Real-world outcomes in refractory chronic graft-*versus*-host disease: the Italian multicenter experience with belumosudil

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Abstract

Chronic graft-*versus*-host disease (cGvHD) remains a major late complication of allogeneic hemato-poietic stem cell transplantation, leading to impaired quality of life and late non-relapse mortality. Belumosudil, an oral ROCK2 inhibitor with immunomodulatory and antifibrotic properties, represents a novel treatment for steroid-refractory or steroid-dependent cGvHD. We conducted a retrospective, multicenter study of 80 patients treated with belumosudil across 29 Italian transplant centers through a compassionate use program. Patients were heavily pretreated (74% with ≥3 prior lines, 84% previously exposed to ruxolitinib), with severe disease in 86% and a median of three organs involved. The best overall response rate was 62.5%, while overall response rates were 52.6%, 57.6%, and 55.0% at three, six, and 12 months, respectively. Median time to response was three months, and the 12-month duration of response was 83.4%. Failure-free survival at 12 months was 67.5%. Responses were observed in all involved organs. Patient-reported outcomes assessed through the National Institutes of Health Severity Index Score (0-10 scale) showed meaningful improvements (≥-2 points) in 33%, 36%, and 29% of patients at three, six, and 12 months, respectively. Treatment was well tolerated. These real-world findings confirm the effectiveness of belumosudil in patients with cGvHD refractory to multiple lines of immunosuppressive therapy.

Introduction

Chronic graft-*versus*-host disease (cGvHD) remains the most common and disabling late complication after allogeneic hematopoietic stem cell transplantation (alloHSCT), with an incidence ranging from 30% to 70% depending on patient, donor and transplant characteristics.[1,2] It is the leading cause of late non-relapse mortality (NRM)[3] and morbidity, impairing patients' quality-of-life[4] due to its multi-organ damage.[5]

The first-line treatment of cGvHD is based on systemic corticosteroids,[6] but responses are often suboptimal, and relapse or treatment-dependency is frequent.[7] Approximately half of patients require second- or third-line systemic therapies due to steroid refractoriness or intolerance.[8] In recent years, ruxolitinib has been introduced as a second-line treatment for cGvHD that is refractory/resistant to steroid therapy.[9,10] Despite the excellent response, the 3-year failure-free survival (FFS) is 56.5%, indicating the need for additional effective treatments.[11] Further strategies are, therefore, desirable for treatment of cGvHD. Historically, therapeutic options, such as extracorporeal photopheresis,[12] ibrutinib,[13,14] and other immune-suppressive drugs have shown limited efficacy and negligible impact on fibrotic manifestations, which are often the most debilitating.

Belumosudil is a selective oral Rho-associated coiled-coil kinase 2 (ROCK2) inhibitor that modulates both immune responses and fibrogenesis. By down-regulating STAT3 phosphorylation and promoting STAT5-mediated regulatory T-cell expansion, it restores immune balance by shifting the Th17/Treg axis. In addition, ROCK2 inhibition reduces fibroblast activation and collagen production, contributing to its anti-fibrotic activity.[15,16]

The pivotal phase II ROCKstar trial on the use of belumosudil in patients with steroid-refractory cGvHD beyond the second-line treatment demonstrated an overall response rate (ORR) of 74-77%, with durable responses recorded across all organ systems and a median duration of response of 54 weeks.[17] These results were further supported by other worldwide clinical trials[18-21] and real-world studies[22-26] which confirmed its efficacy and tolerability in more diverse and heavily pretreated populations. An overview of the main studies on belumosudil is provided in Table 1.

Despite its growing clinical use, real-world evidence on belumosudil remains limited in the European setting. Here, we present data from an Italian multicenter cohort of patients with either steroid-refractory or steroid-dependent cGvHD treated with belumosudil within a compassionate use program, aiming to evaluate its clinical activity and tolerability in routine clinical practice.

Methods

Study design and patients

This retrospective, multicenter, observational study included 80 consecutive patients with moderate or severe cGvHD who received belumosudil through the Italian compassionate use program between June 2023 and April 2025 as part of 29 stem cell transplant programs. Eligible patients were required to have a diagnosis of moderate or severe cGvHD according to the 2014 National Institutes of Health (NIH) consensus criteria,[27] and to have failed at least two prior lines of systemic therapy. There was no age restriction. Key exclusion criteria included active relapse of the underlying hematologic malignancy at belumosudil initiation, uncontrolled infection, severe cytopenia (platelet count <50x10^9/L or neutrophil count <1.5x10^9/L), severe renal impairment (eGFR <30 mL/min/1.73 m^2), hepatic cytolysis (AST/ALT >3 x upper limit of normal [ULN]), hyperbilirubinemia (>1.5 x ULN), active hepatitis B, hepatitis C, or HIV infection, onset of cGvHD after donor lymphocyte infusion, and any secondary malignancy other than non-melanoma skin cancer. Corticosteroid and immune-suppressive therapy doses were required to be stable for at least two weeks prior to belumosudil initiation. Women of childbearing potential

Table 1. Summary of prospective clinical trials and retrospective real-world studies evaluating the efficacy and tolerability of belumosudil.

Protocol	N	LOT m	Prior ruxolitinib %	ORR 6 mo (PR+CR) %	BOR %	DOR	TTR	FFS % (mo)	Organ response %	AE (≥G3)/ drug-related (≥G3) %	SAE/ drug-related %
KD025 trial Jagasia (2021)[18] Prospective phase II	54	3	2	-	65	35 w	>75% within 8 w	76 (6) 47 (12)	Skin 30 Eyes 50 Mouth 70 Liver 50 Lung 25 j/f 70 UGI 100 LGI 100 Esoph 75	98 (61)/56 (NA)	43/0
ROCKstar trial Cutler (2021)[17] Prospective phase II	132	3	29	72 (70+2)	76	54 w	5 w	75 (6) 56 (12)	Skin 37 Eyes 42 Mouth 55 Liver 39 Lungs 26 j/f 72 UGI 53 LGI 69 Esoph 45	99 (54)/67(NA)	38/5
Chinese trial Wang (2024)[20] Prospective phase II	30	3	53	-	73	NR	4.3 w	73 (6) 56 (12)	Skin 40 Eyes 27 Lungs 15 j/f 78 Mouth 55 UGI 67 Liver 67 LGI (NA) Esoph 60	96.7 (36.7)/ 63.3 (NA)	36.7/13.3
Japanese trial Inamoto (2024)[19] Prospective phase II	21	1	0	75 (75+0)	85.7	NR	4.1 w	NR estimated 95 (6) 87 (12)	Skin 55 Eyes 20 Mouth 67 Lung 0 j/f 80	85.7 (28.6)/38.1 (4.8)	28.6/4.8
Real-world data											
German-Swiss Heidenreich (2025)[24] Retrospective compassionate use	33	4	97	28 (28+0)	42	6 mo	3 mo	NR 76 (6) 64 (12)	Skin 21 Mouth 33 Eyes 29 GI 67 Liver 0 j/f 25 Lung 23	≥ 9 (27)	-
Canadian Desai (2024)[22] Retrospective compassionate use	37	4	NA	69	-	-	-	71.9 (6)	-	-	-
USA Raju (2024)[25] Retrospective FDA approval	66	-	Most	59.5 (55+4.5)	-	-	-	Median 20 mo 79 (6) 72 (12)	-	No G3 AE observed	-

Continued on following page.

