Poster G-459

Baseline biopsy characteristics in an IgA nephropathy clinical trial of ravulizumab: A prespecified analysis of the SANCTUARY trial

Katherine Garlo,[1] Kara Rice,[1] Andreas Kateifides,[1] Matt Larochelle,[1] Stephen Nolan,[1] Thainá Jehá,[1] Huma Wasim,[1] Youssef MK Farag[1]

[1]Alexion, AstraZeneca Rare Disease, Boston, MA, USA

INTRODUCTION

- Immunoglobulin A (IgA) nephropathy is the most frequent primary glomerulonephritis and complement activation plays a key role in pathogenesis[1,2]
- Diagnosis of IgA nephropathy is based on kidney biopsy; the MEST-C Oxford classification provides information on disease severity and prognosis[1,3]
  - MEST-C: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C)[3]
- Glomerular complement component C3 staining also has prognostic value[4]
- Clinical trials for IgA nephropathy are often limited by the lack of a central pathology laboratory to minimize interpersonal variation in histological scoring
- Inclusion of a central pathologist to confirm the diagnosis and MEST-C are strengths of the SANCTUARY trial (NCT04564339)[5]
- Biopsies obtained >1 year before trial enrolment may be adequate for diagnostic purposes but information from MEST-C scoring is no longer current
  - A recent biopsy within 1 year of trial enrolment is important for histologic interpretation
- This prespecified analysis reports the baseline biopsy characteristics of patients with IgA nephropathy enrolled in the phase 2 SANCTUARY trial of ravulizumab

A phase 3 trial of ravulizumab in adults with IgA nephropathy (I CAN study, NCT06291376; EU CT 2023-507851-31-00) is ongoing

OBJECTIVES

- To assess baseline MEST-C scores and complement C3 staining in patients enrolled in the SANCTUARY trial of ravulizumab in IgA nephropathy
- To assess agreement between local and central pathology biopsy readings
- To assess treatment effect at Week 26 by baseline local pathology MEST-C scores
- To assess baseline proteinuria by MEST-C scores and complement C3 staining

CONCLUSIONS

- This prespecified analysis of the SANCTUARY trial reported MEST-C scoring and glomerular complement staining from biopsies prior to treatment, based on local pathology (38 sites) and central pathology, for which there was strong interobserver agreement on E, S, and C scores and comparatively lower agreement on M and T
- More than a third of patients had biopsy evidence of active inflammation, as indicated by E lesions. On central pathology, the vast majority had at least some degree of tubular atrophy/interstitial fibrosis. Most patients had positive complement staining
- Ravulizumab had a generally similar proteinuria reduction treatment effect across the MEST-C categories. However, sample sizes were small

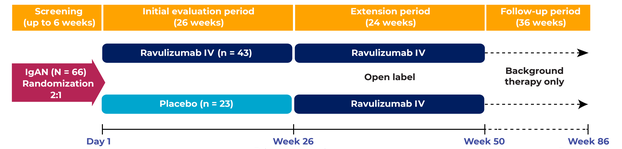
Poster presented at the National Kidney Foundation Spring Clinical Meetings, April 10–13, 2025

Corresponding author name and email address: Katherine Garlo (Katherine.Garlo@alexion.com)

METHODS

- The SANCTUARY trial design is depicted in **Figure 1**; patients were enrolled from 38 sites across 11 countries
- IgA nephropathy diagnosis was based on a kidney biopsy using a local pathology report obtained any time prior to Day 1
- A central pathology laboratory reviewed biopsies performed within 1 year prior to randomization
  - Light microscopy slides were sent to the central pathology lab; digital images were sent in cases where slide shipment was not possible
- Kidney biopsies were evaluated and scored based on MEST-C (Oxford) classification; glomerular complement C3 staining was also conducted
- Kappa statistics were used to evaluate the percent agreement between local and central pathology for MEST-C scores
  - Kappa values ranged from 0 to 1 (no agreement: ≤0, slight agreement: 0.01 – 0.20, fair agreement: 0.21 – 0.40, moderate agreement: 0.41 – 0.60, strong agreement: 0.61 – 0.80, almost perfect agreement: 0.81 – 1.00)
- **Assessments**
  - Baseline biopsy characteristics for MEST-C and glomerular C3 staining by local and central pathology assessment
  - Percent agreement between local and central pathology MEST-C scores
  - Treatment effect on change in proteinuria at Week 26 by baseline local pathology MEST-C scores
  - *Post hoc*: baseline proteinuria by biopsy characteristics based on central pathology scores

Figure 1. Study schematic*



*Key eligibility criteria for the phase 2 SANCTUARY trial: aged 18 – 75 years, biopsy-proven IgA nephropathy diagnosis, eGFR ≥30 mL/min/1.73 m², mean proteinuria ≥1 g/day at screening (based on 2 complete 24-hour urine collections during the screening period), and on stable maximally tolerated renin-angiotensin system inhibitor.

