Belumosudil for Chronic Graft-versus-Host Disease (cGVHD) After 2 or More Prior Lines of Therapy: The ROCKstar Study

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Learning Objectives

Describe	pathophysiology, standard of care, and treatment gaps for chronic graft-versus-host disease (cGVHD)
Discuss	evidence supporting belumosudil for cGVHD
Identify	current place in therapy and clinical implications of belumosudil

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cGVHD Background

- Major complication after allogeneic hematopoietic stem cell transplant (HSCT)
- Leading cause of morbidity and nonrelapse mortality (NRM) in survivors > 2 years
- Incidence is 30-50% despite prevention strategies
- Steroid refractory cGVHD is common and a poor prognostic
- Characterized by immune-mediated tissue damage, fibrosis, and pleiotropic organ manifestations

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REFERENCE

cGVHD

Definition

- Previously ≥ 100 days post transplant
- Specific syndrome involving, for example, scleroderma, dry eyes, dry mouth, bronchiolitis obliterans ***anytime post-transplant***
- Can overlap with acute GVHD

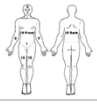
Diagnosis

- Physical Exam
- Clinical Assessment

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN[4]

Please complete for new diagnosis and follow-up with cGVHD (e.g. Day +100, 180, annually, at start of any new cGVHD flare)

Name:_____ MRN:_____ Current Weight: _____Kg Today's Date: _____

Component	Findings		Scoring (see skin score worksheet)
Skin 	Erythematous rash of any sort		% BSA (max 100%)
	Moveable sclerosis		% BSA (max 100%)
	Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis		% BSA (max 100%)
	Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer		Location: _____ Largest dimension: _____cm
Eyes Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: mm of wetting	Left Eye: mm of wetting	

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Filipovich AH, et al. Biol Blood Marrow Transplant. 2005 Dec;11(12):945-56.
Georgia Cancer Center. BMT.09.07. 2020.

Severity Grading

Severity	Mild	Moderate	Severe
Number of organs	1 - 2	≥ 3	≥ 3
Severity of organs	1 (excluding lung)	≥ 3 organs – 1 1 organ (not lung) – 2 Lung – 1	3 (or lung 2)

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Jagasia MH, et al. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.
Wolff D, et al. Biol Blood Marrow Transplant. 2010 Dec;16(12):1611-28.

First-Line Treatment

Prednisone 1 mg/kg/day

- with or without tacrolimus, sirolimus, or cyclosporine

Mild cGVHD

- Topical Immunosuppressants or systemic steroids

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Wolff D, et al. Biol Blood Marrow Transplant. 2010 Dec;16(12):1611-28.

Previous Studies

Study (date)	Design	Population	Intervention	Outcome
CNI – K, et al. Blood. 2002.	Prospective, randomized	• Newly diagnosed • Extensive • PLTs ≥ 100,000 • N=287	• PRED + CSP • PRED	TRM at 5 years • CSP (17%) vs. Non-CSP (13%) No difference in OS, recurrent malignancy, secondary therapy, discontinuation of IST Avascular necrosis: 13% vs 22% (p = 0.04) CSP may reduce steroid toxicity, but not TRM
Steroids – S, et al. Blood. 1988.	Prospective, randomized, double-blind, placebo-controlled	• Newly diagnosed • Extensive • N=179	• PRED + placebo (Group 1) • PRED + AZA (Group 2) • PLTS < 100,00, PRED (Group 3)	Median duration of 2 years NRM • Group I (21%), II (40%), III (58%) • I v. II p = 0.003; I v. III p = 0.002 Survival at 5 years • Group I (61%), II (47%), III (26%) • I v. II P = 0.03; I v. III p = 0.001 Infection rate: III > II > I

CNI (calcineurin inhibitor), PLTs (platelets), CSP (cyclosporine), PRED (prednisone), AZA (azathioprine), PLTs (platelets), NRM (non-relapse mortality), TRM (transplant-related mortality), OS (overall survival), IST (immuno-suppressive therapy)

Koc S, et al. Blood. 2002; 100:48-51.
Sullivan KM, Blood. 1988;72:546-554.

Previous Studies cont.

