

17-19 NOVEMBRE 2021

SFGM-TC
2021



Centre de
Congrès Prouvé
Nancy

Multipotent Mesenchymal Stromal Cells for Poor Graft Function after Allogeneic Hematopoietic Cell Transplantation: a Multicenter Prospective Study

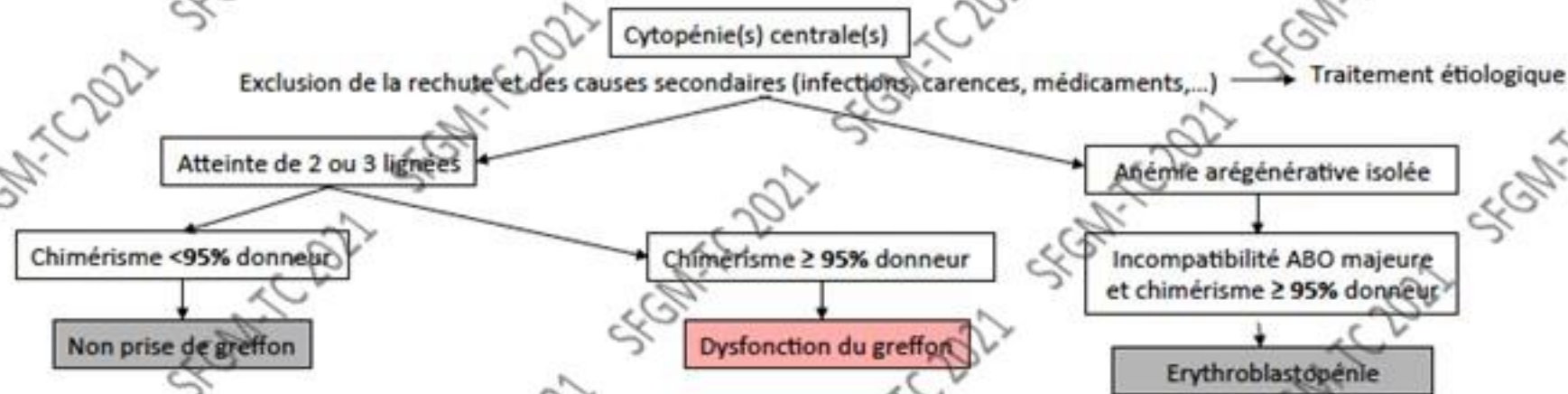
S. Servais, G. Baron, C. Lechanteur, E. Baudoux, A. Briquet, D. Selleslag, J. Maertens, X. Poire,
W. Schroyens, C. Graux, R. Schots, R. Zachée, A. Ory, J. Herman, T. Kerre and Y. Beguin
on behalf of the Transplantation Committee of the Belgian Hematology Society

Introduction

Poor graft function (PGF) after alloHCT

= Persistent cytopenias after alloHCT despite complete engraftment

(SFGM-TC workshop (« Ateliers d'harmonisation de Lille » 2021)



- Rare complication of alloHCT
- Significant morbidity / mortality (infections, bleeding complications, iron overload)

- Treatment options:



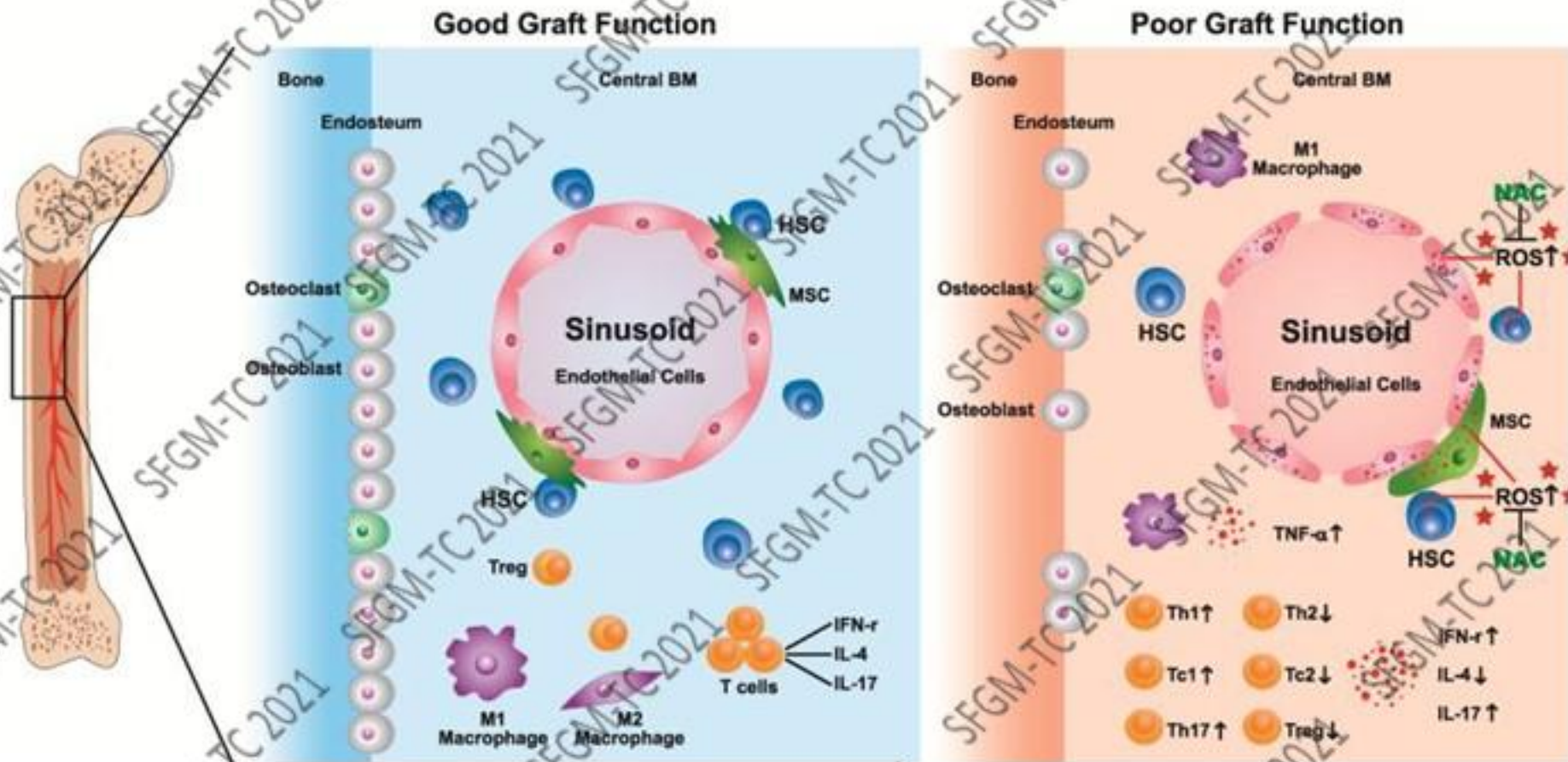
↑ Toxicity
↑ TRM

Feasibility

Low/transient efficacy

Introduction

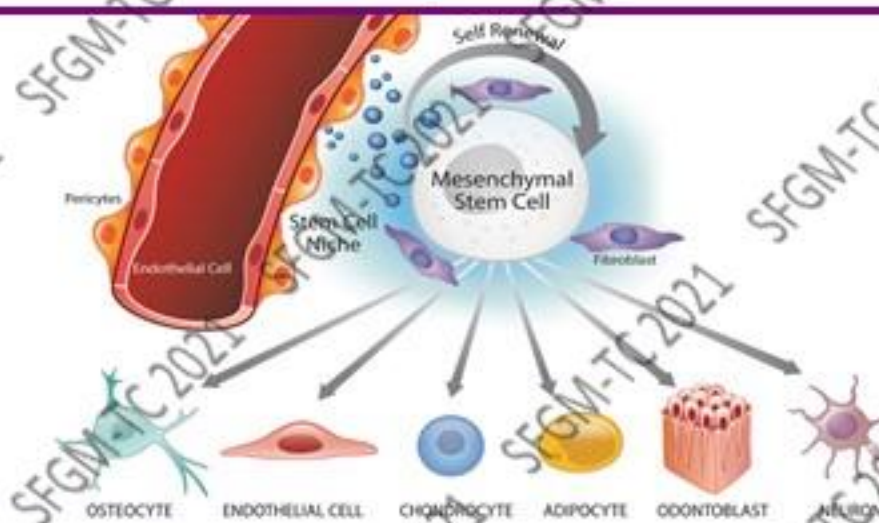
Damaged HSC niches in transplanted patients with PGF



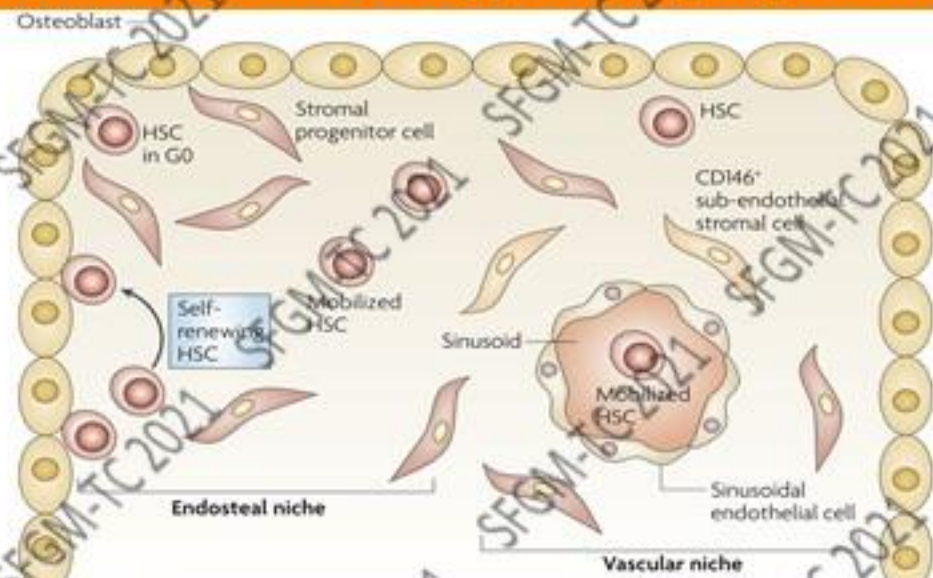
Kong et al. *Semin Hematol* 56 (3) 215-220 (2019)

