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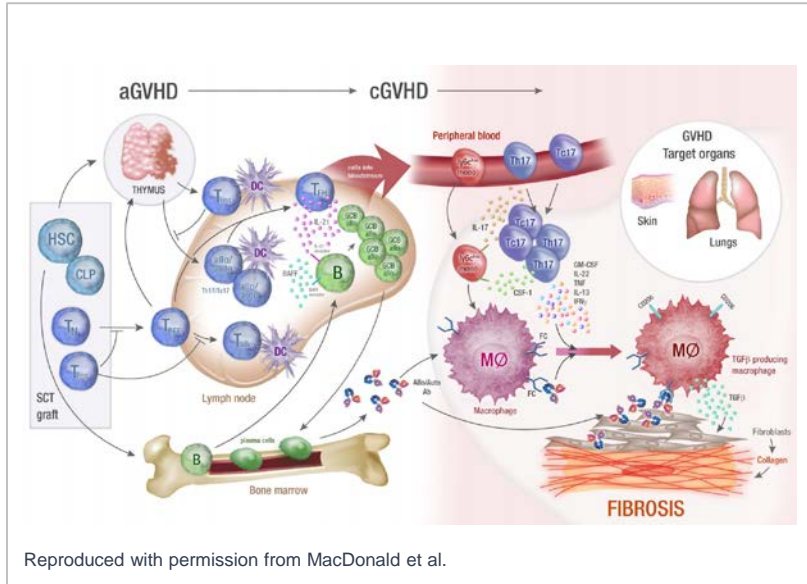
Follow-up Analysis of KD025-213 (the ROCKstar Study): A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Patients With cGVHD

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cGVHD, chronic graft-versus-host disease.

The Pathophysiology of cGVHD



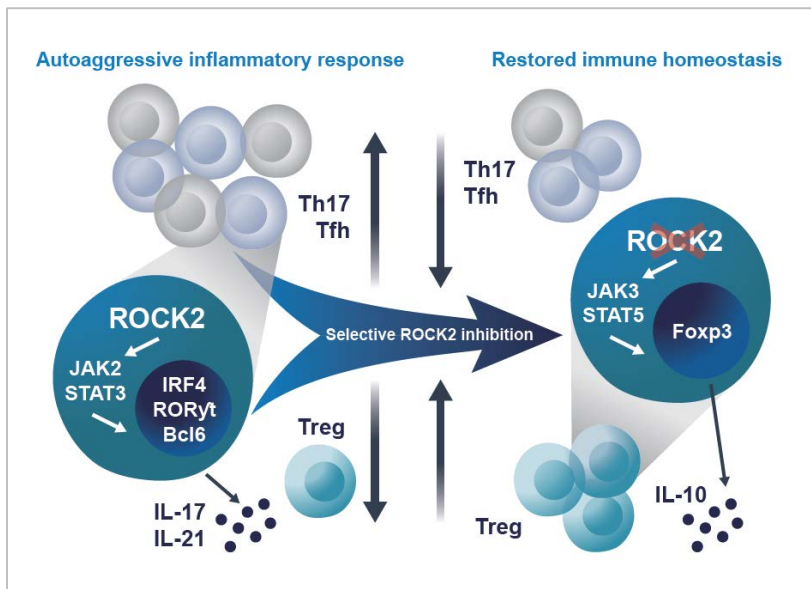
Chronic GVHD is driven by both immune and fibrotic processes

- Chronic GVHD involves both T cells and B cells
 - Overproduction of pro-inflammatory IL-21 and IL-17 cytokines
 - Overactivation of Tfh cells and B cells, leading to the overproduction of antibodies
 - Deficiency of Treg cells, leading to the lack of appropriate regulation of immune response
- Macrophages activate profibrotic mediators and contribute to fibrosis

Ab, antibody; aGVHD, acute graft-versus-host disease; allo, alloreactive; auto, autoreactive; BAFF, B-cell-activating factor; CLP, common lymphoid progenitor; CSF-1, colony-stimulating factor 1; DC, dendritic cell; Fc, receptor for immunoglobulins; GCB, germinal center B [cell]; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-host disease; HSC, hematopoietic stem cell; IFN- γ , interferon- γ ; IL-13, interleukin 13; IL-17, interleukin 17; IL-21, interleukin 21; IL-22, interleukin 22; mono, monocyte; SCT, stem cell transplant; T_{allo}, alloreactive T [cell]; Tc17, cytotoxic 17 T [cell]; T_{EFF}, effector T [cell]; Tfh, follicular helper T [cell]; TGF β , transforming growth factor- β ; Th17, type 17 helper T [cell]; T_N, naive T [cell]; TNF, tumor necrosis factor; Treg, regulatory T [cell].