Study (date)	Design	Population	Intervention	Outcome
MMF – M, et al. Blood. 2009.	Double-blind, randomized multicenter trial	• Within 14 days of cGVHD s/s • CNI +/- PRED • N=230	• MMF (1000 mg with CSP or 750 mg BID) • Placebo • First-line	Resolution of cGVHD at 2yr • MMF (23%) vs. placebo (18%) Death • MMF vs. placebo • HR 1.99 (95% CI; 0.9-4.3)
Thalidomide – A, et al. Biol Blood Marrow Transplant. 2001.	Prospective randomized, open-lab trial	• Extensive cGVHD • N=54	• CSP + PRED +THAL (200-800 mg/day) • CSP + PRED	Response rate (P = 0.5) at 1yr • Thal (85%) vs. no thal (73%) Survival at 1yr • Thal (66%) vs. no thal (74%)
Thalidomide – K, et al. Blood. 2000.	Randomized, placebo-controlled, double-blind trial	• PRED + CSP/TAC • Poor prognosis: TCP or acute to chronic • N=51	• THAL 200-800 mg/day • Placebo • First-line	Drug Discontinuation (P = 0.2) • Thalidomide(92%); 53 days • Placebo (65%); 245 days Safety • Neutropenia • Neurologic symptoms

MMF (mycophenolate mofetil) TCP (thrombocytopenia), CSP (cyclosporine), PRED (prednisone), THAL (thalidomide), TAC (tacrolimus)

Martin PJ, et al. Blood. 2009;113:5074-5082.
Arora M, et al. BIBiol Blood Marrow Transplant. 2001;7:265-273.
Koc S, et al. Blood. 2000;96:3995-3996.

Bottom Line

Agent	Advantages	Disadvantages
Steroids	Sufficient as single agent in mild Best efficacy first-line	Osteoporosis, avascular necrosis of the bone, diabetes
CNI	Steroid sparing Severe or moderate CNI dependent	Renal toxicity, hypertension Only in combination with steroids
MMF	-	GI complaints, infectious and relapse risk Failed to improve efficacy
Azathioprine	-	Hematologic toxicity, infectious risk Mortality
Thalidomide	Concomitant relapse of multiple myeloma	Neurotoxicity, sedation, constipation, thrombosis

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Wolff D, et al. Biol Blood Marrow Transplant. 2010 Dec;16(12):1611-28.

Non-Responders

- Only half of patients respond to first line therapy . . .

Term	Action	Steroid and Dose	Time
Steroid-refractory	Progression despite	prednisone ≥ 1 mg/kg/day	≥ 1 week
	Persistence despite	prednisone at ≥ 0.5 mg/kg/day or 1 mg/kg every other day	≥ 4 weeks
Steroid-dependent	Steroids onboard to prevent recurrence or progression	prednisone doses > 0.25 mg/kg/day or >0.5 mg/kg every other day	≥ 2 unsuccessful attempts to taper, separated by at least 8 weeks

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Wolff D, et al. Biol Blood Marrow Transplant. 2010 Dec;16(12):1611-28.

Trial Challenges

- Limited patient population
- Endpoint variation for first-line treatment trials
- Poorly defined response criteria
- Variable selection criteria, baseline disease, and assessment timepoints

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Martin PJ, et al. Biol Blood Marrow Transplant. 2015 Aug;21(8):1343-59.

Second Line Therapy

Trial-and-Error System

- CNI (cyclosporine, tacrolimus)
- Extracorpeal photopheresis (ECP)
- mTOR inhibitors (e.g., sirolimus)
- Monoclonal antibodies (e.g., rituximab, alemtuzumab)
- Chemotherapy (e.g. methotrexate, cyclophosphamide, pentostatin)
- Tyrosine kinase inhibitors (e.g., imatinib, ruxolitinib, ibrutinib)
- Hydroxychloroquine
- Etanercept
- Interleukin-2

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Martin PJ, et al. Biol Blood Marrow Transplant. 2015 Aug;21(8):1343-59.

Ibrutinib - FDA Approved

Study (date)	Design	Population	Intervention	Outcome

Ibrutinib – M, et al. Blood. 2017.	Multicenter, open-label, single-arm study	• Moderate - severe
		• Glucocorticoid-refractory
		• Glucocorticoid-dependent
		• Failed ≤ 3 prior LOT
		• N=42
			• Ibrutinib 420 mg daily	Median follow-up 13.9 months
				• Best overall response (67%)
				• Sustained response ≥ 20 weeks (71%)
				• Median corticosteroid dose reduction
				  • 0.29 mg/kg/day to 0.12 mg/kg/day (week 49)
				• Discontinued steroids (n=5)
				• Safety
				  • Common: fatigue, diarrhea, muscle spasms, nausea, bruising
				  • ≥ Grade 3, ≥ 10%: fatigue, diarrhea, pneumonia
				  • ≥ Grade 3, ≥ 5%: pyrexia, headache, hyperglycemia, hypokalemia

Ibrutinib

LOT (lines of therapy)

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Miklos D, et al. Blood. 2017 Nov 23;130(21):2243-2250.

