Disclosure

Astra Zeneca, Gilead, Abbvie, Neovii, Novartis

Actualités de la greffe et la thérapie cellulaire

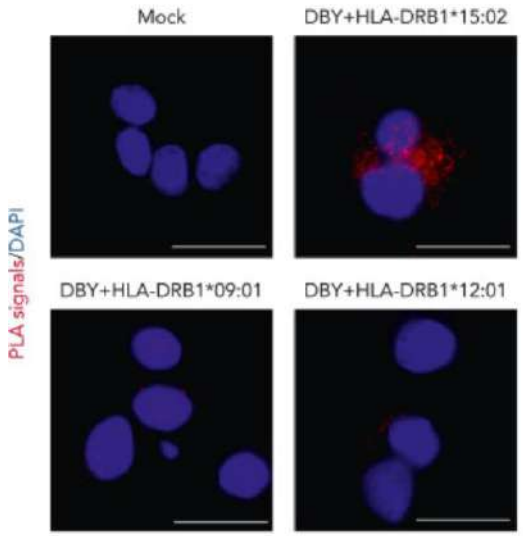
Revue de la littérature 2022-2023

Receveur H/Donneur F fdr GVH+++

Ag HY organes genitaux, coeur, intracellulaire

Comment est il présenté aux organes cibles GVH?

HLA DRB1 15:02 présente AgHY à la surface des cellules

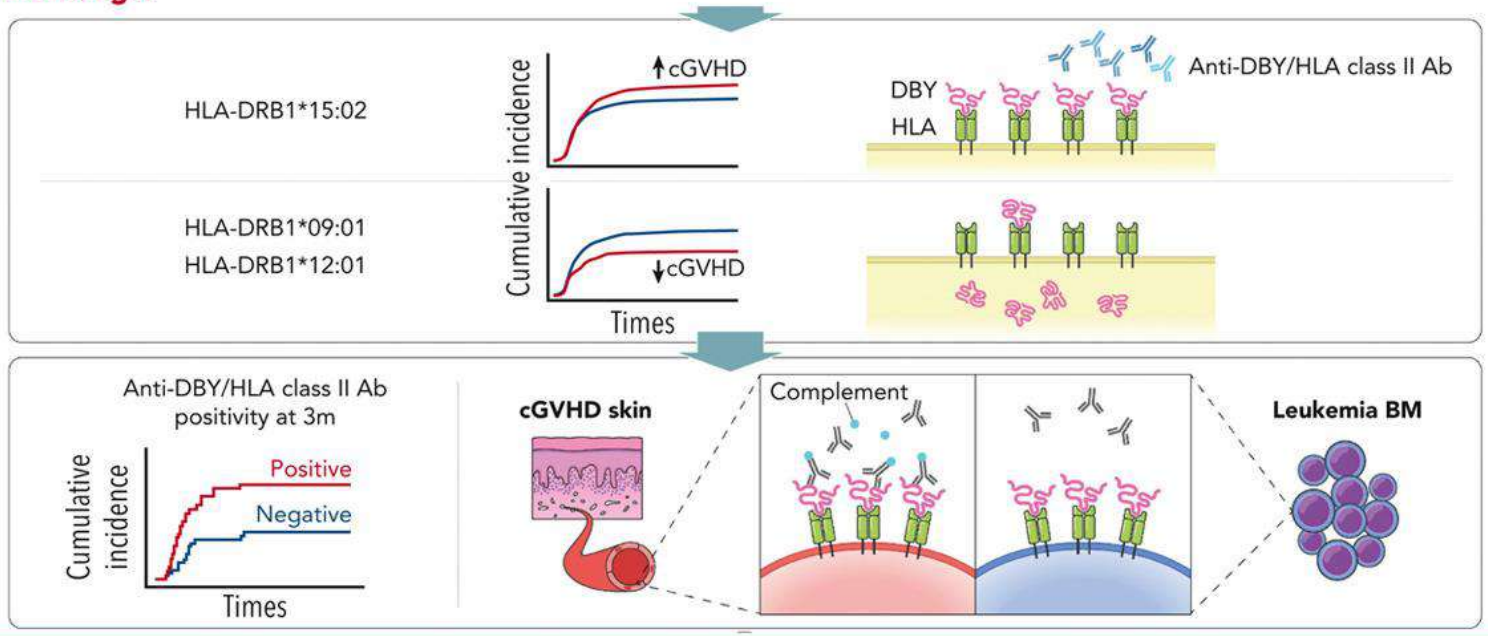


Antibody-Mediated Pathogenesis of Chronic GVHD through DBY/HLA Class II Complexes and Induction of a Graft-Versus Leukemia (GVL) Effect

Context of Research: Alloantibodies against H-Y antigens, encoded on the Y-chromosome, are well-described risk factors for GVHD in female-to-male transplantation. How H-Y antigens emerge at affected organ levels remains elusive.

Patients and Methods: Analysis of nationwide transplantation registry and in vitro studies

Main Findings:

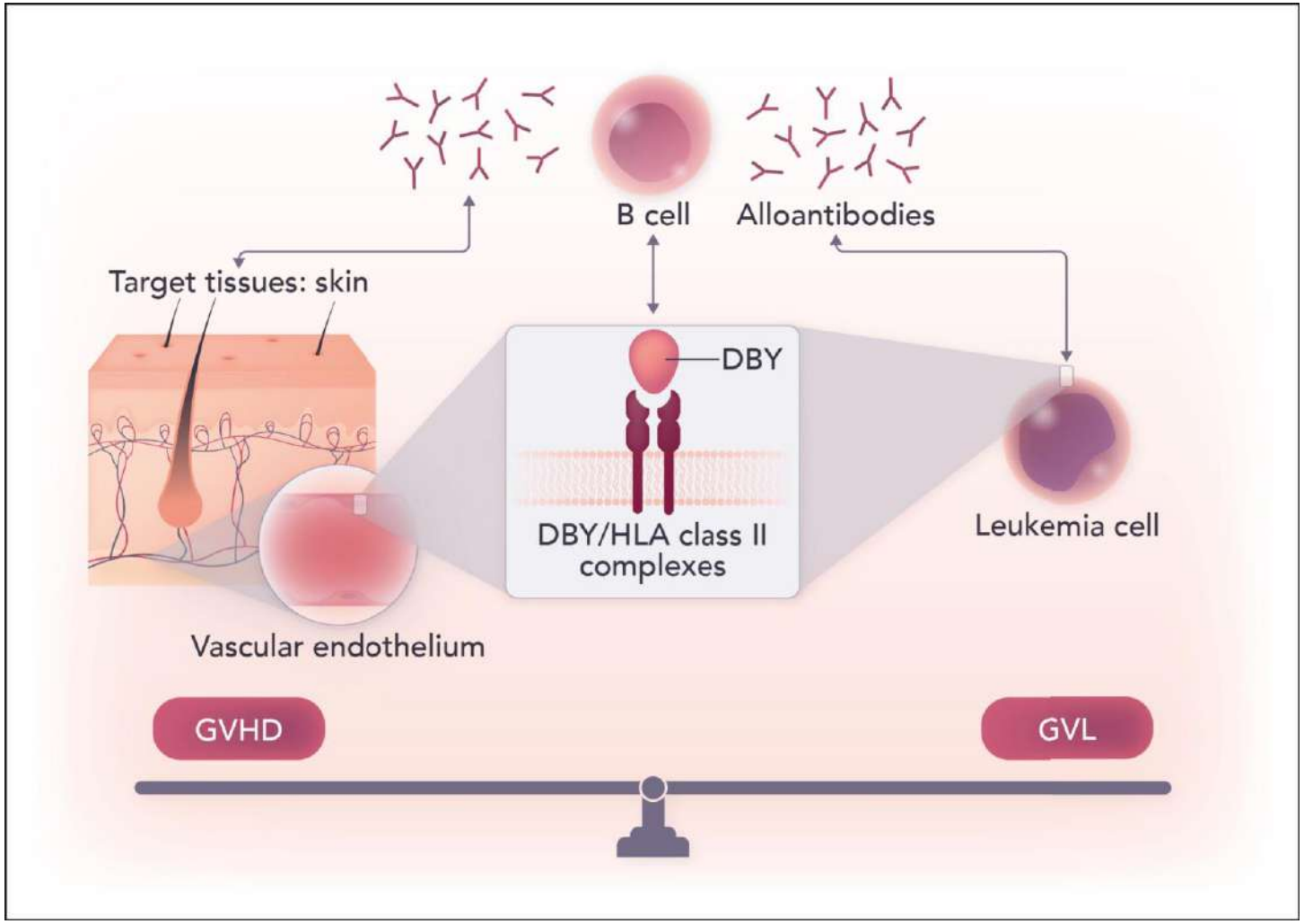


Conclusions: 1) Specific HLA alleles are related to chronic GVHD risk depending on DBY presenting capability; 2) Anti-DBY/HLA complex antibodies directly contribute to chronic GVHD pathogenesis.

*Umino et al. DOI: 10.1182/**blood**.2023019799*

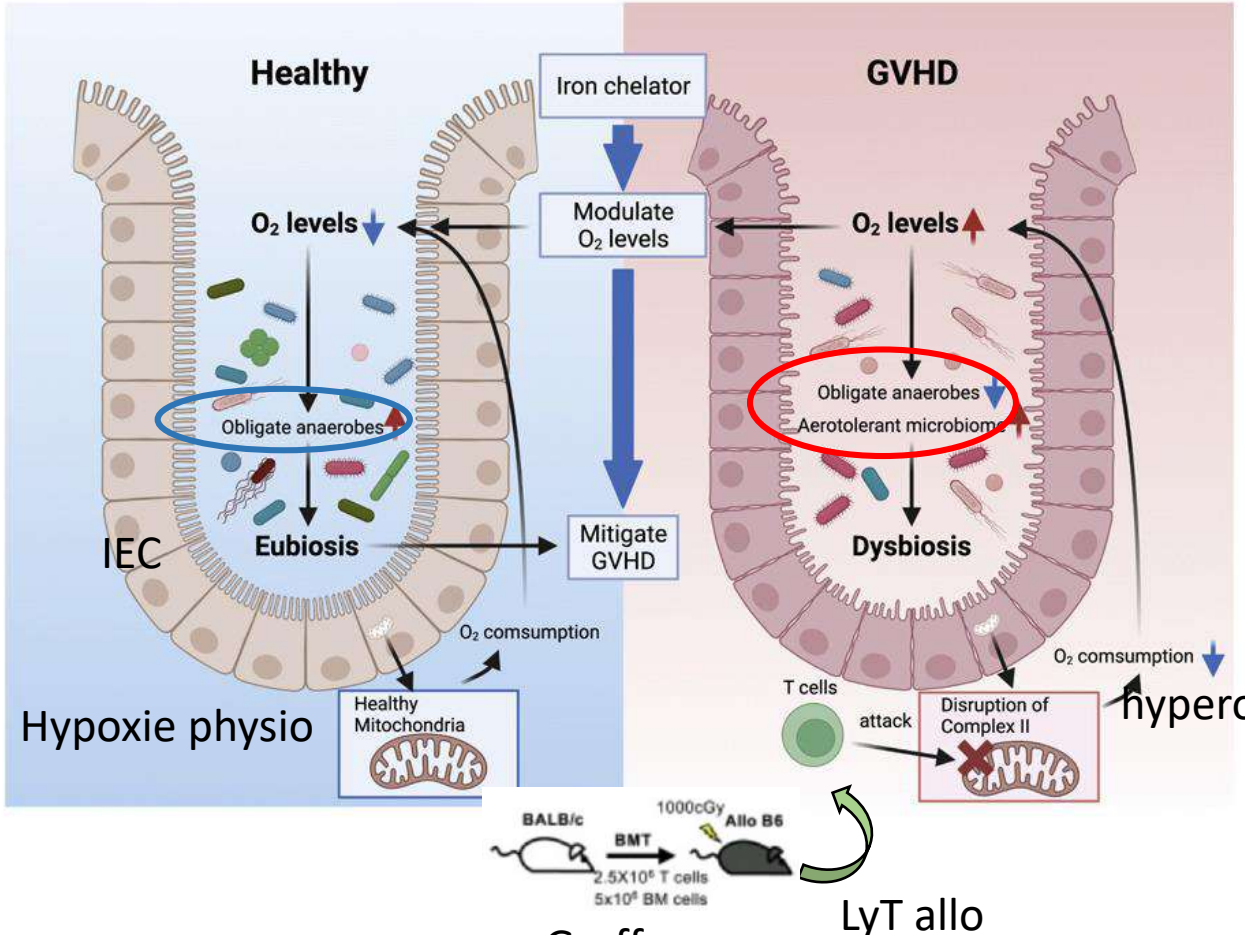
Blood Visual Abstract

W“H-Y” antigen/HLA complexes in chronic GVHD



Noa G. Holtzman,Steven Z. Pavletic, W“H-Y” antigen/HLA complexes in chronic GVHD, Blood, 2023,

Ambient oxygen levels regulate intestinal dysbiosis and GVHD severity after allogeneic stem cell transplantation



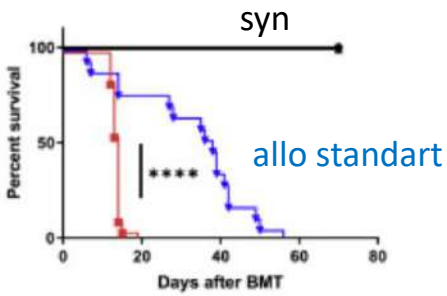
La dysbiose est la conséquence et non la cause de la GVH

Chelateur du fer (diminue l'excès O2 lum int en diminuant la réaction de Fenton)
ou
Apport eubiose post greffe

⬇

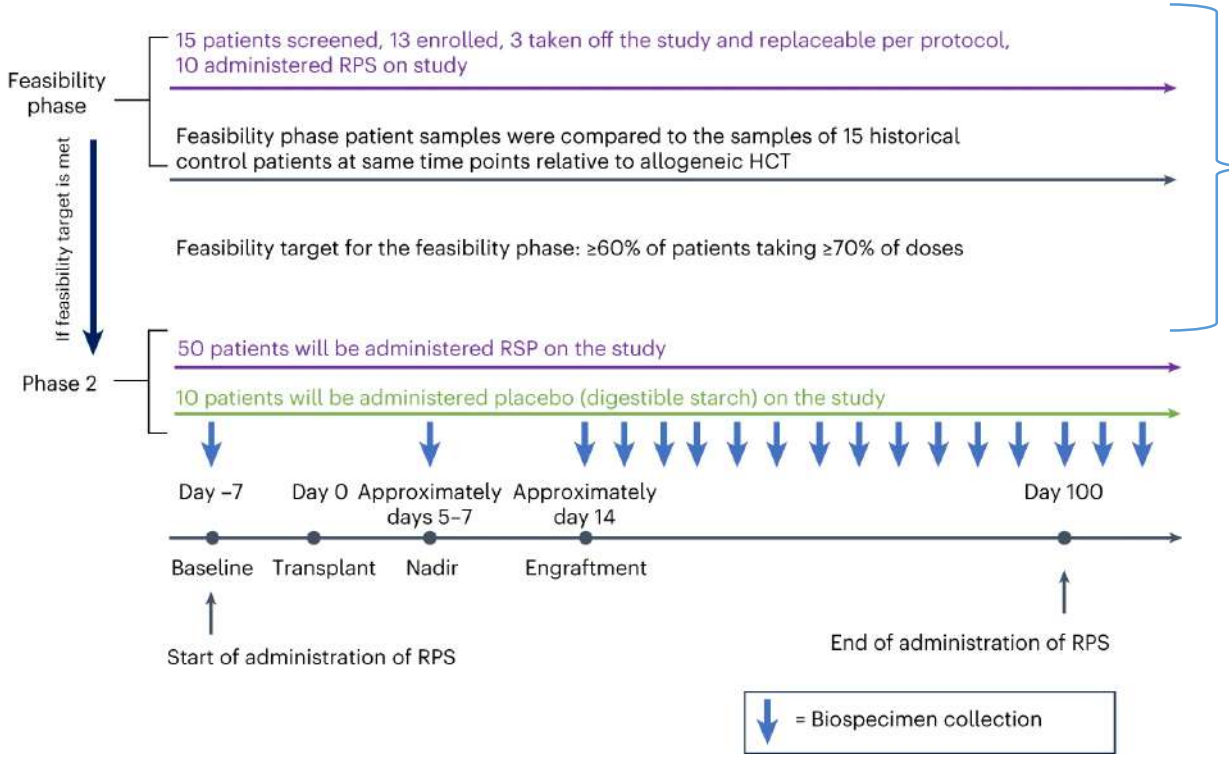
dim GVH

Germ Free: l'absence de microbiote aggrave GVH



Seike Immunity 2023

Feasibility of a dietary intervention to modify gut microbial metabolism in patients with hematopoietic stem cell transplantation



n=10 allo MRD
Ingestion de 20g/j de prébiotiques de J-7 à J100 (amidon de pomme de terre résistants aux enzymes et favorisant les bacteries productrices de butyrate ACC protection barriere muqueuse et energie pour IEC et microbiote)

faisable, augmentation du butyrate dans les selles

Riwes, Nat med 2023

Randomized Double-Blind Phase II Trial of Fecal Microbiota Transplantation Versus Placebo in Allogeneic Hematopoietic Cell Transplantation and AML

adultes, allo pour LAM (n=49 vs n=25) ou induction chimio LAM (n=18 vs n=8)

sortie d'aplasie, stop ATB 48h

Rando 2:1 → Placebo

Rando 2:1 → TMF orale, 5 capsules, répétables

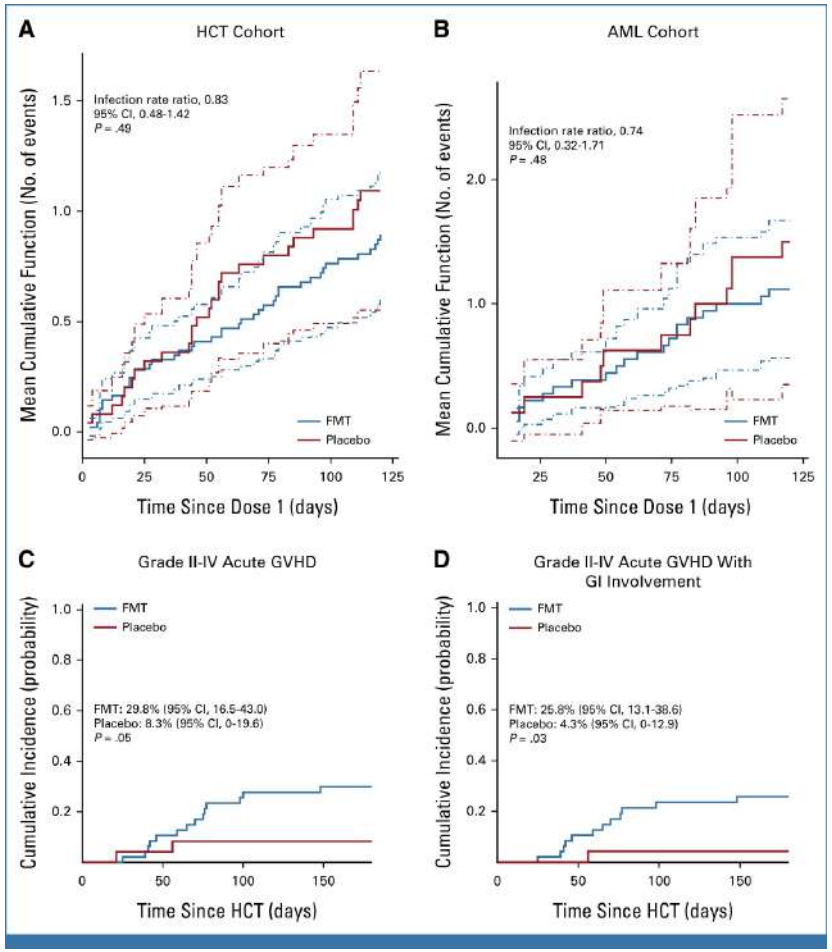
primary end point: taux d'infections dans les 4 mois après dose 1

+ de RIC (63.3% v 36.0%) et moins de cyclophosphamide-PT (PTCy)dans le bras FMT

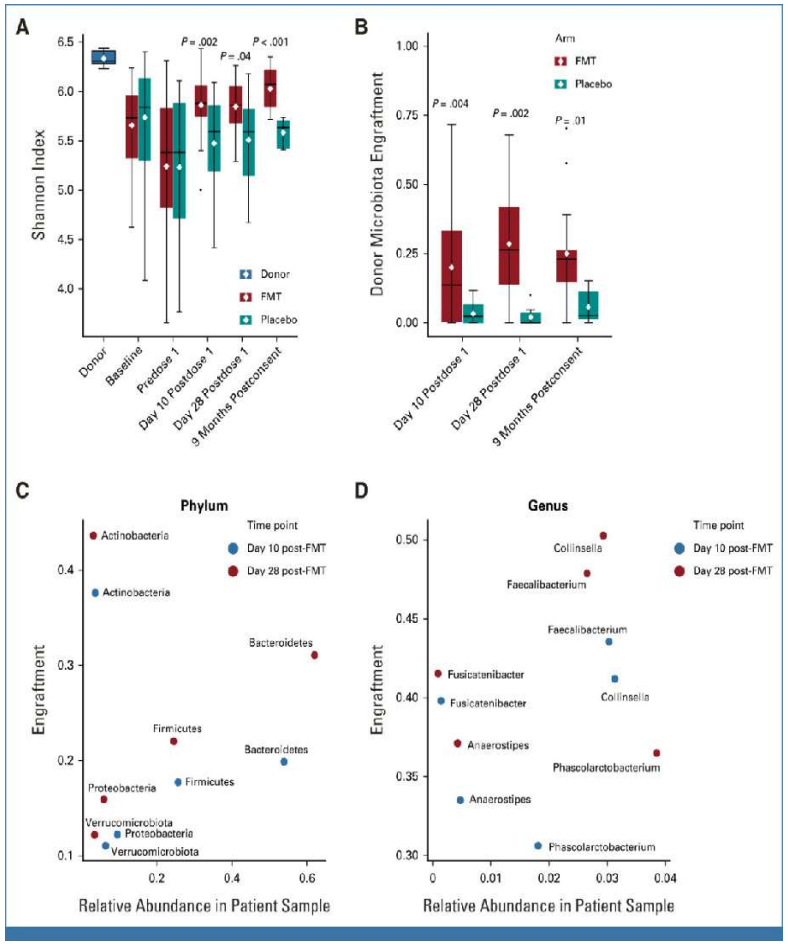
33/34 MAC ont reçu du PTCy

Rashidi , JCO 2023

La TMF ne diminue pas les infections ni la GVH

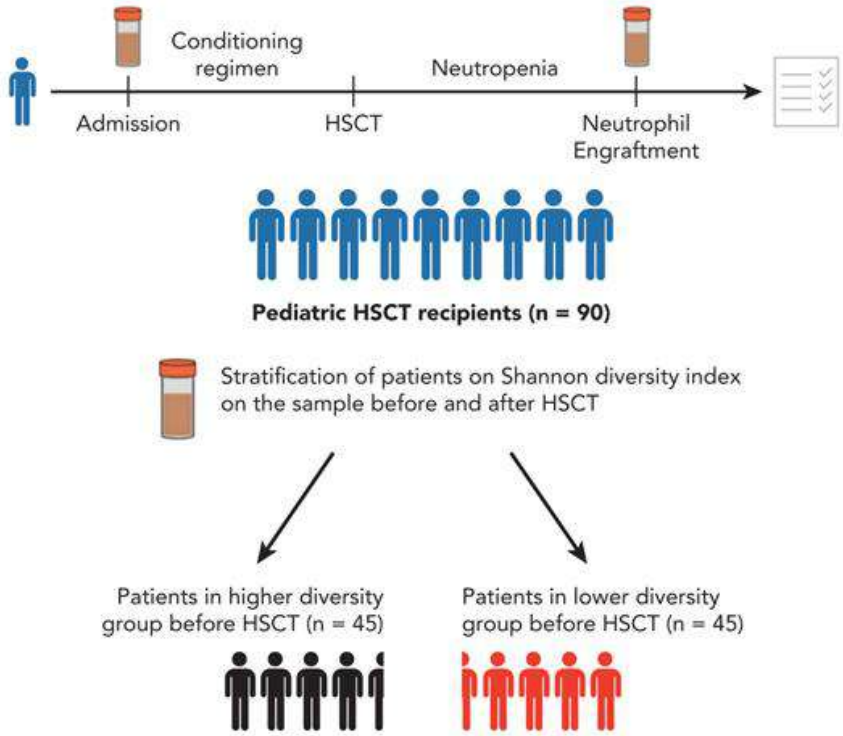


Amélioration de la dysbiose et phénotype donneur

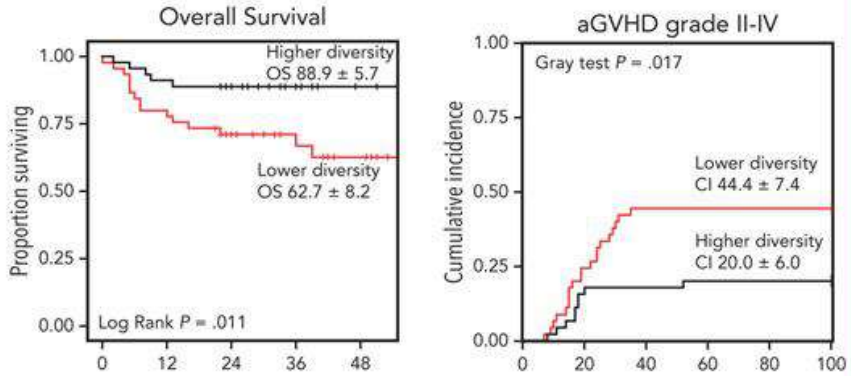


Gut Microbiota Diversity Before Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) as a Predictor of Mortality in Children

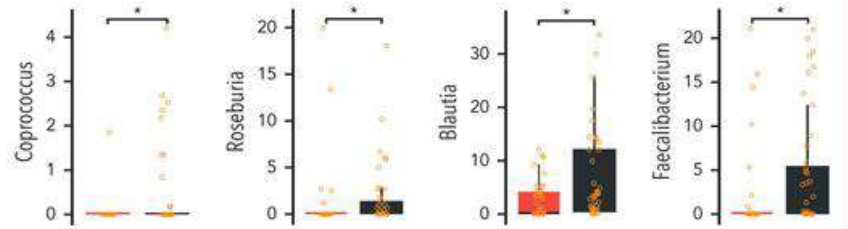
Patients and Methods



Main Outcomes



Gut microbiota composition at genus

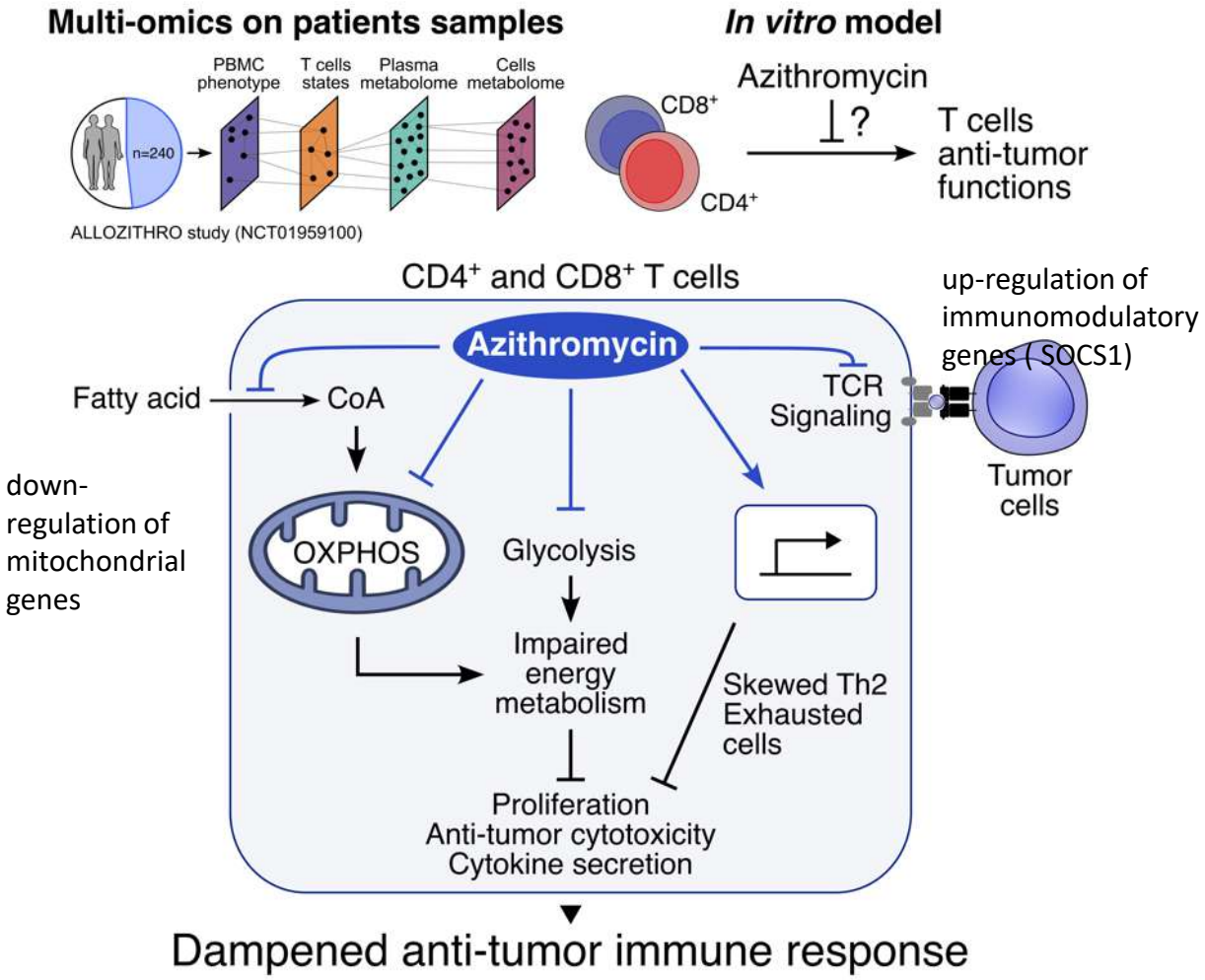


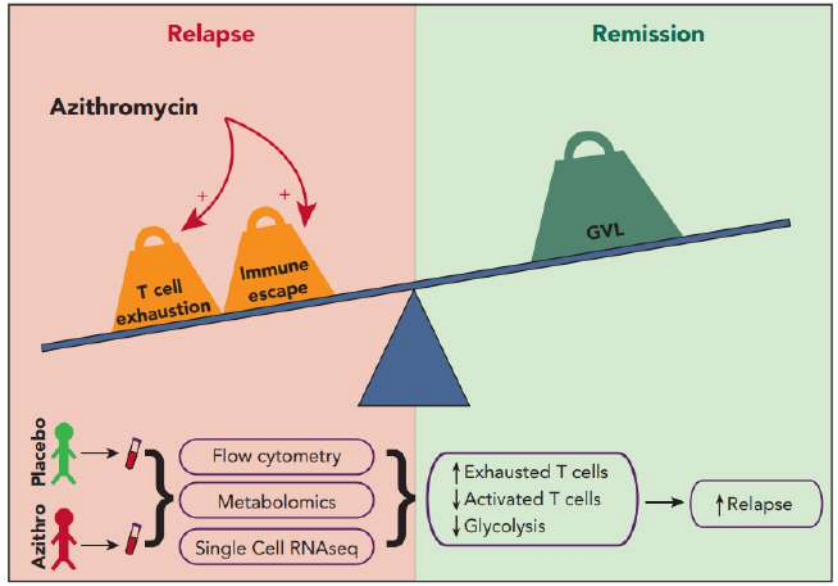
Conclusion: **Higher pre-transplant microbiota diversity correlates with better overall survival, a lower incidence of acute GVHD, and a higher abundance of short-chain fatty acid (SCFA)-producing taxa.**

