Graft Versus Host Disease

BHS Course 2026

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UZ LEUVEN

KU LEUVEN

DISCLOSURE

HS reports having received personal fees from Incyte, Novartis, MAAT Pharma, Mallinckrodt Pharmaceuticals, Sanofi, BeiGene and the Belgian Hematological Society (BHS), as well as research funding from Sanofi, all paid to her institution and not directly related to this work.

She has also received non-financial support from Pfizer, Sanofi, AbbVie, the EBMT (European Society for Blood and Marrow transplantation) the IACH (International Academy for Clinical Hematology) and the CIBMTR (Center for International Bone Marrow Transplantation Research).

HS acknowledges the support of the UZ Leuven Klinische onderzoeks- en opleidingsraad (KOOR) of the University Hospitals of Leuven, Belgium.

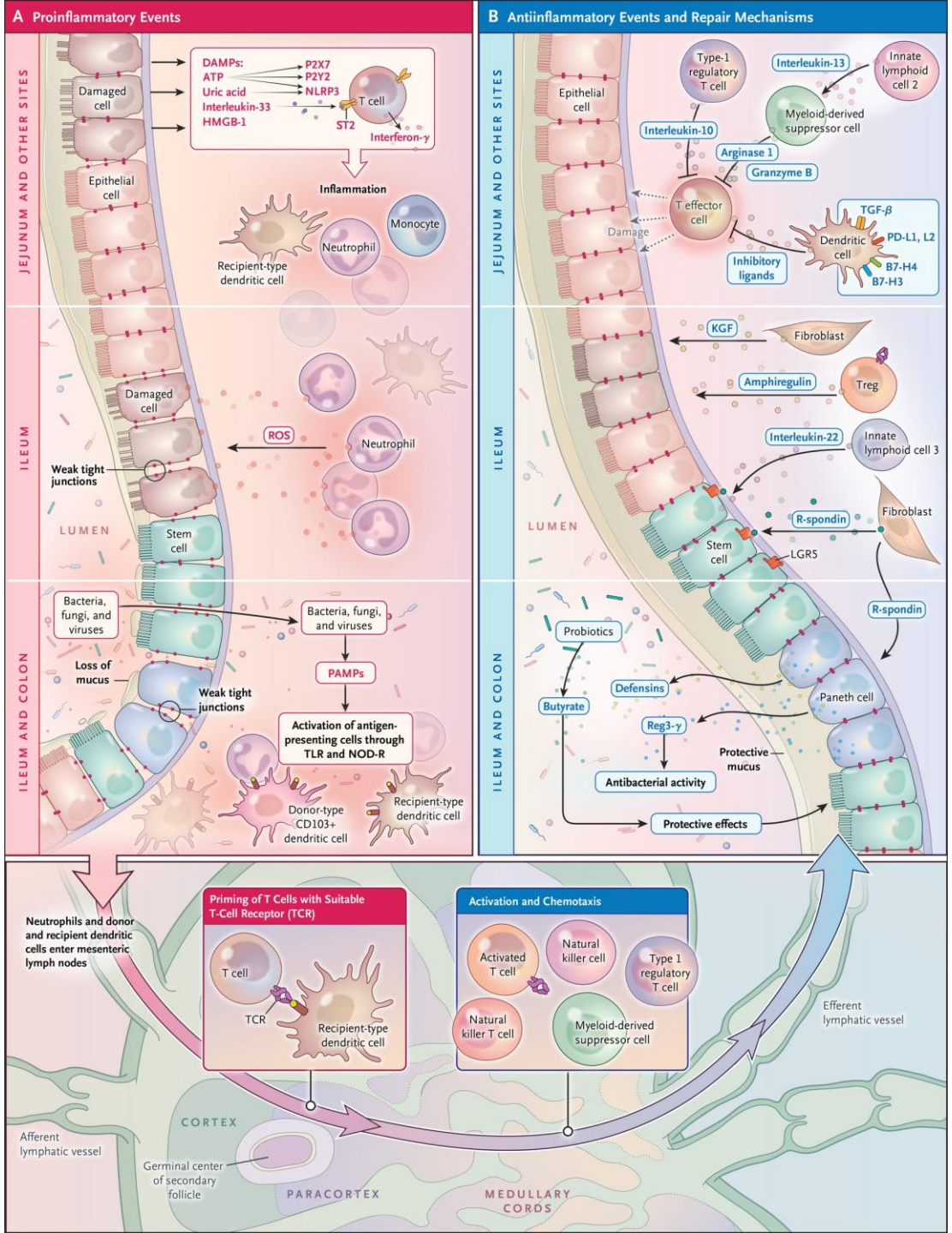
What’s in a name?

Graft versus Host Disease

Graft-versus-host disease (GvHD) refers to a clinical syndrome caused by the response of transplanted donor allogeneic cells to histocompatibility antigens expressed on tissues of the transplantation recipient.

Physiopathology of acute GVHD

Acute GVHD



Damage associated molecular patterns (DAMPs)
&
Pathogen associated molecular patterns (PAMs)

↓

inflammatory cascade

↓

activation of neutrophiles, monocytes, dendritic cells & T cells

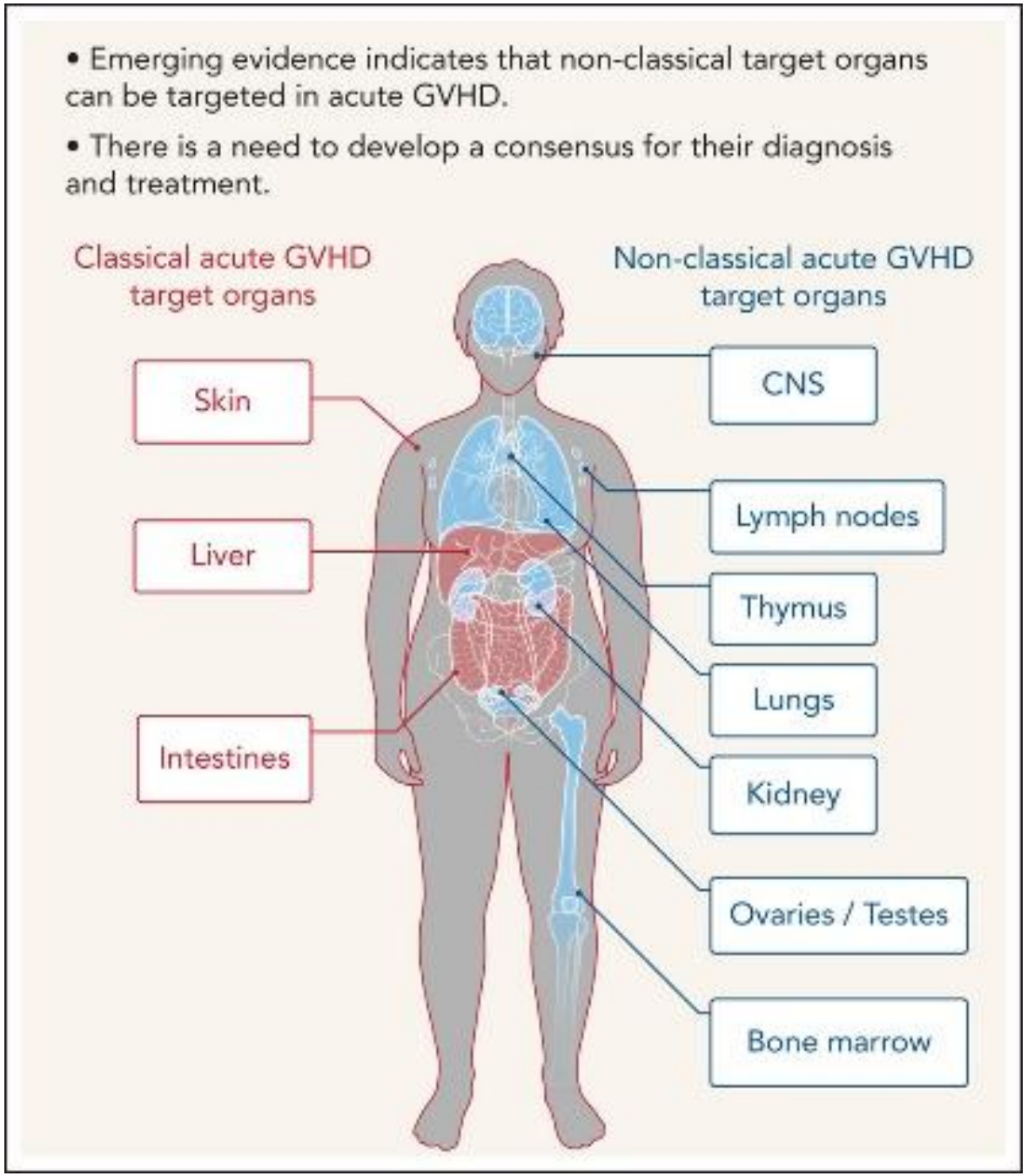
↓

Organ damage

Zeiser R et al. NEJM, 2017.