Protocol	N	LOT m	Prior ruxolitinib %	ORR 6 mo (PR+CR) %	BOR %	DOR	TTR	FFS % (mo)	Organ response %	AE (≥G3)/ drug-related (≥G3) %	SAE/ drug-related %
City of Hope Medcal Center Modi (2025)[26] Retrospective FDA approval	45	3	71.1	-	46.7	-	108.5 days	Median 11.2 mo	Skin 14.7 Mouth 23.8 Eyes 33.3 j/f 23.5 Lung 16.7 Liver 40 GI 0	*Infectious AE 42 (27)	-
French Michonneau (2025)[23] Retrospective compassionate use	68	3	95.5	45.6 (35.3+10.3)	57.3	-	-	NR 89.1 (6) 80.4 (12)	Skin 53.7 Gut 50 Liver 72.7 Lung 17.4 Mouth 70.4 Eyes 46.7 j/f 50	N=10 AE	-

AE: adverse event; BOR: best overall response rate; CR: complete response; DOR: duration of response; Esoph: esophagus; FDA: US Food & Drug Administration; FFS: failure-free survival; G: Grade; GI: gastrointestinal tract; j/f: joint and fascia; LGI: lower gastrointestinal tract; LOT: lines of treatment; m: median; mo: months; NA: not available; NR: not reached; ORR: overall response rate; PR: partial response; SAE: serious adverse event; TTR: time to response; UGI: upper gastrointestinal tract; w: weeks.

were required to use effective contraception. Demographic, clinical, and laboratory data were collected retrospectively from medical records. All data were pseudonymized in accordance with local data protection regulations.

Ethics statement

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Boards and Ethics Committees of all participating centers.

Treatment

Belumosudil was administered orally at an initial dose of 200 mg once daily (with the exception of 2 pediatric patients treated with 100 mg due to physician's choice), with escalation to 200 mg twice daily in cases of concomitant proton pump inhibitor (PPI) use, in accordance with the compassionate use protocol. Concomitant immunosuppressive therapy was permitted. Belumosudil was continued until progression of cGvHD, unacceptable toxicity, relapse of the underlying malignancy, patient withdrawal or death, or at the discretion of the treating physician. Adverse events (AE) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Response evaluation, time-to-event endpoints and patient-reported outcomes

Response was assessed by the treating physician at three, six, and 12 months following belumosudil initiation, according to the NIH consensus criteria[28] for cGvHD. Responses were classified as complete response (CR: resolution of all cGvHD manifestations), partial response (PR: improvement in at least one organ without worsening in the others), stable disease (SD: no change in organ involvement), or progressive disease (PD: worsening in any organ or involvement of a new organ).[28] The overall response rate (ORR) was defined as the proportion of evaluable patients achieving CR or PR at specified time points (three, six, or 12 months). Patients who developed PD at a given time point were classified as being in PD at all subsequent time points, irrespective of treatment discontinuation. Best overall response (BOR) was defined as the proportion of patients achieving CR or PR at any time point during follow-up. Time to response was defined as the interval from belumosudil initiation to the first documented response (CR or PR). Duration of response (DOR) was defined as the time from first response (CR or PR) to disease progression or initiation of a new systemic therapy. FFS was defined as the time from belumosudil initiation to the first occurrence of one of the following events: relapse of the underlying disease, death from any cause, progression of cGVHD, start of a new systemic therapy and/or increase of current immunosuppression.[29] Overall survival (OS) was defined as the time from belumosudil initiation to death from any cause. Patient-reported outcomes (PRO) were assessed using the form B of the NIH Severity Index Score (SIS),[28] a validated composite tool that captures patients' subjective perception of symptom burden and functional impact on a numerical scale ranging from 0 (best) to 10 (worst). The SIS was calculated at three, six, and 12 months after belumosudil initiation. Variations in SIS were categorized as follows: improvement (SIS ≤ –2), stability (SIS ±1), and worsening (SIS ≥ +2).

Statistical analysis

Categorical variables were summarized as counts and percentages, continuous variables as medians and ranges.

Comparisons between groups were performed using Fisher's exact test (categorical variables) and Mann-Whitney U or Kruskal-Wallis test (continuous variables). Survival outcomes (OS, FFS, DOR, time to response) were estimated using the Kaplan-Meier method and compared with the log-rank test.30 Two-sided $P<0.05$ was considered statistically significant. All analyses were performed using R (version 4.4.2) in RStudio (version 2025.05.0+496).

Results

Patients' characteristics

Patients' median age at transplantation was 45 years (range: 10-77), including 3 (4%) pediatric patients. Most patients were male (N=46, 58%). Underlying diagnoses included acute myeloid leukemia (AML, 33%), acute lymphoblastic leukemia (ALL, 27%), myelodysplastic syndrome (MDS, 6%), myeloproliferative neoplasm (MPN, 6%), chronic myeloid leukemia (CML, 8%), Hodgkin lymphoma (HL, 10%), non-Hodgkin lymphoma (NHL, 9%), plasma cell dyscrasia (1%). Most patients (59%) underwent transplantation in late disease phase (with early phase defined as either any disease in first complete remission or CML in chronic phase). Peripheral blood was the predominant stem cell source (86%), and the most common donors were matched relatives (39%), followed by matched unrelated donors (29%), HLA-haploidentical family donors (20%), and mismatched unrelated donors (12%). Myeloablative conditioning was administered in 75% of patients. GvHD prophylaxis included serotherapy in 41%, post-transplant cyclophosphamide (PT-Cy) in 30%, and other approaches in 29%. Approximately 73% of patients developed previous acute GvHD (grade I 19%, grade II 55%, grade III 21%, grade IV 5%).

The median time from HSCT to belumosudil treatment was 54.6 months (range: 5-204) and the median time from cGvHD diagnosis to belumosudil initiation was 42.6 months (range: 1-193). The median follow-up time of patients treated with belumosudil was 9.1 months (range: 1-20).

