



Thérapies innovantes en hématologie

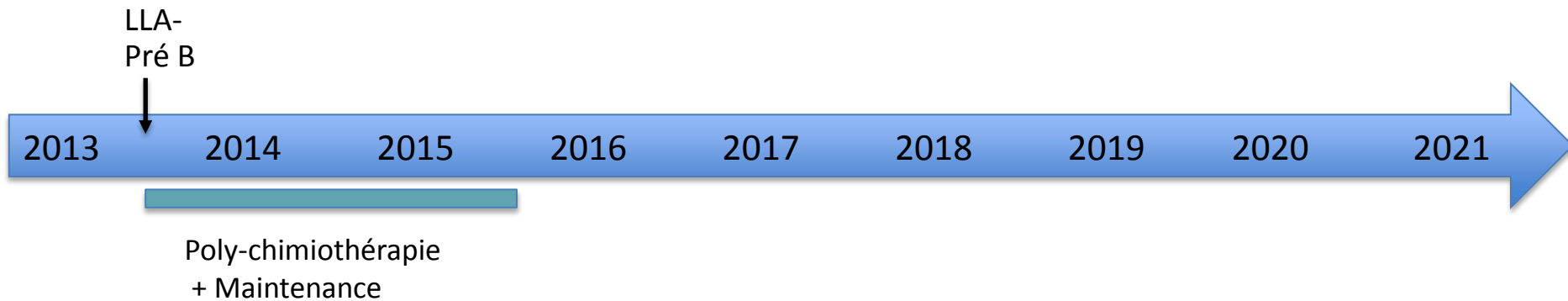
Prof Frédéric Baron
Hématologie clinique & GIGA-I3
CHU-ULiège



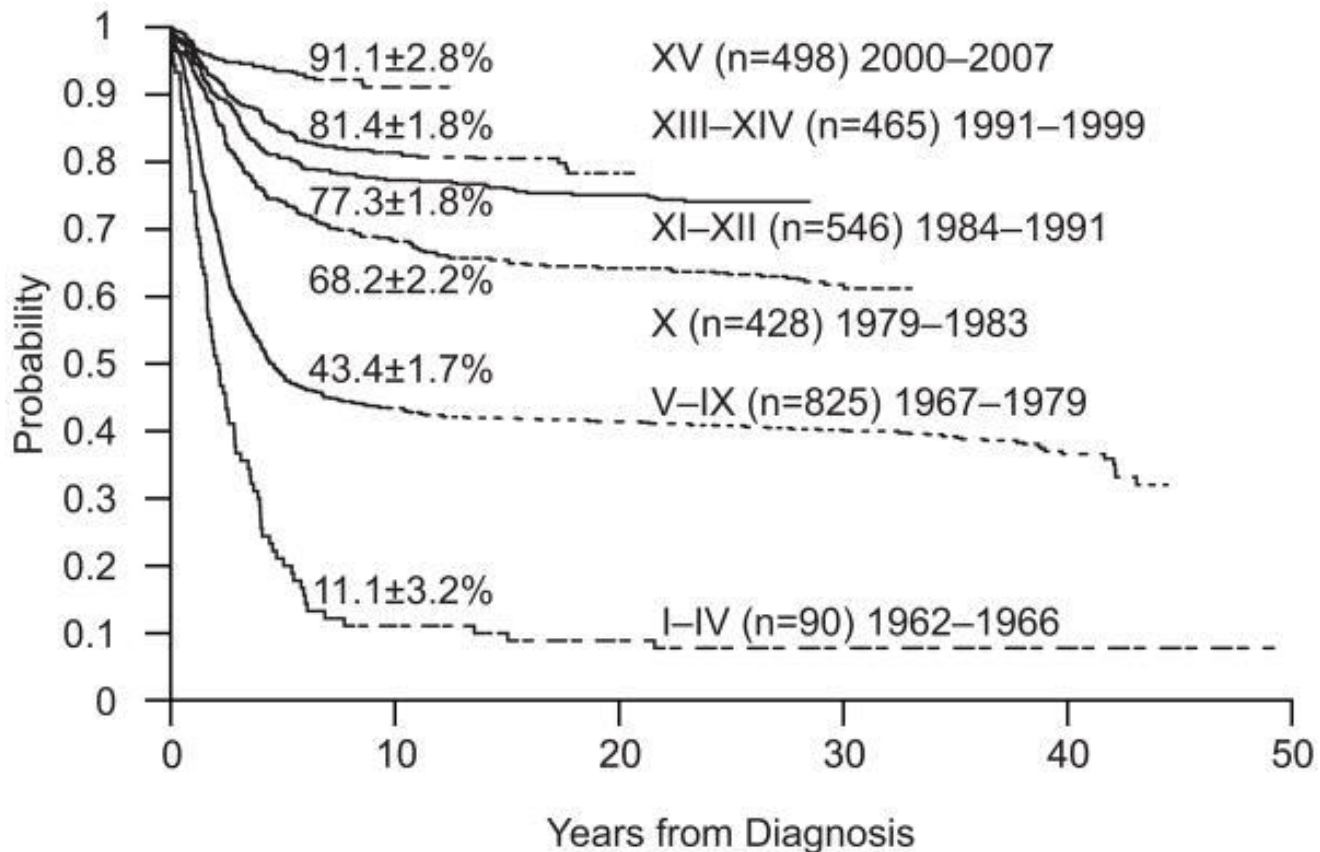
Cas 1

Leucémie lymphoblastique aigue (LLA) enfant

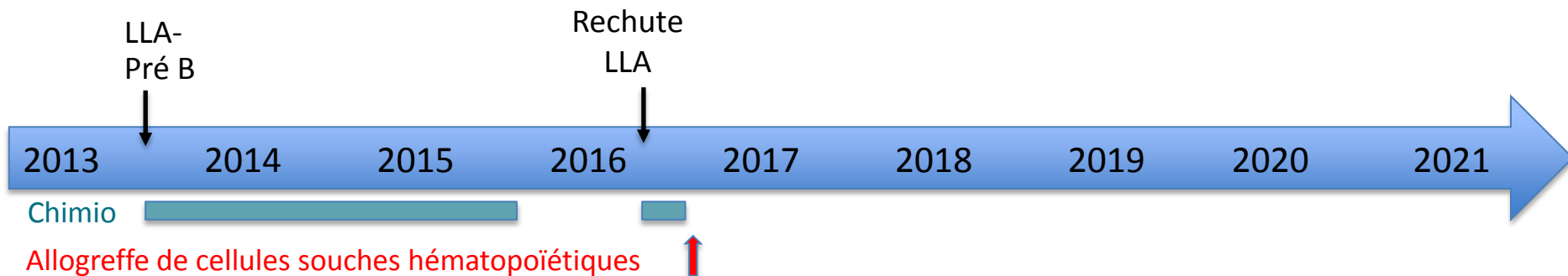
Cas clinique



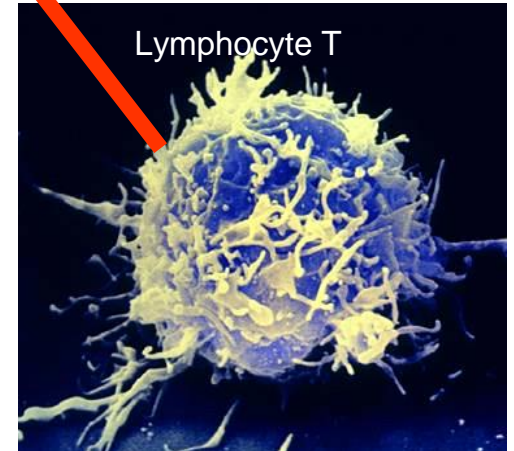
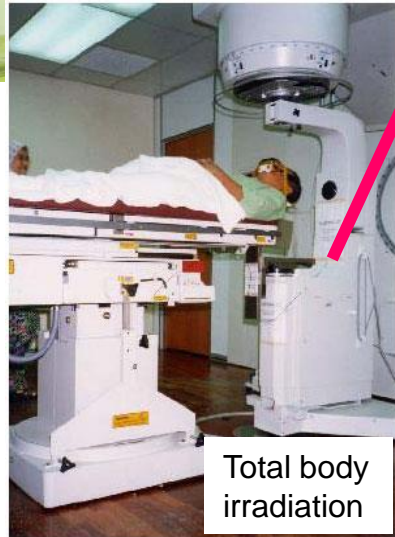
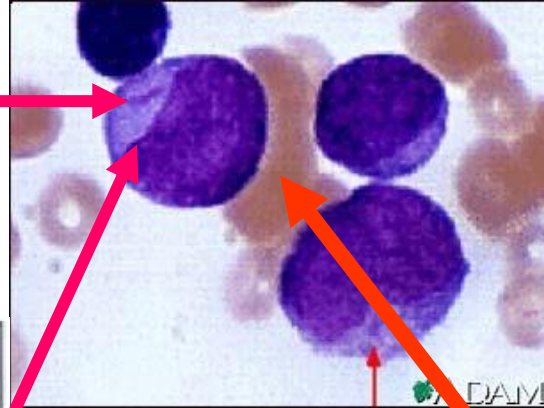
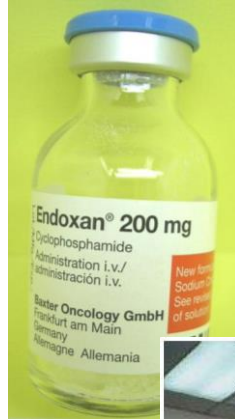
Evolution survie LLA enfants (St Jude Children Memphis)



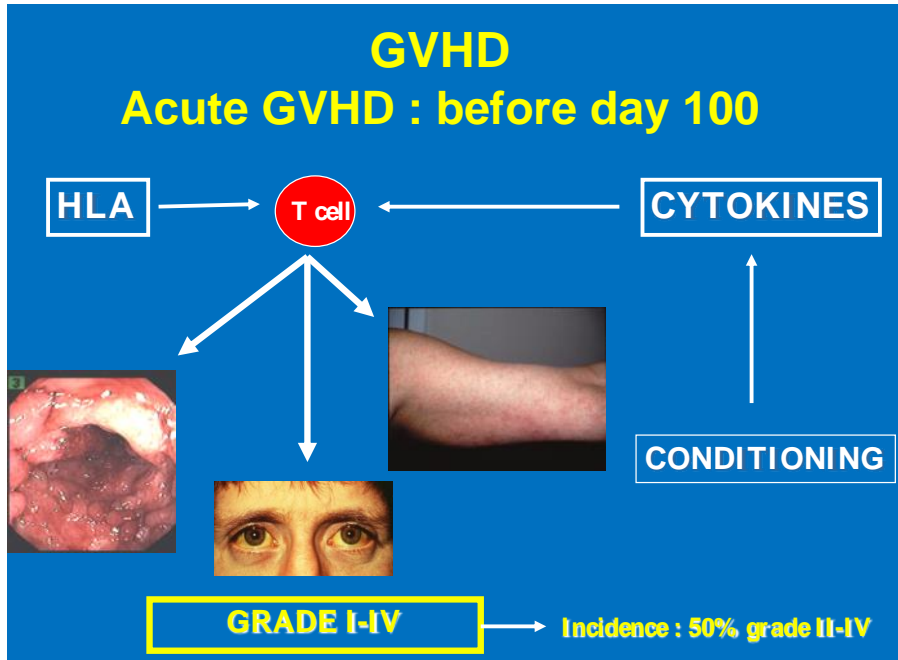
Cas clinique



Allogreffe de cellules souches hématopoïétiques



Maladie du greffon contre l'hôte (GVHD)

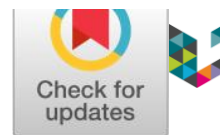


Chronic GVHD

This section displays various clinical manifestations of Chronic GVHD, each with a corresponding image and label:

- Ocular sicca (eye image)
- Oral ulcers (mouth image)
- Nail dystrophy (nail image)
- Skin sclerosis (skin image)
- Deep sclerosis (skin image)
- Bronchiolitis obliterans (lung histology image)
- Loss of bile ducts (liver histology image)
- Fasciitis (muscle image)
- Skin ulcers (skin image)

A central image of a man's torso shows skin manifestations. A green box lists associated symptoms: Infections, Disability, Quality of life, Endocrine, Metabolism, Nutrition, Pain. Another green box at the bottom right states: Spectrum of manifestations in chronic GVHD.

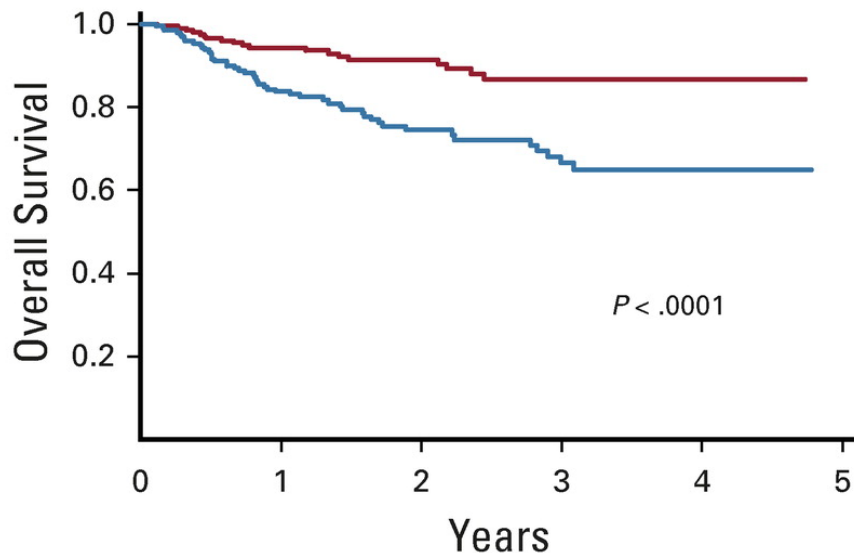


original reports

Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study

Christina Peters, MD¹; Jean-Hugues Dalle, MD, PhD²; Franco Locatelli, MD, PhD³; Ulrike Poetschger, PhD⁴; Petr Sedlacek, MD⁵; Jochen Buechner, MD, PhD⁶; Peter J. Shaw, MD⁷; Raquel Staciuk, MD⁸; Marianne Ifversen, MD, PhD⁹; Herbert Pichler, MD¹; Kim Vettenranta, MD, PhD¹⁰; Peter Svec, MD, PhD¹¹; Olga Aleinikova, MD, PhD¹²; Jerry Stein, MD¹³; Tayfun Güngör, MD¹⁴; Jacek Toporski, MD¹⁵; Tony H. Truong, MD, MPH¹⁶; Cristina Diaz-de-Heredia, MD¹⁷; Marc Bierings, MD, PhD¹⁸; Hany Ariffin, MD, PhD¹⁹; Mohammed Essa, MD²⁰; Birgit Burkhardt, MD, PhD²¹; Kirk Schultz, MD²²; Roland Meisel, MD²³; Arjan Lankester, MD, PhD²⁴; Marc Ansari, MD²⁵; and Martin Schrappe, MD, PhD,²⁶ on behalf of the IBFM Study Group; Arend von Stackelberg, MD,²⁷ on behalf of the IntReALL Study Group; Adriana Balduzzi, MD,²⁸ on behalf of the I-BFM SCT Study Group; Selim Corbacioglu, MD,²⁹ on behalf of the EBMT Paediatric Diseases Working Party; and Peter Bader, MD³⁰