Ruxolitinib

Study (date)	Design	Population	Intervention	Outcome

Ruxolitinib – Z, et al. N Engl J Med. 2021.	Prospective, Phase 3, multicenter, randomized controlled trial	• Moderate - Severe
		• Glucocorticoid-refractory
		• Glucocorticoid-dependent
		• ≥ 12 yo
		• N=329
			• Ruxolitinib 10 mg twice daily
			• Investigator Choice (IC)
			• Randomized 1:1
			• Stopped:
			  • 47% ruxolitinib for toxicity
			  • 74% IC lack of efficacy
				At week 24
				• Overall response:
				  • Ruxolitinib (49.7%) vs. IC (25.6%)
				  • OR – 2.99; P<0.001
				• Median failure free survival
				  • Ruxolitinib (>18.6 mo) vs. IC (5.7mo)
				  • HR – 0.37; P<0.001
				• Lee symptom scale response
				  • Ruxolitinib (24.2%) vs. IC (11%)
				  • OR 2.62; P=0.001
				• Safety (≥ grade 3, ≥ 10%)
				  • Thrombocytopenia (15.2% vs 10.1%)
				  • Anemia (12.7% vs. 7.6%)

Ruxolitinib > Investigator Choice

Mo (month), OR (odds ratio), HR (hazard ratio)

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Zeiser R, et al. N Engl J Med. 2021 Jul 15;385(3):228-238.

Cost-Effectiveness

Study (date)	Design	Population	Intervention	Outcome

Steroid refractory – Y, et al. Biol Blood Marrow Transplant. 2018.	Meta-analysis	• Sole therapy for Steroid Refractory cGVHD
		• 1/2000 – 5/2016
		• 41 Studies
		• N=1047
			• Tacrolimus
			• Sirolimus
			• Rituximab
			• Ruxolitinib
			• Hydroxychloroquine
			• Imatinib
			• Bortezomib
			• Ibrutinib
			• ECP
			• Pomalidomide
			• Methotrexate (MTX)
				• Complete response (CR)
				  • Rituximab or MTX (7-30%)
				• Overall response rate (ORR)
				  • Tacrolimus or ruxolitinib (30-85%)
				• Cost per CR
				  • Ruxolitinib ($1,187,657)
				  • MTX ($680)
				• Cost per ORR
				  • MTX ($453)
				  • Ibrutinib ($242,236)
				• Most cost-effective
				  • MTX for all organ systems
				• Least cost-effective
				  • Pomalidomide & Imatinib

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Yalniz FF, et al. Biol Blood Marrow Transplant. 2018;24(9):1920-1927.

Gaps in Therapy

- Treatment is a balance between efficacy of regimen and toxicity of agents
  - Agents with minimal toxicity for long-term use are needed
  - IST can increase the risk of infection, secondary malignancy, and organ toxicities
- Effective, targeted agents are lacking

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Yalniz FF, et al. Biol Blood Marrow Transplant. 2018;24(9):1920-1927.

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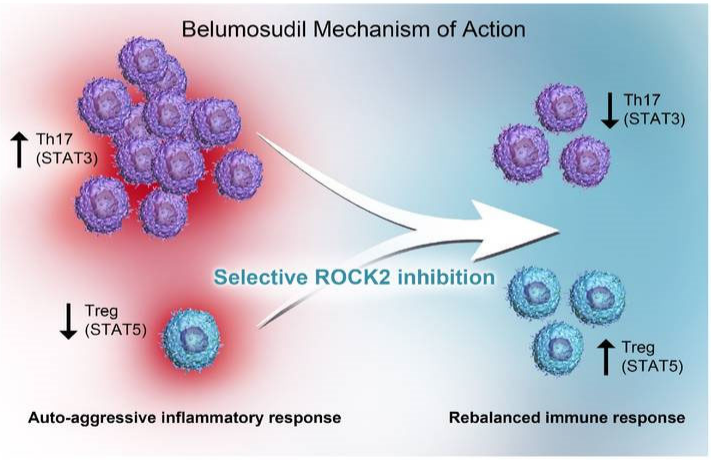
Blood. 2021 Jul 15:blood.2021012021. Epub ahead of print. PMID: 34265047.

