MOFFITT CANCER CENTER
BLOOD AND MARROW TRANSPLANT AND CELLULAR IMMUNOTHERAPY

LATE COMPLICATIONS OF ALLOGENEIC TRANSPLANT: CHRONIC GRAFT VS. HOST DISEASE

Asmita Mishra, MD and Marian Dam, DNP

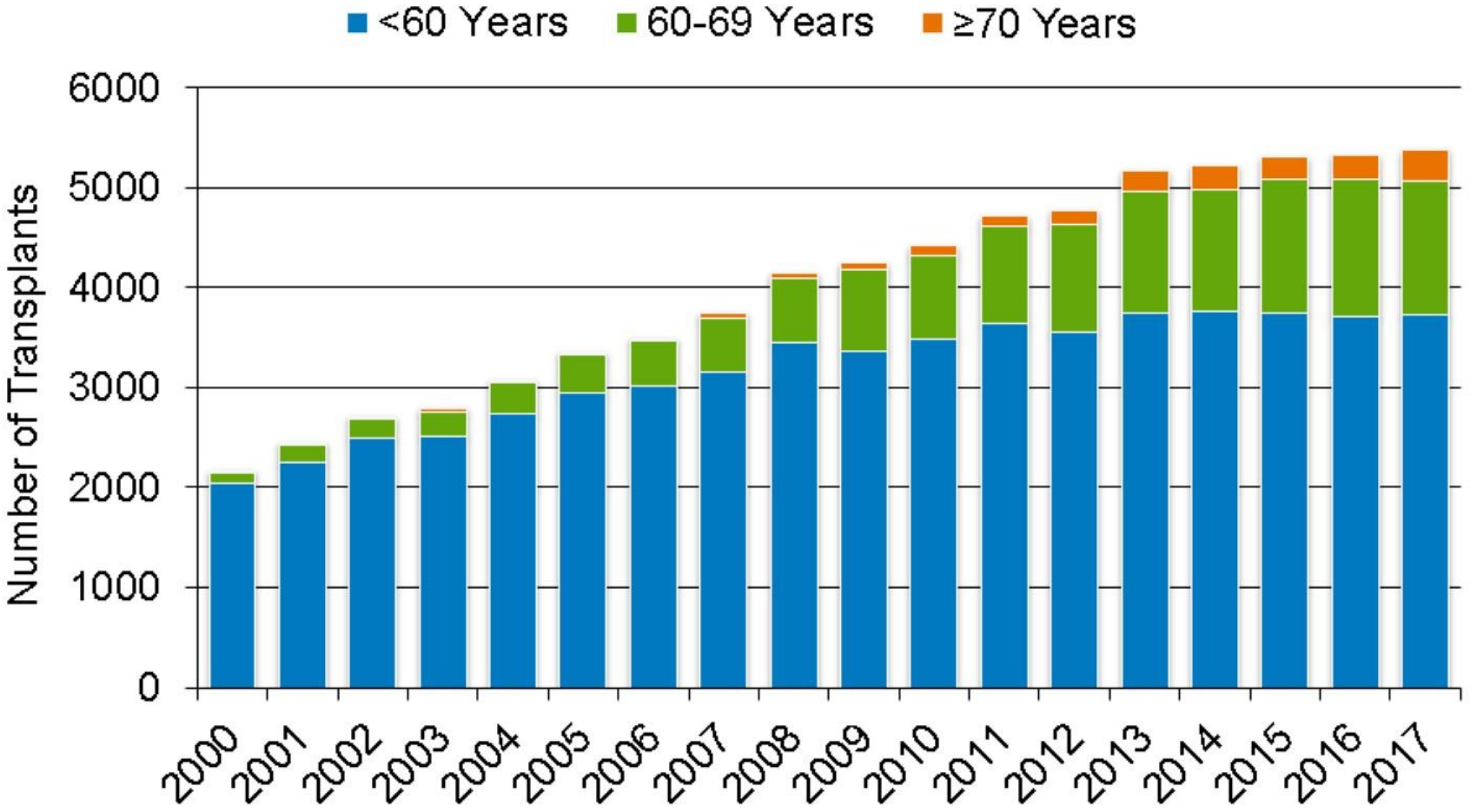
FLASCO 2019 Great Strides Together

May 17, 2019

OPTIMIZING SUCCESS AFTER TRANSPLANT

- **Understanding the problem at hand**
- **Identification and grading of chronic GVHD**
- **Therapy for chronic GVHD**

Trends in Allogeneic HCT in the US by Recipient Age^



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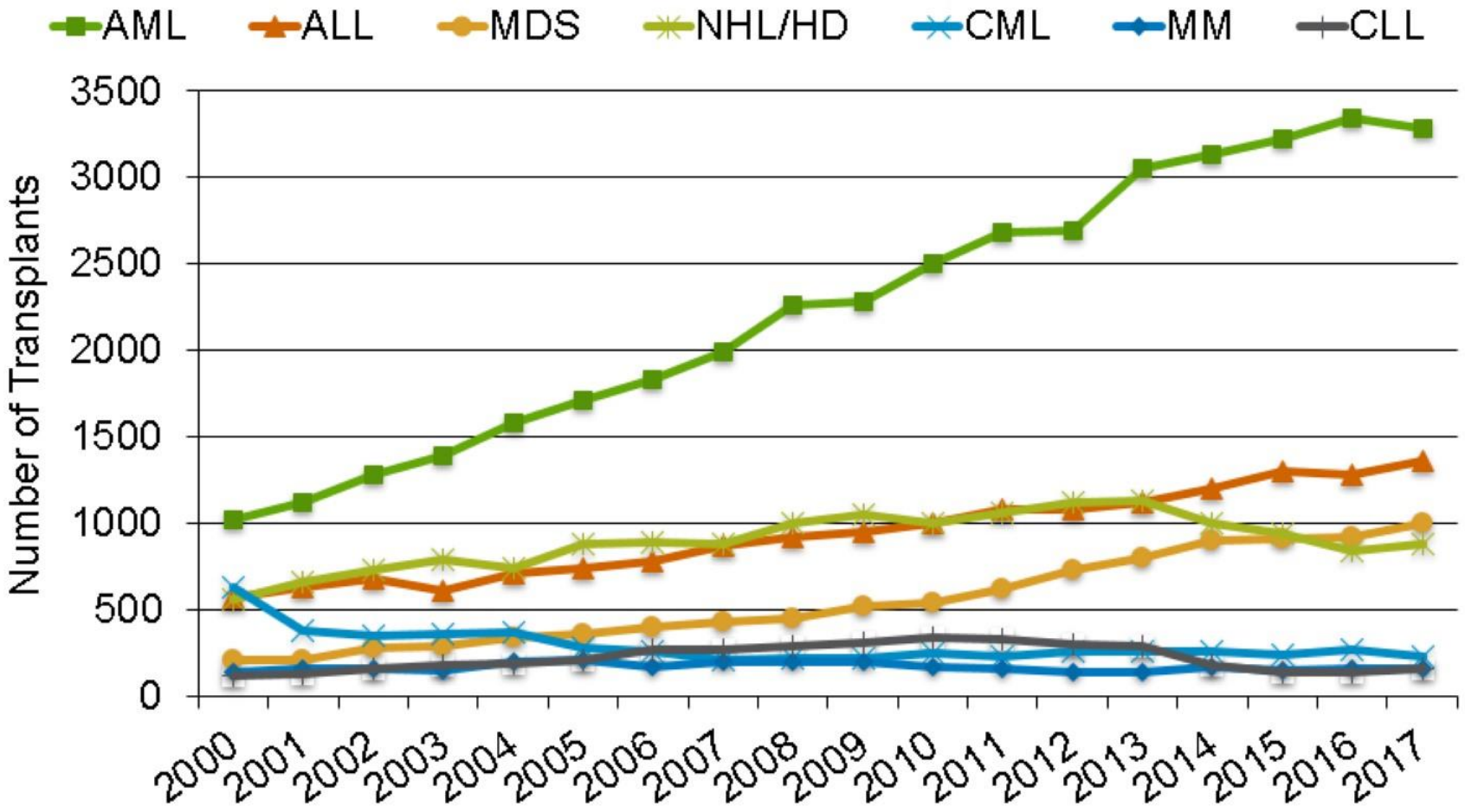
^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Selected Disease Trends for Allogeneic HCT in the US