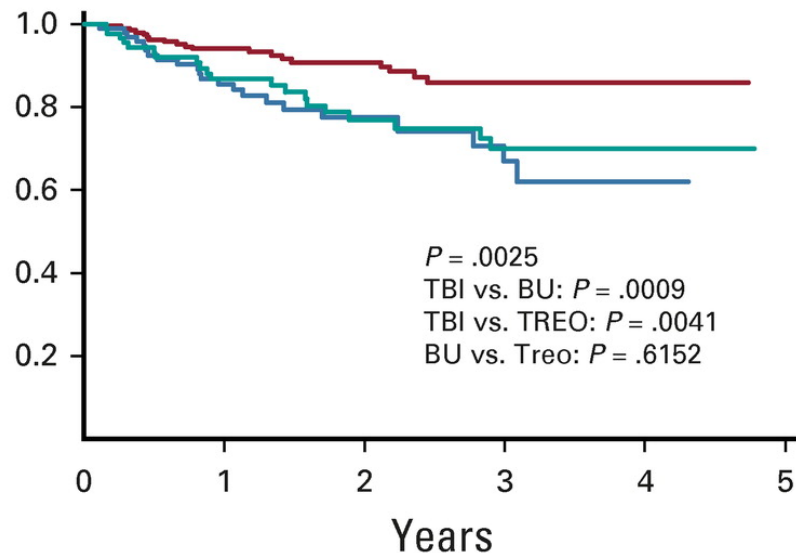
Intention-to-Treat Population



At risk	212	173	105	65	27
	201	145	85	47	17

	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

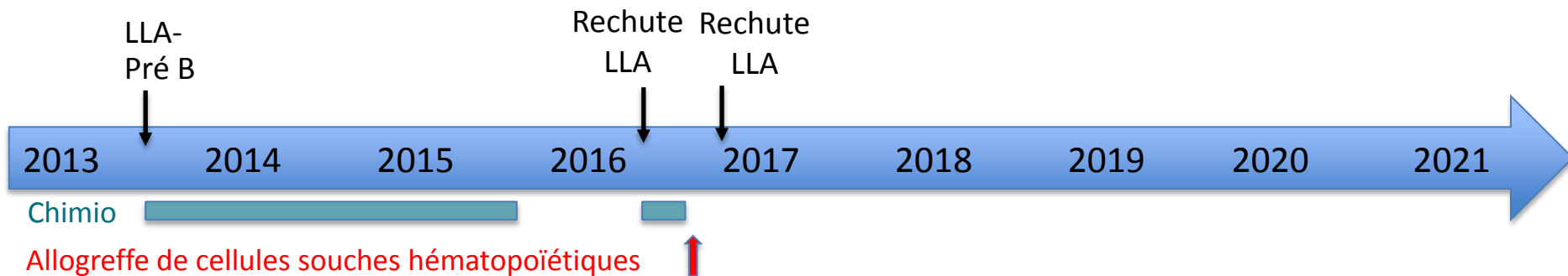
Modified As-Treated Population



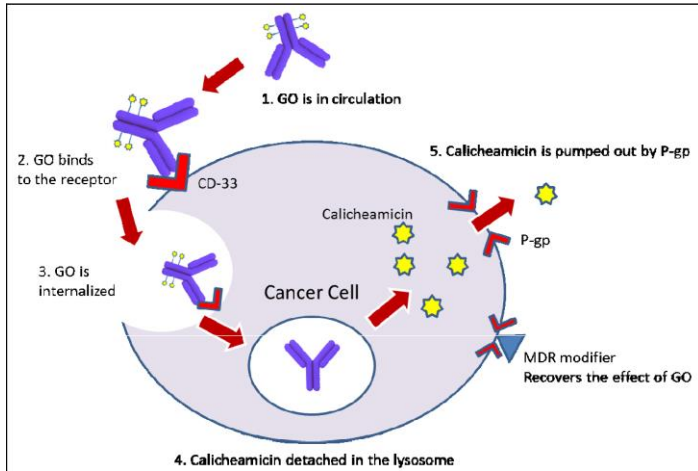
	194	161	97	61	25
	96	72	38	19	5
	90	67	44	27	11

	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
Treo	90	90	20	0.77 (0.65-0.85)

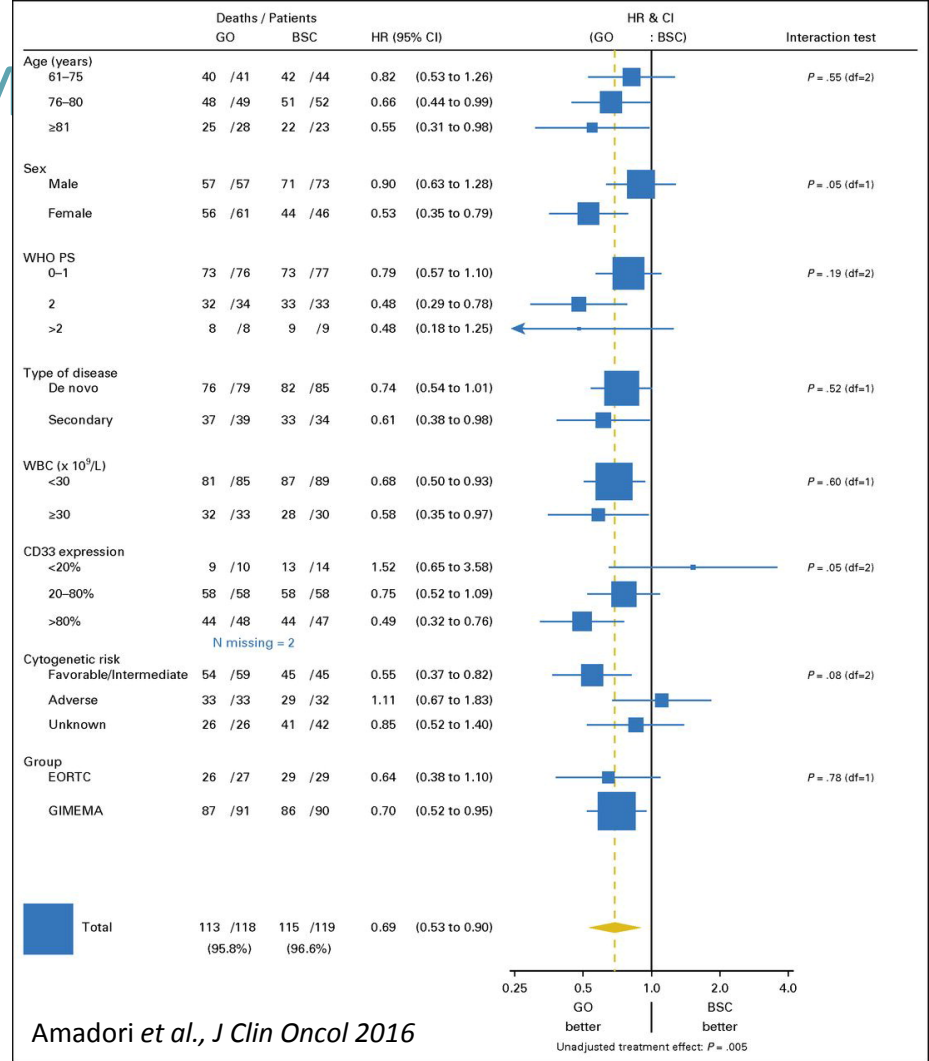
Cas clinique



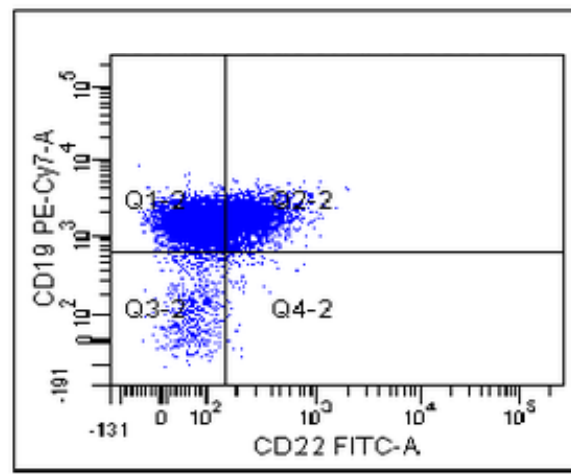
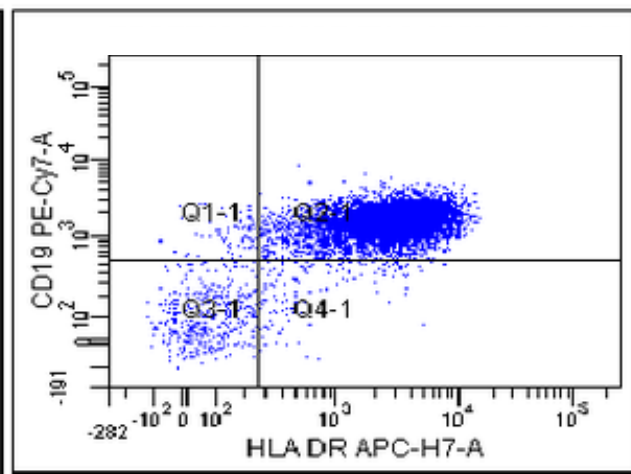
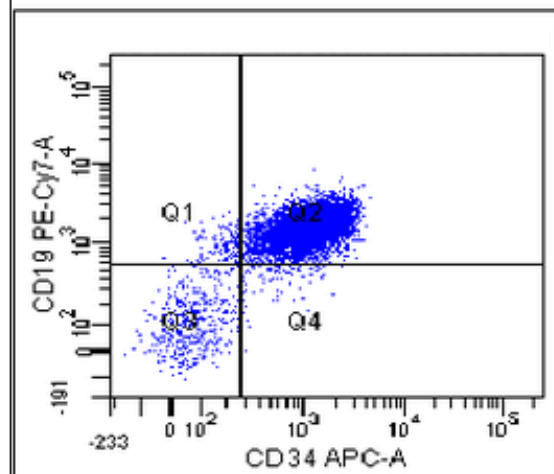
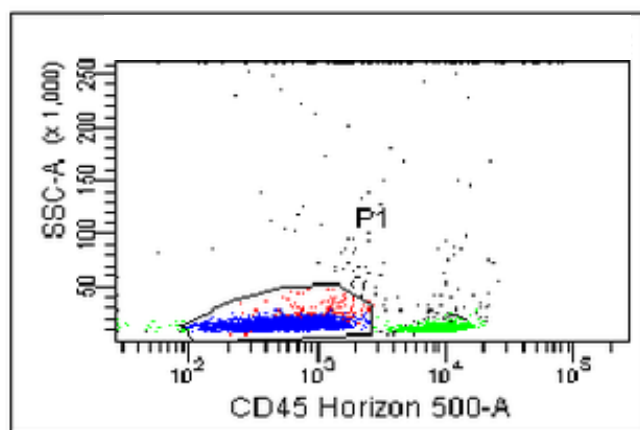
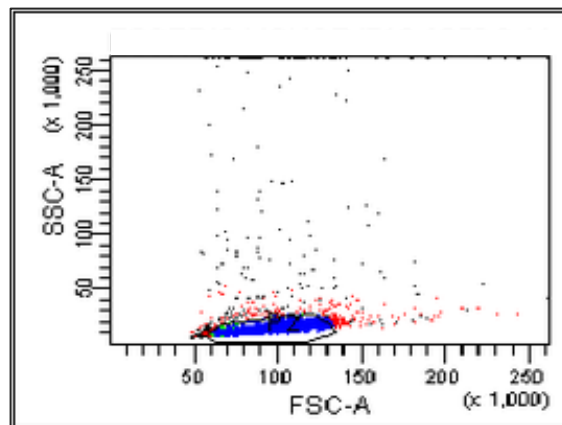
Gemtuzumab ozogamycin (M



