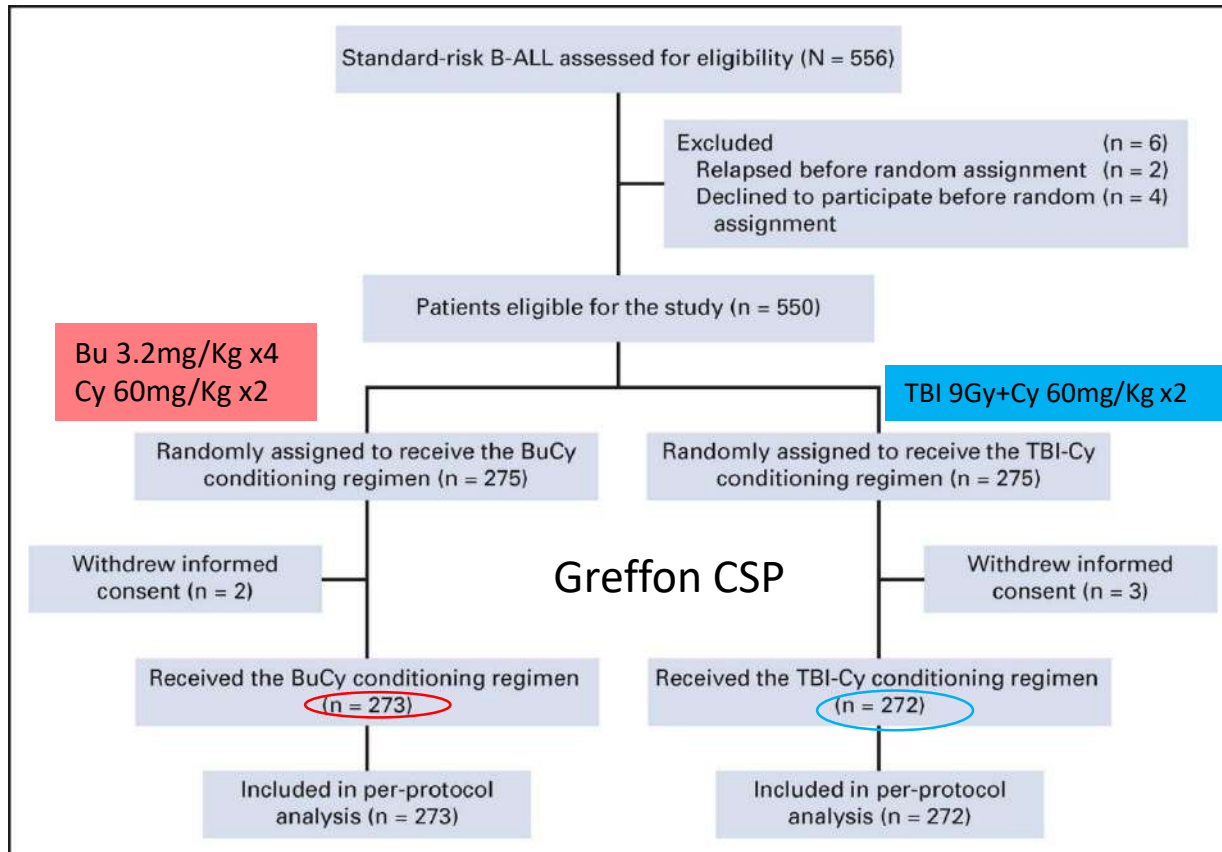


# Actualités en greffe et thérapie cellulaire

2021-2022

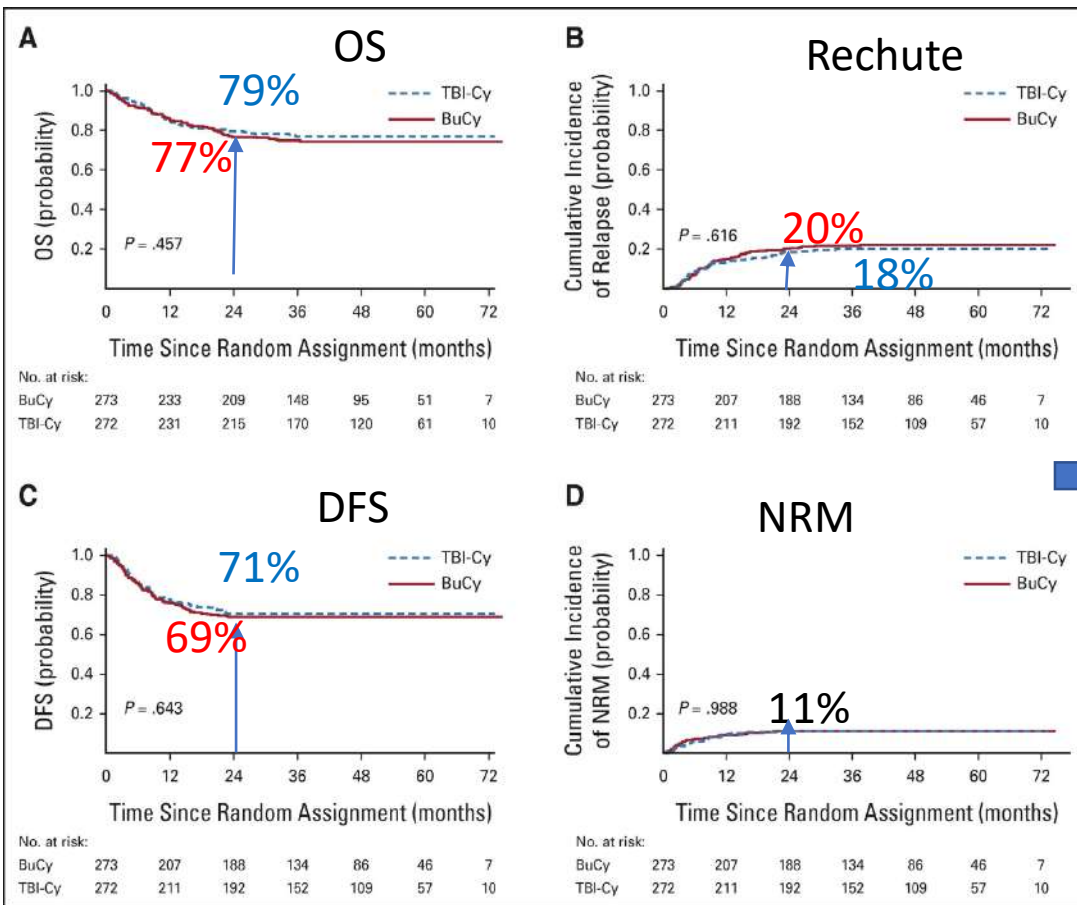
LAL

## Etude rando phase 3 Bu-Cy vs TBI-Cy LAL-B adulte

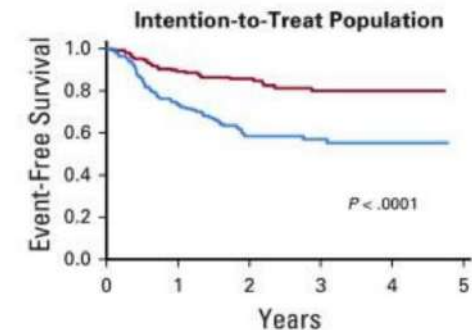


Phase 3 rando, 13 centres Chine  
14-65 ans  
LAL-B en RC1  
Risque standard cytogénétique

Item	BuCy	TBI-Cy
No. of patients	273	272
Patient age, years, median (range)	26 (14-59)	27 (14-61)
Sex, No. (%)		
Female/male	115 (42.1)/158 (57.9)	97 (35.7)/175 (64.3)
Donor, No. (%)		
MUD/MSD	68 (24.9)/205 (75.1)	76 (27.9)/196 (72.1)

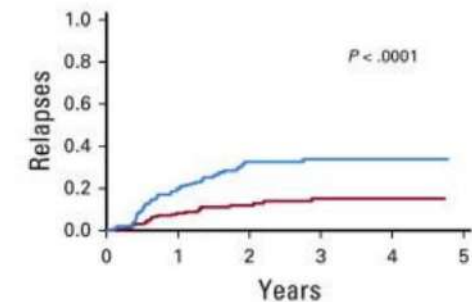


Pas de différence entre Bu-Cy et TBI-Cy LALB RC1 risque standard



At risk	0	1	2	3	4	5
TBI	212	163	99	61	25	
CHC	201	130	68	40	14	

	Patients	Eval.	Events	2-year EFS
TBI	212	209	31	0.86 (0.79-0.90)
CHC	201	200	72	0.58 (0.50-0.66)



MRD + phéno >10<sup>-3</sup> ou PCR >10<sup>-4</sup>

MRD phéno + si >10<sup>-4</sup>

MRD status after induction, No. (%)	Bu-Cy	TBI-Cy
Positive v negative	98 (35.9)/175 (64.1)	89 (32.7)/183 (67.3)
MRD status at HSCT, No. (%)	Bu-Cy	TBI-Cy
Positive v negative	48 (17.6)/225 (82.4)	39 (14.3)/233 (85.7)

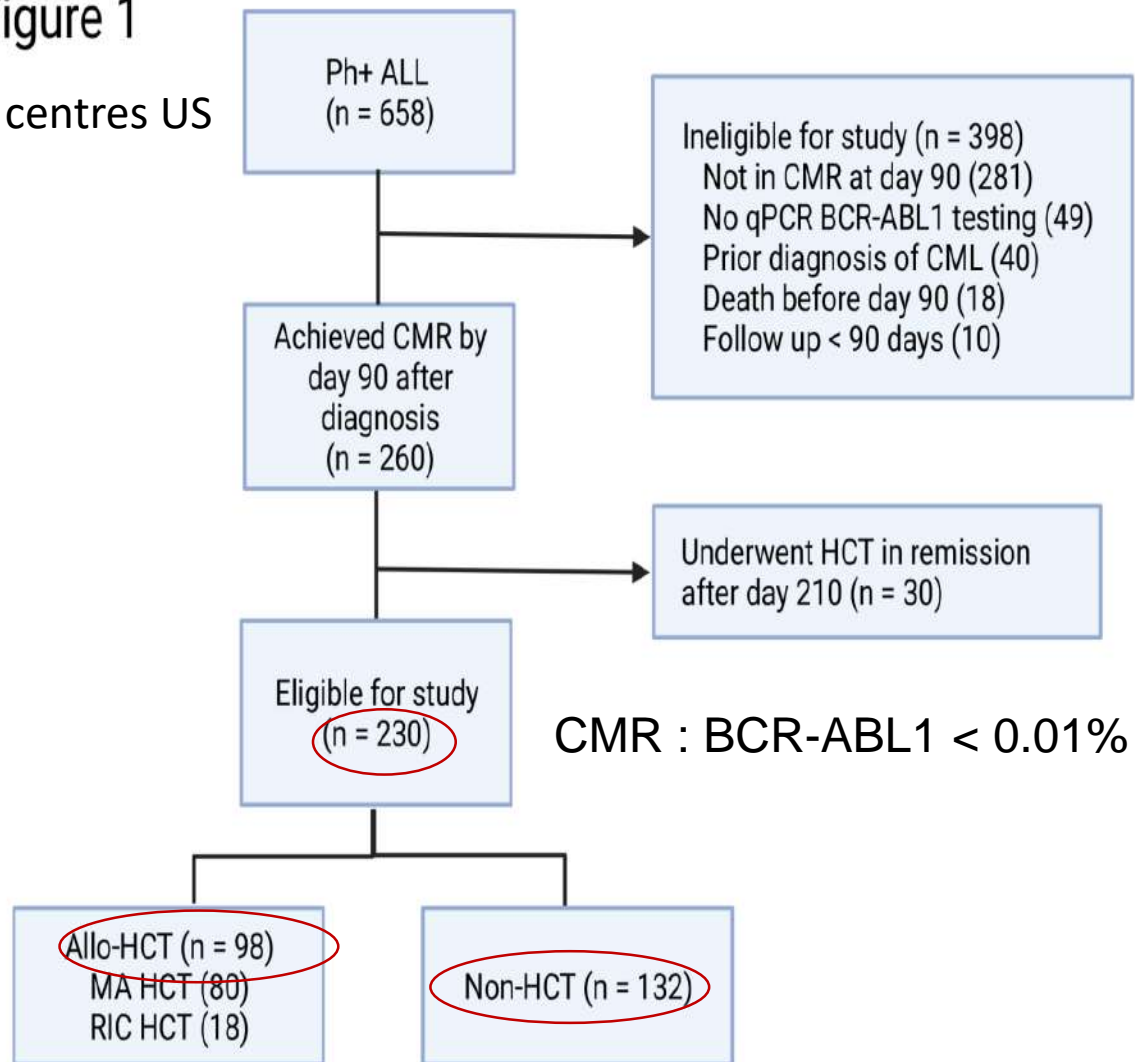
Zhang JCO 2022

MRD pre-HSCT <sup>a</sup>	all	TBI	chimio
MRD-negative (PCR)	135 (33%)	72 (34%)	63 (31%)
MRD-positive (PCR)	132 (32%)	61 (29%)	71 (35%)
MRD-negative (flow cytometry)	57 (14%)	32 (15%)	25 (12%)
MRD-positive (flow cytometry)	12 (3%)	9 (4%)	3 (1%)

43% MRD + et 57% MRD neg à la greffe

# The Role of Allogeneic Transplant for Adult Ph+ ALL in CR1 with Complete Molecular Remission: A Retrospective Analysis

Figure 1  
5 centres US

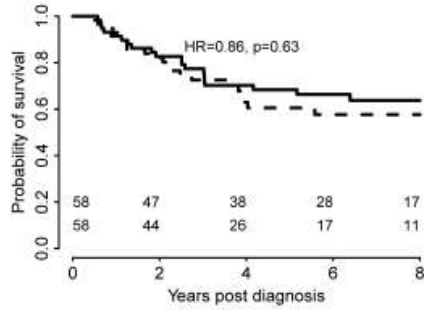


# Propensity Matched Analysis ITT

Pas d'avantage de survie de l'allo chez LALphi+ RC1 réponse moléculaire complète (BCR-Abl)

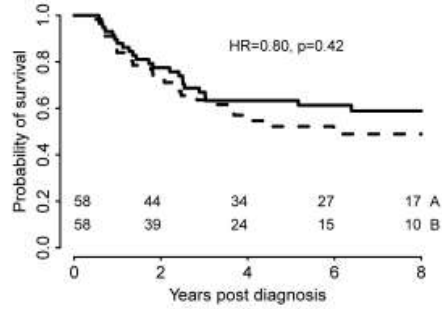
— A. ALLO-HCT  
- - - B. non-HCT

A. overall survival (OS)

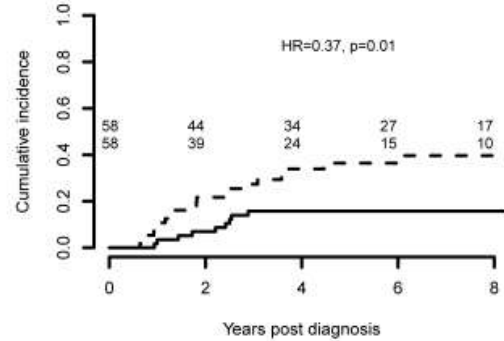


**OS et RFS id**

B. relapse-free survival (RFS)

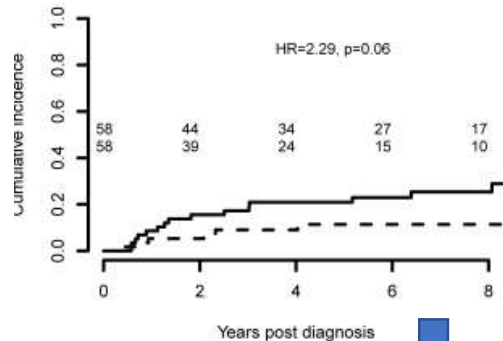


C. Relapse



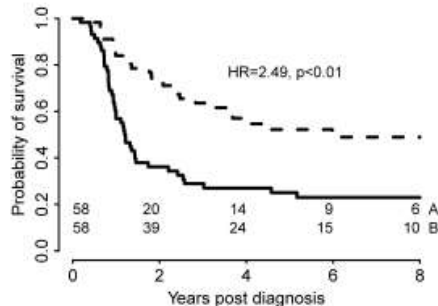
**Aug rechute si non allo  
Allo MAC dim rechute**

D. non-relapse mortality (NRM)



**Aug NRM si allo MAC**

E. GvHD & relapse-free survival (GRFS)



**Aug GRFS si non allo**

Sous groupe **RIC**: aucun bénéfice  
Devenir id aux non greffés

**Biais**  
 Induction et conso intensive  
 Retrospectif: sélection allo (+ jeunes, + fit mais + graves?)  
 Possibilité de rattrapage: blina, ino, CART, allo en RC2  
 Différents ITK utilisés



Nécessité de rando allo vs pas allo si RCM



GRAAPH 2022

*Ghobadi, Juillet 2022 Blood*

Haplo et HLA

M=Match ou MM sens HVG isolé

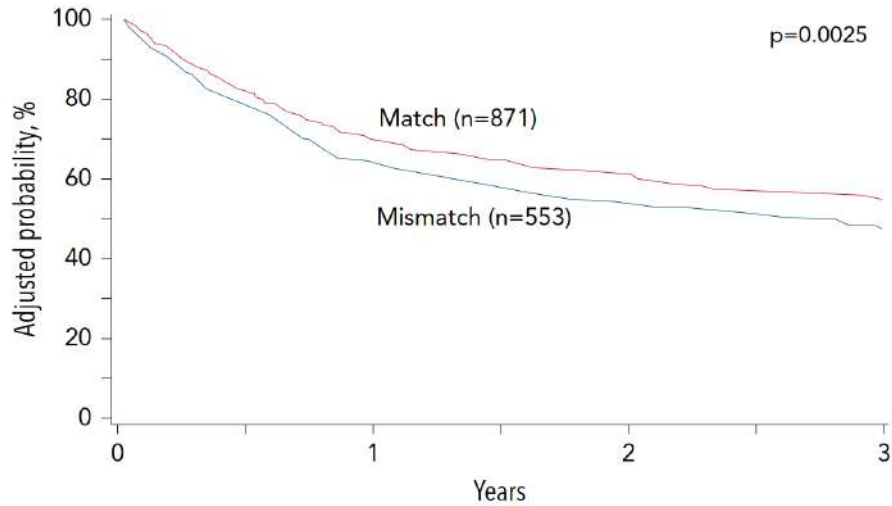
MM=Mismatch sens GVH

HLA-B leader peptide (Petersdorf, Lancet hematol 2020)

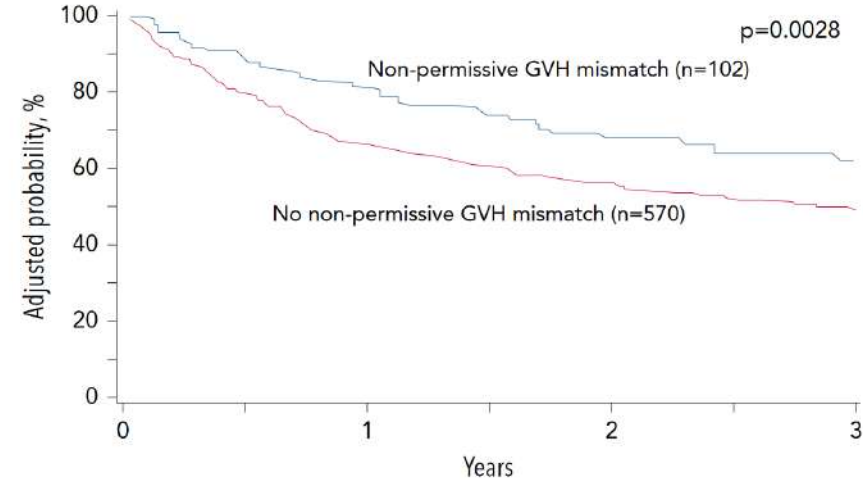
# HLA et greffes Haplo avec HD-Cy

1434 LA/MDS CIBMTR

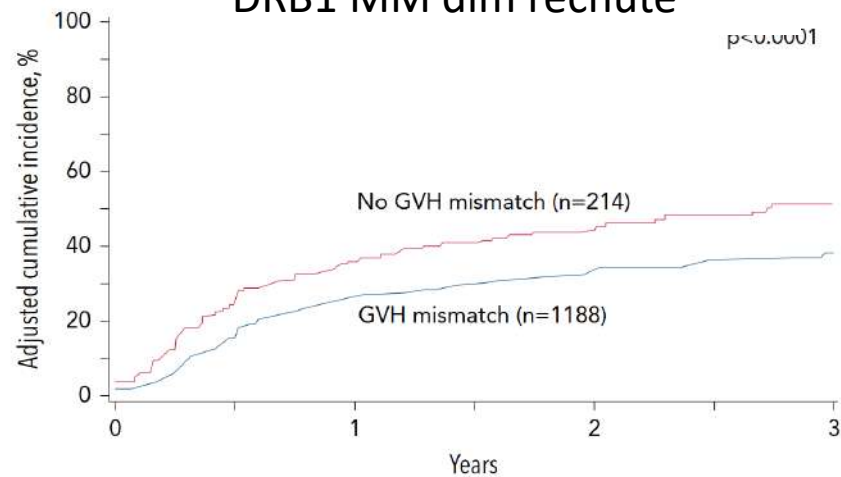
### HLA-B Match aug OS



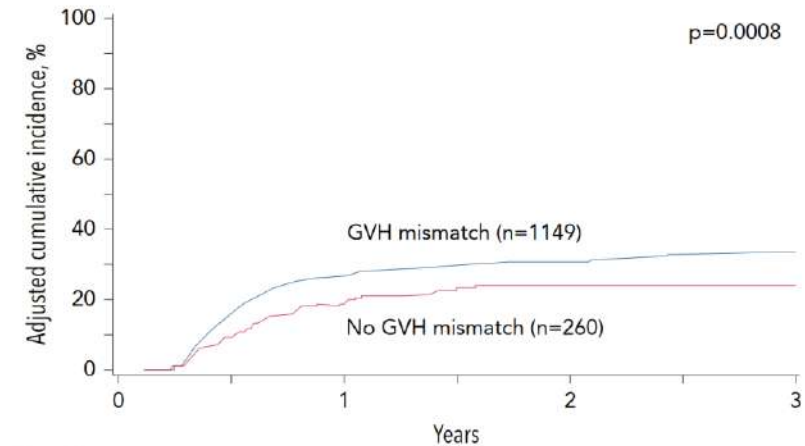
### DPB1 MM non permissif aug OS



### DRB1 MM dim rechute



### HLA-C Match dim GVHc



**Meilleur donneur Matché**

HLA-B M leader peptide (OS, DFS, rechute)

HLA C (GvHc)

