



Allogreffe de CSH: une plateforme d'immunothérapie

Marie Thérèse Rubio, MD, PhD

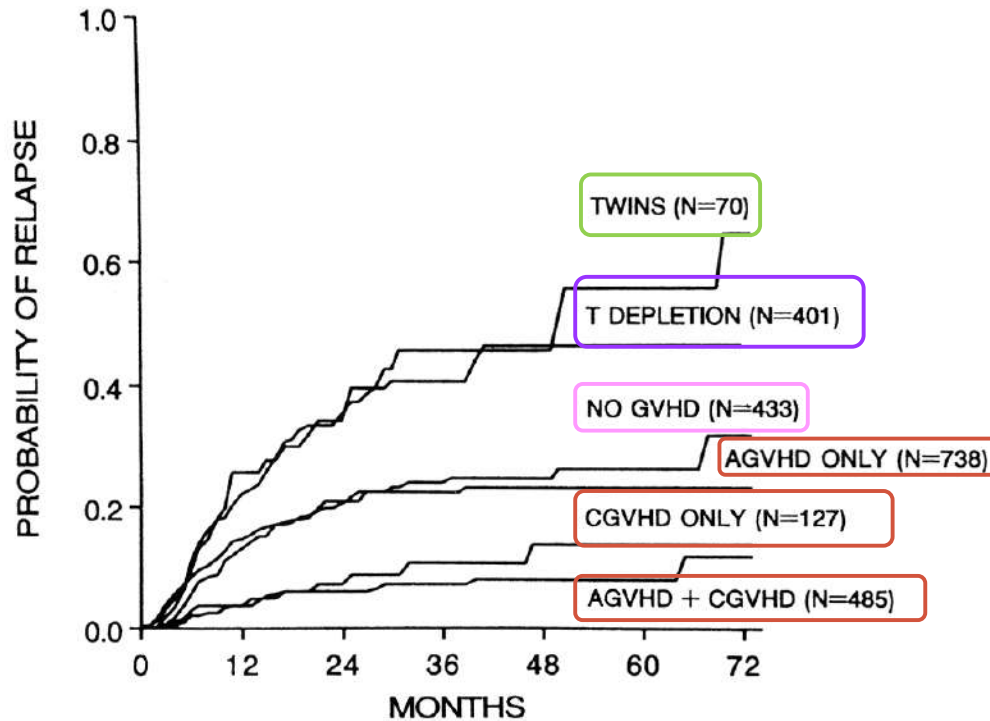
Service d'Hématologie clinique

Hôpital Brabois, CHRU Nancy

m.rubio@chru-nancy.fr

Allogreffe = immunothérapie anti-tumorale via les lymphocytes T du donneur (Effet GVL)

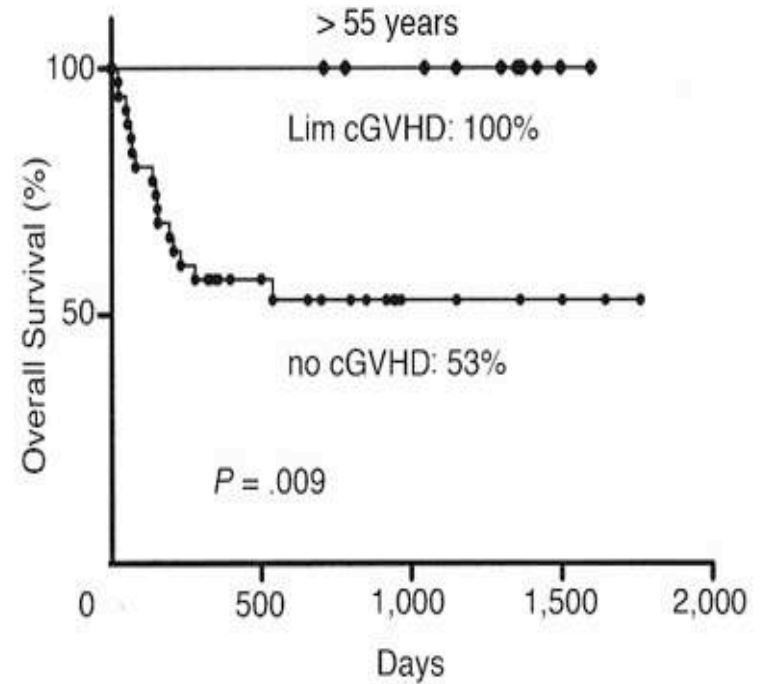
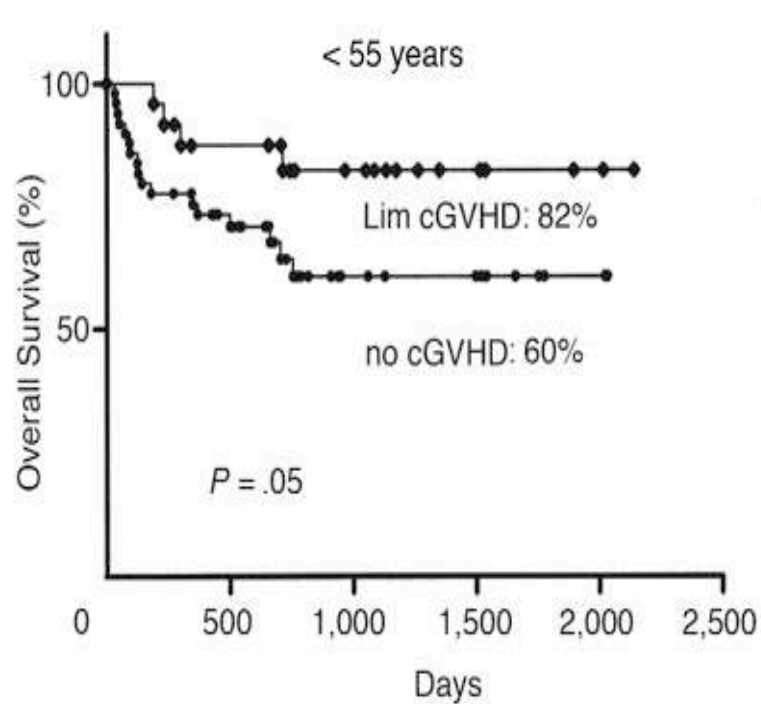
- Risque de rechute réduit chez les patients ayant reçu des CSH allogéniques par rapport aux greffes des CSH syngéniques et autologues
- Risque de rechute diminué chez les patients développant une GVH, notamment chronique