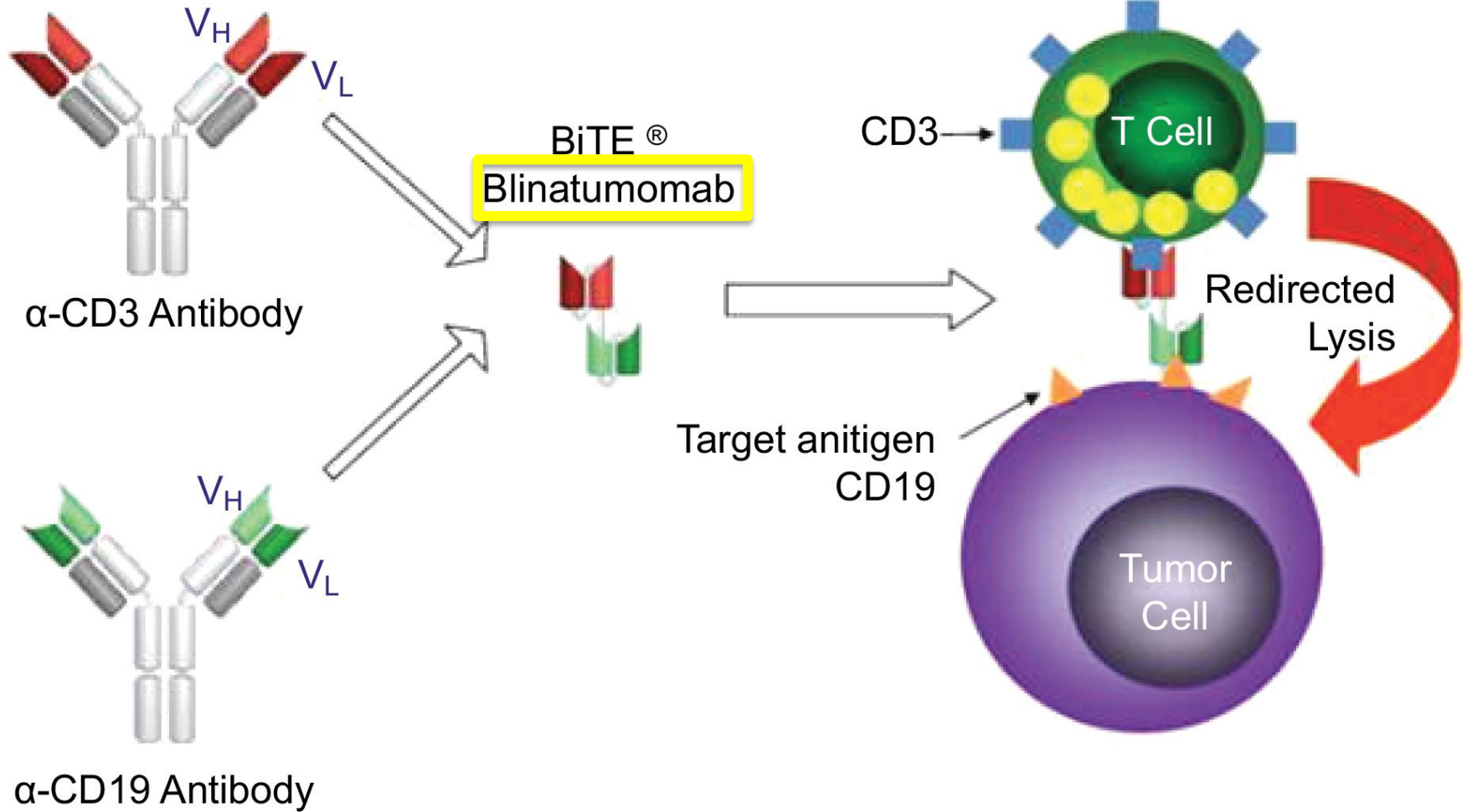
Shefet-Carasso *et al.*



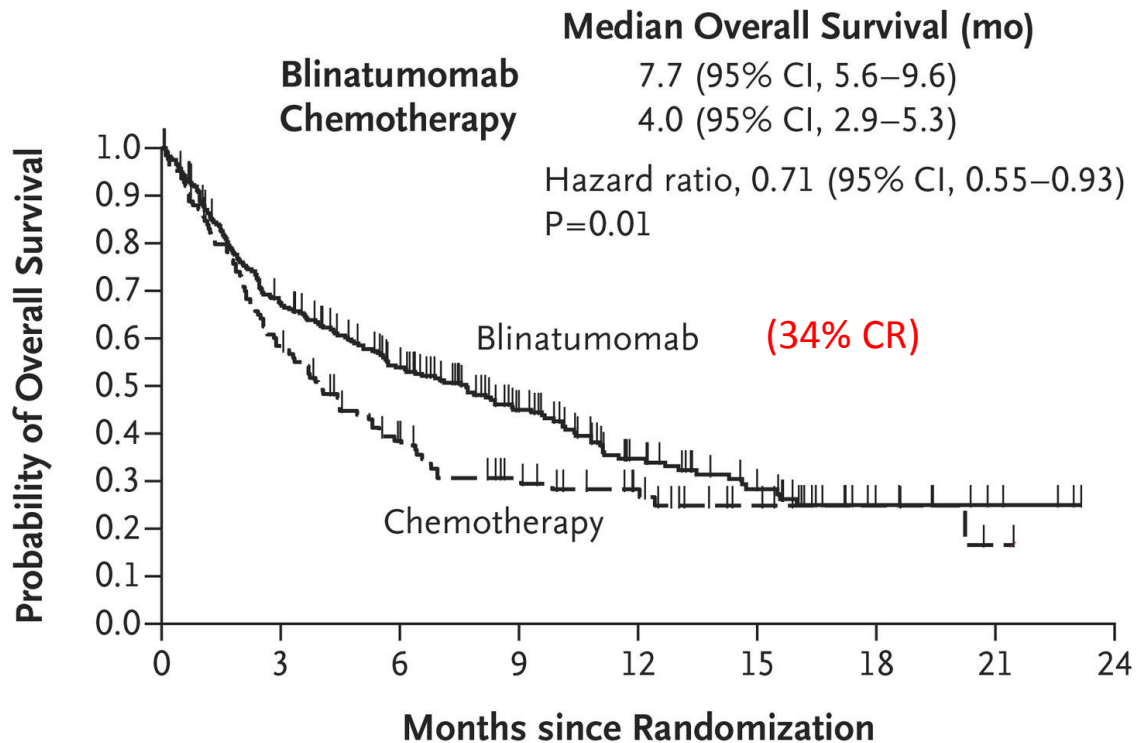
Amadori *et al.*, *J Clin Oncol* 2016



Bi-specific T-cell engager (BiTE)



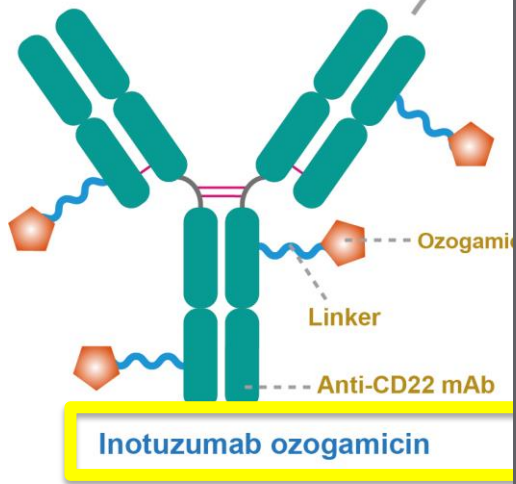
A Overall Survival



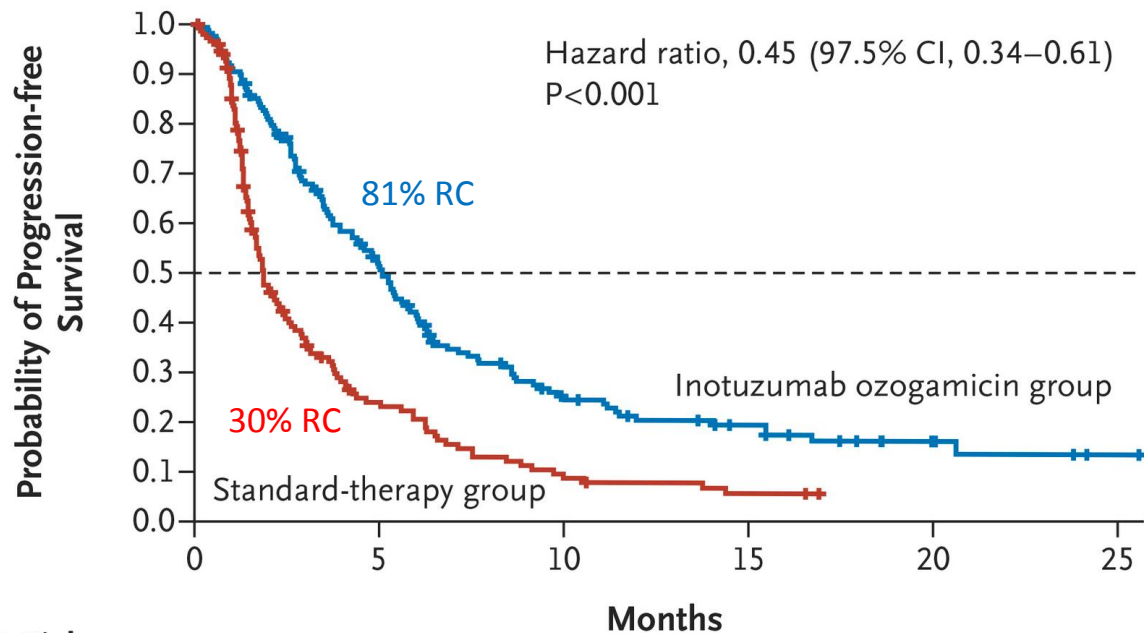
No. at Risk

Blinatumomab	271	176	124	79	45	27	9	4	0
Chemotherapy	134	71	41	27	17	7	4	1	0

Kantarjian et al.
NEJM 2017



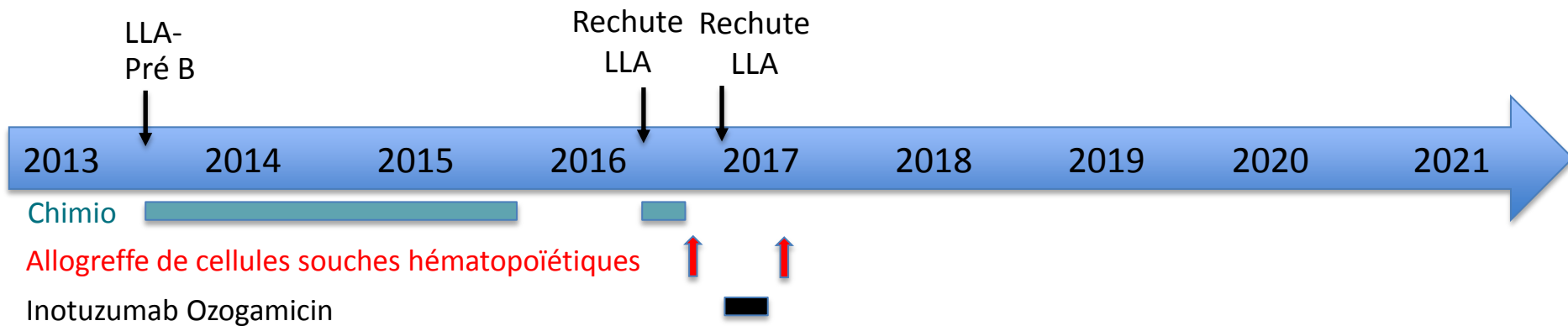
B Progression-free Survival



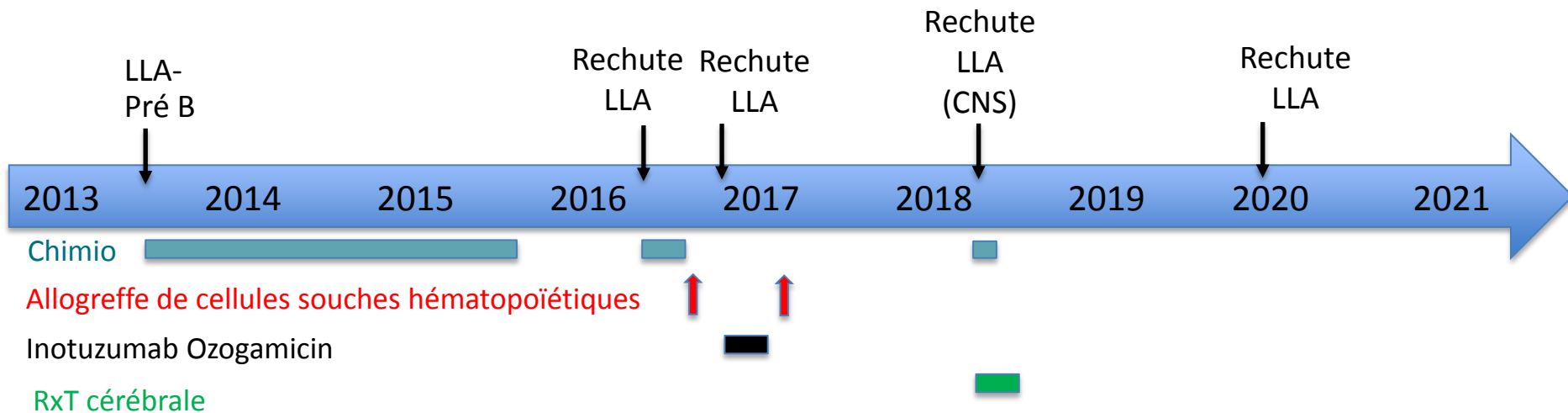
No. at Risk

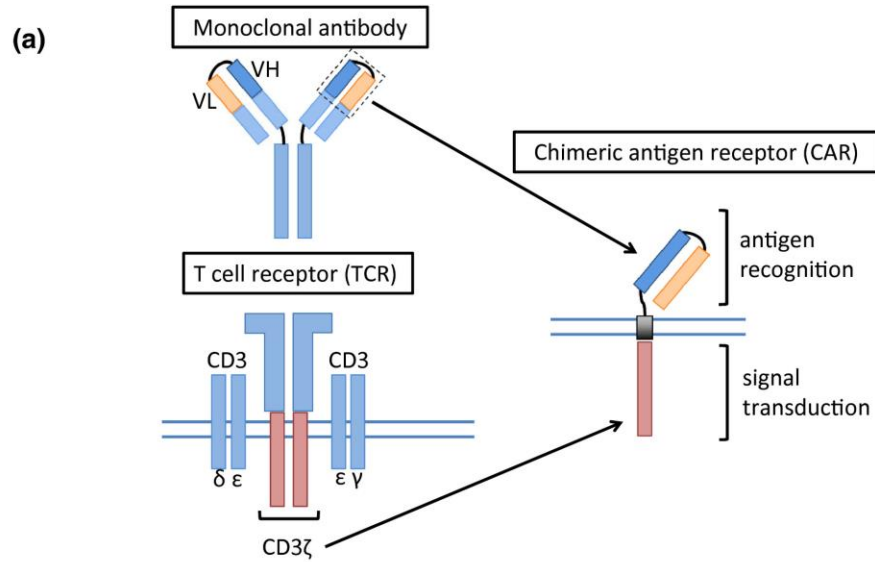
Inotuzumab ozogamicin group	164	72	28	16	6	1
Standard-therapy group	162	24	6	2	0	0