TYPICAL
aGvHD manifestations :

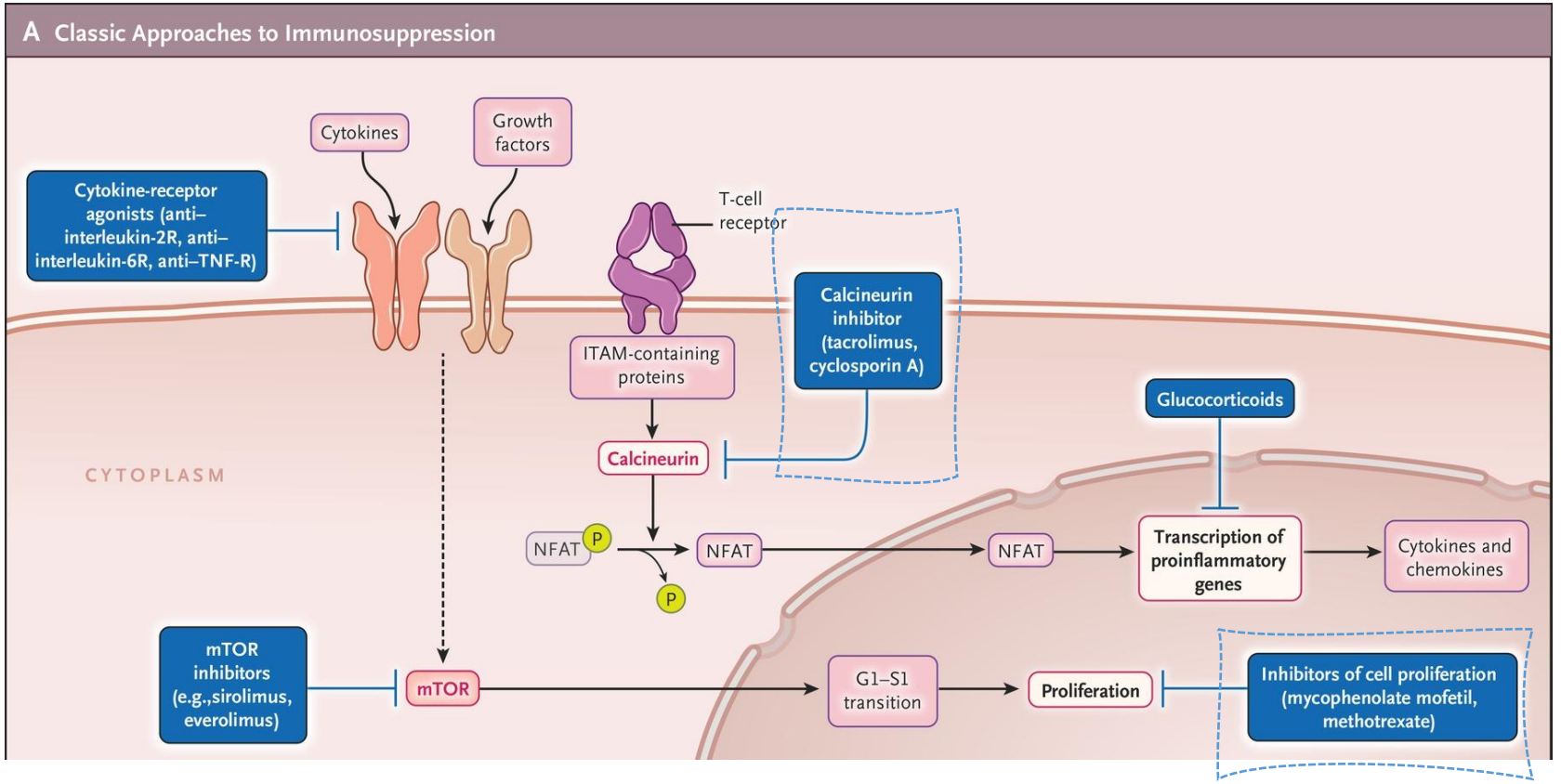
- GI: anorexia with weight loss, nausea, vomiting, and diarrhea
- Skin: inflammatory maculopapular erythematous skin rash
- Liver: elevated bilirubin



Zeiser R et al. Blood, 2021.

Preventing GVHD

GVHD – prevention



Prevention of GVHD typically relies on a combination of a calcineurine inhibitor (during 3-6 months) with a short course of either MTX or MMF.

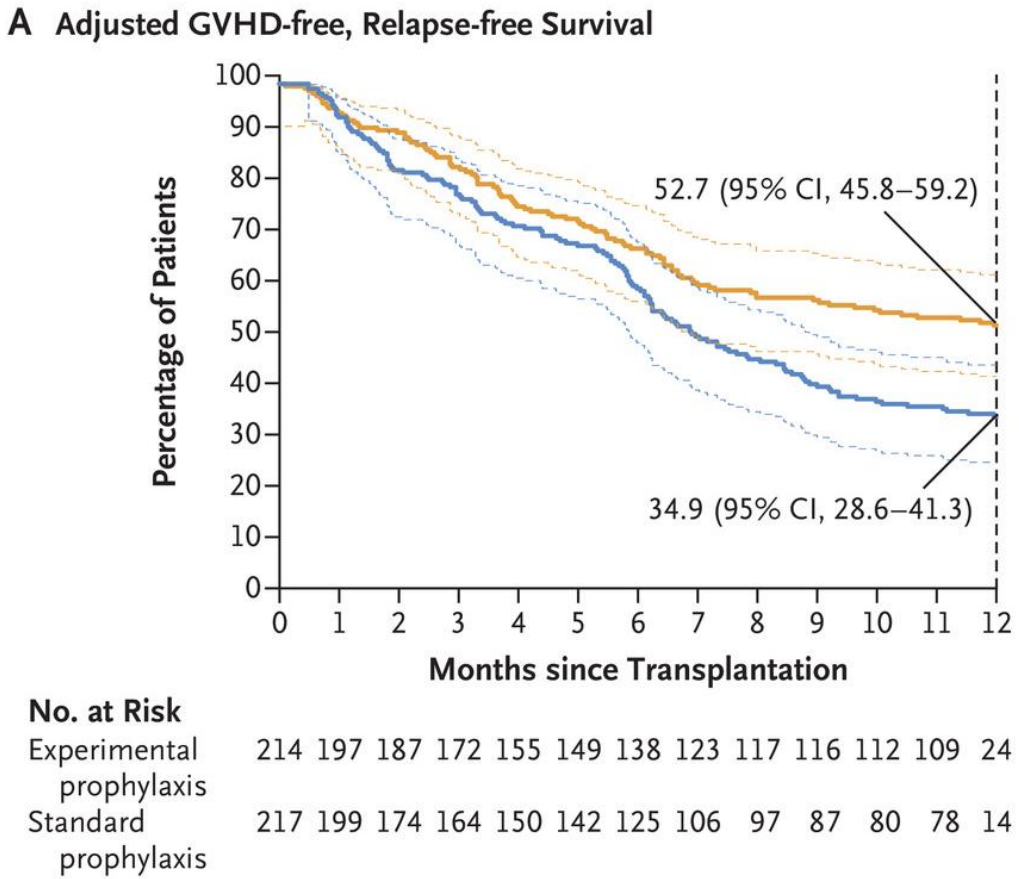
Anti-thymoglobuline (ATG) or Alemtuzumab can also be used in addition.

More recently, High dosis post transplant Cyclophosphamide (PTCY) has also been used.

(In vitro Depletion of T cells of the graft is also an option.)

Zeiser R et al. NEJM 2017.

Effect of Post-Cy in reduced intensity (US)



Tac-MTX-PostCy

Tac-MMF

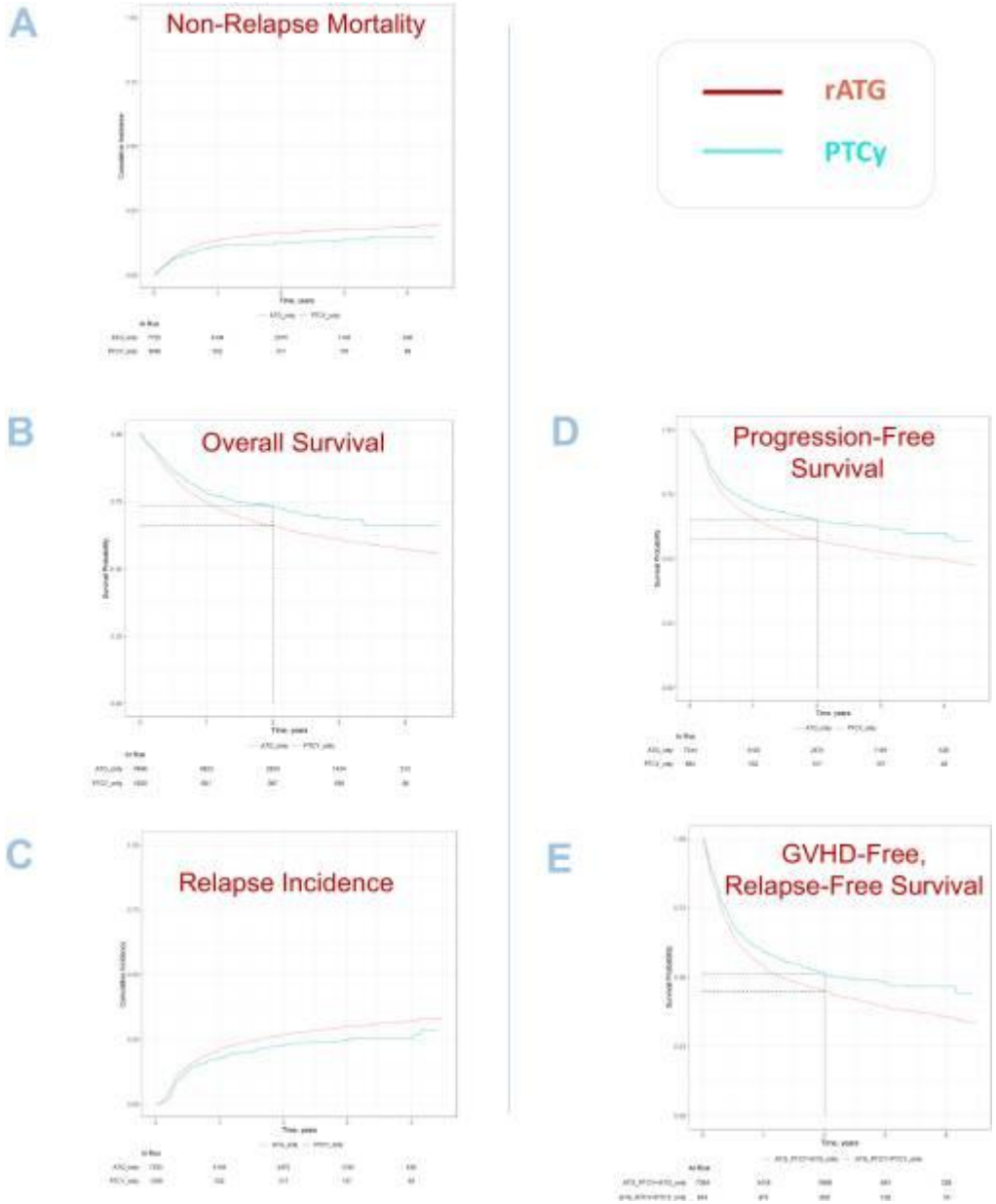
Randomized BMT CTN trial data
Adult
N=428

