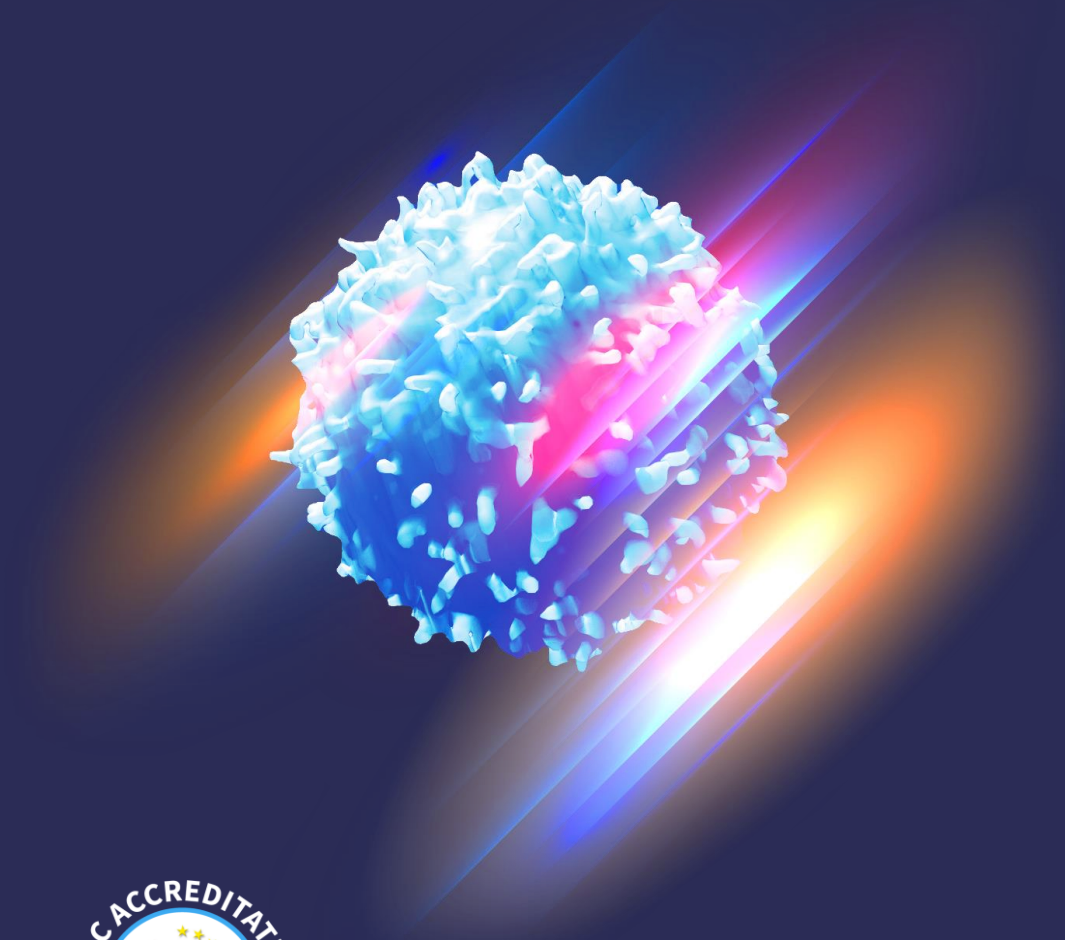
The role of ECP in the management of GvHD

November 29, 2022

Chair: Mohamad Mohty
Speakers: Hildegard Greinix, Daniel Wolff



EBAC ACCREDITATION
EBAC®
2 CME CREDITS

Brought to you by Scientific Education Support

Key considerations for the use of ECP in GvHD

Professor Mohamad Mohty, MD, PhD
Clinical Hematology and Cellular Therapy Department,
Hôpital Saint-Antoine and Sorbonne University,
Paris, FR

