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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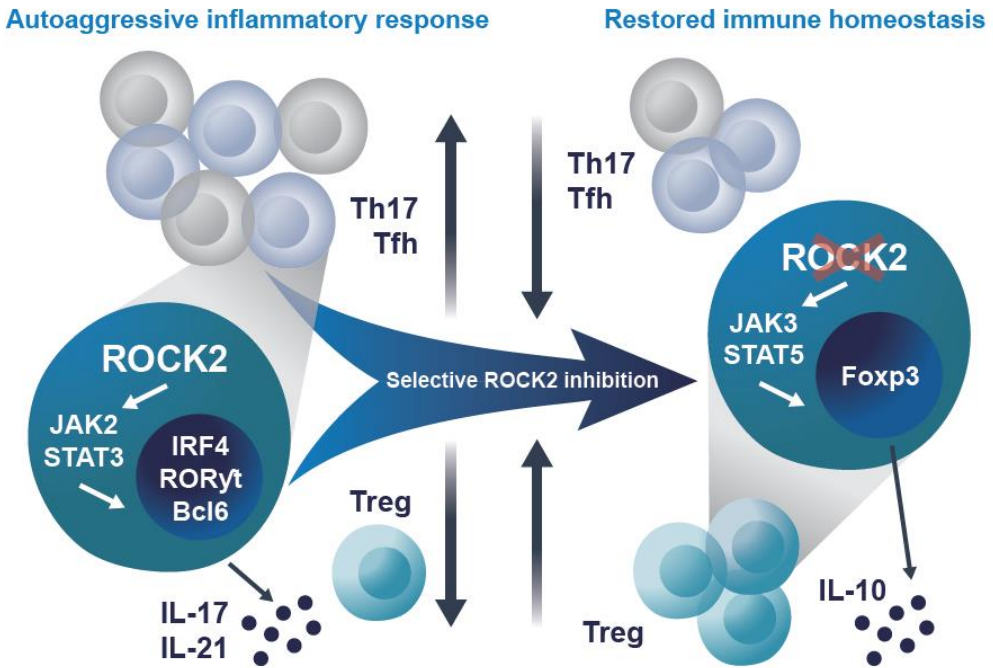
ROCK2 Plays a Key Role in Immune Diseases



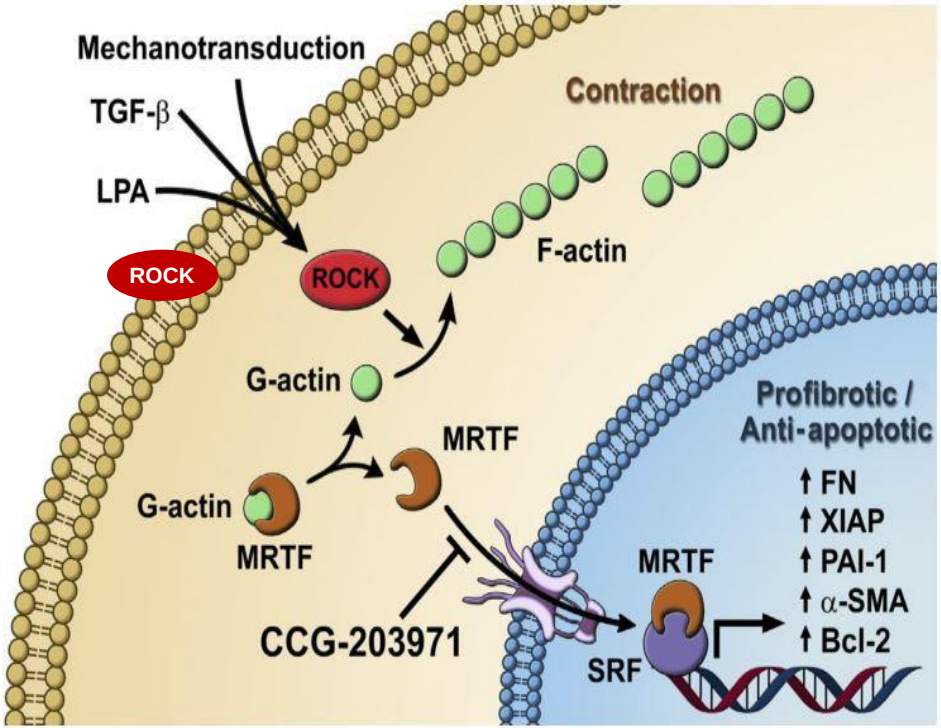
ROCK2 inhibition rebalances immune response to treat immune dysfunction

