KD025 for Patients with Chronic Graft Versus Host Disease (cGVHD): Long-term Follow-up of a Phase 2 Study (KD025-208)

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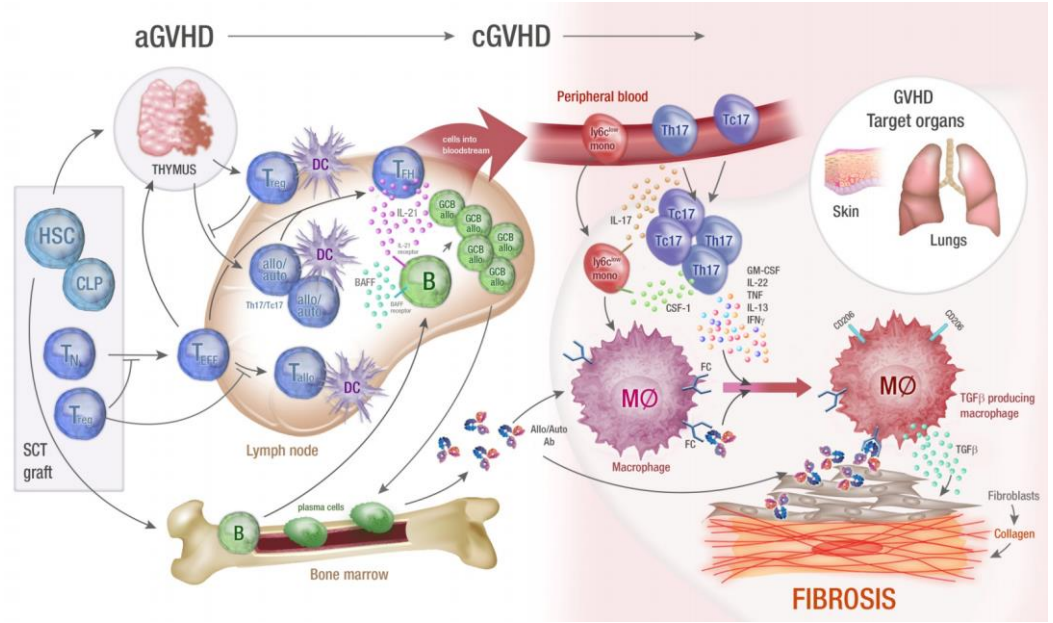
Pathophysiology of Chronic GVHD (cGVHD)

cGVHD is Driven by Immune Cells and Pro-inflammatory Cytokines

- **cGVHD involves both T cells and B cells**
  - Overproduction of pro-inflammatory cytokines IL-21 and IL-17
  - 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

