

Y-a-t-il une place pour la thérapie cellulaire dans la LLC ?

SFGM-TC, Nancy, 2021



EA 7283
CIC-INSERM 1405



Olivier TOURNILHAC, *CHU Clermont Ferrand*

LLC

1/3 jamais traitée

1/3 traitement tardif

1/3 traitement précoce



Sous population de patients à haut risque

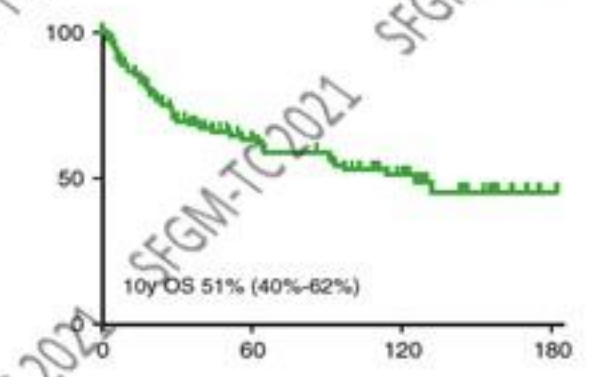
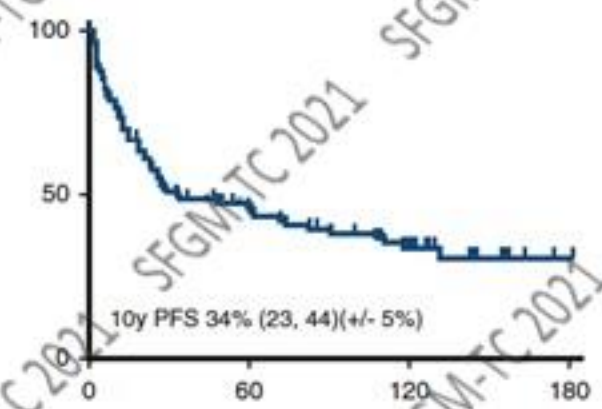
Biologie : altération de *TP53*, caryotype complexe

Rechute précoce aux thérapeutiques

Allogreffe pour les CLL : Quelques données du passé

Allogreffe (RIC) : avant ère des inhibiteurs de BTK/BCL2

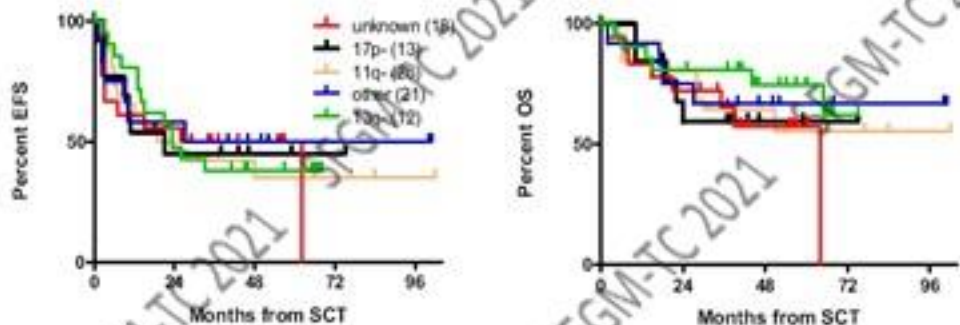
	Schetelig JCO 2003 (n = 30)	Sorror JCO 2008 (n = 82)	Dreger Blood 2010 (n = 90)	Khouri Cancer 2011 (n = 86)	Michallet Exp. He. 2013 (n = 40)
Âge	54 (35-65)	56 (42-72)	53 (27-65)	58 (38-72)	50 (12-63)
Cond.	FB + ATG	F/TBI	FC ± ATG	FCR	FC ± R
Suivi (a)	3,7 (2,1-5,6)	5 (3-7,9)	3,8 (0,6-8,5)	3,1 (0,5-10,9)	3,3 (0,4-5,9)
	3-5 ans (%)				
SSP/SSE	38	39	38	46	58
OS	58	50	51	55	69
Rechute	45	38	39	22	30
cGVH ext.	55	49	56	42	41
NRM	23	23	17	27	15



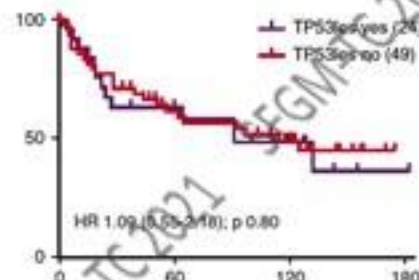
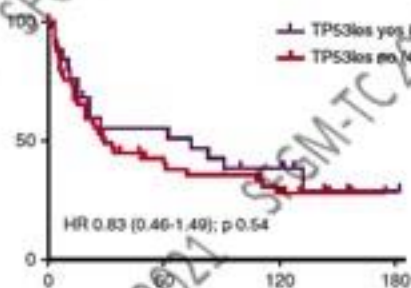
Kramer, Blood, 2017

Impact des facteurs biologiques péjoratifs

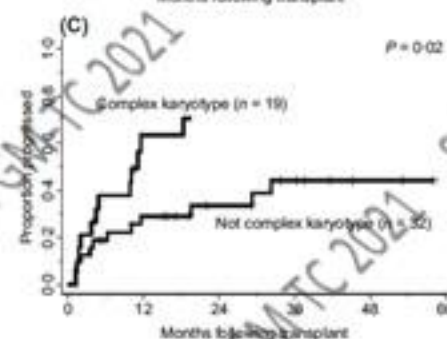
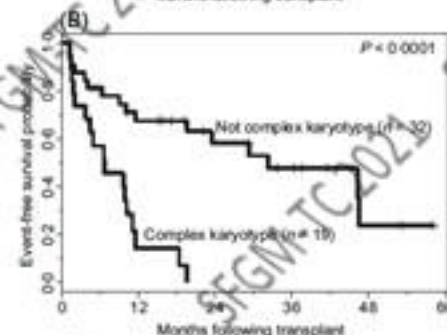
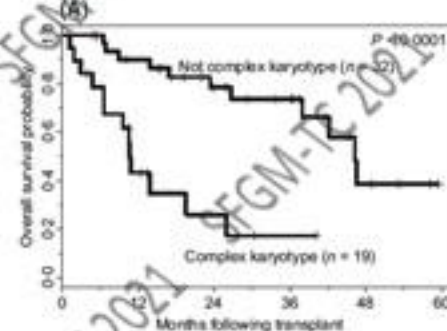
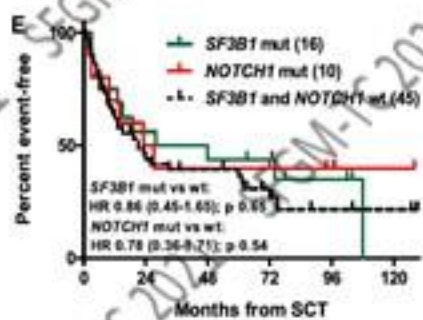
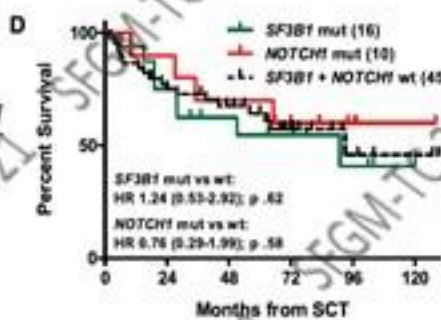
FISH



TP53



SF3B1
NOTCH1



Caryotype
complexe

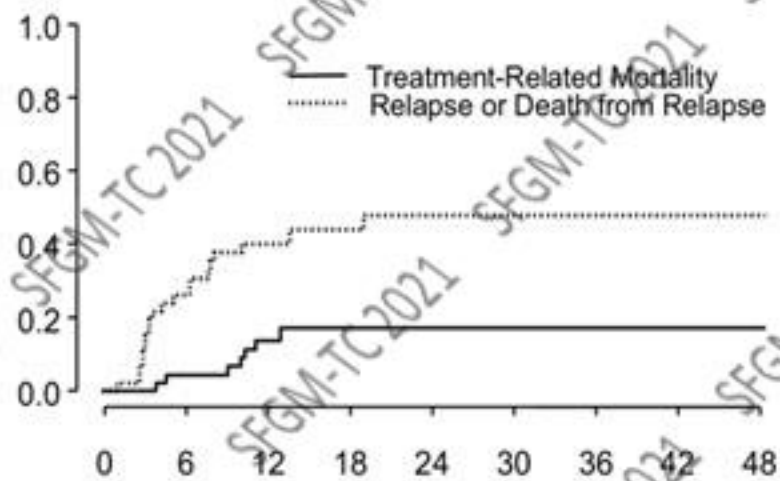
Jagłowski, BJH, 2012

Dreger, Blood, 2010, 2013, 2017

Morbidité et Mortalité

cGVH extensive **20-56%**

Mortalité : **30-50%**

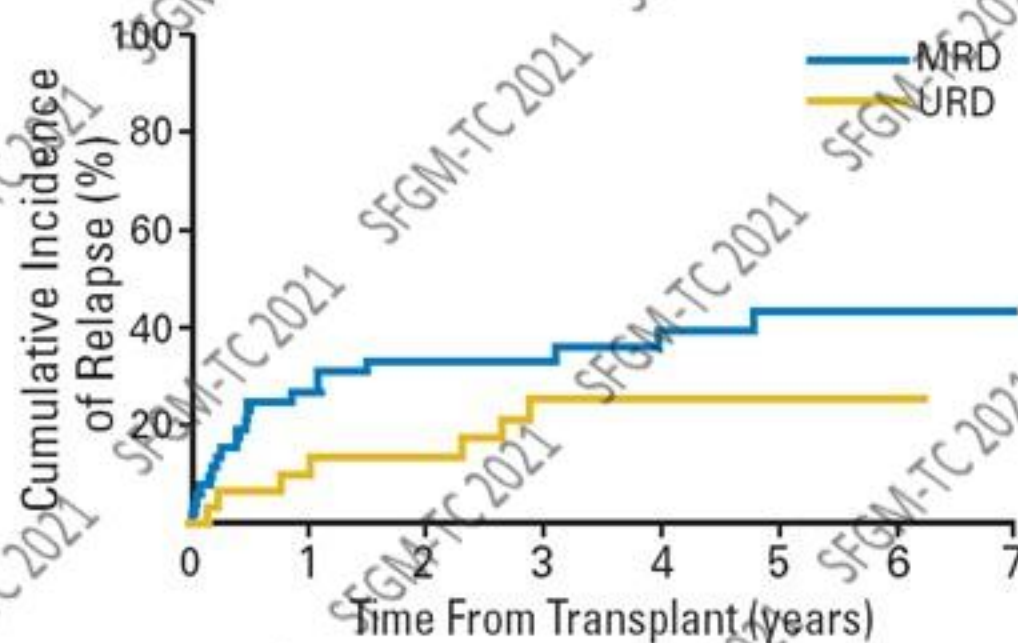


Brown, BBMT, 2006

Rechutes post allogreffe

Maximum 2-3 ans
Rechutes tardives

30-40%

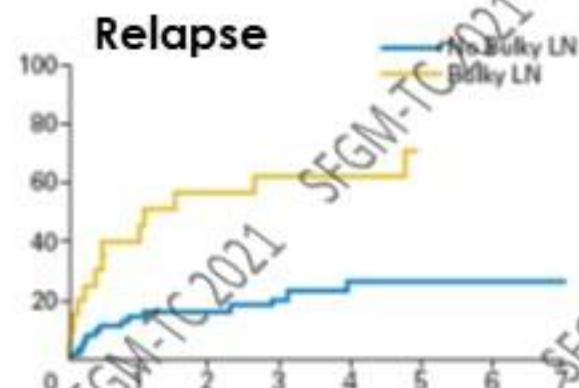


Sorrer, JCO, 2008

Allogreffe pour les CLL : Adaptation des pratiques

- **BCRi/BCL2i : "bridge"**
- BCRi/BCL2i post-allo « salvage »
- Stratégies "MRD-driven"
- Indications ?

