1/ Hey #NephTwitter, today, we'll be talking about the use of felzartamab in membranous nephropathy, but first, let's talk about a bigger idea:

The biopsy tells us where the damage is, but not where the disease process lives.

2/ This thread is brought to you by Gerren Hobby. I'm a private practice nephrologist in Arkansas and I'm excited to talk about membranous nephropathy today.

3/ Let's dive in with a quiz:

What is the mechanism of rituximab?

a. anti-CD38
b. anti-CD20
c. anti-CD3
d. anti-CD19

4/ The correct answer is (b) anti-CD20.

Rituximab binds the CD20 antigen on pre-B and mature B lymphocytes, then depletes them via complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9676507/

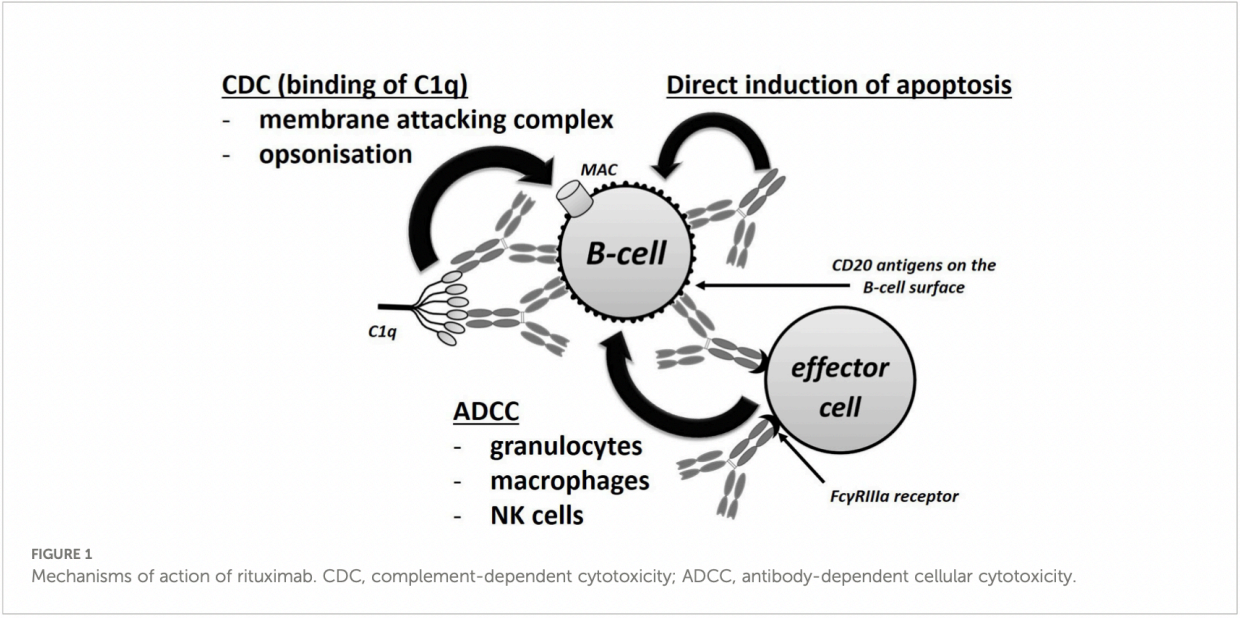
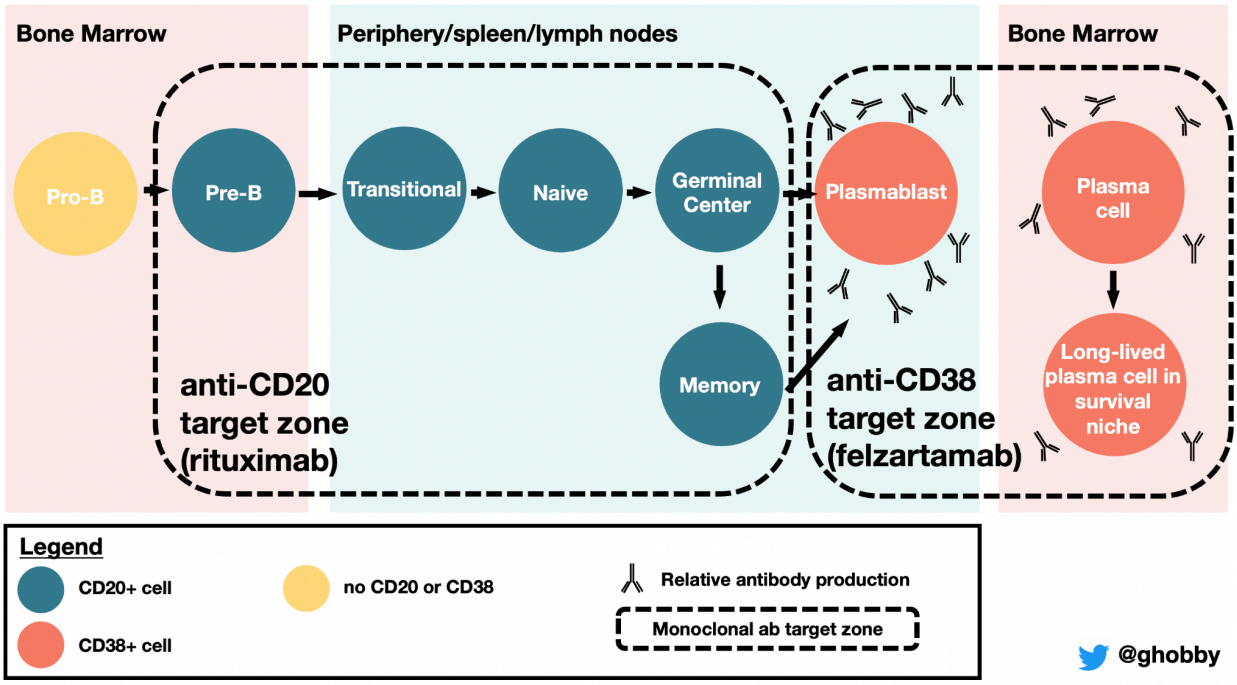


