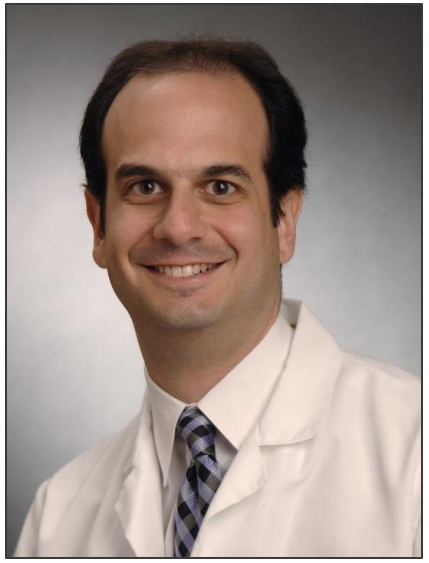
Introduction to Chronic Graft-versus-Host Disease



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Dana-Farber Cancer Institute

Celebrating a Second Chance at Life Survivorship Symposium

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Introduction to Chronic Graft-versus-Host Disease

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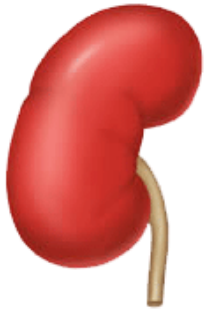
HARVARD MEDICAL SCHOOL

Chronic GVHD - Background

- >50% of ‘Related’ and ‘Unrelated’ donor recipients
  - Incidence increasing as early transplant-related outcomes improve
  - Exception: Cord transplant and Haplo transplant, where incidence is lower
- Very important cause of morbidity in the later post-transplant period
- Median 2-3 years of treatment
- Associated with quality of life and functional deficits

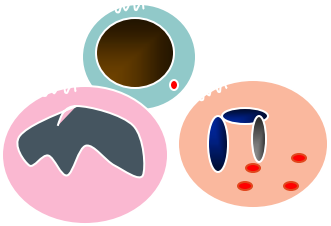
GVHD

- Caused by the interaction between the transplanted immune system (Graft) and recipient tissues (Host)

