

Efficacy and Safety of Axatilimab at 3 Different Doses in Patients with Chronic Graft-Versus-Host Disease (cGVHD) and Related Bronchiolitis Obliterans Syndrome (BOS): Results of a Pivotal Phase 2 Study

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BACKGROUND

BOS, the only recognized lung manifestation of cGVHD, affects up to 10% of all recipients of allogeneic hematopoietic stem cell transplantation and has poor prognosis, with a 5-year overall survival rate of approximately 50%¹

Available cGVHD treatments have limited activity in BOS^{2,3}; thus, there is an urgent need for novel, well-tolerated treatments that can stabilize or reverse disease-associated pathology and improve quality of life²

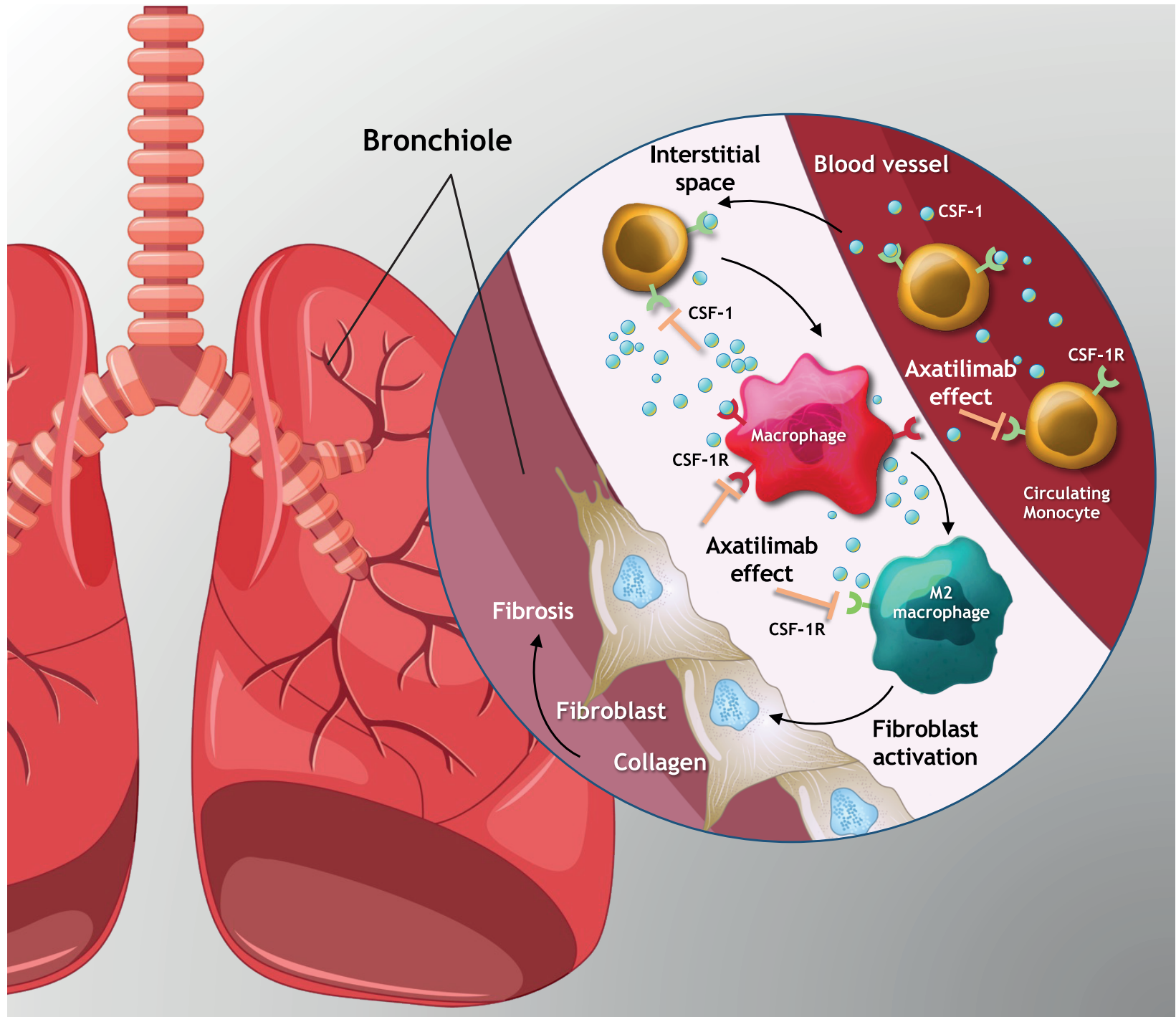
Colony stimulating factor-1 receptor (CSF-1R) signaling is a key regulator of pathogenic macrophages; preclinical data indicated CSF-1R blockade ameliorated BOS⁴

