What is Chronic Graft-Versus-Host Disease?

Chronic GVHD affects multiple organs with inflammation and fibrosis, leading to significant symptoms, patient burden, and mortality[1-3]

Chronic GVHD is a common long-term complication of allo-HSCT[4]

30-50%

of allo-HSCT recipients experience chronic GVHD[4]

Chronic GVHD leads to a significantly lower health-related QoL, including[5-10]

- Decreased functional status
- Inability to work or resume social roles

Chronic GVHD is associated with significant morbidity[11-14]

Chronic GVHD is associated with severe and frequent infections[11-13]

Chronic GVHD leads to debilitating fibrotic organ damage that can be irreversible[14]

Chronic GVHD is a leading cause of non-relapse mortality following allo-HSCT[15]

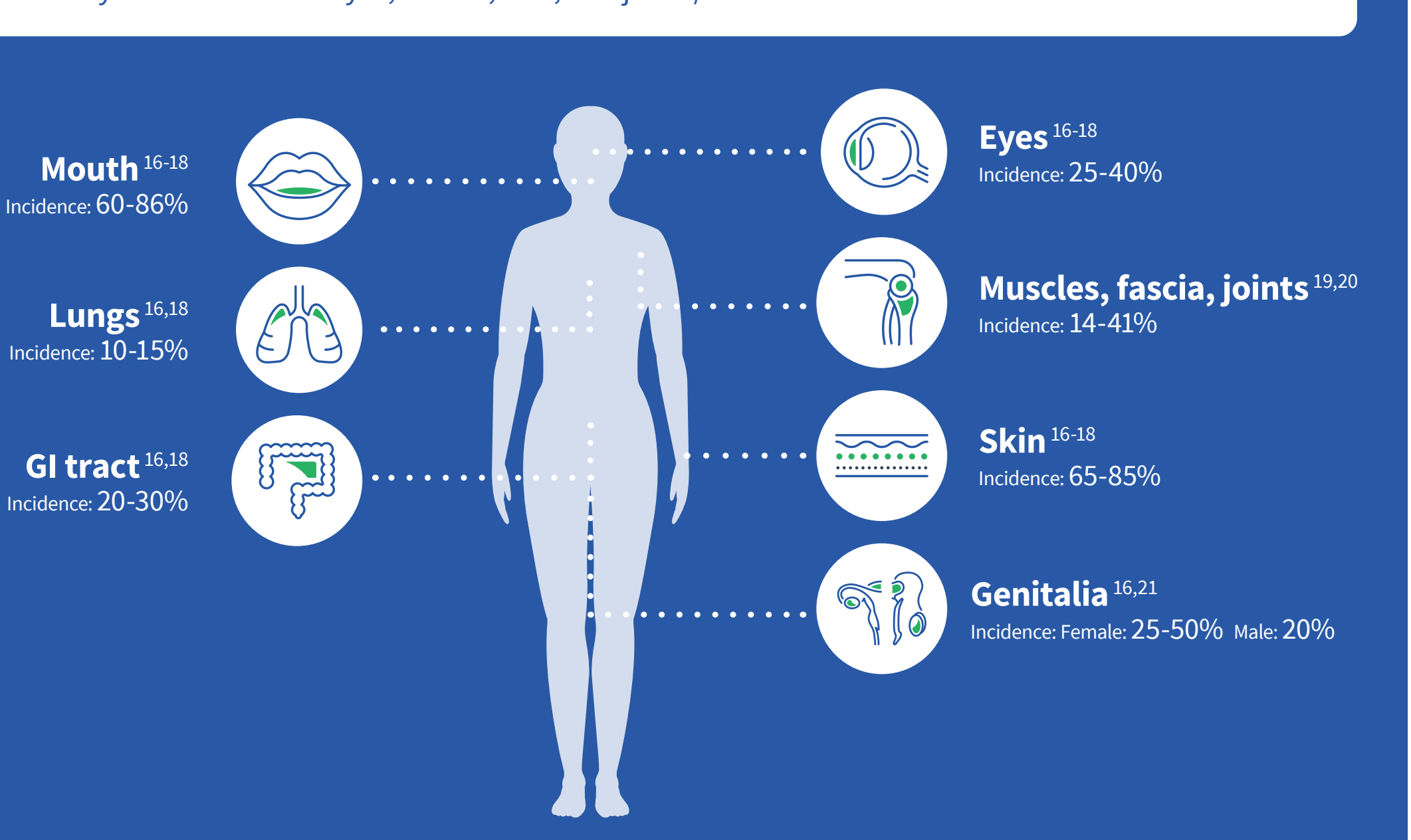
38%

of NRM is associated with chronic GVHD

NRM from chronic GVHD is frequently associated with organ failure and infection

Clinical Presentation of Chronic GVHD

- Chronic GVHD is associated with chronic inflammation and subsequent tissue fibrosis that affects multiple organs[16]
- It most commonly manifests in the eyes, mouth, skin, and joints/fascia[16]



