Actualités 2018

Marie Thérèse Rubio
CS de la SFGM-TC

Montpellier, 21 Novembre 2018

Les grands axes

- **Apport de la génomique** en allogreffe : MRD pré-greffe et mécanismes d'échappement post-greffe ?
- **Sorafenib** et réponse anti-leucémique en post-greffe
- **Transplantation de microbiote fécal** (TMF) et allogreffe
- **CAR-T cells :**
  - Confirmations dans les LAL en multicentrique
  - Mécanismes de résistance
  - Nouvelles AMM et ATU
  - CAR-T dans les LAM : ça avance ?
  - CAR iNKT !!!
- **Nouvelle formulation de chimiothérapie** dans la LAM: Vixeos

blood®

Measurable residual disease monitoring by NGS before allogeneic hematopoietic cell transplantation in AML.

Thol F[1], Gabdoulline R[1], Liebich A[1], Klement P[1], Schiller J[1], Kandziora C[1], Hambach L[1], Stadler M[1], Koenecke C[1], Flintrop M[1], Pankratz M[1], Wichmann M[1], Neziri B[1], Büttner K[1], Heida B[1], Klesse S[1], Chaturvedi A[1], Kloos A[1], Göhring G[2], Schlegelberger B[2], Gaidzik VI[3], Bullinger L[3,4], Fiedler W[5], Heim A[6], Hamwi I[1], Eder M[1], Krauter J[7], Schlenk RF[8], Paschka P[3], Döhner K[3], Döhner H[3], Ganser A[1], Heuser M[1].

1 Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation and.
2 Department of Human Genetics, Hannover Medical School, Hannover, Germany.
3 Department of Internal Medicine III, University of Ulm, Ulm, Germany.
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Blood 2018 132:1703-1713

- 96 patients allogreffés en RC

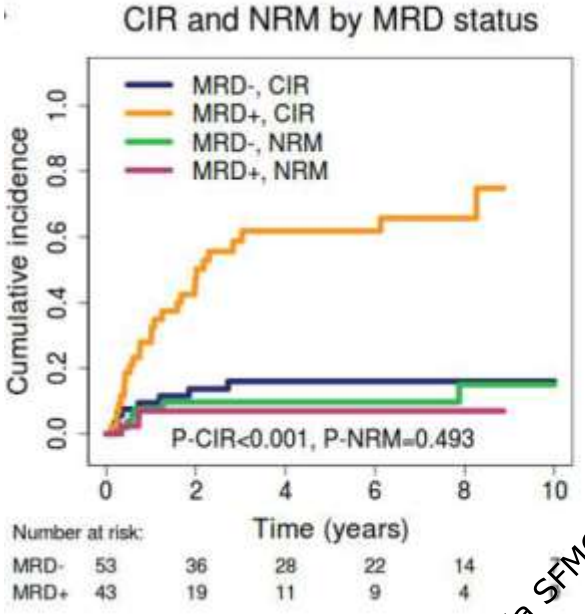
- 93% des LAM en RC ont des mutations détectables en NGS

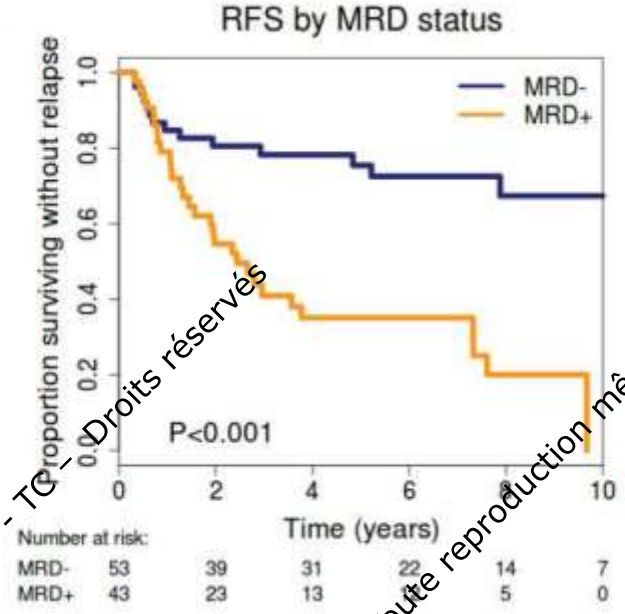
- Mutations suivies en NGS:

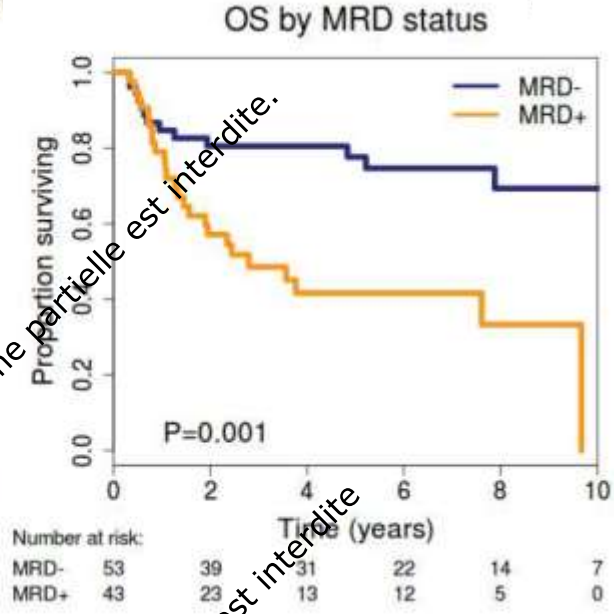
  IDH2 (n=17), RUNX1 (n=17), NRAS (n=12), FLT3 (n=11), TP53 (n=8), IDH1 (n=7), KRAS, SF3B1, STAG2 (n=6 each), EZH2 (n=5), BCOR, BCORL1, PTPN11, TET2, WT1 (n=4 each), PHF6, (n=3), RAD21, ETV6 (n=2 each), CBL, DDX41, KDM6A, SETBP1, SMC3, STAG1 (n=1 each).

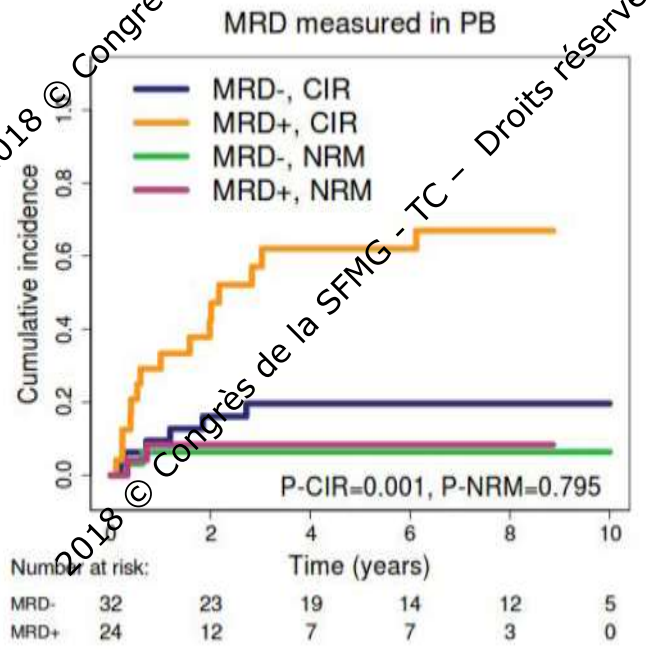
  NPM1, DNMT3A suivis en PCR classique

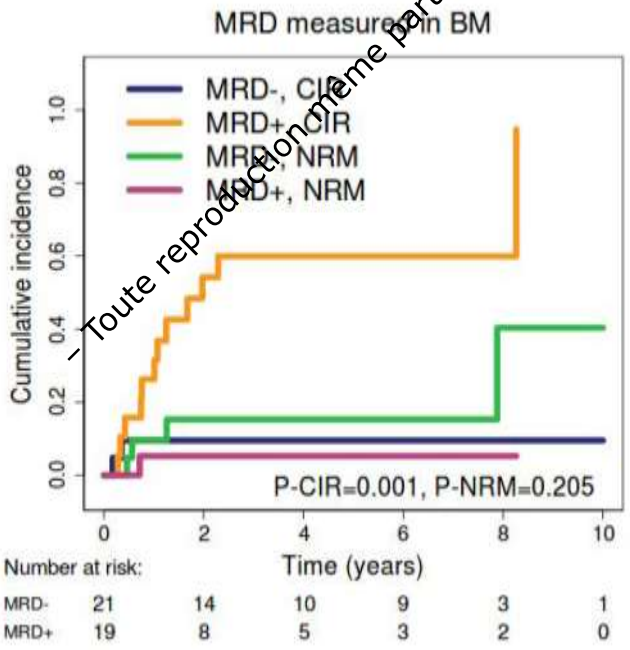
- At HSCT : 43 patients MRD + vs 53 MRD neg
  - MRD +: ELN plus haut risques
  - 95% RC1 dans les 2 groupes
  - Age et caractéristiques de la greffe comparables











Endpoint	Variables in the model	Univariate analysis				Multivariate analysis		
		HR	95% CI	P		HR	95% CI	P
CIR	MRD positive vs negative	5.58	2.47-12.59	<0.001		5.67	2.30-14.0	<0.001
	DNMT3A mutant vs wildtype	0.41	0.17-0.97	0.042		0.33	0.12-0.89	0.029
	FLT3 ITD present vs absent	0.91	0.38-2.15	0.828		3.70	1.36-10.10	0.011
	NPM1 mutant vs wildtype	0.19	0.04-0.81	0.025		0.22	0.06-0.77	0.018
RFS	MRD positive vs negative	3.56	1.86-6.81	<0.001		3.41	1.72-6.75	0.001
	Age above 60 years vs 18-60 years	1.89	1.02-3.49	0.043		2.23	1.15-4.33	0.017
	KRAS mutant vs wildtype	2.13	1.03-4.39	0.041		3.51	1.64-7.50	0.001
	TP53 mutant vs wildtype	2.74	1.31-5.79	0.008		2.26	1.09-4.70	0.029
OS	MRD positive vs negative	3.06	1.54-6.12	0.002		3.00	1.41-6.38	0.004
	Conditioning MAC vs RIC	0.54	0.28-1.02	0.056		0.37	0.20-0.69	0.002
	KRAS mutant vs wildtype	2.84	1.33-6.05	0.007		5.58	2.68-11.62	<0.001
	TP53 mutant vs wildtype	3.57	1.67-7.61	0.001		3.97	1.90-8.29	<0.001

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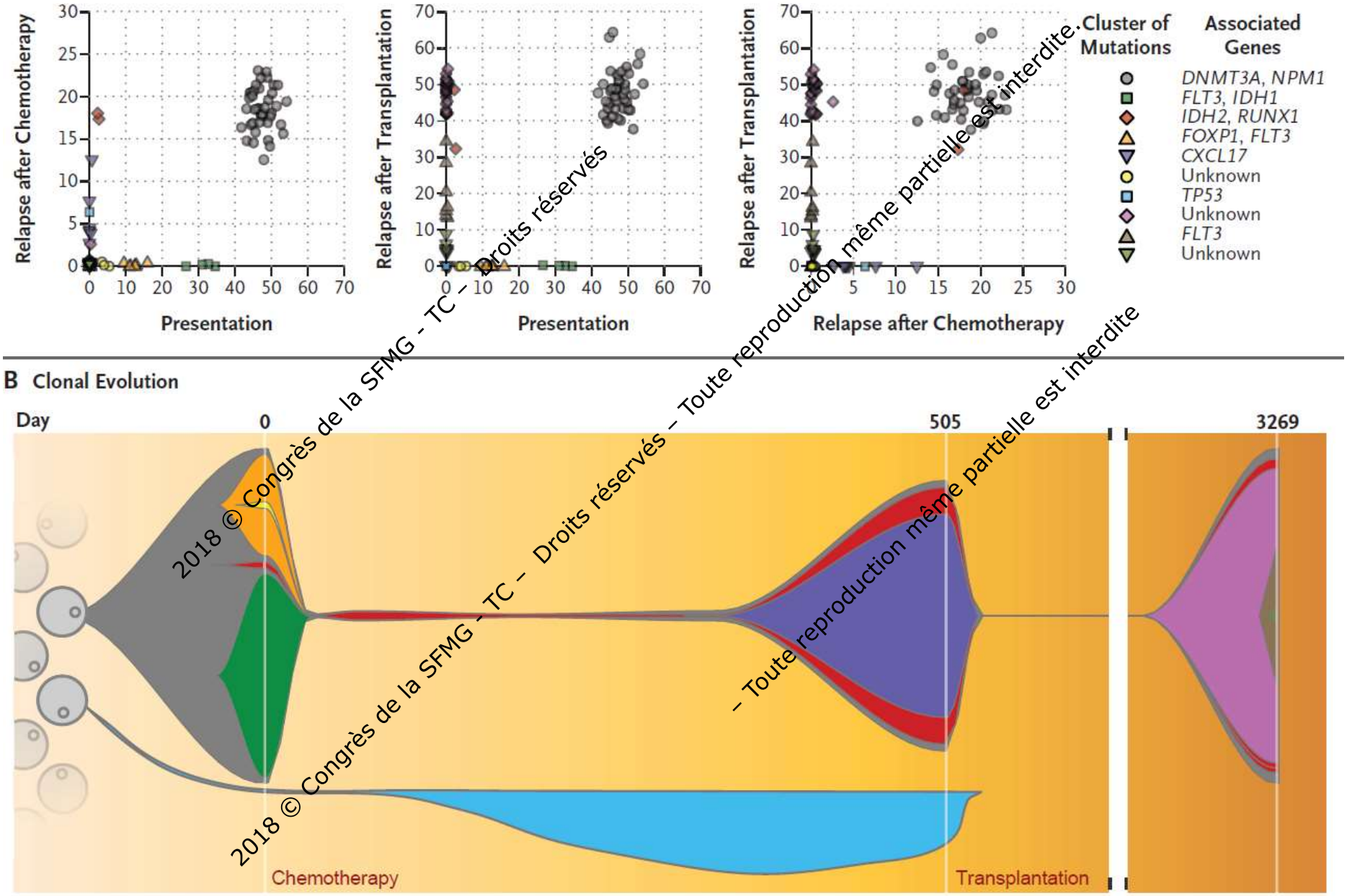
The NEW ENGLAND JOURNAL of MEDICINE

