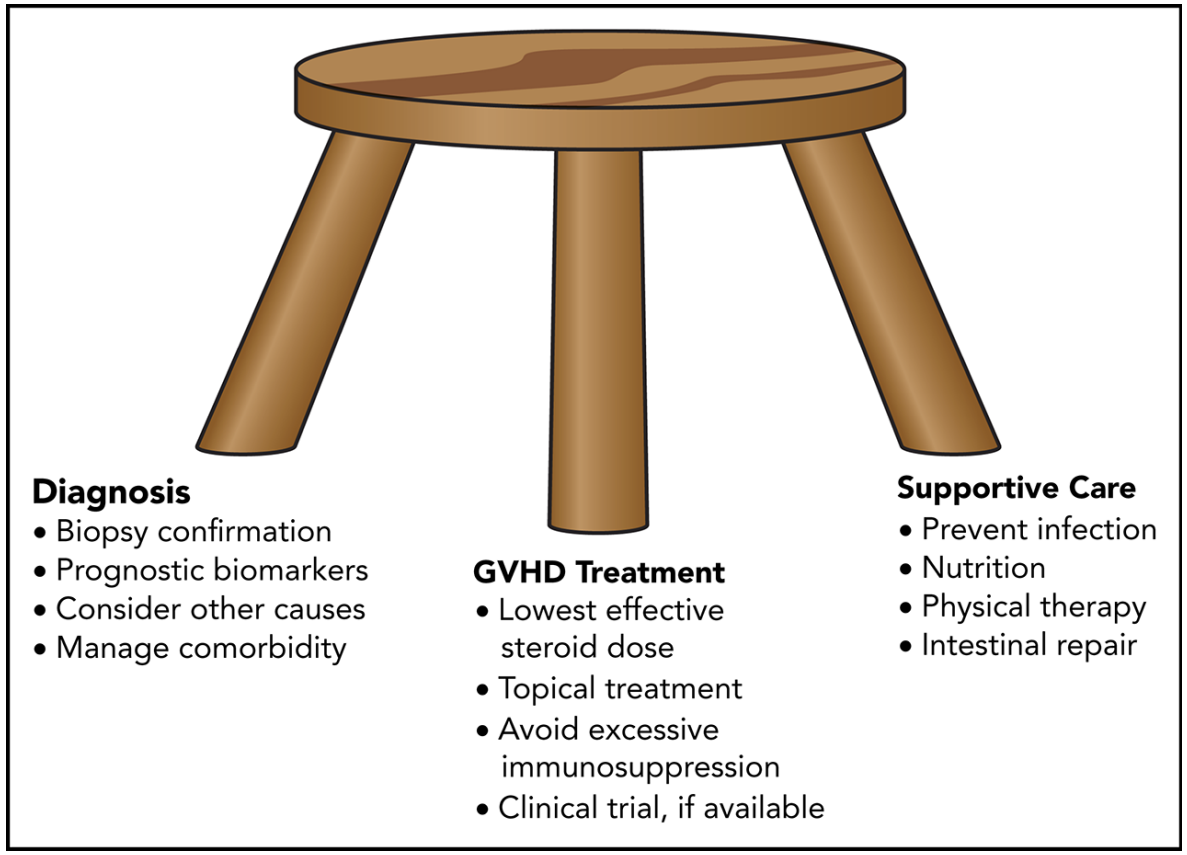
SR aGvHD
Progression of aGvHD within 3 to 5 days of therapy onset with ≥2 mg/kg/day of prednisone
Failure to improve within 5 to 7 days
Incomplete response after more than 28 days of immunosuppressive treatment, including steroids

SR aGvHD Treatment Options	
Ruxolitinib (category 1)	Extracorporeal photopheresis (ECP)
Alemtuzumab	Infliximab
Alpha-1 Antitrypsin	mTOR (sirolimus)
ATG	Mycophenolate mofetil
Basiliximab	Pentostatin
CNI (tacrolimus/cyclosporine)	Tocilizumab
Etanercept	Vedolizumab
Clinical Trial	

aGvHD, acute graft-versus-host disease; SR aGvHD, steroid refractory acute graft-versus-host disease; ATG, anti-thymocyte globulin; CNI. calcineurin inhibitor

NCCN Guidelines. Hematopoietic Cell Transplantation. Version 1.2024

SR-aGvHD Considerations



GvHD, graft-versus-host disease; SR aGvHD, steroid refractory acute graft-versus-host disease

Martin PJ. *Blood.* 2020;135(19):1630-1638.

REACH1

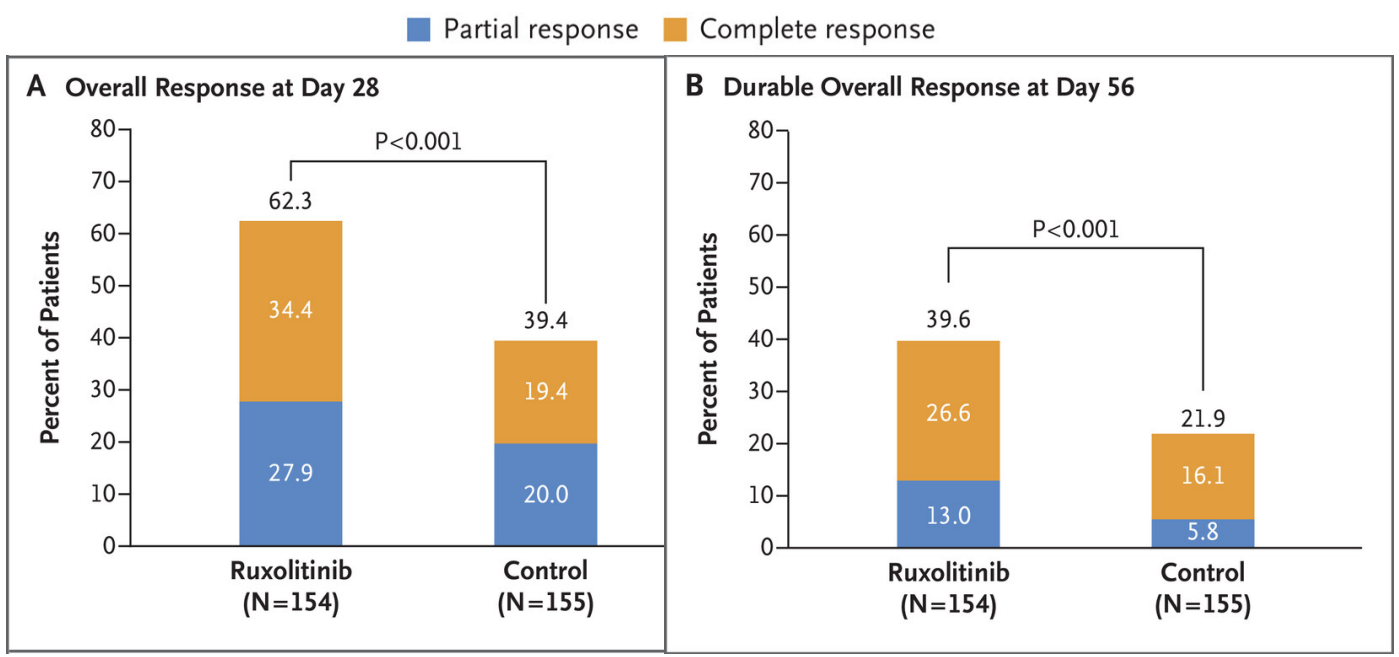
- REACH1: Multicenter, open-label, single-arm Phase 2 trial
  - ≥12 years old; Grade 2-4 SR-aGvHD
  - Ruxolitinib: 5 mg BID
  - N=71 patients

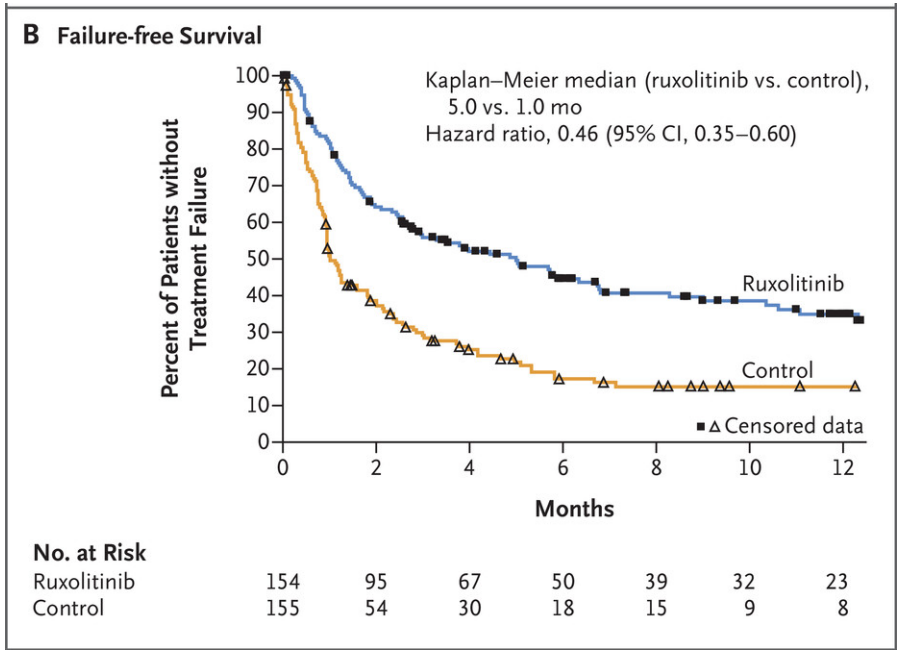
Response at Day 28 by grade of aGvHD				
Response	**Grade 2 (N=23)**	**Grade 3 (N=34)**	**Grade 4 (N=14)**	**All Patients (N=71)**
ORR	19 (82.6)	14 (41.2)	6 (42.9)	39 (54.9)
CR	11 (47.8)	7 (20.6)	1 (7.1)	19 (26.8)
VGPR	4 (17.4)	2 (5.9)	1 (7.1)	7 (9.9)
PR	4 (17.4)	5 (14.7)	4 (28.6)	13 (18.3)

Jagasia M, et al. *Blood.* 2020;135(20):1739-1749.

