

OBINUTUZUMAB INDUCES HISTOLOGIC REMISSION AND DEEP KIDNEY PARENCHYMAL B-CELL DEPLETION IN PATIENTS WITH LUPUS NEPHRITIS: EXPLORATORY ANALYSES OF THE PHASE III REGENCY TRIAL

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BACKGROUND

- Obinutuzumab is a recombinant, humanized, glycoengineered type II anti-CD20 IgG1 monoclonal antibody that leads to greater B-cell depletion compared with type I anti-CD20 antibodies¹
- The REGENCY trial (NCT04221477)² randomized adults with active lupus nephritis (LN) to placebo^a or obinutuzumab^a
 - At Week 76, significantly more obinutuzumab^a-treated participants vs placebo^a-treated participants achieved clinical complete renal response (CRR) (46.4% vs 33.1% [adjusted difference, 13.4%; 95% CI, 2.0% to 24.8%]; $P=0.0232$)²; this led to US Food and Drug Administration approval for obinutuzumab^a to treat LN

^aPlus standard therapy (ST) consisting of mycophenolate mofetil (MMF) plus glucocorticoids.

OBJECTIVE

This exploratory analysis aimed to evaluate the effect of obinutuzumab^a vs placebo^a on tissue-level changes in kidney inflammation between baseline and post-Week 76 paired kidney biopsies from the REGENCY trial by assessing histologic remission and kidney tissue-level B-cell depletion and antibody-secreting cells

^aPlus ST consisting of MMF plus glucocorticoids.

METHODS

- All enrolled study participants had a kidney biopsy performed in the 6 months before or during screening, with an optional post-Week 76 kidney biopsy
- Paired baseline and post-Week 76 native kidney biopsies (up to study Week 80) were collected from 64 study participants (32 obinutuzumab^a; 32 placebo^a)
- Blinded, central reads of baseline and post-Week 76 biopsies were evaluated by Arkana Laboratories and classified as per the 2018 ISN/RPS LN classification and the NIH activity index (AI) and chronicity index
- Proportions of participants achieving histologic remission (AI=0) or near-histologic remission (AI≤1) were determined^b
- CD79a+/CD138- B cells and CD138+/CD79a+/Ki67-plasma cells^c were quantified on formalin-fixed, paraffin-embedded tissue sections by multiplex immunofluorescence microscopy and digital whole-slide image analysis
- Treatment group comparisons of absolute change from baseline at Week 76 were assessed using an ANCOVA model with baseline B-cell/plasma cell counts and stratification factor (Black vs Other) as independent variables

^aPlus ST consisting of MMF plus glucocorticoids; ^bStudy participants with AI≤1 or AI=0 at baseline and who received rescue therapy or glucocorticoid-only rescue prior to Week 76 were considered non-responders; ^cFor 64 study participants, both baseline and post-Week 76 biopsy specimens were available to assess histologic remission; for 29 (obinutuzumab=14; placebo=15) out of those 64, unstained slides were available to perform the B-cell and antibody-secreting-cell analysis.

CONCLUSIONS

- The endpoint of clinical CRR (driven by attainment of UPCR <0.5 g/g) can overlook patients who have achieved histologic remission; returning the kidney to a non-inflamed immunologically inactive state is the goal of LN treatment
- Histologic remission (AI=0) was achieved more frequently in the obinutuzumab^a group compared with the placebo^a group (adjusted difference, 30.75%)
- More than half of the clinical CRR non-responders in the obinutuzumab^a group achieved histologic remission (AI=0) (adjusted difference, 44.9%) compared with the placebo^a group
- Obinutuzumab^a almost completely depletes B cells from the kidney parenchyma and reduces the number of intra-renal plasma cells by about half; in contrast, there was no change in intra-renal B cells or plasma cells in the kidneys of study participants treated with placebo^a
- These data suggest that obinutuzumab mediates favorable outcomes in LN beyond the traditional clinical trial endpoint of clinical CRR

^aPlus ST consisting of MMF plus glucocorticoids.