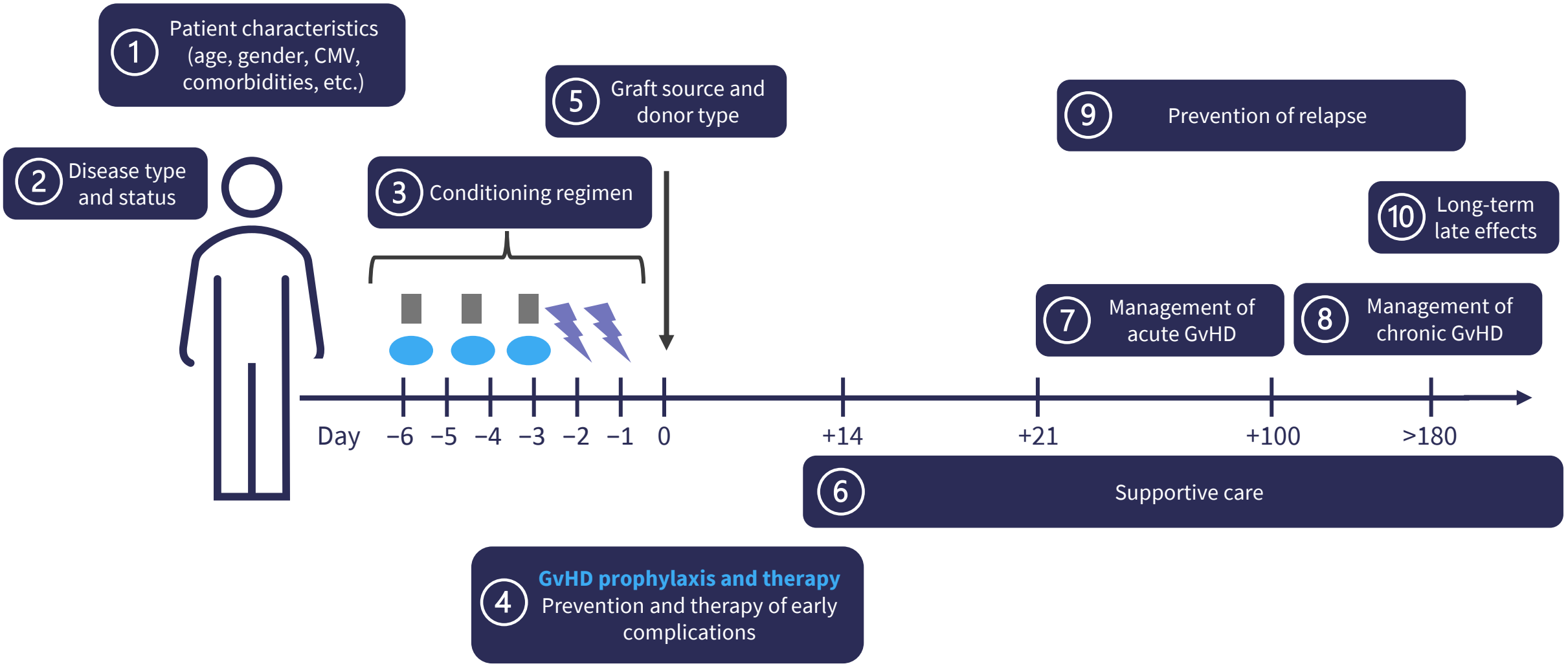
Disclosures

Mohamad Mohty

- The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):
  - Research grant(s)/in kind support: Celgene, Janssen, Sanofi, Jazz Pharmaceuticals
  - Participation in accredited CME/CPD/consultant/strategic advisor (honoraria): Adaptive Biotechnologies, Amgen, BMS, Celgene, Janssen, Takeda, Novartis, Sanofi, Stemline-Menarini, Therakos, Mundipharma
  - Holder of patents/shares or stocks related or unrelated to this presentation: No
  - Non-financial interests: None

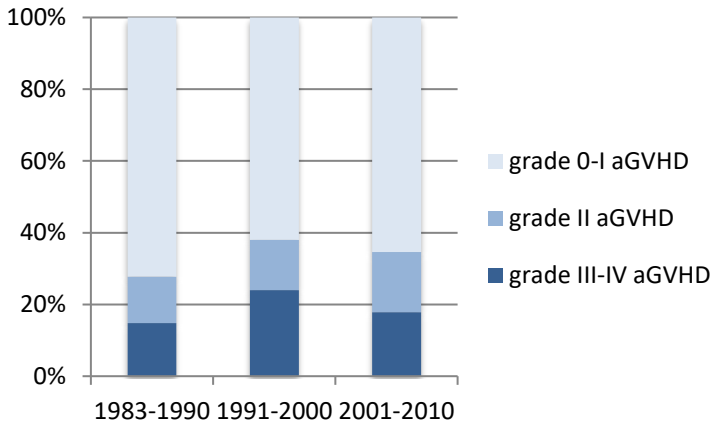
Introduction

The allogeneic stem cell transplant process

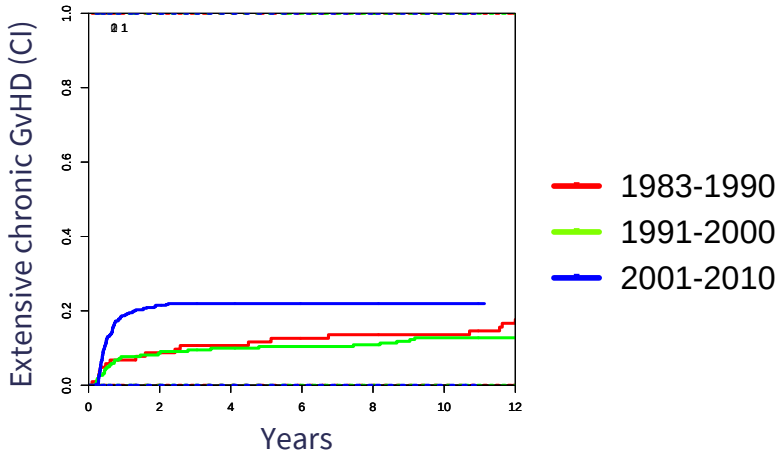


CMV, cytomegalovirus; GvHD, graft-versus-host disease.
Adapted from Mohty M, Malard F. *J Clin Oncol.* 2021;39(18):1951-1954.

