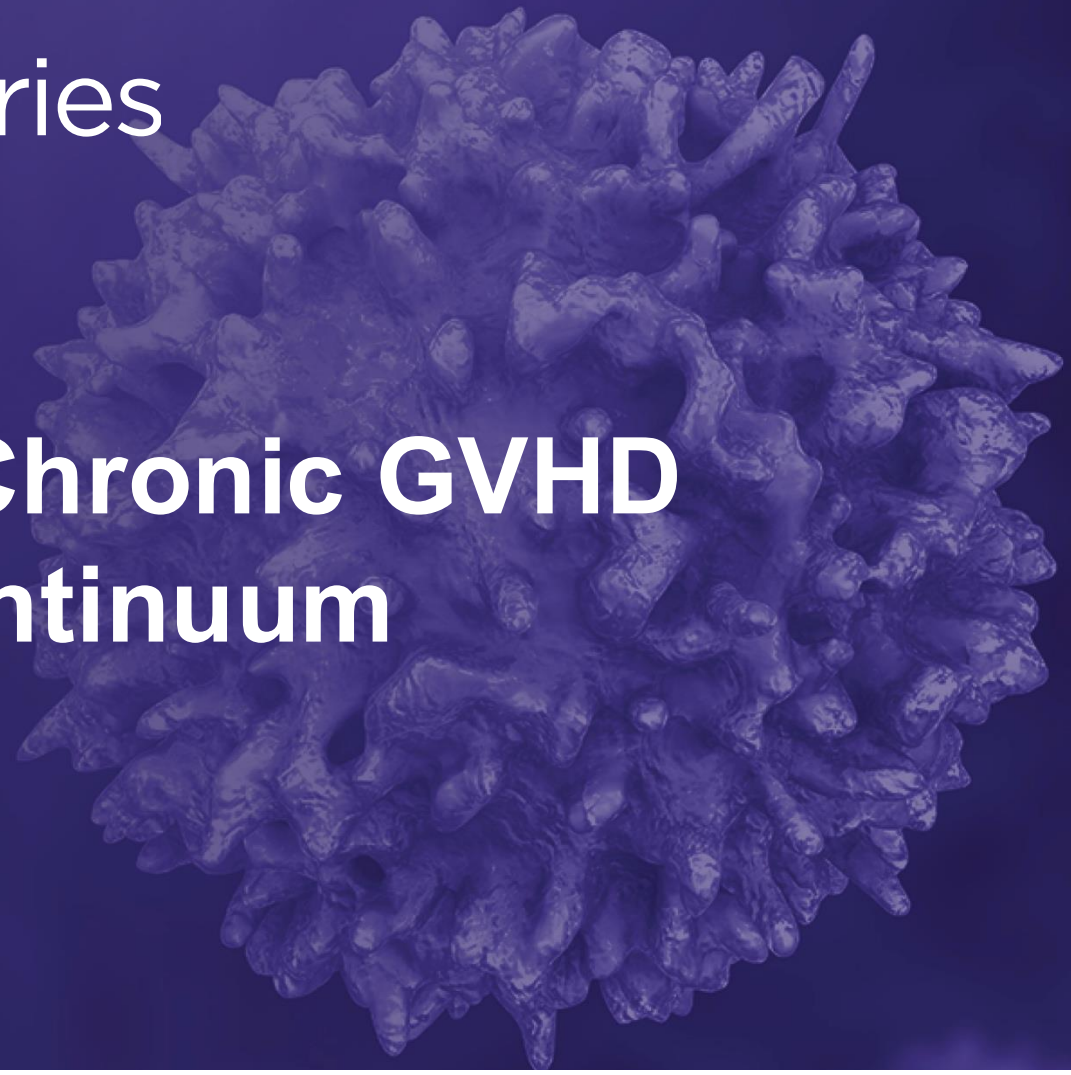
JADPRO Clinical Case Series

Managing Patients With Chronic GVHD Across the Treatment Continuum



SUPPORTED BY Incyte

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Program Agenda

- Review the pathophysiology of cGVHD
- Outline the importance of sustained GVHD monitoring post allogeneic stem cell transplant
- Discuss treatments and sequencing for cGVHD

GVHD Basics

Risk Factors/Impacts[1]

- HLA matching
- Stem cell source (peripheral blood > bone marrow > cord blood)
- Donor pregnancy history
- Disparities
  - Sex
  - Blood type
  - Age
  - CMV
- History of aGVHD
- MAB vs. RIC transplant
- Post-transplant cyclophosphamide

Statistics[1]

- Acute GVHD (aGVHD) incidence: 35-50% of all allo-HSCT recipients
- Chronic GVHD (cGVHD) incidence: 33-50% of all allo-HSCT recipients
- An analysis of claims data showed ~15,000 patients are currently experiencing active cGVHD in the United States[2]

aGVHD; acute graft vs. host disease; allo-HSCT, allogeneic hematopoietic stem cell transplant; CMV, cytomegalovirus; HLA, human leukocyte antigen; MAB, myeloablative; RIC, reduced intensity

1. Akashoshi Y, et al. *Blood Adv.* 2023;7(16):4479-4491; 2. Vadakkel G, et al. *Bone Marrow Transplant.* 2024;59(10):1360-1368.

