Myechild01

UK-France clinical trial
in Children with Acute Myeloid Leukemia
French Cytogenetic Data
on September 9th 2019
and
New cytogenetic stratification

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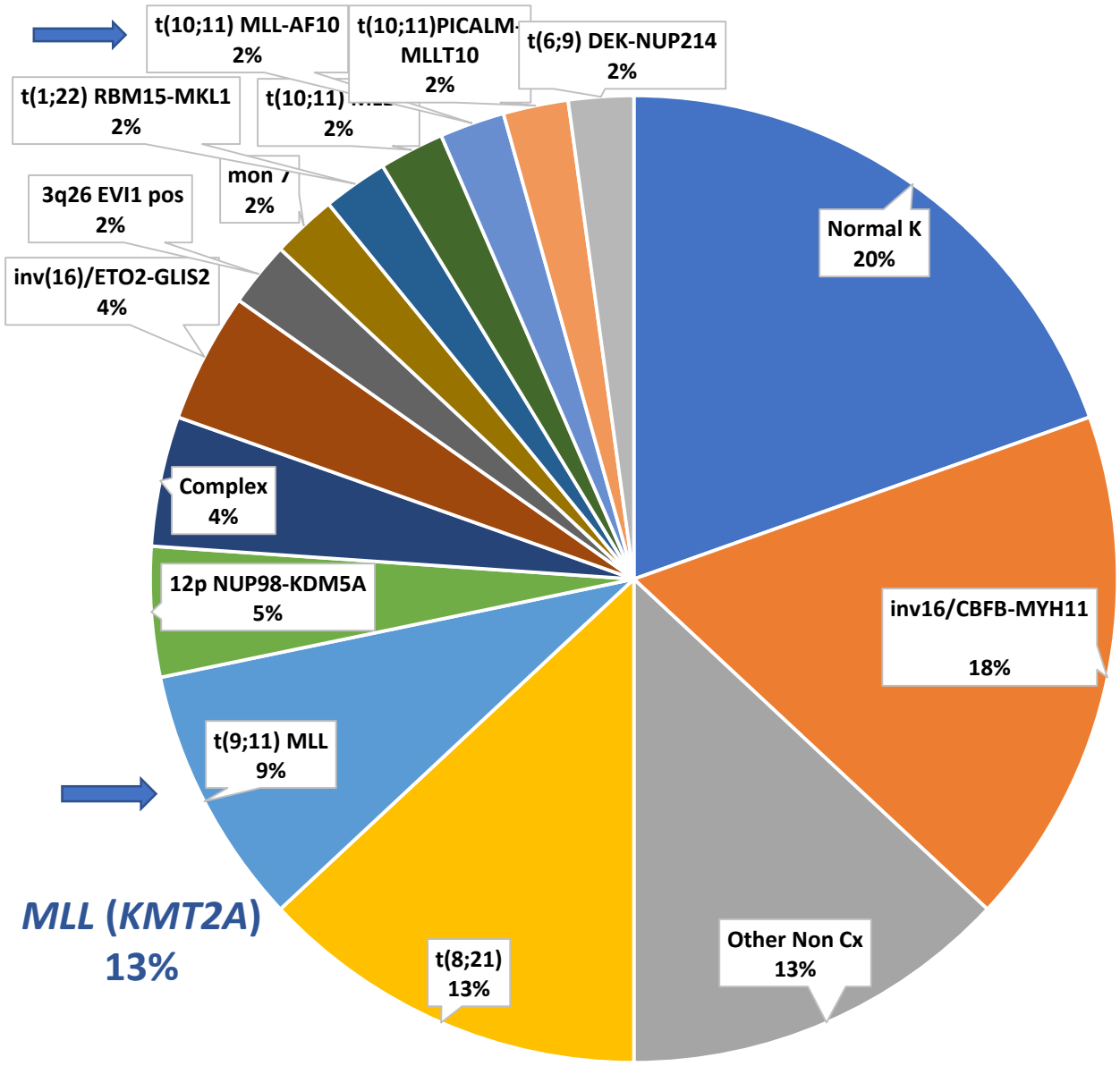
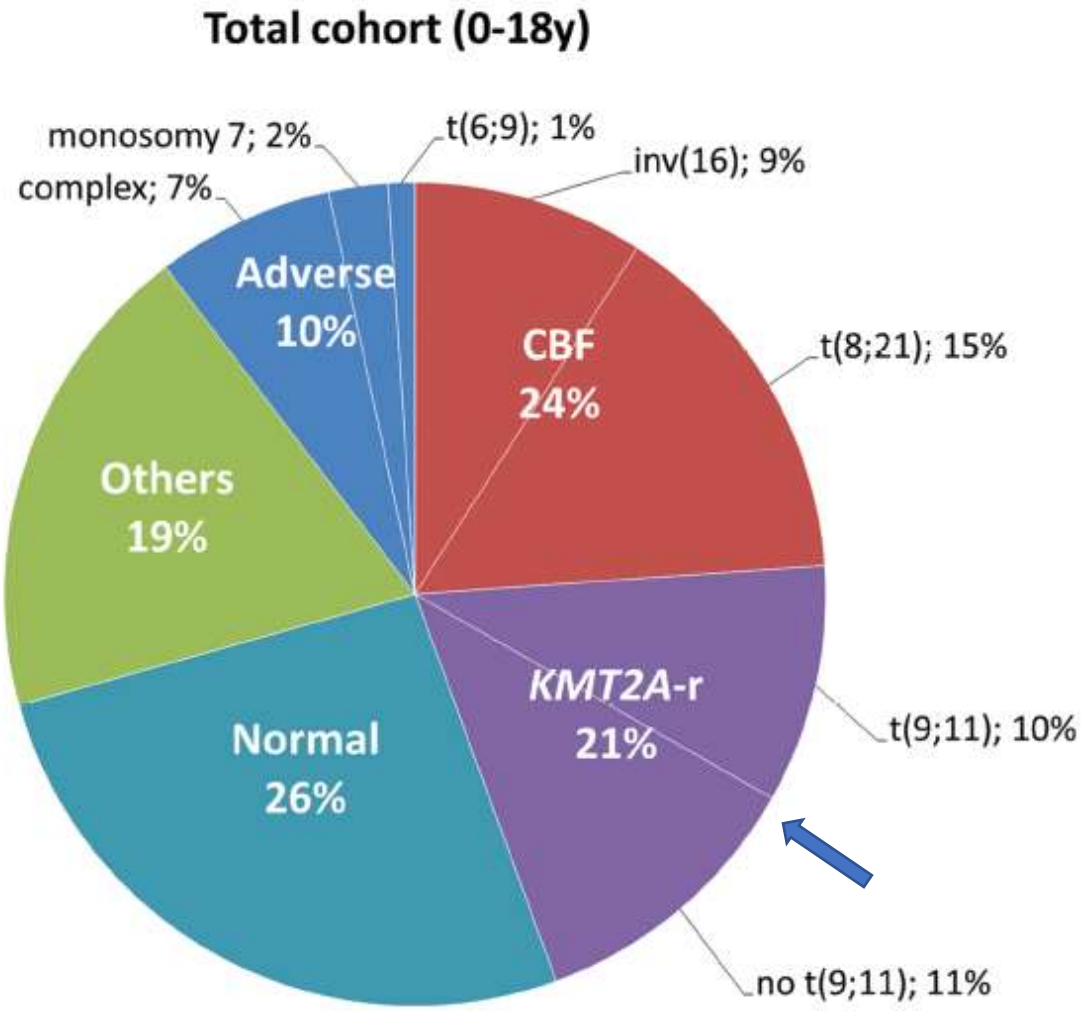
Myechild01 46 French pts on Sept 9th 2019