A median of 3.0 (range: 1-11) prior systemic lines of cGvHD therapy were administered before be-lumosudil, with 74% of patients having received ≥3 lines, 98% treated with prednisone, and 84% with ruxolitinib. At the time of belumosudil initiation, 86% of patients had severe cGvHD (as per NIH criteria), with a median of 3 organs involved (range: 1-6). The most frequently affected sites were the skin (69%), lungs (64%), eyes (62%), and mouth (42%). Other organ involvement included joints and fascia (29%), gastrointestinal tract (30%), liver (12%), and genital tract (11%). Detailed infor-mation on organ severity scores is presented in Table 2. At baseline, 66% of patients received belumosudil at 200 mg daily and 31% at 400 mg daily, adjusted according to concomitant PPI use.

Concomitant immune-suppressive/immune-modulating treatment at belumosudil initiation included prednisone

Table 2. Clinical characteristics of the study population.

Patients	N=80
Prior systemic cGvHD therapy, N (%)	
N of lines, mean (range)	3.6 (1-11)
≥3 lines	59 (74)
≥4 lines	38 (48)
≥5 lines	19 (24)
Prednisone	78 (98)
Ruxolitinib	67 (84)
ECP	52 (65)
CNI	31 (39)
Imatinib	19 (24)
MMF	16 (20)
Rituximab	10 (13)
Ibrutinib	7 (9)
Sirolimus	6 (8)
Other	23 (29)
NIH cGvHD severity at belumosudil initiation, N (%)	
Moderate	11 (14)
Severe	69 (86)
Organ involment at belumosudil initiation, N (%)	
N of organs involved, median (range)	3 (1-6)
Skin, yes - BSA, score 3 - sclerotic score, 3	55 (69) - 29 (36) - 24 (30)
Joints, yes - Joints, score 3	23 (29) - 5 (6)
GI general, yes - GI general, score 3	11 (14) - 4 (5)
Eyes, yes - Eyes, score 3	50 (62) - 7 (9)
Mouth, yes - Mouth, score 3	34 (42) - 0
Lungs, yes - Lungs, score 3	51 (64) - 15 (19)
Liver, yes - Liver, score 3	10 (12) - 1 (1)
Genital tract, yes - Genital tract, score 3	9 (11) - 2 (3)
Concomitant systemic cGvHD therapy at belumosudil initiation, N (%)	
Prednisone	47 (59)
Ruxolitinib	27 (34)
ECP	19 (24)
CNI	14 (18)
MMF	4 (5)
Ibrutinib	1 (1)
Sirolimus	1 (1)
Prednisone-equivalent dose at baseline, median, mg/kg/d (range)	0.3 (0.03-2)
Concomitant other therapies at belumosudil initiation, N (%)	
PPI	47 (59)
Azole	40 (50)
Belumosudil dose at baseline, mg, N (%)	
100	2 (3)
200	53 (66)
400	25 (31)
Treatment discontinuation, N (%)	21 (26)
AE	9 (11)
Voluntary withdrawal	2 (3)
Progression of cGvHD	5 (6)
Death of patient	3 (4)
Other	2 (3)
Median time of discontinuation, days (range)	125 (8-455)

AE: adverse event; BSA: body surface area; cGvHD: chronic graft-*versus*-host disease; CNI: calcineurin inhibitor; ECP: extracorporeal photopheresis; GI: gastrointestinal tract; MMF: mycophenolate mofetil; N: number; NIH: National Institutes of Health; PPI: proton pump inhibitor.

(59%), ruxolitinib (34%), extracorporeal photopheresis (24%), calcineurin inhibitors (18%), and mycophenolate mofetil (5%). Median time of treatment with belumosudil was 8.7 months (range: 0.2-20).

Response evaluation

The BOR was 62.5% (PR 61.2%, CR 1.3%). The ORR was 52.6% at three months (PR 51.3%, CR 1.3%), 57.6% at six months (PR 56.1%, CR 1.5%), and 55.0% at 12 months (PR 52.5%, CR 2.5%) (Figure 1). The 12-month DOR was 83.4% (95%CI: 72.8-95.5%) (Figure 2A). The median time to response was three months (95%CI: 2.69-3.09) (Figure 2B). Notably, 2 patients achieved a late response, occurring between 12 and 24 months from treatment initiation; they all had severe cGvHD at treatment initiation with mostly skin sclerotic and moderate-severe joints/fascia involvements. They both achieved organ response in joints/fascia together with a reduction of sclerotic extension.

In a subgroup analysis considering the pre-exposure to ruxolitinib, at three months, we recorded 56.5% ORR in all patients already exposed to ruxolitinib (N=67), 58.5% in those who were treated with ruxolitinib and discontinued it before belumosudil start (N=40), and 38.5% in ruxolitinib naive patients (N=13). At six months, those ORR became 61.8%, 67.7%, and 40.0% respectively.

Organ specific responses are shown in Figure 3. In addition to the stringent NIH criteria reported in Figure 3, clinical improvement evaluation was also recorded for the lung involvement in order to test if a clinical benefit could be found even in the absence of an objective modification (i.e., improvement of Forced Expiratory Volume in 1 Second [FEV1] value). In particular, among the 51 patients with lung involvement, we recorded a clinical evaluation of response, as assessed by the Lung Symptom Scale (LSS), equal to 39%, while the ORR calculated strictly by the NIH criteria (where FEV1 evaluation, available in our series for 44 of the 51 patients, is prioritized over the clinical evaluation) was only 10%.

Overall survival and failure-free survival

The 12-month OS probability was 95.5% (95% CI: 90.6-100%) (Figure 2C). The median FFS was 18.07 months (95% CI: 12.71-not achieved [NA]), with FFS probabilities equal to 89.1% (95%CI: 82.3-96.6%) and 67.5 % (95%CI: 55.9-81.6%) at six and 12 months, respectively (Figure 2D).

A subgroup analysis was exploratorily conducted to assess the impact of either concomitant ruxolitinib administration during the initial three months of belumosudil treatment or extracorporeal photopheresis (ECP). FFS of these patients are shown in Figure 4A and B.