Trajectory of GVHD

Acute GVHD

- Classic aGVHD presents within the first 100 days of transplant
- Presenting symptoms of the skin, liver, or GI tract and differ from cGVHD
- Persistent, recurrent, or late-onset aGVHD can manifest ≥100 days after transplantation

Chronic GVHD

- Classic cGVHD presents after day 100 post-transplant
- Presentation differs from aGVHD and resembles autoimmune disorders with multi-organ system involvement
- Overlap syndrome can present at any time post-transplant with features of both acute and chronic GVHD

1. Vandenhove B, et al. *Belgian Journal of Hematology.* 2020;11(4):159-173; 2. Valliant AAJ, et al. *StatPearls.* June 7, 2024.

Case 1: Biomarkers and Underlying Pathophysiology of cGVHD

Mr. Parker is a 66-year-old with AML

- Next-generation sequencing results:
  - t(11;19) MLLT3 translocation
  - *KMT2A* rearrangement
  - *FLT3*-ITD mutation
- Treated with anthracycline, high-dose cytarabine (7+3), midostaurin
- Achieved an MRD– remission
- Underwent haploidentical SCT (donor = his son), with myeloablative fludarabine, melphalan, TBI conditioning

AML, acute myeloid leukemia; MRD, measurable residual disease; SCT, stem cell transplant; TBI, total body irradiation.

Case 1 *continued*

- Received GVHD prophylaxis with post-transplant cyclophosphamide, tacrolimus, MMF
- Post-transplant course included:
  - Developed grade 3 mucositis
  - Gram-negative bacteremia with a mucosal barrier infection
- Engrafted by day 19, discharged to follow-up in BMT clinic

BMT, Blood and Marrow Transplant; MMF, mycophenolate mofetil.

1. Ansuinelli M, et.al. *Blood.* 2024;144(Supplement 1):1041; 2. Abedin S, et al. *Blood Adv.* 2025;9(14):3495–3501.

Case 1: aGVHD History

- Day +65
  - Maculopapular rash on 27% BSA
  - Mild nausea
  - Biomarker elevation: ST2 (9794 ng/dL) and REG3a (8848 ng/dL)
  - Skin biopsy showed apoptotic bodies, confirming aGVHD*
  - Initiated prednisone 1 mg/kg
- Day +100
  - Tapered off steroids, GVHD CR
  - AML in remission
  - Initiated azacitidine and midostaurin

CR, complete response; BSA, body surface area.

*See MAGIC criteria for acute GVHD staging/grading via Acute & Chronic GVHD Guidance. BMT CTN. March 13, 2023.

Case 1: cGVHD History

- Day +225
  - Increased blasts in peripheral blood, bone marrow biopsy showed relapse
  - Planned DLI
- Day +270
  - Taste changes, tongue sensitivity, lichen planus
    - Treated with dexamethasone mouth rinses
  - Noted difficulty with dorsiflexion; skin tightness around ankles
    - Initiated prednisone 1 mg/kg and physical therapy

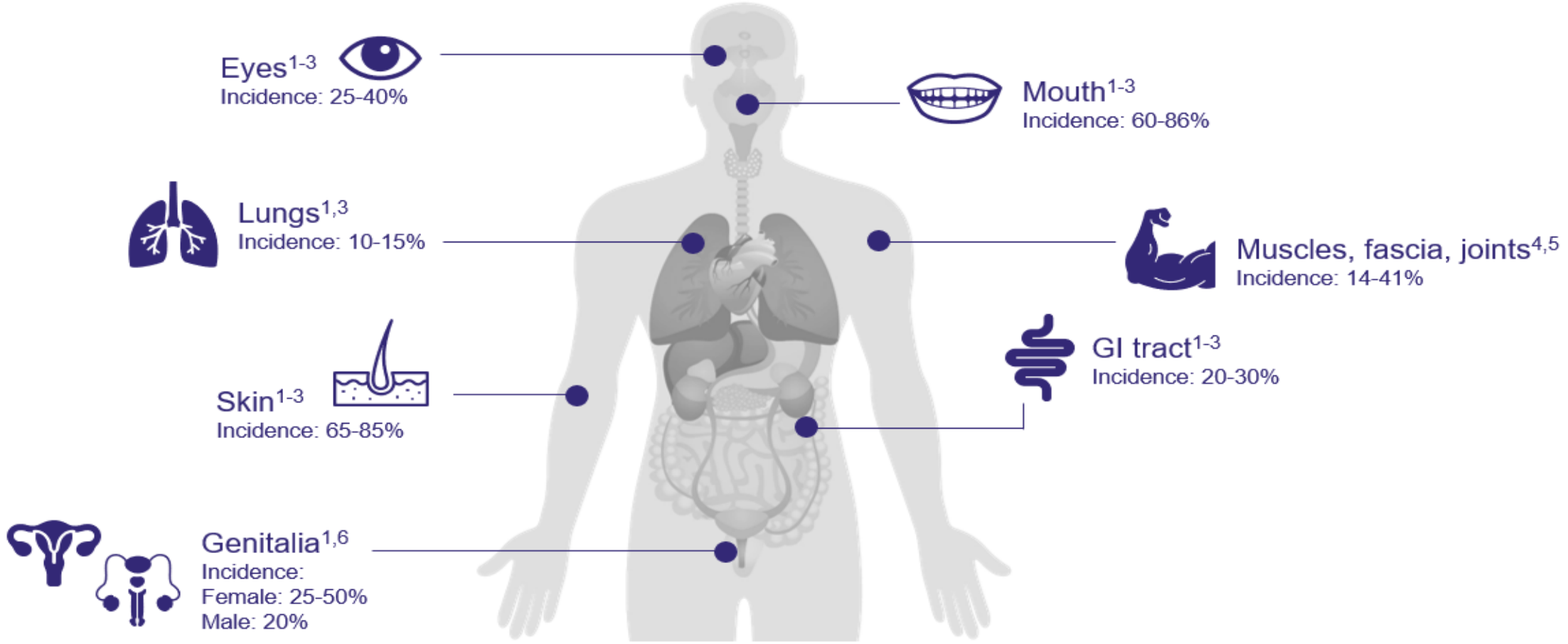
Staging/Grading of cGVHD

	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):				

DLI, donor lymphocyte infusion.

