IV Russian Conference on Malignant Lymphoma", Moscou October 24-25 2007

T-CELL NHL, MODERN THERAPY STRATEGY

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Gela

WHO classification of mature T/NK cell neoplasms (CD1-, tdt-, CD3+ s/c)

leukemic	nodal	extranodal
prolymphocytic	PTCL, unspecified	nasal-type
LGL	angioimmunobl.	enteropathy-type
NK cell	anaplastic large	hepatosplenic
ATL/L		subcut. panniculitis
		primary cutan. anaplastic
		mycosis/Sezary

International PTCL classification project

	Europe	North America	East Asia	N
N	288	320	454	1062
PTCL-NOS	20%	33%	22%	266
AILT	30%	16%	18%	216
Adult T-cell leukemia/lymphoma (ATLL)	1%	2%	26%	126
Nasal NK/T-cell lymphoma	3%	6%	14%	90
ALCL, ALK+	9%	13%	4%	86
ALCL, ALK-	11%	7%	2%	67
Enteropathy-type T-cell lymphoma	11%	6%	2%	57
NK/T-cell lymphoma, nasal type	2%	3%	5%	38
6	100%	100%	100%	

EUROPEAN APPROACH

- Until Rituximab era, similar treatments approaches were used between B and T cell lymphomas:

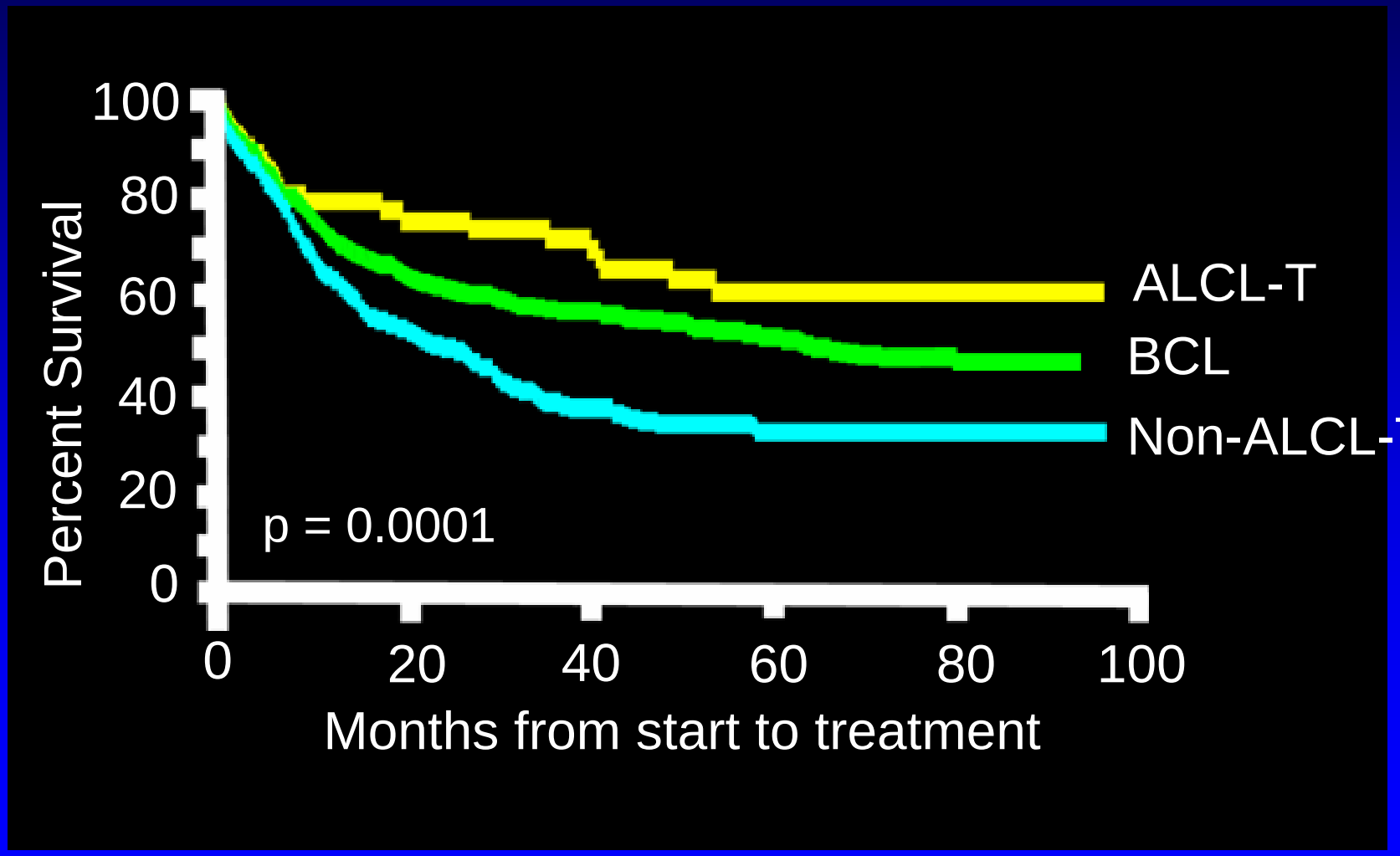
- - CHOP
- OR in Europe more intensive treatment
  - GELA Intensive chemotherapy with ACVBP:
    < 65 yr ACVBP + Consolidation with ASCT IPI 2-3
  - DSHNHL: CHOEP/CHOP; CHOP-14; MEGA- CHOEP
  - ITALY: HDS with ASCT

- Is the International Prognostic Index adequate?
  IPI vs PIT, additional marker, Ki67, CD30, Alk

- Is there a prognostic difference between T cell subtypes?

Messages from retrospective studies

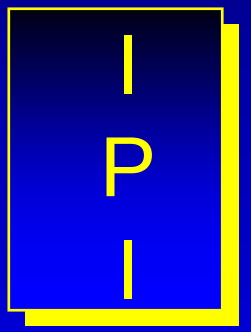
OS OF 228 NON-ALCL CELL AND 60 ALCL T-CELL LYMPHOMA PATIENTS COMPARED WITH 1,595 DIFFUSE BCL PATIENTS: LNH 87

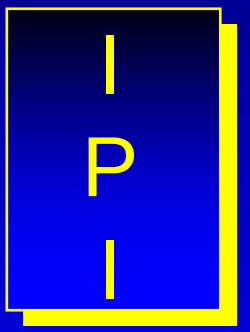


(C. Gisselbrecht et al., Blood 92 : 76-82, 1998)

PERIPHERAL T CELL LYMPHOMA
Cox's analysis survival

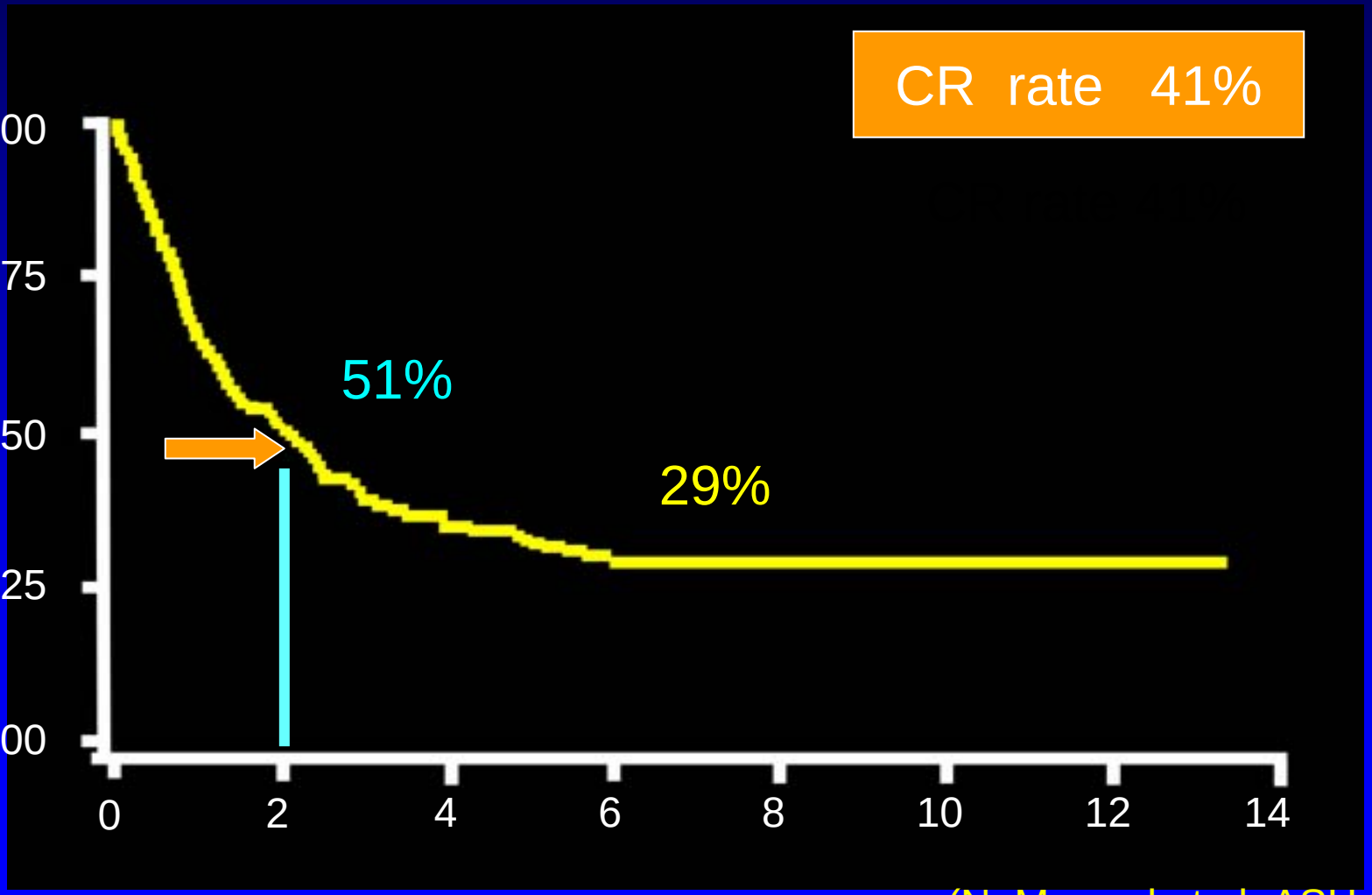
	All T/B p	T large cell/all	T non ALC/ B all	T non ALC/ B non ALC
❖ Age	0.0001	0.0001		
❖ Stage	0.0001	0.0001		
❖ PS	0.0001	0.0001		
❖ LDH	0.0001	0.0001		
❖ IPI 1	---	---	0.0001	0.0001
❖ T all	0.003	---		
❖ Large T cell	---	0.01		
❖ T non ALC	---	---	0.0004	0.0007





Gisselbrecht et al Blood1998

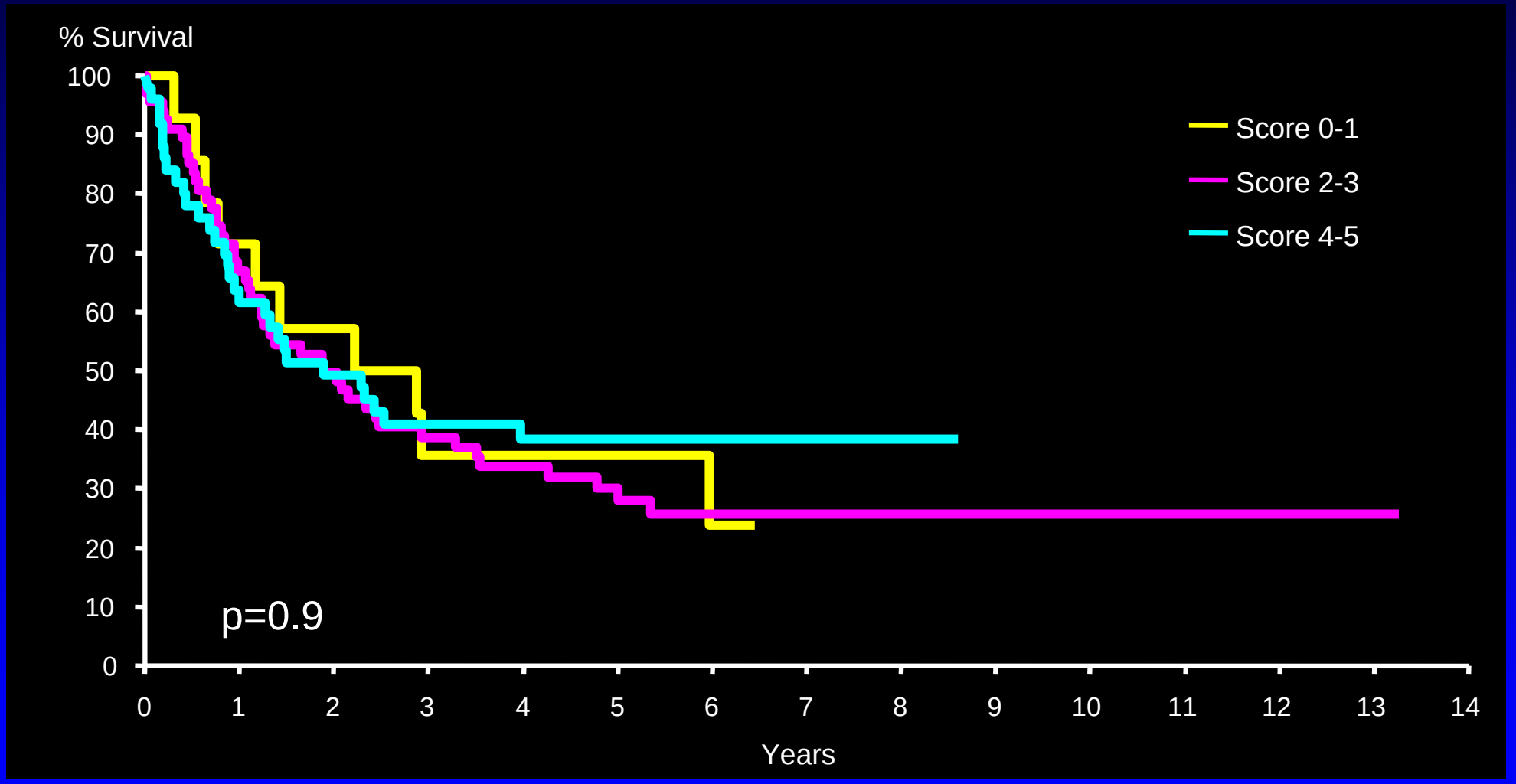
OVERALL SURVIVAL OF THE 156 PATIENTS WITH ANGIOIMMUNOBLASTIC T-CELL LYMPHOMAS: LNH 87-LNH93



