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Cell Therapies for Lupus Nephritis
Can we cure LN?

Brad H. Rovin MD, FASN

Disclosures

Dr. Rovin has the following relevant financial relationships
All relevant financial relationships have been mitigated

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This presentation involves comments or discussion of unapproved or off-label, experimental or investigational use of Cyclophosphamide, MMF, AZA, Rituximab, CSA, Voclosporin, Belimumab, Obinutuzumab

ARTICLES
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Check for updates

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉

5 refractory lupus patients with LN treated with CAR T therapy who all went into remission within a few months and had minimal adverse events

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CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.

Two-year results: 100% CRR in 3 months and no LN relapses off all immunosuppression!

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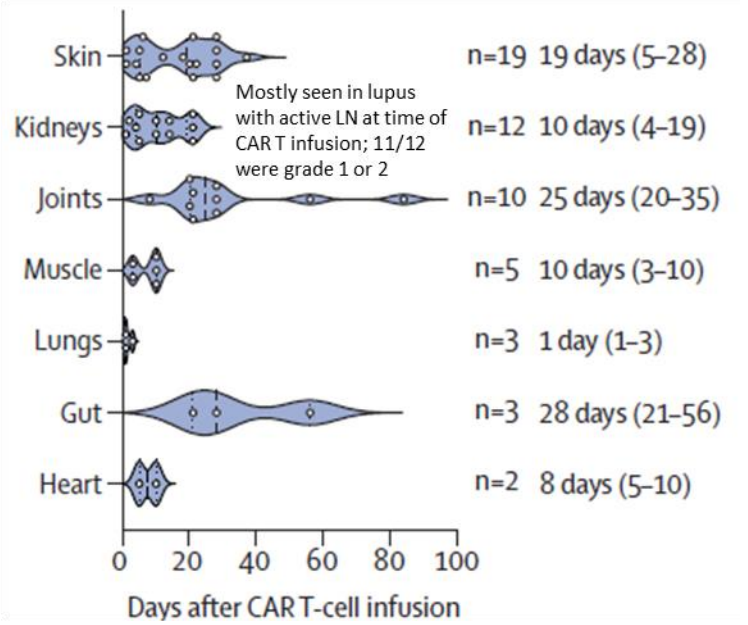
I was skeptical about…SAFETY

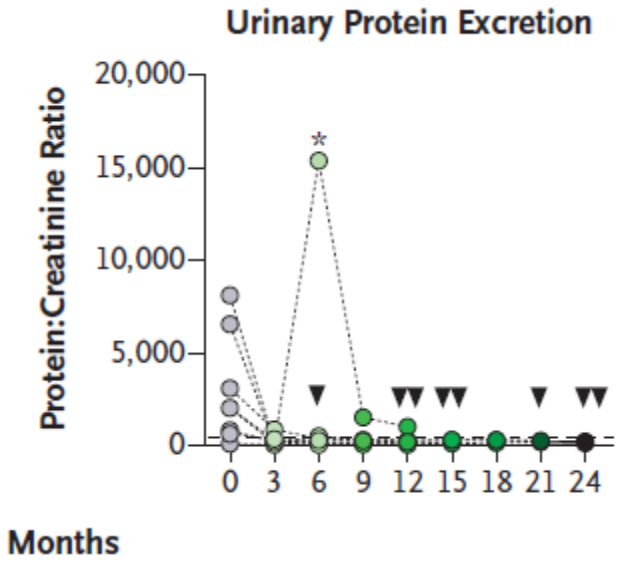
- An LN patient with very active, refractory disease dosed with CABA-201 in late June experienced a protocol-defined dose-limiting toxicity of Grade 4 ICANS, which resolved rapidly following standard management (*Source: Cabeletta Press Release*)
- Patients treated in US have not all gone into remission, some have not responded, others have relapsed (*Source: Data presented at meetings*)
- On November 28, 2023 the FDA released a statement regarding T cell malignancies in recipients of CAR T therapies for hematologic malignancies. 20 cases of T cell malignancies with a denominator of >30,000 patients
- Now we have a new syndrome postulated to be due to the rapid death of infiltrating B cells in tissues caused by CAR Ts called local immune effector cell-associated toxicity syndrome (LICATS). This occurs when B cells are still absent, CAR T are present, and follows the organs involved in the original disease. For the kidney in LN this meant increase in SCr or proteinuria. One patent who did not recover kidney function was biopsied and found to have TMA presumed to be from CMV reactivation and this complicated LICATS



Nonetheless, for such a rigorous protocol safety has been very good; the patient who had grade 4 ICANS, in an interview, said her disease is controlled and she would do it again, even having had a severe complication

Mueller et al, NEJM, 2024; Hagen et al, Lancet Rheum, 2025

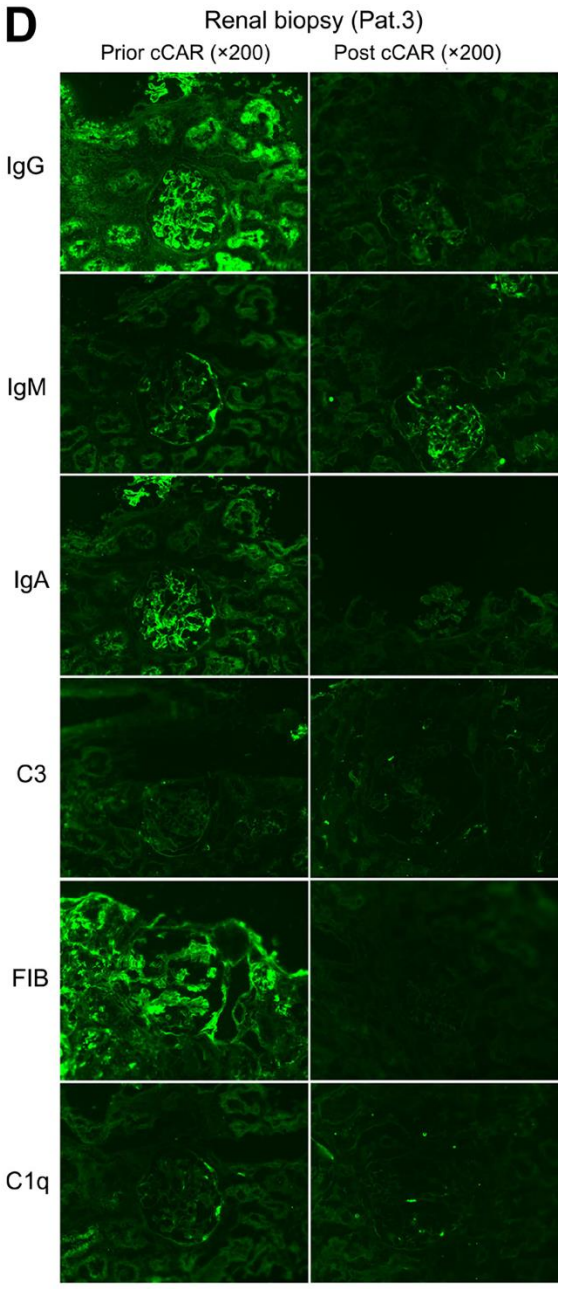
I was skeptical about…CRR in refractory LN!



