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

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

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Authors' contributions

*FB and MR contributed equally as co-first authors. AR and FL designed the study and revised the manuscript; FB designed the study and wrote the paper. MR collected data, did the statistical analysis and wrote the paper. MTLS collected data e revised the PROs 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, MT recruited patients, collected data, revised the manuscript. All the co-authors approved the present version of the manuscript.

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Running head

Italian compassionate use of belumosudil in cGvHD

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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)

Key points: #1 Durable, multi-organ responses were achieved in heavily pretreated patients with refractory chronic GvHD after belumosudil therapy; #2 Treatment was well tolerated, with significant patient-perceived improvements in about one-third of patients.

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Conflict-of-interest statements

FB participated to advisory board and received speaker fees from Neovii, Jazz pharmaceuticals, Sanofi, Novartis, Kite, Gilead, BMS, MSD, Amgen, Janssen, Takeda, Pfizer. MTLS participated to advisory board and received speaker fees from Novartis, Pfizer, Mallinckrodt/Therakos, Sanofi, Medac, Incyte. NP: Sanofi: Advisory board, Novartis: Advisory board. MA: Scientific Advisory Board for Vertex Pharmaceuticals Inc. and Novartis Steering Committee member for Vertex Pharmaceuticals Inc. AP: Tilliots: Consultant, Gilead Kite: Advisory Board/ Speakers, Novartis: Advisory Board/Speakers, Amgen: Speaker, Medaac: Speaker. AR has received honoraria for lectures or presentations from Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Omeros, Sanofi, Italfarmaco; support for attending meetings and/or travel from Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Omeros; participated on a Data Safety Monitoring Board or Advisory Board from Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Roche, Omeros, Sanofi, 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 in an advisory board for Amgen and Vertex. All the other authors declare no conflicts of interest related to this manuscript.

Abstract

Chronic graft-versus-host disease (cGvHD) remains a major late complication of allogeneic hematopoietic 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 -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 was 52.6%, 57.6%, and 55.0% at 3, 6, and 12 months, respectively. Median time to response was 3 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 NIH Severity Index Score (0–10 scale) showed meaningful improvements (≥-2 points) in 33%, 36%, and 29% of patients at 3, 6, 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 (allo-HSCT), 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%, this observation pointing out 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 downregulating 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.

Patients and 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 at 29 stem cell transplant programs. Eligible patients were required to have a diagnosis of moderate or severe cGvHD according to the 2014 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 hematological malignancy at belumosudil initiation, uncontrolled infection, severe cytopenia (platelet count $<50 \times 10^{\square}$/L or neutrophil count $<1.5 \times 10^{\square}$/L), severe renal impairment (eGFR <30 mL/min/1.73 m²), hepatic cytolysis (AST/ALT >3× upper limit of normal [ULN]), hyperbilirubinemia (>1.5× 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 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 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 two 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 (AEs) 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 3, 6, 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 (3, 6, 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. Failure-free survival (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 (PROs) were assessed using the form B of 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 3, 6, and 12 months after belumosudil initiation. Variations in SIS were categorized as follows: improvement (SIS ≤ -2), stability (SIS ± 1) and worsening (SIS $\geq +2$).

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 values <0.05 were considered statistically significant. All analyses were performed using R (version 4.4.2) in RStudio (version 2025.05.0+496).

Results

Patient 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%. Roughly 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 belumosudil, 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 (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%). For detailed information on organ severity scores, please refer to **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 (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% (61.2% PR, 1.3% CR). The ORR was 52.6% at 3 months (51.3% PR, 1.3% CR), 57.6% at 6 months (56.1% PR, 1.5% CR), and 55.0% at 12 months (52.5% PR, 2.5% CR) as shown in **figure 1**. The 12-month DOR was 83.4% [95% CI: 72.8–95.5%], **figure 3A**. The median time to response was 3 months (95% CI: 2.69–3.09, **figure 3B**). 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 6 months, those ORRs became 61.8%, 67.7% and 40.0% respectively.

The organ specific responses are illustrated in **figure 2**. In addition to the stringent NIH criteria reported in the figure 2, 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 FEV1 value). In particular, among the 51 patients with lung involvement, we recorded a clinical evaluation of response, assessed by LSS, equal to 39%, while the ORR calculated stringently 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 (OS) and Failure free survival (FFS)

The 12-month OS probability was 95.5% (95% CI: 90.6–100%, **figure 3C**). The median FFS was 18.07 months (95% CI: 12.71–NA), with FFS probabilities equal to 89.1% (95% CI: 82.3–96.6%) and 67.5 % (95% CI: 55.9 -81.6%) at 6 and 12 months, respectively (**figure 3D**).

