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Cancer Institute

Update in Transplantation and Graft-vs.-Host Disease

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MEDICAL SCHOOL



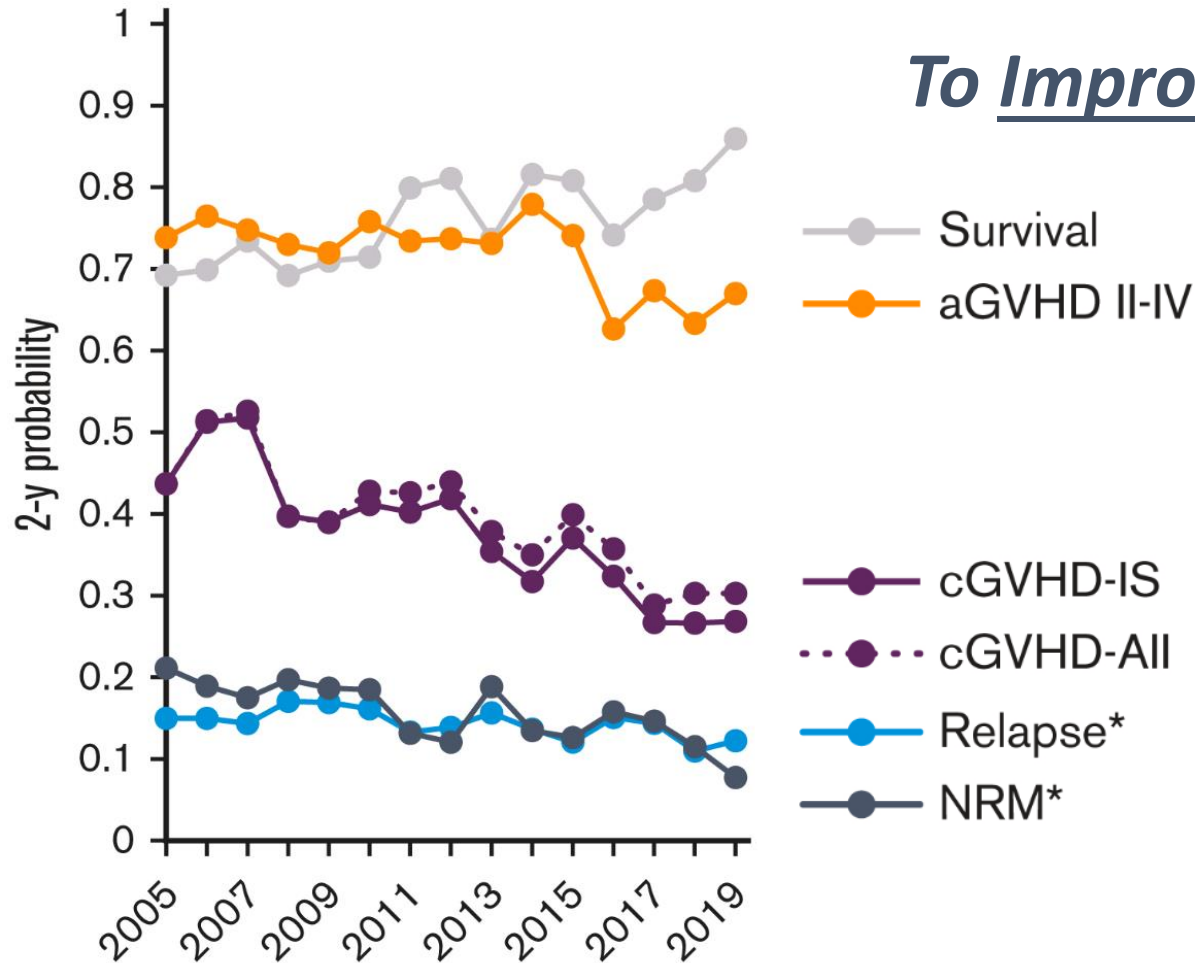
Disclosures

Consulting Fees/Honoraria: Sanofi, Incyte, Syndax, CSL Behring, CareDx

Consulting Fees/Equity: Cimeio, Oxford Immune Algorithmics, OrcaBio



BMT Outcomes Continue To Improve Over Time

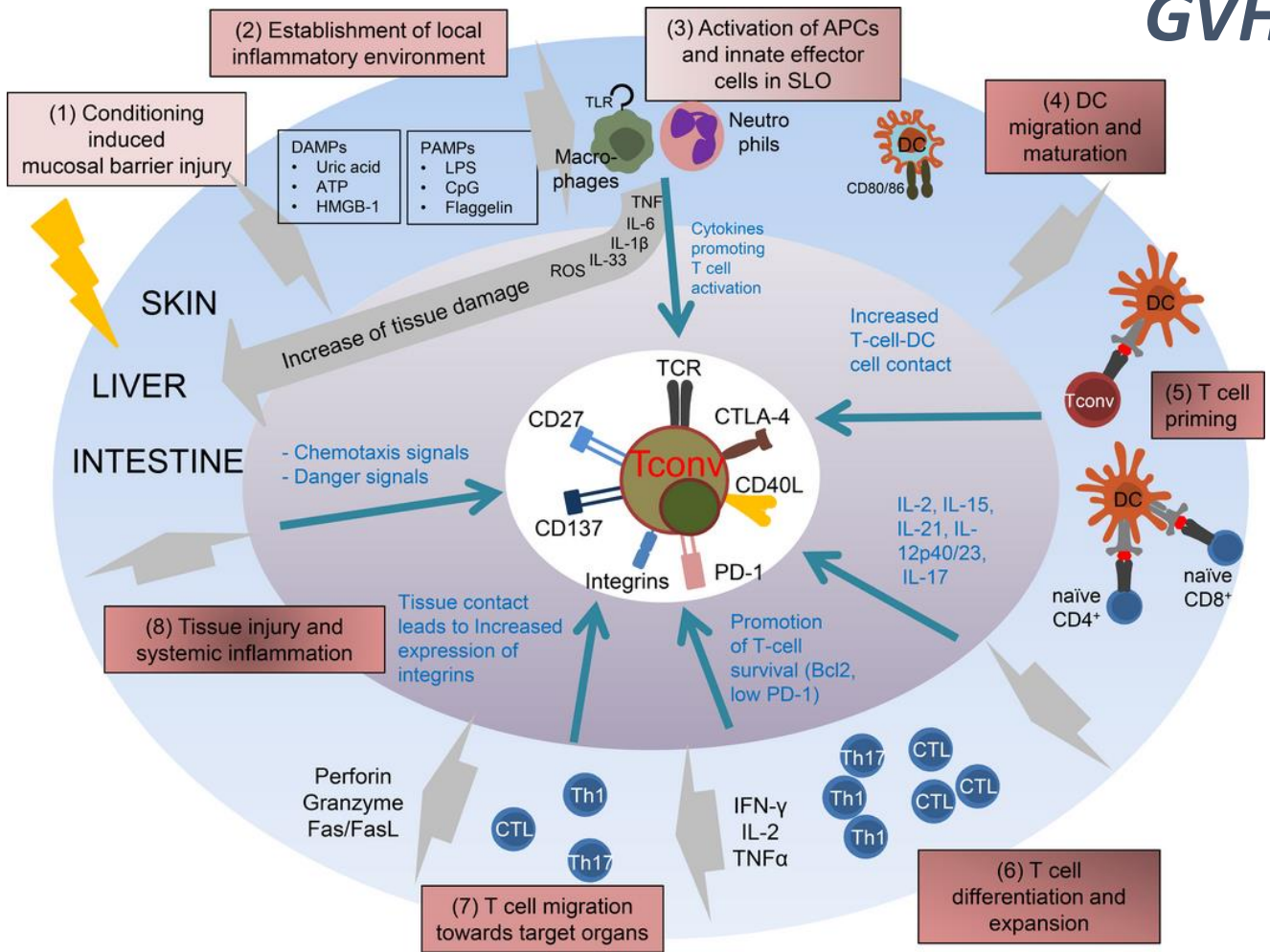




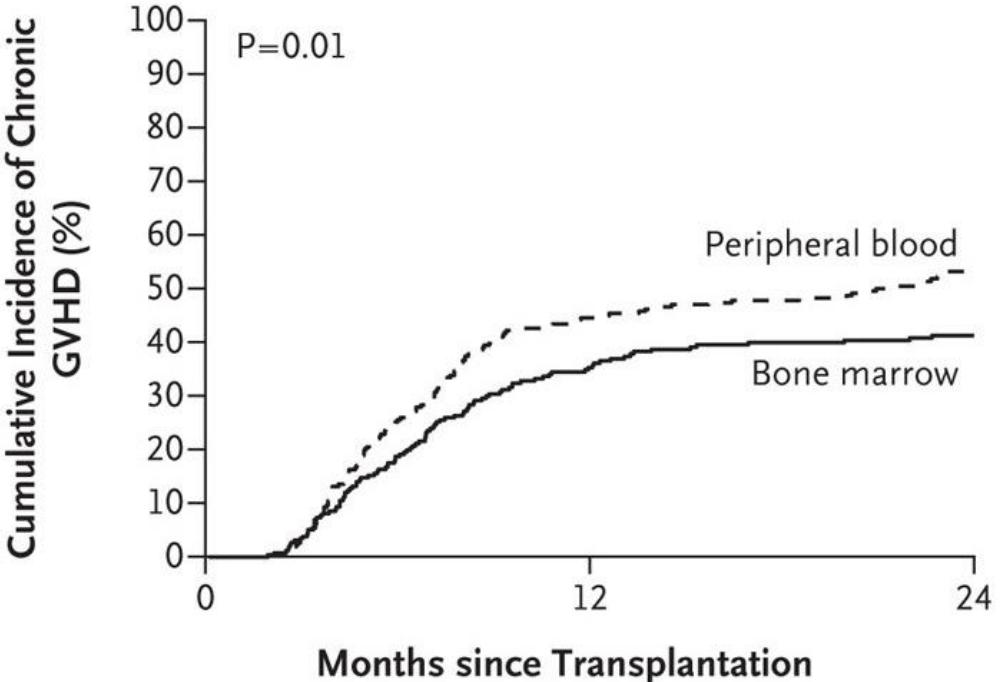
Stem Cell Transplantation - Critical Areas of Improvement

