Oral Abstract Session

Session Title: Glomerular Diseases: Clinical and Translational Studies [OR1402]

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Session Room: Room 103 (Pennsylvania Convention Center)

Abstract Publication #: TH-OR27

Your Presentation Time: 5:24 PM to 5:33 PM (9 minutes total: 6 minutes for presentation, 3 minutes for Q&A)

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Safety and Efficacy of Felzartamab in Primary Membranous Nephropathy (PMN): Final Analysis of the M-PLACE Study

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ASN Kidney Week 2023

Disclosures of Interest

Dr. Rovin has the following relevant financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

Affiliation / Financial Interest	Organization
Research Grants	NIH
Medical/Scientific Advisor	Biogen, Lilly, GSK, Genentech/Roche, Pfizer, BMS, BioMarin, Aurinia, Travere, EMD-Serono, HiBio, Biocryst, Alexion, Novartis, AstraZeneca, Kezar, Otsuka, Calliditis, Galapagos, Horizon, Resonance, Omeros, Biocryst, RILITE Foundation, Exagen, Jannsen, Equilium, Vistera, Kyverna, Alpine, Gilead, Sana, Artiva

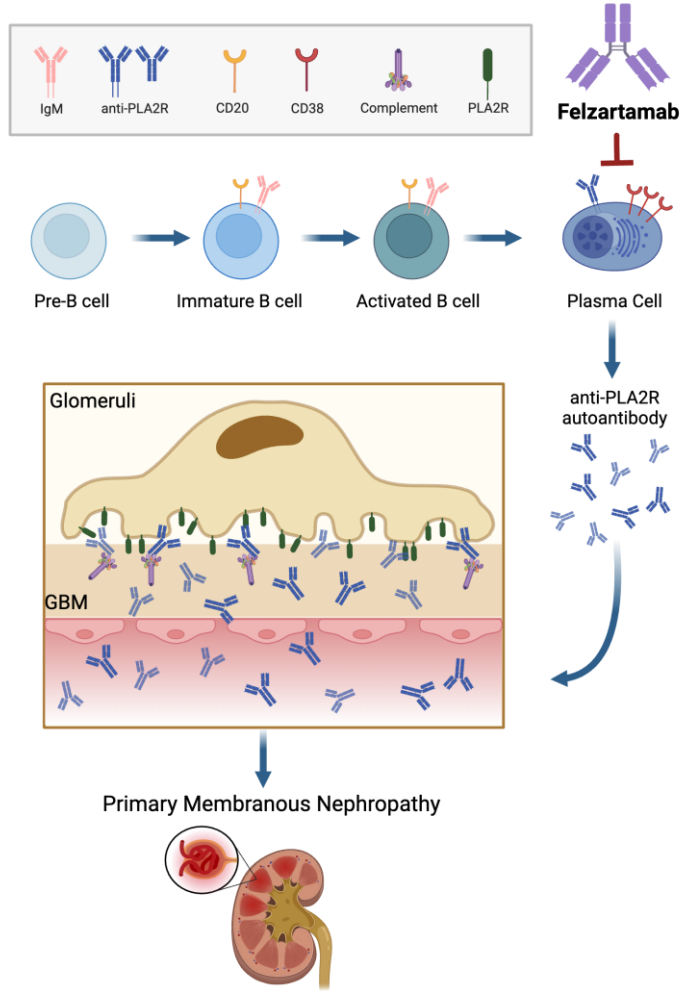
Mechanism of felzartamab in PMN

PMN: autoantibody (AAb) disease that results in podocyte injury

- PMN is a rare autoantibody-driven kidney disease that is the most common cause of nephrotic syndrome in adults
- AAbs (anti-PLA2R in 70-80% of pts) bind to podocyte PLA2R and form immune complexes that activate complement, resulting in podocyte injury, thickening of GBM, and impaired glomerular function
- High anti-PLA2R AAb titers are associated with severe disease, longer time to disease remission, and decreased response to anti-CD20 rituximab treatment
- AAbs are secreted by autoreactive CD20-/CD38+ plasma cells and plasmablasts

Felzartamab depletes plasma cells, key producers of AAbs

- Felzartamab is an investigational, fully human IgG1 monoclonal anti-CD38 antibody that depletes plasmablasts and plasma cells via antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis
- By targeting plasma cells and plasmablasts, felzartamab may reduce level of pathogenic AAbs, prevent glomerular immune complex deposition between basement membrane and epithelial podocytes, and potentially halt progression of PMN