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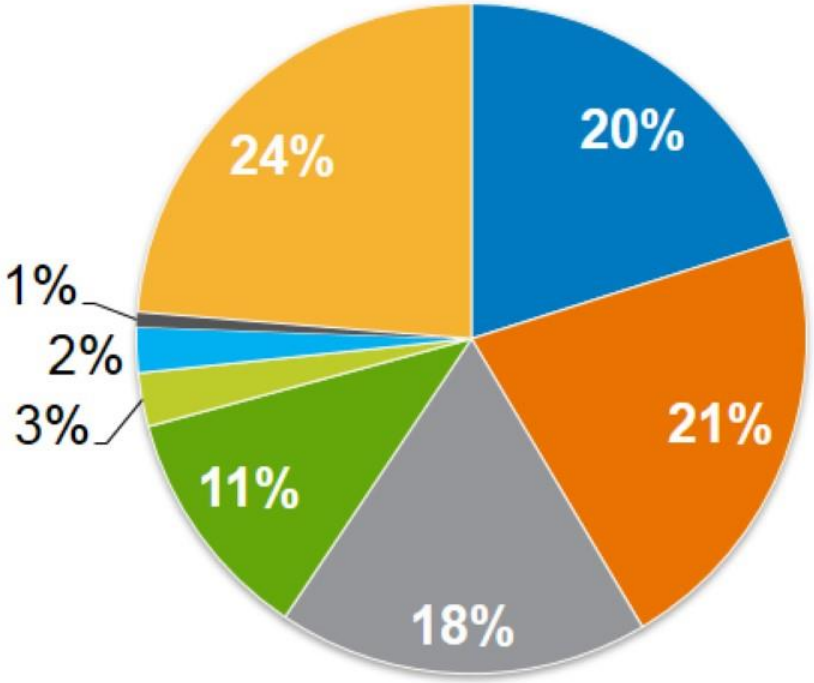
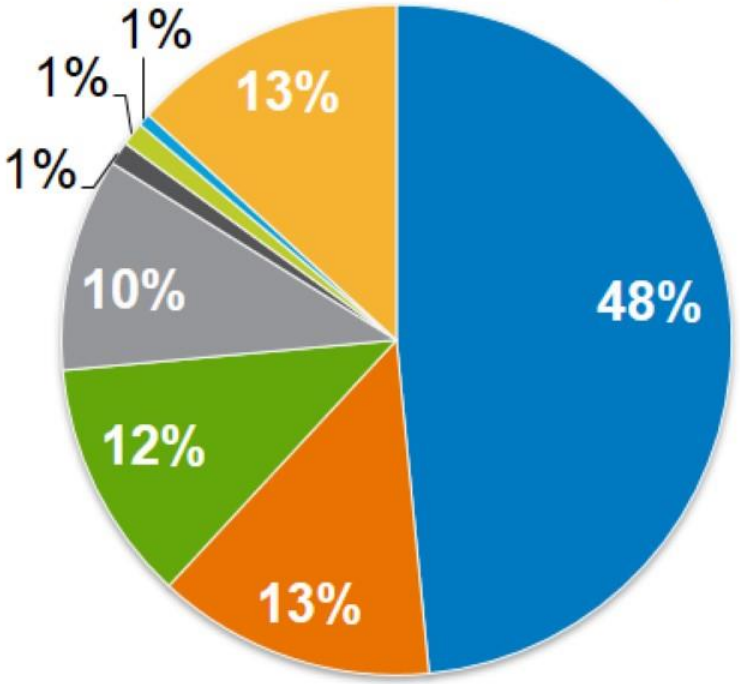
Causes of Death after Unrelated Donor HCT done in 2015-2016

Died within 100 days post-transplant



- Primary Disease
- Infection
- Organ Failure
- GVHD
- Hemorrhage
- Graft Rejection
- Second Malignancy
- Other

Died at or beyond 100 days post-transplant*



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- Other

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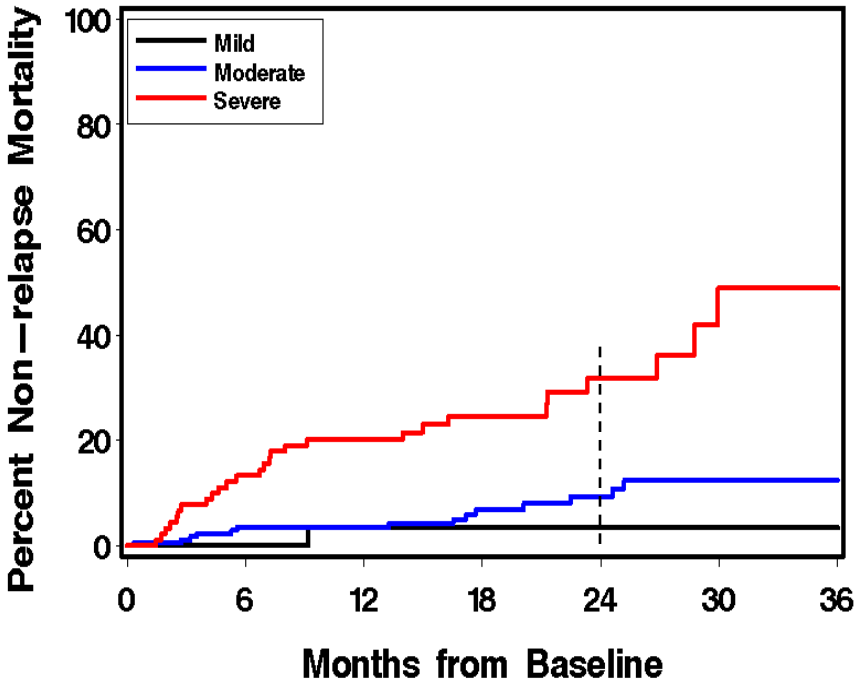
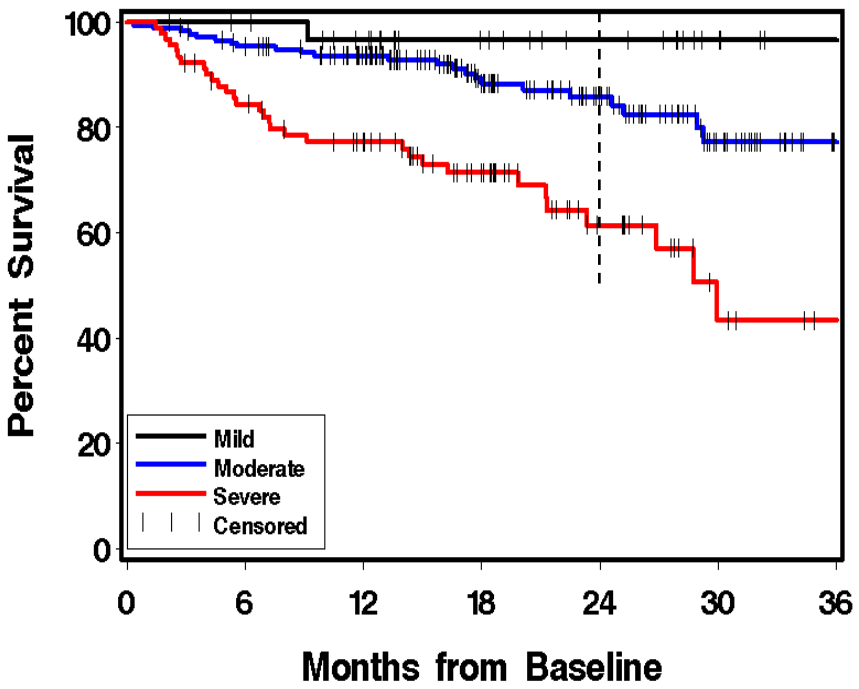
*Data reflects 3-year mortality

