Standard therapy of PTCL-NOS, ALCL and AITL A work in progress

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T-cell Lymphomas: Bologna, 2015

BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

Challenges in the study and management of PTCLs

- Rare and diverse
- Lack of (good) models to study PTCLs
- Treatment paradigms borrowed from DLBCL

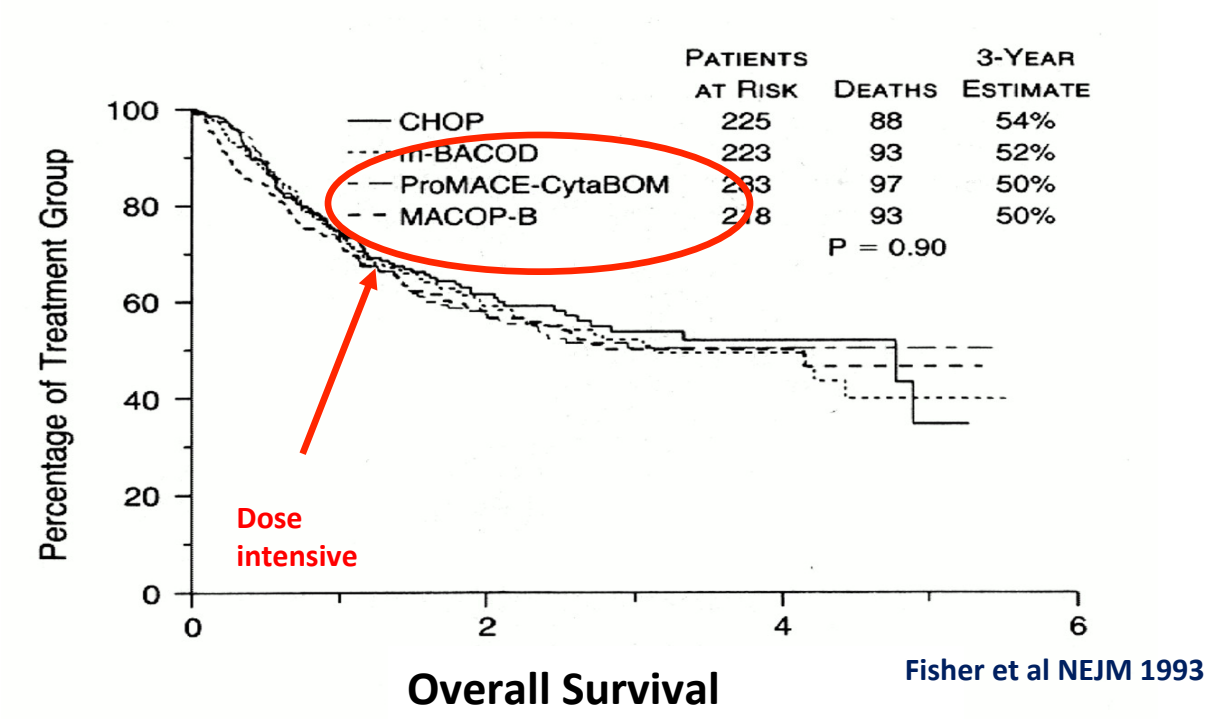
  - CHOP 'standard'

  - New therapies often added to CHOP
- Role of upfront transplant and patient selection unclear ➔ no RCTs
- Clinically, most are aggressive but some have more indolent course

  - PTCL-NOS thyroid with autoimmune thyroiditis (Yoshida BJH 2014)

  - Indolent T-cell LPD GI tract (Perry Blood 2014)

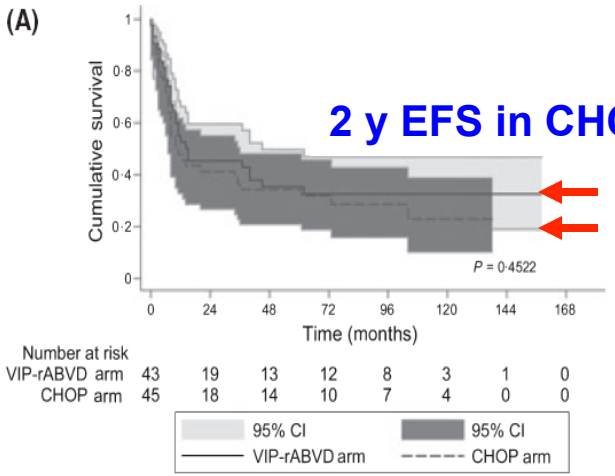
CHOP is the standard therapy for PTCL…. by default



Fisher et al NEJM 1993

Reminder: SWOG study performed during era of Working Formulation classification

RCTs are far and few between

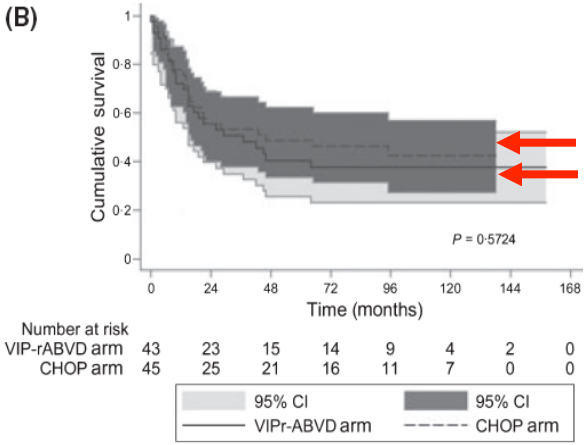


2 y EFS in CHOP ~ 41% (5 y ~35%)

VIP-rABVD

CHOP

GOELAMS Phase 3 study CHOP vs VIP-rABVD no difference in EFS of OS



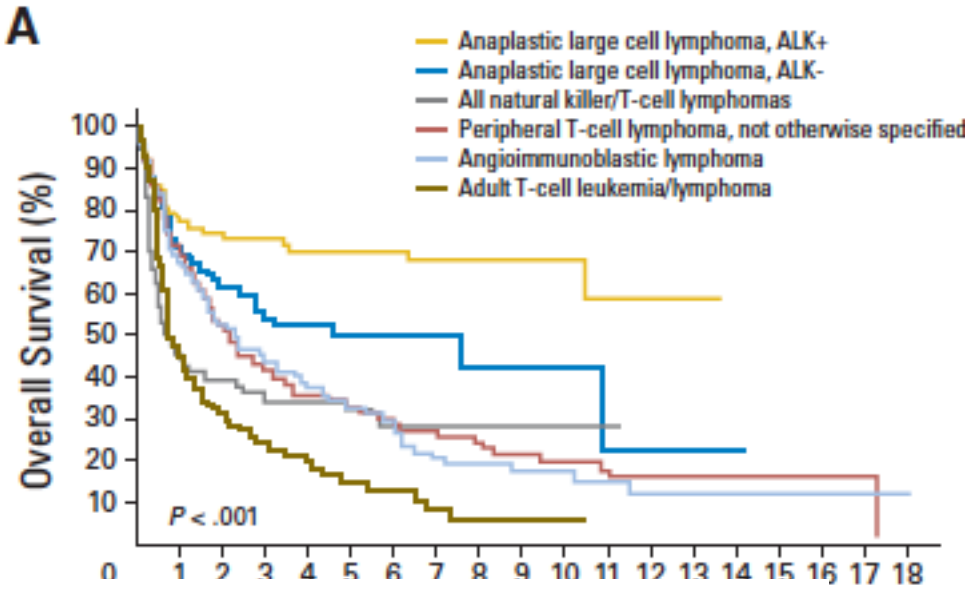
CHOP

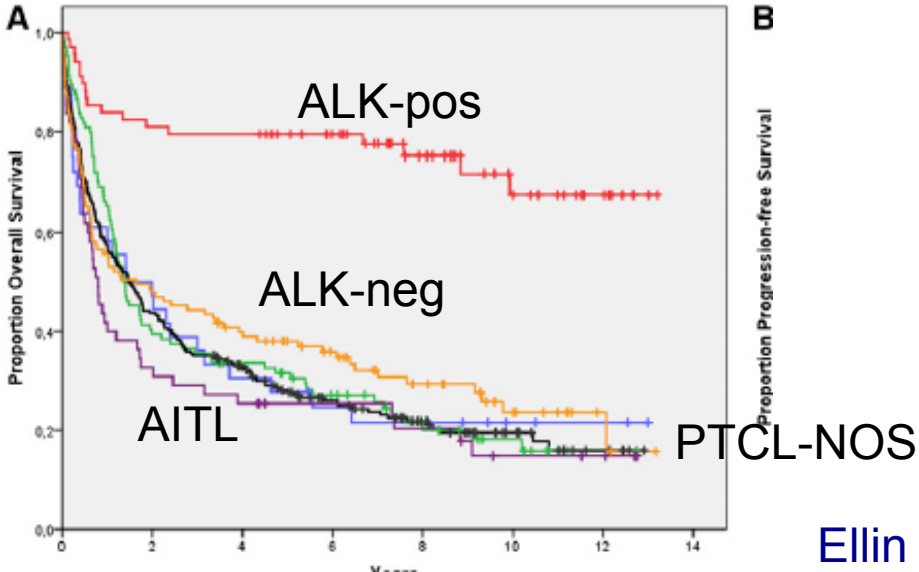
VIP-rABVD

2 y OS in CHOP ~ 55% (5 y ~50%)

Provides benchmark of outcome of patients with PTCL in a clinical trial

Real world outcomes of PTCL following (mostly) anthracycline-based therapy





PTCL (ITLP)	5 y PFS	5 y OS
ALK-pos ALCL	60%	70%
ALK-neg ALCL	36%	49%
PTCL-NOS	20%	32%
AITL	18%	32%

PTCL (Nordic)	5 y PFS	5 y OS
ALK-pos ALCL	63%	79%
ALK-neg ALCL	31%	38%
PTCL-NOS	21%	28%
AITL	20%	31%