Introduction

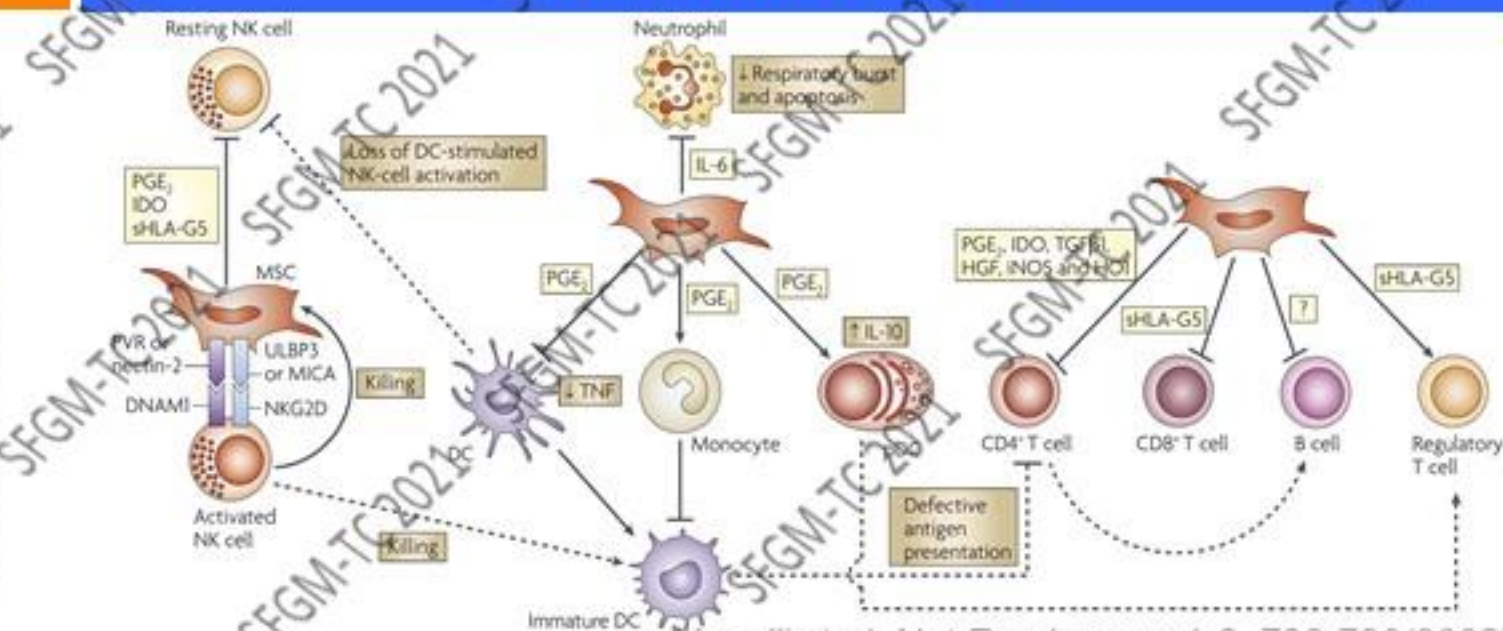
Multipotent mesenchymal stromal cells (MSCs)



Hematopoietic supportive properties



Immunomodulation



Aim

**Single IV infusion of BM-derived MSCs
to improve PGF after alloHCT?**

Belgian multicenter prospective study

(ClinicalTrial.gov#NCT00603330)



BHS

Methods

Patients

8 Belgian centers

30 patients (6 years)

Inclusion criteria:

- **Poor graft function** after alloHCT:
 - At least **2 cytopenias**
with at least **1 severe cytopenia:** ANC < $0.5 \times 10^9/L$ (+/- G-CSF)
Hb < 8.0 g/dL
Platelet count < $20 \times 10^9/L$
or transfusion dependence
 - Cytopenia duration **≥ 2 weeks**
 - **> d+42** after alloHCT
- Full-donor chimerism (> 95%)
- Absence of disease relapse
- Absence of any other identifiable cause of cytopenia

Methods

MSCs

- Production and cryopreservation at the Laboratory of Cell and Gene Therapy (LTCG), ULiege, Belgium
- Bone marrow-derived MSCs**
- Unrelated third-party donors** (≥ 18 y)
- MSC dose: **$1 - 2 \times 10^6$ cells/kg** recipient's weight, **single IV infusion**

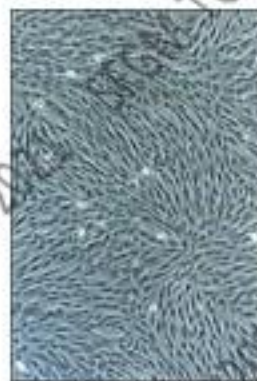


Bone marrow collection



Mononuclear cell isolation

Ficoll



Culture

DMEM-GLX + 10% FBS
37°C, 5% CO₂, 90% hum

3 passages
(+/- 4 weeks)



Freezing
Banking
Releasing

EBMT and
ISCT criteria

Methods

End-points

- Hematological response prospectively recorded at days **0, +30, +60, +90, +120, +150, +180** after MSC infusion:
 - **ANC**
 - **Number of Tx (RBC and plt concentrates)**
 - **Primary end-point: response within 90 days after MSC infusion**
 - **Hematological recovery:** - $ANC \geq 1 \times 10^9/L$
 - Sustained independance from RBC and plt Tx (for at least 30 days)
 - **Complete response (CR)** = recovery of 3 lineages
 - **Partial response (PR)** = recovery of at least 1 lineage
- Overall response (OR = CR + PR)**

Methods

End-points

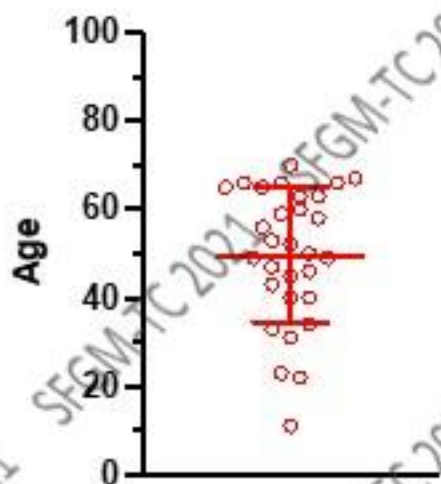
- Response at day +180 after MSC infusion
- Overall survival at day +365 after MSC infusion
- Safety