Safety and tolerability

Among patients who discontinued the drug, the median time to belumosudil withdrawal was 125 days (range: 8-455). Treatment discontinuation occurred in 21 patients (26%), primarily due to adverse events (AE, 11%), patient decision (3%), progression of cGvHD (6%), patient death (4%) or other reasons (3%). Causes of death were respiratory failure in 2 patients with severe lung cGvHD and one bacterial sepsis in a patient with predominant gastrointestinal involvement. A total of 28 non-infectious AE were reported, including 10 (36%) grade ≥3 and 2 (7%) classified as serious adverse events (SAE). The most frequent AE included alanine aminotransaminase (ALT) / glutamate-pyruvate transaminase (GGT) elevations, fatigue, pleuritis/pneumothorax, abdominal pain, myalgia, headache, diarrhoea, hematologic toxicity,

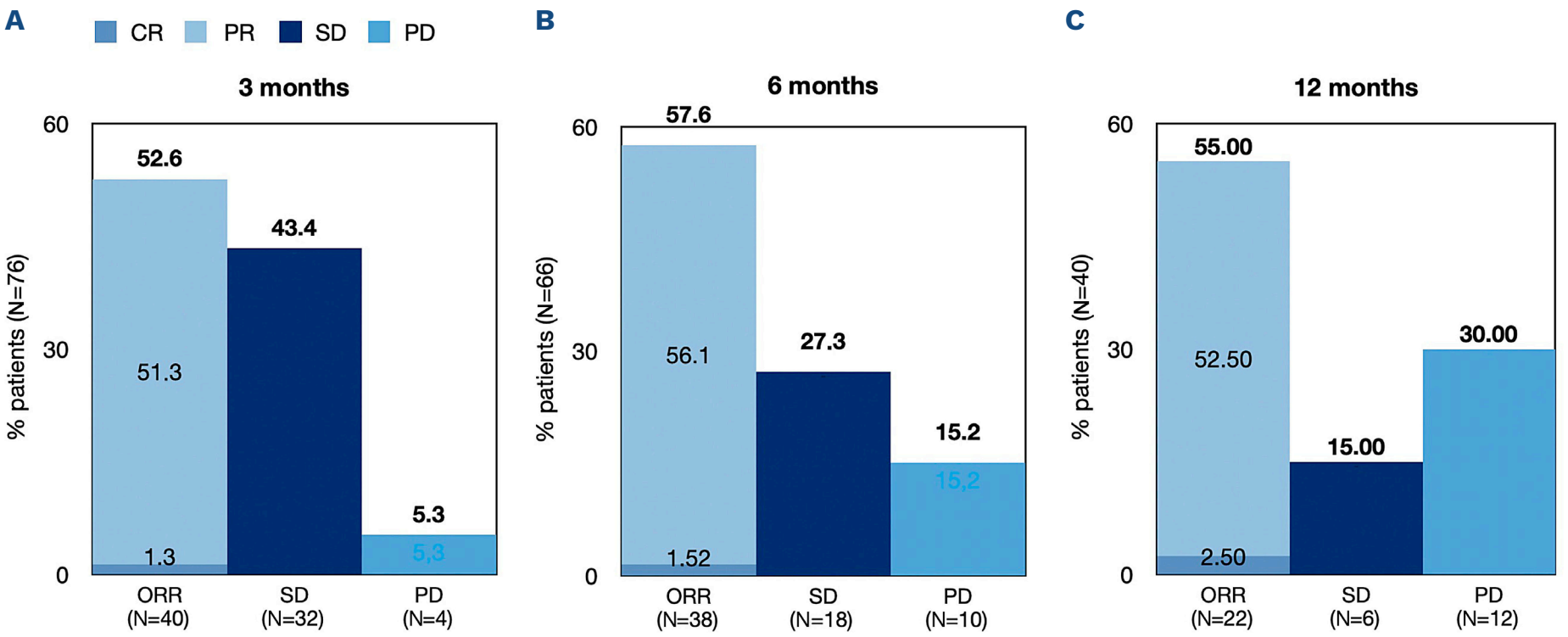

Figure 1. Overall response rate at three, six, and 12 months. Stacked bar plots show the distribution of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) among evaluable patients at three months (N=76) (A), six months (N=66) (B), and 12 months (N=40) (C). Overall response rate (ORR) was defined as the sum of CR and PR.

esophagitis, tachycardia, fever, pericarditis, and retinal artery occlusion. The drug was discontinued due to AE in 9 patients. When analyzed according to concomitant therapies, 8 of 23 patients (34.7%) receiving both belumosudil and ruxolitinib experienced AE, whereas 3 of 15 (20%) of those treated with concomitant ECP developed AE. A small subset of patients (N=4) received the triple combination of belumosudil, ruxolitinib, and ECP; none experienced AE. Among patients treated with belumosudil without concomitant therapies at baseline (N=31), AE occurred in 6 cases (19.4%).

Infectious complications accounted for 47 distinct events, 12 (25%) of which were grade ≥3. Among patients receiving ruxolitinib concomitantly, 11 infectious events occurred, including 6 bacterial (54.5%), 4 viral (36.4%), and one fungal (9.1%). In those receiving belumosudil and ECP, 17 events were observed: 4 bacterial (23.5%), 11 viral (64.7%), one fungal (5.9%), and one of unknown origin (5.9%). In patients treated with both ruxolitinib and ECP, 3 infectious events occurred, consisting of one bacterial (33.3%) and 2 infections of unknown origin (66.7%). Finally, among patients receiving belumosudil without other concomitant therapies, 13 infectious events were recorded, including 7 viral (53.8%), 4 bacterial (30.8%), and 2 of unknown origin (15.4%).

Viral infections represented the majority (49%), followed by bacterial (36%) and fungal (5%) etiologies. No secondary cancers were reported during the observation period.

Patient-reported outcome

Due to the limited availability of data on the LSS,[31] PRO were assessed using the NIH Severity Index Score (SIS), which is included in the NIH Patient Self-Report Form B (0-10 scale used to quantify patient-perceived symptom severity in cGvHD).[28] A SIS variation of 2 points in comparison with the baseline was considered significant[28] to define both improvement (reduction of 2 or more points) or worsening (increasing of 2 or more points) (Figure 5) at three months (N=58), 33% of patients reported an improvement ≥2 points