- 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, retineic-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

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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

ROCKstar: Pivotal Trial of Belumosudil (KD025) in cGVHD

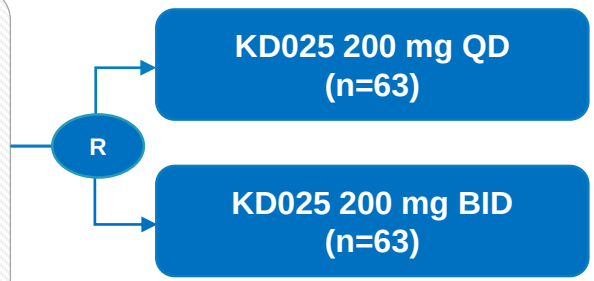
ROCKstar (KD025-213): A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects With cGVHD After At Least 2 Prior Lines of Systemic Therapy

Key Eligibility Criteria

- 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)



Treat to clinically significant progression

Primary Endpoints:

- ORR, per 2014 NIH criteria

Key Secondary Endpoints:

- Safety
- Duration of response
- Lee Symptom Score (QoL measurement)
- Changes in corticosteroid and calcineurin dose
- FFS
- OS

ROCKstar: Advanced, Heavily Pretreated Patient Population

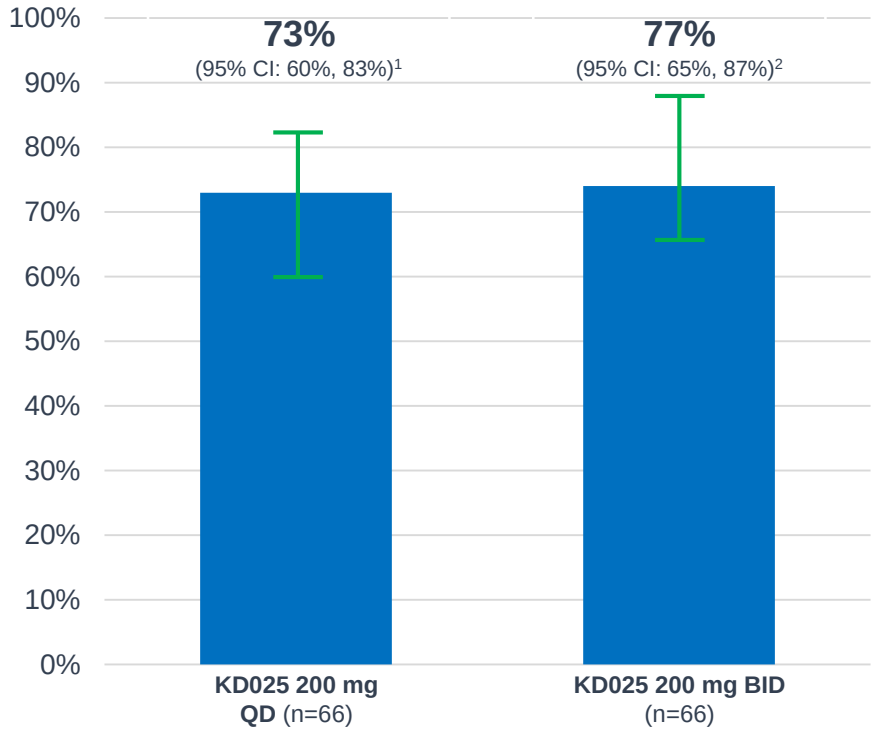
Demographics and Baseline Characteristics

Demographics	KD025 200 mg QD (n=66)	KD025 200 mg BID (n=66)
Median age [years (range)]	53 (21-77)	57 (21-77)
Male (%)	64	50
Median prior lines of therapy	3	4
Median time from cGVHD diagnosis to enrollment (months)	25	30
NIH Severe cGVHD[1] [n (%)]	46 (70%)	43 (65%)
Median prednisone dose (mg/kg/day)	0.2	0.2
≥4 Organs involved [n (%)]	33 (50%)	35 (53%)
Prior ibrutinib treatment[1]	22 (33%)	23 (35%)
Prior ruxolitinib treatment	20 (30%)	18 (27%)
Refractory to line prior to enrollment, excluding unknown / missing	79% (44/56)	65% (35/54)

