

# Microtransplantation de cellules souches hématopoïétiques

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Dr Raynier Devillier, MD, PhD

Congres Annuel de la SFGM-TC: Session Clinique 17/11/2021



# Microtransplantation de CSH vs. Allogreffe de CSH

Allogreffe de CSH

- **Transplantation de 2 systèmes**

- ✓ Hématopoïétiques
- ✓ Immunitaires

Conditionnement  
Immunosuppresseur



Patient

CSH



Donneur



# Microtransplantation de CSH vs. Allogreffe de CSH

Allogreffe de CSH

Conditionnement  
Immunosuppresseur

- **Transplantation de 2 systèmes**

- ✓ Hématopoïétiques
- ✓ Immunitaires

- **Mise en place d'une chimère**



Patient



Donneur

CSH

# Microtransplantation de CSH vs. Allogreffe de CSH

Allogreffe de CSH

Conditionnement  
Immunosuppresseur



Patient

CSH



Donneur

- **Transplantation de 2 systèmes**

- ✓ Hématopoïétiques
- ✓ Immunitaires

- **Mise en place d'une chimère**

- Effet **graft-versus-leukemia (GVL)**
- Effet **graft-versus-host (GVH)**



# Microtransplantation de CSH vs. Allogreffe de CSH

Microtransplantation de CSH

Chimiothérapie  
anti-tumorale

- **Pas de prise de greffe**

« *non engrafting alloreactive cellular therapy* »



Patient



Donneur

CSH



# Microtransplantation de CSH vs. Allogreffe de CSH

Microtransplantation de CSH

Chimiothérapie  
anti-tumorale



Patient

CSH



Donneur

- **Pas de prise de greffe**  
« *non engrafting alloreactive cellular therapy* »
- Mise en place d'un **microchimérisme**

# Microtransplantation de CSH vs. Allogreffe de CSH

Microtransplantation de CSH

Chimiothérapie  
anti-tumorale



Patient

CSH

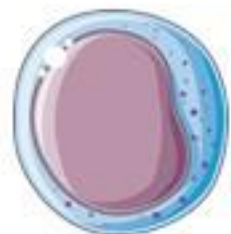


Donneur

- **Pas de prise de greffe**  
« *non engrafting alloreactive cellular therapy* »
- Mise en place d'un **microchimérisme**
- **Effet antitumoral**
- **Sans GVH**

# Mécanisme d'action possible de la microtransplantation

Receveur



NK cells



CD8+ T cells



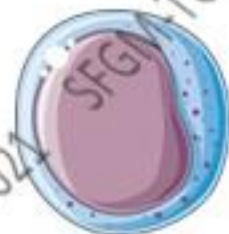
Leukemic cells

lyse directe ?

Donneur



T cells



NK cells

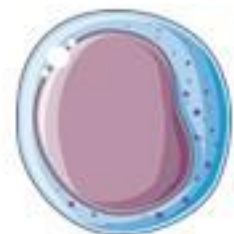


# Mécanisme d'action possible de la microtransplantation

**Receveur**

**1. Alloréactivité bi directionnelle**

**Donneur**



NK cells



CD8+ T cells



Leukemic cells

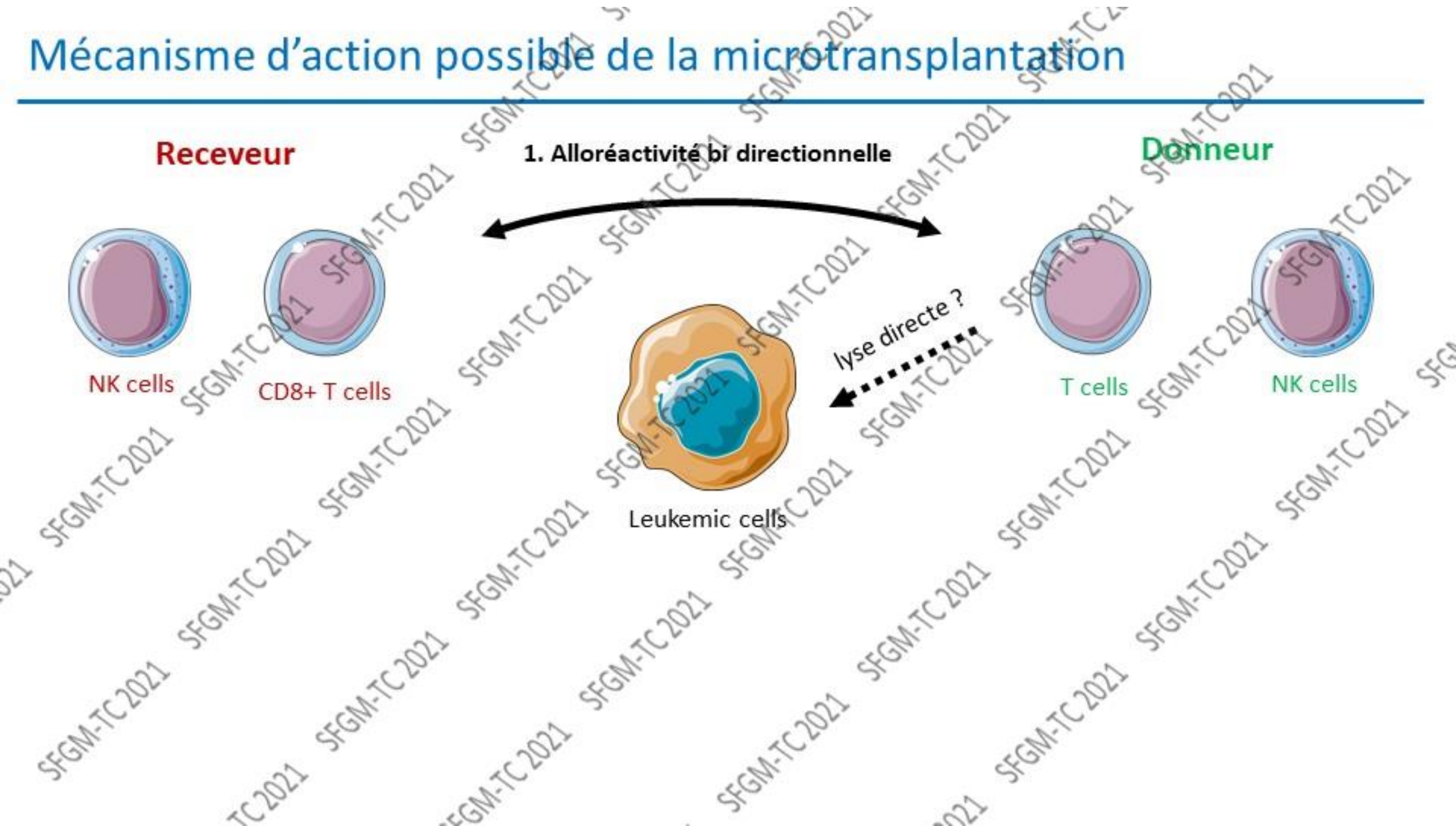
lyse directe ?



T cells



NK cells

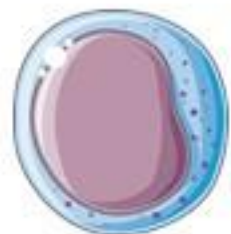


# Mécanisme d'action possible de la microtransplantation

**Receveur**

**1. Alloréactivité bi directionnelle**

**Donneur**



NK cells



CD8+ T cells

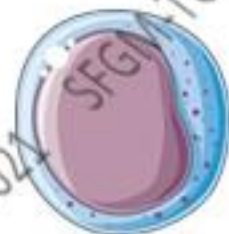


Leukemic cells

lyse directe ?



T cells



NK cells



CPA

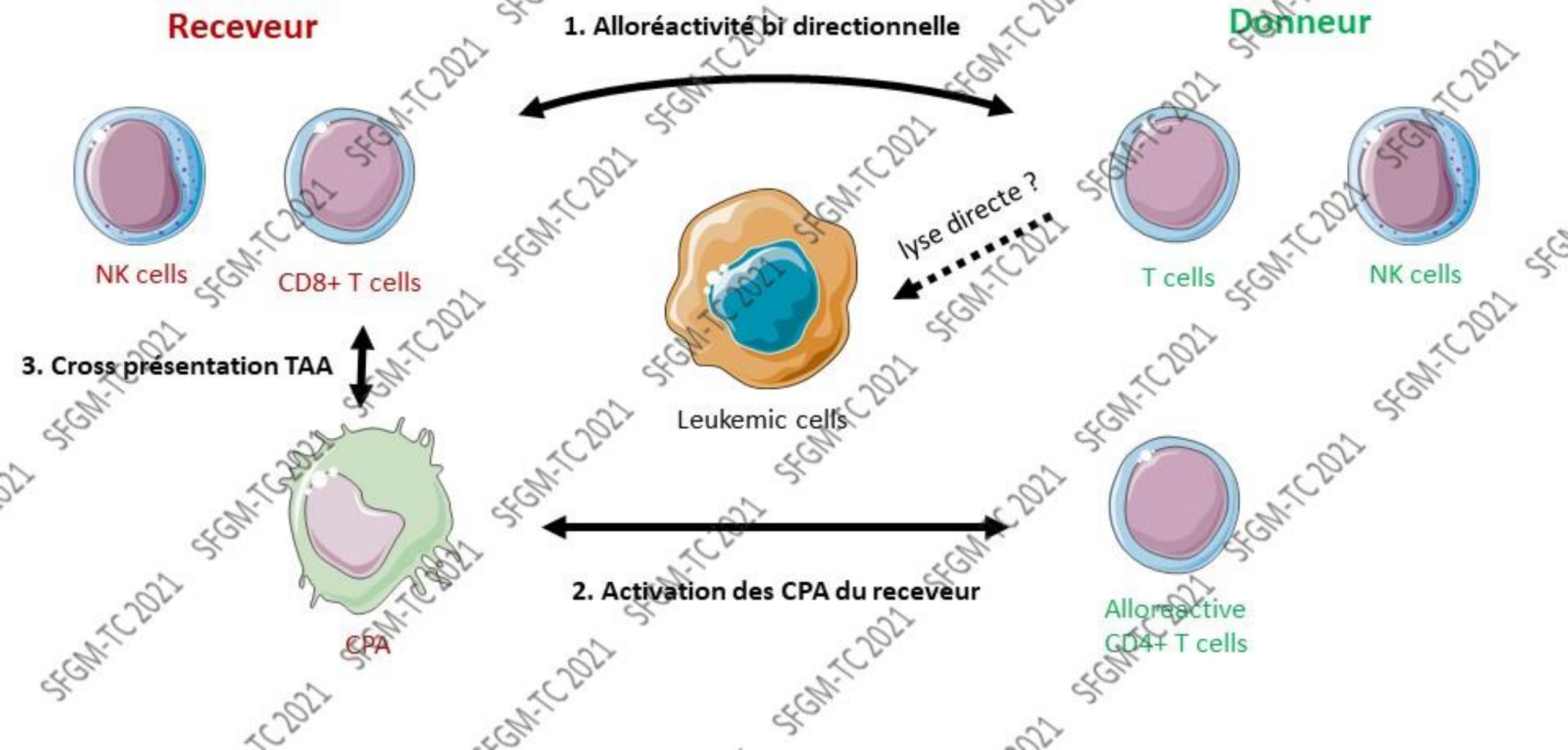
**2. Activation des CPA du receveur**



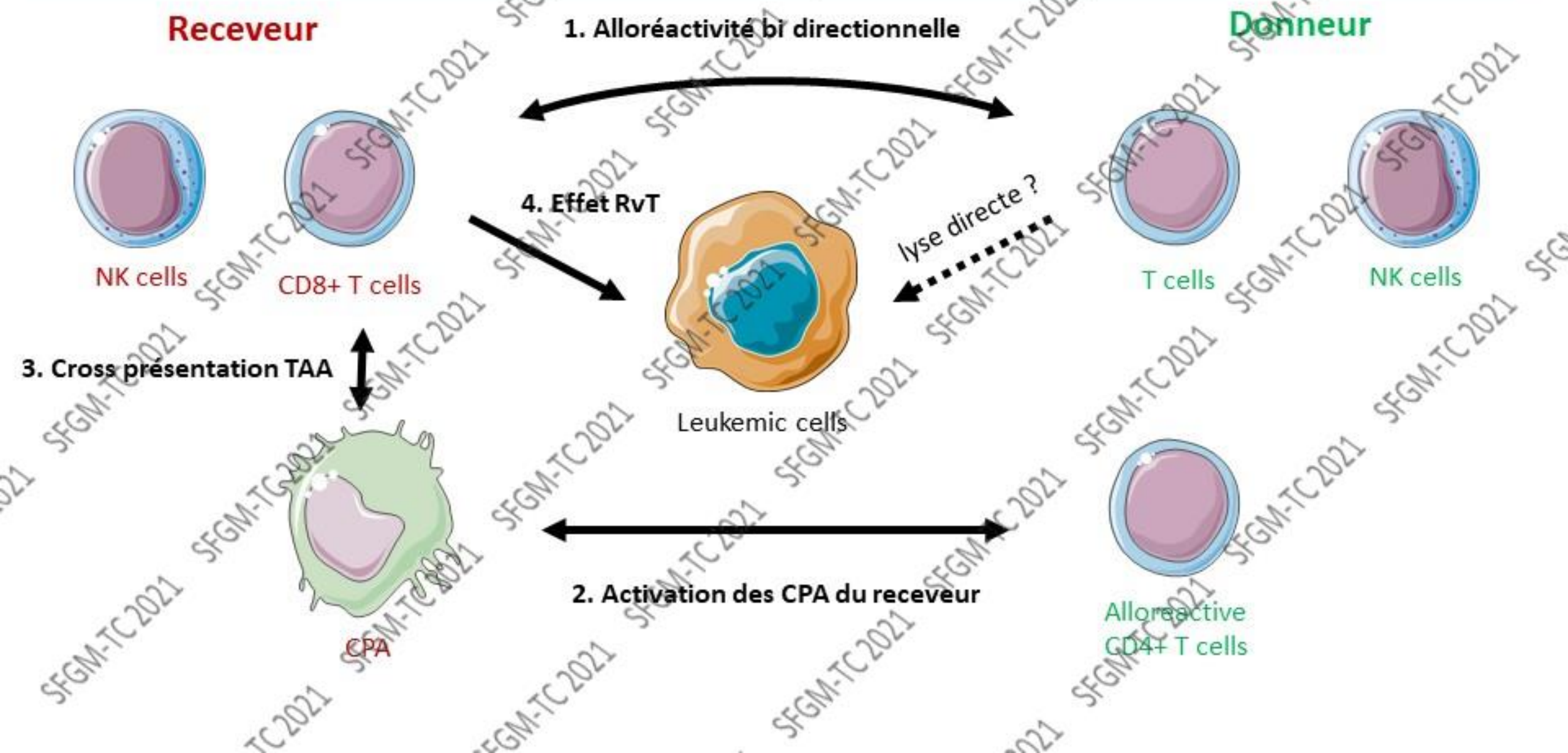
Alloreactive  
CD4+ T cells



# Mécanisme d'action possible de la microtransplantation



# Mécanisme d'action possible de la microtransplantation





# Mécanisme d'action possible de la microtransplantation

Receveur

1. Alloréactivité directionnelle

Donneur

## The Allogeneic Effect Revisited: Exogenous Help for Endogenous, Tumor-Specific T Cells

Heather J. Symons,<sup>1,2</sup> Moshe A. Levy,<sup>1,3</sup> Jie Wang,<sup>1</sup> Xiaotao Zhou,<sup>1</sup> Gang Zhou,<sup>1</sup> Sarah E. Cohen,<sup>1</sup> Leo Luznik,<sup>3</sup> Hyam I. LoSitsky,<sup>1,3</sup> Ephraim J. Fuchs<sup>1,3</sup>

