PF1035

Dynamics of Overall and Organ-Specific Responses to Axatilimab in Chronic Graft-Versus-Host Disease: Analysis From the AGAVE-201 Study

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Introduction

- Chronic graft-versus-host disease (cGVHD) is characterized by inflammatory and fibrotic pathology affecting multiple organs and leading to substantial impairment[1-3]
- Axatilimab, an anti–colony-stimulating factor 1 receptor monoclonal antibody, targets monocytes and macrophages that are critical for inflammation and fibrosis in cGVHD[4]
- In the pivotal AGAVE-201 study (NCT04710576), axatilimab 0.3 mg/kg once every 2 weeks (Q2W) had robust clinical activity and was generally well tolerated in patients with cGVHD, with treatment-related adverse events that were mostly low grade and reversible[5]
- Dynamics of clinical responses and symptom improvements following axatilimab treatment for cGVHD need further investigation

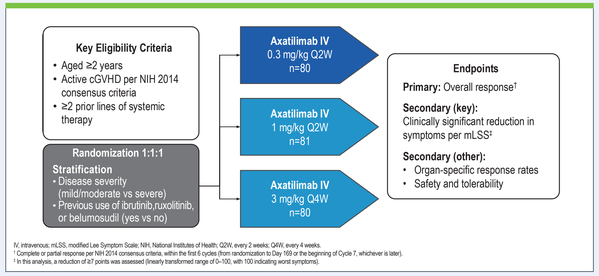
Objective

- To assess the timing/dynamics of clinical responses and symptom improvements among patients with cGVHD who achieved responses with axatilimab in AGAVE-201

Methods

- AGAVE-201 was a phase 2, open-label, multicenter, randomized study to evaluate safety and efficacy of axatilimab in patients with recurrent/refractory cGVHD (**Figure 1**)
- This analysis focuses on patients who achieved overall, organ-specific, or modified Lee Symptom Scale (mLSS) responses

Figure 1. AGAVE-201 Study Design



IV, intravenous; mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health; Q2W, every 2 weeks; Q4W, every 4 weeks.
† 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).
‡ In this analysis, a reduction of ≥7 points was assessed (linearly transformed range of 0–100, with 100 indicating worst symptoms).

- Cumulative incidences of clinical responses per National Institutes of Health (NIH) 2014 consensus criteria (overall and organ-specific) and a ≥7-point improvement in mLSS summary score (threshold considered to be clinically meaningful) were assessed among patients who achieved a response
- Comparisons of time to response (TTR) for 2014 NIH consensus criteria and individual mLSS items (**Table 1**) were assessed among patients with both responses

Table 1. Organ-Specific mLSS Assessments

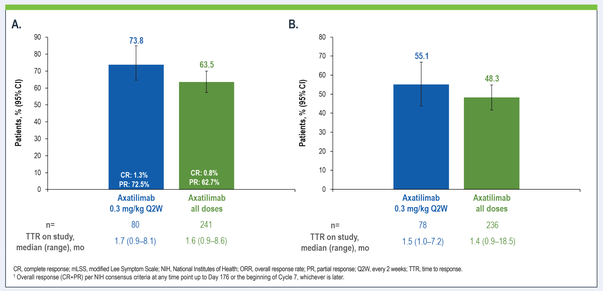
Organ	Patient-reported mLSS assessments† (≥1-point improvement)
Esophagus	• Swallowing liquids • Swallowing solids
Eyes	• Visual clarity • Eye dryness
Joints/fascia	• Joint/muscle aches • Joint movement
Lung	• Shortness of breath at rest • Shortness of breath with exercise
Mouth	• Oral ulcers
Skin	• Skin thickening

mLSS, modified Lee Symptom Scale.
† mLSS items are not validated as single measures.

Results

- AGAVE-201 met its primary endpoint, with an overall response rate by NIH consensus criteria in the 0.3 mg/kg Q2W group of 73.8% at any time up to 6 months (**Figure 2A**); the key secondary endpoint was also met, with 55.1% of patients having a ≥7-point improvement in mLSS (**Figure 2B**)

Figure 2. (A) ORR† and (B) ≥7-Point Improvement in mLSS in the First 6 Cycles in AGAVE-201



CR, complete response; mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health; ORR, overall response rate; PR, partial response; Q2W, every 2 weeks; TTR, time to response.
† Overall response (CR+PR) per NIH consensus criteria at any time point up to Day 176 or the beginning of Cycle 7, whichever is later.

