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Axatilimab for Chronic Graft-Versus-Host Disease: Responses in Fibrosis-Dominant Organs in AGAVE-201

Carrie L. Kitko,[1] Corey Cutler,[2] Zachariah DeFilipp,[3] Stephanie J. Lee,[4] Wendy Ingram,[5] Jennifer White,[6] Helene Schoemans,[7,8] Laetitia Souchet,[9] Daniel Wolff,[10] Simona Sica,[11,12] Avichai Shimoni,[13] Britnie Thomas,[14] Vedran Radojcic,[15] Chuan Tian,[14] Amandeep Salhotra,[16] Jose A. Perez-Simon[17]

[1]Vanderbilt University Medical Center, Nashville, TN, USA; [2]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Fred Hutchinson Cancer Center, Seattle, WA, USA; [5]University Hospital of Wales, Cardiff, United Kingdom; [6]The University of British Columbia, Vancouver General Hospital, Vancouver, BC, Canada; [7]Department of Hematology, University Hospitals Leuven, Leuven, Belgium; [8]Department of Public Health and Primary Care, ACCENT VV, KU Leuven - University of Leuven, Leuven, Belgium; [9]Clinical Hematology Unit, Groupe Hospitalier Pitié-Salpêtrière, AP-HP Sorbonne Université, Paris, France; [10]University Hospital of Regensburg, Regensburg, Germany; [11]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [12]Università Cattolica Sacro Cuore, Rome, Italy; [13]Chaim Sheba Medical Center, Tel-Hashomer and Sackler Medical School Tel-Aviv University, Tel-Aviv, Israel; [14]Incyte Corporation, Wilmington, DE, USA; [15]Syndax Pharmaceuticals, Inc, Waltham, MA, USA; [16]City of Hope Medical Center, Duarte, CA, USA; [17]Hospital Universitario Virgen del Rocío Instituto de Biomedicina de Sevilla (IBIS), CSIC, University of Sevilla, Seville, Spain

Introduction

- Colony-stimulating factor-1 receptor (CSF-1R)–dependent monocytes and macrophages contribute to the multiorgan inflammation and fibrosis that drives chronic graft-versus-host disease (cGVHD)[1]
- Axatilimab is an investigational, high-affinity anti–CSF-1R monoclonal antibody[2]
- In the AGAVE-201 study, axatilimab 0.3 mg/kg every 2 weeks (Q2W) resulted in the highest response rate and most manageable safety profile[3]

Objective

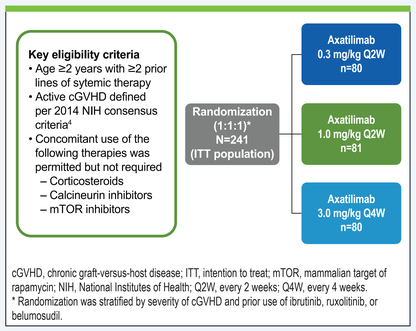
- To evaluate fibrosis-dominant organ-specific responses and changes in patient-reported symptom burden as well as safety, with an emphasis on infections

Methods

Patients and Study Design

- AGAVE-201 (NCT04710576) was a phase 2, open-label, multicenter, randomized study to evaluate safety and efficacy of axatilimab in patients with recurrent/refractory cGVHD (**Figure 1**)

Figure 1. AGAVE-201 Study Design



cGVHD, chronic graft-versus-host disease; ITT, intention to treat; mTOR, mammalian target of rapamycin; NIH, National Institutes of Health; Q2W, every 2 weeks; Q4W, every 4 weeks.
* Randomization was stratified by severity of cGVHD and prior use of ibrutinib, ruxolitinib, or belumosudil.

