MarketVue®

Membranous Nephropathy

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1. DISEASE OVERVIEW

An autoimmune nephropathy characterized by thickening glomerular capillary walls and proteinuria

Membranous nephropathy (MN) is a slowly progressive, autoimmune glomerular disease that affects kidney function and is the cause of up to a third of nephrotic syndrome cases in adults.[1] Patients experience generalized swelling and decreased serum albumin levels, proteinuria, chronic fatigue, and possible progression to end-stage renal disease (ESRD). MN is distinguished by a thickening of glomerular capillary walls caused by immune deposits consisting of immunoglobulin (IgG), antigens, and membrane attack complexes (MACs), which prevents the kidneys from filtering blood effectively. There are two types of MN: primary (pMN) and secondary (sMN). Primary MN accounts for ~80% of cases and the underlying mechanism is not well-understood, whereas sMN accounts for the remaining ~20%, and is associated with the use of NSAIDs or other pre-existing diseases such as Lupus, HIV, Hepatitis B or C, and HPV.[1] Certain autoantigens serve as specific markers of MN. Most membranous nephropathy patients are diagnosed with an antigen-specific form of MN. The most common form is associated with the phospholipase A2 receptor (PLA2R) antigen, however other associated antigens include NELL1, THSD7A, SEMA3B, PCDH7, and HTRA1 (Figure 1.1.).

Membranous nephropathy can occur in all ages and ethnicities, although the average age of onset is typically between 50-60 years. The disease is much rarer in children, usually occurring as secondary to another disease. It predominately affects males over females (2:1) for unknown reasons.[1] The first indication of kidney impairment is typically the detection of protein in the urine (proteinuria), usually coupled with other symptoms, such as generalized edema. Bloodwork can confirm the presence of specific antibodies associated with the disease, such as the phospholipase A2 receptor (PLA2R) antigen that is present in ~70% of pMN cases.

Membranous nephropathy disease outcomes roughly follow the rule of thirds, with up to a third (~5-30%) of untreated patients undergoing spontaneous remission, 25-40% maintaining high levels of proteinuria despite ongoing treatment, and ~40% progressing to ESRD (Table 1.1.).[2] Complications include hypertension, an increased risk of life-threatening thromboembolic and cardiovascular events, malignancies such as cancers, and the risk for relapse even after kidney transplantation.

> *""This is like a relatively rare condition, but it's so often missed from the nephrology standpoint, I always feel like, 'Oh, my God, this is such a simple thing to diagnose. Why was the urine missed? Why was a urine not done?' I just wish that there was more awareness of nephrotic syndrome as a cause for fluid overload or even as a thrombotic risk, you know, that ER physicians or other doctors are looking for that more."* **- Nephrologist, U.S.**

Figure 1.1. Percentage of antigen-specific MN type among patients[3,4,5]

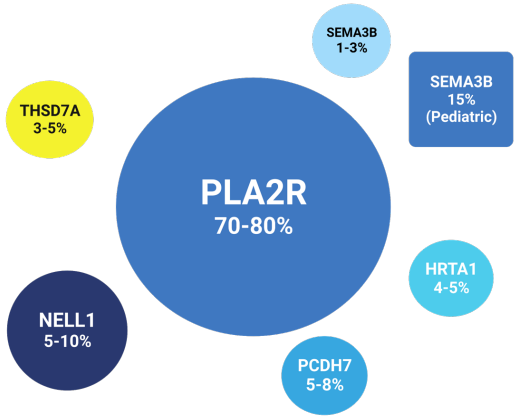


Table 1.1. Rule of thirds patient outcomes[2]

1	**Spontaneous complete remission** ~5 – 30% of patients
2	**Persistently high proteinuria** ~25 – 40% of patients
3	**Progression to ESRD** ~40% of patients

NEPHROTIC SYNDROME IN MEMBRANOUS NEPHROPATHY

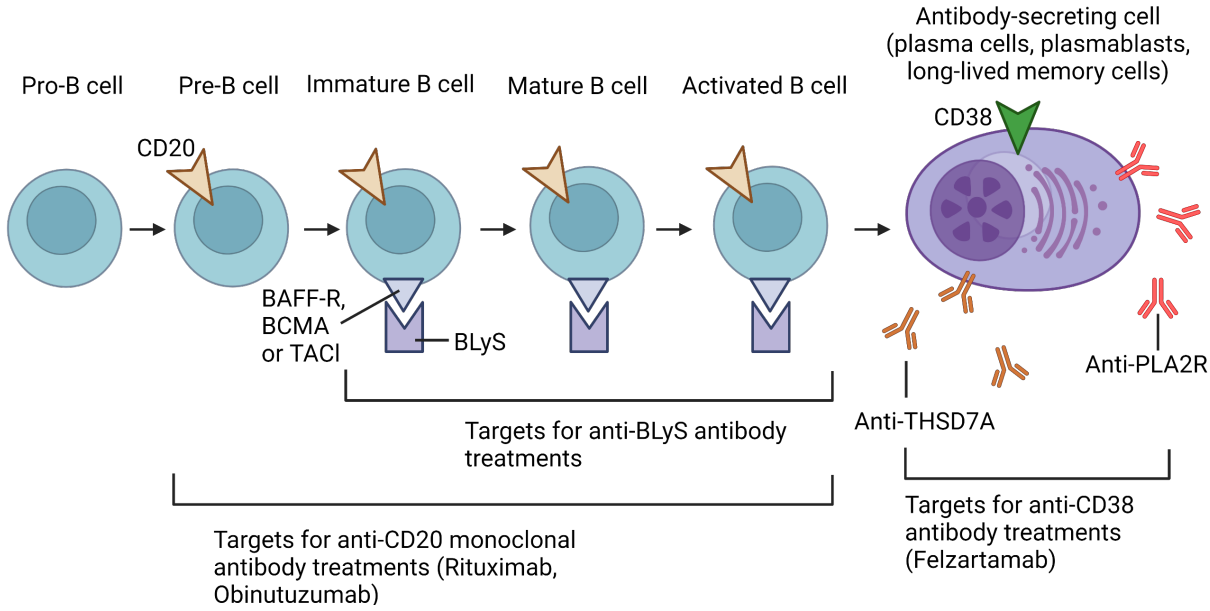
Nephrotic syndrome is a hallmark of membranous nephropathy. pMN is the most common cause of nephrotic syndrome in non-diabetic adults. Symptoms of nephrotic syndrome include significant proteinuria, low blood protein (albumin) levels, and edema. The majority (66%) of patients with MN present with nephrotic syndrome, and the remaining 33% present with asymptomatic proteinuria[1].

1. Figure created with BioRender.com based on Ronco, P, et al. Nat Rev Dis Primers. 2021 Sep 30;7(1):69. 2. Gupta, S, et al. BMC Nephrology. 2017;18(1):201. 3. Figure created using BioRender.com based on Tesar, V, et al. Frontiers in Immunology. 2021;12. 4. Sethi, S, et al. J Am Soc Nephrol. 2021;32(5):1249-1261. 5. Sethi, S. Journal of the American Society of Nephrology. 2021;32(2):268.

Underlying pathology dictates current and future targets for therapy

In the first stage of MN disease pathophysiology, small, electron-dense subepithelial immune complexes containing IgG, antigens, and MAC accumulate in the glomerular basement membrane, leading to cytoskeletal and structural changes at the level of the podocyte that cause leaking of protein into the urine. Over time, the basement membrane thickens, and forms spike-like projections into the subepithelial deposits, which characterizes the beginning of stage 2, wherein these deposits become surrounded by basement membrane and develop into intramembranous deposits. The final stage is characterized by an irregularly thickened glomerular basement membrane incorporating the deposits. Antigens, such as PLA2R, contribute to the disease by binding to the glomerular basement membrane and accumulating in the formation of the immune complexes. Antigens CD20 and CD38 are expressed on developing B cells and antibody-secreting cells (such as plasmablasts and plasma cells) and are targets of monoclonal antibody treatments (e.g., rituximab, felzartamab) that work by preventing antibody production (including auto-antibodies), and subepithelial deposition and accumulation of auto-antibodies in the glomerular basement membrane. (Figure 1.2.).[1]

Figure 1.2. Targets for monoclonal antibody treatments[2]



On using kidney biopsies

"I think the majority of patients are still being diagnosed for the first time on kidney biopsy, and the presentation is such that they'll present with proteinuria. Very often it's nephrotic syndrome, so proteinuria over, you know, 3.5 g and then low serum albumin, edema, so an adult who presents with that will very often just go straight to biopsy. And the one sort of exception to that, which is really an evolving kind of aspect of the field, is the use of PLA2R, and really that's the only antibody that is adequate for diagnosing membranous without a kidney biopsy." – **Nephrologist, U.S.**

"For the most part, people are still doing biopsies because it's not only for diagnostic purposes, right? So biopsies can also give you some other indications, for example, the extent of scarring and fibrosis in the kidney tissue, right? You want to see how much fibrosis and scarring you have. This information you may not get from the biomarker testing at the serology level, but you will get it from the kidney biopsy, and sometimes you'd be surprised how much information kidney biopsy gives you." – **Nephrologist, U.S.**

1. Ruggenenti, P, et al. *Nat Rev Nephrol.* 2017;13(9):563-579. 2. Figure created with BioRender.com based on Ronco, P, et al. Nat Rev Dis Primers. 2021 Sep 30;7(1):69.

