

KZR-616, A Selective Inhibitor of the Immunoproteasome: Preclinical and Clinical Mechanism of Action Studies in Lupus Nephritis

Tony Muchamuel¹, Janet L Anderl¹, R Andrea Fan¹,
Dustin McMinn¹, Brian Tuch², Henry WB Johnson¹,
Christopher J Kirk¹

¹Kezar Life Sciences, South San Francisco, CA, USA; ²BT Consulting, Brisbane, CA, USA



Disclosures

Employees and Shareholders of Kezar Life Sciences

Tony Muchamuel

Janet L Anderl

R Andrea Fan

Dustin McMinn

Henry WB Johnson

Christopher J Kirk

Consultant for Kezar Life Sciences

Brian Tuch



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Dustin McMinn

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R Andrea Fan

Eric Lowe

Janet L Anderl

Brian Tuch

Clinical

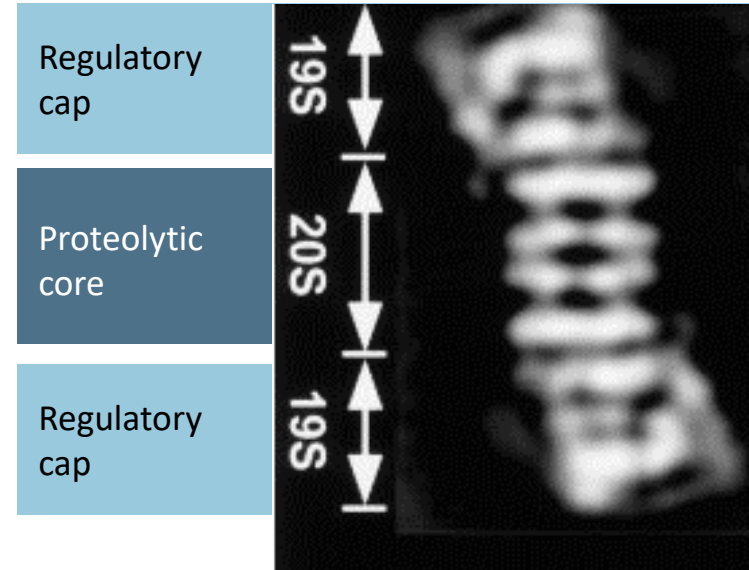
Darrin Bomba



The Proteasome: Primary Means of Intracellular Protein Degradation

- Ubiquitously expressed and highly conserved
- Controls cellular functions via protein degradation
 - Degradation of misfolded/damaged proteins
 - Regulates cellular function (eg, cell cycle) via targeted protein degradation
- Validated target in plasma cell neoplasms
 - Bortezomib (VELCADE®)
 - Carfilzomib (KYPROLIS®)
 - Ixazomib (NINLARO®)
- 2 major forms of the **20S core**
 - Constitutive proteasome
 - Immunoproteasome

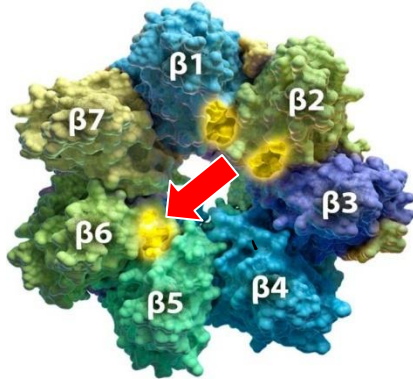
Proteasome Structure



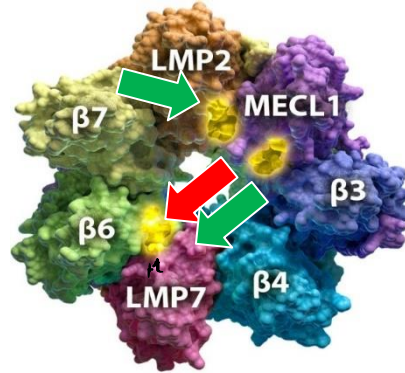
Walz, et al. *J Struct Biol.* 1998;121(1):19-29.