- Reducing Toxicity from Conditioning
- Prevention of Acute and Chronic GVHD
- Treatment of Acute and Chronic GVHD
- Prevention and Treatment of Relapse

GVHD Prevention

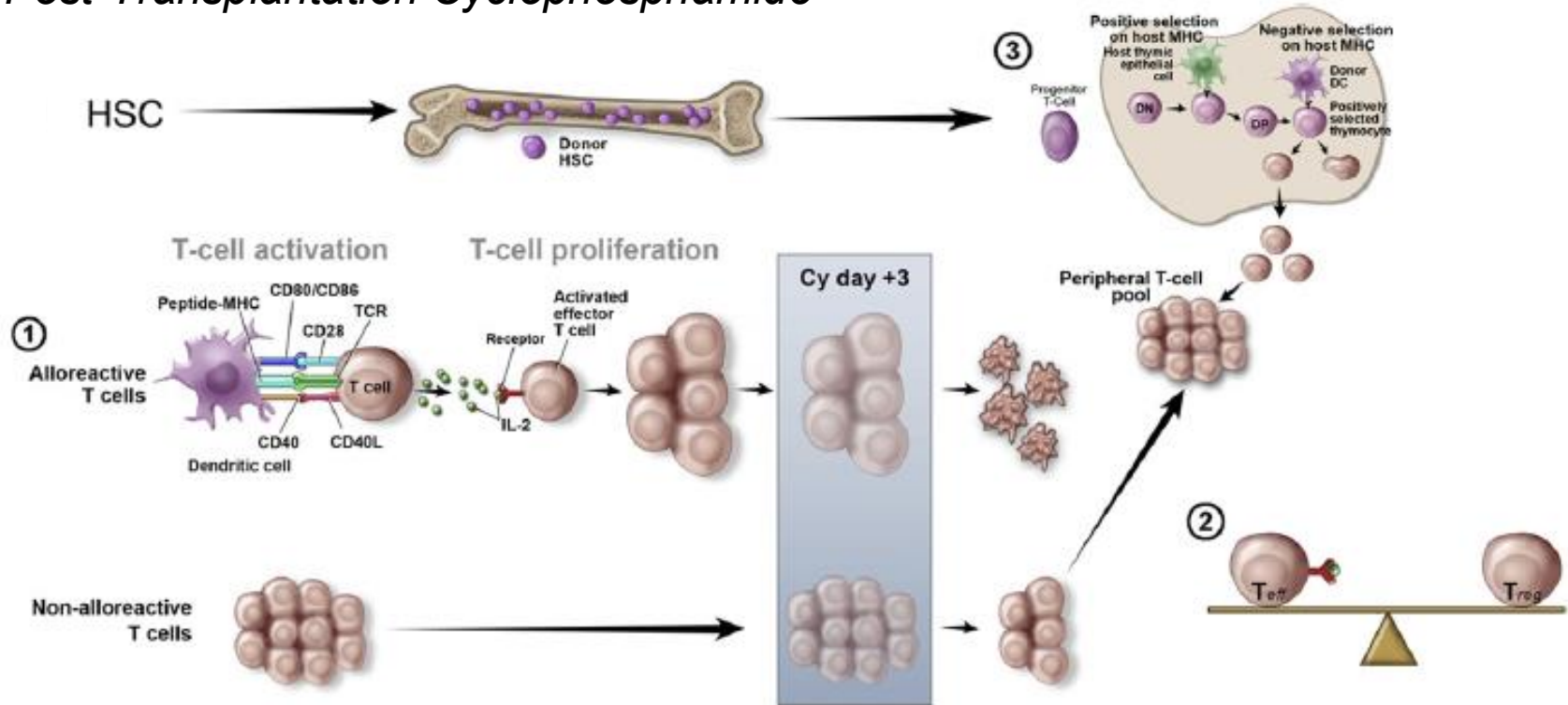


GVHD Prevention



GVHD Prevention - PTCy

Post-Transplantation Cyclophosphamide





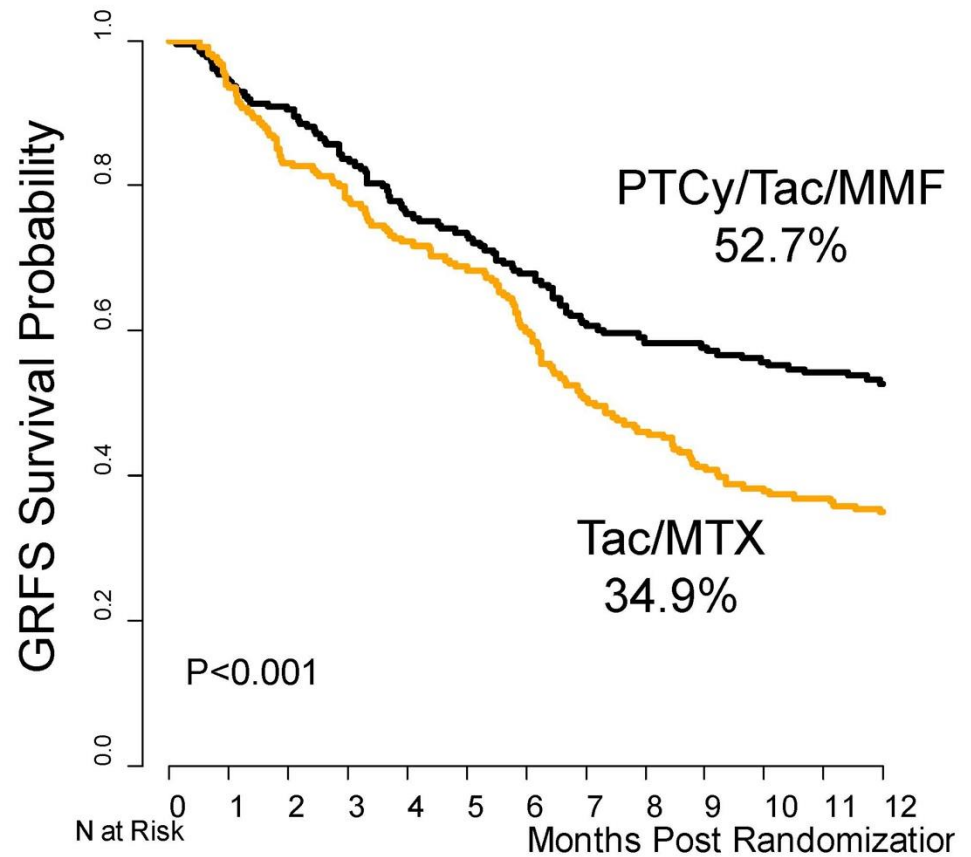
**BMT CTN 1703: A Randomized, Multicenter, Phase III
Trial of Tacrolimus/Methotrexate versus Post-Transplant
Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil
in Non-Myeloablative/Reduced Intensity Conditioning
Allogeneic Peripheral Blood Stem Cell Transplantation**

