ACUTE T CELL LEUKEMIA/LYMPHOMA N° 10620
ANAPLASTIC LARGE CELL LYMPHOMA N° 10630

Conventional treatment or New approaches

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VIENNA 2012 ESMO congress

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Disclosure slide

- ESMO policy requires that all Speakers show a Disclosure slide at the start of their presentation.
- I have no Conflicts of Interest to declare

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GROUPE D'ÉTUDE DES LYMPHOMES DE L'ADULTE

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2008 WHO Classification of PTCL

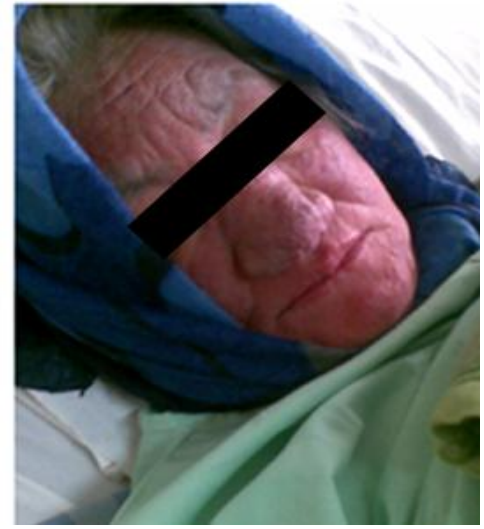
20 Distinctive Subtypes

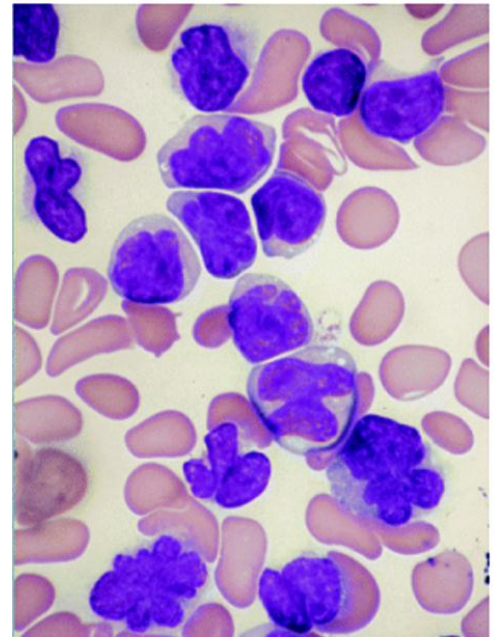
Cutaneous	Extranodal	Nodal	Leukemic
Mycosis Fungoides (MF)	NK/TCL Nasal Type	Peripheral TCL-NOS	Adult T-Cell Leukemia/ Lymphoma
Sézary Syndrome	Enteropathy-Associated TCL	Anaplastic Large Cell Lymphoma (ALK +)	T-cell Prolymphocytic Leukemia
Primary Cutaneous $CD30^+$ T-Cell Disorders	Hepatosplenic TCL	Anaplastic Large Cell Lymphoma (AL -)	T-Cell Large Granular Lymphocytic Leukemia
Primary Cutaneous ALCL	Subcutaneous Panniculitis-Like TCL	Angioimmunoblastic TCL	
Primary Cutaneous γδ TCL	Systemic EBV+ T-cell childhood lymphoprolif		
Primary Cutaneous CD8+ aggressive epidermotropic	Hydroa Vacciniforme-like		
Primary Cutaneous CD4+ small/medium			

Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008.

Adult T cell leukemia/lymphoma (ATL)

- **Aggressive proliferation of mature activated T cells**
- **Secondary to HTLV-I infection**
- **Poor prognosis due to an intrinsic resistance to chemotherapy and the associated severe immunosuppression**
- **Malignant hypercalcemia**
- **Frequent visceral involvement**





ATL SURVIVAL DATA

	Smoulder. n=45	Chronic n=152	Lymphoma n=156	Acute n=465
Alive%	77.8	55.9	27.6	19.4
Non Treat %	66.7	28.9	3.2	9.2
Med Surv	N.R.	24.3	10.2	6.2
2 Y. Surv %	77.7	52.4	21.3	16.7
4 Y. Surv %	62.8	26.9	5.7	5.0

Shimoyama et al 1992

Chemotherapy for ATL

Polychemotherapy

- 1st Generation (PR+CR=15-30%)
- VEPA (VCR, CPM, PDN, ADM),
- VEPAM (VEPA+MTX)
- 2d Generation (Sequential chemotherapies) (CR+PR=45%)
- VEPA-B (VEPA + bleo)/M-FEPA (VDS, CPM, PDN, ADM)/VEPP-B (VCR, CPM,Procarbazine, PDN, Bleo)
- RCM + Growth Factors
- CDE (continuous infusions)
- LSG15 (Yamamda et al , 2001) (in acute ATL: CR<20%, median 10.5 m, renal failure excluded)

→ 4 years Survival < 10%

Do we have new treatments?

- For smouldering and chronic ATL? Wait and watch

  Is there a place for antiviral agents and interferon?
- For acute, and lymphoma ATL?

  Allogenic transplantation: MAC or RIC

  New agents

A nationwide survey of adult T-cell leukemia/lymphoma (ATL) newly diagnosed over the last decade in Japan

Hiroo Katsuya[1], Kenji Ishitsuka[1], Atae Utsunomiya[2], Shuichi Hanada[3], Tetsuya Eto[4], Yukiyoshi Moriuchi[5], Yoshio Saburi[6], Takeharu Yamanaka[7], Junji Suzumiya[8], and Kazuo Tamura[1]

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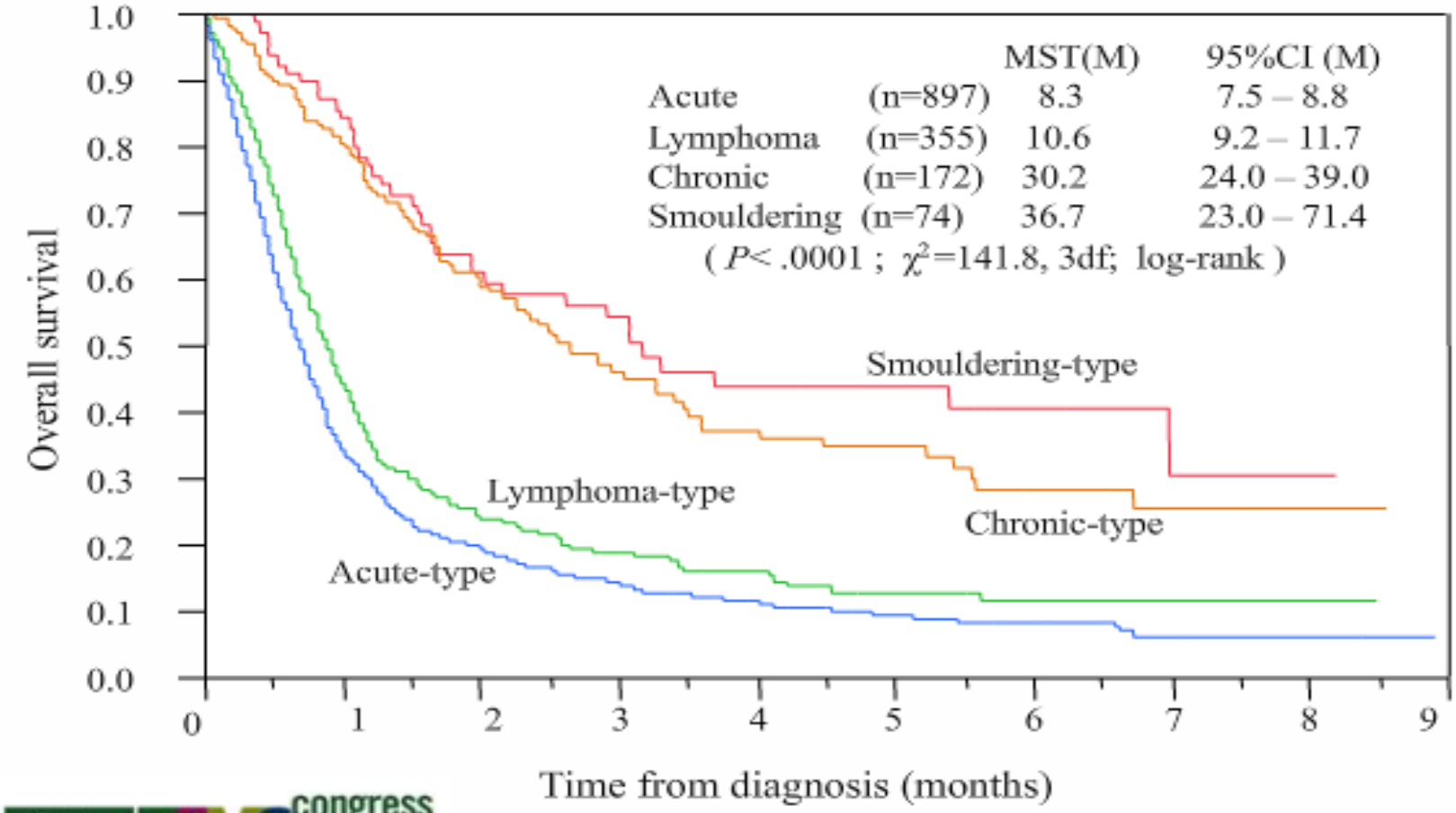
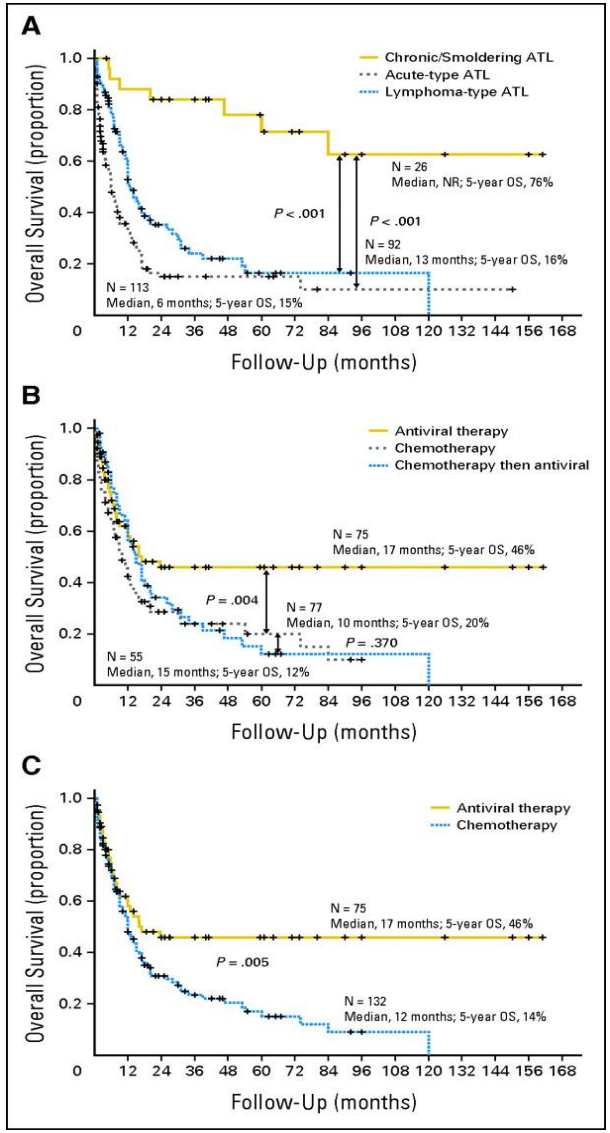
8) Cancer Center, Shimane University, Izumo, Japan