MacDonald KPA et al. *Blood*. 2017;129(1):13-21. doi:10.1182/blood-2016-06-686618

ROCK2 Plays a Key Role in Immune Diseases



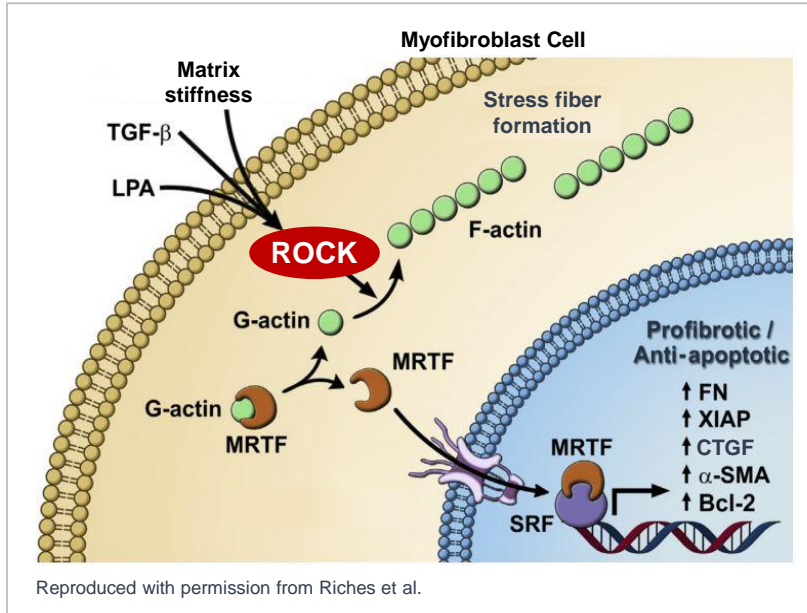
ROCK2 inhibition rebalances immune response to treat immune dysfunction

- ROCKs are serine-threonine kinases
- **Two isoforms:** ROCK1 and ROCK2
- ROCK2 inhibition rebalances the immune system
 - Downregulates pro-inflammatory Th17 cells
 - Increases Treg cells

Bcl6, B-cell lymphoma 6; Foxp3, forkhead box protein P3; IRF4, interferon regulatory factor 4; JAK2, Janus-associated kinase 2; JAK3, Janus-associated kinase 3; ROCK, rho-associated coiled-coil-containing protein kinase; ROCK1, rho-associated coiled-coil-containing protein kinase-1; ROCK2, rho-associated coiled-coil-containing protein kinase-2; RORγt, retinoic-acid-receptor-related orphan nuclear receptor gamma t; STAT3, signal transducer and activator of transcription 3; STAT5, signal transducer and activator of transcription 5.

Zanin-Zhorov A et al. *Proc Natl Acad Sci USA*. 2014;111(47):16814-16819. doi:10.1073/pnas.1414189111

ROCK Is an Intracellular Integrator of Profibrotic Signals



ROCK regulates multiple profibrotic processes, including myofibroblast activation

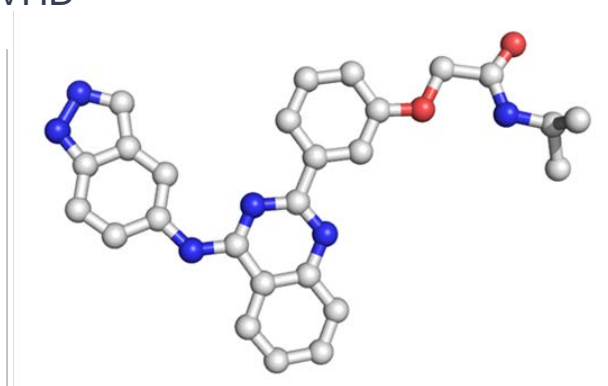
- ROCK is downstream of major profibrotic mediators
- ROCK mediates stress fiber formation
- ROCK regulates transcription of profibrotic genes

α-SMA, α-smooth muscle actin; Bcl-2, B-cell lymphoma 2; CTGF, connective tissue growth factor; FN, fibronectin; LPA, lysophosphatidic acid; MRTF, myocardin-related transcription factor; SRF, serum response factor; XIAP, X-linked inhibitor of apoptosis.