ROCK2 Plays Key Role in Immune Diseases

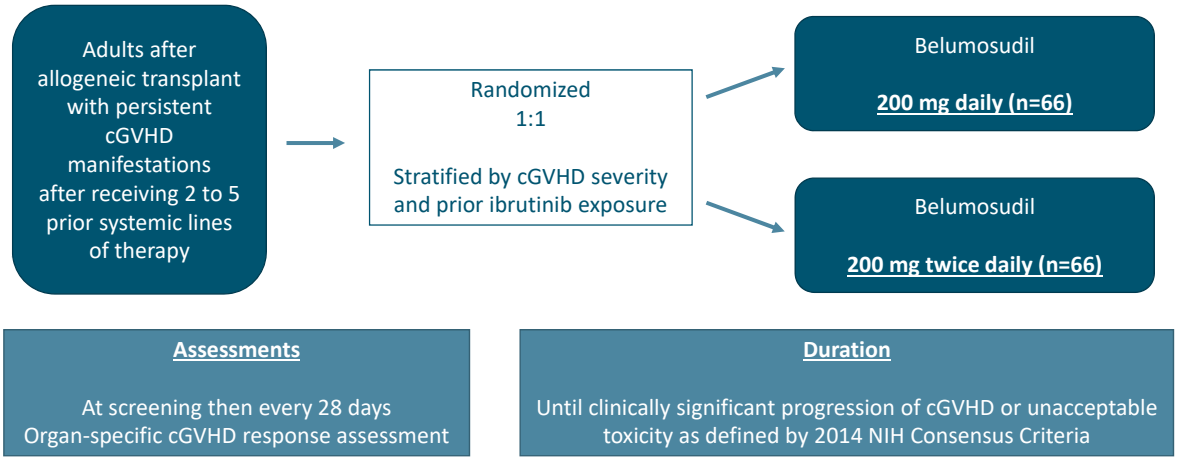
ROCK2 Inhibition Rebalances Immune Response to Treat Immune Dysfunction[1,2]

- **ROCK2 inhibition rebalances the immune system:**
  - Downregulates pro-inflammatory Th17 cells
  - Increases regulatory T (Treg) cells



[1]Proc Natl Acad Sci, 2014
[2]Blood, 2016

Study Design



Assessments

At screening then every 28 days
Organ-specific cGVHD response assessment

Duration

Until clinically significant progression of cGVHD or unacceptable toxicity as defined by 2014 NIH Consensus Criteria

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Cutler CS, et al. Blood. 2021 Jul 15. Epub ahead of print.

Patient Criteria

Inclusion	Exclusion
• ≥ 12 years • Persistent cGVHD • Received 2 – 5 systemic lines of therapy • Glucocorticoid therapy • Stable steroid dose ≥ 2 weeks • Karnofsky ≥ 60 or Lansky ≥ 60 if 12-15 years	• Cancer relapse • Histological relapse • Histological relapse of the underlying cancer • Current treatment with ibrutinib (28 day washout) • active hepatitis B virus or hepatitis C virus or history of HIV • QTc(F)>480ms • FEV1 ≤ 39% or has lung score of 3

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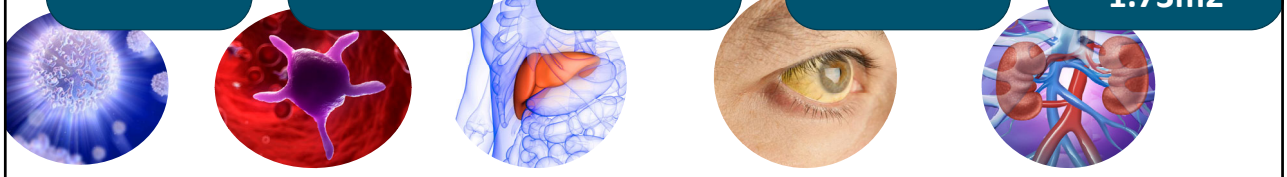
Cutler CS, et al. Blood. 2021 Jul 15. Epub ahead of print.

