Actualités greffe et en thérapie cellulaire 2024

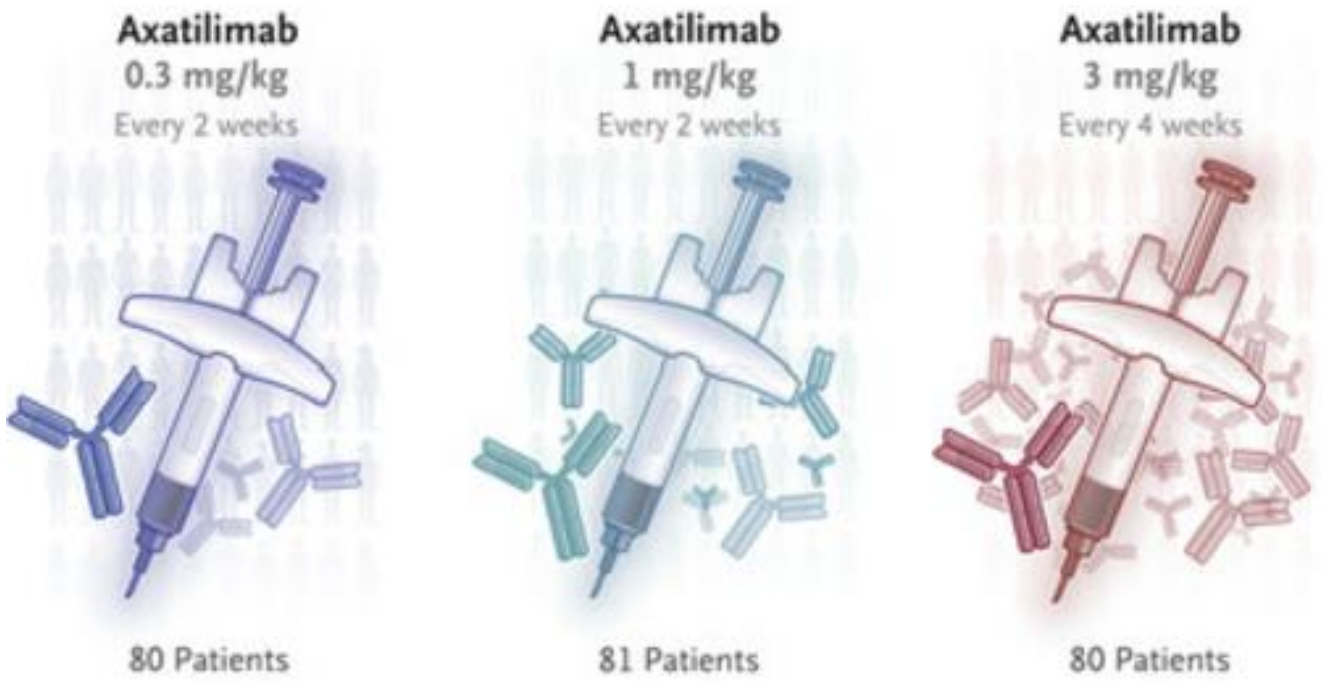
GVH

Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease

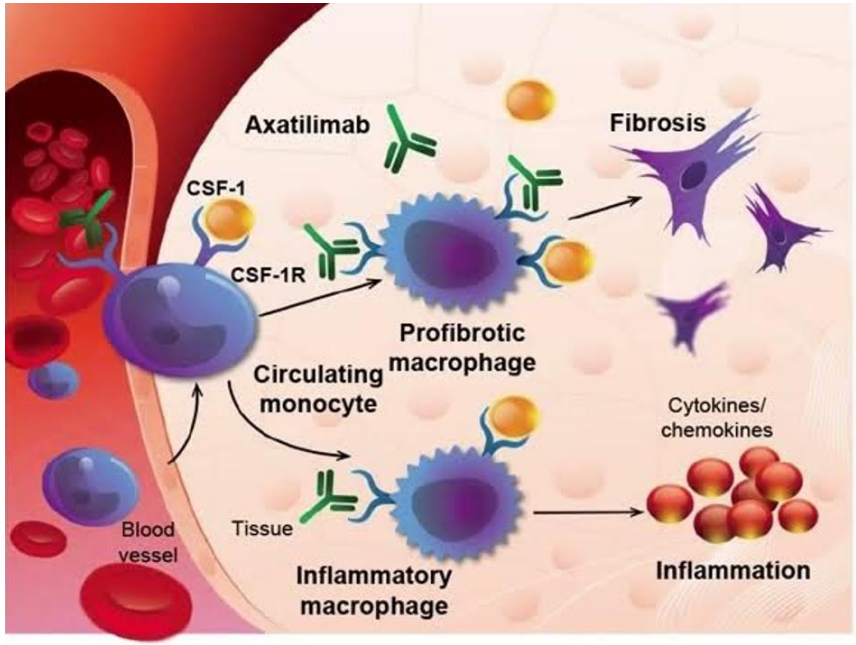
AGAVE-201 phase 2

GVHDc rec/ref, 80% severe, sclerotique, med 4 lignes (2-15), 80% ibru, ruxo, belumosudil

N=241



inhib CSF1-R sur les mono/macrophages

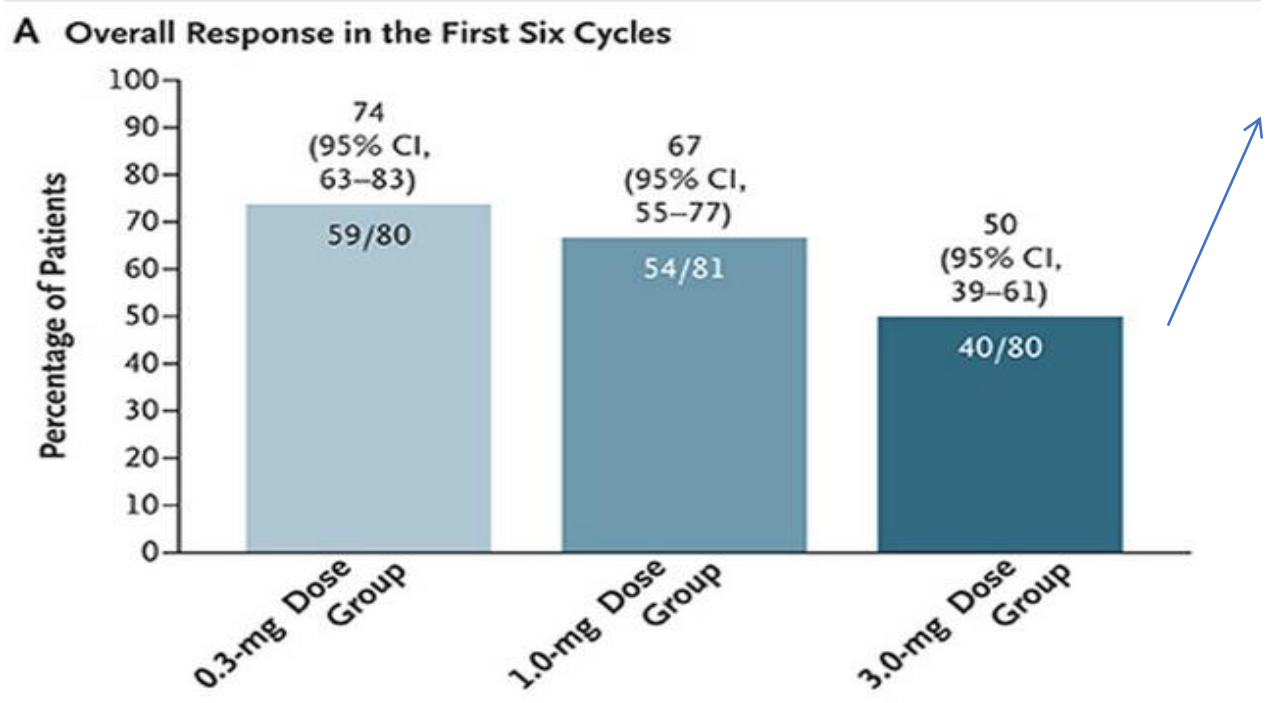


Inhibe la voie monocyte-macrophages profibrotiques et inflammatoires

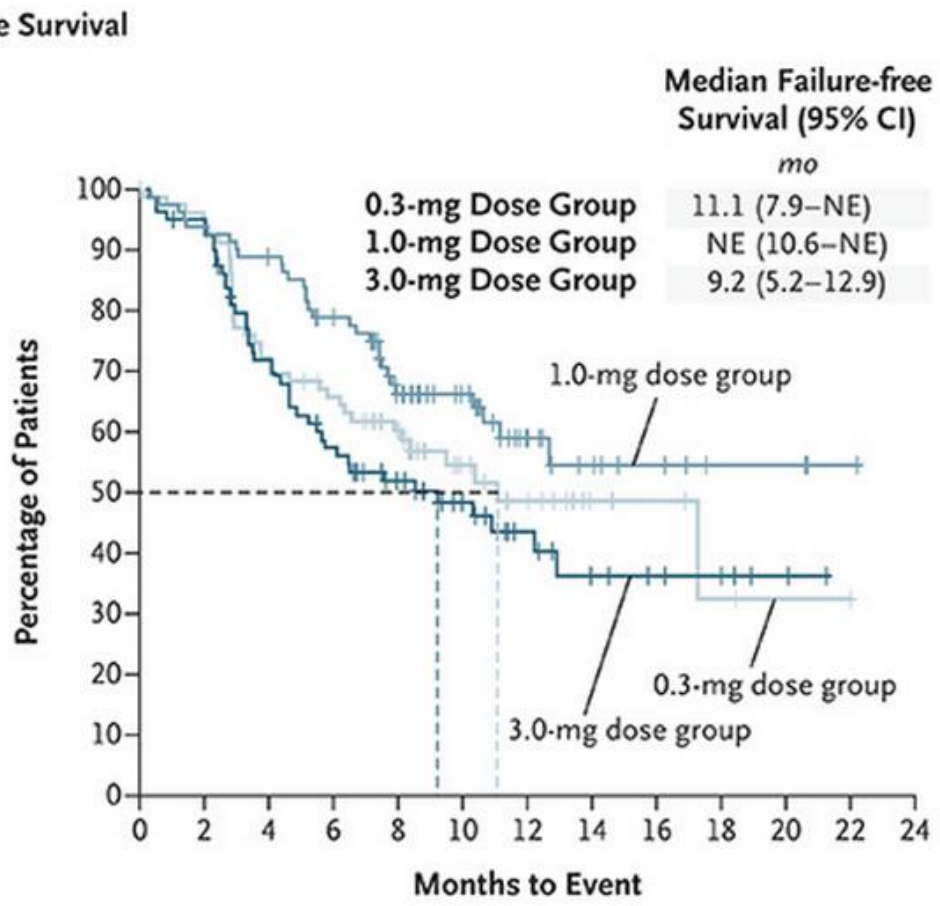
Wolf, NEJM 2024

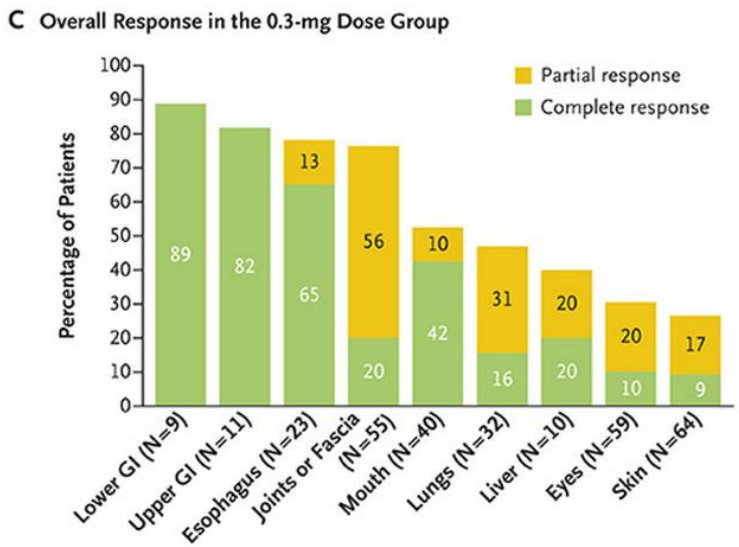
AGAVE-201

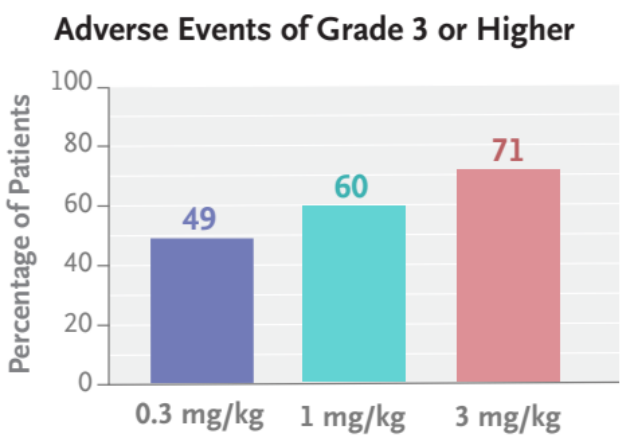
Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease



doses 3mg/Kg: déplétion prolongée monocytes et aug CSF1 circulants, favo inflamma (effet paradoxal)?







Bio, oed periorbitaire, infections virales

Wolf, NEJM 2024

Vedolizumab for the prevention of intestinal acute GVHD after allo HSCT: a randomized phase 3 tria

Vedolizumab: gut-selective anti-$\alpha_4\beta_7$ integrin monoclonal antibody that reduces gut inflammation by inhibiting migration of GI-homing T lymphocytes

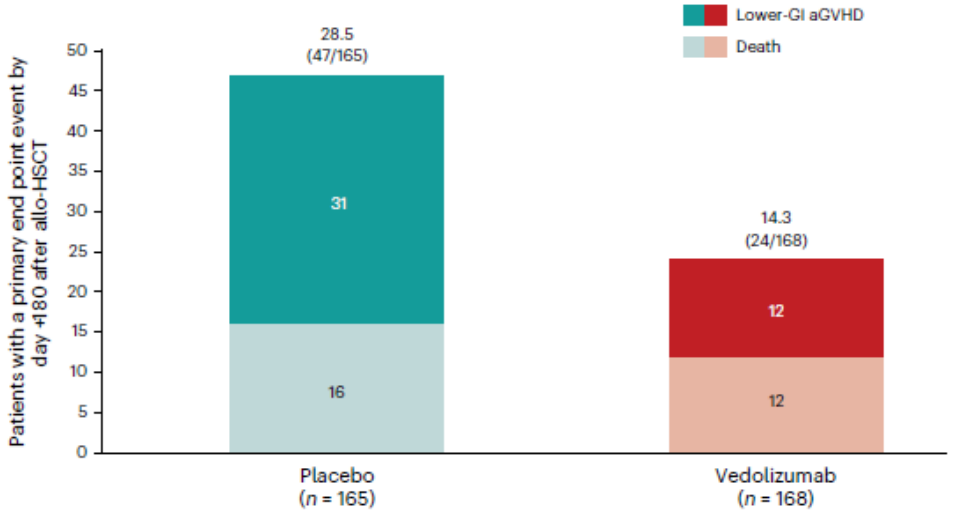
300 mg or placebo intravenously on day −1 and days +13, +41, +69, +97, +125 and +153

CNI + MTX ou MMF

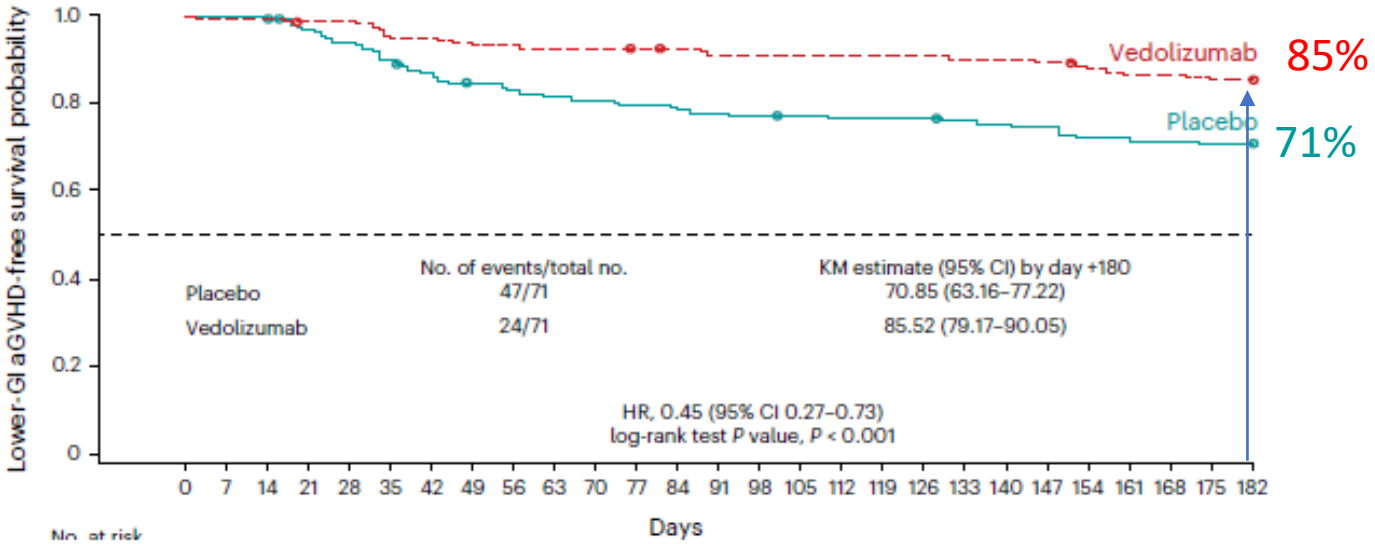
Stratification 8/8, 7/8, RIC/MAC, PB/Moelle, ATG, âge

N=165 placebo

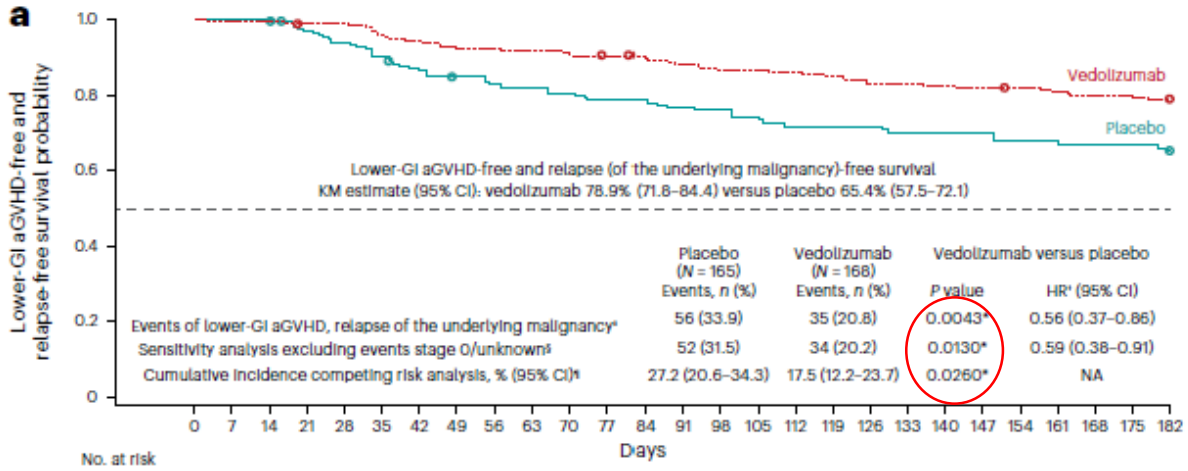
N=168 vedo

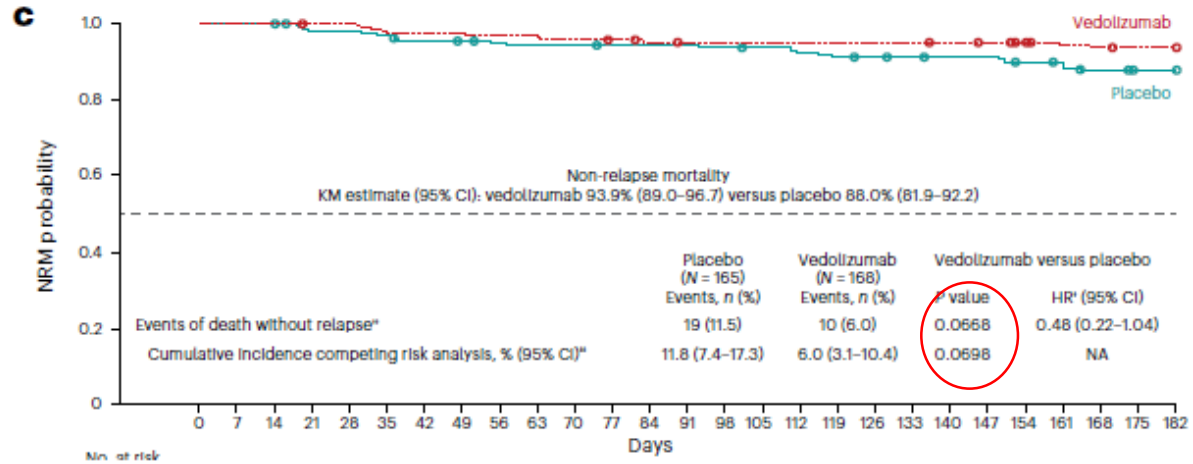


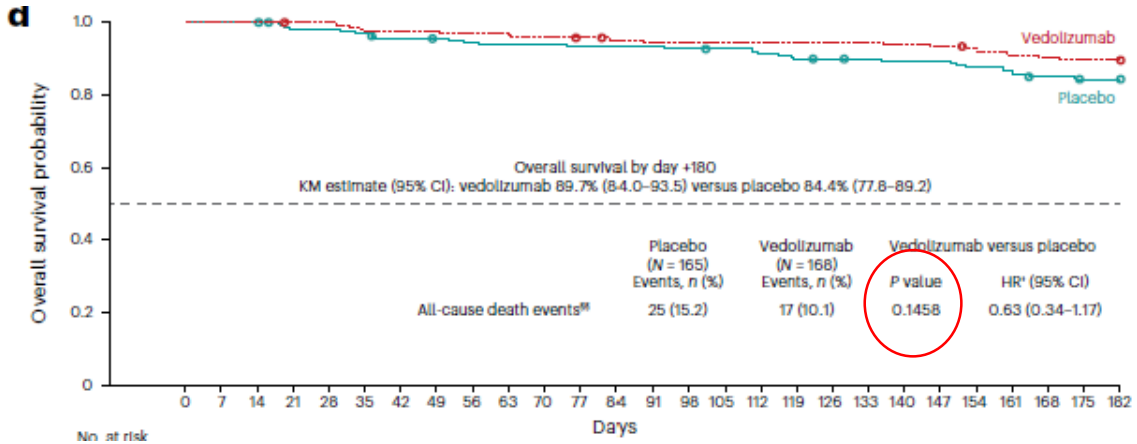
Obj primaire:survie à 6 mois sans GVHa dig



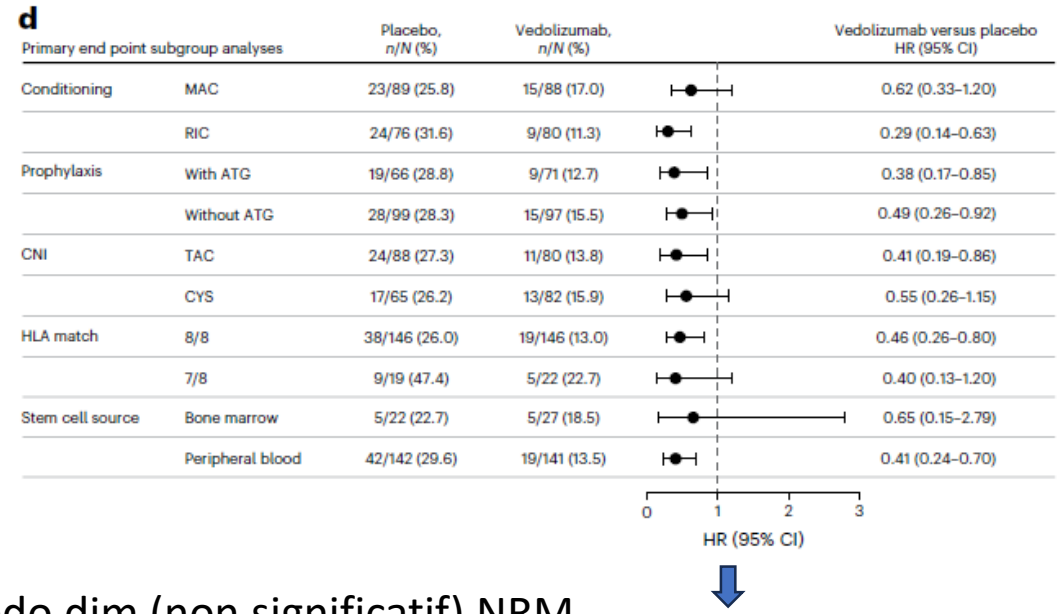
Chen, Nature Medicine 2024







Vedo améliore survie 6 mois sans GVHa dig basse et sans rechute



Vedo dim (non significatif) NRM

Avantage Vedolizumab quelles que soient les conditions

Pas de difference de survie

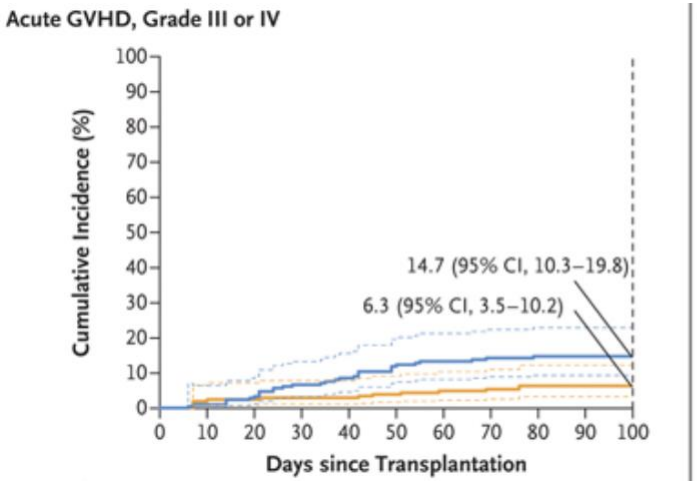
Chen, Nature Medicine 2024

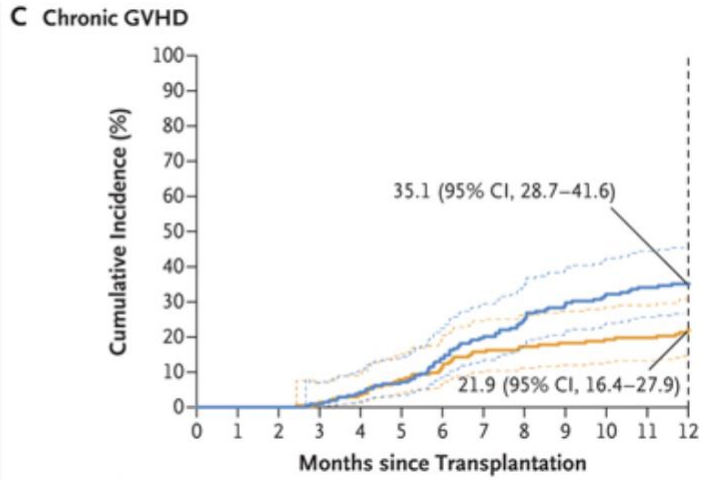
Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