The Immunoproteasome Is a Unique Form of the Proteasome

Constitutive proteasome



Immuno- proteasome





Unique N-terminal threonine protease active sites

Ubiquitous Expression
(eg, heart and liver)

Immune System
(eg, lymphocytes)

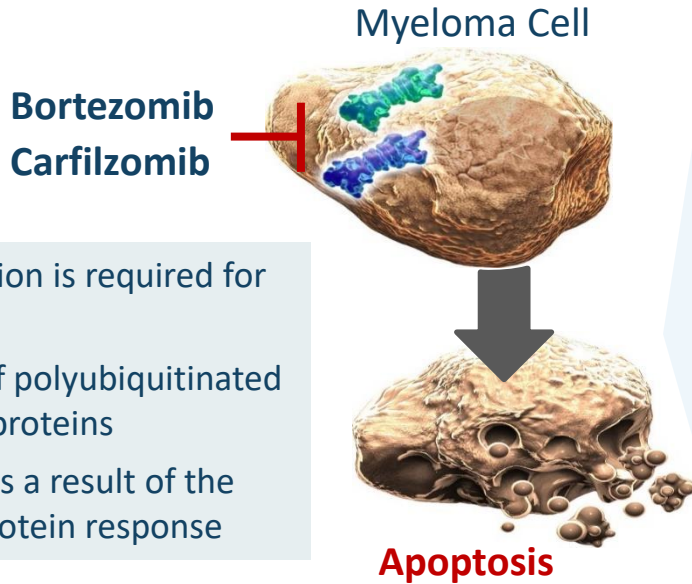
- Immunoproteasome active site subunits induced in nonimmune cells upon exposure to inflammatory cytokines (eg, interferon- γ)
- Expression is increased in multiple autoimmune disorders

-  Chymotrypsin-like: Targets of approved proteasome inhibitors (bortezomib/carfilzomib/ixazomib)
-  Targets of KZR-616



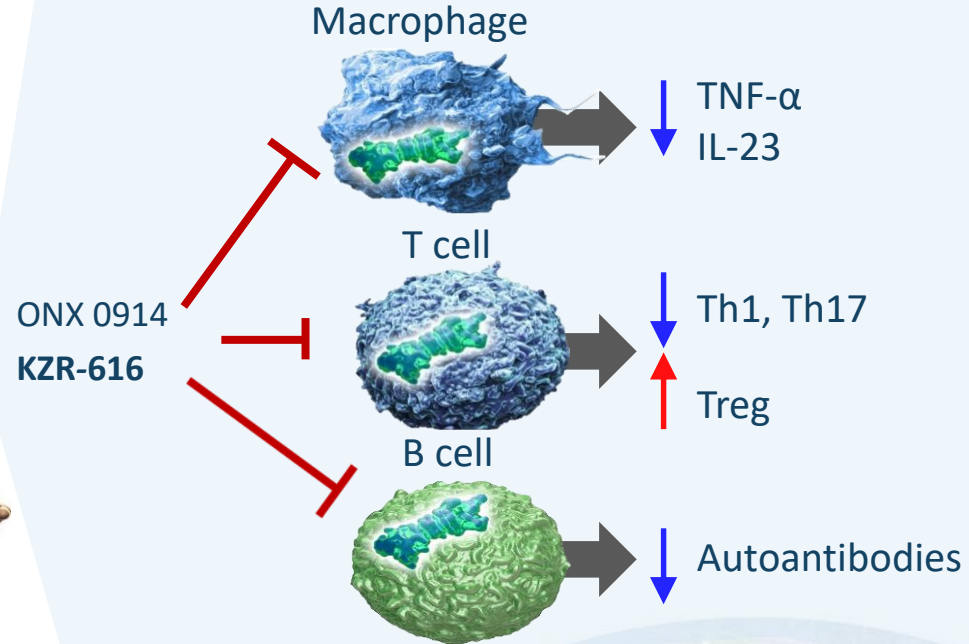
Distinct Cellular Effects of Dual Proteasome Inhibition Versus Selective Immunoproteasome Inhibition

