Longitudinal Assessment of Biomarkers in NOBILITY, a Randomized, Phase II Clinical Trial of Obinutuzumab for Treatment of Proliferative Lupus Nephritis

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C.M. Looney, A. Mao and **T. Schindler** are employees and shareholders of F. Hoffmann-La Roche Ltd.

H. Raghu, V.G. Anania and **J.A. Ross Terres** are employees of Genentech, Inc., and shareholders of F. Hoffmann-La Roche Ltd.

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B-Cell Depletion for the Treatment of Proliferative Lupus Nephritis

B cells are central to lupus nephritis pathogenesis,[1] and formation of T- and B-cell complexes and production/deposition of immune complexes within the kidney lead to inflammation and tissue damage in patients with lupus nephritis[2]

Randomized controlled trials of type I anti-CD20 antibodies (eg, rituximab) showed inconsistent clinical responses that were hypothesized to be due to incomplete B-cell depletion in blood and/or tissues[3-6]

Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody[7] with **enhanced B-cell depletion vs other anti-CD20s** due to

- **Glycoengineering:** up to 100x antibody-dependent cytotoxicity[8,9]
- **Type II binding conformation:** greater direct cell death, reduced internalization and less reliance on complement-dependent cytotoxicity[8,9]

Hypothesis: Enhanced B-cell depletion with obinutuzumab would increase the rate of complete renal response when added to background standard of care (SOC) compared with SOC alone in patients with lupus nephritis

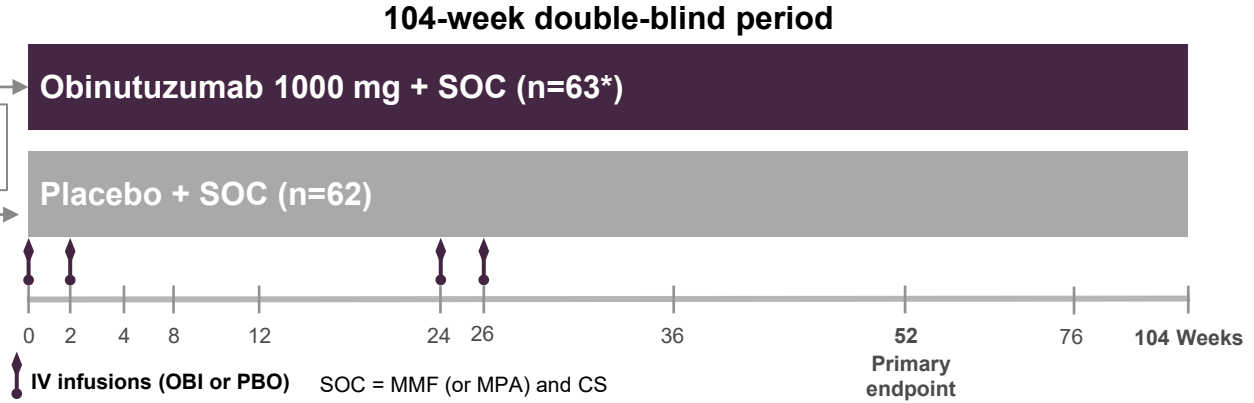
Obinutuzumab is currently not indicated for the treatment of lupus nephritis.

1. Parodis I, et al. *Front Med (Lausanne)*. 2022;9:952304. 2. Parikh SV, et al. *Am J Kidney Dis*. 2020;76:265-281. 3. Rovin BH, et al. *Arthritis Rheum*. 2012;64:1215-1226. 4. Mysler EF, et al. *Arthritis Rheum*. 2013;65:2368-2792. 5. Vital EM, et al. *Arthritis Rheum*. 2011;63:3038-3047. 6. Reddy V, et al. *Arthritis Rheumatol*. 2015;67:2046-2055. 7. Gazyva (obinutuzumab). Prescribing information. Genentech, Inc.; 2022. 8. Herter S, et al. *Mol Cancer Ther*. 2013;12:2031-2042. 9. Mössner E, et al. *Blood*. 2010;115:4393-4402.