(N. Mourad et al.,ASH 2006)

Overall Survival by Complete IPI: AIL

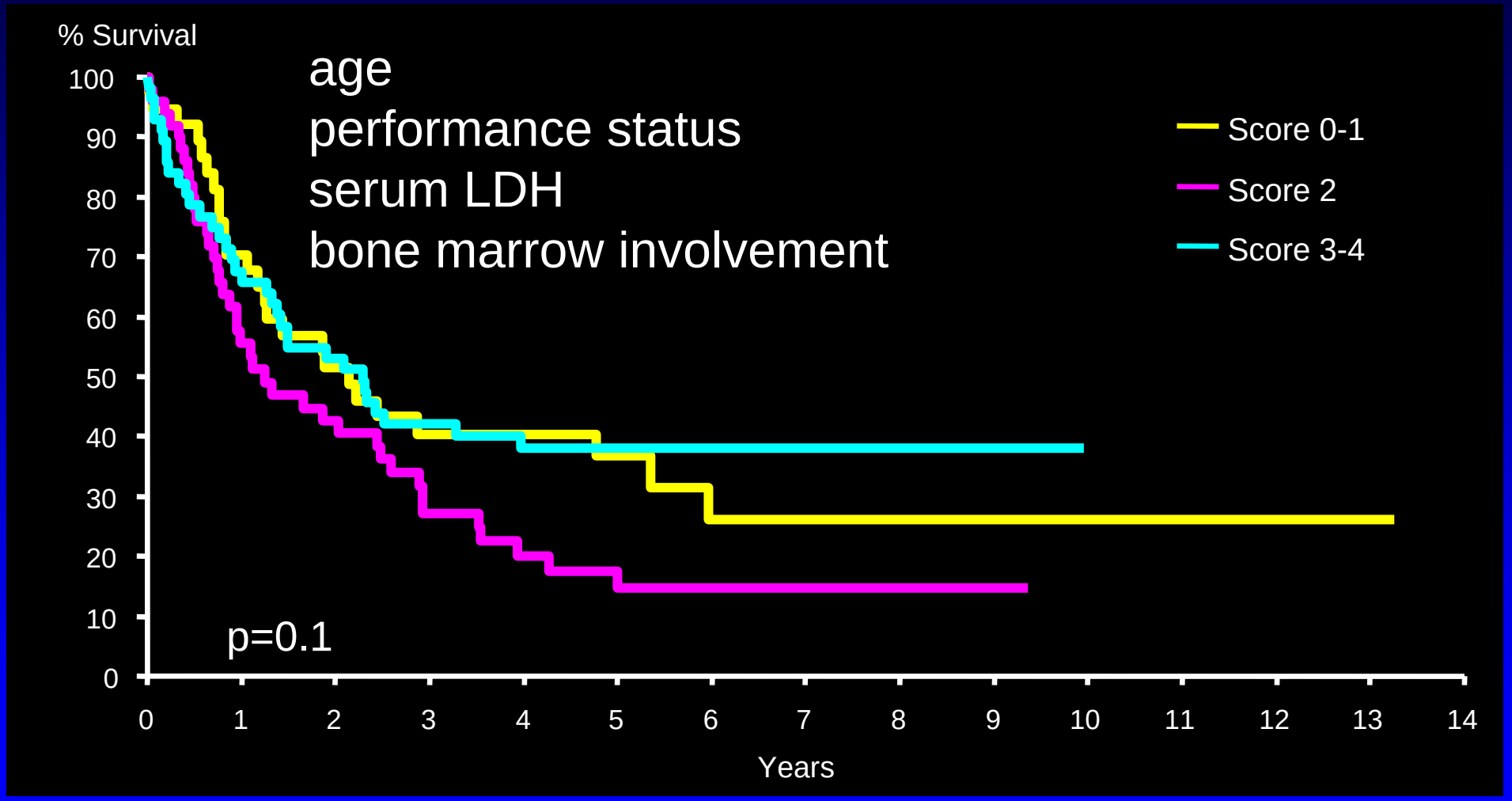
LNH 87-LNH93



N. Mourad et al ASH 2006

Overall Survival by PIT AIL

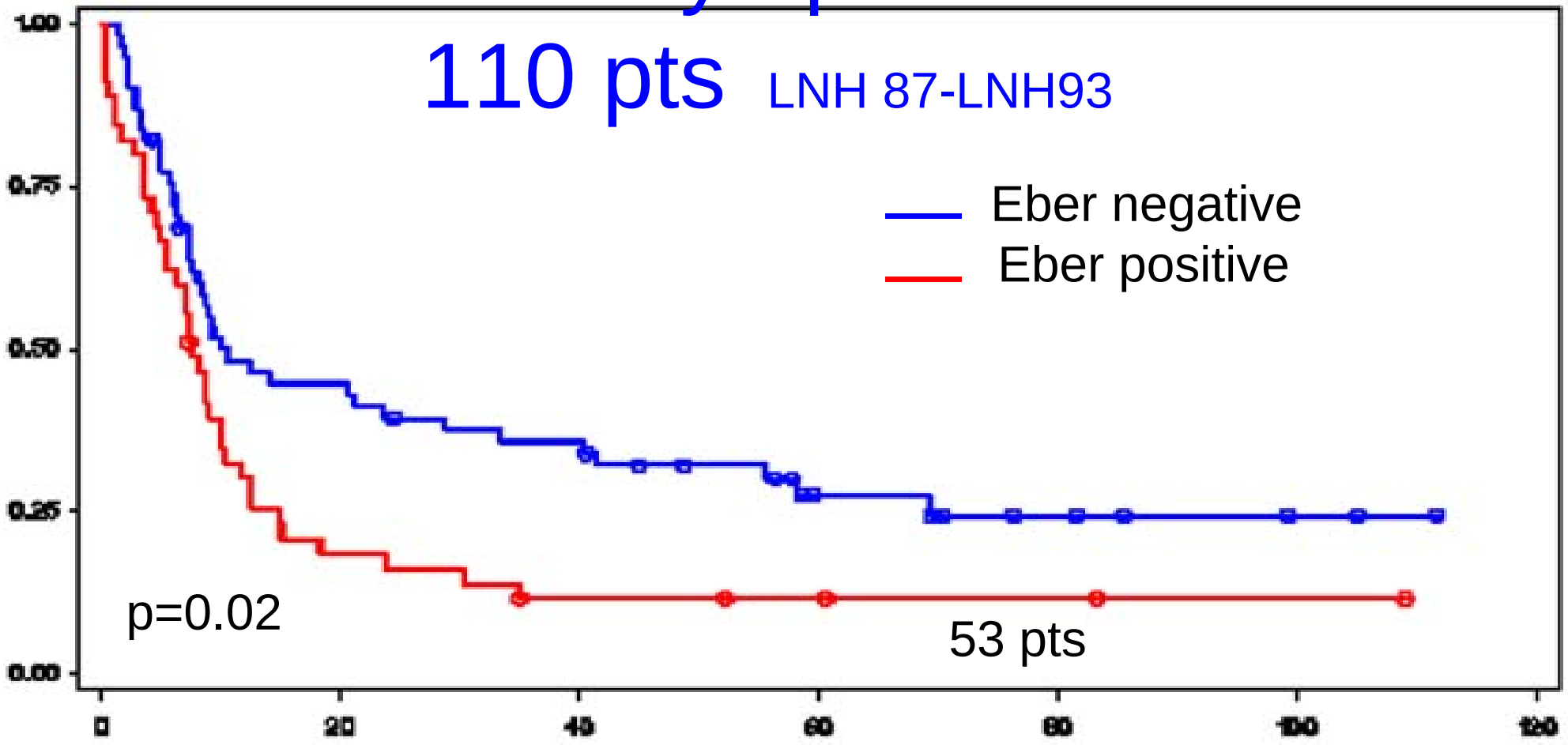
LNH 87-LNH93



N. Mourad et al ASH 2006

T-cell nodal lymphoma NOS

110 pts LNH 87-LNH93



Event Free Survival

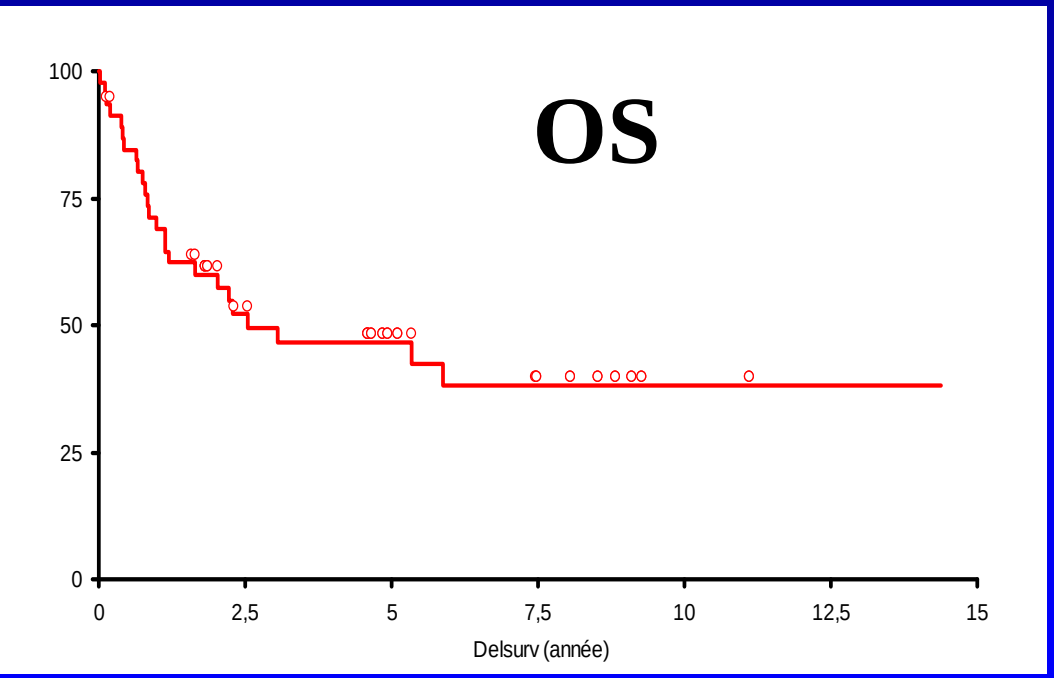
Dupuis J. et al Blood 2006

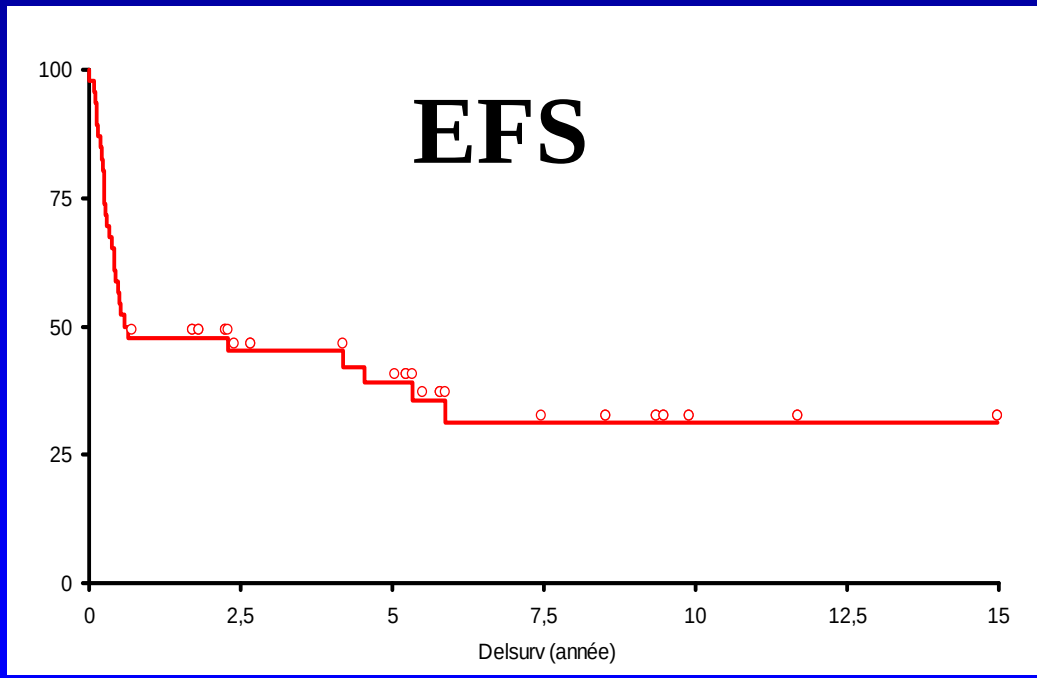
Nasal Type NK/T Lymphoma n= 48

- Stage I-II : 38/48 (79%)
- PS ≤ 1 : 28/47 (60%)
- LDH ≥ 1N : 34/48 (71%)
- IPI ≤ 1 : 31/47 (66%)

1st Line chemotherapy:

CR rate 50%





Belhadj K. et al Blood 2006

WHERE IS THE PROBLEM ?
COMPLETE RESPONSE TO TREATMENT

I.P.I		T CR %	B CR %	p
Score	0	82	81	0.7
	1	73	71	0.7
	2	58	63	0.4
	3	35	52	0.001

(C. Gisselbrecht et al., Blood 92 : 76-82, 1998)

