

ROCK2 Inhibition With Belumosudil (KD025) for the Treatment of Chronic Graft-Versus-Host Disease

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PURPOSE The rho-associated coiled-coil-containing protein kinase-2 (ROCK2) signaling pathway regulates the Th17/regulatory T cells balance and controls profibrotic pathways. Selective ROCK2 inhibition with belumosudil (KD025) may offer a novel approach to the management of chronic graft-versus-host disease (cGVHD).

PATIENTS AND METHODS A phase IIa, open-label, dose-finding study of belumosudil enrolled 54 patients with cGVHD who had received one to three prior lines of therapy (LOTs). The primary end point was overall response rate (ORR).

RESULTS The median time from cGVHD diagnosis to enrollment was 20 months. Seventy-eight percent of patients had severe cGVHD, 50% had ≥ 4 organs involved, 73% had cGVHD refractory to their last LOT, and 50% had received ≥ 3 prior LOTs. With an overall median follow-up of 29 months, the ORR (95% CI) with belumosudil 200 mg once daily, 200 mg twice daily, and 400 mg once daily was 65% (38% to 86%), 69% (41% to 89%), and 62% (38% to 82%), respectively. Responses were clinically meaningful, with a median duration of response of 35 weeks, and were associated with quality-of-life improvements and corticosteroid (CS) dose reductions. CS treatment was discontinued in 19% of patients. The failure-free survival rate was 76% (62% to 85%) and 47% (33% to 60%) at 6 and 12 months, respectively. The 2-year overall survival rate was 82% (69% to 90%). Belumosudil was well-tolerated, with low rates of cytopenia. There were no unexpected adverse events and no apparent increased risk of infection, including cytomegalovirus infection and reactivation.

CONCLUSION Belumosudil treatment resulted in a high ORR and overall survival rate and demonstrated quality-of-life improvements, CS dose reductions, and limited toxicity. Data from the study indicated that belumosudil may prove to be an effective therapy for patients with treatment-refractory cGVHD.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is an immune-mediated inflammatory and fibrotic disorder.¹ It is a leading cause of morbidity,² mortality,^{2,3} and impaired quality of life (QOL)⁴ after an allogeneic hematopoietic cell transplant (alloHCT).²⁻⁴ cGVHD affects up to 70% of all alloHCT recipients,^{2,5-10} with an incidence of 20%-50% in children,⁹ who survive more than 100 days after alloHCT.¹⁰ It is the leading cause of nonrelapse mortality beyond 2 years after alloHCT.¹⁰

The estimated prevalence of cGVHD is 14,000 patients in the United States (as of 2016).¹¹ Of those patients, approximately 40% have severe disease.^{12,13} In addition, 42% of patients have ≥ 4 organs involved at the time of diagnosis.¹⁴

Patients with cGVHD have substantial impairment in QOL,^{4,15,16} as assessed by the Lee Symptom Scale (LSS), which measures the effect of cGVHD on patients' functioning and well-being.¹⁶ Only one third of

patients who have cGVHD and start systemic treatment will be alive, in remission and off immunosuppressive therapy by 5 years.¹²

The pathophysiology of cGVHD can be separated into three phases: early inflammation because of tissue injury, a dysregulated adaptive immune system, and chronic inflammation and aberrant tissue repair with fibrosis.⁸

First-line therapy for National Institutes of Health (NIH)-defined moderate to severe cGVHD is corticosteroids (CSs) alone or in combination with sirolimus or a calcineurin inhibitor.¹⁷ However, up to 70% of patients require additional lines of therapy (LOTs).^{11,12,18} Furthermore, the long-term use of CS is associated with significant side effects.^{18,19}

Management of cGVHD continues to evolve with the advent of targeted therapies. In 2017, the US Food and Drug Administration approved ibrutinib, a Bruton's Tyrosine kinase inhibitor, for the treatment of adults with

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Protocol

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cGVHD after failure of ≥ 1 systemic LOTs.²⁰ In patients with cGVHD who were required to have either $> 25\%$ body surface area erythematous rash or an NIH mouth score of > 4 ,²¹ a study with ibrutinib reported an overall response rate (ORR) of 67% and a discontinuation rate because of treatment-emergent adverse events (TEAEs) of 43%.²² There remains an opportunity to study other treatment options for patients who have failed ≥ 1 LOTs.

Belumosudil is an oral selective rho-associated coiled-coil-containing protein kinase-2 (ROCK2) inhibitor. ROCK2 has been shown to be activated in a Th17-skewed milieu, leading to the upregulation of signal transducer and activator of transcription 3 (STAT3) phosphorylation and the consequent increased expression of Th17-specific transcription factors, such as RAR-related orphan receptor and interferon regulatory factor 4.²³ Moreover, selective ROCK2 inhibition restores immune homeostasis and shifts the Th17/regulatory T cells (Tregs) balance toward Tregs via an STAT5-dependent mechanism.^{23,24} Belumosudil demonstrated a significant reduction of lung and skin fibrosis in animal models of bronchiolitis obliterans syndrome and sclerodermatous cGVHD, respectively,²⁴ which was consistent with the central role of ROCK in facilitating multiple fibrotic pathways.²⁵

Based on the biologic rationale and compelling preclinical data, a phase IIa study was conducted to evaluate the safety and efficacy of belumosudil in patients with cGVHD.

PATIENTS AND METHODS

Patient Eligibility

This phase IIa, dose-finding, open-label study was conducted at seven centers in the United States. Eligible patients were allogeneic bone marrow transplant or alloHCT recipients of age ≥ 18 years with persistent cGVHD manifestations after having received one to three prior systemic LOTs and who were receiving CS treatment with or without a calcineurin inhibitor and/or concurrent extracorporeal photopheresis. Belumosudil was continued until cGVHD progression or unacceptable toxicity.

Study Design and Treatment

Patients were enrolled into three sequential cohorts: cohort one received belumosudil 200 mg once daily, cohort two received belumosudil 200 mg twice daily (twice a day), and cohort three received belumosudil 400 mg once daily. Sixteen patients were planned for each of the cohorts. Before enrollment of the subsequent cohort, safety data in each previous cohort were analyzed after eight patients reached 2 months of treatment to assure that there was no safety signal. The 2-month timeframe was selected because all clinically significant belumosudil-related adverse events (AEs) to date had occurred in ≤ 36 days of starting belumosudil. No safety concerns were identified, allowing for planned dose escalation.