[1]*Stratification factor*

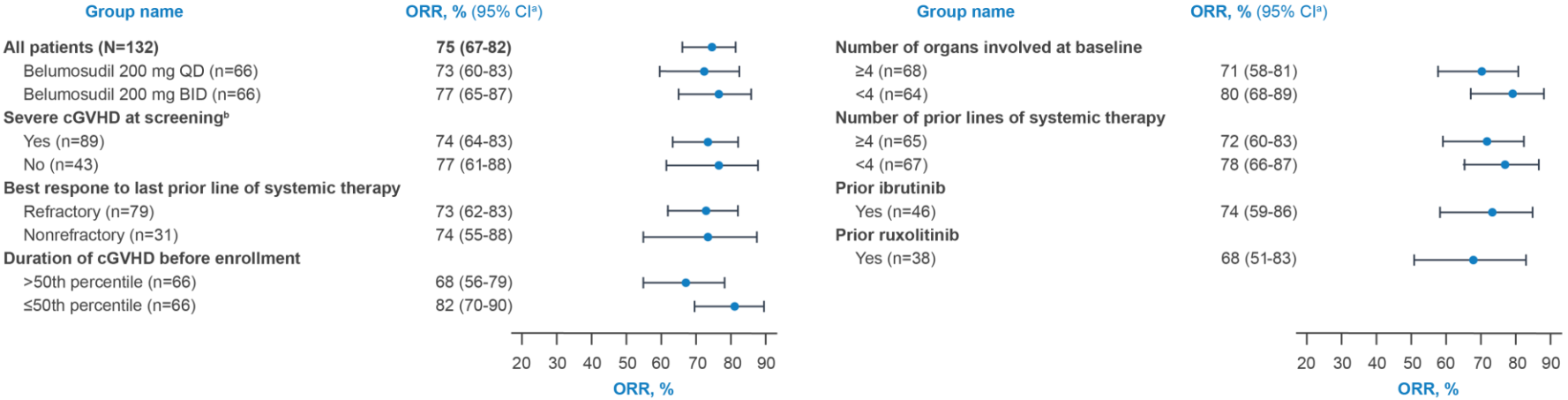
ROCKstar Met Primary Endpoint

- **Belumosudil achieved clinically meaningful and statistically significant ORRs in both arms**
- **Complete Responses (CRs) observed in all affected organ systems**
- **Seven patients have achieved an overall CR**



