1/Hello #NephTwitter! Excited to bring you this #tweetorial (#xtorial) from @KIReports

2/Authored by Dr Priya John from Hyderabad, India.

Before we begin this #Tweetorial, check out this excellent blog from @KIReports exploring how obinutuzumab is redefining treatment in rituximab resistant membranous nephropathy.

https://www.kireportscommunity.org/post/beyond-rituximab-obinutuzumab-redefines-treatment-in-resistant-membranous-nephropathy

#MedTwitter #nephtwitter @ISNkidneycare #XTwitter

3/What is resistant MN in (Detectable anti-PLA2R at baseline) according to KDIGO 2021

A. Persistent high/unchanged serum anti-PLA2R levels after one line of IST

B. Proteinuria at 6 months

C. Persistent high/unchanged anti-PLA2R after two lines of IST

D. High anti-PLA2R at baseline

PMID: 34556256

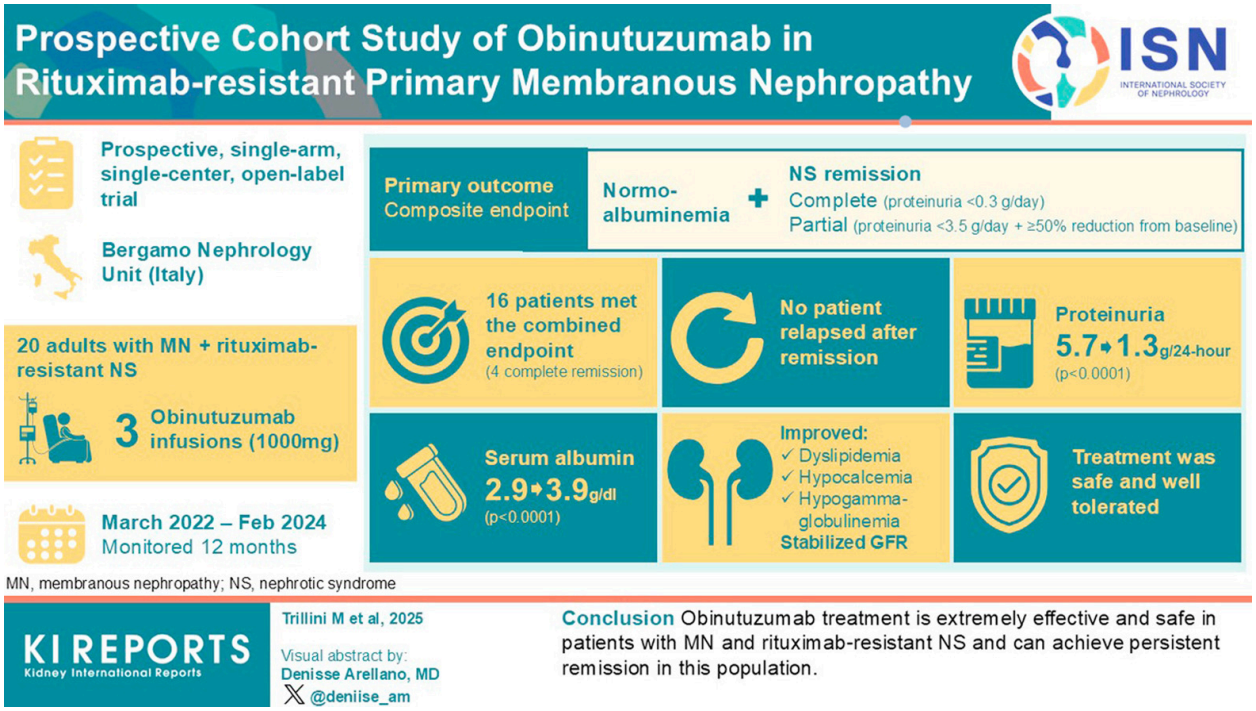
4.Defining resistance harder -anti-PLA2R –ve patients

- ☐ Persistent NS (>6 months, low albumin) → suggests resistance
- ☐ Low-grade proteinuria + normal albumin → Secondary FSGS
- ☐ Persistent proteinuria + partially low albumin → uncertain status
- ☐ Kidney biopsy (small dense deposits) → indicates ongoing disease activity

5. This Tweetorial focuses on obinutuzumab and its emerging role in improving outcomes in resistant membranous nephropathy.