2. EPIDEMIOLOGY & PATIENT POPULATIONS

United States and EU5

DISEASE DEFINITION

For this report, we define diagnosed membranous nephropathy (MN) as primary membranous nephropathy (PMN). diagnosed by kidney biopsy and the exclusion of conditions which can cause secondary glomerulonephritis (drug toxicity, infection, other autoimmune diseases etc.).[1,2,3]

Figure 2.1. Range of prevalent cases of primary MN by region

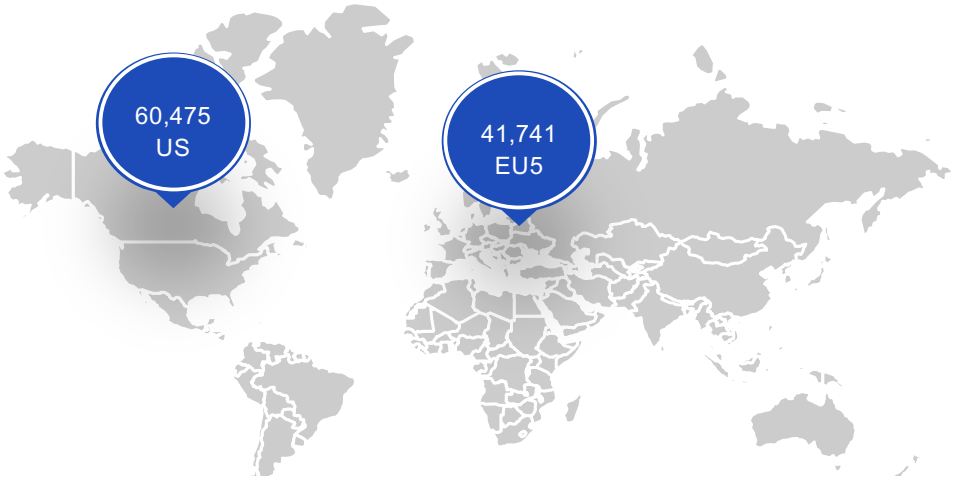


Table 2.1 Diagnosed Incident and Prevalent Populations of Primary MN in the U.S. and EU5[1]

Ages 18+	US	FR	GE	IT	SP	UK	Total G6
Diagnosed MN incident rate per 100,000	1.40	0.93	0.80	1.04	0.98	1.09	1.18
Diagnosed MN incident cases	3,686	484	557	530	381	593	6,230
Diagnosed MN prevalence rate per 100,000	22.97	15.26	13.13	17.06	16.08	17.88	19.32
Diagnosed MN prevalent cases	60,475	7,942	9,132	8,694	6,246	9,78	102,216
% PLA2R Positive	70%	70%	70%	70%	70%	70%	70%
Prevalent PLA2R MN cases	42,332	5,559	6,809	6,392	6,086	4,372	29,219

For the incidence of primary MN, we used country-specific sources when available. For the United States, we used a population study by Sim et al. which estimated the incidence of primary MN in an ethnically diverse U.S. population[2]. For France, Germany, Italy, and the UK we also used country-specific sources (See Chapter 7 – Methodology). Due to the lack of country-specific data for Spain we averaged the incidence of primary MN in France and Italy. Most of the studies reporting incidence of primary MN exclude younger individuals due to lack of cases. For this reason, we report the incidence of primary MN only in individuals aged 18 and above. When necessary, we adjusted the rates of each study to reflect this age cutoff. Due to very little epidemiological data available which reports the prevalence of primary MN, we estimated the size of this population by applying the proportion of primary glomerulonephritis cases which are MN to a prevalence rate of primary glomerulonephritis from a U.S. study and extrapolated this to EU5 countries (for further details see Chapter 7 – Methodology). Here we also report the proportion of individuals with primary MN who are positive for the most common autoantibody: PLA2R.

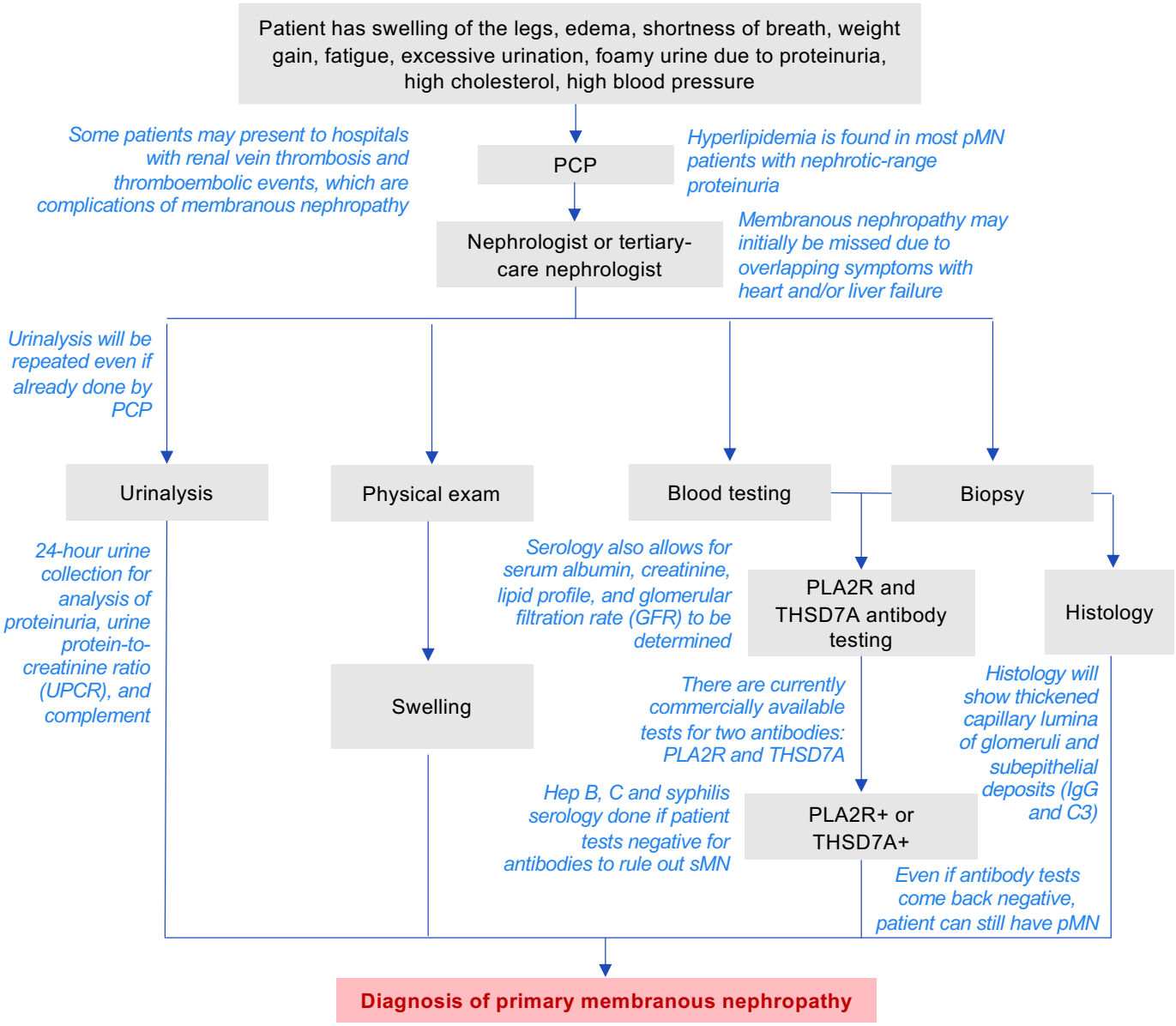
1. REACH primary market research; see Section 7 on methodology.
2. Sim JJ, et al American Journal of Kidney Diseases. 2016 Oct 1;68(4):533-44.

3. DIAGNOSIS & CURRENT TREATMENT

DIAGNOSIS OVERVIEW[1]

Most membranous nephropathy (MN) patients will initially be seen by a PCP/GP before being referred to either a community nephrologist or one specializing in glomerular diseases. Although most nephrologists are comfortable diagnosing and treating MN, patients may occasionally be referred by a general nephrologist to an academic or larger, tertiary center with a glomerular disease clinic. The signs and symptoms of MN include severe edema, foamy urine, weight gain, fatigue, and a loss of appetite. The results of the diagnostic workup make a clear distinction between primary and secondary MN, and this informs treatment. Primary MN is considered idiopathic but is typically attributed to the presence of an auto-antibody and the absence of a secondary cause. Secondary MN can be due to infections, neoplasms, drugs, heavy metal poisoning, autoimmune diseases, stem cell transplants, graft versus host disease, and diabetes; it is most efficiently treated by resolving the underlying secondary cause.

Figure 3.1. Diagnostic pathway for membranous nephropathy patients[1,2,3]



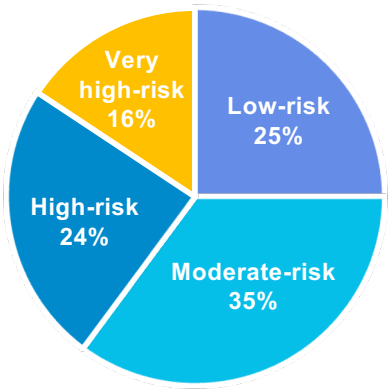
1. REACH primary market research; see Section 7 on methodology 2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4934807/
3. https://emedicine.medscape.com/article/239799-workup#c4

Diagnostic testing for antibodies is replacing the old gold-standard kidney biopsy

Interviewed nephrologists report once MN is suspected, the diagnostic process is relatively straightforward, and patients typically receive a timely diagnosis. Within the last ten years, the availability of reliable antibody testing for the PLA2R and THSD7A antigens has revolutionized the diagnostic workup process. The revised KDIGO 2021 guidelines have dropped the requirement for a kidney biopsy as confirmation for MN in patients who are PLA2R+ and have nephrotic syndrome. However, although the number of kidney biopsies has decreased, many nephrologists continue to utilize them because they can provide important information regarding renal scarring and fibrosis, which can be valuable information, especially in the minority of patients who may have antibodies for which there currently are no commercially available tests.

Once patients receive a diagnosis, they are often categorized based on the risk of progressive loss of kidney function (Table 3.1 and Figure 3.2.). Per surveyed nephrologists, approximately one third of their patients are moderate risk, while another ~40% are high or very-high risk. This categorization determines approaches to treatment and is prognostic.