Overall survival for clinical subtypes



Kaplan and Meier overall survival (OS).



Meta-Analysis on the Use of Zidovudine and Interferon-Alfa in Adult T-Cell Leukemia/Lymphoma Showing Improved Survival in the Leukemic Subtypes

Effect of first line antiviral therapy: all patients

Bazarbachi A et al. JCO 2010;28:4177-4183

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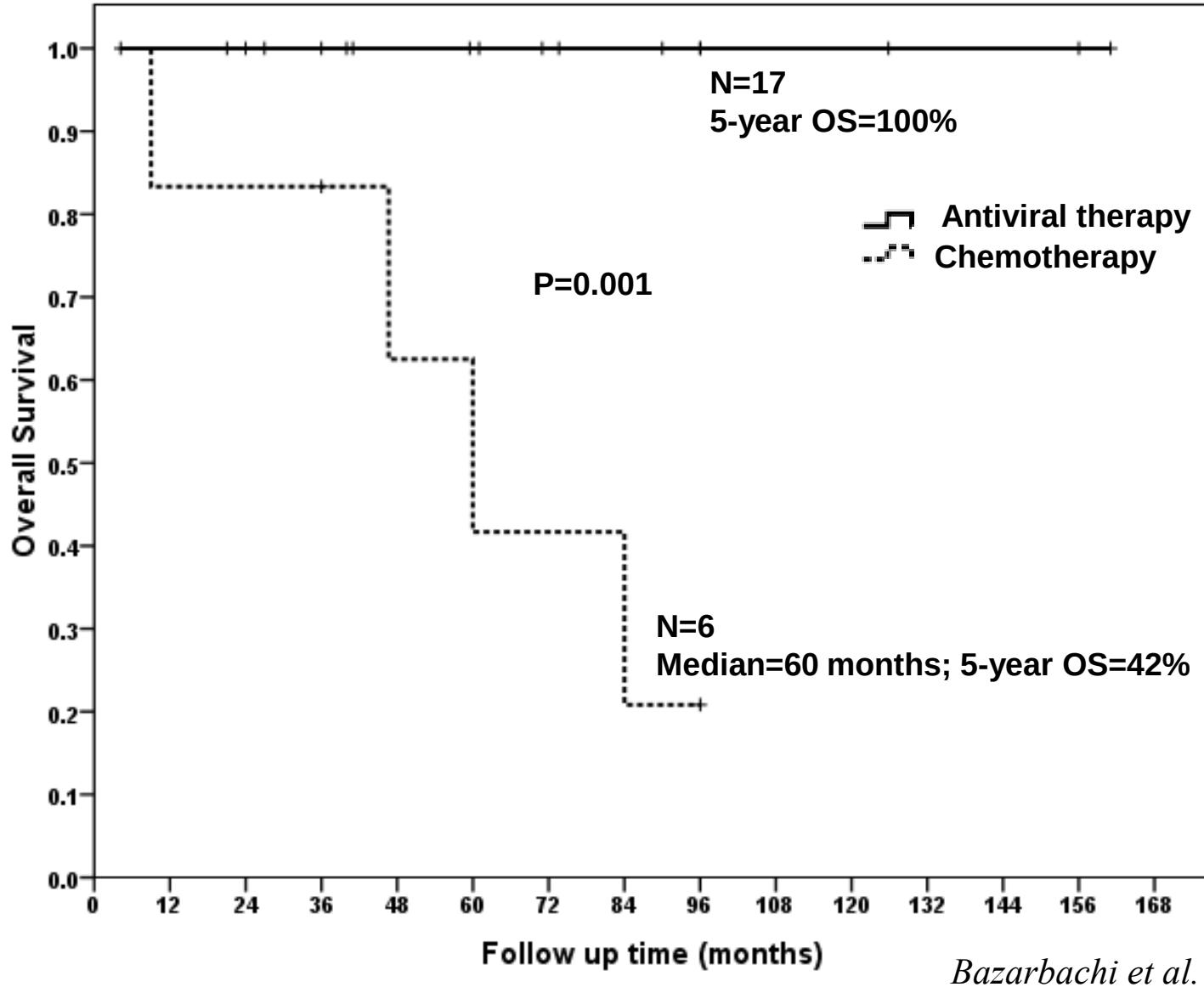
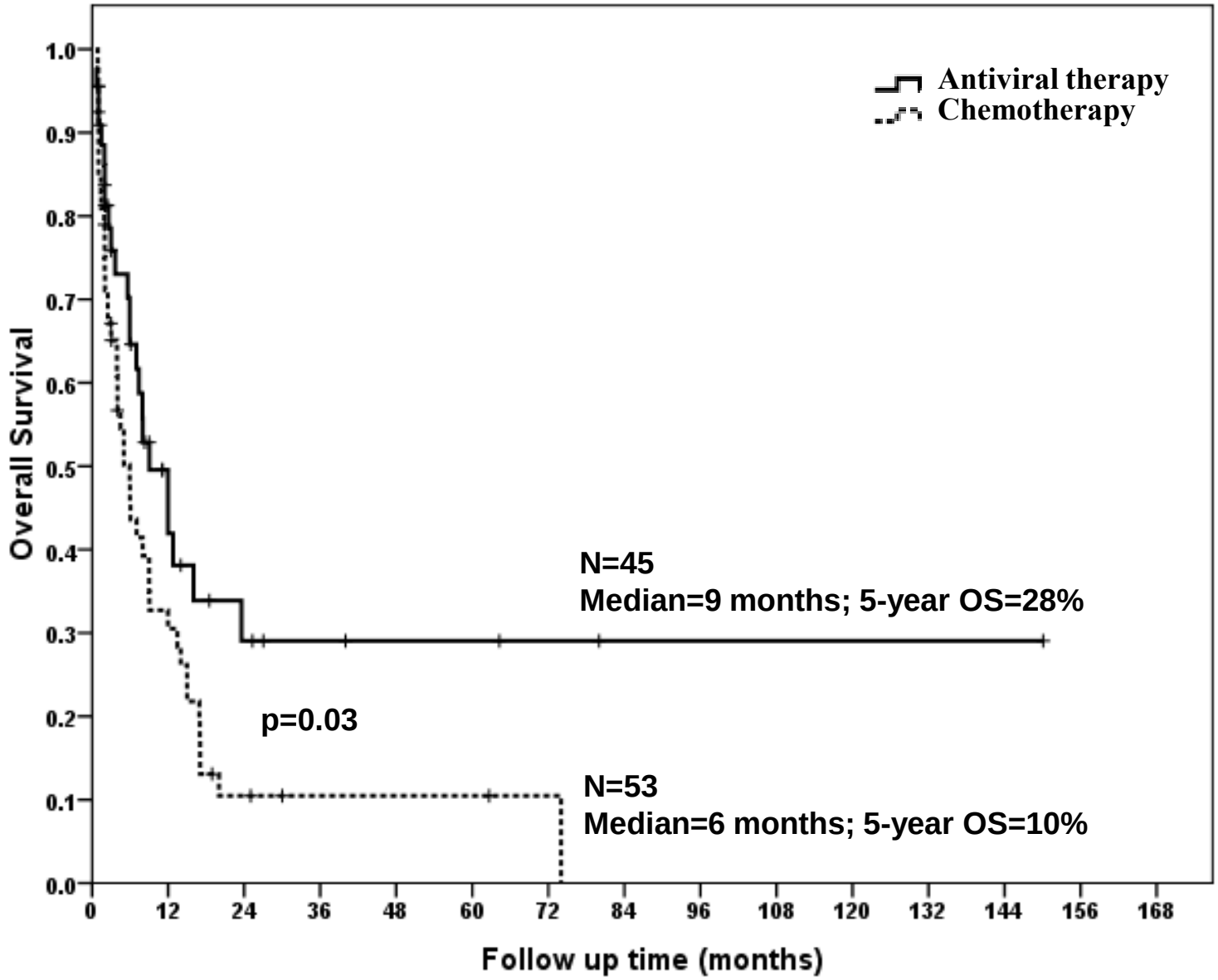
First line antiviral therapy resulted in 100% long term survival in chronic/smouldering ATL