FIGURE 1
Mechanisms of action of rituximab. CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity.

5/ Rituximab

- Reduces the upstream B-cell population that replenishes antibody-producing B cells
- Does not directly deplete the antibody-producing plasmablasts, plasma cells, or long-lived plasma cells

https://pmc.ncbi.nlm.nih.gov/articles/PMC11497632/



6/ Since we are trying to reduce antibody production in membranous nephropathy, rituximab has found a useful home in KDIGO treatment regimens

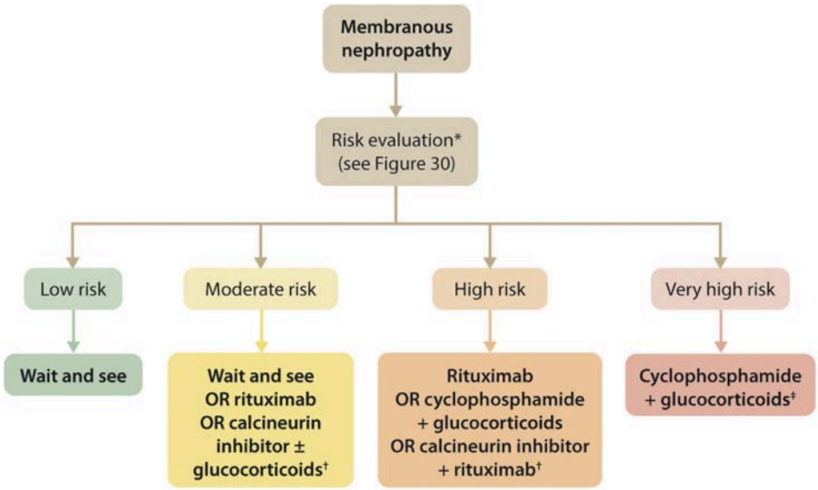


Figure 31 | Risk-based treatment of MN. *See Practice Point 3.2.1 and Figure 30 for a detailed description of risk evaluation. †Calcineurin inhibitor (CNI) monotherapy is considered less efficient. Treatment with CNI for 6–12 months with rapid withdrawal is associated with a high relapse rate. Still, its use may be considered in patients with normal eGFR and moderate risk of progression, since many of these patients will develop a spontaneous remission. The use of CNI will shorten the period of proteinuria. In patients with high risk of progression, addition of rituximab after 6 months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of anti-PLA2R antibodies after CNI treatment. ‡There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure. If eGFR falls below 50 ml/min per 1.73 m^2, the doses of cyclophosphamide should be halved. In patients who do not tolerate or can no longer use cyclophosphamide, rituximab could be offered. Consultation with an expert center is advised. eGFR, estimated glomerular filtration rate; MN, membranous nephropathy; PLA2R, M-type phospholipase A2 receptor.

