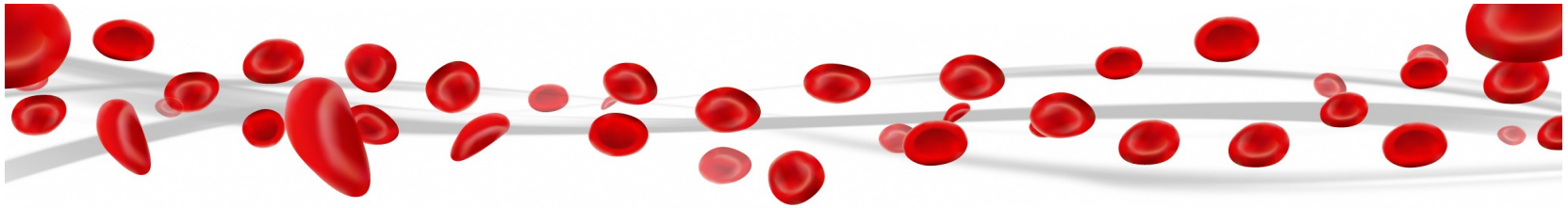


Thursdays Webinars

EuroBloodNet

Management of T-cell Prolymphocytic Leukemia

ERN-EuroBloodNet subnetwork : Lymphoid malignancies

Olivier TOURNILHAC

Service d'hématologie et de thérapie cellulaire

CHU Estaing

Clermont-Ferrand – France

26 May 2022

Co-funded by the Health Programme of the European Union

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

Lysa

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

Astra-Zeneca

Abbvie

Janssen

Roche

Sandoz

Secura-Bio

Gilead

Blueprint

Incyte

Travel grants

Research grants

Honorarium (advisory board, symposium, expertise)

Learning objectives of the webinar

1. What is T-PLL ?
2. How to diagnose T-PLL ?
3. Disease management focusing on actual available tools

T-cell prolymphocytic leukemia

- **Clinical presentation**
- Diagnostic
- Molecular features
- Prognosis
- Management

A new clinico-pathologic entity has been recognized

PROLYMPHOCYTIC LEUKÆMIA OF B AND T CELL TYPE

D. CATOVSKY, J. GALETTO, A. OKOS, D. A. G. GALTON, EVE WILTSHAW, G. STATHOPOULOS

Medical Research Council Leukæmia Unit, Royal Postgraduate Medical School, Department of Chemotherapy, Royal Marsden Hospital, and Department of Immunobiology, Chester Beatty Research Institute, London

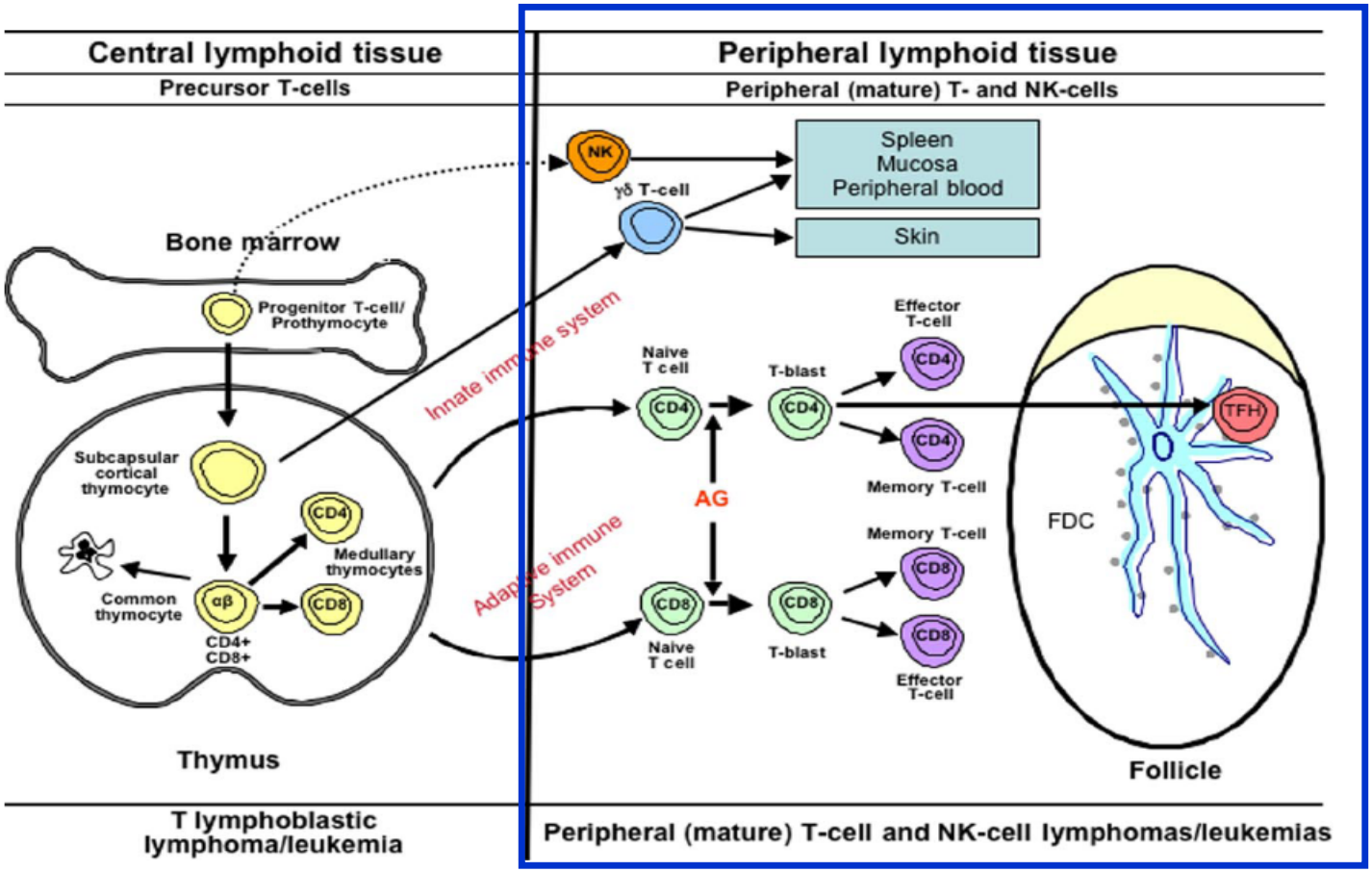
Summary B and T cell markers were studied in four patients with prolymphocytic leukæmia. Three patients demonstrated B-lymphocyte features: a high proportion of cells with surface immunoglobulins and C3 receptors but a low proportion of cells forming rosettes with sheep red blood-cells. The fourth patient had distinct T-lymphocyte characteristics: negative surface immunoglobulins, low proportion of cells with C3 receptors, and more than half of the neoplastic prolymphocytes forming rosettes with sheep red blood-cells. There were no clinical or hæmatological differences among these cases. This is the second unequivocal report of a lymphoproliferative disease of the T-cell type in man and the first of a T prolymphocytic leukæmia.

The Lancet, 1973

Courtesy of Marco Herling

What are we talking about ?

mature T-cell neoplasms



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WHO Classification of Tumours

Leukemic	Extra-nodal		Nodal
	Cutaneous	Other	
T-PLL T-LGL ATL/L (HTLV-1) Aggressive NK Chronic NK LPD Systemic EBV+ T-lymph Hydroa vaccineforme-like T-LPD	Mycosis fungoides Sezary syndrome Primary cut. CD30+ LPD Subcut panniculitis-like (αβ) Primary cut. γδ Primary cut aggressive CD8+ Primary cut small/medium CD4+ *Primary cutaneous acral CD81*	• Extranodal NK/T nasal-type • EATL (EATL #1) • MEITL (EATL #2) • *Indolent T-LPD of the GI tract* • Hepatosplenic (HSTL)	• PTCL TFH phenotype - AITL - F-PTCL - other nodal TFH PTCL • PTCL, NOS • ALCL, ALK + • ALCL, ALK – • *Breast-implant-associated ALCL*

Tissues. International Agency for Research on Cancer,
Swerdlow SH, 2017

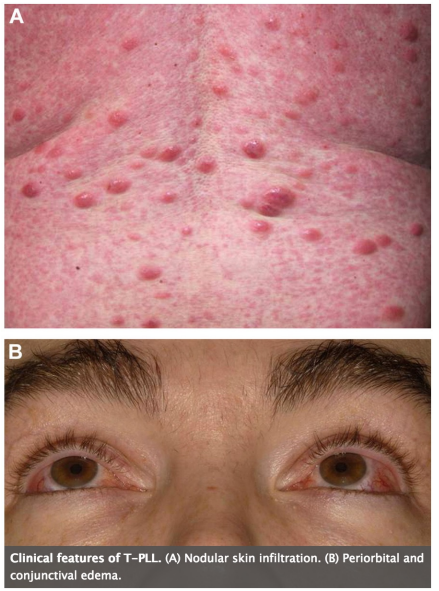
T-PLL : Rare : incidence 2/1 000 000
2% of « matures » leukemias

Clinical presentation

- Median age 65-70 years

- Typical presentation : aggressive, widely disseminated disease
  - Progressive lymphocytosis which can reach extremely high levels
  - Splenomegaly and adenopathy
  - Cytopenia “stage C”
  - B-symptoms (frequency ?)