Figure 3.2. Percentage of MN patients by risk category according to surveyed nephrologists (n=26)[1]



"We can send off a primary membranous panel, so that includes PLA2R antibody testing, and I'm blanking on the other complete name, but it's one of the antibodies that have been discovered as a cause of primary membranous, which I believe is thrombospondin, if I remember correctly, so we can send out the primary membranous antibody testing, but even if the antibodies are going to come back positive, I'm still planning to biopsy this patient, so I'll be getting the patient ready for a kidney biopsy at the same time."
– **Nephrologist, U.S.**

"If they have a strong marker for like PLA2R, then people are moving away from requiring a biopsy for diagnosis. However, if the antibody level is low or if they don't have one, then yes, we do still have to resort to kidney biopsy for the diagnosis." – **Nephrologist, U.S.**

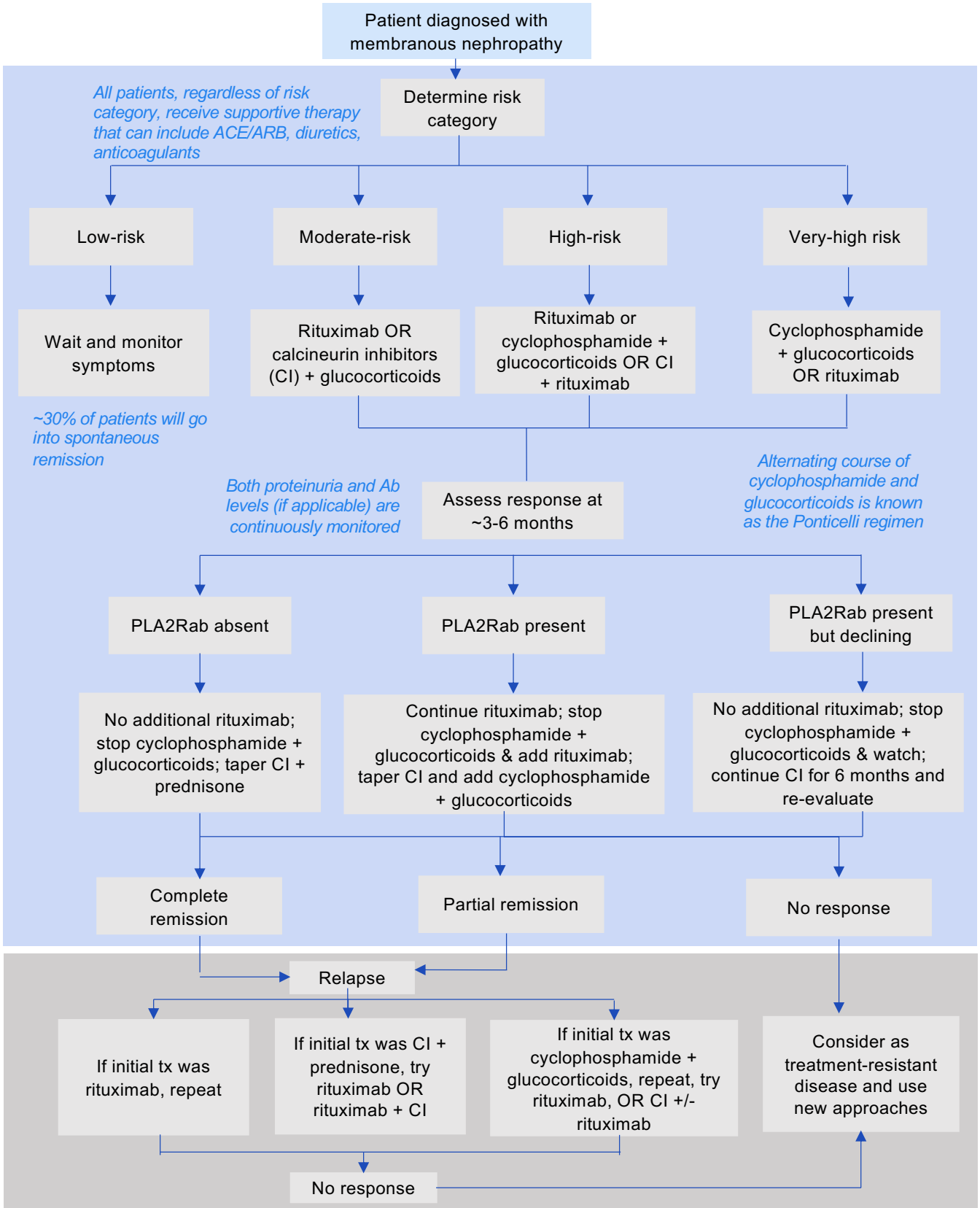
"I think a lot of us will still find value in the biopsy and will still do the biopsy unless there are major contraindications." – **Nephrologist, U.S.**

Table 3.1. KDIGO 2021 clinical criteria for assessing risk of progressive loss of kidney function[2]

Low-risk	Moderate-risk	High-risk	Very high-risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria, >3.5 g/d and decrease <50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73m^2 and/or proteinuria >8g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and decrease <50% after 6 months of conservative therapy with ACEi/ARB AND at least 1 of the following: • Serum albumin <25 g/l • PLA2R ab level >50 RU/ml • Urinary α_1 –microglobulin >40μg/min • Urinary IgG > 1μg/min • Urinary β_2 –microglobulin >250 mg/d • Selectivity index >0.20	• Serum creatinine > 1.5mg/dL • eGFR decrease >20% attributed to MN • Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained OR • High risk AND PLA2R ab >150 RU/ml

1. REACH primary market research; see Section 7 on methodology
2. Table adapted from KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

Treatment flow for primary membranous nephropathy[1,2]



1. REACH primary market research; see Section 7 on methodology 2. KDIGO Clinical Practice Guidelines for Management of Glomerular Diseases https://www.kidney-international.org/article/S0085-2538(21)00562-7/fulltext

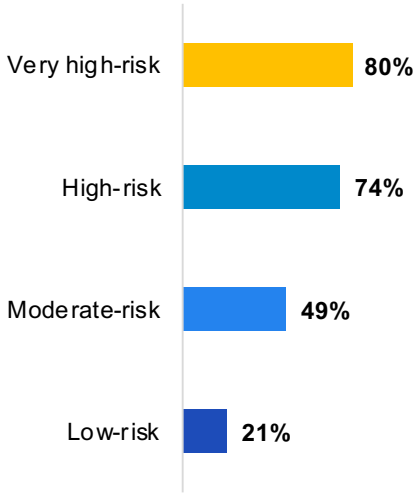
Immunosuppressive therapy is the mainstay of treatment for moderate, high, and very high-risk MN patients

Standard of Care (SOC)

While there are no FDA-approved therapies for MN, interviewed nephrologists report there are relatively consistent guidelines for approaches to treatment[2]. There are essentially two types of therapies for MN patients: supportive and immunosuppressive. The goals of supportive therapy are to control blood pressure and edema, as well as prevent secondary complications such as cardiovascular issues and blood clots. Supportive therapies include RAS blockade (ACE inhibitors or ARBs), diuretics, and anticoagulation drugs. Patients are also recommended to follow a low-sodium and moderate-protein diet. The majority of low-risk patients will only receive supportive therapy, given that they are more likely to go into spontaneous remission and the benefits of immunosuppressive therapy are generally not seen to outweigh the risks. Nevertheless, all patients, regardless of risk category, will receive some form of supportive therapy.

The most commonly prescribed immunosuppressive therapies include rituximab, calcineurin inhibitors, and cyclophosphamide combined with steroids. Patients who are at a higher risk for severe nephrotic syndrome, as evidenced by persistent proteinuria despite supportive treatment and high or climbing antibody titers, are candidates for immunosuppressive therapy. Thus, most moderate, high, and very-high-risk patients receive some form of immunosuppressive therapy.

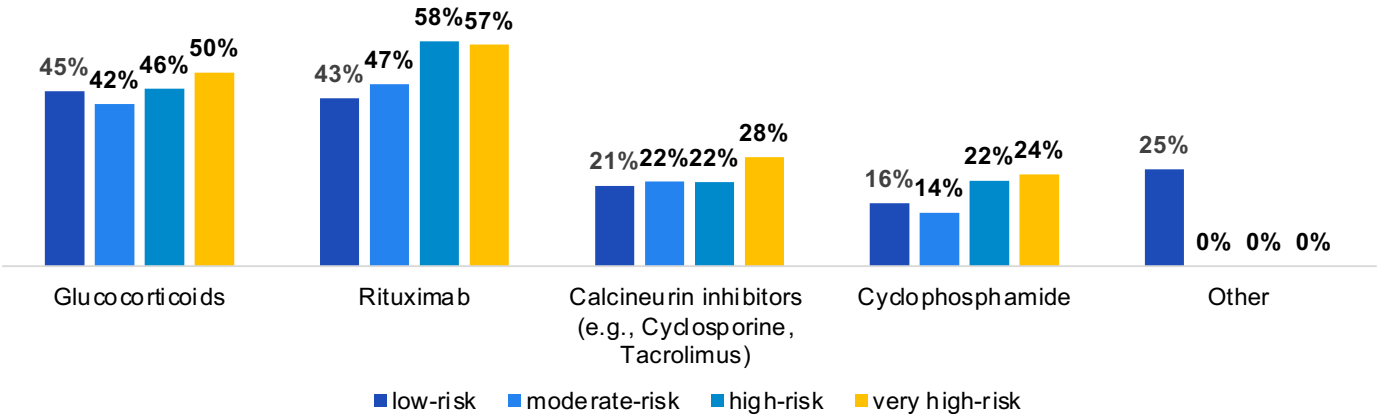
Figure 3.3. Percentage of MN patients treated with immunosuppressive therapy by risk category[1]



According to both interviewed and surveyed nephrologists, provided it is not contraindicated, rituximab is the preferred immunosuppressive therapy for MN patients, regardless of risk classification. Interviewed nephrologists frequently cited the MENTOR trial (NCT01180036) as influential in how and why they use rituximab compared to other immunosuppressive therapies. In this open-label, multicenter RCT, 130 patients were randomized to receive either rituximab or cyclosporine. Rituximab was dosed at 1 g for 2 doses, 2 weeks apart, with redosing at 6 months as needed, while cyclosporine was dosed at 3.5 mg/kg/day. This study demonstrated rituximab was superior to cyclosporine at inducing complete or partial remission at 2 years, as defined by proteinuria: 60% of the patients in the rituximab group achieved either complete or partial remission, compared to 20% in the cyclosporine group[3].

As this study was a relatively large RCT of two commonly used off-label treatments for MN, interviewed nephrologists find these results compelling and have led them to preferentially treat with rituximab given its efficacy in inducing some form of remission, even though patients may require repeated doses at 6 and 12 months. When thinking about tradeoffs between the three different immunosuppressive therapies used in MN, interviewed nephrologists predominantly reported that rituximab is their first choice when it comes to overall safety, efficacy, and dosing convenience, though they acknowledge the speed of onset with rituximab is often slow and there is room for improvement in the proportion of patients who achieve and maintain complete remission.

Figure 3.4. Nephrologist-reported current treatment share for immunosuppressive-treated MN patients[1]



1. REACH primary market research; see Section 7 on methodology
2. https://www.kidney-international.org/article/S0085-2538(21)00562-7/fulltext
3. https://www.nejm.org/doi/full/10.1056/NEJMoa1814427

Achieving partial or complete remission is the ultimate goal of treatment

OVERVIEW

Although membranous nephropathy itself is not considered a life-threatening disease, nephrotic syndrome, which can result if membranous nephropathy is not treated and controlled, can lead to life-threatening complications. The hallmarks of nephrotic syndrome are protein in the urine, not enough protein in the blood, too much fat or cholesterol in the blood, and edema. If this progression is not controlled, nephrotic syndrome can lead to an aggressive decline in GFR and kidney function, leading to secondary complications of membranous nephropathy that include life-threatening thromboembolic events, such as pulmonary embolisms. Interviewed nephrologists also state that some patients may need to be hospitalized to receive diuretics because they are so swollen, which greatly affects their quality of life. Thus, once diagnosed, all membranous nephropathy patients are receiving some form of drug therapy.