Mouth[16-18] Incidence: 60-86%

Lungs[16,18] Incidence: 10-15%

GI tract[16,18] Incidence: 20-30%

Eyes[16-18] Incidence: 25-40%

Muscles, fascia, joints[19,20] Incidence: 14-41%

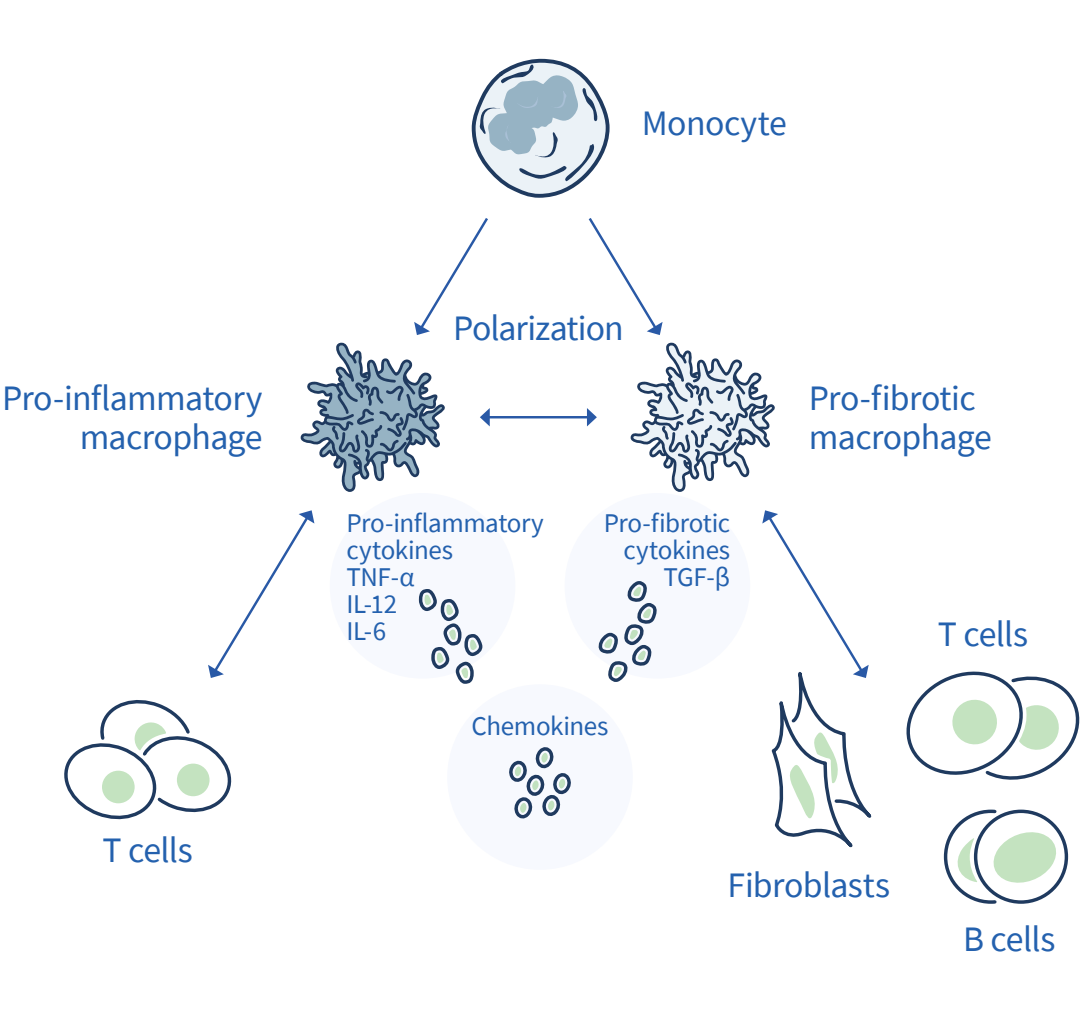
Skin[16-18] Incidence: 65-85%

Genitalia[16,21] Incidence: Female: 25-50% Male: 20%

Monocytes and Macrophages in Chronic GVHD

Inflammation[22]