Laboratory Parameters

ANC	PLT	LFTs	Tbili	*GFR
≥ 1.5	≥ 50,000	≤ 3 x ULN	≤ 1.5 x ULN	≥ 30 mL/min 1.73m2



*using the Modification of Diet in Renal Disease-4 variable formula

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Cutler CS, et al. Blood. 2021 Jul 15. Epub ahead of print.

Acceptable Concurrent Treatments

- Concomitant corticosteroids
- Calcineurin inhibitors
- Sirolimus
- Mycophenolate mofetil
- Methotrexate
- Rituximab
- Extracorporeal photophoresis

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Cutler CS, et al. Blood. 2021 Jul 15. Epub ahead of print.

Outcomes

Primary

Best overall response rate at any time

Secondary

- Failure free survival
- Overall Survival
- Duration of response
- Change in Lee Symptom Scale
- Change in corticosteroid dose
- Change in cGVHD global severity rating
- Change in symptom activity

Safety

- Adverse event
- Serious adverse event
- Relative dose intensity

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Statistical Analysis

- 90% Power
  - 63 subjects per treatment arm, 10% dropout
  - ORR with 95.5% confidence interval lower bound of 30%
- Multiplicity analysis - Hochberg procedure
- Modified intent to treat population: ≥ 1 dose (goal n=126)
  - Interim (IA) - 2 months with one sided alpha of 0.0025
  - Primary – 6 months with one sided alpha of 0.0225 (0.025 if IA significant)
  - Follow-up – 12 months
- Descriptive – ITT population

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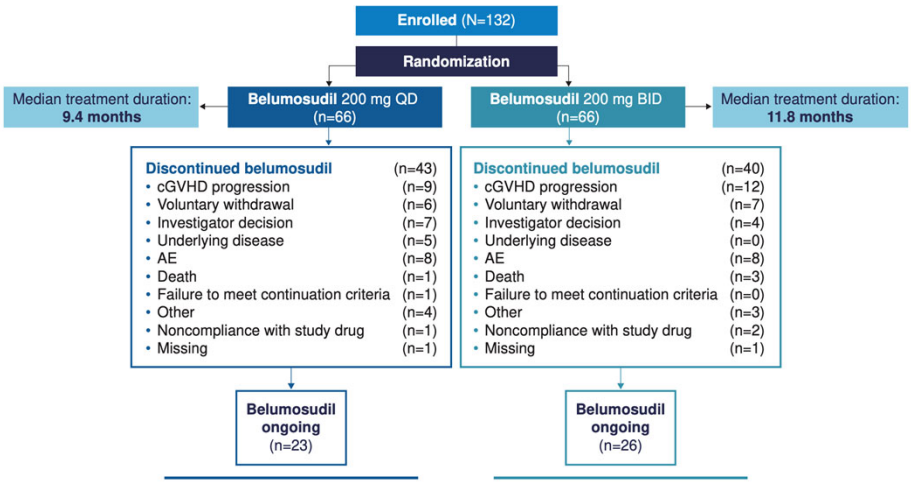
Enrollment



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Baseline Characteristics

Characteristic	Total (n=132)
Age, median (IQR), years	56 (21-77)
Median Karnofsky performance status, n (%)	
60 to 70	29 (22)
80 to 90	95 (72)
100	8 (6)
NIH cGVHD severity, n (%)	
Severe	89 (67)
Moderate	41 (31)
Mild	2 (2)
Organ involvement	
Median # of organs involved, n (range)	4 (0-7)
Skin, n (%)	110 (83)
Lungs, n (%)	27 (36)
Liver	12 (10)

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Baseline cGVHD Therapy

Therapy	Total (n=132)
Prior lines of therapy (LOT), median	3
Refractory to prior LOT, n (%)	79 (72)
Prior LOT type, n (%)	
CNI	87 (66)
Sirolimus	62 (47)
Ruxolitinib	38 (29)
Ibrutinib	45 (34)
MMF	33 (25)
Rituximab	28 (21)
ECP	63 (48)
Concomittant therapy, n (%)	
CNI	49 (37)
ECP	39 (30)
Sirolimus	35 (27)
MMF	13 (10)
Prednisone-equivalent dose at enrollment, mg/kg/day, median (range)	0.2 (0.03-1.07)