A subgroup analysis was exploratorily conducted to assess the impact of either concomitant ruxolitinib administration during the initial 3 months of belumosudil treatment or ECP. The FFS of those patients are shown in **figure 4A e 4B**.

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 AEs (11%), patient decision (3%), progression of cGvHD (6%), patient death (4%) or other reasons (3%). Causes of death were respiratory failure in two patients with severe lung cGvHD and one bacterial sepsis in a patient with predominant gastrointestinal involvement.

A total of 28 non-infectious AEs were reported, including 10 (36%) grade ≥3 and 2 (7%) classified as serious adverse events (SAEs). The most frequent AEs included ALT/GGT elevations, fatigue, pleuritis/pneumothorax, abdominal pain, myalgia, headache, diarrhoea, hematologic toxicity, esophagitis, tachycardia, fever, pericarditis, and retinal artery occlusion. The drug was discontinued due to AEs in 9 patients. When analyzed according to concomitant therapies, 8 of 23 patients (34,7%) receiving both belumosudil and ruxolitinib experienced AEs, whereas 3 of 15 (20%) of those treated with concomitant ECP developed AEs. A small subset of patients (n = 4) received the triple combination of belumosudil, ruxolitinib, and ECP, with none experiencing AEs. Among patients treated with belumosudil without concomitant therapies at baseline (n = 31), AEs 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 1 fungal (9.1%). In those receiving belumosudil and ECP, 17 events were observed: 4 bacterial (23.5%), 11 viral (64.7%), 1 fungal (5.9%), and 1 of unknown origin (5.9%). In patients treated with both ruxolitinib and ECP, 3 infectious events occurred, consisting of 1 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 second cancers were reported during the observation time.

Patient reported outcome (PROs)

Due to the limited availability of data on the Lee Symptom Scale[31], PROs were assessed using the 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 point) or worsening (increasing of 2 or more point): as shown in **figure 5**, at 3 months (n = 58), 33% of patients reported an improvement ≥2 points compared with the baseline, 60% remained stable or had minimal change, and 7% experienced a worsening ≥2 points compared with the baseline. At 6 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 in the different time points is reported in **supplementary figure 1**. A moderate concordance between NIH-defined clinical responses and PROs was found. Specifically, at 3 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 6 months, among 47 patients with available PRO data, 29 had a clinical response, with 16 showing concordance (55.2%). At 12 months, PROs 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 multicentre, 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 3 months to 57.6% at 6 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 belumosudil's use in advanced 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, two 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 month: the apparent increase of PD at 12 months can be explained by the progression of patients being in SD, as well as by the inclusion in this category of those progressed at the previous timepoints.

Organ-specific response data revealed variable efficacy across the involved sites. Cutaneous involvement, in particular the sclerotic one, 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 eruptions 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 proposed mechanism of ROCK2 inhibition[1,32]. Mucosal sites also demonstrated remarkable responses, particularly the oral cavity and esophagus, with ORRs of 67% and 86%, respectively. Responses in upper and lower gastrointestinal involvement reached 100%, though these were observed in a very small subgroup and 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 for 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 a 34% of patients in this cohort with FEV1 lower than 40% predicted, 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, the FFS was 89.1% at 6 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 were observed combining belumosudil and ECP in a little 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 fascial 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 any conclusions about the combined use of two treatments as an alternative to

monotherapy. Further studies are needed to clarify the possible synergistic effect of association therapies.

As shown in **table 3**, the safety profile of belumosudil was reassuring, with only 10 non-infectious grade ≥3 AEs reported, accounting for 36% of all non-infectious AEs. Treatment-related discontinuation occurred in 11% of the patient population. Infectious AEs were the most frequently reported complication, accounting for 47 episodes overall. Viral infections represented the leading aetiology (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 AEs were recorded, of which only 5 (11%) were considered related to belumosudil, including 2 SAEs. 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 PROs 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 $\geq$ -2 points. This is the first analysis reporting PROs 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 pertaining to 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 concomitant immunomodulatory drugs are under the treating physician control 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 positioning in the evolving landscape of cGvHD management.