Cas clinique

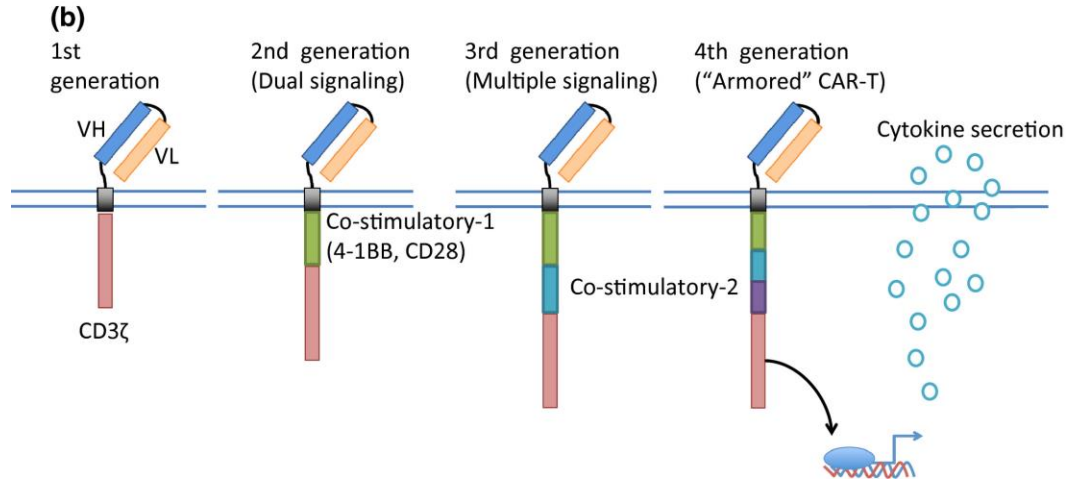


Cas clinique



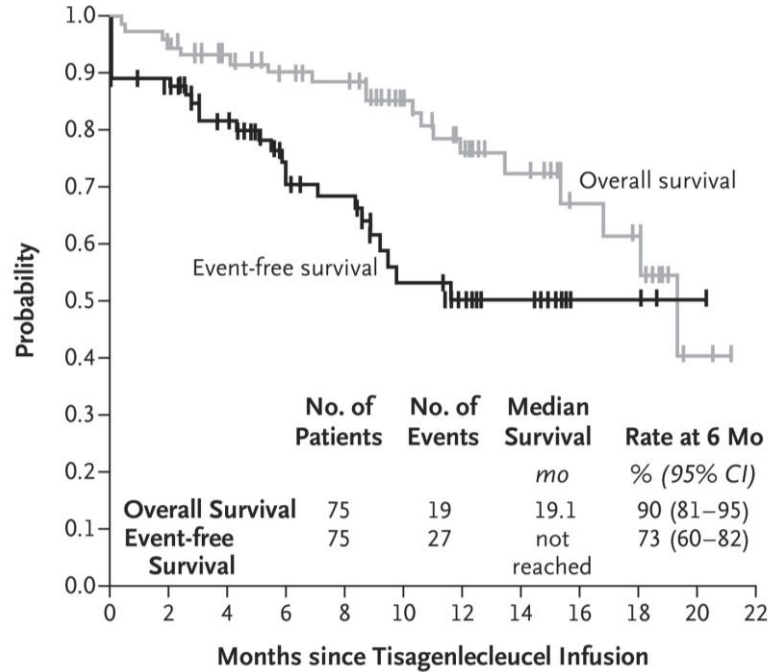


Chimeric antigenic receptor (CARs) (CD19) T cells





B Event-free and Overall Survival

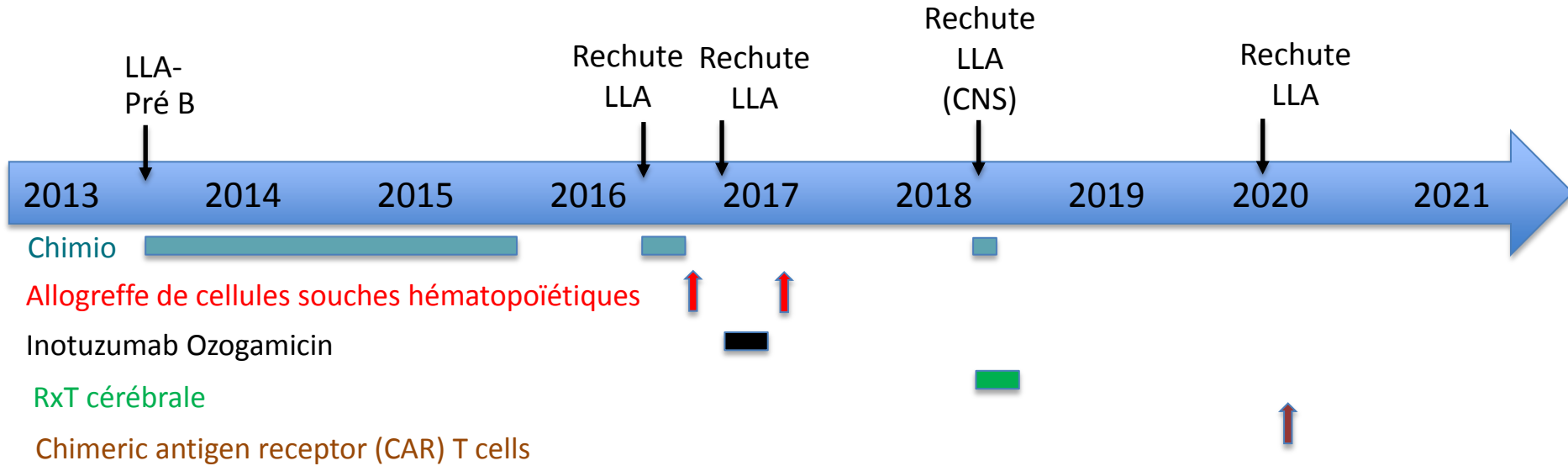


No. at Risk

Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

Maude *et al.*,
NEJM 2018

Cas clinique





Préparation

J-60	Collecte PBMC
J-55	Chimiothérapie
J-6	Unité stérile
J-5	Cyclophosphamide + fludarabine
J-4	Cyclophosphamide + fludarabine
J-3	Cyclophosphamide + fludarabine
J 0	Infusion CAR

Complications des CARs (CRS)



20%

Symptôme ou signe	Grade 1	Grade 2	Grade 3	Grade 4
Paramètres				
Température $\geq 38.0^{\circ}\text{C}$	oui	oui	oui	oui
Hypotension - adulte ≤ 100 mmHg, - enfant $< 70 + (2 \times \text{âge (en années)})$	non	Ne nécessitant pas d'amines (réponse au remplissage)	Nécessitant une amine vasopressive (hors vasopressine) Noradrénaline ≤ 0.25 $\mu\text{g}/\text{kg}/\text{min}$ sur 24h	Nécessitant Noradrénaline > 0.25 $\mu\text{g}/\text{kg}/\text{min}$ sur 24h ou ≥ 0.50 $\mu\text{g}/\text{kg}/\text{min}$ ≥ 1 h ou plusieurs vasopresseurs (hors vasopressine)
Hypoxie (besoin d'O₂ pour SpO₂ > 90%)	non	FiO ₂ < 40% ou oxygénothérapie aux lunettes < 6 L	FiO ₂ $\geq 40\%$ ou oxygénothérapie au masque ou lunettes haut débit	Pression positive requise (CPAP, BiPAP, ventilation mécanique)

Complications des CARs (ICAN)



Symptôme ou signe	Grade 1	Grade 2	Grade 3	Grade 4
Score ICE	7-9 (déficience légère)	3-6 (déficience modérée)	0-2 (déficience sévère)	Score impossible à réaliser
Niveau de conscience	Eveil spontané	Eveil à la voix	Eveil seulement sur stimulus tactile	Eveil requérant des stimuli tactiles vigoureux ou répétitifs, stupeur ou coma
Convulsion	NA	NA	Crise convulsive partielle ou généralisée ou crise non convulsive à l'EEG, avec réponse rapide après intervention thérapeutique	Crise convulsive prolongée (> 5 min) ou convulsions cliniques ou électriques répétitives sans retour à la ligne de base avec traitement
Signes moteurs	NA	NA	NA	Atteinte motrice focale profonde telle qu'hémiplégie ou parapésie
Augmentation de la pression intracrânienne*	NA	NA	Œdème focal/local à l'imagerie neurologique	Œdème cérébral diffus, signes de décérébration ou décortication, paralysie nerf VI, œdème papillaire ou triade de Cushing

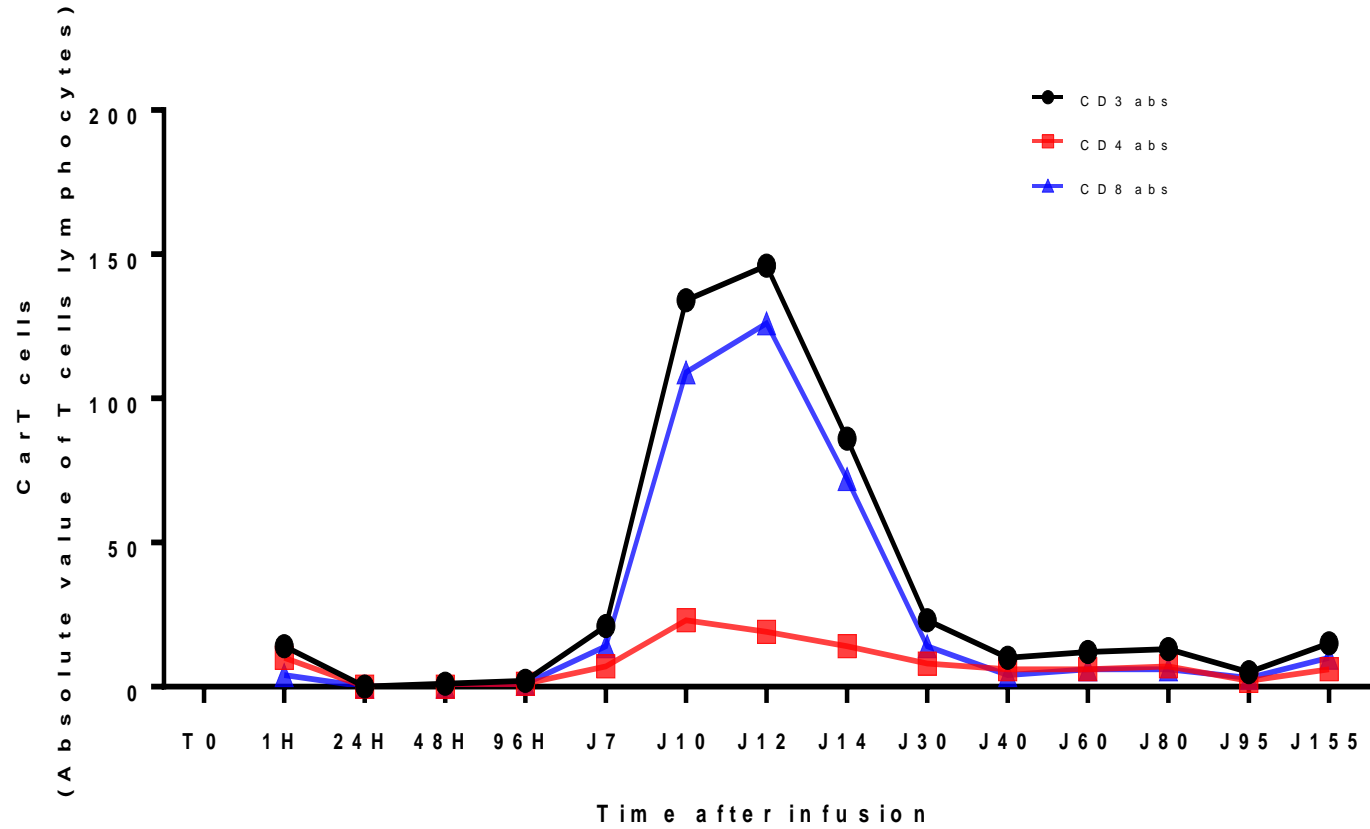


Préparation

J-60	Collecte PBMC
J-55	Chimiothérapie
J-6	Unité stérile
J-5	Cyclophosphamide + fludarabine
J-4	Cyclophosphamide + fludarabine
J-3	Cyclophosphamide + fludarabine
J 0	Infusion CAR

Complications

J2	CRS grade 1
J3	CRS grade 2
J12	QS
Cytopenias	
B-cell aplasia	



Cas clinique # 2

Maladie de Hodgkin

Cas clinique



HK scléro-
nodulaire
stade IV



RP



Progression

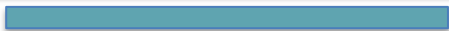


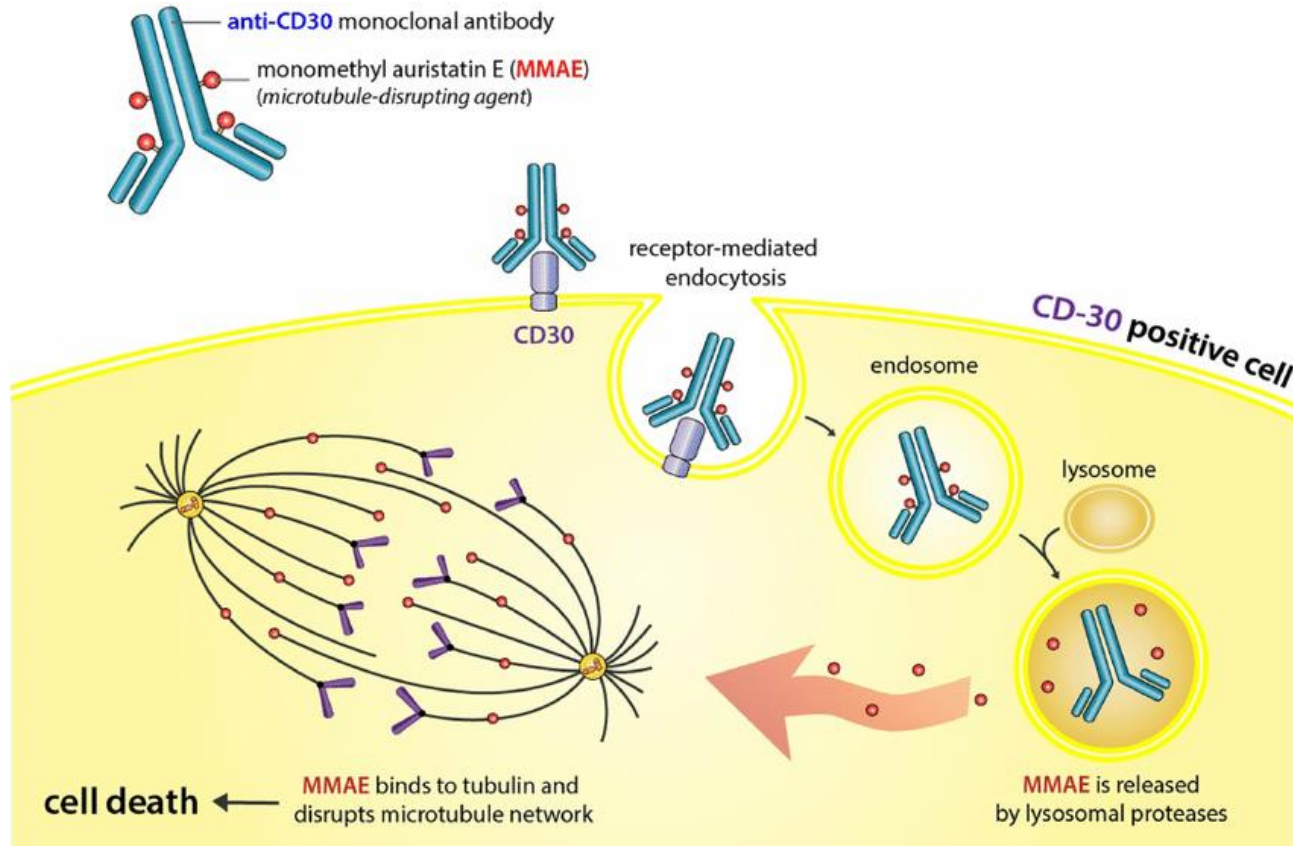
2019

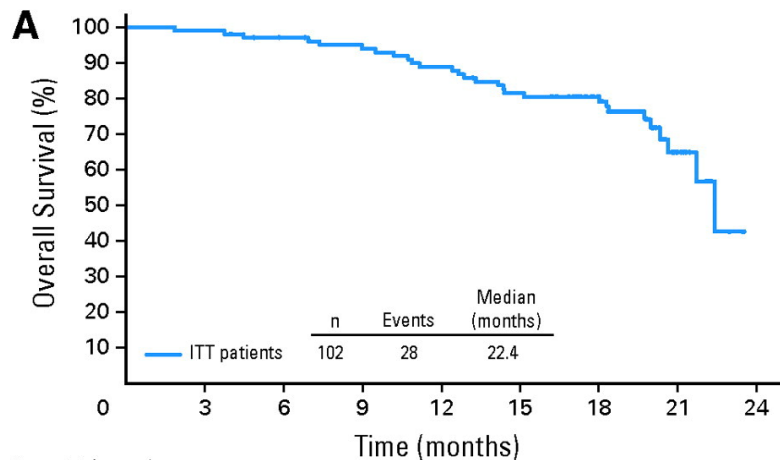
2020

Jan. Fev. Mar. Avr. Mai. Jun. Juil. Aout Sept. Oct. Nov. Dec Jan. Fev. Mar. Avr. Mai. Jun. Jui. Aout Sept. Oct. Nov. Dec