Etude rando 1:1 phase 3

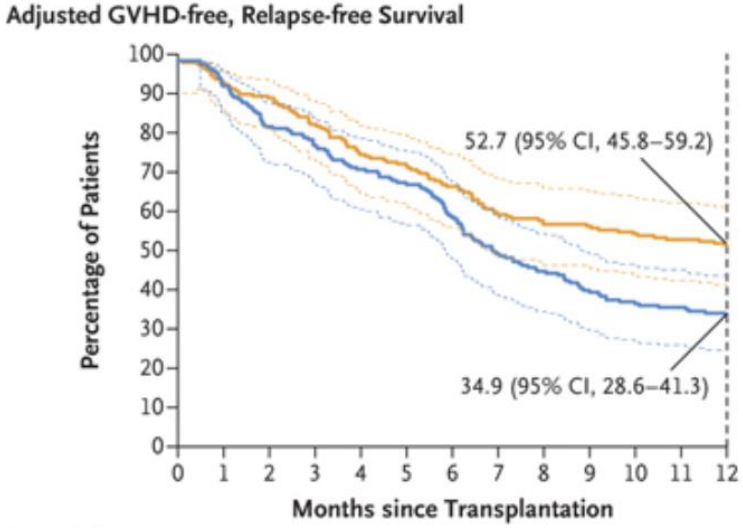
MUD (70%), MRD (30%) RIC, med 64y, 50%LAM, 30% MDS

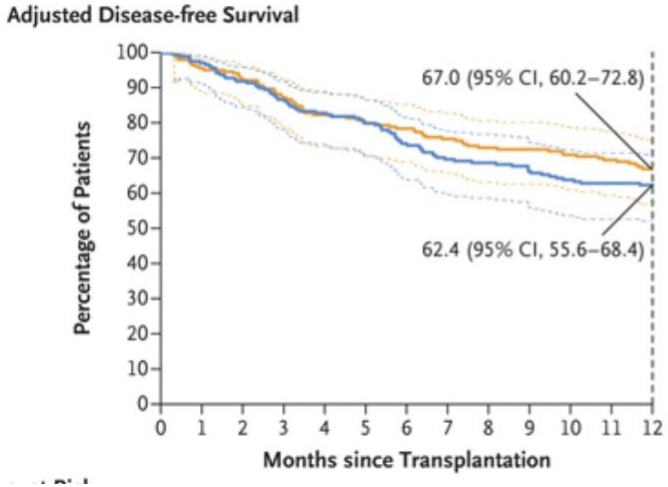
CyPT+Tacro+MMF n=217 > Tacro+MTX n=217

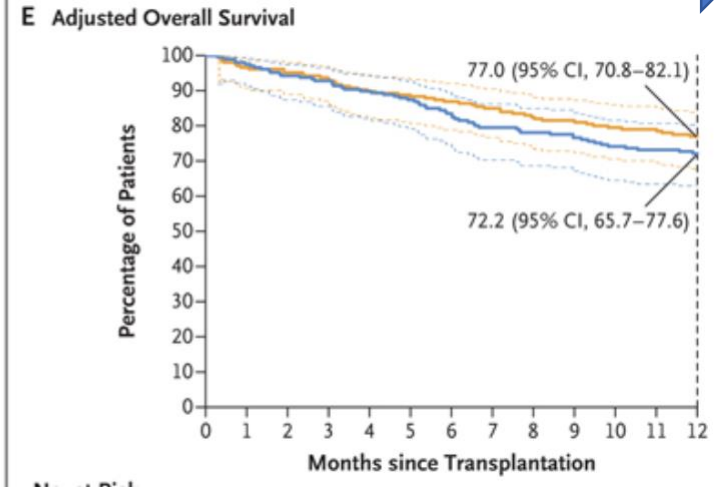




obj primaire GRFS 1y



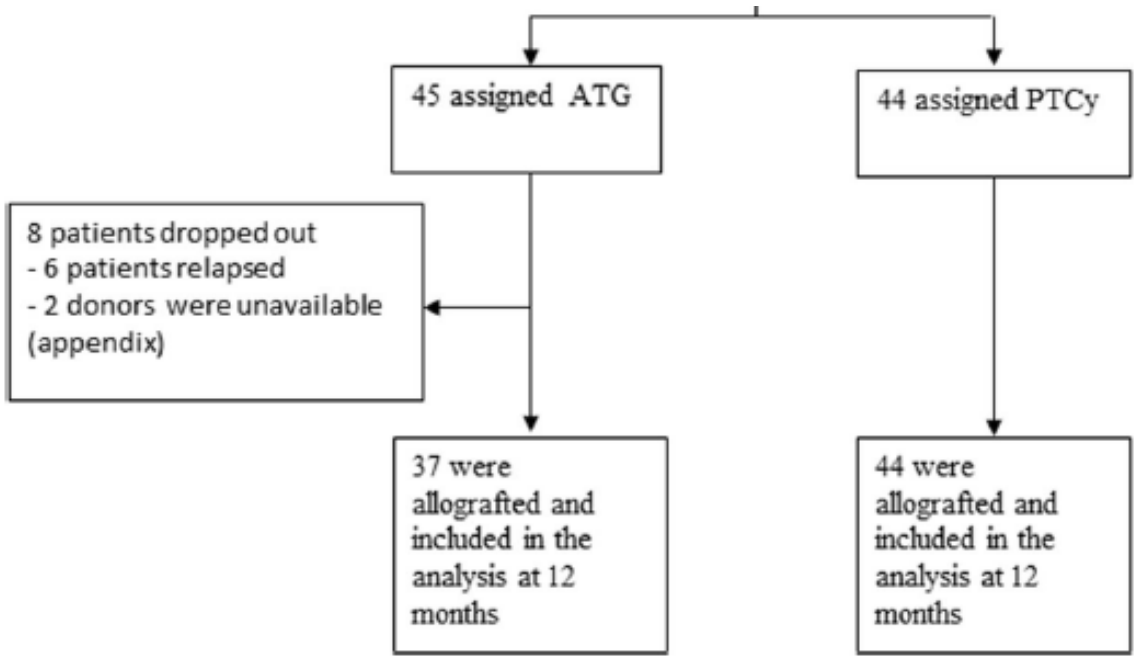


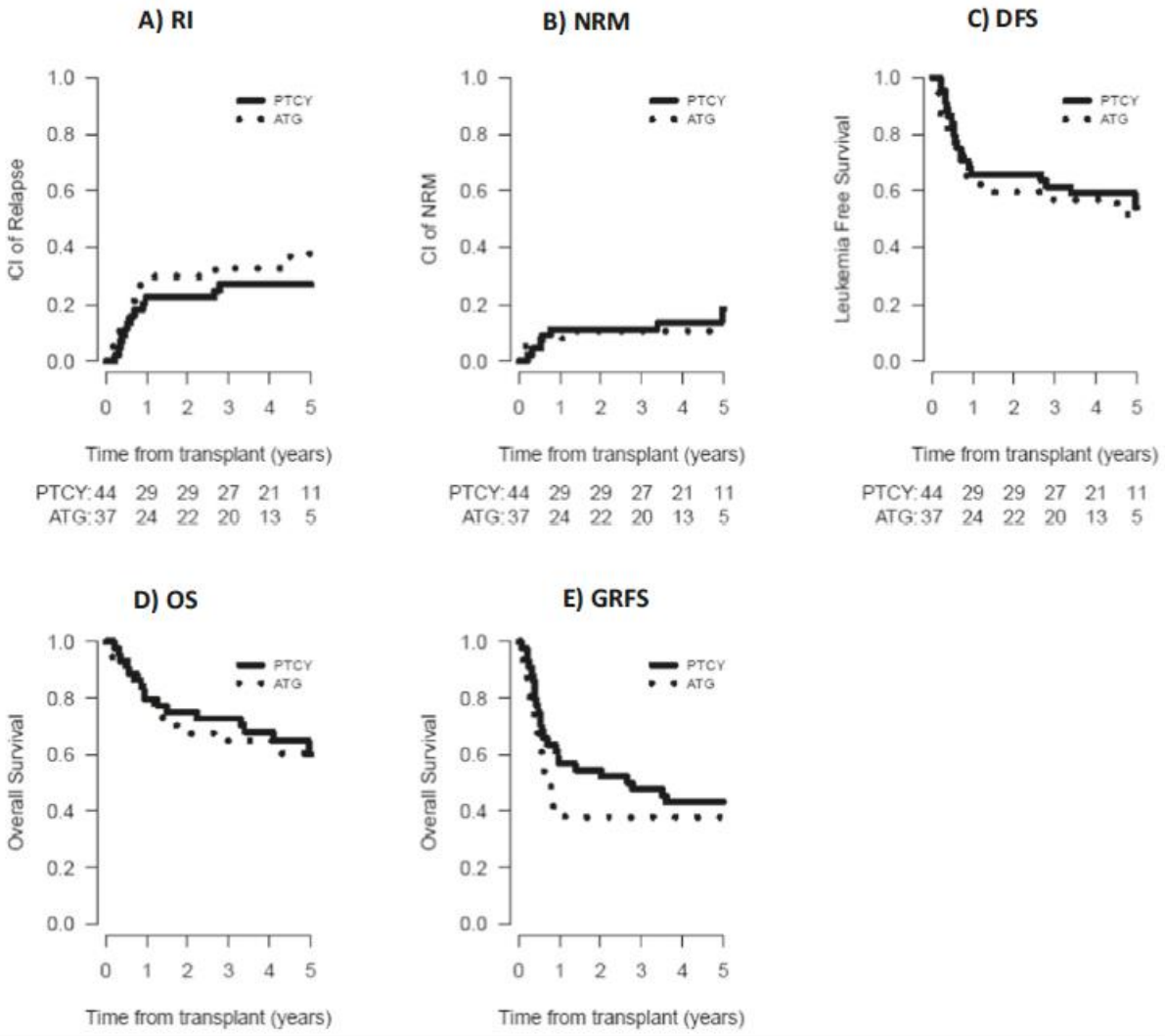


Bolanos-Meade, NEJM 2023

Cy_PT vs ATG
RIC, MUD ou MRD
final analysis of a randomized, open-label, multicenter, phase 2 trial

FB2

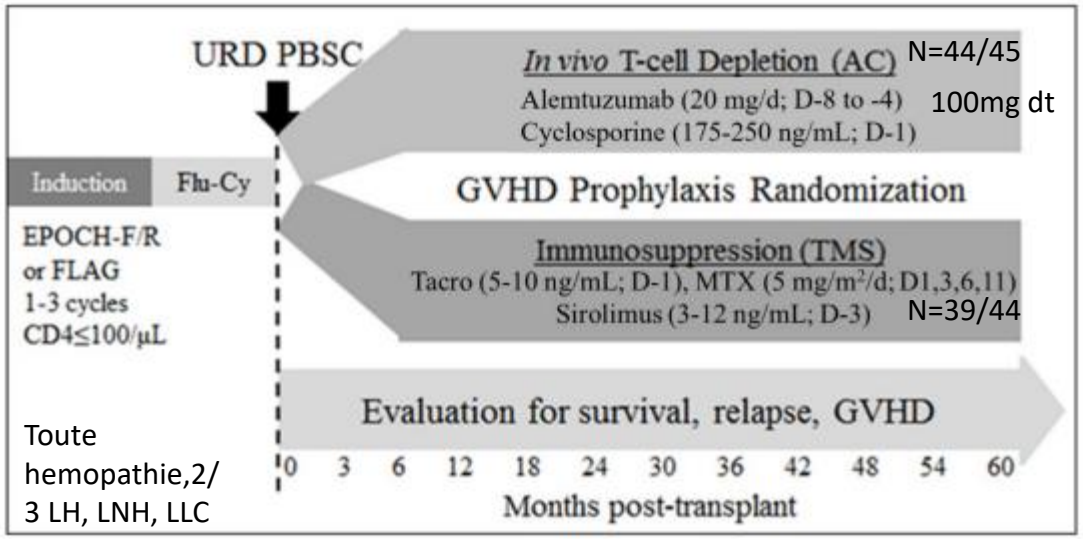




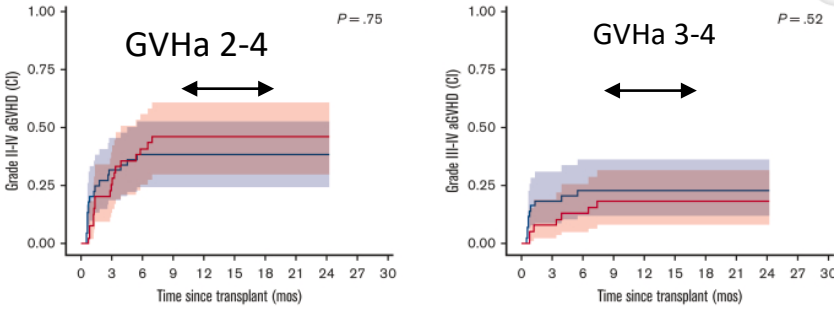
Brissot, Blood Cancer J , 2024

High-dose alemtuzumab and cyclosporine (AC) vs tacro, metho, and sirolimus (TMS) for chronic GVHD prevention

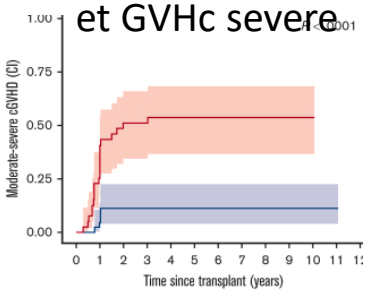
8/8 ou 7/8

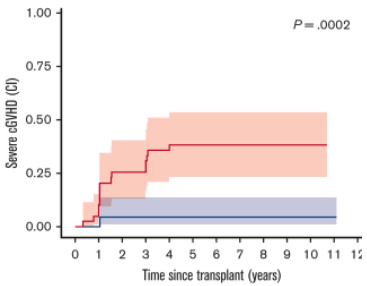


Toute hemopathie,2/ 3 LH, LNH, LLC

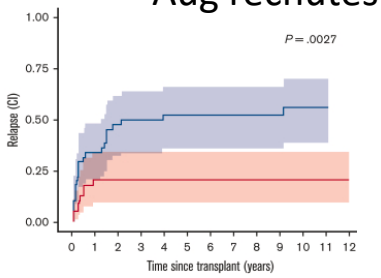


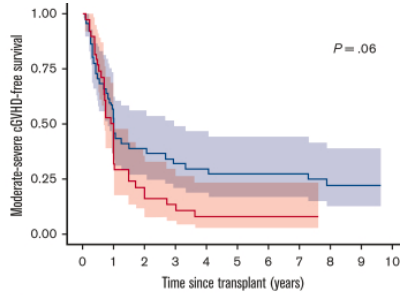
Nette dim GVHc et GVHc severe

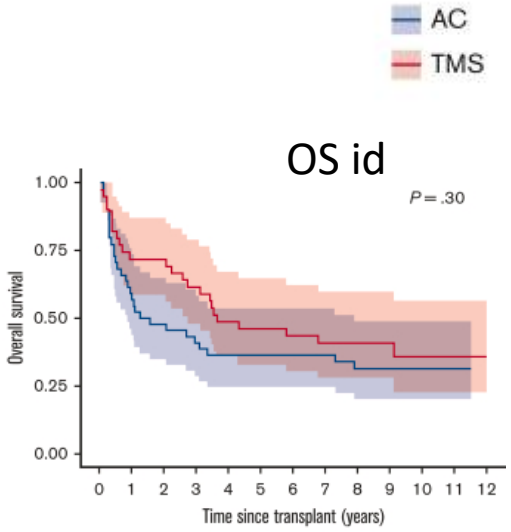




Aug rechutes







Reconstitution immune:
AC dim CD4 naives, dim CD8-Tscm aug ratio Treg/T naive, dim CD8

Alemtuzumab à fortes doses previent très efficacement de la GVHc mais augmente les rechutes et les infections (CMV, 3 PTLD vs 1 etc) sans benefice de survie chez des patients RIC + UD + CSP
Intérêt surtout pour les hémopathies non malignes?

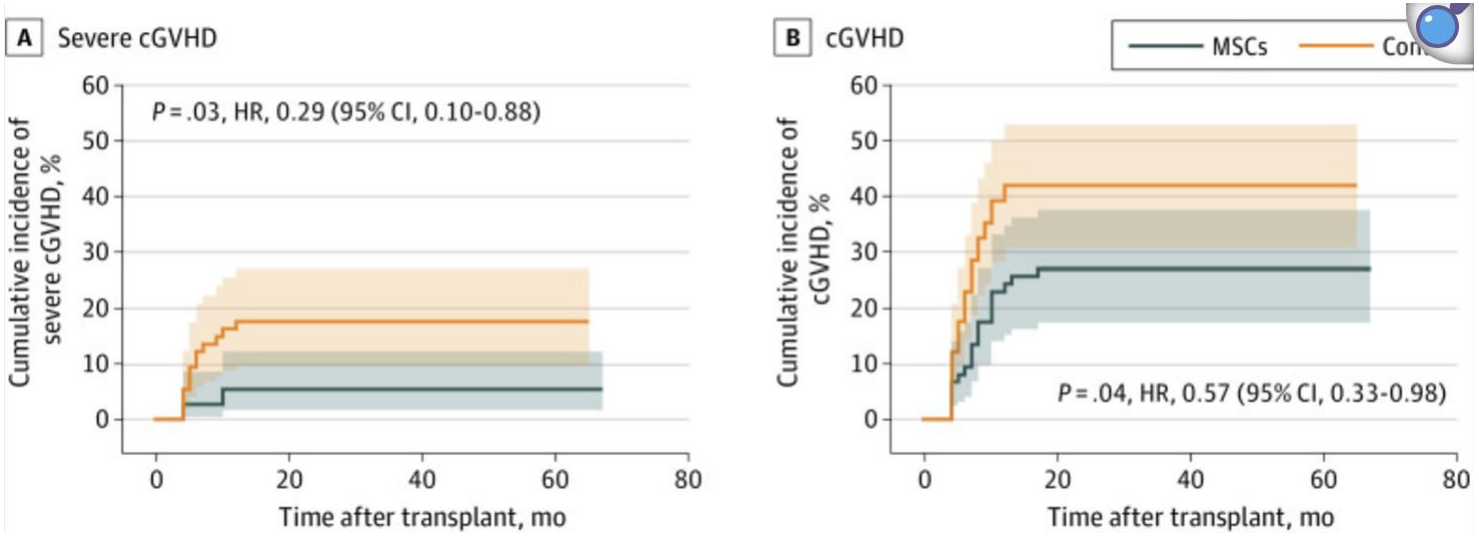
Holtzman, Blood Adv 2024

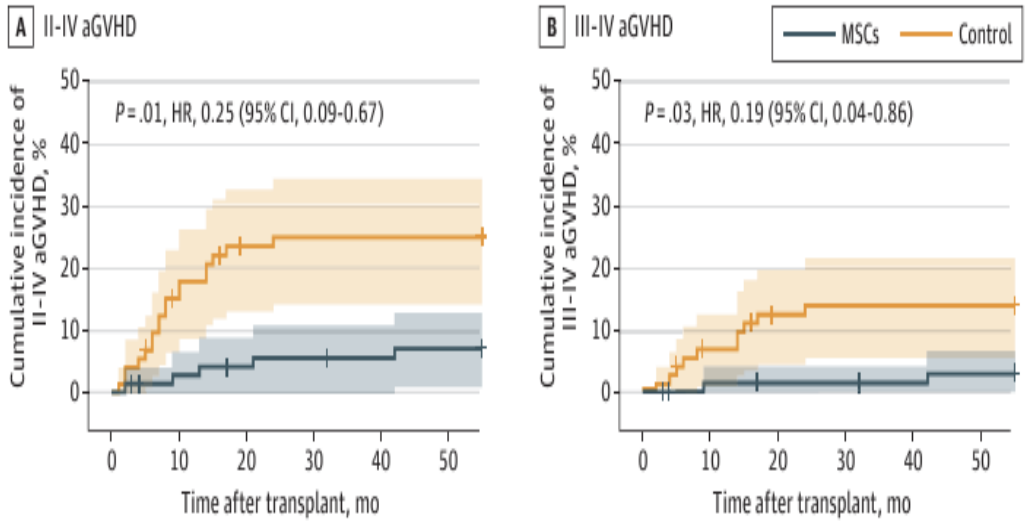
Mesenchymal Stem Cells for Prophylaxis of Chronic GVHD After Haploidentical SCT

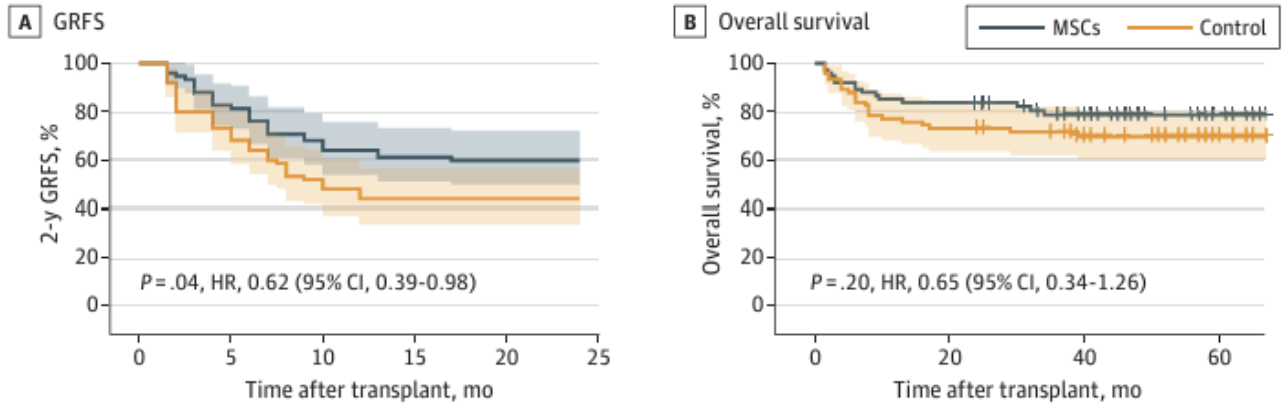
Beijing protocole Me-CCNU, Ara-C, Bu, CTX + CSP+G-BM
MMF CsA MTX

→ N=74, MSCs (**MSC group**) (1 × 10^6 cells/kg/ 2 sem à partir de J45 [4 doses total])

→ N=74, Prophylaxie standard (**control group**).







Rechute idem 10/groupe

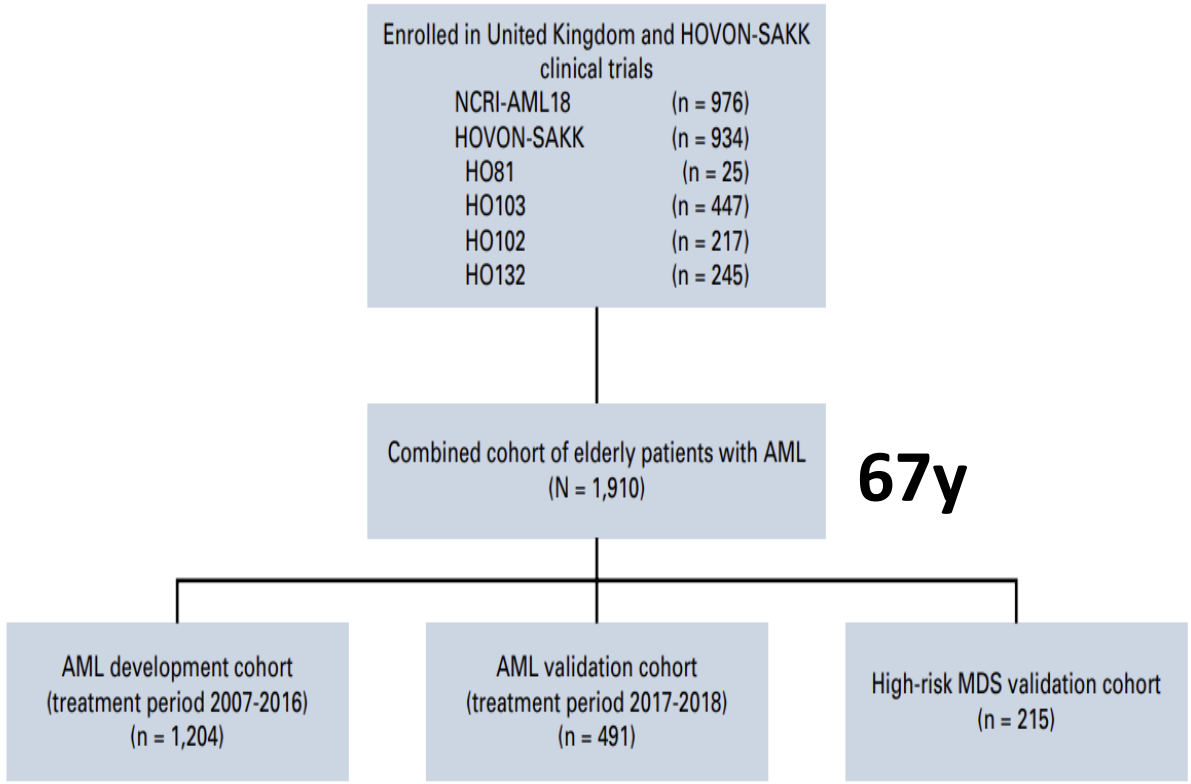
Huang, JAMA Oncol 2023

LAM

Risk Stratification in Older Intensively Treated Patients With AML

Mutations des sujets jeunes

Trouver une nouvelle classification sujets âgés?