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Tables

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	Organ response	AE (≥ G3)/ Drug related (≥ G3)	SAE/drug related
KD025 trial (Jagasia, 2021) **Prospective Phase 2**	54	3	2%	/	65%	35 w	>75% within 8 w	76% (6 mo) 47% (12 mo)	skin 30%, eyes 50%, mouth 70%, liver 50%, lung 25%, j/f 70% uGI 100% loGI 100% esoph 75%	98 % (61%)/56 (NA)	43%/0
ROCKstar trial (Cutler, 2021) **Prospective Phase 2**	132	3	29%	72 % (70+2)	76%	54 w	5 w	75% (6 m) 56% (12 m)	skin37%, eyes 42%, mouth 55%, liver 39%, lungs 26%, j/f 72%, uGI 53%, loGI 69%, esoph 45%	99% (54%)/67%(NA)	38%/5%
Chinese trial (Wang, 2024) **Prospective Phase 2**	30	3	53%	/	73%	NR	4,3 w	73% (6 m) 56% (12 m	skin 40%, eyes 27%, lungs 15% j/f 78%, mouth 55%, uGI and liver 67%, loGI -- esoph 60%	96,7% (36,7%)/ 63,3% (NA)	36,7%/13,3%
Japanese trial (Inamoto, 2024) **Prospective Phase 2**	21	1	0	75% (75+0)	85,7%	NR	4,1 w	NR *estimated 95 (6 m) 87 (12 m)	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, 2024) **Retrospective**	33	4	97%	28% (28+0)	42%	6 m	3 m	NR 76% (6 m)	skin 21%, mouth 33%, eyes 29%, GI 67%, liver 0%, j/f 25%, lung	≥ G3 27%	/

Compassionate use								64% (12 m)	23%		
Canadian (Desai, 2024) **Retrospective Compassionate use**	37	4	NA	69%	/	/	/	71,9% (6m)	/	/	/
USA Raju (2024) **Retrospective FDA approval**	66	/	most	59,5 (55+4,5)	/	/	/	median 20 m 79% (6 m) 72% (12 m)	/	No G3 AE observed	/
City of Hope Medcal Center Modi (2024) **Retrospective FDA approval**	45	3	71,1%		46,7%	/	108,5 days	median 11,2 m	skin 14,7%,mouth 23,8%, eyes 33,3%, j/f 23,5%, lung 16,7%, liver 40%, GI 0%	*Infectious AEs 42% (27%)	/
French (Michonneau, 2025) **Retrospective Compassionate use**	68	3	95,5%	45,6% (35,3+10,3)	57,3%	/	/	NR 89,1% (6m) 80,4% (12m)	skin 53,7%, gut 50%, liver 72,7%, lung 17,4%, mouth 70,4%, eyes 46,7%, j/f 50%	N=10 AEs	/

LOT: lines of treatment; ORR: overall response rate; BOR: best overall response rate; DOR: duration of response; TTR: time to response; FFS: failure free survival; AE: adverse event; SAE: serious adverse event; PR: partial response; CR: complete response; NR: not reached; NA: not available; uGI: upper gastrointestinal tract; loGI: lower gastrointestinal tract; esoph:esophagus; j/f: joint and fascia.

Table 2. Clinical characteristics of the study population

Patients	N=80
Prior systemic cGvHD therapy	
N. of lines, mean	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	
Moderate	11 (14)
Severe	69 (86)
Organ involment at Belumosudil initiation	
Number of organ 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	
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 (range), mg/kg/d	0,3 (0,03-2)
Concomitant other therapies at Belumosudil initiation	
PPI	47 (59)
Azole	40 (50)
Belumosudil dose at baseline, mg	
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)
Time of discontinuation, median (days)	125 (8-455)

cGvHD: chronic graft versus host disease; ECP: extracorporeal photopheresis; CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; NIH: National Institutes of Health; PPI: proton pump inhibitor.

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
Increase 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	N
Any infection	47
Grade ≥3	12
Drug-related infection	5
Drug related SAE	2
Aetiology	
Bacterial	17 (36)
Virus	23 (49)
Fungal	2 (4)
Uknown	5 (11)
Site	
Bacteremia	3 (6)
Mouth	1 (2)
Respiratory	34 (72)
Eye	2 (4)
Urinary and genitalia	3 (6)
Other	4 (10)

AE: adverse event, SAE: serious adverse event, ALT: alanine aminotransaminase, GGT: glutamate-pyruvate transaminase.

Figure legends

Figure 1. Overall response rate at 3, 6, 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 3 months (n = 76), 6 months (n = 66), and 12 months (n = 40). Overall response rate (ORR) was defined as the sum of CR and PR.