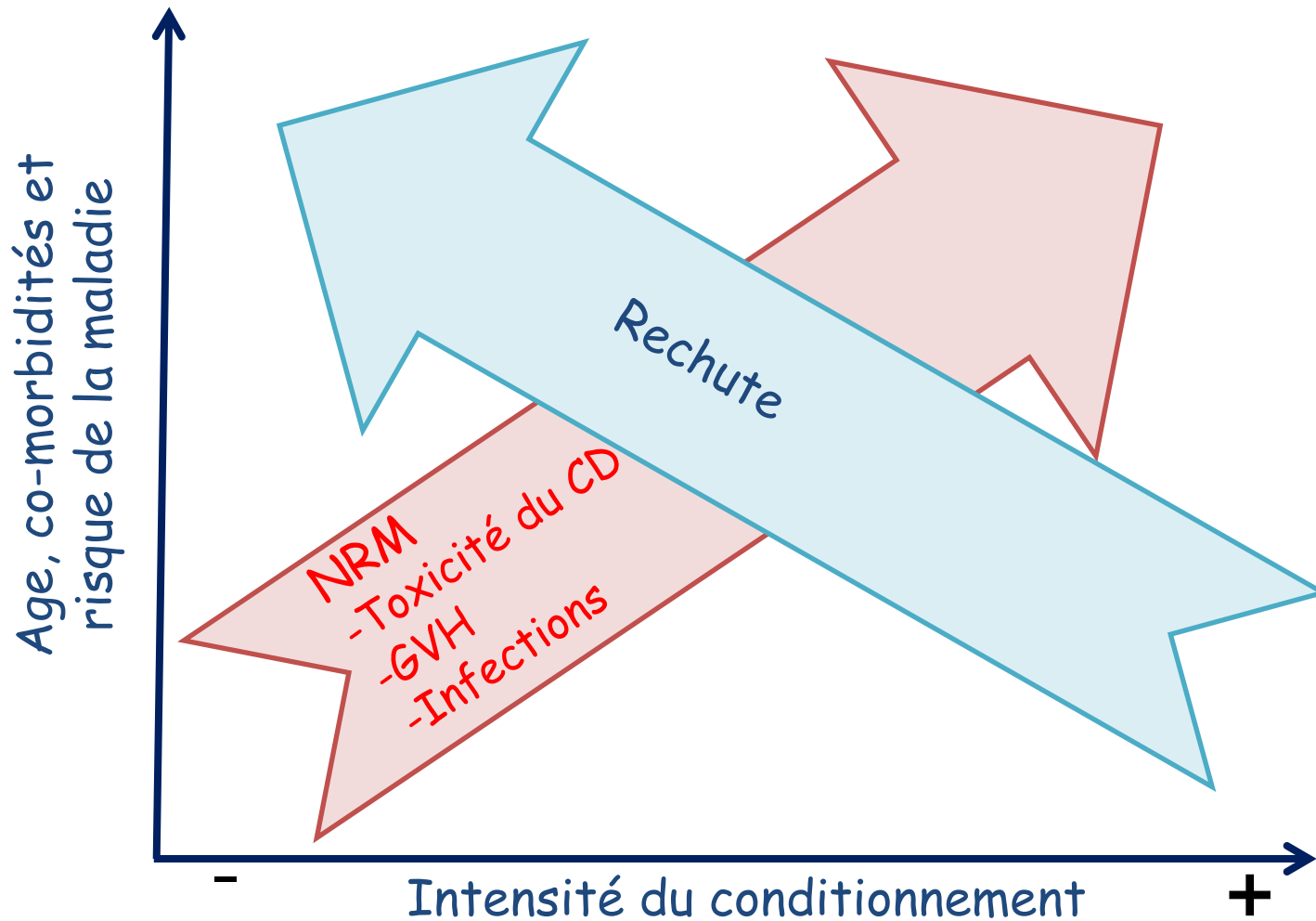
Horowitz, Blood 1990

- Effets bénéfiques des injections de lymphocytes du donneur (DLI) en cas de rechute (20 à 80% de réponse)

GVH chronique: impact sur la survie



Le problème non résolu de la greffe de CSH: balance entre NRM et risque de rechute

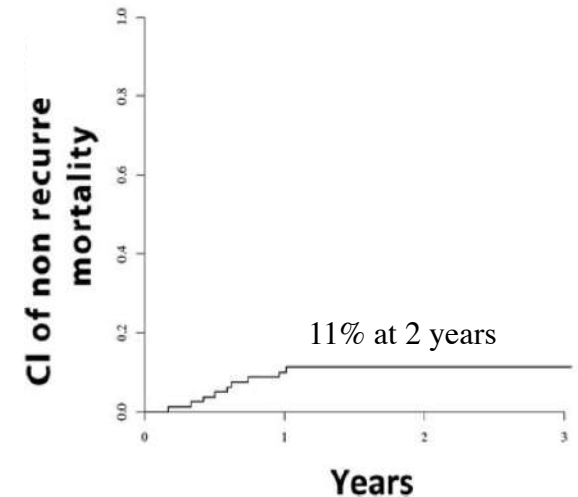
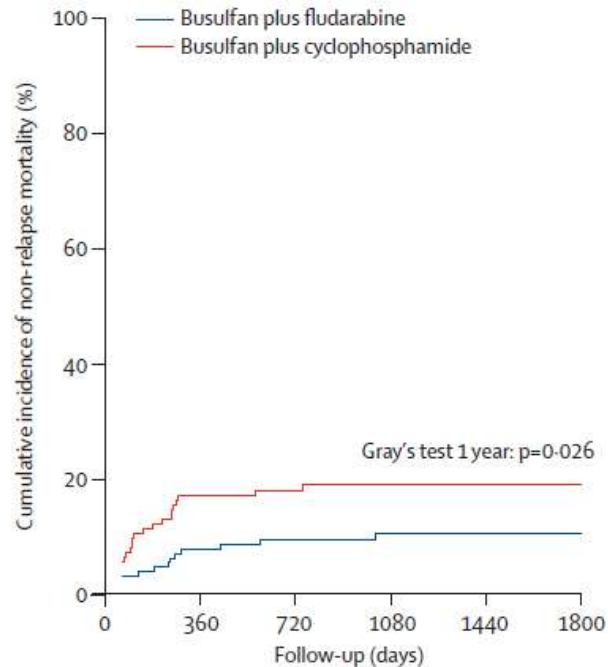
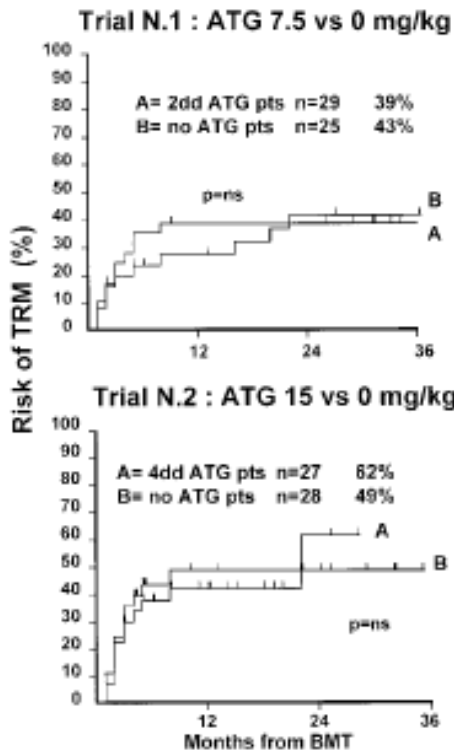


Diminution de la NRM grâce aux CDT réduits et l'amélioration du typage HLA

CDT: TBI-Cy MAC ,
BM grafts, HLA 8/8
Greffes entre 1995 and 2000

CDT MAC: Bu-Cy2 vs FB4
CSP HLA 10/10
Greffes entre 2008 et 2012

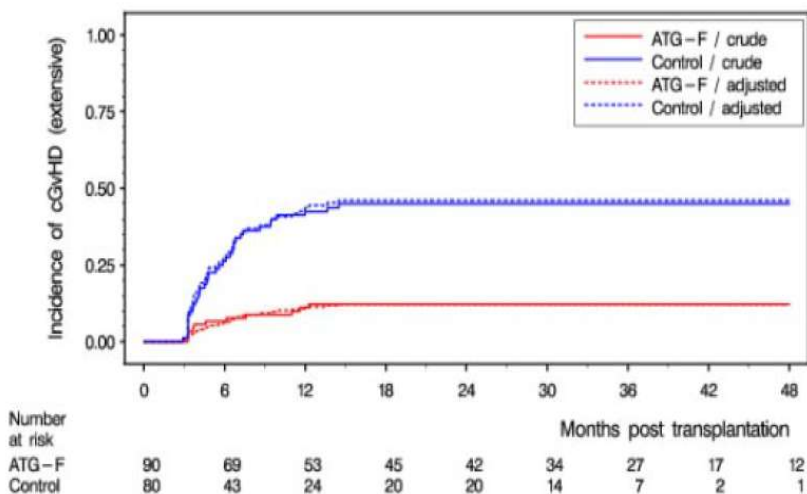
CDT RTC: FB3-SAL
CSP HLA 10/10
Greffes entre 2009 et 2011