2. Activation des CPA du receveur

Allogénique  
T cells

# Mécanisme d'action possible de la microtransplantation

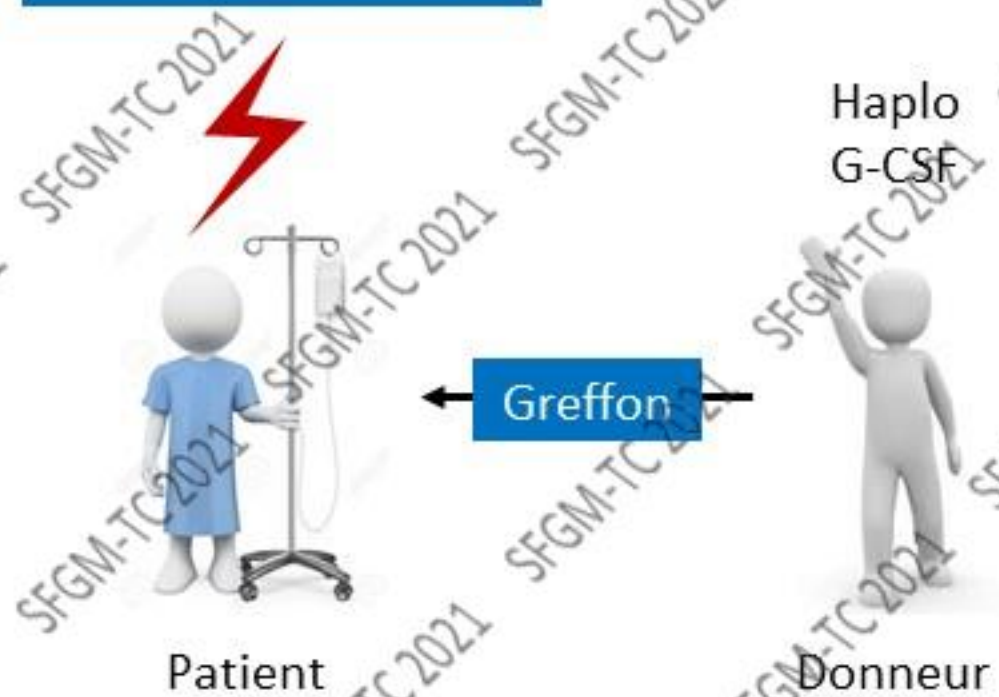
## Nonengraftment Haploidentical Cellular Immunotherapy for Refractory Malignancies: Tumor Responses without Chimerism



Gerald A. Colvin,<sup>1</sup> David Berz,<sup>1</sup> Mathalagu Ramanathan,<sup>2</sup> Eric S. Winer,<sup>1</sup> Loren Fast,<sup>1</sup> Gerald J. Eiftenbein,<sup>3</sup> Peter J. Quesenberry

BBMT 2009

Irradiation Corporelle  
Totale 100 cGy





# Mécanisme d'action possible de la microtransplantation

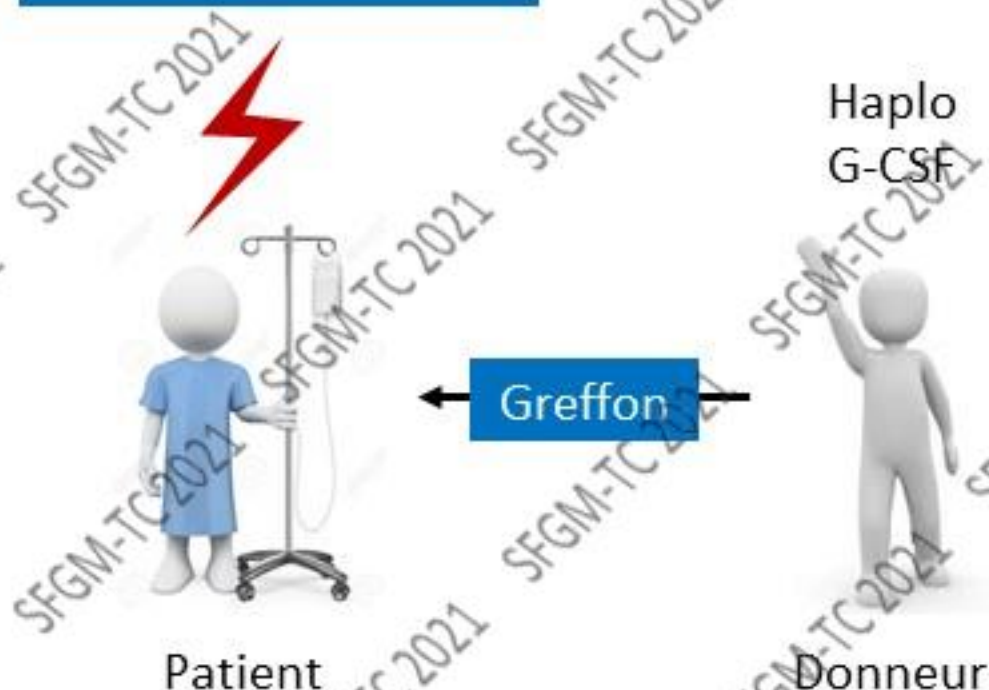
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BBMT 2009

Irradiation Corporelle  
Totale 100 cGy



Syndrôme de relargage cytokinique (CRS)  
“Haplo immunostrom (HIS)”

- Fièvre (100%)
- Rash cutané (60%)
- Diarrhée (73%)

# Mécanisme d'action possible de la microtransplantation

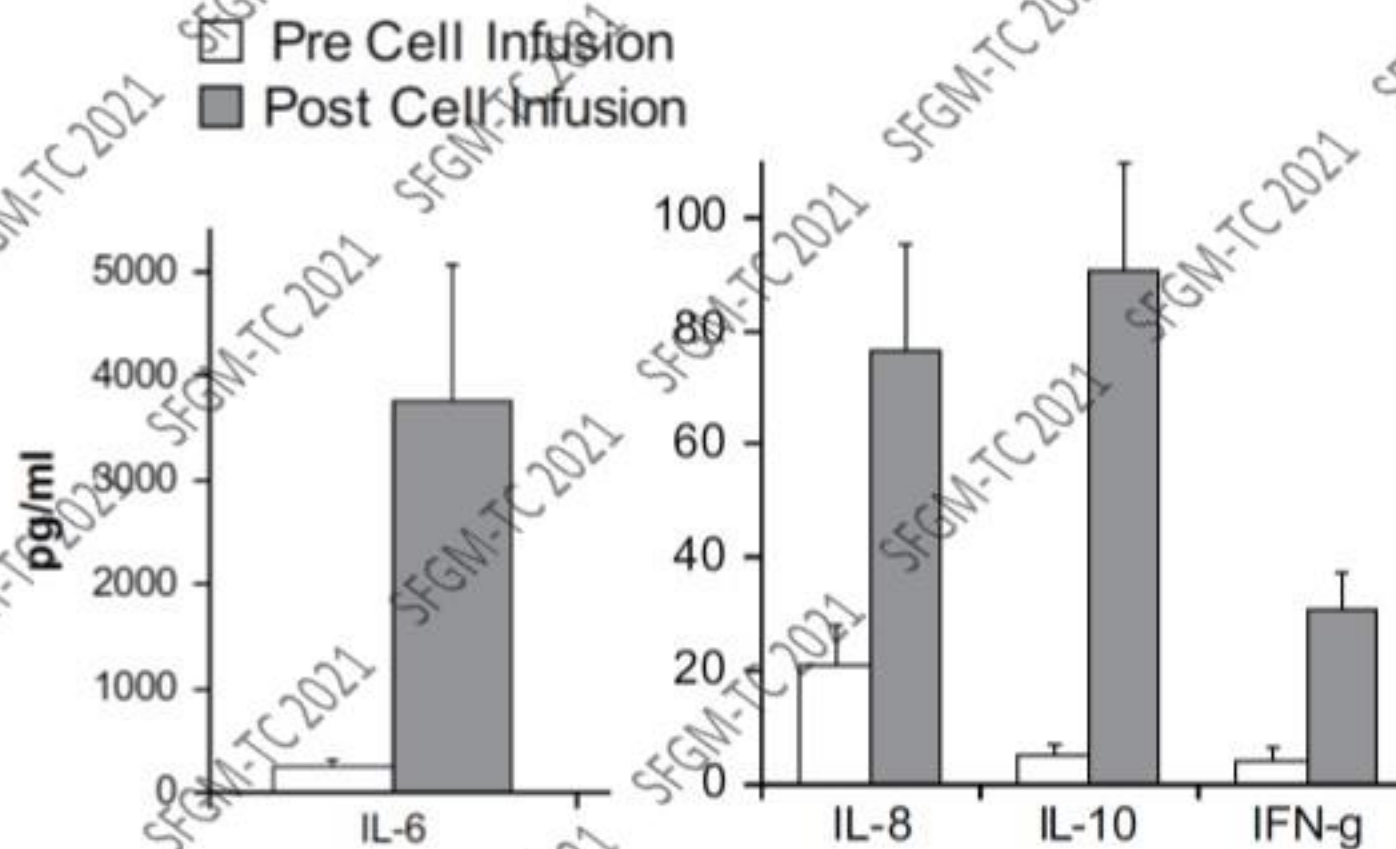
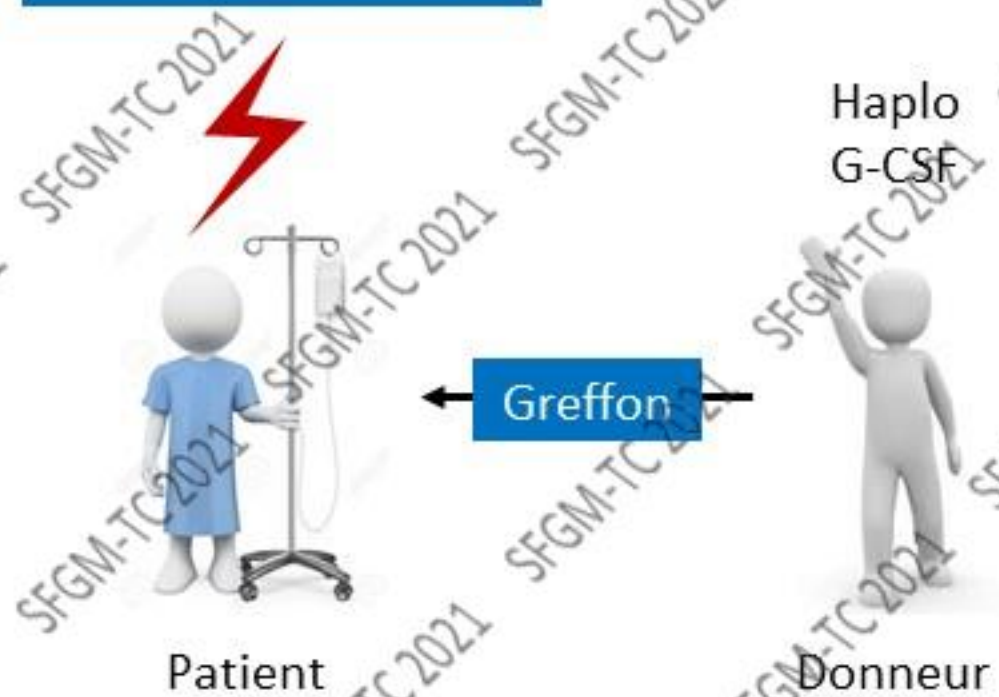
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BBMT 2009

Irradiation Corporelle  
Totale 100 cGy

Effet Dose – Réponse ?

Haplo  
G-CSF

Greffon

Cell Dose and Response Dose Level	Number of Patients	Response
$1 \times 10^6$ CD3 <sup>+</sup> cells/kg	4	0
$1 \times 10^7$ CD3 <sup>+</sup> cells/kg	4	0
$3 \times 10^7$ CD3 <sup>+</sup> cells/kg	4	2 (stable disease)
$1 \times 10^8$ CD3 <sup>+</sup> cells/kg	8	2
$2 \times 10^8$ CD3 <sup>+</sup> cells/kg	21	10