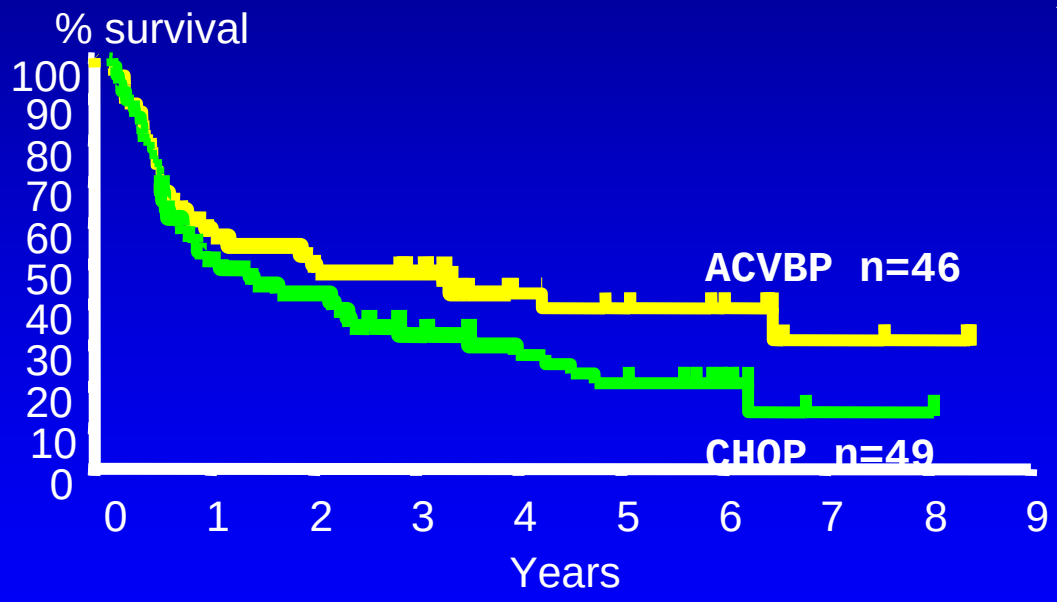
PERIPHERAL T CELL LYMPHOMA

International Prognostic index	n	%	5 y survival (%)	p
Score 0				
T	32	13	81	0.5
B	214	8	84	
Score 1				
T	46	21	58	0.5
B	324	26	63	
Score 2				
T	72	33	34	0.01
B	381	31	52	
Score 3				
T	99	45	24	0.1
B	502	41	34	

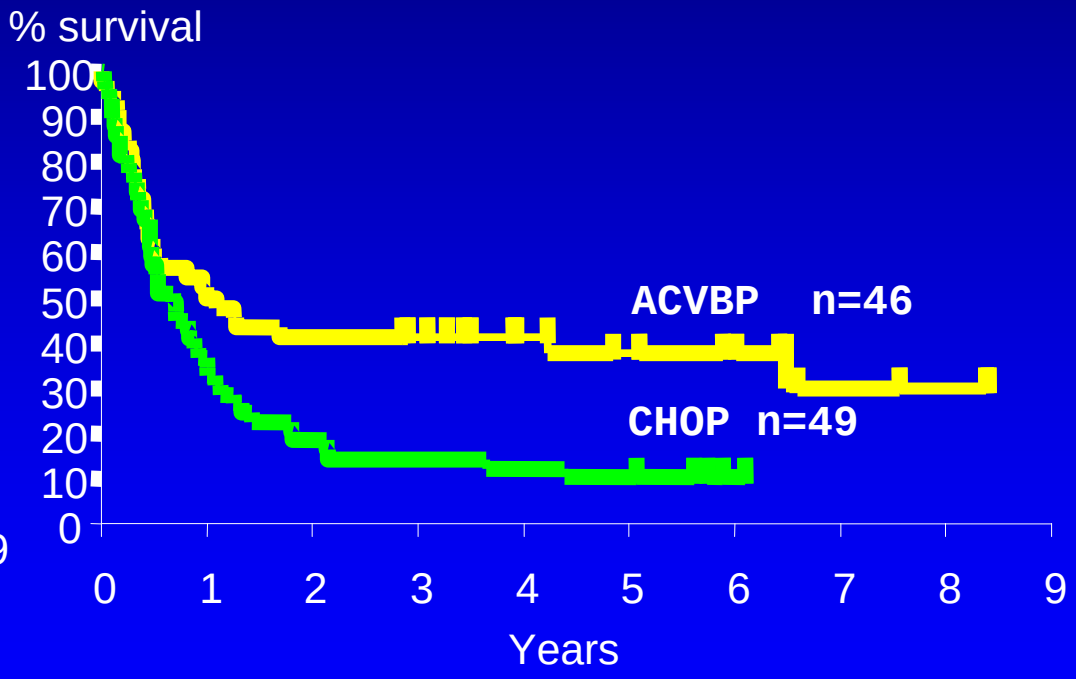
(C. Gisselbrecht et al., Blood 92 : 76-82, 1998)

ARE INTENSIVE REGIMEN BETTER?

OVERALL SURVIVALCHOP:ACVBP T CELL LYMPHOMA LNH 93-5 STUDY



EVENT FREE SURVIVALCHOP:ACVBP T CELL LYMPHOMA LNH 93-5 STUDY



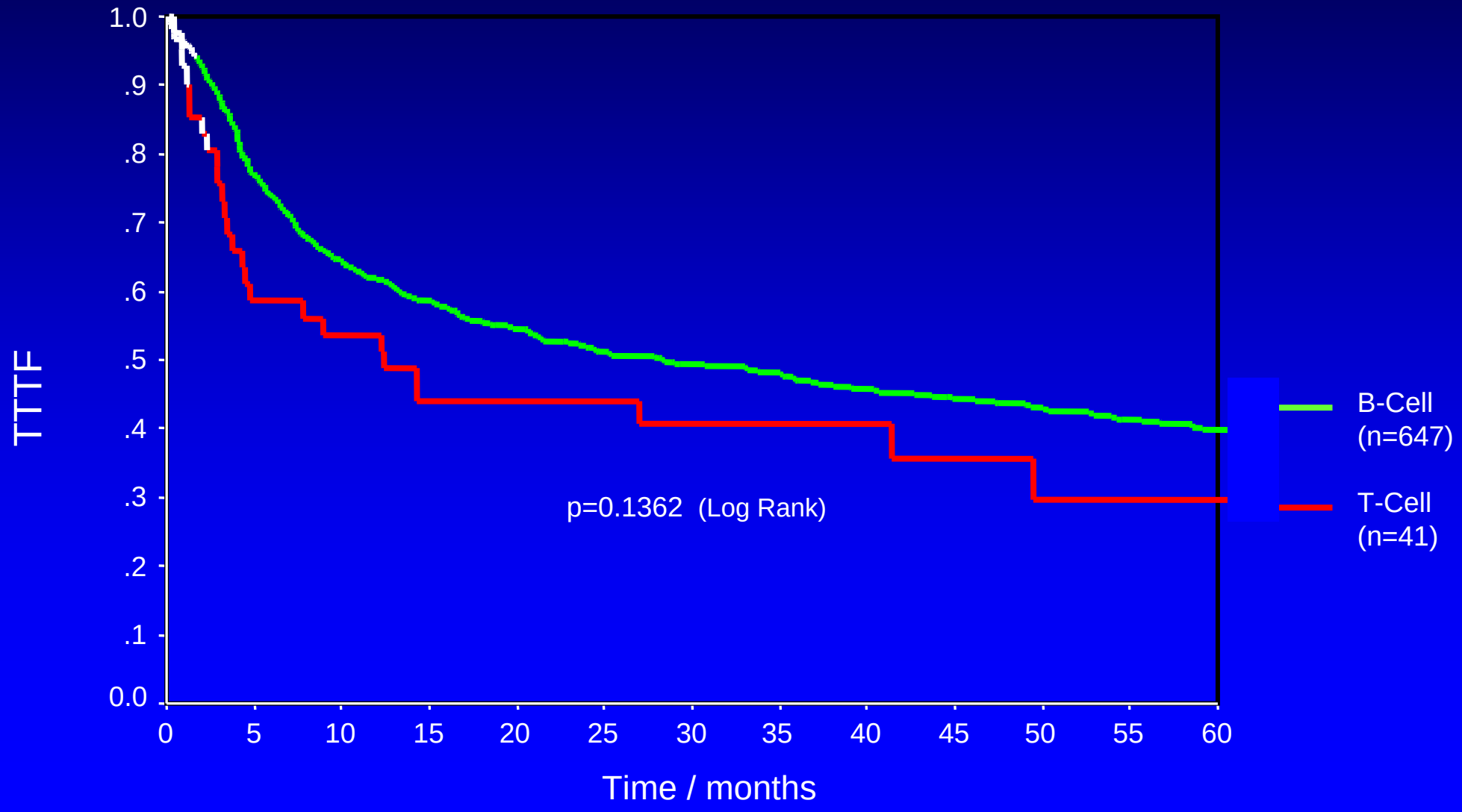
(Tilly et al, Blood 2003)

ARE INTENSIVE REGIMEN BETTER?

DSHNHL

NHL-B2 – Trial

Pts > 60 years (n=689) ; CHO/E/P 14 vs 21



SPECIFIC CHEMOTHERAPY TREATMENTS FOR T-CELL LYMPHOMA ?

- CHEMOTHERAPY REGIMENS :

- None of the chemotherapy regimens used in retrospective analysis has been clearly proven to be effective

- Phase II studies are necessary with w ell defined evaluation criteria, to explore new combination.
  Adapted to histological subtypes??

First goal : → To achieve a high remission rate.

- Dedicated phase II

GELA studies: Ara C - Platinum (ESHAP) based regimen
Burkitt type of regimen not fully explored

New generation:
Gemcitabine combination
ACVBP velcade- R CHOP (AIL)- Campath-CHOP

LNH 98T8

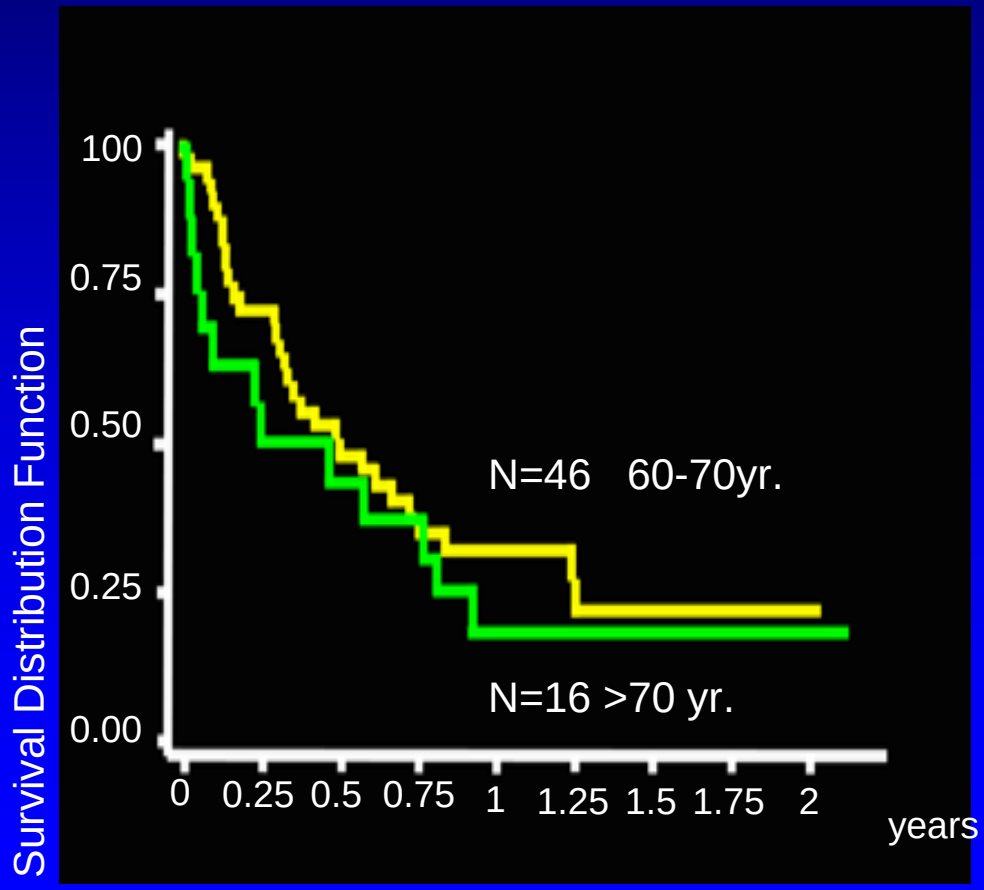
ESHAP X 6 CYCLES (Q 3 WKS) + 13 CIS RÉTINOÏQUE ACID (ROACCUTANE®) 0,5 MG/KG/D 12 M

T-CELL LYMPHOMA > 60 YR/ >70YR : EVENT FREE SURVIVAL

inclusion 77 patients

evaluable 58 patients

Tt completed	41%
CR + CRu	33%
Progression	38%
EFS 2 years	21%
OS 2 years	36%
Toxic deaths 19% (29 % pts > 70)	



R Bouabdallah

LNH 98T7

Inclusion 89 patients
Evaluable 83 pts

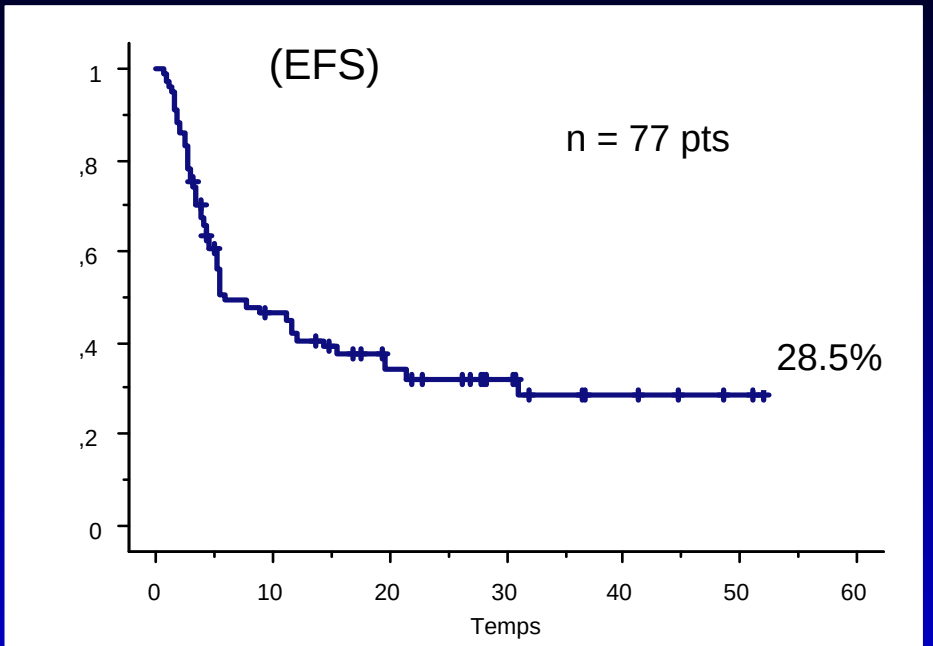
induction completed	72%
RC	30%
RCu	22%
Progression	27%
EFS median	6 m
OS median	26 m
toxic deaths 6%	