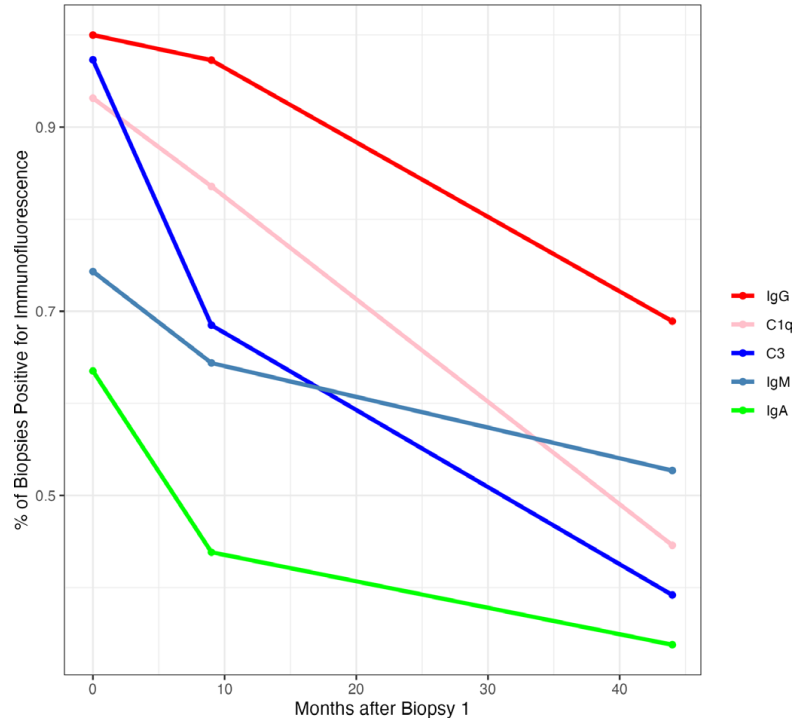
- Resolution of proteinuria at 3 months in refractory LN hard to explain besides hemodynamically
  - Refractory suggests patient had it for a while and several treatments failed
  - An inflamed kidney develops scarring and nephron loss over time leading to fixed proteinuria that will not go away simply by controlling inflammation
- But if a kidney can remodel maybe damage-related proteinuria can resolve (disappear????)
- Can CAR T therapy lead to remodeling of kidney scar? That would be great. *We need tissue*
- Can kidney remodel in 3 mos of CAR T therapy? That would be great. *Need pre/post tissue*
- The trajectory of proteinuria after CD19-BCMA CAR T seems more likely.

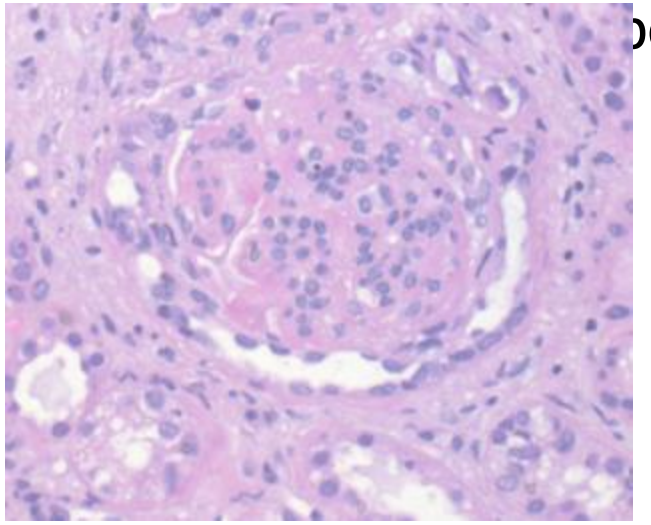
Mueller et al, NEJM, 2024; Wang et al, ARD, 2024

Post-CAR T kidney biopsy



- This is a pre-CAR T (CD19-BCMA) and post (6 months) CAR T biopsy but only IF is given
- This is an unusual biopsy for active LN pre-tx: no C3, C1q
- The fact that IgG disappears in 6 months is remarkable
- Under usual therapy it can take ...pear



