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Belumosudil achieves clinical response in chronic graft-*versus*-host disease with varying organ-specific response kinetics: an analysis from the phase II ROCKstar trial

Alaa Ali[1], Lauren Rota[2], Kathy Marshall[2], Yu Yao[3], Ran Ji[2], Zachariah DeFilipp[4]

[1]Department of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center and Research Institute, Tampa, FL, USA

[2]Sanofi, Morristown, NJ, USA

[3]Sanofi, Cambridge, MA, USA

[4]Hematopoietic Cell Transplant and Cellular Therapy Program, Mass General Brigham Cancer Institute, Boston, MA, USA

Corresponding author: Zachariah DeFilipp - zdefilipp@mgh.harvard.edu

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AA has participated in advisory boards and has been a consultant for Kite Pharma. LR, KM, YY, and RJ are employees of Sanofi and may hold shares and/or stock options in the company. ZD has received research support from Incyte Corporation, Kura Oncology, Inc, REGiMMUNE, and Taiho Oncology, Inc, and consulting fees from Forte Biosciences, Inc, Incyte Corporation, Inhibrx, MaaT Pharma, Medexus Pharmaceuticals, Inc, Mesoblast Ltd, REGiMMUNE, and Sanofi.

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Contributions

AA and ZD conceived and designed the study, analyzed and interpreted data, drafted and reviewed the manuscript and approved its final version. LR, KM, YY and RJ analyzed and interpreted data, reviewed the manuscript and approved its final version.

Data sharing

Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org.

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To the Editor,

Chronic graft-versus-host disease (cGVHD), an autoimmune-like alloimmune disease that follows allogeneic hematopoietic-cell transplantation, presents with heterogeneous organ involvement and variable clinical manifestations, ranging from inflammatory syndromes to progressive fibrosis across multiple tissues.[1] cGVHD pathophysiology is commonly viewed as a sequence of early tissue injury, followed by dysregulated immune responses, and ultimately fibrotic repair.[1,2] Belumosudil is an oral selective inhibitor of Rho-associated coiled-coil containing protein kinase 2 (ROCK2) that is approved in several countries, including the United States, United Kingdom and Canada for the treatment of cGVHD after failure of ≥2 lines of previous therapy, based on the results of the randomized phase II ROCKstar trial (ClinicalTrials.gov Identifier: NCT03640481).[3] The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines, with institutional review board approval; all patients provided informed written consent. In this trial, belumosudil was associated with high overall response rates (200 mg once-daily [QD] cohort: 74%; 200 mg twice-daily [BID] cohort: 77%), with responses observed in all organ manifestations and an overall median time to response (TTR) of 5 weeks (range, 4-66).[4] However, data regarding the timing of improvement in individual organs and patterns of early *vs.* late responses have not been explored. In this secondary analysis of ROCKstar, we aimed to describe organ-specific response kinetics by evaluating TTR and patterns of organ-specific improvement over the first year of belumosudil therapy in participants with long-term follow-up. Our goal was to refine clinical expectations for belumosudil in cGVHD and support organ-specific management approaches.

ROCKstar enrolled recipients of allogeneic hematopoietic stem cell transplant aged ≥12 years with persistent cGVHD manifestations after receiving 2 to 5 prior lines of systemic therapy. Participants were randomized to receive belumosudil 200 mg QD or BID. For the current analysis, the study population was limited to clinical responders, defined as participants who achieved a complete or partial response in ROCKstar, assessed by the 2014 National Institutes of Health (NIH) consensus response criteria for cGVHD.[5] Treatment was given in 28-day cycles and responses assessed on Day 1 of Cycles 2–5 and on Day 1 of every other Cycle thereafter. TTR was defined as the time from treatment initiation to the first documented partial or complete response. Late responses were defined as those occurring beyond 24 weeks of treatment. Organ-level response was evaluated only in participants with involvement of that organ at baseline. Cumulative response rates were evaluated at 12, 24 and 48 weeks to characterize organ-specific kinetics over the first year of treatment. Response assessments performed after initiation of new systemic therapy were excluded. Participants who initiated new systemic therapy prior to achieving a response were truncated at that time point.

This analysis includes 20 participants enrolled in a biomarker cohort[6] after the August 19, 2020, ROCKstar data cutoff (N=152); 114 (75%) were identified as responders. The median age was 55 years (range, 18-77 years). Baseline cGVHD severity was mild in 0.9%, moderate in 29.8%, and severe in 69.3% of responders. The median number of organs involved was 4 (range, 1-7) (**Table 1**). Participants had received a median of 3 prior systemic therapies, and 59.6% were refractory to their most recent line of treatment. Organ involvement at baseline was as follows: skin (n=95, 83.3%); joints/fascia (n=86, 75.4%); eyes (n=85, 74.6%); mouth (n=68, 59.6%); lungs (n=37, 32.5%); esophagus

(n=26, 22.8%); upper gastrointestinal (GI) tract (n=14, 12.3%); liver (n=12, 10.5%); and lower GI tract (n=10, 8.8%) (**Table 1**). Median follow-up was 30.4 months (range, 2.6-40.5 months). Baseline organ severity/function scores are summarized in **Table 1**.