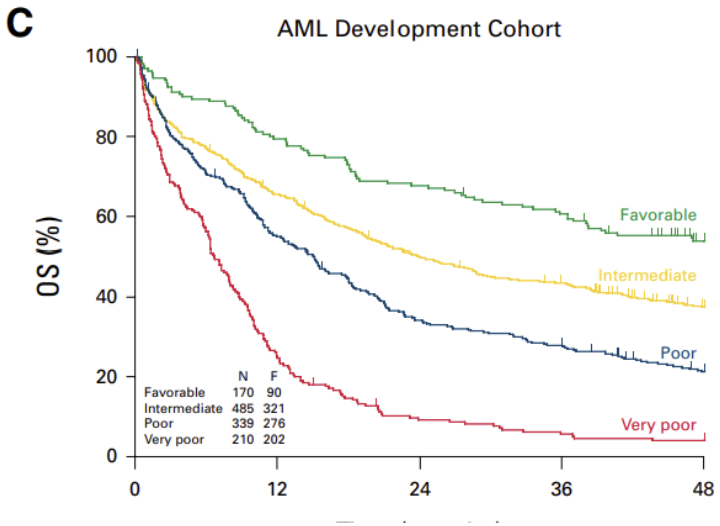
9

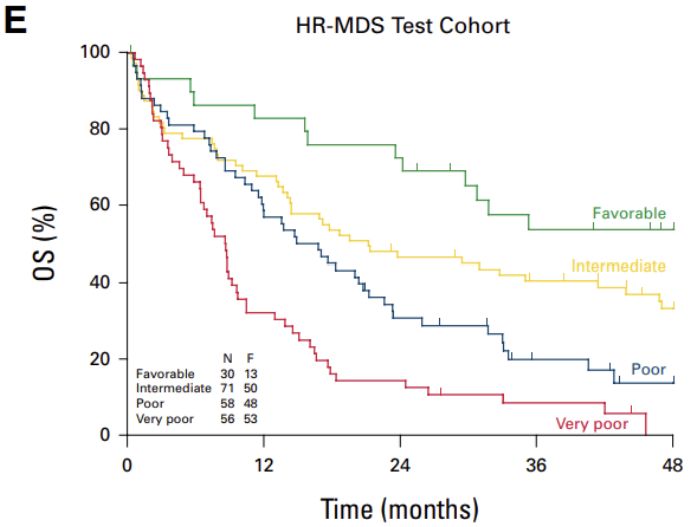
Variable	HR	95%CI	Weight
TP53 mutation	2.42	1.83-3.21	3
Monosomal karyotype	2.06	1.56-2.73	3
Age >65 (years)	1.50	1.31-1.72	2
RUNX1 mutation	1.49	1.26-1.76	1
FLT3-ITD	1.36	1.13-1.65	1
ASXL1 mutation	1.32	1.10-1.58	1
DNMT3A mutation	1.25	1.07-1.45	1
WBC >20 (10e9/L)	1.22	1.03-1.44	1
Male sex	1.15	1.00-1.32	1

age, sex, WBC count, gene mutations, and cytogenetic abnormalities → Machine learning

Favorable	(0-1pt)
Int	(2-3pts)
Poor	(4-5pts)
Very poor	(6-10pts)

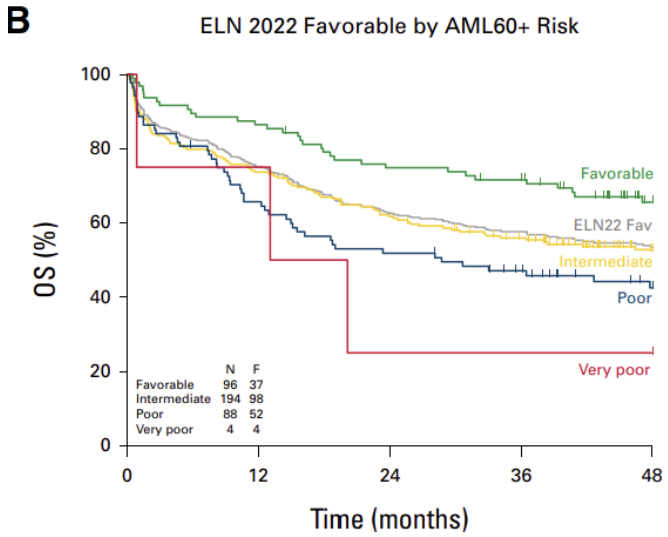
Versluis, JCO 2024

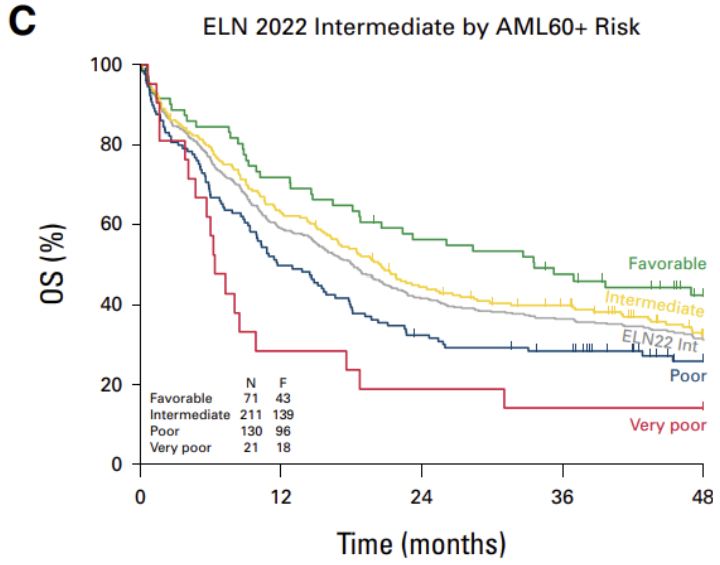


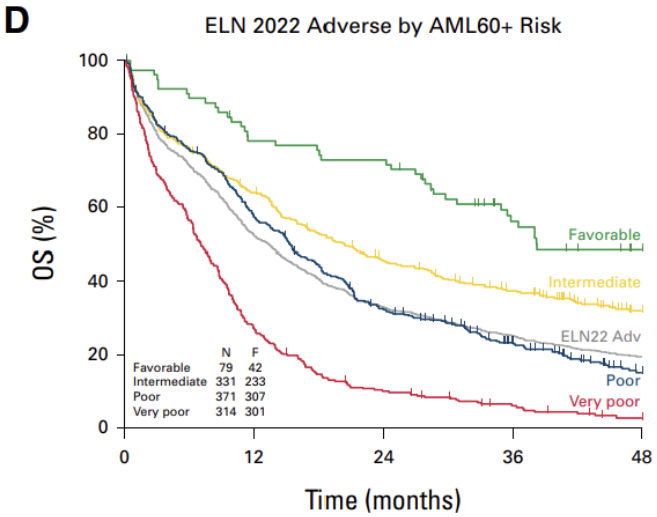


Score AML60+ stratification efficace du risque

Favorable	(0-1pt)
Int	(2-3pts)
Poor	(4-5pts)
Very poor	(6-10pts)

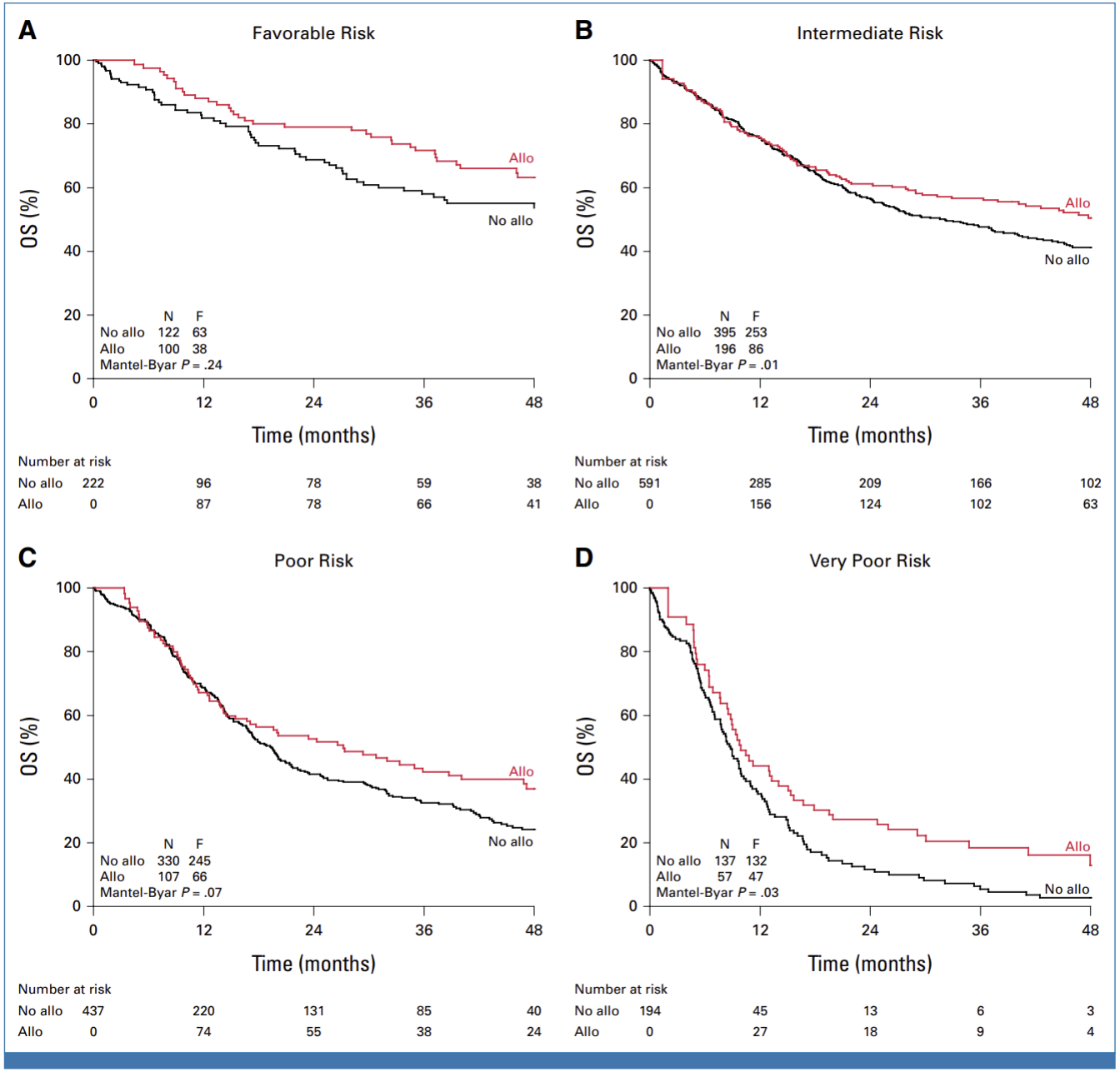






Score AML60+ identifie des sous groupes dans les groupes ELN2022

Versluis, JCO 2024



OS of allo-HCT versus no allo-HCT in first CR in AML60+ risk groups

Intérêt allo dans les LAM int et very poor risk

Versluis, JCO 2024

Remission induction versus immediate allogeneic haematopoietic stem cell transplantation for patients with relapsed or poor responsive acute myeloid leukaemia (ASAP): a randomised, open-label, phase 3, non-inferiority trial

ITT:140 allo d'emblée
Disease control

27% chimio (+severes)
69% watch and wait

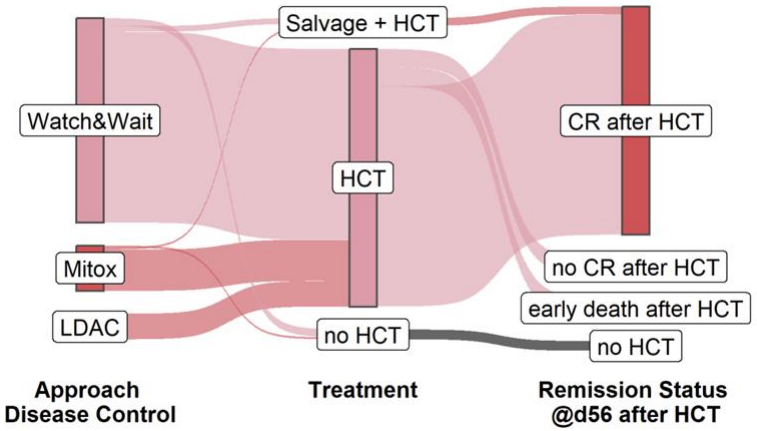
138 per protocol
135 (96%) allo à 16 sem
Délai rando allo 4.4 sem

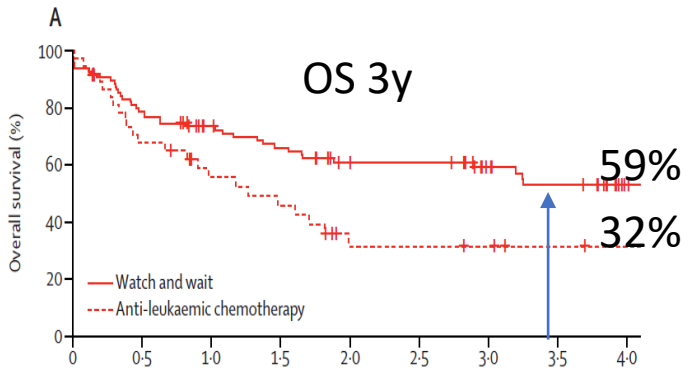
FLAMSA RIC ou Flu MEL TBI8Gy
SAL, ciclo, MMF

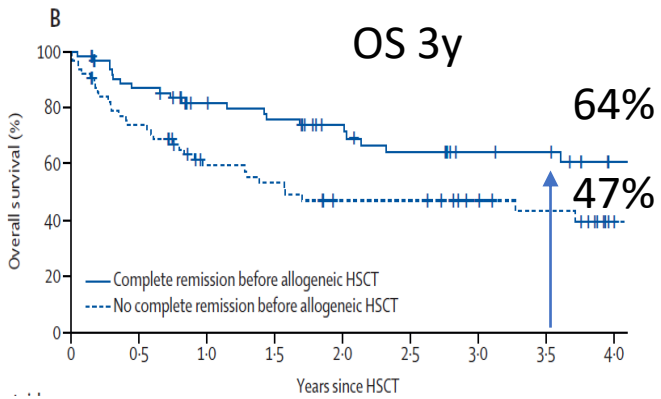
ITT:141 chimio (HAM:HD ARAC-Mitox)
Remission induction
1 cure puis allo

134 per protocol
128 allo, 124 (93%) à 16 sem
Délai rando-allo 7.9 sem
65 en RC (51%) Bu Cy ou FB2 ou Fluda TBI8y
SAL ciclo MTX
63 (49%) pas en RC dont 45 (71%) allo seq

N=281 LAM 1ere rec ou ref après 1 cure induction. 61 ans, 30% blastes



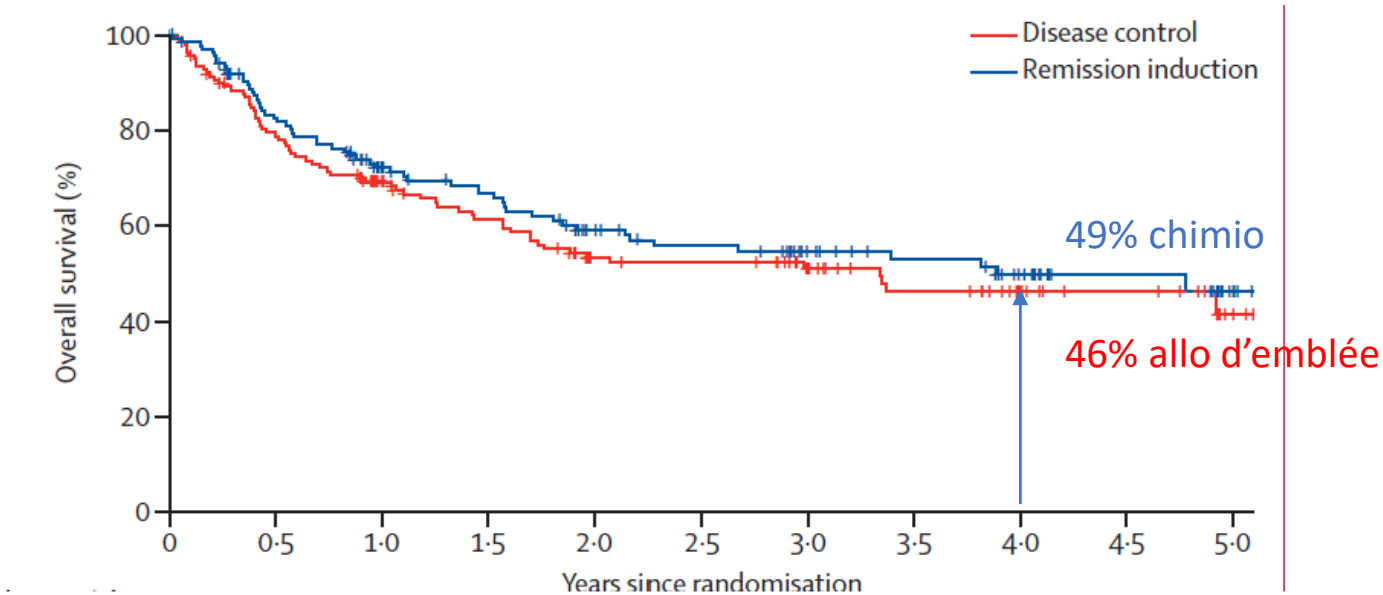




Stelljes, Lancet Haematol 2024

	Allo d'emblée Disease control	Chimio Remission induction	
Objectif primaire: non infériorité taux de RC à J56 post allo	116 (83%)	112 (79%)	→ >2.5%: objectif non atteint
NRM post allo 4 ans	23%	23%	
Rechute 4 ans	36%	34%	
Nb jours hospit avant allo	15j	42j	(p<0·0001)

ASAP



FU 37 mois

Stelljes, Lancet Haematol 2024

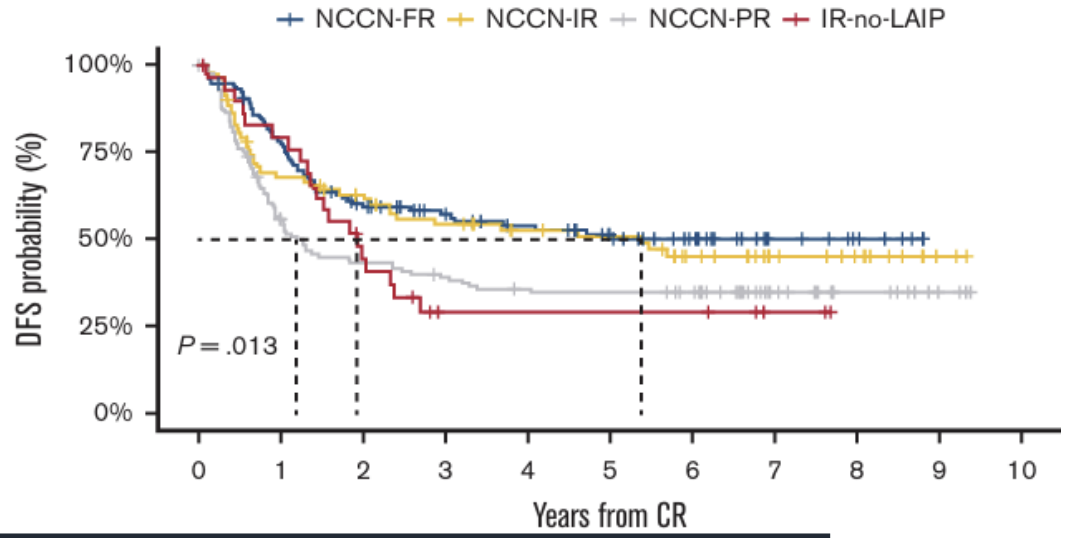
MRD et LAM

Risk-adapted **MRD**-directed therapy for young adults with AML: 6-year update of the **GIMEMA** AML1310 trial.

n=515 LAM, 49y, strat selon groupe de risque Reco NCNN et **MRD** pour les intermediaires **par cytométrie**, seuil ≥0.035%

Favorable (FR), n=138
NPM1+ FLT3-ITD– or CBF+ sans c-Kit mutations) → Auto SCT

poor-risk (PR) , n=188
adverse karyotype or FLT3-ITD+ → Allo SCT

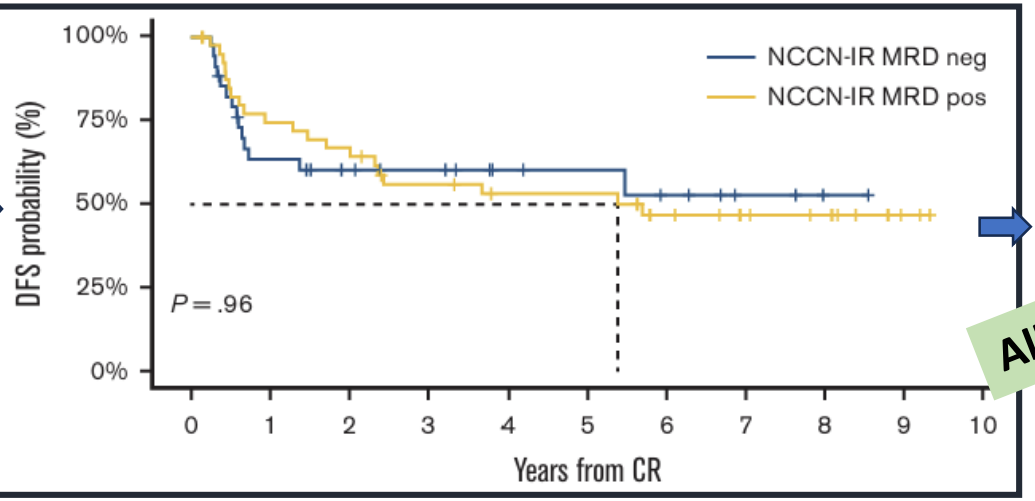


NCNN

Int (IR), n=127
int karyotype ou FLT3-TKD+ ou c-kit mutated CBF+

MRD+ → Allo SCT

MRD- → Auto SCT



MRD n… …= MRD+ allo

Allo int ne bénéficie qu'aux MRD+

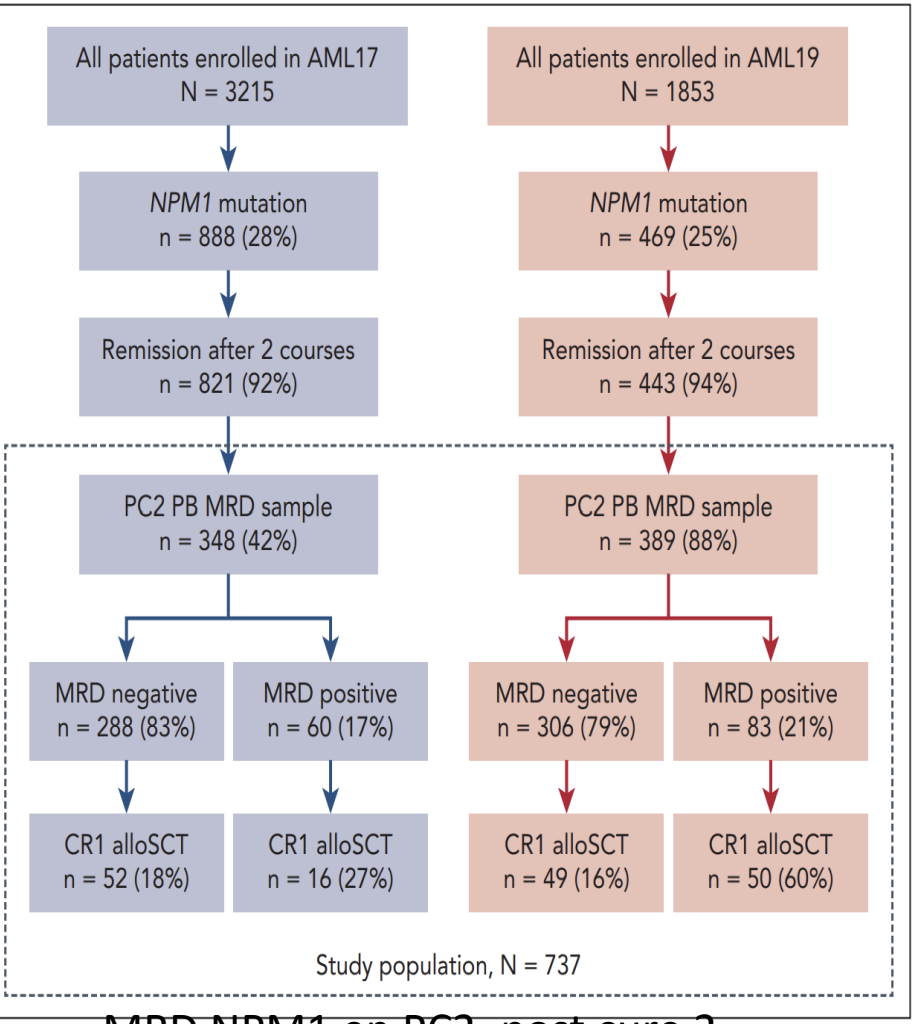
Concordance ELN 2017

(IR-no-LAIP),n=47 → Auto SCT

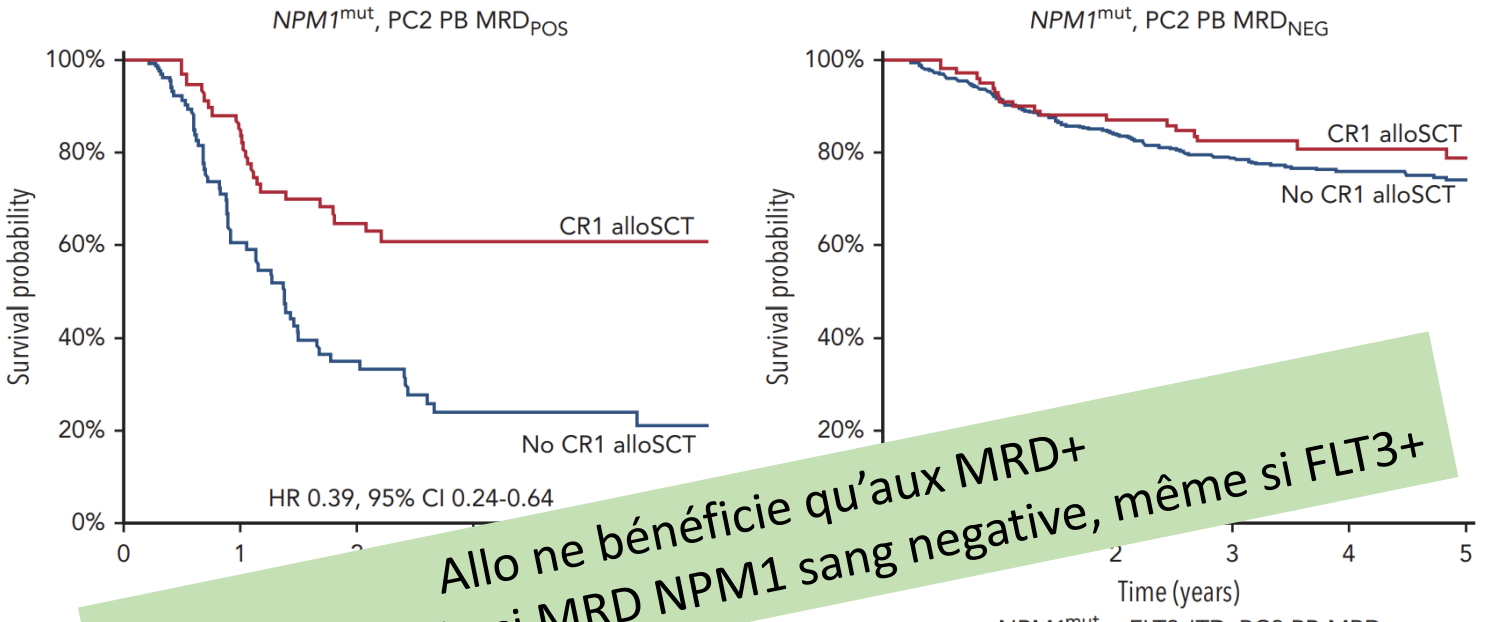
Venditti, Blood adv 2024

Postinduction molecular MRD identifies patients with NPM1 AML who benefit from allogeneic transplant in first remission

