«Nuovi farmaci nella GVHD acuta e cronica»

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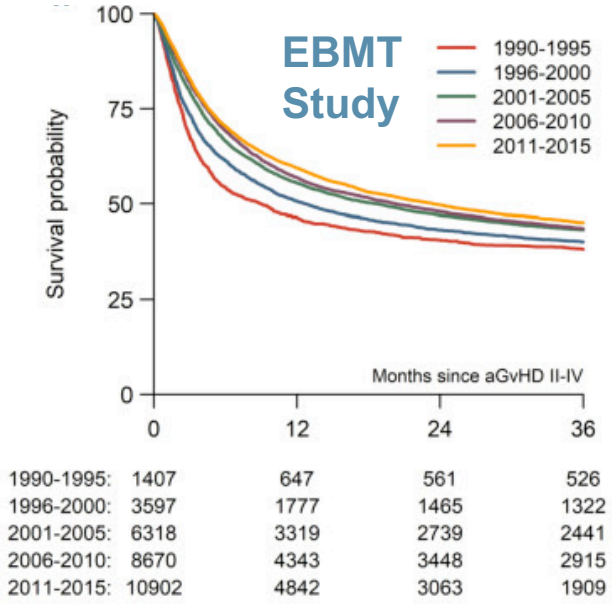
Disclosures

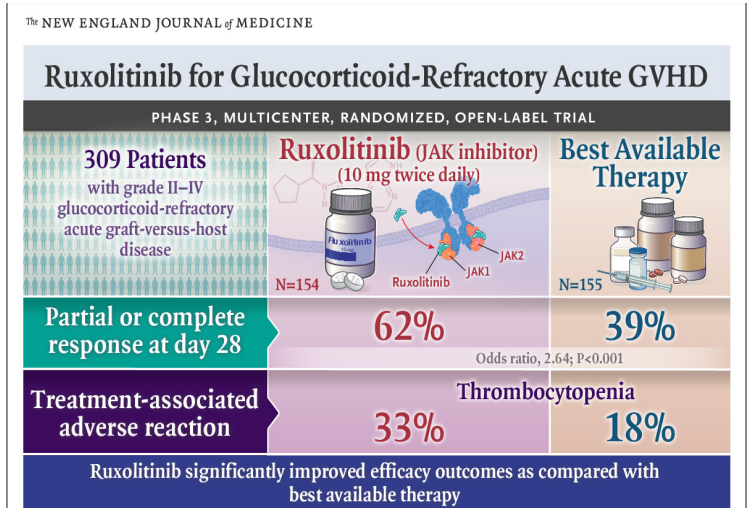
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MEDAC					**X**		

Acute Graft-*versus*-host disease in the modern era: are things getting better?

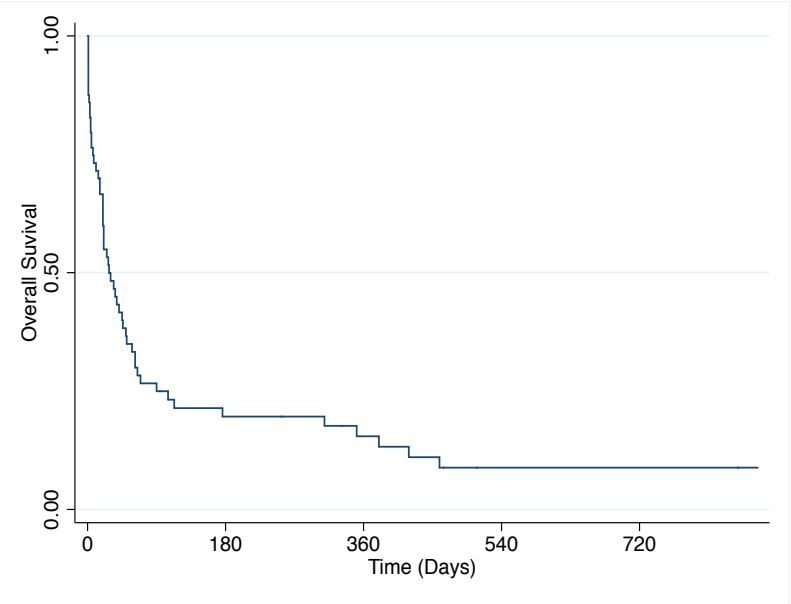


1990-1995:	1407	647	561	526
1996-2000:	3597	1777	1465	1322
2001-2005:	6318	3319	2739	2441
2006-2010:	8670	4343	3448	2915
2011-2015:	10902	4842	3063	1909

Incidences of aGvHD grades II-IV by 100 days significantly decreased from 40% (1990-1995) to 28% (2011-2015)



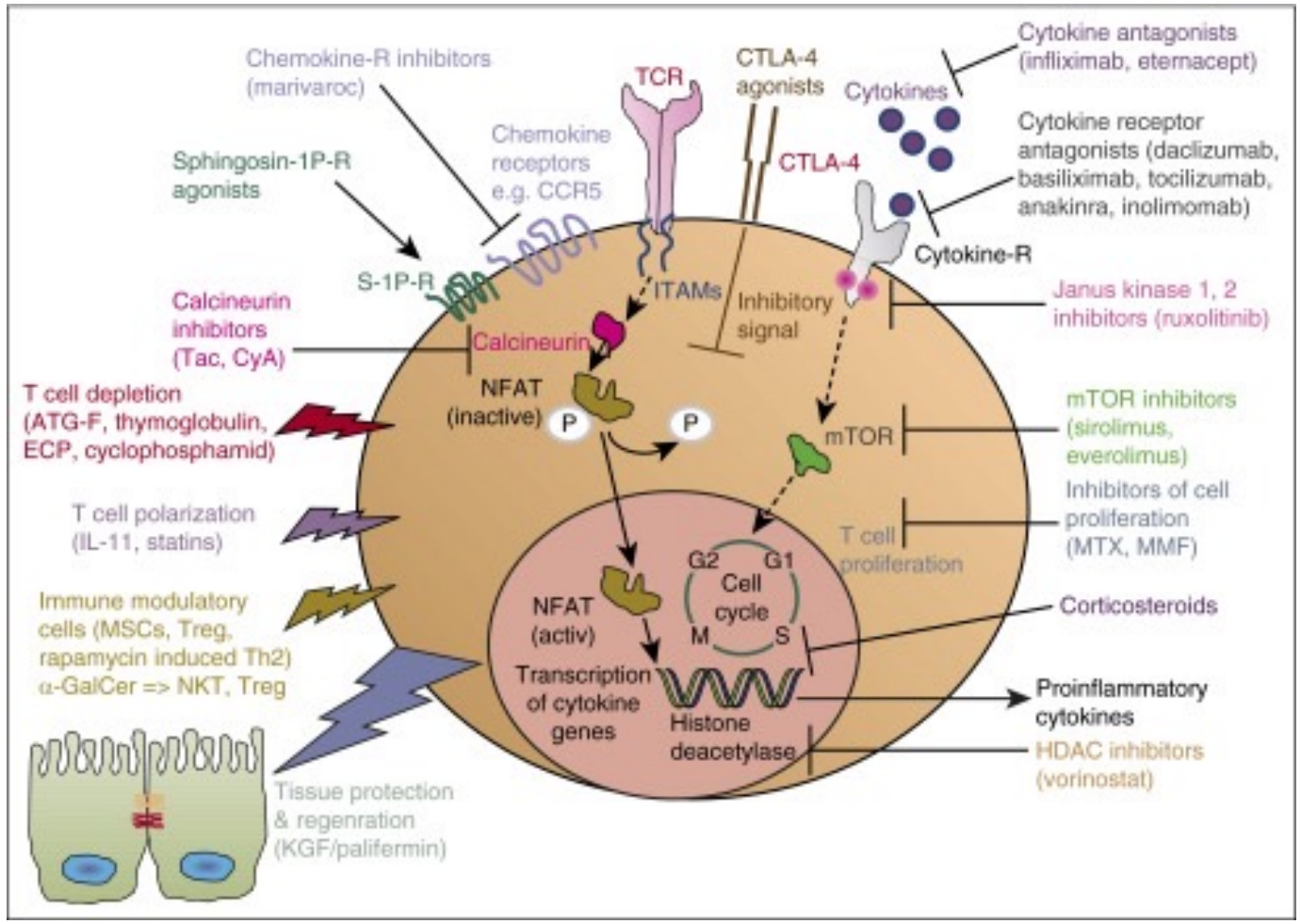
- FFS Ruxolitinib 1 year: 41%
- No significant difference in NRM and OS (11.1 months vs. 6.5 months)



Ruxolitinib for SR-aGVHD results in resistance or intolerance in 1/5 of patients

Greinix HT, Haematologica. 2022; Zeiser R, Blood Adv. 2020; Abedin S, Br J Haematol. 2021.