Overall, responses to belumosudil occurred early in most participants included in the responder population (n=114). The median overall responder TTR was 4.4 weeks (range, 3.7-80.1 weeks), and 65.8% of participants achieved a response by week 8, increasing to 86.8% by week 12 and 94.7% by week 24 (**Supplementary Figure 1**). Only 5.3% of responses occurred after week 24. Importantly, organ systems exhibited different response trajectories. The shortest median TTR was observed in the lower GI tract at 4.1 weeks (**Figure 1**). In general, TTR in lung, mouth, and skin was longer compared to other organs and this trend was observed in the overall population, and in the 200 mg QD and 200 mg BID cohorts (**Figure 1**; **Supplementary Figure 2**). Organs with the most rapid responses were lower GI (80% at 12 weeks), upper GI (78.6% at 12 weeks), and joints/fascia (74.4% at 12 weeks); in these organs, late responses were rare or absent. In contrast, only 10.8% of participants with lung cGVHD achieved a response by week 12, with cumulative responses increasing to 21.6% by week 24 and 40.5% by week 48 or later; nearly half of all lung responses (46.7%) occurred after week 24. Ocular involvement showed a similar delayed-response pattern; although 35.3% of participants responded by week 12, nearly one-third of all ocular responses (29.8%) were first documented after week 24. The mouth and skin exhibited intermediate response kinetics. Mouth involvement showed a moderately delayed pattern, with 45.6% of participants responding by week 12 and 69.1% by week 24. Skin involvement improved more slowly, with 29.5% responding by week 12 and 40.0% by week 24 (**Figure 2**). When stratified by

dose (200 mg QD cohort and the 200 mg BID cohort) cumulative response rate patterns were similar (**Supplementary Figure 3**).

These findings from clinical responders in ROCKstar highlight organ-specific response kinetics to belumosudil therapy for cGVHD and underscore the need for organ-tailored response expectations. Patients with lung and ocular involvement experience low rates of early response, with a more substantial proportion experiencing improvement later in the treatment course. As a result, early fixed timepoint assessments may be insufficient for these organs, and response evaluation may need to be delayed in patients with stable disease or improvement in other organ systems before considering alternative therapies. Non-systemic treatment for ocular and oral cGVHD was allowed and collected in the ROCKstar trial, and may have contributed to observed responses in these organs. Across trials and supported by recent meta-analytic data,[7] lung and ocular cGVHD consistently demonstrate lower response rates at fixed early timepoints;[7,8] however, higher best response rates observed with some agents (including belumosudil[8]) suggest delayed response kinetics in these organs rather than true treatment refractoriness. As the number of available treatment options for cGVHD continues to expand, further study of organ-specific response kinetics may help inform more individualized, organ-directed therapeutic strategies. The results of this analysis also reinforce the broader concept that, in a dynamic and multiphase disease such as cGVHD, clinical trials of novel therapies should move beyond early fixed timepoint or binary response assessments toward longitudinal and composite endpoints (including organ specific).[7,9]

Whether the delayed responses observed in certain organs reflect pharmacokinetic factors that limit drug distribution or underlying biological mechanisms remains unclear. It is plausible that organs in which fibrotic remodeling predominates may require a longer duration of treatment before meaningful improvement becomes detectable.[10,11] The late lung and ocular responses we observed illustrate why fixed early timepoints in clinical trials may underrepresent treatment benefit in selected organs. Delayed responses were only observed in participants who remained on treatment with sufficient follow-up; participants who discontinued, relapsed, or were lost to follow-up before a late response could occur are not represented in these estimates. ROCK2 signaling plays a central role in multiple fibrotic pathways.[12] In contrast, earlier responses to ROCK2 inhibition in other organs may reflect more immediate effects on inflammatory pathways, including downregulation of interleukin 17/21–driven inflammation and rapid rebalancing of effector and regulatory T-cell programs.[13,14]