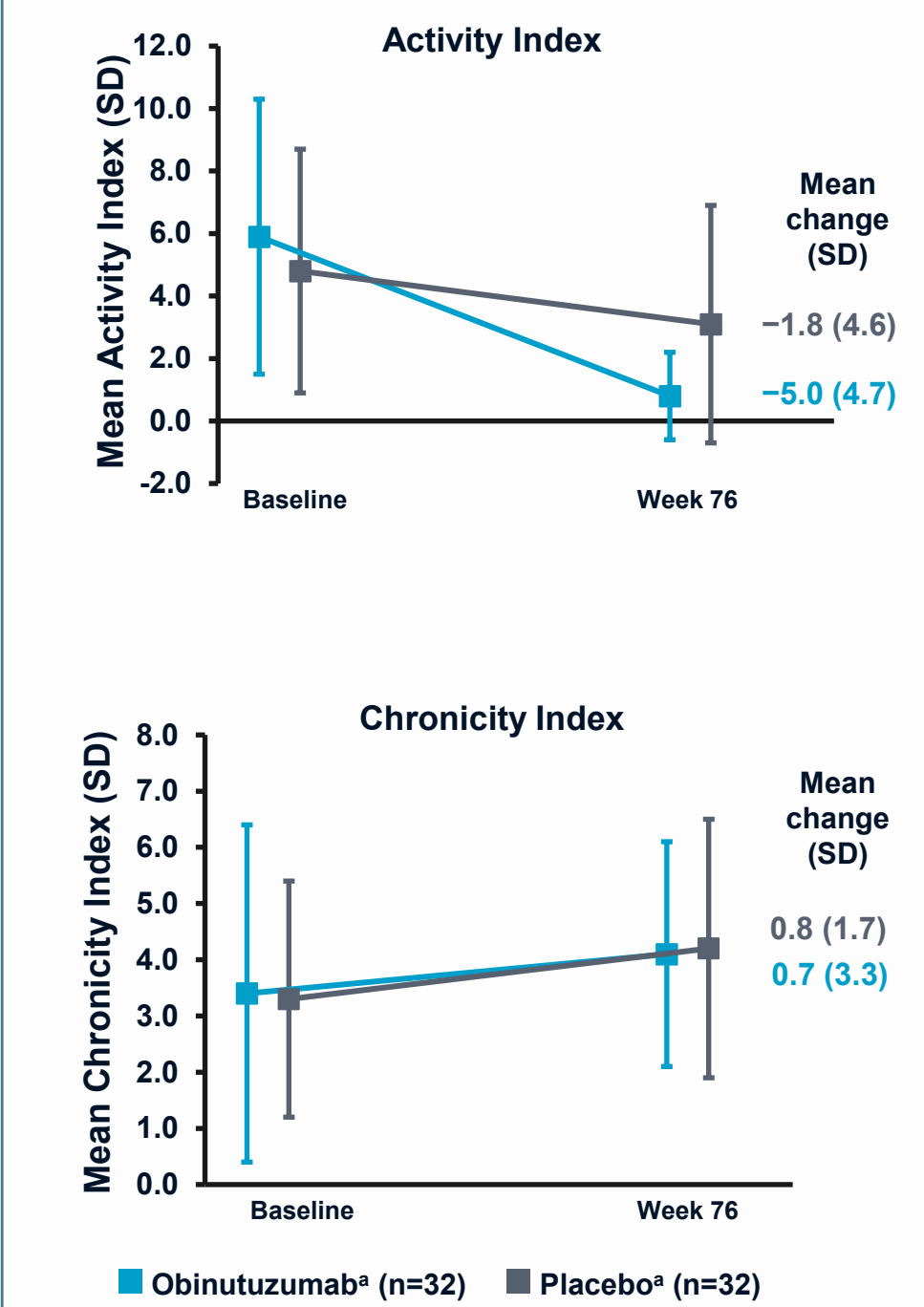
RESULTS

Table 1. Baseline Characteristics of the REGENCY Repeat Kidney Biopsy Cohort Were Generally Balanced and Consistent With the Overall ITT Population