Impact of pre-ASCT « status » on ASCT outcome



Sorrer, JCO, 2008

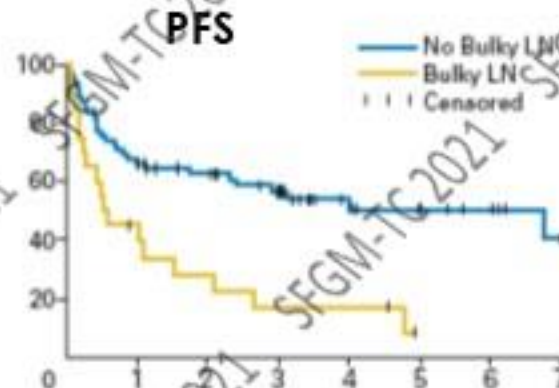
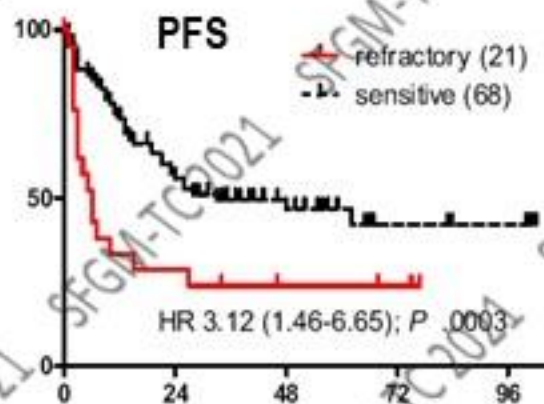


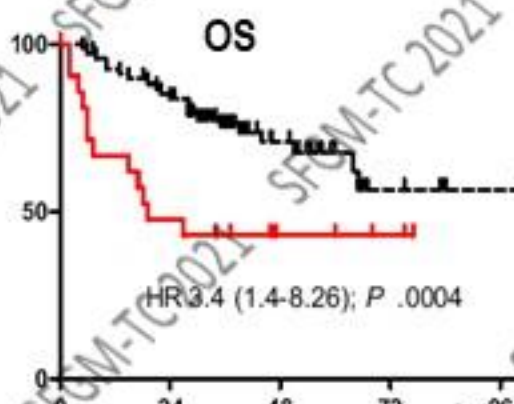
Table 6. RIC: clinical outcomes by risk score

Risk score	N	5-Year OS % (95% CI)	5-Year PFS % (95% CI)	5-Year relapse % (95% CI)
0	14	91 (51, 99)	83 (45, 95)	17 (2, 45)
1	25	78 (54, 90)	63 (38, 80)	15 (3, 35)
2	19	63 (38, 80)	24 (17, 46)	61 (32, 80)
≥3	18	22 (7, 43)	6 (0.4, 22)	72 (42, 88)
P-value		<0.0001	<0.0001	0.00002

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning.



Dreger, Blood, 2010



- LDH >N
- Lymphocytes >1000/uL
- SD/PD
- HTC ≥1

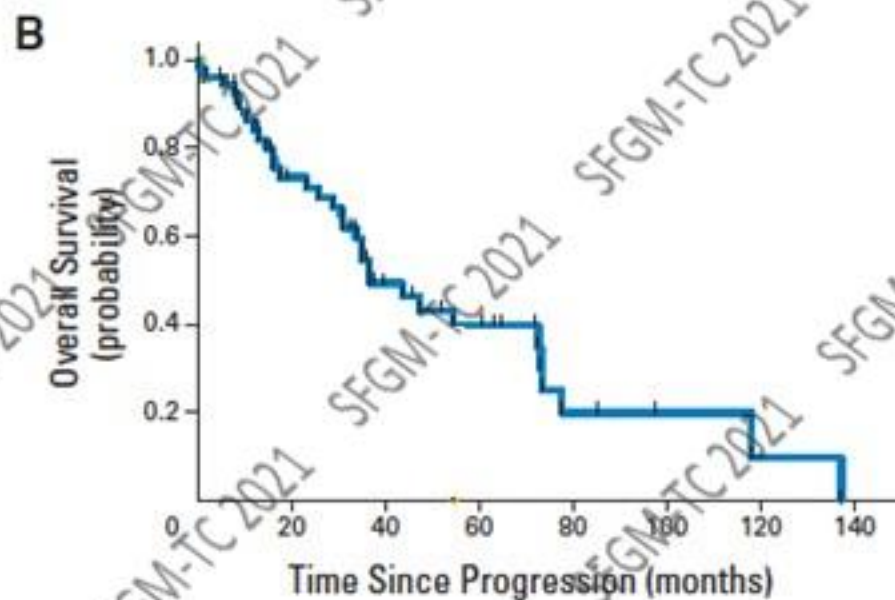
Brown, Leukemia, 2013

Allogreffe pour les CLL : Adaptation des pratiques

- . BCRI/BCL2i : "bridge"
- . **BCRI/BCL2i post-allo « salvage »**
- . Stratégies "MRD-driven"
- . Indications ?

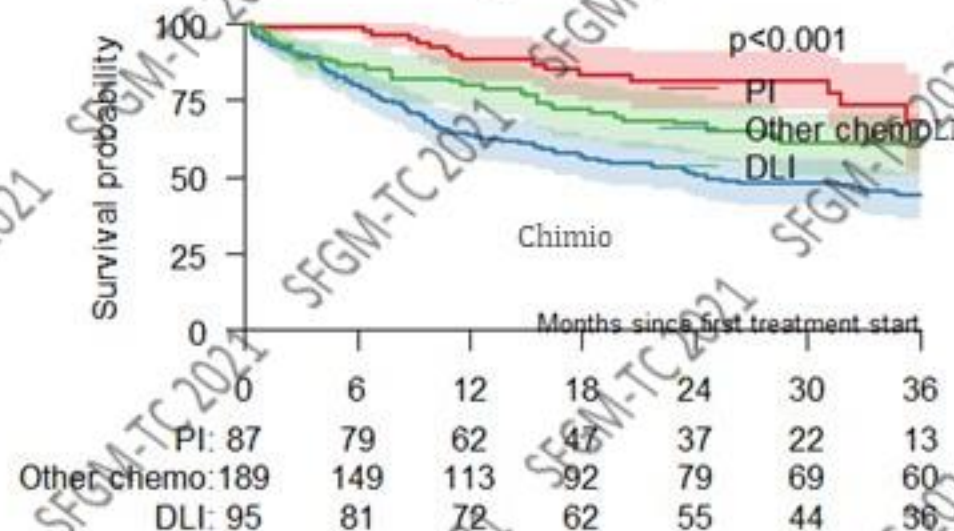
Pronostic des rechutes post allogreffe

72 rechute après allogreffes
[1998 - 2011]



Rozowski, JCO, 2015

626 rechutes post allogreffe
[2010 - 2016]



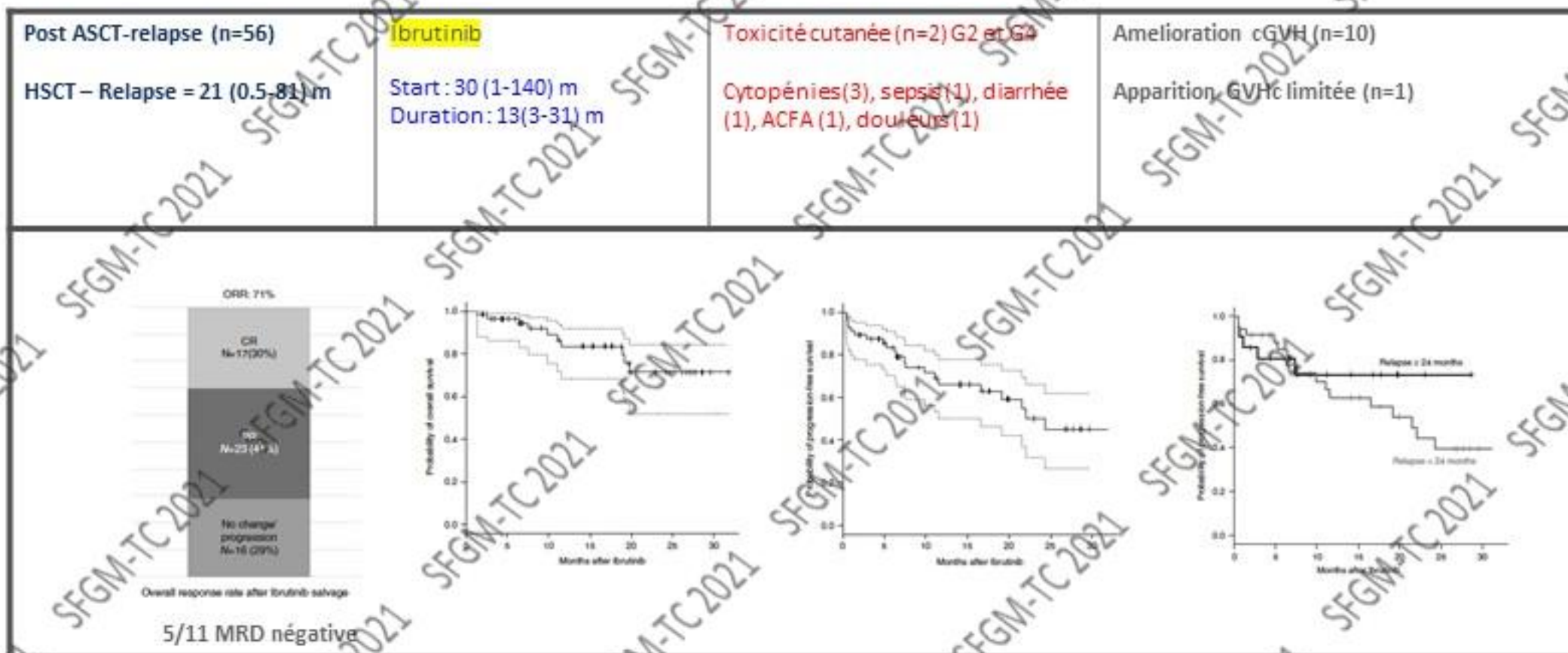
OS à 3 ans = 46% (IC95% 41-50)

Univariate

Rechute [2014 et 2016] ($p=0.02$)
Intervalle > 12 mois ($p < 0.001$)
Absence de del17p ($p=0.01$)