This analysis has several strengths, including the use of systematically collected organ-level data from a multicenter registration trial and the application of standardized 2014 NIH response criteria. However, it is limited by its post hoc design and by the inclusion of responders only. In addition, responses were not stratified by baseline disease severity or by the number of organs involved, factors known to influence treatment outcomes; for example, pulmonary responses are typically more frequent in patients with lower baseline lung severity. Furthermore, NIH response criteria may underestimate clinically meaningful improvement compared with patient-reported outcomes or symptom-based instruments, such as the Lee Symptom Scale, particularly in fibrotic skin involvement.[15] This limitation may help explain why skin demonstrates notable late responses without exhibiting the

more pronounced delayed-response phenotype observed in the lungs and eyes. The analysis did not evaluate the evolution of initial responses (e.g., partial response to complete response) or treatment failures. The evolution of response has previously been reported, and these additional data complement the primary ROCKstar publication.[4] Generalizability may be limited for some organs due to small patient numbers (e.g., lower GI, upper GI, and liver). Despite these limitations, our findings provide clinically relevant insights that complement the original trial results and offer practical guidance for setting organ-specific treatment expectations. Belumosudil achieved clinical response across all involved organs in cGVHD, with varying organ-specific response kinetics. These data from clinical responders in ROCKstar underscore the importance of managing clinical expectations and tailoring treatment duration based on organ-specific response dynamics.

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Table 1. Baseline characteristics (mITT responder population).

Characteristic	200 mg QD (n=57)	200 mg BID (n=57)	Overall N=114
Age, median (range), years	52 (21-77)	57 (17-77)	55 (18-77)
Male, n (%)	37 (64.9)	27 (47.4)	64 (56.1)
Race, n (%)			
White	46 (80.7)	50 (87.7)	96 (84.2)
Black or African American	7 (12.3)	0	7 (6.1)
Asian	1 (1.8)	2 (3.5)	3 (2.6)
American Indian or Alaska Native	0	2 (3.5)	2 (1.8)
Unknown	3 (5.3)	3 (5.3)	6 (5.3)
Ethnicity, n (%)			
Not Hispanic or Latino	51 (90.5)	44 (77.2)	95 (83.3)
Hispanic or Latino	6 (10.5)	11 (19.3)	17 (14.9)
Not reported	0	1 (1.8)	1 (0.9)
Unknown	0	1 (1.8)	1 (0.9)
Karnofsky performance status, n (%)			
60	0	2 (3.5)	2 (1.8)
70	6 (10.5)	11 (19.3)	17 (14.9)
80	32 (56.1)	22 (38.6)	54 (47.4)
90	16 (5.3)	18 (31.6)	34 (29.8)
100	3 (5.3)	4 (7.0)	7 (6.1)
BMI, mean (SD), kg/m^2	27.1 (4.9)	27.1 (6.0)	27.1 (5.4)
Height, mean (SD), cm	172.8 (10.5)	168.1 (11.5)	170.7 (11.1)
Number of previous allogeneic HSCT, n (%)			
1	55 (96.5)	54 (94.7)	109 (95.6)
2	2 (3.5)	3 (5.3)	5 (4.4)
Prior aGVHD, n (%)			
Yes	36 (63.2)	45 (78.9)	81 (71.1)
No	20 (35.1)	12 (21.1)	32 (28.1)
Missing	1 (1.8)	0	1 (0.9)
NIH cGVHD severity at screening, n (%)			
Mild	1 (1.8)	0	1 (0.9)
Moderate	14 (24.6)	20 (35.1)	34 (29.8)
Severe	42 (73.7)	37 (64.9)	79 (69.3)
Number of organs involved, n (%)			
0	0	0	0
1	1 (1.8)	0	1 (0.9)
2	6 (10.5)	13 (22.8)	19 (16.7)
3	20 (35.1)	16 (28.1)	36 (31.6)

≥4	30 (52.6)	28 (49.1)	58 (50.9)
Median (range)	4 (1-7)	3 (2-7)	4 (1-7)
Involvement at baseline, n (%)			
Skin	49 (86.0)	46 (80.7)	95 (83.3)
NIH score			
0	0	0	0
1	6 (12.2)	3 (6.5)	9 (9.5)
2	8 (16.3)	13 (28.3)	21 (22.1)
3	35 (71.4)	30 (65.2)	65 (68.4)
Joints and fascia	45 (78.9)	41 (71.9)	86 (75.4)
NIH score			
0	0	0	0
1	14 (31.1)	17 (41.5)	31 (36.0)
2	24 (53.3)	21 (51.2)	45 (52.3)
3	7 (15.6)	3 (7.3)	10 (11.6)
Eyes	44 (77.2)	41 (71.9)	85 (74.6)
NIH score			
0	0	0	0
1	19 (43.2)	11 (26.8)	30 (35.3)
2	14 (31.8)	15 (36.6)	29 (34.1)
3	11 (25.0)	15 (36.6)	26 (30.6)
Mouth	32 (56.1)	36 (63.2)	68 (59.6)
Total NIH modified OMRS score			
0	0	1 (2.8)	1 (1.5)
1	8 (25.0)	16 (44.4)	24 (35.3)
2	12 (37.5)	6 (16.7)	18 (26.5)
3	6 (18.8)	1 (2.8)	7 (10.3)
4	3 (9.4)	5 (13.9)	8 (11.8)
5	1 (3.1)	2 (5.6)	3 (4.4)
6	1 (3.1)	0	1 (1.5)
7	1 (3.1)	3 (8.3)	4 (5.9)
8	0	0	0
9	0	0	0
10	0	0	0
11	0	2 (5.6)	2 (2.9)
12	0	0	0
Lungs	19 (33.3)	18 (31.6)	37 (32.5)
NIH score			
0	1 (5.3)	1 (5.6)	2 (5.4)
1	11 (57.9)	12 (66.7)	23 (62.2)
2	7 (36.8)	5 (27.8)	12 (32.4)
3	0	0	0