	Obinutuzumab ^a			Placebo ^a		
	ITT Population (N=135)	Kidney Biopsy Cohort (N=32)	Kidney Tissue B-Cell Cohort (N=14)	ITT Population (N=136)	Kidney Biopsy Cohort (N=32)	Kidney Tissue B-Cell Cohort (N=15)
Mean age (SD), years	33.0 (10.5)	28.9 (7.6)	28.2 (7.3)	32.7 (10.0)	33.3 (10.4)	32.8 (7.6)
Female sex, n (%)	114 (84.4)	29 (90.6)	14 (100)	115 (84.6)	25 (78.1)	13 (86.7)
Hispanic or Latino ethnicity, n (%)	71 (52.6)	24 (75.0)	12 (85.7)	85 (62.5)	22 (68.8)	12 (80.0)
eGFR, mL/minute/1.73 m ² , mean (SD)	102.8 (29.3)	114.2 (25.1)	117.9 (32.5)	101.9 (32.2)	103.1 (33.0)	112.7 (30.4)
24-hour UPCR, g/g, mean (SD)	3.14 (2.99)	2.49 (1.64) ^b	2.50 (1.97)	3.53 (2.76)	3.13 (2.52)	2.86 (2.02)
Prior history of LN, n (%)	81 (60.0)	16 (50.0)	1 (7.1)	76 (55.9)	16 (50.0)	1 (6.7)
SLEDAI-2K, mean (SD)	12.1 (8.1)	9.4 (4.6)	9.7 (4.8)	12.4 (6.7)	10.0 (4.8)	10.3 (4.2)
Anti-dsDNA positive (>120 KU/L), n (%)	57 (42.2)	12 (37.5)	7 (50.0)	61 (44.9)	12 (37.5)	8 (53.3)
C3 complement <0.9 g/L, n (%)	77 (57.0)	11 (34.4)	6 (42.9)	76 (55.9)	14 (43.8)	5 (33.3)
C4 complement <0.1 g/L, n (%)	32 (23.7)	5 (15.6)	4 (28.6)	42 (31.1)	12 (37.5)	4 (26.7)
B-cell count per mm ² tissue, mean (SD)	NA	NA	42.81 (69.59)	NA	NA	16.08 (17.85)
Plasma cell count per mm ² tissue, mean (SD)	NA	NA	44.03 (71.82)	NA	NA	29.94 (37.70)

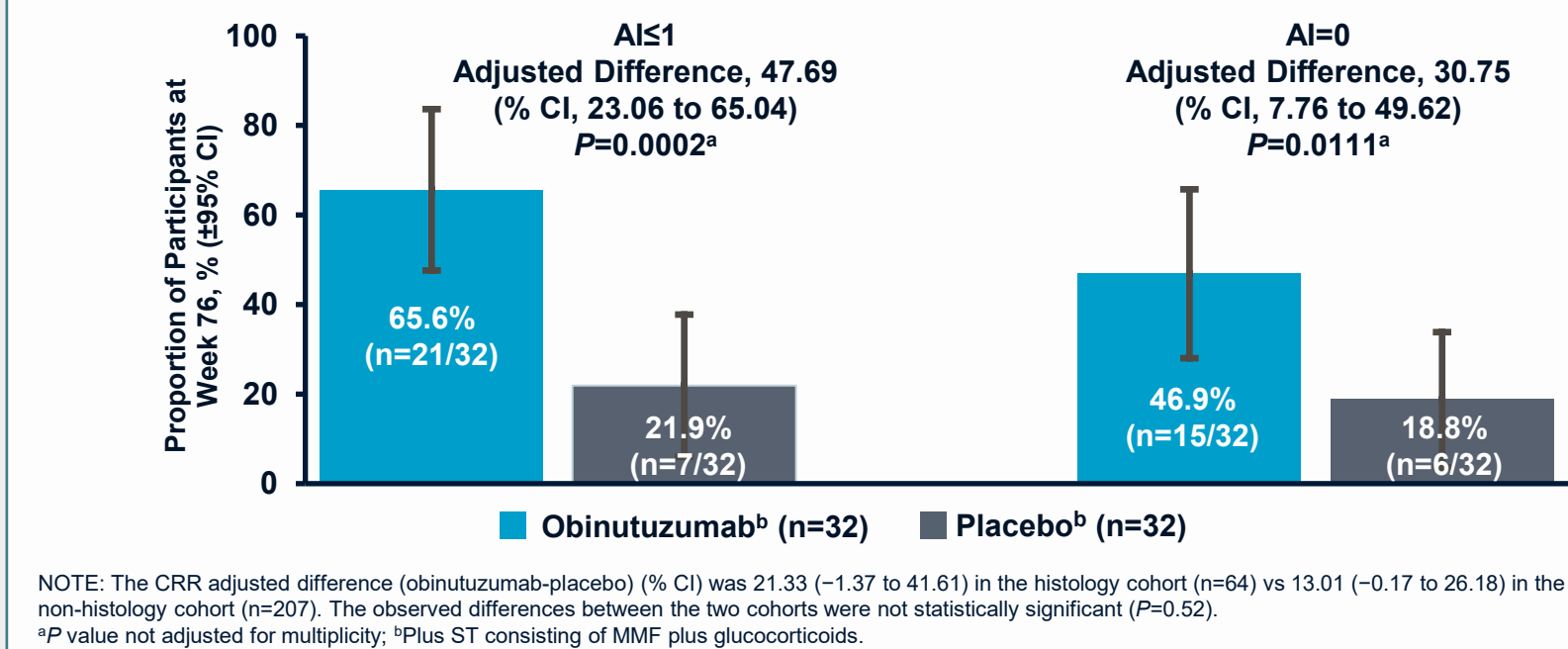
^aPlus ST consisting of MMF plus glucocorticoids.