Activity of axatilimab, a humanized anti-CSF-1R monoclonal antibody (Figure 1), in cGVHD and related BOS was previously shown in a phase 1/2 study (NCT03604692)^{5,6}

In AGAVE-201, a pivotal phase 2, open-label, randomized, multicenter study of axatilimab in patients with recurrent/refractory cGVHD (NCT04710576), treatment with axatilimab given at a dose of 0.3 mg/kg intravenously (IV) every 2 weeks (Q2W) resulted in a cGVHD overall response rate (ORR) of 74% and the best safety profile among the 3 doses tested⁷

Here, we present a subgroup analysis of the efficacy and safety of axatilimab treatment in patients with cGVHD-related BOS enrolled in AGAVE-201 at all 3 dose levels

Figure 1. Mechanism of action of axatilimab



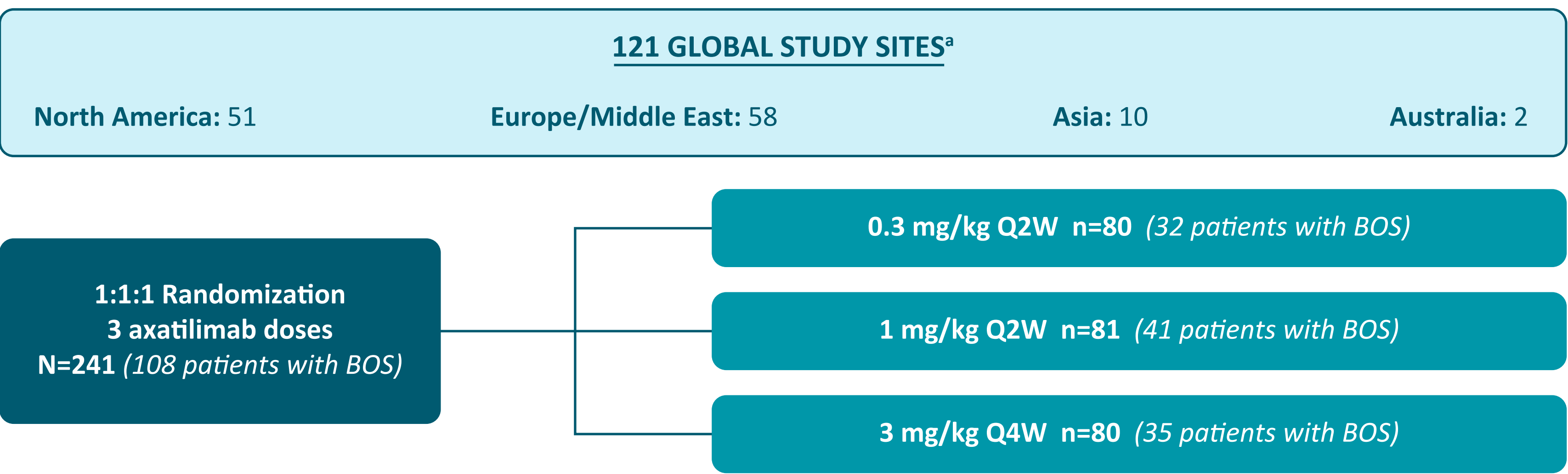
CSF-1, colony stimulating factor-1; CSF-1R, colony stimulating factor-1 receptor.