Bazarbachi et al. J. Clin. Oncol. 2010

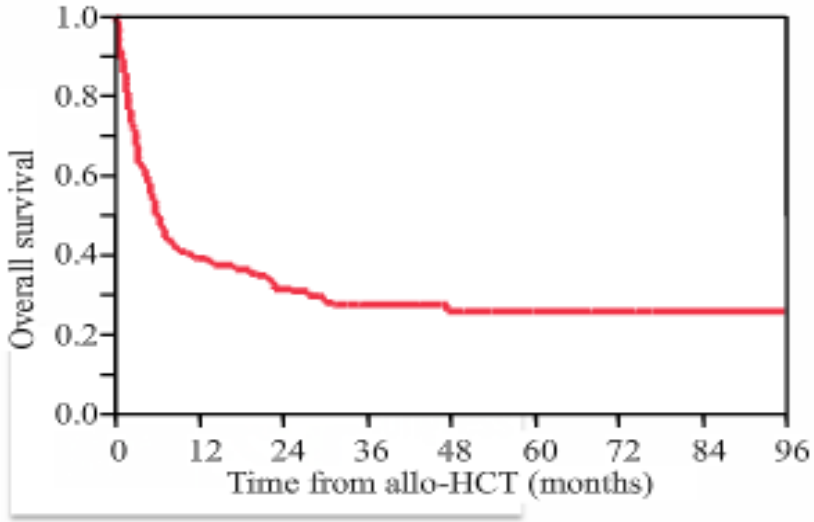
Antiviral therapy improves OS in acute ATL



Bazarbachi et al. J. Clin. Oncol. 2010

Allo-HCT 227 pts

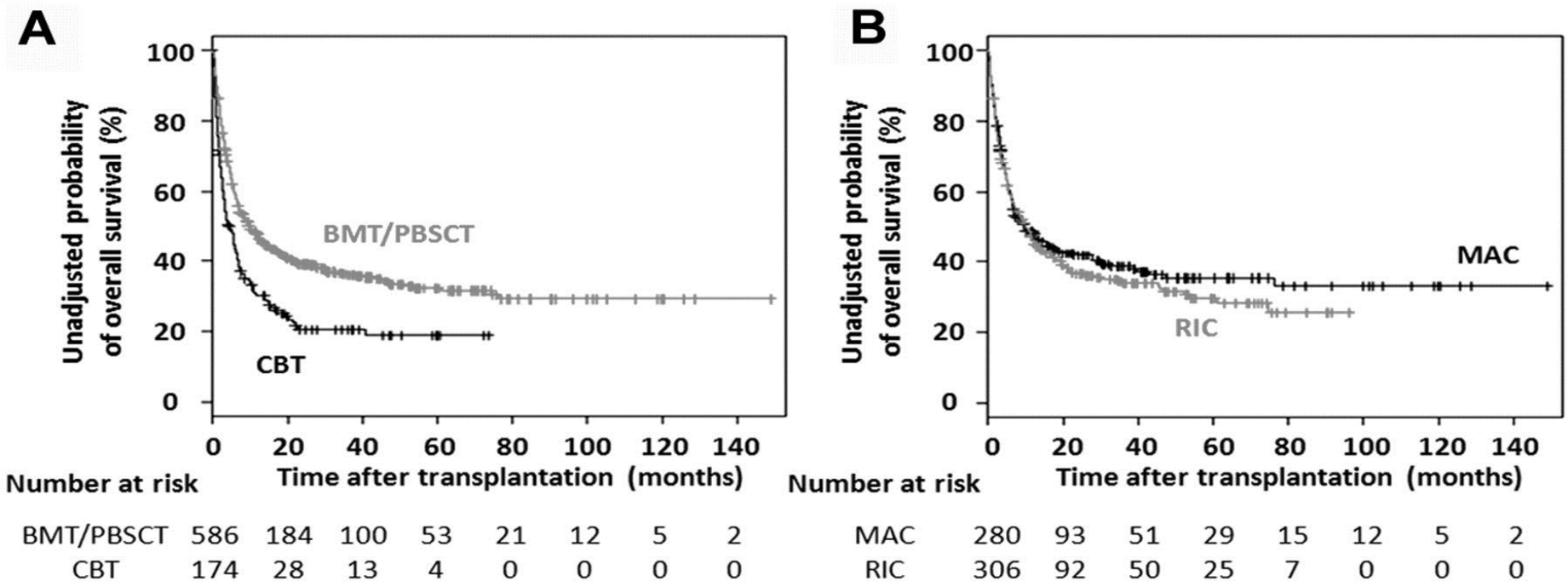
- Median age of patients treated with allo-HCT was 52 years.
- 33% of patients were received allo-HCT in patients with less than 65 years in acute- and lymphoma-type ATL.
- MST and 5 years-OS were 6.2 months and 26.0 %.



	n	%
Donor		
Unrelated	116	51.1
Sibling	103	45.4
Uncertain	8	3.5
Source of stem cells		
Bone marrow	110	48.5
Peripheral blood	72	31.7
Cord blood	37	16.3
Uncertain	8	3.5
Disease status		
First remission	106	46.7
First refractory	58	25.6
First relapse	37	16.3
Others	18	7.9
Uncertain	8	3.5

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

OS of ATL patients receiving allogeneic HSCT. (A) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT, PBSCT, or unrelated CBT. (B) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT or PBSCT with MAC or RIC.



Ishida T et al. Blood 2012;120:1734-1741

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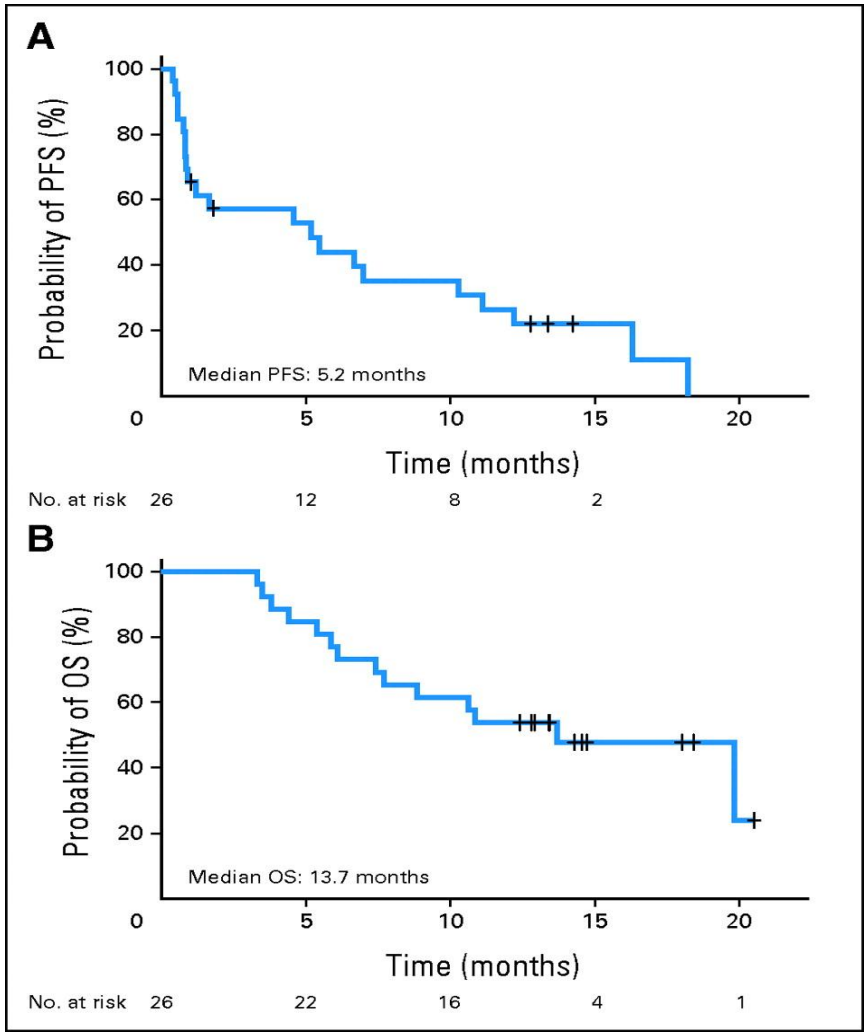
Kaplan-Meier curves of estimated (A) progression-free survival (PFS; median, 5.2 months) and (B) overall survival (OS; median, 13.7 months).