Jagasia MH, et al. 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401.e1.

Clinical Presentation of cGVHD



cGVHD, chronic graft-versus-host disease; GI, gastrointestinal.

References: 1. Jagasia MH, et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401. **2.** Vigorito AC, et al. *Blood*. 2009;114(3):702-708. **3.** Lee SJ, et al. *Blood*. 2002;100(2):406-414. **4.** Vukic T, et al. *Croat Med J*. 2016;57(3):266-275. **5.** Inamoto Y, et al. *Biol Blood Marrow Transplant*. 2012;18(10):1517-1524. **6.** Hamilton BK, et al. *Bone Marrow Transplant*. 2017;52(6):803-810.

The 3 Phases of cGVHD Are Facilitated by Distinct Immune Mediators[1,2]

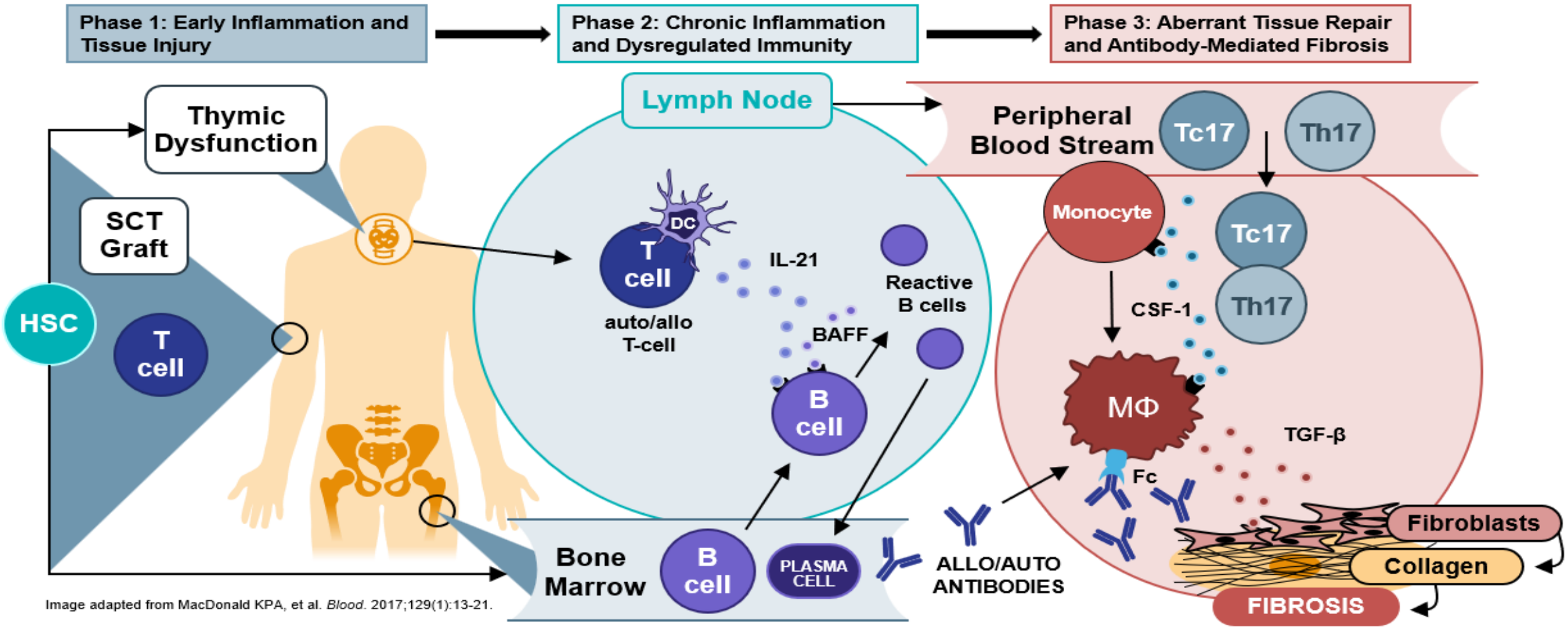


Image adapted from MacDonald KPA, et al. *Blood*. 2017;129(1):13-21.

BAFF, B-cell–activating factor; cGVHD, chronic graft-versus-host disease; CSF-1, colony-stimulating factor 1; DC, dendritic cell; GVHD, graft-versus-host disease; HSC, hematopoietic stem cell; IL, interleukin; MΦ, macrophage; SCT, stem cell transplant; Tc17, T-cytotoxic 17; TGFβ, transforming growth factor β; Th17, T-helper 17.

References: 1. Cooke KR, et al. *Biol Blood Marrow Transplant*. 2017;23(2):211-234. **2.** MacDonald KPA, et al. *Blood*. 2017;129(1):13-21.

