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

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Clinical

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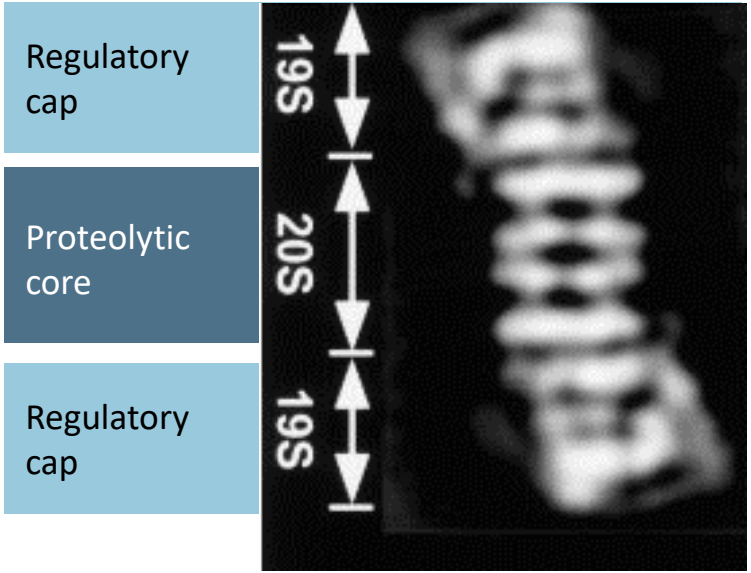
The Proteasome:
Primary Means of Intracellular Protein Degradation

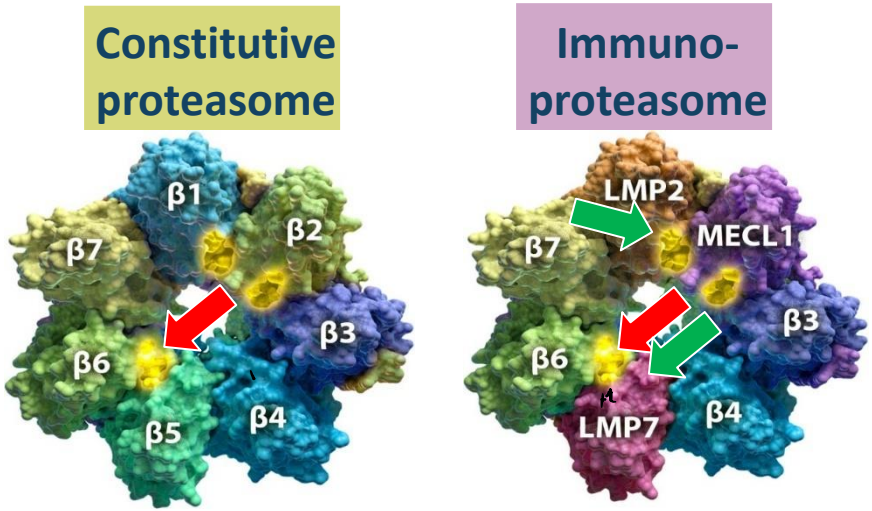
- Ubiquitously expressed and highly conserved
- Controls cellular functions via protein degradation
  - Degradation of misfolded/damaged proteins
  - Regulates cellular function (eg, cell cycle) via targeted protein degradation
- Validated target in plasma cell neoplasms
  - Bortezomib (VELCADE®)
  - 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



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

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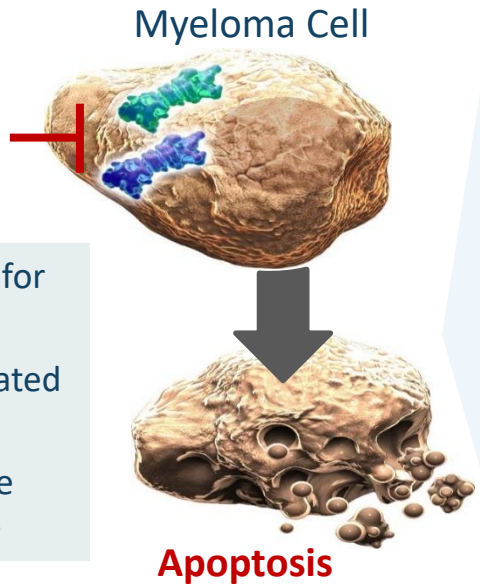
Groettrup M, et al. *Nat Rev Immunol.* 2010;10(1):73-78.