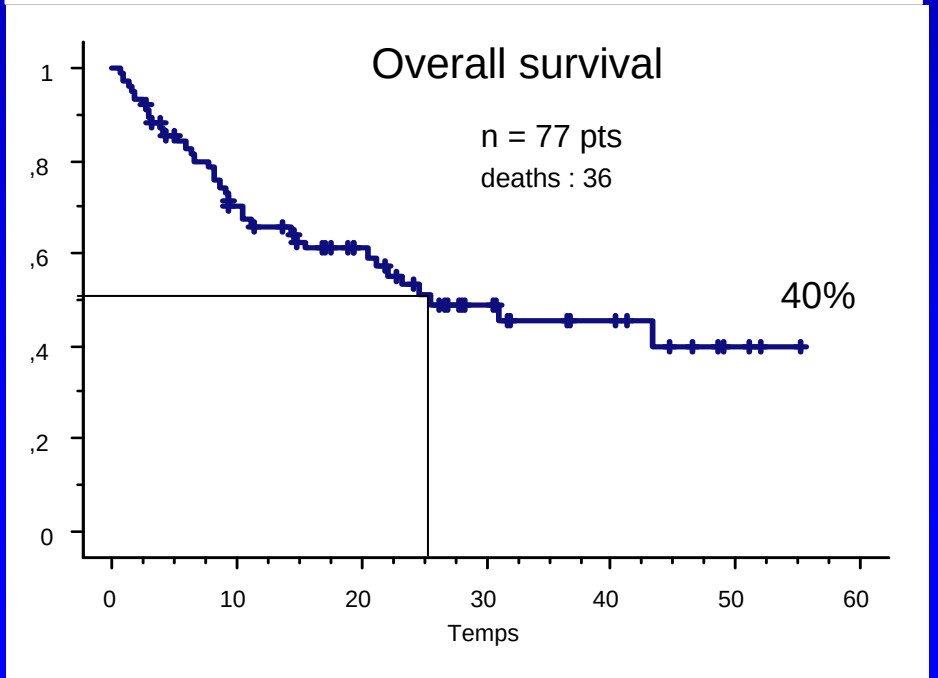
Induction

D1	COPADM/dexa
D22	CYVE/dexa
D43	COPADM/dexa
D64	CYVE/dexa

Burkitt's type

(Delmer et al., ASCO 2003)





Gela
GROUPE D'ÉTUDE DES LYMPHOMES DE L'ADULTE

We need new drugs !!!

V-ACVBP (ACVBP + Velcade 1,5 mg/m² D1 & D5)

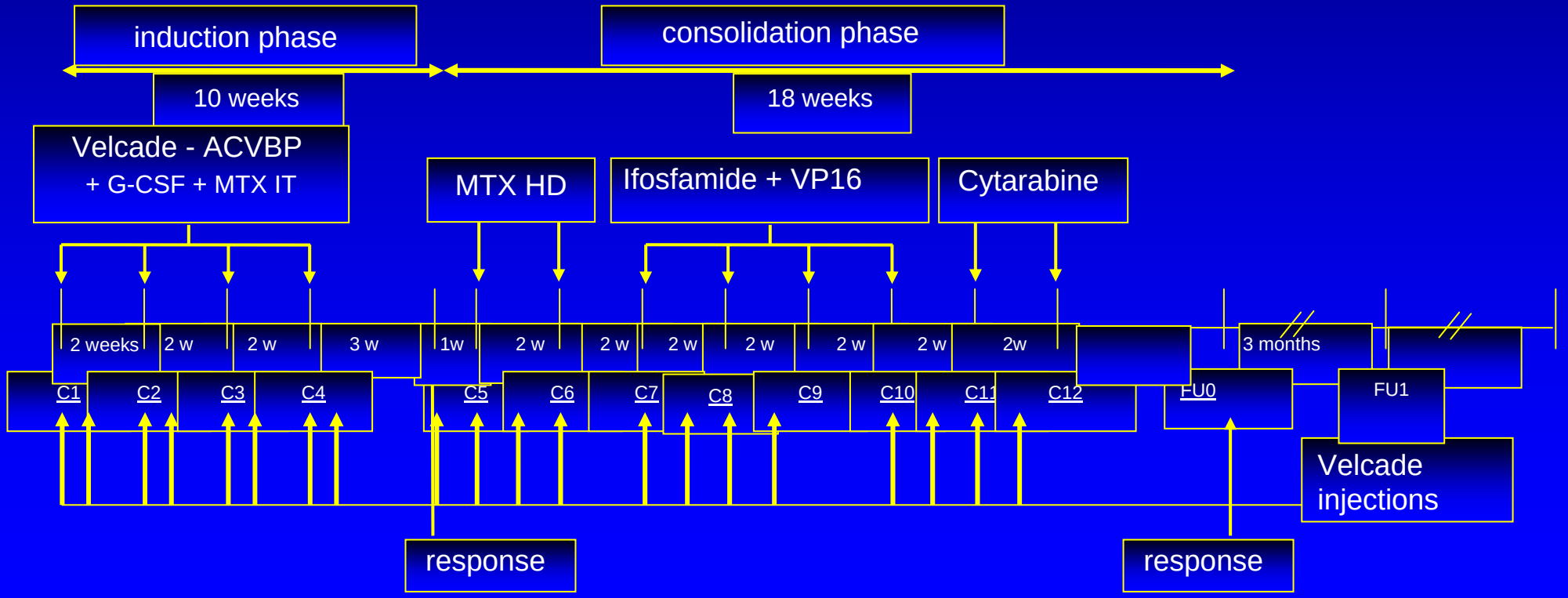
drugs	dose		D1	D2	D3	D4	D5	D6 to D13
Prednisone	60 mg/m²	IV/per os	X	X	X	X	X	
Doxorubicine	75 mg/m²	IV	X					
Cyclophosphamide	1200 mg/m²	IV	X					
Vindesine	2 mg/m²	IV	X				X	
Bleomycine	10 mg	IV	X				X	
Methotrexate	15 mg	IT		X				
VELCADE	1.5 mg/m2	IV	X				X	
G-CSF	5 µg/kg/d	SC						X

Gela
GROUPE D'ÉTUDE DES LYMPHOMES DE L'ADULTE

LNH04-1T

Non anaplastic T CELL
Lymphoma patients 18 - 65 yrs
Non previously treated

Phase II study: 60 patients
Main objective EFS

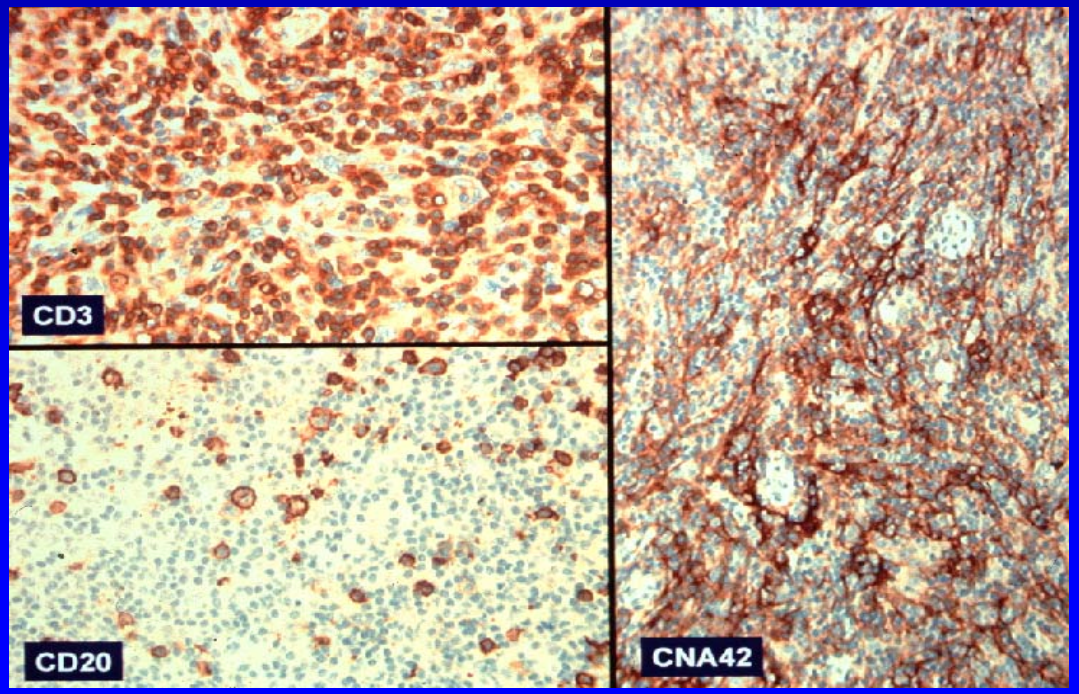


Gela
GROUPE D'ÉTUDE DES LYMPHOMES DE L'ADULTE

We need new ideas !!!

protocol RAIL

CHOP + rituximab in T-cell angioimmunoblastic lymphoma



C. Haioun

EUROPEAN APPROACH

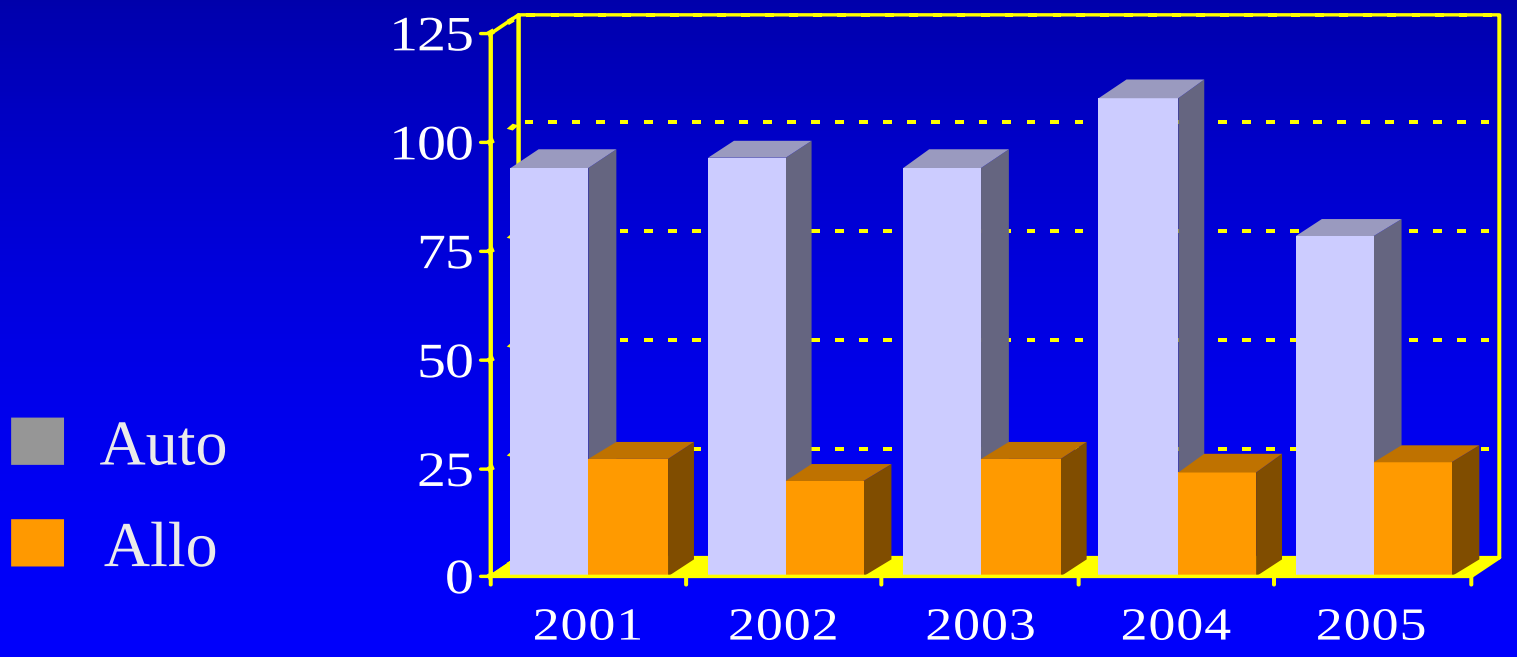
PTCL TREATMENT

- PTCL are difficult diseases and progress should be made to establish better treatment and to better understand the biology of the diseases.
- An European Network is emerging for academic studies and to help the development of new drugs.
- Two directions : transplantation- Campath CHOP

- **IMPACT OF AUTOLOGOUS STEM CELL TRANSPLANTATION**
- **AT LEAST AS GOOD! AS STANDARD CHEMOTHERAPY**
- **REGISTRY DATA ARE ENCOURAGING ALSO FOR AUTO AND RIC ALLO**

EBMT REGISTRY
Auto/Allo SCT for Periph T-cell Lymphoma

	Autologous	Allogeneic	Total
Peripheral T-cell	472	126	598



IN AGRESSIVE LYMPHOMA, THE UNFAVORABLE PROGNOSIS ASSOCIATED WITH THE T-CELL PHENOTYPE IS NOT OVERCOME BY HDT

A RETROSPECTIVE STUDY OF 330 PATIENTS (T-CELL PHENOTYPE,16%) RESPONDER TO ACVBP INDUCTION AND RECEIVING HDT WITH ASCT

LNH 87- 93 ASCT cohort

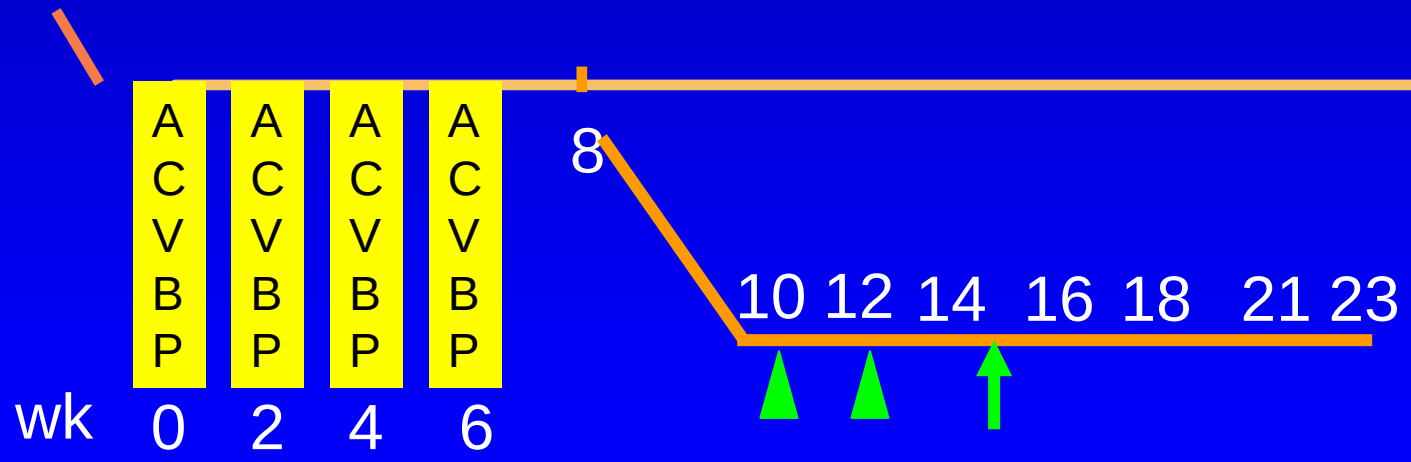
N = 916

541 responders

268 randomized => 198 ASCT

N=391

236 CR/CRu (60%) => 132 ASCT



(N.Mounier et al. JCO 2004)

Up front autoTransplantation in aggressive lymphomas:

- Prognostic factors affecting results in a cohort of 330 aggressive B or T cell lymphoma patients treated with ACVBP + ASCT after remission (CR).

