Treatment of SLE With or Without Nephritis With the Immunoproteasome Inhibitor KZR-616: Initial Results of the MISSION Study

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Samir V. Parikh, MD[1]; Richard Furie, MD[2]; Darrin Bomba[3]; Ken Harvey[3]; Christopher Kirk, PhD[3]; MK Farmer, MD[3]

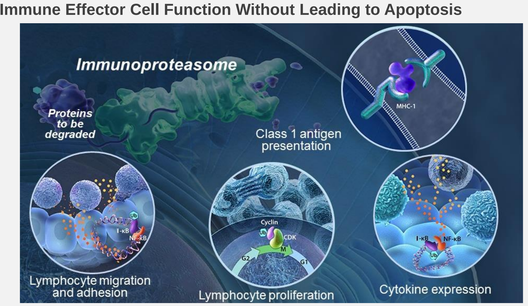
[1]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [2]Northwell Health, Great Neck, NY, USA; [3]Kezar Life Sciences, South San Francisco, CA, USA

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease, and lupus nephritis (LN) is one of its most severe manifestations.[1,2] LN is a primary cause of death and disability in patients with SLE,[3] and development of safer, more targeted therapies for SLE/LN is needed.[1,2] KZR-616 is a selective immunoproteasome inhibitor in development for the treatment of severe autoimmune diseases, including LN.[4] The primary target of KZR-616 is the immunoproteasome (**Figure 1**), found in cells of the immune system.[4] Selective targeting of the immunoproteasome by KZR-616 is expected to normalize the immune response. As the first selective immunoproteasome inhibitor to be studied in clinical trials, KZR-616 has a unique mechanism of action.[4]

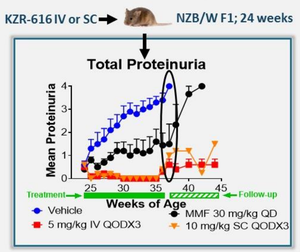
Early preclinical and clinical studies support the use of KZR-616 for LN **(Figure 2;** also see presentation FR-OR38).[5,6] In murine models of SLE/LN, administration of KZR-616 was shown to prevent renal damage through various markers.[5,6] The phase 1b/phase 2 MISSION study (NCT03393013) is designed to assess the safety, tolerability, and efficacy of KZR-616 in patients with SLE with or without nephritis. The phase 1b portion of MISSION is now fully enrolled; interim results through May 4, 2020, are reported here; the phase 2 portion is actively enrolling.

Figure 1. The Immunoproteasome Is Involved in Multiple Aspects of Immune Effector Cell Function Without Leading to Apoptosis



Abbreviations: CDK, cyclin-dependent kinases; G1, growth phase 1; G2, growth phase 2; I-kB, inhibitor of nuclear factor kappa B; M, mitosis; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Ub, ubiquitin.

Figure 2. KZR-616 Blocks LN Disease Progression in NZB/W F1 Mice



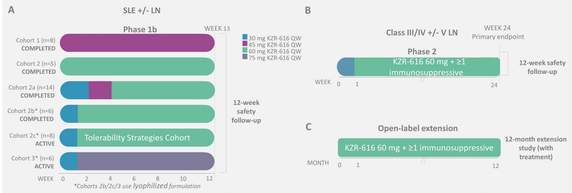
Abbreviations: IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; NZB/W F1, New Zealand black x New Zealand white first filial generation; QD, once a day; QODX3, every third day; SC, subcutaneous.

Methods

- In this 2-part ongoing multicenter study, patients received KZR-616 (**Figure 3**)
  - Part 1: Phase 1b, open-label multiple dose-escalation study of KZR-616 subcutaneous (SC) weekly (QW) in patients with SLE with or without nephritis
  - Part 2: Phase 2, open-label responder analysis of KZR-616 60 mg SC QW in patients with active proliferative LN (not reported here)
- Patients in the phase 1b portion fulfilled the 2012 Systemic Lupus International Collaborating Clinics Classification Criteria and had SLE Disease Activity Index 2000 (SLEDAI-2K) ≥4 at screening; it was recommended that patients receive stable background medications (eg, ≤20 mg/d prednisone equivalent, ≤25 mg/wk methotrexate, ≤20 mg/d leflunomide)

Methods (cont'd)

Figure 3. MISSION Study Design for the Phase 1b (A), Phase 2 (B), and Open-Label Extension (C) Study



Numbers indicate the total currently enrolled for each cohort; results from the May 4, 2020, data cutoff include 6 patients from Cohort 2c and no patients from Cohort 3.
Abbreviations: LN, lupus nephritis; QW, weekly; SLE, systemic lupus erythematosus.