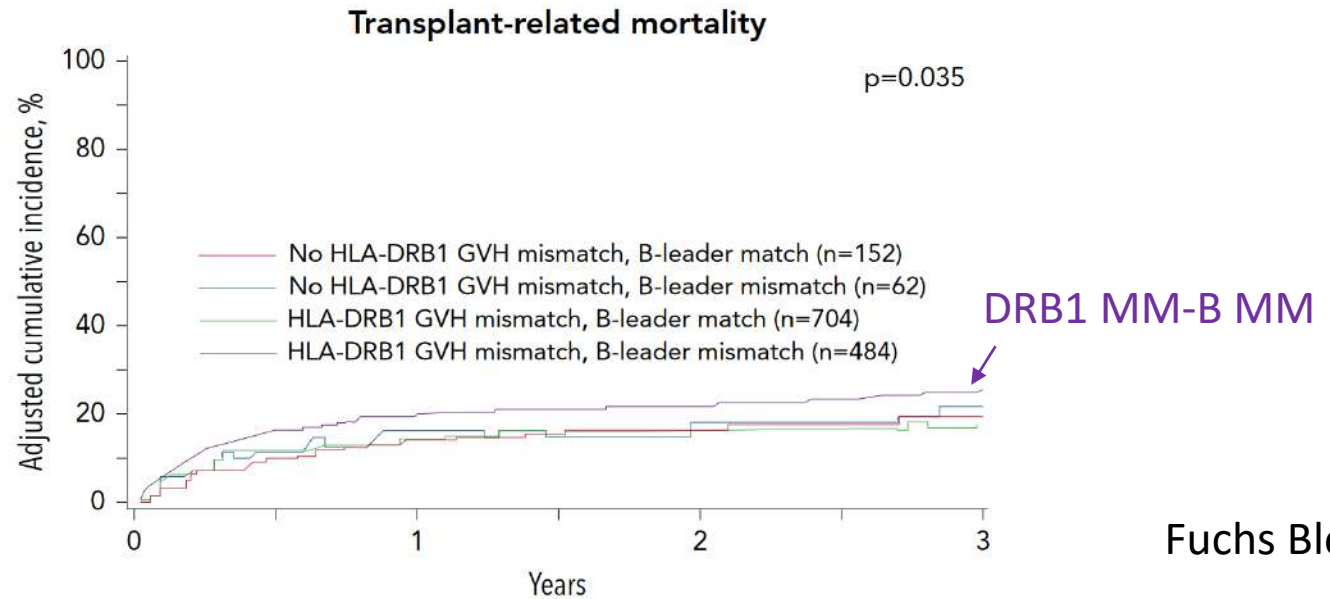
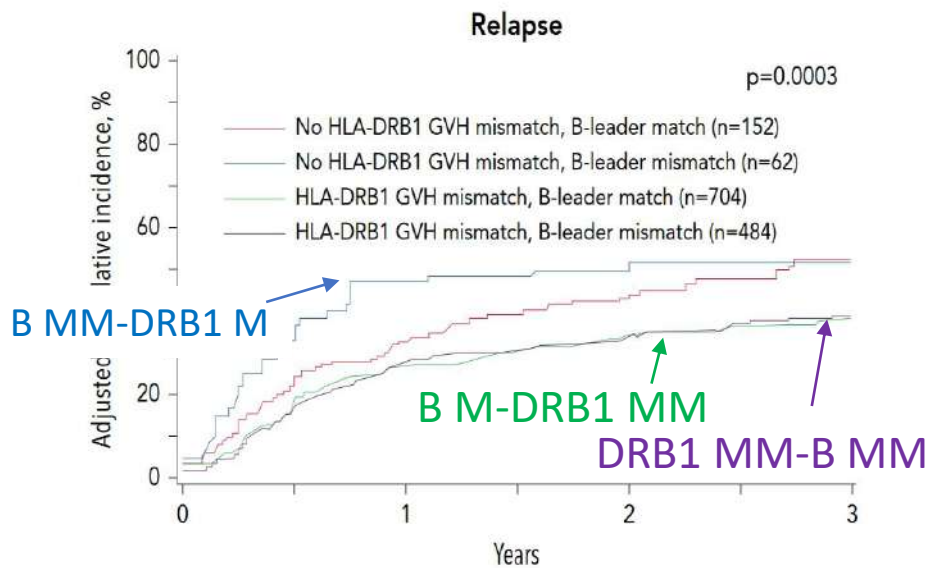
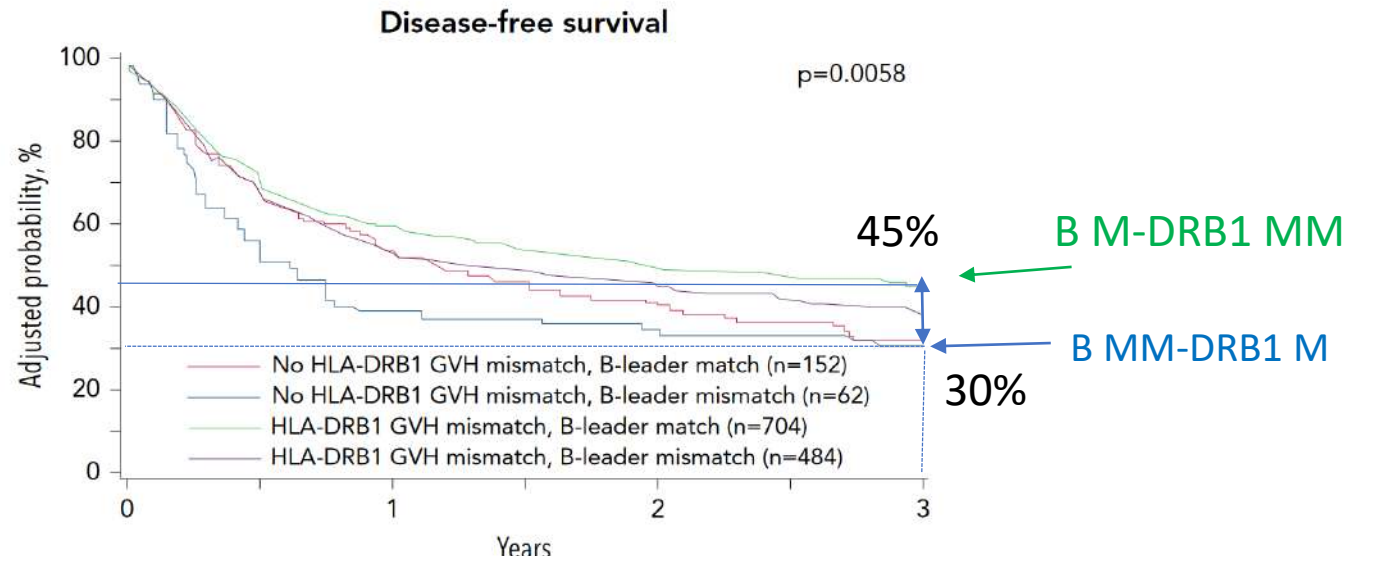
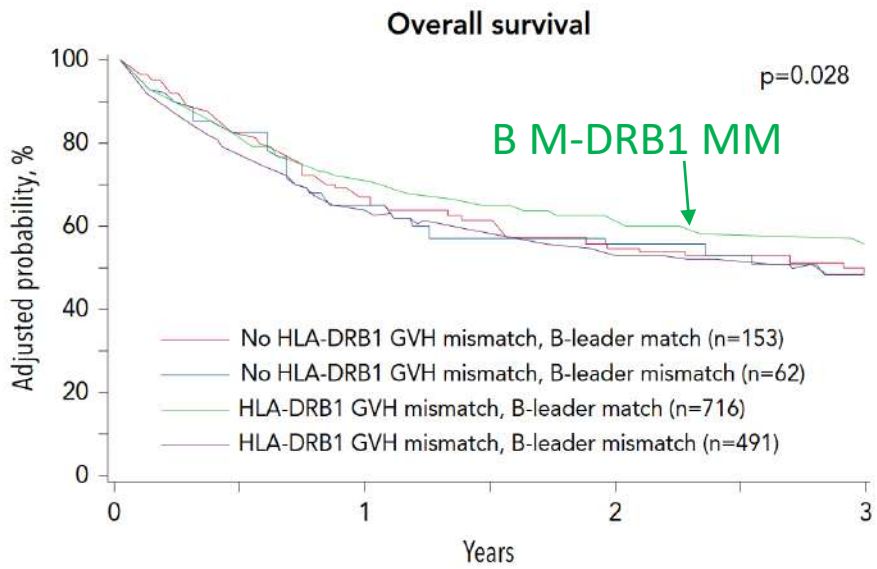
HLA-DQB1 (DFS)

**Mismatch**

HLA-DRB1 (rec)

HLA-DPB1 MM non permissive (OS)





DISCUSSION sur l'effet HDCy-PT haplo

Pas de rôle du MM HLA sur la GVHa  
Déplétion précoce T alloréactifs Cy HD-PT?

Pas de rôle du MM HLA-C sur la rechute  
Déplétion des NK KIR+ alloréactifs par CyHD-PT?

MM HLA-C augmente la GVHc  
Effet retardé du CyHD-PT sur la déplétion thymique des clones HLA C MM?

**Meilleur donneur Matché**

HLA-B M leader peptide (DFS, rechute)  
HLA C (GvHc)  
HLA-DQB1 (DFS)

**Mismatch**

HLA-DRB1 (rec)  
HLA-DPB1 MM non permissive (OS)

Déjà observé MMUD  
Petersdorf Lancet Haematol 2020

Nécessité d'outils pour classer les leader peptide HLA-B (comme C1, C2 et KIR, HLA-E et NKG2A)

MUD  
MMDP non permissif sens GvH aug GVHa 2-4 /3-4 et TRM  
Effet ++ HDCy-PT sur GVHa

MMDP permissif ou pas aug GVL (MUD: préférer MMDP permissif ou MM DP sens HVG)  
Oran Blood 2018

Cyclophosphamide fortes  
doses post transplant  
prophylaxie GVH

HD-CyPT

# Randomized Phase III Prophylaxie GVH sans inhibiteur de calcineurine dans les greffes HLA matchées avec MAC hémopathies malignes

MAC

CD34 Selection Arm (PBSC)		Post-Transplant Cy Arm (BM)	Control Arm (BM)
<b>A</b>	<b>Total Body Irradiation (TBI)/ Cyclophosphamide/Thiotepa/rATG</b> <ul style="list-style-type: none"> <li>TBI (1375 cGy)</li> <li>Cyclophosphamide (120 mg/kg)</li> <li>Thiotepa (10 mg/kg)</li> <li>rATG (5mg/kg)</li> </ul>	<b>C</b> <b>Busulfan/Cyclophosphamide (Bu/Cy)</b> <ul style="list-style-type: none"> <li>Busulfan (16 mg/kg PO or 12.8 mg/kg IV)</li> <li>Cyclophosphamide (100 mg/kg)</li> </ul>	<b>G</b> <b>Busulfan/Cyclophosphamide (Bu/Cy)</b> <ul style="list-style-type: none"> <li>Busulfan (16 mg/kg PO or 12.8 mg/kg IV)</li> <li>Cyclophosphamide (120 mg/kg)</li> </ul>
<b>B</b>	<b>Busulfan<sup>2</sup>/Melphalan/Fludarabine/rATG</b> <ul style="list-style-type: none"> <li>Busulfan (9.6 mg/kg IV)</li> <li>Fludarabine (125 mg/m<sup>2</sup>)</li> <li>Melphalan (140 mg/m<sup>2</sup>)</li> <li>rATG (5mg/kg)</li> </ul>	<b>D</b> <b>Busulfan<sup>2</sup>/Fludarabine (Bu/Flu)</b> <ul style="list-style-type: none"> <li>Busulfan (16 mg/kg PO or 12.8 mg/kg IV)</li> <li>Fludarabine (160 mg/m<sup>2</sup>)</li> </ul>	<b>H</b> <b>Busulfan<sup>2</sup>/Fludarabine (Bu/Flu)</b> <ul style="list-style-type: none"> <li>Busulfan (16 mg/kg PO or 12.8 mg/kg IV)</li> <li>Fludarabine (160 mg/m<sup>2</sup>)</li> </ul>
	<b>E</b> <b>Cyclophosphamide/Total Body Irradiation (Cy/TBI)</b> <ul style="list-style-type: none"> <li>Cyclophosphamide (100 mg/kg)</li> <li>TBI (1200-1420 cGy)</li> </ul>	<b>I</b> <b>Cyclophosphamide/Total Body Irradiation (Cy/TBI)</b> <ul style="list-style-type: none"> <li>Cyclophosphamide (120 mg/kg)</li> <li>TBI (1200-1420 cGy)</li> </ul>	
	<b>F</b> <b>Total Body Irradiation/Etoposide (TBI/Etoposide)</b> <ul style="list-style-type: none"> <li>TBI (1200-1320 cGy)</li> <li>Etoposide (60 mg/kg)</li> </ul>	<b>J</b> <b>Total Body Irradiation/Etoposide (TBI/Etoposide)</b> <ul style="list-style-type: none"> <li>TBI (1200-1320 cGy)</li> <li>Etoposide (60 mg/kg)</li> </ul>	

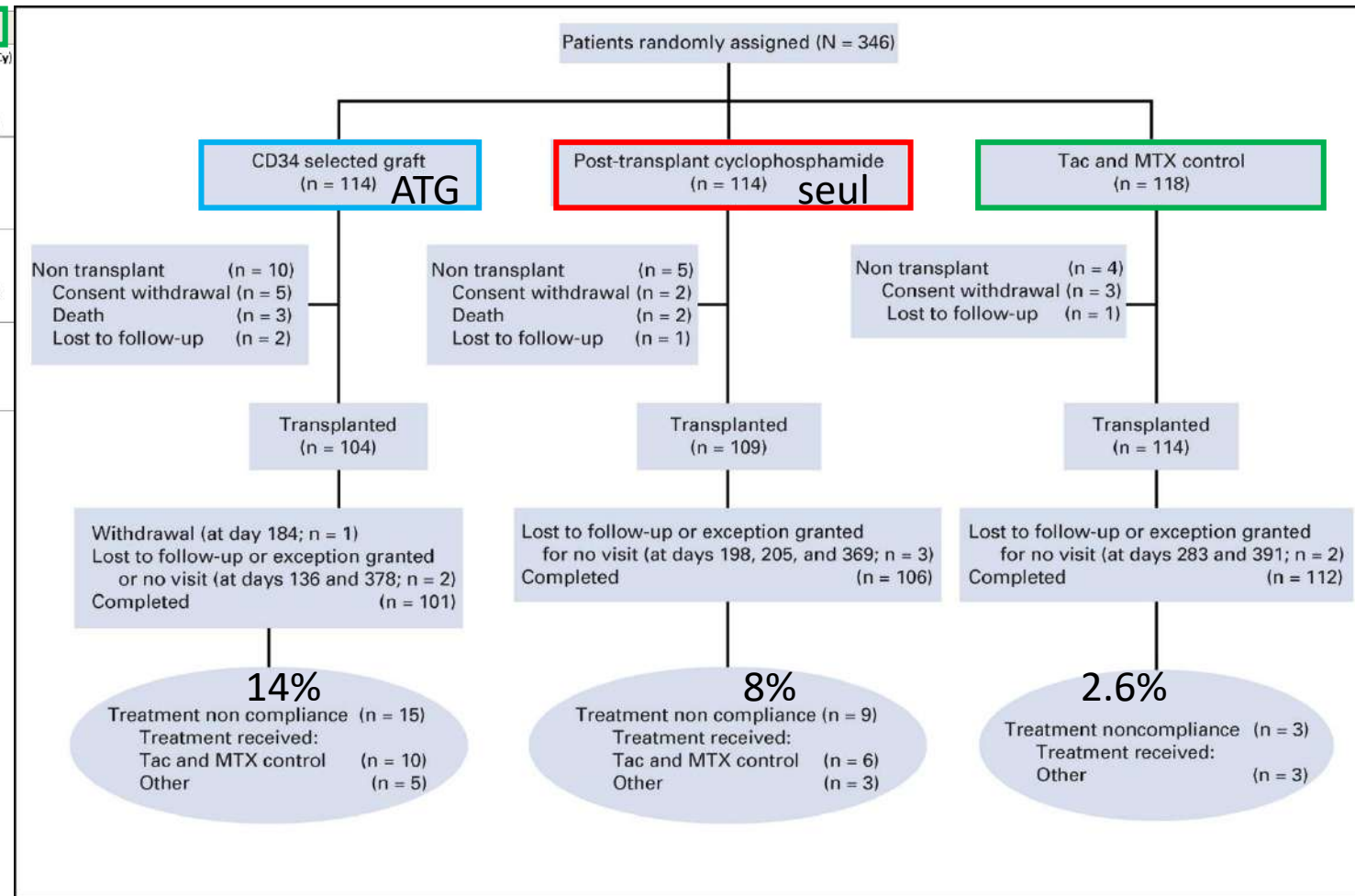
Age 51 ans (13-66)

26 centres US+Allemagne

61.3% LAM , 20-25% LAL, 33.2% high DRI, 62%

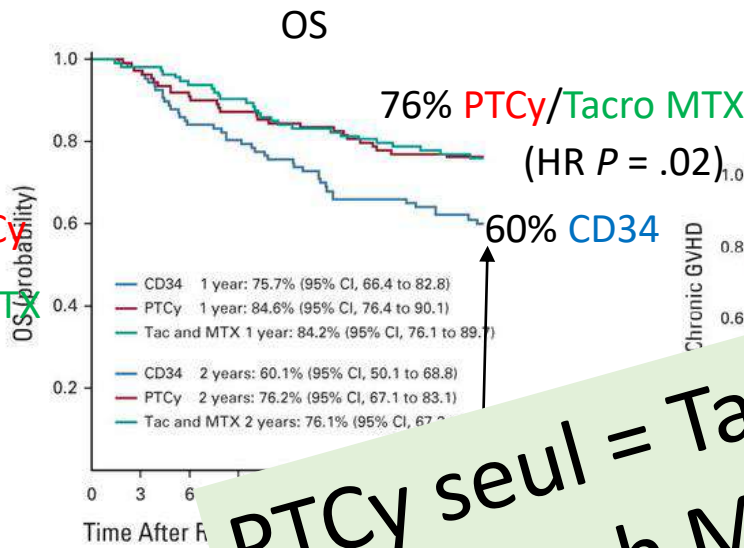
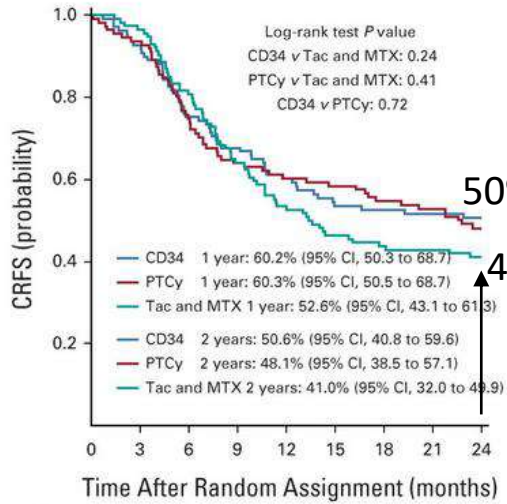
MUD 8/8, 38% MRD, and the median time from diagnosis to HCT was 5 months

90% MO dans les groupes HDCy et Tacrp MTX



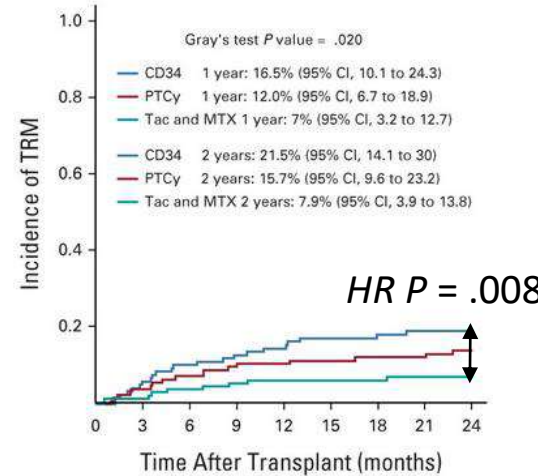


**A** CRFS=GVHc mod sev rel free survival **B**

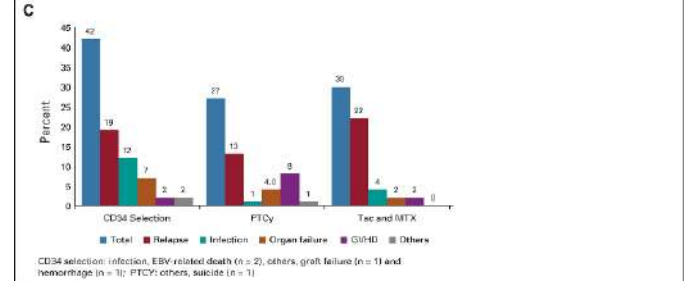
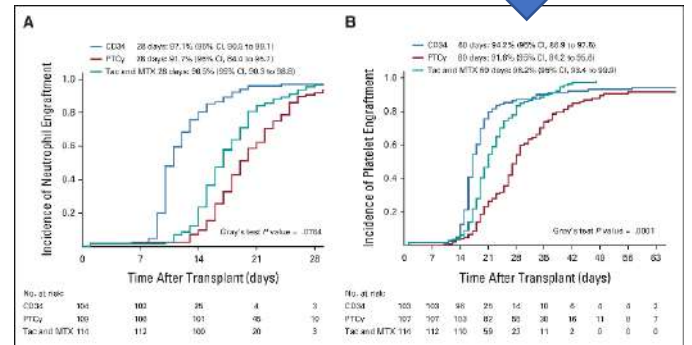
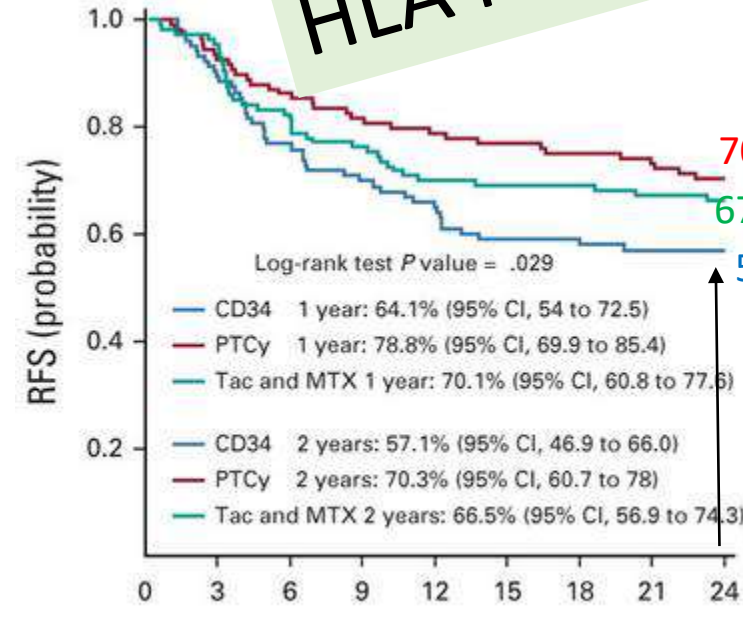
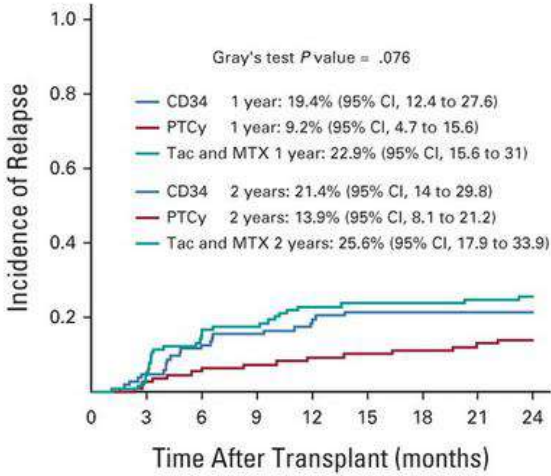


Peu de GVHc mod sev avec CD34

TRM élevée CD34 (infections)



**PTCy seul = Tacro MTX  
 HLA match MAC+BM**



# HAPLO vs MUD

Même prophylaxie HD-Cy PT + ciclo/MMF

LA/MDS

RIC

vs

1211 **haplo**  
 56% CSP  
 62 ans  
 70% caucasiens  
 50% TBI

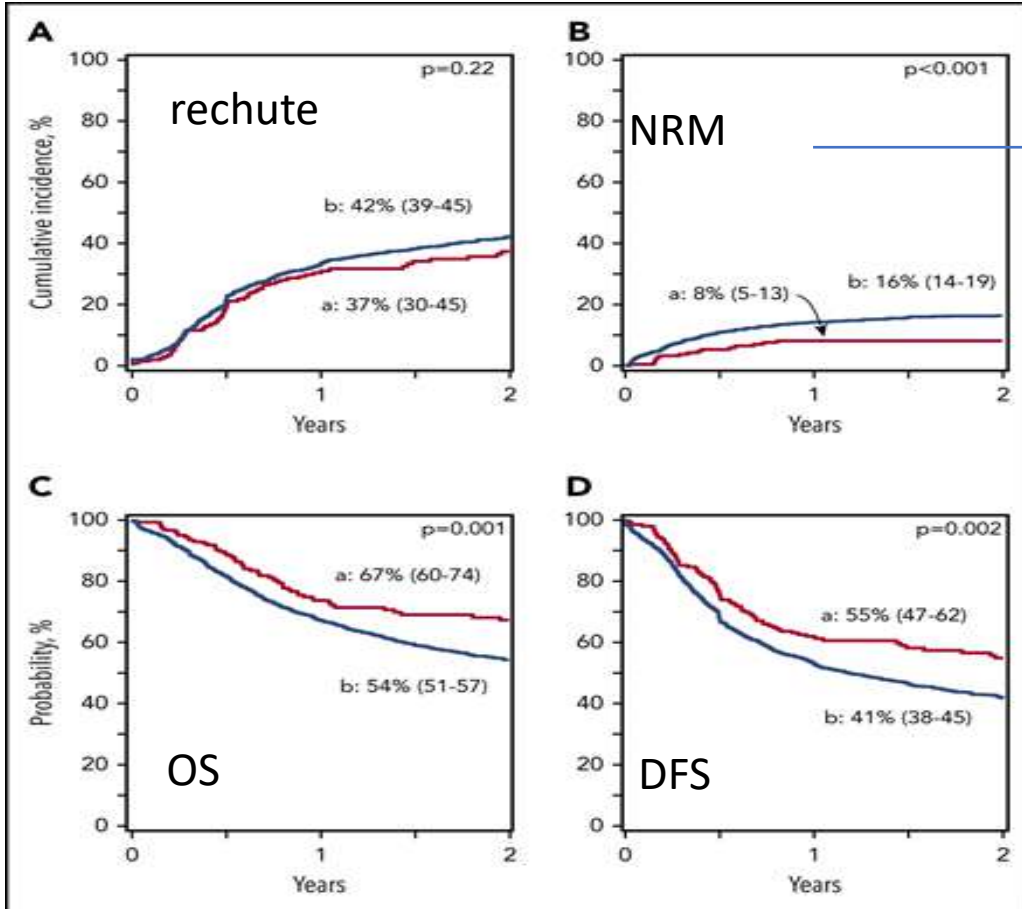
187 **MUD**  
 84% CSP  
 65 ans  
 95% caucasiens  
 34% TBI