N=737, 52y, 87% caryo N, 40% FLT3ITD ht ratio,

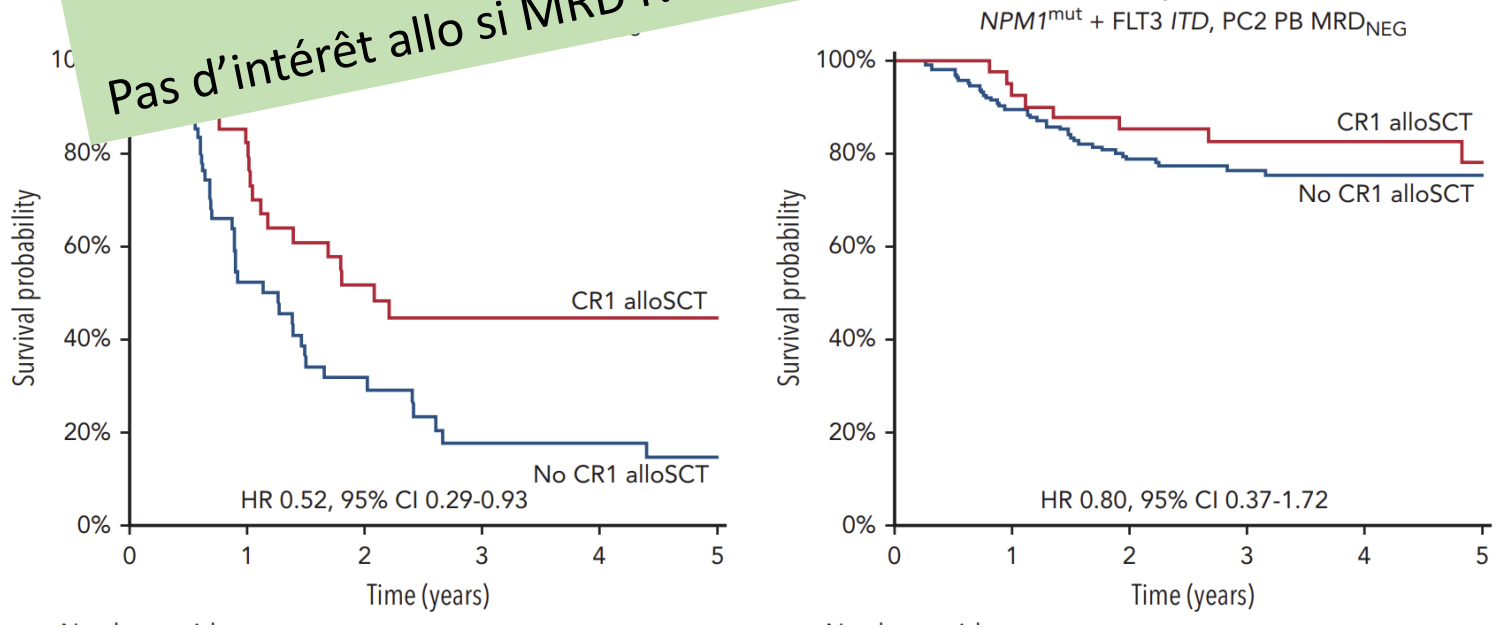


MRD NPM1 en PC2=post cure 2



Allo ne bénéficie qu'aux MRD+

Pas d'intérêt allo si MRD NPM1 sang negative, même si FLT3+

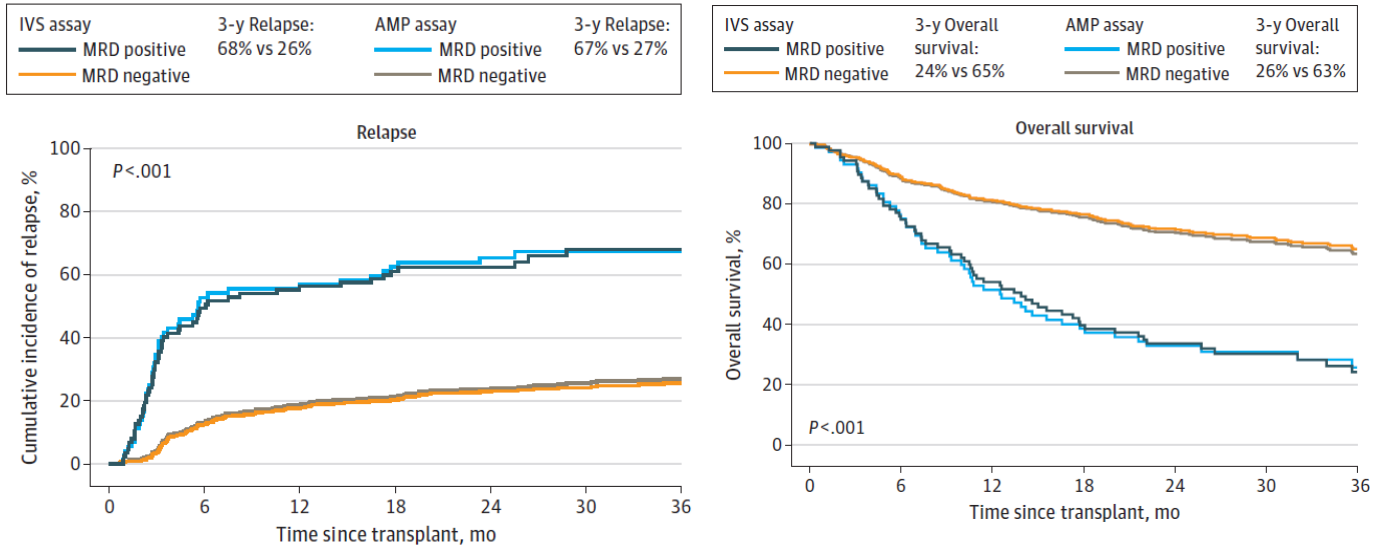


Othman, Blood 2024

Measurable Residual FLT3 ITD Before Allogeneic Transplant for AML

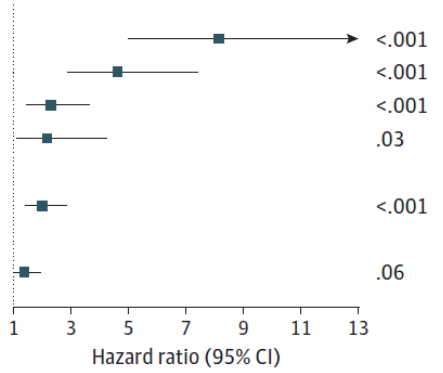
Etude Pre-MEASURE, cohorte 537 LAM FLT3 ITD adultes multicentriques CIBMTR: DNA sequencing MRD SANG FLT3ITD pré allo. Impact MRD pré allo sur le devenir

VAF FLT3 ITD>1x10-4 sang pré allo corrélée à rechute+++ et OS dim

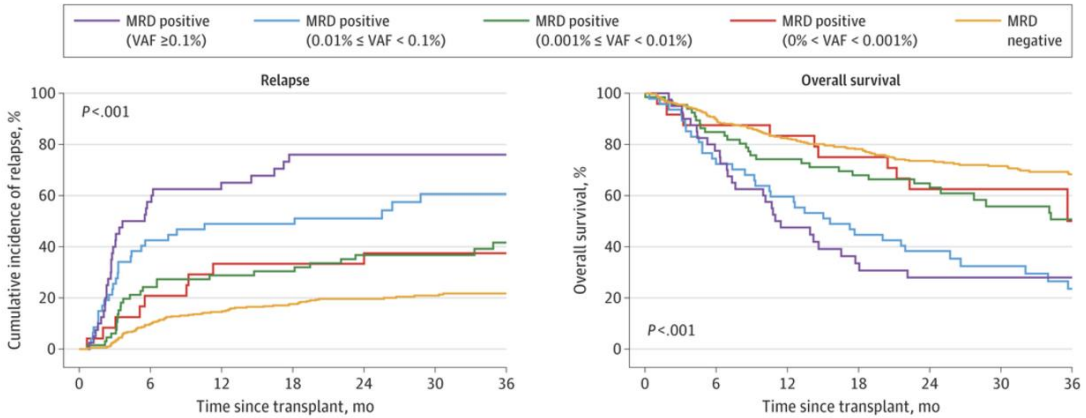


Multivariée risques compétitifs

Measure	Hazard ratio (95% CI)	P value
FLT3-ITD MRD positive		
VAF ≥0.1%	8.15 (5.01-13.26)	<.001
0.01% ≤ VAF < 0.1%	4.62 (2.88-7.42)	<.001
0.001% ≤ VAF < 0.01%	2.30 (1.46-3.63)	<.001
0% < VAF < 0.001%	2.16 (1.10-4.24)	.03
Conditioning intensity		
RIC/NMA	2.01 (1.41-2.86)	<.001
NPM1 baseline		
Positive	1.38 (0.99-1.92)	.06



+ la MRD est élevée + le risque augmente



RIC sans melphalan ou NMA ont + de risque de rechute et de DC à n'importe quel niveau de MRD comparé aux MAC ou Melphalan

Dillon, JAMA oncol 2024

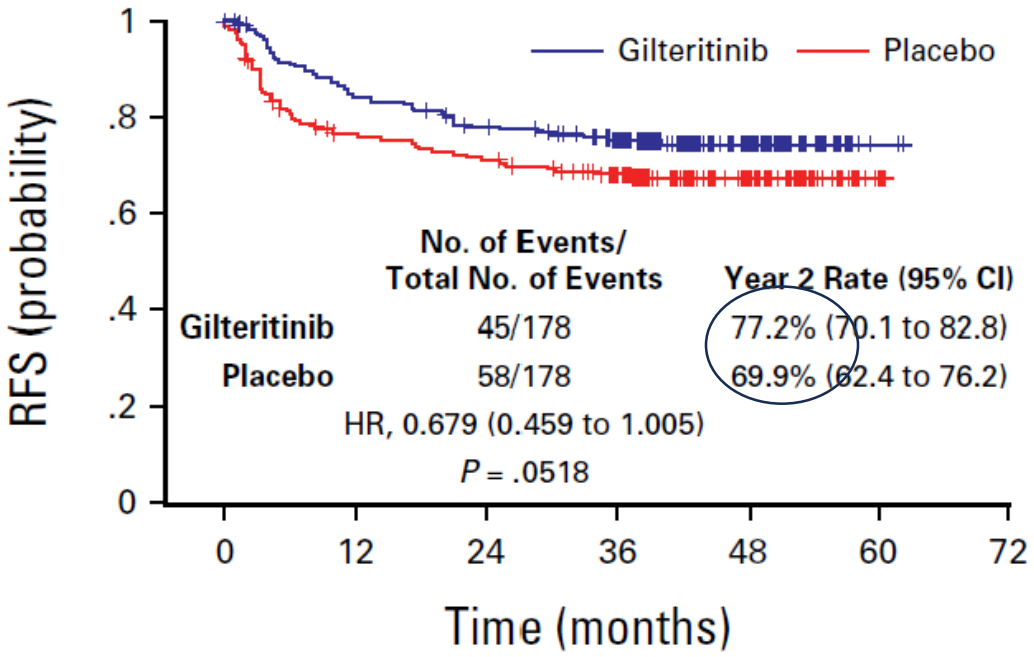
Gilteritinib as Post-Transplant Maintenance for AML With Internal Tandem Duplication Mutation of *FLT3*

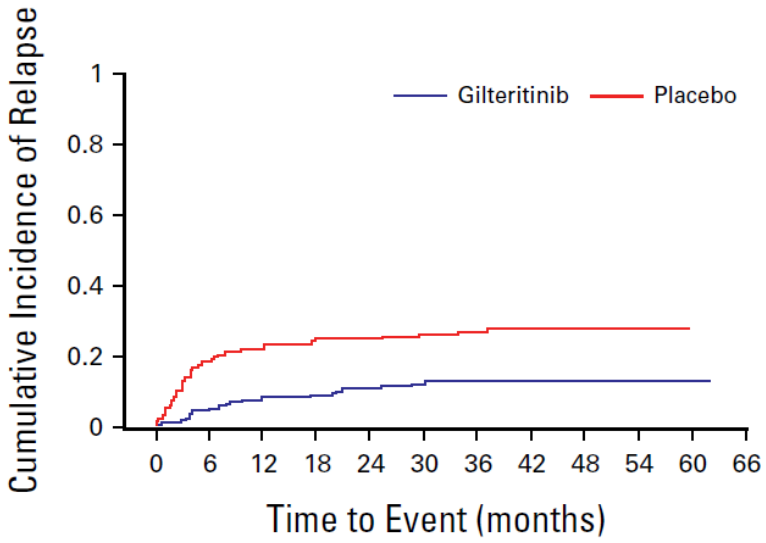
n=356 LAM FLT3-ITD en RC1, 53 ans
2/3 intermed, 34% NPM1+ , 60% MAC
Rando J30 à J90 post allo

→ N=178 placebo

→ N=178 Gilteritinib
120mg/j x2 ans

Objectif primaire: RFS 2y P=0.0518





Levis, JCO 2024

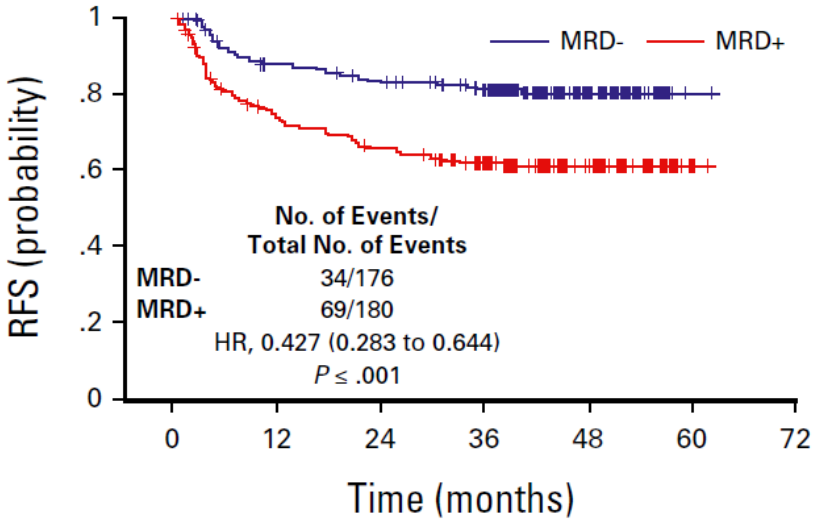
Gilteritinib as Post-Transplant Maintenance for AML With Internal Tandem Duplication Mutation of *FLT3*

2 MRD FLT3 ITD medull. péri SCT: avant allo et à la rando. Détectable si >1x10-6 mais MRD + si > 1x10-4

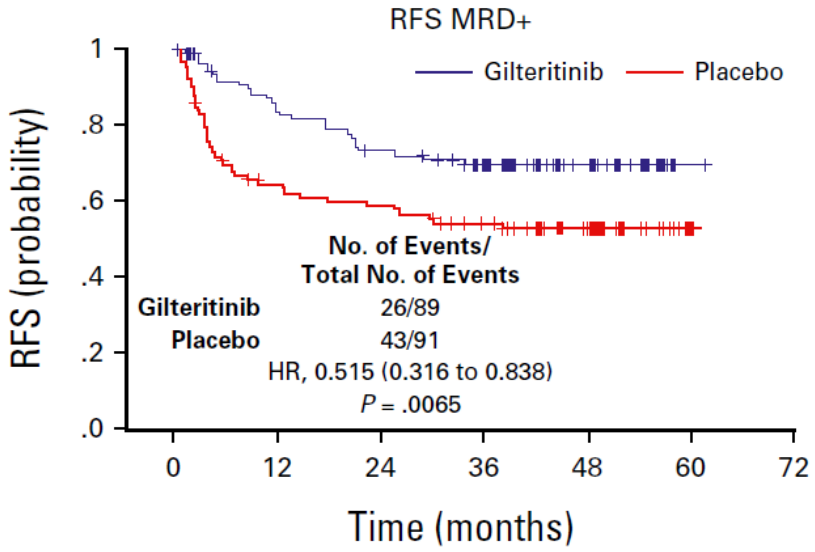
MRD, No. (%)	Gilte	Placebo
Pre-HCT MRD ≥ 10^{-4}	39 (21.9)	36 (20.2)
Pre-HCT MRD ≥ 10^{-6}	82 (46.1)	82 (46.1)
Pre- or post-HCT MRD ≥ 10^{-6}	89 (50)	91 (51.1)

50% des patients avaient une MRD FLT3 + en péri SCT

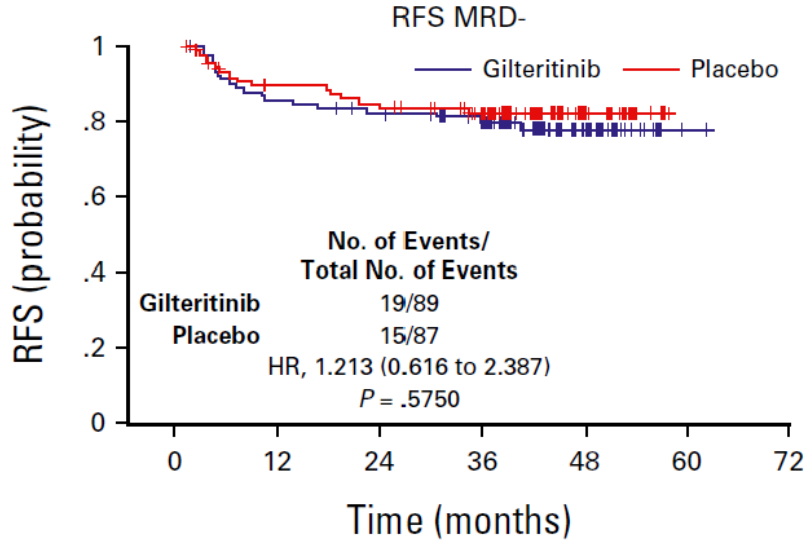
La MRD impacte la RFS indépendamment du bras alloué



Gilteritinib bénéficie aux MRD+



…mais pas aux MRD neg



Levis, JCO 2024

The menin inhibitor revumenib in *KMT2A*-rearranged or *NPM1*-mutant leukaemia

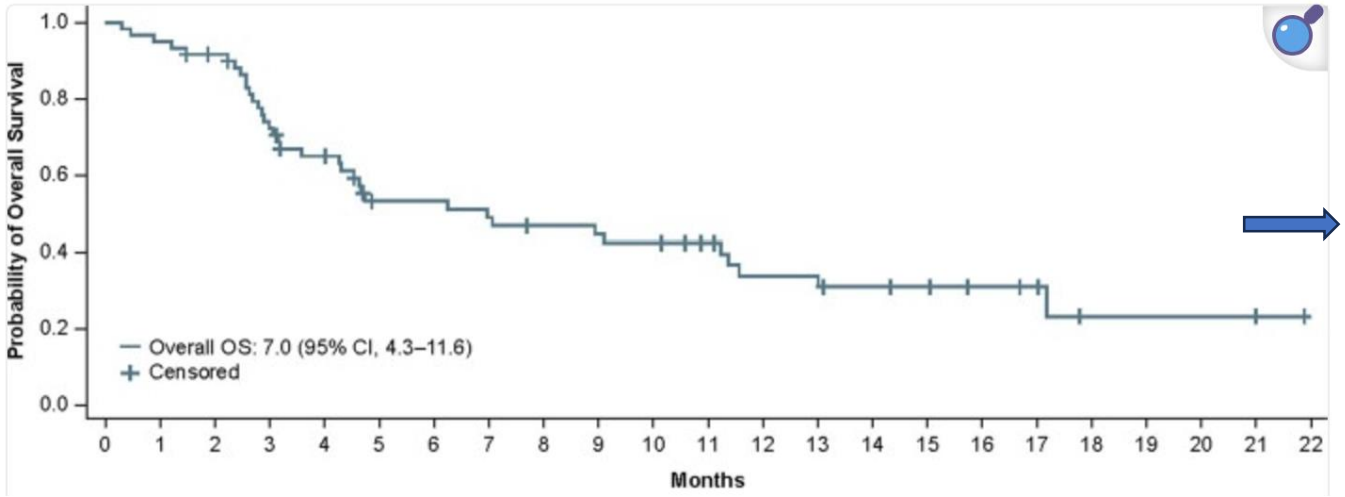
30% RC/RCH

Phase 1
N=68 LAMR/R, 88% KMT2A (n=46) ou NPM1 (n=14)
N=60 adultes, 50y (19-79y); n=8 enfants, 2.5y

Response	Efficacy population (*n* = 60)	*KMT2A*r (*n* = 46)	Mutated *NPM1* (*n* = 14)
Overall response*	32 (53%)	27 (59%)	5 (36%)
Median time to first morphologic response (range), months	0.95 (0.9–3.7)	0.95 (0.9–3.7)	0.99 (1.0–1.9)
Best response*			
CR/CRh	18 (30%)	15 (33%)	3 (21%)
CR	12 (20%)	9 (20%)	3 (21%)
CRh	6 (10%)	6 (13%)	0
Median time to CR or CRh (range), months	1.9 (0.9–4.9)	2.0 (0.9–4.9)	1.9 (1.0–1.9)

Tolérance
Prolongation of the QT interval (56%) don't 13% grade 3, nausea (50%), vomiting (40%) and febrile neutropenia (31%) .
Grade 3: diarrhées, Hca, sd lyse, cytopénies

FU med 12 mois OS med 7 mois

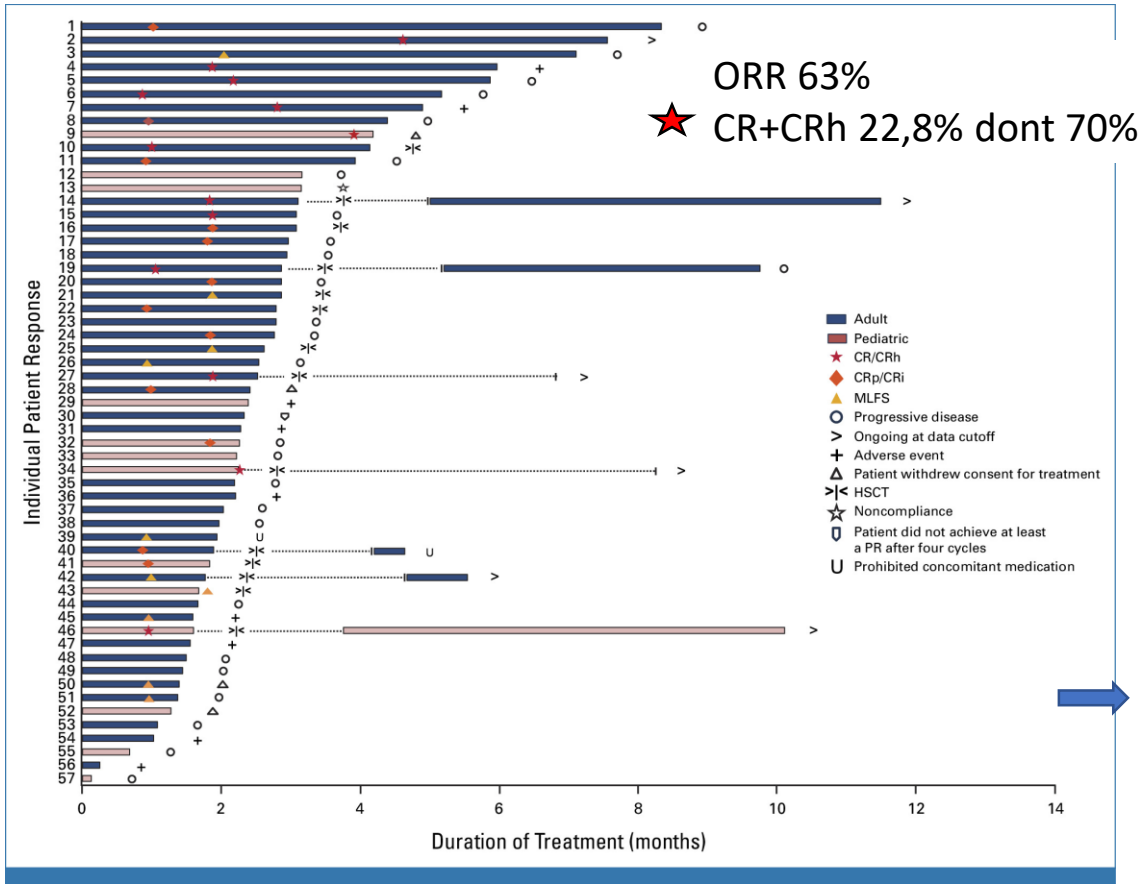


Bridge vers allo (n=12, 18%) dont 9 en RC au dernier fu

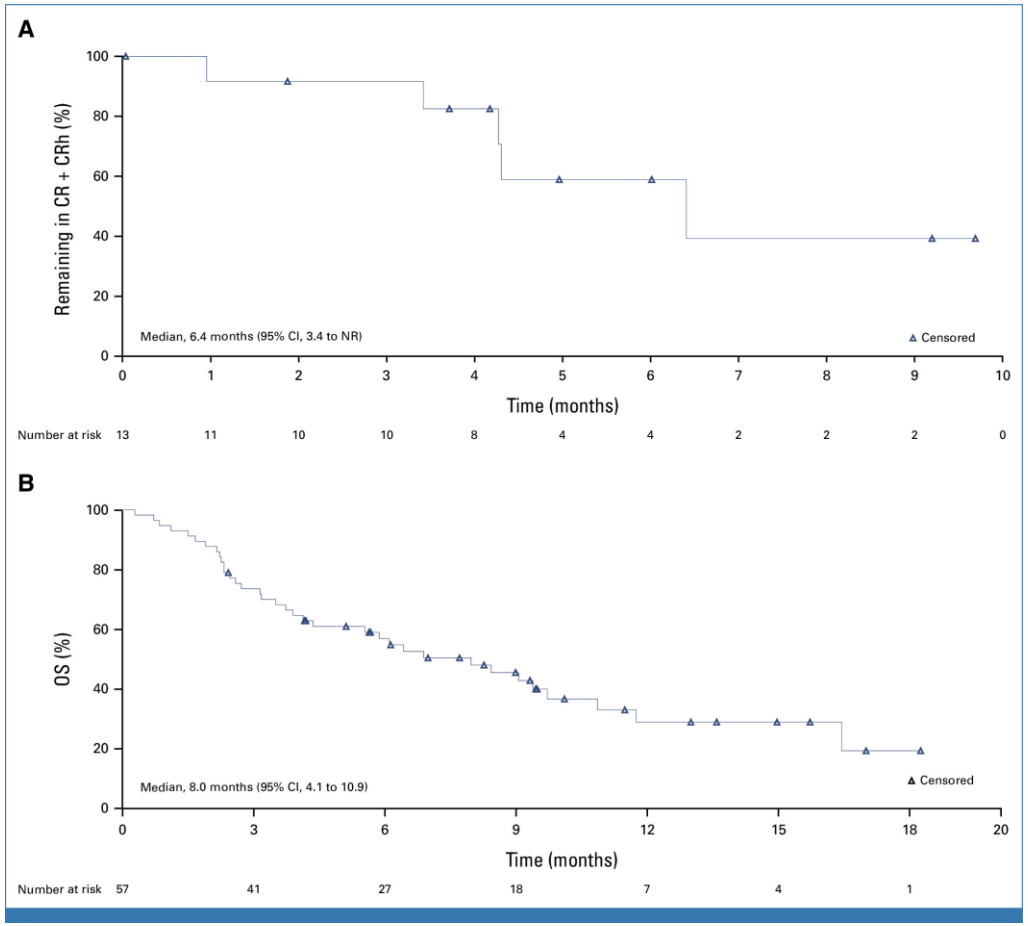
Issa GC, Nature 2023

Menin Inhibition With Revumenib for *KMT2A*-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101)