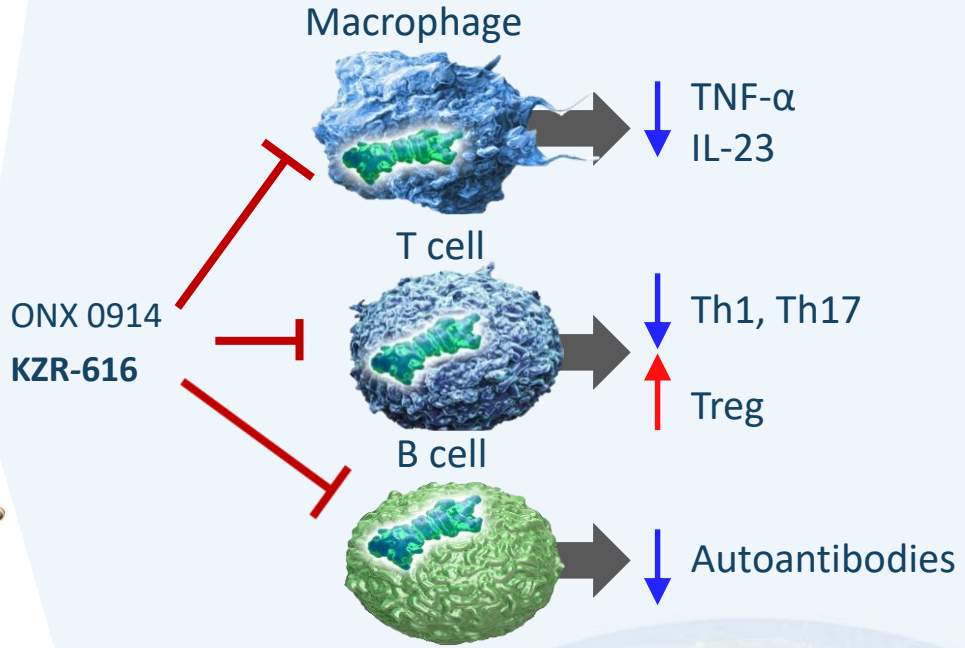
Distinct Cellular Effects of Dual Proteasome Inhibition Versus Selective Immunoproteasome Inhibition

Dual-targeting Proteasome Inhibitors[1]



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

Selective Immunoproteasome Inhibitors[2-4]

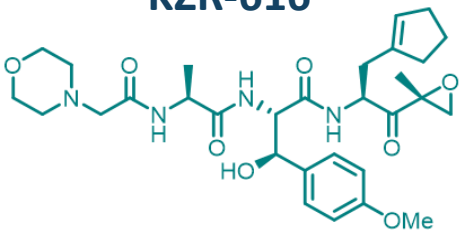


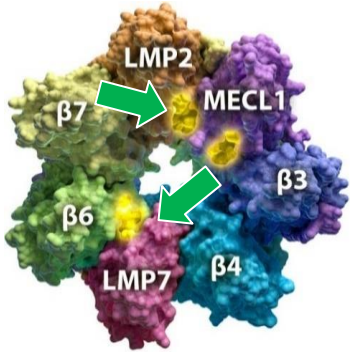
1. Parlati F, et al. *Blood*. 2009;114(16):3439-3447. 2. Muchamuel T, et al. *Nat Med*. 2009;15(7):781-787. 3. Ichikawa HT, et al. *Arth Rheum*. 2012;64(2):493-503.
4. Khalim KW, et al. *J Immunol*. 2012;189(8):4182-4193.
Abbreviations: IL, interleukin; TNF, tumor necrosis factor; Th, T helper; Treg, regulatory T cells.

