

**Peripheral T-cell Lymphoma:  
What is the Best Therapeutic Strategy and  
When Should Transplantation be Utilized?**

**“NEW AGENTS”**

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# Is There an “R-CHOP” for TCL?

## Alemtuzumab- anti-CD52 antibody

- N = 14, Rel/Refr-Phase II, standard dosing (30 mg iv 3x/week)<sup>1</sup>
- 10 PTCL, nos, RR 36% (3CR/2PR)
- 5 deaths-closed early (TB, zoster, aspergillus)
  
- N = 10, Phase II -10 mg x 12 doses (4 weeks)<sup>2</sup>
- PTCL nos 6, CTCL 4
- Response 50% in PTCL, CR2/PR1
- Less toxic

## Denileukin diftitox-fusion protein-IL2-diphtheria toxin

- N = 27, (PTCL 19) Phase II, standard dosing<sup>3</sup>
- 48%RR , not myelosuppressive

<sup>1</sup> Enblad G, et al. *Blood*. 2004;103:2920-2924. <sup>2</sup>Zinzani PL, et al. *Haematologica*. 2005;90:702-703.

<sup>3</sup> Dang NH, et al. *Br J Haematol*. 2007;136:439-447.

# Alemtuzumab and CHOP Chemotherapy as First-line Treatment of PTCL: Results of a GITIL Prospective Multicenter Trial

**A-30 mg + CHOP Q 4 weeks x 8  
N=24 (PTCL/AITL 20)**

**IPI 0-1 33%**

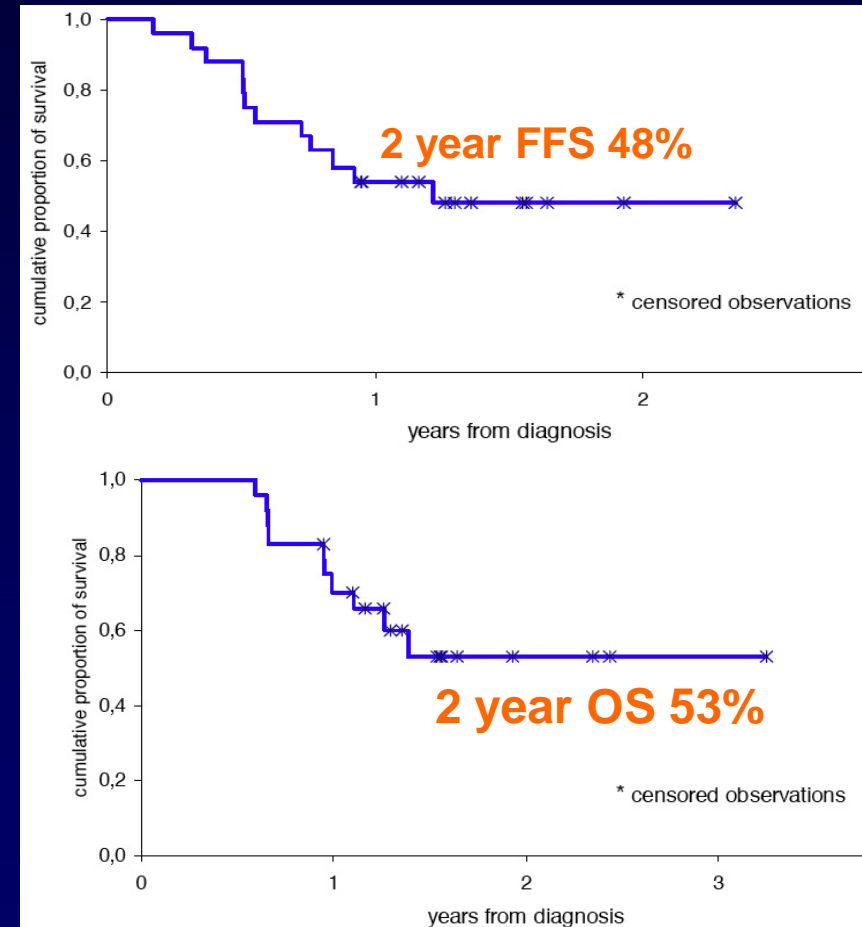
**2-3 58%**

**4-5 8%**

**CR ALL 70.8%**

**PTCL 50%**

**AITL 100%**



# Alemtuzumab Plus CHOP as Front-line Chemotherapy for Patients with PTCL: A Phase II Study

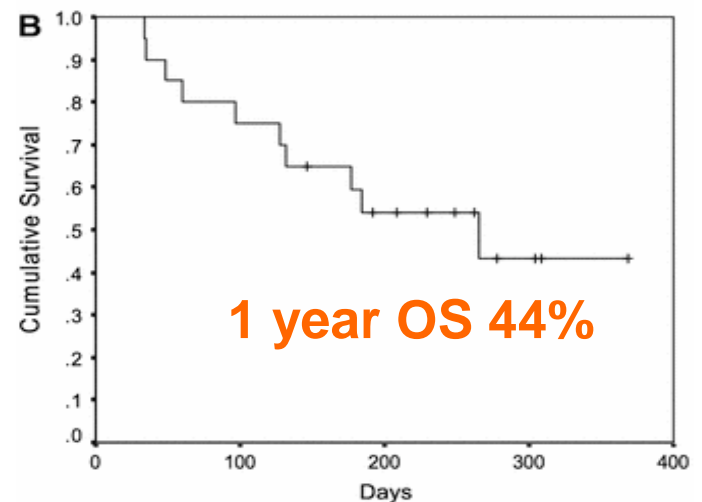
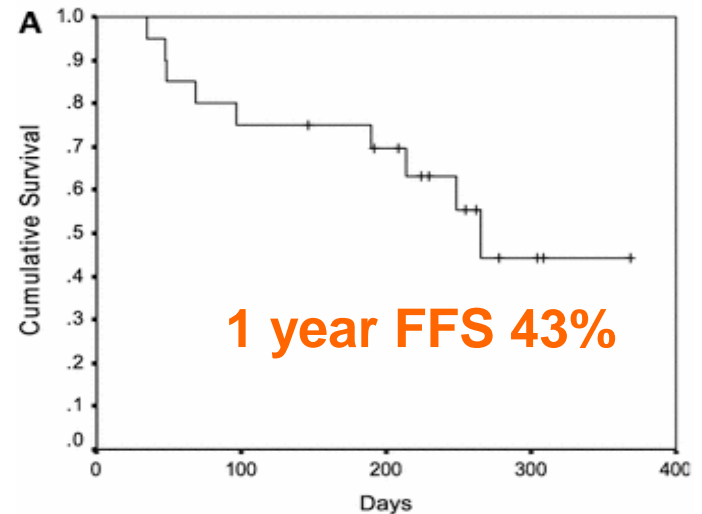
**A-30 mg + CHOP Q 3 weeks x 6**  
**N = 20 (PTCL/AITL 13)**

