Le cellule mesenchimali nella terapia della GVHD refrattaria dell'adulto

GITMO 7-8-May-2026

Prof. Domenico Russo
Unit of Blood Diseases and Bone Marrow Transplantation,
Department of Clinical and Experimental Science, University of Brescia,
ASST Spedali Civili di Brescia, Brescia, Italy.

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Unità di Malattie del Sangue e Trapianto Midollo Osseo - Programma Terapie Cellulari e Ricerca in Ematologia
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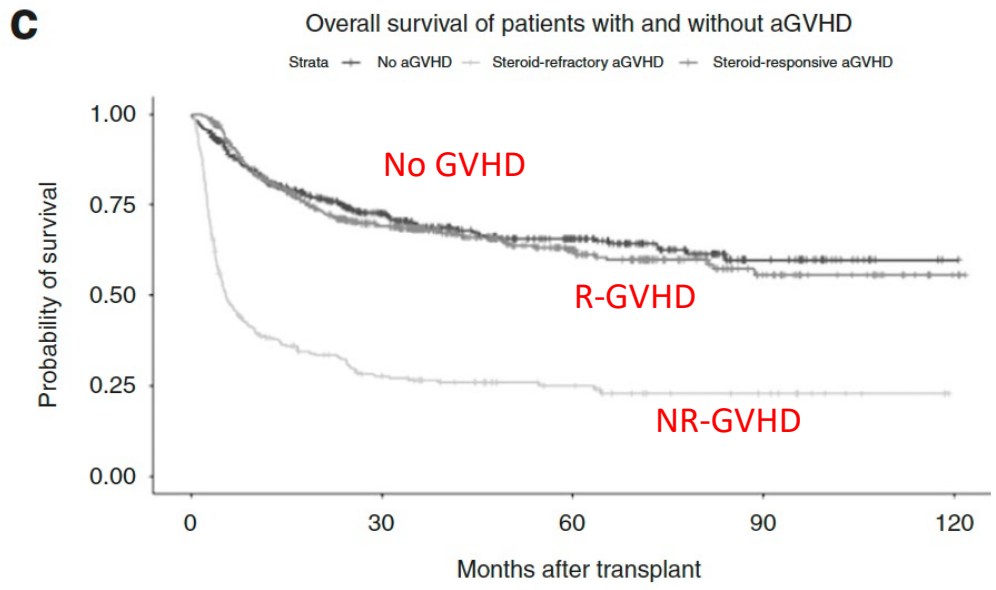
Disclosures of Name Surmane

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Medac	x				x	x	
Gilead					x	x	
MSD					x	x	
BMS						x	
J&J						x	
Abbvie						x	

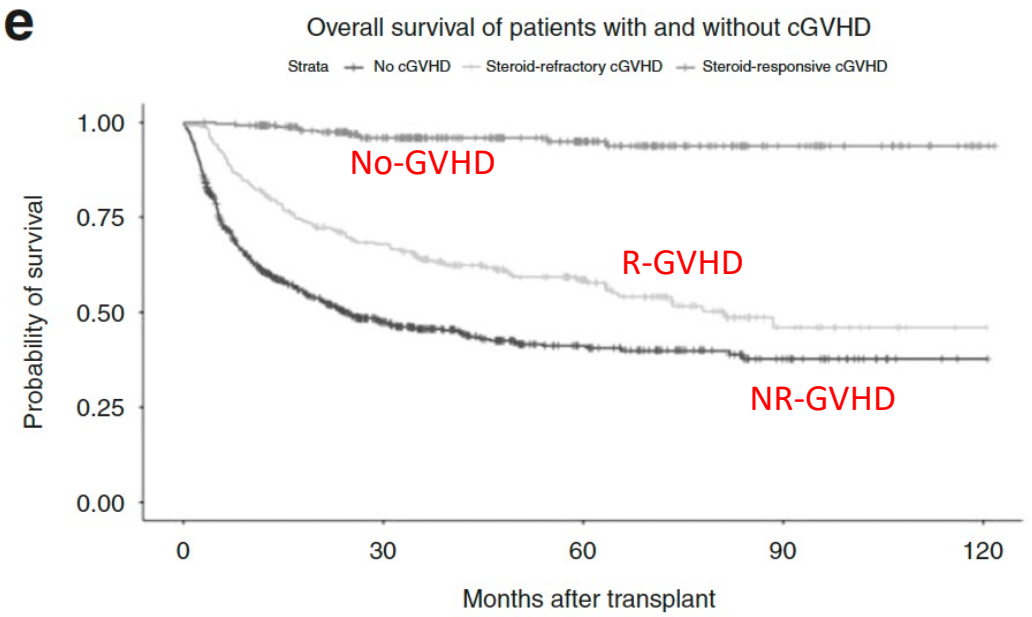
SR-aGVHD unmet need



Number at risk (number censored)

No aGVHD	479 (0)	233 (138)	112 (231)	27 (310)	1 (336)
Steroid-refractory aGVHD	233 (0)	51 (15)	26 (36)	12 (48)	0 (60)
Steroid-responsive aGVHD	505 (0)	251 (112)	98 (249)	29 (311)	3 (337)