Chronic GVHD causes late HCT mortality



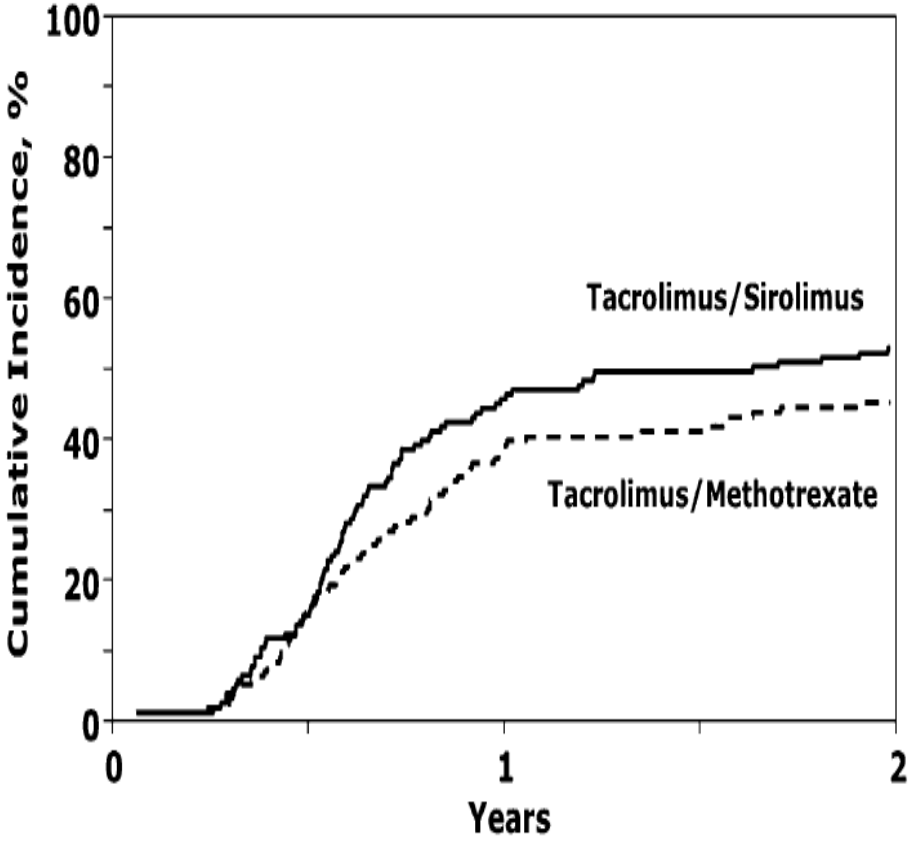


	NRM	OS
severe	**32%**	**62%**
moderate	**9%**	**86%**
mild	**3%**	**97%**

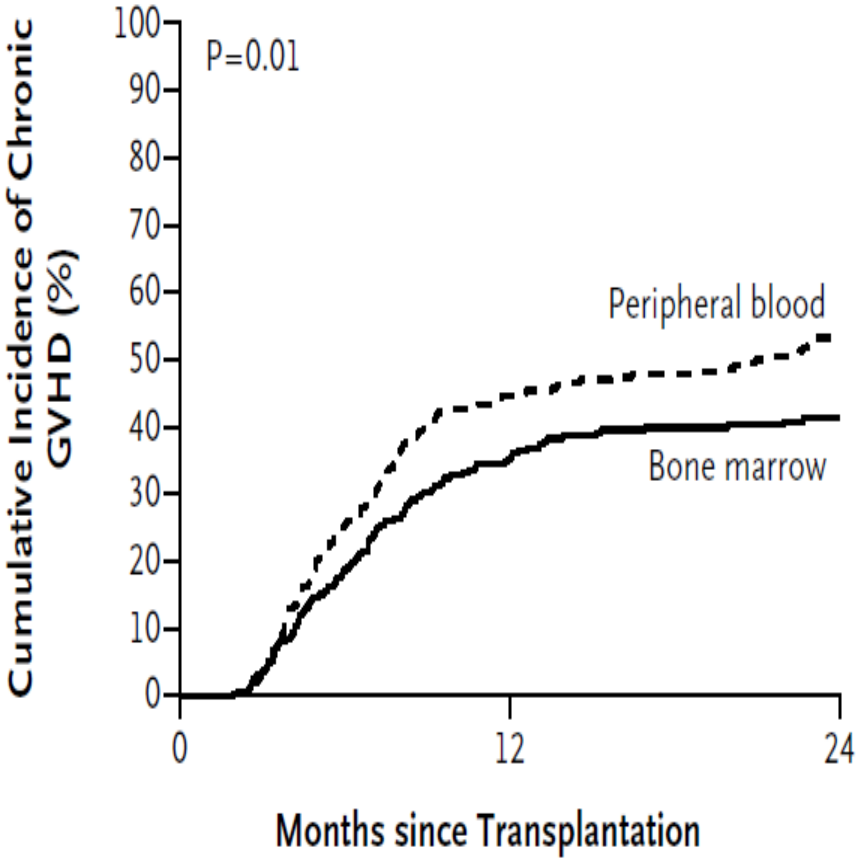
Arai. Blood 2011

Chronic GVHD remains major obstacle to HCT success

BMT CTN 0402



BMT CTN 0201



Cutler, Blood 2014
Anasetti, NEJM 2012

OPTIMIZING SUCCESS AFTER TRANSPLANT

- **Understanding the problem at hand**
  - Long term transplant specific issue
  - Impacts many transplanted patients
  - Major cause of death after transplant

- **Identification and grading of chronic GVHD**

Chronic GVHD Diagnosis

- Major proposed changes in diagnosis, classification, and severity grading following 2005 **NIH** Consensus Conference
- Distinction of acute and chronic
- Definitions of classic vs. overlap chronic
- Individual organ severity grading, summarized in global composite score of mild, moderate, severe

Table 2. Categories of acute and chronic graft-versus-host disease (GVHD). Reprinted from Filipovich et al.[7]

Category	Time of symptoms after HCT or DLI	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute	≤ 100 days	Yes	No
Persistent, recurrent or late-onset acute	> 100 days	Yes	No
Chronic GVHD			
Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Filipovich. BBMT, 2005.

Mild	• 1 or 2 organs or sites (except lung) with score 1
Moderate	• 3 or more organs with score 1 • At least 1 organ or site with score 2 • Lung score of 1
Severe	• At least 1 organ or site with score 3 • Lung score 2