Ellin Blood 2014

Guideline recommendations primary therapy

NCCN Guidelines First line therapy of PTCLs	
ALK+ ALCL	CHOP21
	CHOEP21
ALK-ALCL	CHOEP21
PTCL-NOS	CHOP14
AITL	CHOP21
	DAEPOCH
	HyperCVAD

Consider consolidation HDC/ SCT (exception IPI 0 or 1)

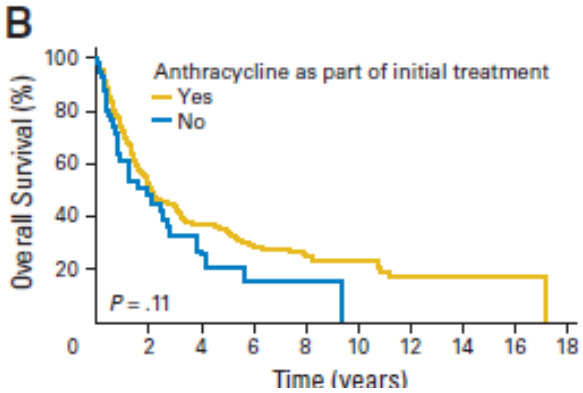
ESMO Guidelines First line therapy of PTCLs	
ALCL	CHOP21
PTCL-NOS	CHOEP21
AITL	'CHOP-like'

Consider consolidative HDC/ ASCT in IPI or PIT $\geq$ 2 if PR or CR

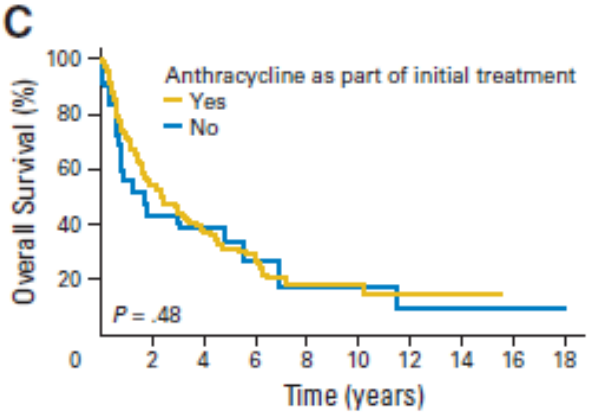
Ongoing Phase 3 studies: CHOP is the comparator

Study	PTCL	Standard	Experimental
Echelon 2	CD30 + PTCL (primarily ALCL)	CHOP (+ ASCT by discretion)	CHP+ Brentuximb
Ro-CHOP	All	CHOP	Romidepsin-CHOP
ACT 1	All < 61 y (not ALCL)	CHOP14 + ASCT	CHOP14+Alemtuzumab + ASCT
ACT 2	All > 60 y (not ALCL)	CHOP14	CHOP14-Alemtuzumab
UK	All	CHOP	Gem-P
China	All	CHOP	GDP-thalidomide

Role of anthracyclines?



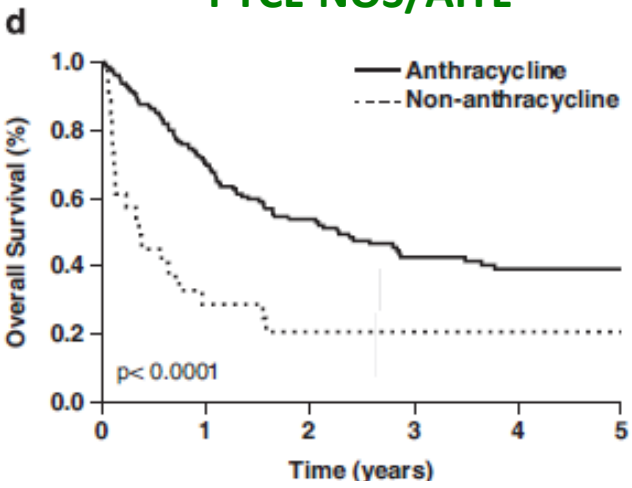
PTCL-NOS



AITL

Vose ITLP JCO 2010

PTCL-NOS/AITL



Briski Cancer J. 2015

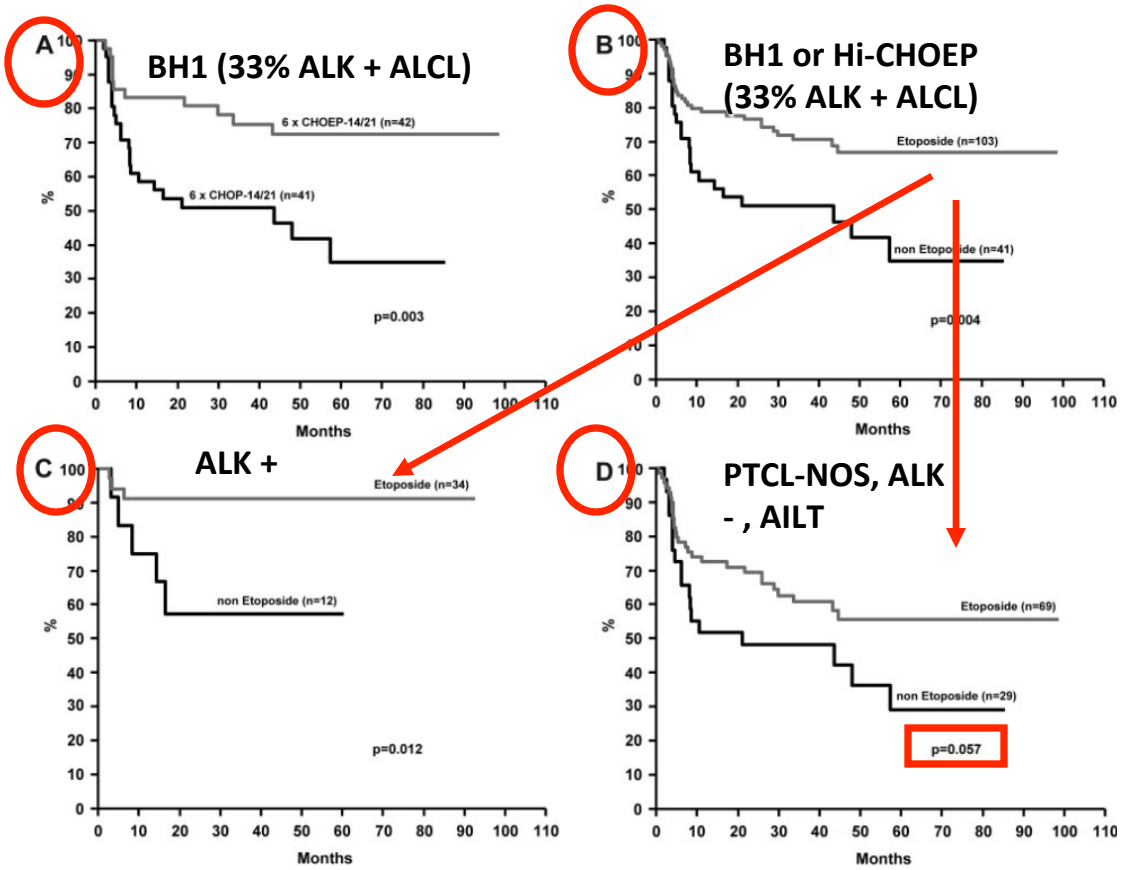
Role of anthracyclines unclear in PTCLs

Is the addition of etoposide the answer?

Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group

Norbert Schmitz,[1] Lorenz Trümper,[2] Marita Ziepert,[3] Maike Nickelsen,[1] Anthony D. Ho,[4] Bernd Metzner,[5] Norma Peter,[6] Markus Loeffler,[3] Andreas Rosenwald,[7] and Michael Pfreundschuh[8]

Schmitz JCO 2010



No OS difference observed, not adjusted for prognostic factors

Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry

Fredrik Ellin,[1,2] Jenny Landström,[2] Mats Jerkeman,[3] and Thomas Relander[3]

[1]Department of Internal Medicine, Kalmar County Hospital, Kalmar, Sweden; [2]Department of Oncology, Lund University, Lund, Sweden; and [3]Department of Oncology, Skane University Hospital, Lund, Sweden

Ellin Blood 2014

	OS (n = 248)		PFS (n = 243)	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.003 (0.984-1.023)	.730	1.000 (0.982-1.018)	.998
Male gender	1.60 (1.12-2.29)	.010	1.66 (1.16-2.35)	.005
Ann Arbor III-IV	1.56 (1.03-2.31)	.028	1.54 (1.05-2.25)	.028
Extranodal involvement >1	1.55 (1.03-2.35)	.037	1.57 (1.04-2.35)	.030
WHO PS >0	1.78 (1.23-2.57)	.002	1.81 (1.26-2.60)	.001
PTCL NOS	1.00	—	1.00	—
ALKneg ALCL	0.81 (0.50-1.25)	.307	0.78 (0.50-1.21)	.261
AITL	0.90 (0.59-1.39)	.643	0.90 (0.59-1.38)	.628
EATL	1.92 (1.18-3.14)	.009	1.52 (0.95-2.45)	.083
TCL U	1.98 (0.96-4.09)	.066	2.05 (0.99-4.24)	.052
Etoposide	0.81 (0.53-1.25)	.341	0.87 (0.57-1.32)	.507
Auto-SCT ITT	0.58 (0.40-0.84)	.004	0.56 (0.39-0.81)	.002

For all PTCL patients up to age 70 y, no benefit of CHOEP

But, if age cut-off moved to < 60 y, addition of etoposide was associated with an improved PFS (P=.008) but not OS (P=.052)

CHOEP VS. CHOP GIVES BETTER RESULTS IN FIRST-LINE THERAPY OF T-CELL LYMPHOMA. A RETROSPECTIVE ANALYSIS FROM CZECH LYMPHOMA STUDY GROUP (CLSG) DATABASE