AUGMENT-101 phase I/II : revumenib for patients with R/R leukemias with *KMT2A*r or *NPM1* mutation. 86% LAM, 12% LAL Analyse interimaire n=57/95 Inclus KMT2A
45% rechute post allo, 80% ref (primo ou rel)
Âge med 37 ans (1.3-75y)
44% >=3 lignes, 2/3 ont eu venetoclax, FU 6 mois
228% sd differenciation, 15% grade 3, 1 grade 1, stop ttt n=7



ORR 63%
★ CR+CRh 22,8% dont 70% MRD neg



14 allo **>I<** (25% pop ; 39% des répondeurs) dont 7 ont eu revumenib post transplant et 5/7 l'ont toujours

Issa GC, JCO 2024

Early Results of the Phase I/II Study Investigating the All-Oral Combination of the Menin Inhibitor Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax in Acute Myeloid Leukemia (SAVE)

N=7, phase I/II, investigator-initiated trial of the all-oral combination of revumenib, venetoclax and the hypomethylating agent ASTX727 in children and adults with relapsed/refractory (R/R) acute myeloid leukemia (AML) (NCT05360160).
27y med
100% ORR (n=7/7) don't 3/7 MRD neg (43%), 3 allo (2 vivants et 1 TRM)
QTc et sd de differenciation résolutifs

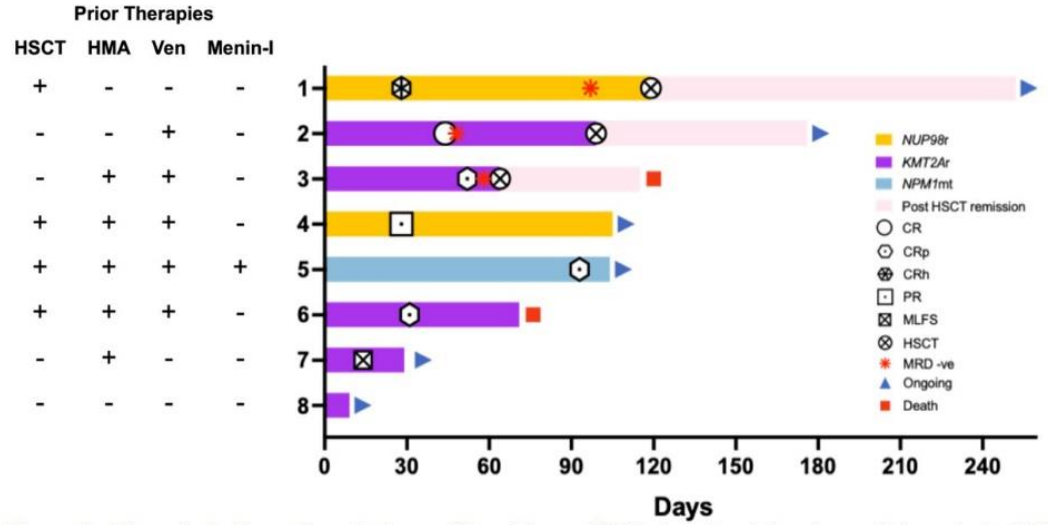


Figure 1: Characterization of remissions. Abbreviations: HSCT, hematopoietic stem cell transplant; HMA, hypomethylating agent; Ven, venetoclax; Menin-I, menin inhibitor

Issa GC, Blood 2023 supp

SMP

LMMC

Management of adult patients with CMML undergoing allo-HCT: recommendations from the EBMT PH&G Committee

AML defined by mutations includes AML with mutated *NPM1* (WHO 2022, pas de seuil blastesand AML with mutated bZIP *CEBPA* (ICC-2022 [≥10% blasts required]).[14] As such, patients with CMML harboring these mutations should be considered and treated as AML.

When mutations in *TP53*, *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *STAG2*, *U2AF1*, or *ZRSR2* are present, ICC-2022 proposes a new disease category MDS/AML defined by 10% to 19% blasts, that can be treated either as MDS or as AML.[14] This however, does not affect patients with CMML as yet.

CPSS-Mol genetic risk group

Variable score points	CPSS cytogenetic risk group	ASXL1	NRAS	RUNX1	SETBP1
0	Normal karyotype, isolated -Y	Unmutated	Unmutated	Unmutated	Unmutated
1	All other abnormalities	Mutated	Mutated	–	Mutated
2	Trisomy 8, complex karyotype (≥3 abnormalities), abnormalities of chromosome 7	–	–	Mutated	–

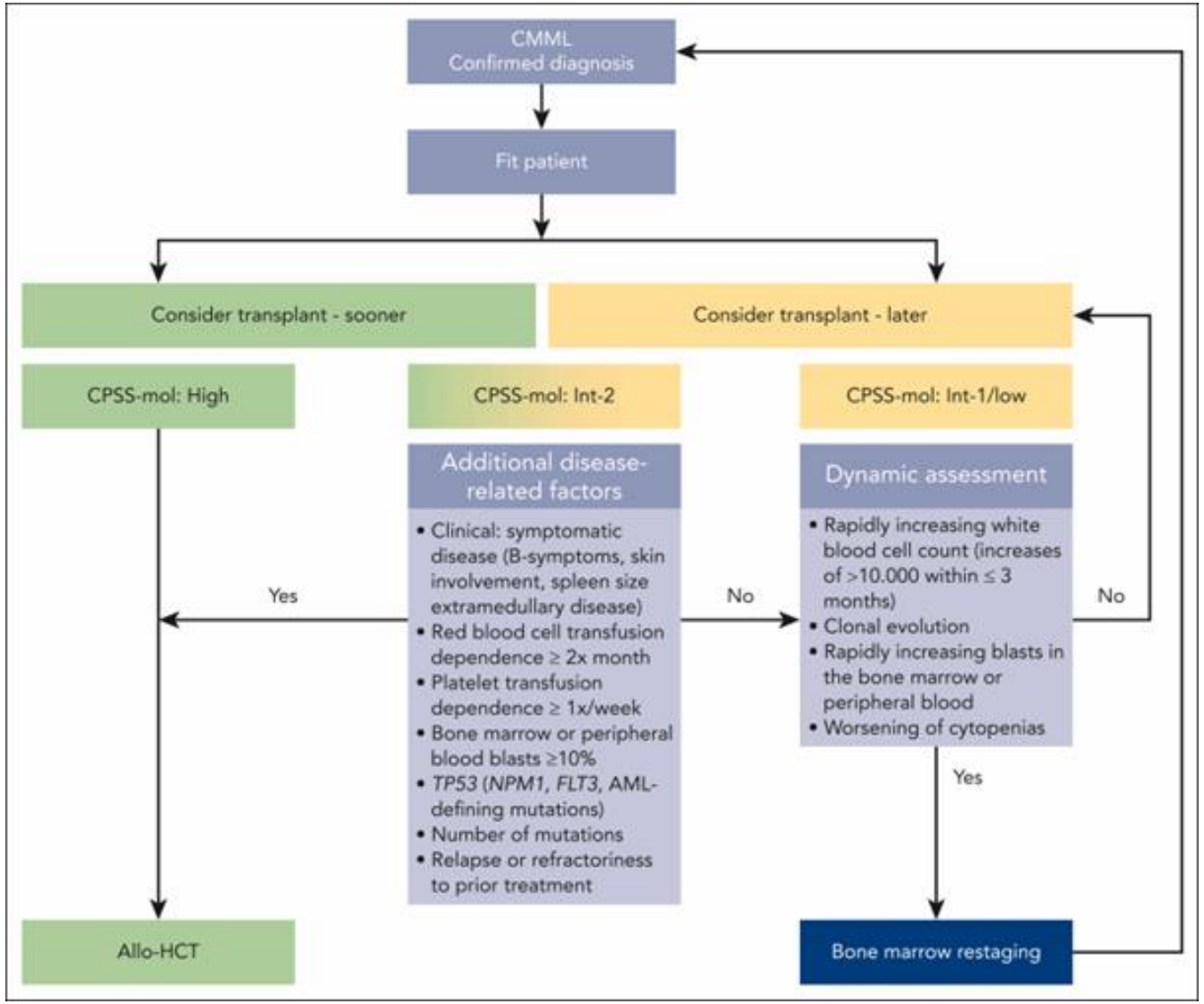
Genetic risk group category	
Total score points	**CPSS genetic risk group**
0	Low
1	Intermediate-1
2	Intermediate-2
≥3	High

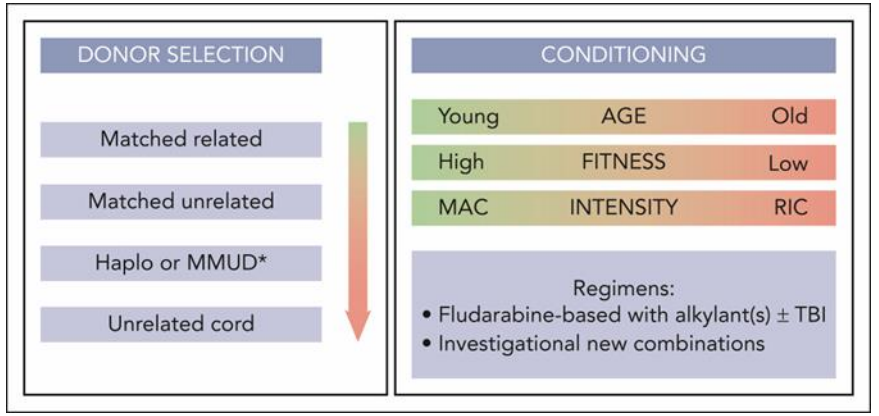
CPSS-Mol score

Score points	Genetic risk group*	Bone marrow blasts	WBC count	Red blood cell transfusion dependency
0	Low	<5%	$<13 \times 10^9$/L	No
1	Intermediate-1	≥5%	$\geq 13 \times 10^9$/L	Yes
2	Intermediate-2	–	–	–
3	High	–	–	–

CPSS-Mol risk group category			
Total score points	**CPSS-Mol risk group**	**Median overall survival,† mo**	**Cumulative incidence of transformation to AML at 48 mo,† %**
0	Low	Not reached	0
1	Intermediate-1	64-68	3 (8)
2-3	Intermediate-2	30-37	21 (24)
≥4	High	17-18	48 (52)

Onida, Blood 2024





Onida, Blood 2024

Donor types and outcomes of transplantation in myelofibrosis: a CIBMTR study

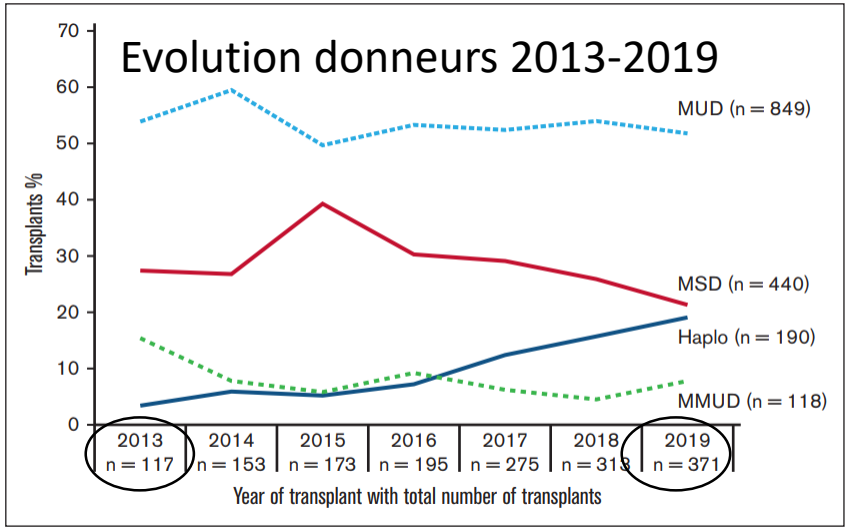
F.U 46m

D+vieux

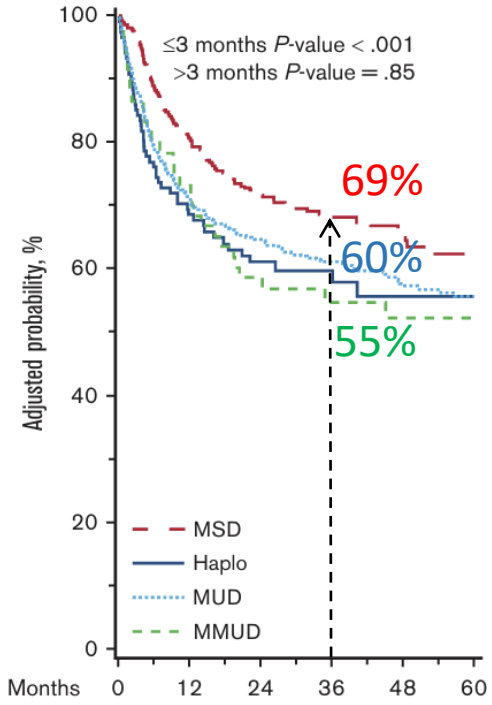
non white
DIPSS +ht
+ RIC,NMA

D+ jeunes

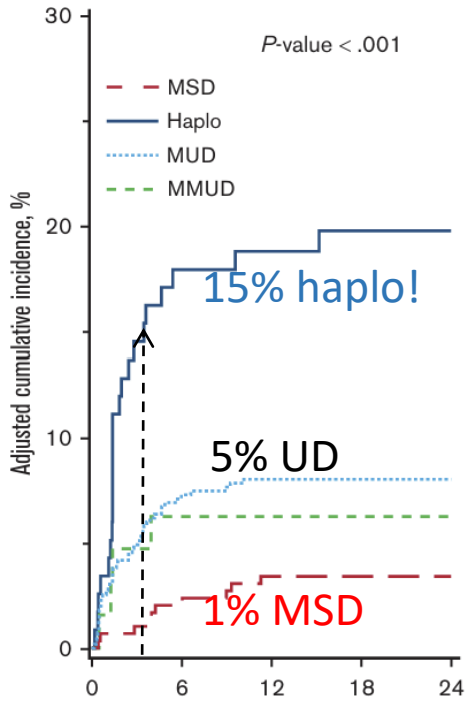
D+ jeunes
R+ jeunes



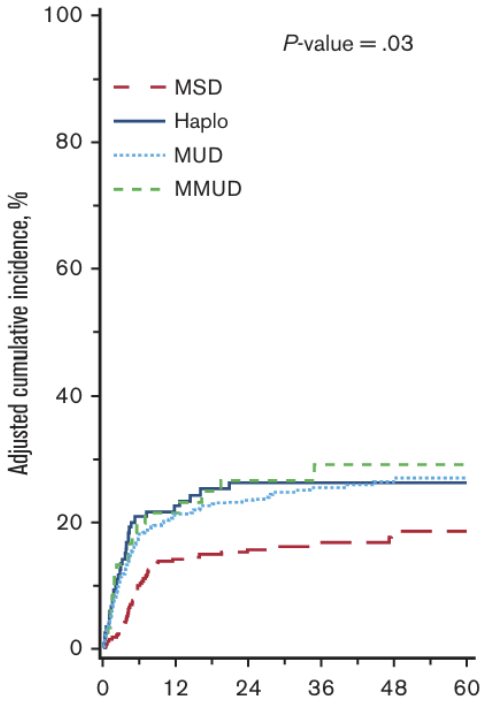
OS



Graft failure D100



NRM

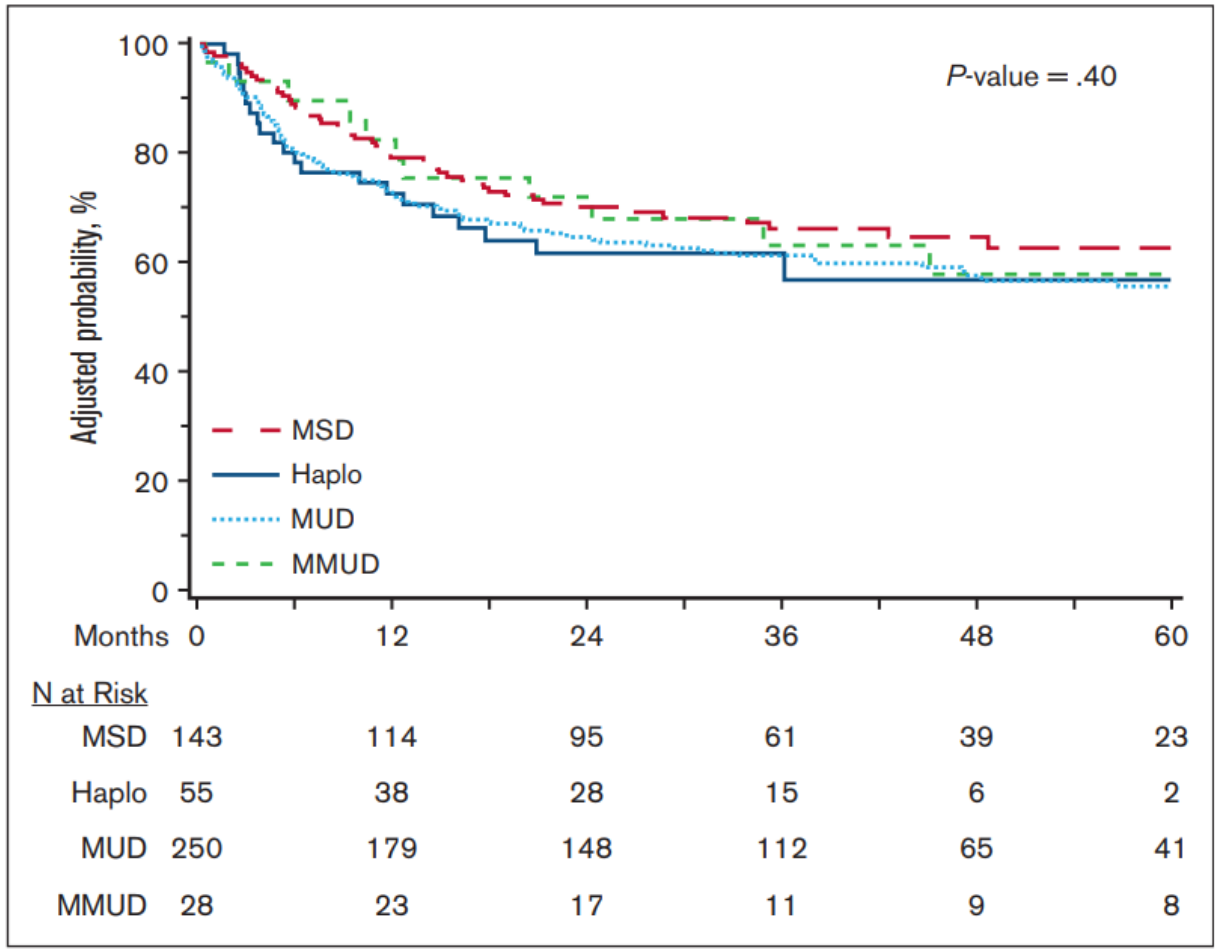


Fdr graft failure (8%)
délai à allo (31 mois vs 27)
Hb <10g/dl
plaq <50 000/mm3
DIPSS int 2 ou high
SMG
CDT NMA (Haplo: 30% de NMA)

Jain, Blood adv 2024

délai Dg à allo-SCT: 25(MSD) à 33(haplo) mois

Meilleure OS si allo<24 mois du Dg



CONCLUSION

DIPSS int-1 ou +
Allo avec n'importe quel donneur dans les 24 mois du Dg
Eviter les CDT NMA (haplo)
Diminuer la taille de la rate

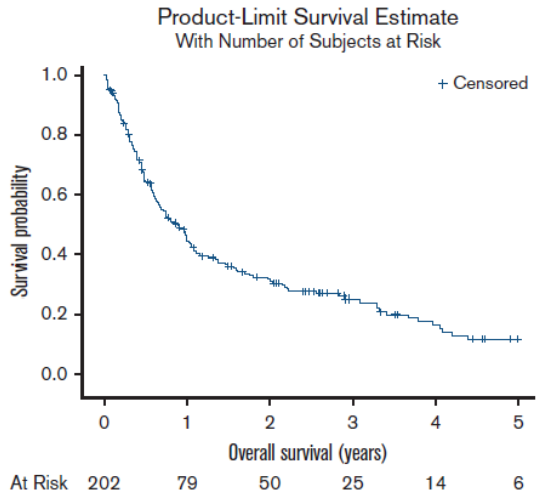
Jain, Blood adv 2024

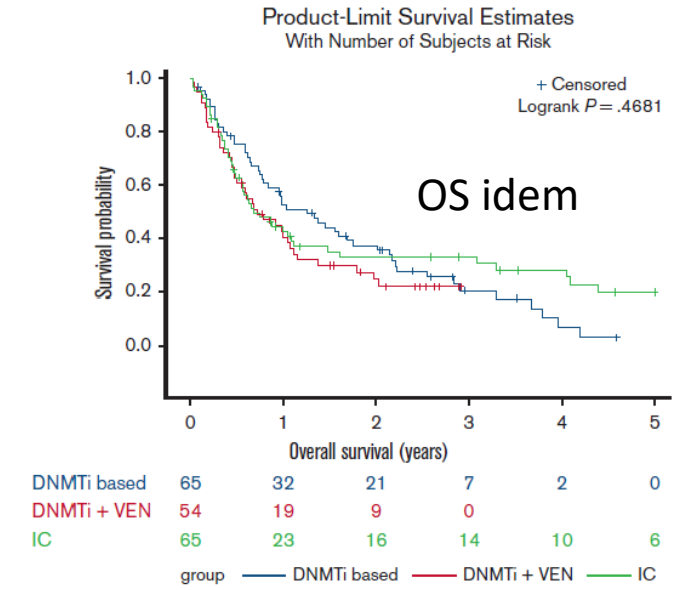
Treatment approach and outcomes of accelerated/ blast-phase myeloproliferative neoplasms in the current era

Etude retrospective 9 centres US+Canada, adultes SMP >10% blastes, accéléré/acutisé depuis 2017. N=202, 1/3 MF primitive, 69 ans

Median follow-up court (0.75 ans) mais OS med 0.86 ans

Driver mutation	N = 202
JAK2	124 (61%)
CALR	33 (16%)
MPL	18 (9%)
Triple-negative	27 (13%)
2017 ELN risk at MPN-AP/BP diagnosis	n = 189
Favorable	5 (2.6)
Intermediate	58 (30.7)
High risk	126 (66.7)
Mutations at MPN-AP/BP diagnosis	n = 166
ASXL1	52 (31%)
TP53	43 (26%)
SRSF2	39 (23%)
IDH2	24 (14%)
EZH2	15 (9%)
U2AF1	12 7%)
IDH1	11 (7%)





Comparaison chimio intensive (IC) (n=65,32%) vs DNMTi+VEN (n=27%) vs DNMTi (32%)

+ jeunes 63 ans vs 70)

