Raising the Bar: Striving to Improve Initial Therapy of PTCL

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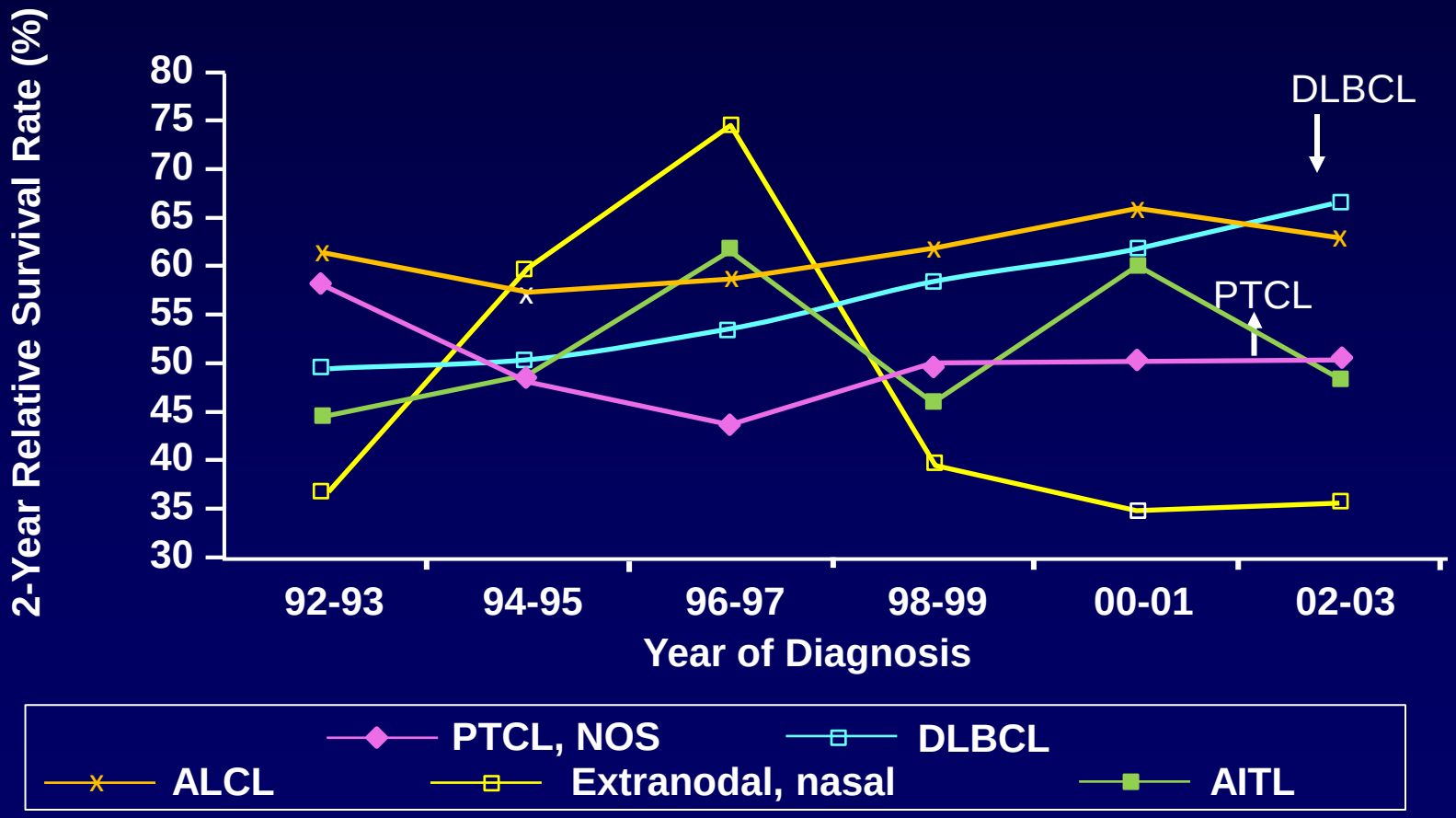
No Improvement in Outcome in A Decade of Patient Treatment 1992-2003

2-Year Relative Survival



Abouyabis AN, et al. *Leuk Lymphoma*. 2008;49(11):2099-2107.

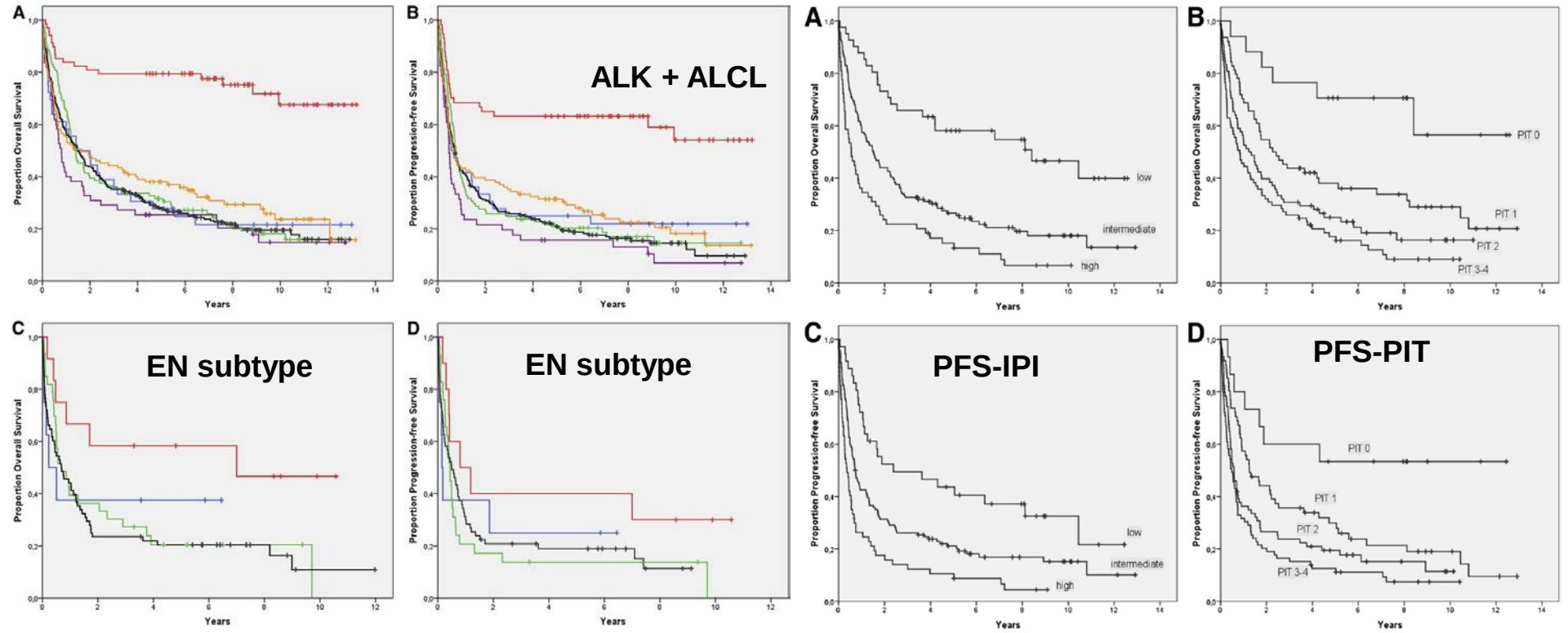
Outcomes of PTCL in Modern Era Swedish Lymphoma Registry: Patients Treatment 2000-2009

Overall Survival (OS) Nodal Subtype

Progression-Free Survival (PFS) Nodal Subtype

OS International Prognostic Index (IPI)

OS Prognostic Index for PTCL-U (PIT)

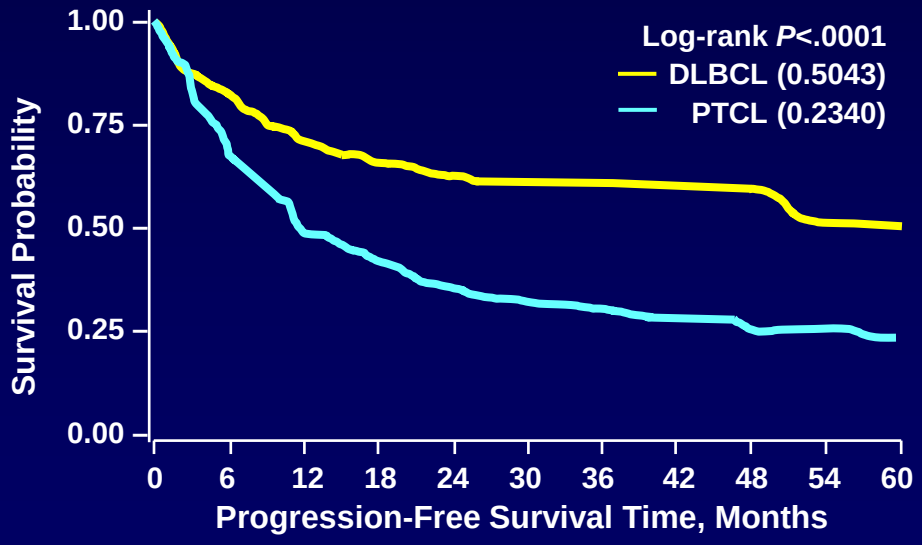


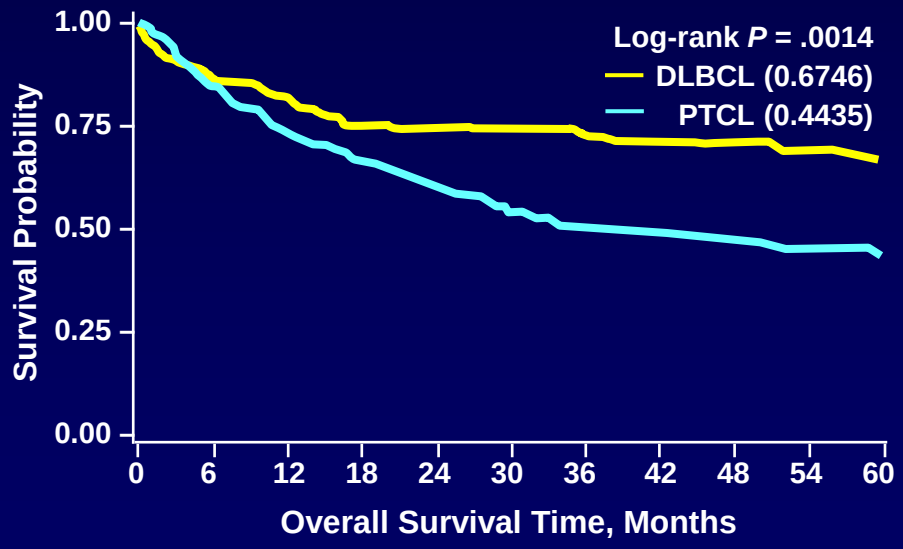
Ellin F, et al. *Blood* 2014;124(10):1570-1577.

PFS and OS of PTCL Compared to Matched Diffuse Large B-Cell Lymphoma (DLBCL) Patients in the Modern Era (US study)

Patient treatment 2000-2011

Achieving a complete response (CR) to front-line therapy significant on multivariate analyses





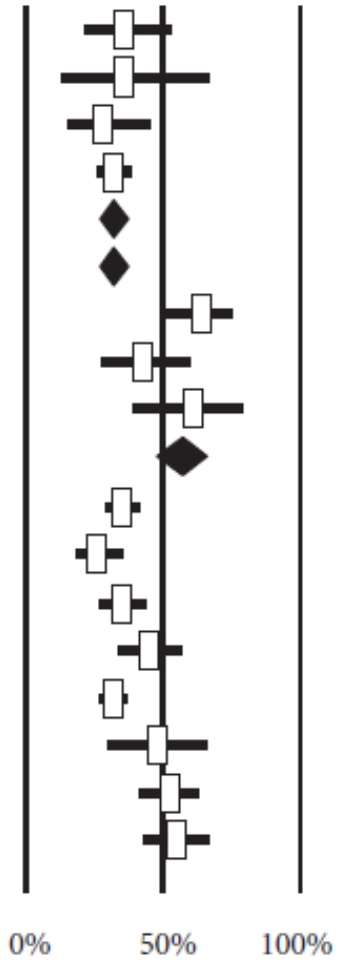
Abramson JS, et al. *Ann Oncol*. 2014;25(11):2211-2217.