[1]p<0.0001; [2]p<0.0001

The ROCKstar Study: Responses Observed Across All Key Subgroups

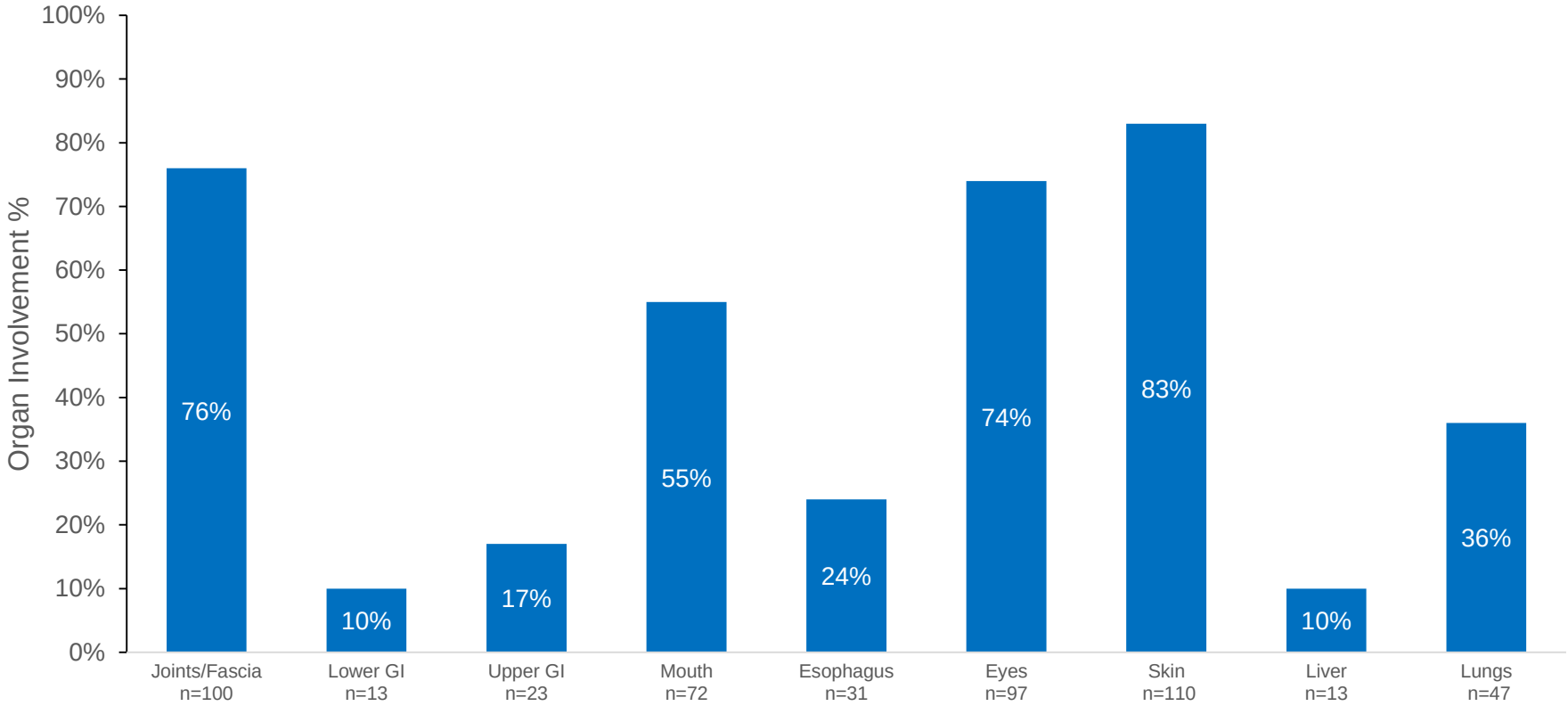


[a] CI is calculated using the Clopper-Pearson interval (exact) method.
[b] Indicates stratification factors.

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

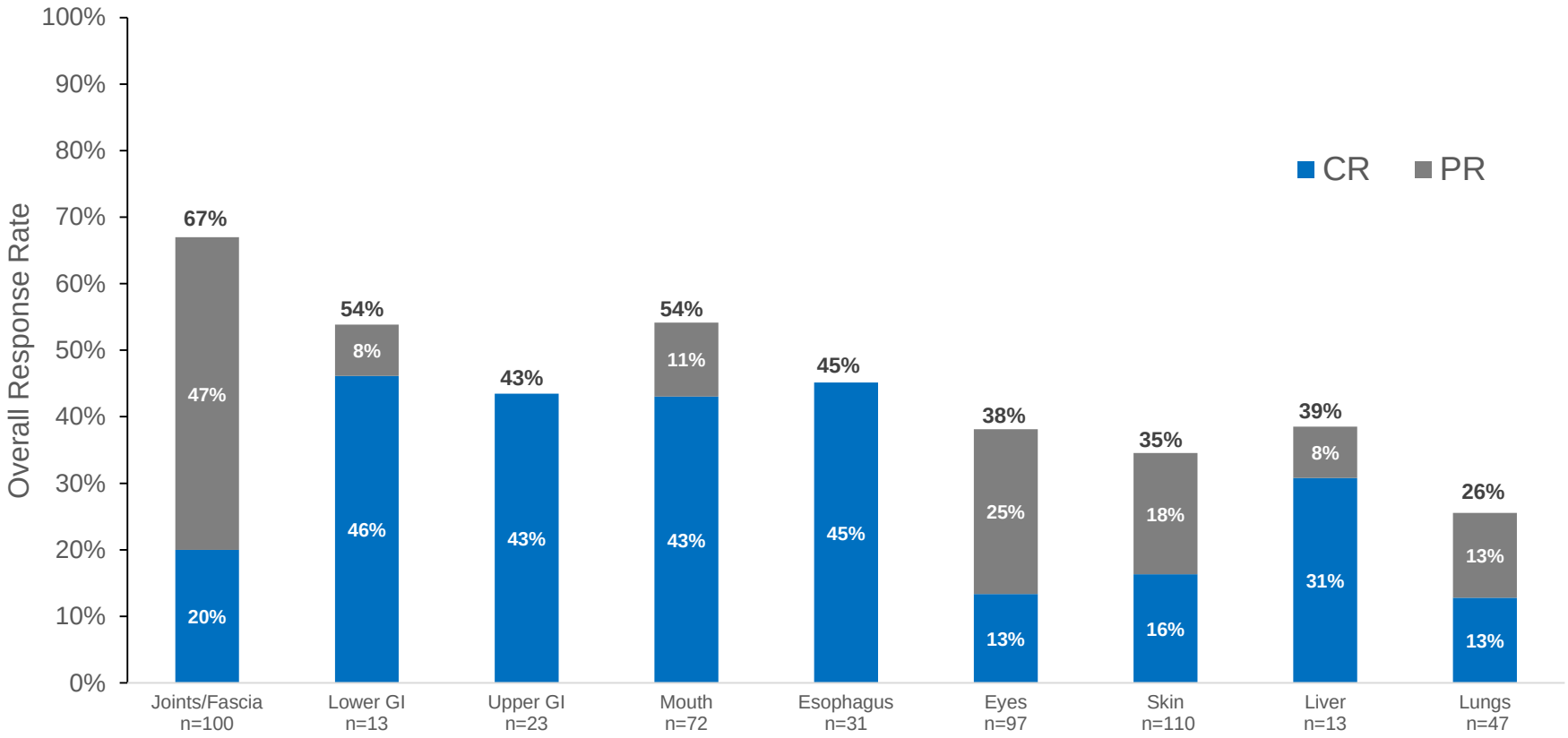
Pooled responses across arms, unless stated.