Incidences of acute and chronic GvHD over time



Malard F. *Bio Blood Marrow Transplant.* 2014;20(8):1217-1223.



Malard F. *Bio Blood Marrow Transplant.* 2014;20(8):1217-1223.

	1983–1990	1991–2000	2001–2010	p value
CI of acute GvHD at Day 100				
Grade 2–4	27.2%	37.6%	34.8%	0.17
Grade 3–4	14.6%	24.0%	18.1%	0.07
CI of extensive chronic GvHD at 2 years	8.7%	8.6%	21.5%	0.0005

- The incidence of acute GvHD has remained stable over decades
- Extensive chronic GvHD significantly increased in the 2001–2010 decade

aGvHD, acute graft-versus-host disease; CI, cumulative incidence; GvHD, graft-versus-host disease.
Malard F. *Bio Blood Marrow Transplant.* 2014;20(8):1217-1223.

First-line treatment of acute GvHD

First-line treatment

- Stage I–II cutaneous acute GvHD (Grade I): topical steroids
  - If no improvement: corticosteroids 1 mg/kg/day
- Grade II acute GvHD: corticosteroids 1–2 mg/kg/day
- **Grade III–IV acute GvHD: corticosteroids 2 mg/kg/day**

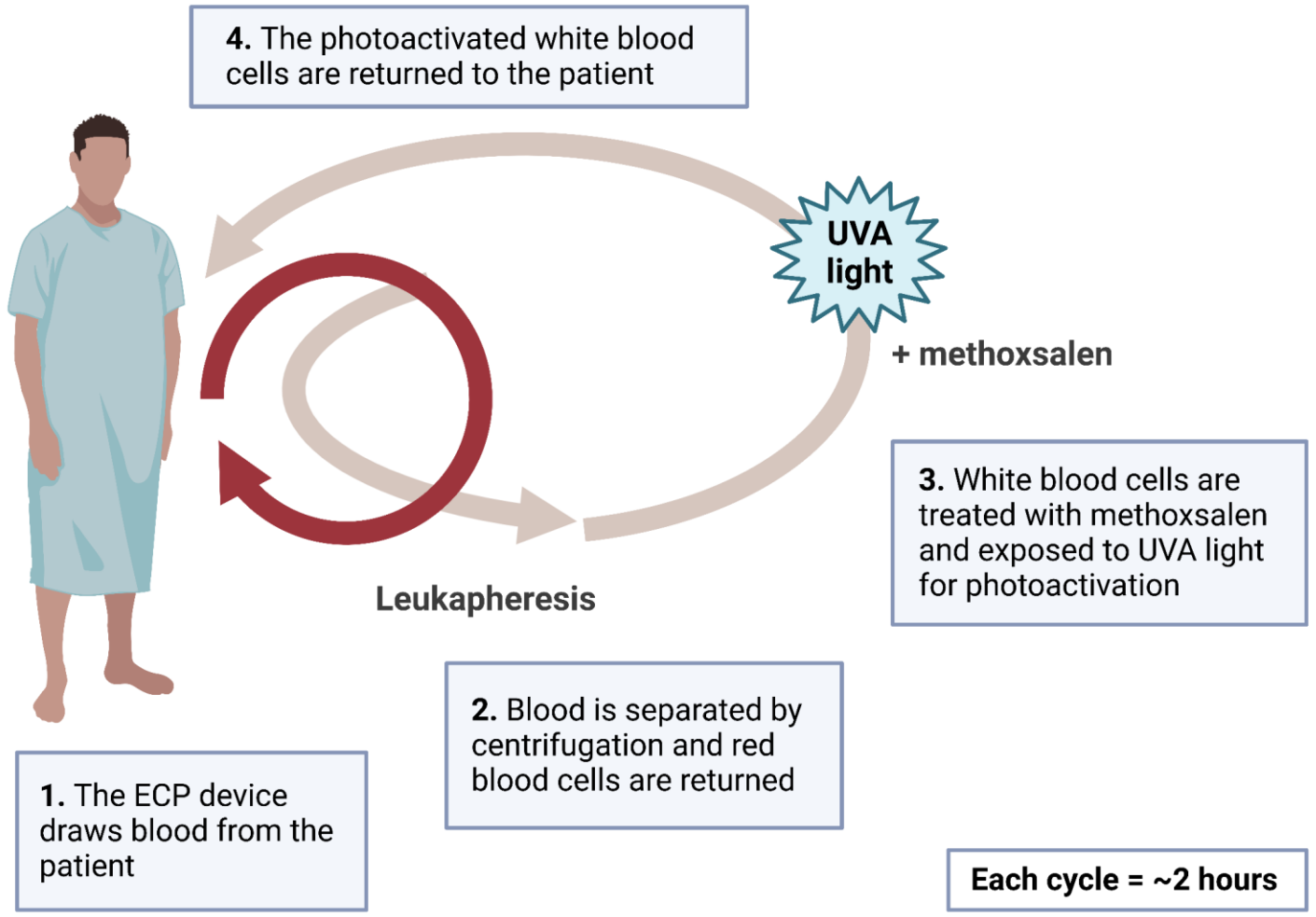
➢ CR rate, approximately 50%

➢ Unmet medical need: need to improve first-line treatment

CR, complete response.