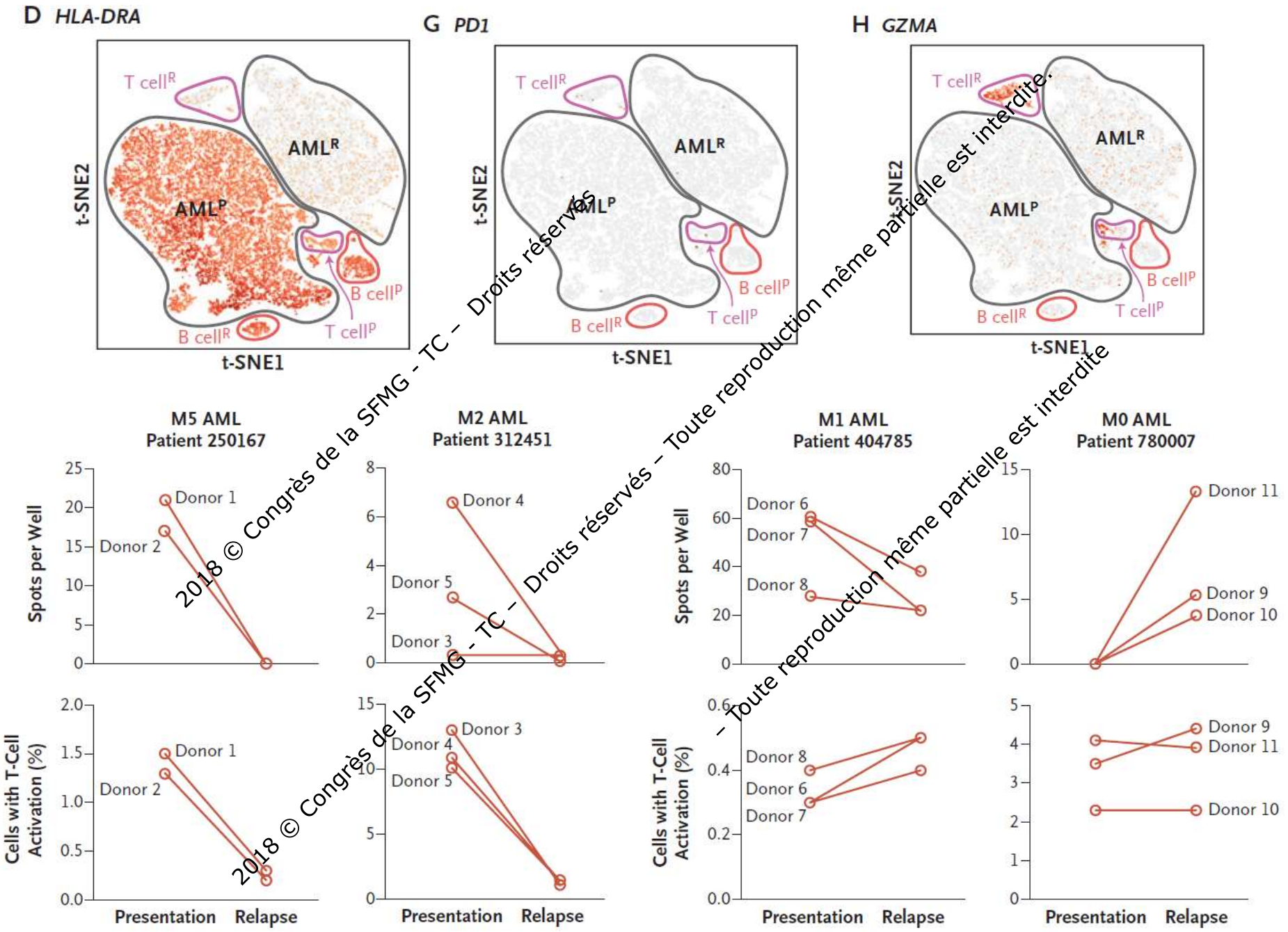
ORIGINAL ARTICLE

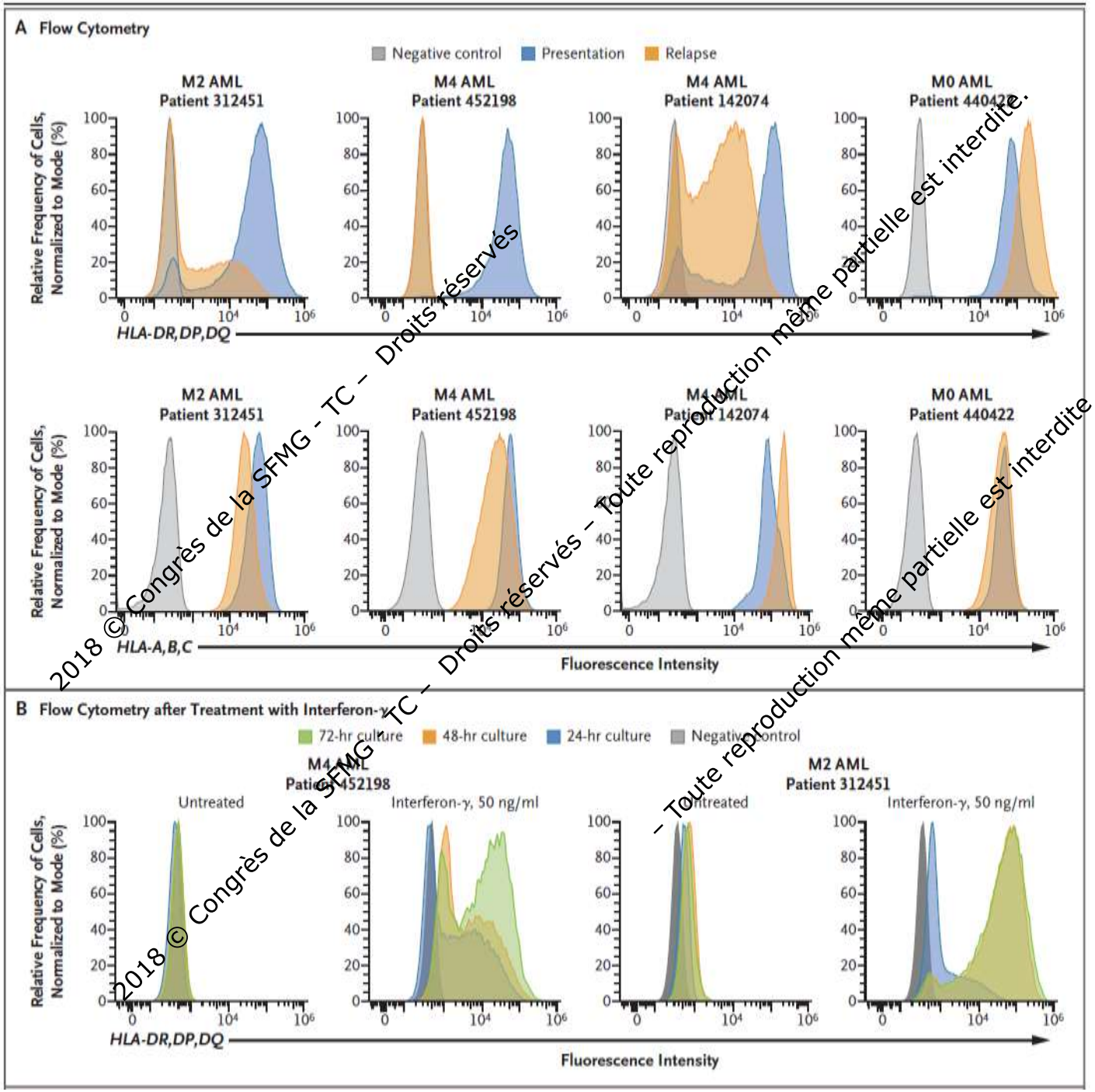
Immune Escape of Relapsed AML Cells after Allogeneic Transplantation

M.J. Christopher, A.A. Petti, M.P. Rettig, C.A. Miller, E. Chendamarai, E.J. Duncavage, J.M. Klco, N.M. Helton, M. O'Laughlin, C.C. Fronick, R.S. Fulton, R.K. Wilson, L.D. Wartman, J.S. Welch, S.E. Heath, J.D. Baty, J.E. Payton, T.A. Graubert, D.C. Link, M.J. Walter, P. Westervelt, T.J. Ley, and J.F. DiPersio

N Engl J Med. 2018 Oct 31. doi: 10.1056/NEJMoa1808777.







The Oncologist®

Hematologic Malignancies

Interferon-α Is Effective for Treatment of Minimal Residual Disease in Patients with t(8;21) Acute Myeloid Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation: Results of a Prospective Registry Study

Xiao-Dong Mo,[a] Yu Wang,[a] Xiao-Hui Zhang,[a] Lan-Ping Xu,[a] Chen-Hua Yan,[a] Huan Chen,[a] Yu-Hong Chen,[a] Ya-Zhen Qin,[a] Kai-Yan Liu,[a] Xiao-Jun Huang[a,b]

[a]Peking University People's Hospital, Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, People's Republic of China; [b]Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, People's Republic of China

The Oncologist 2018;23:1–9

42 patients MRD + receiving IFNα after allo vs historical controls MRD+ without IFN

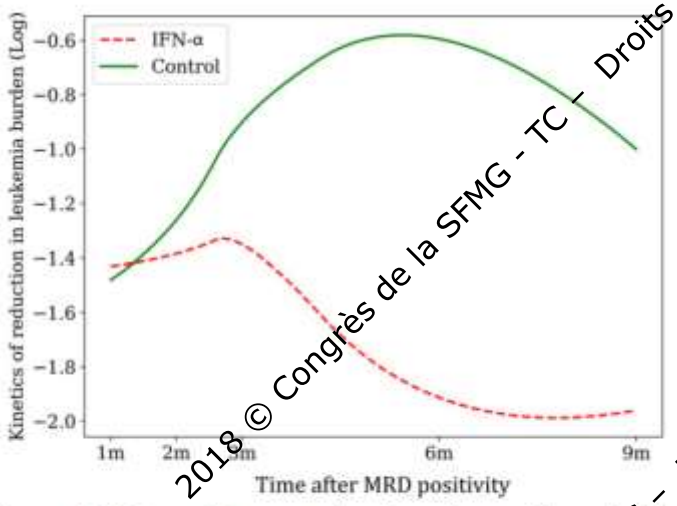
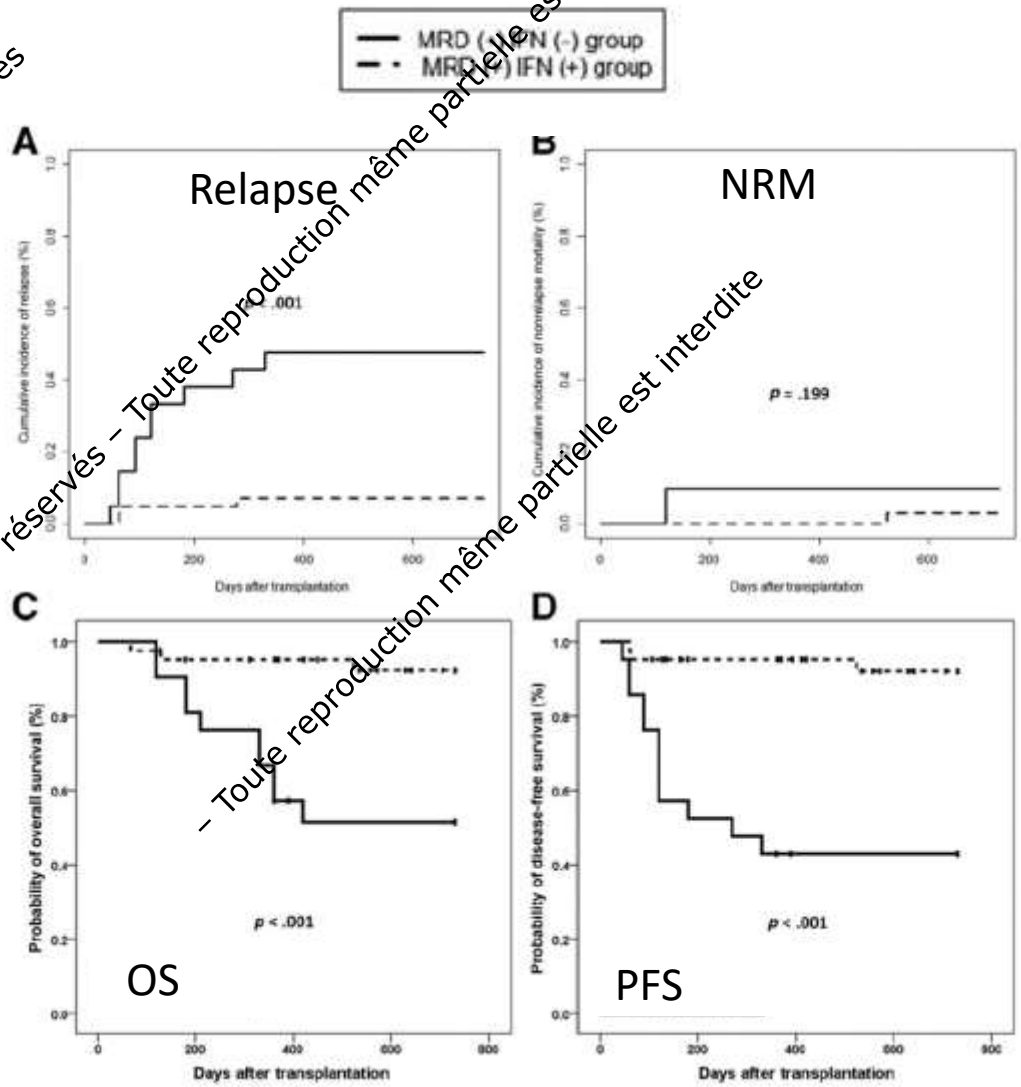


Figure 4. MRD evolution over time in patients with and without IFN-α treatment. Abbreviations: IFN-α, interferon-α; MRD, minimal residual disease.



