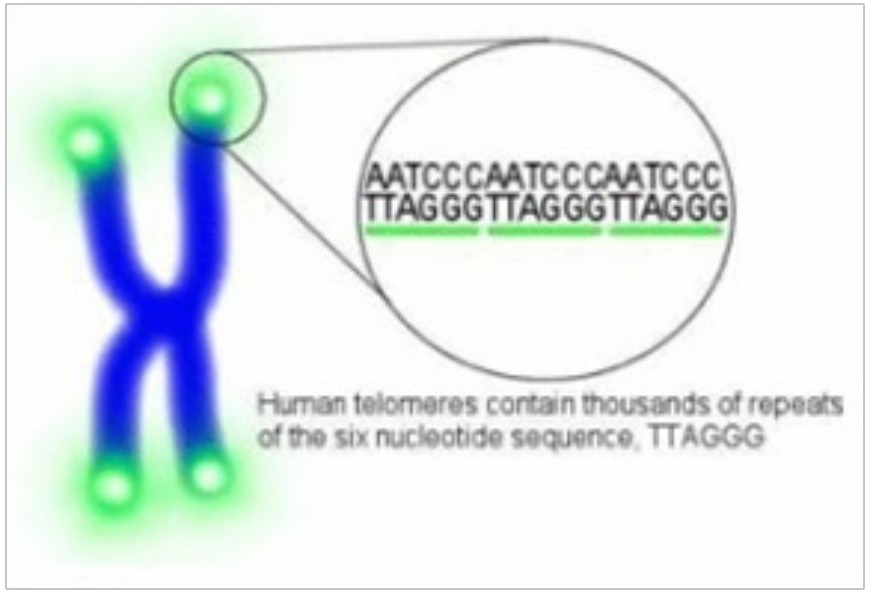
Actualités
HSCT et Téloméropathies

Mony Fahd

03/10/2025



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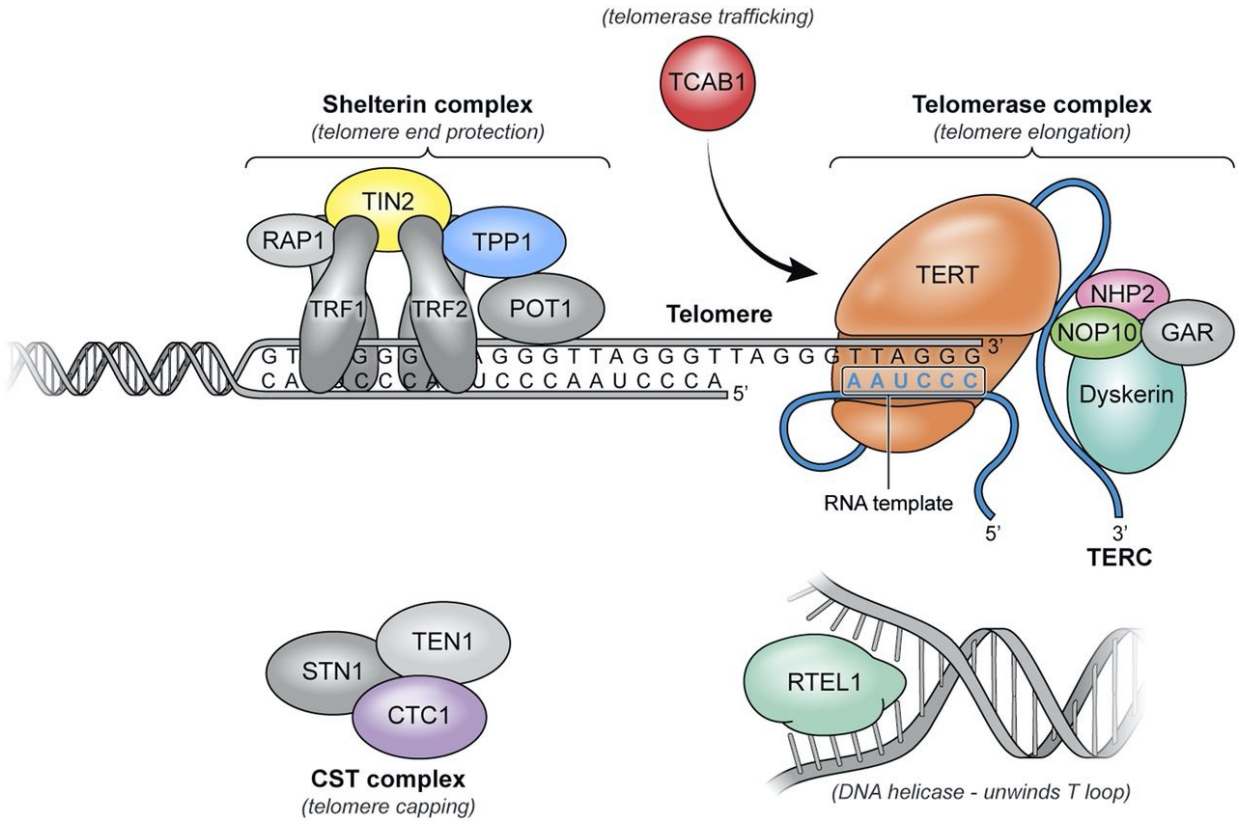
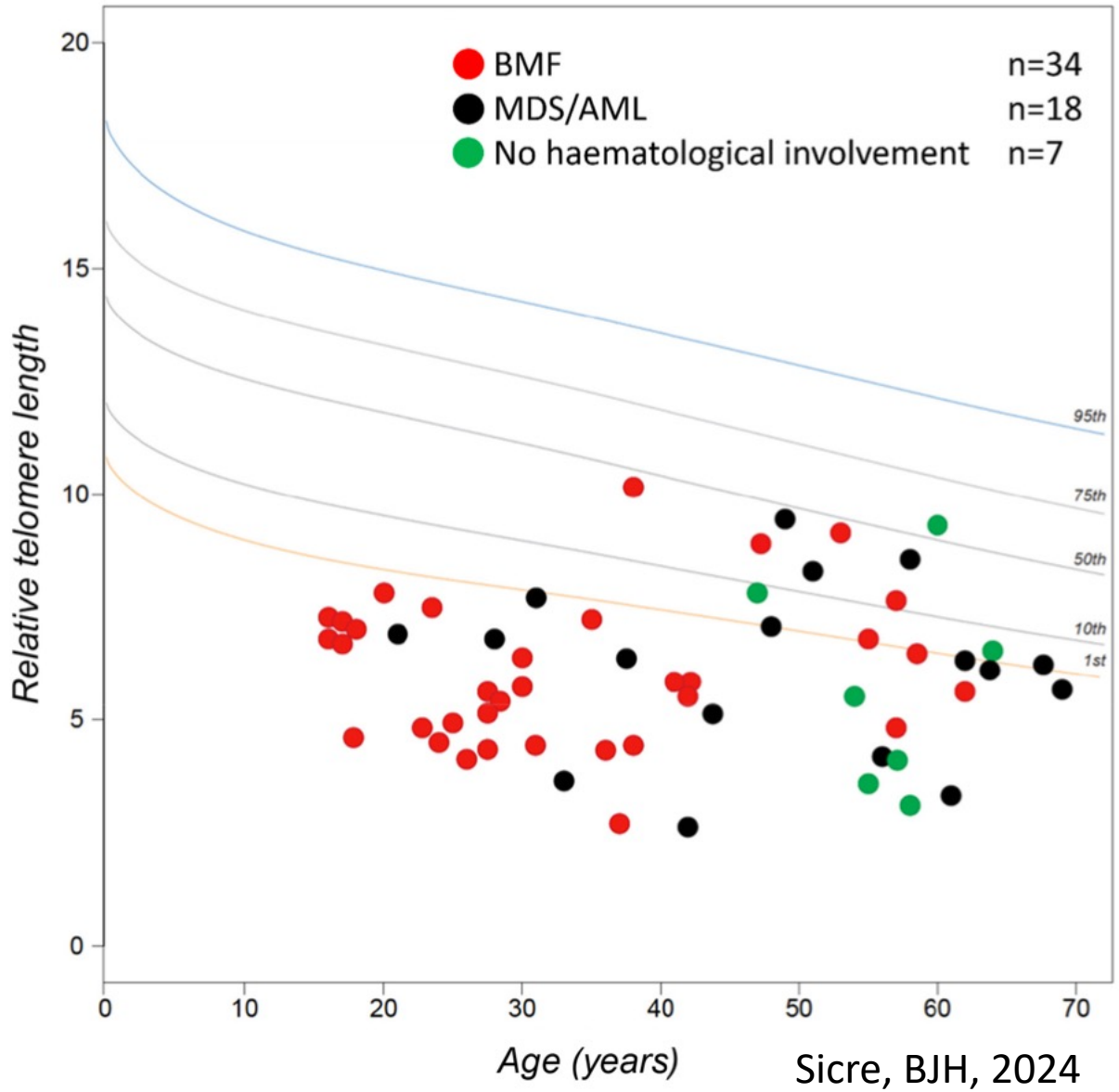
Telomere biology Disorders TBD

Gènes en cause: tous impliqués dans la synthèse/ maintenance/ protection des télomères