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 LMP2[1]
- 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

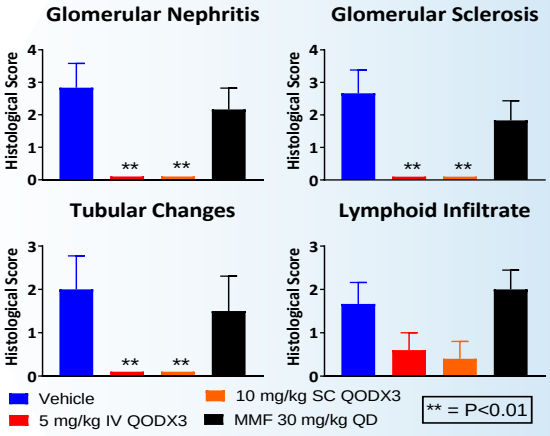


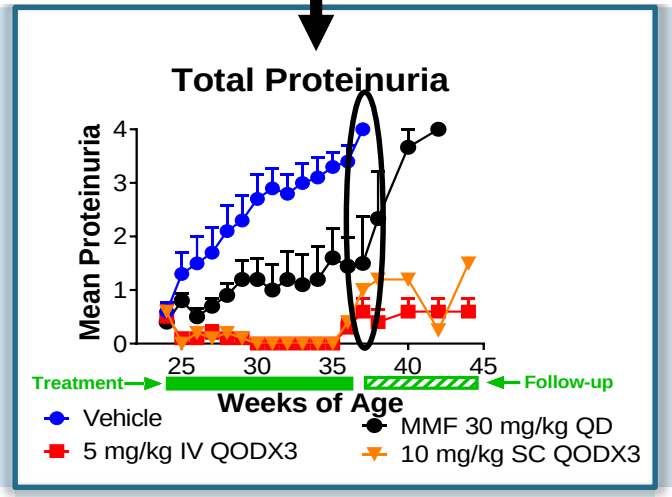


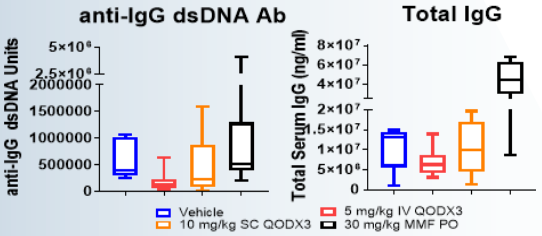
1. Johnson CN, et al. *J Med Chem*. 2018;61(5):1774-1784.
Abbreviation: LMP, low–molecular mass protein.

