MSU Rare Disease Day
February 29, 2020
MK Farmer, MD
Today’s Objectives

• Introduction to Kezar
• Idiopathic Inflammatory Myopathy Overview
• The science behind KZR-616
• Why we think KZR-616 has the potential to treat Polymyositis (PM) and Dermatomyositis (DM)
• Human data from KZR-616 clinical trials to date
• The PRESIDIO trial in PM and DM
Who are we?
DM and PM are chronic autoimmune diseases characterized by inflammation of the muscles and associated tissues.

DERMATOMYOSITIS AND POLYMYOSITIS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>DM and PM</td>
<td>Chronic autoimmune diseases characterized by inflammation of the muscles and associated tissues.</td>
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<tr>
<td>Also referred to</td>
<td>as idiopathic inflammatory myopathies.</td>
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<tr>
<td>Likely triggered by</td>
<td>genetic and environmental factors.</td>
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<tr>
<td>Muscle weakness and</td>
<td>fatigue are common.</td>
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<tr>
<td>DM is characterized</td>
<td>by rash and skin manifestations.</td>
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<tr>
<td>Significant complications</td>
<td>occur leading to organ system problems—lung, GI, heart, joints, Raynaud’s, constitutional.</td>
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<tr>
<td>No approved treatments but</td>
<td>steroids are used.</td>
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CLASSIFICATION CRITERIA

<table>
<thead>
<tr>
<th>Classification Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>Definite PM or DM</td>
<td>4 criteria</td>
</tr>
<tr>
<td>Probable PM or DM</td>
<td>3 criteria</td>
</tr>
<tr>
<td>Possible PM or DM</td>
<td>2 criteria</td>
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- Proximal muscle weakness
- Elevated serum levels of skeletal muscle enzymes
- Myopathic changes on EMG
- Muscle biopsy evidence of inflammation
- Skin rash

https://understandingmyositis.org/myositis/myositis/
Idiopathic Inflammatory Myopathies (IIM) and Examples of Diseases that May Include Myositis

Idiopathic Inflammatory Myopathy (IIM)
• Dermatomyositis (DM)*
• Amyopathic Dermatomyositis (ADM)
• Polymyositis (PM)*
• Sporadic Inclusion Body Myositis (sIBM)
• Immune-Mediated Necrotizing Myopathy (IMNM)*
• Juvenile Dermatomyositis (JDM) and Juvenile Polymyositis (JPM)

* = permitted for inclusion into trial

Examples of Diseases that may include myositis as a feature:
• Antisynthetase Syndrome (ASS)* -- features include interstitial lung disease (ILD), having PM or DM, polyarthritis (inflammation of multiple joints), Raynaud’s, mechanic hands
• Mixed Connective Tissue Disease (MCTD)

https://understandingmyositis.org/myositis/myositis/
Antibodies are associated with certain features of myopathy/myositis

http://www.indianjrheumatol.com/article.asp?issn=0973-3698;year=2018;volume=13;issue=3;spage=186;epage=194;aulast=Malaviya
How do we treat idiopathic inflammatory myopathies?

• Steroids are often the first-line treatment for autoimmune diseases including idiopathic inflammatory myopathies
• Steroids reduce inflammation causing the muscle weakness and also suppress the overactive immune system
• Risks of taking steroids long-term are not insignificant
• Other medications called immunosuppressants often added to steroids to both reduce the steroid dose (“steroid-sparing” properties) and further suppress the overactive immune system
• Examples of immunosuppressants include azathioprine, methotrexate, mycophenolate, leflunomide, tacrolimus
• Both steroids and immunosuppressants work for some, but also have side effects that can be serious, including infections

We need better treatments!
The body is comprised of different organs, each with specific functions.
Organs are composed of cells; cells are composed of different functional units called organelles, each with a specific function.

https://biochemicalminds.wordpress.com/2014/01/31/dont-be-cell-fish-learn-about-cells/
What is a proteasome?

- A proteasome is an organelle and also a protein found in cells of the body.
- They break down damaged and unneeded proteins—"garbage disposal".
- Proteasomes are part of a major mechanism by which cells regulate proteins and also destroy damaged proteins.
- Proteins are tagged for destruction with a small protein called ubiquitin.
- The degradation process yields peptides which are further broken down into amino acids (the building blocks of proteins) which are "recycled" and used for making new proteins.

https://en.wikipedia.org/wiki/Proteasome
The proteasome is an organelle found within all cells.
The immunoproteasome is a unique type of proteasome expressed only in the immune system and where inflammation occurs.