REACH2

- REACH2: Phase 3: Multicenter, open-label, randomized trial
  - ≥12 years old; Grade 2-4 SR-aGvHD
  - Ruxolitinib: 10 mg BID (N=154) versus BAT (N=155)





BAT, best available therapy

Zeiser R, et al. *N Engl J Med*. 2020;382(19):1800-1810.

Ruxolitinib Refractory aGvHD?

- 45%/38% of patients = no response in REACH1/2

Ruxolitinib Refractory aGvHD Definition
Progression of GvHD compared with baseline after ≥5 to 10 days of treatment (objective increase in stage/grade or new organ involvement)
Lack of improvement in GvHD (PR or better) after at least 14 days of treatment
Loss of response: Objective worsening of GvHD defined by increase in stage, grade, or new organ involvement at any time after initial improvement

Mohty M, et al. *Blood.* 2020;136(17):1903-1906.

Alpha-1 Antitrypsin for SR-aGvHD

- AAT = 52-kDa circulating protease inhibitor

- Mechanism of action:
  - ↓ inflammatory cytokines
  - ↓ $T_{effector}$: T_{reg} ratios
  - ↓ DAMPs
  - ↓ Inhibits TLR activation and NF-kB in DCs

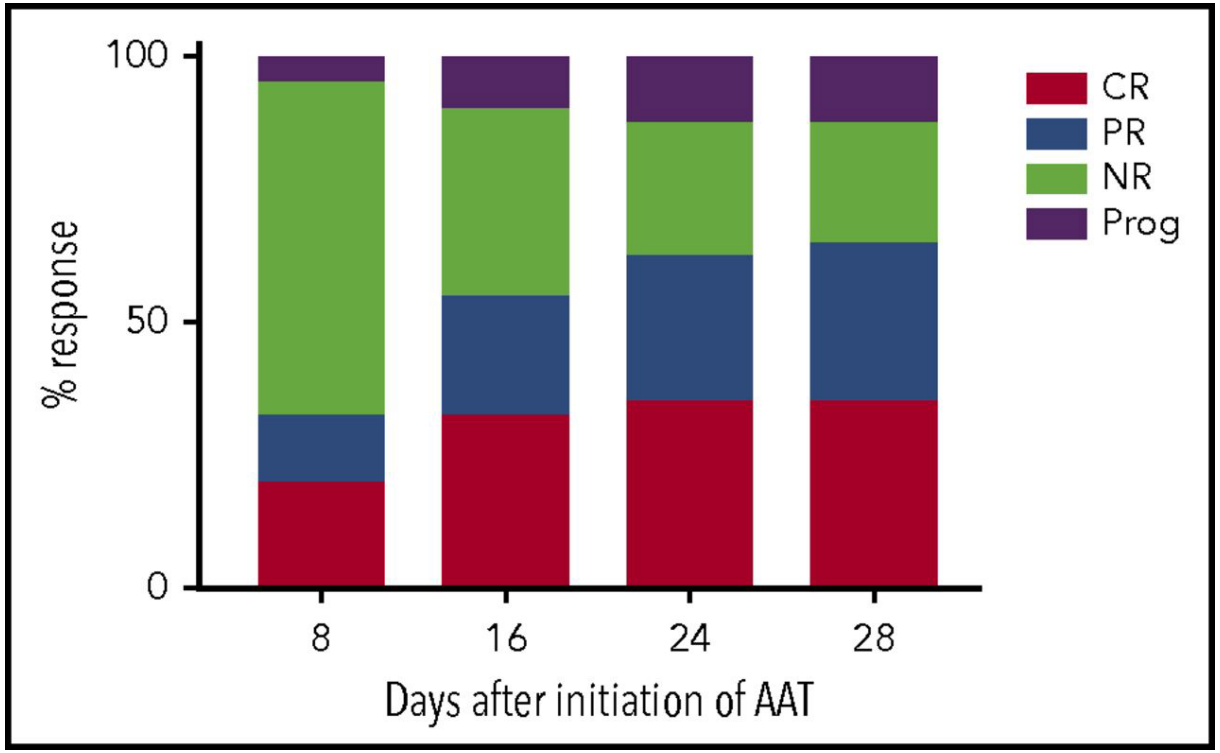
- Administered IV 60 mg/kg/dose twice weekly x 8 doses

AAT, alpha-1 antitrypsin; DAMPS, damage-associated molecular patterns; DCs, dendritic cells; TLR, toll-like receptors

Magenau JM, et al. *Blood.* 2018;131(12):1372-1379.

Alpha-1 Antitrypsin for SR-aGvHD

- Day 28 ORR = 26/40 patients (65%)
  - CR = 14 patients (35%)
  - PR = 12 patients (30%)
- Day 60 ORR = 19/40 patients (47.5%)
  - CR = 14 patients (35%)
  - PR = 19 of 26 initial responders (73%)

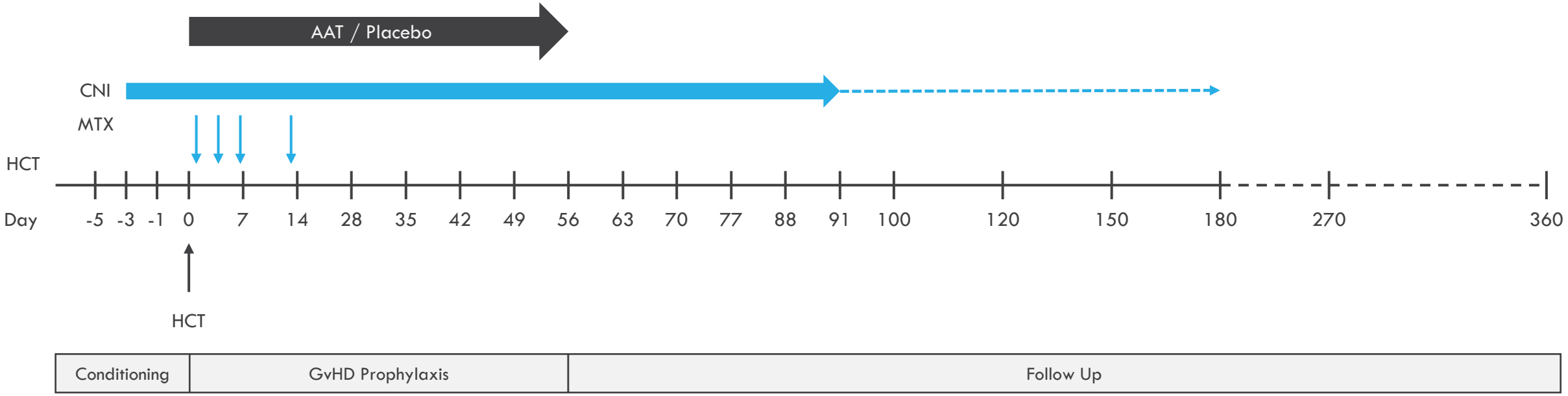


ORR, overall response rate; CR, complete response; PR, partial response; NR, no response; Prog, progression

Magenau JM, et al. *Blood.* 2018;131(12):1372-1379.