Moins blastiques

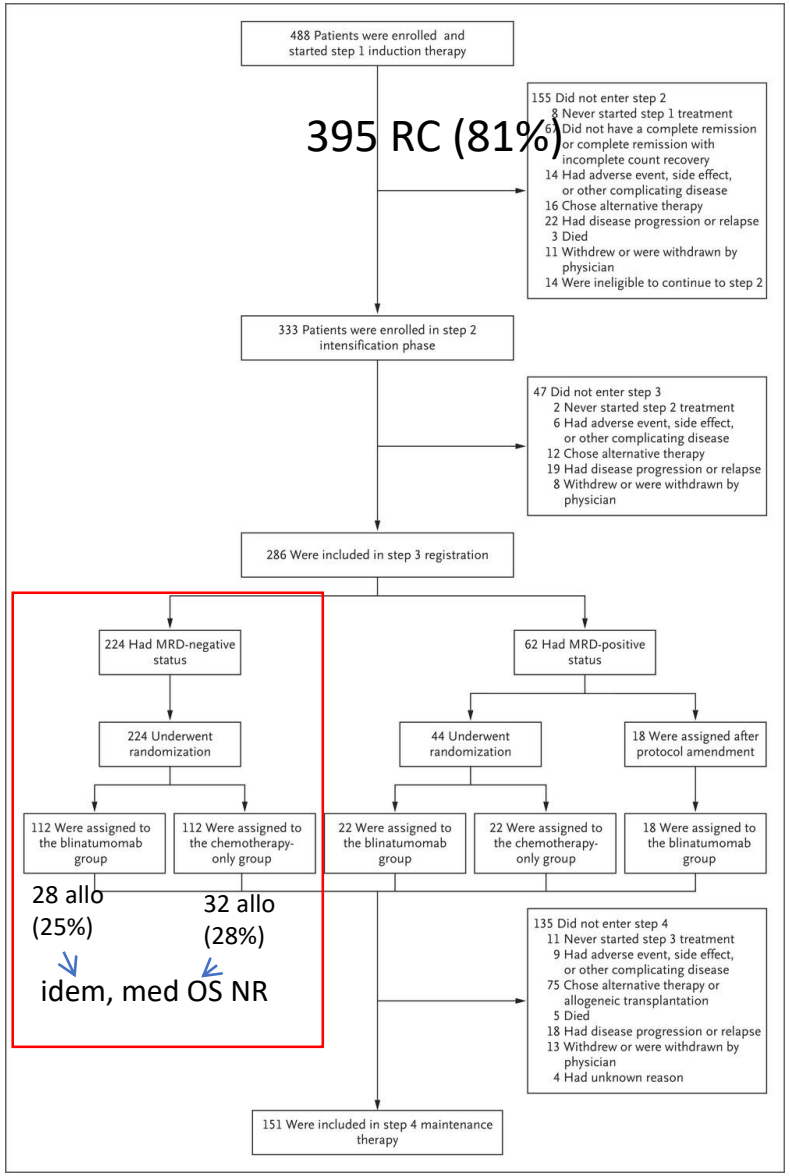
Taux de RC/RCi

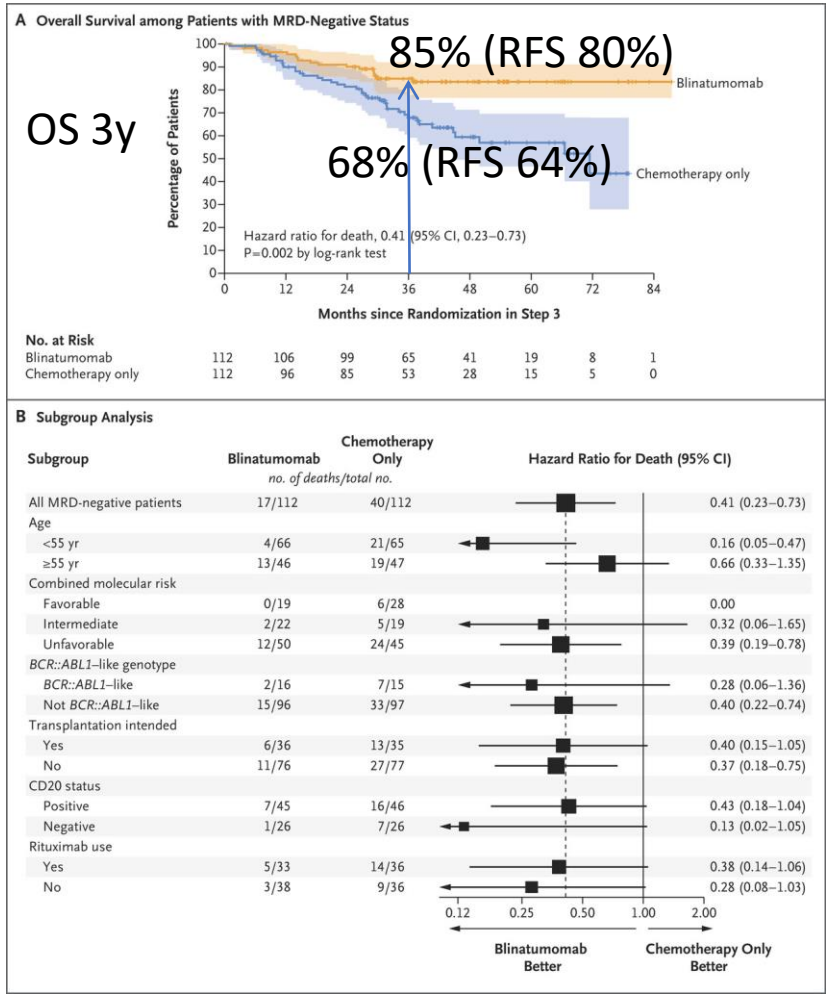
Patel, Blood adv 2024

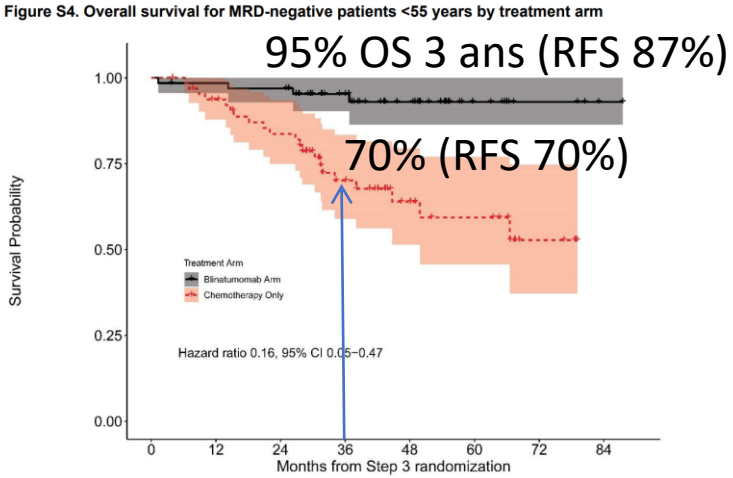
LAL

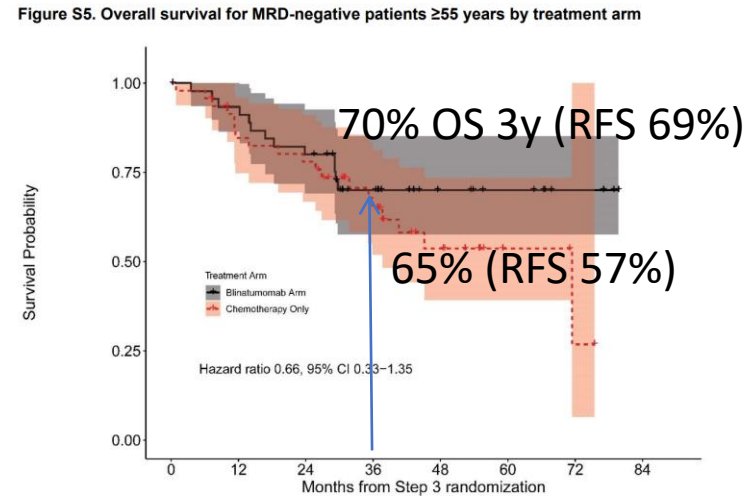
Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

FU med 42 mois









Litzow, NEJM 2024

RESEARCH SUMMARY

Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia

van der Sluis IM et al. DOI: 10.1056/NEJMoa2214171

CLINICAL PROBLEM

Infants with acute lymphoblastic leukemia (ALL) diagnosed in the first year of life have a poor prognosis, and those with rearrangement of the gene *KMT2A* have the worst outcomes, with 6-year event-free survival of 36%. Outcomes in these infants have not improved despite intensification of chemotherapy and the use of allogeneic hematopoietic stem-cell transplantation, which underscores the need for new therapies.

CLINICAL STUDY

Design: A phase 2, multinational, prospective, single-group study evaluated whether adding one course of blinatumomab — a bispecific T-cell engager molecule targeting CD19 — to chemotherapy would be safe and efficacious in infants with newly diagnosed *KMT2A*-rearranged ALL.

Intervention: 30 infants <1 year of age with *KMT2A*-rearranged ALL received 1 month of standard chemotherapy followed by one cycle of blinatumomab (15 μg per square meter of body-surface area per day) given as a 4-week continuous infusion, after which standard treatment was resumed. The primary end point was clinically relevant toxic effects, defined as any toxic effect that was possibly or definitely attributable to blinatumomab and that resulted in permanent discontinuation or death.

RESULTS

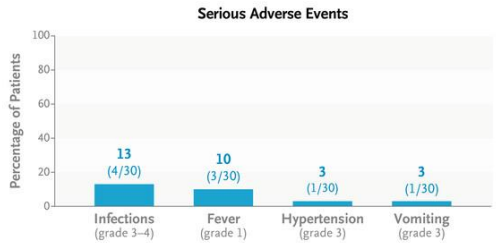
Safety: No clinically relevant toxic effects occurred. Ten serious adverse events were reported in nine patients.

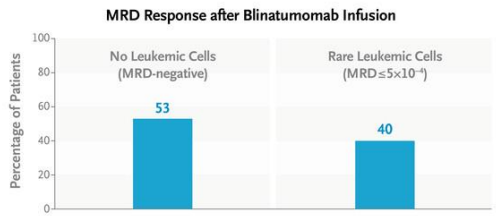
Efficacy: More than 90% of the patients were minimal residual disease (MRD)–negative or had only low levels of leukemic cells after the blinatumomab infusion. After a median follow-up of 26.3 months, 2-year disease-free survival was 81.6% and overall survival was 93.3% — higher than the values seen among historical controls treated with the same chemotherapy regimen.

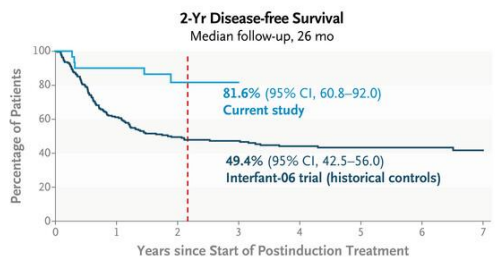
LIMITATIONS

- Follow-up was relatively short.
- Randomization was not allowed, owing to the rarity of the disease and probable poor outcomes without blinatumomab.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

Among infants <1 year of age with *KMT2A*-rearranged ALL, the addition of blinatumomab to standard chemotherapy appeared to be safe and was associated with high efficacy in terms of MRD response and 2-year disease-free and overall survival.

GRAAPH-2014

objectif primaire: RMM BCR-ABL

Evaluable patients

N = 155 /265 prévus

n = 77 n = 78

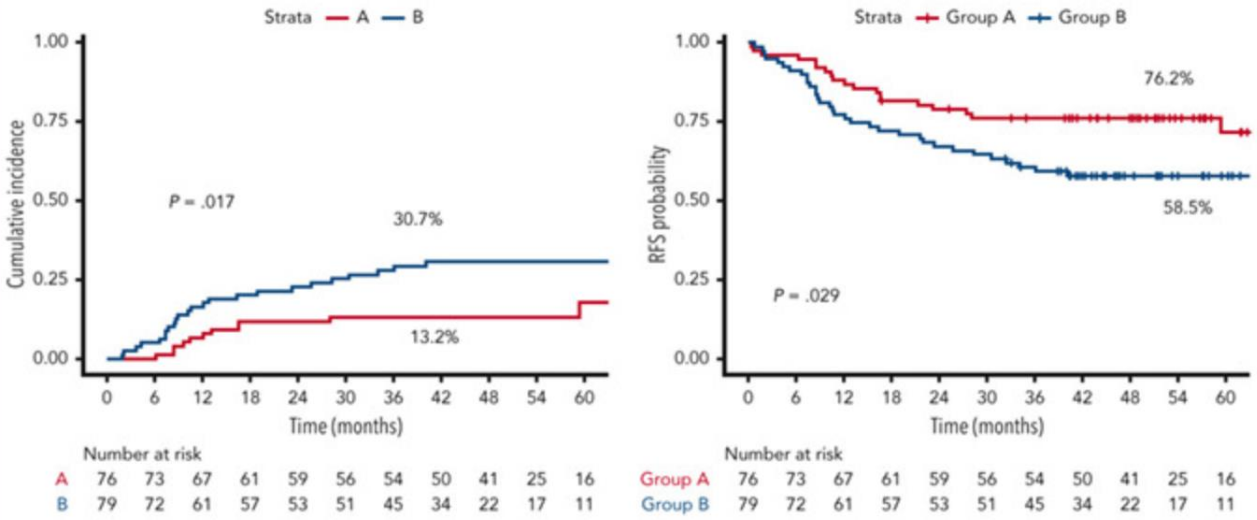
AraC arm — No AraC arm

Cycle 1: induction	NILOTINIB 800, VCR, DEX	MRD1
Cycle 2	NILOTINIB 800 HD-MTX HD AraC / NILOTINIB 800 HD-MTX	MRD2
Cycle 3	NILOTINIB 800, VCR, DEX	MRD3
Cycle 4	NILOTINIB 800 HD-MTX HD AraC / NILOTINIB 800 HD-MTX	MRD4
Interphase (max2)	NILOTINIB 800, 6MP, MTX	
Intensification	HSCT : ALLO/AUTO	
Maintenance	IMATINIB 600	

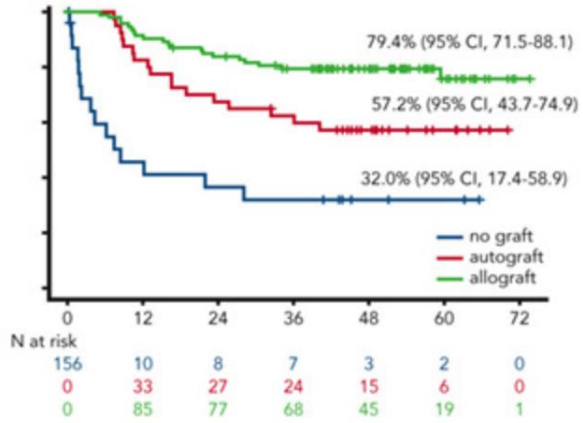
n=133 (85%) SCT, 93 allo (60%)
40 auto (25%)

Primary end point
MRD4 : noninferiority
(MMR: 71.1% in arm A and 77.2% in arm B)

Increased relapse incidence and decreased 4-year RFS in the arm without ARA-C



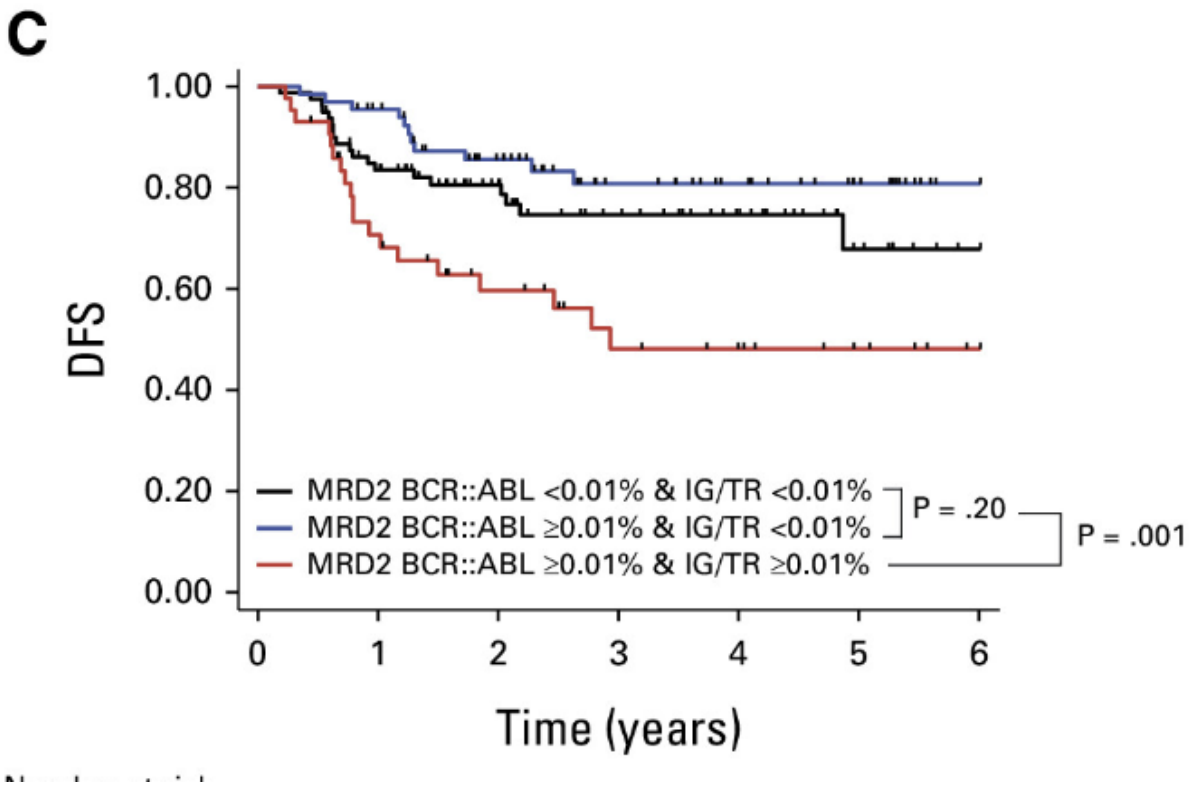
Better RFS in allogeneic stem cell transplantation patients

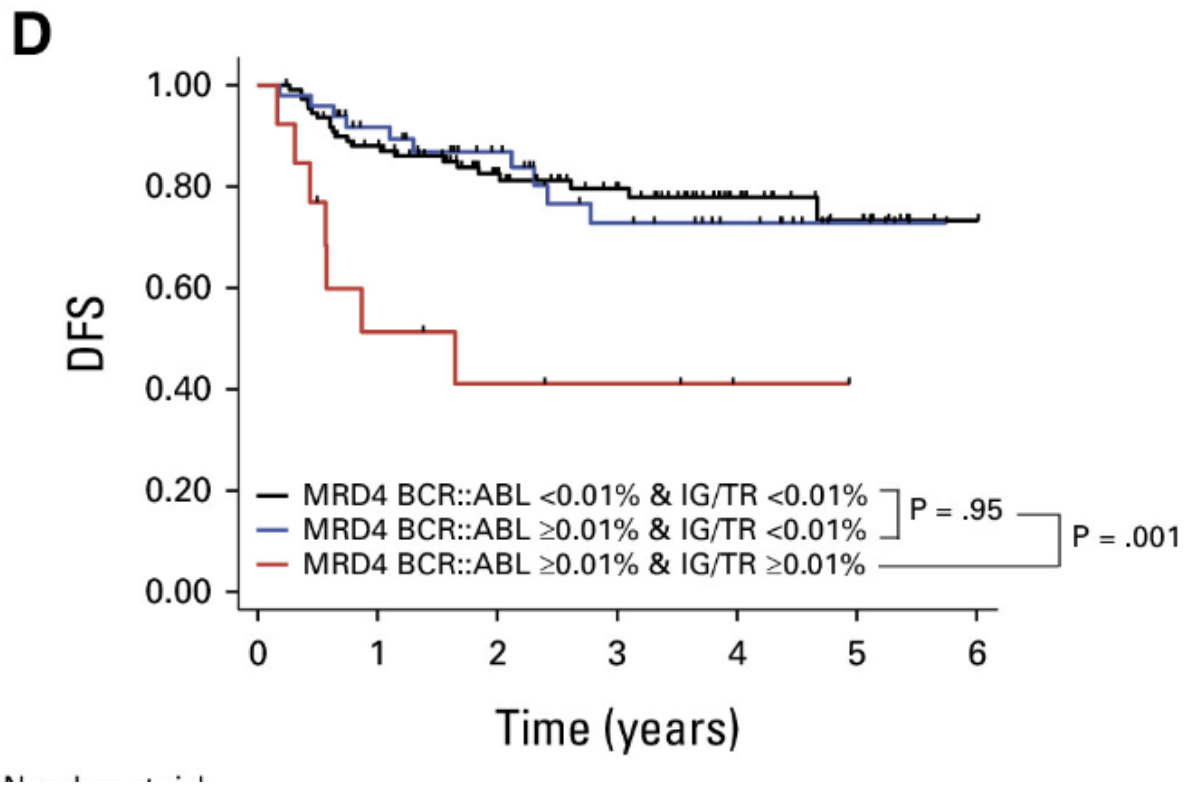


Chalandon, Blood 2024

Significance of Measurable Residual Disease in Adult Philadelphia Chromosome–Positive ALL: A GRAAPH-2014 Study

La MRD IgTCR négative est de bon prc
MRD Bcr Abl + n'impacte pas





Kim, JCO 2024

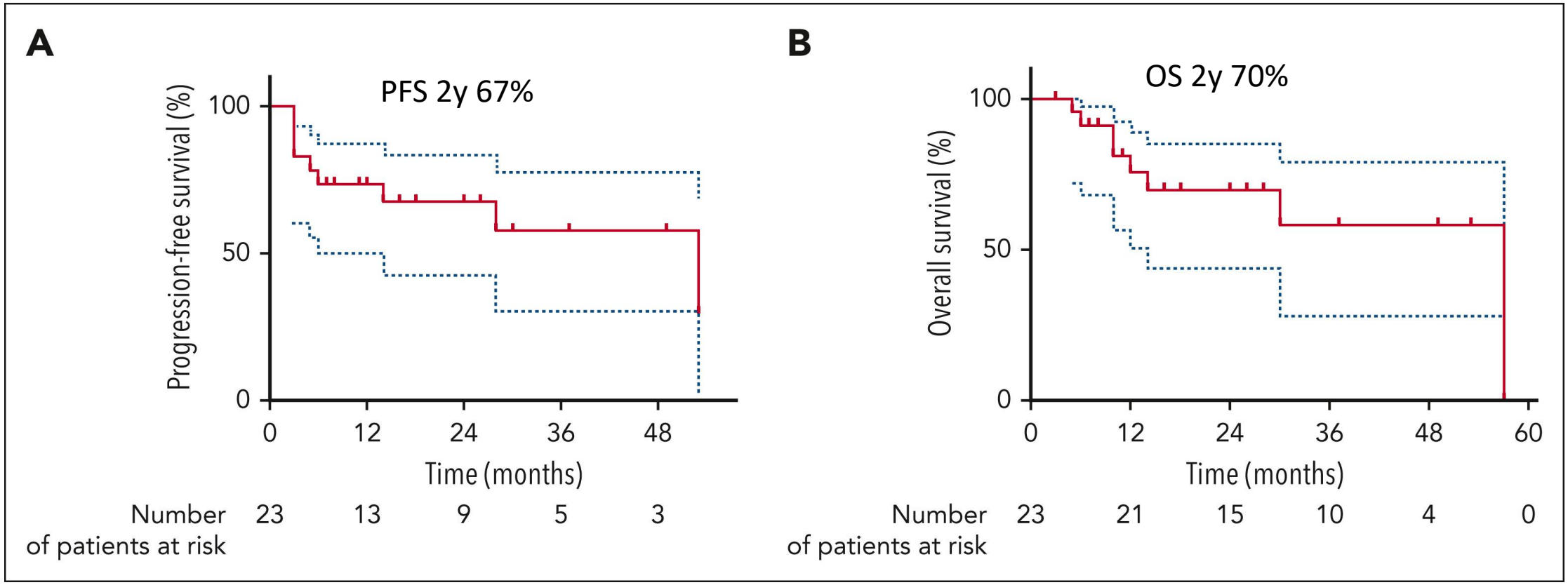
CART

High efficacy of CD19 CAR T cells in patients with transformed Waldenström macroglobulinemia

fu med 28 months 67.5%
âge med 65 ans

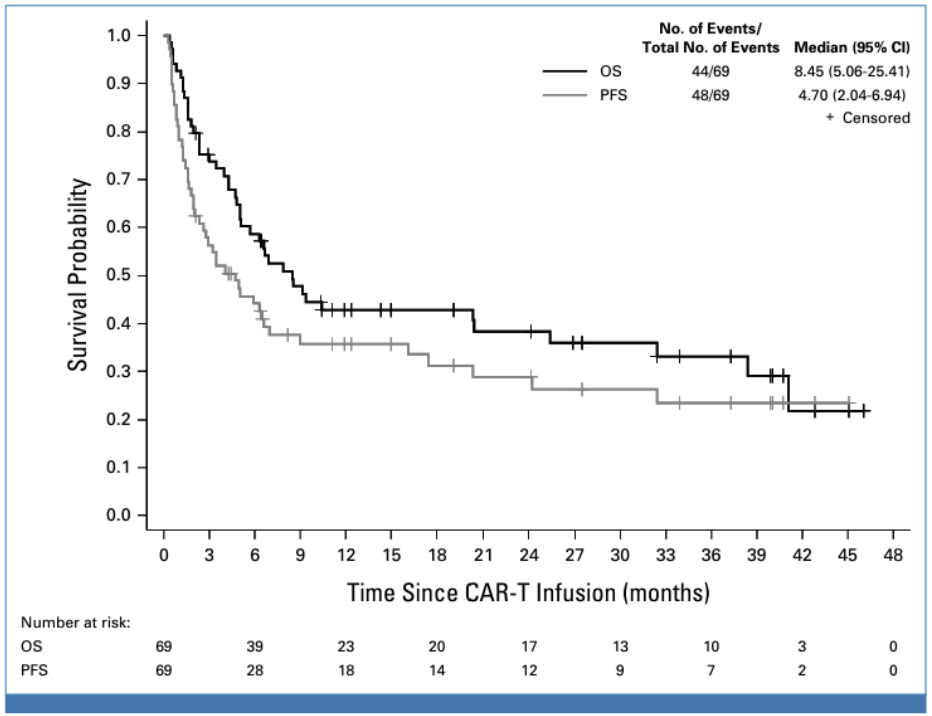
61% axi-cel, 39% Tisa-cel

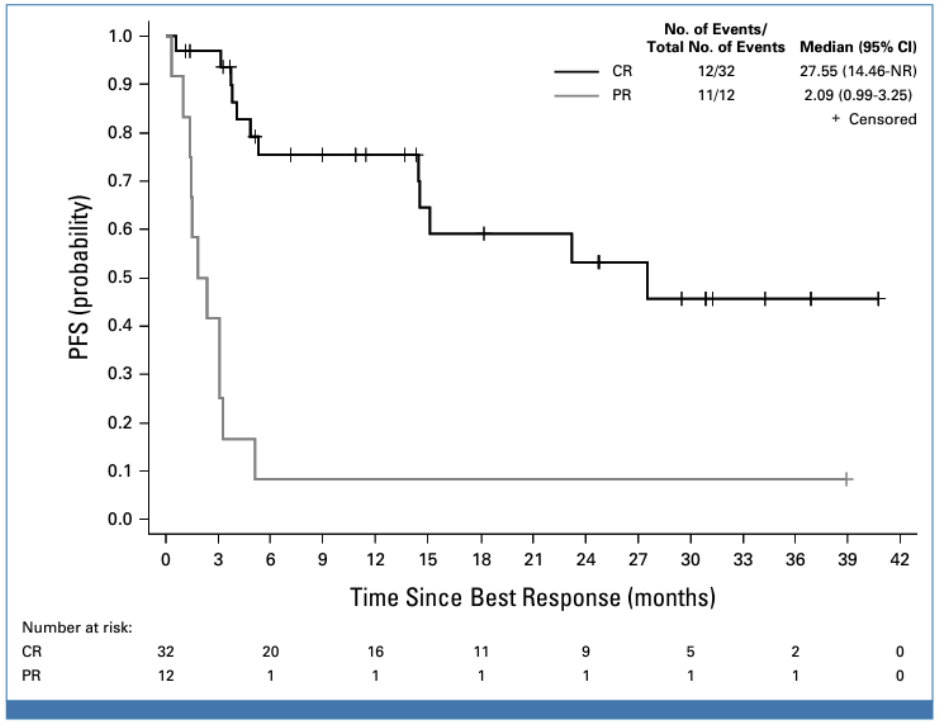
n=23 (19 DESCART , 4 US)



Durot, Blood 2025

Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter Transformation
An International, Multicenter, Retrospective Study





	Taux de RC	PFS 2y	NRM 1y
DLBCL	40-53%	40%	
Richter	46%	29%	13% (infections)
LLC	18%		

Résultats littérature

Kittai, JCO 2024

CAR-T LALB adulte

- Adultes LAL-B R/R ≥18 aux US et ≥26 ans EU **Brexu-cel approuvé depuis 2023**

ZUMA-3 phase 1/2 :n=55, 73% CR/CRi (91% «real world») ; OS 47 mois pour les répondeurs avec FU 3 ans

Hadjivassileva T, et al. EU CAR T 2023. Abstract 34; Roloff G, et al. J Clin Oncol. 2023;41:555-567