SR-cGVHD unmet need

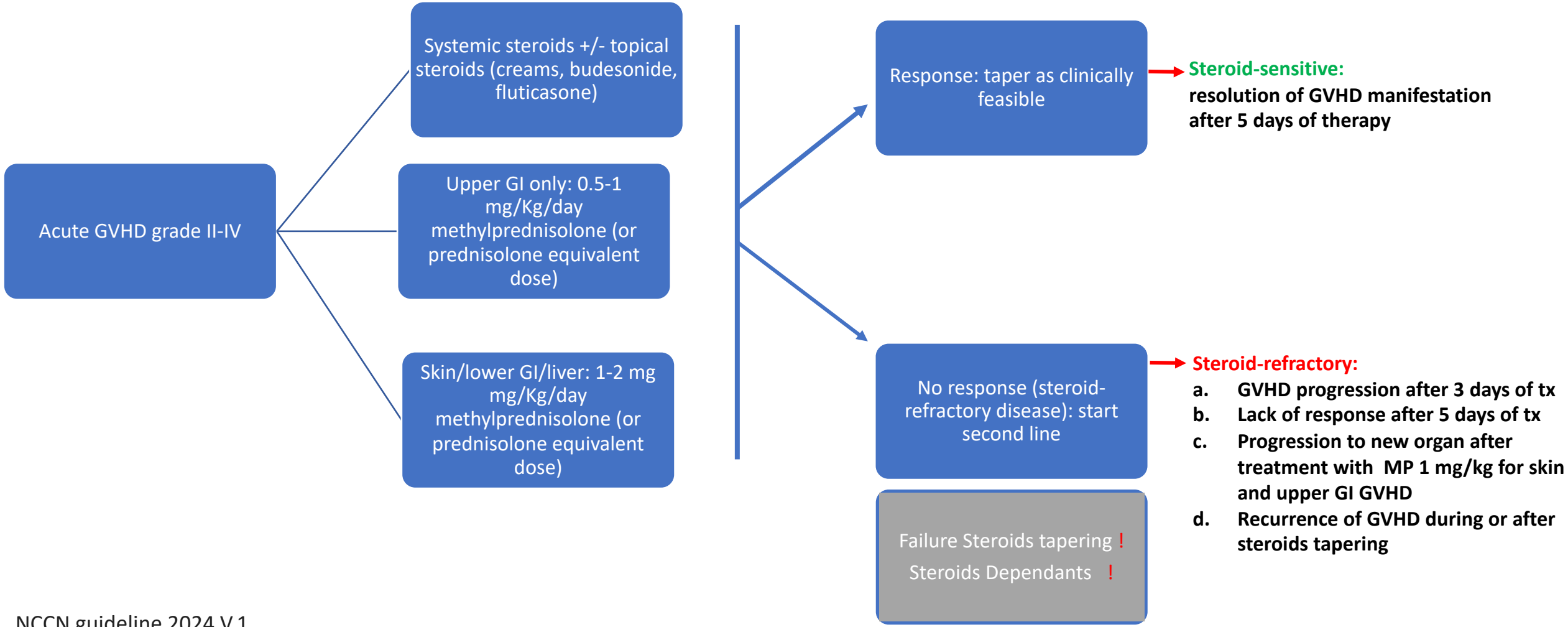


Number at risk (number censored)

No cGVHD	707 (0)	199 (177)	74 (283)	23 (330)	1 (352)
Steroid-refractory cGVHD	243 (0)	152 (14)	75 (73)	17 (121)	1 (137)
Steroid-responsive cGVHD	257 (0)	174 (74)	87 (160)	28 (218)	2 (244)

Pagliuca S et al. - *Bone Marrow Transplantation (2021) 56:38–49*

NCCN guideline 2024 V.1



NCCN guideline 2024 V.1
Penack O et al. Lancet Haematol. 2024 Feb;11(2):e147-e159.
Mohty M et al . Blood. 2020 Oct 22;136(17):1903-1906.
Van Lint MT et al . Blood. 1998 Oct 1;92(7):2288-93.

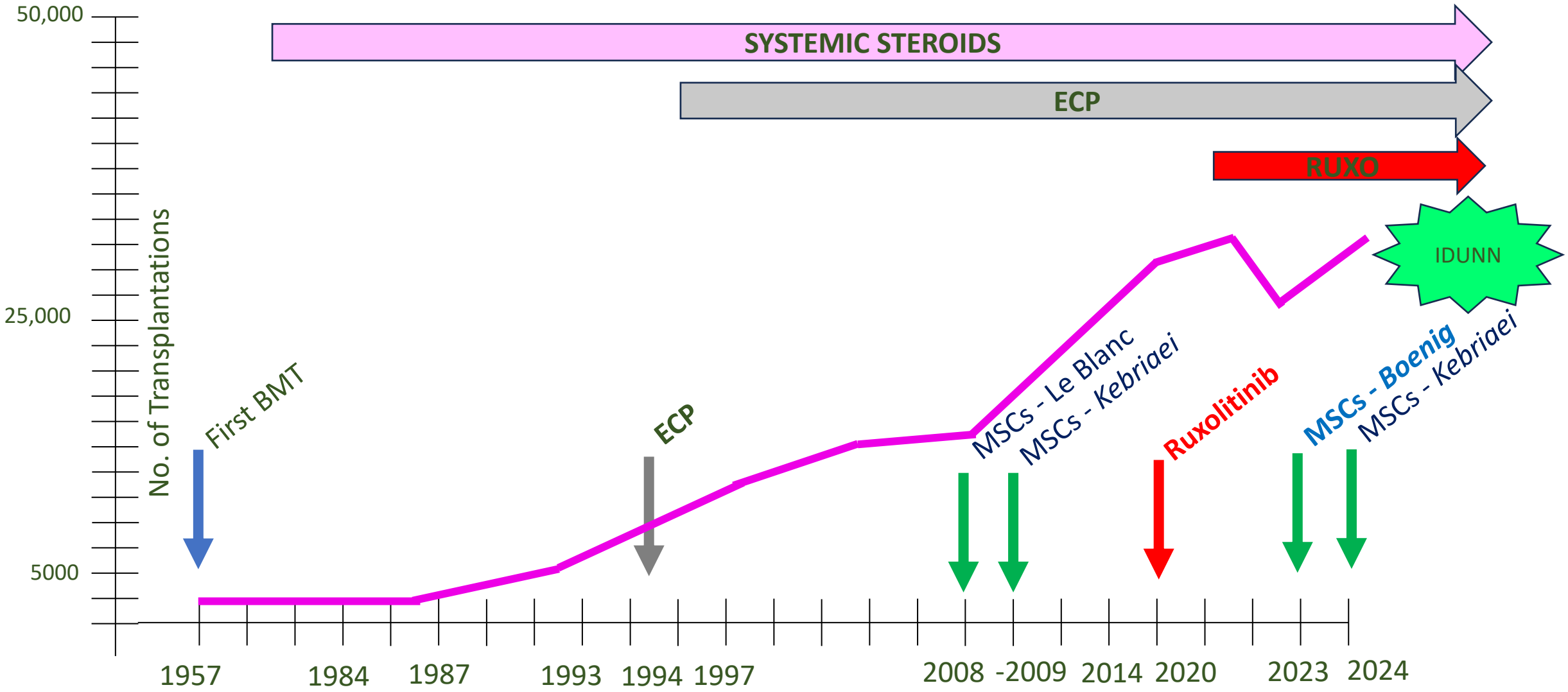
NCCN guideline 2024 V.1

Second line treatment for aGVHD

Acute GVHD

- **Ruxolitinib**
- **Extracorporeal photopheresis (ECP)**
- Antithymocyte globulin (ATG)
- Alpha-1 antitrypsin (AAT)
- Calcineuin inhibitors
- Etanercept/Infliximab
- Sirolimus
- MMF
- **MSCs**
- Pentostatin
- Tocilizumab

ALLO-HSCT – GVHD across Two Centuries
MSCs



Owsianowski M et al. Successful treatment of chronic graft-versus-host disease with extracorporeal photopheresis. Bone Marrow Transplant. 1994;14(5):845-848.
Pierelli L et al. Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. Transfusion 2013;53(10): 2340-2352.
Dignan F et al . Diagnosis and management of chronic graft-versus-host disease. Br J Haematol 2012 Jul;158(1):46-61. 4 – clinicaltrial.gov