AAT – aGvHD Prophylaxis

- A Phase 2/3, Multicenter, randOmized, Double-blind, placebo-controlled, stUdy to evaLuate the safety and efficacy of Alpha-1 AntiTrypsin for the prEvention of graft-versus-host-disease in patients receiving hematopoietic cell transplant (MODULAATE Study)

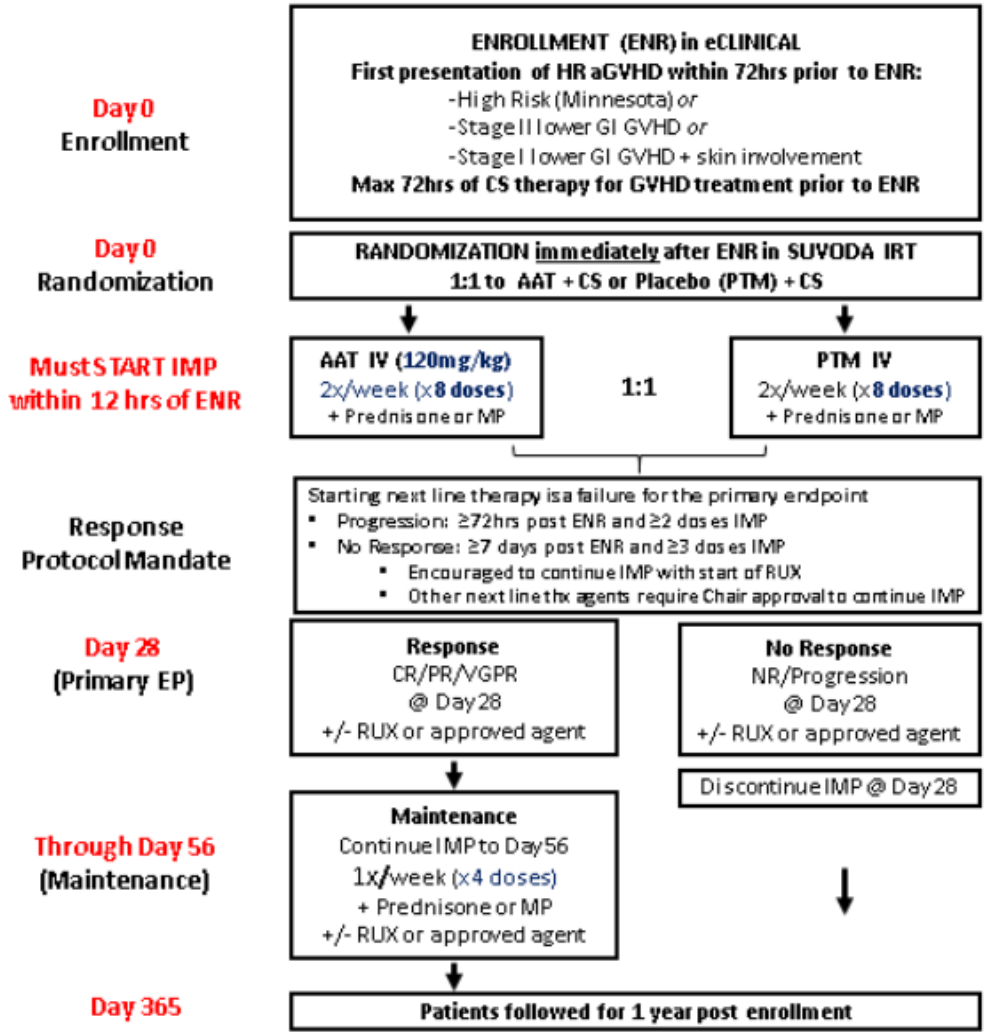


MTX, methotrexate; HCT, hematopoietic stem cell transplant

MODULAATE Study – NCT03805789

AAT for aGvHD (BMT CTN 1705)

- Phase 3, double-blind, placebo controlled
- AAT 120 mg/kg 2x/week + corticosteroids (max 72 hours)
- Primary objective: Compare CR/PR rates at day 28
- Active, not recruiting



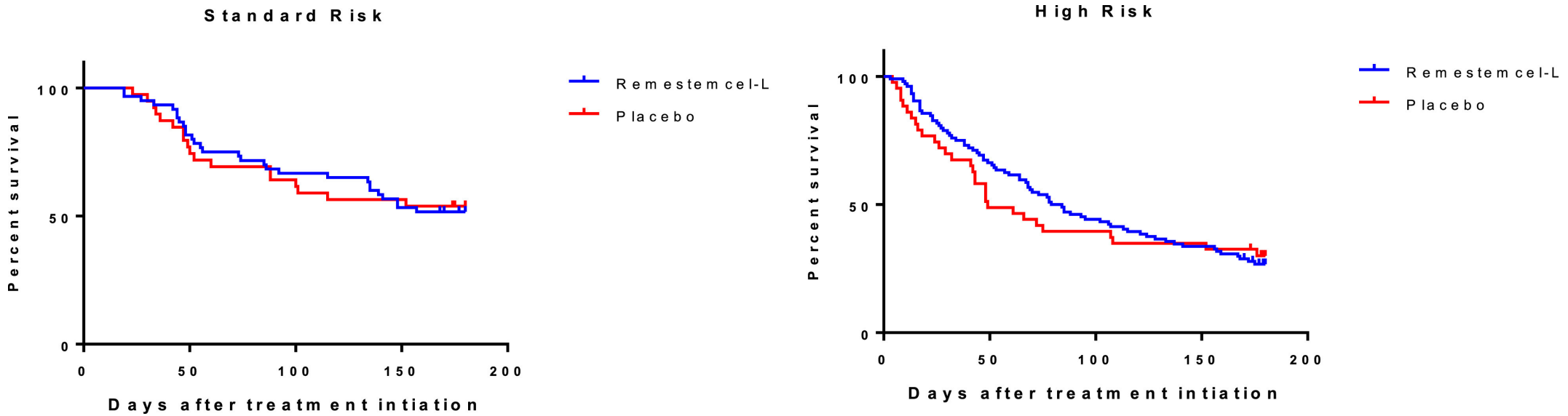
BMT CTN 1705; NCT04167514

Mesenchymal Stromal Cells for SR-aGvHD

- Mesenchymal stromal cells (MSCs) – multipotent, heterogenous, and nonhematopoietic cell population
  - Secrete cytokines and regulatory molecules
  - Promote anti-inflammatory and regenerative effects
  - Repair/replace damages tissue
- Variable success rates for SR-aGvHD
- Well tolerated

Elgaz S, et al. *Transfus Med Hemother.* 2019;46(1):27-34.

Mesenchymal Stromal Cells for SR-aGvHD



All patients, Day 28 ORR: **MSCs 58% vs 54%; *P*=.59**
High-risk GvHD, Day 28 ORR: **MSCs 58% vs 37%; *P*=.03**
Age <18, Day 28 ORR: **MSCs 64% vs 23%; *P*<0.05**
Any liver involvement, Day 28 ORR: **MSCs 55% vs 26%; *P*<0.05**

Kebriaei P, et al. *Biol Blood Marrow Transplant*. 2020;26(5):835-844.

Vedolizumab for SR-aGvHD

- Targets α4β7 integrin expressed on lymphocytes
- Inhibits interaction between α4β7 integrin and MAdCAM-1
- Prevents migration of T cells to GI mucosa
- Variable success for SR-aGvHD
- Dosing varies, 300 to 600 mg Q1-2 weeks

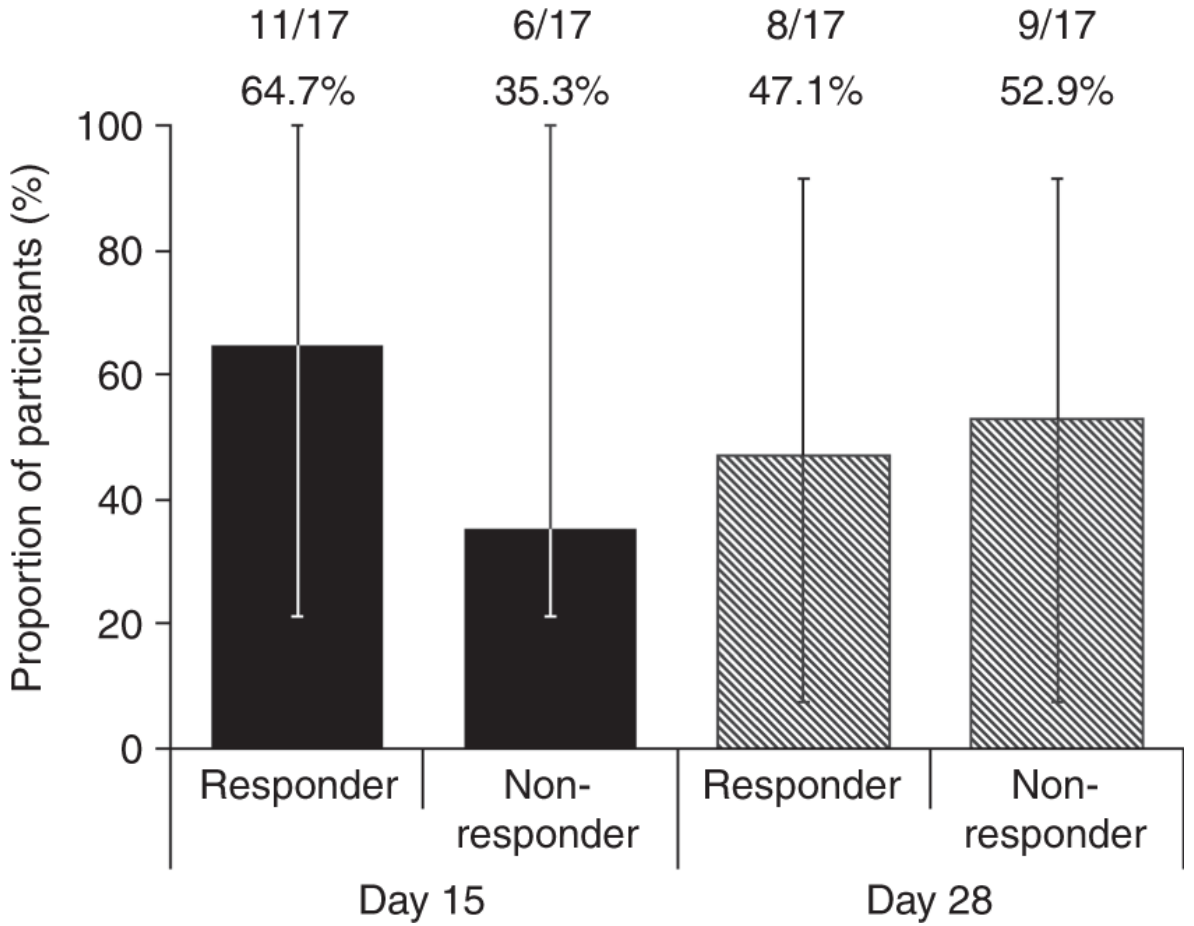
GI, gastrointestinal; MAdCAM-1, mucosal addressin cell-adhesion molecule-1

Fløisand Y, et al. *Bone Marrow Transplant.* 2021;56(10):2477-2488.
Mehta RS, et al. *Transplant Cell Ther.* 2021;27(3):272.