Bolanos-Meade et al NEJM 2023; 2338-2348

PTCY vs ATG MUD in Europe

Better OS	73.1% vs. 65.9%; p = 0.001, HR 0.82
Less NRM	12.1% vs. 16.4%; p = 0.016, HR 0.72.
Less Relapse	22.8% vs. 26.6%; p = 0.046; HR 0.87
Less cGVHD	28.4% vs. rATG 31.4%; p = 0.012; HR 0.77

PTCY n=1039; ATG n=7725

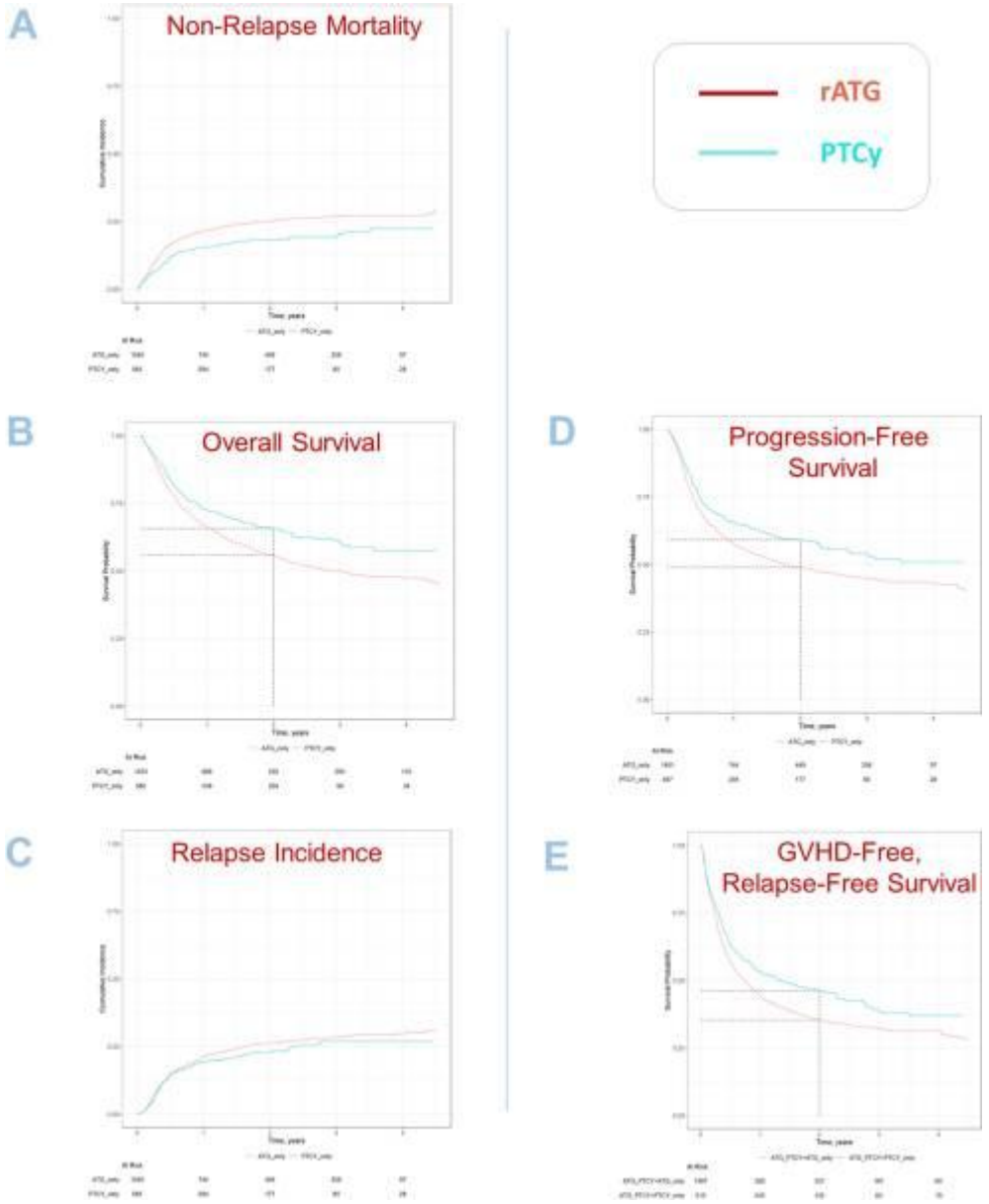


Penack et al, Leukemia 2024 May;38(5):1156-1163.

PTCY vs ATG
MMUD in Europe

Better OS 65.7% vs. 55.7%; p < 0.001, HR 0.77
Less NRM 18% vs. 24.9%; p = 0.028, HR 0.74.
(relapse & GVHD idem)

PTCY n= 583; ATG n=1540

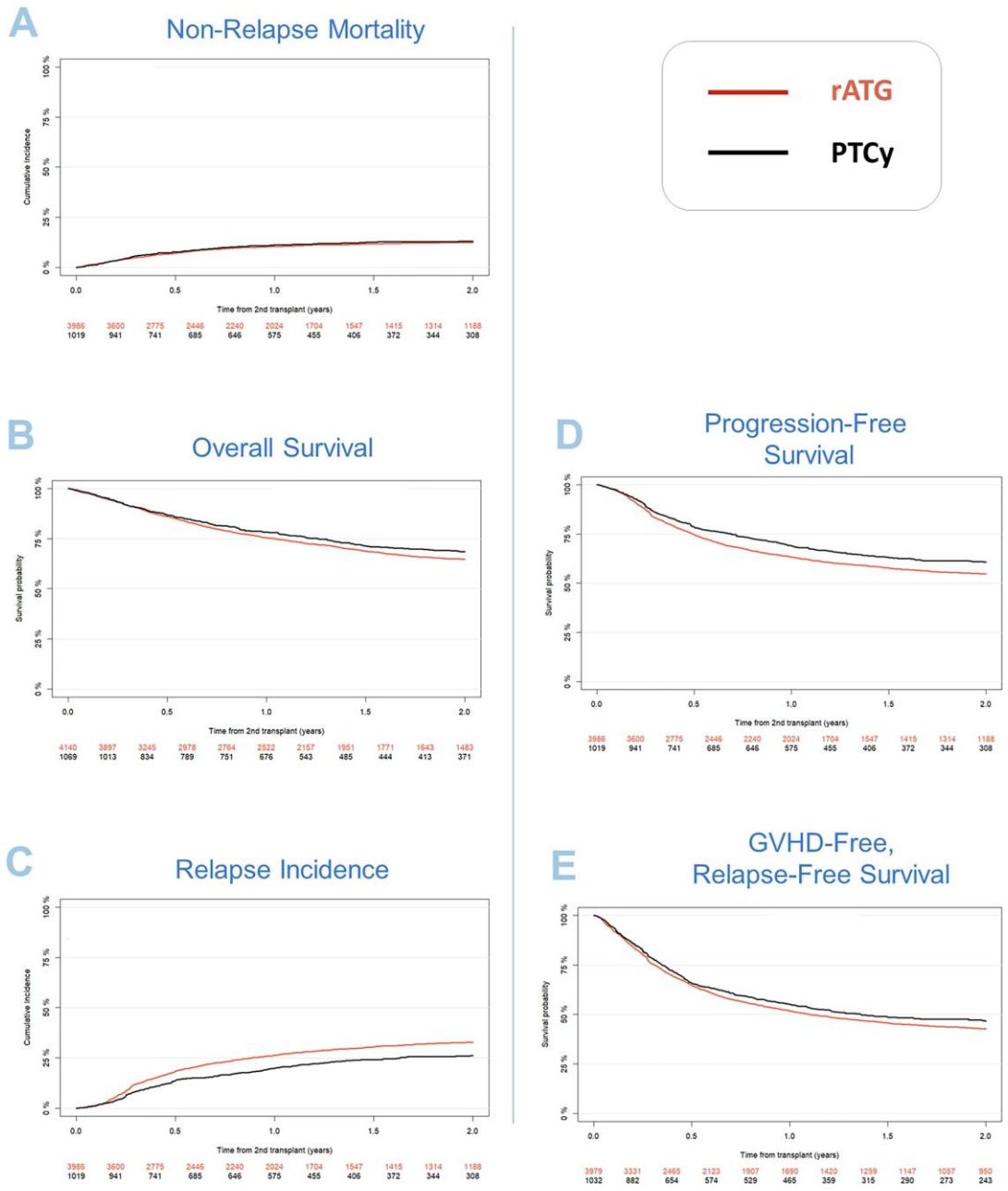


Penack et al, Blood Cancer J 2024 - 15;14(1):45

PTCY vs ATG
Matched siblings in Europe

Less Relapse 26.2% vs. 32.8%; HR 0.78, p = 0.003
(OS, NRM & GVHD idem)

