LMNH T

Thérapeutiques innovantes et hémopathies malignes
AIH Marseille, Sept 2013

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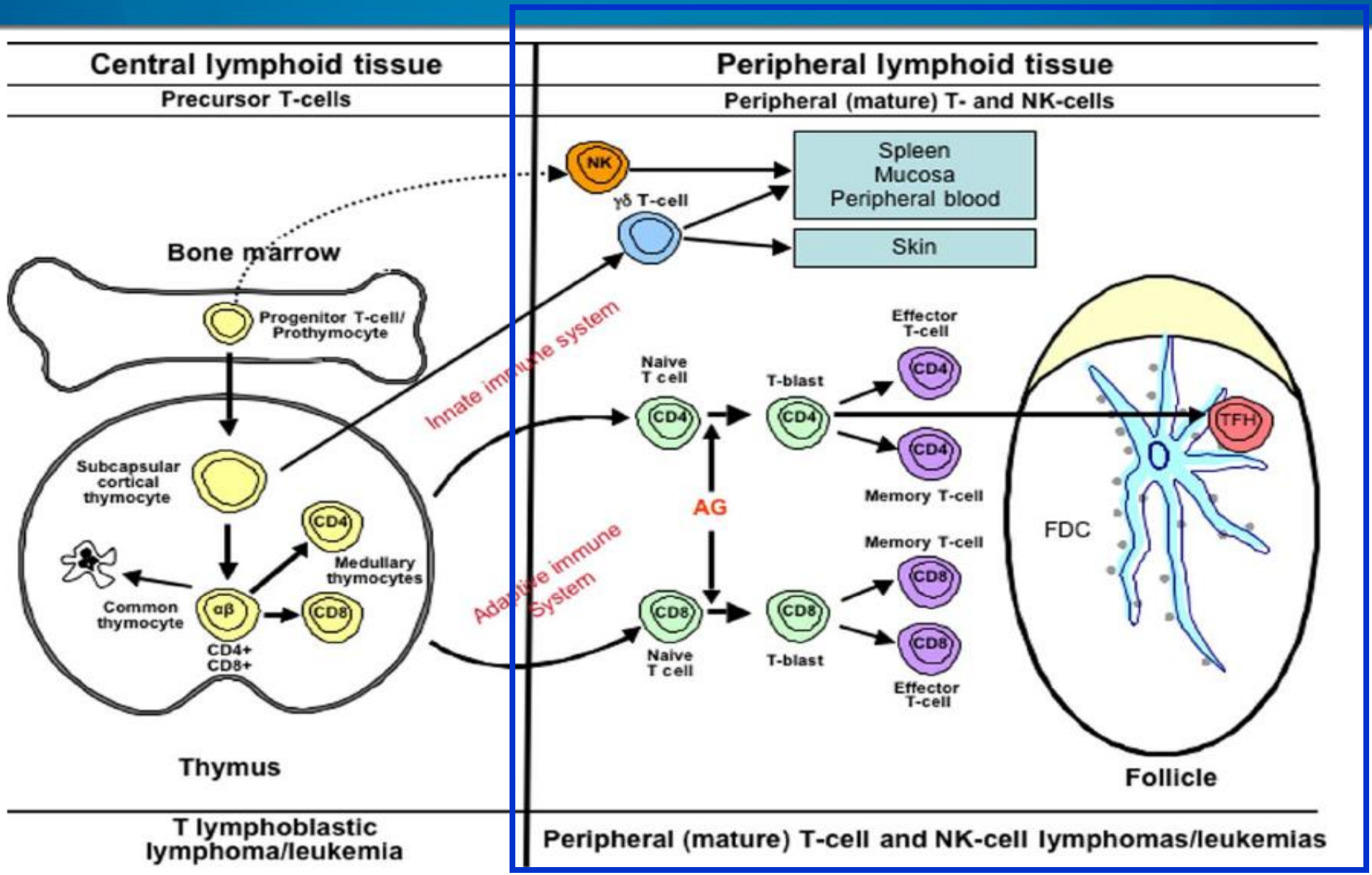
HEMOPATHIES DE PHENOTYPE T/NK :

- **5-6% des hémopathies lymphoïdes**
- **10-15% des lymphomes**
- **6000 nouveaux cas / an (USA)**
- **Facteurs géographiques**
  - ***ex HTLV1 ; NK/T nasal type ; EATL***

Devesa, Cancer Res. 1992 ; Morton, Blood 2006

ORIGINE PERIPHERIQUE



ALGORYTHME

« Lymphomes de phénotype T/NK »

→ ***Lymphoblastiques ?***

↓

NON

↳ **Lymphome T périphérique**

Cutané ?
Mycosis
Fungoides
Sezary
CD30 cut
Autres

↓

incluent
MF transformés

Leucémiques ?
ATLL
LGL
T-PLL

Autres ?

<u>Sous types fréquents et nodaux</u>

PTCL-NOS « lymphome T périphérique, sans autre précision »

ALCL, ALK+ et ALK(-) « lymphome anaplasique a grandes cellules »

AITL « lymphome T angio-immunoblastique (LAI) »

<u>Sous type rares et extranodaux</u>

. Lymphome T/NK de type nasal
. Lymphomes T associés aux entéropathies
. Lymphome T hépato-splénique
. Lymphome T « panniculite-like »

PRESENTATION CLINIQUE DES PTCL : globalement

Table 2. Clinical Characteristics of PTCL and Diffuse BCL Patients

Parameter	PTCL (n = 288) (%)	BCL (n = 1,595) (%)	*P* Value
Age ≤60 yr	64	59	.1
Male	69	53	.001
Female	31	47	
Stage			
I-II	22	42	.001
III-IV	78	58	
B-symptoms	57	40	.001
PS >1	28	25	.1
ENS >1	37	30	.01
BM positive	31	17	.001
Bulk >10 cm	26	41	.001
Hepatomegaly	21	11	.001
Splenomegaly	34	20	.001
Skin lesions	21	4	.001
LDH >NI	51	57	.05
β_2-microglobulin >NI	50	34	.001
Hemoglobin <10 g/dL	21	13	.001
Platelets <100 × 10^9/L	9	3	.001
Eosinophils ≥0.8 × 10^9/L	14	2	.001
Gammaglobulin >20 g/L	8	3	.001

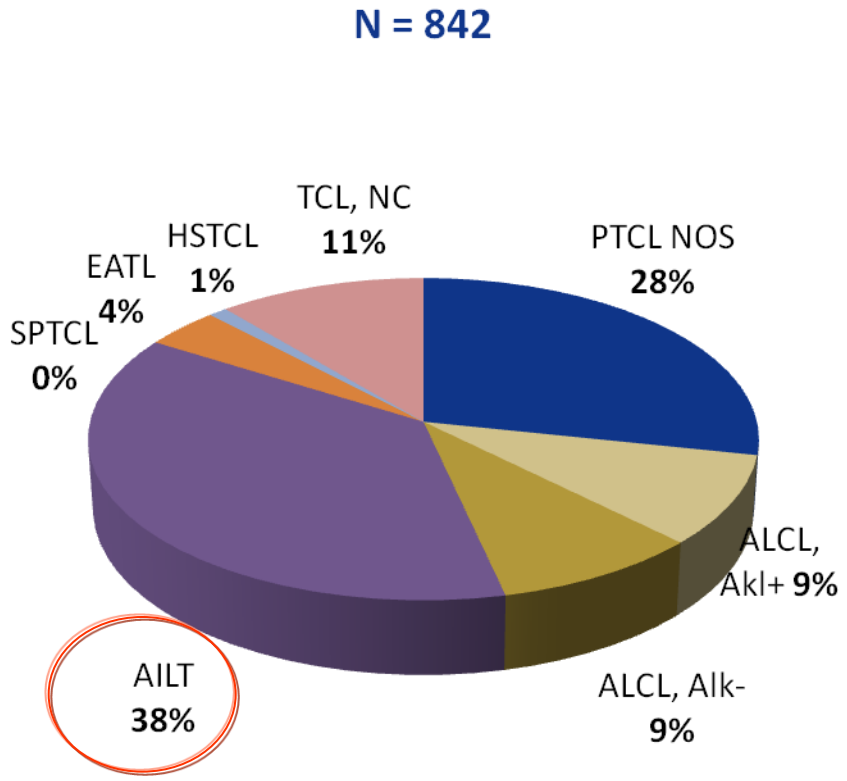
PARTICULARITES :

- **Clinique**
  - Sexe masculin
  - Disséminé
  - Signes généraux (B)
  - Pas très « tumoral »
  - Prurit
- **Biologique**
  - Hypergammaglobulinémie polyclonale
  - Eosinophilie
  - SAM possible
- **Evolutives**
  - Gravité, dès la pris en charge
  - Evolution fluctuante « rémissions spontanées »
  - Grande cortisensibilité …initiale

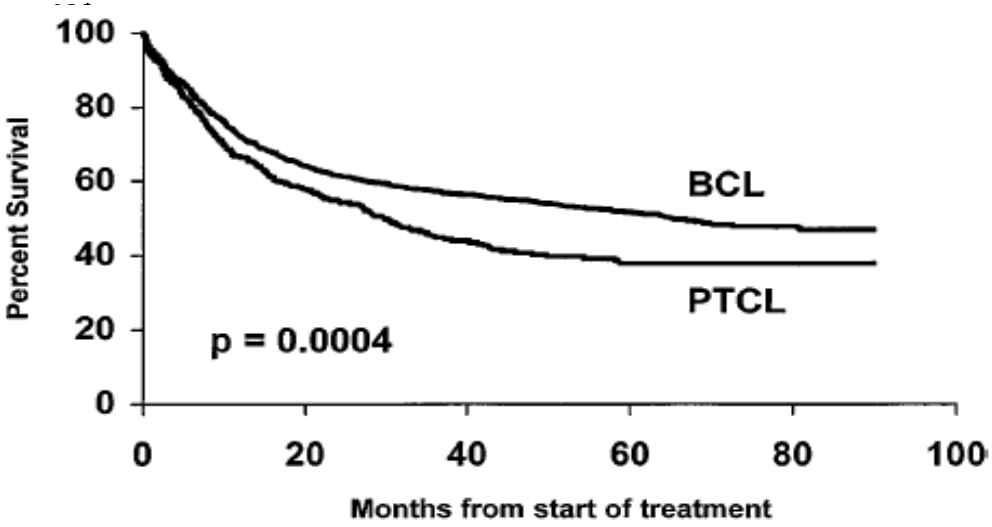
Gisselbrecht, 1999

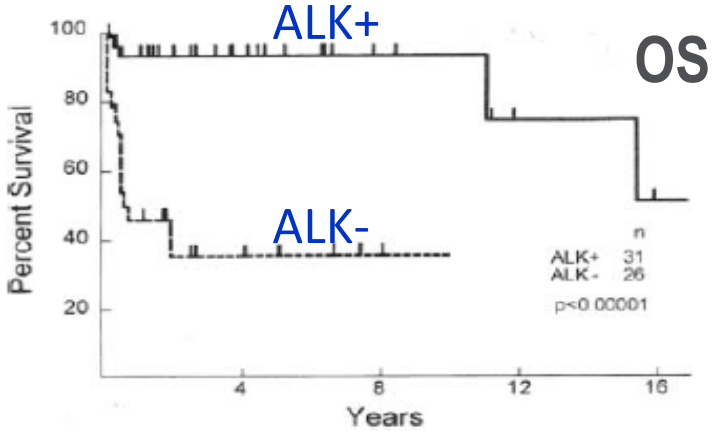
DIAGNOSTIC DIFFICILE

- Impératifs techniques :
  - Histologie
  - IHC étendue (CXCL13, PD1, granzyme…)
  - Et si besoin
    - Cytométrie en flux
    - Cytogénétique
    - Biologie moléculaire
- Communication
  - Clinique / chirurgie / pathologie
- Relecture : **lymphopath**



PRONOSTIC : HISTOLOGIE

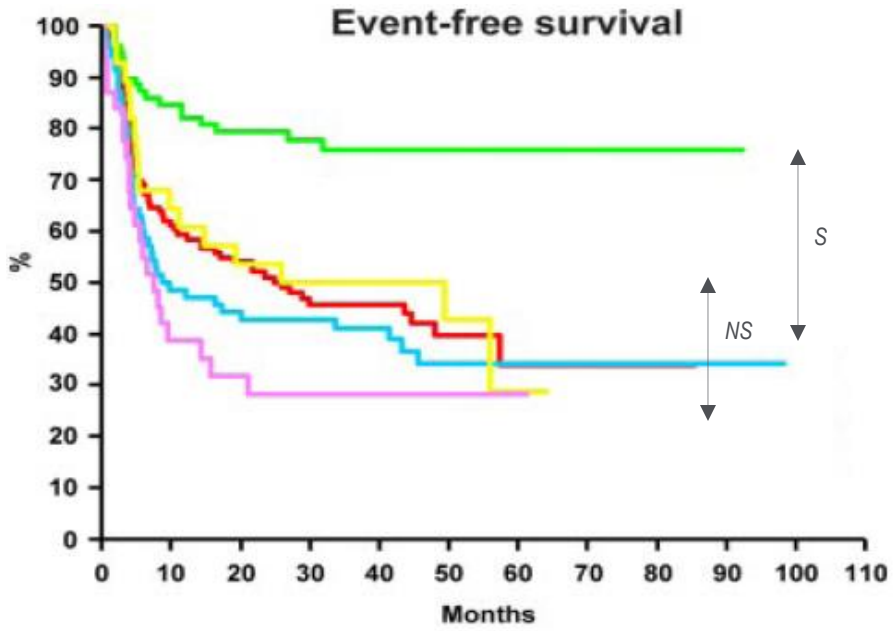


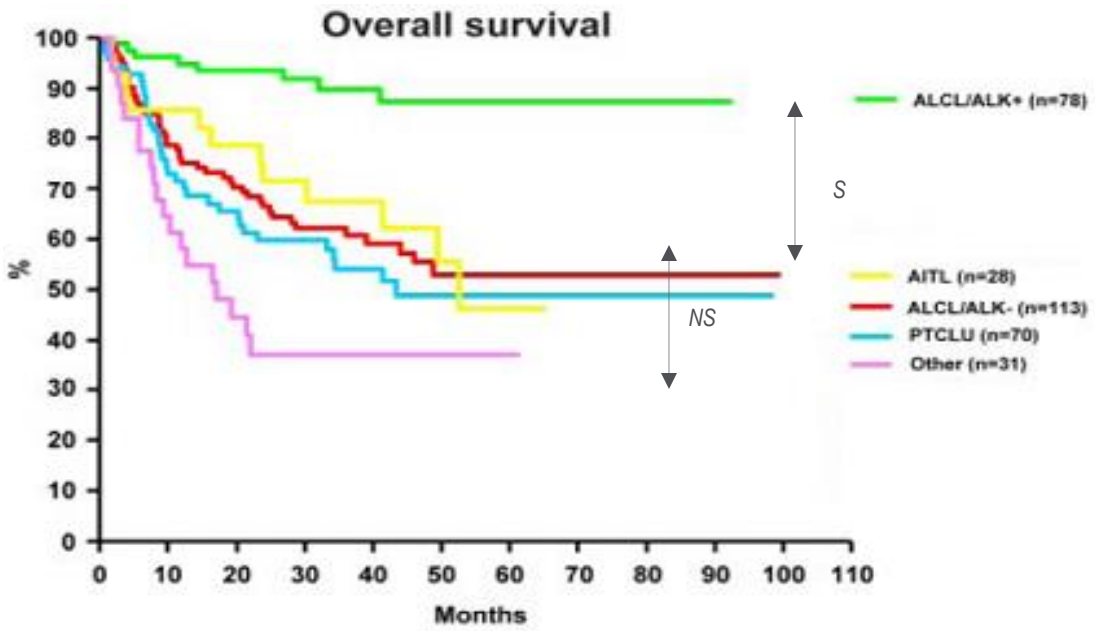


Gascoyne, 1999

Gisselbrecht, 1999
PTCL = 288
BCL = 1595
Traitement : LNH87
(3 groupes, étude randomisée)
1987-1993