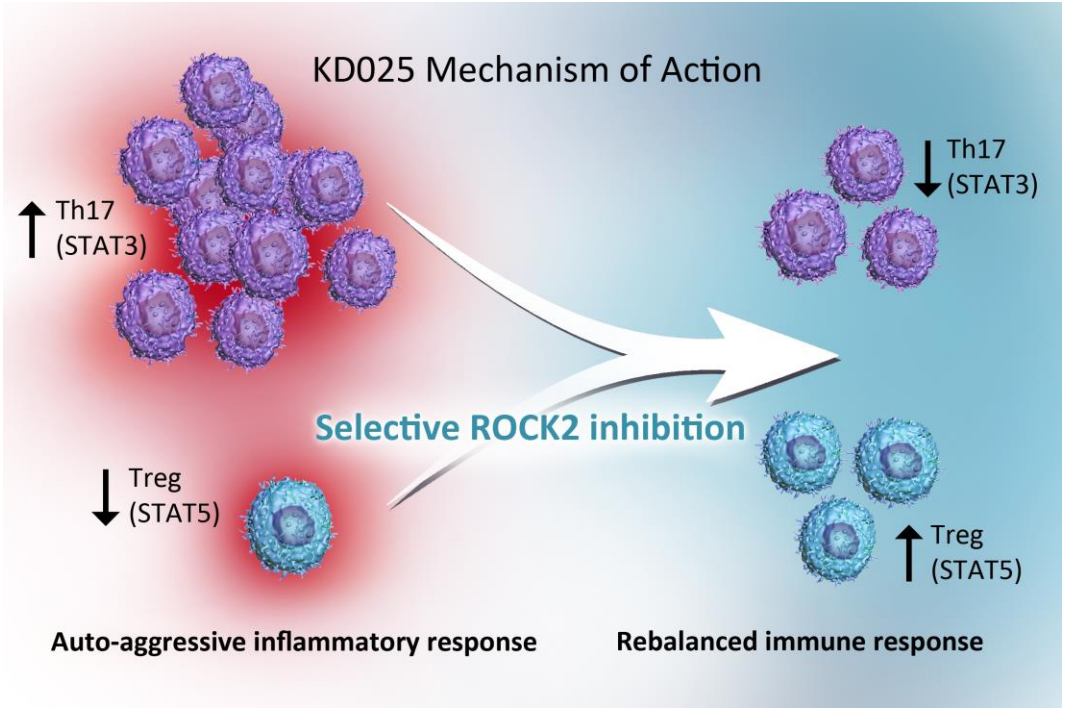


Blood, 2017

ROCK2 Plays Key Role in Autoimmune and Inflammatory Disease

ROCK2 Inhibition Rebalances Immune Response to Treat Immune Dysfunction[1,2]

- **ROCK2 inhibition downregulates pro-inflammatory Th17 responses and increases Treg function**
  - Reduces STAT3 phosphorylation and increases STAT5 phosphorylation
- **ROCK2 inhibition re-establishes immune homeostasis**

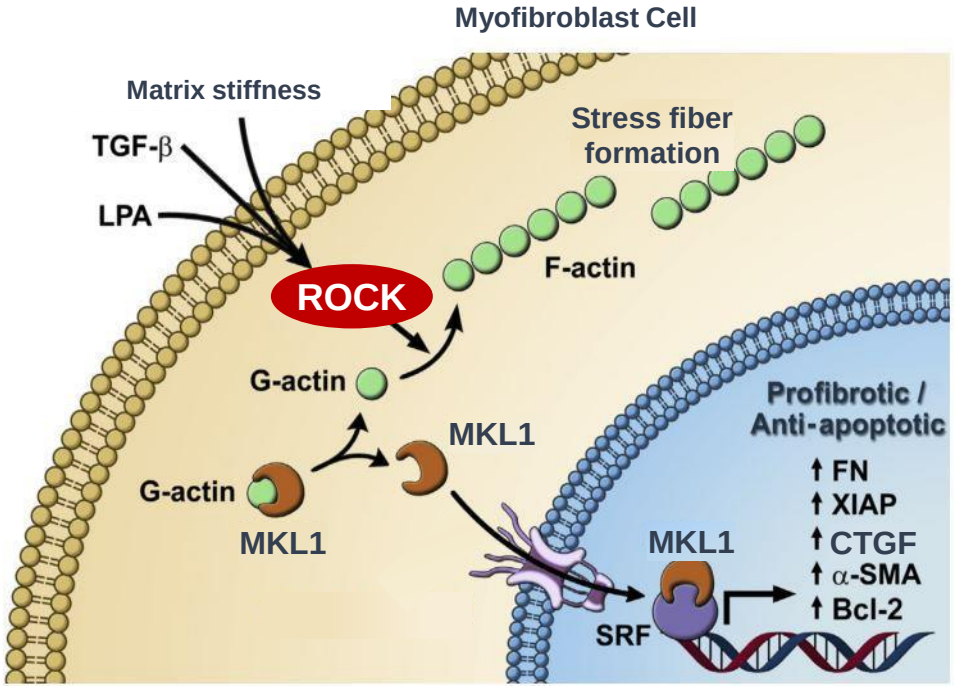


[1]*Proc Natl Acad Sci*, 2014; [2]*Blood*, 2016

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 regulates fibroblast differentiation to myofibroblasts, a pathological cell type in fibrosis
- ROCK mediates stress fiber formation
- ROCK regulates transcription of pro-fibrotic genes



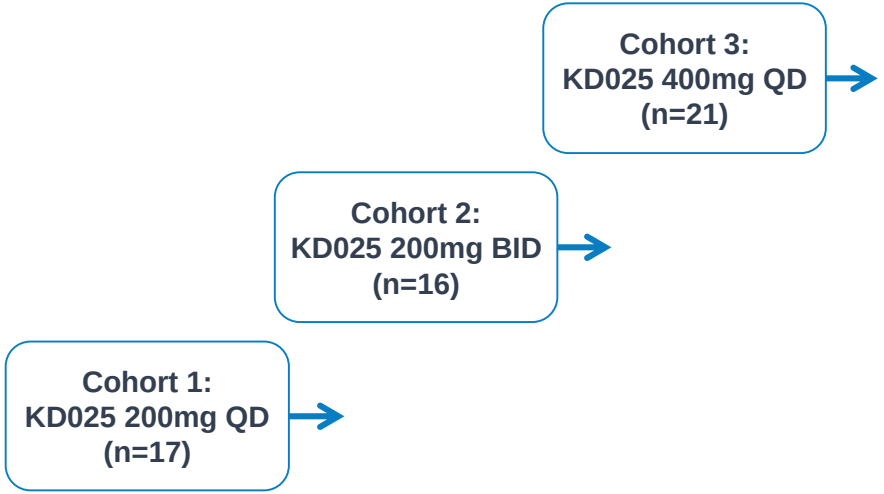
Am J Pathol, 2015

KD025-208: Design and Key Endpoints

All data as of 30 June, 2019; Median duration of follow up: 24 months

Key Eligibility Criteria:

