RAMBAM
Health Care Campus

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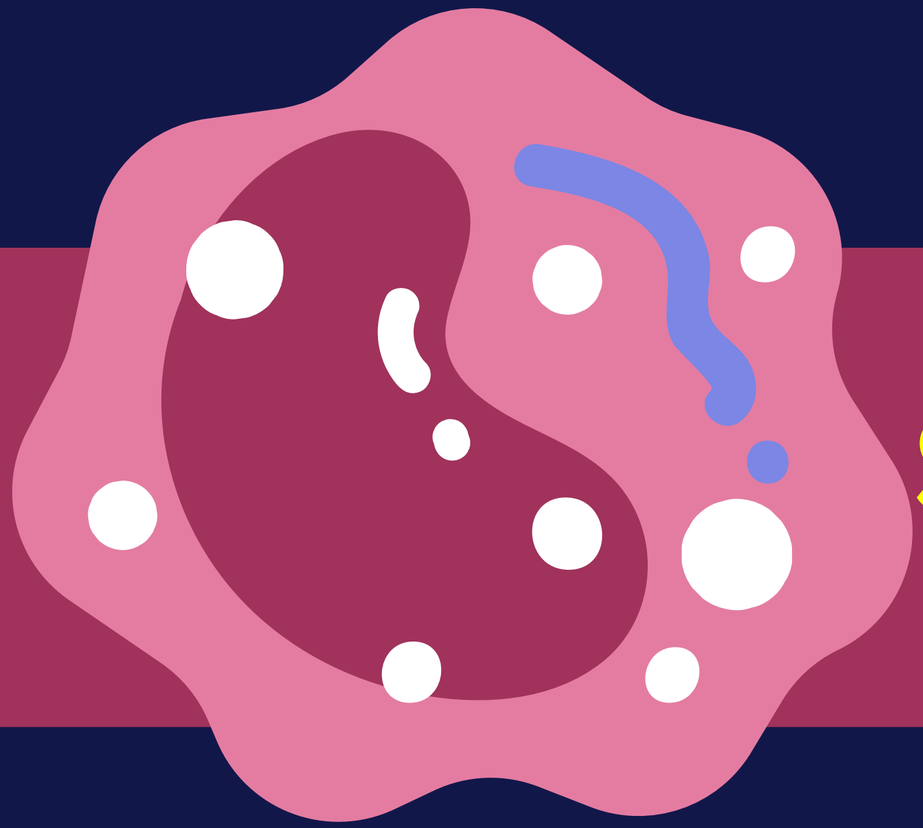
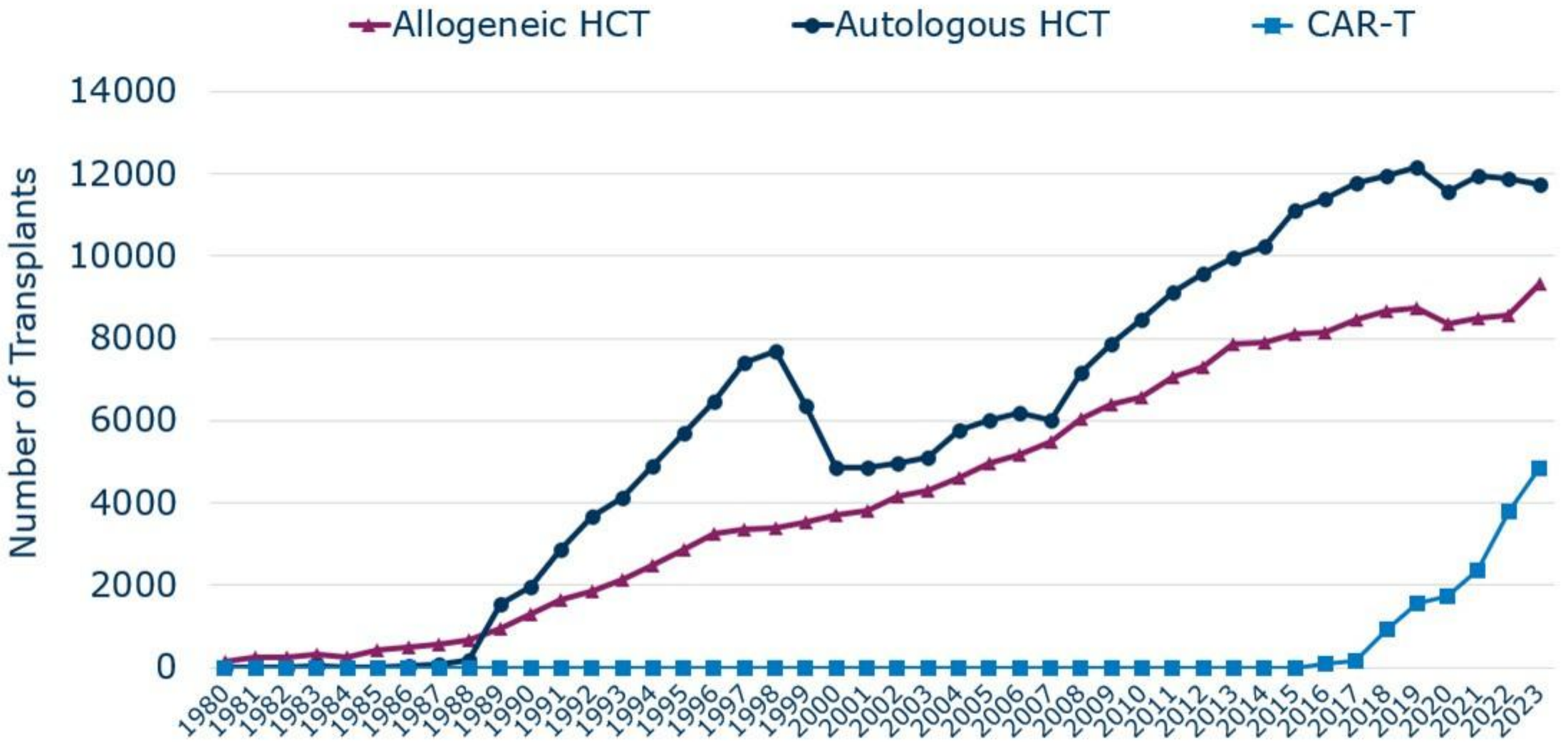


Stem Cell Complications
Fellows -11.25

Tsila Zuckerman
Rambam Health Care Campus

Number of 1st Cellular Therapies Reported to CIBMTR in the US



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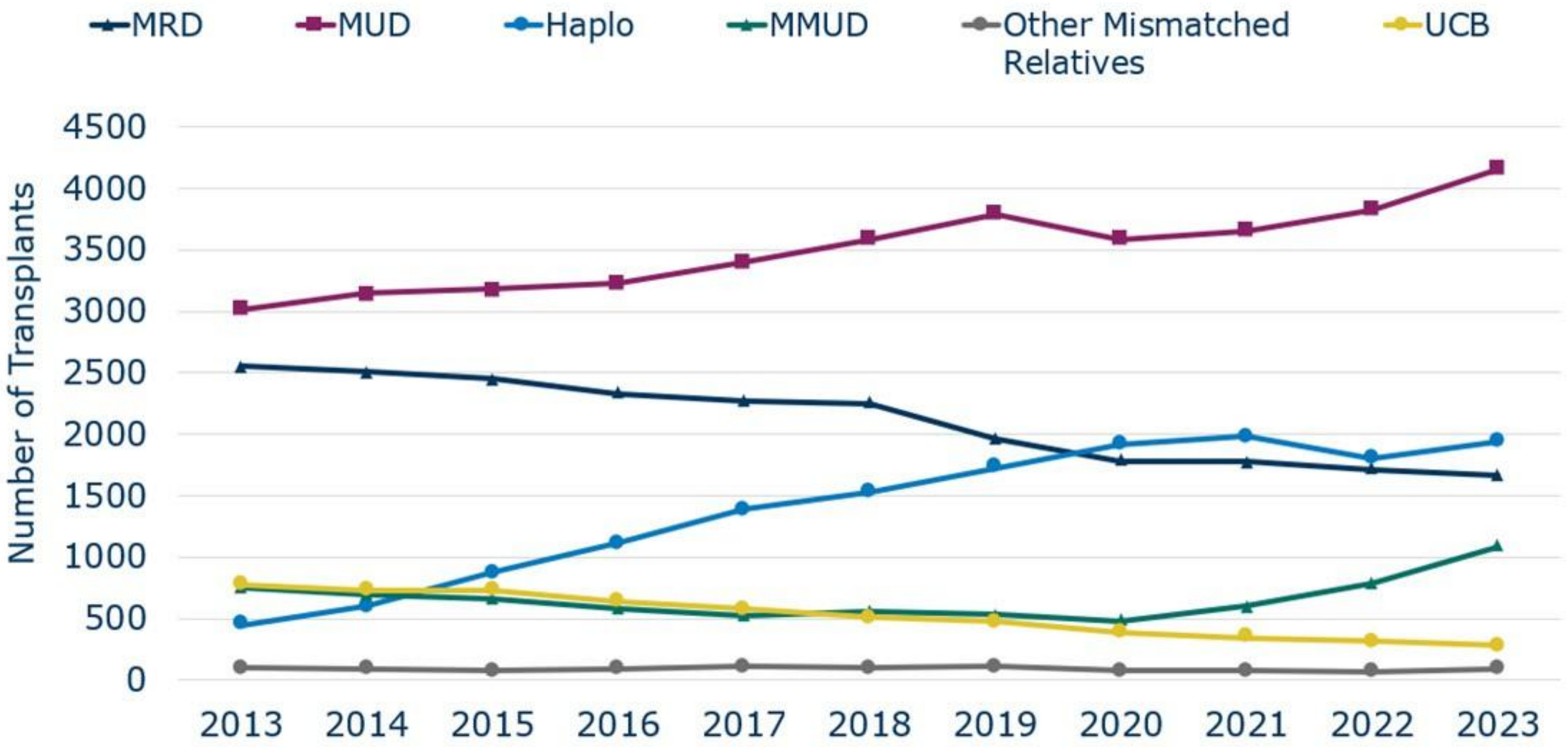
Number of Allogeneic HCTs in the US by Donor Type



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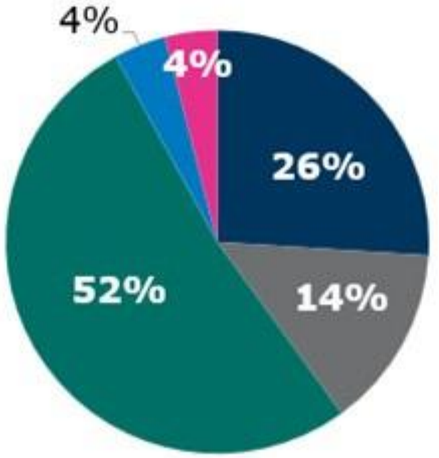
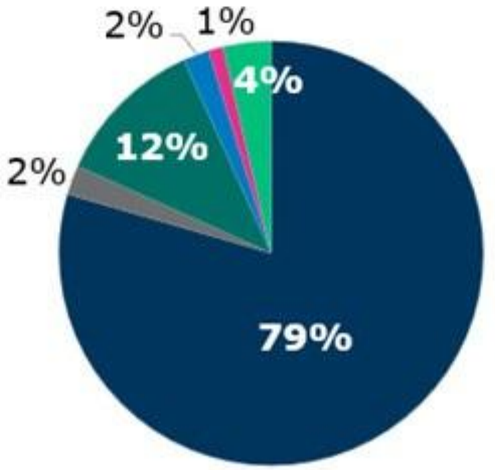
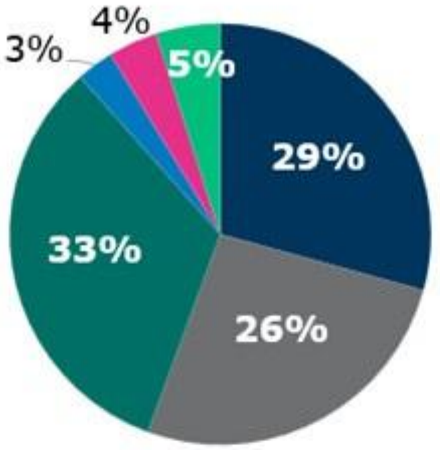
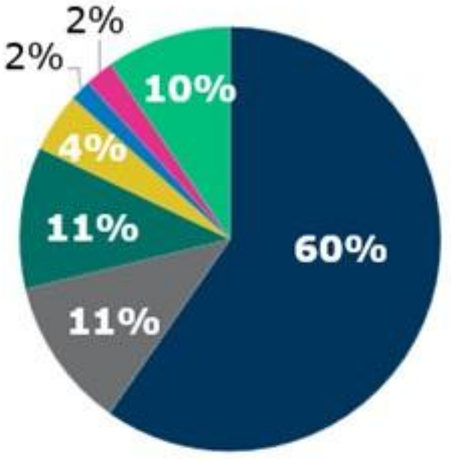
Abbreviations: MRD, matched related donor; MUD, matched unrelated donor; Haplo, ≥2 HLA antigen mismatch; MMUD, mismatched unrelated donor ≤ 7/8 HLA allele match; UCB, umbilical cord blood

Causes of Death after Autologous HCTs in the US, 2019-2023

	Died within 100 days post-transplant	Died at or beyond 100 days post-transplant*
Age <18 years Total transplants = 2545	 n=50	 n=358
Age ≥18 years Total transplants = 56717	 n=774	 n=5847

- Primary disease
- Organ failure
- Hemorrhage
- Graft rejection
- GVHD
- Infection
- Malignancy subsequent to HCT
- Other
- Not reported

*Data reflects 10-year mortality.

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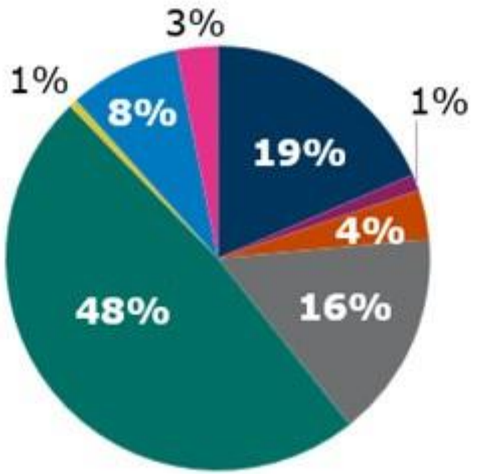
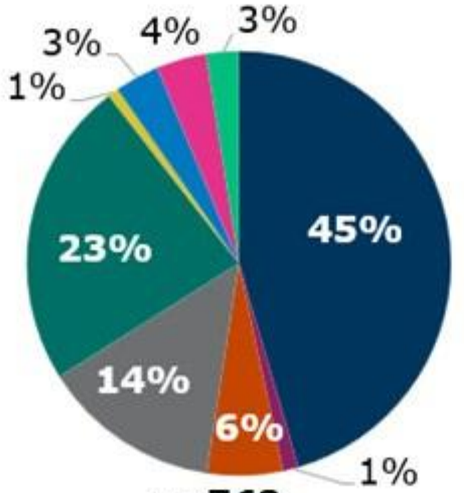
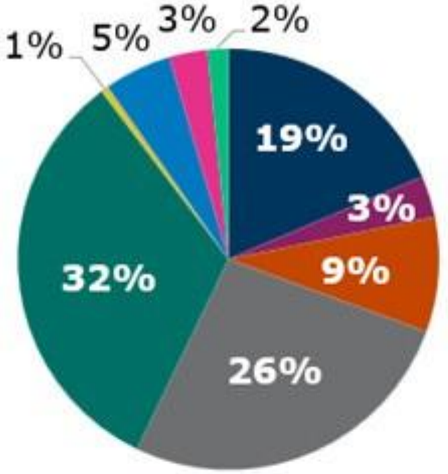
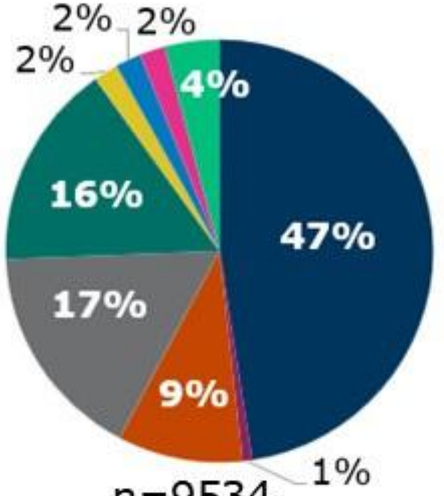
Causes of Death after Allogeneic HCTs in the US, 2019-2023

	Died within 100 days post-transplant	Died at or beyond 100 days post-transplant*
Age <18 years Total transplants = 6264	 n=318	 n=763
Age ≥18 years Total transplants = 36710	 n=3007	 n=9534

- Primary disease
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- Other
- Not reported

*Data reflects 10-year mortality.

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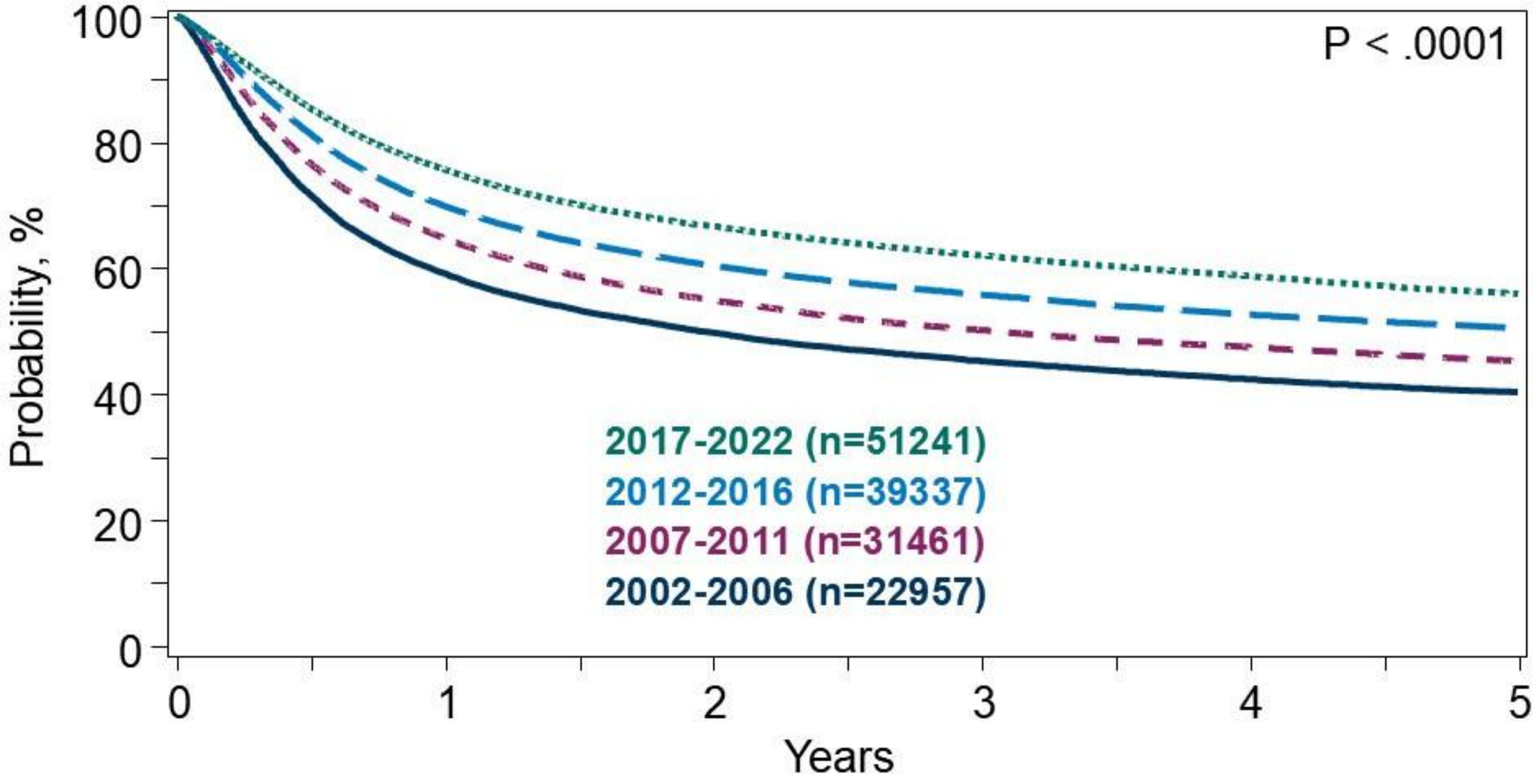
Trends in Survival after Allogeneic HCTs, in the US, 2002-2022



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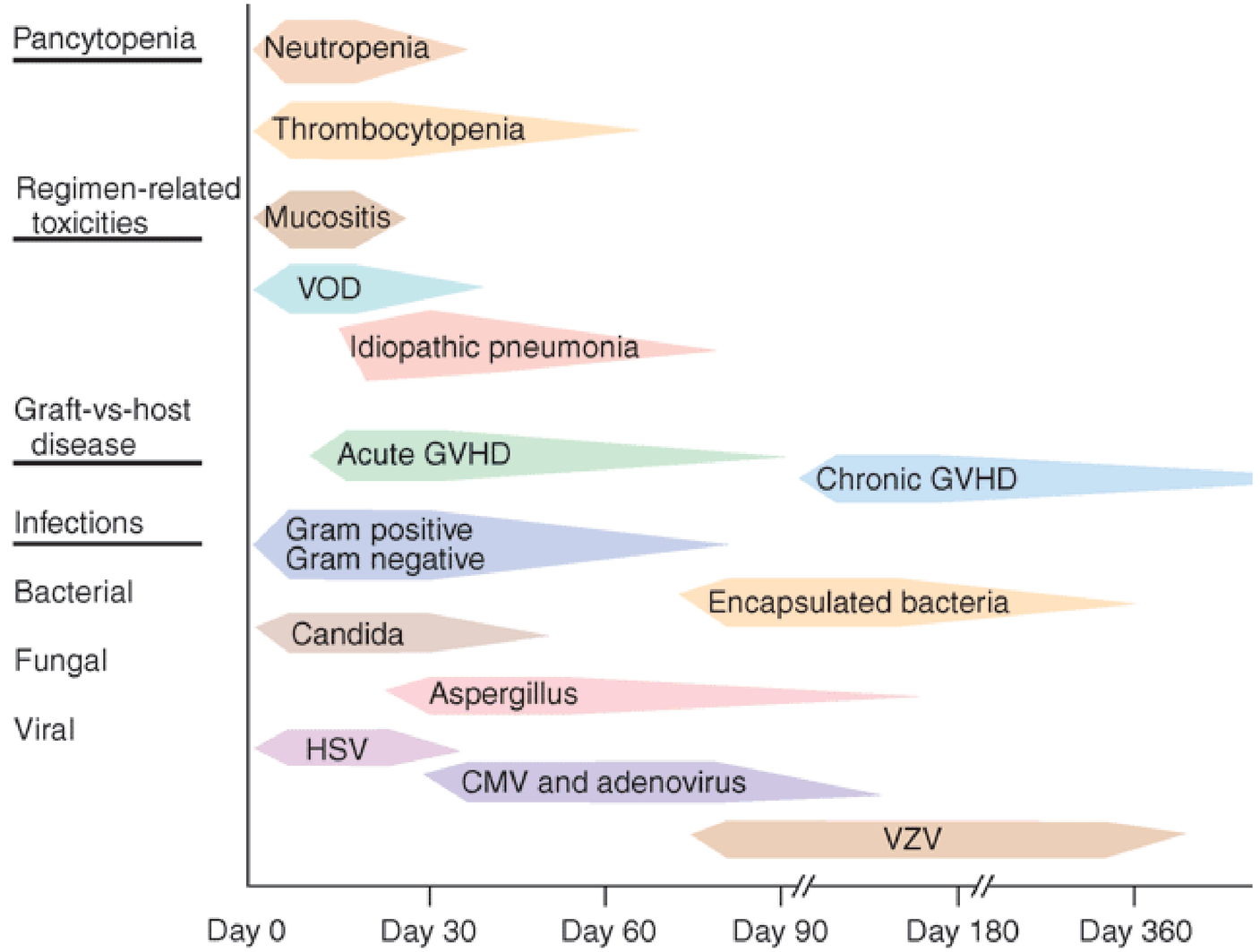
Transplant Complications on a Time Scale

- Pre-engraftment period (from the start of the conditioning regimen to neutrophil recovery).
- Early post-engraftment period (from neutrophil recovery to post-transplantation day 100).
- Late post-engraftment period (day 100 and beyond).