PRONOSTIC : HISTOLOGIE





Schmitz, 2010
PTCL = 320
Traitement : phase II et phase III, CHOP like (38 MEGACHOEP)
1993-2007

- Meilleur pronostic des ALCL-ALK+ (UV et MV)
- Pas de différence ***prouvée*** entre les autres sous groupes

PRONOSTIC : PRESENTATION CLINIQUE

- Tableaux cliniques plus graves que les lymphomes B
  - Signes B, dissémination, notamment moelle, foie, peau, rate
- Gravité « intrinsèque »
  - Moins bon pronostic à IPI égal

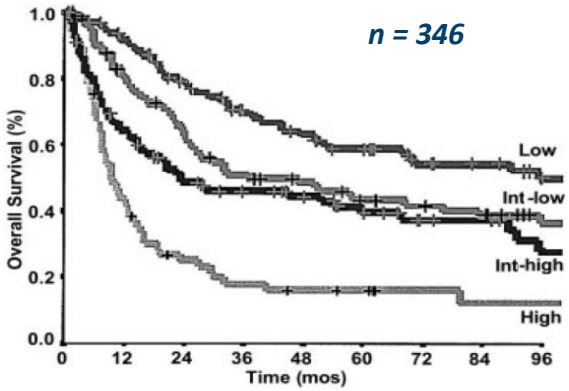
Table 4. Outcome of PTCL Categories Compared With BCL Patients

	Cell Type	n	CR (%)	*P* Value	5-yr OS (%)	*P* Value
IPI score*						
0 factors	B	216	81	.7	84	.1
	T	35	82		77	
1 factor	B	319	71	.7	63	.7
	T	45	73		60	
2 factors	B	359	63	.4	53	.01
	T	63	58		36	
3 factors	B	539	52	.001	35	.03
	T	118	35		23	

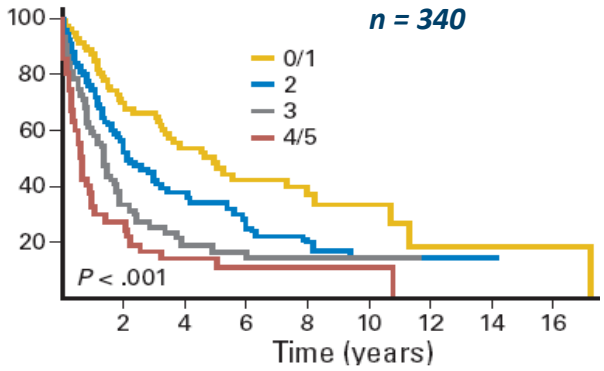
Gisselbrecht, 1999

PRONOSTIC : IPI

PTCL

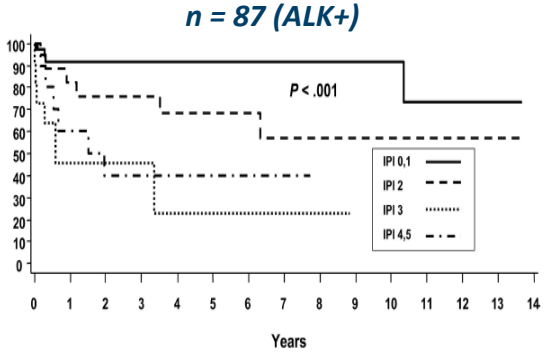


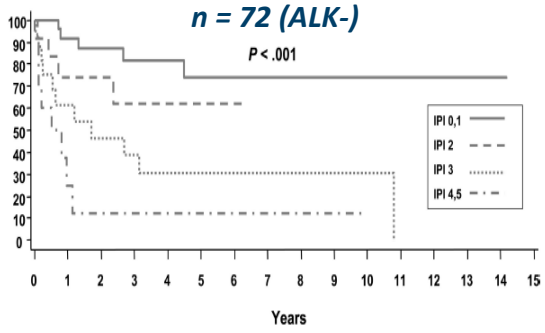
Gallamini, 2004 (1989-2001)



Savage, 2008 (1990-2002)

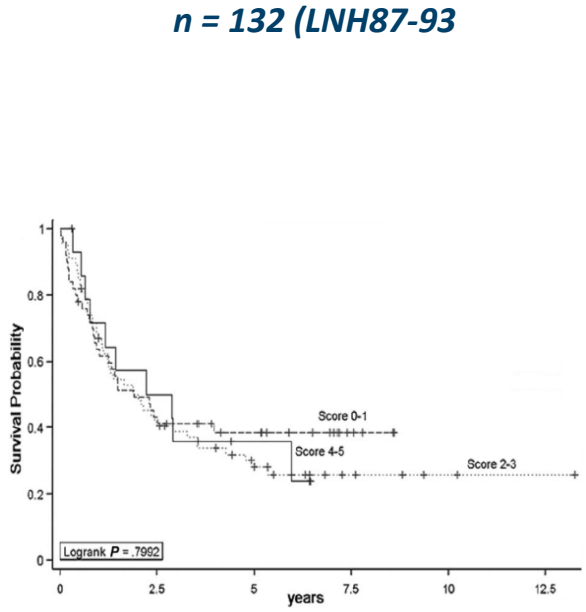
ALCL





Savage, 2008 (1990-2002)

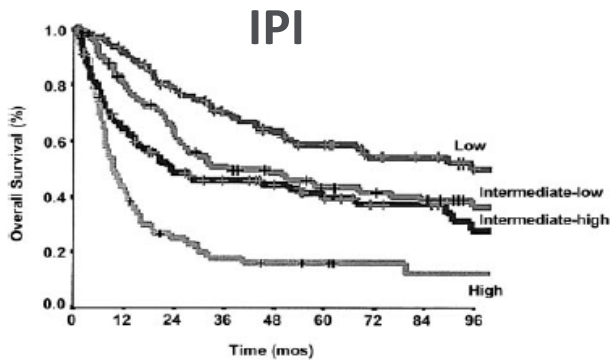
AITL

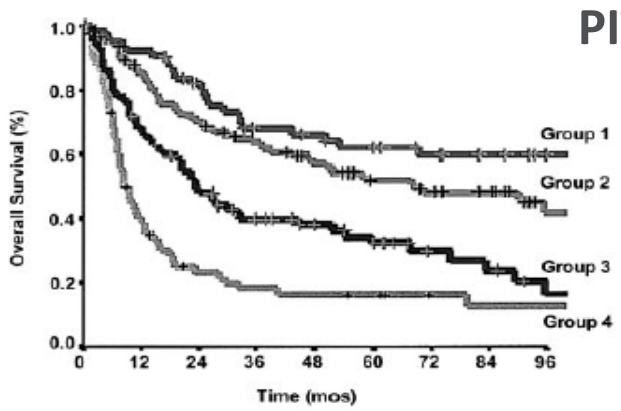


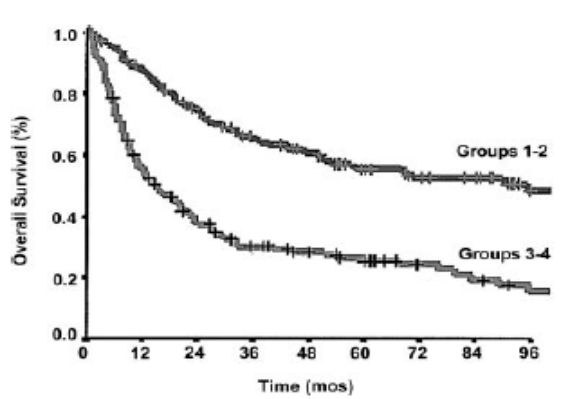
Mourad, 2008 (1987-1999)

PRONOSTIC : AUTRES SCORES

IPI	PIT	ITCL	Ki67	PIAI
Age > 60	Age > 60	Age > 60	Age > 60	Age > 60
PS ≥ 2	PS ≥ 2	PS ≥ 2	PS ≥ 2	PS ≥ 2
LDH	LDH	/	LDH	/
ExNod ≥ 2	BM+	/	/	ExNod ≥ 2
III-IV	/	/	/	B-symptoms
/	/	Plt <150	/	Plt <150
			Ki67>80%	/
/	**PTCL NOS**	**PTCL-NOS et AITL**	**PTCL NOS**	**AITL**
	Gallamini, 2004	**Vose , 2005a**	**Went, 2006**	**Federico, 2013**







PTCL (n=346)

Gallamini, 2004

STADE ANATOMIQUE

n = 95 (1985 – 1996)

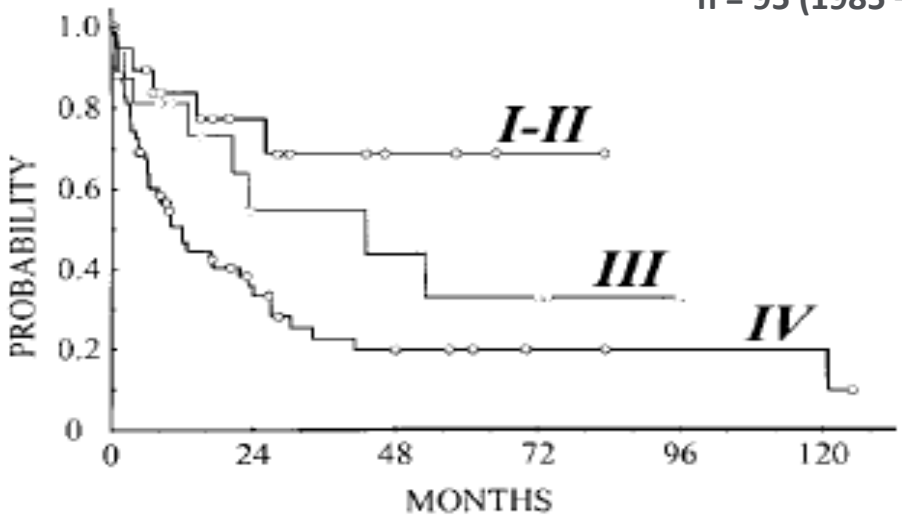


Figure 4. Survival of 95 patients with peripheral T-cell lymphoma unspecified according to the initial Ann Arbor stage ($P < 0.01$).

↓

PTCL-NOS

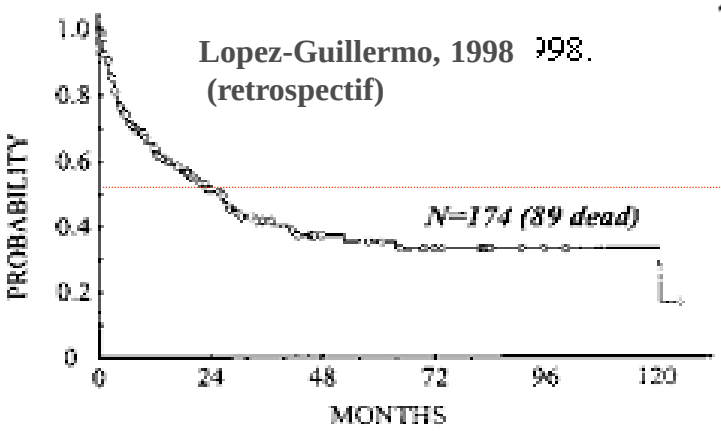
> 90% CHOP like

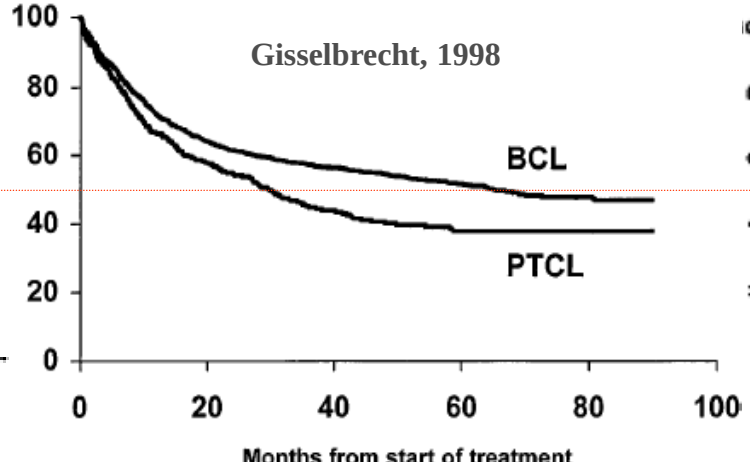
Lopez-Guillermo, 2005a

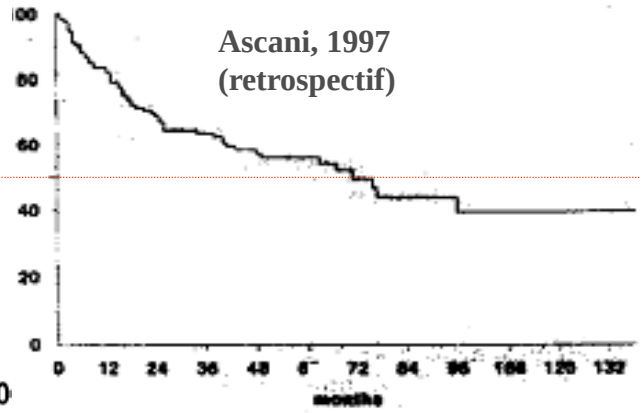
PRONOSTIC

- Inférieur aux DLBCL
  - Présentation + grave
  - Moins bon pronostic à IPI égal
- Sous type histologiques :
  - ALCL-ALK+
  - PTCL = ALCL-ALKneg = AILT
  - Autres entités (plus graves ?)
- IPI pas toujours discriminant, mais a utiliser, faute de mieux
  - Autres score PIT, Ki67 etc : pas mieux
- Rares stades limités : mieux