- Adults with steroid-dependent or steroid-refractory cGVHD
- Have persistent active cGVHD after at least 2 months of steroid therapy
- 1-3 prior lines of treatment for cGVHD
- Receiving glucocorticoid therapy +/- calcineurin inhibitor therapy for cGVHD



Three cohorts enrolled sequentially, following safety assessment of previous cohort

Key Endpoints:

- ORR, per 2014 NIH criteria
- Safety and tolerability of KD025 in patients with cGVHD
- Duration of response (DOR)
- Response by organ system
- Changes in corticosteroid and calcineurin inhibitor dose

KD025-208: Demographics and Baseline Characteristics

- 50% of all patients had ≥4 organs affected - Included both inflammatory and fibrotic manifestations
- 65% of all patients had received ≥2 prior lines of cGVHD therapy
- 73% refractory to prior line of therapy[3]

Demographics and Baseline Characteristics	Cohort 1 (n=17)	Cohort 2 (n=16)	Cohort 3 (n=21)
Median age [years (range)]	50 (20-63)	55 (30-75)	46 (25-75)
Male (%)	76	56	57
Median time cGVHD diagnosis to study (months)	26	18	16
Organ Involvement			
≥4 organs involved	8 (47)	10 (63)	9 (43)
Eyes	14 (82)	11 (69)	17 (81)
Skin	13 (76)	12 (75)	15 (71)
Mouth	13 (76)	11 (69)	11 (52)
Joints and fascia	11 (65)	11 (69)	12 (57)
Lungs	4 (24)	3 (19)	10 (48)
Upper GI	2 (12)	4 (25)	2 (10)
Esophagus	2 (12)	0 (0)	4 (19)
Lower GI	1 (6)	2 (13)	1 (5)
Liver	0 (0)	2 (13)	0 (0)
Severe cGVHD[1]	12 (71)	14 (88)	16 (76)

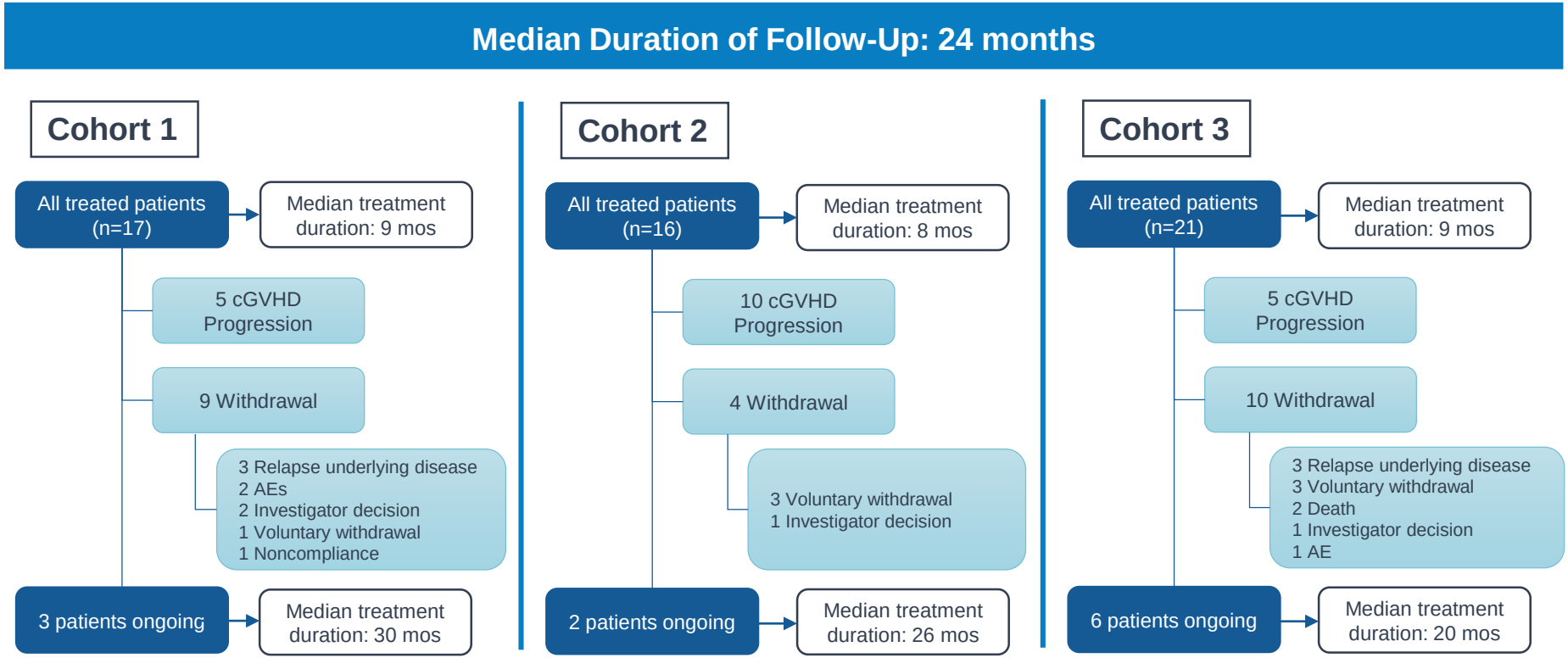
Prior Therapies[2]	Cohort 1 (n=17)	Cohort 2 (n=16)	Cohort 3 (n=21)
Median prednisone dose at BL (mg/kg/day)	0.22	0.19	0.15
Prior lines of therapy			
Median	3	2	2
≥2 prior lines of therapy [n (%)]	15 (88)	8 (50)	12 (57)
Refractory to prior line of therapy[3]	11/15 (73)	9/13 (69)	15/20 (75)