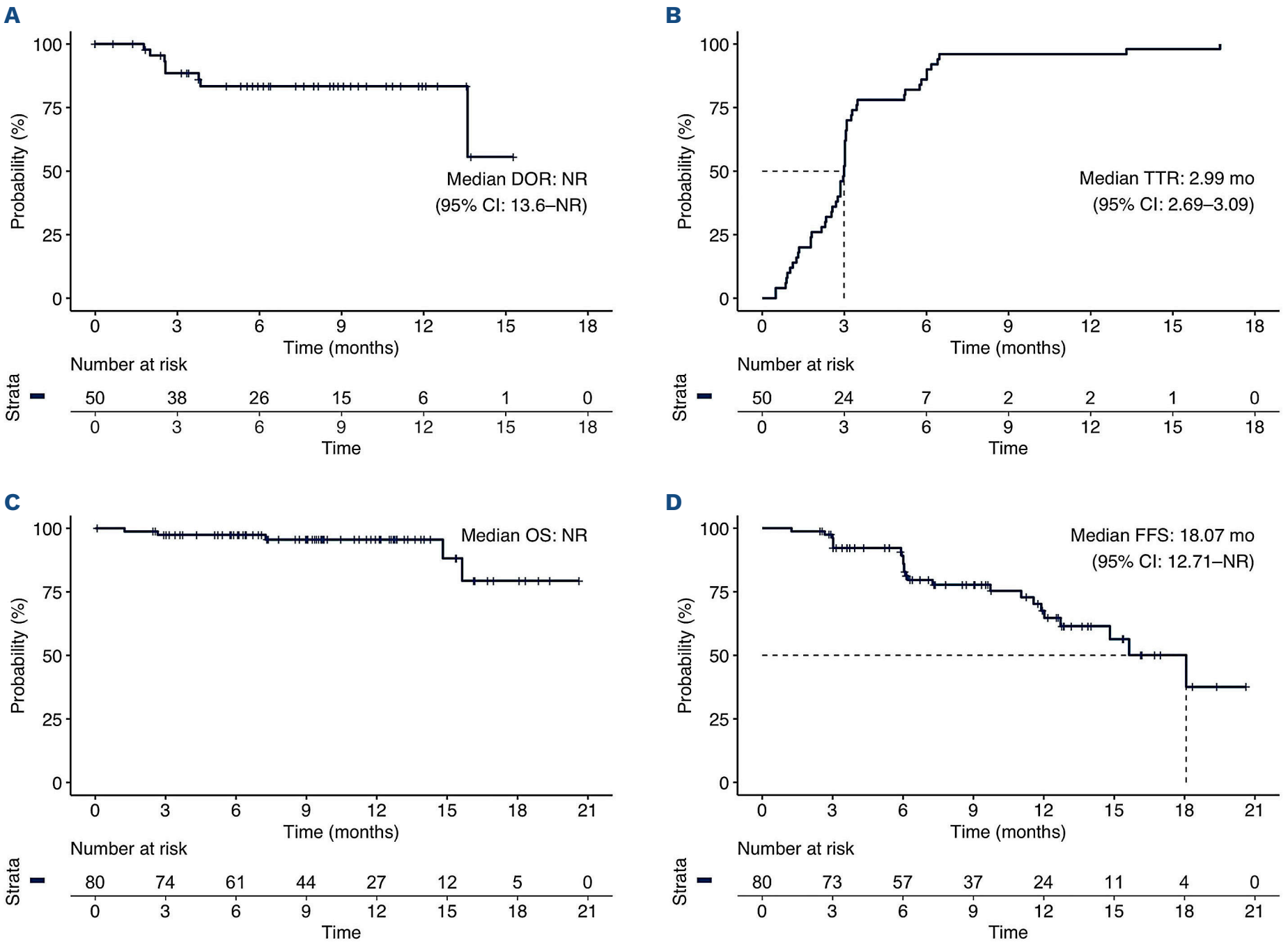

Figure 2. Time-to-events outcomes. Kaplan-Meier curves showing (A) duration of response (DOR), (B) time to response (TTR), (C) overall survival (OS), and (D) failure-free survival (FFS) in patients treated with belumosudil. CI: Confidence Interval; mo: months; NR: not reached.

compared with the baseline, 60% remained stable or had minimal change, and 7% experienced a worsening ≥2 points compared with the baseline. At six months (N=47), 36% showed a significant improvement, 62% were stable, and only 2% experienced significant worsening. At 12 months (N=21), 29% of patients showed a significant improvement, 52% remained stable, while 19% reported a worsening of symptoms. The trend of the overall population at the different time points is reported in *Online Supplementary Figure S1*. A moderate concordance between NIH-defined clinical responses and PRO was found. Specifically, at three months, among patients with available PRO data (N=58), 31 achieved a clinical response (CR or PR), and 16 of these showed concordance between clinical and PRO responses (51.6%). At six months, among 47 patients with available PRO data, 29 had a clinical response, with 16 showing concordance (55.2%). At 12 months, PRO were available for 21 patients; of the 14 patients who achieved a clinical response, 6 demonstrated concordance between clinical and PRO responses (42.8%).

Discussion

In this Italian multicenter, retrospective, real-world study, we evaluated the efficacy and safety of belumosudil in 80 patients with either moderate or severe cGvHD treated with belumosudil within a compassionate use program. To the best of our knowledge, this is the largest European cohort to date, including a particularly high proportion of patients exhibiting severe disease (86%), multi-organ involvement (median 3 organs), and having failed multiple lines of previous therapies (74% with ≥3 prior systemic therapies, 84% previously treated with ruxolitinib). Despite these high-risk features, belumosudil showed encouraging clinical activity. The BOR was 62.5%, while ORR ranged from 52.6% at three months to 57.6% at six months and 55.0% at 12 months, in line with outcomes from clinical trials and other real-world experiences. (See also Table 1.)

The rapid median time to response (3 months) and the durable nature of response (12-months DOR rate of 83.4%) further support the use of belumosudil in advanced disease settings. Interestingly, responses were largely partial, which may reflect the patient population predominantly composed by heavily pre-treated patients. Notably, despite the rapid onset of response, 2 patients achieved a late response, occurring 12 months after treatment initiation, suggesting that belumosudil may exert delayed therapeutic effects in selected individuals, possibly due to gradual and progressive modulation of fibrotic pathways. The ORR rate remains quite stable for at least the first 12 months. The apparent increase of PD at 12 months can be explained by

