APPENDIX: SCOPE OF COVERAGE

Issues that all breakout groups should consider during their discussions

- What is B cell depletion, what is deep B cell depletion, and how shall we define and measure these? Please consider peripheral versus tissue (e.g., lymph node) depletion and need for or use of biopsies in these definitions.
- The term "immune reset" is being used a lot lately. What does that mean?
- What endpoints should be sought when using cell therapies and T cell engagers given that these therapies present safety risks beyond what we usually consider with more conventional therapeutics? For example, consider the ideas of drug-free remission and relapses.
    - Even with more "conventional" B cell targeted therapy, what responses are we looking for?
- Safety concerns when using B cell depleting therapies (alone or with other immunomodulatory therapies), and consideration for chronic use as may be needed in some situations
    - Please include infection prevention, monitoring Ig levels, threshold for IVIG replacement, administration of vaccinations, fertility, and pregnancy considerations
- Is there a scientific rationale of preferring one B cell therapy approach over another (e.g., efficacy, safety, patient and physician preference, cost)? Are there situations when B cell therapy should not be first choice?
- How do we think about combining B cell therapies with other immunosuppressives or even with other B cell therapies? How do we think about sequencing B cell therapies? How do we think about withdrawing B cell therapies? How do we think about preventing relapse?
- Please consider children and adults in your discussions.

Issues to consider when formulating research agenda

- Understand the B cell subsets and autoantibody profiles and how they contribute to disease
- How do we begin to decide how to match patients with their needed depth of B cell depletion?
- Are there other areas of key unmet need?

Breakout Group 1: IgA Nephropathy (IgAN)

1. What is the ideal approach for managing IgAN with B cell therapies: B cell depletion (anti-CD19, anti-CD20), plasma cell depletion (anti-CD38), B cell modulation (anti-BAFF, anti-APRIL, anti-BAFF/APRIL), or combinations of these therapies? What about sequential versus continuous therapy, and what about an induction-maintenance concept? How to sequence drugs, and when to taper them? Consider potential differences between IgAN and IgAV.
2. In IgAN, is the preferred target galactose-deficient IgA1 (Gd-IgA1) or antibodies to Gd-IgA1 (IgG/IgA anti-Gd-IgA1), and how should the target dictate B cell therapeutic choice? Or rather assess total IgA in serum?
3. How do anti–B cell therapies compare with other available approaches in IgAN (e.g., Nefecon, systemic corticosteroids, complement inhibitors)? Should B cell therapies be combined with other IgAN therapies, and what combinations would be appropriate? What are the indications to start B cell therapies in IgAN?
4. What biomarkers or histological features are needed to appropriately guide B cell therapies in IgAN, including but not limited to circulating B cell levels, tissue B cell levels, B cell subsets, and/or B cell growth or maturation factors (e.g., APRIL/BAFF)?
5. Is there a role for very deep B cell depletion in IgAN (e.g., therapy with CAR T cells or T cell engagers)?
6. How do the efficacy and safety of B cell therapies for IgAN compare to the newly approved or soon-to-be approved therapies (e.g., targeted-release mucosal glucocorticoids, endothelin antagonists, and complement inhibitors)?

Breakout Group 2: Primary Membranous Nephropathy (MN)

1. What are the B cell therapies that have proven to be effective in MN (e.g., anti-CD20)? Is there also a role for plasma cell therapy (i.e., anti-CD38) and/or B cell modulation with APRIL/BAFF, BAFF, or CD40/CD40L inhibitors? Who should receive B cell therapy? How should one dose it (i.e., induction/maintenance/duration), and when and how should it be tapered?
2. Are B cell therapies single treatments for MN, or should they be combined with other immunosuppressive therapies?
3. Since anti-PLA2R antibodies have been considered a biomarker for MN, how should these and other MN autoantibodies be integrated into B cell management of MN? Are there additional biomarkers that should/could be considered when using B cell therapies, including but not limited to circulating B cell levels, tissue B cell levels, and B cell subsets? Does the approach to B cell therapies differ between patients who are anti-PLA2R-positive versus -negative (or with another antigen or unknown antigens)?
4. How do efficacy and safety of B cell therapies for MN compare to traditional immunosuppressive therapies (e.g., calcineurin inhibitors [CNI], cytotoxics)?
5. In patients treated with anti-CD20 who do not respond, how should therapy be approached?
6. Is there a role for very deep B cell depletion (e.g., CAR T, T cell engagers, CAAR NK) in MN?

Breakout Group 3: Podocytopathies

1. Which podocytopathies would be most amenable to B cell–directed therapy?
2. What is the role of B cell depletion (e.g., anti-CD19, anti-CD20), plasma cell depletion (anti-CD38), B cell modulation (anti-BAFF, anti-APRIL, anti-BAFF/APRIL), or combinations of thereof in the treatment of podocytopathies? Is there a role of targeting CD40?
3. How do anti–B cell therapies compare with other available approaches (e.g., steroids, CNI, MMF, cytotoxic therapy) for the treatment of podocytopathies with respect to safety and efficacy?
4. What biomarkers are needed to appropriately monitor B cell therapies in podocytopathies, including but not limited to circulating B cell levels, tissue B cell levels, B cell subsets, and antibodies?
    a. How could these strategies be used for patient monitoring from a safety and efficacy standpoint?
    b. How could they help in determining timing and dosing of patient retreatment?
5. Is there a role for very deep B cell depletion (e.g., CAR T or T cell engagers, bi-specific antibodies) in podocytopathies?
6. What are the differences between adults and children with podocytopathies in terms of their response to B cell modulating agents and in terms of the safety profile of these agents?
7. What are the risks of using B cell–modulating agents in treating immune-mediated podocytopathies? In what way and for how long should a patient with an immune-mediated podocytopathy be monitored after having received a B cell–modulating agent?

Breakout Group 4: Lupus Nephritis (LN), ANCA-Associated Vasculitis (AAV), and Other Systemic Diseases

1. As B cell therapies have proven to be effective in systemic diseases (e.g., anti-CD20, anti-BAFF, anti-CD38, anti-CD40, CAR T cell therapy), in which order and combination should B cell agents be commenced? Is it possible to recommend a hierarchical order of increasing B cell depletion therapies in systemic diseases dependent on disease subtype and severity (e.g., rituximab, obinutuzumab, belimumab, CAR T, extrarenal manifestations)? What are the disease-specific considerations?
2. The B cell therapies used in systemic diseases provide varying degrees of B cell depletion, both circulating and in tissue. What biomarkers or histological features are already in use, and which are needed to monitor degree of depletion, efficacy and safety?
3. How do efficacy and safety of B cell therapies for systemic diseases compare to other disease-modifying agents (e.g., MMF, cyclophosphamide)?
4. What precautions (e.g., vaccinations) should be exercised and in which vulnerable populations (e.g., preexisting malignancy) during B cell therapy administration?
5. How should B cell therapies be combined with other available immunosuppressants/immunomodulatory therapies for systemic diseases?
6. When should one consider avoiding or discontinuing B cell therapy in systemic diseases?
7. The aim is restoring immune tolerance. Is a cure realistic with cell-based therapies and if so, should cell therapy be offered to patients only after failing other therapies or at time of disease diagnosis?