PMCID: PMC12857323

VA by Denisse Arleno



6.A word about rituximab resistance:

Primary Resistance : Treatment-naïve patients

Causes: altered B-cell subsets, low CD20, high $CD19^{+}CD20^{-}$ cells

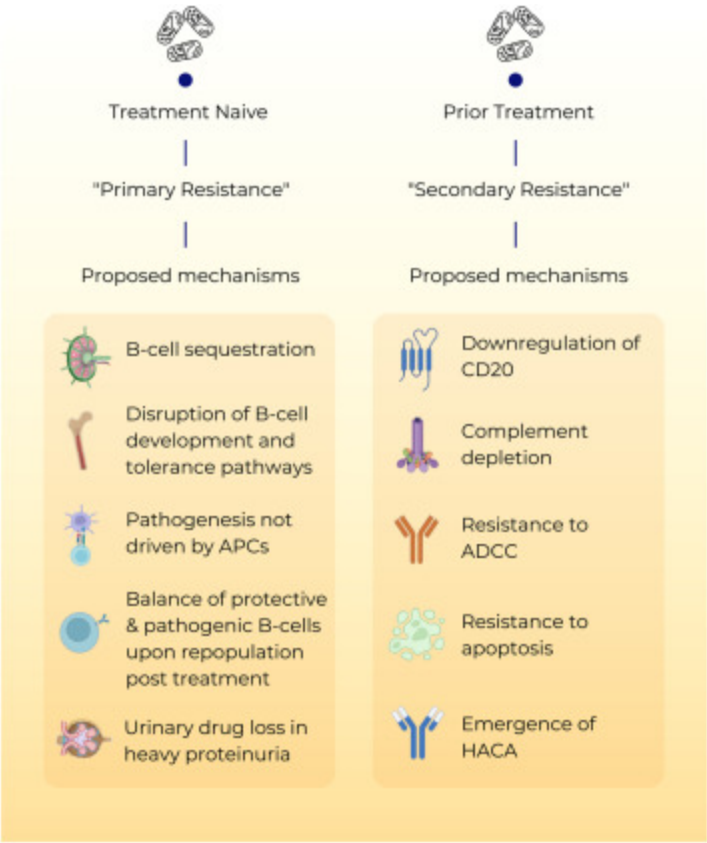
Heavy proteinuria → drug loss → poor response

Secondary Resistance After repeated exposure

↓ CD20, complement resistance

Impaired ADCC, apoptosis resistance

PMID: 38495600



7.What about Human antichimeric antibodies(HACA)

- ☐ Antibodies against rituximab (mouse-derived component)
- ☐ More common in autoimmune diseases
- ☐ Effects:
  - ☐ Increased infusion reactions
  - ☐ Poor B-cell depletion
  - ☐ Early B-cell reconstitution
  - ☐ Higher relapse rates
- ☐ Detection: ELISA
- ☐ Testing best done before rituximab dose
- ☐ Immune complexes may cause false negatives