Dreger, EBMT, 2020

Ibrutinib post allogreffe

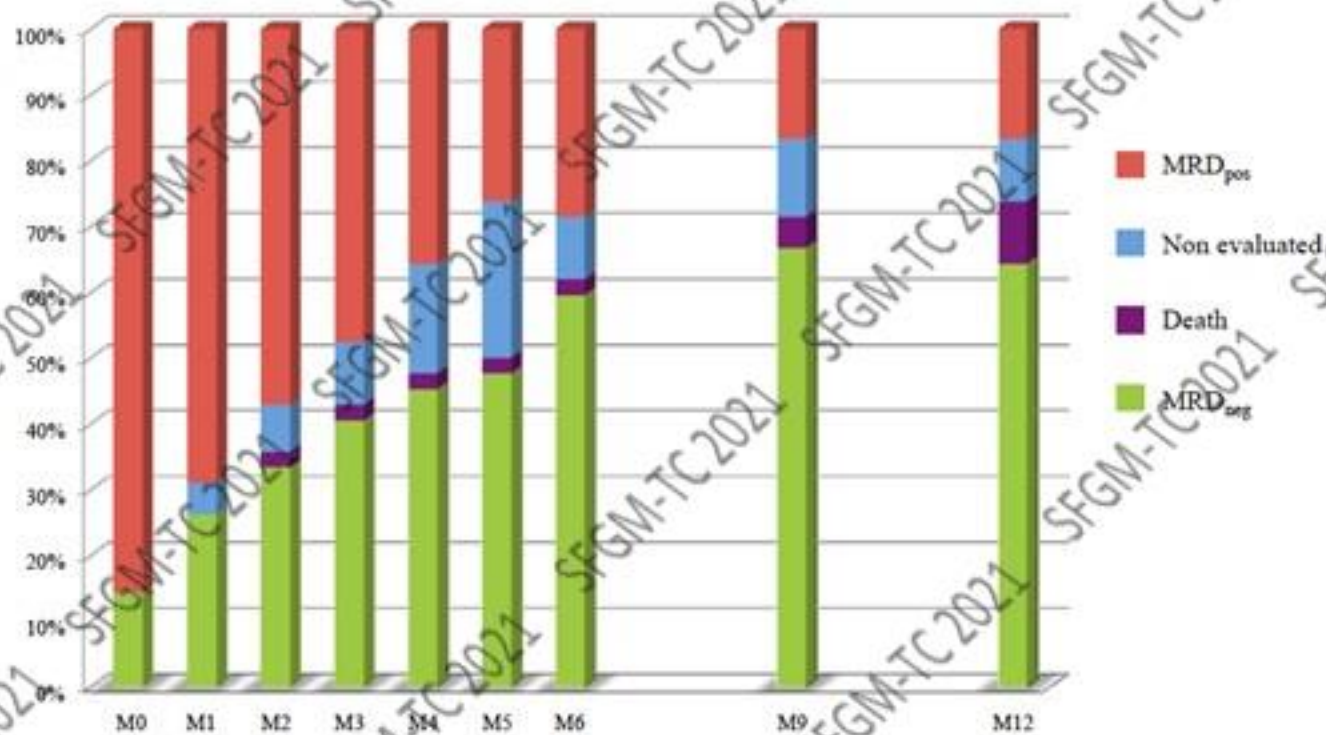
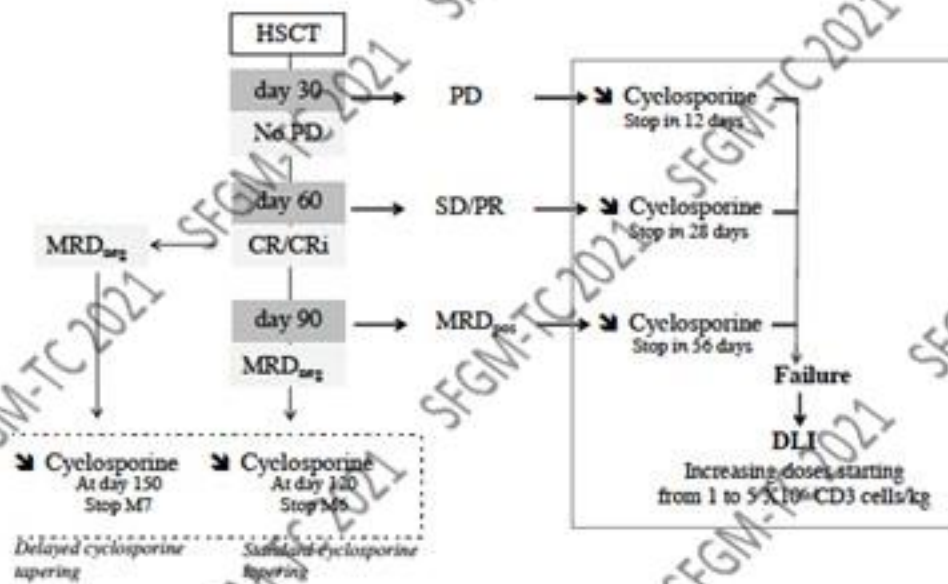


Allogreffe pour les CLL :

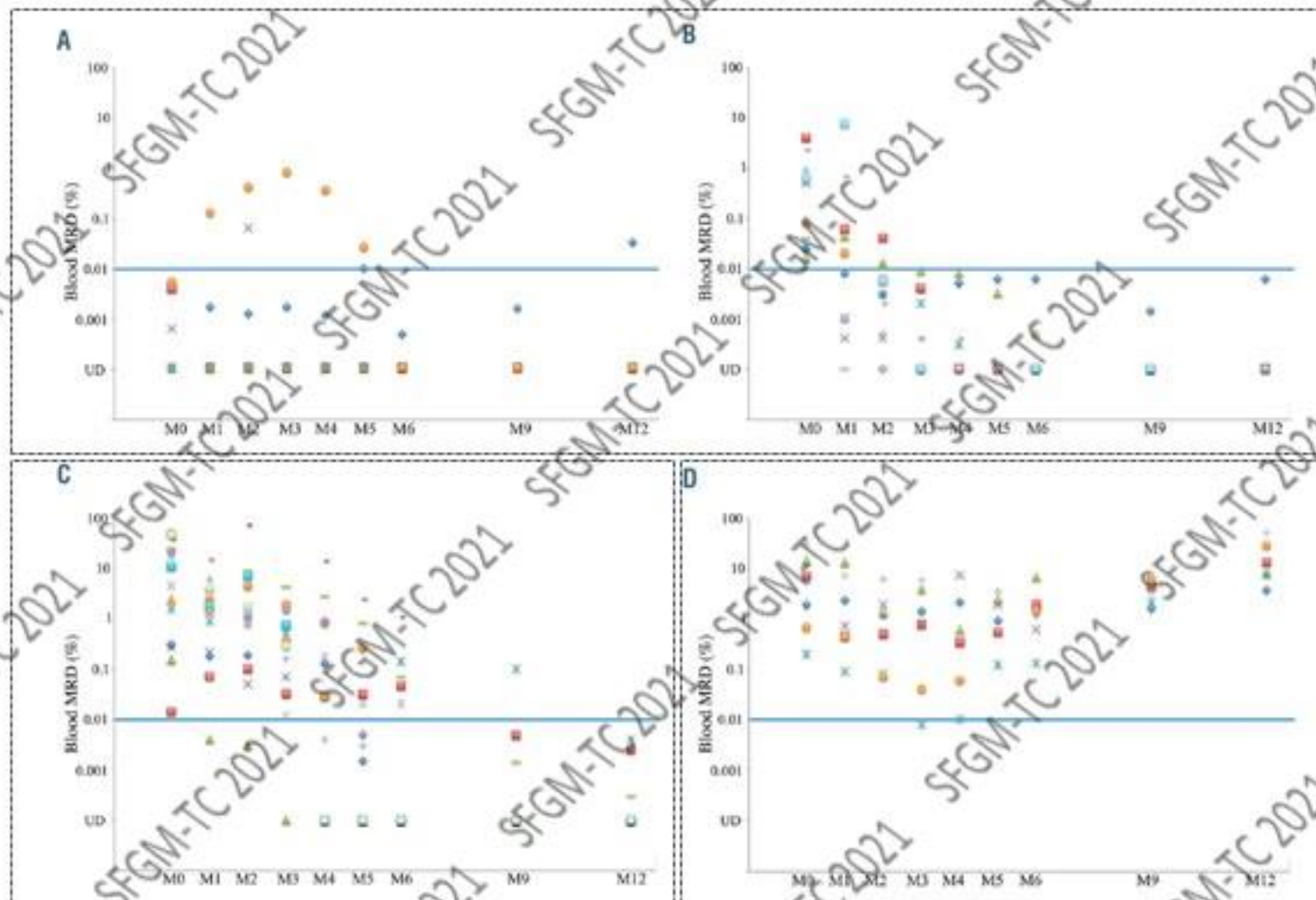
Adaptation des pratiques

- BCRI/BCL2i : “bridge”
- BCRI/BCL2i post-allo « salvage »
- **Stratégies “MRD-driven”**
- Indications ?

Stratégies post-allo « MRD-driven » : RICAC-PMM



RICAC-PMM : ≠ chemins mènent à la MRD -



A+B : n = 17
Rechutes = 4
(12 ; 13 ; 19 ; 34)

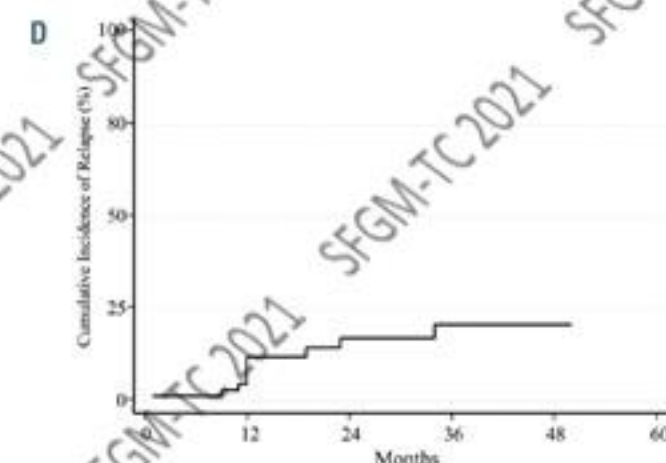
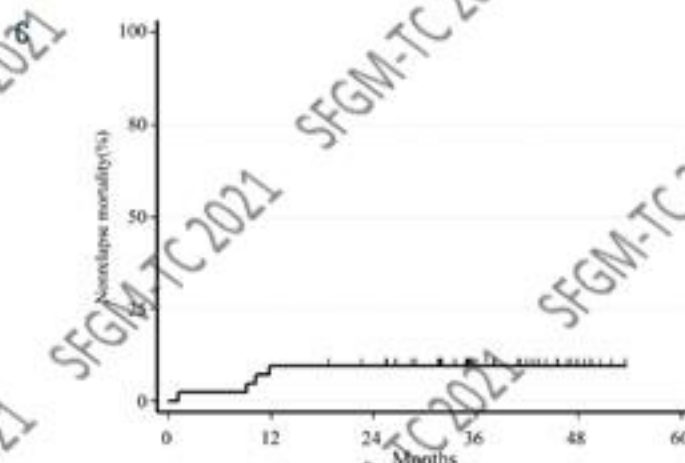
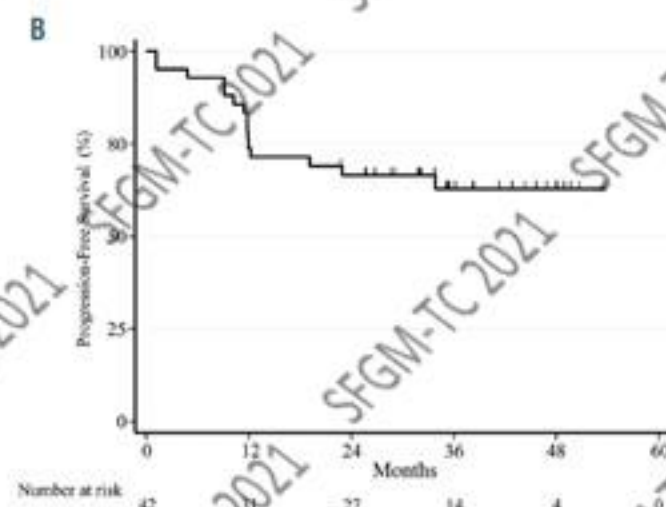
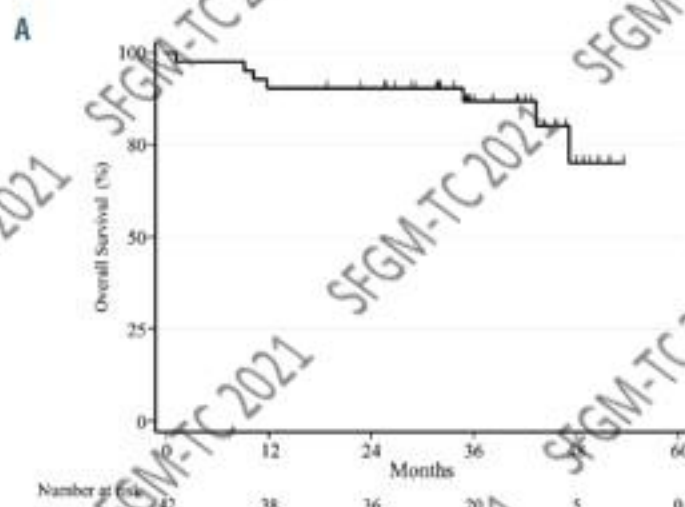
C : n = 15
Rechutes = 2
(13 ; 34)