Figure 1. The Mean Change in Activity Index Was Greater With Obinutuzumab vs Placebo Treatment at Week 76



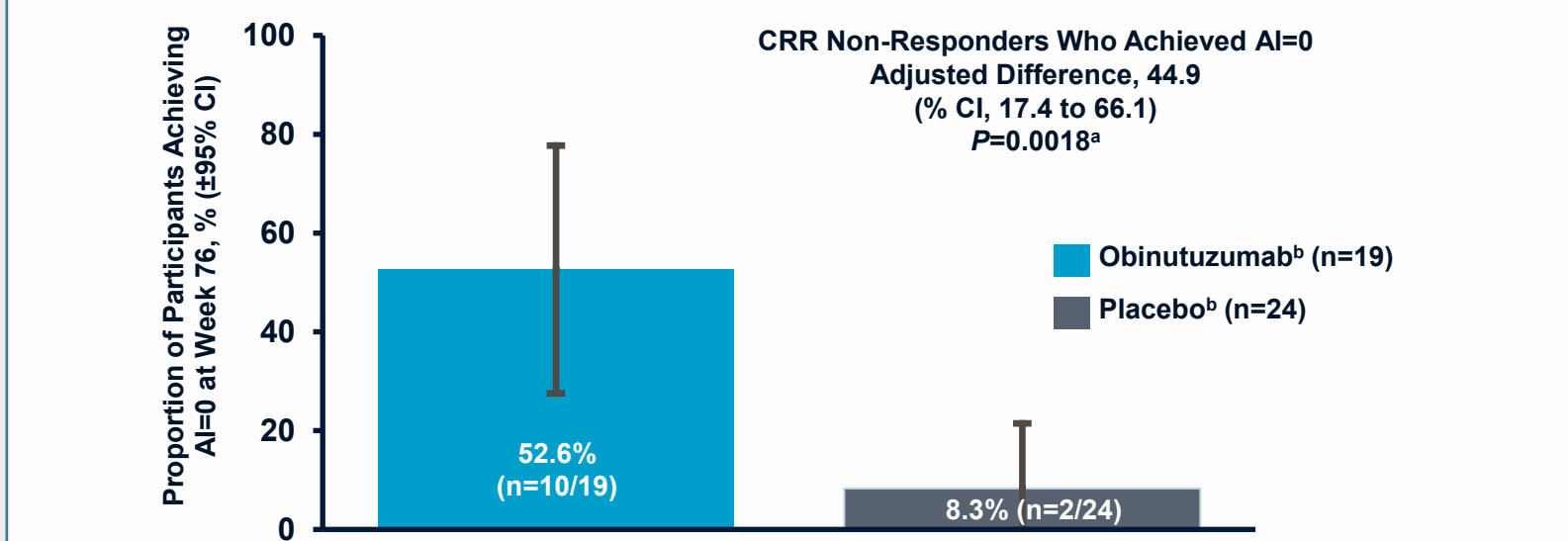
^aPlus ST consisting of MMF plus glucocorticoids.