Mohty M, et al. *Blood.* 2020;136(17):1903-1906. Penack O, et al. *Lancet Haematol.* 2020;7:e157-167.

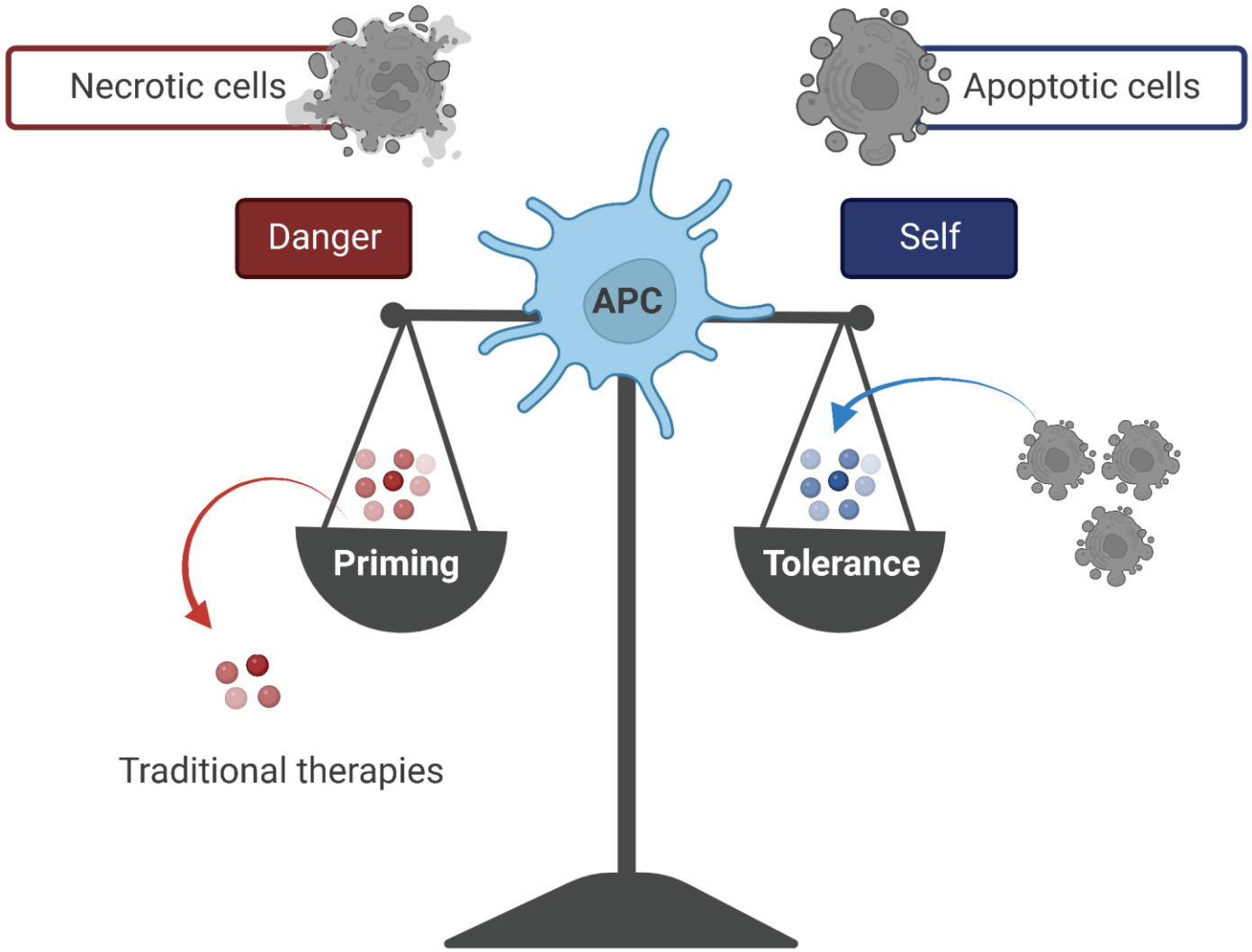
What is extracorporeal photopheresis (ECP)?



Created using BioRender.com.

UVA, ultraviolet A.

Mechanism of action of ECP



Adapted from Peritt. *BBMT.* 2006;12(1 Suppl 2):7-12.
Created using BioRender.com.

APC, antigen presenting cell; ECP, extracorporeal photopheresis.