*Masetti et al. DOI: 10.1182/**blood**.2023020026*

***Blood* Visual Abstract**

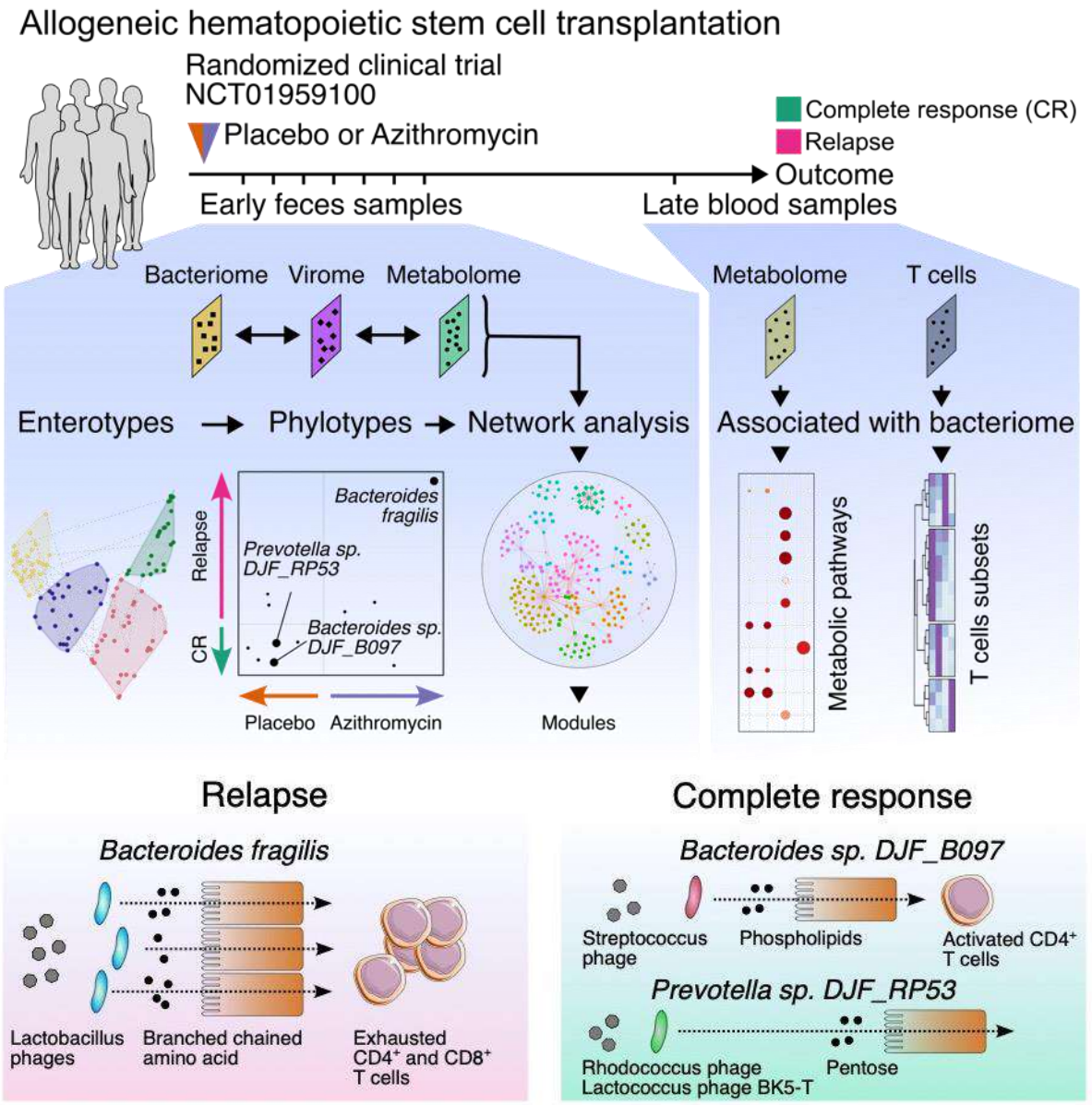
Azithromycin disruptes immune and metabolic networks and dampens immune response





Vallet et al., Blood, 2022

Circulating T cell profiles associate with enterotype signatures underlying hematological malignancy



Enterotypes are associated with:

- Plasma metabolic pathways
- Circulating immune subsets

Bacteria species associated with hematologic response are correlated with blood immune substets

- *Bacteroides fragilis* and exhausted T cells **PD1+Tox+TIGIT+**
- *Bacteroides sp. DJF_B097* and activated T cell **CD4+ KLRG1+**

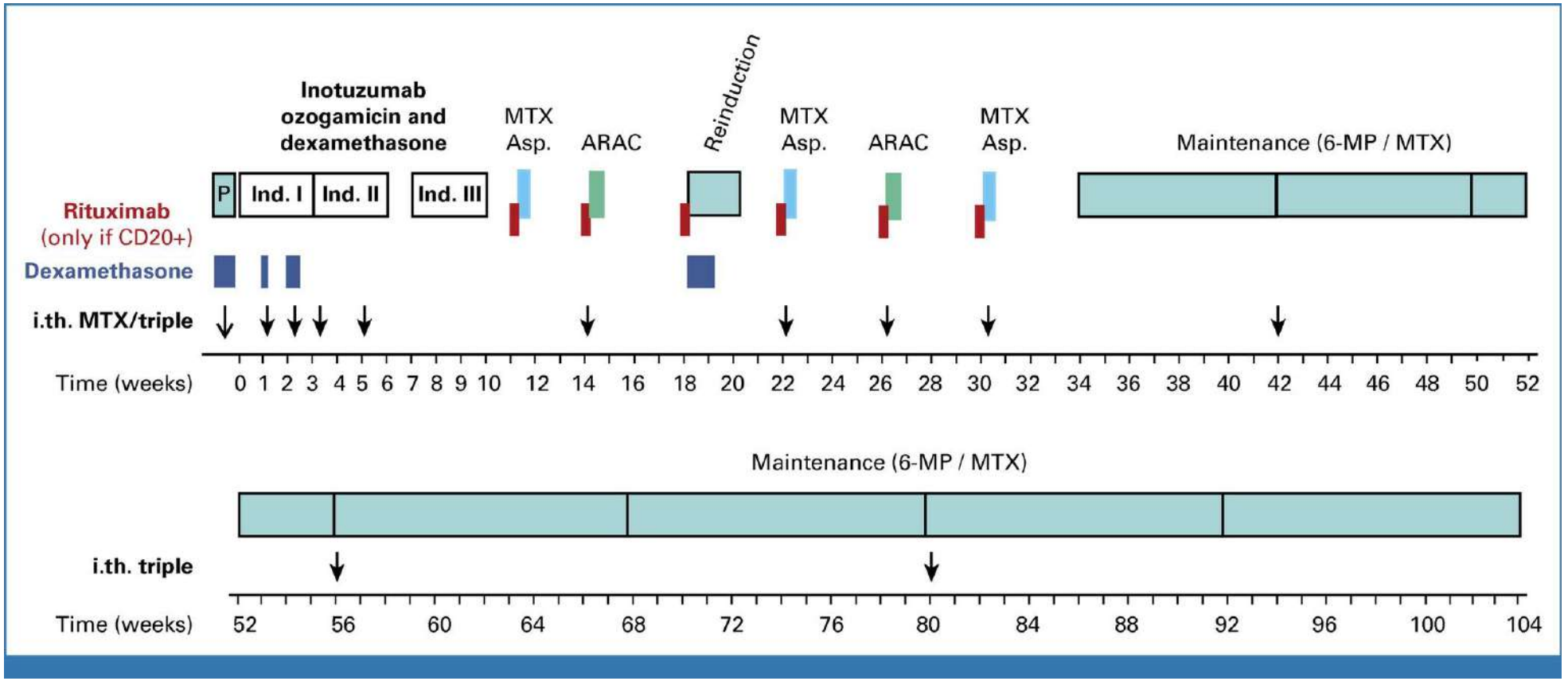
Vallet et al., Cell Host and Microbe, 2023

LAL sujet âgé

Inotuzumab Ozogamicin as Induction Therapy for Patients Older Than 55 Years With Philadelphia Chromosome–Negative B-Precursor ALL

64 years (range, 56-80)

The open-label, phase 2 INITIAL-1 trial of the GMALL

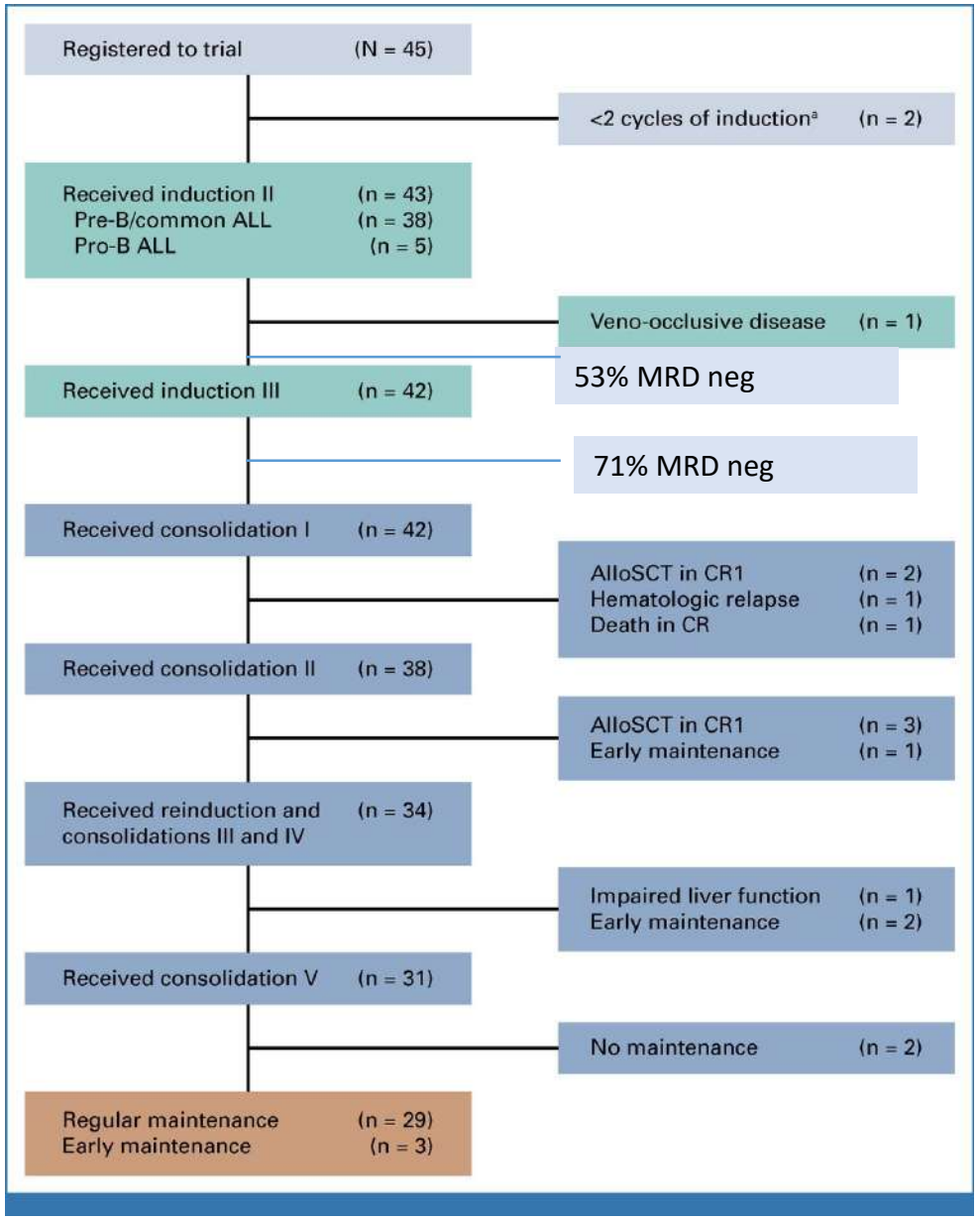


Ino J1-J8-J15 + dexa
3 cycles 28j

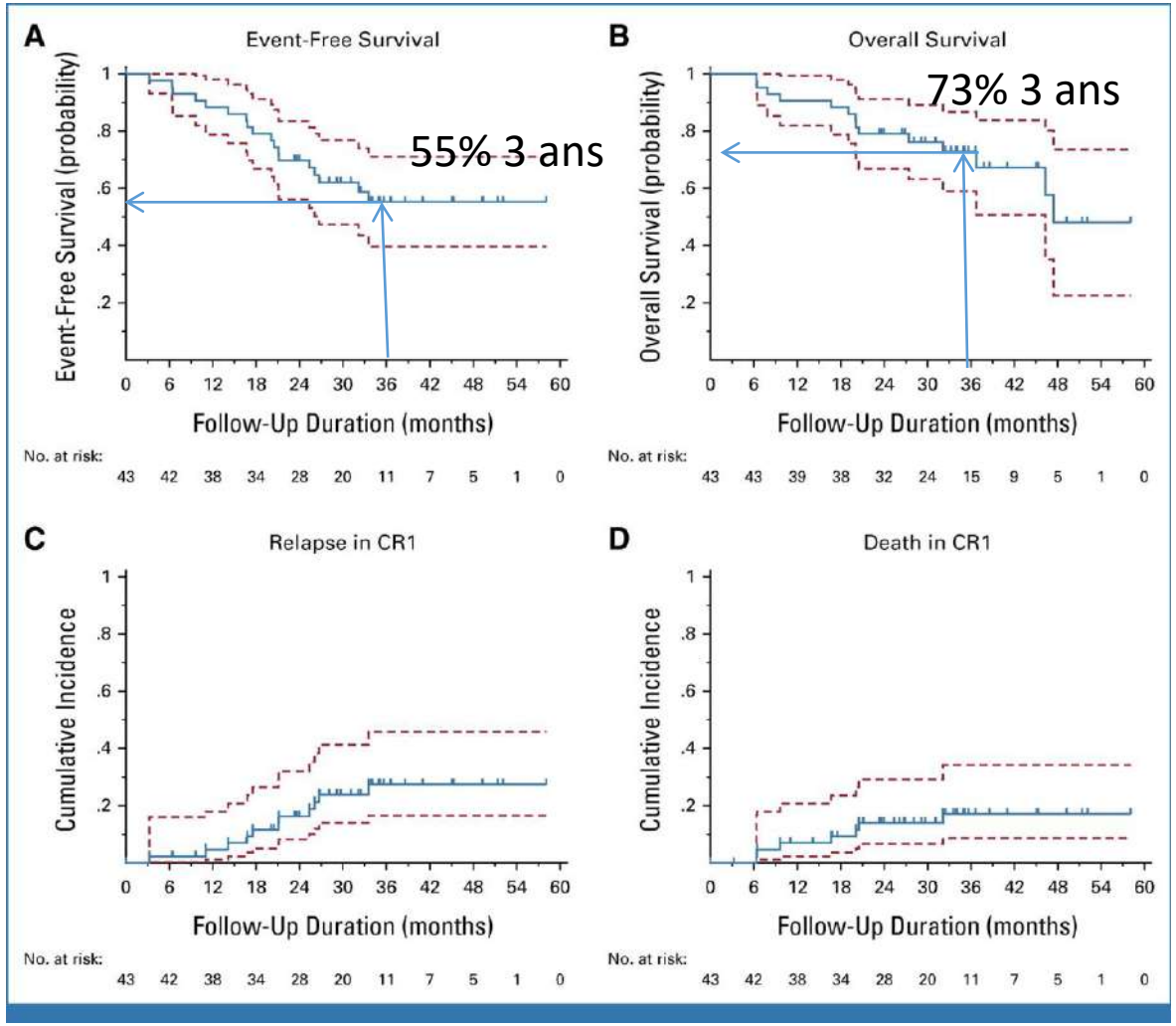
5 conso

reinduction
Ida/AraC/CPM/Dex

Matthias Stelljes, JCO 2023

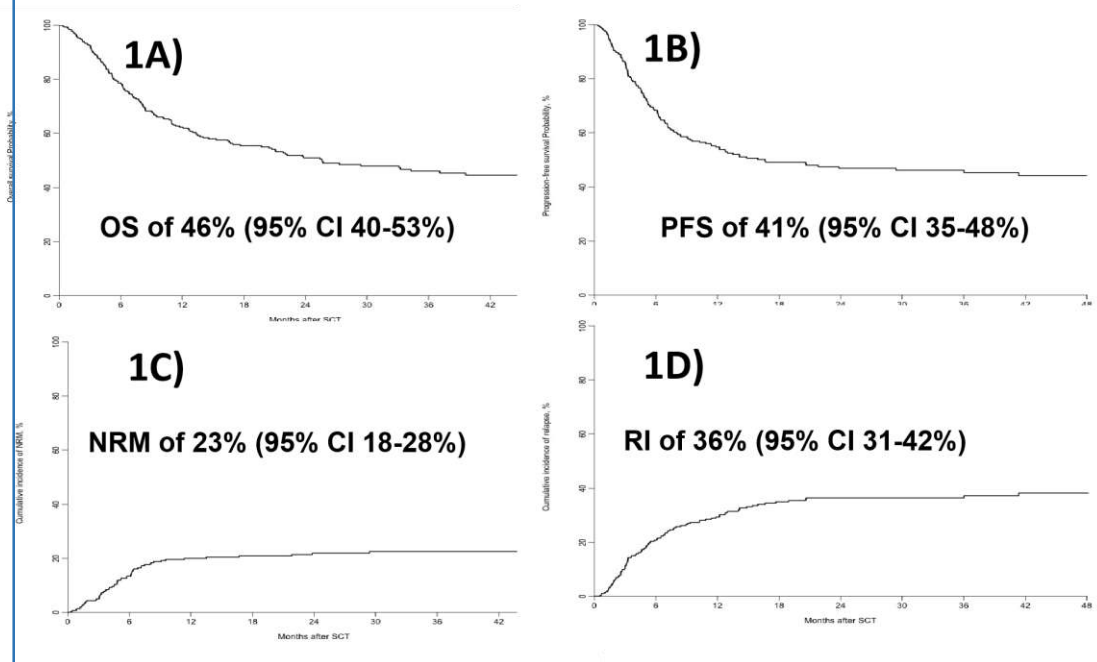


median follow-up of 2.7 years



Matthias Stelljes, JCO 2023

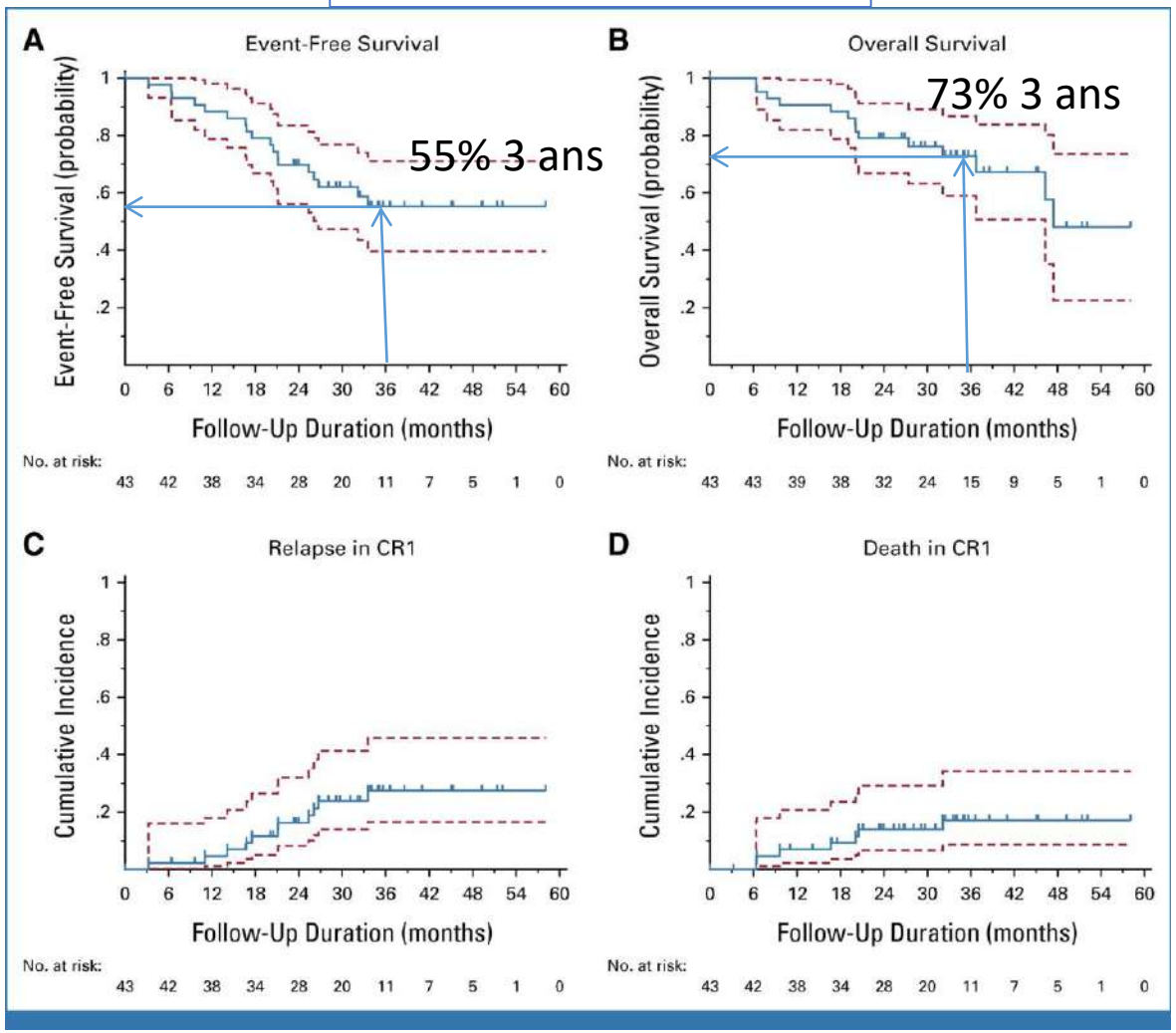
Devenir à 3 ans des allo LAL >60 ans
étude rétrospective SFGM-TC (n=316)



50% LALB Phi+
71% RC1, 23%RC2 et +
âge med 64 ans
2012-2022

Chalandon, ASH 2023

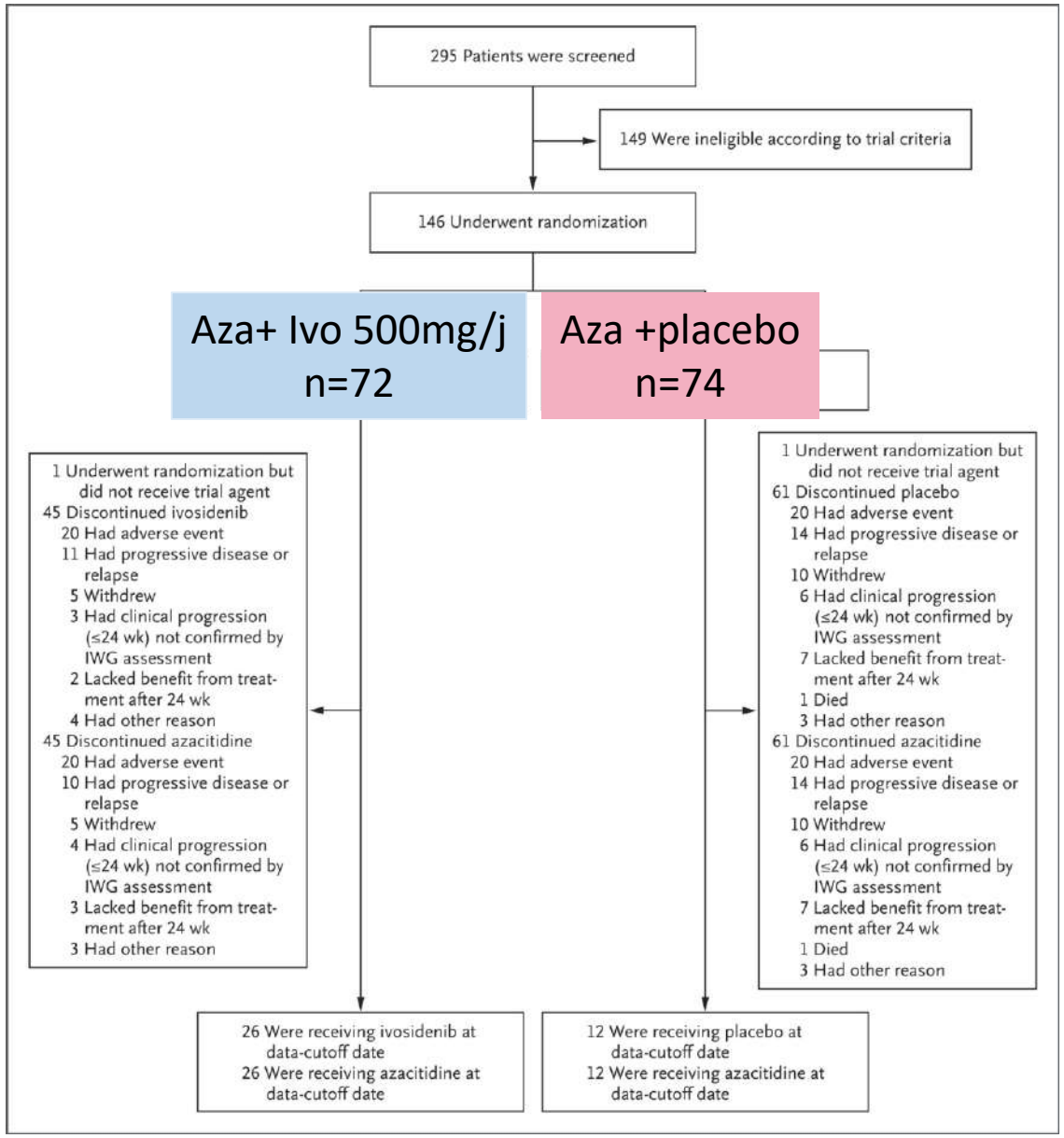
Inotuzumab, med 64 ans



Matthias Stelljes, JCO 2023

LAM/MDS

Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia



IDH1 =6-10% LAM

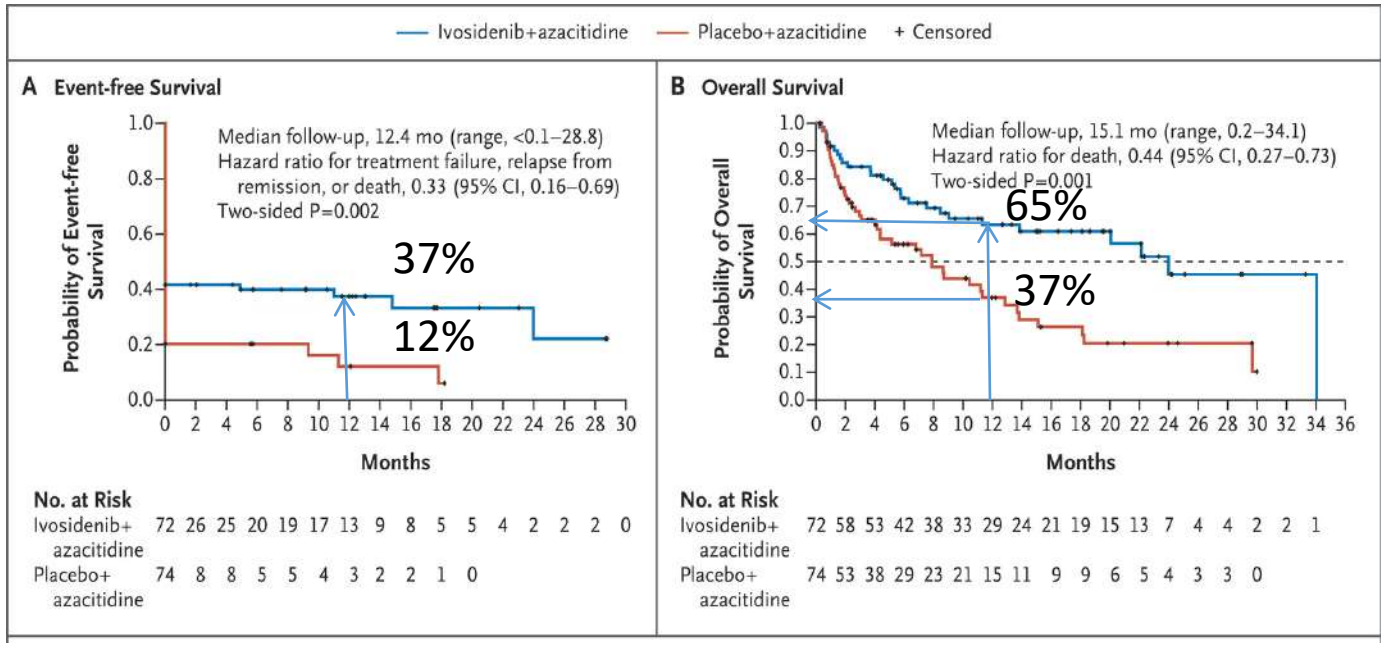
Phase 3 double aveugle, rando, **AGILE**

objectif primaire: EFS

LAM IDH1+ unfit chimio int, med 76 ans
3/4 int
1/4 défavo
Follow up med 12.4 mois

Montesinos, NEJM 2023

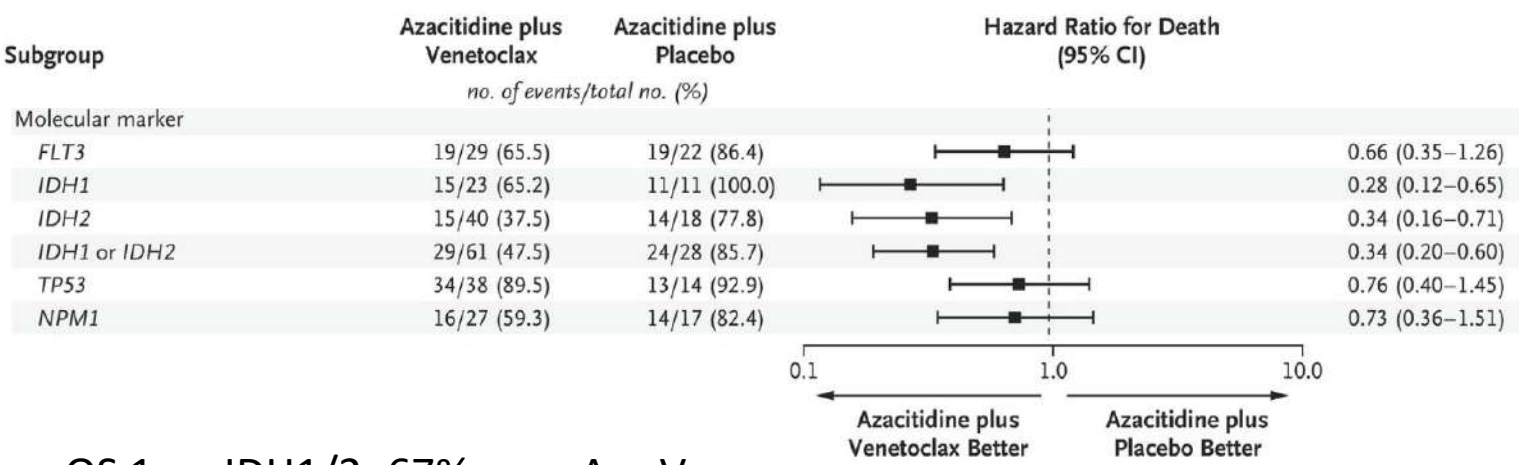
47% RC ivo vs 15% aza



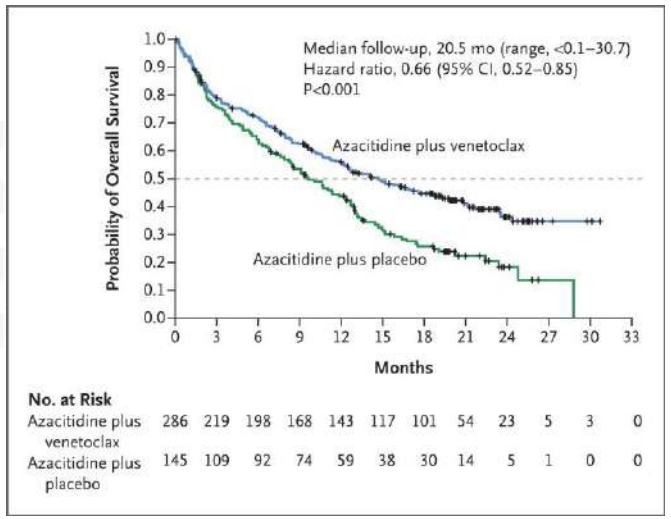
01/08/2023 Autorisations d'accès précoce (AAP)
« Traitement en association avec l'azacitidine des patients ayant une leucémie aiguë myéloïde nouvellement diagnostiquée avec mutation IDH1 R132, non éligibles à la chimiothérapie intensive et aux alternatives disponibles»

en 1ere ligne LAM IDH1+: Ivo ou Aza ven?