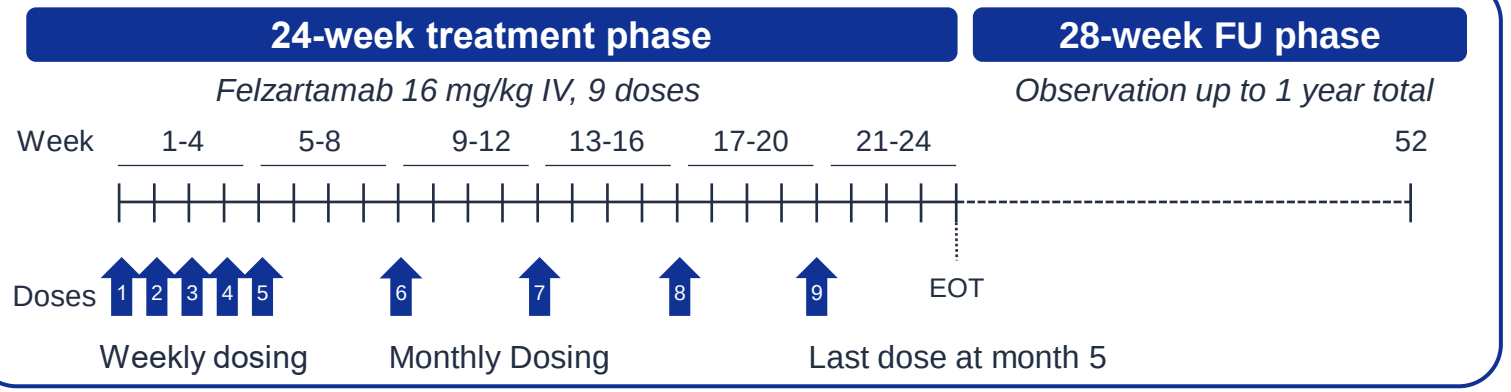


M-PLACE study design

Phase Ib/IIa, PoC, open-label trial assessing assess safety and tolerability, efficacy, and PK of felzartamab in patients with anti-PLA2R autoantibody positive MN *(NCT04145440)**

Cohort 1
Newly dx & relapsed

Cohort 2
Refractory



KEY INCLUSION CRITERIA

- Active and anti-PLA2R AAb positive MN in need of IST
- UPCR ≥3.0 g/g or proteinuria ≥3.5 g/24h
- eGFR ≥50 mL/min/1.73m2
- No remission despite proper treatment with ACE inhibitor and ARBs

Cohort 1:
- Newly diagnosed or relapsed patients
- Serum anti-PLA2R >50.0 RU/mL

Cohort 2:
- Refractory subjects to prior IST (no immunologic remission) and serum anti-PLA2R AAb > 20.0 RU/mL
- No promising standard therapeutic options as documented by investigator

PRIMARY ENDPOINT

- Incidence and severity of TEAEs

KEY SECONDARY and EXPLORATORY ENDPOINTS

- Reduction of serum anti-PLA2R AAb titer
- Changes in proteinuria and serum albumin
- Changes in quality of life
- Changes in kidney function
- Serum concentrations of felzartamab and anti-drug antibodies

* Countries: Australia, Belgium, France, Italy, Netherlands, Poland, Spain, South Korea, United States