Beyond Ruxolitinib in acute GvHD



Zeiser R, Blazar BR.,Blood. 2016 Jun 23;127(25):3117-26.

Acute GVHD[1]

The following agents are often used in conjunction with the original immunosuppressive agent.

FDA-approved category 1 agents

- **Ruxolitinib (category 1)[c,2]**

Alternative agents (listed in alphabetical order)

- **Alemtuzumab[3,4]**
- **Alpha-1 antitrypsin[5]**
- **ATG[6]**
- **Basiliximab[7]**
- **Calcineurin inhibitors (CNIs) (eg, tacrolimus, cyclosporine)**
- **Etanercept[8]**
- **Extracorporeal photopheresis (ECP)[d,9]**
- **Infliximab[10]**
- **mTOR inhibitors (eg, sirolimus)[11,12]**
- **Mycophenolate mofetil[13,14]**
- **Pentostatin[15-17]**
- **Tocilizumab[18-21]**
- **Urinary-derived human chorionic gonadotropin/ epidermal growth factor (uhCG/EGF)[22]**
- **Vedolizumab[23]**

NCCN Guidelines Version 3.2025

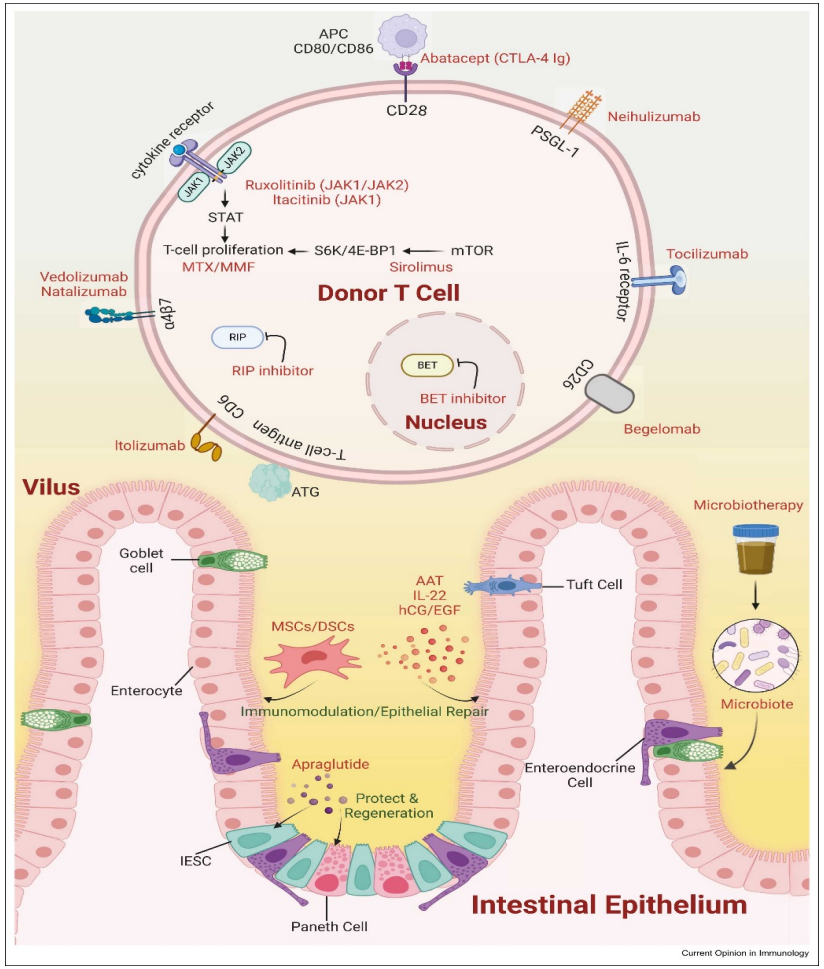
Emerging agents for Ruxolitinib-Refractory acute GvHD

Monoclonal antibodies
- Apraglutide
- Basiliximab
- Begelomab
- Itolizumab
- Natalizumab
- Neihulizumab (ALTB-168)
- Tocilizumab
- Vedolizumab

Targeted treatment
- Receptor-interacting protein kinase 1 inhibitor (RIP1)
- Bromodomain and extra-terminal domain (BET)

Immune modulation

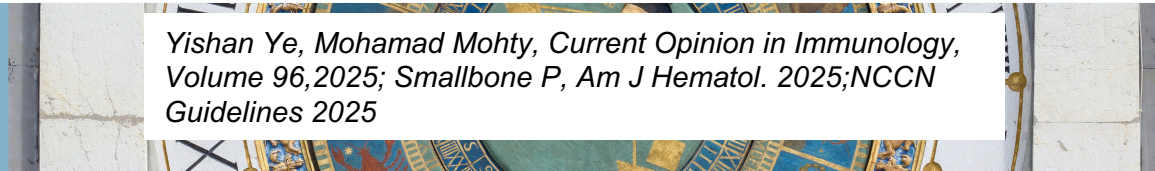
Decidual stromal cells
Fecal Microbiota Transplantation (FMT)
Interleukin-22
Mesenchymal Stromal Cells (MSCs)
Urinary-derived human chorionic gonadotropin (uhCG)
α1-Antitrypsin (AAT)



Yishan Ye, Mohamad Mohty, Current Opinion in Immunology, Volume 96,2025,102649,ISSN 0952-7915,

Emerging agents for acute GvHD

DRUG/TREATMENT	MECHANISM	STUDY DESIGN	RESULTS	NOTES
MONOCLONAL ANTIBODY				
Apraglutide	Glucagon-like peptide 2	STARGAZE, phase 2 (n=31 pts)	Day 28 ORR: 58%; CR 25.8%; Day 28 lower-GI ORR: 54.8%, CR 29%, 42% all organ ORR	SR-lower GI aGvHD + Ruxolitinib
Begelomab	Monoclonal antibody directed against CD26	Phase 1/2 (n=69 pts)	Day 28 ORR: 75% in the prospective cohort, 61% in compassionate use patient Day 28 CR: 11% in prospective cohort, 12% compassionate use patients	SR-aGvHD (No previous Ruxolitinib) 1 y OS=50% (prospective) 1y OS=33% (compassionate)
		Phase II/III	Terminated early due to lack of accrual	/
Itolizumab	Monoclonal antibody against the costimolatory receptor CD6	EQUATE Phase 1b/2	Day 29 CR: 55%, ORR 68% for newly diagnosed grade III-IV acute GI GvHD	aGvHD **First line** + steroids
		EQUATOR Phase 3	Trial recruiting	aGvHD **First line**
Natalizumab	Anti-a4 α4β7 antibody	Single arm Phase 2 (n=21)	Day 28 ORR for new onset acute GI aGvHD: 57% 6 month OS 52%	aGvHD **First line** 300 mg, 2nd dose repeated 4 weeks later
		Phase 2 (n=75)	Day 28 ORR for new onset acute GI aGvHD: 60% No difference in overall or CR between Nata+corticosteroids and corticosteroids alone	SR-aGvHD +corticosteroids
Neihulizumab	Immune checkpoint agonistic antibody that binds to human CD162 (PSGL-1)	Phase 1	Day 28 ORR:69% (cohort 1 3 o 6 mg) ORR 50% (cohort 2 6 mg/kg followed by weekly doses of 4 mg/kg for 3 weeks)	SR-aGvHD 3-6 mg/kg single dose
Tocilizumab	IL-6 receptor blocker	Phase 1/2	Terminated for safety by the data and safety monitoring board	SR-GvHD (no Ruxo) Median survival 26 days
		Tocilizumab+Itacitinib	Terminated Early due to under-recruitment	SR-GvHD
Vedolizumab	Monoclonal antibody targeting integrin α4β7	Phase 2 (n=20 pts)	Failed to meet the primary efficacy end point	SR-GI GvHD (60% received Ruxo) 80% infections!