ROCKstar: Organ Involvement at Baseline



Pooled involvement across arms

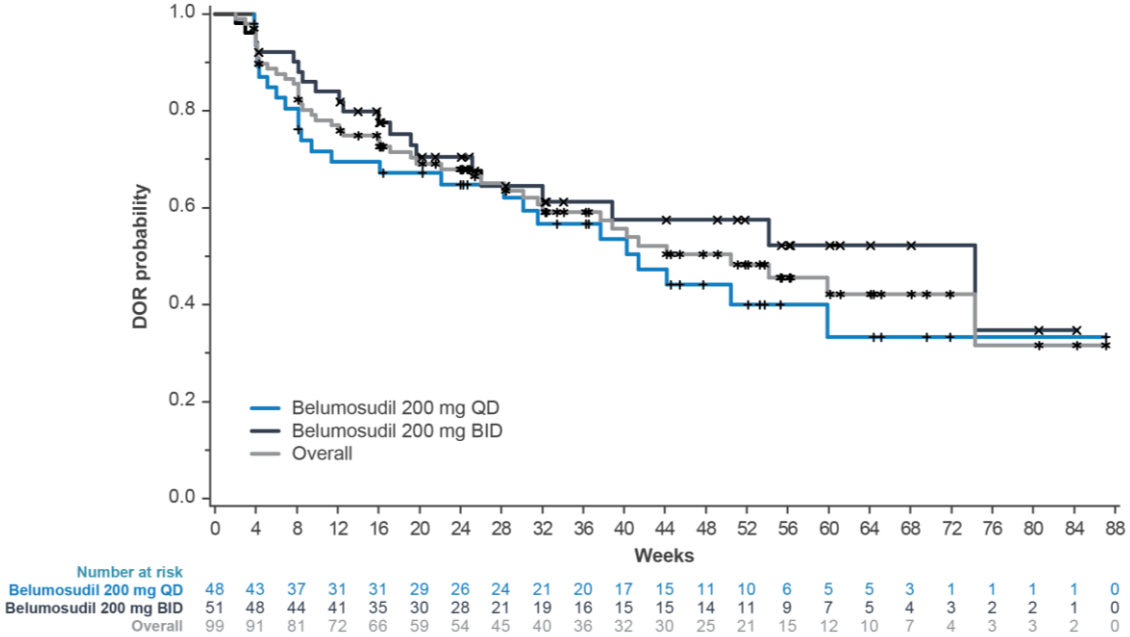
ROCKstar: Complete Responses Observed in All Organ Systems



Pooled responses across arms

The ROCKstar Study: DOR

Kaplan-Meier plot of DOR



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.

