Revolutionizing the Treatment of Autoimmune Disorders and Malignancies

John Fowler, Co-Founder and CEO

Jefferies Healthcare Conference
June 7, 2017
Kezar Life Sciences – Executive Summary

Corporate Background
- Founded in 2015 to develop novel small molecules targeting protein degradation and protein secretion
- Lead program licensed from Onyx / Amgen
- Discovery program in Protein Secretion underway, UCSF research collaboration

Lead Program: KZR-616
- First-in-class selective inhibitor of the immunoproteasome - unique immunomodulatory activity
- Builds on 10+ years of research at Proteolix and Onyx, long patent coverage
- Strong safety profile: not immunosuppressive, better tolerated than proteasome inhibitors KYPROLIS and VELCADE
- Entered the clinic in late 2016; achieved desired target inhibition levels in Phase 1a

Near-Term Milestones
- IND filing in Q4 2017
- Phase 1b/2 trial launches in Q1 2018
- Initial efficacy data in patients presenting in 2H 2018
- 1st Protein Secretion clinical candidate expected in 2018
Timeline of the immunoproteasome program

2004
- Proteolix closes Series A; Chris Kirk joins
- Carfilzomib discovered

2005
- Phase 1 begins in Multiple Myeloma

2006
- 1st selective immunoproteasome inhibitor discovered

2007
- Onyx acquires Proteolix for ~$650M

2008
- Led by Chris, Proteolix/Onyx scientists publish 4 papers; demonstrating efficacy of immunoproteasome inhibitors in mouse models of RA, T1D, Lupus, MS and IBD

2009
- Kyprolis approved to treat Multiple Myeloma

2010
- New and improved molecules, including KZR-616, discovered

2011
- Kezar Life Sciences closes $23M Series A

2012
- Amgen acquires Onyx for $10.4 billion

2013
- KZR-616 Phase 1 begins; desired PD and safety profile established in Q2 2017

2014

2015

2016

2017
Immunoproteasome Inhibition is broad acting and well tolerated

**Strong Safety Profile**
- Avoids systemic toxicities common to dual proteasome inhibitors VELCADE and KYPROLIS
- Avoids immunosuppression common with most biologics
- Well tolerated in animals and in healthy volunteers

**Immunomodulatory activity**
- Blocks cytokine production in innate immune cells (TNF-α, IL-23, IL-6)
- Induces disease remission in mouse autoimmunity models
- Likely responsible for excellent activity in SLE & LN patients treated with VELCADE

**Immunoproteasome**
- Proteins to be degraded
- Validated, Well-Understood Target

**Immunomodulatory activity on**
- T-cells (↓ Th1 & Th17, ↑ Treg)
- B-cells (↓ plasma cells & ↓ autoantibodies)
Kezar enjoys a deep pipeline with a robust drug discovery effort

<table>
<thead>
<tr>
<th>Program</th>
<th>Target Indications</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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<tbody>
<tr>
<td><strong>KZR-616</strong>: Preclinical and Phase 1a &amp; 1b</td>
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<td></td>
<td></td>
<td>GMP CMC &amp; GLP Tox</td>
<td>Phase 1a</td>
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<td></td>
<td>Lupus Nephritis</td>
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<td>Dermatomyositis / Polymyositis</td>
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<td>Orphan/Unmet Need Indication TBD</td>
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<td><strong>Protein Secretion: Cotransins</strong></td>
<td>Oncology / Autoimmune</td>
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<tr>
<td><strong>Selective Protein Secretion Inhibitor (SPSI) 1</strong></td>
<td>Immuno-oncology</td>
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<td>SPSI 2</td>
<td>Autoimmune</td>
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<td>SPSIs 3&amp;4</td>
<td>TBD</td>
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<td>SPSIs 5&amp;6</td>
<td>TBD</td>
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The immunoproteasome is a unique type of proteasome expressed only in the immune system and at sites of inflammation.

- Primary targets of approved drugs VELCADE™ & KYPROLIS™
  - Immunoproteasomes are in non-immune cells following cytokine exposure
  - Expression is increased in patients with autoimmune disorders

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Groettrup, Kirk, and Basler *Nat Rev. Immunol.* 2010
Unlike dual-targeting proteasome inhibitors, selective immunoproteasome inhibitors only modulate immune responses and do not induce cell death.

**Dual-Targeting Proteasome Inhibitors**
- **VELCADE™** (bortezomib)
- **KYPROLIS™** (carfilzomib)

**Selective Immunoproteasome Inhibitors**
- **KZR-616**
  - Macrophage: TNF-α, IL-23
  - T-cell: Th1, Th17
  - B-cell: auto-Ab

**Myeloma Cell**
- Toxic protein buildup
- Apoptosis
Inflammatory disorders are currently treated one cytokine or one cell at a time: But the immunoproteasome covers them all.

Macrophage

T-cell

B-cell

KZR-616

Cytokines
- TNF-α
- IL-1β
- IL-6
- IL-23
- IL-17

Auto-Antibodies

Humira, et al.
Kineret
Actemra
Stelara
Stelara
Cosentyx

Orencia

Rituxan
Immunoproteasome inhibition simultaneously decreases inflammatory T-cell activity and increases Treg function.