Belumosudil was administered orally in 28-day cycles until disease progression or unacceptable toxicity. Progression was defined per the 2014 NIH cGVHD Consensus Criteria.²⁶ Long-term follow-up was conducted via telephone every 8 weeks until study closeout. After 4 weeks of belumosudil therapy, CS could be tapered at the investigators' discretion.

Screening was conducted within 28 days of the first study dose. Response was initially assessed after two cycles; however, this was amended to evaluate response on day 1 of each cycle, starting at cycle 2 day 1.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional review board/independent ethics committee at each center approved the study. All patients provided written informed consent.

The study was registered with ClinicalTrials.gov identifier (NCT02841995) and sponsored by Kadmon Corporation, LLC. All authors reviewed and approved the submitted manuscript.

Study End Points

The primary efficacy end point was ORR, defined as the proportion of patients who achieved either a complete response (CR) or partial response (PR), per the 2014 NIH cGVHD Consensus Criteria, at any time point.²⁶ Only response assessments before the next LOT after belumosudil were counted toward ORR. All responses were assessed by the investigators.

Secondary end points included the number and the percentage of patients with steroid-dependent cGVHD who had a best response of PR or CR, duration of response (DOR), response rate by organ system, LSS score, CS dose reductions, time to next treatment (TTNT), failure-free survival (FFS), and overall survival (OS). The safety and tolerability of belumosudil were evaluated via AE assessments, physical examinations, vital sign measurements, laboratory tests, and electrocardiograms throughout the study. Predose samples were collected for pharmacodynamic (PD) evaluation, which included the assessment of immune cell subtypes in peripheral blood.

Statistical Analysis

With a sample size of 16 patients per cohort, the study had a $> 90\%$ probability of ≥ 1 study participants experiencing an AE with an underlying rate of $\geq 14\%$, which was derived from the probability calculations of the assumed sample size. Assuming a best ORR of 25%, which was determined to be clinically meaningful, the study was expected to have approximately 90% probability to show a response in ≥ 2 patients per cohort. This study was not powered to show significant differences between cohorts with respect to efficacy, AEs, or PD analyses. The primary analysis was conducted using the safety population, defined as enrolled patients who received ≥ 1 dose of study medication. The

TABLE 1. Baseline Demographics and Clinical Characteristics

Characteristic	Cohort 1	Cohort 2	Cohort 3	Total (N = 54)
	KD025 200 mg Once Daily (n = 17)	KD025 200 mg Twice a Day (n = 16)	KD025 400 mg Once Daily (n = 21)	
Median age, years (range)	50 (20-63)	55 (30-75)	46 (25-75)	52 (20-75)
Male, n (%)	13 (77)	9 (56)	12 (57)	34 (63)
Indication for transplant, n (%)				
AML	3 (18)	8 (50)	9 (43)	20 (37)
ALL	3 (18)	2 (13)	3 (14)	8 (15)
MDS	2 (12)	2 (13)	2 (10)	6 (11)
Non-Hodgkin lymphoma	3 (18)	0	2 (10)	5 (9)
Other non-Hodgkin lymphoma	0	2 (13)	1 (5)	3 (6)
Others	6 (35)	2 (13)	4 (19)	12 (22)
Conditioning intensity, n (%) ^a				
Myeloablative	9 (53)	5 (31)	10 (48)	24 (44)
Nonmyeloablative	7 (41)	8 (50)	10 (48)	25 (46)
Unknown	1 (6)	3 (19)	1 (5)	5 (9)
Stem-cell source, n (%) ^a				
Peripheral blood	15 (88)	15 (94)	18 (86)	48 (89)
Bone marrow	0	0	1 (5)	1 (2)
Cord blood	1 (6)	0	0	1 (2)
Unknown	1 (6)	1 (6)	2 (10)	4 (7)
HLA matching of donor or recipient, n (%) ^a				
Matched	14 (82)	13 (81)	18 (86)	45 (83)
Partially matched	3 (18)	3 (19)	2 (10)	8 (15)
Unknown	0	0	1 (5)	1 (2)
CMV-positive serostatus (donor/recipient), n (%)				
+/+	4 (24)	4 (25)	6 (29)	14 (26)
+/-	1 (6)	3 (19)	0	4 (7)
-/+	6 (35)	4 (25)	6 (29)	16 (30)
-/-	3 (18)	4 (25)	6 (29)	13 (24)
At least 1 unknown	3 (18)	1 (6)	3 (14)	7 (13)
Median time from cGVHD diagnosis to enrollment, months (range)	26.4 (0.0-130.7)	18.0 (1.0-69.9)	16.0 (1.0-161.9)	20.0 (0.0-161.9)
cGVHD severity, n (%) ^b				
Severe	12 (71)	14 (88)	16 (76)	42 (78)
Moderate	5 (29)	2 (13)	4 (19)	11 (20)
Mild	0	0	1 (5)	1 (2)
Organ involvement				
Median No. of organs involved, n (range)	3 (2-6)	4 (1-7)	3 (2-7)	4 (1-7)
≥ 4 organs involved, n (%)	8 (47)	10 (63)	9 (43)	27 (50)
Eyes, n (%)	14 (82)	11 (69)	17 (81)	42 (78)
Skin, n (%)	13 (77)	12 (75)	15 (71)	40 (74)
Mouth, n (%)	13 (77)	11 (69)	11 (52)	35 (65)
Joints and/or fascia, n (%)	11 (65)	11 (69)	12 (57)	34 (63)
Lungs, n (%)	4 (24)	3 (19)	10 (48)	17 (32)

(continued on following page)

TABLE 1. Baseline Demographics and Clinical Characteristics (continued)

Characteristic	Cohort 1 KD025 200 mg Once Daily (n = 17)	Cohort 2 KD025 200 mg Twice a Day (n = 16)	Cohort 3 KD025 400 mg Once Daily (n = 21)	Total (N = 54)
Upper GI, n (%)	2 (12)	4 (25)	2 (10)	8 (15)
Esophagus, n (%)	2 (12)	0	4 (19)	6 (11)
Lower GI, n (%)	1 (6)	2 (13)	1 (5)	4 (7)
Liver, n (%)	0	2 (13)	0	2 (4)
Median Karnofsky performance status, n (%)				
≤ 50	0	0	1 (5)	1 (2)
60-70	4 (24)	4 (25)	6 (29)	14 (26)
80-90	13 (77)	12 (75)	14 (67)	39 (72)
100	0	0	0	0
Prior therapy characteristics				
Median prior LOTs, n	3	2	2	3
≥ 2 prior LOTs, n (%)	15 (88)	9 (56)	14 (67)	38 (70)
Refractory to prior LOT, n (%) ^a	11/15 (73)	9/13 (69)	15/20 (75)	35/48 (73)

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; LOT, line of therapy; MDS, myelodysplastic syndrome.