Reasons for Poor Outcomes

- Diagnosis difficult
  - Needs expert pathology
- Treated like B-cell NHL
  - CHOP or anthracycline-based therapy
  - Multidrug resistance (MDR)
  - Doxorubicin and vincristine are substrates
- Outcome of patients who fail front-line therapy is poor
- Not one disease
  - Molecular studies show distinct biological entities

Front-Line Anthracycline-Based Therapy for PTCL Meta-Analysis: OS In Older Series

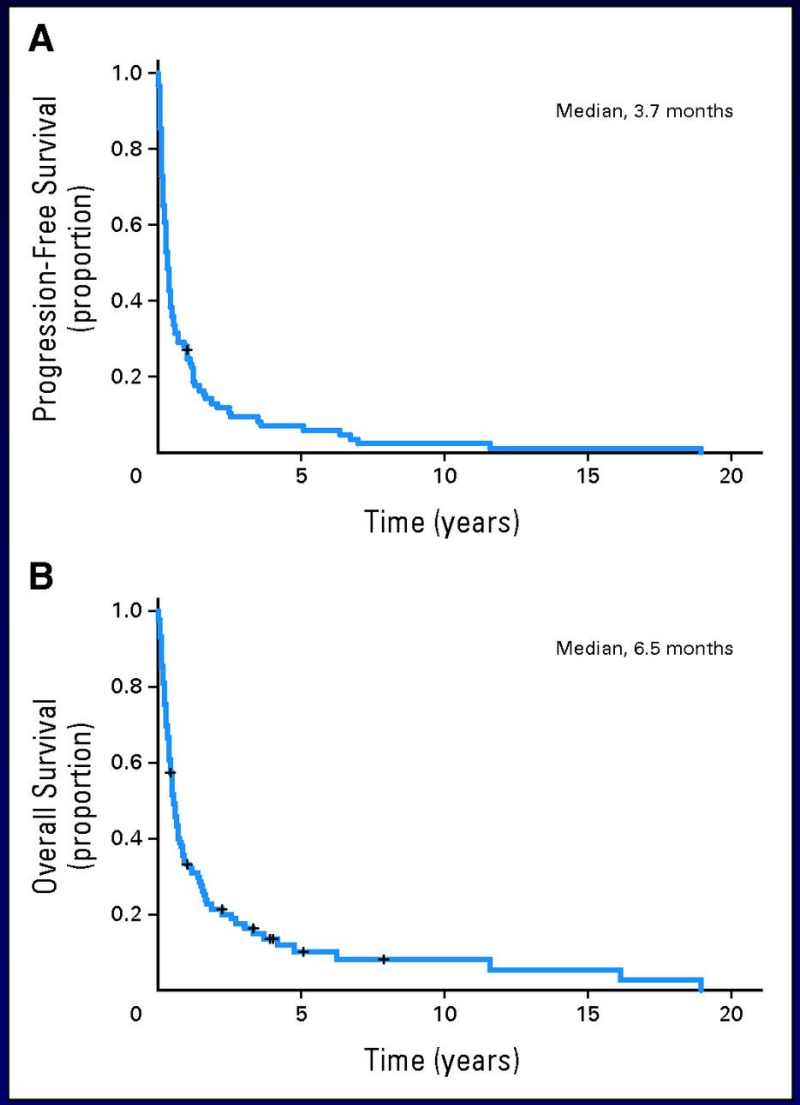
PTCL subgroup	Study, year		5-year OS rate	95% CI		5-year OS rate and 95% CI
AITL	Pautier et al., 1999 [24]		0.360	0.217	0.534	
	Savage et al., 2004 [32]		0.360	0.134	0.672	
	Sonnen et al., 2005 [36]		0.280	0.155	0.451	
	Vose et al., 2008 [1]		0.320	0.264	0.381	
	AITL summary estimate	Fixed	0.321	0.272	0.375	
		Random	0.321	0.272	0.375	
ALCL	Gisselbrecht et al., 1998 [4]		0.640	0.512	0.751	
	Savage et al., 2004 [32]		0.430	0.275	0.600	
	Sonnen et al., 2005 [36]		0.610	0.394	0.790	
	ALCL summary estimate	Fixed	0.573	0.479	0.662	
Non-ALCL PTCL	Gisselbrecht et al., 1998 [4]		0.350	0.291	0.414	
	Rudiger et al., 2002 [29]		0.260	0.182	0.357	
PTCL-NOS	Savage et al., 2004 [32]		0.350	0.269	0.440	
	Sonnen et al., 2005 [36]		0.450	0.338	0.567	
	Vose et al., 2008 [1]		0.320	0.273	0.371	
PTCL combined	Karakas et al., 1996 [13]		0.480	0.303	0.663	
	Kim et al., 2002 [27]		0.526	0.415	0.633	
	Reiser et al., 2002 [28]		0.550	0.429	0.665	

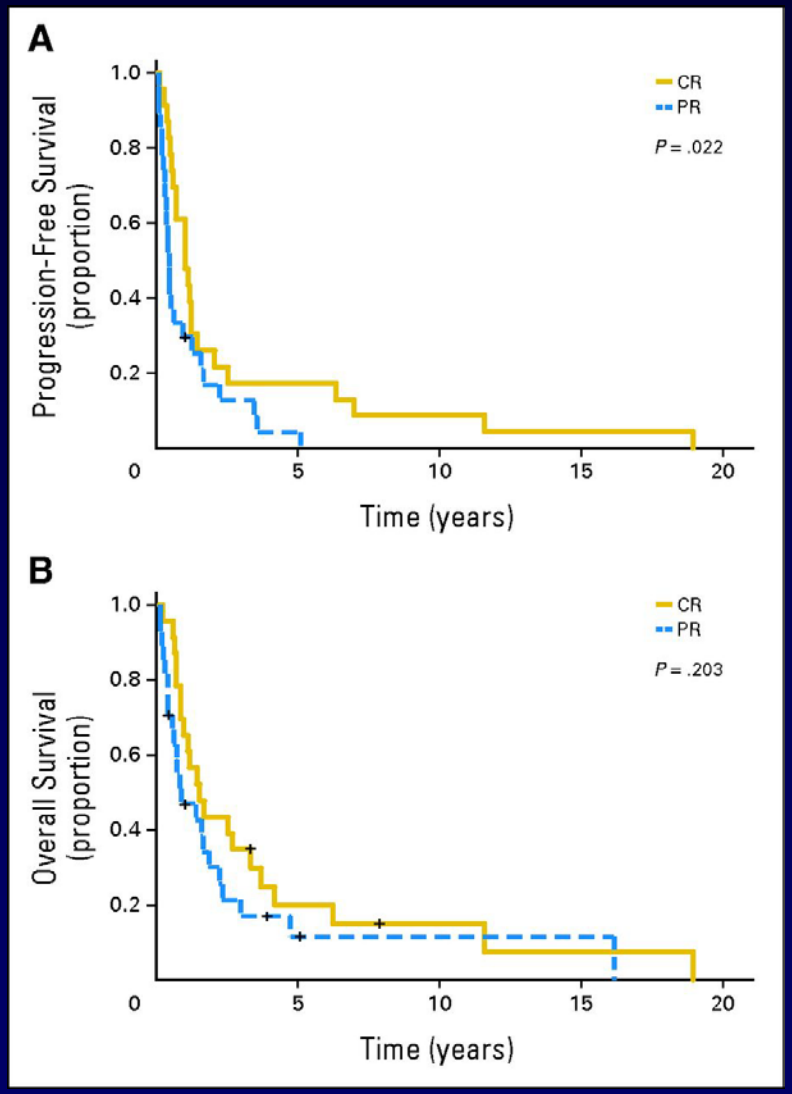


ALCL excluded: Estimated 5-year OS ~ 37 % (95% CI 35%, 39%)

Abouyabis AN, et al. *ISRN Hematol.* 2011;2011:623924.

Poor Outcome (Second PFS and OS) After Relapse or Progression of PTCL





Mak V, et al. *J Clin Oncol*. 2013;31(16):1970-1976.

Raising the Bar: Striving to Improve Initial Therapy of PTCL

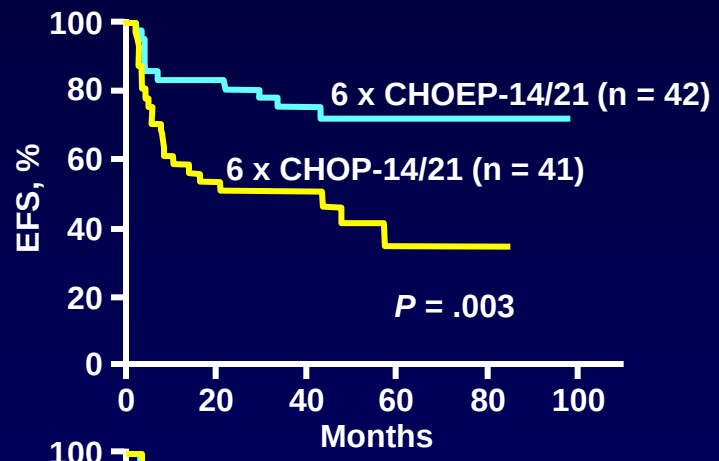
- Adding etoposide to anthracycline-based regimen
- Adding rationally targeted drugs to CHOP
- Consideration of transplant as consolidation
- Alternative to CHOP (nonanthracycline-based regimen)
- Adding novel agents to front-line setting

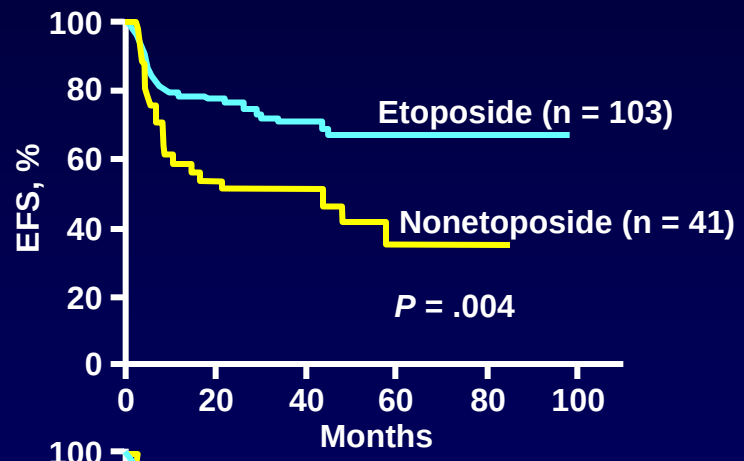
Raising the Bar: Striving to Improve Initial Therapy of PTCL

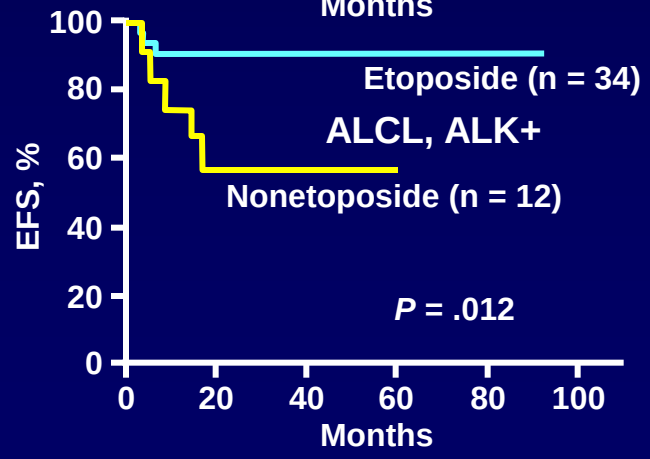
- **Adding etoposide to anthracycline-based regimen**

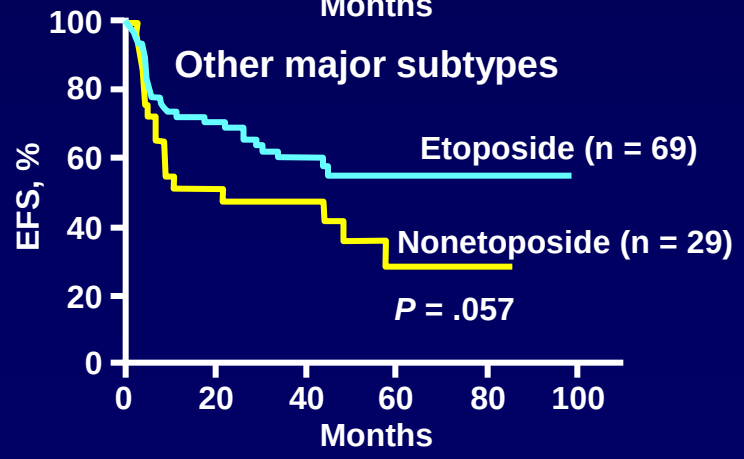
Event-Free Survival (EFS) of Younger Patients With PTCL: GHGNHLSG

18-60 years of age, lactate dehydrogenase (LDH) ≤ upper normal value (UNV)





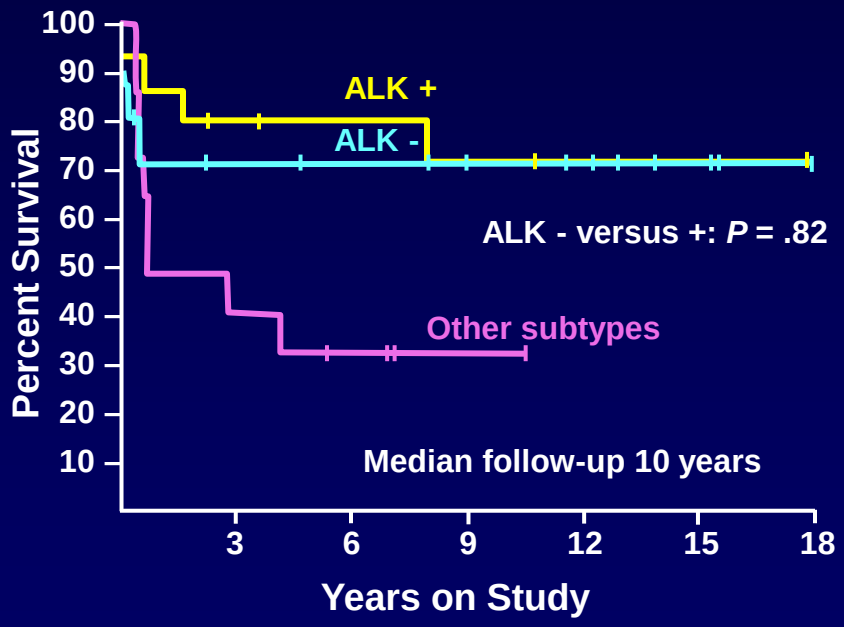




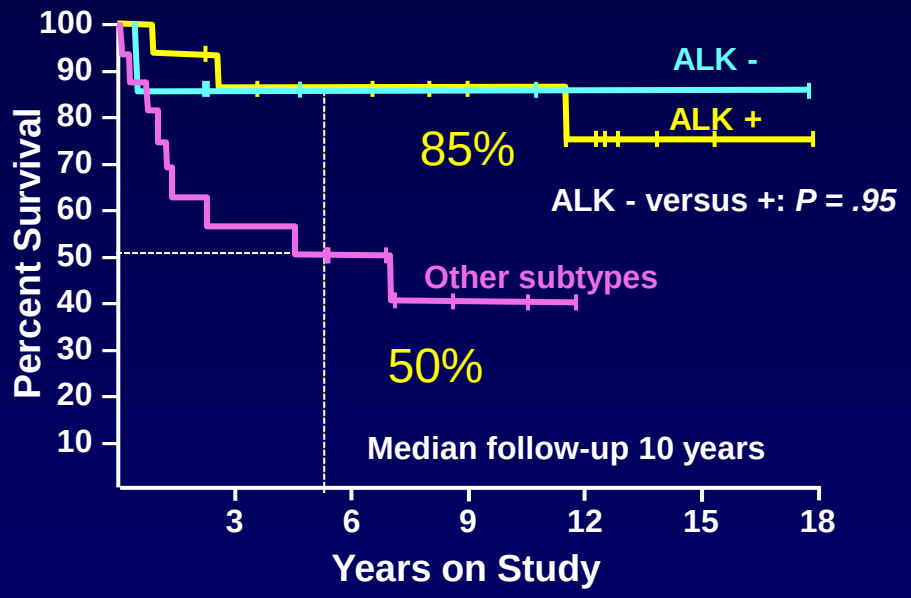
Schmitz N, et al. *Blood*. 2010;116(18):3418-3425.