METHODS

AGAVE-201 was conducted at 121 sites across the world (Figure 2)

Overall, 241 patients were randomized 1:1:1 to receive IV axatilimab at:
– 0.3 mg/kg Q2W (n=80)
– 1 mg/kg Q2W (n=81)
– 3 mg/kg every 4 weeks (Q4W, n=80)

Figure 2. Study sites and cohort overview for AGAVE-201



BOS, bronchiolitis obliterans syndrome; Q2W, every 2 weeks; Q4W, every 4 weeks.

*Clinical trial sites were located in the United States, Canada, the United Kingdom, Belgium, France, Germany, Italy, Poland, Spain, Greece, Israel, Taiwan, Singapore, South Korea, and Australia.

cGVHD-associated BOS diagnosis and response criteria followed the 2014 National Institutes of Health (NIH) cGVHD Consensus:
– Diagnosis criteria: obstructive lung defect with forced expiratory volume in 1 second (FEV₁) <75% predicted, ratio of FEV₁ to vital capacity (FEV₁/VC) <0.7, evidence of air trapping, and absence of an infection⁸
– There were no restrictions on percent predicted FEV₁ in the inclusion criteria for this study, and patients with BOS of any severity were included
– Response criteria: either ≥10% absolute improvement in percent predicted FEV₁ or NIH lung symptom score improvement by 1 point⁹

The primary efficacy endpoint was cGVHD ORR in the first 6 cycles (24 weeks)

Exploratory subgroup analysis endpoints included BOS response and time to first BOS response, and improvements in shortness of breath (SOB) symptoms and percent predicted FEV₁

Safety endpoints included frequency and severity of treatment-emergent adverse events (TEAEs)

BASELINE CHARACTERISTICS

For the overall population (N=241), the median age was 53 years (range, 7–81 years) and 63% (151/241) were male

BOS was present in 45% (108/241) patients enrolled in AGAVE-201 (Table 1)

Table 1. Baseline demographic and pretreatment characteristics of patients in AGAVE-201

Patient characteristic	Overall population (N=241)	Patients with BOS (n=108)		
		0.3 mg/kg Q2W (n=32)	1 mg/kg Q2W (n=41)	3 mg/kg Q4W (n=35)
Number of prior systemic cGVHD therapies, median (range)	4 (2–15)	4 (2–10)	4 (2–10)	4 (2–12)
Number of organs involved, median (maximum)	4 (8)	4 (8)	4 (7)	4 (7)
≥4 organs involved, n (%)	130 (54)	19 (59)	26 (63)	21 (60)
Lung involvement at baseline, n (%)	108 (45)	32 (100)	41 (100)	35 (100)
FEV ₁ ≤39% ^a	36 (39)	14 (47)	15 (42)	7 (26)
NIH cGVHD lung symptom score of ≥3 ^{b,c}	26 (25)	8 (25)	10 (26)	8 (23)

BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; FEV₁, forced expiratory volume in 1 second; NIH, National Institutes of Health; Q2W, every 2 weeks; Q4W, every 4 weeks.

^aAmong patients with lung involvement and corresponding percent predicted FEV₁ at baseline.

^bSevere lung symptoms (shortness of breath at rest, requiring oxygen) related to cGVHD per the 2014 organ scoring of cGVHD developed by the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease.⁸

^cAmong patients with lung involvement and corresponding NIH lung symptom score >0 at baseline.

ORR AND BOS RESPONSE

The primary ORR endpoint was met in all cohorts
– ORR and BOS response rate were highest at the 0.3 mg/kg dose (Table 2)
– The median time to first BOS response was <3 months