Defucosylated Anti-CCR4 Monoclonal Antibody (KW-0761) for Relapsed Adult T-Cell Leukemia-Lymphoma: A Multicenter Phase II Study

anti chemokine receptor 4
26 patients evaluable
Response rate 50%
8 complete response 31%

Ishida T et al. JCO 2012;30:837-842

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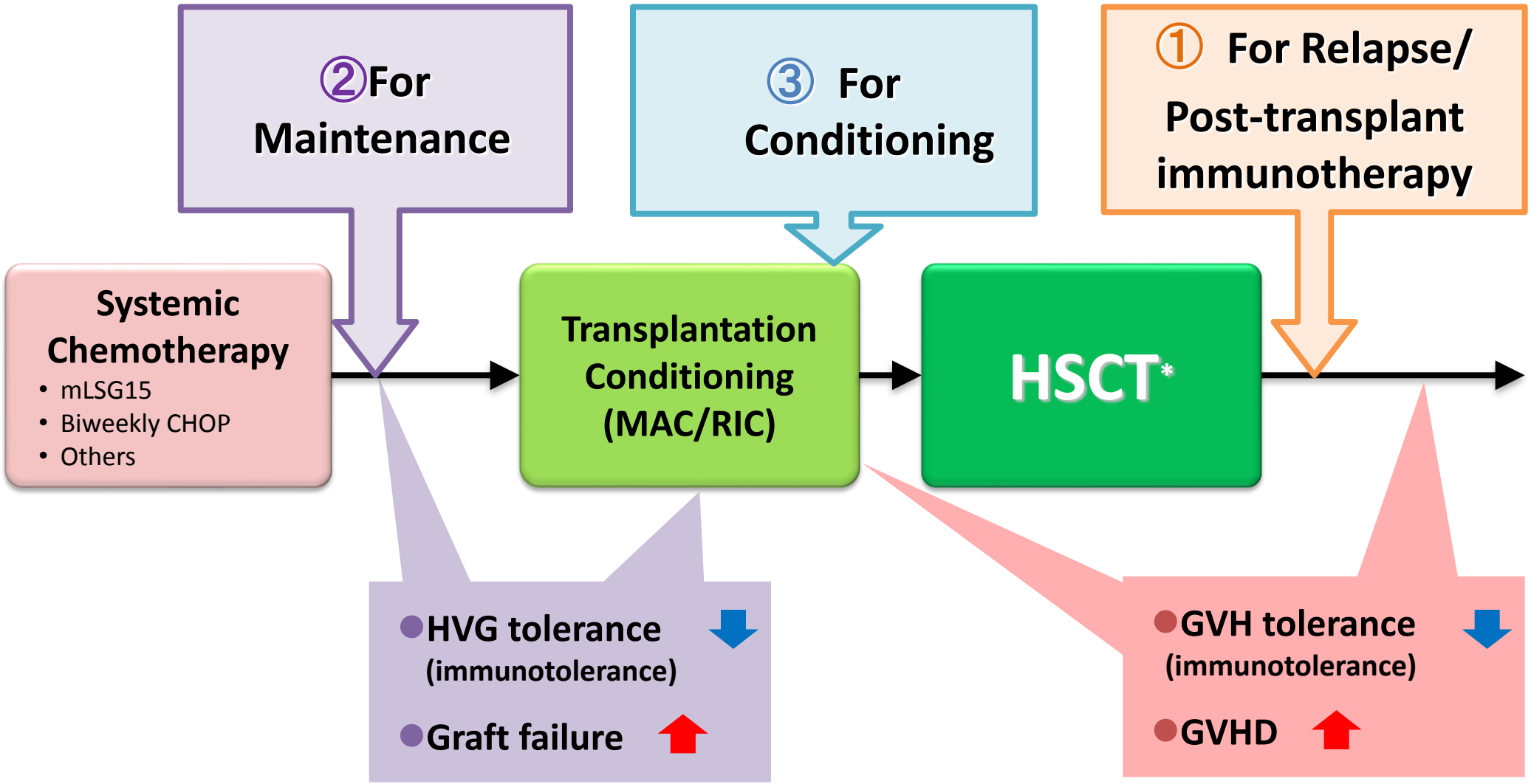
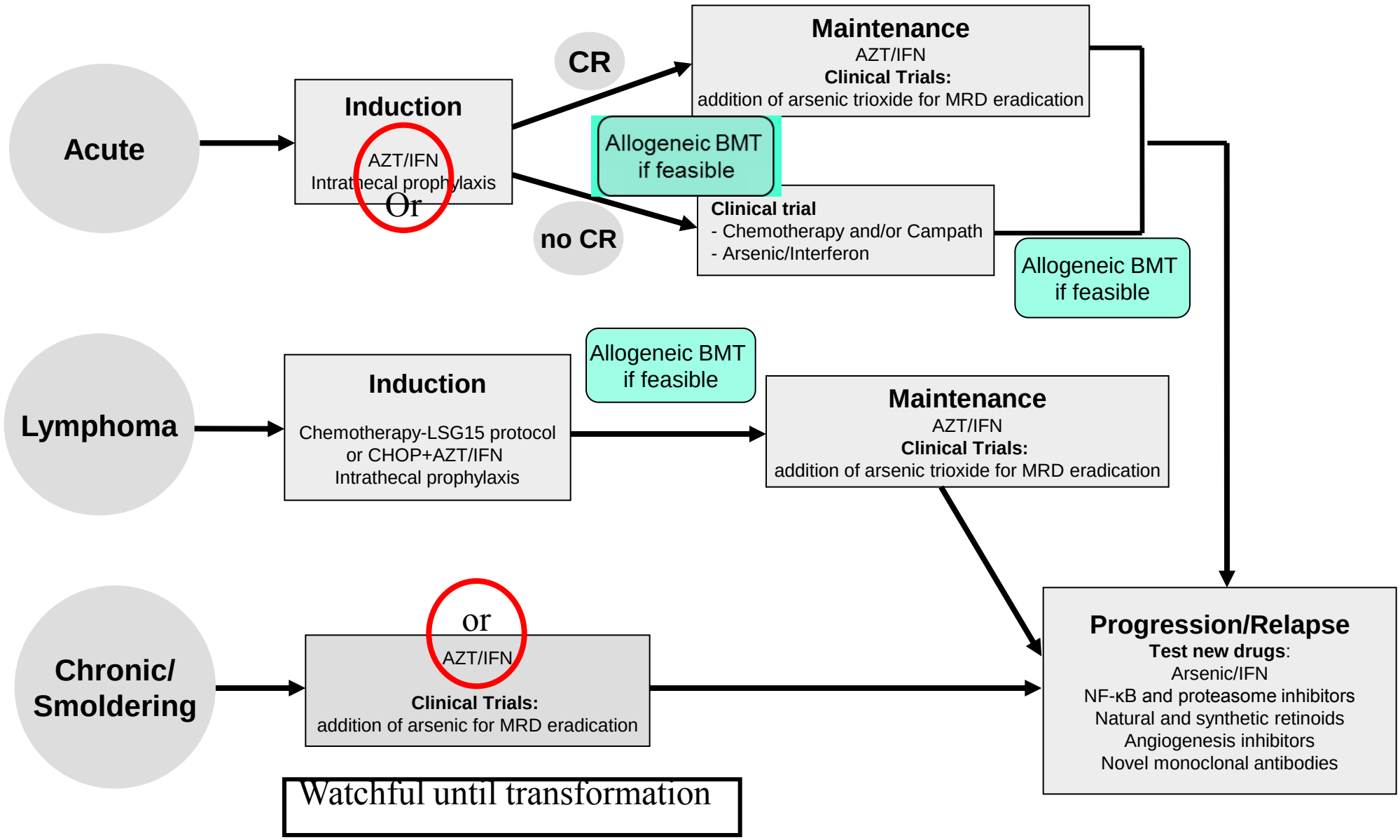
Possible Use of Mogamulizumab in allo-HSCT for ATL Pts



By Courtesy of Dr.Ogura

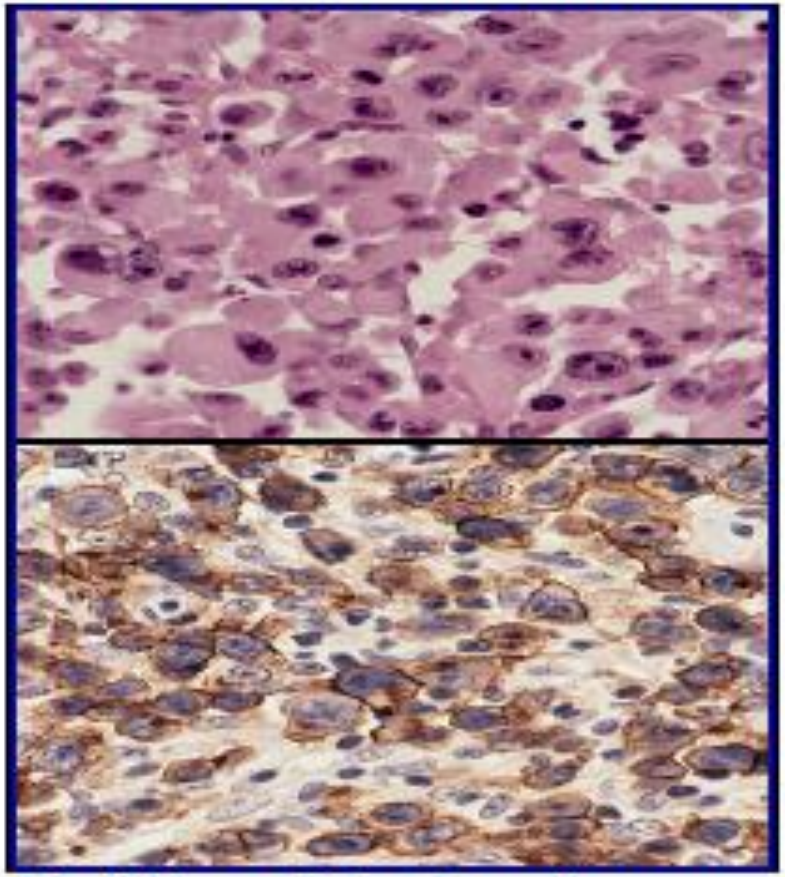
*: HSCT: Hematopoietic Stem Cell Transplantation