Phase II Study of Dose-Adjusted EPOCH in PTCL Patient Treatment 1999-2009

Progression-Free Survival



Overall Survival

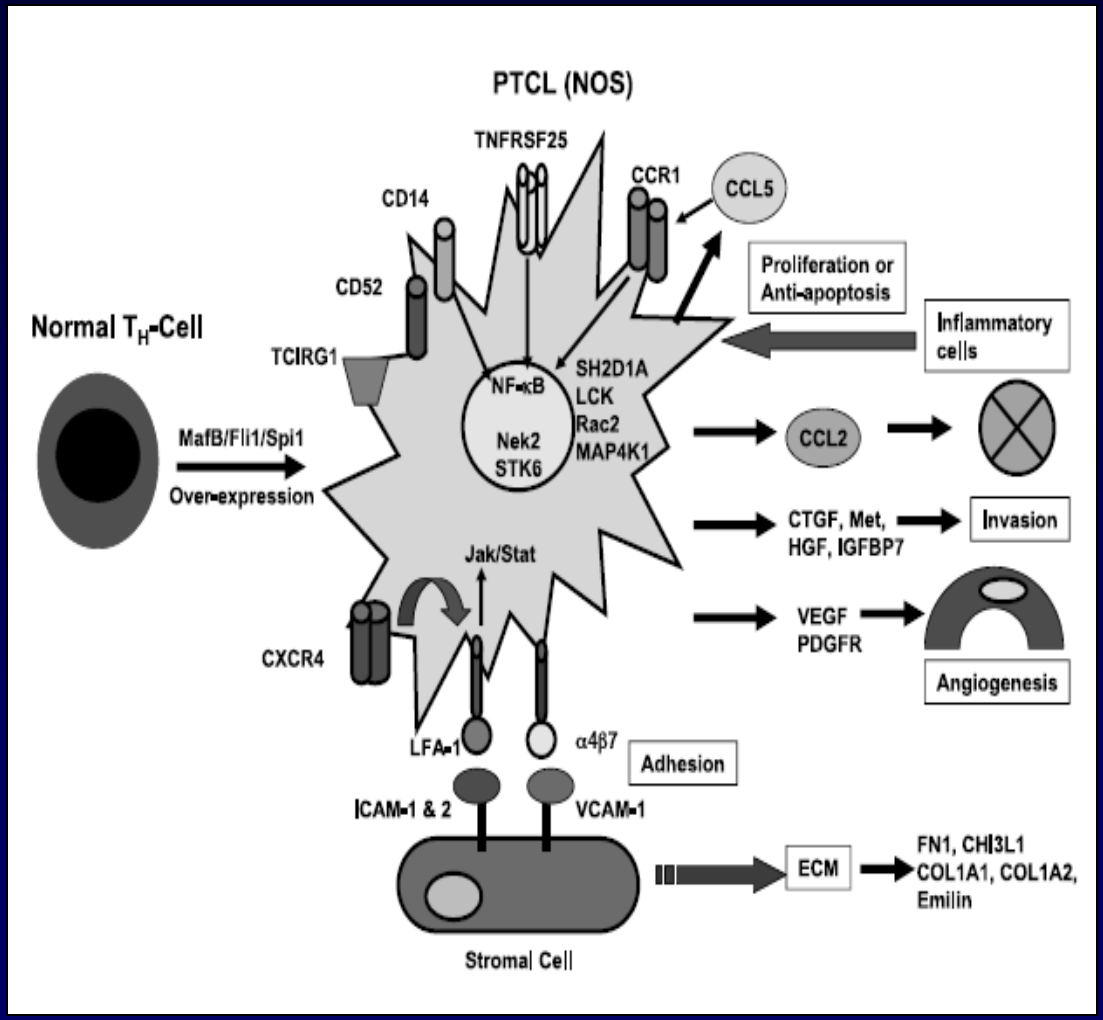


Dunleavey K, et al. *Blood.* 2011;118: Abstract 1618.

Raising the Bar: Striving to Improve Initial Therapy of PTCL

- **Adding rationally targeted drugs to CHOP or anthracycline-based therapy**

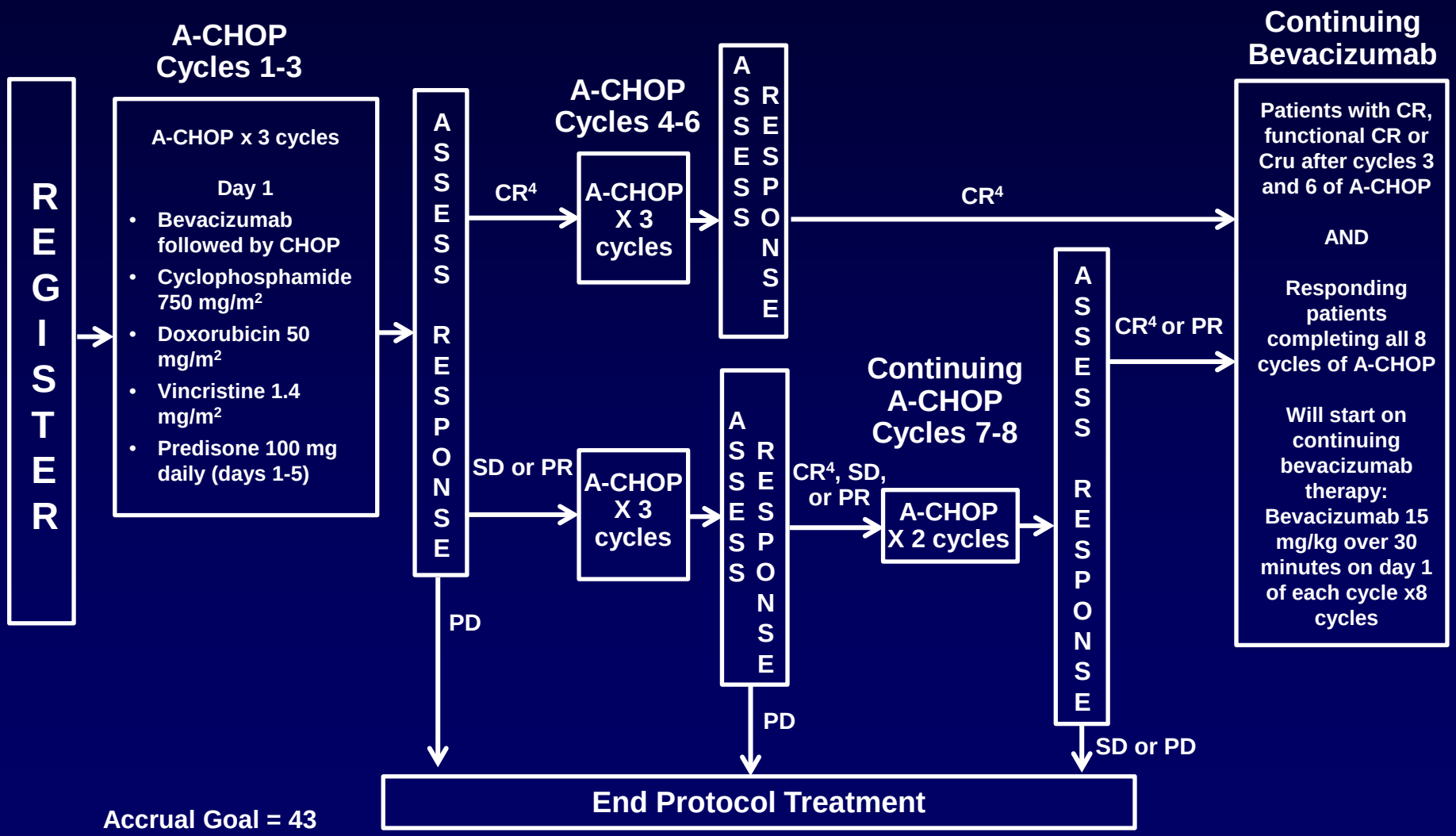
Genes Overexpressed in PTCL



- Vascular biology
- Protein ubiquination
- *MDR* related
- Regulation of transcription
- Chemo taxis
- Immune response

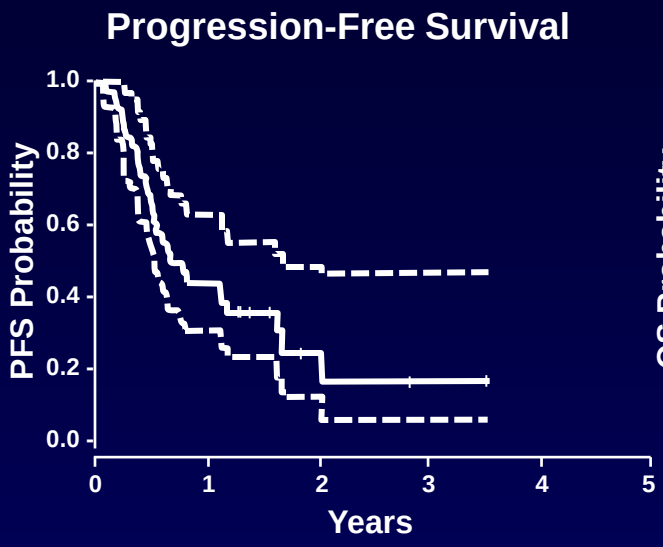
Mahadevan D, et al. *Mol Cancer Ther*. 2005;4(12):1867-1879.

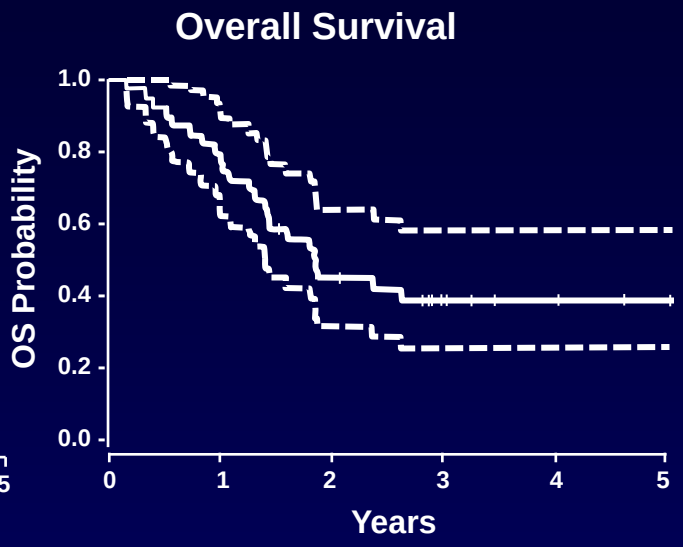
Phase II Study of Bevacizumab and CHOP (A-CHOP) for PTCL ECOG 2404