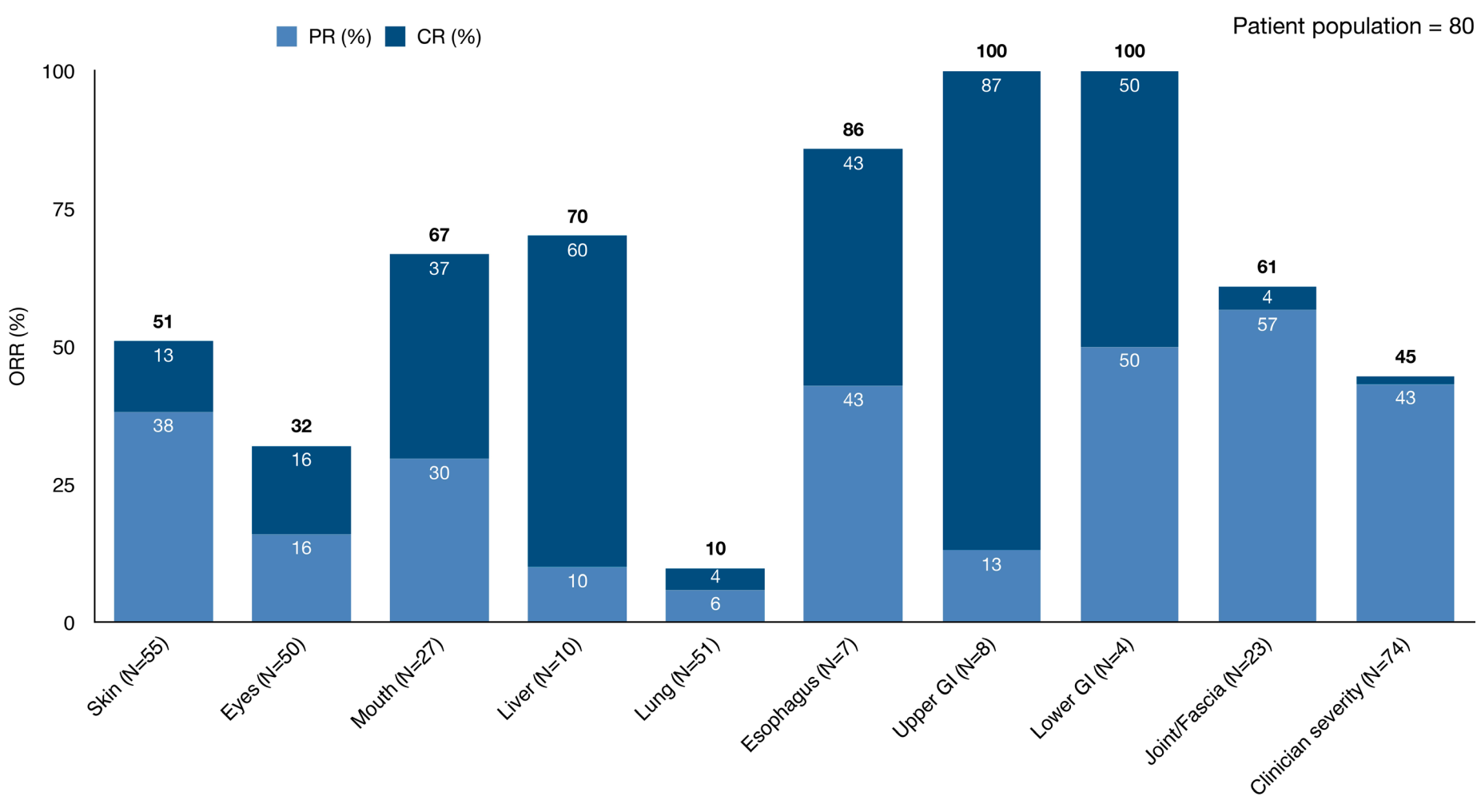

Figure 3. Organ-specific responses to belumosudil. Bars show the proportion of patients achieving partial response (PR, light blue) and complete response (CR, dark blue) across involved organs, according to National Institutes of Health criteria. Number above the bars indicates the percentage of overall responders. N indicates the number of evaluable patients for each organ. ORR: overall response rate.

the progression of patients being in SD, as well as by the inclusion in this category of those who had progressed at the previous timepoints.

Organ-specific response data revealed variable efficacy across the involved sites. Cutaneous involvement (in particular, sclerotic, which remains one of the most debilitating and treatment-resistant manifestations of cGvHD) showed encouraging signs of response with belumosudil. As per the established cGvHD response criteria, cutaneous involvement was assessed using the NIH skin score, which provides an overall estimate for response evaluation by taking the worst score between the percentage of body surface area (BSA) and the skin feature score.[28] In our analysis, to better dissect the effect of belumosudil on sclerotic manifestations, we distinguished between overall BSA involvement (including superficial skin eruption moveable and non-movable sclerosis) and isolated skin sclerosis (including only moveable and non-movable sclerosis). A skin response was observed in 36% of evaluable BSA cases and in 48% of patients with skin sclerotic features. These results support the potential antifibrotic effect of belumosudil in this challenging subset, consistent with its

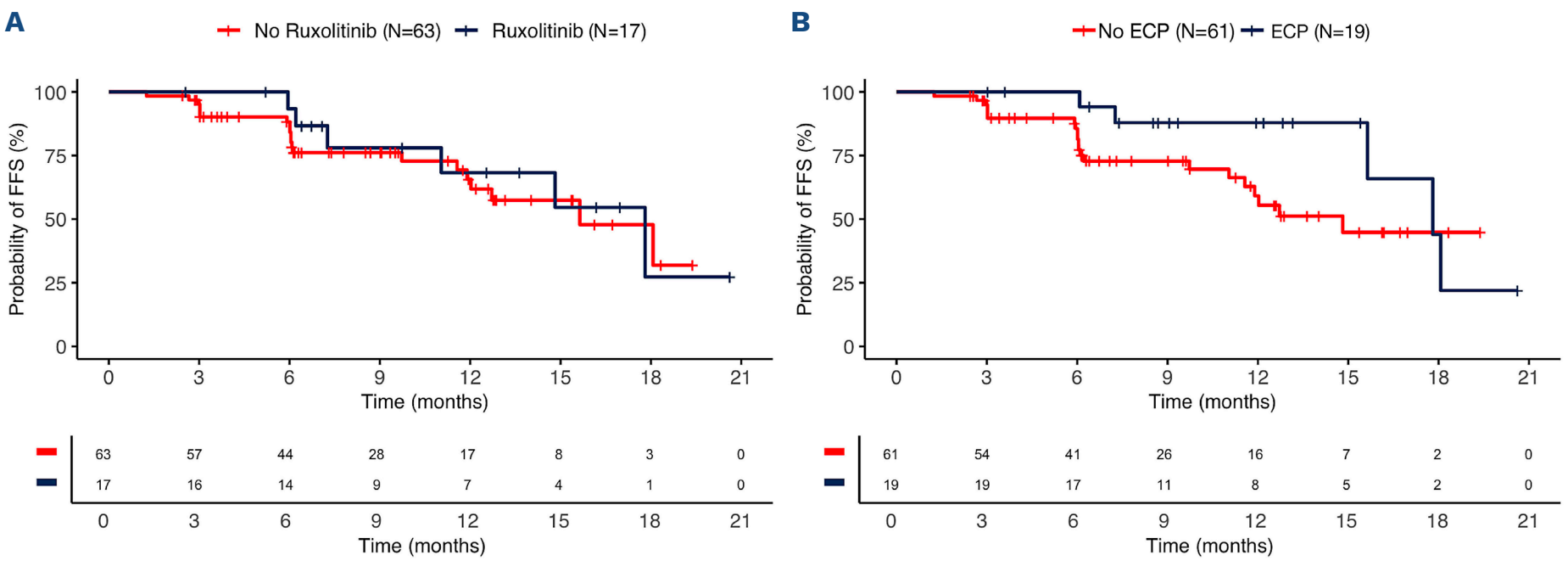

Figure 4. Failure-free survival by concomitant use of either ruxolitinib or extracorporeal photopheresis. Failure-free survival (FFS) by concomitant use of either (A) ruxolitinib or (B) extracorporeal photopheresis. Kaplan-Meier curves of failure-free survival (FFS), stratified by concomitant ruxolitinib during the first three months of therapy and extracorporeal photopheresis (ECP). N: number.