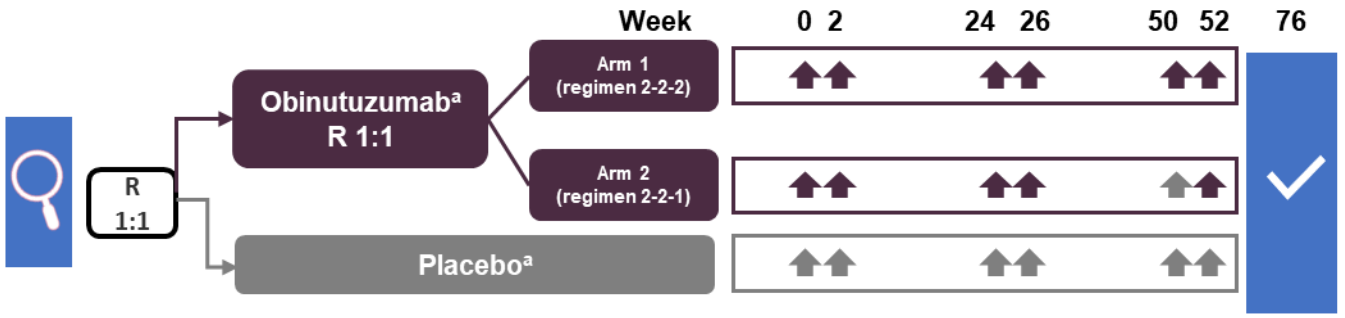


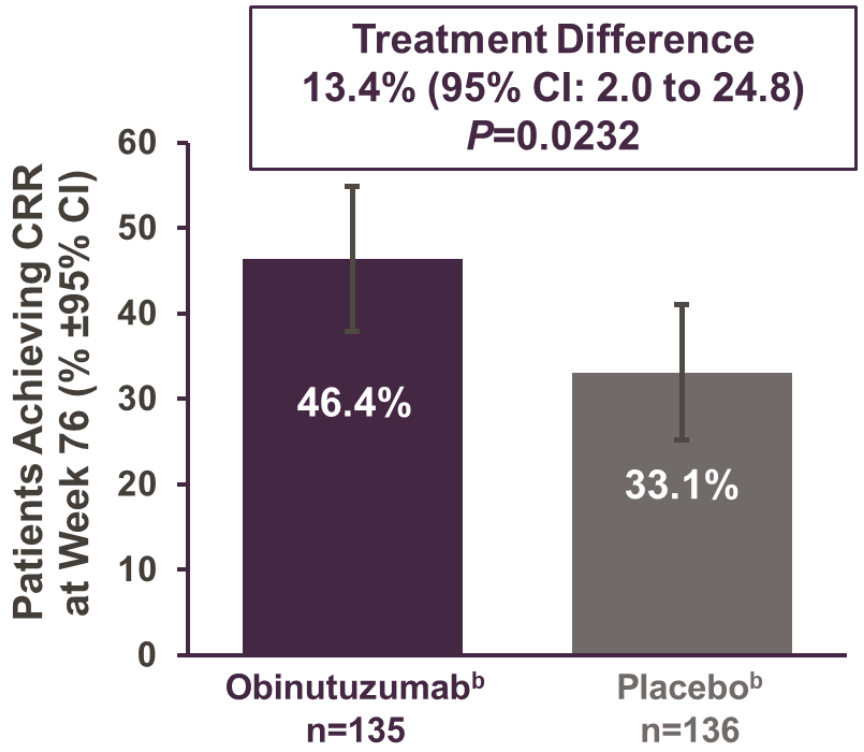
This is a glomerulus 30 days post-treatment with CD19 CAR T; histology is not impressive for a rapid remodel!

Wang et al, ARD, 2024; Malvar, Lup Sci Med, 2023; Tur et al ARD, 2024

- I was skeptical about…immune reset
- Honestly, I am not really sure I know what immune reset is
- I thought maybe it means when immune cells re-populate they are different, maybe less auto-reactive
- I thought exploring the differences between B cell depletion with anti-CD20 and B cell depletion with cell therapy may provide insight