Esophagus	18 (31.6)	8 (14.0)	26 (22.8)
NIH score			
0	0	0	0
1	12 (66.7)	7 (87.5)	19 (73.1)
2	6 (33.3)	0	6 (23.1)
3	0	1 (12.5)	1 (3.8)
Upper GI	9 (15.8)	5 (8.8)	14 (12.3)
NIH score			
0	0	0	0
1	7 (77.8)	3 (60.0)	10 (71.4)
2	1 (11.1)	1 (20.0)	2 (14.3)
3	1 (11.1)	1 (20.0)	2 (14.3)
Liver	9 (15.8)	3 (5.3)	12 (10.5)
ALT			
ALT ≤1 x ULN	3 (33.3)	0	3 (25.0)
ALT >1 x ULN to ≤2 x ULN	3 (33.3)	0	3 (25.0)
ALT >2 x ULN to ≤3 x ULN	3 (33.3)	2 (66.7)	5 (41.7)
ALT >3 x ULN	0	0	0
Lower GI	4 (7.0)	6 (10.5)	10 (8.8)
NIH score			
0	0	0	0
1	3 (75.0)	4 (66.7)	7 (70.0)
2	1 (25.0)	2 (33.3)	3 (30.0
3	0	0	0
Number of prior LOT, n (%)			
1	0	0	0
2	19 (33.3)	12 (21.1)	31 (27.2)
3	13 (22.8)	14 (24.6)	27 (23.7)
4	15 (26)	16 (28.1)	31 (27.2)
5	9 (15.8)	13 (22.8)	22 (19.3)
≥6	1 (1.8)	2 (3.5)	3 (2.6)
Median	3	4	3
Previous treatment with ruxolitinib	19 (33.3)	19 (33.3)	38 (33.3)
Refractory to last systemic therapy prior to enrollment, n (%)	38 (66.7)	30 (52.6)	68 (59.6)

Totals may not sum to 100% due to rounding.

Abbreviations

aGVHD: acute graft-versus-host disease; ALT, alanine transaminase; BMI: body mass index; cGVHD: chronic graft-versus-host disease; GI: gastrointestinal; HSCT:

hematopoietic stem cell transplant; LOT: line of therapy; mITT, modified intention to treat; NIH: National Institutes of Health; OMRS, oral mucosa rating scale; SD: standard deviation; ULN, upper limit of normal.