NOBILITY: Study Design

Key inclusion criteria:
- ISN/RPS class III or IV (± V) LN by biopsy within 6 months
- UPCR >1 g/g on 24-hour collection

CRR: a composite measure requiring UPCR <0.5, normal renal function (serum creatinine ≤ ULN) without worsening of baseline serum creatinine by >15% and inactive urinary sediment (<10 RBCs/HPF without RBC casts)



Primary endpoint: percentage of patients achieving CRR† (Week 52)
Key secondary endpoints: overall renal response (CRR† or PRR‡); changes in levels of dsDNA, C3 and C4; improvements in UPCR; and exploratory analyses at Weeks 76 and 104
Prespecified α level = 0.2

MMF (MPA): target dose of 2.0-2.5 g/day of MMF (or equivalent)
Corticosteroids: 1-3 infusions of methylprednisolone 1000 mg IV prior to randomization and oral prednisone 0.5 mg/kg tapered to 7.5 mg/day by Week 12 and held.

Key exclusion criteria: rapidly progressive glomerulonephritis, eGFR <30 mL/min/1.73 m^2 , >50% of glomeruli with sclerosis

CRR, complete renal response; CS, corticosteroids; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; HPF, high-power field; ISN, International Society of Nephrology; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; OBI, obinutuzumab; PBO, placebo; PRR, partial renal response; R, randomization; RBC, red blood cell; RPS, Renal Pathology Society; SOC, standard of care; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.
*One patient randomly assigned to obinutuzumab did not receive obinutuzumab due to pregnancy. †A composite measure requiring a UPCR of <0.5, normal renal function (serum creatinine ≤ ULN) without worsening of baseline serum creatinine by >15% and inactive urinary sediment (<10 RBCs/HPF without RBC casts).‡A composite measure requiring ≥50% reduction in UPCR from baseline to a value of <1 (to <3 if baseline UPCR was ≥3), serum creatinine not increased by >15% from baseline and urinary sediment <10 RBCs/HPF or ≤50% increase over the baseline value.
ClinicalTrials.gov. Accessed March 1, 2024. https://www.clinicaltrials.gov/study/NCT02550652. Furie RA, et al. *Ann Rheum Dis*. 2022;81(1):100-107.