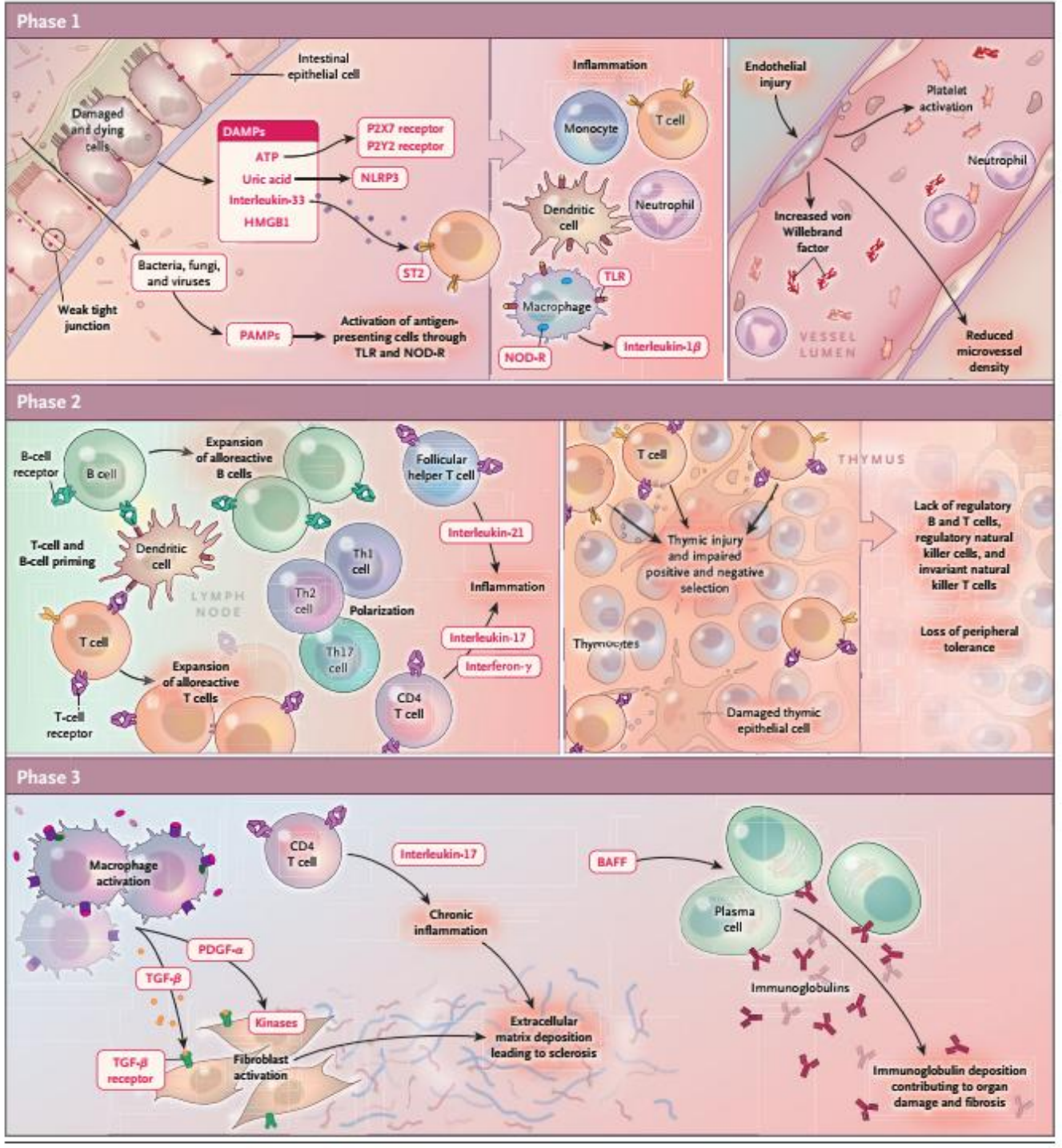
PTCY n= 1069 ; ATG n= 4140



Penack et al, Leukemia 2025: 1503-1511

Physiopathology of chronic GVHD

Chronic GVHD



Damage associated molecular patterns (DAMPs)
&
Pathogen associated molecular patterns (PAMs)

↓

inflammatory cascade

↓

activation B & T cells

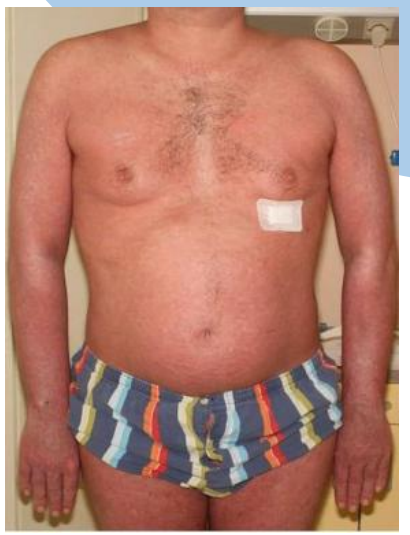
↓

fibrotic cascade

Zeiser R et al. NEJM, 2017

Classic or late aGvHD

- GI: anorexia with weight loss, nausea, vomiting, and diarrhea
- Skin: inflammatory maculopapular erythematous skin rash
- Liver: elevated bilirubin

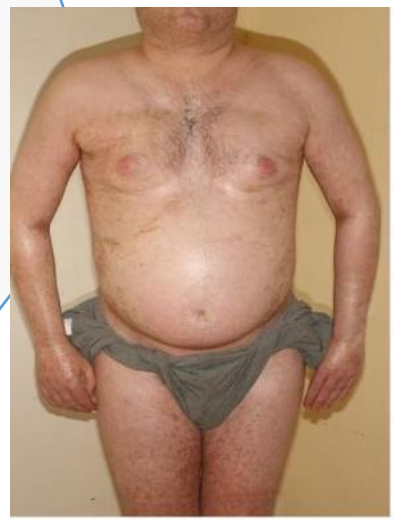


Overlap cGvHD

Classic cGvHD

cGvHD manifestations meeting NIH 2014 diagnostic criteria:

- Skin, nails, scalp, and body hair
- Mouth
- Eyes
- Genitalia
- Esophagus
- Lungs
- Muscles and fascia



Schoemans HM, et al. Bone Marrow Transplant. 2018;1401-15

You’re not sure how to evaluate cGVHD?

SMMuGGLLE your way out !