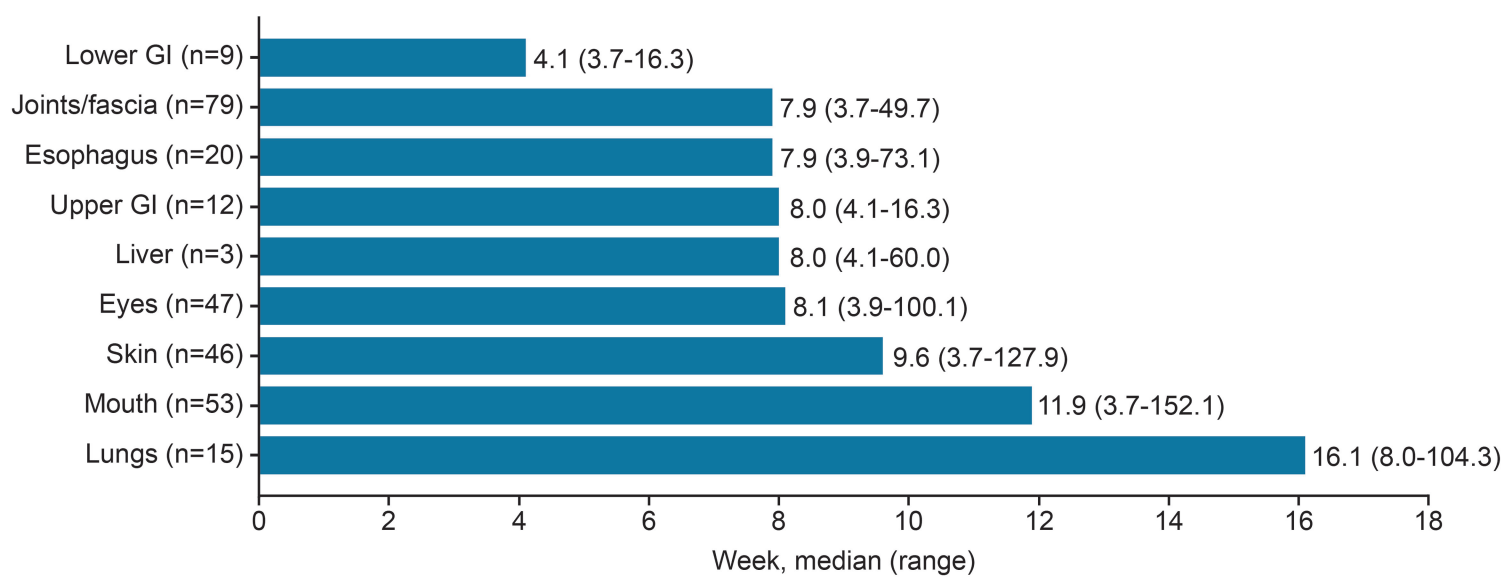
Figure legends

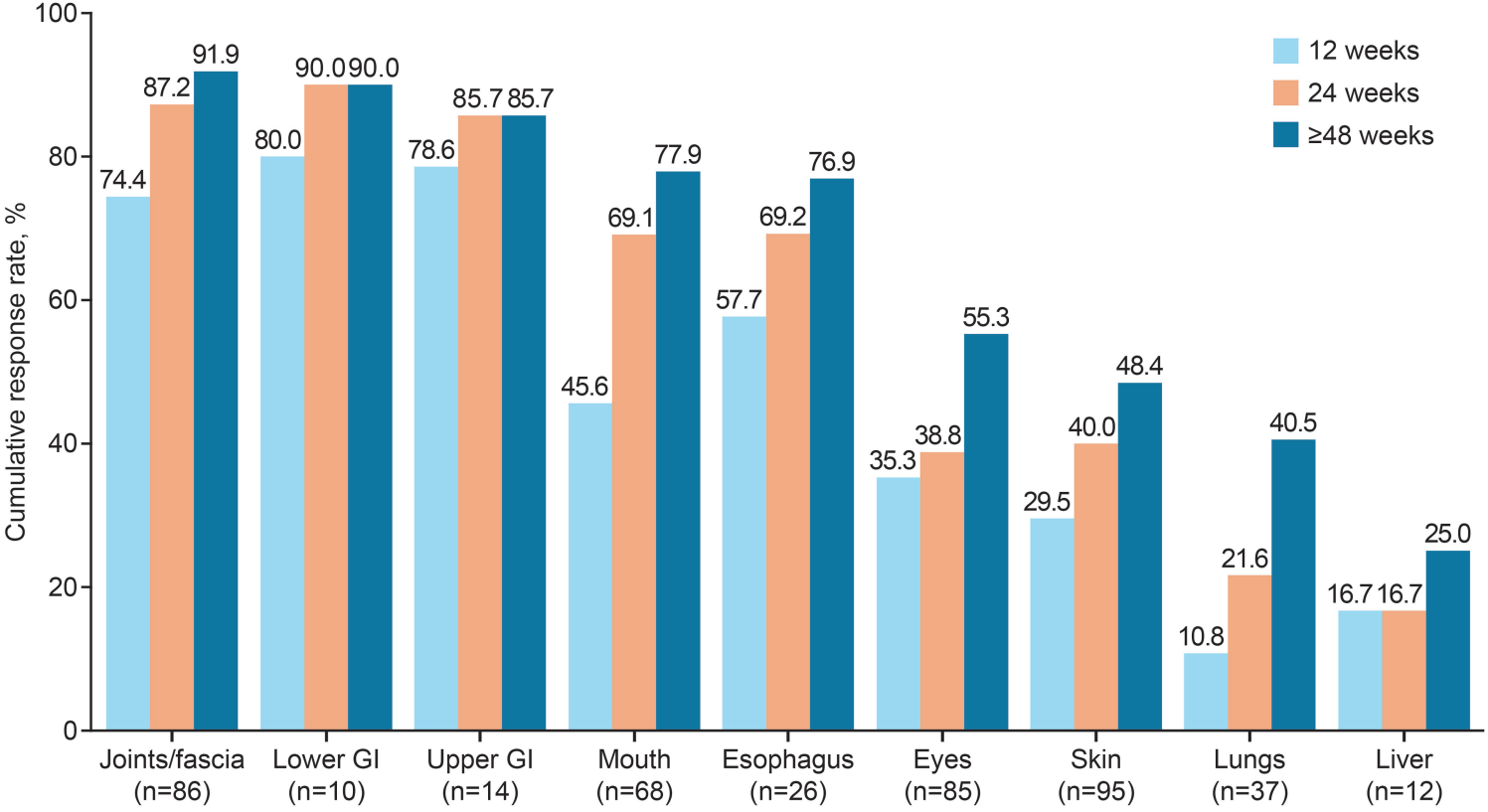
Figure 1. Organ-specific TTR to belumosudil (200 mg QD or BID). GI: gastrointestinal; TTR: time to response.