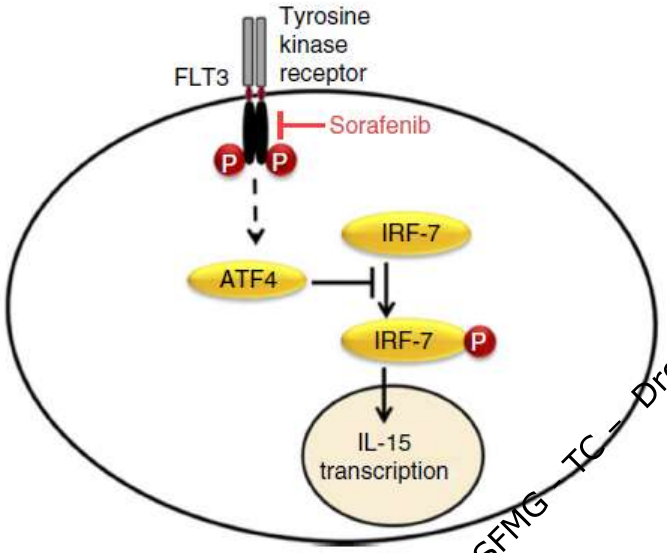
31% de GVHA aigue post-IFN
7% de GVH aigue de grade ≥ 3

nature medicine

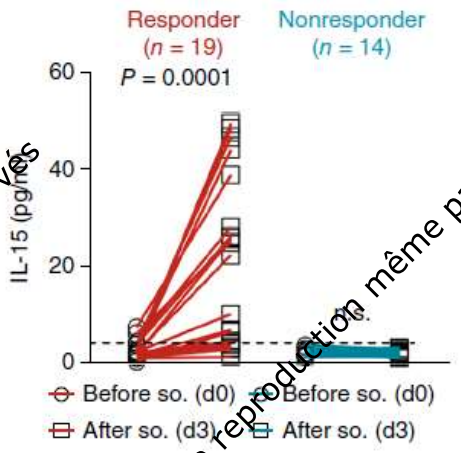
Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells

Jacqueline Schnell[42], Florian Kuchenbauer[42], Donald Bunjes[43], Ronjon Chakraverty[43,44], Simon Richardson[43,44], Saar Gill[45], Nicolaus Kröger[46], Francis Ayuk[46], Luca Vago[47–49], Fabio Ciceri[47–49], Antonia M Müller[50], Takeshi Kondo[51], Takanori Teshima[51], Susan Klaeger[7,52], Bernhard Kuster[52], Dennis (Dong Hwan) Kim[53], Daniel Weisdorf[54], Walter van der Velden[55], Daniela Dörfel[56], Wolfgang Bethge[56], Imken Hilgendorf[57], Andreas Hochhaus[57], Geoffroy Andrieux[25,27,58], Melanie Börries[25,27,58], Hauke Busch[25,27,58,59], John Magenau[60], Pavan Reddy[60], Myriam Labopin[61], Joseph H Antin[62], Andrew S Henden[63,64], Geoffrey R Hill[63–65], Glen A Kennedy[65], Merav Bar[66], Anita Sarma[67], Donal McLornan[67], Ghulam Mufti[67], Betul Oran[68], Katayoun Rezvani[68], Omid Sha[69], Robert S Negrin[69], Arnon Nagler[70], Marco Prinz[21,26], Andreas Burchert[24], Andreas Neubauer[22,23], Dietrich Beelen[15], Andreas Mackensen[20], Nikolas von Bubnoff[1], Wolfgang Herr[4], Burkhard Becher[7], Gerard Socié[35,36], Michael A Caligiuri[71], Eliana Ruggiero[47–49], Chiara Bonini[47–49], Georg Häcker[6], Justus Duyster[1], Jürgen Finke[1], Erika Pearce[3], Bruce R Blazar[72] & Robert Zeiser[1,26]

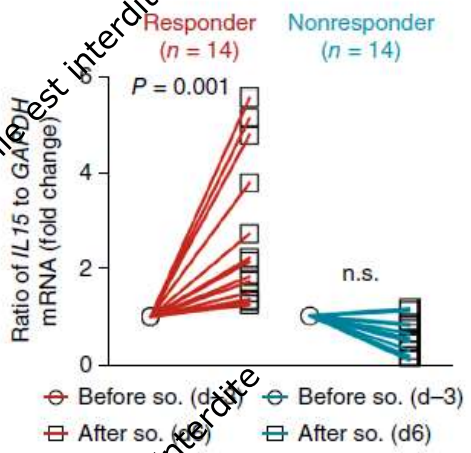
doi:10.1038/nm.4484



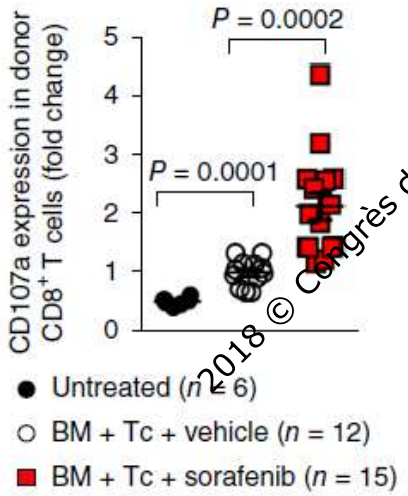
Serum patient

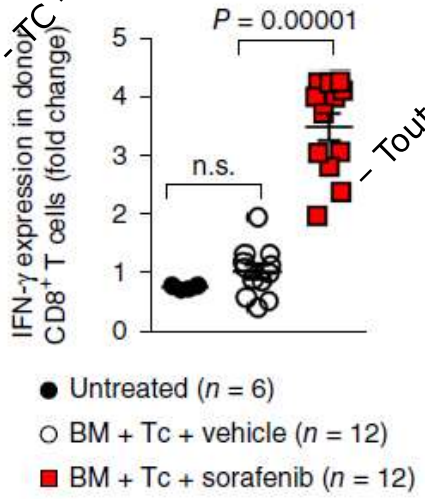


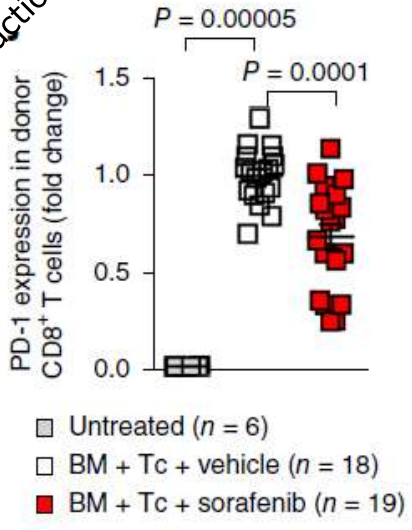
Cellules leucémiques



IL-15 produit par les cellules leucémiques après traitement par Sorafenib induit une population T CD8+ cytotoxique produisant de l'IFN-γ, PD1 faible avec une activité anti-leucémique







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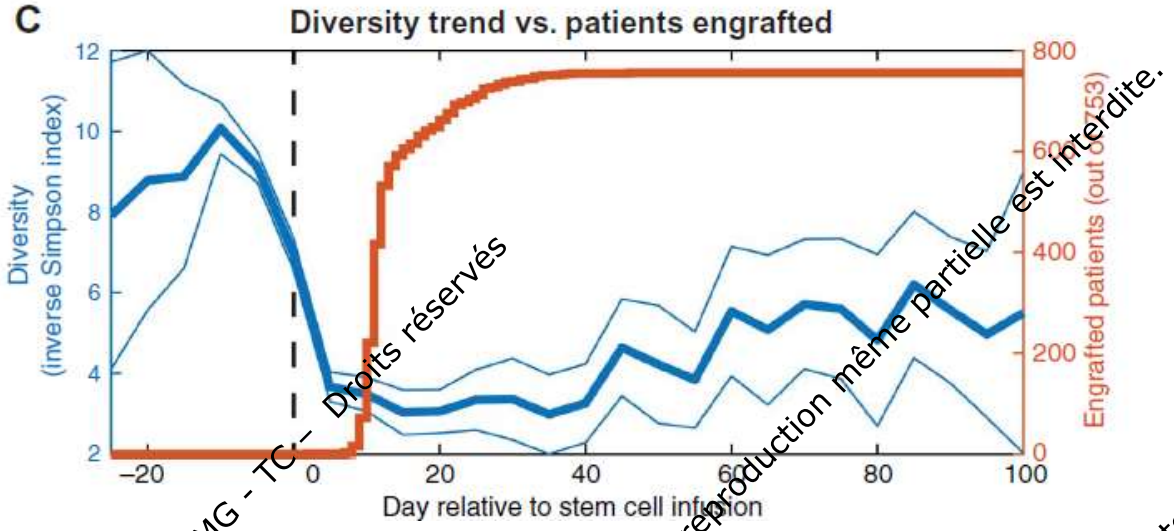
GUT MICROBIOTA

Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant

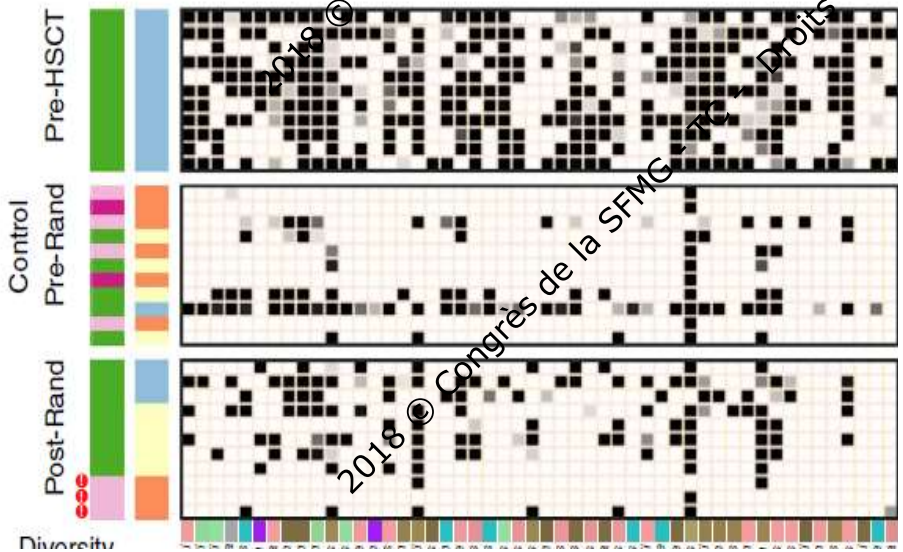
Ying Taur[1], Katharine Coyte[1,2,3], Jonas Schluter[1], Elizabeth Robilotti[1], Cesar Figueroa[1], Mergim Gjonbalaj[1], Eric R. Littmann[1], Lilan Ling[1], Liza Miller[1,4], Yangtsho Gyaltshen[1,5], Emily Fontana[1], Sejal Morjaria[1], Boglarka Gyurkocza[1], Miguel-Angel Perales[1], Hugo Castro-Malaspina[1], Roni Tamari[1], Doris Ponce[1], Guenther Koehne[1], Juliet Barker[1], Ann Jakubowski[1], Esperanza Papadopoulos[1], Parastoo Dahi[1], Craig Sauter[1], Brian Shaffer[1], James W. Young[1,6,7], Jonathan Peled[1], Richard C. Meagher[1], Robert R. Jenq[8], Marcel R. M. van den Brink[1,6], Sergio A. Giralt[1], Eric G. Pamer[1]*, Joao B. Xavier[1]*

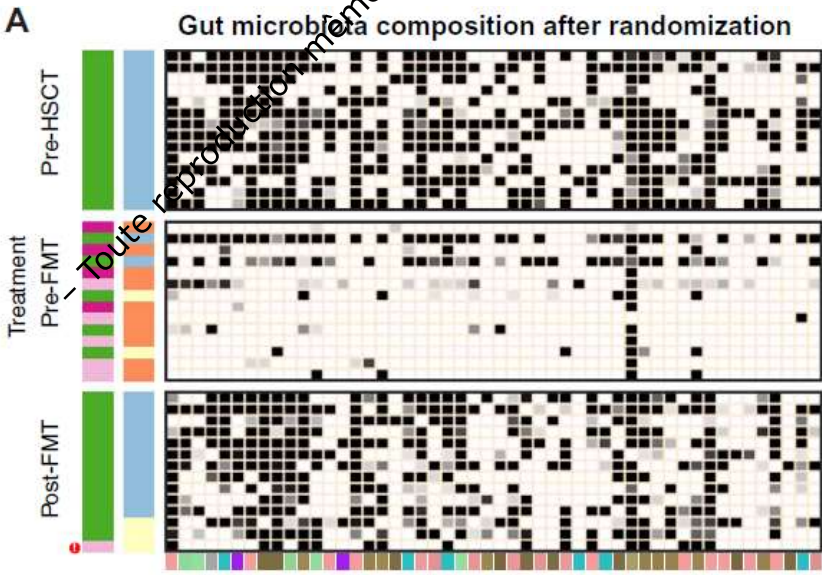
[1]Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. [2]Department of Zoology, University of Oxford, Oxford, UK. [3]Division of Infectious Diseases and Division of Gastroenterology, Department of Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, USA. [4]Washington University in St. Louis School of Medicine, St. Louis, MO 63110, USA. [5]American Museum of Natural History, New York, NY 10024, USA. [6]Weill Cornell Medical College, New York, NY 10065, USA. [7]Rockefeller University, New York, NY 10065, USA. [8]University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
*Corresponding author. Email: pamere@mskcc.org (E.G.P.); xavierj@mskcc.org (J.B.X.)