Top-line results of the phase III REGENCY trial

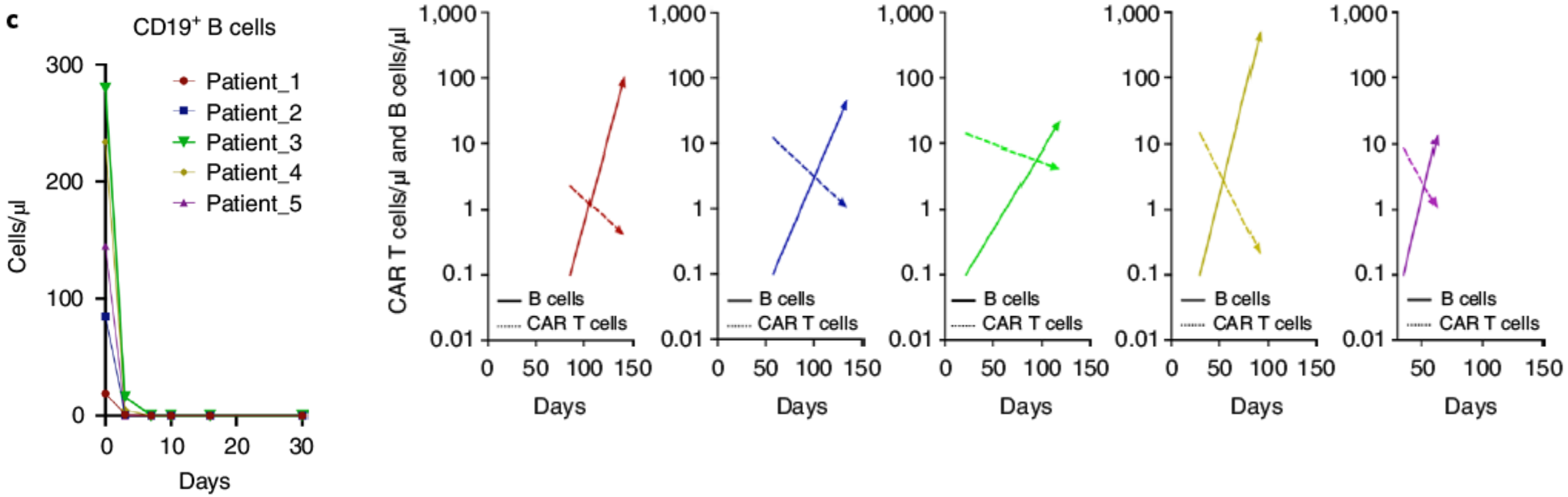


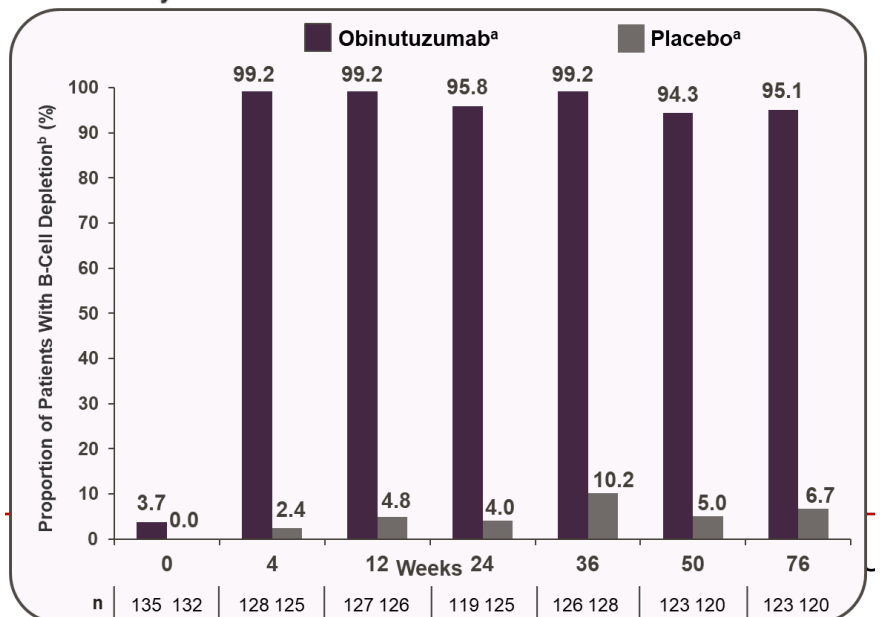


Note: These are NOT refractory LN patients

Furie et al, NEJM, 2025

CAR T and Obi result in deep *peripheral* B cell depletion

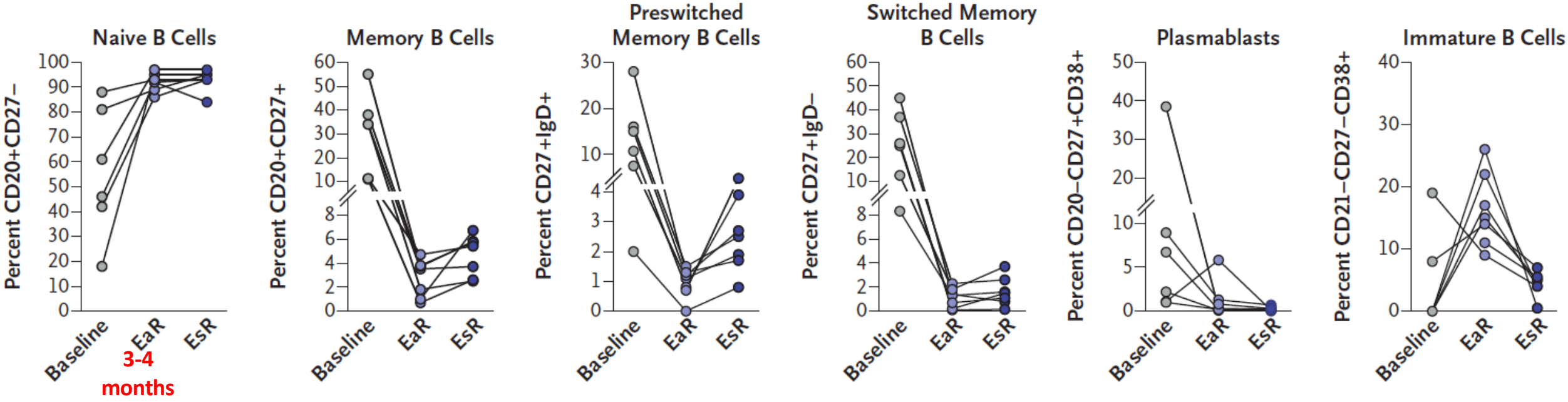




- CAR T cell-mediated B cell depletion is profound, rapid and VERY SHORT-LIVED!
- Obi-mediated B cell depletion is profound, rapid, and VERY LONG-LIVED!

Mackensen et al, Nat Med, 2022; Furie et al, Ann Rheum Dis, 2021

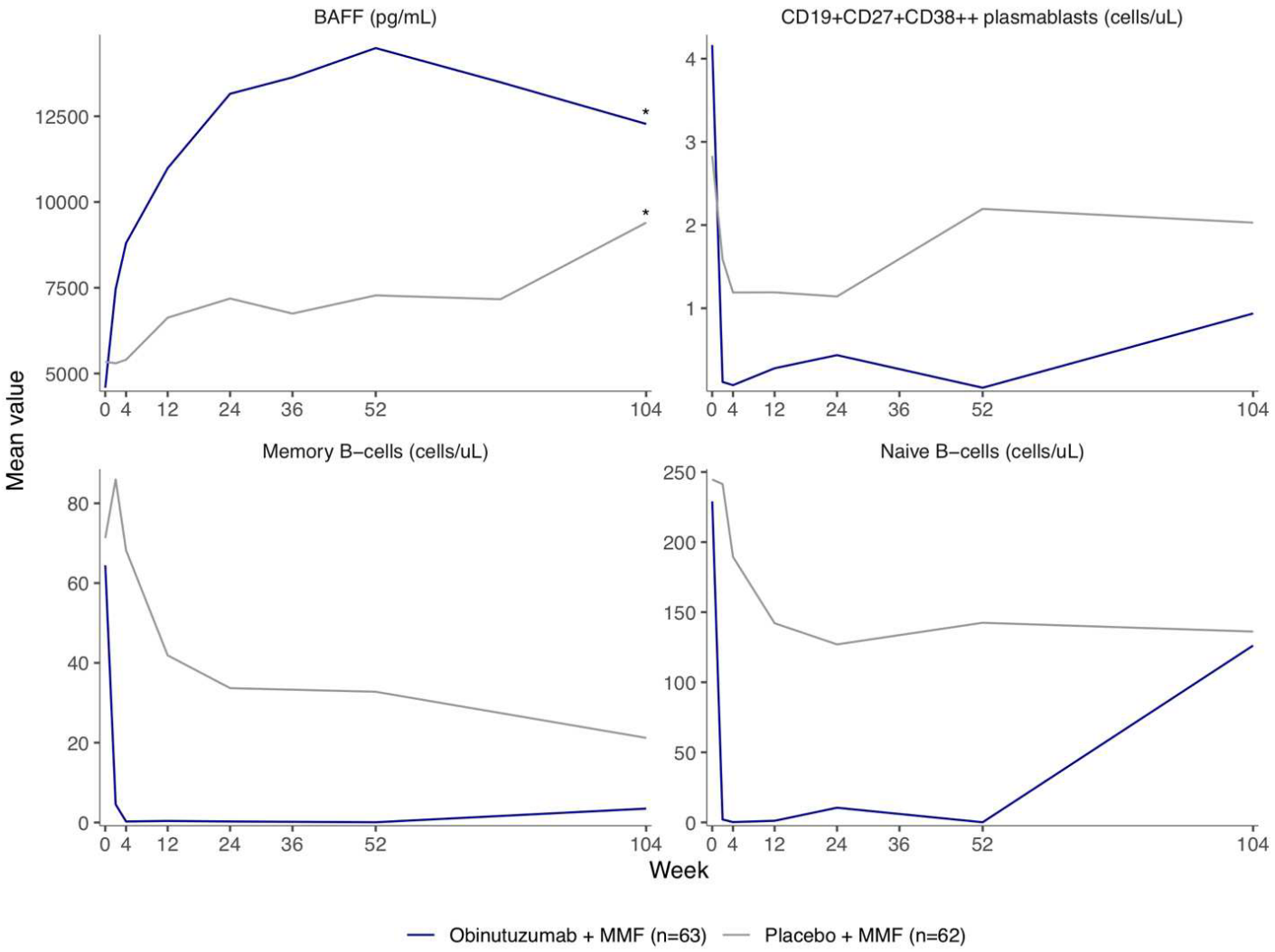
B cell reconstitution after CD19 CAR T



- **A prominent feature of B cell re-constitution after CAR T is the increased population of naïve B cells with fewer memory B cells**