Vedolizumab for SR-aGvHD

- Day 28: 35.3% had OR in all organs involved
  - OR in aGvHD in 64.7% (n=11) at Day 15 and 47.1% (n=8) at Day 28
- CR = 11.8% (n=2) in all organs at Day 15
  - CR = 5.8% (n=1) at Day 28
  - CR = 23.5% (n=4) at Day 43

Note: Study stopped accruing early due to premature discontinuation of study drug and observed mortality



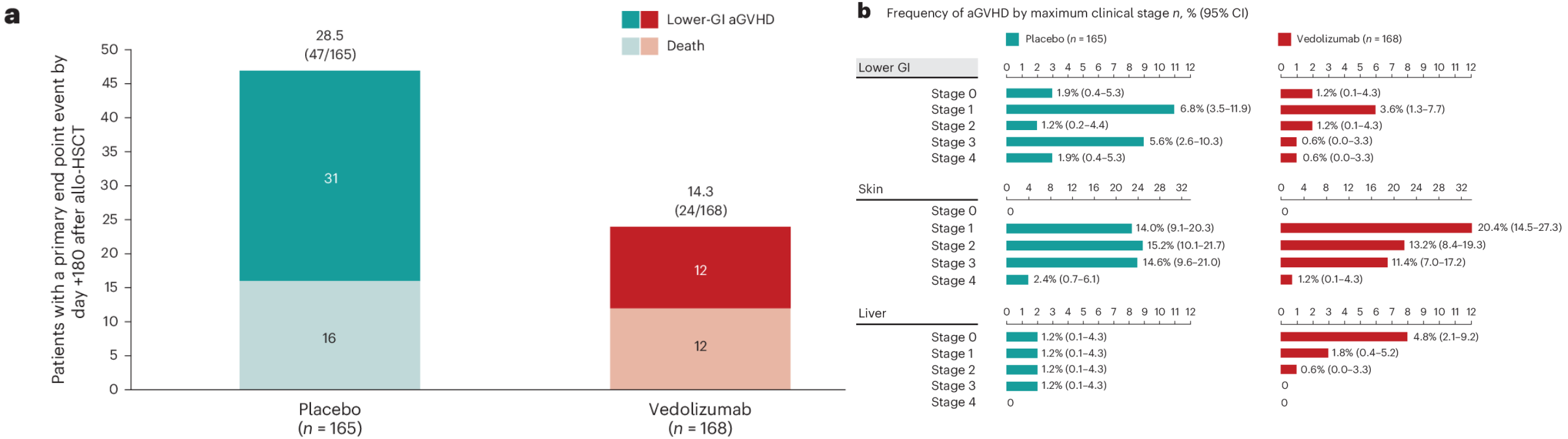
Fløisand Y, et al. *Bone Marrow Transplant*. 2021;56(10):2477-2488.

Vedolizumab aGvHD Prophylaxis

- Phase 3, randomized, placebo controlled
- Vedolizumab 300 mg IV on D-1, +13, +41, +69, +97, +125, +153
- Added to CNI + MTX or MMF
  - ATG permitted (capped at 25% of total enrollment)
- Age ≥12, weight ≥30 kg, 8/8 or 7/8 HLA-matched unrelated PB or BM

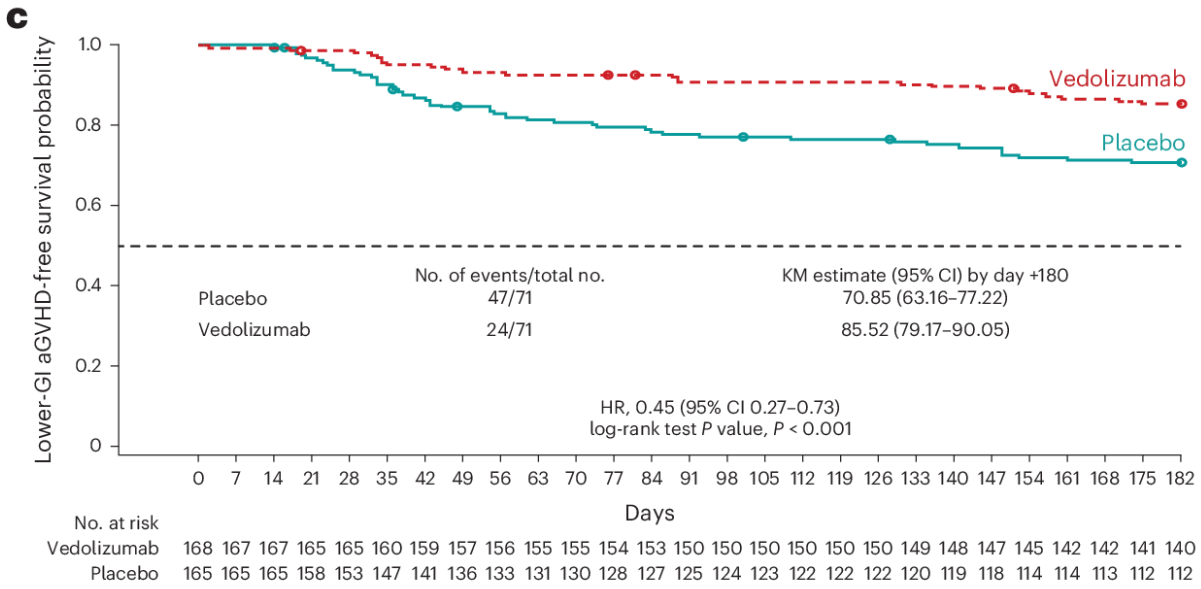
Chen Y, et al. *Nat Med*. 2024;30(8):2277-2287.

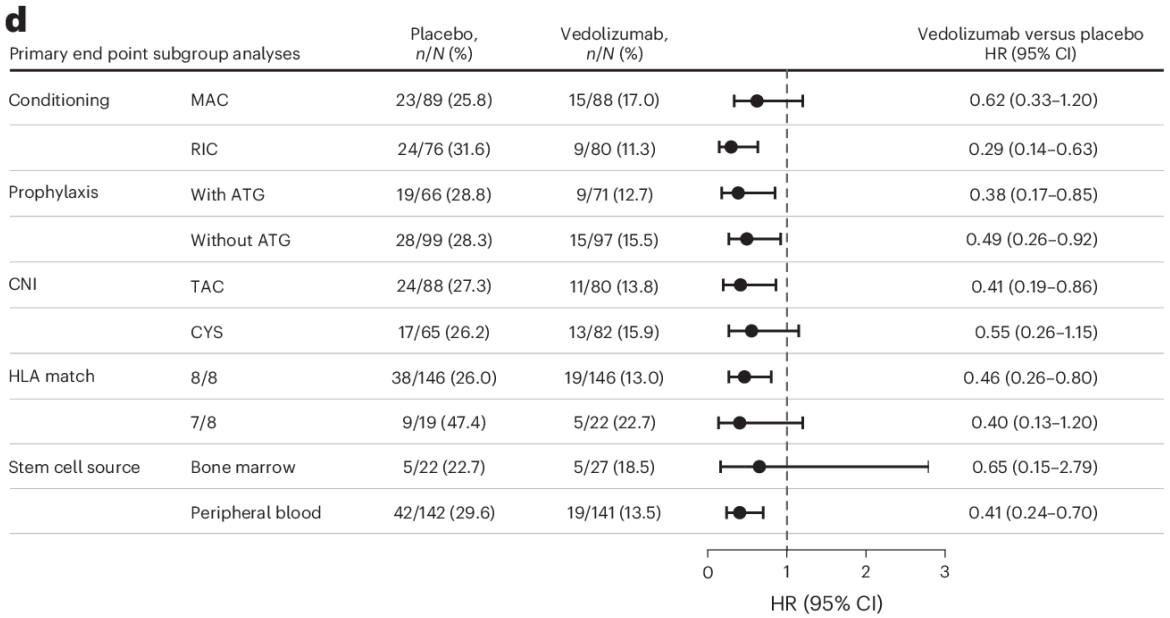
Vedolizumab aGvHD Prophylaxis



Chen Y, et al. *Nat Med.* 2024;30(8):2277-2287.