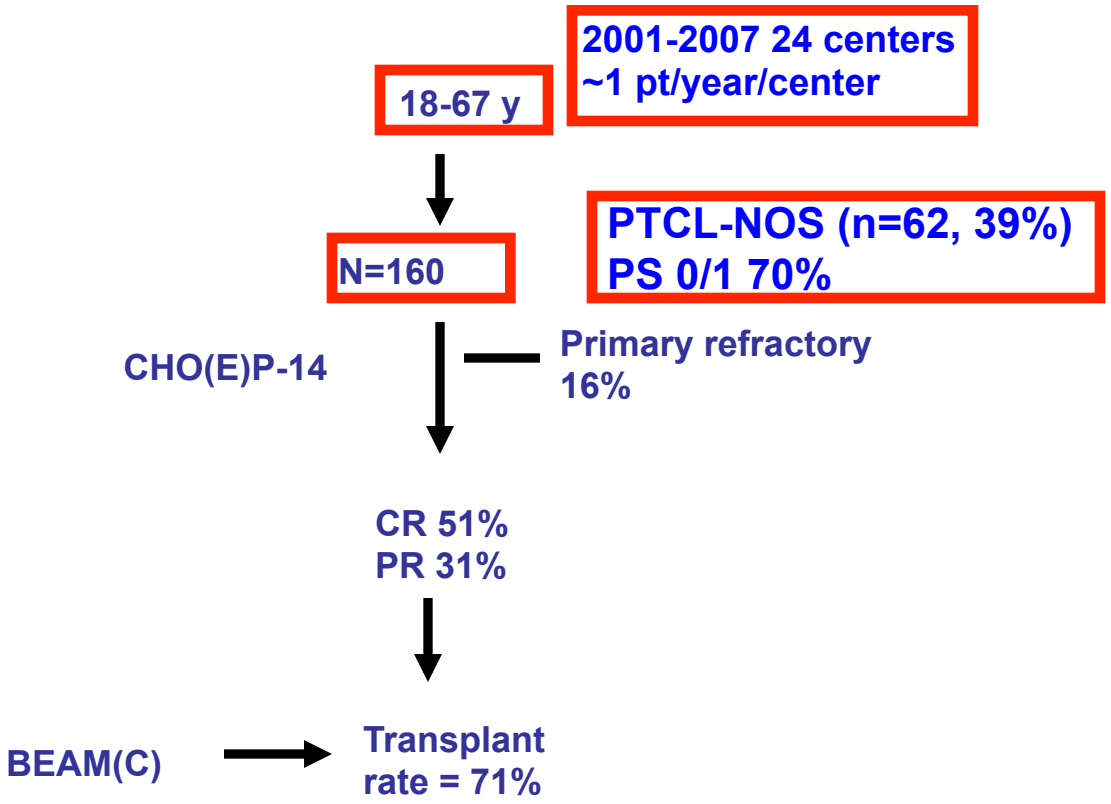
A. Janikova, Brno (Czech Republic) **Lugano 2015**

Should all patients undergo upfront consolidative autoSCT?

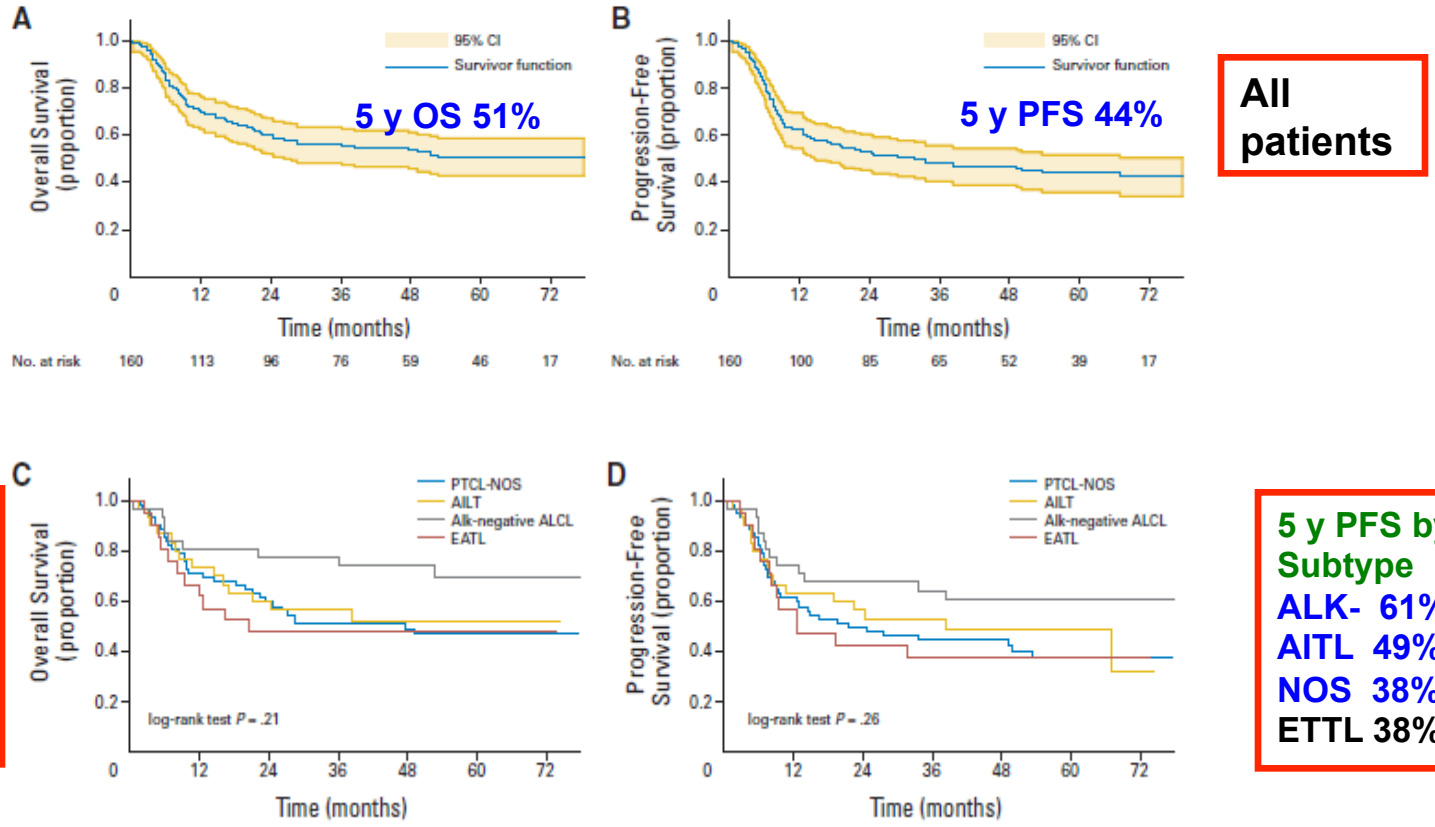
Upfront Autologuos Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01

Francesco d'Amore, Thomas Relander, Grete F. Lauritzsen, Esa Jantunen, Hans Hagberg, Harald Anderson, Harald Holte, Anders Österborg, Mats Merup, Peter Brown, Outi Kuittinen, Martin Erlanson, Bjørn Østenstad, Unn-Merete Fagerli, Ole V. Gadeberg, Christer Sundström, Jan Delabie, Elisabeth Ralfkiaer, Martine Vornanen, and Helle E. Toldbod

D'Amore JCO 2012



Upfront transplant in PTCL



All patients

5 y OS by Subtype
ALK- 70%
AITL 49%
NOS 52%
ETTL 48%

5 y PFS by Subtype
ALK- 61%
AITL 49%
NOS 38%
ETTL 38%

d' Amore JCO 2012

TEN YEARS MEDIAN FOLLOW-UP OF THE NORDIC NLG-T-01 TRIAL ON CHOEP AND UPFRONT AUTOLOGOUS TRANSPLANTATION IN PERIPHERAL T-CELL LYMPHOMAS

F. d'Amore, Aarhus (Denmark)

Lugano 2015

What is the outcome of PTCL patients that achieve a CR post standard chemotherapy vs ASCT?

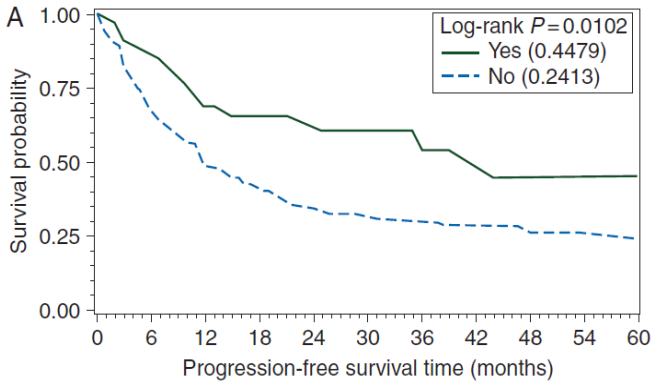
Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy

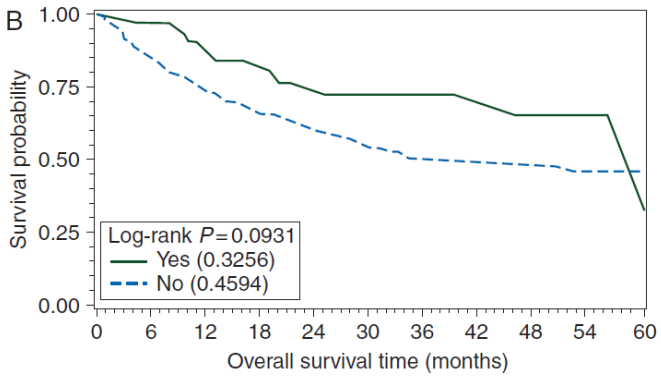
J. S. Abramson[1], T. Feldman[2], A. R. Kroll-Desrosiers[3], L. S. Muffly[4], E. Winer[5], C. R. Flowers[6], F. Lansigan[7], C. Nabhan[4], L. J. Nastoupil[6], R. Nath[3], A. Goy[2], J. J. Castillo[8], D. Jagadeesh[3], B. Woda[3], S. T. Rosen[9], S. M. Smith[4] & A. M. Evens[10*]