BLOOD & MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1703 PRIMARY ENDPOINT:

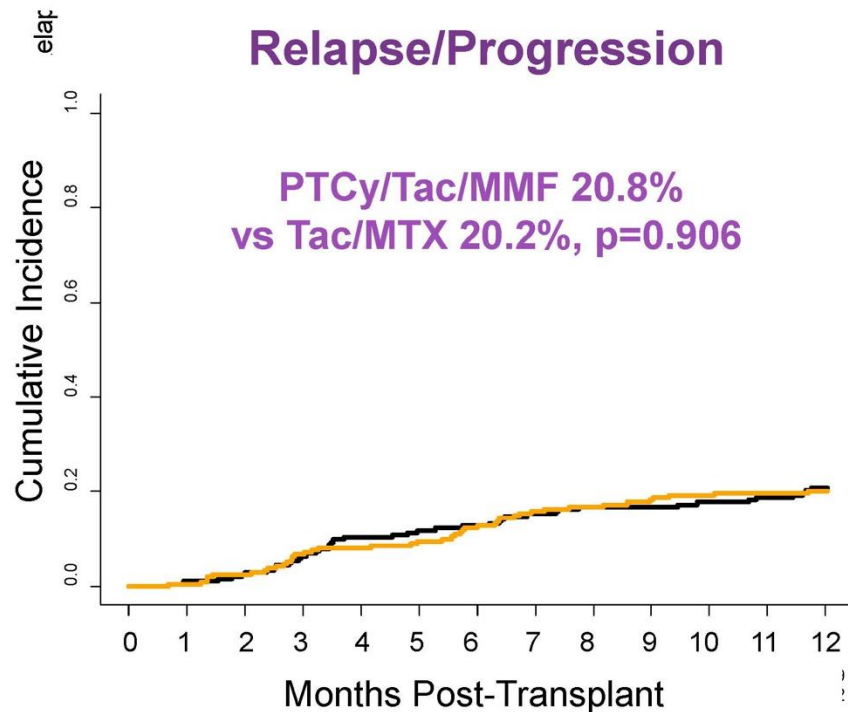
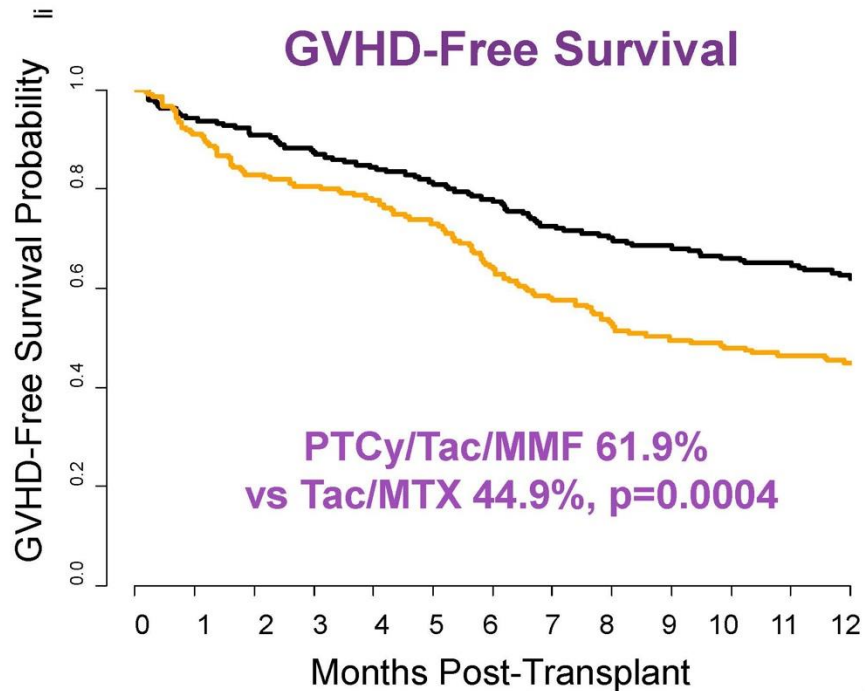
1 Year GVHD-Free, Relapse
Free Survival SUPERIOR with
PTCy/Tac/MMF

Hazard ratio 0.641
 $p < 0.001$



	0	1	2	3	4	5	6	7	8	9	10	11	12
PTCy	214	197	187	172	155	149	138	123	117	116	112	109	24
Tac/MTX	217	199	174	164	150	142	125	106	97	87	80	78	14