ELAM02 n= 385 pts



Marceau-Renaut *et al.* **HemaSphere** (2018) 2:1

APPENDIX 1 – RISK GROUP STRATIFICATION

Cytogenetic and molecular abnormalities

Good Risk cytogenetic and molecular abnormalities

- t(8;21)(q22;q22)/*RUNX1-RUNX1T1*
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- Mutation of *NPM1* without *FLT3*-ITD
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Intermediate Risk Cytogenetic abnormalities

- t(9;11)(p21;q23)/*MLL-MLLT3*
- t(11;19)(q23;p13.3)/*MLL-MLLT1*
- All other *MLL* rearrangements not classified as high risk
- All other abnormalities which are neither good or poor risk

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- -5/del(5q)
- -7
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- inv(16)(p13.3q24.3)/*CBFA2T3-GLIS2*
- *FLT3*-ITD without NPM1 or CBF

t(10;11)(p11~14;q23)
non MLL-MLLT10 ?

Other poor risk categories

- Secondary leukaemia without good risk cytogenetics
- Induction failure after course 1: morphological failure confirmed by flow MRD in Good Risk /Standard Risk patients

Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel

*Ursula Creutzig,[1] *Marry M. van den Heuvel-Eibrink,[2] Brenda Gibson,[3] Michael N. Dworzak,[4] Souichi Adachi,[5] Eveline de Bont,[6] Jochen Harbott,[7] Henrik Hasle,[8] Donna Johnston,[9] Akitoshi Kinoshita,[10] Thomas Lehrnbecher,[11] Guy Leverger,[12] Ester Mejstrikova,[13] Soheil Meshinchi,[14] Andrea Pession,[15] Susana C. Raimondi,[16] Lillian Sung,[17] Jan Stary,[18] Christian M. Zwaan,[2] †Gertjan J. L. Kaspers,[19] and †Dirk Reinhardt,[1] on behalf of the AML Committee of the International BFM Study Group

Table 4. Genetically defined prognostic groups in pediatric AML

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	complex karyotype#
	*WT1*mut/*FLT3*-ITD**
	t(9;22)(q34;q11.2)††

Frequencies, response rates, and outcome measures should be reported by genetic group, and, if sufficient numbers are available, by specific subsets indicated.

*t(15;17)/*PML-RARA* is treated separately from other AMLs.

†In particular in DS patients and infants with acute megakaryoblastic leukemia, analysis of *GATA1s* mutations should be included. Identification of *GATA1s*-associated leukemia in trisomy 21 mosaicism can prevent overtreatment.

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#Three or more chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions.

**There are differences in the risk allocation of *FLT3*-ITD considering the allelic ratio.

††t(9;22) is rare, but it is included because its poor prognostic impact is known.

Case TNO195 (Caen) : t(10;11)(p12;q23) MLL positive : no fusion transcript

- **7 month-old boy**
- **24/04/2019 : AML-M1 , WBC 25x10^9/L**
- **Karyotype : 46,XY,t(10 ;11)(p11.2~12;q23)[13]/46,XY[9]**
- **FISH MLL positive :**

.ish t(10;11)(D10Z1+,3'KMT2A+;5'KMT2A+)[16].nuc ish(KMT2Ax2)(5'KMT2A sep 3'KMT2Ax1)[160/200]

- **RT-MLPA and Marshalek's lab : no fusion transcript**
- **NGS : normal (no mutation)**

Question : Intermediate risk assignment at diagnosis ?