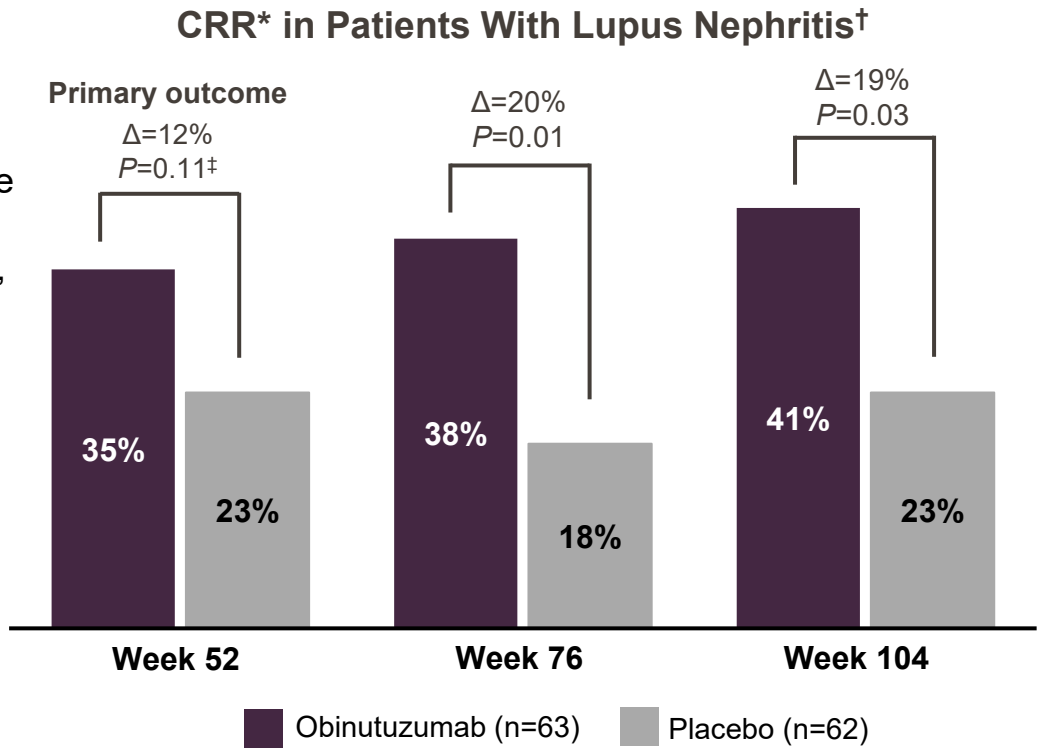
NOBILITY: Clinical Efficacy

Key results

- Primary and secondary endpoints were met at Week 52
- Greater complete renal responses (CRR) were observed through Week 104 (differences of 12%, 20% and 19% at Weeks 52, 76 and 104, respectively)

Conclusion

- Obinutuzumab administered with SOC was superior to SOC alone in achieving CRR in patients with proliferative lupus nephritis
- Response to obinutuzumab was sustained through 104 weeks, 18 months after the last obinutuzumab treatment



CRR, complete renal response.
*A composite measure requiring a UPCR of <0.5, normal renal function (serum creatinine ≤ ULN) without worsening of baseline serum creatinine by >15% and inactive urinary sediment (<10 RBCs/HPF without RBC casts). †The Δ values may not exactly correspond to the subtraction of the patient percentages due to rounding. ‡The prespecified α level was 0.2.
Furie RA, et al. *Ann Rheum Dis*. 2022;81(1):100-107.

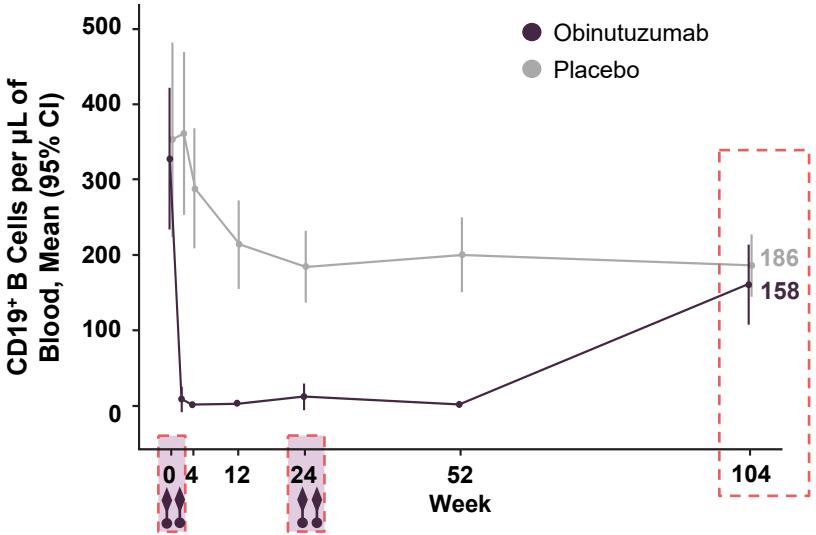
Objectives

This post hoc analyses investigated the relationships between $CD19^+$ B cells/subsets in blood and the clinical response, as well as the effects of obinutuzumab on serological responses in patients with lupus nephritis

NOBILITY PD Data: CD19+ B-Cell Depletion/Repletion in Blood

Demonstration of B-cell depletion capabilities of obinutuzumab in blood by high-sensitivity flow cytometry (LLOQ = 0.4 cells/µL ≈20x more sensitive than conventional TBNK flow cytometry)