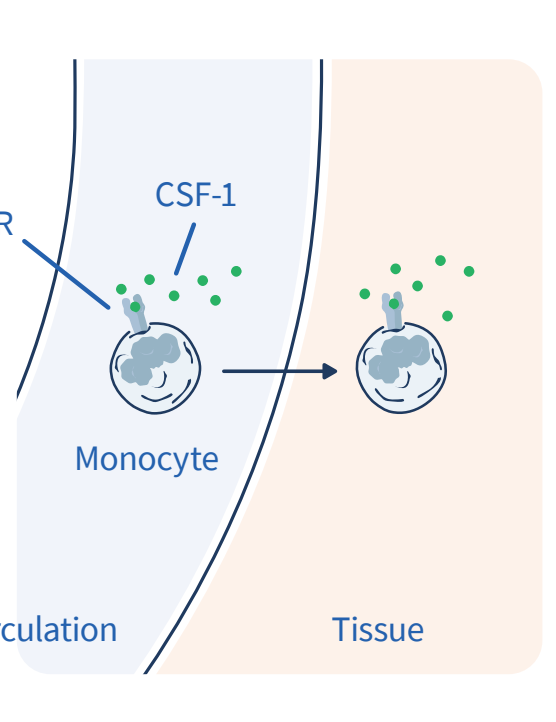
- Monocytes and macrophages are present in chronic GVHD and secrete chemokines and pro-inflammatory cytokines
- Activated macrophages can induce donor T cells to polarize and differentiate, impacting immune homeostasis and leading to chronic inflammation
- Chronic inflammation can lead to dysregulated tissue repair and fibrosis



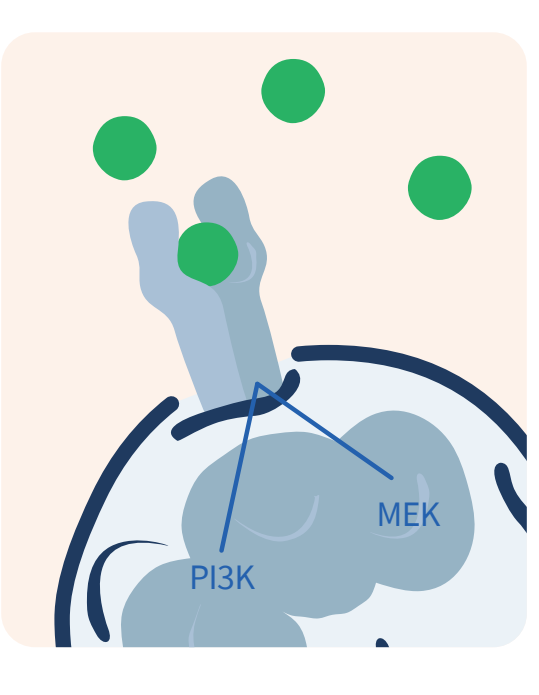
Fibrosis[22]

- Pro-fibrotic macrophages can interact with T cells, B cells, and fibroblasts to drive chronic GVHD
- Pro-fibrotic macrophages secrete cytokines that lead to fibroblast activation and collagen deposition, promoting aberrant tissue repair and fibrosis

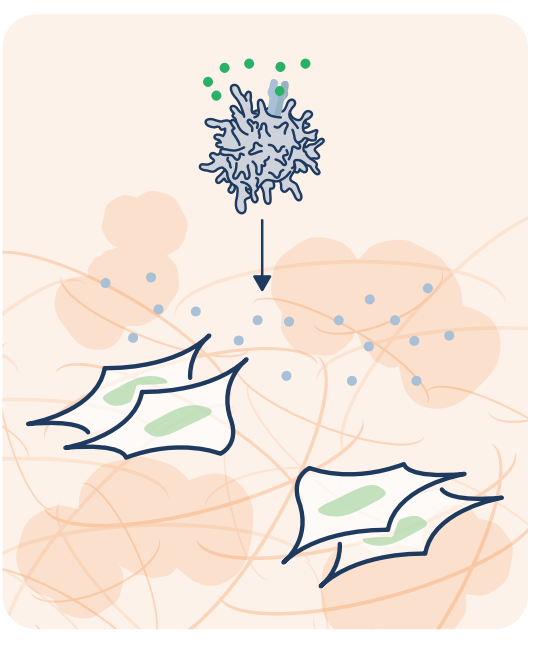
CSF-1R Signaling in Chronic GVHD



CSF-1R signaling promotes the infiltration of monocytes from circulation into tissue[23,24]