Pre Engraftment Complications

- Pancytopenia.
- Gastrointestinal toxicities.(mucositis ,nausea, vomiting)
- Hemorrhagic Cystitis.(Therapy related/Viral related (BK ,adeno))
- Organ dysfunction.
- Endothelial Damage Syndrome .
- Infections related to neutropenia :gram-positive and gram-negative bacteria, herpes simplex virus, candidiasis, and invasive aspergillosis

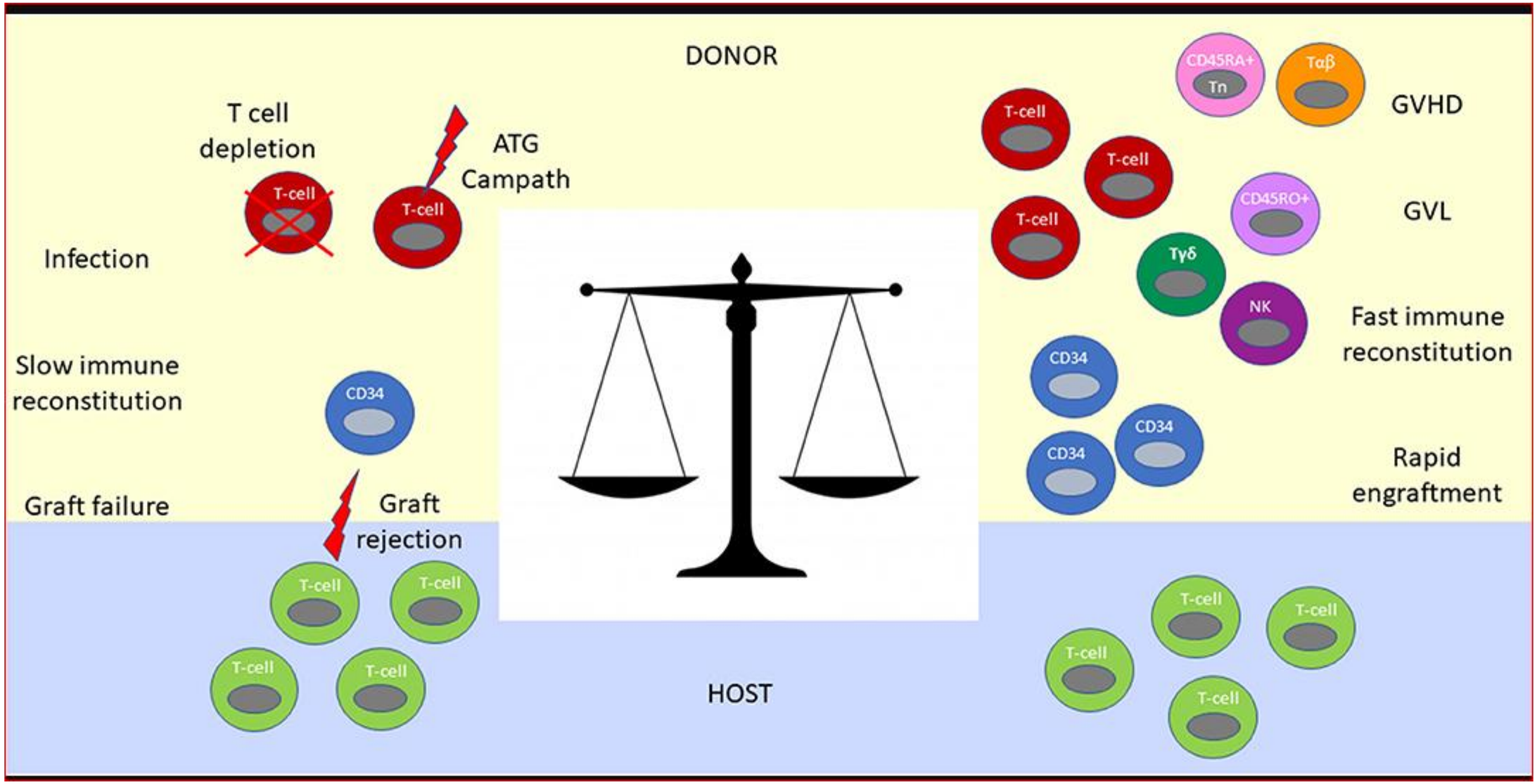
Early Post Engraftment

- Graft failure. Primary / Secondary.
- ABO MM complications.
- Acute GVHD.
- Impaired Immunity . Risk of opportunistic infections (*PCP*,CMV ,RSV, Influenza ,adeno, Aspergillus).

Late Post Engraftment

- Chronic GVHD
- Impaired immunity
- Cardiovascular disease
- Metabolic disorders including diabetes, dyslipidemia.
- Hypothyroidism
- Osteoporosis
- Secondary malignancies
- Gonadal and reproductive dysfunction
- Neuropsychiatric disorders

Graft Function–Graft Failure



Graft Function–Graft Failure

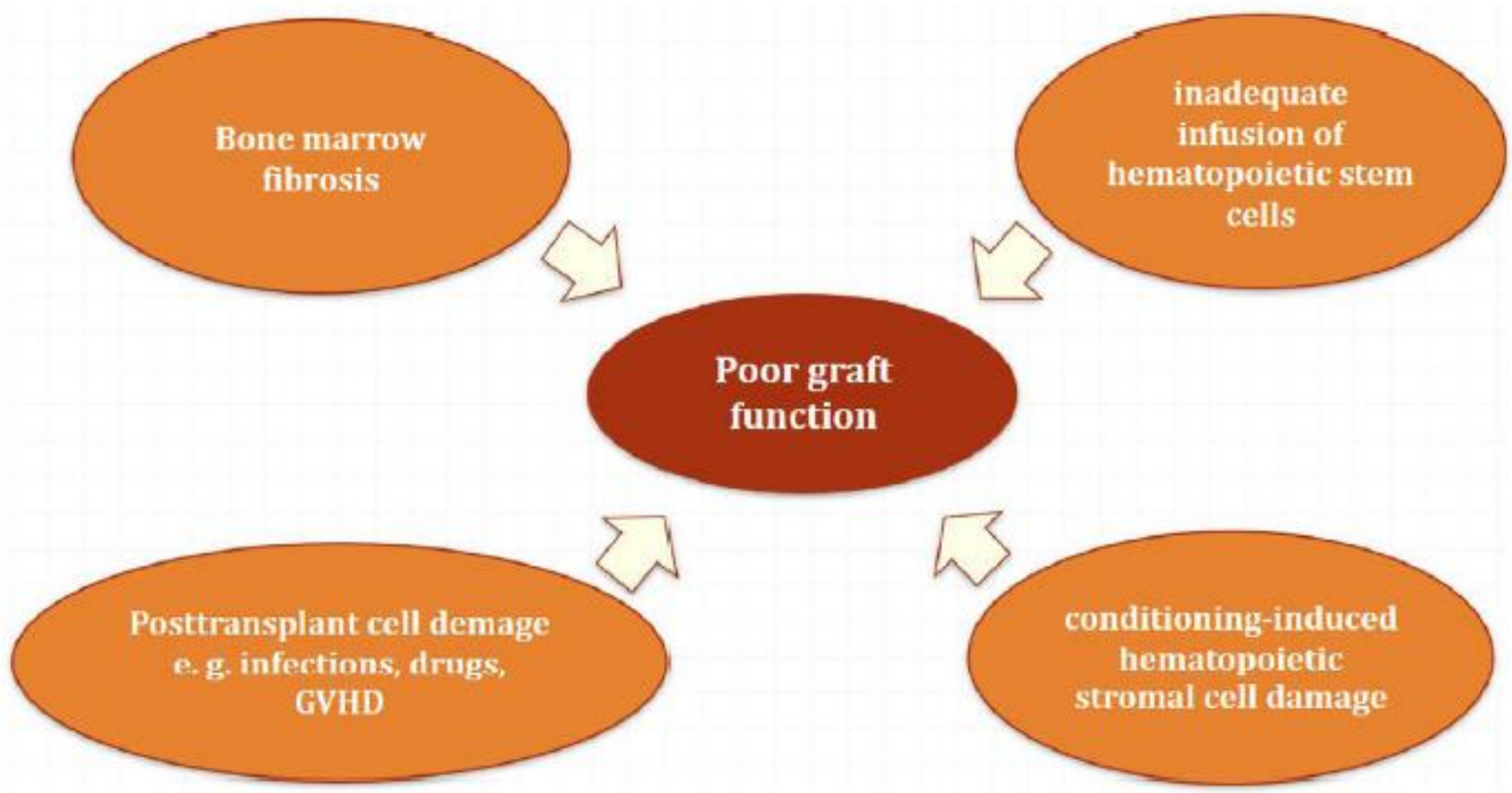


Fig. 2. Mechanisms of Poor Graft Function in allo-HSCT.

Ozdemir. ZN .Transfusion and Apheresis Science, 2018-04-01, Volume 57, Issue 2, Pages 163-167

Graft failure-definitions

- **GF**: lack of donor HSCT engraftment
- **Primary GF** (in MAC SCT) : Failure to achieve a threshold of ANC 0.5x109/L by day 28 with associated cytopenia and absence of initial donor engraftment
- IN NMA SCT: the above by day +42
- **Secondary GF**: Loss of previously functioning graft with loss of full donor chimerism.
- **Graft Rejection**: GF caused by immune mediated process by host cells
- **Poor graft function**: severe cytopenia of at least two cell lines or dependence on blood/plt transfusion/growth factors with full donor chimerism.

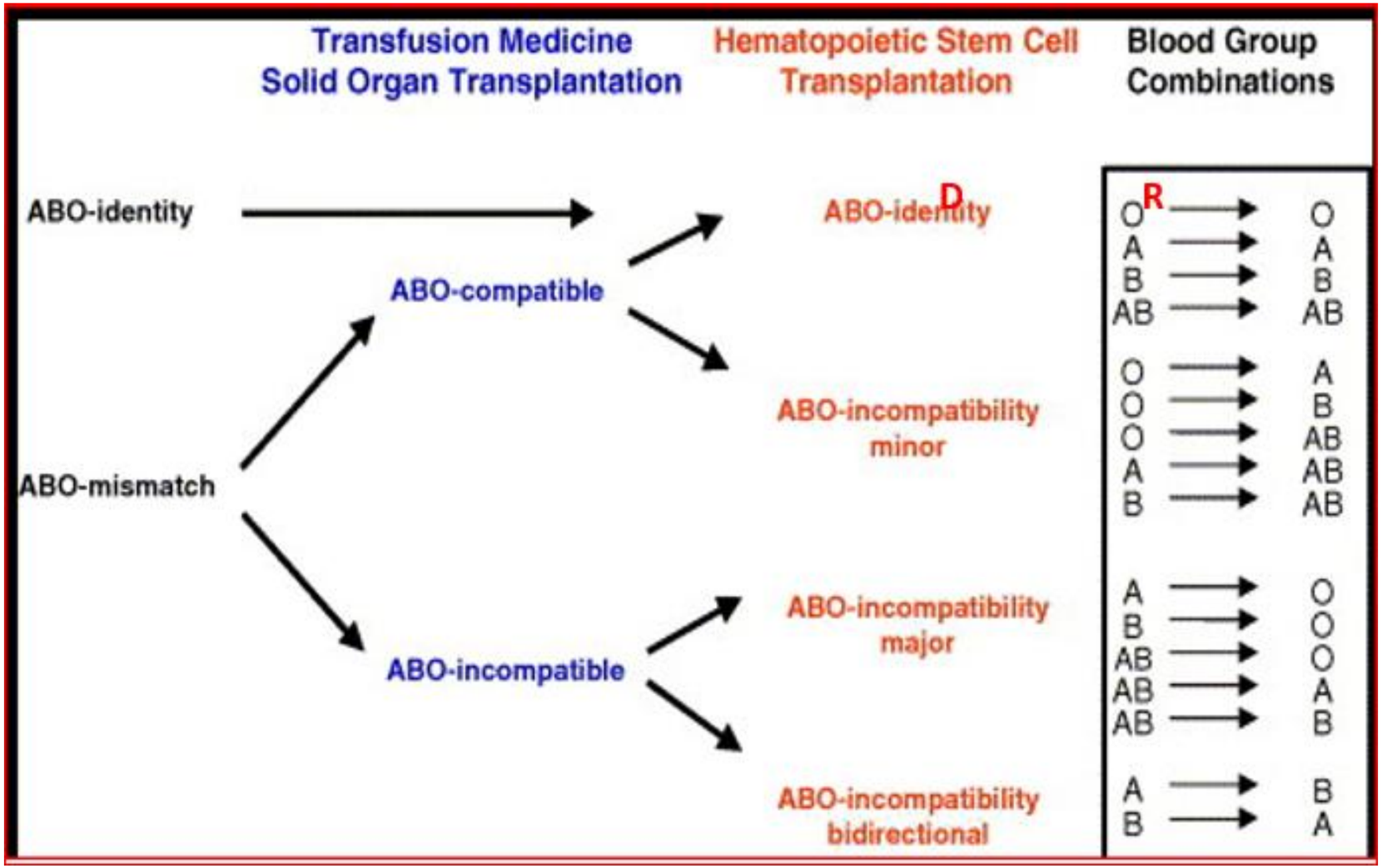
Risk Factors for Graft failure

Immunologic risk factors	Disease/Patient/Donor related	Graft chara
HLA disparity between donor and recipient (Haploidentical > MUD & MMD > MSD)	Underlying disease (Non-malignant; Aplastic anemia, Hemoglobinopathies > Malignant)	Graft source (cord blood
Presence of pre-HSCT donor specific antibodies (DSAs)	Advanced disease in hematologic malignanicies	Low CD34 +
Graft manipulation (Ex-vivo T Cell depletion)	Extensive marrow fibrosis; Myelofibrosis	Storage tech (cryopreserv
Intensity of conditioning regimen (RIC > MAC)	Splenomegally (MPD, MDS)	
Major ABO incompatibility	Extensive pre-transplantation chemotherapy and/or irradiation	
History of extensive transfusion	Iron overload	
Infections (Viral)	Advanced recipient age	
Graft versus Host Disease (GvHD)	Advanced donor age	
Post-transplantation immune suppression regimen	Female donor grafts for male recipients	

Treatment of Graft failure

- Stem cell boost
- 2nd SCT
- Growth factors (erythropoietin/GCSF)
- TPO

ABO Mismatch



ABO Mismatch

molytic complications due to ABO incompatibility

ity	Complications	Prevention	Management
	Acute hemolysis	Graft manipulation (RBC reduction through apheresis or sedimentation) Reduction of recipient's isohemagglutinins (TPE and/or immunoadsorption, incompatible blood transfusions) Hydration	Hydration; transfusions
	Pure red cell aplasia	TPE/immunoadsorption	Transfusions; Others (EPO, rit modulation of immunosuppr
	Acute hemolysis	Graft manipulation (plasma reduction through centrifugation)	Hydration; transfusions
	PLS with delayed hemolysis	Monitoring	Transfusions; RBC exchange

BO incompatibility: combination of both major and minor ABO incompatibilities.
anti-thymocyte globulin; DLI, donor-lymphocyte infusion; EPO, erythropoietin; PLS, passenger lymphocyte syndrome; RBC, red blood cell; a

Graft Versus Host Disease

Causes of Death after Allogeneic HCTs in the US, 2019-2023

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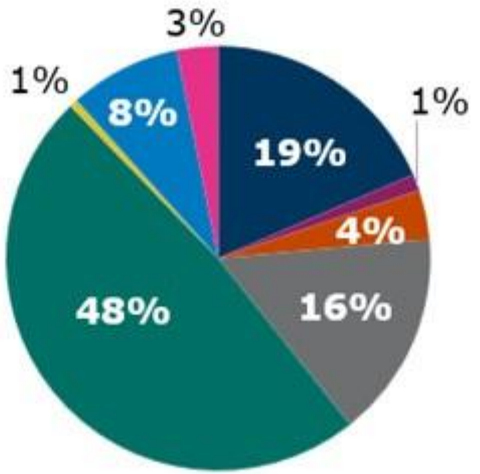
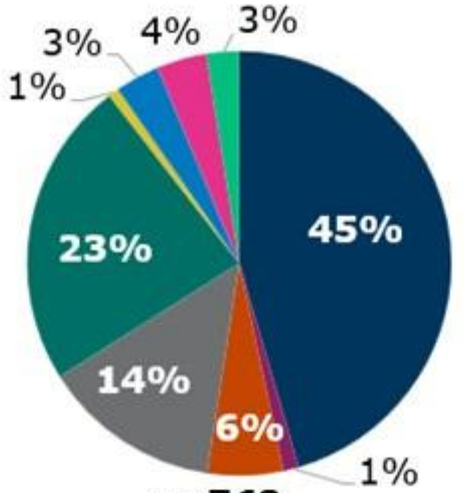
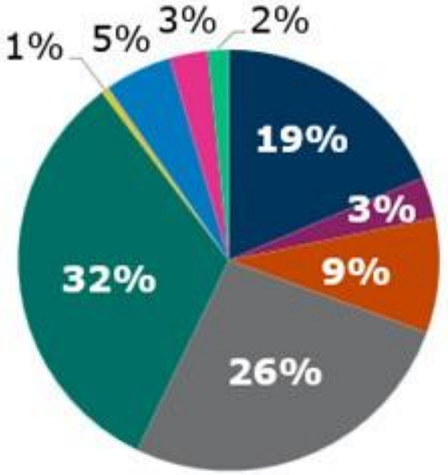
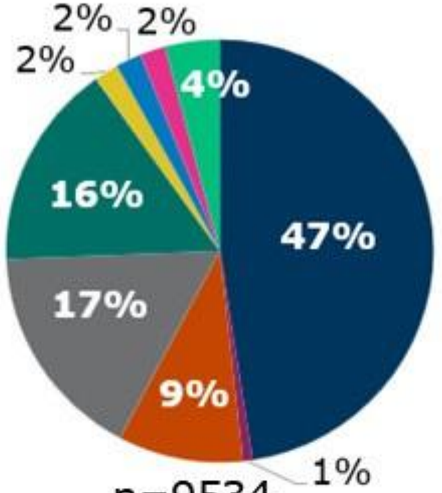
Age <18 years Total transplants = 6264	 n=318	 n=763
Age ≥18 years Total transplants = 36710	 n=3007	 n=9534

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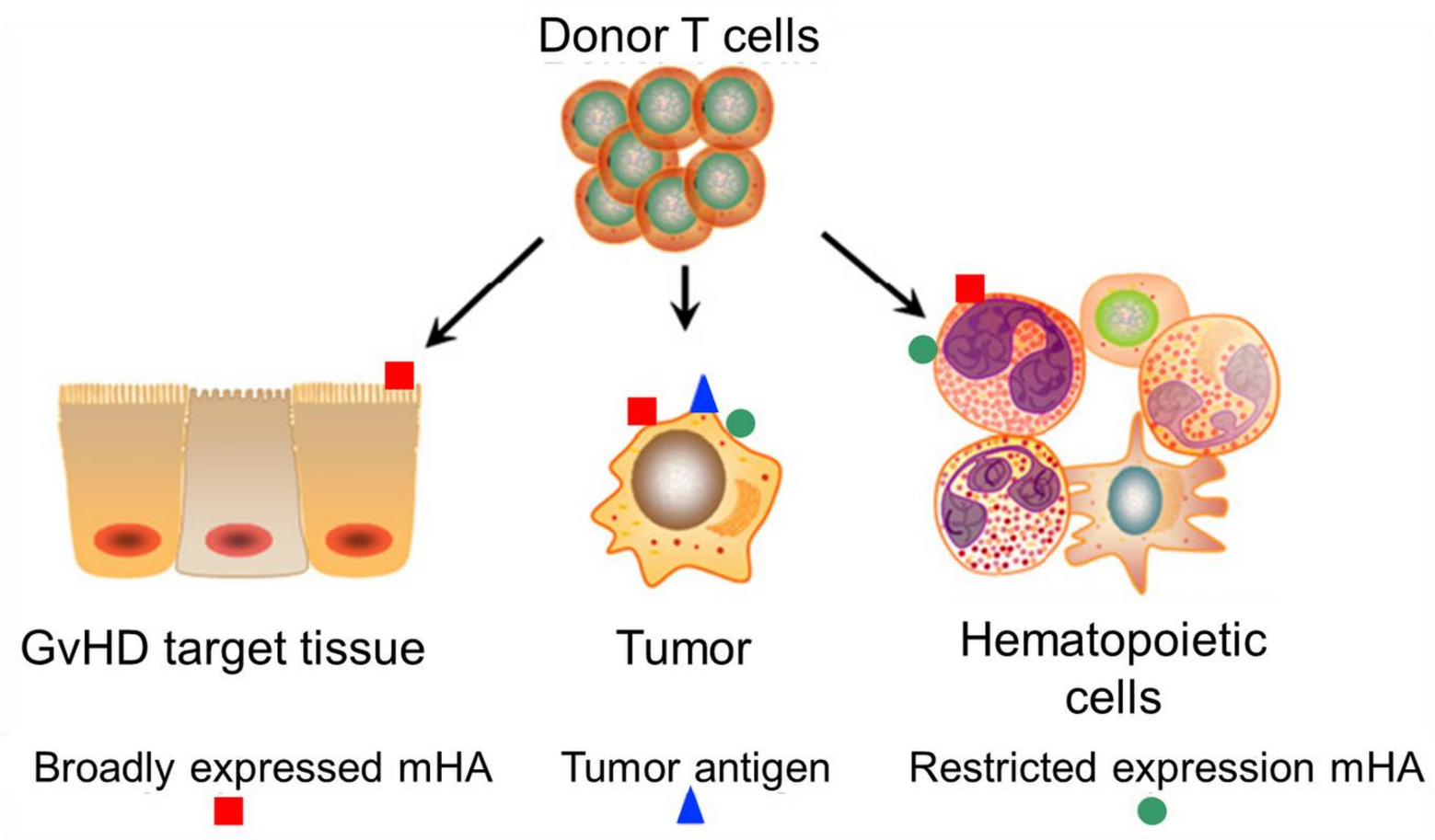
Immunology of Stem Cell Transplantation

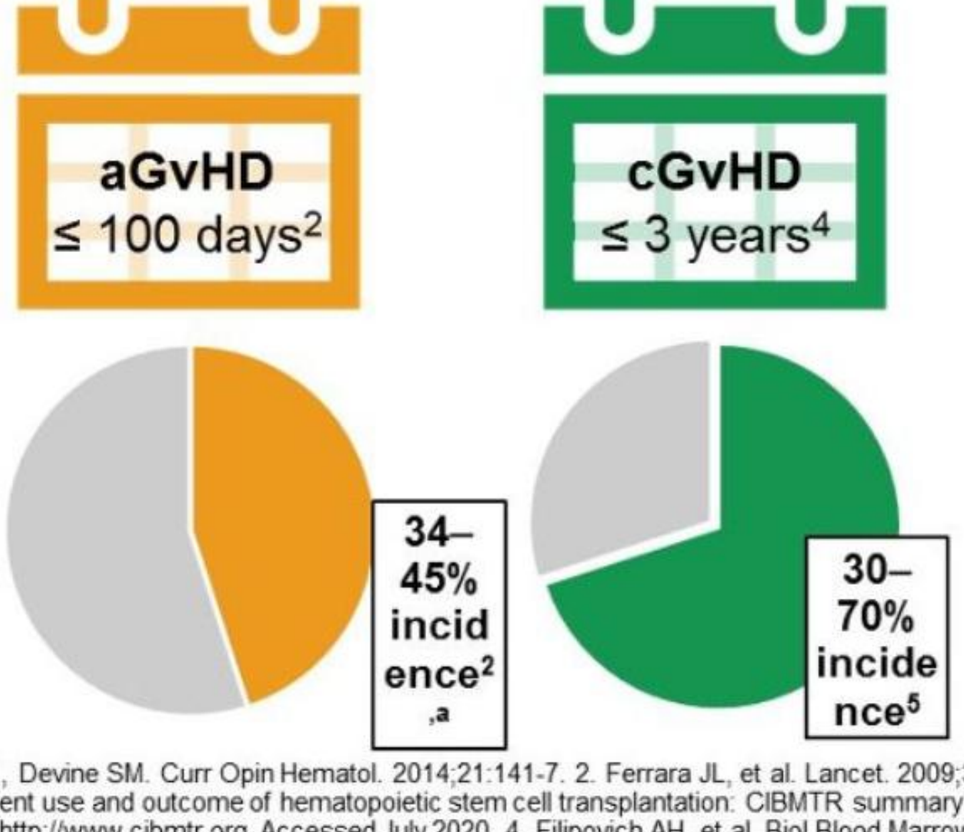


GvHD occurs in approximately 50% of patients receiving allo-SCT[1]

GvHD is a major cause of morbidity and mortality[2]

GvHD is the cause of death in 18–20% of patients receiving allo-SCT[3]

GvHD can manifest as acute or chronic GvHD[1]

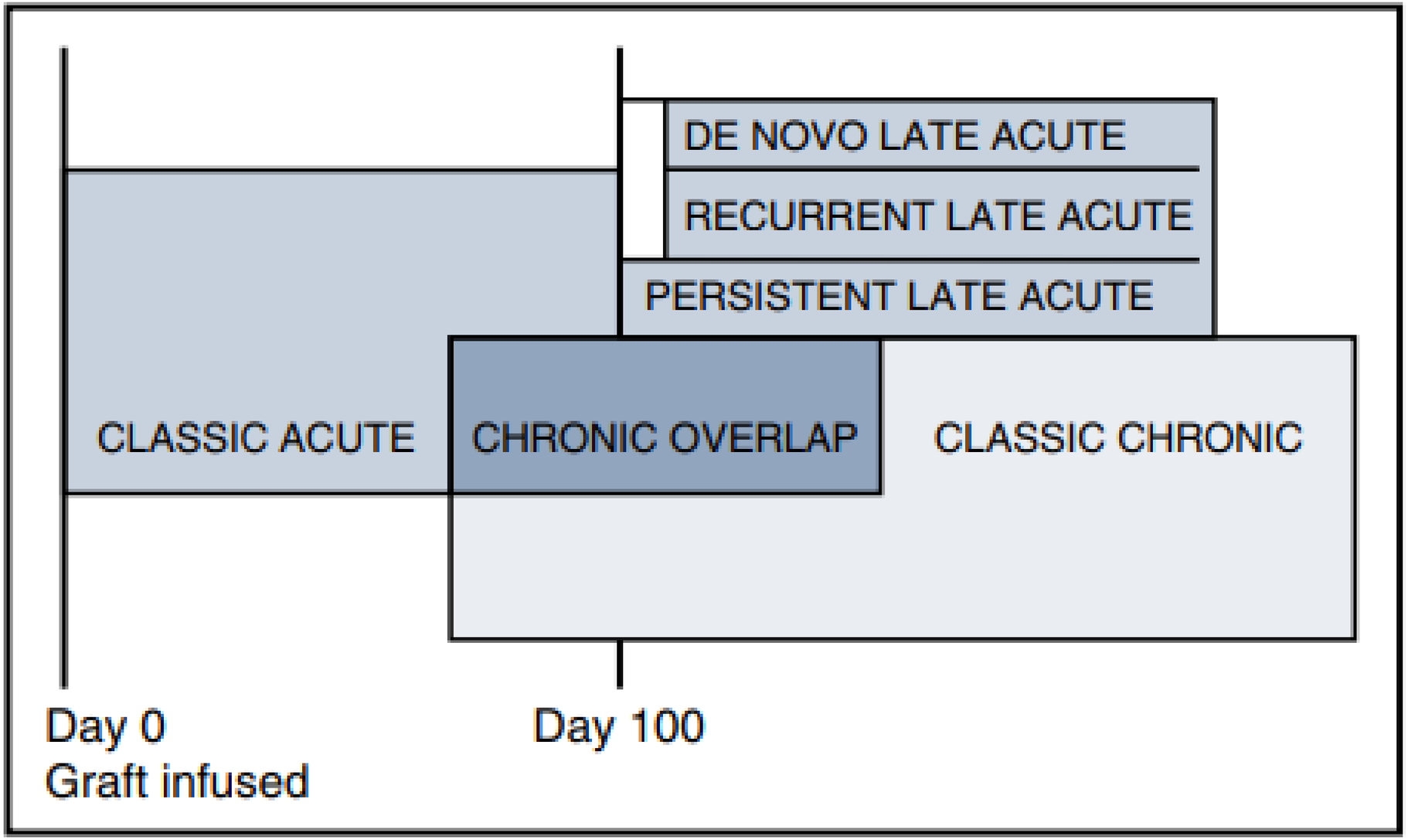


[a] Fully HLA-matched grafts.

aGvHD, acute graft-versus-host disease; allo-SCT, allogeneic stem cell transplantation; cGvHD, chronic graft-versus-host disease; GvHD, graft-versus-host disease; HLA, human leukocyte antigen.