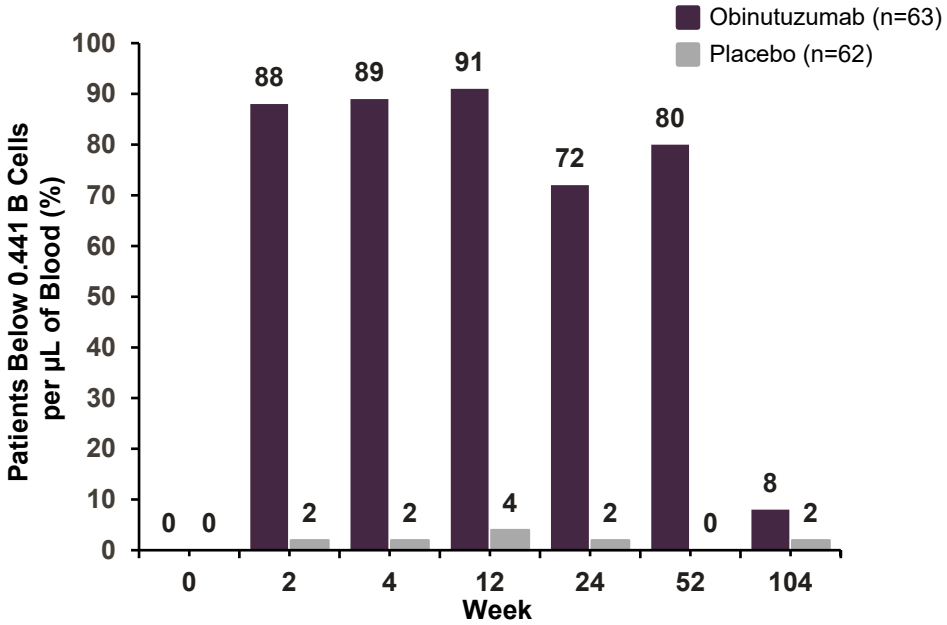
Total CD19+ B Cells



Obinutuzumab, n=	48	56	53	54	54	51
Placebo, n=	48	47	56	47	54	42

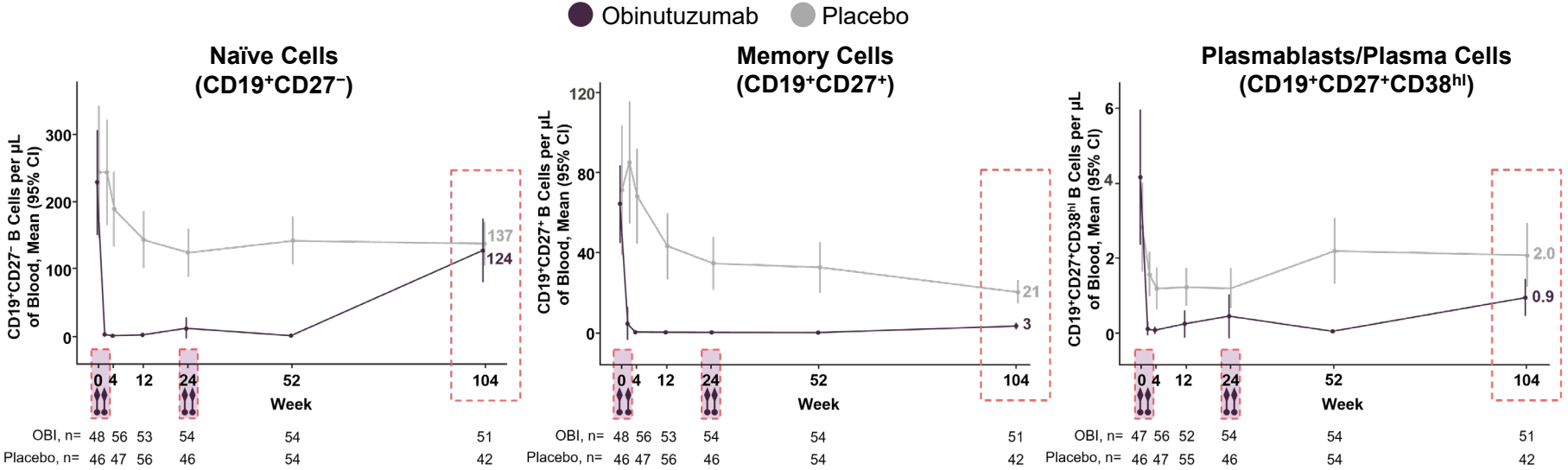
IV infusions (obinutuzumab or placebo) at Weeks 0, 2, 24 and 26.