1ère LIGNE : CHOP Like





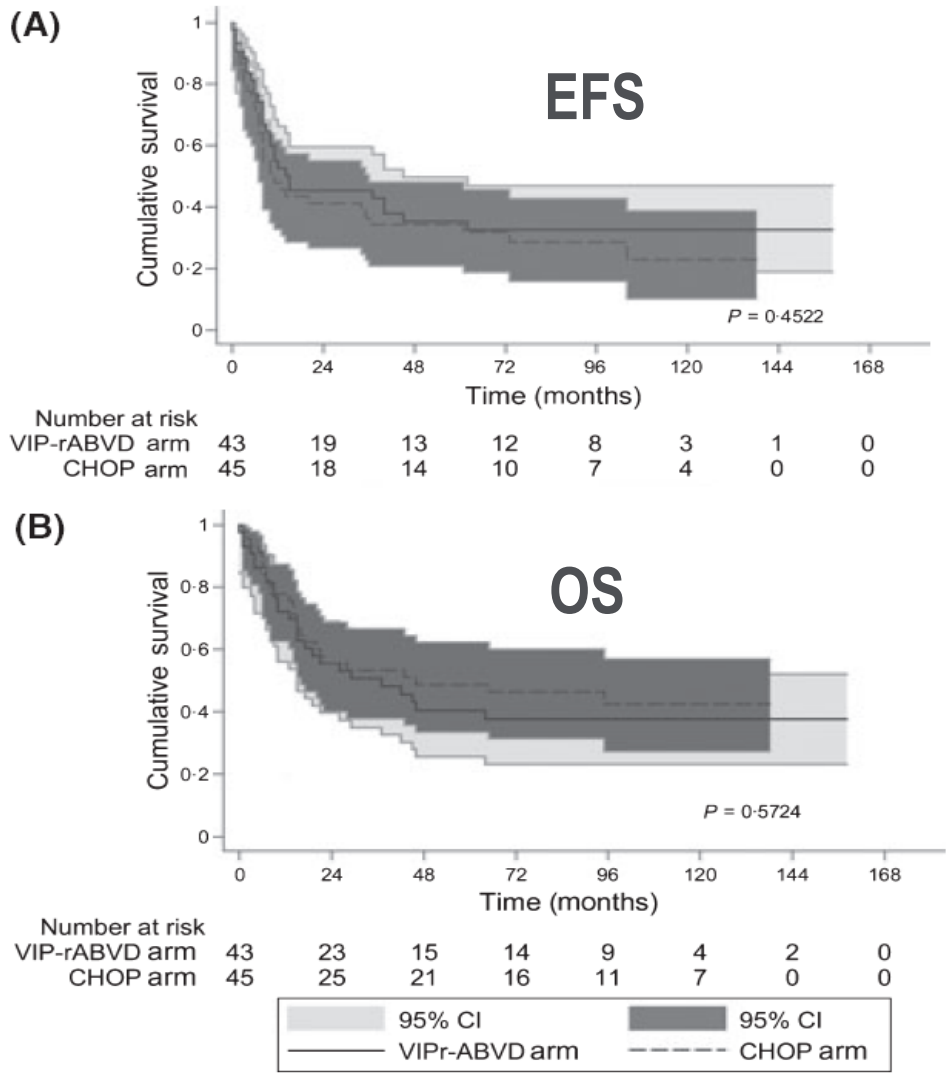


Metanalysis, OS=38% à 5 ans
(Aouyabas 2011)

1ère LIGNE AUTRES POLYCHIMIOTHERAPIES

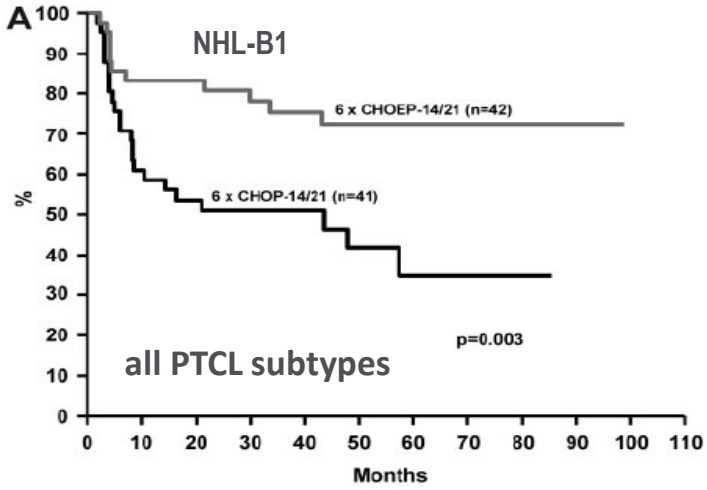
- GOELAMS LTP95
  - 6 VIP/rABVD vs 8 CHOP21 +/- irradiation (des stades I-II et/ou > 5 cm)

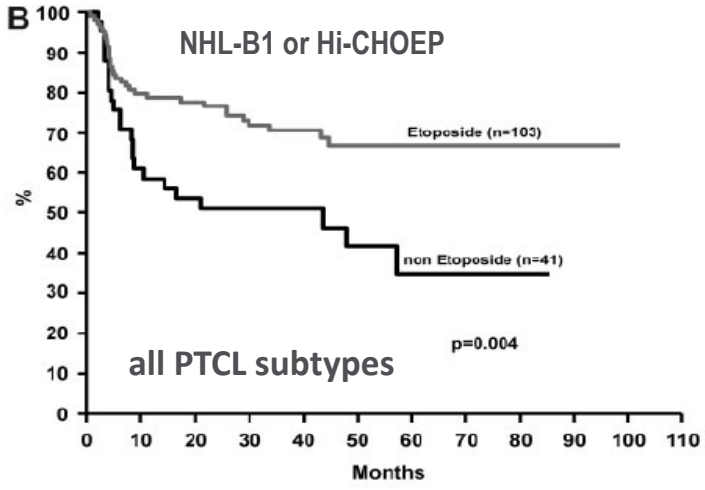
- **N= 88 (dont 10 ALK+)**
- **ORR = 60%**
- **EFS : 2 ans 40%**
- **OS 2 ans : 40%**
- **Aucune différence entre les 2 bras**

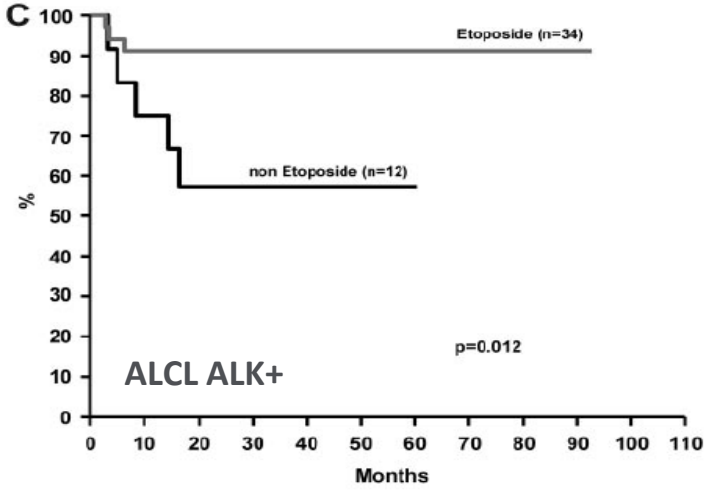


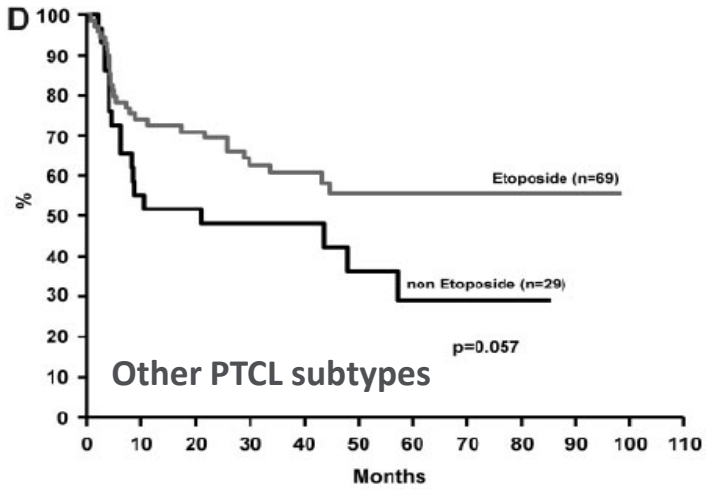
Simon, 2010

1ère LIGNE : ROLE DE L'ETOPOSIDE









Patients 18-60 ans
LDH normales

Schmitz, 2010

1st LINE : POLYCHEMOTHERAPY : WHEN DOES IT FAIL ?

Toxicity ⇗ | Toxic death
Treatment delayed

« CHOP-like » — CR (50 - 70%) — OS 5y (25 - 45%)

⇘ ≥ 30% Primary refractory

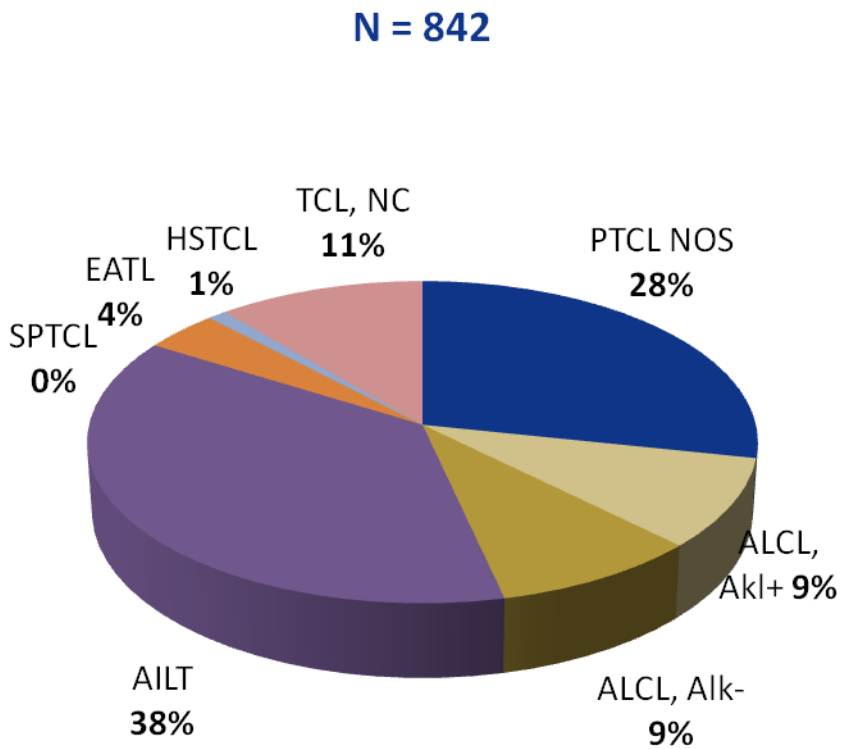
⇘ ≥ 40% Relapse

PFS = 2,8 m

OS = 5,5 m

Mak ASH 2011

Il faut faire mieux, mais comment ?



Parrens et al. ASH 2012

Diversité

Approches
« ciblées »
et/ou
« dépendante des sous types »

CHIMIOTHERAPIES / RADIOTHERAPIE

- Irradiation
- Asparaginase
- Bendamustine
- Pralatrexate
- Gemcitabine
  - … clofarabine, nelarabine, forodesine
- Bortezomib…

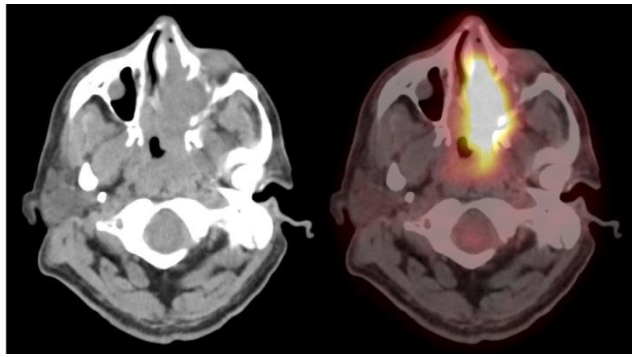
IRRADIATION !!