Apport du SAL: prévention de la GVHc extensive : meilleure qualité de vie

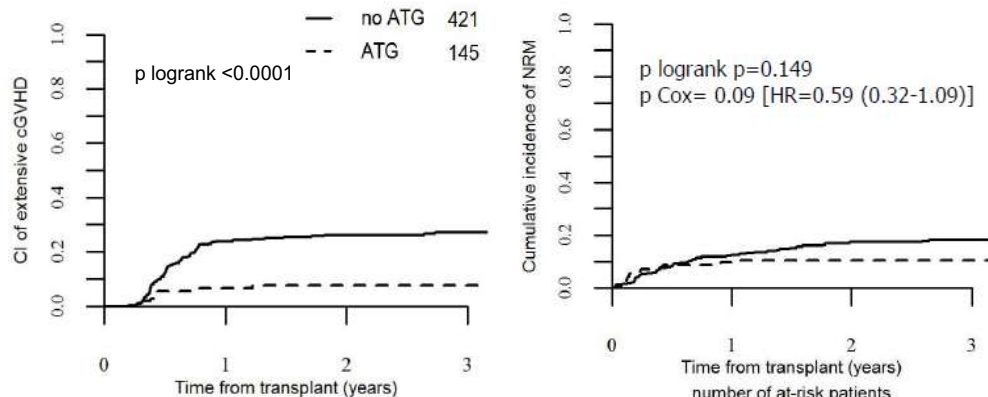
Phase III randomisée, MAC +/- ATG-F;
LAM en RC1, donneur phéno 10/10

Etude rétrospective, FB4 +/- ATG;
LAM en RC1, donneur géno-identique

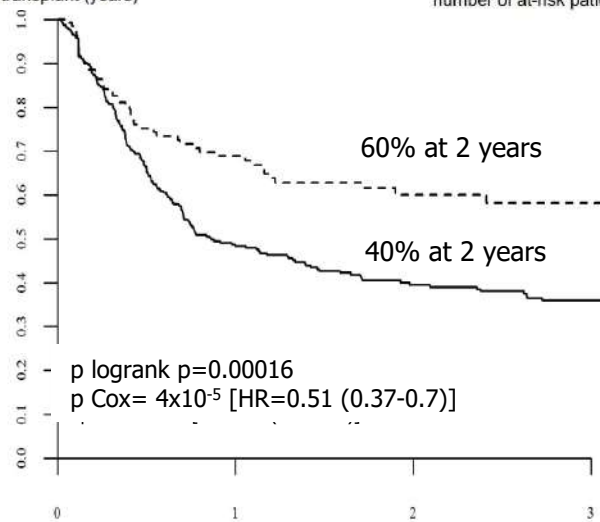


Extensive chronic GVHD

3-year CI, 12.2% to 45.0%; HR =0.20,
95% CI, 0.10 to 0.39, $P < .0001$



GRFS



Faisabilité des greffes haplo-identiques grâce à une prophylaxie de la GVH par Endoxan post-greffe

Study	Nb of pts	SC source	CDT	aGvHD II-IV	cGvHD	NRM	Relapse	OS
Bashey JCO 2013	101	PB	Mix	30 %	38 %	4 %	33 %	64 %
Raiola BBMT 2014	92	BM	Mix	14 %	15 %	18 %	35 %	52 %
Solomon BBMT 2015	30	PB	MAC	43 %	56 %	3 %	24 %	78 %
Ciurea Blood 2015	104	BM	MAC	30%	14%	44%	45%	42%
Blaise BBMT 2016	31	PB	RIC	23 %	13 %	10 %	23 %	70 %
Bashey BBMT 2016	116	PB	Mix	41 %	31 %	17 %	29 %	57 %

En retrospectif : résultats comparables aux greffes HLA compatibles

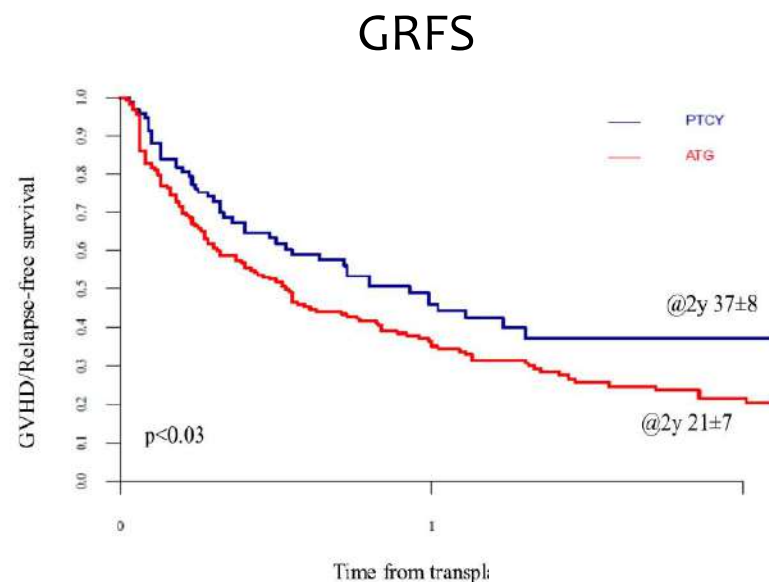
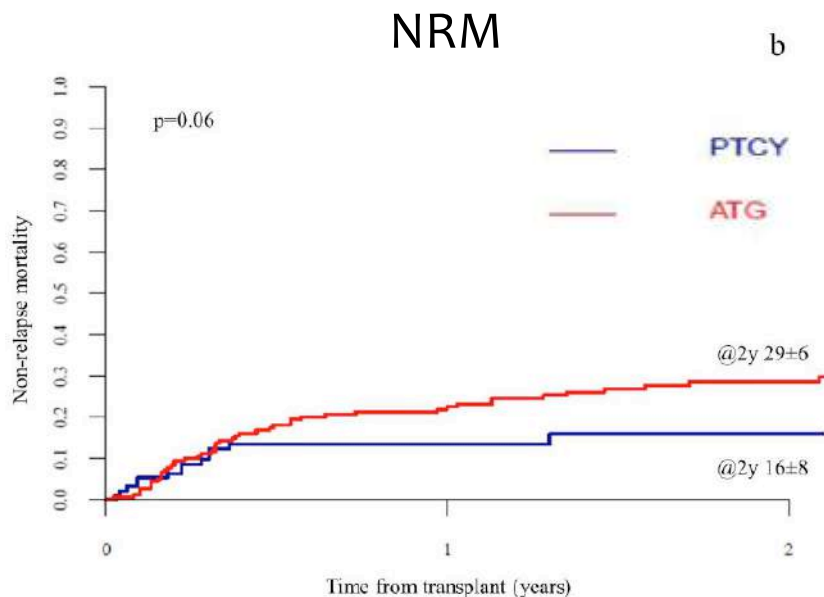
En prospectif: Etudes SFGM-TC:

- ✓ Hapломудelderly: Haplo = phéno 10/10 chez > 55 ans
- ✓ Etude MACHAPLOMUD en cours chez les < 55 ans