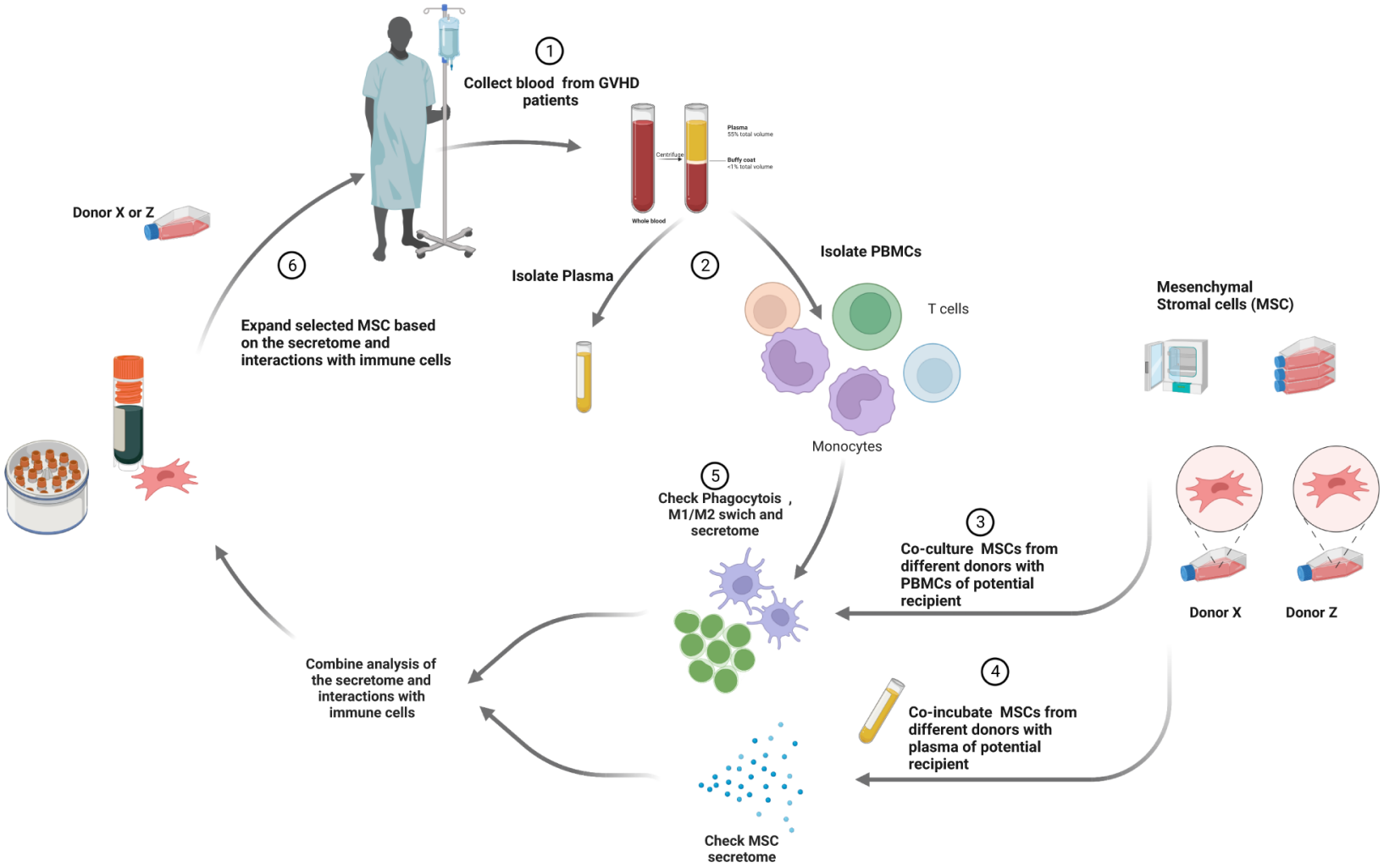
Yishan Ye, Mohamad Mohty, Current Opinion in Immunology, Volume 96,2025; Smallbone P, Am J Hematol. 2025;NCCN Guidelines 2025

Emerging agents for acute GvHD

DRUG/TREATMENT	MECHANISM	STUDY DESIGN	RESULTS	NOTES
TARGETED TREATMENT				
RIP-1 inhibitor (GDC-9264)	Receptor interacting protein kinase (apoptosis in the gut)	Phase 1	Termined for business reason	In combination with SOC for the treatment of aGvHD
BET inhibitor (PLX51107)	Bromodomain and extraterminal domain (BET) proteins	Phase 1b/2	Termined due to sponsor reason	
IMMUNOMODULATION				
Decidual stromal cell	Stromal cells derived from the placenta	Retrospective study (n=38)	ORR 81% , CR 42%	Grade I-IV SR-aGVHD
		Phase 1/2	Results awaited	SR-aGVHD
Fecal Microbiota Transplantation (FMT)	Transplantation of fecal suspension from a healthy donor	HERACLES Study, phase 2 (MaaT013)	Day 28 GI ORR:38% (24 pts); Compassionate use patients (n=154) Day 28 ORR rate: 49%; Steroid and ruxolitinib refractory (n=58) Day 28 GI ORR: 59%; 1-year OS:72%	SR-RR-GI aGvHD
		Metanalysis (n=242 pts)	ORR all 54% ORR GI 64%	
IL-22 (F-652)	Recombinant human IL22 molecule (Tissue-protective IL-10 family cytokine)	Phase 2 (n=27)	Day 28 ORR for new onset lower-GI aGvHD: 70%	aGvHD first line treatment “peribiotics”
Mesenchymal stromal cells (MSCs)	Multipotent progenitor cells	Phase 3	Day 28 ORR:83% Median failure-free survival: 11.3 months	SR-Agvhd CNI+Basiliximab +/- MSC
Urinary-derived human chorionic gonadotropin (uhCG)/EGF		Phase 1 (n=26 pts)	Day 28 CR:62% (I line), 54% (II lines)	
		Phase 2 (n=22)	Day 28 ORR:73%, CR 50%	
α1-Antitrypsin (AAT)	Circulating protease inhibitor – increase Tregs	Phase 2 (n=40)	Day 28 ORR 65%; CR 35%; Responses sustained in 73% of patients without intervening IS	60 mg/kg twice weekly for 8 doses

Yishan Ye, Mohamad Mohty, Current Opinion in Immunology, Volume 96,2025; Smallbone P, Am J Hematol. 2025;NCCN Guidelines 2025

Mesenchymal stromal cells (MSCs) in acute GvHD



BLOOD SPOTLIGHT | OCTOBER 16, 2025

Remestemcel-L-rknd (Ryoncil): the first approved cellular therapy for steroid-refractory acute GVHD

Aaron Etra, James L. M. Ferrara, John E. Levine

Check for updates

Blood (2025) 146 (16): 1897–1901.

https://doi.org/10.1182/blood.2025028553

Article history

Share Tools

Abstract

Until recently, the JAK1/2 inhibitor ruxolitinib (Jakafi) was the only therapy for steroid-refractory acute graft-versus-host disease approved by the US Food and Drug Administration (FDA) for use in patients aged >12 years. The FDA has now approved a potent mesenchymal stromal cell product, remestemcel-L-rknd (Ryoncil), for children aged ≤18 years, showing 70% response rates and ~70% 6-month survival. In this spotlight, we highlight this important advance in the field.

Clinical Study

Efficacy of Cell Therapy with allo-**MSC**s in patients with **G**vhd **R**esistant to **R**uxolitinib second line therapy: A Phase IIB Clinical Trial

(MSC-GRR2 Study)

Clinical Study Protocol

Version 1.0 – 29 May 2025

Sponsor

ASST degli Spedali Civili di Brescia

Principal Investigator

Prof. Domenico Russo

Fecal Microbiota Transplantation in acute GvHD

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Early Access Program (EAP)

- In France: Authorized by the French regulator (ANSM) with Governing protocol for use
- In other countries in Europe: compassionate use

Data from 173 patients treated from July 2018 to Oct 2024, in 27 European sites (France, Italy, Spain, Austria, Switzerland, Germany)

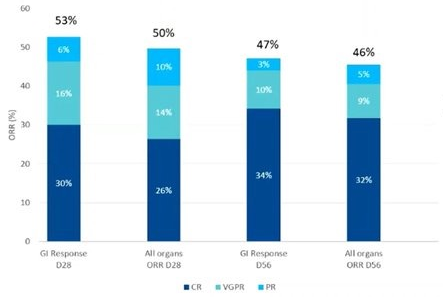
Main inclusion criteria

- Steroid refractory / dependent
- Acute GVHD with gut involvement, grade II to IV
- Any line of treatment
- ≥ 12 hours discontinuation of systemic antibiotics surrounding MaaT013 administration
- Patient not eligible to clinical trial (ARES - NCT04769895- recruitment completed in Oct 2024)