Assessments

- The primary endpoint of the study was overall response rate in the first 6 cycles; the endpoint was met if the lower bound of 95% CI was >30%
- Organ-specific responses were measured using the 2014 National Institutes of Health cGVHD consensus guidelines[5]
- Additional clinician-reported assessments included photographic range of motion (P-ROM), reduction in sclerotic body surface area (BSA), and improvement in skin/joint tightening/severity
- Modified Lee Symptom Scale organ subdomain analyses were performed to identify changes in symptom burden associated with fibrosis[6]
- Safety and tolerability were also assessed with an emphasis on infections, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), and invasive fungal infections

Results

Patients

- Demographics and baseline characteristics were similar across cohorts (**Table 1**)
- A high proportion of patients had severe disease with multiorgan involvement

Table 1. Demographics and Baseline Clinical Characteristics

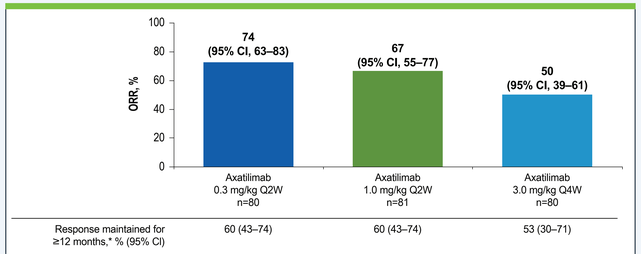
	Axatilimab 0.3 mg/kg Q2W (n=80)	Axatilimab 1.0 mg/kg Q2W (n=81)	Axatilimab 3.0 mg/kg Q4W (n=80)	Overall (N=241)
Age, median (range), y	50 (7–76)	56 (26–81)	53 (7–79)	53 (7–81)
Patients with severe disease, n (%)	63 (79)	64 (79)	65 (81)	192 (80)
Number of organs involved, median (max)	4 (8)	4 (7)	3 (7)	4 (8)
Organs involved at baseline, n (%)				
Skin	64 (80)	63 (78)	66 (83)	193 (80)
Sclerotic skin*	60 (94)	60 (95)	60 (91)	180 (93)
Skin features score of 3†	46 (77)	48 (80)	55 (92)	149 (83)
Joints/fascia	55 (69)	56 (69)	51 (64)	162 (67)
Lung	32 (40)	41 (51)	35 (44)	108 (45)
NIH cGVHD lung symptom score of 3‡	8 (25)	10 (26)	8 (23)	26 (25)
FEV1 ≤39%§	14 (47)	15 (42)	7 (26)	36 (39)
Esophagus	23 (29)	18 (22)	20 (25)	61 (25)

cGVHD, chronic graft-versus-host disease; FEV1, forced expiratory volume in the first second; NIH, National Institutes of Health; Q2W, every 2 weeks; Q4W, every 4 weeks.
* Denominator includes patients with skin involvement. † Denominator includes patients with sclerotic skin. ‡ Denominator includes patients with baseline evaluation of NIH lung symptom score. § Denominator includes patients with baseline evaluation of FEV1.

Overall Response Rate

- Substantial clinical responses were observed in the 0.3 mg/kg Q2W cohort (**Figure 2**)

Figure 2. ORR (NIH 2014 Criteria) in the First 6 Cycles

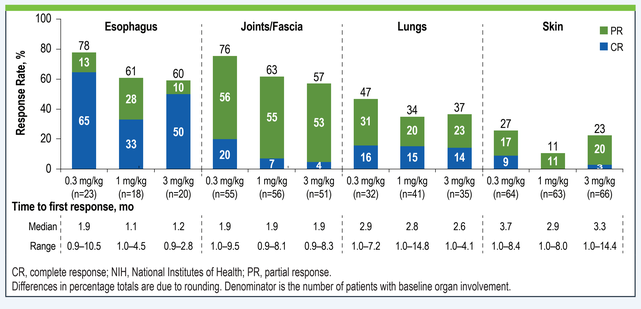


NIH, National Institutes of Health; ORR, overall response rate; Q2W, every 2 weeks; Q4W, every 4 weeks.
* Based on Kaplan–Meier estimate of 12-month event-free probability.

Responses in Fibrosis-Dominant Organs

- Responses were seen in all organs, including organs that can have fibrotic manifestations (**Figure 3**)
- Lungs and skin had slightly prolonged time to first response

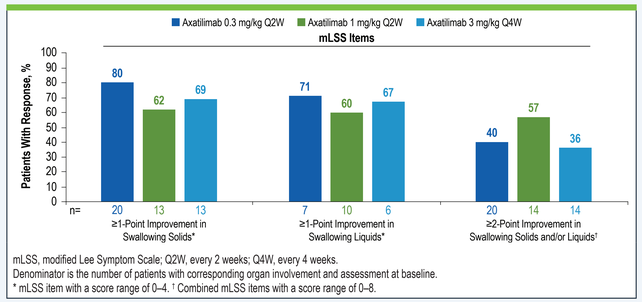
Figure 3. Responses (NIH 2014 Criteria) in Fibrosis-Dominant Organs (Best Response at Any Time)



CR, complete response; NIH, National Institutes of Health; PR, partial response.
Differences in percentage totals are due to rounding. Denominator is the number of patients with baseline organ involvement.