Patients With B Cells Below LLOQ



Blood samples for flow cytometry were drawn before administration of study drug on dosing days. Depletion in the placebo group was due to accidental or intentional obinutuzumab exposure.
IV, intravenous; LLOQ, lower limit of quantitation; PD, pharmacodynamics; TBNK, T, B and natural killer cell.

NOBILITY PD Data: B-Cell Subsets Depletion/Repletion in Blood



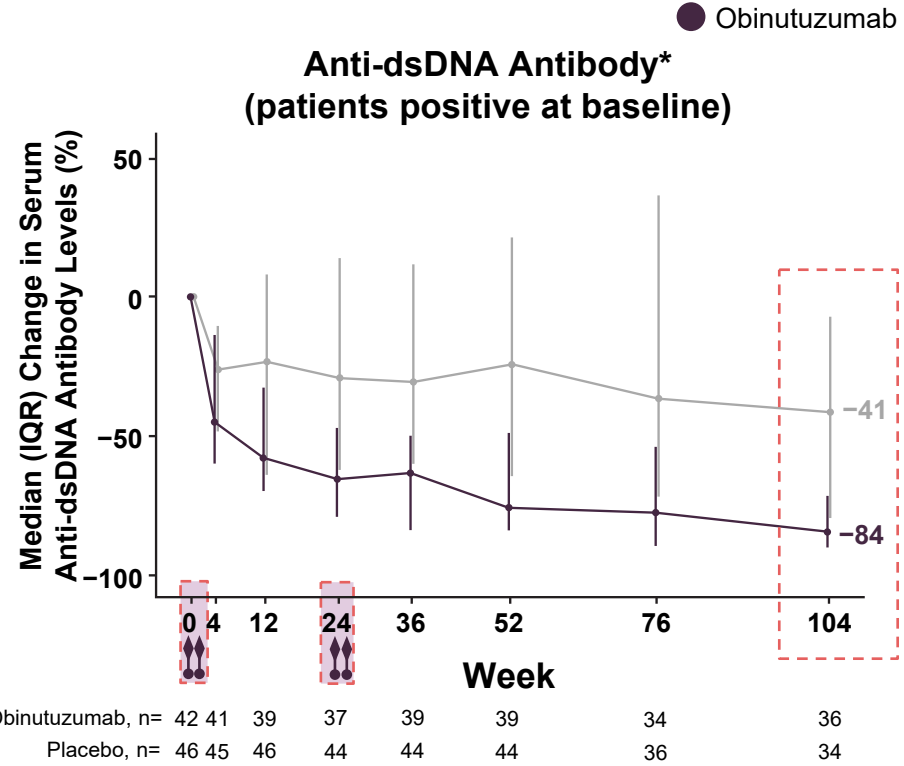
IV infusions (obinutuzumab or placebo) at Weeks 0, 2, 24 and 26.