Improved GVHD outcomes not at expense of relapse





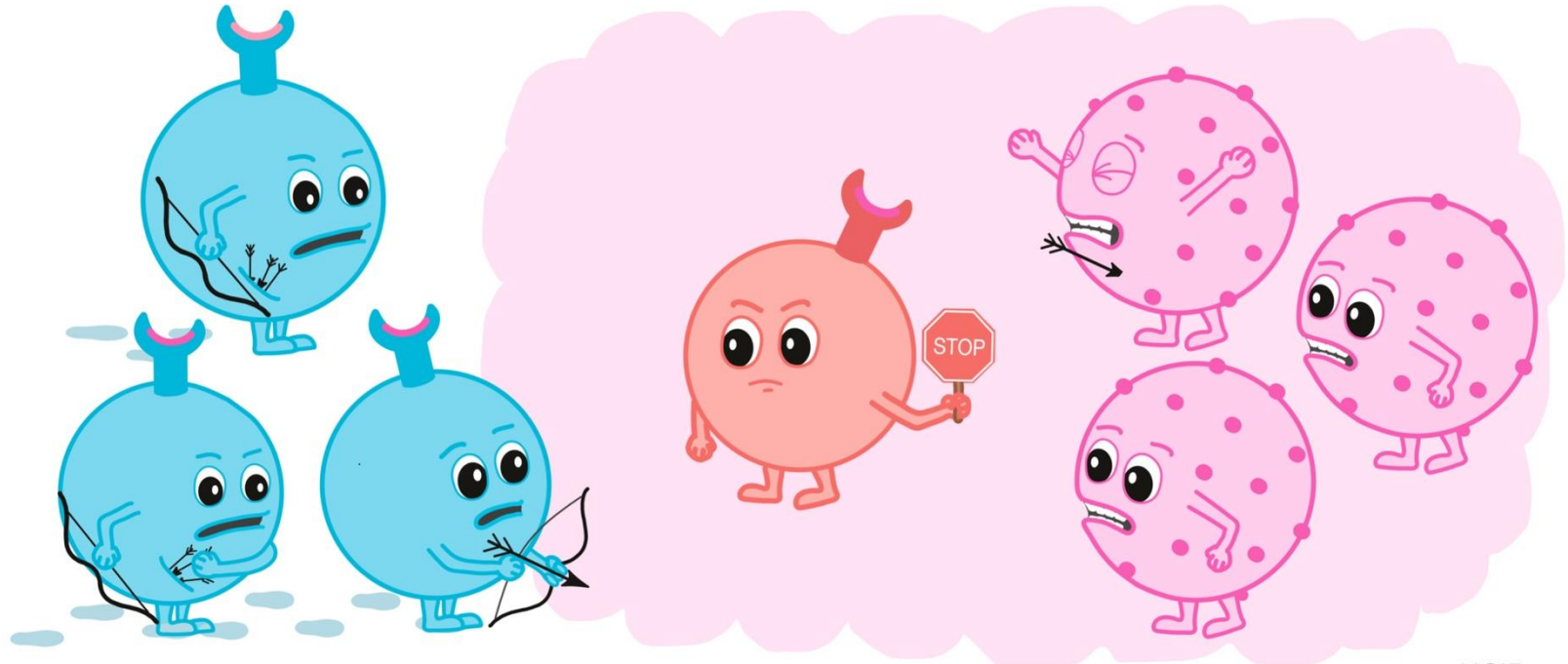
GVHD Prevention - PTCy

- PTCy – Now STANDARD of CARE in Reduced Intensity Transplantation and Haploidentical Transplantation
- Not quite yet the standard in Ablative Transplantation
- MULTIPLE Trials ongoing to improve upon PTCy ongoing



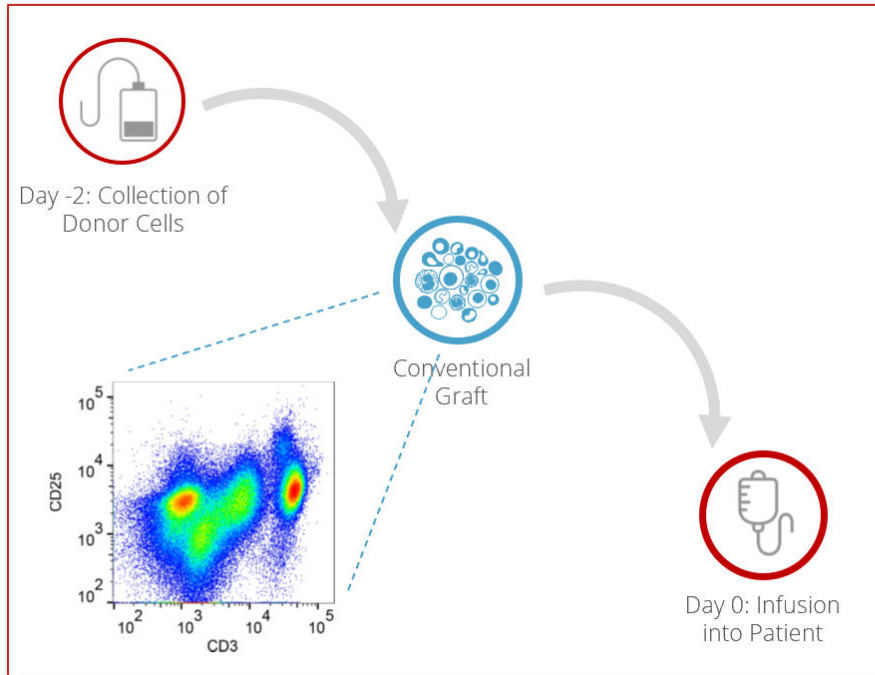
Regulatory T Cells – The Brakes of the Immune System

regulatory T cells slow down or suppress immune responses



GVHD Prevention - OrcaBio

Conventional transplant

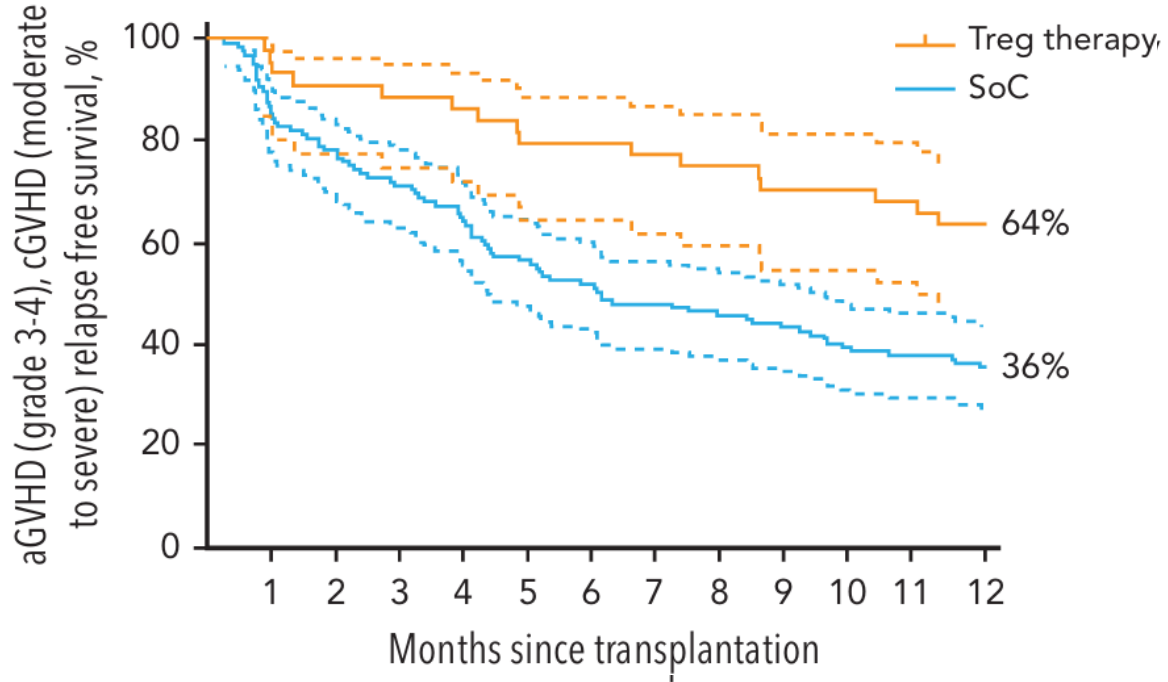


[Eddinger et al. Nature Medicine 2003 Sep;9\(9\):1144-50.](#) | [Trzonkowski et al. Clin Immunol. 2009 Oct;133\(1\):22-6.](#)

[Di Ianni M, et al. Blood. 2011;117\(14\):3921-3928.](#) | [Brunstein, et al. Blood 2016 Feb 127 \(8\):1044-51.](#) | [Kellner H, et al.](#)

[Oncotarget 2018 Nov 2;9\(86\):35611-35622.](#)