ROCKstar: CS, CNI Dose Reductions and QoL Improvements

CS and CNI Dose Reductions

- 21% of patients have completely discontinued CS
- 64% achieved corticosteroid dose reductions
  - Observed in responders and non-responders
- 45% of patients were able to reduce their CNI dose, and 22% discontinued CNI therapy

Quality of Life (QoL) Improvements as Measured by Lee cGVHD Symptom Scale (LSS) Score

- 60% of patients experienced clinically meaningful improvement (≥7 point reduction) in LSS score
- LSS improvements observed in responders and non-responders

CNI, calcineurin inhibitor; CS, corticosteroid.

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

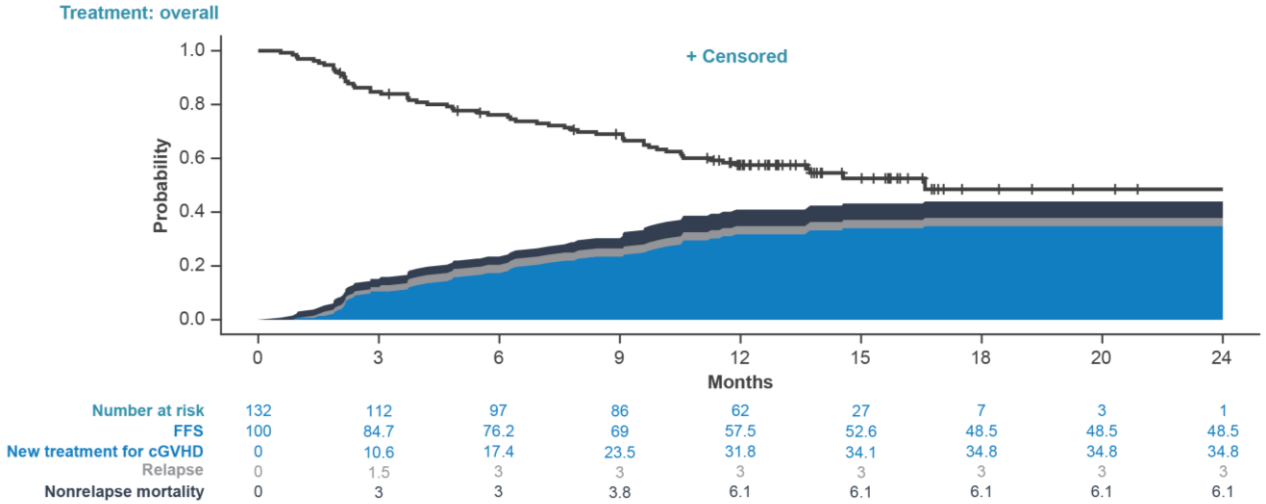
Safety overview	Belumosudil 200 mg QD (n=66)	Belumosudil 200 mg BID (n=66)	Overall (N=132)
Median duration of treatment, mo	9.4	11.8	10.4
Any AE, n (%)	65 (99)	66 (100)	131 (99)
Grade ≥3 AE, n (%)	37 (56)	34 (52)	71 (54)
SAE, n (%)	27 (41)	23 (35)	50 (38)
Drug-related AE, n (%)			
Any related AE	49 (74)	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.

ROCKstar: Failure Free Survival

Kaplan-Meier plot of FFS



Number at risk	132	112	97	86	62	27	7	3	1
FFS	100	84.7	76.2	69	57.5	52.6	48.5	48.5	48.5
New treatment for cGVHD	0	10.6	17.4	23.5	31.8	34.1	34.8	34.8	34.8
Relapse	0	1.5	3	3	3	3	3	3	3
Nonrelapse mortality	0	3	3	3.8	6.1	6.1	6.1	6.1	6.1

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

The ROCKstar Study: Conclusions

- **Belumosudil was well tolerated and achieved clinically meaningful outcomes**
- **75% ORR 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
- **50-week median duration of response**
- **Well tolerated**

Acknowledgements

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Thanks!

EBMT