Riches DWH et al. *Am J Pathol.* 2015;185(4):909-912. doi:10.1016/j.ajpath.2015.01.005

Rationale for Belumosudil (KD025) in cGVHD

- Belumosudil, an investigational drug, is an oral selective ROCK2 inhibitor¹
 - More than 550 individuals have received belumosudil in ongoing and completed studies
- Targets both the immune and the fibrotic pathophysiology of cGVHD¹
- Preclinical data in sclerodermatous mouse model¹
- KD025-208 study
 - Phase 2a study of belumosudil showed an ORR of 65% in patients with cGVHD after receiving 1 to 3 prior lines of systemic therapy^{2,3}
 - Data from this study led to
 - FDA Breakthrough Therapy Designation for belumosudil for the treatment of adult patients with cGVHD after failure of ≥ 2 lines of systemic therapy
 - The ROCKstar Study (KD025-213)



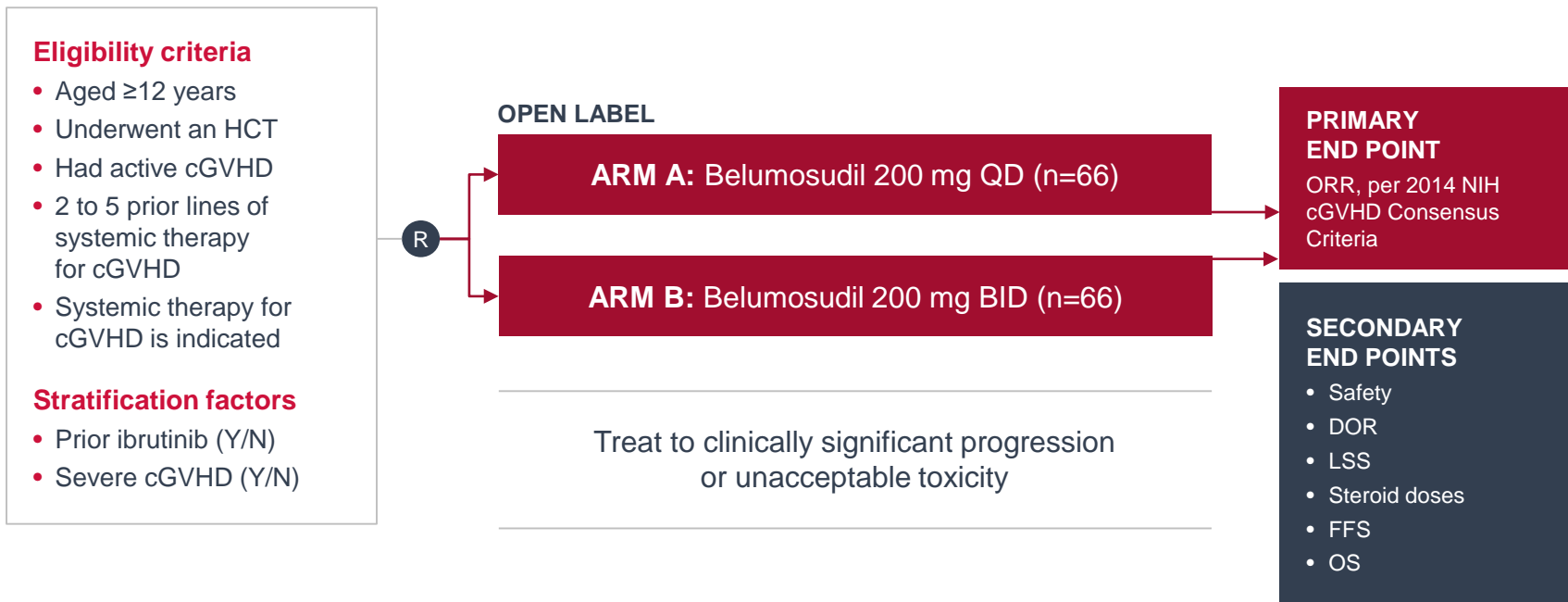
The chemical structure of belumosudil

ORR, overall response rate.

1. Flynn R et al. *Blood*. 2016;127(17):2144-2154. doi:10.1182/blood-2015-10-678706 2. Data on file. Kadmon Pharmaceuticals, LLC; 2018. 3. Data on file. Kadmon Pharmaceuticals, LLC; 2020.