- Alternate presentations :
- extranodal, including typical (albeit non constant) involvement :
  - pleural (peritoneal) effusion,
  - peripheral edema, particularly periorbital and/or conjunctival
  - skin lesions which include skin nodules, maculopapular rash, (rare) erythroderma
  - CNS (more frequent at relapse)
- (very) indolent forms eventually evolving to a more aggressive form.



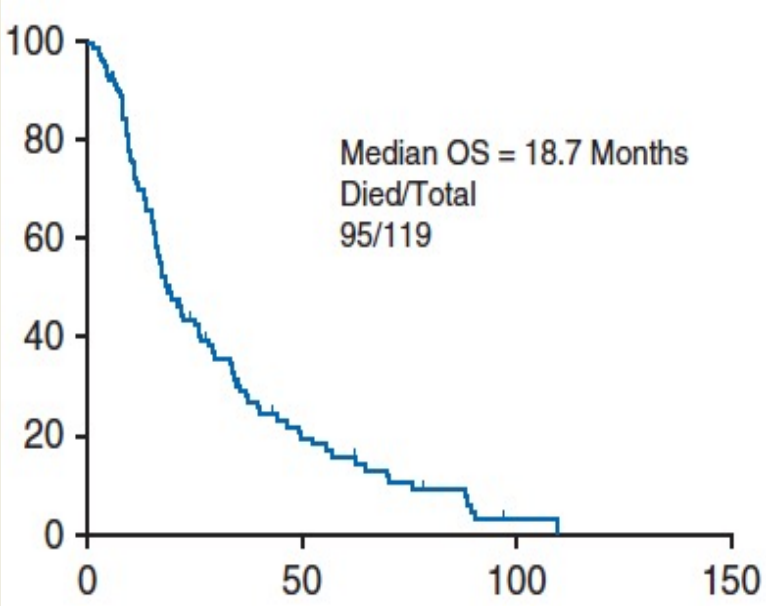
Clinical features of T-PLL. (A) Nodular skin infiltration. (B) Periorbital and conjunctival edema.

Dearden, Blood, 2012

Matutes, Blood 1991; Garand, BJH 1998; Ravandi, Clin Lymphoma Myeloma 2005; Khullar, Int J Dermatol 2017; Krassas, Ocul Immunol Inflamm; Jain, Ann Oncol 2017.

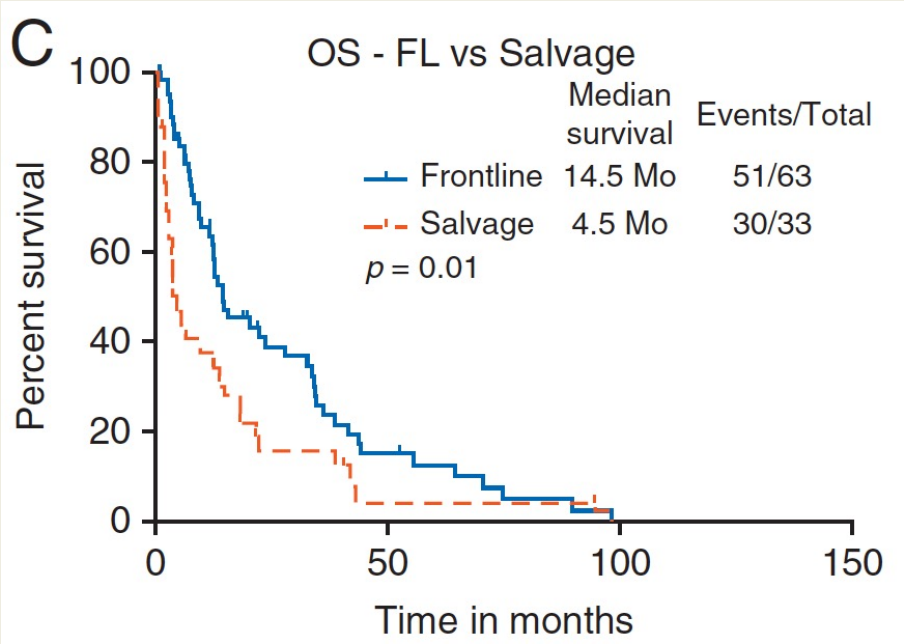
Clinical presentation

Overall survival (n=119)



Untreated patients

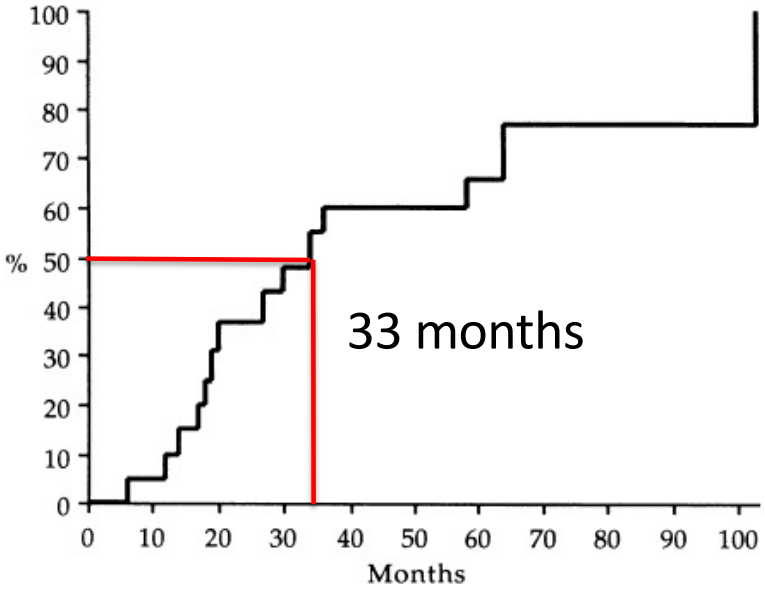
➡ time to 1st line = 2.3 m (0.1 – 52)

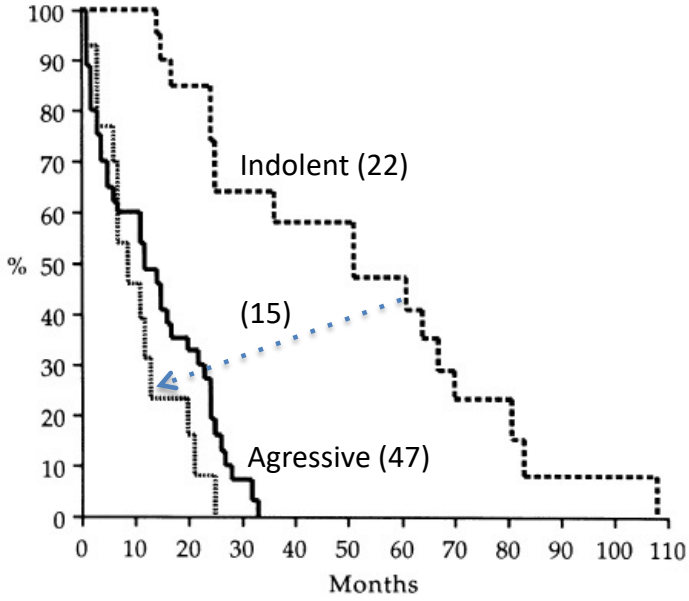


Jain, Ann Oncol, 2017

Clinical presentation

“Indolent” or”non-active” forms





Progression : 62% @ 36 months

Garand, BJH, 1998

Clinical presentation

	Matutes (n=78)	Garand #1 (n=25)	Garand #2 (n=53)	Jain #3 (n=75)	Jain #4 (n=43)
Timing	*Diagnostic*	*Diagnostic*	*Diagnostic*	*Before 1L*	*Before R/R trt*
Age	69 (33-91)	72 (49-96)	69 (35-98)	63 (35-87)	64 (39-83)
PS ≥ 2	/	/	/	12%	26%
Adenopathy	53%	5%	64%	55%	63%
Splenomegaly	73%*	11%	81%	31%	51%
Skin	27%	0%	25%	28%	28%
Hepatomegaly	40%	5%	43%	9%	15%
Effusion	14%	0%	19%	11% (Pl)	14% (Pl)
Other extra-nodal	/	0%	13%	/	/
Leucocytes	/	19 (10-52)	64 (12-715)	48 (2-800)	115 (1.7-547)
Platelets	51% (<100)	10% (<100)	36% (<100)	146 (3-450)	67 (11-356)
Hemoglobin	36% (<10)	0% (<10)	15% (<10)	13.3 (7.3-18)	10.7 (7.2-14.7)

#1 : Cohort agressive ; : #2 : Cohort indolent ; #3 : Front line, #4 : Relapse. * splenomegaly >10 cm (51%)

Matutes, Blood1991; Garand, BJH1998; Jain, Ann Oncol 2017.