GVHD Prevention - OrcaBio



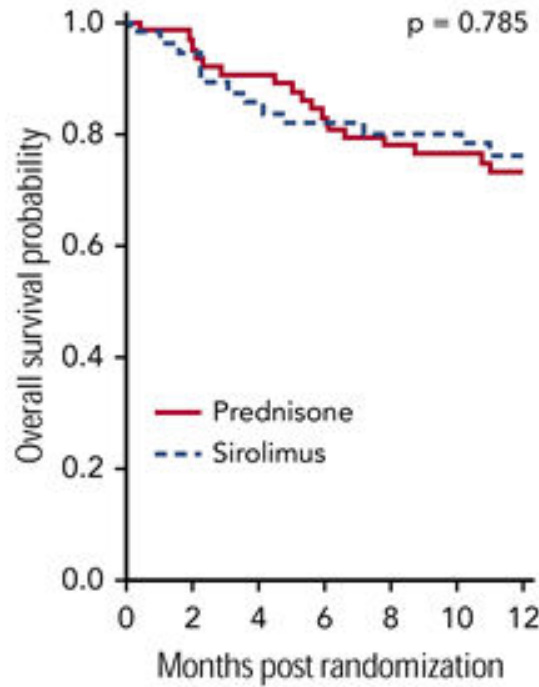
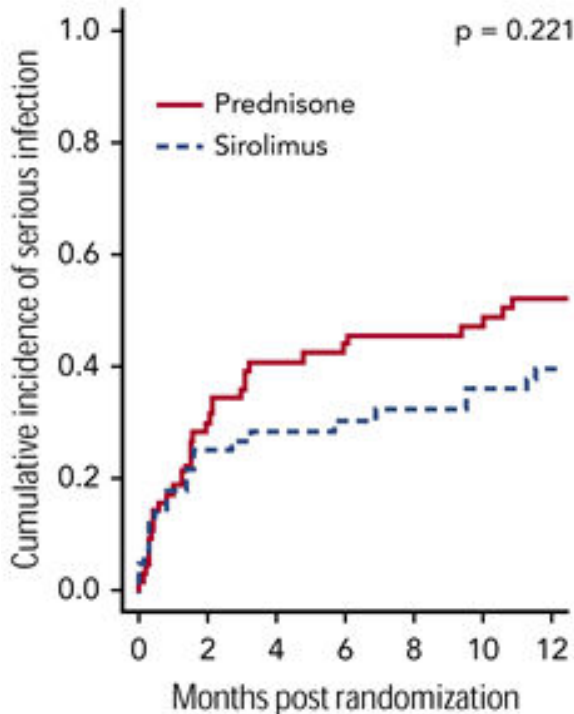
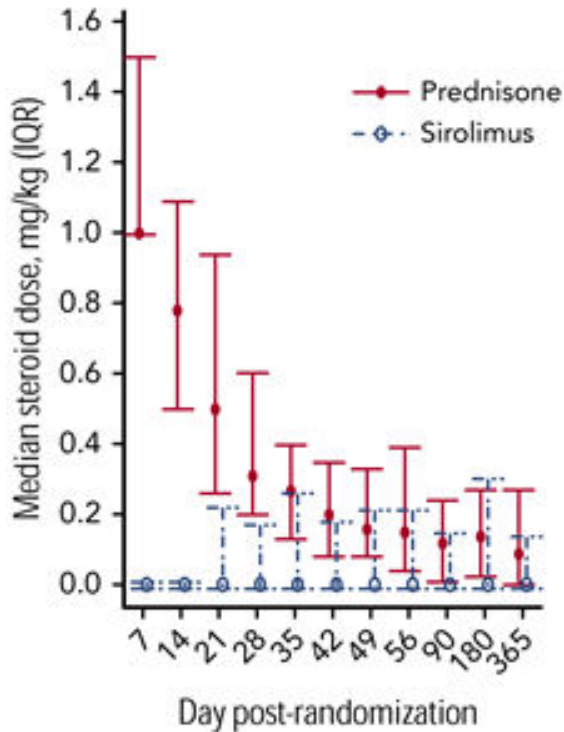


Therapy of Acute GVHD

- Corticosteroids – First line
 - Toxic: Diabetes, High BP, High Cholesterol, Insomnia, Mood changes
 - Only MODERATELY effective:
 - 50% Durable Response
 - 25% Resistant immediately
 - 25% Recur with tapering
- 2nd Line Therapy Required by Many