Mueller et al, NEJM, 2024; Venhoff et al, Autoimmunity, 2014;

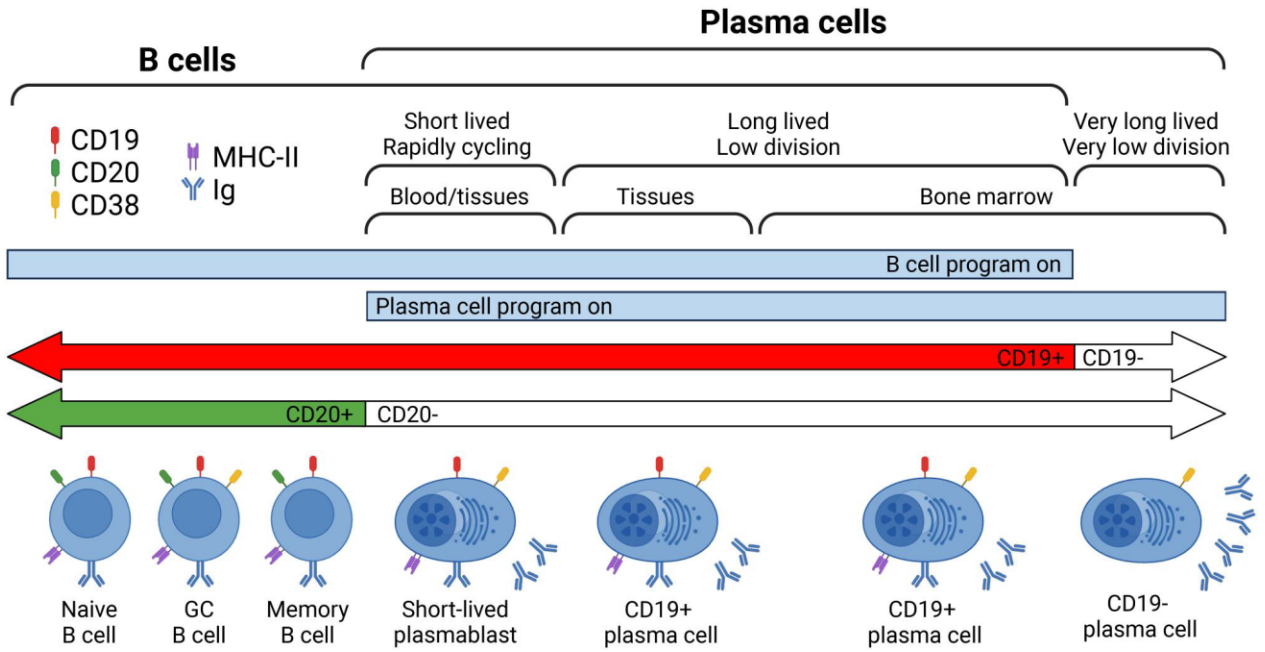
B cell reconstitution after obinutuzumab

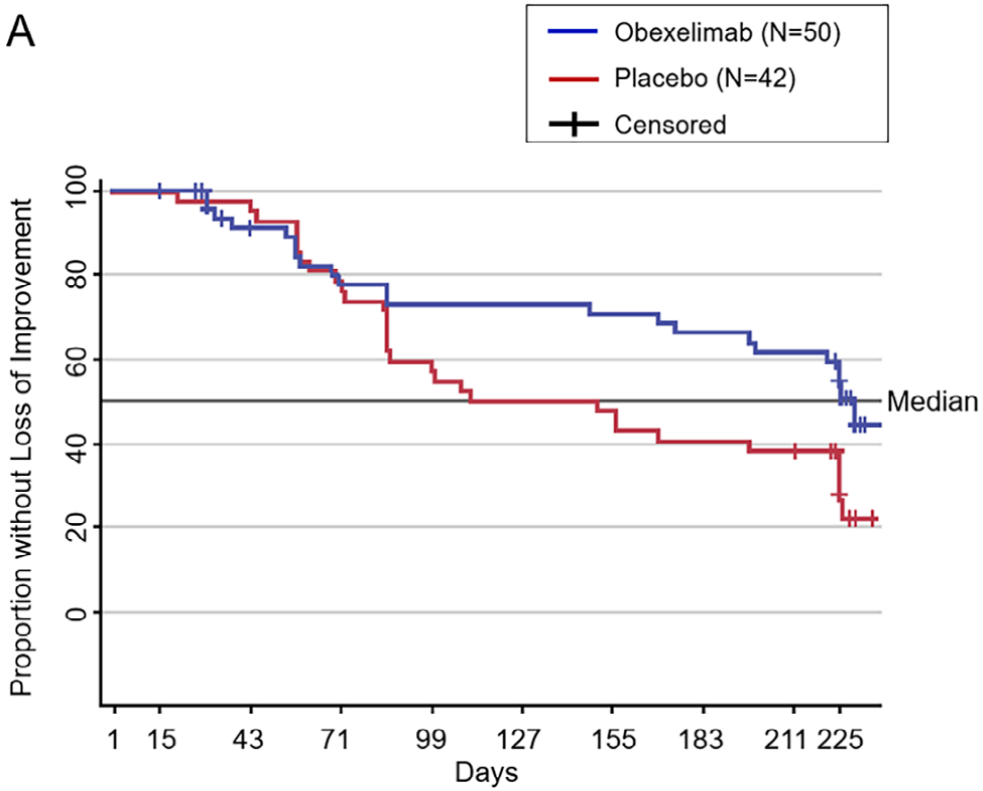


So why aren't OBI results more similar to CAR T results?

Furie et al, Ann Rheum Dis, 2021

Should we target CD19 instead of CD20?