Bazarbachi et al. How I treat ATL **Blood 2011;118:1736-1745**

ALCL: Clinical Characteristics

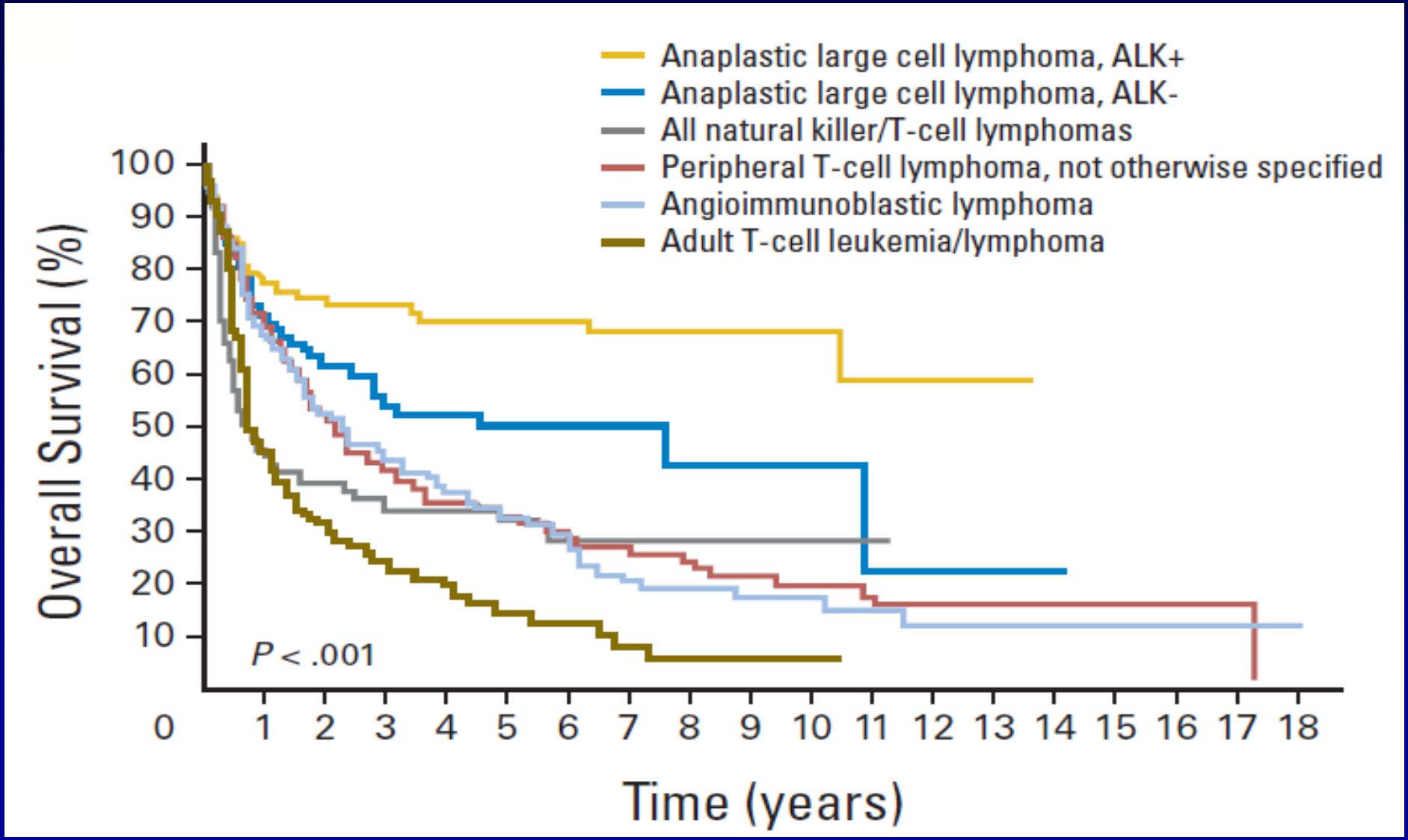
Uniform expression of CD30



Large malignant cells with abundant cytoplasm and pleomorphic, often **Horse-shoe** shaped nuclei

- 3% of adult, 10-20% of childhood NHL
- ~70% present with advanced stage
- Lymphadenopathy and B symptoms common
- Extranodal involvement
  - Skin (21%), bone (17%), lung (11%), marrow (10%), liver (8%)
  - Rare in gut and CNS
- TCR (γ/δ) gene rearrangements 90%
- Frequently t (2;5) and ALK positive
- *WHO 2008 classification: 2 clinical entities, ALK+ and ALK-, with distinct molecular signature*

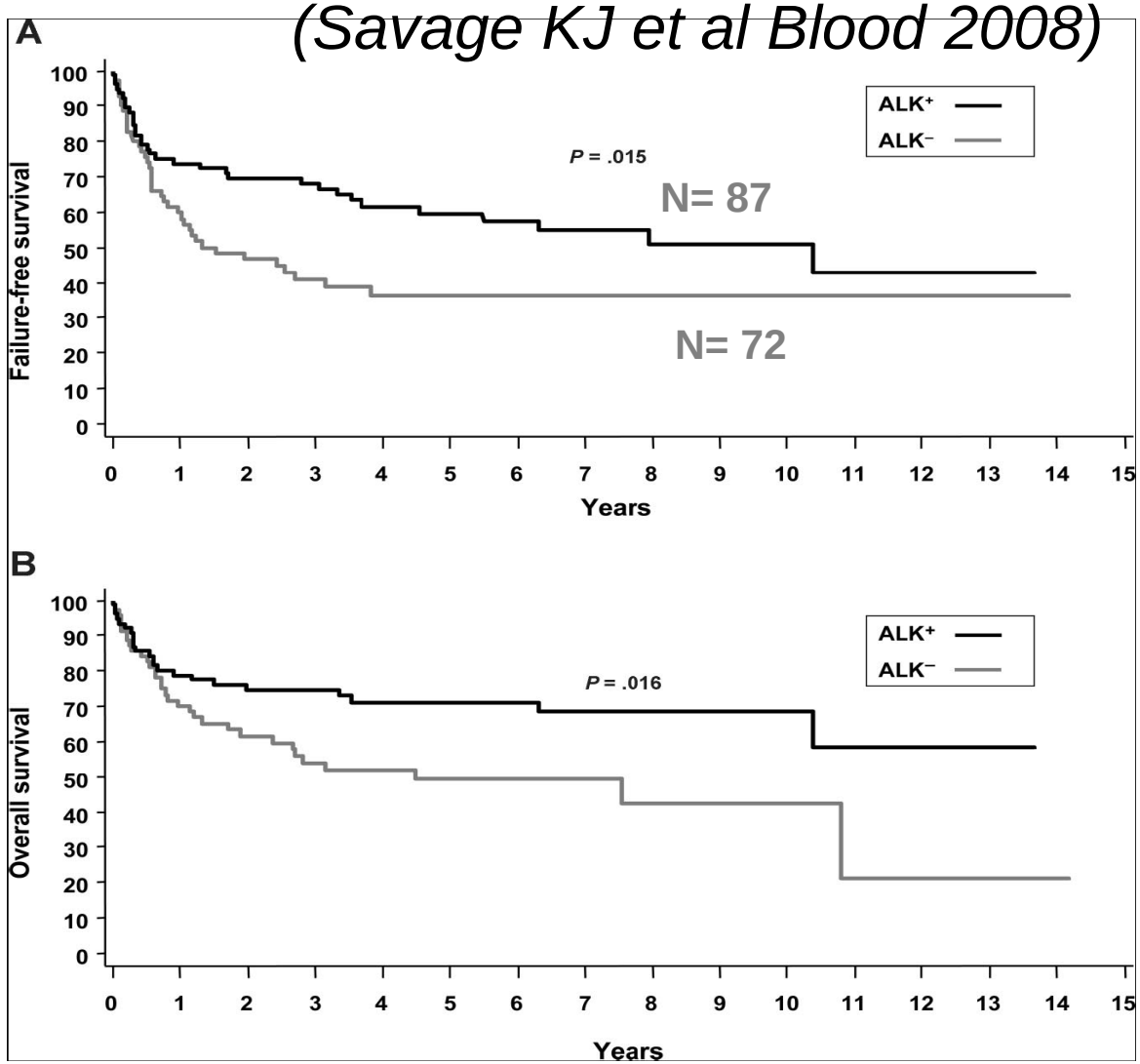
Survival Is Different Within Subtypes of T-Cell Lymphoma



Reproduced with permission from International T-cell Lymphoma Project. *J Clin Oncol.* 2008. 26; 25: 4124-4130.