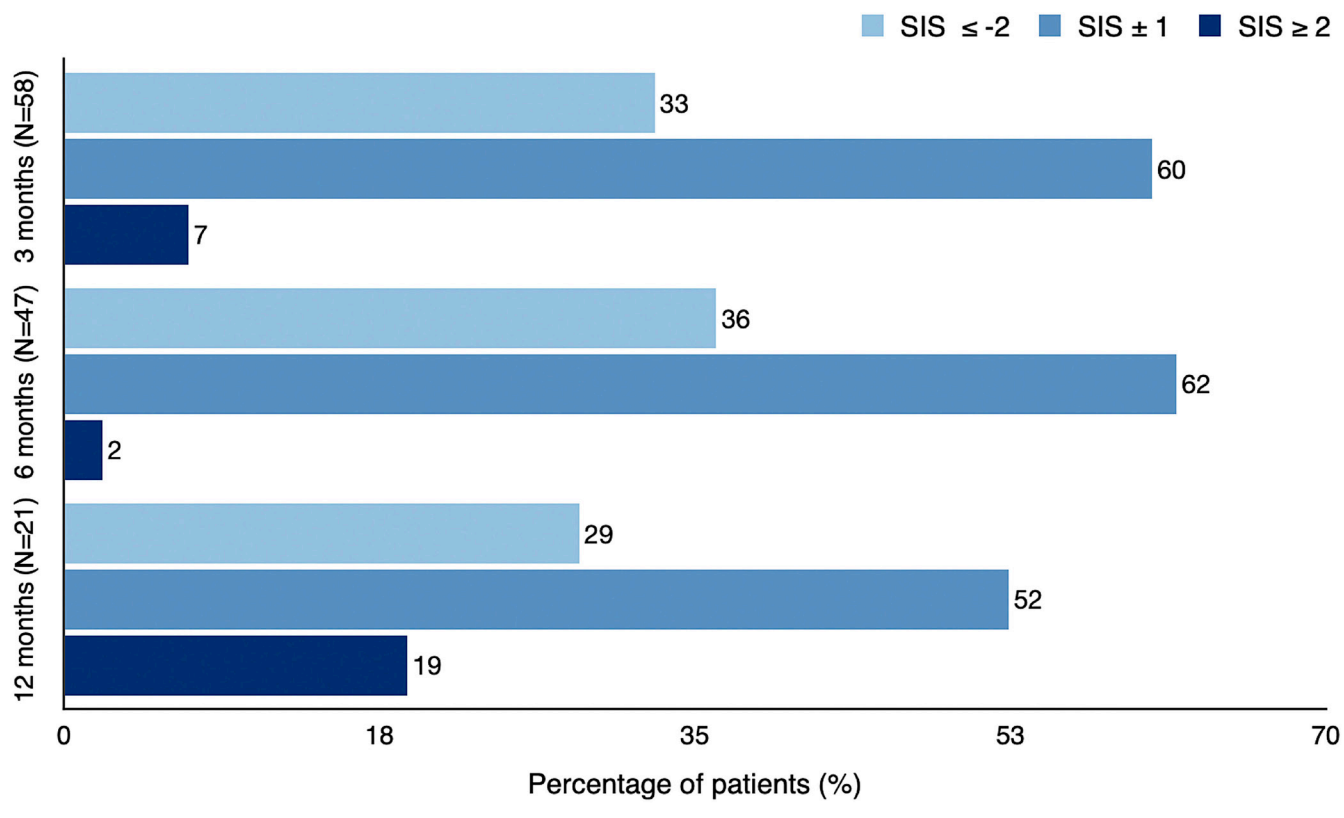

Figure 5. Analysis of patient-reported outcomes. Patient-reported outcomes (PRO) were assessed using the National Institutes of Health Severity Index Score (SIS) (0-10) at three, six, and 12 months after belumosudil initiation. Changes from baseline were classified as improvement (≤ –2 points), stability (±1 point), or worsening (≥ +2 points).

proposed mechanism of ROCK2 inhibition.[1,32] Mucosal sites also demonstrated remarkable responses, particularly the oral cavity and esophagus, with ORR of 67% and 86%, respectively. Responses in upper and lower gastrointestinal involvement reached 100%, though these were observed in a very small subgroup, for which this finding should be interpreted with caution. Liver involvement was found to be particularly sensitive to belumosudil, achieving an ORR of 70% with a clear predominance of CR. Overall, these data suggest that belumosudil may provide meaningful benefit in both inflammatory and fibrotic cGvHD manifestations, at least regarding skin involvement.

Lung involvement, by contrast, remained a therapeutic challenge with only 10% of ORR if assessed according to NIH response criteria; nonetheless, a clinical benefit was achieved in this patient population as displayed by the ORR of 39% according to the lung symptom score (lung SS), highlighting a discrepancy between functional measures and patient-perceived improvement, which can be expected in a so heavily advanced disease population where the organ damage is unlikely to be reverted.

In addition, considering the 34% of patients in this cohort with FEV1<40%, which was an exclusion criteria in the registration trial,[17] our results can be considered aligned with prior studies that documented poor responsiveness in advanced bronchiolitis obliterans syndrome (BOS), particularly in stage 3 disease, reinforcing the potential value of earlier intervention. Overall, this organ-level analysis suggests that belumosudil may induce an immunomodulatory and antifibrotic effect that is more effective in certain compartments or at earlier disease stages.

Importantly, FFS was 89.1% at six months and 67.5% at 12 months. These results are particularly relevant in a population with extensive exposure to prior treatments and high disease severity, although the lack of further lines of therapy can 'positively' impact the shape of FFS curves. Moreover, our findings are comparable to those reported within prospective clinical trials,[17-20] despite the broader heterogeneity typical of real-world cohorts.