Skin

Mouth

Muscles/fascia

G-I / esophagus

Genital

Liver

Lungs

Eyes

‘Chronic’ GVHD

E

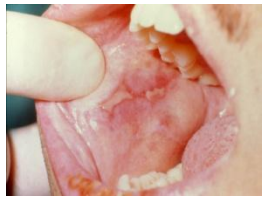
M

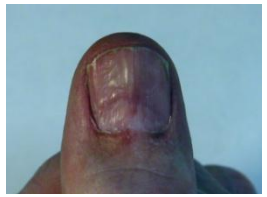
L

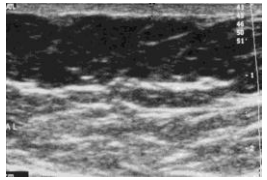
L

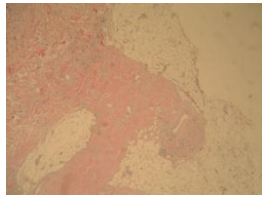
Mu

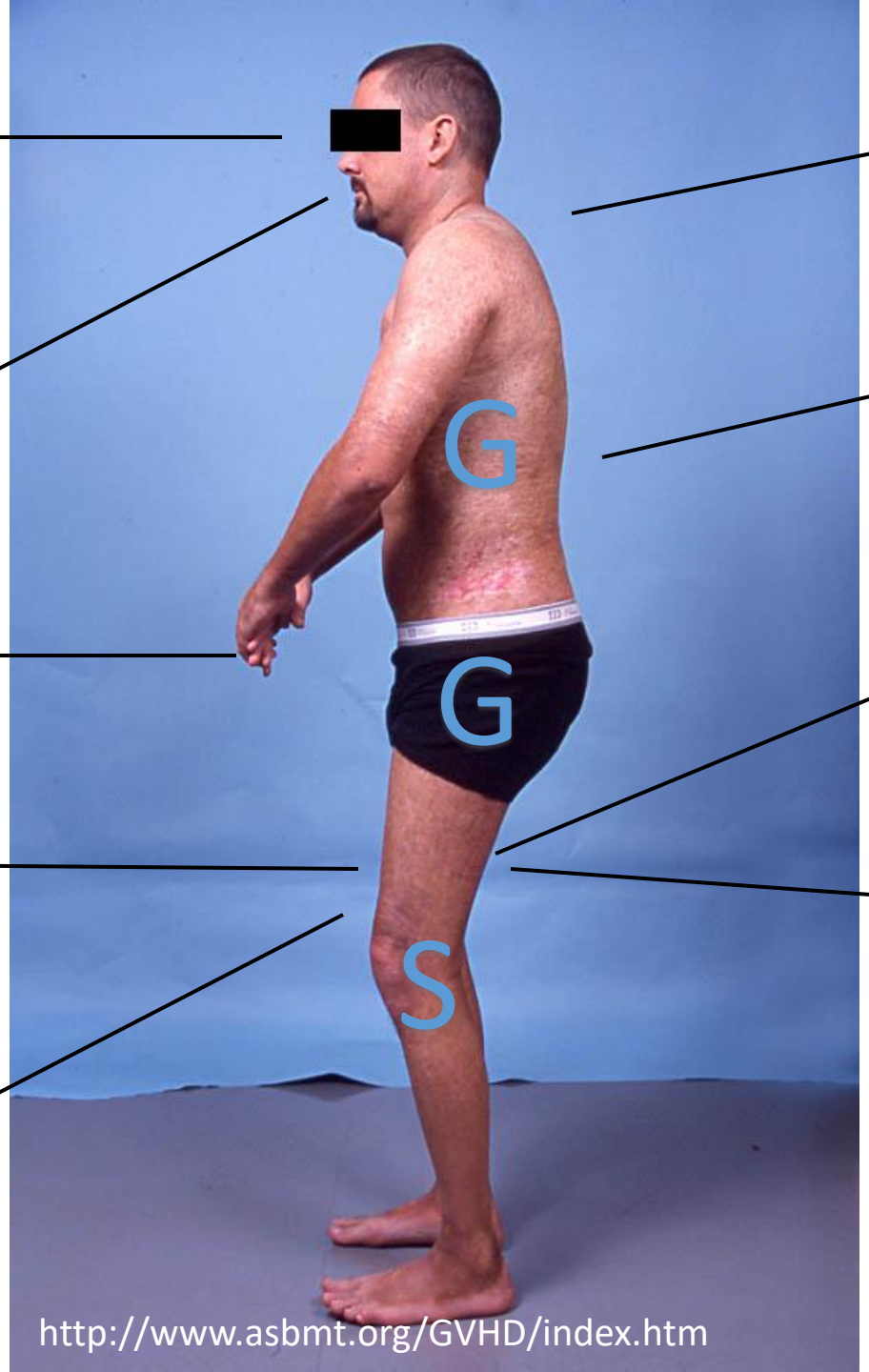

Ocular sicca


Oral ulcers

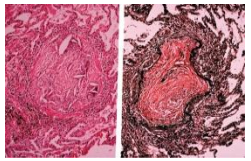

Nail dystrophy

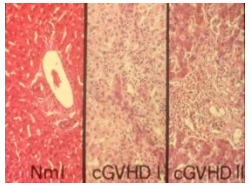

Skin sclerosis


Deep sclerosis

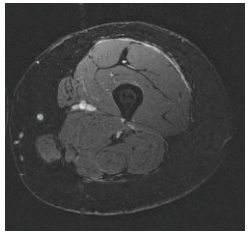


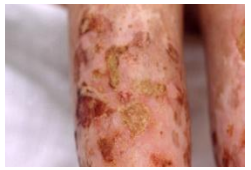
http://www.asbmt.org/GVHD/index.htm


Bronchiolitis obliterans



Loss of bile ducts


Fasciitis

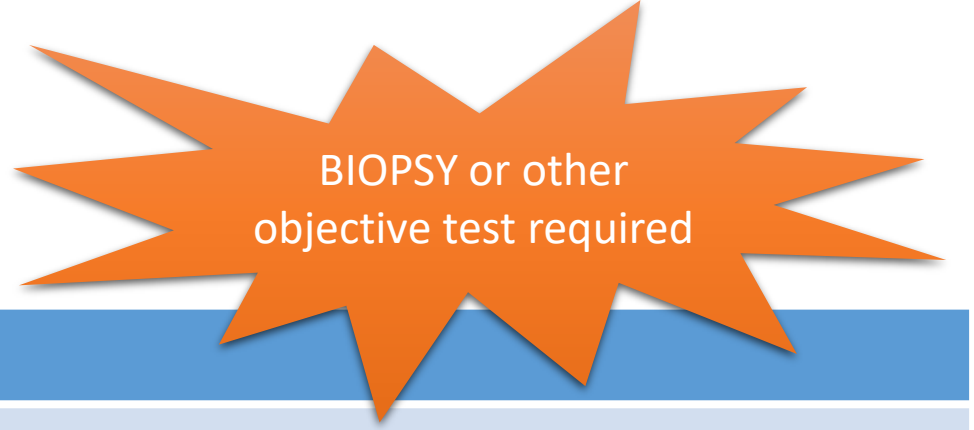

Skin ulcers

Diagnostic Signs of chronic GvHD

Organ	Feature
Skin	Poikiloderma, lichen planus-like, morphea-like, lichen sclerosus-like, sclerotic features
Mouth	Lichen planus-like
Eyes	-
Genitalia	Lichen planus-like, lichen sclerosus-like
GI Tract	Esophageal web, strictures or stenosis in esophagus
Liver	-
Lung	Bronchiolitis obliterans (BOS) with positive lung biopsy
Muscles, fascia, joints	Fasciitis, joint stiffness or contractures sec. to fasciitis or sclerosis

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

Distinctive Signs of chronic GvHD



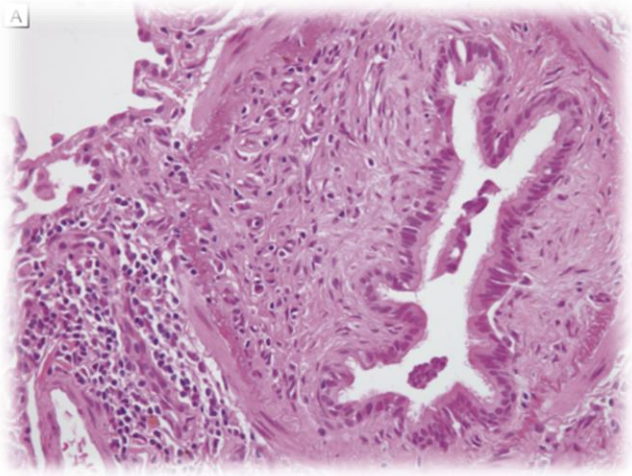
Organ	Example
Skin	Hypo/Hyper pigmentation, alopecia …
Mouth	Hyper keratosis, Sicca, …
Eyes	Sicca, …
Genitalia	Ulcerations, …
GI Tract	-
Liver	Increased liver enzymes (AP and/or ALT) or bilirubine, …
Lung	Impaired lung function with signs of BOS, …
Muscles, fascia, joints	Myositis, …

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

GVHD of the lungs - BOS
Bronchiolitis Obliterans Syndrome

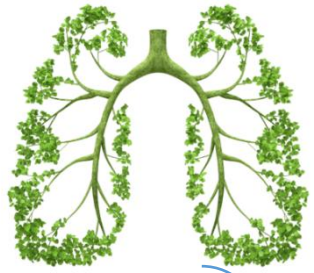
Peribronchial proliferation between epithelium and smooth muscle

Airtrapping ➔ Obstruction



AJR 2012;199:581-587.

Bronchiolitis Obliterans Syndrome



- FEV1<75% of predicted with ≥10% decline over less than 2 years.
- FEV1/FVC < 0.7 or the fifth percentile of predicted.
- Absence of respiratory tract infection.

ALL THREE

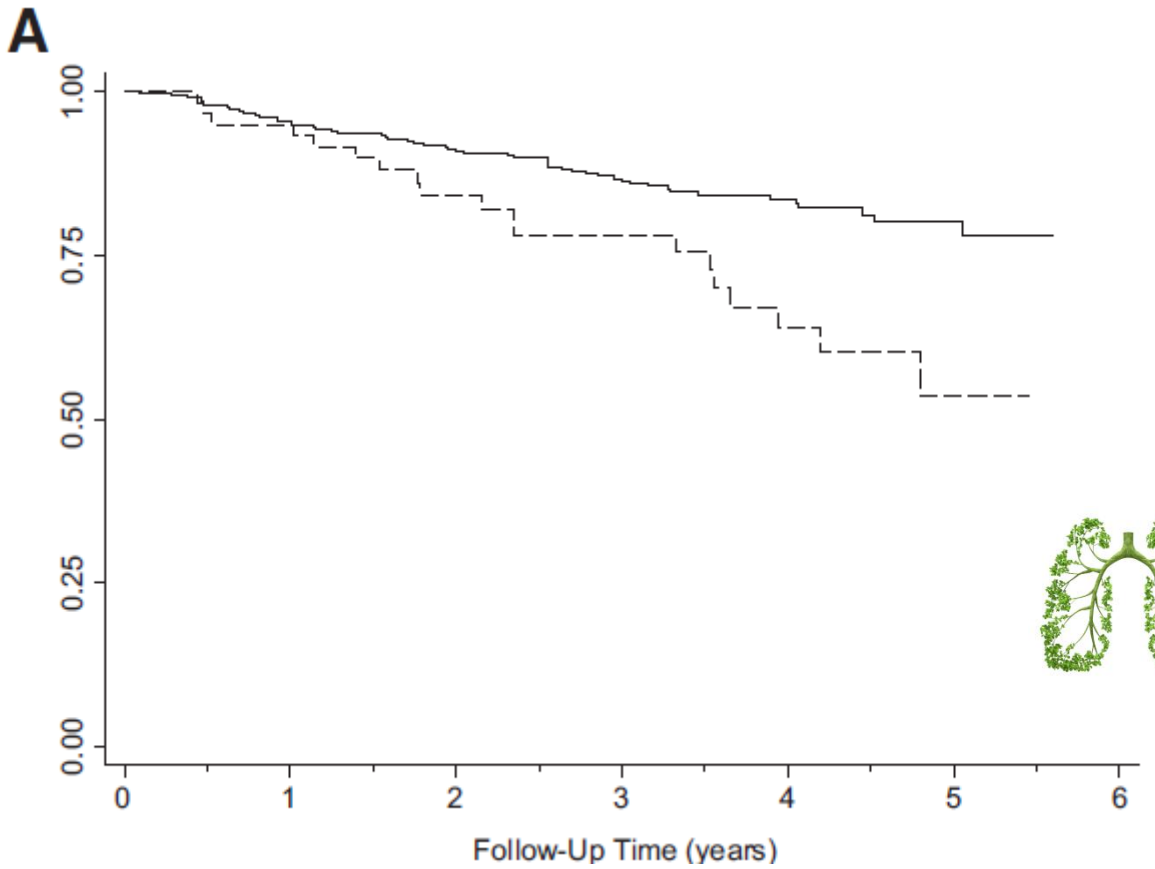
+

One of the 2 supporting features of BOS

- Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by HR-CT OR
- Evidence of air trapping by PFTs: RV >120% of predicted OR RV/TLC elevated outside the 90% CI

