Interim Analysis of KD025-213: A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) after at Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Corey Cutler, MD, MPH¹, Stephanie Lee, MD, MPH², Sally Arai, MD³, Marcello Rotta, MD⁴, Behyar Zoghi, MD⁵, Aravind Ramakrishnan, MD⁶, Aleksandr Lazaryan, MD, MPH, PhD⁷, David A Eiznhamer, PhD⁸, Olivier Schueller, PhD⁸, Zhongming Yang, PhD⁸, Laurie S. Green, MEd⁸, Sanjay K. Aggarwal, MD⁸, The ROCKstar Study Group⁹, Bruce R. Blazar, MD¹⁰, Steven Z. Pavletic, MD¹¹ and Madan Jagasia, MD¹²

¹ Department of Hematologic Malignancies, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, ² Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, ³ Stanford University, Stanford, CA, ⁴ James Cancer Center, Ohio State University, Columbus, OH, ⁵ Texas Transplant Institute, Methodist Hospital, San Antonio, TX, ⁶ Blood and Marrow Transplant, Texas Transplant Institute at St. David's South Austin Medical Center, Austin, TX, ⁷ Blood and Marrow Transplantation and Cellular Immunotherapy, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, ⁸ Kadmon Corporation, LLC, New York, NY, ⁹ The ROCKstar Study Group, New York, NY, ¹⁰ Division of Pediatric Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN, ¹¹ Experimental Transplantation and Immunology Branch, Center for Cancer Research (CCR), National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, ¹² Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN

2020 TCT | Transplantation and Cellular Therapy Meetings
cGVHD is Driven by Immune Cells and Pro-inflammatory Cytokines

- cGVHD involves both T cells and B cells
  - Overproduction of pro-inflammatory IL-21 and IL-17 cytokines
  - Over-activation of T follicular helper (Tfh) cells and B cells, leading to over-production of antibodies
  - Deficiency of regulatory T (Treg) cells, leading to a lack of appropriate regulation of immune response

Blood. 2017 Jan 5;129(1):13-21
ROCK2 Plays Key Role in Immune Diseases

ROCK2 Inhibition Rebalances Immune Response to Treat Immune Dysfunction\textsuperscript{1,2}

- Rho-associated coiled-coil kinase (ROCK) is a serine/threonine kinase
  - Two isoforms: ROCK1 and ROCK2\textsuperscript{1}

- ROCK2 inhibition rebalances the immune system
  - Downregulates pro-inflammatory Th17 cells
  - Increases regulatory T cells

\textsuperscript{1}Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):16814-9; \textsuperscript{2}Blood. 2016 Apr 28;127(17):2144-54
ROCK is an Intracellular Integrator of Pro-Fibrotic Signals

ROCK Regulates Multiple Profibrotic Processes, Including Myofibroblast Activation

- ROCK is downstream of major pro-fibrotic mediators
- ROCK mediates stress fiber formation
- ROCK regulates transcription of pro-fibrotic genes

Rationale for KD025 in cGVHD

- **KD025 is an orally available, selective inhibitor of ROCK2**
  - Over 550 individuals have received KD025 in ongoing and completed studies

- **Targets both immune and fibrotic pathophysiology of cGVHD**

- **Preclinical data in sclerodermatous mouse model** \(^1\)

- **Study KD025-208** \(^2\)
  - Phase 2a study of KD025 showed an Overall Response Rate (ORR) of 65% with KD025 in cGVHD patients after 1-3 prior lines of systemic therapy (see Poster #275, TCT 2020)

  - Data from this study led to:
    - FDA Breakthrough Therapy Designation for KD025 for the treatment of adult patients with cGVHD after failure of two or more lines of systemic therapy
    - KD025-213 (The ROCKstar Study) \(^3\)

\(^1\)Blood. 2016 Apr 28;127(17):2144-54; \(^2\)NCT02841995; \(^3\)NCT03640481
KD025-213: Study Design and Endpoints

Arm B: KD025 200mg BID (n=63)
- Ages ≥12
- 2-5 prior lines of systemic therapy for cGVHD
- Systemic therapy for cGVHD is indicated

Stratification Factors
- Prior ibrutinib (Y/N)
- Severe cGVHD (Y/N)

Open label

Arm A: KD025 200mg QD (n=63)

Primary Endpoint
ORR, per 2014 NIH criteria

Secondary endpoints
- Safety
- DOR
- Lee Symptom Scale
- Steroid doses
- FFS
- OS

Treat to clinically significant progression or unacceptable toxicity
# KD025-213: Statistical Analysis Plan