Table 3.2. Treatment goals for MN[1]

1	Lower PLA2R antibody levels
2	Lower proteinuria to achieve either complete or partial remission
3	Control nephrotic syndrome to minimize secondary complications

Upon initiation of treatment, the primary goal is to lower antibody levels to zero (in patients who have auto-antibodies that can be reliably detected with a commercially available assay, i.e., those who are PLA2R+ or THSD7A+). This is a goal because high antibody titers tend to correlate strongly with severe proteinuria. Thus, by lowering antibody levels, proteinuria should eventually reduce to an acceptable level and ideally resolve completely, which is another goal of MN treatment. Interviewed nephrologists state that proteinuria is an indicator of kidney injury and is associated with long-term decline in kidney function. However, proteinuria alone cannot be always used as a reliable marker since many things can affect proteinuria. This factor, combined with the fact that there are no other known diseases associated with PLA2R antibodies, gives interviewed experts confidence that reducing PLA2R antibody titers is an accurate prognostic biomarker for eventual proteinuria reduction, as assessed by complete or partial remission.

> *"So the goal of therapy again has changed a little bit. It used to be proteinuria reduction and preservation of GFR, which are still goals of therapy, but now more recently if they do have a serologic marker, then we would want to normalize that serologic marker."* – **Nephrologist, U.S.**
>
> *"When you look at antibody reduction, the one thing I think is that you still want to have a complete remission. You really still want to see antibody levels really disappear."* – **Nephrologist, U.S.**

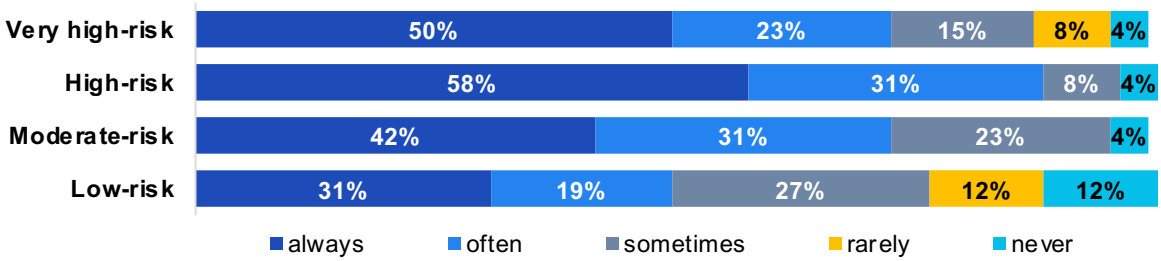
Table 3.3. Key terms to know for MN[2]

Term	Definition
Complete remission	Reduction in urine protein to <0.3 g/day (UPCR <300 mg/g or 30 mg/mmol) confirmed by two values at least 1 week apart, with normal serum albumin and renal function
Partial remission	Reduction in urine protein to <3.5 g/day (UPCR <3,500 mg/g or 350 mg/mmol) and ≥50% reduction from peak values, confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of serum albumin, and stable renal function
Relapse	New symptoms of nephrotic syndrome after achieving either complete or partial remission

1. REACH primary market research; see Section 7 on methodology 2. Table adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4934807/

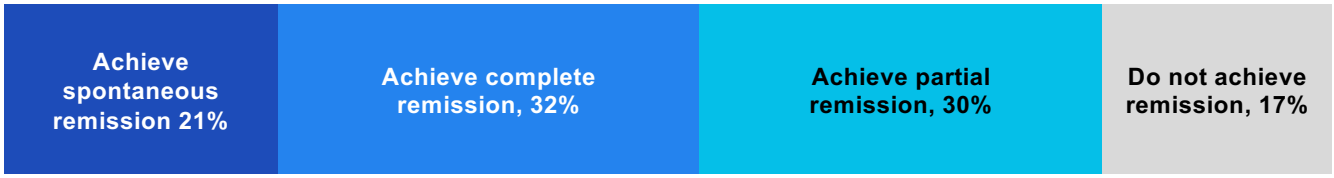
Immunologic remission precedes clinical remission

Figure 3.5. Percentage of nephrologists monitoring antibody levels in PLA2R+ pts throughout treatment[1]



Given the correlation between PLA2R antibody titer and severity of disease, the majority of nephrologists always or often monitor antibody levels throughout treatment, especially in those who are high or very-high risk (Figure 3.5). While both antibody levels and proteinuria are used to guide therapy, there is a lag between immunologic responses and complete remission as determined by proteinuria reduction. Interviewed experts we spoke to state that patients initially presenting with a high anti-PLA2R titers who experience significant reductions after several months of treatment may still have elevated proteinuria that will continue to decrease over the next several months. Furthermore, interviewed nephrologists report that in their experience, patients whose antibody titers decrease to undetectable or near undetectable levels on commercial assays will frequently go on to achieve complete remission, with up to 1/3 of patients achieving spontaneous remission without needing any immunosuppressive therapy (surveyed nephrologists put this number at closer to ~20%, Figure 3.6). Thus, it is generally accepted amongst nephrologists that falling PLA2R antibody titers (either spontaneously or as a result of immunosuppressive treatment) is indicative of an impending remission, although the ideal goal is antibody levels that are undetectable in the patient.

Figure 3.6. Nephrologist-reported proportion of MN patients achieving different disease responses[1]



Although surveyed nephrologists estimate that almost two-thirds of MN patients will achieve either partial or complete remission (Figure 3.6), interviewed nephrologists explain that there can be variability in the timing, extent, and durability of remission depending on the type of immunosuppressive therapy. Cyclophosphamide tends to induce the highest rates of both partial and complete remission, and it can do so relatively quickly, usually within 3 months. However, due to its toxicity, it is more often reserved for high and very high-risk patients (Figure 3.5). Interviewed nephrologists report that between 60-70% of patients achieve remission with rituximab, but its onset is much slower and can take upwards of 6 months to a year to induce remission. Thus, even though physicians largely prefer to rituximab, when a patient has a rapid decline in kidney function or other significant symptoms, cyclophosphamide is used. Although calcineurin inhibitors can induce remission within a few months, they come with concerns over long-term toxicity and higher relapse rates according to interviewed nephrologists. Overall, surveyed nephrologists estimate that approximately one third of their MN patients relapse after achieving complete remission (Figure 3.7).

Figure 3.7. Time to remission and proportion of patients who relapse following complete remission according to surveyed nephrologists

8 months is the average duration of treatment before a membranous nephropathy patient is able to achieve complete remission

32% is the proportion of membranous nephropathy patients who will experience a relapse after achieving complete remission

1. REACH primary market research; see Section 7 on methodology

Upsides and downsides of current immunosuppressive membranous nephropathy treatments

Treatment	Upsides	Downsides
Rituximab	• Steroid-sparing • Most patients do not completely fail treatment and will achieve either complete or partial remission • Overall less immunosuppression than other therapies since most pts will achieve some form of remission • No long-term risk of malignancy or increase in cardiovascular mortality • Dosing is straightforward, infrequent	• Slow onset of action • Optimal dose and timing is uncertain, with many patients needing repeated doses every 6 months • Black box label for fatal infusion-related reactions, severe mucocutaneous rxns, Hep B reactivation, PML • Rarely, patients can experience serum sickness and/or anaphylaxis • Myelosuppression and increased risk of opportunistic infections due to broad immunosuppression • Hypogammaglobulinemia • Lab monitoring required • Lower rates of remission than cyclophosphamide + glucocorticoids
Calcineurin inhibitors	• Steroid-sparing • Relatively low cost compared to rituximab • Relatively effective at inducing remission	• Long-term nephrotoxicity • Long-term neurotoxicity • Myelosuppression and increased risk of opportunistic infections due to broad immunosuppression • Side effects include hair growth, gingiva hyperplasia, diabetes, hypertension, and liver dysfunction • Higher rates of relapse than rituximab • Lab monitoring required
Cyclophosphamide + glucocorticoids (e.g., Ponticelli regimen)	• Relatively low cost compared to rituximab • Most effective at inducing remission (partial or complete) amongst currently available immunosuppressive therapies • Faster onset of action than rituximab • Can rapidly prevent progression towards renal failure	• Significant side effects of corticosteroids include: hypertension, obesity, headache, nausea, osteoporosis, ulcers, cataracts, psychological disturbances, infections, sepsis, and serum electrolyte disturbances • Corticosteroids contraindicated in elderly patients with comorbidities such as hypertension, diabetes, obesity • Myelosuppression and increased risk of opportunistic infections due to broad immunosuppression • Side effects of cyclophosphamide include: anemia, nausea, anorexia, cystitis, and hair loss • Risk of infertility in younger patients • Leukocytopenia • Thrombocytopenia • Increased risk of malignancy, including blood and bladder cancers • Lab monitoring required

Physician perspectives on current treatment regimens

Table 3.4. KOL insights on current regimens[1]