Montesinos NEJM 2023



OS 1 an IDH1/2: 67% avec Aza Ven



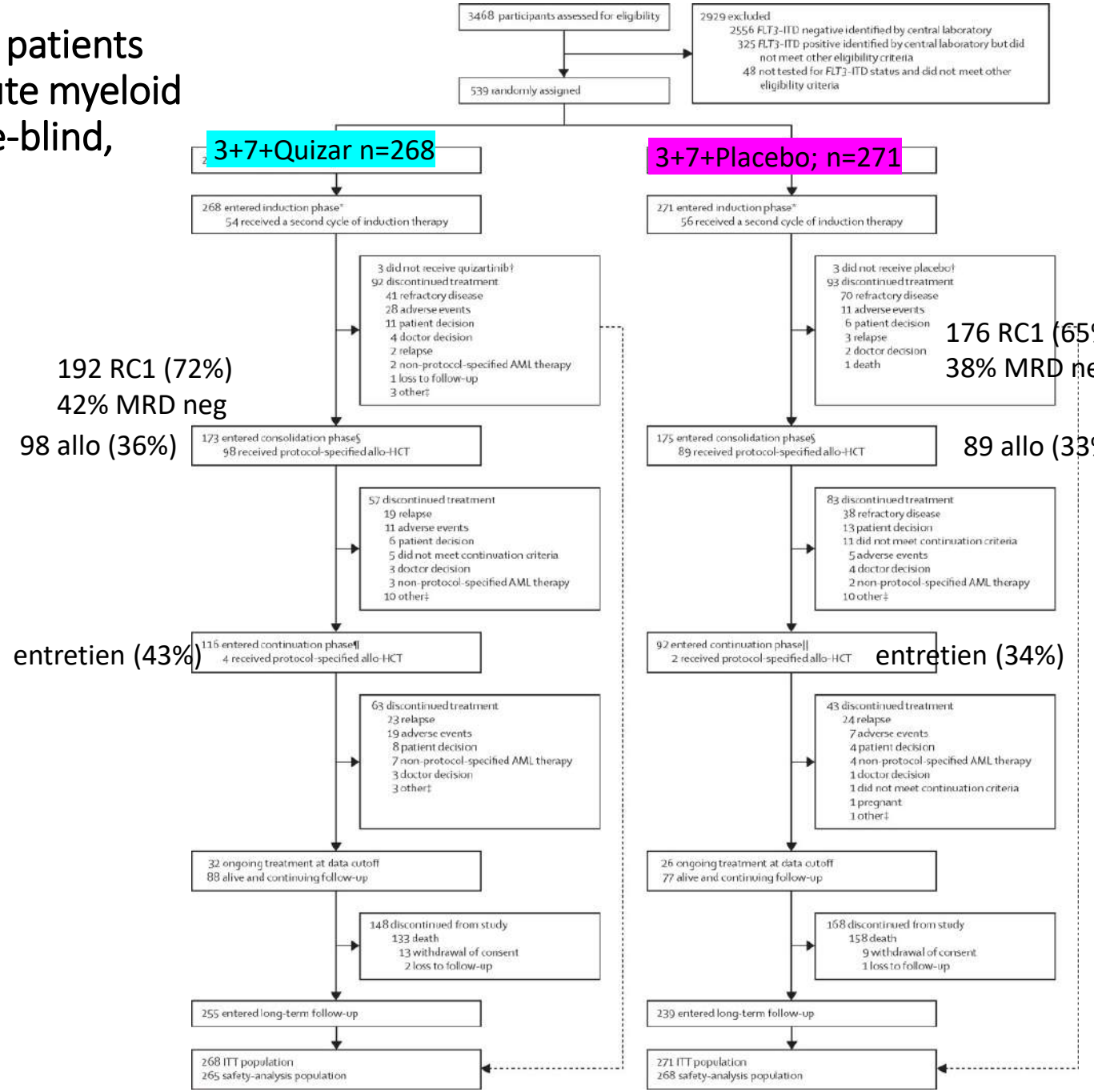
VIALE-A

DiNardo NEJM 2020

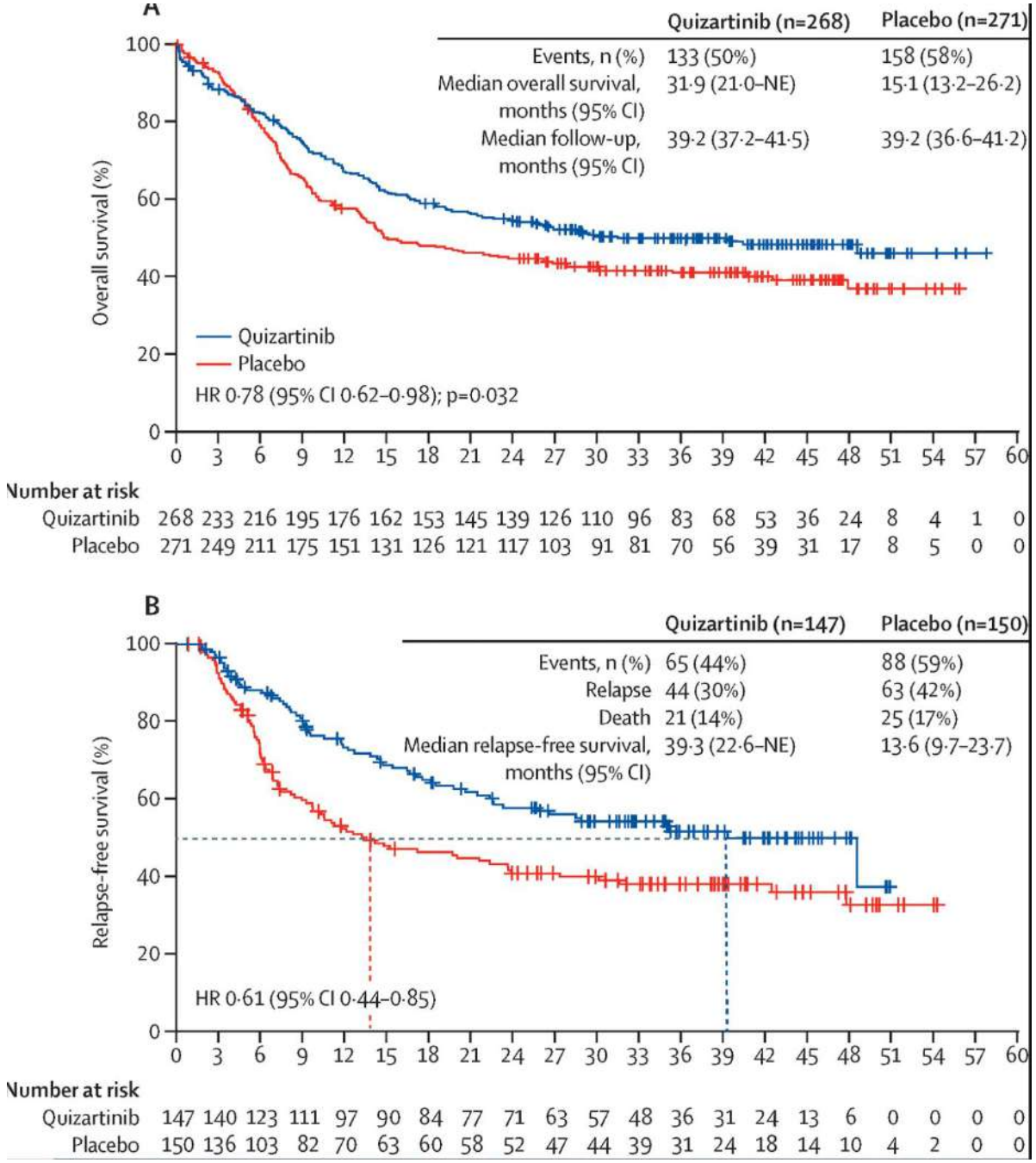
Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial

Rationnel
Midaustorin (Ratify) multikinase inh type 1, <60 ans
35%dim risque décès FLT3-TKD vs 20% FLT3-ITD

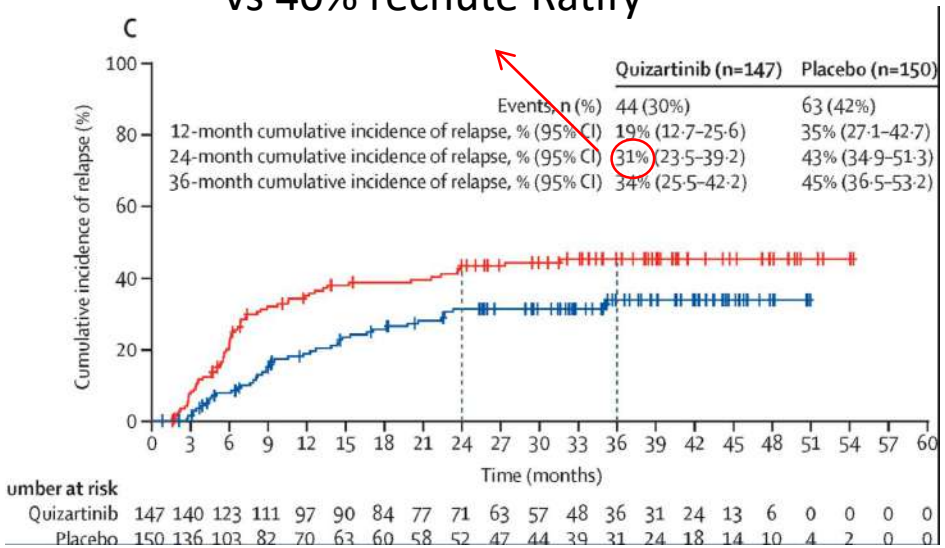
Quizar: inhib sélectif **FLT3ITD** type 2
18-75 ans, med 56 ans , 40% 60-75 ans
MRD évaluée sur FLT3ITD



Erba, Lancet 2023



vs 40% rechute Ratify



Amélioration de l'OS, EFS, rechute avec Quizar

Quizar, le nouveau standard?

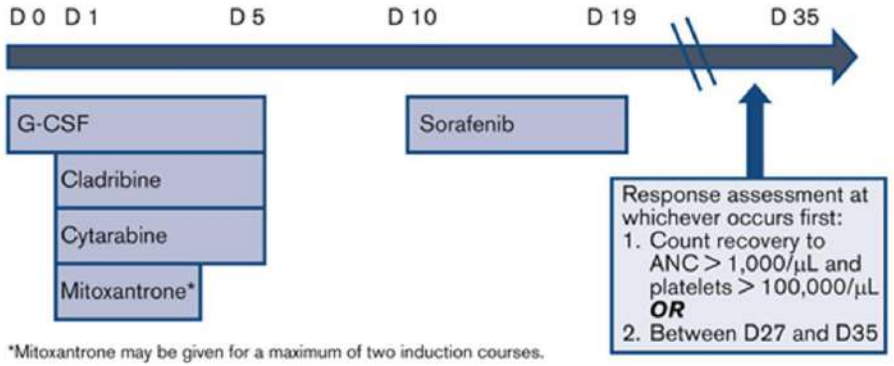
Erba, Lancet 2023

Phase 1/2 study of sorafenib added to cladribine, high-dose cytarabine, G-CSF, and mitoxantrone in untreated AML

med 48 ans
39% int; 34% adv
34 (83%) ont obtenu CR MRD–
63% allo, pas d'entretien

Treatment Schema

n=81, 18-60 ans (med 50 ans), LAM



*Mitoxantrone may be given for a maximum of two induction courses.

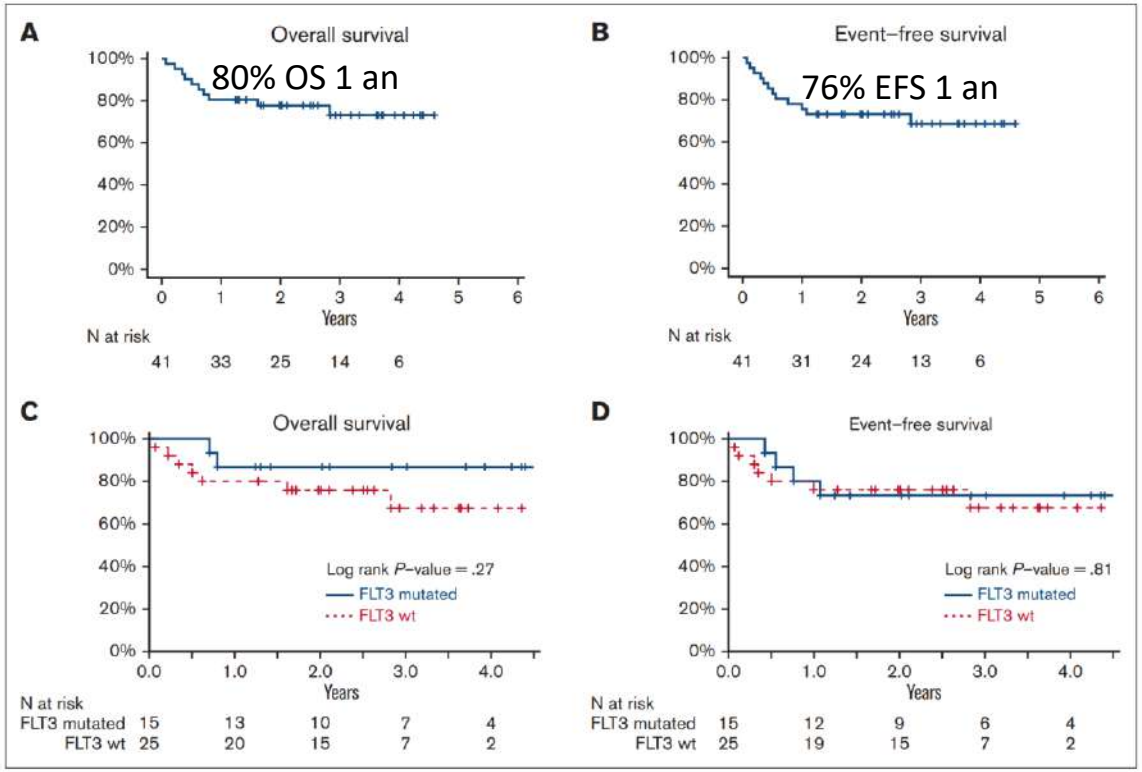
Dose Escalation Schema

Dose Level	G-CSF (SQ, Do-D5)[1]	Cladribine (IV, D1-D5)[2]	Cytarabine (IV, D1-D5)[2,3]	Mitoxantrone (IV, D1-D3)[2]	Sorafenib (PO, D10-D19)
1	5 µg/kg	5 mg/m^2	2 g/m^2	10 mg/m^2	200 mg PO BID
2	5 µg/kg	5 mg/m^2	2 g/m^2	12 mg/m^2	200 mg PO BID
3	5 µg/kg	5 mg/m^2	2 g/m^2	15 mg/m^2	200 mg PO BID
4	5 µg/kg	5 mg/m^2	2 g/m^2	18 mg/m^2	200 mg PO BID
5	5 µg/kg	5 mg/m^2	2 g/m^2	18 mg/m^2	400 mg AM, 200 mg PM
6	5 µg/kg	5 mg/m^2	2 g/m^2	18 mg/m^2	400 mg BID
−1	5 µg/kg	5 mg/m^2	2 g/m^2	18 mg/m^2	200 mg QD

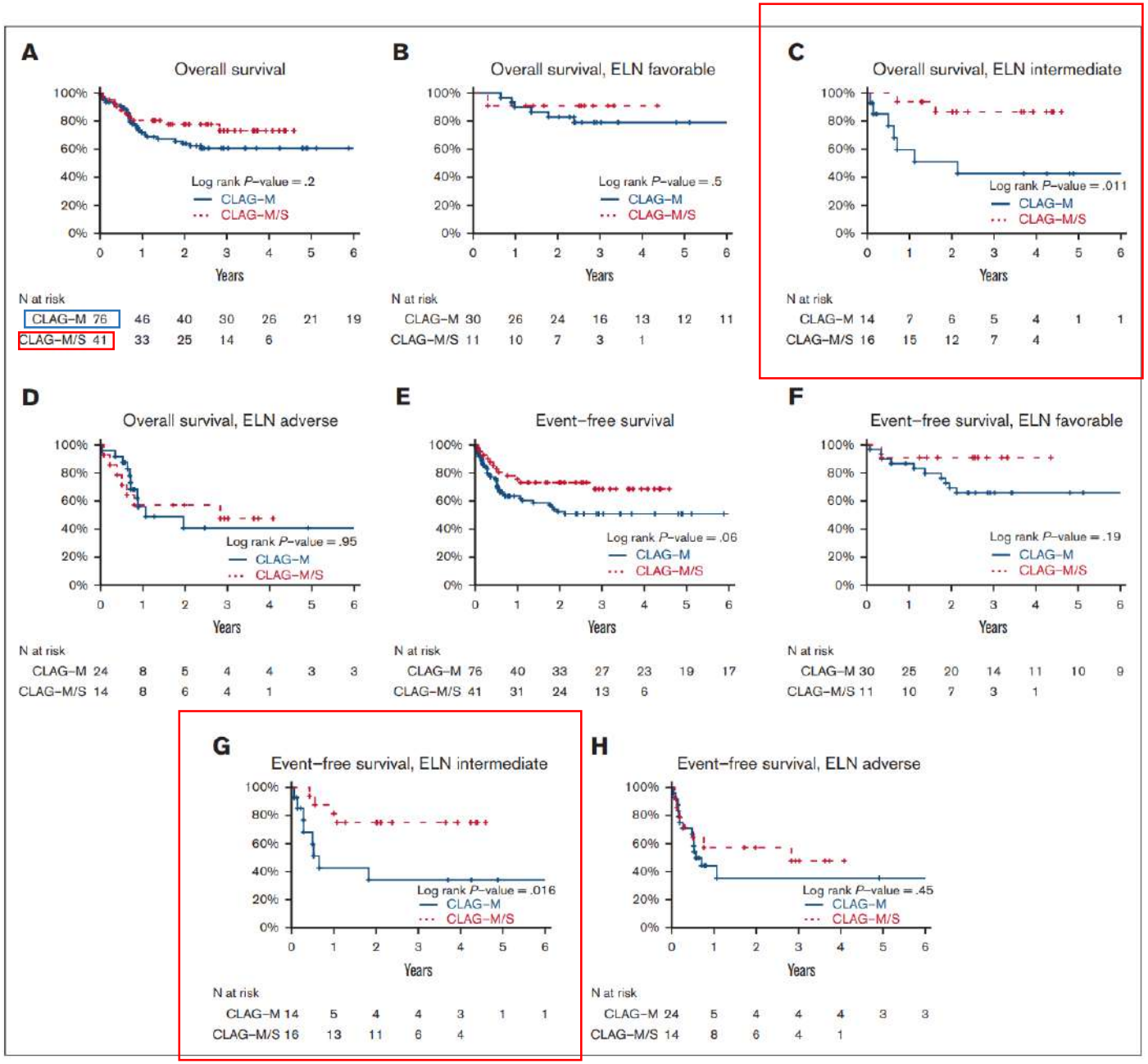
dernier pallier dose RP2D

OS et EFS des 41 pts traités au RP2D de CLAG-M/sorafenib

Pas de différence FLT3+ ou neg



Anna B. Halpern,Blood Adv, 2023



Comparaison rétrospective matchée

Arac+Cladribine+GCSF-mitox (CLAG-M) vs CLAG-M + Sorafenib (CLAG-M/S)

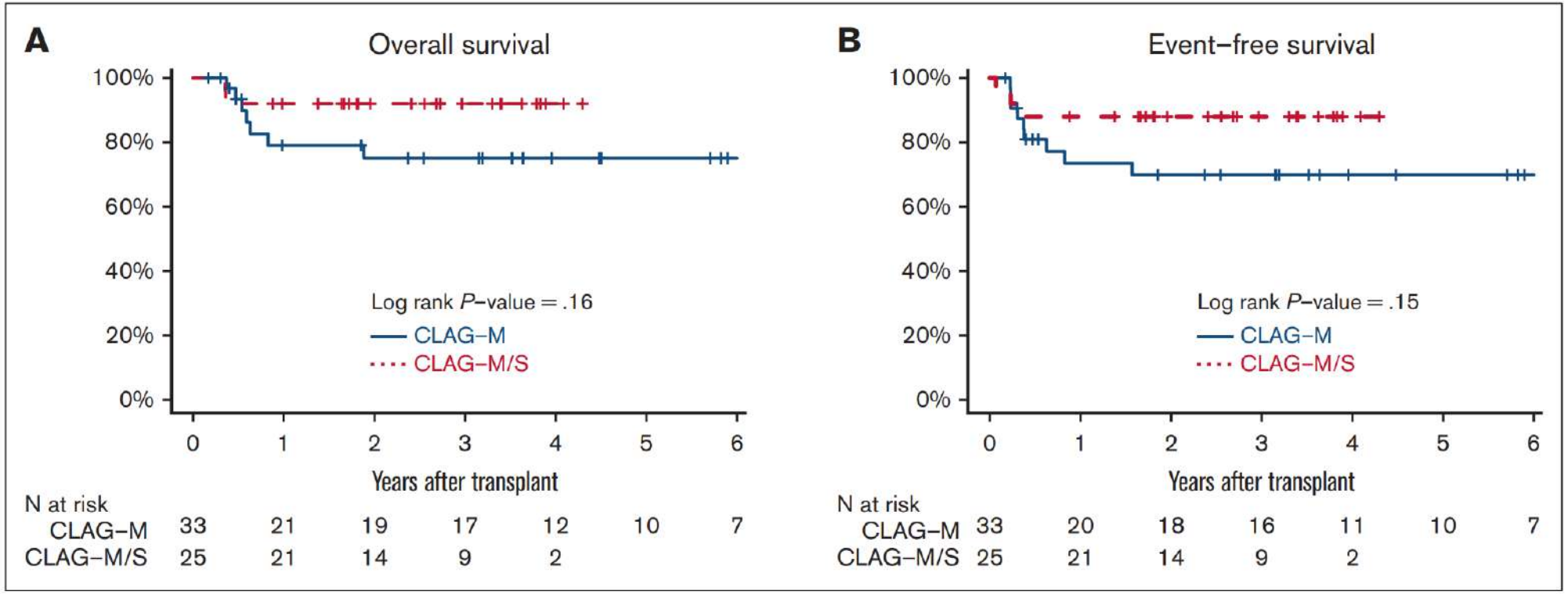
Avantage OS et EFS pour CLAG-M+Sorafenib surtout LAM int

Un peu + d'allo en RC1 dans CLAG M/S:même résultats après multivariées incluant allo comme covariable temps dépendants

Anna B. Halpern,Blood Adv, 2023

Estimate of posttransplant OS and EFS for the patients who recieved CLAG-M/sorafenib vs CLAG-M alone

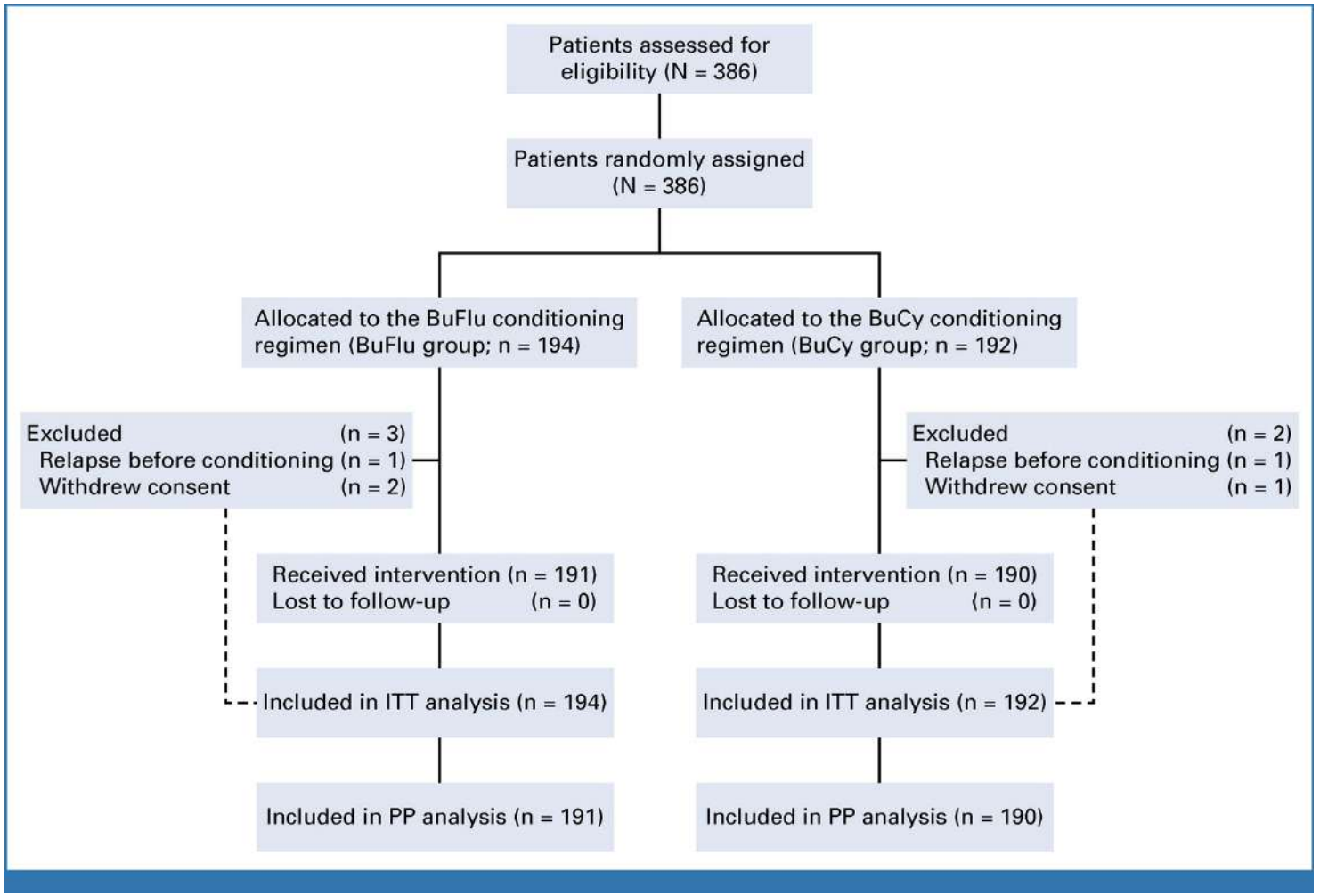
63% d'allo dans le groupe RP2D CLAG-M/S dont 61% en RC1
58% allo dans CLAG-M dont 43% en RC1
Pas de maintenance post allo



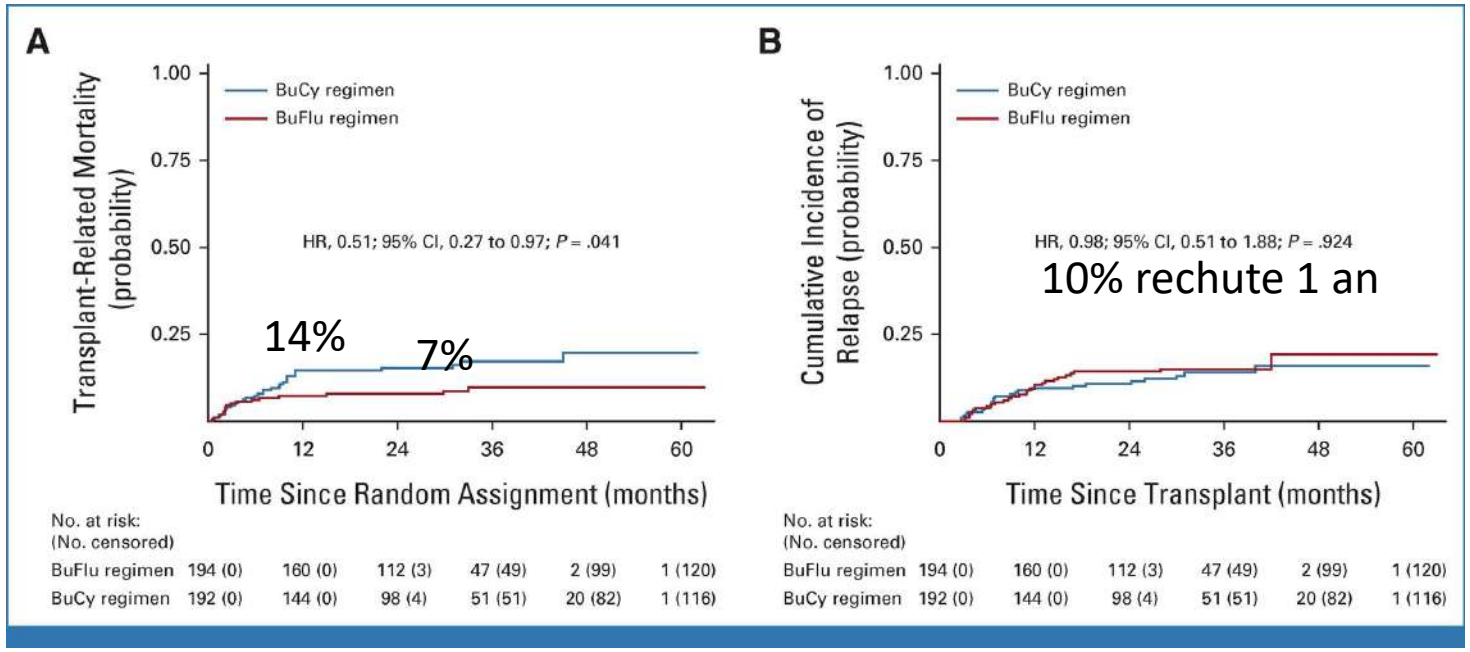
Anna B. Halpern,Blood Adv, 2023

FB4 vs Bu-Cy HAPLO LAM
Multicenter Randomized Phase III Trial

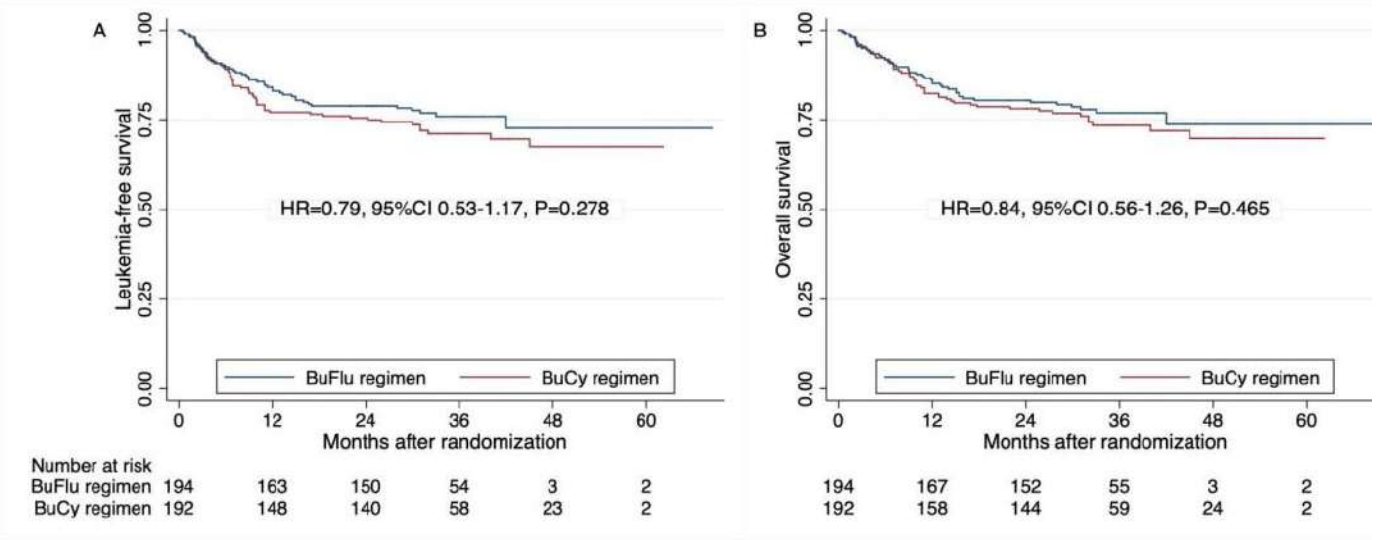
G-BM+CSP
Prévention GVH: ATG 7.5mg/Kg, ciclo, MTX, MMF
MRD évaluée flow cyto
G-CSF-DLI préemptives si MRD+ (n=81/92)
ou decitabine si GVH (n=11/92)
+/-sorafenib (n=25)
Age médian 37 ans
MRD neg 63% à la greffe
LAM RC1 85%
55% high risk
30% int
13% low risk



Lung et al, JCO 2023



GVHa 2-4 40%
GvH 3-4 10%
GvHc 40%
PNN: 12-13 jours
Plaq: 13-14j
3 rejets



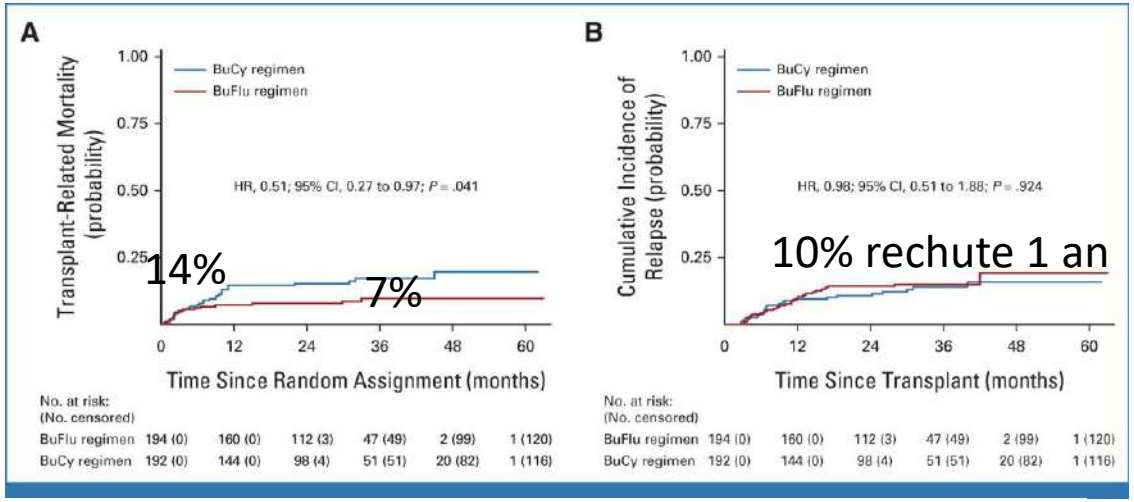
Supplementary Figure 2. Kaplan-Meier curves of leukemia-free survival (A) and overall survival (B).