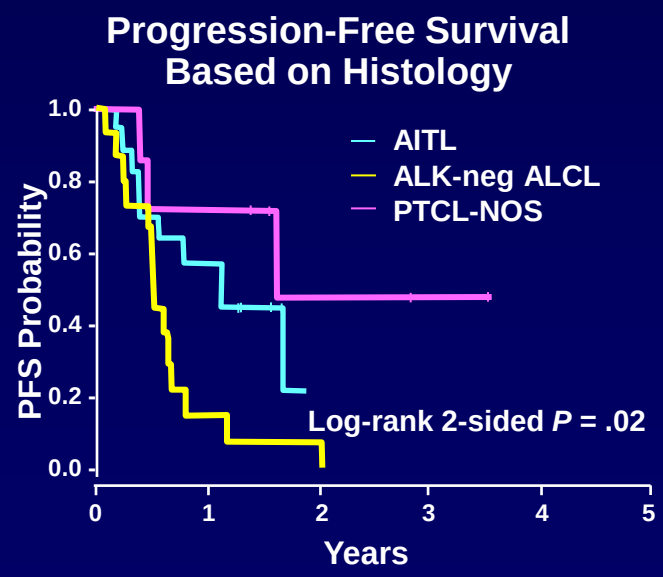


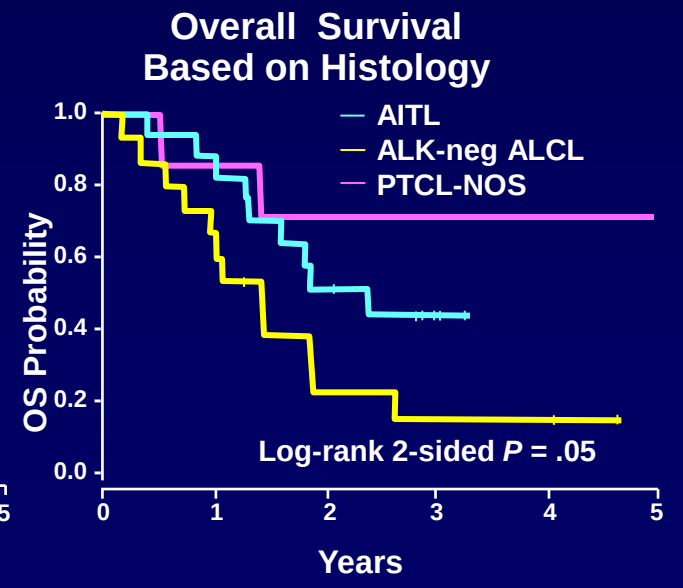
Accrual Goal = 43

Phase II Study of Bevacizumab and CHOP (A-CHOP) ECOG 2404





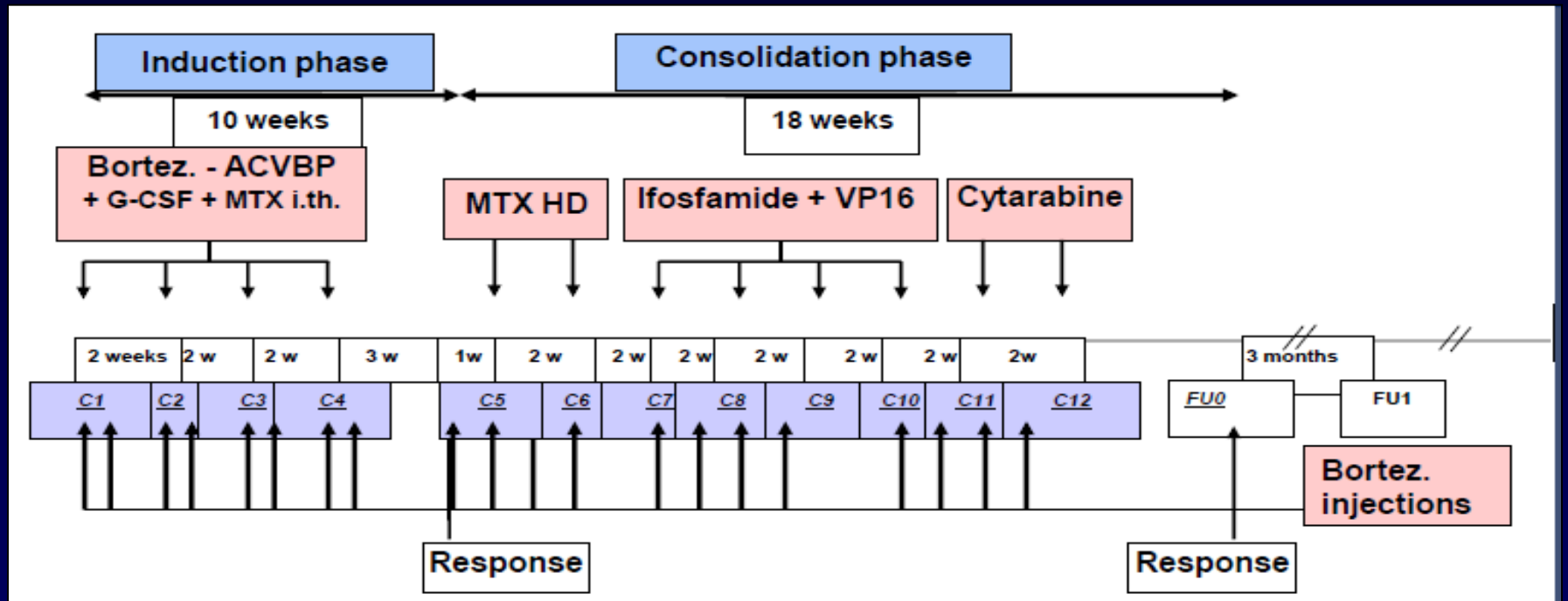




- ORR 90% BUT not durable
- 1-year PFS 44%
- EF monitored after A-CHOP <u>before</u> bevacizumab
- 22 pts rec'd at least 4 cycles of A-CHOP
- Cardiac toxicity in 5/22 pts (22%)
- Gr 3-4 CHF in 4 pts (18%)

Advani AS, et al. *Br J Haematol*. 2011;153(4):504-507; Ganjoo K, et al *Leuk Lymphoma.* 2014;55(4):768-772.

GELA-LNH05-1T
Delmer et al ASCO 2009 # 8554



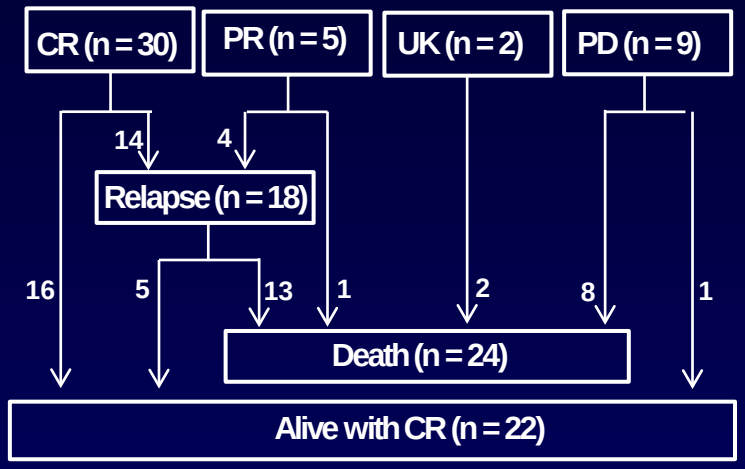
- Age 18 - 65 years
- PTCL except ALCL
- Non previously treated
- Phase II study
- Main objective EFS
- Written consent

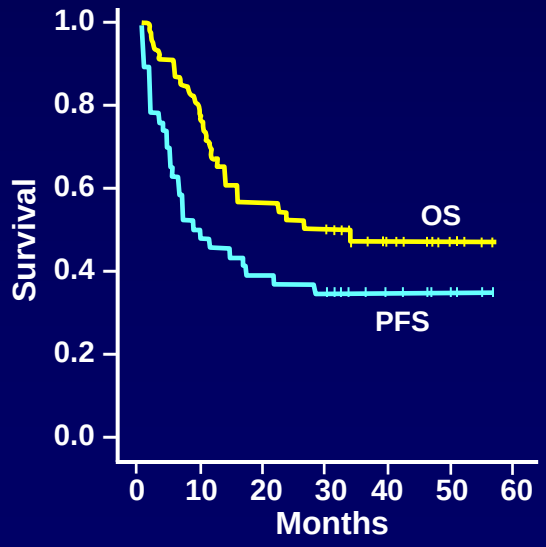
CR 49% (similar to results with ACVBP alone), more toxicity

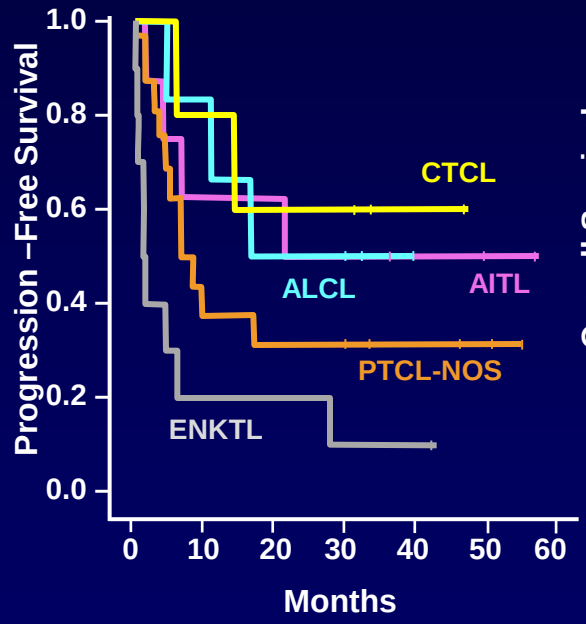
Delmer A, et al. *J Clin Oncol.* 2009;27(15s): Abstract 8554.

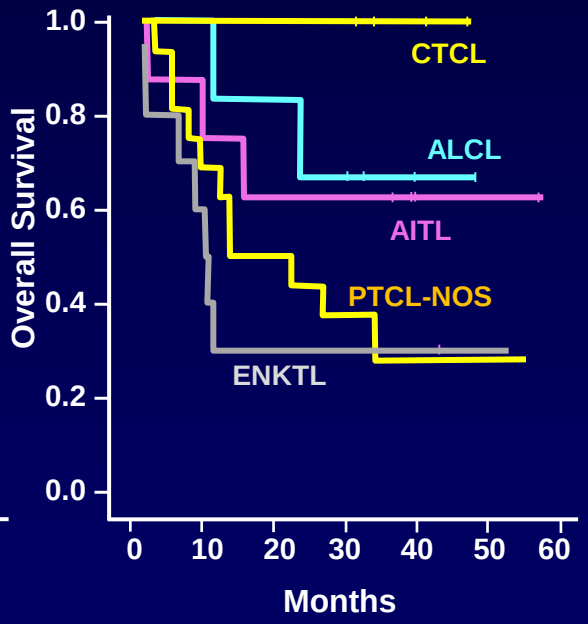
Bortezomib+CHOP as First-Line for Stage 3-4 PTCL

ORR 76%, CR 65%, 3-year PFS 37%, OS 47%









Kim SJ, et al. *Eur J Cancer.* 2012;48(17):3223-3231.

Raising the Bar: Striving to Improve Initial Therapy of PTCL

- **Consideration of transplant as consolidation**

What Are the Data Supporting ASCT for PTCL?

No randomized clinical trial comparing chemotherapy vs ASCT

- **Retrospective data from prospective randomized trials for aggressive lymphomas**
  - **GELA pooled analysis with matched controls no advantage to ASCT[1]**
- **Prospective data**
  - **Variable front-line chemotherapy**
  - **Variable preparative regimen for ASCT**
  - **Variable inclusion criteria**

1. Mounier N, et al. *Ann Oncol.* 2004;15(12):1790-1797.

ASCT in PTCL: Upfront Treatment Prospective PTCL Restricted Trials

Citation	Patients , n	Age, y	Regimen	Tx rate	CR/PR, %	OS, %	FU
Corradini ***Leukemia* 2006**	62 Incl ALK + ALCL	43	1. APO → DHAP → HD Mito./Mel 2. MACOP-B → HD AraC/Mito → BEAM	74	72	34 Alk- ALCL 21	12 y
Rodriguez ***Eur J Hematol* 2007**	26	44	MegaCHOP/IFE → BEAM	73	81	73	3 y
D'Amore ***JCO* 2012**	160	55	CHOEP-14 → BEAM/BEAC	70	82	50	5 y
Mercadal ***Ann Onc* 2008**	41	47	HighCHOP/ ESHAP altern. → BEAM/BEAC	41	59	39	4 y
Reimer ***JCO* 2009**	83	47	CHOP → DexaBEAM/ESHAP → HD Cy + TBI	66	71	48	3y
Ahn **ASH 201**			+Etop				3y

~ 25%-60% do not get to ASCT, OS ~ 50%

Adapted from Reimer P, et al. *Adv Hematol.* 2010;2010:320624.

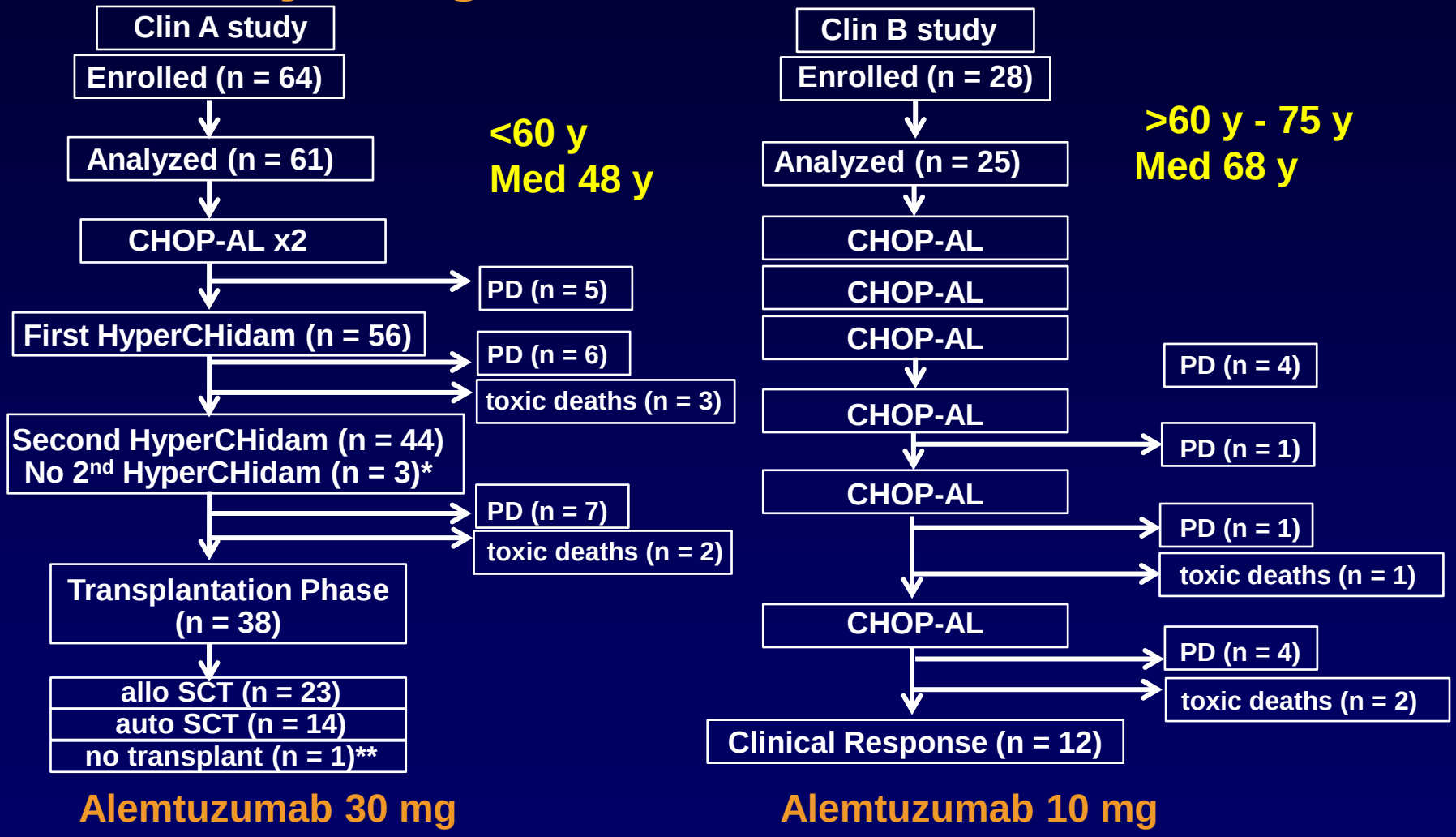
ASCT in PTCL
Summary of Prospective Trials