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

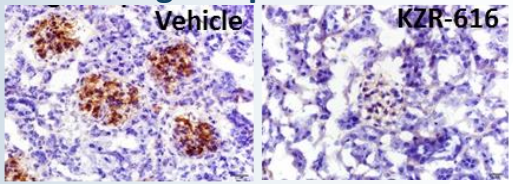
KZR-616 IV or SC →  NZB/W F1; 24 weeks

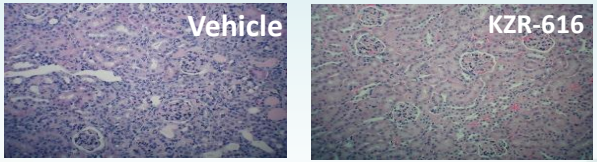






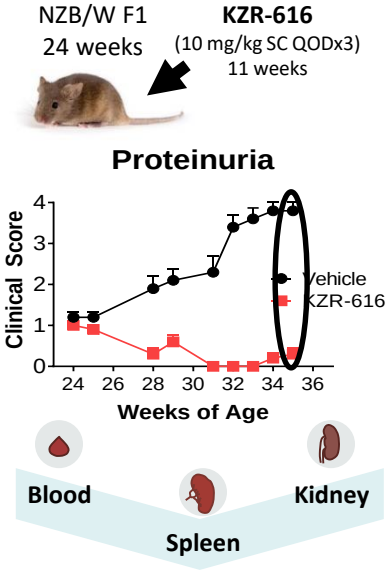
IgG Deposition



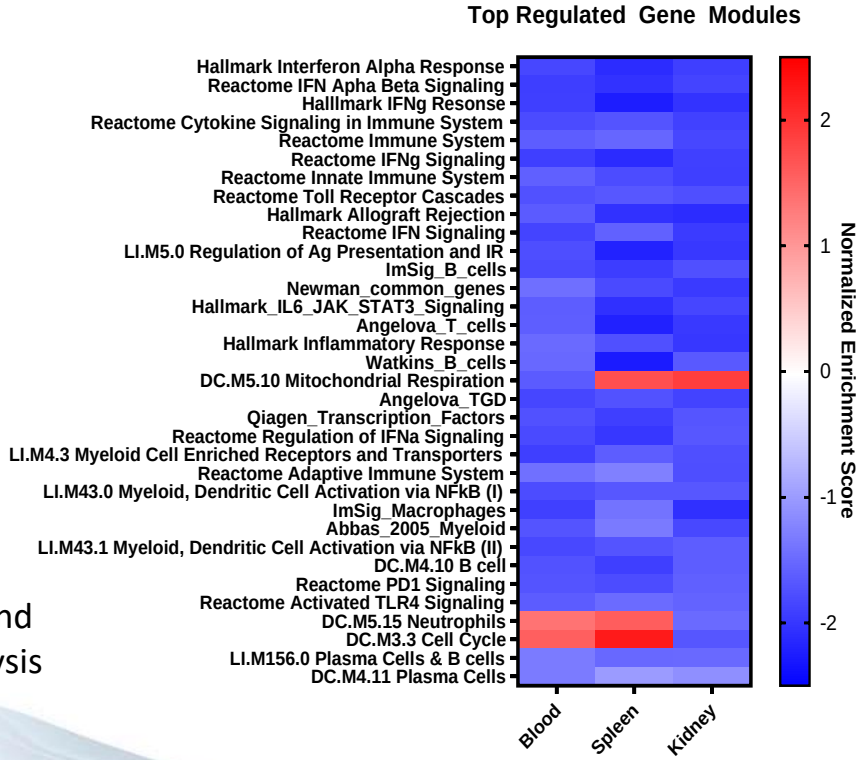


Abbreviations: dsDNA, anti–double stranded DNA antibody; IgG, immunoglobulin G; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; NZB/W F1, New Zealand black x New Zealand white first filial generation; QD, once a day; QOD, every other day; QODX3, every third day; SC, subcutaneous.

KZR-616 Treatment Results in Inhibition of Immune Response Pathways



RNA Sequencing FGSEA and Ingenuity® Pathway Analysis



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**

Previously identified

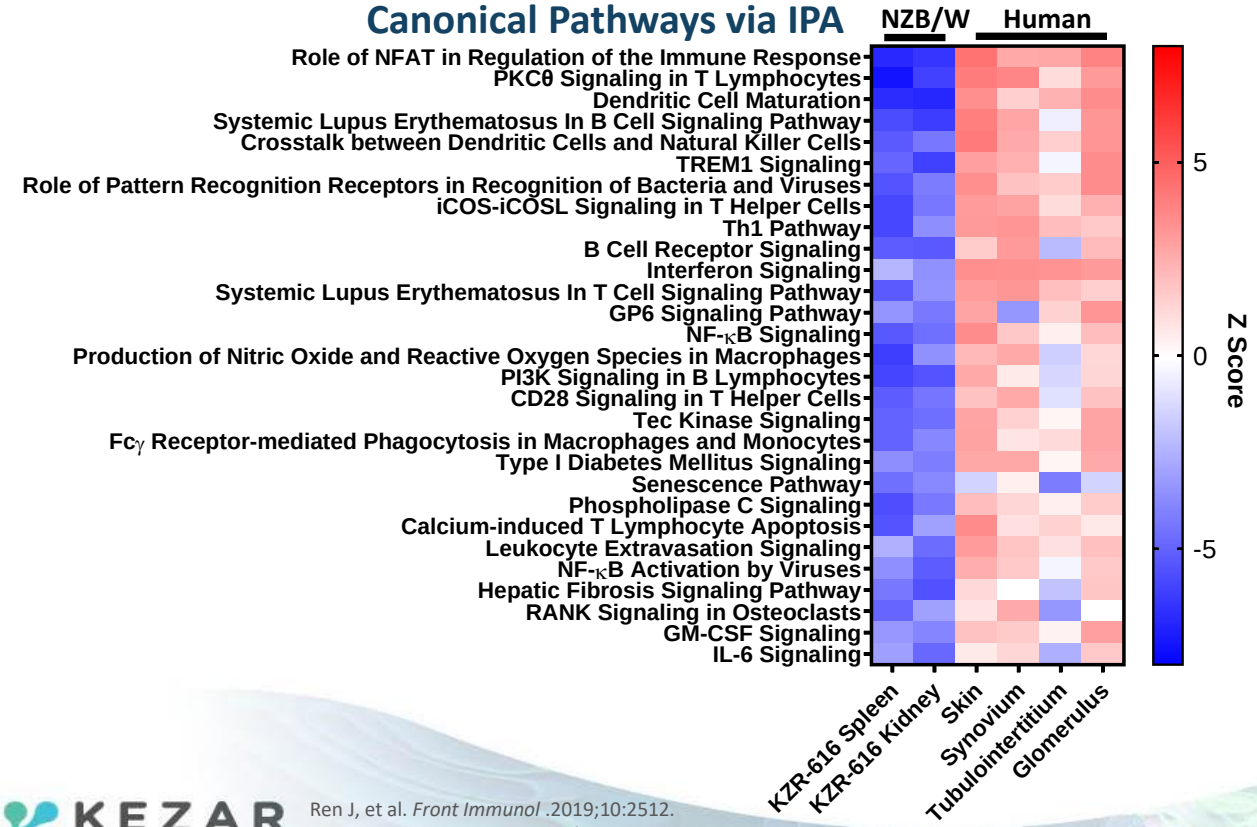
- PKCθ signaling
- SLE in B cell signaling
- TREM1 signaling
- BCR signaling
- SLE T cell signaling