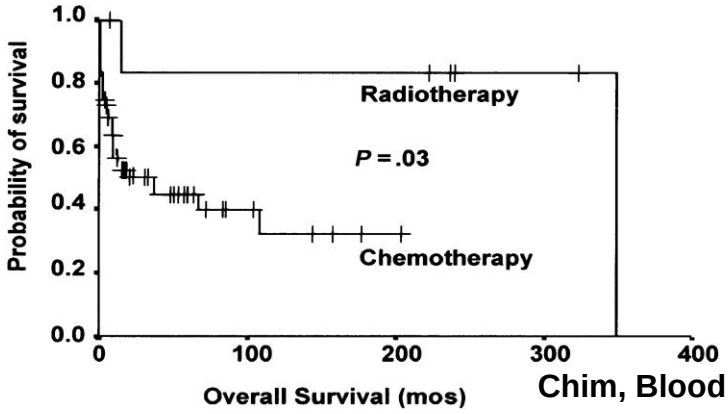
des LNH T/NK nasal (CD3e+, CD56+, EBV+)

➔ *Early irradiation (45-55 Gy) for localized disease*

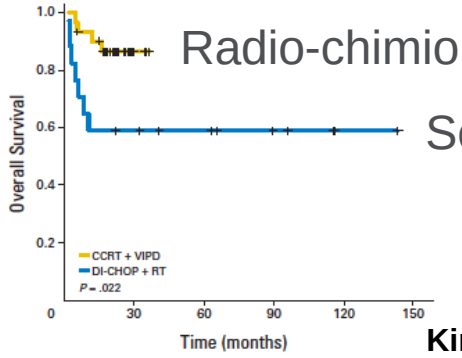
Modality	N	Chemotherapy	CR rate	Survival	Year
RT	90	-	66 %	5y OS 38 %	1998
RT	92	-	66 %	5y OS 40 %	2000
Cx -> +/− RT	40	CHOP etc.	72 %	5y OS 29 %	2004
Cx -> RT	43	CHOP-B	44 %	3y OS 48 %	2006
Cx -> RT	53	CHOP etc.	49 %	2y OS 76 %	2007
RT -> Cx	133	CHOP etc.	-	5y OS 75 %	1998
	28		-	5y OS 35 %	
RT -> Cx	105	CHOP etc.	87 %	5y OS 78 %	2006
SCRT	27	2/3 dose DeVIC	77 %	2y OS 78 %	2009
SCRT	30	Cisplatin (+ VIPD)	80 %	2y OS 86 %	2009

Suzuki, Current Onc Report 2012





Chim, Blood 2004



Radio-chimio

Sequential

Kim, JCO, 2009

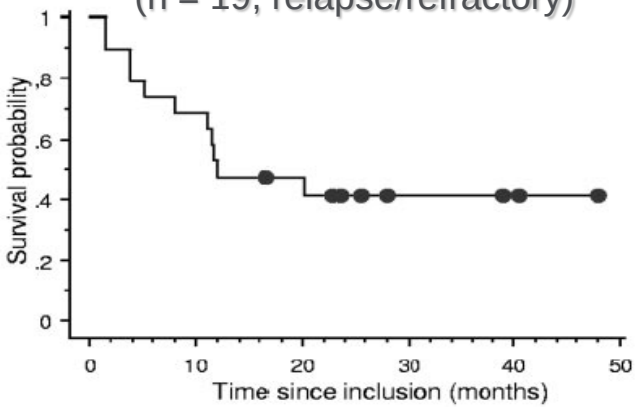
ASPARAGINASES

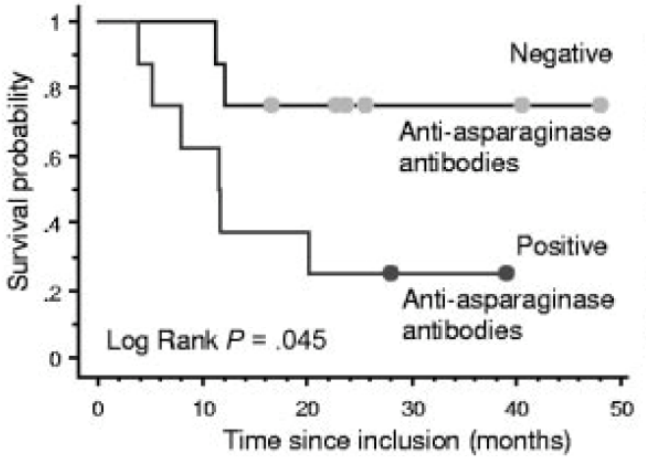
↳ *Enzymes (E. coli ; E. chrysanthemi)*

si LNH T/NK nasal (CD3ε+, CD56+, EBV+)

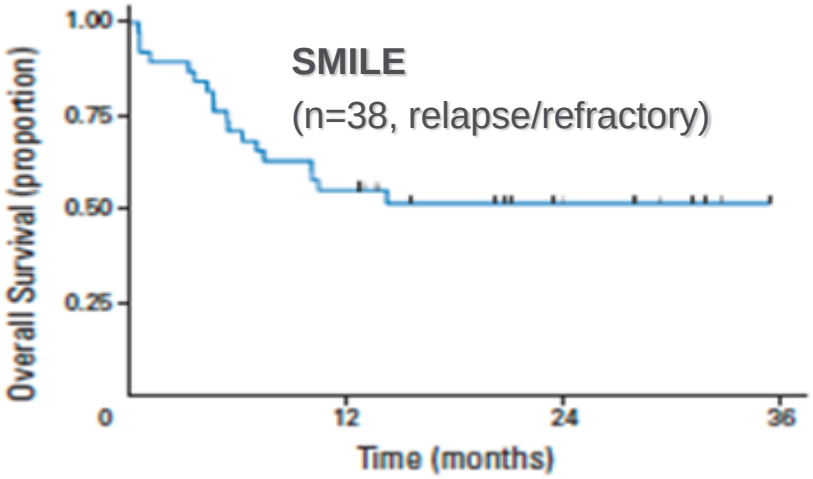
L-aspa/MTX/dexa

(n = 19, relapse/refractory)





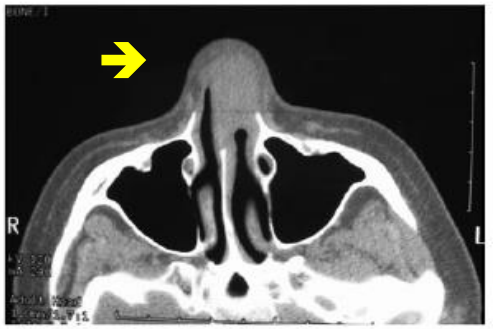
Jaccard, Blood 2011

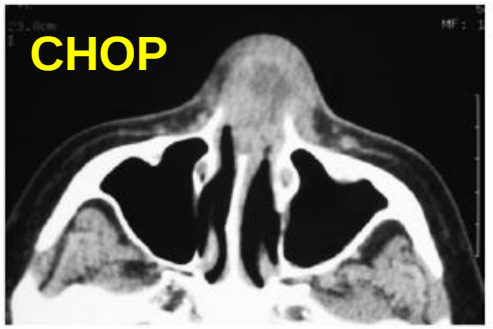


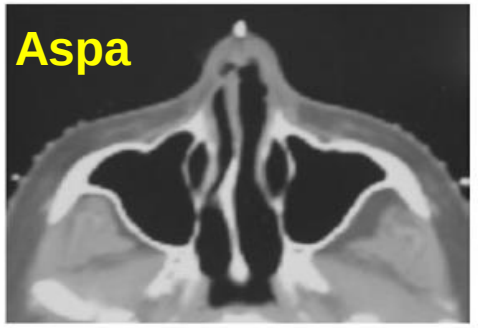
SMILE

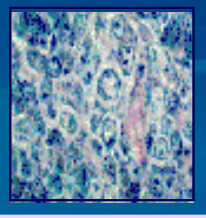
(n=38, relapse/refractory)

Kim, JCO, 2011









PROTOCOLE SWAN (swich asparaginase)

PHASE 2 MULTICENTRE STUDY FOR PREVIOUSLY UNTREATED NK/T NASAL-TYPE LYMPHOMA

Rationale / principles :

- ➔ *Early irradiation for localized disease*
- ➔ *Radio sensitizing agent*
- ➔ *L-asparaginase based polychemotherapy, addition of gemcitabine*
- ➔ *Intensification for disseminated disease*
- ➔ *Successive L-asparaginase switches*

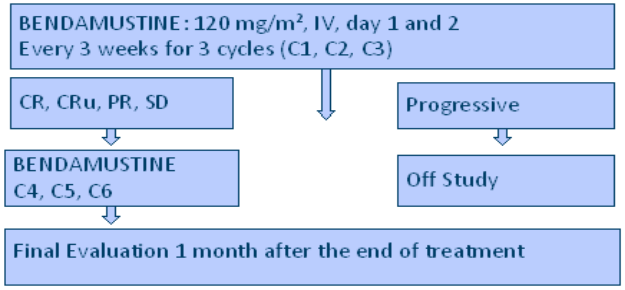
To increase PFS as main objective

BENDAMUSTINE

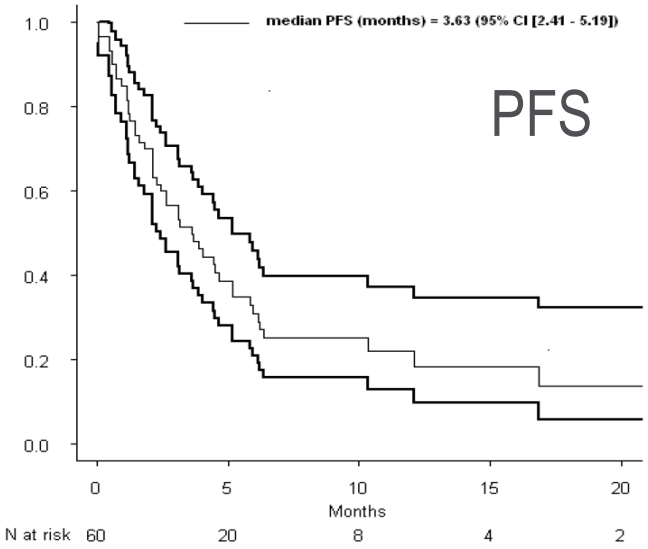
Alkylant

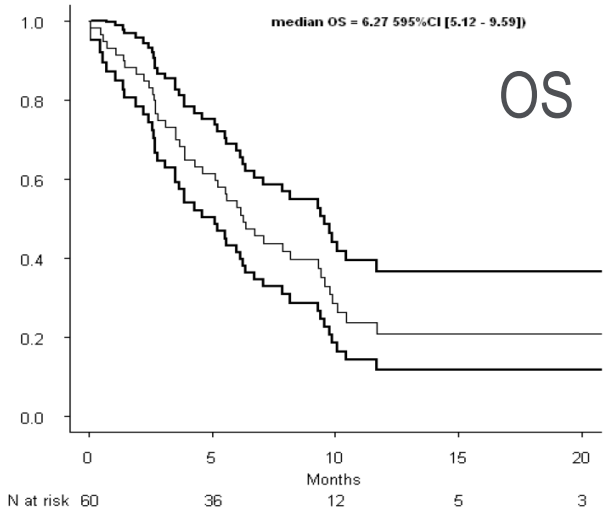
BENTLY phase II (GOELAMS)

Rechutes/ref (n=60)	ORR = 50%	Toxicité Grade 3-4
PTCL = 58 ; CTCL = 2	CR = 28%	. neutropénie 18%,
		. thrombopénie 24%
		. mucite 6%
		. infection 20%



- FU médian : 6 mois
- DOR = 3,5 (1-21) mois
- Décès = 43 (86% LNH)



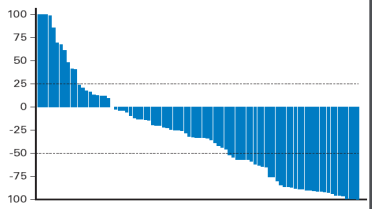


Damaj 2012, JCO

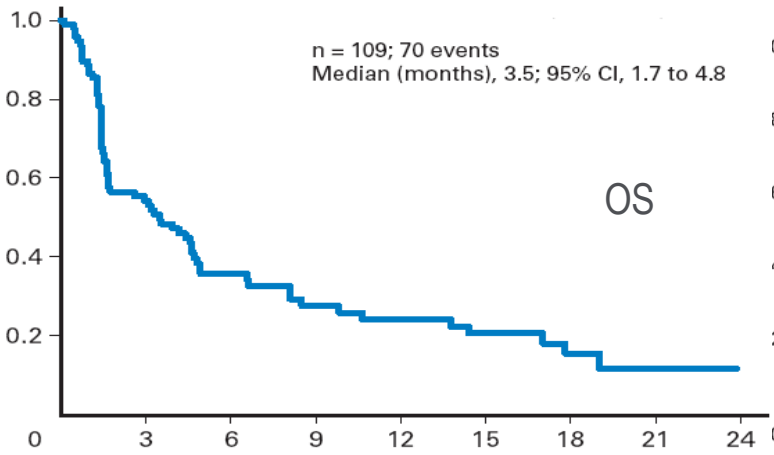
PRALATREXATE

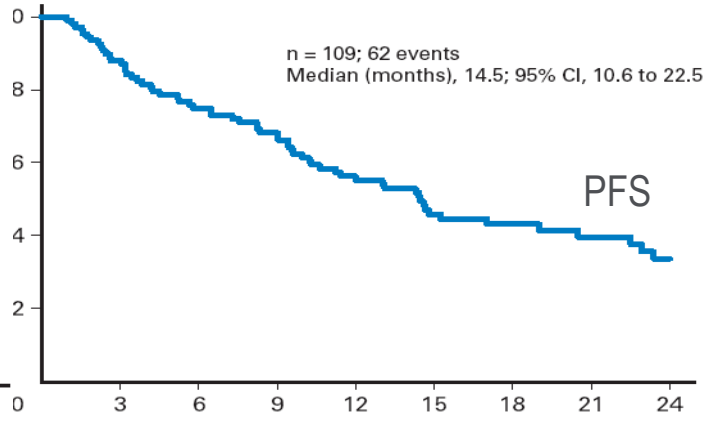
antifolique, transfert et retention cellulaire

PROPEL phase II

Rechutes/ref (n=60)	Réponses app. à 46 (37-349) jours	Toxicité Grade 3-4
PTCL = 59 ; CTCL = 12	ORR = 29%	. neutropénie 22%,
[30 mg/m2/sem x 6 IV] cycles 7 sem	CR/CRu = 11% 	. thrombopénie 33%
+ vit B12 + folates		. mucite 22%
Until Tox or PD		

- FU médian : 18 mois
- DOR 10,5 mois (3,4-?)
- Other >? AITL





O'Connor, 2011, JCO

PRALATREXATE

antifolique, ↑ transfert et retention cellulaire

La suite…

- Approuvé par la FDA
- Refusé par l'EMEA
- Développement en association
  - Simultanée (lymphomes en rechutes) : phase I/ IIa
    - gemcitabine + pralatrexate
  - Séquentielle (PTCL/CTCL première ligne) : phase III, international, NCT01420679
    - CHO(E)P like +/- pralatrexate : n = 549

GEMCITABINE

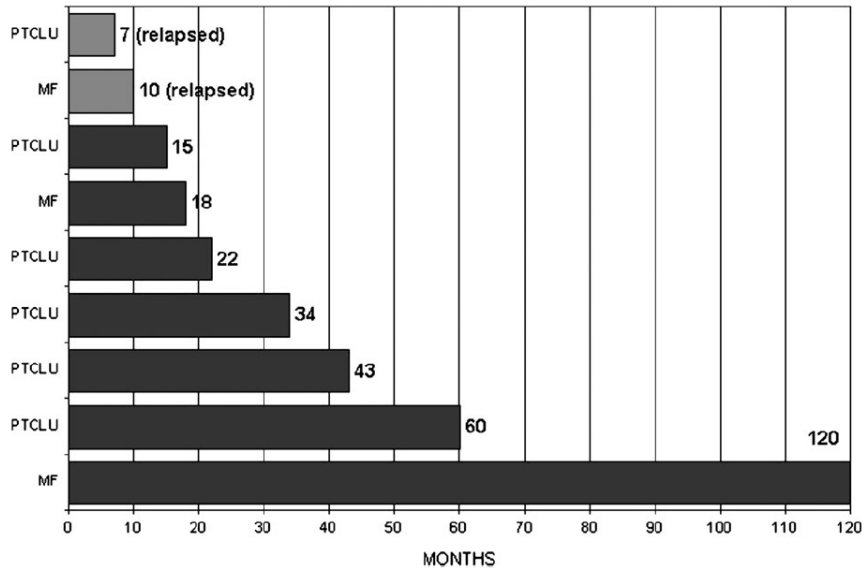
antimétabolite analogue de la déoxycytidine