**Active Autoimmune Disease**

**Immune System in Balance With Immunoproteasome Inhibition**

**Experiment:** Expose differentiated human CD4+ T-cells to an immunoproteasome inhibitor for 1 hour, then wash away drug.

**ONX 0914:**

- **Th1:** 
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- **Th17:** 
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- **Treg:** 
  - 0
  - 100
  - 200
  - 300
  - 400
  - 500

E. Suzuki, manuscript in preparation (AAI 2010)
A single dose of an immunoproteasome inhibitor ameliorates inflammation in a mouse RA model

**ONX 0914**

**Disease model**

**Active site profile**

**Collagen Antibody Induced Arthritis**

Clinical Score

Day of Study

0 3 6 9 12 15

0 2 4 6 8 10 12 14 16

Vehicle ONX 0914

**Subunit Inhibition Profile**

% Activity

LMP7 LMP2 MECL1 Betz

**Paw mRNA**

**Reduced Expression of Inflammatory Cytokines**

Expression

Vehicle ONX 0914

TNF-α IL-6 IL-1β

Muchamuel et al. Nat Med. 2009
Immunoproteasome inhibition is superior to anti-TNF-α therapy in mouse models of RA

Anti-Collagen Ab Model (CAIA)
- T/B-cell independent

Collagen Immunization Model (CIA)
- T/B-cell Dependent

Muchamuel et al. Nat Med. 2009
Both 45 mg and 60 mg doses in our Phase 1a study achieved our desired proteasome subunit inhibition profile.

<table>
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<tr>
<th>Target Subunit Inhibition Profile</th>
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<tr>
<td>Beta5</td>
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<tr>
<td>&lt;80%</td>
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### Figures

- **Beta5**
  - % Activity (vs. Day 1 Predose)
  - Avoid Excessive Inhibition
- **LMP7**
  - Desired Inhibition Levels
- **LMP2**
  - 30 mg
  - 45 mg
  - 60 mg

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**KEZAR LIFE SCIENCES**
Preclinical and Phase 1a data provides further confirmation of a positive long-term safety profile for KZR-616

- Well tolerated in 3 month GLP rat and monkey studies
- Animal models showed no immunosuppression
- VELCADE AND KYPROLIS patients (>100k treated) show no immunosuppression (PML, TB, Lymphoma)
- KZR-616 is safer than KYPROLIS and VELCADE after 1 month of treatment at the same levels of immunoproteasome inhibition
  - Full labs from Phase 1a MAD cohorts confirm no hematologic AEs (thrombocytopenia, neutropenia, anemia) seen with dual inhibitors
  - No kidney or liver function abnormalities noted
  - No prolonged cases of fatigue, myalgia, or GI issues
  - No peripheral neuropathy
- PK and PD are consistent across subjects and with repeat dosing
Kezar will launch a Phase 1b/2 trial and generate data in patients at multiple points in 2018 and 2019.

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<thead>
<tr>
<th>2018</th>
<th>2019</th>
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<td>Q1</td>
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<td>Q2</td>
<td>Q2</td>
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<td>Q3</td>
<td>Q3</td>
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<td>Q4</td>
<td>Q4</td>
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**Phase 1b dose escalation (n=6 / cohort)**
*Refractory Polyarthritis*
3 months treatment (weekly SC)

- Includes SLE, LN, RA, PsA, Sjögren’s, Myositis
- Minimum of 4 swollen/tender joints to be enrolled
- Safety & secondary endpoints for disease response

**Phase 1b expansion (n=10 / cohort)**
*Individual Indications*
1-3 cohorts

**Phase 2 Lupus Nephritis, (n=48)**
*MMF & Prednisone +/- KZR-616*
Two dose levels tested, plus placebo (1:1:1)
3 months treatment with follow-up
Readout expected 1H 2020
VELCADE is active in patients with severe SLE and lupus nephritis, highlighting the potential for immunoproteasome inhibition in these indications

- Treatment capped at < 3 months to avoid peripheral neuropathy (off-target effect of VELCADE)
- Further VELCADE development limited by neuropathy and systemic toxicities
- Activity in other diseases (e.g. Sjogrens, ITP) demonstrate broad potential of immunoproteasome inhibition

**SLEDAI Response in SLE Patients**

- Median SLEDAI
  - Baseline: 14
  - Post-treatment: 4
  - Durable reduction in SLEDAI improvements

**Renal Response in LN Patients**

- Median proteinuria
  - Baseline: 2.2 g/day
  - Post treatment: 0.87 g/day
  - Continued reduction in proteinuria seen post treatment

Selective immunoproteasome inhibition resulted in equivalent efficacy as dual inhibitors - but at much better tolerated doses

Selective immunoproteasome inhibition induced similar improvements in autoantibody reduction, blockade of IFN-α production, and reduced plasma cell formation as dual inhibitors

Immune proteasome inhibition is as effective as VELCADE in mouse models of lupus nephritis and SLE

Ichikawa et al. Arthritis and Rheumatism 2011
Despite historical challenges in lupus nephritis, KZR-616 is well positioned for potential success there and in other unmet needs