ECP: Some history

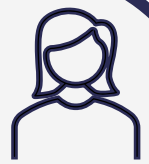
- 1987: Edelson, *et al*. ➔ CTCL
- 1988: First ECP system approved in the US by the FDA
- 1994: Owsianowski, *et al*. ➔ First case of GvHD treated with ECP reported
- PubMed search of “photopheresis GvHD” ➔ 287 articles (as of August 31, 2022)

CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; GvHD, graft-versus-host disease.
Edelson, et al. *N Engl J Med.* 1987;316(6):297-303. Owsianowski, et al. *Bone Marrow Transplant.* 1994;14(5):845-848.

Case no. 1

ECP + steroids as first-line treatment of skin predominant acute GvHD

Case no. 1



- 60-year-old female, no prior medical history, no comorbidities (Sorror index = 0), diagnosed with high-risk AML in March 2019
- Achieved first CR after induction and consolidation

AML, acute myeloid leukemia; CR, complete response.

Case no. 1

- Given the high-risk disease, an allogeneic stem cell transplant from her HLA-identical sister was decided
- Conditioning regimen: fludarabine 150 mg/m^2, IV busulfan 9.6 mg/kg, and anti-human thymocyte immunoglobulin/kg total dose
- GvHD prophylaxis: cyclosporine alone
- G-CSF-mobilized PBSCs were used

G-CSF, granulocyte-colony stimulating factor; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell.

Case no. 1

- ANC and platelets recovery occurred at Day 18
- At Day 24: appearance of a skin rash + erythema covering >70% of the BSA
- No GI or liver manifestations of GvHD

ANC, absolute neutrophil count; BSA, body surface area; GI, gastrointestinal.

What is your treatment approach for such a patient with acute GvHD?

- A) Wait and watch
- B) Local dermo-corticosteroids alone
- C) Corticosteroids 1 mg/kg/day
- D) ECP alone
- E) Other

ECP, extracorporeal photopheresis; GvHD, graft-versus-host disease.

ECP + steroids as first-line treatment of skin predominant aGvHD

- ECP: first-line treatment in skin predominant aGvHD
- Retrospective study (n = 37)
  - ECP + steroids 1 mg/kg: n = 26 (ECP started at a median of 7 days (0–14) after CS)
  - ECP + topical steroids: n = 11 (Stage I or Stage II at high risk of relapse)
- ECP
  - Twice a week (n = 23) or once a week in case of difficult venous access (n = 14) until achievement of VGPR
  - Every 2–4 weeks until CR
  - No maintenance
- CsA was continued in all patients but one

aGvHD, acute graft-versus-host disease; CR, complete response; CS, corticosteroids; CsA, cyclosporine A; ECP, extracorporeal photopheresis; VGPR, very good partial response.
Sestili, et al. *Cytotherapy.* 2020;22(8):445-449.

ECP + steroids as first-line treatment of skin predominant aGvHD: Patients characteristics

Revised Glucksberg criteria	Stage I	Stage II	Stage III	Stage IV
Skin, n (%)	3 (8%)	22 (59%)	12 (32%)	0
Gastrointestinal tract, n (%)	6 (16%)	0	0	0
Liver, n (%)	2 (5%)	2 (5%)	0	0
Overall grade	17 (46%)	18 (49%)	2 (5%)	0

aGvHD, acute graft-versus-host disease; ECP, extracorporeal photopheresis.
Sestili, et al. *Cytotherapy.* 2020;22(8):445-449.

ECP + steroids as first-line treatment of skin predominant aGvHD: Safety

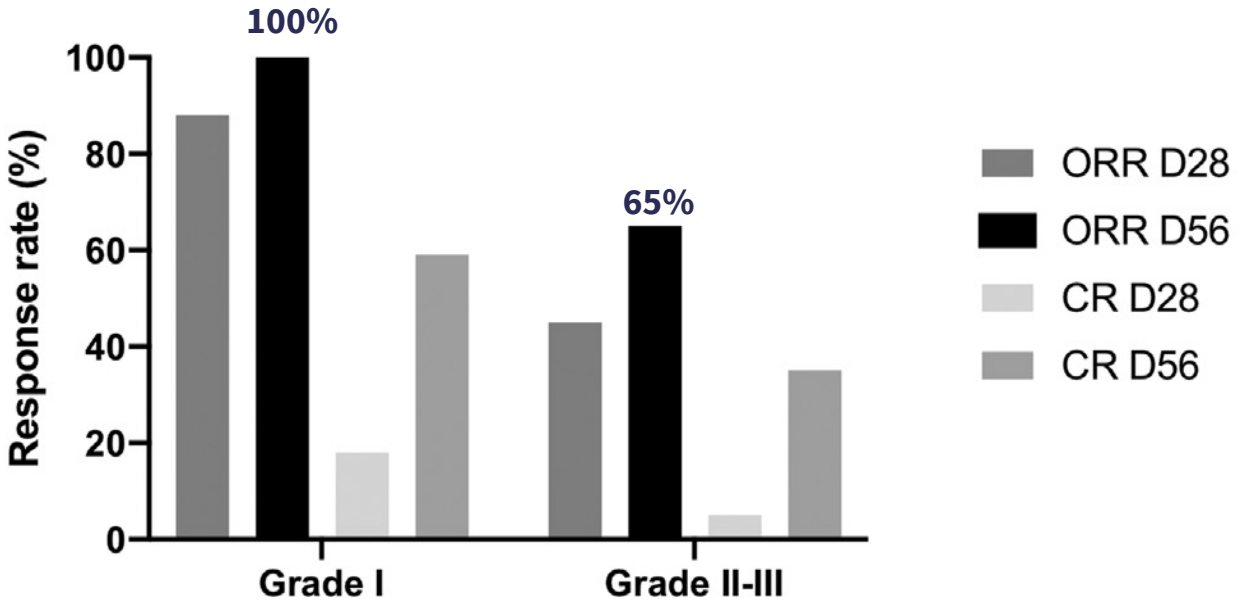
- Median number of ECP: n = 13 (range, 3–36)
- Reasons for ECP discontinuation:
  - Complete resolution of aGvHD (n = 17)
  - Venous access issue (n = 3)
  - Relapse of underlying disease (n = 7)
  - Absence of response (n = 2) and patient choice (n = 1)
- No serious adverse events
- Bacterial infections: n = 5
- Viral infections: n = 13
- Fungal infections: n = 1
- **Fatal infection in one patient**