MAC

vs

825 **Haplo**  
 74% CSP  
 45 ans  
 70% caucasiens  
 55% LAM/13%MDS

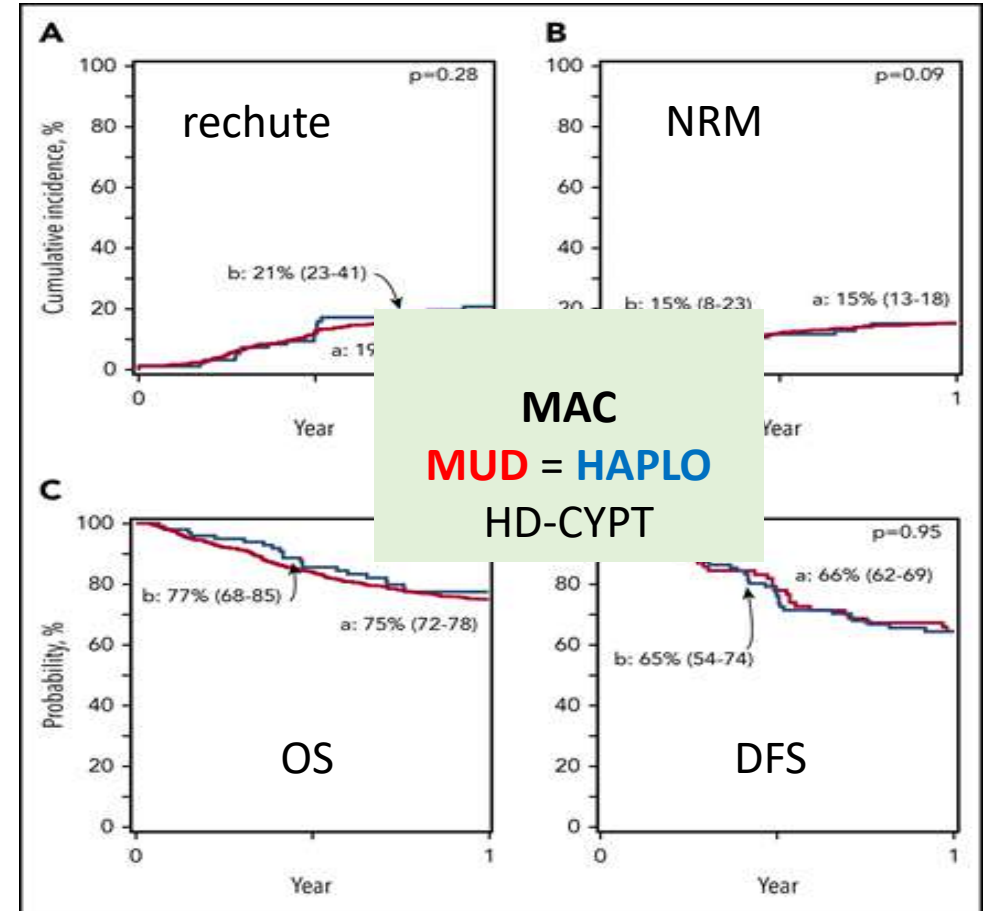
97 **MUD**  
 88% CSP  
 50 ans  
 90% caucasiens  
 48%LAM/24%MDS



**Haplo** **MUD**  
 9% GVHa 3-4 vs 4%  
 Retard PNN et plaq  
 11% rejet vs 3%



**RIC**  
**MUD > HAPLO**  
 HD-CYPT



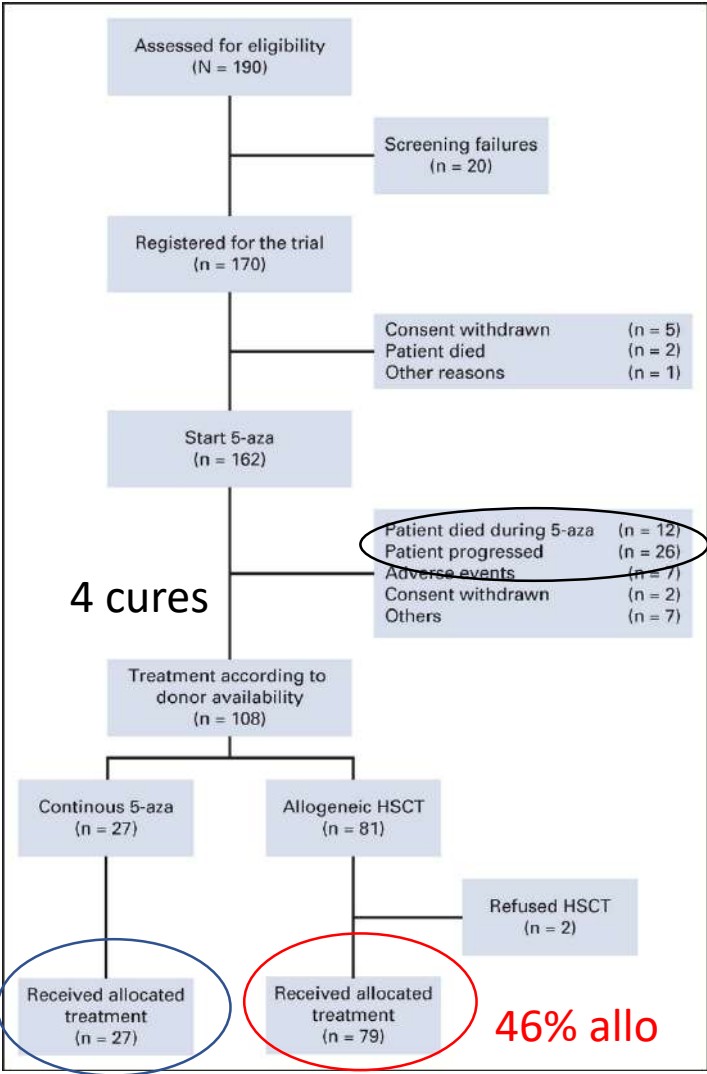
**MAC**  
**MUD = HAPLO**  
 HD-CYPT

# LAM/MDS

Sujet âgé

55-70 ans  
 MDS ou LMMC (WBC < 13 G/L) IPSS int-II ou high-risk or int-I +  
 high-risk cytogenetics ou LMMC acutisée + blastes ≤ 30%

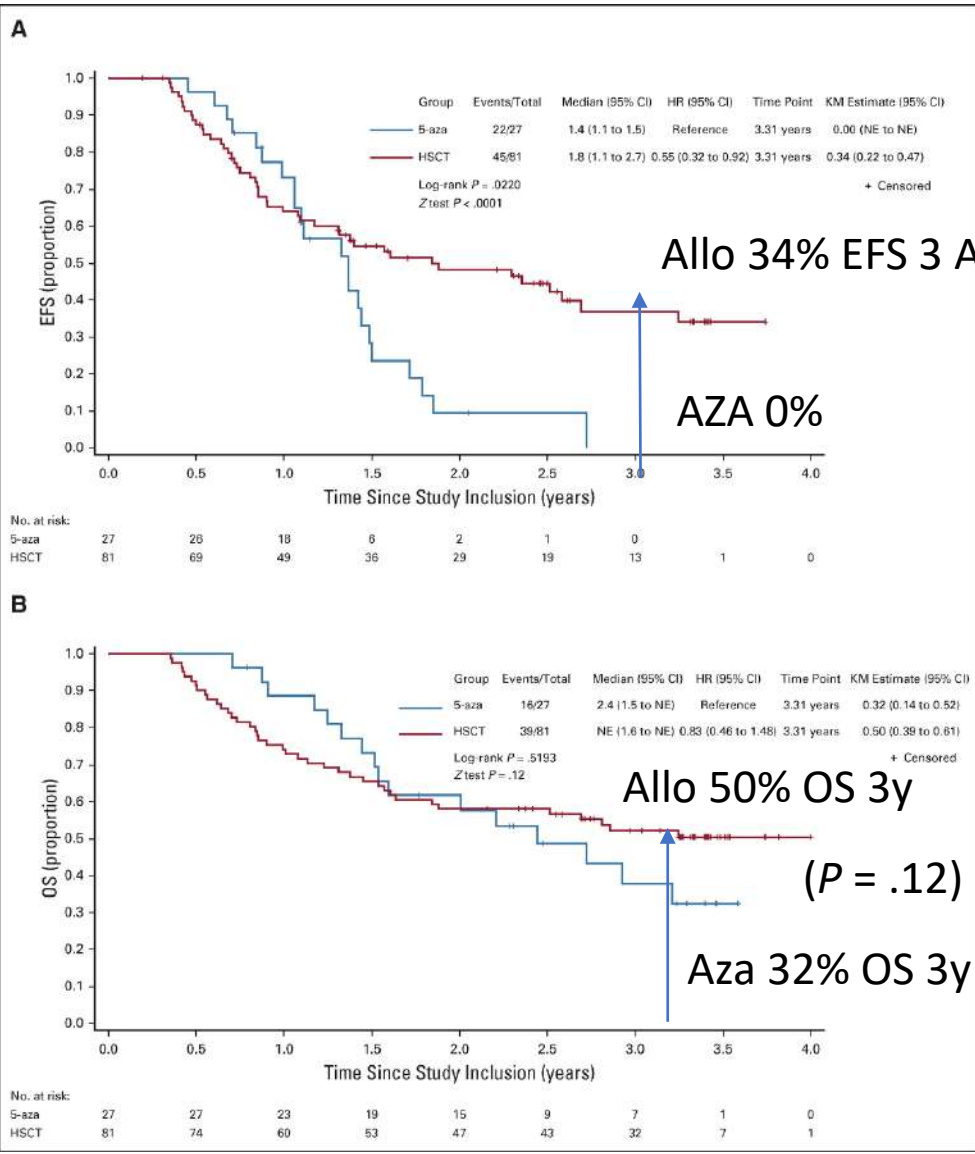
# 5-Azacytidine Treatment vs allo 10/10 (donor/no donor) MDS avancée sujet âgé VidazaAllo



¼ patients perdus avant allo  
 Intérêt du bridging?

46% allo

N=65 MUD (82%), TRM 19% 1 an  
 FB2 ou Flamsa  
 Ciclo+MTX ou MMF +/- ATG si MUD



Allo 34% EFS 3 ANS

AZA 0%

Allo 50% OS 3y

(P = .12)

Aza 32% OS 3y

Bénéfice >65 ans  
 ou répondeurs à  
 Aza

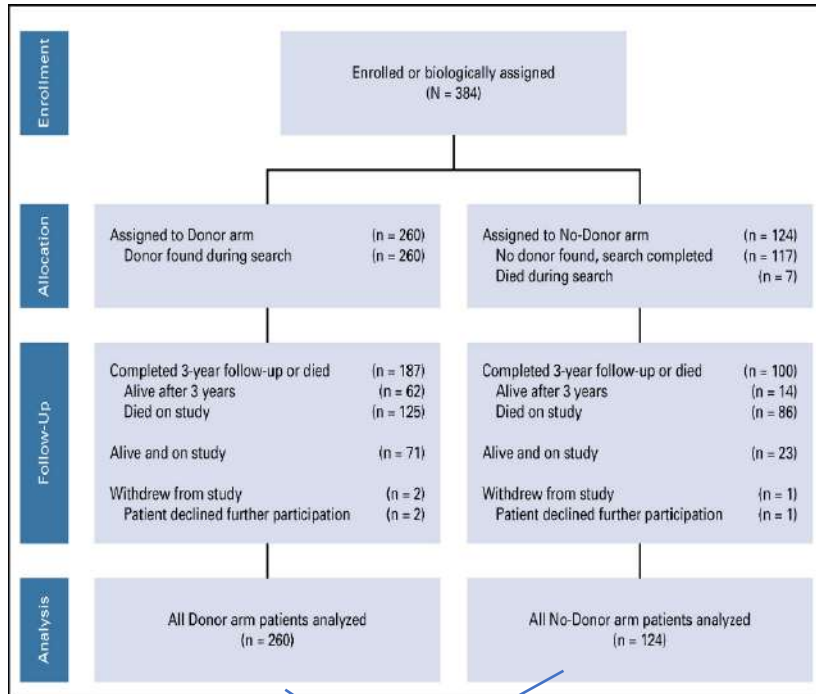
Hypothèse 50% vs 30%

Mais manque de  
 puissance car 27% Aza  
 vs 40% attendus



# Allogreffe CSH MDS haut risque 50-75 ans Donor vs no donor

Essai multicentrique prospectif non rando  
allo RIC vs hypomethylant ou best supp care  
Pts 50-75 ans  
De novo MDS int-2 ou high risk  
Bras donor si 8/8 MD  
Bras no donor si zero donneur dans les 90 j



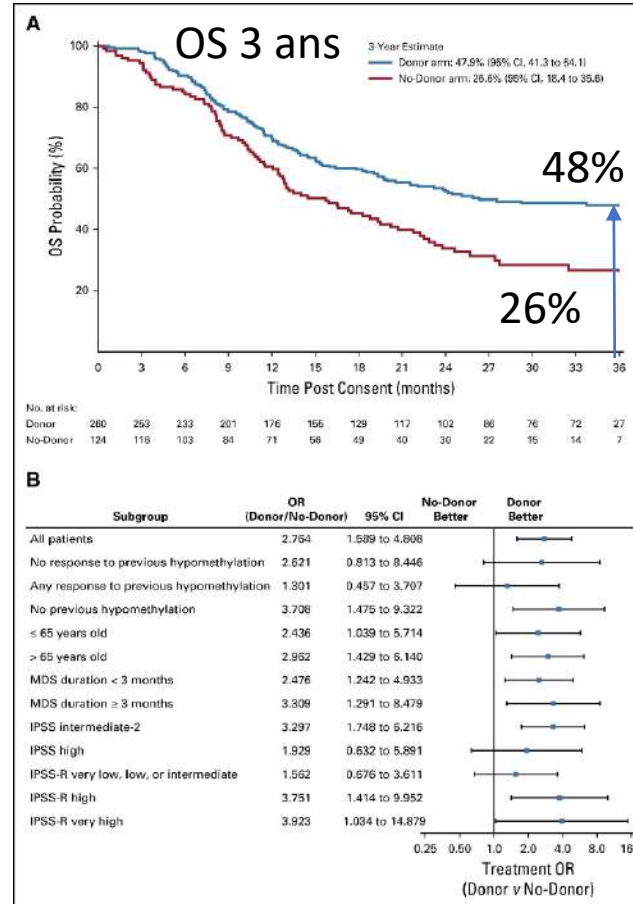
10% (n=26) MAC

25% allo (n=31)

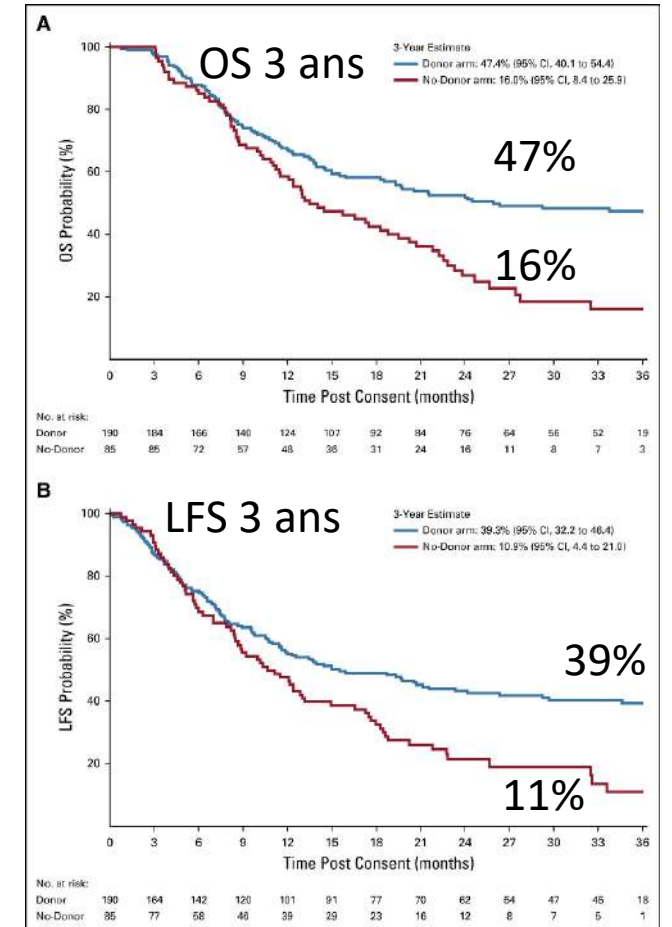
17% non allo (n=44)

Non compliance 26%

ITT

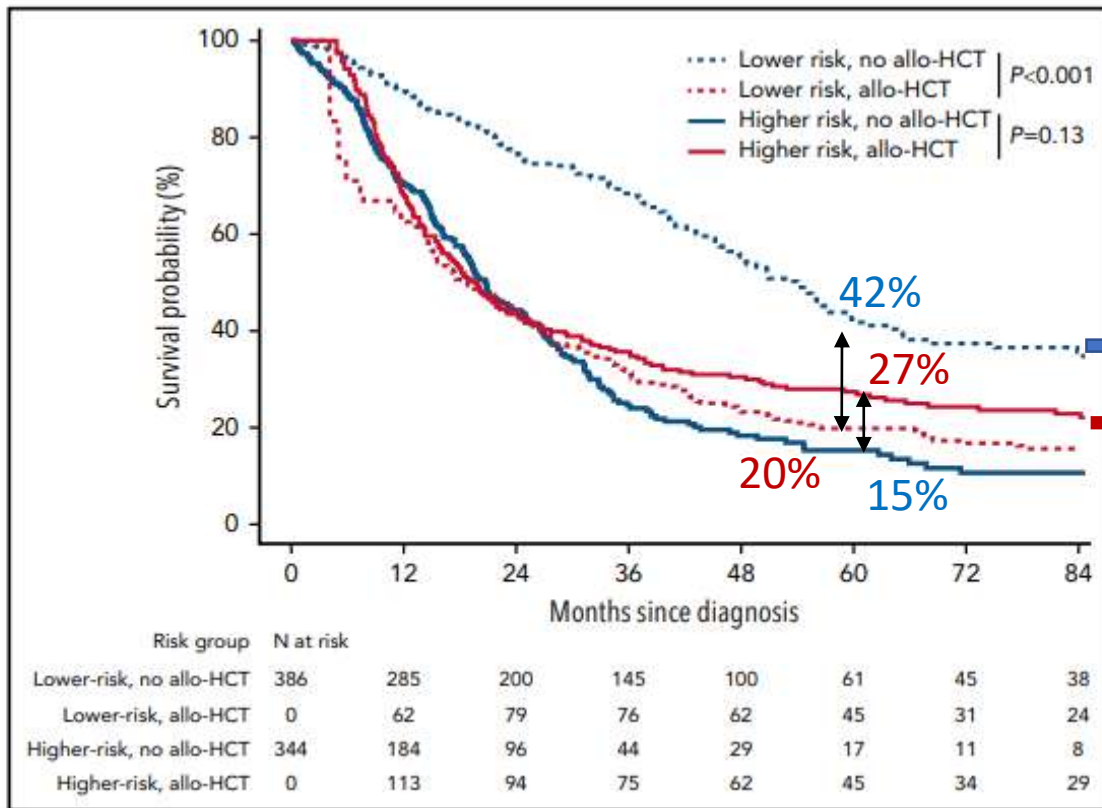


As treated



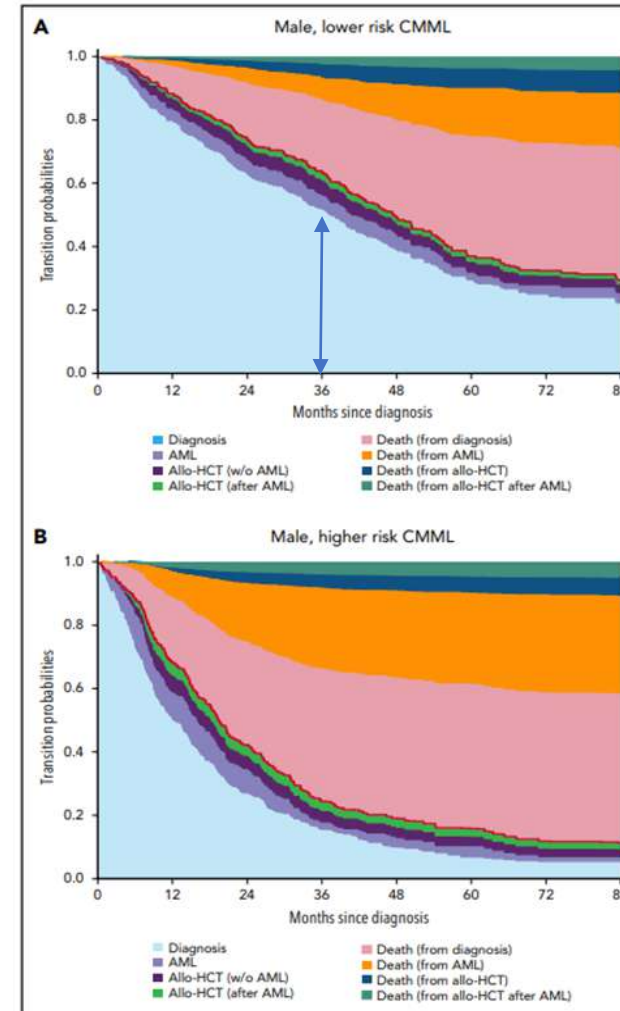
# Rôle de l'allo dans la LMMC

Simon-Makuch survival curves according to CMML risk group



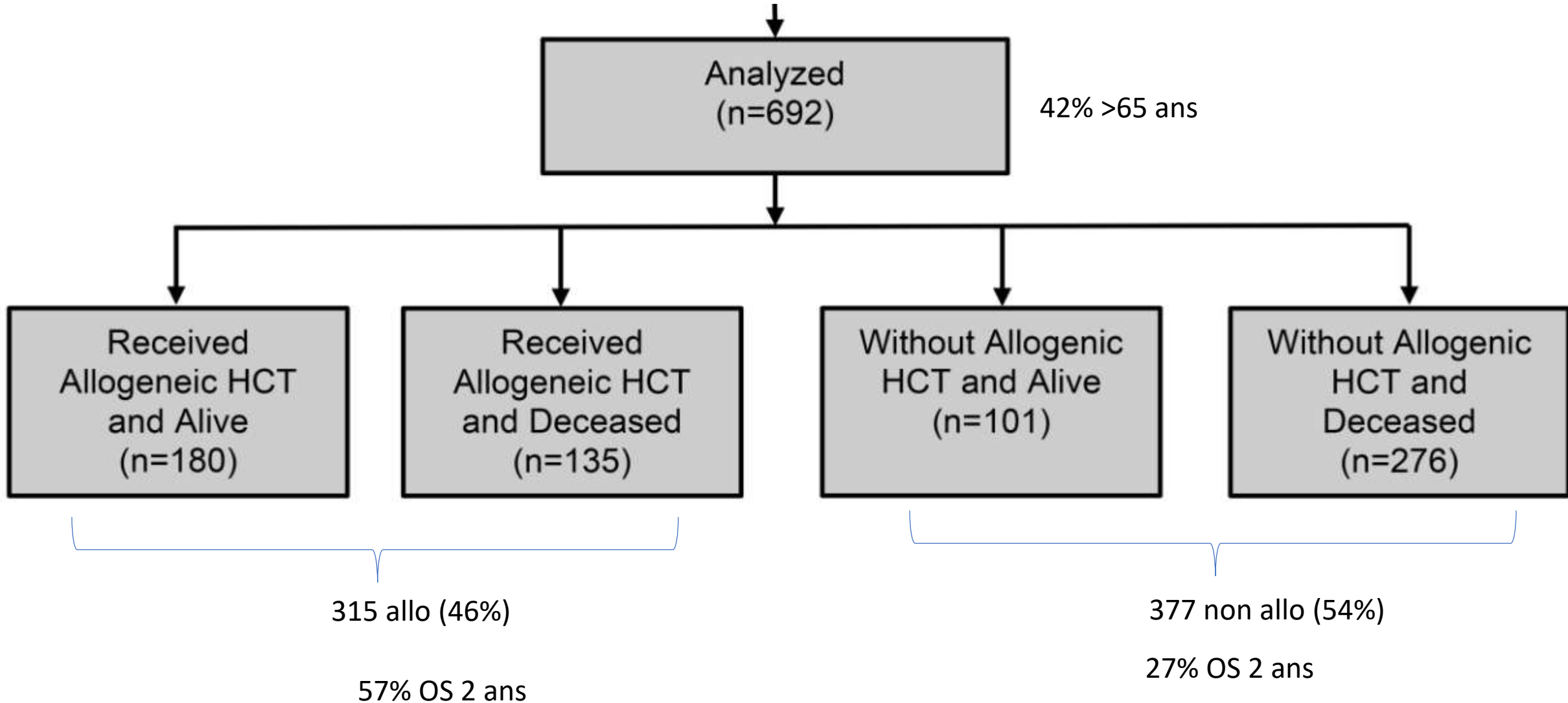
Pas d'intérêt  
allo bas risk  
(low-int1)  
Intérêt  
allo ht risk  
(int2 ou ht  
risk)

Multi états Homme 60 ans



# An 8-year pragmatic observation evaluation of the benefits of allogeneic HCT in older and medically infirm AML patients

Etude prospective multicentrique observationnelle US



# Association mortalité et allogreffe

Avantage allo

Pas d'avantage allo sauf LAM ht risque

	Unadjusted		Adjusted*	
	HR (95% CI)	P	HR (95% CI)	P
All patients (n=692)	0.71 (0.57 - 0.88)	0.002	0.85 (0.66 - 1.09)	0.19
Patients aged ≥65 (n=295)	0.65 (0.46 - 0.90)	0.01	0.79 (0.53 - 1.16)	0.22
Patients with augmented HCT-CI scores ≥4 (n= 353)	0.63 (0.46 - 0.86)	0.0004	0.84 (0.58 - 1.21)	0.34
Patients with ELN intermediate risk (n=296)	0.55 (0.40 - 0.77)	0.0004	0.81 (0.55 - 1.17)	0.26
Patients with ELN adverse risk (n=248)	0.37 (0.25 - 0.54)	<0.0001	0.58 (0.38 - 0.89)	0.01
Patients who achieved CR1 (n=510)	0.85 (0.67 - 1.09)	0.20	0.96 (0.72 - 1.27)	0.75
Patients who did not achieve CR1 (n=182)	0.27 (0.15 - 0.51)	<0.0001	0.45 (0.22 - 0.90)	0.02

\*Adjusted for the augmented HCT-CI, age, ELN cytogenetic risk, relapsed/refractory AML at enrollment, post-treatment CR1 status, treatment intensity, sum PHQ-9, KPS, ADL, FACT-G, and 4-MWT (post-treatment CR1 status, sum PHQ-9, KPS, ADL, FACT-G, and 4-MWT modeled as time-dependent variables, with missing indicator to account for those without data).