Novel prognostic subgroups in childhood 11q23/*MLL*-rearranged acute myeloid leukemia: results of an international retrospective study

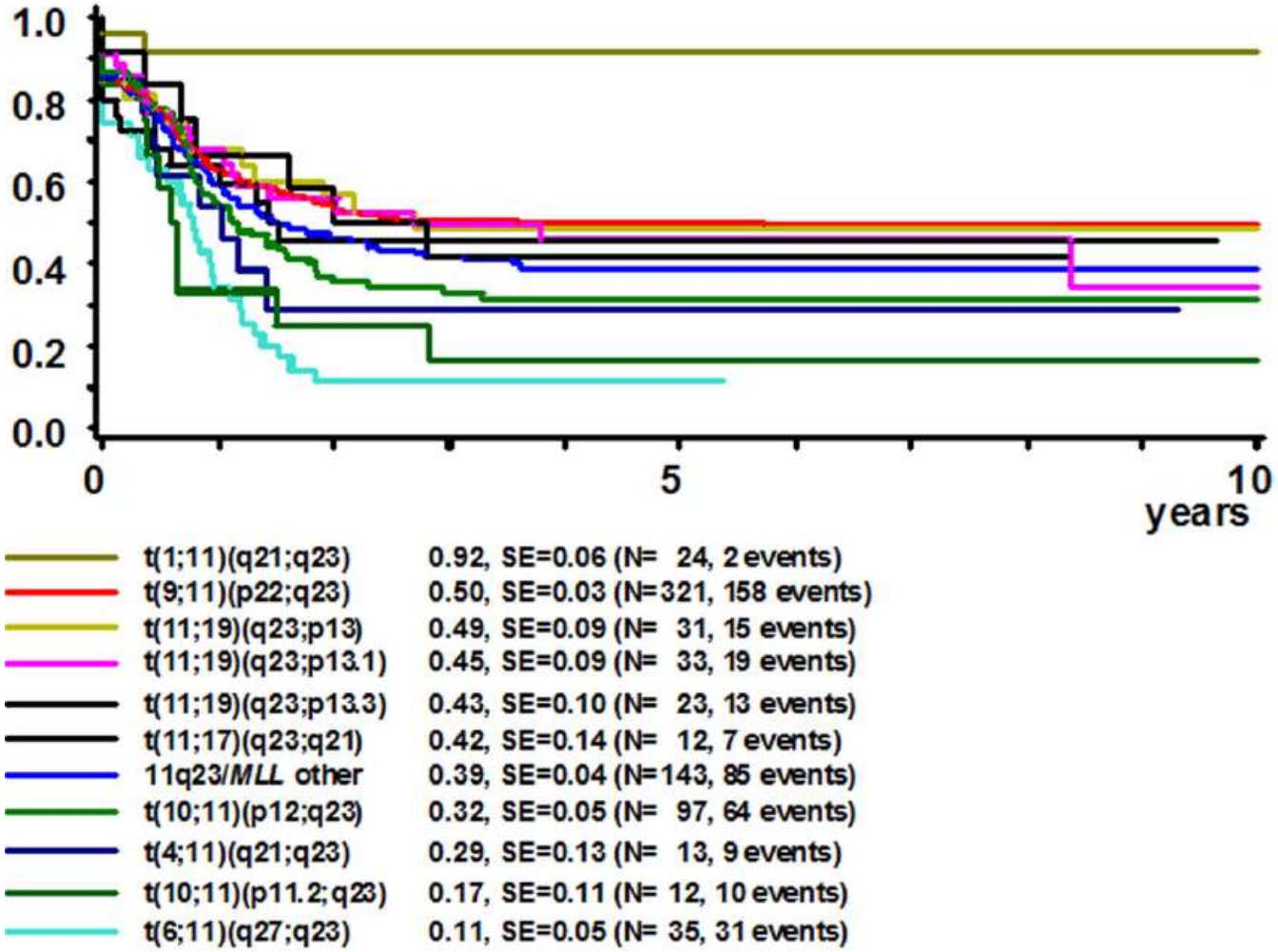


Figure 2. Survival curves for patients with 11q23/*MLL*-rearranged pediatric AML grouped on the basis of different translocation partners. (A) Event-free survival curves.

Balgobind BV et al, Blood, 2009

Novel prognostic subgroups in childhood 11q23/*MLL*-rearranged acute myeloid leukemia: results of an international retrospective study