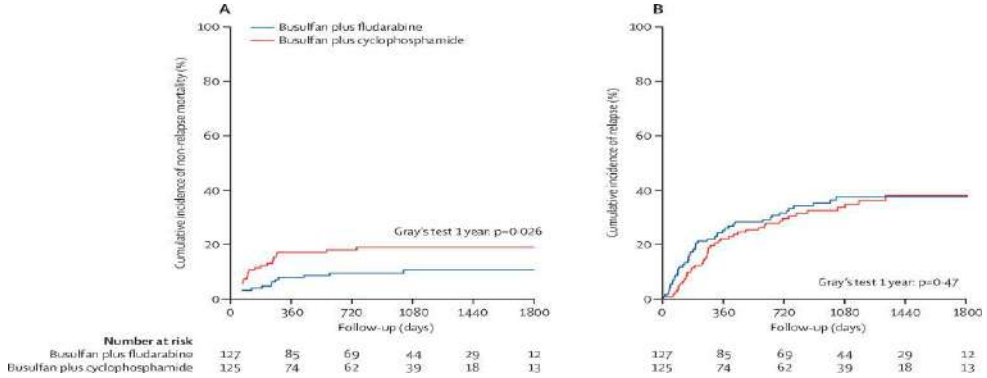
FB4 vs Bu-Cy

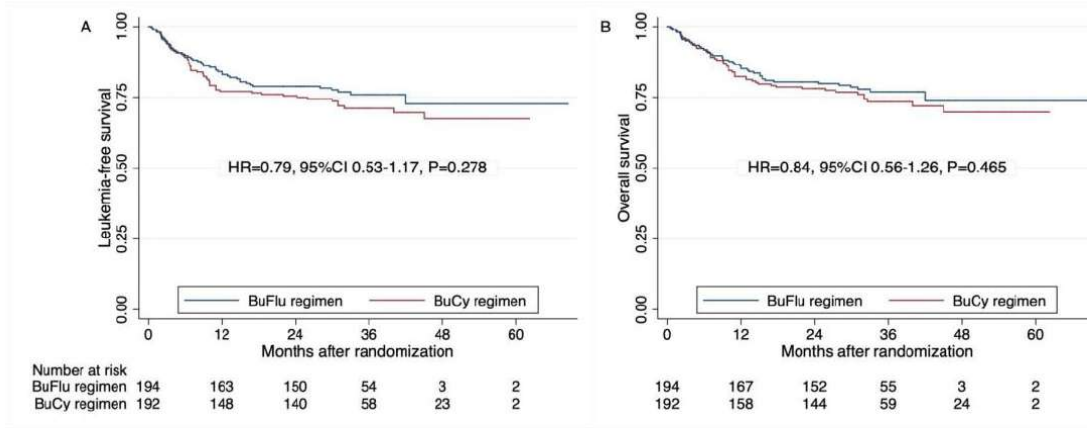
rando phase 3

Ling, JCO 2023, **Haplo**
âge median **35 ans**
ciclo+MTX+ATG+**MMF/ G-DLI**

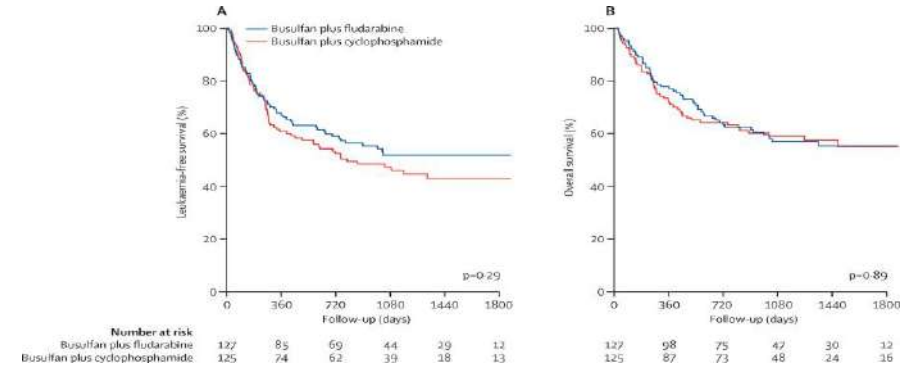
Rambaldi, Lancet oncol 2015 **Matchées**
âge median **50 ans**
ciclo+ MTX +/- ATG MUD



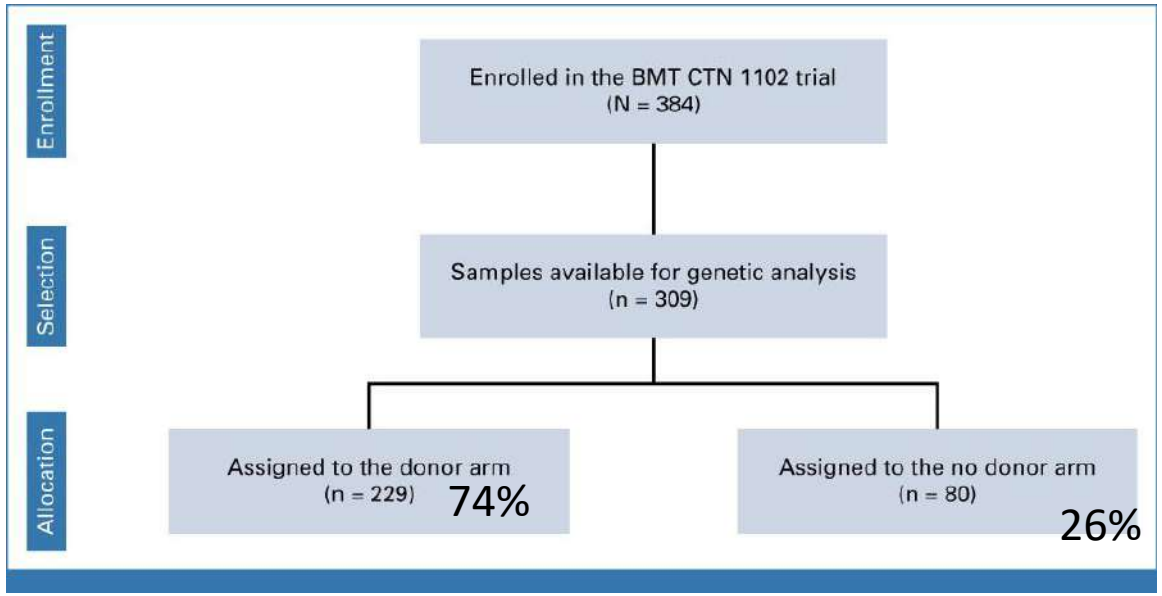




Supplementary Figure 2. Kaplan-Meier curves of leukemia-free survival (A) and overall survival (B).



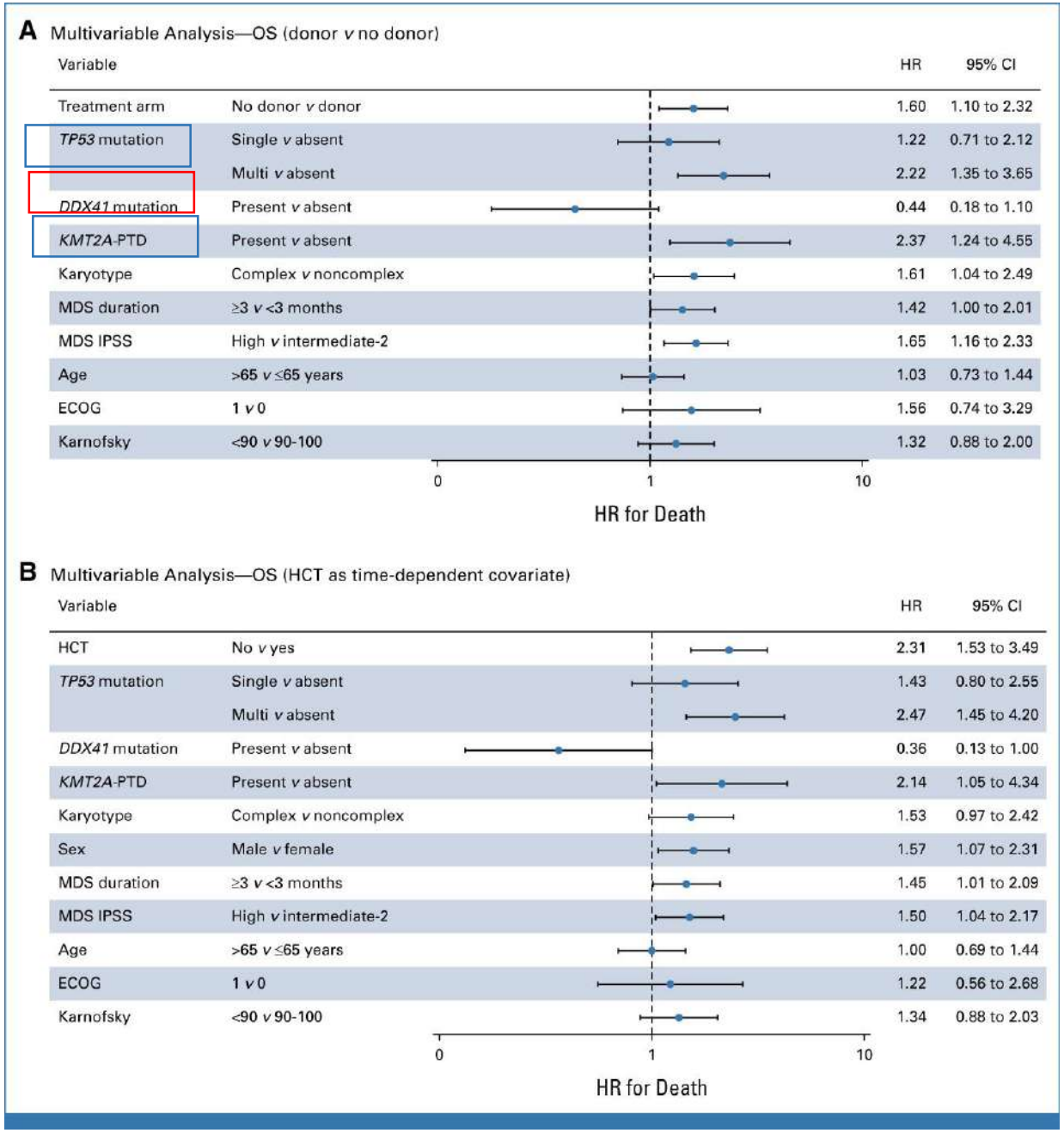
Allogeneic Hematopoietic Cell Transplantation Improves Outcome in Myelodysplastic Syndrome Across High-Risk Genetic Subgroups: Genetic Analysis of the Blood and Marrow Transplant Clinical Trials Network 1102 Study



follow up med chez survivants 32 mois

IPSS		
Intermediate-2	206	66.7%
High	103	33.3%
IPSS-R		
Very low, low, intermediate	95	30.7%
High	109	35.3%
Very high	105	34.0%
IPSS-M		
Very low	26	8.4%
Low	42	13.6%
Moderate low	42	13.6%
Moderate high	45	14.6%
High	85	27.5%
Very high	69	22.3%
Karyotype		
Complex	201	65.0%
Non-complex	78	25.2%
Missing	30	9.7%

Jurjen Versluis, JCO 2023



TP53+ 28% allo, 29% non allo

Table S3. Univariate analysis of Overall Survival by Mutation

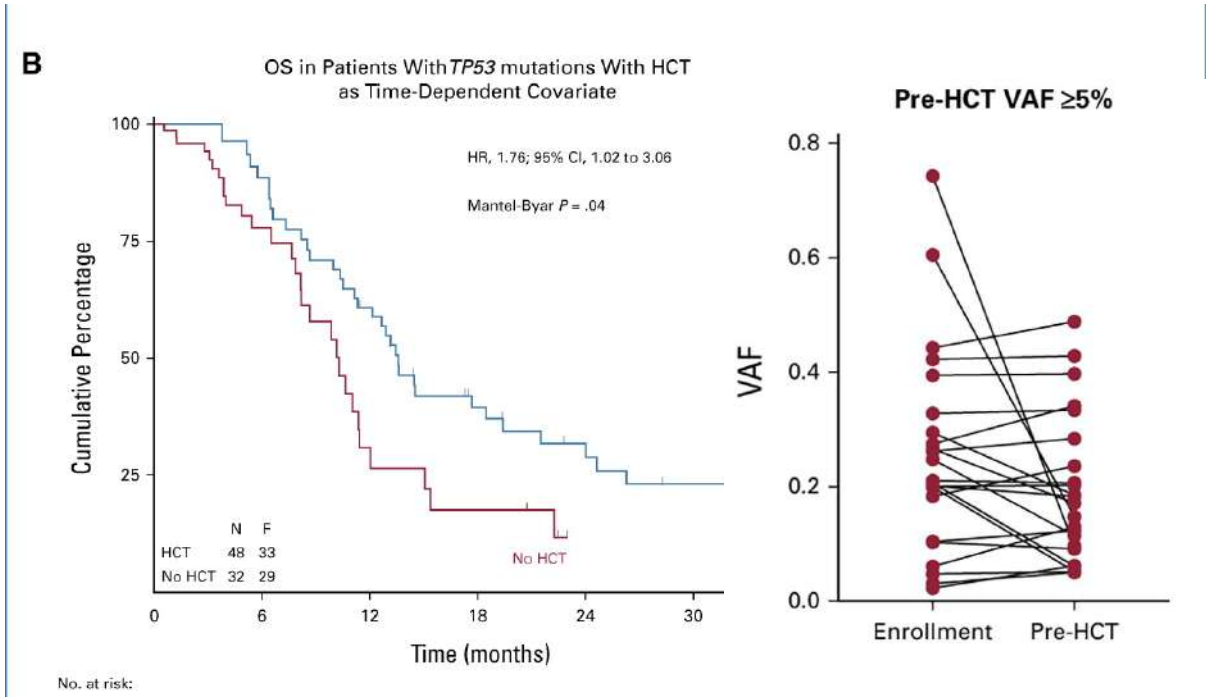
Mutation (present vs. absent)*	**HR (death)**	**95% CI**	***P* value**
TP53	2.55	1.86–3.50	<.001
KMT2A-PTD	2.21	1.22–3.99	.009
NRAS	1.73	0.85–3.52	.133
BCOR	1.18	0.60–2.32	.623
ETV6	1.16	0.57–2.36	.685
TET2	1.03	0.67–1.58	.883
DNMT3A	0.95	0.61–1.48	.819
SETBP1	0.94	0.42–2.13	.886
EZH2	0.92	0.38–2.23	.847
U2AF1	0.79	0.48–1.29	.349
SRSF2	0.74	0.47–1.17	.202
ASXL1	0.72	0.50–1.06	.096
RUNX1	0.67	0.42–1.09	.105
SF3B1	0.67	0.30–1.51	.336
STAG2	0.57	0.34–0.96	.034
IDH2	0.54	0.22–1.31	.172
DDX41	0.39	0.17–0.87	.022

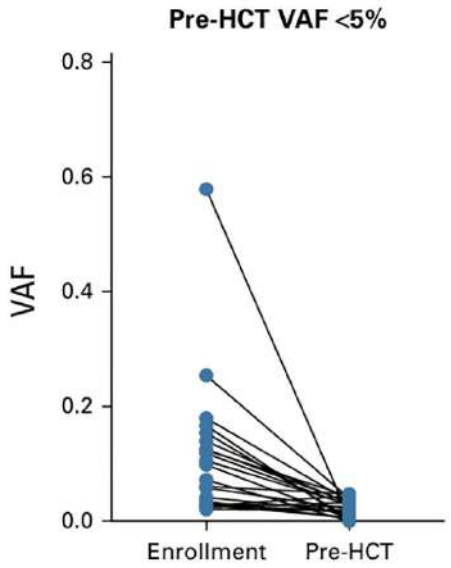
* Listed mutations are present in ≥10 patients

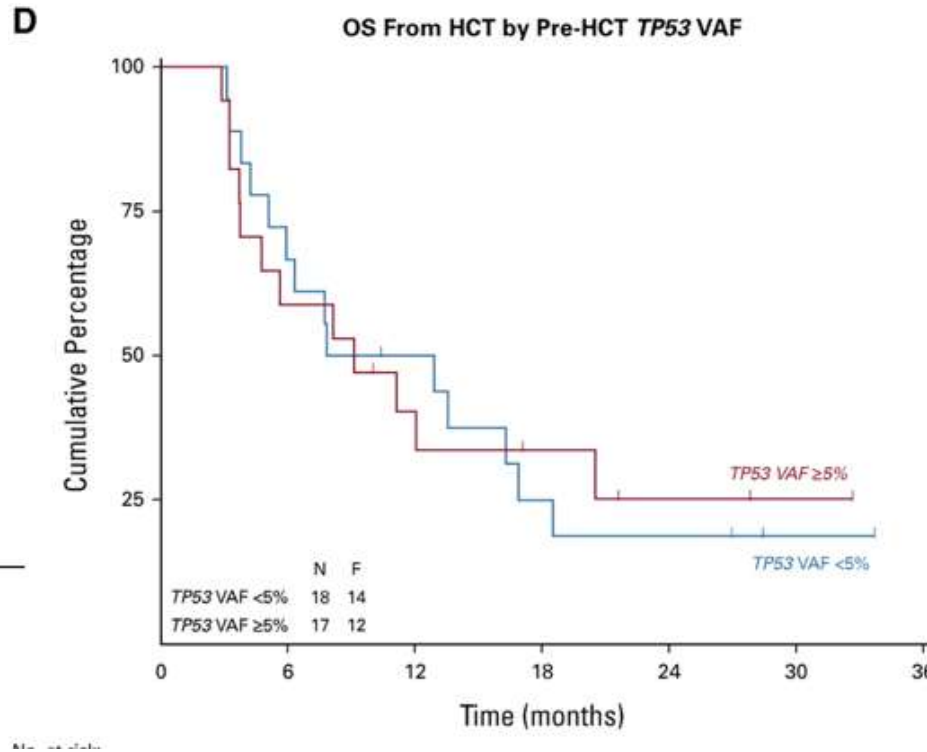
DDX41 7% (n=23 dont 20 allo
1 rechute (TP53+)= 4%
5 TRM=25% (0 FB2)
DFS: 70%

n= 87 TP53 (55% multihit),
55 allo, 32 non allo

pas d'impact de la clearance pré SCT de TP53

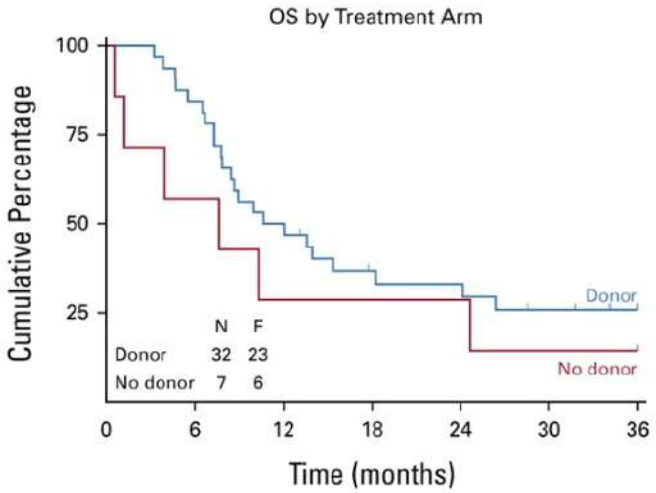


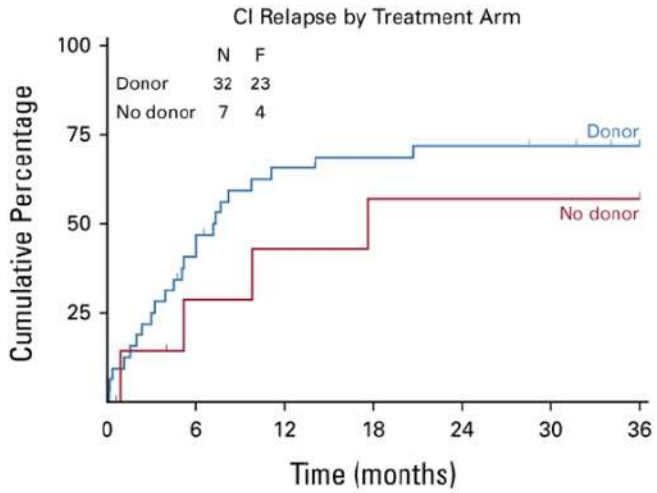




Jurjen Versluis, JCO 2023

IPSS-M Very High Risk—*TP53* Mutation Present

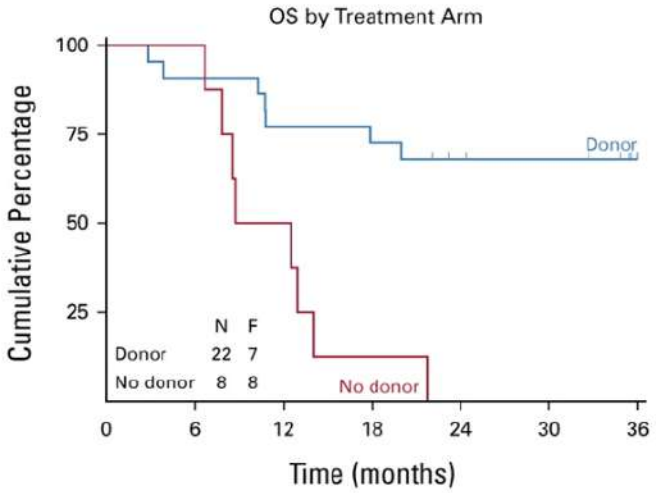


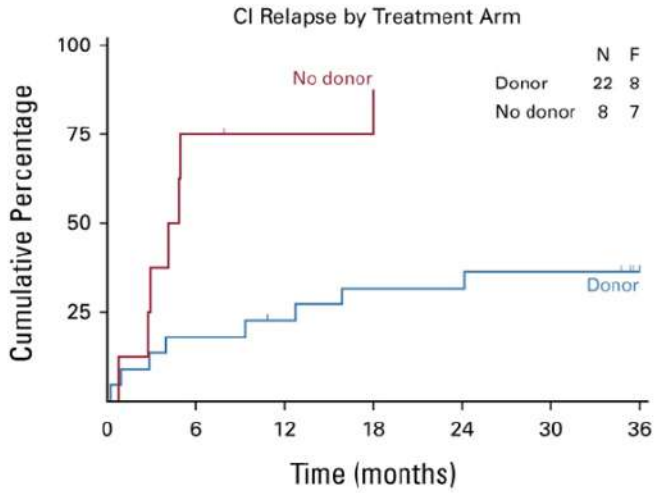


No. at risk:							
Donor	32	27	16	10	9	6	2
No donor	7	4	2	2	2	1	1

No. at risk:							
Donor	32	17	8	6	5	4	1
No donor	7	3	2	1	1	1	1

IPSS-M Very High Risk—*TP53* Mutation Absent





No. at risk:							
Donor	22	20	17	16	13	12	4
No donor	8	8	4	1	0	0	0

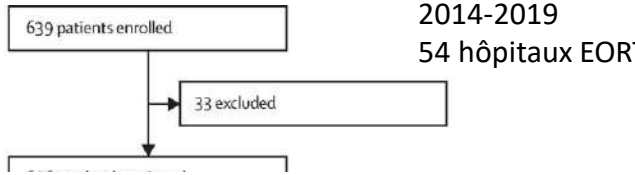
No. at risk:							
Donor	22	16	13	11	11	10	4
No donor	8	2	1	1	0	0	0

Jurjen Versluis, JCO 2023

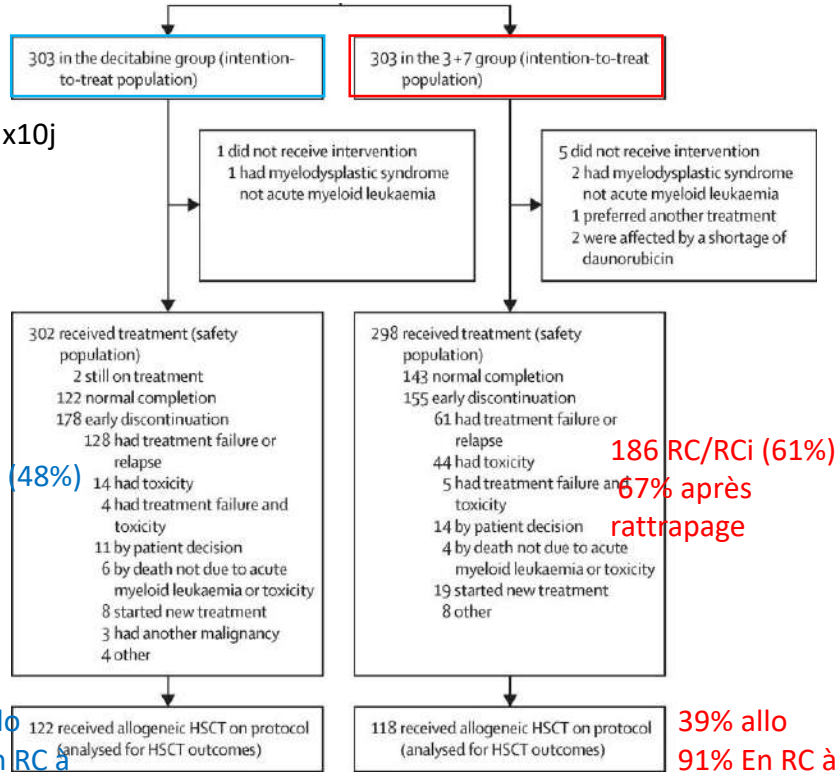
10-day decitabine versus 3 + 7 chemotherapy followed by allografting in older patients with acute myeloid leukaemia: an open-label, randomised, controlled, phase 3 trial

med follow up 4 ans

2014-2019
54 hôpitaux EORTC, GIMENA, MDS group



67 ans med, 1/3>70 ans



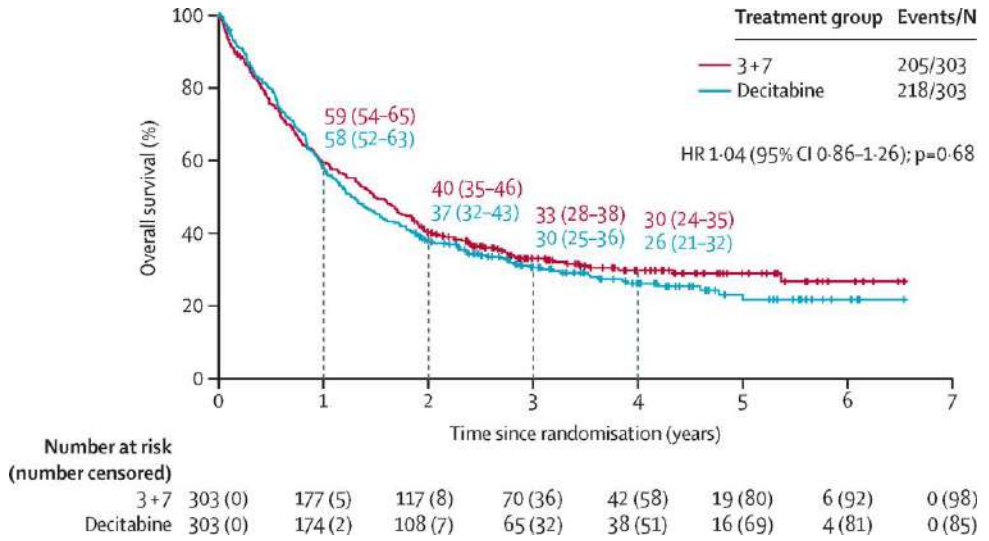
20mg/m2 x10j

145 RC/RCi (48%)
60% après rattrapage

186 RC/RCi (61%)
67% après rattrapage

40% allo
75% en RC à allo

39% allo
91% En RC à l'allo



LAM bon prc (NPM1) ou int → chimio
>30G/L GB → chimio

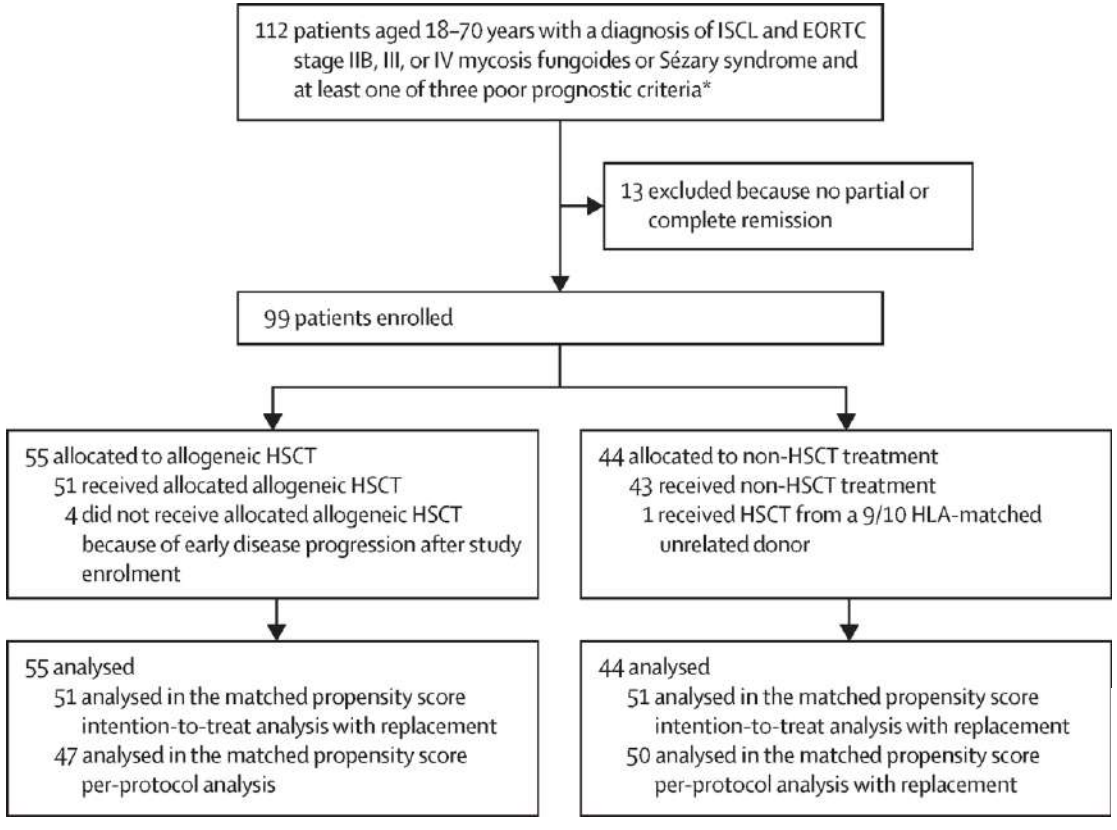
LAM défavo monosomal → decitabine (RC id)
>70 ans → decitabine (TRM dim)

vénéto? inh FLT3?