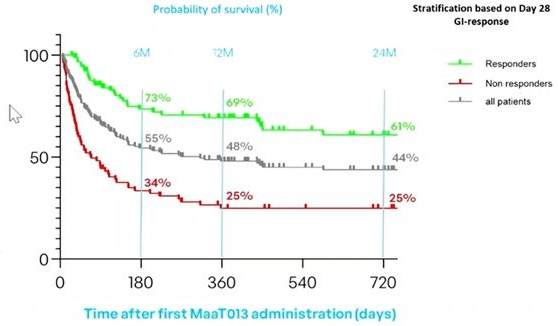
Patients Characteristics

Gender, n (%)	Male	96 (55%)
	Female	77 (45%)
Age at first MaaT013 administration (years)	Median [range]	59 [12;77]
Number of previous lines of treatment, n	Median [range]	2 [1;6]
Steroid status	Steroid refractory aGvHD	142 (82%)
	Steroid dependent-aGvHD	31 (18%)
Type of aGvHD	Classical	107 (62%)
	Late onset	17 (10%)
	Hyper-acute	22 (13%)
	Overlap syndrome and cGvHD	27 (16%)
GvHD grading (MAGIC), n (%)	I	0
	II	23 (13%)
	III	85 (49%)
	IV	65 (38%)

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD response (all EAP patients, n=173)



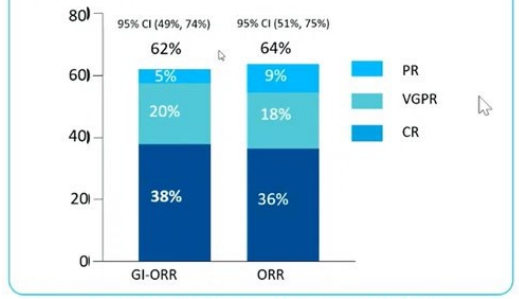
Sustainable response at D56



Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastrointestinal; M: months

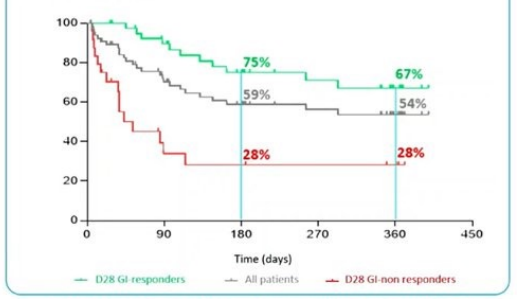
Phase 3 ARES: Strong Response to MaaT013 in aGvHD in 3L

Topline Results



Primary endpoint met with a significant GI-ORR ($p < 0.0001$)

Probability of Survival by D28 Response



Response-driven prolonged survival, with 54% probability 1-year OS compared to *Abedin et al. 2021*, 1-year OS of 15% in 3L

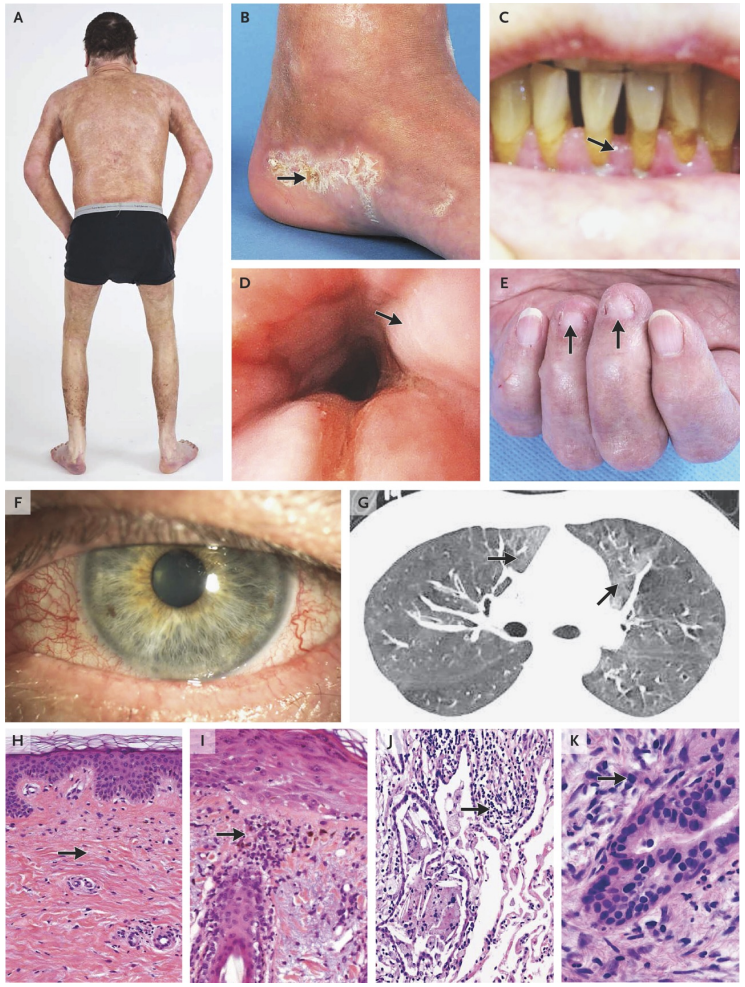
Ongoing safety monitoring until the 1-year follow-up, 1-year OS expected in late H2 2025 & Final results expected in Q1 2026

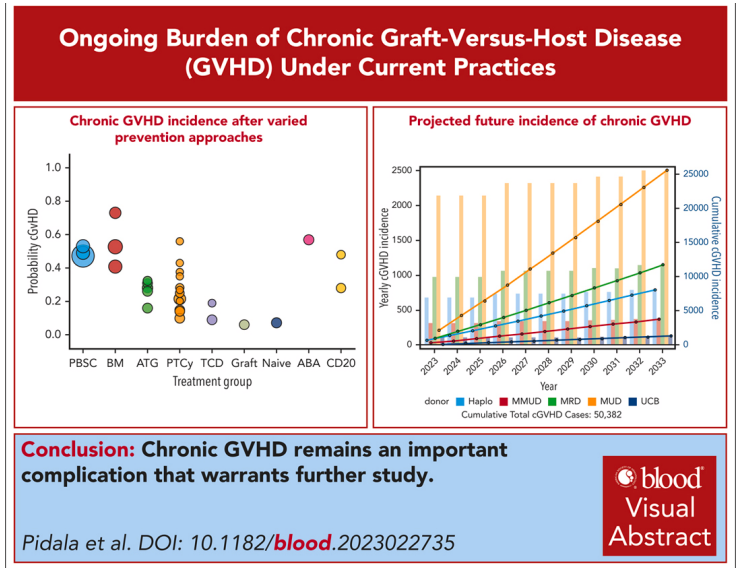
MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Conclusions

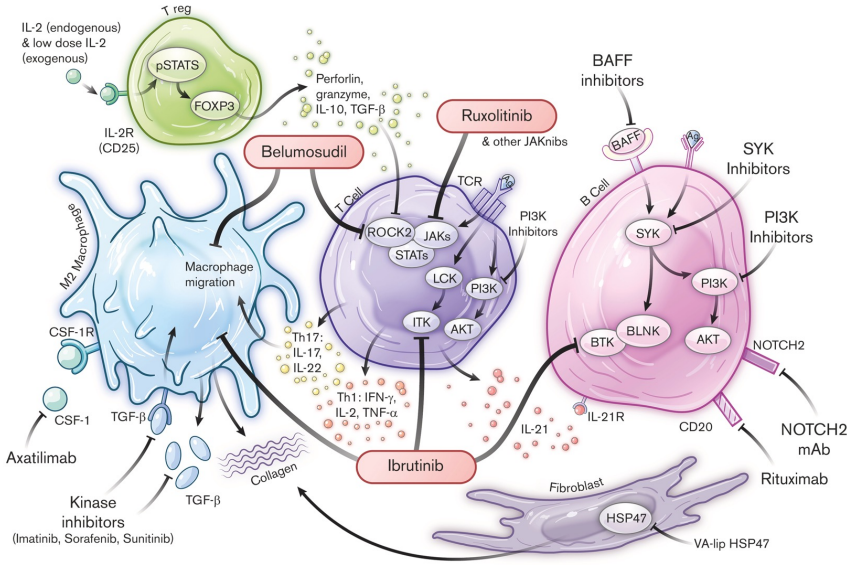
- EAP & Phase 3 results are consistent and confirm the high efficacy of MaaT013 for SR- and SD-GI- aGvHD
- High overall survival in this severe population
- Innovative mechanism of action based on immune modulation
- Favorable safety profile observed
- Phase 3 ARES Trial OS data are expected in late H2 2025

Abbreviations: ORR, overall response rate; GI, gastro-intestinal; SR-aGVHD, steroid-refractory acute graft-versus-host disease; SD-aGVHD, steroid-dependent acute graft-versus-host disease

Chronic GvHD: unresolved complication or ancient history?