EDX post-greffe et greffes HLA 9/10

Etude rétrospective de l'ALWP de l'EBMT

MAC and RIC, majorité de greffon de CSP

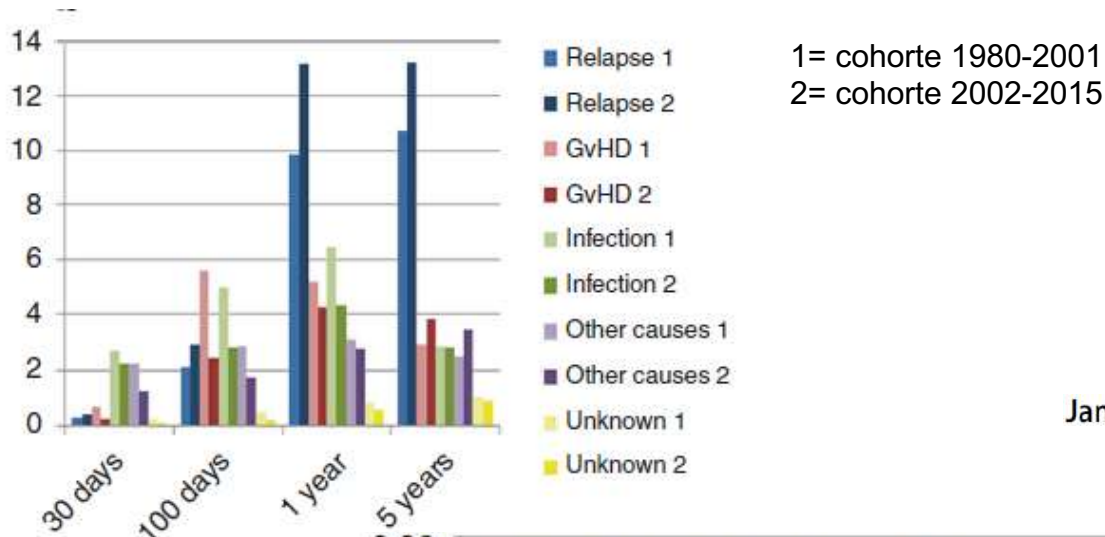


Battaglia et al. Blood 2019; online July 3

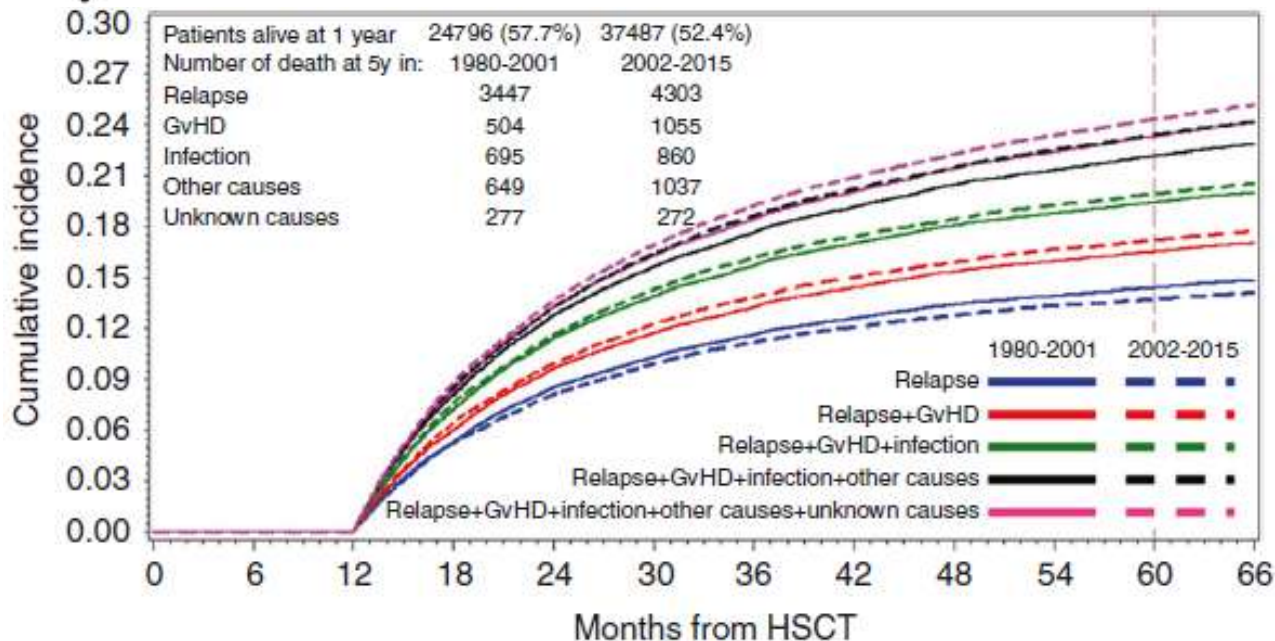
Diminution de l'incidence de GVH aigue Grade III-IV

Etude en cours SFGM-TC: Altergref : Haplo vs 9/10 avec EDX post-greffe en prophylaxie de la GVH dans les 2 bras

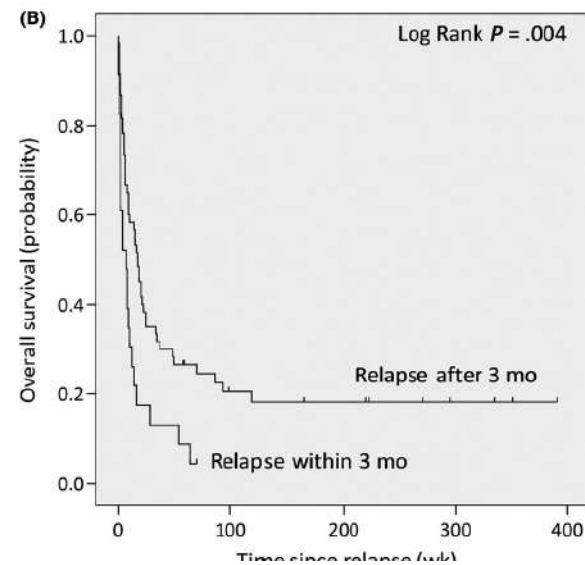
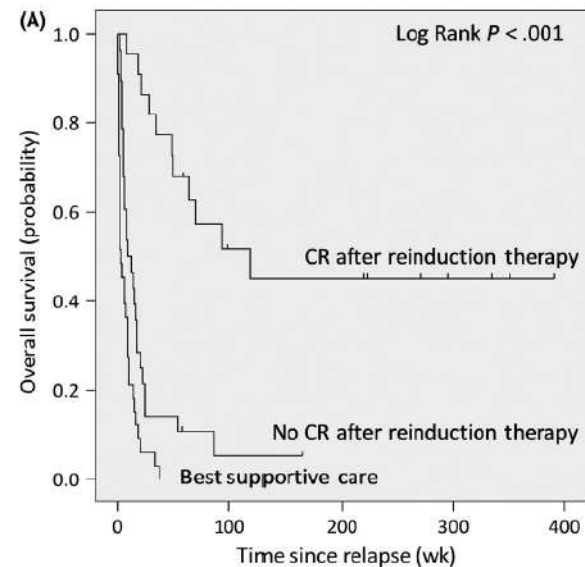
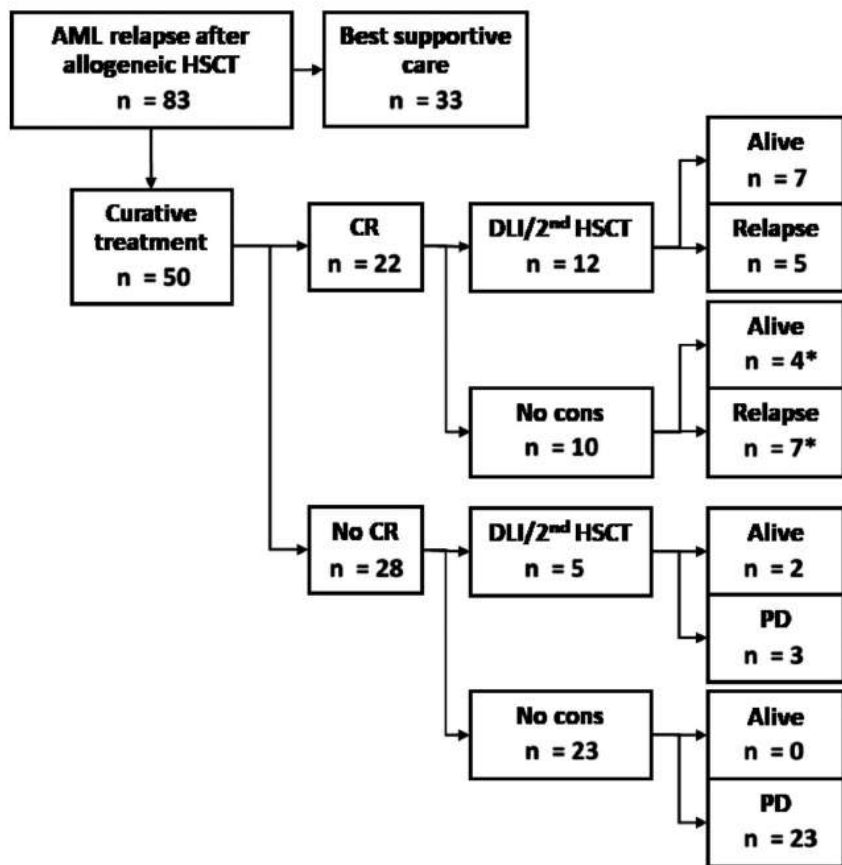
La rechute représente la principale cause de décès après allogreffe