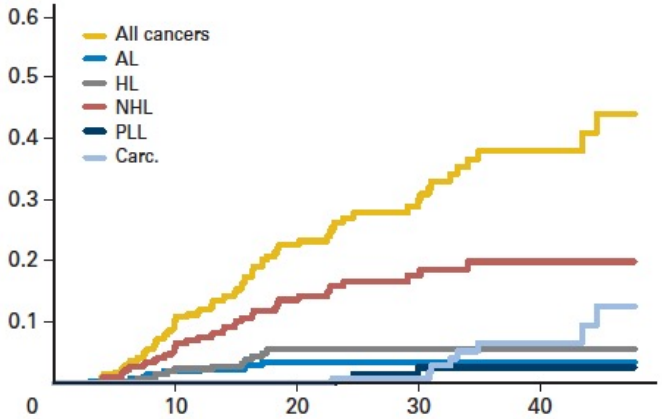
Clinical presentation

Ataxia-Telangiectasia

- *ATM* bi-allelic mutation
- Ataxia, telangiectasia, high αFP, radiosensiitivity
- Cancer predisposition

Rétrospective French cohort (n=279 ; FU 15 y) : 70 cancers

LNH	38
Hodgkin	12
Solid	9
LA	8
T-PLL	3



Incidence 68/100000

Suarez, JCO, 2014

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Thursdays Webinars

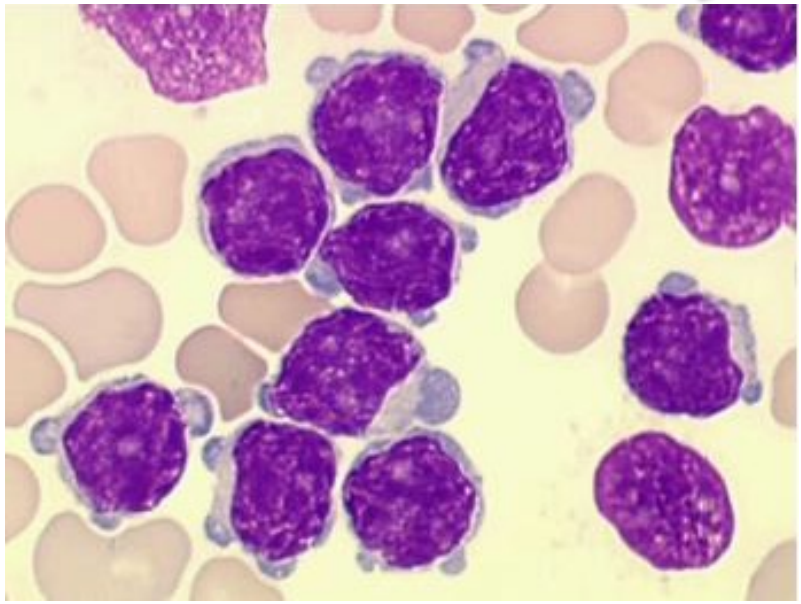
T-cell prolymphocytic leukemia

- Clinical presentation
- **Diagnostic**
- Molecular features
- Prognosis
- Management

Cytology : classical (75%)

Blebs !

Median size
High N/C
Condensed chromatin
1 nucleole
Basophilia
No granule
Blebs

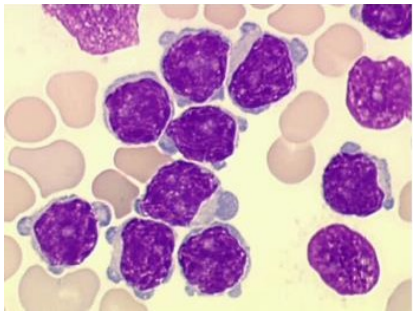


C. Debord

Cytology : variants

Classical (75%)

Medium size
Nucleole visible
Chromatin mod. condensed

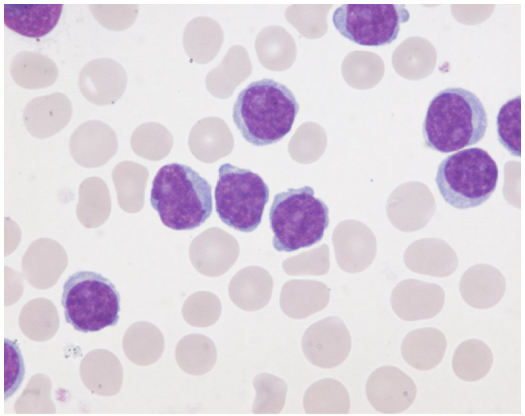


C. Debord

Clearly PLL

Small cell (20%)

Small size
Nucleole non visible
Chromatine condensed

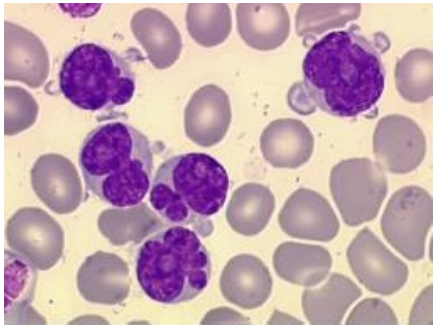


K. Laribi

CLL like

Cerebriform/flower (5%)

Nucleus irregular



C. Debord

Could be mistaken for …Sezary…ATLL..

Flow cytometry

Classical Panel

- **Positive** for CD3, possibly low
- **Negative** for CD1a and TdT
- **Positive** for CD45 various isoforms
- **Positive** for CD2, CD5, CD7(++)
- **Variable** expression of CD4 and CD8
  - Usually CD4+ (60%)
  - Double positive CD4+/CD8+ (25%)
  - Rare CD8+ (15%)
  - Very rare double negative (<5%)

Clonality :
TRBC1

Additional markers

CD16 : negative
CD56 : negative
CD25 : negative (80%)
CD38 : positive (20-50%)
CD26 : rarement+ faible

CD52 : positive
TCR$\alpha\beta$: positive
TCL1 : positive → Cytometry (permeabilization) → IHC
HLADR : negative
CD30 : négative

CD158k : ?

Staber, Blood, 2019

Cytogenetics

Abnormal karyotype (>90%) ; complex karyotype (70-80%)		
14q11 et 14q32.1 locus TRA/D and ***TCL1A*** **and** ***TCL1B*** genes	inv(14)(q11;q32) t(14;14)(q11;q32)	>70%
14q11 et Xq28 locus TRA/D and ***MTCP1*** gene	t(X;14)(q28;q11)	<10%
8 Gain ***MYC*** gene 8p deletion	i(8)(q10) t(8;8)(p11-12;q12) Trisomy 8	75%
11q23 ***ATM*** gene	Deletion	70%
17p ***TP53*** gene	Deletion	20-30%
Other **Loss :** 7q34-36 (*EZH2*) (53%), 22q (37%), 13q14q21 (31%), 17q (25–29%), 6q (25.5%), 20q11.23 (25.5%), 9q21 (23.5%), 12p13 (*CDKN1B*) (23.5%) **Gain :** 22q (29%), 5p (22–62%), 7q (22%), 17q (20%), 6p (20–25%)		

Is the karyotype normal ?

- 71 yo woman, isolated slowly progressive lymphocytosis (>4 G/L) : 5,5 G/L. in 2019
- Cytology : medium sized celles, highN/C, basophily, irragular nucleus, nucleoled
- Phenotype : TdT negative, CD2+, CD3+, CD7+, CD4+ , CD8neg
- Pending diagnosis….

CYTOGENETIQUE
Sang

Caryotype :

Comptage cellulaire : 18.10⁶ cellules — Marquage chromosomique : GTG

Conditions de culture	Résolution (nb de bandes)	Nombre de mitoses caryotypées
72h + PHA	300-400	21

Cytogénétique moléculaire :

Conditions de culture : 72h + PHA

Nom des sondes	Locus	Sonde témoin	Fournisseur
LSI TRA/D Break Apart Rearrangement Probe	14q11.2	/	Vysis
XCP 8 rouge	peinture	/	Metasystems
XCP X vert	peinture	/	Metasystems

Formule chromosomique des cellules examinées :

46,X,der(X)t(X;1)(p22;q21),add(7)(q34),der(14)add(14)(p11)inv(14)(q11q32),
add(21)(p11)[7]/46,XX,der(8)t(8;8)(p23;q11),inv(14)(q11q32)[4]/46,XX[10].ish
der(X)(wcpX+),der(8)(wcp8+)[10],inv(14)(q11)(5'TRA+)(q32)(3'TRA+)[11],der(?)t(?;X)
(wcpX+)[10].nuc ish(TRAx2)(5'TRA sep 3'TRAx1)[46/100]

Diagnostic

Blood T-cell proliferation

Clinic / Cytology

Cytometry / Cytogenetics

Major criteria	Minor criteria (at least 1 required)
• >5 × 10⁹/L cells of T-PLL phenotype in peripheral blood or bone marrow	• Abnormalities involving chromosome 11 (11q22.3; *ATM*)
• T-cell clonality (by PCR for TRB/TRG, or by flow cytometry)	• Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
• Abnormalities of 14q32 or Xq28 OR expression of *TCL1A/B*, or *MTCP1**	• Abnormalities in chromosome 5, 12, 13, 22, or complex karyotype
	• Involvement of T-PLL specific site (eg, splenomegaly, effusions)

*Cases without TCL1A, TCL1B, or MTCP1 rearrangement or their respective overexpression are collected as TCL1-family negative T-PLL.