^aDenominator excludes patients with unknown status (six patients in total).

^bDisease severity was determined using the Physician-reported Global cGVHD Activity Assessment Form.

Clopper-Pearson (exact) method was used to construct the two-sided 95% CI for ORR. The Kaplan-Meier (K-M) method was used to calculate estimates of FFS and OS.

RESULTS

Patients

Fifty-four patients in total were enrolled in sequential cohorts between September 2016 and March 2018: 17 patients in cohort 1, 16 patients in cohort 2, and 21 patients in cohort 3. As of the data cutoff for this analysis, February 19, 2020, the median duration of follow-up was 36 months in cohort 1, 32 months in cohort 2, and 24 months in cohort 3. The overall median duration of follow-up was 29 months (range, 1-39 months).

Demographics and baseline characteristics were overall comparable across cohorts (Table 1, Appendix Table A1, online only). The median age at baseline was 52 years (range, 20-75 years). The median time from cGVHD diagnosis to treatment was longest in cohort 1 at 26 months (compared with 18 months and 16 months in cohorts 2 and 3, respectively). Seventy-eight percent of patients had severe cGVHD per investigator assessment. Half of the patients had involvement of ≥ 4 organs, and more patients in cohort 3 had lung involvement (48%) compared with those in cohorts 1 (24%) and 2 (19%). The baseline median CS dose (mg/kg/d prednisone equivalent) was 0.22, 0.19, and 0.17 across cohorts, respectively. Patients in cohort 1 had received a median of three prior LOTs,

whereas patients in cohorts 2 and 3 had received a median of two prior LOTs. Seventy-three percent (35 of 48, data not available for six patients) of patients were refractory to their last LOT before study enrollment.

The CONSORT diagram (Fig 1) shows patient disposition. The median duration of treatment was 8.5 months (range, 2-39 months) in cohort 1, 7.5 months (range, 1-35 months) in cohort 2, and 9 months (range, 1-29 months) in cohort 3. Twenty-eight percent of patients have received > 18 months of belumosudil.

Seven patients (13%) remained on belumosudil at the time of this analysis. Reasons for discontinuing belumosudil included cGVHD progression (n = 22), voluntary withdrawal by patients (n = 8), relapse of underlying disease (n = 7), investigator decision (n = 3), AEs considered to be possibly treatment related (n = 3), and death (n = 2).

Efficacy

Overall response rate. In the safety population (N = 54), the ORR (95% CI) was 65% (51% to 77%). The ORR (95% CI) was similar across cohorts: 65% (38% to 86%) in cohort 1, 69% (41% to 89%) in cohort 2, and 62% (38% to 82%) in cohort 3 (Table 2). Efficacy data for subgroups and secondary end points are presented as pooled data across cohorts.

Responses were achieved across key subgroups, with ORRs of 60% (25 of 42) in patients with severe cGVHD, 66% (23 of 35) in patients who had received ≥ 2 prior