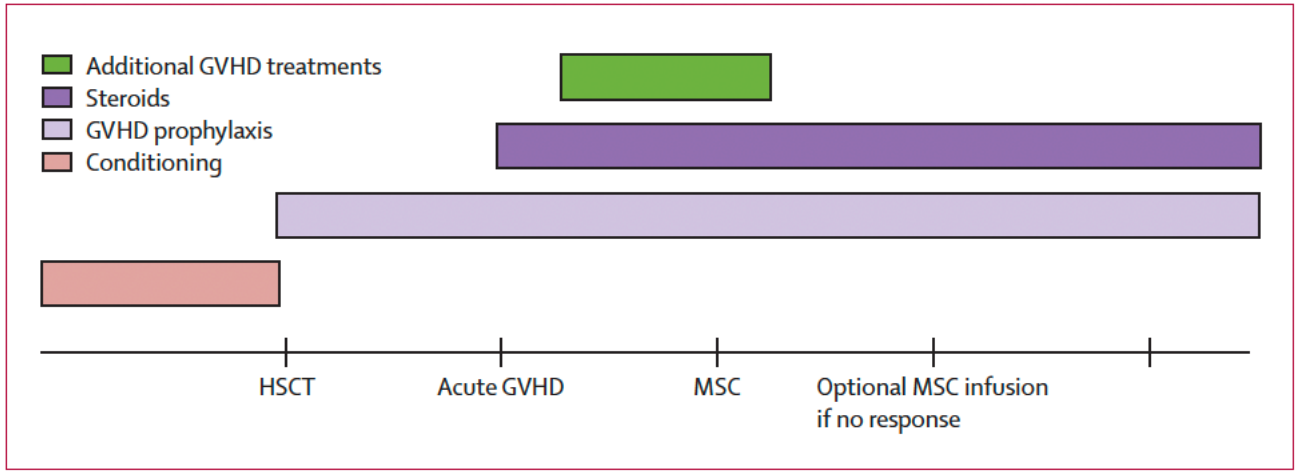
MSCs for treatment of SR-GVHD: a phase II study

	Number of patients
GVHD severity	
GVHD II, III, IV	5, 25, 25
Organ involvement	
One: skin, gut, liver	3, 6, 1
Two: gut+skin/gut+liver/liver+skin	15, 7, 4
Three	19
GVHD confirmed on biopsy	
Skin, gut, liver	10, 31, 2
GVHD treatment before MSC infusion	
Ciclosporin or tacrolimus	55 (53)*
Prednisolone ≥2 mg/kg	55 (55)*
MMF	10 (10)*
Daclizumab + infliximab	4
Daclizumab alone	1 (3)*
Etanercept and PUVA	1
Extracorporeal photochemotherapy	10 (8)*
Cyclophosphamide	3
ATG	2†
Rituximab	1 (1)*
Previous failed therapy	
First line	55
Second line	33
Third line	14
Fourth line	4
Fifth line	2

	Children (n=25)	Adults (n=30)	All patients (n=55)
Complete response	17	13	30
Partial response	4	5	9
Stable disease	2	1	3
Progressive disease	2	11	13
Overall response	21	18	39
Survival*	13	8	21
Limited chronic GVHD	2	0	2
Extensive chronic GVHD	4	2	6

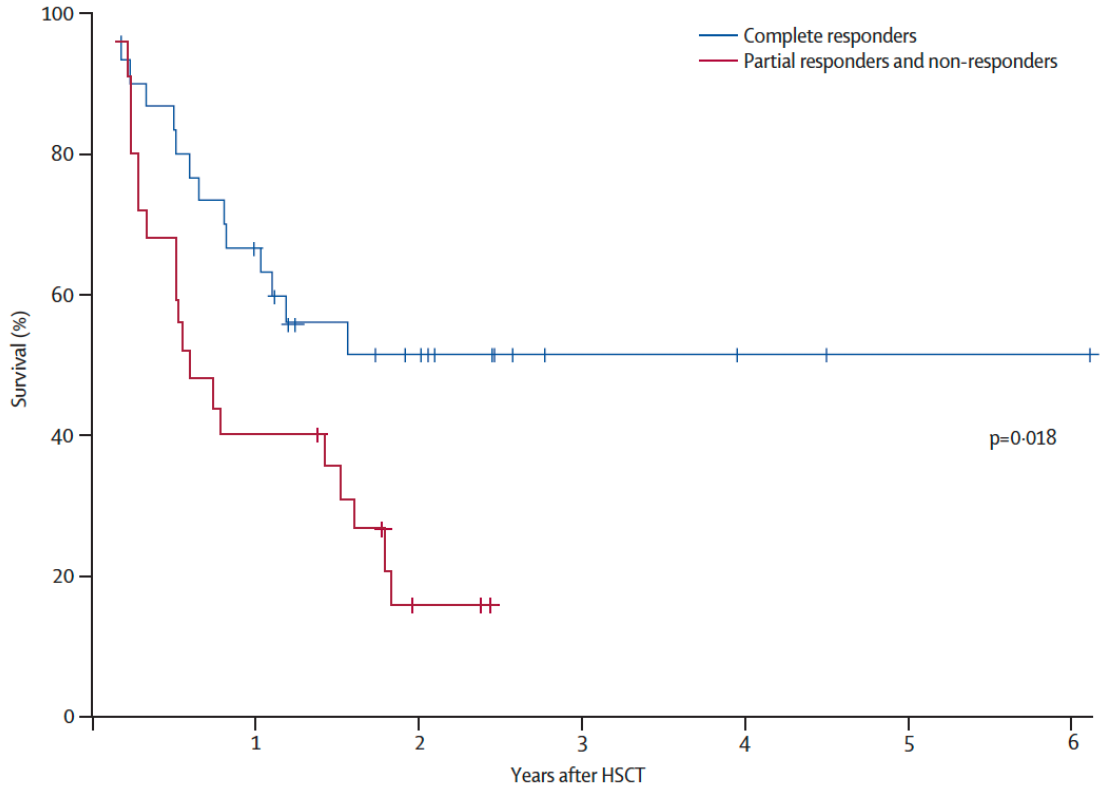
*At last data collection, March, 2007.