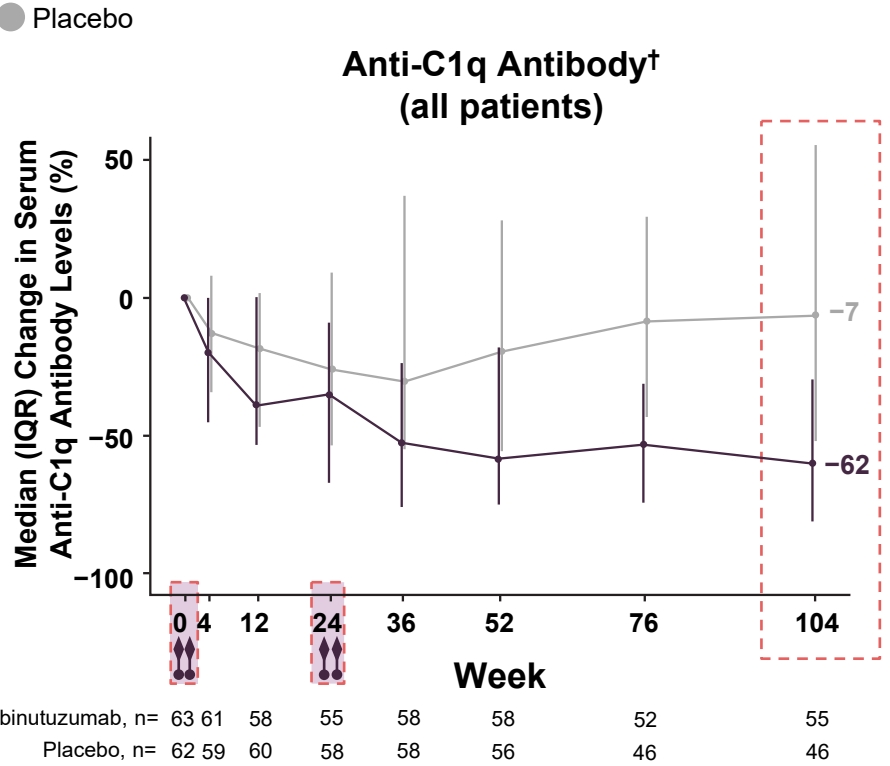
At Week 104, naïve B cells were replenished, whereas memory B cells and plasmablasts/plasma cells remained low in the blood of patients treated with obinutuzumab

Obinutuzumab was associated with an increased prevalence of low IgM, but not low IgG levels compared with baseline and was not associated with reduced concentrations of pre-existing protective antibodies to influenza A, influenza B, tetanus, mumps and rubella[1]

Ig, immunoglobulin; IV, intravenous; OBI, obinutuzumab; PD, pharmacodynamics. 1. Furie RA, et al. *Ann Rheum Dis*. 2022;81(1):100-107.