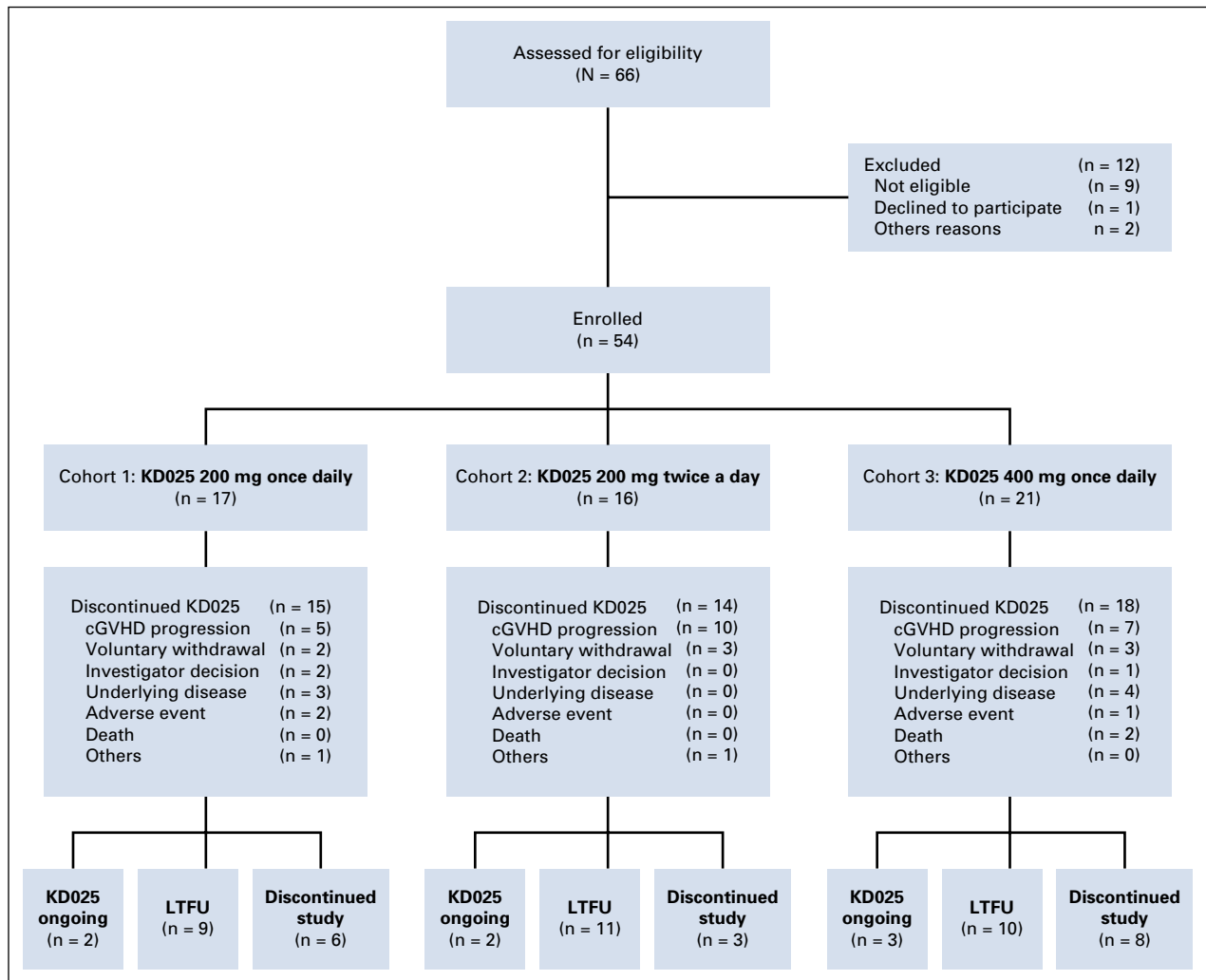


FIG 1. CONSORT diagram. cGVHD, chronic graft-versus-host disease; LTFU, long-term follow-up.

systemic LOTs, 63% (22 of 35) in patients who were refractory to their last LOT before enrollment, and 70% (19 of 27) in patients with ≥ 4 organs involved (Fig 2). All responses at the patient level were PR; however, organ-specific analyses showed that CR was achieved across all affected organs, with the exception of the lungs, where PR was the best response achieved (Appendix Figs A1 and A2, online only).

Responses were generally rapid, with $> 75\%$ of all responses achieved by the first response assessment at week 8 (Appendix Fig A3, online only). Four of 35 responses occurred after 24 weeks of belumosudil treatment, with late organ responses observed in the lungs, joints and/or fascia, and eyes (Appendix Fig A4, online only). Among responders, the K-M median DOR across cohorts was 35 weeks (Fig 3A). The K-M median DOR was 38 weeks for patients who had received ≥ 2 prior systemic LOTs.

Time to next treatment. The K-M median TTNT was 14 months (Fig 3B). Subsequent systemic cGVHD

therapies included tacrolimus, sirolimus, ibrutinib, ruxolitinib, extracorporeal photopheresis, and mycophenolate mofetil.

FFS and OS. The FFS rate (95% CI) was 76% (62% to 85%), 47% (33% to 60%), and 33% (21% to 46%) at 6, 12, and 24 months, respectively (Fig 3C). FFS was defined as the time from the first dose of belumosudil to a failure event.²⁷ Reasons for failure included initiation of a new systemic therapy ($n = 27$), relapse of the underlying disease ($n = 7$), and death ($n = 2$). An important end point is the percentage of patients achieving FFS with response (CR/PR) at 12 months,²⁸ which was 24% in this study. The OS rate (95% CI) was 91% (79% to 96%) and 82% (69% to 90%) at 12 and 24 months, respectively (Fig 3D).

QOL assessment. Clinically meaningful improvement in LSS score, defined as a decrease of ≥ 7 points in the LSS summary score,¹⁶ during belumosudil treatment was observed in 50% of patients. Thirty-five percent of all patients (37% of responders and 32% of nonresponders) reported a

TABLE 2. Efficacy and CS Reduction

Efficacy End Point	Cohort 1 KD025 200 mg Once Daily (n = 17)	Cohort 2 KD025 200 mg Twice a Day (n = 16)	Cohort 3 KD025 400 mg Once Daily (n = 21)	Total (N = 54)
ORR, % (95% CI)	65 (38 to 86)	69 (41 to 89)	62 (38 to 82)	65 (51 to 77)
Subgroup analyses, n/N (% , 95% CI)				
≥ 2 prior LOTs	10/15 (67, 38 to 88)	5/8 (63, 25 to 92)	8/12 (67, 35 to 90)	23/35 (66, 48 to 81)
Refractory to previous LOT	7/11 (64, 31 to 89)	6/9 (67, 30 to 93)	9/15 (60, 32 to 94)	22/35 (63, 45 to 79)
≥ 4 organs involved	4/8 (50, 16 to 84)	8/10 (80, 44 to 98)	7/9 (78, 40 to 97)	19/27 (70, 50 to 86)
Severe cGVHD ^a	8/12 (67, 35 to 90)	9/14 (64, 35 to 87)	8/16 (50, 25 to 75)	25/42 (60, 43 to 74)
Clinically significant improvement (LSS) ^b				
Overall, n (% , 95% CI)	9 (53, 28 to 77)	7 (44, 20 to 70)	11 (52, 30 to 74)	27 (50, 36 to 64)
Responder, n/N (% , 95% CI)	8/11 (73, 39 to 94)	3/11 (27, 6 to 61)	9/13 (69, 39 to 91)	20/35 (57, 39 to 74)
Nonresponder, n/N (% , 95% CI)	1/6 (17, 0.4 to 64)	4/5 (80, 28 to 99)	2/8 (25, 3 to 65)	7/19 (37, 16 to 62)
Proportion with CS reduction, n (% , 95% CI)	13 (76, 50 to 93)	9 (56, 30 to 80)	14 (67, 43 to 85)	36 (67, 53 to 79)
Mean percent change in CS dose from baseline, %				
Overall	-50	-36	-47	-45
Responder	-63	-36	-63	-55
Nonresponder	-26	-37	-19	-26
CS discontinuation, n (% , 95% CI)	4 (24, 7 to 50)	2 (13, 2 to 38)	4 (19, 5 to 42)	10 (19, 9 to 31)

Abbreviations: cGVHD, chronic graft-versus-host disease; CS, corticosteroid; LOT, line of therapy; LSS, Lee Symptom Scale; ORR, overall response rate.

^aDisease severity was determined using the Physician-reported Global cGVHD Activity Assessment Form.

^bChanges in cGVHD symptom burden were measured by the LSS. Clinically meaningful improvement in symptom burden was defined as a decrease of at least seven points in LSS summary score.