Demographics and baseline characteristics

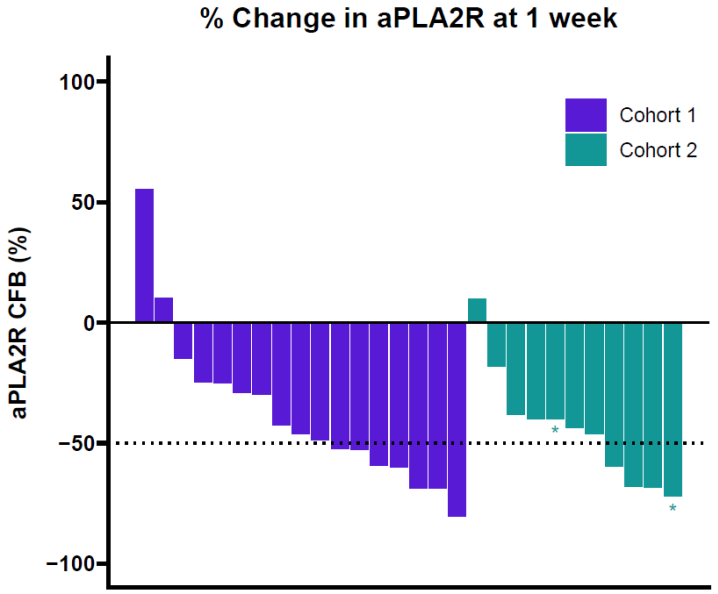
	Cohort 1 Newly Diagnosed / Relapsed (n=18)	Cohort 2 Refractory (n=13)	All Patients (n=31)
Mean (SD) age, y	59.2 (11.3)	55.0 (12.5)	57.5 (11.8)
Sex, n (%)			
Male	13 (72.2)	11 (84.6)	24 (77.4)
Female	5 (27.8)	2 (15.4)	7 (22.6)
Baseline disease status, n (%)			
Newly diagnosed	15 (83.3)	0	15 (48.4)
Relapsed	3 (16.7)	0	3 (9.7)
Refractory	0	13 (100)	13 (41.9)
Prior IST, n (%)			
0	16 (88.9)	0	16 (51.6)
1	0	7 (53.8)	7 (22.6)
≥2	2 (11.1)	6 (46.2)	8 (25.8)
Rituximab	1 (5.6)	11 (84.6)	12 (38.7)
Cyclophosphamide	1 (5.6)	6 (46.2)	7 (22.6)
Tacrolimus	2 (11.1)	4 (30.8)	6 (19.4)
Anti-PLA2R AAb titer, RU/mL*	207.9 (118.9)	301.5 (377.6)	247.1 (259.3)
Proteinuria (24-hour UPCR), g/g*	6.2 (2.0)	6.7 (2.5)	6.4 (2.2)
eGFR, mL/min/1.73 m^2*	64.8 (21.9)	53.7 (15.6)	60.2 (20.0)
Serum albumin, g/L*	25.9 (5.4)	28.0 (4.2)	26.8 (5.0)

*Baseline, mean (SD)

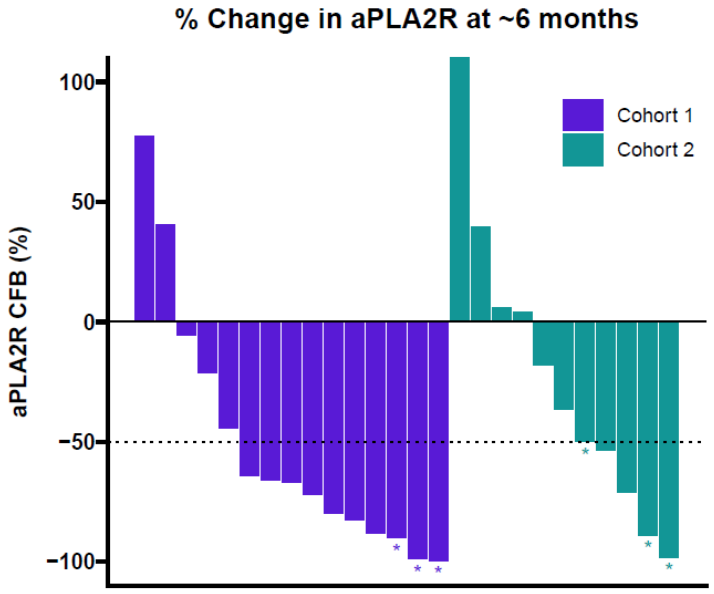
Safety and tolerability

	Cohort 1 Newly Diagnosed / Relapsed (n=18)	Cohort 2 Refractory (n=13)	All Patients (n=31)
Patients with any TEAE, n (%)	15 (83.3)	12 (92.3)	27 (87.1)
Patients with any grade 3 or 4 TEAE, n (%)	3 (16.7)	5 (38.5)	8 (25.8)
Patients with any serious TEAE, n (%)	2 (11.1)	3 (23.1)	5 (16.1)
Patients with any TEAE leading to treatment discontinuation, n (%)	3 (16.7)	2 (15.4)	5 (16.1)
Patients with a pre-defined TEAE of special interest, n (%)	4 (22.2)	2 (15.4)	6 (19.4)
Allergic reaction	1 (5.6)	1 (7.7)	2 (6.5)
Grade ≥3 infection	1 (5.6)	0	1 (3.2)
Grade ≥3 infusion-related reaction	1 (5.6)	0	1 (3.2)
Grade ≥3 neutropenia (ANC <1.0 × 10^9/L)	1 (5.6)	1 (7.7)	2 (6.5)
TEAEs occurring in ≥4 patients overall, n (%)			
Infusion-related reaction	1 (5.6)	8 (61.5)	9 (29.0)
Hypogammaglobulinemia	7 (38.9)	1 (7.7)	8 (25.8)
Peripheral edema	2 (11.1)	4 (30.8)	6 (19.4)
Nausea	4 (22.2)	1 (7.7)	5 (16.1)
Bronchitis	0	4 (30.8)	4 (12.9)