Figure 2. More Study Participants Achieved Near-Histologic Remission (AI≤1) or Histologic Remission (AI=0) With Obinutuzumab vs Placebo Treatment at Week 76



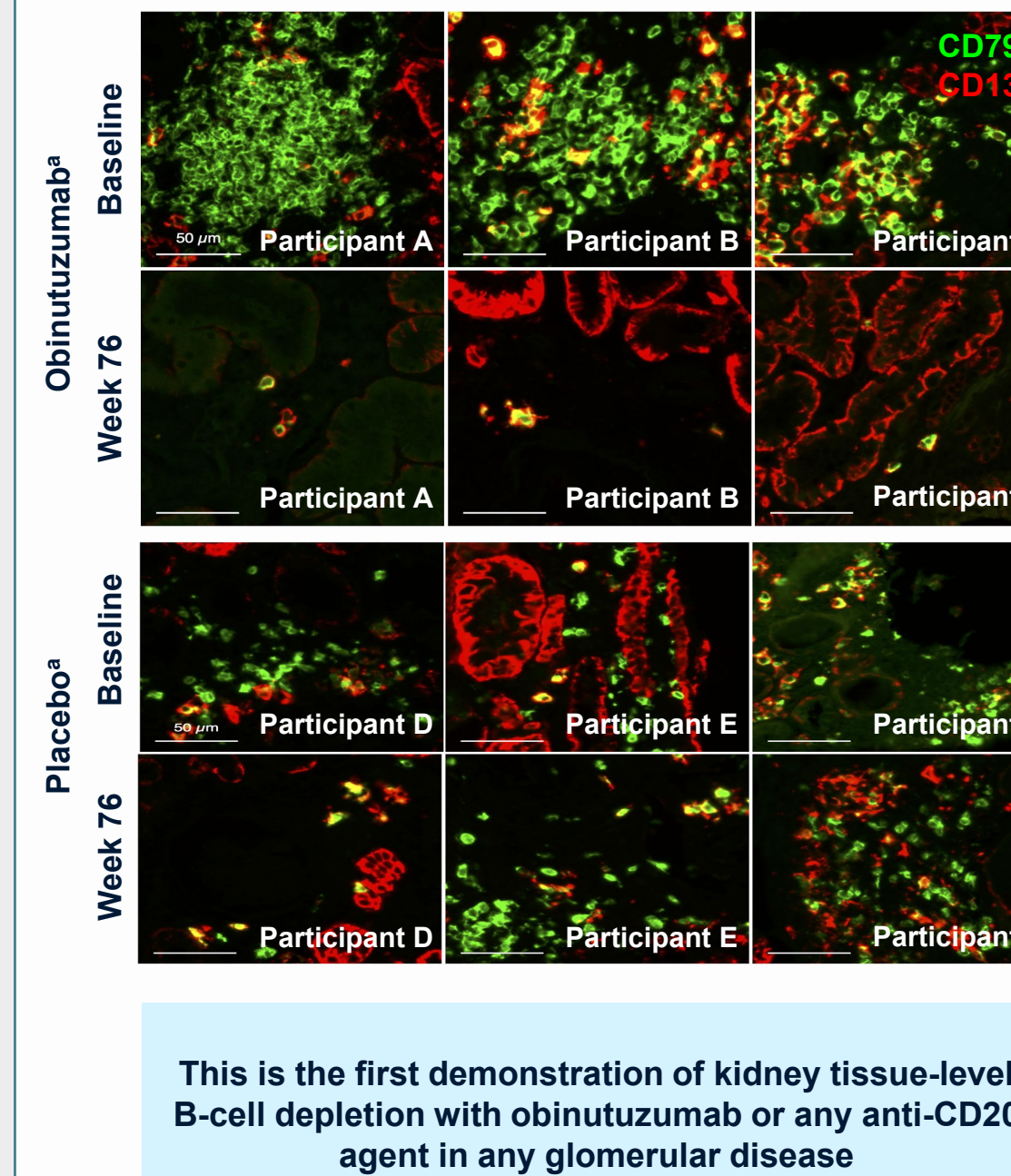
NOTE: The CRR adjusted difference (obinutuzumab-placebo) (% CI) was 21.33 (-1.37 to 41.61) in the histology cohort (n=64) vs 13.01 (-0.17 to 26.18) in the non-histology cohort (n=207). The observed differences between the two cohorts were not statistically significant ($P=0.52$). ^aP value not adjusted for multiplicity; ^bPlus ST consisting of MMF plus glucocorticoids.