Some of the patients, while starting belumosudil, continued ruxolitinib therapy, the only drug available and approved in Italy in refractory/resistant cGvHD, overlapping the two drugs for a median time of 4.8 months (N=27, 17, 11, and 3 at baseline, 3, 6, and 12 months, respectively), with the goal of preventing any cGvHD flare and to leverage a potential synergistic effect. No significant impact on FFS was observed in patients receiving concomitant ruxolitinib during the first three months, suggesting that belumosudil can be safely combined with JAK inhibitors without compromising efficacy, but, apparently, without any additive or synergic effect. This finding is supported by recent real-world studies: a single-center retrospective analysis on a small sample size (N=14) reported a 71% ORR with the combination, including responses in fibrotic organs and no excess toxicity.[33] Similarly, a study of 20 patients treated with both agents showed a 55% ORR and good tolerability, even in those refractory to prior lines.[34] Another retrospective cohort (N=14) described encouraging survival outcomes and low non-relapse mortality without safety concerns.[35] With the limitation of a real-world experience, these data reinforce the safety of the ruxolitinib-belumosudil combination in advanced cGvHD. Similarly, no significant difference in FFS was observed combining belumosudil and ECP in a small proportion of the patient population. A recent report described 13 patients with cGvHD treated with belumosudil plus ECP, showing encouraging clinical responses (particularly in skin and facial manifestations) together with a favorable safety profile.[36] However, the limited number of patients reported and the retrospective nature of the study prevent us from drawing any conclusions about the combined use

Table 3. Non-infectious and infectious adverse events in the study population

Non-infectious AE	N
Any AE	28
Grade ≥3	10
Drug-related AE	16
SAE	2
Drug-related SAE	1
Increased ALT/ GGT	5
Fatigue	4
Pleuritis/pneumothorax	3
Abdominal pain	3
Myalgia	2
Headache	2
Diarrhea	2
Hematotoxicity	2
Esophagitis	1
Tachycardia	1
Fever	1
Pericarditis	1
Retinal artery occlusion	1
Infectious AE	
Any infection	47
Grade ≥3	12
Drug-related infection	5
Drug-related SAE	2
Etiology infectious AE, N (%)	
Bacterial	17 (36)
Virus	23 (49)
Fungal	2 (4)
Uknown	5 (11)
Site infectious AE, N (%)	
Bacteremia	3 (6)
Mouth	1 (2)
Respiratory	34 (72)
Eye	2 (4)
Urinary and genitalia	3 (6)
Other	4 (10)

AE: adverse event; ALT: alanine aminotransaminase; GGT: glutamate-pyruvate transaminase; N: number; SAE: serious adverse event.

of two treatments as an alternative to monotherapy. Further studies are needed to clarify the possible synergistic effect of association therapies.

The safety profile of belumosudil was reassuring, with only 10 non-infectious grade ≥3 AE reported, accounting for 36% of all non-infectious AE (Table 3). Treatment-related discontinuation occurred in 11% of the patient population. Infectious AE were the most frequently reported complication, accounting for 47 episodes overall. Viral infections represented the leading etiology (49%). The respiratory tract was the most commonly affected site (72%), with other involvement including genitourinary, ocular, and oral mucosa. A total of 12 grade ≥3 infectious AE were recorded, of which only 5 (11%) were considered related to belumosudil, including 2 SAE. No treatment-related deaths were recorded. These findings are reassuring given the underlying immunocompromised state of the population, and are aligned with previous real-world and trial-based safety reports.

In addition to clinical endpoints, we assessed the PRO using the NIH SIS, a tool that captures functional status and symptom burden also in a real-world setting. At each of the three time points, one-third of patients reported meaningful symptomatic improvement defined as SIS > -2 points. This is the first analysis reporting PRO for cGvHD patients treated with belumosudil in a large real-world setting. These data suggest that belumosudil benefit may extend beyond organ response as per NIH criteria, a concept echoed in other studies where subjective response rates exceeded objective ones, particularly in fibrotic or sclerotic involvement.[22]

Several limitations of this study should be acknowledged. The retrospective design and limited follow-up may underestimate long-term toxicities and sustained efficacy. Moreover, response assessment was not centrally adjudicated and relied on assessment of treating physicians, which can potentially introduce variability in outcome reporting. Finally, in a compassionate use program, administration of concomitant immunomodulatory drugs is at the discretion of the treating physician and can represent a further selection bias. Nevertheless, the multicenter nature and real-world context of this analysis enhance its external validity and support the generalizability of our findings.

In conclusion, this real-world Italian experience confirms that belumosudil is an effective and well-tolerated option for patients with refractory/resistant, highly pretreated, moderate-to-severe cGvHD in a real-world setting, even for the self-assessment endpoints. The consistency of our results with those from clinical trials and other national cohorts reinforces its role in the therapeutic armamentarium for advanced cGvHD. As ongoing trials explore belumosudil in earlier treatment lines and in combination regimens, future data will help refine its role in the evolving landscape of cGvHD management.

Disclosures

FB participated on advisory board and received speaker fees from Neovii, Jazz Pharmaceuticals, Sanofi, Novartis, Kite, Gilead, BMS, MSD, Amgen, Janssen, Takeda and Pfizer; MTLS participated on advisory board and received speaker fees from Novartis, Pfizer, Mallinckrodt/Therakos, Sanofi, Medac and Incyte; NP reports advisory board for Sanofi and Novartis; MA reports Scientific Adviso-ry Board for Vertex Pharmaceuticals Inc. and Novartis Steering Committee member for Vertex Pharmaceuticals Inc; AP reports consultancy for Tilliots, Advisory Board/Speaker for Gilead Kite and Novartis, and Speaker for Amgen and Medaac; AR has received honoraria for lectures or presentations from Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Omeros, Sanofi and Italfarmaco, support for attending meetings and/or travel from Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead and Omeros, and participated on a Data Safety Monitoring Board or Advisory Board for Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Roche, Omeros, Sanofi and Italfarmaco; FL has received honoraria from and/or has been a member of the speakers bureau for Novartis, Jazz Pharmaceuticals, Sanofi, Sobi, Miltenyi, bluebird bio, Inc., Amgen, Medac, Neovii and BMS, and has participated on an advisory board for Amgen and Vertex. All the other authors have no conflicts of interest to disclose.

Contributions

AR and FL designed the study and revised the manuscript; FB designed the study and wrote the paper; MR collected data, carried out the statistical analysis, and wrote the paper; MTLS collected data and revised the PRO data; PC, NP, AG, LP, MA, GM, GP, AA, CN, MM, NM, MF, LS, FZ, LC, AP, AB, LG, CS, FE, LF, JM, PA, AS, RDM, DS, MM and MT recruited patients, collected data, and revised the manuscript. All the authors approved the final version of the manuscript for publication.

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Data-sharing statement

The data of this study will be available from the corresponding author upon reasonable request for a period of 5 years following publication. In addition, the dataset will be accessible via the following DOI (10.5281/zenodo.17492672).

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