Newly identified

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

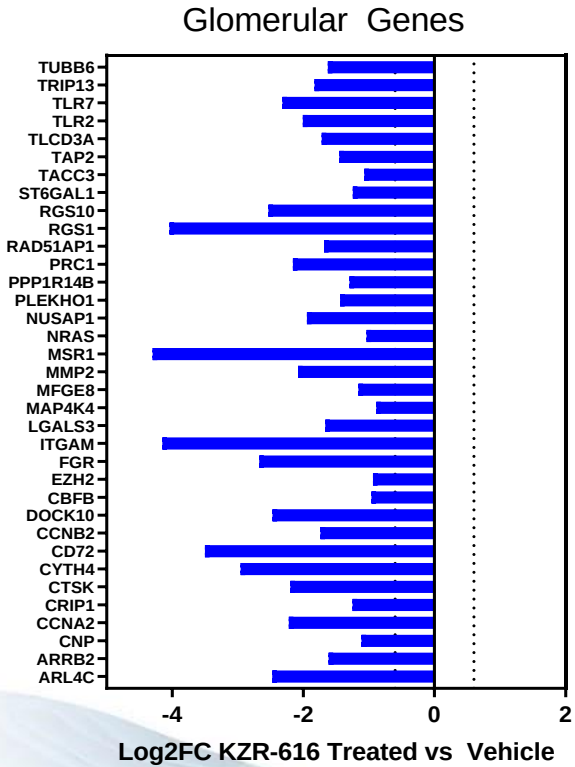
- Spleen
- Kidney

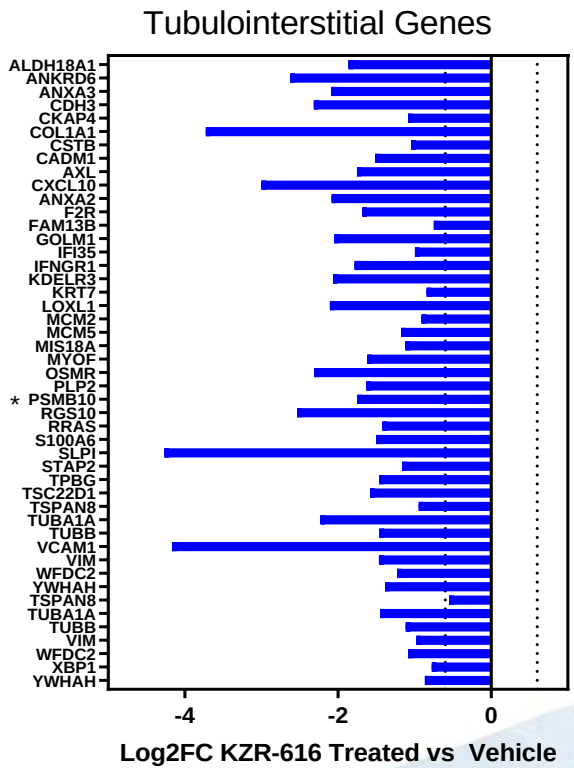
Human tissues from patients with active SLE