[1]Defined as at least 1 organ with NIH Activity Assessment score of 3, or lung score ≥2 at baseline

[2] ECP was not counted as a prior systemic therapy

[3] Status unknown for 6 subjects

KD025-208: Patient Disposition



KD025-208: Safety and Tolerability

- **AEs were overall consistent with those expected in cGVHD patients receiving corticosteroids**
- **No apparent increased risk of infection**
  - No CMV infection reported

Safety Overview, n (%)	Cohort 1 (n=17)	Cohort 2 (n=16)	Cohort 3 (n=21)	ITT (n=54)
Median weeks of treatment	37	33	39	36
Any Adverse Event (AE)	17 (100)	16 (100)	20 (95)	53 (98)
Grade 3/4 AE	9 (53)	11 (69)	10 (48)	30 (56)
SAE	5 (29)	6 (38)	12 (57)	23 (43)
Drug related AE				
Any related AE	7 (41)	9 (56)	14 (67)	30 (56)
Related AE leading to discontinuation[1]	2 (12)	0	1 (5)	3 (6)
Related Grade ≥3 event	1 (6)	4 (25)	2 (10)	7 (13)
On study deaths[2]	0	0	4 (19)	4 (7)

Commonly Reported AEs, n (%)	Cohort 1 (n=17)	Cohort 2 (n=16)	Cohort 3 (n=21)	ITT (n=54)
All Grade, in ≥20%				
Upper respiratory tract infection	9 (53)	9 (56)	7 (33)	25 (46)
Diarrhea	6 (35)	5 (31)	7 (33)	18 (33)
Nausea	6 (35)	4 (25)	8 (38)	18 (33)
ALT / AST increased (SMQ Broad)	8 (47)	7 (44)	3 (14)	18 (33)
Fatigue	5 (29)	3 (19)	9 (43)	17 (32)
Dyspnea	3 (18)	6 (38)	7 (33)	16 (30)
Headache	4 (24)	3 (19)	6 (29)	13 (24)
Edema	3 (17)	4 (25)	6 (29)	13 (24)
Cough	1 (6)	4 (25)	7 (33)	12 (22)
Hypertension	5 (29)	2 (13)	4 (19)	11 (20)
Grade ≥3, in ≥5%				
Dyspnea	1 (6)	2 (13)	5 (24)	8 (15)
Lung Infection / Pneumonia	1 (6)	2 (11)	5 (24)	8 (15)
ALT / AST increased (SMQ Broad)	2 (12)	3 (19)	0	5 (9)
Hypoxia	1 (6)	1 (6)	3 (14)	5 (9)
Hyperglycemia	2 (12)	0	2 (10)	4 (7)
Anemia	2 (12)	1 (6)	0	3 (6)