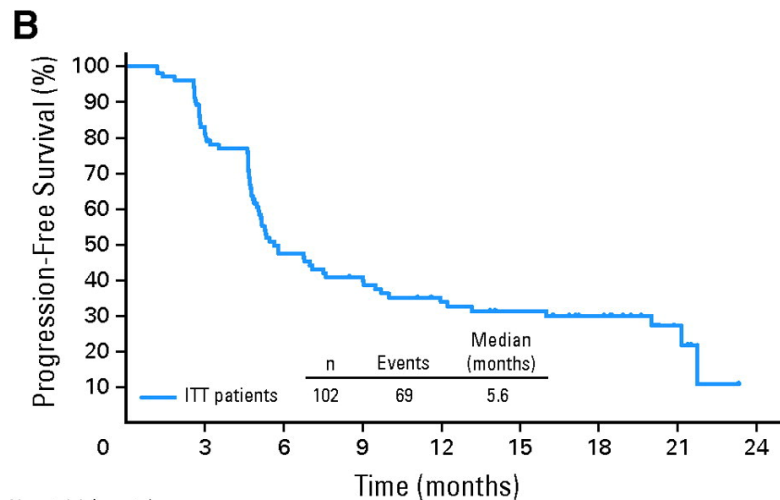
Chimio







No. at risk (events)
102 (0) 101 (1) 96 (3) 91 (6) 86 (11) 78 (18) 59 (19) 14 (26) 0 (28)



No. at risk (events)
102 (0) 80 (19) 43 (51) 36 (57) 27 (63) 23 (65) 18 (66) 5 (67) 0 (69)

Younes *et al.*, J
Clin Oncol 2012



Cas clinique

HK scléro-
nodulaire
stade IV

Progression

RP

RC

2019

2020

Jan. Fev. Mar. Avr. Mai. Jun. Jul. Aout Sept. Oct. Nov. Dec Jan. Fev. Mar. Avr. Mai. Jun. Jul. Aout Sept. Oct. Nov. Dec

Chimio

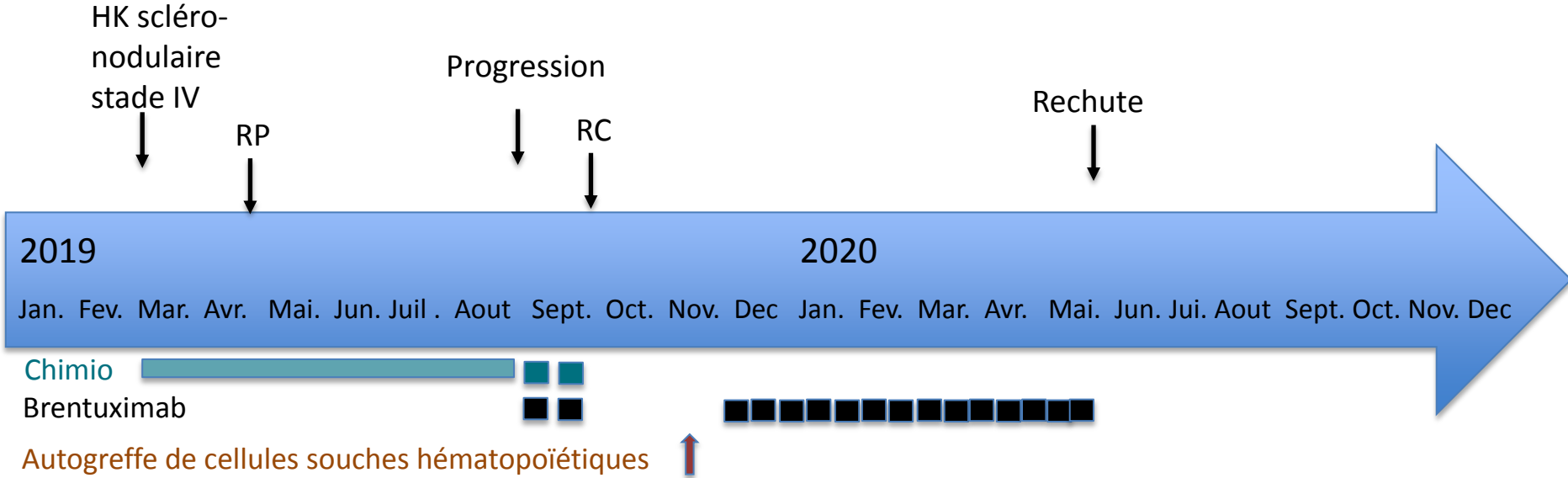
Brentuximab

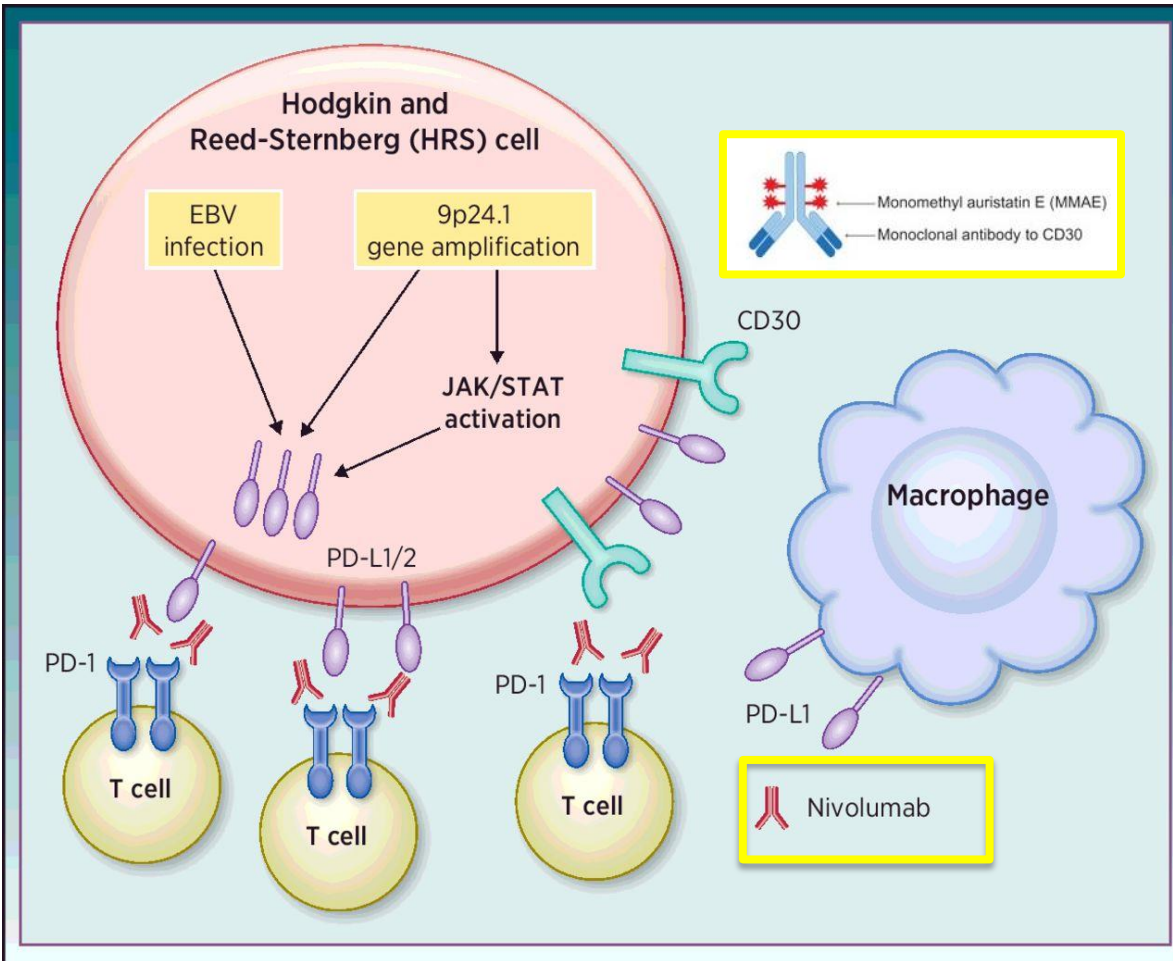
Autogreffe de cellules souches hématopoïétiques

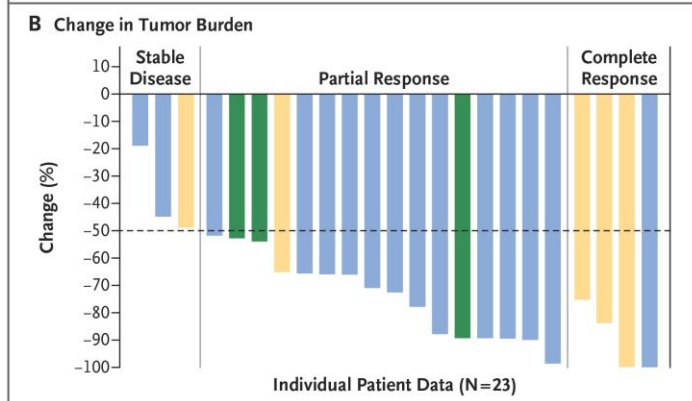
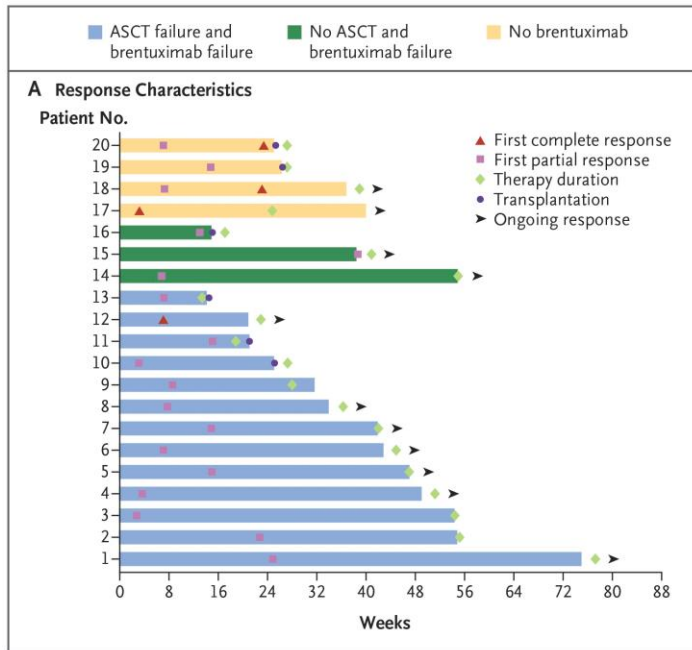