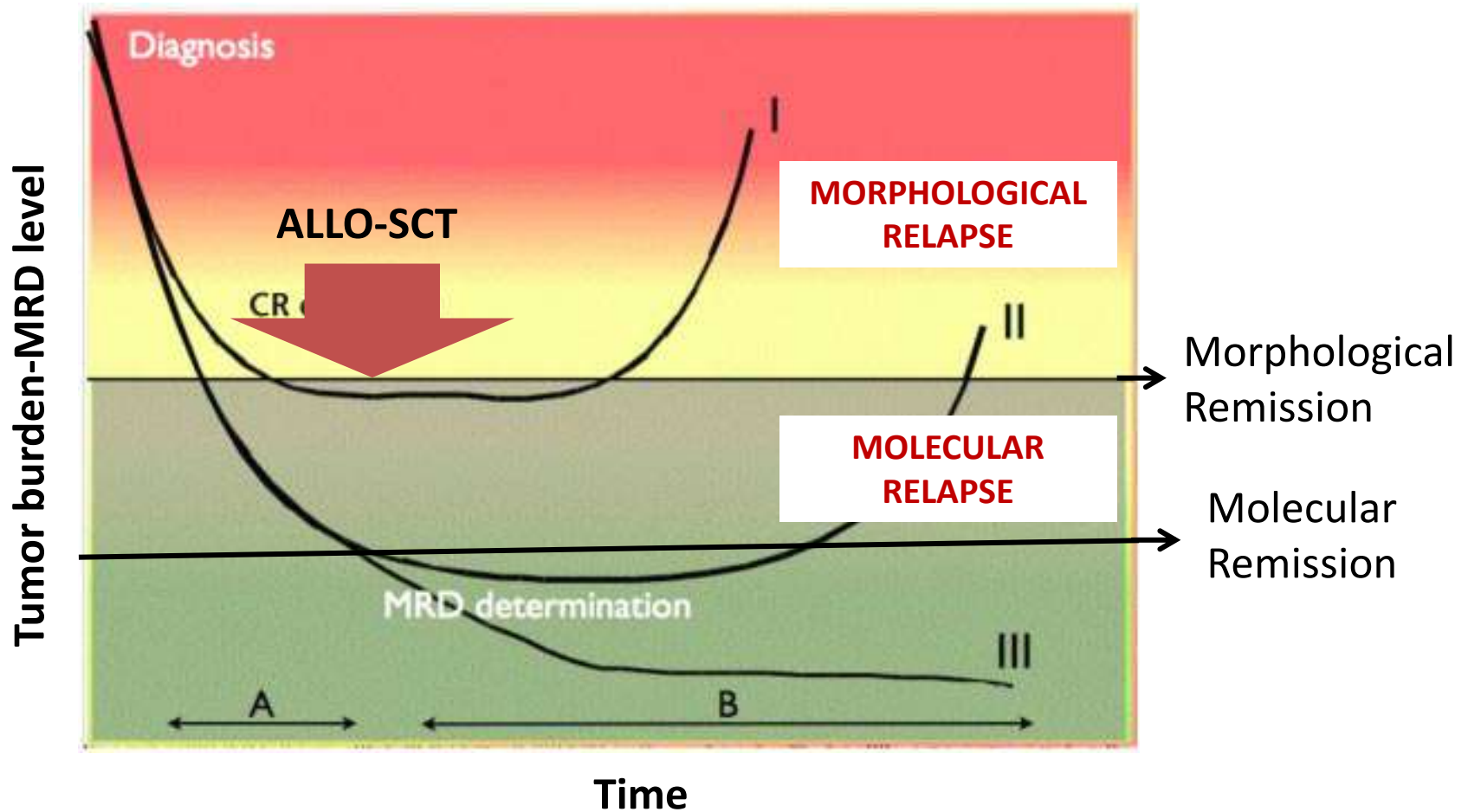
Jan Styczyński Bone Marrow Transplantation (2020) 55:126–136



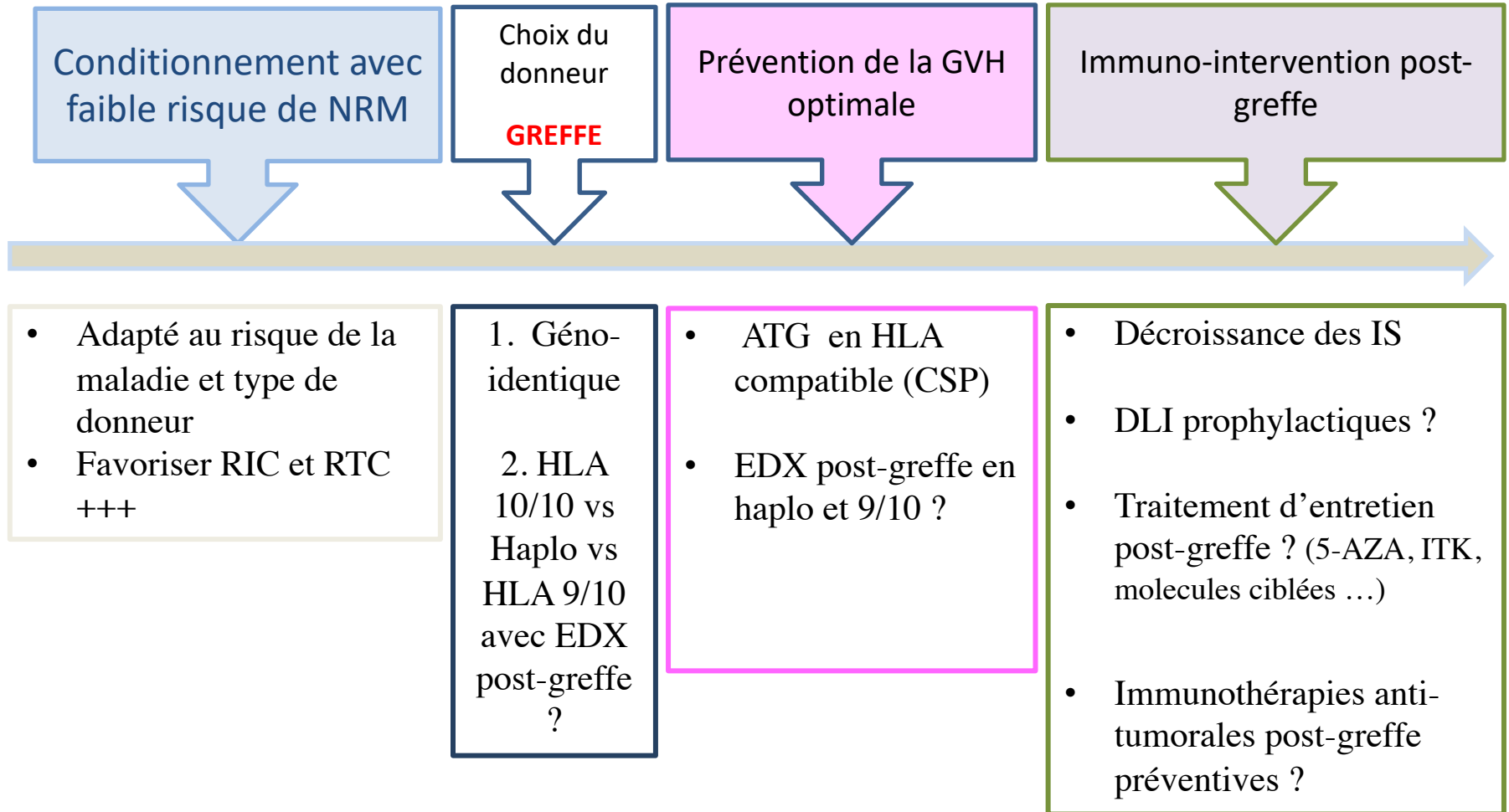
Mauvais pronostic de la rechute post-allogreffe



