PS2029

The Effects of Prior Lines of Therapy on Clinical Outcomes for Patients With Chronic Graft-Versus-Host Disease Receiving Axatilimab: A Post Hoc Analysis of AGAVE-201

Presented at the
European Hematology Association (EHA) 2025 Congress
Milan, Italy • 12–15 June 2025

Carrie L. Kitko, MD,[1] Rohtesh Mehta, MD, MPH, MS,[2] Gizelle Popradi, MDCM,[3] Eduardo Olavarria, MD, PhD,[4] Dries Deeren, MD, PhD,[5] Britnie Thomas, PhD,[6] Valkal Bhatt, PharmD,[6] Shuyuan Lou, PhD,[6] Vedran Radojcic, MD,[7] Catherine J. Lee, MD, MS[2]

[1]Vanderbilt University Medical Center, Nashville, TN, USA; [2]Fred Hutchinson Cancer Center, Seattle, WA, USA; [3]McGill University Health Center—Research Institute, Montreal, QC, Canada; [4]Imperial College Healthcare NHS Trust, London, United Kingdom; [5]Algemeen Ziekenhuis Delta Roeselare-Menen, Roeselare, Belgium; [6]Incyte Corporation, Wilmington, DE, USA; [7]Syndax Pharmaceuticals, Inc., New York, NY, USA

Introduction

- Chronic graft-versus-host disease (cGVHD) is characterized by inflammatory and fibrotic pathology that affects multiple organs with varying severity and leads to significant impairment[1-3]
- Patients commonly receive ≥3 lines of therapy (LOT) in cGVHD, which can include treatments approved by the US Food and Drug Administration (FDA), such as ruxolitinib, belumosudil, and ibrutinib[4]
- Axatilimab, an anti–colony-stimulating factor 1 receptor (CSF-1R) monoclonal antibody, targets monocytes and macrophages that are critical to cGVHD pathogenesis[5]
- In the pivotal AGAVE-201 study (NCT04710576), the FDA-approved axatilimab dose of 0.3 mg/kg once every 2 weeks (Q2W)[6] had robust clinical activity and was generally well tolerated in patients with cGVHD, with treatment-related adverse events that were mostly low grade and transient[7]
  - It is unknown how prior FDA-approved agents may affect the efficacy of axatilimab for cGVHD; additional investigation regarding the optimal timing and sequencing of cGVHD therapies is warranted

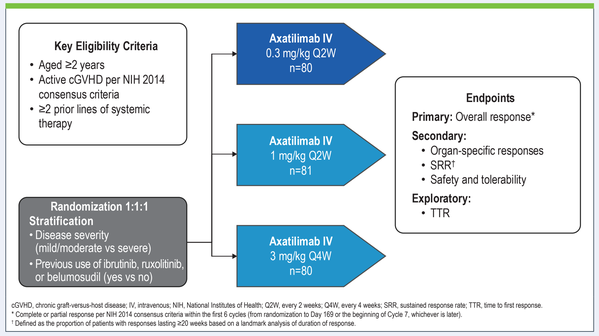
Objective

- To evaluate the effects of prior LOT on clinical outcomes among patients treated with axatilimab for cGVHD in AGAVE-201

Methods

- In AGAVE-201, patients were randomized 1:1:1 to intravenous axatilimab (0.3 mg/kg Q2W; 1 mg/kg Q2W; 3 mg/kg every 4 weeks [Q4W]; **Figure 1**)
- Endpoints included
  - Overall response rate (ORR)
  - Time to first response (TTR)
  - Sustained response rate (SRR; defined as the proportion of patients with responses lasting ≥20 weeks based on a landmark analysis of duration of response)
  - Organ-specific responses based on 2014 National Institutes of Health cGVHD consensus criteria
- Reponses were assessed post hoc by number of prior LOT and last therapy (ruxolitinib, belumosudil, and other therapies [all therapies other than ruxolitinib, including belumosudil])
- LOT were clinically adjudicated for this analysis

Figure 1. AGAVE-201 Study Design



cGVHD, chronic graft-versus-host disease; IV, intravenous; NIH, National Institutes of Health; Q2W, every 2 weeks; Q4W, every 4 weeks; SRR, sustained response rate; TTR, time to first response.
* Complete or partial response per NIH 2014 consensus criteria within the first 6 cycles (from randomization to Day 169 or the beginning of Cycle 7, whichever is later).
† Defined as the proportion of patients with responses lasting ≥20 weeks based on a landmark analysis of duration of response.