1. Jaglowski SM, Devine SM. Curr Opin Hematol. 2014;21:141-7. 2. Ferrara JL, et al. Lancet. 2009;373:15
3. Pasquini MC, Zhu X. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, Available from: http://www.cibmtr.org. Accessed July 2020. 4. Filipovich AH, et al. Biol Blood Marrow Trans 2005;11:945-56. 5. Jagasia MH, et al. Biol Blood Marrow Transplant. 2015;21:38

GVHD Classification



GVHD Biology

Initially described in mice as **secondary disease** occurring after recovery from TBI-induced damage

Definitions by Billingham (1966) are still valid for all manifestations of GvHD (GvHD after allogeneic SCT, after transfusion, after Organ Tx):

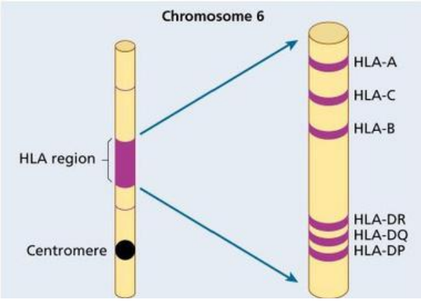
1. Graft must contain immunocompetent cells
2. Host expresses major or minor antigens absent on the donor
3. Host is incapable of rejecting the donor cells

Donor T Cells Responds to Foreign Recipient Antigens

- The HLA system :genetically determined highly polymorphic proteins encoded by the MHC

  Class I – A,B,C : proteins expressed on all nucleated cells with different density

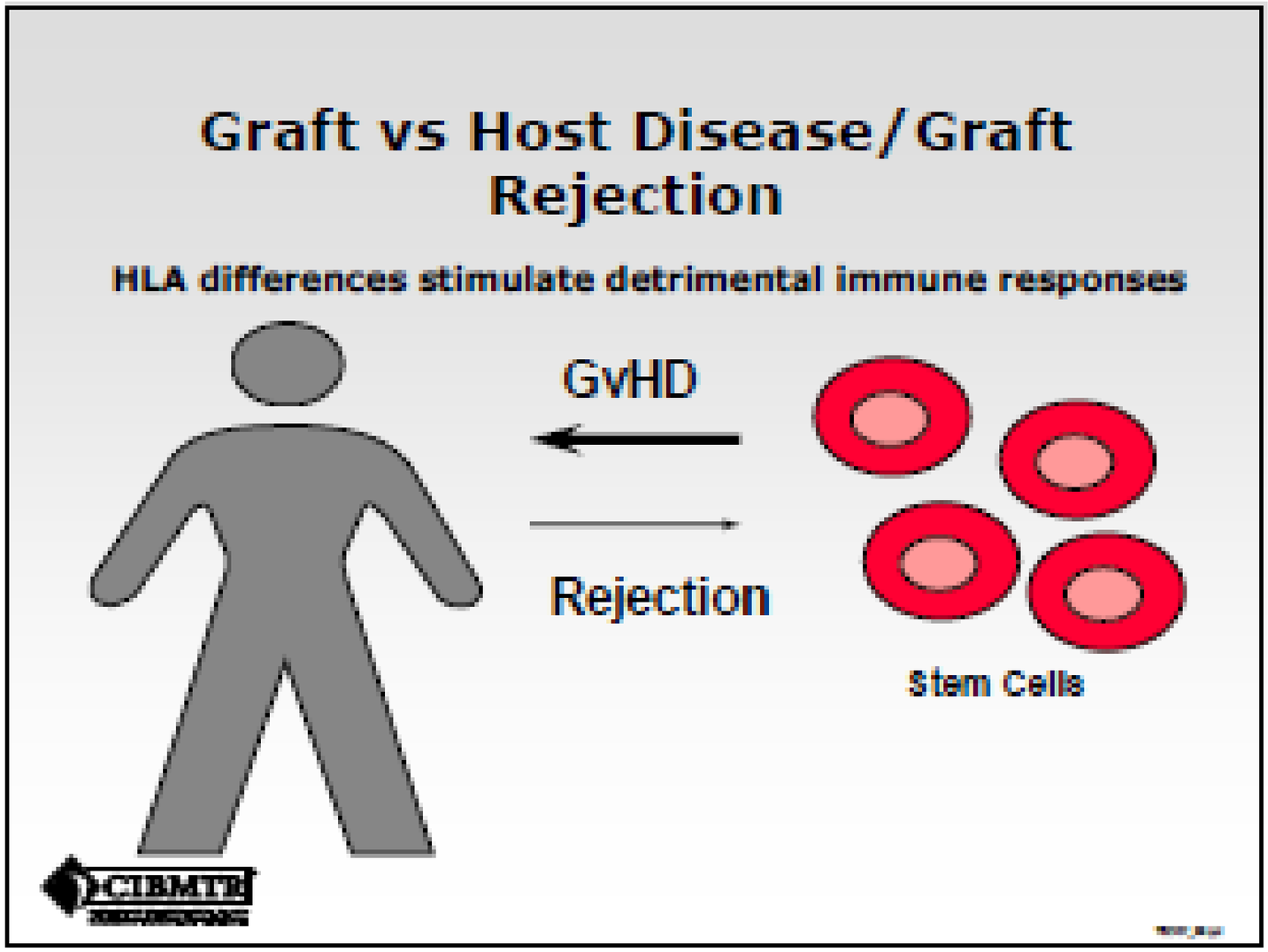
  Class II- DR,DQ : proteins expressed mainly on hematopoietic cells



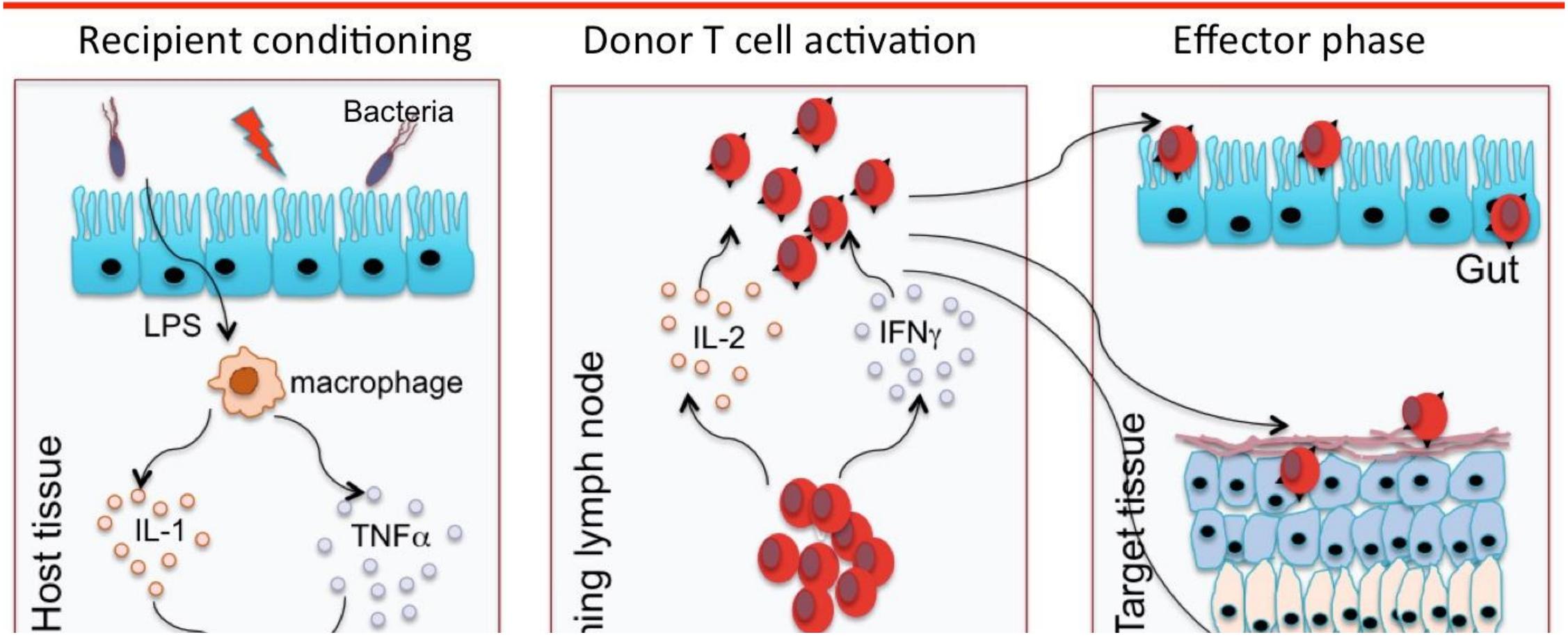
- Genetic determinants outside the HLA system: minor histocompatibility antigens

- Polymorphism in both donor and recipient for various cytokines involved in the cytokine storm of aGVHD: TNF,IFN,IL-10.

Role of T cells in Stem Cell Transplantation

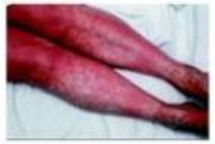


Patho-physiology of GVHD

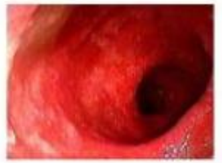


Clinical features of aGvHD

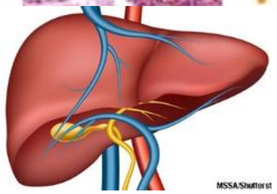
Target organs of aGvHD[1]



Skin
- Maculopapular rash
- Hands, feet
- Pain, itch
- Erythroderma, bullae

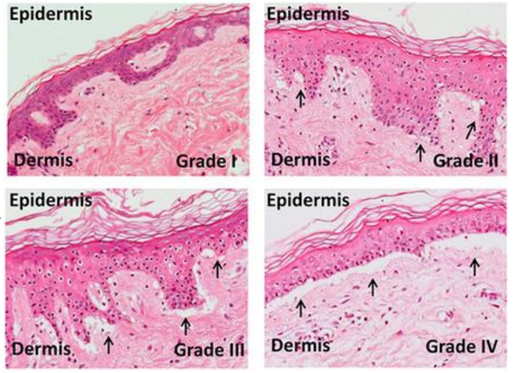


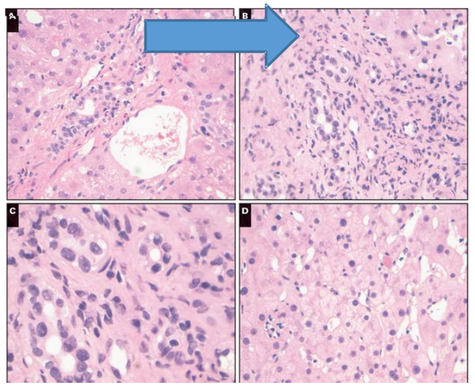
GI tract
- Diarrhea
- Watery, green
- Pain, bleeding

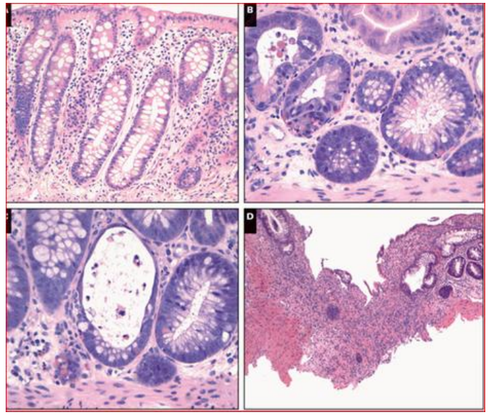


Liver
- Cholestatic ALP/GGT
- Jaundice

Key risk factors for aGvHD







1. Ferrara J

kaline phosphatase; GGT, gamma glutamyltransferase; GI, gastrointestinal.

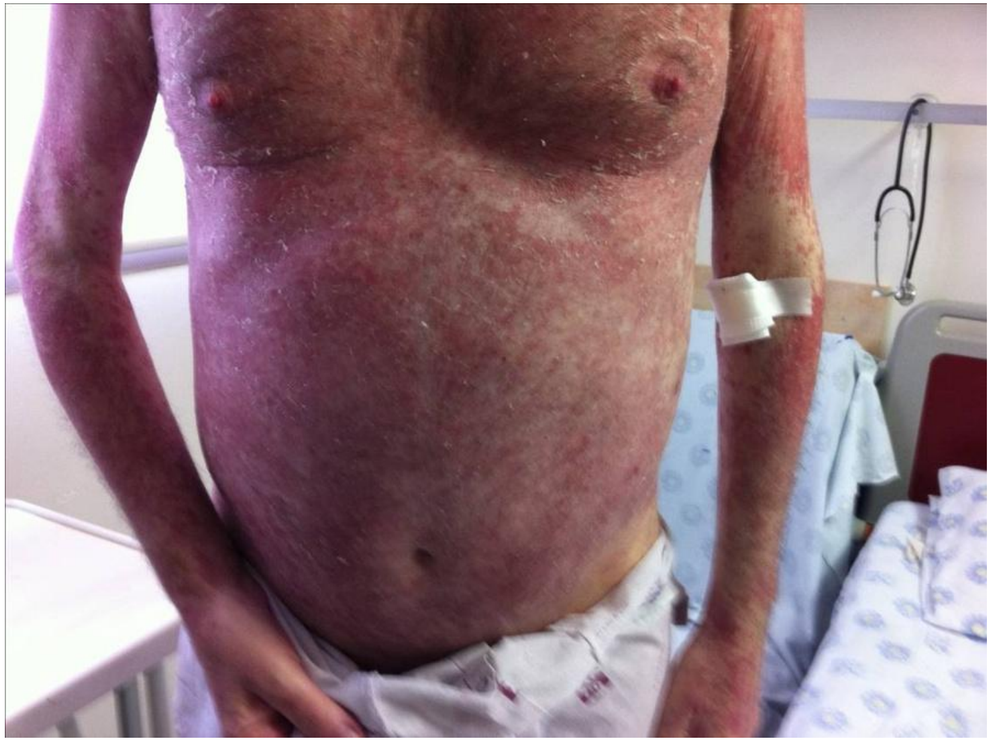
Staging of aGVHD

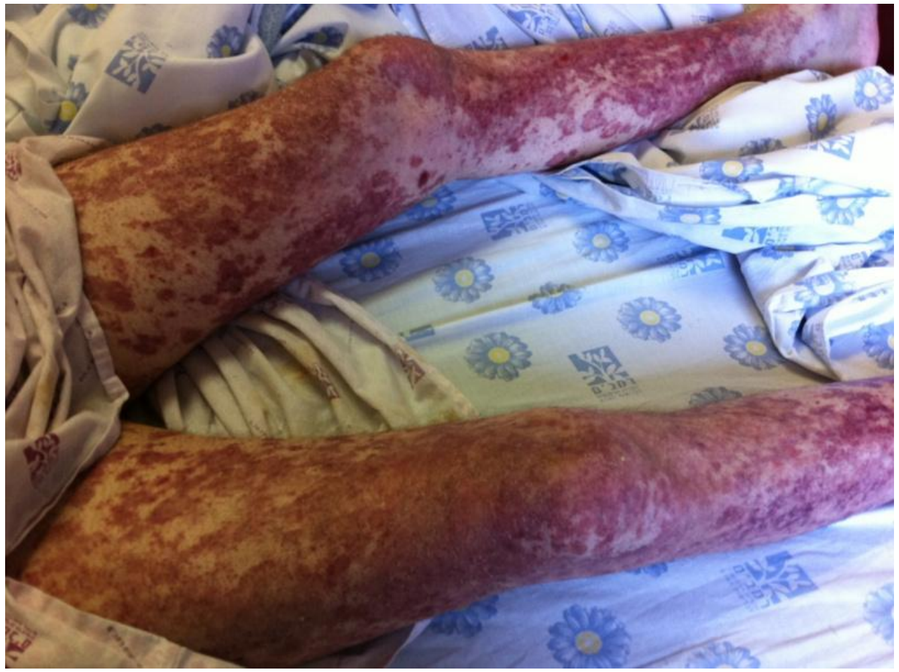
Stage	skin	liver	GIT
I	Rush <25%	Bilirubin 2-2.9mg/dl	Diarrhea 500-1000cc/d /Bx of UGIT involvement
II	Rush 25-50%	Bilirubin 3-6mg/dl	Diarrhea 1000-1500cc/d
III	Rush >50%	Bilirubin 6.1-15 mg/dl	Diarrhea 1500-2000cc/d
IV	Generalized +bullae	Bilirubin>15mg/dl	Diarrhea>2000cc/d ,abdominal pain, ileus

Grading of aGVHD

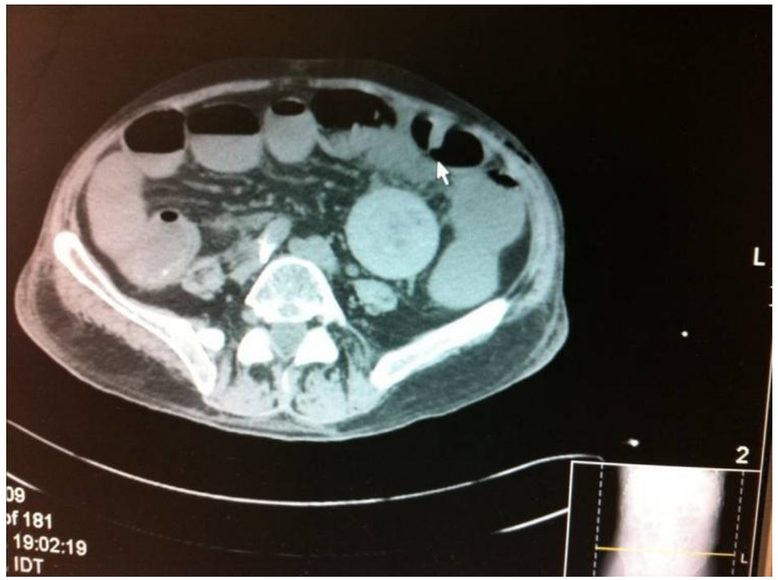
Organ Stage	Skin	Liver	GIT
I	Stage1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	-	Stage 2-3	Stage 2-4
IV	Stage4	Stage 4	-

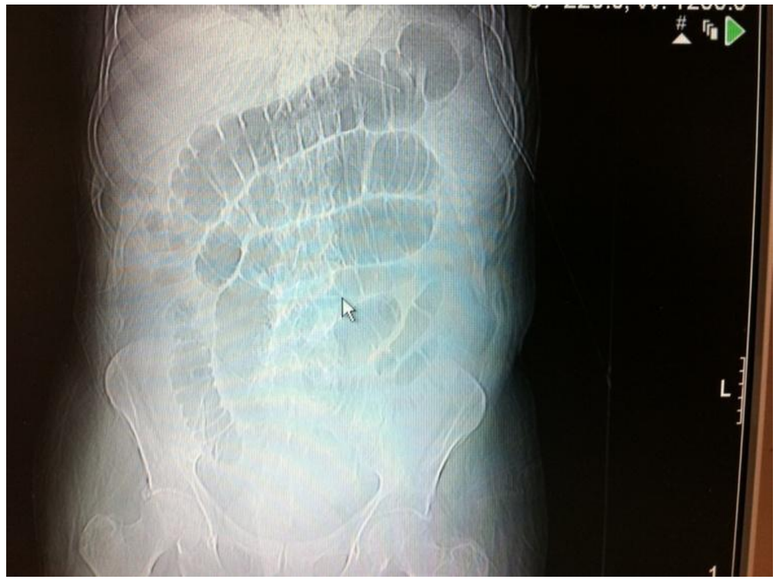
Skin aGVHD Grade IV

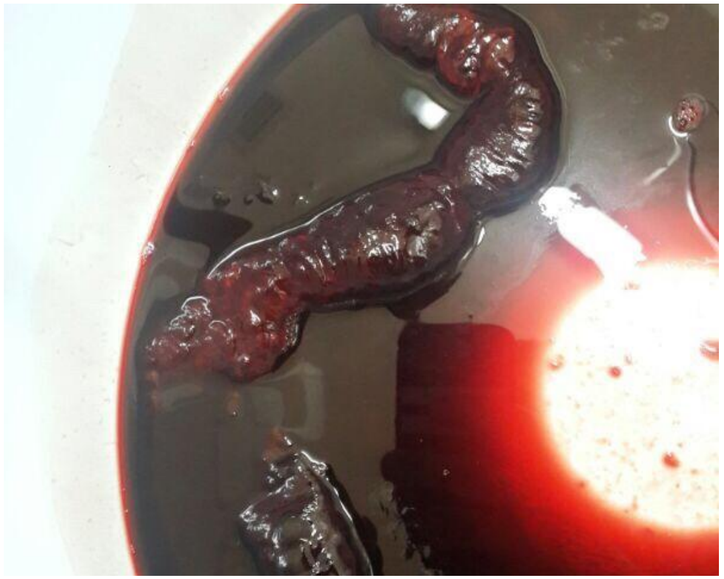




GIT GVHD grade 4







GVHD Risk Factors

- HLA Disparity
- Transplant from unrelated donor
- Donor/ recipient gender disparity: Female to male
- Recipient (donor?) age.
- Stem cell source (peripheral blood>> BM)
- Allo immunized donor(pregnancy, blood transfusion)
- CMV serological disparity
- Presence of aGVHD

EBMT European Society for Blood and Marrow Transplantation

Prophylaxis and management of GvHD

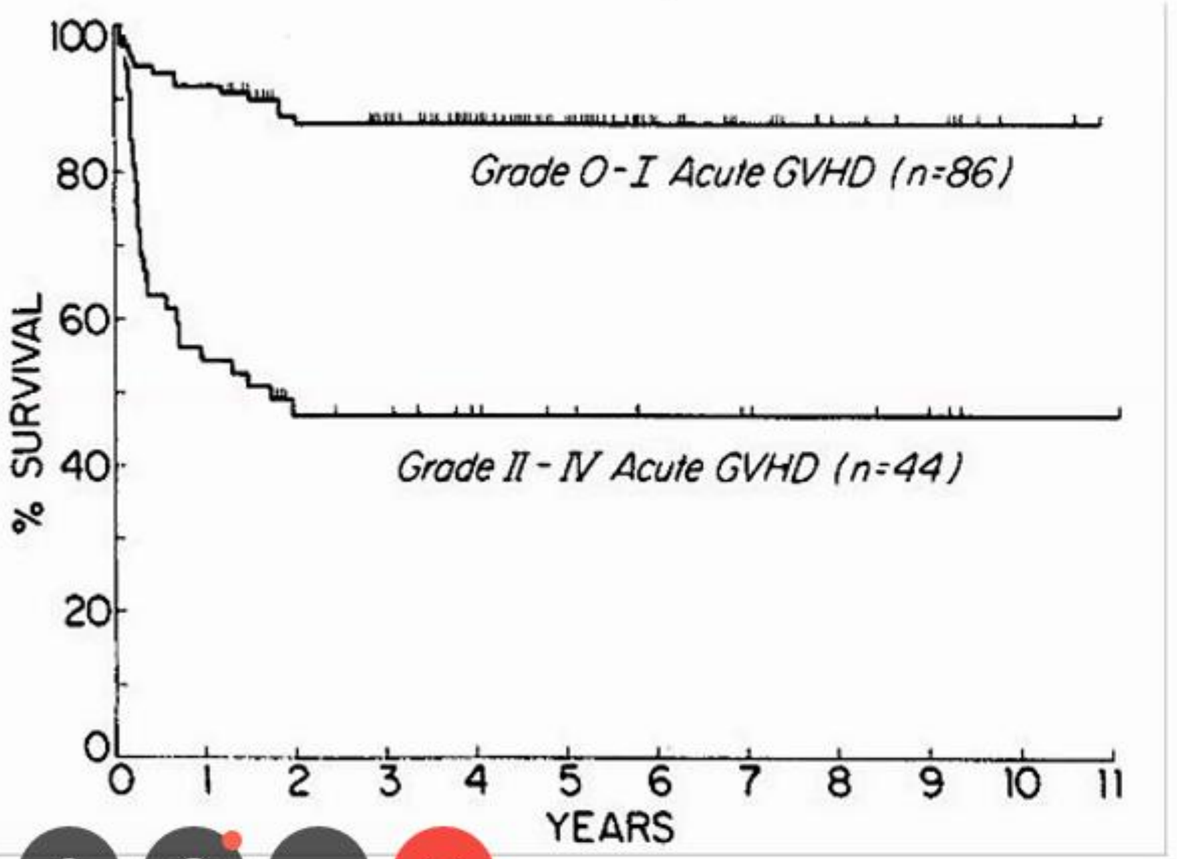
Olaf Penack, MD

EBMT Transplant Complications Working Party

Charité Universitätsmedizin Berlin, Germany

Prophylaxis of GvHD, Why?