Lubbert, Lancet hematol 2023

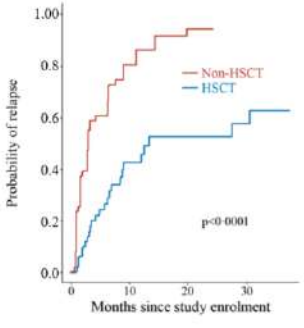
Allogeneic transplantation in advanced cutaneous T-cell lymphomas (CUTALLO): a propensity score matched controlled prospective study

A de Masson, Lancet 2023



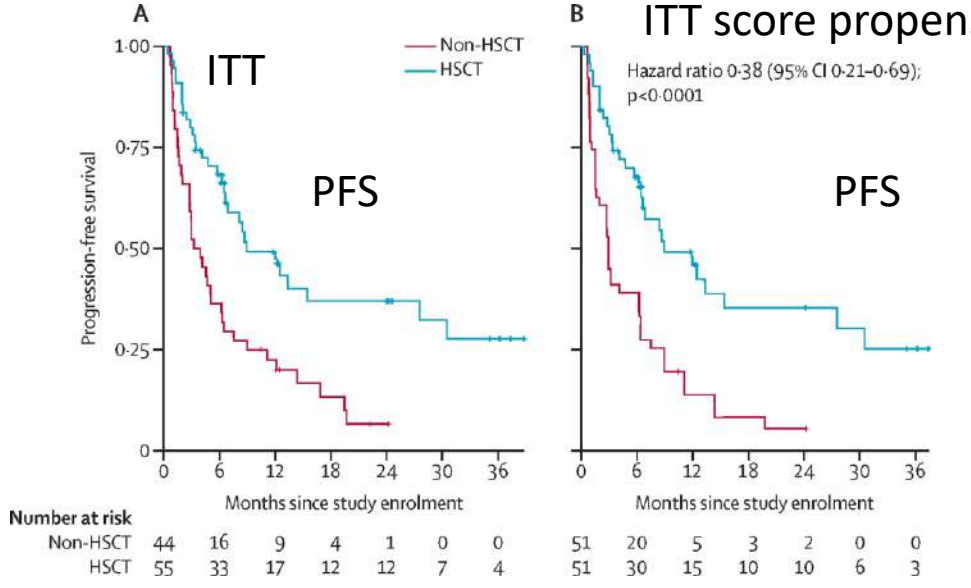
20% RC cut à l'inclusion
MSD ou MUD ou haplo RIC
pas d'ATG

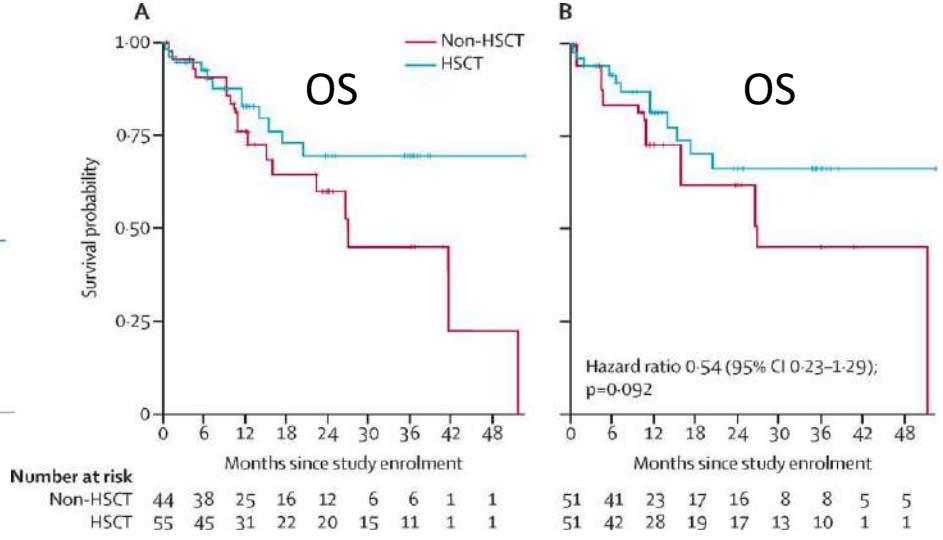
14% RC cut à l'inclusion



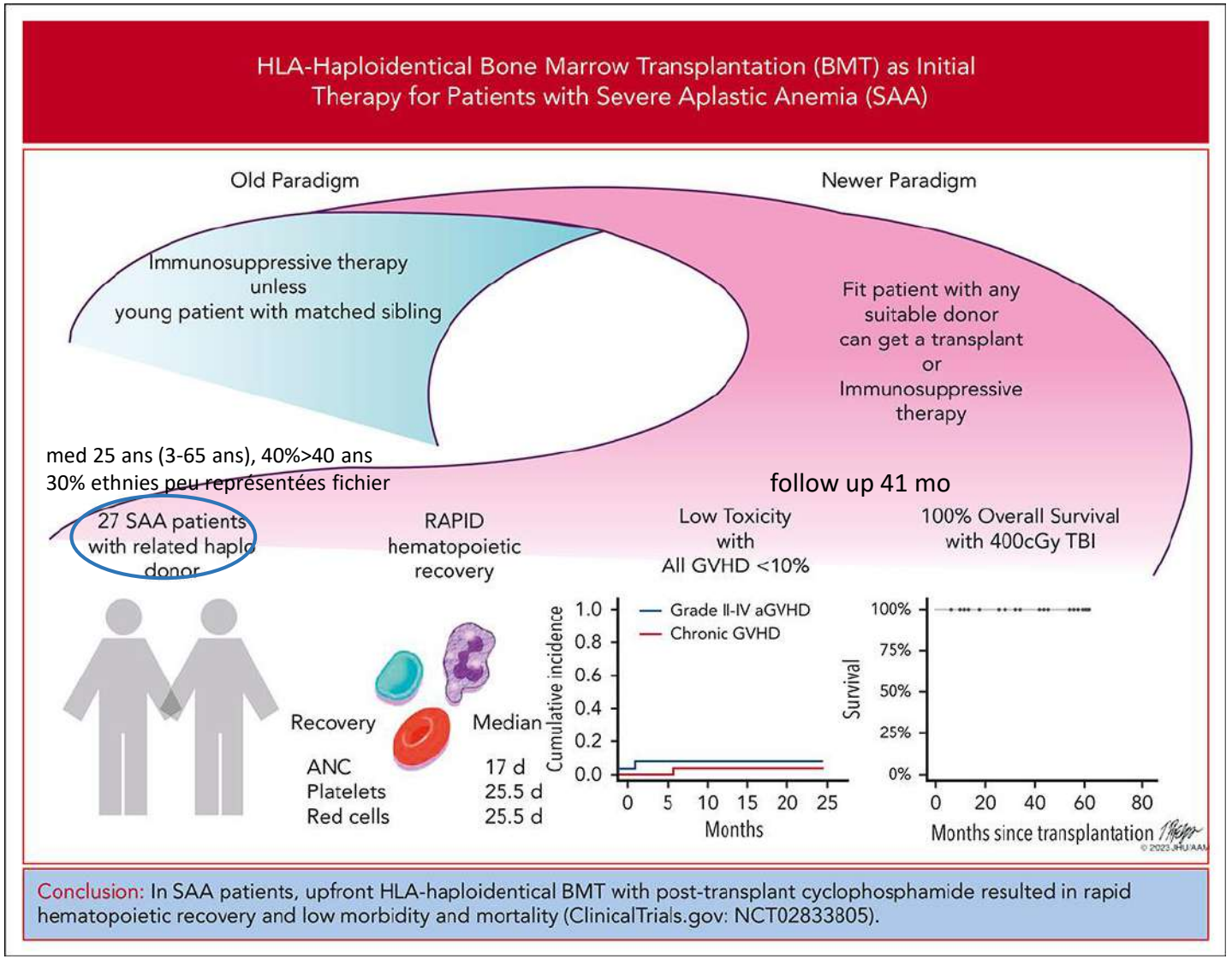
Rechute 1 an :47%allo vs 86% non allo
NRM 1 an:8.5% allo vs 0% non allo

ITT score propension





Greffe haplo 1ere ligne pour les aplasies médullaires sévères



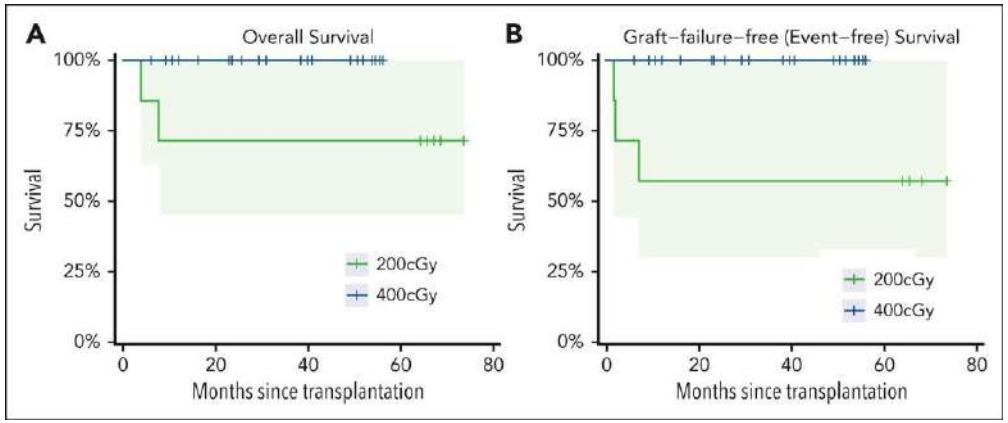
Inclusion:
AA sévère:2 critères/3 (PNN <0.5 × 109/L, plaq <20 × 109/L ou reticulocyte <60 × 109/L)

Exclusion
Donneur géno si R<25 ans
DSA>1000 MFI
Fanconi, telomères courts, -7
Atcd de traitement IMS

Rabbit ATG (rATG; Thymoglobulin) 0.5 mg/kg J −9 , 2 mg/kg J−8 and −7
Fludarabine 30 mg/m2 IV daily J −6 à J−2 (dt 150 mg/m2)
Cyclophosphamide 14.5 mg/kg IV J −6 à J −5
TBI 200 cGy on day −1 puis aug 400cGy après 7 premiers patients (3 rejets dont 2 DC)

Prévention GVH: HD-Cy PT 50mg/Kg J3, J4 + Tacro (1 an puis réduit 6 mois) et MMF (J5-J35)

Moelle
4x108 CNT/Kg



DeZern; Blood 2023

Infectieux

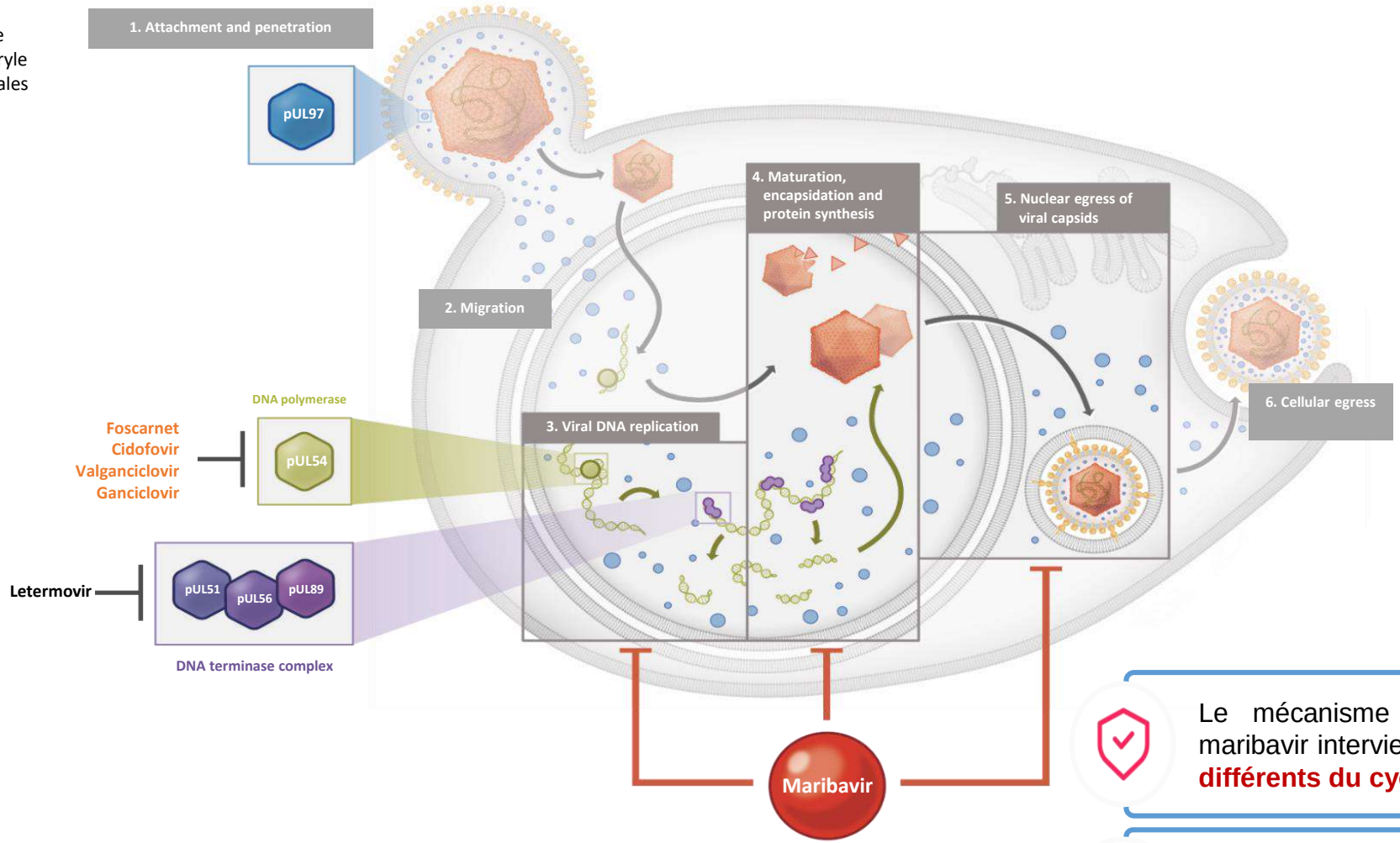
Le processus de réplication CMV

La protéine kinase CMV UL97 est une sérine/thréonine kinase qui phosphoryle un certains nombres de protéines virales et cellulaires, y compris pUL44[1,2]

La protéine kinase UL54 (ADN polymérase) est ciblée par les médicaments antiviraux GCV, VGCV, FOS[3] et CDV[4]

Complexe de terminaison d'ADN CMV - l'holocomplexe d'encapsidation fonctionnel est un hétéro-oligomère composé des protéines pUL56, pUL89 et pUL51[3], protéines contribuant au processus de clivage et d'emballage de l'ADN

- LET cible un mécanisme dépendant de l'interaction de pUL56, pUL89 et pUL51[3]



Le mécanisme d'action multi-cible du maribavir intervient au niveau de **3 points différents du cycle de vie viral**

Haut niveau de spécificité au CMV, réduisant **les effets non spécifiques/non désirés**

1. Prichard MN. Rev Med Virol. 2009;19:215–29; 2. Wolf DG, et al. Proc Natl Acad Sci USA. 2001;98:1895–900; 3. Ligat G, et al. FEMS Microbiol Rev. 2018;42:137–45; 4. El Chaer F, et al. Blood. 2016;128:2624–36; 5. Crough T, Khanna R. Clin Microbiol Rev. 2009;22:76–98; 6. van Damme E, et al. Front Microbiol. 2014;5:218; 7. Mettenleiter TC, et al. Virus Res. 2009;143:222–34; 8. Fishman JA. Am J Transplant. 2013;13(suppl 3):1–8.

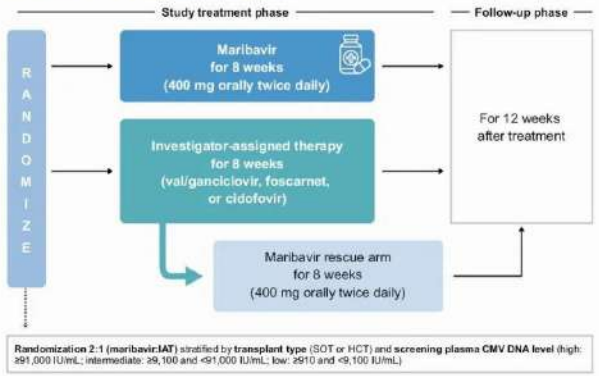
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

Robin K. Avery, Sophie Alain, Barbara D. Alexander, Emily A. Blumberg, Roy F. Chemaly, Catherine Cordonnier, Rafael F. Duarte, Diana F. Florescu, Nassim Kamar, Deepali Kumar, Johan Maertens, Francisco M. Marty, Genovefa A. Papanicolaou, Fernanda P. Silveira, Oliver Witzke, Jingyang Wu, Aimee K. Sundberg, and Martha Fournier, for the SOLSTICE Trial Investigators

INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

STUDY DESIGN



STUDY ENDPOINTS

The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

PRIMARY ENDPOINT (WEEK 8)

Adjusted difference (95% CI): 32.8 (22.80–42.74)

A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

KEY SECONDARY ENDPOINT (WEEK 16)

Adjusted difference (95% CI): 9.5 (2.02–16.88)

A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

SAFETY

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.

Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).

Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).

One patient per treatment group had fatal treatment-related TEAEs.

CONCLUSIONS

Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

CMV, cytomegalovirus; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid-organ transplant; TEAE, treatment-emergent adverse event.

ClinicalTrials.gov: NCT02931539
This study was funded by Takeda Development Center Americas, Inc., Lexington, MA

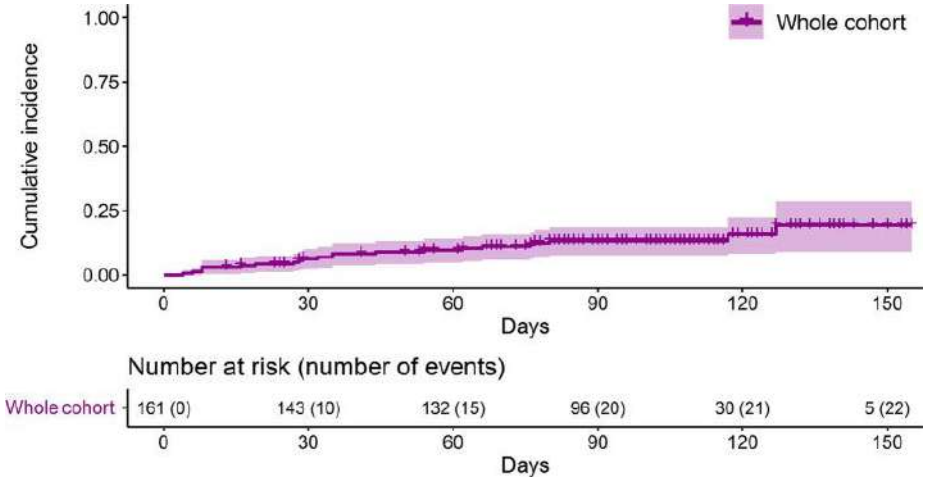
Mars 2023
Avis favorable au remboursement dans « le traitement de l'infection et/ou de la maladie à cytomégalovirus (CMV) réfractaire (avec ou sans résistance) à un ou plusieurs traitements antérieurs, y compris le ganciclovir, le valganciclovir, le cidofovir ou le foscarnet chez les patients adultes ayant reçu une greffe de cellules souches hématopoïétiques (GCSH) ou une greffe d'organe solide (GOS). »
Realiser genotypage de resistance

ACCES PRECOCE

Avery, Clin Inf Dis 2022

Expérience SFGM-TC du tixagevimab/cilgavimab (AZD7442) en prophylaxie primaire , vague omicron

n=161 adultes allogreffés
med 58 ans
73% avaient été vaccinés
critère ATU: séro IgG anti S <264 BAU
88% avaient 1 ou + fdr non réponse
Déc 2021-Avril 2022:AZD7442 150+150 mg
med follow up 105 jours

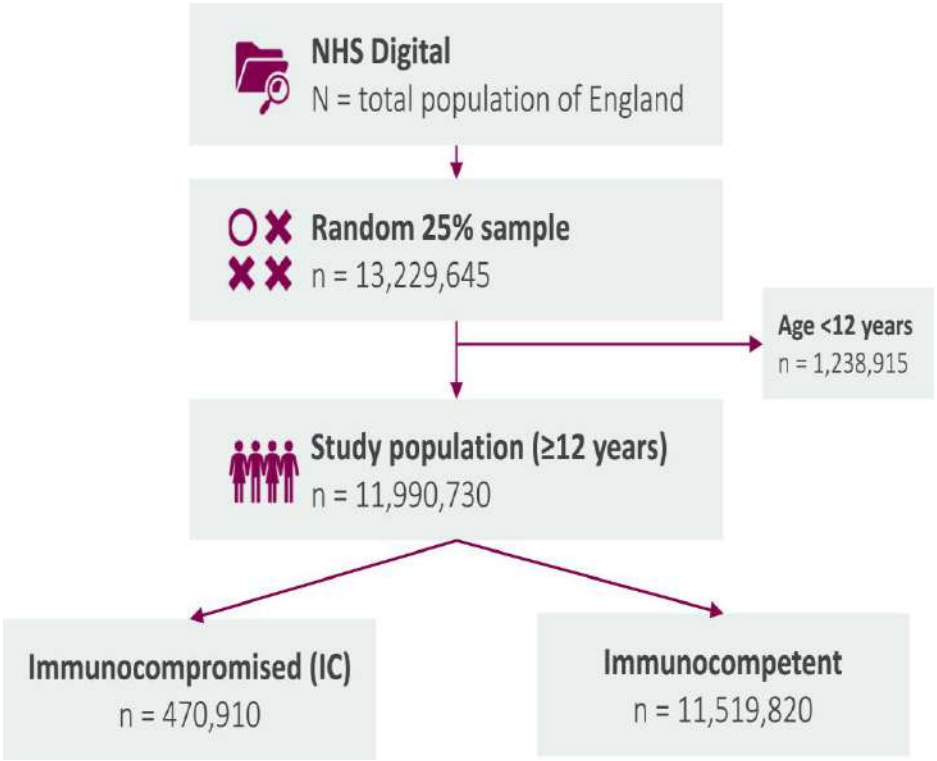


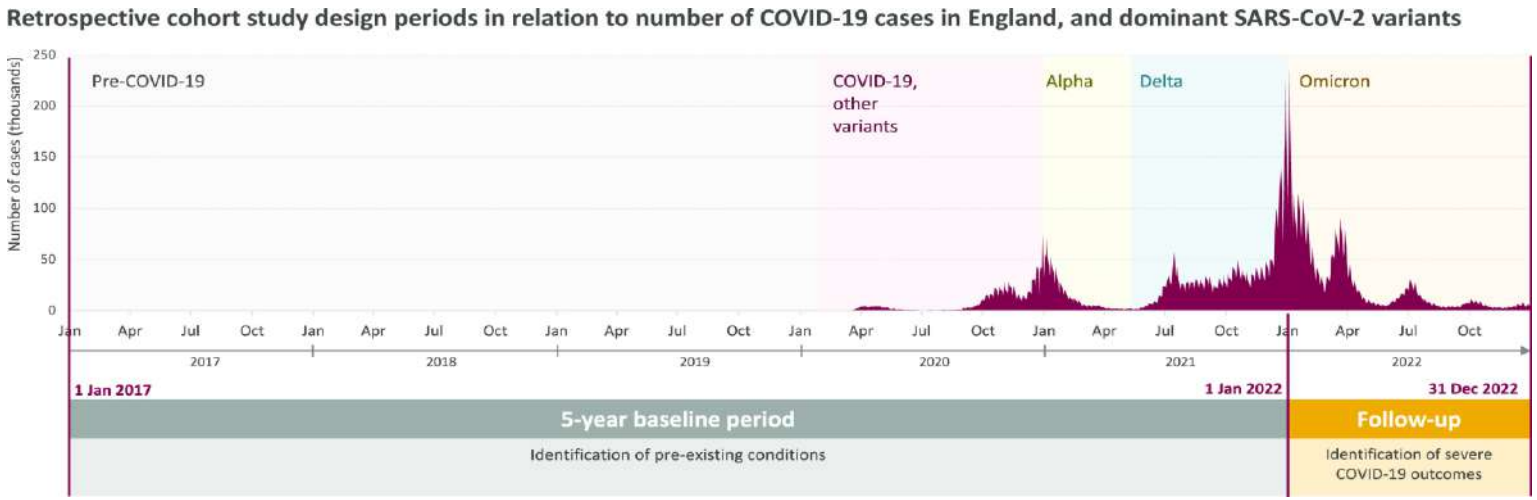
que serait il passé sans prophylaxie?
Omicron est il sévère chez les IMD?