MONOTHERAPIE

Rechutes/ref	Réponses (PTCL)	Toxicité Grade 3-4 absente
PTCL = 20; CTCL =19	ORR = 55%	. Neutropénie (G1-2) = 38%
[1,2 mg/m²/sem J1;8;15]	CR = 30% (soit 9 RC)	. Thrombopénie (G1-2) = 46%
cycles 21 j	PR = 25%	
3 à 6 cycles		

Evolution des 9 RC

	Age	Diagnosis	Stage	Previous treatments	Duration (months)
1	66	PTCL	III	CHOP; RT; DHAP	15
2	48	MF	IV	PUVA; CVP; Campath; Bexa	18
3	50	PTCL	IV_{SKIN}	CHOP; RT	22
4	69	PTCL	III	CHOP; IEV; RT	34
5	68	PTCL	III	RT; CHOP; Campath	43
6	71	PTCL	IV_{SKIN}	CHOP; Campath	60
7	75	MF	IV	PUVA; RT; CVP	120



Zinzani, 2010, Ann Oncol

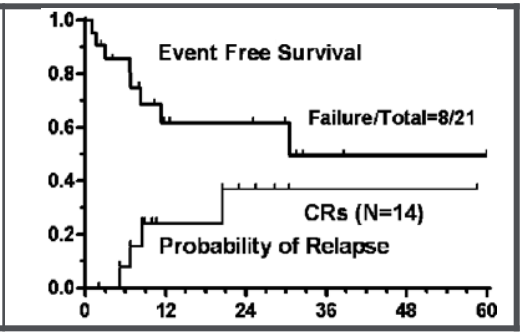
GEMCITABINE

antimétabolite analogue de la déoxycytidine

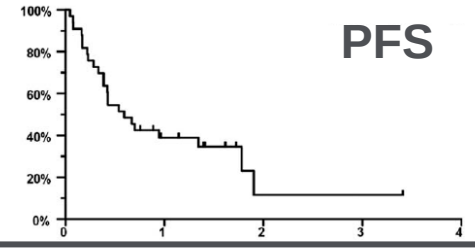
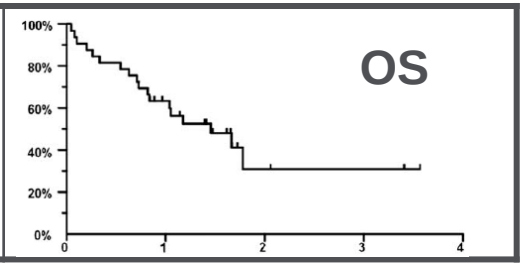
ASSOCIATIONS

Rechutes/ref	Réponses	Toxicité Grade 3-4	➔ Phase IIR 1re ligne
PTCL = 16	ORR = 55%	. Neutropénie = 69%	$CHOP_{21}$ vs $Gem\text{-}P_{28}$
[GEM + PLAT + MP] ***Gem-P***	CR = 19% PR = 25%	. anémie = 11%	UK (n=182)

Arkenau, 2007, Haematologica

1ère ligne	Réponses (3 cures)	Toxicité Grade 3-4	
PTCL = 16, CTCL = 5	ORR = 86%	. Infection = 33%	
[GEM + IFO + OXALI] ***Gifox***	CR = 67% PR = 19%	. Thrombopénie = 38%	
ASCT si eligible			

Corazzelli, 2012, ASH

1ère ligne /rechutes	Réponses (6 cures)		
PTCL = 33 (26/7)	ORR = 39%		
[GEM + ETO + PLAT + MP] ***Pegs***	CR = 24% PR = 15%		

Mahadevan, 2012, Cancer

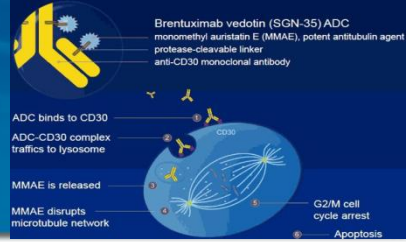
ANTICORPS MONOCLONAUX

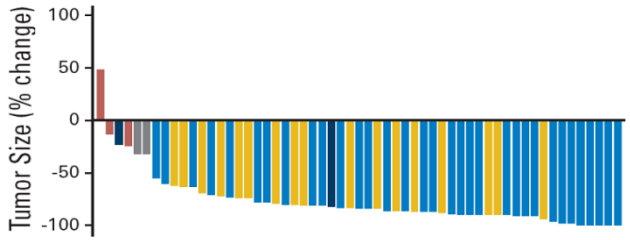
MONOTHERAPIES	Cible	ORR	CR	Auteur	Note
Alemtuzumab	CD52	50	33	*Zinzani, 2005*	Exp. CD52 variable 6 – 100% (ALCL = 6%)
Brentuximab	CD30	86	57	*Pro, 2012*	Exp. CD30 variable 30 – 100% (ALCL = 100%)
Daclizumab	CD25	?	?	*Berkowitz*	ATLL
Denileukin-diftitox	CD25	48	22	*Dang 2007*	
Mogamulizumab	CCR4	50	31	*Ishida 2012*	ATLL+++, mais CCR4 exprimé aussi dans les PTCL
Siplizumab	CD2	19	0	*O'Mahony 2009*	Lymphoprolifération EBV induites
Zanolimumab	CD4	21	10	*D'Amore, 2010*	La plupart des PTCL-NOS et les AITL sont CD4+

BRENTUXIMAB

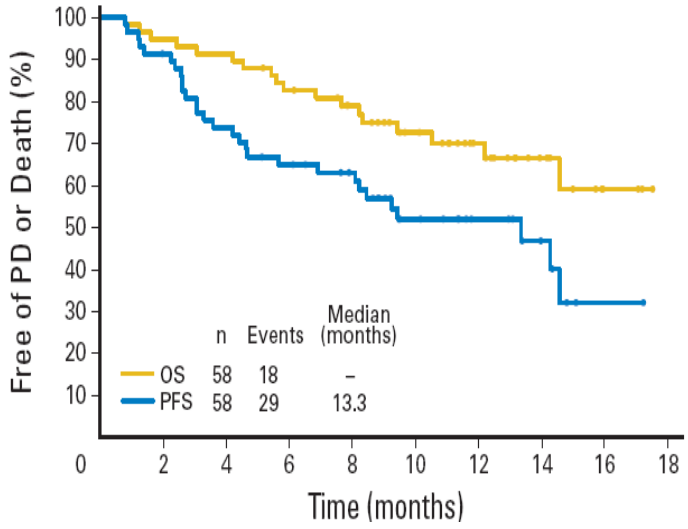
anti-CD30 conjugué monomethyl-auristatine

Phase II



Rechutes/ref	Réponses	Toxicité Grade 3-4
ALCL = 58 ; 2/3 alk(-) **[1,8 mg/m2/sem x 3 IV]** **Maximum 16 doses** I	ORR = 86% CR = 59% 	. Neutropénie 21% . Thrombopénie 14% . Neuropathie 12% (41% G1-4) survenue / transitoire

- FU médian : 22,8 mois (0,8 -32)
- DOR 13,2 mois (0-28)
  - DOR si CR : NR
- ASCT post brentuximab
  - 9 allo
  - 9 auto



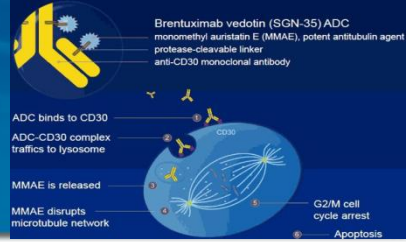
OS : NR*

PFS : 14.6 m*

Pro, 2012, JCO et *update ASH 2010

BRENTUXIMAB

anti-CD30 conjugué monomethyl-auristatine



EXPRESSION DU CD30 DANS LES PTCL

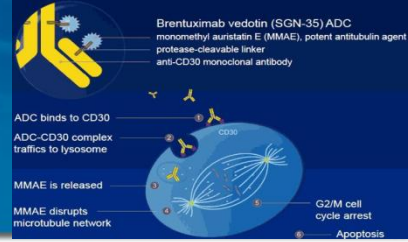
% of CD30 tumour cells	ALCL		PTCL N = 49	AITL N = 48	ENKTL N = 10	EATL N = 7	HTLV I N = 3
	ALK+ N = 61	ALK– N = 17					
0–<5%			15	16	7	7	1
5–24%			15	26	1		0
25–49%			5	2	1		1
50–75%			3	4	0		1
>75%	61	17	11	0	11		0
Positive cases (>5%)	100%	100%	69%	66.6%	30%	0	66.6%
Positive cases with strong expression (>50%)	100%	100%	28.5%	8.3%	10%	0	33.3%

Bossard, Lugano 2013

BRENTUXIMAB

anti-CD30 conjugué monomethyl-auristatine

La suite…



- **AMM (25/10/2012) : ALCL, CD30+, confirmé (IHC), rechute/réfractaire après ≥ 1 ligne**

- **Autres PTCL (monothérapie)**

Rechutes/ref PTCL = 29 (AITL/PTCL) **[1,8 mg/m2/sem x 3 IV] until DP or Tox**	ORR = 36% (AITL 50%) CR = 28% (AITL 36%)	Toxicité Grade 3-4 . Neuropathies = 10% . Neutropénies	DOR NR

Oki, 2013, Lugano

Rechutes/ref **(NCT01421667)** B-NHL = 35 et PTCL = 18 (AITL =9) **[1,8 mg/m2/sem x 3 IV] until DP or Tox**	ORR = 27% (AITL 60%) CR = NA% (AITL 22%)

Jacobsen, 2012, ASH

- **Développement (combinaison, PTCL, 1ère ligne) [CHOP21 vs BTX-CHP21] x 6-8 *Echelon2***

O'Connor, 2013, Lugano

ALEMTUZUMAB

anti-CD52

- **Monothérapie**

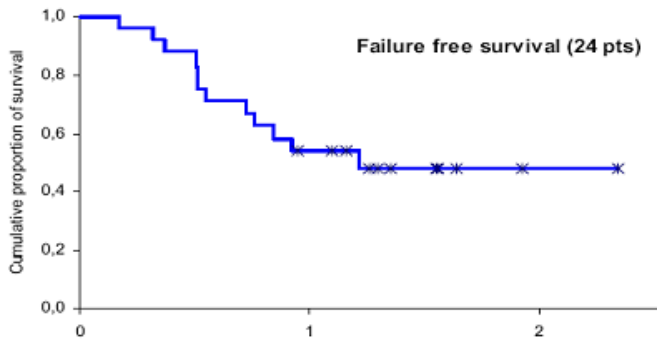
Rechutes/ref **PTCL + CTCL (env. 50)**	ORR = 36 à 55% CR = 20%	TRM = 0 à 36%	Lundin 2003 Emblad 2004 Zinzani 2005

- **Associations**

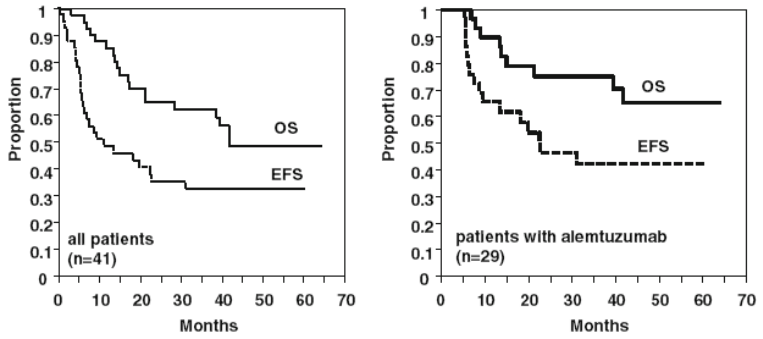
Rechutes/ref et 1ères lignes **PTCL (env. 150)** DA-EPOCH Pentostatine CHO(E)P FC-doxo ESHAP / DHAP HyperCVAD	ORR = 33 à 90% CR = 33-80%	TRM = 0 – **50%** CMV, EBV, champignons..	Wilson 2005 Itragumtornchai 2006 Gallamini 2007 Kim 2007, 2012 Ravandi 2009 Weidman 2010 Kuan 2013 Binder 2013

ALEMTUZUMAB

anti-CD52

1ère ligne	Réponses	Toxicité Grade 3-4	
PTCL = 28 **[CHOP28 + ALZ 30 mg J1]** **8 cures**	ORR = 75 % CR = 71%	CMV react = 17% Aspergillose = 2 LEMP = 1 Staph = 1 TRM = 4%	

Gallamini, Blood, 2007

1ère ligne	Réponses	Toxicité Grade 3-4	
PTCL = 41 **[CHO(E)P14 x 6** **+ in CR/PR consolidation** **ALZ 133 mg over 4 w]** **(2003-2006 DSHNHL)**	ORR = 63 % CR = 59%	après alemtuzumab CMV react = 2 Aspergillose = 1 Levure 1 Sepsis (BG-) = 2 TRM = 2%	

Binder, Ann Hematol, 2013

ALEMTUZUMAB

anti-CD52

La suite…

- **Retrait d'AMM pour la LLC/T-PLL (août 2012) ATU**

- **Polémique sur l'expression du CD52 dans les lymphomes T**
  - Immunohistochimie : pas des expression dans 70% des PTCL
    Rodig, 2006 ; Chang, 2007 ; Pittaluga , 2007
  - Transcriptome : plus faible expression p/r Lc T normal, surtout PTCL CD30+
    Gallamini, 2007 ; de Leval 2007
  - Cytométrie : PTCL : 90-100% sont CD52 sauf les ALCL (10%)
    Geissinger 2009 ; Jiang 2009

- **Poursuite difficile du développement en combinaison, PTCL sauf ALCL, 1ère ligne**
  - ACT1 (<60 ans) : A-CHOEP14 vs CHOP14 puis BEAM et autogreffe
  - ACT2 (≥ 60 ans) : A-CHOP14 vs CHOP14 (participation du LYSA)

AUTRES MOLECULES

- HDACi
  - Romidespin (Coiffier 2012 ; ORR 25%)
  - Belinostat (Zain 2010 ; ORR 32%)
  - Vorinostat
- Inhibiteurs de kinases
  - Aurora kinase : alisertib (Friedberg, 2011 : ORR 57%)
  - Crisotinib (ALK)
- Lenalidomide (Dueck, 2012 ; ORR 30%) : →
- Everolimus (Kim, 2011)
- Plitidepsin (Ribrag 2013 ; ORR 21%)