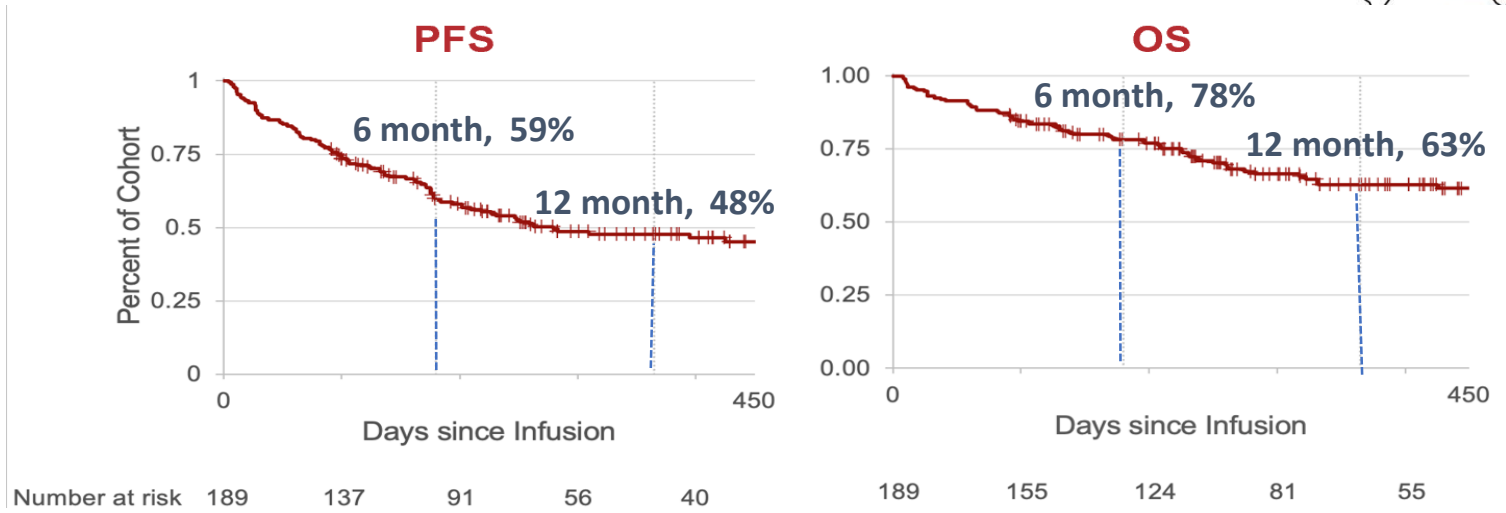
Outcomes After Brexucabtagene Autoleucel Administered as a Standard Therapy for Adults Rel/Ref

Roloff, JCO 2024

Median age, years (range)	46 (18-81)
Female (%)	43
Ph+ / Ph-neg / Ph-like (%)	29 / 53 / 18
Median # lines of therapy (range)	4 (2-12)
Prior Blinatumomab (%)	59
Prior Inotuzumab (%)	48
Prior Allogeneic HCT (%)	41
Disease Burden at Apheresis	
Active disease (%)	50
CR with MRD + / unknown (%)	27
CR with MRD – (%)	15
CNS 2-3 (%)	35 (19)
Extramedullary disease (%)	43 (23)

ROCCA 30 Centres US (N=189pts, F.U 11.4Mo)

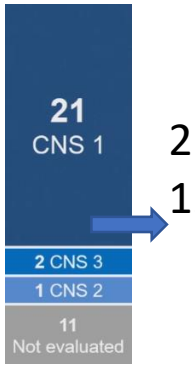
- **CR/CRi 90% dont 79% MRD neg**



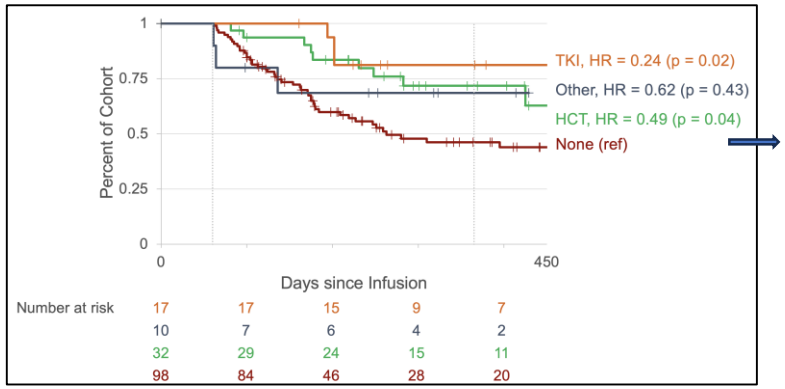
CRS: 84%
Grade 3-4: 11%

ICANS: 56%
Grade 3-4:31%

Réponse SNC (n=35 SNC +)



21 réponses/24 évaluables
12 réponses sans bridge IT



ITK ou Allo Aug OS

	N=64
Age, median (range)	43.5y (22-69)
Baseline, N(%)	
WBC > 50 G/L	9/56 (16)
CNS 2/3	6/62 (10)
Ph-postive ALL	20/64 (31)
Prior lines , N (%)	
1	5/64 (8)
2	27/64 (42)
3+	32/64 (50)
Prior therapy , N(%)	
alloHSCT, N (%)	43/64 (67)
inotuzumab, N(%)	9/64 (14)
blinatumomab, N(%)	42/64 (66)
Before CAR T cell , >N(%)	
CNS 2/3	12/62 (19)
% BM blast >25%	8/36 (22)

Efficacy and tolerance of brexucabtagene autoleucel in adults with R/R B-ALL: a GRAALL study from the DESCAR-T registry

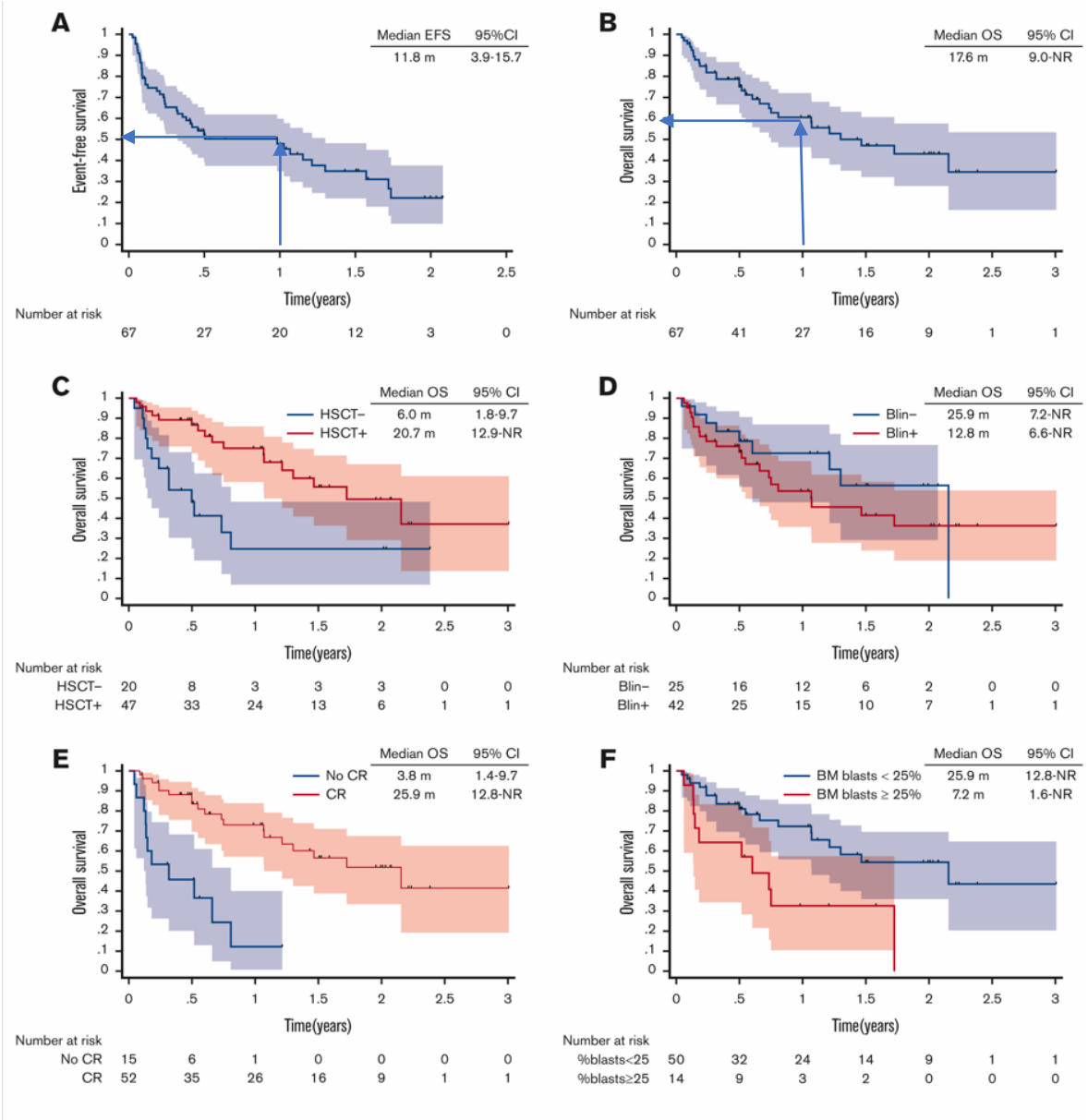
Mai 2019-Fev 2023 80 adultes LAL-B R/R ont eu leucaphérèse pour Brexu-Cel en accès précoce, 64 pts injectés (80%)

Follow up 18 mois

Rabian, Blood Adv 2024

Rabian et al. ASH 2023 Abstract #3498

EFS 1 an 52% et OS 60% idem US mais rechutes ++ (37% des répondeurs)



	N=64
CRS, N(%) / grade 3+	48/62 (77) / 4/62 (6)
ICANS, N (%) / grade 3+	28/62 (45) / 5/62 (8)
CR	49/64 (77)
CR with MRD neg	23/25 (92)

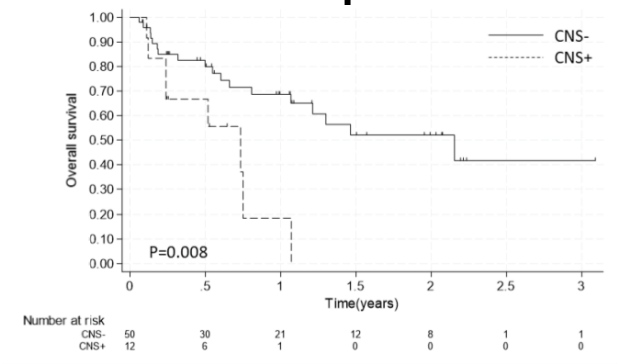
Moins d'ICANS sévère

Bridge vers allo pour n=8 (dont 4 seconde allo) en RC

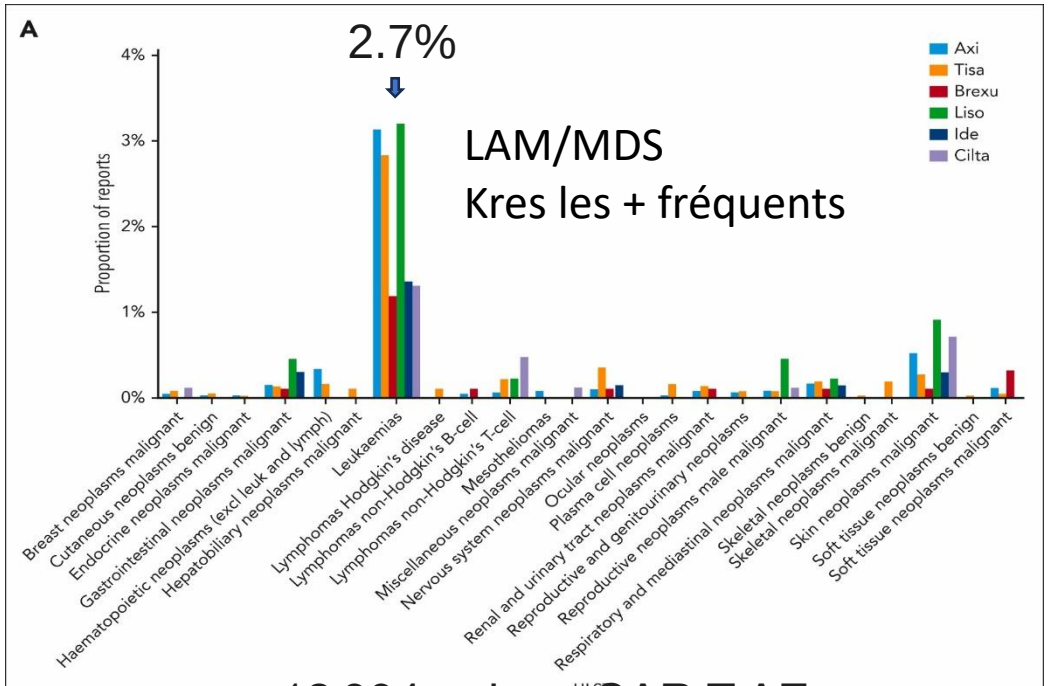
Atcd allo >1 an meilleure OS
Pas de benefice du blina pré CART (perte CD19?)

Blastes <25% pré LD meilleure OS

Mauvais prc des SNC+

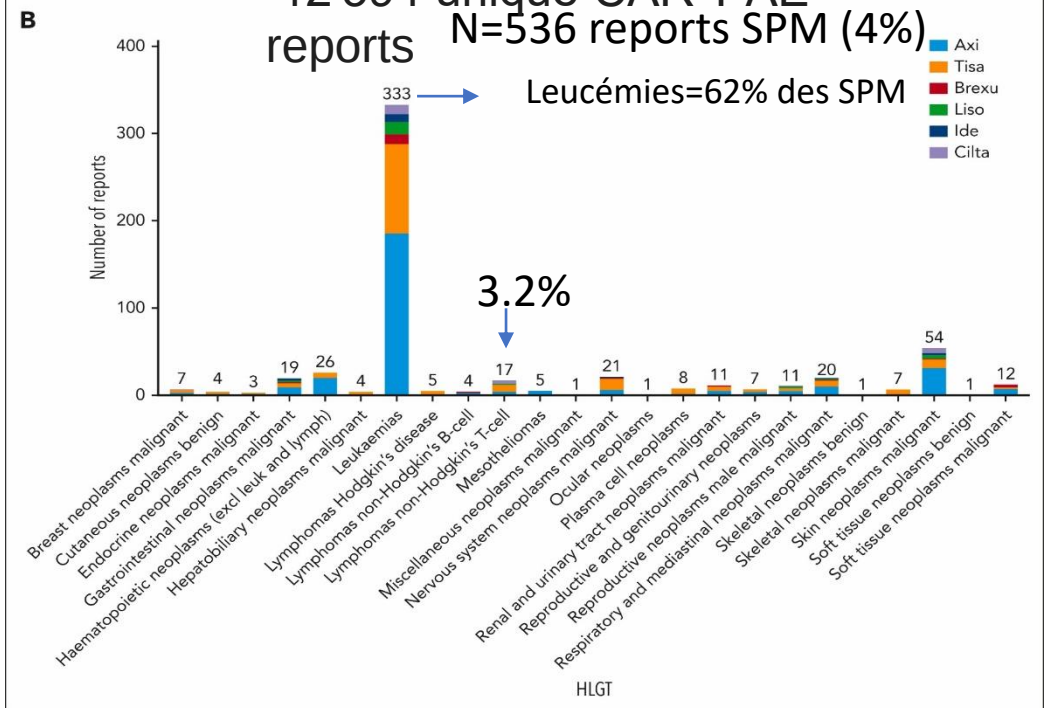


Rabian Blood Adv 2024



12 394 unique CAR T AE reports

N=536 reports SPM (4%)



Second primary malignancies (SPM) after commercial CAR T-cell therapy: analysis of the FDA Adverse Events Reporting System

cancers primitifs 2res (SPMs) rapportés dans la litterature :

Tisa-cel :LAL-B ELIANA and ENSIGN: 2.2% , DLBCL JULIET: 0%

Axi cel: ZUMA-1 and ZUMA-7 : <1% and 4.7%

Brexucabtagene autoleucel :ZUMA-3 trial: 0%

Liso-cel :TRANSCEND NHL 8.1% ; TRANSFORM 3.3%

Cilta-cel :CARTITUDE-1 :25.8% (n=16* puis 6** de + /97pts)
Sidana, Blood 2025: real life n= 20/236 SPM (8.5%)

Ide-cel: KarMMa-1 :0%

**Martin et al, JCO 2023*
***Munshi N, et al. S202: Cartitude-1 final results: phase 1B/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma.HemaSphere 2023;7(S3):e6102468*

Autres reports CD19 et BCMA CART 3,5 a 4,5%

Elsallab Blood, 2024.

Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy

Dec 2023 FDA: 22 cas d'hémopathies malignes T: Lymphomes T, LGL, PTCL, T cut

Apparition dans les 2 ans post CART (1-19 mois) , 50% la 1ere année

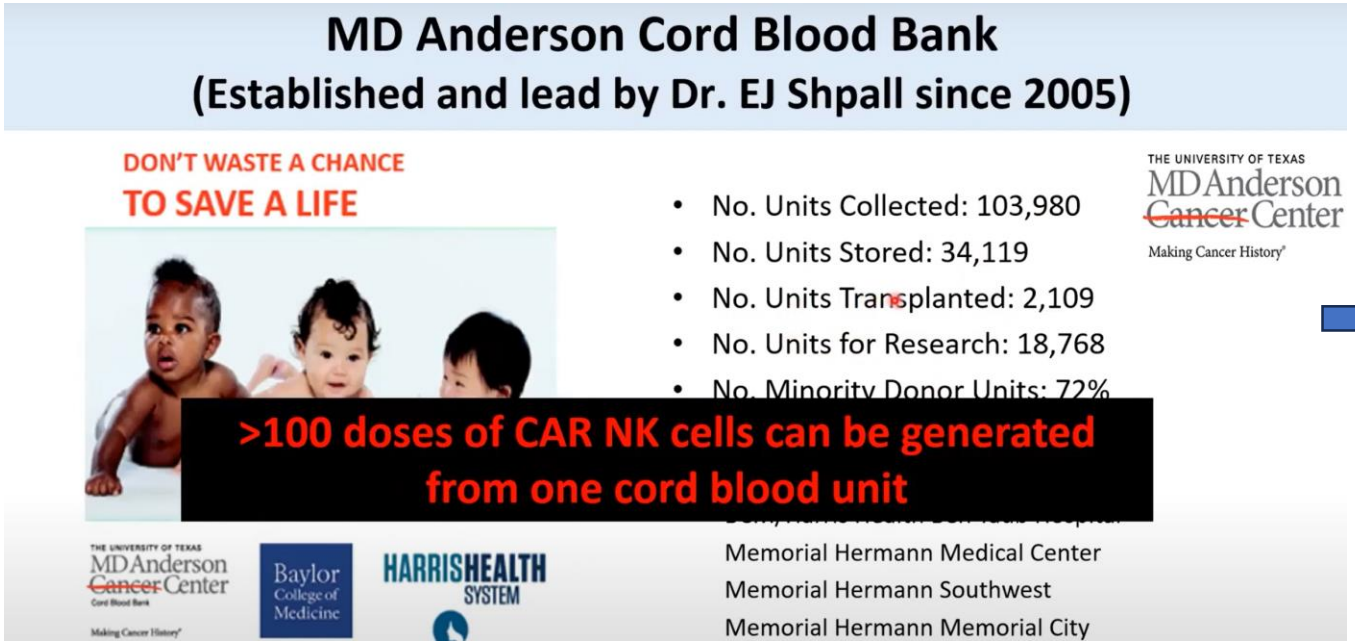
n=3 séquençage génétiques: détection du transgene CAR

Complication rare : 22 sur 27 000 doses sur les 6 CAR-T approuvés: 0.08%

Verdun, NEJM 2024

Safety, efficacy and determinants of response of allogeneic CD19-specific CAR-NK cells in CD19⁺ B cell tumors: a phase 1/2 trial

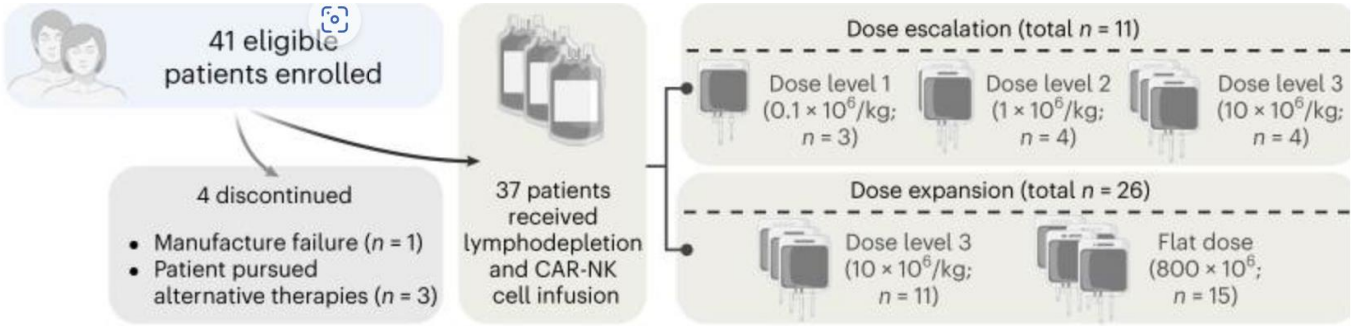
MD Anderson, CAR allogénique NK issu de sang de cordon, CD28-iCasp9-IL15



Optimal cords: Time to freezing =<24hr; NRBC=<8E7
Suboptimal cords: Time to freezing >24hr; NRBC>8E7

Marin, Nat Med 2024

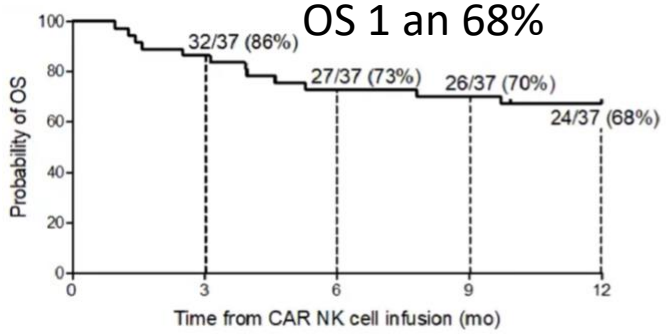
Safety, efficacy and determinants of response of allogeneic CD19-specific CAR-NK cells in CD19⁺ B cell tumors: a phase 1/2 trial



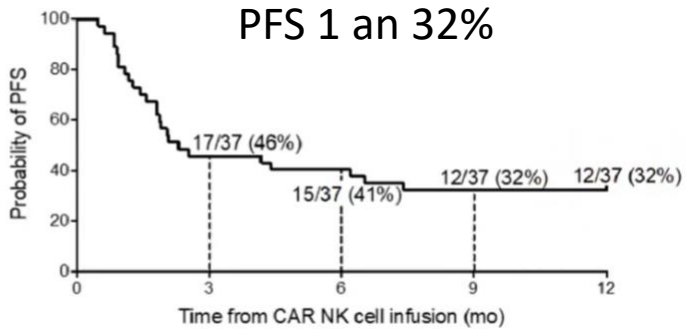
Pas de DLT
1x107/Kg
N=11 , NEJM, Liu 2020

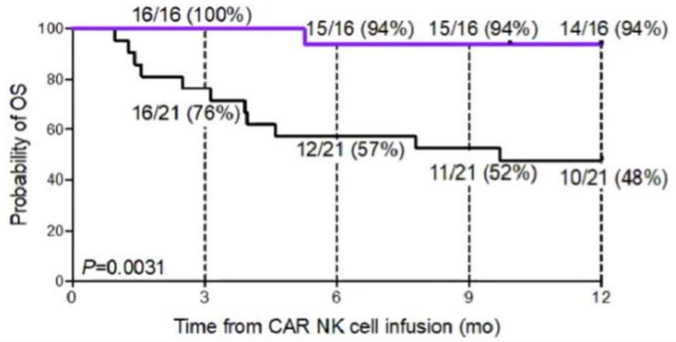
Dose unique 8x108
(=1x107 pour 80kg)
Pas de thérapie post CAR

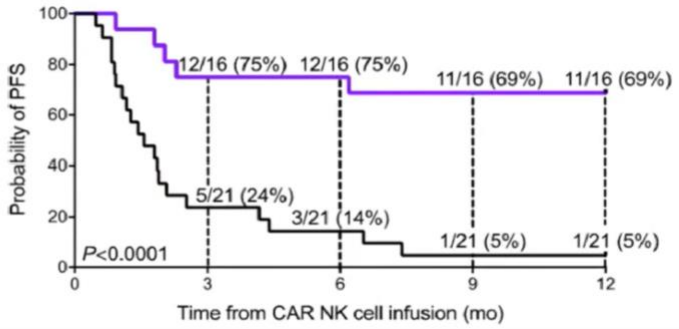
OS 1 an 68%



PFS 1 an 32%







Sub-Cs Opt-Cs

Optimal cords: Time to freezing =<24hr; NRBC=<8E7
Suboptimal cords: Time to freezing >24hr; NRBC>8E7

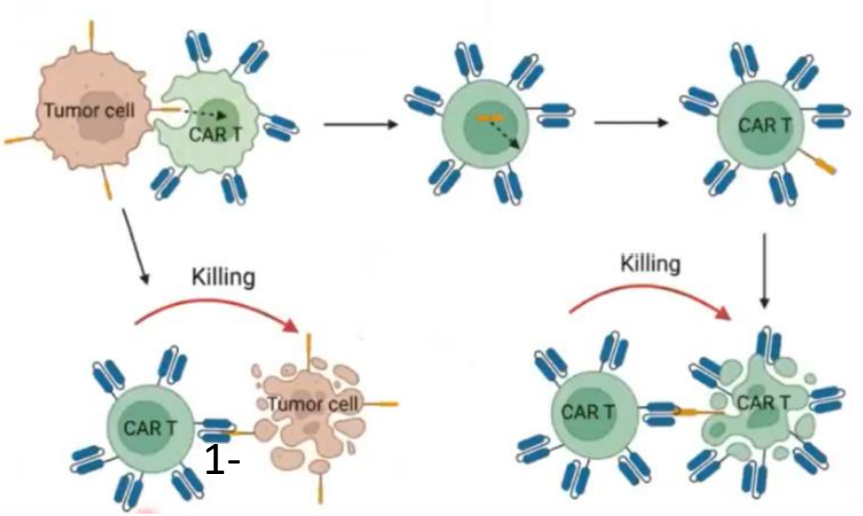
➡ Résultats encourageants
Très peu de toxicité
0 GVHD, 0 ICANS, 1 CRS grade 1