Dual-targeting Proteasome Inhibitors¹



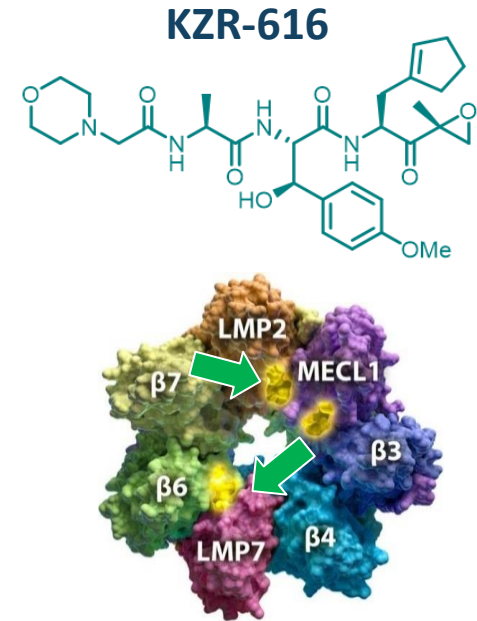
- Dual inhibition is required for cell death
- Induction of polyubiquitinated (unfolded) proteins
- Cell death as a result of the unfolded protein response

Selective Immunoproteasome Inhibitors²⁻⁴



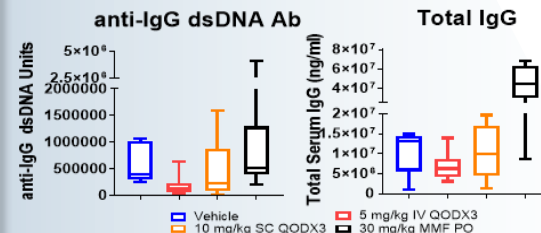
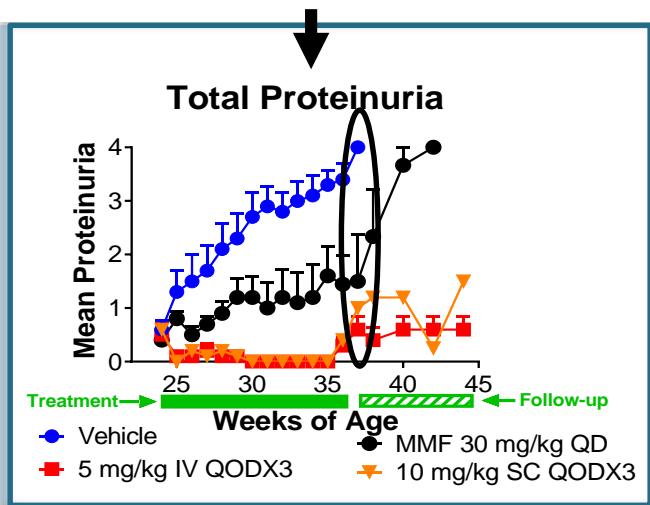
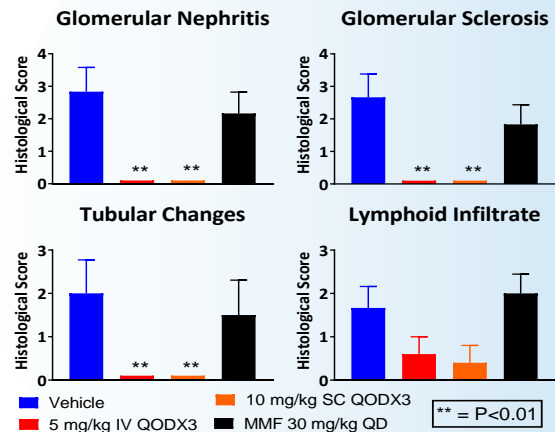
KZR-616: A First-in-class Selective Inhibitor of the Immunoproteasome

- Derived from medicinal chemistry efforts focused on potent and selective inhibition of LMP7 and LMP2¹
- Results from phase 1 healthy volunteer studies (N=100):
 - Consistent pharmacokinetics and pharmacodynamics with repeat subcutaneous (SC) administration
 - Target inhibition achieved at doses ≥ 30 mg/kg
 - Biologic activity established; consistent with preclinical models