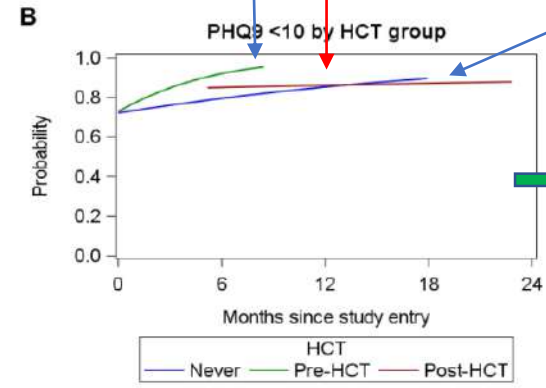
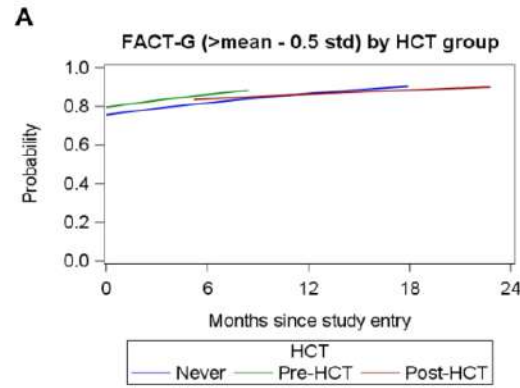
**Note:** 4-MWT=NIH Toolbox 4-Meter Walk Gait Speed Test; ADL=activities of daily living; CR1=first complete remission; ELN=European LeukemiaNet; FACT-G=Functional Assessment of Cancer Therapy-General; HCT-CI=Hematopoietic Cell Transplantation-Specific Comorbidity Index; KPS=Karnofsky Performance Status; PHQ-9=Patient Health Questionnaire-9; PWB=Physical Wellbeing subscale.

# Evolution des scores de qualité de vie au cours du temps

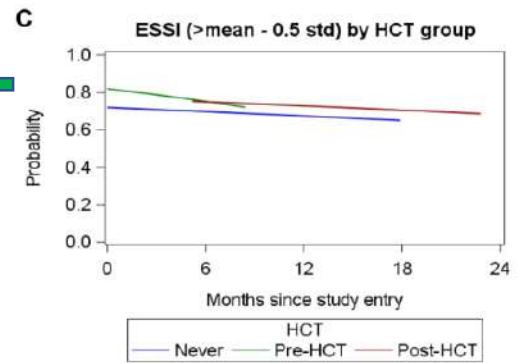
Avant la greffe

Après greffe

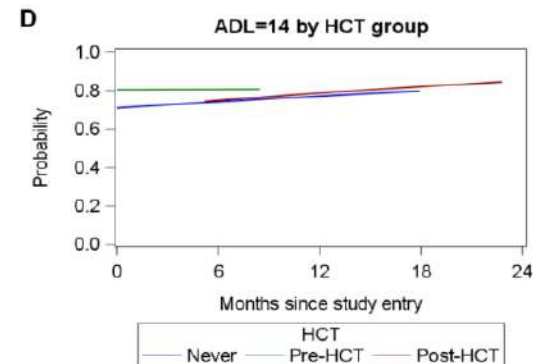
Jamais greffés



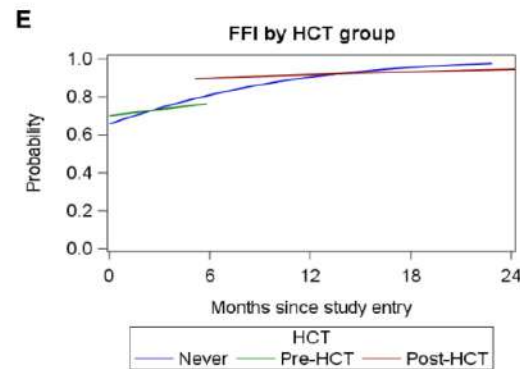
Meilleur évolution score PHQ9 (dépression) avant la greffe par rapport à jamais greffé



Diminution ESSI (social) avant la greffe par rapport aux non greffés



Aucune différence évolution des scores Non greffés vs post allogreffe

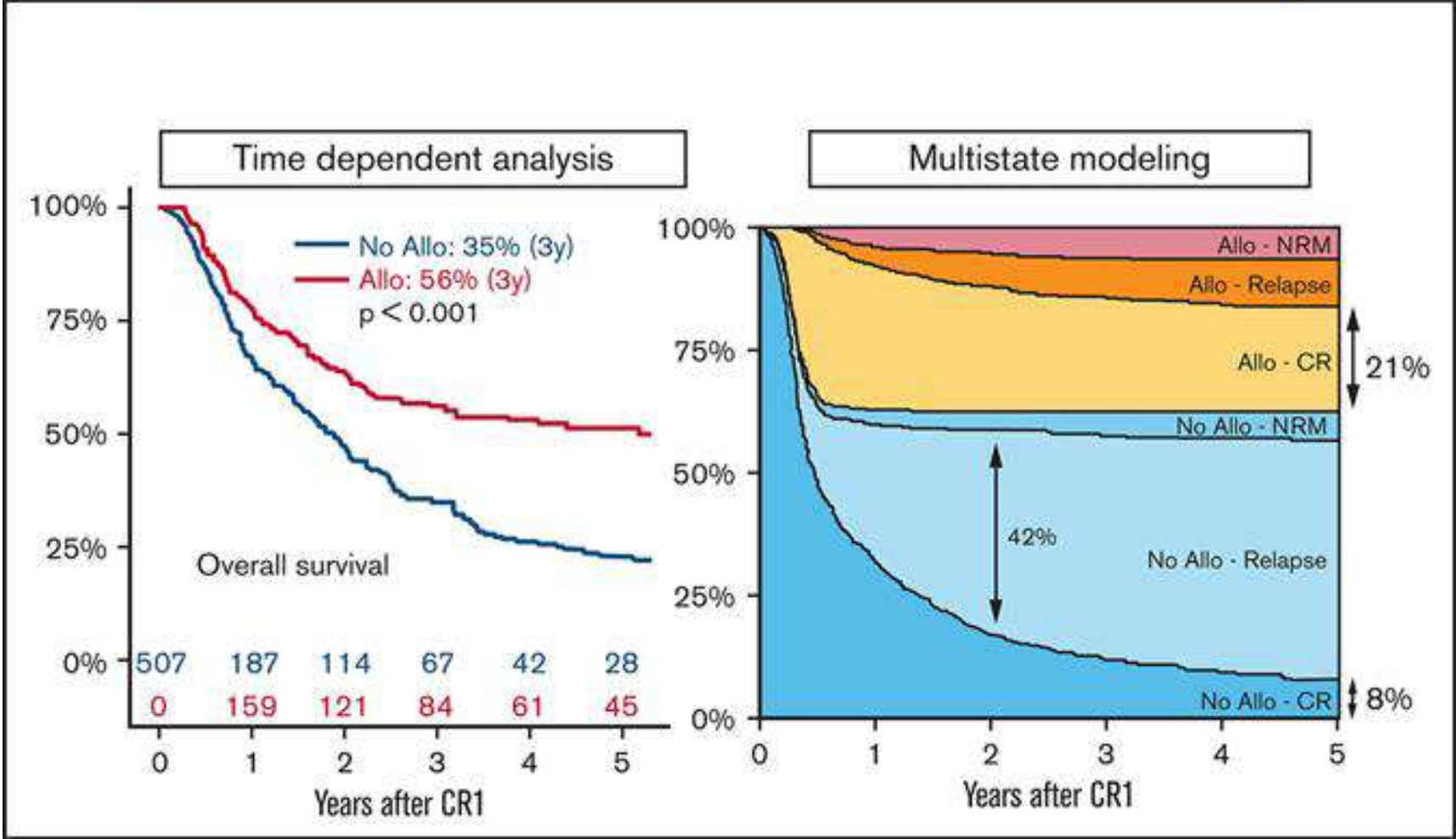


FACT-G=Functional Assessment of Cancer Therapy-General  
 PHQ-9=Patient Health Questionnaire-9 (dépression)  
 ESSI=ENRICH Social Support Inventory (social)  
 ADL=activities of daily living  
 FFI=Fried Frailty Index;



**In-depth time-dependent analysis of the benefit of allo-HSCT for elderly patients with CR1 AML: a FILO study. Blood Adv 2022**

R Devillier, E Forcade, A Garnier, S Guenounou, S Thepot, G Guillerm, P Ceballos, Y Hicheri, PY Dumas, P Peterlin, M Hunault-Berger, MC Béné, A Bouvier, P Chevallier, D Blaise, N Vey, A Pigneux, C Récher, A Huynh.



60-70 ans

N=369 int

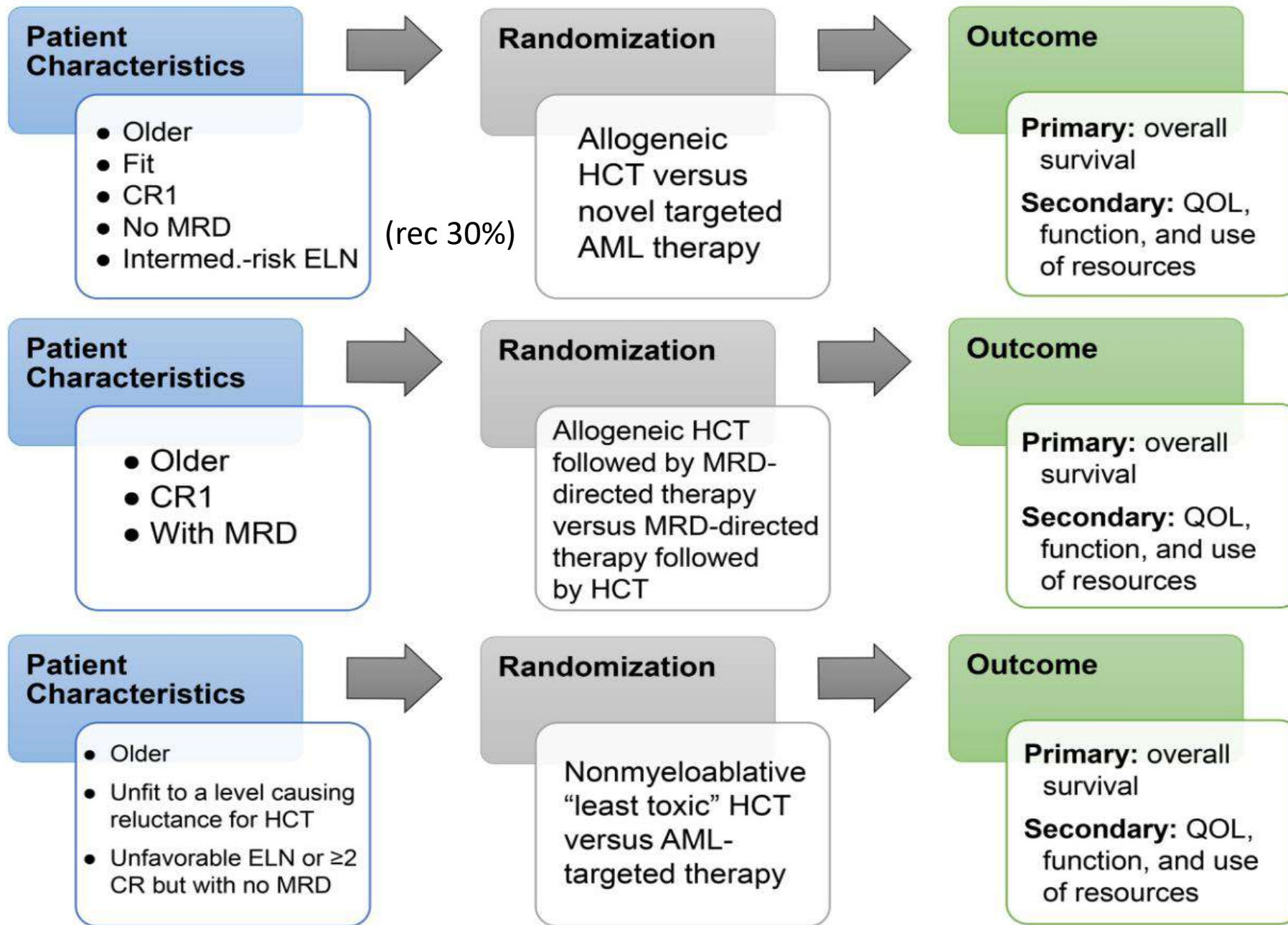
N=138 défav

203 allo



Pas d'évaluation des comorbidités, fragilité, fonctions cognitives etc

Figure 3, Sorror et al.



Proposition d'essais rando

Thérapeutiques ciblées hors  
allo LAM âgés?

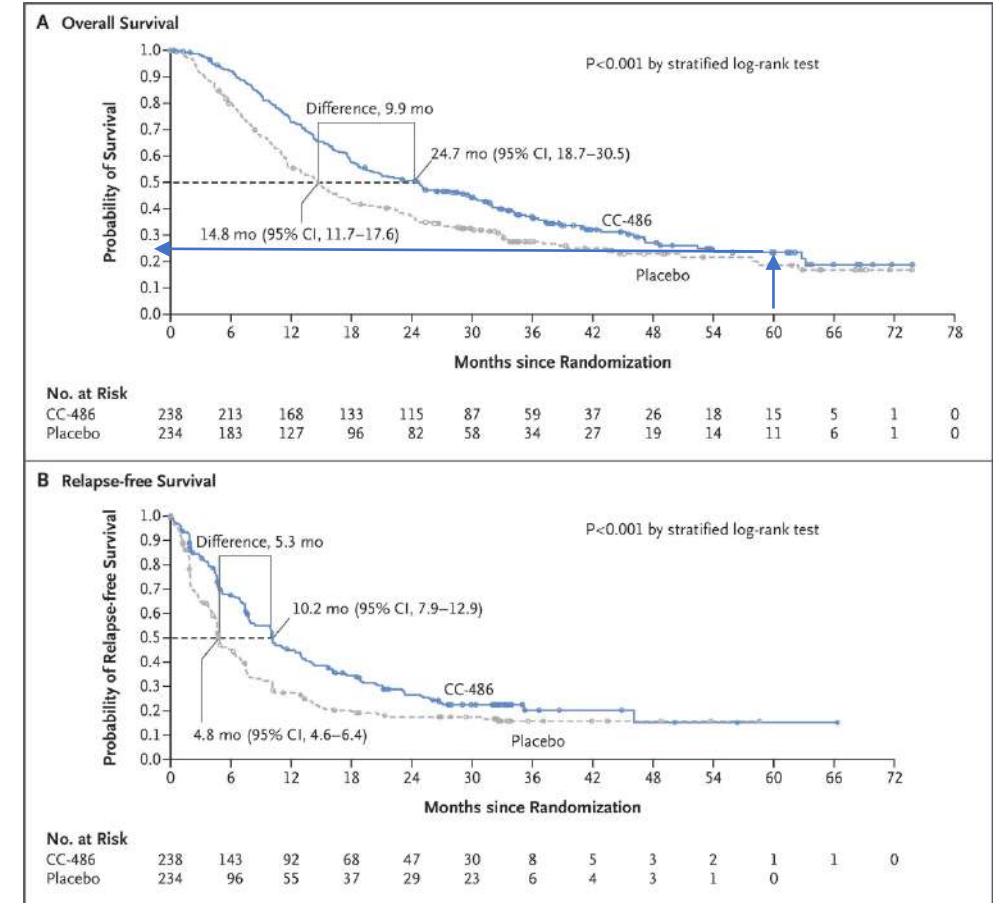
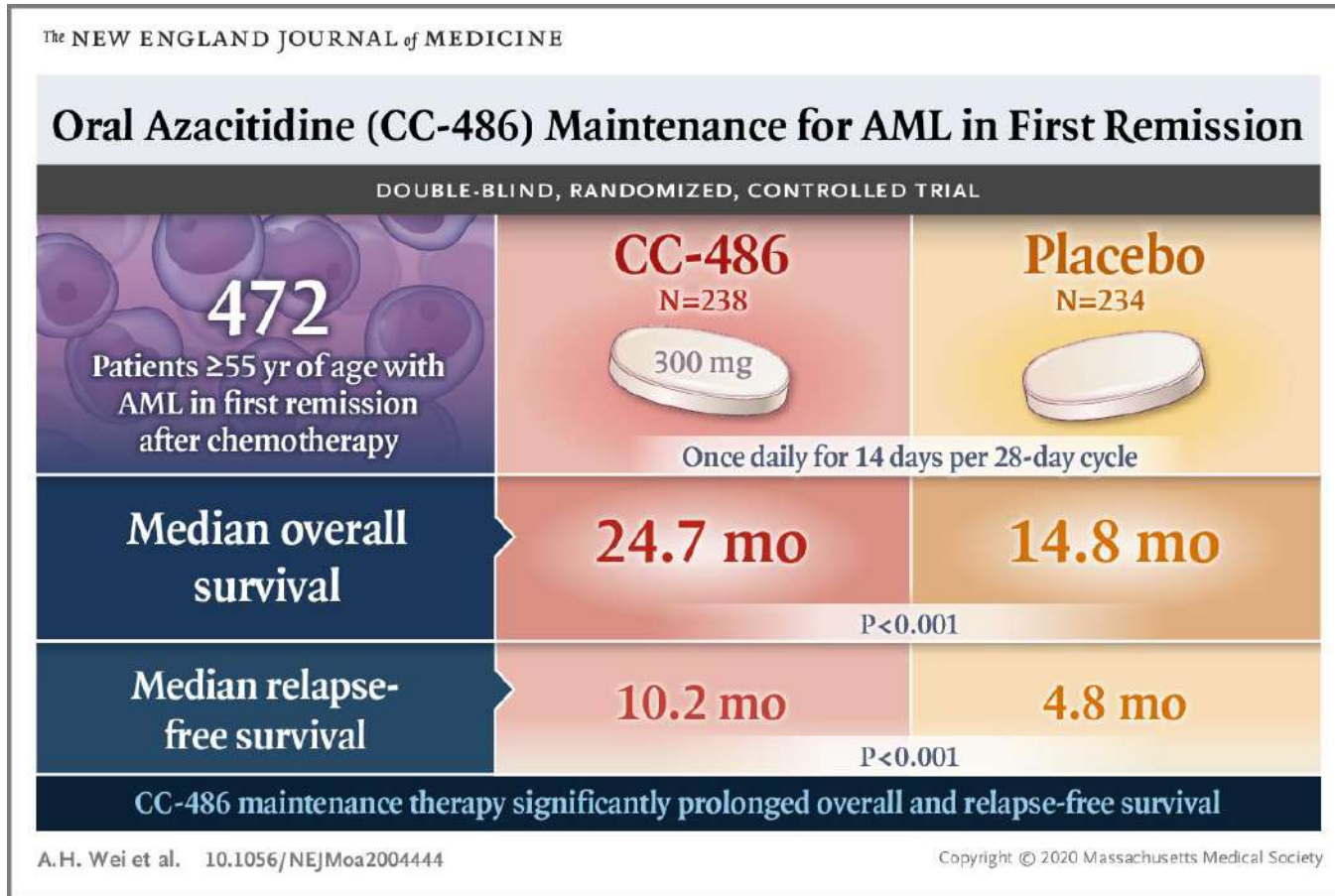
MRD?



# Oral azacitidine prolongs survival of patients with AML in remission independently of MRD status

Gail, Blood, 2022

Rappel: QUAZAR AML-001 [NCT01757535](https://clinicaltrials.gov/ct2/show/study/NCT01757535)