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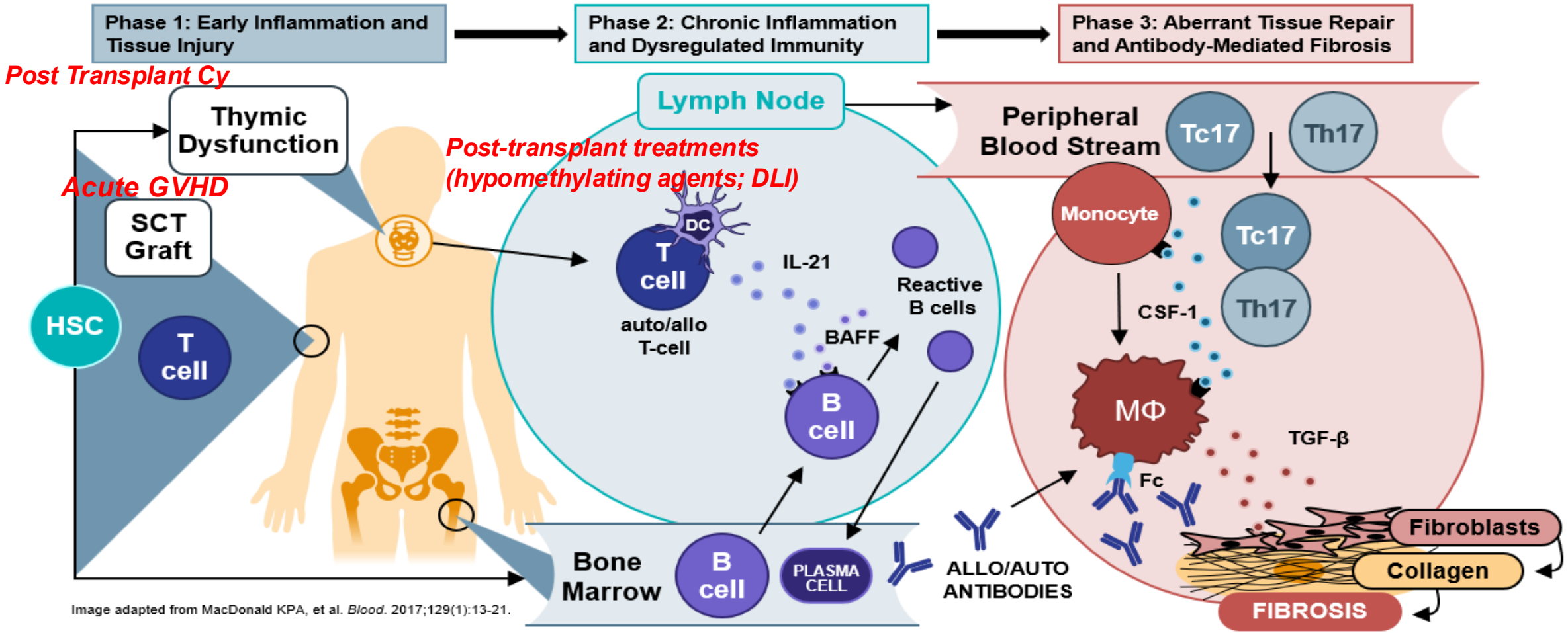

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Audience Response Question #1: GVHD Pathophysiology

How much does the biology and pathophysiology of cGVHD impact your treatment plan?

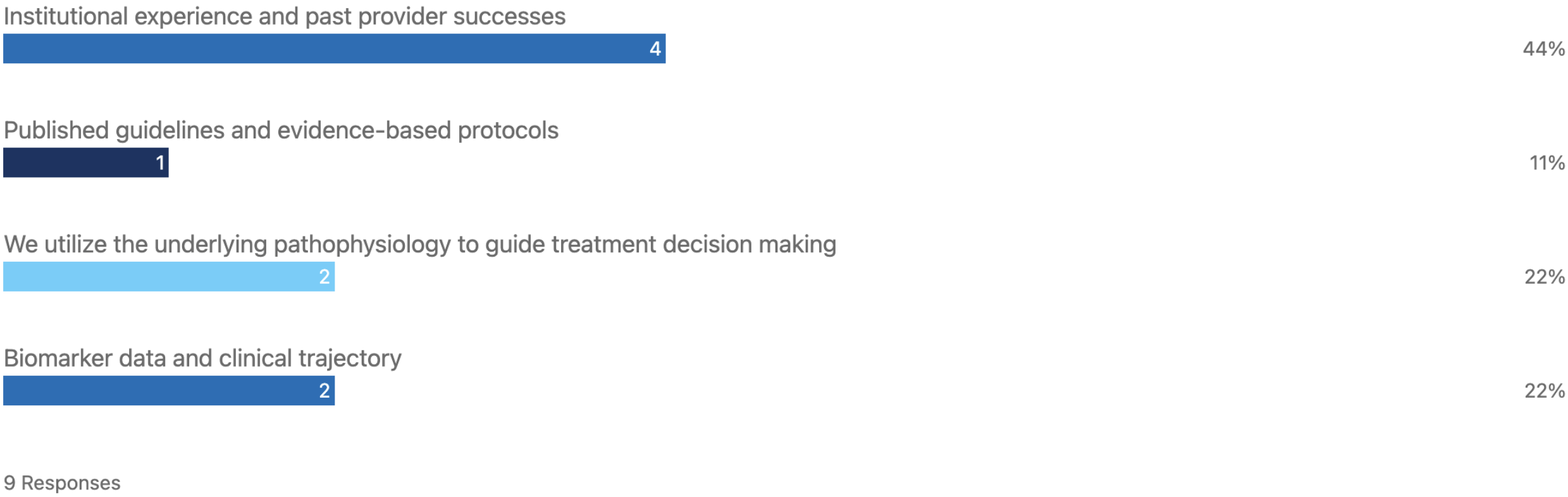
A. Not at all
B. A lot
C. Depends on the patient and testing results.
D. I had not considered pathophysiology before but might consider that more going forward.