**IPI L-LI 60%**

**HI-H 40%**

**CR ALL 65%**

**PTCL 80%**



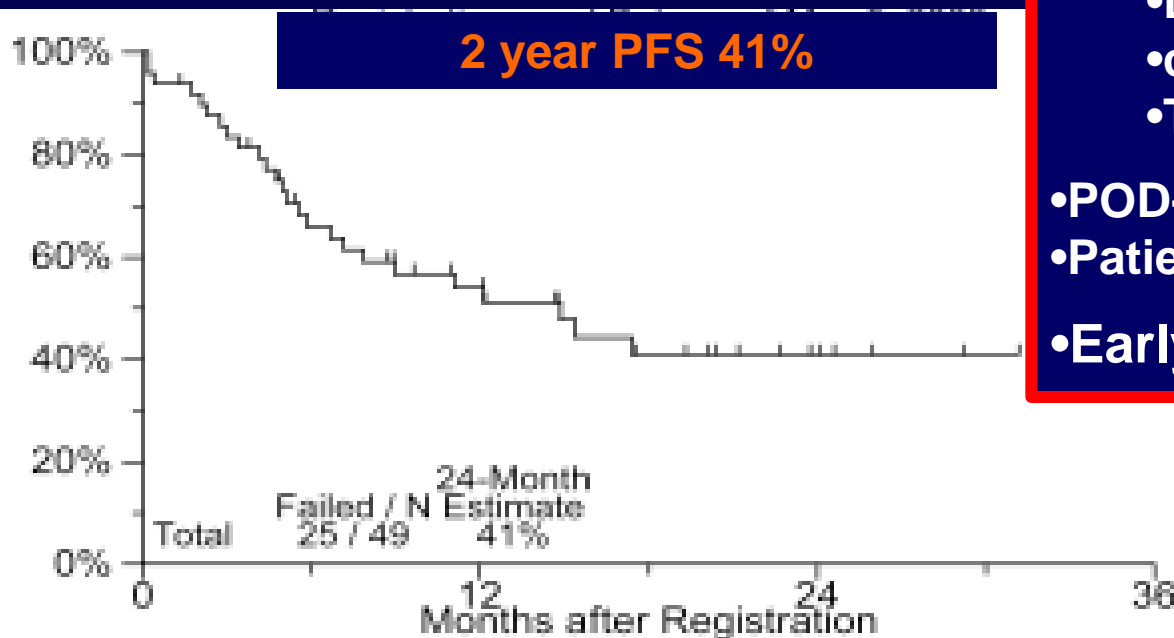
# Issues with Alemtuzumab + CHOP

- **Toxicity**
  - **Gallamini A, et al**
  - **Grade 4 Infection-17%**
  - **Sepsis, Aspergillosis, JC virus, PCP**
  - **Kim JG, et al**
  - **Toxicity-Grade 3-4**
    - **Neutropenia 90%, Lymphopenia 95%,  
Febrile neutropenia 55%**
    - **Infectious deaths 10%**
    - **Study halted early due to SAE**
- **Heterogeneity of CD52 expression**
  - **Series of PTCL 35-40%\***
  - **Down-regulated in PTCL?**
  - **Varies by technique: Flow vs. Immunohistochemistry**

# Phase II Study of Denileukin Diftitox + CHOP in PTCL: "CONCEPT" Trial Interim Results

- Phase II, newly diagnosed aggressive PTCL
- 18mcg/kg/d D1-2, CHOP D3
- N = 49 (80% PTCL/AITL/ALCL)
- CR 75.7%, ORR 86.5%

- 7 D/C due to Adverse Events
  - anaphylaxis
  - pneumonia
  - pneumonitis
  - LFTs
  - cardiac arrest x 2
  - TLS/rhabdo
- POD-7
- Patient request
- Early Discontinuation 20 (41%)



Foss HD, et al. 10<sup>th</sup> ICML Lugano, June 5, 2008.

