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groups. Mechanistic analyses of circulating B cells at week 48 showed differences in the relative proportions of B cell subpopulations between RC and RCB groups and fewer ANA +B cells in the RCB group (figure 1).

Conclusions Treatment with anti-BAFF following anti-CD20 did not improve clinical outcome at week 48; (ii) anti-BAFF delayed blood B cell reconstitution following B cell depletion; (iii) anti-BAFF following anti-CD20 was not associated with hypogammaglobulinemia or an increase in serious infections and (iv) the reconstituted B cell populations differed between the RCB and RC groups. Further analyses at 96 weeks will address how anti-BAFF therapy affects quantitative and qualitative recovery of B cells as well as long-term clinical outcome.

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KZR -616, A SELECTIVE INHIBITOR OF THE IMMUNOPROTEASOME, ATTENUATES THE DEVELOPMENT OF MURINE LUPUS

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Background The proteasome inhibitor bortezomib, which inhibits both the constitutive proteasome and immunoproteasome, has been used successfully to treat patients with systemic lupus erythematosus (SLE), but adverse effects limit its use. The immunoproteasome is a distinct class of proteasome found predominantly in immune effector cells. KZR-616 selectively inhibits the LMP7 and LMP2 subunits of the immunoproteasome and is currently being studied in patients with SLE and lupus nephritis (LN). Here we describe the clinical, cellular, and molecular effects of KZR-616 in a mouse model of SLE.

Methods Immunoproteasome inhibition was measured in mice following administration of KZR-616 by quantitation of proteasome active site occupancy. The therapeutic effect of KZR-616 treatment was examined in the NZB/W F1 model of SLE. The degree of proteinuria (0-4 scale) was used to evaluate the severity of nephritis. Serum anti-double-stranded deoxyribonucleic acid (dsDNA) was measured by enzyme-linked immunosorbent assay (ELISA). Kidneys were harvested and

stained with hematoxylin and eosin (H and E) and anti-immunoglobulin G (IgG). Ribonucleic acid (RNA) was extracted from spleens and kidneys and examined by RNA sequencing analysis.

Results KZR-616 administration mice resulted in selective inhibition of LMP7 and LMP2 by 91% and 71%, respectively, similar to levels of inhibition seen *in vitro*. KZR-616 treatment in diseased mice resulted in complete resolution of proteinuria and statistically significant reductions in anti-dsDNA production and an absence of renal IgG deposition compared to vehicle treated animals. Proteinuria levels did not significantly increase 8 weeks after KZR-616 treatment discontinuation. Histologic analysis following 12 weeks of treatment revealed complete prevention of glomerular nephritis and sclerosis. Immunoproteasome inhibition decreased expression of genes involved in plasma cell differentiation, antibody secretion, and glomerular and tubulointerstitial renal pathology in diseased mice treated with KZR-616.

Conclusions KZR-616 effectively blocks disease progression in a mouse model of SLE. Durable disease remission in animals was achieved at well-tolerated doses. Inhibition of the immunoproteasome attenuated gene expression associated with immune effector cell function and glomerular injury. These experimental data support the ongoing clinical evaluation of KZR-616 in patients with LN.

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EXAMINING THE TRANSCRIPTIONAL IMPACT OF LIGANDED ESTROGEN RECEPTOR ALPHA IN THE INFLAMMATORY MILIEU OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Systemic lupus erythematosus (SLE) disproportionately affects females (9:1) over males. Despite significant research effort, the exact mechanisms behind this compelling sex bias are undefined. Our prior studies demonstrate a significant role for estrogen receptor alpha (ER) mediated