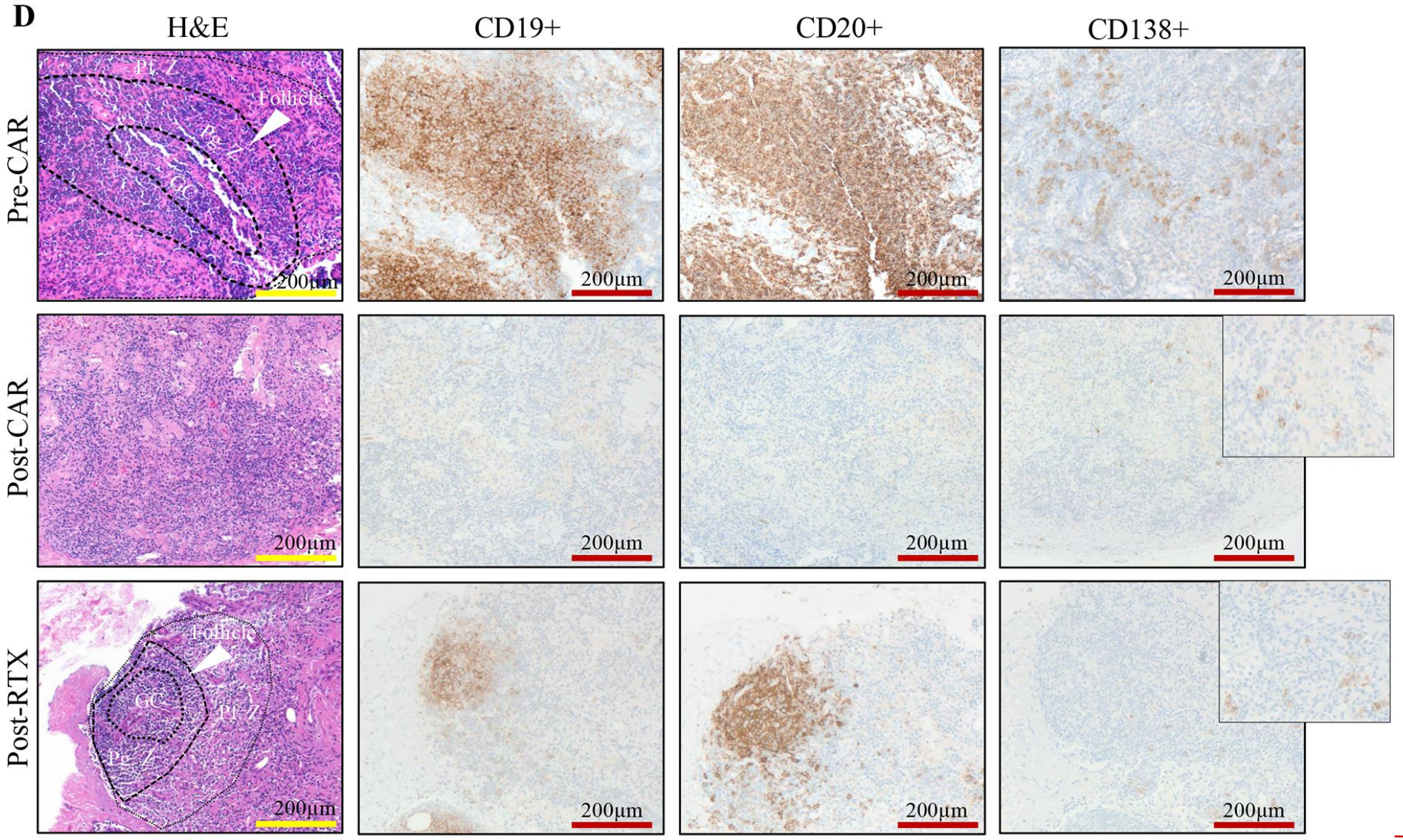
Testing of the fully humanized anti-CD19 monoclonal antibody obexelimab was stopped after phase II in lupus as endpoints were not achieved…

But this was a maintenance of improvement study and the anti-CD19 is not a B cell depleting agent (although B cells fell by 50%) but more of an inactivating antibody. Patient sorted by gene modules showed differential results with good results in those with ↑ B cell genes and ↓ inflammation genes

Suan et al, J Immunol, 2025; Merril, Arth Rheum, 2023

Is tissue the issue?

Lymph nodes after CAR T treatment for autoimmune disease



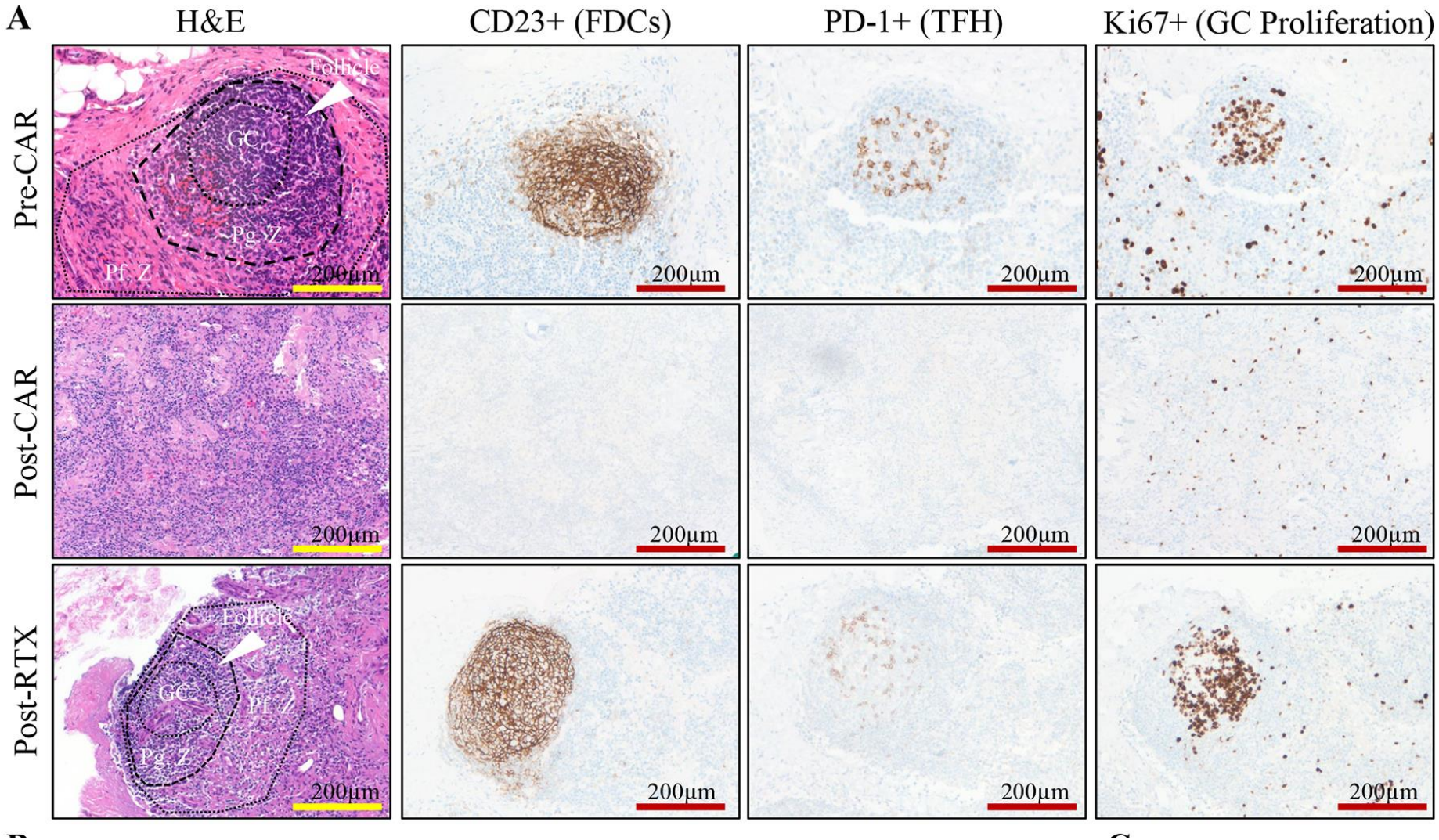
Inguinal lymph node biopsies were taken about 60 days after CD19 CAR T and 100 days after rituximab therapy