Results

Patients (n = 30)

Results

Patients (n = 30)

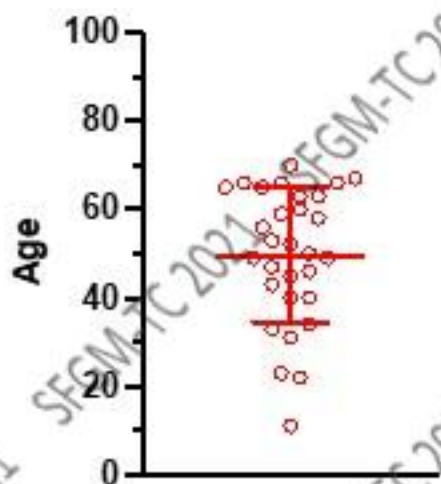


Median 51
(11-70) y

| | n | (%) |
|---|------------|---------------|
| AML/ MDS | 20 | (67) |
| Primary/secondary MF | 4 | (13) |
| Other malignancy | 6 | (20) |
| RIC regimen | 19 | (63) |
| PBSC / BM / UCB | 26 / 3 / 1 | (87 / 10 / 3) |
| Graft CD34 ⁺ cell dose, median (range), x10 ⁶ /kg | 5.5 | (1.8-13) |
| HLA-matched SIB | 6 | (5) |
| HLA-matched UD | 11 | (37) |
| HLA-haploidentical RD | 7 | (23) |
| HLA-mismatched UD | 6 | (5) |
| D/R ABO major (+/- minor) IC | 11 | (37) |
| Prior II-IV aGVHD | 6 | (20) |
| Prior CMV infection | 6 | (20) |
| Prior donor stem cell boost | 5 | (17) |

Results

Patients (n = 30)



| | n | (%) |
|--|------------|---------------|
| AML/ MDS | 20 | (67) |
| Primary/secondary MF | 4 | (13) |
| Other malignancy | 6 | (20) |
| RIC regimen | 19 | (63) |
| PBSC / BM / CB | 25 / 5 / 1 | (87 / 10 / 3) |
| Graft CD34 ⁺ cell dose, median (range), x10 ⁶ /kg | 5.5 | (1.8-13) |
| HLA-matched SIB | 6 | (5) |
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Results

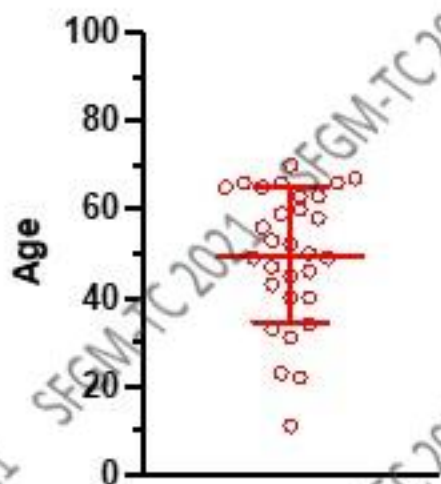
Patients

Most patients cumulated risk factors for PGF

| Patient ID | Risk factors for PGF |
|------------|---------------------------|
| 1 | RIC, URD, HLA |
| 2 | HLA |
| 3 | - |
| 4 | CD34, RIC, HLA |
| 5 | URD, CMV |
| 6 | CD34, HLA |
| 7 | RIC, HLA |
| 8 | RIC, ABO |
| 9 | RIC |
| 10 | HLA, aGVHD |
| 11 | RIC, URD, ABO, CMV, aGVHD |
| 12 | HLA, aGVHD |
| 13 | HLA |
| 14 | RIC, URD, CMV |
| 15 | RIC |
| 16 | RIC, URD |
| 17 | RIC, URD |
| 18 | HLA, CMV, aGVHD |
| 19 | RIC, URD, HLA, ABO |
| 20 | URD, aGVHD |
| 21 | RIC, URD, HLA |
| 22 | RIC, URD |
| 23 | CD34, RIC, URD, ABO |
| 24 | RIC, URD, HLA, CMV |
| 25 | CD34, RIC, UCB, URD, HLA |
| 26 | RIC |
| 27 | RIC, ABO |
| 28 | URD, HLA, aGVHD |
| 29 | CD34, URD, CMV |
| 30 | RIC, URD, ABO |

Results

Patients (n = 30)



| | n | (%) |
|---|----------|-------------|
| AML/MDS | 20 | (67) |
| Primary/secondary MIP | 4 | (13) |
| Other malignancy | 6 | (20) |
| RIC regimen | 19 | (63) |
| PBSC / BM / UCB | 23 / 1 | (81) / (3) |
| Graft CD34+ cell dose, median (range), $\times 10^6$ | 5.5 | (1.8-13) |
| HLA-matched SIB | 6 | (5) |
| HLA-matched UD | 11 | (37) |
| HLA-haploidentical RD | 7 | (23) |
| HLA-mismatched UD | 6 | (5) |
| D/R ABO major (+/- minor) IC | 11 | (37) |
| Prior II-IV aGVHD | 6 | (20) |
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| Prior donor stem cell boost | 5 | (17) |