MULTIVARIATE SURVIVAL ANALYSIS OVERALL SURVIVAL

CHARACTERISTICS	Relative risk	CI 95 %	p-value
AGE			
Above vs.below 35	1.65	[0.97;2.80]	0.06
EXTRANODAL INVOLVEMENT			
> 1 SITE vs 0-1 site	2.22	[1.36;3.63]	0.014
BONE MARROW INVOLVEMENT			
Present vs. absent	1.73	[1.04;2.88]	0.035
Histology			
Non Anaplastic T vs others	2.98	[1.62;5.46]	0.0006

- matched comparison with a cohort of patients treated with ACVBP without ASCT in prospective GELA studies.

»

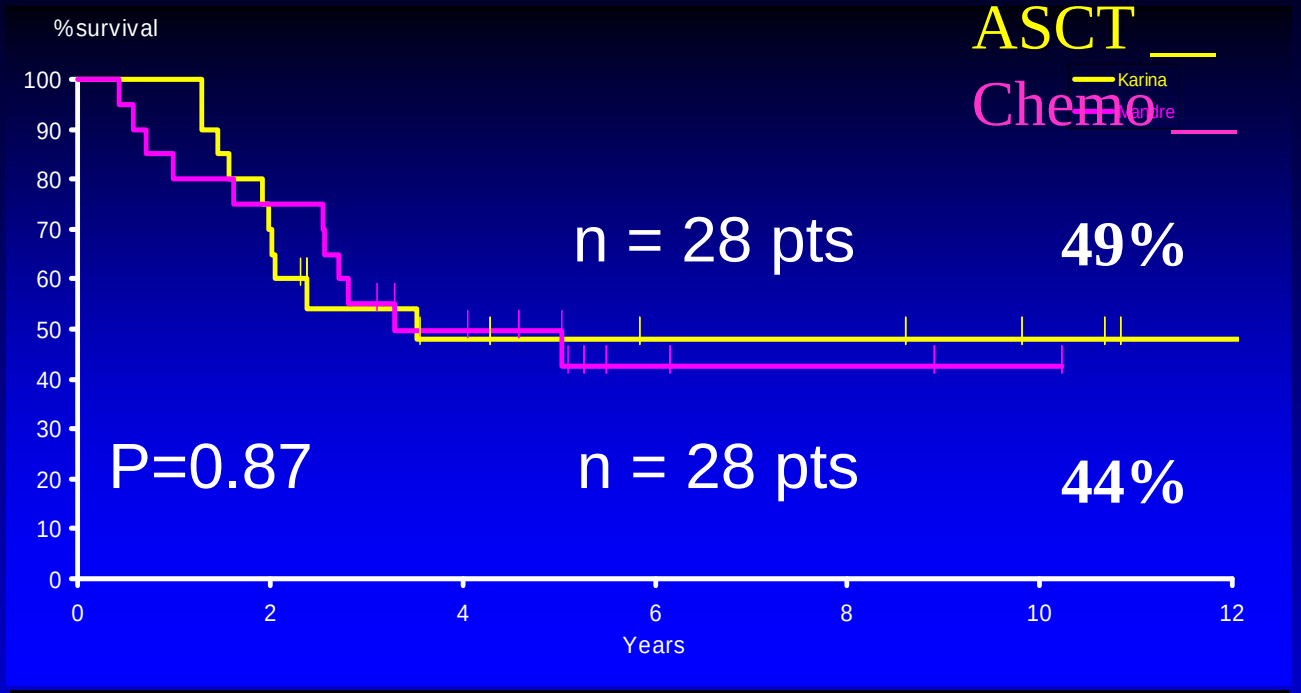
N. Mounier JCO 2004; Ann Oncol 2004

Up front autoTransplantation in T cell lymphomas

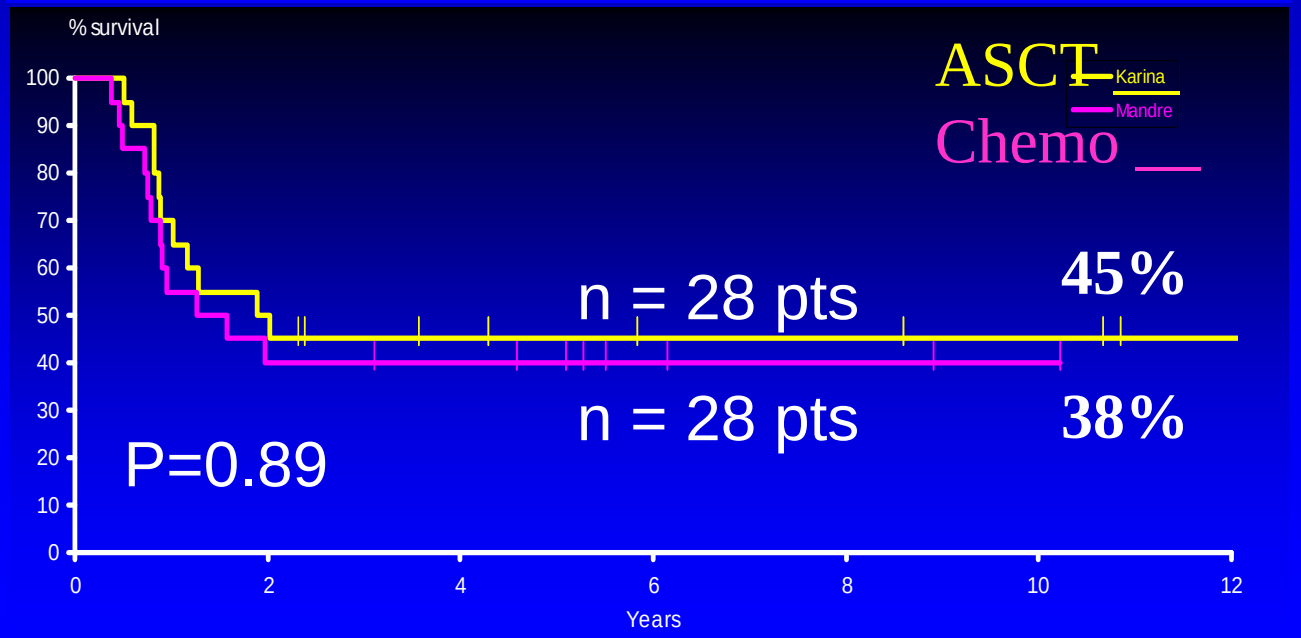
Matching
graft / non graf t
Consolidation

T non anaplastic
Lymphoma

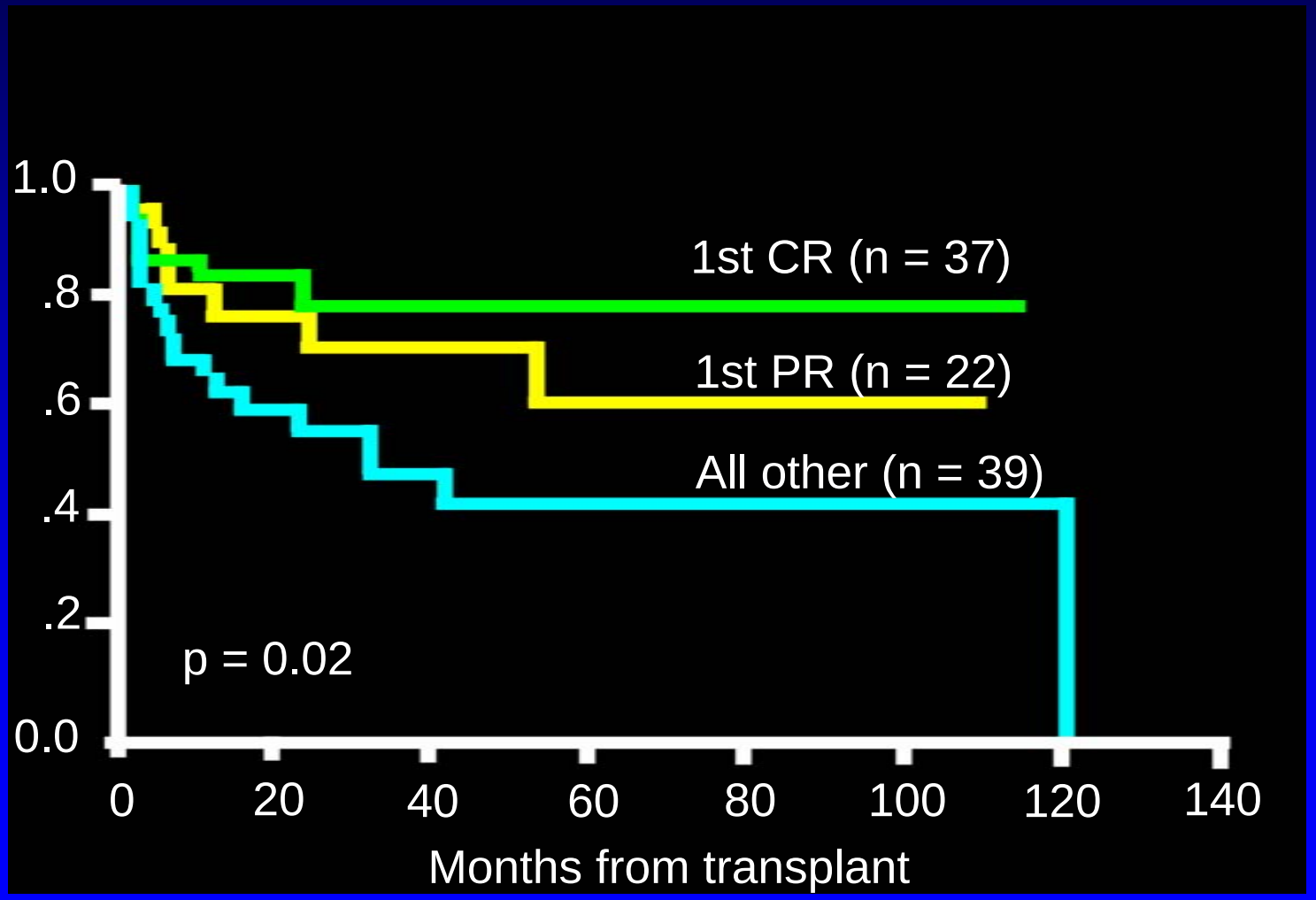
OS



EFS



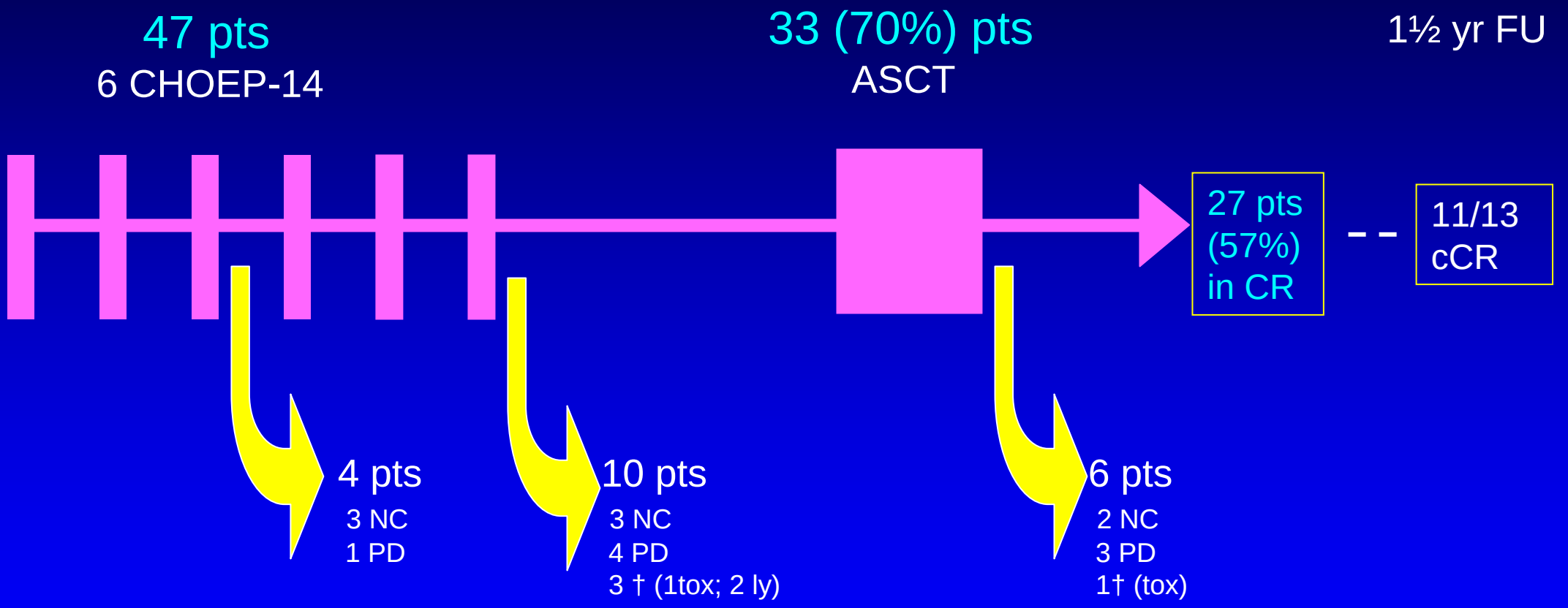
HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN PERIPHERAL T-CELL LYMPHOMA: THE GEL-TAMO EXPERIENCE