Jagasia MH et al, BBMT 2015;21:389-401

BOS is associated with high mortality



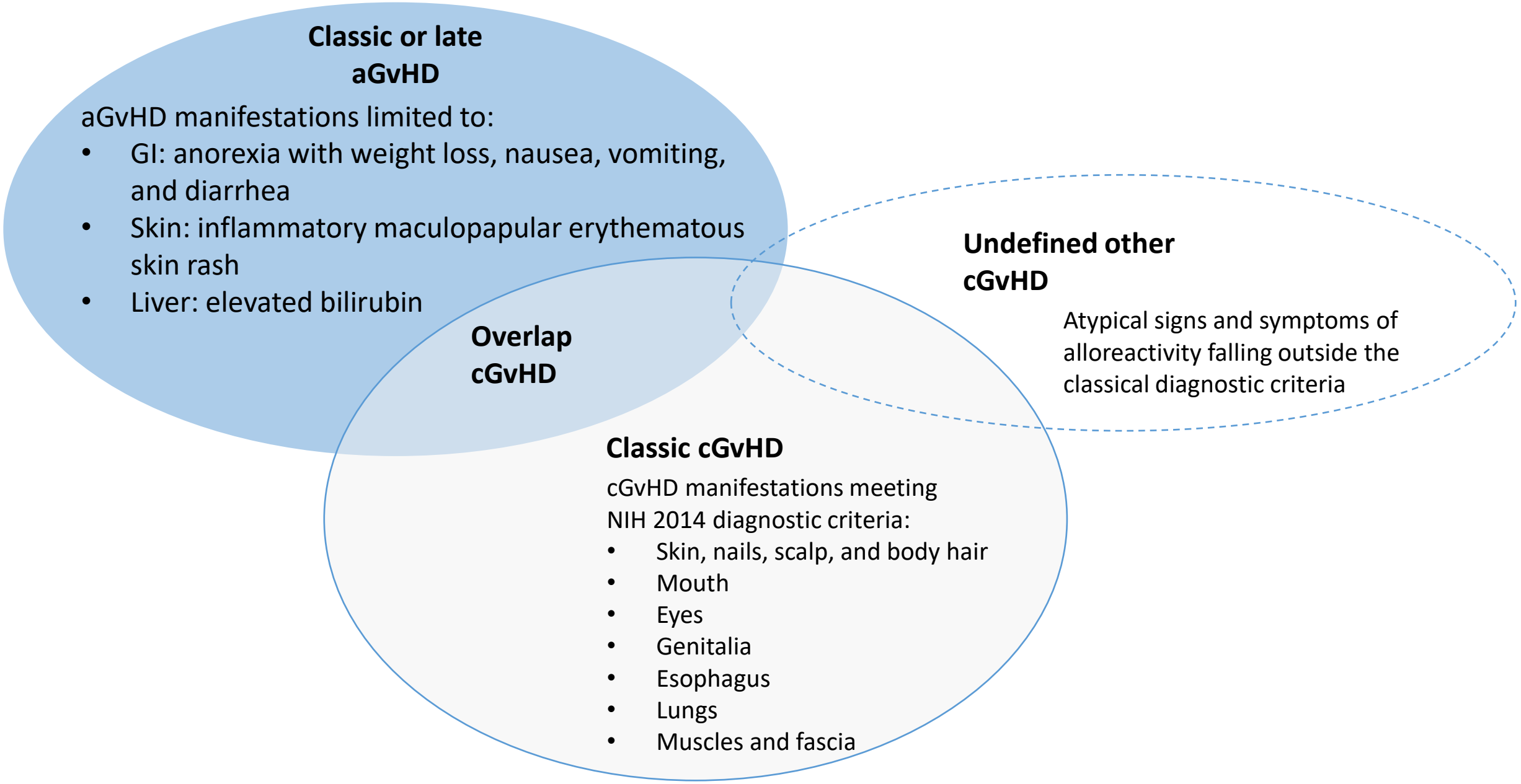
No BOS

BOS

FEV1 <75%
FEV1/FVC <0.7
+ air trapping

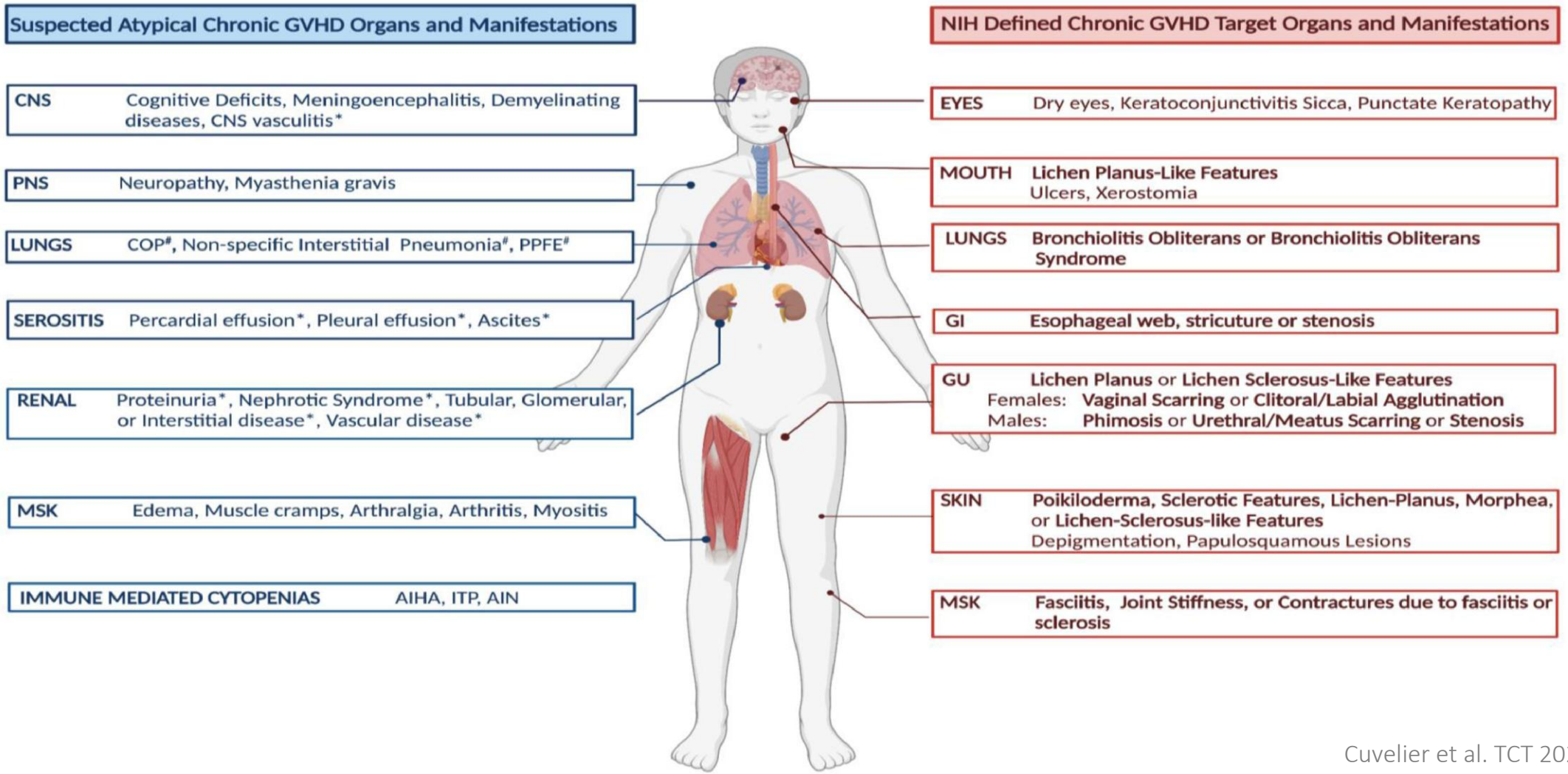
Seattle Fred Hutch 2002-2006
946 alloTx followed by PFTs

Au et al, BBMT 2011, 1072-1078
Palmer J et al. BBMT 2014;20:337-44
Abedin et al. Biol Blood Marrow Transplant. 2015 Jun;21(6):1127-31.



Schoemans HM, et al. Bone Marrow Transplant. 2018;1401-15

Atypical ‘other GVHD’



Cuvelier et al. TCT 2022; 426-445

Treating GVHD

There are at least 4 ways of staging acute GVHD individual organ severity…

Organ Severity Stage acute GvHD	Original Glucksberg[13]	Modified Glucksberg or "Keystone criteria"[14]	IBMTR[15]	MAGIC
Skin				
0	no rash			
1	Rash <25% of BSA			
2	Rash 25% to 50% of BSA			
3	Rash >50% of BSA			
4	Generalized erythroderma with bullous formation			Generalized erythroderma (>50% BSA) plus bullous formation and desquamation **>5% of BSA**
Liver				
0	Total serum bilirubin < 34 µmol/L (<2.0mg/dL) or AST/SGOT 150-750 IU	Total serum bilirubin < 34 µmol/L (<2.0mg/dL)		
1	Total serum bilirubin 34-50 µmol/L (2.0 to 3mg/dL)			
2	Total serum bilirubin 51-102 µmol/L (3.1 to 6mg/dL)			
3	Total serum bilirubin 103-255 µmol/L (6.1 to 15mg/dL)			
4	Total serum bilirubin >255 µmol/L (>15mg/dL)			
Upper GI				
0	NA	no persistent nausea with histologic evidence of GvHD in the stomach or duodenum		**no or intermittent*** anorexia or nausea or vomiting
1	NA	persistent nausea **with histologic evidence of GvHD** in the stomach or duodenum		**persistent*** anorexia or nausea or vomiting
Lower GI				
0	Diarrhea <500 mL/day			Diarrhea <500 mL/day or <3 episodes/day for adults** [a]
1	Diarrhea >500 mL/day			Diarrhea 500-999 mL/day or 3-4 episodes/day for adults** [b]
2	Diarrhea >1000 mL/day			Diarrhea 1000-1500 mL/day or 5-7 episodes/day for adults** [c]
3	Diarrhea >1500 mL/day			Diarrhea >1500mL/day or >7 episodes/day for adults** [d]
4	Diarrhea >2000 mL/day	severe abdominal pain with/without ileus		Severe abdominal pain **with/without ileus or grossly bloody stools (regardless of stool volume)**
Karnofsky index				
	>30%	NA		
	<30%	NA		

Glucksberg et al, Transplantation; 295-304

Przepiorka D et al, BMT 1995; 825-828
Rowlings PA et al. Br J Haematol 1997; 855-864

Harris et al, BBMT 2016; 4-10

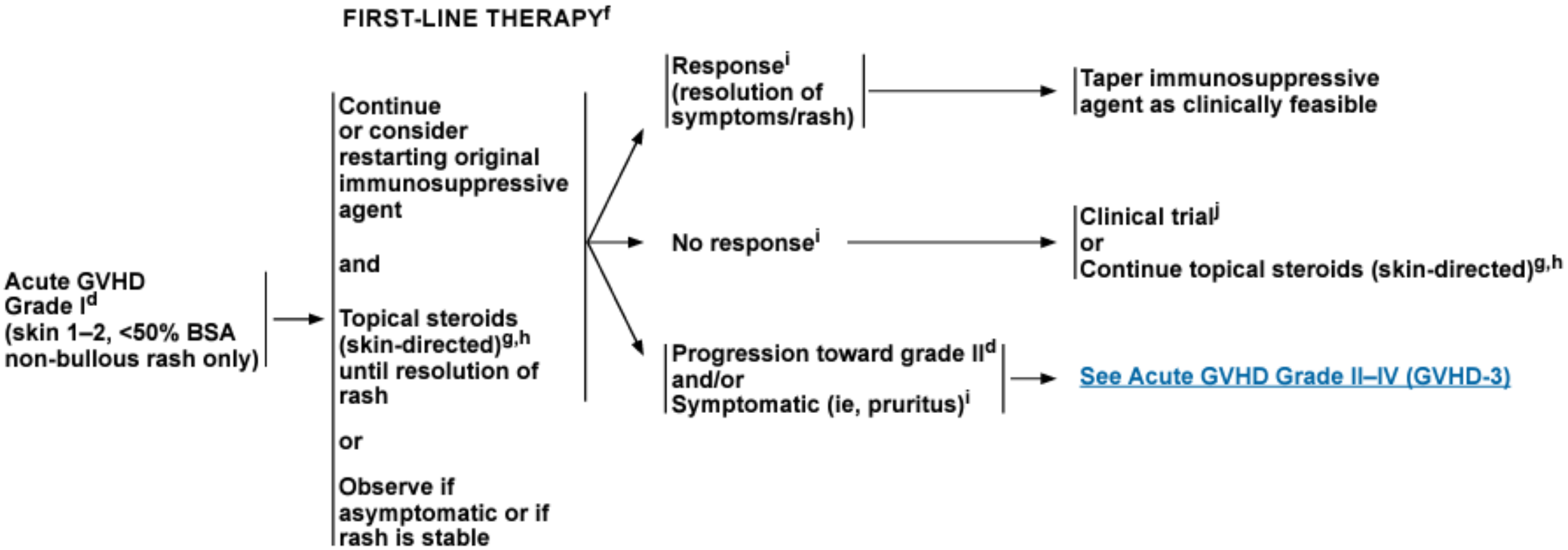
Schoemans et al, BMT 2018; 1401-1415

Acute overall GvHD scoring (I-IV) – MAGIC

GRADE		SKIN	LIVER	GI
0	NONE	0	0	0
I	Mild	1 or 2	0	0
II	Moderate	3	1	1
III	Severe	-	2 or 3	2 or 3
IV	Life threatening	4	4	4