- ~25%-60% do not get to ASCT due to disease progression during primary therapy
- ~20% relapse within the first year after ASCT
- Additional ~10% relapse by 2 years post ASCT
- Does ASCT as consolidation improve results or just select for healthier people with chemosensitive disease?
  - Factors (high-risk disease) predict for poor outcome after chemotherapy and ASCT

Alemtuzumab (A) + Chemotherapy First-Line Treatment of PTCL

Citation	n	PTCL	A dose, mg	Chemo	ORR/CR	% PFS/EFS	% Toxicity
Gallamani *Blood* 2007	24	14	30	CHOP-28	75/71 (50% PTCL)	48 (2 yr)	17% G4 infection
Kim *Cancer Chemother Pharmacol* 2007	20		30	CHOP	80/65	43 (1 yr)	10% death infection
Kluin-Nelemans *Annals of Oncol* 2011	20	10	30x3	CHOP-14	90/60	27 (2 yr)	15% EBV=LPD2 0% TRM

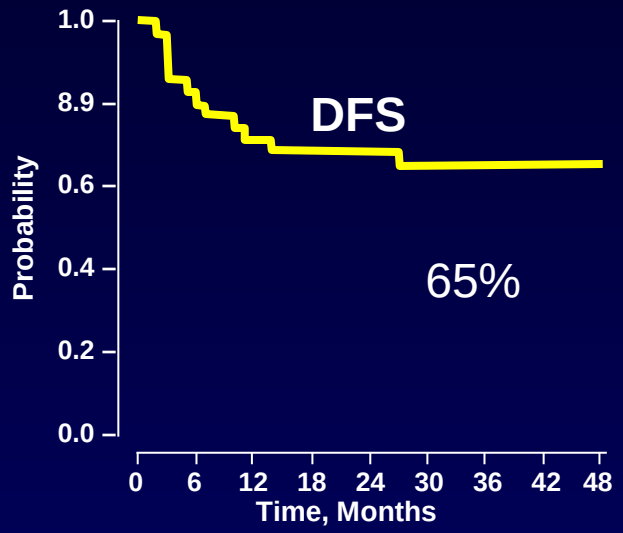
Phase II Study of Intensified Chemoimmunotherapy With or Without SCT in Newly Diagnosed Patients With PTCL

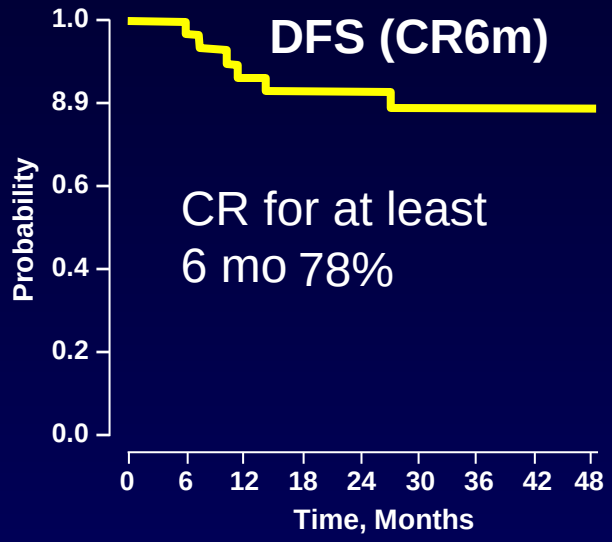


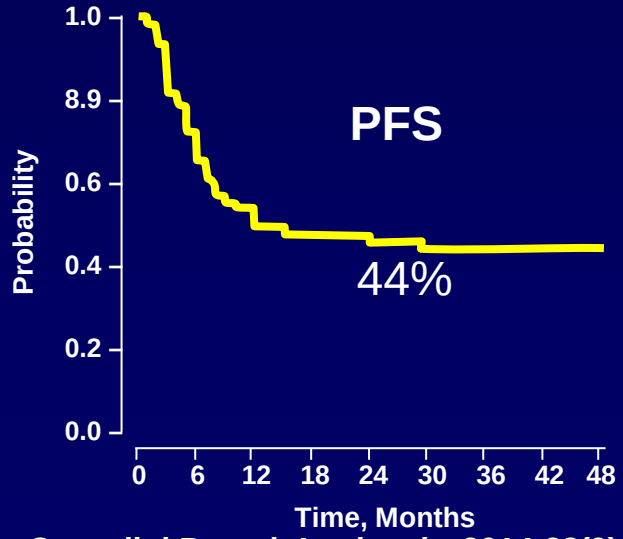
*these 3 patients underwent transplantation after 1 cycle HyperCHidam; **physician decision

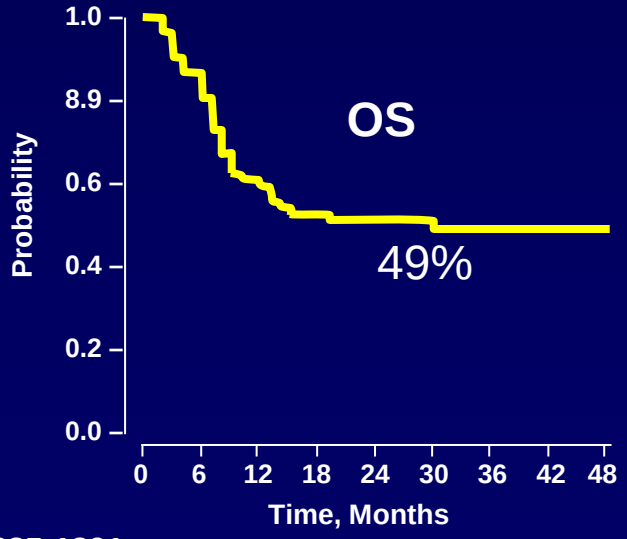
Corradini P, et al. *Leukemia.* 2014;28(9):1885-1891.

Results Arm A: Estimated 4-Year Outcomes Median Follow-Up 40 Months, 62% Received SCT









No diff auto vs allo

4-y OS 92% vs 69%

***P* = 0.8**

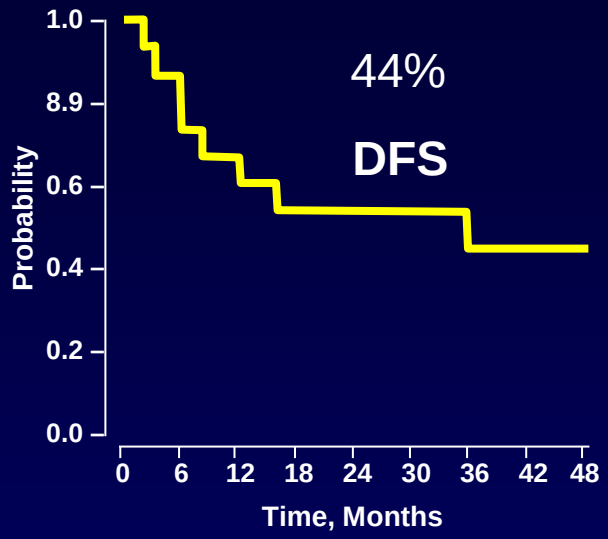
4-y PFS 70% vs 69%

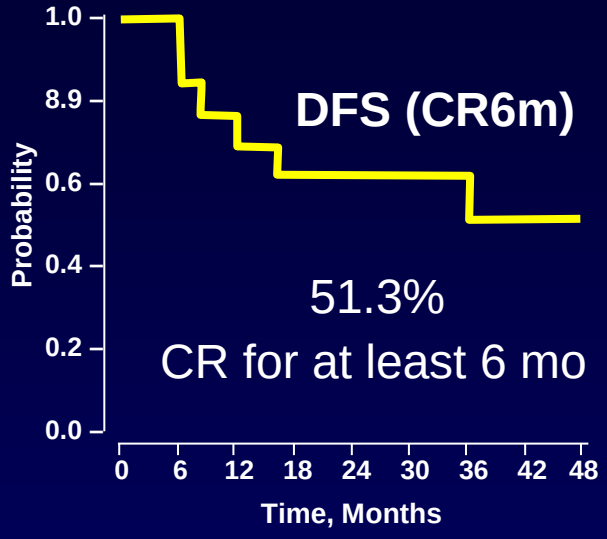
***P* = 0.9**

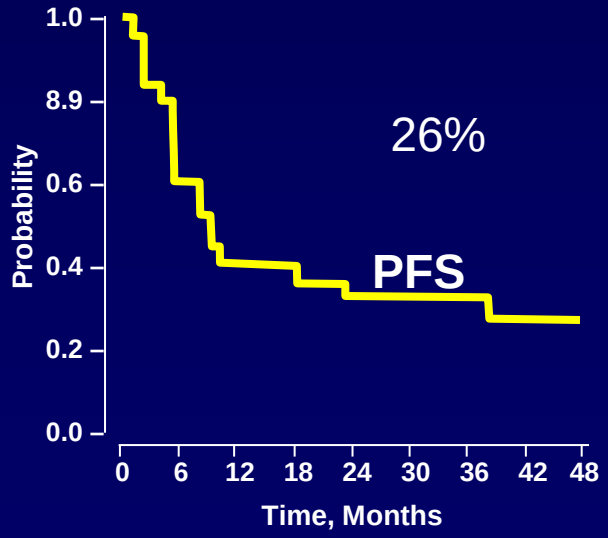
CMV 14%

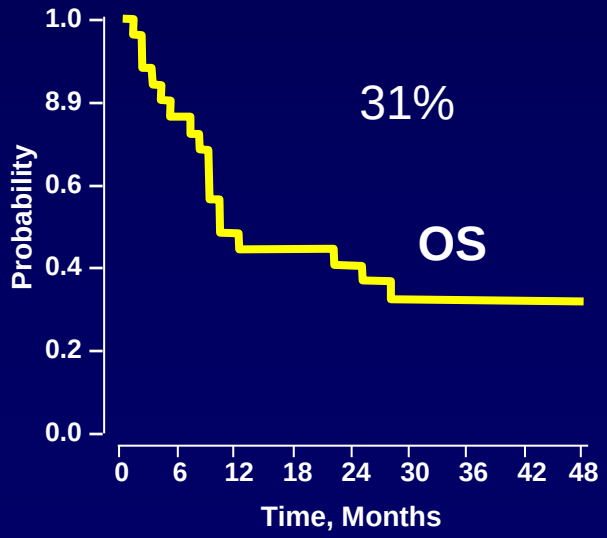
Corradini P, et al. *Leukemia.* 2014;28(9):1885-1891.