- Synovium
- Skin
- Tubulointerstitium
- Glomerulus

Ren J, et al. *Front Immunol* .2019;10:2512.
GEO accession # GSE36700 and GSE72535.
Abbreviations: IPA, Ingenuity Pathway Analysis; NZB/W, New Zealand black x New Zealand white; SLE, systemic lupus erythematosus.

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





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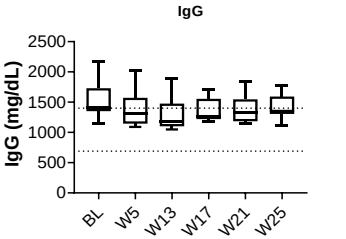
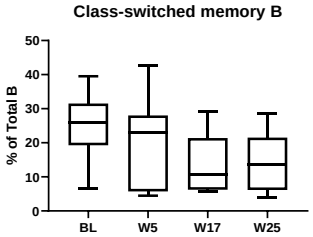
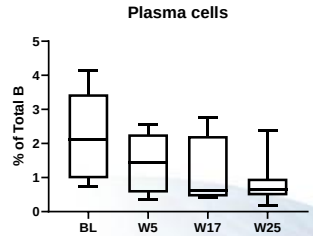
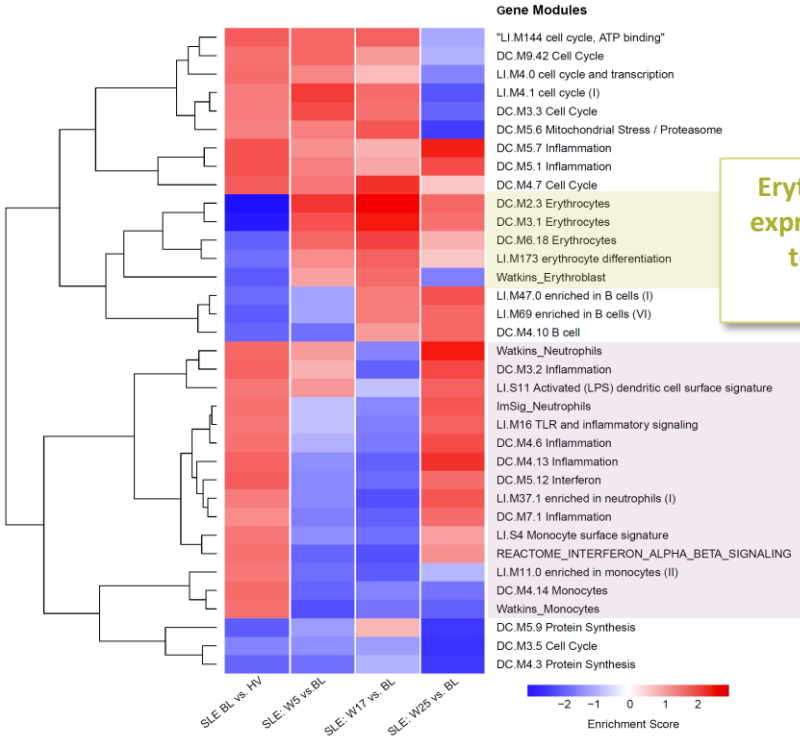
Gene list from Berthier, CC et al. *J Immunol*. 2012;189(2):988-1001.
Abbreviations: LN, lupus nephritis; Log2FC, log2 fold change.