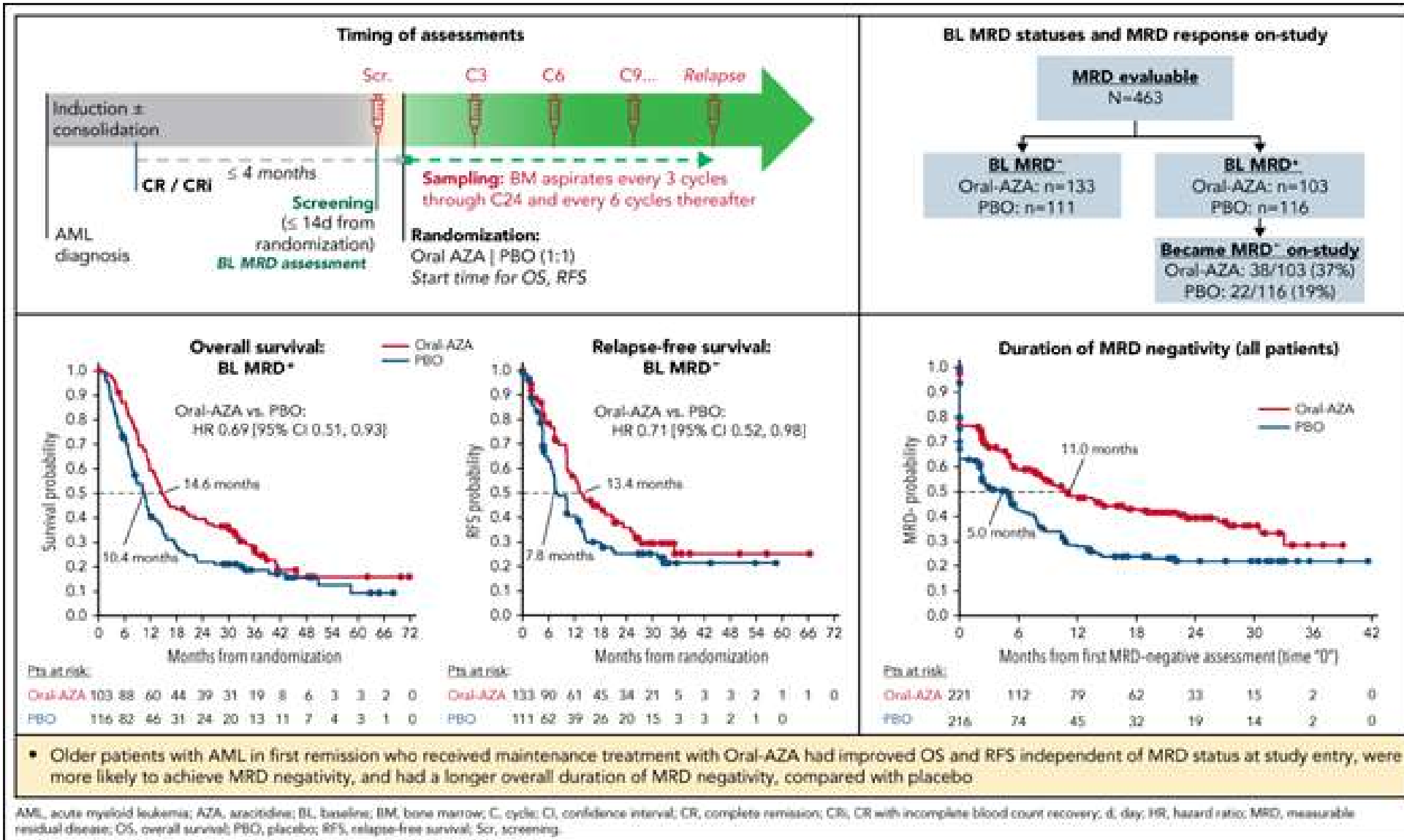


Wei, NEJM 2020



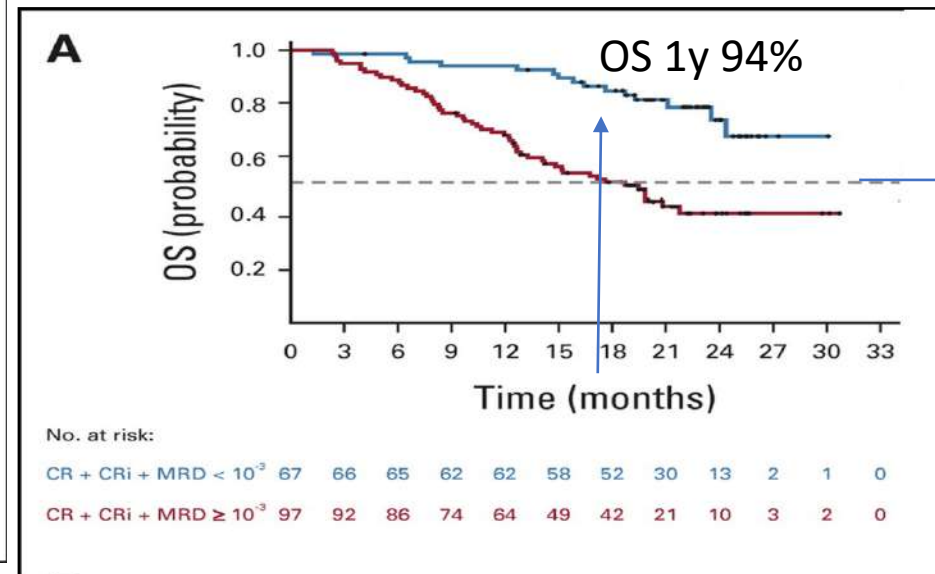
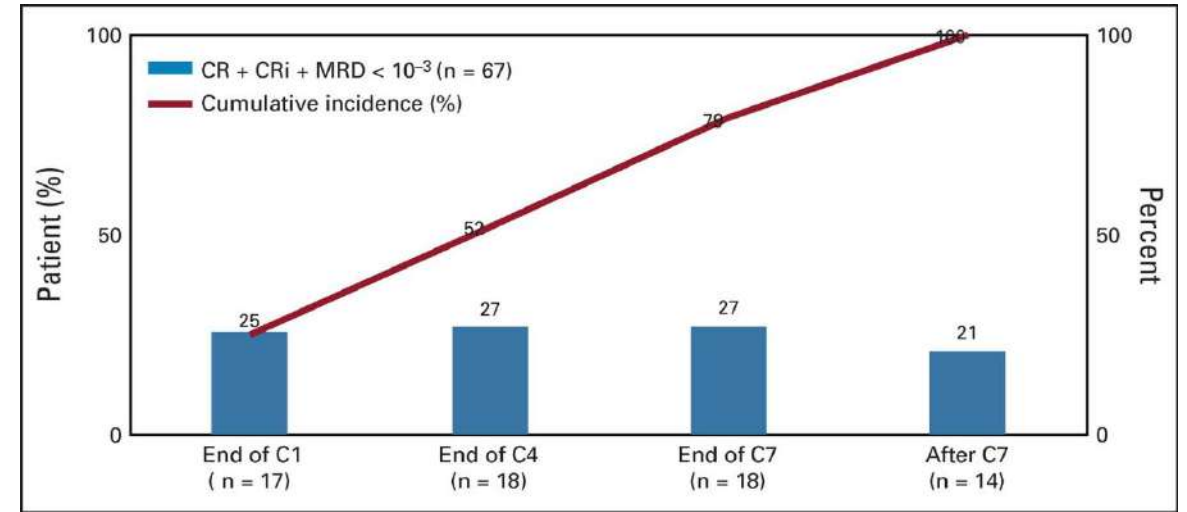
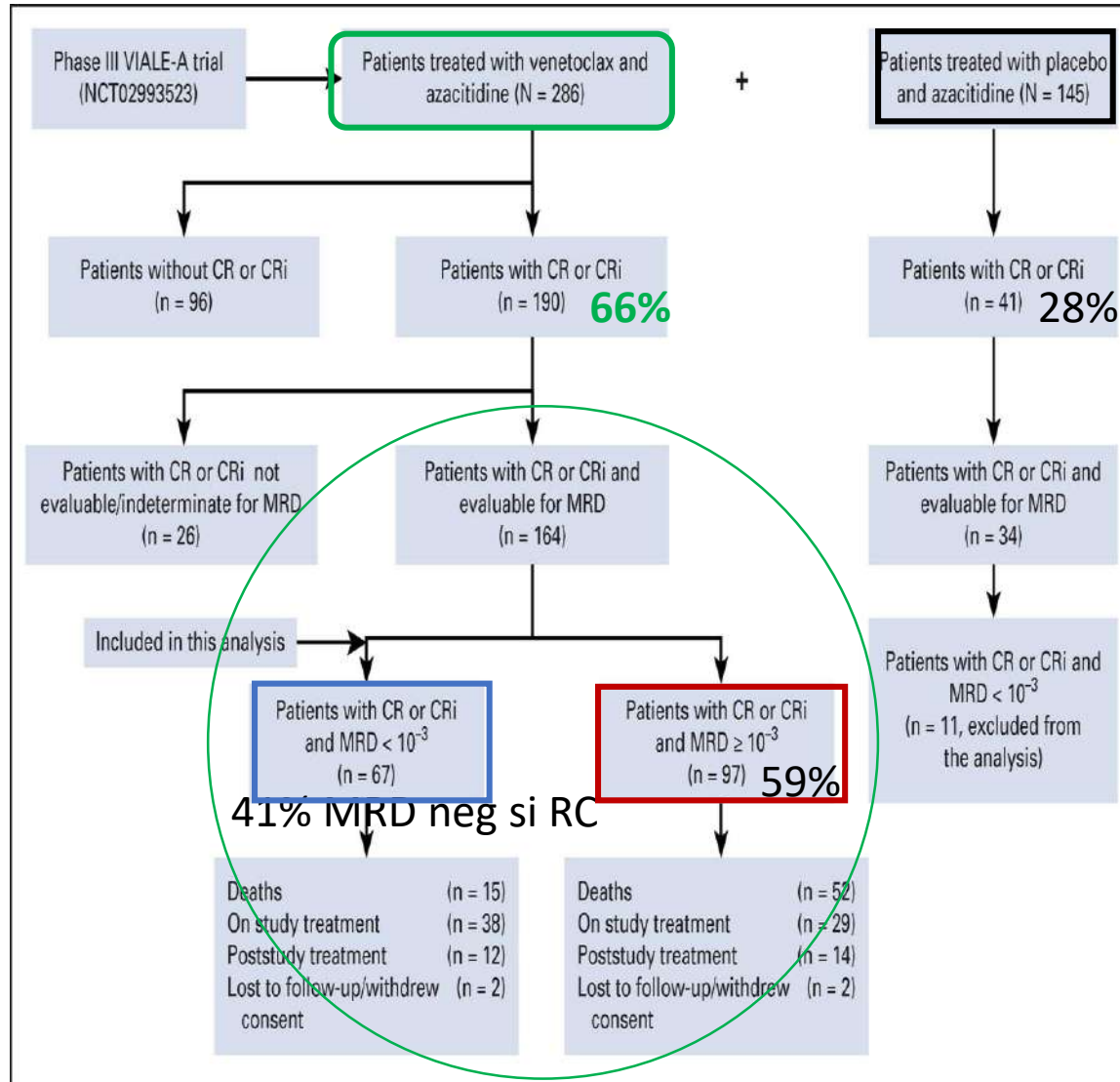
Rôle du statut MRD baseline ? Impact du CC-486 sur la MRD ?

# Oral azacitidine prolongs survival of patients with AML in remission independently of MRD status



25% of MRD responders achieved MRD negativity >6 months after starting oral-AZA

# MRD et prc des patients LAM traités par Aza-Ven (VIALE-A)



Médiane survie non atteinte si MRD neg, même cytogénétique défavo

Prc idem si MRD neg + tardive

# Phase II Triplet: Veneto + Cladribine+ AraC low dose (LDAC) en alternance avec 5-AZA, sujets âgés LAM de novo

## Induction

CLAD 5 mg/m<sup>2</sup>/j J1-5 iv

LDAC (20 mg x2/j) J1-10 ss cut

Venetoclax J1-21. 400 mg x1/j ( 100 mg si posa ou vorico)

Conso: idem sauf CLAD (5 mg/m<sup>2</sup>) J1-3

Cycles 3 and 4 : 5-AZA (75 mg/m<sup>2</sup> IV or SQ), once daily on D1-7.

Puis **alternance** 2 cycles triplet/ 2 cycles AZA jusqu'à C18

## Phase 2

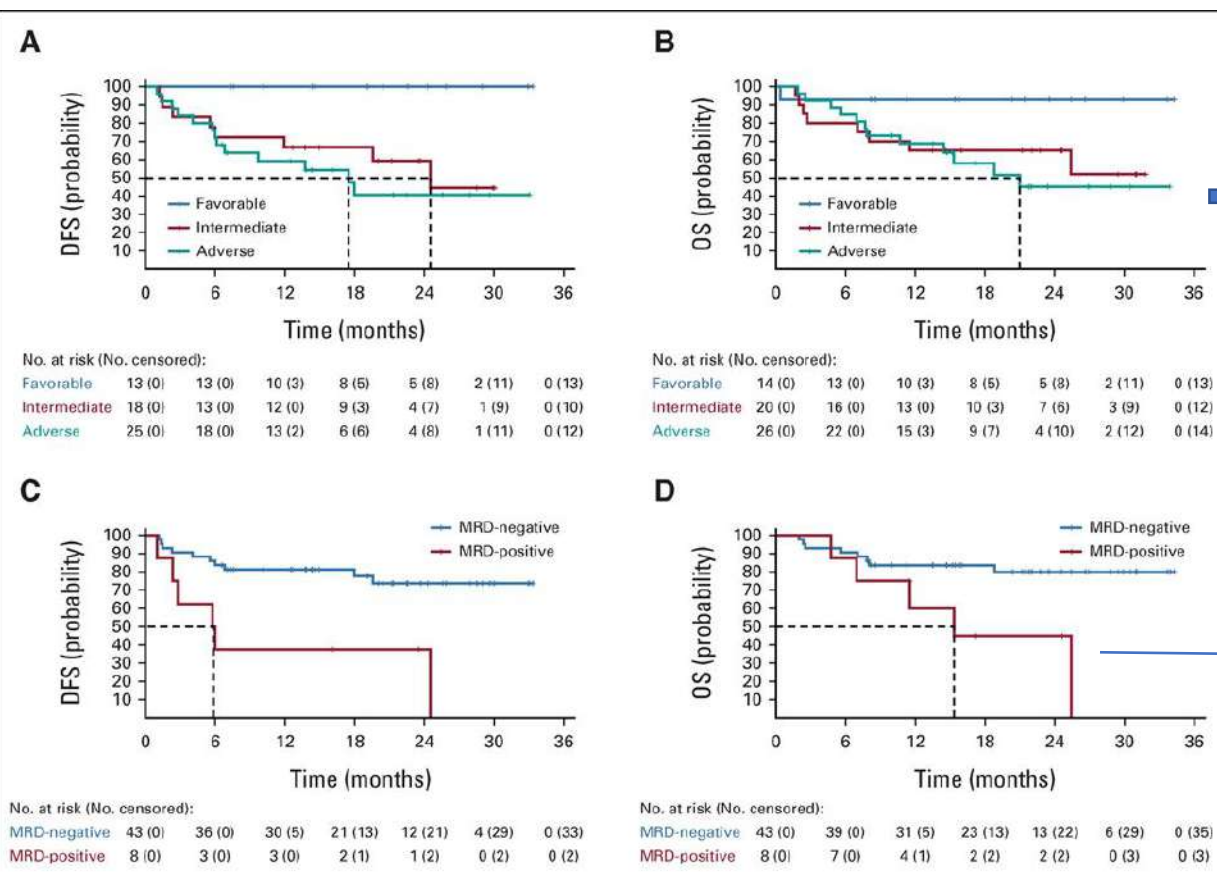
N=60 , 68 ans (57-84), LAM 33% int 43% adverse

RC 93%, MRD neg 84%

1 DC à l'induction (2%)

FU 22 mo, med OS et DFS non atteinte

50% OS 3 ans même adverse  
Intérêt allo?



Allo si MRD pos?

## Eprenetapopt (APR-246) + Azacitidine in *TP53* MDS et LAM (20-30% blastes)

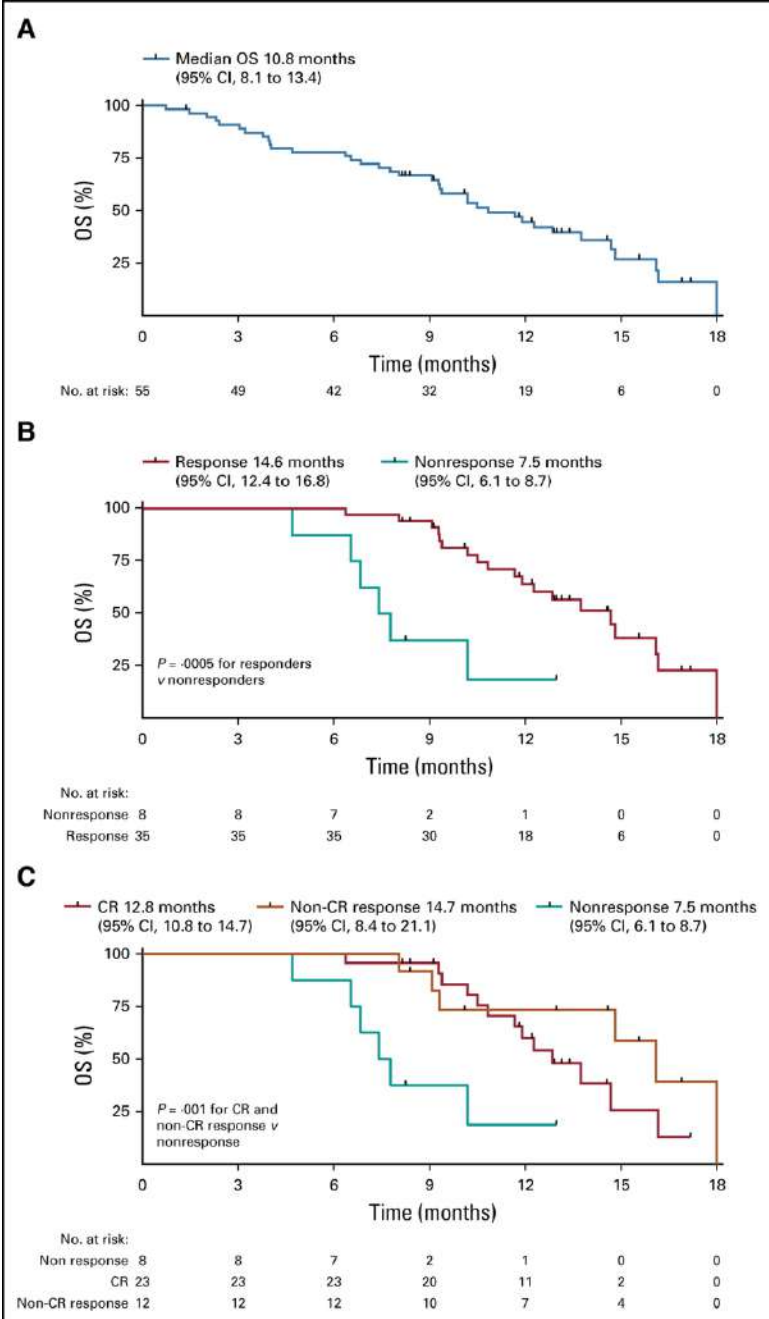
N=55 (40 MDS/11 LAM) , med 66 ans

ORR 71%, dont 44% CR et **38% avec négativation TP53**

durée med RC 7.3 mois

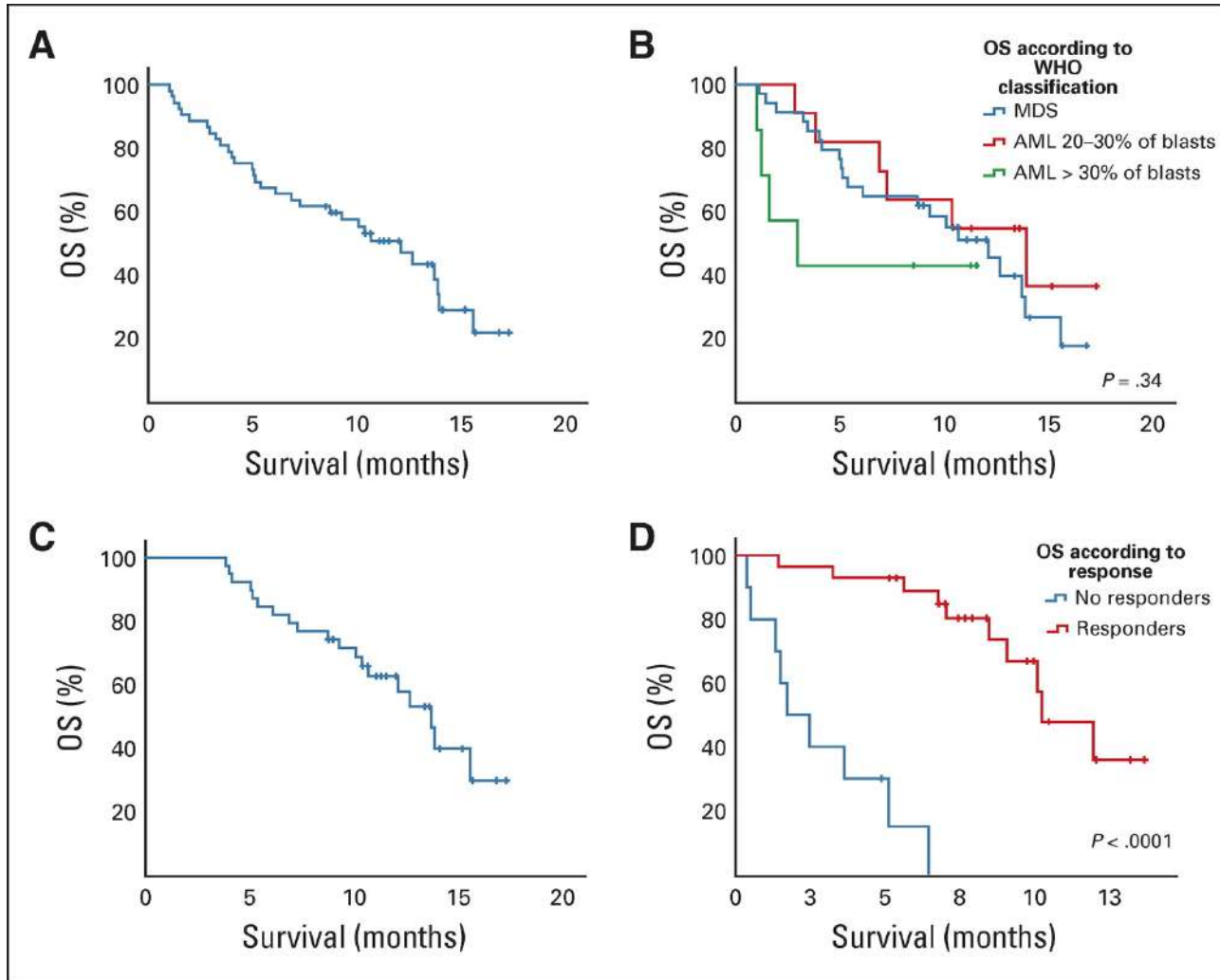


**35% allo (19/55) avec OS med 14.7 mois**  
**Pas de benefice de l'allo sur la survie**  
**Avantage si au moins 4 cycles reçus avant l'allo**





# Eprenetapopt Plus Azacitidine in *TP53*-Mutated MDS/AML : A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM)



N= 34 MDS / 18 LAM

ORR 62%  
47% CR  
Durée réponse 10 Mois

ORR 33%  
17% CR  
(27% si <30% blastes mo  
0% si >30% blastes mo)  
Durée réponse 12 Mois

34% RC , 30% NGS nég  
Meilleur OS si dim VAF<5%  
8% allogreffes

Assessed for eligibility  
(N = 84)

Excluded pre-HCT (n = 29)  
Active disease (n = 8)  
Patient/physician decision (n = 14)  
Death (n = 2)  
Other reasons (n = 5)

Received HCT  
(n = 55)

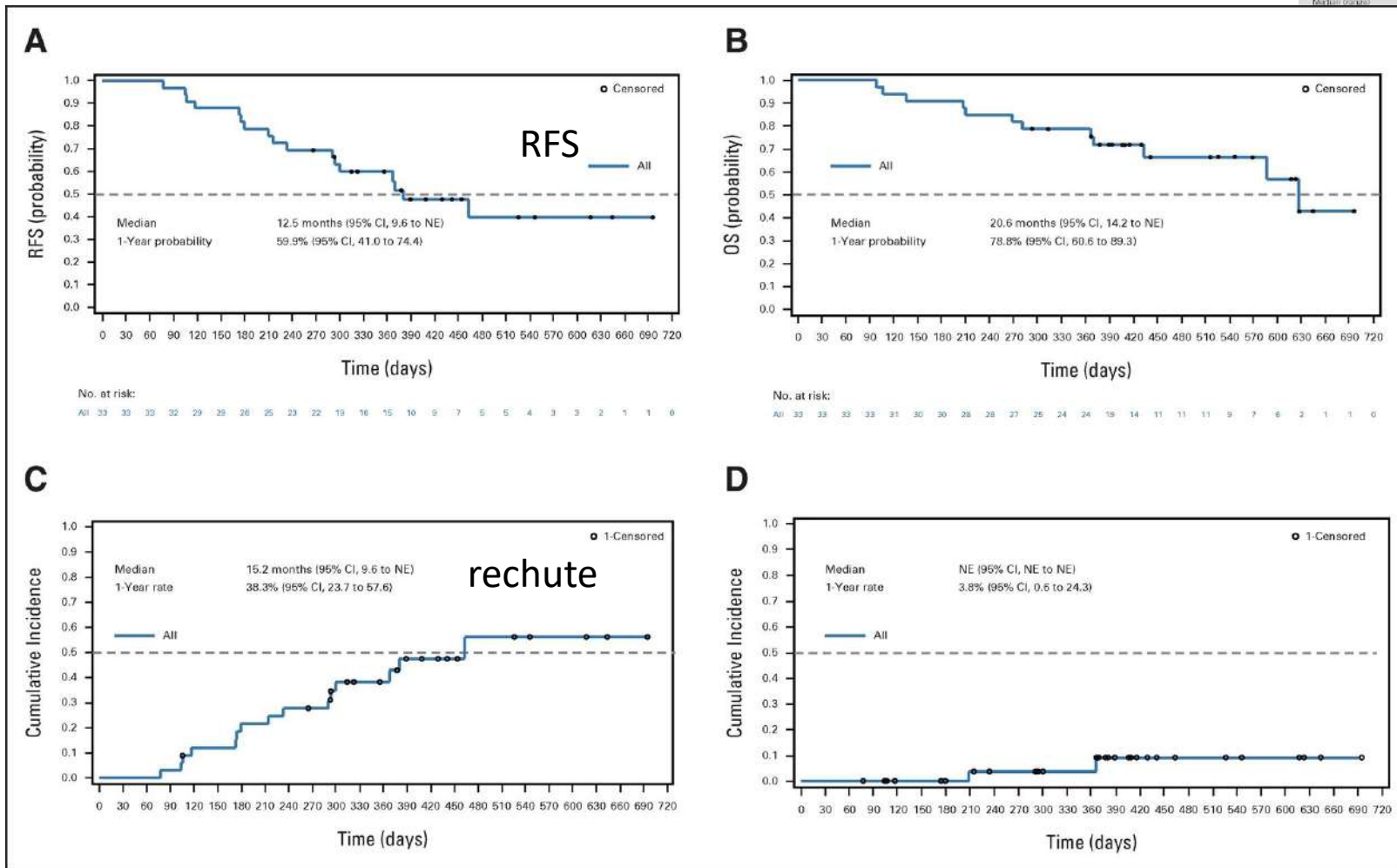
Excluded post-HCT (n = 22)  
Relapsed disease (n = 2)  
Patient/physician decision (n = 9)  
Did not meet eligibility criteria (n = 11)  
Cytopenias (n = 5)  
Organ dysfunction (n = 4)  
Other reasons (n = 2)

Received maintenance  
(n = 33)

Discontinued study (n = 11)  
Death (n = 11)  
Discontinued eprenetapopt (n = 31)  
Completed 12 planned cycles (n = 13)  
Evidence of relapse (n = 10)  
Patient refusal (n = 2)  
Physician decision (n = 2)  
Patient decision (n = 2)  
Adverse event (n = 1)  
Unacceptable toxicity (n = 1)  
Discontinued azacitidine (n = 31)  
Completed 12 planned cycles (n = 13)  
Evidence of relapse (n = 10)  
Physician decision (n = 3)  
Patient refusal (n = 2)  
Patient decision (n = 2)  
Unacceptable toxicity (n = 1)

Analyzed  
(n = 33)

# Eprenetapopt Plus Azacitidine After Allogeneic Hematopoietic Stem-Cell Transplantation for *TP53*-Mutant Acute Myeloid Leukemia and Myelodysplastic Syndromes



Not reported	1 (3)
Hispanic or Latino ethnicity, No. (%)	
Yes	1 (3)
No	17 (52)
Not specified	15 (45)
Karnofsky performance status, No. (%)	
≥ 90	12 (36)
≤ 70 to < 90	21 (64)
Received HMA any time before HCT, No. (%)	
Yes	26 (79)
No	7 (21)
Received induction chemotherapy before HCT, No. (%)	
Yes	12 (36)
No	23 (64)
No. of prior chemotherapies received	
Median (range)	1 (0-4)