Case 1 Poll: When determining treatment for chronic GVHD, which of the following most influences your choice of intervention? (Choose the one answer that best aligns with your practice.)

A. Institutional experience and past provider successes
B. Published guidelines and evidence-based protocols
C. We utilize the underlying pathophysiology to guide treatment decision making
D. Biomarker data and clinical trajectory

Results from Case 1 Polling

When determining treatment for chronic GVHD, which of the following most influences your choice of intervention (Choose the one answer that best aligns with your practice)?



Clinical Pearls

- Unlike acute GVHD, chronic GVHD often presents as features resembling autoimmune and fibrotic disorders, involving multiple organ sites such as the skin, eyes, lungs, joints, and genitalia.
- Recognizing its heterogeneous and progressive nature is key—early signs like dry eyes, skin changes, or joint stiffness may precede more severe manifestations.
- Understanding the immune-mediated pathophysiology helps guide individualized treatment strategies targeting inflammation, fibrosis, and immune modulation.

Case 2: Critical Role of Sustained Monitoring for Post-Transplant Chronic GVHD Symptoms

JB is a 28-year-old male with high-risk ALL

- Patient lived far (1000+ miles) from where he was diagnosed. Moved for treatment and transplant.
- Treatment
  - COG protocol
    - MRD+
  - Blinatumomab
    - Obtained MRD– remission
  - Allogeneic stem cell transplant
    - Conditioning regimen: Cy/TBI

ALL, acute lymphocytic leukemia; MRD, measurable residual disease; COG, Children's Oncology Group; Cy, cyclophosphamide; TBI, total body irradiation.

Key Considerations for This Case

AYA Population

- ~85,480 AYAs aged 15-39 expected to be diagnosed with cancer in 2025 in the US[1]
- Consider psychosocial needs of AYAs with a cancer diagnosis as they struggle with loss of independence; social isolation and a desire for normalcy
- Autonomy is affected
  - Adherence to treatments
  - Asserting their independence
  - Overwhelmed by logistics and decisions

Transitioning Care From Transplant Center

- Need for patients to get back home
- Complexities of monitoring for complications post allo-HSCT
- Referring offices may be unfamiliar with post-transplant care
- cGVHD can be difficult to diagnose and symptoms usually overlap with other benign conditions
- 2020 NIH consensus guidelines[2] recommend empowering patients to participate in their own monitoring and reporting of symptoms for improved outcomes

allo-HSCT, allogeneic hematopoietic stem cell transplant; AYA, adolescents and young adults;

1. Adolescents and Young Adults with Cancer. National Cancer Institute. 2. Kitko CL, et al. *Transplant Cell Ther.* 2021;27(7):545-557.

Case 2: aGVHD History

- Day +40: aGVHD
  - Flat confluent rash, >80% BSA (late reporting)
  - Initiated topical triamcinolone 0.5% and prednisone 1 mg/kg
  - 1-month taper off prednisone with clinical CR
- Day +89: aGVHD flare
  - Macular popular rash, 32% BSA (mother intervened earlier)
  - Re-initiated prednisone 1 mg/kg
  - 1-month taper off prednisone with clinical CR
- Day +180: Standard GVHD prophylaxis tacrolimus was stopped after institutional protocol taper schedule
  - MRD–
  - No signs of GVHD or other post-transplant complications
  - Moved back to his pretransplant residence >1000 miles from transplant center

BSA, body surface area; CR, complete remission; MRD, measurable residual disease.

Case 2: cGVHD History

- Transitions of care and other factors impacted the early recognition and diagnosis of cGVHD in this patient
- 2+ years post-transplant he presented back at the transplant center
  - Deep sclerosis in upper arms, lower legs, abdomen, back, and sides of the chest, >50% BSA
  - Diagnosed with extensive skin presentation of cGVHD
    - cGVHD skin score was a 3 due to the deep sclerotic features[1]
  - Treatment
    - Prednisone
      - Became steroid dependent
    - UVA-1 phototherapy
    - Ruxolitinib and topical treatments (being seen in a heme/derm clinic)
      - Improvement seen in upper arms, lower legs; could dorsiflex

Steroid-dependent:
Repeated symptom flares during taper of corticosteroids <0.25 mg/kg/day

1. Jagasia MH, et al. *Biol Blood Marrow Transplant.* 2015;21(3):389-401.e1.

Case 2 *continued*

- After 1 year, no additional benefit seen from current treatment
  - ECP added
    - Required moving back near transplant center
  - Stable skin disease on arms and legs; mild improvement of sclerotic features on abdomen, sides
- 14 months later, abdomen, chest, and back beginning to become hidebound, with signs of fibrotic changes
  - Discontinued ECP
  - Belumosudil
    - Was recommended to remain near transplant center for close evaluation

ECP, extracorporeal photopheresis.

