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

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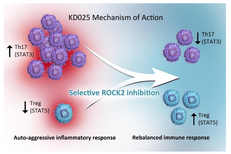
INTRODUCTION

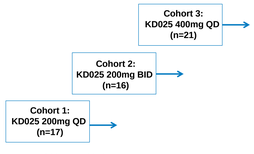
KD025 is an orally available Rho-associated coiled-coil kinase 2 (ROCK2) selective inhibitor in clinical development for inflammatory and fibrotic disease indications. KD025 has been shown to downregulate pro-inflammatory T helper 17 (TH17) cells and T follicular helper cells while upregulating Treg cells, as well as decrease collagen deposition and myofibroblast formation and proliferation. Therefore, KD025 may potentially impact the immunologic and fibrotic components of cGVHD.



METHODS

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



Data as of 30 June, 2019

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

Cohorts enrolled sequentially following safety assessment of previous cohort.

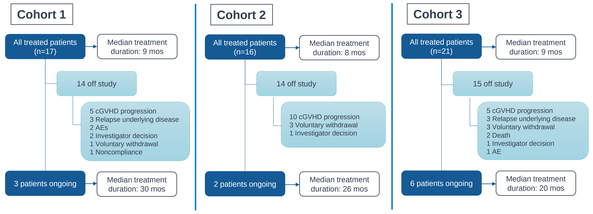
RESULTS

Baseline Characteristics

	Cohort 1 (n=17)	Cohort 2 (n=16)	Cohort 3 (n=21)	mITT (n=54)
Median (range) age, yrs	50 (20-63)	55 (30-75)	46 (25-75)	52 (20-75)
Male/Female (%)	76/24	56/44	57/43	63/37
Median time cGVHD diagnosis to enrollment, mos	26.4	18.0	16.0	20.0
Median time transplant to enrollment, mos	39.0	29.0	26.7	30.3
≥4 organs involved (n (%))	8 (47)	10 (63)	9 (43)	27 (50)
Severe cGVHD (n (%))	12 (71)	14 (88)	16 (76)	42 (78)
Median prednisone dose at BL (mg/kg/day)	0.22	0.19	0.17	0.19
Median prior lines of therapy	3	2	2	2
≥2 prior lines of therapy (n (%))	15 (88)	9 (56)	14 (67)	38 (70)

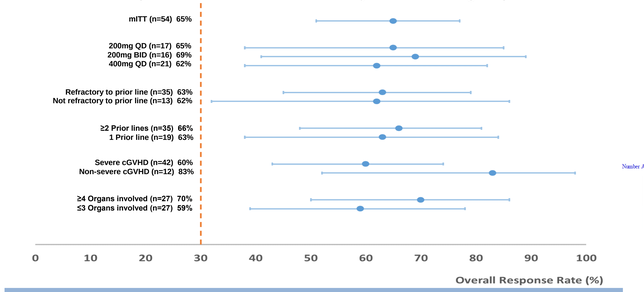
Patient Disposition

Median Duration of Follow-Up: 24 months



Overall Response Rate

ORR of 65% Across All Three Cohorts
Responses Achieved Across Key Patient Subgroups



Duration of Response (DOR)

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

DOR: determined from time of first documented response.
Event:
- Documented loss of response
- Initiation of new systemic cGVHD therapy
- Death

Censoring:
- Last documented response assessment

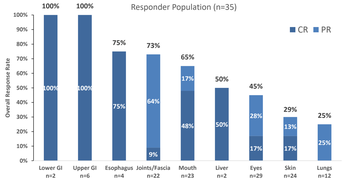
Time to Response

- Responses were rapid: >75% of responders achieved a response by Week 8 assessment
- 4/35 responses occurred after 24 weeks of treatment with KD025

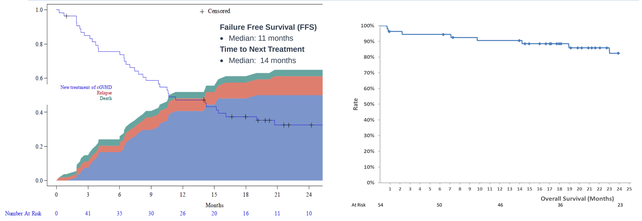
Late responses included:
- Lung at 67 weeks
- Eye at 35 weeks

Responses Across Organ Systems in Responders

- Complete responses (CRs) observed in: lower GI, upper GI, esophagus, joints/fascia, mouth, liver, eyes, skin
- Partial responses (PRs) observed in lungs



Failure Free Survival (FFS) and Overall Survival (OS)



Corticosteroid Dose Reductions

	Cohort 1	Cohort 2	Cohort 3
Patients with corticosteroid dose reduction, n (%)	13 (76)	9 (56)	14 (67)

- 67% achieved corticosteroid dose reductions
- Median corticosteroid dose reduction: 50%
- Corticosteroid dose reductions observed in responders and non-responders
- 19% of patients have completely discontinued steroids

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

Lee cGVHD Symptom Scale Score

	Cohort 1	Cohort 2	Cohort 3
Patients with improvement in LSS Score, %	59%	44%	52%

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

SAFETY

Safety Overview, n (%)	Cohort 1	Cohort 2	Cohort 3	mITT
Median months of treatment	8.5	7.5	9.0	8.4
Any Adverse Event (AE)	17 (100)	16 (100)	20 (95)	53 (98)
Grade 3/4 AE	9 (53)	10 (63)	14 (67)	33 (61)
SAE	5 (29)	6 (38)	12 (57)	23 (43)
Drug-related events (per investigator)				
Any related AE, n (%)	7 (41)	8 (50)	14 (67)	29 (54)
Any related grade 3+ event	1 (6)	3 (19)	2 (10)	6 (11)
Any related SAE	0	0	0	0
On study deaths	0	0	4 (19)	4 (7)

Commonly Reported AEs

All Grade AEs in ≥30%, n (%)	Cohort 1	Cohort 2	Cohort 3	mITT
URTI	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)

Grade 3 / 4 AEs in ≥5% , n (%)	Cohort 1	Cohort 2	Cohort 3	mITT
Dyspnea	1 (6)	2 (13)	4 (19)	7 (13)
ALT/AST increased (SMQ Broad)	2 (12)	2 (13)	0	4 (7)
Hyperglycemia	2 (12)	0	2 (10)	4 (7)
Hypoxia	1 (6)	1 (6)	2 (10)	4 (7)
Anemia	2 (12)	1 (6)	0	3 (6)
Lung Infection/Pneumonia	0	1 (6)	2 (10)	3 (6)

CONCLUSIONS

- **KD025 was well tolerated:**
  - AEs consistent with those expected in cGVHD patients receiving corticosteroids
- **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
  - 1-year FFS: 47%, 2-year FFS: 32%
  - 6-month FFS with PR/CR: 37%

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