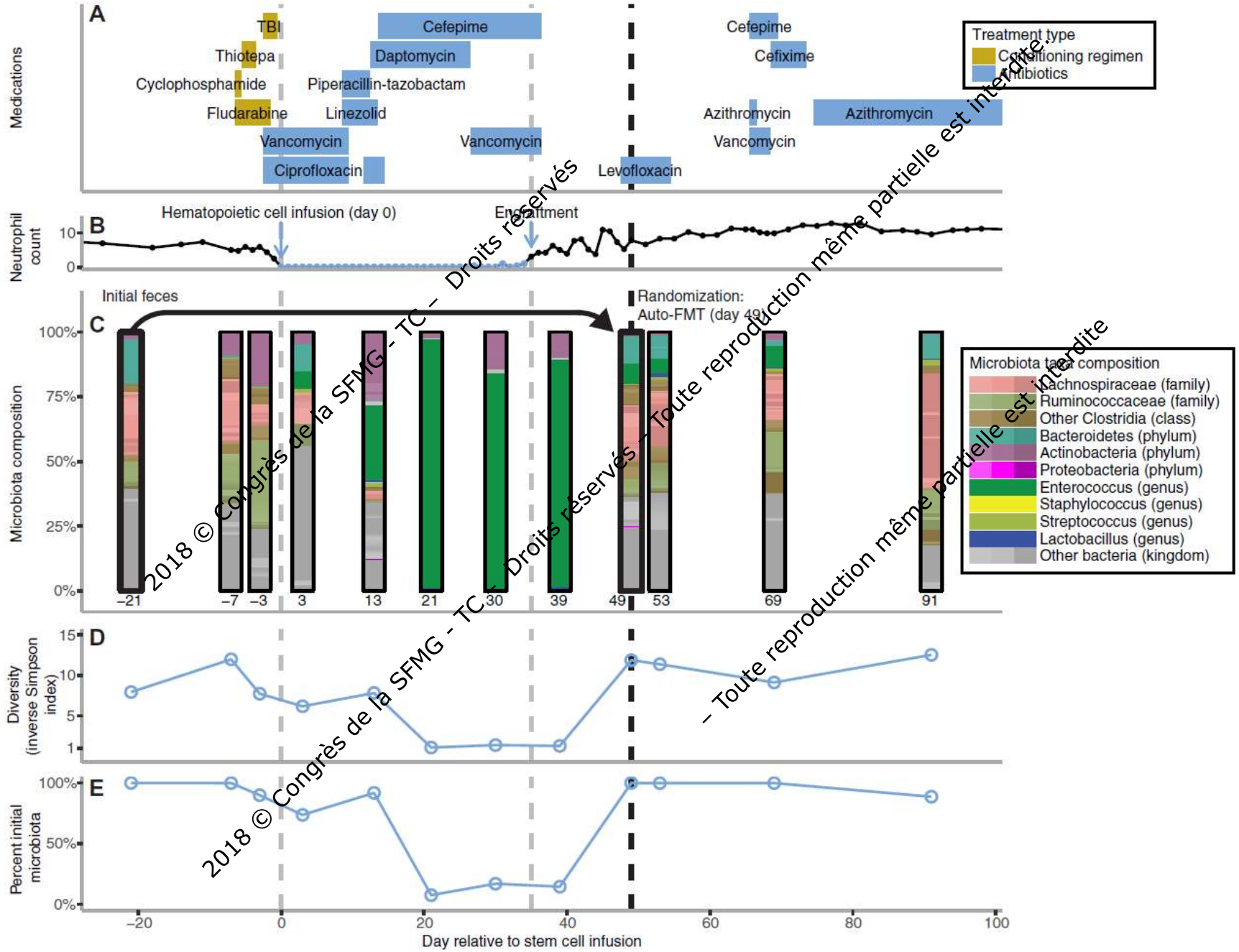


A randomized controlled clinical trial of auto-FMT to restore the gut microbiota

14 FMT vs 11 no FMT







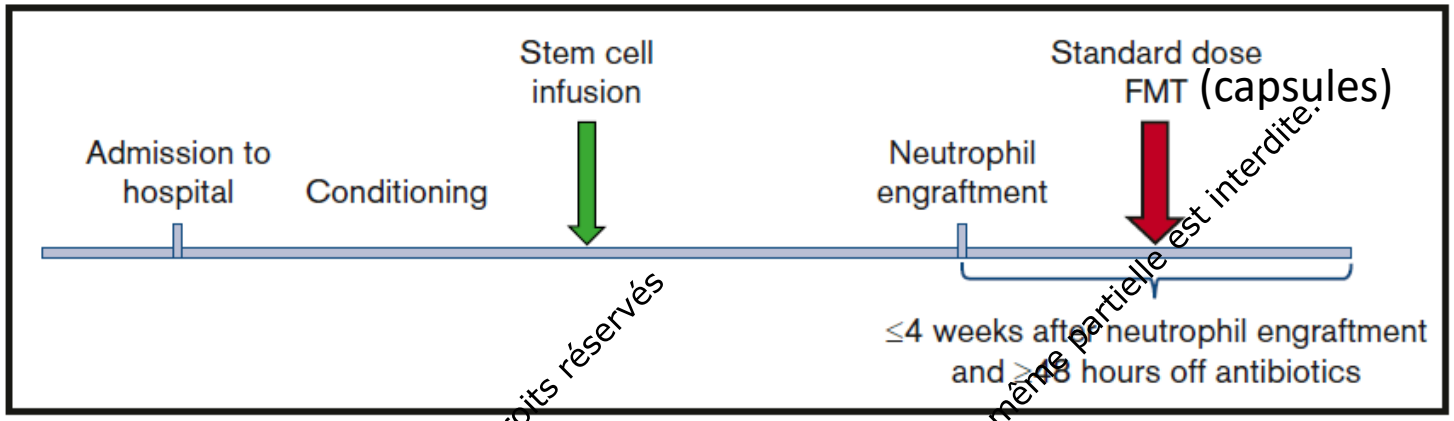
REGULAR ARTICLE

blood advances

Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity

Zachariah DeFilipp,[1] Jonathan U. Peled,[2,3] Shulin Li,[4] Jasmin Mahabamunuge,[5] Zeina Dagher,[1] Ann E. Slingerland,[2,3] Candice Del Rio,[1] Betsy Valles,[1] Maria E. Kempner,[1] Melissa Smith,[1] Jami Brown,[1] Bimalangshu R. Dey,[1] Areej El-Jawahri,[1] Steven L. McAfee,[1] Thomas R. Spitzer,[1] Karen K. Ballen,[6] Anthony D. Sung,[7] Tara E. Dalton,[7] Julia F. Messina,[8] Katja Dettmer,[9] Gerhard Liebisch,[10] Peter Oefner,[9] Ying Taur,[3,11] Eric G. Pamer,[3,11] Ernst Holler,[12] Michael K. Mansour,[5] Marcel R. M. van den Brink,[2,3] Elizabeth Hohmann,[5] Robert R. Jenq,[13,14,*] and Yi-Bin Chen[1,*]

[1]Blood and Marrow Transplant Program, Massachusetts General Hospital, Boston, MA; [2]Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Department of Medicine, Weill Cornell Medical College, New York, NY; [4]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; [5]Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA; [6]Division of Hematology/Oncology, University of Virginia School of Medicine, Charlottesville, VA; [7]Division of Hematologic Malignancies and Cellular Therapies and [8]Division of Infectious Diseases, Duke University School of Medicine, Durham, NC; [9]Institute of Functional Genomics, University of Regensburg, Regensburg, Germany; [10]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Regensburg, Germany; [11]Infectious Disease Service and Center for Microbes, Inflammation and Cancer, Memorial Sloan Kettering Cancer Center, New York, NY; [12]Department of Hematology and Oncology, Internal Medicine III, University Medical Center, Regensburg, Germany; and [13]Department of Genomic Medicine and [14]Department of Stem Cell Transplantation Cellular Therapy, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX



Major eligibility criteria:
Adult patients (≥18 year of age) receiving allogeneic transplant
8/8 HLA-matched related or unrelated donor or haploidentical donor
Myeloablative or fludarabine/melphalan conditioning regimen
Any GVHD prophylaxis
No history of IBD, delayed gastric emptying syndrome, active GI infection
No acute GI GVHD prior to FMT

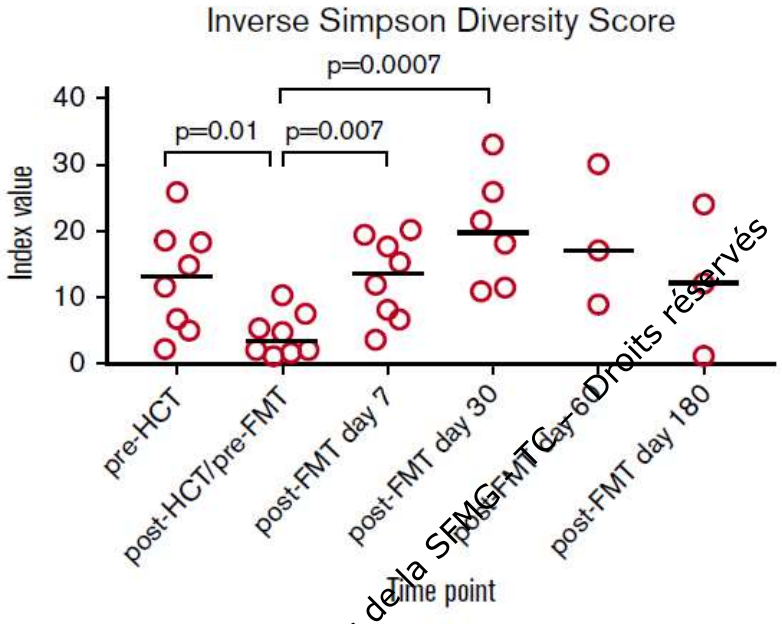
Number of patients enrolled on study prior to HCT: **18**

- Patient withdrew consent prior to HCT (**n=1**)
- Patients developing acute GI GVHD prior to FMT (**n=3**)

Number of patients eligible to receive FMT: **14**

- Patient with persistent HCT-related GI toxicity (**n=1**)

Number of patients receiving FMT: **13**



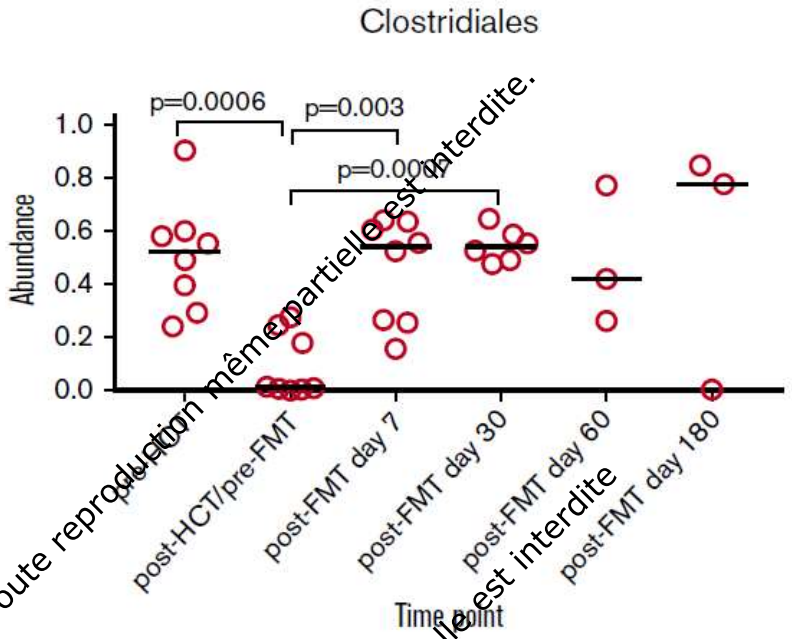


Table 2. Clinical outcomes

Outcome	Value
Patients receiving FMT, n	13
Median time from allo-HCT to FMT (range), d	27 (19-45)
Median follow-up (range), mo	15 (13-20)
C difficile colitis, n	1
Bacteremia, n	1
Grade 3-4 acute GVHD, n	2
Deaths, n	2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

N Engl J Med 2018;378:439-48.
DOI: 10.1056/NEJMoa1709866

- **ELIANA : first global multi-center CAR T cell trial**
  - Cell processing of CTL019 therapy at Novartis facility
  - U.S. manufactured cell therapy with global supply
  - 25 sites across 11 countries (North America, Europe and Asia Pacific)
  - Site training program: CTL019 -specific logistics and patient management
- **Key eligibility criteria**
  - **Inclusion: B-cell ALL, age 3–21*; bone marrow with ≥5% lymphoblasts**
  - Exclusion: Isolated extra-medullary disease relapse; prior CD19-directed or gene therapy
- **Lymphodepleting chemotherapy prior to infusion**
  - Fludarabine (30 mg/m^2 i.v. daily for 4 doses)
  - Cyclophosphamide (500 mg/m^2 i.v. daily for 2 doses)
- **Target CTL019 dosing (single infusion)**
  - 2.0–5.0 x 10^6/kg for patients ≤50kg
  - 1.0–2.5 x 10^8 for patients >50 kg