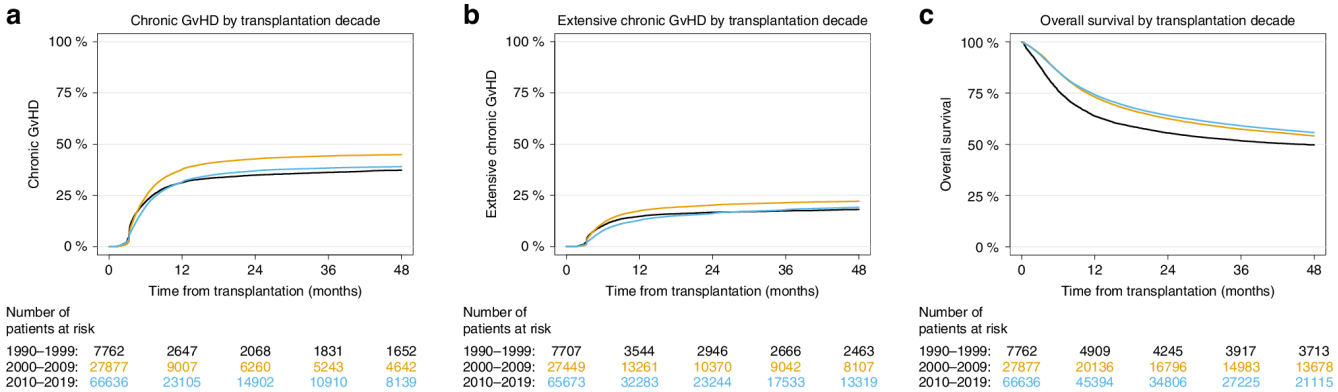


- Affects about 30-70% of recipients of allogeneic transplant
- Incidence depends on several factors including graft source, composition and GvHD prophylaxis
- Is associated with an increased risk of TRM and decreased overall survival and QoL
- Pre ruxolitinib era: chronic SR-cGvHD FFS 45% at 1 year and 31% at 2 years
- Ruxolitinib: Overall response at week 24 greater than BAT (49.7% vs. 25.6%), longer median FFS (>18.6 months vs. 5.7 months) and higher symptom response (24.2% vs. 11.0%)

Arai et al, BBMT, 2014;Wingard et al, JCO, 2011; Zeiser R, Blazar BR. N Engl J Med. 2016; Buxbaum N, Blood Adv. 2023.

Chronic GvHD: unresolved complication or ancient history?

Over 3 transplantation decades: EBMT data



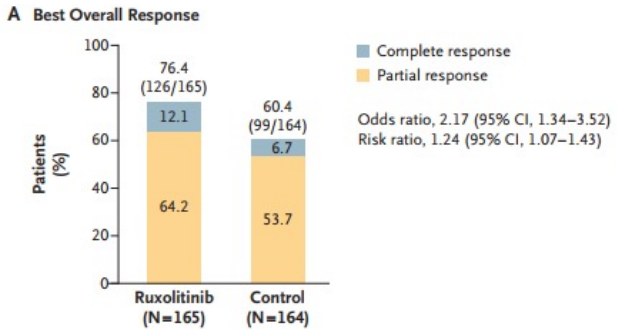
Pulanic D, Peric Z.,Bone Marrow Transplant. 2025

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

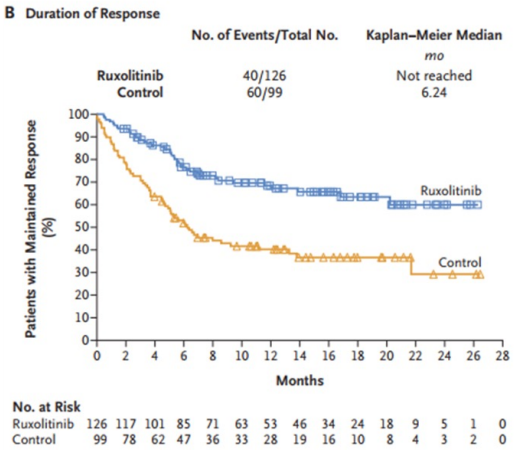
Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease

