Safety, Tolerability, and Efficacy of Axatilimab, a Colony-Stimulating Factor 1 Receptor (CSF-1R) Humanized Antibody, in Advanced Chronic Graft-versus-host Disease–Related Bronchiolitis Obliterans Syndrome

Vedran Radojcic, MD; Carrie L. Kitko, MD; Antonio Di Stasi, MD; Mukta Arora, MD, MS; Mohammad Abu Zaid, MD; Michael L. Meyers, MD, PhD; Peter Ordentlich, PhD; Timothy O'Toole, MS; Yifan Huang, PhD; Bruce R. Blazar, MD; Trent P. Wang, DO; Amandeep Salhotra, MD; Iskra Pusic, MD; Stephanie J. Lee, MD, MPH; and Zachariah DeFilipp, MD

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Disclosures

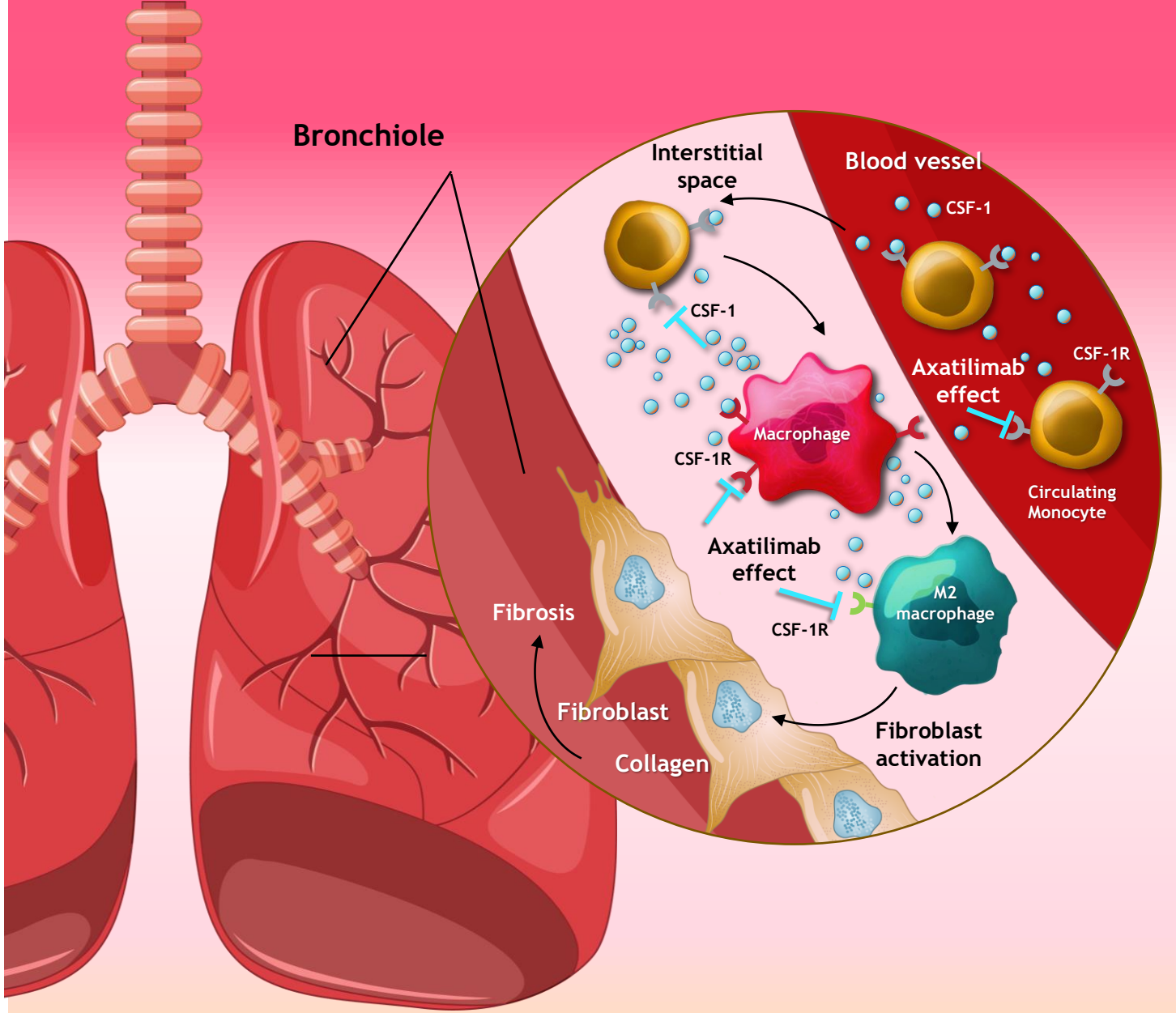
- The presenting author has stock options in and is a full-time employee of Syndax Pharmaceuticals