[1] Cohort 1: Headache; Diarrhea. Cohort 3: Fatigue

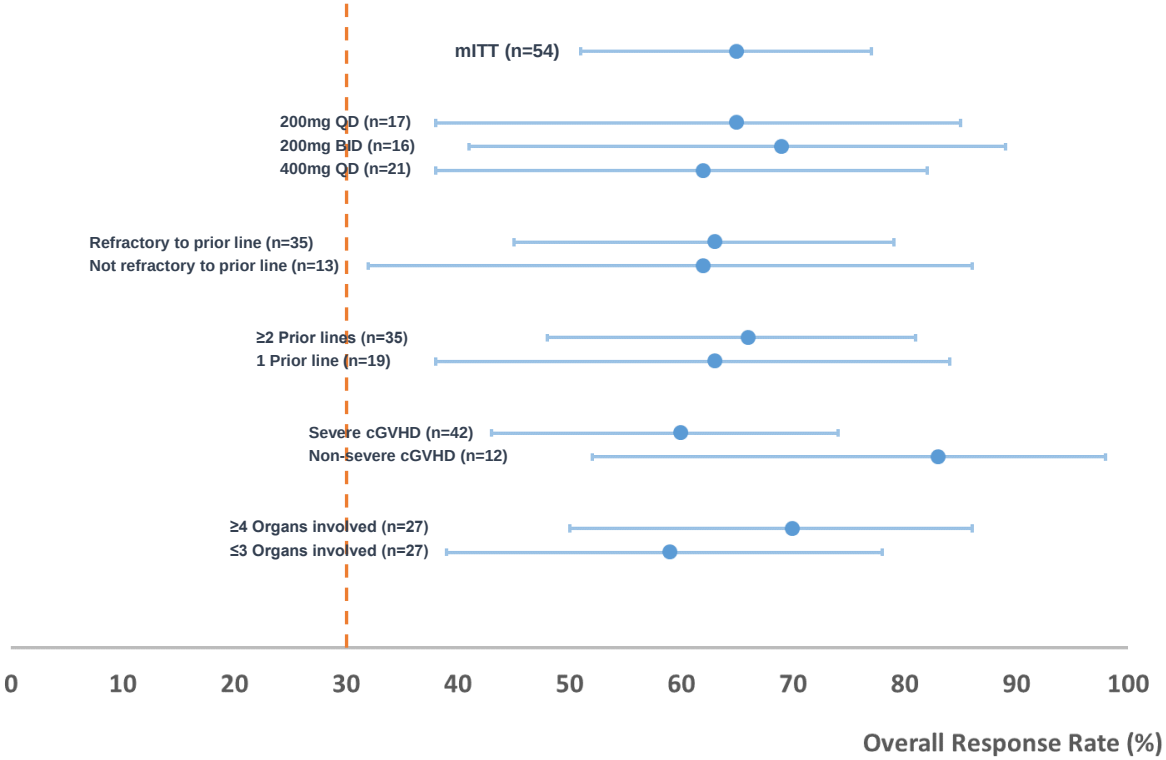
[2] Relapse of Leukemia; Lung infection; Cardiac arrest; cGVHD Progression. All considered not related to KD025

KD025-208: Overall Response Rate (ORR)

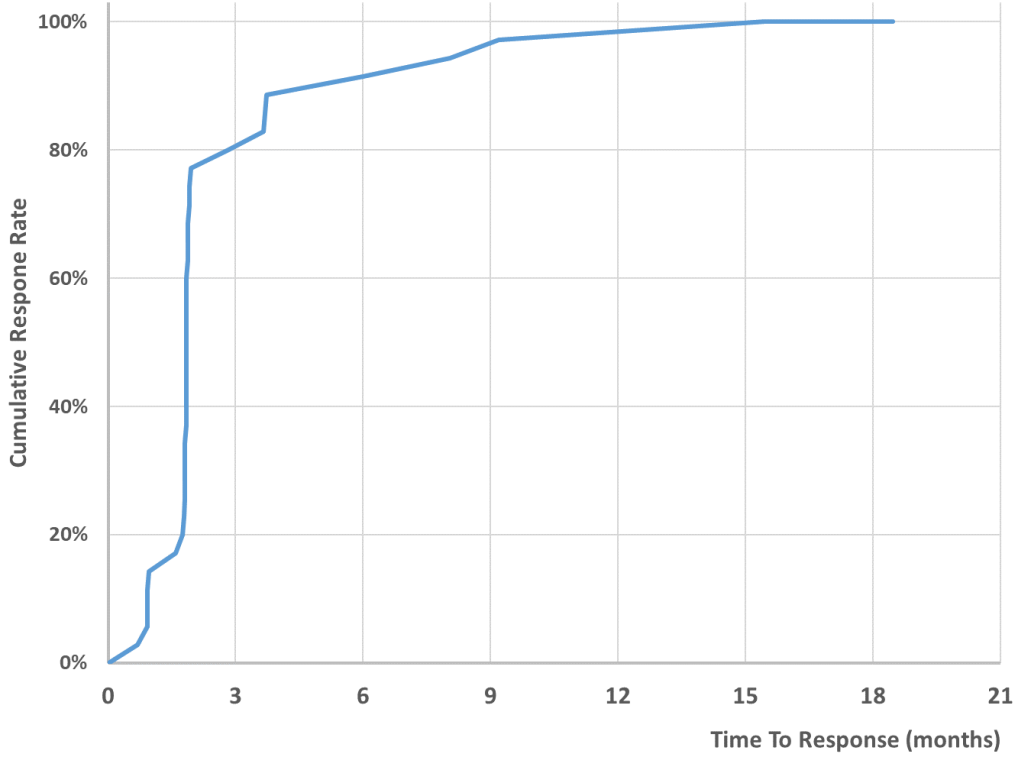
	n	ORR	95% CI
mITT	54	65%	(51, 77)
200 mg QD	17	65%	(38, 86)
200 mg BID	16	69%	(41, 89)
400 mg QD	21	62%	(38, 82)