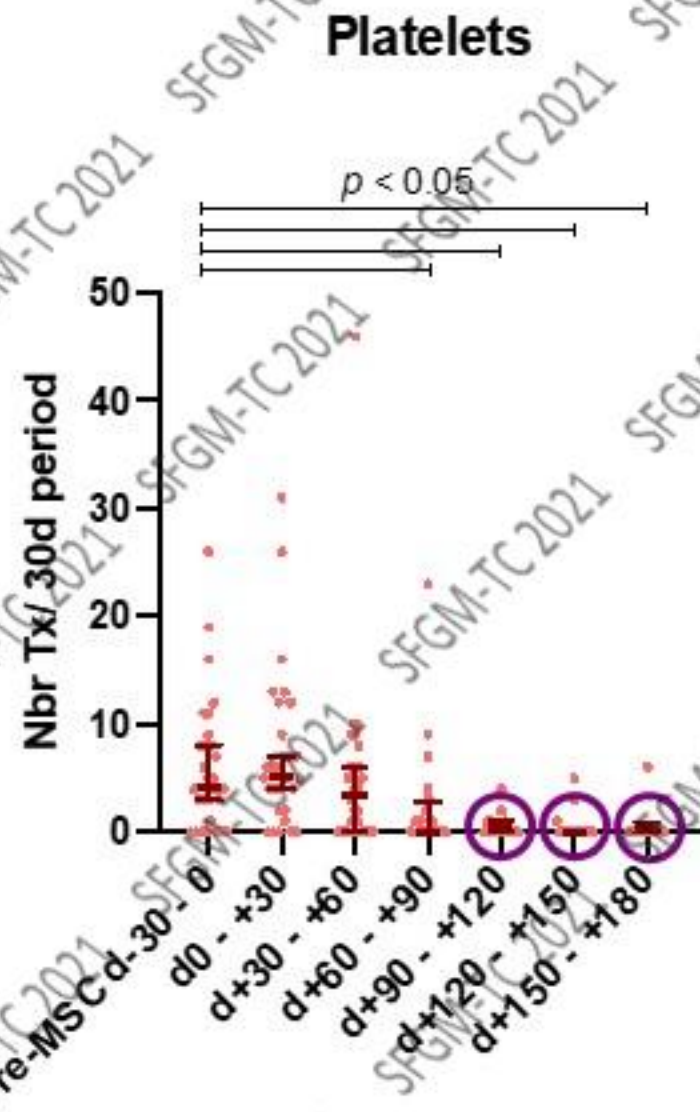
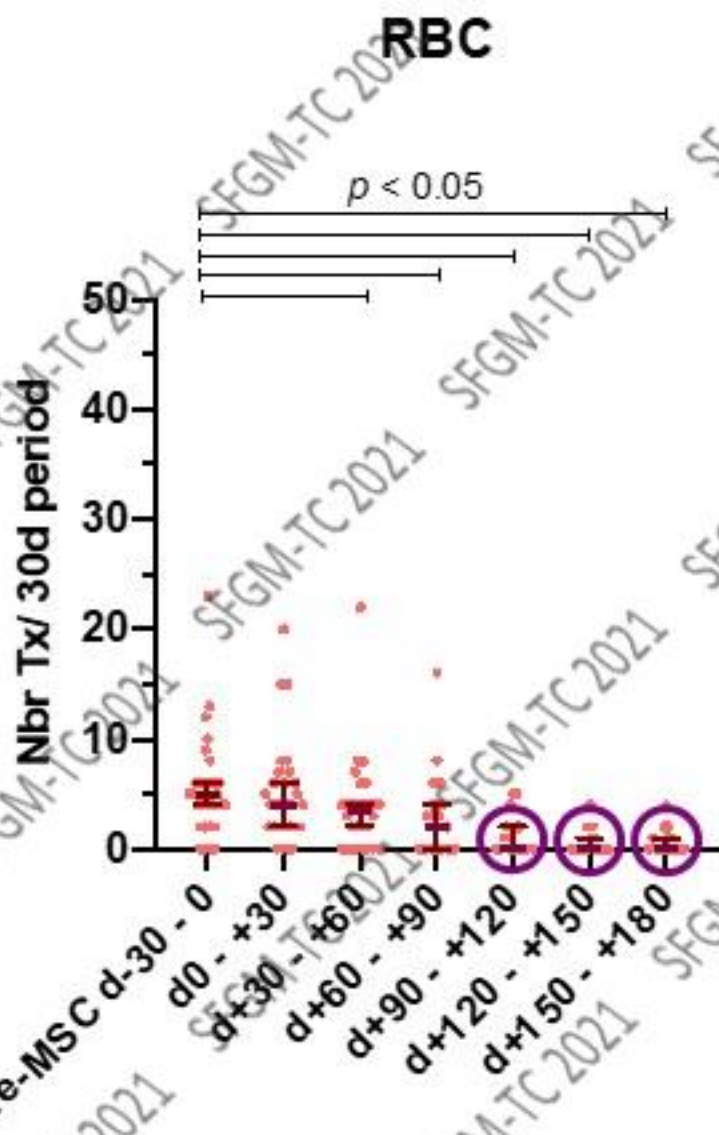
Results

Patients (n= 30)

| | n | (%) |
|---|-----|----------|
| Anemia | 26 | (87) |
| Thrombocytopenia | 22 | (73) |
| Neutropenia | 5 | (17) |
| Primary PGF | 22 | (73) |
| Secondary PGF | 8 | (27) |
| Delay between HCT and MSC, median (range), days | 159 | (42-595) |