➡ Excellents résultats si NK provenant d'un cordon optimal

Marin, Nat Med 2024

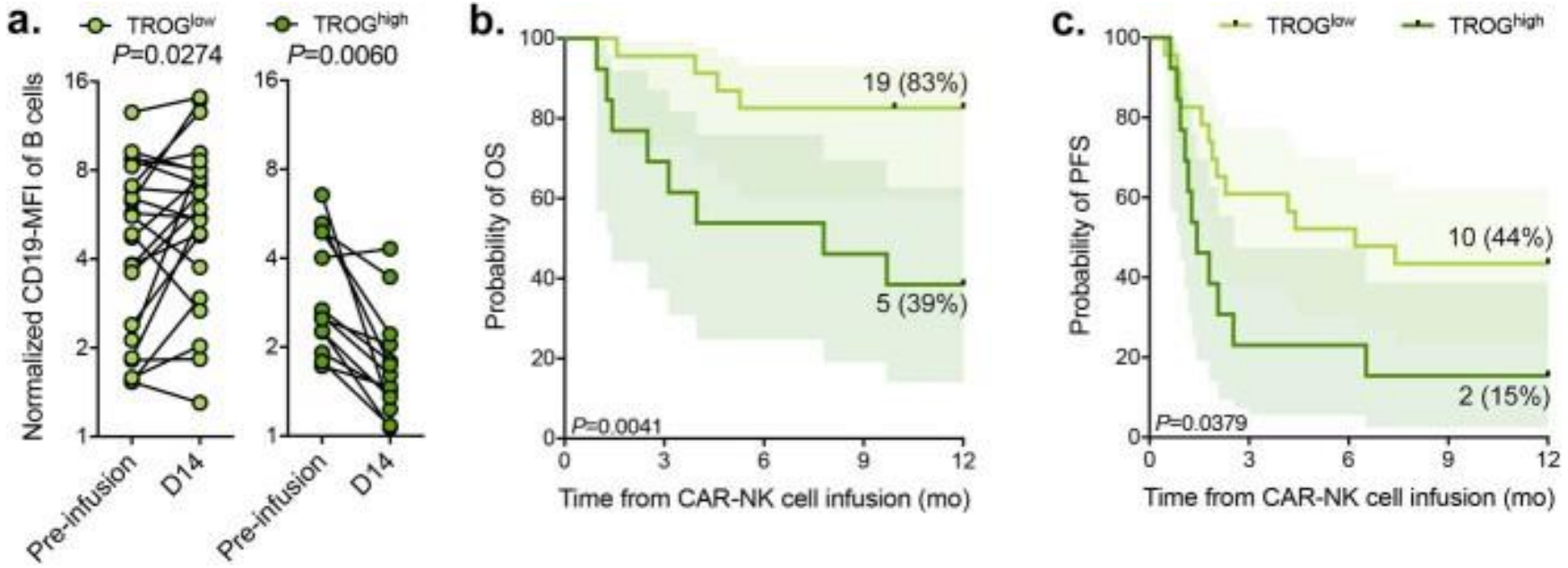
CAR T cell trogocytosis and cooperative killing regulate tumour antigen escape

Hamieh Nature 2019



1-L'antigène tumoral (ex CD19) est capté par le CAR et exprimé à sa surface
2-Fratricidie CAR/CAR trogocyté CD19+
3-la cible exprime moins l'Ag

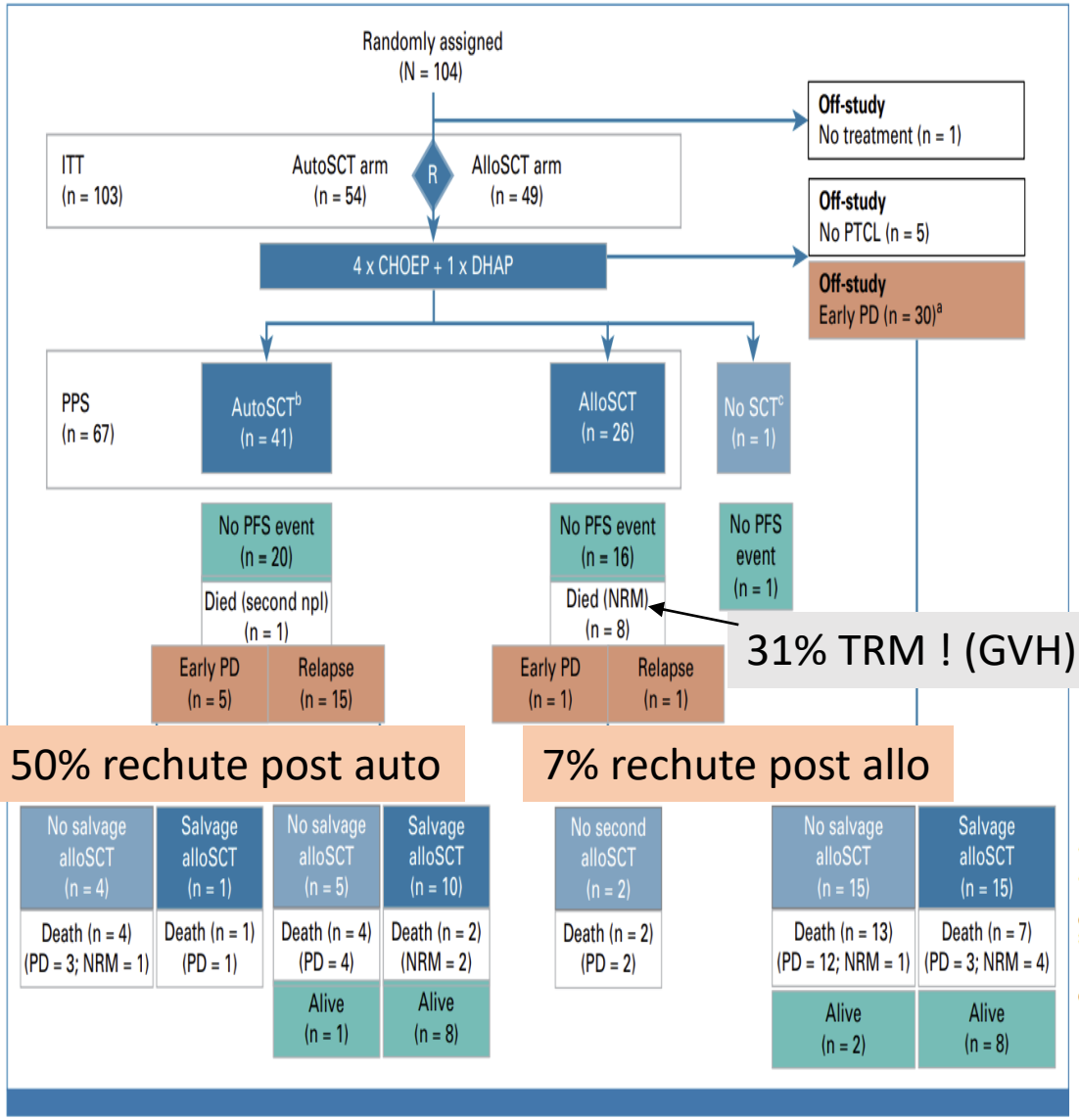
L'expression de l'antigène trogocyté (TROG) sur les CAR19 + NK est associéé à une réduction de l'expression du CD19 sur les B cells et est associée à un mauvais prc post CAR19/IL-15 NK-cell



Marin, Nat Med 2024

LYMPHOMES T

Long-Term Follow-Up of the Prospective Randomized AATT Study (Auto or Allo Transplantation in Peripheral T-Cell Lymphoma)

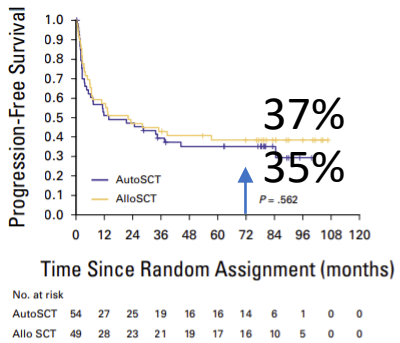


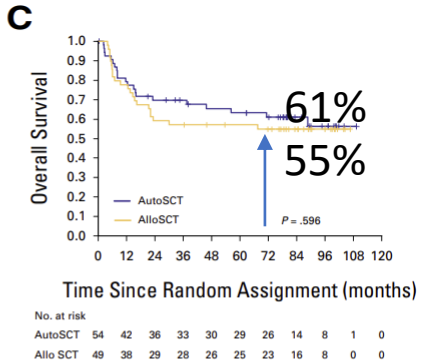
31% TRM ! (GVH)

50% rechute post auto

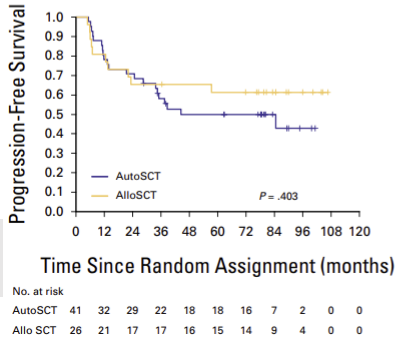
7% rechute post allo

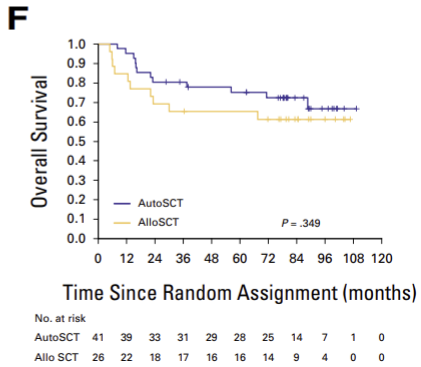
Tournilhac, JCO 2024





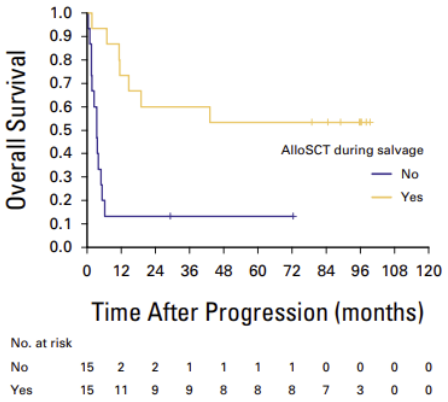
Survie identique
Allo=auto 1ere ligne

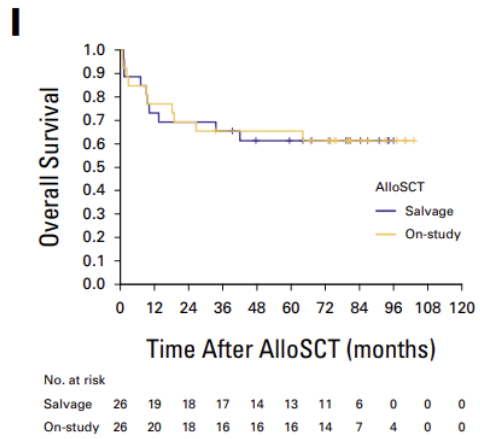




PFS post auto à 37% à 7ans
OS post auto 61% 7y

50% des rechutes post auto ont été allogreffés





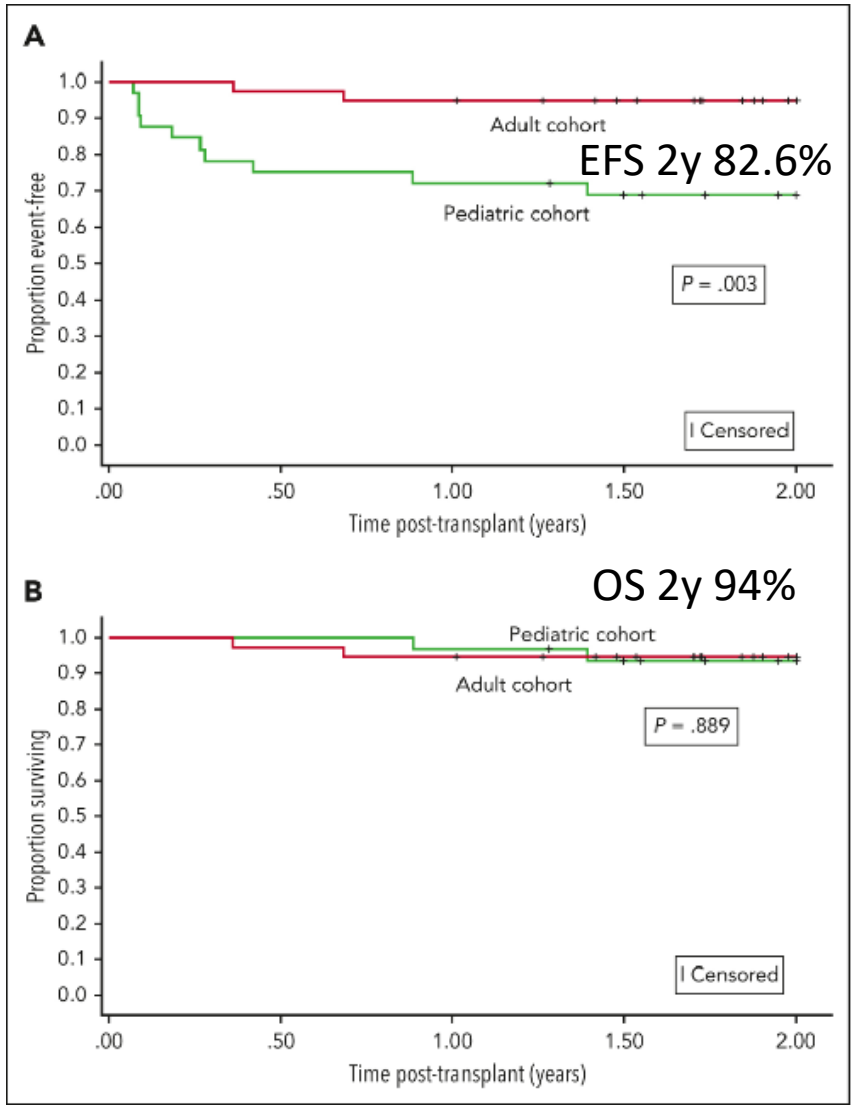
OS allo en RC1=allo en RC2

Allo:pas en 1ere ligne mais +++ en cas de rec/ref

Pathologies non malignes

Vanderbilt Global Haploidentical BMT Learning Collaborative

An international learning collaborative phase 2 trial for haploidentical bone marrow transplant in sickle cell disease

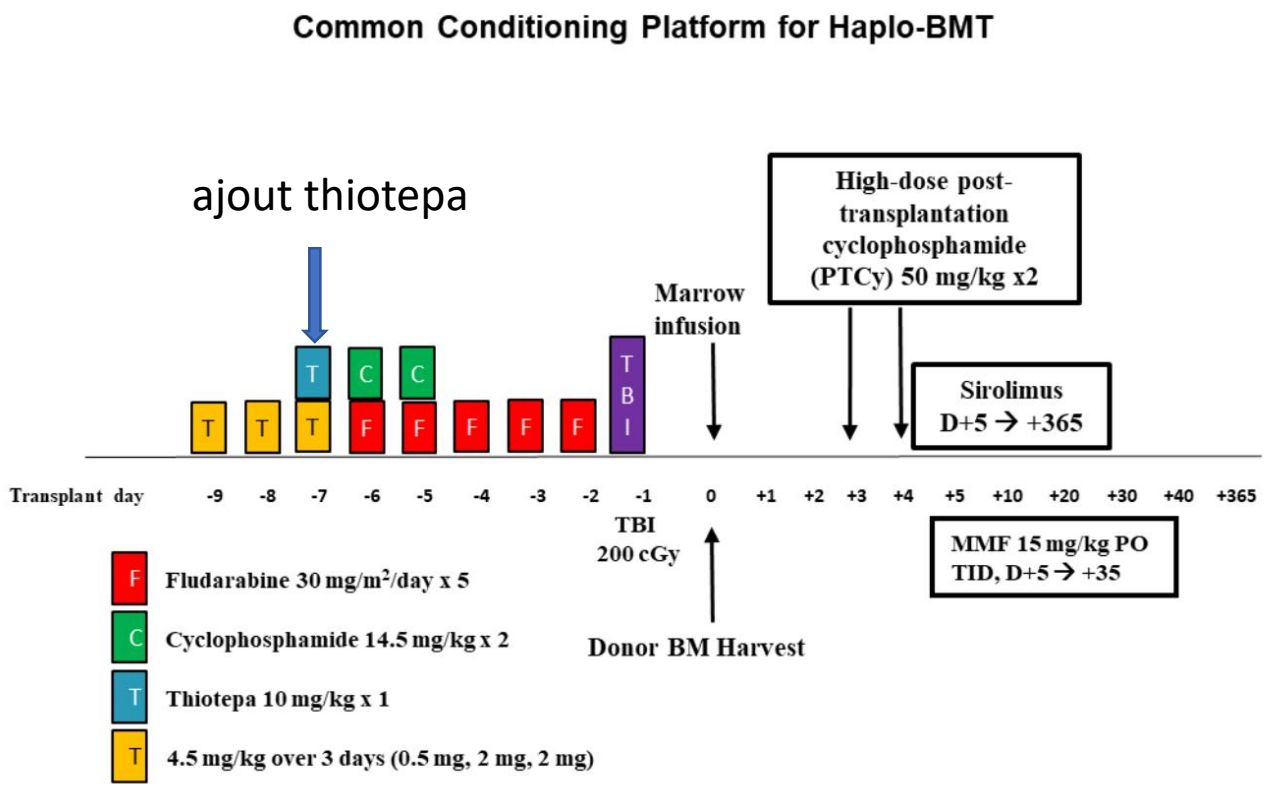


EFS 2y 82.6%

OS 2y 94%

n=38 adultes

n=32 enfants



Kassim, Blood 2024

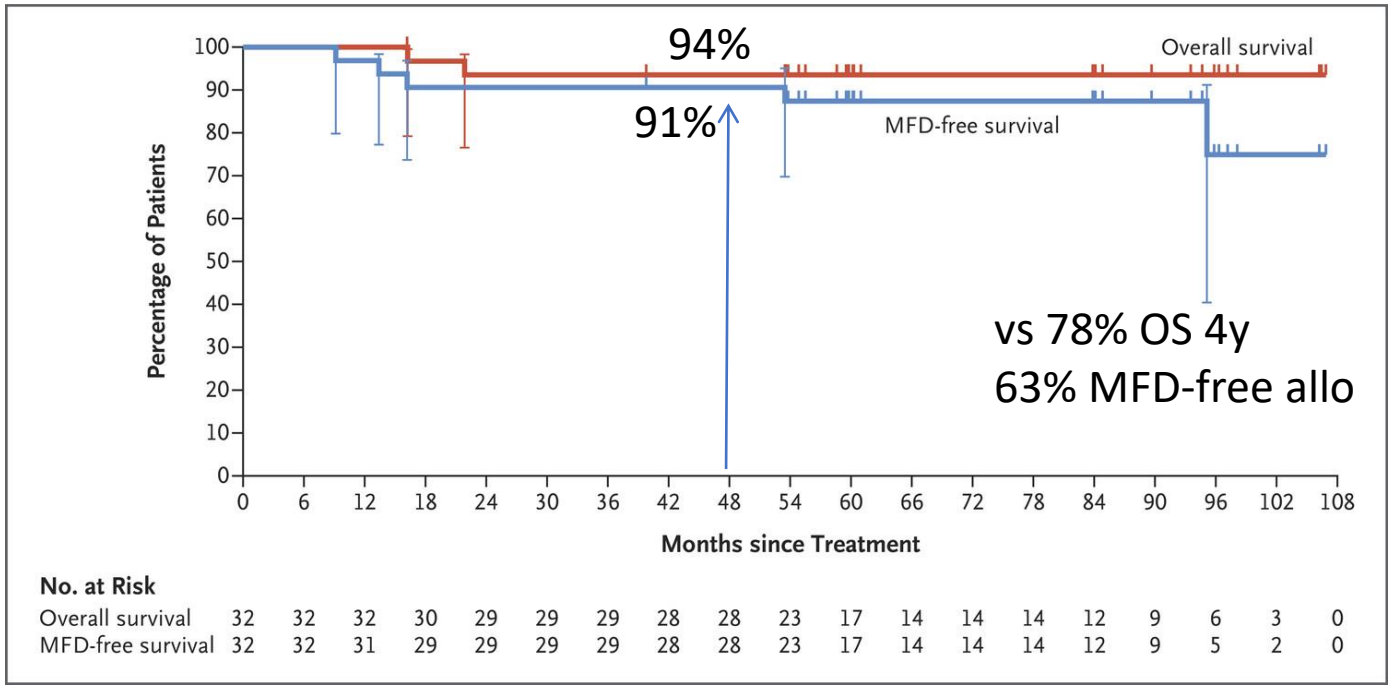
Lentiviral Gene Therapy for Cerebral Adrenoleukodystrophy

Adrenoleukodystrophy is an X-linked metabolic disease caused by pathogenic variants in ABCD1 that lead to a deficiency in peroxisomal transporter ATP-binding cassette domain 1 (ABCD1 or adrenoleukodystrophy protein)1,2 and the accumulation of saturated very-long-chain fatty acids. Cerebral adrenoleukodystrophy develops in approximately 35% of affected boys before adulthood.1,3 Progressive white-matter inflammation and demyelination lead to the loss of cognitive and neurologic function, and early death ensues

ALD102
n=32, 6 ans med
FU 60 mois
eli-cel: CSP autologues (GCSF ou plerixafor) transduites vecteur lentiviral Lenti-D ABCDE, CDT MAC Bu Cy

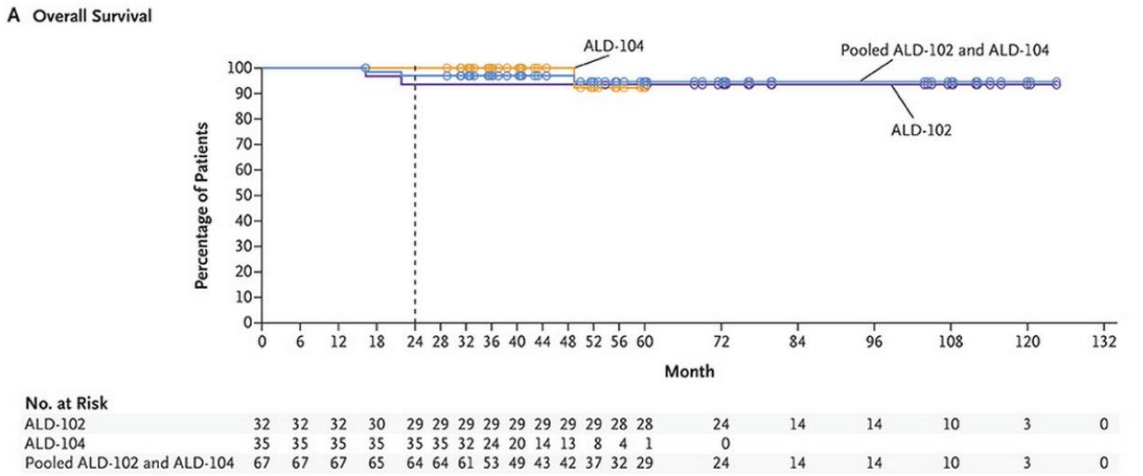
Patients were eligible for the study if they had cerebral adrenoleukodystrophy confirmed by biochemical and genetic testing and if they had signs of early-stage cerebral disease with gadolinium enhancement on MRI of the brain that were characteristic of adrenoleukodystrophy,17 a neurologic function score of 0 or 1 (range, 0 to 25, with higher scores indicating more severe deficits), and a Loes score of 0.5 to 9. The Loes score is a nonlinear, semiquantitative scale for the assessment of adrenoleukodystrophy white-matter lesions and atrophy on MRI; scores range from 0 to 34, with higher scores indicating more extensive disease, and a score of less than 0.5 considered to be normal. Both the Loes score and the neurologic function score have been validated for patients with adrenoleukodystrophy.18,19 Patients were excluded from the study if they had a sibling who was HLA-matched and was willing and able to donate cells for HSCT.

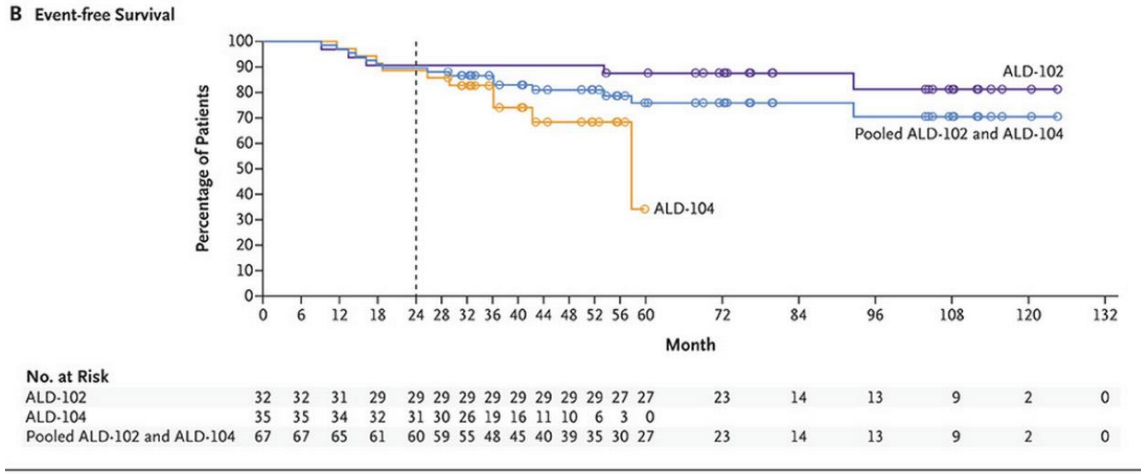
OSand Survival Free of Major Functional Disabilities

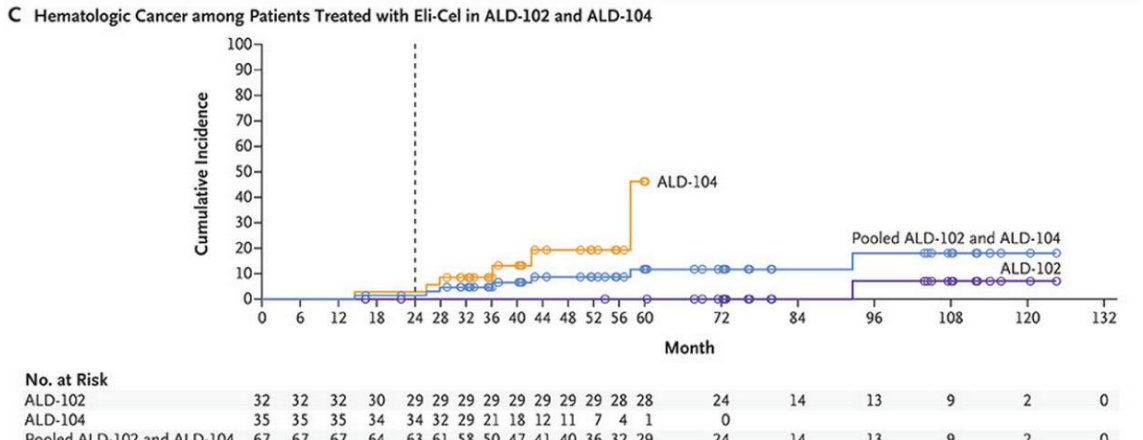


vs 78% OS 4y
63% MFD-free allo

Eichler, NEJM 2024







Hematologic Cancer after Gene Therapy for Cerebral Adrenoleukodystrophy

ALD-102 n=32

GCSF ou Plerixafor

Bu-Cy

n=1 (GCSF)

ALD-104 n=35

Plerixafor

Bu-Flu

n=6

eli-cel (ABCD1)

Lenti D lentivirus, contient promoter enhancer pour faire exprimer gène ABCD1 microglie, macrophages cerebraux, HSC

7 hémopathies myéloides (10%)
(âge 5-13 ans):
MDS (n=2), MDS-EB (n=3), LAM (n=1) , -7 n=1, n=6
somatic mutations (KRAS , NRAS , WT1 , CDKN2A or CDKN2B , or RUNX1)
14-92 mois post injection
insertion du vecteur Lenti-D lentiviral dans des proto oncogenes MECOM-EVI1 or PRDM166
5 allo, 1 DC GVHD

FU med 60.2 mo, 26 of 32 patients (81%) were alive without major functional disabilities

Duncan, NEJM 2024