# New Regimens: Comparison to CHOP

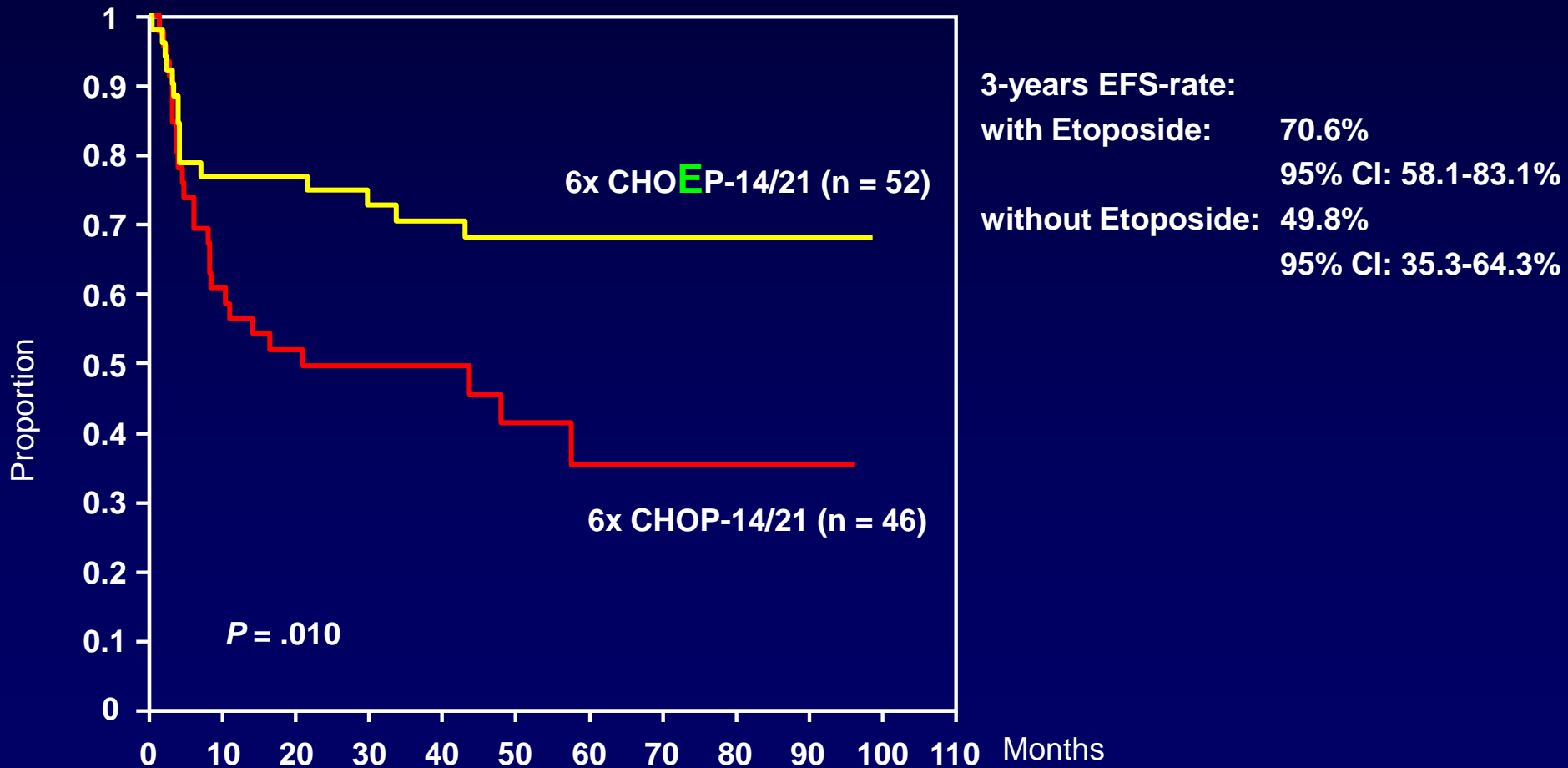
- **GOELAMS VIP/ABVD vs. CHOP8**
  - No difference EFS or OS<sup>1</sup>
- **DSHNHL NHLB1  $\leq$  60y, LDH normal**
  - CHOP(E) (14 or 21)
  - Subgroup analysis of PTCLs (n = 98)<sup>2</sup>
    - younger pts ( $\leq$ 60 yrs) with good-risk disease (LDH  $\leq$  N) showed significantly better 3-yrs-EFS (71 vs. 50%) when etoposide (ETO) was added to CHOP-14 or -21 ( $P = .010$ )

<sup>1</sup>Gressin R, et al. *Blood*. 2006;108:Abstract 2464.

<sup>2</sup>Schmitz N, et al. 10<sup>th</sup> ICML Lugano, June 5, 2008; Abstract 94.

# T-cell Lymphomas in DSHNHL Trials

Results from the NHL-B1 trial ( $\leq 60$  years, LDH  $\leq N$ , n = 98)  
Event-free survival: role of **etoposide**



## **And There Are so Many New Drugs, or at least drugs new to PTCL**

- **CD 52-alemtuzumab**
- **IL2 R-Denileukin  
Diftitox**
- **Pentostatin**
- **L-Asparaginase**
- **Nelarabine**
- **Clofarabine**
- **Vorinostat**
- **Bortezomib**