Survival after diagnosis
of acute GvHD
in aplastic anemia



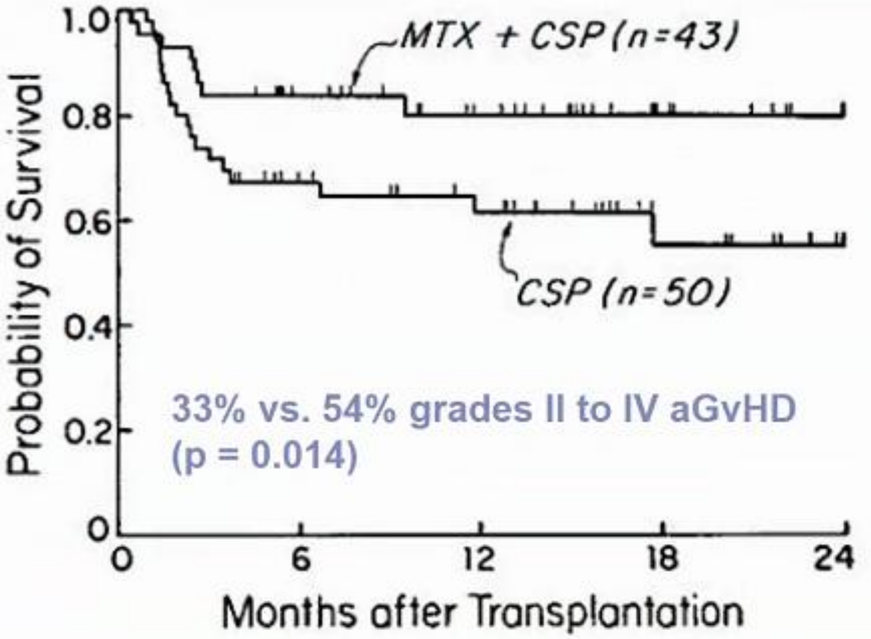
Storb [illegible]. N Engl J Med 1983; 308:302-307

Prophylaxis of GvHD

100%

Patients undergoing MRD/MUD allogeneic SCT should receive GvHD prophylaxis with a calcineurin inhibitor plus an antimetabolite

Myeloablative: MTX



Storb et al. N Engl J Med. 1986 Mar 20;314(12):729-35

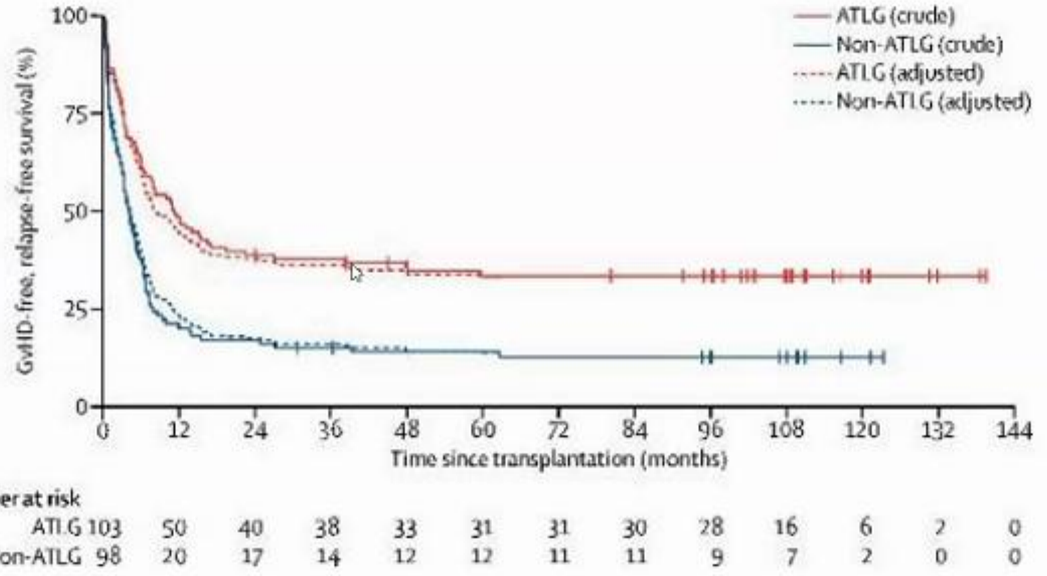
Prophylaxis of Acute GvHD

100%

ATG is recommended for preventing GvHD in patients undergoing MUD allogeneic SCT

Matched Unrelated Donors

Reduction of chronic GvHD in several randomized studies



Finke et al. Lancet Haematol 2017;4: e293–301

Reduced incidence of chronic GvHD

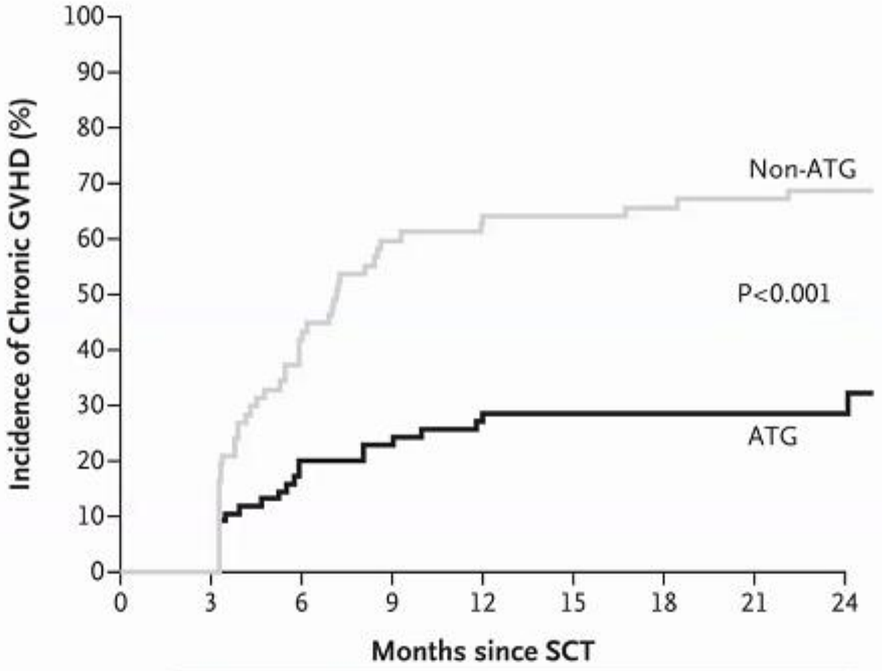
Prophylaxis of Acute GvHD

95%

ATG can be recommended for preventing GvHD in patients undergoing MRD allogeneic SCT

Matched Unrelated Donors

Reduction of chronic GvHD in randomized studies and retrospective analyses

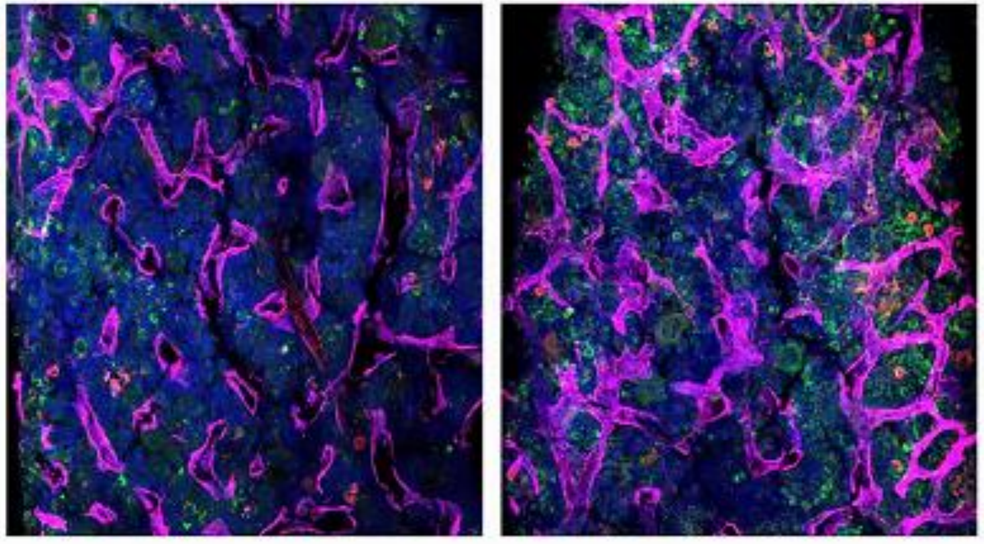


Kröger et al. N Engl J Med. 2016 Jan 7;374

Reduced incidence of chronic GvHD

EBMT GvHD Recommendations

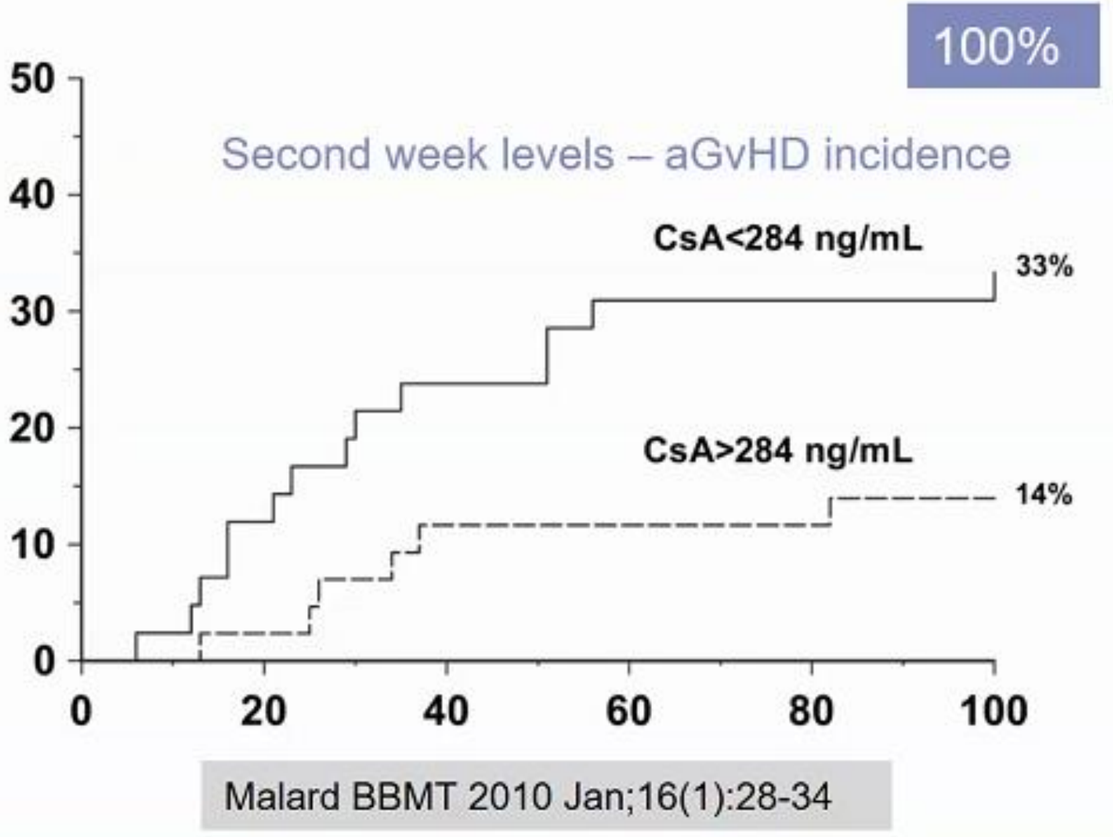
- Prophylaxis of GvHD
- **Drug management**
- Treatment of acute GvHD
- Treatment of chronic GvHD



Drug Management

CsA target concentration in the first weeks post-transplantation should be 200-300 mcg/L in order to efficiently prevent aGvHD

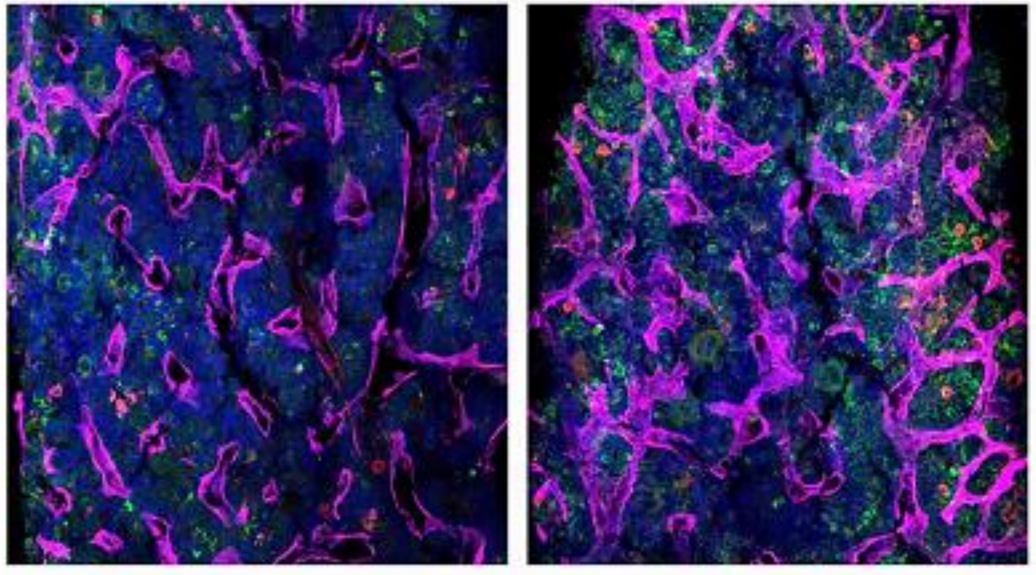
Retrospective studies proved that higher CsA levels in the first weeks post-transplantation were associated with lower frequency of aGvHD



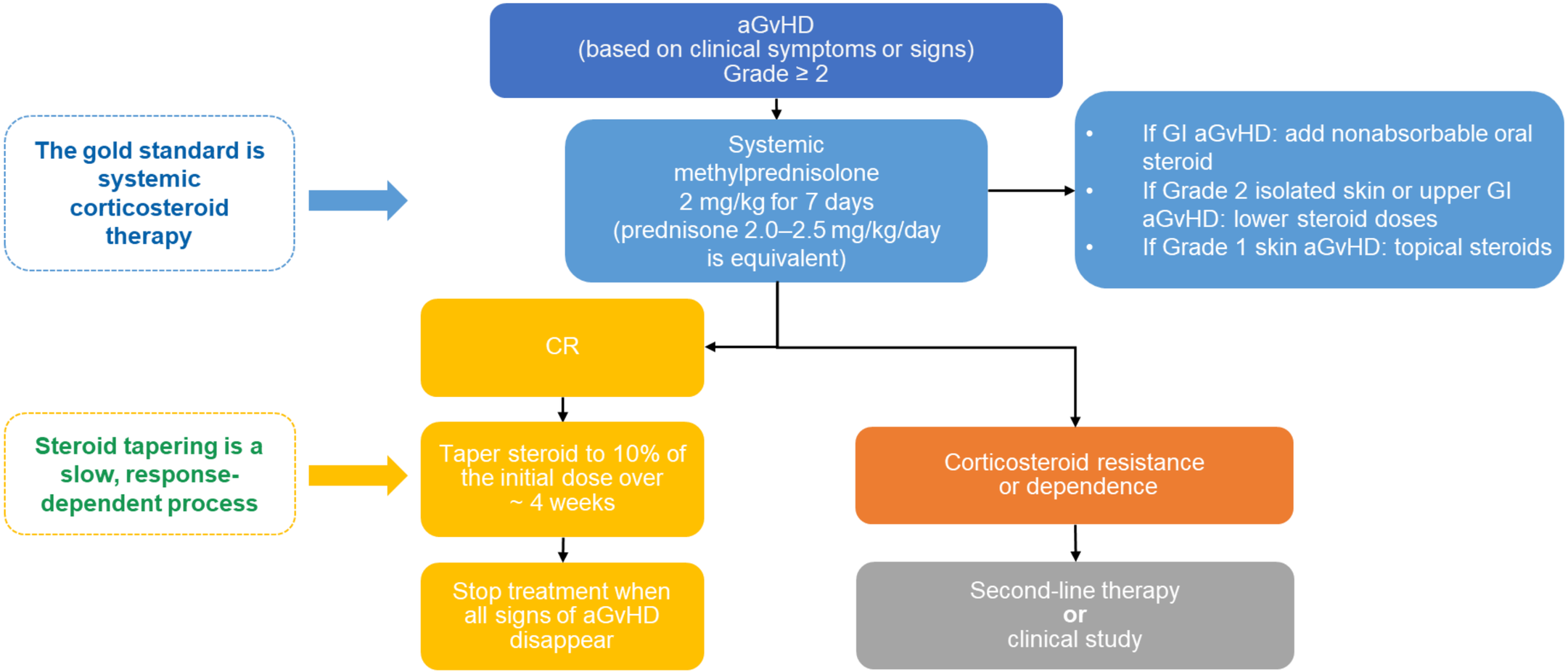
High cyclosporin levels in the first weeks after allo-SCT reduce aGvHD incidence

EBMT GvHD Recommendations

- Prophylaxis of GvHD
- Drug management
- **Treatment of acute GvHD**
- Treatment of chronic GvHD



EBMT 2020 Treatment Guidelines: Acute GvHD

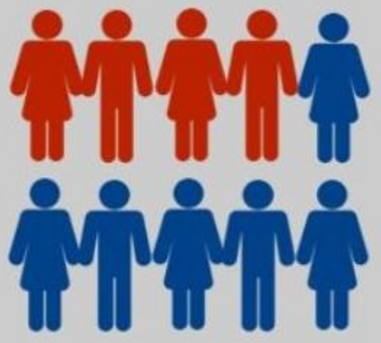


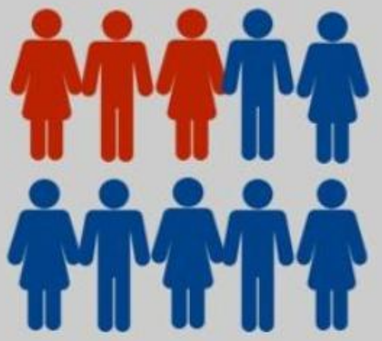
CR, complete response.

Penack O, et al. Lancet Haematol. 2020;7:e157-67.

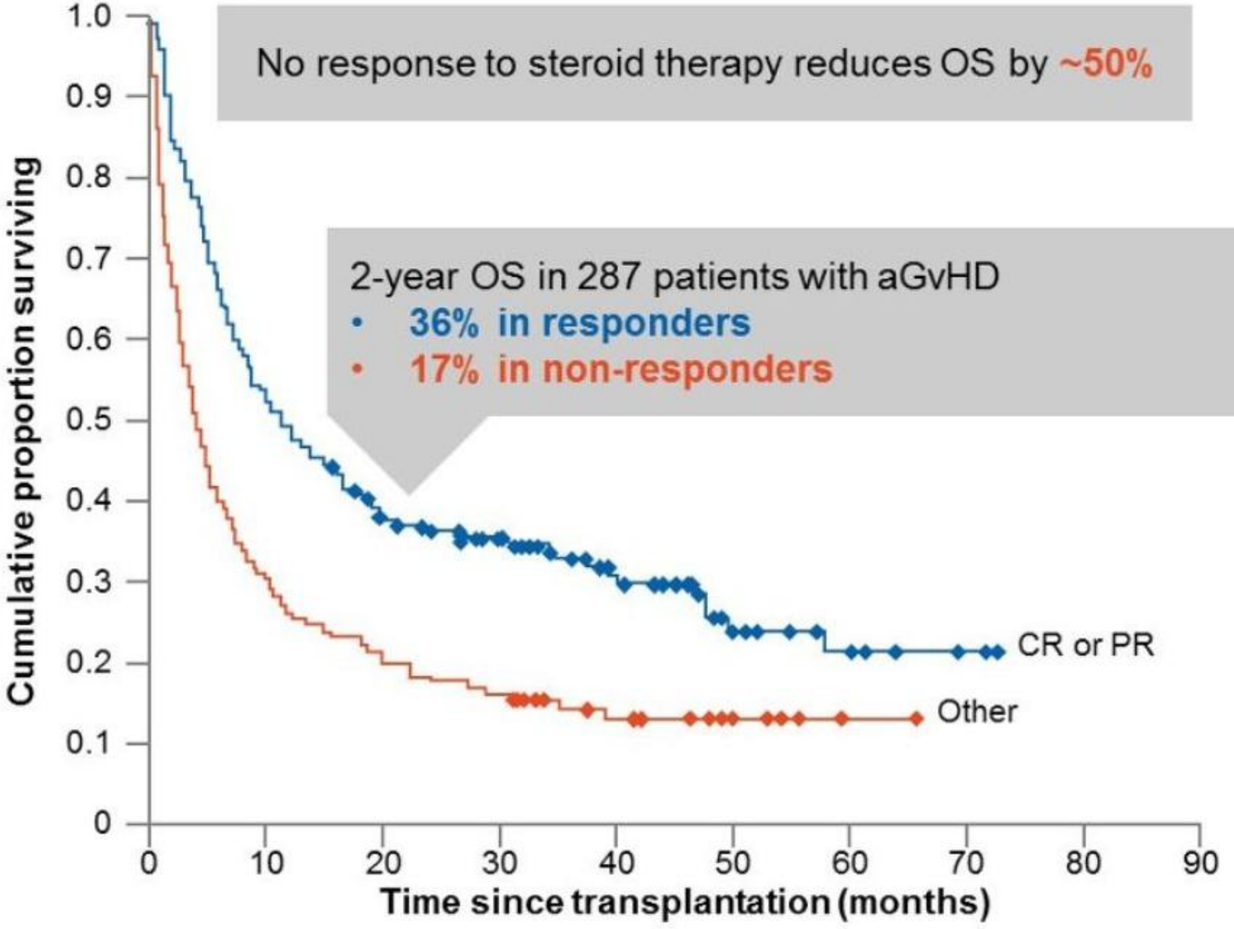
Response to steroids in patients with aGvHD

Steroids are effective in **only 40%** of patients with aGvHD





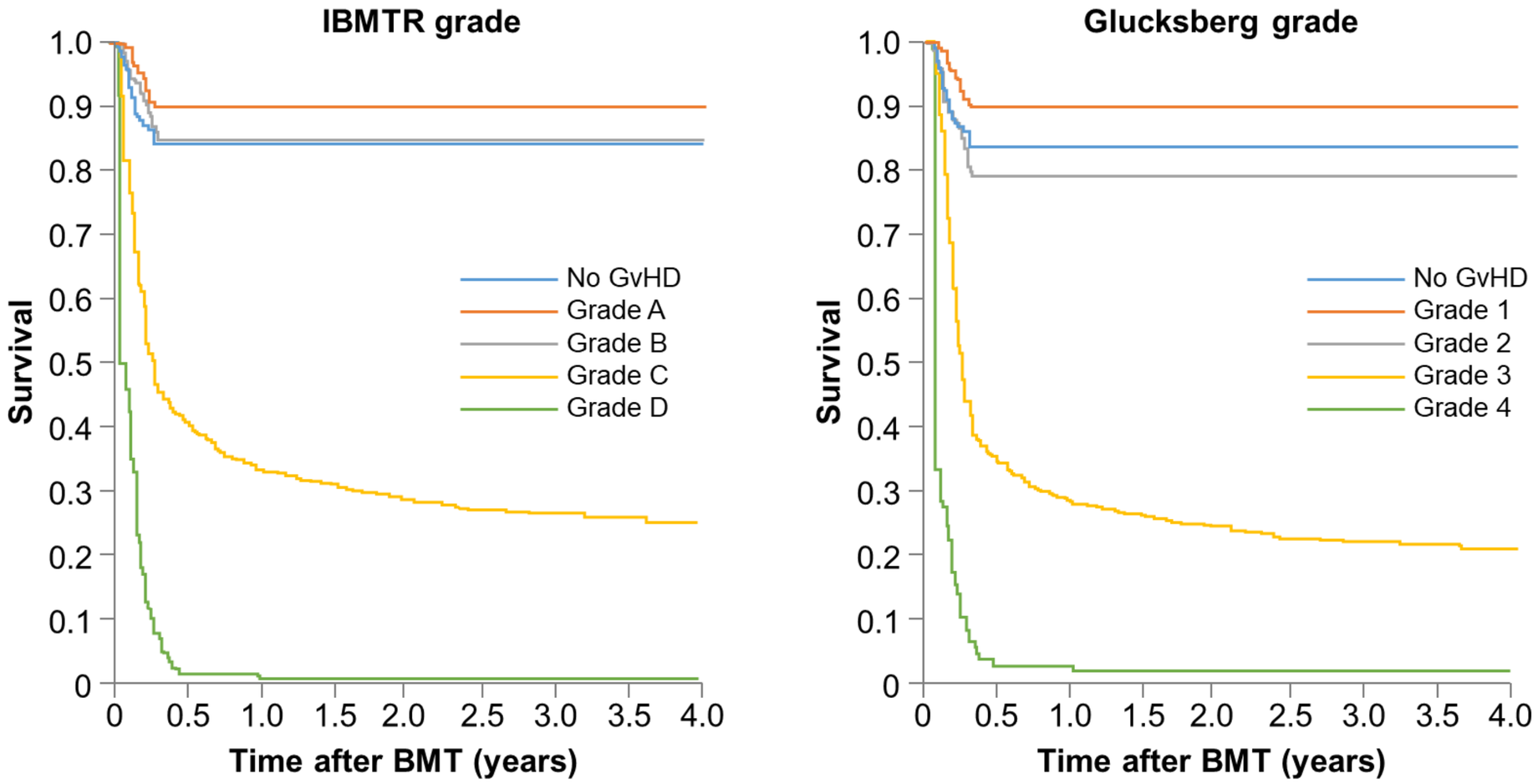
Only 30% of patients with aGvHD have a long-lasting response to steroids



OS, overall survival; PR, partial response.