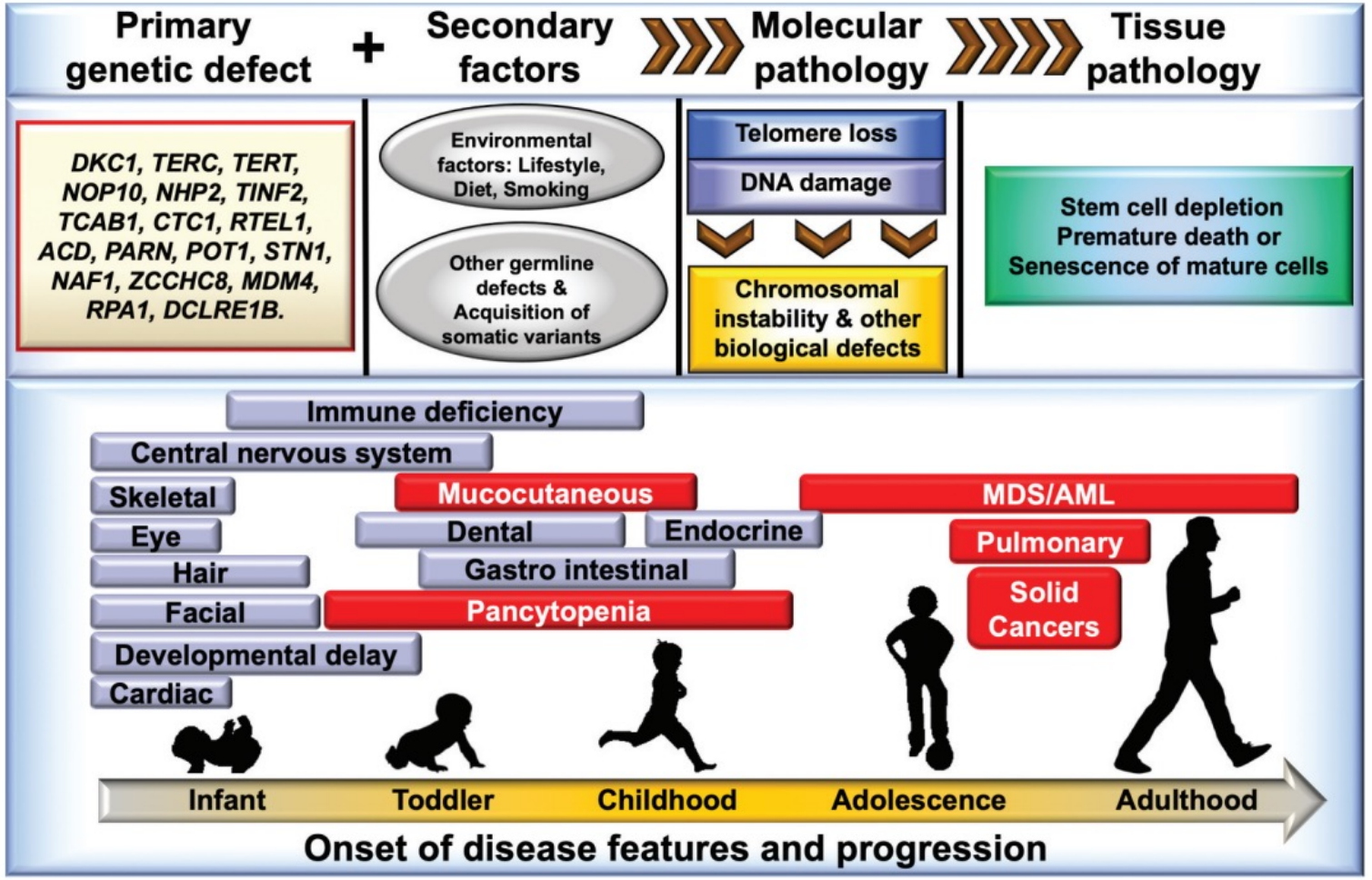




Sicre, BJH, 2024

TBD et profil évolutif?

- Corrélation Génotype/Phénotype
- Anticipation génétique
- Pénétrance incomplète
- SGR

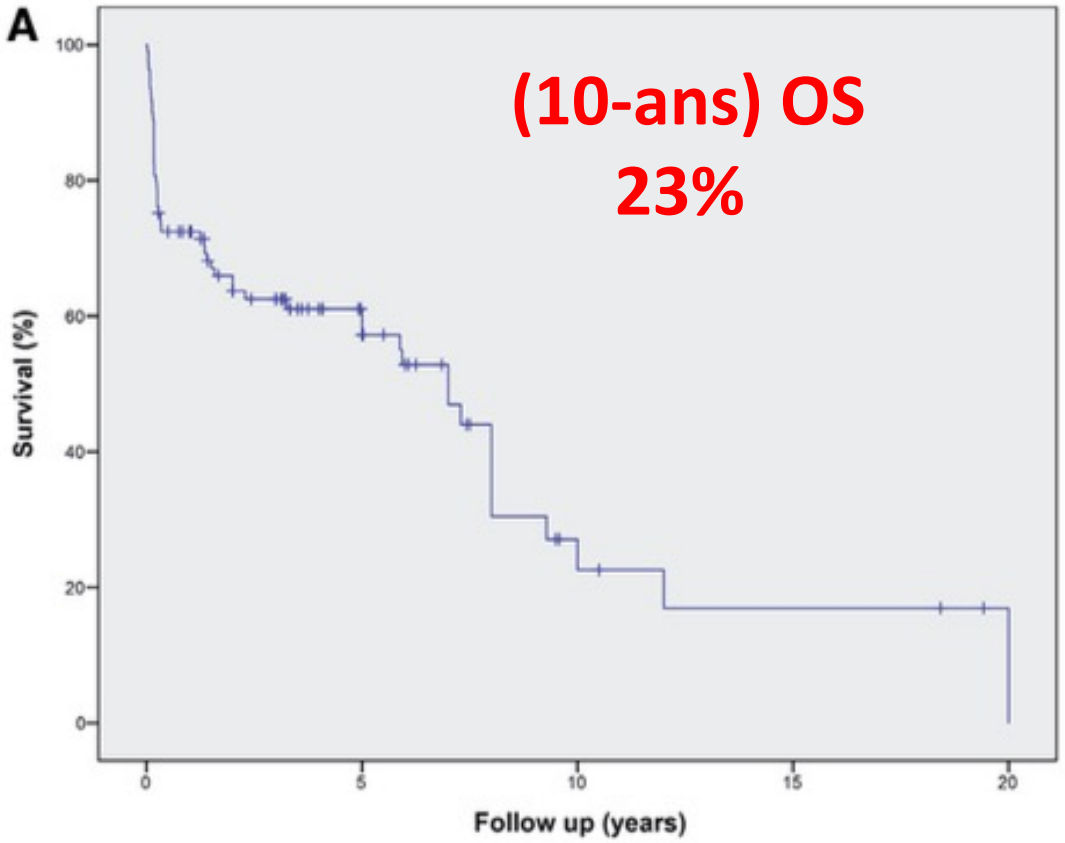


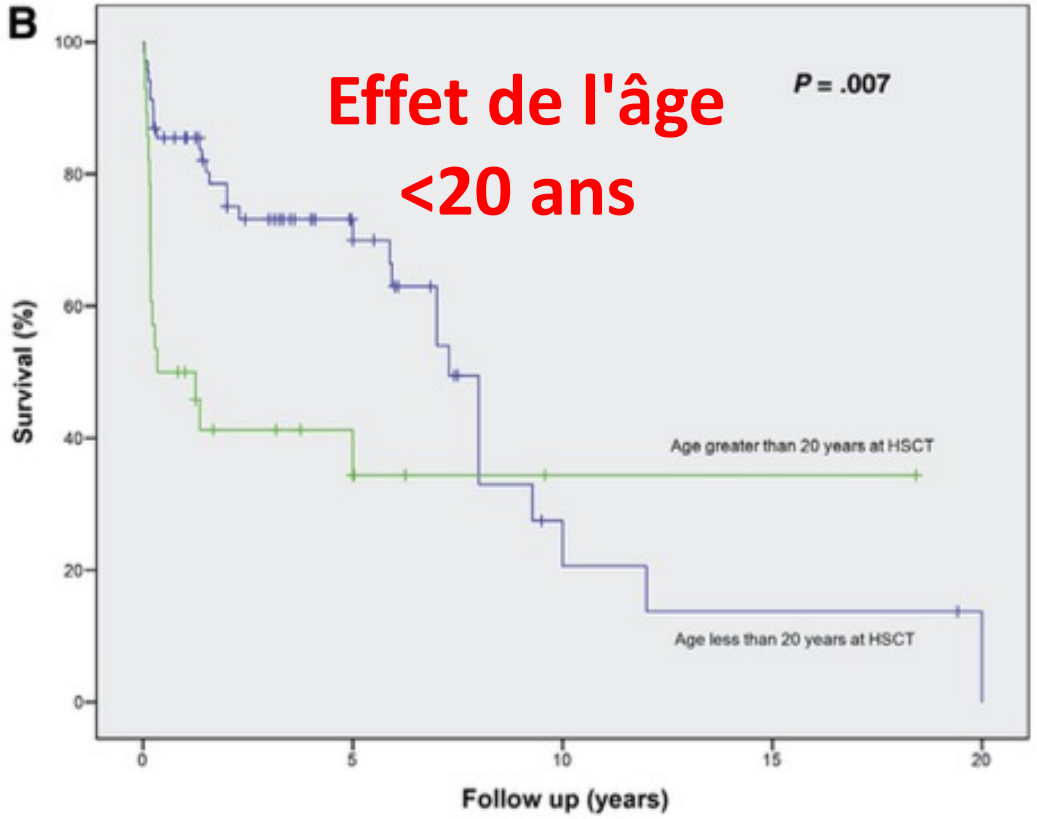
Dokal, 2022

Survival after hematopoietic stem cell transplantat in patient with dyskeratosis congenital: systematic review of the literature