N numbers refer to organ-specific responders within overall responder population. Median (minimum–maximum) values are shown for TTR.

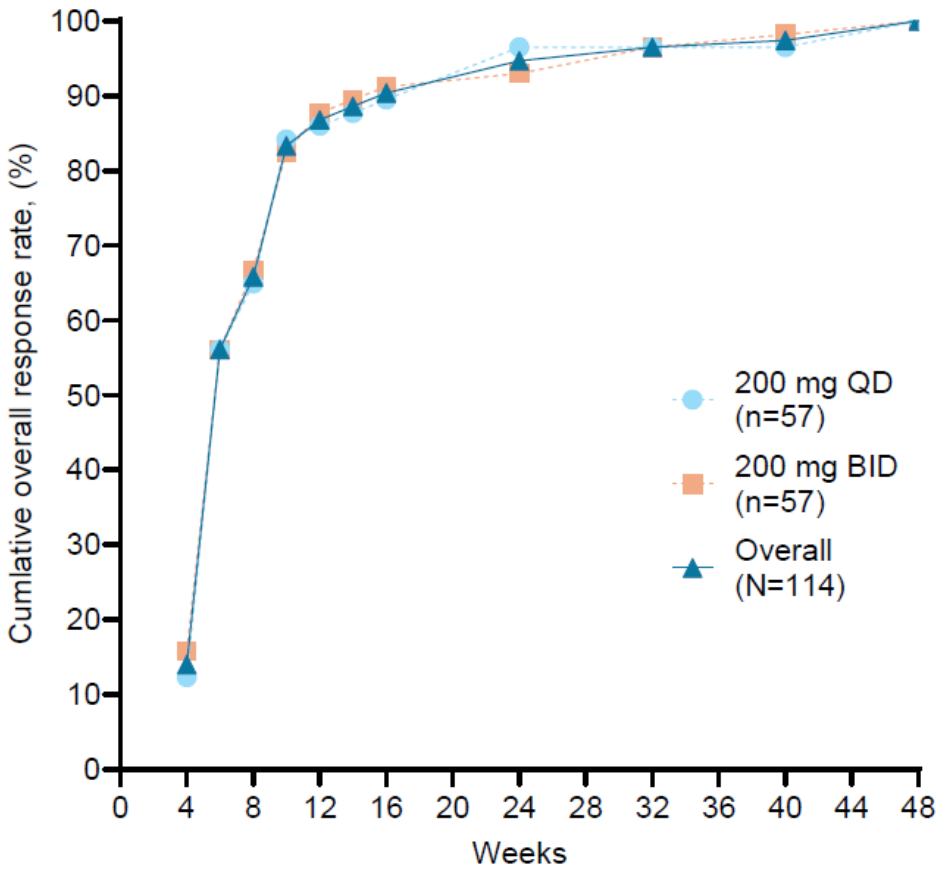
Figure 2. Organ-specific cumulative response rates to belumosudil (200 mg QD or BID). GI: gastrointestinal.