Figure 3. More Than Half of the Clinical CRR Non-Responders in the Obinutuzumab Group Achieved Histologic Remission (AI=0) at Week 76



Study participants achieving AI=0 at Week 76 are considered as participants with an event except for the following who were considered non-responders: participants with AI=0 at baseline; participants who received rescue therapy or glucocorticoid-only rescue prior to Week 76. ^aP value not adjusted for multiplicity; ^bPlus ST consisting of MMF plus glucocorticoids.

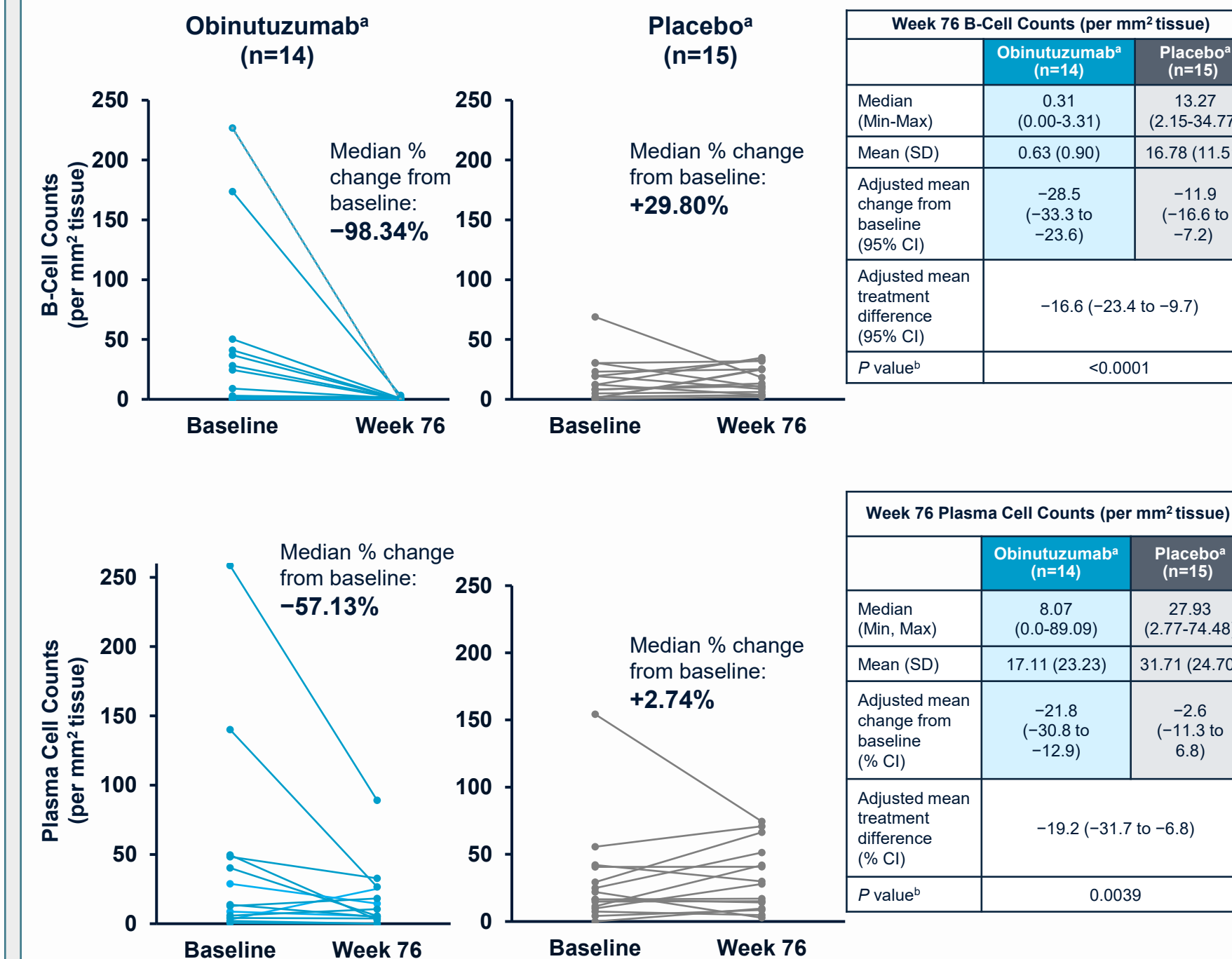
Figure 4. Obinutuzumab-Induced Kidney Tissue Depletion of B Cells and Plasma Cells in the REGENCY Trial