Anaplastic large cell lymphoma: ALK positive versus ALK negative

(Savage KJ et al Blood 2008)



International peripheral T cell and NK/T cell lymphoma study

Anaplastic ALK- and PTCL-NOS
Savage KJ Blood 2008: 5496-5504

PTCL-NOS: n=331 : 31% CD30+,only 4,5% >80% CD30+

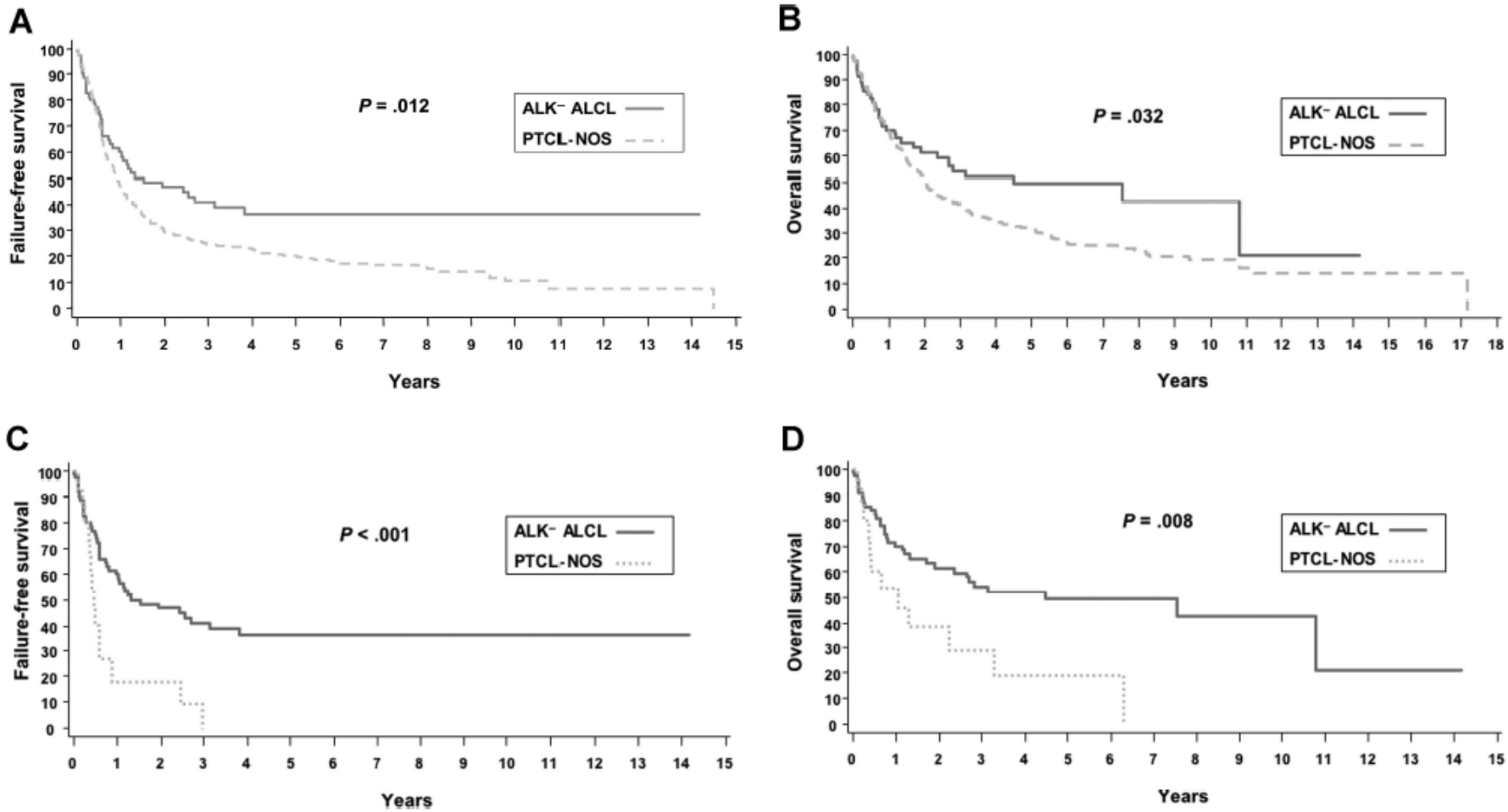


Figure 3. Survival of ALK⁻ ALCL and PTCL-NOS. (A) FFS of ALK⁻ ALCL and PTCL-NOS. (B) OS of ALK⁻ ALCL and PTCL-NOS. (C) FFS of ALK⁻ ALCL and PTCL-NOS (CD30⁺ ≥ 80% cells). (D) OS of ALK⁻ ALCL and PTCL-NOS (CD30⁺ ≥ 80% cells).

What are the Long Term Outcome and the Prognostic Factors in 138 Adults with Systemic Anaplastic Large-Cell Lymphoma?

Characteristic	ALK+	ALK-	*p*
n=138	64 (46%)	74 (54%)	
Age			
Median (y)	31.5	56	< .0001
Less than 60 y	92 %	64 %	< .0001
Less than 40 y	66 %	23 %	< .0001
B symptoms	52 %	55 %	.778
Performance status			.020
0 or 1	84 %	67 %	
More than 1	16 %	33 %	
Ann Arbor stage			.191
I or II	44 %	33 %	
III or IV	56 %	67 %	
No. of extranodal sites			.405
0 or 1	77 %	70 %	
More than 1	23 %	30 %	
IPI score			.030
0,1	55 %	39 %	
2	22 %	13 %	
3	18 %	27 %	
4,5	5 %	21 %	
Elevated LDH	46 %	53 %	.401
β2 microglobulin > 3 mg/L	12 %	33 %	.017