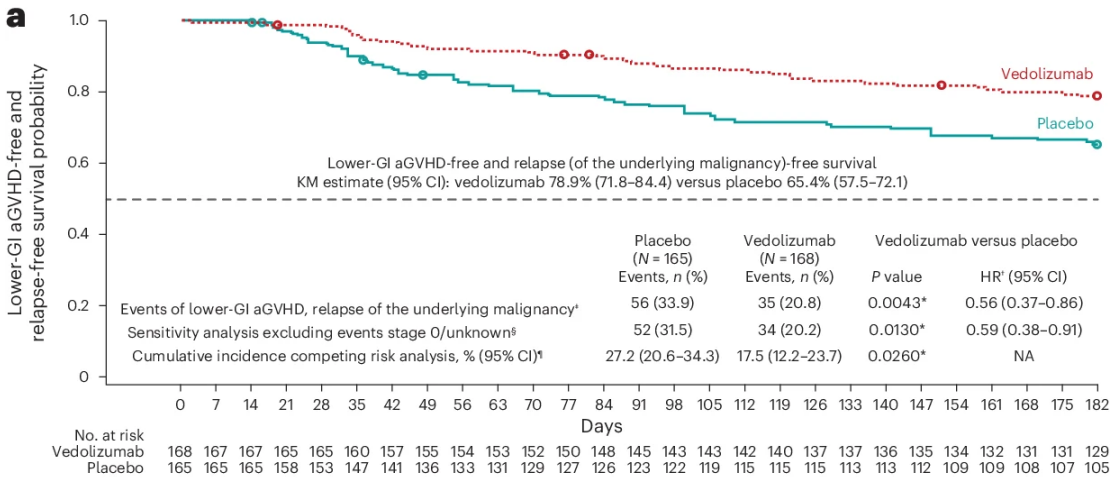
Vedolizumab aGvHD Prophylaxis

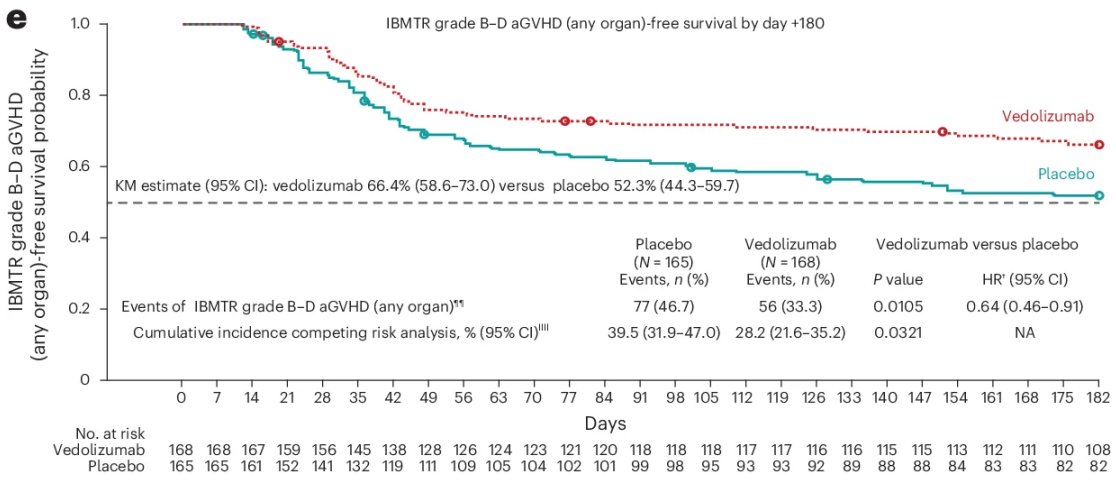




Chen Y, et al. *Nat Med.* 2024;30(8):2277-2287.

Vedolizumab aGvHD Prophylaxis





Chen Y, et al. *Nat Med.* 2024;30(8):2277-2287.

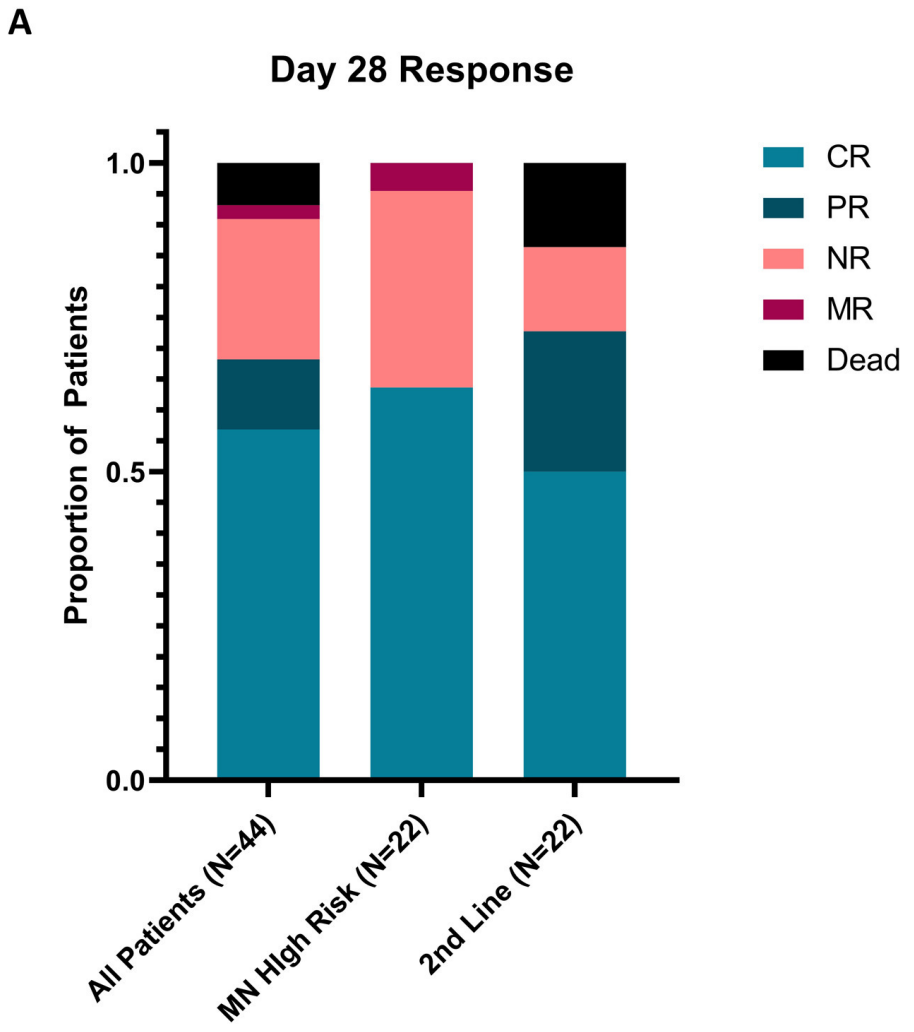
Beta-hCG for SR-aGvHD

- Impaired healing of damaged tissues = poor aGvHD outcomes
- Human chorionic gonadotropin (hCG) = epidermal growth factor
- Promote resolution of tissue damage in aGvHD
- Promotes T_{reg} expansion
- 2000 to 5000 units/m^2 of uhCG/EGF SQ every other day

Holtan S, et al. *Transplant Cell Ther.* 2023;29(8):509.
Holtan S, et al. *Blood Adv.* 2020;4(7):1284-1295.