aGvHD, acute graft-versus-host disease; ECP, extracorporeal photopheresis.
Sestili, et al. *Cytotherapy.* 2020;22(8):445-449.

ECP + steroids associated with high response rate

n = 37

	All
ORR	81%
CR	59%
VGPR	22%
Median time for ORR	15.5 days (6–56)
Median time for CR	52 days (15–144)
Median number of ECP required to achieve CR	8 (2–26)



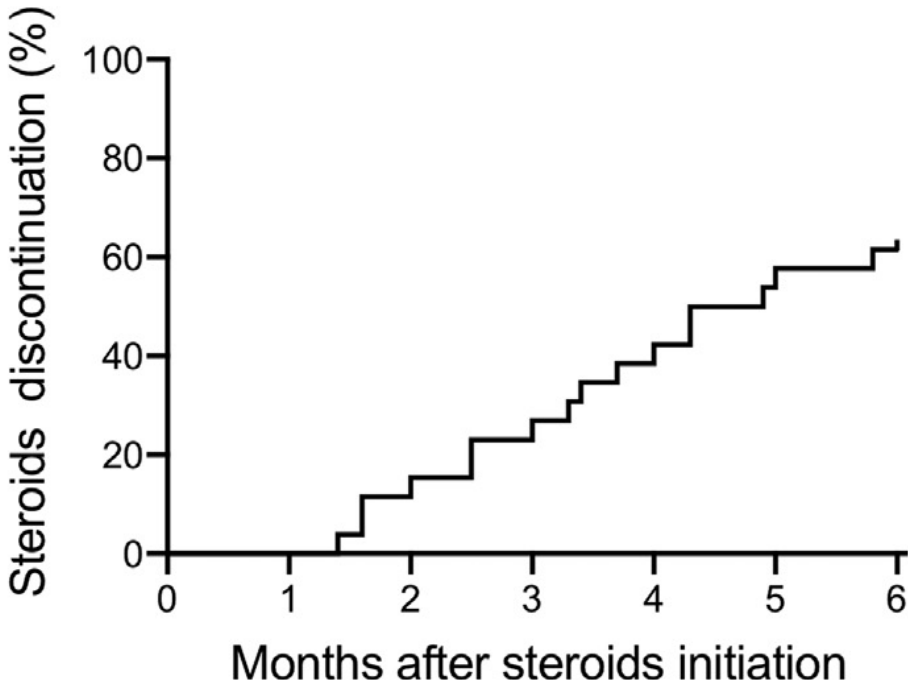
Sestili, et al. Extracorporeal photopheresis as first-line strategy in the treatment of acute graft-versus-host disease after hematopoietic stem cell transplantation: A single-center experience. *Cytotherapy.* 2020;22(8):445-449. DOI: 10.1016/j.jcyt.2020.03.003

- ECP + topical steroids: 100% CR (n = 11)
- ECP + steroids: 42% CR and 31% VGPR (n = 26)
- 7 treatment failures: progression before Day 56, n = 3; stable disease at Day 56, n = 4