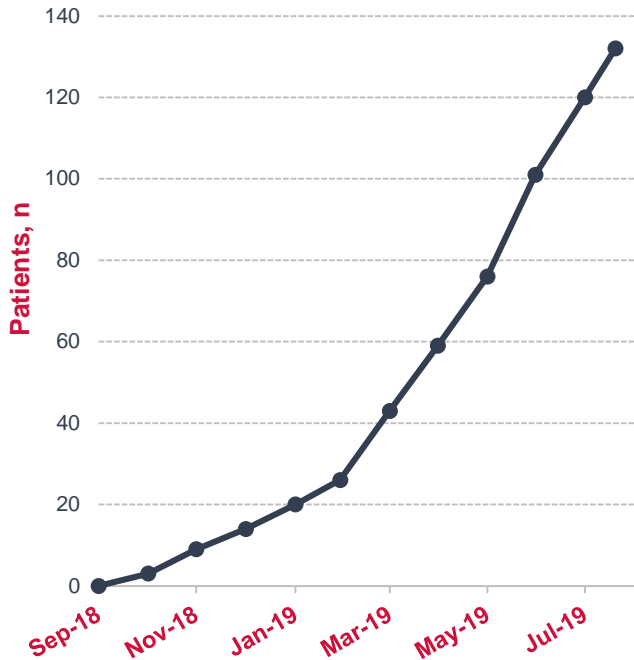
The ROCKstar Study: Study Design and End Points



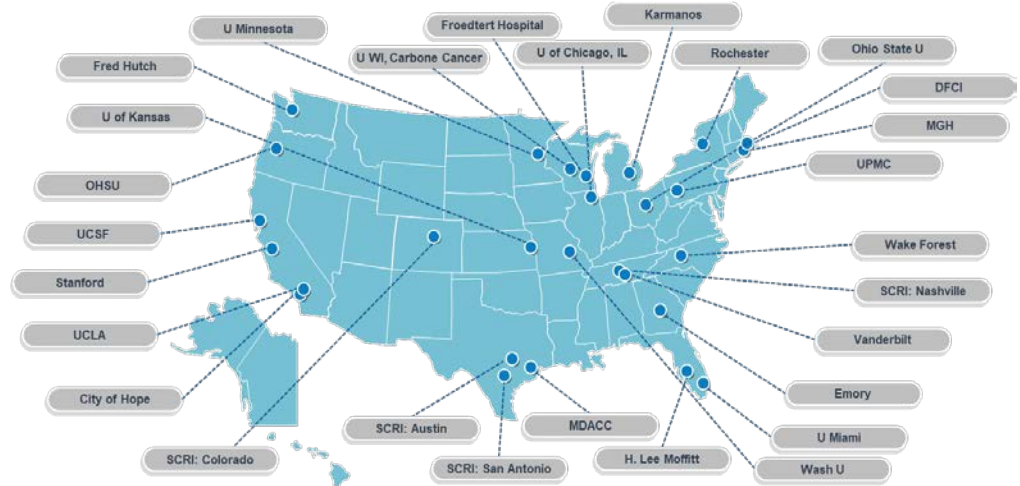
BID, twice a day; DOR, duration of response; FFS, failure-free survival; HCT, hematopoietic cell transplant; LSS, Lee Symptom Scale; NIH, National Institutes of Health; OS, overall survival; QD, every day. These data come from an analysis of the ROCKstar study as of August 2020.



The ROCKstar Study: Fully Enrolled in <10 Months



- 28 US sites
- **Enrollment period:**
October 2018 to August 2019



The ROCKstar Study: Diverse Patient Population

Select Demographics and Baseline Characteristics

Demographics	Belumosudil 200 mg QD (n=66)	Belumosudil 200 mg BID (n=66)
Median age, y (range)	53 (21-77)	57 (21-77)
Male, %	64	50
Median prior lines of therapy, n	3	4
Median time from cGVHD diagnosis to enrollment, mo	25	30
NIH moderate cGVHD, n (%)	18 (27)	23 (35)
NIH severe cGVHD, ^a n (%)	46 (70)	43 (65)
Median prednisone dose, mg/kg/d	0.19	0.20
≥4 organs involved, n (%)	33 (50)	35 (53)
Prior ibrutinib treatment, ^a n (%)	22 (33)	23 (35)
Prior ruxolitinib treatment, n (%)	20 (30)	18 (27)
Refractory to last prior line of systemic therapy, n (%)	44 (79)	35 (65)

^aStratification factor.

These data come from an analysis of the ROCKstar study as of August 2020.