- LN enjoys a quantitative measurement of therapeutic benefit
  - Ongoing and planned Phase 3 trials are using renal response (total and/or complete response) as primary endpoints
- VELCADE induces a rapid improvement in renal function in LN patients
  - Improvements in proteinuria seen within 3 months
- Current LN competition focused on B-cell targeted therapies and immunosuppressive small molecules
  - Likely challenges will include response rate (biologics) and / or risk/benefit profile (immunosuppressive agents)
- Diseases involving dysfunction of multiple immune system components or cytokines are well suited to the broad activity of immunoproteasome inhibition
  - Biologic therapies targeting an individual cell type or cytokine (e.g. ENBREL or RITUXAN) do not induce a sufficient depth of response to provide clinical benefit
25-50 million people in the US suffer from more than 100 diagnosed autoimmune disorders. KZR-616 has potential efficacy across much of this spectrum, which could lend itself to strategic partnerships.

### Partial list of autoimmune disorders (beyond those currently targeted for development)

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<tr>
<th>Large Market</th>
<th>Orphan/Small Market</th>
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<tr>
<td>Systemic Lupus Erythematosus (SLE)</td>
<td>Amyloidosis</td>
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<tr>
<td>Sjögren’s Syndrome</td>
<td>Thrombocytopenic Purpura</td>
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<td>Psoriatic Arthritis</td>
<td>Inclusion body myositis</td>
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<td>Rheumatoid Arthritis</td>
<td>Uveitis</td>
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<tr>
<td>Psoriasis</td>
<td>Takayasu’s Arteritis</td>
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<td>Crohn’s Disease</td>
<td>Buerger’s Disease</td>
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<tr>
<td>Ankylosing Spondylitis</td>
<td>Cutaneous Vasculitis</td>
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<td>Type 1 Diabetes</td>
<td>Kawasaki Disease</td>
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<tr>
<td>Multiple Sclerosis</td>
<td>Polyarteritis Nodosa</td>
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<tr>
<td>Polymyalgia Rheumatica</td>
<td>Behcet’s syndrome</td>
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<tr>
<td>Graves’ Disease</td>
<td>Churg-Strauss Syndrome</td>
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### Selected pharma with strategic focus in inflammation / immunology

- Bristol-Myers Squibb
- Pfizer
- Abbvie
- Celgene
- Sanofi
- AstraZeneca
- GSK
- Genentech
Kezar’s Series A financing was supported by a strong group of investors

- $23M raised in June 2015, Series B closing mid-2017
- Institutional Investors:
  - MORNINGSIDE
  - OMEGA FUNDS
  - AJU I.B INVESTMENT
  - Cormorant Asset Mgmt.
  - EcoR1 CAPITAL
  - 9W

- Individual Investors (partial list):
  - Franklin Berger, Founder, FMB Research
  - Matt Fust, former CFO, Onyx Pharmaceuticals and Jazz Pharmaceuticals
  - Susan Molineaux, CEO, Calithera Biosciences
  - Ted Love, MD, CEO, Global Blood Therapeutics
  - Paul Klingenstein, Founder, Aberdare Capital Management
Kezar benefits from a strong board and advisory group

Board of Directors

- Jean-Pierre Sommadossi, PhD, Chairman; Pharmasset, Idenix, Atea
- Gerald Chan, ScD; Morningside Group
- Franklin Berger, MBA; FMB Research, JP Morgan
- Michael Kauffman, MD, PhD; Karyopharm, Onyx, Proteolix, Millennium
- John Fowler, MBA; Kezar Life Sciences
- Chris Kirk, PhD; Kezar Life Sciences

Clinical and Scientific Advisors

- Stanford Peng, MD, PhD; Stemcentrx, Roche, Alpine Biosciences
- Maria Dall’Era, MD; UCSF
- Marcus Groettrup, PhD; Univ. of Konstanz
- Kenneth Kalunian, UCSD
- John Looney, MD; Univ. of Rochester
- Reinhard Voll, MD, PhD; Univ. of Freiburg
- David Wofsy, MD; UCSF
- Jack Taunton, PhD; Kezar Co-Founder, UCSF, HHMI
Kezar Life Sciences – Executive Summary

• Kezar Life Sciences is a clinical stage biotechnology company developing highly novel therapeutics targeting protein degradation and protein secretion to address unmet need in autoimmunity and oncology.

• **Lead Product Candidate - KZR-616**
  • First-in-class selective inhibitor of the immunoproteasome - a unique form of proteasome expressed only in the immune system and at sites of inflammation
  • Supported by 10+ years of preclinical work performed at Proteolix and Onyx
  • Entered the clinic in late 2016; achieved desired target inhibition levels
  • Strong safety profile: avoids immunosuppression, suitable for chronic administration
  • Broad immunomodulatory profile is unique and powerful
  • Patent protection to 2034+

• **Near-Term Milestones**
  • IND in Q4 2017
  • Phase 1b/2 trial begins in Q1 2018
  • Initial efficacy data in patients presenting in 2H 2018
  • 1st Protein Secretion clinical candidate expected in 2018