Results

- The demographics and baseline clinical characteristics of patients in AGAVE-201 are summarized in **Table 1**

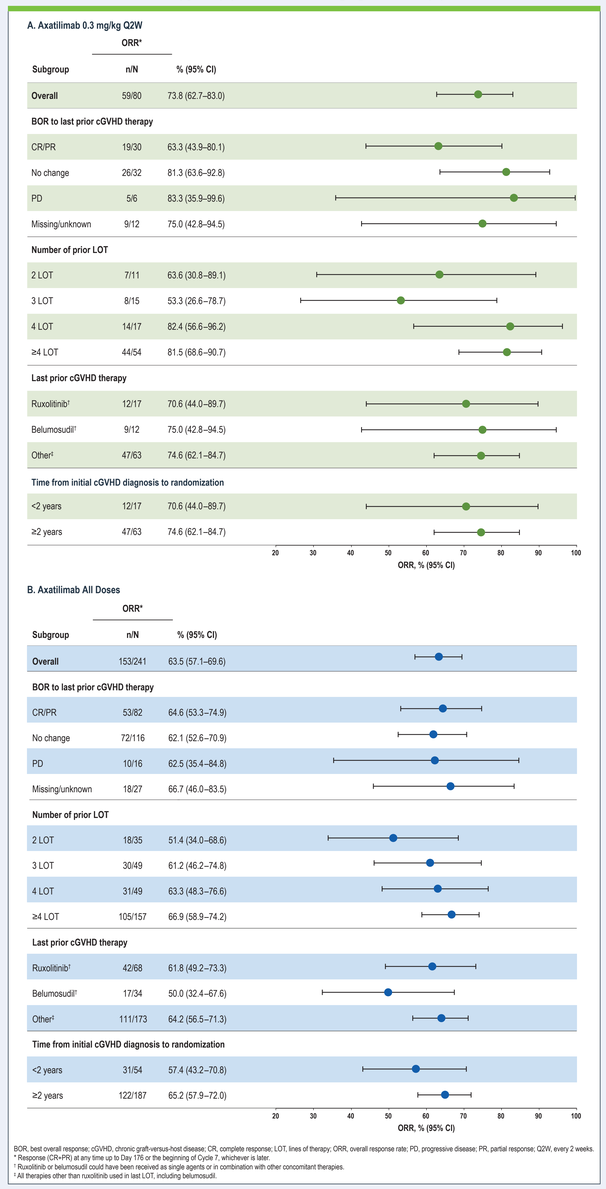
Table 1. Patient Demographics and Baseline Clinical Characteristics

	Axatilimab 0.3 mg/kg Q2W (n=80)	Axatilimab all doses (N=241)
Age, median (range), y	50.0 (7–76)	53.0 (7–81)
Male, n (%)	47 (58.8)	151 (62.7)
Time from cGVHD diagnosis to randomization, median (range), y	3.9 (0.4–17.6)	4.0 (0.4–17.6)
Number of organs involved at baseline, median (maximum)	4.0 (8)*	4.0 (8)*
Severe disease, n (%)	63 (78.8)	192 (79.7)
Number of prior LOT, median (range)	4.0 (2–12)	4.0 (2–15)
Prior cGVHD therapy,‡ n (%)	67 (83.8)	204 (84.6)
Ruxolitinib	57 (71.3)	179 (74.3)
As last prior LOT	17 (21.3)	68 (28.2)
In 1st LOT	4 (5.0)	15 (6.2)
In 2nd LOT	26 (32.5)	59 (24.5)
In 3rd LOT	20 (25.0)	58 (24.1)
In ≥4th LOT	24 (30.0)	97 (40.2)
Belumosudil	16 (20.0)	56 (23.2)
As last prior LOT	12 (15.0)	34 (14.1)
In 2nd LOT	1 (1.3)	3 (1.2)
In 3rd LOT	3 (3.8)	14 (5.8)
In ≥4th LOT	13 (16.3)	41 (17.0)
Ibrutinib	27 (33.8)	75 (31.1)
As last prior LOT	5 (6.3)	14 (5.8)
In 1st LOT	1 (1.3)	6 (2.5)
In 2nd LOT	4 (5.0)	10 (4.1)
In 3rd LOT	4 (5.0)	12 (5.0)
In ≥4th LOT	19 (23.8)	54 (22.4)