RESULTS AND INTERPRETATION

- Local pathology MEST-C score and C3 staining on biopsies prior to Day 1 are shown in **Table 1**

Table 1. Baseline biopsy characteristics – local pathology*

Category	Ravulizumab n (%)	Placebo n (%)	Total n (%)
MEST-C score			
M-score	n = 37	n = 20	n = 57
M0	14 (37.8)	7 (35.0)	21 (36.8)
M1	23 (62.2)	13 (65.0)	36 (63.2)
E-score	n = 36	n = 20	n = 56
E0	19 (52.8)	14 (70.0)	33 (58.9)
E1	17 (47.2)	6 (30.0)	23 (41.1)
S-score	n = 37	n = 20	n = 57
S0	5 (13.5)	2 (10.0)	7 (12.3)
S1	32 (86.5)	18 (90.0)	50 (87.7)
T-score	n = 36	n = 20	n = 56
T0	22 (61.1)	11 (55.0)	33 (58.9)
T1	14 (38.9)	8 (40.0)	22 (39.3)
T2	0	1 (5.0)	1 (1.8)
C-score	n = 27	n = 20	n = 47
C0	15 (55.6)	14 (70.0)	29 (61.7)
C1	11 (40.7)	6 (30.0)	17 (36.2)
C2	1 (3.7)	0	1 (2.1)
Glomerular C3 staining	n = 37	n = 21	n = 58
0/1+	18 (48.6)	6 (28.6)	24 (41.4)
2+/3+	19 (51.4)	15 (71.4)	34 (58.6)

*Full analysis set.

- 30 of the 66 patients (45%) had a biopsy within 1 year prior to randomization
  - Within 3 months prior: 9 patients (30%); 3 to 6 months prior: 9 patients (30%); between 6 and 12 months prior: 12 patients (40%)
- **Table 2** reports MEST-C score and C3 staining among patients with a biopsy within 1 year prior to randomization and with central pathology data available

Table 2. Baseline biopsy characteristics – central pathology – among patients with biopsy ≤1 year prior to randomization

Category	Ravulizumab n (%)	Placebo n (%)	Total n (%)
MEST-C score			
M-score	n = 11	n = 8	n = 19
M0	6 (54.5)	4 (50.0)	10 (52.6)
M1	5 (45.5)	4 (50.0)	9 (47.4)
E-score	n = 11	n = 8	n = 19
E0	5 (45.5)	7 (87.5)	12 (63.2)
E1	6 (54.5)	1 (12.5)	7 (36.8)
S-score	n = 11	n = 8	n = 19
S0	0	0	0
S1	11 (100)	8 (100)	19 (100)
T-score	n = 11	n = 8	n = 19
T0	2 (18.2)	0	2 (10.5)
T1	8 (72.7)	8 (100)	16 (84.2)
T2	1 (9.1)	0	1 (5.3)
C-score	n = 11	n = 8	n = 19
C0	6 (54.5)	6 (75.0)	12 (63.2)
C1	5 (45.5)	2 (25.0)	7 (36.8)
C2	0	0	0
Glomerular C3 staining	n = 11	n = 9	n = 20
0/1+	7 (63.6)	2 (22.2)	9 (45.0)
2+/3+	4 (36.4)	7 (77.8)	11 (55.0)

- Both local and central pathology MEST-C scores were available for 24 patients (except for C-scores), regardless of biopsy age **(Table 3)**
  - IgA nephropathy was confirmed as the primary diagnosis by central pathology in all cases
- Strong agreement between local and central pathology scores was noted for E, S, and C (**Table 3**)
  - Agreement for M and T was comparatively lower