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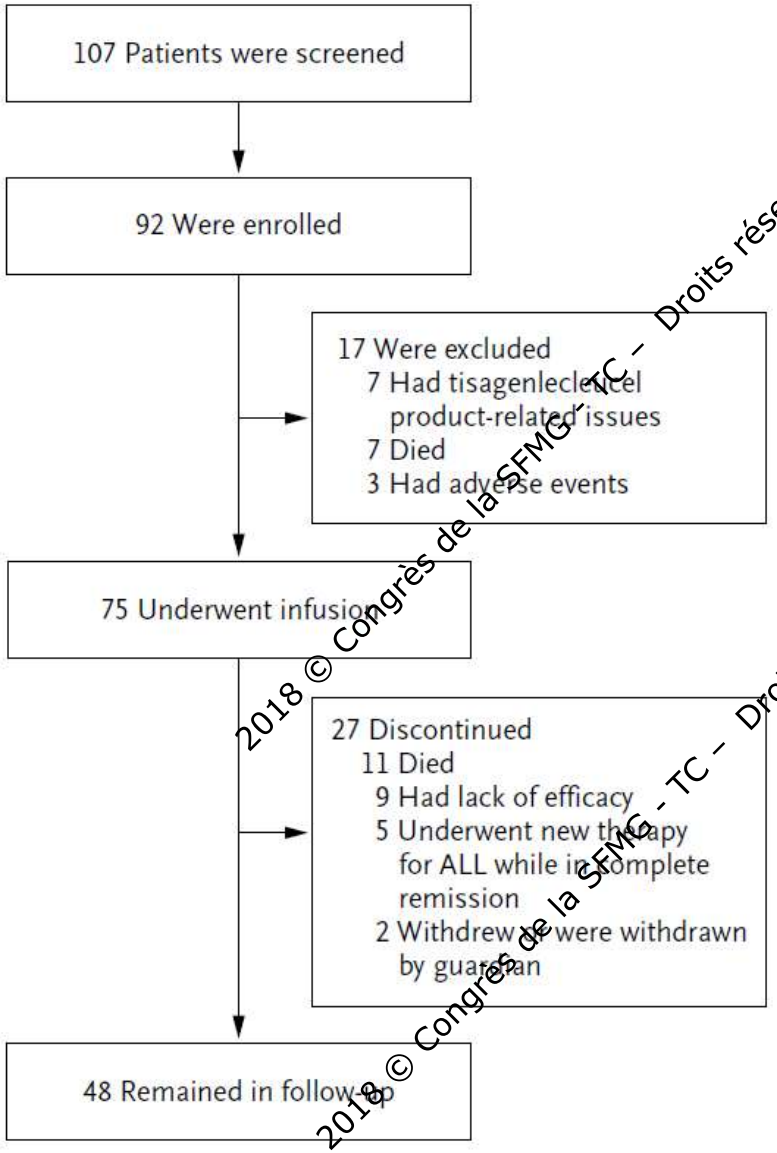


Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

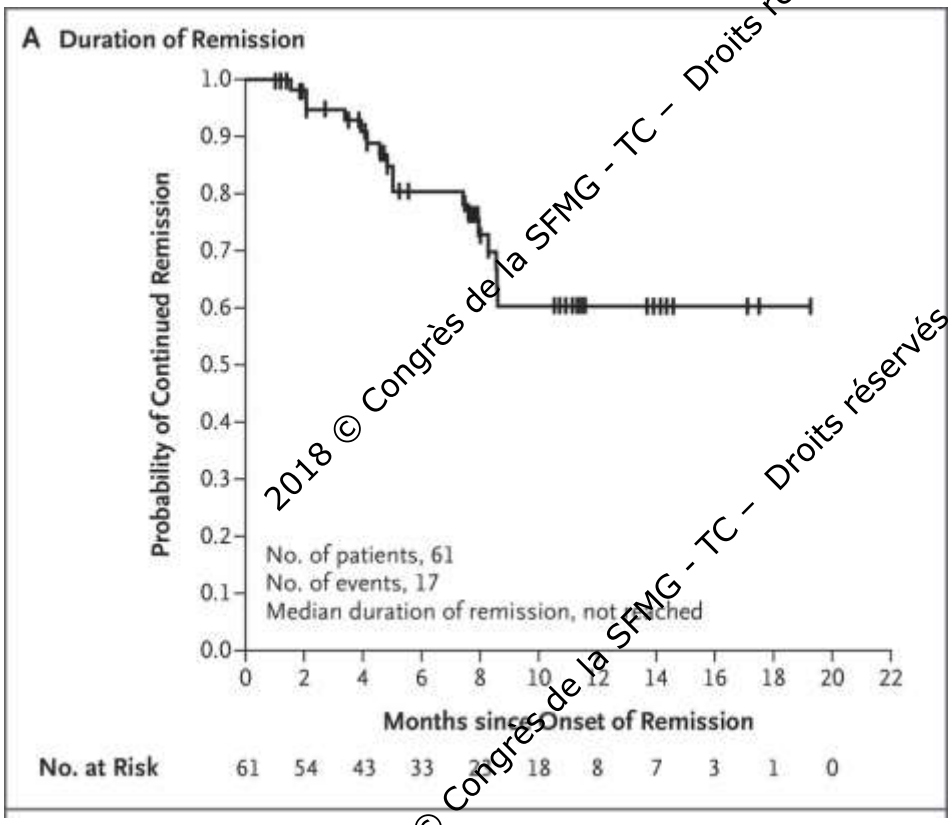
Type of Event	Any Grade (N=75)	Grade 3 (N=75)	Grade 4 (N=75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0

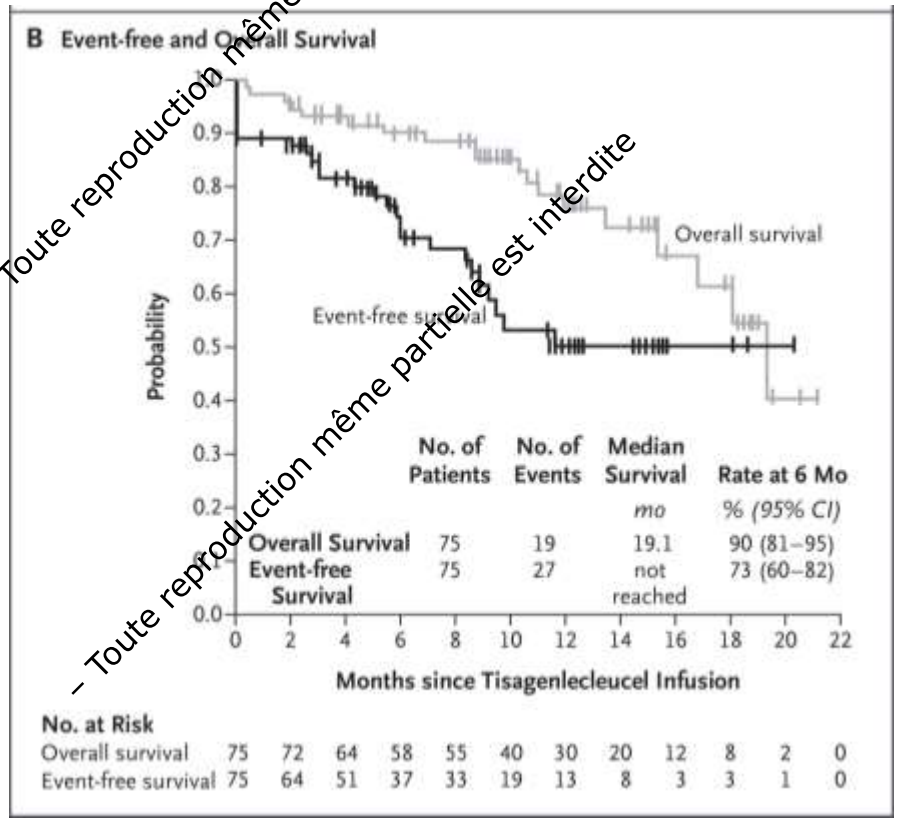
* The criteria for defining adverse events of special interest were based on experience from ongoing clinical studies. The cytokine release syndrome includes the Medical Dictionary for Regulatory Activities preferred terms "cytokine release syndrome," "cytokine storm," "shock," "macrophage activation," and "hemophagocytic lymphohistiocytosis." Neurologic events include the standardized Medical Dictionary for Regulatory Activities query terms "noninfectious encephalopathy" and "delirium."

MFU : 13 months

ORR: 81% (CR: 60% Cri:21%)

When CR/Cri: 95% MRD neg at D28





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

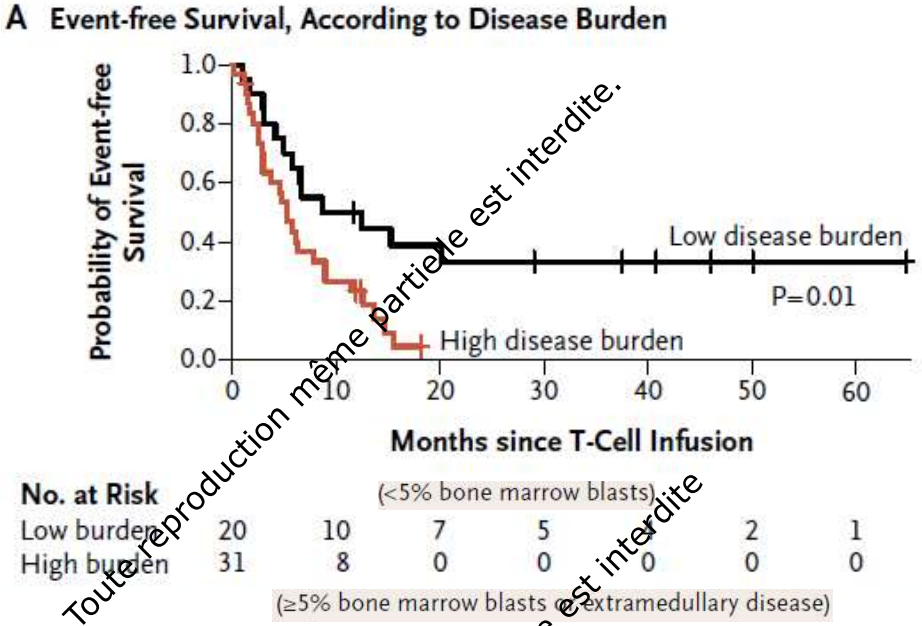
Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

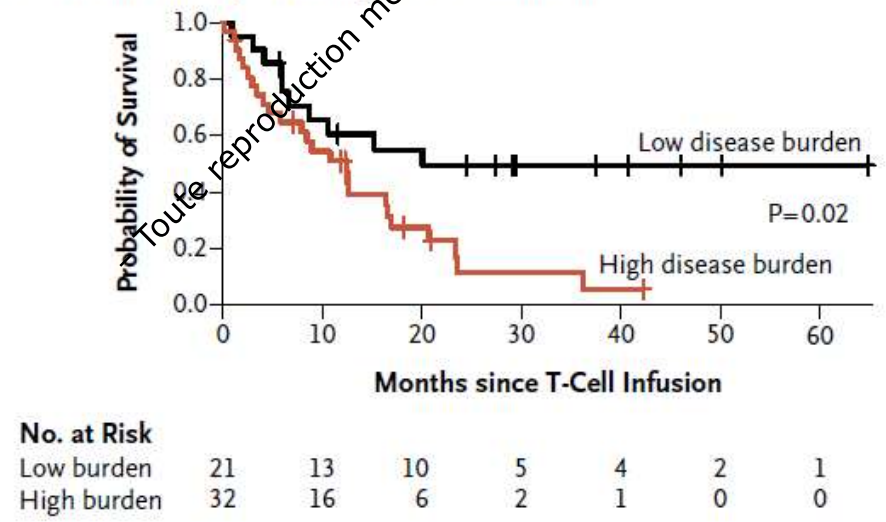
Jae H. Park, M.D., Isabelle Rivière, Ph.D., Mithat Gonen, Ph.D., Xiuyan Wang, Ph.D., Brigitte Sénéchal, Ph.D., Kevin J. Curran, M.D., Craig Sauter, M.D., Yongzeng Wang, Ph.D., Bianca Santomasso, M.D., Ph.D., Elena Mead, M.D., Mikhail Roshal, M.D., Peter Maslak, M.D., Marco Davila, M.D., Ph.D., Renier J. Brentjens, M.D., Ph.D., and Michel Sadelain, M.D., Ph.D.

N Engl J Med 2018;378:449-59.
DOI: 10.1056/NEJMoa1709919

Table 1. Characteristics of the 53 Patients at Baseline.*

Characteristic	Value
Age	
Median (range) — yr	44 (23–74)
Distribution — no. (%)	
18–30 yr	14 (26)
31–60 yr	31 (58)
>60 yr	8 (15)
No. of previous therapies — no. (%)	
2	21 (40)
3	13 (25)
≥4	19 (36)
Primary refractory disease — no. (%)	
Yes	12 (23)
No	41 (77)
Previous allogeneic HSCT — no. (%)	
Yes	19 (36)
No	34 (64)
Previous treatment with blinatumomab — no. (%)	
Yes	13 (25)
No	40 (75)
Pretreatment disease burden†	
Median bone marrow blasts (range) — %	63 (5–97)
Bone marrow blasts — no. (%)	
≥5%	27 (51)
<5% with extramedullary disease	5 (9)
≥0.01% and <5%	15 (28)
<0.01%	6 (11)
Philadelphia chromosome–positive — no. (%)	
Yes	16 (30)
No	37 (70)





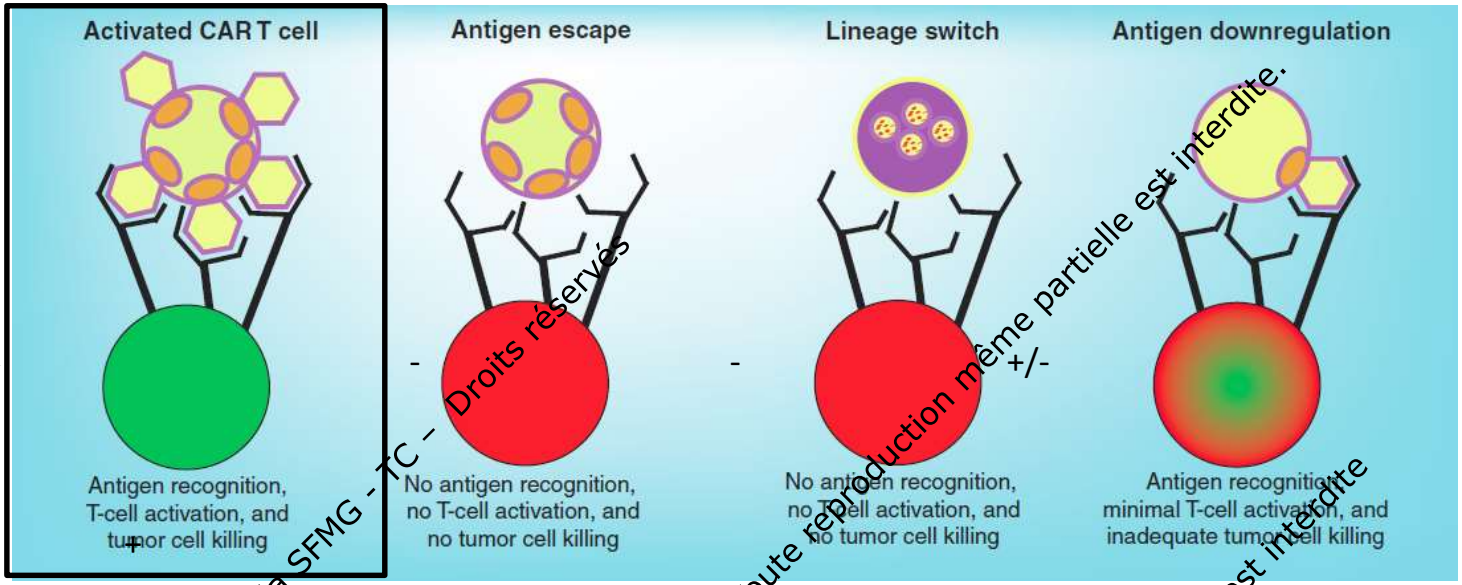
Tumor Antigen Escape from CAR T-cell Therapy

