(PF1125) THE SAFETY AND EFFICACY OF BELUMOSUDIL AND RUXOLITINIB COMBINATION IN RUXOLITINIB REFRACTORY CGVHD

Topic: 23. Stem cell transplantation - Clinical

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Background

Despite therapeutic advances with JAK and ROCK inhibitors in chronic GVHD (cGVHD), durable responses remain limited. Patients with advanced cGVHD after multiple prior therapies require simultaneous targeting of multiple pathways. Preclinical data support synergistic effects through dual JAK/ROCK pathway inhibition, potentially overcoming resistance mechanisms.

Aims

To evaluate the safety and efficacy of combination therapy with belumosudil and ruxolitinib in patients with cGVHD refractory to ruxolitinib.

Methods

We conducted a multicenter study across four centers, enrolling 57 patients with ruxolitinib-refractory cGVHD (63.2% severe NIH-grade; 66.7% with ≥5 prior therapies). Eligible patients had progression or suboptimal response after ≥3 months of ruxolitinib. The primary endpoint was 6-month overall response rate (ORR), with secondary endpoints including best overall response (BOR), failure-free survival (FFS), adverse events, symptom improvement, and corticosteroid reduction.

Results

At median follow-up of 364 days, 3 month-ORR was 59.6% (95%CI 47.7-70.5) , with a BOR of 75.4% (63.2–84.7). The 6-month ORR was 50.9% (38.1–63.7), with a BOR of 68.4% (56.4–80.5). Patients with lung involvement (63.2%) showed 83.3% symptom-based response (including 29.2% complete responses) versus 3.7% FEV1 improvement. Twelve-month FFS was 94.5% (87.1-100). Corticosteroid doses were successfully reduced in 86.4% of patients. Following three months of combination therapy, 23 patients successfully discontinued ruxolitinib; nonetheless, 22.8% (13.8–35.3) of patients ultimately required next-line immunosuppressive therapy. The combination demonstrated a favorable safety profile, with grade ≥3 pneumonia occurring in only 5.3% of patients and no treatment-related discontinuations or severe hematologic toxicity observed.

Variables	N= 57

Age, median(range),y	42(17-68)
male	29(50.9%)
Disease, n(%)	
AML	26 (45.6%)
ALL	21 (36.8%)
MDS	5 (8.8%)
Others	5 (8.8%)
Donor type, n(%)	
MSD	12 (21.1%)
HRD	35 (61.4%)
URD	10 (17.5%)
Conditioning intensity, n(%)	
MAC	51 (89.5%)
RIC	6 (10.5%)
Median time of cGVHD diagnosis from transplantation	215 (68-1512) days
Median time from cGVHD diagnosis to initiating ruxolitinib	138 (0-3636) days
Median time from initiating ruxolitinib to adding belumosudil	287 (69-2471) days

Median time from cGVHD diagnosis to ruxolitinib & belumosudil combination	574 (82-4001) days
Median follow up from ruxolitinib & belumosudil combination	364 (162-777) days
NIH cGVHD severity at the strat of R+B, n(%)	
Severe	n=36 (63.2%)
Moderate	n=21 (36.8%)
Median systemic LOTs before R+B	5 (3-8)
≥5 prior LOTs	40 (70.2%)
Median number of organs involved with cGVHD at the start of R + B	4(2-7)
≥4 organs involved	37 (64.9%)
Organ involvement, n(%)	
skin	30 (52.6%)
eyes	46 (80.7%)
mouth	40 (70.2%)
esophagus	17 (29.8%)
Upper gastrointestinal	6 (10.5%)
Lower gastrointestinal	2 (3.5%)
liver	6 (10.5%)

lung	36 (63.2%)
Joints/fascia	29 (50.9%)
Vulvo/vaginal	22 (38.6%)
Prior systemic cGVHD therapy type	
Corticosteroids	57 (100.0%)
Cyclosporin	55 (96.5%)
Tacrolimus	36(63.2%)
Mycophenolate mofetil	33 (57.9%)
Ruxolitinib	57 (100.0%)
Methotrexate	24 (42.1%)
Imatinib	5 (8.8%)
Mesenchymal stem cells	18 (31.6%)
Others	7 (12.3%)

Table1 Baseline patient demographics and clinical characteristics

Summary/Conclusion

These results confirm the clinically meaningful efficacy and safety of dual JAK/ROCK inhibition in this heavily pretreated population. These findings support the mechanistic rationale for concurrent pathway inhibition and warrant prospective validation in randomized controlled trials.