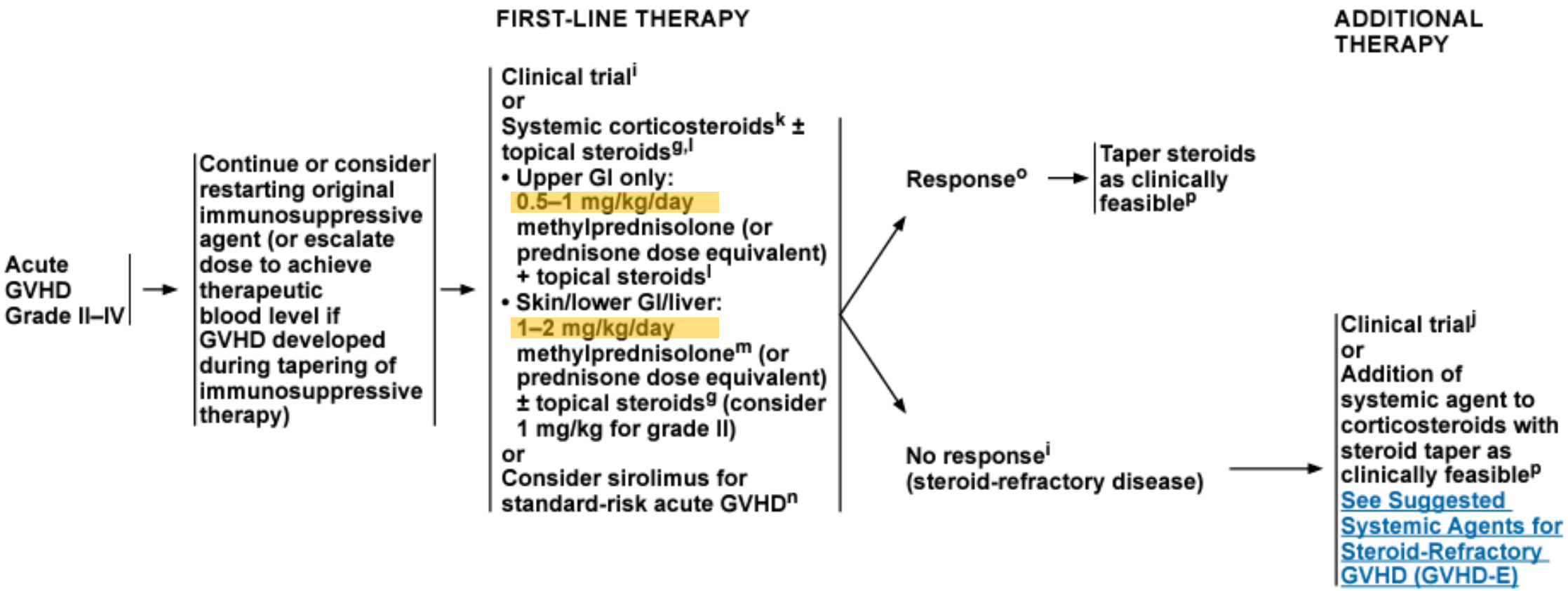
Harris et al, BBMT 2016
Schoemans et al, BMT 2018; 1401-1415

First-line Therapy of Acute GvHD – grade I



NCCN Guidelines Version 3.2025

First-line Therapy of Acute GvHD – grade II-IV



[n] Standard-risk acute GVHD as defined by clinical risk score and biomarker status cf CTN1501 trial: Pidala J, et al. Blood 2020;135:97-107.

NCCN Guidelines Version 3.2025

Proposed terminology for Steroid response

Steroid	aGVHD	
Refractoriness or Resistance	Progression within 3-5 days of therapy onset with ≥ 2mg/kg/day of prednisone **OR** Failure to improve within 5-7days of treatment initiation **OR** Incomplete response after more than 28 days of immunosuppressive treatment including steroids	
Dependence	Inability to taper prednisone below 2mg/kg/day **OR** Recurrence of GVHD activity during steroid taper	
Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

Schoemans et al, BMT 2018;1401-1415

Steroid refractory acute GVHD treatment

!!! consider a clinical Trial !!!!

Ruxolitinib* (Zeiser et al NEJM 2020)

Alemtuzumab
Alpha-1antitrypsin (AAT)
Anti-Thymoglobulin (ATG)
Basiliximab
Calcineurine inhibitors
Etanercept
Extracorporeal photopheresis (ECP)
Fecal transplantation
Infliximab
mTor inhibitors (sirolimus, …)
Mycophenolate mofetil
Pentostatin
Tocilizumab

Selection of agent based on:

Institutional preference
Physician experience
Toxicity profile
Effect of prior treatment
Drug interactions
Accessibility
Patient tolerability

Penack, Lancet Hematology 2024
NCCN guidelines, 2025.

* FDA approved for GVHD treatment

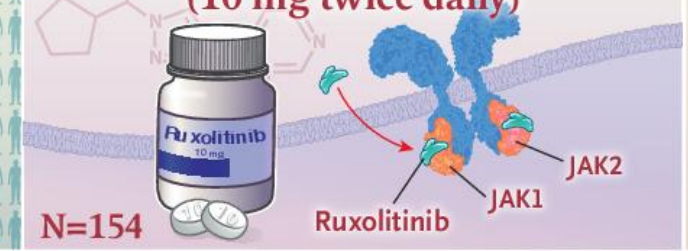
The NEW ENGLAND JOURNAL of MEDICINE

Ruxolitinib for Glucocorticoid-Refractory Acute GVHD

PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL TRIAL

309 Patients
with grade II–IV glucocorticoid-refractory acute graft-versus-host disease

Ruxolitinib (JAK inhibitor)
(10 mg twice daily)



N=154

Best Available Therapy

N=155

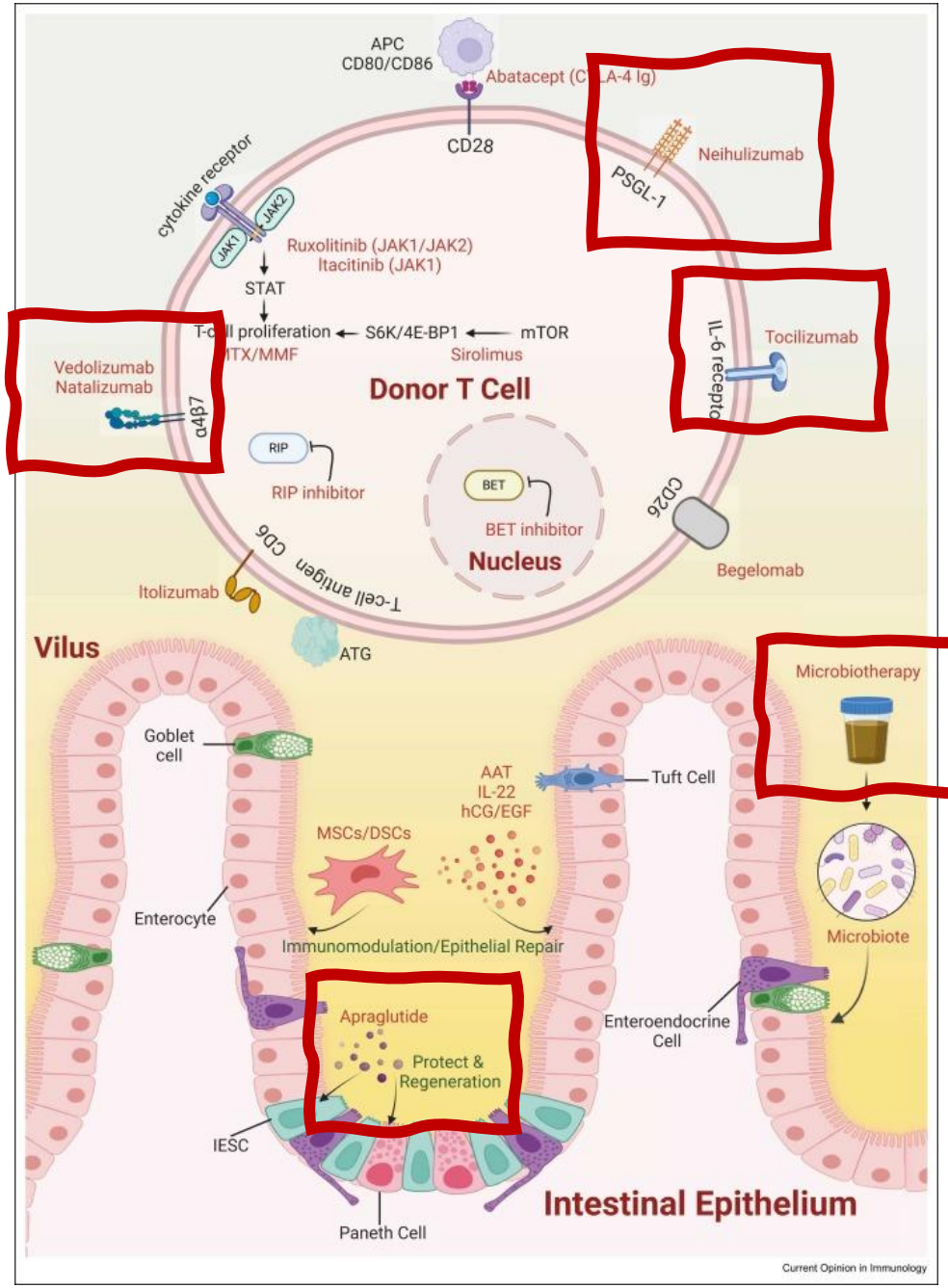
	Ruxolitinib	Best Available Therapy
Partial or complete response at day 28	62%	39%
	Odds ratio, 2.64; P<0.001	
Treatment-associated adverse reaction	Thrombocytopenia 33%	18%