Barbaro, BBMT, 2016

N=109
36 études
1976-2013





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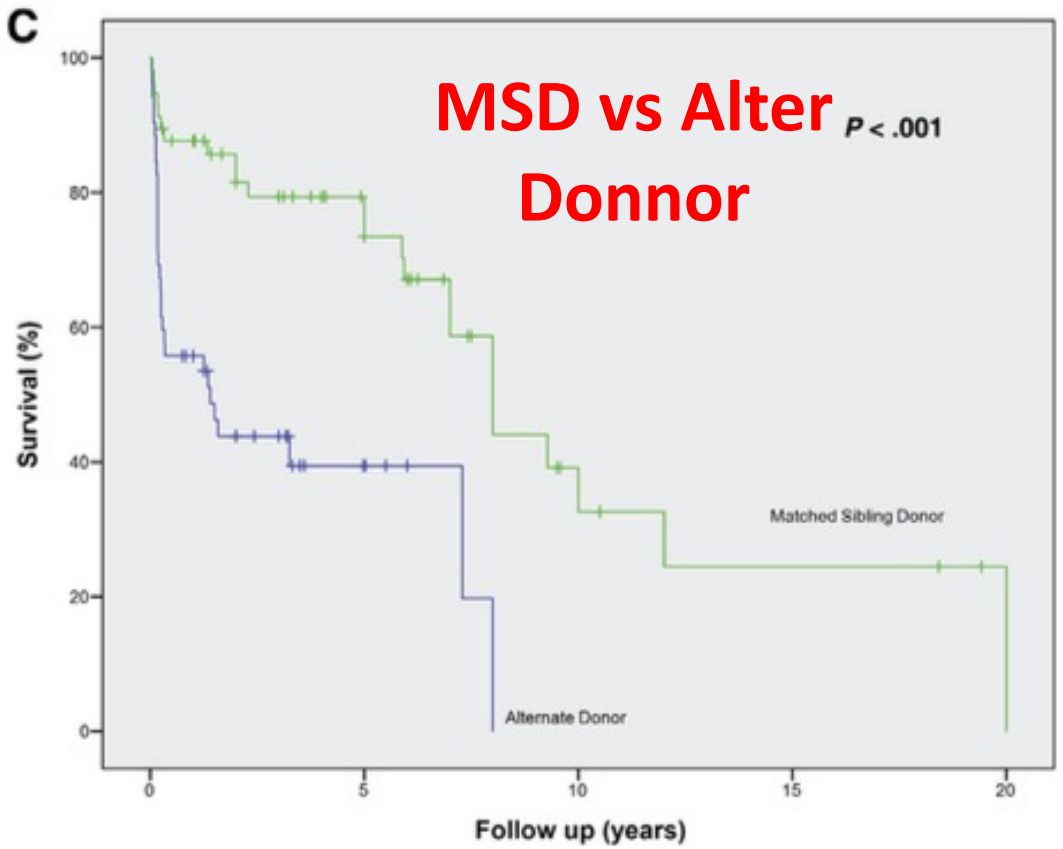
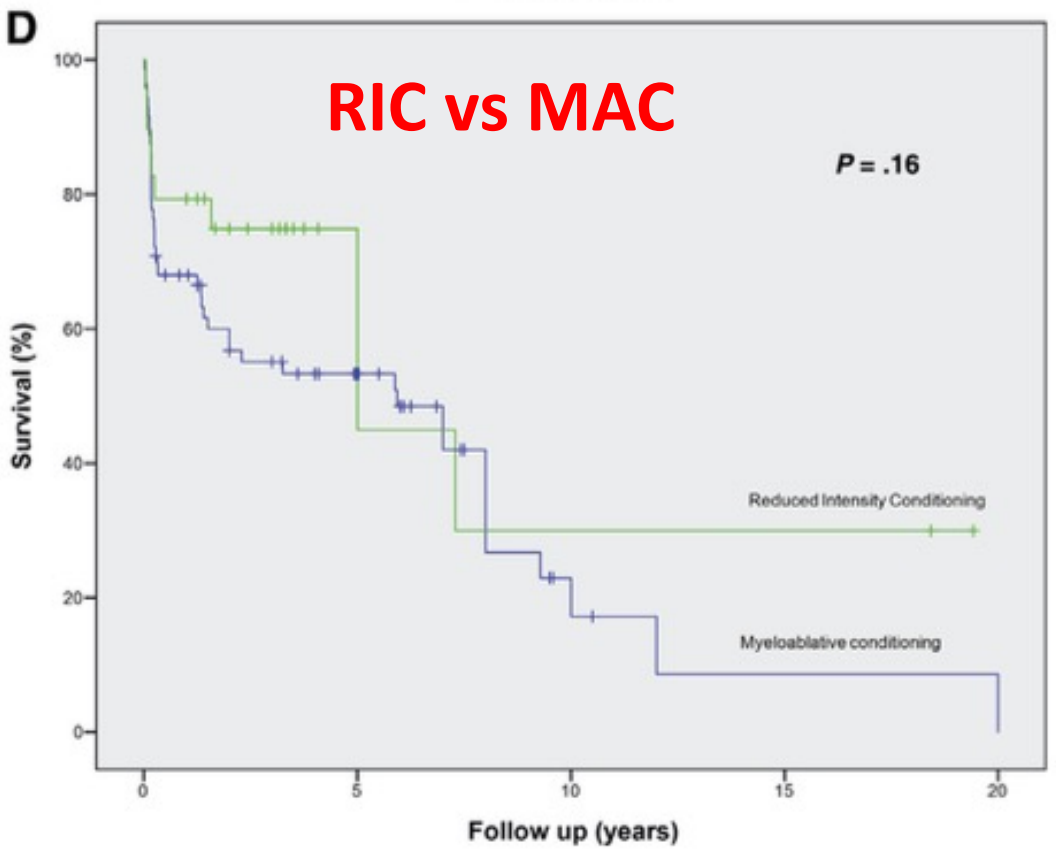




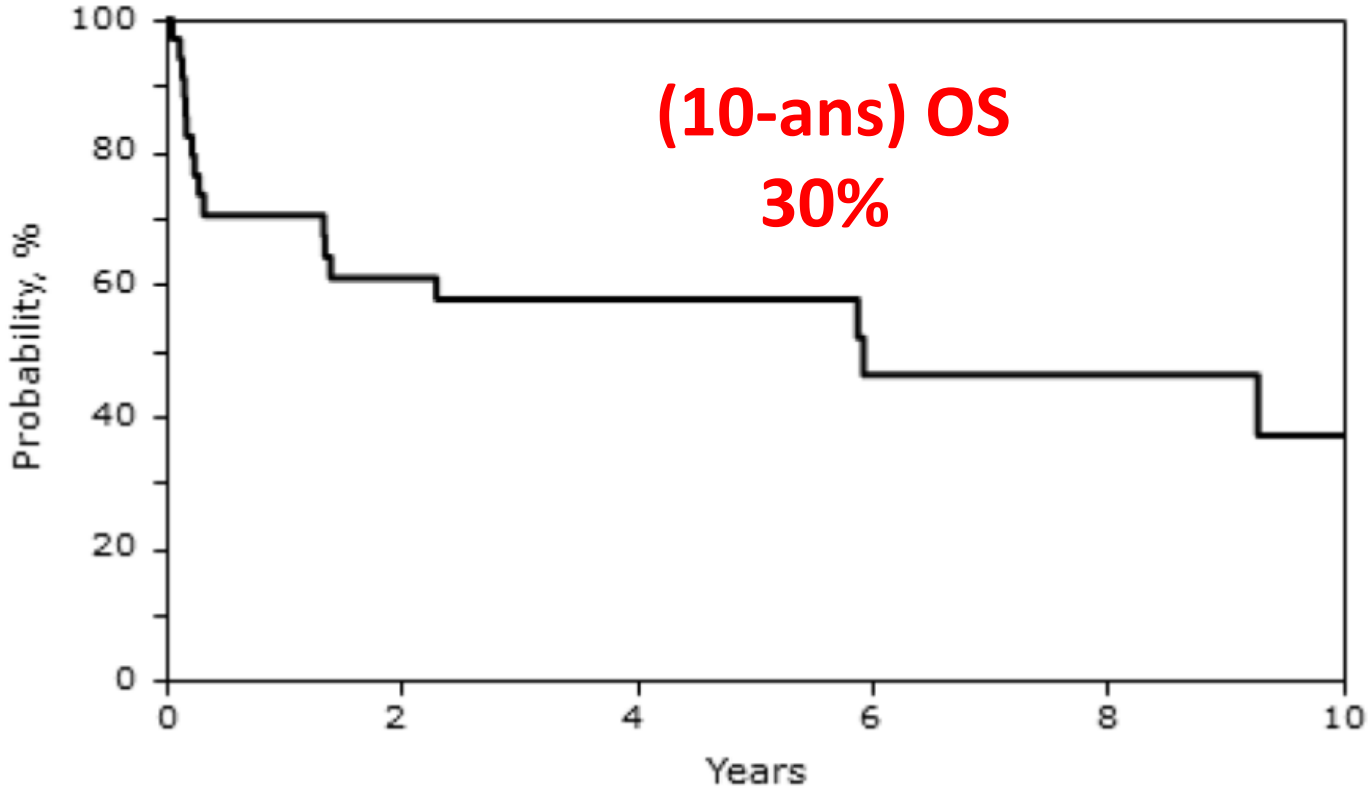
Outcome of allogenic hematopoietic cell transplant in patients with in dyskeratosis congenital

N=34
26 centres
1981-2009

Savage, 2013 Biol Blood Marrow Transplant

- CIBMTR
- 32 HSCT après1989
- Age 2- 35 Mediane 13 ans
- 20 pts DCD
  - 10 DCD < 4 mois (59%)
  - 6 DCD>5 ans
- 10 rejets 2aires

- FR RIC vs MAC
  MSD/MUD vs MMD



Outcome of stem cell transplantation in dyskeratosis congenital

Fioredda, BJH, 2018

N=94
EBMT/EWOG
1979-2015

EBMT, EWOG-MDS, + US: 1 centre

- 79 pts > 2000
- Age à la greffe(Med): 5,8a (0-33,5)
- Délai diagnostic/greffe: > 2 ans: 59%
- Mutation connue: 36%

(*TINF2*: 47%, *DKC1*: 26%, *TERC*: 12%, *TERT*: 12%)

- BMF 94pts
- MDS 8/55 pts
- CDT NMAC

Outcome of stem cell transplantation in dyskeratosis congenital

Fioredda, BJH, 2018

N=94
EBMT/EWOG
1979-2015

- Rejets 17 %
  - 1 aires 5%
  - 2 aires 12%
- aGvHD (grade II–IV) 18%
- cGvHD 31% à 12 mois PG et 35% à 36 mois PG
- Taux de mortalité 41%
- Analyse multivariée:
  - Age<20 ans
  - MSD ou MUD