TPLL-ISG Diagnostic criteria
Staber, Blood, 2019

T-PLL

T-PLL Classique

All 3 major criteria

T-PLL « TCL-family negative »**

2 major criteria (1 and 2) and ≥ 1 minor criteria

	Cytometry	other
T-ALL	TdT+, CD1a+	
T-LGL	CD8+, CD57+, CD16+	
ATLL	CD4+, CD25+	HTLV1+
Sezary	CD7-, CD4+, CD25+, CD158k+, CD26+	Cytology possibly confusing
Leukemic PTCL*	CyTCL1-	TCL1- (IHC), NGS signatures (TFH, HSTL…)
Other entities	Thyroïd/lymphocytosis T-cell lymphoproliferation TCUS	

Other tools

Targeted NGS (*ATM, JAK/STAT, TP53*…)

Extended flow cytometry panel

Tissue Histology : TCL1 IHC

Hybridation in situ *TRC A/D*
TCL-1 break-apart at 14q32
MTCP 1 at Xq28

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T-cell prolymphocytic leukemia

- Clinical presentation
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- **Molecular features**
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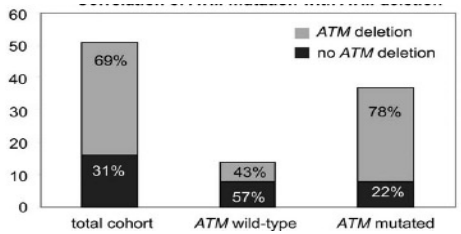
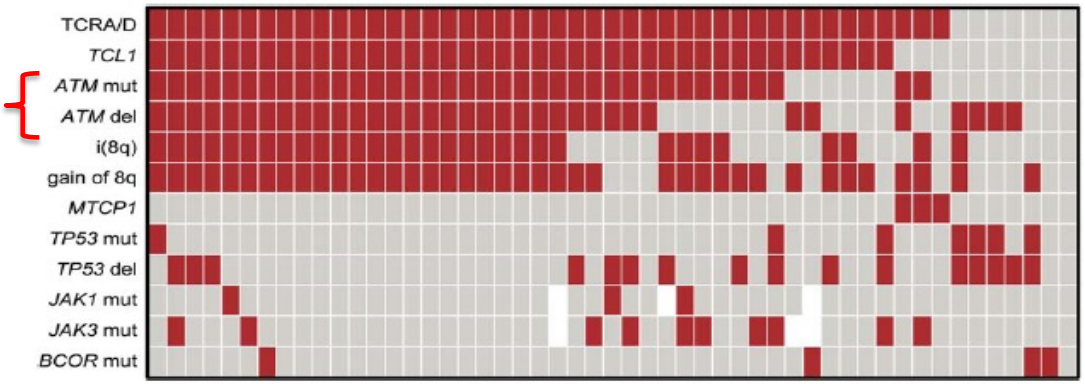
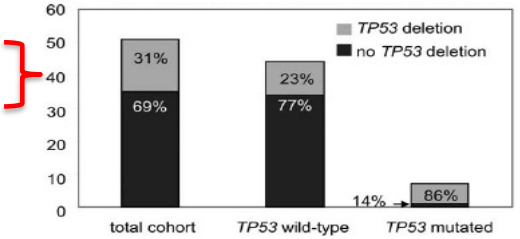
Molecular landscape



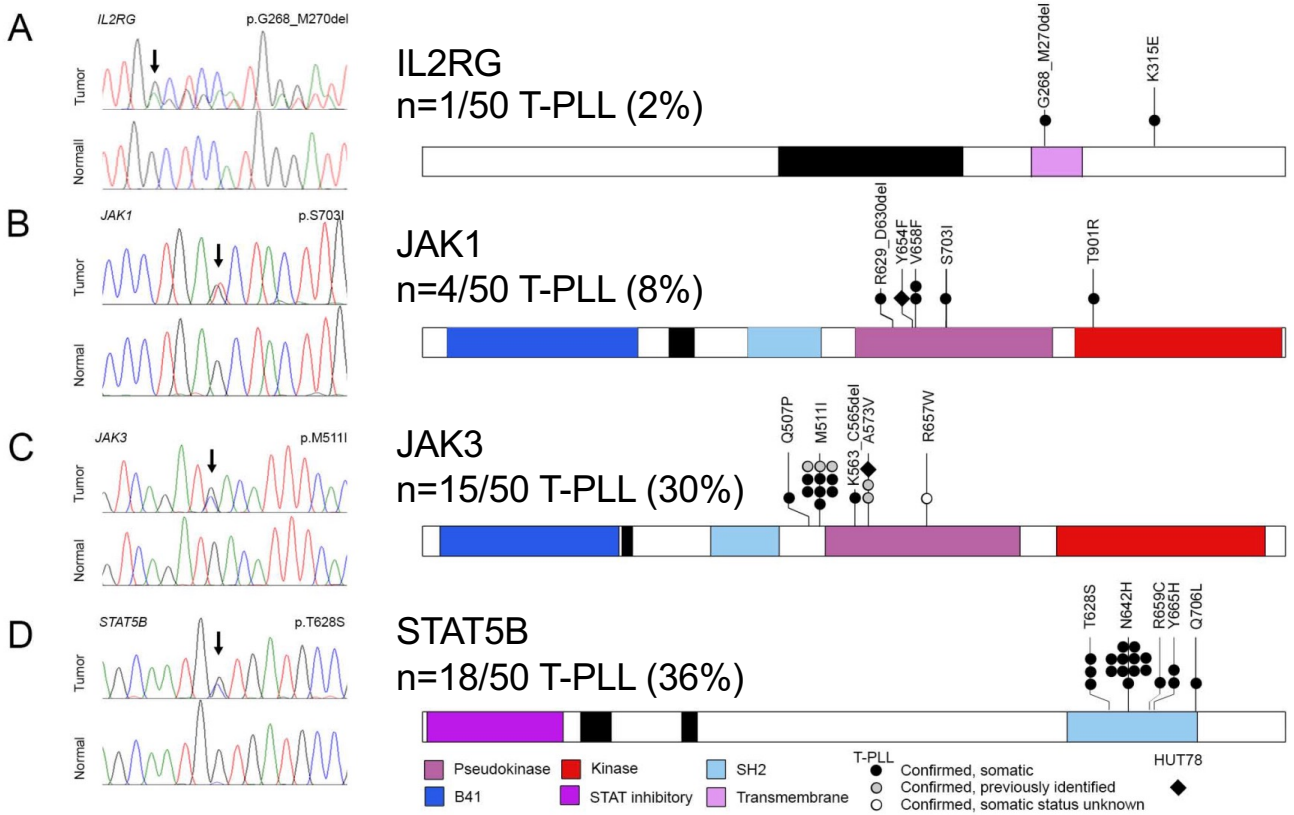




DNA damage	JAK/STAT pathway
***ATM* (75%)**	**IL2RG (2%)**
***TP53* (25%)**	***JAK1* (10%) … pseudokinase domain**
SAMHD1 (20%)	***JAK3* (30%) … pseudokinase domain**
	***STAT5B* (30%)**

Kiel, 2014 ; Stengel, 2016

Molecular landscape



Kiel, 2014

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Molecular landscape

DNA damage/repair	Env. 100%
ATM mutation	70%
ATM deletion (11q)	70%
TP53 mutation	15%
TP53 deletion (17p)	20-30%
SAMHD1 mutation	18%
HERC2 mutation	12%
HERC1 mutation	9%
JAK/STAT Pathway	**75%**
IL2RG mutation	2%
JAK1 mutation	10%
JAK3 mutation	30%
STAT5B mutation	30%

Epigenetic regulation	
EZH2 deletion (del 7q34-36)	50%
EZH2 mutation	12%
TET2 mutation	3-19%
PR2M2	12%
KTM2B	9%
KTM2E	9%
ARID4B	6%
EP300	6%
BCOR	3-19%
Other	
CDKN1B deletion (del 12p13)	*25%*
CHEK2 mutation	*3-10%*
FBXW10 mutation	