Responses observed across key subgroups

- Refractory to prior line: 63%
- ≥2 Prior lines of therapy: 66%
- Severe cGVHD: 60%
- ≥4 Organs involved: 70%

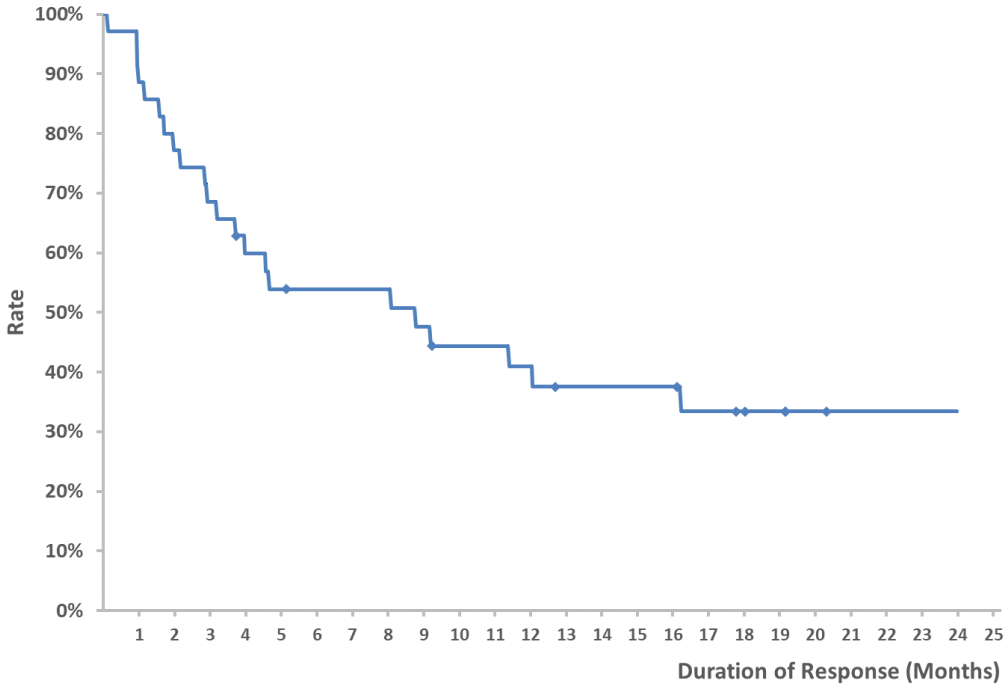


KD025-208: Time to Response



- **Amongst responders, 75% of responses occurred by week 8 assessment**
- **4/35 responses occurred after 24 weeks of treatment with KD025**
  - Late responses included:
    - Lung at 67 weeks
    - Eye at 35 weeks

KD025-208: Duration of Response (DOR)



- **Kaplan-Meier median DOR of 35 weeks (8 months) in mITT responder population**
- **51% of responders maintained a response for ≥ 20 weeks**

DOR is determined from time of first documented response.

Event:
- Documented loss of response
- Initiation of new systemic cGVHD therapy
- Death

Censoring:
- Last documented response assessment

KD025-208: Responses Across Organ Systems with Advanced Involvement

- **Responses across organ systems have been presented previously**
- **Here we present responses for organs with advanced involvement at baseline**

Organ	Baseline Criteria	N	Organ-Specific Response Rate
Skin	NIH score = 3	23	17%
Eyes	NIH score = 3	14	29%
Joints and Fascia	NIH score = 3 or P-ROM < 20	13	69%
Lung	NIH score ≥ 2	9	22%
Mouth	Modified Oral Mucosa Rating Scale (OMRS) ≥ 9	1	100%
Upper GI	NIH score = 3	1	100%
Lower GI	NIH score = 3	-	-
Esophagus	NIH score = 3	-	-
Liver	NA	-	-
Global Severity Rating (GSR)	Baseline GSR ≥ 8	15	60%