CSF-1R signaling activates intracellular pathways associated with the survival, proliferation, migration, and differentiation of monocytes and macrophages[25]



In the tissue, CSF-1R-dependent macrophages promote fibrosis during chronic GVHD[23,24,26]

Allo-HSCT, allogeneic HSCT; CSF-1, colony-stimulating factor 1; CSF-1R, colony-stimulating factor 1 receptor; GI, gastrointestinal; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IL, interleukin; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; QoL, quality of life; NRM, non-relapse mortality; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

What is Axatilimab-csfr?

A humanized anti-CSF-1R antibody that attaches to CSF-1R on the surface of monocytes and macrophages to block CSF-1R signaling[27]

Blocking CSF-1R signaling suppresses the activation, proliferation, and survival of monocytes and macrophages that contribute to inflammation and fibrosis in chronic GVHD[23,27]

Indication:

NIKTIMVO™ (axatilimab-csfr) is a CSF-1R-blocking antibody indicated for the treatment of chronic GVHD after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg[28]

Axatilimab-csfr was evaluated in the AGAVE-201 study[29,30]

AGAVE-201

An open-label, randomized, phase 2 study of axatilimab-csfr in chronic GVHD[30]

Study Design[30]

Eligibility criteria

Inclusion

- ≥2 years of age[a]
- HSCT with refractory[b] or recurrent[c] active chronic GVHD despite at least 2 lines of systemic therapy
- KPS ≥60 (≥16 years)
- Lansky PS ≥60 (<16 years)

Exclusion

Treatments for chronic GVHD, other than corticosteroids or either a CNI or an mTOR inhibitor, were prohibited

Treatment Period

Randomization 1:1:1

0.3 mg/kg IV q2w
n=80

1.0 mg/kg IV q2w
n=81

3.0 mg/kg IV q4w
n=80

Treatment for up to 2 years
until disease progression or unacceptable toxicity

Patients achieving sustained responses on the q2w dosing schedule (0.3 mg/kg or 1.0 mg/kg) were allowed to shift to a q4w schedule after 6 cycles

Primary Endpoint

- ORR in the first 6 cycles (up to day 169) as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in chronic GVHD

Key Secondary Endpoint

- Proportion of patients with a clinically significant (≥5 and ≥7 point improvement) in mLSS

Other Secondary Endpoints

- DOR[d]
- BOR[e]
- Organ-specific response rate[e]
- Number of patients with TEAEs

[a] Age inclusion criteria differ by country. [b] Defined as meeting all of the following criteria: 1) development of 1 or more new sites of disease while being treated for chronic GVHD 2) progression of existing sites of disease despite at least 1 month of standard or investigation therapy for chronic GVHD 3) no response within 3 months on prior therapy for chronic GVHD and treating physician believes a new systemic therapy is required. [c] Active, symptomatic disease (after an initial response to prior therapy) as defined, based on the NIH 2014 consensus criteria, by organ-specific or global assessment or for which the physician believes that a new line of systemic therapy is required. [d] DOR is defined as the time from initial partial response or complete response until documented progression of chronic GVHD, start of new therapy, or death for any reason. [e] Organ-specific response is defined as the number of participants with objective response for the nine individual organs based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in chronic GVHD (skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs and joints and fascia).