C, Cycle; cGVHD, chronic graft-versus-host disease; D, Day; FDA, US Food and Drug Administration; LOT, lines of therapy; Q2W, every 2 weeks; TEAE, treatment-emergent adverse event.
Randomization was stratified by prior use (yes/no) of ≥1 FDA-approved cGVHD therapy (ibrutinib, ruxolitinib, and belumosudil).
* No patients in the study had 0 organs involved. Data on organ involvement were not available for 2 patients: 1 patient assigned to the 0.3 mg/kg dose due to a serious adverse event that resulted in that patient's withdrawal of consent before C1D1; and 1 patient assigned to the 3 mg/kg dose who had a baseline assessment on C1D7.
‡ Includes FDA-approved therapies received for cGVHD prior to AGAVE-201 (ibrutinib, ruxolitinib, and belumosudil).

- The most common prior cGVHD therapies during any LOT were prednisone (76.8%), ruxolitinib and ruxolitinib phosphate (54.8% and 19.5%, respectively), extracorporeal photopheresis (56.4%), tacrolimus (40.2%), ibrutinib (31.1%), mycophenolate mofetil (29.5%), sirolimus (29.5%), rituximab (26.1%), belumosudil (23.2%), and ciclosporin (17.8%)
- Across all doses, ORRs with axatilimab were similar for patients whether their best response to last prior treatment was a complete or partial response, no change, or progression (**Figure 2**)
- ORRs were consistent, with slight increases among patients who received a greater number of prior LOT
- ORR in the 68 patients treated with ruxolitinib in last LOT was 62%
  - The median TTR for these patients was 1.9 (range, 0.9–5.8) months and SRR was 43% (95% CI, 31%–55%)
- ORR in the 34 patients treated with belumosudil in last LOT was 50% **(Figure 2)**
  - The median TTR for these patients was 1.9 (range, 0.9–3.9) months, and SRR was 26% (95% CI, 13%–44%)
- Responses in patients with any therapy other than ruxolitinib in last LOT are also shown in **Figure 2**
- Owing to low patient numbers when assessing the single-dose cohort of 0.3 mg/kg Q2W, organ-specific response rates were assessed across all doses **(Figure 3)**
- Across all organs, response rates were numerically similar between patients who received ruxolitinib as last LOT compared with all other prior therapies **(Figure 3)**
- Organ-specific response rates were generally greater with ruxolitinib as last LOT compared with belumosudil as last LOT, except in the eyes, where responses were numerically similar (**Figure 3**); these analyses were not powered to evaluate statistical differences

Figure 2. Overall Response by Best Response to Last Prior cGVHD Therapy, Number of Prior LOT, and Last Prior cGVHD Therapy for (A) Axatilimab 0.3 mg/kg Q2W and (B) Axatilimab All Doses

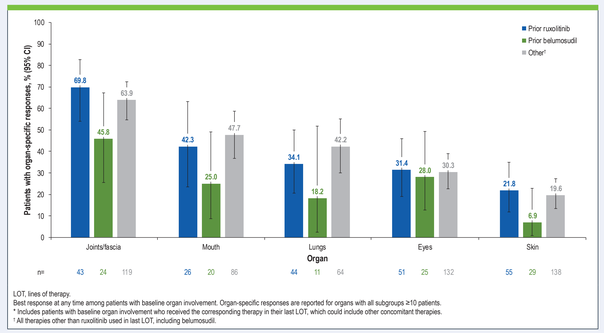


BOR, best overall response; cGVHD, chronic graft-versus-host disease; CR, complete response; LOT, lines of therapy; ORR, overall response rate; PD, progressive disease; PR, partial response; Q2W, every 2 weeks.
* Response (CR+PR) at any time up to Day 176 or the beginning of Cycle 7, whichever is later.
† Ruxolitinib or belumosudil could have been received as single agents or in combination with other concomitant therapies.
‡ All therapies other than ruxolitinib used in last LOT, including belumosudil.