- Demographics and baseline characteristics (**Table 2**) were similar across treatment groups and between responders and the overall patient population

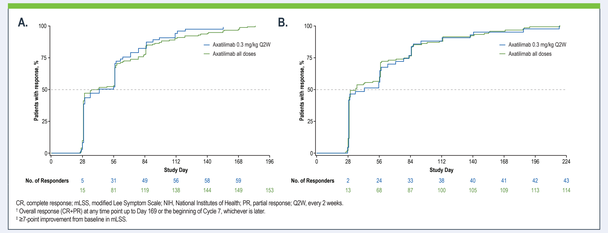
Table 2. Patient Demographics and Baseline Characteristics

Characteristic	Responders† (n=153)	All patients (N=241)
Age, median (range), y	52.0 (7–76)	53.0 (7–81)
Male, n (%)	95 (62.1)	151 (62.7)
Race, n (%)		
White	133 (86.9)	200 (83.0)
Asian	7 (4.6)	16 (6.6)
Black	1 (0.7)	5 (2.1)
Not reported	10 (6.5)	16 (6.6)
Other‡	2 (1.3)	4 (1.7)
Ethnicity, n (%)		
Not Hispanic or Latino	132 (86.3)	215 (89.2)
Hispanic or Latino	17 (11.1)	19 (7.9)
Not reported/unknown	4 (2.6)	7 (2.9)
Prior cGVHD therapy, n (%)	130 (85.0)	204 (84.6)
Ruxolitinib	117 (76.5)	179 (74.3)
Ibrutinib	53 (34.6)	75 (31.1)
Belumosudil	30 (19.6)	56 (23.2)
Number of organs involved at baseline, median (maximum)	4.0 (8)§	4.0 (8)§
Involved organs, n (%)		
Skin	130 (85.0)	193 (80.1)
Eyes	121 (79.1)	183 (75.9)
Joints and fascia	117 (76.5)	162 (67.2)
Mouth	75 (49.0)	112 (46.5)
Lungs	65 (42.5)	108 (44.8)
Esophagus	44 (28.8)	61 (25.3)
Liver	28 (18.3)	40 (16.6)
Upper GI	23 (15.0)	28 (11.6)
Lower GI	17 (11.1)	18 (7.5)
Time from cGVHD diagnosis to randomization, median (range), y	4.0 (0.4–17.6)	4.0 (0.4–17.6)
Severe disease, n (%)	121 (79.1)	192 (79.7)

C, cycle; cGVHD, chronic graft-versus-host disease; D, day; GI, gastrointestinal; Q2W, every 2 weeks; Q4W, every 4 weeks.
† Subgroup comprises patients who achieved overall response within the first 6 treatment cycles.
‡ Includes American Indian or Alaskan Native, and Native Hawaiian or Pacific Islander.
§ No patients in the study had 0 organs involved. Data on organ involvement were not available for 2 patients: 1 patient randomized to 0.3 mg/kg dose Q2W due to a serious adverse event that resulted in that patient's withdrawal of consent before C1D1, and 1 patient randomized to 3 mg/kg Q4W who had a baseline assessment on C1D7.

- Most patients who achieved an overall clinical response (**Figure 3A**) and/or ≥7-point improvement in mLSS (**Figure 3B**) in the first 6 treatment cycles did so by Day 56

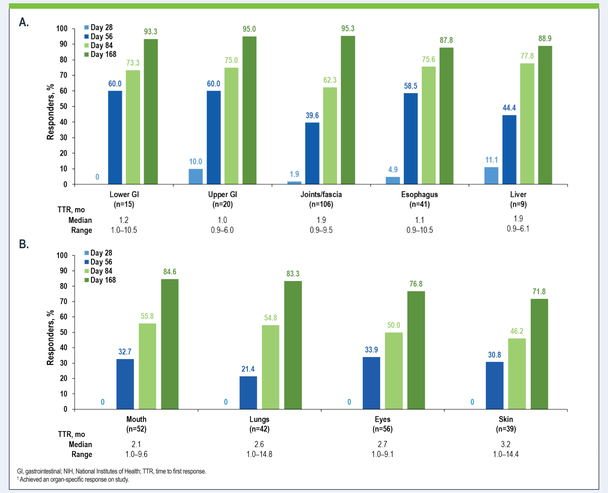
Figure 3. Time to (A) Overall NIH† and (B) mLSS‡ Responses in Cycles 1–6



CR, complete response; mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health; PR, partial response; Q2W, every 2 weeks.
† Overall response (CR+PR) at any time point up to Day 169 or the beginning of Cycle 7, whichever is later.
‡ ≥7-point improvement from baseline in mLSS.

- The lower GI, upper GI, joints/fascia, esophagus, and liver were fastest to respond to treatment (**Figure 4A**), with median TTR ranging between 1.0 and 1.9 months
- Mouth, lungs, eyes, and skin were slower to respond to treatment (**Figure 4B**), with median TTR ranging between 2.1 and 3.2 months

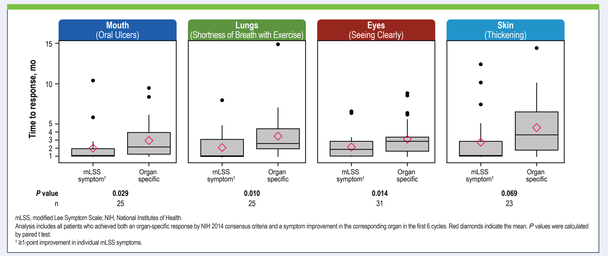
Figure 4. NIH 2014 Organ-Specific Responders† (All Axatilimab Doses) Stratified by (A) Faster and (B) Slower Organ-Specific Responses



GI, gastrointestinal; NIH, National Institutes of Health; TTR, time to first response.
† Achieved an organ-specific response on study.