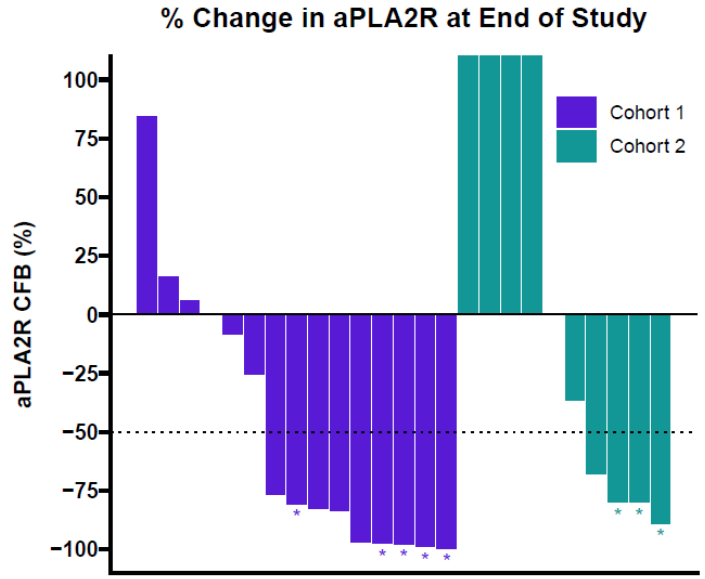
Felzartamab resulted in rapid, deep, and durable reductions in anti-PLA2R AAb



- 22 of 25 (88.0%) had reductions in anti-PLA2R AAb titer (mean change: −40%)



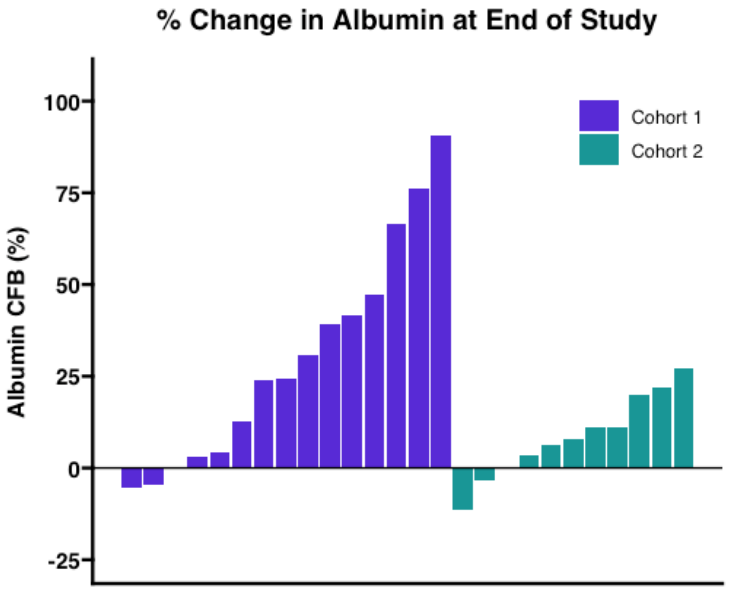
- 20 of 26 (76.9%) had reductions in anti-PLA2R AAb titer