Cas clinique



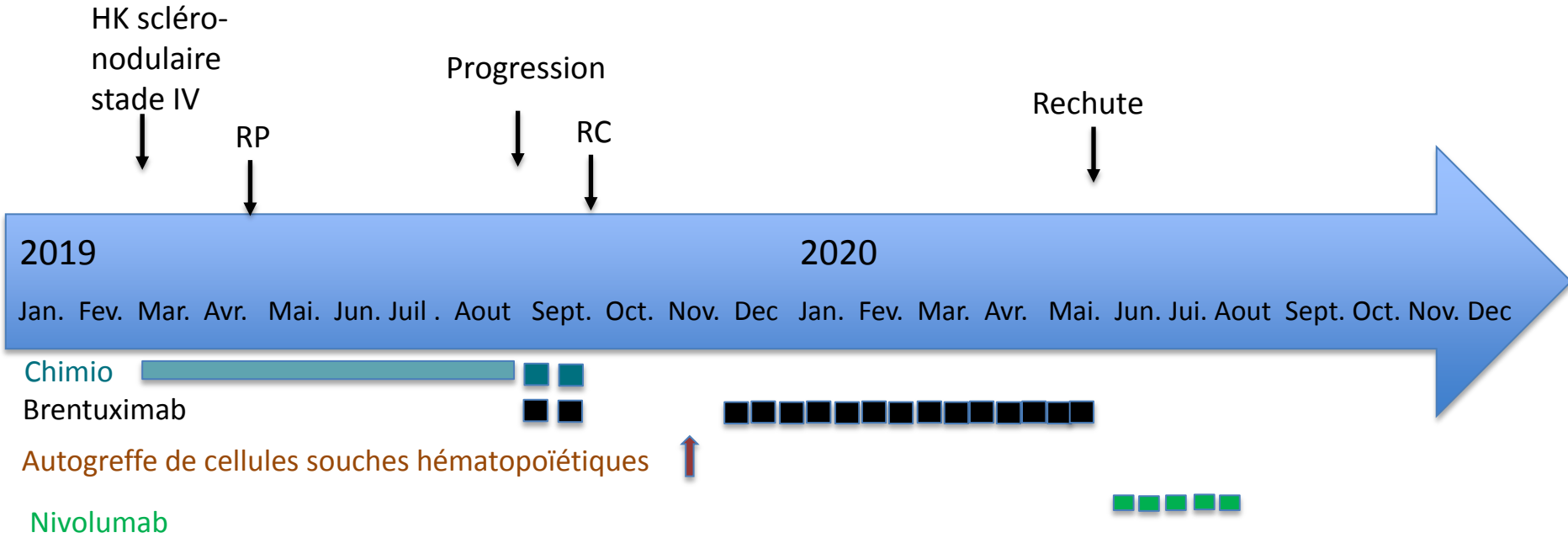




Ansell *et al.*, N
Engl J Med 2015

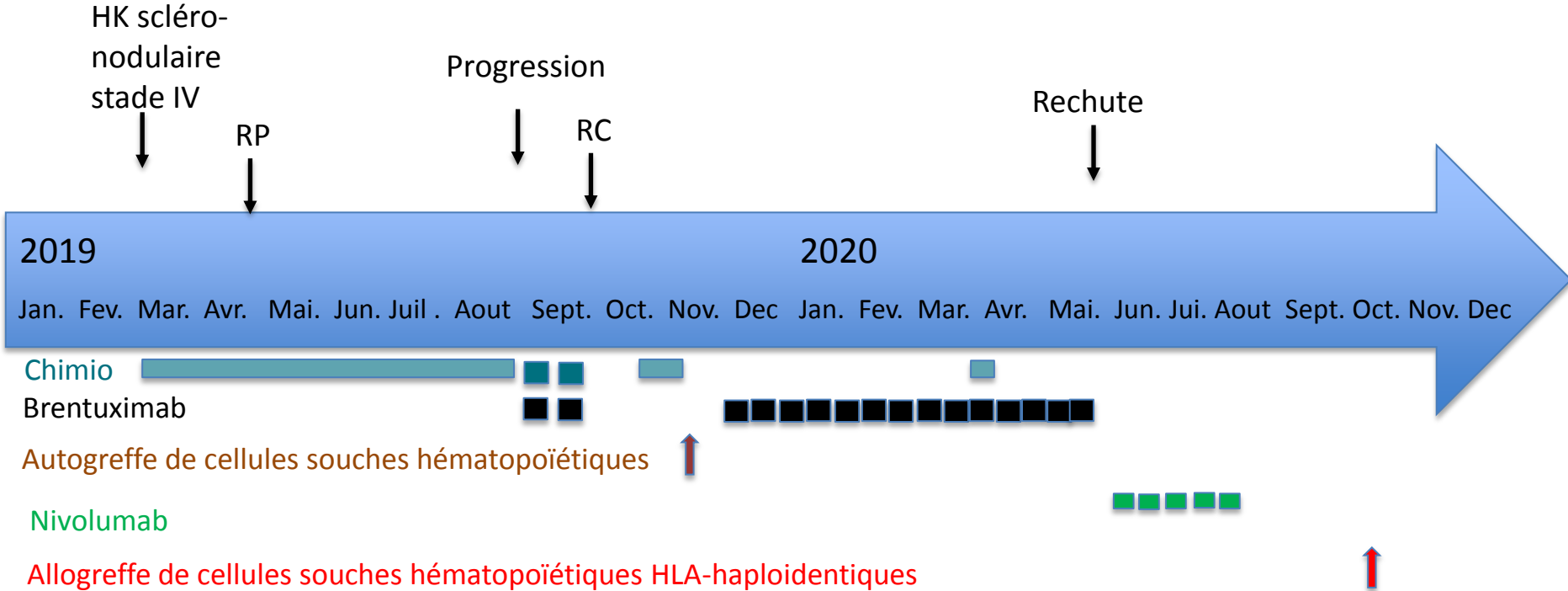


Cas clinique





Cas clinique





Greffes HLA-haploidentiques

Maman

A22	A12
B44	B15
DR32	DR11

Papa

A32	A31
B27	B16
DR15	DR32

Frère

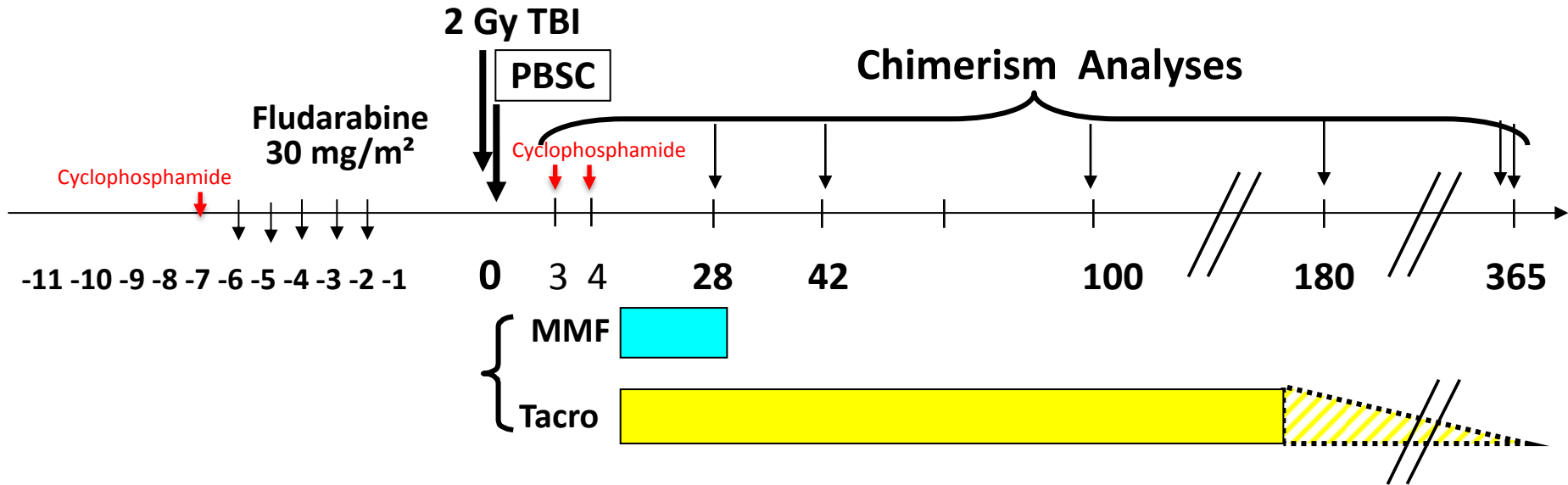
A22	A31
B44	B16
DR32	DR32

Patient

A22	A32
B44	B27
DR32	DR15



Greffe non-myéloablatifve HLA-haploidentifve



1. PTCy mitigates xenoGVHD



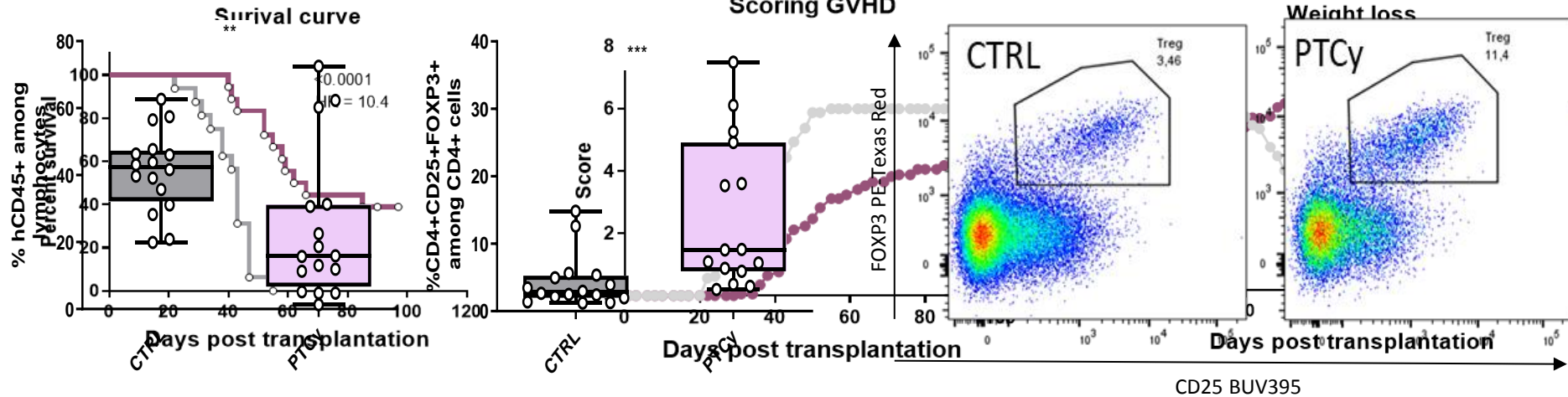
D0: 20×10^6 human PBMCs i.v.

D3: cyclophosphamide 100 mg/kg i.p injection

D21: Facs analysis for blood immune reconstitution

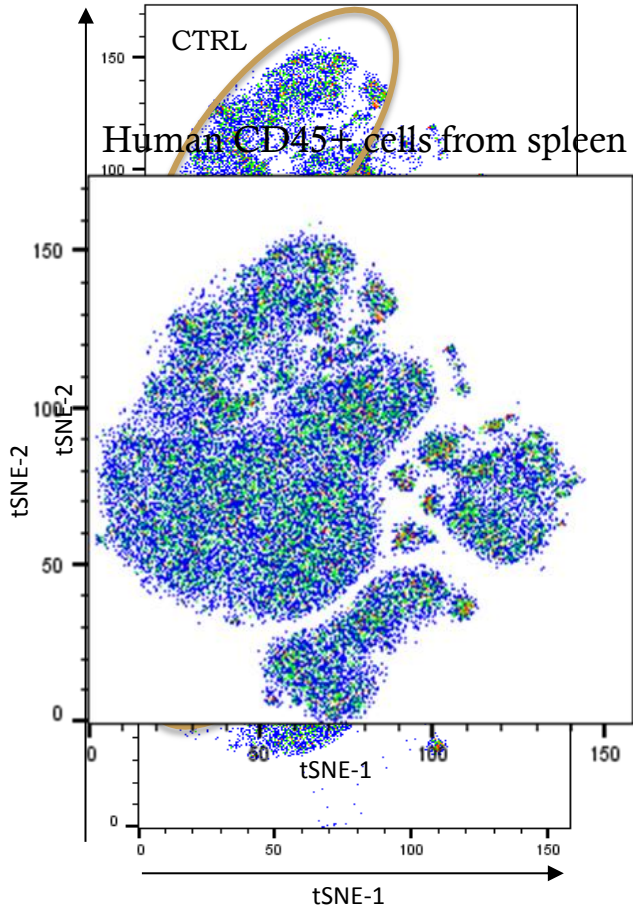
Survival and scoring

- GVHD score:
- Hunching (2)
 - Anemia (2)
 - Mobility loss (2)
 - Weight loss (2)
- ➔ Sacrifice score 6/8