The ROCKstar Study: Safety and Tolerability

Commonly reported AEs, n (%)	Belumosudil 200 mg QD (n=66)	Belumosudil 200 mg BID (n=66)	Overall (N=132)
All grades in ≥20% of patients			
Fatigue	30 (46)	20 (30)	50 (38)
Diarrhea	23 (35)	21 (32)	44 (33)
Nausea	23 (35)	18 (27)	41 (31)
Cough	20 (30)	17 (26)	37 (28)
Upper respiratory tract infection	17 (26)	18 (27)	35 (27)
Dyspnea	21 (32)	12 (18)	33 (25)
Headache	13 (20)	18 (27)	31 (24)
Liver-related AEs	12 (18)	19 (29)	31 (24)
Peripheral edema	17 (26)	13 (20)	30 (23)
Vomiting	18 (27)	10 (15)	28 (21)
Muscle spasms	13 (20)	13 (20)	26 (20)
Grade ≥3 in ≥5% of patients			
Pneumonia	6 (9)	4 (6)	10 (8)
Hypertension	4 (6)	4 (6)	8 (6)
Hyperglycemia	3 (5)	3 (5)	6 (5)

- AEs were overall consistent with those expected in patients with cGVHD receiving corticosteroids and other immunosuppressants
 - There was 1 reported case of Epstein-Barr virus and 1 reported case of CMV reactivation

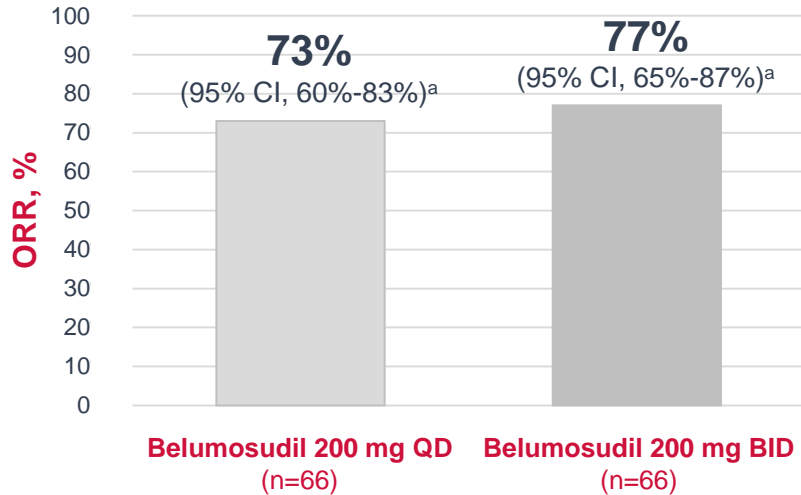
Safety overview	Belumosudil 200 mg QD (n=66)	Belumosudil 200 mg BID (n=66)	Overall (N=132)
Median duration of treatment, mo	9.4	11.8	10.4
Any AE, n (%)	65 (99)	66 (100)	131 (99)
Grade ≥3 AE, n (%)	37 (56)	34 (52)	71 (54)
SAE, n (%)	27 (41)	23 (35)	50 (38)
Drug-related AE, n (%)			
Any related AE	49 (74)	40 (61)	89 (67)
Related SAE	5 (8)	2 (3)	7 (5)
On study deaths,^a n (%)	4 (6)	4 (6)	8 (6)

^a **Belumosudil QD:** aspiration pneumonia; hemoptysis; MODS/septic shock; relapse AML.
Belumosudil BID: cardiac arrest (2); infection; respiratory failure.

AE, adverse event; AML, acute myeloid leukemia; MODS, multiple organ dysfunction syndrome; SAE, serious adverse event.

The ROCKstar Study: Primary End Point Met

Belumosudil achieved clinically meaningful and statistically significant ORRs in both arms