NOBILITY: Serum Autoantibody Levels

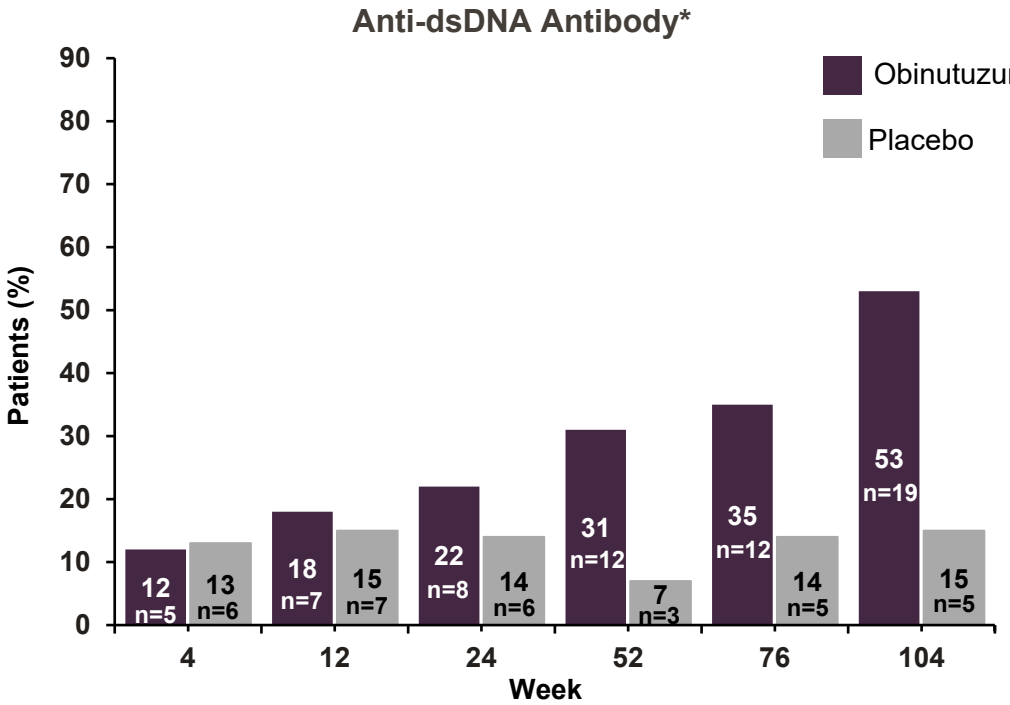




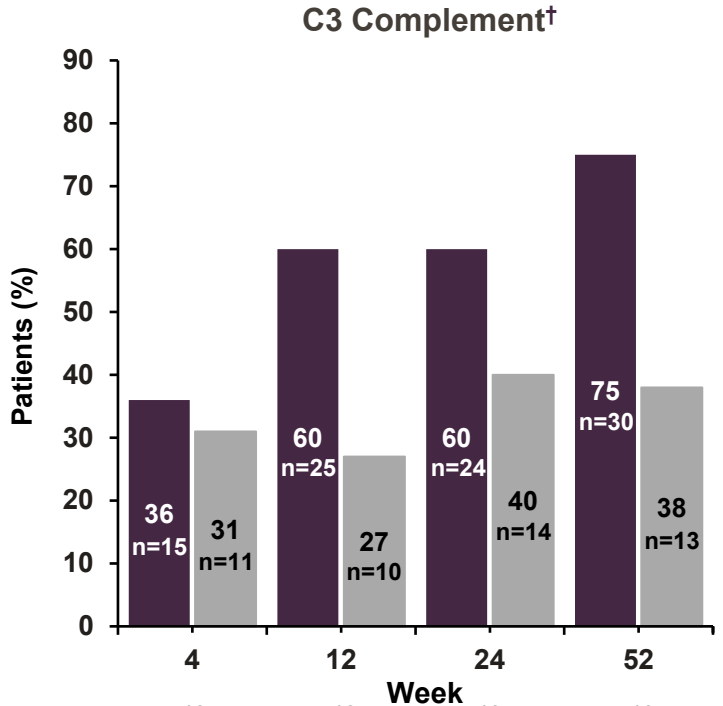
IV infusions (obinutuzumab or placebo) at Weeks 0, 2, 24 and 26.

dsDNA, double stranded DNA; IV, intravenous. *Anti-dsDNA antibody levels measured by Inova QUANTA Lite® ELISA and positivity defined as >30 IU/mL. †Anti-C1q antibody levels measured by ELISA at National Jewish Health Laboratories (reported as % of standard). Normal human reference range is ≤ 7.0% of standard.

NOBILITY: Normalization of Serologies



Obinutuzumab, n=	41	39	37	39	34	36
Placebo, n=	45	46	44	44	36	34



Obinutuzumab, n=	42	42	40	40
Placebo, n=	36	37	35	34

dsDNA, double stranded DNA; IV, intravenous.
*Anti-dsDNA antibody levels measured by Inova QUANTA Lite® ELISA and positivity defined as >30 IU/mL. †Normal C3 level defined as ≥90 mg/dL.
‡Normal C4 level defined as ≥16 mg/dL.