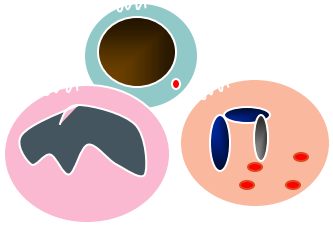


Transplanted Organ

Rejection

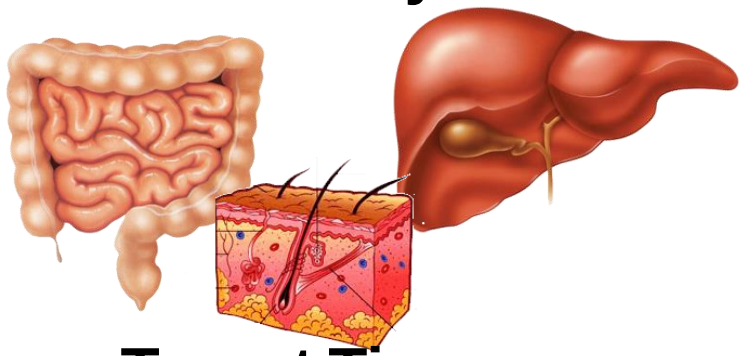


Immune System



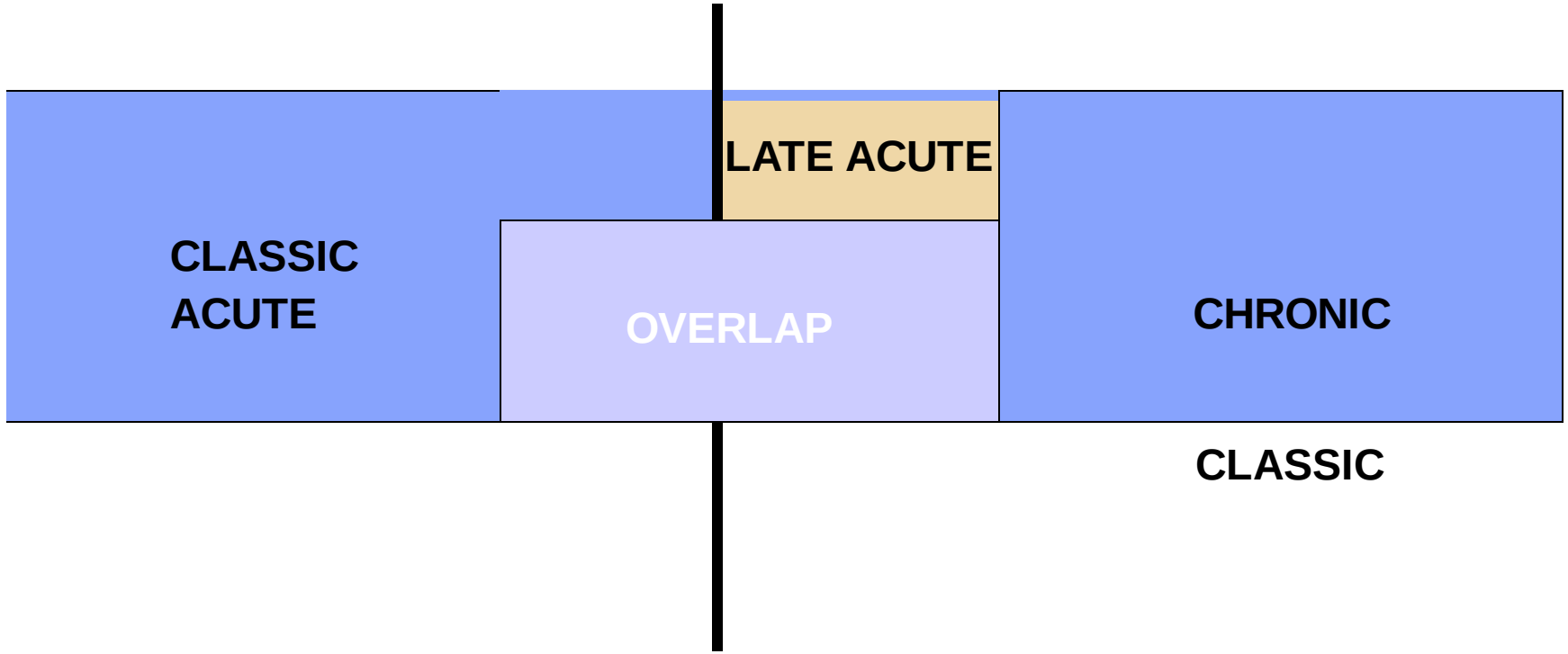
Transplanted Organ

GVHD

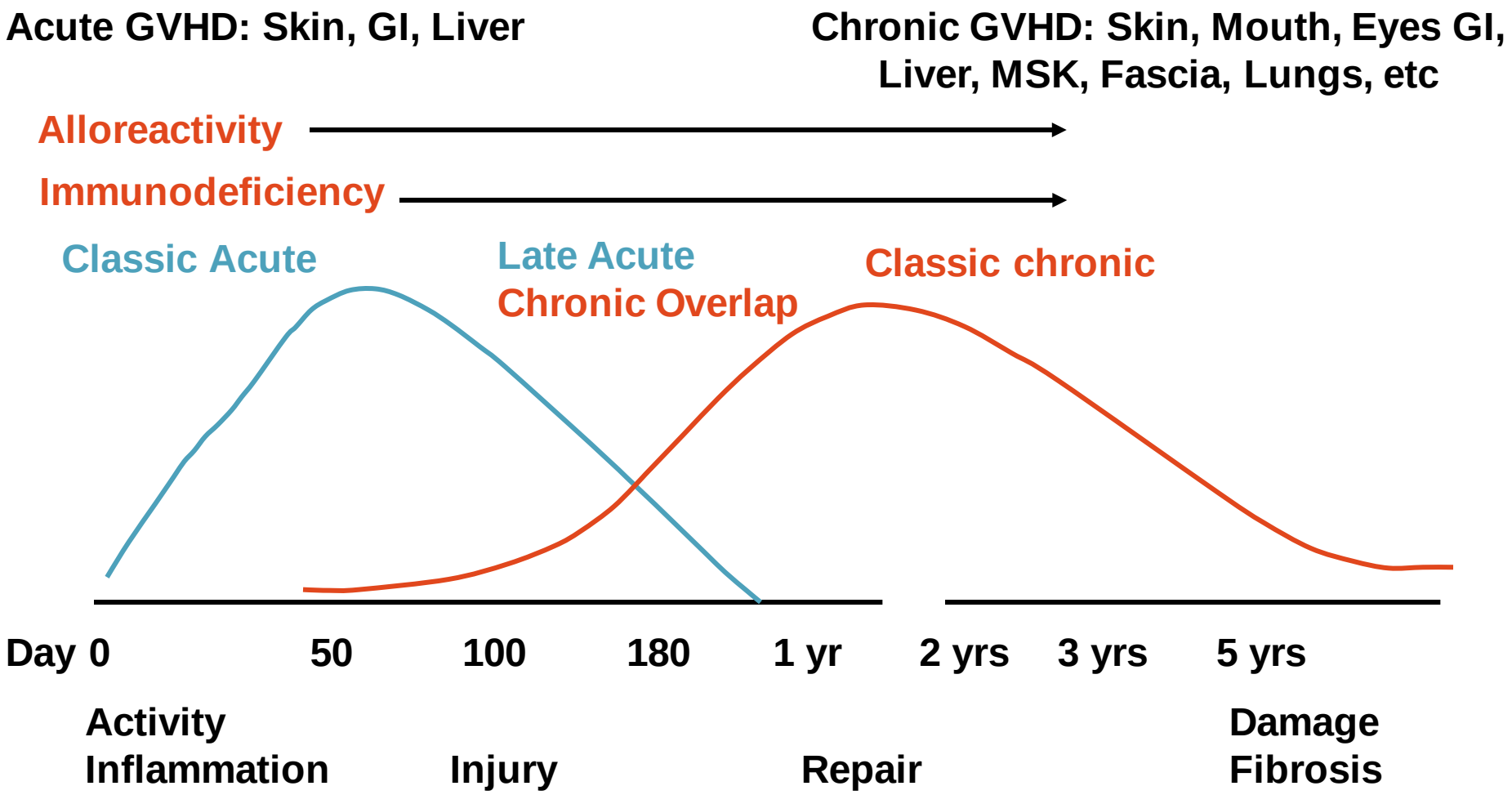


Target Tissues

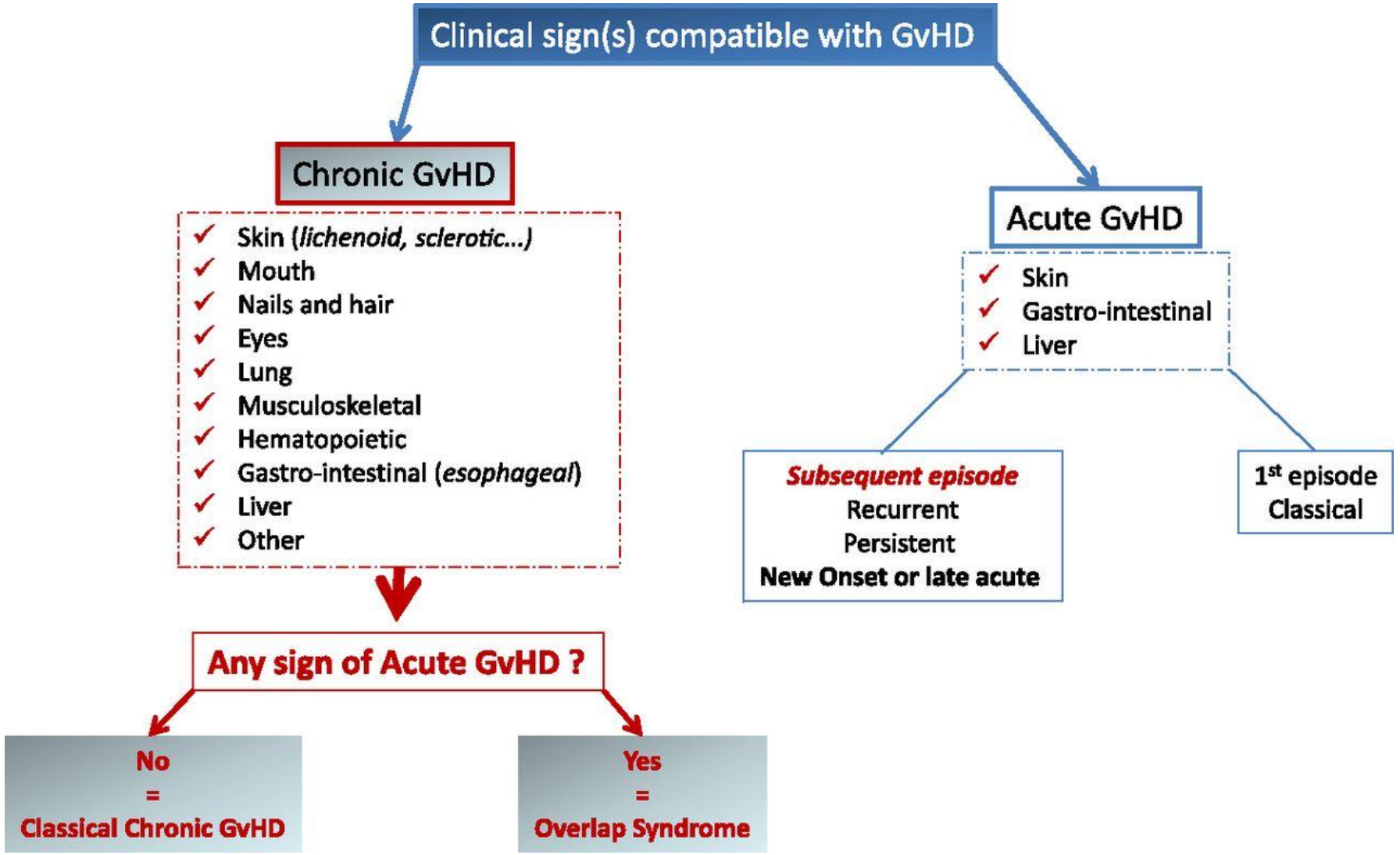
Acute and Chronic GVHD



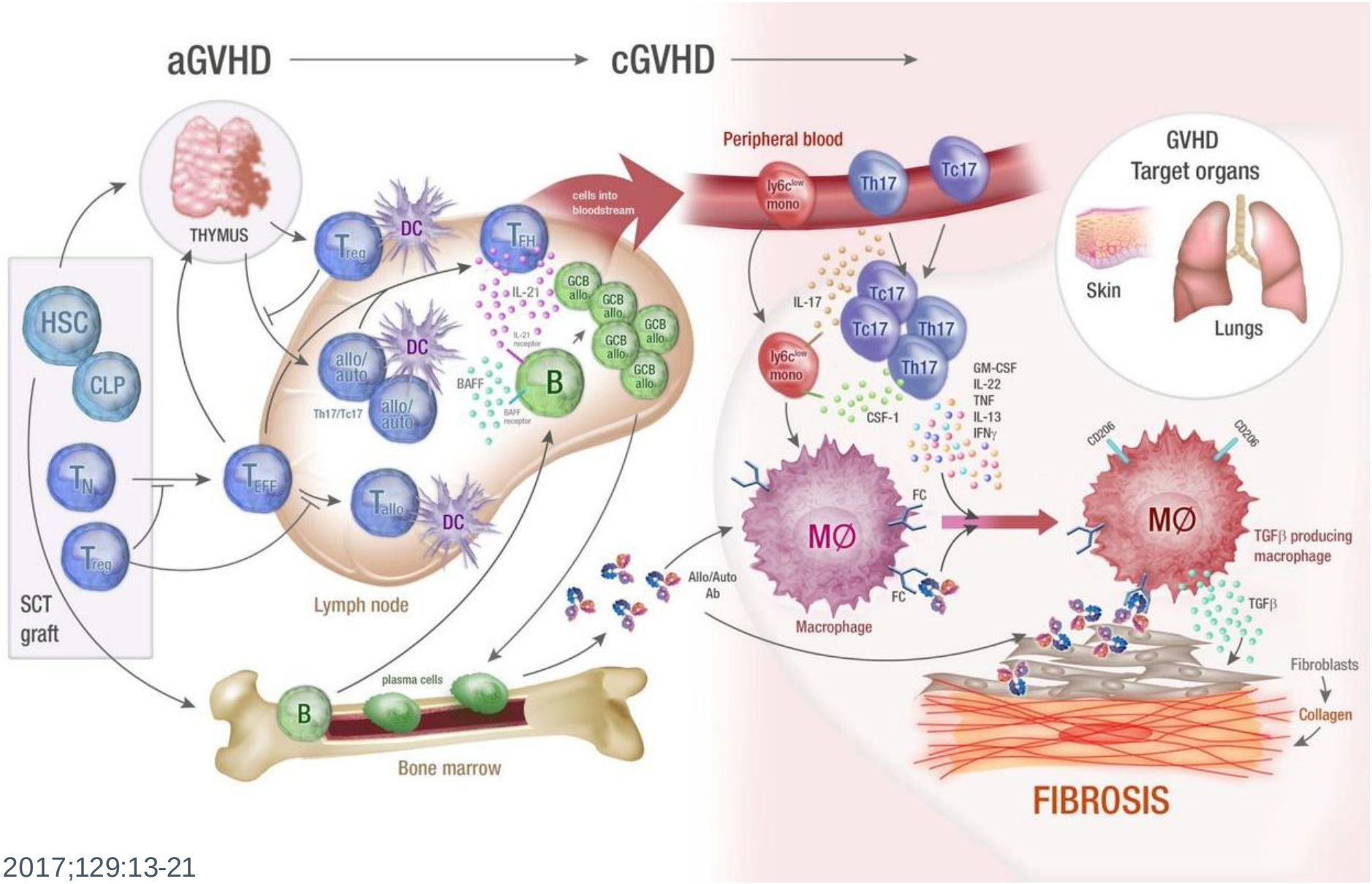
GVHD after Allogeneic Hematopoietic Cell Transplant (HCT)



GVHD Classification



GVHD Pathology: Acute and Chronic GVHD



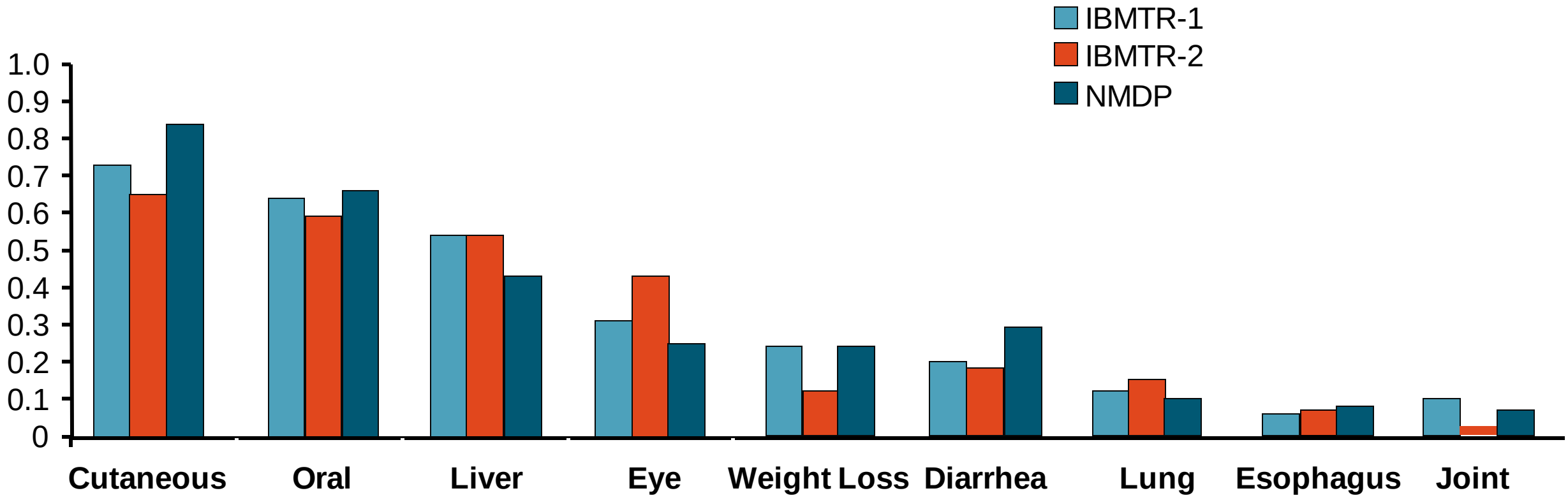
MacDonald *et al*, Blood 2017;129:13-21

3 Biologic Phases of Chronic GVHD

Phase 1: Acute Inflammation & Tissue Injury	Phase 2: Chronic Inflammation & Dysregulated Immunity	Phase 3: Aberrant Tissue Repair & Fibrosis
Innate Immunity ▪ Cytokines ▪ TLR agonists ▪ Neutrophils ▪ Platelets ▪ Vascular inflammation	**Adaptive Immunity** ▪ Thymic injury and dysfunction ▪ T-cells ▪ B-cells ▪ NK cells ▪ Antigen-presenting cells ▪ Regulatory cells – T_{REG}, B_{REG} – IL-10 producing regulatory T-cells	**Innate & Adaptive** ▪ TGFβ ▪ PDGFα ▪ TNFα ▪ IL-17 ▪ Macrophages ▪ Fibroblasts

Cooke KR, et al. Biol Blood Marrow Transplant. 2017;23:211-234.