Denominators reflect all participants with baseline involvement of the specified organ. Percentages reflect cumulative response rates calculated using the number of participants with baseline involvement of the specified organ as the denominator. Longer follow-up in this analysis (median 30.4 months) compared with the primary ROCKstar publication (median 14 months) accounts for differences in organ-specific response rates within responder population.[4]

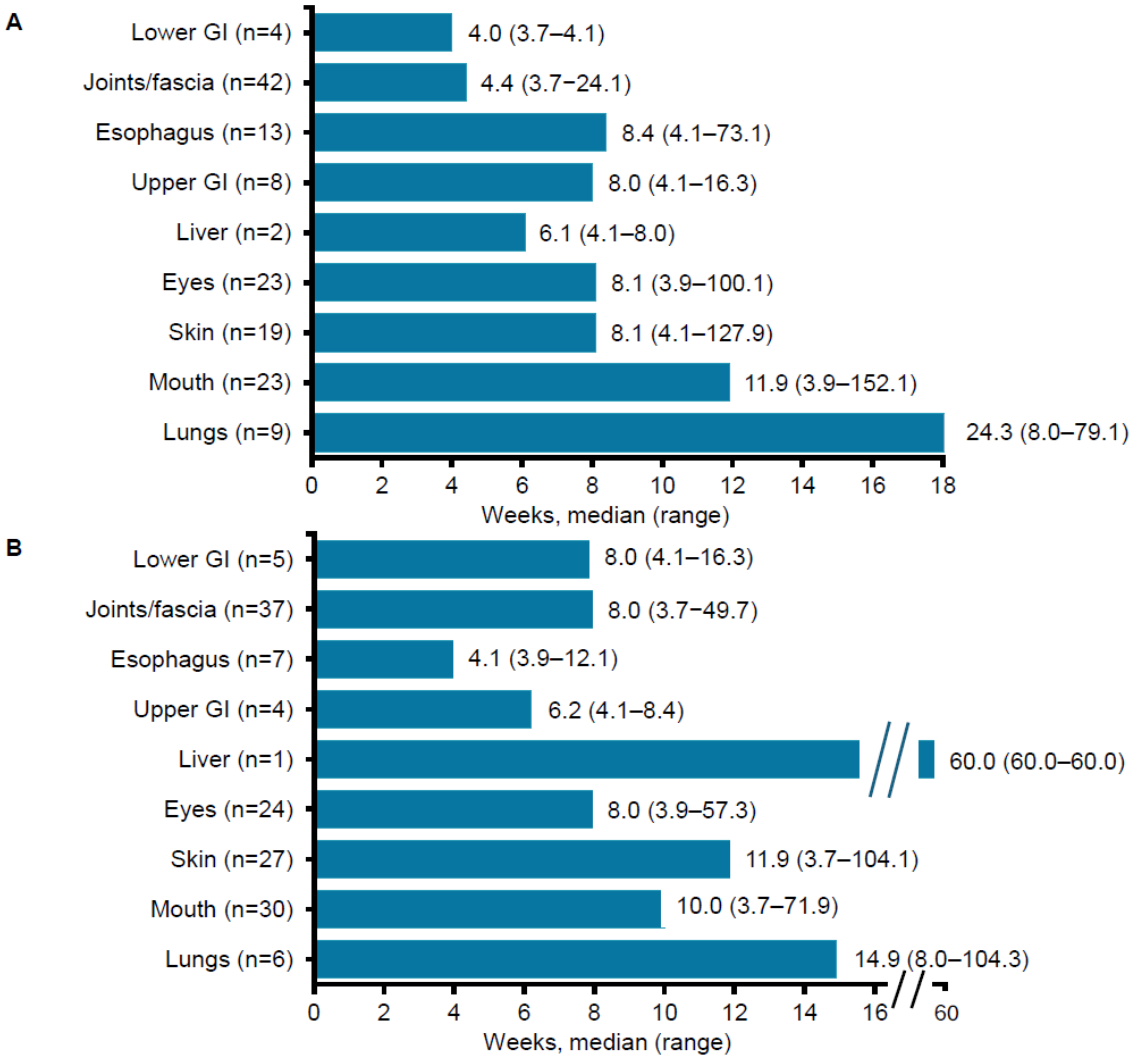

Lower GI (n=9)
4.1 (3.7-16.3)
Joints/fascia (n=79)
7.9 (3.7-49.7)
Esophagus (n=20)
7.9 (3.9-73.1)
Upper GI (n=12)
8.0 (4.1-16.3)
Liver (n=3)
8.0 (4.1-60.0)
Eyes (n=47)
8.1 (3.9-100.1)
Skin (n=46)
9.6 (3.7-127.9)
Mouth (n=53)
11.9 (3.7-152.1)
Lungs (n=15)
16.1 (8.0-104.3)
0
2
4
6
8
10
12
14
16
18
Week, median (range)


12 weeks
24 weeks
≥48 weeks
Cumulative response rate, %
100
80
60
40
20
0
74.4
87.2
91.9
80.0
90.0
90.0
78.6
85.7
85.7
45.6
69.1
77.9
57.7
69.2
76.9
35.3
38.8
55.3
29.5
40.0
48.4
10.8
21.6
40.5
16.7
16.7
25.0
Joints/fascia (n=86)
Lower GI (n=10)
Upper GI (n=14)
Mouth (n=68)
Esophagus (n=26)
Eyes (n=85)
Skin (n=95)
Lungs (n=37)
Liver (n=12)