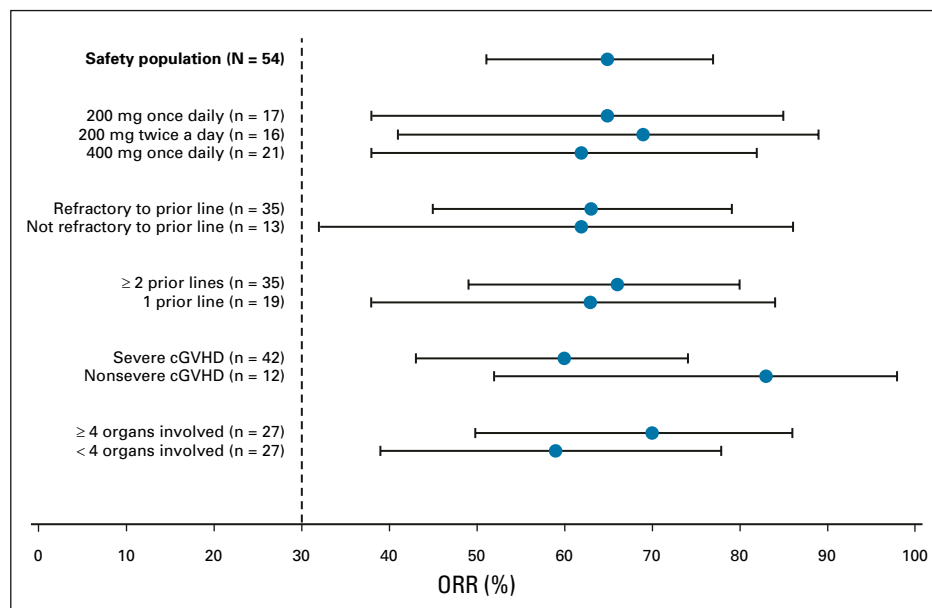


FIG 2. Forest plot for subgroup analyses of ORR in the safety population. Note that subgroups were defined based on baseline assessment. cGVHD, chronic graft-versus-host disease; ORR, overall response rate.

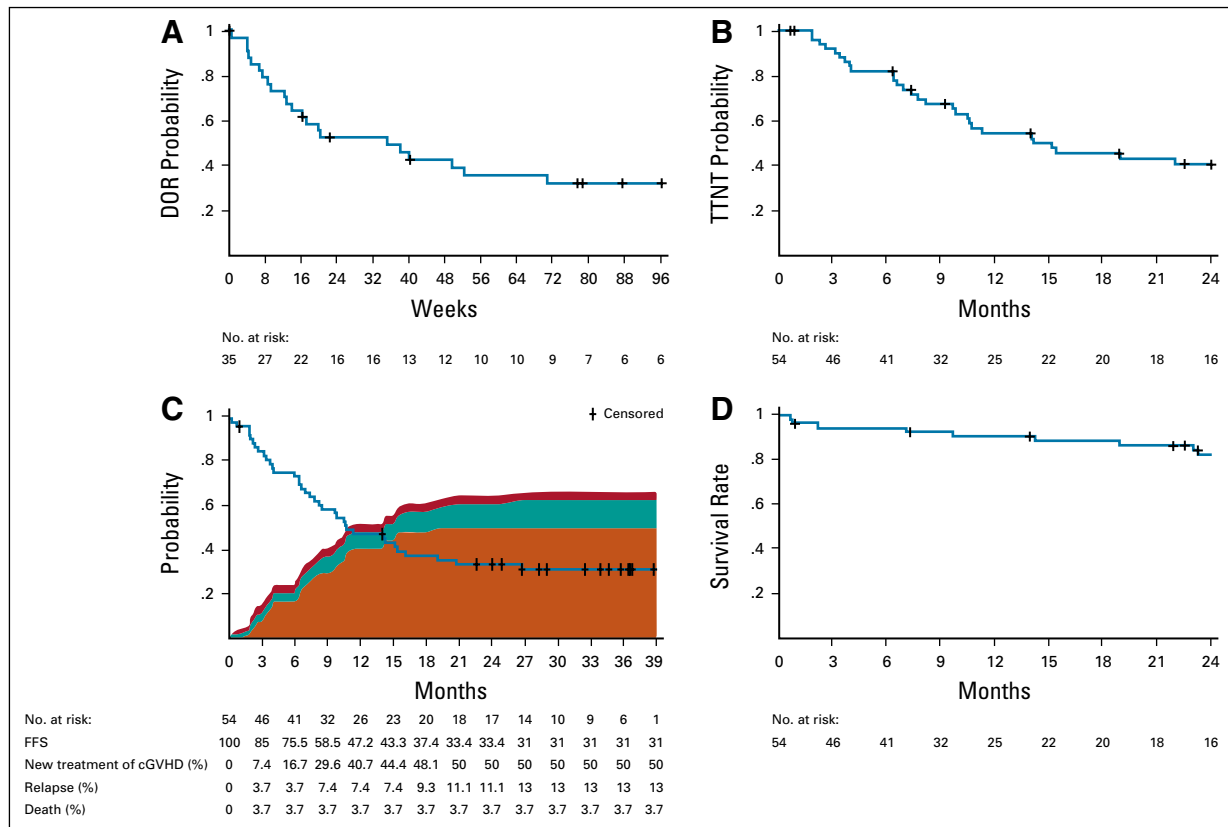


FIG 3. Durability of response to belumosudil in patients with cGVHD. Kaplan-Meier curves of estimated (A) DOR for responders, (B) time to next cGVHD systemic treatment (TTNT) in the safety population, (C) FFS in the safety population (including reasons for failure), and (D) overall survival in the safety population. DOR was defined as the time from response until documented progression. FFS was defined as the time from first dose of study drug to the start of another cGVHD systemic treatment, relapse of the underlying disease, or death.^{28,29} cGVHD, chronic graft-versus-host disease; DOR, duration of response; FFS, failure-free survival; TTNT, time to next treatment.

clinically meaningful improvement in LSS score on consecutive assessments.

CS sparing. During belumosudil treatment, 67% of patients reduced CS dose and 19% completely discontinued CS. The mean CS dose was reduced by 45%. The median time to CS discontinuation was 29 weeks (range, 8-77 weeks). The mean CS dose reduction was 55% in responders and 26% in nonresponders (Table 2).

Safety

Belumosudil was well-tolerated, with > 56 patient-years of belumosudil exposure. The median relative dose intensity was 98% overall. The percentage of patients with a relative dose intensity > 95% was 77%, 63%, and 71% across cohorts, respectively. Dose reductions occurred in 9% of patients, and the median duration of reduction was 97 days (range, 21-859 days). Dose interruptions occurred in 41% of patients, and the median duration of interruption was 10 days (range, 2-39 days).