7/ The problem is that around 30% of membranous nephropathy cases are do not respond to rituximab, although not all nonresponse is due to true rituximab resistance

https://pmc.ncbi.nlm.nih.gov/articles/PMC3402291/

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Rituximab in Idiopathic Membranous Nephropathy

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ABSTRACT

Selective depletion of B cells with the mAb rituximab may benefit the autoimmune glomerular disease idiopathic membranous nephropathy (IMN). Here, we describe our experience treating 100 consecutive IMN patients with persistent nephrotic syndrome with rituximab. We defined complete remission as persistent proteinuria <0.3 g/24 h and partial remission as persistent proteinuria <3 g/24 h, each also having >50% reduction in proteinuria from baseline. During a median follow-up of 29 months after rituximab administration, 65 patients achieved complete or partial remission. The median time to remission was 7.1 months. All 24 patients who had at least 4 years of follow-up achieved complete or partial remission. Rates of remission were similar between patients with or without previous immunosuppressive treatment. Four patients died and four progressed to ESRD. Measured GFR increased by a mean 13.2 (SD 19.6) ml/min per 1.73 m^2 among those who achieved complete remission. Serum albumin significantly increased and albumin fractional clearance decreased among those achieving complete or partial remission. Proteinuria at baseline and the follow-up duration each independently predicted the decline of proteinuria. Furthermore, the magnitude of proteinuria reduction significantly correlated with slower GFR decline (P=0.0001). No treatment-related serious adverse events occurred. In summary, rituximab achieved disease remission and stabilized or improved renal function in a large cohort of high-risk patients with IMN.

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8/ If we are cutting off the upstream supply of plasma cells with rituximab, then why do some pts not respond to rituximab?

Perhaps, one reason could be the continued antibody production due to something called CD38+ (but CD20 negative) long-lived plasma cells.

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Prospective Cohort Study of Felzartamab in Rituximab-Resistant Primary Membranous Nephropathy

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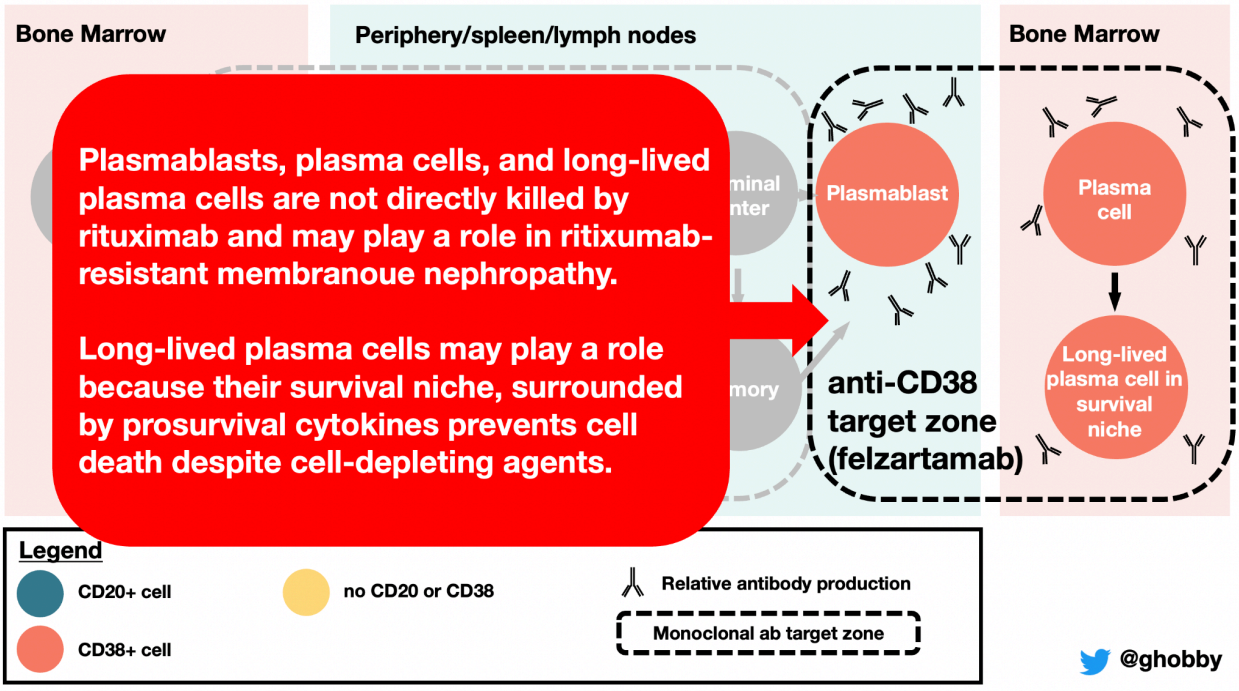
https://www.kireports.org/article/S2468-0249%2826%2902700-2/fulltext