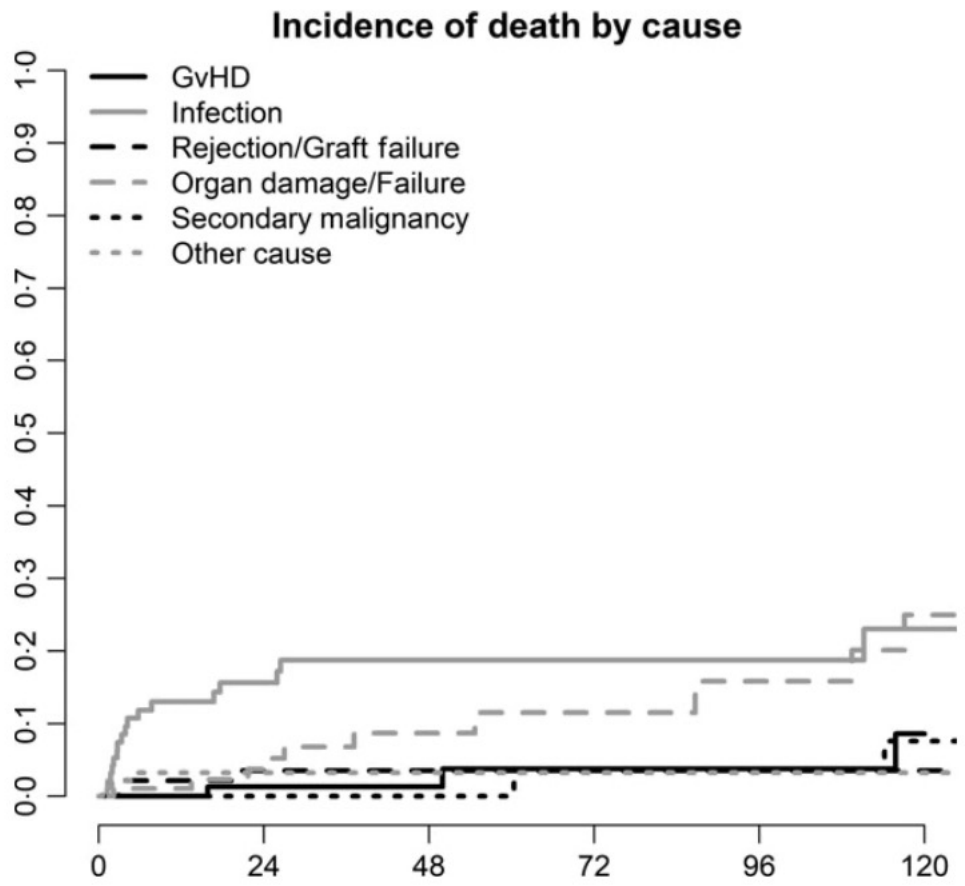


Fig 2. Cumulative incidence of causes of death. GvHD, graft-versus-host disease.

Outcome of stem cell transplantation in dyskeratosis congenital

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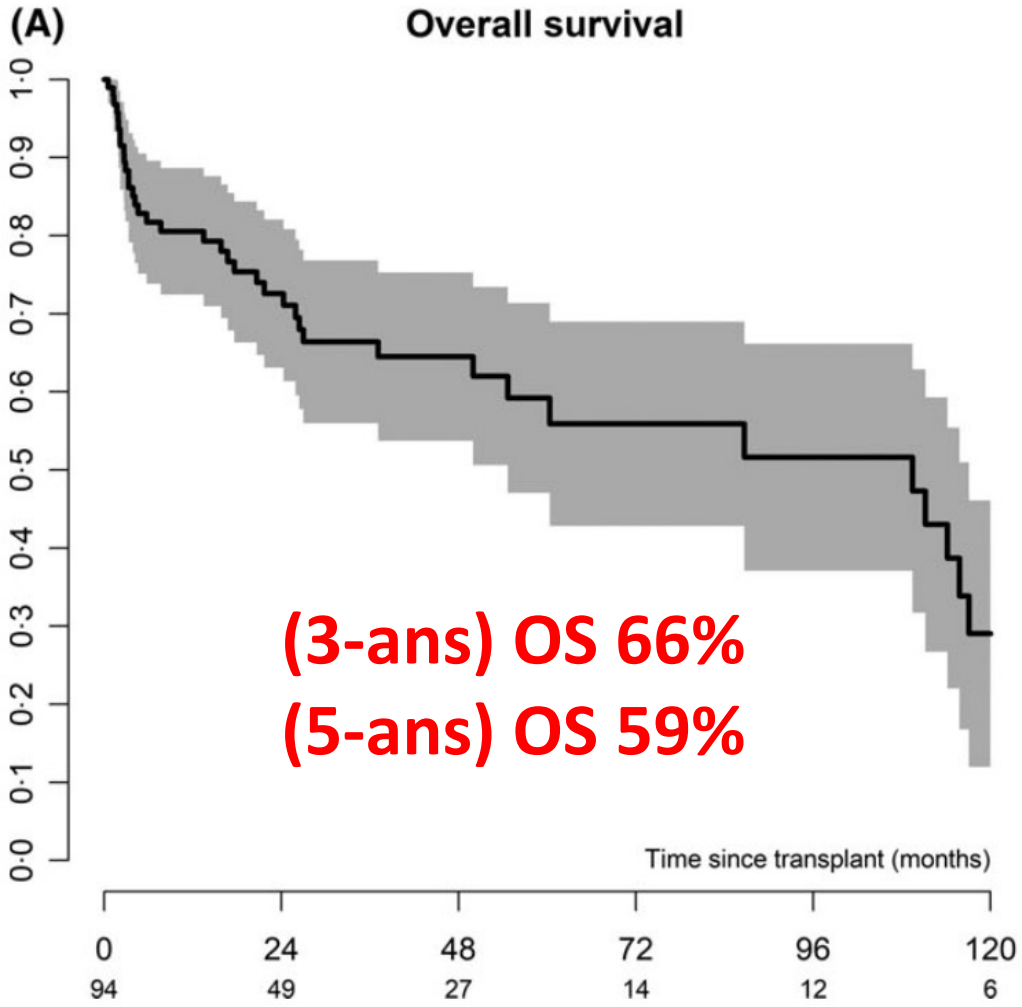
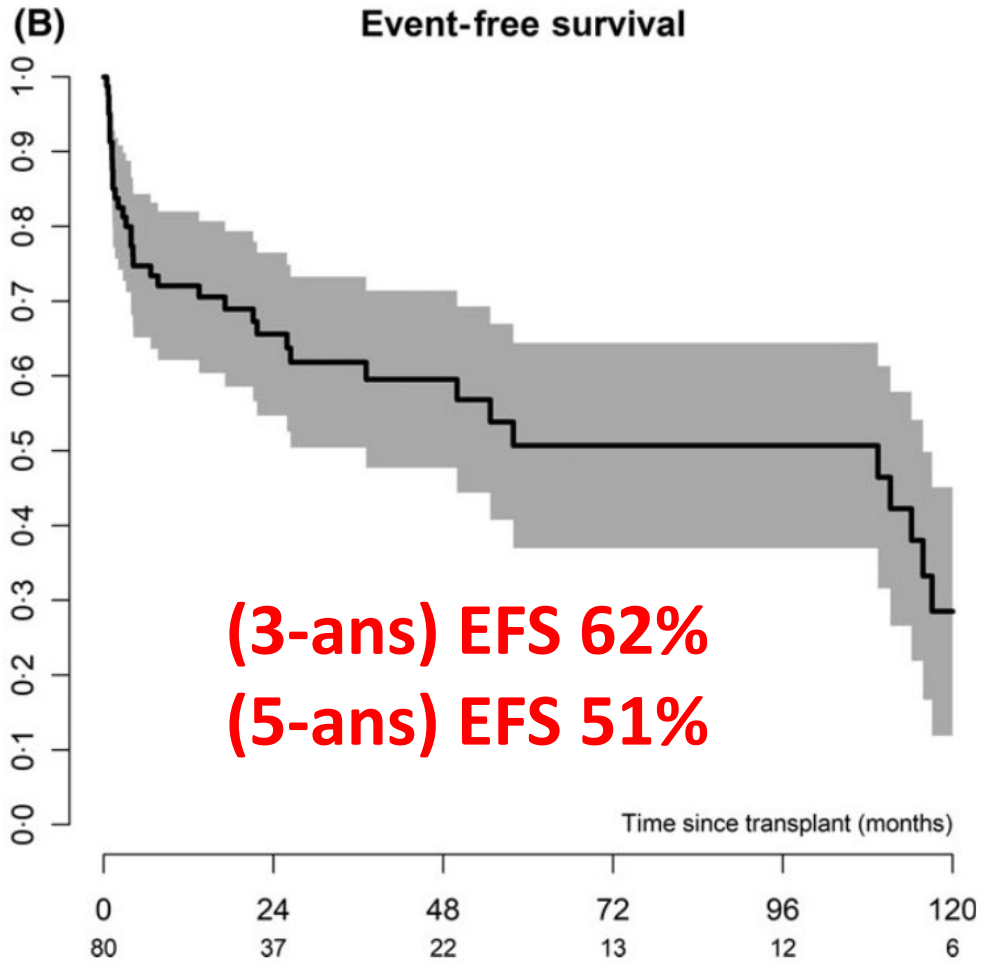