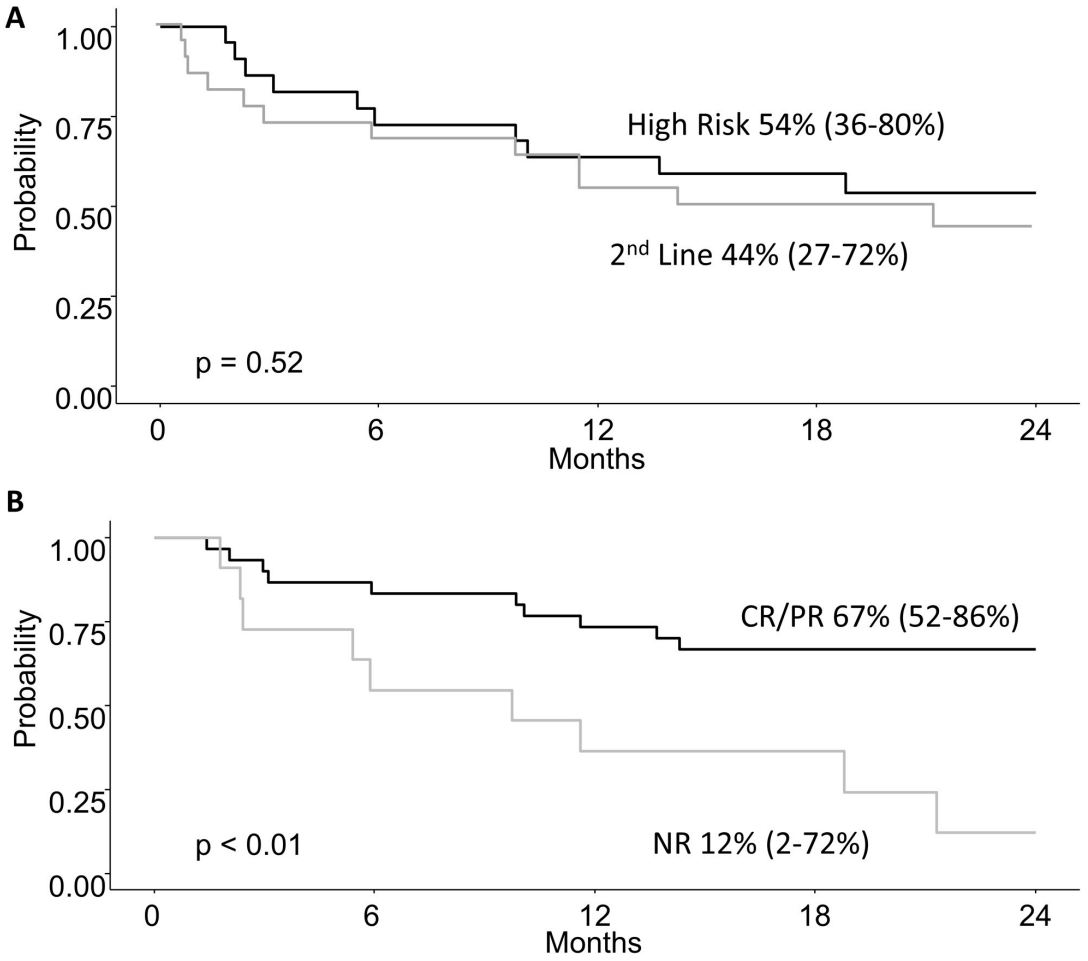
Beta-hCG for SR-aGvHD (NCT02525029)

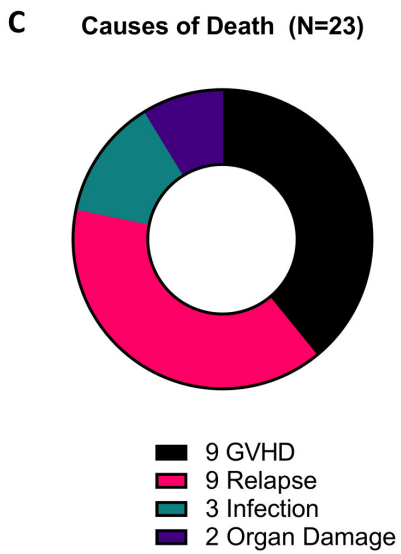
- Day 28 ORR = 68%
  (57% CR; 11% PR)
- MN high-risk ORR = 64% (all CRs)
  - N=22
- 2nd line therapy ORR = 73%
  (50% CR; 23% PR)
  - N=22



Holtan S, et al. *Transplant Cell Ther*. 2023;29(8):509.

Beta-hCG for SR-aGvHD (NCT02525029)





Holtan S, et al. *Transplant Cell Ther*. 2023;29(8):509.

Lithium for Acute GI-GvHD

- Immunosuppression targets systemic GvHD
  - Fails to resolve mucosal injury of gut

- Lithium promotes intestinal epithelial repair
  - Inhibits GSK3
  - Promotes β-cantenin-mediated transcription
  - Activates Wnt pathway

- Epithelial stem cell replication
- Crypt genesis/proliferation

GI-GvHD, gastrointestinal graft-versus-host disease; GSK3, glycogen synthase kinase-3

Martin PJ. *Blood.* 2020;135(19):1630-1638.
Steinback G, et al. *PLoS One.* 2017;12(8):e0183284.

Lithium for Acute GI-GvHD

- Lithium carbonate ER 450 mg
  - Target trough 0.5 - 1.0 mmol/L
- All patients had severe GI-GvHD
- 10/20 = CR; 8 survived >1 year
- Early lithium (<3 days) improved response

Characteristic	Survivors (N = 8)	Nonsurvivors (N = 12)
lithium started ≤ 3 days after endoscopic diagnosis of denuded mucosa, N (%)	8 (100)	4 (33)
Salvage therapy for refractory GVHD ≥ 7 days before lithium, N (%)	0 (0)	7 (58)
lithium started ≤ 3 days after endoscopy and no salvage therapy for GVHD ≥ 7 days before lithium, N (%)	8 (100)	2 (17)
lithium started ≤ 3 days after endoscopy and given for ≥ 19 days, N (%)	8 (100)	1 (8)

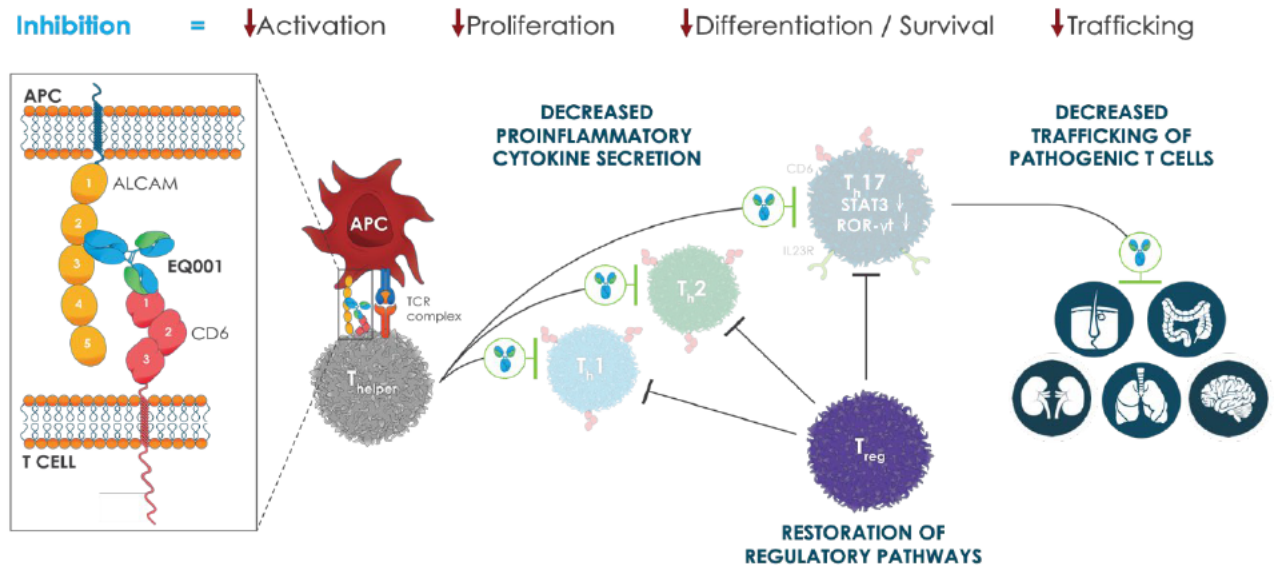
https://doi.org/10.1371/journal.pone.0183284.t004

Steinback G, et al. *PLoS One.* 2017;12(8):e0183284.

Itolizumab aGvHD Treatment (EQ-100-02)

- Itolizumab targets CD6 on T cells
  - Costimulatory membrane glycoprotein
  - Blocks binding of CD6 to ALCAM
- Age ≥12, weight ≥40 kg, Grade III-IV aGvHD or Grade II LGI

Figure 1: Blockade of CD6 Co-stimulation by Itolizumab Inhibits Optimal T-Cell Activation and Attenuates a Proinflammatory Response



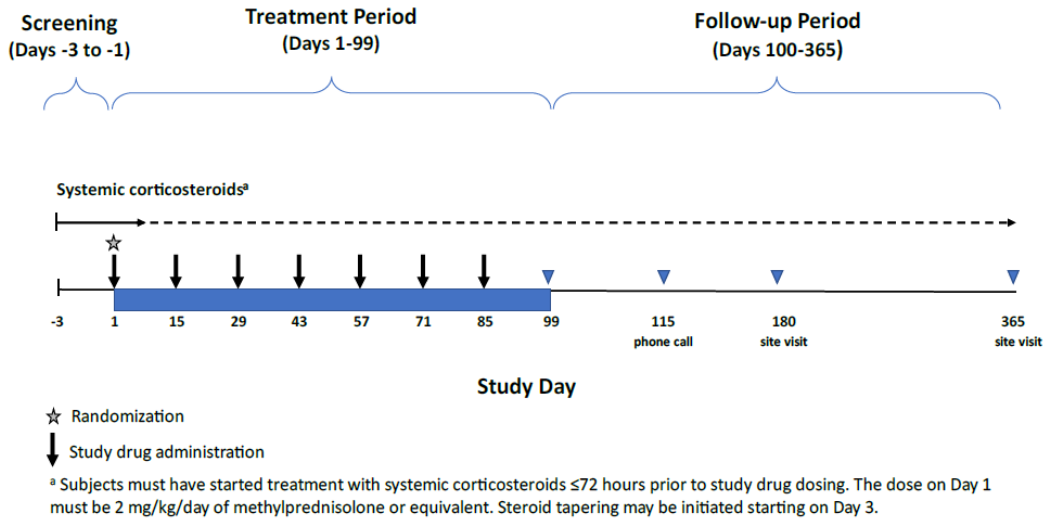
ALCAM, activated leukocyte cell adhesion molecule

Protocol Number: EQ-100-02, Version 6 Equillium, Inc.
Phase 3 Study of Itolizumab as initial therapy for aGvHD.