Background

- BOS is a difficult-to-treat manifestation of cGVHD with a poor prognosis[1]
- CSF-1/CSF-1R signaling is a key regulator of fibrosis-mediating macrophages[2]
- In preclinical studies, CSF-1R blockade ameliorated BOS[2]
- Axatilimab is an investigational humanized monoclonal antibody that inhibits CSF-1R signaling and may control fibrosis in BOS

BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; CSF-1R, colony-stimulating factor 1 receptor.

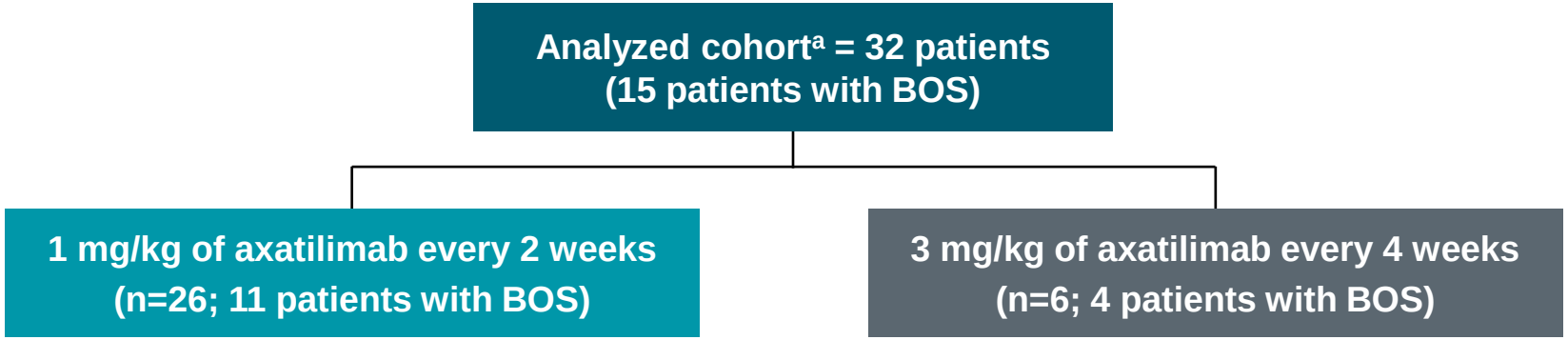
1. Chien et al. *Biol Blood Marrow Transplant.* 2010;16:S106-S114. **2.** Alexander et al. *J Clin Invest*. 2014;10:4266-4680. **3.** MacDonald et al. *Blood.* 2017;129:13-21.



Mechanism of action of axatilimab.[3]

Study Design and Methods

The phase 1/2 study evaluated safety and efficacy in patients with cGVHD (NCT03604692)[1]



- Doses described in this study are currently being evaluated in phase 2 AGAVE-201 study (NCT04710576)
- BOS definition followed the NIH cGVHD criteria[2]: obstructive lung defect with FEV_1 <75% predicted, FEV_1/VC <0.7, evidence of air trapping, and absence of an infection
- BOS response was defined by the NIH consensus criteria as either[3]:
  - ≥10% absolute improvement in percent predicted FEV_1
  - Lung symptom score improvement by 1 point
- BOS response and time to first BOS response were evaluated

AE, adverse event; BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; FEV_1, forced expiratory volume in 1 second; HCT, hematopoietic cell transplantation; NIH, National Institutes of Health; ORR, overall response rate; VC, vital capacity. [a]Cohort presented here is inclusive of only a subset of patients who were evaluated in the phase 1/2 study. Full study design can be seen in Kitko et al. *J Clin Oncol.* 2022;41:1864-1875.

1. Kitko et al. *J Clin Oncol.* 2022;41:1864-1875. **2.** Jagasia et al. *Biol Blood Marrow Transplant*. 2015;21:389-401. **3.** Lee et al. *Biol Blood Marrow Transplant*. 2015;21:984-999.