KZR-616 Blocks LN Disease Progression in NZB/W F1 Mice

KZR-616 IV or SC →  NZB/W F1; 24 weeks



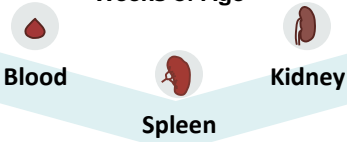
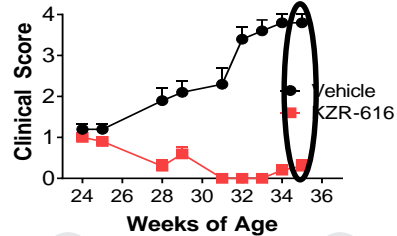
KZR-616 Treatment Results in Inhibition of Immune Response Pathways

NZB/W F1
24 weeks

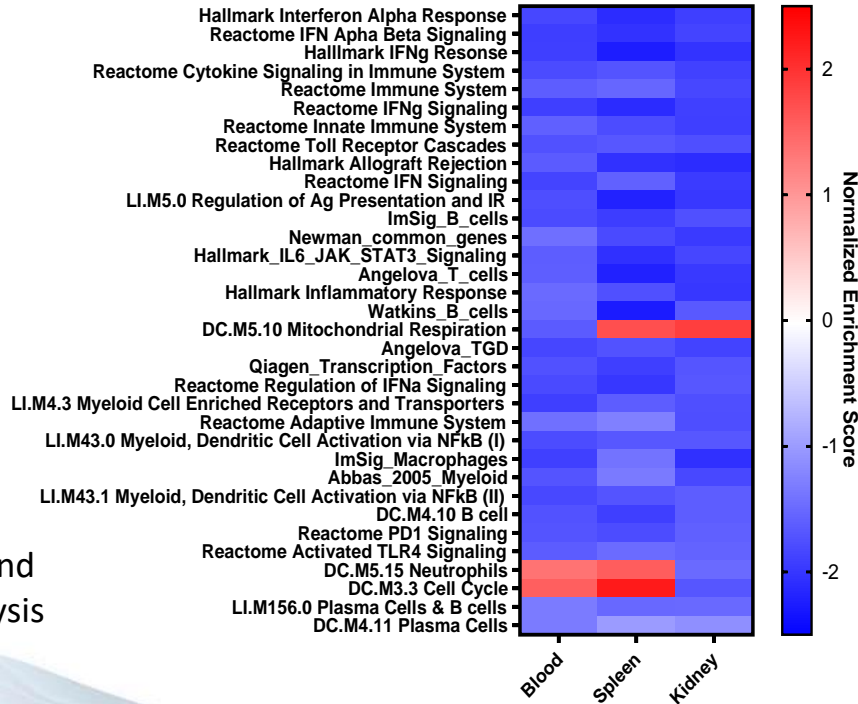
KZR-616
(10 mg/kg SC QODx3)
11 weeks



Proteinuria



Top Regulated Gene Modules



Reduced by FSGEA

- Cytokine signaling
- Innate and adaptive immune response
- IL6, JAK, STAT3 signaling
- Type I interferon
- B cells and plasma cells

Reduced by IPA Analysis

- Th1 pathway
- IL-6 signaling
- NF-κB signaling (indirect)
- CD28 signaling
- PKCθ signaling
- SLE in B cell signaling
- TREM1 signaling
- BCR signaling
- SLE T cell signaling