Rituximab
"The problem with rituximab, it does work, but it does take a lot of time to work. It can be three or four months before you see a benefit of rituximab just because it's a B-cell-depleting agent, so if my patient is having very significant symptoms, rapid decline in the kidney function, and I need to induce remission as fast as possible, I have to do cyclophosphamide." – **Nephrologist, U.S.**
"Hepatitis B positivity is a contraindication for using rituximab, and there are some situations where I have to go back and do cyclophosphamide despite the side effects." – **Nephrologist, U.S.**
"It's been cited in a variety of studies. Probably the most pivotal study was the MENTOR study that was published in the New England Journal of Medicine, and there the dosing was the 1 g separated by two weeks, repeated at six months. That is what I do in practice, what most of my colleagues do in practice. It's just way more convenient. It'll eliminate circulating B cells in the vast majority of patients. It may be overkill, and there are some studies that have looked at can you do lower doses and still do okay, but when you look at like the complexity needed to do smaller regimens, you know, get one and then we'll check your B cells and we'll decide whether to have you come back. Realistically, a lot of times we don't do that– **Nephrologist, U.S.**
"I've had pretty good efficacy with rituximab, you know, with good rates of remission. I've also had success with cyclophosphamide in the past. However, a couple of my patients had side effects to rituximab as far as one had an allergic reaction. Another one had something called serum sickness which required hospitalization, and that means they can never get rituximab again, so it does have different side effects than cyclophosphamide, I would say." – **Nephrologist, U.S.**
"In my experience, rituximab has worked extremely well. I think that I've not had a patient fail rituximab, although I do have patients that don't have a complete response to rituximab." – **Nephrologist, U.S.**
Calcineurin inhibitors (e.g, Cyclosporine, Tacrolimus)
"If the Rituxan doesn't work, then the next line I would probably try is the calcineurin inhibitors. I use tacrolimus and not cyclosporine, which is what they studied for the MENTOR trial, because tacrolimus, I think it has a better side-effect profile, so I will use tacrolimus." – **Nephrologist, U.S.**
"My concern with calcineurin inhibitors, which I have seen and it's been shown, is that when we stop it for membranous, there's a very high percentage of relapse.." – **Nephrologist, U.S.**
"If the renal function is on the lower side, so maybe EGFR less than 50 or 60, and that's just my gestalt, I would be hesitant to start them on calcineurin inhibitor because these have further detrimental effects on like say hyperkalemia and, you know, renal vasoconstriction, so I'm a little hesitant about using tacrolimus as the renal function is worsening." – **Nephrologist, U.S.**
"I rarely use those now. I do use cyclosporine if they are very, very proteinuric, so, you know, let's say they have like more than 5 g of proteinuria, they're already very hypoalbuminemic, and they have good kidney function, I might put them on a calcineurin inhibitor, at least temporarily, to quickly reduce their proteinuria." – **Nephrologist, U.S.**
Cyclophosphamide + glucocorticoids
"Cyclophosphamide, I have used it, but I try to save that because one, my patients don't want it, and two, you know, it's associated with other concerning risks such as increased risk of malignancy including blood, bladder cancers, leukemias, hemorrhagic cystitis, and like pretty bad bone marrow suppression, so because it has all those side effects, yes, I've used it especially if they don't respond to rituximab and I'm concerned that their kidney function is just declining. I will use it, but I don't use it as a first line." – **Nephrologist, U.S.**
"So cyclophosphamide has been the standard therapy. The problem is the side effects you get with the chemotherapy including leukopenia, GI symptoms, hair loss, all of those." – **Nephrologist, U.S.**
"Cyclophosphamide, efficacy seems to be the best, but it's really the tolerability. You know, my younger patients do worry about infertility." – **Nephrologist, U.S.**

1. REACH primary market research; see Section 7 on methodology

Key treatment dynamics that will shape disease management and drug use in MN

Table 3.5. Must-know membranous nephropathy treatment dynamics

Nephrologists are comfortable monitoring PLA2R antibody titers and using reduction in these levels to guide treatment decisions – Given the correlation between antibody status and proteinuria levels, nephrologists we spoke to say they are generally comfortable making treatment decision based on antibody titer reductions. Additionally, KOLs are largely willing to accept reductions in titers as evidence of efficacy in proof-of-concept studies. However, PLA2R and THSD7A are currently the only biomarkers with commercially available assays, excluding ~20-25% of MN patients who are positive for other identified antibodies. Availability of reliable testing for additional MN antibodies will provide additional biomarkers for disease prognosis and to guide treatment for these patients as well as to allow clinical trials to measure antibody responses in a broader group of patients to track treatment responses in proof-of-concept and pivotal studies.

Emerging therapies will need to differentiate themselves based on efficacy, onset of action, and antigen-specific mechanisms of action. With no FDA-approved therapy for MN, nephrologists are looking for something that can induce complete, durable remission in the majority of patients. Currently, most nephrologists rely on rituximab as the go-to immunosuppressive therapy. However, its slow onset of action combined with less-than-ideal rates of inducing durable remission leaves room for a better therapy. Obinutuzumab, another anti-CD20 inhibitor, has an opportunity to differentiate itself on both efficacy and onset of action. Moreover felzartamab, an anti-CD38 inhibitor, is exciting to some nephrologists because it represents a different target, with potential to deliver promising results in patients who are currently refractory to or relapsed following anti-CD20 treatments. Interviewed experts hypothesize anti-plasma-cell therapies could be promising in patients who are refractory to current immunosuppressive treatments, since they may have autoantibody-producing plasma cells rather than immature B cells.

Figure 3.8. Important dynamics of membranous nephropathy market evolution

Today

"With immunosuppression, like my first thing I probably give is Rituxan, rituximab, and this is based on the MENTOR trial that was published in New England Journal of Medicine several years ago." – ***Nephrologist, U.S.***

1

Rituximab will continue to be the backbone of treatment. Nephrologists report there is currently nothing as effective as rituximab in inducing remission while causing relatively few long-term side effects

2024 – 2026

Approval of the first treatment for MN is on the horizon. Obinutuzumab is in Ph 3 trials and felzartamab has reported positive Ph 2 data and it appears that FDA-approved therapies for MN may become available in the next several years.

2

"Other anti-CD20s are not really exciting. You know, it's like you have a Ferrari, and now you want a Lamborghini, but it's still a car. It's not like you have a car and now you have a plane. It's not that level. It's kind of a one-off where, you know, anti-CD20 has worked, so you use another anti-CD20 antibody which may have, you know, an additional 5% efficacy, but it's not a game-changer."
– ***Nephrologist, U.S.***

2030+

"So if we think that the PLA2R is a specific pathway that's causing primary membranous, I would want to know if there's a specific way of targeting that pathway and then hopefully have less systemic side effects."
– ***Nephrologist, U.S.***

3

New, more targeted mechanisms of action? While the late-stage pipeline is sparse, there are a number of therapies in earlier stages with varied MoAs. Physicians ideally hope for a rapid and efficacious antigen-specific therapy.

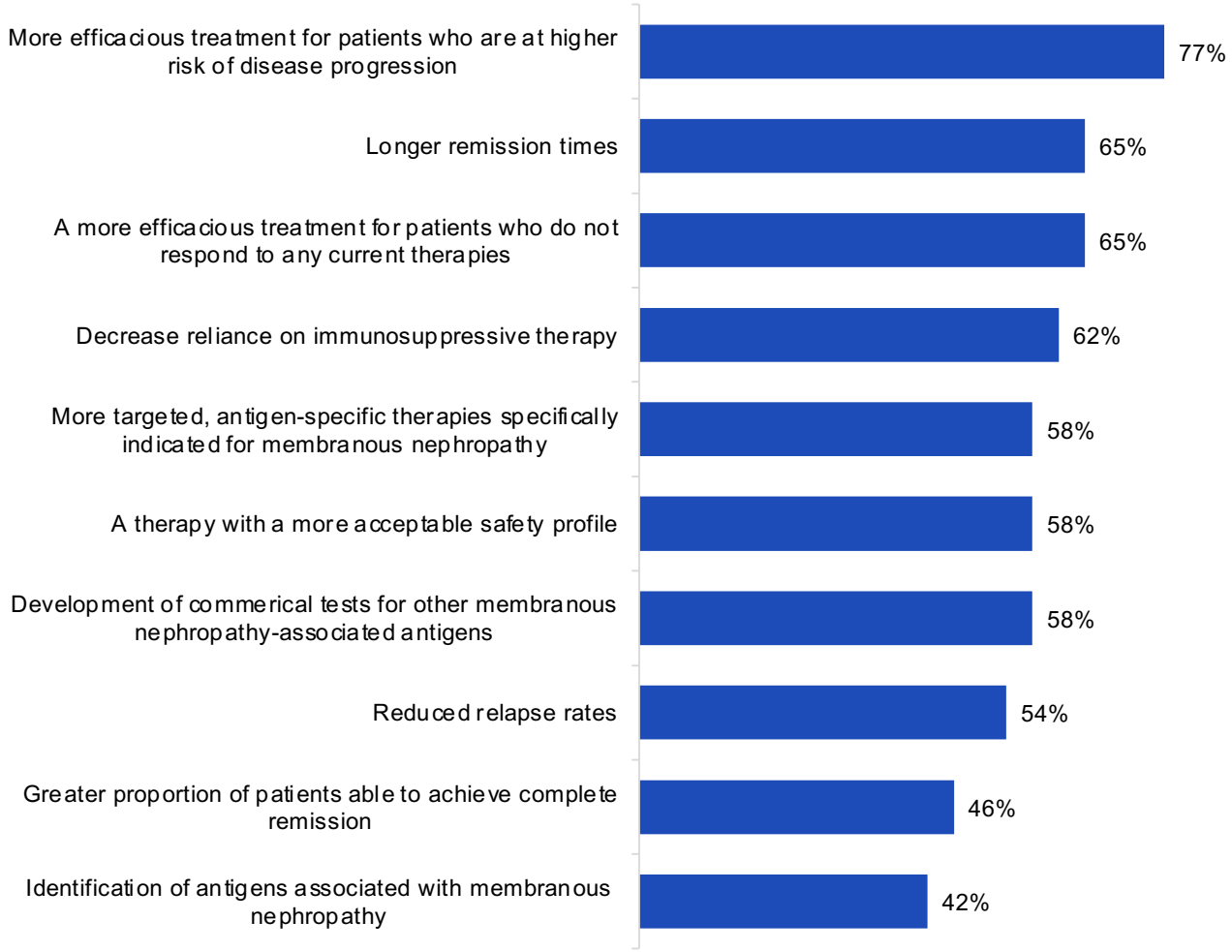
4. UNMET NEED

OVERVIEW

Given there are no approved therapies indicated specifically for membranous nephropathy, there remain multiple unmet needs. Both interviewed and surveyed nephrologists agree that there is a large need for more efficacious therapies for all membranous nephropathy patients, meaning therapies that will reduce proteinuria and induce either partial and/or complete remission at a greater rate than current treatments. However, surveyed nephrologists are particularly concerned for those patients who are at a higher risk for disease progression or are refractory to all other currently available immunosuppressive treatments. Physicians would also like to see more antigen-specific therapies in the near future. Additionally, interviewed and surveyed nephrologists are also interested in therapies that can induce longer periods of remission given that upwards of a third of patients who achieve either remission will ultimately relapse at some point (Figure 3.7), although the time to relapse is highly variable. Thus, it is not surprising that nearly two-thirds cite a therapy with longer remission times, and more than half say that therapies with reduced relapse rates are important needs in MN (Figure 4.1).

Figure 4.1. Nephrologist-reported unmet needs in membranous nephropathy[1]

How would you rate the following unmet needs for membranous nephropathy treatments?
Use a scale where 1 = Not at all important and 7 = Extremely important.



Percentage of nephrologists (n=26) rating unmet need as 'important' – a score of "6" or "7"

1. REACH primary market research; see Section 7 on methodology

Physician insights on the most urgent unmet needs for membranous nephropathy

"One is the need for more specific therapy for membranous and possibly even based on the antigen. At one point, would we have different treatments based on different antigens? That's possible. I don't know, but there is going to be much more the subsets of membranous."

- Nephrologist, U.S.