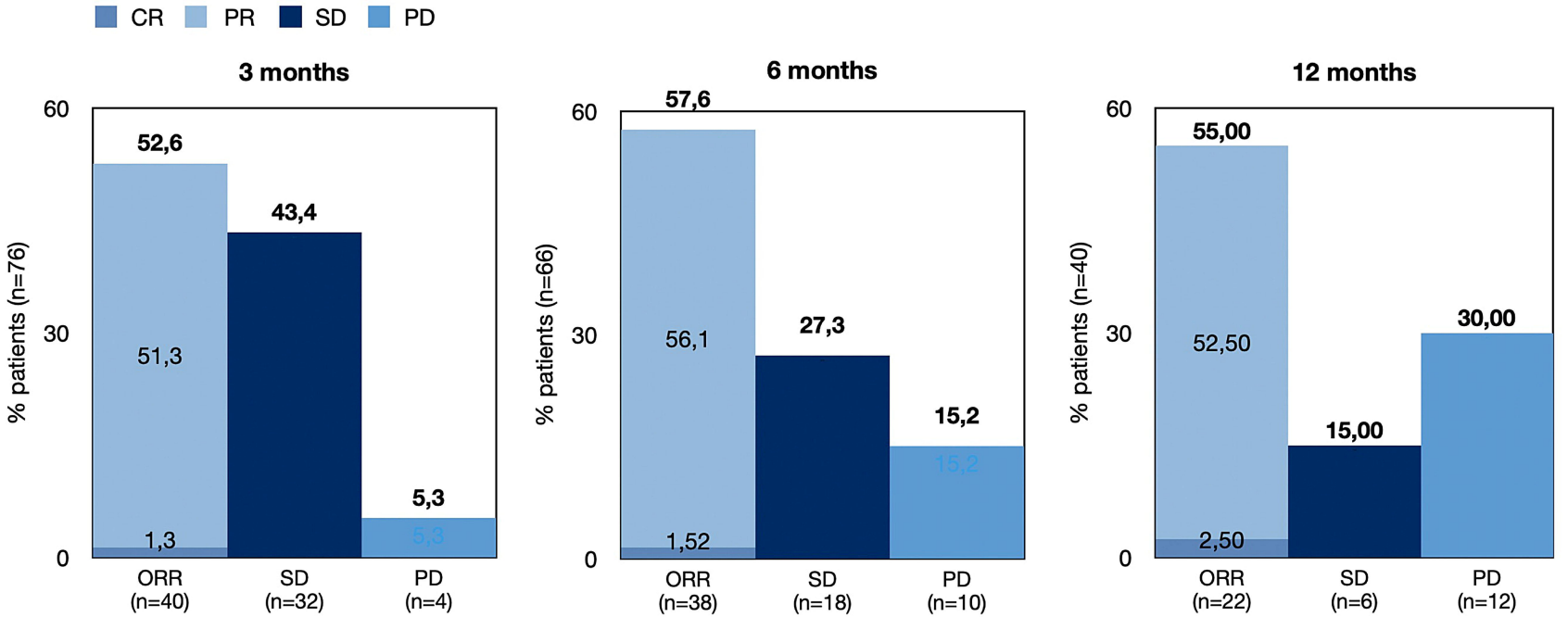
Figure 2. Organ-specific responses to belumosudil. Bars show the proportion of patients achieving partial response (PR, light blue) and complete response (CR, dark blue) across involved organs, according to NIH criteria. Numbers above the bars indicate the percentage of overall responders; n indicates the number of evaluable patients for each organ.

Figure 3. 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. NR: not reached. Mo: months.

Figure 4. Failure-free survival by concomitant use of either ruxolitinib (panel A) or ECP (panel B). Kaplan–Meier curves of failure-free survival (FFS), stratified by concomitant ruxolitinib during the first 3 months of therapy and ECP. ECP: extracorporeal photopheresis.

Figure 5. Analysis of patient-reported outcomes. Patient-reported outcomes (PROs) were assessed using the NIH Severity Index Score (SIS) (0–10) at 3, 6, and 12 months after belumosudil initiation. Changes from baseline were classified as improvement (≤ -2 points), stability (± 1 point), or worsening ($\geq +2$ points).