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Results

	200 mg qday (n=66)	200 mg BID (n=66)	Total (n=132)
ORR, % (95% CI)	74 (62-84)	77 (65-87)	76 (68-83)
Within 6 months	71 (59-82)	73 (60-83)	72 (64-80)
CR, n (%)	2 (3)	1 (2)	3 (2)
PR, n (%)	45 (68)	47 (71)	92 (70)
Clinically significant improvement in LSS, n (%)	39 (59)	41 (62)	80 (61)
Responder	34 (69)	36 (71)	70 (70)
Non-responder	5 (29)	5 (33)	30 (31)
Steroid reduction, n (%)	42 (64)	44 (67)	86 (65)
Δ from BL, mean, %	-43	-48	-45
Responder	-49	-22	-54
Non-responder	-22	-10	-16
Discontinuation, n (%)	13 (20)	15 (23)	28 (21)
TTR, median, weeks (range)	NR	NR	5 (4-66)
Responder DOR, median, weeks	NR	NR	54
2-year OS, % (95% CI)	NR	NR	89 (82-93)

ORR (overall response rate), CR (complete response), PR (partial response), LSS (lee symptom scale), BL (baseline), TTR (time to response), DOR (duration of response), OS (overall survival), NR (not reported)

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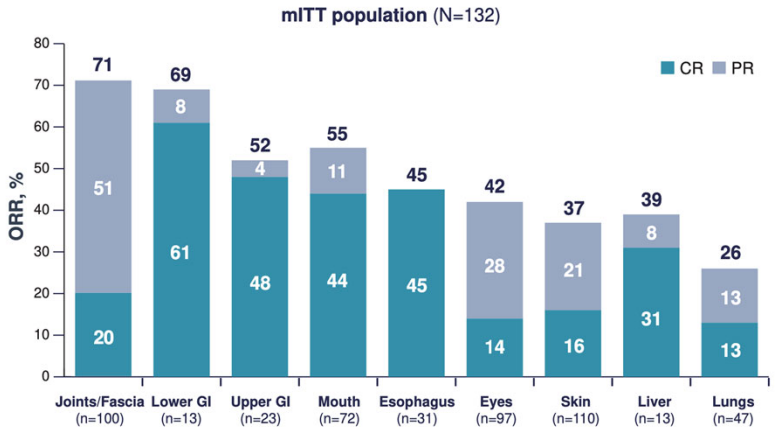
Organ System Response



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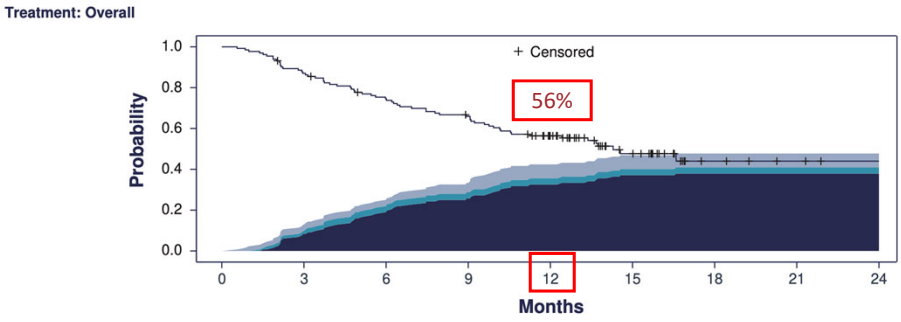
Failure Free Survival



Number at risk	132	114	96	84	62	26	7	3	1
EFS	100	87	74.6	65.9	56.4	47.7	44	44	44
New treatment for cGVHD	0	8.3	18.9	25.8	32.6	37.1	37.9	37.9	37.9
Relapse	0	1.5	3	3	3	3	3	3	3
Death	0	3	3	4.5	6.8	6.8	6.8	6.8	6.8

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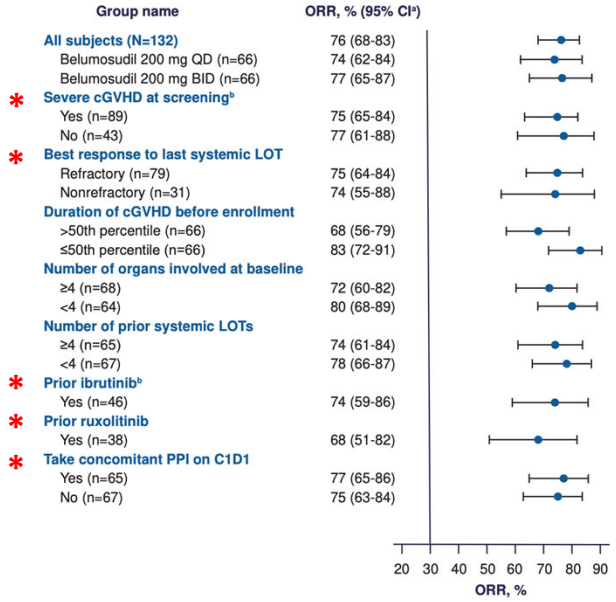
Subgroup Analysis

- ORR maintained across subgroup analysis

Figure 2.