Patient

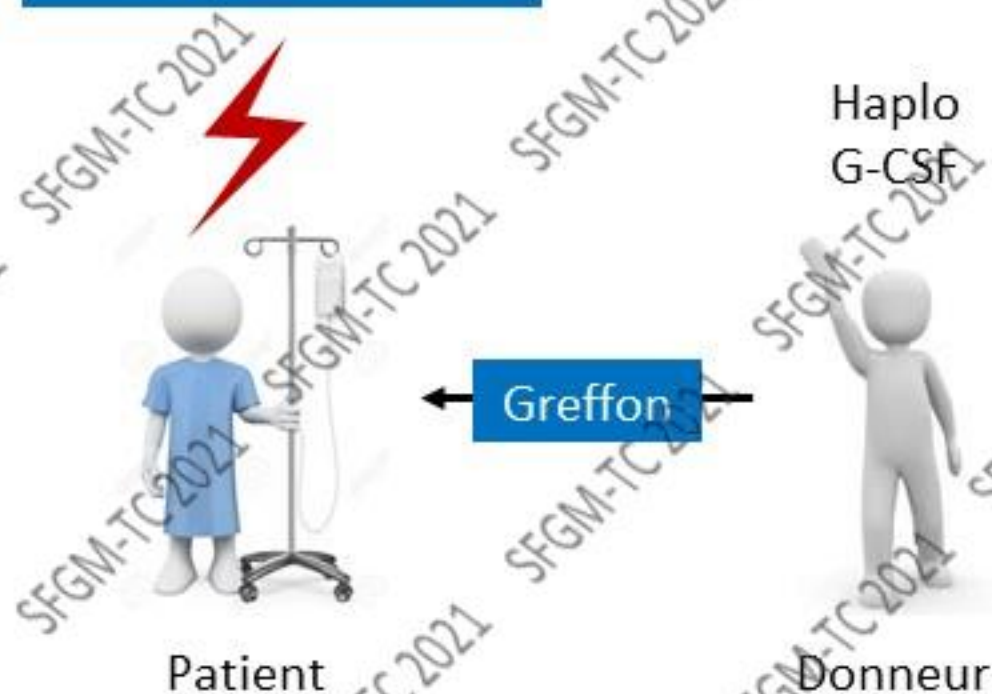
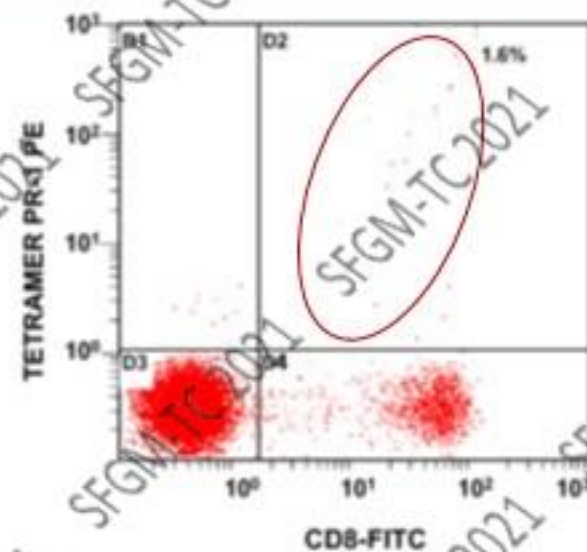
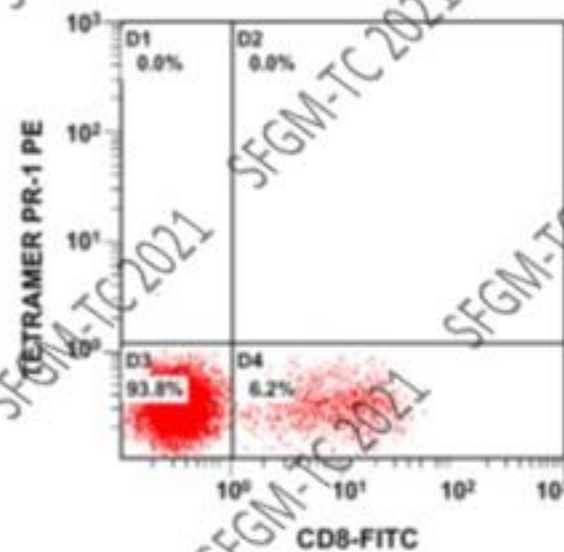
Donneur

# Mécanisme d'action possible de la microtransplantation

## A Pilot study of allogeneic cellular therapy for patients with advanced hematologic malignancies

Daniel J. Medina<sup>a</sup>, Mecide Gharibo<sup>a</sup>, Philip Savage<sup>b</sup>, Alan Kohler<sup>c</sup>, Mercy Kuriyan<sup>d</sup>, Binaifer Balsara<sup>e</sup>, Monika Anand<sup>c</sup>, Dale Schaar<sup>a</sup>, Tracy Krimmel<sup>a</sup>, Kara Saggiono<sup>a</sup>, Jacqueline Manago<sup>a</sup>, Lois Talty<sup>c</sup>, Liesel Dudek<sup>c</sup>, Stephanie Grospe<sup>a</sup>, Arnold Rubin<sup>a</sup>, Roger K. Strair<sup>a,\*</sup>

Irradiation Corporelle  
Totale 100 cGy



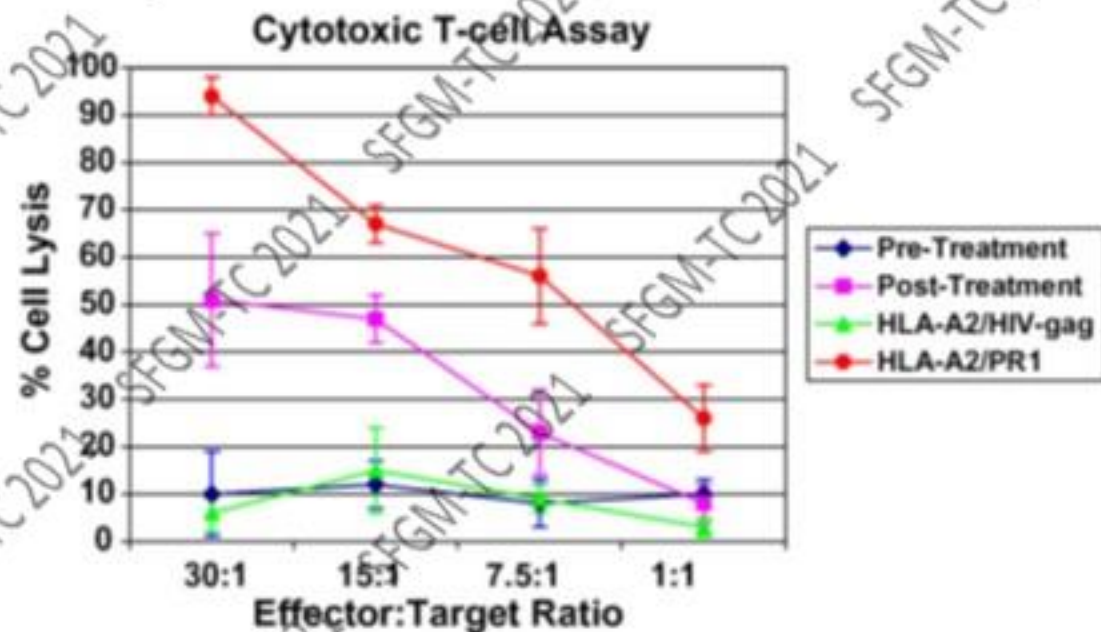
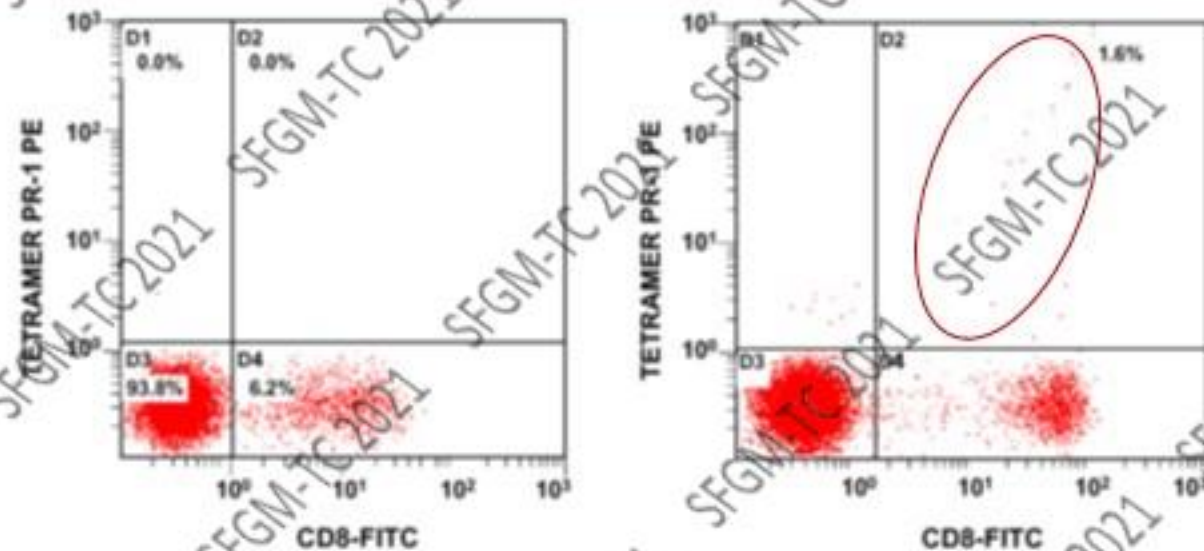
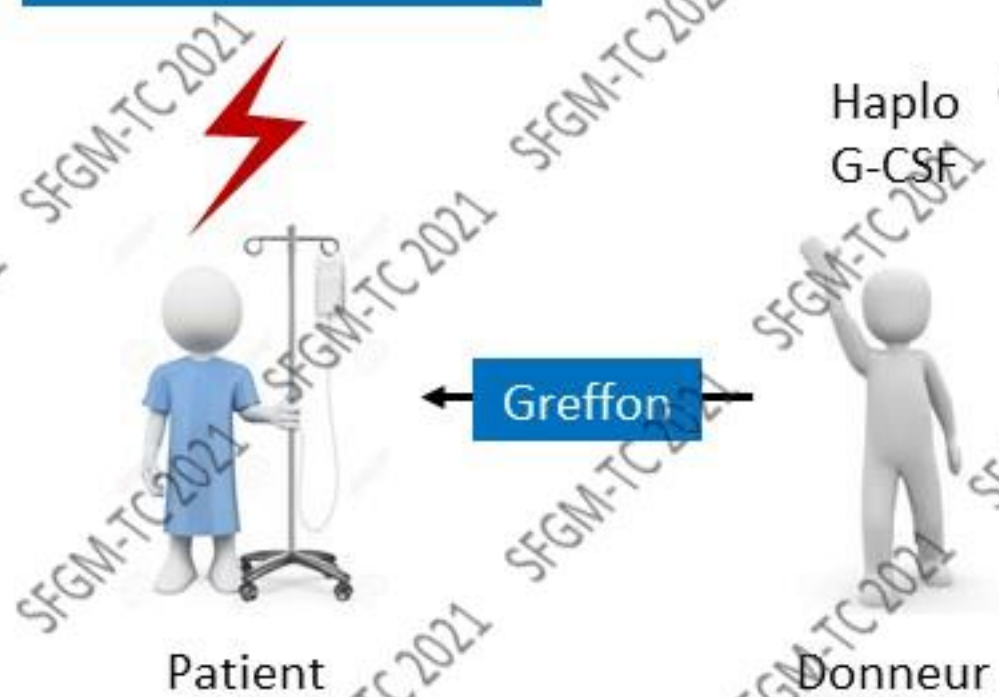


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Irradiation Corporelle  
Totale 100 cGy



## Résultats Cliniques: MST vs Chimiothérapie Intensive

Infusion of HLA-mismatched peripheral blood stem cells improves the outcome of chemotherapy for acute myeloid leukemia in elderly patients

Mei Guo,<sup>1</sup> Kai-Xun Hu,<sup>1</sup> Chang-Lin Yu,<sup>1</sup> Qi-Yun Sun,<sup>1</sup> Jian-Hui Qiao,<sup>1</sup> Dan-Hong Wang,<sup>1</sup> Guang-Xian Liu,<sup>1</sup> Wan-Jun Sun,<sup>2</sup> Li Wei,<sup>1</sup> Xue-Dong Sun,<sup>1</sup> Ya-Jing Huang,<sup>2</sup> Jun-Xiao Qiao,<sup>2</sup> Zheng Dong,<sup>1</sup> and Hui-Sheng Ai<sup>1</sup>

*Guo Blood 2011*

- LAM
- Age > 60 ans
- Première ligne



Chimio  
N=28

Chimio + MST  
N=30



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Adaptée par Cornillon et al., bull cancer 2019

## Résultats Cliniques: MST vs Chimiothérapie Intensive

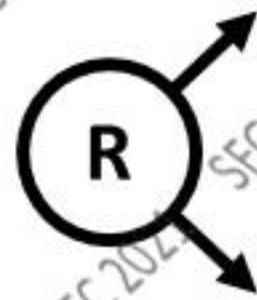
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Guo Blood 2011

- LAM
- Age > 60 ans
- Première ligne

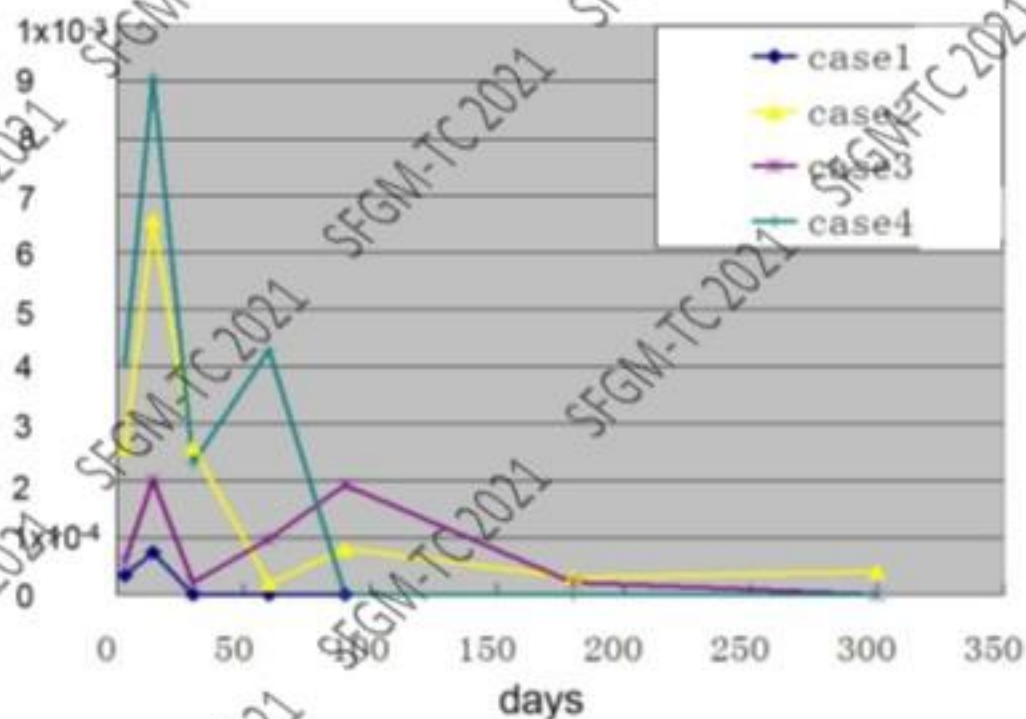
- Pas de GVH
- Pas de prise de greffe
- Microchimérisme