(J. Rodriguez, et al., Ann. Oncol., 2003)

Preliminary results – NLG-T-01

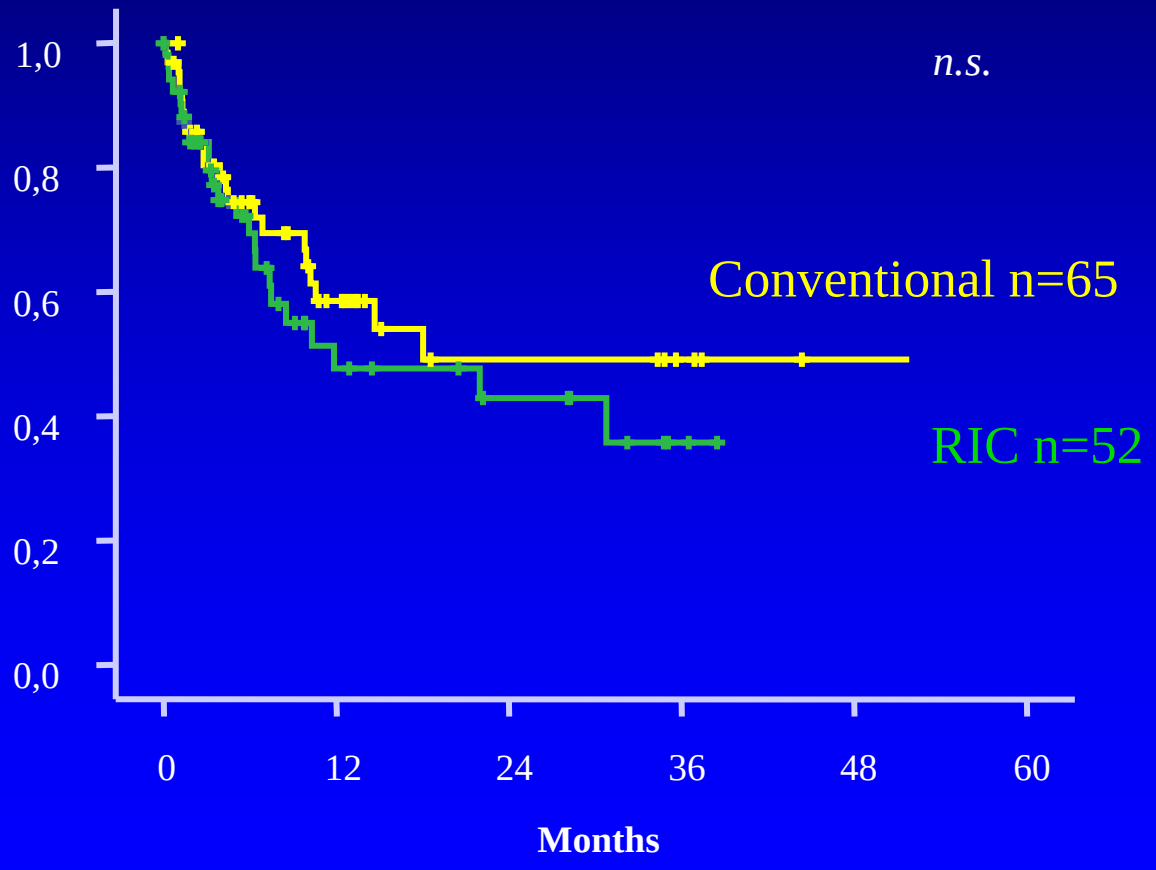
N_{tot}=64; N_{eval}=47 (17 under treatment)



NB: 4/5 enteropathy-type pts = PD
2/2 (PTCLu) late relapses in BM

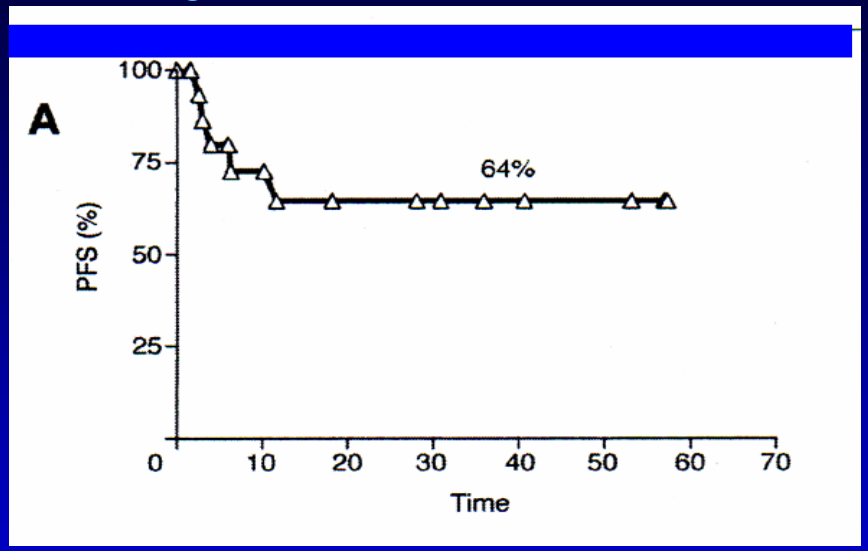
Courtesy F d'Amore

EBMT REGISTRY
Allo SCT for Periph T-cell L: OS by conditioning

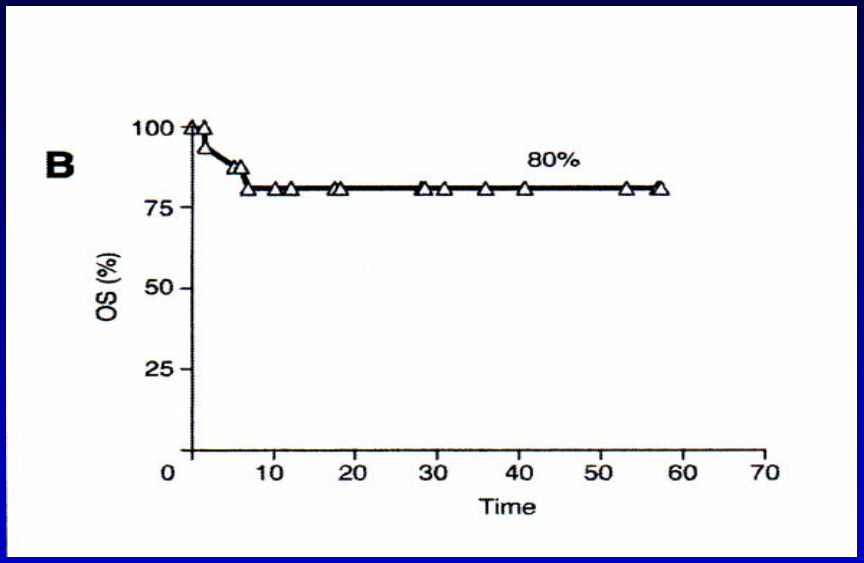


SURVIVAL AND TRANSPLANT-RELATED MORTALITY (TRM) CURVES.

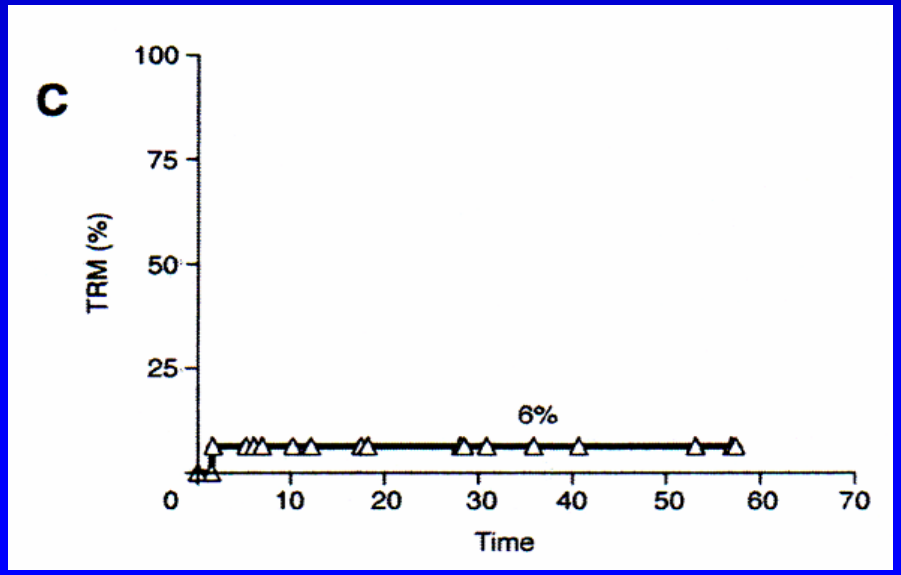
Progression Free survival



Overall survival



TRM curve of patients who received allograting



JOURNAL OF CLINICAL ONCOLOGY

(P. Corradini, JCO, 2004)

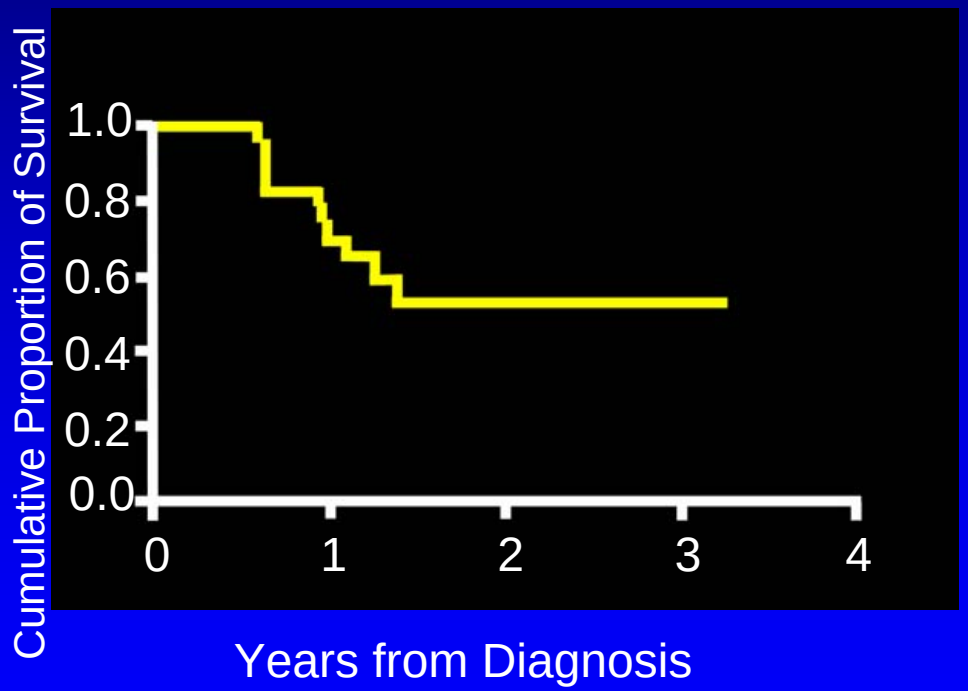
Combination chemotherapy-alemtuzumab

- A growing clinical experience with the combination alemtuzumab + CHOP/CHOP-like:
  Gallamini, Hovon, BNLI, DSHNHL ..
  or +fludarabine-based chemotherapy: Weidmann

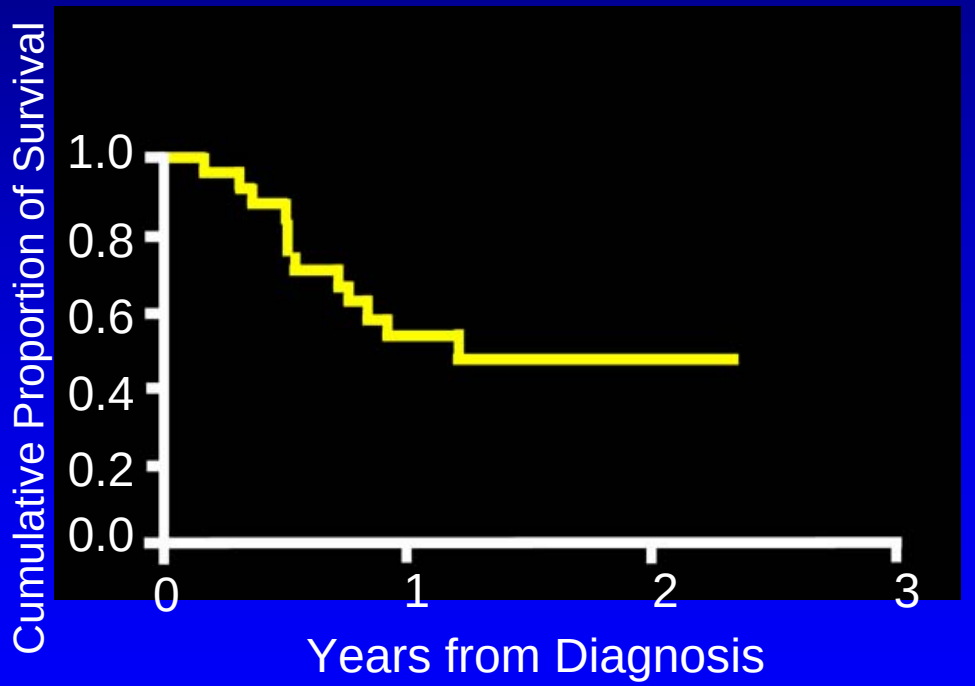
- (>100 patients treated so far) experience is accumulating through ongoing phase II clinical studies.
-
- Toxicity was reduced with monitoring and prophylaxis of viral infections. A-CHOP is manageable.
- Alemtuzumab dose in association is between 30mg to 60 mg per cycle, depending on the chemotherapy used.