Diagnostic Manifestations

SKIN
- Poikiloderma
- Lichen-planus
- Sclerosis
- Morphea
- Lichen sclerosis

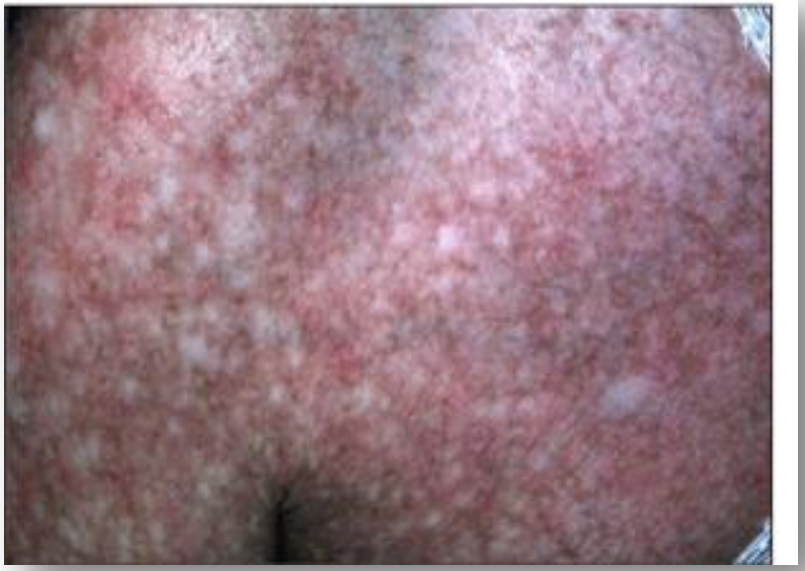
MOUTH/EYES
- Lichen-planus
- Dry eyes

GI
- Esophageal web, stricture
- Liver abnormalities

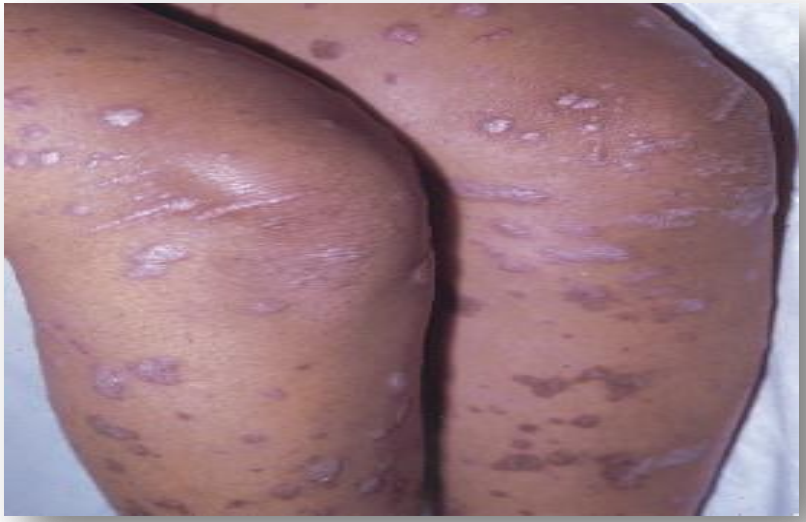
JOINTS
- Fasciitis
- Contractures or joint stiffness

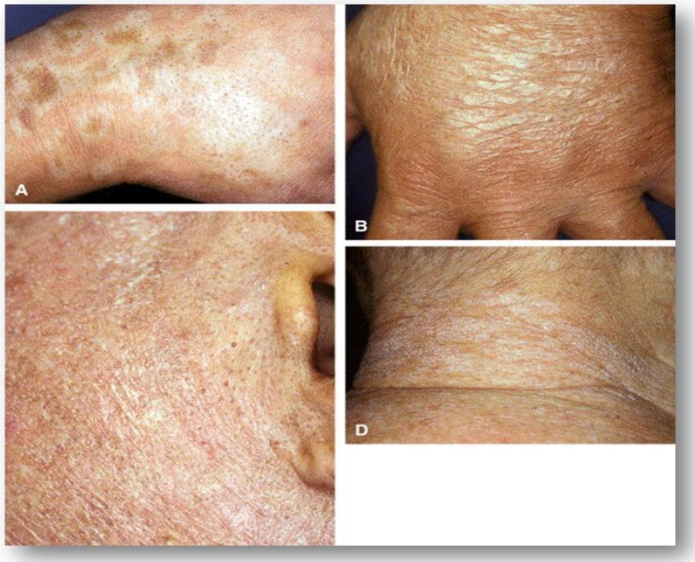
LUNG
- Bronchiolitis obliterans

GENITAL
- Lichen planus
- Lichen sclerosis
- Vaginal scarring
- (male – phimosis, or urethral/meatus stenosis)



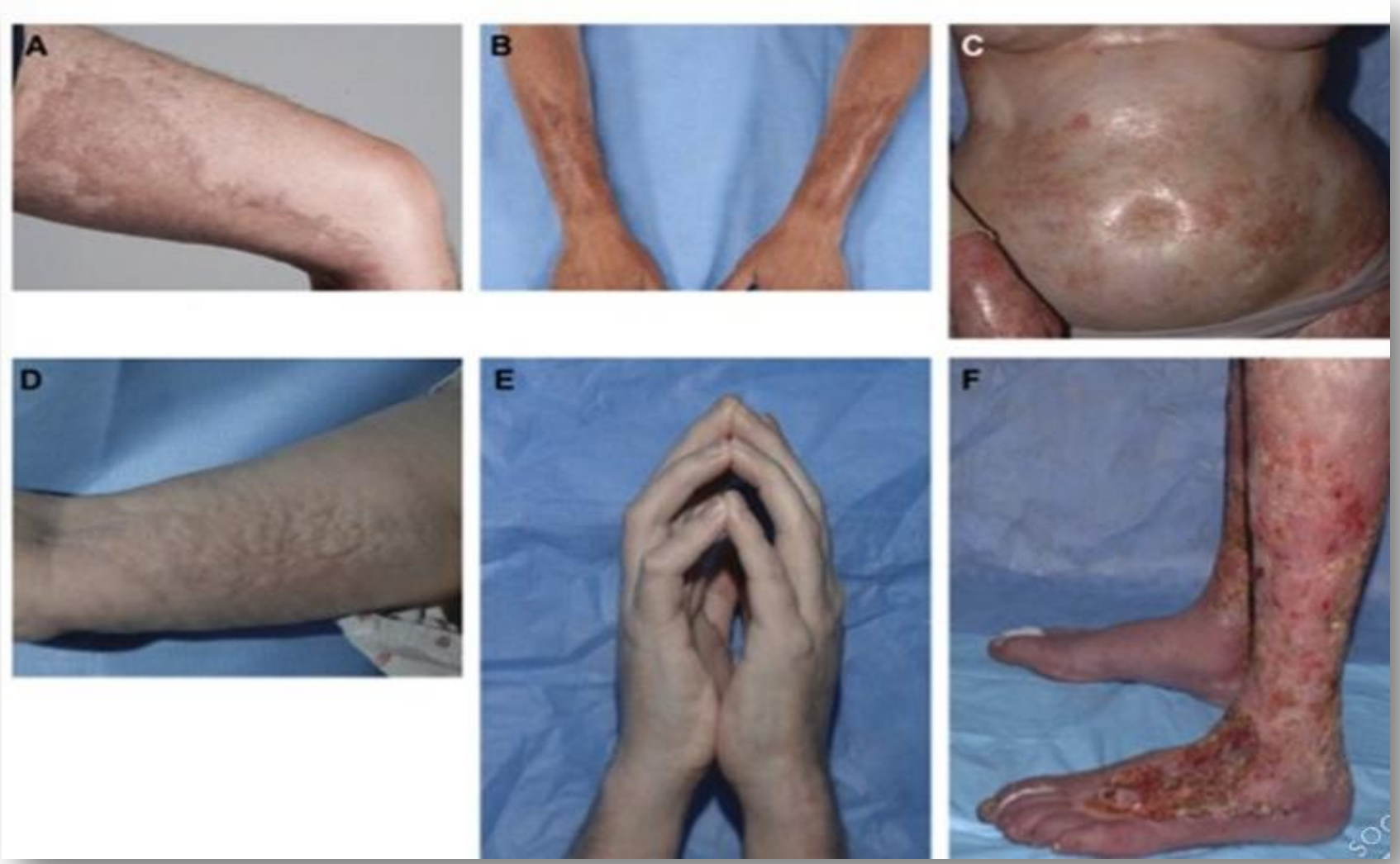
Poikiloderma: Atrophy and pigmentary changes





Lichen sclerosis: discrete to coalescent gray to white moveable papules or plaques, with shiny appearance and leathery
consistency