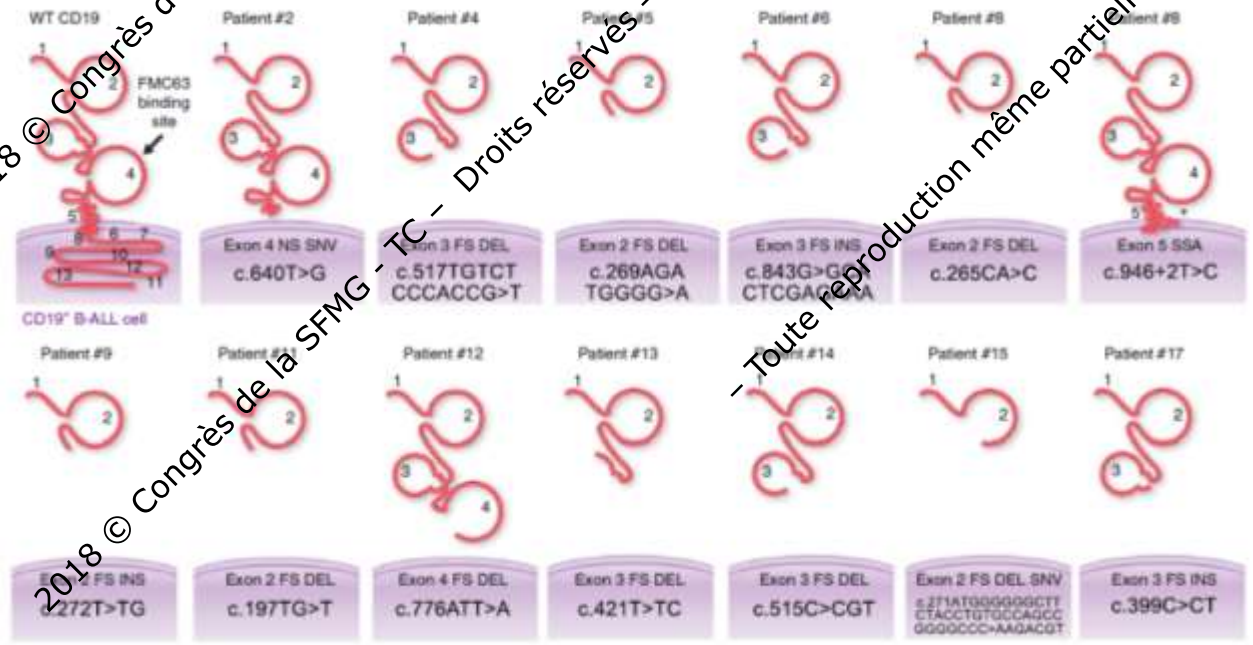
Robbie G. Majzner[1] and Crystal L. Mackall[1,2,3]

Cancer Discov; 8(10); 1–8. ©2018 AACR.

Table 1. A summary of antigen escape in CD19 CAR trials for ALL

Trial	Population	CD19 CAR construct	Relapse rate	CD19-negative relapse rate
Children's Hospital of Philadelphia phase I	Pediatric	FMC63-4-1BB-ζ	36% (20/55)	24% (13/55)
Novartis phase II (ELIANA)	Pediatric	FMC63-4-1BB-ζ	33% (20/61)	25% (15/61)
Seattle Children's Research Institute phase I	Pediatric	FMC63-4-1BB-ζ	45% (18/40)	18% (7/40)
NCI phase I	Pediatric	FMC63-CD28-ζ	29% (8/28)	18% (5/28)
Memorial Sloan Kettering phase I	Adult	SJ25C1-CD28-ζ	57% (25/44)	9% (4/44)
Fred Hutchinson Cancer Center phase I	Adult	FMC63-4-1BB-ζ	31% (9/29)	7% (2/29)





Orlando et al, Nat Med 2018

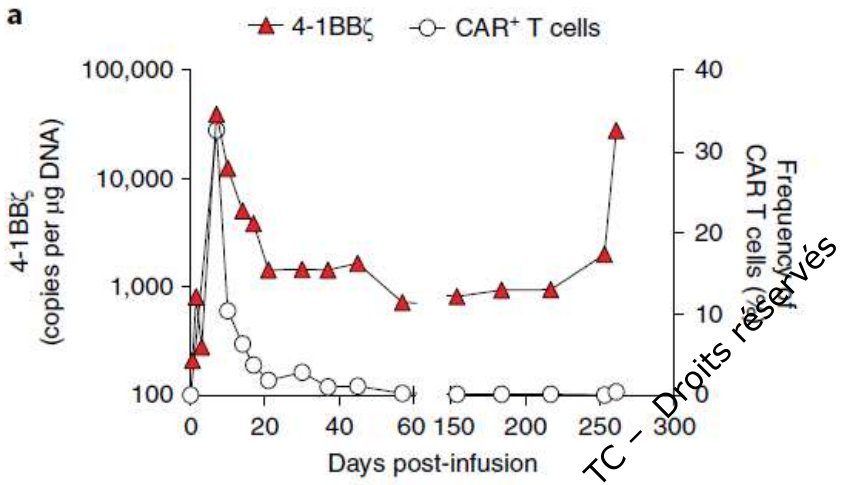
nature medicine

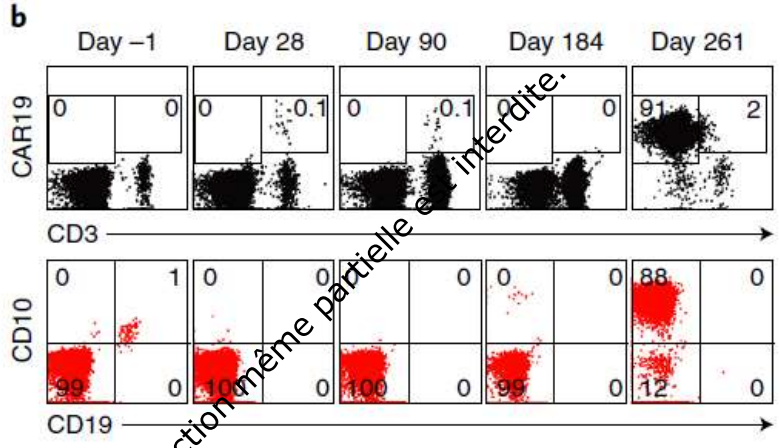
BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-018-0201-9

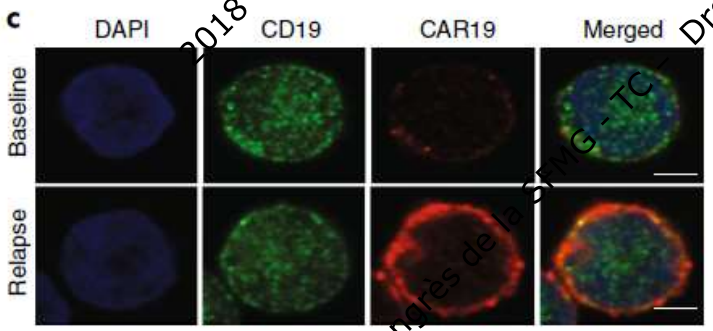
Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell

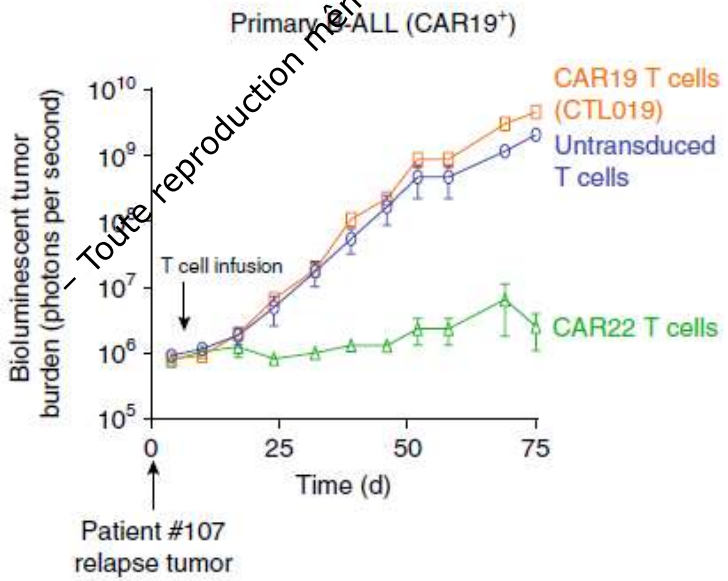
Marco Ruella[1,2,3,4,5,11], Jun Xu[1,2,3,11], David M. Barrett[6,11], Joseph A. Fraietta[1,2,3,4], Tyler J. Reich[1], David E. Ambrose[1], Michael Klichinsky[1,7], Olga Shestova[1], Prachi R. Patel[1], Irina Kulikovskaya[1], Farzana Nazimuddin[1], Vijay G. Bhoj[1,2,3], Elena J. Orlando[8], Terry J. Fry[9], Hans Bitter[8], Shannon L. Maude[6], Bruce L. Levine[1,2,3], Christopher L. Nobles[10], Frederic D. Bushman[10], Regina M. Young[1], John Scholler[1], Saar I. Gill[1,3,5], Carl H. June[1,2,3,4*], Stephan A. Grupp[6], Simon F. Lacey[1,2,3,12] and J. Joseph Melenhorst[1,2,3,12*]





Ectopic CAR19 expression on B-ALL cells masks CD19 and creates CTL019-resistant leukemia.





AMM européennes - CAR-T cells

ont obtenu une AMM européenne le 28 août 2018:

- Kymriah ® (tisagenlecleucel, Novartis):

-chez les patients de moins de 26 ans comme traitement de la leucémie lymphoblastique aiguë à cellules B réfractaire ou récidivante

-chez les adultes atteints de lymphome diffus à grandes cellules B en rechute ou réfractaires à au moins deux lignes de thérapie systémique.

- Yescarta® (axicabtagene ciloleucel, Kite-Gilead) pour le traitement de :

-patients adultes atteints d'un lymphome diffus à grandes cellules B (LDGCB)

-ou d'un lymphome médiastinal primitif à grandes cellules B (LMPGCB),

-réfractaires ou en rechute, après au moins deux lignes de traitement systémique

Leukemia

CAR T-cells targeting FLT3 have potent activity against FLT3−ITD+AML and act synergistically with the FLT3-inhibitor crenolanib

Hardikkumar Jetani, Irene Garcia-Cadenas, Thomas Nerreter, Simone Thomas, Julian Rydzek, Javier Briones Meijide, Halvard Bonig, Wolfgang Herr, Jordi Sierra, Hermann Einsele, Michael Hudecek

Wang et al. Journal of Hematology & Oncology (2018) 11:60
https://doi.org/10.1186/s13045-018-0603-7

Journal of Hematology & Oncology

RESEARCH Open Access

Targeting FLT3 in acute myeloid leukemia using ligand-based chimeric antigen receptor-engineered T cells

Ying Wang†, Yingxi Xu†, Shisai Li, Jia Liu, Yanyan Xing, Haiyan Xing, Zheng Tian, Kejing Tang, Qing Rao, Min Wang* and Jianxiang Wang*

Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

A Novel Anti-LILRB4 CAR-T Cell for the Treatment of Monocytic AML

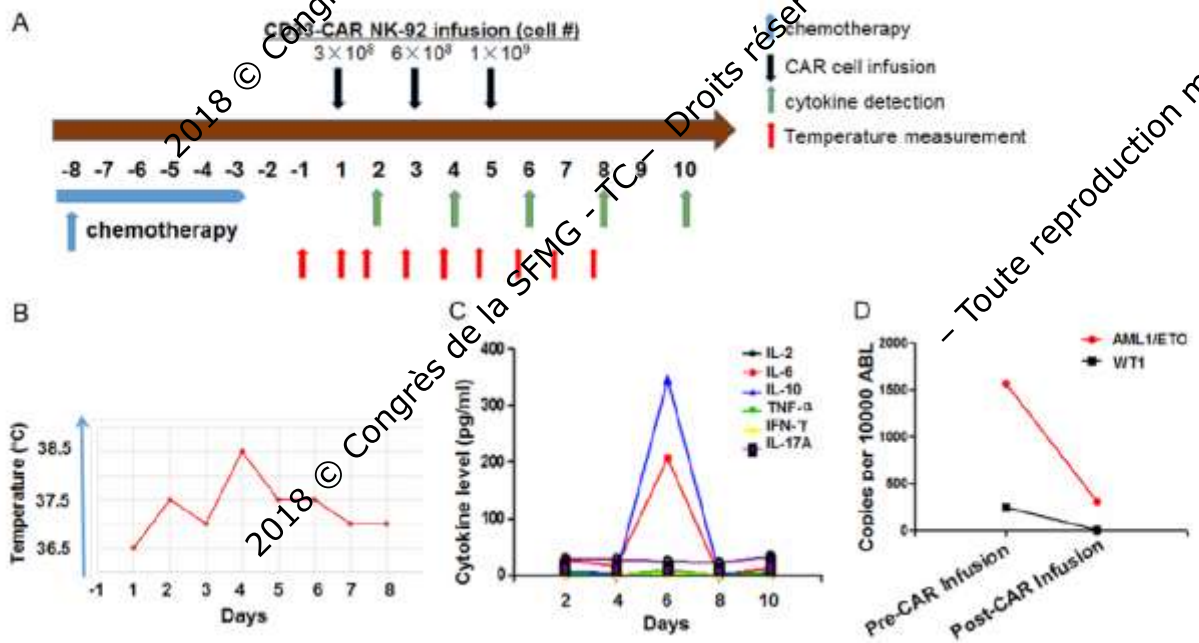
Samuel John,[1,5] Heyu Chen,[2,5] Mi Deng,[2,5] Xun Gui,[3] Guojin Wu,[2] Weina Chen,[4] Zunling Li,[2] Ningyan Zhang,[3] Zhiqiang An,[3] and Cheng Cheng Zhang[2]