This is the first demonstration of kidney tissue-level B-cell depletion with obinutuzumab or any anti-CD20 agent in any glomerular disease

B cell-rich areas from study participants with the highest baseline B-cell counts from obinutuzumab^a or placebo^a groups at baseline and Week 76^a. B cells are CD79a⁺ (green) and CD138⁺ (red). Antibody-secreting cells are CD79a⁺ (green) and CD138⁺ (red), the large majority of which are plasma cells and Ki67⁺ (not shown). Renal tubular epithelium cells are CD138⁺ (red) and CD79a⁻. ^aPlus ST consisting of MMF plus glucocorticoids.

Figure 5. Obinutuzumab Treatment Resulted in Complete/Near-Complete Depletion of B Cells and Reduction in Plasma Cells in the Kidneys of Study Participants With LN at Week 76



^aPlus ST consisting of MMF plus glucocorticoids; ^bP values are from a post hoc analysis; formal claims of statistical significance cannot be made.

REFERENCES

- Tobinai K, et al. *Adv Ther*. 2017;34:324-356.
- Furie RA, et al. *N Engl J Med*. 2025;392:1471-1483.

ABBREVIATIONS

AI, activity index; ANCOVA, analysis of covariance; CI, confidence interval; CRR, complete renal response; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; ISN/RPS, International Society of Nephrology/Renal Pathology Society; ITT, intention-to-treat; LN, lupus nephritis; MMF, mycophenolate mofetil; NA, not available; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; ST, standard therapy; UPCR, urine protein-to-creatinine ratio.

DISCLOSURES

B.H.R. has received consulting fees from F. Hoffmann-La Roche Ltd/Genentech Inc. E.M. and T.S. are employees and shareholders of F. Hoffmann-La Roche Ltd. C.D.A., H.R., C.C., P.S.C., J.P.G., B.Y., A.T., T.A.O. and W.F.P. are employees of Genentech, Inc. and shareholders of F. Hoffmann-La Roche Ltd. V.A. has received consulting fees and/or reported professional services for F. Hoffmann-La Roche Ltd, GlaxoSmithKline and Novartis. M.B.S., G.A., T.B., L.F.P. and E.H.A. have nothing to disclose. F.I.P. has received consulting fees and/or research support from AbbVie, Amgen, Eli Lilly, F. Hoffmann-La Roche Ltd, Janssen, Novartis, Pfizer and Takeda. J.A. has received consulting fees and/or reports professional services for AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd, Horizon Therapeutics and Kezar. J.R. has received consulting fees and/or reported professional services for AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd and Horizon Therapeutics. R.A.F. has received research support and consulting fees from Chugai Pharmaceutical Co., Ltd., F. Hoffmann-La Roche Ltd, Genentech, Inc. and GlaxoSmithKline; is a consultant for AstraZeneca, EMD Serono, Novartis, Biogen, and BMS; is an investigator for AstraZeneca, Novartis, Biogen, BMS, and Kyverna; and is a speaker for AstraZeneca. C.L. has received support and/or consulting fees from Calliditas Therapeutics AB and Novartis. A.M. has received consulting fees and/or reports professional services for Bristol Myers Squibb, F. Hoffmann-La Roche Ltd, GlaxoSmithKline, Kezar, Novartis and Pfizer.

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