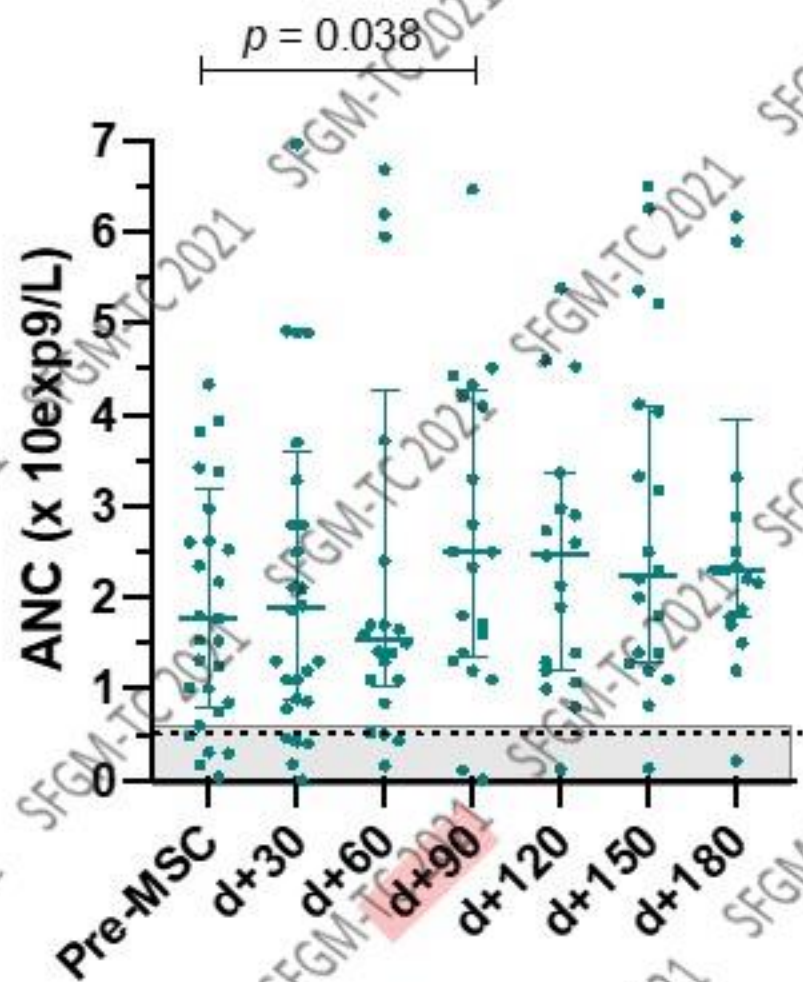
Results

RBC and platelet transfusions

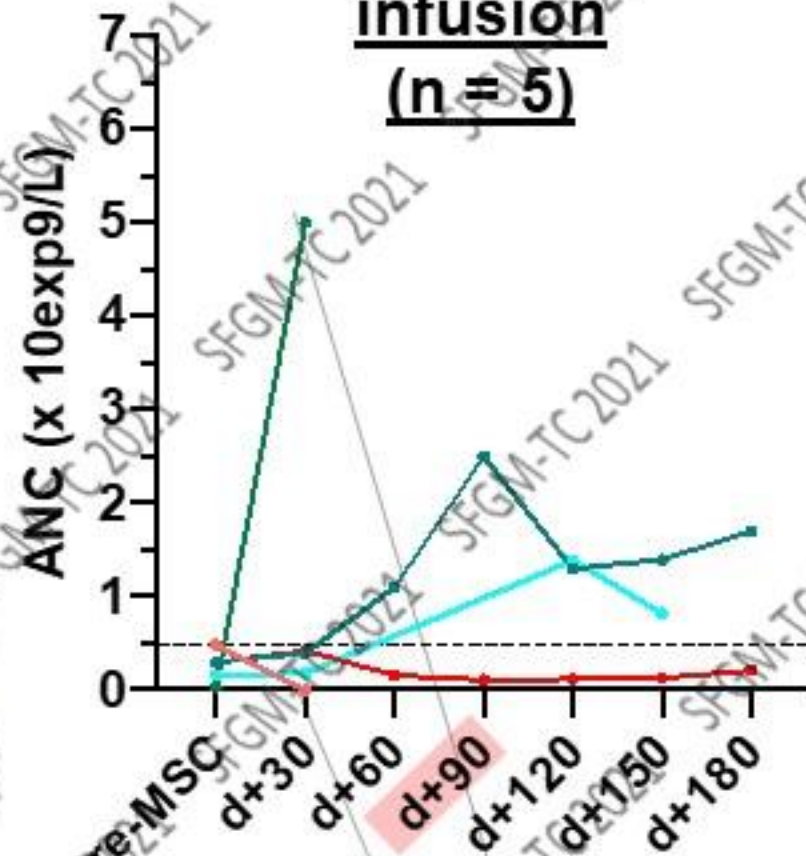


Results

ANC



ANC < 0.5 x 10⁹ at MSC infusion (n = 5)