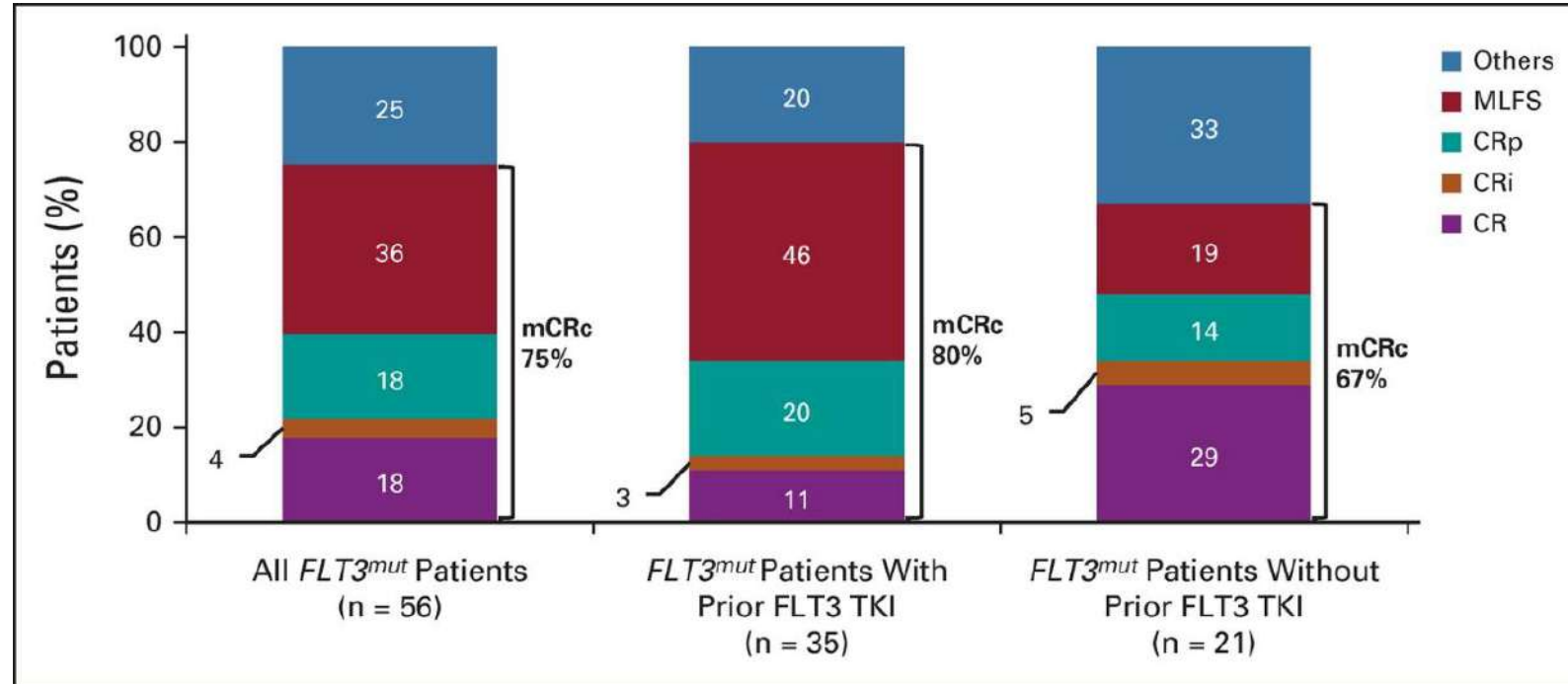
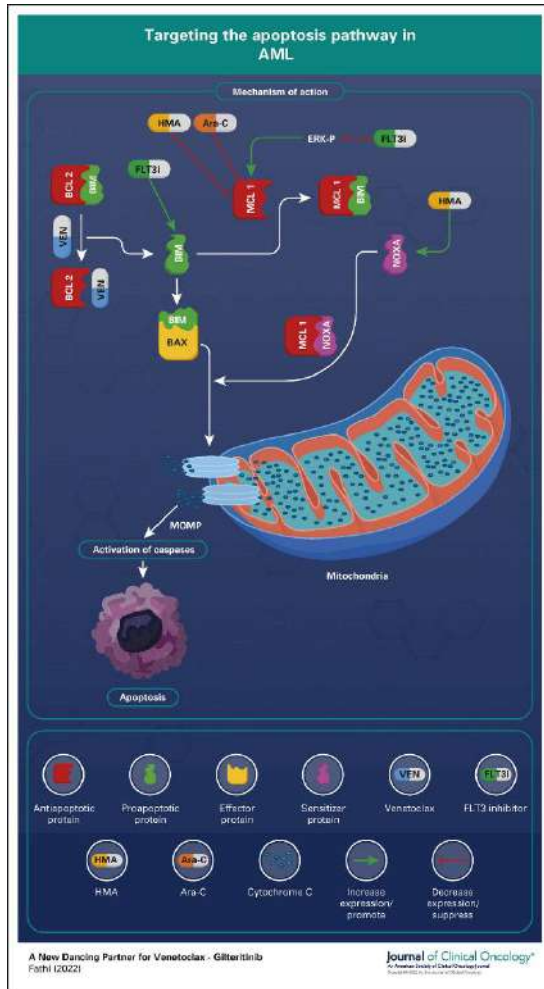
	21 (64)
	6 (18)
	3 (9)
	3 (9)
	22 (67)
	11 (33)
	4 (12)
	18 (55)
	5 (15)
	6 (18)
	31 (94)
	2 (6)
	19 (58)
days	58 (41-74)
	19 (44-53)
	24 (73)
	7 (21)
	2 (6)
CT by the	24 (83)
	9 (31)
	13 (45)
T (reasoning for	19 (58)
	9 (27)
	4 (12)
	1 (3)
y (pre-HCT	22 (5 (5-7)

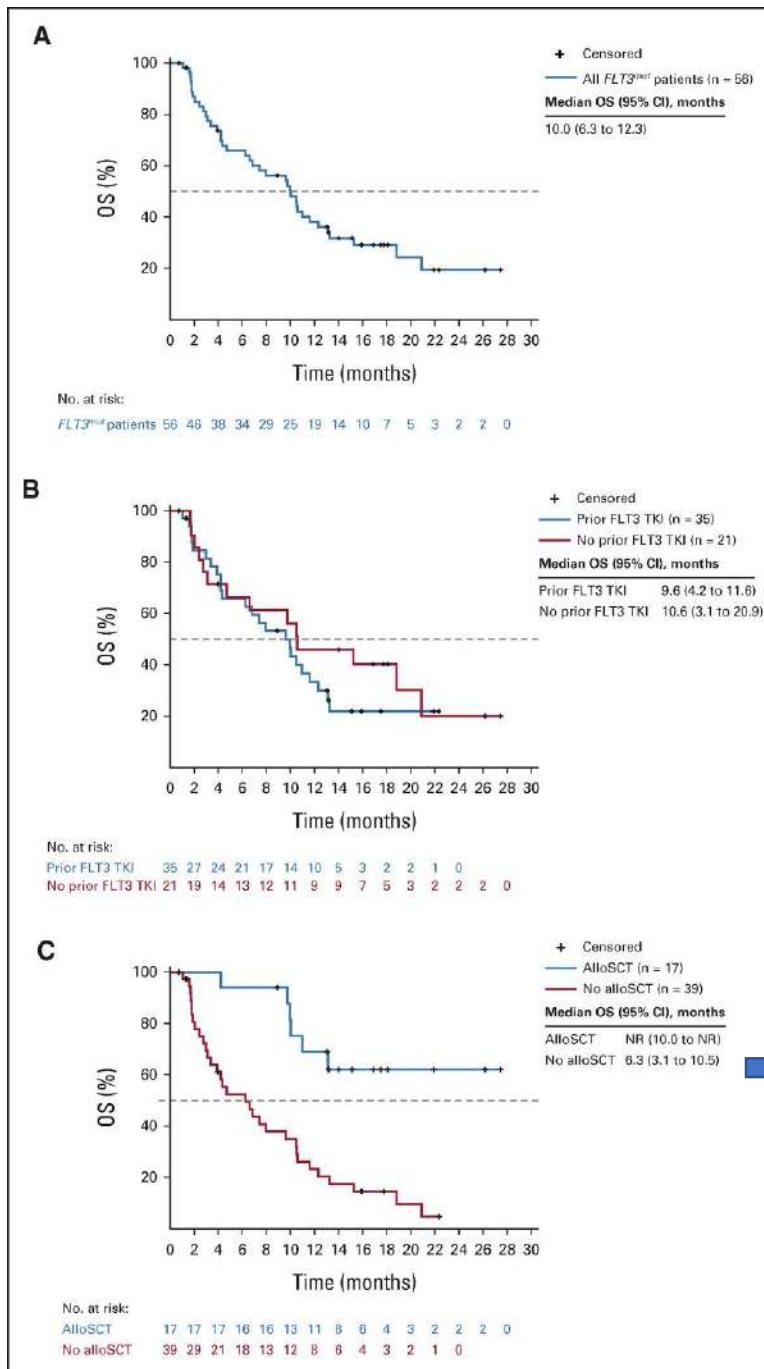




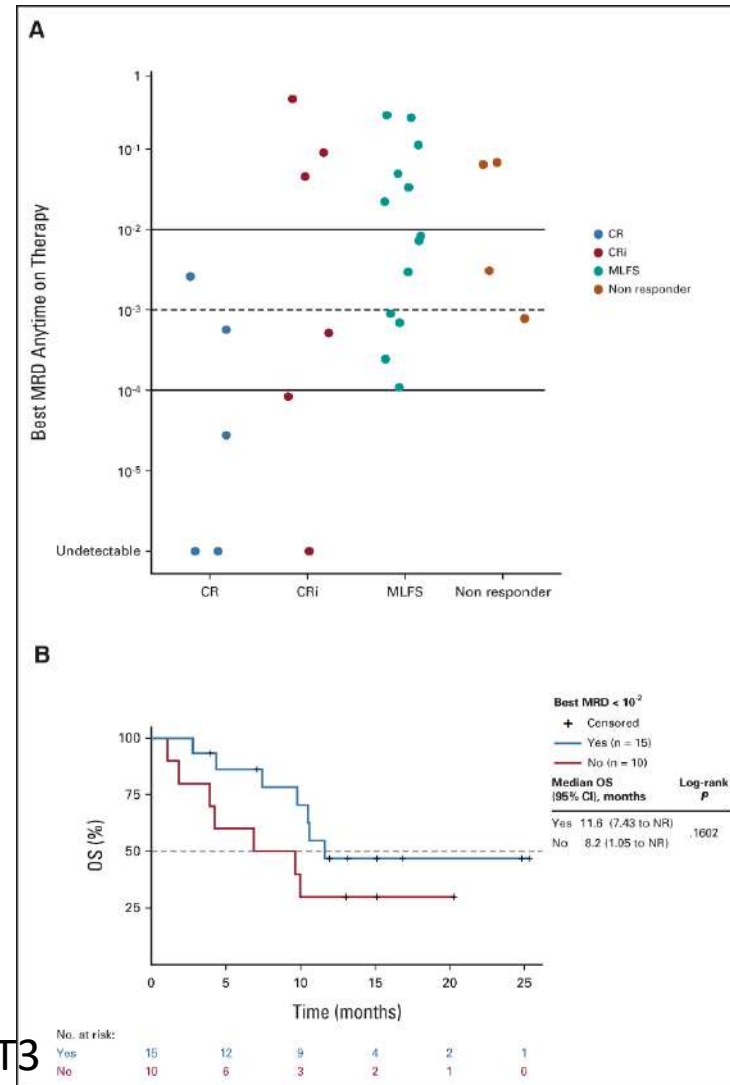
# A New Dancing Partner for Venetoclax: Gilteritinib

# Venetoclax Plus Gilteritinib for *FLT3*-Mutated Relapsed/Refractory Acute Myeloid Leukemia



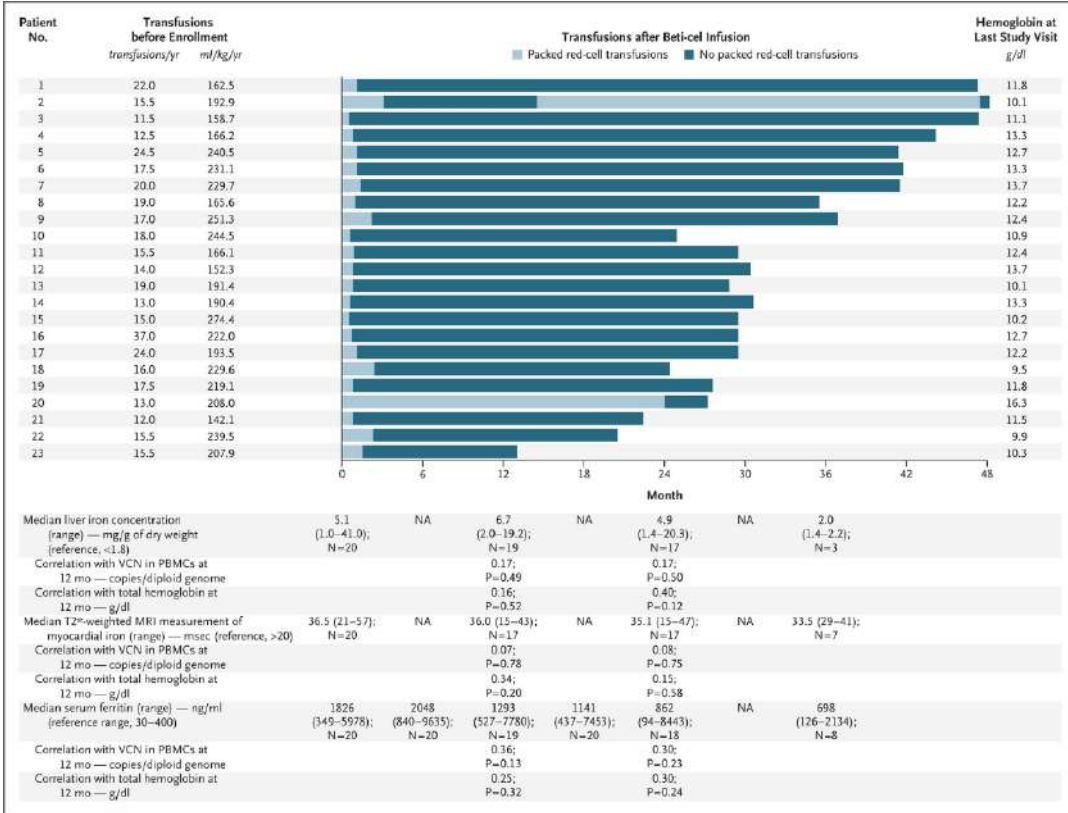


Grand bénéfice de l'allogreffe LAM FLT3 R/R rattrapée par Gilter venetocla



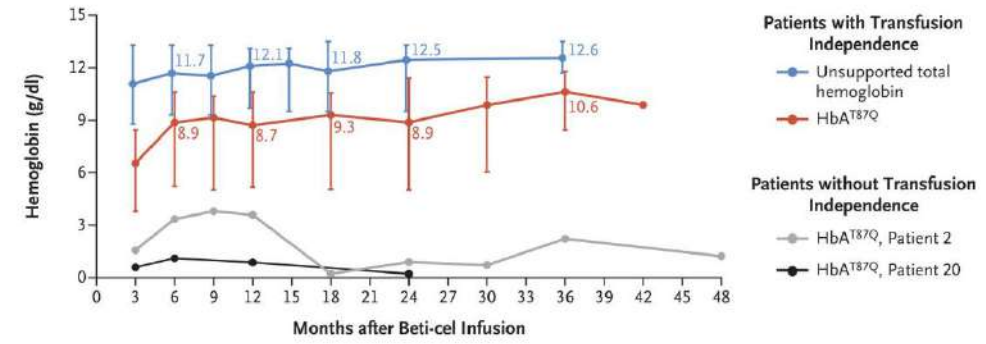
# Thérapie génique et Hémoglobinopathies

# Betibeglogene Autotemcel Gene Therapy for Non- $\beta^0/\beta^0$ Genotype $\beta$ -Thalassemia



Locatelli NEJM

A



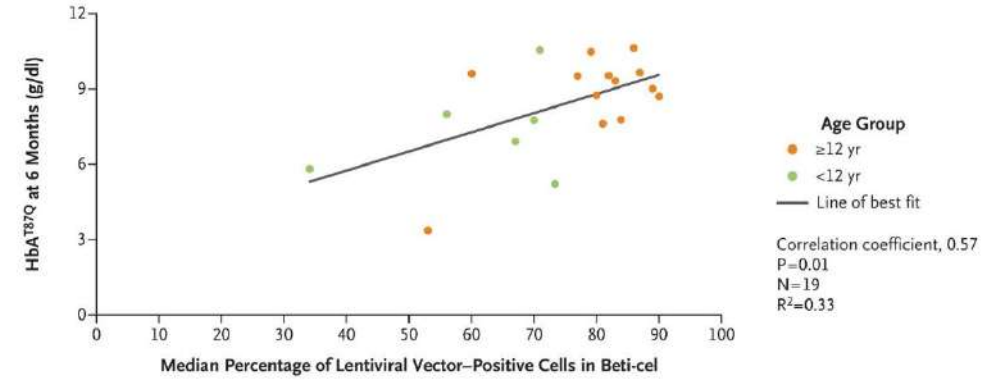
Patients with Transfusion Independence

Unsupported total hemoglobin	12	20	20	19	18	17	NR	8	NR	NR
HbA <sup>T87Q</sup>	20	18	20	20	19	18	11	7	2	NR

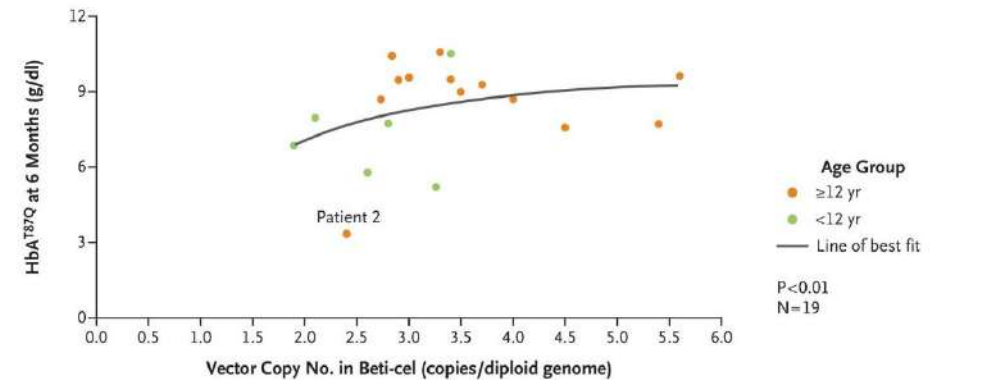
Patients without Transfusion Independence

HbA <sup>T87Q</sup>	2	2	1	2	1	2	1	1	NR	1
---------------------	---	---	---	---	---	---	---	---	----	---

B



C



# Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

THE NEW ENGLAND JOURNAL OF MEDICINE  
RESEARCH SUMMARY

## Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

Kanter J et al. DOI: 10.1056/NEJMoa2117175

### CLINICAL PROBLEM

Patients with sickle cell disease often have vaso-occlusive events, progressive vasculopathy, and chronic hemolytic anemia, which are associated with an increased risk of complications and early death. HLA-matched sibling allogeneic hematopoietic stem-cell (HSC) transplantation is one treatment option, but its potential use is limited. Gene therapy with lentiviral gene autotransfer (LentiGlobin) — consisting of autologous transplantation of hematopoietic stem and progenitor cells transduced with a lentiviral vector encoding a modified  $\beta$ -globin gene, resulting in the production of the antickling hemoglobin HbA<sup>T87Q</sup> — presents another therapeutic option.

### CLINICAL TRIAL

**Design:** An unpre-specified interim analysis of a phase 1-2 trial evaluated the efficacy and safety of LentiGlobin in patients with sickle cell disease.

**Intervention:** 35 patients received a single infusion of LentiGlobin and were followed for up to 36 months. Efficacy outcomes included levels of total hemoglobin, HbA<sup>T87Q</sup>, and hemolysis markers and the incidence of vaso-occlusive events.

### RESULTS

**Efficacy:** During a median follow-up of 12.3 months, median total hemoglobin increased and HbA<sup>T87Q</sup> expression was observed in most red cells. Markers of hemolysis were reduced overall. Among 25 patients who met criteria for evaluation of vaso-occlusive events, 3 had events after infusion; there were no severe events, a reduction from the rate during the 2 years before infusion.

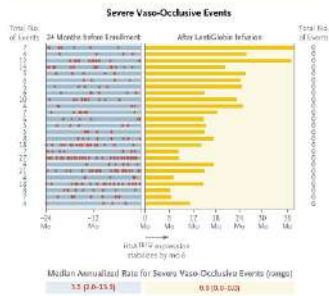
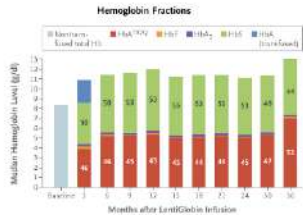
**Safety:** One third of patients had serious adverse events after infusion, the most frequent were abdominal pain, drug withdrawal syndrome, nausea, and vomiting. In 3 patients, adverse events were judged to be related to LentiGlobin infusion.

### LIMITATIONS AND REMAINING QUESTIONS

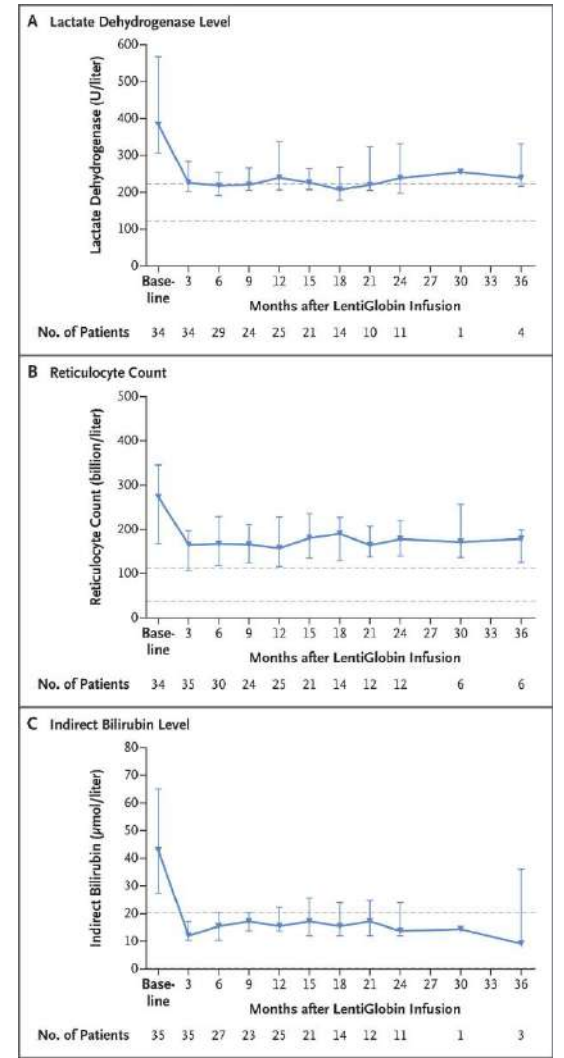
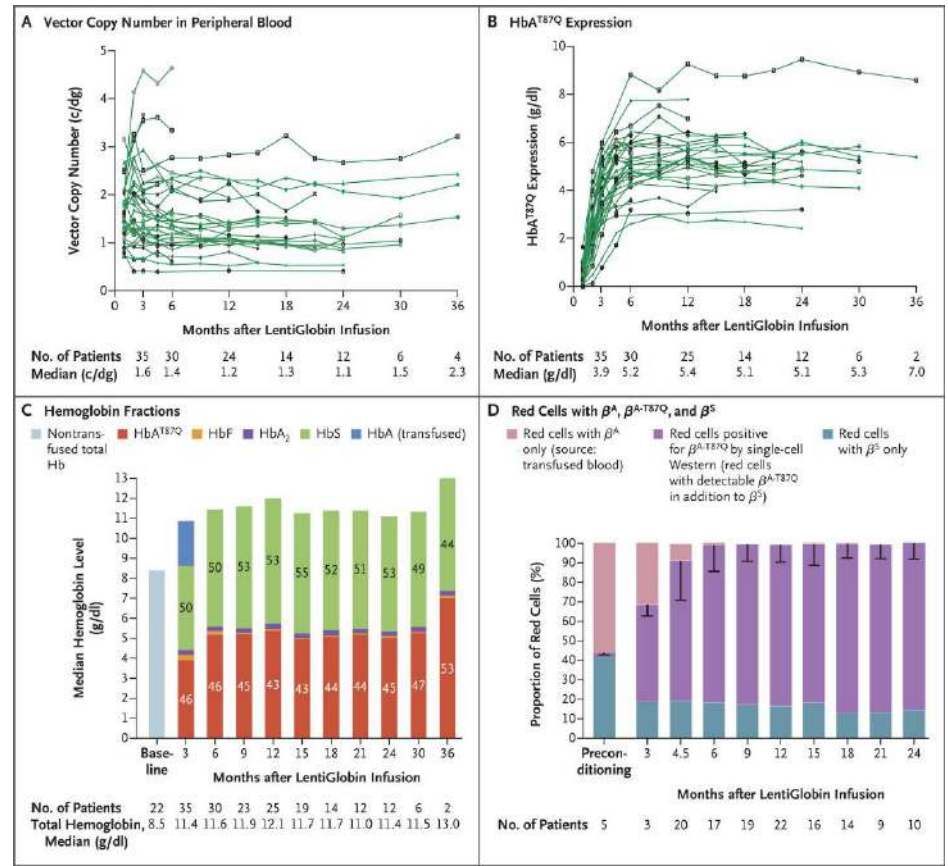
Limitations of the study include the following:

- The small number of patients
- Limited duration of follow-up
- The lack of a control group

Links: Full Article | NEJM Quick Take | Editorial



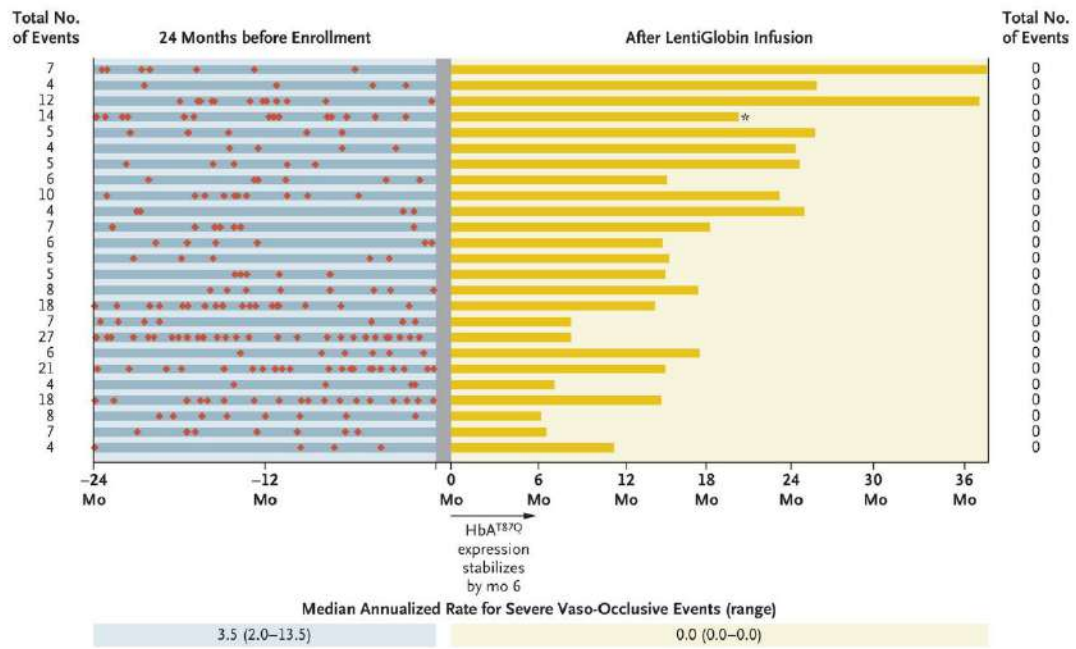
**CONCLUSIONS**  
One-time gene therapy with LentiGlobin resulted in sustained production of the antickling hemoglobin HbA<sup>T87Q</sup> in patients with sickle cell disease.