Table 3. Agreement between local and central pathology for MEST-C scores

Category	Local pathology n (%)	Central pathology n (%)	Percent agreement (%)	Kappa statistic* (95% CI)
M-score	n = 24	n = 24	75.0	0.50 (0.20, 0.80)
M0	6 (25.0)	12 (50.0)		
M1	18 (75.0)	12 (50.0)		
E-score	n = 24	n = 24	87.5	0.75 (0.48, 1)
E0	13 (54.2)	14 (58.3)		
E1	11 (45.8)	10 (41.7)		
S-score	n = 24	n = 24	91.7	0.63 (0.16, 1)
S0	4 (16.7)	2 (8.3)		
S1	20 (83.3)	22 (91.7)		
T-score	n = 24	n = 24	66.7	NA
T0	10 (41.7)	4 (16.7)		
T1	14 (58.3)	18 (75.0)		
T2	0	2 (8.3)		
C-score	n = 22	n = 22	90.9	0.81 (0.57, 1)
C0	12 (54.5)	14 (63.6)		
C1	10 (45.5)	8 (36.4)		

*An unweighted kappa statistic and corresponding 95% CI is represented.

- Baseline mean proteinuria was similar across MEST-C and glomerular C3 staining categories **(Table 4)**

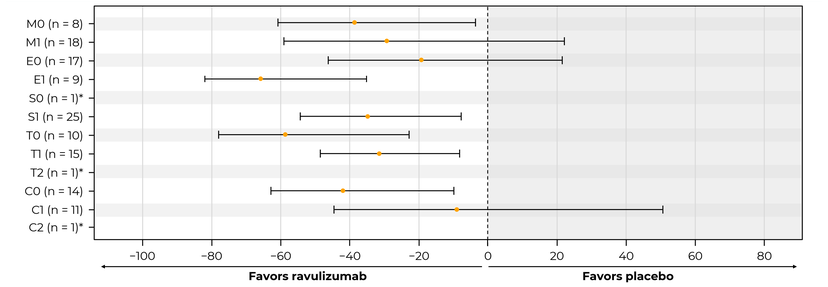
Table 4. Baseline proteinuria by biopsy characteristics (central pathology scores)*

Category	Baseline 24-hour UPCR (g/g)	
	Mean (SD)	Median (Q1, Q3)
MEST-C score		
M0 (n = 10)	1.29 (0.53)	1.16 (0.93, 1.64)
M1 (n = 9)	1.21 (0.39)	1.26 (0.97, 1.38)
E0 (n = 12)	1.24 (0.54)	1.09 (0.84, 1.64)
E1 (n = 7)	1.28 (0.31)	1.26 (1.09, 1.64)
S1 (n = 19)	1.25 (0.46)	1.23 (0.93, 1.64)
T1 (n = 16)	1.27 (0.50)	1.25 (0.84, 1.64)
C0 (n = 12)	1.28 (0.53)	1.30 (0.86, 1.64)
C1 (n = 7)	1.20 (0.34)	1.15 (0.93, 1.64)
Glomerular C3 staining		
0/1+ (n = 9)	1.22 (0.52)	1.23 (0.76, 1.38)
2+/3+ (n = 11)	1.28 (0.40)	1.26 (0.97, 1.64)

*Data are included for categories with ≥5 patients, who had biopsy within 1 year before randomization.

- In general, a similar treatment effect on proteinuria was observed across MEST-C categories **(Figure 2)**

Figure 2. Treatment effect (90% CI) on change in proteinuria (24-hour UP) from baseline to Week 26 based on local pathology MEST-C score at baseline, in patients with biopsy ≤1 year prior to randomization



*Insufficient sample size.

Abbreviations

C3, complement component 3; CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IV, intravenous; MEST-C, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and crescents; NA, not available; Q1, first quartile; Q3, third quartile; SD, standard deviation; UP, urine protein; UPCR, urine protein:creatinine ratio.

Acknowledgments

Writing assistance for this poster was provided by Neetu Menghani, PhD, and Aiman Lakdawala, MSc, CMPP® from Indegene Ltd., Bangalore, India, with funding from Alexion, AstraZeneca Rare Disease.

Funding

This study was funded by Alexion, AstraZeneca Rare Disease.

Disclosures

All authors are employees and shareholders of Alexion, AstraZeneca Rare Disease.

References

1. Rajasekaran A, et al. *Am J Med* Sci. 2021;361(2):176–194.
2. Rizk DV, et al. *Front Immunol*. 2019;10:504.
3. Trimarchi H, et al. *Kidney Int*. 2017;91(5):1014–1021.
4. Xie M, et al. *J Nephrol*. 2023;36(2):495–505.
5. Lafayette R, et al. *J Am Soc Nephrol*. 2024 Oct 25.