Results Arm B: Estimated 4-Year Outcomes Median Follow-Up 48 Months Stopped Early Due to Poor OS







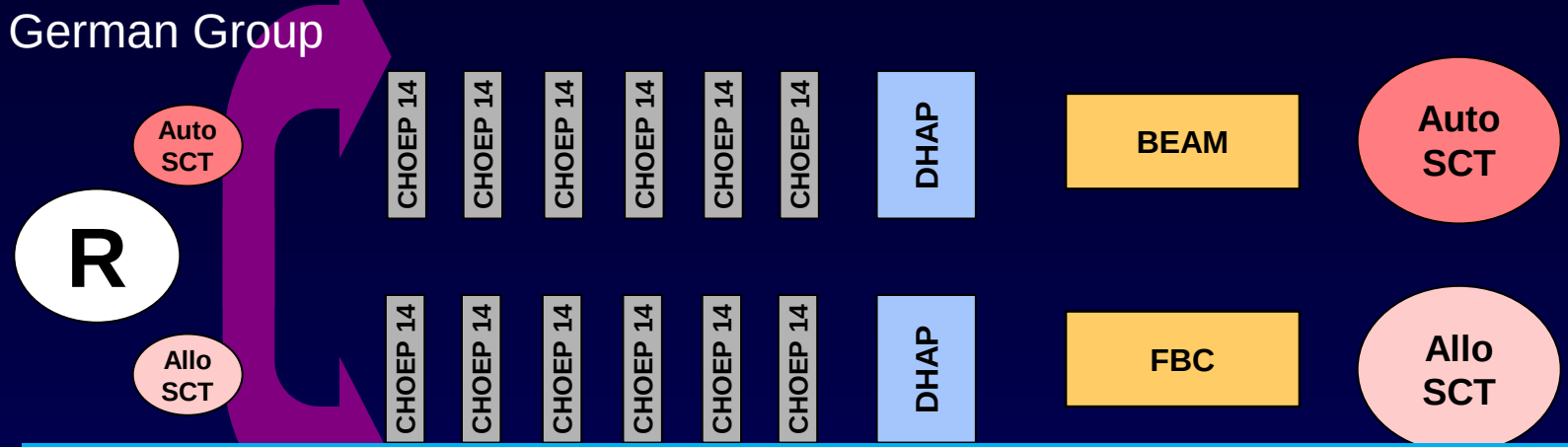


Conclusions:

- Alemtuzumab cannot be safely used with SCT
- Allo transplant not recommended outside trial
- Alemtuzumab low dose also toxic

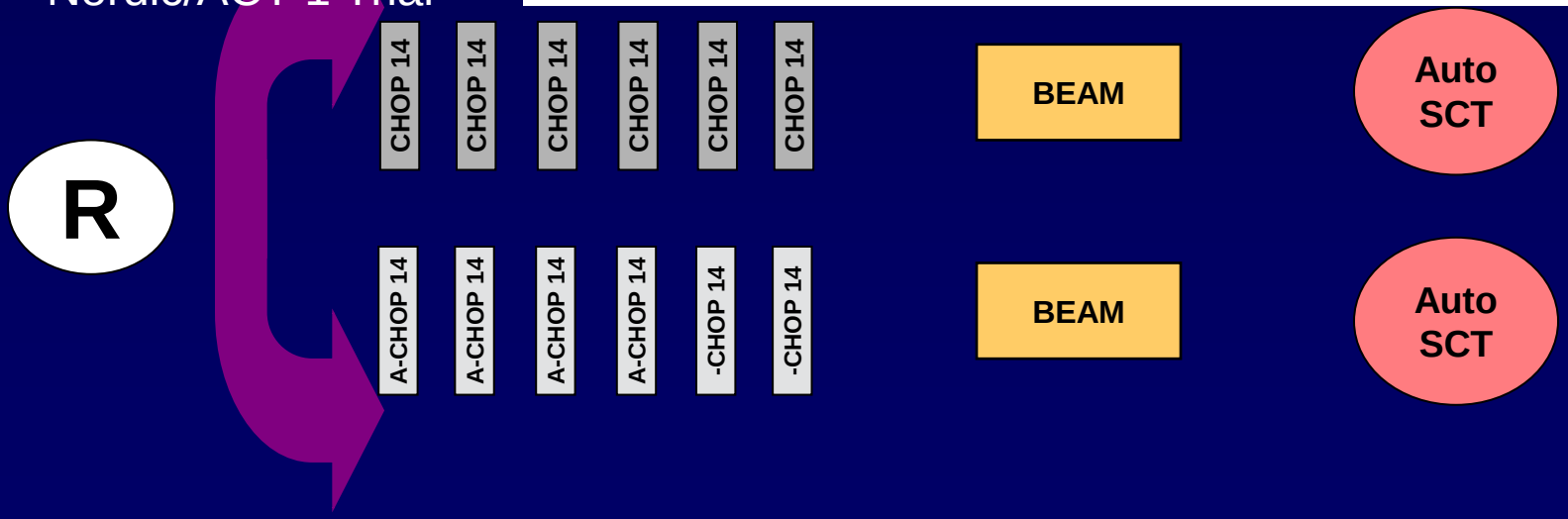
Corradini P, et al. *Leukemia.* 2014;28(9):1885-1891.

Ongoing Phase III Trials



No trial addressing chemo versus transplant

A = Alemtuzumab 30 mg



Raising the Bar: Striving to Improve Initial Therapy of PTCL

- **Alternative to CHOP (nonanthracycline based regimen)**

S0350 Regimen (PEGS): Phase II Trial in PTCL Cisplatinum, Etoposide, Gemcitabine Plus Solumedrol

Rationale: Use non MDR substrates due to high P glycoprotein expression in PTCL (non adriamycin- or vincristine-based regimen)

- **PEGS schema: administered q 21 days**
  - **Cisplatinum: 25 mg/m^2 IV d1-4**
  - **Etoposide: 40 mg/m^2 IV d1-4**
  - **Gemcitabine: 1000 mg/m^2 IV d1**
  - **Solumedrol: 250 mg IV d1-4**

Objectives: ORR, 2-y PFS, OS, tolerability
Molecular studies (GEP), P glycoprotein assessment

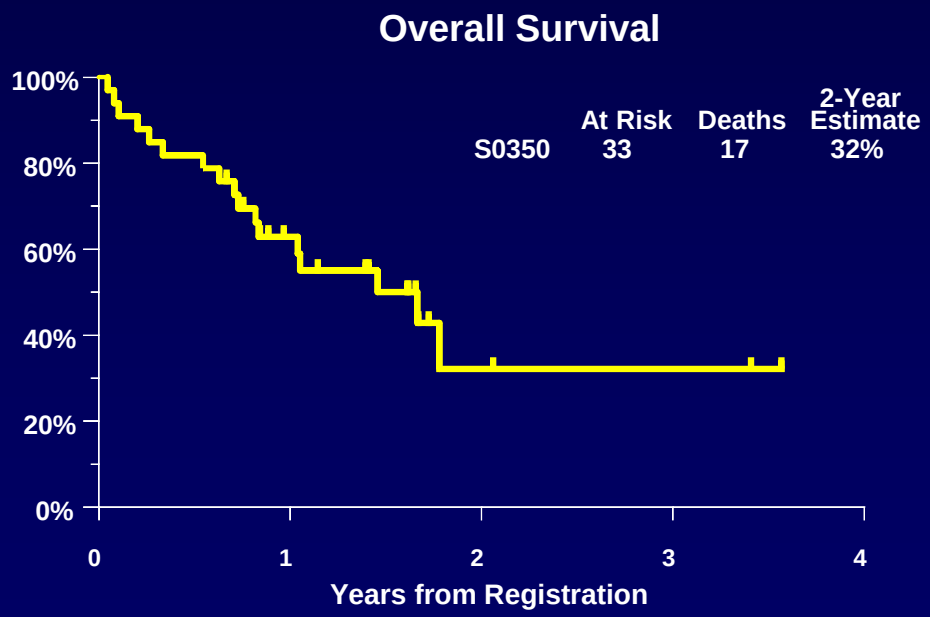
Accrual 6/55 over 2 years

Amended to include relapsed disease

Response

- ORR [CR + PR] = 39% [13/33] , average Rx 5.5 cycles
- 2-year OS = 32% (95% CI: 8%-56%)
- Median OS = 17 mo (95% CI: 15 mo to 20 mo)

Response	N (%)	Histologic Subtype
CR	6 CONFIRMED (18%) 2 UNCONFIRMED (6%) TOTAL = 8 (24%)	PTCL (NOS) = 4 ALCL (ALK-) = 2 PTCL (NOS) = 2
PR	5 (15%)	PTCL (NOS) = 3 ALCL (ALK-) = 1 AITL = 1
STABLE	4 (12%)	

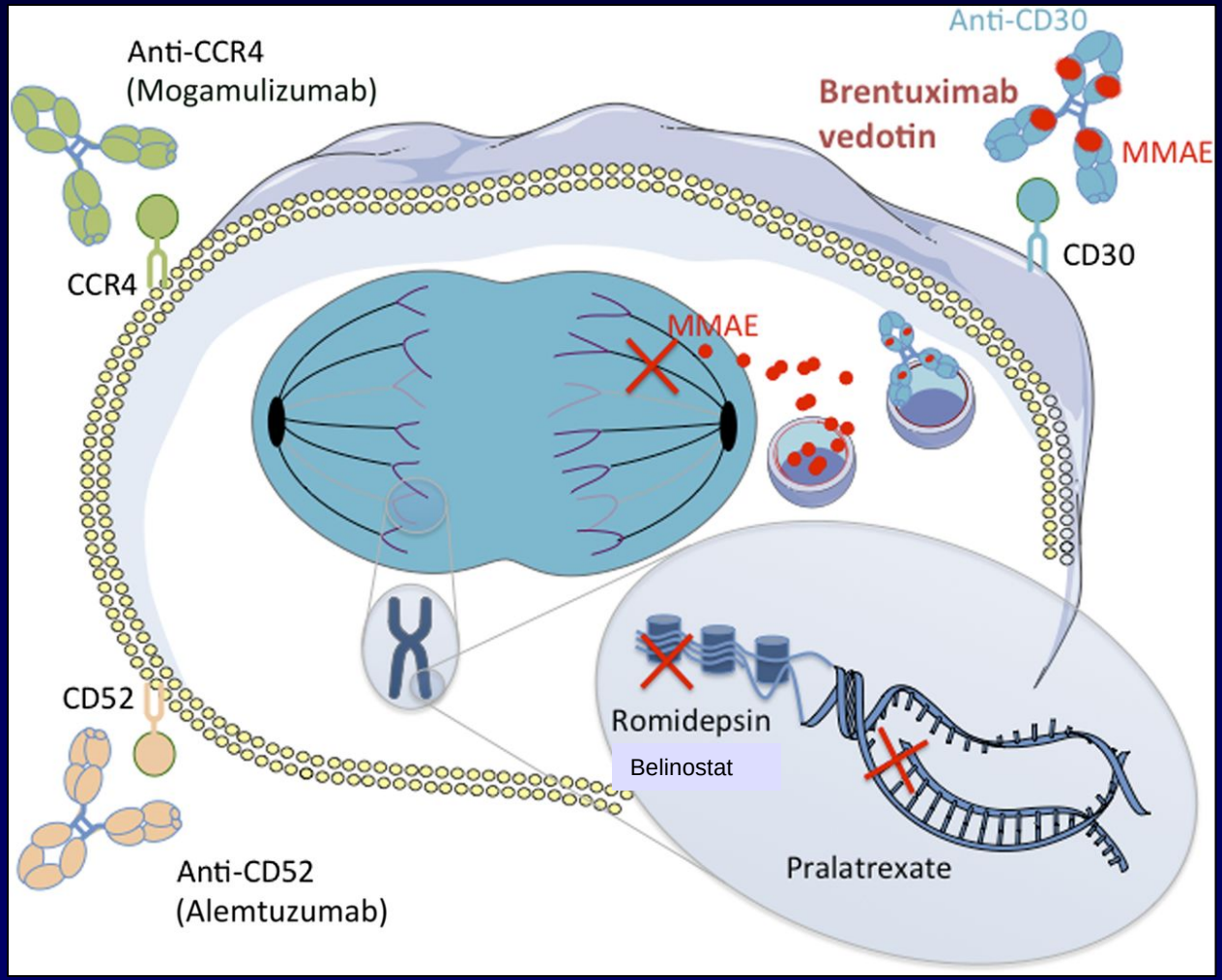


Mahadevan D, et al. Presented at the 2010 International Conference on Malignant Lymphoma.

Raising the Bar: Striving to Improve Initial Therapy of PTCL

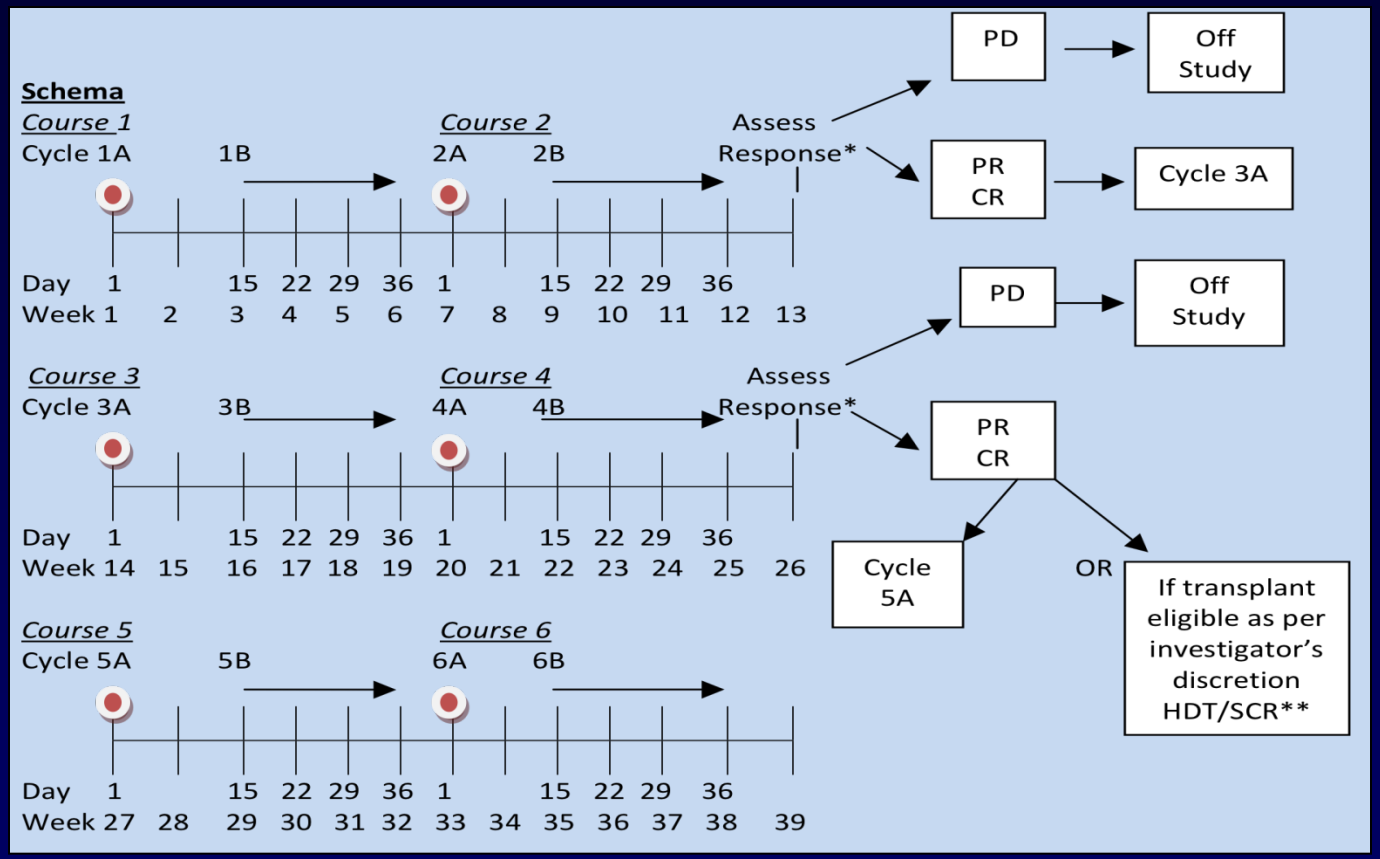
- **Adding novel agents to front-line setting**

Mechanisms of Action of New Drugs in PTCL



Adapted from Bachy E, et al. *Blood*. 2014;123(20):3059-3060.