CHOP, CAMPATH 1H,
24 Peripheral T Cell Lymphoma patients
First line treatment
CR rate 70%

Overall Survival (24 pts)



Failure free Survival (24 pts)



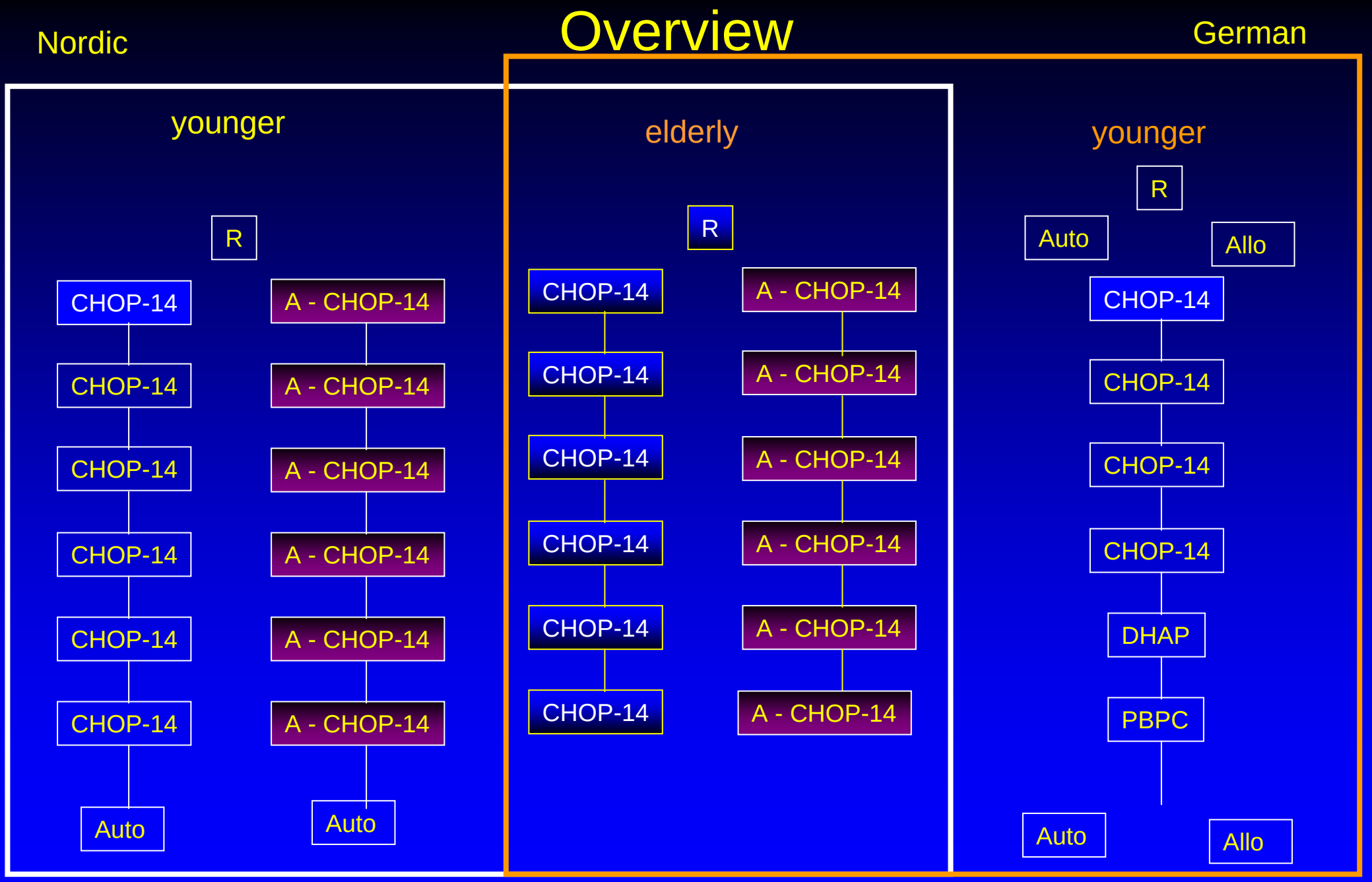
(A. Gallamini, et al., Blood 2007)

EUROPEAN PERSPECTIVE

- TOWARD A MULTICENTRIC RANDOMIZED STUDY

- Participating countries and groups:
- Nordic lymphoma group F. d'amore , Germany DSHNHL L. Trümper , N Schmitz
- HOVON, GELA GOELAMS, GELTAMO, IIL, NCRI, ALLG, SAKK, CLG, PLG, Israel, Austria,Portugal, Russia, ….several pending
- Pathologists and clinicians wi ll work together to assure diagnosis and to study biological aspects of this rare disease.

Overview

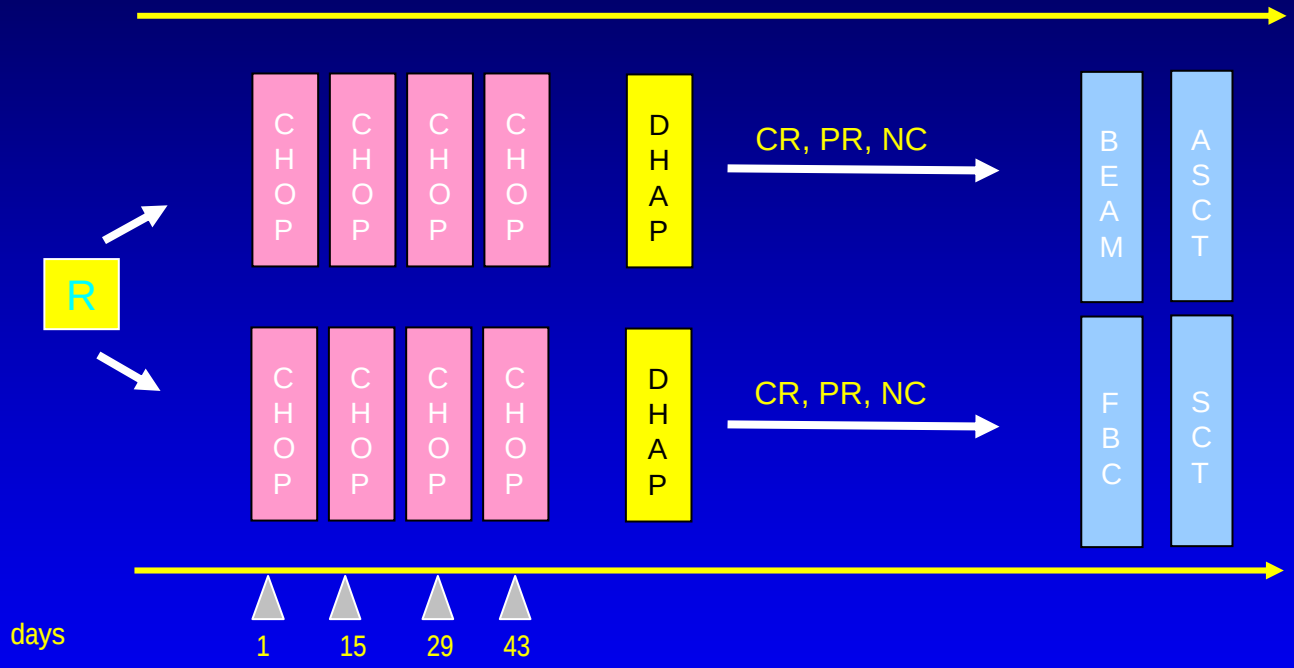


Alemtuzumab: 30mg S/C d 1,2

first-line treatment of PTCL (d60 yrs)

PTCL
- non-cutaneous PTCL
- except alk-positive ALCL

- IPI t 2



R = At diagnosis, patients are r andomized to allogeneic or autolog ous transplantation. Donor search (family or unrelated) will be initiated only in pa tients randomized to allogeneic transplantation. Patients randomized to allogeneic tx but without a donor will receive autol ogous tx. Peripheral blood stem cells are harvested after DHAP in patients who will receive au tologous tx (randomized or crossed over).

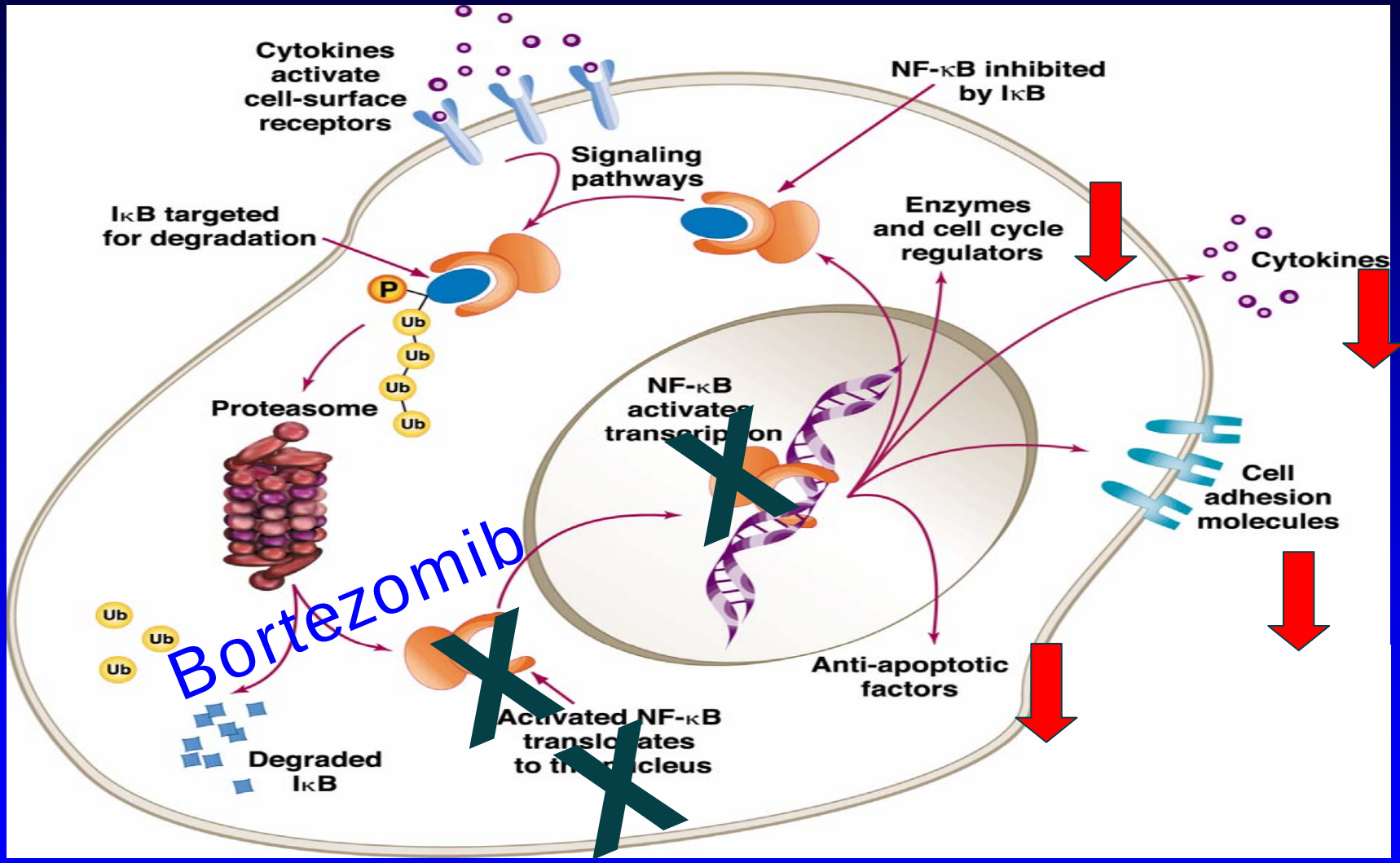
Chair: N.Schmitz

New drugs for T cell Lymphomas

New insights to the biology of cancer help to find new targets for therapeutic agents

- Monoclonal antibodies
- Signal Transduction
- Transcription regulation
- Angiogenesis Inhibitors
- Microenvironment
- Protéasome Inhibitors
- Cell cycle Modifiers
- Apoptosis Inhibitors
- Antigene expression Modulators
- Dendritic Cells
- Vaccines
- Gene therapy …

Bortésomib = Protéasome Inhibitor



Bortezomib in Refractory CTCL
Phase II

- N = 15 – 12 evaluable patients
- Dose : 1.3 mg/m ^{2} IV D 1, 4, 8 and 11 every 21 days X 6 cycles

Results

Efficacy

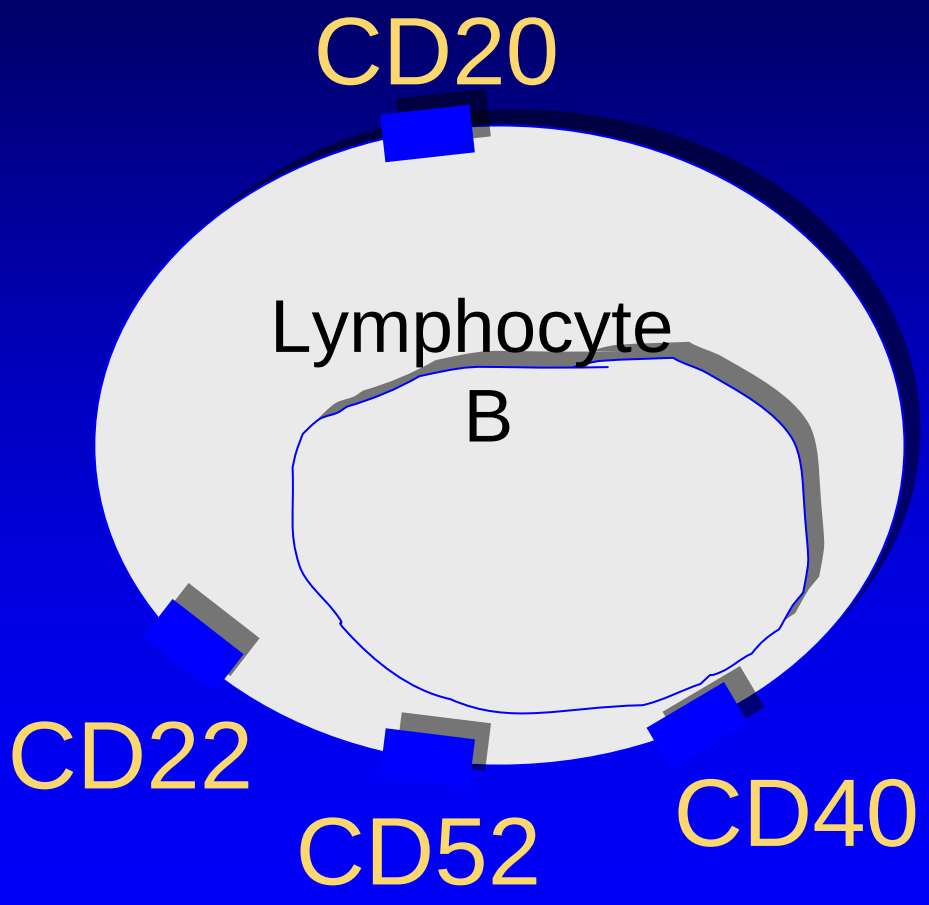
- ORR = 8 (67%) : CR = 2 PR = 6 (+ 2 PR in PTCL)
- Median TTF = 9 months (range, 3-10)