David Sibon, et al Journal of clinical oncology in press 2012

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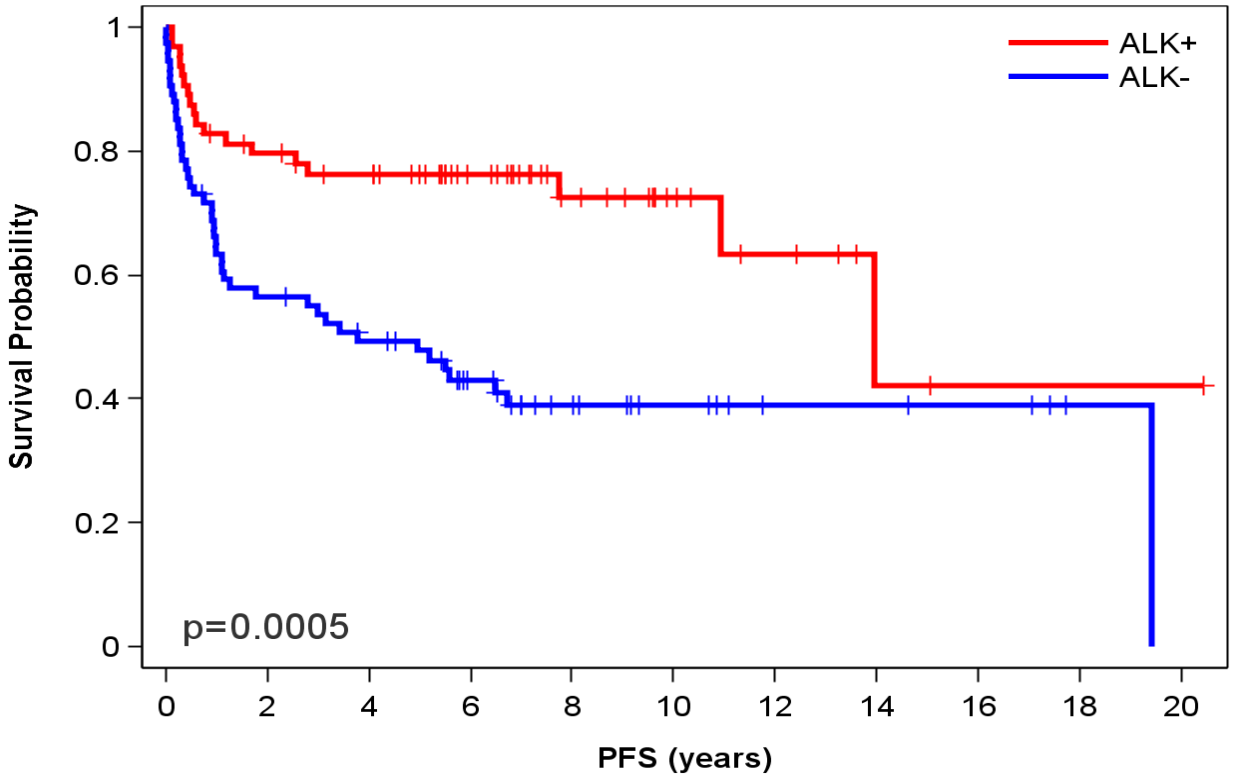
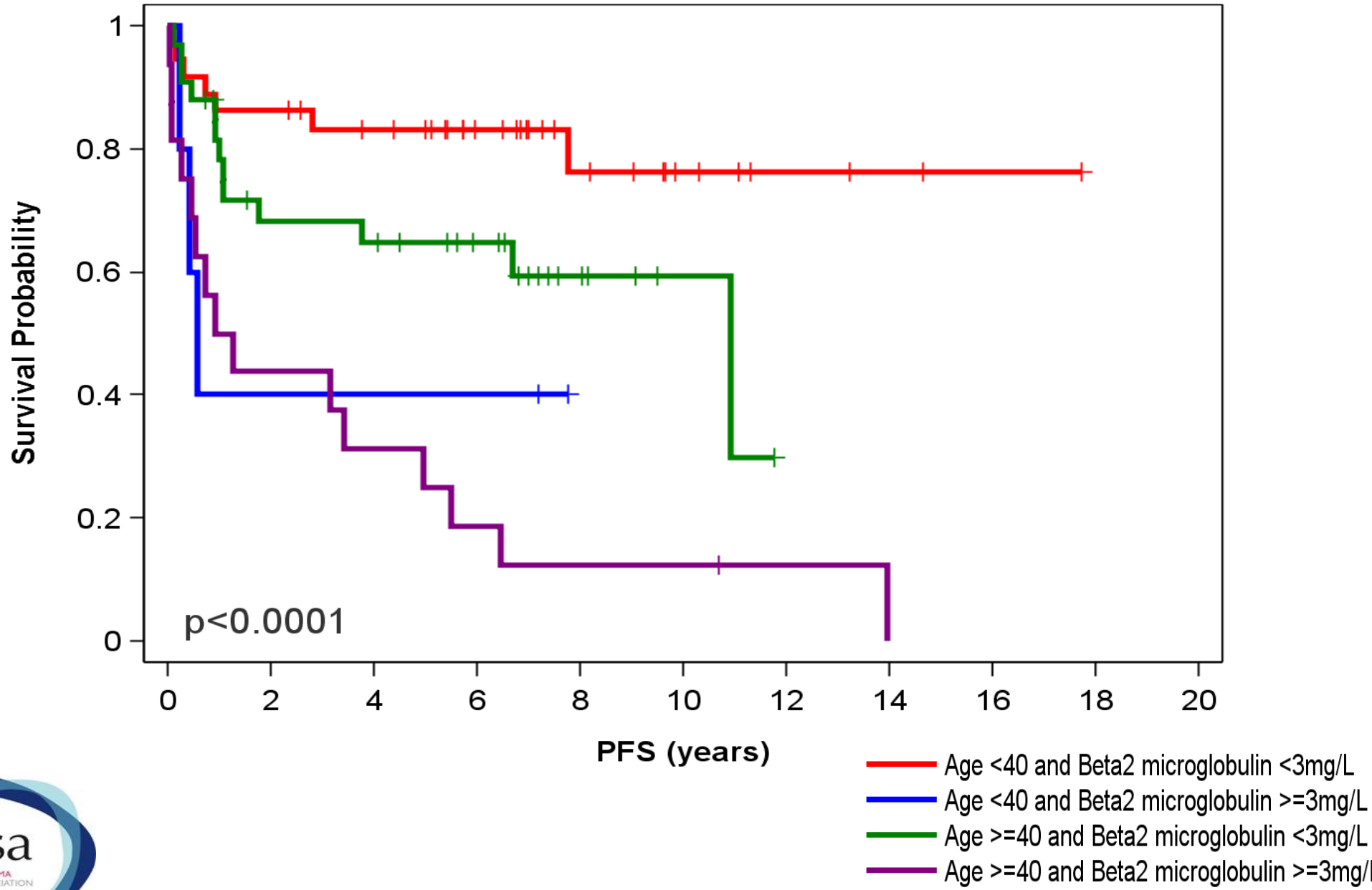
Prognostic impact of ALK on PFS



	ALK+	ALK-	*p*
8-y PFS	72%	39%	.0005



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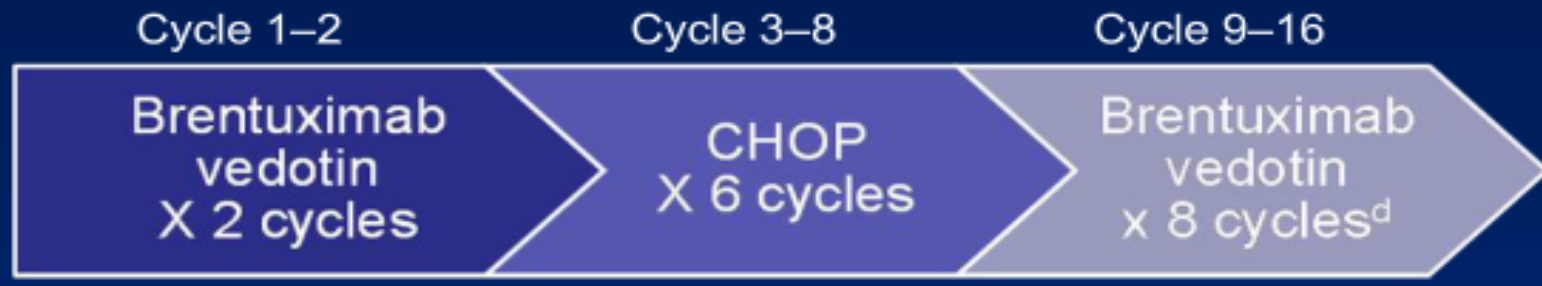
Phase 1, Multicenter, Open-Label Study of Brentuximab Vedotin as Frontline Treatment[a]

- Arm 1 of a 3-arm study[b]
  - Brentuximab vedotin (1.8 mg/kg) in sequence with CHOP[c]



- Arm 1 objectives
  - Primary: Safety and tolerability
  - Secondary: Investigator assessment of response (per Cheson 2007)

a Data are preliminary
b Arms 2 and 3 investigated combination therapy with brentuximab vedotin and CHP (CHOP without vincristine)
c Each treatment cycle = 3 weeks
d Patients who achieve a PR or CR after completion of induction therapy (end of Cycle 8) are eligible to continue brentuximab vedotin

Phase 1 Brentuximab vedotin CHOP brentuximab

Demographics and Baseline Characteristics

	N=13
Age[a]	62 (23–81)
Gender	9 M / 4 F
ECOG status, n	
0–1	11
2	2
ALK status[b], n	3 positive/10 negative
Disease stage[c], n	
I/II	5
III/IV	7
IPI score, n	
0–1	5
2–3	5
4–5	3

a Median (range)
b ALK-positive patients must have IPI score ≥2
c Disease stage for 1 patient is missing

Response to first-line treatment

	ALK+	ALK-
CR	77%	57%
CRu	9%	11%
PR	3%	8%
SD	2%	1%
PD	9%	8%
Death	0%	15%

	ALK+	ALK-	*p*
ORR	89%	76%	.04

Phase 1 Brentuximab vedotin CHOP brentuximab

	ORR	CR	
Alk-/+	100%	38% 67%	2cycl End Tt

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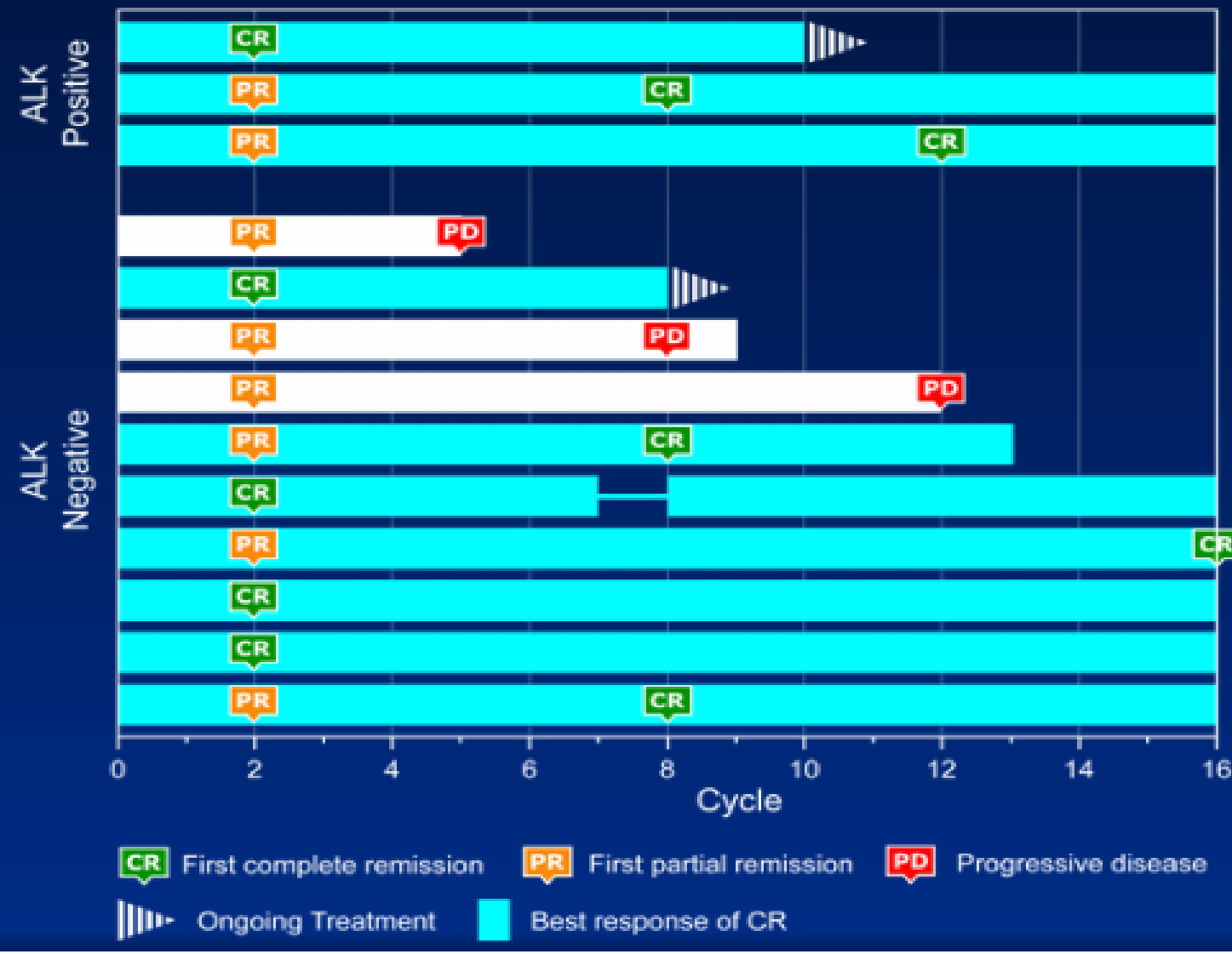
Initial Responses by Cycle