Baseline Characteristics and Patient Demographics (ITT Population)[29,30]

Total patients enrolled	241
Median age (range 7-81)	53
Time from chronic GVHD diagnosis to randomization, median (max), years	4 (18)
Number of prior systemic chronic GVHD therapies, median (max)	4 (15)
Prior ibrutinib, ruxolitinib, and/or belumosudil, n (%)	204 (85)
Patients with severe disease, n (%)	192 (80)
Number of organs involved, median (max)	4 (8)
Organs involved at baseline, n (%)	
Skin	193 (80)
Sclerotic skin	180 (93)
Skin features score of 3	149 (83)
Joints/fascia	162 (67)
Lung	108 (45)
NIH chronic GVHD lung score of 3	26 (25)
FEV1 ≤39% Patients with severe lung disease were not excluded from the study	36 (39)
Esophagus	61 (25)
Patients receiving systemic corticosteroids at baseline, %	65%
Mean dose	19.4 mg

BOR, best overall response; CNI, calcineurin inhibitor; DOR, duration of response; FEV1, forced expiratory volume; KPS, Karnofsky Performance Scale; mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health; ORR, overall response rate; PS, performance status; q2w, every 2 weeks; q4w, every 4 weeks; TEAEs, treatment-emergent adverse events.

AGAVE-201 Efficacy: 0.3 mg/kg q2w Cohort

Primary Endpoint: Overall Response Rate[30]

74% **Responded to axatilimab-csfr**

59 of 80 patients in this cohort had a response

Time to Response[30]

Median time to response was 1.7 months (range 0.9-8.1)

Duration of Response[30]

60%

of responses were maintained for

≥12 months

(95% CI 43-74)[a]

[a] Based on Kaplan–Meier estimate of 12-month event-free probability.

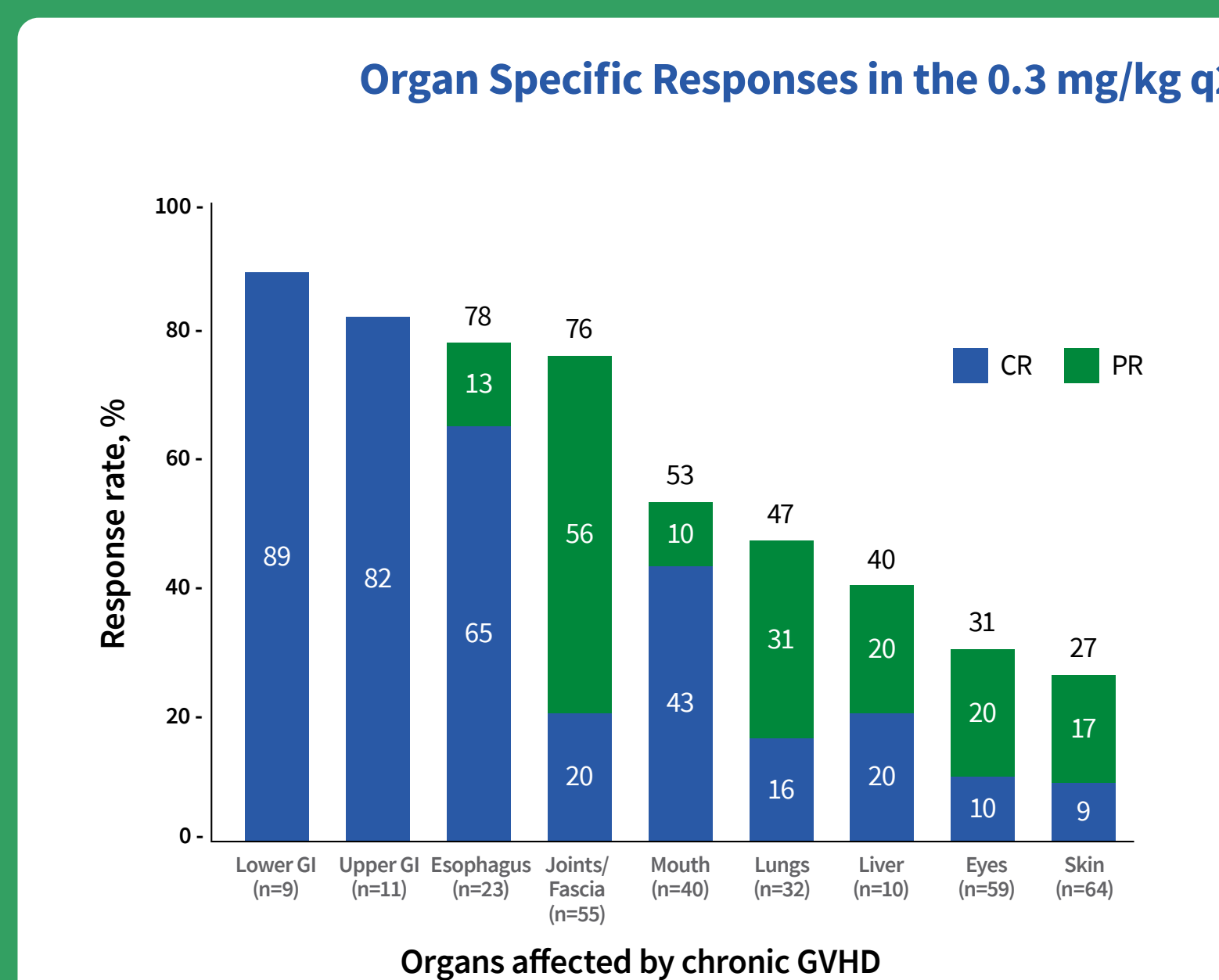
Modified Lee Symptom Scale Score Improvement in the 0.3 mg/kg q2w Cohort[30]