CEOP-P As Front-Line Therapy for Patients With Stage II- IV Peripheral T-Cell NHL



Cycle A

Cyclophosphamide 750 mg/m^2 d1 IV
Etoposide 100 mg/m^2 d1-3$^{\#}$ IV
Vincristine 1.4 mg/m^2 (capped at 2 mg) d1 IV
Prednisone 100 mg PO d1-5
*Pegfilgrastim 6 mg d4 wk 1 of each course SQ
$^{\#}$Etoposide can be given PO on d2 and d3 at double dose of 100 mg/m^2 BID

Cycle B

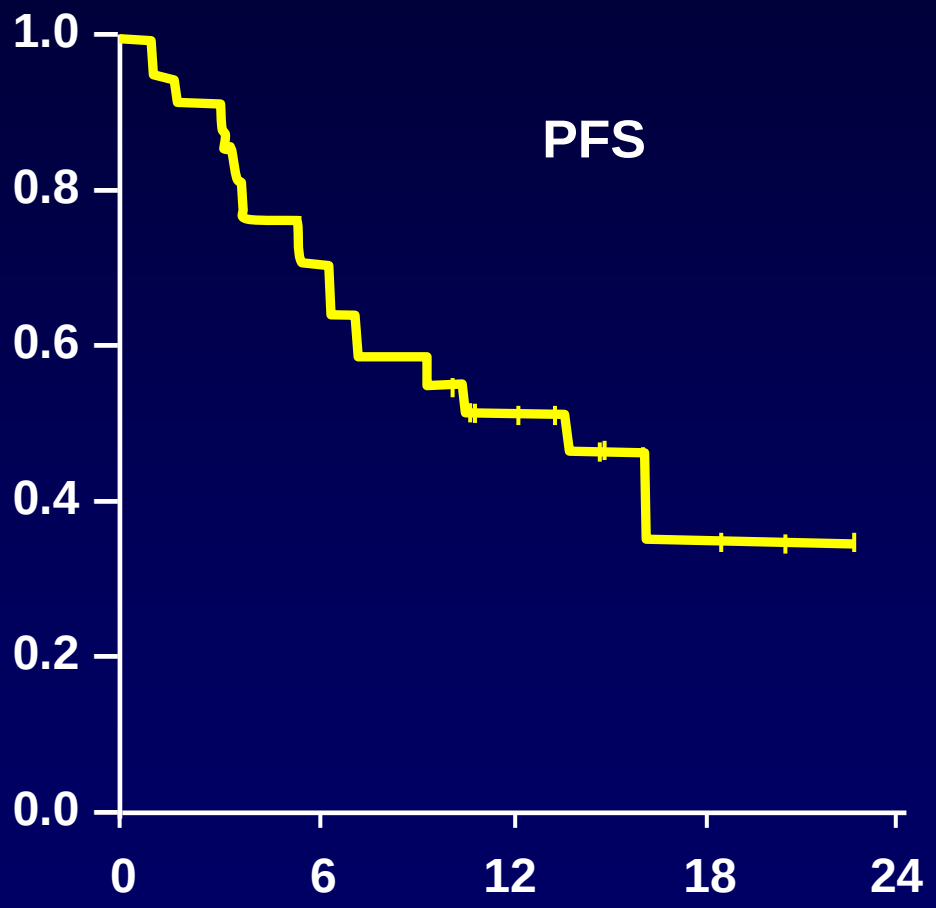
Pralatrexate 30 mg/m^2 d1 IV q wk x3
*Filgrastim (G-SCF) 300 mcg d30 of each course SQ (optional, per institutional standards)

SCHEMA NOTE: Patients achieving SD after 4 courses (1, 2, 3, 4) will receive 2 additional courses (5, 6) and then be reevaluated for response post course 6. *Pegfilgrastim/filgrastim are suggested/optional per MD choice.

**HDT/SCR, high-dose therapy/stem-cell rescue (see section 5.7)

CEOP-P: Results

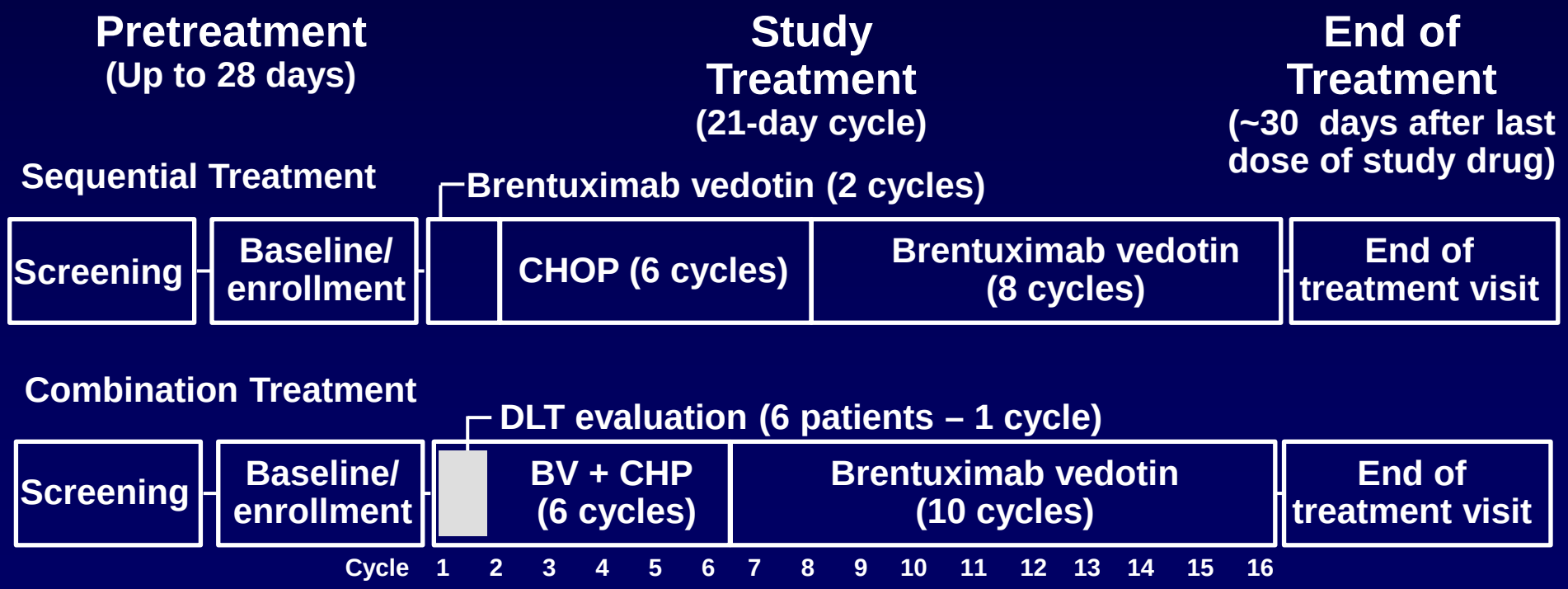
- CR rate (50%) at end of therapy suggests the regimen useful per study design
  - Primary statistical aim of improving CR from 40%-60% not met
- Estimated 1- and-2 year PFS are 50% and 34% respectively.
- -Age <60 y, a low IPI score, achieving a CR, and consolidation with ASCT were statistically significant for better PFS
- Estimated 1- and 2-year OS is 64%
- Defining optimal front-line therapy in PTCL continues to be a challenge and an unmet need



Advani RH, et al. *Blood.* 2013;122: Abstract.

Brentuximab Vedotin Administered Concurrently or Sequentially With Multiagent Chemotherapy As Front-Line Treatment of ALCL and Other CD30-Positive Mature T-Cell and NK-Cell Lymphomas

Med age 56, 69% stage 3-4, 73% ALCL



Fanale MA, et al. *J Clin Oncol.* 2014;32(28):3137-3143.

Response After Sequential or Combination Treatment

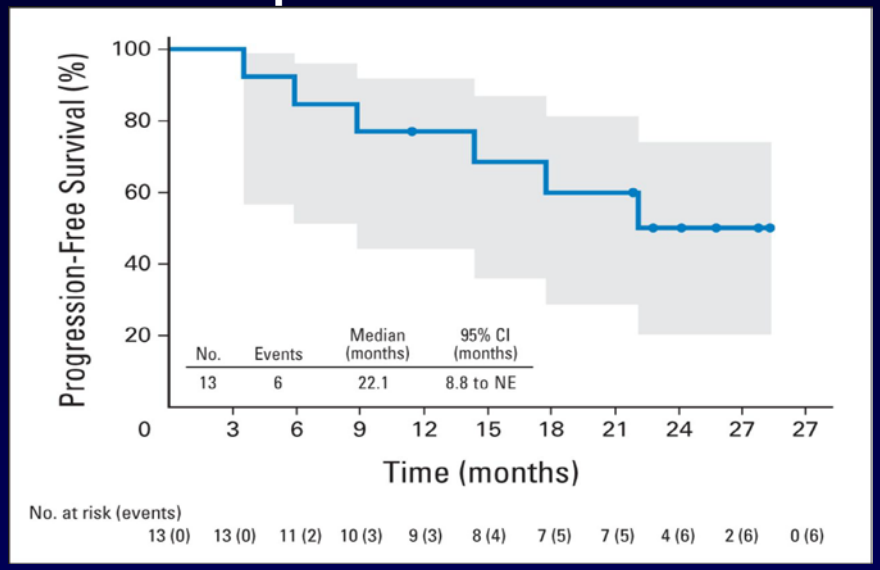
	Sequential ALCL n = 13		Combination					
			ALCL n = 19		Non-ALCL n = 7		Total n = 26	
Response	No.	%	No.	%	No.	%	No.	%
Objective response	11	85	19	100	7	100	26	100
Complete remission	8	62	16	84	7	100	23	88
Partial remission	3	23	3	16	0		3	12
Stable disease	0		0		0		0	
Progressive disease	2	15	0		0		0	

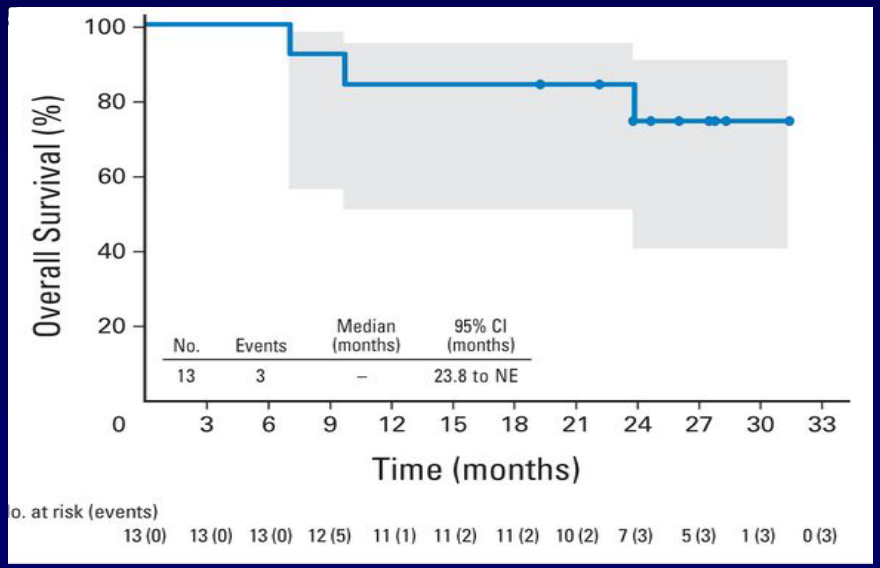
Response assessment per investigator at cycle 8 (sequential treatment), cycle 6 (combination treatment), or at last available response assessment for patients who discontinued treatment before these timepoints.

Fanale MA, et al. *J Clin Oncol.* 2014;32(28):3137-3143.