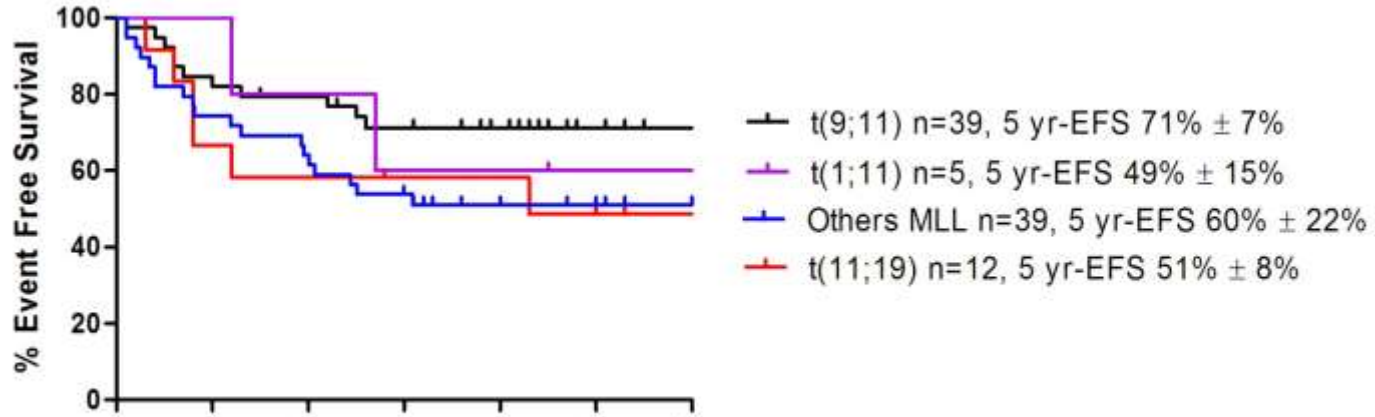
Brian V. Balgobind,[1] *Susana C. Raimondi,[2,3] *Jochen Harbott,[4] Martin Zimmermann,[5] Todd A. Alonzo,[3] Anne Auvrignon,[6] H. Berna Beverloo,[7,8] Myron Chang,[9] Ursula Creutzig,[10] Michael N. Dworzak,[11] Erik Forestier,[12] Brenda Gibson,[13] Henrik Hasle,[14] Christine J. Harrison,[15] Nyla A. Heerema,[3,16] Gertjan J. L. Kaspers,[17-19] Anna Leszl,[20] Nathalia Litvinko,[21] Luca Lo Nigro,[22] Akira Morimoto,[23,24] Christine Perot,[6] Rob Pieters,[1] Dirk Reinhardt,[5] Jeffrey E. Rubnitz,[2] Franklin O. Smith,[3,25] Jan Stary,[26] Irina Stasevich,[21] Sabine Strehl,[11] Takashi Taga,[23,27] Daisuke Tomizawa,[23,28] David Webb,[18,29] Zuzana Zemanova,[30] †C. Michel Zwaan,[1,17] and †Marry M. van den Heuvel-Eibrink[1,17]

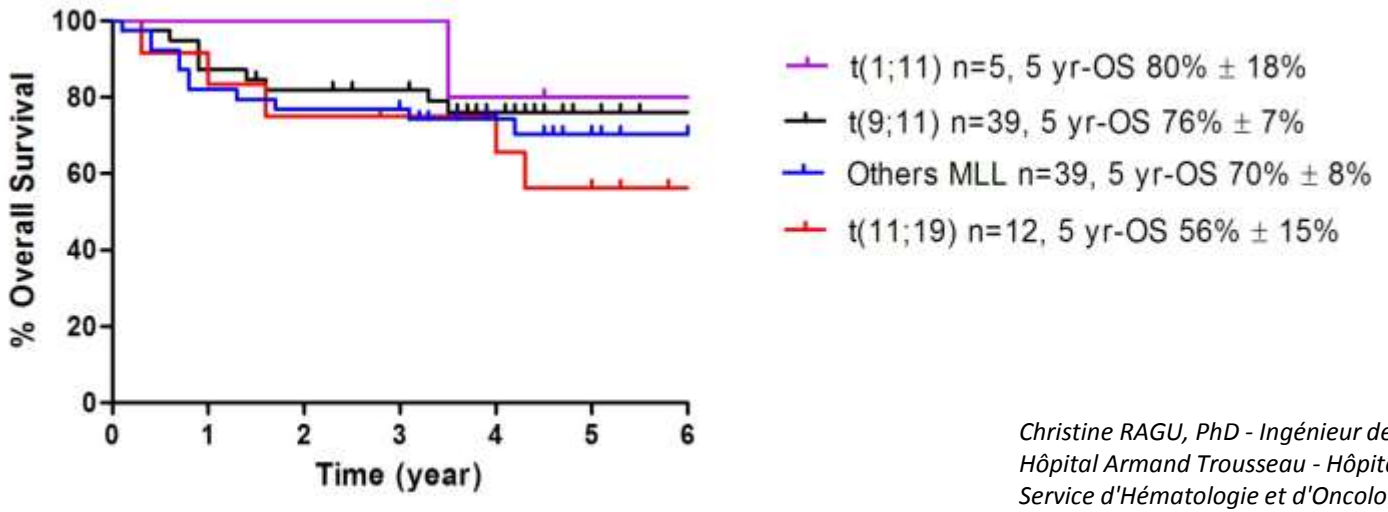
Patients with a t(1;11)(q21;q23) showed independent favorable outcome with overall survival at 5 years of 100% ± 0%, and an event-free survival of 92% ± 5%. Several rearrangements were identified as predictors of poor clinical outcome, including t(6;11)(q27;q23), t(10;11)(p11.2;q23), t(4;11)(q21;q23), and t(10;11)(p12;q23).