Chronic GVHD: Organ Involvement



Adapted from Lee SJ, et al. Biol Blood Marrow Transplant. 2002;8:32-39.

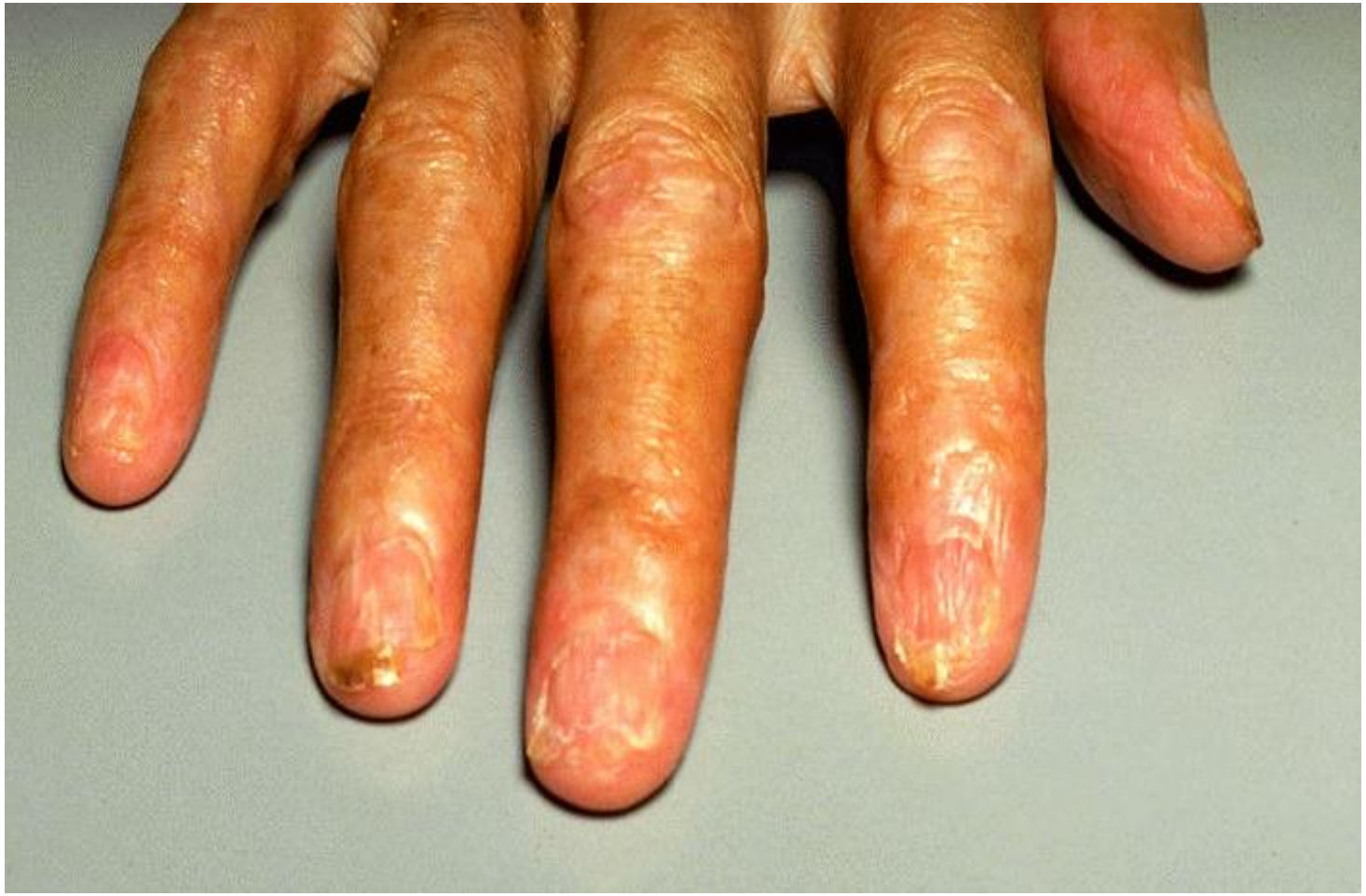
GVHD Signs and Symptoms

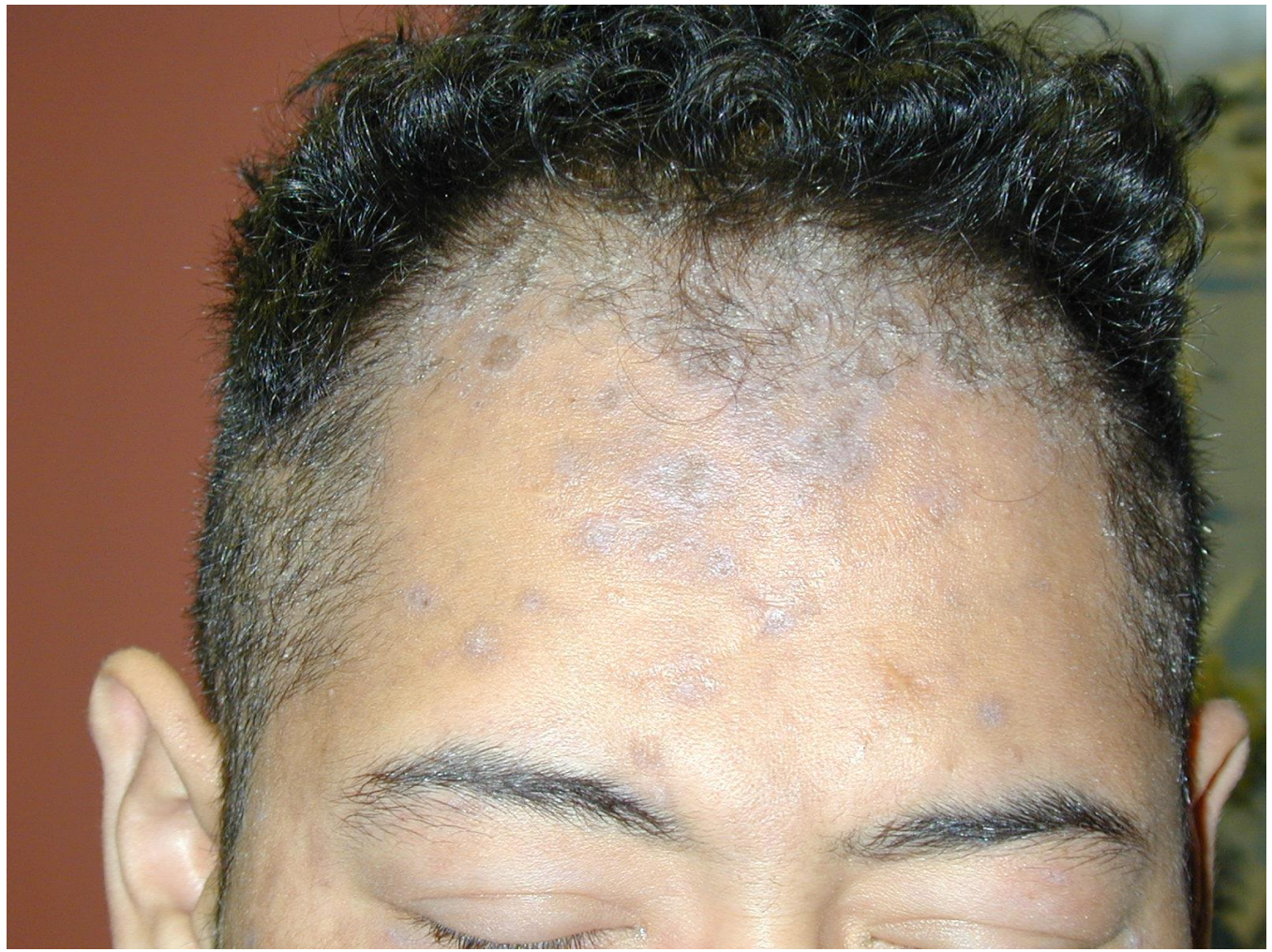
Skin and related structures	**Skin**: Hyper/hypopigmentation, lichenoid, sclerodermal, papulosquamous, ichthyosiform and psoriasiform changes; atrophy, poikiloderma, and ulcers	Pruritus, dryness, pain, infection, rigidity, decreased range of motion, photosensitivity
	Nails: Dystrophy, longitudinal ridging, onycholysis, pterygium, destruction	Nail and hair loss
	Scalp: Scaling, fibrosis, scarring and non-scarring alopecia, papulosquamous changes	
Mouth	Lichenoid changes, erythema, ulcers, xerostomia, fibrosis, leukoplakia; dental caries	Pain, odynophagia, dysphagia, dysgeusia, dryness, sensitivity to food
Eyes	Keratoconjunctivitis sicca, corneal ulcerations	Pain, dryness photophobia
Musculoskeletal	Polymyositis, muscle weakness, myalgias, arthritis, arthralgias, fasciitis	Weakness, arthralgias, myalgias, decrease ROM
GI tract	**Upper**: Abnormal motility, esophageal fibrosis, ulcerations, strictures **Lower**: Mucosal abnormalities/malabsorption, submucosal fibrosis	Odynophagia and lower dysphagia, pain, heartburn, nausea, anorexia, vomiting, abdominal pain, diarrhea/malabsorption, dehydration, weight loss