D : n = 7
Rechutes = 5 (RT=3)
(1 ; 9 ; 11 ; 12 ; 12)

RICAC-PMM : résultats



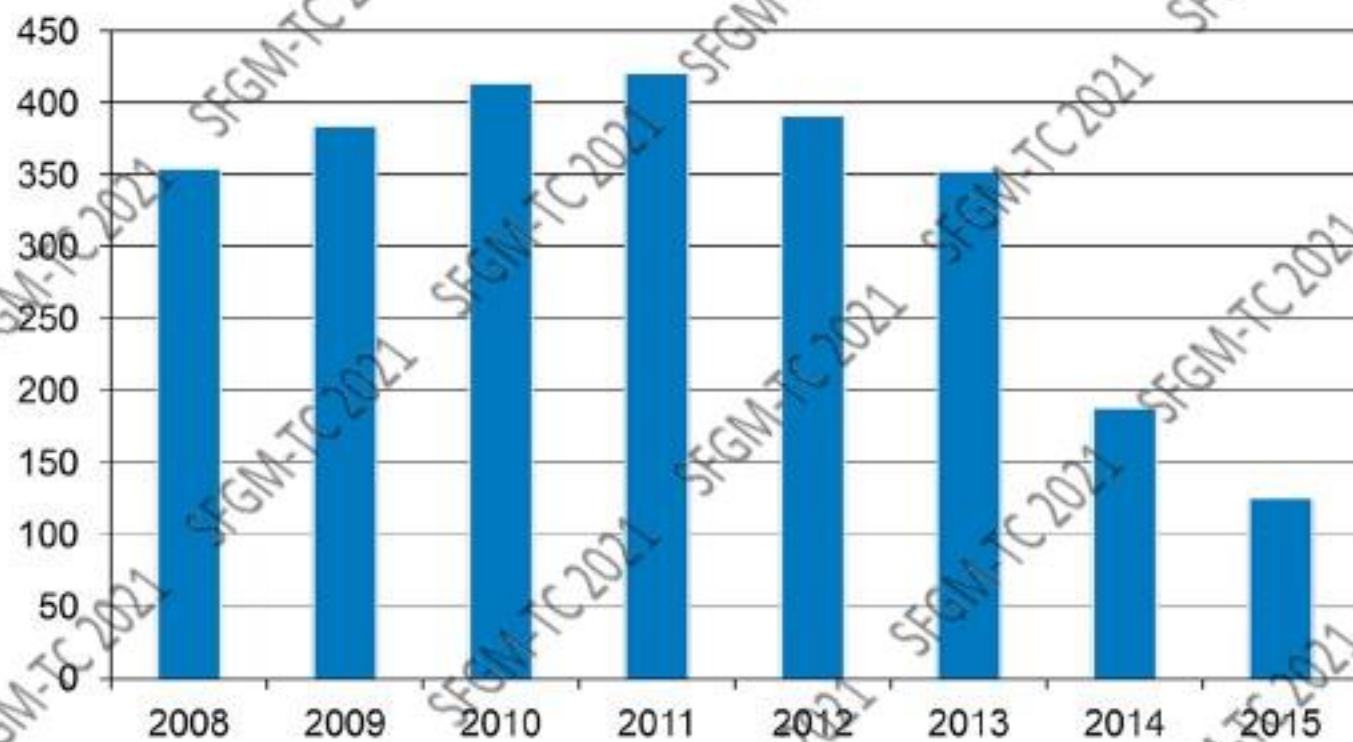
	Patient (n=42)
Sex	
Female	10
Male	32
Median age at transplant: y (range)	58.6 (40.6 - 68.6)
Median time between diagnostic and HSCT: y (range)	4.5 (0.2 - 14.7)
Indication for HSCT: n	
del(17)p and/or TP53 mutation, 1 st line	11
del(17)p and/or TP53 mutation, in relapse	16
Purine analogs refractoriness without TP53 abnormality	3
Early relapse (<2 y) after fludarabine based combination or autologous transplant without TP53 abnormality	12
Median prior treatment lines: n (range)	2 (1-5)
Last line before HSCT: n	
Alemtuzumab +/- Dexamethasone	17
Bendamustine based combination (B, BR, BOMP)	14
R-CHAC	6
Ibrutinib	3
Deliasib + rituximab	1
Rituximab	1
Median time between last line and HSCT: d (range)	63 (7-179)
Prior exposure to alemtuzumab: n	20
Median interval between alemtuzumab (last line) and HSCT: d (range)	85 (37-179)
HSCT done ≤ 60 days post alemtuzumab: n	6
Disease status at transplantation: n	
CR/CR1	8
PR	34
Lymph node ≥ 15 mm*	25
Lymph node ≤ 15 mm	17
	*All < 50 mm
Donor type (HLA 10/10): n	
HLA Matched sibling	16
HLA Matched unrelated	26



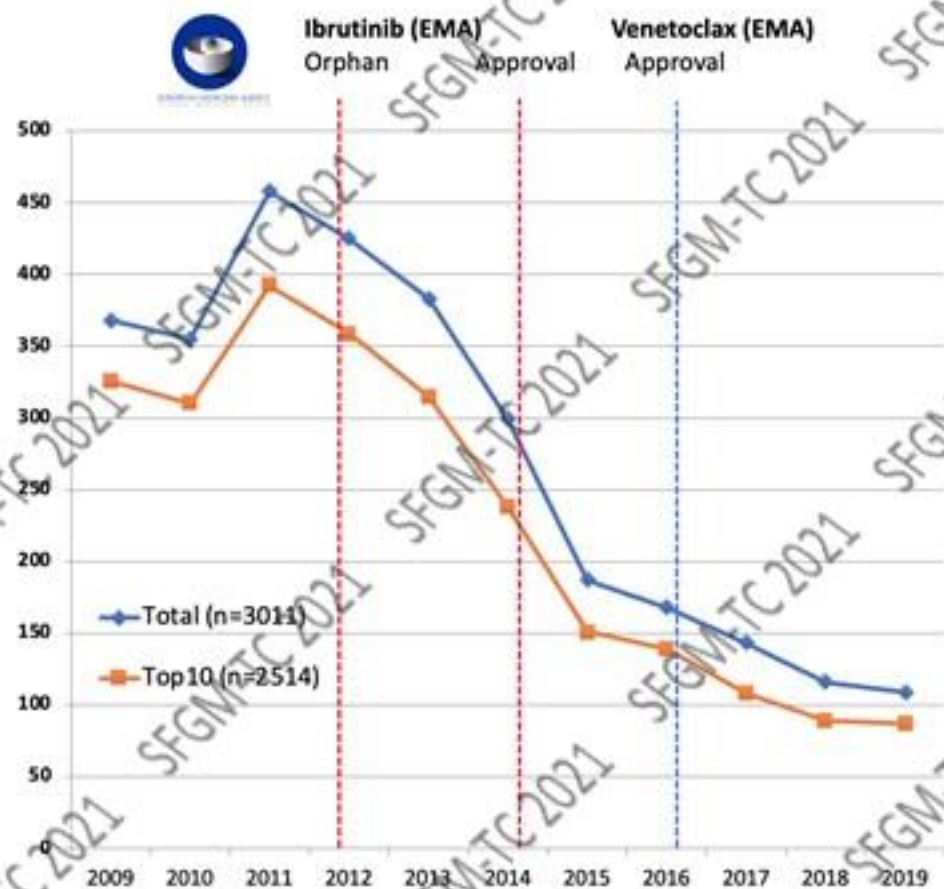
Allogreffe pour les CLL : Adaptation des pratiques

- . BCRI/BCL2i : “bridge”
- . BCRI/BCL2i post-allo « salvage »
- . Stratégies “MRD-driven”
- . **Indications ?**

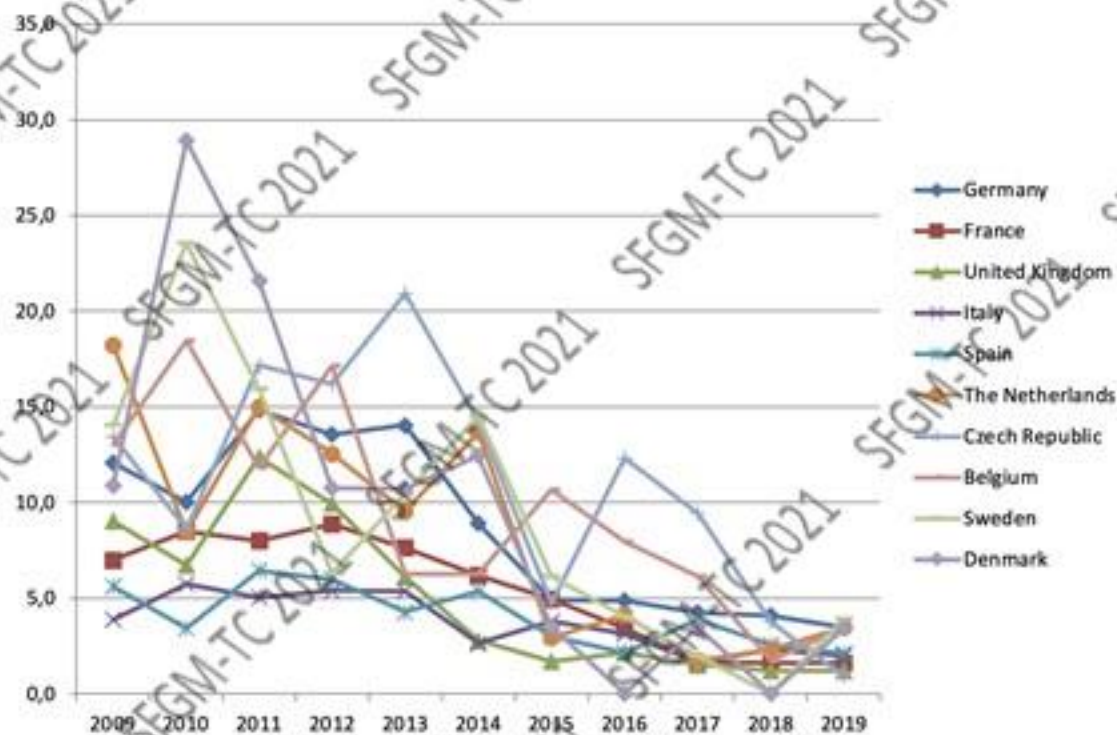
Allogreffe et LLC : évolution des indications CIBMTR



Allogreffe et LLC : évolution des indications EBMT



Allogreffe pour LLC par an et par 10^{e7} hab.