- **Lenalidomide**
- **Temsirolimus**
- **CSA**
- **Sorafenib**
- **Pralatrexate**
- **Depsipeptide**
- **Everolimus**
- **Syk inhibitors**
- **Enzastaurin**
- **Anti-CD 4**
- **Anti-CD 2**
- **Anti-CD 30 -naked or  
conjugated**
- **Chemokine receptors**
- **Fodosine**
- **Plitidepsin**
- **Others...**

# Newer Drugs

- **Gemcitabine**

- N = 13 (5 MF, 8 PTCL) phase II days 1, 8, and 15 of a 28-day schedule at the dosage of 1200 mg/m<sup>2</sup> for a total of three courses
- PTCL 5/8 RR, 1CR, 4 PR<sup>1</sup>

- **Bortezomib**

- CTCL/PTCL skin N = 12 (10 MF)<sup>2</sup>
- RR all=8/12 (67%)PTCL-50%1/2 CR
- Phase I +CHOP<sup>3</sup>
- CHOP +1.6 mg/m<sup>2</sup>/dose of bortezomib on days 1 and 8 every 3 weeks
- N = 13 complete remission in 8 (61.5%)

- **Nelarabine**

- CALGB 1.5 g/m<sup>2</sup> N = 19, CTCL 11/PTCL 8<sup>4</sup>
- RR 10.5% (2PR 1-MF/1-ALCL)

<sup>1</sup>Zinzani PL, et al. *Ann Oncol*. 1998 ;9(12):1351-1353. <sup>2</sup>Zinzani PL, et al. *J Clin Oncol*. 2007;25(27):4293-4297.