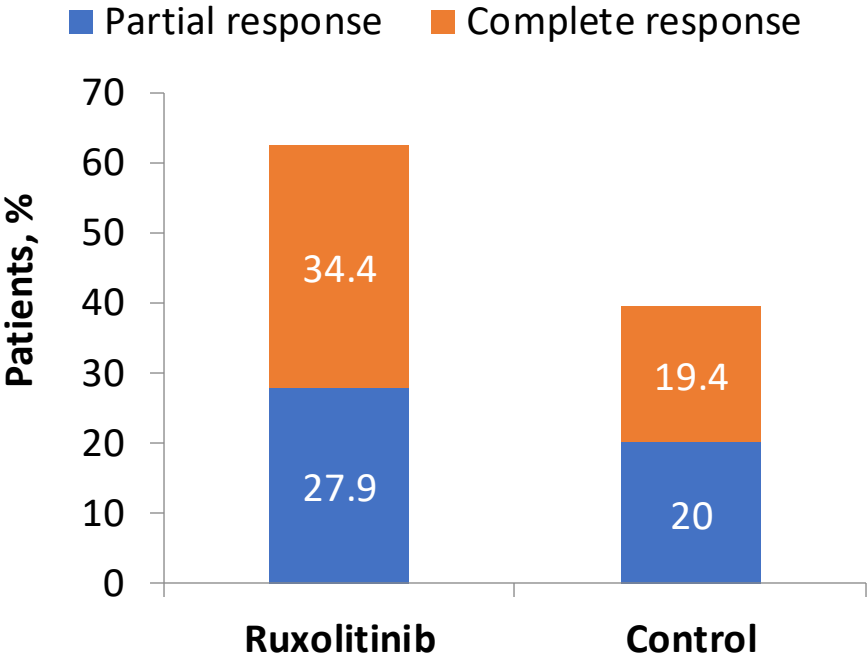
Avoiding Steroids in Acute GVHD

Sirolimus vs Prednisone



Acute GVHD Treatment – REACH2 Trial of Ruxolitinib

Overall Response at Day 28

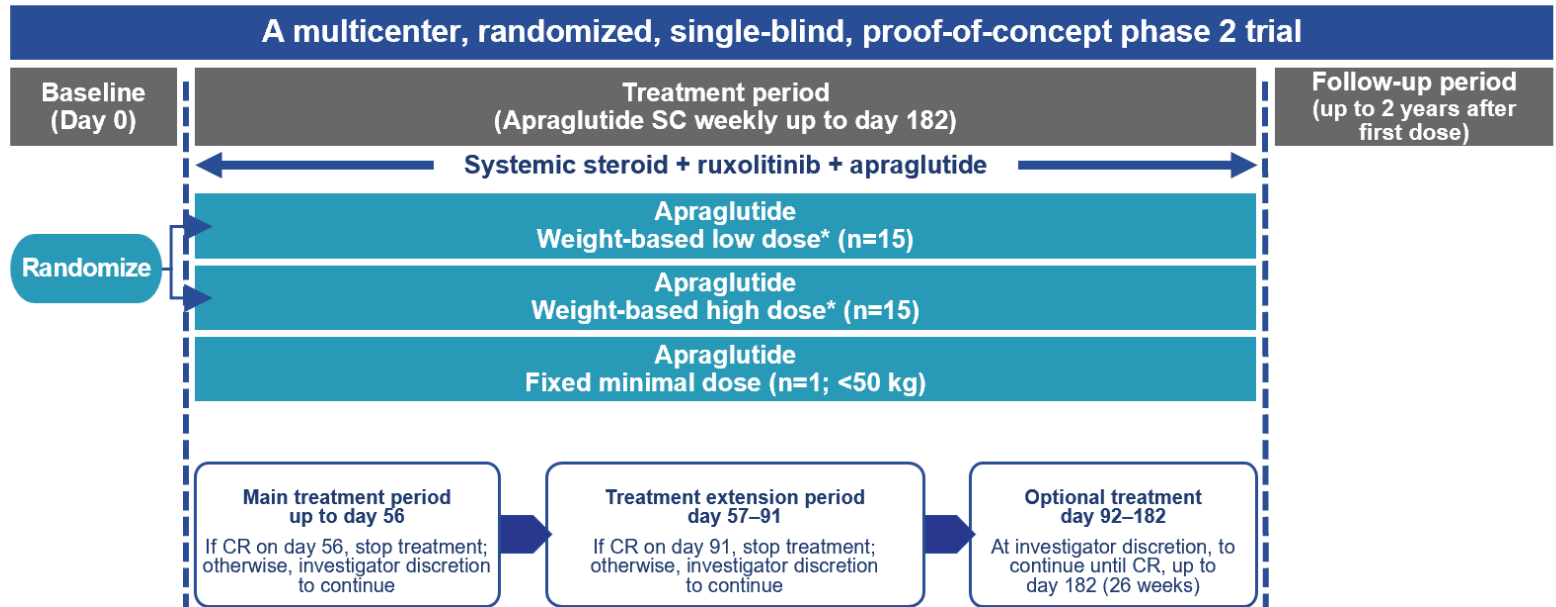




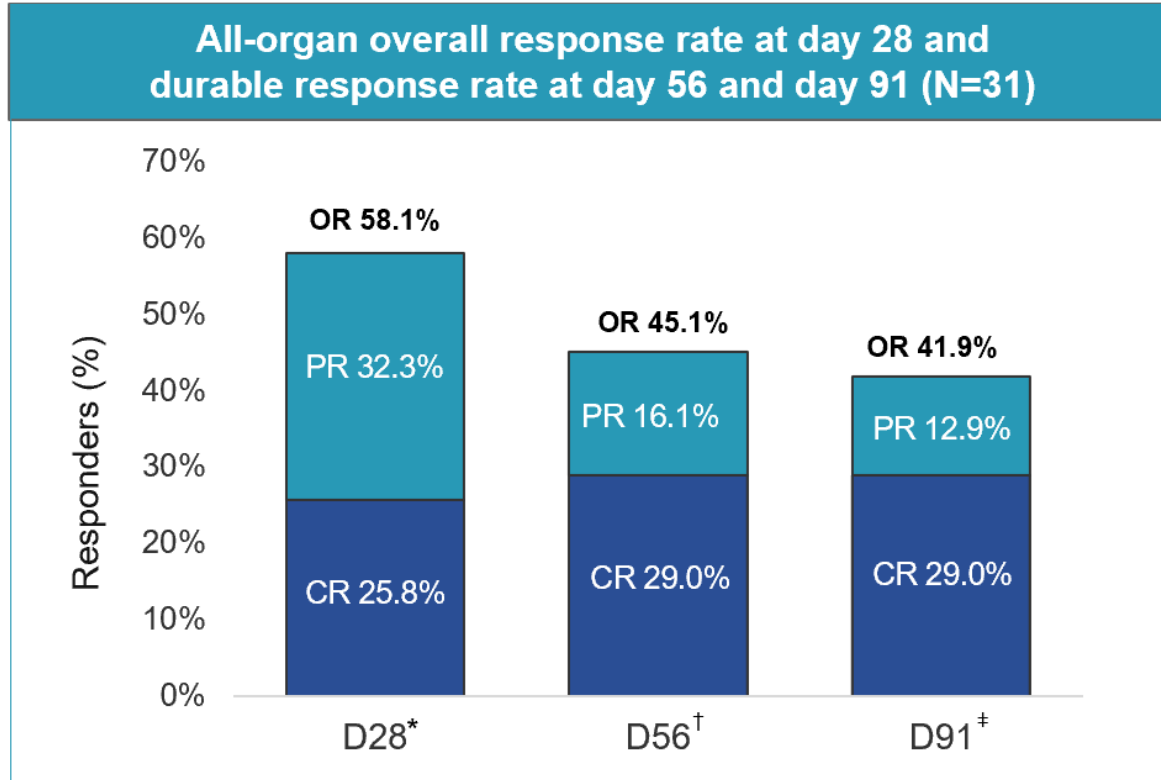
Acute GVHD Treatment – Ruxolitinib + Apraglutide

STARGAZE study design

Study aim: To assess the safety and efficacy of apraglutide in combination with ruxolitinib in patients with SR, lower-GI aGvHD



Acute GVHD Treatment – Ruxolitinib + Apraglutide



FDA Approved Agents in Chronic GVHD

Ibrutinib

Mode of action

Selectively inhibits BTK and inhibits IL-2 ITK

Treatment effects in cGvHD

ITK inhibition favors the formation of Th-1 immune responses

Approval

FDA

Indication

Second-line treatment for adult patients with cGvHD, after failure of 2 systemic lines of therapy

Belumosudil

Mode of action

Selectively inhibits ROCK2¹

Treatment effects in cGvHD

Can block the promotion of inflammatory and fibrotic processes¹

Approval

FDA, MHRA³⁻⁴

Indication

Management of cGvHD in adults and children ≥ 12 years, after failure of ≥ 2 systemic lines of therapy³

Ruxolitinib

Mode of action

Inhibits JAK1 and JAK2¹

Treatment effects in cGvHD

Can disrupt cytokine and growth factor signaling pathways¹

Approval

FDA, EMA⁵⁻⁶

Indication

Treatment of aGvHD and cGvHD in certain adults and children ≥ 12 years⁵

Axatilimab

Mode of action

Targets CSF-1R on monocytes and macrophages⁷

Treatment effects in cGvHD

Mediation of inflammation and fibrosis⁸

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Second-line treatment for adult and pediatric patients with cGvHD, after failure of ≥ 2 systemic lines of therapy⁹

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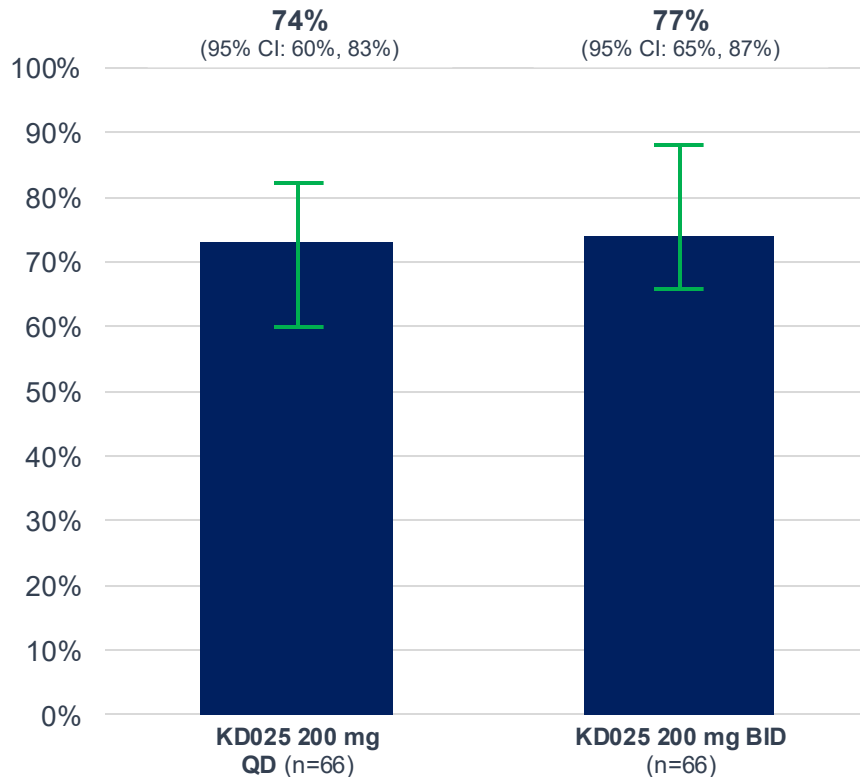
FDA⁹