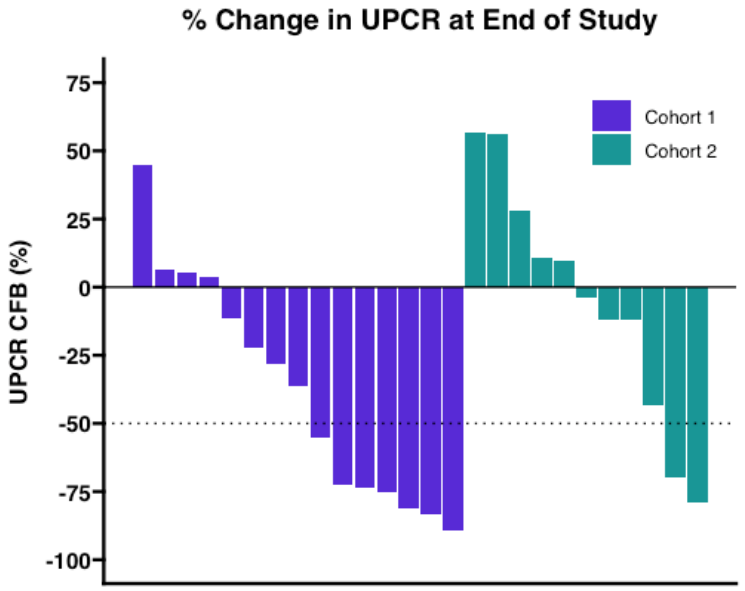


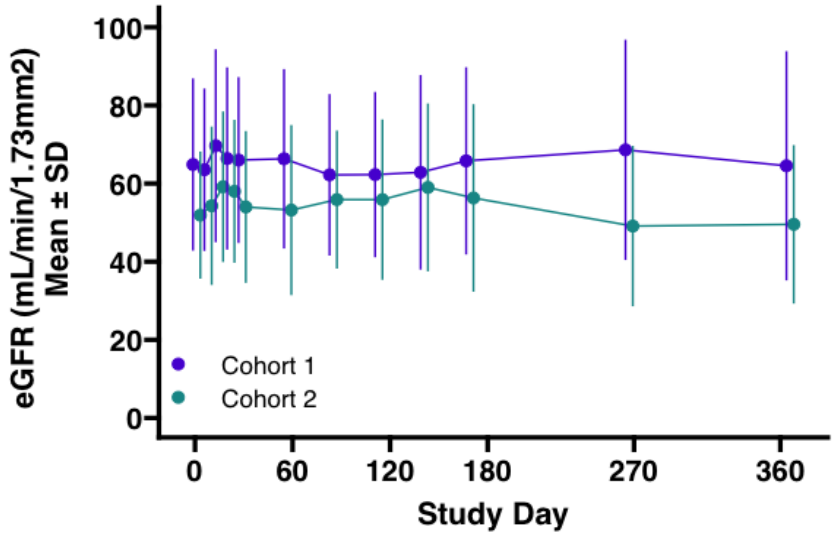
- 17 of 26 (65.4%) had reductions in anti-PLA2R AAb titer
  - 8 (30.8%) achieved immunologic complete response (ICR, <14 RU/mL)
  - 6 (23.1%) achieved immunologic partial remission (IPR, reduction by at least 50%)

* Patients achieved an ICR
End of Study: ~12 months for most patients

Reductions in anti-PLA2R AAb resulted in improvements in serum albumin and UPCR, with stable eGFR







- 20 of 26 (76.9%) had increases in serum albumin
  - 9 (34.6%) (Cohort 1, n=7; Cohort 2, n=2) within normal range

- 17 (65.4%) (Cohort 1, n=11; Cohort 2, n=6) had decreases from baseline in 24-hour UPCR
  - 9 (34.6%) achieved partial remission by EOS (Cohort 1, n=7; Cohort 2, n=2)
  - Anti-PLA2R AAb reductions at 3 months preceded decreases in UPCR by 12 months with stronger correlation in Cohort 1 (r = 0.7) vs Cohort 2 (r = 0.15)

- eGFR remained stable

Conclusions

- In patients with high-risk anti-PLA2R+ PMN, felzartamab demonstrated rapid (1 week) and durable (continued after last dose) reduction of anti-PLA2R AAb titer with high rates of immunologic response
- Reductions in 24-hour UPCR in most patients by last study visit with ~ 1/2 of efficacy-evaluable patients in Cohort 1 with proteinuria partial remission by 1 year
    - Proteinuria partial remission observed even in patients refractory to cyclophosphamide and rituximab
- In some heavily refractory patients (Cohort 2), attenuated benefit after treatment discontinuation suggests need for longer duration of felzartamab treatment and/or combination therapy
- Favorable safety profile and observed efficacy, along with ability to mount humoral response to vaccination, warrant further investigation of felzartamab as therapeutic option in PMN
- Future studies will assess efficacy and safety of greater than one course in PMN, as well as efficacy of felzartamab in patients with PMN who have lower levels of anti-PLA2R AAb autoantibodies or other autoantibodies over longer follow-up period

Back-up

Reductions in IgG were modest and transient

Reductions in serum IgG were monitored due to the mechanism of felzartamab. Reductions in serum IgG were modest and recovered to 16.7% (SD, 51.7%) above baseline at EOS