Itolizumab aGvHD Treatment (EQ-100-02)

- Primary objective:
  Efficacy of itolizumab versus placebo in combination with steroids

- Itolizumab 1.6 mg/kg IV load, 0.8 mg/kg/dose every 2 weeks



Protocol Number: EQ-100-02, Version 6 Equillium, Inc.
Phase 3 Study of Itolizumab as initial therapy for aGvHD.

CARE TEAM FORUM®

Interprofessional Care

Panel Discussion

Meet Paul

20-year-old Male

Homozygous SS Sickle Cell Disease

Pain Crises

Multiple in early childhood

2017 x 3 admissions

Acute Chest Syndrome

2001, 2015, 2017

Infection

EBV pharyngitis (2004)

Strep Pneumococcal Bacteremia (2004)

Neurologic Complications

Silent infarct (2010)

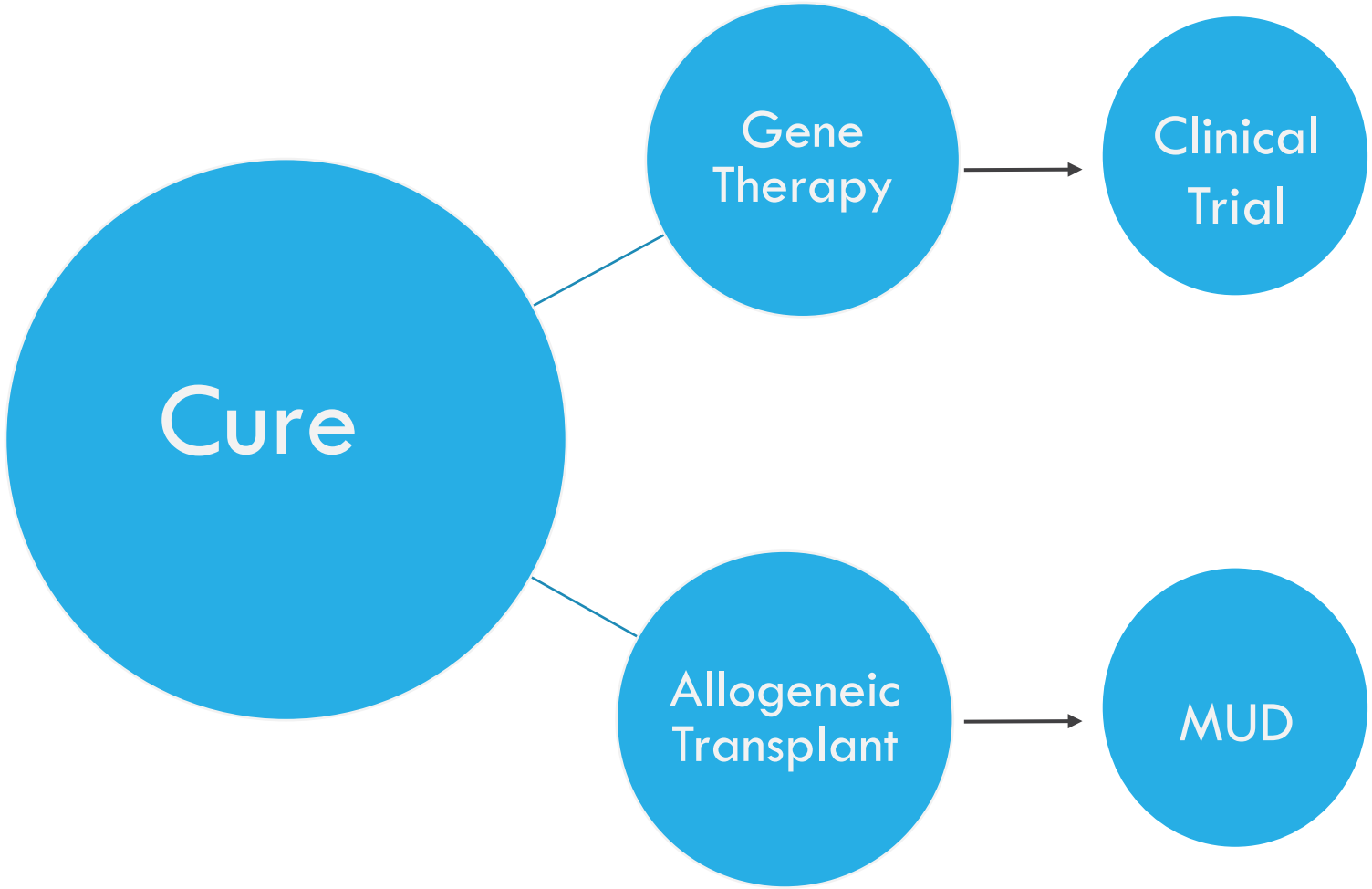
CV & Renal Complications

Tricuspid regurgitation, PAC

Proteinuria

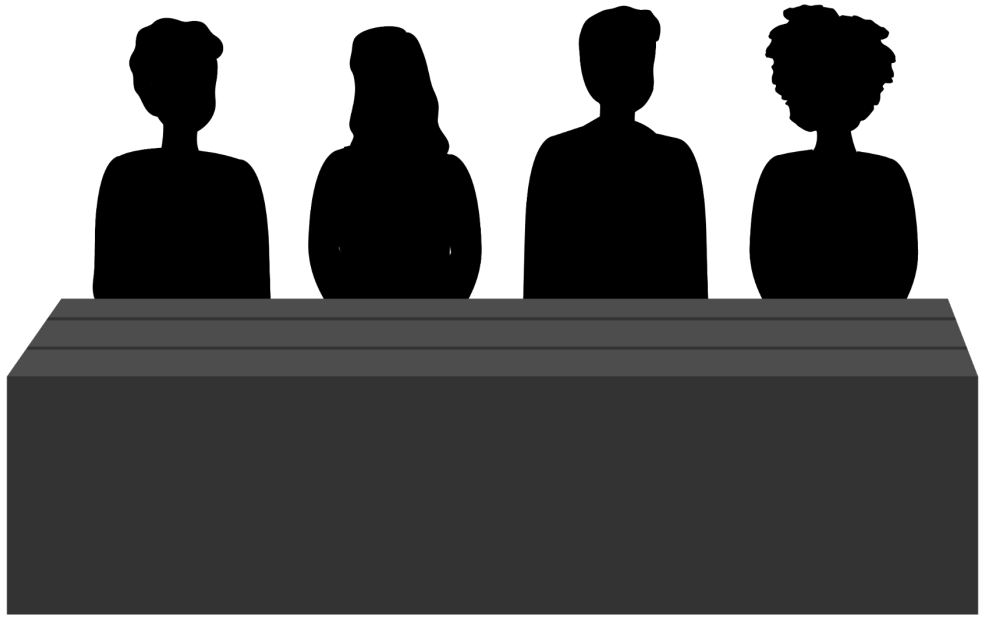
Hydroxyurea Maintanence Therapy (2002-)

Treatment Options



Discussion

- How did you make the decision of BMT versus gene therapy?
- What kind of pre-BMT education do you recall?
- Which transplant related complications do you recall hearing about in your pretransplant consultation?



Initial Hospital Course

March 25, 2019

Admission

Pain crisis with line placement

Conditioning: FluBuThymo per CTN 1503

Partial exchange transfusions x 2

April 5, 2019

8/8 matched, unrelated donor bone marrow transplant

Cell Dose: 2.3 million CD34/kg

April 18, 2019

Neutrophil Engraftment

Discharge (Day +31)

April 26, 2019

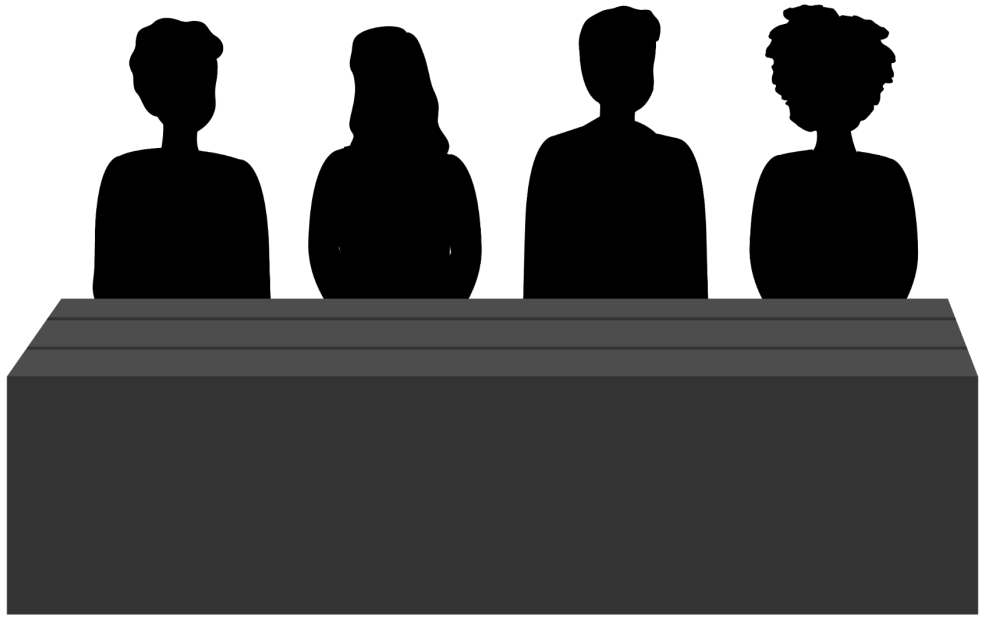
Hospital Course Complications

N/V/D, mucositis, febrile neutropenia, neuropathic pain

GvHD Prophylaxis: Tacrolimus, Methotrexate

Discussion

- Was there anything significant that you recall about your initial hospitalization?
- Can you describe your family and support system?
- What role did the team members play in your care?