Characteristic	Number (%)
All patients	341 (100)
Median age, years (range)	62 years (18–95)
Gender	
Female	141 (41)
Male	200 (59)
Histology	
PTCL-NOS	107 (31)
ALCL, ALK +	23 (7)
ALCL, ALK−	43 (13)
ALCL, ALK unknown	22 (6)
AITL	77 (23)

Characteristic	Number (%)
Initial systemic treatment ($n = 341$)	
CHOP-like	237 (70)
HyperCVAD/MA	20 (6)
Other regimen[b]	61 (18)
Palliative care only	23 (7)
SCT in first remission ($n = 318$)	
Yes	33 (10)
No	285 (90)
Radiation in first remission ($n = 318$)	
Yes	68 (21)
No	250 (79)

Upfront ASCT in the treatment of PTCLs

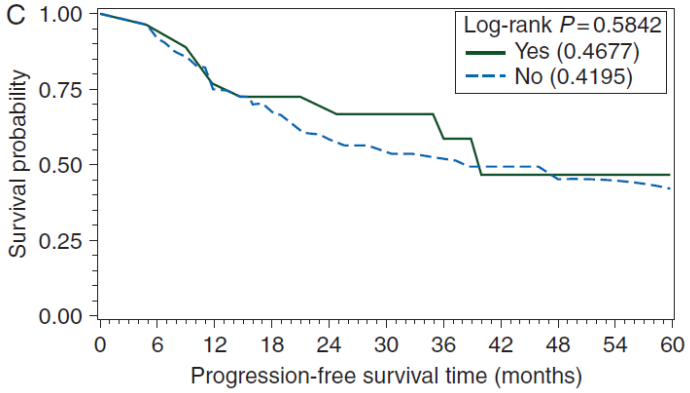


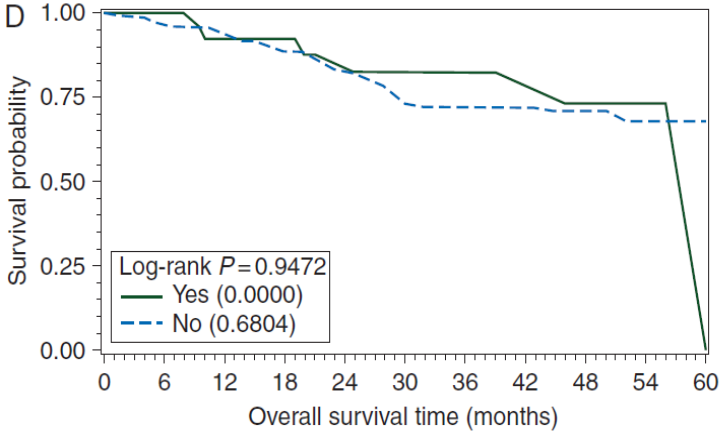


ASCT

No ASCT

But, no difference if comparison confined to CR patients only



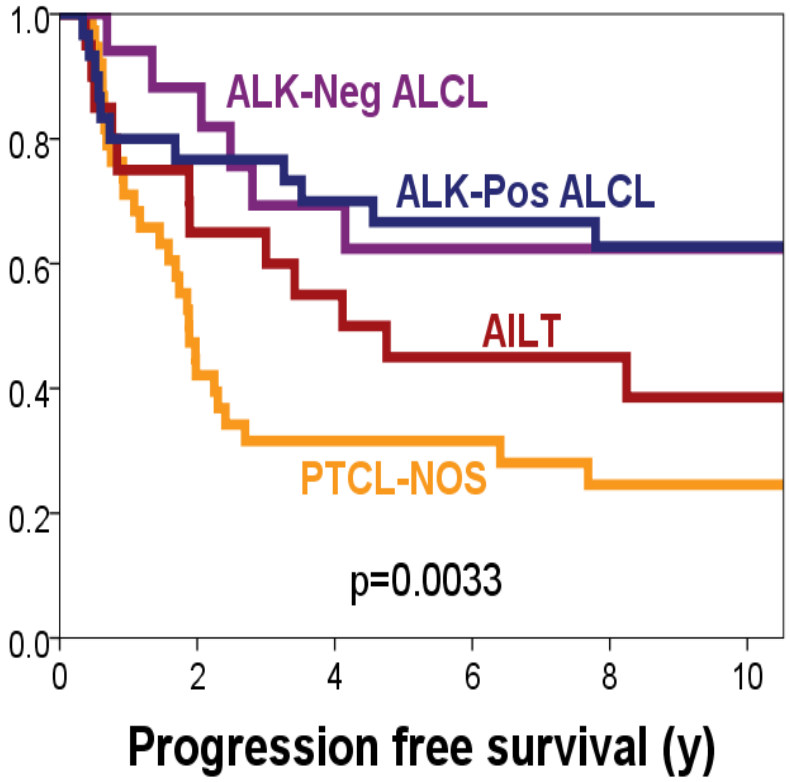


ASCT

No ASCT

Caveat: All PTCL subtypes included – is there a correlation between histologic subytpe and benefit of up-front transplant?

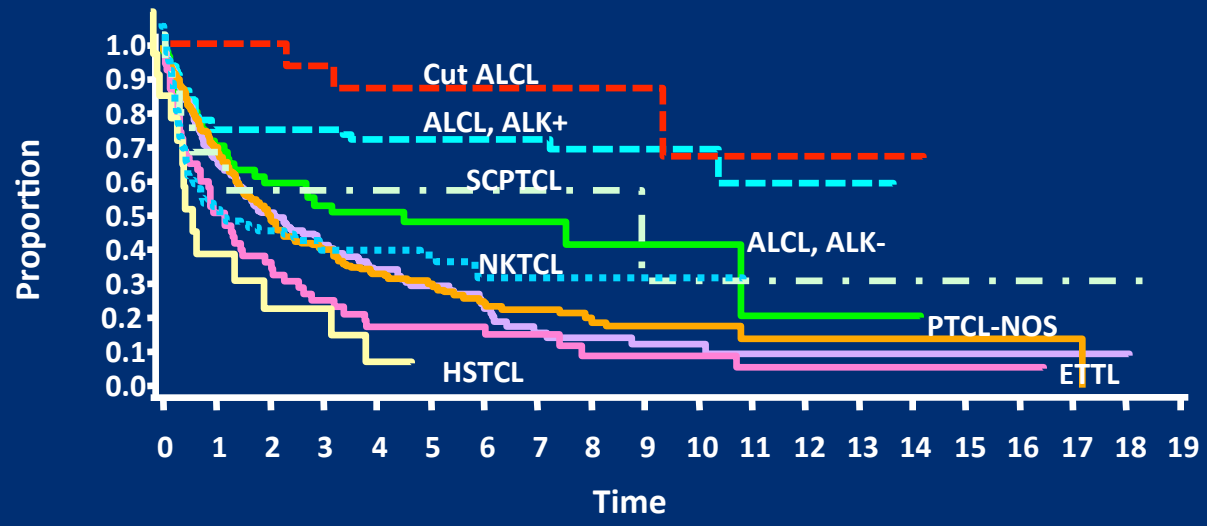
PFS of PTCL patients in CR following front-line chemotherapy



5-year PFS (%)	
ALK-POS	67
ALK-NEG	62
AITL	45
PTCL-NOS	32

BCCA Lavoie ASCO 2014

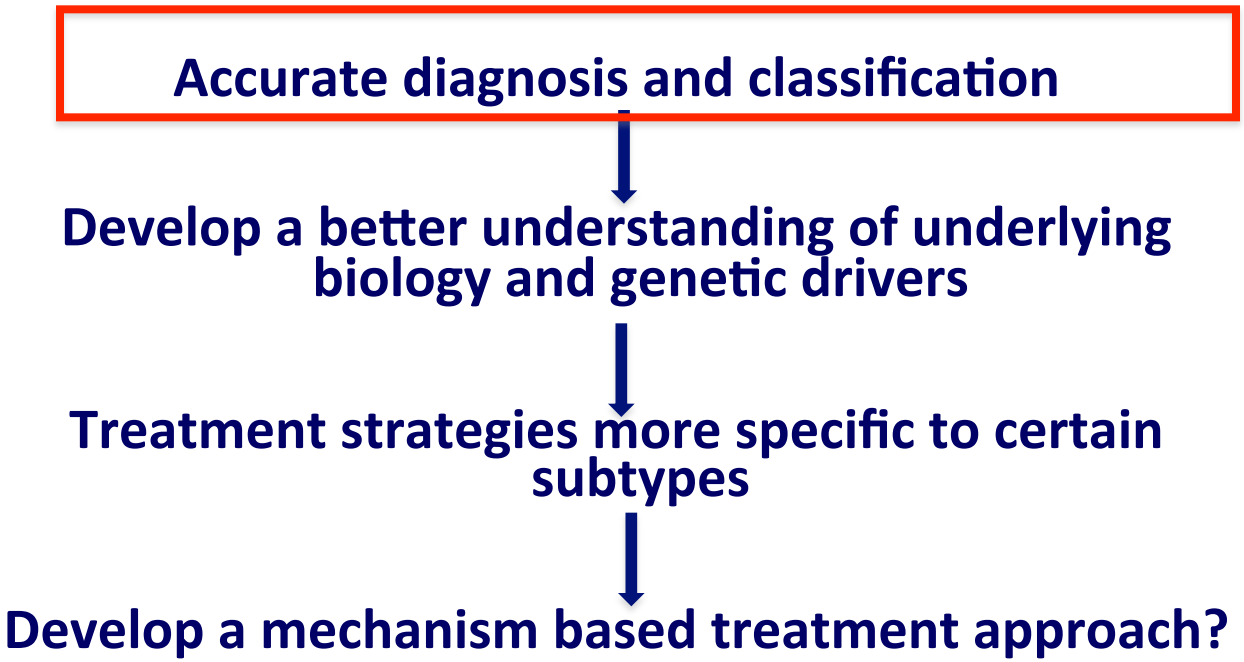
Survival of PTCL Subtypes: Disease Heterogeneity



What about biological and genetic heterogeneity within subtypes which may impact treatment selection?