Magenau J, Reddy P. Leukemia. 2014;28:2283-91. Murray J, et al. Graft-Versus-Host Disease (GvHD). In: The European Blood and Marrow Transplantation Textbook for Nurses. Springer International Publishing, Switzerland; 2018: 221-51. Figure reproduced from Westin JR, et al. Adv Hematol. 2011;2011:601953. Copyright © 2011 Westin et al. https://creativecommons.org/licenses/by-nc/3.0/ Different color lines.

Probability of survival according to maximum GvHD score



BMT, bone marrow transplant.

Cahn J-Y, et al. Blood. 2005;106:1495-500.

Definition of Steroid Refractory aGVHD

Steroid Resistance:

- Progression in any organ within 3,4 or 5 days of therapy onset with ≥ 2mg/kg/d of prednisone equivalent.
- Failure to improve within 5 or 7 days of treatment initiation.
- Incomplete response after ≥ 28 days of immunosuppressive treatment including steroids .

Steroid Dependence:

- Inability to taper prednisone under 2mg/kg/d after an initialy successful treatment of at least 7 days.
- Recurrence of GVHD activity during steroid tapering.

Response to Second-line Therapy for Steroid-refractory Acute GvHD

- Response 28 days after initiation of second-line therapy for SR-aGvHD[1,a]

Response, n (%)	Patients with SR-aGvHD (N = 203)
CR	**47 (23)**
PR	31 (15)
NR[b]	125 (62)

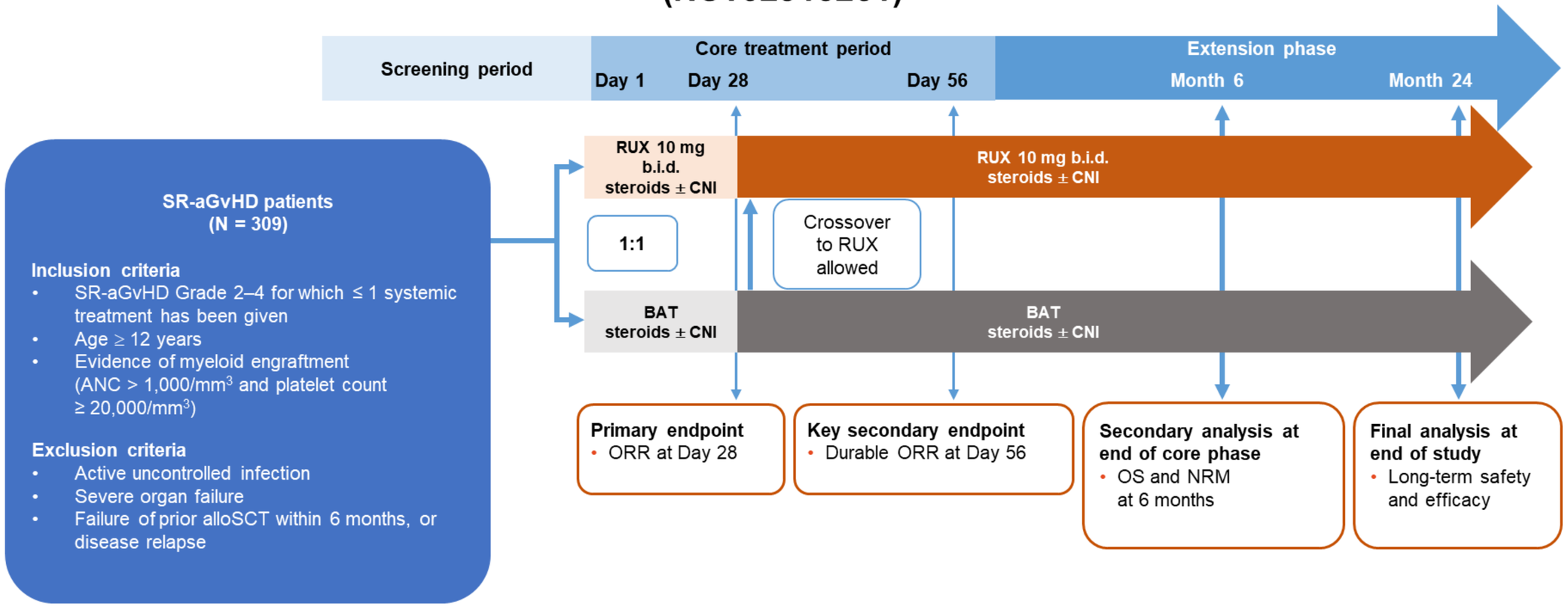
- 6-month OS in patients with SR-aGvHD ranged from 17 to 86%[2]
- **2 years** after diagnosis of SR-aGvHD (N = 203)[1]
  - **OS 25%**
  - NRM 65%
    - 69% due to aGvHD (mostly due to infections [70%])
    - 18% relapse of underlying malignancy

[a] Second-line therapy included ATG, etanercept, or MMF.
[b] Includes 37 patients (18%) who died within 28 days of initiation of second-line therapy.
NR, no response; NRM, nonrelapse mortality; SR, steroid refractory.

1. Rashidi A, et al. Biol Blood Marrow Transplant. 2019;25:2297-302.
2. Martin PJ, et al. Biol Blood Marrow Transplant. 2012;18:1150-63.

REACH2: Study Design

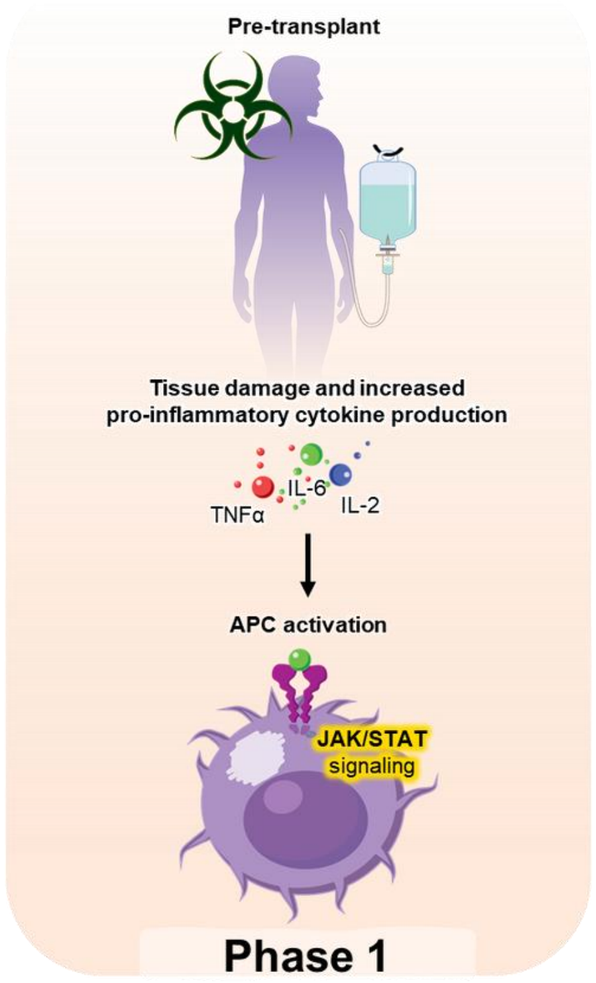
Phase 3, randomized, open-label, multicenter study to evaluate the safety and efficacy of RUX (10 mg b.i.d.) vs investigator-determined BAT in patients with SR-aGvHD after alloHSCT (NCT02913261)

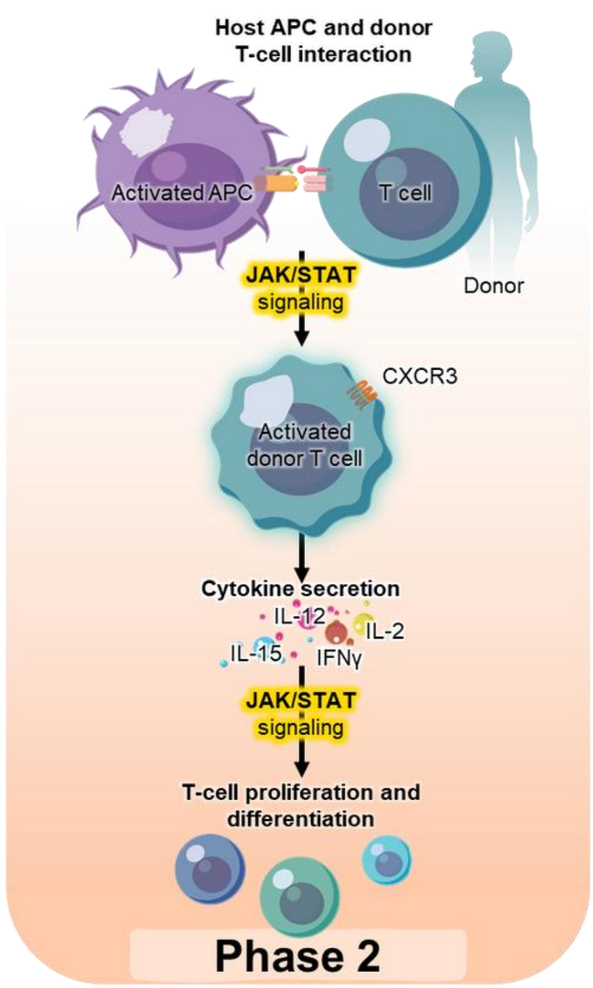


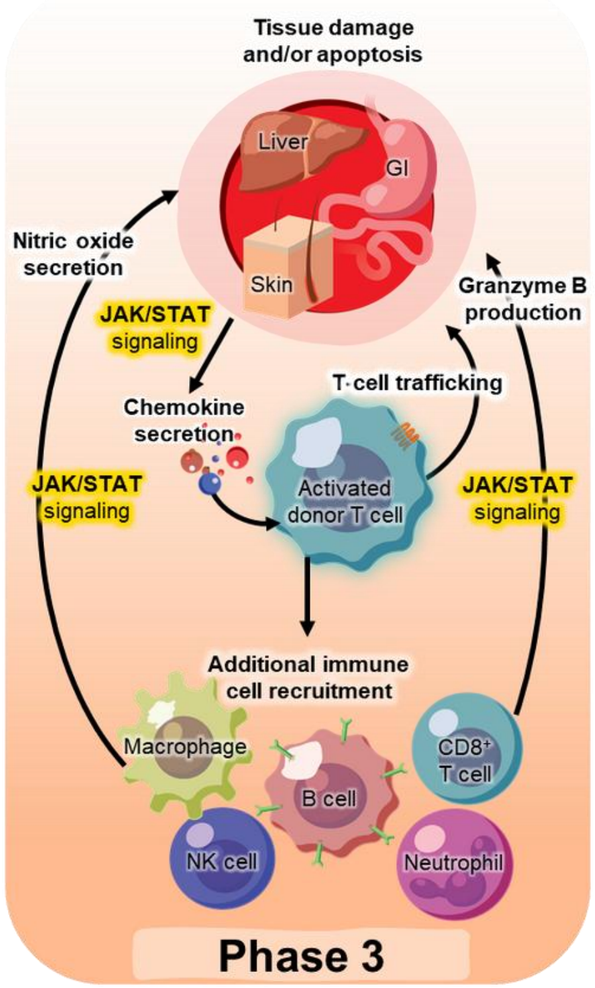
ANC, absolute neutrophil count; BAT, best available therapy; b.i.d., twice daily; ORR, overall response rate.

NCT02913261. Available from: https://clinicaltrials.gov/ct2/show/NCT02913261.
Zeiser R, et al. Oral presentation at EHA 2020; abstract S255.

JAK/STAT Signaling Plays a Role in aGvHD



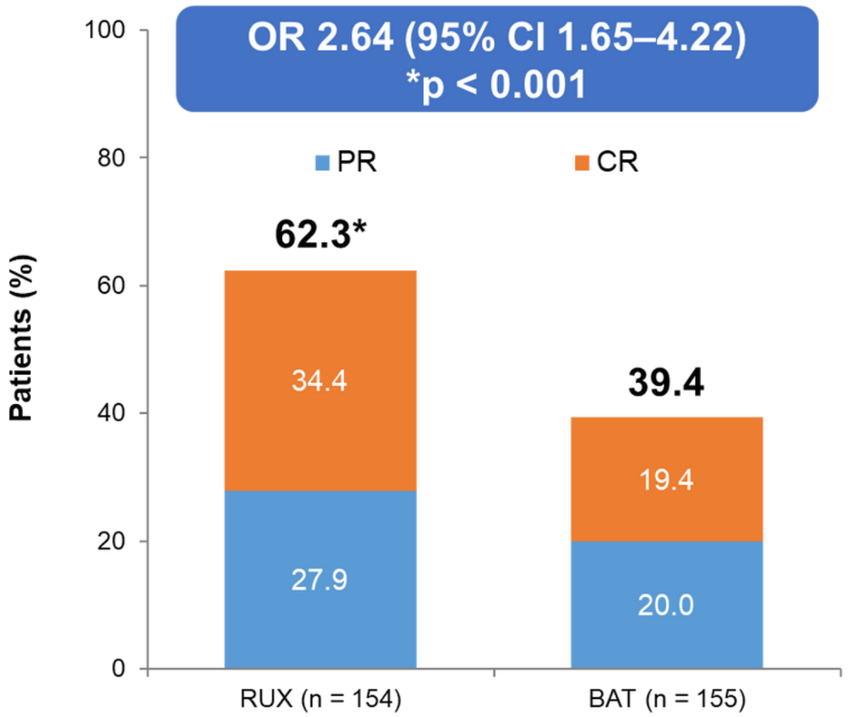




APC, antigen-presenting cell; CXCR3, C-X-C motif chemokine receptor 3; GI, gastrointestinal; IFNγ, interferon gamma; IL, interleukin; JAK, Janus kinase; NK, natural killer; STAT, signal transducer and activator of transcription; TNFα, tumor necrosis factor alfa.

1. Schroeder MA, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1125-1134. 2. Abboud R, et al. *Ther Adv Hematol*. 2020 Jun 2;11:2040620720914489. 3. Magenau J, et al. *Br J Haematol*. 2016;173(2):190-205.

REACH2: Overall Response Rate at day 28 was Significantly Higher for Ruxolitinib Vs Best Available Therapy

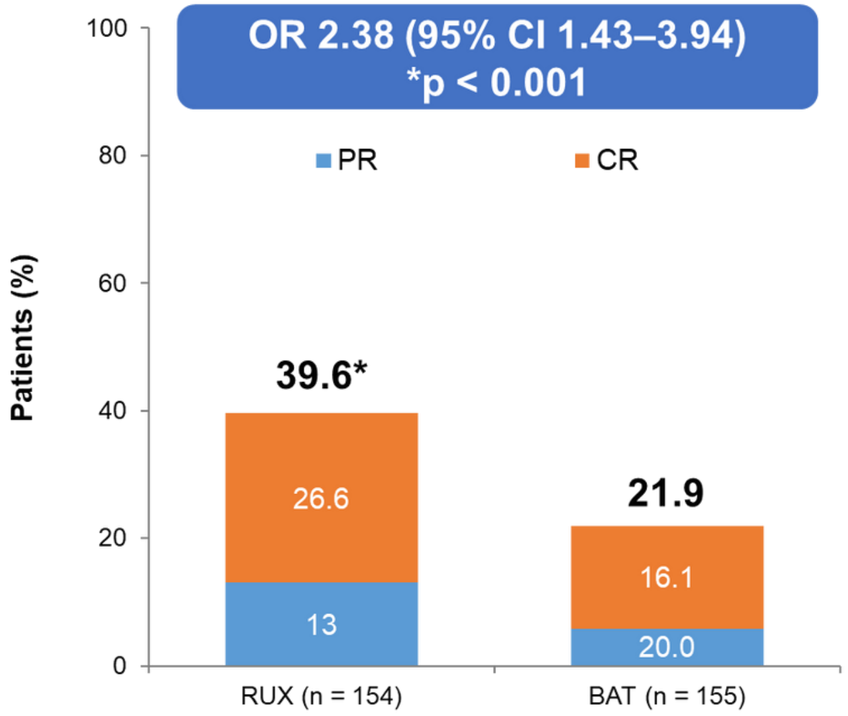


	RUX (n = 154)	BAT (n = 155)
Responders, n (%)		
CR	53 (34.4)	30 (19.4)
PR	43 (27.9)	31 (20.0)
Nonresponders, n (%)		
NR	7 (4.5)	10 (6.5)
Mixed response	10 (5.5)	17 (11.0)
Progression	4 (2.6)	13 (8.4)
Other[a]	1 (0.6)	7 (4.5)
Unknown	36 (23.4)	47 (30.3)

[a] Other: patient with additional systemic therapies along with CR/PR per investigator assessment.
CI, confidence interval; OR, odds ratio.

Zeiser R, et al. Oral presentation at EHA 2020; abstract S255.

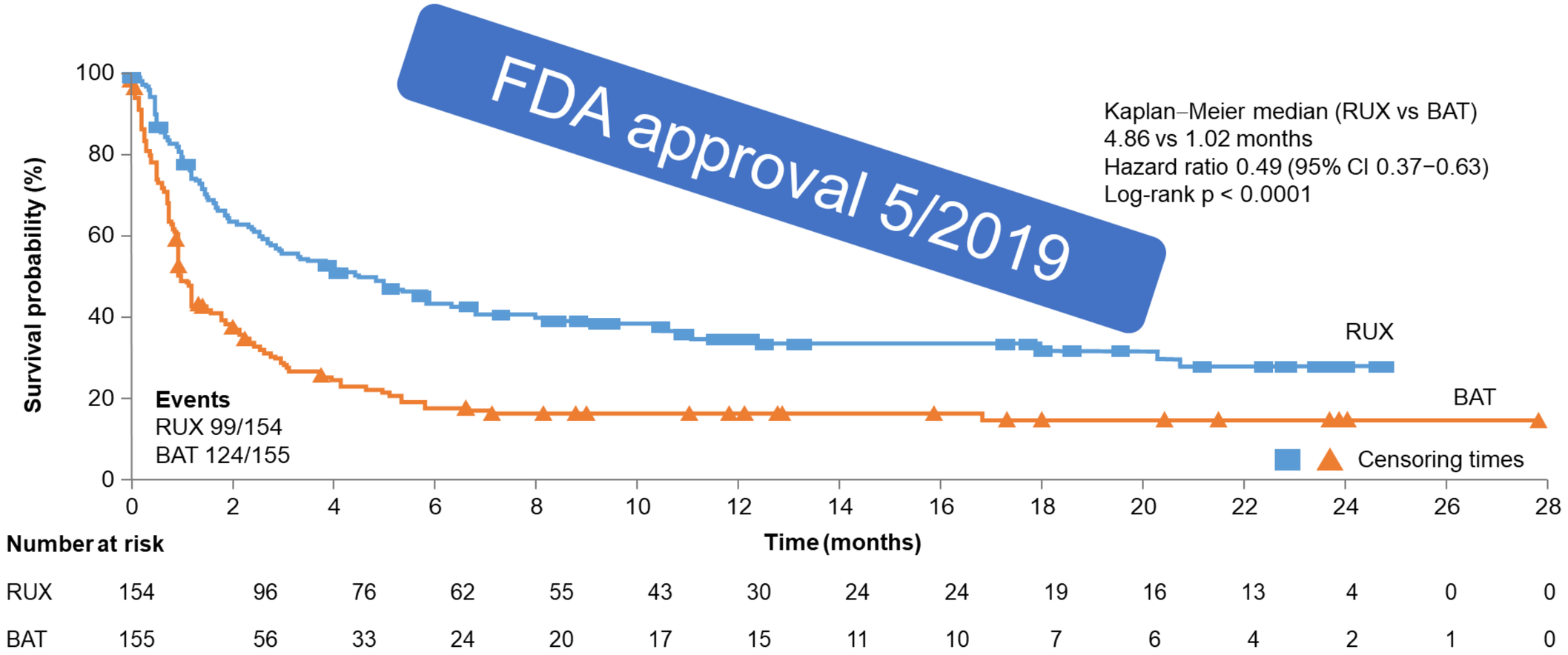
REACH2: Durable Overall Response Rate at Day 56 was Significantly Higher for Ruxolitinib Vs Best Available Therapy



	RUX (n = 154)	BAT (n = 155)
Responders, n (%)		
CR	41 (26.6)	25 (16.1)
PR	20 (13.0)	9 (5.8)
Nonresponders, n (%)		
NR	1 (0.6)	1 (0.6)
Mixed response	5 (3.2)	4 (2.6)
Progression	0	0
Other[a]	0	1 (0.6)
Unknown	29 (18.8)	21 (13.5)

[a] Other: patient with additional systemic therapies along with CR/PR per investigator assessment.

REACH2: Failure-free Survival



Number at risk

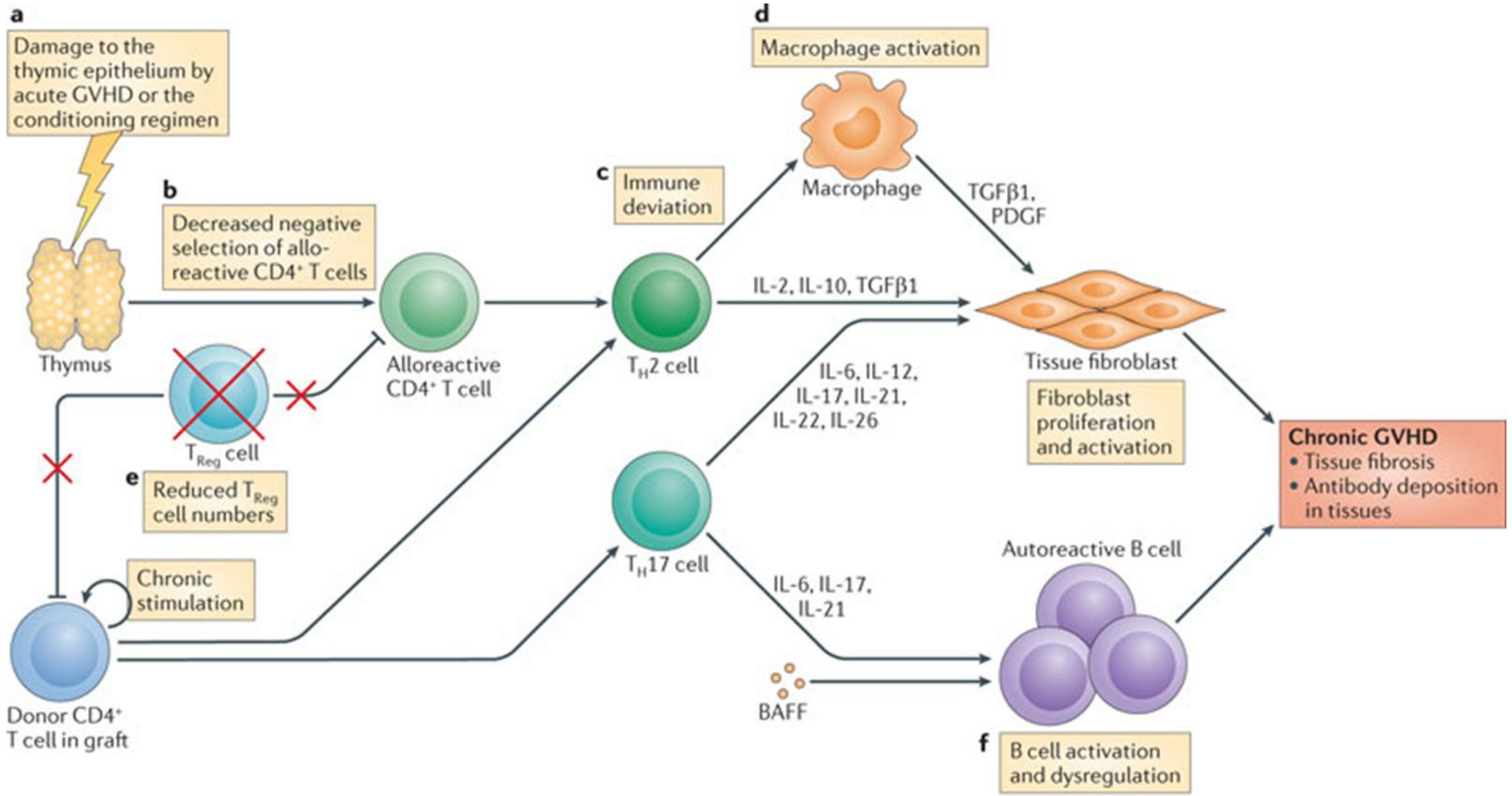
RUX	154	96	76	62	55	43	30	24	24	19	16	13	4	0	0
BAT	155	56	33	24	20	17	15	11	10	7	6	4	2	1	0

[a] The event included hematologic disease relapse/progression, NRM, or addition of new systemic aGvHD treatment.
FDA, Food and Drug Administration.

Mohty M, et al. Oral presentation at EBMT 2021; abstract OS8.