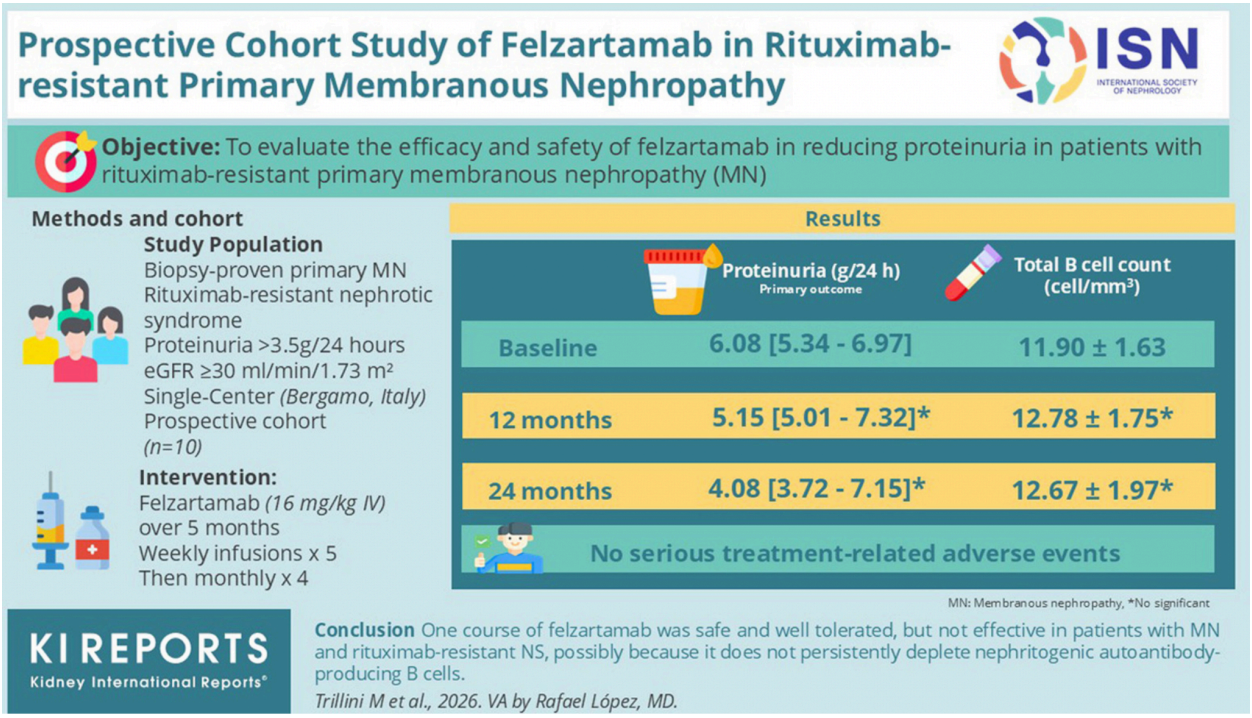
9/ Ever wonder why CMV IgG, varicella IgG, or HBV surface Ab can persist years after exposure?

That's the work of long-lived plasma cells: CD38+ antibody factories that settle into bone marrow survival niches – cytokine "cocoons" that let them produce antibodies for decades.



10/ The authors examined if depleting these long-lived plasma cells via the anti-CD38 monoclonal antibody, felzartamab, could help in rituximab-resistant primary membranous nephropathy

✅Single-arm
✅Single-center
✅open-label



11/ The result… a negative trial. Felzartamab did not decrease proteinuria or albuminuria.