Chimio  
N=28

Chimio + MST  
N=30

Microchimérisme: PCR sur région Chromosome Y





## Résultats Cliniques: MST vs Chimiothérapie Intensive

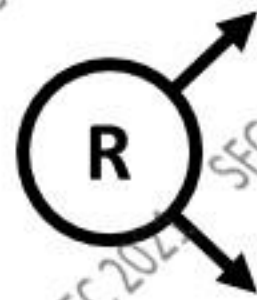
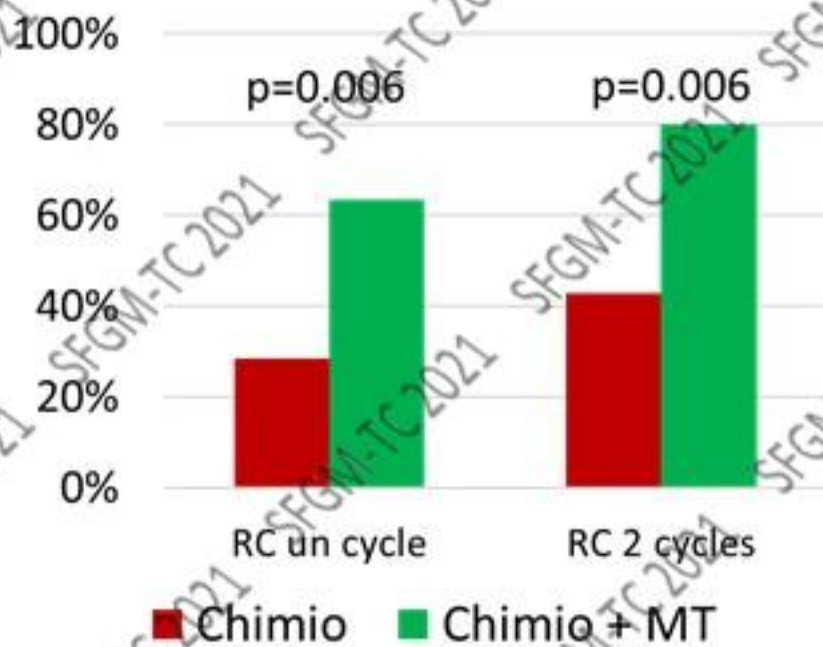
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Guo Blood 2011

- LAM
- Age > 60 ans
- Première ligne

Taux de Rémission Complète



Chimio  
N=28

Chimio + MT  
N=30

# Résultats Cliniques: MST vs Chimiothérapie Intensive

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Guo Blood 2011

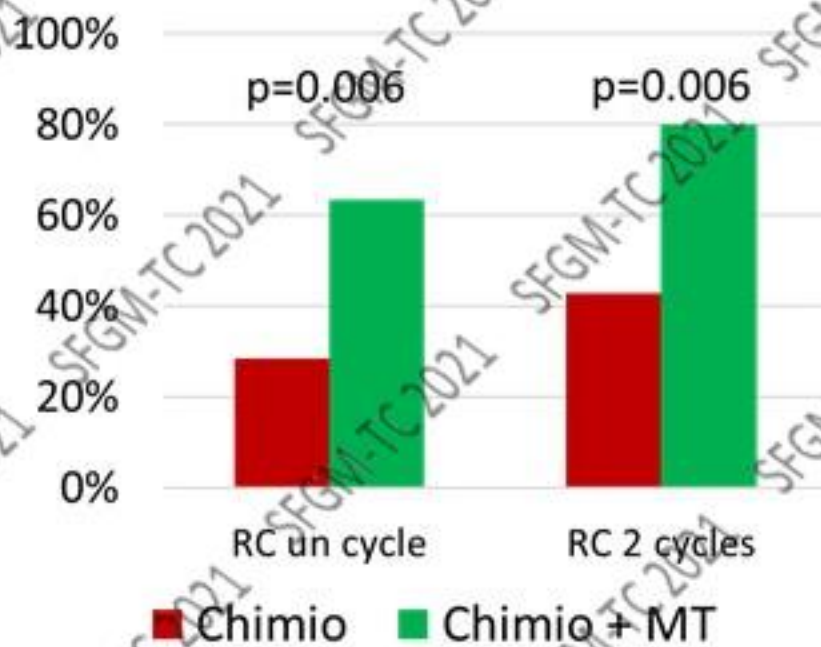
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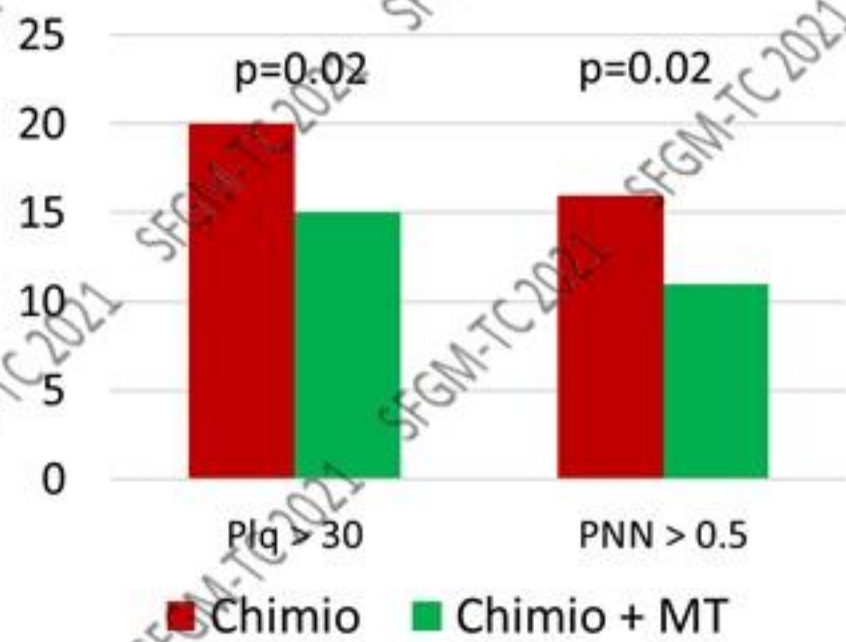
Chimio  
N=28

Chimio + MT  
N=30

### Taux de Rémission Complète



### Récupération Hématologique





## Résultats Cliniques: MST vs Chimiothérapie Intensive

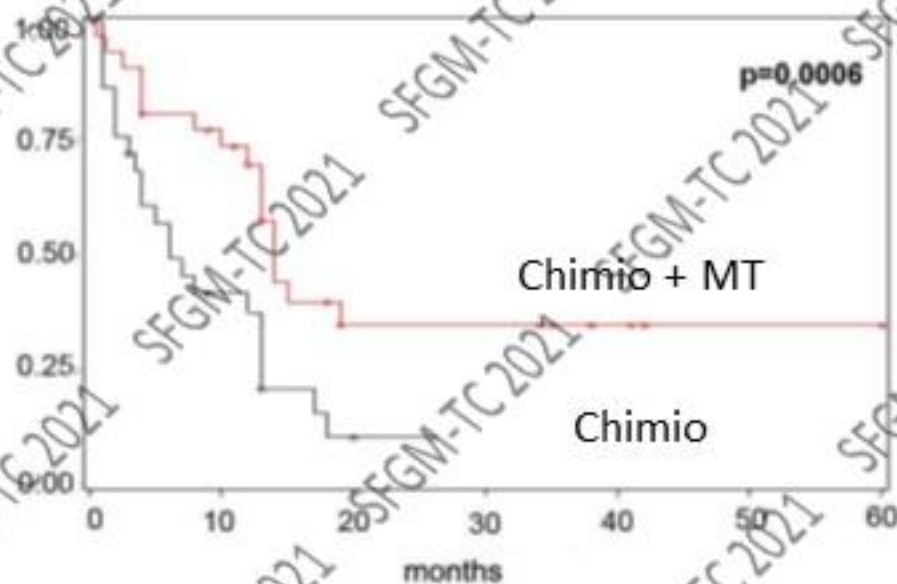
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Guo Blood 2011

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Survie Globale



Chimio  
N=28

Chimio + MT  
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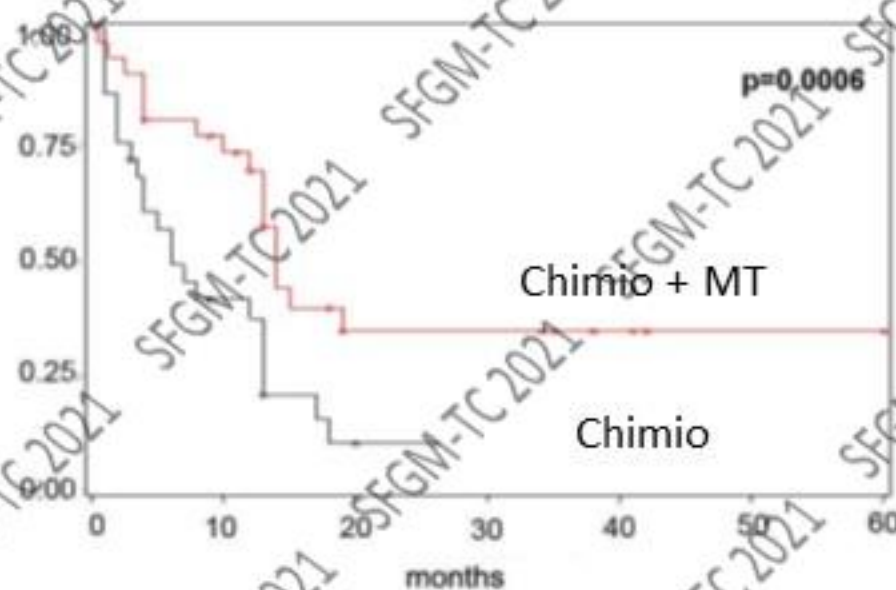
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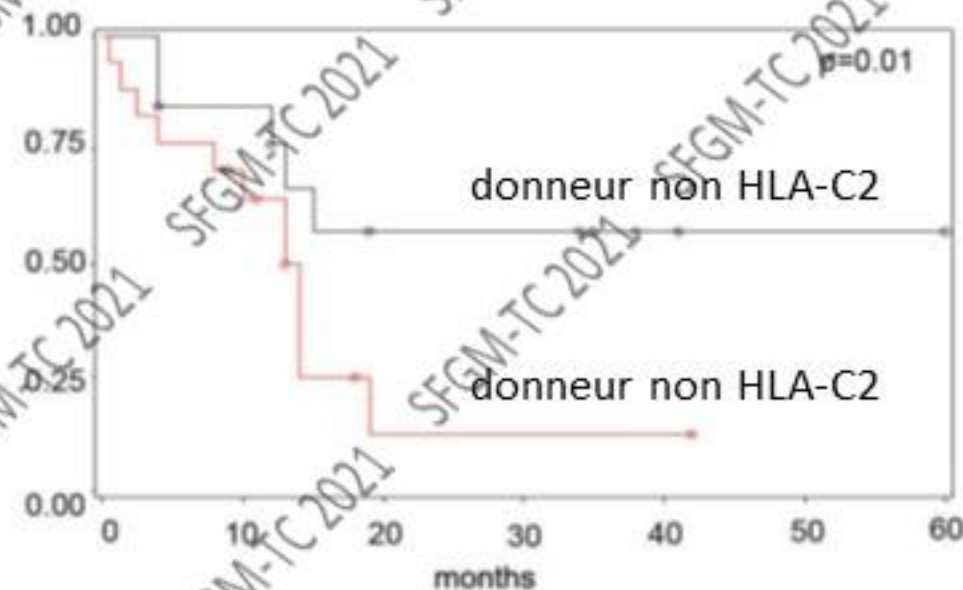
Chimio  
N=28

Chimio + MT  
N=30

Survie Globale



Survie Globale dans le bras Chimio + MT





# Résultats Cliniques: MST en induction et consolidation ?

JAMA Oncology | Original Investigation

## HLA-Mismatched Microtransplant in Older Patients Newly Diagnosed With Acute Myeloid Leukemia Results From the Microtransplantation Interest Group

Guo et al. JAMA Oncol 2017

**N = 185**

- AML
- Age > 60y
- MST à l'induction
- MST en consolidation

# Résultats Cliniques: MST en induction et consolidation ?

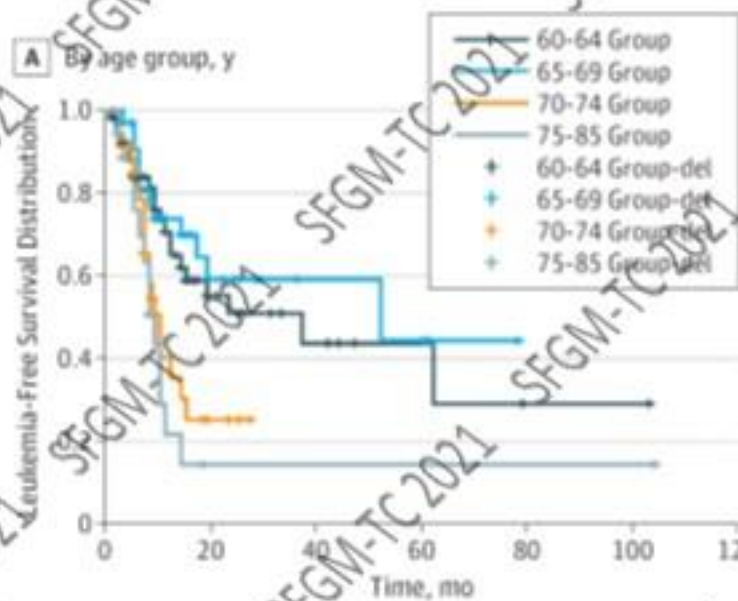
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- AML
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- MST en consolidation



No. at risk	0	20	40	60	80	100	120
60-64 Group	52	14	6	3	1	0	0
65-69 Group	33	4	2	0	0	0	0
70-74 Group	34	0	0	0	0	0	0
75-85 Group	19	1	0	0	0	0	0



# Résultats Cliniques: MST en induction et consolidation ?

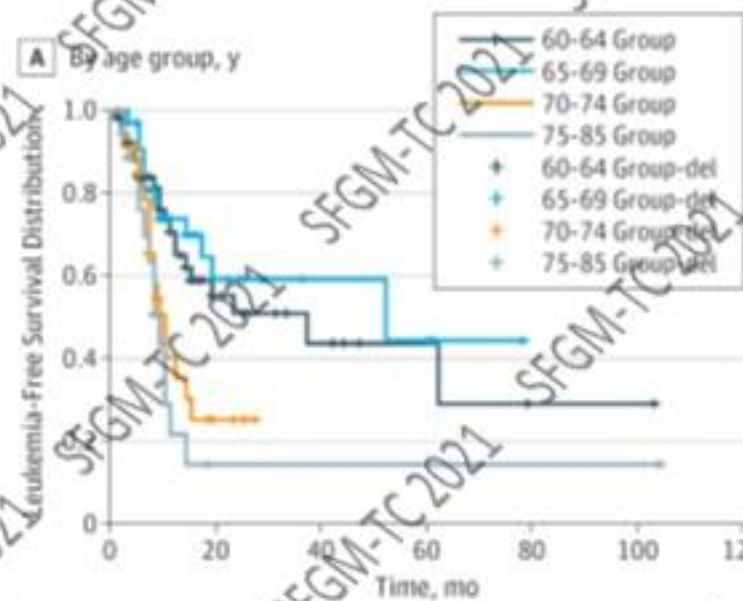
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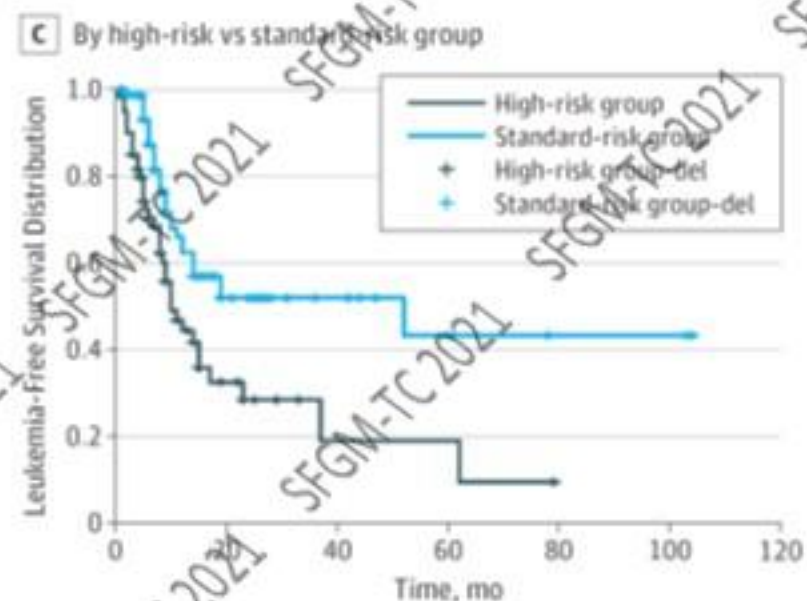
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70-74 Group	34	0	0	0	0	0	0
75-85 Group	19	1	0	0	0	0	0