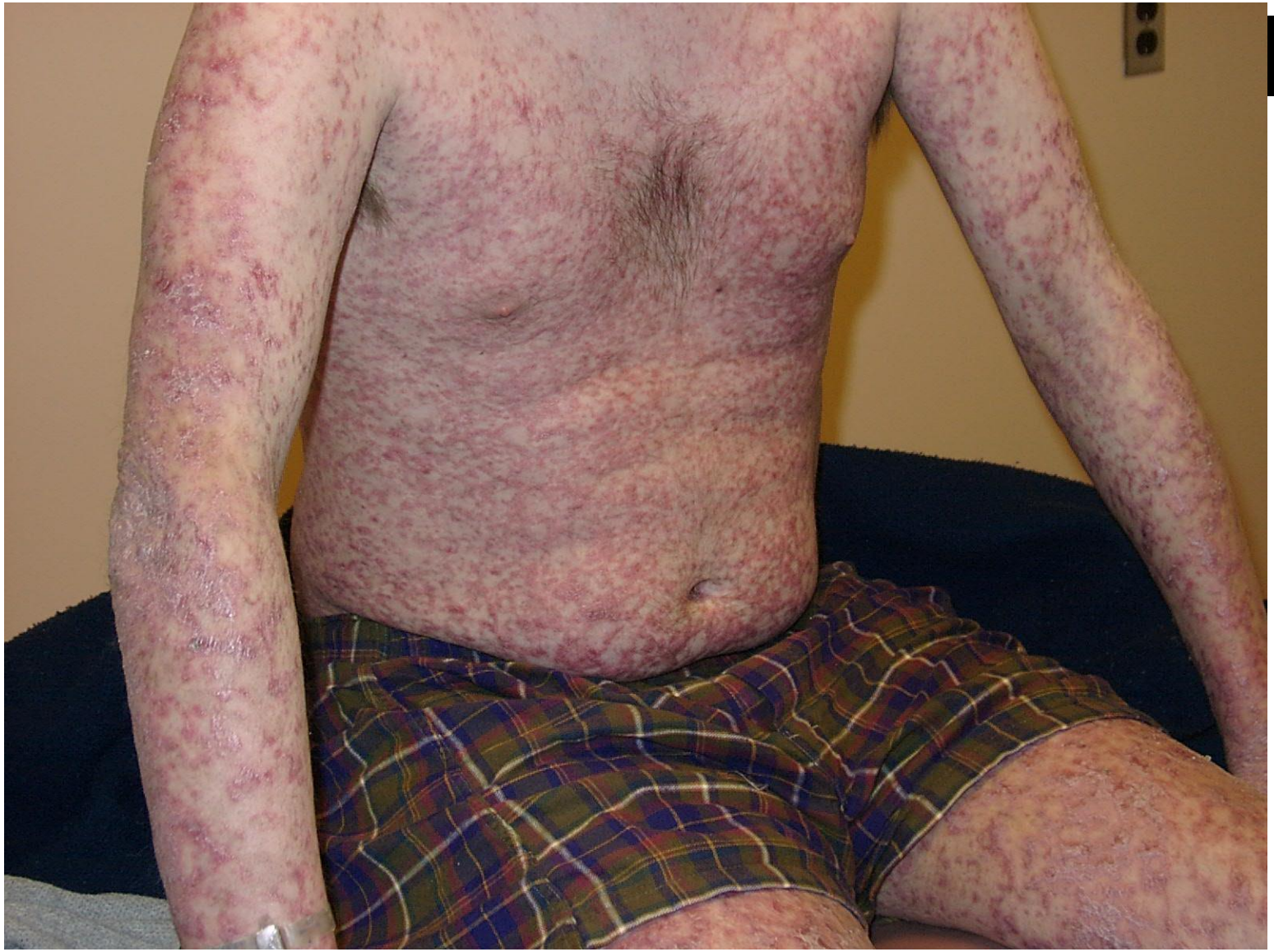
GVHD Signs and Symptoms, Continued

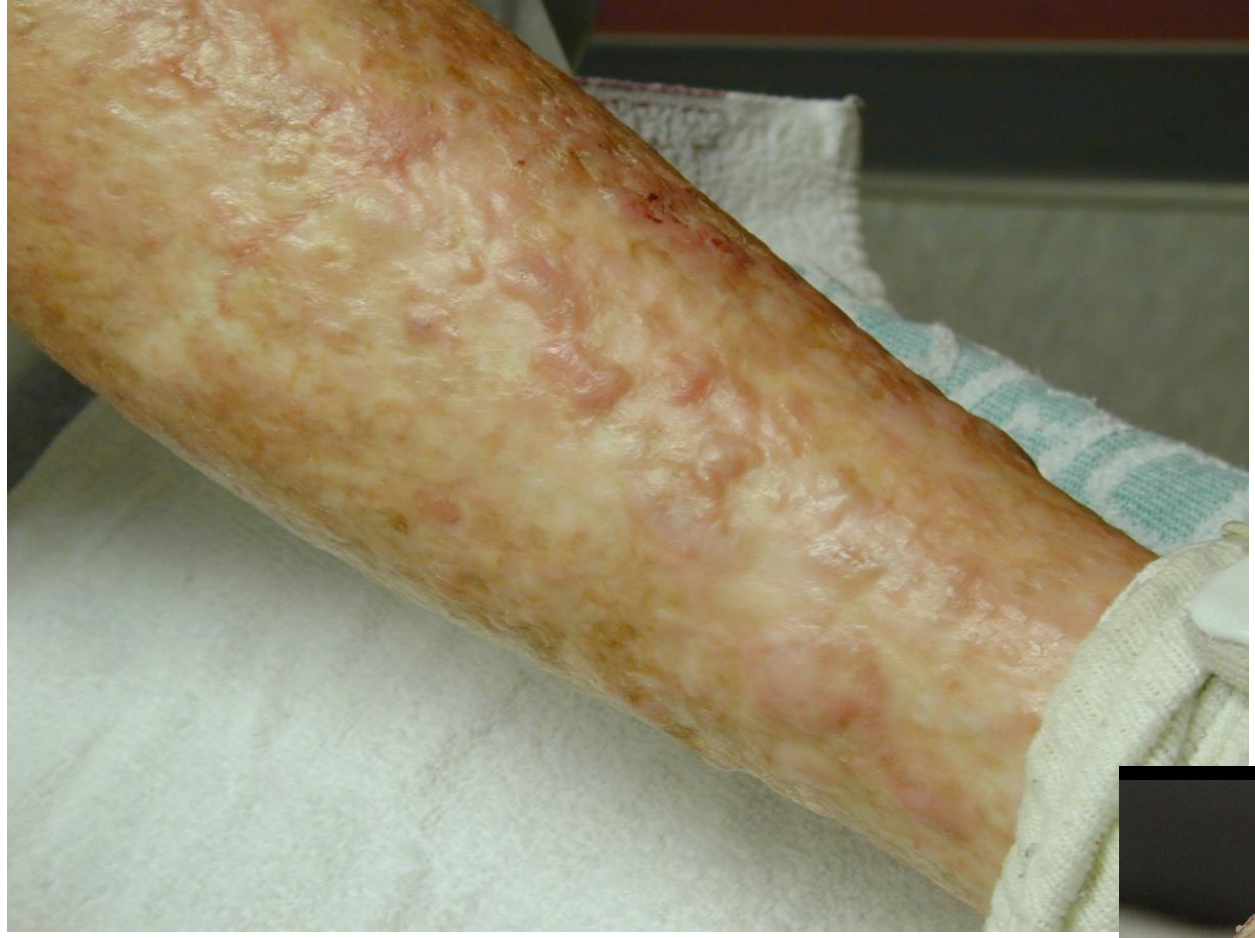
Liver	Hyperbilirubinemia, elevated ALP, elevated ALT/AST, fibrosis	Fatigue, jaundice, pruritus
Lung	Obstructive (BO/BOOP) or restrictive (scleroderma of the chest) dysfunction; air trapping, bronchiectasis, pneumothorax, pneumomediastinum, subcutaneous emphysema; microbial colonization or pneumonia	Dyspnea, wheezing, productive or non productive cough
Neurologic	Neuropathy, myasthenic syndromes	Pain, burning, dysesthesias, paresthesias, muscle weakness
Vaginal mucosa	Erythema, lichenoid changes, dryness, ulcers, strictures/stenosis	Pain, burning, dryness, dyspareunia
Serosal	Serositis, pericardial, pleural and peritoneal effusions	Dyspnea, chest pain, pleuritic pain, abdominal pain, ascites
Hematopoietic	Isolated or combined cytopenias, eosinophilia, hemolysis	Fatigue, fever, infection, bleeding
Immunologic	Repeated infections of various etiologies, lymphopenia, hyper/hypogammaglobulinemia	Increased susceptibility to infection