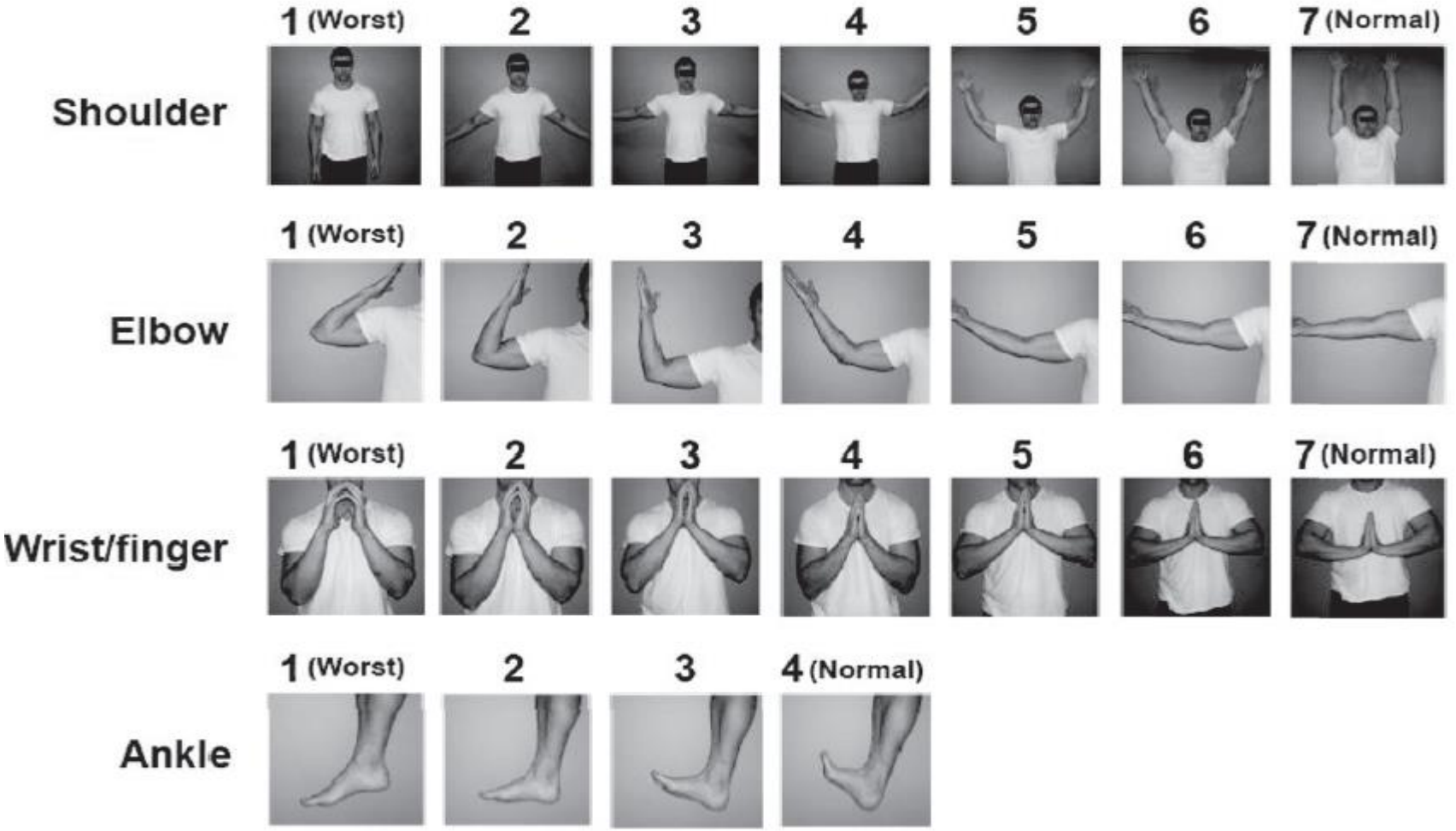
Lichen planus: Erythematous/violaceous flat-topped papules or plaques with or without surface reticulation or silvery/shiny appearance
on direct light



Cutaneous sclerosis: thickened or tight skin, ranges from superficial sclerosis (thickened skin) to deep sclerosis (hidebound) -> at most severe, limited mobility, Ulceration, and poor wound healing

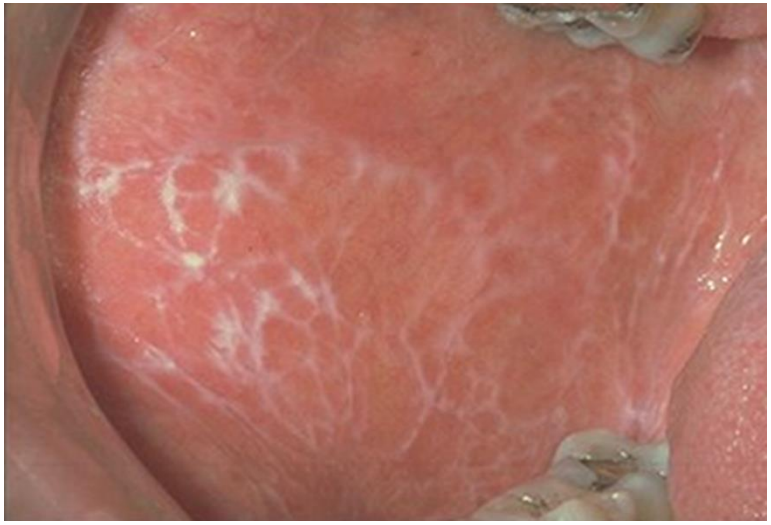
Morphea: localized, patchy area of moveable skin with leathery-like consistency, often with dyspigmentation

P-ROM

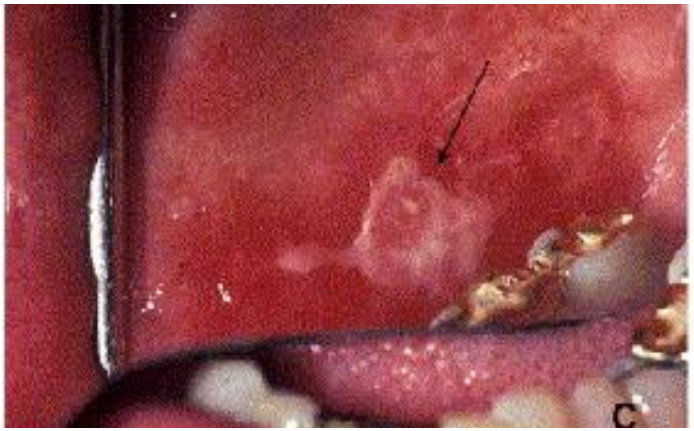

Shoulder
1 (Worst)
2
3
4
5
6
7 (Normal)
Elbow
1 (Worst)
2
3
4
5
6
7 (Normal)
Wrist/finger
1 (Worst)
2
3
4
5
6
7 (Normal)
Ankle
1 (Worst)
2
3
4 (Normal)

NIH Mouth Score

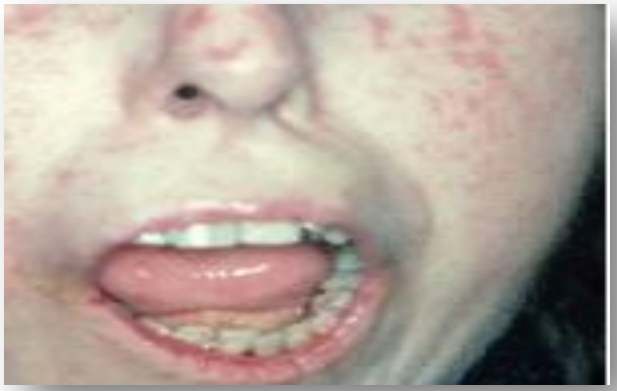
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				



Lichen planus-like changes: white lines and lacy-appearing lesions on the buccal mucosa, tongue, palate, or lips