AEs were consistent with those expected in a population of patients with advanced cGVHD receiving CS. AEs reported in ≥ 20% of patients were upper respiratory infection

(46%), diarrhea (33%), fatigue (33%), nausea (33%), increased liver function tests (33%), dyspnea (30%), headache (24%), peripheral edema (24%), cough (22%), and hypertension (20%) (Table 3). Serious AEs were reported in 43% of patients, and serious AEs reported in > 1 patient were dyspnea (7%), lung infection (6%), hypoxia (4%), and influenza-like illness (4%). Sixty-one percent of patients had a grade ≥ 3 AE, with the most common being dyspnea (13%), increased liver function tests (7%), hyperglycemia (7%), and hypoxia (7%) (Table 3).

Grade ≥ 3 cytopenias were reported in two patients (4%). These occurred at relapse of underlying malignancy in patients who had otherwise maintained normal blood counts during their belumosudil treatment.

No cases of cytomegalovirus (CMV) infection or reactivation were reported with belumosudil.

Three patients discontinued belumosudil because of potentially drug-related AEs (cohort 1: diarrhea and headache; cohort 3: fatigue). Four patients, all in cohort 3, died during the study—secondary to relapse of leukemia, pneumonia (unknown pathogen), cardiac arrest, and cGVHD progression—with none of the deaths attributed to

TABLE 3. Safety Overview

AE, No. (%)	Cohort 1 KD025 200 mg Once Daily (n = 17)	Cohort 2 KD025 200 mg Twice a Day (n = 16)	Cohort 3 KD025 400 mg Once Daily (n = 21)	Total (N = 54)
Any AE	17 (100)	16 (100)	20 (95)	53 (98)
Grade \geq 3 AE	9 (53)	10 (63)	14 (67)	33 (61)
Drug-related AE	8 (47)	8 (50)	14 (67)	30 (56)
SAE	5 (29)	6 (38)	12 (57)	23 (43)
Death	0	0	2 (10)	2 (4)
Drug-related SAE	0	0	0	0
All grade in \geq 20%				
URI	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)
Fatigue	6 (35)	3 (19)	9 (43)	18 (33)
ALT/AST increased	11 (65)	5 (31)	2 (10)	18 (33)
Dyspnea	3 (18)	6 (38)	7 (33)	16 (30)
Peripheral edema	3 (18)	4 (25)	6 (29)	13 (24)
Headache	4 (24)	3 (19)	6 (29)	13 (24)
Cough	1 (6)	4 (25)	7 (33)	12 (22)
Hypertension	5 (29)	2 (13)	4 (19)	11 (20)
Grade \geq 3 in \geq 5%				
Dyspnea	1 (6)	2 (13)	4 (19)	7 (13)
Lung infection or pneumonia	1 (6)	2 (13)	2 (10)	5 (9)
ALT/AST increased	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)

Abbreviations: AE, adverse event; SAE, serious adverse event; URI, upper respiratory tract infection.

belumosudil. There was no dose response with respect to the observed AEs.

PD Analyses

In exploratory PD analyses of peripheral blood mononuclear cells across cohorts, the percentage of CD4⁺ Tregs demonstrated an increasing trend early on by cycle 2 day 1 of belumosudil treatment. A simultaneous decrease in Th17 cells was also observed. The Th17 cells continued to decrease through C4D1 and C6D25. The percentage of CD4⁺ Tregs continued to increase through C4D1 and C7D1, as shown in [Figure 4](#). Because of the small sample size, correlative data with steroid dose were limited for any statistical analysis.

DISCUSSION

This study was the first to evaluate belumosudil treatment in patients with cGVHD. All phenotypes of cGVHD, without requirements for inflammatory or fibrotic manifestations, were included. Patients with advanced multiorgan cGVHD

treated with belumosudil achieved an ORR of 65%, with QOL improvements, CS dose reductions, and limited toxicity. With relatively small sample sizes, there was no difference in the ORR across cohorts.

Belumosudil achieved response rates that were meaningful and consistent across subgroups, including patients with severe cGVHD, patients who had received \geq 2 prior systemic LOTs, patients who were refractory to their last LOT before enrollment, and patients with \geq 4 organs involved. The ORR among patients with nonsevere cGVHD was 83%, suggesting that further studies of how belumosudil may benefit patients earlier in their disease are indicated. All responses at the patient level were PR; no CR was achieved. However, given the severity and extent of fibrotic cGVHD manifestations in this patient population, achieving CR in all organs was not expected, as some advanced fibrotic changes in the eyes, mouth, lungs, or joints and/or fascia can be irreversible. CR was observed in all organs except the lungs, where PR was achieved.

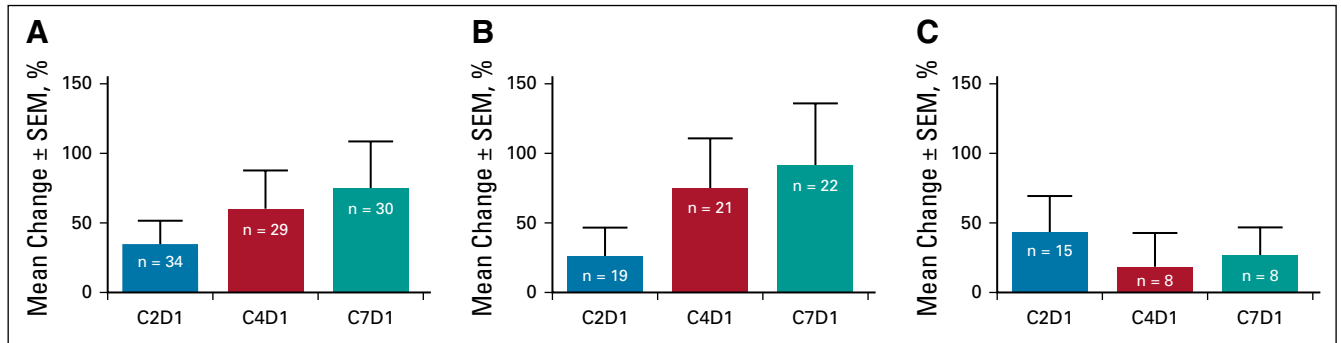


FIG 4. Changes in percentage of CD4⁺ Tregs following treatment with belumosudil compared with baseline. (A) Tregs (all), (B) Tregs (responders), and (C) Tregs (nonresponders). Predose peripheral blood samples were collected on C1D1, C2D1, C4D1, C7D1, and end-of-treatment visits. C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; C4D1, cycle 4 day 1; C7D1, cycle 7 day 1; Tregs, regulatory T cells.