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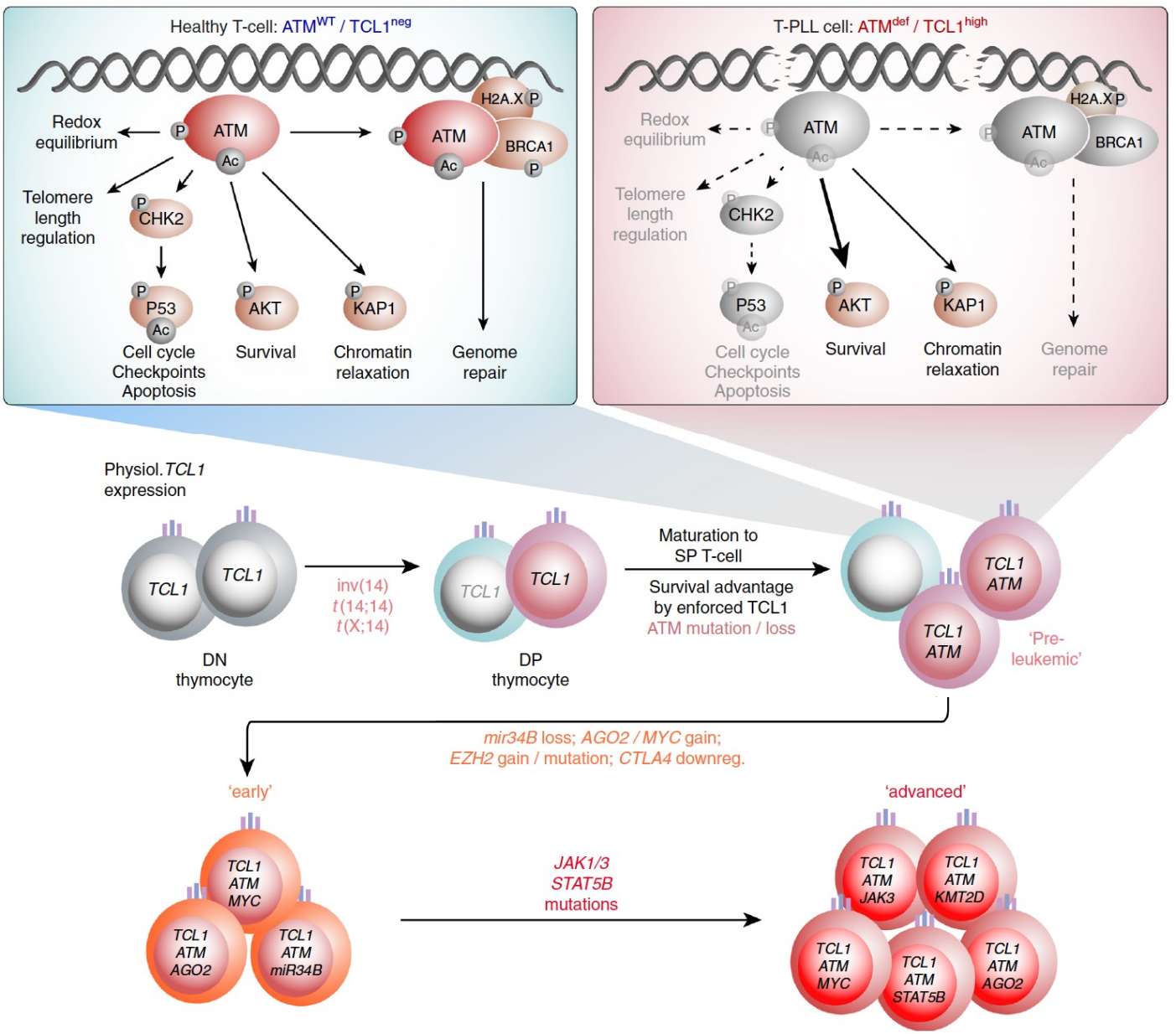
Kiel, Blood 2014; Bellanger, Leukemia, 2014; Bergman, Genes Chromosomes Cancer 2014 ;
Stengel, Genes Chromosomes Cancer 2016;
Johansson, Blood Cancer J 2018;
Lopez, BJH 2016.

Proposed clonal evolution

For « classical T-PLL »



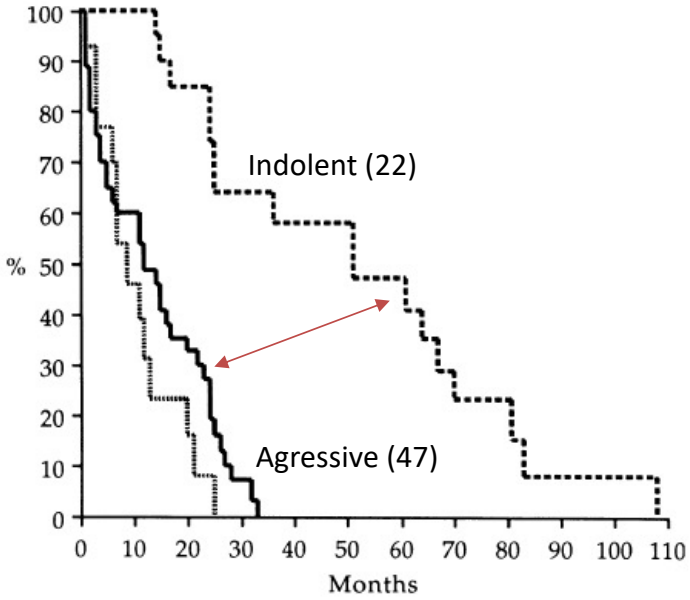
Schrader, Nat Com, 2018

T-cell prolymphocytic leukemia

- Clinical presentation
- Diagnostic
- Molecular features
- **Prognosis**
- Management