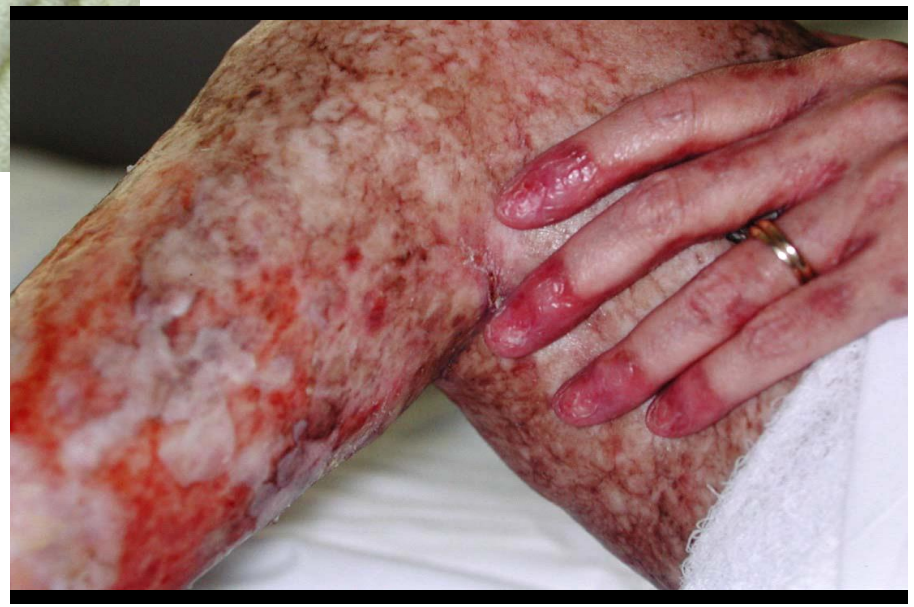
Chronic GVHD: Skin Involvement



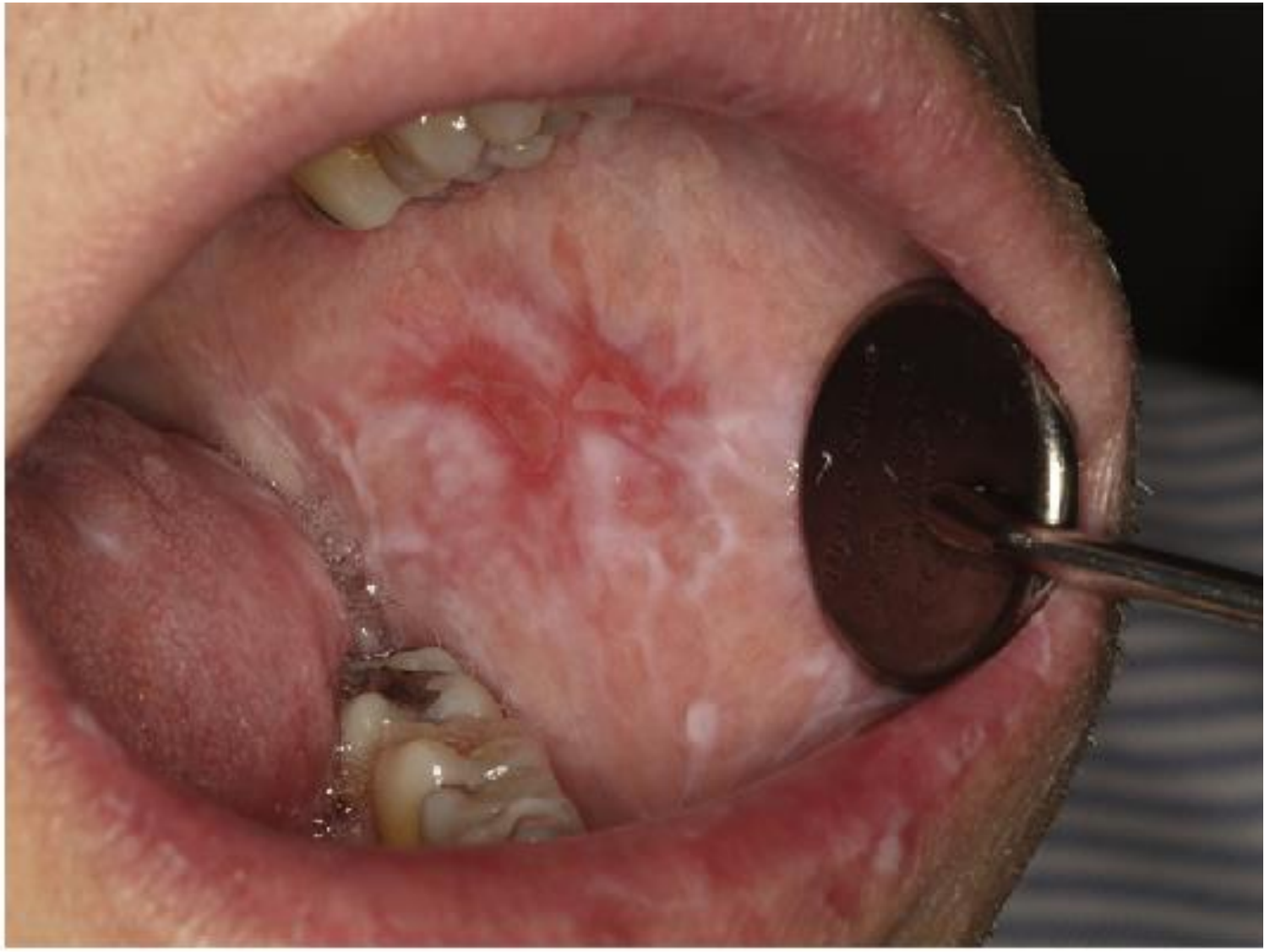




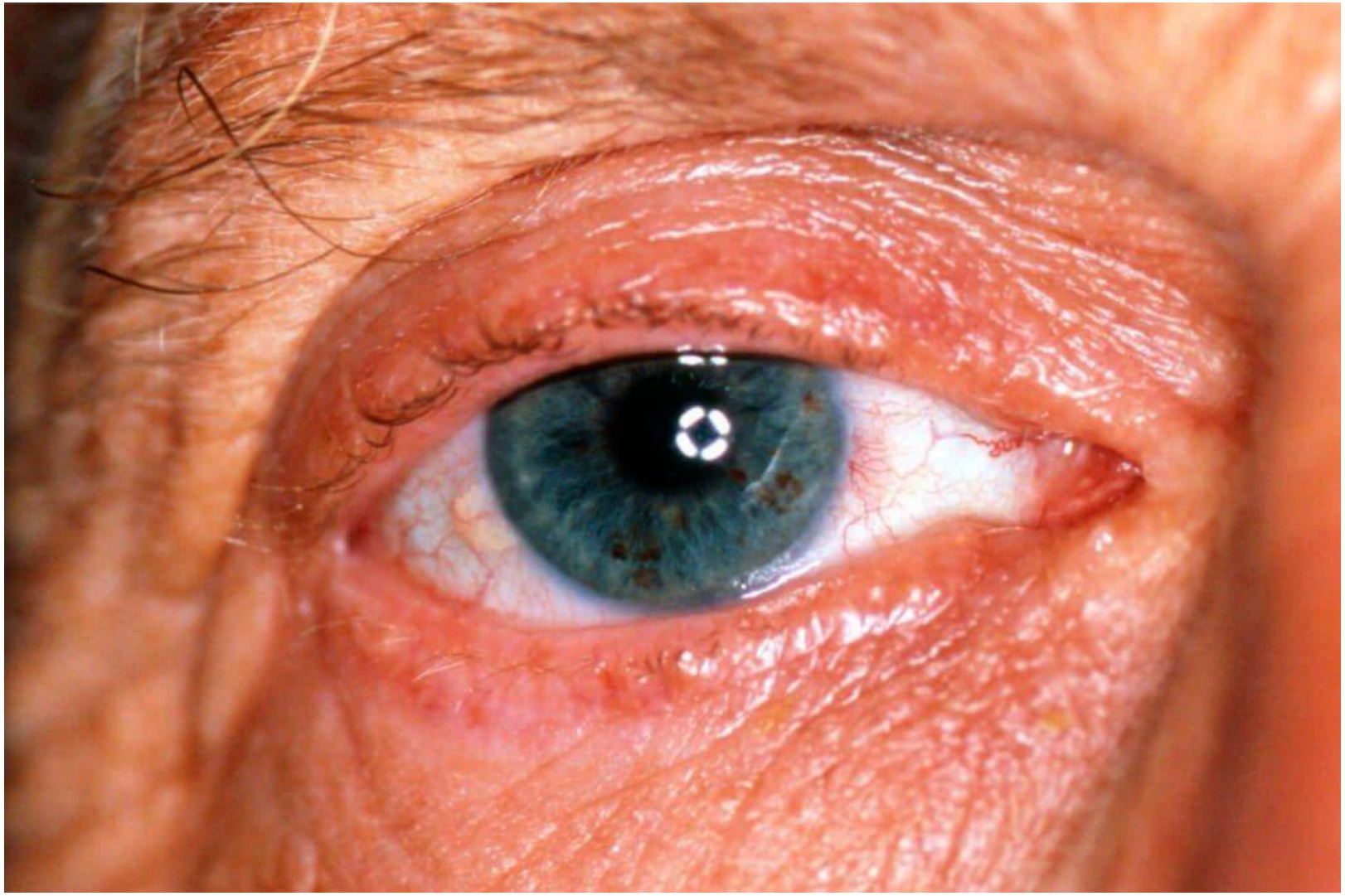




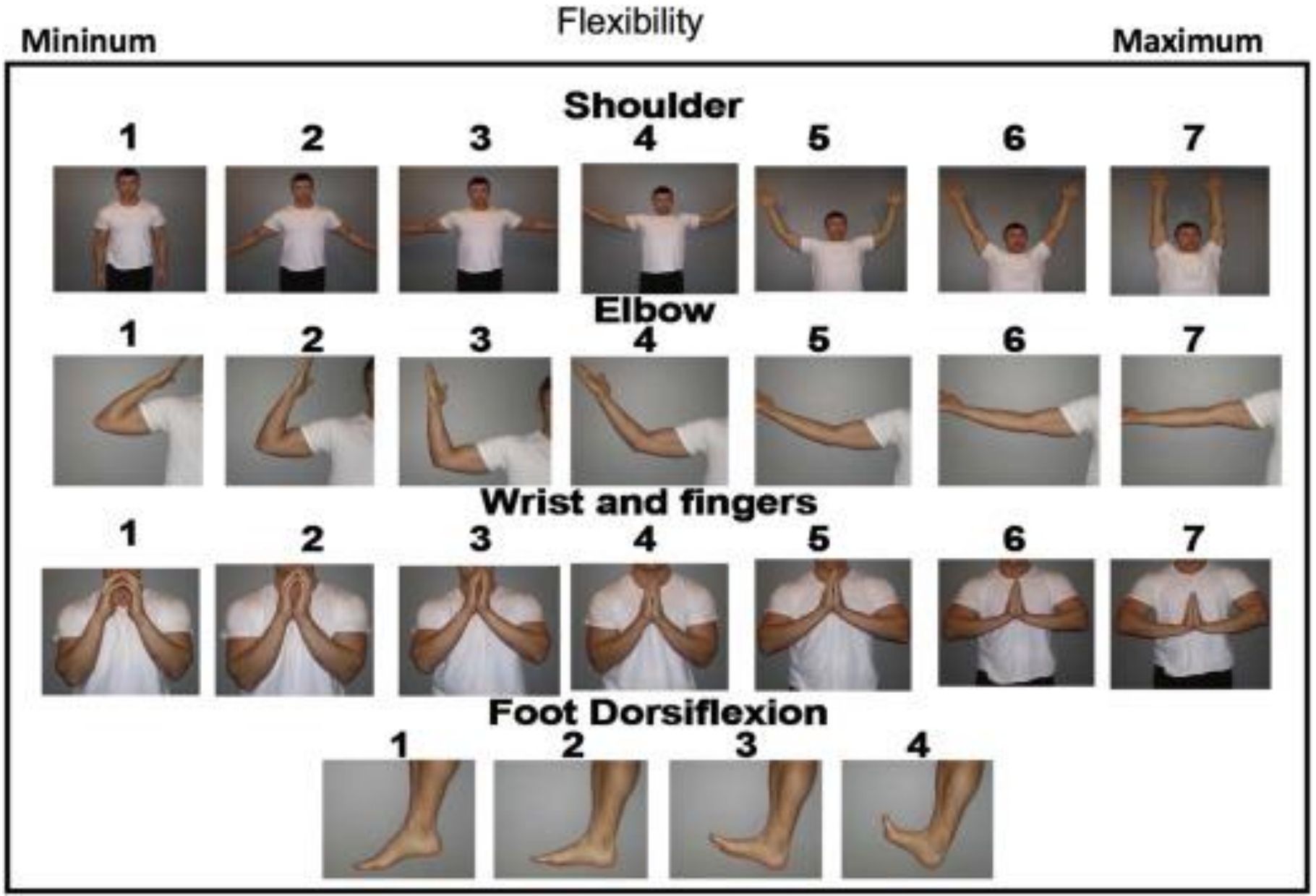
Chronic GVHD: Mouth Involvement

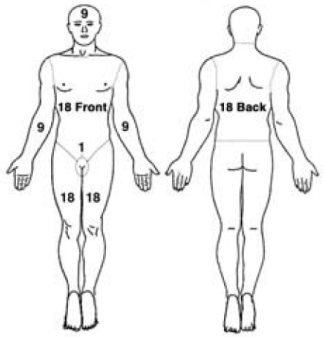


Chronic GVHD: Eye Involvement



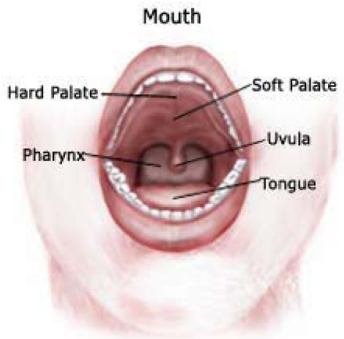
Chronic GVHD: Fascia Involvement



Component	Findings	Scoring (see skin score worksheet)
Skin 	Erythematous rash of any sort	% BSA (max 100%)
	Moveable sclerosis	% BSA (max 100%)
	Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis	% BSA (max 100%)
	Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer	Location: _____ Largest dimension: _____cm