14% de COVID, pas de forme sévère, pas de décès
profil plutôt favorable au vu de la littérature
intérêt de doubler les doses? (PRECOVIM)

Jondreville, J Hematol Oncol 2022

Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study





3.9% de la pop anglaise
>80% ont reçu 3 doses ou + vaccin

22% hospit COVID ➡ aug risque 1.3 à 13.1
28% USI COVID
24% décès COVID ➡ aug risque 1.3 à 19.9

pop + à risque: transplantés d'organe solide

➡ OMICRON reste une infection sévère

Evans, The Lancet Regional Health - Europe in press

CAR

Cette Ford Mustang électrique est vendue plus de 300.000 euros

TRANSFORM

Rando

N=92 SOC
3 chimio puis auto si reponse

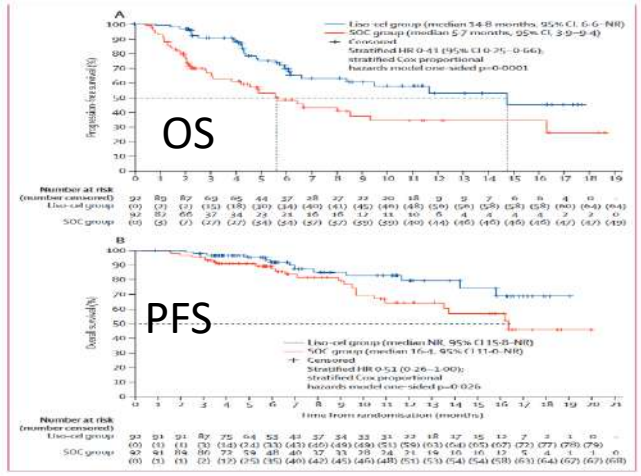
92 CART
Liso-cell

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

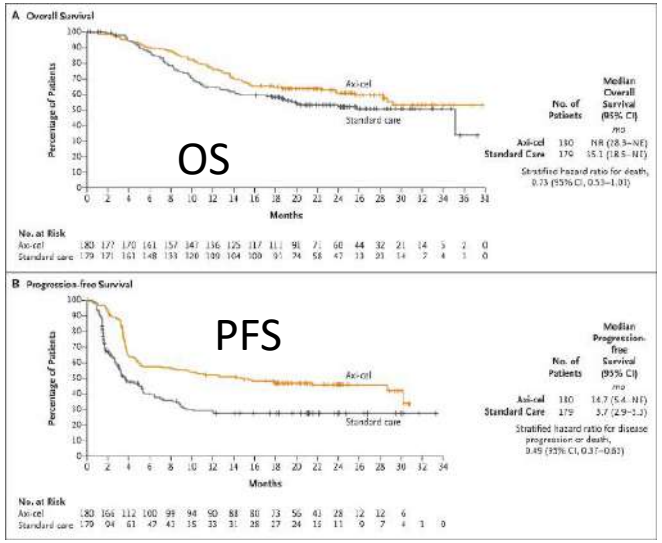
Certains ref ont reçu des CART

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%

CART>auto
2de ligne



Locke, NEJM 2022

BELINDA

Rando

N=160 SOC
3 chimio puis auto si reponse

162 CART
Tisa-cell

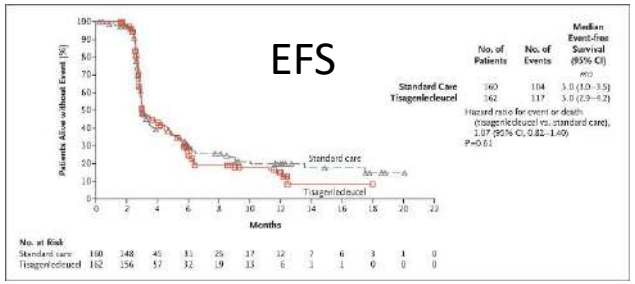
81 Tisa-cel
3ieme ligne

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

CART=auto
2de ligne



Bishop NEJM 2022

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: Primary analysis of phase 3 TRANSFORM study (Abramson et al)

- **Primary endpoint:** EFS (per IRC)
  Key secondary endpoints: CR rate (per IRC), PFS (per IRC), OS
- **Eligibility:** Adult patients with R/R LBCL ≤ 12 months after first-line therapy intended for ASCT

Patients with R/R LBCL | N = 184

Open-label, Phase 3 Trial Randomized 1:1

Liso-cel
n = 92
100 × 10^6 CAR$^+$ T cells

58 (63%) received bridging therapy
89 (97%) received liso-cel

SOC
n = 92
3 cycles of platinum-based immunochemotherapy + HDCT/ASCT

43 (47%) completed full SOC treatment
61 (66%) approved for crossover to receive liso-cel as 3rd line therapy after SOC failure

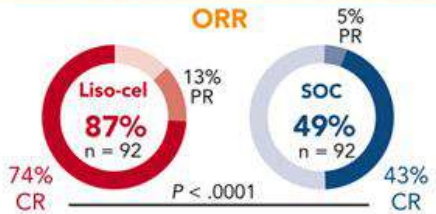
Efficacy

Median EFS, PFS, and OS

Stratified HR	18-month rate diff.
EFS: HR, 0.356; not retested	+31.8%
PFS: HR, 0.400; *P* < .0001	+29.4%
OS: HR, 0.724; *P* = .0987	+12.5%

Median follow-up: 17.5 months

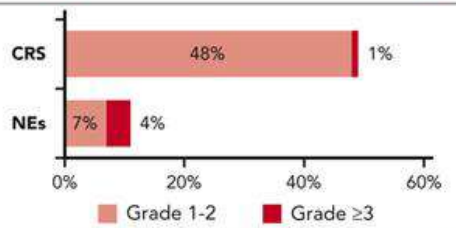
ORR



Safety

Grade ≥3 TEAEs

	Liso-cel	SOC
Serious AEs	48%	49%
Deaths due to TEAEs	2%	2%

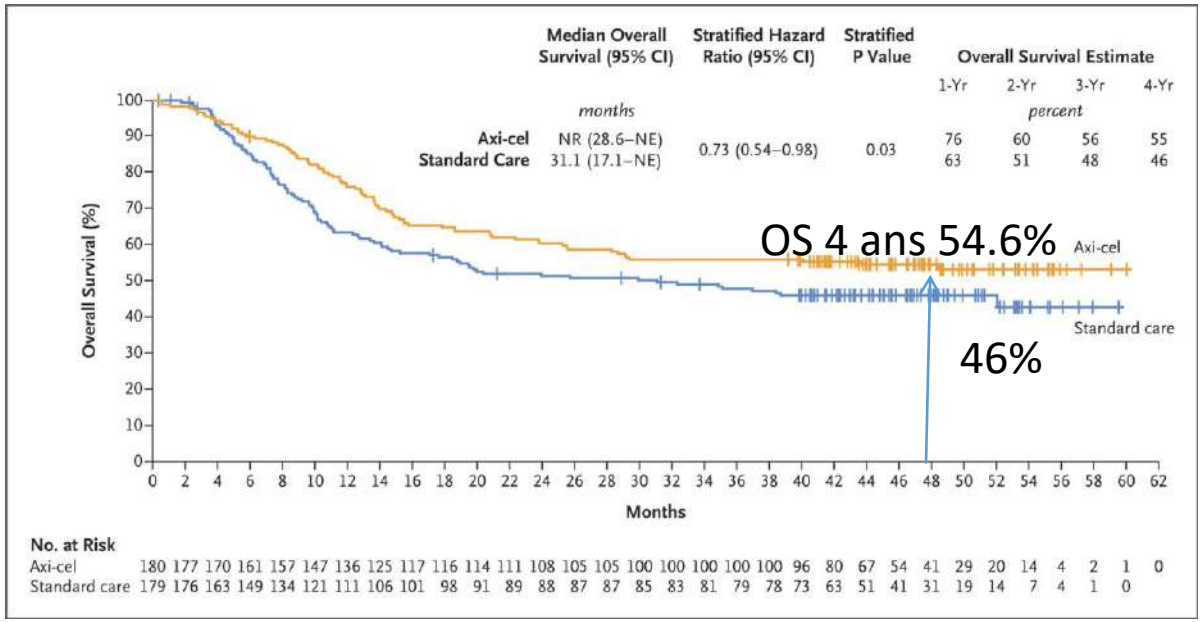


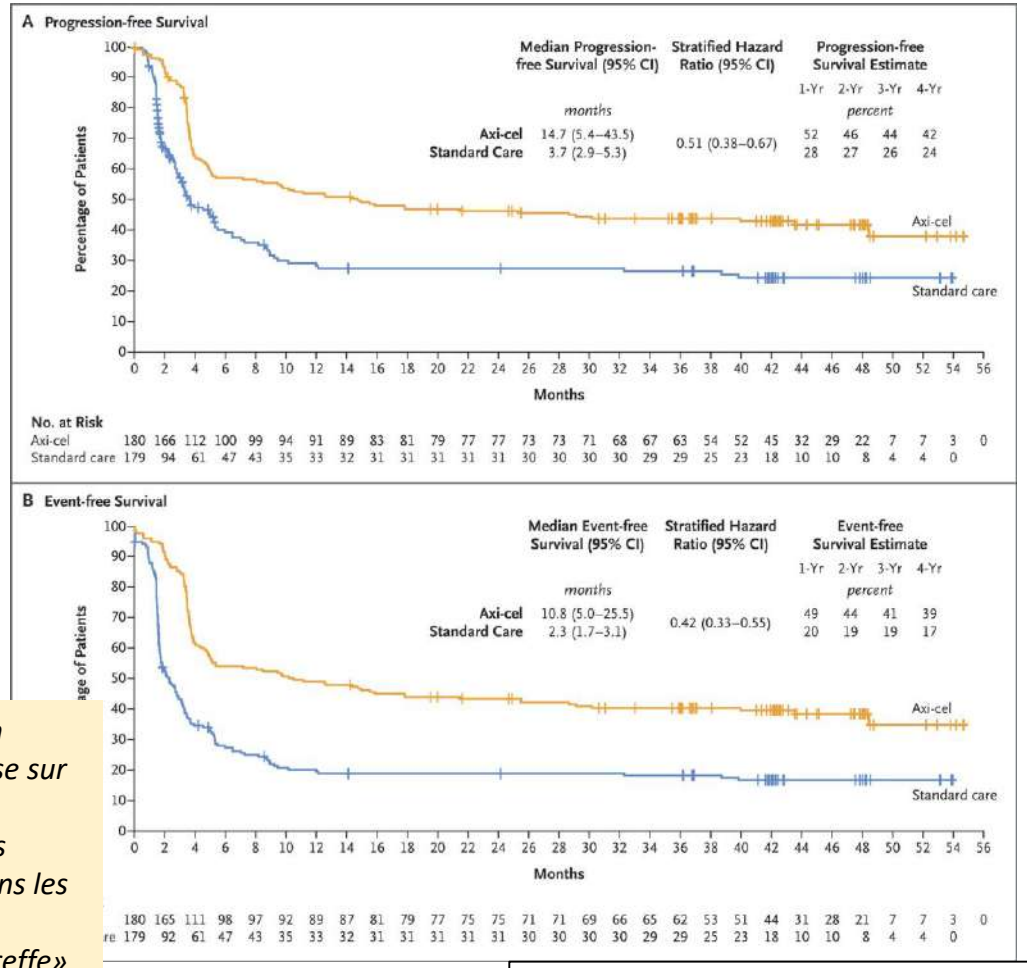
No Grade 4 or 5 CRS or NEs

No prophylactic corticosteroids or vasopressors used

ASCT, autologous hematopoietic stem cell transplantation; CR, complete response; CRS, cytokine release syndrome; EFS, event-free survival; HDCT, high dose chemotherapy; IRC, independent review committee; NE, neurological event; ORR, objective response rate; PFS, progression-free survival; R/R, primary refractory or early relapsed; OS, overall survival; SOC, standard of care; TEAE, treatment-emergent adverse event.

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma (ZUMA-7)





11 2d cancers (8 Axi-cell (4.4%) /3 chimio)

Arm	Patient	Preferred Term	Toxicity Grade	Serious AE
Axi-Cel	1	Spindle cell sarcoma	2	Yes
	2	Hepatocellular carcinoma	3	Yes
	3	Acute myeloid leukemia (transformed from myelodysplastic syndrome)†	5	No‡
	4	Lung adenocarcinoma	5	Yes
	5	Adenocarcinoma of colon	3	Yes
	6	Myelodysplastic syndrome§	3	Yes
	7	Anal squamous cell carcinoma	3	Yes
	8	Plasma cell myeloma	1	Yes
Standard Care	9	Ductal adenocarcinoma of pancreas	3	Yes
	10	Metastatic malignant melanoma	3	Yes
	11	Bladder transitional cell carcinoma	3	Yes
		Adenocarcinoma of colon‖	3	Yes

* New or secondary malignancies are reported here irrespective of potential relationship to

Le médicament YESCARTA :autorisation d'accès précoce pré-autorisation de mise sur le marché (AMM) dans l'indication « traitement des patients adultes atteints deDLBCL, réfractaires ou en rechute dans les 12 mois après la fin d'un traitement de première ligne et éligibles à une autogreffe»

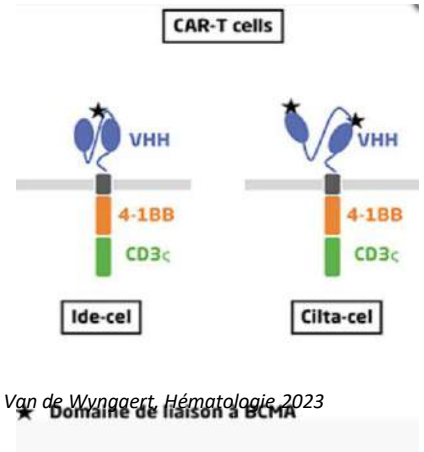
med follow up 47 mois (vs 24.9 dans la 1ere publi)
56% bras auto ont reçu CART 3ieme ligne

ALYCANTE
DLBCL,»unfit» à l'auto 1ere rechute: meilleure RC 82%
Houot, EHA abst s233

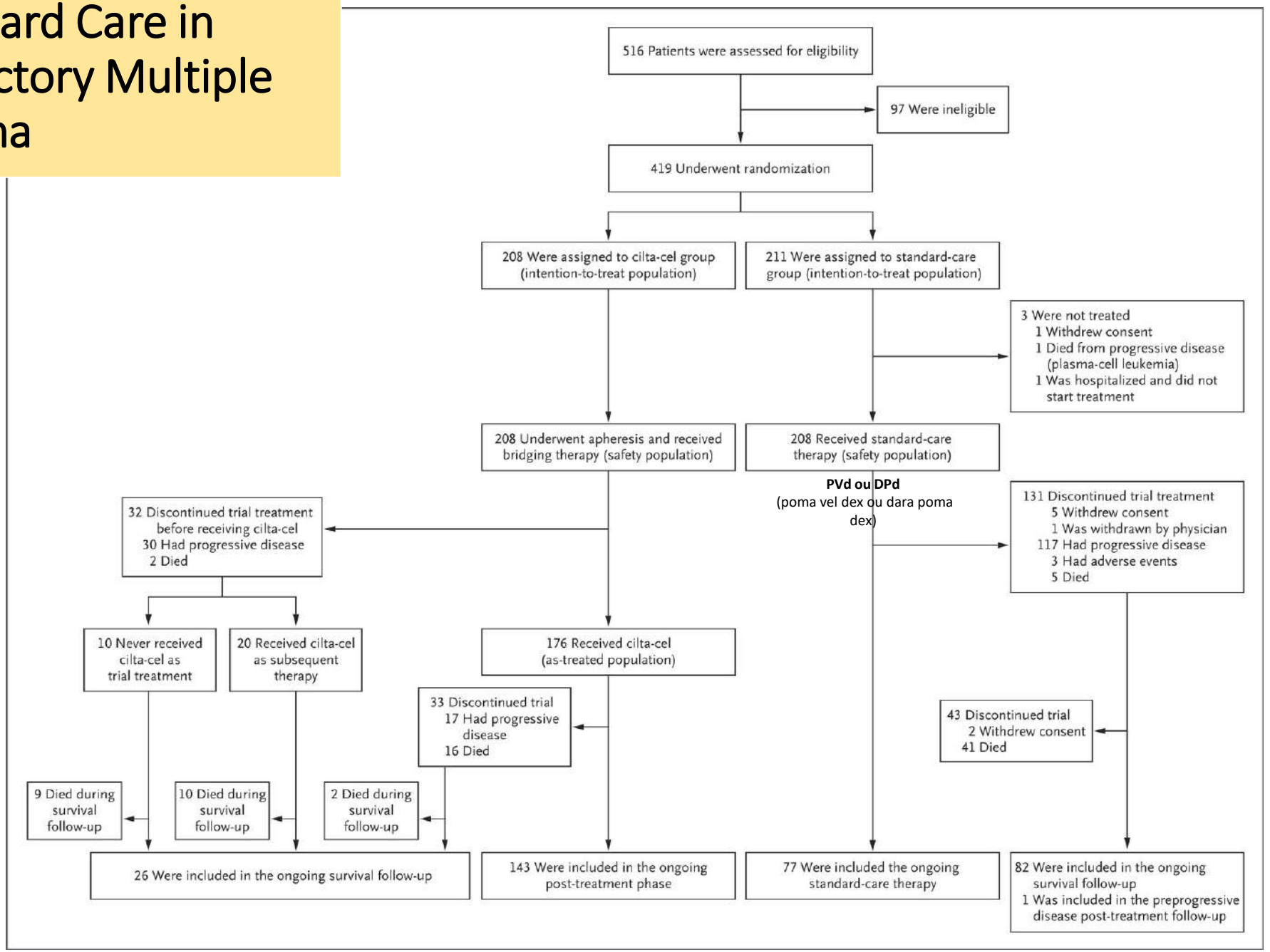
Jason R. Westin, NEJM 2023

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

Phase 3 rando MM ref Lenalidomide:
Cilta-cel vs SOC
1 à 3 L de ttt dont 1 IP et 1 IMiD
60% ht risque cytogénét
25% triple ref (- avancés que CARTITUDE-1)
critère ppal: SSP
suivi med 15.7 mois

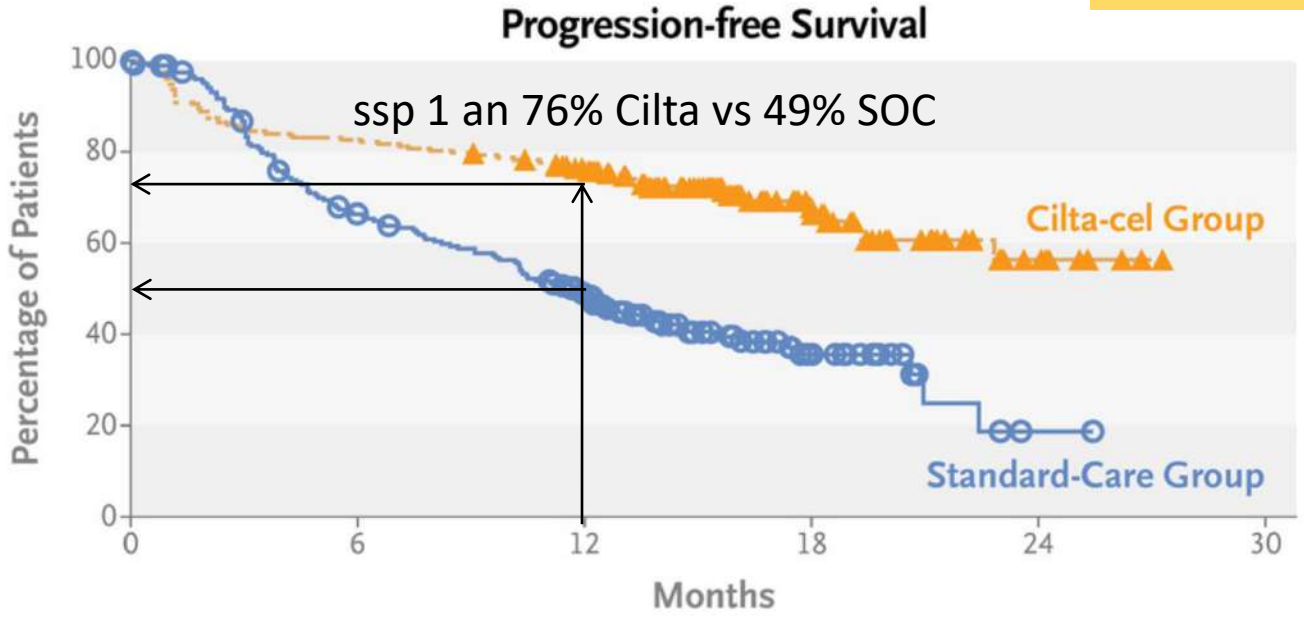


Van de Wyngaert, Hématologie 2023



San-Miguel, NEJM 2023

CARTITUDE-4

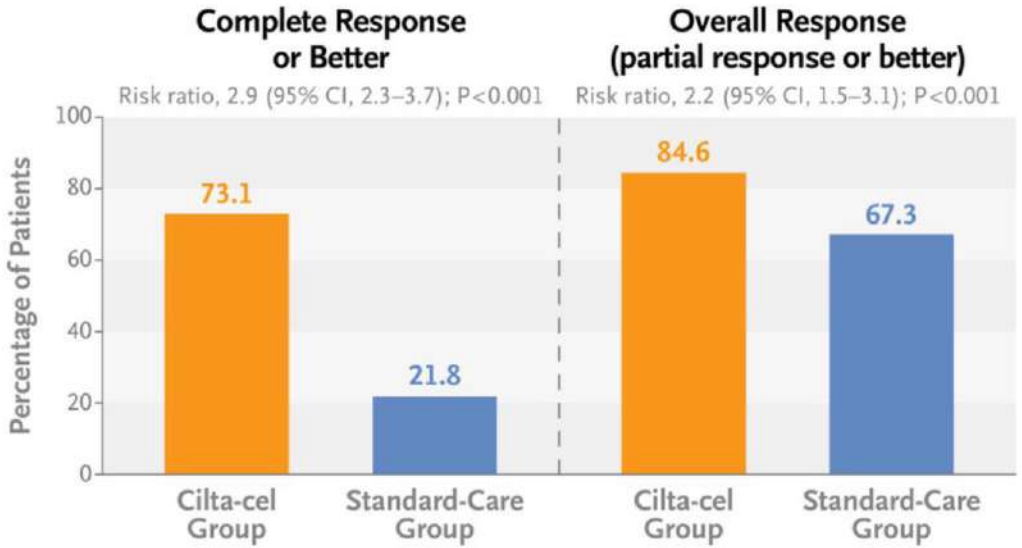


ssp 1 an 76% Cilta vs 49% SOC

dim du risque de progression ou de décès de 74%

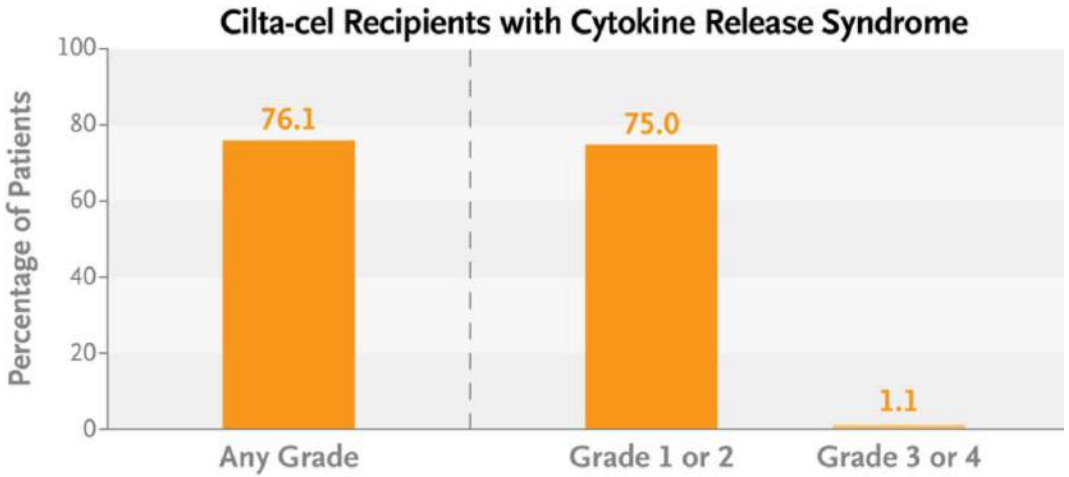
...à comparer avec anti-CD38+carfilzomib

CARTITUDE-6: rando vs autogreffe



RC 58.2%
MRD neg 60.6%

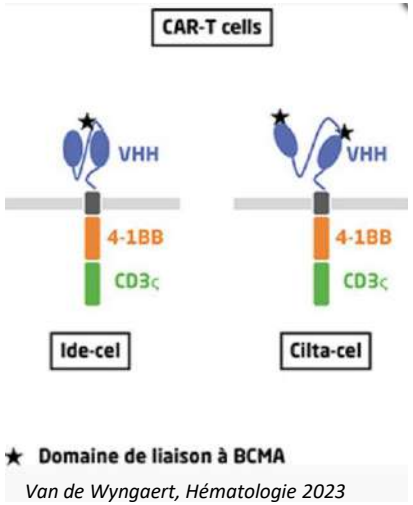
RC 15.2%
MRD neg 15.6%



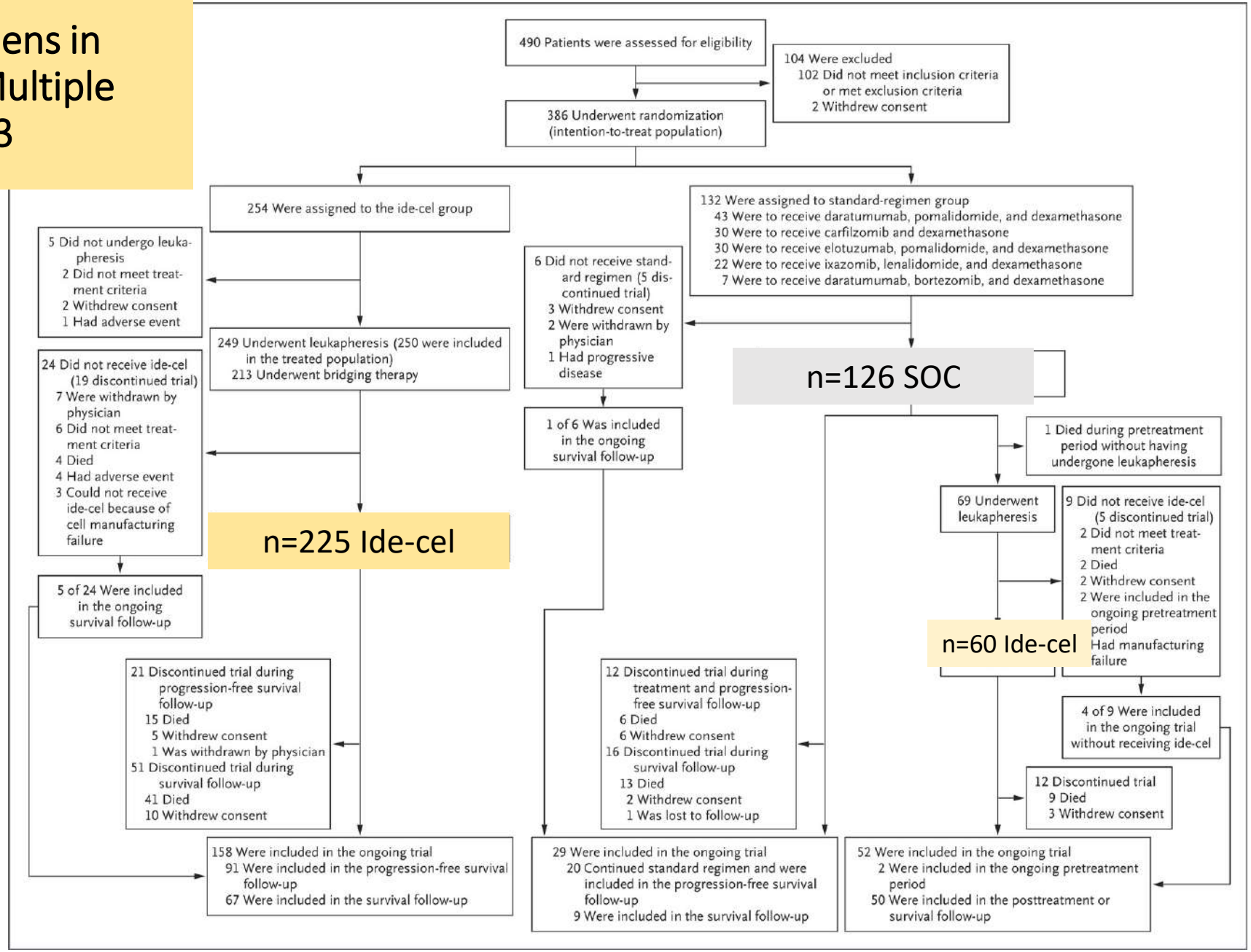
+ d'anémie et thrombopénie gr 3-4 avec Cilta-Cel
mais pas = d'infections
20% Icans 3% gr 3-4
warning: 10% de sd parkinson et para paires crâniennes tardif

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma KARMMa-3

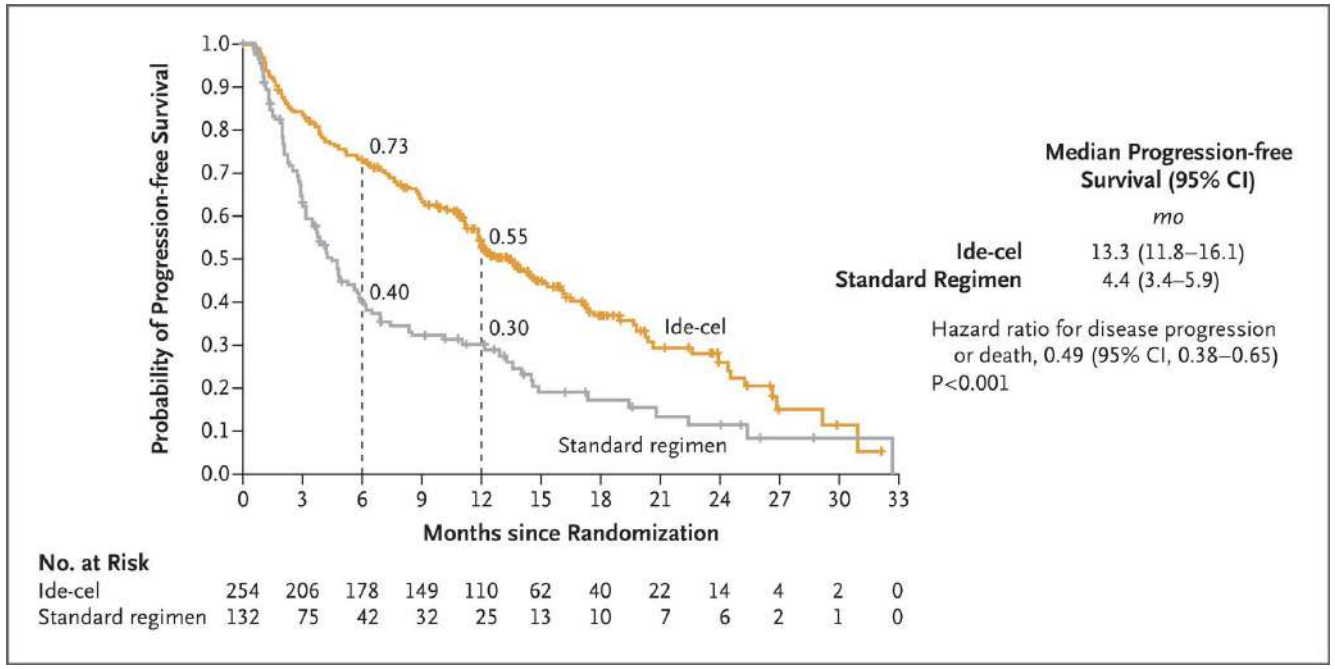
Phase 3 rando MM rec/ref
Ide-cel vs SOC
2 à 4L de ttt dont au moins 2 cyles Dara+ IMiD+IP
60% ht risque cytogénét
66% triple ref; 95% ont eu dara
dose: 150×106 to 450×106 CAR
primary end point: PFS



Van de Wyngaert, Hématologie 2023

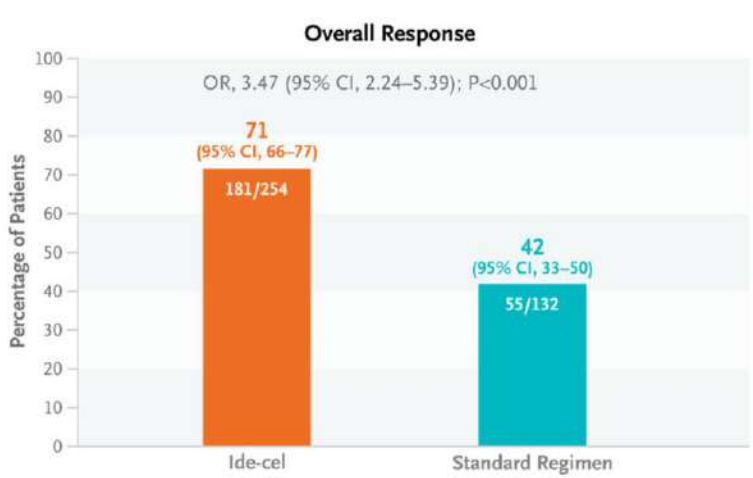


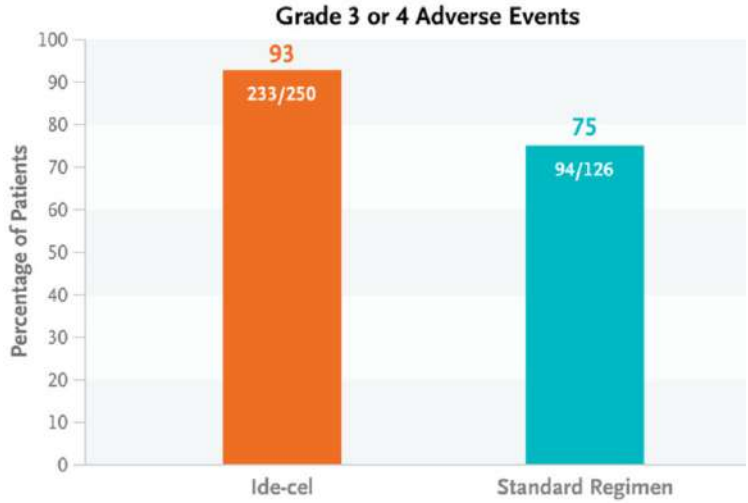
Rodriguez-Otero, NEJM 2023



➡ dim du risque de progression ou de décès de 51%

Approbation Europe et Remboursement France Ide-Cel (Abecma)
patients adultes atteints d'un myélome multiple en rechute et réfractaire ayant reçu au moins trois traitements antérieurs, incluant un agent immunomodulateur, un inhibiteur de protéasome et un anticorps anti CD38, et dont la maladie a progressé pendant le dernier traitement.