"I think the unmet need is development of these tests for other antigens because I do think going into the future, you know, it's going towards like personalized medicine where instead of membranous, we'll say, 'This is PLA2 membranous,' or, 'This is malignancy-related membranous that's related to a different antigen,' maybe something called NELL antigen that may be associated with that or lupus-related antigen…so I think going forward, I know we're headed towards that, something where we can actually personalize it, but I think the unmet thing is one, identify the antigens, which is in the works, but also making them available for testing. I think when PLA2 became commercially available, it really did change the course of how we treated these patients, so I do believe the future of membranous is going to be a more personalized level."

- Nephrologist, U.S.

"So for the most part, what we're dealing with, if you're going to ask me what is the unmet need, we're still dealing with overall Immunosuppressive therapy. Cyclophosphamide is used for membranous, used for lupus, used for ANCA vasculitis, but there is the unmet need of having a lot of side effects with the [immunosuppressive therapies] that we have like cyclophosphamide."

- Nephrologist, U.S.

"The third unmet need is that there is still a small subset of the patients who would not respond to any of those [immunosuppressive] agents."

- Nephrologist, U.S.

"[The unmet need] would be more like the targeted therapies that, you know, cancer treatment has where you have molecules or therapies directed to a specific pathway, to a specific target. We're discovering all these antibodies that could possibly be leading to the disease process in membranous, but we really don't have any targeted therapies. That's what I would think, yeah."

-Nephrologist, U.S.

"So I certainly think that longer remission would be something. You know, as I said, rituximab is very good at inducing a response, but a lot of times that response is partial and not complete. In fact, partial is probably more common than complete response is, and so one, higher rate of complete response, and two, certainly longer duration of remission."

-Nephrologist, U.S.

1. REACH primary market research; see Section 7 on methodology

5. PIPELINE ANALYSIS

OVERVIEW

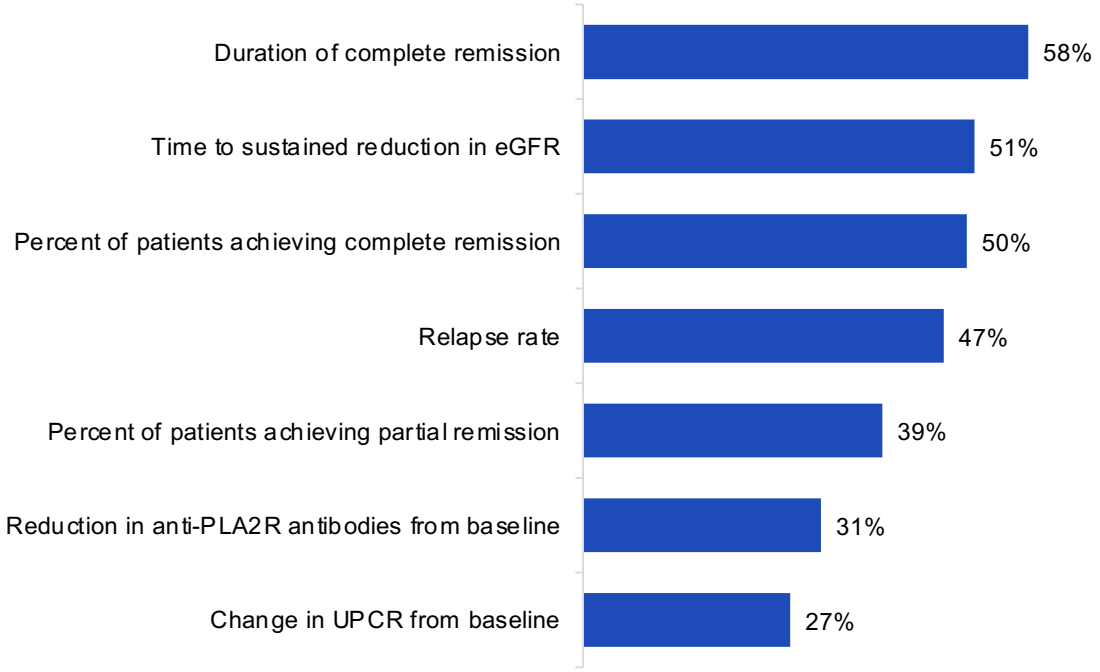
The development pipeline for membranous nephropathy is relatively active with current candidates targeting a variety of mechanisms (Table 5.1.). Several therapies currently in development for MN are already approved in other indications including pegcetacoplan (Apellis' Empaveli, a C3 complement inhibitor approved for paroxysmal nocturnal hemoglobinuria and geographic atrophy), obinutuzumab (Roche's Gazyva, a CD20 inhibitor approved for CLL and follicular lymphoma) and efgartigimod (argenx's Vyvgart, an FcRn inhibitor approved for gMG in patients who are AChR positive), which recently posted a Phase 2 study that will enroll patients in China[2].

Beyond these therapies, felzartmab is notable as it is a novel therapy targeting CD38 and is currently in Phase 2 for MN. Felzartamab was previously developed by Morphosys, however in June 2022, the company out-licensed worldwide development and commercialization rights to felzartamab outside of China to Human Immunology Biosicences (HIBio)[3]. In April 2023, HIBio announced positive Phase 2 data for felzartmab from two trials, M-PLACE and NewPLACE (see Table 5.1. and Figures 5.2. and 5.3. for additional details).

Given that other therapies for serious nephrological conditions (e.g., IgA nephropathy) have received accelerated approval on the basis of proteinuria reduction from baseline, it is important to understand what trial outcomes matter to nephrologists in MN. Notably, nephrologists who treat MN are most focused on the timing and duration of complete remission and relapse rates as the most important outcomes for a pivotal MN trial and find the reduction from baseline in disease markers like anti-PLA2R or the urine protein creatinine ratio (UPCR) less impactful. This is likely due to the fact MN patients, particularly those who are high or very-high risk, may have significantly elevated antibody titers and proteinuria at baseline. Experts we spoke to point out that while reduction of these values from baseline is important, many patients will not achieve complete and durable remission unless antibody levels become undetectable, and proteinuria decreases to <0.3g/day. Similarly, interviewed nephrologists report that "in the nephrology community, people have the general acceptance and understanding that if a study showed as a primary outcome significant urine protein reduction, then this would translate over months and years to improvement in the GFR.".

Figure 5.1. Nephrologist-reported most important outcomes for a pivotal trial in MN[1]

Please rank three of the following outcomes in terms of how important they are in a pivotal trial for an emerging therapy for membranous nephropathy.



Percentage of nephrologists (n=26) ranking outcome among their top 3

1. REACH primary market research
2. https://clinicaltrials.gov/ct2/show/NCT05810961
3. https://hibio.com/news/morpho-sys-and-hi-bio-enter-into-equity-participation-and-license-agreements-for-felzartamab-and-mor-210

The MN pipeline is active with various mechanisms being studied

Table 5.1. Comparison of ongoing trials of therapies for MN[1]

Company / Drug	MOA	Dose form & frequency	**Primary** & Secondary Endpoint(s)	Comments
Hoffman-La Roche Obinutuzumab	CD20 mAb	IV; infusion at week 0, Week 2, Week 24, and Week 26	**% of pts who achieve CR at wk 104** % of pts who achieve overall remission at wk 104 % of pts who achieve CR at wk 76	• Phase 3 study • Estimated primary completion date is January 2025 • Eligible pts have diagnosis of primary membranous nephropathy, UPCR > 4 g/g, and eGFR > 40 mL/min/1.73m^2
Cerium Pharmaceuticals SNP-ACTH (1-39)	Adreno-corticotropic hormone (ACTH) therapy	SC; 3 mg or 5 mg injection 3x/week	**Change in urinary protein** **Change in anti-PLA2R antibody levels** **Complete response of PMN**	• Phase 3 study • Estimated primary completion date March 1, 2025 • Eligible pts have eFGR > 40 mL/min/1.73m^2 and a positive anti-PLA2R antibody test
BeiGene Zanubrutinib	BTK inhibitor	Oral; capsules once or twice daily	**Reduction in UPCR** **# of pts achieving CR** # of pts with treatment failure # of pts with immunological response	• Phase 2/3 study • Est primary completion: Dec 2028 • Eligible pts have UPCR > 3.5 g/g and Anti-PLA2R antibody > 50 RU/mL at confirmation assessment • While BeiGene is the trial sponsor, MN is not listed in the company pipeline as a target indication
Argenx Efgartigimod	FcRn inhibitor	IV; q1w, 4-week long cycle	**Change from baseline to wk 24 in urine protein creatinine ratio in anti-PLA2R population**	• Phase 2 study • Being conducted in China • Eligible pts have diagnosis of MN confirmed by renal biopsy • No explicit mention of eligibility being based on a positive anti-PLA2R antibody test
Apellis Pegcetacoplan (APL-2)	C3 inhibitor	SC; daily infusion for 16 weeks	**Proteinuria reduction** CR at wk 48 Stabilization or improvement in glomerular filtration rate from baseline to wk 48	• Phase 2 study • Primary completion date: Apr 2020 • Eligible pts have a positive test for anti-PLA2R antibodies and UPCR > 2.4 g/g • IC-MPGN and C3G are listed as target indications in the company pipeline but MN is not mentioned
HI-Bio Felzartamab (MOR202)	CD38 mAb	IV; 6 treatment cycle of 28 days each, dosing occurs weekly in Cycle 1 and q4w for Cycles 2-6, total of 9 doses	**Adverse Events** Effect of MOR202 on serum anti-PLA2R antibodies Immunogenicity of MOR202	• Phase 2 study - MPLACE • Actual primary completion date was January 19, 2022 • Eligible pts have UPCR > 3 g/g or proteinuria > 3.5 g/24h, active anti-PLA2R antibody positive, eGFR > 50 mL/min/1.73m^2
HI-Bio Felzartamab (MOR202)	CD38 mAb	IV; 5 or 2 doses of MOR202	**% change of anti-PLA2R antibody levels**	• Phase 2 study - NewPLACE • Estimated primary completion date January 11, 2024 • Eligible pts have UPCR > 3.0 g/g or proteinuria > 3.5 g/24h, eGFR > 50 mL/min/1.73m^2, anti-PLA2R antibodies / 50 RU/mL

1. Clinicaltrials.gov 2. https://acelyrin.com/press/acelyrin-announces-acquisition-of-valenza-bio

Table 5.1. Comparison of ongoing trials of therapies for MN (continued)