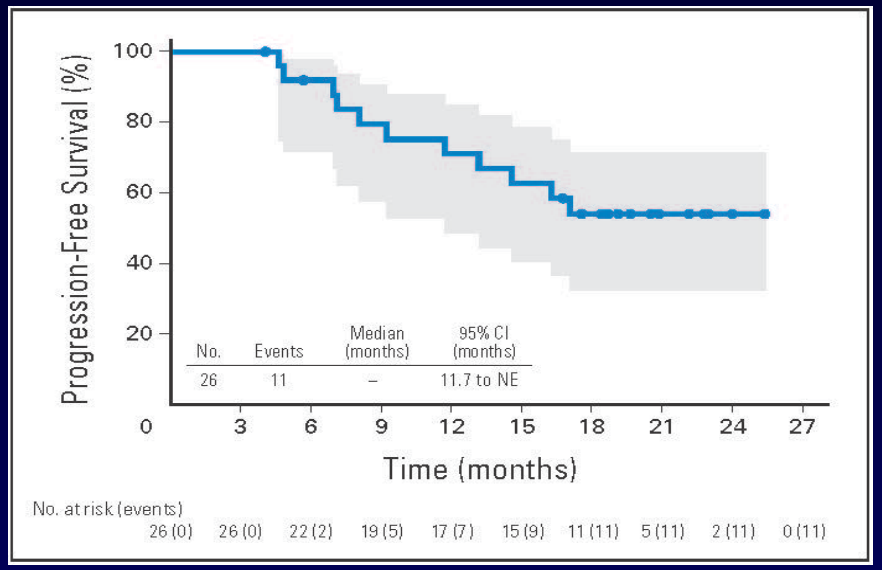
Outcomes

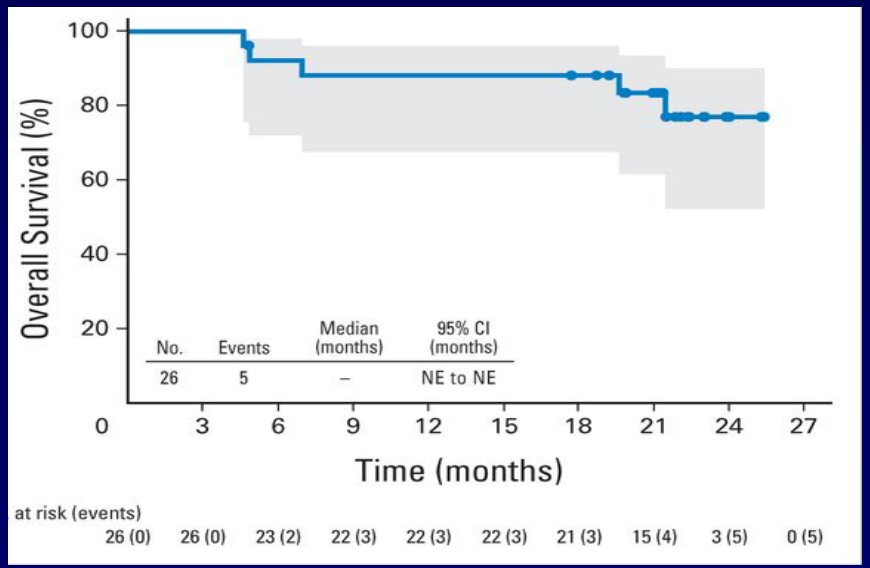
Sequential Treatment





Combination Treatment

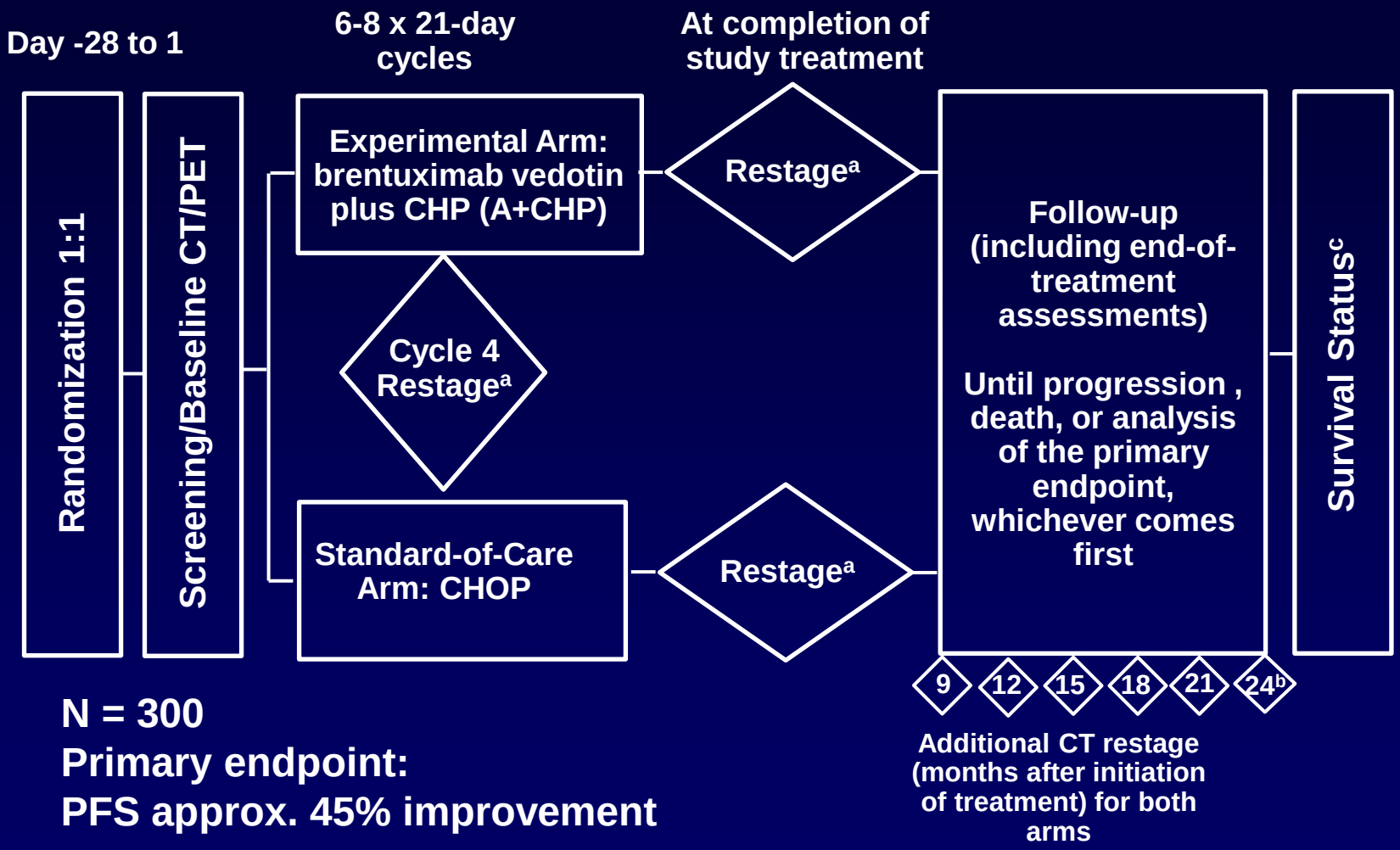




Fanale MA, et al. *J Clin Oncol.* 2014;32(28):3137-3143.

Echelon-2 Trial

PTCL-CD30+ (≥ 10%) if ALK+ ALCL IPI ≥2



N = 300

Primary endpoint:

PFS approx. 45% improvement

[a]CT and PET scans required

[b]Additional CT scans every 6 months thereafter until progression per investigator, death, or analysis of the primary endpoint, whichever comes first

[c]For patients with documented progression, continued follow-up for survival every 6 months until death or study closure, whichever comes first

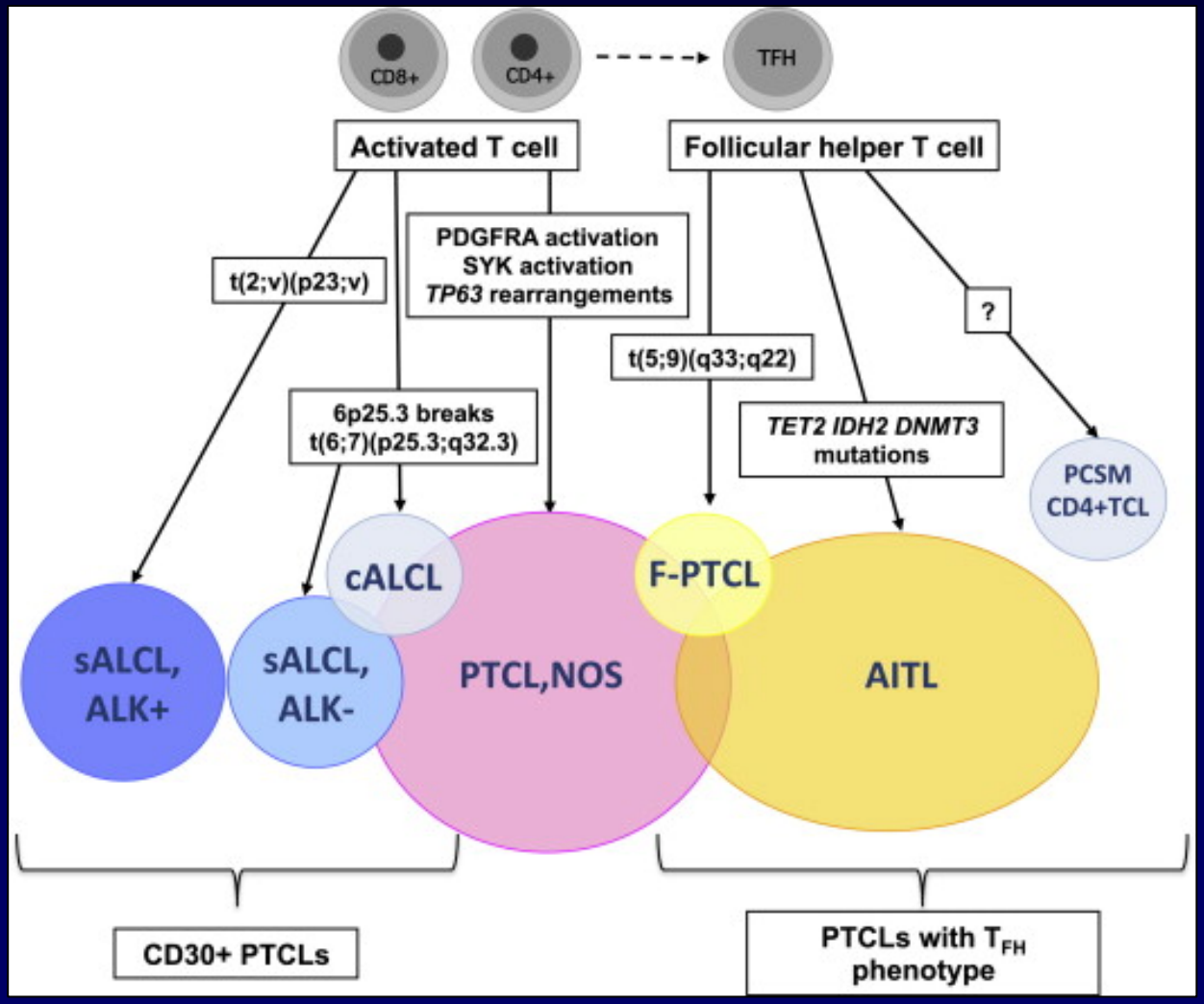
Other Ongoing Phase III Trials Front-Line Therapy of PTCL

Study	Population	Endpoint	Setting
Immunotherapy			
Alemtuzumab + chemo vs chemo	Newly diagnosed PTCL	EFS	Induction
Antimetabolite			
Pralatrexate maintenance vs observation	Newly diagnosed PTCL	OS	Maintenance: Closed due to poor accrual
Histone deacetylase inhibitor			
Romidepsin + CHOP vs CHOP	Newly diagnosed PTCL	PFS	Induction

Raising the Bar: Striving to Improve Initial Therapy of PTCL

- **Significant advances in biology have led to well defined molecular subsets**

Putative Cellular Derivation and Known Oncogenic Pathways for the Main Nodal and Selected PTCL Entities



Philippe G, et al. *Semin Hematol.* 2014;51(1):5-16.

Potential Molecular Targets for Future Therapeutic Interventions in PTCL

Target	Function	Rationale	Agent	References
BCL2	Antiapoptotic	Overexpressed in PTCL; correlates with poor prognosis	ABT-199	Rassidakis et al, Souers et al
IDH2	Metabolic enzyme	Mutated in AITL and PTCL-NOS; produced 2HG, which blocks chromatin-modifying enzymes	Mutant IDH2 inhibitor	Cairns et al, Wang et al
BRD4	Epigenetic "reader"	BRD4 inhibition kills AML with mutant IDH2 (preclinical)	JQ1; iBET	Chen et al
FYN	Kinase	Activating mutations in AITL and PTCL-NOS	Dasatinib	Couronne et al
JAK2/STAT3	Kinase	Pathway activation in AITL and PTCL-NOS	Ruxolitinib	Maurer et al
JAK3	Kinase	Activating mutations in NKTCL	Tofacitinib	Koo et al
PI3Kδ and γ	Kinase	Promote growth/survival in PTCL	IPI-145	Horwitz et al
MTOR	Kinase	Promotes growth/survival in PTCL	Everolimus	Kim et al
PDGFRα	Kinase	Pathway activation in PTCL	Imatinib	Piccaluga et al

Intlekofer AM, et al. *Int J Hematol*. 2014;99(3):249-262.

Q1: What Would You Recommend As Initial Therapy?

1) CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
2) CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
3) Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, prednisone)
4) Brentuximab vedotin
5) Gemcitabine + cisplatin-based regimen

Q2: What Would You Do Next?

1) Observation without further therapy
2) Consolidate with high-dose therapy (HDT) and autologous stem cell transplant (ASCT)
3) Type siblings for possible allogeneic transplant (allo-SCT)
4) Start maintenance brentuximab vedotin

Take-Home Message

- Standard CHOP; does not work well for most subtypes
- Clinical trial should always be first choice
- Off trial: etoposide-based regimen for ALCL or pts less than age 60 y for other histologies
- If CR (PTCL-NOS, ALK – ALCL, AILT), consider consolidation with SCT
- Improved understanding of biology and has offered some clarity to the broader term ‘PTCL’
  - Specific entities defined
  - Molecular-based prognostic markers identified
- Potential new targets identified that provide a rationale for new approaches to therapy