- Patients received KZR-616 45 mg (Cohort 1) or 60 mg (Cohort 2) SC QW for 13 weeks; those in Cohort 2a received doses of 30 mg, 30 mg, 45 mg, 45 mg, and 60 mg; those in Cohorts 2b and 2c received an initial dose of 30 mg followed by the target dose of 60 mg; those in Cohort 3 received an initial dose of 30 mg before stepping up to 75 mg
  - In Cohorts 2c and 3 and for the first 2 doses, patients received prophylactic oral electrolyte solution, nonsedating antihistamines, and antiemetics and/or dose escalation
- Safety and tolerability were assessed through May 4, 2020, in the safety population (patients receiving any study drug)
- Exploratory efficacy measures and biomarkers were evaluated, including at weeks 1 (baseline), 13 (end of treatment), and 25 (end of study)
- Efficacy was assessed in patients who completed the study as of May 4, 2020
  - Individual data from a patient with LN who completed week 25 after May 4, 2020, were also included to provide a more complete analysis of the 2 patients with active proliferative LN at study entry
- Gene expression from phase 1 studies[7]
  - RNA sequencing was performed using Illumina TruSeq® with whole blood collected in PAXgene® RNA tubes
  - Raw data were processed with the robust standard error of the mean R package; differential expression was modeled using DESeq2, and a variety of gene modules[8] examined using fast gene set enrichment analysis

Interim Results

Patient Enrollment and Demographics

- Phase 1b: As of September 24, 2020, the study is fully enrolled
- As of the May 4, 2020, update, 23 patients completed the phase 1b study
- Mean age was 52.0 years; mean SLE disease duration was 96.2 months; 94.9% were women
  - Concomitant medications most commonly used among patients included hydroxychloroquine (HCQ; n=19, 48.7%), prednisone (n=25, 64.1%), paracetamol (n=10, 25.6%), folic acid (n=13, 33.3%), and ondansetron (n=6, 15.4%)
  - Among those taking prednisone, the average dose was 7.8 mg/d

Safety

- Most patients had mild (87.2%) or moderate (30.8%) adverse events (AEs); the most common AEs were injection-site erythema, nausea, and vomiting (**Table 1**)
  - There were no reports of peripheral neuropathy or prolonged hematologic AEs and no clinically significant laboratory abnormalities
  - Four serious AEs were reported: one each of thrombotic microangiopathy, herpes zoster, systemic inflammatory response, and viral infection complicated by chest pain
- No discontinuations have been observed to date in the later cohorts

Disease Activity

- Mean values of all 7 measures of disease activity improved in patients who completed 13 weeks of treatment (**Table 2**)
  - These improvements were maintained or enhanced during the follow-up period, as indicated by numerically lower scores at week 25 than at baseline (**Table 2**)

Biomarkers

- Of 6 patients with elevated anti–double-stranded DNA antibody (anti-dsDNA) levels at baseline, all showed reduced levels at week 13, and levels for 3 patients had reduced by >60%. The effect persisted after discontinuation of investigational drug (**Table 3**)

Interim Results (cont'd)

Table 1. KZR-616 Safety and Tolerability, With No Discontinuations in Later Cohorts (Safety Population)

Measures, No. (%)	Cohort 2a[a] (n=14)	Cohort 2b (n=6)	Cohort 2c (n=6)	All patients[b] (Cohorts 1-2c) (N=39)
Common TEAEs	12 (85.7)	4 (66.7)	5 (83.3)	34 (87.2)
Injection site reactions	9 (64.3)	2 (33.3)	4 (66.7)	25 (64.1)
Nausea	5 (35.7)	1 (16.7)	2 (33.3)	14 (35.9)
Vomiting	4 (28.6)	1 (16.7)	1 (16.7)	12 (30.8)
TEAEs ≥ grade 3	2 (14.3)	1 (16.7)	0 (0.0)	4 (10.3)
Infectious TEAEs ≥ grade 3	1 (7.1)	1 (16.7)	0 (0.0)	2 (5.1)
Infectious TEAEs; all grades	5 (37.5)	2 (33.3)	0 (0.0)	8 (20.5)
Serious TEAEs	2 (14.3)	1 (16.7)	0 (0.0)	4 (10.3)
Any study discontinuation	4 (28.6)	0 (0.0)	0 (0.0)	10 (25.6)
Patients receiving prednisone	10 (71.4)	4 (66.7)	2 (33.3)	26 (66.7)

[a]Patients received 4 doses to reach target dose. [b]All patients are inclusive of patients from Cohort 1. Cohorts 2b and 2c (as well as Cohort 3, data not presented) received a lyophilized formulation of KZR-616, prophylactic oral electrolyte solution, nonsedating antihistamines, and antiemetics and/or dose escalation.
Abbreviation: TEAE, treatment-emergent adverse event.