Adapted from
ITLP JCO 2008

Moving forward means going back



PTCL-NOS: The ‘Wastebasket’ Diagnosis

Lymphoma with T-cell phenotype

↓

Features not consistent with ‘specified’

PTCL subtype as defined by the WHO

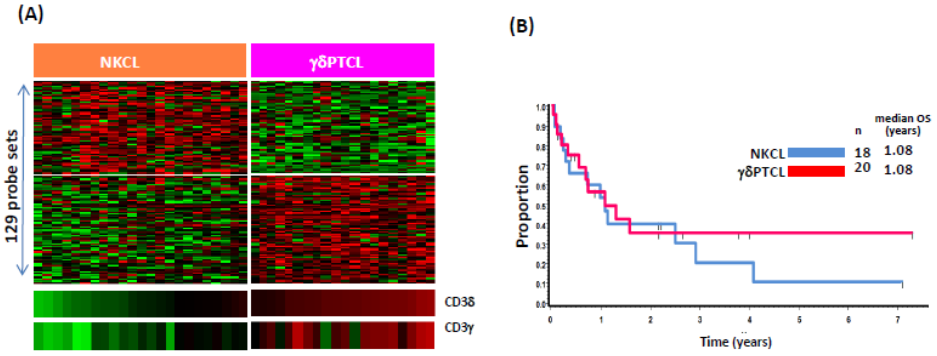
PTCL-NOS

Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma

Javeed Iqbal, George Wright, Chao Wang, Andreas Rosenwald, Randy D. Gascoyne, Dennis D. Weisenburger, Timothy C. Greiner, Lynette Smith, Shuangping Guo, Ryan A. Wilcox, Bin Tean Teh, Soon Thye Lim, Soon Yong Tan, Lisa M. Rimsza, Elaine S. Jaffe, Elias Campo, Antonio Martinez, Jan Delabie, Rita M. Braziel, James R. Cook, Raymond R. Tubbs, German Ott, Eva Geissinger, Philippe Gaulard, Pier Paolo Piccaluga, Stefano A. Pileri, Wing Y. Au, Shigeo Nakamura, Masao Seto, Francoise Berger, Laurence de Leval, Joseph M. Connors, James Armitage, Julie Vose, Wing C. Chan and Louis M. Staudt

BLOOD, 8 MAY 2014 • VOLUME 123, NUMBER 19

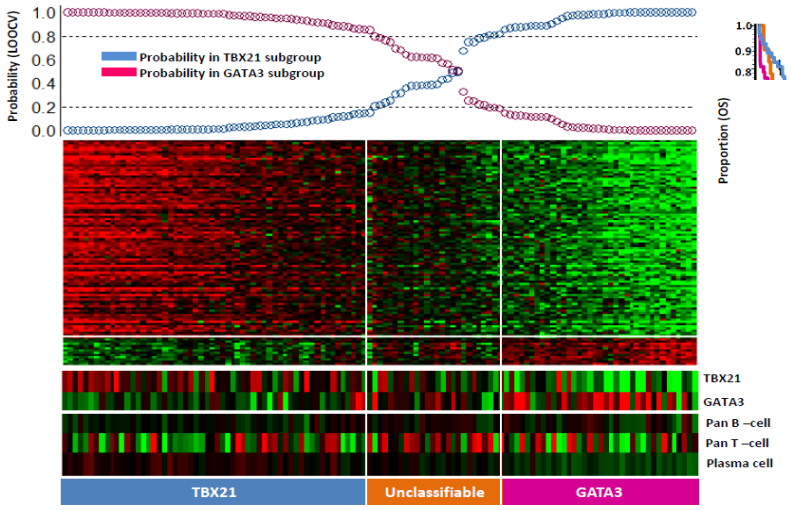
13/150 9% PTCL-NOS have a γδ phenotype → comparable outcome to EN NK/TCL



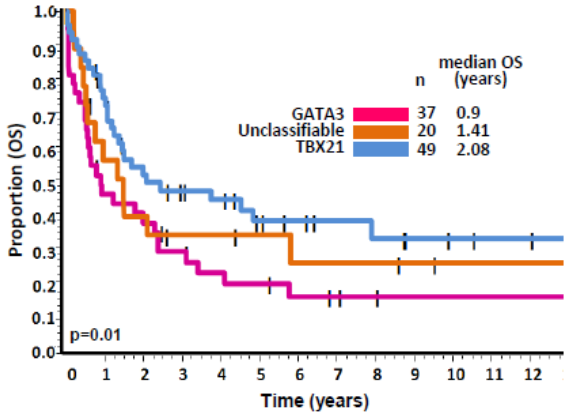
Should treatment approaches in γδ PTCL-NOS mirror those in extranodal NK/T-cell lymphoma ?

Subclassification of PTCL-NOS

Cluster 2
TBX21 (T-bet) and EOMES and targets: CXCR3, IL2RB, CCL3, IFNγ



Cluster 1
GATA3 and targets: CCR4, IL18RA, CXCR7, IK



'GATA3' PTCL-NOS inferior OS vs 'TBX21'

20% unclassified

Reproducibility? Translation therapeutically – differential sensitivity to standard chemotherapy and novel therapies?

PTCL-NOS – not all are aggressive

Primary peripheral T-cell lymphoma, not otherwise specified of the thyroid with autoimmune thyroiditis

Yoshida et al BJH 2014

Case	Age (years)	Sex	Enlarged thyroid	CS	Extra-thyroid lesions	PS	LDH > normal	History of autoimmune thyroiditis	Presence of anti-thyroid antibodies *
1	61	M	Bilateral	IV	PB, BM	1	–	–	+
2	68	M	Bilateral	IIE	Cervical LNs	4	+	+	+
3	63	F	Right	IIE	A cervical LN	1	–	–	–
4	51	M	Bilateral	IV	Cervical LNs, PB	1	–	+	+
5	67	F	Bilateral	IIE	Cervical LNs	1	–	+	+
6	83	M	Bilateral	IV	PB, BM	1	–	+	+

6 cases PTCL-NOS thyroid, known hx thyroiditis in 2/3; PB 50%

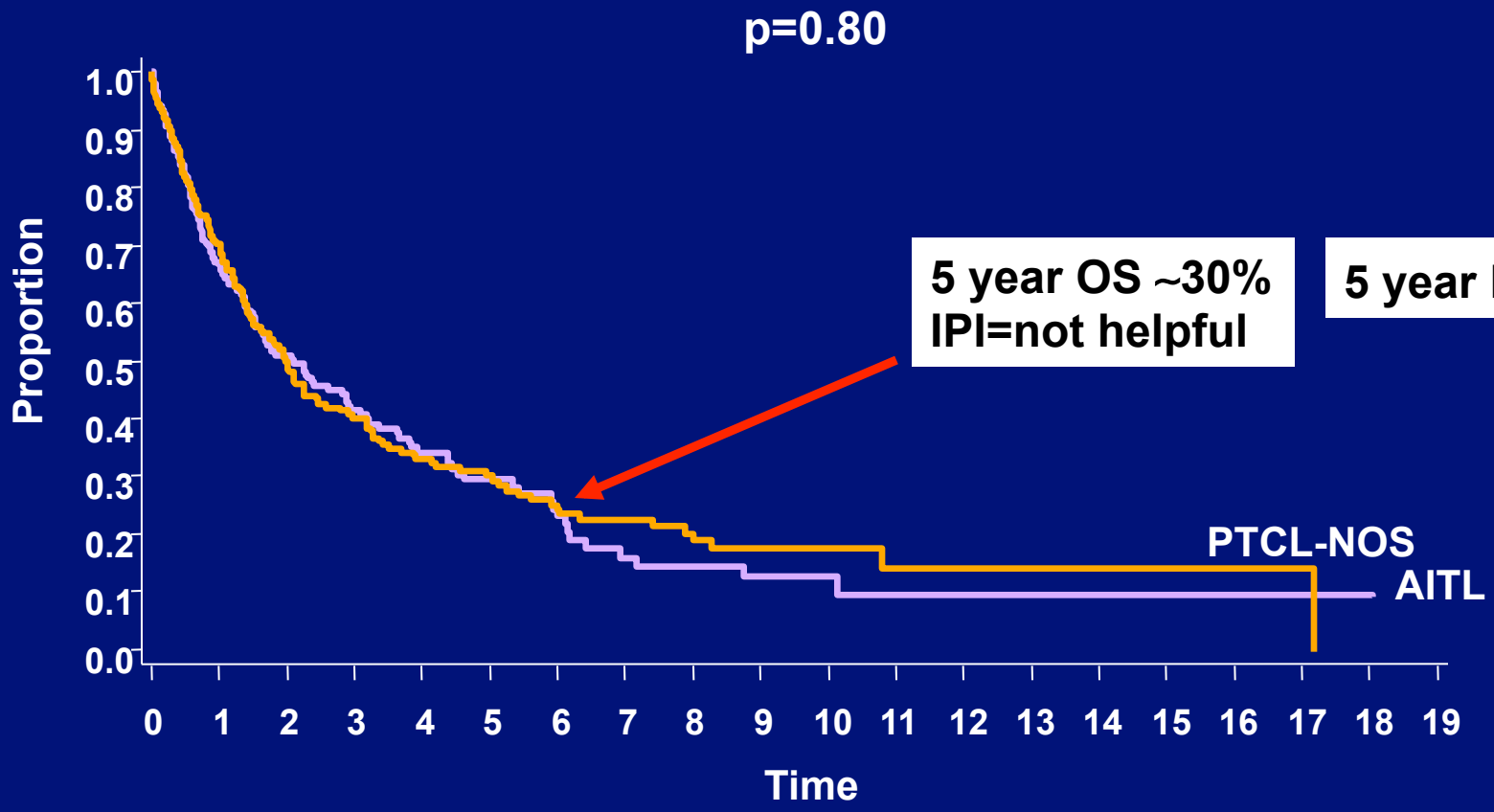
Case	Diagnosis	Size of lymhoma cells	LEL	CD3	CD4	CD8	TIA1	CXCR3	CCR5	CCR4
1	PTCL-NOS	Small to medium	+	+	+	–	–	+	+	–
2	PTCL-NOS	Diffuse, large	–	+	+	–	–	+	+	–
3	PTCL-NOS	Small to medium	+	+	+	–	+	+	–	–
4	PTCL-NOS	Small to medium	+	+	+	–	–	+	–	–
5	PTCL-NOS	Small to medium	+	+	+	–	–	+	–	–
6	PTCL-NOS	Small to medium	–	+	+	–	–	+	–	+