Previously identified

Newly identified

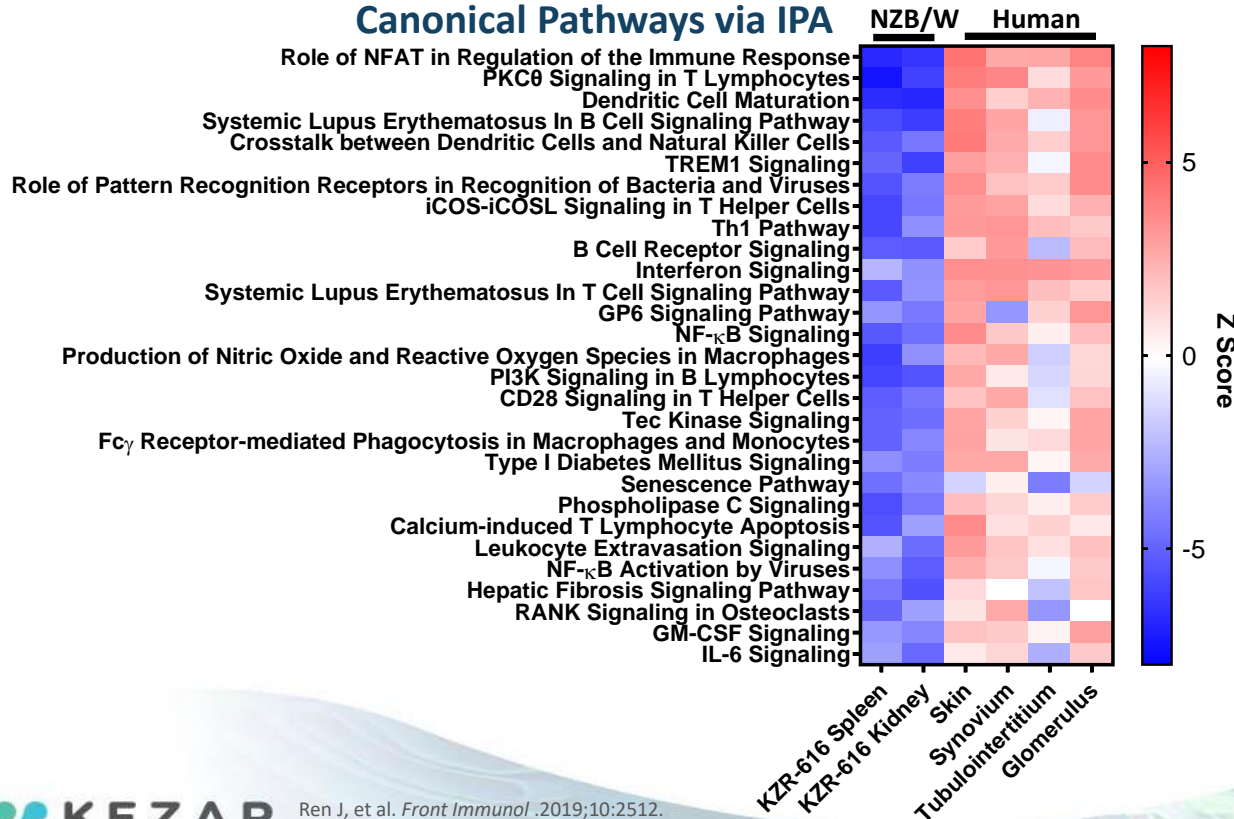
RNA Sequencing FGSEA and Ingenuity® Pathway Analysis

Abbreviations: BCR, B cell receptor; CD, cluster of differentiation; FGSEA, fast gene set enrichment analysis; IL, interleukin; IPA, ingenuity pathway analysis; JAK, janus kinase; NF-κB, nuclear factor kappa B; NZB/W F1, New Zealand black x New Zealand white first filial generation; PKC, protein kinase C; QODX3, every third day; SC, subcutaneous; SLE, Systemic lupus erythematosus; STAT, signal transducer and activator of transcription; Th, T helper; TREM, triggering receptor expressed on myeloid cells.



KZR-616 Treatment Decreases Lupus Gene Signature Pathways in NZB/W Mice That Are Increased in Active Human SLE