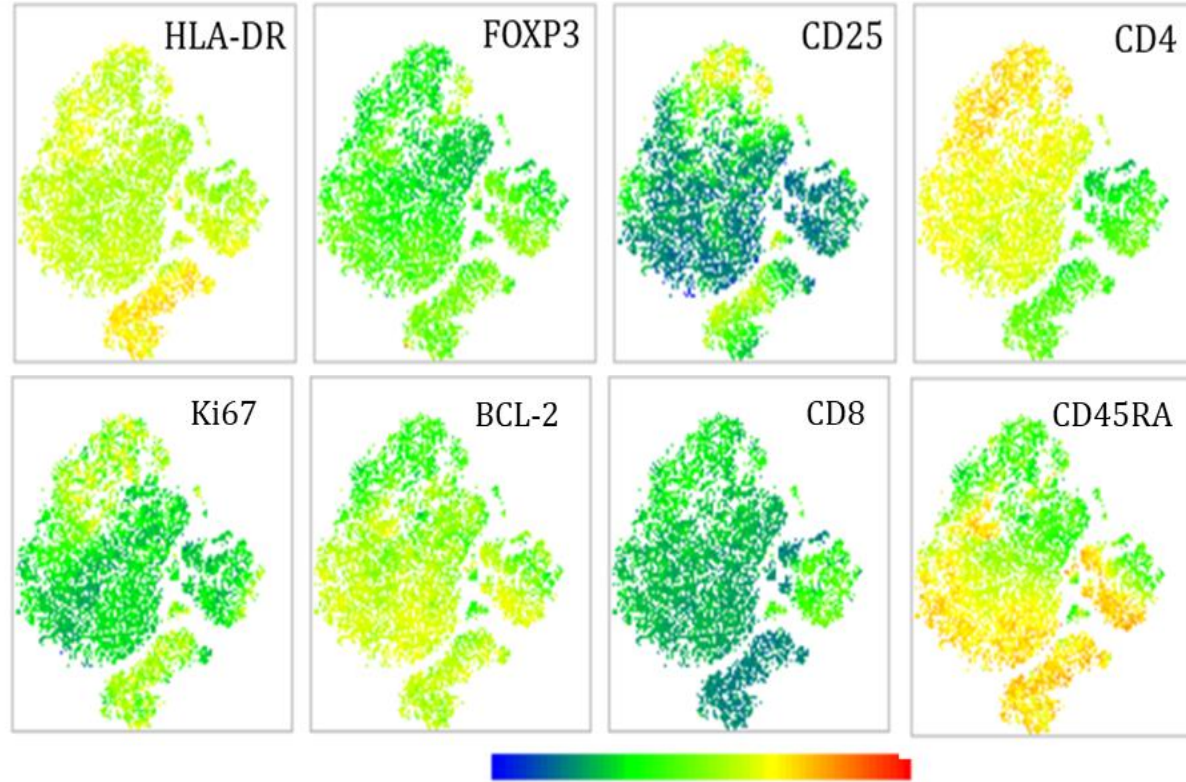


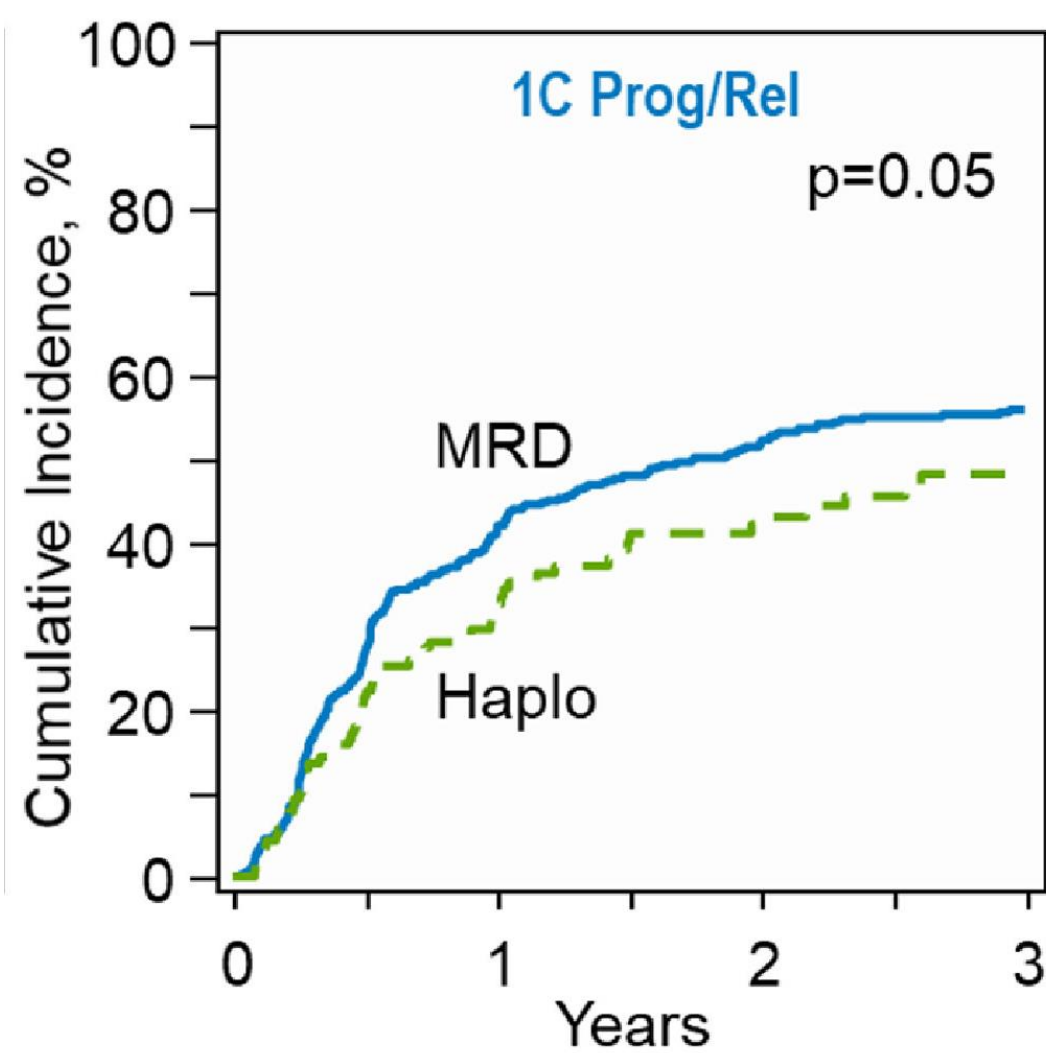
CD25 BUV395

2. PTCy kills proliferative and activated T cells



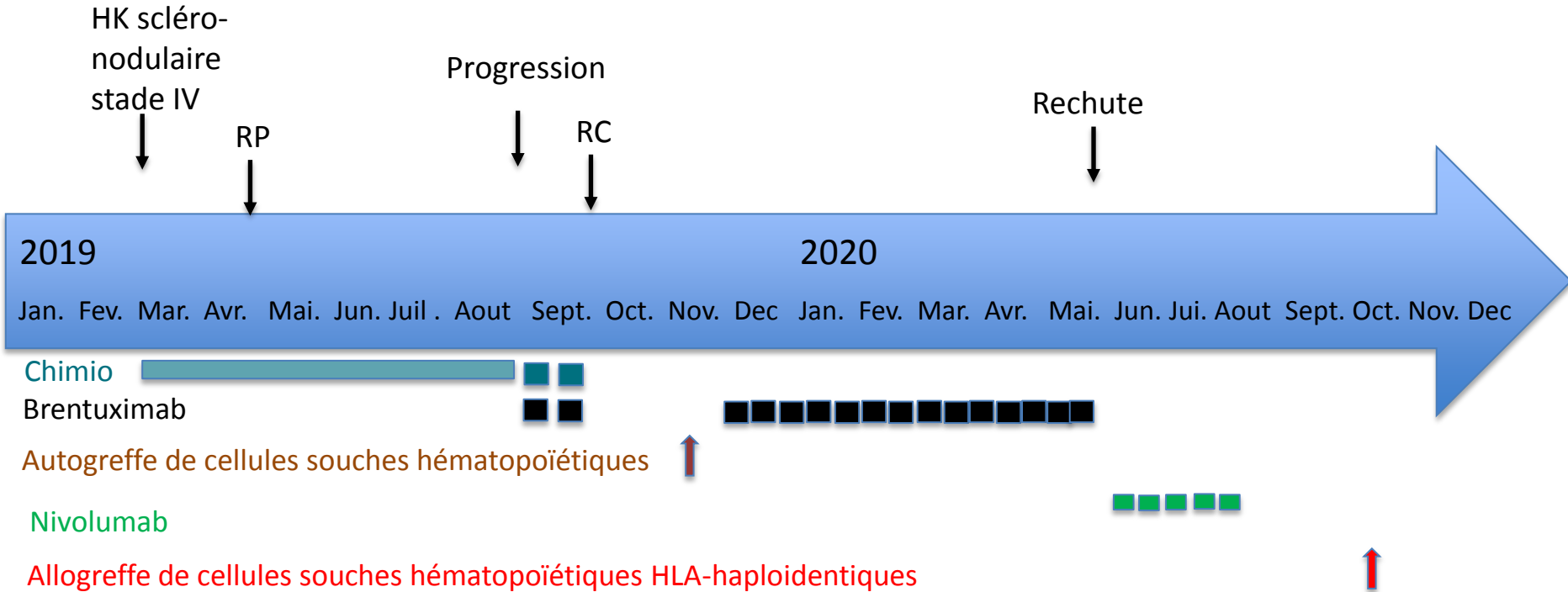
- ❖ PTCy kills proliferative and activated T cells and increases the frequencies of naive and BCL-2⁺ T cells







Cas clinique



Cas clinique #3

Leucémie myéloblastique aigue (LMA)



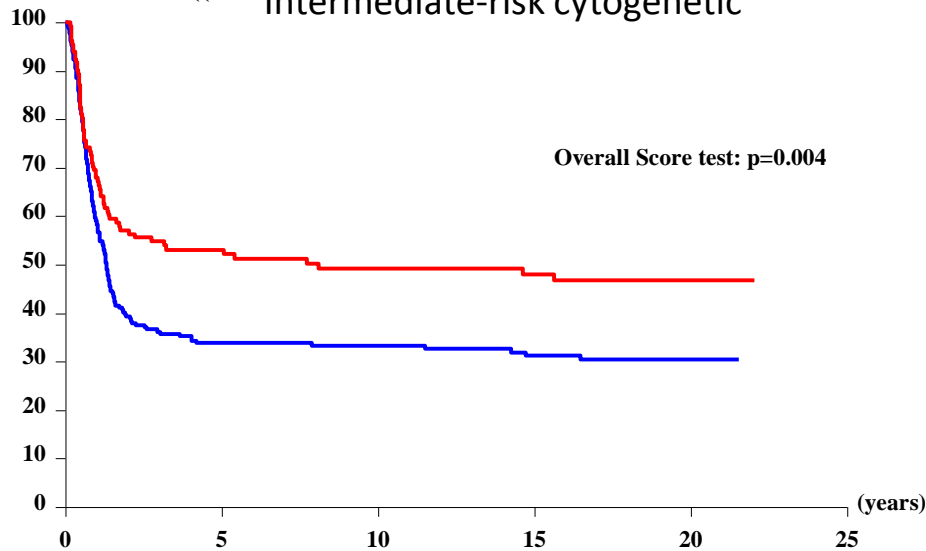
Cas clinique

- ▶ Homme 65 ans
- ▶ 10/2015: LMA (cytogénétique nle, NPM1 et FLT3 non mutés)

L'allogreffe de CSH reste le traitement de premier choix pour les patients atteints de LMA

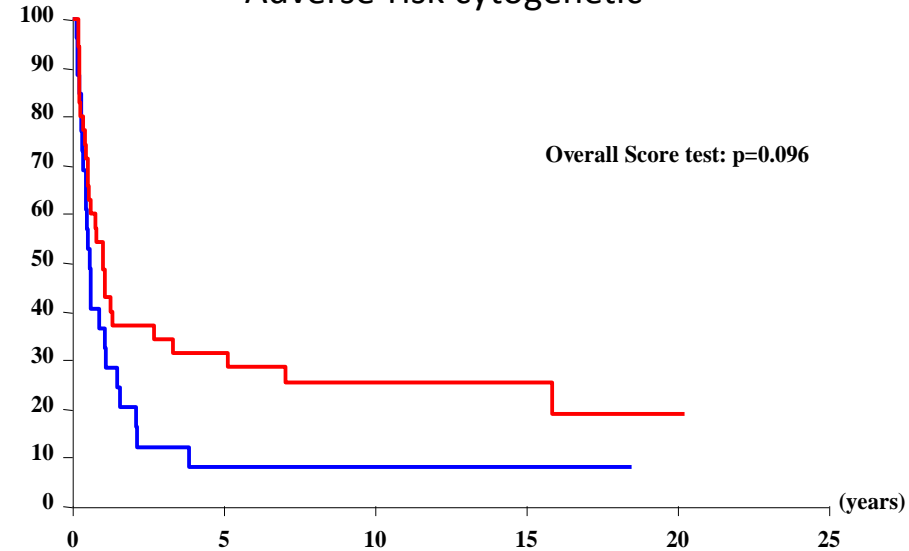


Intermediate-risk cytogenetic



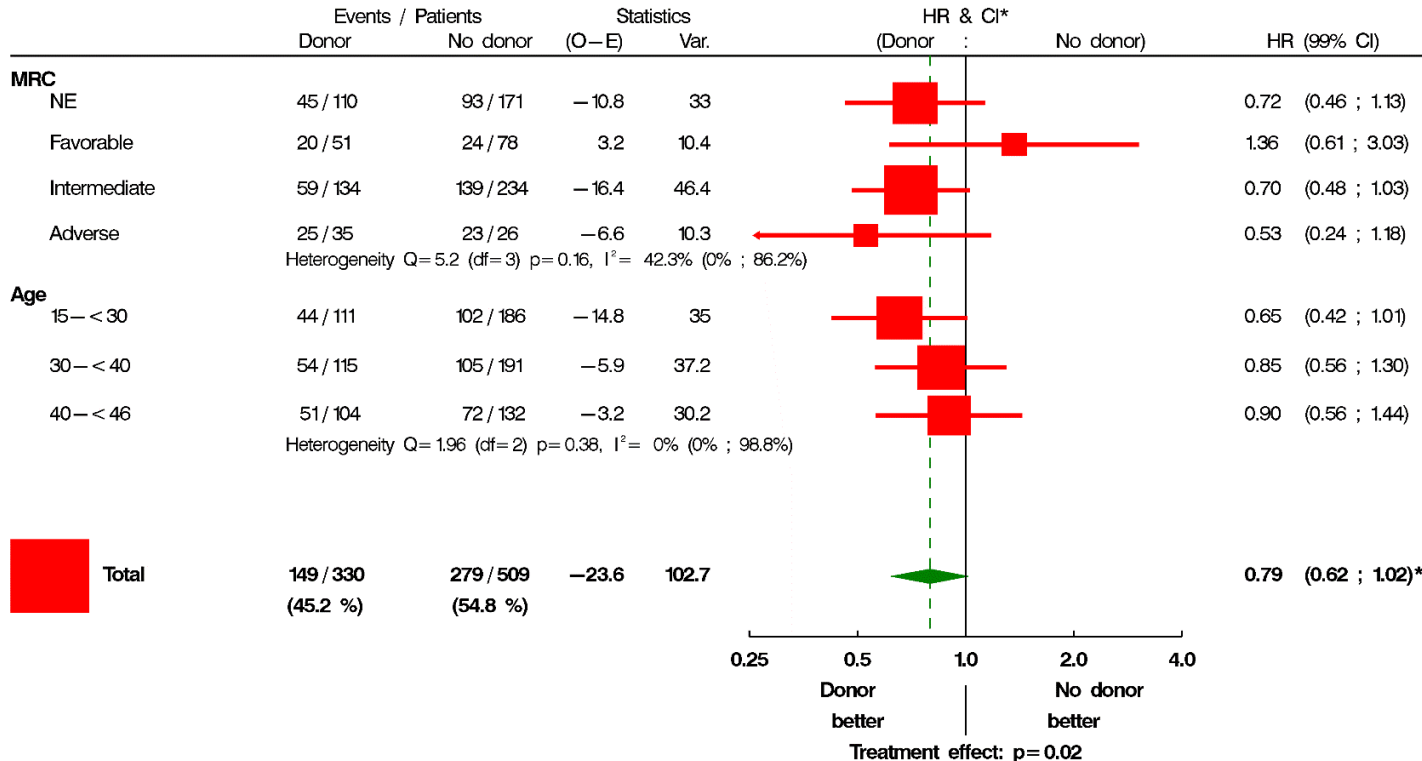
O	N	Number of patients at risk :				Donor
157	234	66	52	46	11	— No
67	134	59	45	39	7	— Yes

Adverse-risk cytogenetic



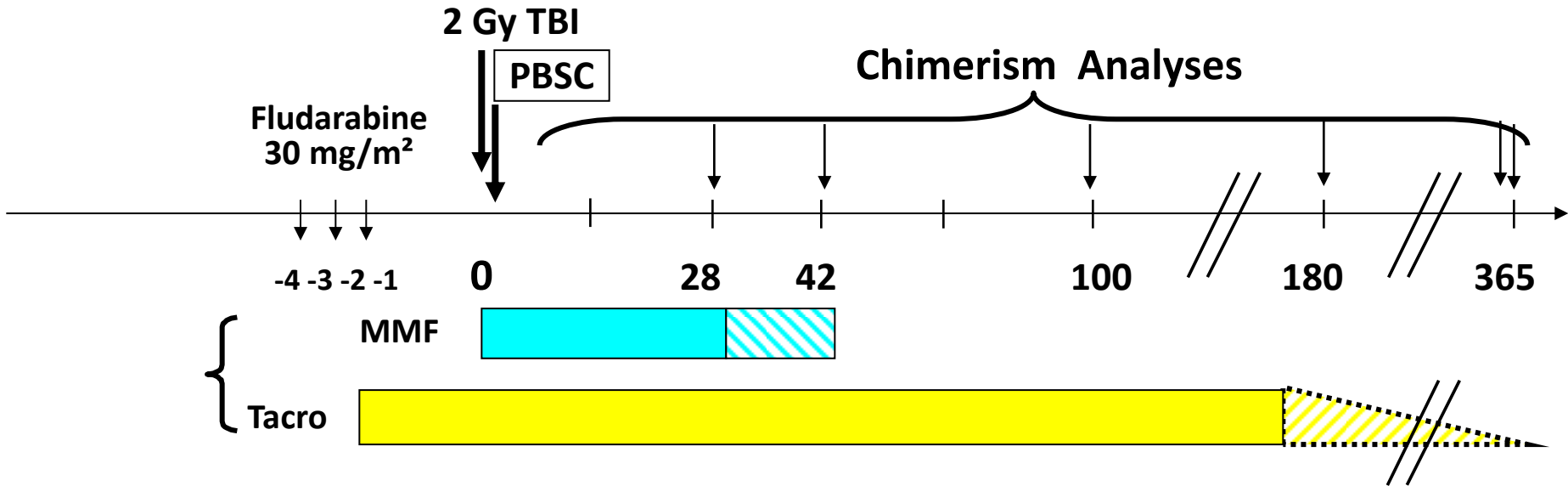
O	N	Number of patients at risk :				Donor
23	26	2	1	1	0	— No
27	35	11	5	5	1	— Yes