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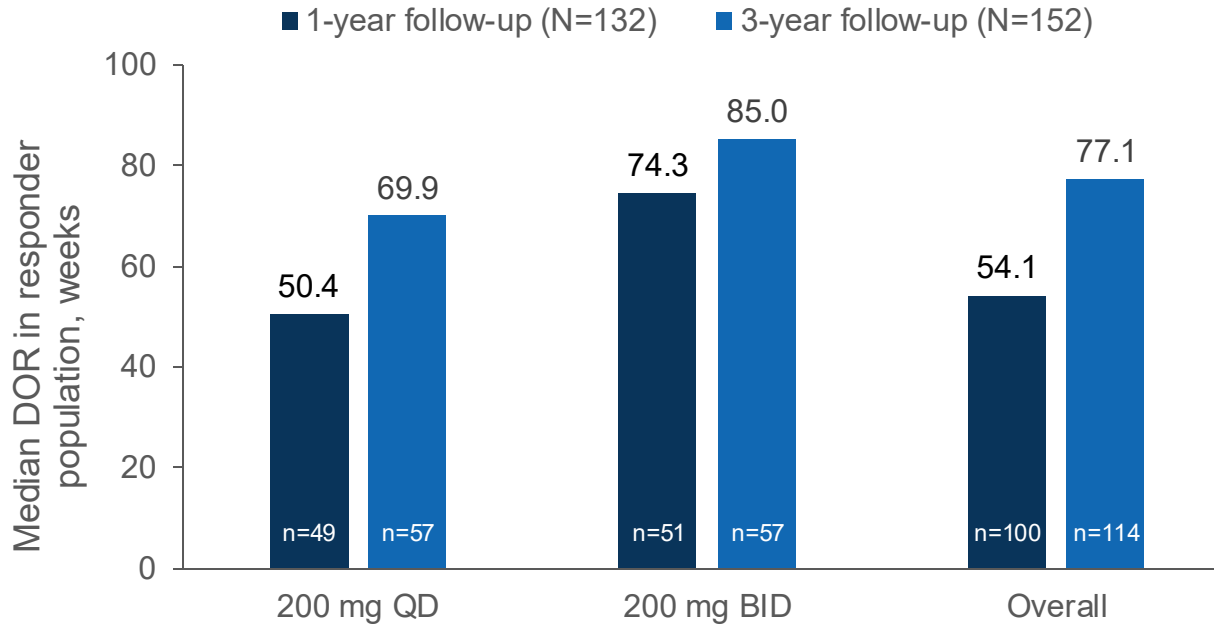
Second-line treatment for adult and pediatric patients with cGvHD, after failure of ≥ 2 systemic lines of therapy⁹

ROCKstar Met Primary Endpoint

- Belumosudil achieved clinically meaningful and statistically significant ORRs in both arms
- Complete Responses (CRs) observed in all affected organ systems
- Seven patients have achieved an overall CR
- 44% of patients have remained on belumosudil therapy for >1 year.
- The median DOR was 54 weeks, and 60% of responders maintained responses for ≥ 20 weeks.

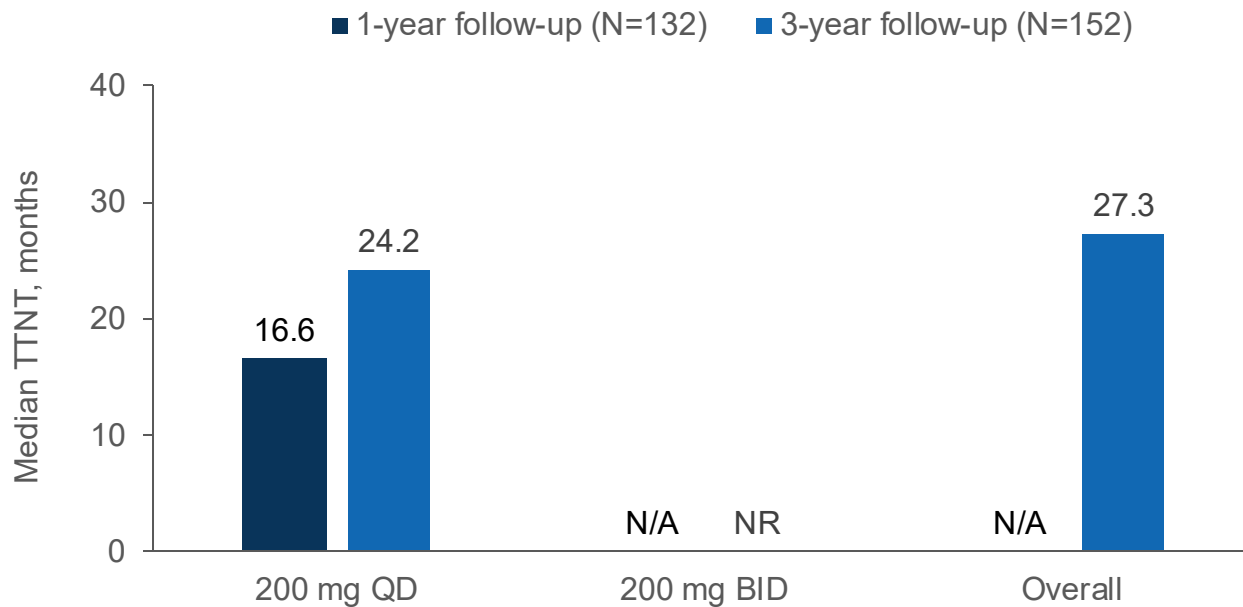


3 Year Follow-Up Median DOR among responders



BID, twice daily; DOR, duration of response; QD, once daily.

3 Year Follow-Up: Median TTNT



mITT population.

BID, twice daily; N/A, not available; NR, not reached; mITT, modified intent-to-treat; QD, once daily; TTNT, time to next treatment.



TDI01 in the Treatment of Moderate to Severe Chronic Graft-Versus-Host Disease: Results from a Multicenter, Open-Label Phase Ib/II Study

Xiaodong Mo¹, Xuejun Zhang², Rong Guo³, Erjie Jiang, Jie Jin, Xiaoyu Zhu, Yicheng Zhang, Shunqing Wang, Zhiming zhang, Jia Wei, Zhuogang Liu, Yuxian Huang, Hai Yi, Xin Wang, Zhiguo Wang, Ming Hou, Xiaojun Huang

¹Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Peking University People's Hospital, Beijing, China

²Department of Hematology, Hebei Institute of Hematology, The Second Hospital of Hebei Medical University, Shijiazhuang, China

³Department of Hematology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

*All clinical investigators are part of the TDI01-cGVHD clinical trial team.

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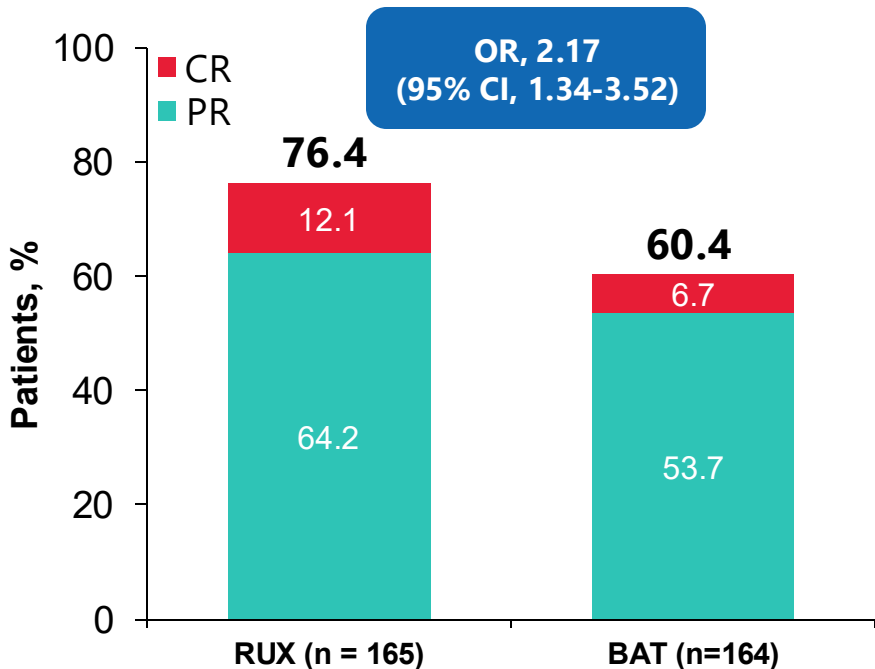
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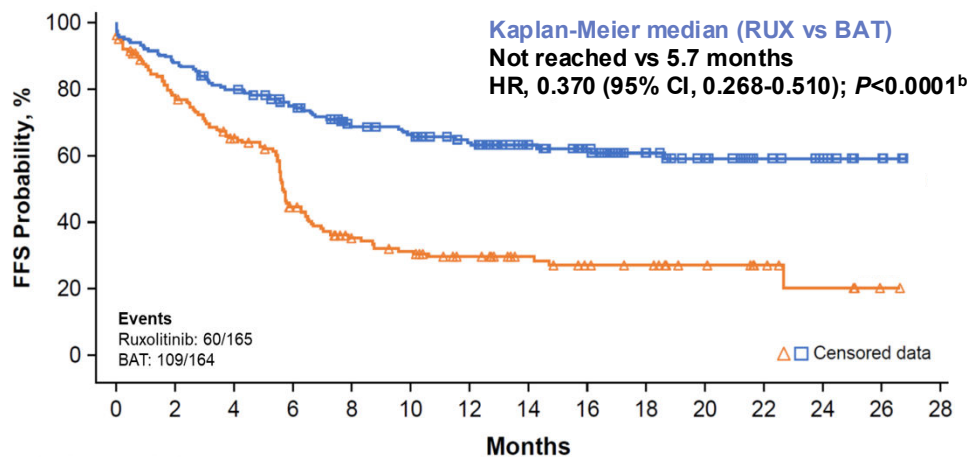
Second-line treatment for adult and pediatric patients with cGvHD, after failure of ≥ 2 systemic lines of therapy⁹