Figure 1


CR
PR
SD
PD
3 months
% patients (n=76)
60
30
0
52,6
43,4
5,3
51,3
1,3
5,3
ORR (n=40)
SD (n=32)
PD (n=4)
6 months
% patients (n=66)
57,6
27,3
15,2
56,1
1,52
15,2
ORR (n=38)
SD (n=18)
PD (n=10)
12 months
% patients (n=40)
55,00
15,00
30,00
52,50
2,50
ORR (n=22)
SD (n=6)
PD (n=12)

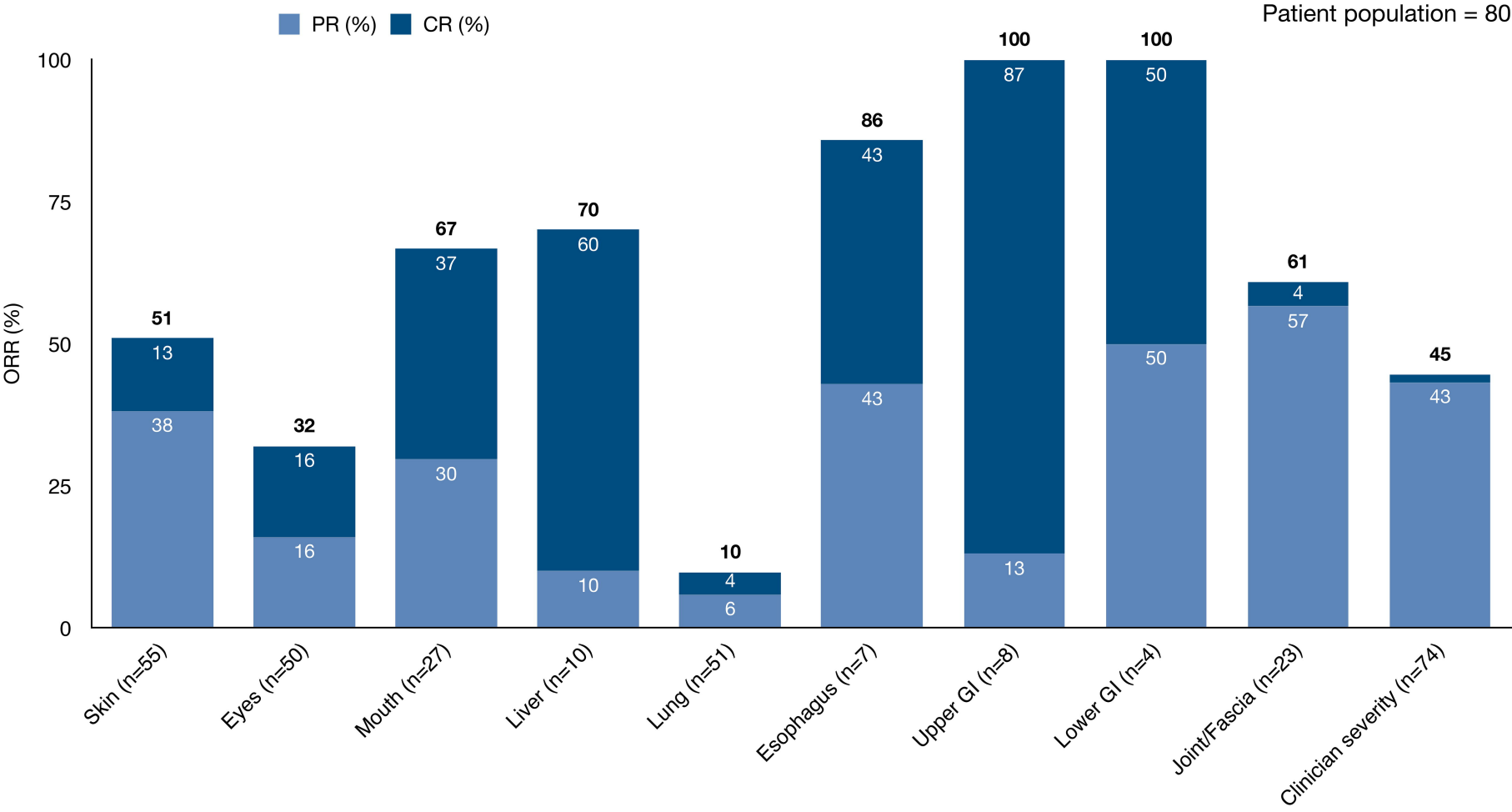

PR (%)
CR (%)
Patient population = 80
ORR (%)
100
75
50
25
0
51
13
38
32
16
16
67
37
30
70
60
10
10
4
6
86
43
43
100
87
13
100
50
50
61
4
57
45
43
Skin (n=55)
Eyes (n=50)
Mouth (n=27)
Liver (n=10)
Lung (n=51)
Esophagus (n=7)
Upper GI (n=8)
Lower GI (n=4)
Joint/Fascia (n=23)
Clinician severity (n=74)