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Safety

	200 mg qday (n=66)	200 mg BID (n=66)	Total (n=132)
Any adverse event, no (%)	65 (99)	66 (100)	131 (99)
Grade ≥ 3 adverse events, no (%)	37 (56)	34 (52)	71 (54)
SAEs	27 (41)	23 (35)	50 (38)
Drug-related SAEs	5 (8)	2 (3)	7 (5)
RDI, median			99.7%

- 200 mg qday – Grade 3 or 4, ≥ 5%
  - Pneumonia (9%)
  - Hypertension (6%)
  - Hyperglycemia (5%)
- 200 mg BID – Grade 3 or 4, ≥ 5%
  - Pneumonia (6%)
  - Hypertension (6%)
  - Hyperglycemia (5%)

SAEs (serious adverse events), RDI (relative dose intensity)

Common (≥ 20%)
Fatigue, diarrhea, nausea, cough, URTI, dyspnea, headache, peripheral edema, vomiting, muscle spasm

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Author's Conclusions

200 mg qday

Sustained, clinically meaningful responses

- regardless of response to prior treatment, severity of cGVHD, number of organs involved

Dosing and formulation are convenient

Well tolerated

- population vulnerable to AEs and IST
- remained on therapy

Improved QOL

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Critiques

- Strengths
  - Well written and designed – concise
  - Novel therapy – needed for this population
  - Response despite difficult to treat population
  - Generalizable - population was clearly defined
- Weaknesses
  - Lack of control group
  - Drop-out

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Reviewer's Conclusions

- Belumosudil is a targeted agent to be considered in patients with refractory cGVHD after ≥ 2 LOTs
- Despite reported percentages of AEs, belumosudil does not appear to significantly increase expected AEs from cGVHD therapy
- Provides convenient dosing for patients
- Further questions
  - Efficacy/safety in earlier stages of cGVHD
  - Cost

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Belumosudil Monitoring/ Management

- Monitoring
  - Pregnancy test at initiation
  - Initial labs: ANC ≥ 1.5, PLTs ≥ 50,000, eGFR ≥ 30
  - Tbili, AST/ALT → at least monthly
  - AEs: infection, infertility, edema, HTN, hyperglycemia
- Management
  - Film-coated – Do not crush
  - Drug-Drug interactions: gastric pH, CYP3A4
  - Administer with a meal

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Test your knowledge

Which of the following statements about the ROCKstar study is true?

A. Patients on concurrent treatment with ibrutinib were included
B. Patients with were randomized after steroids alone
C. Patients were randomized to belumosudil 200 mg daily, 200 mg BID, or best available therapy
D. Patients with known active hepatitis B virus or hepatitis C virus or history of HIV were excluded.

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Knowledge Check

Which of the following statements about the ROCKstar study is true?

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Knowledge Check

DK is a 35 yo female with T-cell non-Hodgkin lymphoma underwent 10/10 HLA-matched unrelated-donor peripheral blood HSCT. At her 25 month visit she was diagnosed refractory, severe cGVHD and is on treatment with tacrolimus, high-dose steroids, and rituximab. Her symptoms have persisted, and she is being considered for Belumosudil.

What is/are pertinent counseling points for Belumosudil?

A. Concurrent therapy with proton pump inhibitors require dose adjustment
B. Infertility risks and contraception in females of reproductive potential
C. Take belumosudil with food
D. All of the above

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Test your knowledge

DK is a 35 yo female with T-cell non-Hodgkin lymphoma underwent 10/10 HLA-matched unrelated-donor peripheral blood HSCT. At her 25 month visit she was diagnosed refractory, severe cGVHD and is on treatment with tacrolimus, high-dose steroids, and rituximab. Her symptoms have persisted, and she is being considered for Belumosudil.

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Questions?

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