No. at risk	0	20	40	60	80	100	120
High-risk group	14	9	2	2	0	0	0
Standard-risk group	20	9	4	2	2	0	0

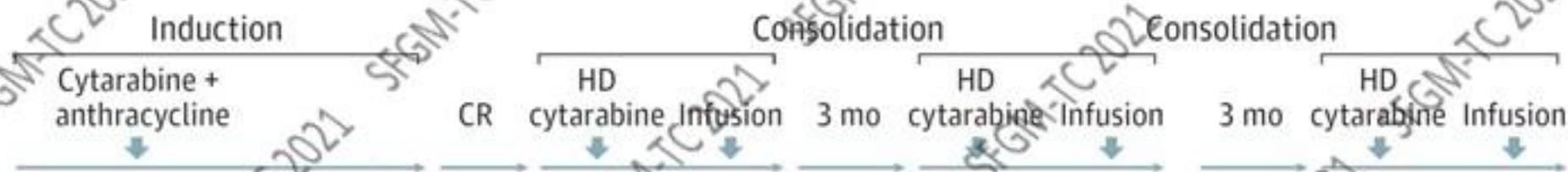
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JOURNAL OF CLINICAL ONCOLOGY



**N = 101**

- LAM Age < 65 ans
- 1<sup>ère</sup> Rémission Complète
- Pas de donneur compatible
- Risque intermédiaire **N=81**
- Risque faible **N=20**



# Résultats Cliniques: MST en consolidation ?

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VOLUME 30 · NUMBER 23 · NOVEMBER 20 2012

JOURNAL OF CLINICAL ONCOLOGY



**N = 101**

- LAM Age < 65 ans
- 1<sup>ère</sup> Rémission Complète
- Pas de donneur compatible
- Risque intermédiaire **N=81**
- Risque faible **N=20**

- Pas de GVH
- 4 chimères mixtes transitoires

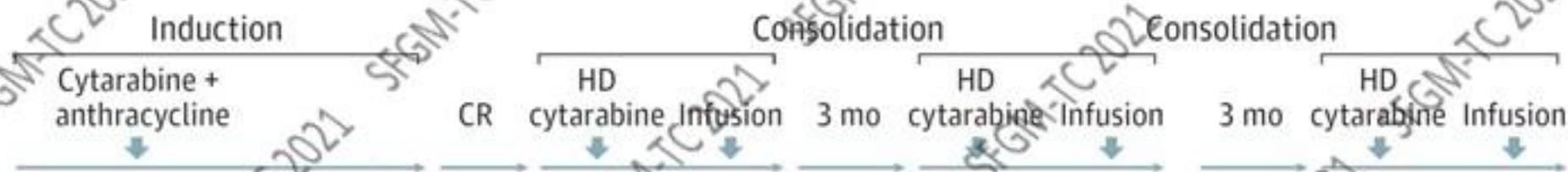
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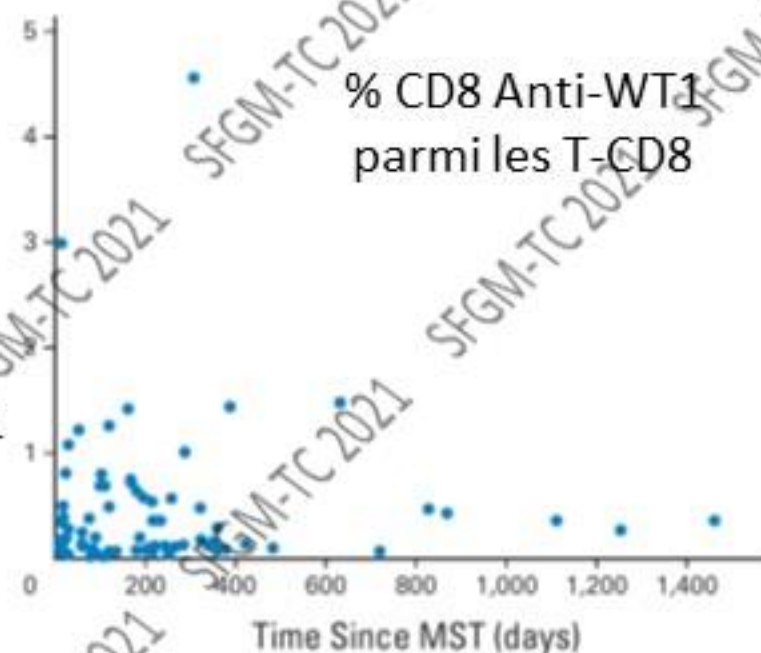
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- 33/39 patients (85%) T Anti-WT1





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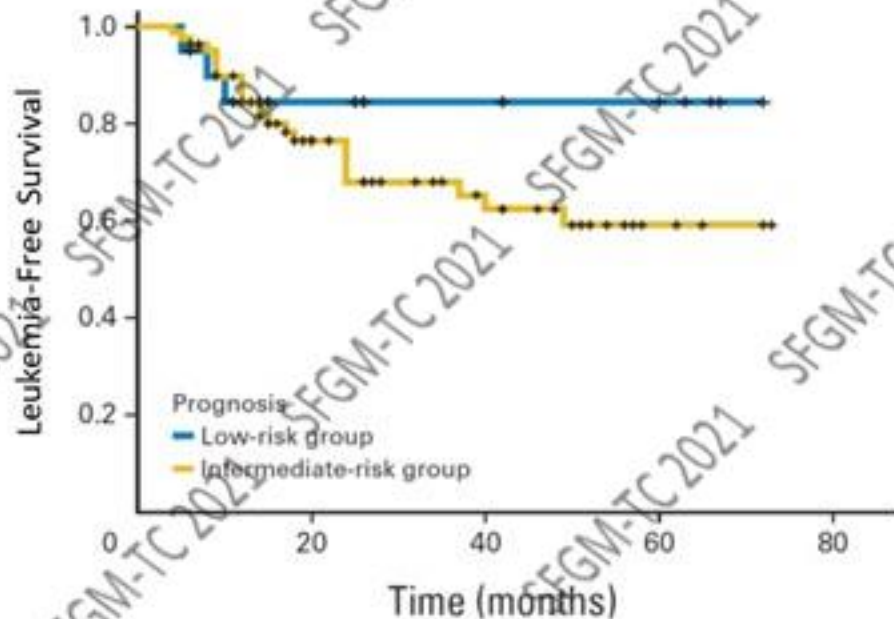
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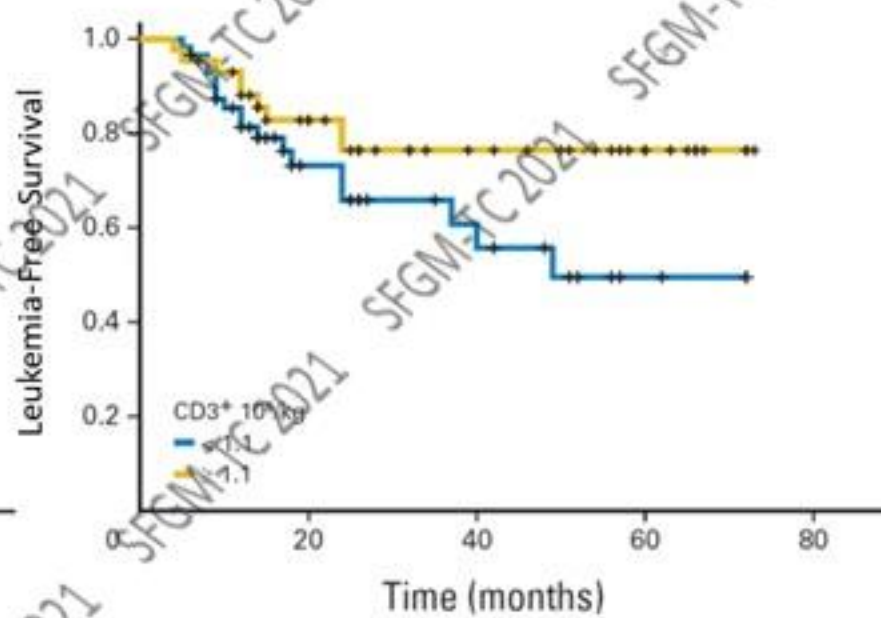
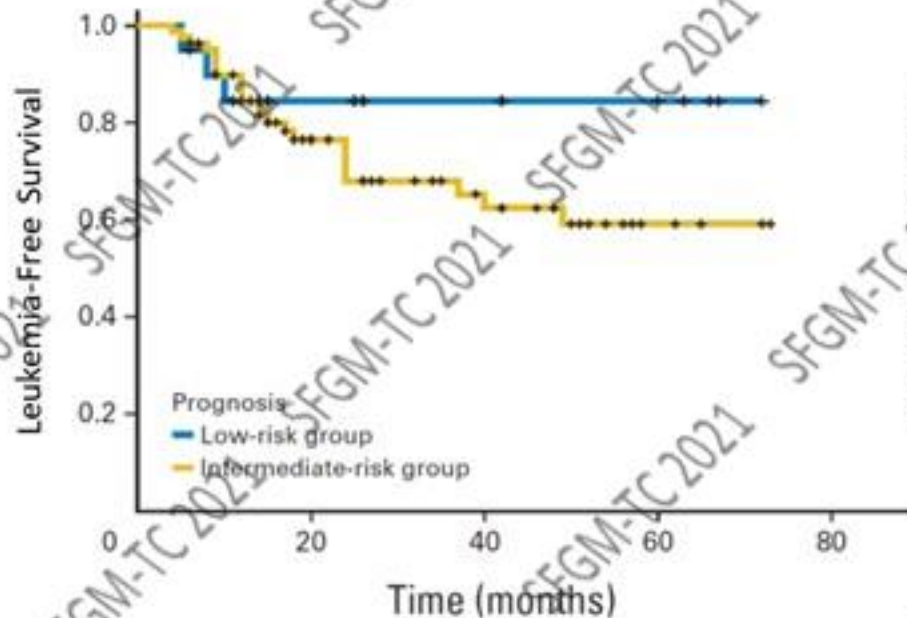
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## Microtransplantation sans chimiothérapie intensive

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Decitabine before Low-Dose Cytarabine-Based Chemotherapy Combined with Human Leukocyte Antigen–Mismatched Stem Cell Microtransplantation Improved Outcomes in Elderly Patients with Newly Diagnosed Acute Myeloid Leukemia

Zhu BBMT 2017

**N = 23**

- LAM
- Age > 60 ans
- Première ligne

**DCAG + MST; 4 cycles**

Decitabine  
Cytarabine  
Aclarubicine  
G-CSF

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- RC post C1: 80%
- Récupération hémato:
  - ✓ PNN: 12 jours
  - ✓ Plq: 14 jours
- Pas de GVH



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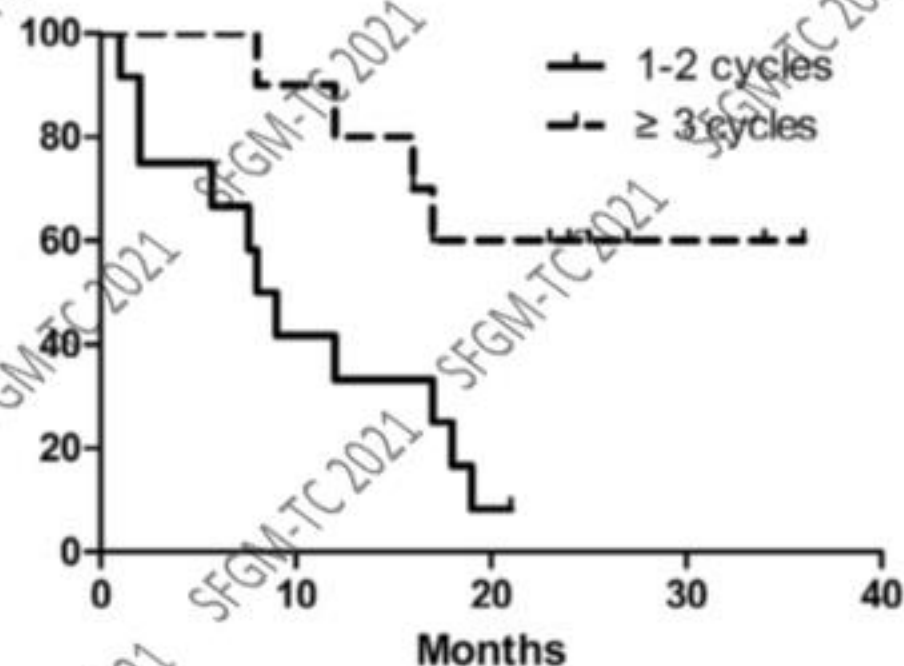
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Survie Globale



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Consolidation therapy with decitabine and intermediate-dose cytarabine followed by HLA-mismatched peripheral blood stem cells infusion for older patients with acute myeloid leukemia in first remission

*Li et al. Leuk Lymph 2018*

**N = 23**

- LAM
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**DAC + IDAC + MST x 3 conso**

vs.