Robert Zeiser, M.D., Nicola Polverelli, M.D., Ph.D., Ron Ram, M.D.,

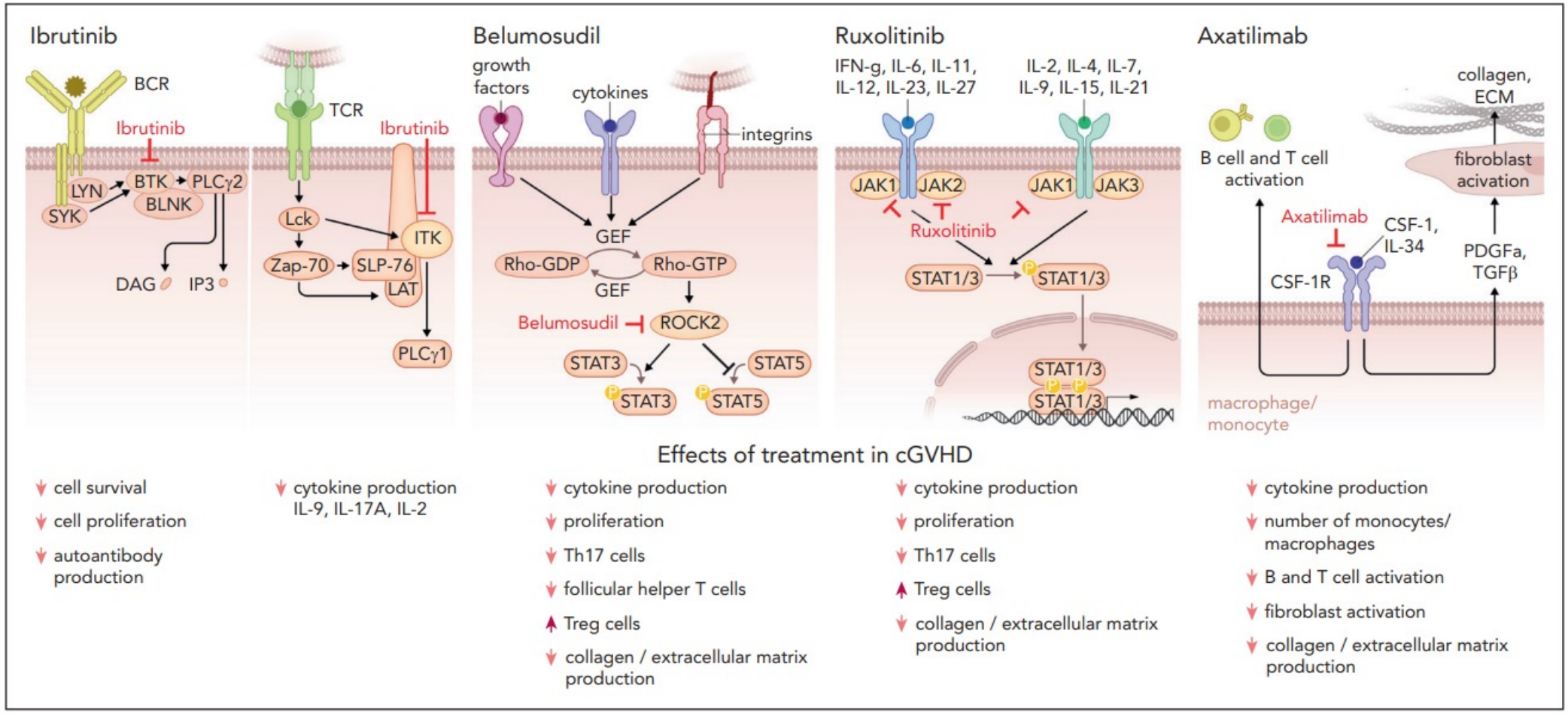


ORR lung: 9%

ORR sclerodermatous: 38%



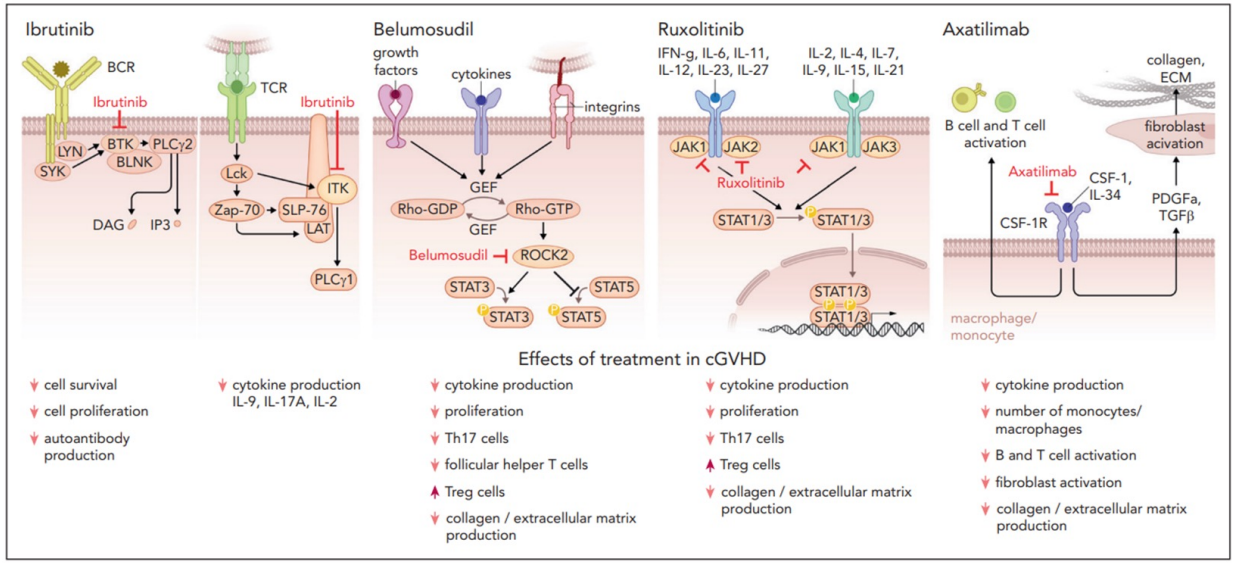
FDA-approved agents for Chronic GvHD



Lee SJ, Zeiser R.,Blood.

FDA-approved agents for Chronic GvHD

Variable	Ibrutinib (adult)[18]	Ibrutinib (pediatric)[16]	Ruxolitinib[17]	Belumosudil[18]	Axatilimab[19]
Approval date (age, y, or weight)	8/2017 (age ≥12)	8/2022 (age ≥1)	7/2021 (≥12)	9/2021 (≥12)	8/2024 (≥40 kg)
Study design					
Design	Phase 1b/2, single arm, open label	Single arm, open label	Randomized, phase 3, open label	Randomized, phase 2, open label, 2 doses	Randomized, phase 2, open label, 3 doses
Comparator	Historical	Adult PK	Best available therapy (N = 10)	Historical	Historical
Primary end point	Best ORR	PK and safety	ORR at 24 wk	Best ORR	Best ORR within 6 cycles (169 d)
Secondary end points	Sustained response ≥20 wk, corticosteroid dose reductions, change in symptoms	ORR by 24 wk, duration of response, survival	Key: FFS, Lee symptom scale Others: organ responses, best ORR, duration of response, corticosteroid dose reductions, survival, change in QOL	Duration of response, change in symptoms, FFS, corticosteroid dose reductions, survival	Key: Lee symptom scale
Key inclusion criteria	Failed 1-3 prior therapy lines Erythema >25% BSA or oral mucosa score >4	Failed ≥1 prior line	Failed 1 prior line	Failed 2-5 prior lines	Failed 2-5 prior lines
Concurrent medications	Allowed	Allowed	Only corticosteroids and/or CNI	Allowed	Only corticosteroids, CNI, and/or mTOR inhibitors
Study design notes	—	Combined report with treatment naive	Crossover allowed after 24 wk	Excluded FEV_1 ≤39% or lung symptom score 3	—
NCT no.	02195869	03790332	03112603	03640481	04710576
Study population					
No. of patients on the agent/approved dose	42	47	165	66	80
Age, median (range), y	56 (19-74)	13 (1-19)	49 (13-73)	53 (21-77)	50 (7-76)
Time since diagnosis, median, mo	14	16	6	25	47
Severe cGVHD, %	?	74	59	70	79
No. of organs, median	2	?	?	4	4
Prior lines of therapy, median	2	2	1	3	4
Prior ibrutinib, %	0	0	0	33	34
Prior ruxolitinib, %	0	28	0	30	71
Prior belumosudil, %	0	0	0	0	20
Follow-up, median, mo	14	20	13	14	8
Efficacy					
Best ORR (CR + PR), %	67	77	76	74	74
CR	—	4% by 20 mo	12% by 13 mo	6% by 12 mo	1% (unknown time)
ORR (PR + CR) at 6 mo, %	—	60	50	—	—
Duration of response	71% at >5 mo	58% at 18 mo	69% at 12 mo	50% at 12 mo	60% at 12 mo
FFS	51% at 18 mo	59% at 18 mo	61% at 18 mo	57% at 12 mo	49% at 12 mo
Clinically meaningful decrease in symptoms	61%	?	24% at 24 wk	59%	60%
Organ responses, %*					
Skin response	88	47	41	37†	26
Joint/fascia response	—	58	38	71†	76
Mouth response	88	59	50	55†	52
Eye response	—	47	26	42†	30
GI response	91	90 (upper)	40 (upper) 53 (lower)	52 (upper)† 69 (lower)†	82 (upper)
Liver response	—	45	24	39†	40
Lung response	—	31	9	26†	47
AEs					
Grade ≥3 TEAEs, %	—	66	57	56	49
Grade ≥3 TEAEs >10%	Pneumonia, fatigue, diarrhea (10%-12%), infection (36%)	Fever (11%)	Cytopenias (9%-15%)	None	Pneumonia (10%)



Lee SJ, Zeiser R. Blood. 2025

Emerging agents for acute GvHD

Agent	Mechanism/ Target	Clinical Trial Identifier	Study Phase	No. of Patients	Line of Therapy	Dosing Schedule	Treatment Response	Toxicity
Baricitinib[53, 56]	JAK 1/2 Inhibitor	NCT02759731	I/II	24	Refractory after 1 line of therapy	Initial: 2 mg once daily[a]	6-month ORR: 79.2% (PR: 66.7%; MR: 12.5%)	• Upper respiratory tract infection (33%) • Hypophosphatemia (21%) • Hypokalemia (17%) • Hypertriglyceridemia (13%) • Nausea (13%)
Abatacept[54]	Selective costimulation modulator inhibiting CD28	NCT01954979	II	36	Refractory after 1 line of therapy	10 mg/kg IV x 6 doses Doses 1–3: every 2 weeks Doses 4–6: every 4 weeks	5-month ORR: 58% (All PR)	• Fatigue (9%) • Neutropenia (6%) • Headache (4%) • Upper respiratory tract infection (3%)
Ixazomib[55]	20S proteasome inhibitor	NCT02513498	II	50	Refractory after 1 line of therapy	4 mg once weekly on days 1, 8, 15 of a 28-day cycle x 6 cycles	6-month ORR: 40% (All PR)	• Nausea • Fatigue • Thrombocytopenia

Emerging agents for acute GvHD

CLINICAL TRIALS AND OBSERVATIONS | JUNE 12, 2025

A first-in-class JAK/ROCK inhibitor, rovadicitinib, for glucocorticoid-refractory or -dependent chronic GVHD