Company / Drug	MOA	Dose form & frequency	**Primary** & Secondary Endpoint(s)	Comments
Reistone SHR1459	BTK Inhibitor	Oral; tablets taken 1x/day for 24 weeks	**Proportion of pts achieving CR or partial remission at wk 24**	• Phase 2 study • Estimated primary completion date June 30, 2023 • Anti-PLA2R antibody > 20 RU/mL, proteinuria > 3.5 g/24h, eGFR > 60 L/min/1.73m^2
Acelyrin VB119	IgG1 mAb	IV; q1w for 6 weeks	**Adverse Events** % of pts with Anti-Drug Antibodies % of pts achieving CR of proteinuria Anti-PLA2R Antibody Assessment	• Phase 1b/2a study • Estimated primary completed date is Oct 2023 • Originally developed by ValenzaBio which was acquired by Acelyrin in January 2023[2] • Following the acquisition this drug is not currently listed in the Acelyrin pipeline • Eligible pts have a positive test for anti-PLA2R antibodies, > 3.5 g/g UPCR and proteinuria > 3.5 g/24h
Alpine Immune Sciences Povetacicept (ALPN-303)	B cell cytokine agonist	SC; q4w	**Adverse Events**	• Phase 1 study • Estimated primary completion date January 2026 • Not specific to MN patients only • Eligible MN pts have UPCR > 3.5 g/g and a positive test for anti-PLA2R antibodies
Alexion gefurulimab (ALXN1720)	C5 inhibitor	SC; infusion, one dose for duration of study	**Serum Concentration of ALXN1720** # of patients with adverse events Serum concentration of free and total C5 # of pts with antidrug antibodies to ALXN1720	• Phase 1 study • Estimated primary completion date April 27, 2023 • Not for MN specifically, can have other diseases that cause proteinuria (Lupus Nephritis, IgAN, Diabetic nephropathy, etc) • Eligible pts have proteinuria > 1 g/24h
Cabaletta Bio PLA2R-CAART	Chimeric AutoAntibody Receptor T cell therapy	N/A	N/A	• Preclinical development • PLA2R-CAART targets B cells that produce anti-PLA2R antibodies[2]

"I think serologic response is going to be the key to all new trials, and I think, you know, we know that we can put membranous patients into remission, but how long do we put them into it, so time to next therapy would be important, although typically that probably wouldn't be in the original trial because, you know, the follow-up time would be too long, but certainly long-term follow-up of these patients would also be very important in terms of data." **- Nephrologist, US**

"I would want to see, you know, pretty significant reduction in proteinuria and improvement in nephrotic syndrome within the first three months of, you know, starting the medication, so if we were looking at a new drug versus placebo versus existing treatment, then I would want to see that significant difference between the two arms." **- Nephrologist, US**

1. Clinicaltrials.gov 2. https://www.cabalettabio.com/pipeline/pla2r-caart

The M-PLACE trial is a phase 1b/2a, proof of concept, open-label, multicenter study to assess felzartamab in anti-PLA2R+ membranous nephropathy patients. The study enrolled two cohorts: Cohort 1 containing newly diagnosed patients and patients who relapsed after a previous therapy, and Cohort 2 containing patients who did not achieve immunologic remission after a previous therapy. Participants received weekly doses of felzartamab IV for 4 weeks, then once every 4 weeks for a total treatment period of 6 months, and study follow-ups to 12 months.

At the American Society of Nephrology (ASN) Annual Meeting in November 2022, interim data from the MPLACE trial were present for 23 out of 31 enrolled patients who had completed the treatment phase. The majority of felzartamab-treated patients (89.3%) showed a reduction in anti-antibody titers within the first week (median reduction of 44.8% from baseline), and most treatment emergent adverse effects (TEAEs) reported were mild to moderate. Of the patients who completed treatment at 6 months (EOT), the majority achieved immunologic partial response and just over one quarter achieved immunologic complete response (Figure 5.3). Only twelve patients had end of study (EOS) UPCR data available at 12 months and, of those patients, one third achieved a greater than 50% reduction from baseline in UPCR.[1]

In April 2023, HIBio announced final results from both the MPLACE and NewPlace studies, citing positive data from both trials and their intention to advance felzartamab into late-stage trials. However, there no specific efficacy data was given in the press release and HIBio stated that they intend to present further results at an upcoming medical meeting.[3]

Figure 5.2. M-PLACE study design[1]

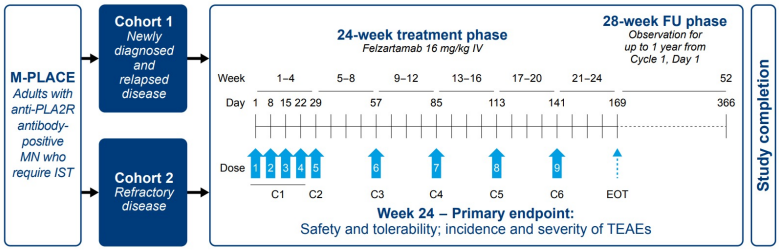
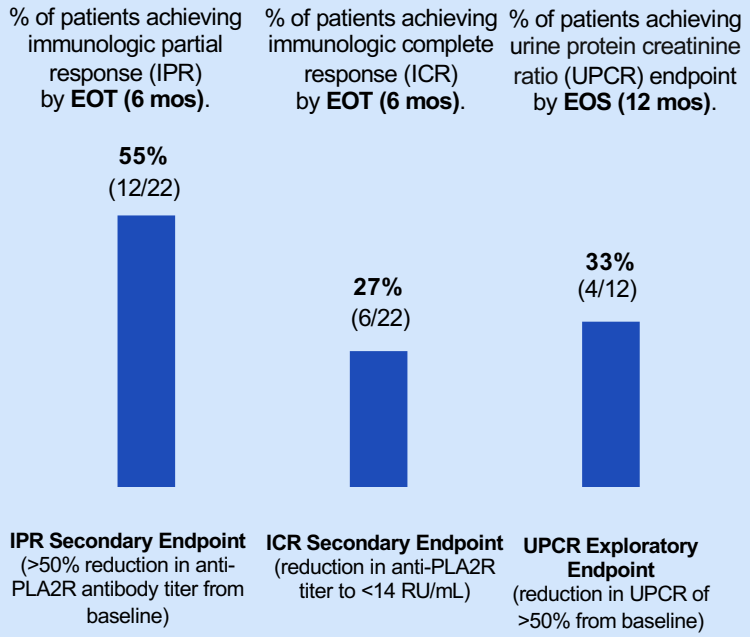


Figure 5.3. Interim results of Ph 1b/2a Trial of Felzartamab in Patients with anti-PLA2R antibody-positive MN (M-PLACE)[1]



"I think because there's such a need for more treatment options, I would welcome it really as long as it's safe. I would definitely enroll my patients in these clinical trials if they came up as long as they're safe, especially for my patients who don't respond, which is about a quarter to 30% of them." – **Nephrologist, U.S.**

"If it's done in the up-front setting, newly diagnosed, and it's in comparison with anti-CD20 antibodies and it's superior, then an anti-CD38 antibody might be the new first-line therapy for membranous, but if it was done in refractory patients, those that are refractory to anti-CD20, then it would be used as second line."
– **Nephrologist, U.S.**

1. Rovin, BH, et al. Abstract SA-PO679, American Society of Nephrology Annual Meeting, November 2022. 2. REACH primary market research; see Section 7 on methodology 3. https://hibio.com/news/hi-bio-announces-positive-phase-2-data-on-felzartamab-for-the-treatment-of-primary-membranous-nephropathy

Physician insights on data from the MPLACE study

On the antibody titer reductions seen in MPLACE study

"I think fundamentally, the level of response looks good, and you see a lot of people who are getting a real substantial decrease, including in refractory patients, and I'd seen this poster at the ASN. I'm not involved directly in this work, but I think when you think about it conceptually, patients with membranous were not responding to treatment in particular, so the refractory group, you have to ask yourself why that is, and what it usually means when they're refractory, very often these days, it means they're not responding to rituximab, sometimes to calcineurin inhibitors, sometimes to cyclophosphamide, so you have to ask yourself why are the antibodies being produced despite this? So the idea being that if you have somebody with membranous who's had it for long enough, it may be that the cells that are producing the PLA2R antibody are now socked in plasma cells and are not kind of immature B cells, and so they've become kind of more established, and so you need an anti-plasma-cell therapy." – **Nephrologist, U.S.**

"When you look at antibody reduction, the one thing I think is that you still want to have a complete remission. You really still want to see antibody levels really disappear, so, you know, those people who 50% - it depends a little bit on where you're starting from, but I think if they still have detectable antibody, that's concerning, and if you're stopping antibody production but you're not kind of getting rid of the initiating cells, you know, are you just kind of delaying the inevitable, or will it bounce back?" – **Nephrologist, U.S.**

On the correlation between antibody levels and UPCR data from MPLACE

"So I mean you do see a correlation, but it's separated in time, so it's not a problem to see proteinuria that persists. In fact, we expect the proteinuria to persist after the antibody levels decrease, so as long as after the antibody levels decrease, eventually the proteinuria comes down, that's fine. That's essentially what we see in membranous. Up to now, that's what we've seen irrespective of how the membranous is treated. By whatever method, if the antibody levels go down, the proteinuria will eventually come down later, and so that's been a very reliable relationship, but it doesn't need to happen right away. In fact, we don't really expect it to happen right away." – **Nephrologist, U.S.**

"Presumably the patients who still have proteinuria after 12 months, and 12 months is a long time, but on the other hand, there are people with proteinuria out farther than that. A lot of patients, it's more in the range of six months or so, but that said, you know, if they're not seeing a proteinuria reduction after that time and the antibody levels are low, then it's one of two things. It's either they're just slow to reach remission, but they are going to reach remission, and we clearly see that happen, or there are some patients who will have ongoing kind of low-level disease activity even despite negative antibody levels, and that may mean that they have, you know, other sorts of something called epitope spreading, or they're making other sorts of antibodies perhaps that are not being picked up by the specific assay, or they just have such a low-level production that the assay doesn't count it as positive, but there's enough antibody being sucked up by the kidney as soon as it's produced that it's still causing disease." – **Nephrologist, U.S.**

Overall thoughts on the MPLACE data

"Is it compelling, so I mean from the standpoint of it's what you'd expect to see, yes. On the other hand, you know, in treating membranous, we're really not looking for kind of a partial treatment. I mean from the standpoint of antibody production, we're really looking to eliminate the production of PLA2R antibodies, so I'm not saying it's not possible to have some clinical benefit to substantially reduce the titers, but we just know that if you don't eliminate the titers, if there's still titer present, that person is going to have chronic disease and persistent disease activity, and actually when you look at patients with persistent disease activity in membranous, they almost universally develop CKD over time, and it's not very fast, but these are people who largely have kidney-limited disease, so, you know, they're often otherwise healthy, and to have persistent chronic kidney disease and progression even to end-stage renal disease, these are the patients who have kind of persistent antibody levels despite treating them and persistent proteinuria, even if it's not full nephrotic syndrome." – **Nephrologist, U.S.**

1. REACH primary market research; see Section 7 on methodology

Physician insights on emerging therapeutic targets in MN

On complement inhibition as an MN target

"If you're not getting rid of the antibody and you're just blocking the downstream effect, that would suggest that you need ongoing therapy, which not all patients with membranous who get treated with rituximab need long-term ongoing maintenance therapy, so I think that depending on, you know, what the trials show and efficacy, off the top of my head knowing what anti-complement drugs do, like I said, it might be only beneficial for a small population of the patients who may have, you know, frequent relapse or they can only get a partial response to anti-CD20 therapy."