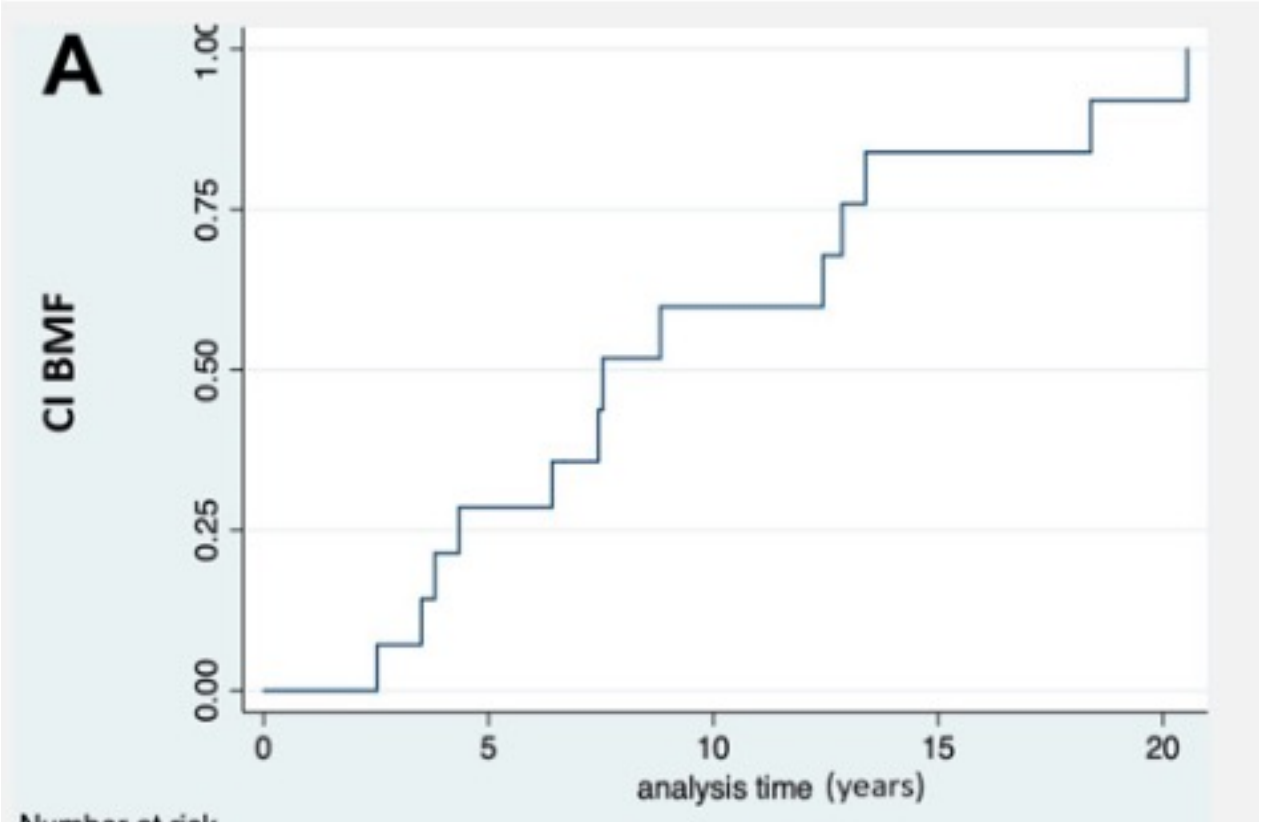
Dyskeratosis congenita: natural history of the disease through the study of a cohort of patients diagnosed in childhood

Diaz-de-Heredia, frontiers in pediatrics, 2023

N=14
4 centres
1998-2020

Cohorte pédiatrique espagnole

- 14pts de 3-17ans
- 12 diag génétique
- BMF 13 pts: âge 3-18 (M8)
- FU médian 9 ans (2-24 ans)
- 8 vivants
  - 6 à 32 ans , med 18 ans
- Pas de cancer

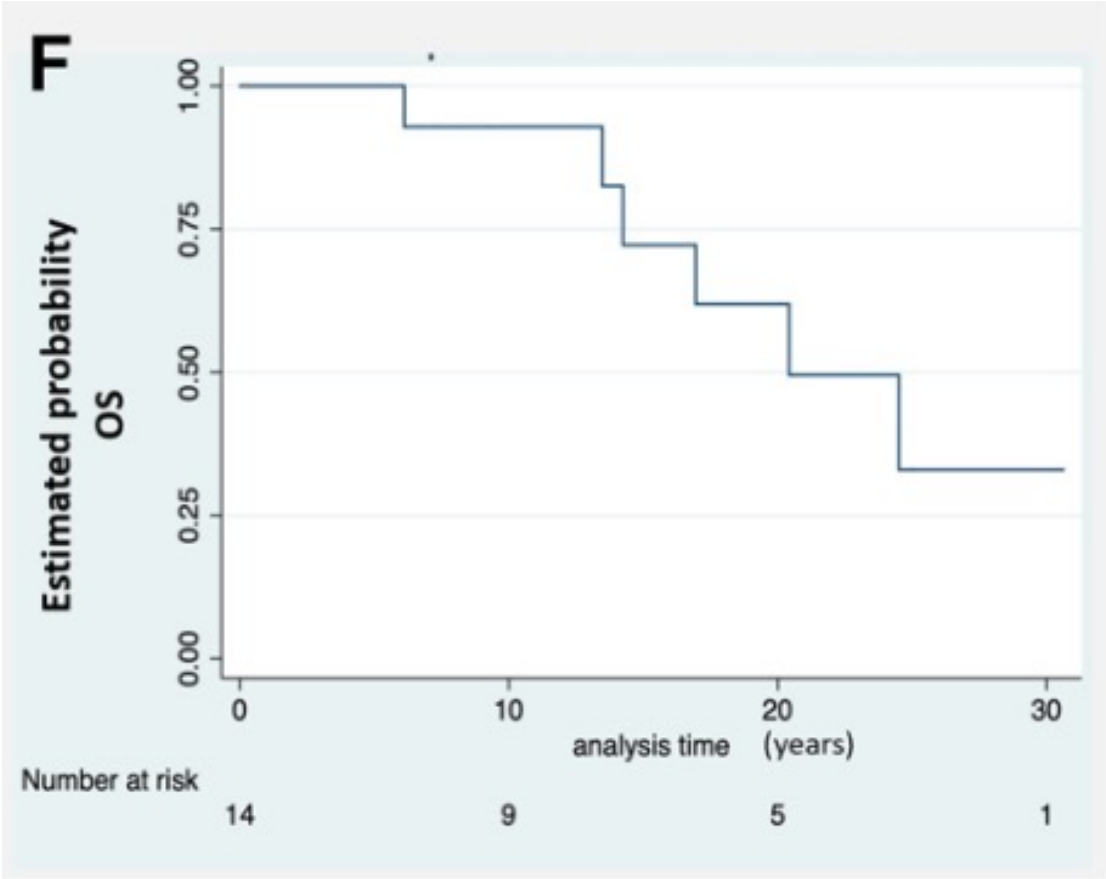


Dyskeratosis congenita: natural history of the disease through the study of a cohort of patients diagnosed in childhood

Diaz-de-Heredia, frontiers in pediatrics, 2023

N=14
4 centres
1998-2020

- 8 HSCT 6a (3-18a)
- 6 pts DCD (dont 4 PG)
  - 1TRM (<J100
  - 4 Infections
  - 1 PF
- Age médian au DC 13 (6-24 ans)



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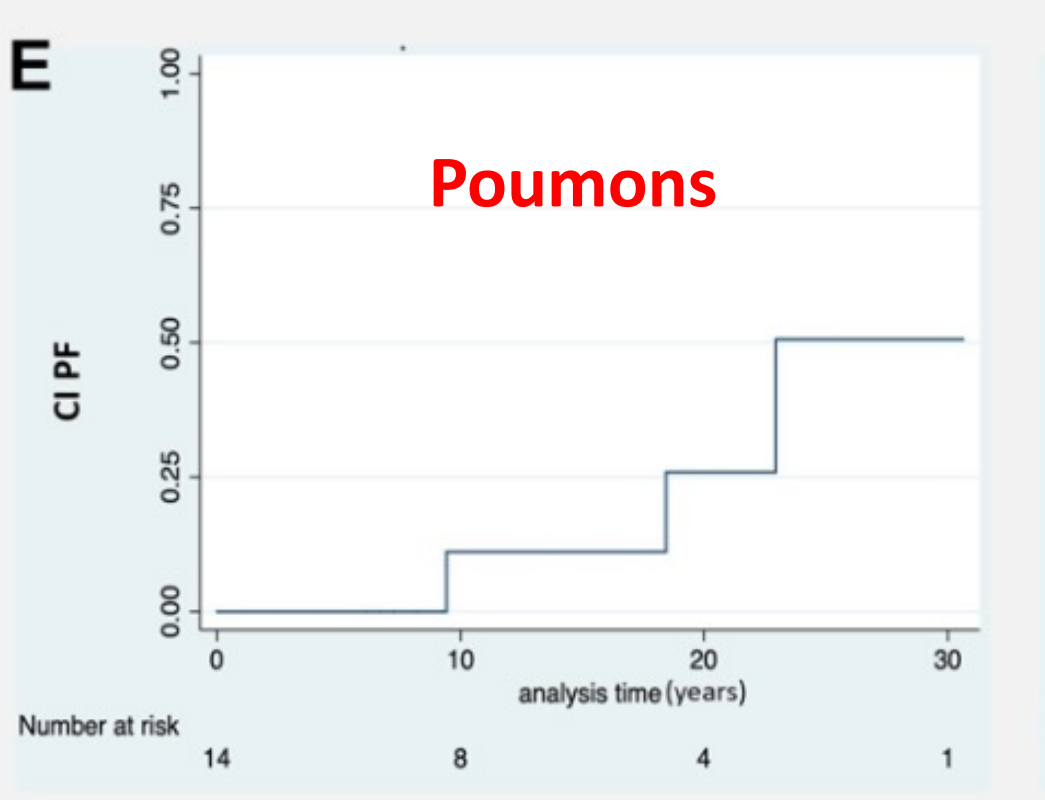
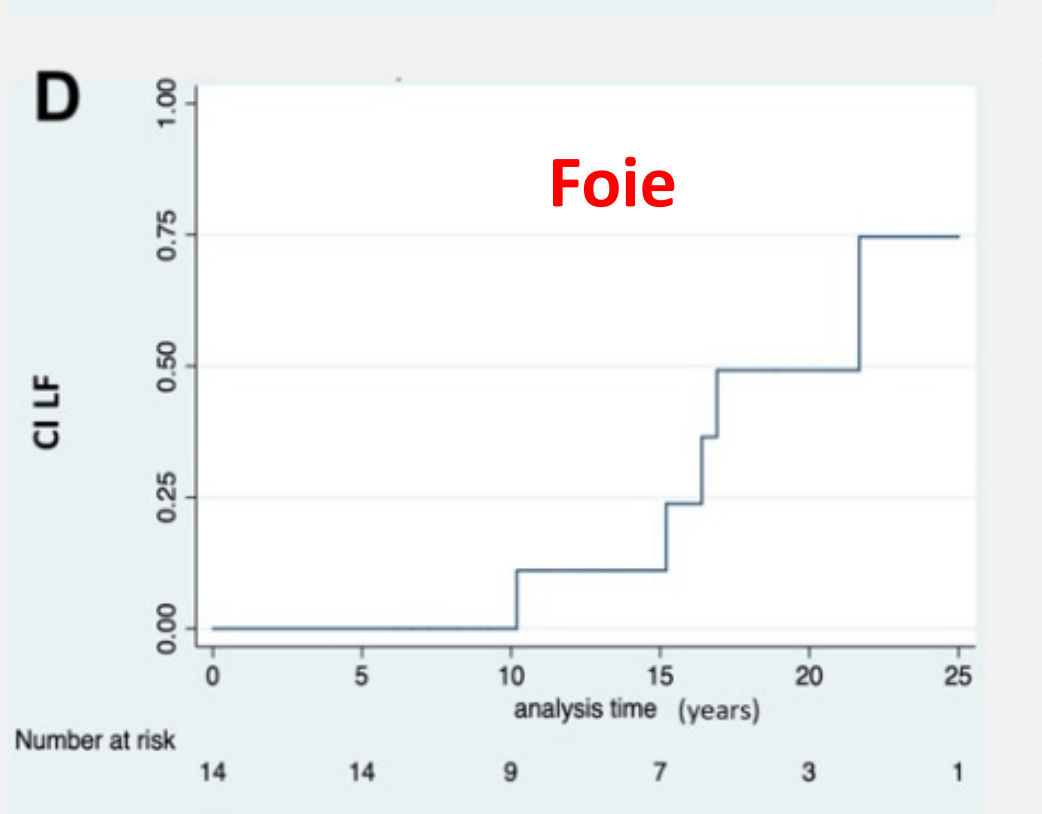