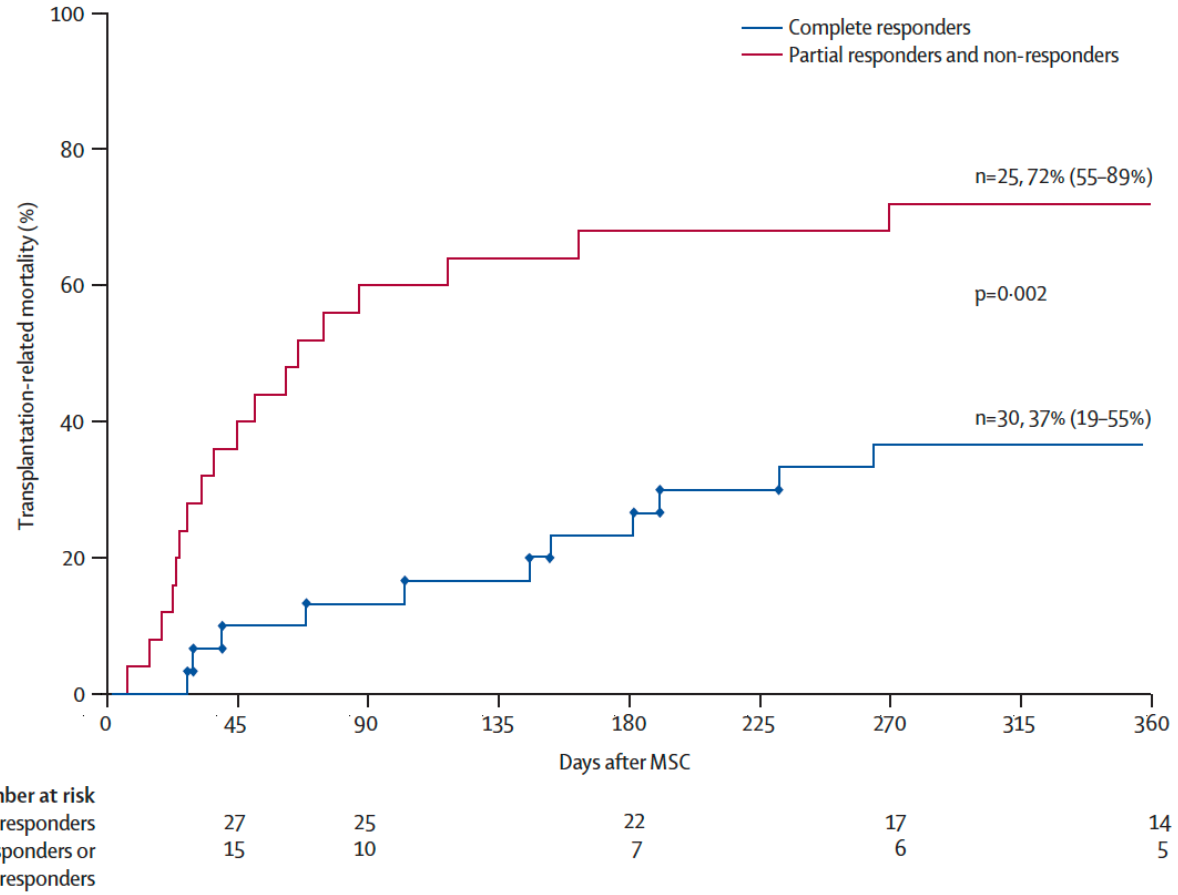
GVHD response and outcome



Le Blanc K et al Lancet. 2008 May 10;371(9624):1579-86.

Mesenchymal Stem Cells for treatment of SR-GVHD: a phase II study





GVHD grade	Responders	Total patients	Response rate
Grade II–III	22	30	73%
Grade IV	17	25	68%
Total	39	55	71%

There was no relation between the treatment given before infusion of MSC and response.

Le Blanc K et al Lancet. 2008 May 10;371(9624):1579-86.

MSCs Added to Corticosteroid Therapy for the Treatment of aGVHD

	High Dose (8×10^6 MSCs/kg) No. Patients	Low Dose (2×10^6 MSCs/kg) No. Patients
Sex		
Male	10	11
Female	5	5
Median Age, years (range)	49 (34-67)	53 (42-67)
Disease		
AML/MDS	8	6
NHL	2	3
CLL	1	3
ALL	3	1
MMF	0	2
MM	1	0
Hodgkin	0	1
Donor		
Related	9	10
Unrelated	6	6
GVHD Grade		
II	10	11
III	4	3
IV	1	2
Stem cell source		
Bone marrow	0	1
PBSC	15	15
Conditioning		
Myeloablative	8	7
Reduced intensity	3	5
Nonmyeloablative	2	2
DLI	2	2
Onset of GVHD		
Median days (range)	37 (14-121)	31 (18-115)
GVHD prophylaxis		
Cyclosporine	3	3
Tacrolimus	4	6
Tacrolimus + MMF or MTX	6	5

Two infusions day 1 and day 3 + PDN for newly diagnosed aGHVD

Table 2. Induction of GVHD Response to Treatment

Response Type	High-Dose (8×10^6 MSCs/kg) No. Patients (%)	Low-Dose (2×10^6 MSCs/kg) No. Patients (%)	Total (N = 31) No. Patients (%)
Complete Response	10 (66.7)	14 (87.5)	24 (77.4)
Partial Response	5 (33.3)	0	5 (16.1)
No Response	0	2 (12.5)	2 (6.5)

Table 4. Summary of Response by Initial Organ System Involved

Organ System No. Patients	Grade	Response	High-Dose 8×10^6 MSCs/kg No. Patients	Low-Dose 2×10^6 MSCs/kg No. Patients	Total No. Patients (%)
Skin only N = 13	II	CR	3	8	11 (85)
		PR	1	0	1 (8)
	III/IV	PR	1	0	1 (8)
GI only N = 11	II	CR	3	2	5 (45)
	III/IV	CR	1	2	3 (27)
		PR	1	0	1 (9)
		NR	0	2	2 (18)
Multiorgan N = 7	II	CR	2	1	3 (43)
	III/IV	CR	1	1	2 (29)
		PR	2	0	2 (29)

Twenty of 22 patients (91%) did not need second-line therapy and were alive at day 90. In contrast, 9 patients required second-line therapy within the first 28 days, and only 3 (33%) survived to day 90 (P 0 .0011).

Kebriaei P et al. Biol Blood Marrow Transplant. 2009 Jul;15(7):804-11.

Limits of MSCs Academic Manifacture

- **Complex ex vivo expansion required**, including multiple culture passages and strict GMP conditions, which increases production time and costs.
- **Manufacturing relies on bone marrow–derived cells expanded with fetal bovine serum and multiple processing steps, introducing variability between donors and batches.**
- **Extensive quality control** is necessary before clinical release (sterility, viral testing, potency assays, viability, immunophenotype), **making production logistically demanding**.
- **Biological heterogeneity and variable responses observed even when cells from the same donor are used in different recipients, suggesting inconsistent potency of MSC products.**

Differences between MSC products

Product	Starting material	Passages	Identity	Quality control	Potency
MC0518 (MSCs-FFM-2018)	8 BM donors	3 passages	**Pos:** CD105, CD73, CD90 **Neg:** CD14, CD34, CD45	Tested for viral pathogens, mycoplasma, sterility, endotoxin, identity, potency, viability	**Mixed lymphocyte reaction (inhibition of T-cell proliferation)**
Remestemcel-L (Kebriaei et al., 2020)	1 BM donor	5 passages	**Pos:** CD105, CD73, CD29, CD44, CD71, CD90, CD106, CD120a, CD124, CD166 **Neg:** CD14, CD34, CD45	Tested for viral pathogens, mycoplasma, sterility, endotoxin, identity, purity, potency, viability	TNFR1 expression + inhibition of IL2Rα on activated T cells
MSCs (Le Blanc et al., 2008)	Multiple BM donors (HLA-identical, haploidentical, third-party)	1–4 passages (mostly P2–P3)	**Pos:** CD73, CD90, CD105 (>90%) **Neg:** CD34, CD45, CD14, CD3	GMP-expanded; tested for sterility, viability (>95%), morphology, absence of pathogens	No standardized potency assay; functional immunomodulation inferred (in vitro lymphocyte suppression described)

Zeiser R et al. Transfus Med Hemother. 2026 Feb 16.
Le Blanc K et al Lancet. 2008 May 10;371(9624):1579-86.