**IDAC x 3 conso**



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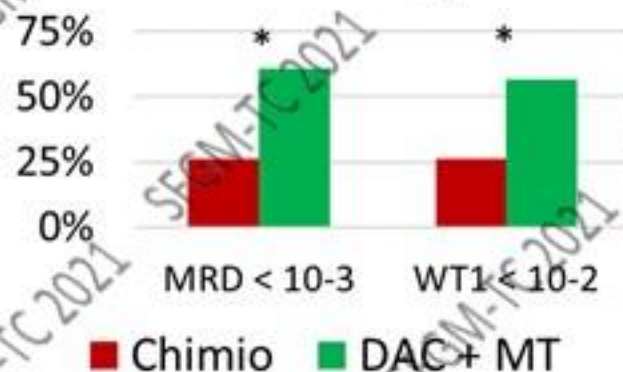
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MRD et WT1 expression





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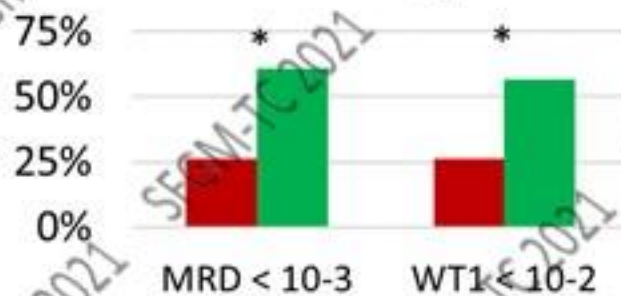
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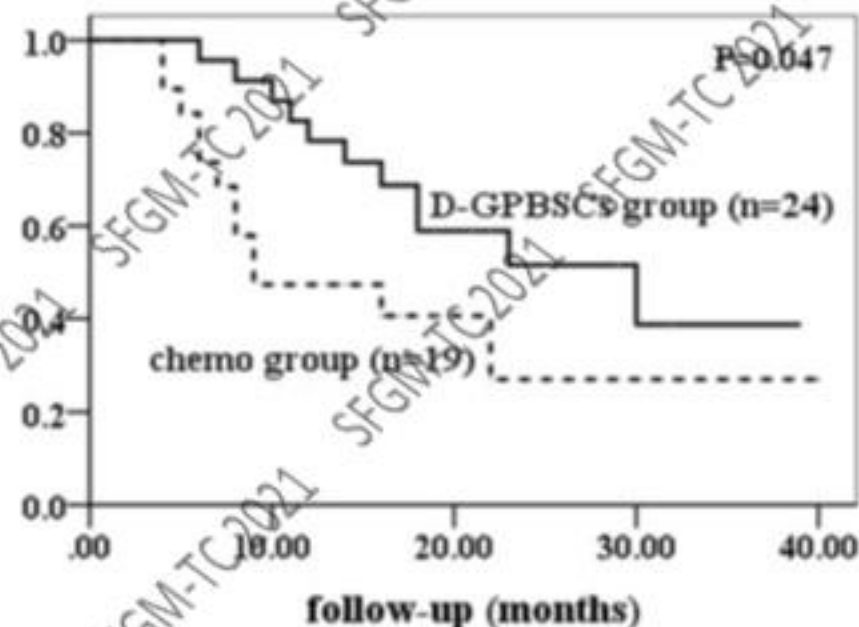


## MRD et WT1 expression



Chimio DAC+MT

## Survie sans leucémie

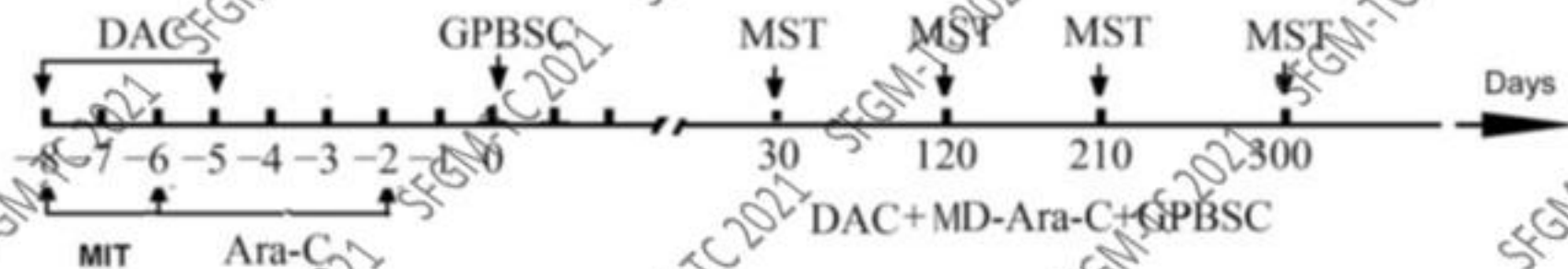


## Microtransplantation pour syndrome myelodysplasique

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Hu et al. SCTM 2016

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- 22 IAM post SMD



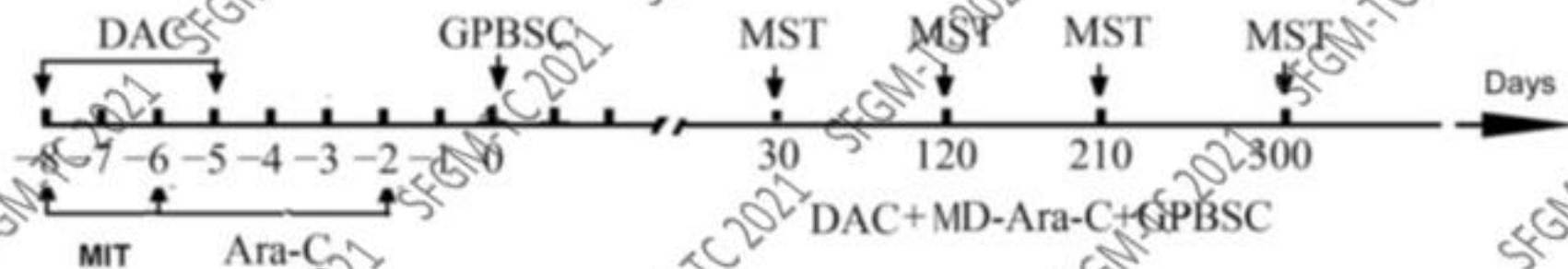


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- Microchimérisme
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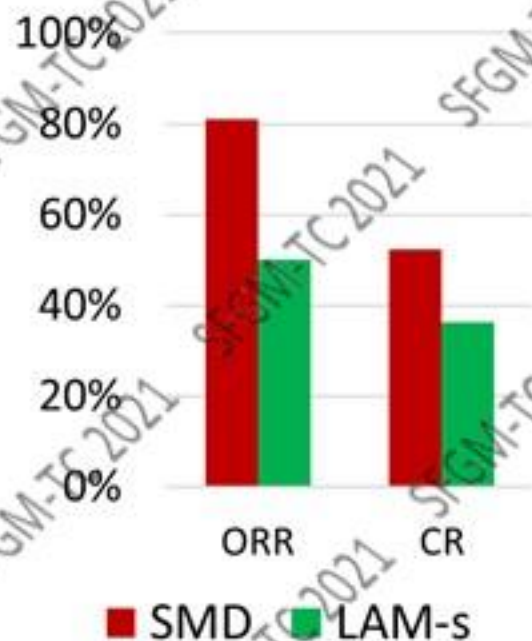
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Taux de Réponses





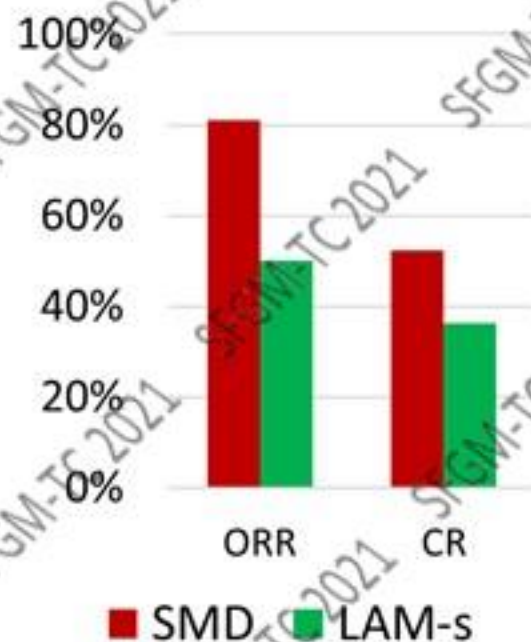
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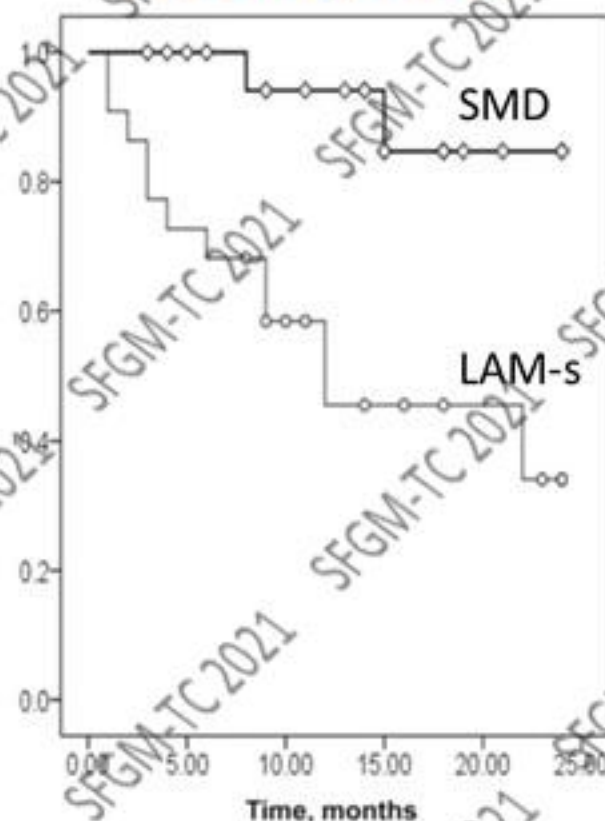
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Survie globale



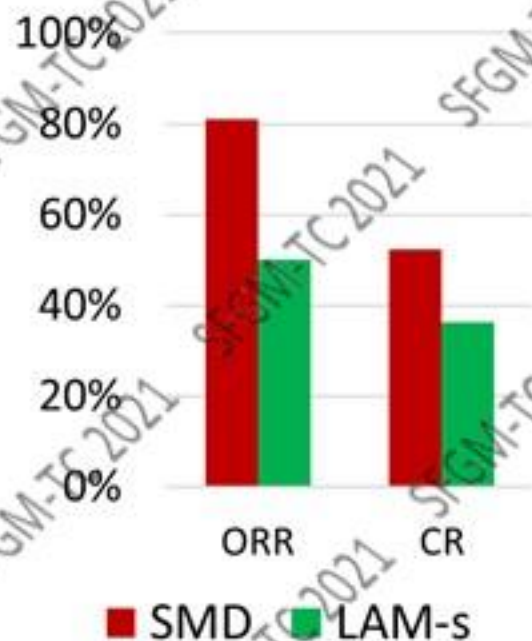
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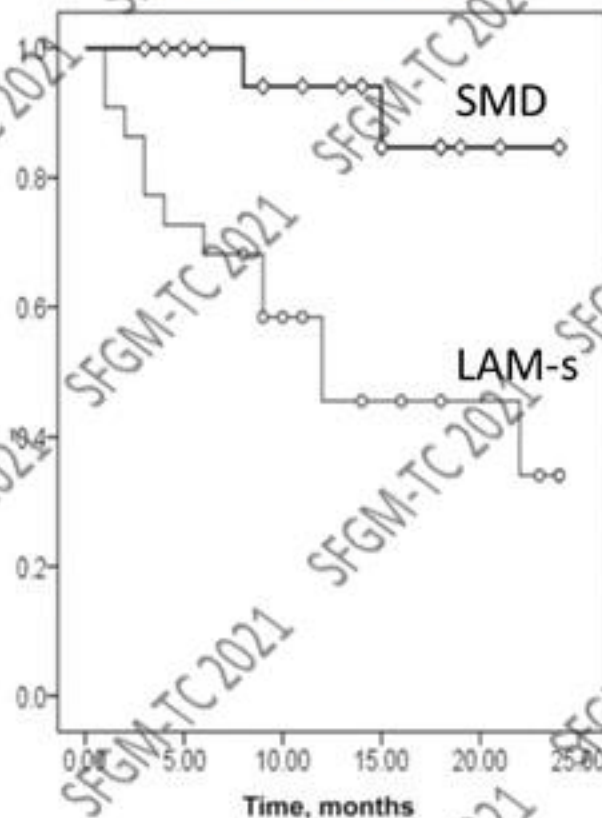
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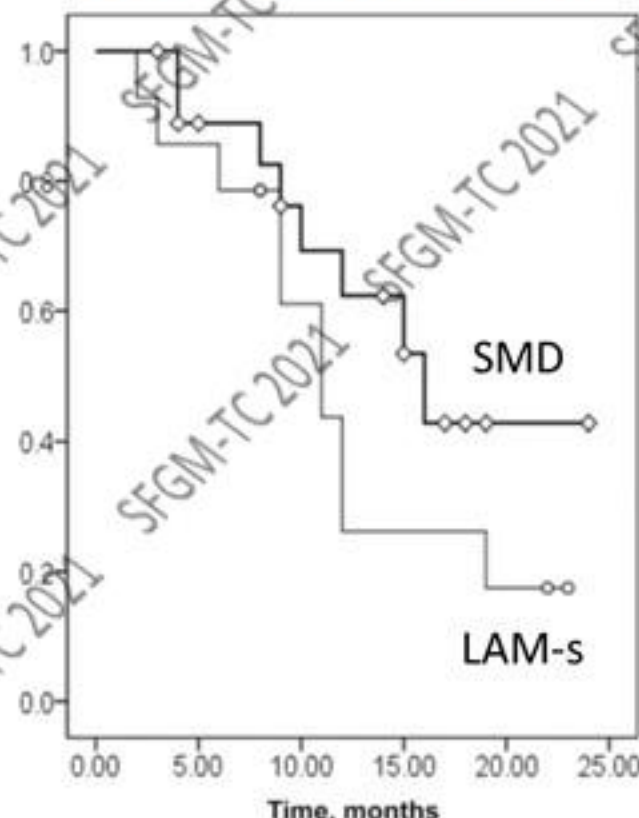
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Survie globale



Survie sans rechute





# Microtransplantation pour syndrome myelodysplasique

## Decitabine With or Without Micro-Transplantation for the Treatment of Intermediate or High-Risk Myelodysplastic Syndrome: A Chinese Single-Center Retrospective Study of 22 Patients

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2021

Groupe Decitabine (DAC) J1 à J5 20 mg/m<sup>2</sup> [N=11]

vs.