Allogreffe : reco. ERIC-EBMT 2014, update 2018

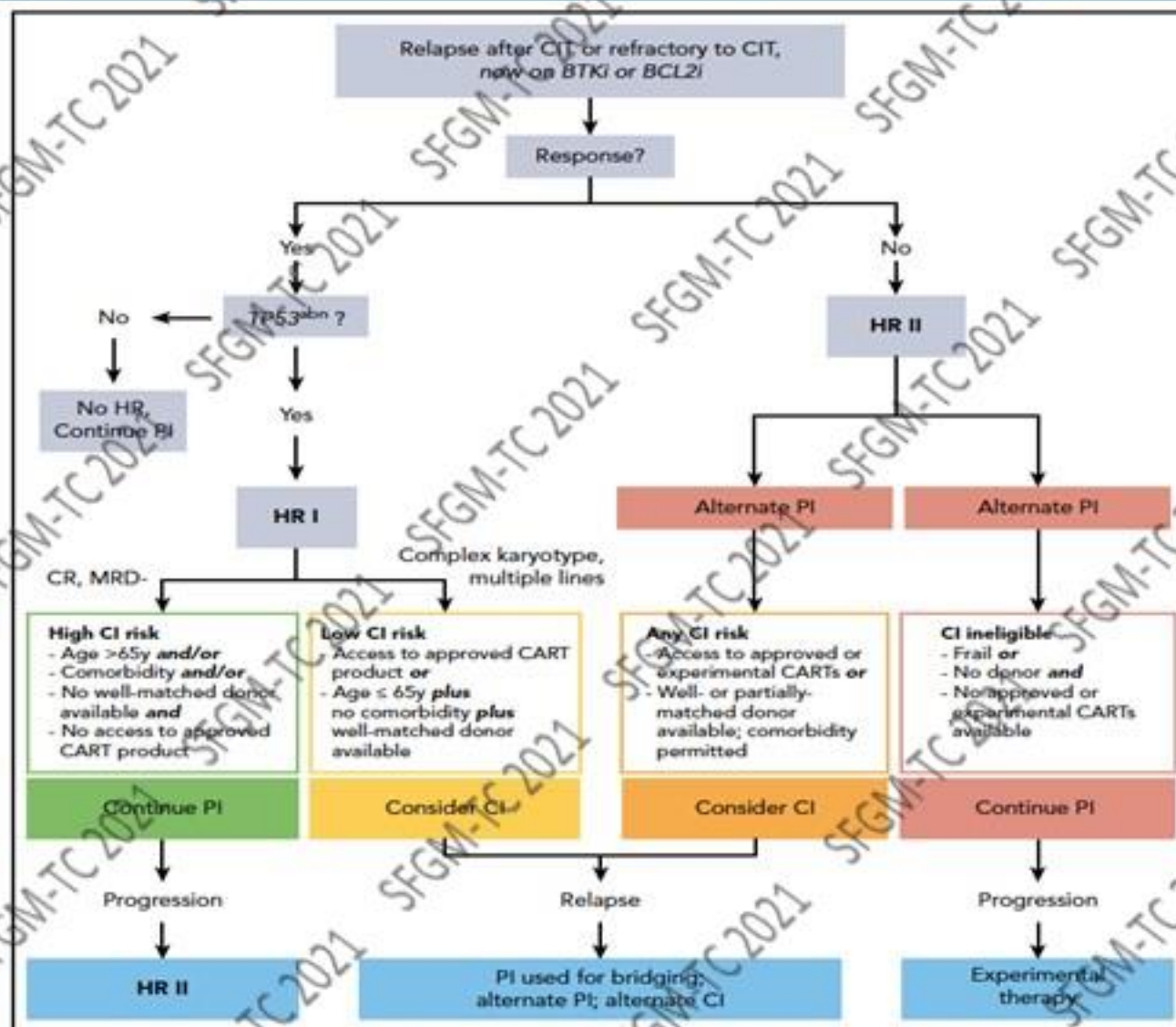


Figure 2. Decision tree for therapy of chemotherapeutic-resistant untransformed CLL according to the revised high-risk concept. Additional factors to be taken into account when considering regular therapy. HR, high risk; TP53abn, TP53 abnormality.

Niveaux d'indication d'allogreffe (2018)

● Niveau 1 :

- Rechute/ Refractaires à ICT
- + altération TP53
- + réponse à BCRI ou BCL2i

« Suggérée, si HLA 10/10 et sans comorbidités »

Dreger, Blood, 2018

● Niveau 2 :

- Rechute/ Refractaires à ICT
- + rechute/refractaire à BCRI ou BCL2i

« Justifiée, même si pas de HLA10/10 et/ou si co-morbidités »

Séquence classique ICT > BTKi

Ibrutinib
après
Immuno-chimio

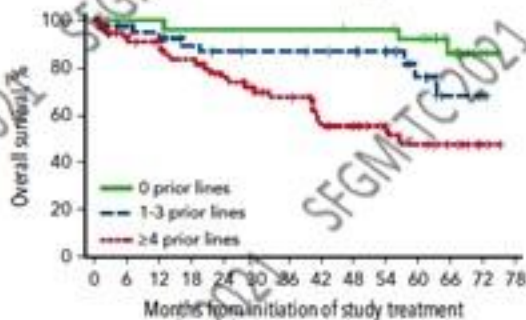
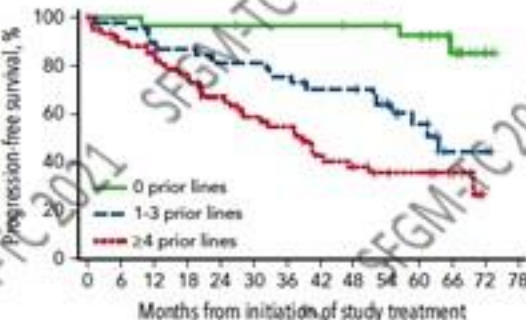
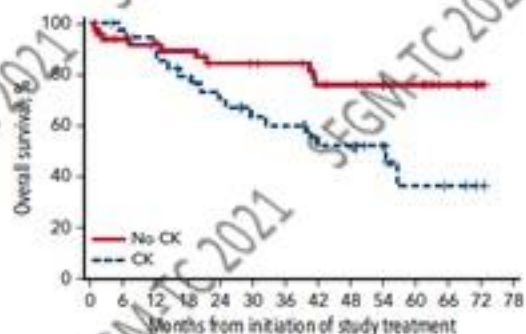
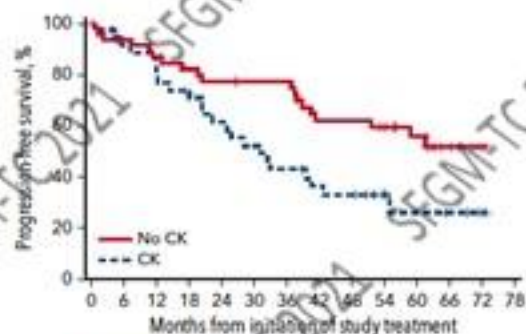
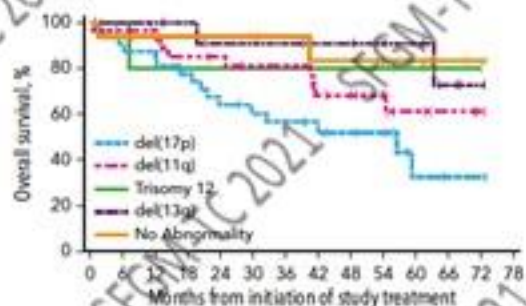
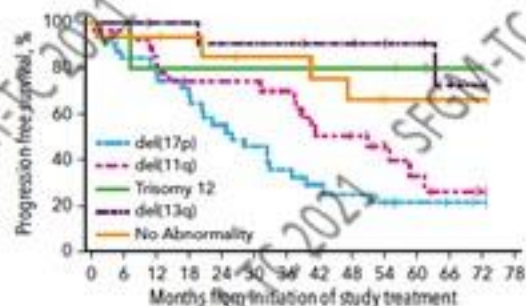
PFS ≥ 50 mois

PFS réduite si :

Altération TP53
Caryotype complexe
≥ 3-4 lignes

Rôle mutations
BTK, PLCγ

Woyach, JCO, 2017
Quinquenel, Blood, 2019



O'Brien, Blood, 2018

Niveau 1
En réponse BCL2i
Si TP53
Si Fit et HLA10/10

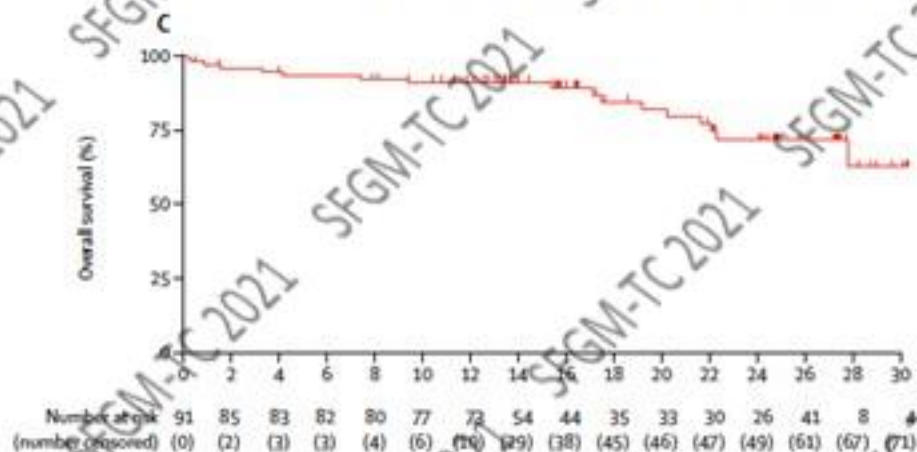
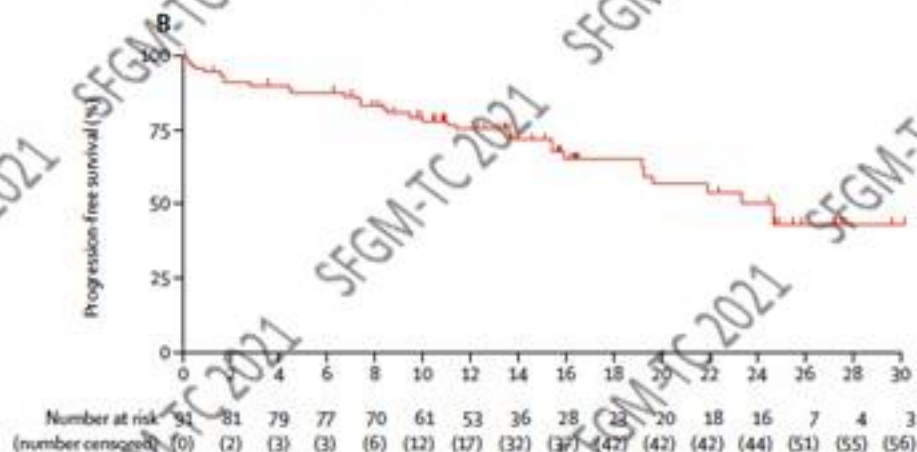
↓
Appliqué ?
Venetoclax +++

Séquence classique ICT > BTKi > BCL2i

Venetoclax
après
Ibrutinib

PFS = 24 mois

Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial



Jones, Lancet Oncology, 2019

Niveau 2

R/R CIT

R/R BTKi



Appliqué?