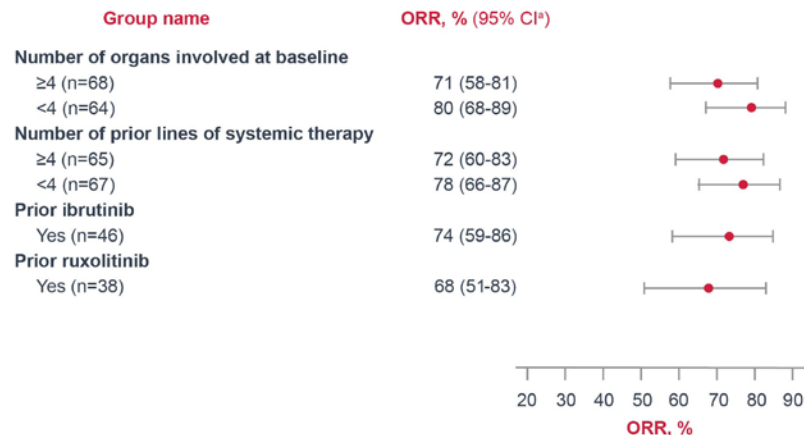
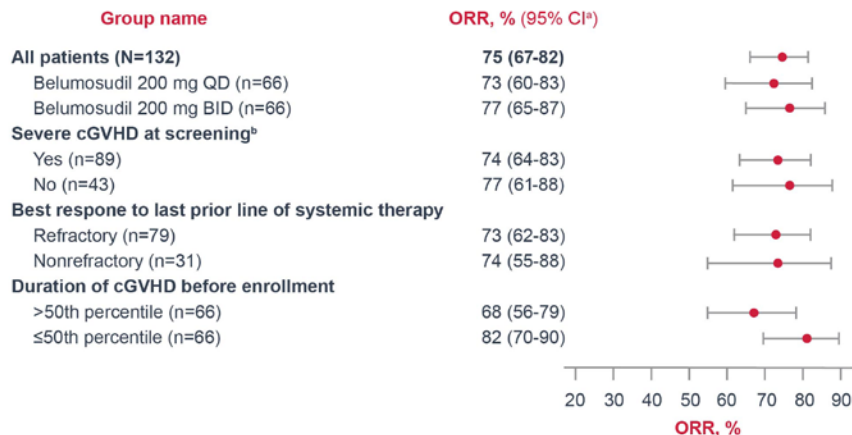
- Follow-up analysis occurred 12 months after last patient was enrolled
- Seven patients achieved a CR in all affected organs
- Statistical significance is achieved if the lower bound of the 95% CI of ORR exceeds 30%

CR, complete response.

^a $P < .0001$.



The ROCKstar Study: Responses Observed Across All Key Subgroups



^aCI is calculated using the Clopper-Pearson interval (exact) method.

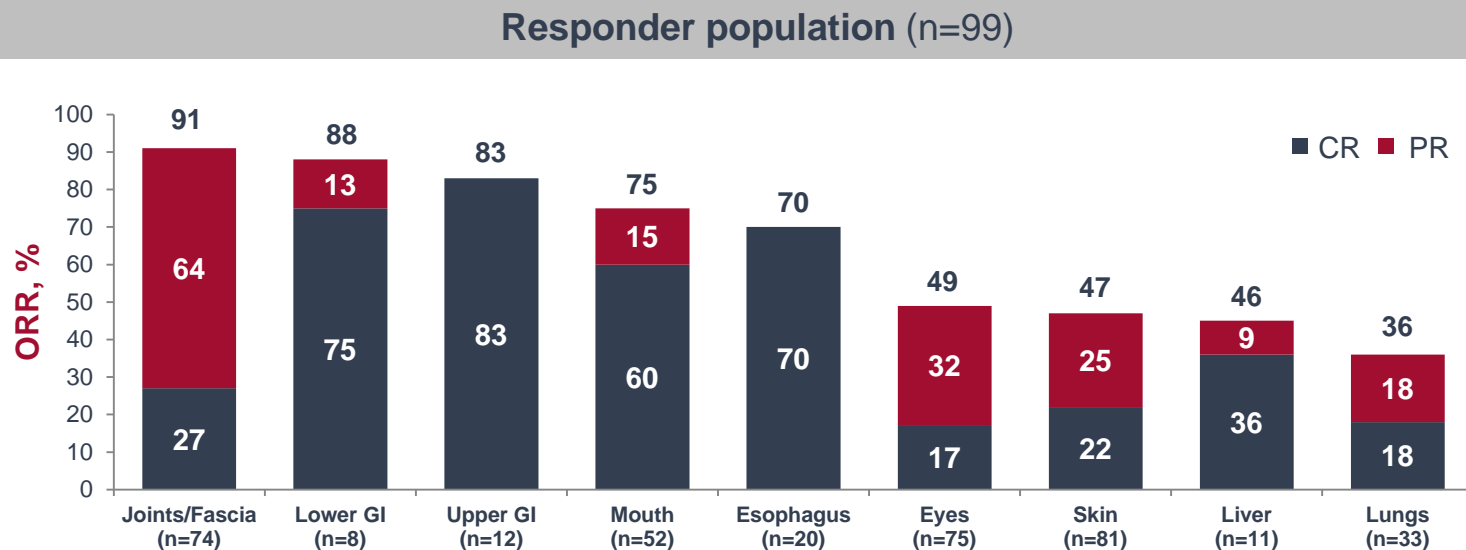
^bIndicates stratification factors.