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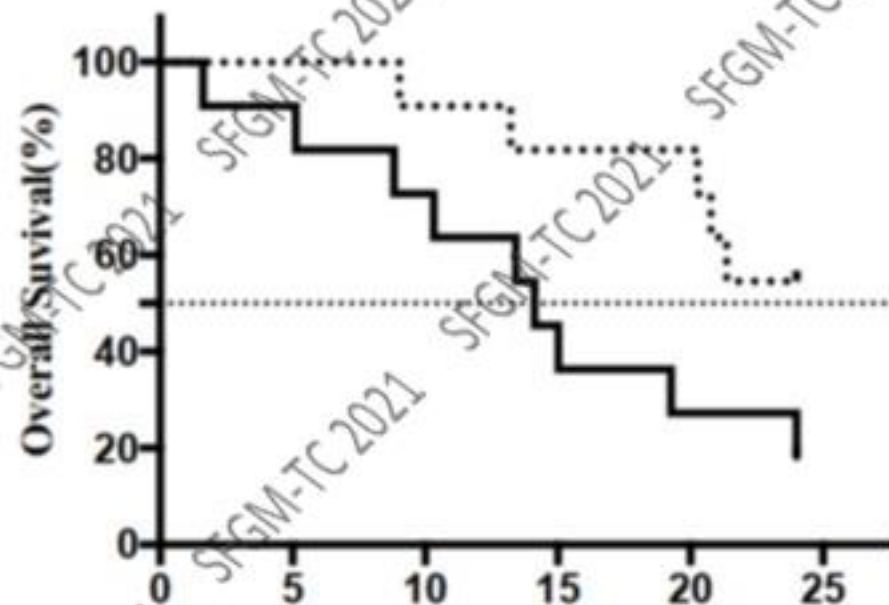
2021

... MST+DAC (n=11)  
— DAC (n=11)  
Log-rank test  $p=0.04$

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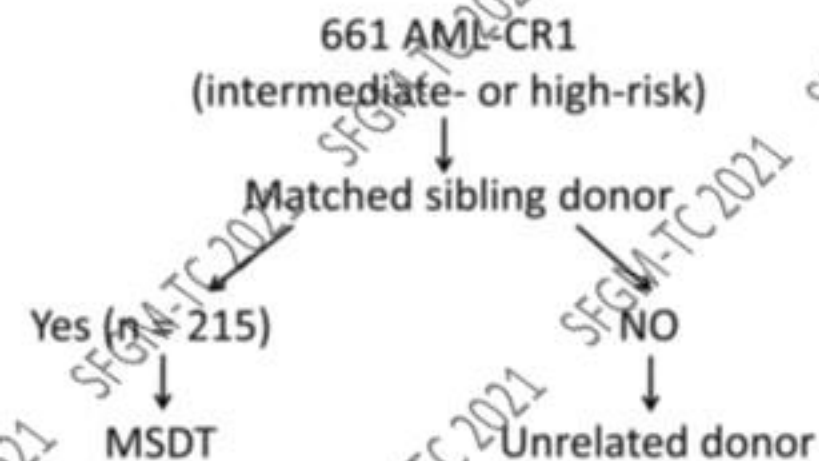




## Résultats cliniques: MST vs. Allogreffe HLA génoidentique

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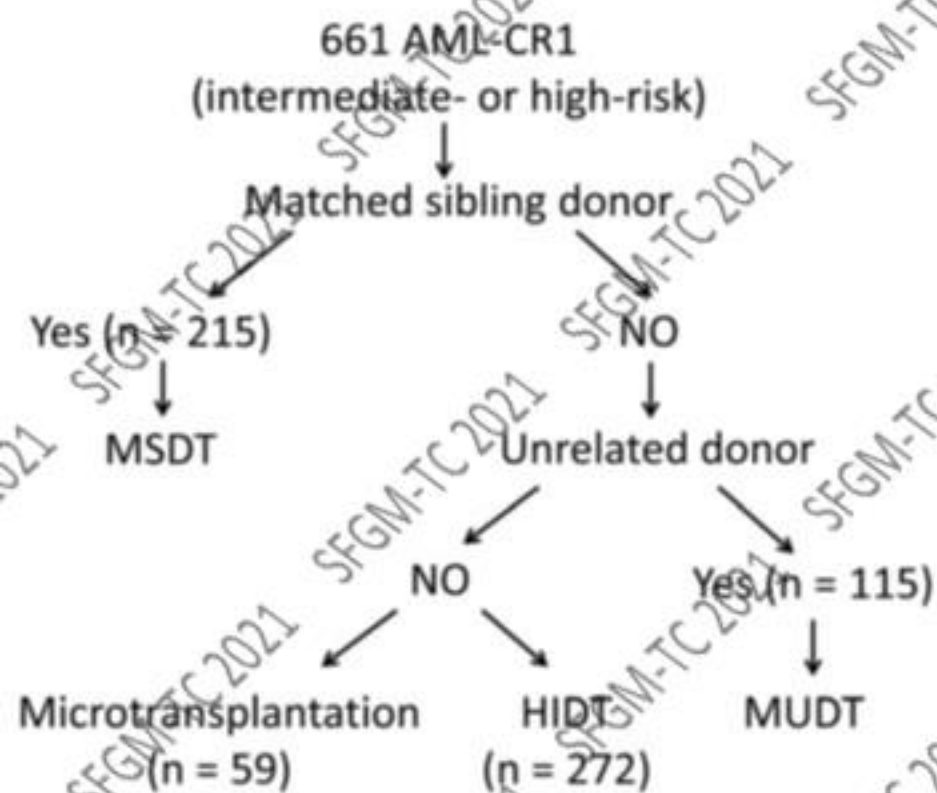
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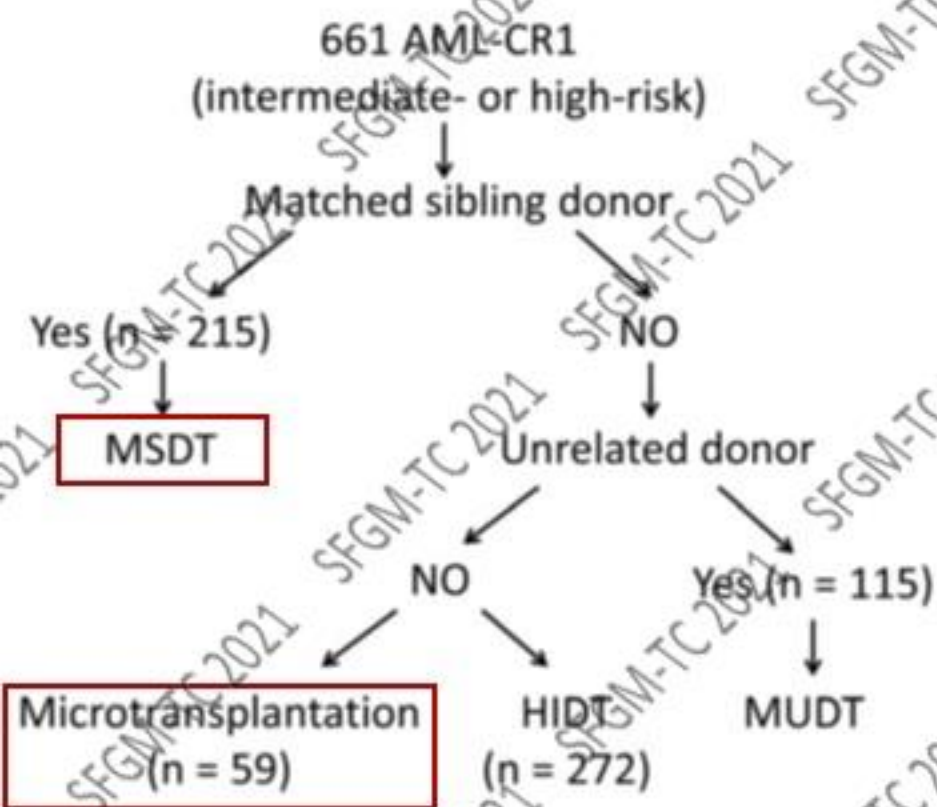




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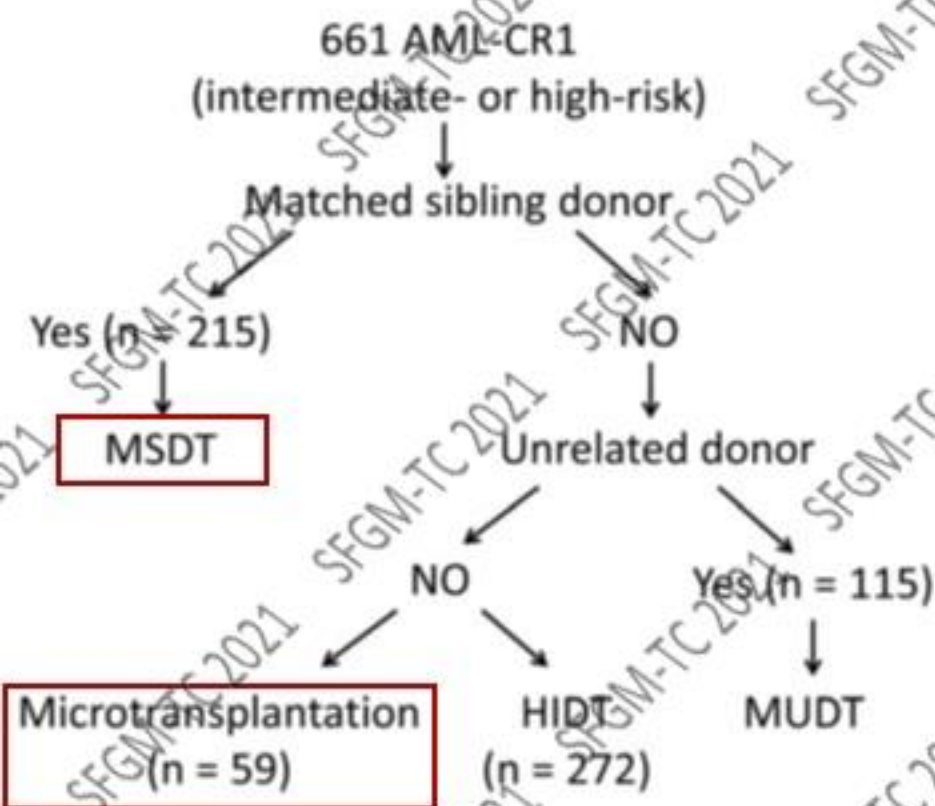
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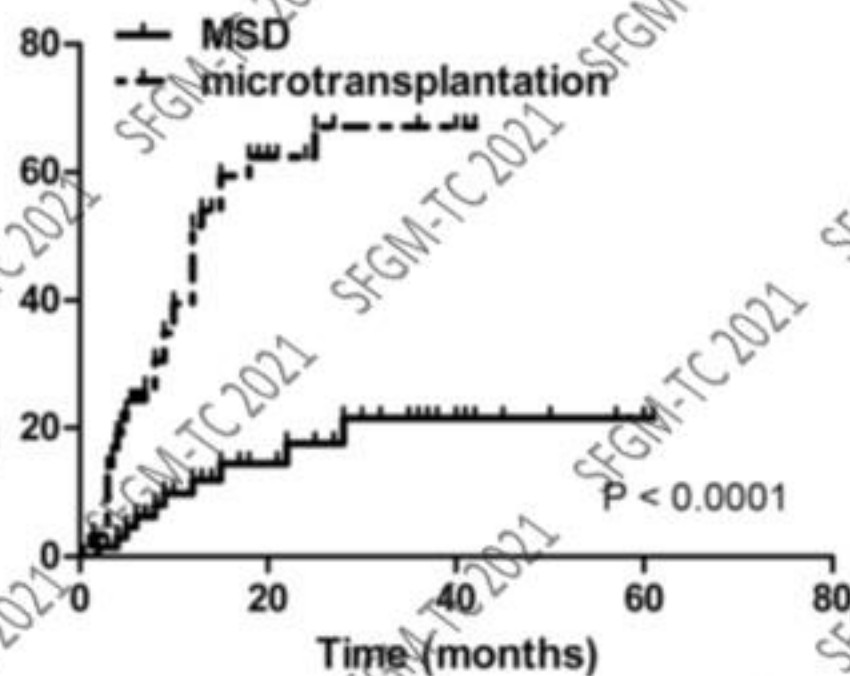
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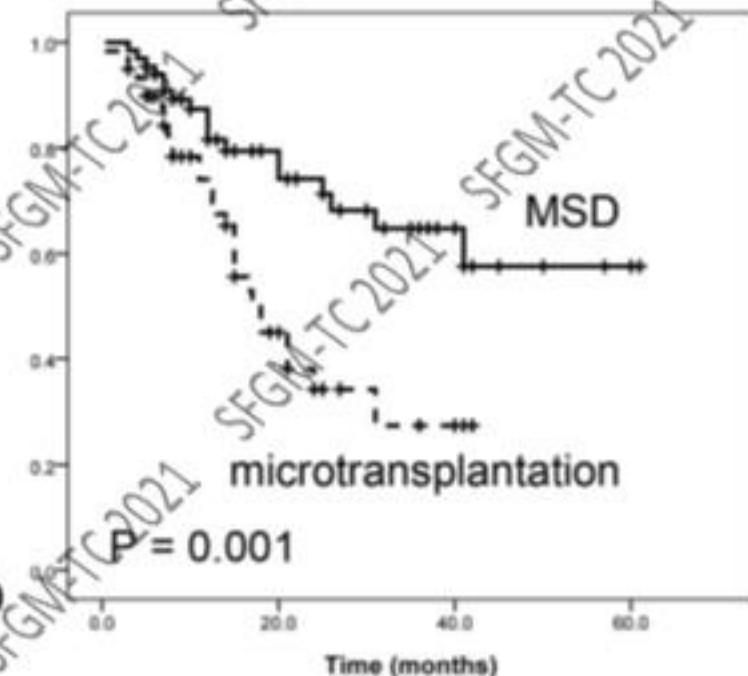
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Incidence de Rechute



Survie Globale





## Quel donneur pour la microtransplantation ?

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### Comparative study of micro-transplantation from HLA fully mismatched unrelated and partly matched related donors in acute myeloid leukemia