Am J Cancer Res 2018;8(6):1083-1089
www.ajcr.us /ISSN:2156-6976/ajcr0078782

Original Article

First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia

Xiaowen Tang[2,3*], Lin Yang[3,4,5*], Zheng Li[1,2,3], Ansel P Nalin[6], Haiping Dai[1,2], Ting Xu[1,2,3], Jia Yin[1,2,3], Fengtao You[3,4,5], Mingqing Zhu[1,2,3], Wenhong Shen[1,2,3], Guanghua Chen[1,2,3], Xiaoming Zhu[1,2,3], Depei Wu[1,2,3], Jianhua Yu[6,7,8]



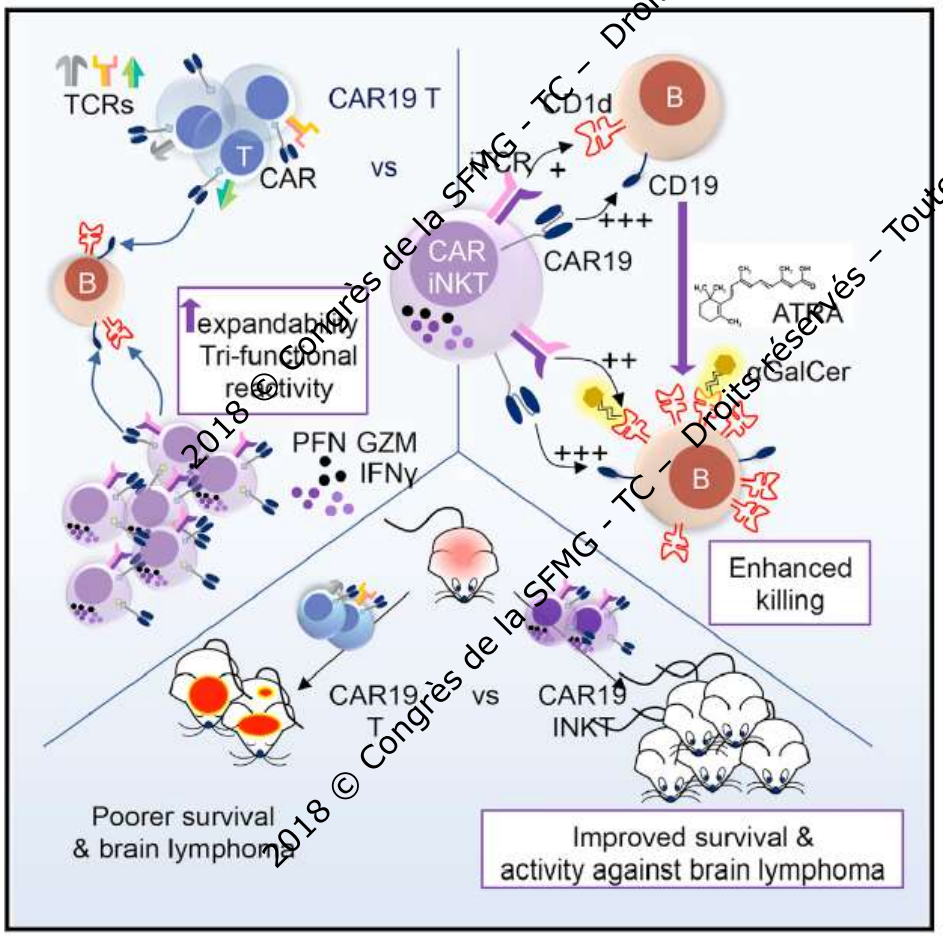
2 RC/3 patients

Rechute précoce chez les 2 répondeurs

Cancer Cell

Enhanced Anti-lymphoma Activity of CAR19-iNKT Cells Underpinned by Dual CD19 and CD1d Targeting

Graphical Abstract



Authors

Antonia Rotolo, Valentina S. Caputo, Monika Holubova, ..., Kikkeri Naresh, Jordan Maher, Anastasios Karadimitris

Correspondence

a.karadimitris@imperial.ac.uk

In Brief

Rotolo et al. show that anti-CD19 chimeric antigen receptor (CAR19)-engineered CD1d-restricted invariant NKT cells (iNKT) are more effective than CAR19-T cells against CD1d-expressing lymphomas, including those in the brain. De-repression of CD1d expression further enhances the anti-tumor efficacy of CAR19-iNKT.

Rotolo et al., 2018, Cancer Cell *34*, 596–610

Phase 3 study

VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

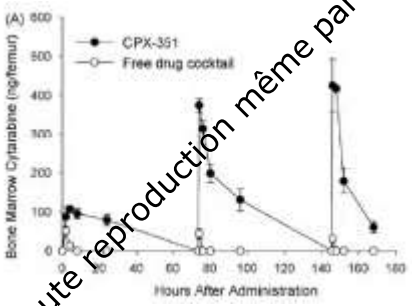
CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

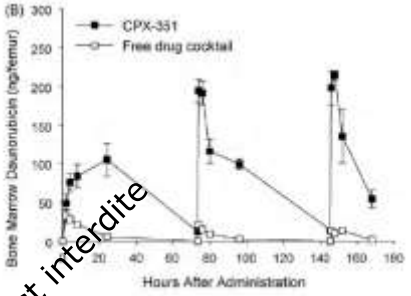
Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ruhan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur E. Louie, and Bruno C. Medeiros

Lancet JE, et al. *J Clin Oncol* 2018;36:2684–92

Dual drug advanced liposomal formulation : Vyxeos®

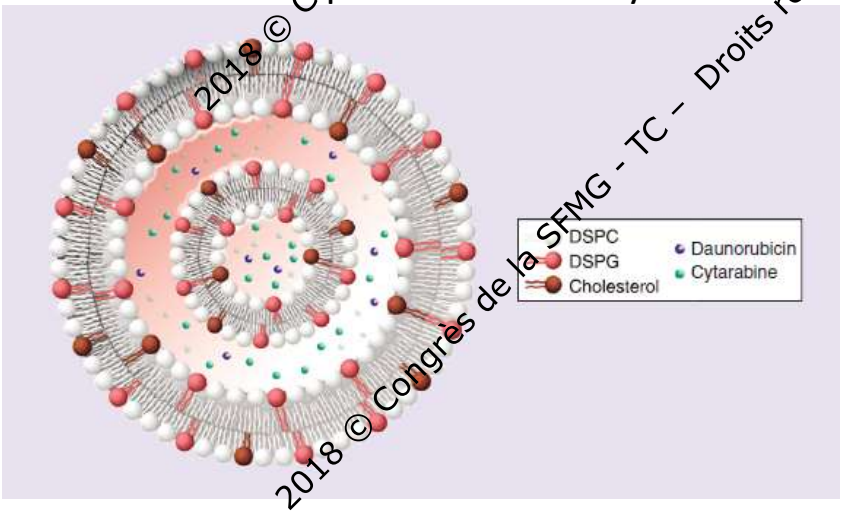
- Bilamellar liposomes,100 nm
- Membrane composed of DSPC:DSPG:cholesterol in a 7:2:1 molar ratio
- Cytarabine and daunorubicin encapsulated in the aqueous space of both vesicles at a 5:1 molar ratio

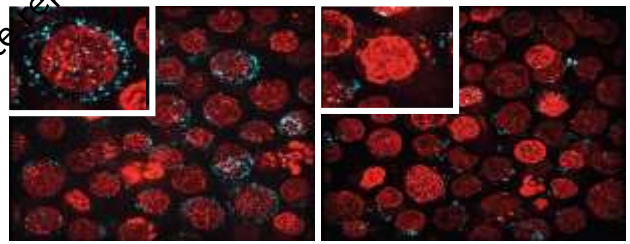




- Vyxeos accumulates in the bone marrow at high concentrations and is preferentially taken up by leukaemic vs normal marrow cells

Schematic representation of Vyxeos®



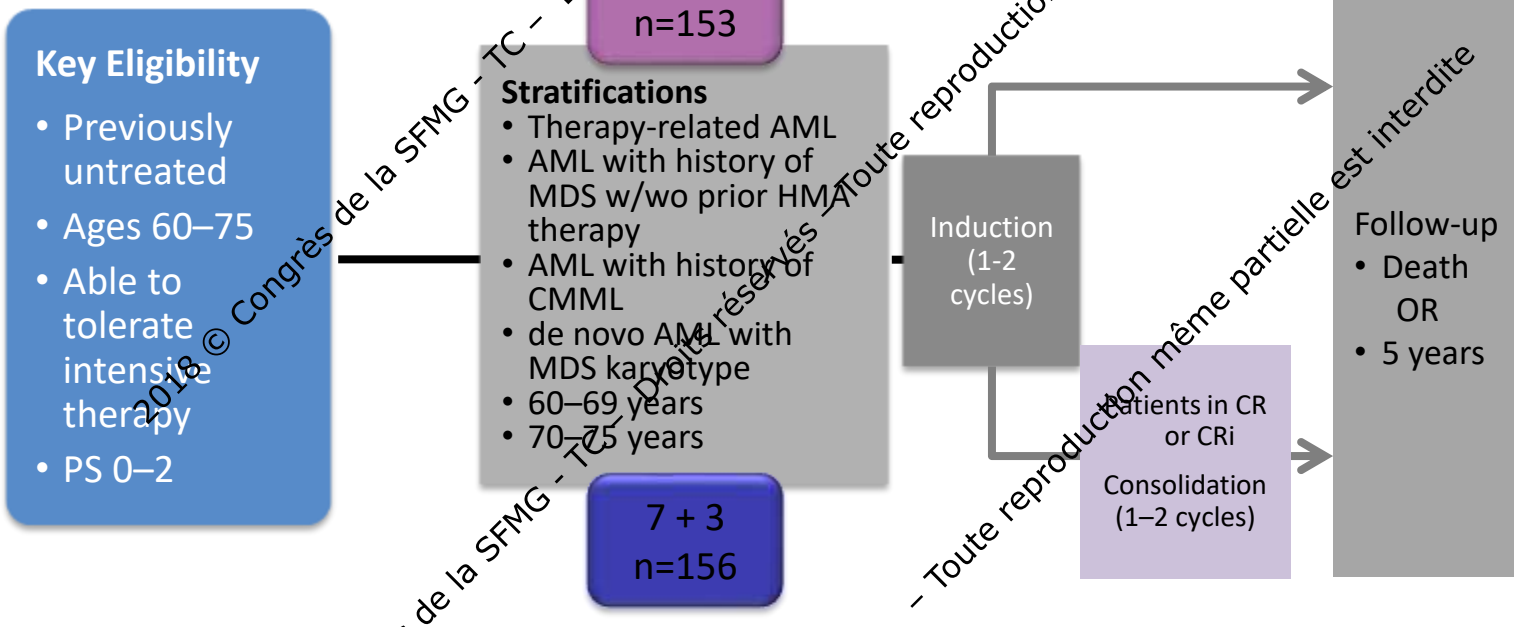


DSPC: Distearylphosphatidylcholine; DSPG: Distearylphosphatidylglycerol

Tolcher AW et al. *Futur Oncol* 2018; 10.2217/fon-2017-0607

Lim WS, et al. Leuk Res 2010;34:1214–23

Phase 3 study of CPX-351 vs standard induction in older patients with newly diagnosed high-risk AML



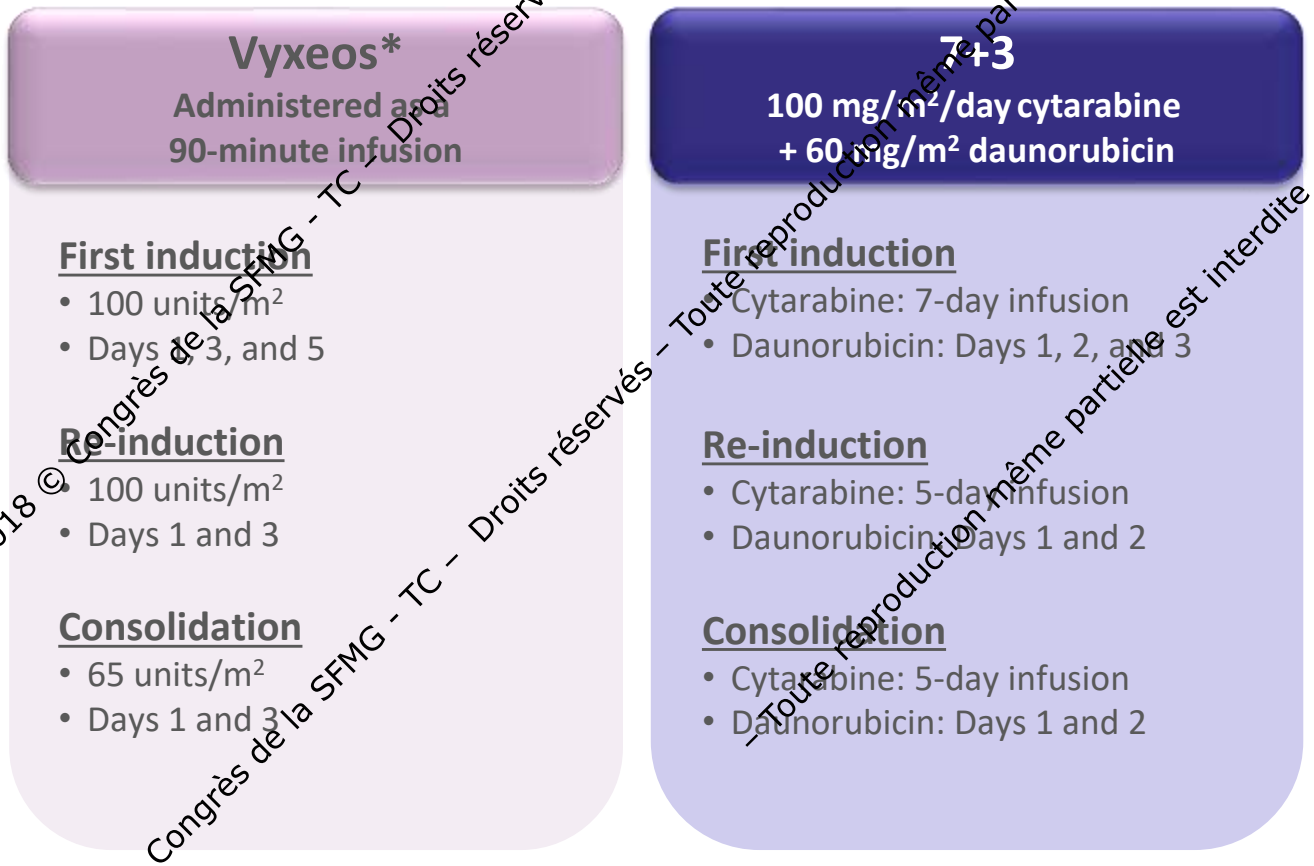
Primary Endpoint: Overall survival

*CPX-351=Vyxeos®

CMML, chronic myelomonocytic leukeamia; CR, complete response; CRi, CR with incomplete bloody count recovery; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; PS, performance status.