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

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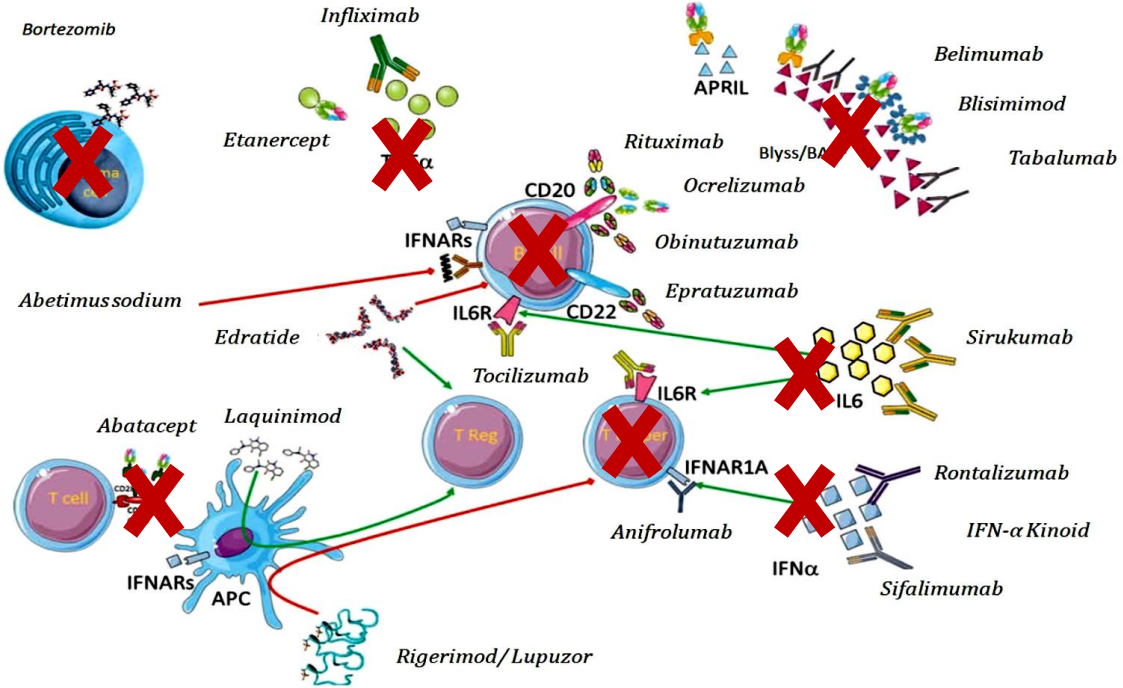
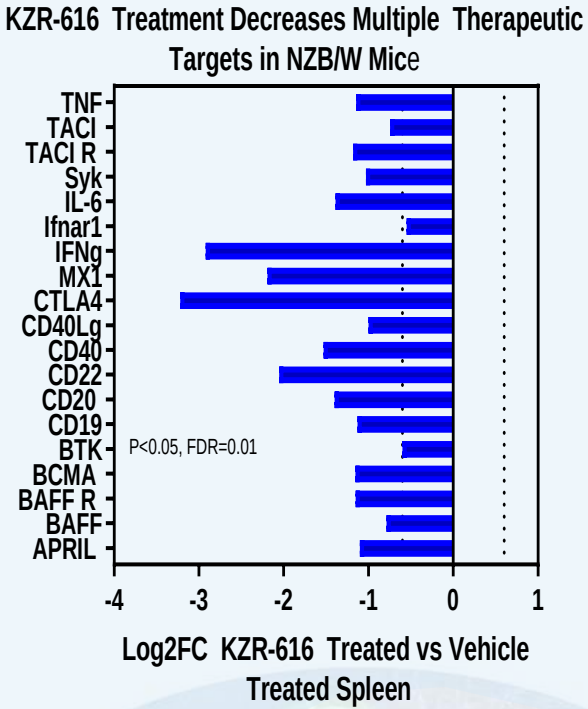
Gene list from Berthier, CC et al. *J Immunol*. 2012;189(2):988-1001.
Abbreviations: BL, baseline; HVs, healthy volunteers; IgG, immunoglobulin G; SLE, systemic lupus erythematosus.

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





Sciascia S, et al. *F1000Res*. 2018;7(F1000 Faculty Rev):970.

Abbreviations: Log2FC, log2 fold change; NZB/W, New Zealand black x New Zealand white; SLE, systemic lupus erythematosus.

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

ENDPOINTS

1°: Efficacy
Number of patients with ≥50% reduction in UPCR

2°:
Safety and tolerability;
additional renal response parameters (eg, CRR);
extra-renal SLE disease indices; PROs

NCT03393013

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.