Table 2. Mean Disease Activity Scores Decreased Over Time With KZR-616 Treatment (Study Completers, n=23)

Scores, Mean (SD)	Baseline	Week 13 (end of treatment)	Week 25 (end of study)
SLEDAI-2K	9.5 (2.8)	6.8 (2.5)	7.0 (2.5)
CLASI-A	5.8 (4.8)	3.4 (3.6)	3.6 (3.9)
Tender joint count	12.0 (7.0)	5.6 (5.2)	5.7 (4.2)
Swollen joint count	8.1 (6.5)	3.0 (4.2)	2.1 (2.7)
Physician Global Assessment	56.0 (23.2)	40.5 (23.0)	38.0 (17.6)
Patient Global Assessment	60.4 (24.7)	40.7 (25.2)	42.5 (20.3)
Patient assessment of pain	61.5 (23.0)	48.1 (26.2)	43.0 (24.2)

Abbreviations: CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 3. Anti-dsDNA Antibody Titers Reduced Over Time for KZR-616 Treatment in Those With Elevated Levels at Baseline

Individual	Mean anti-dsDNA level, IU/mL (baseline)	% Change from baseline, week 13 (end of treatment)	% Change from baseline, week 25 (end of study)
Patient A	1015	−64.0	−82.0
Patient B[a]	87	−20.7	−33.3
Patient C	32	−6.3	−18.8
Patient D[b]	134	−60.4	−54.5
Patient E[a]	90	−76.7	−68.9
Patient F[b]	98	−46.9	−45.9

[a]History of nephritis (inactive at screening). [b]Active proliferative nephritis.
Abbreviation: anti-dsDNA, anti–double-stranded DNA antibody.

Lupus Nephritis (LN)

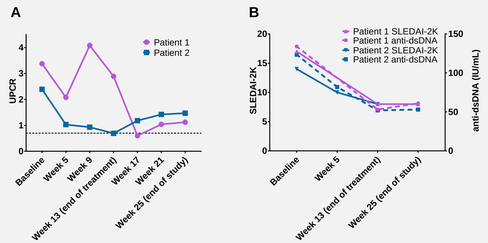
- Two patients in phase 1b had prior renal biopsies with acute proliferative LN resistant to the best available therapy
  - Patient 1 (Cohort 2a, LN class IV/V) had a baseline stable treatment regimen of leflunomide, HCQ, and prednisone (10 mg/d), and prior tacrolimus therapy had failed
  - Patient 2 (Cohort 2c; LN class III) had a baseline stable treatment regimen of mycophenolate mofetil (2 g), HCQ, and prednisone (10 mg/d)
- These 2 patients were the only patients in the phase 1b study with baseline urine protein to creatinine ratio (UPCR) >1; 2 of 2 patients showed a >50% reduction from baseline in proteinuria (**Figure 4A**) and had reductions in SLEDAI-2K and anti-dsDNA levels (**Figure 4B**)
  - After up to 13 weeks of KZR-616 administration, UPCR levels dropped below 0.7 at week 17 in patient 1 and at week 13 in patient 2
- In the 4 patients with a history of nephritis (inactive at enrollment), mean UPCR with KZR-616 treatment was stable at <0.5 throughout the study

Gene Expression

- Several immune-related gene modules with higher enrichment in patients with SLE vs healthy volunteers were downregulated after treatment with KZR-616 (**Figure 5**)
- Erythrocyte gene modules that showed lower enrichment in patients with SLE vs healthy volunteers were upregulated in patients with treatment (**Figure 5**)

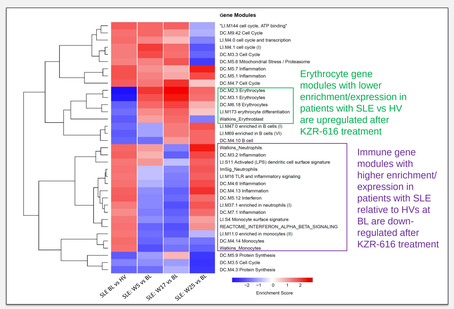
Interim Results (cont'd)

Figure 4. Improvements in UPCR (A), SLEDAI-2K, and Anti-dsDNA (B) Over Time With KZR-616 Treatment in 2 Patients With LN



Dotted line in A indicates a 0.7 UPCR threshold.
Abbreviations: anti-dsDNA, anti–double-stranded DNA antibody; LN, lupus nephritis; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR, urine protein to creatine ratio.

Figure 5. KZR-616 Administration Resulted in Alterations in Abnormal Gene Expression Patterns in SLE Patients



Abbreviations: BL, baseline; HV, healthy volunteer; SLE, systemic lupus erythematosus; W, week.

Conclusions

- KZR-616 is a first-in-class selective immunoproteasome inhibitor with broad therapeutic potential across autoimmune diseases, including LN
- Results from the phase 1b portion of MISSION indicate that KZR-616 60 mg SC QW is well positioned as a long-term treatment option
  - Weekly administration of KZR-616 appears to be safe, and improved tolerability was seen with a dose step-up strategy, use of lyophilized formulation, and use of select premedications
  - KZR-616 is associated with improvements in multiple exploratory efficacy endpoints and reduced expression of key inflammatory genes
- Two of two patients with LN show >50% reduction from baseline in UPCR, as well as improvements in SLEDAI-2K and circulating anti-dsDNA antibody titers, with KZR-616
- The ongoing open-label phase 2 portion of MISSION will further evaluate KZR-616 for the treatment of LN, with a primary study endpoint defined by the number of patients with a ≥50% reduction in UPCR compared with baseline at 6 months

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