Patients With BOS Are More Heavily Pretreated

Patient Characteristics	Analyzed Cohort N=32		Patients with BOS n=15	
	Axatilimab 1 mg/kg q2w n=26	Axatilimab 3 mg/kg q4w n=6	Axatilimab 1 mg/kg q2w n=11	Axatilimab 3 mg/kg q4w n=4
Age, mean (SD)	51.5 (14.6)	59.2 (15.3)	47.1 (14.7)	63.3 (7.5)
Male, n (%)	16 (61.5)	4 (66.7)	6 (54.5)	2 (50.0)
Time from cGVHD diagnosis to study start, years, median (range)	3.3 (0.35, 7.10)[a]	1.6 (0.75, 3.91)[b]	3.8 (1.86, 7.10)	2.6 (1.23, 3.91)
Previous GVHD treatments, median (range)	3.5 (2, 11)	3.5 (2, 9)	6.0 (3, 11)	3.5 (2, 9)

Patients with BOS received a median of 5 (range, 2 to 11) previous cGVHD treatments compared with a median of 3.5 (range, 2 to 11) previous treatments in the full cohort

BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; q2w, 2 doses every 2 weeks; q4w, 2 doses every 4 weeks.

[a]n=25. [b]n=5.

Median Time to Response in Patients With BOS Treated With Axatilimab Was ~2.8 Months[a]

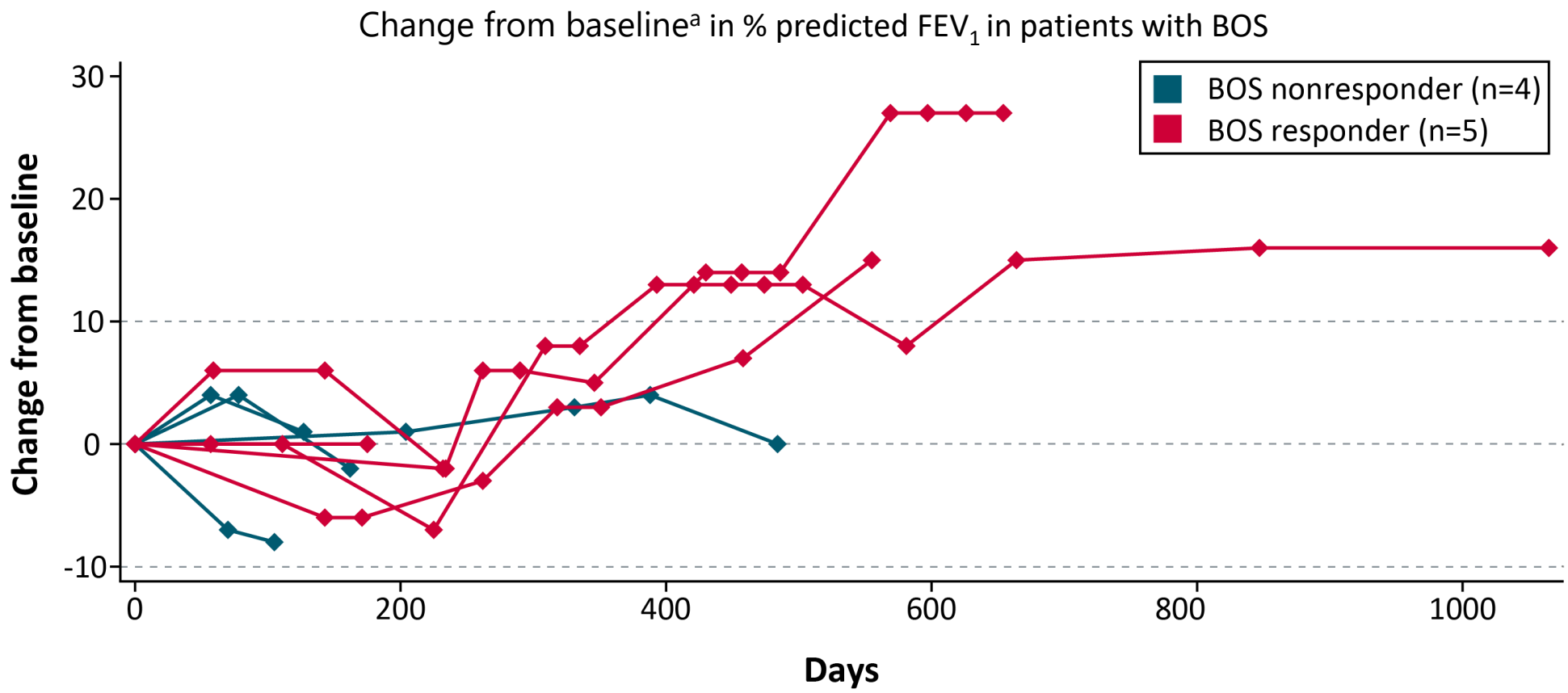
	Patients with BOS n=15	
	Axatilimab 1 mg/kg q2w n=11	Axatilimab 3 mg/kg q4w n=4
BOS response, n		
Total	5	3
FEV_1 (% predicted)	2	1
Symptom	4	3
Symptom only	3	2
Time to BOS response		
Months, median (range)	2.76 (0.95, 18.23)	2.79 (1.94, 2.83)