Critères décisionnels

Critères prédictifs de durée de réponse au Venetoclax

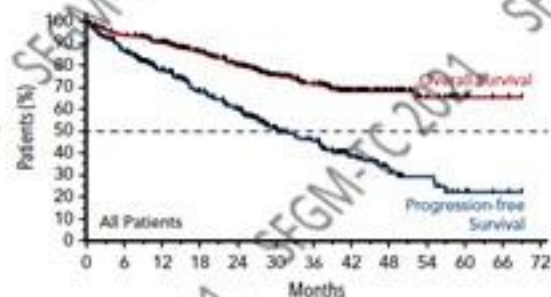
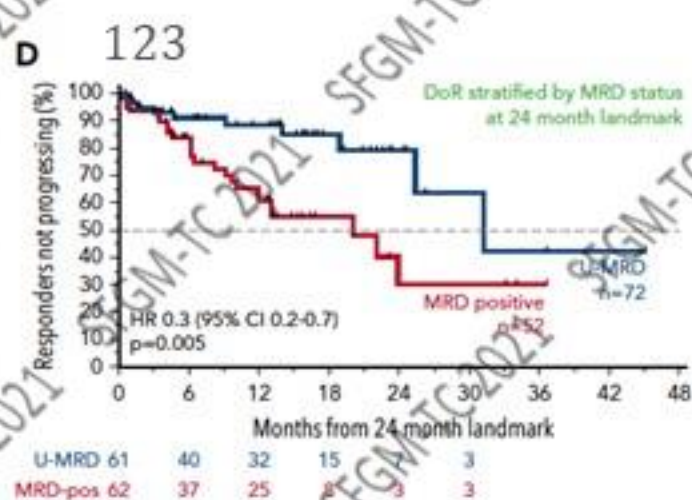
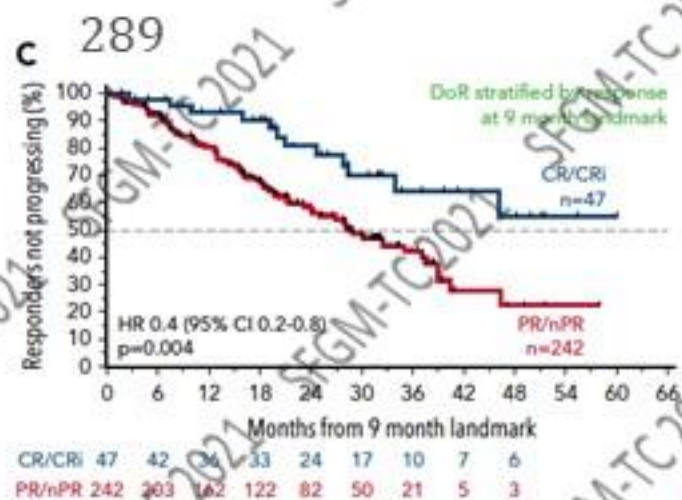
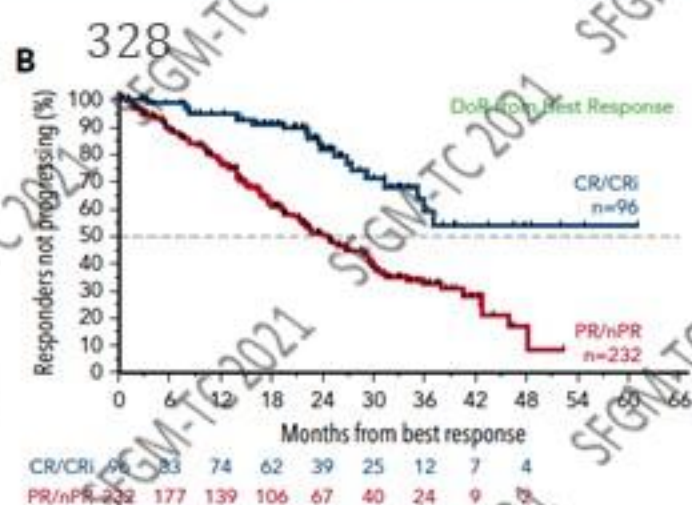
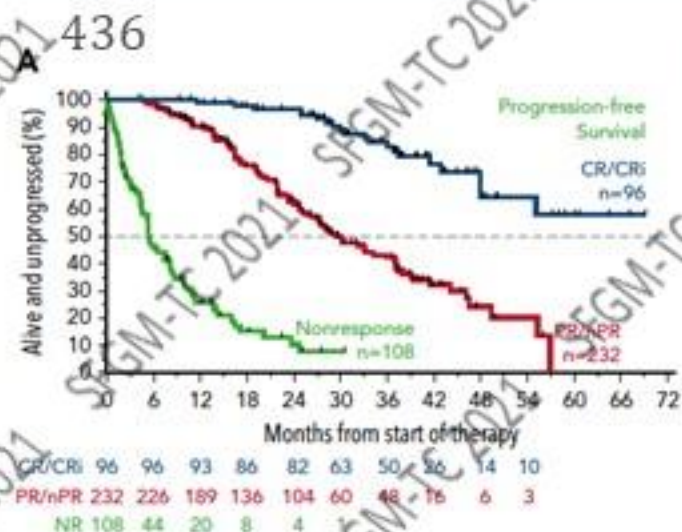
Venetoclax +/- R

N=436

Post BCRi = 34%

R/R BCRi = 26%

PFS = 30 mois



Roberts, Blood, 2019

Critères prédictifs de durée de réponse au Venetoclax

Variable	HR (95% CI) for relapse risk					
	Pretreatment variables only		Pretreatment variables plus response depth (PR vs CR) at 9 mo		Pretreatment variables plus MRD status (pos vs U) at 24 mo	
	All patients (n = 323)	400 mg monotherapy (n = 250)	All patients (n = 311)	400 mg monotherapy (n = 242)	All patients (n = 187)	400 mg monotherapy (n = 159)
Max node size, cm						
≥5 to <10	2.5 (1.73.7)	2.4 (1.53.7)	2.1 (1.43.3)	2.1 (1.33.3)	2.9 (1.75.1)	2.8 (1.65.1)
≥10	2.8 (1.74.6)	2.7 (1.54.8)	2.3 (1.33.9)	2.4 (1.44.3)	3.6 (1.67.9)	3.0 (1.46.8)
Prior therapies						
2 to 3	NI	NI	NI	NI	NI	NI
>3	NI	NI	NI	NI	NI	NI
Fludarabine refractory disease	1.5 (1.12.2)	NI	1.5 (1.12.2)	NI	1.0 (0.61.8)*	NI
Prior BCRi exposure	NI	NI	NI	NI	NI	NI
BCRi refractory disease	2.5 (1.54.1)†	1.9 (1.13.3)	2.3 (1.43.9)†	1.9 (1.13.2)	3.0 (1.65.8)†	2.6 (1.45.0)
TP53 mutation and/or 17p deletion	1.8 (1.22.5)	NI	1.8 (1.22.5)	NI	1.9 (1.03.4)	NI
13q deletion	NI	NI	NI	NI	NI	NI
NOTCH1 mutation	1.8 (1.13.0)	NI	2.0 (1.23.3)	NI	2.6 (1.14.2)	NI
IGHV unmutated	2.1 (1.04.3)	NI	NI	NI	NI	NI
Monotherapy vs combination	0.8 (0.41.5)	—	—	—	—	—
PR/nPR vs CR/CR at 9 mo†	—	—	2.1 (1.14.0)	2.3 (1.010.5)	—	—
PB MRD-pos vs UMRD at 24 mo†	—	—	—	—	3.0 (1.75.2)	3.4 (1.96.3)

Niveau 2

R/R CIT

R/R BTKi



Critères décisionnels

Post thérapeutiques

Réponse Y/N

RC (9 mois)

MRD (24 mois)

Pré-thérapeutiques

BCRi R/R

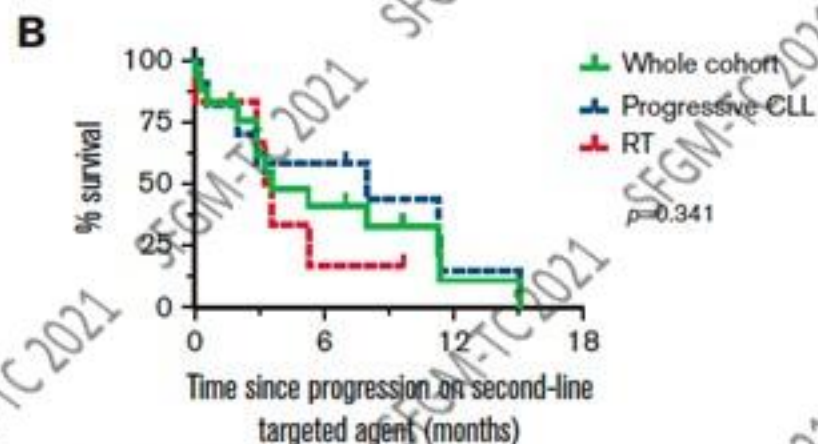
TP53, (NOTCH1)

Bulky ≥5 cm

Caryotype complexe ?

Double réfractaires BCRi/BCL2i

Doubles réfractaires



Lew, Blood Adv, 2021

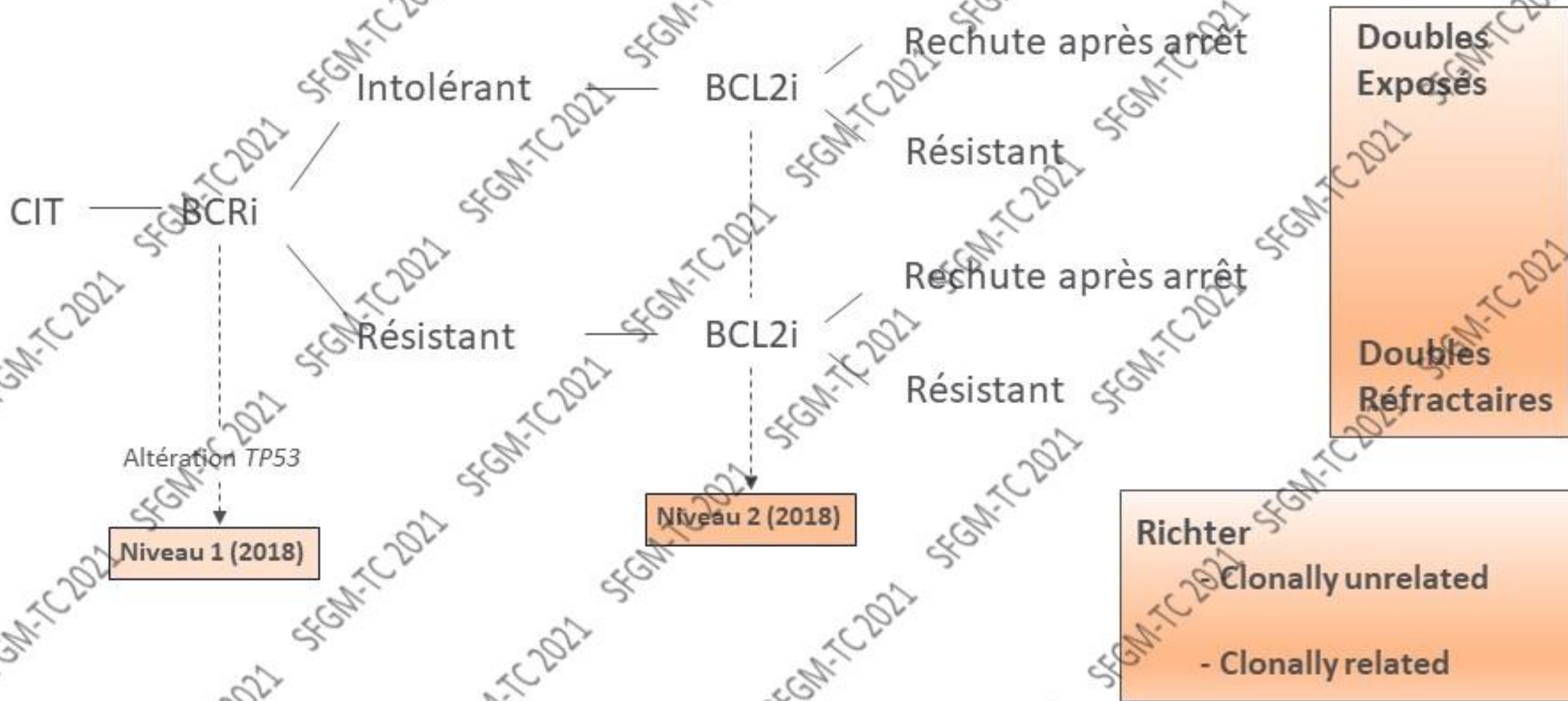
Doubles exposés/réfractaires Post venetoclax