Figure 3

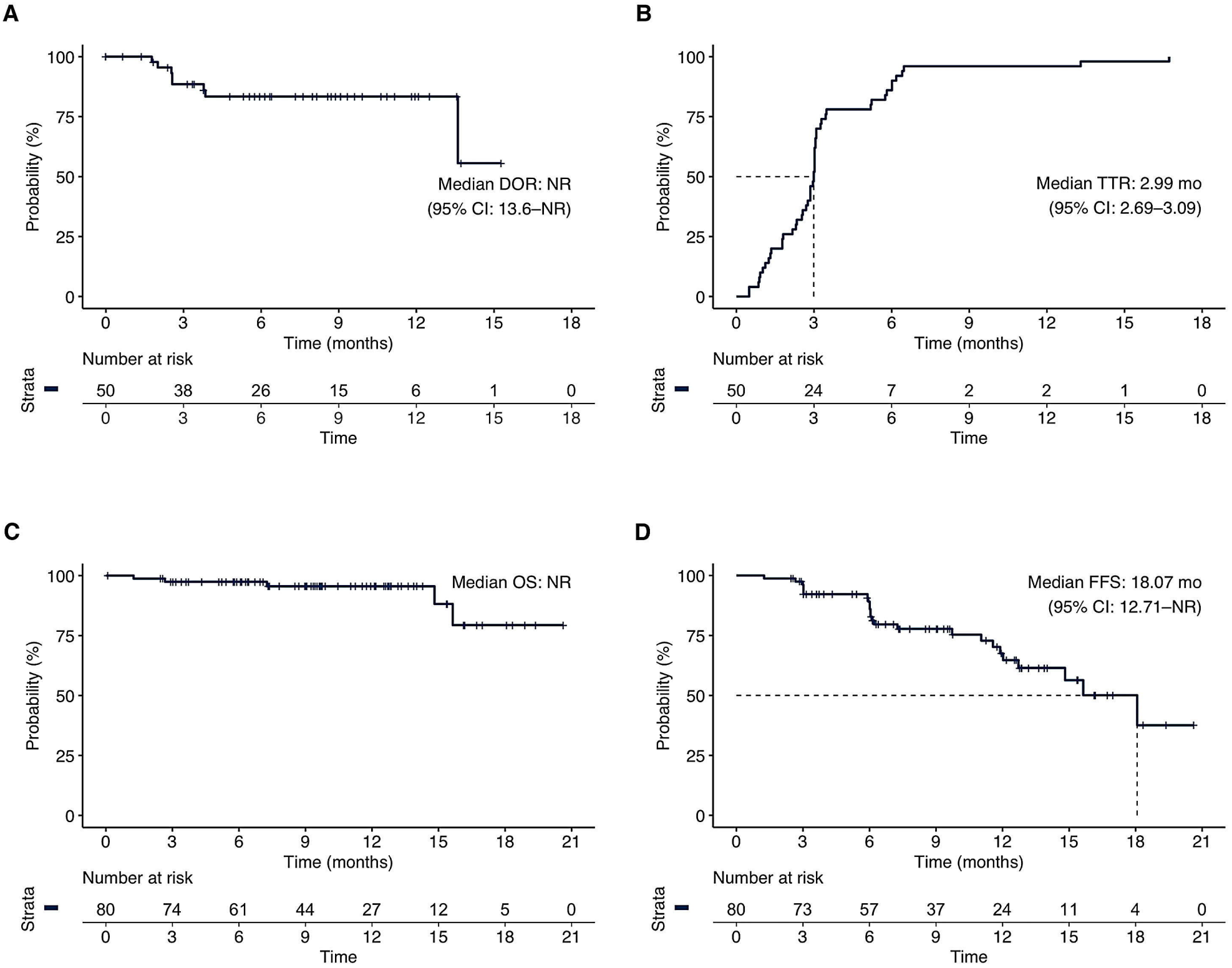

A
Probability (%)
100
75
50
25
0
Median DOR: NR
(95% CI: 13.6–NR)
0 3 6 9 12 15 18
Time (months)
Number at risk
Strata
50 38 26 15 6 1 0
0 3 6 9 12 15 18
Time
B
Probability (%)
100
75
50
25
0
Median TTR: 2.99 mo
(95% CI: 2.69–3.09)
0 3 6 9 12 15 18
Time (months)
Number at risk
Strata
50 24 7 2 2 1 0
0 3 6 9 12 15 18
Time
C
Probability (%)
100
75
50
25
0
Median OS: NR
0 3 6 9 12 15 18 21
Time (months)
Number at risk
Strata
80 74 61 44 27 12 5 0
0 3 6 9 12 15 18 21
Time
D
Probability (%)
100
75
50
25
0
Median FFS: 18.07 mo
(95% CI: 12.71–NR)
0 3 6 9 12 15 18 21
Time (months)
Number at risk
Strata
80 73 57 37 24 11 4 0
0 3 6 9 12 15 18 21
Time