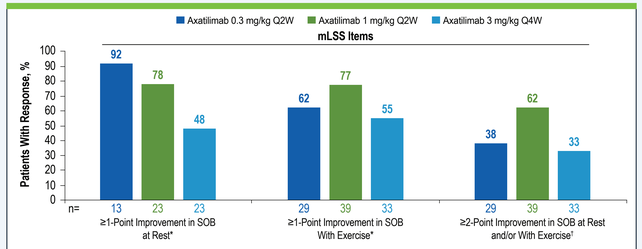
- Improvements were observed in swallowing (**Figure 4**), shortness of breath (**Figure 5**), skin and joints (**Figure 6**), and sclerotic skin (**Figure 7**)

Figure 4. Patient-Reported Improvements in Swallowing (Best Response at Any Time)



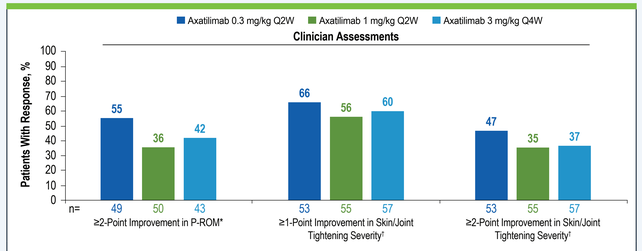
mLSS, modified Lee Symptom Scale; Q2W, every 2 weeks; Q4W, every 4 weeks.
Denominator is the number of patients with corresponding organ involvement and assessment at baseline.
* mLSS item with a score range of 0–4. † Combined mLSS items with a score range of 0–8.

Figure 5. Patient-Reported Improvements in Shortness of Breath (Best Response at Any Time)



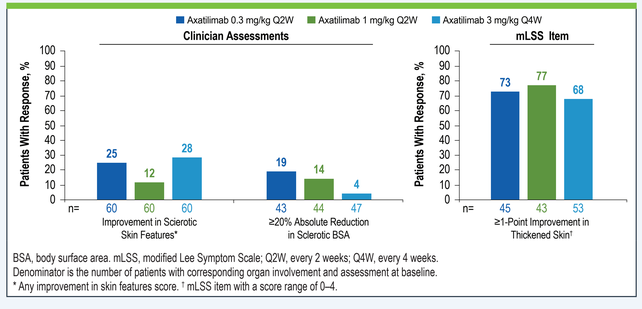
mLSS, modified Lee Symptom Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SOB, shortness of breath.
Denominator is the number of patients with corresponding organ involvement and assessment at baseline.
* mLSS item with a score range of 0–4. † Combined mLSS items with a score range of 0–8.

Figure 6. Clinical Improvements in Skin and Joints (Best Response at Any Time)



P-ROM, photographic range of motion; Q2W, every 2 weeks; Q4W, every 4 weeks.
Denominator is the number of patients with corresponding organ involvement and assessment at baseline.
* Clinician assessment with a score range of 0–25. † Clinician assessment with a score range of 0–10.

Figure 7. Clinical and Patient-Reported Improvements of Sclerotic Skin (Best Response at Any Time)



BSA, body surface area. mLSS, modified Lee Symptom Scale; Q2W, every 2 weeks; Q4W, every 4 weeks.
Denominator is the number of patients with corresponding organ involvement and assessment at baseline.
* Any improvement in skin features score. † mLSS item with a score range of 0–4.