Eyes Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: mm of wetting	Left Eye: mm of wetting

Mouth



Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

Blood Counts	Platelet Count K/uL	ULN K/uL	Total WBC K/uL	ULN K/uL	% Eosinophils %					
Liver Function Tests	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L				

Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*		
Gastrointestinal-Esophageal • Dysphagia OR • Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*		
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*		
Lungs • Bronchiolitis Obliterans	Pulmonary Function Tests with Diffusing Capacity (attach report for person> 5 yrs old)	FEV-1 % Predicted	Single Breath DLCO (adjusted for hemoglobin) % Predicted

Health Care Provider Global Ratings: **In your opinion, do you think that this patient's chronic GVHD is mild, moderate or severe?** 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GVHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** **Most severe cGvHD symptoms possible**	**Over the past month would you say that this patient's cGVHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Functional Performance (in persons >4 years old) • Walk Time • Grip Strength	Total Distance Walked in 2 Minutes: Number of laps: _____ (x 50 feet) + final partial lap: _____ feet = _____ feet walked in 2 minutes	Grip Strength (Dominant Hand) Trial #1 psi	Trial #2 psi	Trial #3 psi	Range of Motion: ○ Not performed ○ Physical Therapy Report Attached

cGVHD Assessment

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† ☐ **SCORE % BSA**				
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 GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
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

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

cGVHD Assessment

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ 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 punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware 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):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ 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 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

cGVHD Assessment

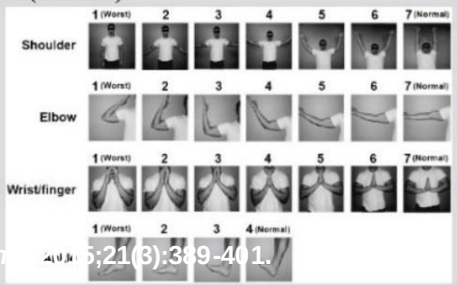
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



Blood Marrow Transplant. 2015;21(3):389-401.

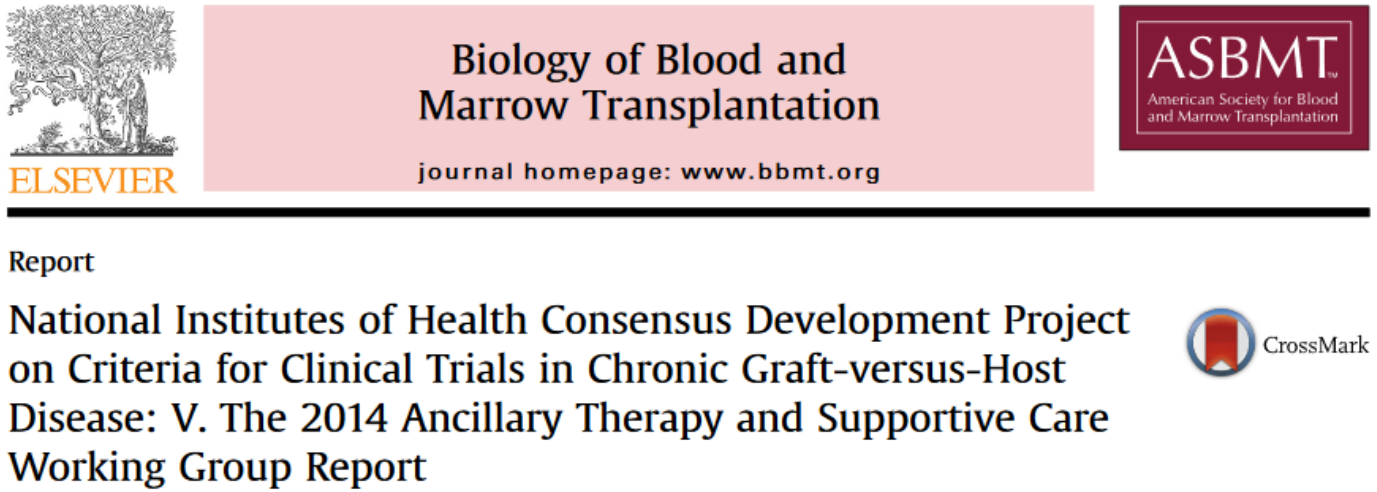
NIH Individual Organ Severity Score

- 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 Strategy

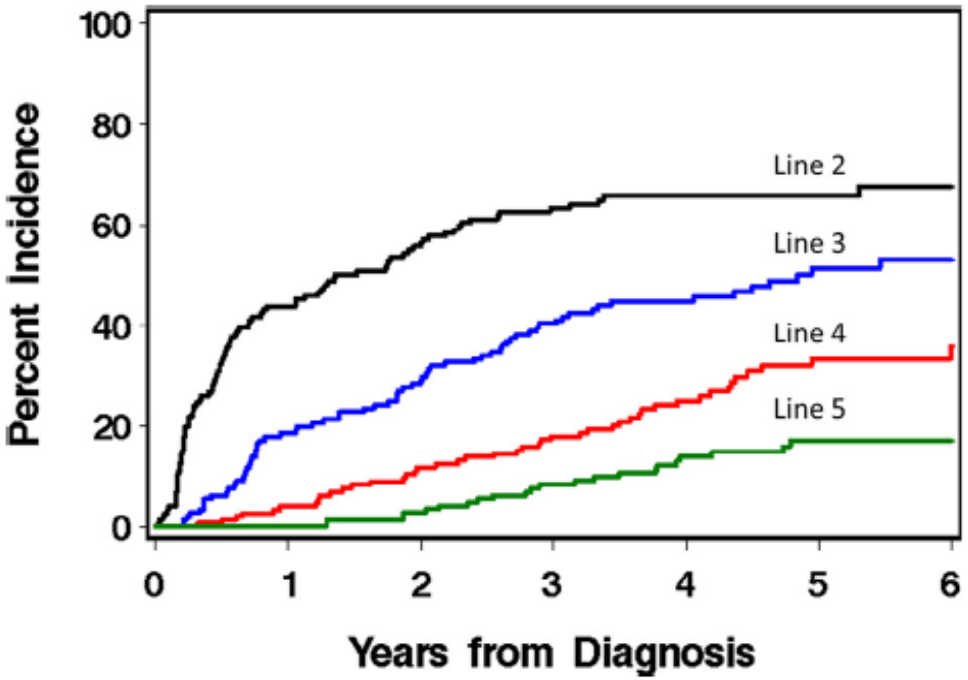
- **Local symptoms → Local Rx**
  - Early identification is crucial
  - Two types of local therapies
    - Supportive
    - Locally immunosuppressive



- **Systemic symptoms or multiple local sites → Systemic Rx**
  - Prednisone 1 mg/kg/day + Tacrolimus *or* Cyclosporine
  - Complete response rate: 50%-55%
  - Median time to discontinue immune therapy: 1.6-2.2 years
  - Additional agents at onset of GVHD: Not shown to be beneficial

Indications for Secondary Treatment of Chronic GVHD

- Progression of symptoms
- No improvement after ~ 1 mo of treatment
- Inability to taper prednisone below 1 mg/kg/day within 4-8 weeks without worsening
- Toxicity



The chance that a patient starting initial therapy for chronic GVHD will never need additional therapy is only 21.3%

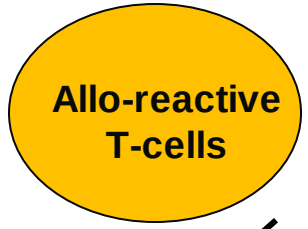
Lee, BBMT 2017

Second-Line Therapy for Chronic GHVD

- After failure of corticosteroids, no current consensus on optimal second-line treatment choice
- Many retrospective and prospective studies suggest high response rates with second-line treatment options
  - Results are hard to interpret because of suboptimal study designs
- Treatment choices are based on:
  - Physician experience
  - Ease of use
  - Need for monitoring
  - Risk of toxicity

Treatment	ORR, %
ECP	65-70
Rituximab	66-86
Imatinib	22-79
Pentostatin	53-56
Mycophenolate mofetil	26-64
mTOR inhibitor	76
IL-2	52

Mechanistic Interventions for the Prevention or Treatment of Chronic GVHD

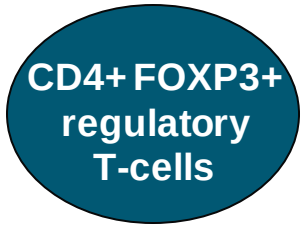


Stem cell graft engineering

- Antithymocyte globulin
- Posttransplant cyclophosphamide
- CD34 selection
- Ex vivo pan–T-cell depletion
- Ex vivo selective T-cell depletion
- Donor IL-2 therapy

Inhibit T-cell signaling

- ITK inhibition: ibrutinib
- JAK1/2 inhibition: ruxolitinib
- ROCK2 inhibition: KD025
- Bortezomib



Treg-sparing therapy

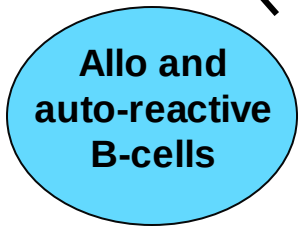
- Sirolimus
- Mycophenolate mofetil
- Ruxolitinib
- Bortezomib

Adoptive Treg Therapy

- Purified donor Treg
- Ex vivo expanded Treg
- Antigen-specific Treg

In vivo Treg expansion

- ECP
- Low-dose IL-2



B-cell depletion in vivo

- Rituximab
- Ofatumumab
- Obinutuzumab

Inhibit B-cell signaling

- BTK inhibition: ibrutinib
- SYK inhibition: fostamatinib

Cutler CS, et al. Blood. 2017;129:22-29.