MSCs-FFM

- **MSCs-FFM** (allogeneic mesenchymal stromal cells from multiple donors)
- MSCs exert their immunomodulatory effects primarily through the secretion of various mediators and metabolic modulators that ultimately suppress lymphocyte activity.
- MSCs, may also contribute to the establishment of an immune-suppressive microenvironment.

PROS of Manifacture

• Standardized manufacturing process using pooled bone marrow mononuclear cells from multi ple donors, reducing donor-to-donor variability and improving product consistency.

• Large-scale production and cryopreservation allow creation of an off-the-shelf cell therapy product that can be rapidly available for patients with severe GVHD.

• Pooling cells from several donors may enhance immunomodulatory potency and functional het erogeneity of the MSC product, potentially improving therapeutic activity

MSC-FFM - Studies and Results

Study / Source	Year	Population	N	CR (%)	PR (%)	ORR (%)	Notes
Magliano et al, Avenoso. **Italian compass. use**	2026	acute GVHD	12	34	66	58 (Day 28)	GI and skin GVHD improved after MSC infusion
Phina-Ziebin et al.	2025	Steroid + ruxolitinib refractory aGVHD	43	21	47	67	Severe GI involvement in most patients
Bonig et al.	2023	Adult and paediatric refractory aGVHD	189	13.5	50	49 (Day 28)	Real-world cohort, heavily pretreated patients
Gruhn et al. / literature review	2021	Pediatric SR-aGVHD	multiple studies	variable	variable	~59–80 after 4 weeks	Higher responses generally observed in children
Bader et al.	2018	Pediatric refractory aGVHD	69	25	61	62.9 (Day 28)	ORR increased to 66.9% at Day 60

MSCs-FFM GVHD grade & Organ response

GVHD Grade	Overall Response Rate (ORR)	Notes
Grade II	**~74% (Day 28)**	Highest response rate among grades
Grade III	**~75% (Day 28)**	Comparable response to Grade II
Grade IV	~53% (Day 28)	Lower response in severe disease

Organ Involvement	Improvement Rate	Notes
Skin	**~69%**	Most consistent response
Liver	**~57%**	Intermediate response
Lower GI	**~59%**	Good response despite severe presentations
Upper GI	~40%	Lower improvement compared with other organs

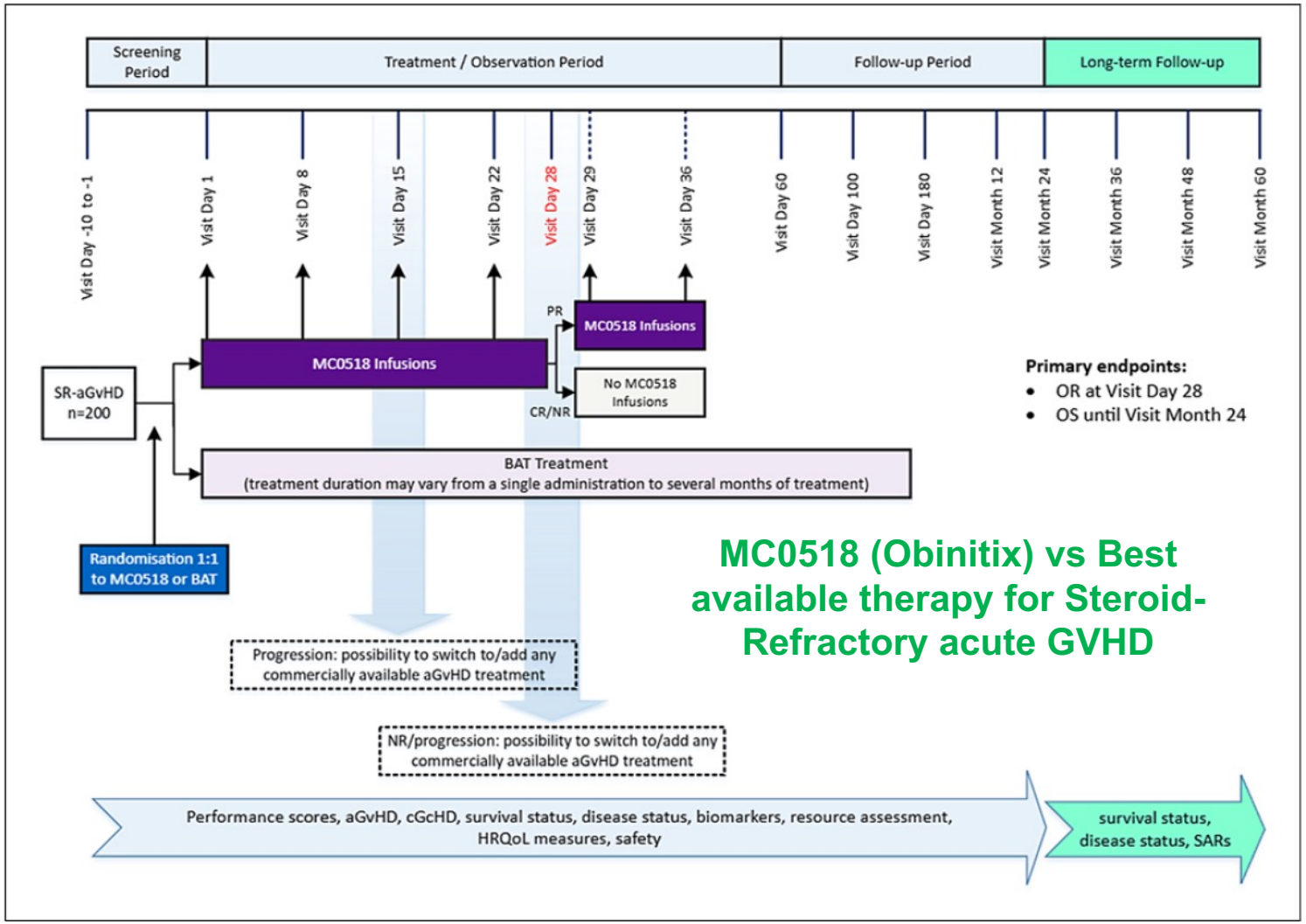
Organ responses evaluated at Day 28 after MSC infusion in refractory aGVHD patients.

Magliano G. et al.; Bader P. et al.; Zeiser R. et al.; Gruhn B. et al.; Phina-Ziebin X. et al.