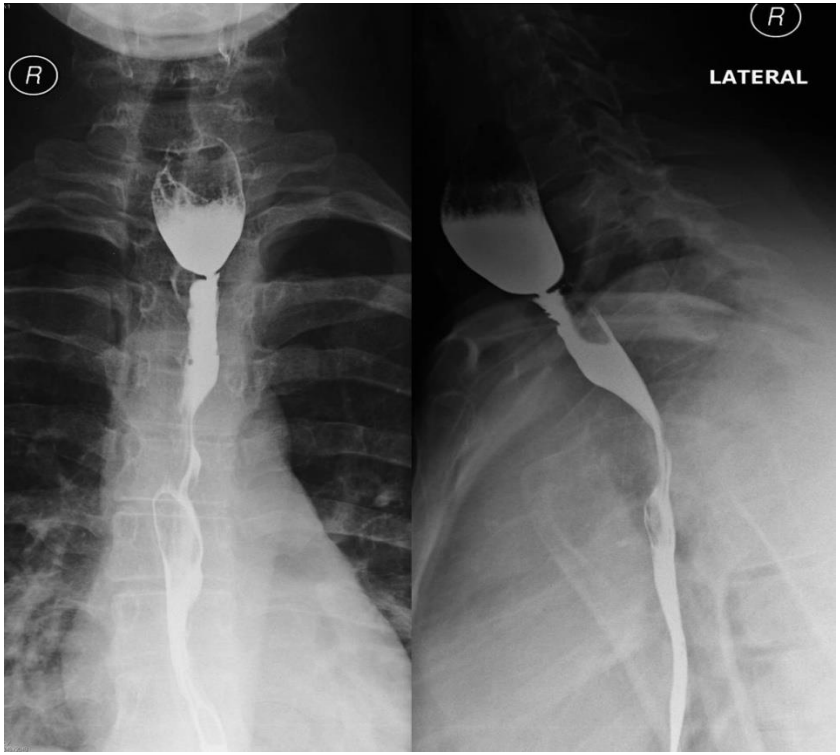
Hyperkeratotic plaques: leukoplakia

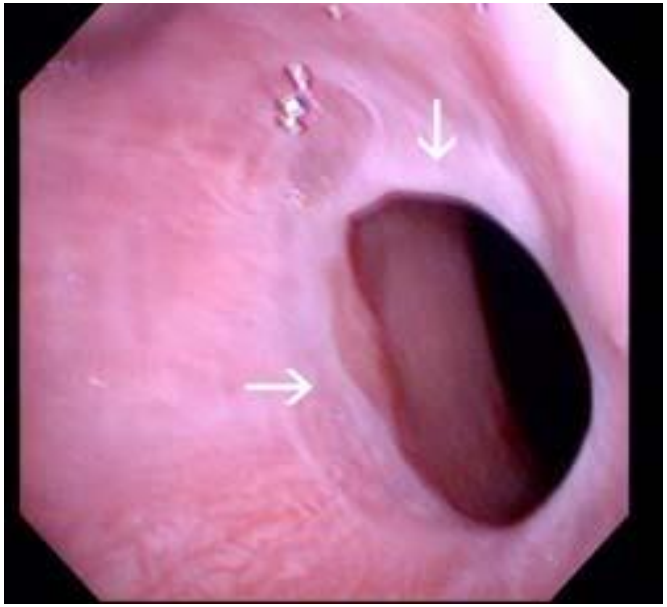


Sclerosis: decreased oral range of motion

NIH GI tract score

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
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):* _____				



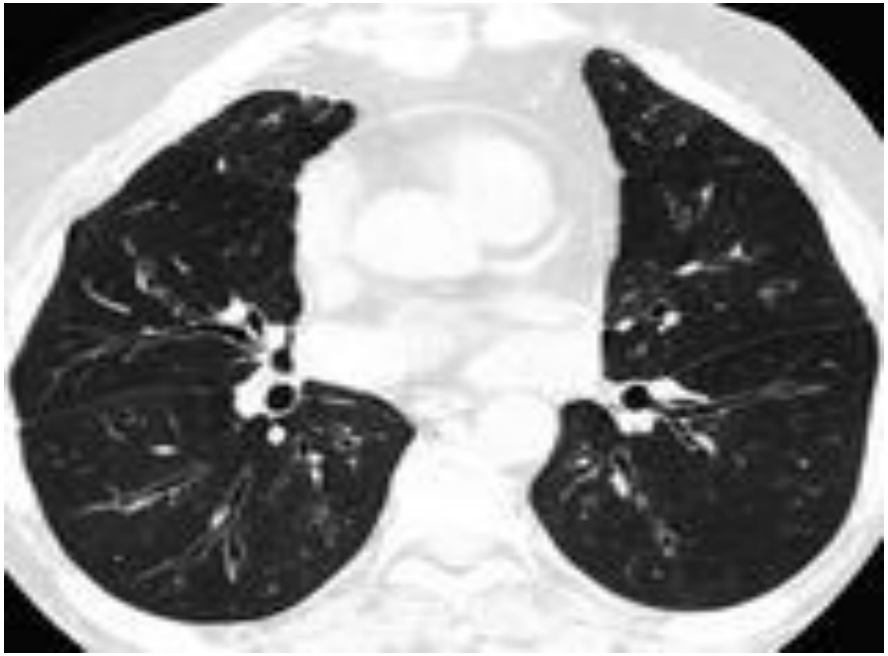


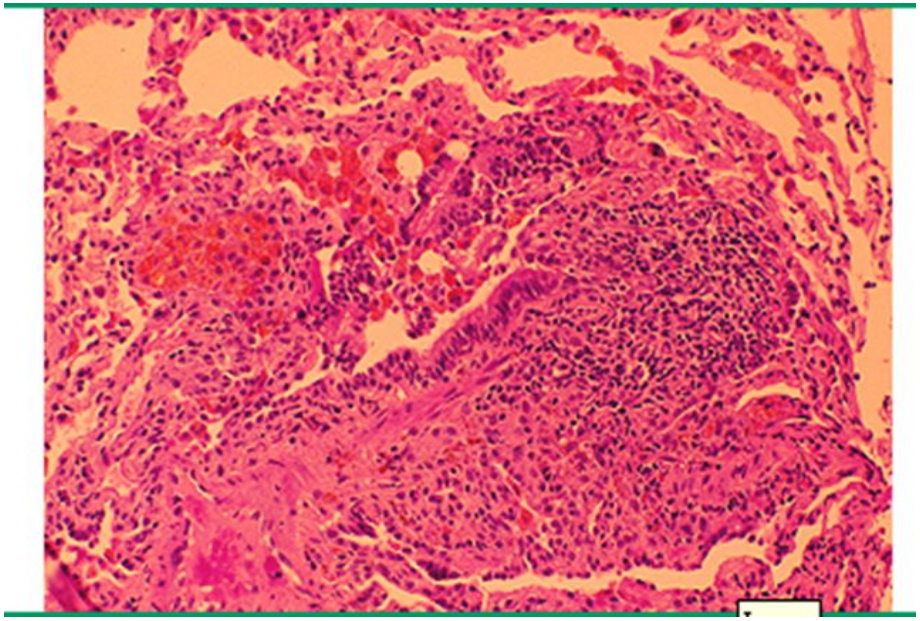
Esophageal web: Barium swallow and endoscopic visualization demonstrate esophageal narrowing due to web

NIH Liver score

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
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):*				

Bronchiolitis Obliterans Syndrome (BOS)





OPTIMIZING SUCCESS AFTER TRANSPLANT

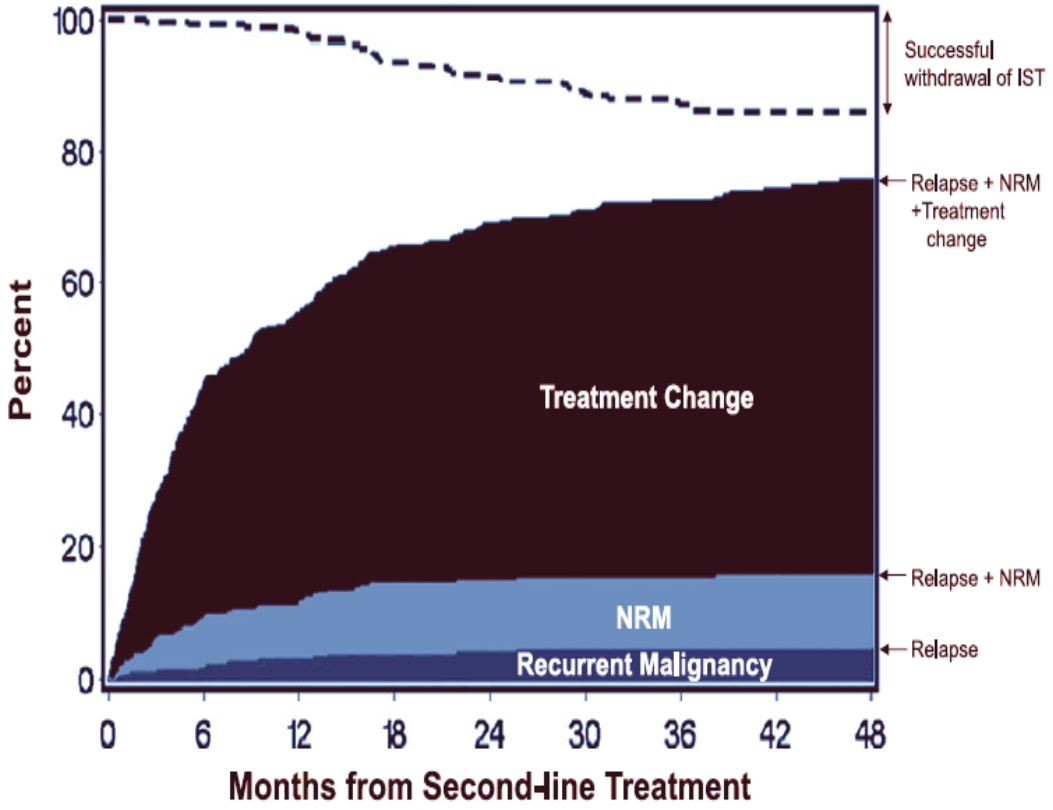
- Understanding the problem at hand

- **Identification and grading of chronic GVHD**
  - Can occur any time but usually 100 days after HCT
  - Any organ can get impacted: skin most common
  - Significant impact on morbidity