Table 2. Efficacy endpoints

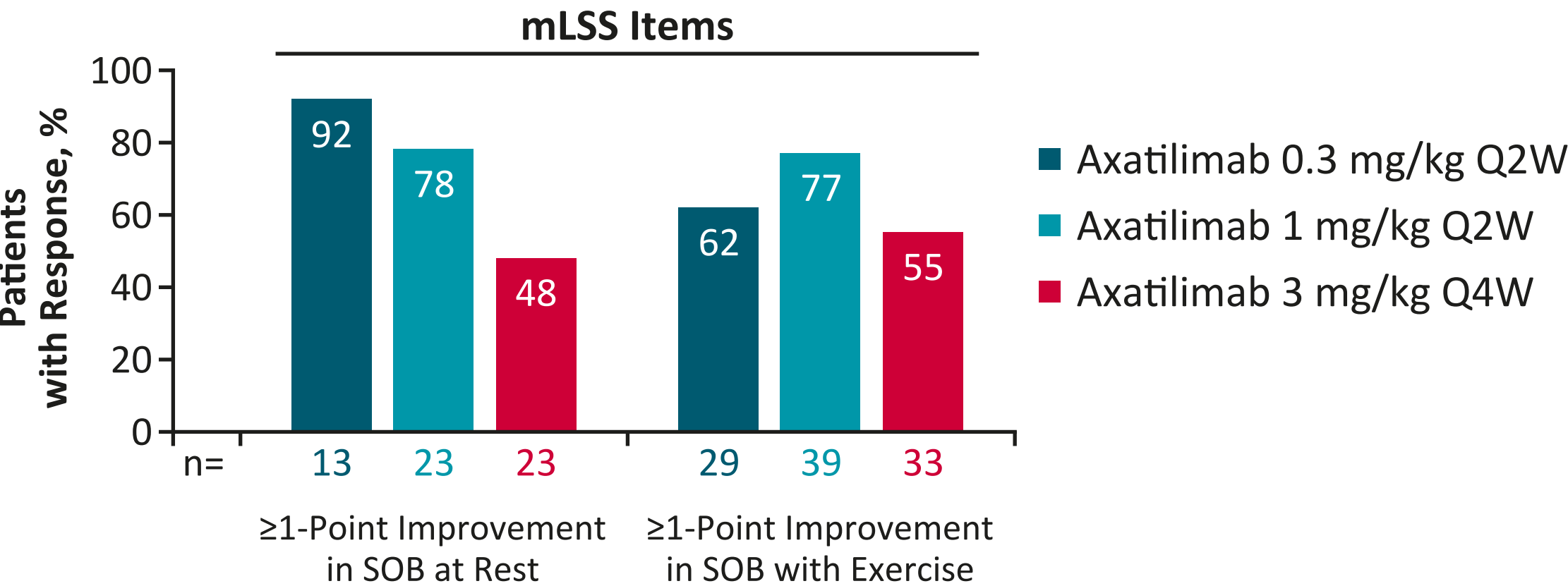
Population and endpoints	0.3 mg/kg Q2W	1 mg/kg Q2W	3 mg/kg Q4W
Overall population, n	80	81	80
ORR, n (%)	59 (74)	54 (67)	40 (50)
Population and endpoints	0.3 mg/kg Q2W	1 mg/kg Q2W	3 mg/kg Q4W
Patients with baseline BOS, n	32	41	35
BOS response, n (%)	15 (47)	14 (34)	13 (37)

BOS, bronchiolitis obliterans syndrome; ORR, overall response rate; Q2W, every 2 weeks; Q4W, every 4 weeks.

PATIENT-REPORTED IMPROVEMENT

A ≥1-point (i.e., clinically meaningful^{9,10}) improvement in the modified Lee Symptom Scale was observed for SOB at rest, and improvement in SOB with exercise, in each cohort (Figure 3)

Figure 3. Patient-reported improvement in shortness of breath^a



mLS, modified Lee Symptom Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SOB, shortness of breath.