CAR T depletes almost all of the B cells as opposed to rituximab

CAR T and rituximab do not eliminate all CD19-CD138 cells*, believed to be final differentiated state plasma cells, likely accounting for lack of hypogammaglobulinemia
*CAR T does eliminate all CD19+CD138 plasmablasts

Tur et al, Ann Rheum Dis, 2024

Lymph node architecture after CAR T treatment



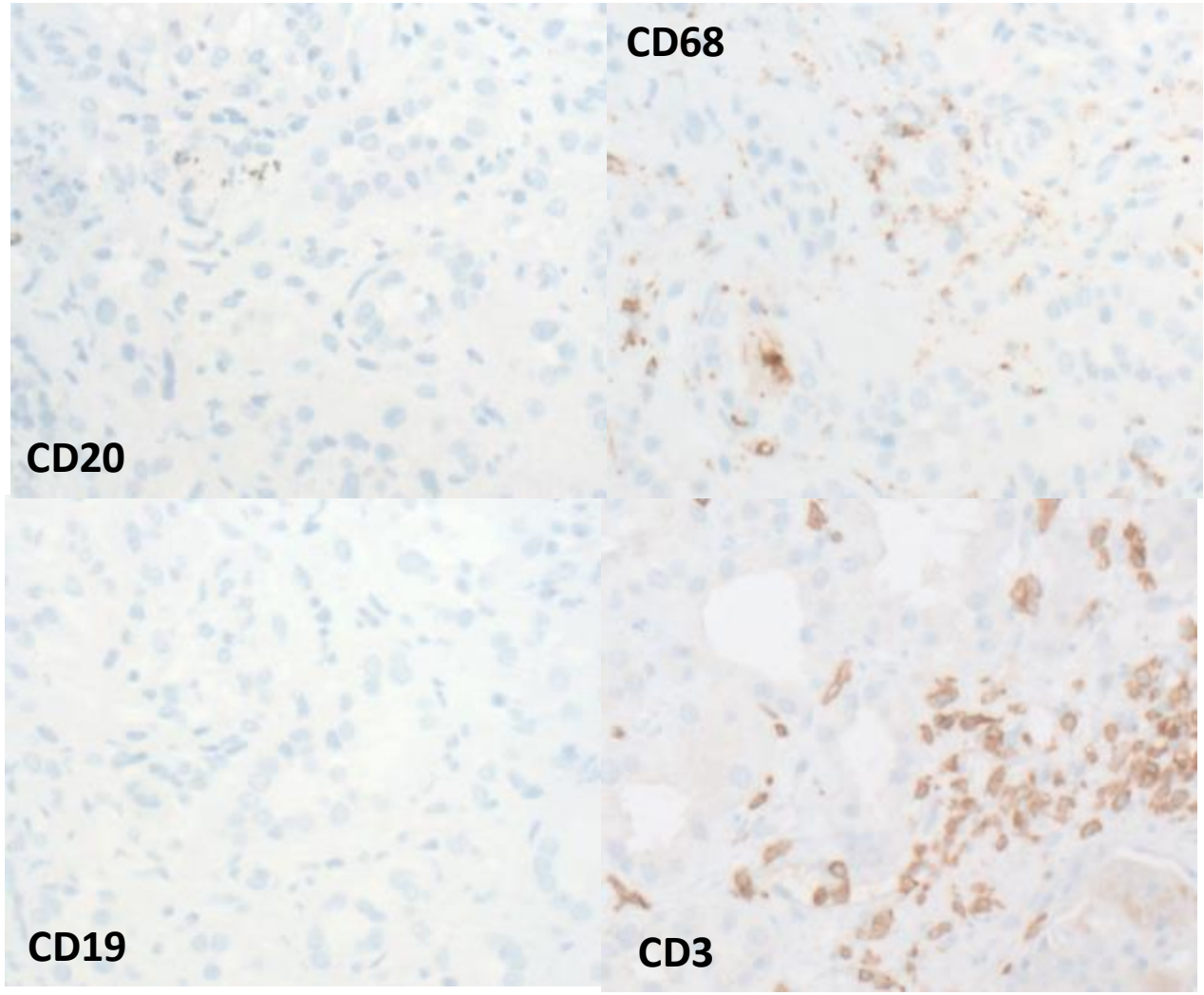
CD19 CAR T cell therapy obliterates the lymphoid follicle structure of the lymph node; note complete disappearance of germinal centers

T follicular helper cells may express CD19, however TFH and follicular dendritic cells likely need B cell help to survive and complete elimination with CAR T deprives these important follicular cells

Lymph node architecture is largely intact after rituximab

Tur et al, Ann Rheum Dis, 2024

Kidney leukocytes after CAR T treatment



CD19 CAR T cell therapy depletes B cells from the kidney 30 days after administration (no pre-treatment tissue ☹)