- **Therapy for chronic GVHD**

Chronic GVHD: Secondary treatment

- Second-line therapy
  - Many IS agents used
  - Frequent failure, multiple lines of therapy
- Many novel agents being evaluated
- Recent FDA approved treatment option available

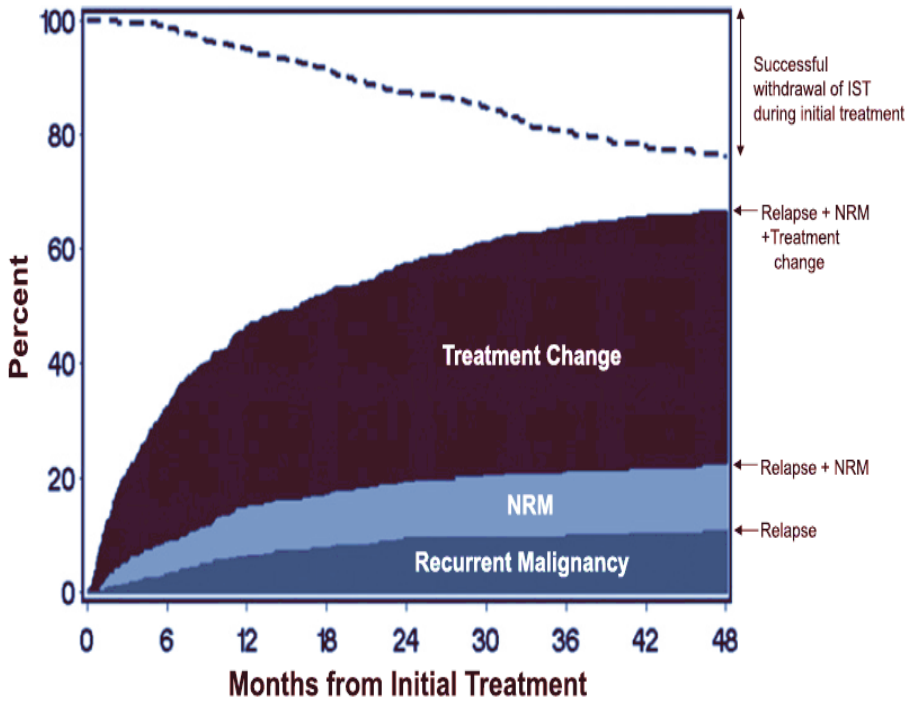


Relapse	3%	4%	4%	5%	5%	5%	5%	5%
NRM	7%	9%	11%	11%	11%	11%	11%	11%
Treatment change	34%	43%	50%	53%	55%	57%	58%	59%
FFS	56%	45%	35%	31%	29%	28%	26%	25%
Withdrawal of IST	1%	2%	6%	8%	11%	13%	14%	15%

Inamoto. Blood 2013

Chronic GVHD: Primary treatment

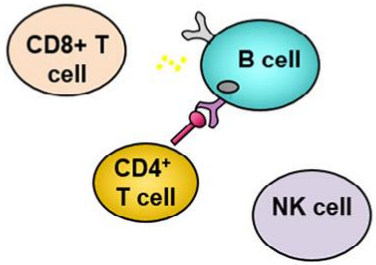
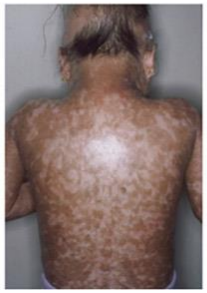
- Standard first-line treatment
  - 1mg/kg/day prednisone
  - CNI – spare steroid exposure
- Expected outcome
  - ORR 6-9 months ~ 60%
  - CR 6-9 months ~ 30%



Relapse	4%	7%	8%	10%	10%	11%	11%	11%
NRM	6%	9%	9%	10%	11%	11%	11%	12%
Treatment change	23%	30%	34%	37%	40%	42%	43%	44%
FFS	68%	54%	48%	43%	39%	36%	35%	34%
Withdrawal of IST	1%	5%	9%	13%	15%	20%	22%	23%

Sullivan. Blood 1988, Arora. BBMT 2001, Martin. Blood 2009, Gilman. BBMT 2012, Inamoto. Blood 2014

Novel agents for chronic GVHD

Phase I Acute inflammation & Tissue injury	Phase 2 Chronic inflammation & dysregulated immunity	Phase 3 Aberrant tissue repair & fibrosis
Innate immunity	Adaptive immunity	Innate & adaptive
		

• Cytokines
• TLR agonists
• Neutrophils
• Platelets
• Vascular inflammation
	• Thymic Injury and dysfunction
	• T cells
	• B cells
	• NK cells
	• Antigen presenting cells
	• Regulatory Cells
	  • Treg, Breg
	  • IL-10 producing regulatory T cells (Tr1)
		• TGFβ
		• PDGFα
		• TNFα
		• IL-17
		• Macrophages
		• Fibroblasts

Cooke, BBMT 2017

Novel agents for chronic GVHD

Drug	*Mechanism*	*Target*
Baricitinib	JAK1/2 inhibitor	T-cell signaling
Carfilzomib	Proteasome inhibitor	T-cell signaling
Ixazomib	Proteasome inhibitor	T-cell signaling
KD025	ROCK2 inhibitor	T-cell signaling
Abatacept	CTLA4-Ig fusion protein	T-cell costimulatory pathway
Ponesimod	S1P1 receptor modulator	T-cell homing
Brentuximab	CD30 antibody-drug conjugate	T-cell responses
Ibrutinib	BTK/ITK inhibitor	B cells
Ofatumumab	Anti-CD20 antibody	B cells
Fostamatinib	Syk inhibitor	B cells
Entospletinib	Syk inhibitor	B cells
Dose escalated IL-2	Induction of T-regs	T-regs
IL-2+T-regs	Induction of T-regs	T-regs and Cellular therapies
Autologous MSCs	Suppressive population	Cellular therapies
Dendritic cells	Suppressive population	Cellular therapies
AZD9668	Neutrophil elastase inhibitor	Non-lymphocyte target
Vismodegib	Hedgehog inhibitor	Non-lymphocyte target
LDE225	Hedgehog inhibitor	Non-lymphocyte target
Pomalidomide	Multiple	Non-lymphocyte target

Im, Leukemia 2017

IBRUTINIB FOR CHRONIC GVHD

- **Multiple targets in GVHD inducing pathways**

✓ Inhibition of Bruton tyrosine kinase in B cells

✓ Interleukein-2 inducible T cells kinase in T cells

- **Multicenter open label study, N=42**
- **Steroid dependent or refractory cGVHD**