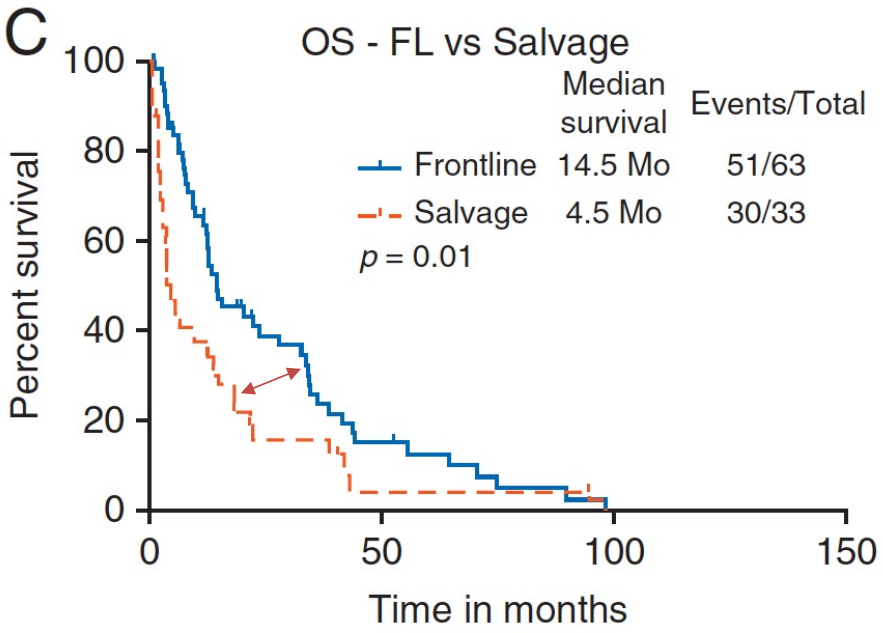
Impact of disease status

Indolent versus active



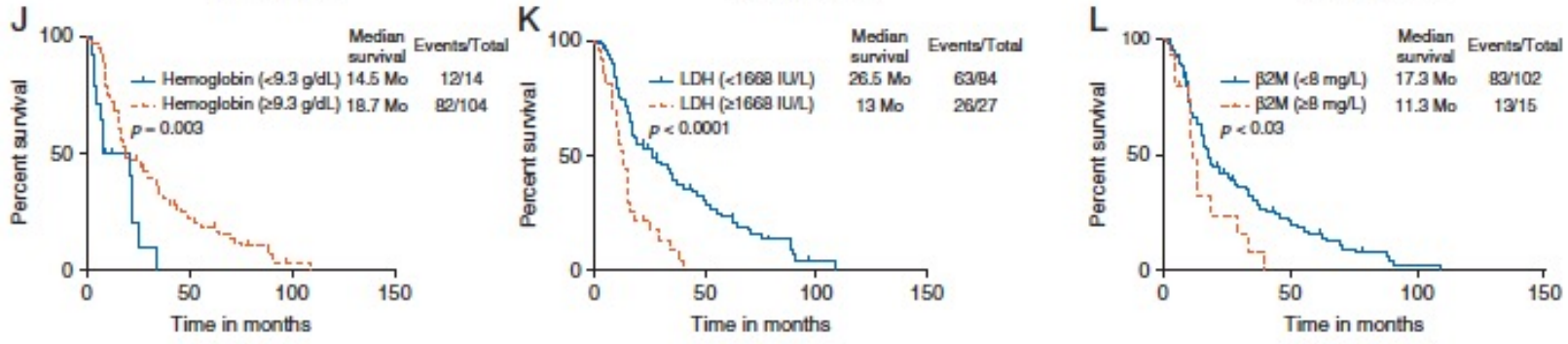
Garand, BJH, 1998

Front line versus Salvage

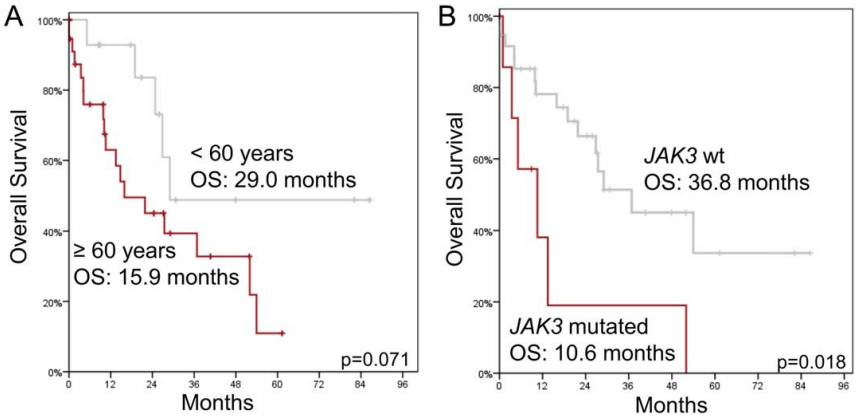


Jain, Ann Oncol, 2017

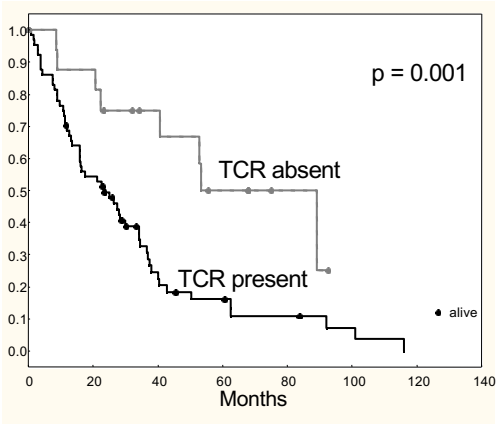
Prognostic



Jain, Ann Oncol, 2017



Stengel, Genes Chromosomes & Cancer, 2016



Herling, Blood, 2008

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T-cell prolymphocytic leukemia

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- **Management**

T-PLL treatment indications

Patients with indolent course : no treatment is recommended, but close follow-up

blood count at least every 3 months and

clinical evaluation at least every 6 months

Patients with active disease are to be treated.

Staging: at least 1 criterion defines active T-PLL (= indication for treatment)		
Disease-related constitutional symptoms	Significant fatigue: ECOG ≥2	
	Unintentional weight loss of >10% of normal body weight in ≤6 mo	
	Drenching night sweats, without evidence of infection	
	Fever greater than 38°C, without evidence of infection	
Symptomatic bone marrow failure	Hemoglobin	<10 g/dL
	Platelet count	<100 × 10⁹/L
Rapidly enlarging lymph nodes, spleen, and liver	>50% in 2 mo; diameter doubling <6 mo	
	Symptomatic enlarged lymph node, spleen, or liver	
Increasing lymphocytosis	If >30 × 10⁹/L: >50% in 2 mo; lymphocyte doubling time <6 mo	
Extranodal involvement	Organ infiltration; peritoneal or pleural effusion, central nervous system involvement	

Staber, Blood, 2019

Retrospective analysis

Alkylator
CHOP
Irradiation
OS<12m
Matutes, Blood, 2001

	Protocole	Ind	n	ORR (%)	CR (%)	PR (%)	PFS (mo.)	OS (mo.)
Mercieca 1994	PENTO	**R/R**	56	45	9	36	6	9
Pawson 1997	PENTO	**R/R**	25	40	3			
	ALZ IV	**R/R**	15	73	60	13	6	8
Keating 2002	ALZ IV	**1L**	4	75	75	0	4.5	7.5
	ALZ IV	**R/R**	72	50	38	12		
Jain 2017	ALZ IV	**1L**	42	81	61	20	11	15
	ALZ IV + PENTO	**1L**	13	82	73	9	4.3	10.4
	ALZ IV	**R/R**	15	46	46	/	3	15
	ALZ IV + PENTO	**RR**	5	75	50	25	2.6	2.6
Herbaux 2014	BENDA	**R/R + 1L**	15	53	20	33	5	8.7

40-45% ORR
In R/R

50% ORR
In R/R+1L

Prospective trials : alemtuzumab based

Reference	Protocole	Ind.	n	age	ORR (%)	CR (%)	PR (%)	PFS (mo.)	OS # (mo.)
Ravandi, JCO, 2009	PENTO + ALZ IV	**R/R**	13	57 (21-79)	69	62	8	7.8	10.2
Hopfinger, 2013	FMC then ALZ IV (TPLL1)	**1L (16)** **R/R (9)**	25	66 (38-78)	68 92	24 48	44 44	11.9	17.1
Pflug 2019	attFCM + ALZ SC puis ALZ SC (TPLL2)	**1L (13)** **R/R (5)**	18	68 (32-78)	69	32	37	7.5	11.5
Dearden 2001	ALZ IV	**R/R**	39	57 (34-78)	76	60	16	6	8
	ALZ IV (Bis)	**R/R+1**	13	58 (43-77)	46	38	8	0-16	n.d.
Dearden 2011	ALZ IV	**1L**	32	62 (36-85)	91	81	10	67% @12m	35% @48m
	ALZ SC	**1L**	9	61 (36-79)	33*	33*	0	67% @12m	33% @48m
	ALZ IV	**R/R**	45	59 (35-81)	74	60	14	26% @12m	18% @48m

* 67% if SC changed for IV or pentostatine addition

Alemtuzumab IV front line : high ORR/CR ; PFS ≥1y but OS <4y

Alemtuzumab : a standrard to be used with caution !

Impact of supportive care +++

- Infusion reaction management : try to improve tolerance

Communication
SC administration better tolerance but loss of efficacy versus IV
Ramp up
Steroids, anti Histaminic, paracetamol

- Infection screening and prevention
  - Cotrimoxazole
  - Valaciclovir
  - CMV screening
- Blood products irradiation
- Hematopoietic growth factors
- Be aware of :
  - Various (any kind !) infectious complications : including CVM/EBV reactivation
  - Immune reconstitution syndrome
  - Negative impact on T-cell engraftment post allogeneic transplantation
  - Risk of drug shortage !

Long survivors post-alemtuzumab : role of transplantation

Overal survival

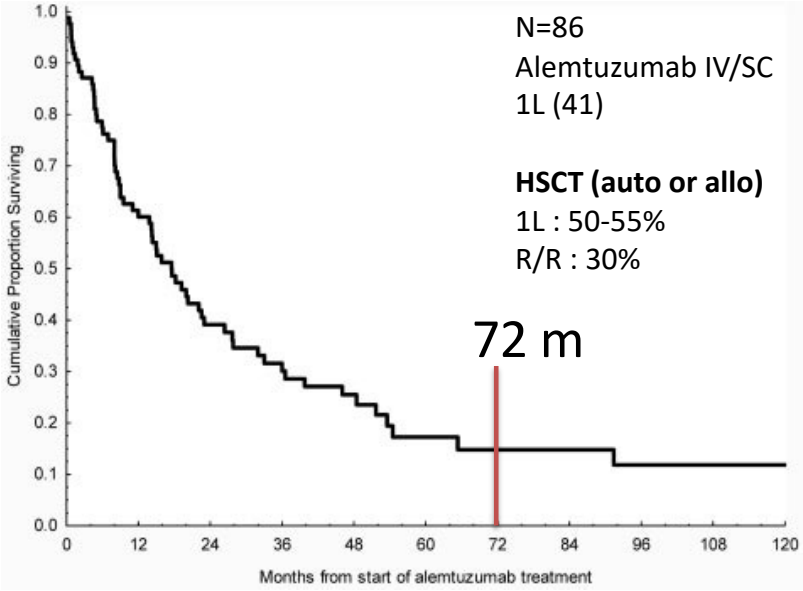

Figure 6. Survival curve for 86 T-PLL patients treated with alemtuzumab. Survivors beyond 72 months are those who received consolidation with a HSCT.