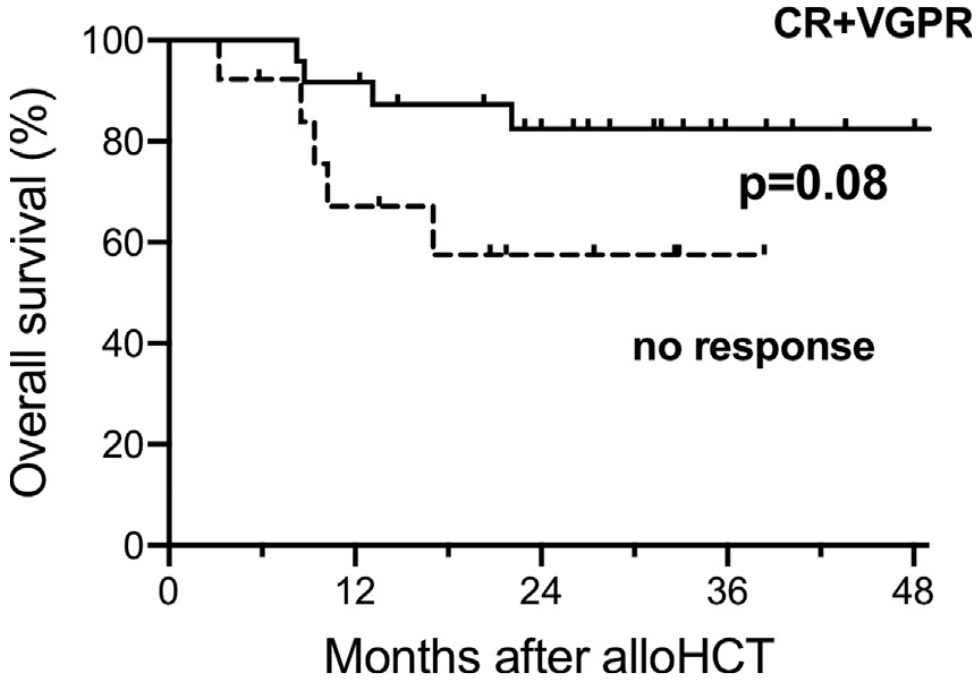
CR, complete response; ECP, extracorporeal photopheresis; ORR, overall response rate; VGPR, very good partial response.
Sestili, et al. *Cytotherapy.* 2020;22(8):445-449.

ECP + steroids is a promising strategy for first-line treatment of skin predominant aGvHD

n = 37



Sestili, et al. Extracorporeal photopheresis as first-line strategy in the treatment of acute graft-versus-host disease after hematopoietic stem cell transplantation: A single-center experience. *Cytotherapy.* 2020;22(8):445-449. DOI: 10.1016/j.jcyt.2020.03.003



Sestili, et al. Extracorporeal photopheresis as first-line strategy in the treatment of acute graft-versus-host disease after hematopoietic stem cell transplantation: A single-center experience. *Cytotherapy.* 2020;22(8):445-449. DOI: 10.1016/j.jcyt.2020.03.003

aGvHD, acute graft-versus-host disease; alloHCT, allogeneic hematopoietic cell transplant; CR, complete response; ECP, extracorporeal photopheresis; VGPR, very good partial response.
Sestili, et al. *Cytotherapy.* 2020;22(8):445-449.

ECP for first-line treatment of aGvHD after haplo-HCT with PTCy

- n = 7 (4 patients treated with ECP alone and 3 patients treated with ECP + CS 1 mg/kg for 1 week)
- 2 × ECP/week for 4 weeks, 2 × ECP/2 weeks for 6 weeks, 2 × ECP/month until clinical improvement

	Patient						
	1	2	3	4	5	6	7
Diagnosis	HL	HL	HL	Ewing	HL	NHL	NHL
Day diagnosis aGvHD	+ 48	+ 66	+ 39	+ 42	+ 32	+ 30	+71
Grade aGvHD	4	2	2	2	2	2	2
Delay GvHD-ECP start, day	2	6	3	1	2	30	4
Steroids	Yes	Yes	/	/	/	Yes	Yes
Full-dose steroids, day	12	7	/	/	/	7	3
Total number of ECP	44	28	40	10	15	9	12
Response	CR	CR	CR	CR	CR	PR	CR
Clinical response after ECP, day	56	2	14	11	8	57	32
CMV reactivation	+	+	/	/	/	/	+
EBV reactivation	/	+	+	/	/	/	/
cGvHD	No	No	Yes	No	No	No	No

- Response: 6 CR and 1 PR
- Median time to CR/PR: 14 days (range, 2–57 days)

aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; CMV, cytomegalovirus; CR, complete response; CS, corticosteroid; ECP, extracorporeal photopheresis; haplo-HCT, haploidentical hematopoietic cell transplant; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PR, partial response; PTCy, post-transplant cyclophosphamide.

Castagna, et al. *BMT.* 2014;49:317-318.

Case 1: Summary

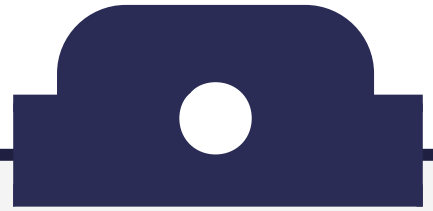
- ECP is feasible and well tolerated in patients with aGvHD (potent immunomodulatory effect)
- Promising results and efficacy in first-line treatment
  - Systemic steroid-free ECP-based treatment for non-severe aGvHD
  - Steroids + ECP for severe aGvHD: steroid-sparing strategy
- Randomized clinical trials are needed to establish the value of ECP in those patients

aGvHD, acute graft-versus-host disease; ECP, extracorporeal photopheresis.