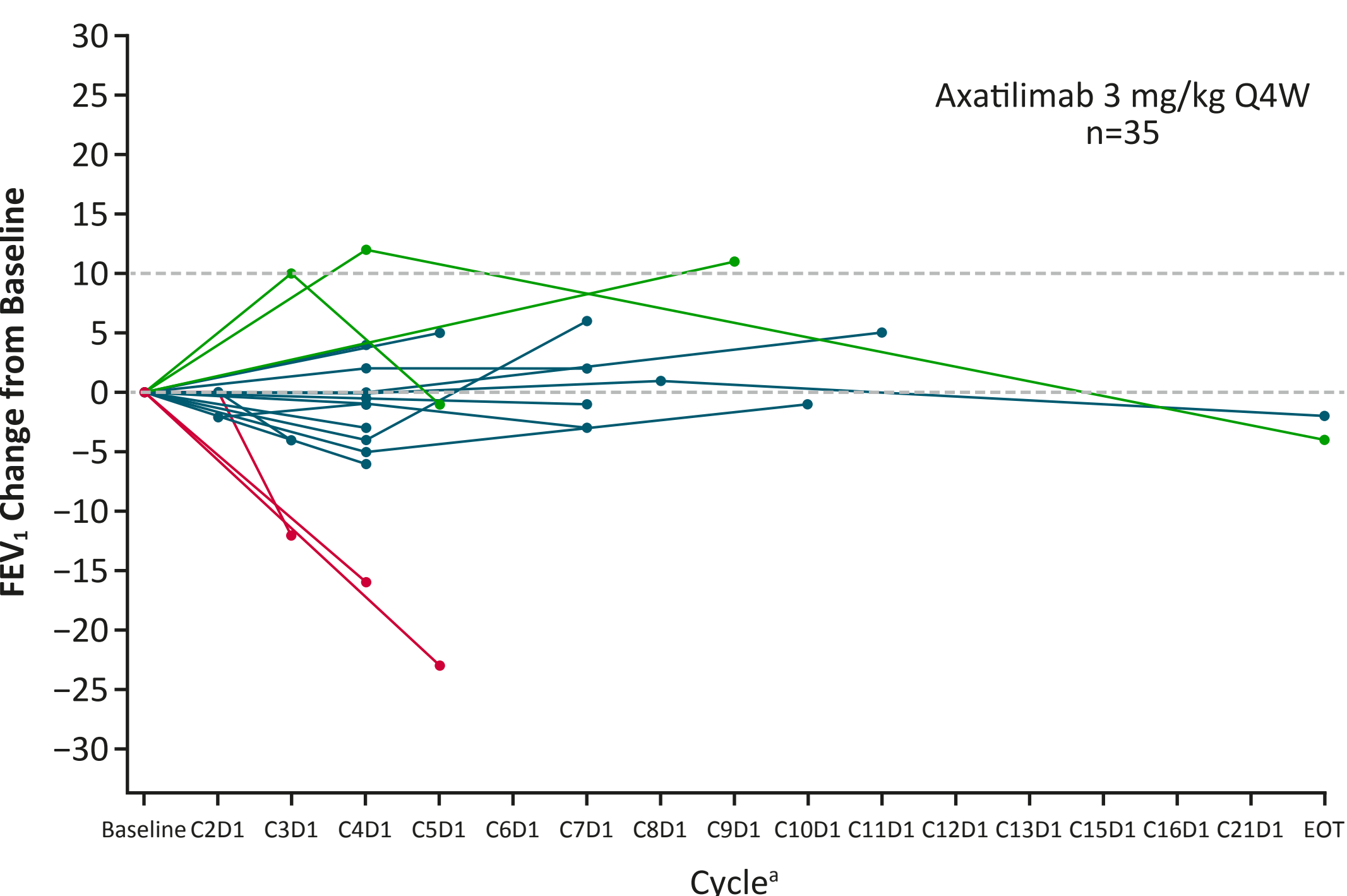
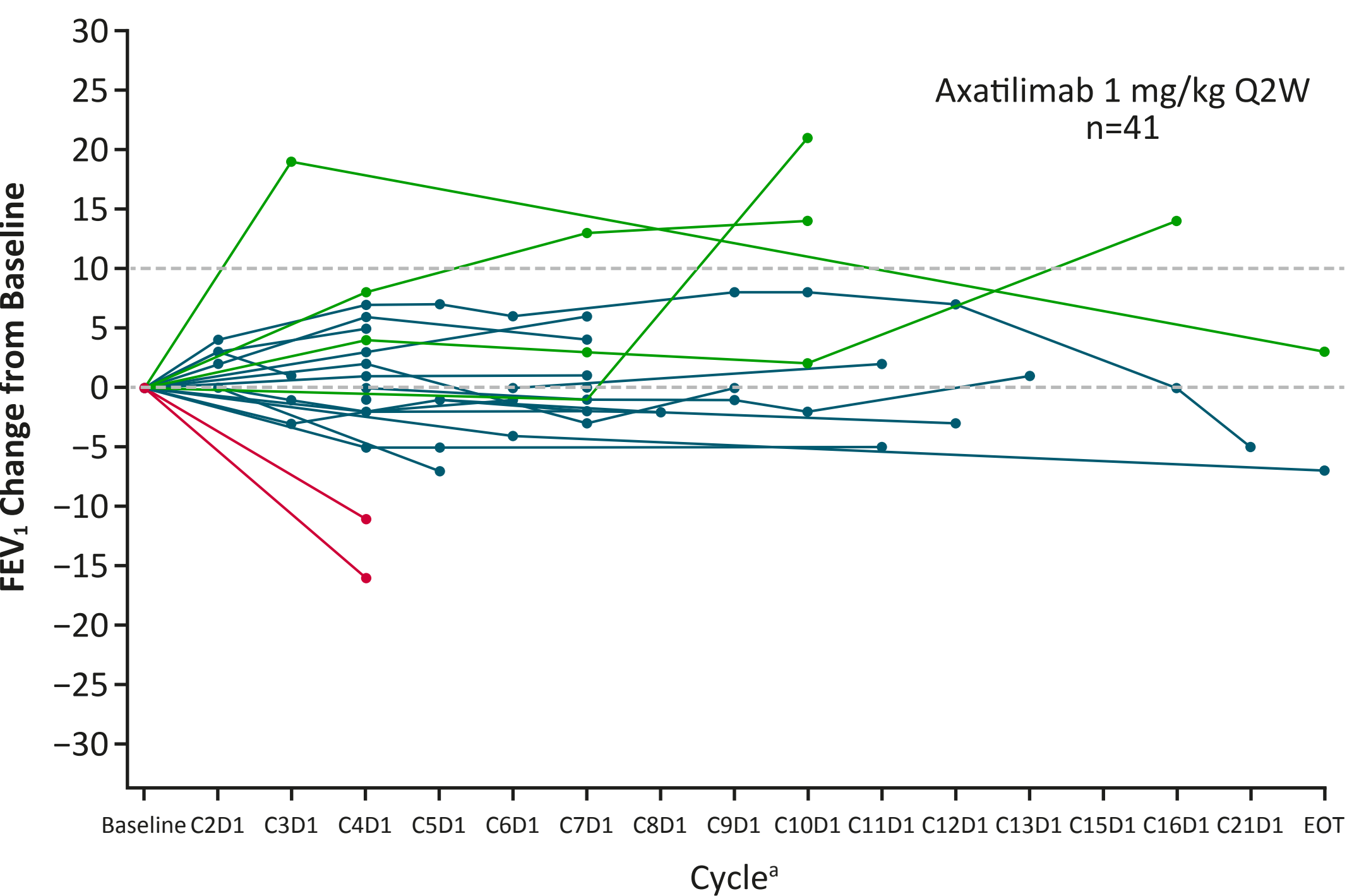