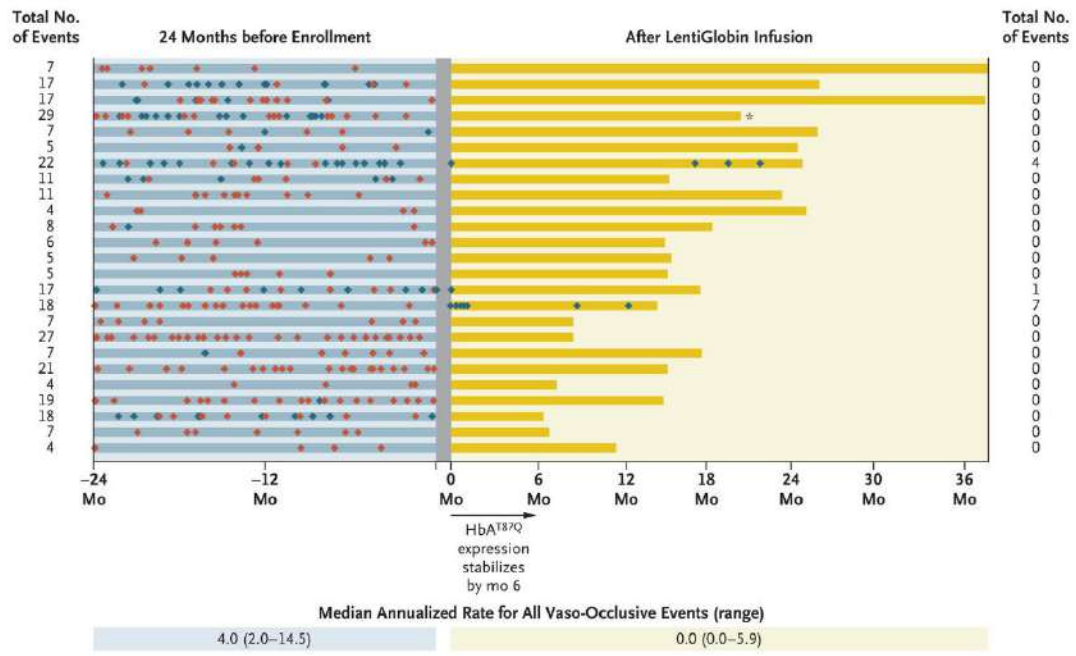


◆ Severe vaso-occlusive event    ◆ All other vaso-occlusive events

**A Severe Vaso-Occlusive Events**



**B All Vaso-Occlusive Events**



Efficacité +++ sur les évènements vaso occlusifs

CAR-T

*Autogrefe vs CART en 2de ligne DLBCL?*

# TRANSFORM

Rando

N=92 SOC  
3 chimio puis auto  
si reponse

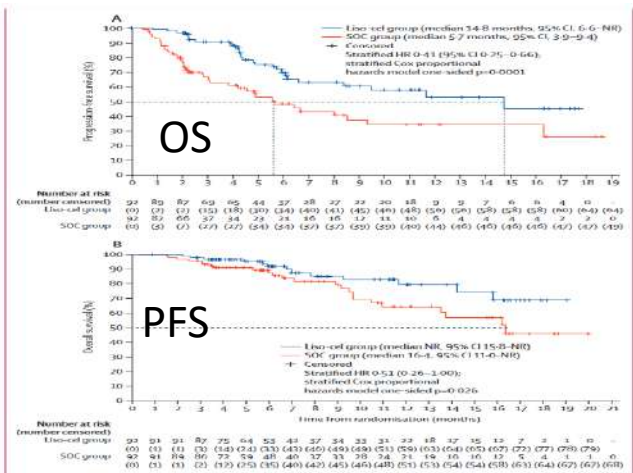
92 CART  
Liso-cell

46 liso-cel  
3ieme ligne

Auto pour 46% (N=42)

CART 98% (n=90)

ORR	48%	vs	86%
RC	39%	vs	66%
EFS 6mo	33%	vs	66%
OS 1y	64%	vs	80%



Kamdar, Lancet 2022

# Zuma 7

Randomisation

N=179 SOC  
3 chimio puis autogreffe si RC

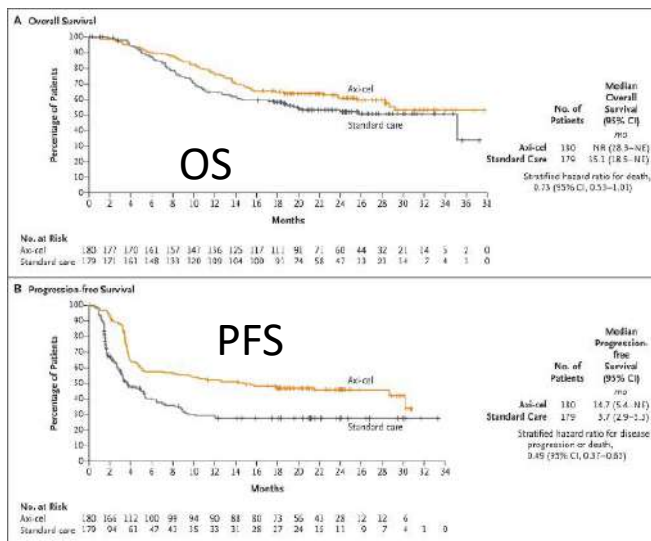
N=180 CART  
Axi-cell

Certains ref  
ont reçu des  
CART

Auto pour 1/3  
(n=62)

CART pour la  
majorité  
(n=170)

ORR	50%	vs	83%
RC	32%	vs	65%
EFS 2y	16%	vs	41%
OS 2y	52%	vs	61%



Locke, NEJM 2022

# BELINDA

Rando

N=160 SOC  
3 chimio puis auto  
si reponse

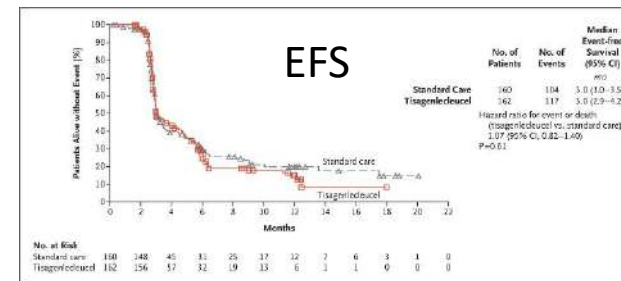
162 CART  
Tisa-cell

81 Tisa-cel  
3ieme ligne

Auto pour 1/3 (N=52)

CART 96% (n=155)

ORR	46%	vs	42%
RC	27%	vs	28%
EFS med	3 mois	vs	3 mois



Bishop NEJM 2022

CART > auto  
2de ligne

CART = auto  
2de ligne



## Comparaison Zuma 7 et BELINDA?

### ZUMA-7 (Axi-cel)

Seul bridge autorisé: corticoïdes

Maladie moins progressive

1/3 auto , 1 seule ligne chimio autorisée

Temps leukapherese/injection court: 13 jours

9% DLBCL type ABC

### BELINDA (Tisa-cel)

N'importe quel bridge (83%)

26% maladie progressive aux CART

1/3 auto alors que 2 lignes autorisées: patients + graves

Temps leukapherese/injection long: 52 jours  
(wash out après le bridge, COVID, centres non US..)

32% DLBCL type ABC (+ mauvais prc)

CART-T en 2de ligne préférable chez patients avec DLBCL pas trop agressif

Axi-cel + efficace que Tisa-cel?

OPEN

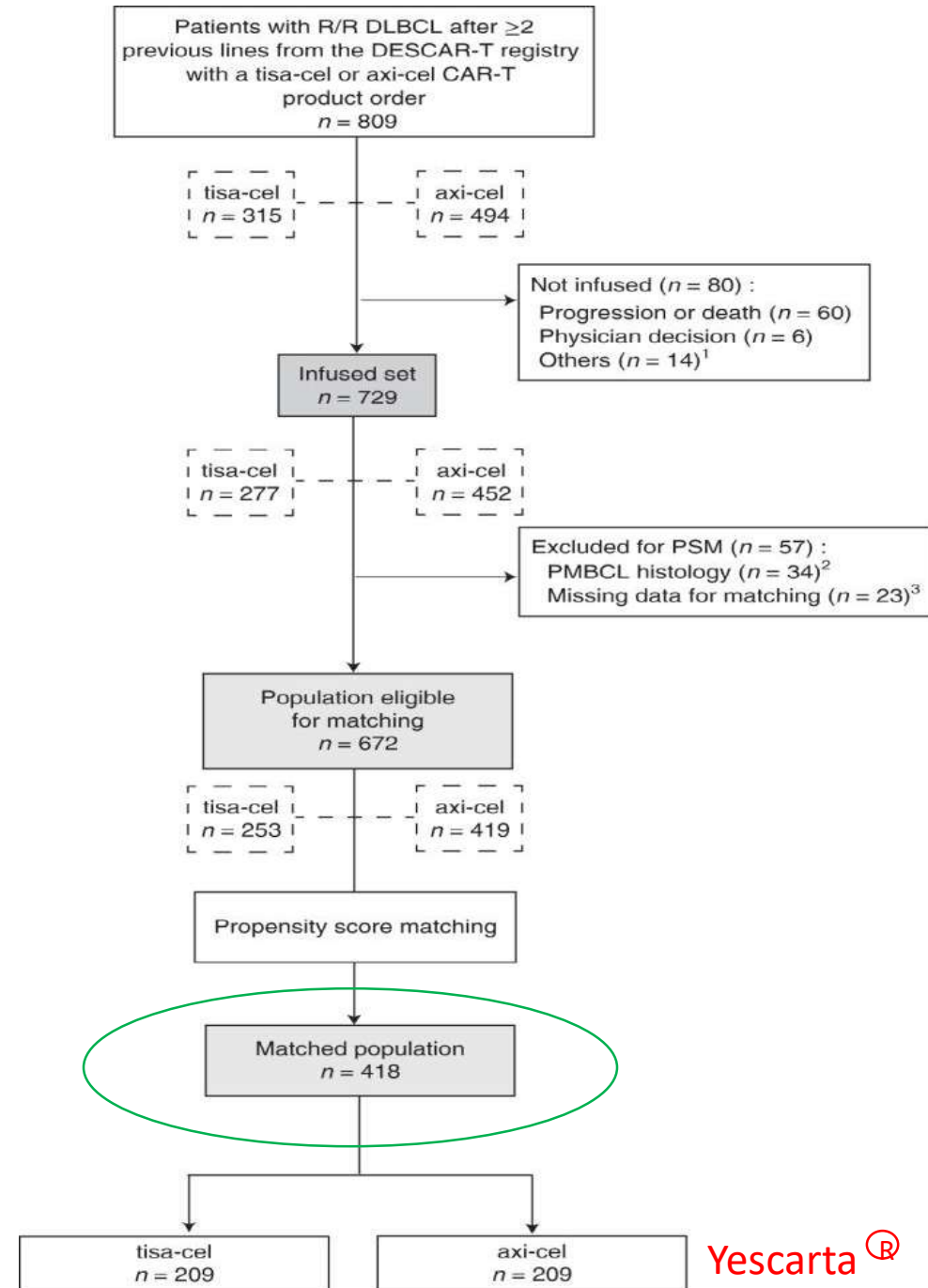
# A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma

Emmanuel Bachy<sup>1,2</sup>, Steven Le Gouill<sup>3</sup>, Roberta Di Blasi<sup>4</sup>, Pierre Sesques<sup>1</sup>, Guillaume Manson<sup>5</sup>, Guillaume Cartron<sup>6</sup>, David Beauvais<sup>7</sup>, Louise Roulin<sup>8</sup>, François Xavier Gros<sup>9</sup>, Marie Thérèse Rubio<sup>10</sup>, Pierre Bories<sup>11</sup>, Jacques Olivier Bay<sup>12</sup>, Cristina Castilla Llorente<sup>13</sup>, Sylvain Choquet<sup>14</sup>, René-Olivier Casasnovas<sup>15</sup>, Mohamad Mohty<sup>16</sup>, Stéphanie Guidez<sup>17</sup>, Magalie Joris<sup>18</sup>, Michaël Loschi<sup>19</sup>, Sylvain Carras<sup>20</sup>, Julie Abraham<sup>21</sup>, Adrien Chauchet<sup>22</sup>, Laurianne Drieu La Rochelle<sup>23</sup>, Bénédicte Deau-Fischer<sup>24</sup>, Olivier Hermine<sup>25</sup>, Thomas Gastinne<sup>26</sup>, Jean Jacques Tudesq<sup>5</sup>, Elodie Gat<sup>27</sup>, Florence Broussais<sup>28</sup>, Catherine Thieblemont<sup>4</sup>, Roch Houot<sup>5</sup> and Franck Morschhauser<sup>7,29</sup>

CART-T commerciaux dans le cadre de l'AMM  
DLBCL à partir de la 3ieme ligne  
Registre DESCART

Follow up med 1 an

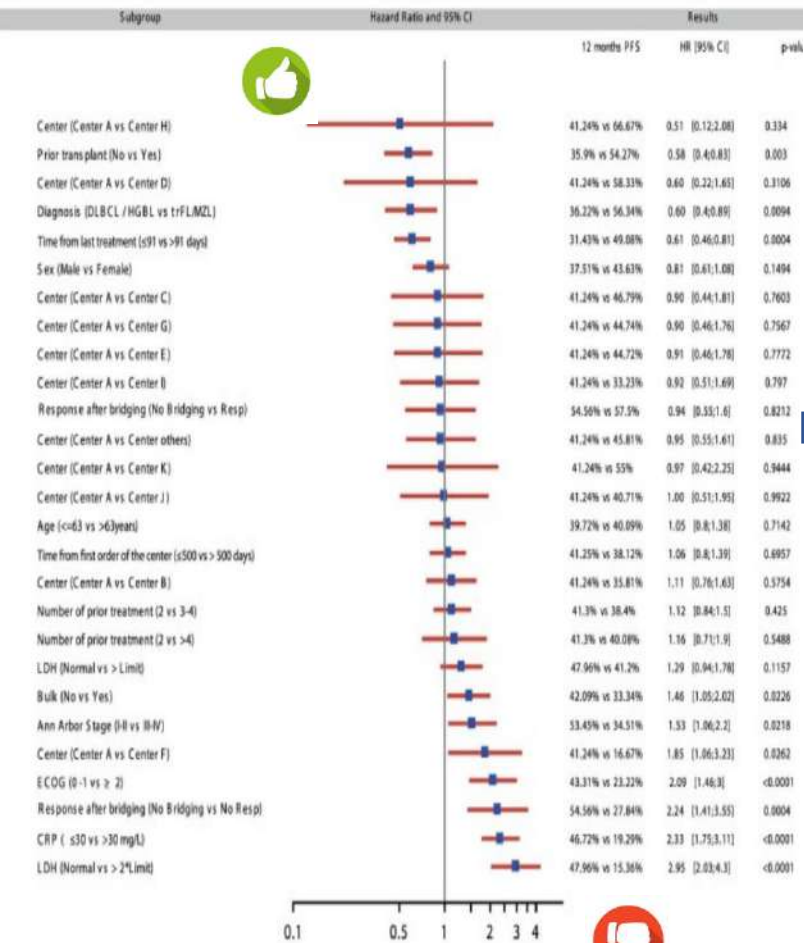
(NCT04328298)



Kymriah®

Yescarta®

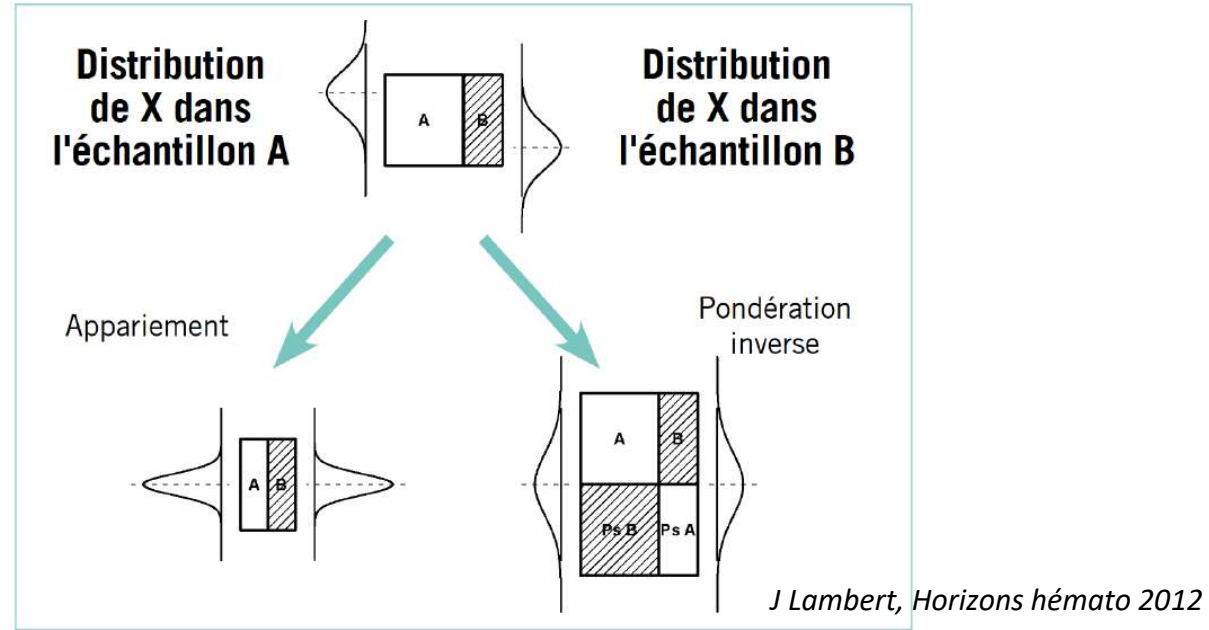
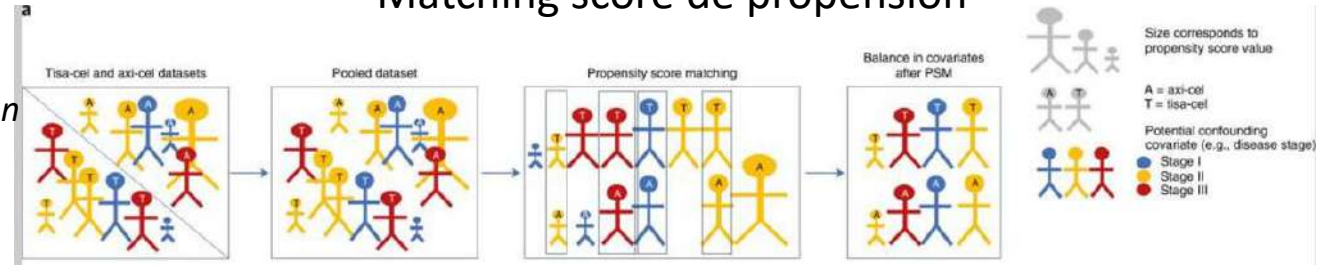
# Univarié



Score de propension: probabilité de recevoir un traitement conditionné par les facteurs de confusions

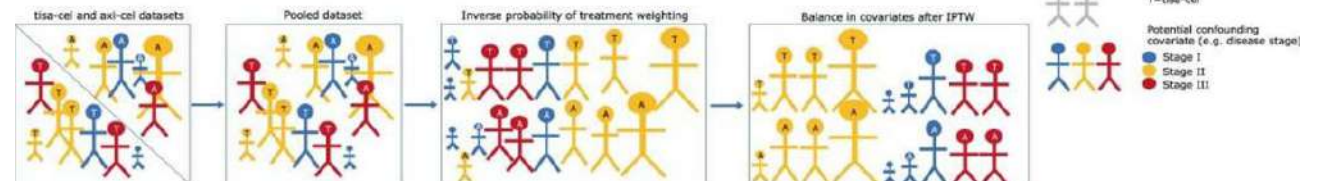
14 variables de confusion (X)

# Matching score de propension



# IPTW, Inverse probability treatment weighting

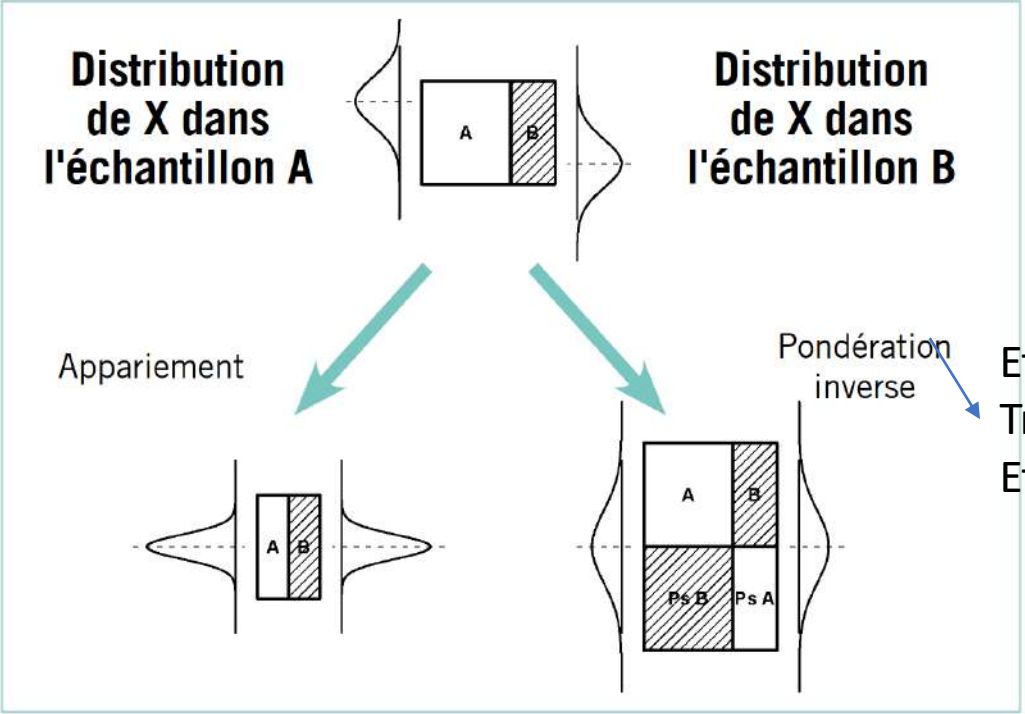
pondérer les observations par l'inverse de la probabilité de recevoir le traitement effectivement reçu