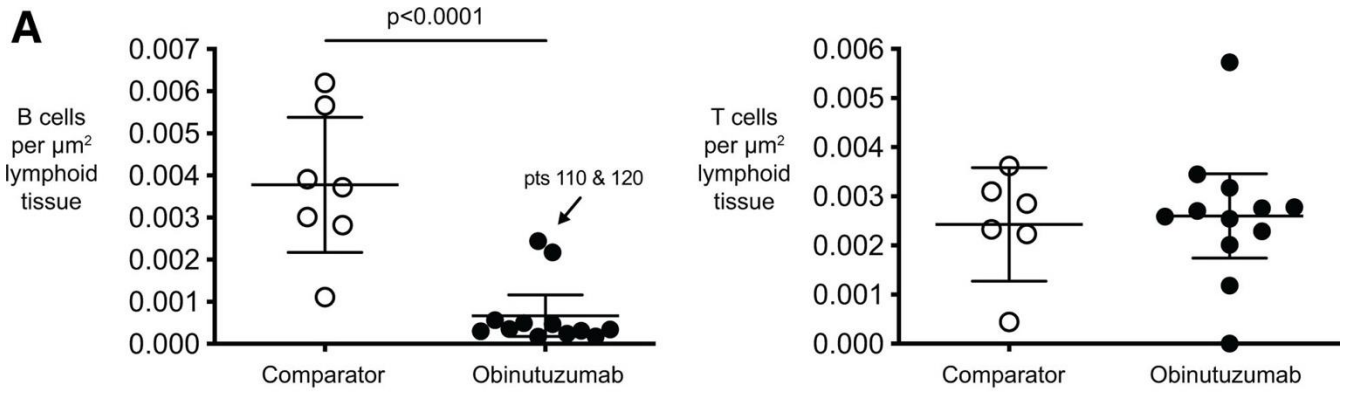
Similar to kidney, lymph node CD3 and CD68 populations were not affected by CAR T treatment

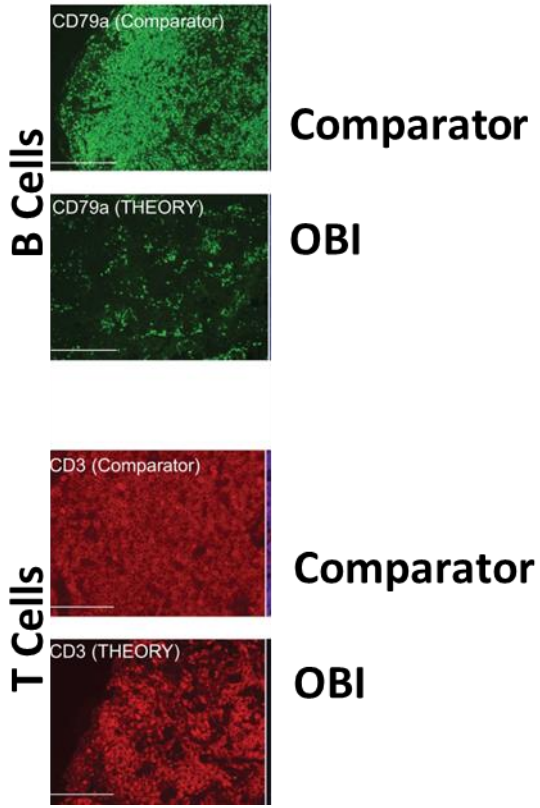
The presence of T cells and other immune cells suggests that the lymphodepleting therapy used to condition for CAR T may not have a major role in the response to CAR T

Tur et al, Ann Rheum Dis, 2024

Lymph nodes after obinutuzumab

THEORY was a phase I trial to look at obi treatment of highly anti-HLA sensitized ESKD patients awaiting transplant. Patients received 1 or 2 doses of obi and effects on peripheral B cells noted. When transplanted, lymph nodes were taken to see what Obi did to tissue B cells. Not clear when obi had been given relative to txp and nodes were from 1 and 2-dose patients; Comparator group was random txp patients not in the trial.



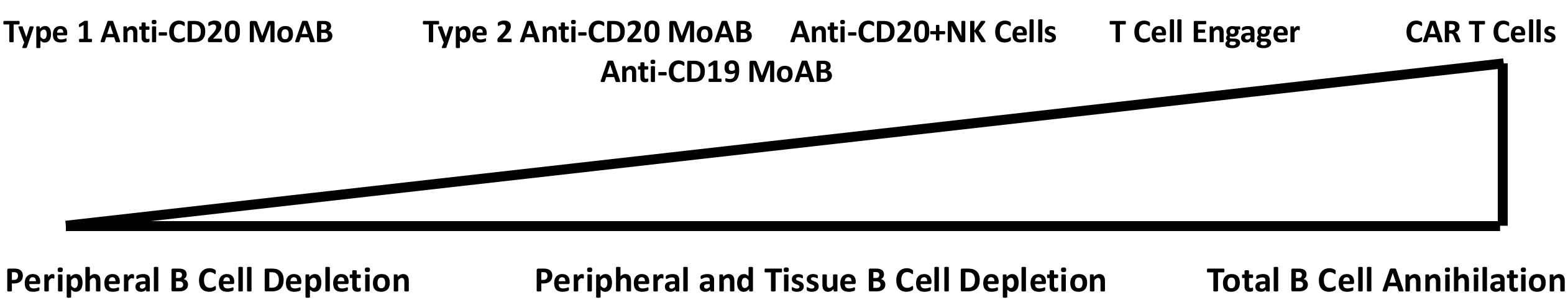


Looney et al, Transplantation Direct, 2023

Cell therapies are evolving…future considerations

- Off the shelf, allogeneic CAR T are already in trial-these have been genetically modified to be hypo-immune so the host immune system does not kill them immediately
- Cell therapies with other cell types are being considered, for example the use of CAR NK to work in conjunction with anti-CD20 antibodies to enhance killing
- Most new protocols are at least considering reduction or elimination of conditioning with CYC-FLU
- Bispecific engineered antibodies that bring B cells into contact with T cells are here and ready to trial in autoimmune diseases-let the patients own T cells do the dirty work without CAR modification!

B Cell Depletion-How Deep is Deep Enough?



- Good or excellent peripheral B cell depletion seems to work well for some patients
- Other patients may respond but flare later
- Some patients will not respond at all
- We have all of the above tools to achieve specific levels of B cell depletion and more choices on the way
- It will be critical to be able to identify the degree of B cell depletion a patient needs *a priori* to treat in a precision fashion and to avoid trial and error use of escalating B cell therapies