CD3+, CD4+, CXCR3+, small-medium sized cells

Case	Initial therapy	Effect of initial therapy	PFS (months)	Spontaneous regression	Therapy at relapse	OS (months)	Outcome
1	Chemotherapy (COP)	PR	57	+*	Radiotherapy (thyroid) 46 Gy	120	Survival without lymphoma
2	Chemotherapy (CHOP)	PR	4	–	Chemotherapy (IT)	5	Death
3	Only biopsy			+		15	Survival without lymphoma
4	Only biopsy			+		97	Survival without lymphoma
5	Chemotherapy (CHOP)	PR	23	–	Chemotherapy (COP)	70	Survival with lymphoma
6	Chemotherapy (THP-COP)	PR	8	+*	Radiotherapy (thyroid) 40 Gy	13	Survival without lymphoma

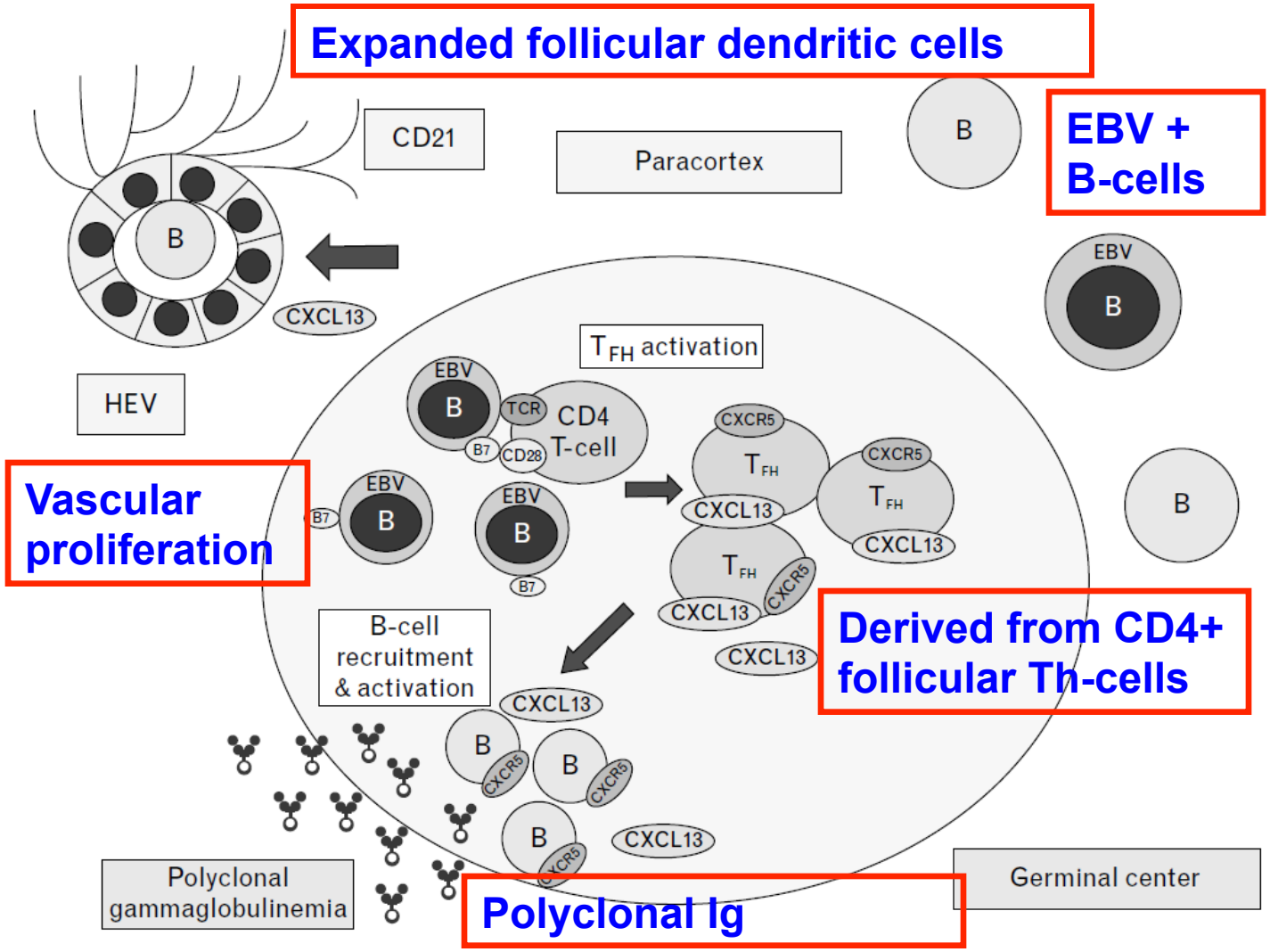
Indolent course, spontaneous remissions observed post RT – observation is reasonable

OS AITL vs PTCL-NOS



Adapted from ITLP
Vose JCO 2008

AITL: Unique biology with immune dysregulation



Dunleavy Curr Opin Hematology 2007

Mutations in epigenetic modifiers in AITL and TFH-cell PTCL-NOS

		TET2	IDH2	DNMT3A	RHOA G_{17V}
AITL	**Palomero 2014**	47%	-	-	67%
	Sakata-Yanagimoto 2014	82.6%	30.4%	26%	70.8%
	Odejide 2014 (targeted)	76%	20%	33%	-
	Yoo 2014	-	-	-	53.3%
	Cairns 2012	-	20%	-	-
PTCL NOS	**Palomero 2014**	38%	-	-	18%
	Sakata-Yanagimoto 2014	48.5%	0	27.3	17.2%
	Cairns 2012	-	0	-	-

Correlation of mutations with response to epigenetic therapies?

AITL ? A different standard therapy

Clues

Responds differentially to therapy

- CHOP + Avastin ECOG

1 year PFS PTCL-NOS vs AITL 15% vs 57.5%

- Lenalidomide

ORR PTCL-NOS vs AITL 22% vs 31%

-HDACs

Durable reponses with romidepsin and belinostat

- Pralaxtrexate

Low ORR

ALCL: Clinical and genetic heterogeneity

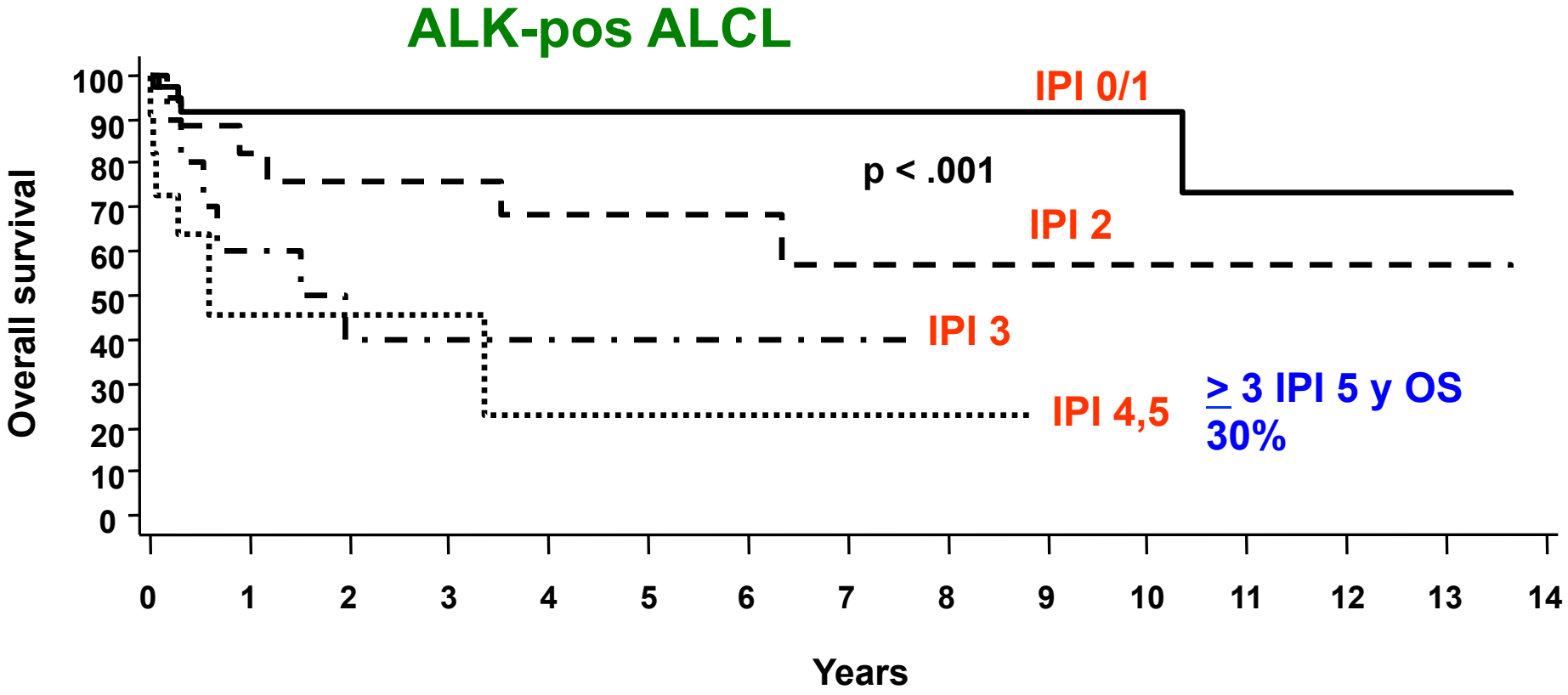
		ALK +	ALK -	ALK +	ALK -	ALK +	ALK -	
Author **n=ALK +** **n=ALK -**	**Median follow-up (yrs)**	**Median age (yrs)**		**Progression free survival (P value)**		**Overall survival (P value)**		**Treatment**
Gascoyne [45] n=36; n=34	4.2	30	61	5yr 82%	5yr 45% <0.001	5yr 79%	5yr 46% <0.0003	Doxorubicin-containing regimen
Falini [9] n=53; n=25	2.1	22*	43*	10yr 82%	10yr 28% <0.0001	5yr 71%	5yr 15%* <0.001	Doxorubicin-containing regimen
Suzuki [46] n=83; n=60	NR	21	57	NR	NR	5yr 70%	5yr 40% 0.0009	Regimens with or without doxorubicin
Ten Berge[27] n=28; n=46	2.1	23	54	5yr 85%‡	5yr 45%‡	5yr 90%	5yr 40% 0.0001	CHOP
Savage [8] n=87; n=72	3.5 ALK+, 1.7 ALK-	34	58	5yr 60%	5yr 36% 0.015	5yr 70%	5yr 49% 0.016	Anthracycline-based regimen
Schmitz [43] n=78; n=113	3.7**	37	50	3yr 75%	3yr 45% NR	3yr 89%	3yr 62% <0.001	CHOP or CHOP + etoposide (CHOEP)
Sibon[11] n=64; n=74	8.0	31	56	5yr 76% 8yr 72%	5yr 48% 8yr 39% <0.001	5yr 86% 8yr 82%	5yr 58% 8yr 49% <0.01	Anthracycline-based regimen
Parilla Castellar [41] n=32; n=73	6.5	27	58	NR	NR	5yr 85%	5yr 52% 0.0025	CHOP/CHOP-like