Belumosudil response kinetics suggest that most responders achieved responses rapidly within 8 weeks after receiving belumosudil.

Belumosudil was well-tolerated, with a median DOR of 35 weeks across all responders. The ability to stay on therapy is dependent on the safety and long-term tolerability profile of the intervention. The median treatment duration was 8 months (range, 1-39 months). Twenty-eight percent of patients remained on belumosudil for > 18 months, with 11 patients remaining on treatment at the time of this analysis. There was no reported CMV infection or reactivation, despite 57% of patients being CMV seropositive. The incidence of TEAEs and grade \geq 3 TEAEs was similar across cohorts.

The combination of well-tolerated therapy and efficacy in inducing responses translated into a 2-year OS rate of 82%, a median TTNT of 14 months, and FFS rates of 76% and 47% at 6 and 12 months, respectively.

In a prospective study conducted by the cGVHD Consortium, the 12-month FFS rate with response (CR/PR) after first-line therapy was 12% to 15%.²⁸ In our study (after 1-3 prior LOTs), the 12-month FFS rate with response was 24%.

Belumosudil therapy was associated with a CS-sparing effect. The current treatment paradigm relies on CS as the mainstay of therapy; however, the related long-term toxicities mandate the use of the lowest possible dose or discontinuation whenever possible. The use of CS is tied to QOL, as the side effect profile of CS contributes to patient symptom burden.^{18,19,30} CS dose reduction was observed across both responders and nonresponders to belumosudil. Approximately 20% of patients were able to discontinue CS during belumosudil treatment. Even in the absence of an NIH-defined response, patients experienced

clinical benefit, as evidenced by improvements in LSS score or reductions in CS doses.

The pathophysiology and clinical phenotype of cGVHD reflect both immune and fibrotic components.⁸ An ideal intervention would target both aspects. Fibrotic cGVHD manifestations, including fasciitis, ocular fibrosis, cutaneous sclerosis, and bronchiolitis obliterans syndrome, are notoriously difficult to treat.^{18,31-33} As a ROCK2 inhibitor, belumosudil has been shown to decrease inflammation, restore immune homeostasis, and decrease fibrosis.^{23,24,34} In our study, responses were achieved in patients with fibrotic manifestations in the lungs, joints and/or fascia, and eyes. These responses were observed in some cases after > 24 weeks of treatment,³⁴ further highlighting the need to sustain effective therapy to achieve clinical benefit, particularly in patients with difficult-to-treat disease.

In summary, belumosudil is a selective ROCK2 inhibitor with a novel mechanism of action that targets both inflammation and fibrosis in cGVHD.²³ Belumosudil was well-tolerated and achieved clinically meaningful responses in patients with cGVHD across all dose regimens evaluated.³⁵ Responses have been durable and associated with QOL improvements and CS dose reductions or discontinuations. These clinical benefits were also seen in patients who did not achieve NIH-defined responses.³⁵ Data from this study are very encouraging, given the unmet needs of patients with cGVHD. These data have led to belumosudil being granted Breakthrough Therapy Designation by the US Food and Drug Administration. Because the lower belumosudil 200-mg once daily dose was equally safe and effective, it has been further compared in a subsequent randomized registration study (ClinicalTrials.gov identifier: [NCT03640481](https://clinicaltrials.gov/ct2/show/study/NCT03640481)) against the 200-mg twice a day dose for final dose recommendation.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**ROCK2 Inhibition With Belumosudil (KD025) for the Treatment of Chronic Graft-Versus-Host Disease**

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APPENDIX

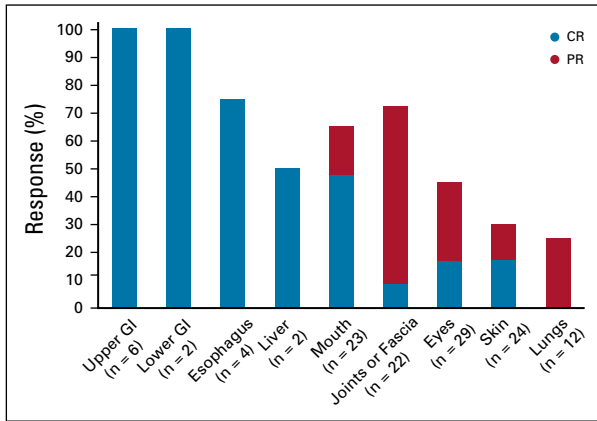


FIG A1. Best individual response by organ system among responders. n = number of responder population for global severity rating and number of specific organs involved at baseline. The percentages are calculated based on the corresponding n. CR, complete response; PR, partial response.