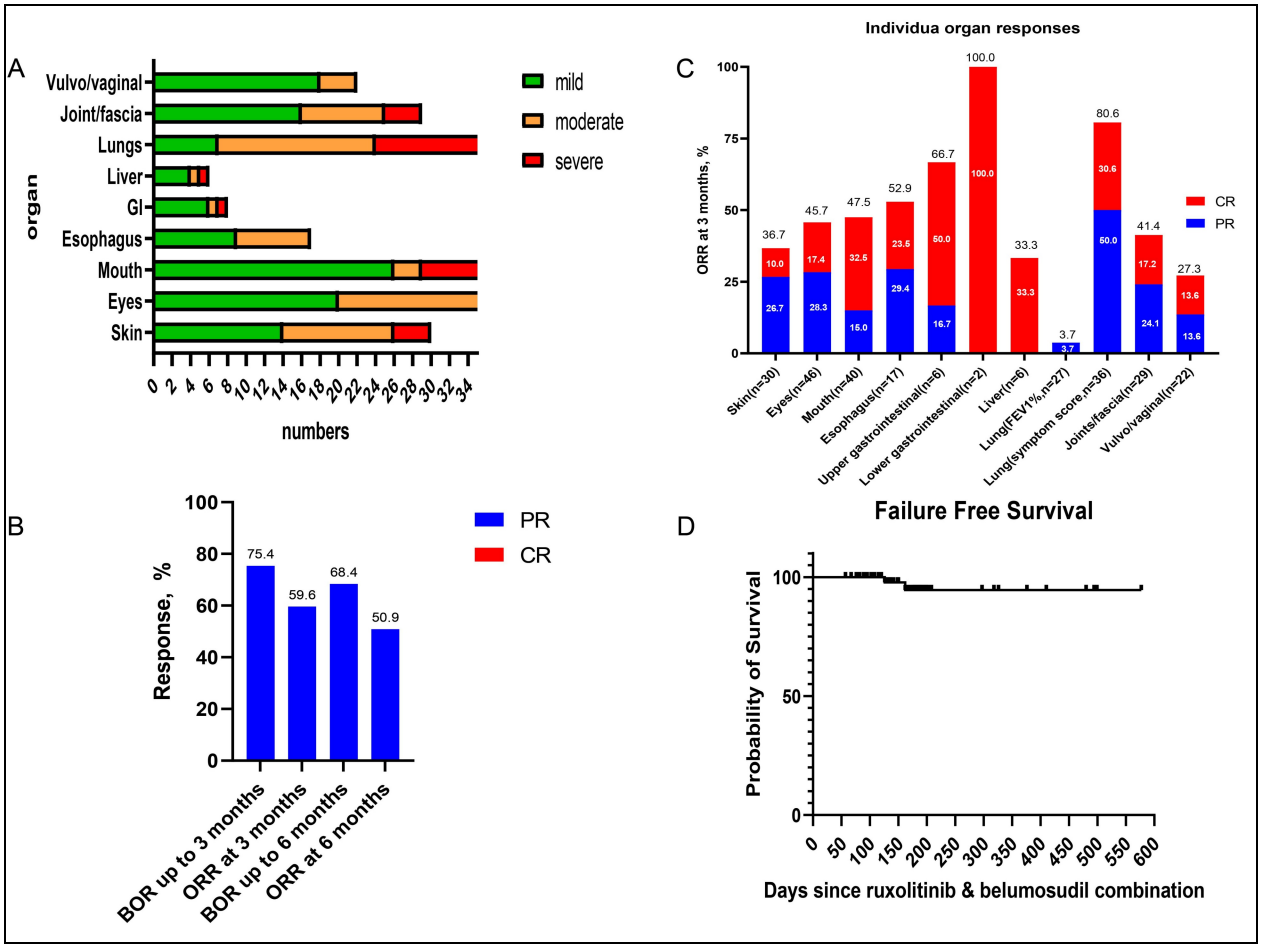

Figure 1 The efficacy of ruxolitinib and belumosudil combination for cGVHD (A) Grade by organ system at start before combination. (B) BOR and ORR to combination therapy. (C) Response to combination ruxolitinib and belumosudil by organ system. (D) Estimated failure free survival.