BLOOD, 17 SEPTEMBER 2009 • VOLUME 114, NUMBER 12

t(9;11)(p22;q23) MLL-AF9/t(11;19)(q23;p13)MLL-ENL/ELL/t(1;11)(q21;q23)MLL-AF1Q
Données ELAM02

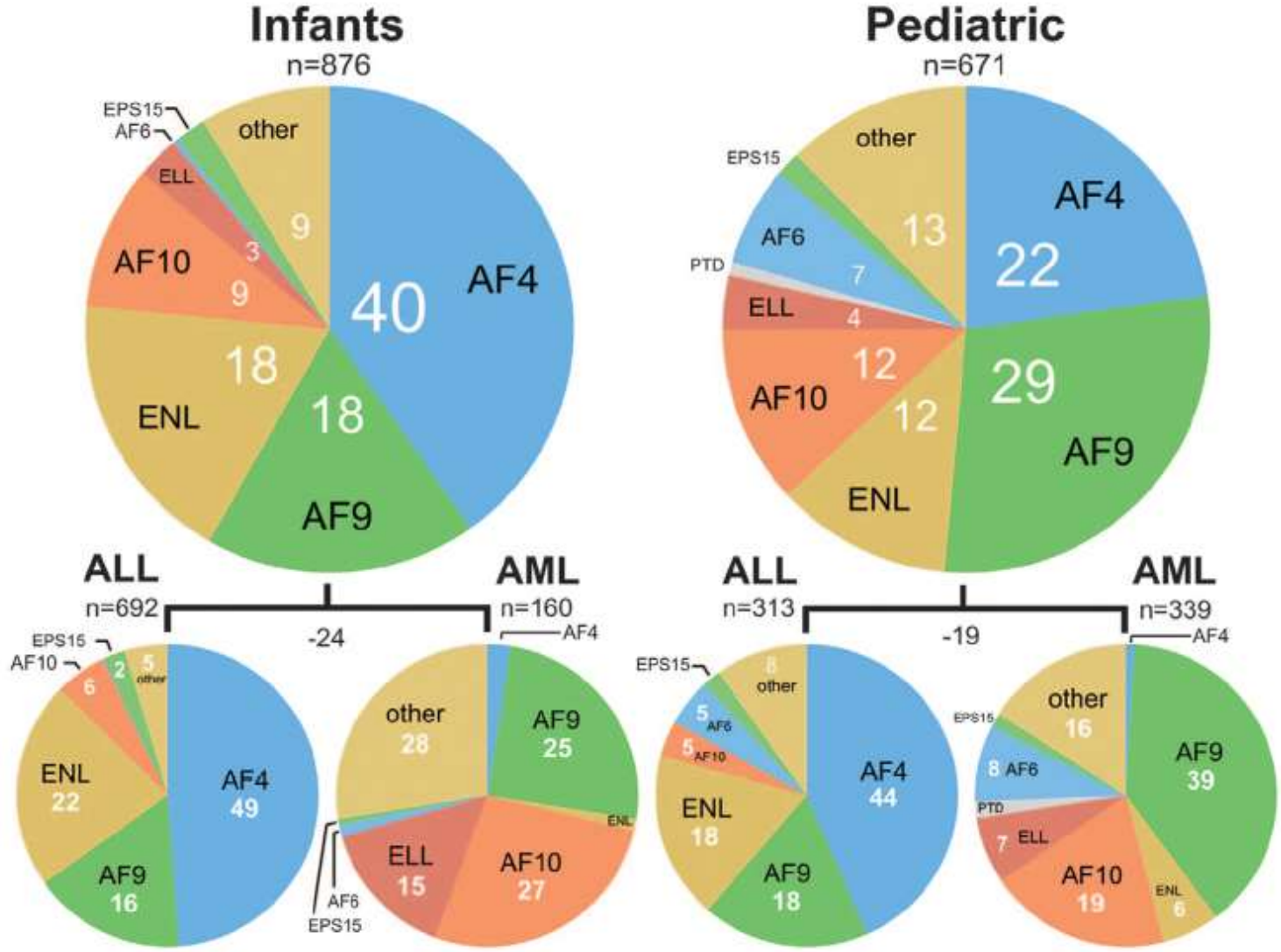
MLL positifs (n=95)
t(9;11) 43% (n=39) dont 70% isolée
t(11;19) 16% (n=12)
t(1;11) 5% (n=5)
« MLL autres » 43% (n=39)





Christine RAGU, PhD - Ingénieur de Recherche Clinique
Hôpital Armand Trousseau - Hôpitaux universitaires Paris Est, AP-HP
Service d'Hématologie et d'Oncologie Pédiatrique

MLL recombinome in acute leukemia



C Meyer *et al* Leukemia (2017)

MLL recombinome in acute leukemia

ins(10;11)(p12;q23)	10p12	*NEBL*	*Cóser et al. (2010)*	AML
ins(10;11)(p12;q23q13)	10p12	*MLLT10/AF10*	Chaplin *et al.* (1995)	AML, t-AML, ALL, T-ALL, BAL
t(10;11)(p11.2;q23)	10p11.2	*ABI1*	Taki *et al.* (1998)	AML

C Meyer *et al* Leukemia (2017)

MLL recombinome in acute leukemia

No partner gene fused to 5′-MLL gene			
t(1;11)(p13.1;q23)	1p13.1	[16]	PMF
t(6;11)(q27;q23)	6q27	Not published yet	AML
t(9;11)(p13.3;q23)	9p13.3	[16]	t-ALL
t(11;11)(q23;q23.3)	11q23.3	[16]	ALL, AML
t(11;11)(q23;q24.3)	11q24.3	[16]	AML
t(11;21)(q23;q22)	21q22	[16]	t-ALL

C Meyer *et al* Leukemia (2017)

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And other t(10;11)(p11~14) with MLL rearrangement

(sept 2019)