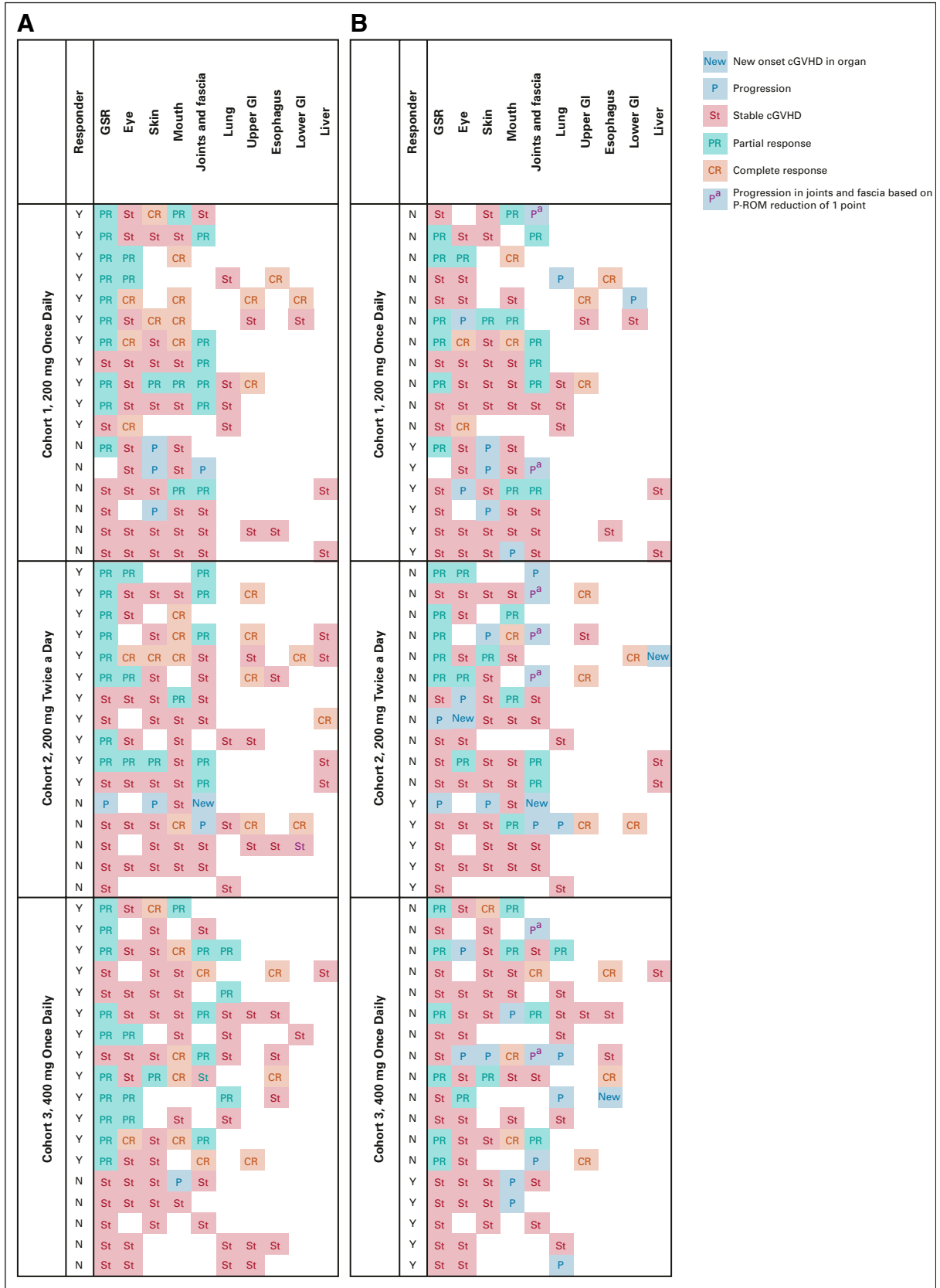


FIG A2. Response and progression heat map for all patients in the safety population. (A) Best response by organ. (B) Organ responses at time of progression or end of study. Of 11 patients with progression in joints, seven had a reduction in P-ROM of just one unit. cGVHD, chronic graft-versus-host disease; CR, complete response; GSR, Global Severity Rating; PR, partial response; P-ROM, photographic range of motion.

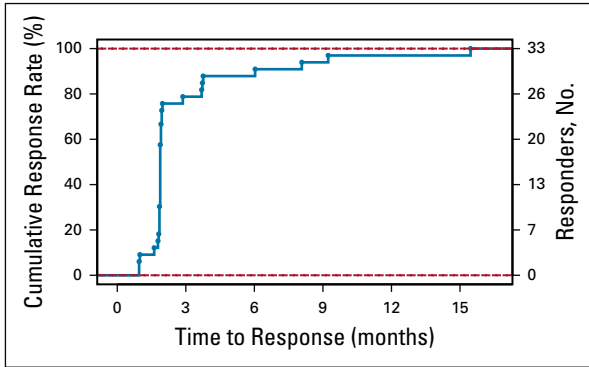


FIG A3. Time to response among belumosudil responders. Percentages are calculated based on the number of responder population.

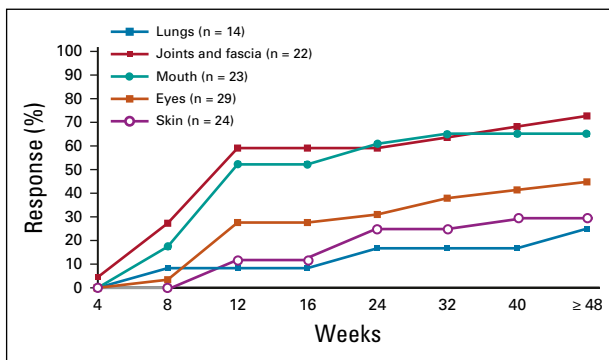


FIG A4. Time to response by selected organs among responders. Percentages are calculated based on the number of responder population.

TABLE A1. Additional Baseline Demographics

Characteristic	Cohort 1 KD025 200 mg Once Daily (n = 17)	Cohort 2 KD025 200 mg Twice a Day (n = 16)	Cohort 3 KD025 400 mg Once Daily (n = 21)	Total (N = 54)
Prior systemic cGVHD therapy type, No. (%)				
CS	17 (100)	16 (100)	21 (100)	54 (100)
Tacrolimus	8 (47)	7 (44)	11 (52)	26 (48)
Sirolimus	10 (59)	8 (50)	6 (29)	24 (44)
Rituximab	8 (47)	3 (19)	5 (24)	16 (30)
ECP	5 (29)	4 (25)	6 (29)	15 (28)
MMF	4 (24)	4 (25)	4 (19)	12 (22)
Cyclosporine	3 (18)	0	2 (10)	5 (9)
Ibrutinib	1 (6)	0	3 (14)	4 (7)
MTX	1 (6)	2 (13)	0	3 (6)
Ixazomib	1 (6)	1 (6)	0	2 (4)
ATG	1 (6)	0	0	1 (2)
Ofatumumab	0	0	1 (5)	1 (2)
Imatinib	1 (6)	0	0	1 (2)
Ruxolitinib	0	0	1 (5)	1 (2)
Continuing systemic cGVHD therapy type				
CS, No. (%)	17 (100)	16 (100)	21 (100)	54 (100)
Mean prednisone equivalent dose at enrollment, mg/kg/d	0.22	0.24	0.28	0.25
CNI, No. (%)	7 (41)	6 (38)	12 (57)	25 (46)
ECP, No. (%)	4 (24)	4 (25)	4 (19)	12 (22)

Abbreviations: ATG, antithymocyte globulin; cGVHD, chronic graft-versus-host disease; CNI, calcineurin inhibitor; CS, corticosteroid; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MTX, methotrexate.