<sup>3</sup>Lee J, et al. *Annals of Oncology*. 2008;19(12):2079-2083. <sup>4</sup>Czuczman MS, et al. *Leuk Lymph*. 2007;48(1):97-103.

# PROPEL - Study Design

<b>Design</b>	Phase 2 single arm, open label, multi-center, non-randomized, international
<b>Target Population</b>	Adult patients with relapsed or refractory PTCL
<b>Number of Patients</b>	Minimum of 100 evaluable patients
<b>Treatment</b>	Pralatrexate 30 mg/m <sup>2</sup> IV x 6 weeks followed by 1 week rest (7 week cycle) in combination with vitamin supplementation
<b>Primary Endpoint</b>	Response rate by IWC (CR + CRu + PR)
<b>Secondary Endpoints</b>	<ul style="list-style-type: none"><li>• Duration of response</li><li>• Progression-free survival</li><li>• Overall survival</li></ul>

# PROPEL - Histology

HISTOPATHOLOGY	Per Independent Central Review (N = 111)		Per Investigator (N = 111)	
	n	%	n	%
PTCL-unspecified	59	53%	51	46%
Anaplastic large cell lymphoma, primary systemic type	17	15%	17	15%
Angioimmunoblastic T-cell lymphoma	13	12%	18	16%
Transformed mycosis fungoides	12	11%	13	12%
Blastic NK lymphoma (w/ skin, LN, or visceral involvement)	4	4%	4	4%
T/NK-cell lymphoma-nasal	2	2%	1	<1%
Extranodal peripheral T/NK-cell lymphoma unspecified	1	<1%	2	2%
Adult T-cell leukemia/lymphoma (HTLV 1+)	1	<1%	2	2%
T/NK-cell leukemia/lymphoma	0	0%	1	<1%
Mycosis fungoides (not transformed)*	1	<1%	0	0%
Inconsistent with T-cell lymphoma*	1	<1%	0	0%
Aggressive T-cell lymphoma	0	0%	1	<1%
Aggressive large cell T-cell lymphoma	0	0%	1	<1%

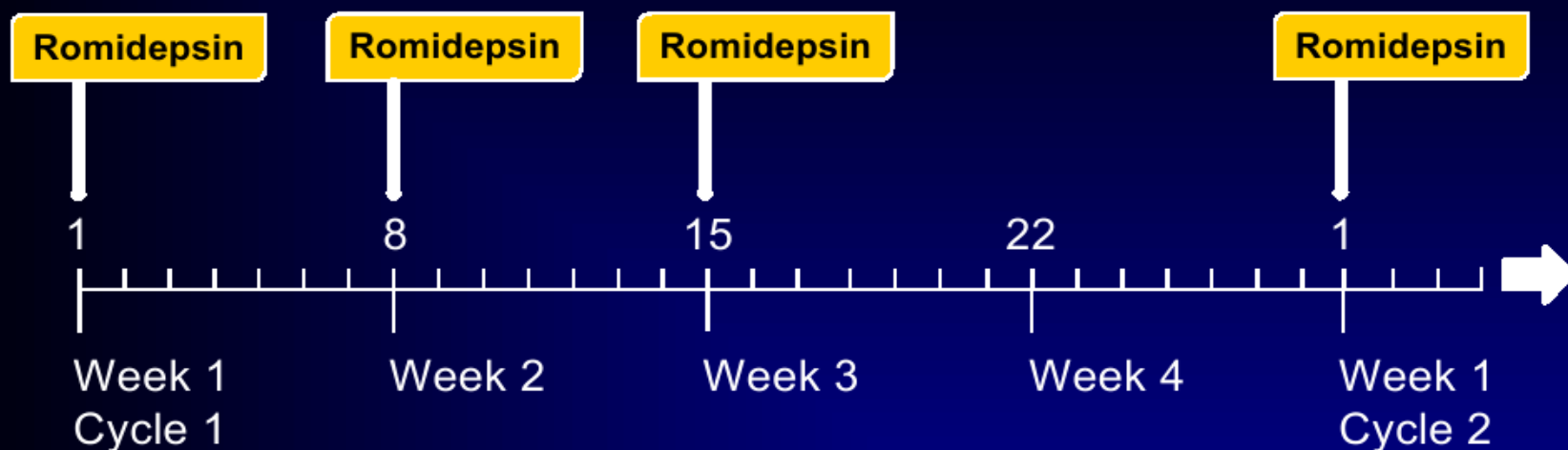
\*Two treated patients excluded from efficacy analysis