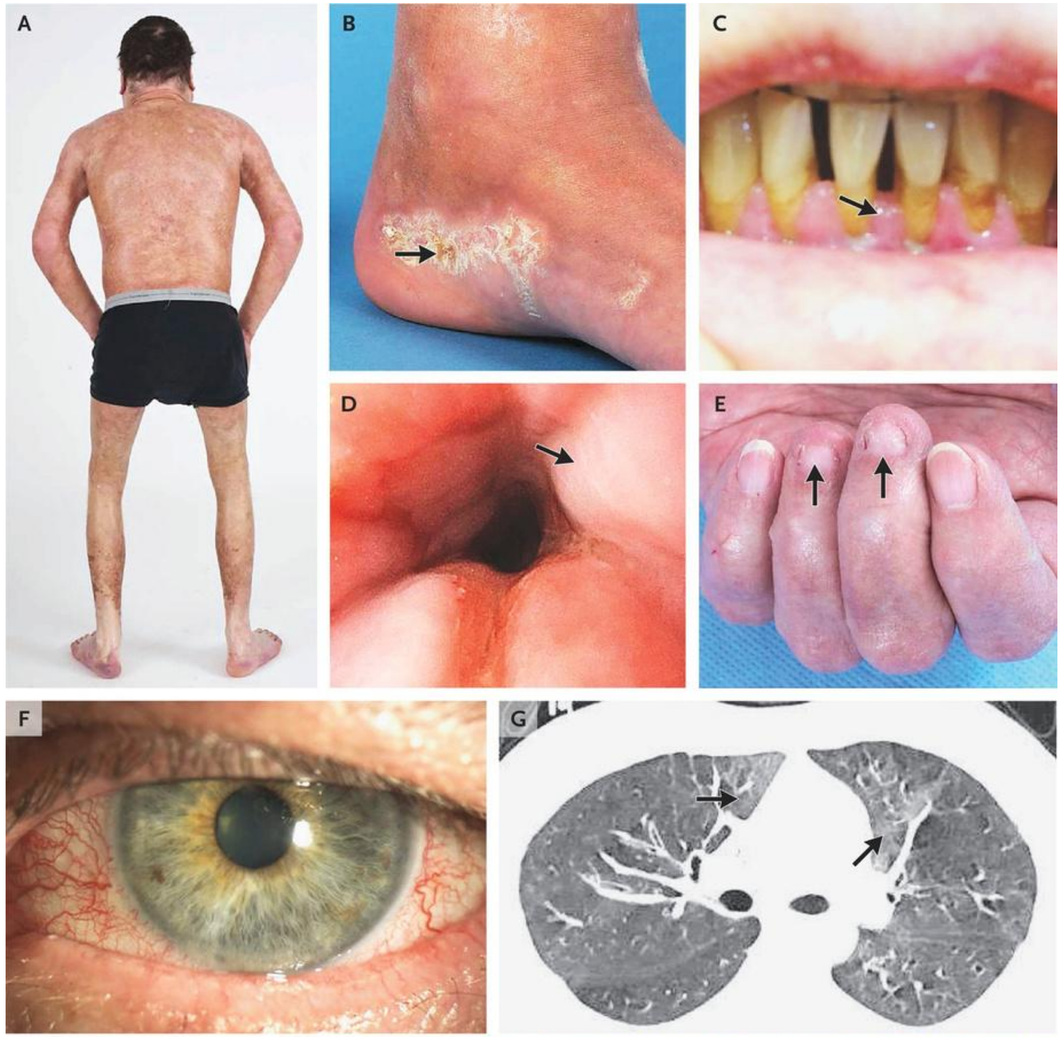
Chronic GVHD

Pathophysiology Chronic GvHD



Blazar B, et al. Nat Rev Immunol. 2012;12:443-58

Clinical and Histopathological Findings in Chronic GVHD



- Skin – 67 percent
- Mouth – 60 percent
- Liver – 52 percent
- Lung – 50 percent
- Eye – 48 percent
- Joints and fascia – 48 percent
- Gastrointestinal tract – 30 percent
- Genitalia – 12 percent

2014 NIH Criteria for Chronic GvHD Diagnosis

A) At least 1 diagnostic manifestation

or

B) 1 distinctive manifestation confirmed by biopsy or testing of same or other involved organ

- **Diagnostic manifestations** sufficient by themselves to establish the diagnosis of cGvHD: skin, mouth, GI tract, lung, fascia, and genitalia (lichen planus or lichen sclerosis, poikiloderma, sclerosis, or esophageal webs)
- There are no diagnostic features of the nails, eyes, or liver
- If the lung is the only site of cGvHD without a distinctive manifestation elsewhere, then a lung biopsy is mandatory

NIH Individual Organ Severity Score

0—No clinical manifestations/symptoms

1—Clinical manifestations with no more than mild disability

2—Clinical manifestations with moderate disability

3—Clinical manifestations with severe disability

Category	Number of Organs	Maximum Severity
Mild	≤2	1 (0 for lung)
Moderate (a)	≥3	1 (0 for lung)
Moderate (b)	Any	2 (1 for lung)
Severe	Any	3 (2 for lung)

	Score 0	Score 1	Score 2	Score 3
SKIN[6] *GvHD features to be scored by BSA:* **Check all that apply:** ❑ Maculopapular rash/ erythema ❑ Lichen planus-like features ❑ Sclerotic features ❑ Papulosquamous lesions or ichthyosis ❑ Keratosis pilaris-like	❑ No BSA involved	❑ 1-18% BSA	❑ 19-50% BSA	❑ >50% BSA
❑ Abnormality present but explained entirely by non-GvHD documented cause (specify):_____				
SKIN FEATURES Score:	❑ No sclerotic features		❑ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ❑ Deep sclerotic features ❑ "Hidebound" (unable to pinch) ❑ Impaired mobility ❑ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis_____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
EYES	❑ No symptoms	❑ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤3 x per day)	❑ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops ≤3 x per day or punctual plugs) **WITHOUT** new vision impairment due to KCS	❑ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
❑ Abnormality present but explained entirely by non-GvHD documented cause (specify):_____				
LUNGS	❑ No symptoms	❑ Mild symptoms (shortness of breath after climbing one flight of steps)	❑ Moderate symptoms (shortness of breath after walking on flat ground)	❑ Severe symptoms (shortness of breath at rest, requiring O_2)

Shoulder

1 (worst) 2 3 4 5 6 7 (normal)

❑ Not done

Elbow

1 (worst) 2 3 4 5 6 7 (normal)

❑ Not done

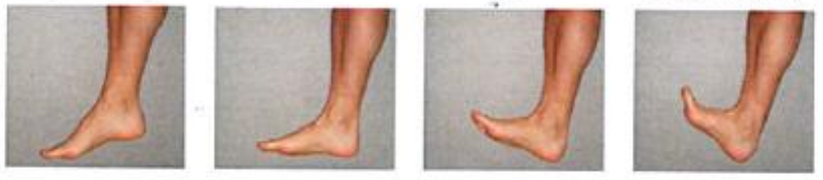
Wrist/finger

1 (worst) 2 3 4 5 6 7 (normal)

❑ Not done

Ankle

1 (worst) 2 3 4 (normal)



❑ Not done

Severity Grading of cGVHD

Table. National Institutes of Health Individual Organ Severity Scoring System

NIH Individual Organ Severity Score

0—No clinical manifestations/symptoms

1—Clinical manifestations with no more than mild disability

2—Clinical manifestations with moderate disability

3—Clinical manifestations with severe disability

Category	Number of Organs	Maximum Severity
Mild	≤2	1 (0 for lung)
Moderate (a)	≥3	1 (0 for lung)
Moderate (b)	Any	2 (1 for lung)
Severe	Any	3 (2 for lung)

Treatment of Chronic GvHD

100%

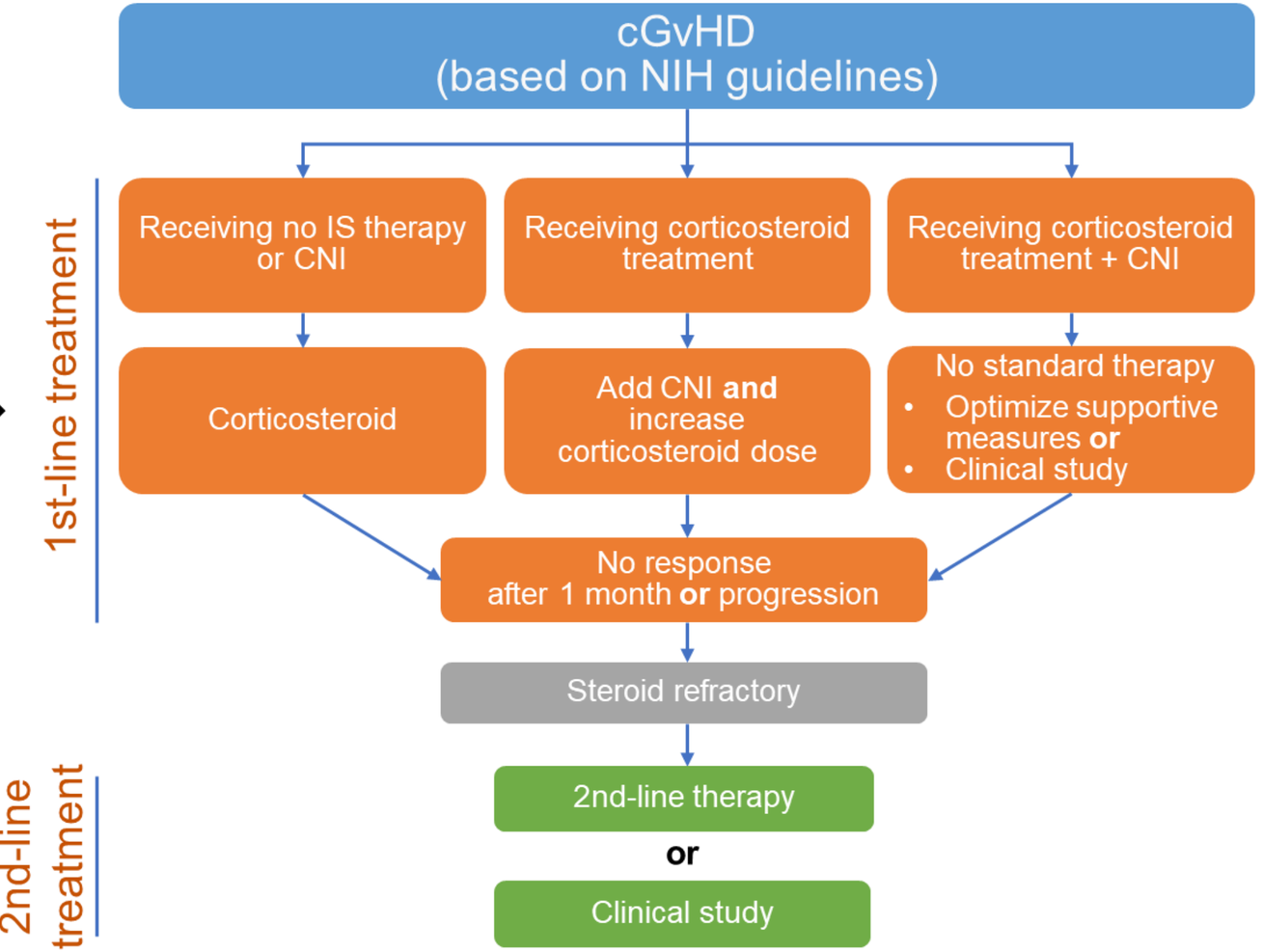
First-line treatment

The first-choice corticosteroid is prednisone at the dose of 1 mg/kg orally

- **Expert opinion, standard practice**
- **Based on non-comparative studies using 1 mg/kg**
- **There are no randomized studies comparing this dose to higher or lower steroid doses**

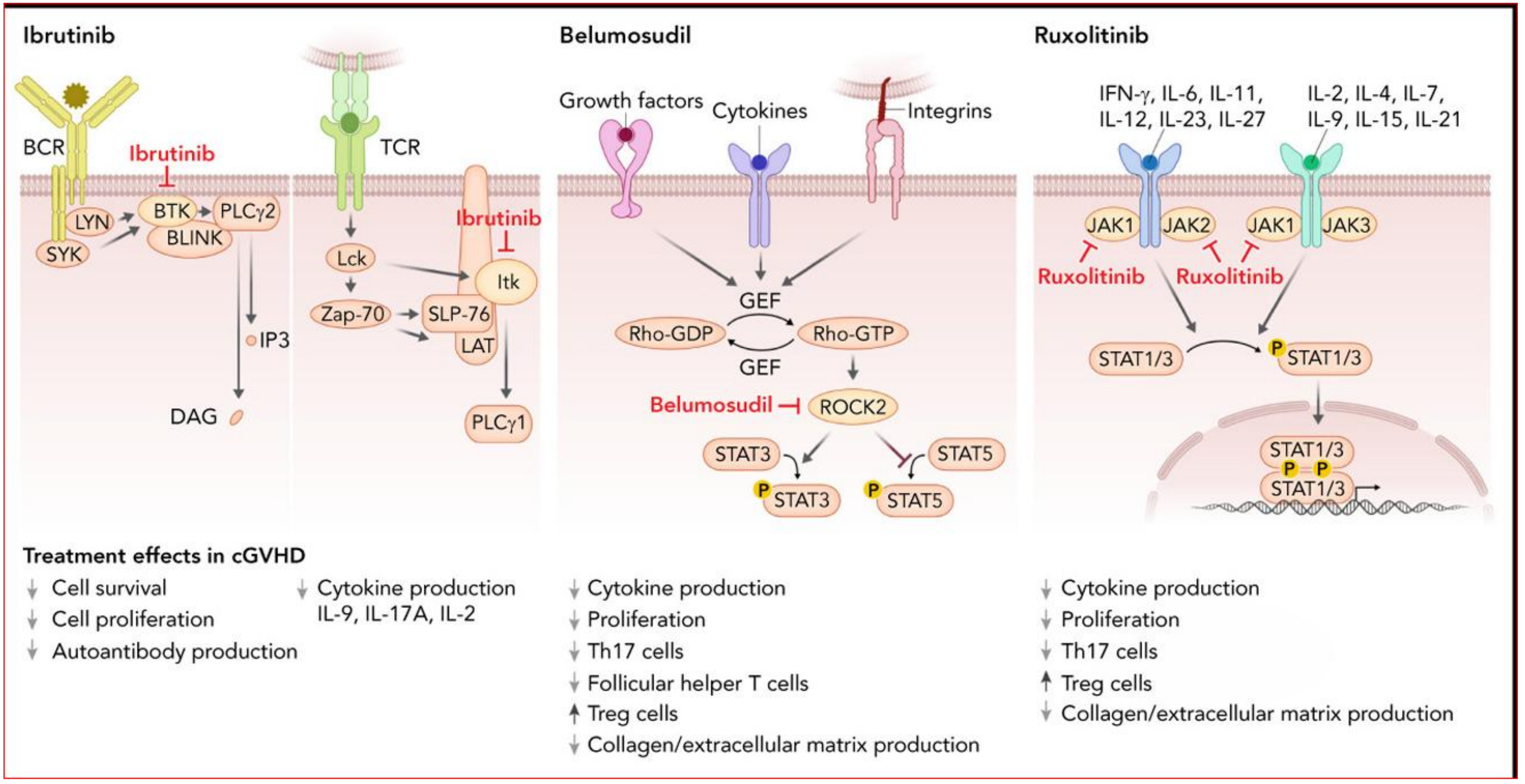
EBMT 2020 Treatment Guidelines: Chronic GvHD

Corticosteroids as 1st-line therapy



CNI, calcineurin inhibitor;
EBMT, European Group for Blood and Marrow Transplantation;
ELN, European LeukemiaNet;
NIH, National Institutes of Health.

Ruutu T, et al. Bone Marrow Transplant. 2014;49:168-73.



Treatment effects in cGVHD

Ibrutinib

- ↓ Cell survival
- ↓ Cell proliferation
- ↓ Autoantibody production
- ↓ Cytokine production IL-9, IL-17A, IL-2

Belumosudil

- ↓ Cytokine production
- ↓ Proliferation
- ↓ Th17 cells
- ↓ Follicular helper T cells
- ↑ Treg cells
- ↓ Collagen/extracellular matrix production

Ruxolitinib

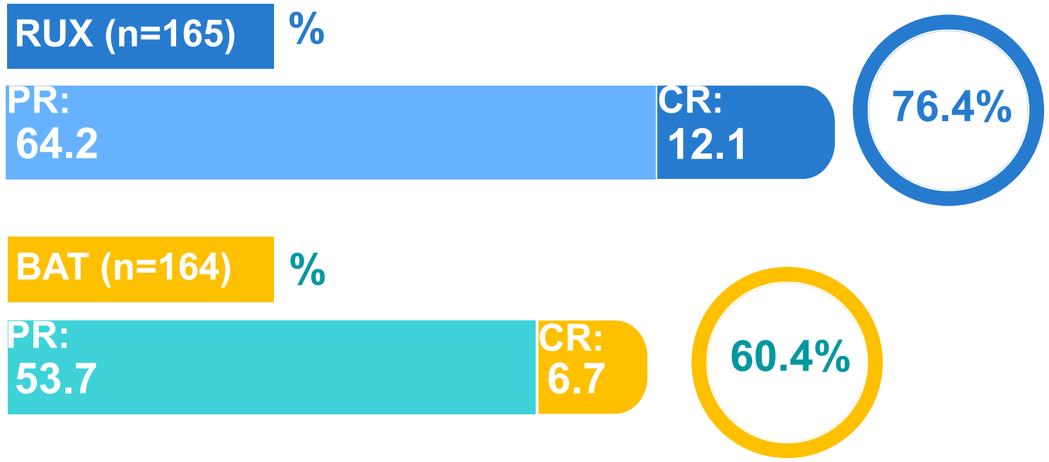
- ↓ Cytokine production
- ↓ Proliferation
- ↓ Th17 cells
- ↑ Treg cells
- ↓ Collagen/extracellular matrix production

Response at any Time was Higher with Ruxolitinib[a]

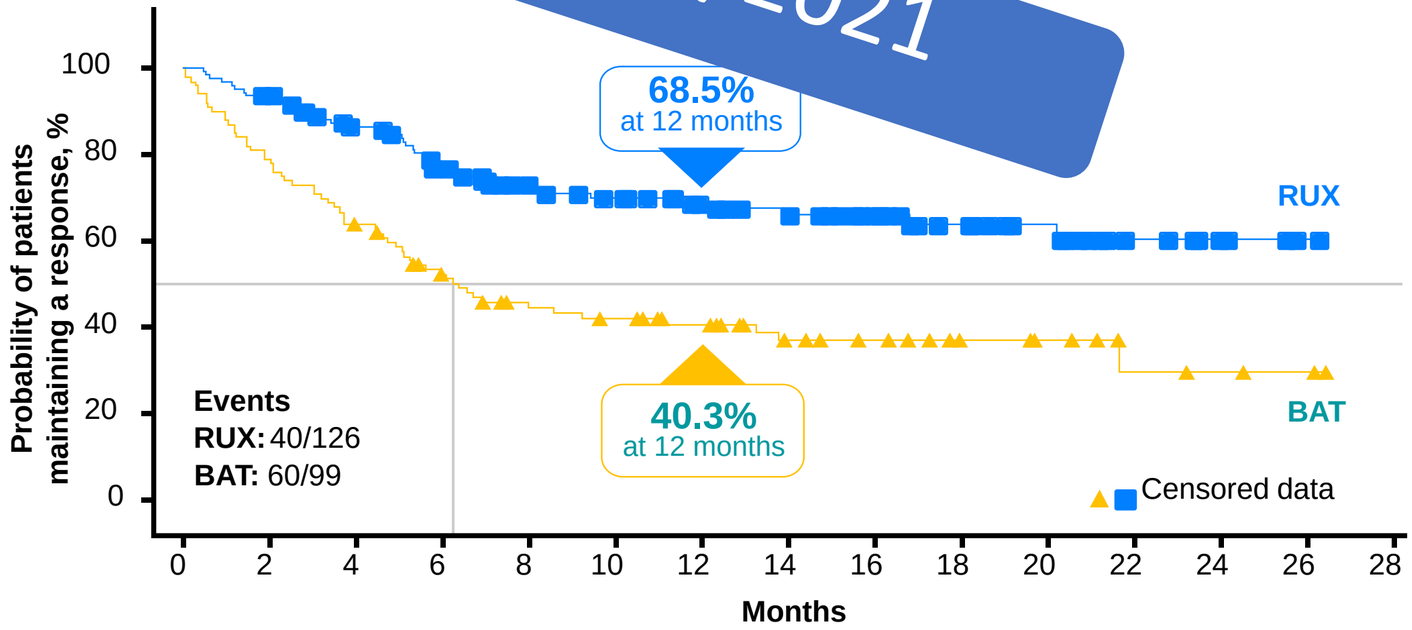
FDA approval 9/2021

Best Overall Response

OR, 2.17 (95% CI, 1.34-3.52)
RR, 1.24 (95% CI, 1.07-1.43)



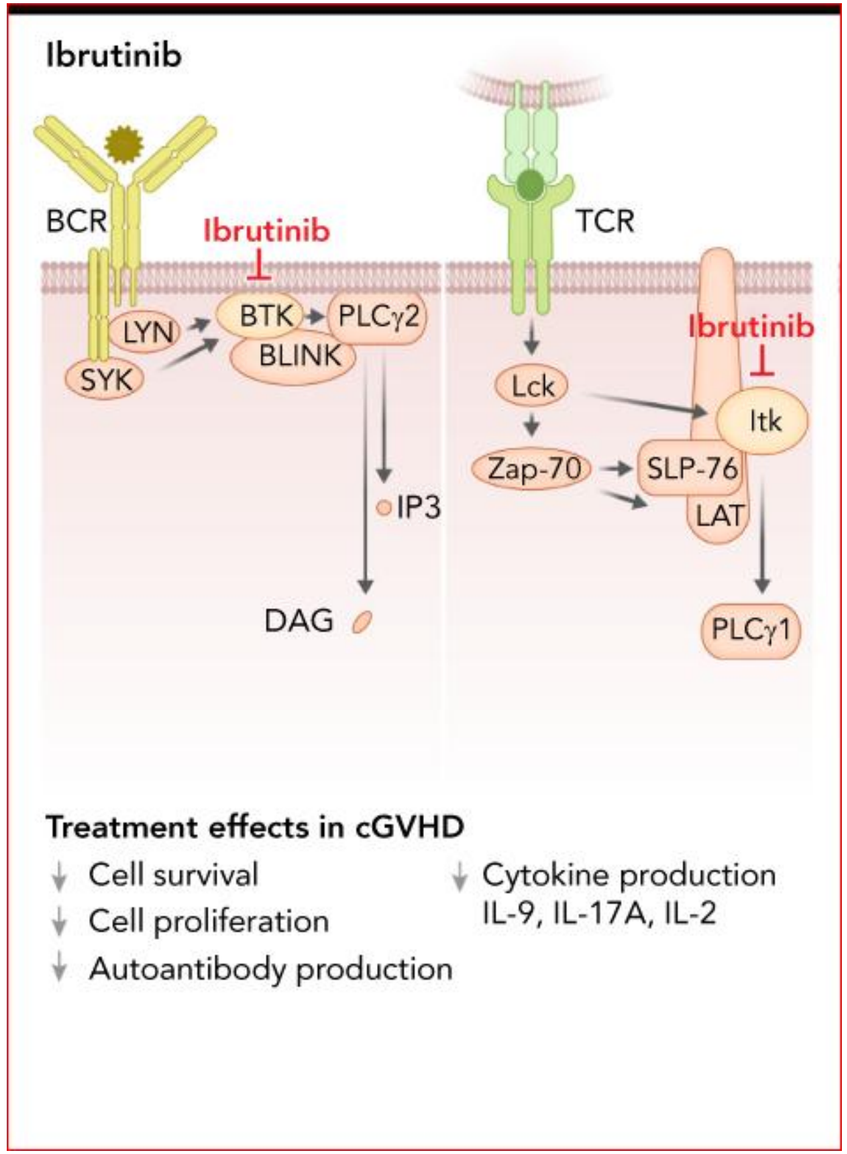
Duration of Response



Median duration of best overall response at any time point was 6.24 months in the BAT arm but was not reached in the RUX arm

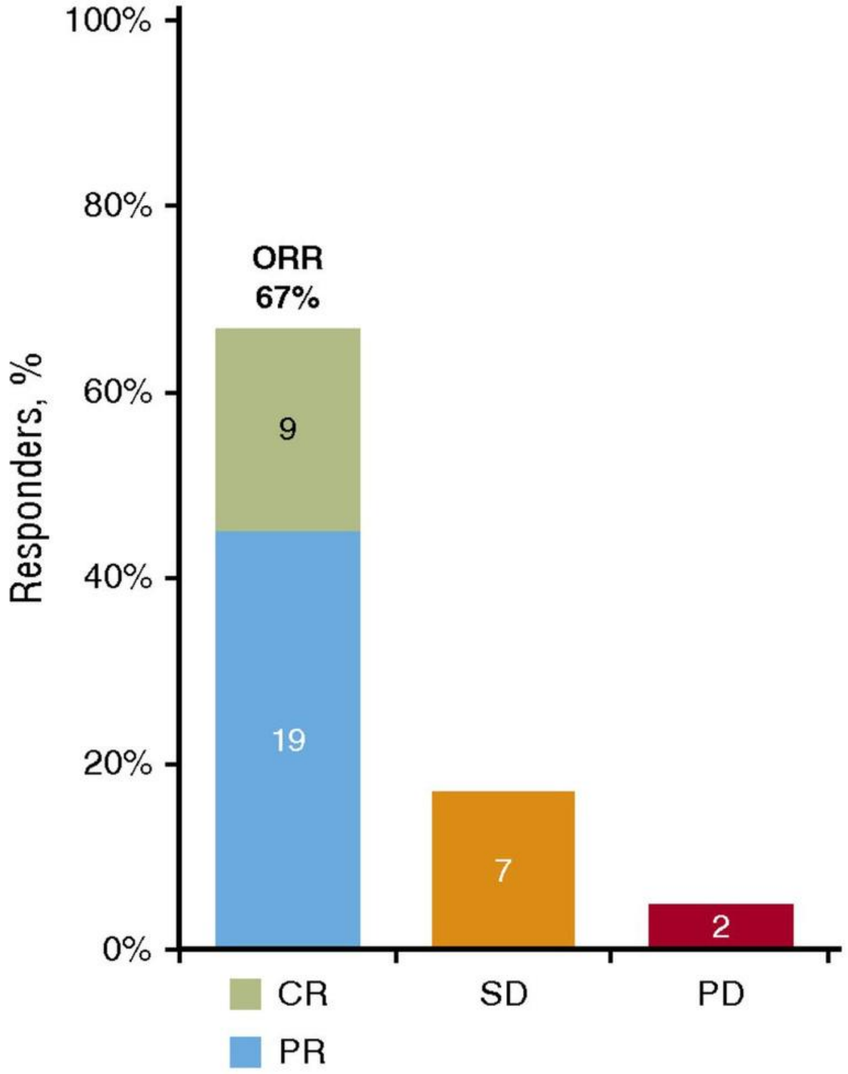
BAT, best available therapy; CR, complete response; OR, odds ratio; PR, partial response; RR, risk ratio; RUX, ruxolitinib.
[a] Among patients who achieved a CR or PR at any time up to week 24. Duration of response from first documented PR or CR.
Zeiser R, et al. *N Engl J Med*. 2021;385(3):228-238.