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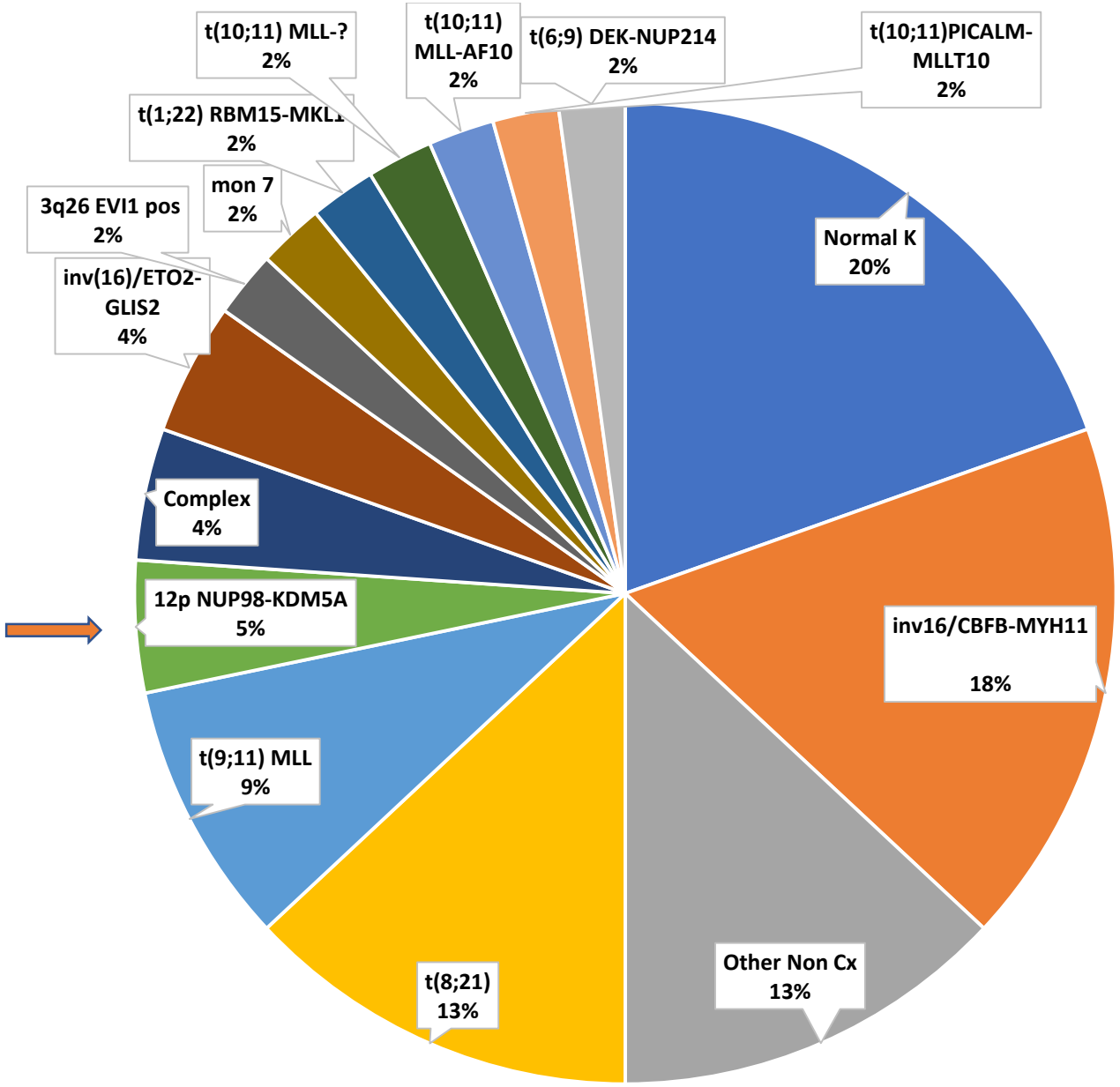
46 French patients on Sept 9th 2019