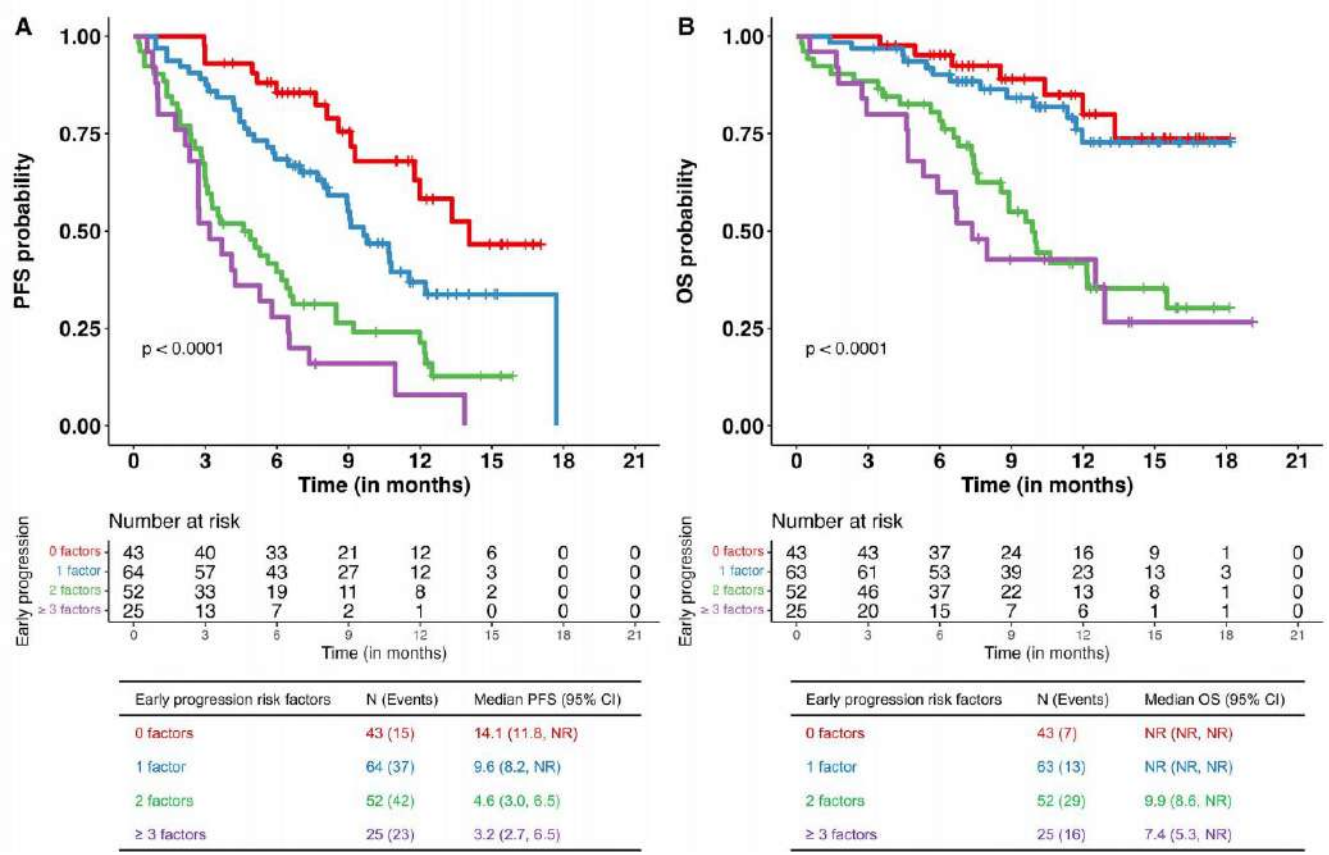


88% CRS, 4% gr 3-4
15% Icans 3% gr 3-4
décès liés au tt: 3% vs 1%

Factors associated with refractoriness or early progression after idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma: U.S. Myeloma Immunotherapy Consortium real world experience

Early progression risk factors :
- **prior BCMA therapy**
-extramedullary disease
-baseline ferritin
- plasma cell leukemia
- t(4;14)

Survival analysis by number of early progression risk factors.



Early progression risk factors	N (Events)	Median PFS (95% CI)
0 factors	43 (15)	14.1 (11.8, NR)
1 factor	64 (37)	9.6 (8.2, NR)
2 factors	52 (42)	4.6 (3.0, 6.5)
≥ 3 factors	25 (23)	3.2 (2.7, 6.5)

Early progression risk factors	N (Events)	Median OS (95% CI)
0 factors	43 (7)	NR (NR, NR)
1 factor	63 (13)	NR (NR, NR)
2 factors	52 (29)	9.9 (8.6, NR)
≥ 3 factors	25 (16)	7.4 (5.3, NR)

Hashmi, Haematologica 2023

Resservez-vous !

*Pr Noël Milpied**

* *Rédacteur en chef.*

Voilà un peu plus de 3 mois environ que le menu gargantuesque de 3 des congrès majeurs pour notre discipline (ASCO®, EHA et ICML- Lugano) a été servi. Un petit creux avant d'attaquer celui bien copieux de l'ASH ?

Quelle meilleure collation pour le combler que de picorer ces immanquables sélectionnés et resservis par des expertes et experts de renom dans leur domaine.

Reprendre un peu de *CAR-T cells* ou de bispécifiques dans les lymphomes ou les myélomes, se remettre en mémoire les thérapies ciblées dans les syndromes myéloprolifératifs, déguster les savoureux résultats des thérapies ciblées dans les leucémies aiguës lymphoblastiques et découvrir le piquant de l'administration du quizartinib dans les leucémies aiguës myéloïdes et son bénéfice inattendu quel que soit le statut mutationnel de *FLT3*.

Se laisser allécher par les résultats des combinaisons thérapie ciblée et chimiothérapie en 1re ligne des lymphomes de Hodgkin, malheureusement encore interdites sur nos tables, ou par l'abandon des chimiothérapies indigestes dans les leucémies lymphoïdes chroniques et les lymphomes du manteau au profit de thérapies, encore une fois ciblées, courtes et légères.

Et pour celles et ceux qui savent déjà tout cela, dégustez le zakouski de *Juliette*, vous y apprendrez que nos amies les bêtes souffrent également d'hémopathies et que le Cavalier King Charles a des plaquettes géantes, pas seulement les oreilles !

Alors, bonne dégustation.

N. Milpied déclare ne pas avoir de liens d'intérêts en relation avec cet éditorial.

Les recalés

Immune effector cell–associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 High: ≥2			

Low risk (HT 0-1)

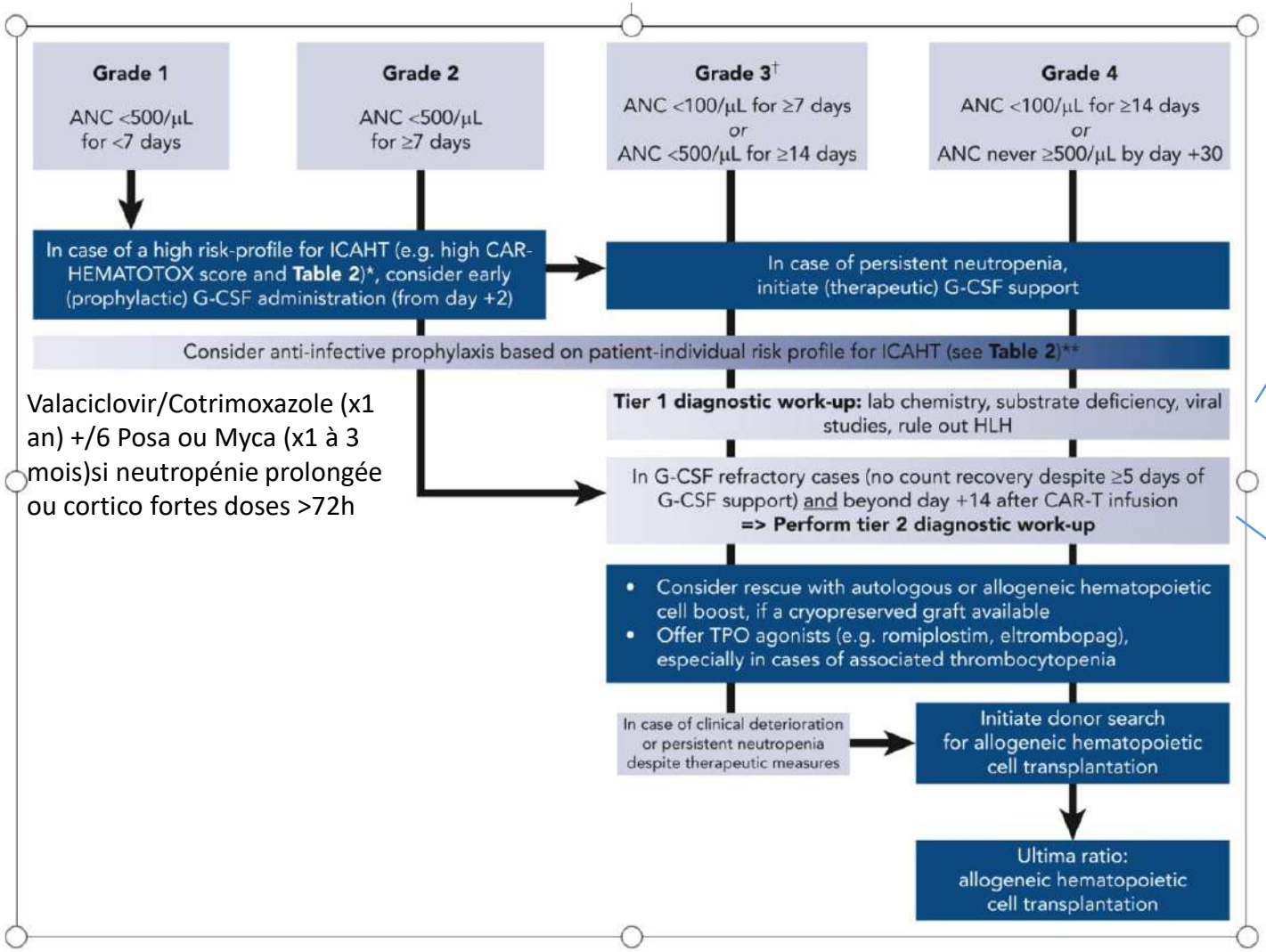
High risk (HT 2-7)

Risk profile

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

Rejeski, Blood 2023



Valaciclovir/Cotrimoxazole (x1 an) +/6 Posa ou Myca (x1 à 3 mois)si neutropénie prolongée ou cortico fortes doses >72h

TIER 1	Lower threshold to perform – minimal workup		
	Poor bone marrow reserve	Prior treatments including allo-HCT, fludarabine, marrow infiltration	Complete blood count (CBC), reticulocyte production index (RPI), peripheral blood smear
	Medication – drug side effects	Check for concomitant myelosuppressive medications	
	Vitamin deficiencies	Vitamin B12, folic acid	Serum levels
	Rule out infections	Bacterial/viral/fungal infections	Blood cultures, CMV PCR, procalcitonin, $CD4^+$ T-cell, IgG, B-cell levels
	Rule out macrophage-activation syndrome*	CRS/MAS or IEC-HS	Serum ferritin, triglycerides

Viral PCR considering the clinical presentation	Parvovirus	Parvovirus B19 PCR
	HHV6, JCV	HHV6, JCV PCR blood/CSF
	EBV, adenovirus, HSV	PCR
Bone marrow disease	(MDS/AML/myelofibrosis) or relapse	BM aspirate, biopsy, flow cytometry, immunohistochemistry, cytogenetics, NGS
	Relapse of leukemia/lymphoma	Flow cytometry peripheral blood / bone marrow, including B-cell panel
Other causes	Other rare hematologic diseases, myeloid diseases, PNH, autoimmune processes	Myeloid panel, GPI-linked structures, direct antiglobulin test (DAT)

Rejeski, Blood 2023

Efficacy and Safety of CD34+ Stem Cell Boost for Delayed Hematopoietic Recovery After BCMA Directed CAR T-cell Therapy

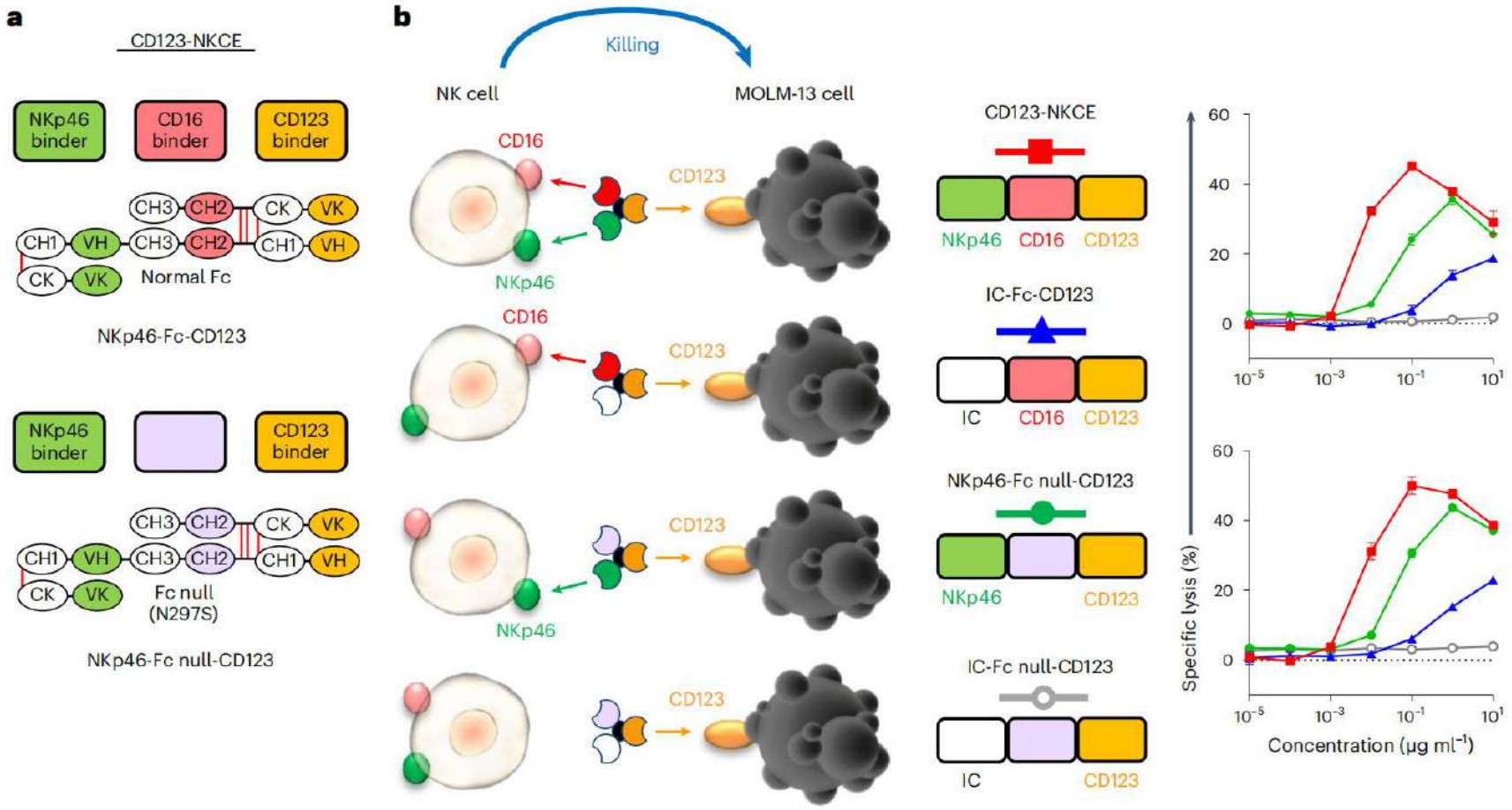
Etude rétrospective 3 centres US
n= 101 patients CART anti BCMA pour MM Rec/ref. med 63 ans
n=19/101 ont reçu un greffon de CSP congelé pour cytopénies persistantes
93% CRS mais 1 seul grade 3
78% ORR à J90 dont 50% RC

Davis et al; Transplantation and Cellular Therapy 2023

	n=19
Prior CAR T-cell dose (cells × 10^6)	
Idecabtagene vicleucel n=18	425.2 (372.1-496.4)
Ciltacabtagene autoleucel, n = 1	48.5
Stem cell boost dose (CD34+ cells × 10^6/kg)	2.75 (1.76-7.38)
Day of stem cell boost post CAR T infusion	53 (24-126)
Day of engraftment after stem cell boost	
Neutrophils	14 (9-39)
Hemoglobin	23 (6-34)
Platelets	17 (12-39)
Indications for stem cell boost	
Pancytopenia	13 (68%)
Pancytopenia and infection	2 (11%)
Anemia and thrombocytopenia	2 (11%)
Thrombocytopenia	1 (5%)
Neutropenia	1 (5%)
Transfusion needs after CAR T	
PRBC transfusion > 7 days	15 (79%)
Platelet transfusion > 7 days	15 (79%)
Days of G-CSF after stem cell boost, median (range)	10 (0-28)
TPO agonist use after stem cell boost	11 (58%)
IVIG use after stem cell boost	7 (36%)

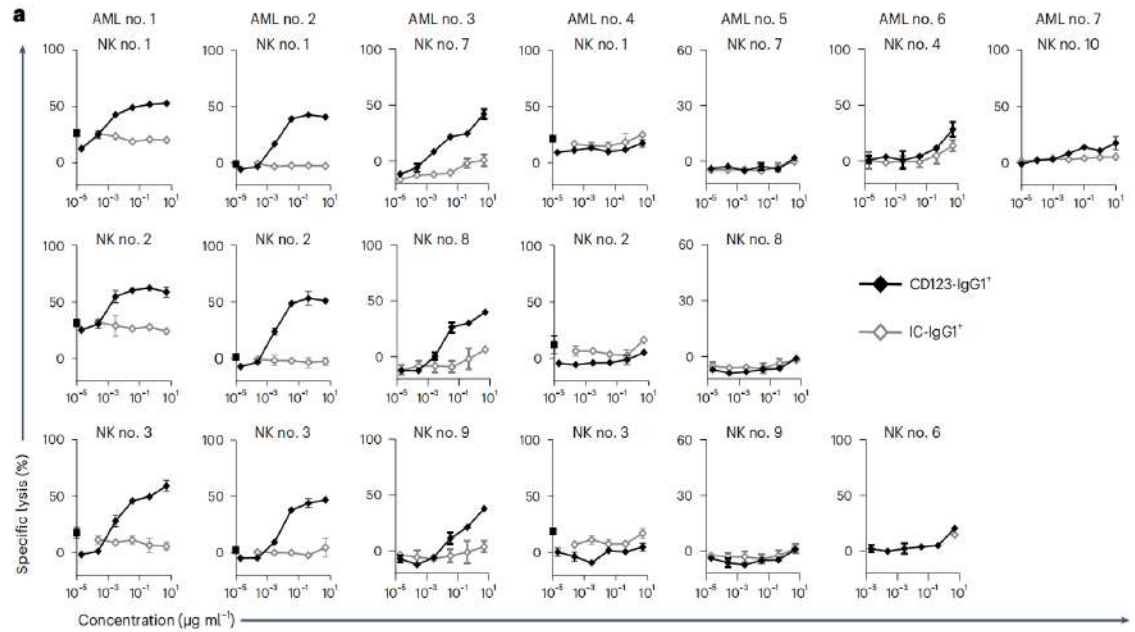
CAR Allogéniques

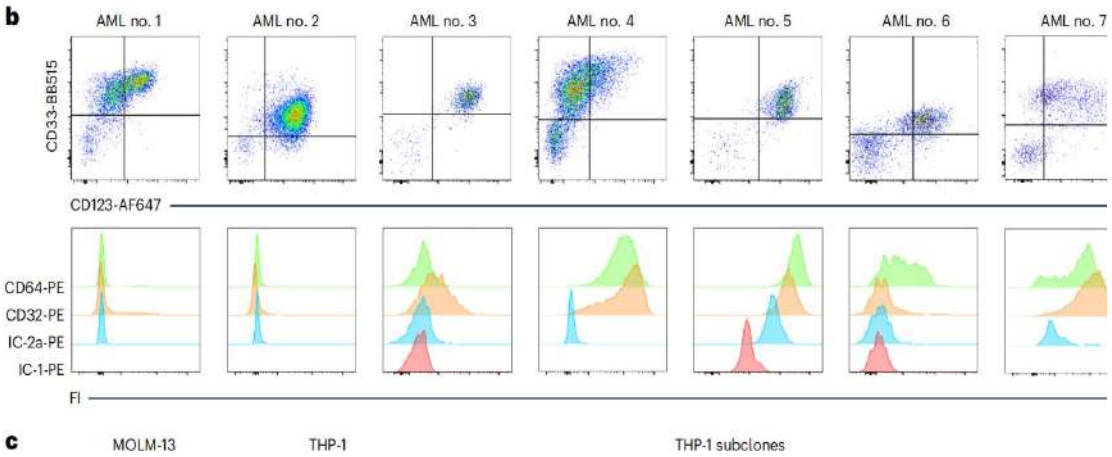
Control of acute myeloid leukemia by a trifunctional NKp46-CD16a-NK cell engager targeting CD123



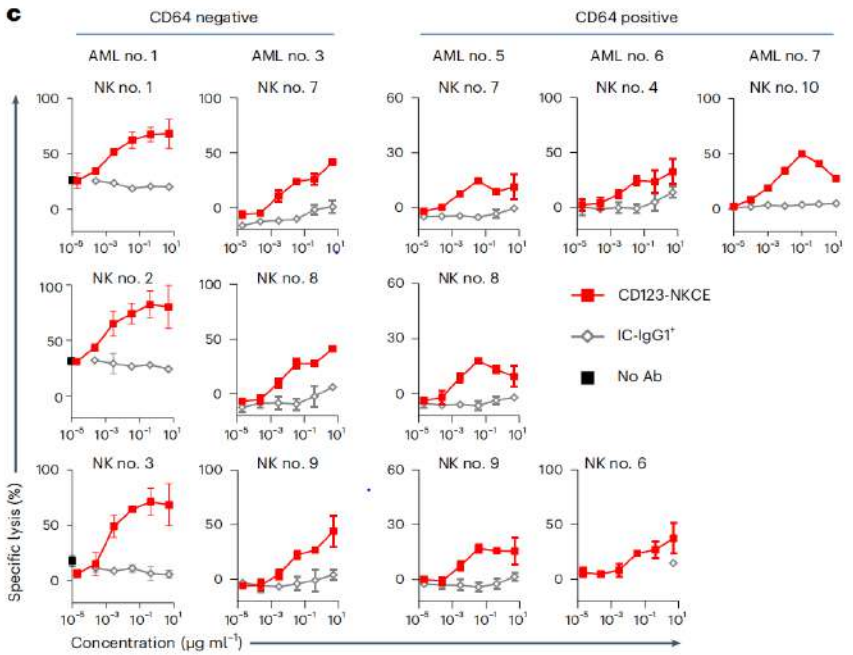
Gauthier Nature Biotechnology 2022

Expression CD64 sur blastes LAM inhibe
Ac anti CD123

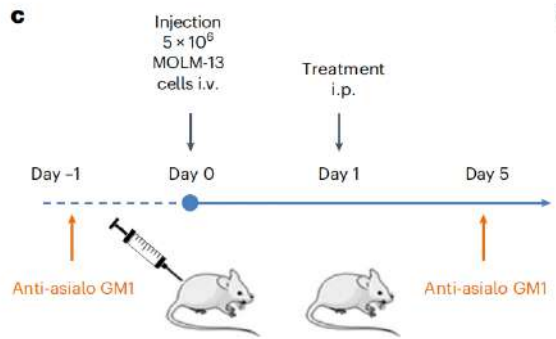


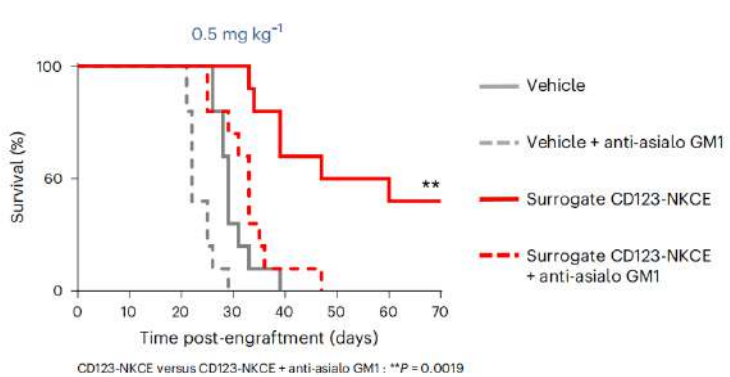


Trispécifique lyse les blastes LAM CD64+ ou -



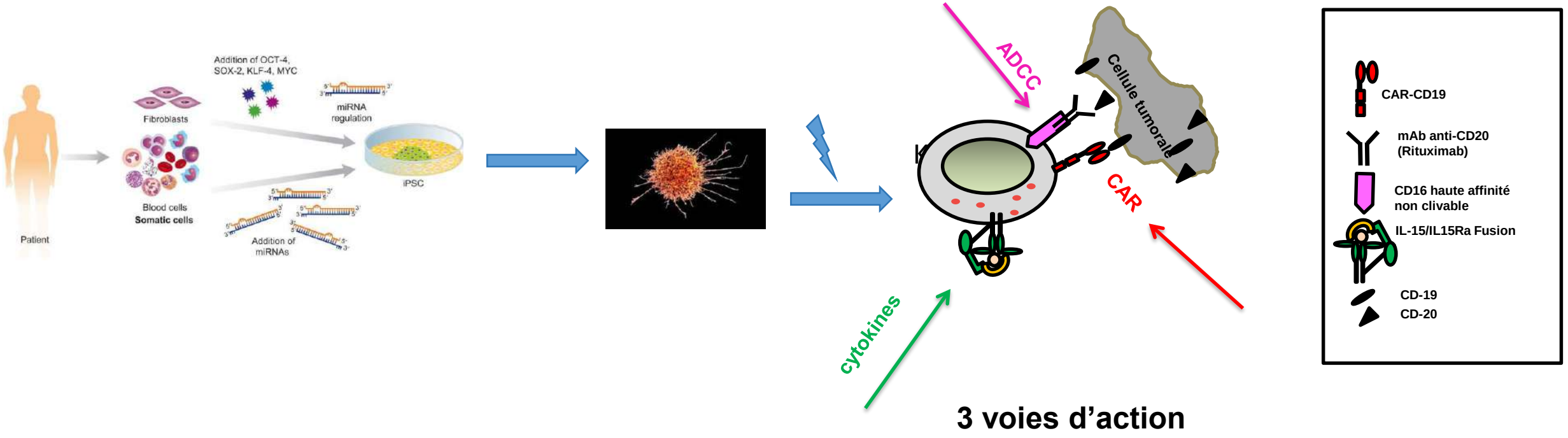
Efficacité in vivo, dépendante des NK

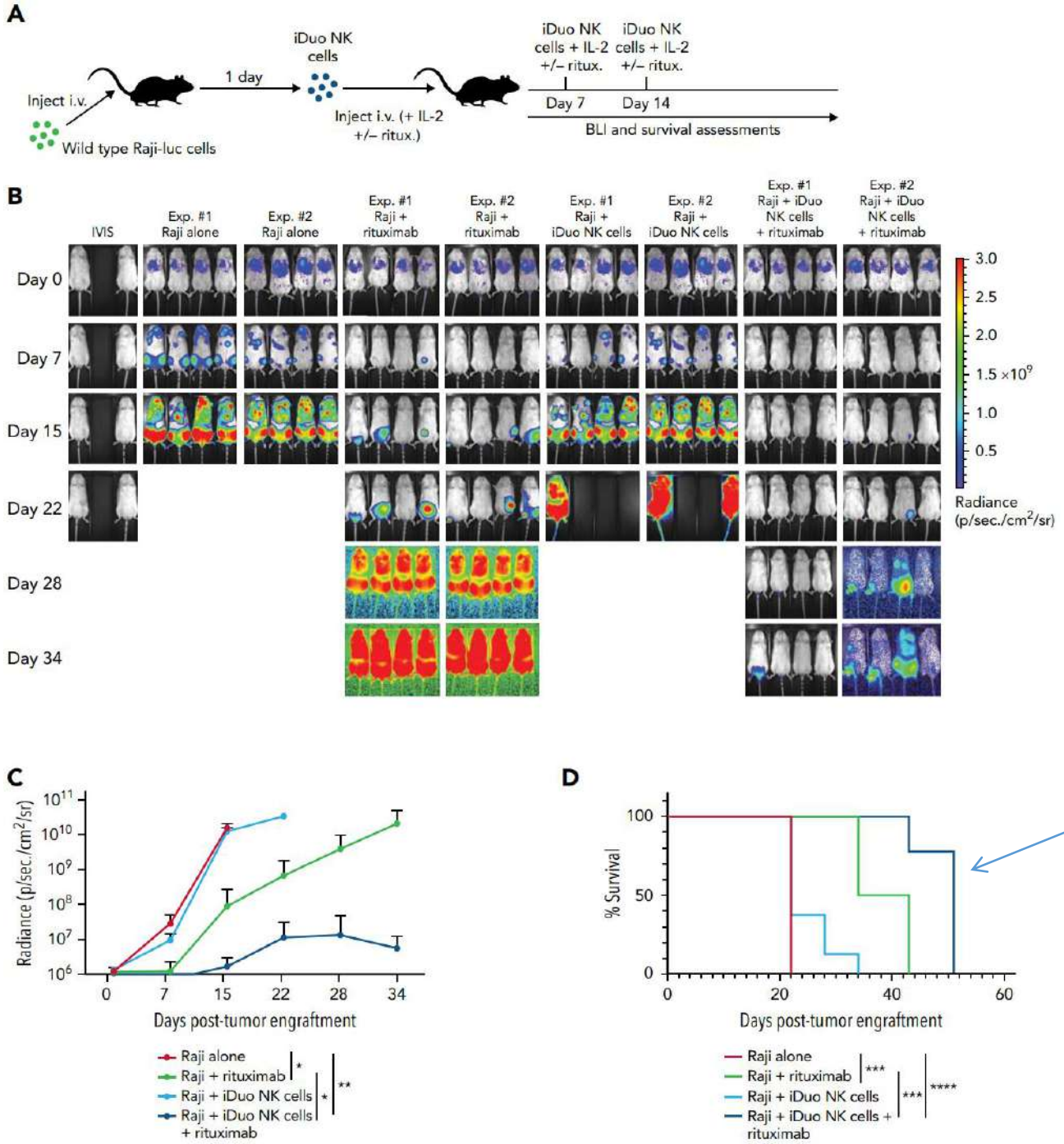




Dual antigen–targeted off-the-shelf NK cells show durable response and prevent antigen escape in lymphoma and leukemia