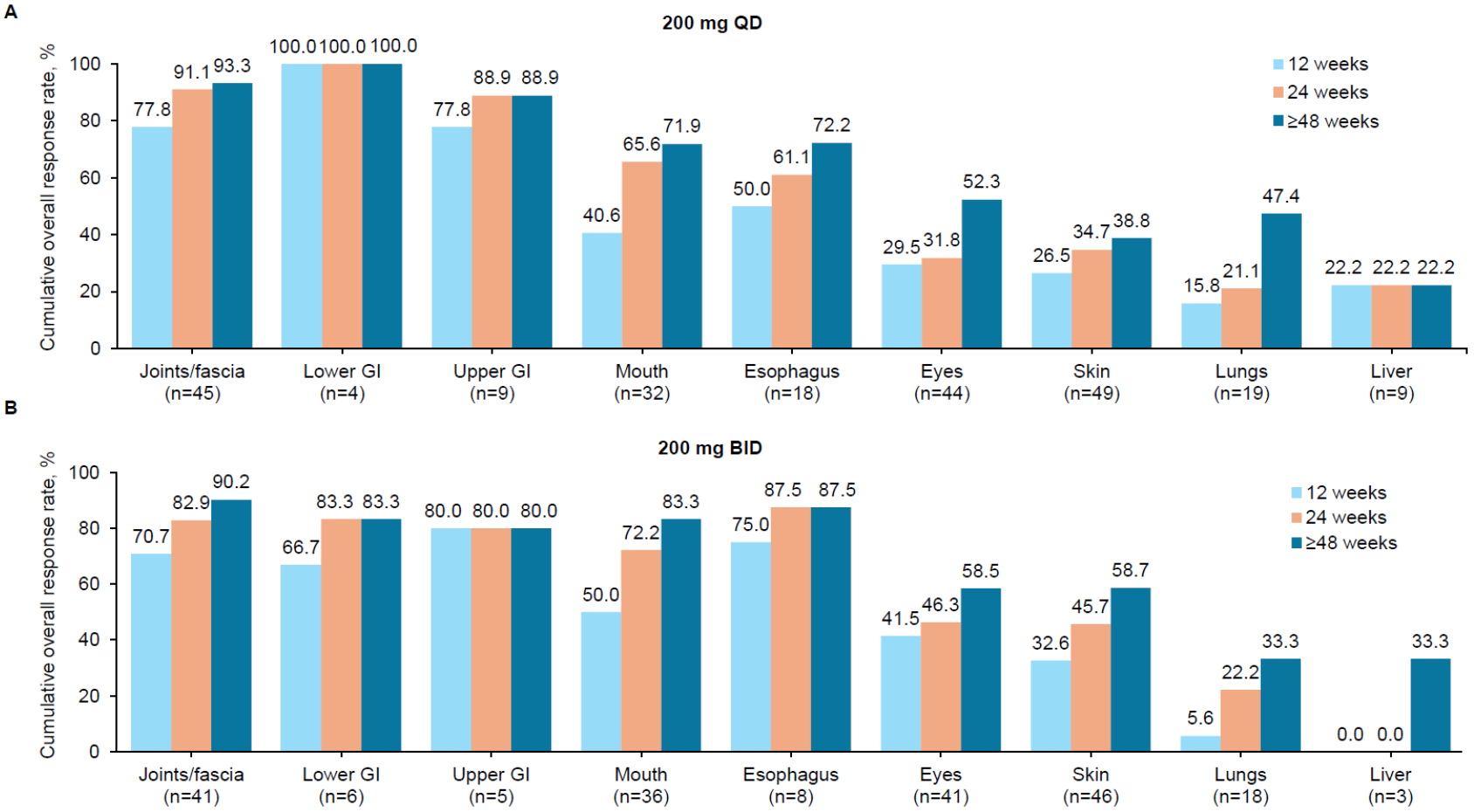
Supplemental materials: Belumosudil achieves clinical response in chronic GVHD with varying organ-specific response kinetics: an analysis from the phase 2 ROCKstar trial



Supplementary Figure 1. Cumulative overall response rate in the responder population.



Supplementary Figure 2. Organ-specific TTR to belumosudil 200 mg QD (A) and 200 mg BID (B). GI: gastrointestinal; TTR: time to response.



Supplementary Figure 3. Organ-specific cumulative response rates to belumosudil 200 mg QD (A) and 200 mg BID (B). BID, twice daily**;** GI: gastrointestinal; QD, once daily.