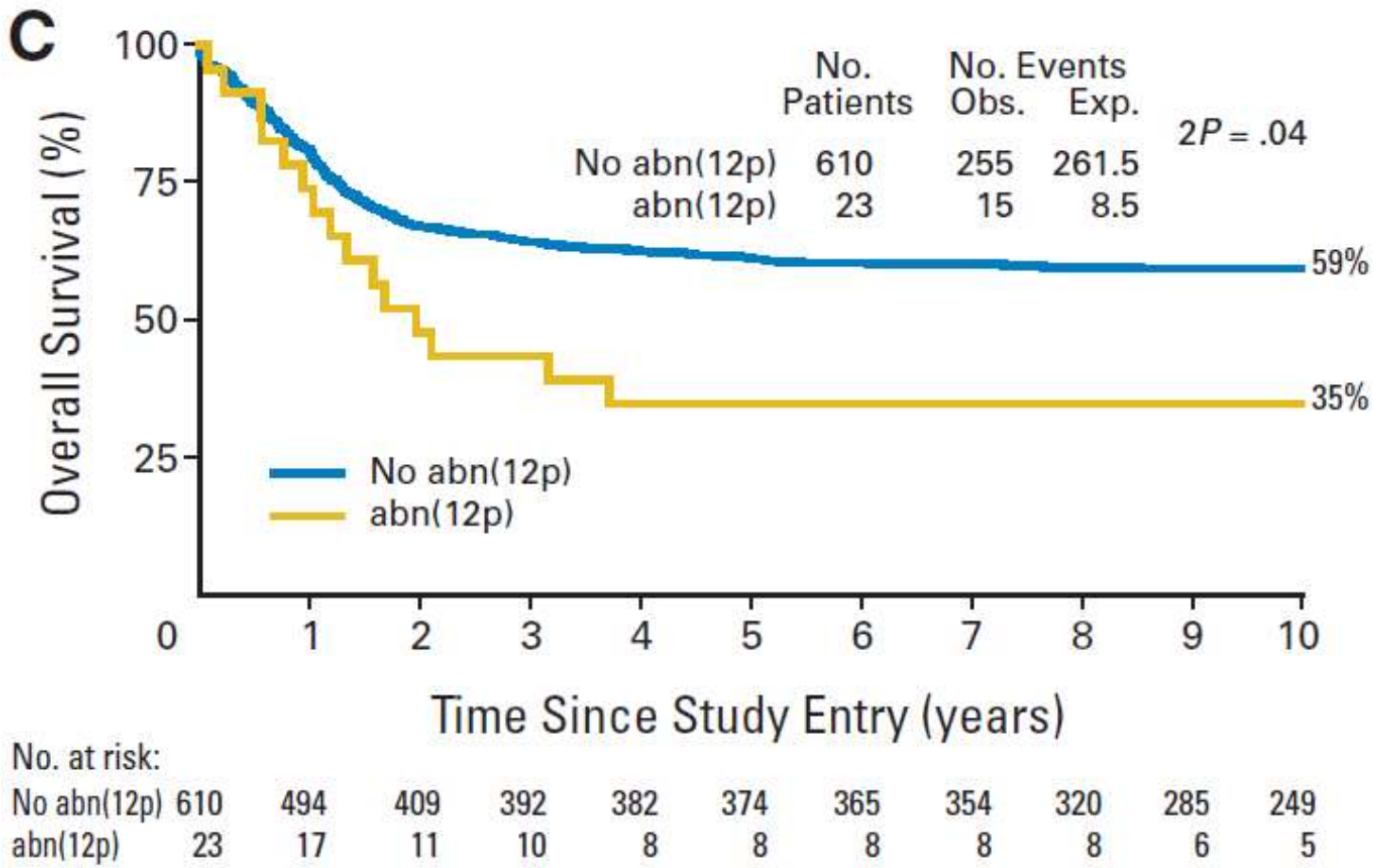


Myechild01

Cytogenetics of Childhood Acute Myeloid Leukemia: United Kingdom Medical Research Council Treatment Trials AML 10 and 12

Christine J. Harrison, Robert K. Hills, Anthony V. Moorman, David J. Grimwade, Ian Hann, David K.H. Webb, Keith Wheatley, Siebold S.N. de Graaf, Eva van den Berg, Alan K. Burnett, and Brenda E.S. Gibson

VOLUME 28 · NUMBER 16 · JUNE 1 2010
JOURNAL OF CLINICAL ONCOLOGY



AMKL

Leucémie Aiguë Mégacaryoblastique (AMKL) 4~15% des nouveaux diagnostics
LAM pédiatrique.

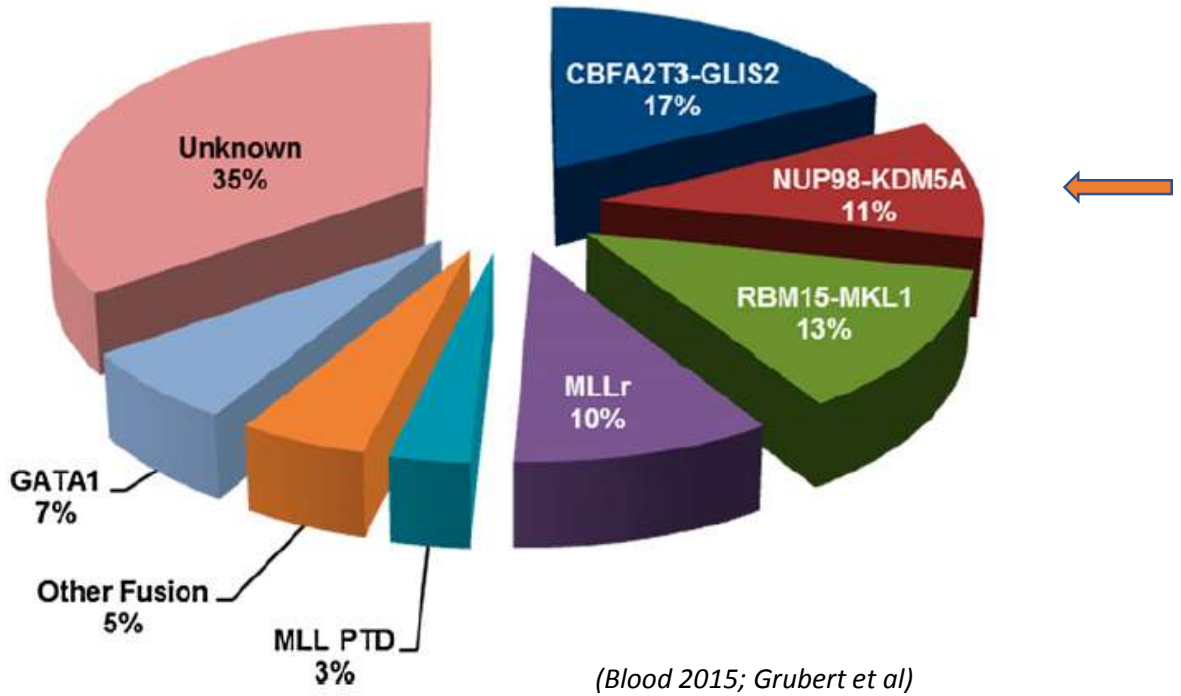
AMKL chez les enfants atteints du **syndrome de Down (DS)** (+21c) sont caractérisée par une mutation **de GATA1** qui coopère avec la trisomie 21, suivie de l'acquisition d'autres mutations somatiques.

