KZR-616, a Selective Inhibitor of the Immunoproteasome, Blocks the Disease Progression in Multiple Models of Systemic Lupus Erythematosus (SLE)

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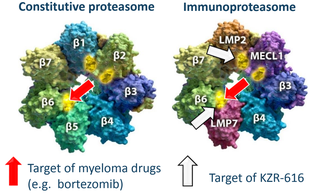
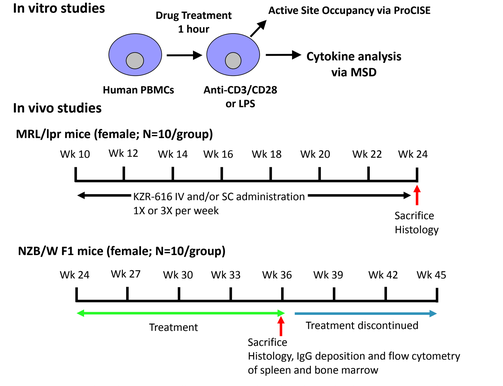
BACKGROUND

- Proteasome Inhibitors (e.g. bortezomib) used to treat multiple myeloma target both forms of the proteasome (Figure 1)
- Bortezomib has been used successfully to treat patients with SLE and lupus nephritis (LN)[1, 2]
- ONX 0914 was the first described selective inhibitor of the immunoproteasome and is effective in mouse models of inflammation[3, 4, 5]
- KZR-616 is an analog of ONX 0914 and has completed Phase 1 studies in healthy volunteers (ACR Abstract# 2587)
- We evaluated the activity of KZR-616 in preclinical models of SLE and LN

Figure 1. Proteasome subunit composition



METHODS



- Human peripheral blood B-cells were stimulated with antibodies to CD40 and IgM in the presence of IL-21 for 6 days. Plasmablast differentiation was confirmed by CD38 staining with flow cytometry. IgG was measured by MSD.
- Cynomolgus monkeys were administered 0 or 4 mg/kg KZR-616 subcutaneously once a week for 13 consecutive weeks. Hematology changes were measured 24 hours, 7 Days and 8 weeks after the last dose (Day 85). T-dependent antibody responses (TDAR) to keyhole limpet hematocyanin (KLH) or Tetanus Toxoid (TT) were measured in cynomolgus monkeys following 4 or 13 weekly administrations of KZR-616 via ELISA.

RESULTS

Figure 2. Inhibition of LMP7 and LMP2 with KZR-616 blocks inflammatory cytokine production in human monocytes and T cells

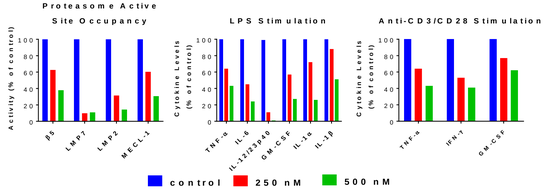


Figure 3. KZR-616 blocks progression of lupus nephritis in MRL/lpr mice

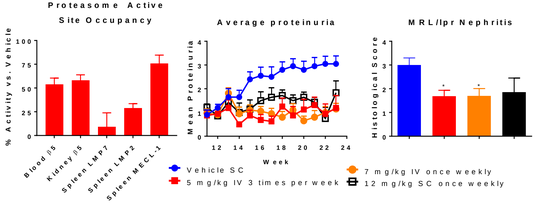


Figure 4. KZR-616 blocks disease progression in NZB/W F1 mice

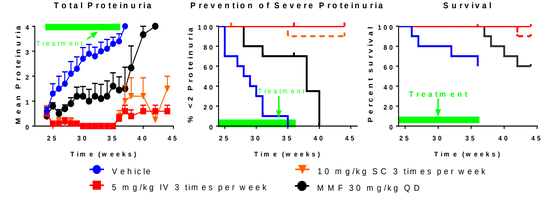


Figure 5. KZR-616 synergizes with MMF to block disease progression in NZB/W F1 mice