**Primary Endpoint: ORR**

Statistical significance is achieved if the lower bound of the 95% CI of ORR exceeds 30%.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interim Analysis</strong></td>
<td>2 months after completion of enrollment 1-sided alpha = 0.0025</td>
</tr>
<tr>
<td></td>
<td>Data cutoff date: 17 October, 2019</td>
</tr>
<tr>
<td></td>
<td>Data presented at TCT, 23 February, 2020</td>
</tr>
<tr>
<td><strong>Primary Analysis</strong></td>
<td>6 months after completion of enrollment</td>
</tr>
<tr>
<td></td>
<td>Expected 2Q 2020</td>
</tr>
<tr>
<td><strong>Follow-up Analysis</strong></td>
<td>12 months after completion of enrollment</td>
</tr>
<tr>
<td></td>
<td>Expected 4Q 2020</td>
</tr>
</tbody>
</table>
KD025-213: Fully Enrolled in Less Than 10 Months

- Enrolled at 28 U.S. sites
- First Patient In: Oct 2018; Last Patient In: Aug 2019
# KD025-213: Advanced Patient Population

## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>KD025 QD (n=66)</th>
<th>KD025 BID (n=66)</th>
<th>Overall (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [years (range)]</td>
<td>53 (21-77)</td>
<td>57 (21-77)</td>
<td>56 (21-77)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64</td>
<td>50</td>
<td>57</td>
</tr>
<tr>
<td>Median prior lines of therapy</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Median time from cGVHD diagnosis to enrollment (months)</td>
<td>25</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>* NIH Severe cGVHD [n (%)]</td>
<td>45 (68%)</td>
<td>42 (64%)</td>
<td>87 (66%)</td>
</tr>
<tr>
<td>Median prednisone dose (mg/kg/day)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>≥4 Organs involved [n (%)]</td>
<td>34 (52%)</td>
<td>35 (53%)</td>
<td>69 (52%)</td>
</tr>
<tr>
<td>* Prior ibrutinib treatment</td>
<td>22 (33%)</td>
<td>23 (35%)</td>
<td>45 (34%)</td>
</tr>
<tr>
<td>Refractory to line prior to enrollment, excluding unknown / missing</td>
<td>81% (42/52)</td>
<td>65% (32/49)</td>
<td>73% (74/101)</td>
</tr>
</tbody>
</table>

* Stratification factor
KD025-213: Patient Disposition

Median Duration of Follow-Up: 5 months

**KD025 QD**

- All treated patients (n=66)
- Median treatment duration: 4.5 mos
- 22 Came off Study
  - 6 Voluntary withdrawal
  - 4 Investigator decision
  - 4 Relapse underlying disease
  - 3 Adverse event
  - 2 cGVHD progression
  - 2 Death
  - 1 Other
- 44 patients ongoing

**KD025 BID**

- All treated patients (n=66)
- Median treatment duration: 4.2 mos
- 23 Came off Study
  - 10 cGVHD progression
  - 4 Adverse event
  - 4 Voluntary withdrawal
  - 3 Investigator decision
  - 1 Death
  - 1 Other
- 43 patients ongoing
KD025-213: Safety and Tolerability

- AEs were overall consistent with those expected in cGVHD patients receiving corticosteroids and other immunosuppressants
- No apparent increased risk of infection
  - No CMV reactivation

<table>
<thead>
<tr>
<th>Safety Overview, n (%)</th>
<th>KD025 QD (n=66)</th>
<th>KD025 BID (n=66)</th>
<th>Overall (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment (months)</td>
<td>4.5</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Any Adverse Event (AE)</td>
<td>64 (97)</td>
<td>61 (92)</td>
<td>125 (95)</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>23 (35)</td>
<td>27 (41)</td>
<td>50 (38)</td>
</tr>
<tr>
<td>SAE</td>
<td>22 (33)</td>
<td>15 (23)</td>
<td>37 (28)</td>
</tr>
<tr>
<td>Drug related AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any related AE</td>
<td>38 (58)</td>
<td>28 (42)</td>
<td>66 (50)</td>
</tr>
<tr>
<td>Related SAE</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>On study deaths(^1)</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