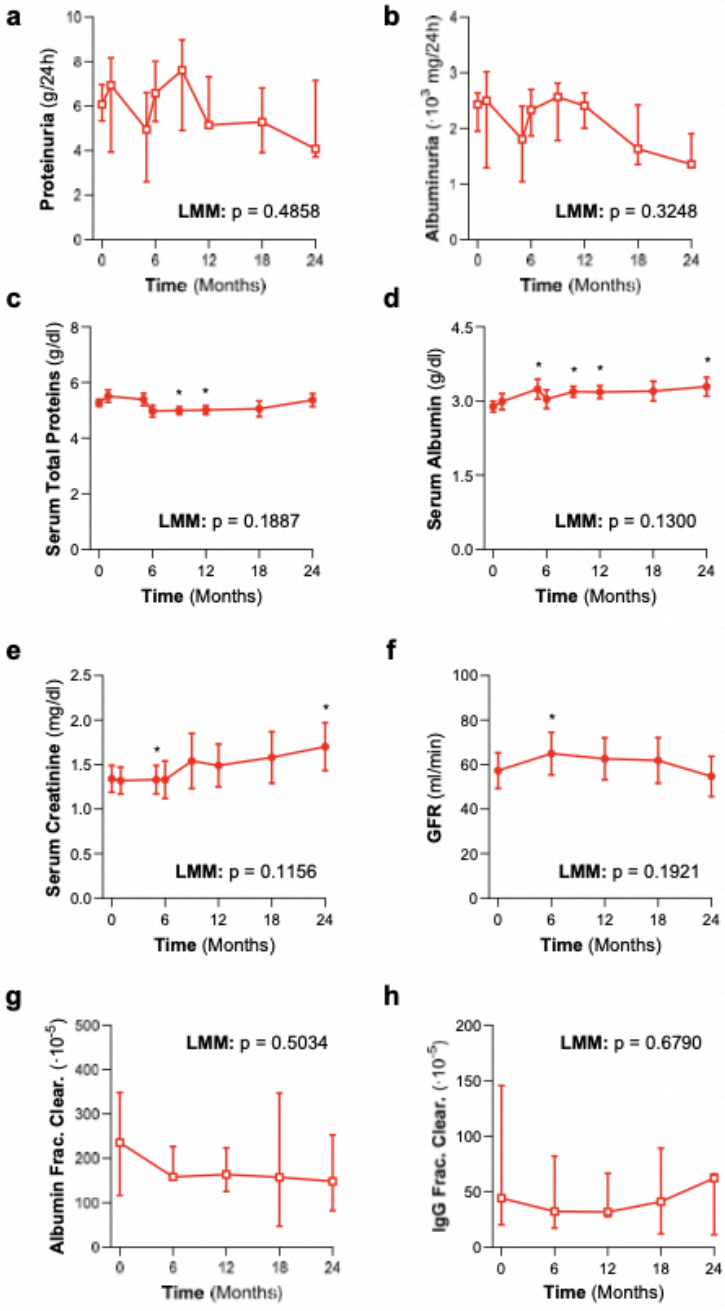


Figure 1. Changes in 24-hour proteinuria; 24-hour albuminuria; serum total protein, albumin, and creatinine levels; GFR; and albumin and IgG fractional clearances after felzartamab treatment compared with baseline (pretreatment) values. (a) 24-hour proteinuria and (b) albuminuria did not significantly change during 24-month follow-up after felzartamab. (c) Serum total proteins levels were significantly lower at 9 and 12 months whereas (d) serum albumin levels were significantly higher at 5, 9, 12, and 24 months after the first felzartamab administration than at baseline. (e) Serum creatinine levels were significantly higher at 5 and 24 months and (f) GFR values were significantly higher at 6 months after the first felzartamab administration than at baseline. (g) Albumin and (h) IgG fractional clearances never differed from baseline. Data are shown as mean ± SEM (solid circle) or as median [q1–q3] (white square). Paired *t* test: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ versus baseline. Data are represented as median [Q1–Q3]. Wilcoxon signed-rank test: $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ versus baseline. Frac., fractional; GFR, glomerular filtration rate; LMM, linear mixed model (within 24 months).

12/ On the surface, this falls into the category of a negative trial of a fancy monoclonal antibody with the take-home message of:

- Stay the course
- Use rituximab or a CNI
- Wait until a better monoclonal antibody comes out

13/ But negative trials are useful, and this one offers a glimpse into MN pathogenesis and perhaps the direction of future trials.

14/ Why didn't felzartamab work?

Possibly:
• Dose wasn't enough
• NK cells also express CD38 and may "soak up" the drug
• NK-cell depletion may impair ADCC
• Long-lived plasma cells may be protected in survival niches

Likely: a combination.

15/ This paper shows where immunosuppression is heading.

We've moved from "steroids for everything" to targeting specific pathways: T cells, B cells, complement.

Now we're refining this to which B-cell population we should target — and when?

16/ It will be exciting to see where the next studies in glomerular disease take us. Be sure to keep in mind these aspects of glomerular pathogenesis as you read upcoming articles. This has been a tweetorial by @ghobby for @KIReports