Audience Response Question #2: Subsequent Therapy

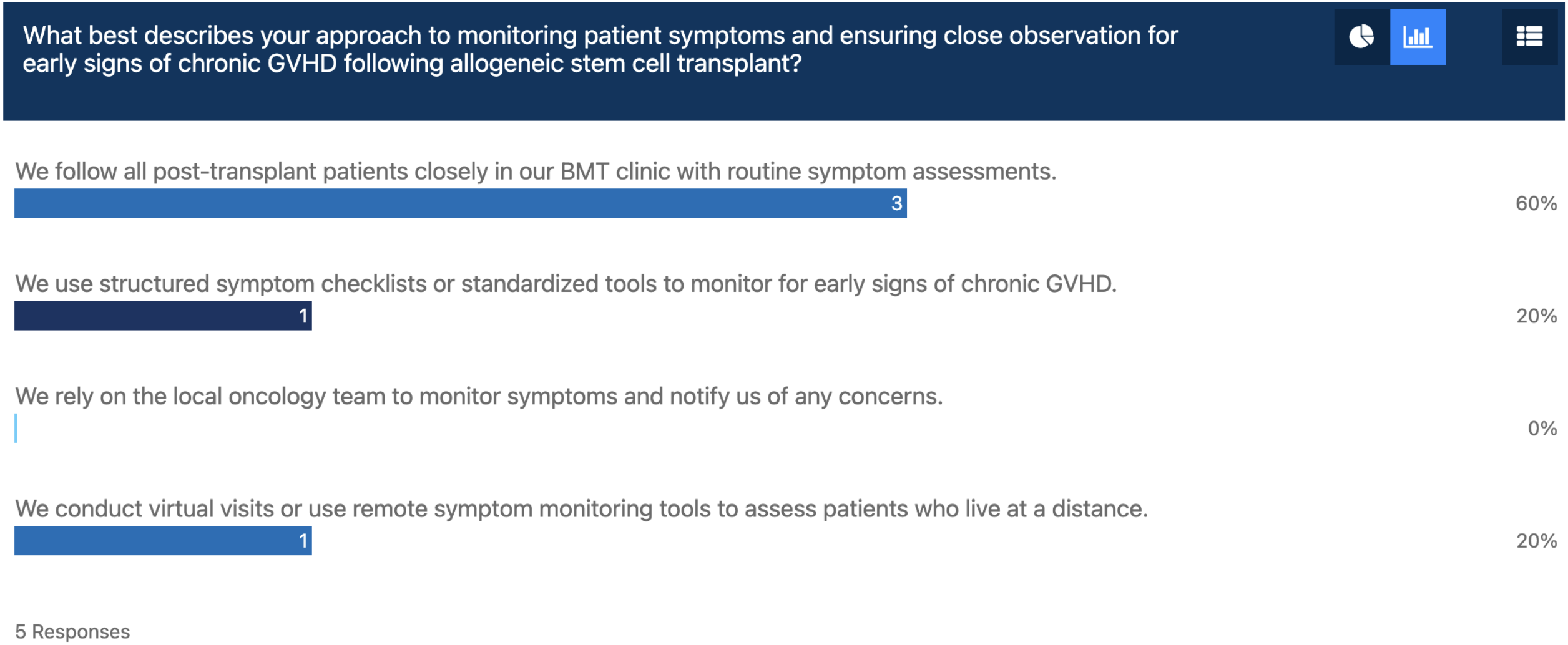
If this patient has new organ involvement or progresses on his current treatment, what would your next treatment choice be?

A. Restart ruxolitinib
B. Re-initiate steroids
C. Axatilimab
D. Sirolimus

Case 2 Poll: What best describes your approach to monitoring patient symptoms and ensuring close observation for early signs of chronic GVHD following allogeneic stem cell transplant?

A. We follow all post-transplant patients closely in our BMT clinic with routine symptom assessments.
B. We use structured symptom checklists or standardized tools to monitor for early signs of chronic GVHD.
C. We rely on the local oncology team to monitor symptoms and notify us of any concerns.
D. We conduct virtual visits or use remote symptom monitoring tools to assess patients who live at a distance.

Results from Case 2 Polling



Clinical Pearls

- Establishing an effective ongoing chronic GVHD assessment protocol at the time that patients transfer away from the transplant center is essential as timely identification and intervention can significantly improve long-term outcomes.
- Managing adolescent and young adult (AYA) patients during this transitional period post-transplant can be particularly challenging, as they often try to exert their independence and may lack full awareness of the long-term risks associated with chronic GVHD.

Audience Response Question #3: Pulmonary GVHD

If your patient has pulmonary GVHD, what treatment plan do you implement?

A. Steroids
B. Ibrutinib
C. Belumosudil
D. Ruxolitinib
E. Axatilimab

Case 3: Multifaceted Presentation of Chronic GVHD Leading to Multiple Lines of Therapy Use

MR is a 33-year-old female with MDS-EB2

- Categorized as high risk, R-IPSS score of 5
- Next-generation sequencing results
  - *WT1* mutation
  - *SAMD9* mutation
- Initial treatment
  - Decitabine/cedazuridine plus venetoclax
    - First hematologic CR

CR, complete remission; MDS-EB-2, myelodysplastic syndrome with excess blasts-2; R-IPSS, Revised International Prognostic Scoring System.