Ruxolitinib Treatment Outcomes

Best Overall Response



Failure-Free Survival



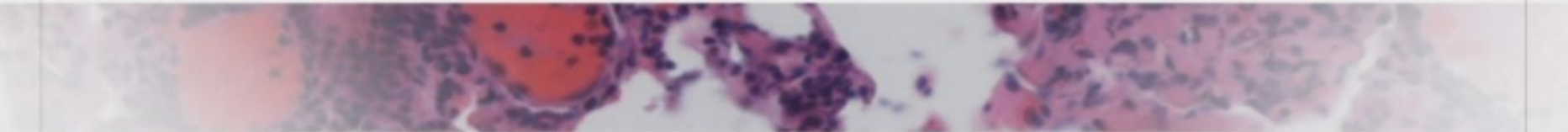
No. of patients at risk

Ruxolitinib	165	145	130	115	92	87	76	58	49	37	27	15	9	4	0
BAT	164	123	100	64	45	39	31	23	17	15	9	6	3	1	0



American Society of Hematology

Helping hematologists conquer blood diseases worldwide



A horizontal band of a microscopic image showing tissue sections with various cellular structures and colors, including shades of red, purple, and pink.

JAK/ROCK Inhibitor Rovadicitinib For Glucocorticoid-Refractory or -Dependent Chronic Graft-versus-Host Disease: Updated Results of Multicenter, Phase 1b/2a Trial

Yanmin Zhao^{1,2,3}, Yi Luo^{1,2,3}, Jimin Shi^{1,2,3}, Shunqing Wang⁴, Caixia Wang⁴, Erle Jiang⁵, Chen Liang⁵, Xiaoyu Zhu⁶, Xuejun Zhang⁷, Fankai Meng⁸, Hua Jin⁹, Yeqian Zhao^{1,2,3}, Jian Yu^{1,2,3}, Xiaoyu Lai^{1,2,3}, Lizhen Liu^{1,2,3}, Huarui Fu^{1,2,3}, Yishan Ye^{1,2,3}, Congxiao Zhang^{1,2,3}, Tao Wang¹⁰, Lifan Tu¹¹, Xunqiang Wang¹¹, He Huang^{1,2,3*}

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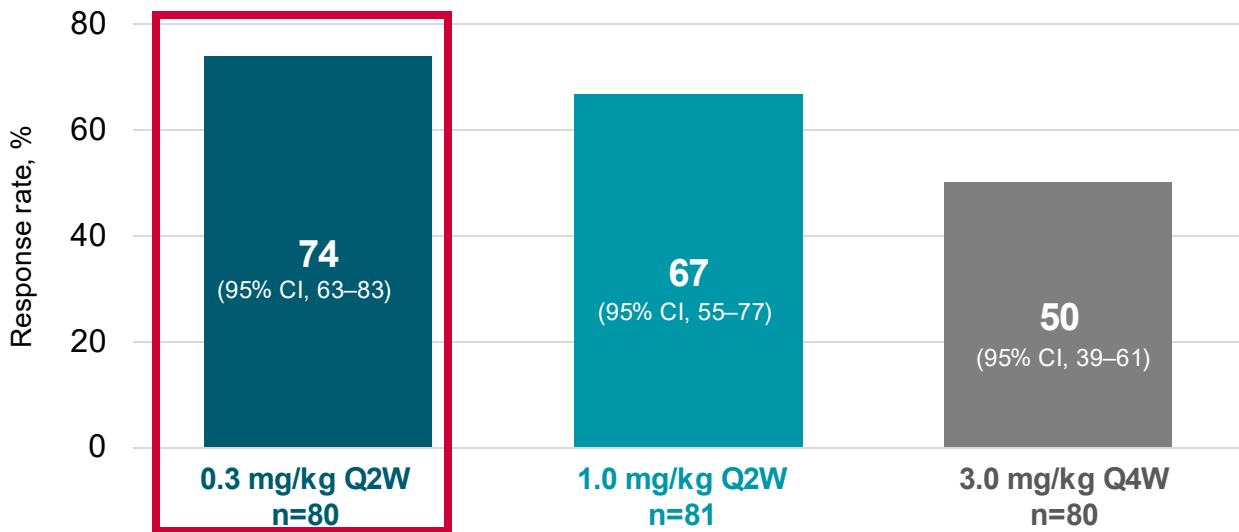
Safety and Efficacy of Axatilimab at 3 Different Doses in Patients with Chronic Graft-Versus-Host Disease (AGAVE-201)

Daniel Wolff*, MD, PhD; Corey Cutler,* MD, MPH, FRCPC; Stephanie J. Lee, MD, MPH; Iskra Pusic, MD; Henrique Bittencourt MD, PhD; Jennifer White MD, MSc, FRCPC; Mehdi Hamadani MD; Sally Arai, MD; Amandeep Salhotra, MD; Jose A. Perez-Simon, MD; Amin Alousi, MD; Hannah Choe, MD; Mi Kwon, MD; Arancha Bermúdez, MD; Inho Kim, MD, PhD; Gerard Socie, MD, PhD; Vedran Radojicic, MD; Timothy O'Toole, MS; Chuan Tian, PhD; Peter Ordentlich, PhD; Zachariah DeFilipp,[†] MD; and Carrie L. Kitko,[†] MD

^{*/†}Authors contributed equally to this work.

Primary Efficacy Endpoint Met in All Cohorts

Overall Response Rates With Axatilimab



Time to response, median months (range)

1.7 (0.9–8.1)

1.9 (0.9–8.6)

1.4 (0.9–5.6)

Response maintained for ≥12 months, % (95% CI)

60 (43–74)

60 (43–74)

53 (30–71)

Q2W, every 2 weeks; Q4W, every 4 weeks.

*Primary endpoint was overall response rate in the first 6 cycles as defined by NIH 2014 Consensus Criteria¹

ORIGINAL ARTICLE

Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease

D. Wolff, C. Cutler, S.J. Lee, I. Pusic, H. Bittencourt, J. White, M. Hamadani, S. Arai, A. Salhotra, J.A. Perez-Simon, A. Alousi, H. Choe, M. Kwon, A. Bermúdez, I. Kim, G. Socié, S. Chhabra, V. Radojicic, T. O'Toole, C. Tian, P. Ordentlich, Z. DeFilipp, and C.L. Kitko, for the AGAVE-201 Investigators*

FDA approves axatilimab-csfr for chronic graft-versus-host disease

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On August 14, 2024, the Food and Drug Administration approved axatilimab-csfr (Niktimvo, Incyte Corporation), a colony stimulating factor-1 receptor-blocking antibody, for the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg.

2 Novel CSF1R Inhibitors

- Pimicotinib
- Vimseltinib

- Both Oral (instead of IV – Axatilimab)
- Both in clinical trials
- Vimseltinib already on the market



Conclusions and Future Directions

- GVHD Care Improving

Acute

- Better prevention
- Better appreciation of the toxicities of therapy
- Better approaches to steroid resistance

Chronic

- Better prevention
- 4 drugs approved
- Multiple drugs in development