Lancet JE et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. J Clin Oncol 2018;36(26):2684-2692

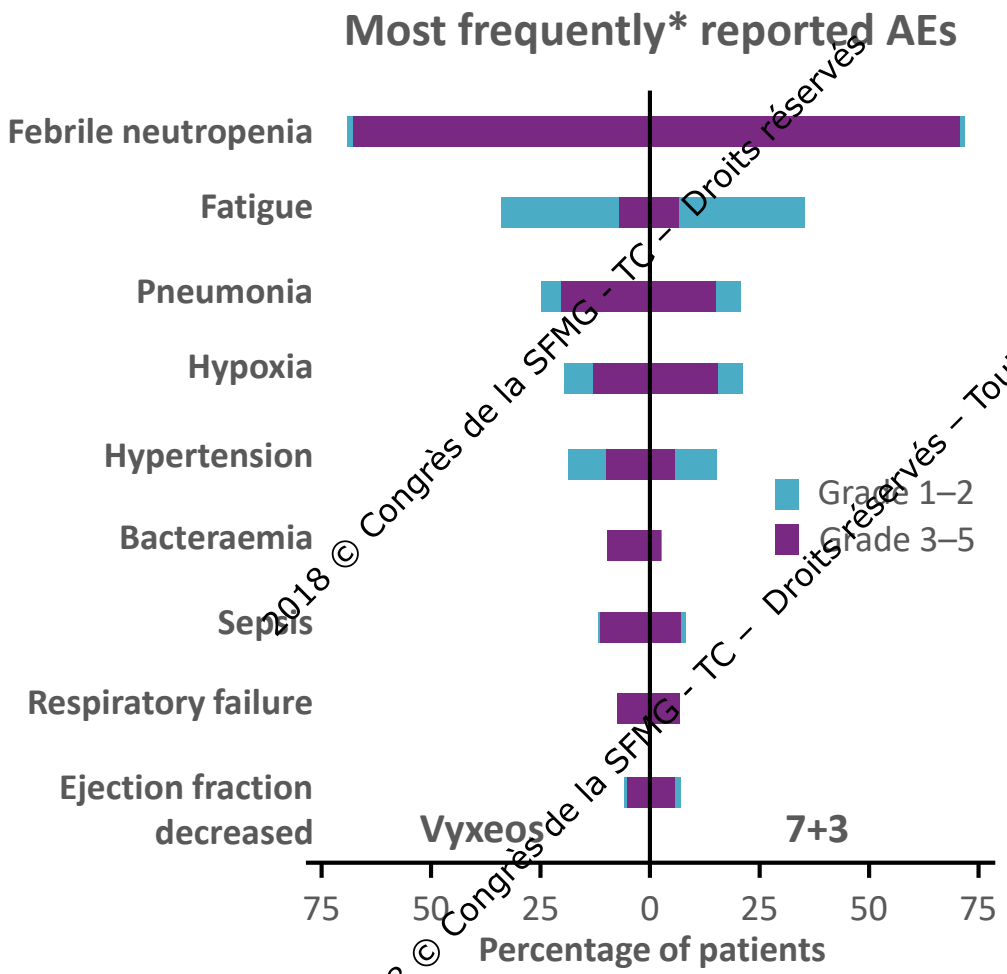
Treatment schedule and dosing



*1 unit = 1 mg cytarabine + 0.44 mg daunorubicin

Lancet JE et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. J Clin Oncol 2018;36(26):2684-2692

Safety

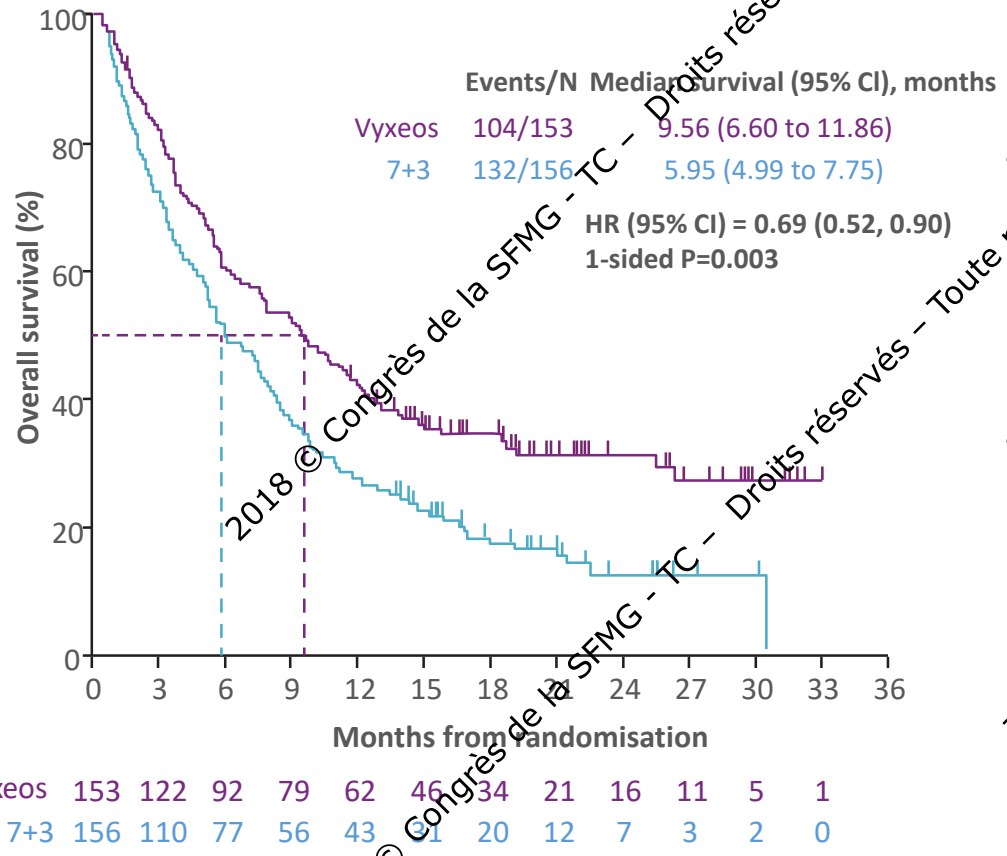


- The types of AEs, proportions of patients who experienced them, and severities of events were comparable between treatment cohorts
- The most frequently reported grade 3–5 AEs were febrile neutropenia, pneumonia, and hypoxia
- The median time to neutrophil (≥500/mL) and platelet (≥50,000/mL) recovery in patients who achieved CR + CRi after initial induction chemotherapy was longer with CPX-351 (35.0 and 36.5 days, respectively) versus 7+3 (29 and 29 days)
- Early mortality rates was :
  - <30 days: 5.9% with CPX-351 vs 10.6% with “7+3”; 2-sided p=0.149
  - <60 days: 13.7% with CPX-351 vs 21.2% with “7+3”; 2-sided p=0.097

*The percentages of patients with grade 1–2 and 3–5 events are shown for all adverse events occurring in >5% of patients in either treatment group as grade 3–5 events;
AE, adverse event

Lancet JE, et al. *J Clin Oncol* 2018;36:2684–92

Vyxeos is the first chemotherapy to significantly increase overall survival vs 7+3 for patients with high-risk AML

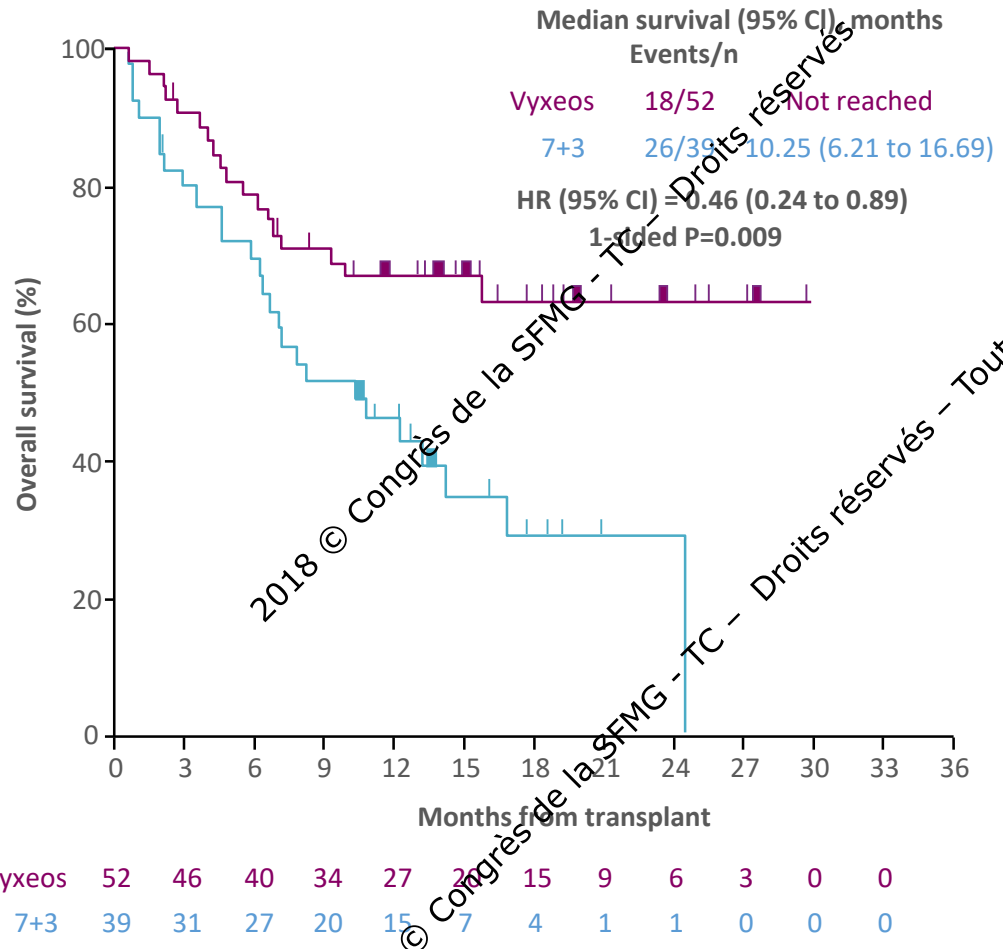


- With a median follow-up of 20.7 months, Vyxeos significantly improved OS vs 7+3
- Kaplan–Meier estimates of OS:
  - 1-year: 41.5% for Vyxeos vs 27.6% for 7+3
  - 2-year: 31.1% for Vyxeos vs 12.3% for 7+3

Lancet JE, et al. *J Clin Oncol* 2018;36:2684–92

CI, confidence interval; HR, hazard ratio; OS, overall survival
7+3, standard cytarabine and daunorubicin

Post-hoc analysis suggests that Vyxeos may improve transplant outcomes for patients vs 7+3



- Vyxeos arm: 34% of patients received transplant
- 7 + 3 arm: 25% of patients received transplant
- An exploratory landmark Kaplan–Meier estimate of overall survival analysis from the time of HSCT favoured Vyxeos

Lancet JE, et al. *J Clin Oncol* 2018;36:2684–92

Vyxeos® :
AMM européenne obtenue le 23 aout 2018

Vyxeos® est indiqué pour le traitement des patients adultes présentant une leucémie aiguë myéloblastique nouvellement diagnostiquée, secondaire à un traitement (LAM-t) ou une LAM avec anomalies associées aux myélodysplasies (LAM-MRC). [1]

LAM-t [2]

- LAM secondaire à un traitement (chimiothérapie et/ou radiothérapie)

LAM-MRC [2]

(AML-MRC selon OMS)

- LAM post-SMD ou post-SMD/SMP
- LAM *de novo* avec anomalies cytogénétiques associées aux myélodysplasies
- LAM avec dysplasie multilignée*

AML-MRC : Acute Myeloid Leukemia - Myelodysplasia-Related Changes / LAM-MRC : LAM avec anomalies associées aux myélodysplasies ; SMD : Syndrome Myélodysplasique ; SMP : Syndrome Myéloprolifératif

*en l'absence de mutation NPM1 ou mutation biallélique CEBPA.

1. Résumé des caractéristiques du produit Vyxeos® en vigueur. 2. Swerdlow S, Campo E *et al*. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, 2017, Lyon, France: IARC, 4e édition. pp:150-2.