Other Health Issues Related to Chronic GVHD

- Long-term survivors of allogeneic BMT with chronic GvHD are 3 times as likely to have 2 or more chronic health conditions

- Specific conditions associated with chronic GvHD include
  - oral and ocular complications
  - pulmonary compromise
  - gastrointestinal complications
  - neurological problems

- Patients with chronic GvHD are 2.7-fold more likely to be frail

Phase 1b/2 Study of Ibrutinib in cGVHD (NCT02195869)

Key eligibility criteria:

- Steroid dependent/refractory
- ≤3 prior treatments for cGVHD
- Other systemic immunosuppressants, if used, were continued
- >25% body surface area with "erythematous rash", by NIH-defined criteria
  or
- >4 total mouth score, by NIH-defined criteria

Patients with cGVHD who have failed frontline steroids (N = 42)

Ibrutinib 420 mg[a] orally continued until progression of cGVHD or unacceptable toxicity

[a]Recommended phase 2 dose identified in phase 1 of the study

Primary end point:

- cGVHD response per 2005 NIH response criteria

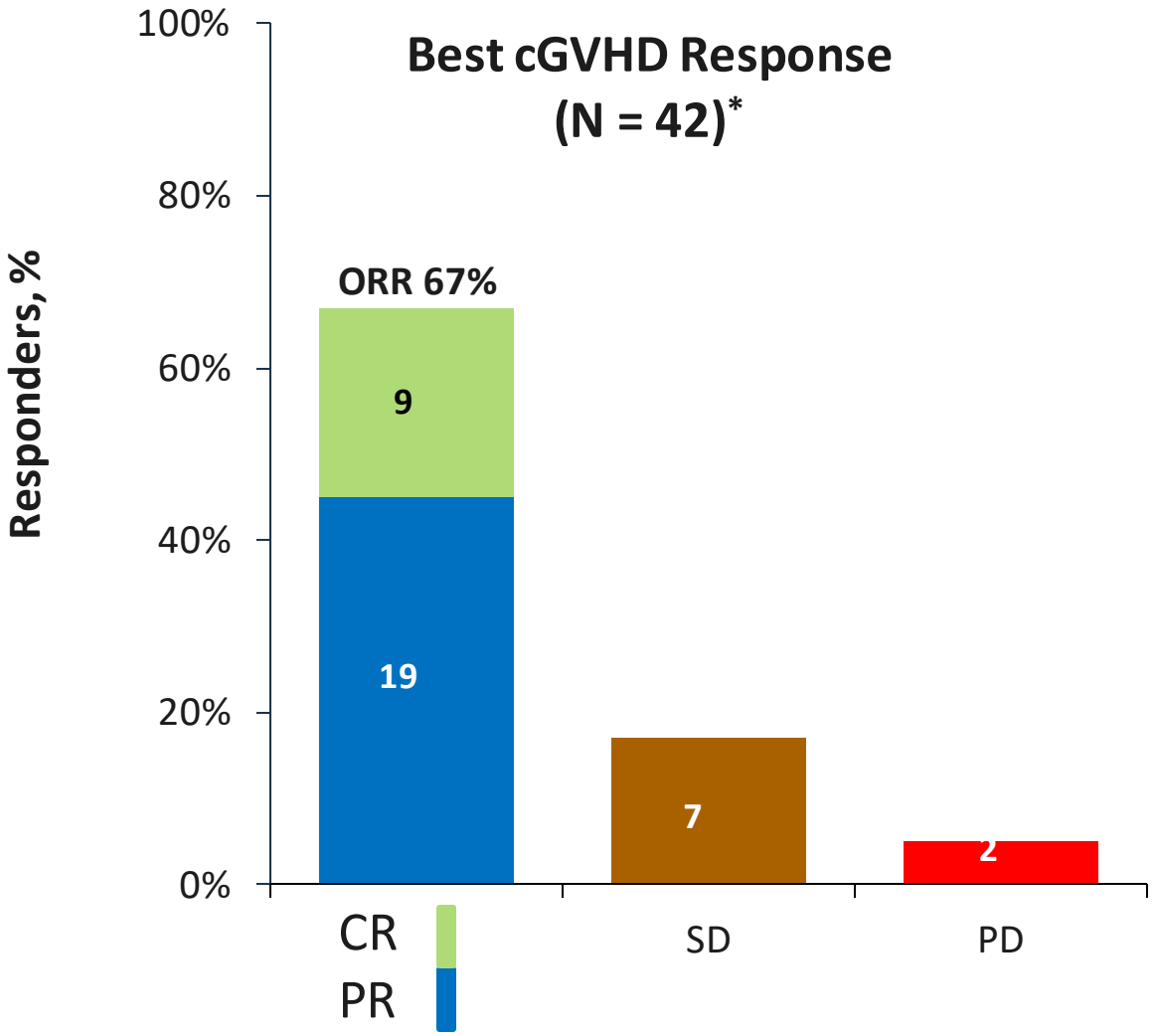
Secondary end points:

- Rate of sustained response
- Change in Lee cGVHD symptom scale
- Changes in steroid requirement over time
- Safety end points

Exploratory end points :

- Effect on lymphoid and myeloid signaling pathways and plasma cytokines and chemokines

Ibrutinib Produced a High Rate of Response That Was Sustained

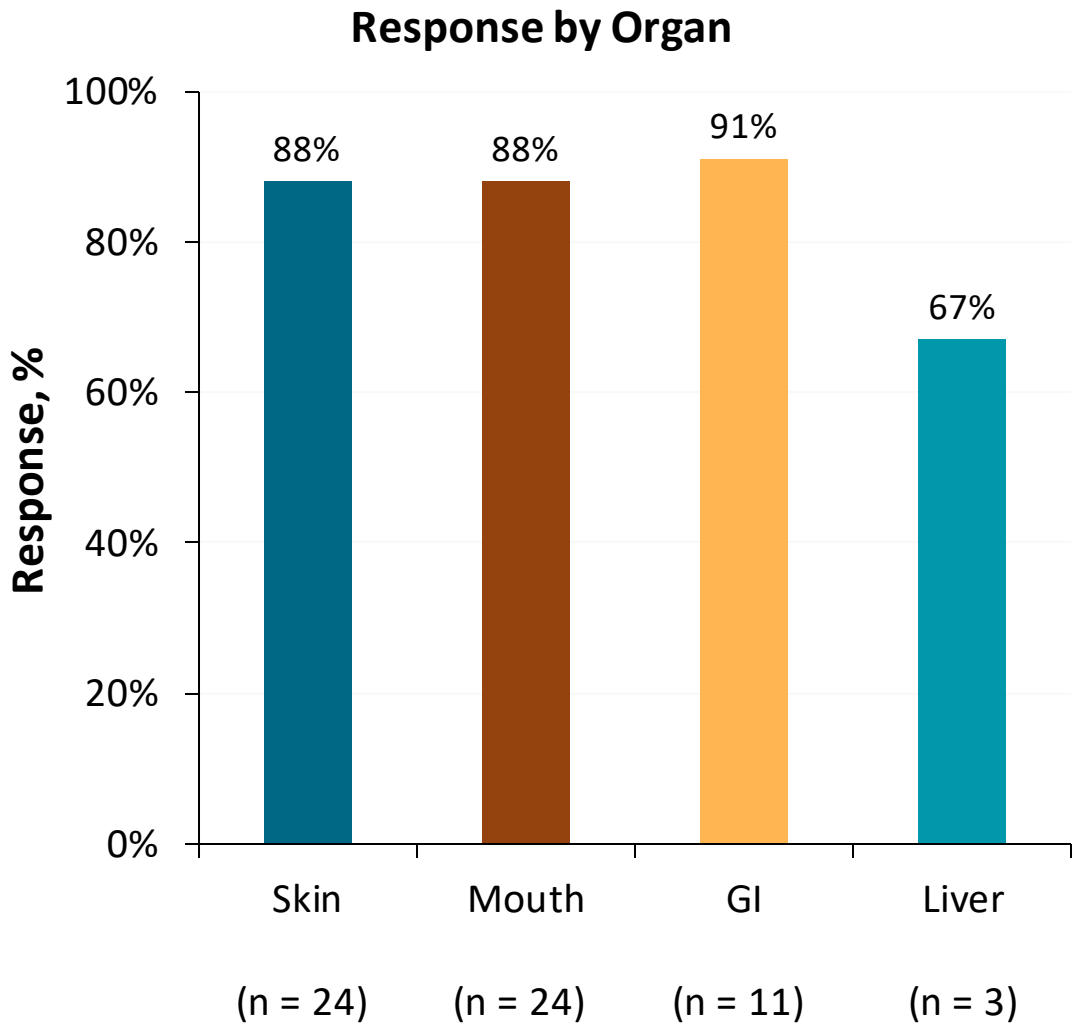


- 1/3 of responders had a CR
- 79% responded at the time of 1st response assessment
- 71% of the 28 responders had a sustained cGVHD response of at least 5 mo

*5 patients had no response assessment during the study but are included in the denominator.

EHA 2017, 1129 cGVHD; Pusic et al.

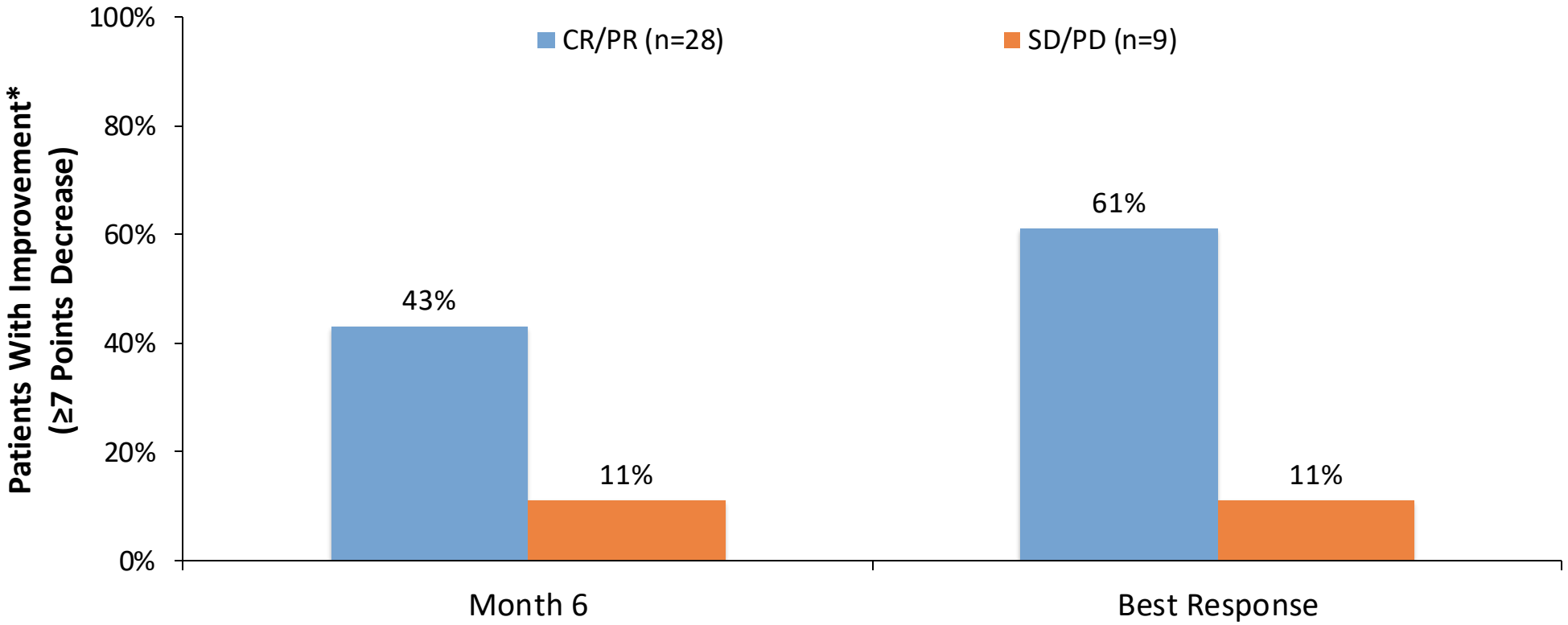
Chronic GVHD Responses Were Observed Across Multiple Organs



- 80% (20/25) of patients with ≥2 involved organs at baseline responded in at least 2 organs
- 56% (5/9) of patients with ≥3 involved organs at baseline responded in at least 3 organs

EHA 2017, 1129 cGVHD; Pusic et al.