Case no. 2

ECP + steroids for the treatment of refractory chronic GvHD

Case no. 2



- 55-year-old black male with MDS received 9/10 RIC URD PBSCT
- CsA + MMF + ATG for GvHD prophylaxis
- Despite the absence of acute GvHD, the patient developed sclerotic chronic GvHD, including eyes and oral involvement around Day 96 after transplant
- The patient was started on prednisone 1 mg/kg/day and continued to receive CsA; 8 weeks after treatment initiation, the patient nearly achieved a partial response and was clearly impacted by chronic GvHD symptoms

ATG, antithymocyte globulin; CsA, cyclosporine A; GvHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MMF, mofetil mycophenolate; PBSCT, peripheral blood stem cell transplant; RIC, reduced-intensity conditioning; URD, unrelated donor.

What is your treatment approach for such a patient with chronic GvHD?

- A) Wait and watch
- B) Introduce ruxolitinib
- C) Introduce ibrutinib
- D) Introduce ECP
- E) Other

ECP, extracorporeal photopheresis; GvHD, graft-versus-host disease.

Indications for second-line therapy of cGvHD

- **Progression** if minimum 1 mg/kg/day of prednisone for 2 weeks
- **Stable disease** if 4–8 weeks on ≥0.5 mg/kg/day of prednisone
- Inability to taper <0.5 mg/kg/day of prednisone
- **Intolerance** of first-line treatment

cGvHD, chronic graft-versus-host disease.
Wolff D, et al. *Biol Blood Marrow Transplant.* 2011;17(1):1-17.

Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease

Daniel Wolff,[1] Michael Schleuning,[2] Stephanie von Harsdorf,[3] Ulrike Bacher,[4] Armin Gerbitz,[5] Michael Stadler,[6] Francis Ayuk,[4] Alexander Kiani,[7] Rainer Schwerdtfeger,[2] Georgia B. Vogelsang,[8] Guido Kobbe,[9] Martin Gramatzki,[10] Anita Lawitschka,[11] Mohamad Mohty,[12] Steven Z. Pavletic,[13] Hildegard Greinix,[14] Ernst Holler[1]

Therapy	Recommendation	Evidence	Comment
Steroids	B	III-1	Serious side effects
Photopheresis	**C-1**	**II**	**Steroid-sparing, excellent safety profile**
mTOR inhibitors	C-1	III-1	↑ TAM with CNI
Cyclosporin / FK506	C-1	III-1	Spare steroids
MMF	C-1	III-1	↑ viral infections, GI toxicity
Imatinib	C-2	III-1	Best in sclerodermoid GvHD and BO
Rituximab	C-2	II	Effective in autoAB-mediated diseases
Total nodal Rx	C-2	III-2	Best in fasciitis and mucocutaneous cGvHD

AB, antibody; BO, bronchiolitis obliterans; CNI, calcineurin inhibitor; GI, gastrointestinal; MMF, mofetil mycophenolate; TAM, transplantation-associated microangiopathia.

Wolff D, et al. *Biol Blood Marrow Transplant.* 2011;17(1):1-17.

Phase II study of ECP in steroid-refractory/dependent/intolerant cGvHD

- The safety and efficacy of ECP together with standard therapy was compared with standard therapy alone in patients with cutaneous manifestations of cGvHD that could not be adequately controlled by corticosteroid treatment.
  - The proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease from baseline in total skin score was 8.3% in the ECP arm at Week 12 and 0% in the control arm.
  - The nonblinded investigator assessment of skin complete or partial responses revealed a significant improvement in favor of ECP ($p < 0.001$).

cGvHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis.
Flowers, et al. *Blood.* 2008;112(7):2667-2674.

Panel discussion

Supportive care in chronic GvHD

Prophylaxis of infections

Pneumococci, *Pneum. jiroveci*

VZV, fungi

IV Ig in severe infections

Vaccinations

No live vaccine

S. pneumoniae, influenza

GvHD, chronic graft-versus-host disease; IV, intravenous; IG, immunoglobulin; VZV, varicella zoster virus.

Supportive care in chronic GvHD

Prevention of osteoporosis

Psychosocial support

Rehabilitation

Dietary support

GvHD, graft-versus-host disease.

Conclusion

Conclusion

- Acute and chronic GvHD remain serious complications of allo-HSCT
- Improved understanding of pathophysiology of GvHD
  - Separation of GvHD from GvL pending
  - Therapy according to immune dysfunction and organ tropism
- Progress in GvHD prevention is still needed
- Need to improve first-line therapy of both acute and chronic GvHD
- Biomarkers for diagnosis and prognosis warranted

allo-HSCT, allogeneic hematopoietic stem cell transplantation; GvHD, chronic graft-versus-host disease; GvL, graft-versus-leukemia.

Thank you