	(n = 44)	(n = 30)	(n = 17)
Nb ligne antérieure	2 (0-8) [†]	4 (1-11)	4 (1-16) [†]
Préexposés BTKi	Non	Oui*	Oui
Préexposés PI3Ki	nd	nd	Non
Altération de TP53	**	***	***
Rattrapage post-vénétoclax	BTKi	BTKi	PI3Ki
ORR (%)	84	54	47
CR (%)	9	10	
FU (m)	10.5	3.5	5
SSP médiane (m)	32	12**	5
SG médiane (m)	ND	ND	ND

* Dont 66 % réfractaires à BTKi, 33 % intolérants à BTKi. ** SSP de 4 mois pour les réfractaires à BTKi, et non atteinte pour les intolérants à BTKi. *** 56 % pour l'ensemble des tests de la cohorte initiale (n = 312), n : n'incluant pas la dernière ligne par vénétoclax.

Mato, Clin Canc Research, 2020

Séquence classique (CIT) > BCRI > BCL2i >>> thérapie cellulaire ?



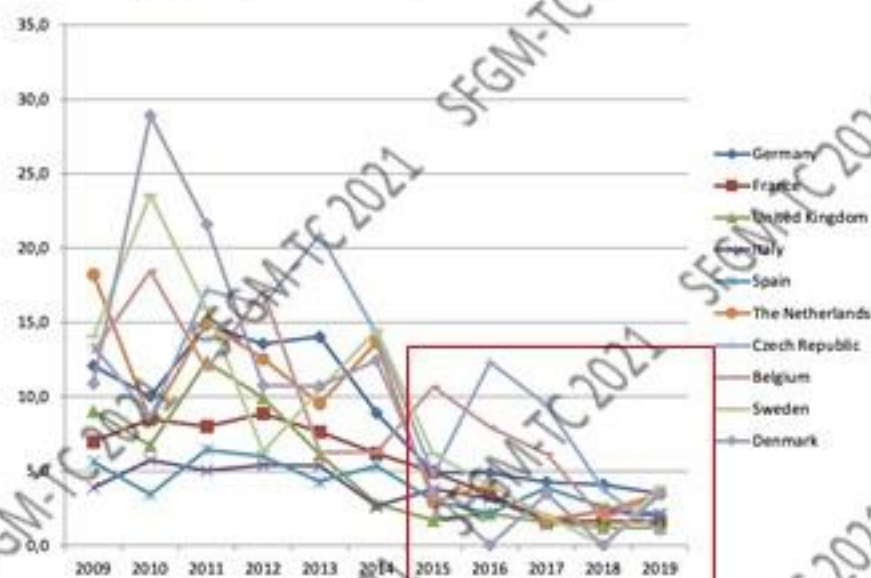
Doubles réfractaires et doubles exposés

BTKi 2nd génération / associations

- **Allogreffe**
- CAR-T/NK
- Bispcifiques

Allogreffe

Allogreffe pour LLC par an et par 10^7 hab.

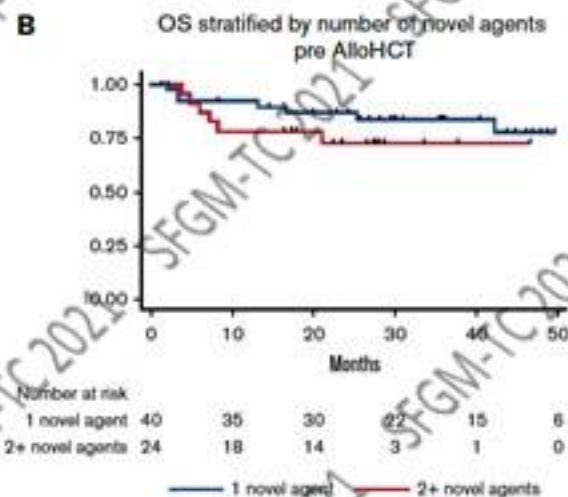
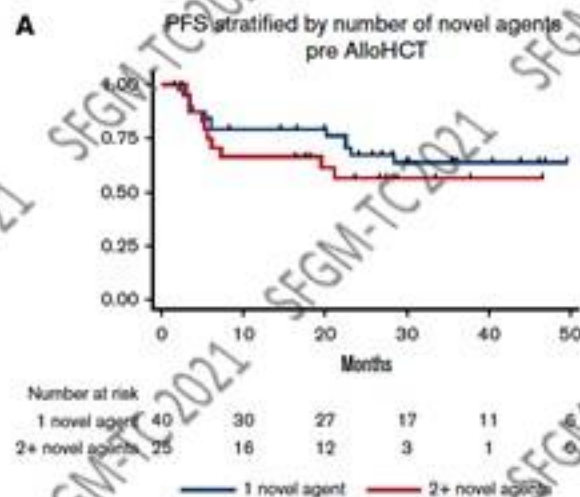


CMWP-EBMT

AlloSCT after Multiple PI (AMPI)

AlloSCT after stopping ibrutinib for intolerance or relapse (ASTIIR)

Venetoclax before and after alloSCT for CLL (VenAC)



Roeker, Blood Adv, 2020

25 with ≥ 2 novel agents

**16 double refractory BCRI/BTKi
Bridge ?**

Doubles réfractaires et doubles exposés

BTKi 2nd génération / associations

- Allogreffe

- **CAR-T/NK**

- Bispcifiques

CAR-T

	Porter (STM 2015)	Frey (JCO 2020)	Gill (ASH 2018)	Turtle (JCO 2017)	Gauthier (Blood 2020)	Siddiqi (ASH 2020)	Wierda (ICML 2021)
Patients (n)	14	38	19	24 (5RT)	19 (4RT)	23 (1RT)	19
CAR-T	CTL019	CART-19	CTL119	JCAR014	JCAR014	JCAR017	JCAR017
With Ibrutinib	no	no	yes	no	yes	no	yes
Median age (y)	66	61	62	61	65	66	61
Previous lines (n)	5 (1-11)	3.5 (2-7)	2 (1-16)	5 (3-9)	5 (1-10)	4 (2-11)	4 (1-10)
Ibrutinib (R/R)	1 (1)	9 (?)	5 (0)	24 (19)	19 (19)	23 (17)	19 (19)
Venetoclax (R/R)	0	1	0	6 (6)	11 (6)	13 (11)	11 (na)
CK (%)	na	na	na	67	74	48	42
TP53 alterations (%)	43	39*	58	Del = 58	Del = 74	Mut = 61 Del = 35	Mut = 82 Del = 42
ORR (%)	57	44*	71*	70	83*	82*	95
CR (%)	29	28*	43*	17	22*	46*	63
MRD(-) BM (%)	29	na	78*	50*	61*	65*	79

*assessment limited to evaluable patients

10 ans de développement
6 études et 156 patients

ORR = 60-95%
CR = 17-63%

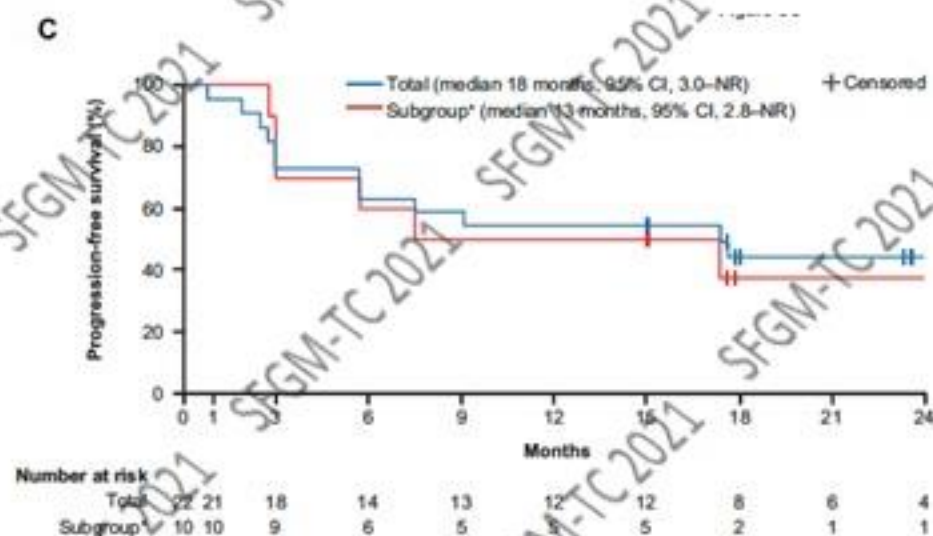
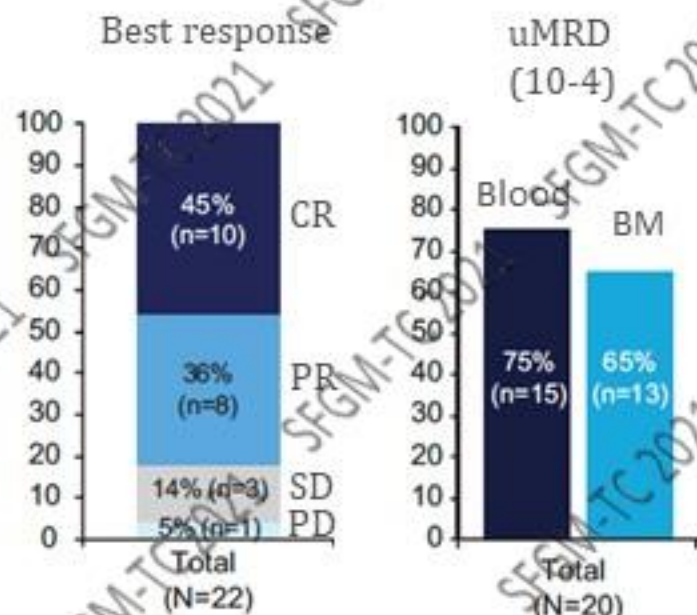
CRS G3 = 5-20%
NT G3 = 5-25%

CAR-T : JCAR17 sans ibrutinib (Transcend 004)