<table>
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<tr>
<th>Constitutive proteasome</th>
<th>Immunoproteasome</th>
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<tr>
<td>Ubiquitous Expression (heart, lung, etc)</td>
<td>Expressed in Immune System (T cells, macrophages, B cells)</td>
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Primary targets of dual proteasome inhibitors bortezomib and carfilzomib

Primary targets of KZR-616

*Active sites inducing protein degradation are highlighted*
Targeting the immunoproteasome represents a unique approach to treat inflammatory disorders

- Proteasome inhibitors (such as bortezomib) are active in animal models of autoimmunity, including lupus and lupus nephritis (Neubert et. al Nat. Med. 2008)
- Bortezomib (a dual proteasome inhibitor approved in myeloma) has been used successfully in the treatment of hard-to-treat autoimmune disorders
- Side effects of bortezomib include problems with different types of blood cells, peripheral neuropathy, and prolonged fatigue, all which prevent long term use
- Selective inhibitors of the immunoproteasome (e.g. KZR-616) can replicate the anti-inflammatory activity of bortezomib without similar side effects in animals
- 20+ peer reviewed scientific articles supporting immunoproteasome inhibitors for the treatment of autoimmune disorders
KZR-616 is Product of Long-term R&D (Research & Development) Effort

Proteasomes discovered

1970s 1980s ...

VELCADe (bortezomib): First FDA approved proteasome inhibitor (multiple myeloma)

1999 2003 2004

First selective immunoproteasome inhibitor discovered

2009

Nobel prize awarded to Ciechanover, Hershko and Rose for proteasome discovery

2015 2016 2019

Kezar Life Sciences formed; KZR-616 nominated for clinical studies

First clinical trial with KZR-616 initiated

PRESIDIO Study Launched
We believe KZR-616 has the potential to treat severe autoimmune diseases

<table>
<thead>
<tr>
<th>Compound</th>
<th>Therapeutic Indication</th>
<th>Development Stage</th>
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<tr>
<td></td>
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<td>Preclinical</td>
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<tr>
<td><strong>KZR-616</strong></td>
<td><strong>Selective Immunoproteasome Inhibition</strong></td>
<td></td>
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<tr>
<td></td>
<td>Autoimmune Hemolytic Anemia (AIHA)/Immune Thrombocytopenia (ITP)</td>
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<tr>
<td></td>
<td>Lupus Nephritis (LN)</td>
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<td></td>
<td>Dermatomyositis (DM)/Polymyositis (PM)</td>
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Immunoproteasome inhibition improved muscle function in a mouse model of polymyositis*

CIM model
- Immunize mice with muscle C protein
- Measure grip strength
- Histologic analysis of biceps muscle

C57Bl/6

13 days

- Mice develop myositis (Sugihara 2007)
- Started treatment with ONX 0914
- ONX 0914 improved muscle function and reduced muscle damage

Day 28 Muscle Histology

Day 21 Enzyme Levels

*data on file

CIM=C protein induced myositis
KZR-616 has been studied in 100 healthy volunteers and in 33 lupus patients

<table>
<thead>
<tr>
<th>KZR 616 in Healthy People</th>
<th>KZR-616 in people with Lupus (SLE) and Lupus Nephritis (LN or kidney disease)</th>
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<tbody>
<tr>
<td>100 healthy volunteers have taken KZR-616</td>
<td>33 patients with lupus or LN have taken KZR-616</td>
</tr>
<tr>
<td>People were able to tolerate many different doses of KZR-616</td>
<td>We looked at 7 different ways to measure disease activity, which included SLEDAI, CLASI, Tender and Swollen Joint Counts, and Patient and Physician reported outcomes</td>
</tr>
<tr>
<td>We haven’t seen the side effects that are normally seen with dual proteasome inhibitors such as bortezomib</td>
<td>The majority of patients that took KZR-616 for at least 1 month had some kind of improvement in their disease activity!</td>
</tr>
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</table>
KZR-616 shows promise for dermatomyositis and polymyositis treatment