Safety

- Adverse events were mostly low grade, reversible, and increased with higher doses
- No CMV, EBV, or invasive fungal infections occurred in the 0.3 mg/kg Q2W cohort (**Table 2**)

Table 2. Infections

	Axatilimab 0.3 mg/kg Q2W (n=79)		Axatilimab 1.0 mg/kg Q2W (n=81)		Axatilimab 3.0 mg/kg Q4W (n=79)	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Viral infection	33 (42)	10 (13)	34 (42)	12 (15)	30 (38)	12 (15)
COVID-19*	13 (16)	3 (4)	19 (23)	6 (7)	12 (15)	7 (9)
EBV	0	0	0	0	4 (5)	1 (1)
CMV†	0	0	1 (1)	0	2 (3)	0
Bacterial infection	10 (13)	5 (6)	12 (15)	6 (7)	12 (15)	6 (8)
Fungal infection	3 (4)	0	7 (9)	3 (4)	6 (8)	0
Invasive fungal‡	0	0	3 (4)	2 (2)	0	0
Mycobacterial infection	1 (1)	1 (1)	0	0	0	0
Unspecified pathogen§	43 (54)	10 (13)	39 (48)	17 (21)	33 (42)	12 (15)
Pneumonia	9 (11)	8 (10)	12 (15)	7 (9)	8 (10)	5 (6)
Treatment-related infections	15 (19)	6 (8)	19 (23)	11 (14)	11 (14)	6 (8)

CMV, cytomegalovirus; EBV, Epstein-Barr virus; Q2W, every 2 weeks; Q4W, every 4 weeks.
Safety population includes all patients who received ≥1 dose of axatilimab.
* Includes COVID-19 pneumonia. † Includes CMV infection, CMV infection reactivation, and cytomegaloviral pneumonia. ‡ Includes bronchopulmonary aspergillosis or *Aspergillus* infection. § Includes infections with unspecified etiology.

Conclusions

- **Responses were noted in all fibrosis-dominant organs**
- **Clinical activity in fibrosis-dominant organs is supported by clinician-reported changes and patient-reported reductions in organ-specific symptom burden**
- **Axatilimab had a generally well-tolerated safety profile**
  - **Opportunistic infections, which are typically common in patients with cGVHD under heavy immunosuppression, were infrequent**

Disclosures

CLK served as an advisory committee member for Horizon Therapeutics and Incyte Corporation. CC served as a consultant for Astellas, Incyte Corporation, Inhibrx, Rigel Pharmaceuticals, Sanofi, and Syndax Pharmaceuticals; served as a data safety monitoring board member for AlloVir and Pluristem Therapeutics; and served as a board of directors/advisory committee member for Cimeio Therapeutics and Oxford Immune Algorithmics. ZD served as a consultant for Incyte Corporation, Inhibrx, MorphoSys, Ono Pharmaceuticals, PharmaBiome AG, and Sanofi; received honoraria from Incyte Corporation and MorphoSys; and received research funding from Incyte Corporation, Regimmune, and Taiho Oncology. SJL received research funding from Amgen, AstraZeneca, Incyte Corporation, Kadmon, Pfizer, and Syndax Pharmaceuticals; served as a consultant for Equillium, Incyte Corporation, Kadmon, Mallinckrodt, and Novartis; received study medication from Janssen; and served as a steering committee member for Novartis and Sanofi. WI received honoraria from Medac Pharma and served as an advisory board member for Gilead, Novartis, Roche, Sobi, and Synairgen. JW received honoraria from Novartis and Sanofi. HS received personal fees from Incyte Corporation, Janssen, Novartis, Sanofi, and the Belgian Hematological Society (BHS) and research grants from Novartis and BHS, all paid to her institution. She also received nonfinancial support (travel grants) from Gilead, Pfizer, EBMT, and Center for International Blood and Marrow Transplant Research (CIBMTR). LS, SS, and A. Shimoni have no disclosures to report. DW received honoraria from Behring, Gilead, Incyte Corporation, Mallinckrodt, Novartis, Sanofi, and Takeda and received research funding from Novartis. BT and CT are employees and shareholders of Incyte Corporation. VR is an employee and shareholder of Syndax Pharmaceuticals. A. Salhotra received research funding from Bristol Myers Squibb, Gilead, Jazz Pharmaceuticals, Kura Oncology, Orca Bio, and Rigel Pharmaceuticals; served as a speakers bureau member for Sanofi; and served as a board of directors/advisory committee member for Swedish Orphan Biovitrum. JAP-S served as a consultant for Incyte Corporation, Novartis, and Sanofi.

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