Protocole REVAIL :
AITL, 1ère ligne, sujet Agé :
lenalidomide + CHOP21 x 8

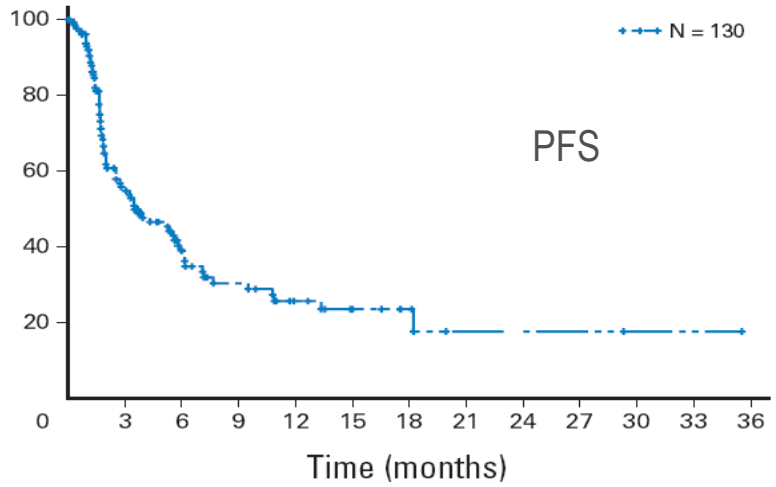
Lysa
THE LYMPHOMA STUDY ASSOCIATION

ROMIDEPSINE

inhibiteur d'HDAC, classe1 bicyclique

Rechutes/ref	Réponses	Toxicité Grade 3-4
PTCL = 130	App. à 1,8 mois (1,4-5,3)	. Neutropénie 22%
[14 mg/m2 IV d1, d8, d15] cycles 4 w	ORR = 25%	. Thrombopénie 25%
6 cycles	CR/CRu = 15%	
if CR/PR/SD until tox. or PD	SD 33%	

- FU médian : 13 mois
- DOR 17 mois (0-34)



Coiffier, JCO, 2012

ROMIDEPSINE

inhibiteur d'HDAC, classe1 bicyclique

La suite…

- Approuvé par la FDA
  - CTCL 2009
  - PTCL après 1 ligne 2011
- Refusé par l'EMEA (nov. 2012)
- Développement en associations

1ères ligne, phase Ib/II PTCL (n=18) **[Ro 12 mg/m2 IV d1, d8 + CHOP21] x 8**	ORR = 78% CR = 66%	Some cardiovascular events	**PFS 12 m = 57%**

Dupuis, 2013, Lugano

1ères ligne, phase III, international, Lysa : RoCHOP$_{21}$x8 vs CHOP$_{21}$x8

PLACE DU TEP

- Informativité

Hodgkin	233	100%
Burkitt	18	100%
MCL	14	100%
Nodal MZL	8	100%
Lymphoblastique	6	100%

DLBCL	216	97%
Follicular	133	95%
PTCL	34	85%
SLL	24	83%
Extranodal MZL	29	55%

Weiler-Sagie, J Nucl Med. 2010

- Evaluation par sous type

PTCL-NOS	**97% (n=34) ;**	**NK/T 80% (n=12) ;**
ALCL	**80% (n=20) ;**	**ATLL 100% (n=9);**
AITL	**72% (n=18) ;**	**EATL 100% (n=2).**

Feeney Am J of Roetgen. 2010

- TEP+ à 4 cures : rôle pronostique ?

1st LINE : POLYCHEMOTHERAPY : WHEN DOES IT FAIL ?

Toxicity ⇗ | Toxic death
Treatment delayed

« CHOP-like » — CR (50 - 70%) — OS 5y (25 - 45%)

⇘ ≥ 30% Primary refractory

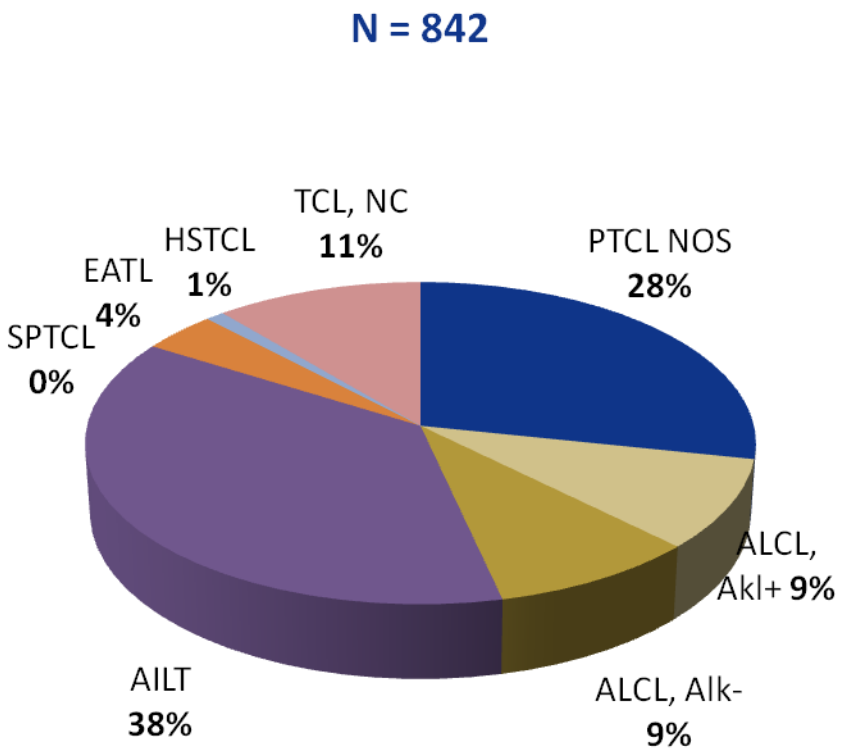
⇘ ≥ 40% Relapse

PFS = 2,8 m

OS = 5,5 m

Mak ASH 2011

Il faut faire mieux, mais comment ?



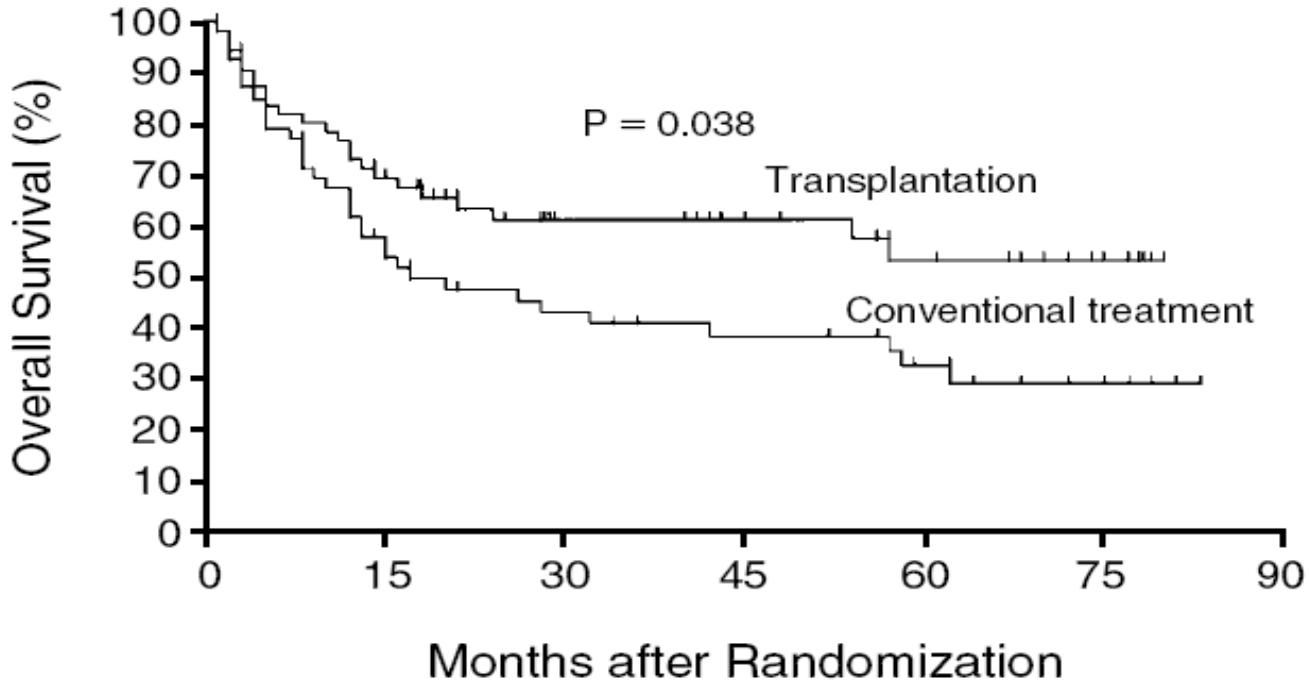
Parrens et al. ASH 2012

Diversité

↓

Thérapie cellulaire

ASCT : the experience of relapsing lymphoma



Philip, NEJM, 1995

ASCT for relapse / refractory PTCL : Retrospective studies

Group/author	Year	*n*	Including ALCL?/ histology	Status at transplant	DFS/EFS/ PFS/RFS	OS	Additional important info /comments
EBMT/Nickelsen	2008	424	Yes (4% ALK$^+$ALCL)	CR/PR 87%	49% (3 y)	62% (3 y)	35% transplanted in CR1
EBMT/Kyriakou	2008	146	AITL only	CR/PR 69%	49% (4 y)	59% (4 y)	69% transplanted in 1st line
MDACC/Beitinjaneh	2011	126	Yes (7% ALK$^+$ALCL)	CR/PR 84%,	30% (4 y)	39% (4 y)	67% transplanted in 2nd line
GELTAMO/Rodriguez	2003	115	Yes (22% ALCL)	CR/PR 94%	60% (5 y)	56% (5 y)	68% transplanted in 2nd line.
GELTAMO/Rodriguez	2003	35	No data	PR 89%, RD	55% (5 y)	37% (5 y)	subgroup of the above GELTAMO
GELTAMO/Rodriguez	2007	74	Yes (31% ALCL)	CR1 100%	63% (5 y)	68% (5 y)	
Mak	2011	38	Yes (no data)	no data	48% (3 y)	55% (3 y)	100% transplanted in 2nd line
City of Hope/Nademanee	2011	67	Yes (16% ALK$^+$ALCL)	CR/PR 70%	40% (5 y)	54% (5 y)	82% transplanted in 2nd line
Prochazka	2011	29	Yes (10% ALK$^+$ALCL)	CR1/PR1100%	52% (2 y)	65% (2 y)	
Hwang	2011	35	Yes (6% ALCL)	CR/PR 74%	No data	70% (3 y)	
Numata	2010	39	Yes (23% ALCL)	CR/PR 82%	61% (5 y)	62% (5 y)	59% transplanted in 1st line
Yang	2009	64	PTCL-NOS only	CR 33%, PR	44% (3 y)	53% (3 y)	56% transplanted in 2nd line
Stanford/Chen	2008	53	Yes (34% ALCL)	CR/PR 81%	25% (5 y)	48% (5 y)	72% transplanted in 2nd line
Cleveland Clinic/Smith	2007	32	Yes (66% ALCL)	CR/PR 74%	18% (5 y)	34% (5 y)	81% transplanted in 2nd line
Fevler	2007	64	Yes (31% ALCL)	CR/PR 78%	50% (3 y)	53% (3 y)	72% transplanted in 1st line
Kim	2007	40	Yes (12% ALCL)	CR 27%, PR	3.6 months	11.5 months	73% transplanted in 2nd line
MSKCC/Kewalramani	2006	24	No ALK$^+$ALCL	CR 63%, PR 27%	24% (5 y)	33% (5 y)	100% transplanted in 2nd line
Vanderbilt/Jagasia	2004	28	Yes (25% ALK$^+$ALCL)	CR/PR 93%	50% (3 y)	69% (3 y)	96% transplanted in 2nd line
EBMT/Schetelig	2003	29	AITL only	CR 45%, PR 38%	37% (5 y)	44% (5 y)	52% transplanted in 2nd line
Song	2003	36	Yes (25% ALCL)	CR 42%, PR 50%	37% (3 y)	48% (3 y)	100% transplanted in 2nd line
MDACC/Rodriguez	2001	29	No data	CR 38%, PR 48%	32% (3 y)	38% (3 y)	100% transplanted in 2nd line
Blystad	2001	40	Yes (35% ALCL)	CR 70%, PR 30%	48% (3 y)	58% (3 y)	58% transplanted in 2nd line
Fanin	1999	64	ALCL only	CR/PR 88%	56% (5 y)	70% (5 y)	53% transplanted in 2nd line

Up to 1000 cases

Various histologies (including CTCL)

Some patients Refractory at ASCT

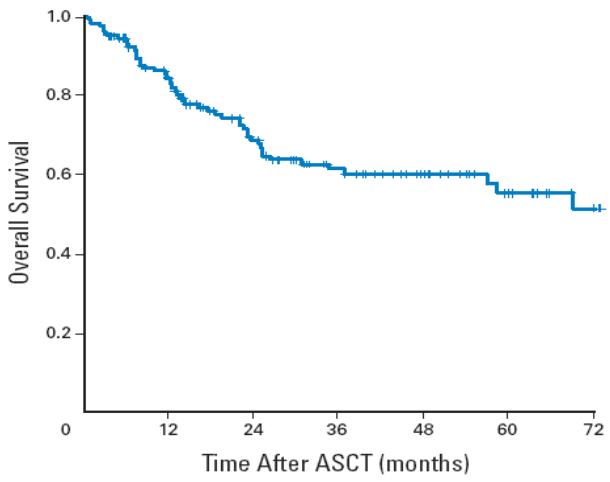
PFS/EFS = 25-60%
OS = 33-70%

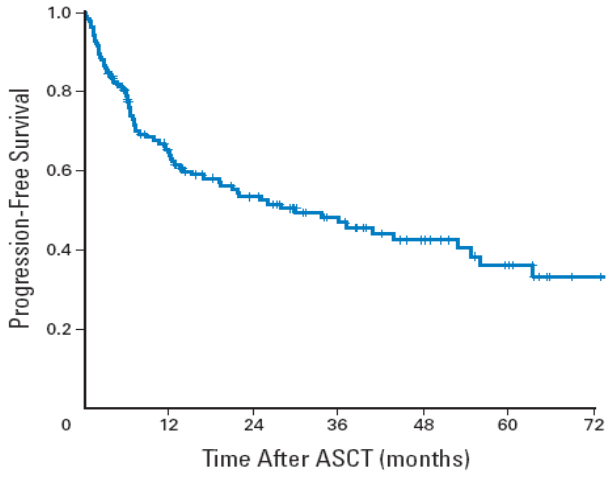
Only 4 published studies only in the relapse setting