Case 3: Transplant Course

- Matched unrelated stem cell transplant
  - 25-year-old male CMV– donor
  - Blood type of both donor and recipient were O+
- Myeloablative conditioning: fludarabine, busulfan, ATG regimen
- Post-transplant course complicated by
  - Deep-vein thrombosis
  - Pulmonary embolism
  - Prolonged cytopenias with blood count stabilization ~60 days post-transplant
  - Tapered off immunosuppression at 6 months post-transplant with no initial GVHD or other symptoms
- 8 months post-transplant
  - Fallen donor chimerisms, concern of losing graft/disease progression, planned DLI with 1 x 10^7 CD3+ cells
  - Low CD3 chimerism persisted, planned additional DLI with 3 x 10^7 CD3+ cells, resulted in full 100% CD3 and CD33 chimerisms

ATG, antithymocyte globulin; DLI, donor lymphocyte infusion.

Case 3: GVHD History

- 4 months post–last DLI
  - Ocular GVHD: dry, gritty eyes
  - Ocular-derived treatment (no systemic immunosuppression)
- 6 months post-DLI
  - Cough, fluctuating shortness of breath
  - Serial PFTs (as part of cGVHD evaluation) noted worsening function, oxygen dependency 24 hr/day
  - Treatment
    - Prednisone 1 mg/kg, FAM, bronchoscopy
    - Tapered steroids over 3 months given side effects
    - Reinitiated tacrolimus and started MMF

Time Point	FEV_1	RV
Baseline	99%	100%
GVHD diagnosis	75%	105%
Most recent measurement (6 months post DLI)	39%	133%

DLI, donor lymphocyte infusion; FAM, fluticasone, azithromycin, montelukast; MMF, mycophenolate mofetil; PFT, pulmonary function test.

Case 3 *continued*

Over the next 4 months:

- Hospitalized several times for acute-onset SOB, chest tightness
- Multiple lines of therapy were implemented with goal of improving pulmonary symptoms
  - Tacrolimus and MMF were discontinued; belumosudil and ruxolitinib were started
  - Prednisone was reinitiated with the goal to taper as soon as her disease allowed, given ongoing side effects
- Stable pulmonary function lasted 6 months, but still required oxygen, difficulty walking for extended periods of time
- Prednisone kept to 0.5 mg/kg/day to prevent flares; deemed steroid dependent

SOB, shortness of breath.

Steroid Response Definitions

- Steroid refractory
  - cGVHD progression while on prednisone at ≥1 mg/kg/day for 1–2 weeks, OR stable cGVHD while on ≥0.5 mg/kg/day for 1–2 months
- Steroid dependent
  - Repeated symptom flares during taper of corticosteroids <0.25 mg/kg/day

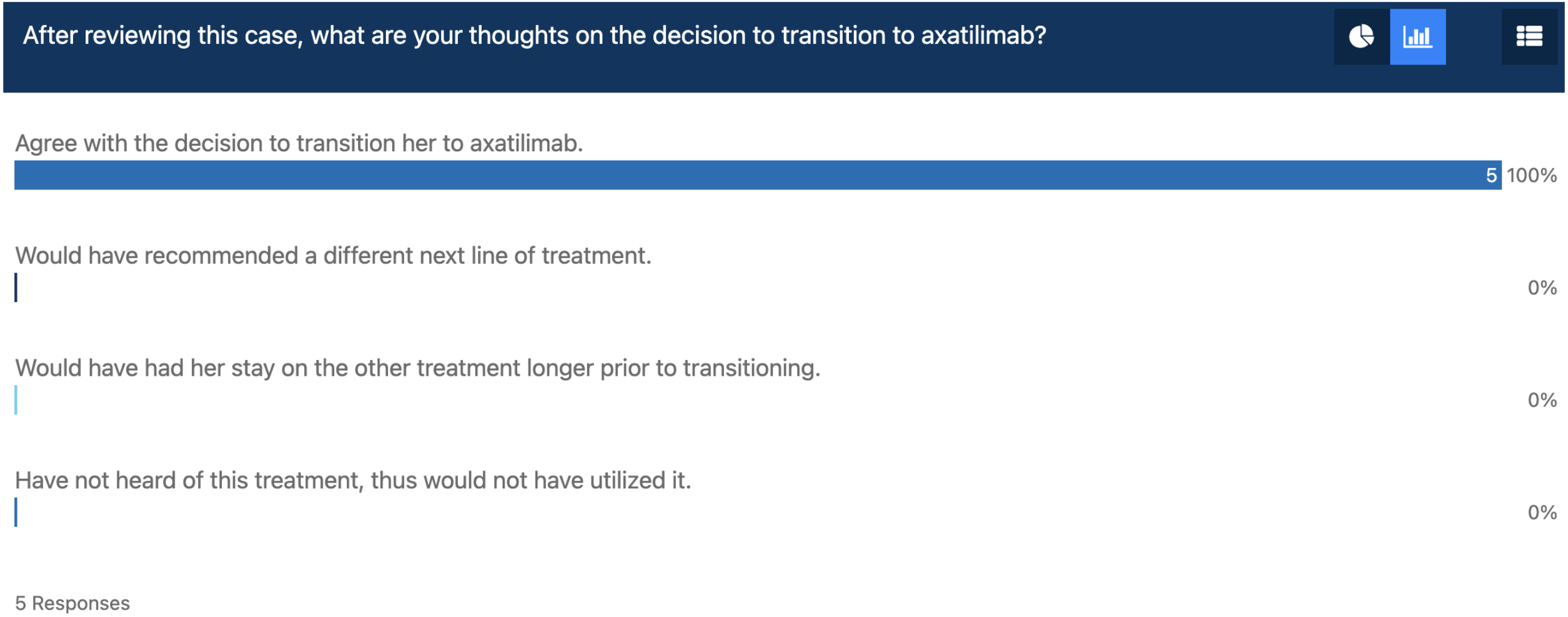
Case 3 *continued*

Because of MDS control and concern for long-term outcomes with lung GVHD:

- Referred to thoracic transplant surgeon for consideration of lung transplant
  - Steroids, debility led to increased weight (80-lb weight loss required before lung transplant could be considered)
- ECP added
  - Minimal benefit, lung function worsened again
- Referred for clinical trial options
  - Initiated on clinical trial of axatilimab, transitioned to standard of care once the drug was approved and commercially available
    - After 6 doses noted significant pulmonary improvement
    - Tapered off oxygen during the day, able to walk on treadmill for 18 min/day for weight management toward lung transplant

MDS, myelodysplastic syndrome; ECP, extracorporeal photopheresis.