Hu Am J Hem 2020

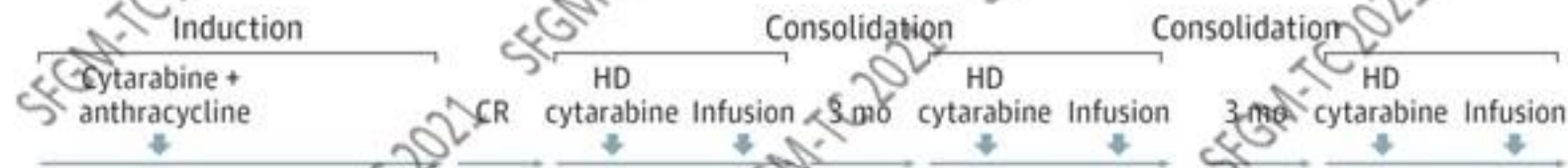
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- 1<sup>ère</sup> Rémission Complète
- MST en consolidation
- Donneur non apparenté  
**N=54**
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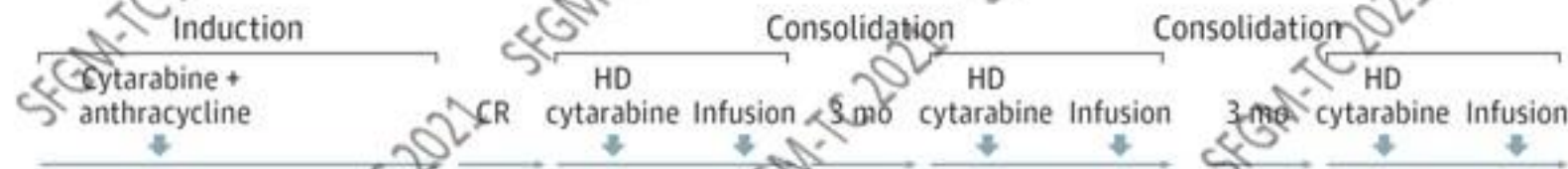
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HLA loci	Unrelated	Haplo
0/10	33 (61.1%)	3 (4.5%)
1/10	7 (13%)	7 (10.5%)
2/10	4 (7.4%)	2 (3.0%)
3/10, 4/10	10 (18.5%)	4 (5.9%)
5-7/10	0	51 (76.1%)



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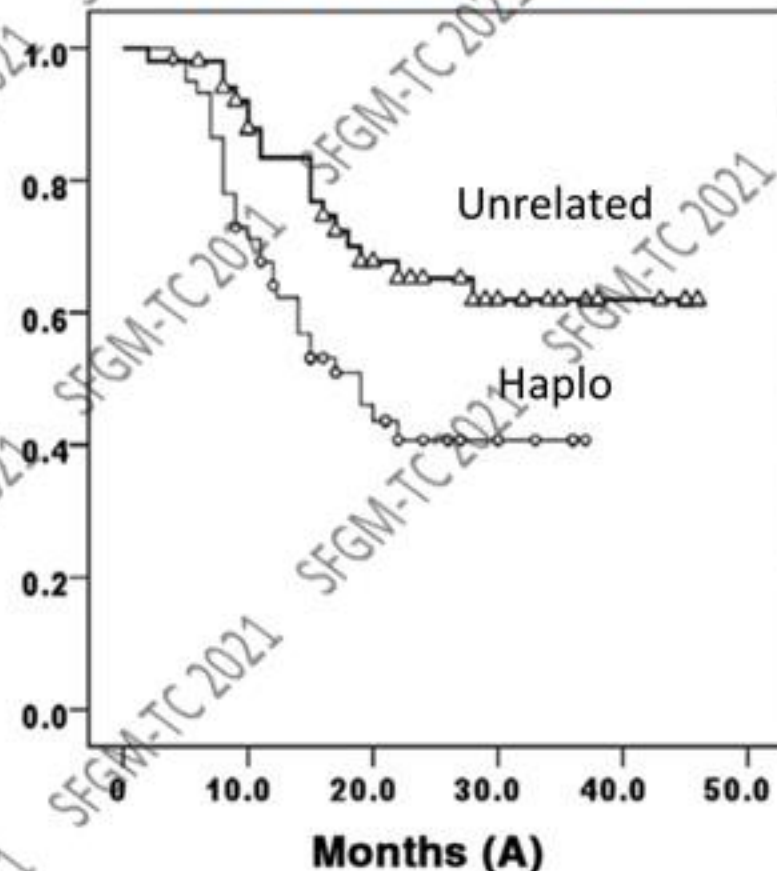
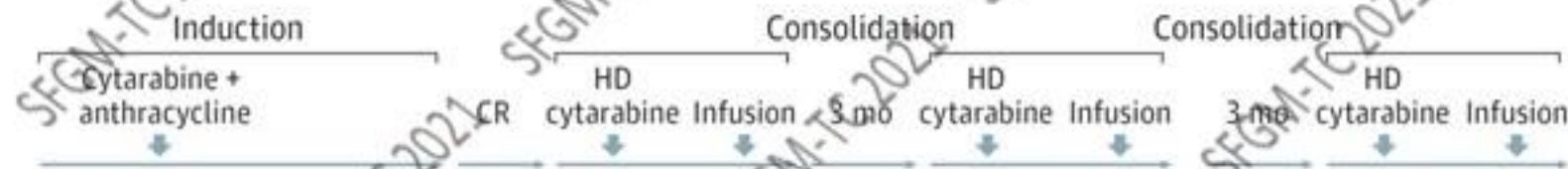
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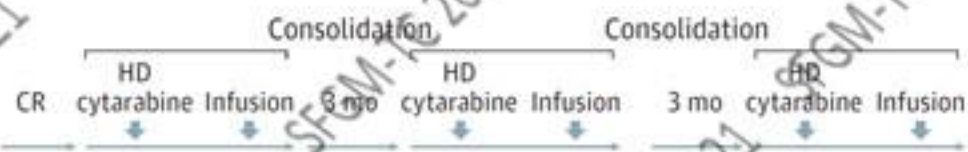


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# Donor Selection in HLA-Mismatched Hematopoietic Stem Cell Microtransplantation for Acute Myeloid Leukemia

N=131

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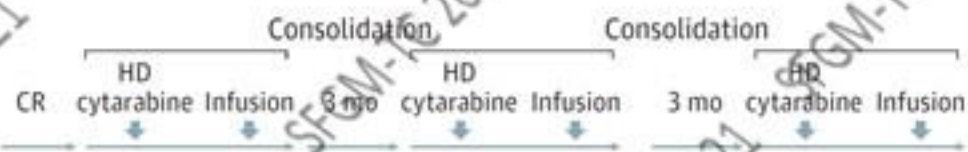


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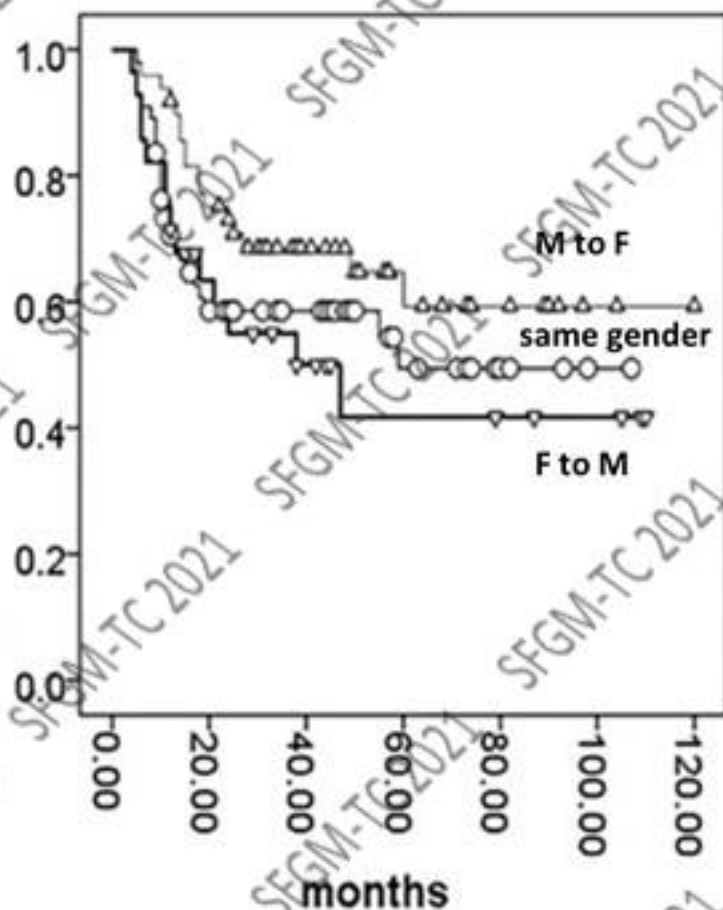
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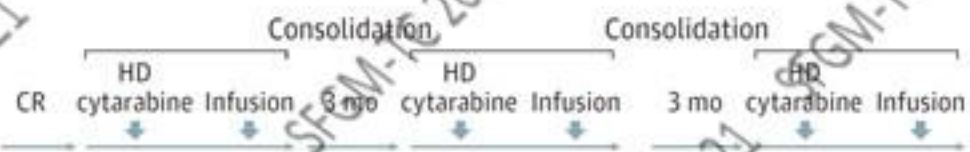


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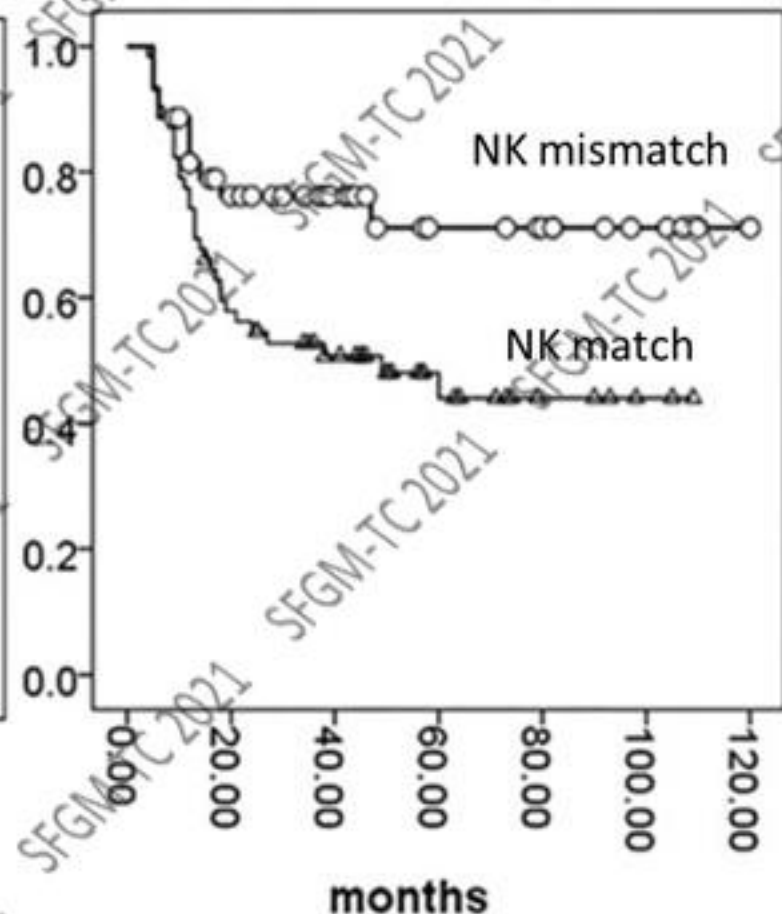
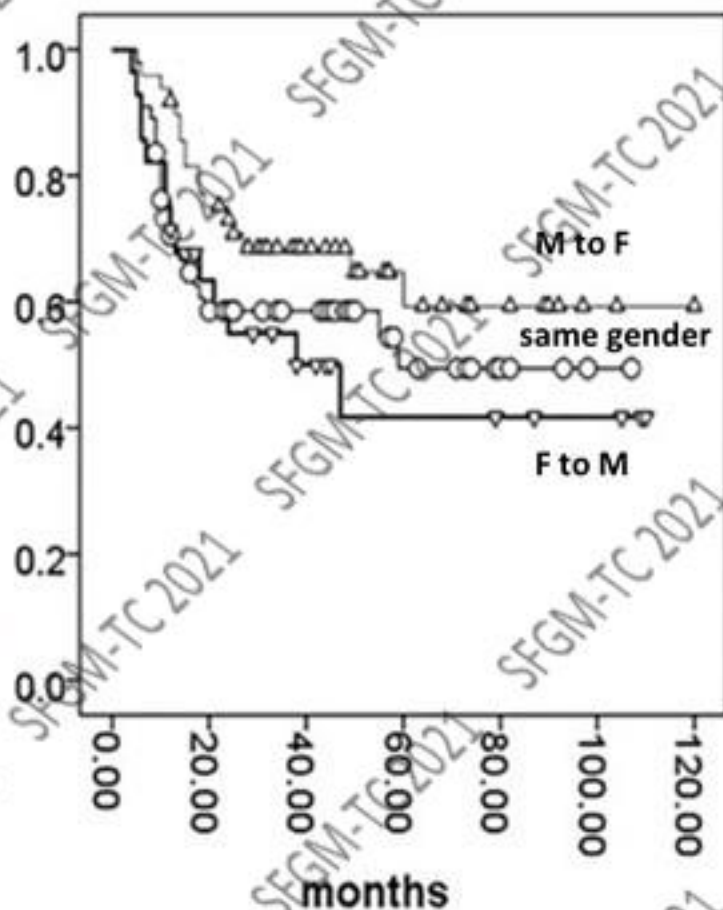
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Hu stem cell dev 2020

Survie sans leucémie



# Microtransplantation: « Bridge to Allo »

## HLA-mismatched microtransplantation for relapsed or refractory acute myeloid leukemia as a bridge to allogeneic hematopoietic stem cell transplantation

BMT 2020

Neeraj Sidharthan<sup>1</sup> · Ephraim Fuchs<sup>2</sup> · Manoj Unni<sup>1</sup> · Ullas Mony<sup>3</sup> · Pavankumar Boyella<sup>4</sup> · Raghuveer Prabhu<sup>1</sup>  
Rema Ganapathy<sup>1</sup> · Veena Shenoy<sup>4</sup> · Geeta Vidyadharan<sup>5</sup>

Case no.	Subject	Relation
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	DLI donor	Unrelated
	BMT donor	Haplo
2	Patient	
	DLI donor	Haplo
	BMT donor	Haplo
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	BMT donor	Haplo
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Age	Status	Salvage	CRS	CR	Outcome
19y	PIF	Intensive	grade II	yes	relapse / death
49y	1st Relapse	Intensive	grade IV	yes	Allo, NRM
42y	1st Relapse	Intensive	no	yes	Allo, CR

# Microtransplantation de CSH

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## Atelier d'harmonisations 2019 : indications et organisation d'une microtransplantation de cellules souches hématopoïétiques



Cornillon et al. Bull Can 2019



## Atelier d'harmonisations 2019 : indications et organisation d'une microtransplantation de cellules souches hématopoïétiques



Cornillon et al. Bull Can 2019

### Indications

Les données actuelles ne sont pas suffisantes pour émettre des recommandations quant aux indications de la MT

*« En aucun cas elle remplace l'allogreffe classique »*

*« La MT reste un traitement en cours d'investigation et reste conseillée dans le cadre d'essais cliniques »*

# Microtransplantation de CSH

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JAMA Oncology | Review

## Microtransplantation for Acute Myeloid Leukemia A Systematic Review

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**CONCLUSIONS AND RELEVANCE** This study suggests that, to date, there are no convincing data on the safety or effectiveness of microtransplantation in persons with AML or MDS. This strategy should be considered investigational and performed in the setting of controlled clinical trials.



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