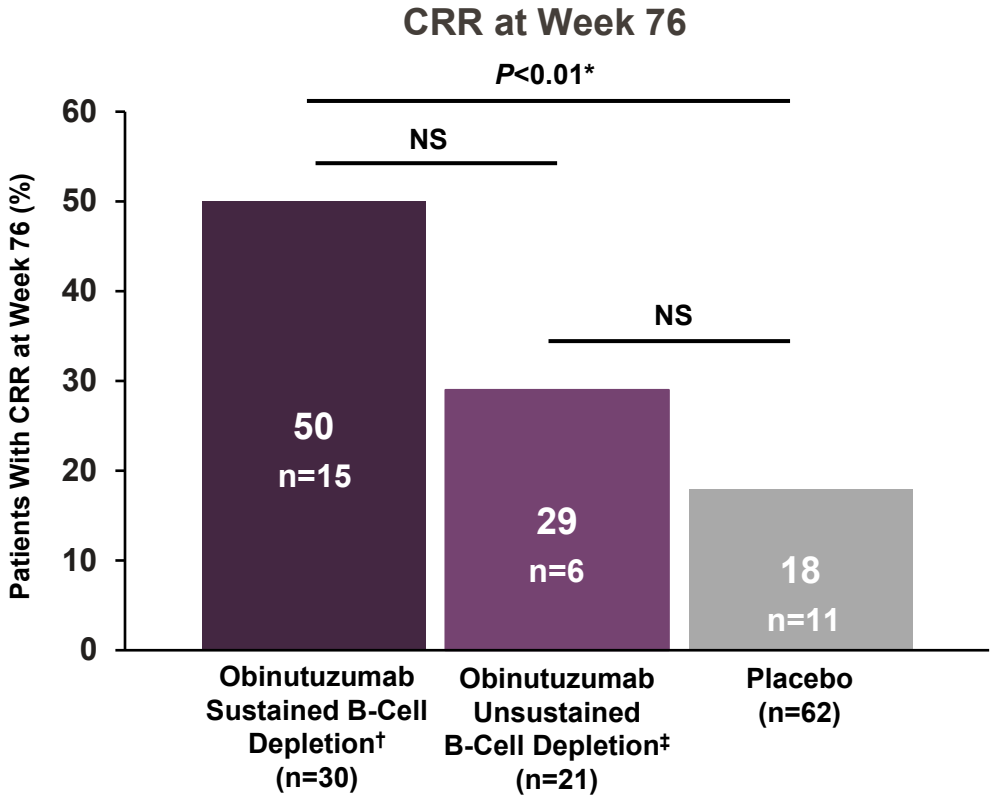
Similar results were observed for normalization of **C4 complement‡**

NOBILITY: Exploration of PD-Efficacy Relationship

Sustained B-cell depletion: undetectable CD19⁺ cells (< LLOQ by HSFC) at Week 24 **and** Week 52

Unsustained B-cell depletion: detectable CD19⁺ cells (> LLOQ by HSFC) at Week 24 **or** Week 52

Patients with **sustained B-cell depletion,** as measured by HSFC, were 72% more likely to achieve CRR at Week 76 (12 months after last obinutuzumab dose)



CRR, complete renal response; HSFC, high-sensitivity flow cytometry panel MRB1.1 with LLOQ of 0.4 cells/uL; NS, not significant; PD, pharmacodynamics.
**P* value determined by Cochran–Mantel–Haenszel test vs placebo. †Sustained B-cell depletion defined as undetectable CD19⁺ B cells (< LLOQ by HSFC) in blood at Weeks 24 and 52. ‡Unsustained B-cell depletion defined as detectable CD19⁺ B cells in blood (> LLOQ by HSFC) at Week 24 or Week 52.

Conclusions

- Treatment with obinutuzumab resulted in rapid and profound depletion of $CD19^+$ total B cells and B-cell subsets in blood
- At Week 104, naïve B cells recovered, whereas memory B cells and plasmablasts/plasma cells remained low in patients treated with obinutuzumab
- Obinutuzumab resulted in earlier and greater improvements in levels of anti-dsDNA antibodies, anti-C1q autoantibodies and complement C3/C4
- Normalization of serologies occured in more patients receiving obinutuzumab than patients receiving placebo
- Patients with sustained B-cell depletion following obinutuzumab treatment achieved greater rates of CRR at Week 76 than those who did not sustain depletion

Data support the hypothesis that obinutuzumab-mediated robust and sustained B-cell depletion will result in better clinical responses vs standard of care in patients with lupus nephritis