Partial BOS response was observed in 53% of patients; no patients with BOS had progression

BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in 1 second; ORR, overall response rate; q2w, 2 doses every 2 weeks; q4w, 2 doses every 4 weeks.

[a]As measured by symptom or FEV_1 improvement.

Most Patients With BOS Had Improvement in FEV_1



[a]Baseline is defined as the latter FEV_1 assessment at screening and C1D1 except for 1 subject, whose baseline is the FEV_1 assessment at C1D15. Percent change in FEV_1 from baseline is shown for 9 patients; 1 additional patient did not show a progression as reported by change in volume (liters). FEV_1 monitoring not mandated by protocol.

BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in 1 second.

Few Patients Discontinued Treatment Owing to AEs or Interrupted Treatment for Any Reason

	Axatilimab 1 mg/kg q2w n=26	Axatilimab 3 mg/kg q4w n=6	Patients with BOS n=15
Axatilimab dose changes due to AE,[a] n (%)			
Discontinuation[b]	2 (7.7)	1 (16.7)	1 (6.7)
Dose decrease	2 (7.7)	1 (16.7)	2 (13.3)
Axatilimab treatment			
Axatilimab cycles started, median (range)	7.5 (1, 39)	7.5 (3, 24)	7.0 (2, 39)
Axatilimab treatment duration, months, median (range)	7.13 (0.95, 40.28)	7.70 (2.79, 27.86)	6.93 (1.41, 40.28)

AE, adverse event.

[a]Except AE of chronic graft-versus-host disease progression. [b]AEs resulting in discontinuation were multiple contusions (due to fall), worsening lower extremity edema, and allergic reaction (1 each).

Axatilimab Demonstrates a Manageable Safety Profile With Treatment-Related On-target Effects of CSF-1R Blockade Observed

All related terms in ≥10%	Axatilimab 1 mg/kg q2w; n=26	Axatilimab 3 mg/kg q4w; n=6	Patients with BOS n=15
Related TEAE, n (%)	19 (73.1)	5 (83.3)	11 (73.3)
AST increase	6 (23.1)	3 (50.0)	4 (26.7)
Fatigue	6 (23.1)	2 (33.3)	3 (20.0)
CPK increase	3 (11.5)	4 (66.7)	5 (33.3)
ALT increase	3 (11.5)	2 (33.3)	2 (13.3)
Amylase increase	4 (15.4)	0	1 (6.7)
Lipase increased	3 (11.5)	3 (50.0)	2 (13.3)
Periorbital edema	3 (11.5)	3 (50.0)	5 (33.3)
Lactate dehydrogenase increased	1 (3.8)	2 (33.3)	3 (20.0)
Nausea	3 (11.5)	1(16.7)	3 (20.0)
At least 1 related grade ≥ 3 TEAE, n (%)	4 (15.4)	2 (33.3)	2 (13.3)
Related infections and infestations	**5 (19.2)**	**1 (16.7)**	**2 (13.3)**

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, blood creatine kinase; CSF-1R, colony-stimulating factor 1 receptor; q2w, 2 doses every 2 weeks; q4w, 2 doses every 4 weeks; TEAE, treatment-emergent adverse event.

Conclusions

- Axatilimab demonstrated clinical activity in BOS
- Axatilimab had a manageable safety profile
  - Adverse events were driven by blockade effect, which indicated on-target macrophage depletion
- Further evaluation is warranted for axatilimab in cGVHD, BOS, and other fibrotic indications, including IPF

BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; IPF, idiopathic pulmonary fibrosis.

Acknowledgements

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Questions?