Dearden, Blood, 2012

Results of allogeneic transplantation

	nb		1L	age	ALZ	Status @T	RIC	UM donors	TRM	CIR	OS
Krishnan BJH, 2010	13	Multicentric (1996-2005)	62%	51 (39-61)	100%	CR/PR (85%) NR (15%)	31%	0%	31%	31%	33%
Wiktor-Jedrzejczak Leukemia, 2012	41	EBMT / RMH (1995-2006)	nr	51 (24-71)	26%	CR/PR (56%) SD/PD (32%)	47%	0%	31% (3y)	47% (3y)	21% (3y)
Guillaume Eur J Hematol, 2015	27	SFGM-TC (2000-2013)	48%	53 (36-65)	63%	CR/PR (89%) SD/PD (11%)	63%	14%	31% (3y)	47% (3y)	36% (3y)
Sellner BMT, 2017	10	Heildelberg (2007-2015)	80%	59 (43-72)	100%	CR/PR (100%)	100%	20%	30%	50%	20%
Dholaria Leuk Research, 2018	11	Lee Moffitt (2006-2016)	82%	56 (43-71)	82%	CR/PR (100%)	27%	27%	34% (4y)	21% (4y)	56% (4y)
Yamasaki, Ann Hematol, 2019	20	JSHCT (2000-2016)				CR/PR (35%) Other (65%)	50%	55%	21% (1y)	70% (3y)	40% (3y)
Wiktor-Jedrzejczak, BMT, 2019	37	EBMT (2007-2012)	72%	56 (47–59)	95%	CR/PR (90%) SD/PD (10%)	65%	0%	32% (4y)	38% (4y)	42% (4y)
Murthy Transplant Cell Ther, 2022	266	CIBMTR (2008-2018)	na	59 (25-76)	na	CR/PR (86%) Other (14%)	71%	26%	32% (4y)	42% (4y)	30% (4y)

TRM	CIR	OS
30%	≥40%	30-40%

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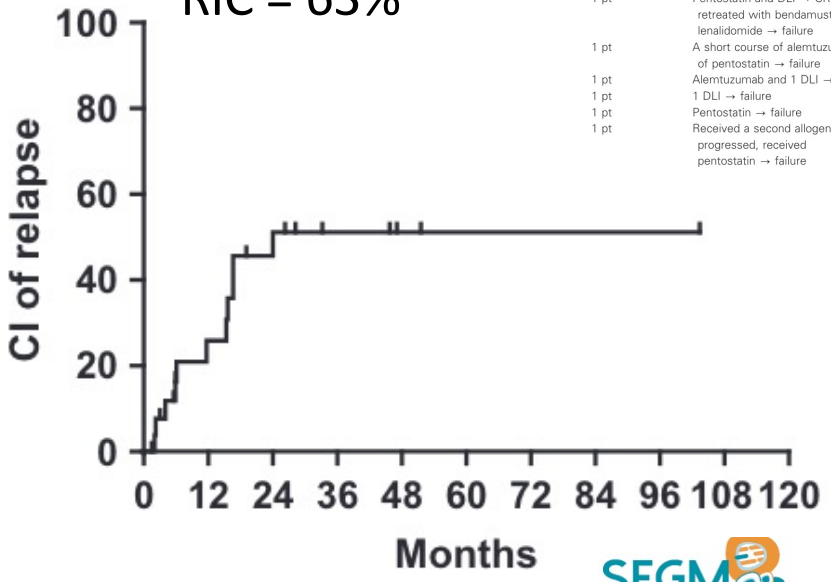
Treatment options

Relapse post allogeneic transplantation : T-PLL ≠ PTCL

N=27 T-PLL
2000-2013
RIC = 63%

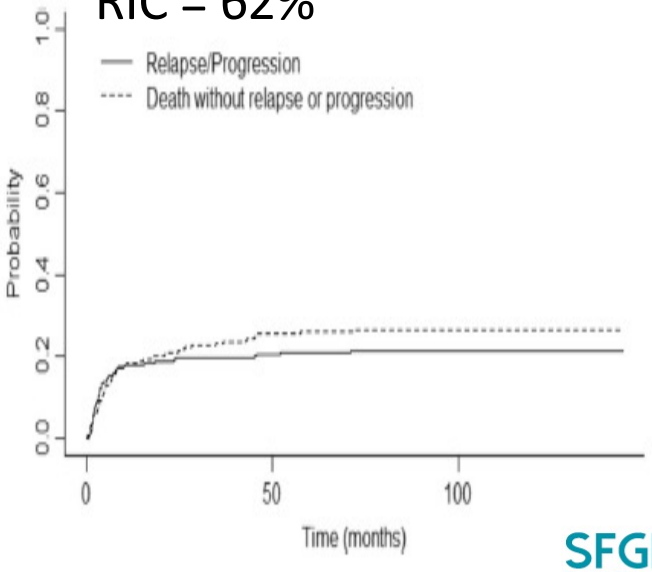
Relapse treatment

1 pt	Alemtuzumab → failure, lenalidomide → failure, bendamustine → failure
1 pt	Lenalidomide and radiotherapy → PR
1 pt	Alemtuzumab and 3 DLI → PR and progressed
1 pt	Alemtuzumab and 2 DLI → CR complicated by an acute grade IV GVHD (died from pulmonary carcinoma)
1 pt	Pentostatin and DLI → CR of short duration, retreated with bendamustine and lenalidomide → failure
1 pt	A short course of alemtuzumab → failure, 2 cycles of pentostatin → failure
1 pt	Alemtuzumab and 1 DLI → failure
1 pt	1 DLI → failure
1 pt	Pentostatin → failure
1 pt	Received a second allogeneic transplantation, progressed, received pentostatin → failure



Guillaume, Eur J Hematol, 2015

N=285 PTCL
2006-2014
RIC = 62%



Mamez, Journal of Hem/Oncol, 2020

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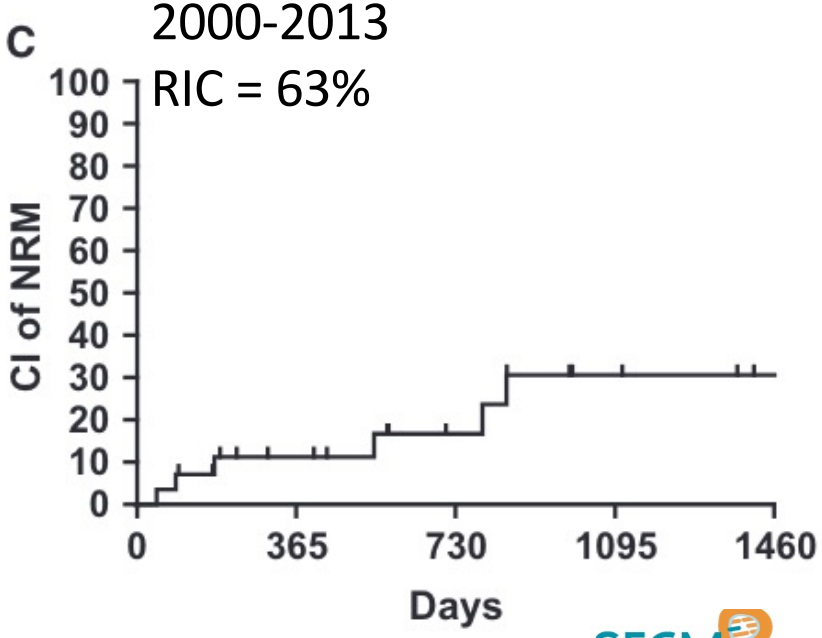
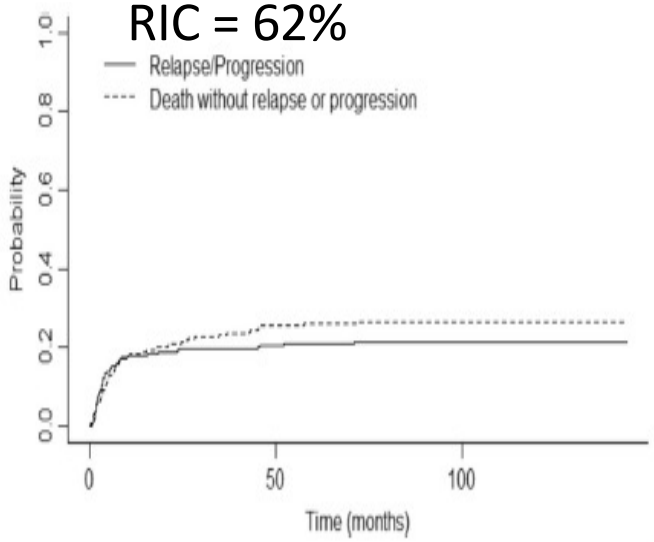
Non relapse mortality

N=27 T-PLL
2000-2013
RIC = 63%



Guillaume, Eur J Hematol, 2015

N=285 PTCL
2006-2014
RIC = 62%



Mamez, Journal of Hem/Oncol, 2020

Allo-HCT in T-PLL : EBMT - Prospective data collection (n=37)

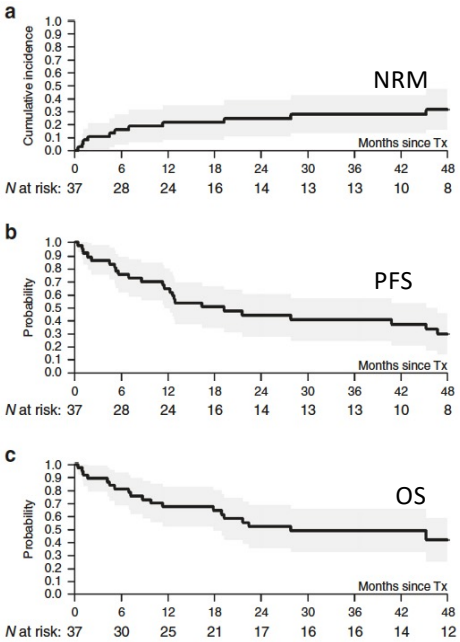
EBMT CMWP 2007-2012

≤65 yo
CR/PR (90%) (CR1=44% ; PR1 =22%)
HLA matched
Alemtuzumab pre-allo (95%) : 75 d (53-152)
MAC 35%