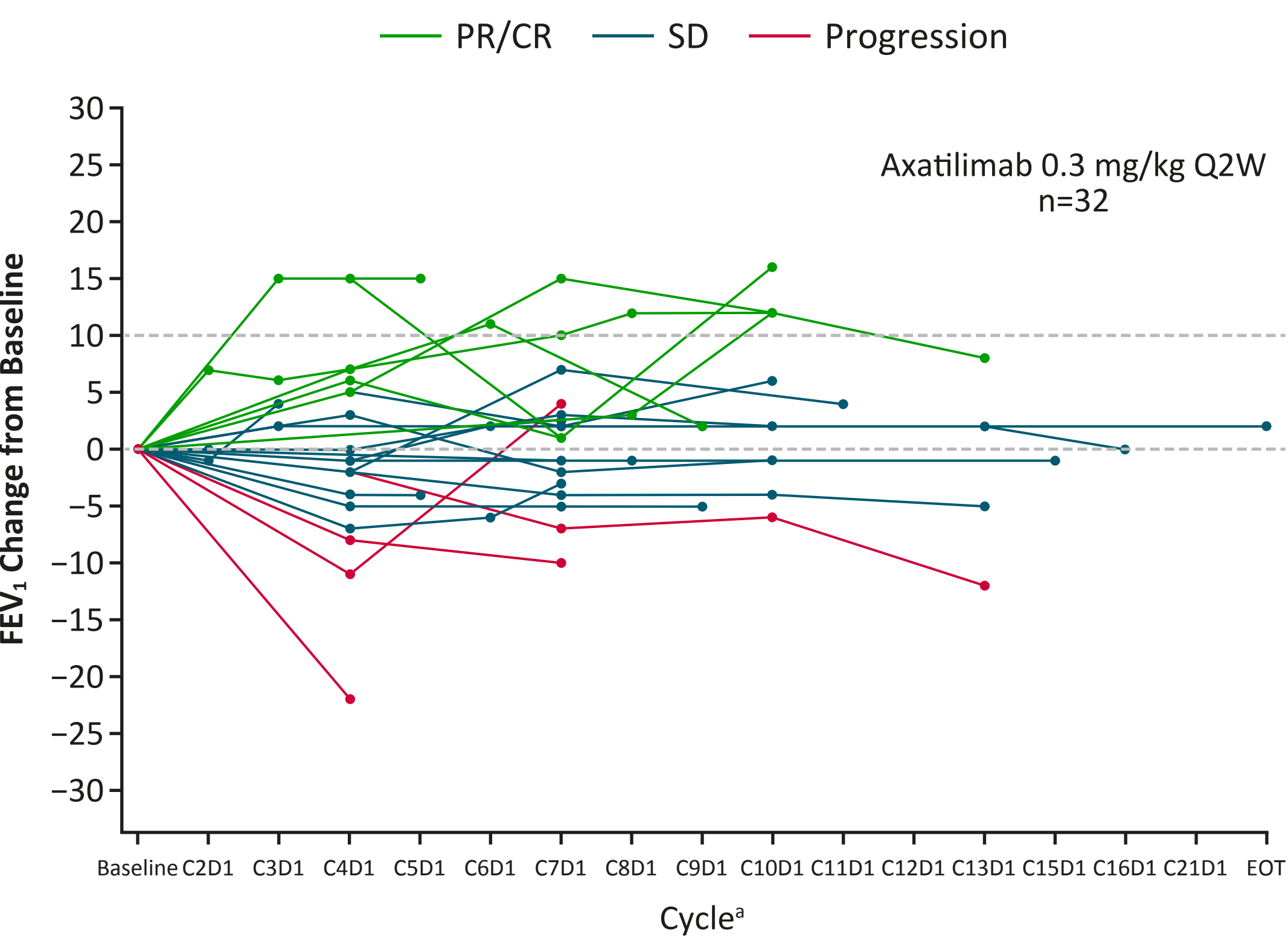
^aCombined mLS items with a score range of 0–4. Denominator is the number of patients with corresponding lung involvement who had an assessment at baseline.