Ibrutinib Produced Clinically Meaningful Improvement in Lee Symptom Scale Score Among Responders



- Consistent with improvement in chonic GVHD symptoms, clinician-assessed and patient-reported reductions in overall chronic GVHD severity were also reported

*5 patients had no Lee symptom scale assessment during the study.

Second-line Chronic GVHD Treatment Options: Ruxolitinib

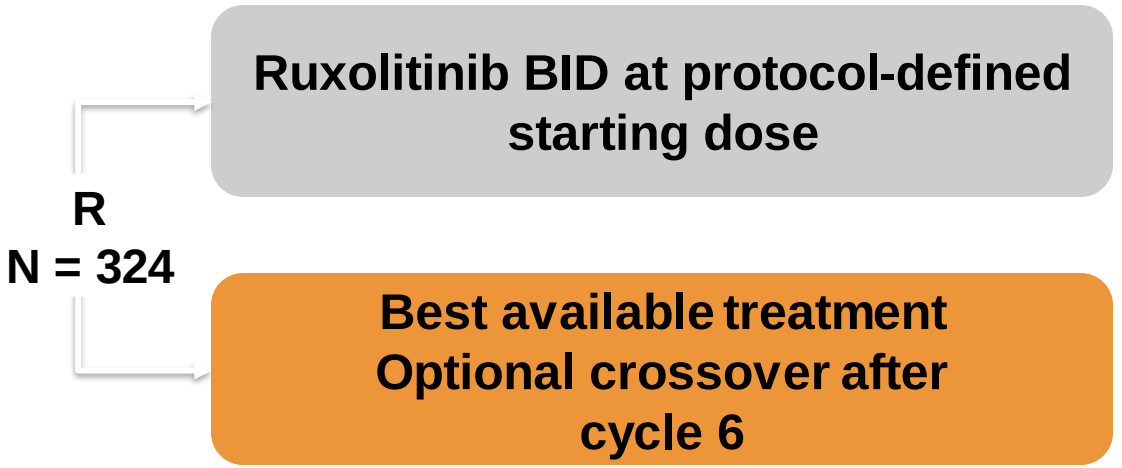
- Europe and US, retrospective survey
- N= 41 steroid-refractory mod-severe cGvHD
- Median follow-up 22.4 weeks
- **ORR: 85.4% (35/41)**
- 5.7% (2/35) cGVHD relapse rate

Key eligibility criteria

- **≥12 years old with moderate to severe steroid-refractory classical cGVHD**
- **Myeloid and platelet engraftment**
- **Only prior treatments, corticosteroids ± CNI for cGVHD**
- **If prior JAK inhibitor for aGVHD, CR or PR, and off for >8 weeks**

REACH3

- **Primary endpoint: ORR**
- **Secondary endpoints: Δ symptom scale score, DOR, OS, ↓ steroid use, QOL, toxicity**



Zeiser R, et al. *Leukemia*. 2015; Zeiser R, Blazar BR. *Blood.* 2016

Interim Analysis of KD025-213: A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) after at Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Corey Cutler, MD, MPH[1], Stephanie Lee, MD, MPH[2], Sally Arai, MD[3], Marcello Rotta, MD[4], Behyar Zoghi, MD[5], Aravind Ramakrishnan, MD[6], Aleksandr Lazaryan, MD, MPH, PhD[7], David A Eiznhamer, PhD[8], Olivier Schueller, PhD[8], Zhongming Yang, PhD[8], Laurie S. Green, MEd[8], Sanjay K. Aggarwal, MD[8], The ROCKstar Study Group[9], Bruce R. Blazar, MD[10], Steven Z. Pavletic, MD[11] and Madan Jagasia, MD[12]

[1] Department of Hematologic Malignancies, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, [2] Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, [3] Stanford University, Stanford, CA, [4] James Cancer Center, Ohio State University, Columbus, OH, [5] Texas Transplant Institute, Methodist Hospital, San Antonio, TX, [6] Blood and Marrow Transplant, Texas Transplant Institute at St. David's South Austin Medical Center, Austin, TX, [7] Blood and Marrow Transplantation and Cellular Immunotherapy, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, [8] Kadmon Corporation, LLC, New York, NY, [9] The ROCKstar Study Group, New York, NY, [10] Division of Pediatric Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN, [11] Experimental Transplantation and Immunology Branch, Center for Cancer Research (CCR), National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, [12] Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN

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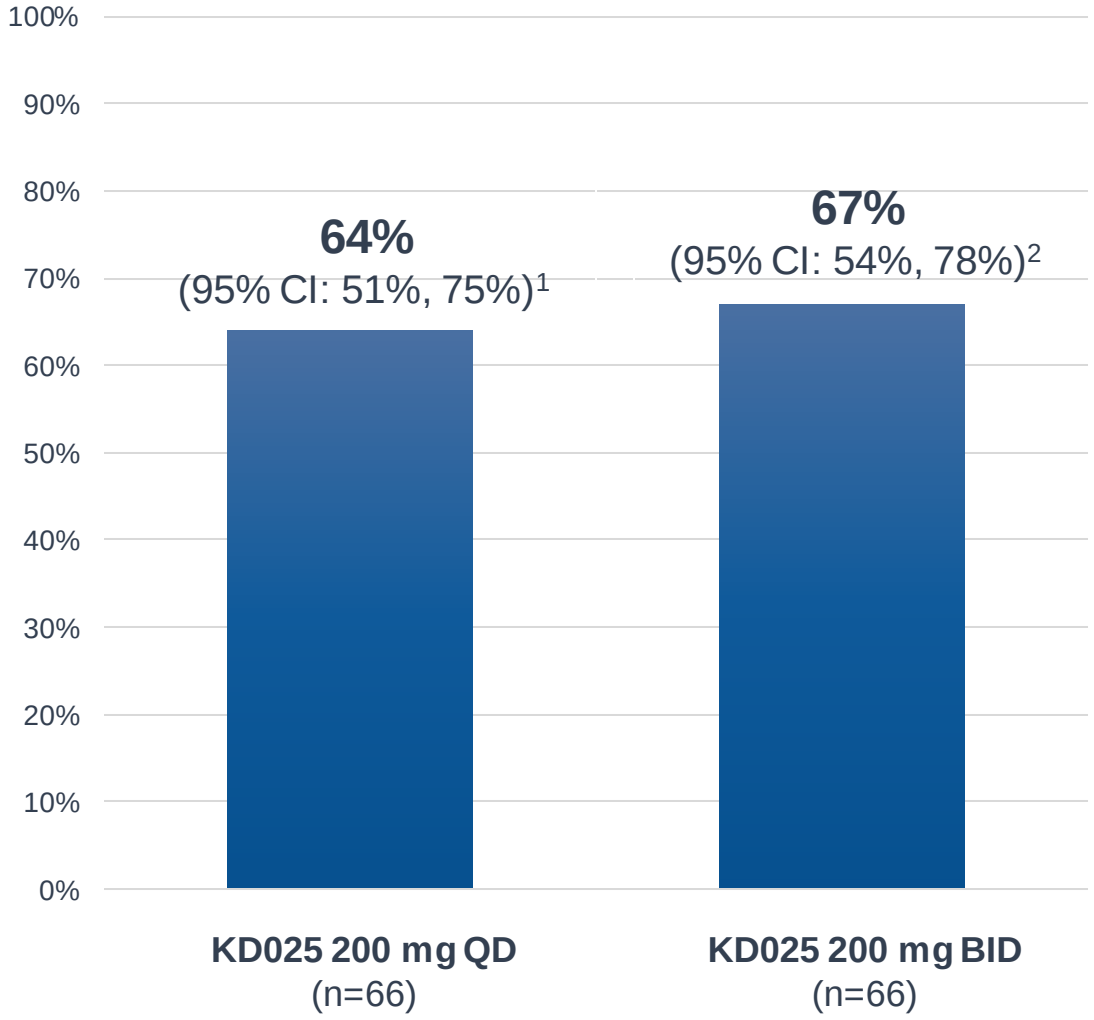
KD025-213: Primary Endpoint Met at Interim Analysis



- **Interim analysis occurred 2 months after last patient was enrolled**
- **KD025 achieved clinically meaningful and statistically significant ORRs in both arms**
  - Statistical significance is achieved if the lower bound of the 95% CI of ORR exceeds 30%
- **Three patients achieved a complete response (CR)**

[1]p<0.0001; [2]p<0.0001

GvHD Treatment-Induced Long-Term Effects

- Immune deficiency
- Cataracts
- Chronic kidney injury
- Steroid-induced diabetes
- Dyslipidemia
- Steroid myopathy
- Adrenal insufficiency
- Osteoporosis
- Neuropathy
- Poor wound healing
- Second malignancies/PTLD

Flowers MED, et al. Long-term follow-up after HSCT: General guidelines for referring physicians. 2019.

Long-Term Morbidity Associated with Chronic Graft versus Host Disease

A Report from the Blood or Marrow Transplant Survivor Study (BMTSS)

M Arora, Y Chen, J Wu, L Hageman, L Francisco, E Ness, M Parman, M Kung, A Bosworth, M Nayar, R Bhatia, SJ Forman, DJ Weisdorf, SH Armenian, S Bhatia

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Frequency of Late Effects in Survivors with and without chronic GVHD

Condition	No cGvHD (%)	cGvHD (%)	P
Ocular	52.4	63.5	0.007
Oral	17	30.9	<0.0001
Pulmonary	11.9	23	0.0005
GI	7.6	12.5	0.05
Neurology	23.1	33.2	0.007
Frailty	6.1	17.1	<0.0001
Endocrine	42.6	48	0.19
Cardiac	7.2	9.9	0.26
Renal	1.8	0.3	0.08
Second malignancy	26.7	26.3	0.91

Conclusions

- Chronic GVHD
  - Common
  - Potentially serious unless caught early

  But……
  - Treatable
  - Lots of advances – drug approvals coming
  - Tons of research……Stay tuned!

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Questions?

Celebrating a Second Chance at Life Survivorship Symposium

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