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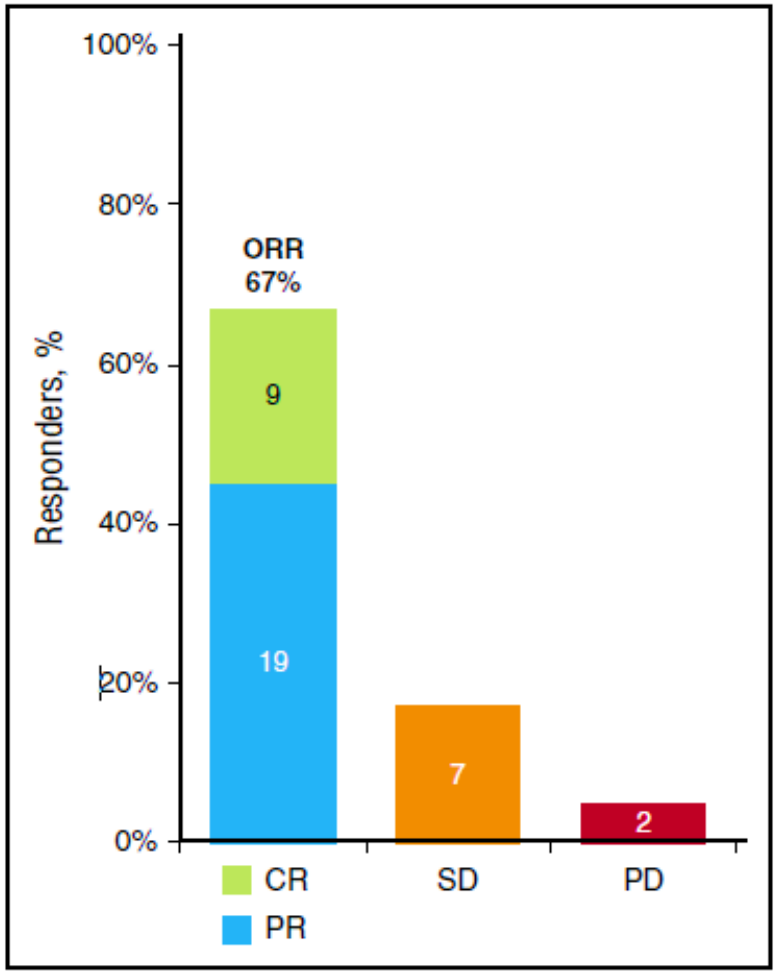
Durable Response with Ibrutinib



	No. of responders	Sustained response rate n (%)
Sustained response of ≥20 wk	28	20 (71)

Organ	No. of responders with organ involvement at baseline	Best ORR, n (%)
Skin	24	21 (88)
Mouth	24	21 (88)
Gastrointestinal	11	10 (91)

Organs showing response	No. of patients with ≥2 involved organs at baseline among responders	Best ORR, n (%)
≥2 organs	25	20 (80)

Adverse event (N = 42)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	5 (12)	14 (33)	5 (12)	0	0
Diarrhea	7 (17)	4 (10)	4 (10)	0	0
Muscle spasms	8 (19)	3 (7)	1 (2)	0	0
Nausea	8 (19)	3 (7)	0	0	0
Bruising	6 (14)	4 (10)	0	0	0

Miklos et al, Blood 2017

Scenario 1

- **39 Y.O. Caucasian Male**
- Disease: AML t (8,21) (q22, q22), relapsed
- DOT: 2015
- Type of transplant: allogeneic matched unrelated
- Donor 43 y.o. M, ABO compatible
- Match grade 10/12 (DPB1 permissive)
- Conditioning: Fludarabine + Busulfan 5300.
- Stem cell source: Peripheral blood.
- GVHD prophylaxis: *Tacrolimus/Sirolimus*

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Post Transplant Complication

- During a routine 2 month follow up patient was found to have approx. 45% maculopapular rash (Gr2 skin) with Gr 2 LFT elevation.
  - Treatment plan was to optimize Tacrolimus/Sirolimus levels
  - Started Prednisone 1mg/kg (~100mg)
    - Topical betamethasone cream

Post Transplant Complication

- **02/20/2016:** Skin GVHD resolved and started steroid taper with weekly visits.
- Recurrence of liver transaminases 2x ULN at prednisone taper dose of 50mg.
  - Moderate GVHD score: Prednisone dose increased to 80mg

- **04/02/2016:** Scleroderma to 25% of BSA Extracorpeal photopheresis (ECP) started 2 times a week.
  - Plan to taper steroid as tolerated every 3 weeks

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Post Transplant Complication

- **01/2017**: Patient remained on GVHD therapy for scleroderma and Grade 2 abnormal liver transaminases. He began to experience irritability, AMS, and probable seizures was referred to Neuro-Oncology.
  - *MRI brain w/wo later revealed enhancement & progression of white matter lesions*
  - Started on levetiracetam 1gm BID and IVIG X 2 days
  - Severe GVHD score: Initiated Ibrutinib

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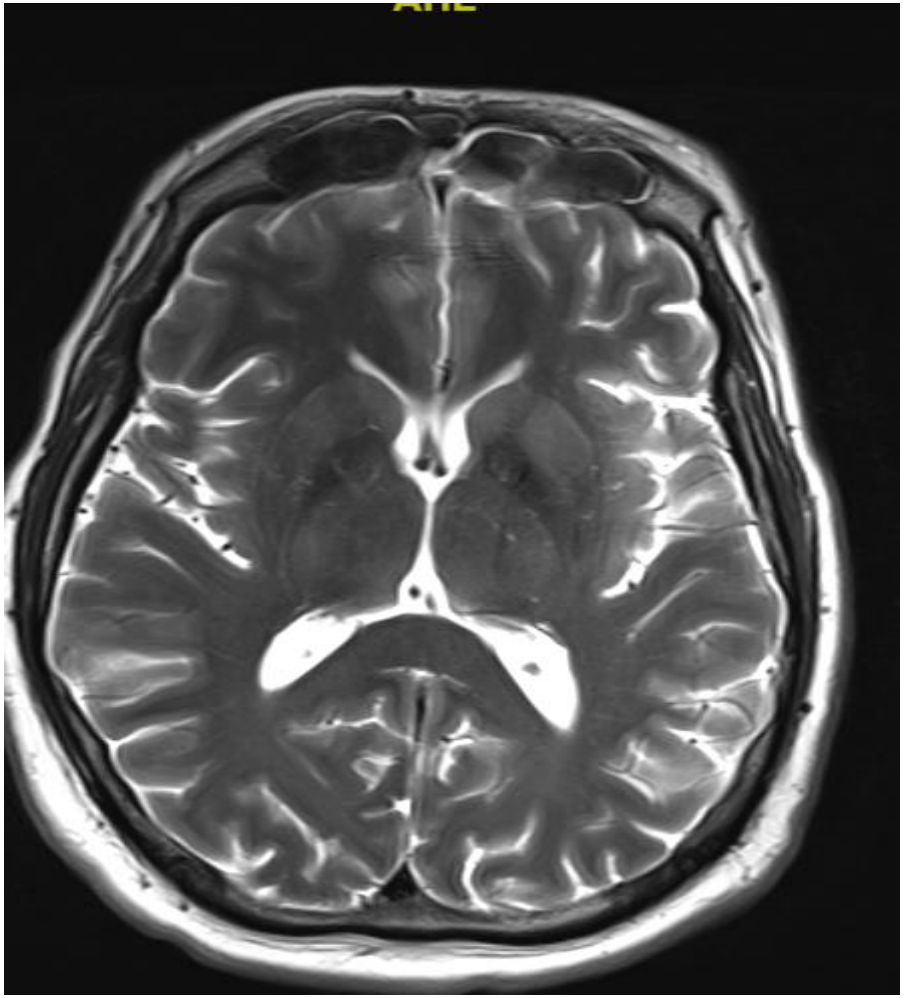
Post Transplant Complication



-Brain (biopsy proven) tissue w/ encephalitis, perivascular inflammation and microglial activation and gliosis

-Predominately CD3+ T-cells, mixture of CD4/CD8 cells

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Long Term Follow-up

- Resolution of brain GVHD as evidenced by MRI. Tapered off levetiracetam.
- GVHD: PR. Now off ECP. Remains on low dose Tacrolimus daily, Sirolimus on alternating days, prednisone 10 mg. Reduced ibrutinib dose due to muscle cramping.
- He now follows up twice a year, attends baseball games with spouse.

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CONCLUSION

- **Understanding the problem at hand**
  - Obstacle to otherwise curative potential of HCT
  - GVHD poses major risks: morbidity including disability, impaired QOL, and death

- **Therapy for chronic GVHD**
  - Steroids remain first line therapy
  - Ibrutinib is the first FDA approved therapy for GVHD

- **CONTACT A FRIEND: asmita.mishra@moffitt.org**

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Acknowledgments

- The Patients
- Moffitt BMT-CI Department

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