Lisocabtagene maraleucel

Patients (n)	23 (1RT)
CAR-T	JCAR017
With Ibrutinib	no
Median age (y)	66
Previous lines (n)	4 (2-11)
Ibrutinib (R/R)	23 (21)
Venetoclax (R/R)	15 (15)
CK (%)	48
TP53 alterations (%)	Mut = 61 Del = 35

15 doubles exposés
11 doubles réfractaires



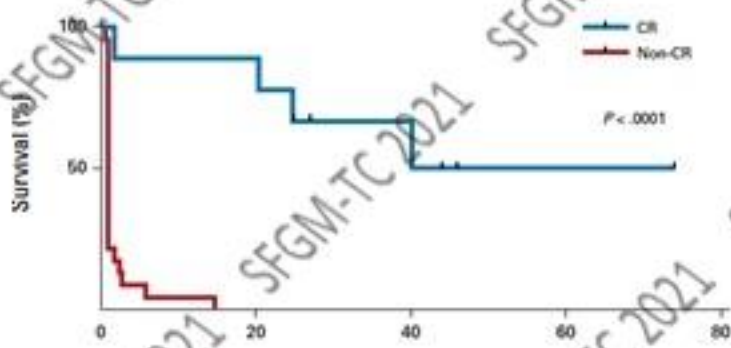
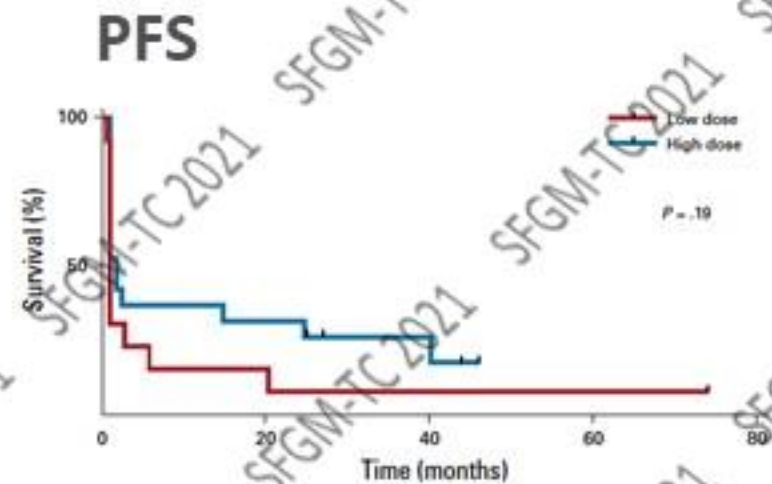
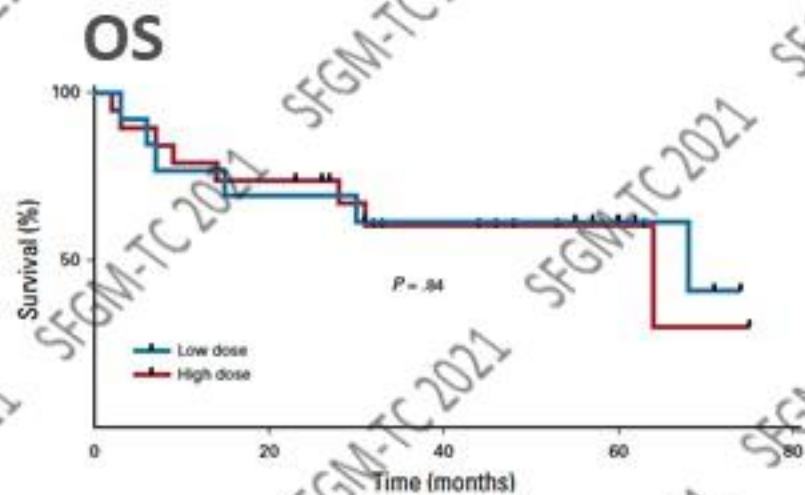
CAR-T : CART-19

N=38 (32 évaluable)

FU = 32 (2-75)

ORR = 44%

CR = 28%



Dysfonction immunitaire

$\gamma\delta$ T cells

- increased number of V δ 1 T cells
- expansion of terminally differentiated memory V γ 9V δ 2 T cells
- low proliferative response of V γ 9V δ 2 cells to stimuli
- reduced V γ 9V δ 2 T cell cytotoxic activity

NK cells

- alterations in activating and inhibitory receptors expression: defective recognition of target cells
- impaired degranulation and cytokine production

iNK cells

- reduced frequency in progressive CLL

Dendritic cells

- Immature phenotype
- Decrease ability to induce T-cell response

Conventional T cells

- increased absolute number
- unbalanced differentiation subset distribution
- decreased TCR repertoire diversity
- impaired immunological synapse
- altered cytokines production
- chronic activation phenotype and overexpression of inhibitory immune checkpoints
- low proliferative capacity
- defective CD8+ T cells cytotoxicity

CLL cells

Tregs

- increased absolute number, especially in advanced disease stages

Th17 cells

- increased absolute number and IL-17 cytokine production
- unbalanced Tregs/Th17 cells

NLC

- Pro-tumorigenic secretion
- Recruitment of myeloid cells and T-cell activation

MDSC

- increased frequency
- recruitment and induction of Tregs

Impact sur les CAR-T autologues

- Exhausted phenotype (CD4)
- Limited proliferative and cytotoxic capacities (CD8)
- Au diagnostic
- Aggravation / thérapeutique

Riches, Blood, 2013

- Capacités d'expansion et de transduction différentes
- Marqueurs d'exhaustion en expansion

Hoffmann, Front Immunol, 2017

- Relation in vitro / efficacité

Fraietta, Nature Med, 2018

CAR-T + ibrutinib ?

	Gill (ASH 2018)	Gauthier (Blood 2020)	Wierda (ICML 2021)
Patients (n)	19	19 (4RT)	19
CAR-T	CTL119	JCAR014	JCAR017
With Ibrutinib	yes	yes	yes
Median age (y)	62	65	61
Previous lines (n)	2 (1-16)	5 (1-10)	4 (1-10)
Ibrutinib (R/R)	5 (0)	19 (19)	19 (19)
Venetoclax (R/R)	0	11 (6)	11 (na)
CK (%)	na	74	42
TP53 alterations (%)	58	Del = 74	Mut = 32 Del = 42
ORR (%)	71*	83*	95
CR (%)	43*	22*	63
MRD(-) BM (%)	78*	61*	79
CRS G3	16%	0%	5%
NT G3	5%	26%	16%
PFS	na	38% @ 12m	na

Amélioration des capacités fonctionnelles ?
Meilleurs résultats ?
Moins de CRS ?

NB : 2 fatal cardiac events

CAR-NK

Table 1. Characteristics of the Patients at Baseline.*

Patient No.	Dose Level cells/kg	Age	Sex	Diagnosis	Previous Lines of Therapy no.	Failure of HSCT, Ibrutinib, or Venetoclax
1	1x10 ⁶	47	Male	Transformed follicular lymphoma	3	Autologous HSCT
2	1x10 ⁶	59	Male	Diffuse large B-cell lymphoma	6	NA
3	1x10 ⁶	59	Female	Chronic lymphocytic leukemia	4	Ibrutinib, venetoclax
4	0.25x10 ⁶	56	Male	Chronic lymphocytic leukemia	5	Ibrutinib
5	1x10 ⁶	61	Male	Chronic lymphocytic leukemia with Richter's transformation	5	Ibrutinib
6	1x10 ⁶	59	Female	Accelerated chronic lymphocytic leukemia	5	Ibrutinib, venetoclax
7	1x10 ⁶	66	Female	Chronic lymphocytic leukemia	4	Ibrutinib
8	1x10 ⁷	64	Male	Transformed follicular lymphoma	1	Autologous HSCT
9	1x10 ⁷	70	Male	Diffuse large B-cell lymphoma	4	Autologous HSCT
10	1x10 ⁷	61	Female	Transformed follicular lymphoma	4	Autologous HSCT
11	1x10 ⁷	60	Male	Follicular lymphoma (focally grade 3B)	4	NA

CAR:

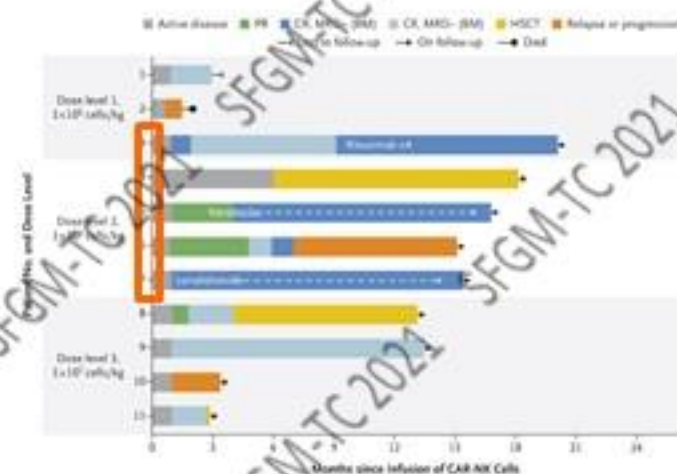
Anti-CD19: recognition
 CD28, CD3ε: signalling endo domain
 IL15: *in vivo* (expansion)
 iCasp9: (suicide)

Cellules NK allogénique (Cord Blood)
 HLA-agnostic
 (+/- KIR matching)
 Lymphodepletion FC

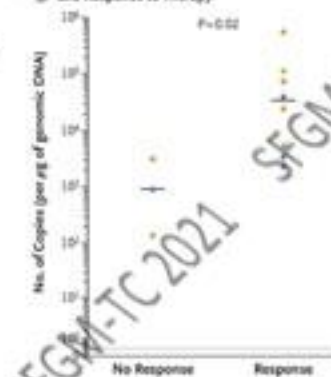
Median FU = 14 m (2-20)

ORR = 73% (n=8)

CR = 3 CLL and 4 lymphoma



Vector Transgene Copies, According to Dose and Response to Therapy



Doubles réfractaires et doubles exposés

BTKi 2nd génération / associations

. Allogreffe

. CAR-T/NK

Bispécifiques

Bispécifiques

NCT00676871	CLL	MEDI-538 (blinatumomab)	
NCT00014560	NHL/CLL	4G7xH22	
NCT04923048	NHL/CLL	G8261 CD3xCD22	
NCT04540796	NHL/CLL	JNJ-75348780 CD3xCD22	
NCT02743546	NHL/CLL	JNJ-64052781 CD3xCD19 duvortuxizumab and ibrutinib	
NCT04763083	MCL/CLL	NVG-111 CD3xROR1	
NCT02290951	NHL/CLL	REGN1979 CD3xCD20 (odronextamab) IV/SC	
NCT02568553	NHL/CLL	CD3xCD19 blinatumomab + lenalidomide	
NCT04806035	NHL/CLL	TG-1801 CD47xCD19 + anti CD20 (ublrituximab)	
NCT04623541	CLL	GEN3013 CD3xCD20 (Epcoritamab) phase 1b/2	R/R CLL ≥2L dont BCRI
NCT05091424	CLL	CD3xCD20 Mosunetuzumab SC phase Ib	R/R CLL ≥2L dont BCRI et/ou VEN

Y-a-t il une place pour la thérapie cellulaire dans la LLC ?

- Oui, mais :

- Laquelle ?

- Allogreffe : résultats robustes mais toxicité connue
- CAR-T : résultats encore discutables (protocoles)

- Quand ?

- Niveau 1 : non, attendre la ligne suivante
- Niveau 2 : oui, selon critères biologiques/réponse
- Doubles réfractaires (attention à la définition) ? oui

- Sachant que :

- Les lignes changent dans la LLC
- La concurrence est rude ... BCRi non covalents, associations, bispécifiques