# PROPEL

## Summary of Response by Central Review: IWC

69% of responders did so after Cycle 1		Pralatrexate (N = 109)		
		n	Percent	95% CI
Best Response	CR+CRu+PR	29	27%	19-36
	CR	10	9%	
	CRu	1	<1%	
	PR	18	17%	
	SD	23	21%	
	PD	40	37%	
	UE	3	3%	
	ND: off-treatment in Cycle 1	14	13%	

# Treatment Schedule



Schedule:

4-hour infusion 14 mg/m<sup>2</sup> on days 1, 8, & 15 every 28 days

# Clinical Results: PTCL

Response	All Pts N = 48 n (%)	All Pts $\geq$ 2 cycles N=34 n (%)
ORR (CR+PR)	15 (31%)	15 (44%)
CR	4 (8%)	4 (12%)
PR	11 (23%)	11 (32%)
SD	7 (15%)	7 (21%)

Median Duration of Response = 9 months (2 - 61+) in 15 pts with CR/PR

# Phase II Clinical Trial of Belinostat (PXD101) in Patients with Recurrent or Refractory CTCL or PTCL

## Study Objectives

- Response rate
- Safety

## Patient Population

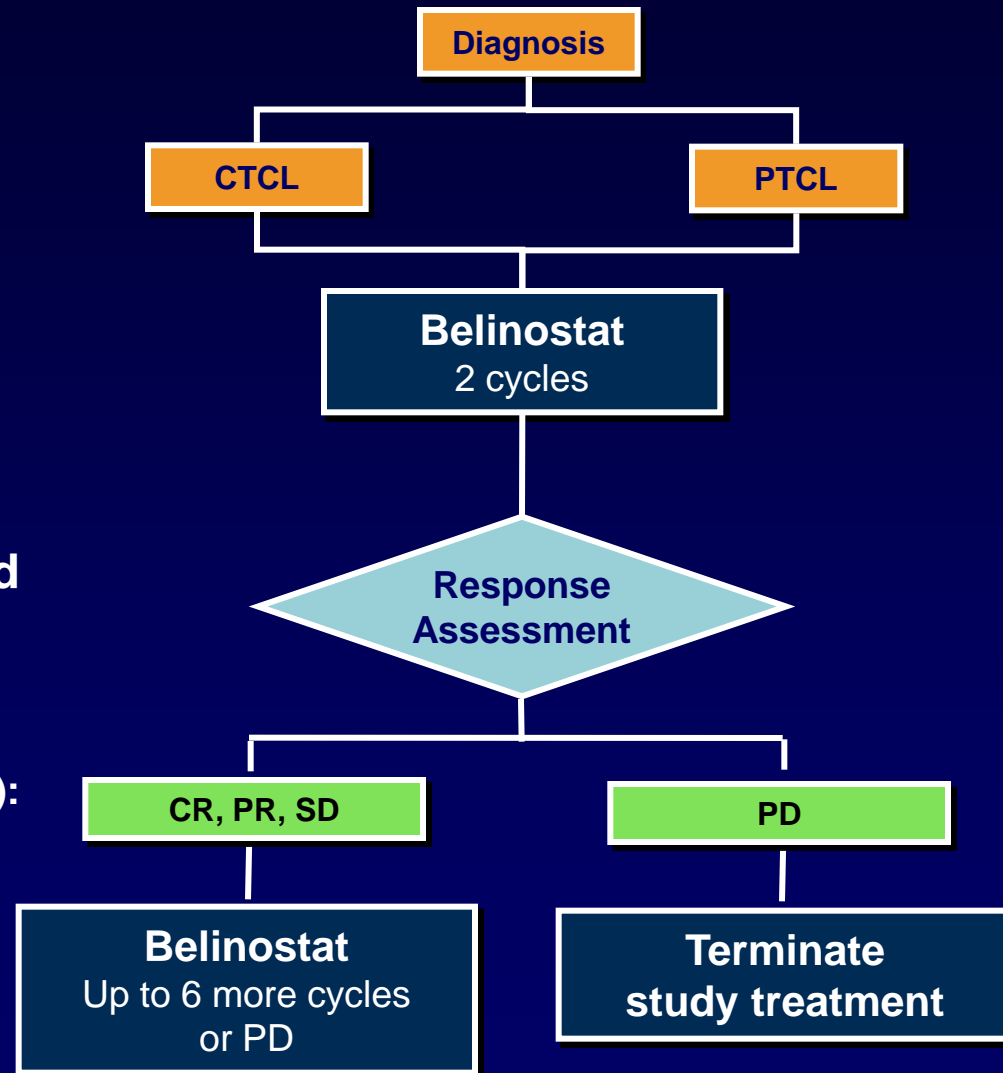
- CTCL or PTCL
- Failed  $\geq 1$  prior line of therapy