Response assessments performed on or after the initiation of a new systemic therapy for cGVHD were excluded from the analysis.

Pooled responses across arms, unless stated.

The ROCKstar Study: Responses Observed Across All Organ Systems

CRs observed in all organs

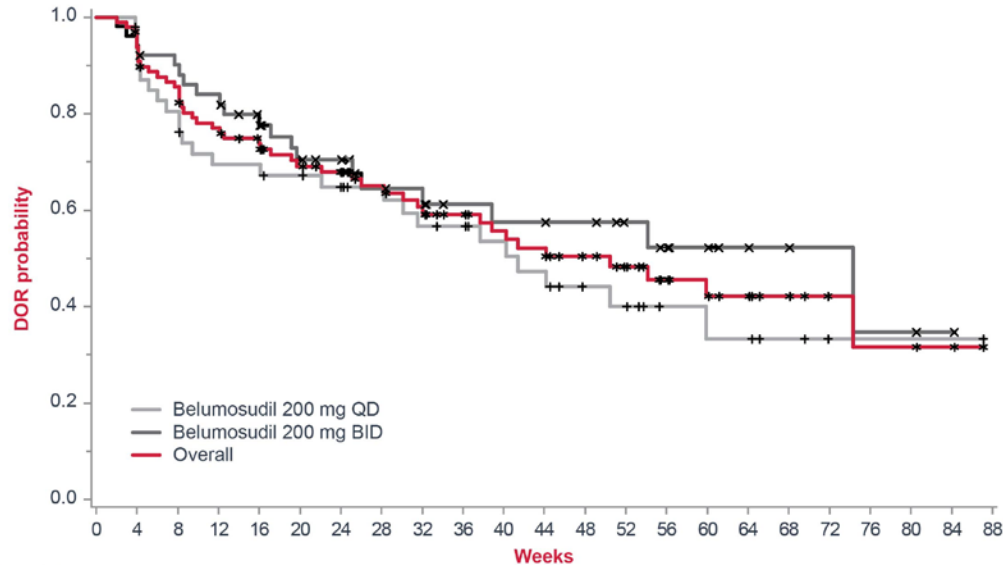


GI, gastrointestinal; PR, partial response.



The ROCKstar Study: DOR

Kaplan-Meier plot of DOR



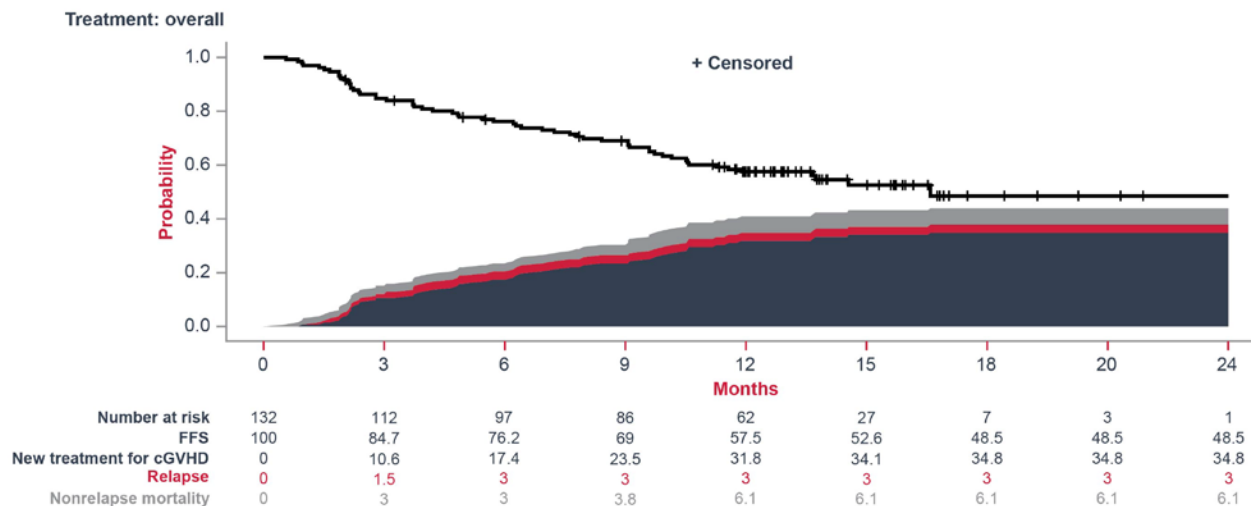
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	
Number at risk																								
Belumosudil 200 mg QD	48	43	37	31	31	29	26	24	21	20	17	15	11	10	6	5	5	3	1	1	1	1	0	
Belumosudil 200 mg BID	51	48	44	41	35	30	28	21	19	16	15	15	14	11	9	7	5	4	3	2	2	1	0	
Overall	99	91	81	72	66	59	54	45	40	36	32	30	25	21	15	12	10	7	4	3	3	2	0	