8. Before we dive into this emerging option for rituximab-resistant MN, what remains the first-line therapy?(KDIGO 2021)

- ☐ Depends of eGFR

- ☐ CNI
- ☐ Cyclophosphamide
- ☐ CNI+Cyclophosphamide

9.KDIGO suggests eGFR based options in rituximab resistant cases

CNI+rituximab if eGFR is stable

Cyclophosphamide+glucocorticoids if eGFR is worsening

Current study looked into other potent CD 20 antibody-Obinutuzumab

10. Is Obinutuzumab Rituximab's smarter sibling?

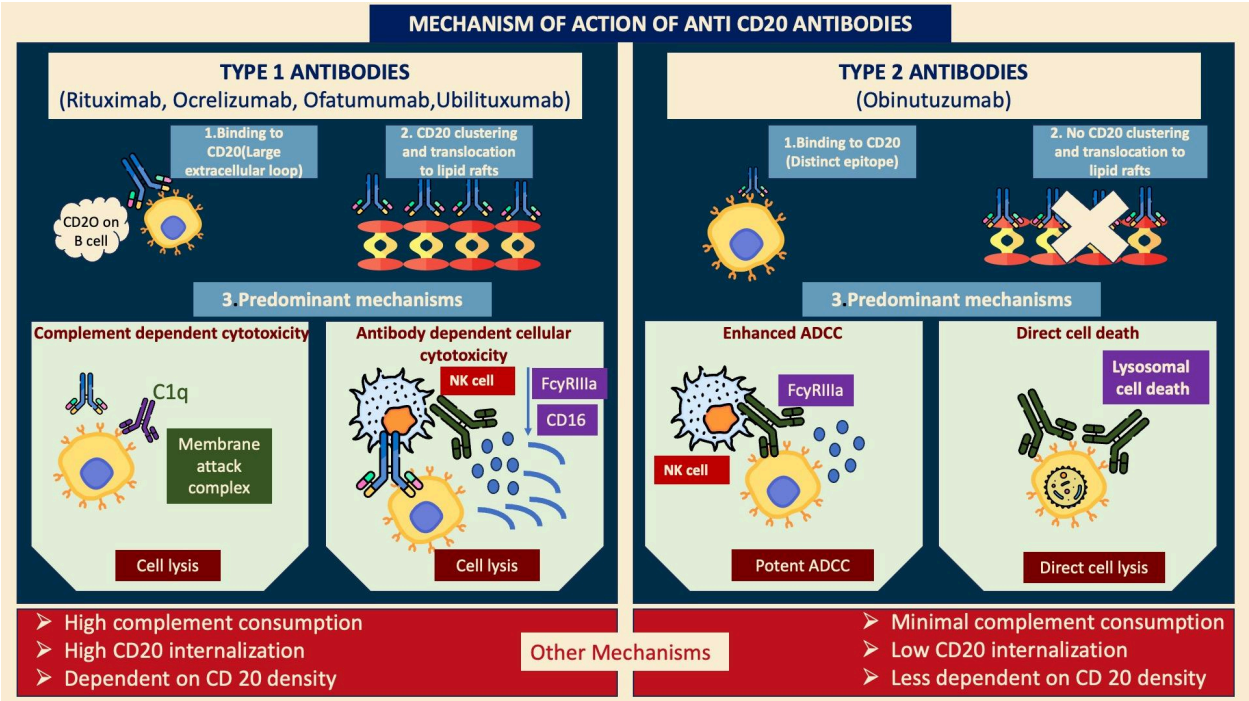
Check this infographic by Dr Priya John

ANTICD20 ANTIBODIES AT A GLANCE

FEATURE	TYPE I *(Rituximab, Ocrelizumab, Ofatumumab, Ublituximab)*	TYPE II *(Obinutuzumab)*
CD 20 binding	Large loop, redistributes CD 20	Different orientation, no redistribution
Lipid raft formation	Present	Absent
Complement activation	Strong	Minimal
ADCC	Moderate ⟶ High in defucosylated agents	Very Strong(defucosylated)
Direct cell death	Weak	Strong(lysosomal, non apoptotic)
CD 20 internalization	High	Low/minimal
Mechanism dominance	CDC>ADCC	ADCC+Direct cell death
Effect of CD55/CD59	Reduced efficacy(complement dependent)	Less affected
CD20 density dependency	High dependence(except ofatumumab)	Less dependence
Complement consumption	High	Minimal
B cell depletion pattern	Circulating B cells(complement driven)	More tissue-based killing
Fc engineering	Present in some	Prominent feature
Defucosylation	Ublituximab(yes)	Obinutuzumab(yes) ⟶ Strong ADCC
Infusion reactions	Moderate----high(highest with rituximab)	High early reactions
Key mechanism	Lipid raft and complement lysis	Direct cell death and ADCC
Clinical implication	Best when complement intact	Best in complement resistant/low CDC states

10. Wait why Obinutuzumab at all? Do we have any advantages?

- ☐ Greater B-cell depletion
- ☐ Higher ADCC activity
- ☐ Direct B-cell killing (lysosomal pathway)
- ☐ Less CD20 internalization → reduced resistance
- ☐ Better tissue (lymphoid) B-cell depletion including memory B cells
- ☐ Lower immunogenicity (humanized → fewer anti-drug antibodies