(IPW, pour Inverse Probability Weighting)

Les deux méthodes visent à obtenir une répartition identique de la covariable X entre les deux groupes

Merci Jordan!



l'effet moyen du traitement chez les traités (ou Average Treatment effect for the Treated : ATT) (proche essai rando)

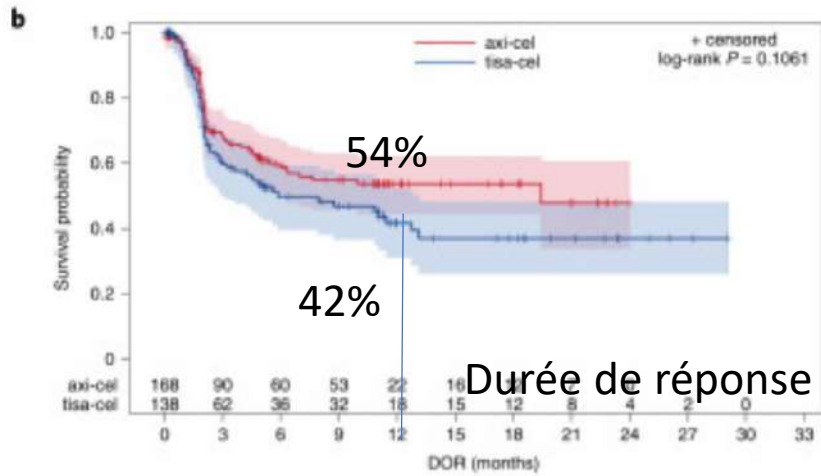
Effet moyen sur toute la population ou Treatment Effect : ATE)

J Lambert, Horizons héματο 2012

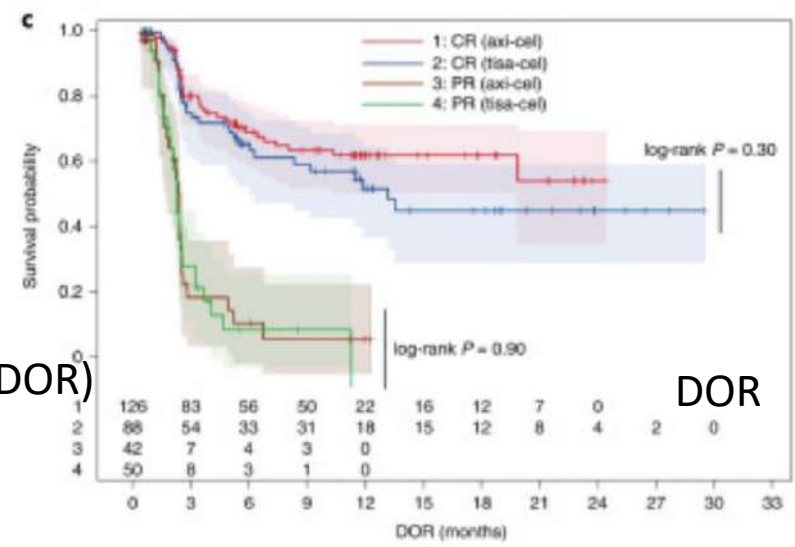
Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants

Allan, J comp eff res; 2020 doi: 10.2217

# Survie selon le CAR-T et après matching par le score de propension

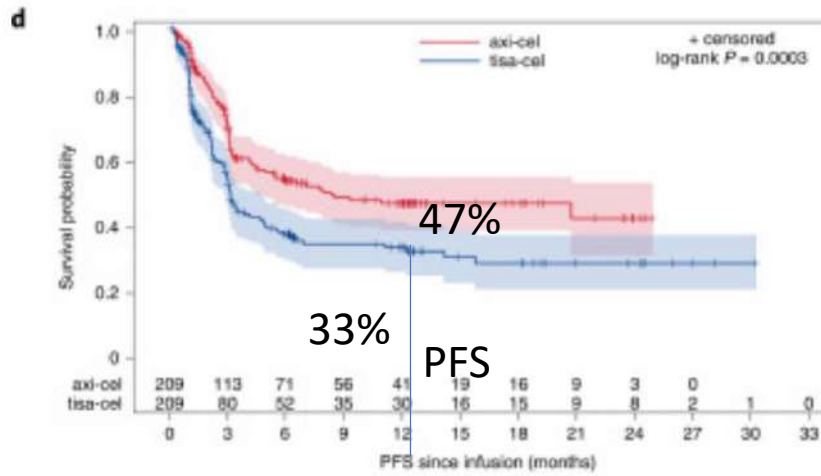


	No. of patients	Event	Censored	Median survival (95% CI)
axi-cel	188	37.5% (83)	62.5% (105)	19.4 (8.3 ; NA)
tisa-cel	138	43.5% (90)	56.5% (78)	5.8 (3 ; 13.1)

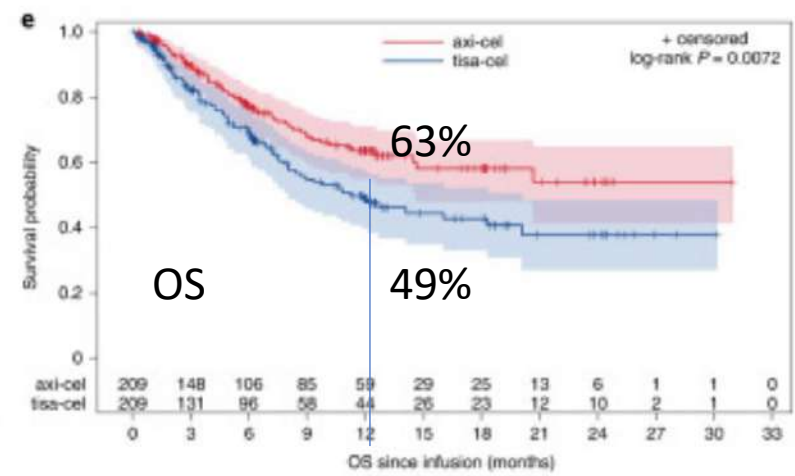


+ de CRS peu graves  
+ grade ≥3 ICANS.  
(14% axi vs 4% tisa)

**Axi-cel > Tisa-Cell  
+ efficace , + Toxique (ICANS)**



	No. of patients	Event	Censored	Median survival (95% CI)
axi-cel	209	43.1% (90)	56.9% (119)	8.2 (4.4 ; NA)
tisa-cel	209	55.5% (116)	44.5% (93)	3.1 (2.8 ; 4.1)



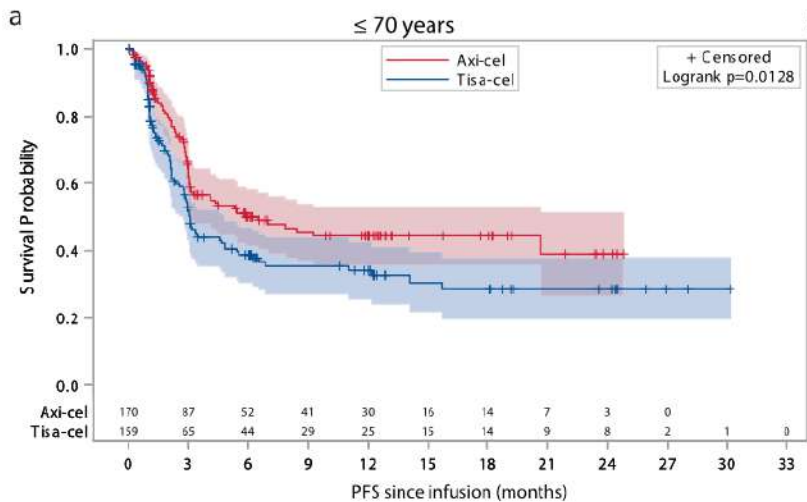
	No. of patients	Event	Censored	Median survival (95% CI)
axi-cel	209	28.2% (59)	71.8% (150)	Not reached (14.7 ; NA)
tisa-cel	209	37.8% (78)	62.2% (130)	11.2 (8 ; 20.1)

ORR: 80.4% vs 66%  
RC: 60.3% vs 42.1%  
(P < 0.001)

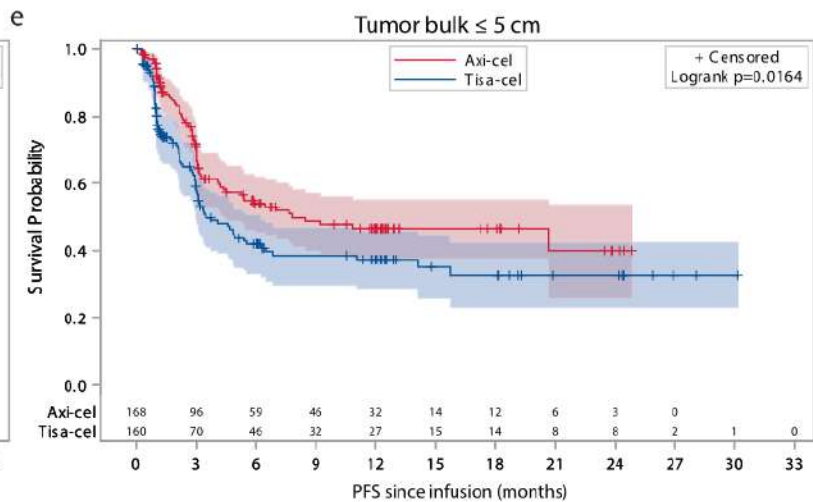
Résultats similaires avec le IPTW



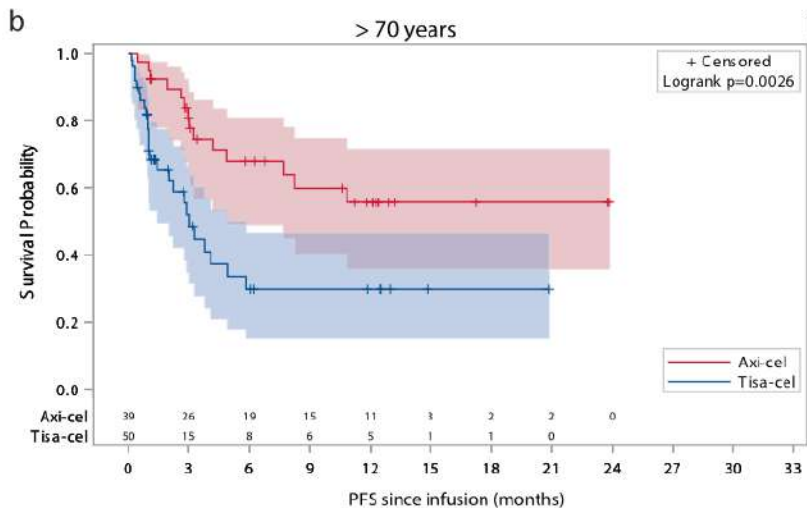
# PFS



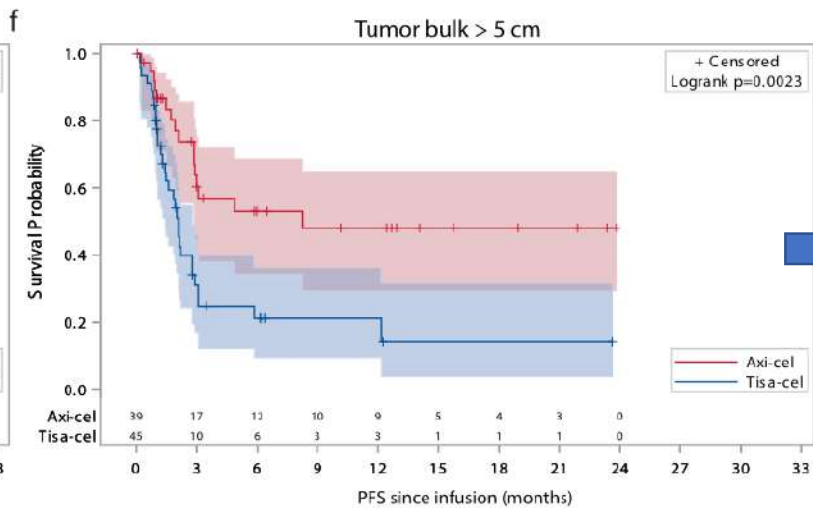
	No. of Subjects	Event	Censored	Median Survival (95%CL)
Axi-cel	170	44.7 % (76)	55.3 % (94)	5.9 (3.1 ; NA)
Tisa-cel	159	56.6 % (90)	43.4 % (69)	3.1 (2.7 ; 4.8)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Axi-cel	168	43.5 % (73)	56.5 % (95)	7.9 (4.4 ; NA)
Tisa-cel	160	51.9 % (83)	48.1 % (77)	3.5 (3 ; 6.2)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Axi-cel	39	35.9 % (14)	64.1 % (25)	Not reached (4.9 ; NA)
Tisa-cel	50	52 % (26)	48 % (24)	3 (1.4 ; 5.8)

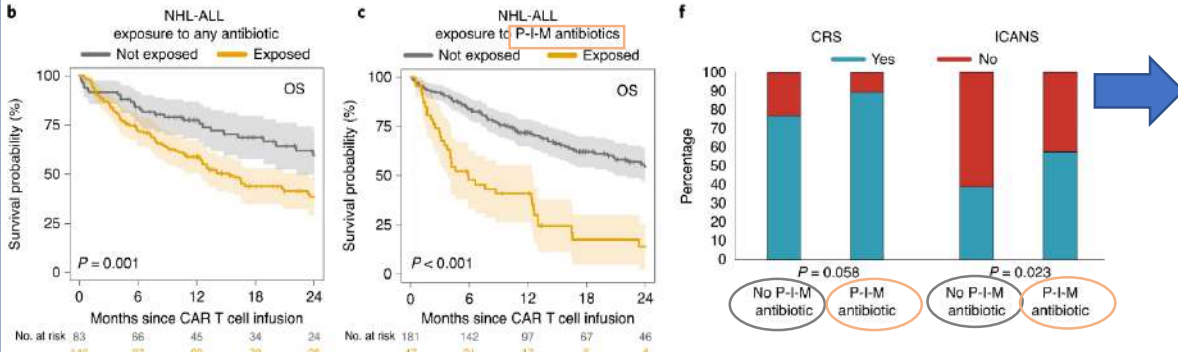


	No. of Subjects	Event	Censored	Median Survival (95%CL)
Axi-cel	39	41 % (16)	59 % (23)	8.2 (2.9 ; NA)
Tisa-cel	45	68.9 % (31)	31.1 % (14)	2.1 (1.4 ; 2.8)

Supériorité d'axi-cell confirmée en PFS et OS  
Même chez les sujets âgés ou bulky

# Gut microbiome correlates of response and toxicity following anti-CD19 CAR T cell therapy

N=228 CART-CD19 LNH/LALB

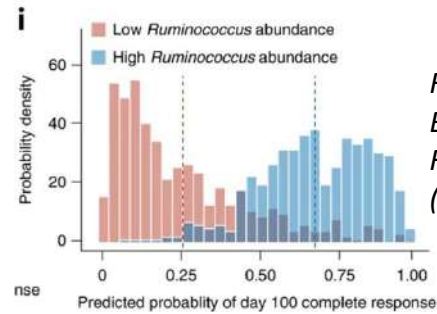
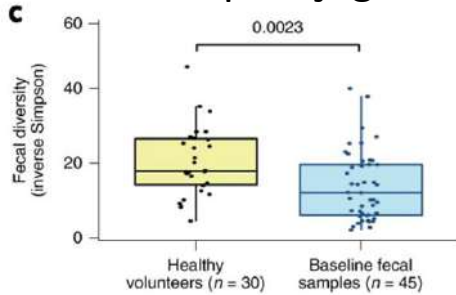


L'exposition aux antibio, surtout à large spectre dans le mois précédant les CART est associée à une dim OS et une aug de la toxicité

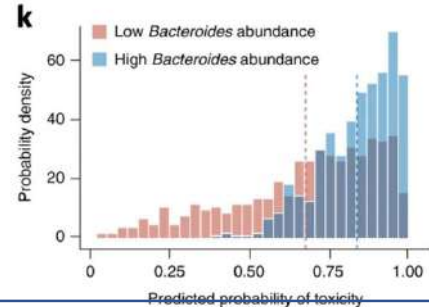
N=48

Collection fecale baseline

Séquençage 16S

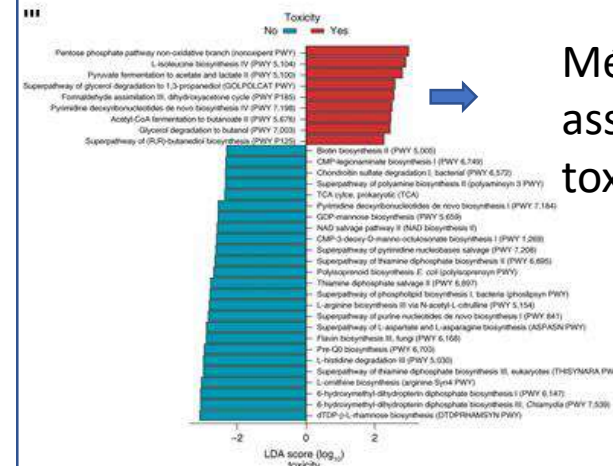


*Ruminococcus*  
*Bacteroides*  
*Faecalibacterium* (clostridia) → Meilleure réponse



*Bacteroides* → Toxicité

## Séquençage métagénomique shotgun



Métabolites associés à la toxicité

Accumulation cellules senescentes → inflammation, dégats chroniques tissus → pathologies liées à l'âge

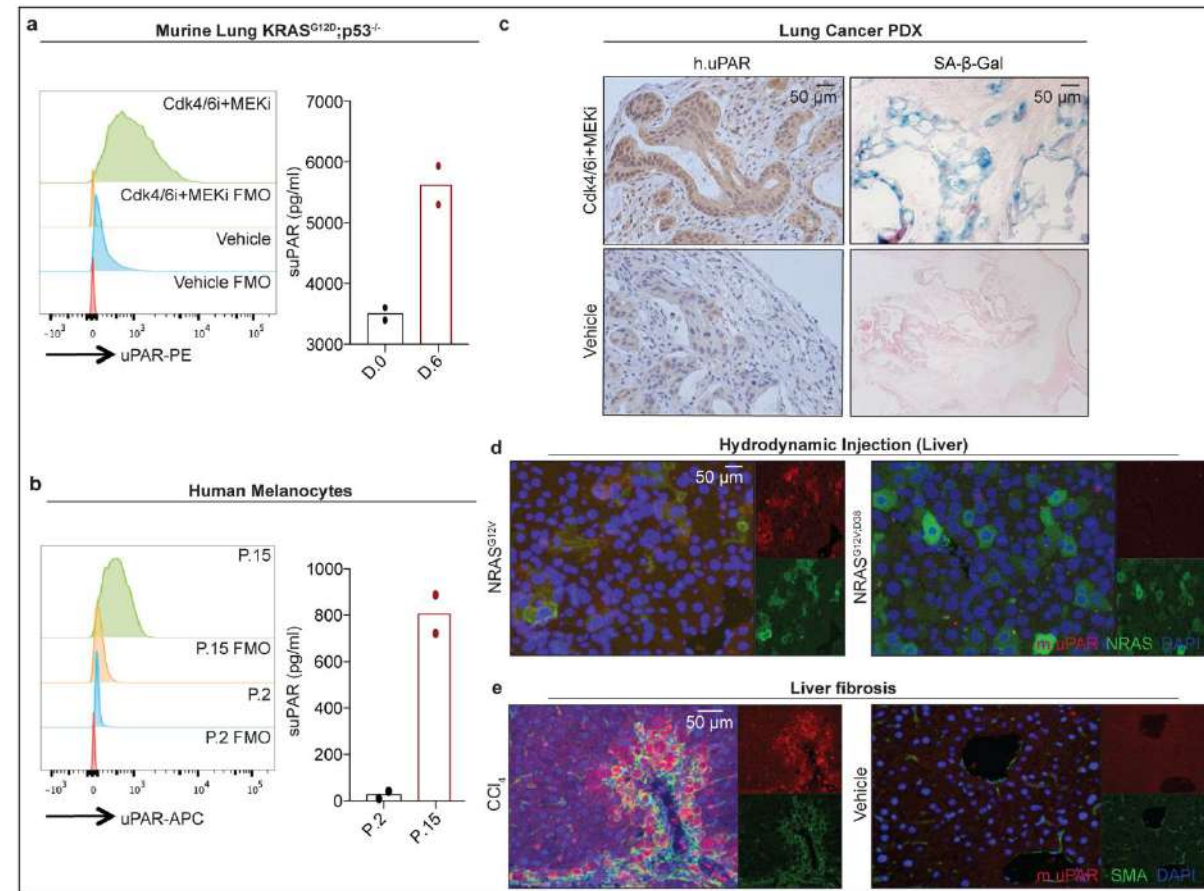
1 Identification protéines de surface uprégulée lors de la sénescence

3 modèles murins de cellules sénescents induites par oncogène, thérapie, culture (adénoK poumon, hépatocytes )

↓  
Séquençage ARN

↓  
Uprégulation gène PLAUR, codant pour **uPAR** (récepteur activateur plasminogène urokinase-type)

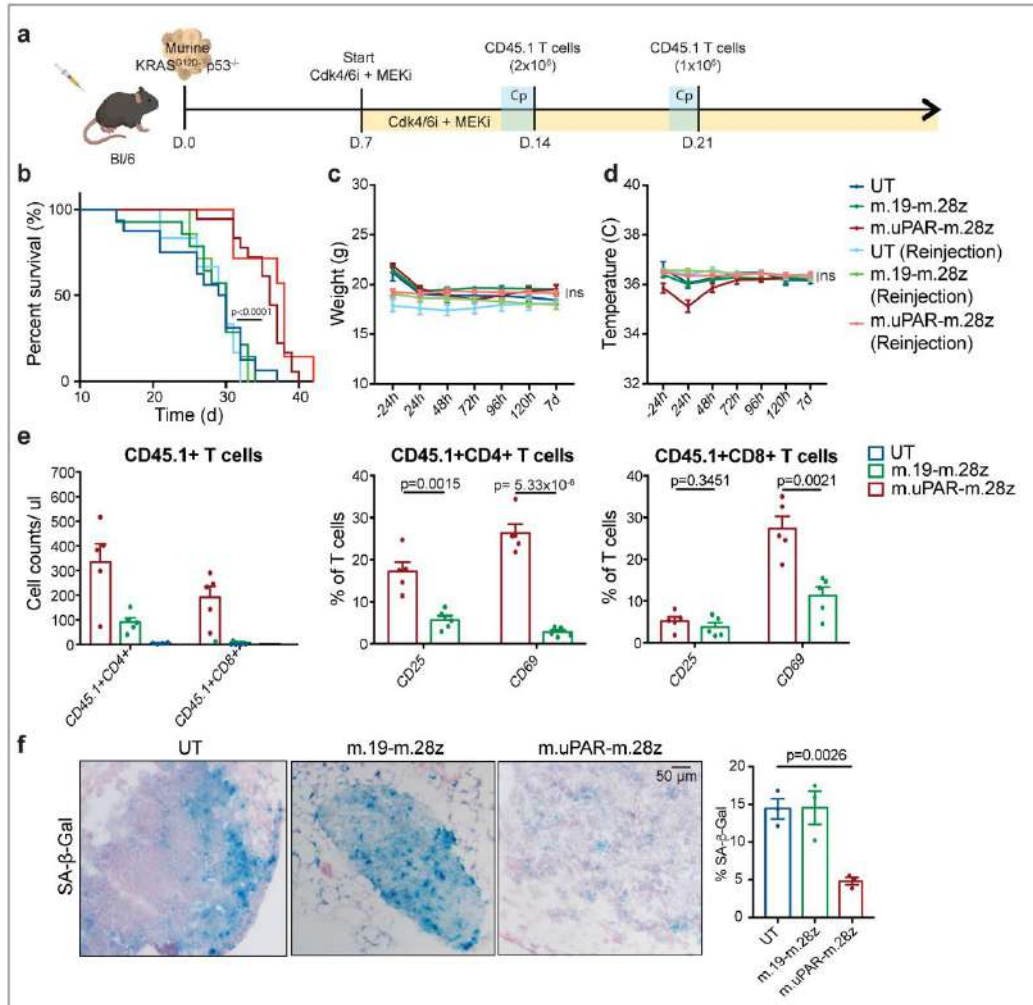
2 Surexpression uPAR à la surface et surnageant de cellules sénescents murines  
Humaines (fibrose hép, plaques d'athérosclérose , K pancreas)





## Construction CART murin anti uPAR-CD28

Senolytic CAR T cells target senescent cells in a  $Kras^{G12D}$ -driven model of lung cancer



Senolytic CAR T cells are therapeutic in NASH-induced liver fibrosis