Safety in the Overall Population (N=239)

- Treatment-emergent adverse events (TEAEs) of any grade occurred in 96.2% of patients in the 0.3 mg/kg Q2W group and 97.9% across all doses; grade ≥3 TEAEs occurred in 49.4% and 60.3% of patients, respectively

Figure 3. Organ-Specific Responses With Axatilimab by Last Prior Therapy*



LOT, lines of therapy.
Best response at any time among patients with baseline organ involvement. Organ-specific responses are reported for organs with all subgroups ≥10 patients.
* Includes patients with baseline organ involvement who received the corresponding therapy in their last LOT, which could include other concomitant therapies.
‡ All therapies other than ruxolitinib used in last LOT, including belumosudil.

- Opportunistic infections (cytomegalovirus, Epstein-Barr virus, and invasive fungal) did not occur in any patients in the 0.3 mg/kg Q2W group and occurred in 10 (4.2%) patients across all doses
- In the 0.3 mg/kg Q2W group and across all doses, 6.3% and 15.5% of patients, respectively, had TEAEs that led to discontinuation of treatment

Conclusions

- **In AGAVE-201, ORRs were consistent with axatilimab regardless of the number of prior LOT received**
  - **Responses were more sustained with ruxolitinib as last prior therapy**
- **Patients who received axatilimab immediately after a regimen with ruxolitinib demonstrated rapid, durable clinical responses**
- **Organ-specific responses to axatilimab were noted regardless of last prior therapy, and there was a trend toward higher organ-specific response rates for those treated in their last LOT with ruxolitinib compared with belumosudil in some organs (joints/fascia, mouth, lungs, and skin)**
- **These findings warrant further investigation and may be attributable to the novel mechanism of action of axatilimab or LOT**
  - **Small patient numbers and mixed treatment regimens may limit interpretation**
- **These data demonstrate the efficacy of axatilimab for steroid-refractory cGVHD after 2 LOT, including patients treated with ruxolitinib as last LOT**

Disclosures

CLK served as an advisory committee member for Incyte Corporation, Sanofi, and Mesoblast; and as a member of the GVHD adjudication team for Alexion, CSL Behring, DSMC, and Incyte Corporation. RM has served on a review panel for OrcaBio and received research funding from CSL Behring, Incyte Corporation, Kadmon, and Syndax. GP has served as a consultant for or received honoraria from AbbVie, Amgen, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Jazz, Kyowa Kirin, Mallinckrodt, Medexus, Merck, Novartis, Paladin, Pfizer, Seagen, Sanofi, Servier, Sobi, and Takeda. EO has no disclosures to report. DD has served as a consultant for Alexion, Bristol Myers Squibb, Incyte, Novartis, Sanofi, Sobi, and Takeda and received research funding from Alexion, Amgen, Novartis, Roche, and Sobi. BT, VB, and SL are employees and shareholders of Incyte Corporation. VR was an employee and shareholder of Syndax Pharmaceuticals at the time this work was conducted. CJL has served as a consultant for and/or received honoraria from Bristol Myers Squibb, CareDx, Fresenius Kabi, Incyte Corporation, Kadmon, Kite, and Sanofi and received research funding from Incyte Corporation.

Acknowledgments

This study was funded by Incyte Corporation (Wilmington, DE) and Syndax Pharmaceuticals (New York, NY). Medical writing support was provided by Rob M. Camp, PhD, from Citrus Health Group (Chicago, IL), and was funded by Incyte Corporation and Syndax Pharmaceuticals.

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Originally presented at TCT 2025.