Ibrutinib for Chronic GvHD

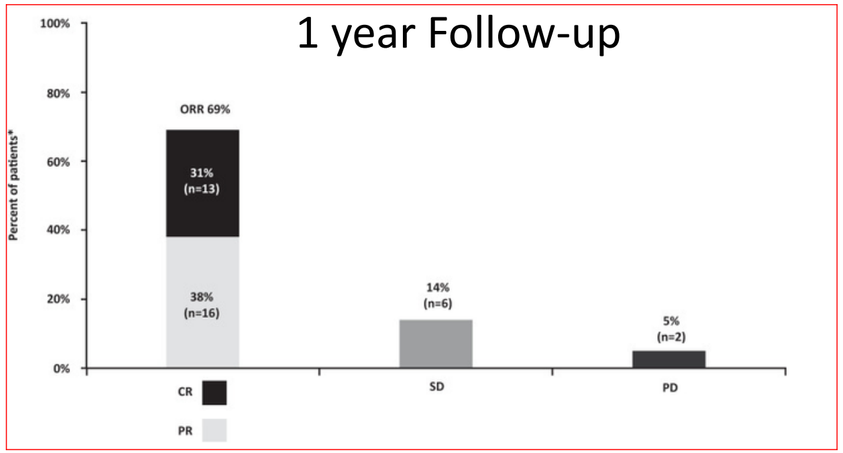


Zeiser R Blood 2022 Mar 17;139(11):1642-1645

Ibrutinib for Chronic GvHD after Failure of Prior Therapy
A phase Ib/II study



- 67% of patients experienced improvements in their cGvHD symptoms
- In 48% of patients in the trial, the improvement of symptoms lasted for up to 5 months or longer



FDA approved 2017
Pediatric approval -2022

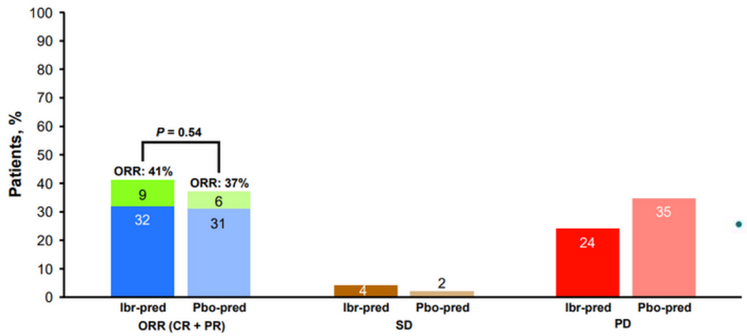
Miklos D, et al. Blood. 2017;130:2243-50
Waller EK BBMT 2019/ 25(10) .

PD, progressive disease; SD, stable disease.

Ibrutinib Vs Placebo in Combination With Corticosteroids in Patients With New-Onset Chronic Graft-Versus-Host Disease (cGVHD): Results From the Randomized, Double-Blind, Phase 3 iNTEGRATE Study

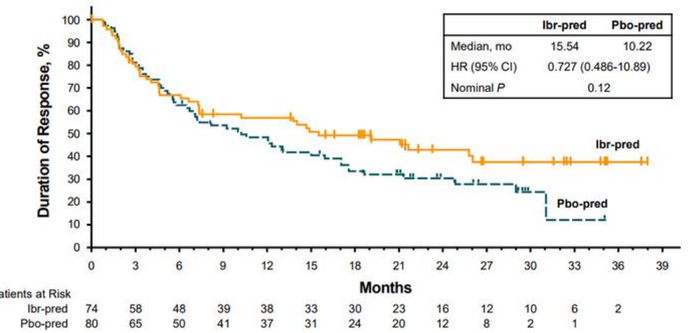
David Miklos, MD, PhD[1]; Mohammad Abu Zaid, MD[2]; Julian P. Cooney, MD, MBBS, FRACP, FRCPA[3]; Jörn Albring, MD[4]; Mary Flowers, MD[5]; Alan P. Skarbnik, MD[6]; Ibrahim Yakoub-Agha, MD, PhD[7]; Bor-Sheng Ko, MD, PhD[8]; Benedetto Bruno, MD, PhD[9]; Edmund K. Waller, MD, PhD, FACP[10]; Jean Yared, MD[11]; Sang Kyun Sohn, MD, PhD[12]; Claude-Eric Bulabois, MD[13]; Takanori Teshima, MD, PhD[14]; David Jacobsohn, MD, ScM[15]; Hildegard Greinix, MD[16]; Ahmad Mokatrin, PhD[17]; Yihua Lee, PhD[17]; Justin Wahlstrom, MD[17]; Lori Styles, MD[17]; and Gerard Socie, MD, PhD[18]

Response Rates at 48 Weeks



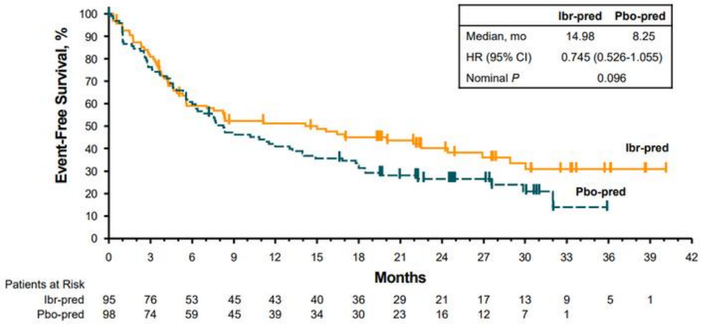
- There were no significant differences in response rates between arms in any of the individual organ systems

Duration of Response[a]



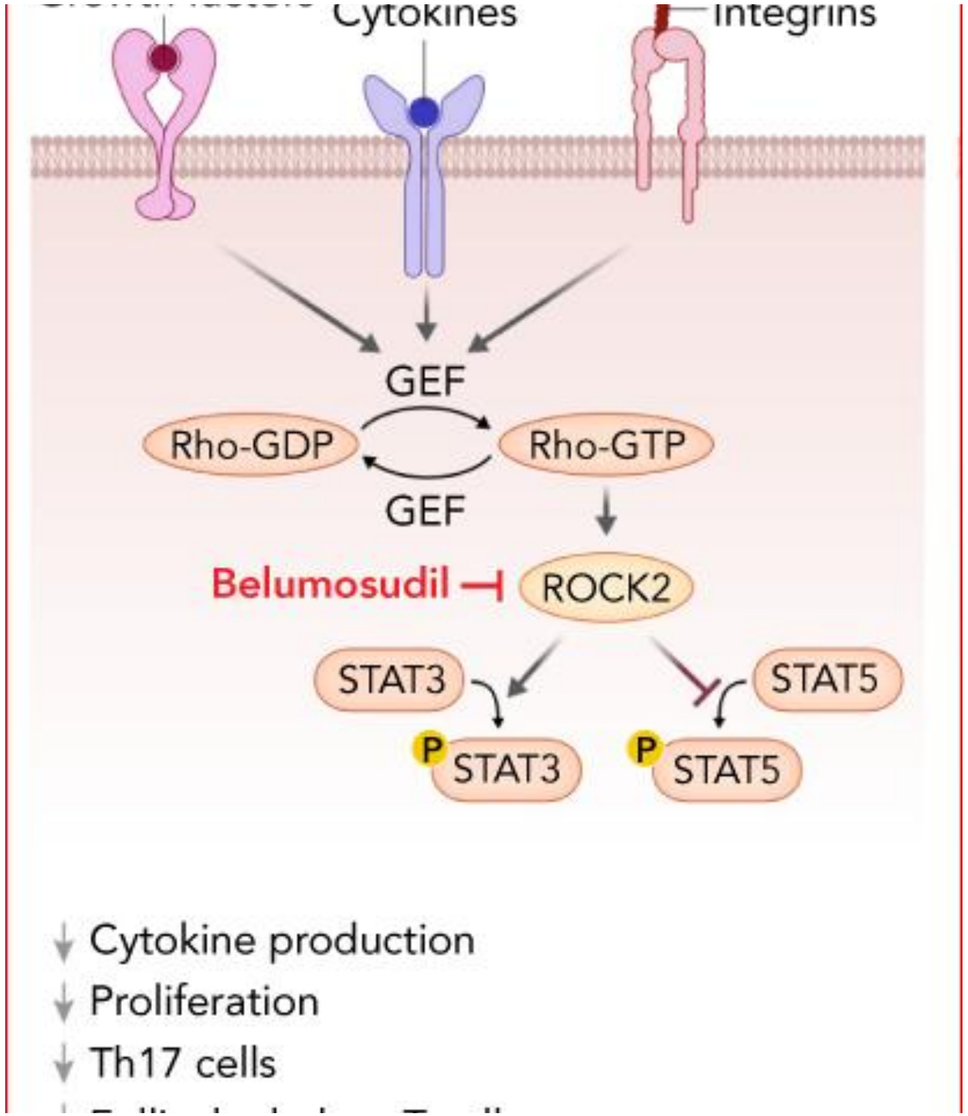
- Trend toward longer DOR was observed in the ibrutinib arm

Event-Free Survival[a]



- Events included death, malignancy relapse, cGVHD progression per NIH criteria, and initiation of subsequent therapy
- Trend toward longer EFS in the ibrutinib arm

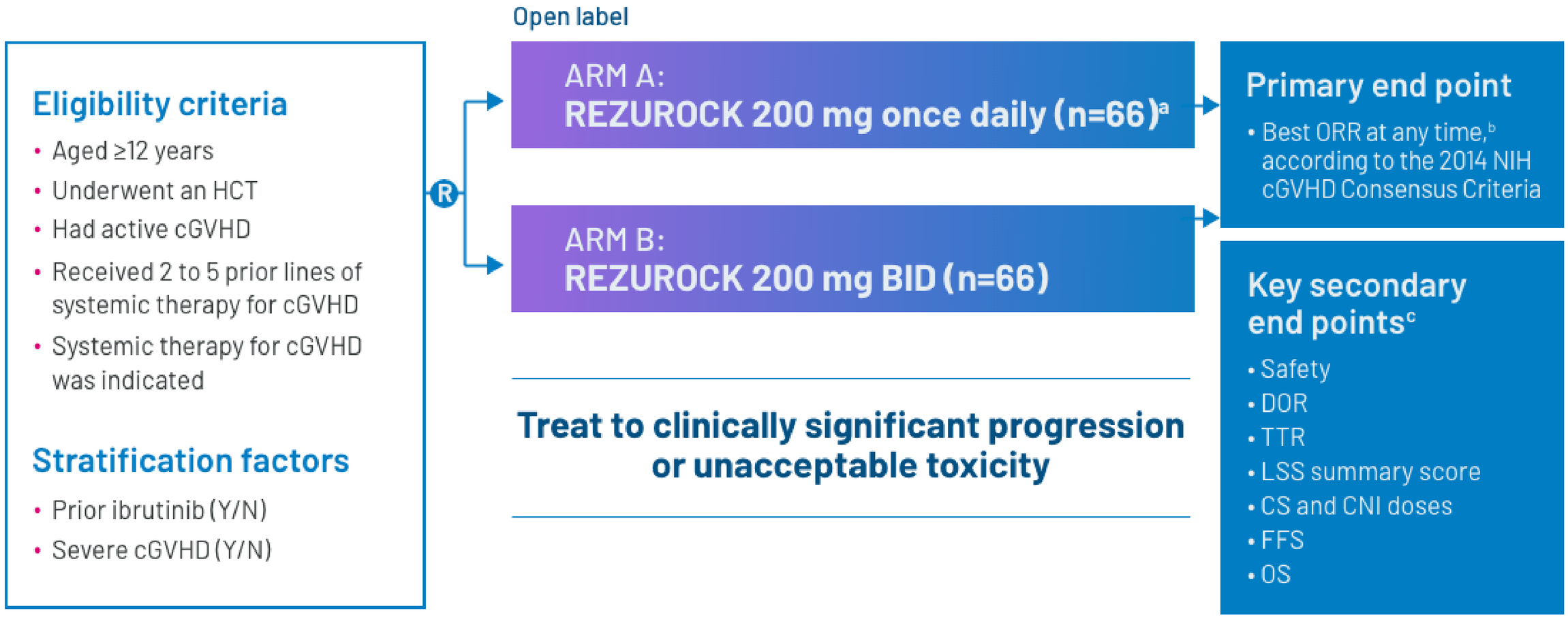
Belumosudil: oral selective ROCK2 inhibitor



Th, T helper cell.

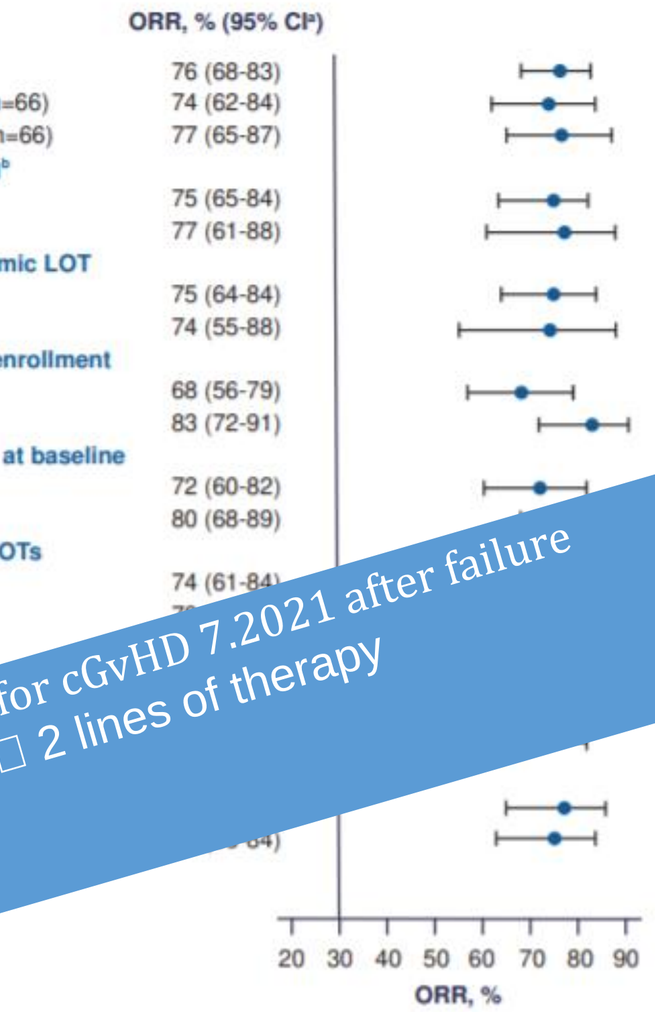
Zeiser R Blood 2022 Mar 17;139(11):1642-1645

Rockstar Study: Phase 2 Randomized Multicenter (28 Centers In USA)



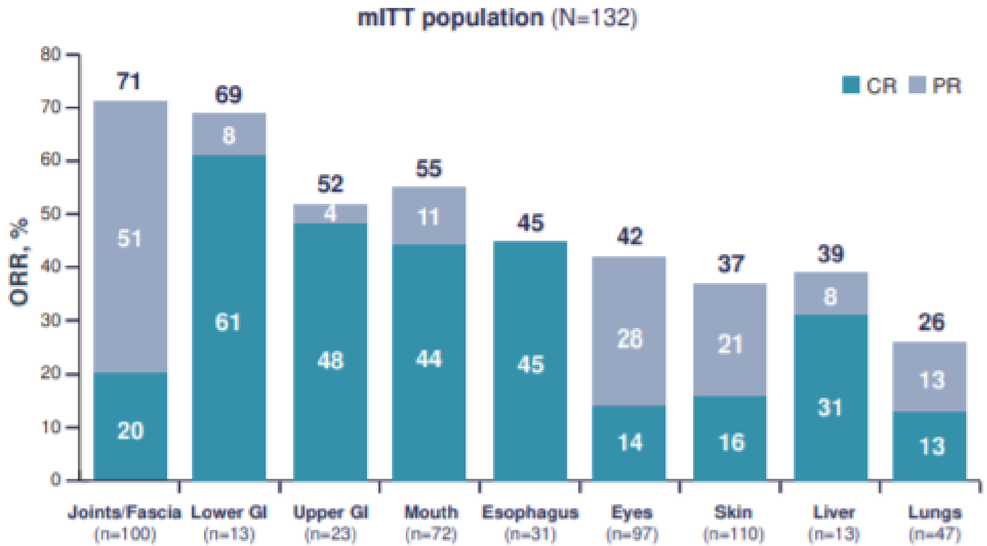
DOR, duration of response; TTR, time to response.

Figure 2.



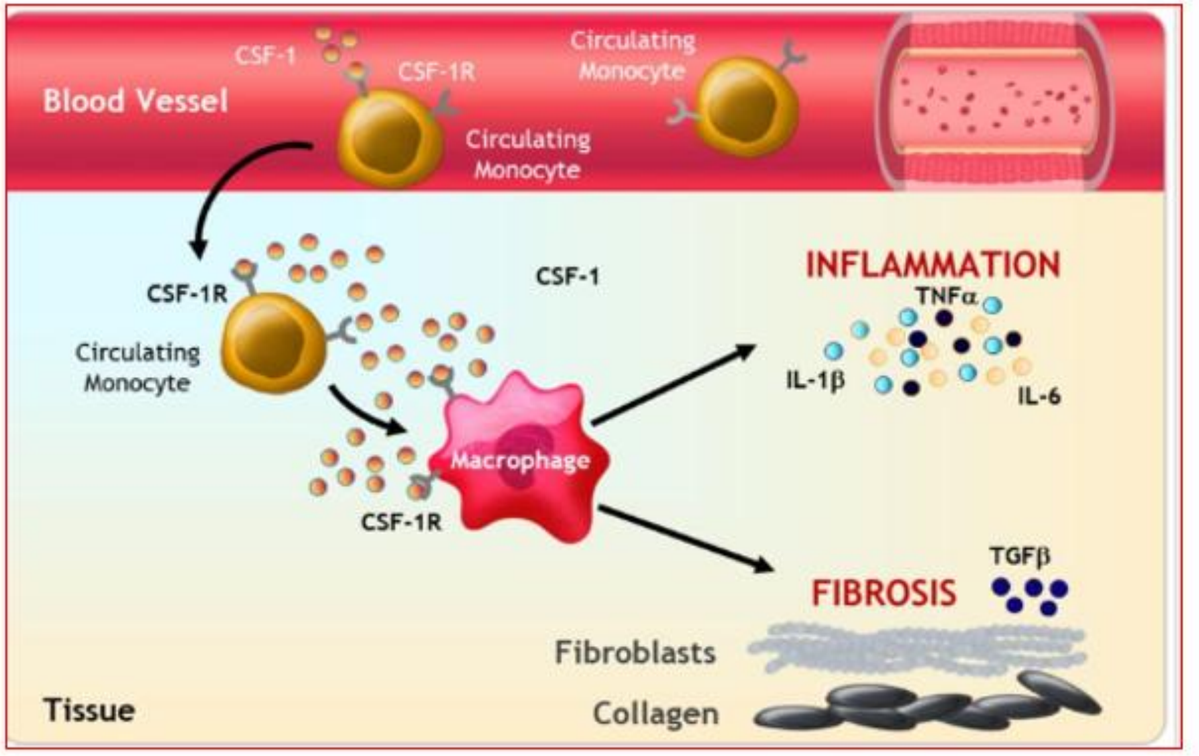
FDA approval for cGvHD 7.2021 after failure of ≥ 2 lines of therapy

Efficacy end point	Belumosudil 200 mg QD (n=66)	Belumosudil 200 mg BID (n=66)	Total (N=132)
ORR, n (%)	49 (74)	51 (77)	100 (76)
95% CI	62-84	65-87	68-83
ORR for responses occurring within 6 months of treatment, n (%)	47 (71)	48 (73)	95 (72)
95% CI	59-82	60-83	64-80
CR, n (%)	2 (3)	1 (2)	3 (2)
PR, n (%)	45 (68)	47 (71)	92 (70)
ORR for responses occurring within 12 months of treatment, n (%)	49 (74)	50 (76)	99 (75)
95% CI	62-84	64-86	67-82
CR, n (%)	4 (6)	2 (3)	6 (5)
PR, n (%)	45 (68)	48 (73)	93 (71)



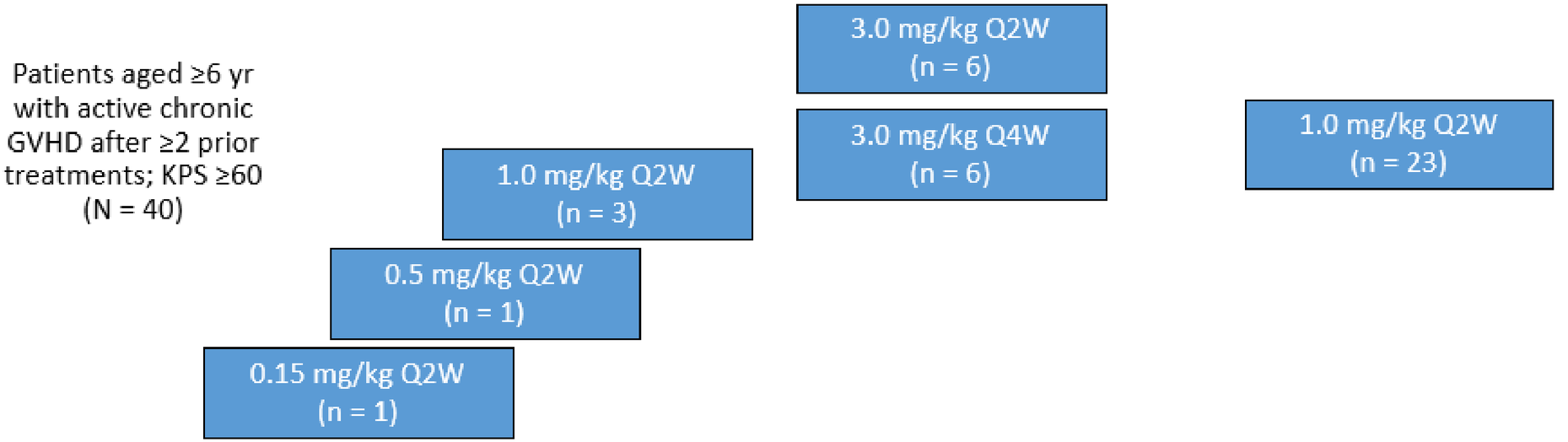
Corey C , Blood, 2021 138 (22).

Axatilimab


Blood Vessel
CSF-1
CSF-1R
Circulating Monocyte
Circulating Monocyte
CSF-1R
Circulating Monocyte
CSF-1
Macrophage
CSF-1R
INFLAMMATION
TNFα
IL-1β
IL-6
TGFβ
FIBROSIS
Fibroblasts
Collagen
Tissue

Axatilimab in Chronic GVHD: Phase I/II

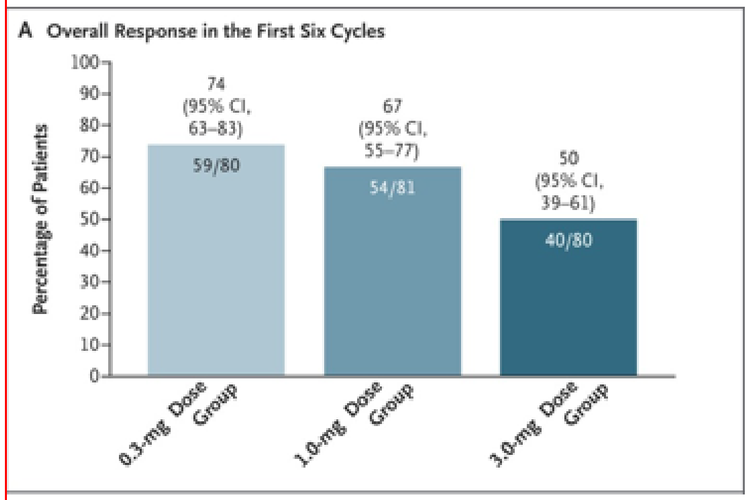
- Phase I/II dose escalation/expansion study

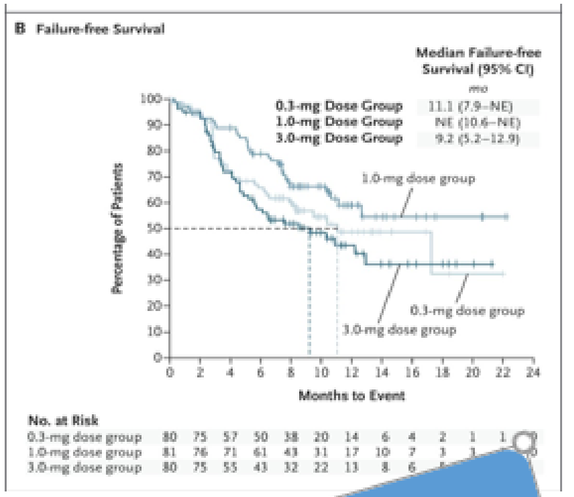


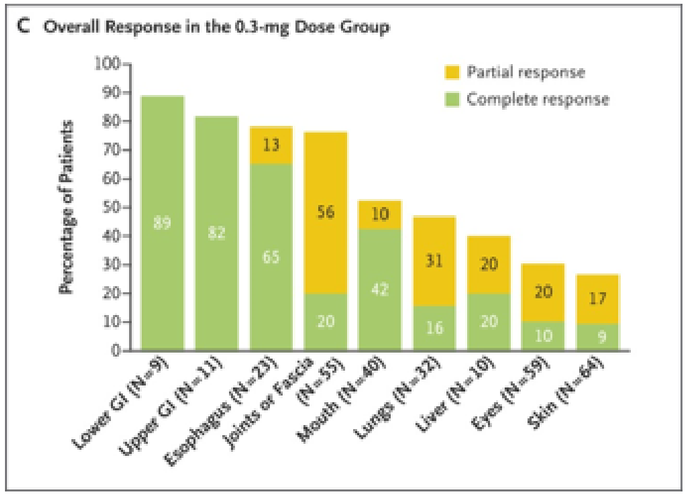
- **Phase I endpoints:** safety, ORR, RP2D (analysis identified as 1.0 mg/kg Q2W)
- **Phase II primary endpoint:** ORR (by 2014 NIH chronic GVHD criteria)

Lee. ASH 2021. Abstr 263.