Hapgood and Savage Epub Blood 2015

Summary of studies: ALK pos better than ALK-neg

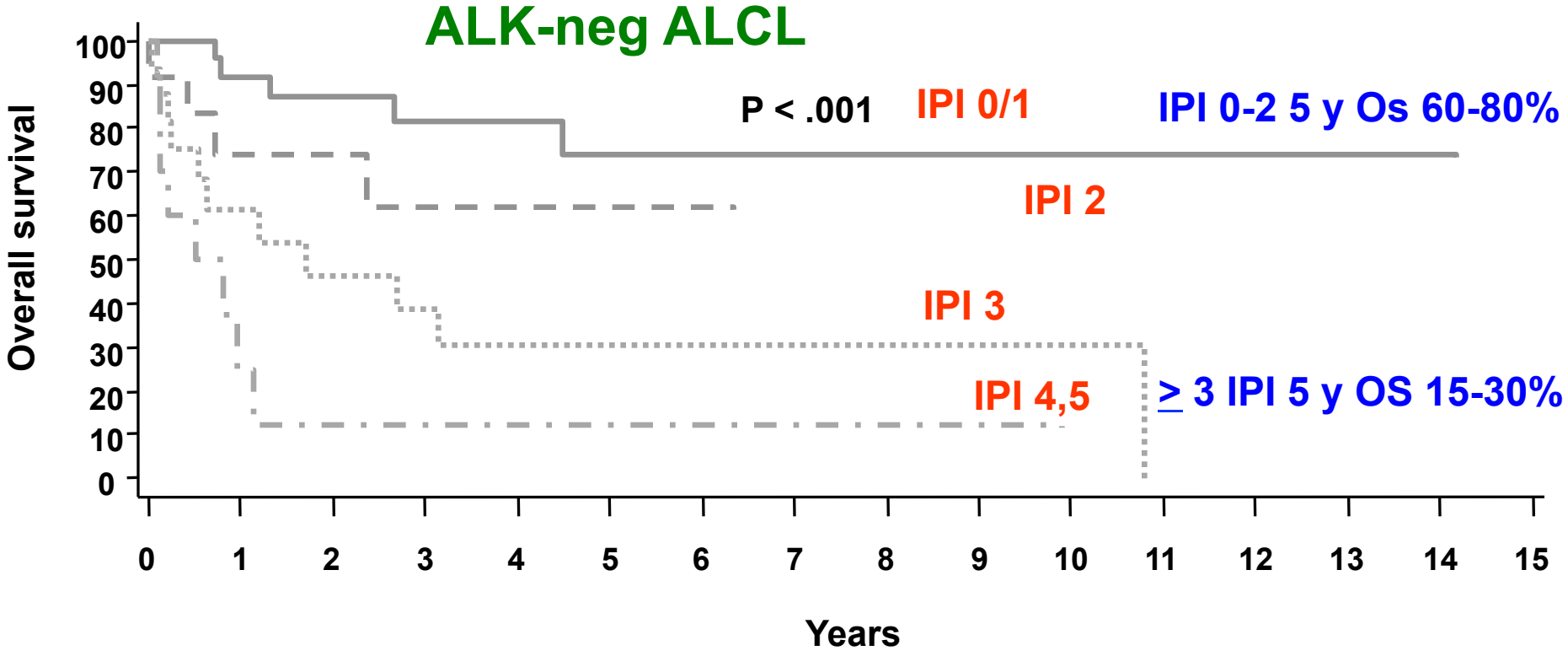
ALK-neg outcome is highly variable 5 yr PFS 28%-48%; 5 yr OS 15%-58%

The IPI matters in ALK+ALCL



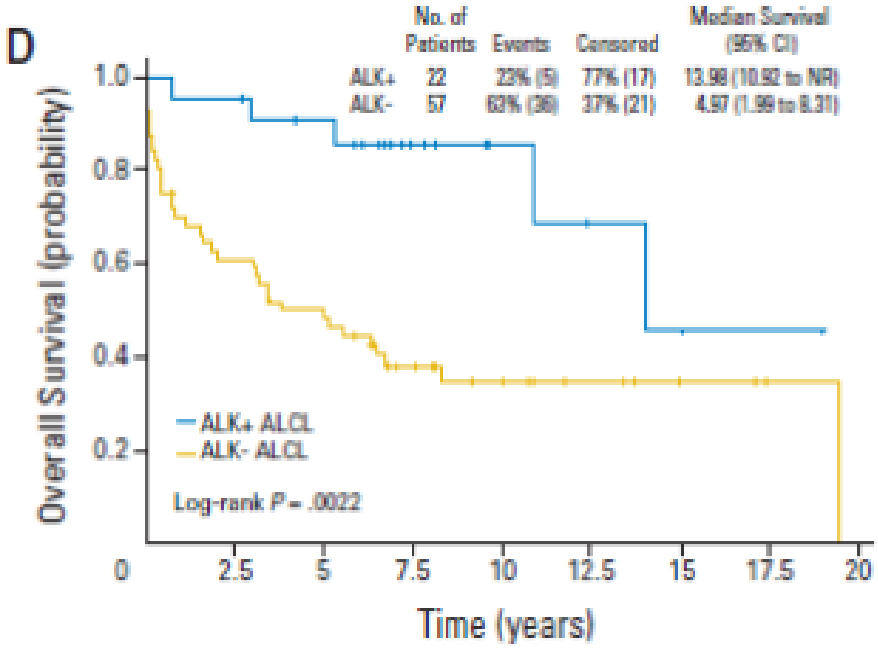
Savage Blood 2008

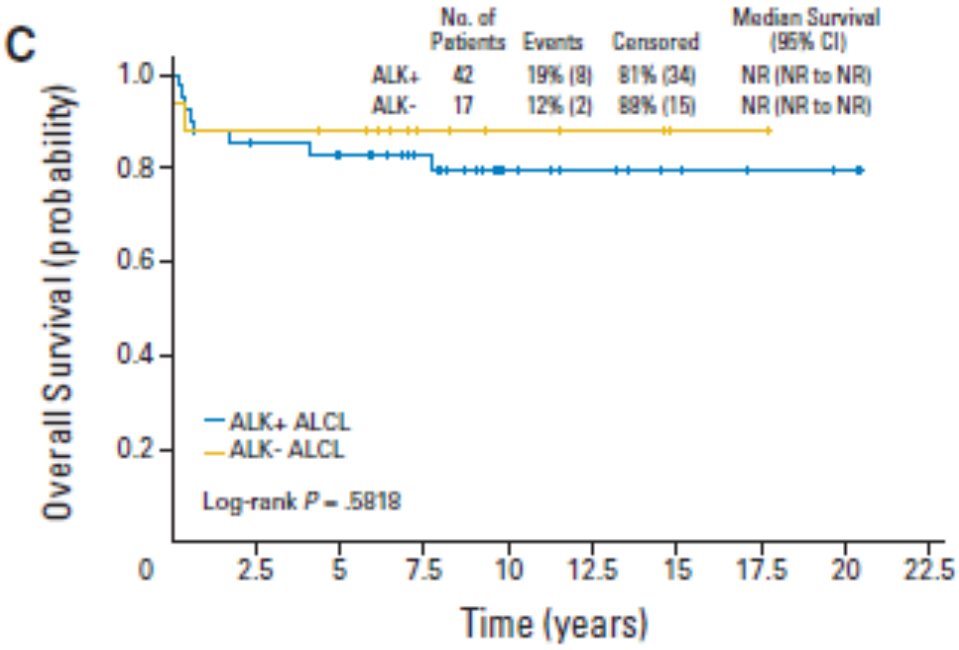
The IPI matters in ALK-neg ALCL



Savage Blood 2008

ALCL: Impact of age





Age > 40 y → ALK + > ALK -

Age < 40 y →ALK+ = ALK-

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

Edgardo R. Parrilla Castellar,[1] Elaine S. Jaffe,[2] Jonathan W. Said,[3] Steven H. Swerdlow,[4] Rhett P. Ketterling,[1] Ryan A. Knudson,[1] Jagmohan S. Sidhu,[5] Eric D. Hsi,[6] Shridevi Karikehalli,[7] Liuyan Jiang,[8] George Vasmatzis,[9] Sarah E. Gibson,[4] Sarah Ondrejka,[6] Alina Nicolae,[2] Karen L. Grogg,[1] Cristine Allmer,[10] Kay M. Ristow,[11] Wyndham H. Wilson,[12] William R. Macon,[1] Mark E. Law,[1] James R. Cerhan,[10] Thomas M. Habermann,[11] Stephen M. Ansell,[11] Ahmet Dogan,[1] Matthew J. Maurer,[10] and Andrew L. Feldman[1]