Canonical Pathways via IPA



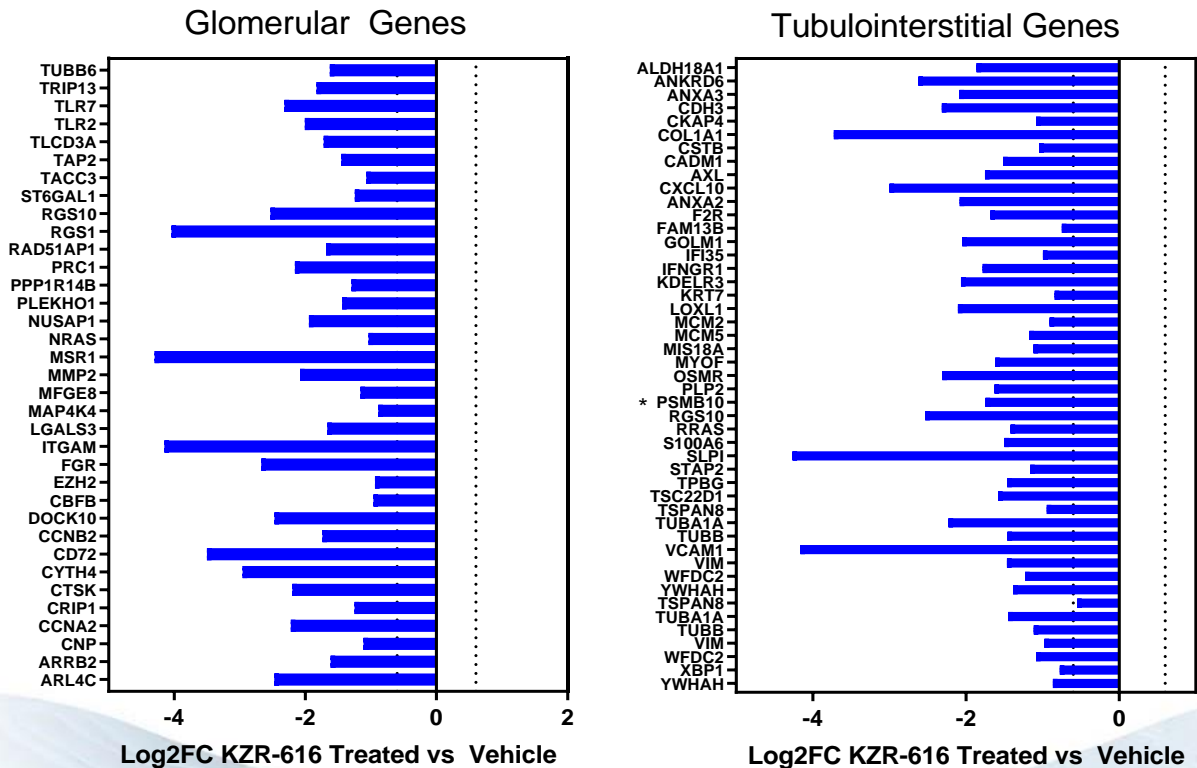
KZR-616–treated NZB/W mice

- Spleen
- Kidney

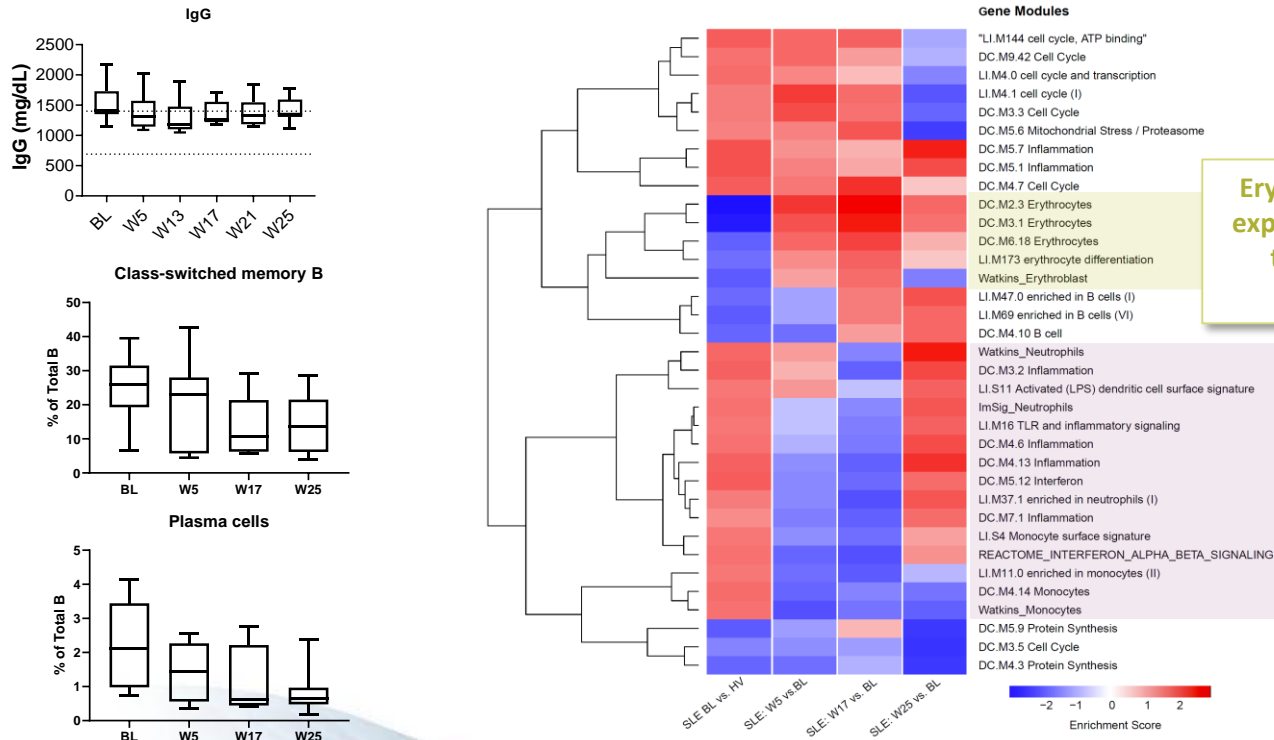
Human tissues from patients with active SLE