Overall, 44% of patients have remained on belumosudil therapy for >1 years.

The median DOR was **50 weeks**, and 60% of responders maintained responses for ≥ 20 weeks.

The ROCKstar Study: FFS

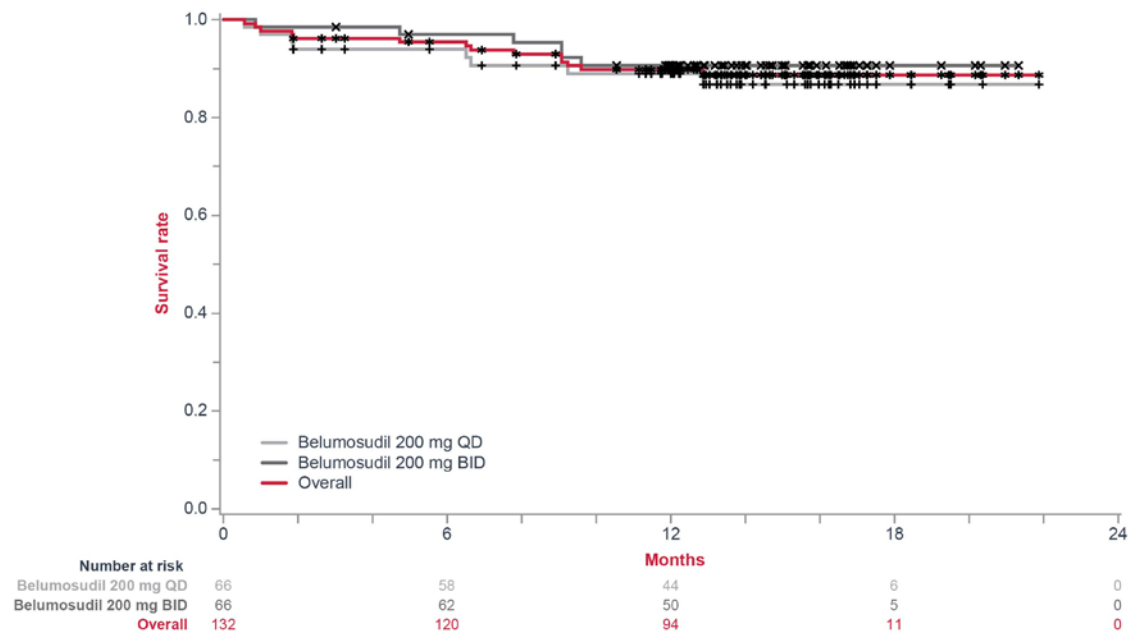
Kaplan-Meier plot of FFS



An FFS rate of **58%** was maintained at 12 months.

The ROCKstar Study: OS

Kaplan-Meier plot of OS



The OS rate
at **24 months**
was 89%
(95% CI, 82%-93%).

The ROCKstar Study: Additional End Points

- Overall, 64% of patients were able to reduce their **CS dose**, and 21% discontinued **CS therapy**
 - The mean CS dose was reduced by 44%; 52% in responders and 17% in nonresponders
- Overall, 45% of patients were able to reduce their **CNI dose**, and 22% discontinued **CNI therapy**
- Overall, clinically meaningful improvement in **LSS score** from baseline was observed in 60% of patients
 - Both responders and nonresponders achieved clinically meaningful improvements in LSS

CNI, calcineurin inhibitor; CS, corticosteroid.



The ROCKstar Study: Conclusions

Belumosudil was well tolerated and achieved clinically meaningful outcomes

- ORR of >70% across QD and BID treatment arms
 - Responses observed across all key subgroups
 - Responses observed in all affected organ systems, including in organs with fibrotic disease
- Additional end point data, including PK and PD data, are expected in 2021

PD, pharmacodynamics; PK, pharmacokinetics.



Acknowledgements

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- Partner CROs