Yared, Canc Treat Rev 2012

ASCT for PTCL : EBMT experience

	Tot.	Age (y)	period	Histology	CR1 (%)	CR/PR* (%)	PFS %	OS %	
Nickelsen ASH 2008	**424**	**51** (17-74)	2000-2005	23% ALCL (incl.ALK+) 28% AITL 42% PTCL 7% other	35	87	**49**	**62**	***4y***
Kyriakou JCO 2006	**146**	**53** (19-72)	1992-2004	100% AILT	69	69	**49**	**59**	***4y***





**Status at transplantation*

ASCT as a part of salvage therapy in PTCL : conclusion

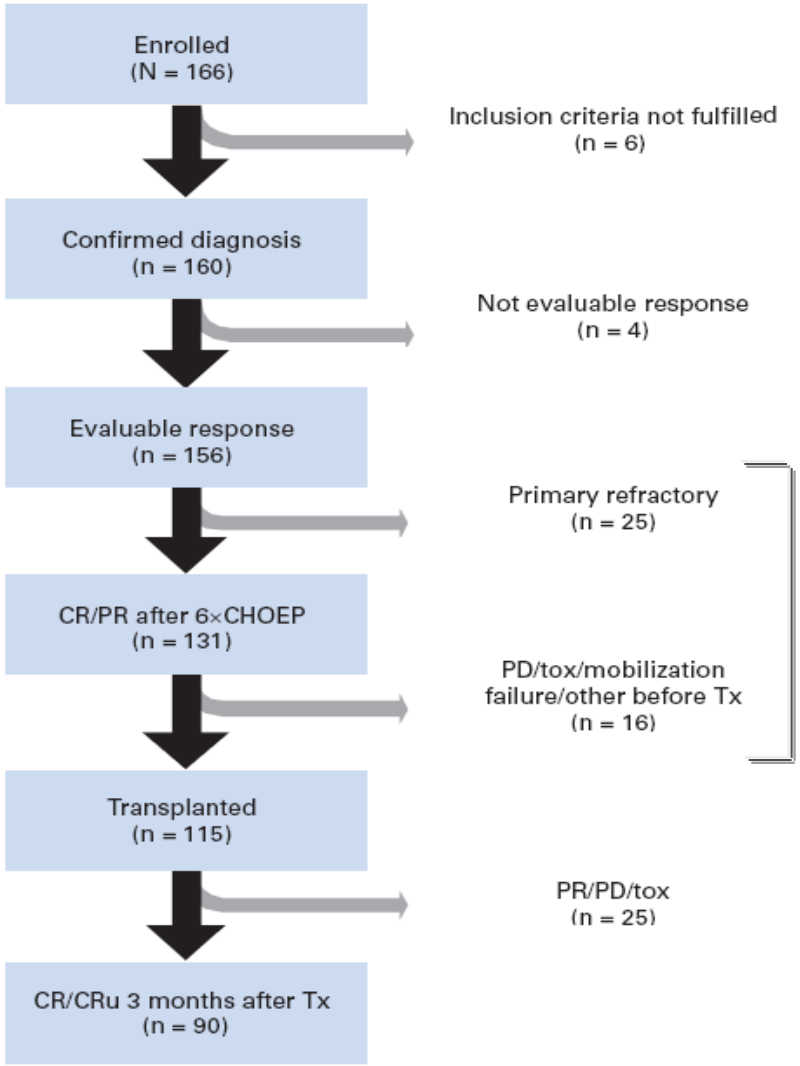
- Feasible up to 65 (-70) years old
- Possible option but only for patients with controlled disease (CR !)
  - No prospective studies :
    - **Only transplanted patients are reported !**
    - **Study including 1st Line and relapsing patients**
  - Very poor results in patients transplanted with refractory disease
- ASCT is clearly challenged with other options !
  - New drugs for frail patients
  - Allogeneic transplantation for fit patients
- The problem #1, is to control a relapsing PTCL !

ASCT 1st line : Prospective Phase II Studies

	Tot.	Age (y)	ALCL (%)	ASCT %	CR/PR* (%)	TRM %	PFS %	OS %		Treatment
Reimer JCO 2009	**83**	**47** (30-65)	13 No ALK+	65	47/26	3	**36**	**48**	***4y***	CHOP21 x 4-6 DexaBEAM or ESHAP x 1-2 **EDX-TBI**
Corradini Leukemia 2006	**62**	42	23 30% ALK+	74	56/16	4.8	**30**	**34**	***12y***	APO DHAPHD Mito/Melo or MACOP-B HD/AraC/Mito **BEAM**
Rodrigues EJH 2007	**26**	44	8 No ALK+	73	73	0	**53**	**73**	***3y***	MEGACHOP/IFE **BEAM**
Mercadal Ann Oncol 2008	**41**	47	1 ALK+	41	49/10	3	**30**	**39**	***4y***	MaxiCHOP/ESHAP altern. **BEAM / BEAC**
Ahn ASH 2011	**46** 25% NK/T	/	na No ALK+	67	50/17	na	**47**	**48**	***5y***	CHOP-like or other. **BuCyVP16**
D'Amore JCO 2012	**160**	**57** (22-67)	31 No ALK+	72	85	4	**44**	**51**	***5y***	CHO(E)P14x6 **BEAM**

*Status at transplantation

ASCT 1st line : NLG-T-01 study



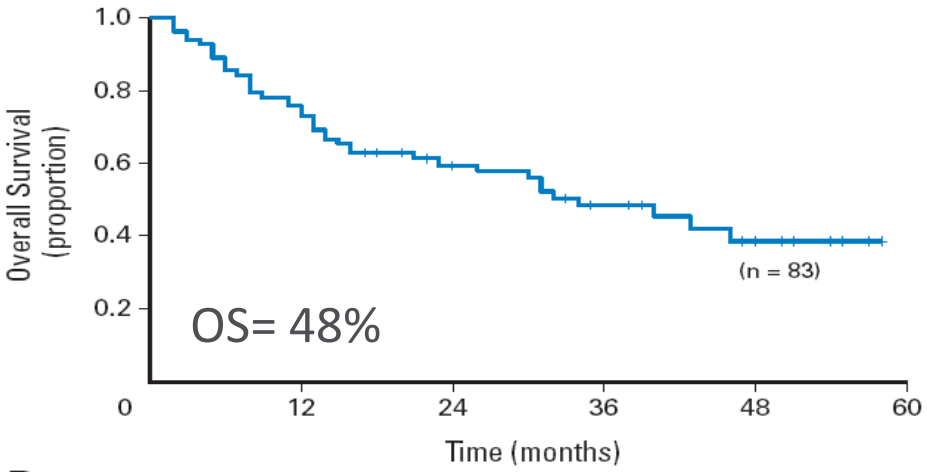
Only 70% proceed to ASCT

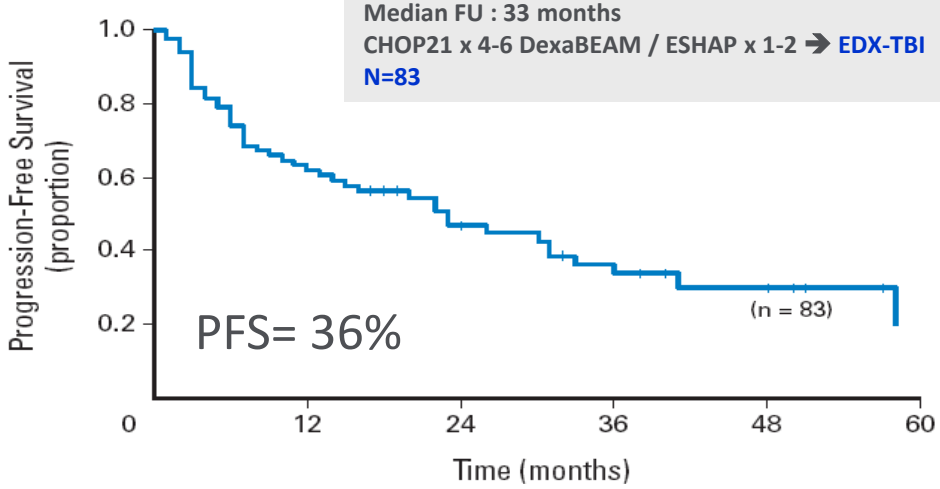
Why not ?

1) No response or early progression
2) Toxicity
3) Mobilisation failure

D'Amore, JCO 2012

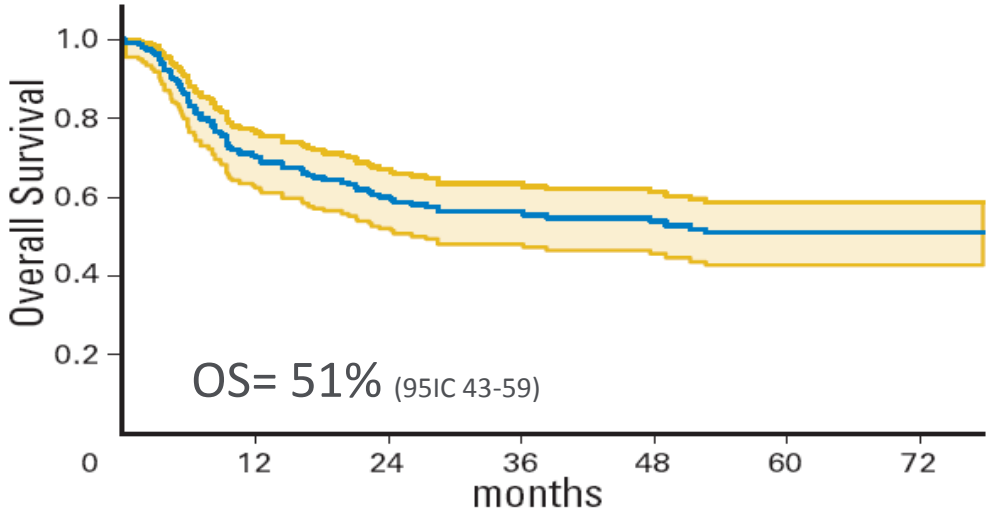
ASCT 1st line : NLG-T-01 and German Studies

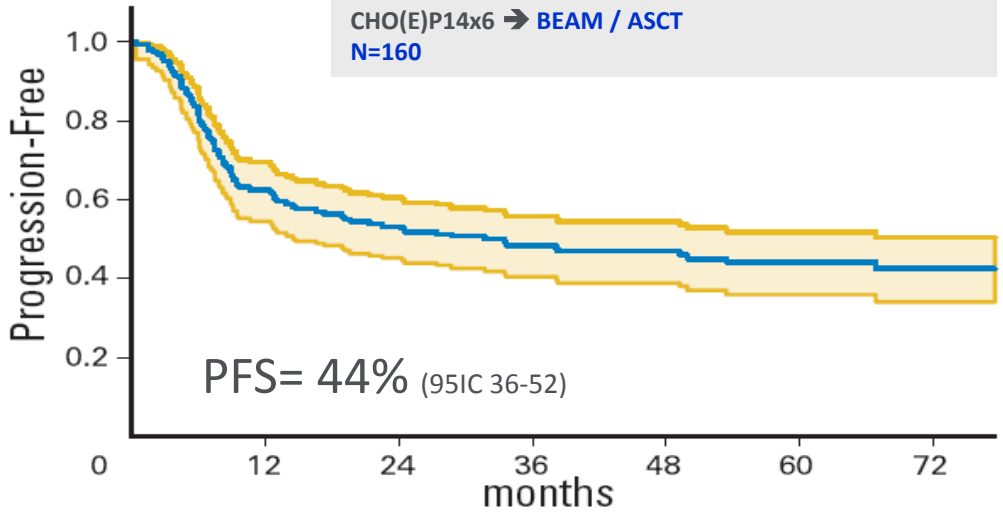




Median FU : 33 months
CHOP21 x 4-6 DexaBEAM / ESHAP x 1-2 ➔ EDX-TBI
N=83

Reimer, JCO 2009

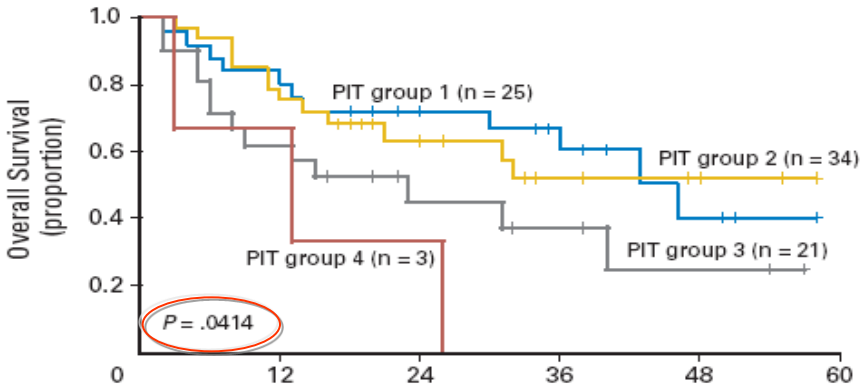


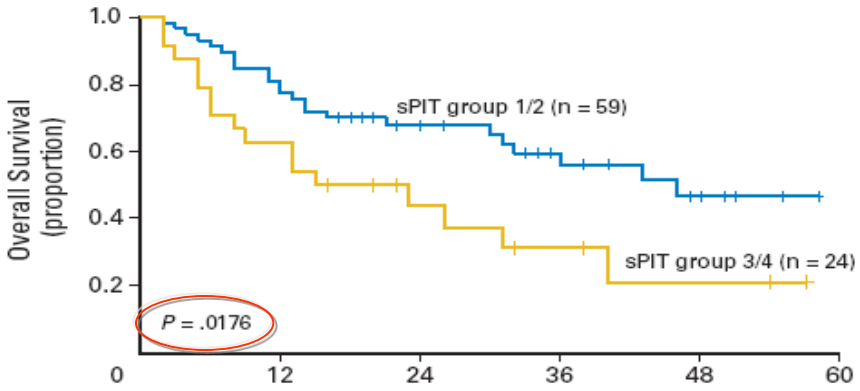


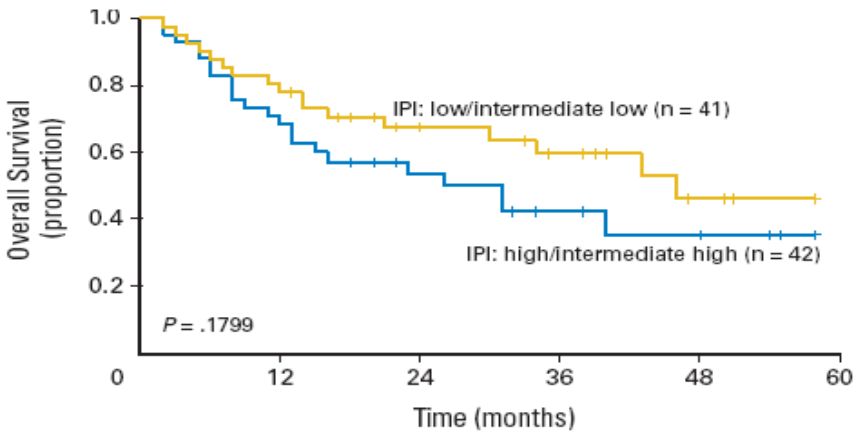
Median FU : 60.5 months
CHO(E)P14x6 ➔ BEAM / ASCT
N=160