Parrilla-Castellar Blood 2014

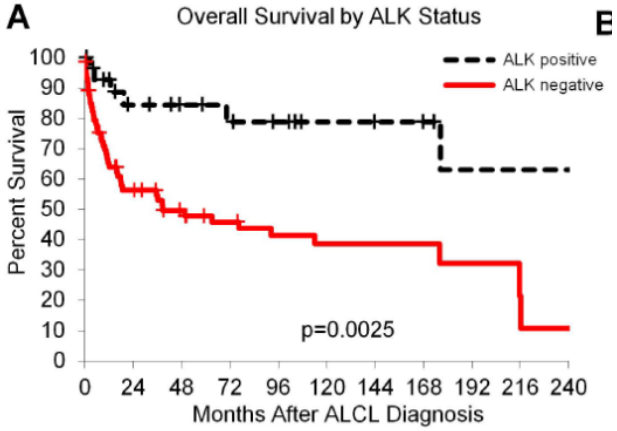
- **2 recurrent rearrangements previously identified in ALK-neg ALCL *DUSP22-IRF4* (6p 25.3 → *DUSP22* rearrangement) *TP63 3q28***

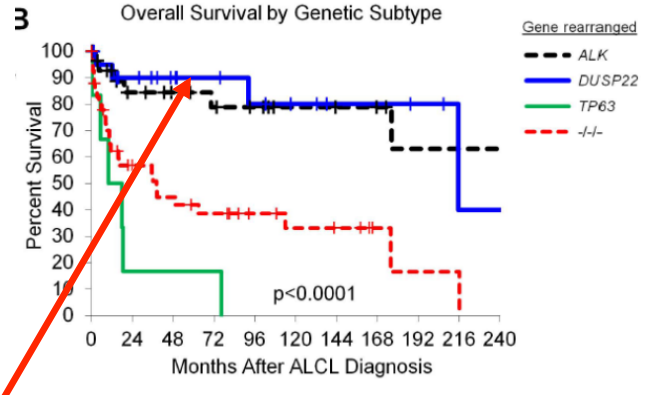
- **Evaluated the prognostic significance *DUSP22* and *P63* in 73 ALK-neg ALCLs and 32 ALK-pos ALCL**

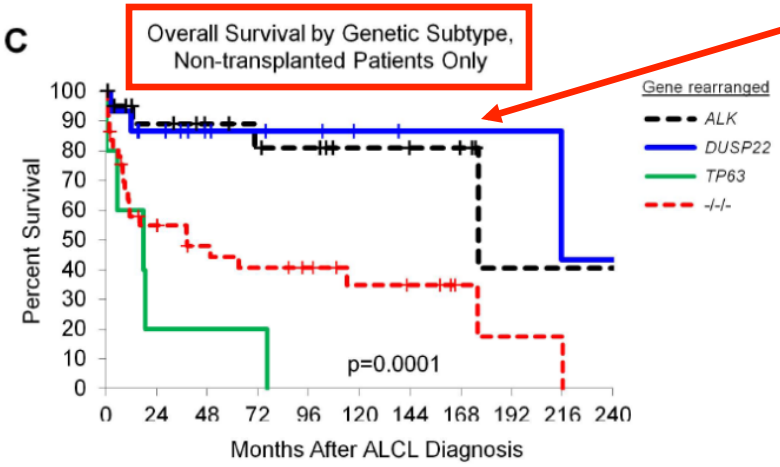
- **22 (30%) *DUSP22* rearrangement; 6 (8%) *TP63* rearrangement → seen only in ALK-neg ALCL; 45% of all ALCLs 'triple negative'**

- ***DUSP22* rearrangement ALK-ALCL cases younger (median age 53.5), classic features of ALCL, cytotoxic markers -**

Survival of ALK-neg ALCL by *DUSP22* and *Tp63* rearrangements







***DUSP22* + *5* y OS 90% including in non-transplanted cases**

-MVA adjusted for IPI, age (*DUSP22*+ HR .58, p=.50)

-*p63* + cases 5 y OS 17%

-' triple –' 5 y OS 42%

ALK-neg ALCL is clinically and genetically heterogeneous – implications in comparing studies and evaluating impact of therapy including ASCT

One size fits all treatment approach is not working

- **Empiric therapy is not working – outcomes have not changed for PTCLs**

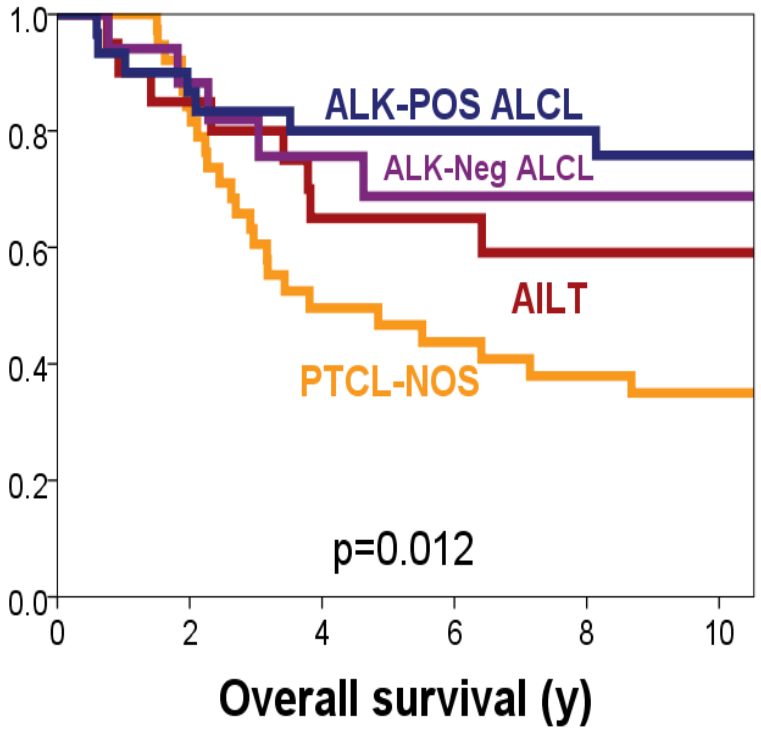
- **CHOP never works for:**
  - Hepatosplenic γδ TCL
  - Extranodal NK/T-cell lymphoma

- **CHOP sometimes works for:**
  - PTCL-NOS and AITL≈ 20-30% ? Which patients

- **CHOP often works for:**
  - ALK-pos ALCL (IPI 0-2)
  - ALK-neg ALCL (young, low risk, ?*DUSP22 +)*

- **Need to understand underlying biology and study PTCL subtypes separately (no more lumping!)**

OS of PTCL patients in CR following front-line chemotherapy



5-year OS (%)	
ALK-POS	80
ALK-NEG	69
AITL	65
PTCL-NOS	47

BCCA Lavoie ASCO 2014

ALLOGENEIC TRANSPLANTATION FOR T-CELL LYMPHOMAS: NO DIFFERENCE IN OUTCOME BETWEEN PATIENTS ALLOGRAFTED UP-FRONT AND IN FIRST CHEMOSENSITIVE RELAPSE

A. Dodero, Milan (Italy)

ALLOGENEIC OR AUTOLOGOUS TRANSPLANTATION AS FIRST-LINE THERAPY FOR YOUNGER PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA - RESULTS OF THE INTERIM ANALYSIS OF THE AATT TRIAL

N. Schmitz, Hamburg (Germany)

Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma

Javeed Iqbal, George Wright, Chao Wang, Andreas Rosenwald, Randy D. Gascoyne, Dennis D. Weisenburger, Timothy C. Greiner, Lynette Smith, Shuangping Guo, Ryan A. Wilcox, Bin Tean Teh, Soon Thye Lim, Soon Yong Tan, Lisa M. Rimsza, Elaine S. Jaffe, Elias Campo, Antonio Martinez, Jan Delabie, Rita M. Braziel, James R. Cook, Raymond R. Tubbs, German Ott, Eva Geissinger, Philippe Gaulard, Pier Paolo Piccaluga, Stefano A. Pileri, Wing Y. Au, Shigeo Nakamura, Masao Seto, Francoise Berger, Laurence de Leval, Joseph M. Connors, James Armitage, Julie Vose, Wing C. Chan and Louis M. Staudt

BLOOD, 8 MAY 2014 • VOLUME 123, NUMBER 19

- **Genes in AITL molecular classification signature: angiogenesis, vascular endothelial functioin or cell migration**

- **34 gene signatures correlated with OS**

Signature cluster	Effect of high expression	Training *P* value	Validation *P* value
P53-induced gene signature	Poor prognosis	.001	.01
Cytotoxic T-cell signature	Poor prognosis	.005	.04
Monocytic/dendritic	Poor prognosis	.011	.01
B cell (GCB cell signature)	Good prognosis	.002	.01
Miscellaneous gene signatures	Good Prognosis	.009	.07