- Synovium
- Skin
- Tubulointerstitium
- Glomerulus

KZR-616 Treatment in Mice Inhibits Genes Upregulated in the Glomerulus and Tubulointerstitium of Patients With LN



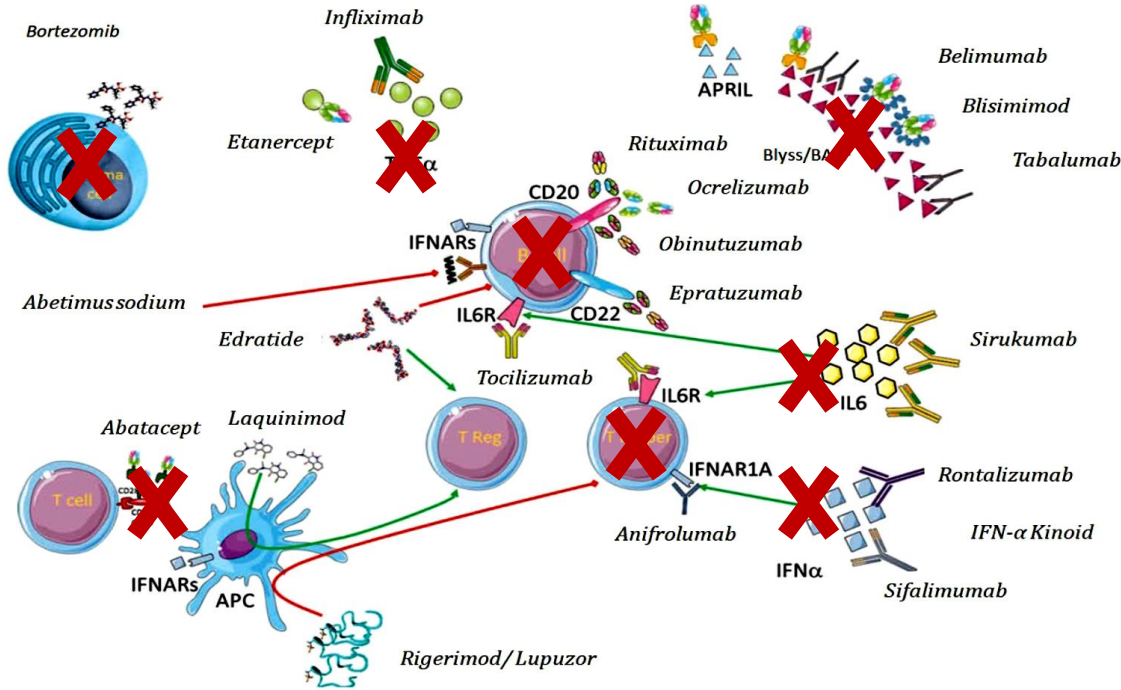
KZR-616 Treatment Decreases IgG Levels and B-Cell Subsets and Affects Multiple Inflammatory Gene Expression Modules in Patients With SLE