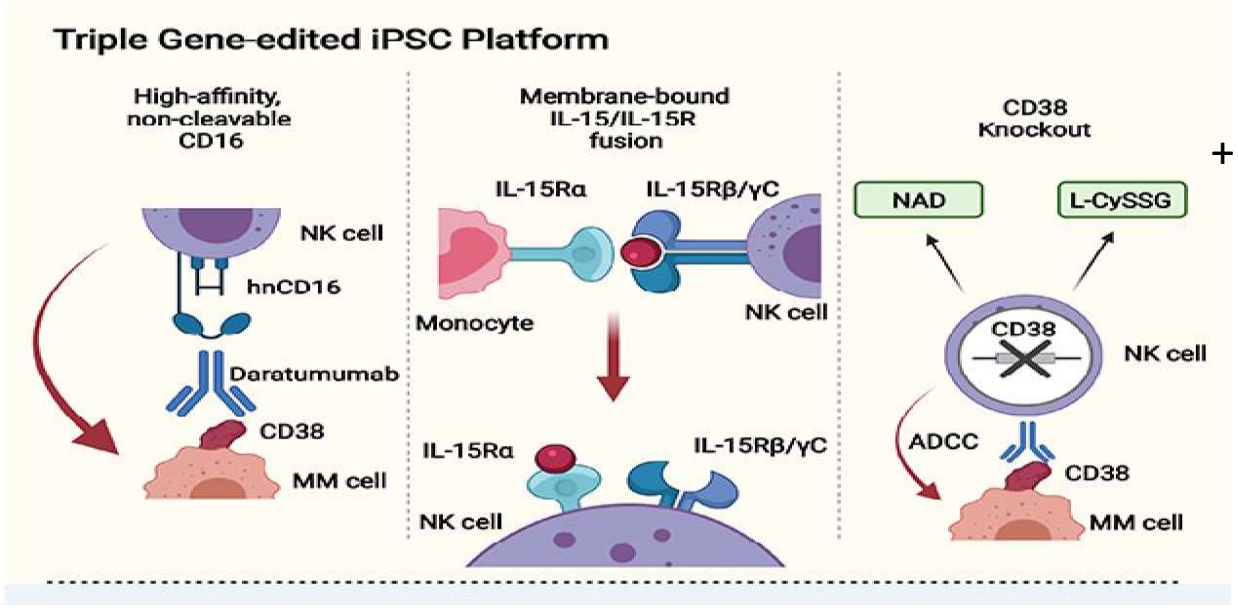
Frank Cichocki, Blood 2022



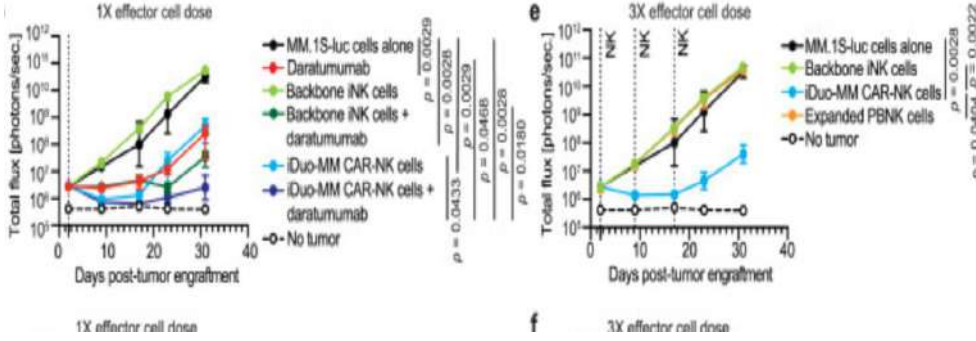


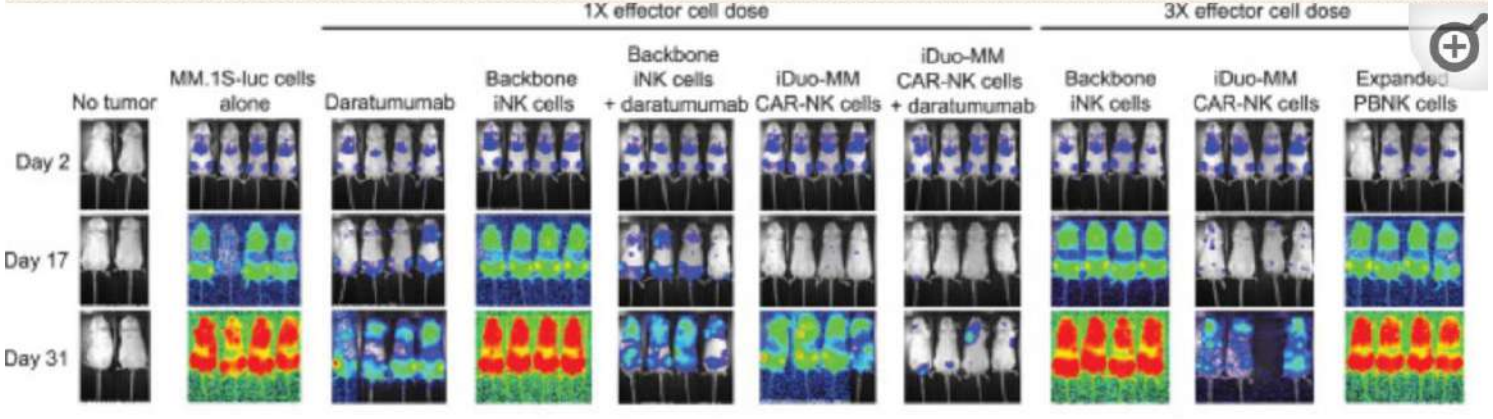
l'activité antitumorale augmente avec le rituximab

Quadruple gene-engineered natural killer cells enable multi-antigen targeting for durable antitumor activity against multiple myeloma



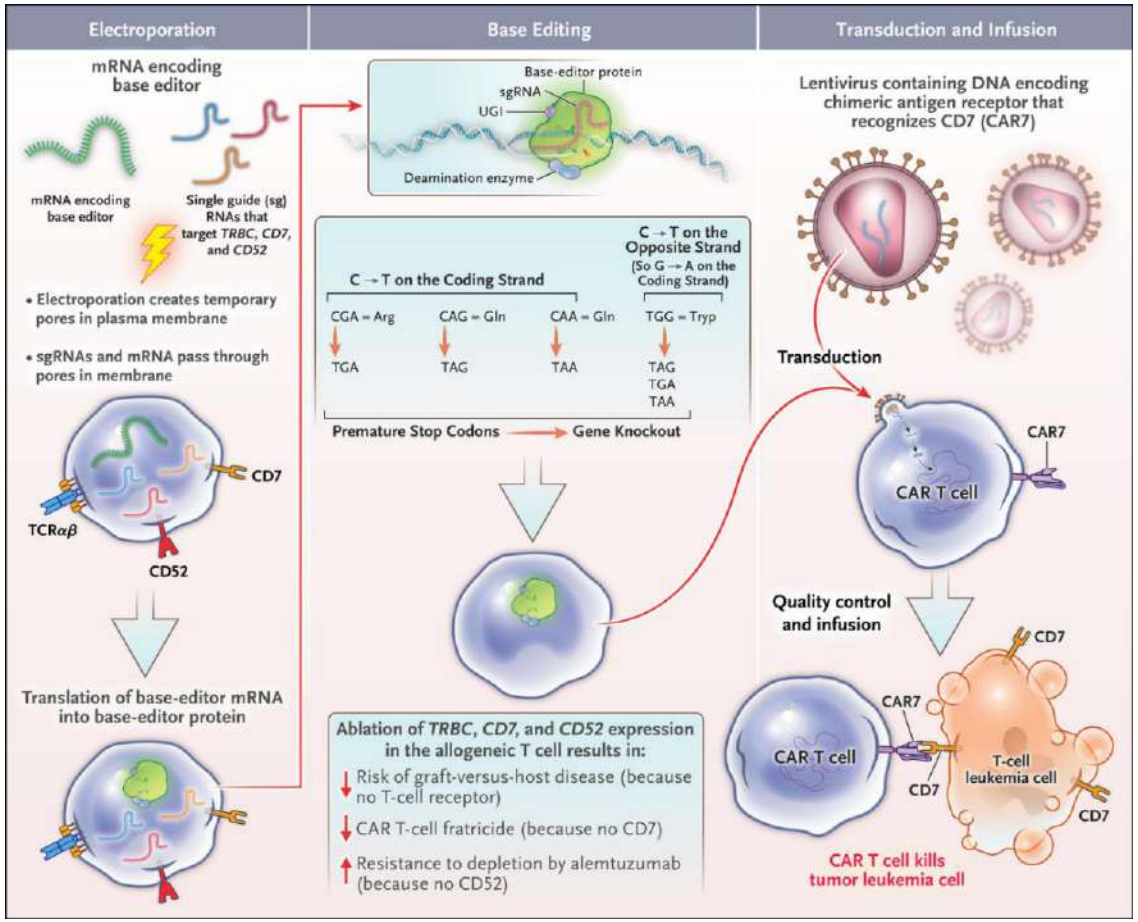
+ CAR BCMA





Cichocki, Nat Commun 2022

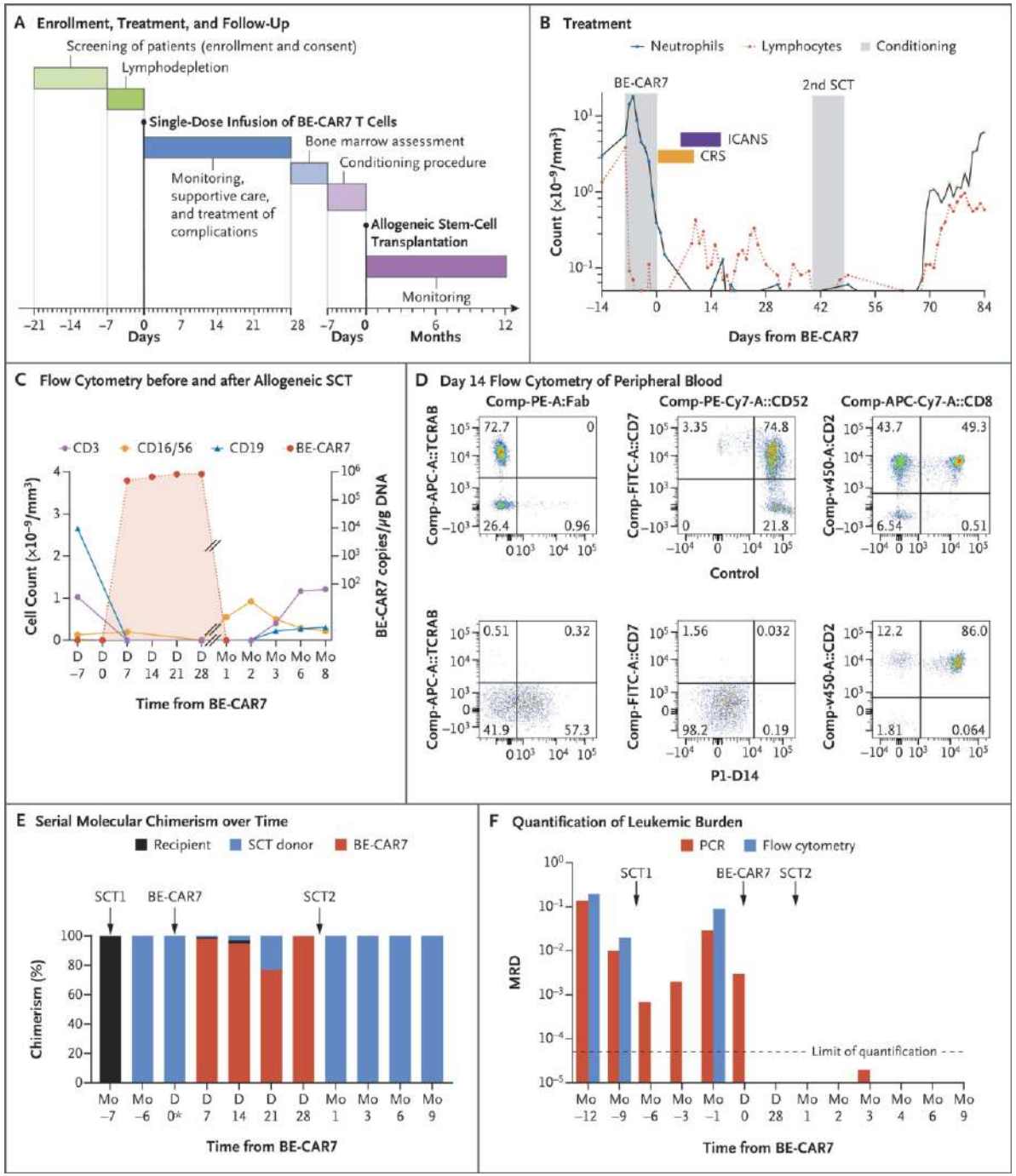
Base-Edited CAR7 T Cells for Relapsed T-Cell Acute Lymphoblastic Leukemia



base editing:inactivation des gènes CD52 ,CD7 receptors et β chain eu αβ T-cell receptor pour échapper à la serothérapie lymphodepletante, CAR7 T-cell fratricide, et GVH respectivement

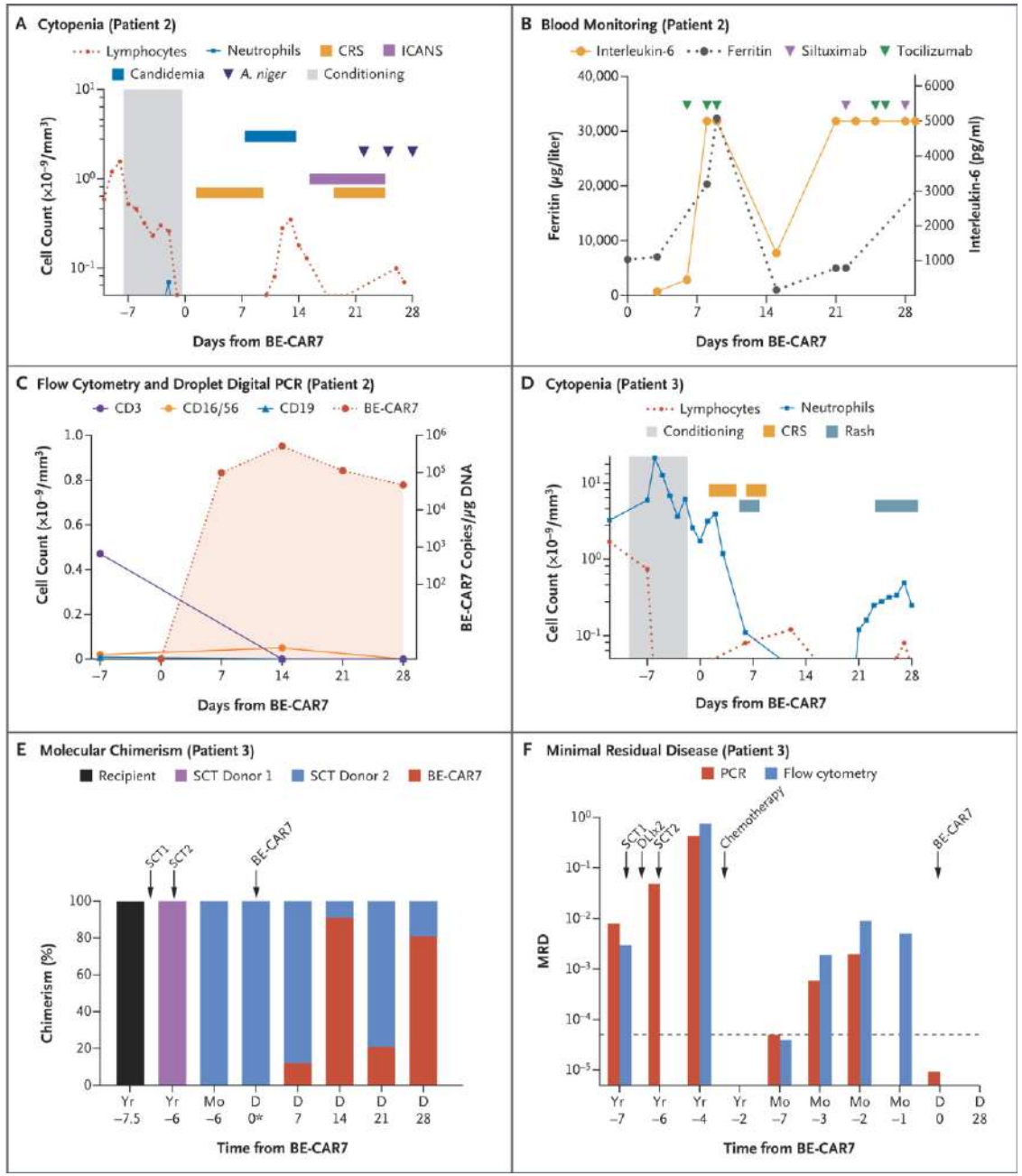
Great Ormond Street Hospital, Londres

Robert Chiesa et al. for the Base-Edited CAR T Group, NEJM Sept 2023



Patients in the study received lymphodepletion with fludarabine (150 mg per square meter of body-surface area), cyclophosphamide (120 mg per kilogram of body weight), and alemtuzumab (1 mg per kilogram) followed by infusion of 0.2×106 to 2.0×106 BE-CAR7 T cells per kilogram (with a maximum of 5×104 per kilogram of TCRαβ+ T cells, to limit the risk of GVHD).

inclusion: 1 enfant LALT rec/ref
pas d'atcd de GVH
pas d'infection active severe
pas d'Ac anti HLA anti CART B7

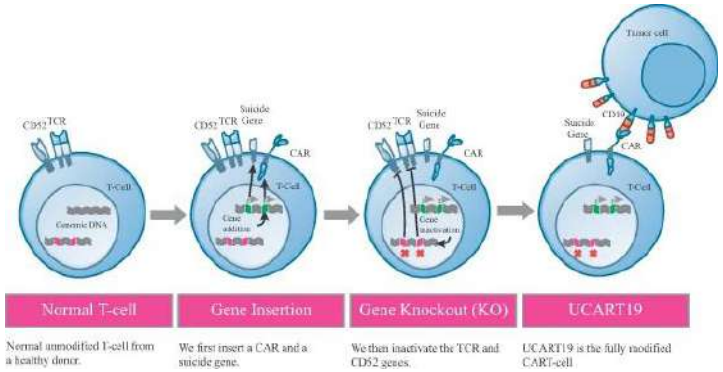


Pt 2 décédé d'IFI (candidémie + aspergillose), grosse masse tumorale

Pt 3 obtention d'une RC3 (atcds de 2 allo, 2de rechute MO + SNC), allo 3 après CAR B7

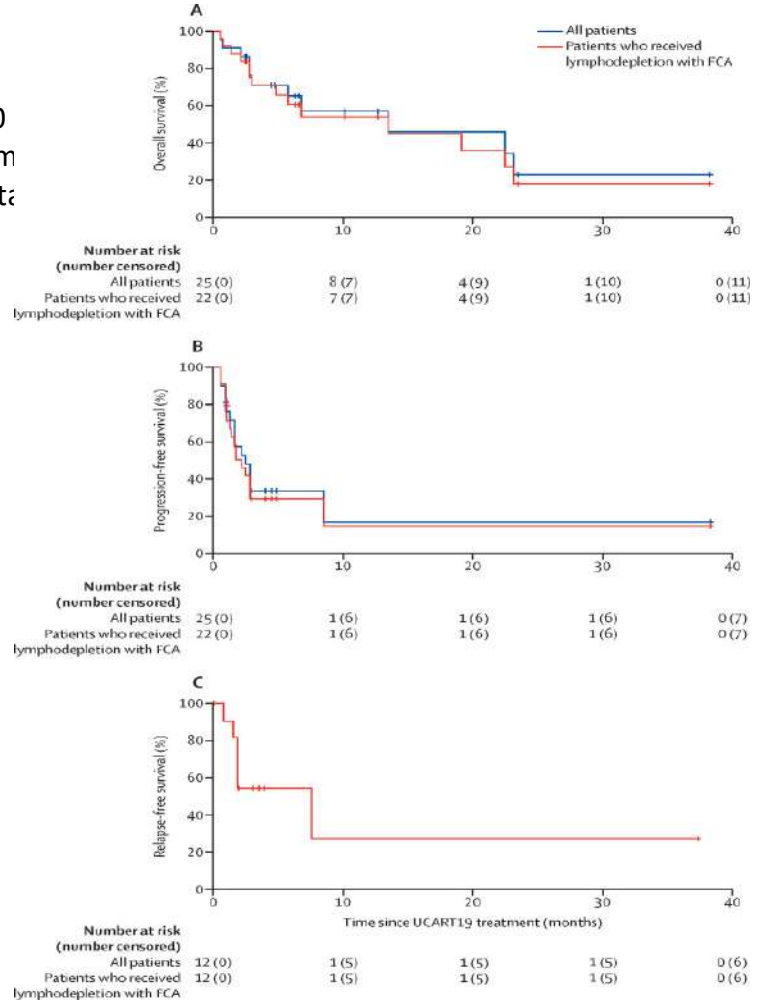
Proof of concept
Très cytopéniant, IMS+++
CRS, ICANS+
nécessité d'allo

UCART19, a first-in-class allogeneic anti-CD19 chimeric antigen receptor T-cell therapy for adults with relapsed or refractory B-cell acute lymphoblastic leukaemia (CALM): a phase 1, dose-escalation trial



LD: fludarabine (30 mg/m2/j x 3 j) and cyclophosphamide (500 mg/m2 /j x 3 days) +/-alemtuzumab (1 mg/kg or 40 mg or 60 m sur 5 days) . UCART19 6 × 106, 6–8 × 107, or 1·8–2·4 × 108 tota

n=25, 37 ans med, follow up 12.8 mois, ORR 48%, med PFS 2.1 mo, OS 13.4 mo
72% atcd allo
80% CRS dont 25% gr 3-4
2 GVHa grade 1
28% infections gr 3 ou +

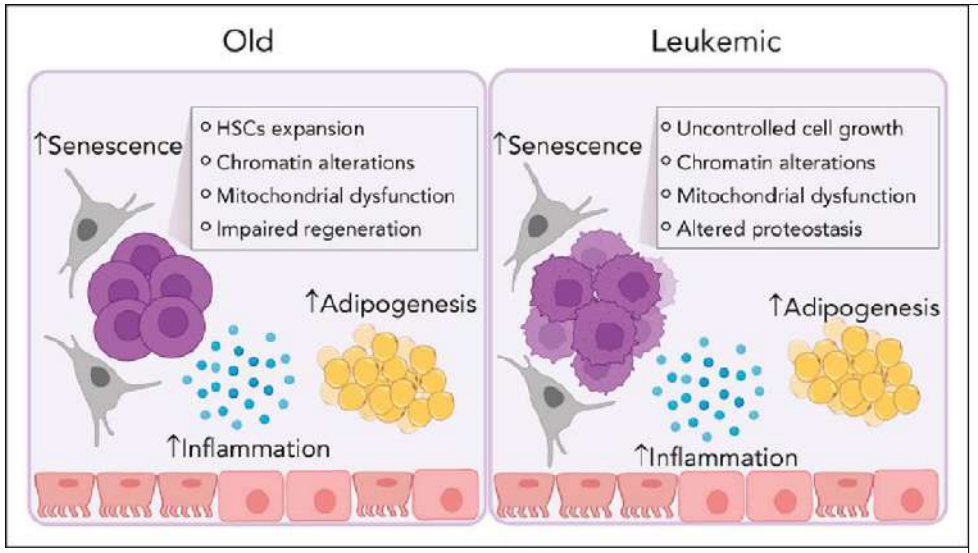


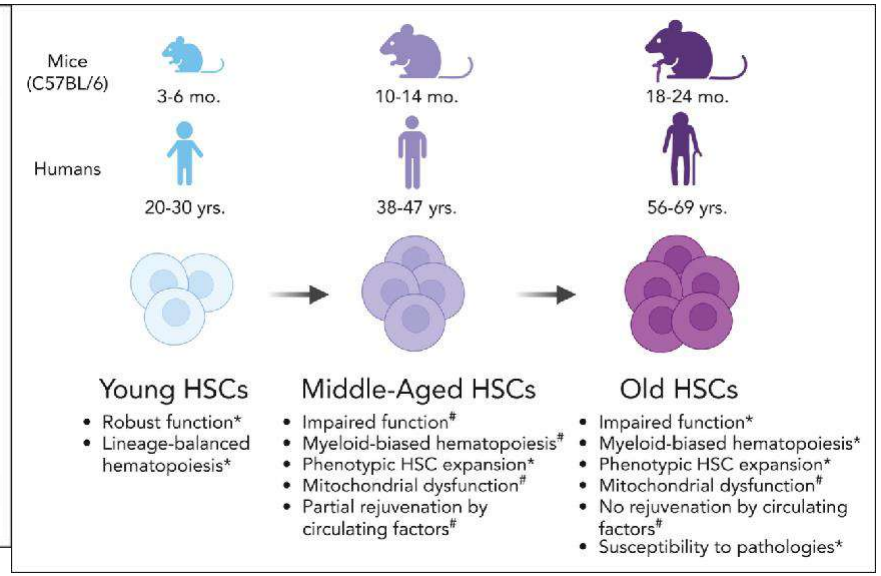
Résultats des CART anti CD19 autologues LALB adulte				
	CTL019	AUTO-1	KTE-X19	MSKCC19-28z
CR	69%	85%	71%	83%
EFS 2 ans	31-49%	48%	med RFS 11.6 mo	med EFS 6 mo

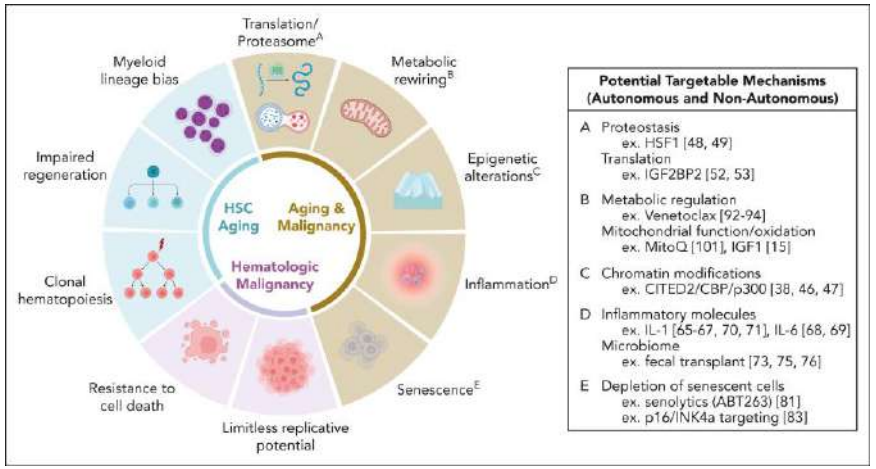
Ruben, Lancet Haematology 2022

Hematopoietic stem cell aging and leukemia transformation

Patricia A. Colom Díaz, Blood 2023







CHIP donneur
GVHc et dim rechute
Frick..Frederik Damm, JCO 2019

Donor CHIP=safe
Kim, Haematologica 2023

CSM pro infla augm GVH dim rec
N De Isla (journée scientifique SFGM 2023)

Impact of Donor Age on Allogeneic Hematopoietic Cell Transplantation Outcomes in Older Adults with Acute Myeloid Leukemia

Diminution rechute MUD

Aug NRM MUD
période 2011-2015

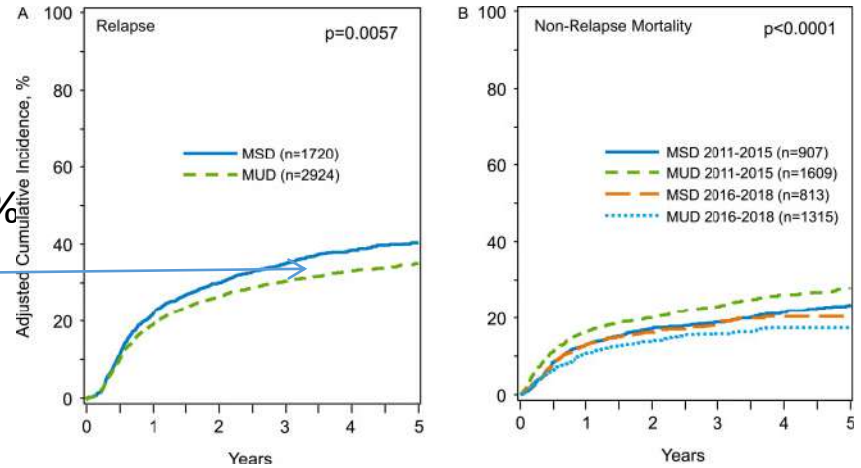
	Younger MUD (≤35)		Older MSD (≥50)		P-value
	N = 2948		N = 1736		
Relapse	HR 0.86	95% CI, 0.77-0.96	HR 1.00		0.005
NRM (2011-2015)	HR 1.24	95% CI, 1.04-1.49	HR 1.00		0.016
NRM (2016-2018)	HR 0.78	95% CI, 0.64-0.96	HR 1.00		0.017
Chronic GVHD	HR 1.18	95% CI, 1.08-1.29	HR 1.00		0.0002
DFS	HR 0.92	95% CI, 0.85-1.01	HR 1.00		0.073
OS	HR 1.02	95% CI, 0.94-1.12	HR 1.00		0.607
5-year Relapse	35%	95% CI, 33%-37%	41%	95% CI, 38%-43%	0.003
5-year DFS	44%	95% CI, 42%-46%	41%	95% CI, 38%-43%	0.045

CIBMTR 2011-2018
R LAM>50 ans n=4784 (62 ans)
MSD >50 ans n=1736 (60 ans)
MUD<35 n=2948 (25 ans)

MUD: - de MAC, - de DF pour RH, + de CMV D/R -/+, + de moelle, + d'ATG/alemtuzumab

MUD jeune > MSD âgé
LAM haut risque

Rechute 5 ans
35% MUD vs MSD 41%
p=.003

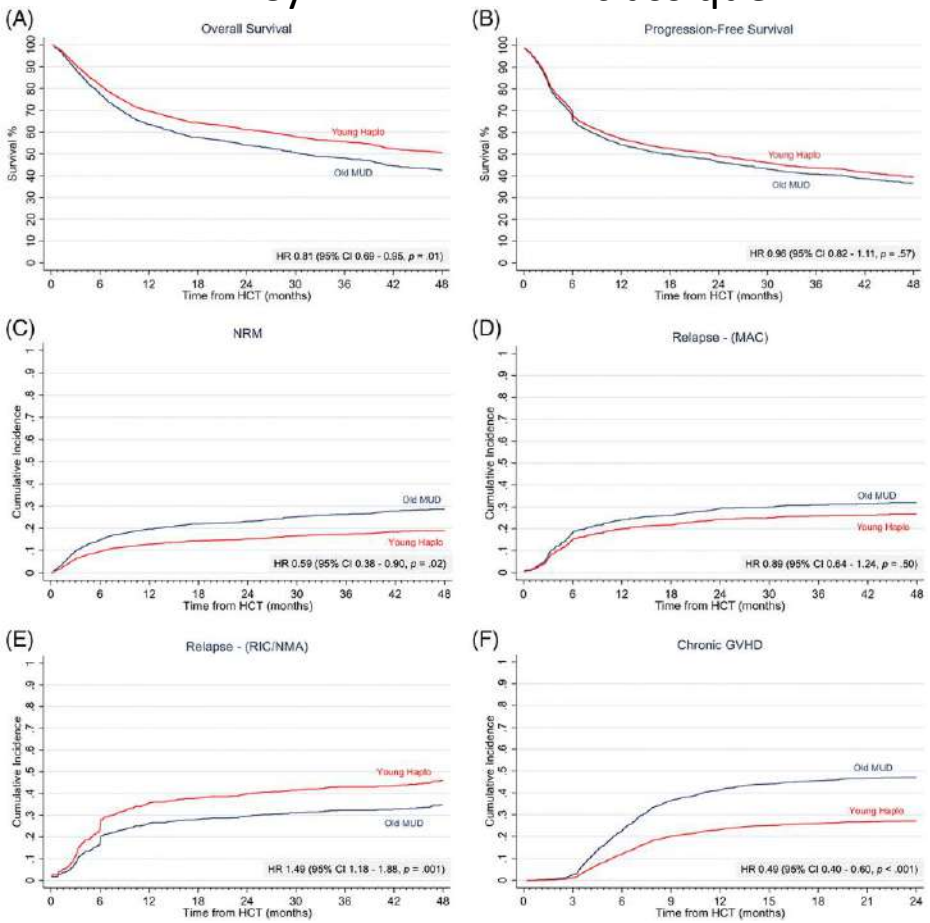


NRM 5 ans (période 2016-2018)
17% MUD vs MSD 20%
p=NS

M Abid, Transplant Cell Ther 2023

Younger haploidentical donor versus older matched unrelated donor for patients with AML/MDS

Jeune Haplo > MUD âgé
HD-CyPT «classique»



CIBMTR, Marcoux Am J Hematol 2023

Choosing Between Older Matched Sibling Donor and Younger Matched Unrelated Donor in Allogeneic Hematopoietic Cell Transplantation: Comparison of Clinical Outcomes in Acute Myeloid Leukemia and Myelodysplastic Syndrome

Monocentrique LAM/MDS, greffon CSP
n=85 MSD >60 ans vs 292 MUD <30 ans
score propension

Devenir idem ⟷

choisir le + rapide et + simple

Pereira, TCT 2023

QUE NOUS RÉSERVE L'AVENIR ?