---

**Commonly Reported AEs, n (%)**

<table>
<thead>
<tr>
<th>All Grade, in ≥10%</th>
<th>KD025 QD (n=66)</th>
<th>KD025 BID (n=66)</th>
<th>Overall (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>20 (30)</td>
<td>12 (18)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (24)</td>
<td>12 (18)</td>
<td>28 (21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (23)</td>
<td>13 (20)</td>
<td>28 (21)</td>
</tr>
<tr>
<td>Liver related investigations (SMQB)</td>
<td>13 (20)</td>
<td>14 (21)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16 (24)</td>
<td>10 (15)</td>
<td>26 (20)</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (18)</td>
<td>9 (14)</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13 (20)</td>
<td>8 (12)</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (15)</td>
<td>9 (14)</td>
<td>19 (14)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (17)</td>
<td>7 (11)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (12)</td>
<td>9 (14)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>9 (14)</td>
<td>7 (11)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>URTI</td>
<td>6 (9)</td>
<td>10 (15)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (17)</td>
<td>4 (6)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (11)</td>
<td>7 (11)</td>
<td>14 (11)</td>
</tr>
</tbody>
</table>

**Grade ≥3, in ≥3%**

<table>
<thead>
<tr>
<th></th>
<th>KD025 QD (n=66)</th>
<th>KD025 BID (n=66)</th>
<th>Overall (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3 (5)</td>
<td>4 (6)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>GGT increased</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

\(^1\) KD025 QD: Aspiration pneumonia; Hemoptysis; MODS/Septic shock; Relapse AML.
KD025 BID: Cardiac arrest.
KD025-213: Primary Endpoint Met at Interim Analysis

- Interim analysis occurred 2 months after last patient was enrolled
- KD025 achieved clinically meaningful and statistically significant ORRs in both arms
  - Statistical significance is achieved if the lower bound of the 95% CI of ORR exceeds 30%
- Three patients achieved a complete response (CR)

<table>
<thead>
<tr>
<th>Arm</th>
<th>ORR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KD025 200 mg QD (n=66)</td>
<td>64%</td>
<td>(51%, 75%)¹</td>
</tr>
<tr>
<td>KD025 200 mg BID (n=66)</td>
<td>67%</td>
<td>(54%, 78%)²</td>
</tr>
</tbody>
</table>

¹p<0.0001; ²p<0.0001
KD025-213: Responses Observed Across All Key Subgroups

- **mITT**
  - 200 mg QD (n=66, 64%)
  - 200 mg BID (n=66, 67%)

- **NIH Severity**
  - Severe (n=87, 61%)
  - Non-Severe (n=45, 73%)

- **Time from Diagnosis to Study**
  - > 50\(^{th}\) Percentile (n=65, 55%)
  - ≤ 50\(^{th}\) Percentile (n=66, 74%)

- **Organs Involved**
  - ≥ 4 (n=69, 64%)
  - < 4 (n=62, 68%)

- **Prior Lines of Therapy**
  - ≥ 4 (n=68, 63%)
  - < 4 (n=64, 67%)

- **Best Response to Prior Line**
  - Refractory (n=74, 68%)
  - Responsive (n=27, 59%)

- **Prior Ibrutinib**
  - Yes (n=45, 62%)
  - No (n=87, 67%)

- **Prior Ruxolitinib**
  - Yes (n=37, 62%)
  - No (n=95, 66%)

Pooled responses across arms, unless stated
KD025 was Well Tolerated and Achieved Clinically Meaningful Outcomes

- **KD025 was well tolerated**
  - No apparent increased risk of infection; no CMV reactivation

- **ORR of 65% across QD and BID arms**
  - Responses observed across all key subgroups
  - Responses observed in all affected organ systems, including in organs with fibrotic disease

- **Additional endpoint data will be available later in 2020 including:**
  - Duration of response
  - FFS, OS
  - Lee Symptom Scale (LSS) reductions
  - Corticosteroid dose reductions
  - PK and PD
Acknowledgements

- Trial patients and their caregivers
- All ROCKstar study investigators and all site staff, nurses, study coordinators
- The KD025-213 Steering Committee:
  - Madan Jagasia, MD (Chair), Vanderbilt University Medical Center, Nashville, TN
  - Steven Z. Pavletic, MD (Co-chair), National Cancer Institute, Bethesda, MD
  - Bruce R. Blazar, MD, Department of Pediatrics, University of Minnesota, Minneapolis, MN
  - Corey Cutler, MD, Dana Farber Cancer Institute, Boston, MA
  - Stephanie Lee, MD, Fred Hutchinson Cancer Research Institute, Seattle, WA
  - Sanjay K. Aggarwal, MD, SVP Clinical Development, Kadmon, Cambridge, MA
- Kadmon Holdings, Inc.
- Partner CROs