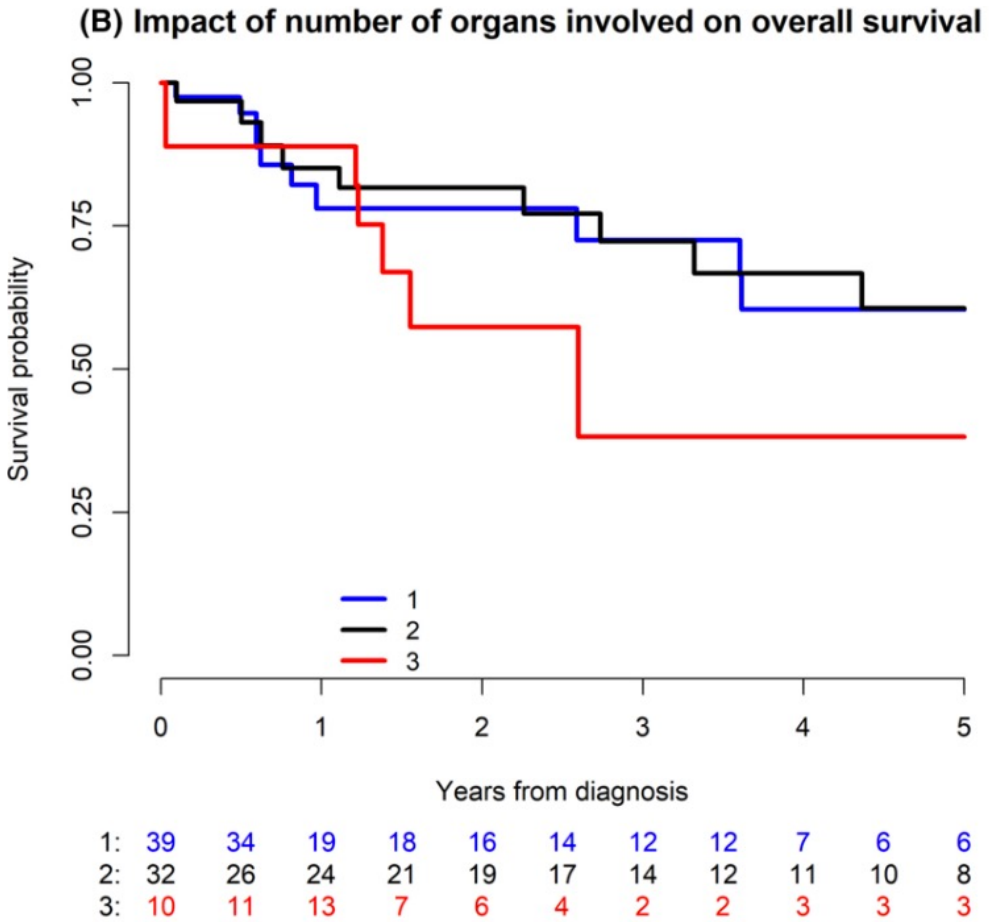


Haematological features of telomere biology disorders diagnosed in adulthood: A French nationwide study of 127 patients

Sicre, BJH, 2024

N=127
CeramiC
2003-2022

- >15 ans
- 93 cas index (âge médian au diag 48 ans)
- 34 apparentés (âge médian au diag 28 ans)
- BMF 62% :
  - Au diag: 10% sévère 17 % MDS 1,6% LAM
  - Au suivi: 3% sévère 5% MDS et 2,4% LAM
- Poumon 30%
- Autres 8%
- 17 HSCT: 9 MDS
  8 sévère BMF



Take Home message HSCT et TBD

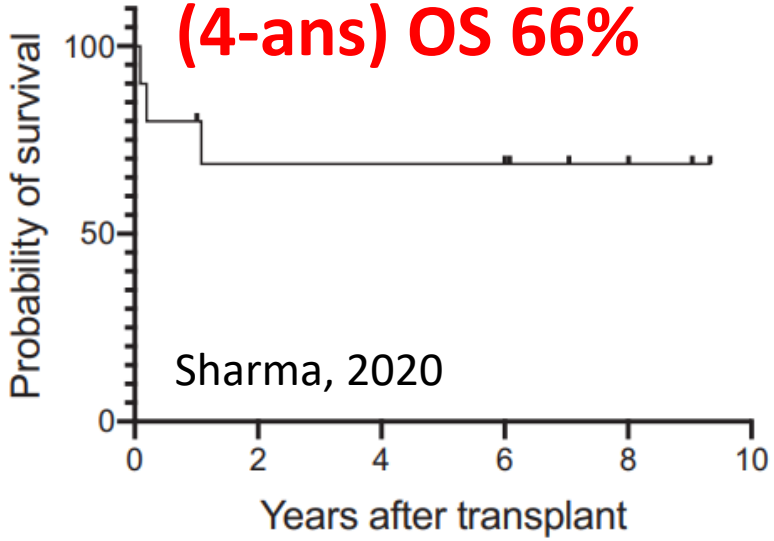
- Les meilleurs résultats de HSCT pour TDB patients
  - patients âgés de moins de 20 ans
  - sans atteinte multi-organe
  - CDT RIC flu based et campath
  - Donneur MSD/MUD
  - Greffon médullaire > CSP et CB
- Pas de greffe pré-emptive (Sévère BMF MDS LAM)
- Evaluation donneur MSD+++

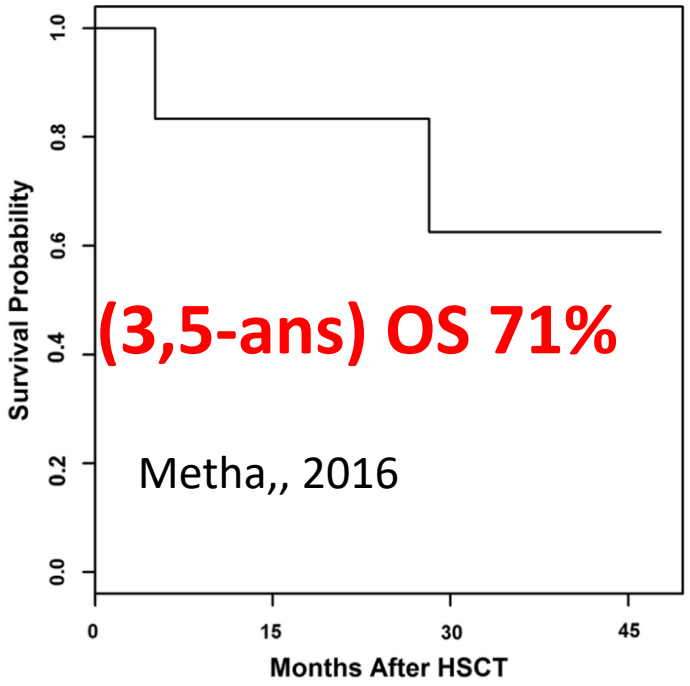
- Que nous apprennent les séries plus récentes?

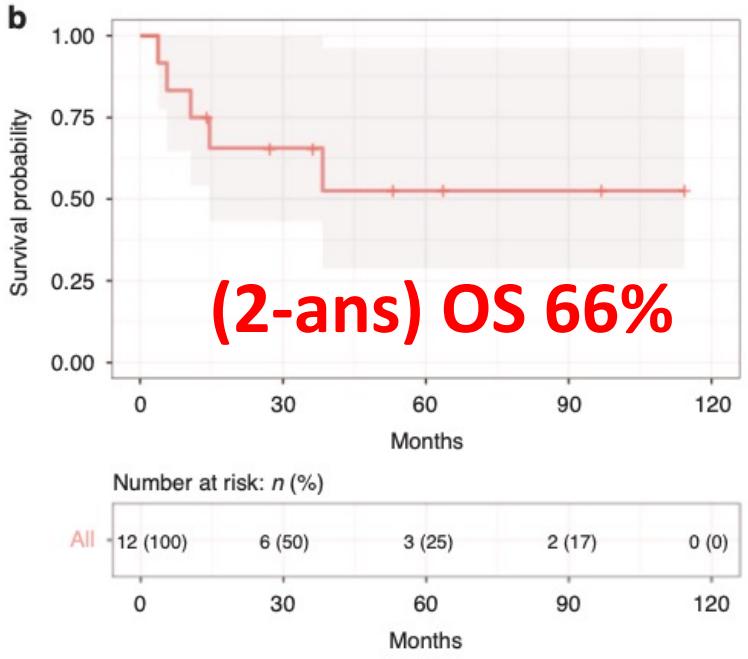
HSCT RIC TBD patient

	Nb pts	Aga à la greffe	Génétique	Statut	Donneur	CDT	Graft	GVH	Complications	Décès	OS
Dietz 2011	6	2-29	Non	BMF	MUD MMUD CB	FCA + TBI 2	1 rejet	2 aGvHD II/III 1 cGvHD	CMV Adv	2DC<J100	66% à 26 M
Metha 2016	7	1,3-12,5a	2 TINF2 1 RETL1 1 DKC1 2 TERT	1 MDS	1 MSD 5 MUD 1 MMUD	Flu Mel Campath		2 aGvHD II/III 1 cGvHD	CMV EBV ADV BK	1 DC <6 mois 1 DC à 28M	71% à 44 M (14 à 57M)
Sharma 2020	9	0.9-15,9a	2 TERT 1 DKC1 1 WRAP53	BMF	2 MSD 6 MUD 2 UCB	Flu Mel Campath (Edx TBI)	1 rejet 2aire	1 aGvHD IV	PTLD VOD MAT	2 DC <J100 1 DC LAM 1	66,6% à 4Y
Sicre 2024	12	17-58a	2 RETL1 4 TERT 3 TERC	5 MDS	1 MSD 1 MMUD 10 MUD	FCA +1 TBI 2		2 aGvHD II/IV 3 cGvHD	CMV EBV	2 DC<6 mois 3 DC<2y	66% 2Y