~87% had mLSS score improvement from baseline

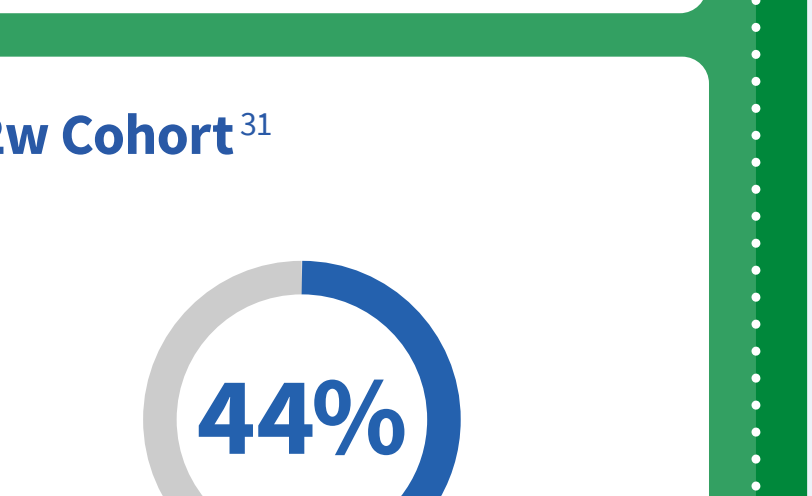
55% had a clinically meaningful change of ≥7-point improvement in mLSS score

1.5 months Median time to ≥7-point mLSS improvement

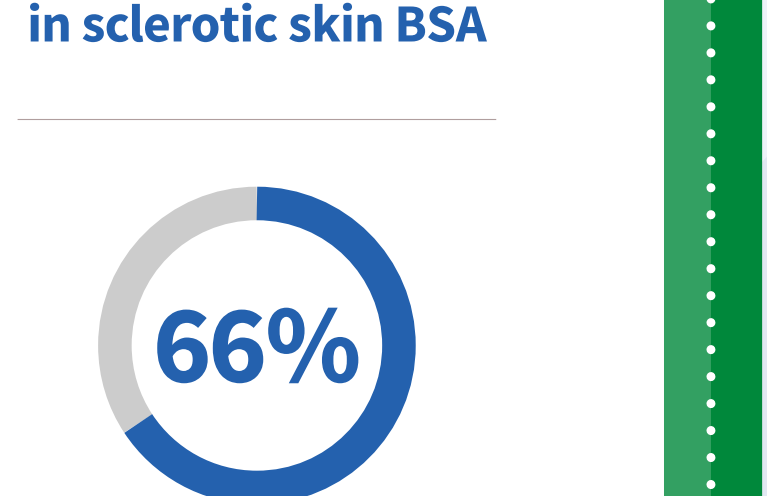
Organ Specific Responses in the 0.3 mg/kg q2w Cohort[31]



Responses were seen in all organs, including organs that can have fibrotic manifestations



Patients with reduction in sclerotic skin BSA



Patients with improvement in skin and joint tightening severity

BSA, body-surface area; CI, confidence interval; CR, complete response; PR, partial response.