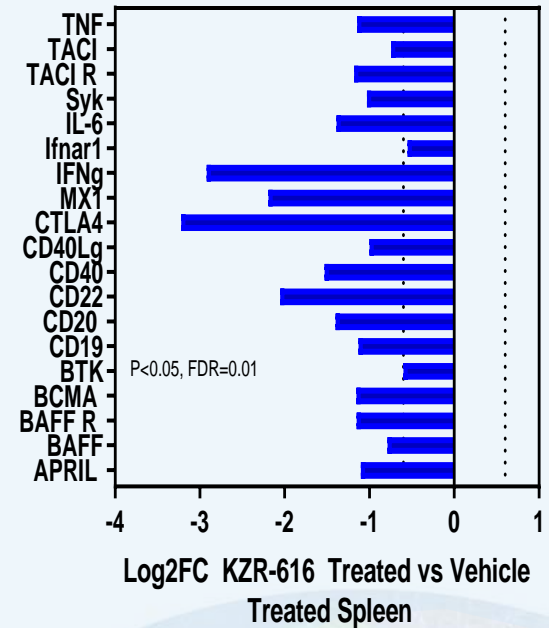
Erythrocyte gene modules have lower expression in patients with SLE relative to HVs and are upregulated after treatment

These immune gene modules have higher expression in patients with SLE relative to HV and are downregulated after KZR-616 treatment

KZR-616 Targets Multiple Points in the Pathogenesis of SLE Targeted by Biological Agents



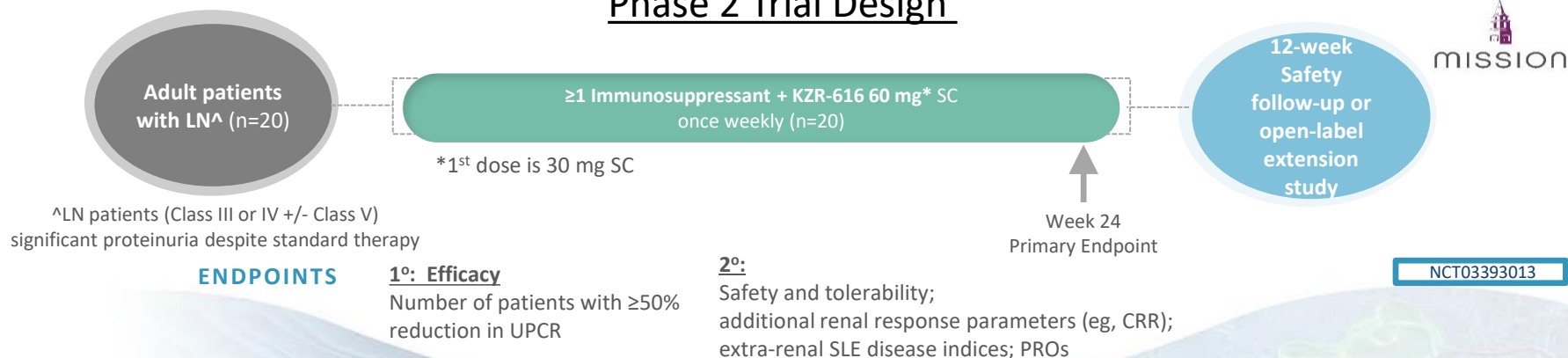
KZR-616 Treatment Decreases Multiple Therapeutic Targets in NZB/W Mice



Summary of KZR-616 Effects in Mouse Models of Lupus

- Highly active in the NZB/W F1 mouse model of SLE/LN
- Effect due in part to depletion of activated B cells and plasma cells
- Gene expression profiling reveals inhibition of multiple gene modules and pathways associated with lupus
- Similar findings demonstrated in SLE patients
- Favorable safety, tolerability, and clinical activity in SLE patients (Abstract #3444277)
- KZR-616 is currently being evaluated in a Phase 2 trial in LN (MISSION)

Phase 2 Trial Design



[^]LN patients (Class III or IV +/- Class V)
significant proteinuria despite standard therapy

ENDPOINTS

1^o: Efficacy

Number of patients with ≥50% reduction in UPCR

2^o:

Safety and tolerability;
additional renal response parameters (eg, CRR);
extra-renal SLE disease indices; PROs

Abbreviations: CRR, complete renal response; LN, lupus nephritis; NZB/W F1, New Zealand black x New Zealand white first filial generation; PRO, patient-reported outcome; SC, subcutaneous; SLE, systemic lupus erythematosus; UPCR, urine protein/creatinine ratio.