-Nephrologist, U.S.

"We know [obinutuzumab] works just like rituximab, only more so. It's a much more potent and long-lasting depletion of B cells. We know that in patients who have diseases that respond to rituximab normally but don't respond to rituximab, many of those patients, refractory patients, will respond to obinutuzumab, so, you know, why not make that analogous to membranous? We've seen it work in other kidney disease like lupus nephritis where there's good phase II data, and there are already, not a ton, but there are case reports of patients with refractory membranous who respond to obinutuzumab, so I think it's much easier imagining repurposing a drug whose risks are known, who is already out there, already FDA approved, already prescribable – it's much easier to imaging repurposing it, especially when it has kind of compelling reasons to think that it might be better."

-Nephrologist, U.S.

"I would like to see a newer therapy target another cell, such as the plasma cell, and that would be some advance. And then the other is, you know, we don't know why PLA2R or any of the other antibodies elicit the response that they do, and so therapy that can limit the autoimmunity of PLA2R, that would be exciting."

-Nephrologist, U.S.

"So if we get down to a PLA2R-specific therapy, I would definitely use that treatment as probably first line for the PLA2R-positive patients. You know, I would definitely switch that to a first-line agent, I would think, but yes, I would reserve it for the people that I'm planning to treat now…If they already had good prognosis, why would I, you know, give them a potential toxic medication and then have more complications from that?"

-Nephrologist, U.S.

"The question would be does kind of interrupting the complement cascade lead to enough of a decrease in local immune signaling that you stop making antibodies, and I don't think that that's been shown, so I think they're so far downstream that there's not going to be a ton of interest and really a ton of justification to say. You know, who wants to be on a pill or a subcu infusion to kind of prevent inflammation in the kidney when you have the opportunity to actually stop the antibody that's producing the inflammation in the first place, because we know that if you stop antibody production that you get really good renal outcomes. The GFR improves. You don't get a lot of scarring, so while complement inhibitors make sense in something like IgA nephropathy or lupus where there's a lot of local glomerulonephritis and proliferation, that's not the case in membranous."

– **Nephrologist, U.S.**

1. REACH primary market research; see Section 7 on methodology

6. VALUE & ACCESS

OVERVIEW

Currently, there are no approved therapies for MN patients. As such, nephrologists are limited to corticosteroids, renoprotective therapies, and immunosuppressive treatments that include rituximab, cyclophosphamide, and calcineurin inhibitors (Table 6.1.).

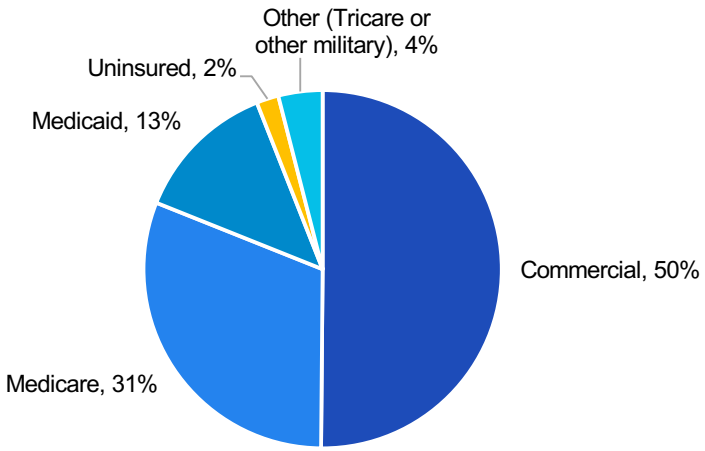
While there are no approved therapies for MN, some therapies have recently been approved in other rare, proteinuric kidney diseases that may serve as an analogue for potential pricing of MN treatments, including Calliditas' novel budesonide formulation (Tarpeyo) which was approved in December 2021 and Travere's sparsentan (Filspari) which was approved in February 2023 by the FDA for use in IgA nephropathy patients[2,3]. Both treatment were granted accelerated approval by the FDA based on reduction of proteinuria to fill an unmet need in a population with serious risk of disease progression.

Sparsentan is a once-daily oral medication and places emphasis on being the first and only non-immunosuppressive therapy approved for the condition and it is priced at $9,900 per month. Currently, Tarpeyo, a delayed-release form of budesonide, is priced at $14,160 per month. This works out to an annual cost for sparsentan of ~$120k and ~$170k for budesonide[4]. As sparsentan enters its first year of approval it will be worth noting whether its lower cost draws budesonide patients away or if patients and providers alike will prefer to continue using Tarpeyo, a re-formulation of an older drug with which they are more familiar. Companies looking to develop a drug in Membranous Nephropathy should consider what measures Travere will take with providers, patients, and payers to educate and expand access.

Table 6.1. MN therapy pricing, U.S.

Type	Drug	Target/Class	List Price (WAC) Per Month or Infusion
Small molecule	Corticosteroids (based on prednisone)	Steroid	$5 - $60
	Cyclosporine	Calcineurin inhibitor	$26 - $67
	Cyclophosphamide (based on oral capsules and oral tablets)	Alkylating antineoplastic agent	$30 - $60
	ACEs (based on lisinopril)	Angiotensin-converting enzyme	$10 - $13
	ARBs (based on irbesartan)	Angiotensin receptor blocker	$30 - $40
Biologics	Rituximab	CD20	$9,902 per 1,000mg infusion

Figure 6.1. Membranous nephropathy patients by insurance type[1]



1. REACH primary market research; see Section 7 on methodology 2. https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-fda-accelerated-approval 3. https://www.fda.gov/drugs/fda-approves-first-drug-decrease-urine-protein-iga-nephropathy-rare-kidney-disease 4. https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-travere-therapeutics-kidney-disorder-drug-2023-02-17/

7. METHODOLOGY

Primary Market Research Approach

Interviews

Participants : 5 U.S. Nephrologists paid an honorarium for participating

Dates: April 2023

Qualitative interviews: 1-hour phone interview

Survey

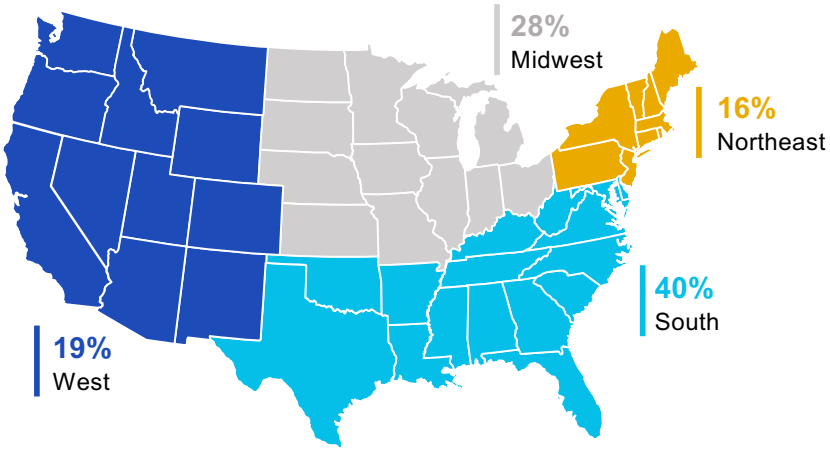
Participants: 26 U.S. Nephrologists (paid an honorarium for participating)

Date: April 2023

Quantitative survey: 15-minute online survey

Participant Screening Criteria		
Respondents had to meet the following requirements to participate in this study survey		
• **Time Spent in Clinical Practice:** More than 75% of time devoted to direct patient care as opposed to non-clinical activities such as research or teaching	• **Time in Practice**: Minimum of 3 years and no more than 30 years.	• **Patient Load:** Physicians had a minimum of 10 MN patients.

Practice Location
Surveyed U.S. Nephrologists



EPIDEMIOLOGY METHODOLOGY

Diagnosed Primary MN Disease Definition. Primary MN is an autoimmune disease that directly affects the filtering membranes (glomeruli) of the kidney For this analysis, we define diagnosed membranous nephropathy (MN) as primary membranous nephropathy (PMN) diagnosed by kidney biopsy and the exclusion of conditions which can cause secondary glomerulonephritis (drug toxicity, infection, other autoimmune diseases etc).[1,2,3]

Diagnosed Primary MN Incidence Estimates. For this analysis we incorporated country-specific population studies for the U.S.,[4] France,[5] Germany,[6] Italy,[7] and the UK.[8] Due to the lack of quality population studies for Spain, we decided to use an average of the incidence of primary MN from France and Italy. Most studies reported the incidence of primary MN as new cases diagnosed by kidney biopsy in individuals aged 18+. When necessary, we adjusted the study reported incidence rates to reflect the incidence of primary MN in individuals aged 18 and above. For France we used the age-specific incidence rates reported by Simon et al. and calculated the overall incidence rate for individuals aged 18+ using the country-specific age populations. We report the final incidence rates per 100,000 persons aged 18+ per country.

Diagnosed Primary MN Prevalence Estimates. For this estimate we found it difficult to find country-specific sources which reported the prevalence rate of primary MN. For this reason, we decided to use a U.S. study which reported the prevalence of primary glomerulonephritis in two healthcare cohorts using ICD-9 codes.[9] From these two cohorts we calculated the overall prevalence rate of primary glomerulonephritis in the U.S. population aged 18 and above. We then averaged the proportion of primary glomerulonephritis cases that are MN from three different studies[4,6,8] and applied this proportion to the overall U.S. primary glomerulonephritis rate. For EU5 we used an incidence: prevalence ratio using the U.S. rates, to extrapolate the prevalence of primary MN per country.

Prevalence of Autoantibodies. Recent evidence suggests that primary MN is driven by autoantibodies specific to native podocyte antigens of the kidney, with the most common autoantibody being PLA2R.[10] The literature suggests that 70% of individuals with primary MN have circulating PLA2R antibodies.[10,1,2,3] We applied this proportion to the prevalent cases per country to estimate the number of individuals who have primary MN and are PLA2R positive.

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