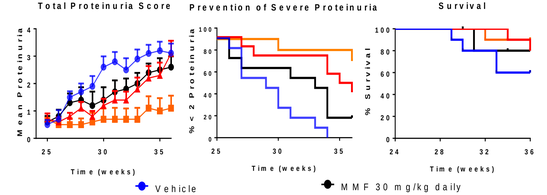


Figure 6. Administration of KZR-616 prevents renal damage in NZB/W F1 mice

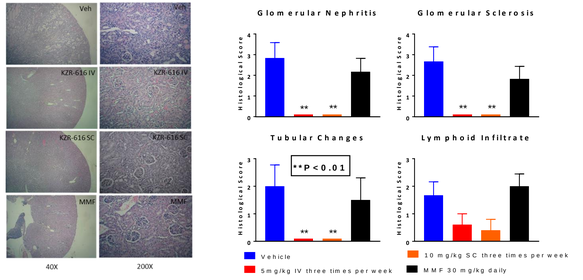


Figure 7. KZR-616 reduces autoantibodies to dsDNA, total IgG levels and IgG deposition in kidneys in NZB/W F1 mice

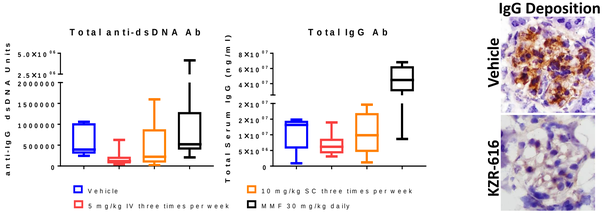


Figure 8. Lymphocyte subpopulations in NZB/W F1 mice following KZR-616 administration

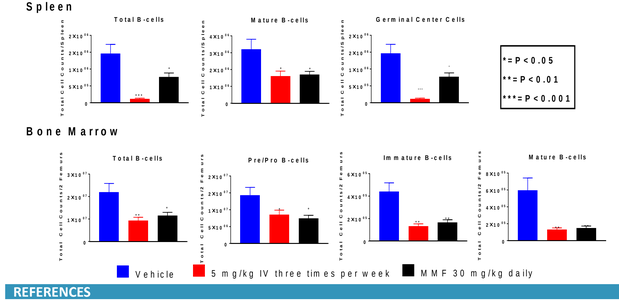


Figure 9. KZR-616 inhibits B cell differentiation in human PBMCs and reduces Short-Lived (SL) and Long-Lived (LL) plasma cells (PC) in NZB/W F1 mice

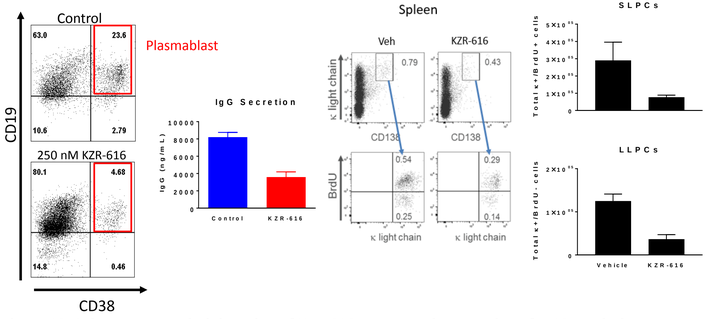
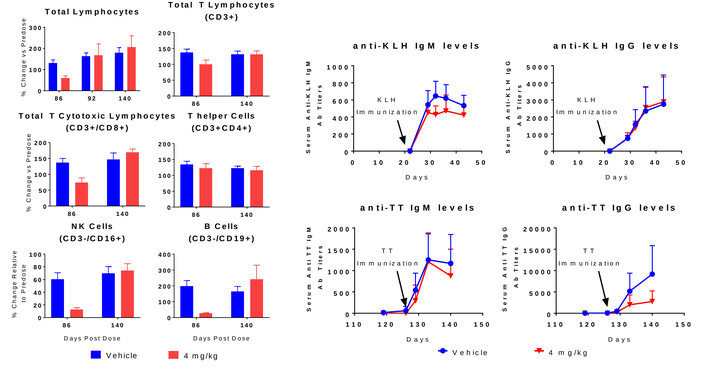


Figure 10. Subcutaneous administration of KZR-616 to cynomolgus monkeys for 13 weeks has no effects on lymphocytes or antibody responses to TT or KLH



CONCLUSIONS

- KZR-616 blocks cytokine production and plasma cell formation
- Complete resolution of proteinuria and reduced autoantibody levels and renal IgG deposition seen following KZR-616 treatment of diseased mice
- Prolonged renal response in mice even after treatment withdrawal
- KZR-616 synergizes with MMF in NZB/W F1 mice
- Effect of KZR-616 is due in part to depletion of activated B-cells and plasma cells
- Phase 1 study of KZR-616 in healthy volunteers shows similar levels of immunoproteasome inhibition to mouse models (Abstract #2587)

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