Post-Transplant Course

Day +40

Grade 1 Skin GvHD

Topical Steroid

Day +63

aGvHD score 0

Steroid weaned

Day +75

Discharged off CNI. Steroids at 1.25 mg/kg/day

Continue ECP for prior skin GvHD

Basiliximab given for GvHD prophy

Day +84 (no aGvHD)

Steroid weaned to 1mg/kg/day

ECP 3x/week

Basiliximab weekly

Day +97

Steroid weaned to 0.4 mg/k/day

ECP weaned to twice weekly

Admission (Day +56 to 61)

Stage 2 Skin

Steroid Pulse (2 mg/kg)

CNI changed d/t Mag Wasting

Day +70

Presented to the ED with severe headache

Neuro exam unremarkable

BP: 182/129

CT: No acute process

MRI: PRES

CSA level therapeutic

Day +78

Letermovir initiated for low level CMV

Day +89

Steroid weaned to 0.7 mg/kg/day

Post-Transplant Course

Day +104

Steroid weaned to 0.25 mg/kg/day

ECP twice weekly

Basiliximab weekly

Day +115 (Admission)

Two-day history of acute diarrhea, cramping abdominal pain, nausea

GPAN, CMV PCR negative

GI consulted; endoscopy scheduled for the next day

Day +117 (Endoscopy)

4 L stool output

Steroids (1 mg/kg/day) initiated post procedure

Day +120

3 to 5 L stool output

Budesonide

ECP & basiliximab ongoing

PCA initiated for pain control

Day +123

Steroids increased to 2 mg/kg/day

Day +129

Stage IV GI GvHD

Infliximab initiated

Day +135

Abdominal pain remains uncontrolled; Ketamine PCA required

Dysuria, hematuria; found to be BK positive.

Day +137

EBV Viremia; Rituximab given

Post-Transplant Course

Day +140

Methadone initiated for pain control

Day + 145

Current therapies: Steroid (systemic & enteral), ECP, Infliximab, basiliximab

Stool volumes ~1 L/day but refractory pain ongoing

Mesenchymal stem cells for compassionate use applied for and approved

Day + 146

Repeat EGD & colonoscopy given degree of pain despite improving stool volumes.

- Regenerating epithelial tissue without crypt apoptosis or lymphocytic infiltrate
- Viral staining negative

Day +151

RRT called for pupil changes, dizziness, altered mental status

- Opioid related

Day +168

Ruxolitinib initiated

Day +175

Mesenchymal stem cell dose #1/8 (compassionate use)

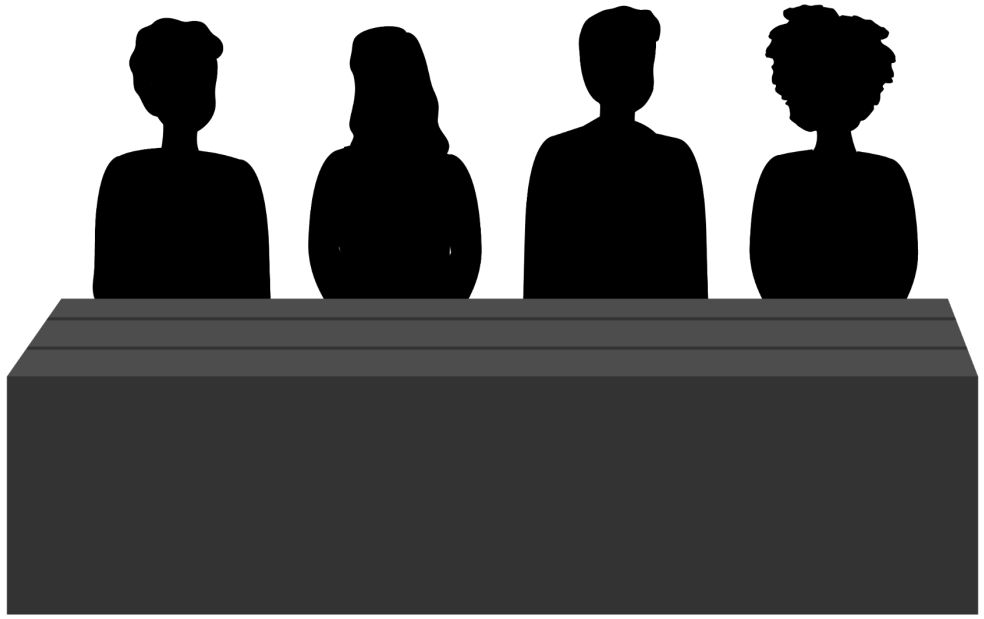
Day +200

DISCHARGED

Systemic steroid, topical steroid, ECP, infliximab, basiliximab, ruxolitinib, mesenchymal stem cells

Discussion

- As an African-American patient, did you hear the team talk about how your skin GvHD may have been easier or harder to identify and treat? If so, please describe your experience as a patient?
- Please describe your fears as you were experiencing steroid refractory GvHD?
- What do you think got you through?
- What were some of the barriers or limitations to your care? Insurance?

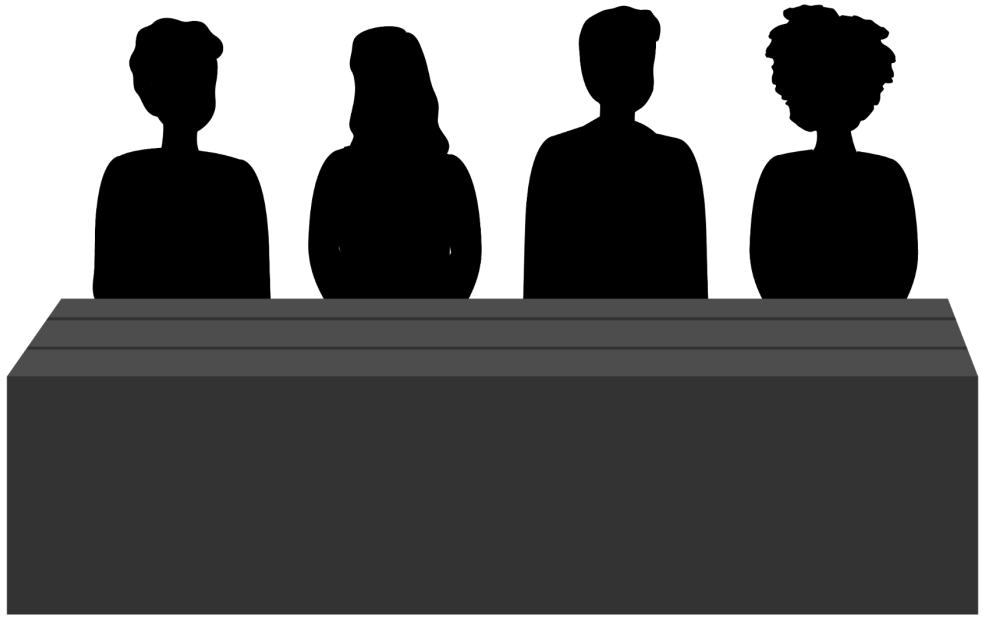



UNIVERSITY OF MICHIGAN
MICHIGAN MEDICINE
PAUL CAMPBELL BSN
NURSE

Paul 2024

Discussion

- Paul, can you share how your experience has influenced the care you provide for BMT patients, as a floor nurse on the same Pediatric BMT Unit that you received your transplant?
- Can you describe what your survivorship/long-term follow-up care currently looks like?
- If you could do this again, would you have chosen BMT versus gene therapy?



Long-term Follow-up

- 5 years post-transplant
- Hemoglobin S: 0%
- Chimerism: 100% donor CD3+ and CD33+
- No evidence of active cGvHD
- Organ function
  - Nephrology: Proteinuria; followed by nephrology
  - Cardiac: Normal ECHO
  - Pulmonary: Restrictive pattern on PFTs
  - Osteopenia noted in femoral neck
  - Endocrine function normal