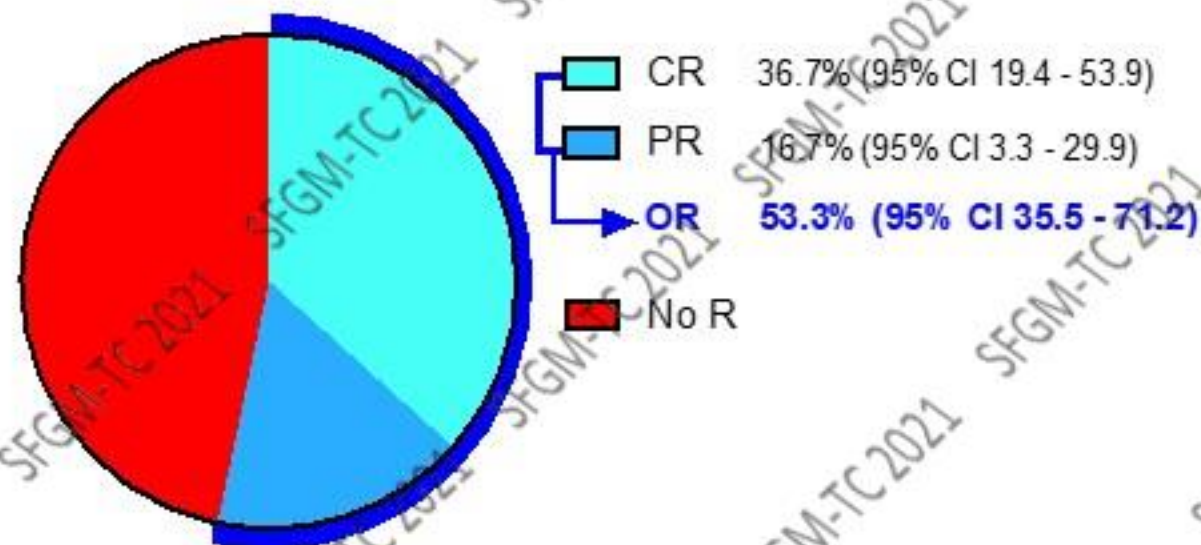


① disease relapse
② 2nd alloHCT for PGF

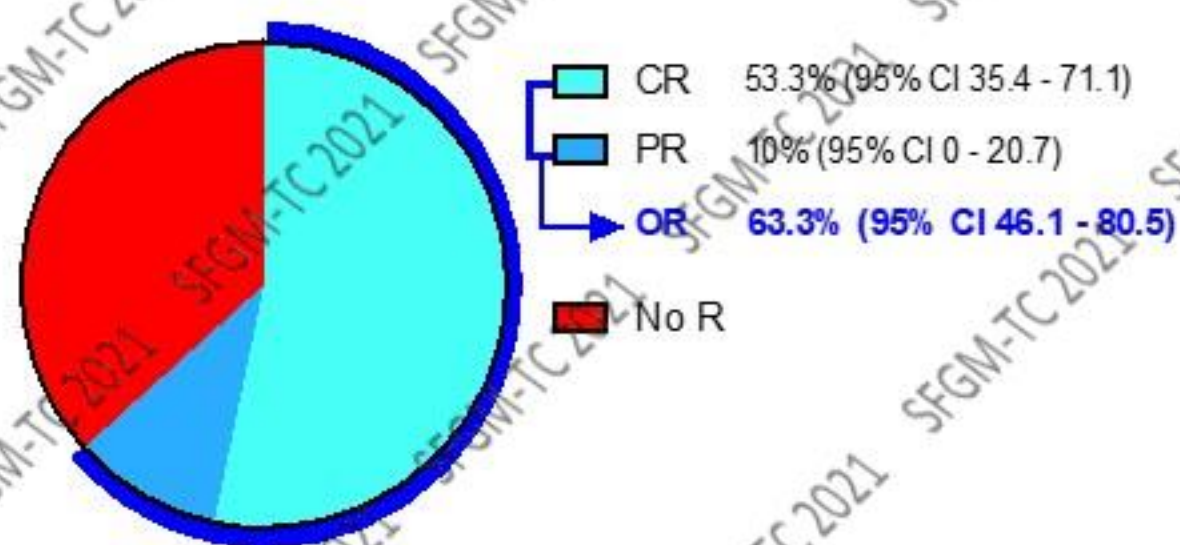
Results

Overall response

d90



d180



Results

Comparison: responders vs non-responders (d90)

No difference

- Patient characteristics (age, gender, disease)
- Transplant characteristics (conditioning, donor, ABO, CMV, CD34⁺ dose)
- Prior aGVHD
- Donor-derived stem cell boost before MSC
- Number of cytopenia(s)
- Primary / secondary PGF
- Delay between HCT and MSC

Results

Comparison: responders vs non-responders (d90)

No difference

- Patient characteristics (age, gender, disease)
- Transplant characteristics (conditioning, donor, ABO, CMV, CD34⁺ dose)
- Prior aGVHD
- Donor-derived stem cell boost before MSC
- Number of cytopenia(s)
- Primary / secondary PGF ($p = 0.061$)
- Delay between HCT and MSC

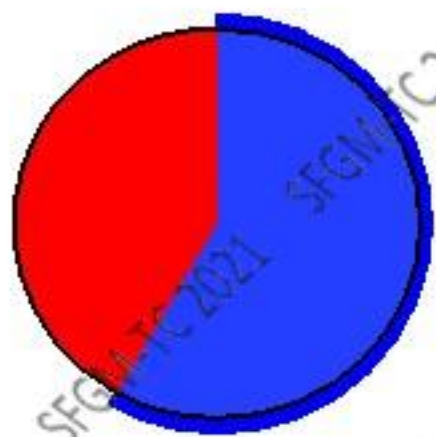
(responders: 122 [42–384] days vs. non-responders: 198 [75–595] days, $p = 0.075$)