MSCs-FFM Safety & Adverse Events

Study / Source	Year	Population	N	Adverse Events	Safety Notes
Magliano G., Avenoso D.	2026	Acute GVHD	12	**None reported**	MSC infusions well tolerated, no complications observed
Phina-Ziebin X. et al.	2025	Steroid + ruxolitinib refractory aGVHD	43	**No MSC-related toxicity reported**	Good safety profile in compassionate use program
Bonig H. et al.	2023	Adult and paediatric refractory aGVHD	133	**5 non-serious adverse drug reactions**	Mild/moderate severity; all resolved
Gruhn B. et al.	2021	Pediatric SR-aGVHD (case + literature)	1 + review	**No infusion-related toxicity reported**	MSC treatment generally well tolerated
Bader P. et al.	2018	Pediatric refractory aGVHD	140	**4 adverse drug reactions in 3 patients**	3 serious, 1 non-serious; overall favourable safety profile

IDUNN trial - Mesenchymal Stromal Cells vs Best Available Therapy in SR-aGvHD



SR-aGVHD defined as:

a) aGvHD progression within 3 to 5 days of therapy onset with >= 2 mg/kg/day of prednisone equivalent or
b) failure to improve within 5 to 7 days of treatment initiation with >= 2 mg/kg/day of prednisone equivalent or
c) incomplete response after > 28 days of immunosuppressive treatment including at least 5 days with >= 2 mg/kg/day of prednisone equivalent

Study Objective

To demonstrate superiority of MC0518 vs BAT

Recruiting N ≈ 210 patients

Zeiser R et al. Transfus Med Hemother. 2026 Feb 16.

MSCs-FFM in Italy

- Not Registered
- Only Compassionate Use: Italian Experience Colleting Data on 14 cases
- Running Proposal: Prospective Phase II B Multicenter Study

Italian Experiences on Compassionate use of MSCS (Obnitix) for R/R acute-GVHD

aGvHD N = 12	Organ Invol N (%)	Prior Therapy lines	MSCs-cycles N	IST at MSC	Response @ last cy N (%)	Side-Ef N (%)	IST – post N (%)	Outcome Aliv/Dead N (%)
Grade								
G3 10 (84%)	Skin 3 (25%)	1 S-1; Rux+ECP; Etanr	3	Rux+CsA+S	SD	0	Rux+FK+S	A
G4 2 (16%)		2 S-2; Rux, Etanr	3	Rux+CsA+S	CR	0	CsA+S	A
		3 S-1; Rux, Etanr	4	Rux+CsA+S	CR	0	Rux+CsA+S	A
	GI 4 (33%)	1 S-2; Rux	4	Rux+S	SD	0	Rux	A
		2 S-2+CsA;Rux	4	S	CR	0	S	D
		3 S-2;Rux; Vedolizumab	4	Rux+S	CR	0	Rux+S	D
		4 S-2; Rux; ECP	2	CsA+S	SD	0	CsA+S	D
	Skin+GI 5 (42%)	1 S-2; Rux	3	Rux	PR	0	-	A
		2 S-2; Rux; ECP	4	S	PR	0	-	A
		3 S-2; Rux; ECP	4	S	SD	0	S	D
		4 S-2; Rux; ECP	4	Rux+ECP+S	SD	0	Rux+S	D
		5 S-2; Rux; ECP	4	Rux+ECP+S	PR	0	ECP	A
		Median prior lines= 3 (2-3)	≥4 = 8 (66%)		CR 4 (34%) PR/SD 8 (66%)	0	10 (83%)	A 7 (58%) D 5 (42%) **Death cause** Infec. 4 (80) GvHD 1 (20)

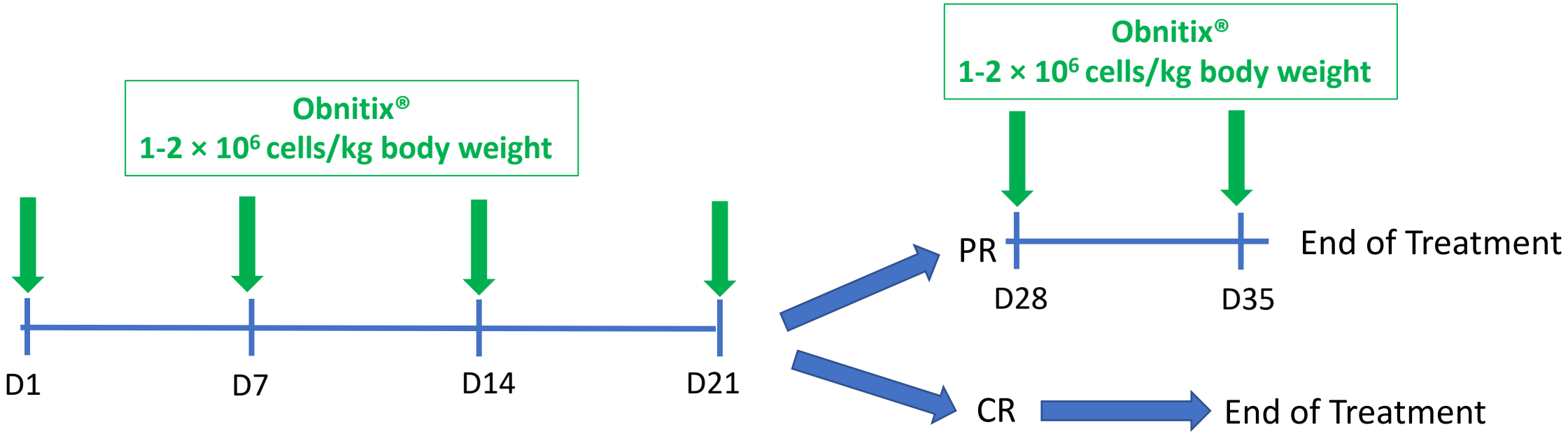
Italian Experiences on Compassionate use of MSCS (Obnitix) for R/R chronic-GVHD

CGvHD N = 2	Organ Invol N (%)	Prior Therapy lines	MSCs-cycles N (%)	IST at MSC	Response @ last cy N (%)	Side-Eff N (%)	IST – post N (%)	Outcome Ali/Dead N (%)
Severity								
Moderate 1 (50%)	Skin +lung =1 (50%)	1 S-2, CSA, ECP, FK, Rux, belumosudil, MTX, imatinib	4	MTX+imatinib+S	PR	0	MTX+imatinib+S	A
Severe 1 (50%)	Skin+eye+GI=1 (50%)	2 S-2, CSA, ECP, MTX, Rux, ibrutinib, belumosudil, MMF	4	MMF+S	PR	0	MMF+S	A
			≥4 = 2/2		PR 2/2	0 0		A 2 (100%) D 0

Enrolling Italian Centres

- **AOU delle Marche, Ancona**
- **ASST Spedali Civili, Brescia**
- **IRCCS Ospedale Policlinico San Martino, Genova**
- **A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo**
- **Fondazione IRCCS Policlinico San Matteo, Pavia**
- **Policlinico Universitario A. Gemelli IRCCS, Roma**
- **Ospedale Universitario S. M. M., Udine**
- **Ospedale dell'Angelo, Venezia Mestre**

Allogeneic Mesenchymal Stromal Cells (allo-MSCs) Infusion in Patients with Ruxolitinib-refractory aGVHD a Phase IIB Clinical Trial : approved by AIFA - 28 April 2026



- **Inclusion criteria:**
- Patient ≥18
- HSCT with any type of donor, stem cell source, GvHD prophylaxis and conditioning regimen
- Patient with aGvHD per modified Glucksberg or MAGIC criteria ≥II-IV grades at the time of diagnosis of refractoriness to steroids and ruxolitinib according to EBMT criteria.