HSCT RIC TBD patient



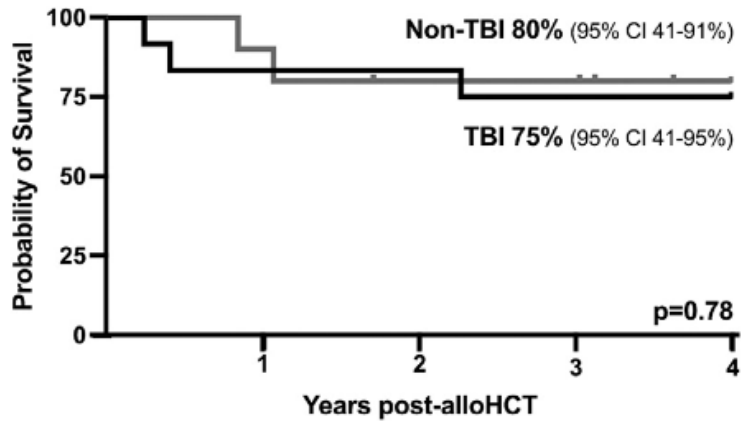




Sicre, 2024

HSCT RIC TBD patient: TBI?

	Nb pts	Aga à la greffe	Génétique	Statut	CDT	Graft	GVH	Complication	Deces	Outcome
DIMITOV 2024	10	1,7-65,9	TERT 2 RTEL1 DKC1 3 TERC 1	3 MDS	FCA	1 rejet Rechute 3 MDS	aGvHD J100 0% cGvHD 10% (4y)	CMV EBV IRpA	1 DC<1N	0S 4Y 80%
	12	2,2-52.2	RTEL1 2 TERC 3 TINF 1 TERT 1	1 MDS	FCA +TBI 2		aGvHD J100 8% cGvHD 17%	CMV EBV Cystite H IRpA h.Dig	1 DC <100 (ADV) 1 DC<1N	0S 4Y 75%



Radiation- and Alkylator-free Bone Marrow Transplantation Regimen for Patients With Dyskeratosis Congenita

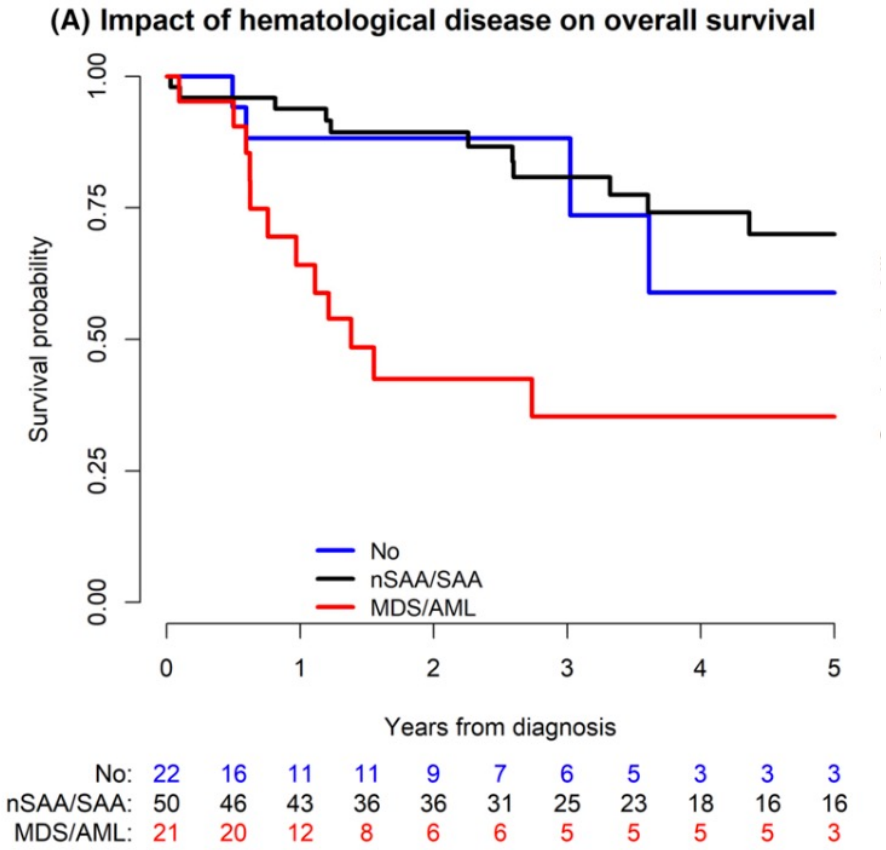
Agarwal

- **ClinicalTrials.gov ID** NCT01659606

- Flu 30mg/m2X6 Campath 0,2mg/kgX5
- BM
- CsA/MMF

- En 2024, ESH- EBMT- EHA
  - OS à 5 ans 85%
  - 3 DC TRM/3 DC disease

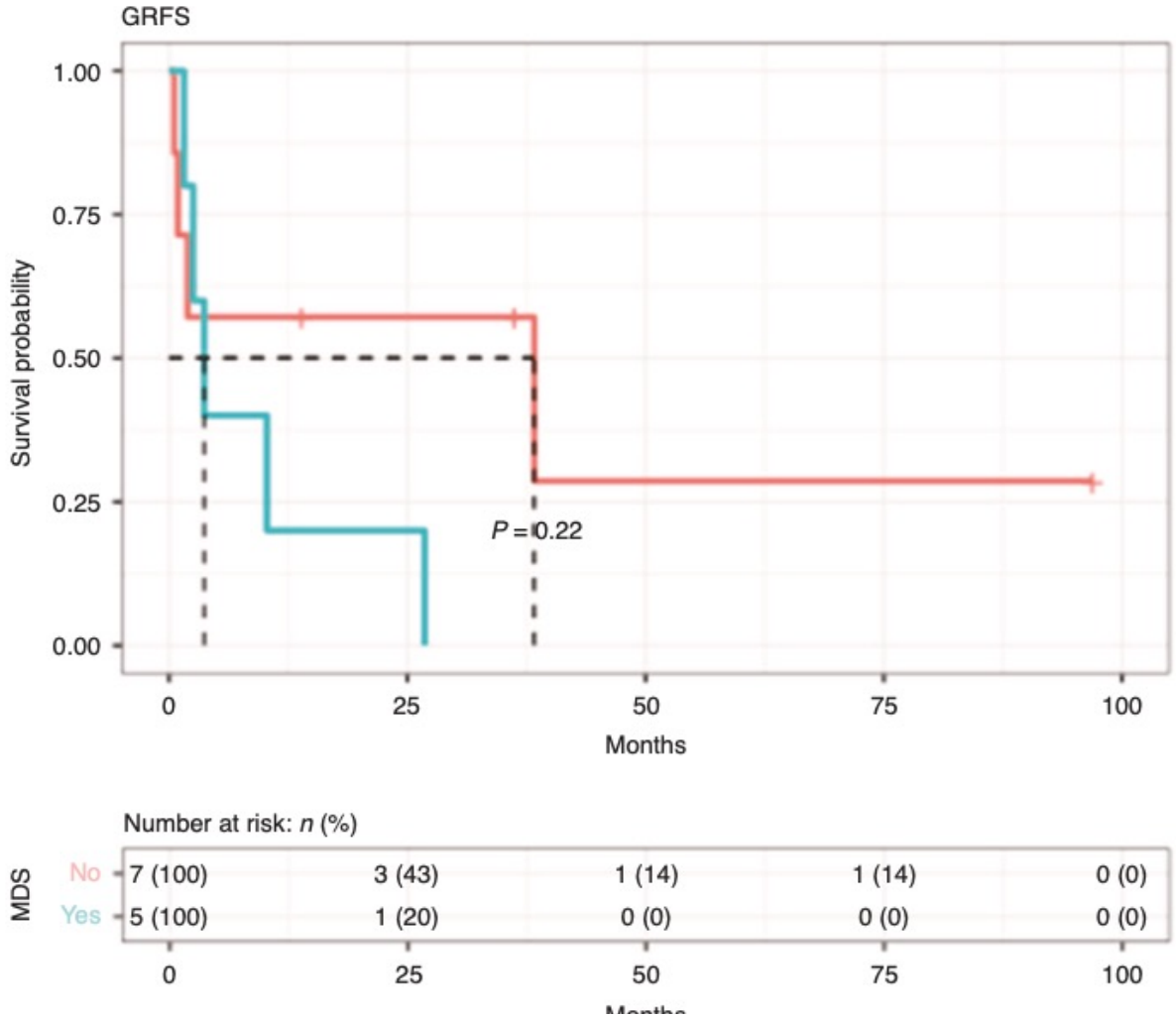
TBD et Evolution clonale



5 patients MDS (5/9, 55.5%)

Rechutent puis DC

Sicre, BJH, 2024



Sicre, BMT, 2024

Analysis of Late Complications Associated With Hematopoietic Stem Cell Transplantation in Patients With Dyskeratosis Congenita

Koike, pediatric blood cancer, 2025

- N=7
- 1985-2020
- Age median 6 ans (2-11)
- Cdt Flu EDX SAL Irradiation thoraco abdominale 3Gy
- Acute complication (Grade II acute GVHD, infection)

- Late Complications PF
  - pulmonary arteriovenous malformations
  - liver fibrosis
  - hepatopulmonary syndrome
- Four patients (57%) died at a median age of 10 (range: 8.2–13.3) years post-HSCT from PF, LF, and intestinal bleeding.