- Selective inhibition of the immunoproteasome occurs without the side effects seen with dual proteasome inhibition
- Encouraging data from laboratory research in animal models of autoimmunity including polymyositis
- Improvement in CLASI skin scores in lupus patients in the MISSION study suggests that skin findings in DM might improve with KZR-616
- Our long term goal is to establish KZR-616 as standard of care for the treatment of severe autoimmune disorders, including DM and PM
- KZR-616 is the only immunoproteasome in clinical trials right now for PM/DM
PRESEIDIO Study:
https://www.kezarlifesciences.com/presidiostudy/

PRESEIDIO
A Phase 2 Study of KZR-616 to Evaluate Safety and Efficacy in Patients with Polymyositis or Dermatomyositis
Robust Phase 2 PRESIDIO Study Design Actively Enrolling Polymyositis and Dermatomyositis Patients

- Adult patients with DM or PM (n=24)

**Treatment Period 1**
- KZR-616 45mg* SC once weekly
- Placebo SC once weekly

*1st 2 doses are 30mg

**Treatment Period 2**
- KZR-616 45mg* SC once weekly
- Placebo SC once weekly

*1st 2 doses are 30mg

Randomize 1:1

Week 16 Endpoint

Week 32 Endpoint

8-week safety follow-up
What is unique about the PRESIDIO study?

- **Everyone gets KZR-616!** Most studies have some or most study participants receiving the active drug, but for PRESIDIO, EVERYONE gets the chance to receive it.

- **Study sites can utilize home health services to administer weekly injections for a majority of study visits**
  - Helpful for those who work or are physically limited
  - Nurse will come to you
  - In close contact with study team

- **Doctor visits, assessments, testing, and KZR-616 are free to the patient**

- **Frequent contact with study site**
Who might qualify for the PRESIDIO study?

DM or PM (including immune-mediated necrotizing myopathy [IMNM])
- Antisynthetase syndrome and secondary Sjögrens
- Stable ILD (interstitial lung disease)
- Use of assistive devices (walker, cane, rollator, etc)

Active disease and some muscle weakness are both required
- Active disease by recent MRI/EMG/muscle biopsy
- Active disease by active DM rash
- Elevated CPK/CK
- Muscle weakness determined by standardized muscle testing

No absolute requirement to be taking medications for myositis, but you can take the following during the study:
- Up to 20 mg per day of prednisone
- One steroid, one immunosuppressant (azathioprine, methotrexate, mycophenolate mofetil, tacrolimus) and one antimalarial (for DM) such as hydroxychloroquine
Who might qualify for the PRESIDIO study?

Who is Eligible for this Study?

To be considered eligible for the PRESIDIO study, participants must:

- Be at least 18 years of age
- Have been diagnosed by a physician with polymyositis or dermatomyositis and currently have active disease with muscle weakness
- Have found that treatments like corticosteroids or immunosuppressants do not work well or cannot be taken due to side effects

Participants must meet other study criteria to take part in the PRESIDIO Study.

For more information, please contact clinicaltrials@kezarbio.com or see the full list of eligibility criteria at ClinicalTrials.gov.
What types of myositis patients would NOT qualify for PRESIDIO?

- Sporadic inclusion body myositis (sIBM), juvenile onset myositis
- Cancer-associated myositis, myositis in overlap with another connective tissue disease are not eligible BUT if you have arthritis as part of your myositis, you still might be eligible!
- Normal muscle strength
- Moderate to severe muscle or lung damage

Medications not permitted during the PRESIDIO study (but you can take them before you start on the study):
  - Prednisone > 20 mg per day
  - More than one immunosuppressant
  - Acthar® gel (repository corticotropin)
  - Immunoglobulin treatment (IVIG [Flebogamma®, Gamunex®, Privigen®, Octagam® and Gammagard® and subcutaneous [sIG: Cuvitru®, HyQvia®, Hizentra®, Gamunex-C®, and Gammaked®]])
We currently have 8 sites in the United States that are able to enroll patients—more to come!

- Irvine, CA
- Austin, TX
- Webster, TX (Houston suburb)
- Kansas City, KS
- Panama City Beach, FL
- Ann Arbor, MI (Detroit suburb)
- Duncansville, PA (80 miles east of Pittsburgh)
- Great Neck, NY (Long Island)
Check back for updates!

https://www.kezarlifesciences.com/presidiostudy/

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A Phase 2 Study of KZR-616 to Evaluate Safety and Efficacy in Patients with Polymyositis or Dermatomyositis