Figure 4

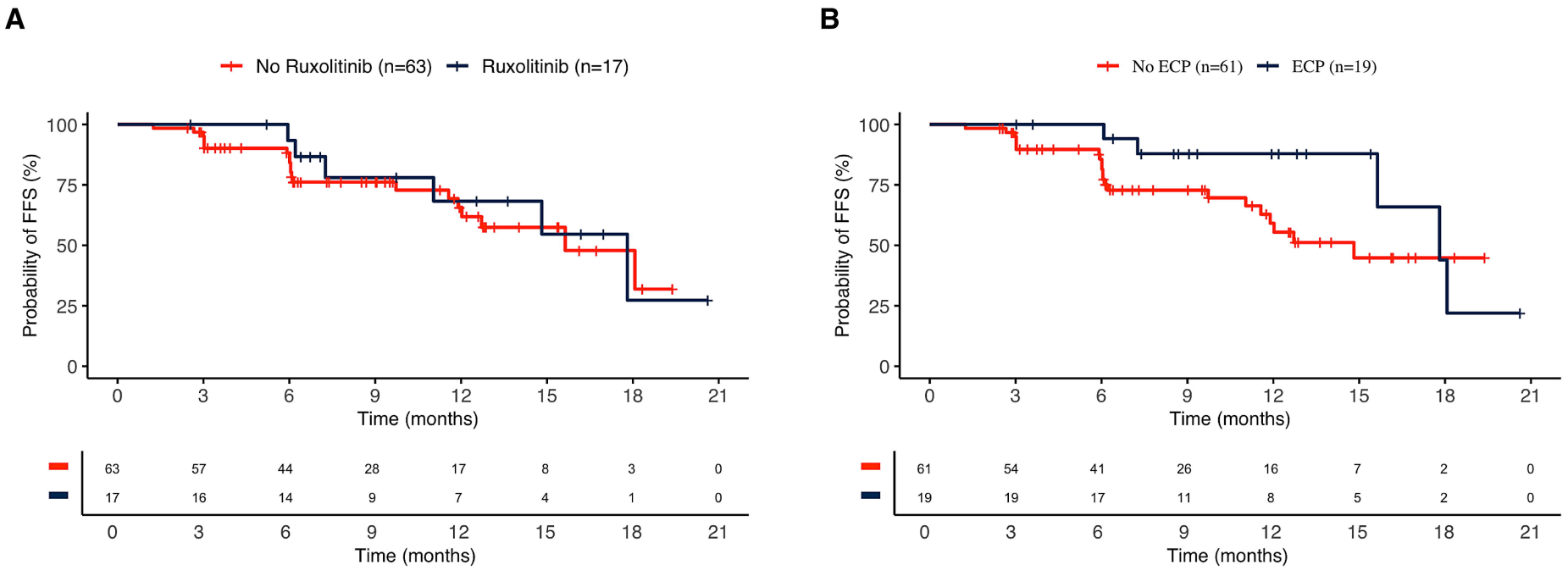
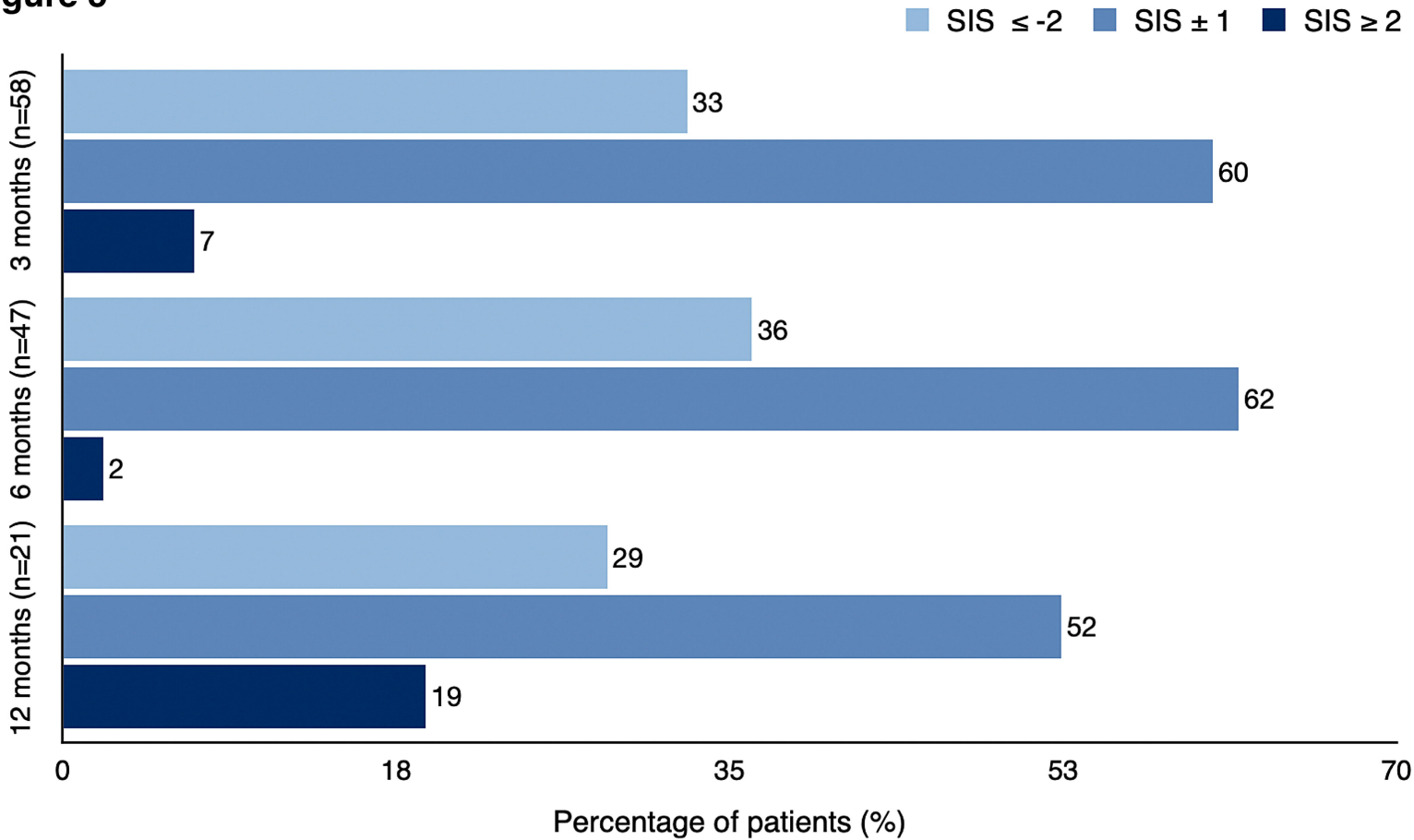