Safety

Treatment Emergent Adverse Events[30]

	Axatilimab-csfr 0.3 mg/kg q2w (n=79)	Axatilimab-csfr 1.0 mg/kg q2w (n=81)	Axatilimab-csfr 3.0 mg/kg q4w (n=79)
Any grade TEAE in ≥20% of total patients			
Fatigue	18 (22.8)	16 (19.8)	21 (26.6)
Headache	15 (19.0)	14 (17.3)	16 (20.3)
COVID-19	13 (16.5)	18 (22.2)	11 (13.9)
Laboratory-based Abnormalities			
AST increase	11 (13.9)	31 (38.3)	43 (54.4)
ALT increase	10 (12.7)	18 (22.2)	31 (39.2)
CPK increase	9 (11.4)	26 (32.1)	49 (62.0)
Lipase increase	9 (11.4)	21 (25.9)	39 (49.4)
Lactate dehydrogenase increase	11 (13.9)	22 (27.2)	32 (40.5)
Amylase increase	3 (3.8)	10 (12.3)	34 (43.0)
Periorbital edema	2 (2.5)	19 (23.5)	24 (29.1)
At least 1 related grade ≥3 TEAE	14 (17.7)	28 (34.6)	37 (46.8)
Fatal TEAE	1 (1.3)[a]	7 (8.6)[b]	6 (7.6)[c]

[a] Dyspnea. [b] Sudden cardiac death, bronchopulmonary aspergillosis, pneumonia (n=2), sepsis, leukemia recurrent, respiratory failure. [c] Leukemia recurrent, dyspnea, respiratory failure, shock hemorrhagic, neutropenic sepsis, pneumonia.

Infections and Infusion-Related Reactions[29]

	Axatilimab-csfr 0.3 mg/kg q2w (n=79)	Axatilimab-csfr 1.0 mg/kg q2w (n=81)	Axatilimab-csfr 3.0 mg/kg q4w (n=79)	Total (N=239)
Any grade infections	58 (73.4)	59 (72.8)	55 (69.6)	172 (72.0)
Viral infections				
BK virus infection	1 (1.3)	0 (0)	0 (0)	1 (0.4)
COVID-19	13 (16.5)	18 (22.2)	11 (13.9)	42 (17.6)
COVID-19 pneumonia	3 (3.8)	1 (1.2)	2 (2.5)	3 (1.3)
Coronavirus infection	2 (2.5)	0 (0)	1 (1.3)	3 (1.3)
Cytomegalovirus infection	0 (0)	1 (1.2)	0 (0)	1 (0.4)
Cytomegalovirus infection reactivation	0 (0)	0 (0)	1 (1.3)	1 (0.4)
Epstein-Barr viremia	0 (0)	0 (0)	1 (1.3)	1 (0.4)
Epstein-Barr virus infection	0 (0)	0 (0)	2 (2.5)	2 (0.8)
Epstein-Barr virus infection reactivation	0 (0)	0 (0)	1 (1.3)	1 (0.4)
Fungal infections				
Aspergillus infection	0 (0)	1 (1.2)	0 (0)	1 (0.4)
Bronchopulmonary aspergillosis	0 (0)	2 (2.5)	0 (0)	2 (0.8)
Candida infection	3 (3.8)	4 (4.9)	2 (2.5)	9 (3.8)
Infusion-related reactions	6 (7.6)	4 (4.9)	1 (1.3)	11 (4.6)

Data are listed as n (%). Participants were counted once under each MedDRA system organ class and preferred term.

No CMV, EBV, or invasive fungal infections occurred in patients who received axatilimab-csfr at 0.3 mg/kg every 2 weeks[29]

Dose Modifications in the 0.3 mg/kg q2w Cohort:[29,30]

6.3% of patients required an axatilimab-csfr dose decrease due to AEs

6.3% of patients discontinued axatilimab-csfr due to AEs

Hematologic Abnormalities[29]

Among all cohorts in AGAVE-201 (N=239)

Blood and lymphatic system disorders:	
Anemia	4.2%
Febrile neutropenia	2.1%
Immune thrombocytopenia	0.4%
Neutropenia	0.4%
Thrombocytopenia	1.3%
	0.8%

Participants were counted once under each MedDRA system organ class and preferred term.

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; COVID, coronavirus disease; CPK, creatine phosphokinase; EBV, Epstein-Barr virus.