Results

Response (d90) according to type of PGF and delay HCT – MSC

$p = 0.061$

Primary

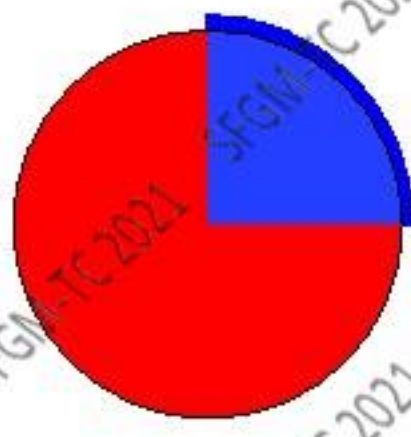


n=22

OR 63.6% (95% CI 43.5 - 83.7)

No R

Secondary



n=8

OR 25% (95% CI 0 - 55.1)

No R

$p = 0.03$

HCT – MSC
 $< 180d$

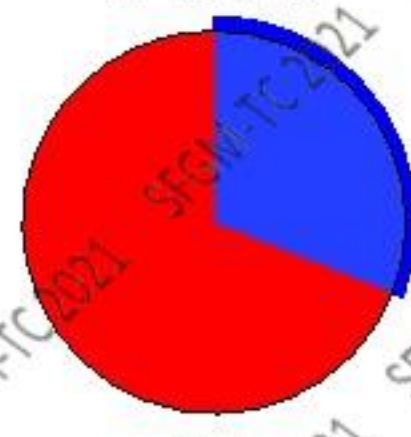


n=17

OR 70.6% (95% CI 48.9 - 92.3)

No R

HCT – MSC
 $\geq 180d$



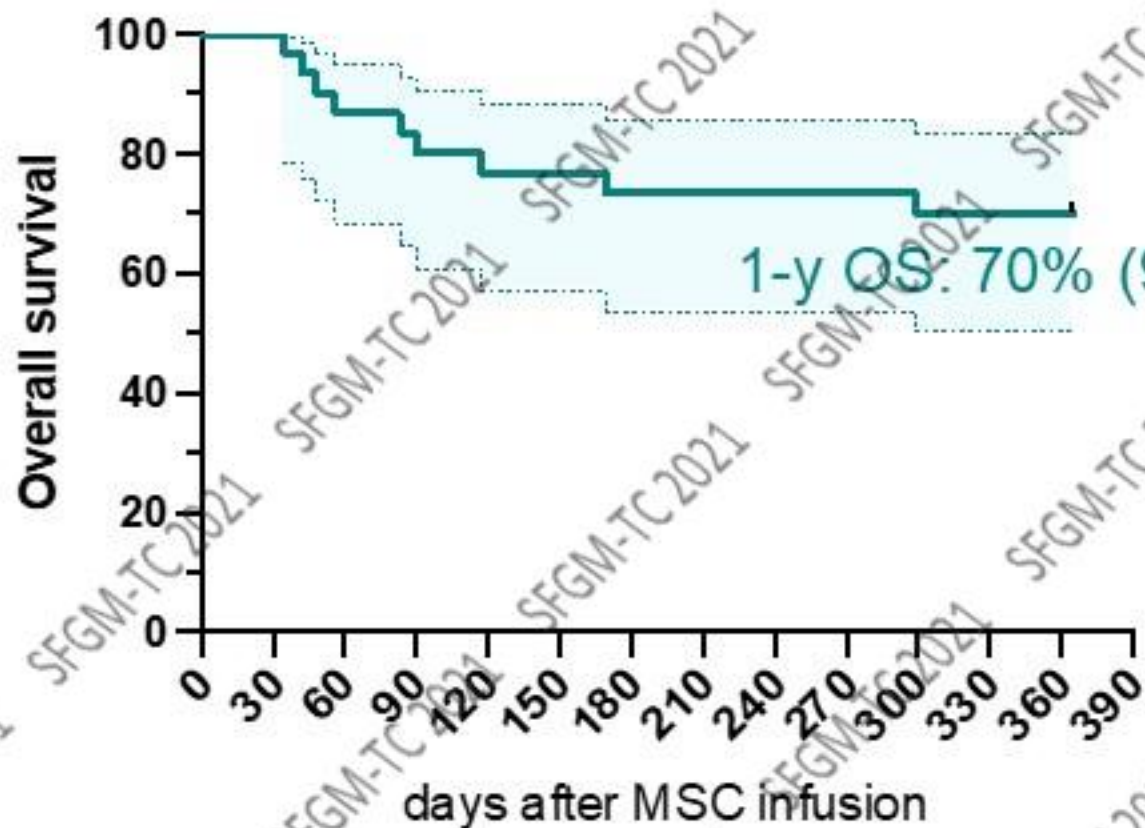
n=12

OR 30.8% (95% CI 5.7 - 55.9)

No R

Results

Overall survival



Responders vs. non responders

(landmark analysis d90) $p=NS$

Primary vs. secondary PGF $p=NS$

Safety: No SAE related to MSC infusion reported

Third-party BM-derived MSCs for PGF after alloHCT:

- **53%** of patients resolved at least one of their cytopenias
- **37%** of patients achieved a complete hematological recovery
- No severe adverse event

Limitations:

- Low number of patients (n=30)
- Absence of a control group – Spontaneous recovery not excluded

→ **Need for further studies**

Acknowledgments

Members of the Laboratory of Cell and Gene Therapy
(LTCG), ULiege

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Brussels, UZA Antwerpen, Clinique Universitaire de Mont-Godinne Yvoir, UZG Gent, AZ VUB
Brussels, ZNA Stuivenberg Antwerp

Patients



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Thank you for your attention