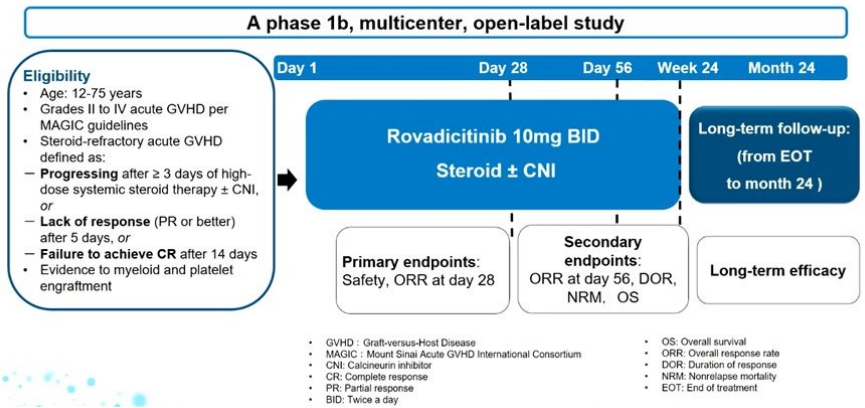
Clinical Trials & Observations

Yanmin M. Zhao, Yi Luo, Jimin M. Shi, Shunqing Q. Wang, Caixia K. Wang, Erlie L. Jiang, Chen Liang, Xiaoyu Y. Zhu, Xuejun J. Zhang, Fankai K. Meng, Hua Jin, Yeqian Q. Zhao, Jian Yu, Xiaoyu Y. Lai, Lizhen Z. Liu, Huarui R. Fu, Yishan S. Ye, Congxiao X. Zhang, Tao Wang, Lifan F. Tu, Xunqiang Q. Wang, He Huang

Drug/pivotal study design	Ibrutinib phase 1b/2, open-label study	Ruxolitinib phase 3 open-label, randomized trial (REACH3)	Belumosudil phase 2 randomized, multicenter registration (ROCKstar Study)	Axatilimab phase 2, multinational, pivotal, randomized study (AGAVE-201)*	Rovadicitinib multicenter, open-label, phase 1b/2a
Target and mechanism of action	BTK inhibitor Reduced activation, proliferation, and survival of B and T cells	JAK1/2 inhibitor Reduced inflammation, increased TREGs, reduced collagen deposition	ROCK2 inhibitor Reduced type 17 and follicular T-helper cells and enhanced regulatory T cells	CSF1R blocking antibody Inhibition of monocyte-driven inflammation and fibrosis	Dual JAK1/2 and ROCK1/2 inhibitor Combined inhibition of inflammatory and profibrotic pathways
Study population	N = 42 Age 18 years 1-3 lines of therapy cGVHD Steroid-refractory: 14% Steroid-dependent: 67% Lung involvement: 5%	N = 329 Age > 12 years 1 prior line Steroid-refractory: 71.4% Steroid-dependent: 28.6% Lung involvement: 44.8% Lung score 3: 8.5%:	N = 132 Age > 12 years 2-5 prior lines of therapy Refractory to prior line treatment: 72% Lung involvement: 36% Lung score 3: excluded Prior rux: 29% Prior ibru: 34%	N = 241 Age > 2 years ≥2 lines of therapy Refractory to last line of treatment: 48% Lung involvement: 40% Prior rux: 74% Prior belu: 23%	N = 44 Age > 12 years ≥1 prior lines of therapy Steroid-refractory: 25% Steroid-dependent: 75% Lung involvement: 59.1% Lung score 3: 23.1% Prior rux: 40.9% Prior belu: 0
Short-term efficacy	BOR (at any time): 67%	BOR until week 24: 76.4%	BOR* (at any time): 76%	ORR in first 6 cycles*: 74%	BOR until week 24: 86.4%
Long-term efficacy	Sustained response beyond 44 weeks: 55%	Median FFS above 18.6 mo	12-mo FFS*: 57%	12-mo FFS*: 64%	12-mo FFS: 85.2%
AEs leading to discontinuation	33%	16.4%	21%	6%*	3.5%*

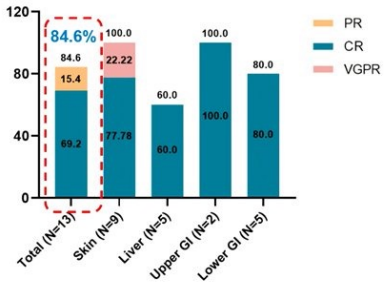
Rovadicitinib for aGVHD: PRECLINICAL → A PILOT STUDY

Study Design



Response outcomes

ORR at day 28 by baseline organ involvement

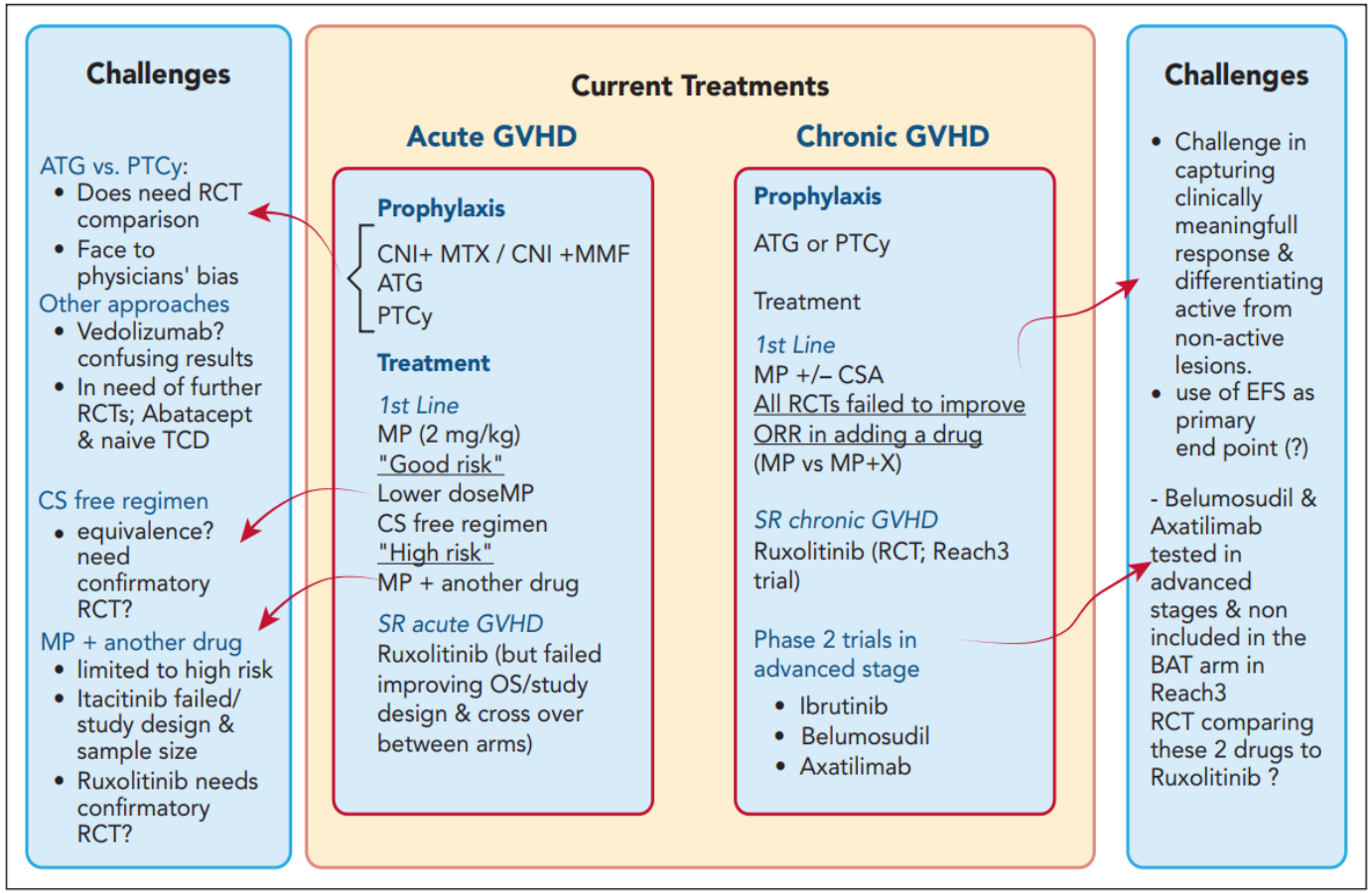


ORR at day 28 by baseline aGVHD grade

Response	Grade II (N=7)	Grade III/IV (N=6)	Total (N=13)
CR	5 (71.43)	4 (66.67)	9 (69.23)
VGPR	2 (28.57)	0	2 (15.38)
PR	0	0	0
Overall response	7 (100)	4 (66.67)	11 (84.62)
95%CI	[59.04, 100.0]	[22.28, 95.67]	[54.55, 98.08]