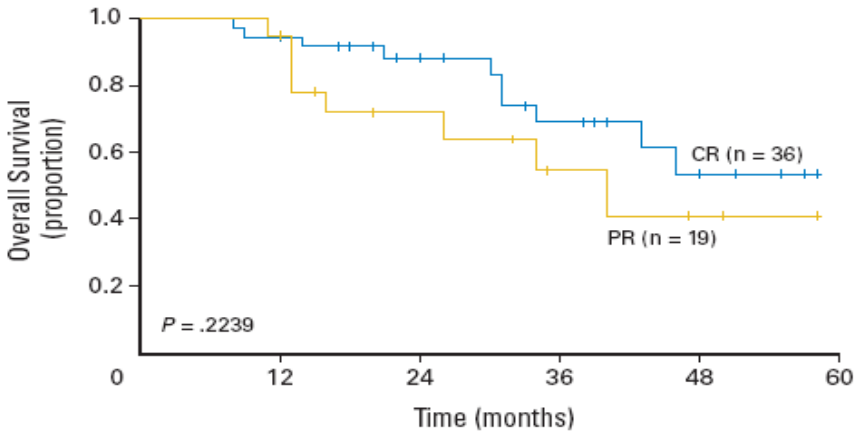
D'Amore, JCO 2012

ASCT 1st line : German study : statistical analysis (UV)





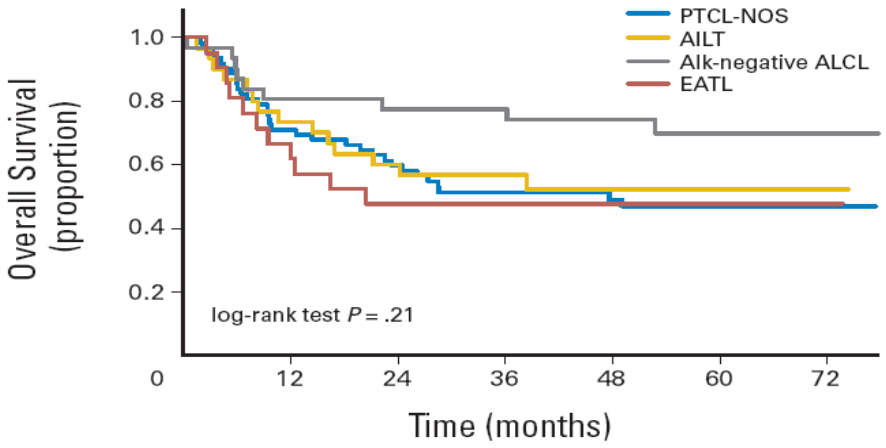


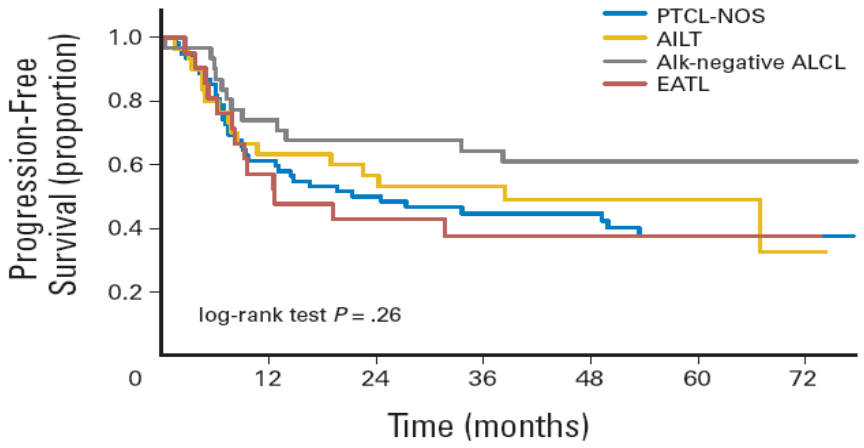


Impact on OS of aaIPI, PIT, CR/PR at transplantation, histological subtype, BM involvement

Reimer, JCO 2009

ASCT 1st line : Impact of of histological subgroup ?





Histologic subtype	Patients No.	Patients %
PTCL-NOS	62	39
ALK-negative ALCL	31	19
AILT	30	19
EATL	21	13
Panniculitis like	6	4
T/NK nasal type	5	3
Hepatosplenic	5	3

5y
OS = 70%
PFS = 61%

D'Amore, JCO 2012

ASCT as 1st Line therapy of PTCL : conclusion

- Feasible up to 65 (-70) years old
- German + Nordic phase 2 studies ➲ 243 patients
  - OS = 50%
  - PFS = 35-45%
- Still 30-35% will not proceed to transplantation
  - Progressive disease
  - Toxicity/mobilization failure

Choice of induction therapy !

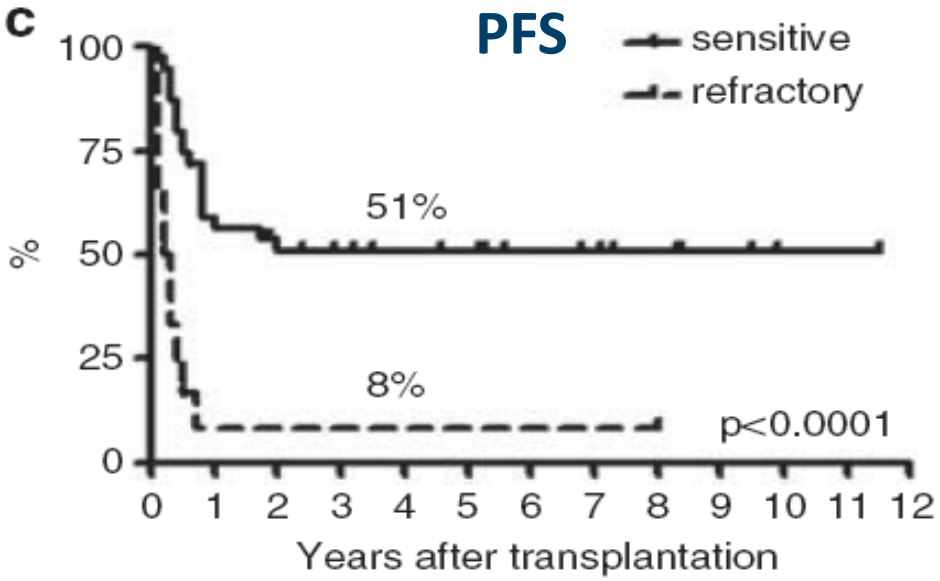
- Recommended treatment ?
  - May be better than CHOP-based polychemotherapy
  - Other strategies in addition or compared to ASCT are warranted

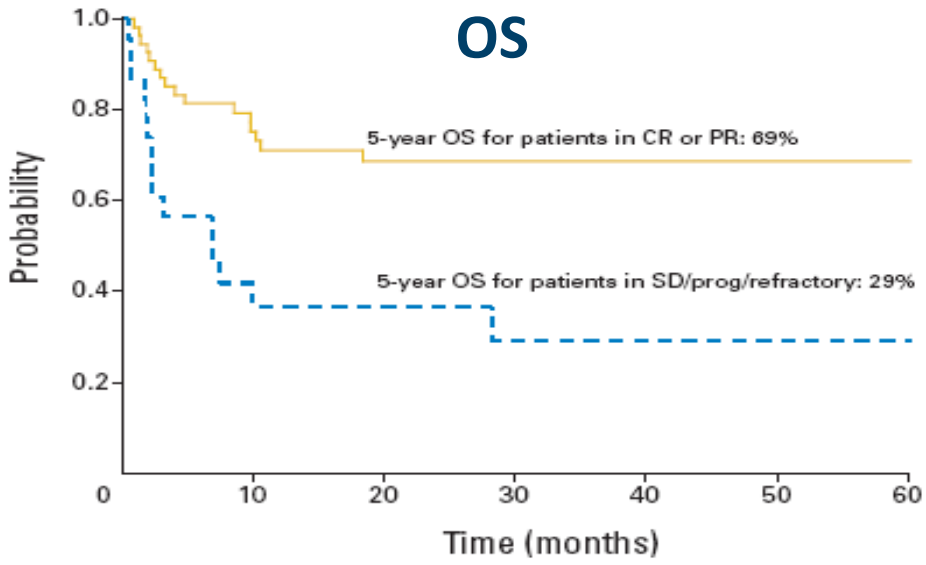
ALLOGREFFE

		PTCL ALCL AITL %	Myelo Ablative %	Relapse %	TRM NRM	OS	PFS EFS	at	Multivariée (facteurs pré allo)
Le Gouill JCO 2008	N=77 rétrospective registre SFGM-TC	84	74	40	33	57	53	*5y*	disease status (OS et EFS) HLA mismatch (OS, EFS et TRM)
Dodero Leukemia 2012	N=52 prospective et rétrospective	83	0	49	12	50	44	*5y*	disease status (OS et PFS) Age > 45 y (OS et PFS)
Jacobsen BJH 2012	N=52 rétrospective	40	60	43	27	59	39	*3y*	Extra nodal (OS et PFS) Allo < 2002 (OS et PFS) HLA mismatch (OS et PFS) Age > 50 y (OS et PFS)
Kyriakou JCO 2011	N=45 rétrospective registre EBMT	100 AITL	56	17	25 (1y)	64	53	*3y*	/

→ *Uniquement rechutes et réfractaires*

ALLOGREFFE : STATUS PRE ALLOGREFFE





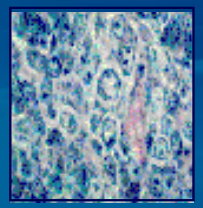
Mini-Allogreffe = 100%
Analyse multivariée
Disease status (OS et PFS)
Age > 45 y (OS et PFS)

Mini-Allogreffe = 27%
Analyse multivariée
Disease status (OS et EFS)
HLA mismatch (OS, EFS et TRM)

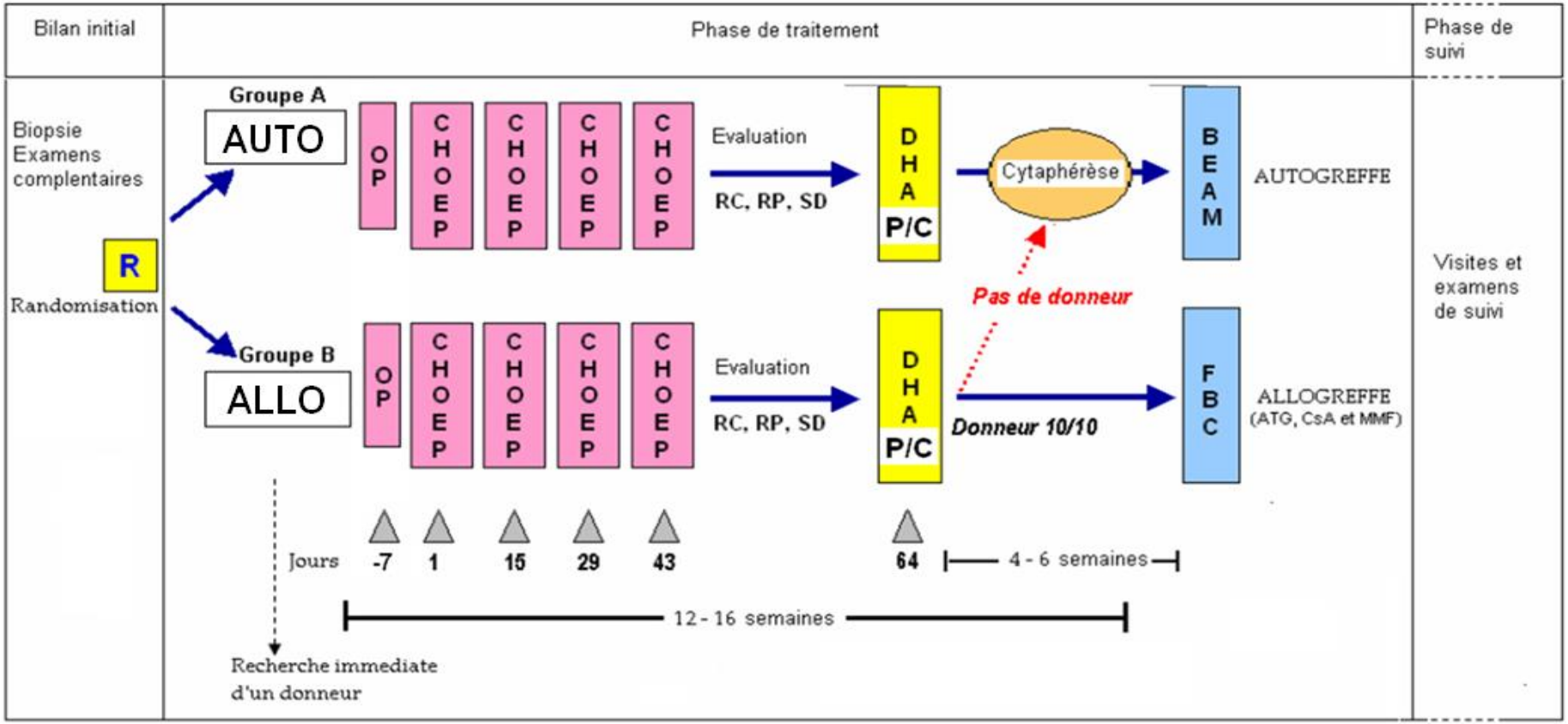
Et pas : nb de lignes, histologie, autogreffe, donor type et délai diagnostic - transplantation

Dodero 2012

Le Gouill 2008



DSHNHL 2006-1A / AATT



PTCL 1ère ligne (sauf ALK+) Hypothèse : Allogreffe : ↗ EFS 3 ans + 25% ?

N=150 (env. 70 patients randomisés, sept 2013)