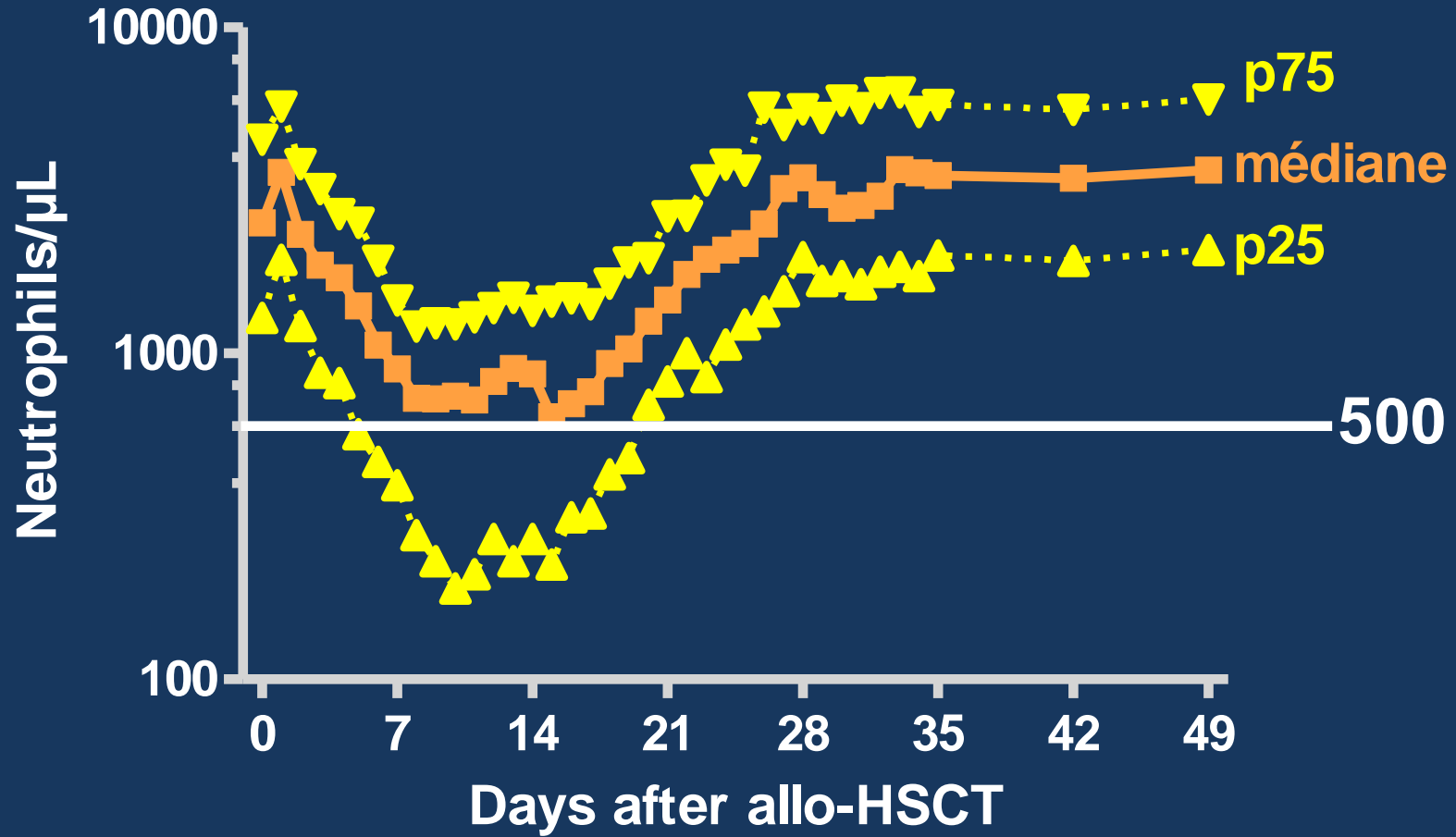
L'allogreffe de CSH reste le traitement de premier choix pour les patients atteints de LMA



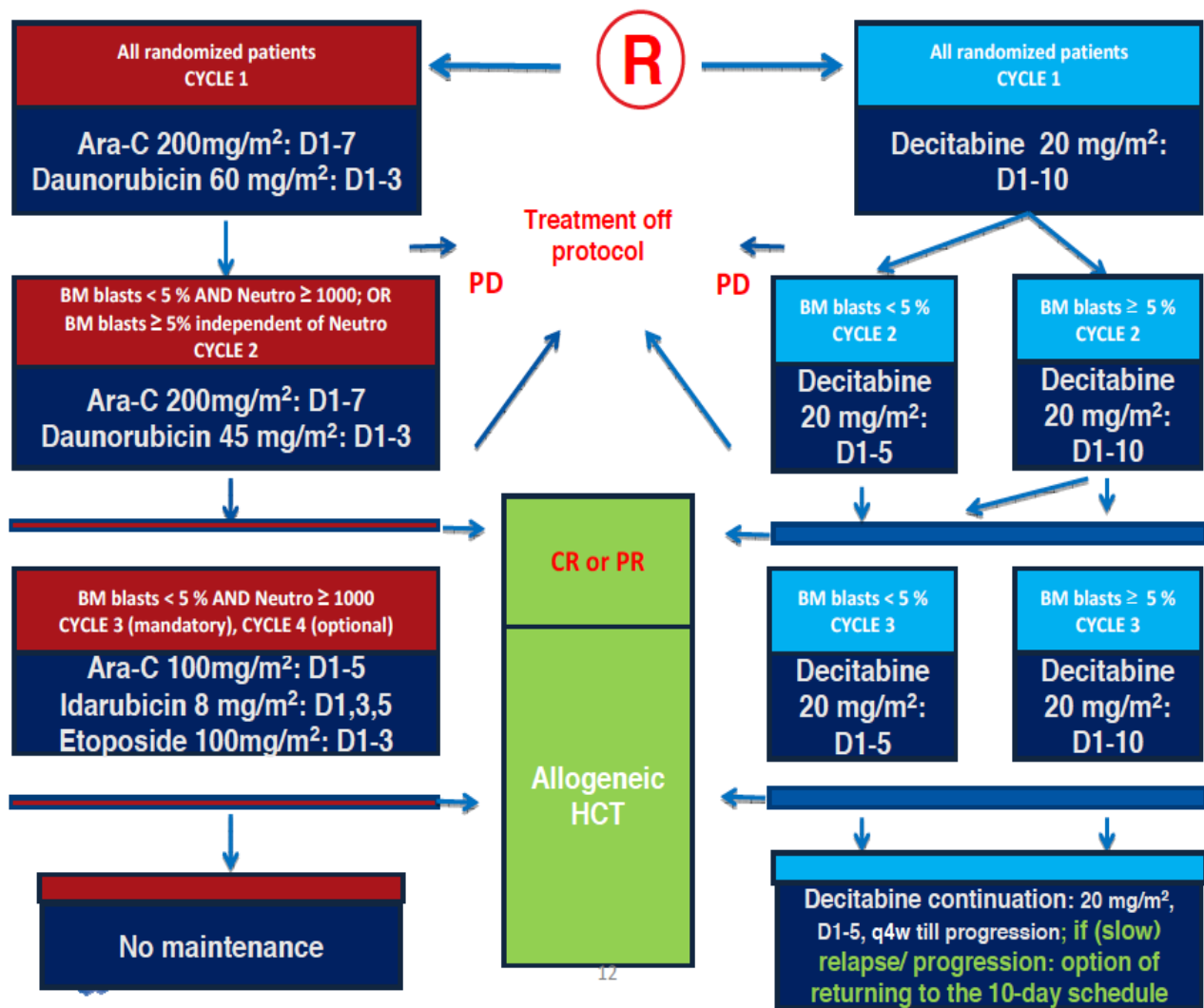


Greffe non-myéloablative (Seattle)





EORTC- GIMEMA AML-21 (M. Lübbert)



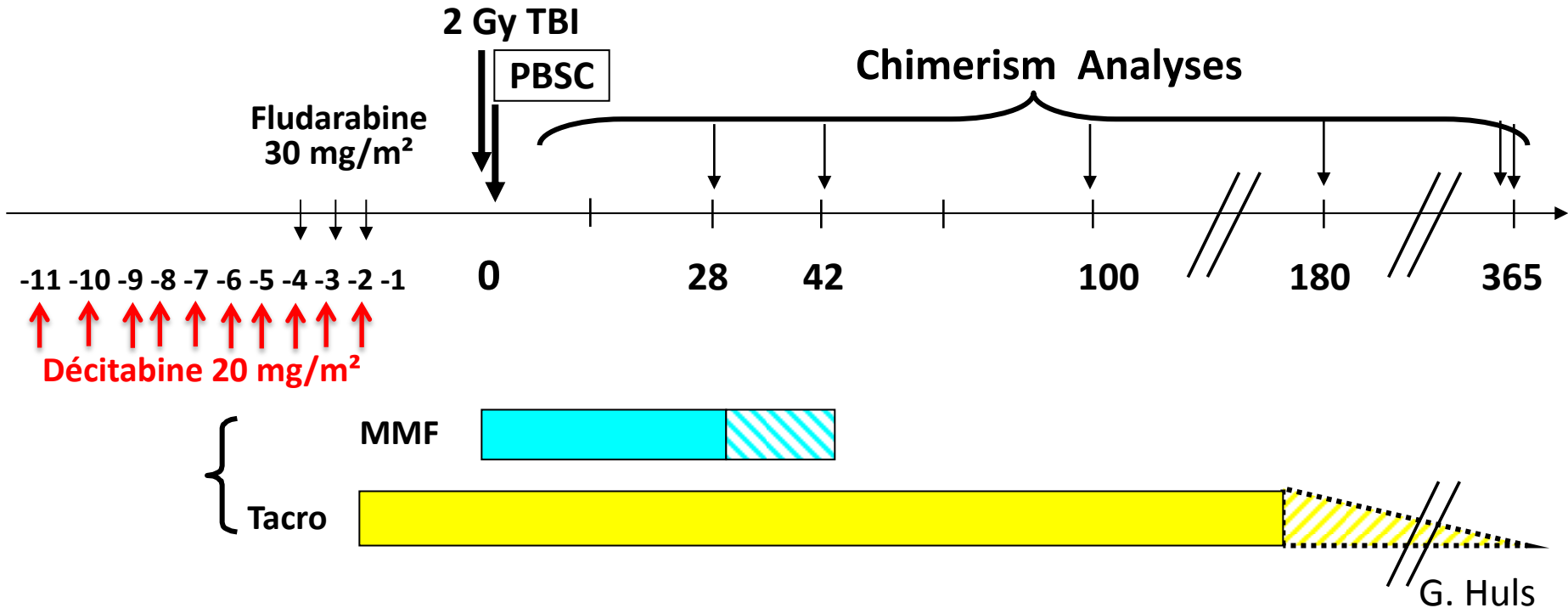


Cas clinique

- ▶ Homme 65 ans
- ▶ 10/2015: LMA (cytogénétique nle, NPM1 et FLT3 non mutés)
- ▶ Inclusion dans protocole EORTC AML-21, randomisé dans le bras décitabine. RC après 2 cures.



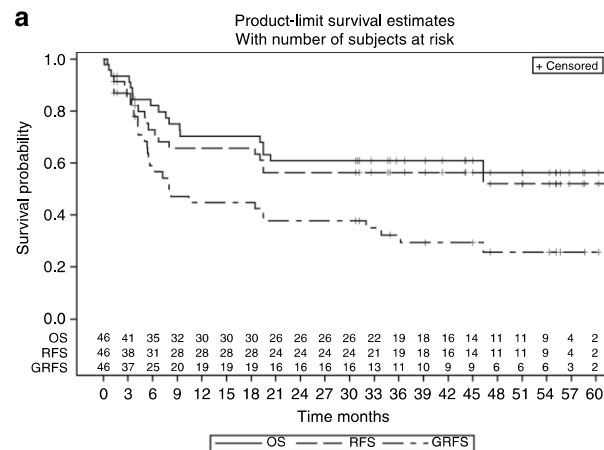
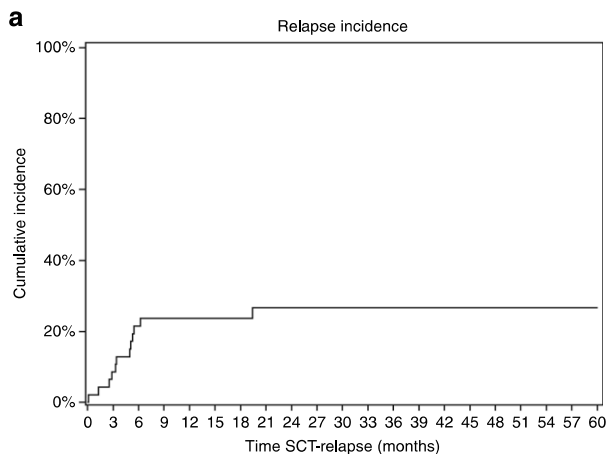
Décitabine + greffe non-myéloablatrice





Low relapse risk in poor risk AML after conditioning with 10-day decitabine, fludarabine and 2 Gray TBI prior to allogeneic hematopoietic cell transplantation

Marjan Cruijssen^{1,6} · Jacobien R. Hilberink² · Walter J. F. M. van der Velden¹ · Joop H. Jansen³ · Brigitte Bär¹ · Nicolaas P. M. Schaap¹ · Anton de Haan⁴ · André B. Mulder² · Marco R. de Groot² · Frédéric Baron⁵ · Edo Vellenga² · Nicole N. M. Blijlevens¹ · Gerwin Huls²

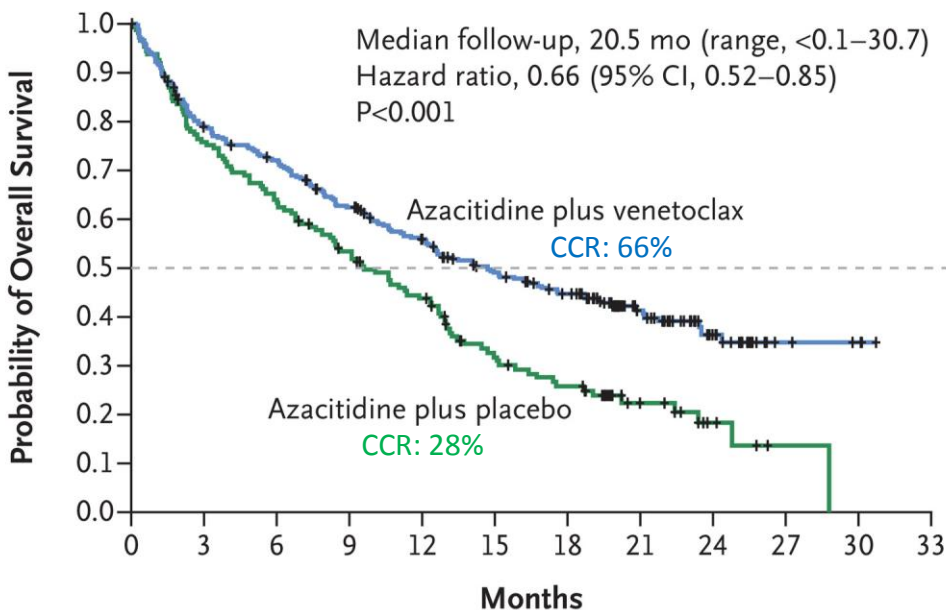




Cas clinique

- ▶ Homme 65 ans
- ▶ 10/2015: LMA (cytogénétique nle, NPM1 et FLT3 non mutés)
- ▶ Inclusion dans protocole EORTC AML-21, randomisé dans le bras décitabine. RC après 2 cures.
- ▶ Allogreffe: mini-décitabine
- ▶ RC depuis lors

Aza (75 mg/m^2) vs Aza + venetoclax (400 mg) dans les LAM du sujet âgé



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0



Take home messages

- ▶ Thérapies ciblées:

Immunothérapie: mab, bite, CARs

Inhibiteurs tyrosines kinases / BCL-2 inhibiteurs

Checkpoint inhibiteurs

- ▶ Progrès allogreffe: greffes non-myéloablatives
et greffes HLA-haploidentiques



FAISONS
GAGNER
LA vie



CENTRE ANTICANCÉREUX PRÈS L'UNIVERSITÉ DE LIÈGE A.S.B.L.



Pr Yves BEGUIN

fnrs

LA LIBERTÉ DE CHERCHER



Fondation contre le cancer



Patients



The future of cancer therapy