Autres options thérapeutiques?

- Androgènes
  - Permet de restaurer une hématopoïèse partiellement
  - Effets secondaires
  - Epuisement

Perspectives: TBD et TG

Study to Evaluate of EXG34217 in Patients With Telomere Biology Disorders With Bone Marrow Failure

NCT04211714

Phase 1/2

Suivi 5 et 24 mois

Clinical Use of ZSCAN4 for Telomere Elongation in Hematopoietic Stem Cells

Authors: Kasiani C. Myers, M.D., Stella M. Davies, M.B.B.S., Ph.D., Carolyn Lutzko, Ph.D., Robin Wahle, M.S., David D. Grier, M.D., Geraldine Aubert, Ph.D., Kevin Norris, Ph.D., +6 , and Minoru S.H. Ko, M.D., Ph.D. Author Info & Affiliations

Published February 25, 2025 | NEJM Evid 2025;4(3) | DOI: 10.1056/EVIDoa2400252 | VOL. 4 NO. 3

4 patients inclus, 2 qui ont mobilisés avec succés

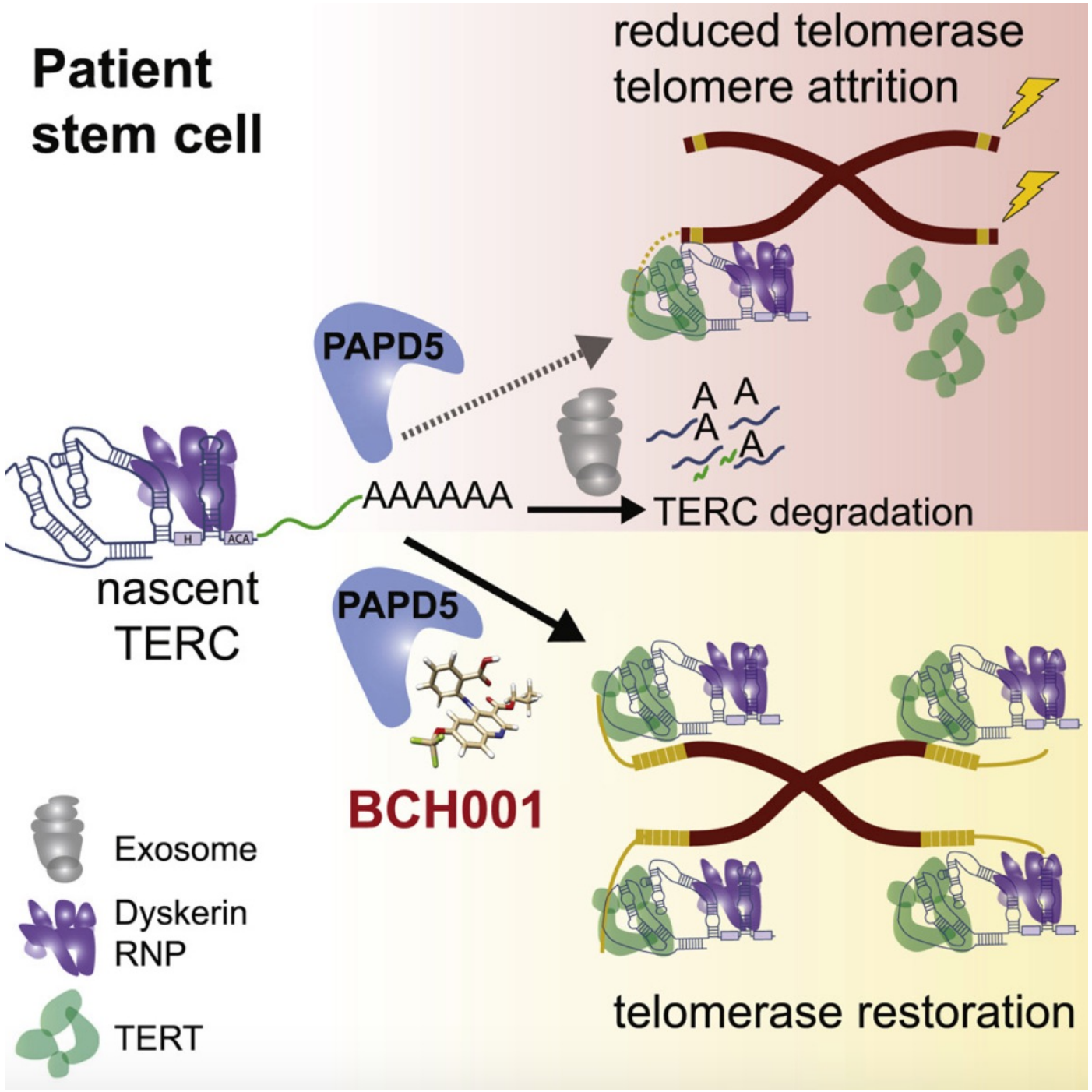
GENE THERAPY | APRIL 7, 2016

Telomerase gene therapy rescues telomere length, bone marrow aplasia, and survival in mice with aplastic anemia

Christian Bär, Juan Manuel Povedano, Rosa Serrano, Carlos Benitez-Buelga, Miriam Popkes, Ivan Formentini, Maria Bobadilla, Fatima Bosch, Maria A. Blasco

Perspectives: Inhibiteurs de PAPD5

Capables de restaurer l'activité télomérase dans les cellules souches



Cas clinique 1: TBD avec SMD

20 ans	23 ans	24 ans			
2018	2021	Janvier 2022	Avril 2022	Mai 2022	
Cytopénies modérées	Diag TBD TERT BMF	Aggravation Cytopénies Monosomie 7	11% blastes BM EFR, TDM thorax, IRM hépatique normaux. Vidaza-ven	Myelo pre greffe moelle pauvre sans EB echec caryotype	

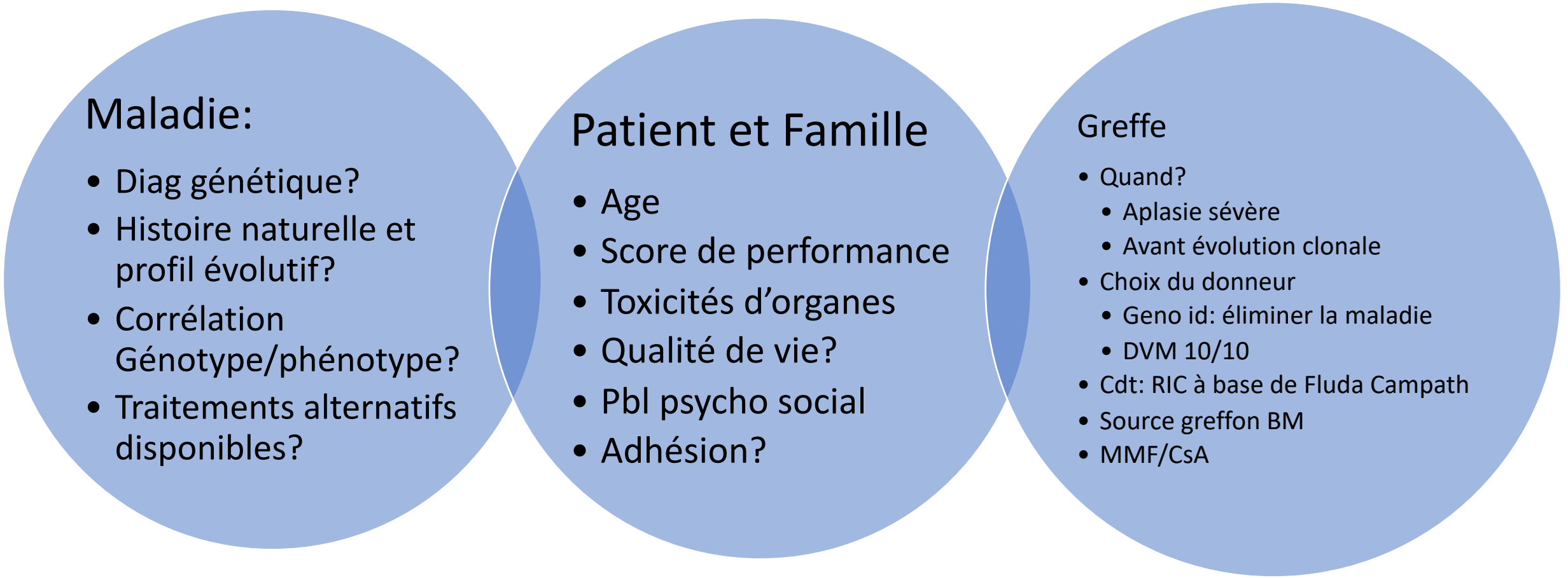
24 ans					27 ans
Mai 2022	Juin 2022	Sept 22	Juin 23	Sept 24	Fev 25
Allogreffe 9/10 (M) Fluda Mel Campath.	Bilan M1 OK GVH grade 2 cortico Se EBV	cGVH CTC Neoral Jakavi	Multiples Infections avec cytopénies	PTLD Ritux Baisse IS	PNP ADV	Lésion intra épithéliale de bas grade de la vulve

Cas clinique 2: TBD NRS

4M	§ M	14 M	22 M	2 ans	2an ½
Mai 19	Juillet 19	Mars 2020	Nov 2020	Janv 2021→ Nov 21	Juin 2021 →Dec 2021
Anémie ferriprive	Bicytopénie	Pancytopénie AMAC Mutation TINF2	Allogreffe Geno Flu EDX Campath Chim 100%D Pas de GVH	Maladie CMV Digestive Hépatique Pulmonaire	Hémorragies Digestives répétées

3 ans	3, 8 ans
2022	Sept 22	Nov 22
Atteinte hépatique débutante HTP sans signes IHC Atteinte pulmonaire: sd interstitiel	Atteinte respiratoire hypoxémiante Récidive hémorragie digestive	Transfert Réa Décès Hypothèse: Sd hépato- pulmonaire

TBD: HSCT or not?



Merci

MaRIH
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