Relapse Rate = 38% (4y)

Rare after 2y (n=2)

Jedrzejczak, BMT, 2019



32% (4y)

30% (4y)

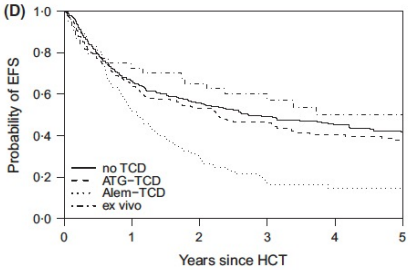
42% (4y)

Univariate analysis

TBI > 6 Gy : lower relapse rate
Interval diag-allo > 12m : lower NRM

But no impact of
Alemtuzumab ≤ 60 days
CR vs PR
MAC (trend RR)

CLL (n=684) ; EBMT



ALZ within 2 weeks

Schetelig, BMT, 2017

T-PLL (n=266) ; CIBMTR

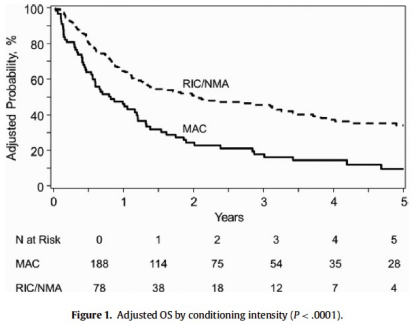


Figure 1. Adjusted OS by conditioning intensity ($P < .0001$).

Murthy, Transplant Cell Ther, 2022

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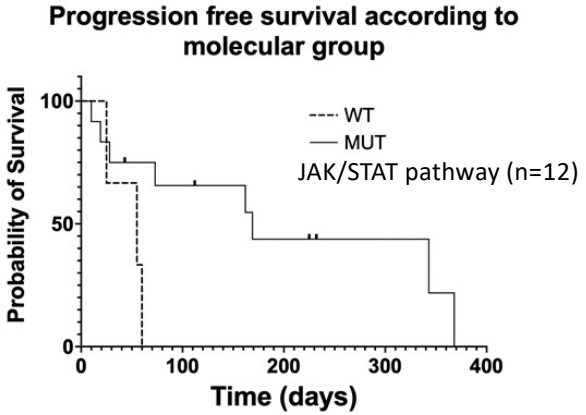
Preliminary Study of Ruxolitinib and Venetoclax for Treatment of Patients with T-Cell Prolymphocytic Leukemia Refractory to, or Ineligible for Alemtuzumab

Charles Herbaux, Stéphanie Poulain, Damien Roos-Weil, Jacques-Olivier Bay, Yann Guillermin, Francois Lemonnier, Kamel Laribi, Sorin Visanica, Jerome Moreaux, Hugo Gonzalez, Maxime Jullien, Abderrazak El Yamani, Houria Debarri, Sophie Godet, Franck Morschhauser, Olivier Tournilhac, Matthew S. Davids, Loic Ysebaert

Blood (2021) 138 (Supplement 1): 1201.

Retrospective study
N=15
Ruxolitinib 15x2 + venetoclax 800
R/R (n=14)
1L (n=1)
. Alemtuzumab Refractory (n=10)
. Alemtuzumab Refractory (n=5)

ORR= 73% (all PR)



Conclusion

T-PLL is a clear entity

Diagnostic is based on 4C : Clinic/Cytology/Cytometry/Cytogenetics

- Apply consensus criteria (Blood, 2019)

Aggressive behavior and poor prognosis

- Possible indolent forms (close W/W)

Molecular landscape : extensively characterized

- Tumor vulnerabilities / targetable mutations ? : example of JAK/STAT mutations

Treatment option include

- Alemtuzumab +/- pentostatin
  - 1st line high ORR, PFS ≥ 1y and OS < 4y
  - Caution !
- Allogeneic transplantation
  - Only curative option (OS = 30-40%)
  - But high Relapse Rate ≥ 40% (including late relapses)
  - And non relapse mortality
- Autologous transplantation
  - Underreported !

Recommandation

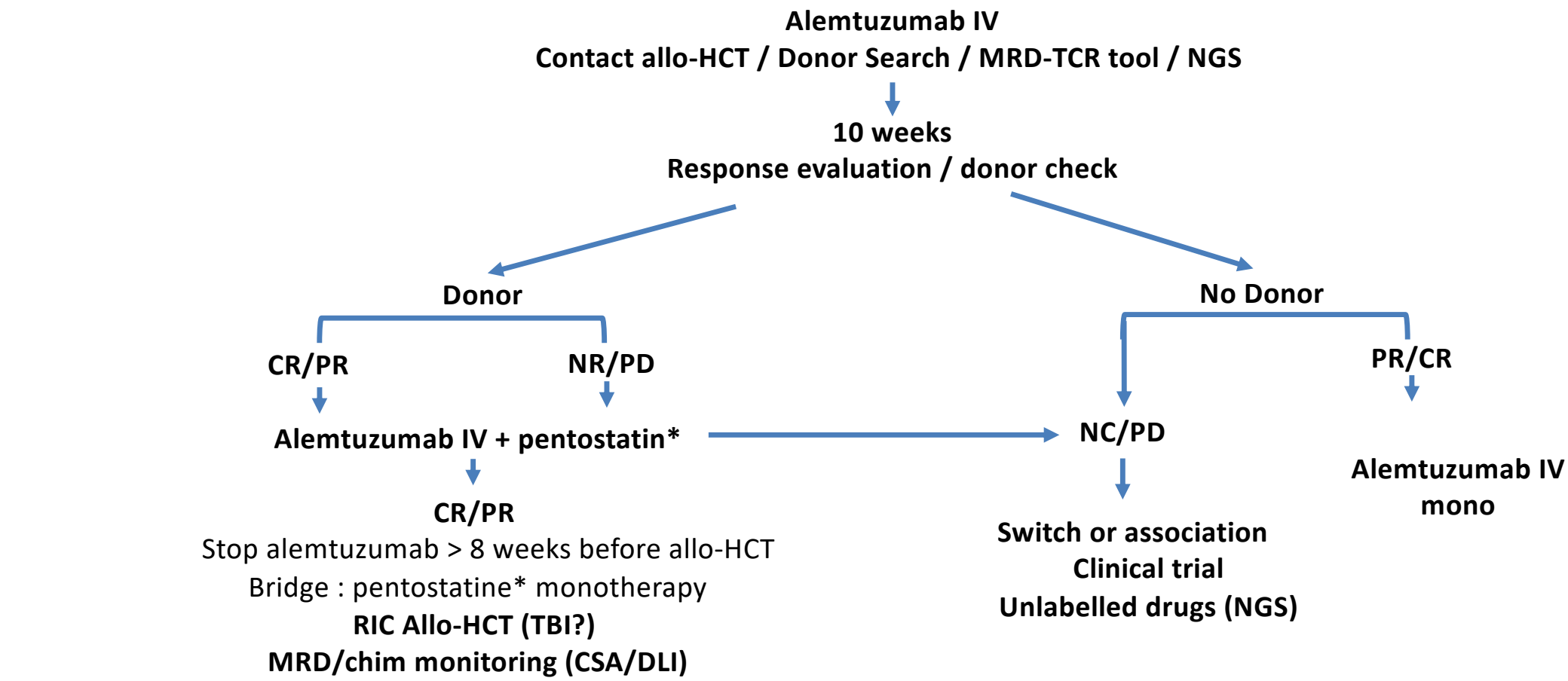
Table 3. PLL management algorithm

	Stable indolent	First line	Consolidation	Relapse/refractory
T-PLL	W & W until progression	IV alemtuzumab +/– PA	Consider autologous or allogenic SCT in all eligible patients	Repeat alemtuzumab (if CD52 positive) PA-based combination Bendamustine Clinical trial Experimental agent (eg, JAK5/STAT5b inhibitors) Consider SCT

W&W indicates watch and wait; BR, bendamustine and rituximab; IV, intravenous; and PA, purine analog.

Dearden, ASH, 2015

Proposal optimization for 1st Line, ≤ 70 y and eligible for allo-HCT



*Alternative : Bendamustine

O. Tournilhac, 2nd T-PLL international study group meeting, Wien, 2022
adapted of Dearden, ASH, 2015 and Blood, 2012

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Take home messages

1. T-PLL diagnostic is based on 4C, with the demonstration of *TCL1* or *MTCP1* genes implication.
2. Molecular landscape has been well described above *TCL1* or *MTCP1* rearrangement discovering potential targetable mutations. This landscape includes very frequent ATM mutations and/or deletion and frequent mutation on JAK/STAT pathway.
3. Aggressive course and poor pronostic : alemtuzumab remains a standard treatment (PFS ≥ 1y) but allogeneic transplantation, the only curative option should be considered in eligible patients.