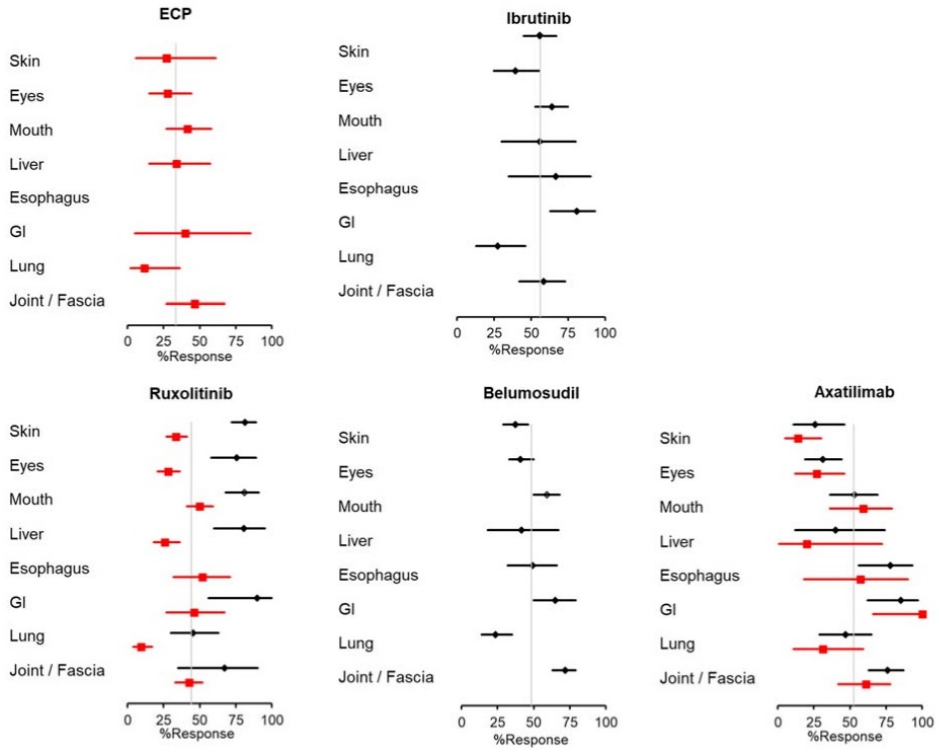
- The median follow-up time was 21.5 (range, 1-269) days. In preliminary efficacy analysis, the **ORR at day 28** in all patients was **84.6%.**
- All 7 patients **(100%)** with grade II aGVHD, achieved CR or VGPR. The ORR was 66% for III-IV aGVHD.

Challenges in GvHD



Socie G, Blood, 2025.

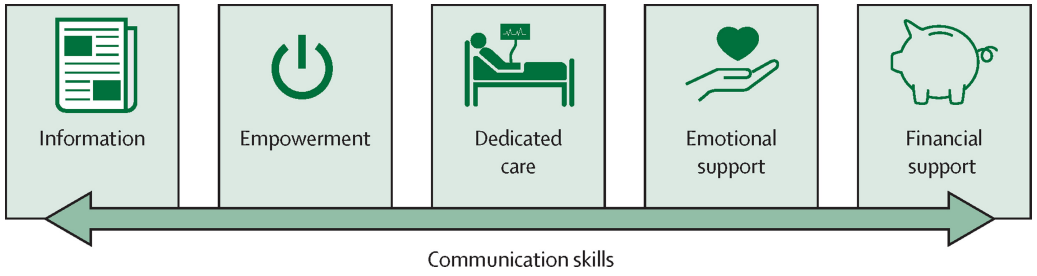
Treatment and organ response

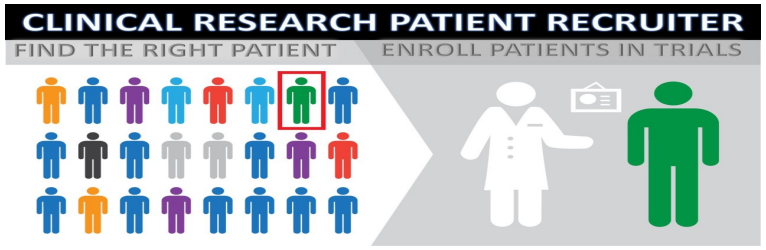


Morishita T, Cells,2025

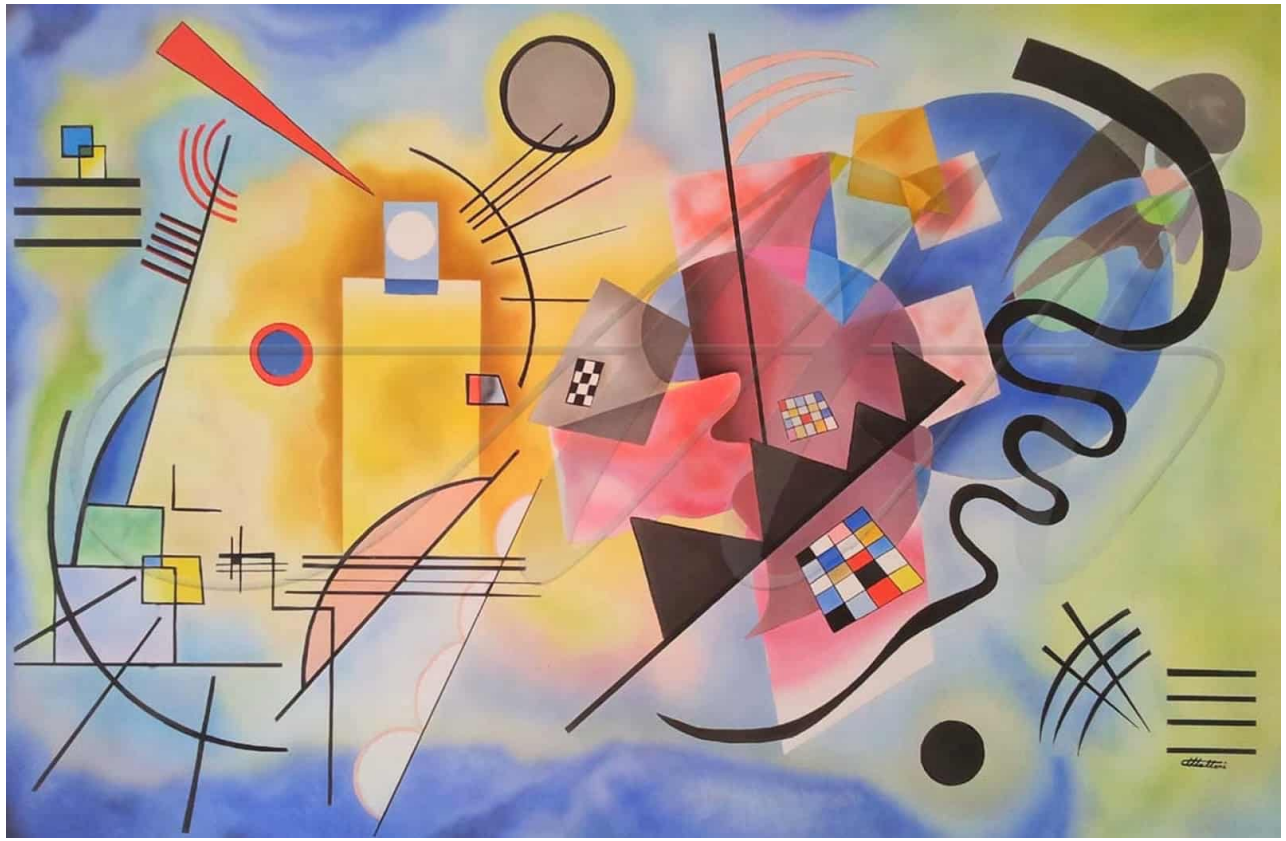
Conclusions

- Establishing the **ideal endpoint for clinical trials** in SR/RR-aGvHD is an essential next step (GvHD-free survival, OS, relapse?) – the endpoint used shoud be recognised by regulatory agencies (FDA-EMA) to ensure the approval of effective treatment for these patients.
- Future trials should also incorporate **biomarkers** to enrich the understanding of baseline patient characteristics and predict populations likely to benefict or deepen insights into the pathophysiology and pharmacodynamics of the study intervention
- The ultimate goal remains to prevent the occurence of SR/RR-GvHD through **effective prophylaxis and optimization of first-line therapy** beyond corticosteroides.
- Future research should focus on **personalized** treatment strategies, integrating biomarkers to guide therapy selection and combining **pharmacologic and non pharmacologic approaches** to achieve durable disease control and improved quality of life for patients with SR-aGvHD.





Grazie per l’attenzione



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