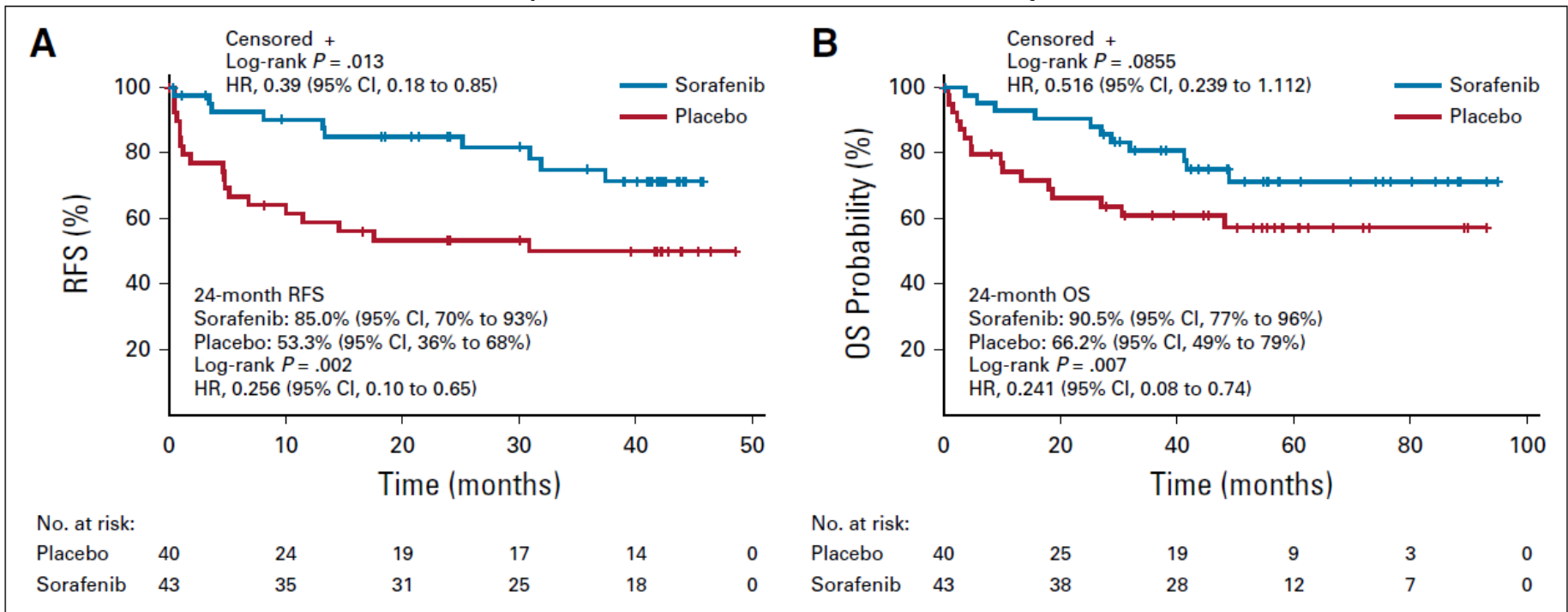
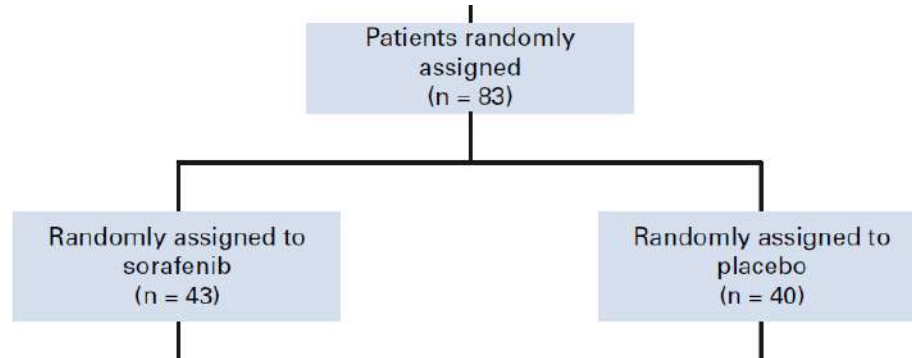
Chez qui faut-il envisager un traitement préventif de la rechute ? Quand intervenir en préventif ?



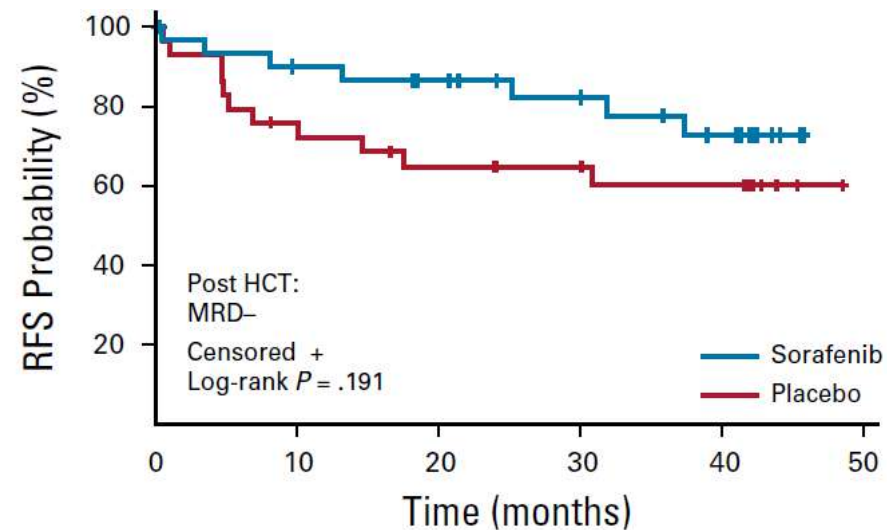
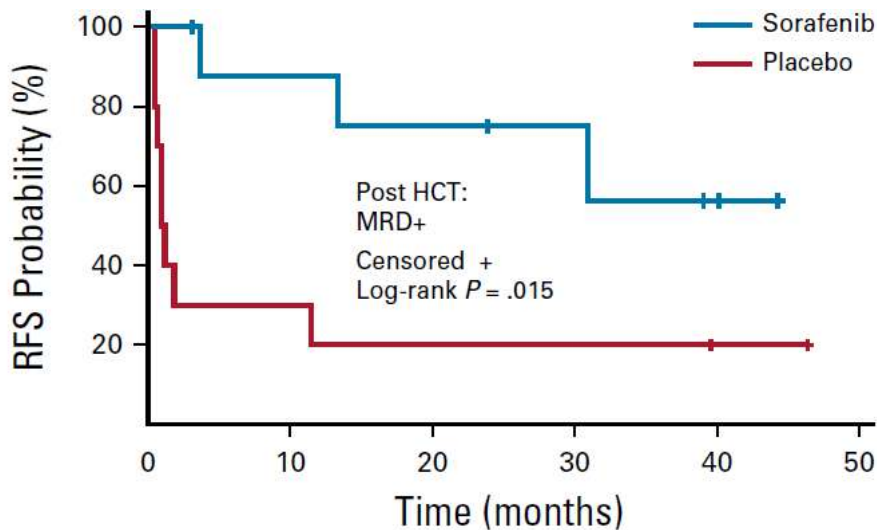
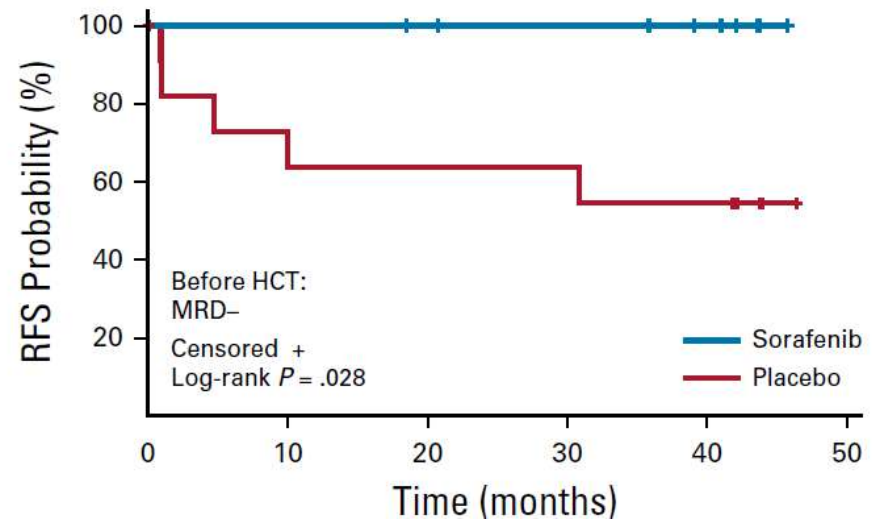
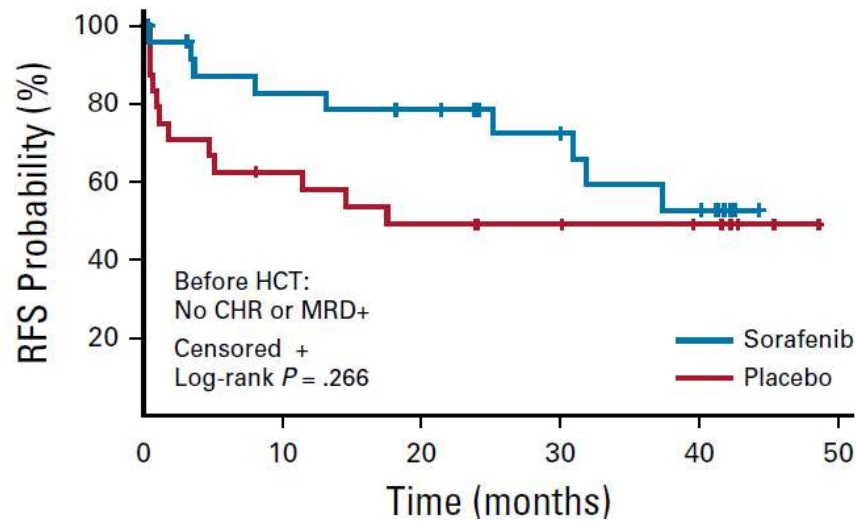
Challenge et avenir de l'allogreffe de CSH: devenir une plateforme d'immunothérapie: les conditions