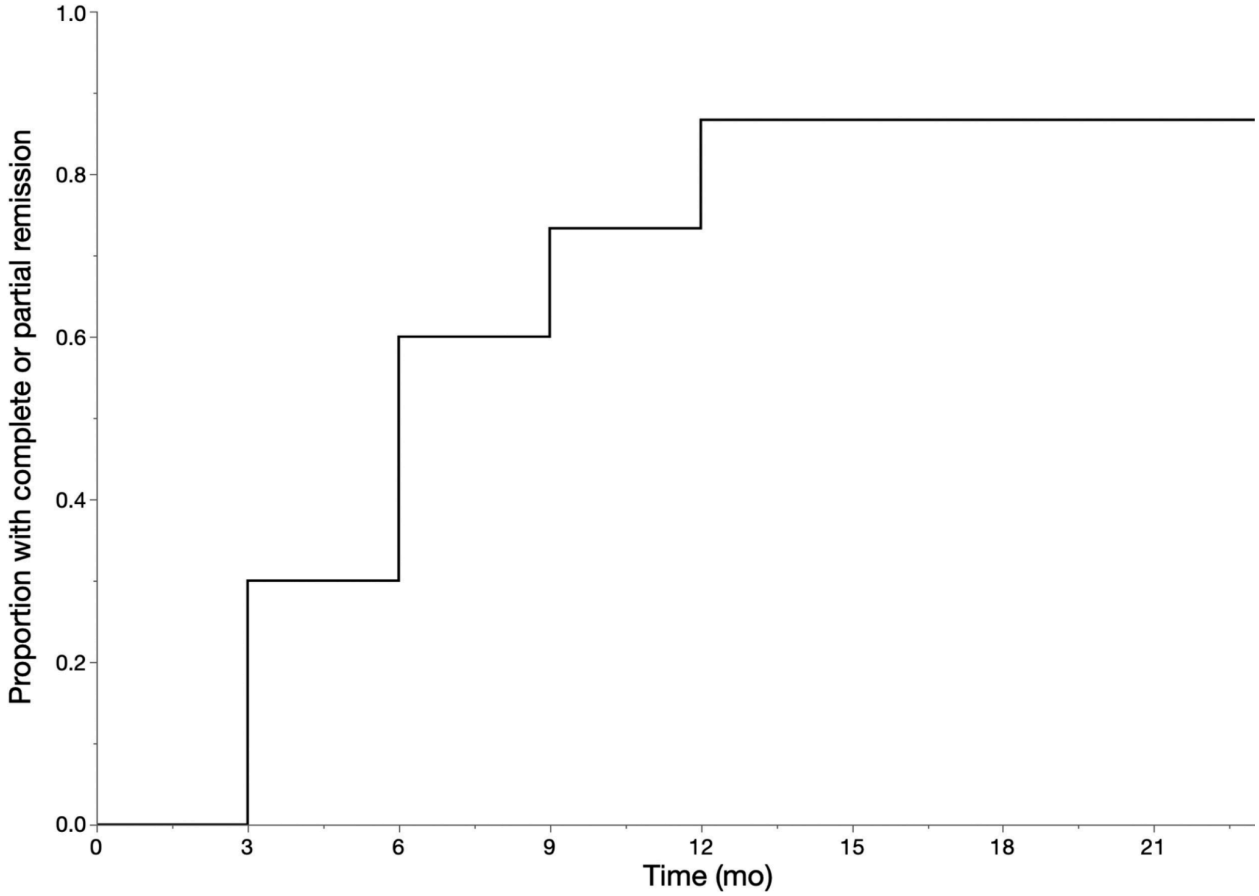
11. Current study by Trillini et al is a

- Prospective, single-center, open-label study
- 20 adults with biopsy-proven primary MN
- All had rituximab-resistant nephrotic syndrome
- Obinutuzumab: 3 doses (total 3000 mg over 4 weeks)
- Follow-up categorized into two cohorts
- Cohort A: 20 patients followed for 12 months
- Cohort B: 10 patients with extended 24-month follow-up