At present

- We don’t have robust data (prospective, long-term) on the efficacy of MSCs while we have substantial data on the safety (tolerance; side effects)
- These data (efficacy and safety) come from esperiences based on the use of MSCs in 2° or 3° Line (either alone or in combination)
- But earlier use of MSCs shloud be considered

Personal Opinion: paradigm shift from treatment to prevention

The greatest value of MSCs may not be only in treating refractory GVHD, but in preventing it from occurring.

Current paradigm

MSC used as **late-line** rescue therapy

Limited patient population

High disease burden already established

Future vision

- MSC used as early immunomodulatory intervention

- 2 line R or in combination
- 1° line + Steroids
- Integration into GVHD prophylaxis platforms

Target:

high-risk patients
alternative donors

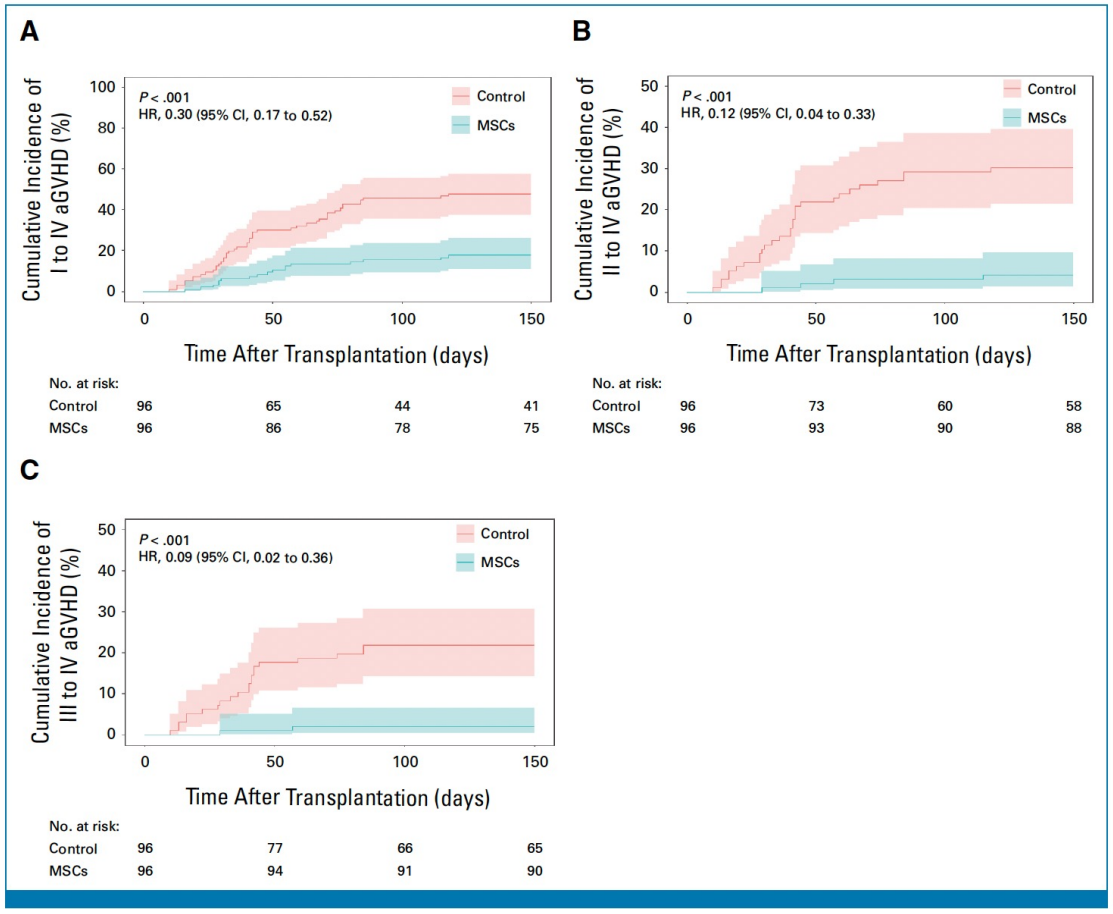
Why this matters?

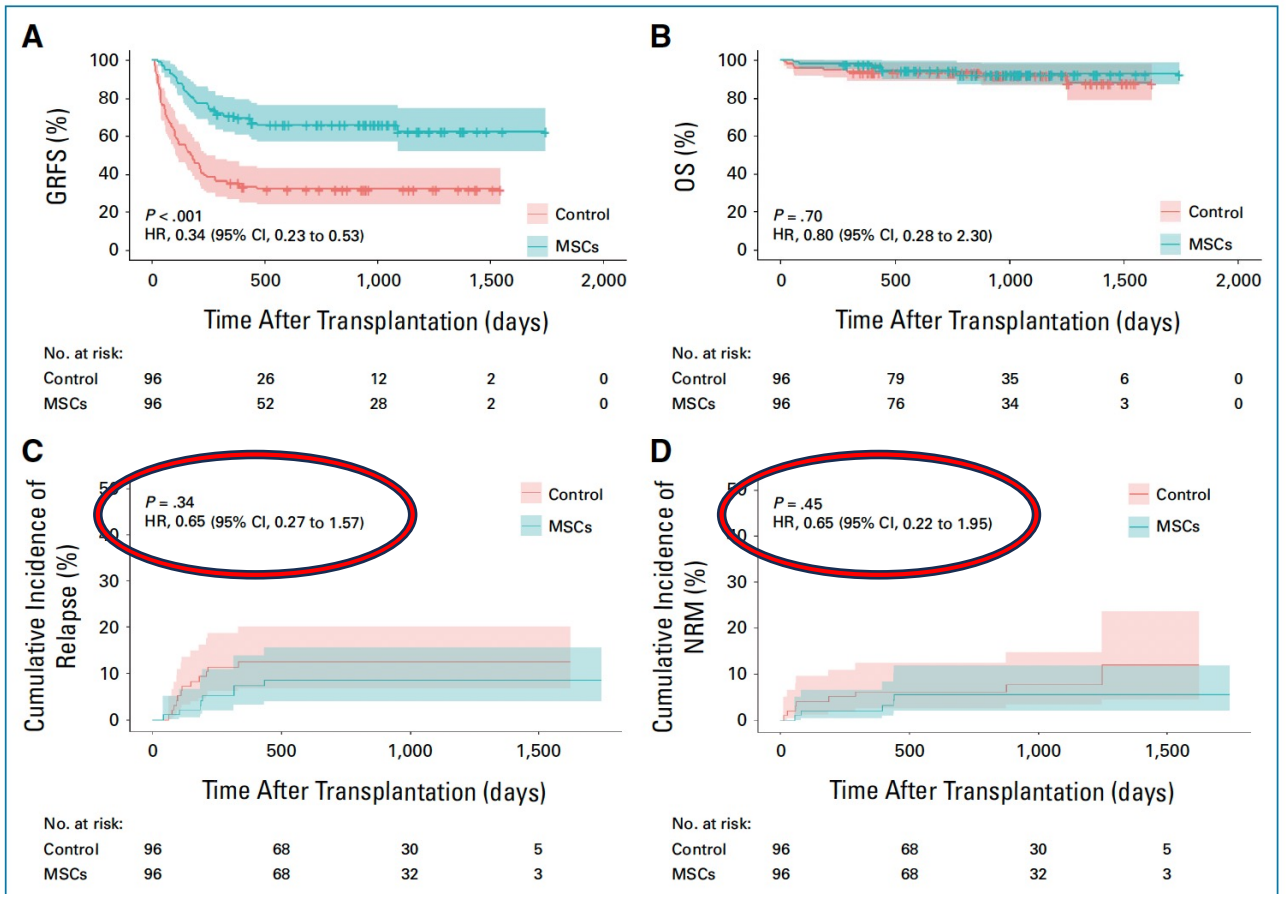
- aGVHD is easier to prevent (treat earlier) than to reverse
- MSC mechanism fits early immune regulation
- Potential to transform clinical outcomes