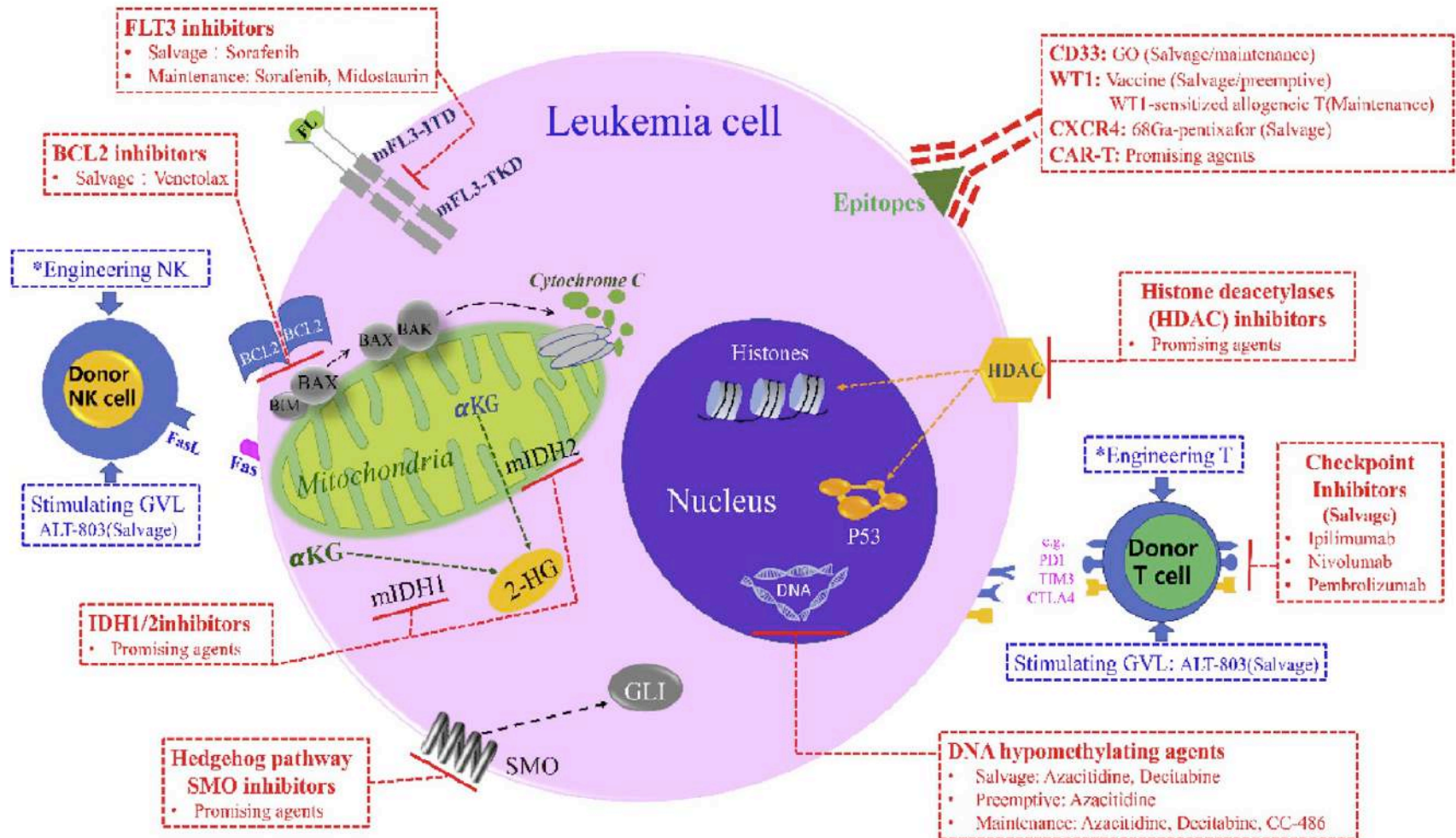
Exemple de maintienane post-allogreffe améliorant la survie post-greffe: inhibiteur de FLT3



Exemple de maintienane post-allogreffe améliorant la survie post-greffe: inhibiteur de FLT3



Les différentes approches d'IMMUNOTHERAPIE/IMMUNOMODULATION POST-ALLOGREFFE



Etudes de maintenance post-allogreffe en cours

Target	Agent	Intervention strategy	Therapy regimen	Identifier (phase)	Status	Complete date	With results
<i>FLT3</i>	Sorafenib	Salvage	+/-DLI	NCT02867891 (no)	Completed	12/2016	Yes
		Maintenance	Mono	NCT01398501 (1)	Completed	8/2016	Yes
		Maintenance	Mono	NCT02474290 (2/3)	Completed	8/2019	Yes
		Maintenance	Mono	NCT01578109 (no)	Active, not recruiting	12/2025	Yes
	Midostaurin	Maintenance	Mono	NCT03247088 (1/2)	Recruiting	7/2022	No
		Preemptive	Mono	NCT03951961 (2)	Not yet Recruiting	12/2023	No
		Maintenance	Mono	NCT01477606 (2)	Active, not recruiting	6/2020	Yes
	Quizartinib	Maintenance	Mono	NCT01883362 (2)	Completed	4/2018	No
		Salvage/maintenance	Mono	NCT02039726 (3)	Active, not recruiting	12/2020	Yes
		Maintenance/ preemptive	Mono	NCT01468467 (1)	completed	3/2015	Yes
Gliteritinib		Maintenance	Mono	NCT02997202 (3)	Recruiting	4/2025	No
<i>BCL-2</i>	Crenolanib	Maintenance	Mono	NCT02400255 (2)	Recruiting	6/2021	No
	Venetolax	Maintenance/ preemptive	+AZA	NCT04161885 (3)	Recruiting	8/2024	No
		Maintenance/ preemptive	+AZA	NCT04128501 (2)	Not yet Recruiting	10/2022	No
	Ivosidenib	Maintenance	Mono	NCT03564821 (1)	Recruiting	7/2024	No
<i>IDH2</i>	Enasidenib	Maintenance	Mono	NCT03515512 (1)	Recruiting	5/2024	No
		Maintenance	Mono	NCT03728335 (1)	Recruiting	12/2020	No