https://pubmed.ncbi.nlm.nih.gov/41624448/

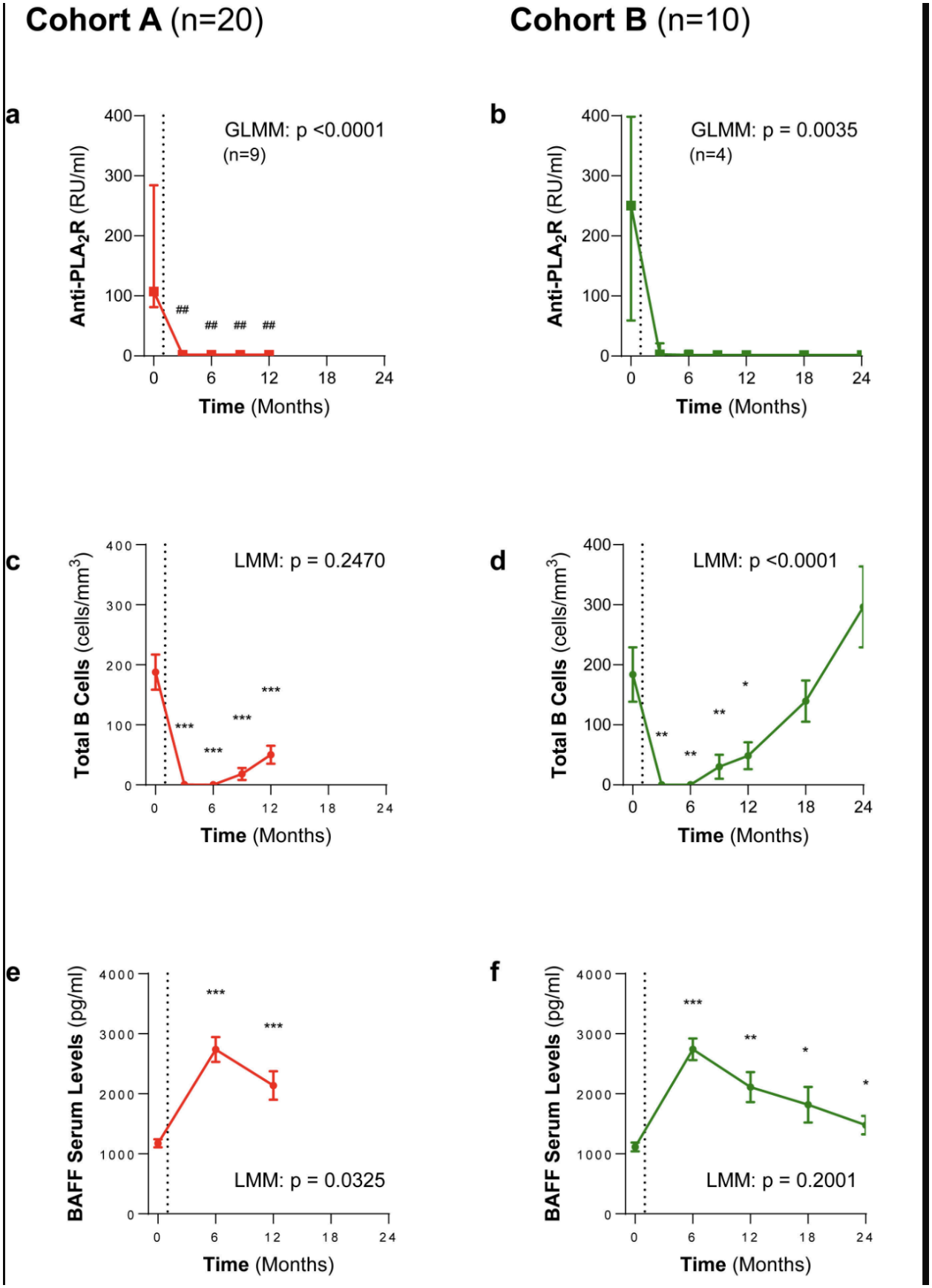
12.Results are astonishing

- **Remission:**
  - 80% at 12 months
  - 85% overall during follow-up
- Significant reduction in proteinuria (~5.7 → 1.3 g/day)
- Serum albumin improved
- No relapses after remission
- GFR remained stable
- Improvement in lipid profile and nephrotic state



13.What about Immunological Findings

- Rapid, near-complete B-cell depletion (3–6 months)
- Gradual recovery by 9–24 months
- No relapse despite B-cell return → “immune reset”
- Sustained suppression of anti-PLA2R antibodies


Cohort A (n=20)
Cohort B (n=10)
a
Anti-PLA2R (RU/ml)
GLMM: p <0.0001
(n=9)
##
Time (Months)
b
Anti-PLA2R (RU/ml)
GLMM: p = 0.0035
(n=4)
Time (Months)
c
Total B Cells (cells/mm3)
LMM: p = 0.2470
***
Time (Months)
d
Total B Cells (cells/mm3)
LMM: p <0.0001
**
*
Time (Months)
e
BAFF Serum Levels (pg/ml)
***
LMM: p = 0.0325
Time (Months)
f
BAFF Serum Levels (pg/ml)
***
**
*
LMM: p = 0.2001
Time (Months)

14. This drug seriously sounds miraculous. What about safety?
No increase in opportunistic infections reported in study
Infusion reactions → mild and manageable
Low immunogenicity → fewer anti-drug antibodies
No significant cytopenias
Renal function remained stable

15. Key takeaways from the study

- Obinutuzumab shows high efficacy in rituximab-resistant MN
- Deep sustained B-cell depletion
- Significant proteinuria reduction &albumin improvement
- Durable remission with no relapses
- True “immune reset”
- Larger studies are needed for long-term validation

16.Thank you for reading along! We hope this #Tweetorial shed light on obinutuzumab’s evolving role in resistant MN.
Follow @KIReports & https://www.kireportscommunity.org/
for more #MedEd in #kidneydisease! #FOAMed #nephtwitter

.