- Symptom and functional improvements in organs that were slower to respond were substantially more rapid relative to their corresponding time to organ-specific NIH clinical response (**Figure 5**)
- Differences between clinical response and symptom improvements were not as substantial for limited joint movement, joint/muscle aches, difficulty swallowing liquids/solid foods, dry eyes, or shortness of breath at rest (data not shown)

Figure 5. Timing of Symptom Improvement Compared With Organ-Specific NIH Response (All Axatilimab Doses)



mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health.
Analysis includes all patients who achieved both an organ-specific response by NIH 2014 consensus criteria and a symptom improvement in the corresponding organ in the first 6 cycles. Red diamonds indicate the mean. *P* values were calculated by paired *t* test.
† ≥1-point improvement in individual mLSS symptoms.

- Similar to the overall patient population, the safety profile of axatilimab in responders was dose dependent (**Table 3**)

Table 3. Safety in Responders†

n (%)	Axatilimab 0.3 mg/kg Q2W (n=59)	Axatilimab 1 mg/kg Q2W (n=54)	Axatilimab 3 mg/kg Q4W (n=40)
TEAE (all grade)	58 (98.3)	53 (98.1)	39 (97.5)
Grade ≥3	28 (47.5)	34 (63.0)	26 (65.0)
TRAEs	42 (71.2)	46 (85.2)	34 (85.0)
Grade ≥3	10 (16.9)	21 (38.9)	17 (42.5)
TEAEs of special interest‡	41 (69.5)	42 (77.8)	28 (70.0)
Grade ≥3	13 (22.0)	20 (37.0)	13 (32.5)
Serious TEAEs	21 (35.6)	24 (44.4)	17 (42.5)
Fatal TEAEs§	0	5 (9.3)	1 (2.5)
TEAEs leading to dose modifications			
Discontinuations	3 (5.1)	16 (29.6)	2 (5.0)
Interruptions	24 (40.7)	20 (37.0)	14 (35.0)
Reductions	4 (6.8)	5 (9.3)	9 (22.5)

Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
Safety population includes all patients who received ≥1 dose of axatilimab.
† Subgroup comprises patients who achieved overall response within the first 6 treatment cycles.
‡ Included infusion-related reactions (eg, hypersensitivity reactions) and infections.
§ 1 mg/kg Q2W: sudden cardiac death, bronchopulmonary aspergillosis, recurrent leukemia, pneumonia (n=2), sepsis; 3 mg/kg Q4W: respiratory syncytial viral pneumonia.

Conclusions

- **In the pivotal AGAVE-201 study, axatilimab 0.3 mg/kg Q2W yielded high response rates and was generally well tolerated in patients with cGVHD**
- **Median times to organ-specific responses with axatilimab ranged from 1.0 to 3.2 months across organs**
  - **Lower GI, upper GI, esophagus, liver, and joints/fascia were fastest to respond, whereas lung, mouth, eye, and skin responses were slower, likely due to fibrotic manifestations**
- **Improvements in specific cGVHD symptoms associated with the lungs, mouth, eyes, and skin were more rapid than the respective organ-specific responses by NIH 2014 response criteria**
- **Overall, these data highlight the potential for rapid onset of clinical activity and symptom improvement with axatilimab in inflammatory and fibrotic manifestations of cGVHD among a heavily pretreated population with long-standing cGVHD**

Disclosures

AS received research funding from Bristol Myers Squibb, Orca Bio, and Rigel Pharmaceuticals and served as a speakers bureau member for Sanofi and Incyte Corporation. HC has received research funding from National Institutes of Health National Cancer Institute; has received honoraria from AbbVie, MJH Life Sciences, and OrcaBio; has received travel support from Actinium Pharmaceuticals; and has served as a consultant and board of directors/advisory committee member and received equipment, materials, or drugs to her institution from Incyte Corporation, Ironwood, Regimmune, and Sanofi. NF has served as a consultant for Sanofi and Omeros; served as a member of advisory committee for Incyte Corporation; and served as a speakers bureau member for Incyte, medical monitor for Blood and Marrow Clinical Trial Network (BMT CTN), and DSMB member for Chronic GVHD Consortium. MK has served as a speakers bureau member for Gilead, Pfizer, and Jazz Pharmaceuticals and served as member of an advisory committee for Sanofi. BT, CT, and SL are employees and shareholders of Incyte Corporation. VR was an employee and shareholder of Syndax Pharmaceuticals at the time the work was completed. DW received honoraria from Behring, Gilead, Incyte Corporation, Mallinckrodt, Novartis, Sanofi, and Takeda and received research funding from Novartis. SJL received research funding from AstraZeneca, Incyte Corporation, Pfizer, and Sanofi; served as a consultant for Incyte Corporation, Sanofi, and Novartis; received study medication from Janssen; and served as a steering committee member for Novartis and Sanofi.

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