A
No Ruxolitinib (n=63)
Ruxolitinib (n=17)
Probability of FFS (%)
100
75
50
25
0
0
3
6
9
12
15
18
21
Time (months)
63 57 44 28 17 8 3 0
17 16 14 9 7 4 1 0
0 3 6 9 12 15 18 21
Time (months)
B
No ECP (n=61)
ECP (n=19)
Probability of FFS (%)
100
75
50
25
0
0 3 6 9 12 15 18 21
Time (months)
61 54 41 26 16 7 2 0
19 19 17 11 8 5 2 0
0 3 6 9 12 15 18 21
Time (months)

Figure 5


SIS ≤ -2
SIS ± 1
SIS ≥ 2
3 months (n=58)
6 months (n=47)
12 months (n=21)
33
60
7
36
62
2
29
52
19
0
18
35
53
70
Percentage of patients (%)

Supplementary figure 1. Longitudinal assessment of Severity Index Score at 3, 6, and 12 months.
Severity Index Score (SIS) for all patients (n = 80) at 3, 6, and 12 months relative to baseline. Each bar represents the individual patient score, categorized as NA (0), improvement (1; SIS ≤ –2), stability (2; SIS ±1), or worsening (3; SIS ≥ +2). *NA: not available.*. All patients (n = 80) are represented across the three time points (3, 6, and 12 months). Values on the x-axis vary according to the SIS, categorized as follows: 0 =NA, 1=improvement (SIS ≤ –2), 2=stability.

Supplementary figure 1