RESULTS

IMPROVEMENT IN PERCENT PREDICTED FEV₁

Improvement in percent predicted FEV₁ was observed in all cohorts (Figure 4)

Figure 4. FEV₁ responses (change from baseline) to axatilimab in all dose cohorts



C, cycle; CR, complete response; D, day; EOT, end of treatment; FEV₁, forced expiratory volume in 1 second; IV, intravenous; PR, partial response; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, stable disease.

^aOne cycle equals 28 days.

Percent predicted FEV₁ values were prioritized for response assessment when available.

SAFETY PROFILE OF AXATILIMAB

TEAE-driven axatilimab discontinuation occurred in 3% (1/31) of patients in the 0.3 mg/kg cohort and 16% (17/108) of all study patients evaluable for safety (Table 3)

TEAEs were dose-dependent in frequency and severity
– Most TEAEs were laboratory abnormalities and consistent with on-target effects of CSF-1R blockade

COVID-19 infections were frequently observed, but did not result in any deaths

Table 3. Overview of safety profile of axatilimab among patients with BOS in AGAVE-201

Adverse event ^a , n (%)	Overall population with BOS (n=108)	0.3 mg/kg Q2W (n=32)	1 mg/kg Q2W (n=41)	3 mg/kg Q4W (n=35)
Any	106 (98)	31 (97)	40 (98)	35 (100)
Grade ≥3	76 (70)	18 (56)	31 (76)	27 (77)
Fatal	11 (10)	1 (3)	6 (15)	4 (11)

TEAEs^b in ≥20% excluding infections and laboratory abnormalities, any grade

Fatigue	22 (20)	7 (22)	9 (22)	6 (17)
Key infections, any grade				
COVID-19	18 (17)	5 (16)	8 (20)	5 (14)
COVID-19 pneumonia	3 (3)	0 (0)	1 (2)	2 (6)
Pneumonia	24 (22)	8 (25)	10 (24)	6 (17)
Upper respiratory tract infection	19 (18)	7 (22)	8 (20)	4 (11)

CSF-1R blockade-driven abnormalities, any grade

Periorbital edema	20 (19)	0 (0)	9 (22)	11 (31)
Laboratory-based abnormalities				
CPK increased	37 (34)	2 (6)	14 (34)	21 (60)
AST increased	35 (32)	4 (13)	15 (37)	16 (46)
Lactate dehydrogenase increased	32 (30)	5 (16)	12 (29)	15 (43)
Lipase increased	28 (26)	0 (0)	11 (27)	17 (49)
ALT increased	27 (25)	4 (13)	11 (27)	12 (34)
Amylase increased	22 (20)	0 (0)	5 (12)	17 (49)

Infusion-related reaction, any grade	4 (4)	3 (9)	1 (2)	0 (0)
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Grade ≥3 TEAEs in ≥5% of overall BOS population

Pneumonia	17 (16)	7 (22)	6 (15)	4 (11)
CPK increased	8 (7)	0 (0)	2 (5)	6 (17)
Respiratory failure	8 (7)	3 (9)	2 (5)	3 (9)
COVID-19	7 (7)	1 (3)	4 (10)	2 (6)
Hypertension	5 (5)	2 (6)	2 (5)	1 (3)
Dyspnea	5 (5)	2 (6)	1 (2)	2 (6)
Leading to dose reduction	13 (12)	3 (9)	4 (10)	6 (17)
Leading to discontinuation of axatilimab	17 (16)	1 (3)	8 (20)	8 (23)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOS, bronchiolitis obliterans syndrome; CPK, blood creatine phosphokinase; CSF-1R, colony stimulating factor-1 receptor; Q2W, every 2 weeks; Q4W, every 4 weeks;

TEAE, treatment-emergent adverse event.

^aThe safety analysis set consisted of all enrolled patients who received ≥1 dose of axatilimab during the study.

^bTEAEs listed by MedDRA system organ class and preferred term version 24.0.

LIMITATIONS

All patients received IV axatilimab and no comparator drug or placebo was included in the study design, which may have introduced investigator or patient-reporting bias for outcomes

The COVID-19 pandemic limited the ability for consistent pulmonary function test monitoring during the study

CONCLUSIONS

Treatment with axatilimab 0.3 mg/kg Q2W demonstrated high ORR, rapid BOS response, and a manageable safety profile in cGVHD and BOS
– Axatilimab demonstrated rapid onset and a robust BOS response rate of 47% (0.3 mg/kg Q2W dose)
– Response rate was higher than that observed with other treatments for cGVHD or chronic lung allograft dysfunction–related BOS^{3,12,13} despite inclusion of large proportion of patients with severe BOS commonly excluded from participation in other studies^{14,15}

Most patients with BOS receiving axatilimab reported clinically meaningful improvements in symptoms of SOB at rest or with exertion

The safety profile of axatilimab in patients with BOS is consistent with that reported for the entire cGVHD cohort and similar to patients without lung cGVHD involvement

Infection rates were comparable with other cGVHD approved modalities^{3,16–18}

Observed antifibrotic activity of axatilimab at the 0.3 mg/kg Q2W dose supports its evaluation in the ongoing phase 2 study in idiopathic pulmonary fibrosis (NCT06132256)

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