Sequential Infusion of Mesenchymal Stem Cell for Graft-Versus-Host Disease Prevention in Haploidentical Hematopoietic Stem Cell Transplantation: An Open-Label, Multicenter, Randomized Controlled Clinical Trial

Han Yao, MD, PhD[1,2,3]; Ruihao Huang, MD[1,2,3]; Haixia Fu, MD[4]; Ren Lin, MD[5]; Yanqi Zhang, MD, PhD[6]; Yimei Feng, MD, PhD[1,2,3]; Yu Wang, MD, PhD[4]; Ting Chen, MD, PhD[1,2,3]; Xiaoqi Wang, MD, PhD[1,2,3]; Lidan Zhu, MD, PhD[1,2,3]; Jia Liu, MD, PhD[1,2,3]; Yuqing Liu, MD, PhD[1,2,3]; Lu Zhao, MD, PhD[1,2,3]; Lu Wang, MD, PhD[1,2,3]; Peiyan Kong, MD, PhD[1,2,3]; Qin Wen, MD, PhD[1,2,3]; Cheng Zhang, MD, PhD[1,2,3]; Li Gao, MD, PhD[1,2,3]; Lei Gao, MD, PhD[1,2,3]; Qifa Liu, MD, PhD[5]; Xiaohui Zhang, MD, PhD[4]; Xiaojun Huang, MD, PhD[4]; and Xi Zhang, MD, PhD[1,2,3]

No-PTCY based





JCO 2025

Sequential Infusion of Mesenchymal Stem Cell for Graft-Versus-Host Disease Prevention in Haploidentical Hematopoietic Stem Cell Transplantation: An Open-Label, Multicenter, Randomized Controlled Clinical Trial

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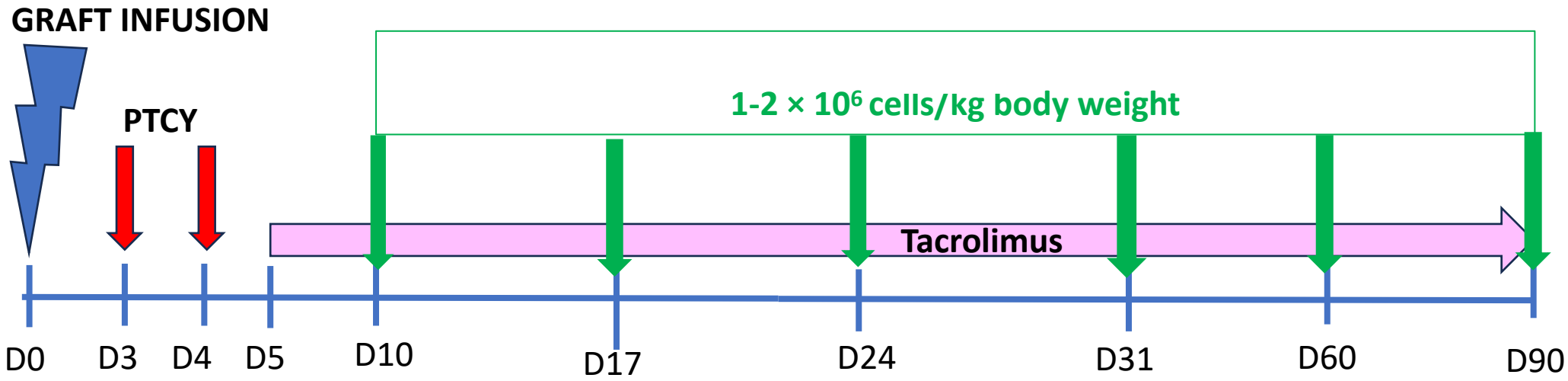
- MSC given at $1x10^6$/kg 4 hours before infusion on day 0;
- Once/ week for the first month after transplantation;
- Once/ 2 weeks for the second month;
- Once/@ third month (total 8 doses)

	Control Group (n = 96), No. (%)	MSC Group (n = 96), No. (%)		Control Group (n = 96), No. (%)	MSC Group (n = 96), No. (%)	
Adverse Event	Any Grade	Any Grade	*P*	Maximum Grade 3/4	Maximum Grade 3/4	*P*
Sepsis	5 (5.2)	5 (5.2)	1.0	2 (2.1)	2 (2.1)	1.0
HC	20 (20.8)	16 (16.7)	.579	12 (12.5)	3 (3)	.031
TMA	6 (6.3)	3 (3.1)	.497	–	–	
Hemorrhage	9 (9.4)	3 (3.1)	.136	0 (0)	0 (0)	1.0
EBV	45 (46.9)	43 (44.8)	1.0	–	–	
CMV	44 (45.8)	41 (42.7)	.771	13 (13.5)	11 (11.5)	.827
VOD	2 (2.1)	1 (1.0)	1.0	–	–	

Allogeneic Mesenchymal Stromal Cells (allo-MSCs) Infusion with PTCY for GVHD prophylaxis



- **Inclusion criteria:**
- Patient ≥60 yy
- HSCT MUD 9/10 or HAPLO, PBSC, any conditioning regimen
- GVHD prophylaxis with PTCY, tacrolimus

Proposal by Daniele Avenoso