Ruxolitinib significantly improved efficacy outcomes as compared with best available therapy

R. Zeiser et al. 10.1056/NEJMoa1917635

Zeiser et al, NEJM; 1800-1810

New therapies for aGVHD



Ye et al, Curr Opnion Immunol 2025

There are at least 4 ways of grading cGVHD severity

Shulman et al. Am J Med. 1980; 204–17
Lee et al. BBMT. 2003; 215–33

Filipovich et al. BBMT 2005; 945–56
Jagasia et al. BBMT 2015; 389–401

Schoemans et al, BMT 2018;1401-1415

	Original Seattle Criteria[21]	Revised Seattle Criteria[22]	NIH	
DIAGNOSIS				
	NA	NA	based on either the presence of specific **diagnostic** signs or **distinctive** signs accompanied by additional confirmation (e.g. biopsy or other objective diagnostic test) in at least one target organ (skin & appendages, mouth, eyes, genitalia, esophagus, lungs and muscles & fascia)	
SEVERITY SCORING				
Limited	Limited **skin** AND/OR limited **hepatic** involvement	Limited **skin** AND/OR limited **hepatic** involvement OR **single organ sicca** syndrome (eyes, mouth, vagina)	Mild	**no more than two organs** with a score* of 1, except for lung
Extensive	Generalized **skin** involvement AND/OR major **hepatic** complications AND/OR an isolated **sicca** syndrome of the eyes, mouth AND/OR any **other** organ involvement	Generalized **skin** involvement AND/OR major **hepatic** complications AND/OR **multiple organs** involved (more than two, including 'nails'), the presence of skin **sclerosis** / **serositis** or **fasciitis**, **bronchiolitis** obliterans, **decreased performance status** (<60% Karnofsky-Lansky index) or **weight loss >15%**	Moderate	any other severity scoring* not included in the mild or severe categories
			Severe	**at least one organ** with a score* of 3 or a lung score* of 2

cGVHD scores according to NIH criteria

Eight organs : Skin Mouth Muscles GI Genital Liver Lung Eyes

Score 0	No problem
Score 1	Minor symptoms without impact
Score 2	Symptoms impacting ADL
Score 3	Symptoms resulting in disability

!! Based on consensus opinion and not on empiric data !!

cGVHD scores according to NIH criteria

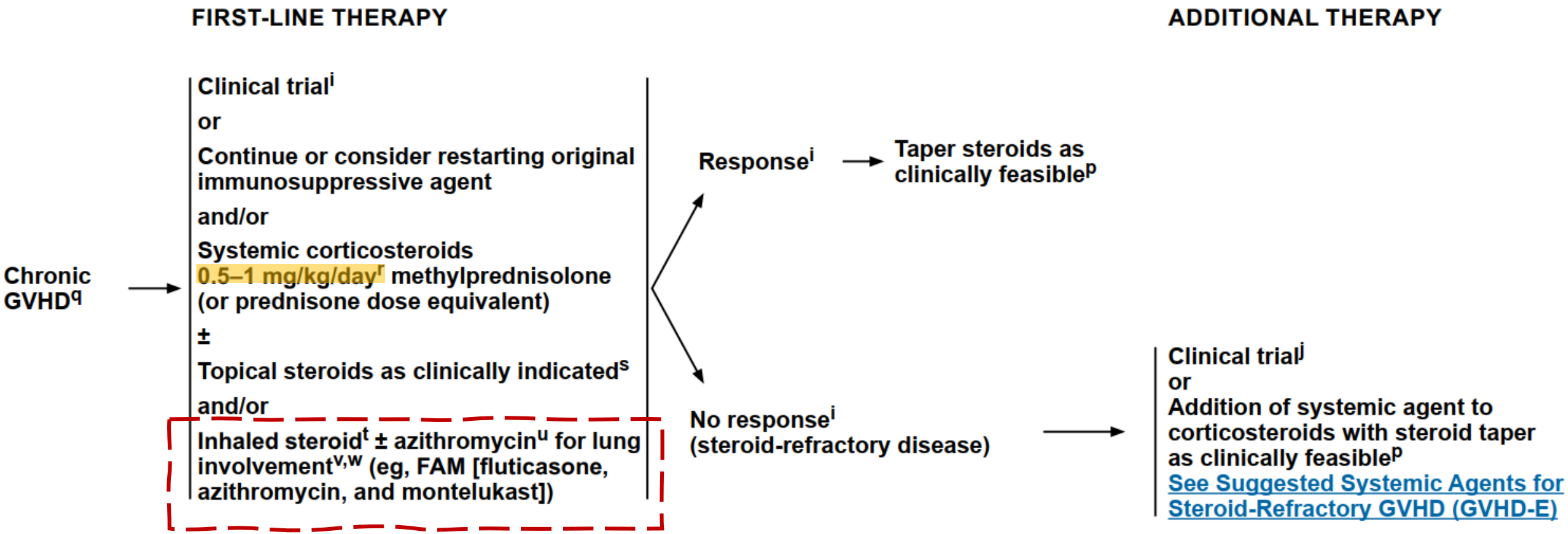
# OF ORGANS	MILD
1	Score 1
2	Score 1
3	

MILD = 1 or 2 organs (but not lung) with maximum Score 1

MODERATE = Lung Score 1 **or ≥** three organs at Score 1 **or** at least one organ at Score 2

SEVERE = Lung Score 2 **or** Score 3 in any organ

Systemic Treatment of moderate/severe cGvHD



NCCN guidelines, 2025

Proposed terminology for Steroid response

Steroid	aGVHD	cGVHD
Refractoriness or Resistance	Progression within 3-5 days of therapy onset with ≥ 2mg/kg/day of prednisone **OR** Failure to improve within 5-7days of treatment initiation **OR** Incomplete response after more than 28 days of immunosuppressive treatment including steroids	Progression while on prednisone at ≥ 1mg/kg/day for 1-2 weeks **OR** Stable disease while on prednisone at ≥ 0.5mg/kg/day for 1-2 months
Dependence	Inability to taper presone below 2mg/kg/day **OR** Recurrence of GVHD activity during steroid taper	Inability to taper prednisone below 0,25mg/kg/day in at least 2 attempts separated by 8 weeks
Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

Schoemans et al, BMT 2018;1401-1415

Steroid refractory chronic GVHD treatment

!!! consider a clinical Trial !!!!

Ruxolitinib* (Zeiser et al NEJM 2021)

Ibrutinib*
Belumosudil*
Axatilimab*

Abatercept
Alemtuzumab
Calcineurine inhibitors
Etanercept
Extracorporeal photopheresis (ECP)
Hydroxychloroquine
Imatinib
Interleukin-2
Methotrexat
mTor inhibitors
Pentostatin
Rituximab

Selection of agent based on:

Institutional preference
Physician experience
Toxicity profile
Effect of prior treatment
Drug interactions
Accessibility
Patient tolerability

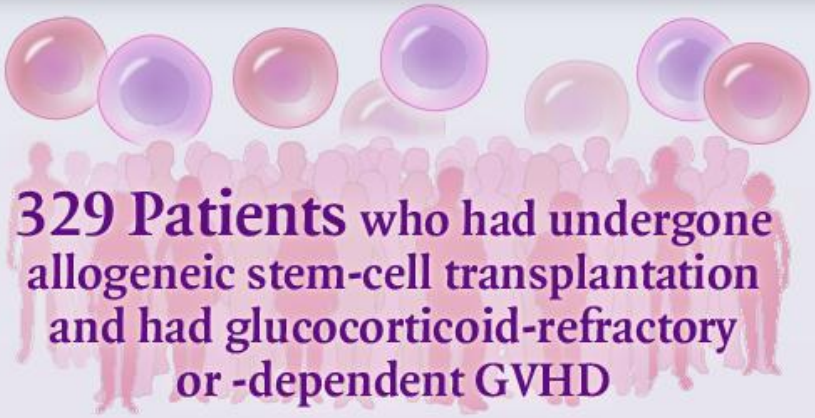
* FDA approved

Penack, Lancet Hematology 2024
NCCN guidelines, 2025

The NEW ENGLAND JOURNAL of MEDICINE

Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease

PHASE 3, OPEN-LABEL, RANDOMIZED TRIAL



329 Patients who had undergone allogeneic stem-cell transplantation and had glucocorticoid-refractory or -dependent GVHD

Ruxolitinib 10 mg twice daily

(N=165)

Investigator's choice of therapy (control)

(N=164)

Overall response (complete or partial response) at week 24	49.7% (82 patients)	25.6% (42 patients)
	OR, 2.99; P<0.001	

Ruxolitinib showed superior efficacy over control but led to a higher incidence of grade ≥3 thrombocytopenia and anemia

R. Zeiser et al. 10.1056/NEJMoa2033122

Zeiser et al, NEJM; 1800-1810

Take home message

Take home message

Prevent it

Recognize it early

Score it (Belgian flag & SMMuGGLLE)

Treat grade II-IV or moderate/severe GVHD with Steroids → Ruxo →…

Beware of highly morbid forms (sclerosis, dry eyes and lungs)

Think of supportive care & impact on QoL (even in mild GVHD)

Top references GVHD

- Physiopathology
  - Zeiser et al 2017 https://pubmed.ncbi.nlm.nih.gov/29171820/ (acute)
  - Zeiser et al 2017 https://pubmed.ncbi.nlm.nih.gov/29281578/ (chronic)

- Diagnosis and scoring
  - Schoemans et al 2018 https://pubmed.ncbi.nlm.nih.gov/29872128/ (summary of recommendations)
  - Kitko et al https://pubmed.ncbi.nlm.nih.gov/33839317/ (early recognition)
  - Cuvelier et al https://pubmed.ncbi.nlm.nih.gov/35662591/ (atypical GVHD)

- Prophylaxis & Treatment recommendations
  - Penack et al 2020 https://pubmed.ncbi.nlm.nih.gov/32004485/ (European guidelines)
  - Penack et al 2024 https://pubmed.ncbi.nlm.nih.gov/38184001/ (European guidelines)
  - NCCN 2023 https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf (US guidelines)

- QoL
  - Pidala et al 2010 https://pubmed.ncbi.nlm.nih.gov/21355084/
  - Kurosawa et al 2017 https://www.sciencedirect.com/science/article/pii/S1083879117305207