Concomitant Medications[29]

The most commonly taken (by > 10% of participants) concomitant medications included:

Concomitant Medication (N=241)

Acyclovir	60.6%	**Cyclosporine**	13.7%
Prednisone	52.3%	**Fluconazole**	11.6%
Posaconazole	24.1%	**Prednisolone**	11.2%
Tacrolimus	20.3%	**Sirolimus**	12.0%
Valacyclovir	14.1%	**Dexamethasone**	10.4%

Summary

- Chronic GVHD affects multiple organs with inflammation and fibrosis leading to significant symptoms, patient burden, and mortality[1-3]
- CSF-1R signaling through monocytes and macrophages can promote inflammation and fibrosis in chronic GVHD[22]
- Axatilimab-csfr is an anti-CSF-1R antibody that blocks CSF-1R signaling[27]
- In AGAVE-201, 74% of patients receiving axatilimab-csfr 0.3 mg/kg q2w had a response, and responses were noted in all fibrosis-dominant organs[30]
- The most common TEAEs were fatigue and headache, and there were no CMV, EBV, or invasive fungal infections at the 0.3 mg/kg q2w dose[29,30]

Warnings and Precautions[28]

Infusion-Related Reactions	Premedicate patients with an antihistamine and antipyretic if they have previously had an infusion-related reaction to axatilimab-csfr, and monitor for symptoms such as fever, chills, rash, flushing, dyspnea, and hypertension, adjusting or discontinuing the infusion based on severity
Embryo-Fetal Toxicity	Axatilimab-csfr may cause fetal harm due to its mechanism of action; verify pregnancy status and advise pregnant women and people of reproductive potential of this risk and instruct use of effective contraception during treatment and for 30 days after the last dose
Lactation	Advise women not to breastfeed during treatment and for 30 days after the last dose of axatilimab-csfr
Pediatric Use	Safety and efficacy are not established for those weighing <40 kg; based on findings of thickening of the growth plate and metaphysis and/or degeneration of the growth plate in the femur in animals, monitor bone growth and development in pediatric patients (<40kg)
Geriatric Use	No overall differences in the safety and efficacy of axatilimab-csfr have been observed between patients ≥ 65 years and younger patients

1. Blazar BR, et al. *Nat Rev Immunol*. 2012;12:443-458. 2. Cutler CS, et al. *Blood*. 2017;129(1):22-29. 3. Cooke KR, et al. *Biol Blood Marrow Transplant*. 2017;23:211-234. 4. Lee SJ. *Best Pract Res Clin Haematol*. 2010;4:529-535. 5. Kitko CL, et al. *Transplant Cell Ther*. 2021;27:545-557. 6. Lee SJ, et al. *Haematologica*. 2018;103:1535-1541. 7. Wong FL, et al. *Blood*. 2010;115:2508-2519. 8. Bevans M, et al. *Biol Blood Marrow Transplant*. 2017;23:538-551. 9. Yu J, et al. *Cancer Med*. 2023;12:3623-3633. 10. Kurosawa S, et al. *Biol Blood Marrow Transplant*. 2019;25:1851-1858. 11. Arai S, et al. *Biol Blood Marrow Transplant*. 2015;21:266-74. 12. Socié G, Ritz J. *Blood*. 2014;124:374-384. 13. Blau O, et al. *Int J Transplant Red Med*. 2017;3:033. 14. Hill GR, et al. *Annu Rev Immunol*. 2021 Apr 26;39:19-49. 15. deFilipp Z, et al. *Blood Adv*. 2021;5:4278-4284. 16. Jagasia MH, et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401. 17. Vigorito AC, et al. *Blood*. 2009;114(3):702-708. 18. Lee SJ, et al. *Blood*. 2002;100(2):406-414. 19. Vukic T, et al. *Croat Med J*. 2016;57(3):266-275. 20. Inamoto Y, et al. *Arthritis Rheumatol*. 2014;66(4):1044-1052. 21. Hamilton BK, et al. *Bone Marrow Transplant*. 2017;52(6):803-810. 22. Hong Y et al. *World J Clin Cases*. 2020 May 26; 8(10): 1793–1805. 23. Alexander KA, et al. *J Clin Invest*. 2014;124(10):4266-4280. 24. MacDonald KPA, et al. *Blood*. 2017 Jan 5;129(1):13-21. 25. Hume DA, MacDonald KP. *Blood*. 2012;119(8):1810-1820. 26. Banovic T, et al. *Blood*. 2005; 106(6):2206-2214. 27. Kitko CL, et al. *J Clin Oncol*. 2023;41(10):1864-1875. 28. NIKTIMVO™ (axatilimab-csfr). Prescribing Information. Incyte Corporation; January 2025. 29. Data on File, Incyte Corporation. 30. Wolff D, et al. Presentation at ASH Annual Meeting. December 10, 2023. 31. deFilipp Z, et al. Tandem 2024. Oral presentation 36.

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