KD025-208: Corticosteroid Dose Reductions

- **19% of patients have completely discontinued corticosteroids**
- **65% achieved corticosteroid dose reductions**
- **Median corticosteroid dose reduction: 50%**
- **Corticosteroid dose reductions observed in responders and non-responders**

	Cohort 1 N=17	Cohort 2 N=16	Cohort 3 N=21
Patients with corticosteroid dose reduction, n (%)	13 (76)	9 (56)	13 (62)

Median corticosteroid dose reduction	Cohort 1	Cohort 2	Cohort 3
All Patients	63%	50%	50%
Responders	75% (n=11)	55% (n=11)	65% (n=13)
Non-Responders	21% (n=6)	33% (n=5)	0 (n=8)

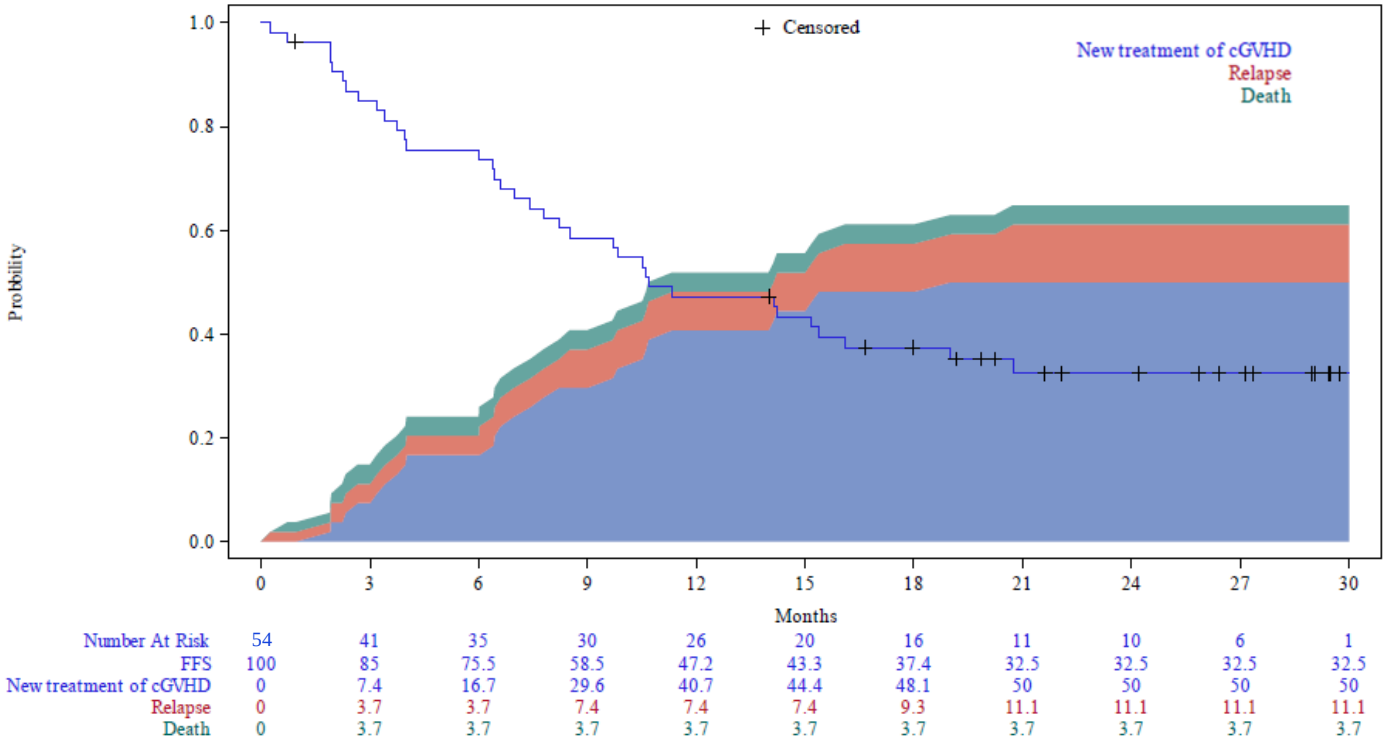
KD025-208: Lee cGVHD Symptom Scale (LSS) Score

- **35% of patients experienced clinically meaningful improvement (≥7 point reduction) on consecutive assessments**
- **LSS improvements observed in responders and non-responders**

	Cohort 1 N=17	Cohort 2 N=16	Cohort 3 N=21
Patients with improvement in LSS Score, %	59%	44%	52%