## Dosing

- Belinostat 1000 mg/m<sup>2</sup> administered as a 30 min IV infusion once daily on days 1-5 every 3 weeks

## Two-Stage Design (by study arm/diagnosis):

- Terminate study arm if  $\leq 1/13$  pts show response; if  $\geq 2/13$  show response continue enrollment
- Simon “optimal” two-stage design to test null hypothesis that the true success proportion is at most 10%



# PTCL: Exposure & Efficacy

- Median Cycles = 3 (1-8)
- ORR in 17 Evaluable Patients = 24%
  - 3 CR (PTCLu IB, IIIA and IIIB)
  - 1 PR (AITL IVB)
  - 4 SD (ALCL IIA,IIB, PTCLu IVB, NK/T IVA)

Characteristic	Result
<i>Time to Objective Response (days), n = 4</i> Median Range	67 36 — 114
<i>Time to Complete Response (days), n = 3</i> Median Range	114 36 — 140
<i>Duration of Objective Response (days), n = 4</i> Median (3 ongoing) Range	+249 +1 — +504
<i>Progression-Free Survival (days), n = 19</i> Median (7 pts without event) Range	+50 14 — +590

# New Drugs

- **Lenalidomide-Phase II, 25 mg D1-21/28 cycle**
  - 4/9 pts responded – ongoing phase II<sup>1</sup>
  - 3/7 pts responded – ongoing phase II (2 CR, 1 PR)<sup>2</sup>
- **RAD001 (6 MF, 7 PTCLU)**
  - 10 mg daily (4 week cycles)
  - ORR 46 % (6 PR); 3 PR in 7 PTCLU<sup>3</sup>
- **Anti-CD4 (Zanolimumab)**
  - 5/21 (24% RR in PTCL-d'Amore ASH 2007 a3409)
  - Z-CHOP (? Future)

<sup>1</sup>Reiman T, et al. *Blood*. 2007;110:Abstract 2579. <sup>2</sup>Zinzani, et al. Clinical Trials.gov Identifier: NCT01036399.

<sup>3</sup>Johnston PB, et al. T-cell Lymphoma Forum, Maui, January 28-30, 2010. <sup>4</sup>d'Amore F, et al. *Blood*. 2007;110:Abstract 3409.

# T-cell Lymphomas: Getting Beyond CHOP

- CHOP will not cure most patients with PTCL?
- Transplantation *may* consolidate remissions
  - But we still need more effective initial therapies

## New combinations and combinations of new agents

### Gemcitabine + bortezomib

2005 Phase I Results of Combination Gemcitabine and Bortezomib for Relapsed/Refractory Nodal T-NHL and Aggressive B-NHL

### Pralatrexate + Bortezomib

Pralatrexate Compliments the Activity of the Proteasome Inhibitor Bortezomib in in Vitro Models of Lymphoid T-Cell Malignancies

### Pralatrexate + Gemcitabine

1570 A Phase 1/2A Open-Label Study of Pralatrexate and Gemcitabine in Patients with Relapsed or Refractory Lymphoproliferative

### HDAC combinations (?)