Overall Response and Failure-free Survival (Intention-to-Treat Population).







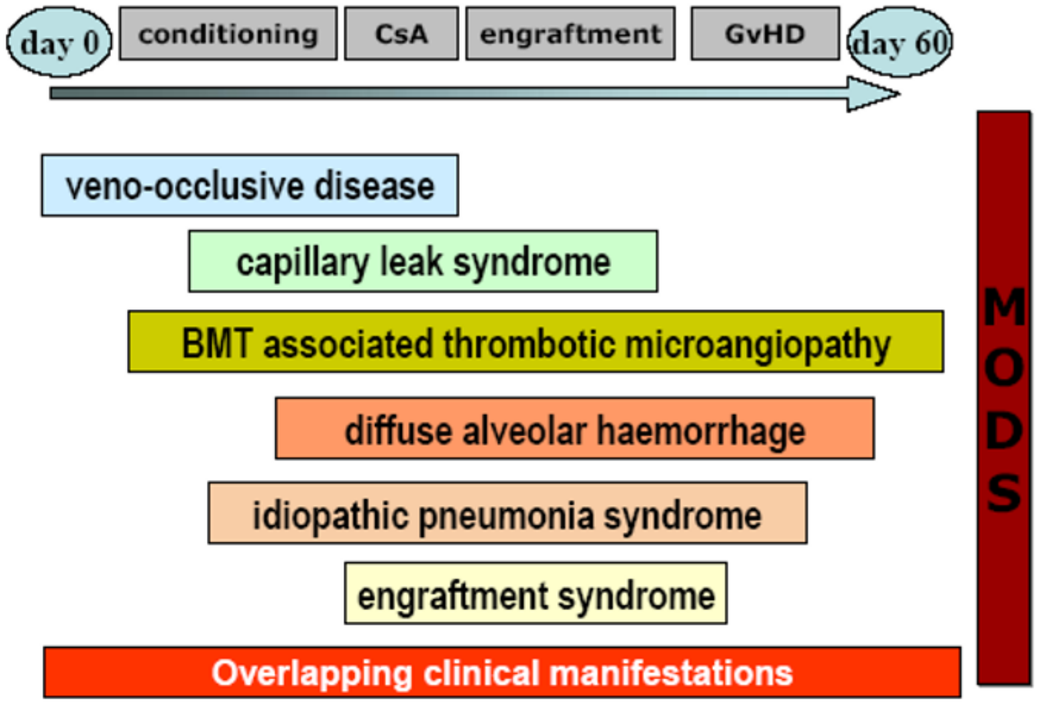
FDA approval for cGvHD 8.2024 after failure of ≥ 2 lines of therapy

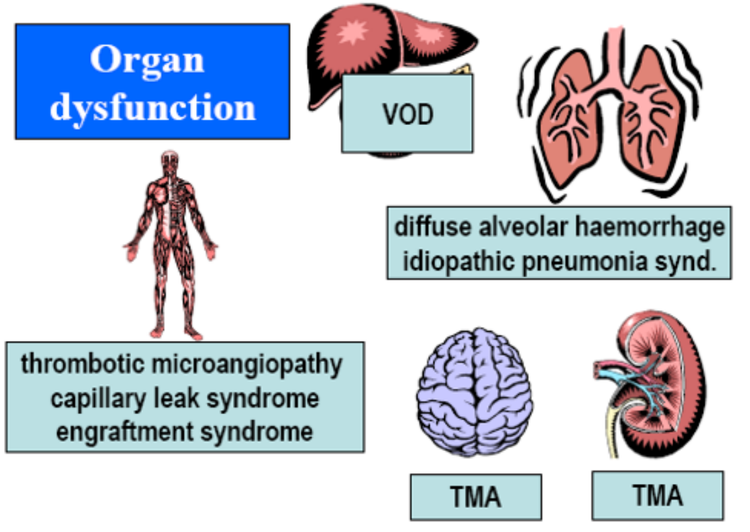
Wolff D .N Engl J Med
Volume 391(11):1002-1014
September 19, 2024

Conclusions I

- GvHD is a major complication post SCT and is associated with significant morbidity and mortality especially when steroid refractory or dependent .
- Recent years have advanced our understanding of the pathophysiology of the disease and resulted in development of targeted therapy
- All treatments are targeting at kinase inhibitors resulting in reduction of growth signals and activation of key cellular proteins involved in cell activation, migration and proliferation.
- Following phase II-III studies FDA approved since 2017 1 treatment in aGVHD and 3 in cGVHD .However only the Ruxolitinib was a a phase III study.

SCT-associated Endothelial Dysfunction / Vascular Endothelial Syndromes





SCT-Associated Endothelial Damage- Pathogenesis

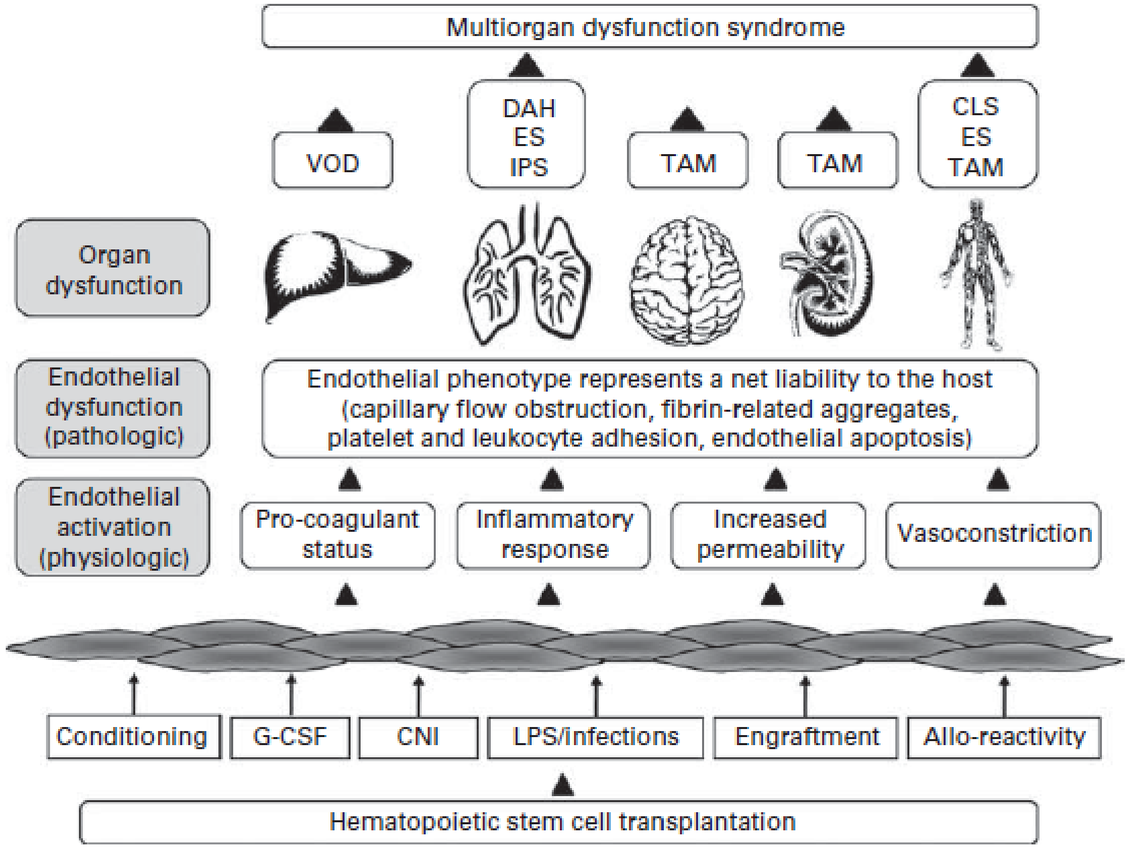


Figure 2 Common pathogenesis of the vascular endothelial syndromes developed early after HSCT. CLS, capillary leak syndrome; CNI, calcineurin inhibitors; DAH, diffuse alveolar haemorrhage; ES, engraftment syndrome; IPS, idiopathic pneumonia syndrome; LPS, lipopolysaccharide; TAM, transplant-associated microangiopathy; VOD, veno-occlusive disease.

הסינדרומים השונים נקבעים לפי השינוי הפנוטיפי הדומיננטי (פרו-אינפלמטורי, פרו-טרומבוטי או פרו-אופטוטי) ומיקומו (סיסטמי או ממוקם לאיבר).

Endothelial syndromes after HSCT
E Carreras and M Diaz-Ricart, BMT (2011) 46, 1495–1502

Clinical Manifestations

Table 2 Clinical manifestations of the vascular endothelial syndromes after HSCT

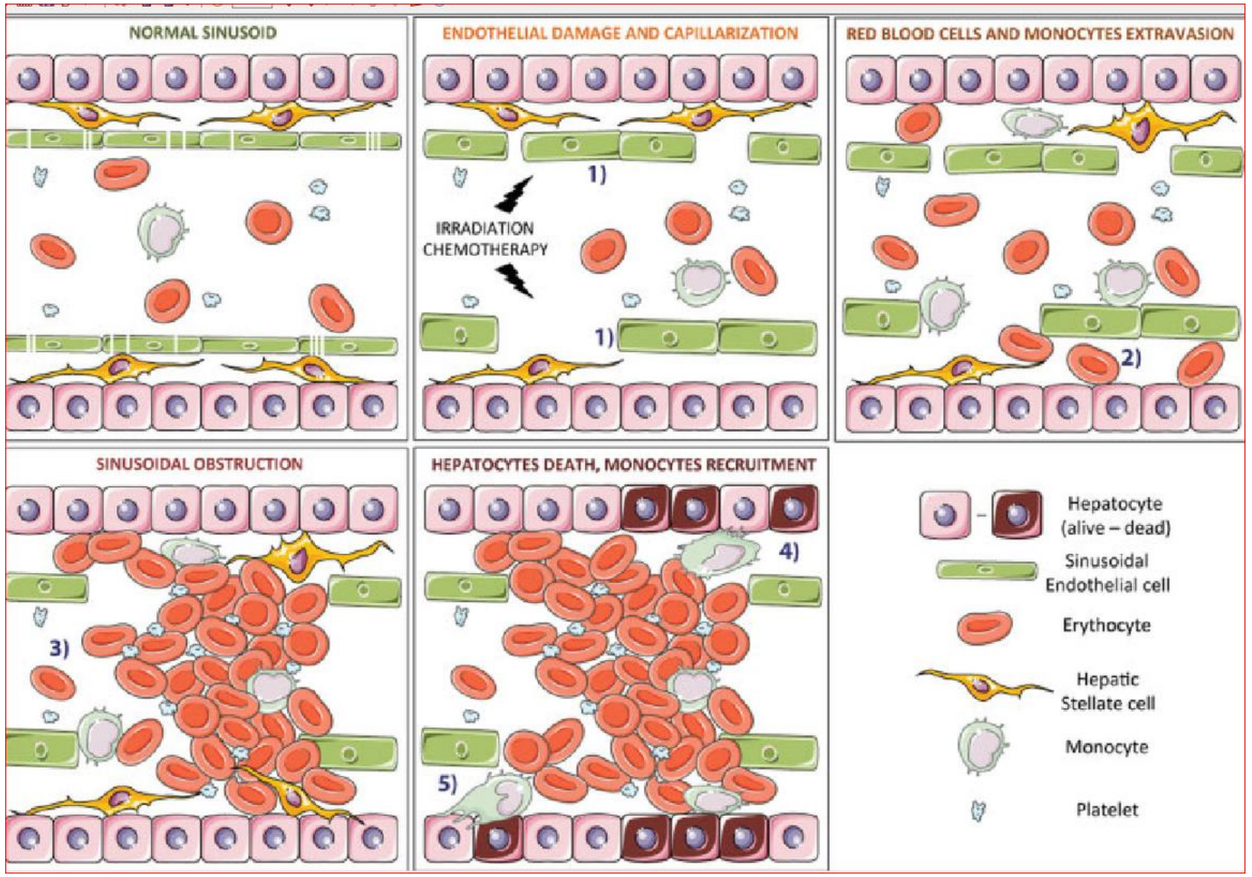
Symptoms and signs	*VOD*	*CLS*	*ES*	*DAH*	*IPS*	*TAM*
Usually starting	0–7	7–10	11–15	11–19	18–23	25–120
on day:						
Fever		✓	✓		✓	✓
Jaundice	✓					
Hepatomegaly	✓					
Weight gain	✓	✓	✓			
Oedemas	✓	✓				
Ascites	✓	✓				
Lung infiltrates	✓	✓	✓	✓	✓	
Dyspnoea	✓	✓	✓	✓	✓	
Hypoxia	✓	✓	✓	✓	✓	
Diarrhoea			✓			
Renal dysfunction	✓	✓	✓			✓
Neurological dysfunction			✓			✓
Evolution to MODS	✓	✓	✓		✓	✓
Predominant in:	allo	auto	auto	allo	allo	allo

Endothelial syndromes after HSCT
E Carreras and M Diaz-Ricart, BMT (2011) 46, 1495-1502

VOD / SOS – introduction

- SOS – the most common and studied from these syndromes, the only one with diagnostic clinical criteria
- Incidence – Allo, MAC – 14%, RIC/Auto- <5% influenced by several risk factors
- High morbidity and mortality, severe VOD - >90% in 100d (McDonald, 93)
- Several therapeutic measures for prevention and treatment – no consensus

SOS Pathogenesis



1.Loss of sinusoidal fenestration and formation of gaps in the endothelial barrier.
2.Endothelial cell round up and red blood cells penetrate the space of Disse.
3. Obstruction of the sinusoidal blood flow.
4.Necrosis of hepatocytes and denudation of endothelial lining.
5. Loss of Kupffer cells and activation of coagulation obstruct larger vessel (centrilobular vein).

SOS Clinical criteria

Usually pediatrics

Usually adults

Modified Seattle criteria Shulman & Hinterberger, 1992	Baltimore criteria Jones et al, 1987
Two of the following criteria must be present within 20 d of transplant	**Bilirubin** must be > 2mg/dl within 21d of transplant **and two of the following** criteria must be present
Bilirubin > 2 mg/dl	hepatomegaly
Hepatomegaly or right upper quadrant pain	ascites
Weight gain (>2% from pre-transplant weight)	Weight gain (>5% from pre-transplant weight)

SOS risk factors

Risk factor	Lower risk<higher risk of SOS
Liver status	Normal < fibrosis, cirrhosis, tumor
Iron overload	Absent < present
Previous drugs	Gemtuzumab ozogamicin (MYLOTARG)
Type of HCT	Autologous < allogeneic (first < second)
Type of donor	HLA identical sibling < unrelated
Grade of compatibility	Match < minor mismatch < major mismatch
Conditioning regimen	
Total dose	RIC < MAC
Busulfan	IV < oral dose targeted < oral non adjusted
Order of administration	Other combinations < Busulfan first than Cy

Carreras, How I Manage SOS after HCT
British Journal of Hematology, 2015, 168, 481-491

SOS Severity Grading

- Retrospective clinical criteria
- Mild – spontaneous resolution
- Severe - >100d or the cause of death
- Nowadays the presence of Multi Organ Failure (MOF) - renal, respiratory or CNS, is considered the most powerful prognostic factor for severe VOD

Grade of SOS

Clinical data/grade	* Mild	* Moderate	* Severe
Rate of change (d)	Slow (over 6-7 d)	Mod (over 4-5 d)	Rapid (over 2-3 d)
Bilirubin (mg/dL)	2-2.99	3-5	5 <
Liver function tests	X normal 3 >	X normal 3-5	X normal 5 <
Weight above baseline	2%	2.1-5%	5% <
Renal function	normal	X normal 2 >	≥X normal 2

* 2 or more of the followings

Carreras, BJH, 2015
Adopted from Chao, 2014

Diagnosis – Methods

- A “rule-out” diagnosis
- Trans-jugular biopsy (not mandatory)
- Hepatic venous gradient pressure (HVGP)
- Ultra-Sound
- Plasminogen activator inhibitor (PAI-1)

Carreras et al. 1993, BMT

VOD/SOS

- Prevention

- **Ursolit** shown to be effective in some randomized studies
- Treatment of possible risk factors (iron overload, hepatitis)
- Selection of conditioning regimen (RIC in high risk patients)
- Avoiding hepato-toxic drugs
- Defibrotide in high-risk children

- Treatment

- Supportive – **Diuresis**
- **Defibrotide – for severe VOD** (תערובת של אוליגונוקלאוטידים חד גדיליים מרירית מעי חזיר) - cure in up to 50% (30-76%)

TA-TMA: Clinical features

- Multisystem, multifactorial disease with hyper-activated complement system -> tissue damage caused by micro-vessel thrombosis, that usually presents 20-100 days post-transplant
- A member of the family of thrombotic microangiopathies (TTP, HUS) **BUT** normal ADAMTS13 levels

HSCT related TMA

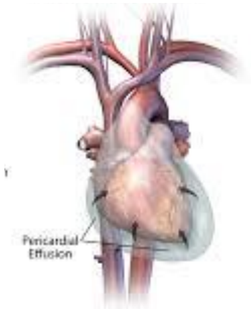
Elevated BP

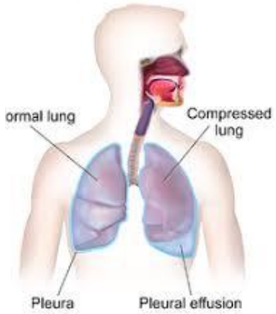
+

AKI + proteinuria

+

Hemolysis(LDH, haptoglobin)
Anemia
Thromobocytopenia
Schistocytes on blood smear





Incidence: 0.5% - 76% (recent studies: 10%-35%)
Mortality rate : 80%-90% if patients develop multi-organ failure

Diagnosis and causes of TMA in HSCT patients (Blood 2014, Laskin B et al)

TA-TMA

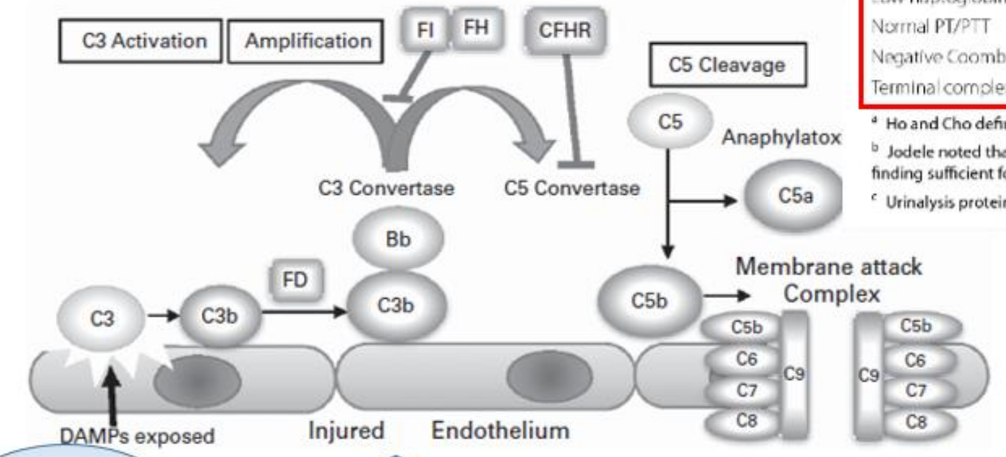
Table 1 Summary of TA-TMA diagnostic criteria

Diagnostic criteria	CTN 2005 Ho [7]	EBMT IWG 2007 Ruutu [8]	Overall TMA 2010 Cho [9]	2016 Jodele [21]
Schistocytes[a]	✓	✓	✓	✓[b]
Elevated LDH	✓	✓	✓	✓
Renal and/or neurologic dysfunction	✓			✓[c]
Thrombocytopenia		✓	✓	✓
Anemia		✓	✓	✓
Low haptoglobin		✓	✓	
Normal PT/PTT	✓	✓	✓	
Negative Coombs test	✓		✓	
Terminal complement activation				✓

[a] Ho and Cho defined increased schistocytes as ≥ 2/HPF. Ruutu defined ≥ 8/HPF as the threshold suggestive of TA-TMA

[b] Jodele noted that histologic evidence of microangiopathy on a tissue specimen may exist in the absence of peripheral blood schistocytosis and considered this finding sufficient for a diagnosis of TA-TMA even in the absence of other any other suggestive clinical features

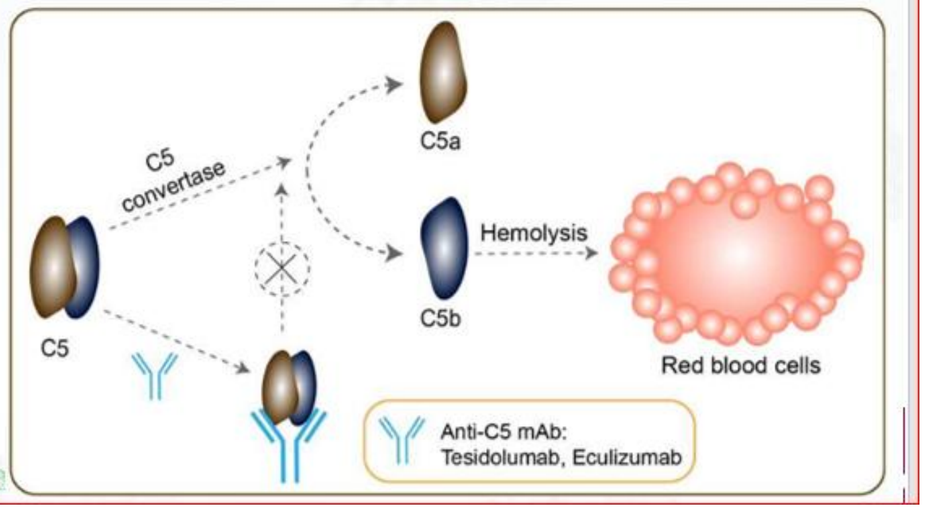
[c] Urinalysis protein concentration of ≥ 30 mg/dL and/or hypertension considered more reliable than serum creatinine as evidence of renal dysfunction



DAMPS=damage-associated molecular patterns

Conditioning regimens
Use of CNI
Infections
aGVHD

Eculizumab



Transplant-associated thrombotic microangiopathy
J Khosla et al. Bone Marrow Transplantation (2018) 129 – 137

Engraftment syndrome

Clinical features

- Within 24 -96 h of engraftment
- High **fever** of non-infectious etiology **+**
  (unresponsive to antibiotics w negative cultures)
- **Skin rash** (>25% b.s.) (R/O allergic reaction)
- **Lung infiltrates or hypoxia**
  (not due to volume overload, congestive heart failure)

- Other: Diarrhea (non-infectious), weight gain, oedemas, ascites, organ dysfunction (renal, neurological, hepatic)
- **Responds well to steroids**

Idiopatic Pneumonia Syndrome

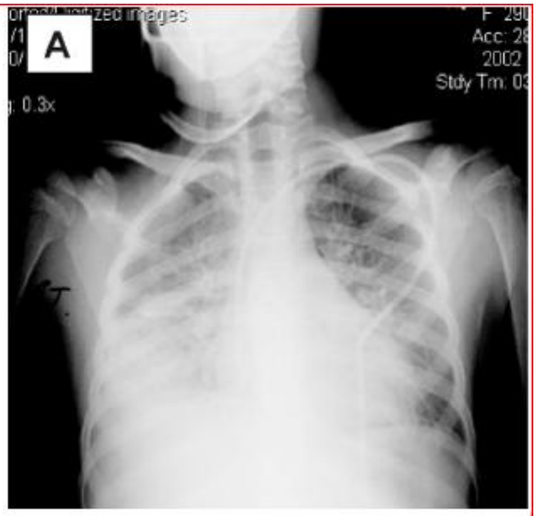
- <10% of allogeneic transplants, uncommon after auto
- Lung insults from toxic effect of conditioning, cell mediated injury, inflammatory cytokines, occult infections

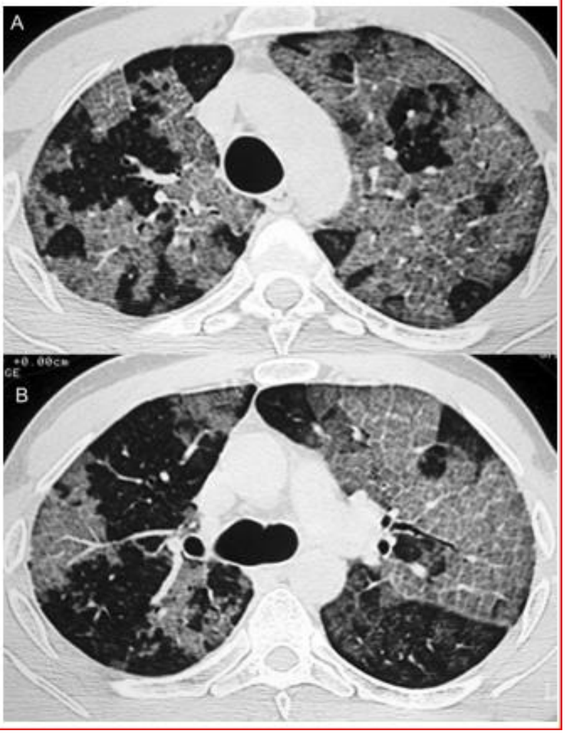
Risk factors: TBI (BCNU, BU, CTX), Age, prior XRT, MTX, unrelated BMT, acute GVHD

Clinical diagnosis: fever, cough, dyspnea, hypoxemia, diffuse alveolar or interstitial lung infiltrates, no pathogen isolated

Treatment: Supportive care, Steroids? Anti-TNF

Outcome: 50-70% die, 97% of those reaching mechanical ventilation





בהצלחה בבחינות

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