Results from Case 3 Polling



Considerations When Determining Treatments

Treatment Options for cGVHD

Target	Therapeutic Intervention	Mechanism and Considerations
T cells	Calcineurin inhibitors (tacrolimus; cyclosporin)	Inhibiting calcineurin, an enzyme that activates T-cells of the immune system. PRES
T cells	Methotrexate	
M-TOR	Sirolimus	Has been thought to preserve regulatory T cells.
T cells of the Immune system	Extracorporeal photopheresis	Immune modulating therapy majorly targeting the enhancement of regulatory T cells. Complex schedule; may need CVC.
IL-6	Steroids	Long term effects on muscles and bones; glucose, etc.
B cells	Rituximab Ibrutinib (BTK inhibitor)	Interleukin-6 (IL-6) is another proinflammatory cytokine involved in the pathogenesis of GVHD. IL-6 promotes B-cell activation and differentiation, as well as inflammatory responses. Antigen recognition by B-cell receptors results in activation of the Bruton tyrosine kinase (BTK) signaling pathway, which leads to survival, proliferation, and migration of B cells.
JAK/STAT	Ruxolitinib	Impacts cytokine signaling and T-cell activation
rho-associated coiled-coil–containing protein kinase 2 (ROCK 2)	Belumosudil	Inhibits aberrant profibrotic signaling
CSF-1R	Axatilimab	IV infusion
Co stimulatory modulatory blocking CD 28	Abatacept	IV infusion
T and B cells	Mycophenolate mofetil	Depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation.

CVC, central venous catheter; M-TOR, mammalian target of rapamycin; PRES, posterior reversible encephalopathy syndrome.

Vadakkel G, et al. *Bone Marrow Transplant.* 2024;59(10):1360-1368.

Considerations in Choice of Therapy

Patient Factors

- cGVHD organ involvement
- Comorbidities
- Graft function
- Underlying malignancy and remission status
- Performance status
- Access to cancer center
- Insurance coverage

Drug-Specific Factors

- Route of administration
- MOA
- Safety profile
- ORR/organ system–specific response rate
- FFS
- TTR

FFS, failure-free survival; MOA, mechanism of action; ORR, overall response rate; TTR, time to response.

NIH Consensus Criteria for Response to GVHD Treatment

It is essential for clinicians to evaluate organ-based responses to treatment and make changes based on response.

Organ Measures	2005 Recommendation	2014 Recommendation
Skin	Skin response is measured using the body surface area of erythematous rash, moveable sclerosis and non-moveable sclerosis	Skin response is measured using the updated NIH Skin Score Detailed collection of type of BSA involvement no longer collected except for non-moveable sclerosis Skin and/or joint tightening is an exploratory measure
	Size of skin ulcers is documented	Presence or absence, not size, of skin ulcer is documented
Eye	Eye response is measured by change in Schirmer's test	Eye response is measured by change in NIH Eye Score
Mouth	Mouth response is measured by change in the Modified Oral Mucosa Score. Scores range from 0–15	Remove mucoceles from the Modified Oral Mucosa Score. Scores range from 0–12
	Oral chronic GVHD is described as "hyperkeratosis" changes	The term "hyperkeratosis" is replaced by "lichen-like" changes
	Patients' symptoms of mouth dryness and mouth pain are captured on 0–10 scales	No longer recommended. Mouth sensitivity is still captured on a 0–10 scale.
GI	Change from a 0 to 1 in the NIH GI and esophagus response measures are considered progression	Change from a 0 to 1 in these measures is no longer considered progression
Liver	Liver response is measured by change in ALT, bilirubin and alkaline phosphatase	Simplification of the definitions of improvement and progression
Lung	Lung response is measured by change in %FEV1 and DLCO after	Lung response is measured by change in %FEV1

Kitko CL, et al. *Transplant Cell Ther.* 2021;27(7):545-557.

Lee SJ, et al. *Biol Blood Marrow Transplant.* 2015;21(6):984-999.

Case 3 Poll: After reviewing this case, what are your thoughts on the decision to transition to axatilimab?

A. Agree with the decision to transition her to axatilimab.
B. Would have recommended a different next line of treatment.
C. Would have had her stay on the other treatment longer prior to transitioning.
D. Have not heard of this treatment, thus would not have utilized it.

Clinical Pearls

- Effective management of chronic GVHD requires ongoing assessment of symptom control, organ involvement, and functional impact.
- Escalation or transition of therapy should be considered when there is progression despite treatment, lack of improvement after an appropriate trial period, intolerable side effects, or emergence of new organ involvement.
- Timely adjustments can help reduce complications and improve quality of life for allogeneic stem cell transplant recipients.

Q & A

Please type your questions for **Chris Rimkus**
into the **question box**.

Thank You