NO PFS AVAILABLE

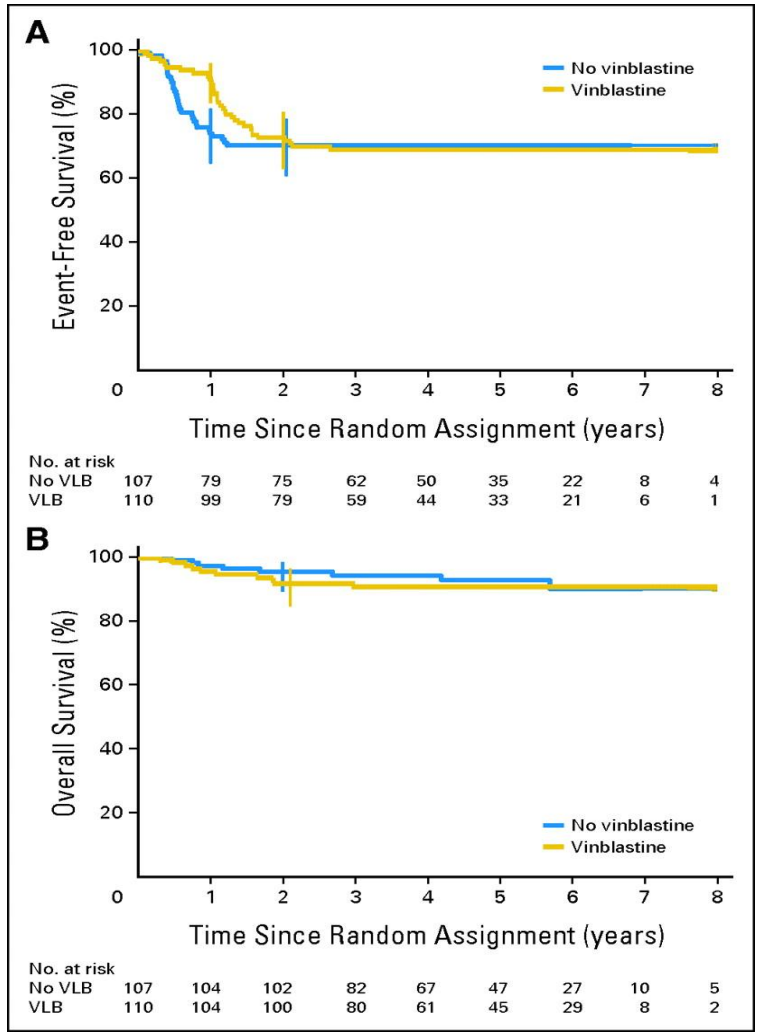


Brentuximab Vedotin (SGN-35) in Relapsed/Refractory ALCL

ALCL	N=58
ALK-negative	72%
Prior chemotherapy regimens*	2 (1-6)
Prior ASCT	26%
Objective response rate	86% (75, 94)
Median duration of OR	12.6 mo (5.7, –)
CR rate	57% (43, 70)
Median DOR patients w/ CR	13.2 mo (10.8, –)
Median PFS	13.3 mo (6.9, –)
Median OS	Not reached

Shustov A., et.al. *Ann.Onc.* 2011; 22(4): Abstr. 125

(A) Event-free survival (EFS) by treatment group.



Vinblastine in Children and Adolescents With High-Risk Anaplastic Large-Cell Lymphoma: Results of the Randomized ALCL99-Vinblastine Trial

Do we need maintenance therapy?

Le Deley M et al. JCO 2010;28:3987-3993

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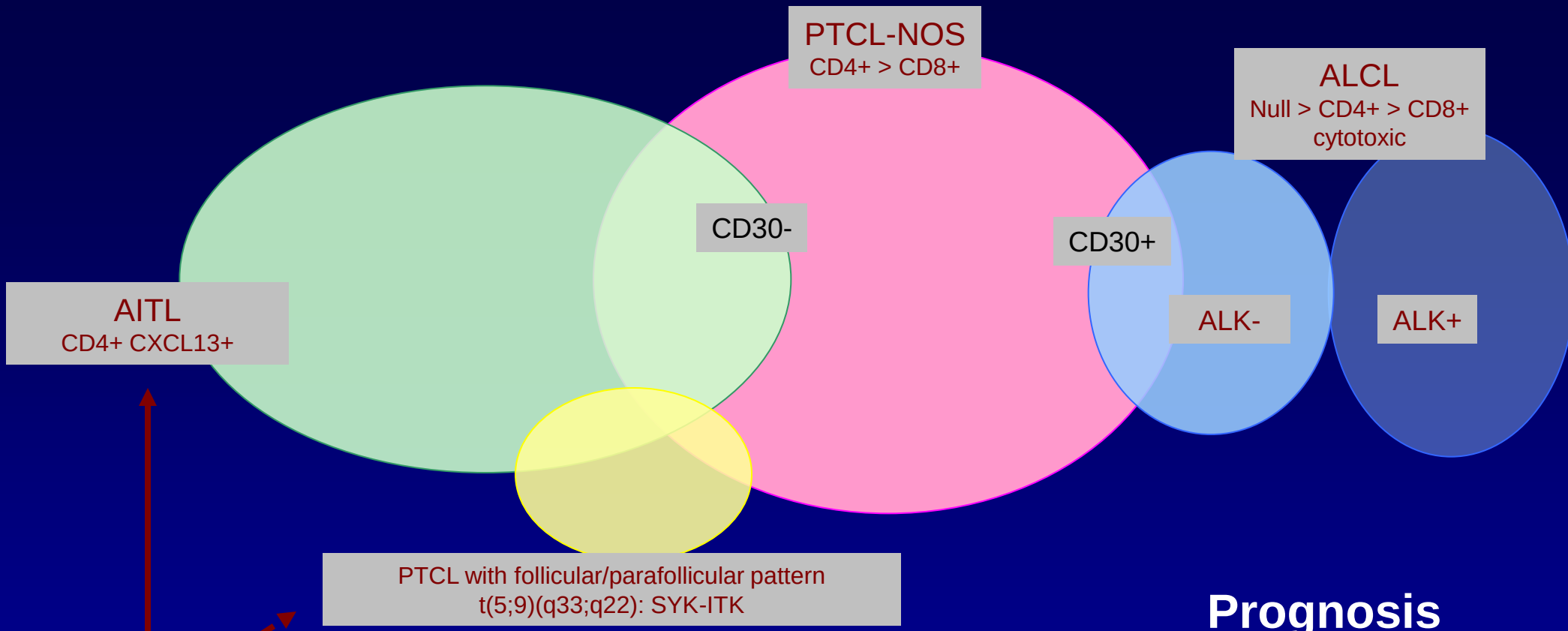
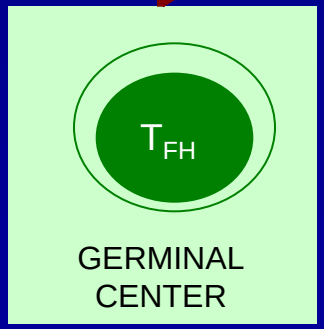
Conclusion

- Not all the ALK+ ALCL have a good prognosis
- Not all the ALK- ALCL have a poor prognosis
- Prominent impact of age and β2 microglobulin in ALK+ and ALK- ALCL
- These two factors could be useful for improving the prognostic assessment of patients with ALCL
- It is important to take in account prognostic parameters in stratifying patients in prospective RANDOMIZED trials for evaluating : transplantation or new drugs





Biology will help emerging treatment options

	Prognosis
Angioimmunoblastic	**Poor**
Peripheral, nos	**Poor**
ALCL, ALK –	**Poor**
ALCL, ALK +	**Favorable**

L de Leval and P Gaulard. *Hematology,* 2008.