Improvement in LSS Score on consecutive assessments	Cohort 1	Cohort 2	Cohort 3
All Patients	29%	31%	43%
Responders	36% (4/11)	18% (2/11)	54% (7/13)
Non-Responders	17% (1/6)	60% (3/5)	25% (2/8)

KD025-208: Failure Free Survival



Number At Risk	54	41	35	30	26	20	16	11	10	6	1
FFS	100	85	75.5	58.5	47.2	43.3	37.4	32.5	32.5	32.5	32.5
New treatment of cGVHD	0	7.4	16.7	29.6	40.7	44.4	48.1	50	50	50	50
Relapse	0	3.7	3.7	7.4	7.4	7.4	9.3	11.1	11.1	11.1	11.1
Death	0	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7

Failure Free Survival (FFS)

- Median: 11 months
- Landmark
  - 12 month FFS: 47%
  - 24 month FFS: 32%
- 6 month FFS with PR/CR: 37%

Time to Next Treatment

- Median 14 months

Overall Survival

- 24 month OS: 83%

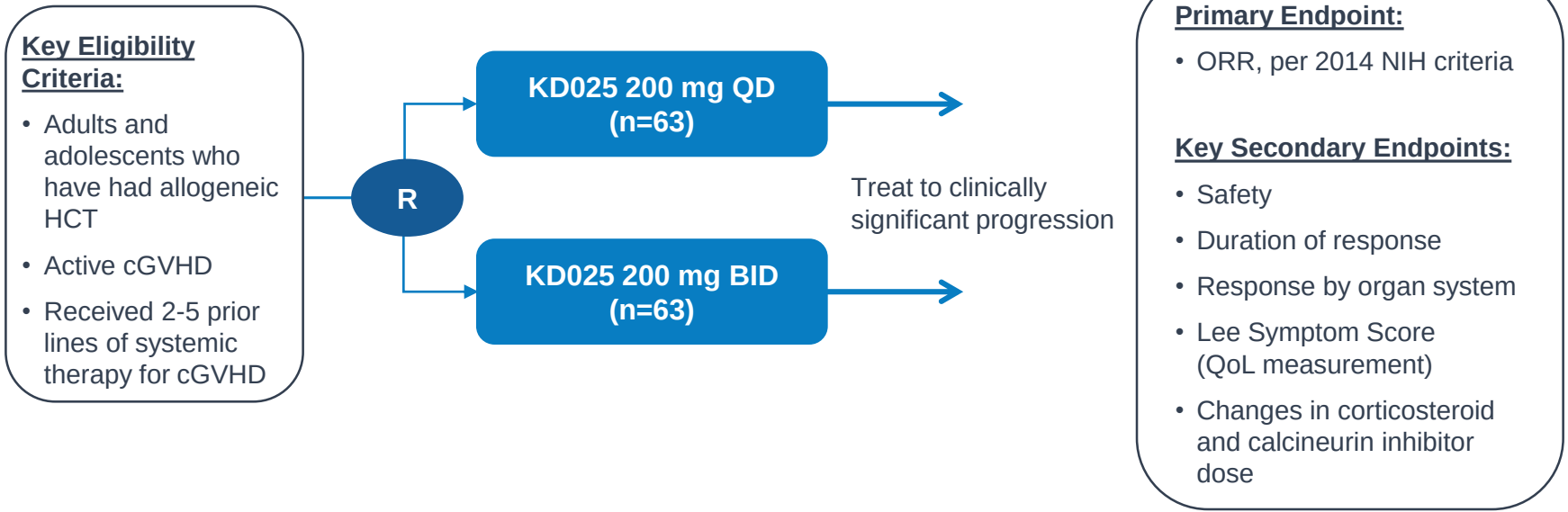
KD025-208: Conclusions

KD025 was Well Tolerated and Achieved Clinically Meaningful Outcomes

- **KD025 was well tolerated:**
  - No apparent increased risk of infection observed
- **ORR of 65% across all three cohorts:**
  - Responses observed across all key subgroups
  - Responses observed in all affected organ systems, including in organs with fibrotic disease
- **Durable and clinically meaningful outcomes:**
  - Median DOR of 35 weeks amongst responders
  - 19% of patients were able to discontinue corticosteroids
  - 35% of patients experienced clinically meaningful improvement in LSS score on consecutive assessments
  - 1 year FFS: 47%
  - 2 year Overall Survival: 83%

KD025-213: Ongoing Pivotal Trial of KD025 in cGVHD

KD025-213 (ROCKstar): A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects With cGVHD After At Least 2 Prior Lines of Systemic Therapy



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