Non-DS-AMKL se caractérise par une chimère oncogénique, comprenant des gènes connus pour jouer un rôle dans l'hématopoïèse normale.

CBFA2T3-GLIS2, fusion
la plus fréquente identifiée
à ce jour dans ce sous-ensemble
de patients => **mauvais pronostic**.

↓

« hauts risques »
MyeChild 01



(Blood 2015; Grubert et al)

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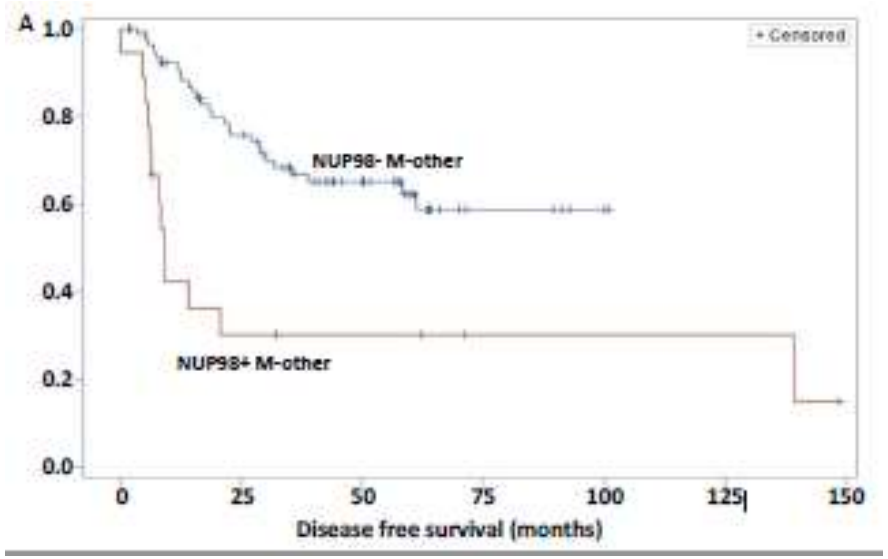
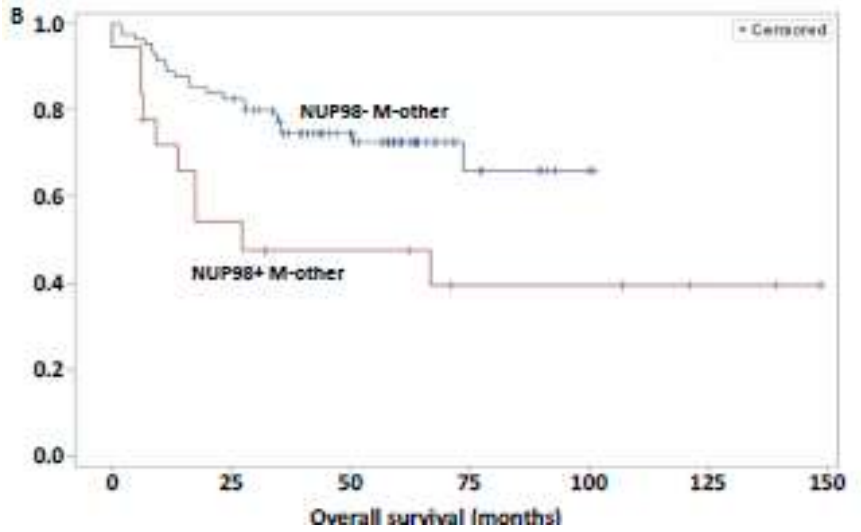
NUP98 is rearranged in 3.8% of pediatric AML forming a clinical and molecular homogenous group with a poor prognosis

Struski S et al, GFCH, Leukemia 2016





La survie sans maladie à 5 ans est de 30% par rapport à 62% dans les NUP98 négatifs (p <0,001), semblable à d'autres publications (*Holllink Ih et al, Blood 2011 et Shiba N et la,Genes Chrom Cancer , 2013*)

La survie globale à 5 ans (OS) à 48% significativement plus faible par rapport au groupe témoin à 72% (p <0,001), légèrement mieux que l'OS à 4 ans rapporté par d'autres publications (20% ou 33) *(Holllink Ih et al, Blood 2011 et Shiba N et al,Gene Chrom Cancer , 2013)*

Après la phase induction :
13/22 patients (72%) sont refractaires,2 patients ont reçu que de la chimiothérapie (rechute à 6 mois et décédés), les autres 11 enfants ont été greffés, donc biais de greffe, les enfants greffés survivent par rapport à ceux traités par la chimiothérapie.

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Including t(11;12)(p15;p13) / *NUP98- KDM5A (JARID1A)*

And other *NUP98*

(sept 2019)

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- Induction failure after course 1: morphological failure confirmed by flow MRD in Good Risk /Standard Risk patients

MyeChild 01

Acknowledgments :

Guy LEVERGER
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Claude PREUDHOMME

Emmanuelle DELABESSE
Audrey GUILMATRE
Maxime FERREBEUF

And other

Pediatricians

Cytogeneticists (GFCH)

Cytologists (GFHC)

Molecular biologists (GBMHM)

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more especially to Christine HARRISON