Etudes de maintenance post-allogreffe en cours

Target	Agent	Intervention strategy	Therapy regimen	Identifier (phase)	Status	Complete date	With results	
DNA methylation	Azacitidine	Salvage	Mono	NCT01083706 (2)	Completed	12/2013	Yes	
		Salvage	Mono	NCT02017457 (2)	Completed	11/2019	Yes	
		Preemptive	Mono	NCT01462578 (2)	Active, not recruiting	8/2020	Yes	
		Preemptive	Mono	NCT03850418 (2)	Recruiting	2/2024	No	
		Preemptive	+DLI	NCT01541280 (2)	Completed	7/2015	Yes	
		Maintenance/ preemptive	+/-DLI	NCT02458235 (2)	Active, not recruiting	4/2020	No	
		Maintenance	Mono	NCT01995578 (2)	Recruiting	11/2021	No	
		Maintenance	Mono	NCT00350818 (1)	completed	8/2010	No	
		Maintenance	Mono	NCT00887068 (3)	completed	8/2018	No	
		Maintenance	+Nivolumab	NCT04128020 (1)	Recruiting	10/2022	No	
		Maintenance	+APR-246	NCT03931291 (2)	Recruiting	9/2021	No	
		Maintenance	+Valproic Acid	NCT02124174 (2)	Recruiting	1/2021	No	
		Maintenance	Mono	NCT01168219 (2)	Active, not recruiting	11/2015	Yes	
	Decitabine	Decitabine	Salvage	+DLI	NCT01758367 (1/2)	Unknown	6/2018	Yes
			Salvage	+2nd HSCT	NCT00002832 (1/2)	Completed	3/2002	No
			Salvage	+Ruxolitinib + DLI	NCT04055844 (2)	Recruiting	1/2025	No
			Preemptive	Mono	NCT03663751 (2)	Recruiting	3/2021	No
			Preemptive	+DLI	NCT03662087 (2/3)	Recruiting	12/2022	No
			Maintenance	Mono	NCT01809392 (2/3)	Unknown	12/2015	No
Maintenance	Decitabine	Maintenance	Mono	NCT01277484 (1)	Unknown	12/2015	Yes	
		Maintenance	Mono	NCT00986804 (1)	Completed	2/2016	Yes	
		Maintenance	+DLI	NCT03771222 (2)	Not yet Recruiting	12/2021	No	

Etudes de maintenance post-allogreffe en cours

Target	Agent	Intervention strategy	Therapy regimen	Identifier (phase)	Status	Complete date	With results
	Guadecitabine	Salvage/preemptive	+DLI	NCT02684162 (2)	Recruiting	6/2021	No
		Maintenance	Mono	NCT03454984 (2)	Not yet Recruiting	3/2022	No
Histone deacetylases	CC-486	Maintenance	Mono	NCT01835587 (1/2)	Completed	5/2017	Yes
		Maintenance	Mono	NCT04173533 (3)	Recruiting	6/2024	No
	Panobinostat	Maintenance	Mono	NCT01451268 (1/2)	Unknown	4/2018	Yes
		Maintenance	Mono	NCT04326764 (3)	Recruiting	10/2023	No
	Vorinostat	Maintenance	+AZA	NCT03843528 (1)	Recruiting	12/2021	No
Epitopes							
CD33	BI 836858	Salvage	+F16IL2	NCT03207191 (1)	Unknown	12/2019	No
	GO	Salvage	Mono	NCT00044733 (2)	Completed	9/2004	Yes
Maintenance		Mono	NCT01020539 (1)	Active, not recruiting	12/2020	No	
Maintenance		Mono	NCT02117297 (2)	Recruiting	12/2022	No	
CD38	33 A	Maintenance	Mono	NCT02614560 (1/2)	Terminated	9/2017	No
	Daratumumab	Salvage	+DLI	NCT03537599 (1/2)	Recruiting	9/2021	No
WT1	DC vaccine	Salvage/preemptive	+DLI	NCT00923910 (1/2)	Completed	11/2016	Yes
		Preemptive	+DEC	NCT01483274 (1)	Completed	6/2015	No
	WT1-sensitized T	Maintenance/preemptive/salvage	+/- (FLU + CTX)	NCT01640301 (1/2)	Active, not recruiting	10/2030	Yes
		Salvage/preemptive	Mono	NCT00620633 (1)	Active, not recruiting	2/2021	No
	CTL	Salvage/preemptive	Mono	NCT00052520 (1/2)	Completed	6/2013	No
		Maintenance	Mono	NCT02895412 (1)	Recruiting	12/2020	No
CD123	Anti-CD123-CART	Salvage	Mono	NCT03114670 (1)	Recruiting	3/2021	No

Etudes de maintenance post-allogreffe en cours

Target	Agent	Intervention strategy	Therapy regimen	Identifier (phase)	Status	Complete date	With results
CTLA-4	Ipilimumab	Salvage	+DLI	NCT00060372 (1)	Completed	4/2008	Yes
		Salvage	Or Nivolumab	NCT01822509 (1)	Active, not recruiting	12/2018	Yes
PD-1	Nivolumab	Salvage	+LEN	NCT01919619 (2)	Recruiting	6/2021	No
		Maintenance	+/-Nivolumab	NCT02846376 (1)	Recruiting	7/2023	No
		Salvage	Mono	NCT03146468 (2)	Recruiting	6/2020	No
		Salvage	+/-Ipilimumab	NCT03600155 (1)	Recruiting	6/2022	No
		Salvage	+Tocilizumab	NCT03588936 (1)	Recruiting	8/2022	No
		Maintenance	Mono	NCT02985554 (1)	Recruiting	3/2022	No
		Maintenance	Mono	NCT04361058 (1)	Recruiting	4/2025	No
Engineering donor T	Pembrolizumab	Salvage	Mono	NCT02981914 (1)	Recruiting	2/2029	No
		Salvage	Mono	NCT03286114 (1)	Recruiting	10/2021	No
Engineering donor T	CD25hi T _{reg} depleted	Salvage	Mono	NCT00675831 (1)	Completed	1/2013	Yes
		Salvage	+Ipilimumab	NCT03912064 (1)	Recruiting	5/2024	No
		Salvage	Mono	NCT01523223 (1)	Completed	10/2016	Yes
Engineering donor NK	CD8 ⁺ CD44hi CD45RA-depleted	Maintenance	Mono	NCT03849651 (2)	Recruiting	7/2025	No
		Salvage	+FLU + Ara-C or DEC	NCT04220684 (1)	Not yet Recruiting	12/2021	No
		Salvage	+CTX + FLU	NCT00526292 (2)	Completed	7/2015	Yes
		Maintenance	Mono	NCT00569283 (1)	Completed	12/2008	Yes
		Maintenance	Mono	NCT01795378 (1/2)	Completed	5/2015	Yes
		Maintenance	Mono	NCT00823524 (1/2)	Completed	2/2013	Yes
		Maintenance	Mono	NCT03300492 (1/2)	Recruiting	1/2023	No
		Maintenance	Mono	NCT04166929 (2)	Recruiting	1/2022	No
		Maintenance	Mono	NCT02727803 (2)	Recruiting	5/2021	No
		Maintenance	Mono	NCT01904136 (1/2)	Recruiting	4/2021	No
	CD4- iNKT	Maintenance	Mono	NCT03605953 (no)	Not yet Recruiting	4/2021	No