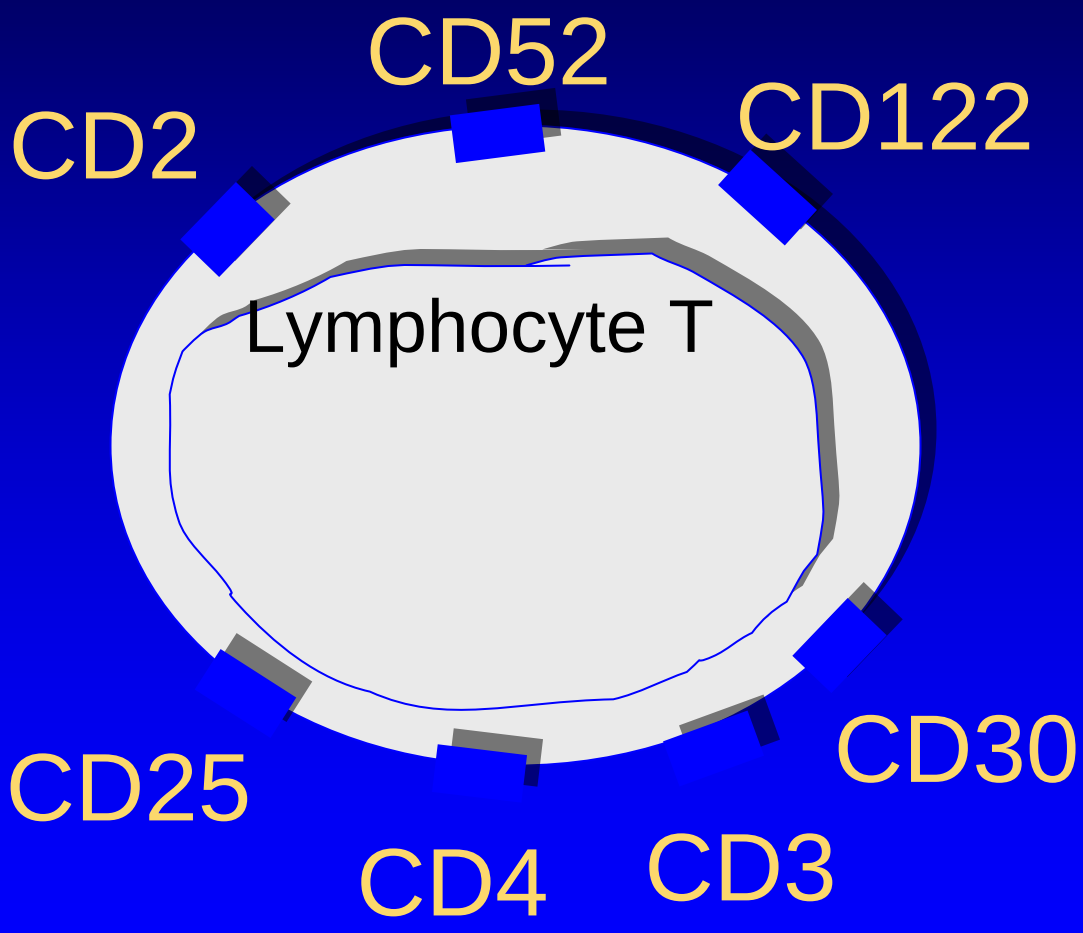
Grade 3 Toxicity

- Neutropenia = 2 (17%)
- Thrombocytopenia = 2 (17%)
- Sensory neuropathy = 1 (8%)

Zinzani, et al. Blood 2006 vol 108 Abstract 2462

Antigens expression





Zanolimumab

- Target : CD4 T lymphocyte

• in PTCL

N= 19 patients at least 1 infusion of zanolimumab - Follow up: at least 6 weeks

- Good tolerance
- Objective response: in 4 patients

d'Amore F, et al. Blood 2006 vol 108 Abstract 2723

• In CD4-+ MF type CTCL (Stage IB-IVB) Refractory or Intolerant to Bexarotene and one Other Standard Therapy

N = 24

- Good tolerance at doses of 4 -14 mg/kg
- Objective response : in 5 / 12 patients

Duvic M, et al. Blood 2006 vol 108 Abstract 2731

SGN-30 (Anti-CD30 mAb) in CD30 + Lymphoproliferative Disorders Phase I

- Target : CD30
- Chimeric monoclonal antibody
  - Blocks the G1 phase
  - \+ Enhance the efficacy of standard ch emotherapies by drug sensitization through growth regulating and proapoptotic pathways
- Phase II trial in patients with refract ory primary cutaneous ALCL (pcALCL) and symptomatic CD30 +ve lymphoproliferative disorders
- N = 19 enrolled
  - ORR = 58% : CR = 5
  - Acceptable tolerance (rash; pruritus)

Duvic M, et al. Blood 2006 vol 108 Abstract 2733

MEDI-507 (Siplizumab) in CD2 +ve T-Cell Lymphoma/Leukemia Phase I

- Target CD2
- CD2 =human T- and NK-cells
- humanized IgG1k class
- Induces apoptosis via antibody-dependent cell-mediated cytotoxicity
- Phase I trial
- 0.7 mg/kg, 3.4 mg/kg or 4.8 mg/kg doses were tested

Casale DA, et al. Blood 2006 vol 108 Abstract 2727

New drugs for T cell Lymphomas

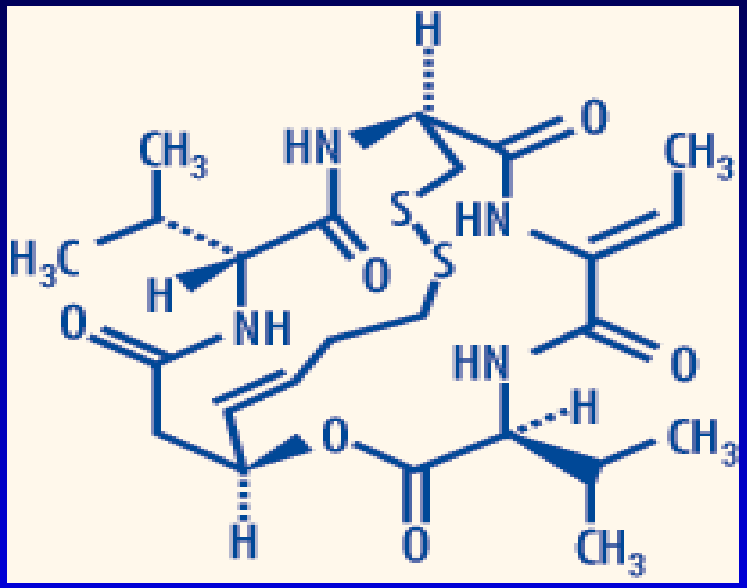
New insights to the biology of cancer help to find new targets for therapeutic agents

- Monoclonal antibodies
- Signal Transduction
- Transcription regulation
- Angiogenesis Inhibitors
- Microenvironment
- Protéasome Inhibitors
- Cell cycle Modifiers
- Apoptosis Inhibitors
- Cytotoxic agents
- Antigene expression Modulators
- Dendritic Cells
- Vaccines
- Gene therapy …

Histone deacetylase inhibitor: Vorinostat in persistant, progressive or refractory CTCL
Olsen et al JCO 2007

- Vorinostat : 400 mg per os until progression
- 74 CTCL MF/SS: 61 IIB, or higher, 30 SS
- Median prior systemic treatments: 3 (22 deniflox)
- Objective response rate: 30%
- Median TTR 56 days- median TTF in responding patients > 300 days. Pruritus relief
- No drug related grade 3 ECG AE. One QTc prolongation
- Phase II on PTCL EU US

Romidepsin (Depsipeptide, FK228) in Patients with Refractory CTCL



Phase II Trial

- Romidepsin is a bicyclic peptide which inhibits both class I and II histone deacetylases
- Early clinical trials have demonstrated activity in T-cell lymphomas
- This single arm phase II trial evaluated the efficacy and safety of Romidepsin in patients with refractory CTCL

Demierre LA, et al. Blood 2006 vol 108 Abstract 2468

Phase II Trial of Romidepsin in CTCL

Demierre LA, et al. Blood 2006 vol 108 Abstract 2468

- N =43
- Romidepsin at 14 mg/m2 as a 4-hour IV infusion on Days 1, 8 and 15 q 28 days, up to 6 cycles

- Results
- Efficacy
  - 38 patients were evaluable for efficacy
  - CR = 3 (8%)
  - PR = 9 (24%)
  - SD = 22 (58%)
  - PD =3 (8%)
  - ORR = 12 (32%)
  - Patients with relief of pruritus = 14 (88%)
  - Median time to response = 8 weeks (range 4-12 weeks)
- Grade 3/4 Adverse Events
  - Nausea (3%) /vomiting (3%), fatigue (6%), diarrhea (3%), pyrexia (6%)
  - Cardiac arrhythmia prolonged QTc interval

•Results on PTCL NCI :

•26 pts: 3CR, 3PR

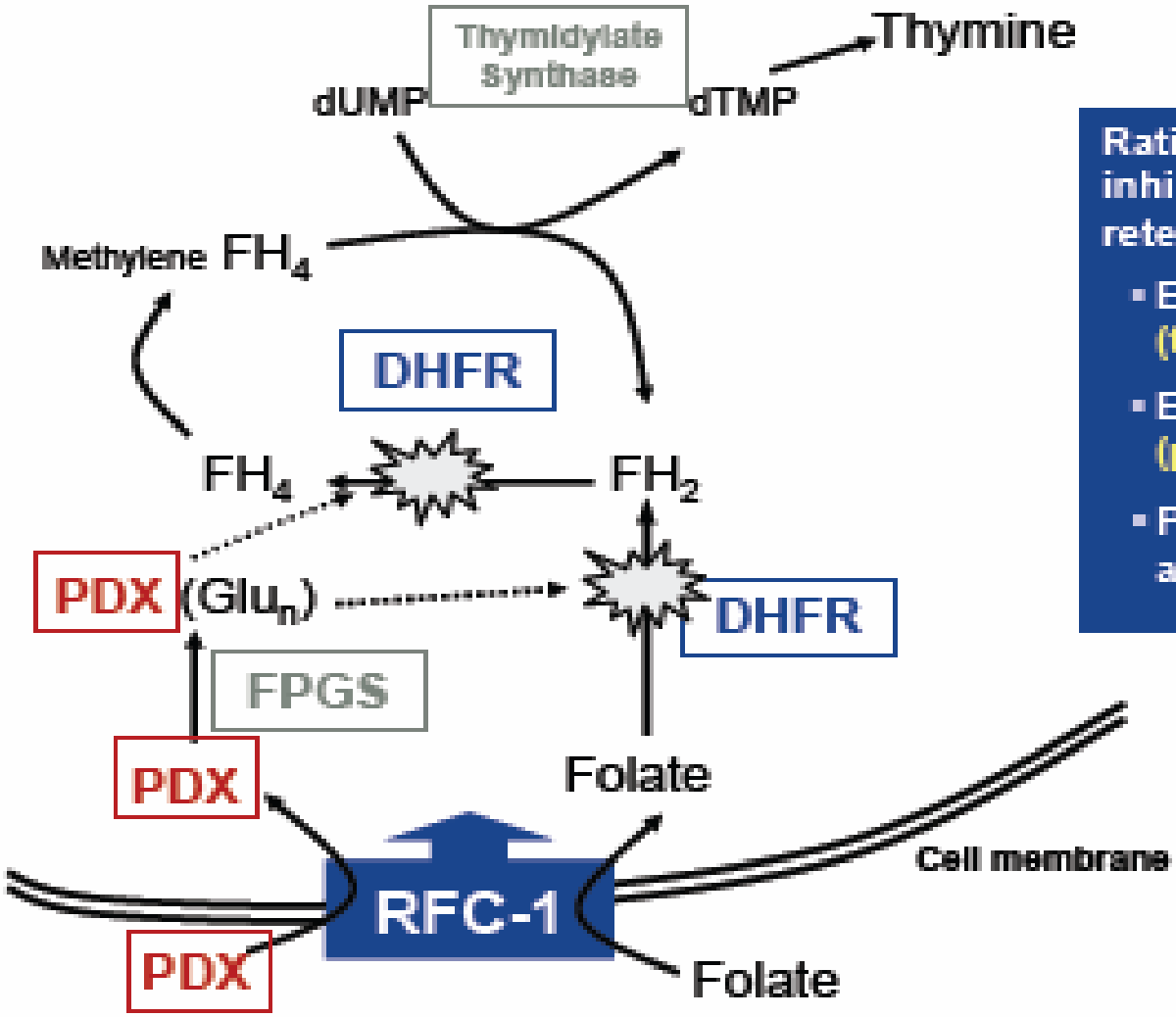
Phase II on PTCL EU US

New drugs for T cell Lymphomas

New insights to the biology of cancer help to find new targets for therapeutic agents

- Monoclonal antibodies
- Signal Transduction
- Transcription regulation
- Angiogenesis Inhibitors
- Microenvironment
- Protéasome Inhibitors
- Cell cycle Modifiers
- Apoptosis Inhibitors
- Cytotoxic agents: antimetabolites
- Antigene expression Modulators
- Dendritic Cells
- Vaccines
- Gene therapy …

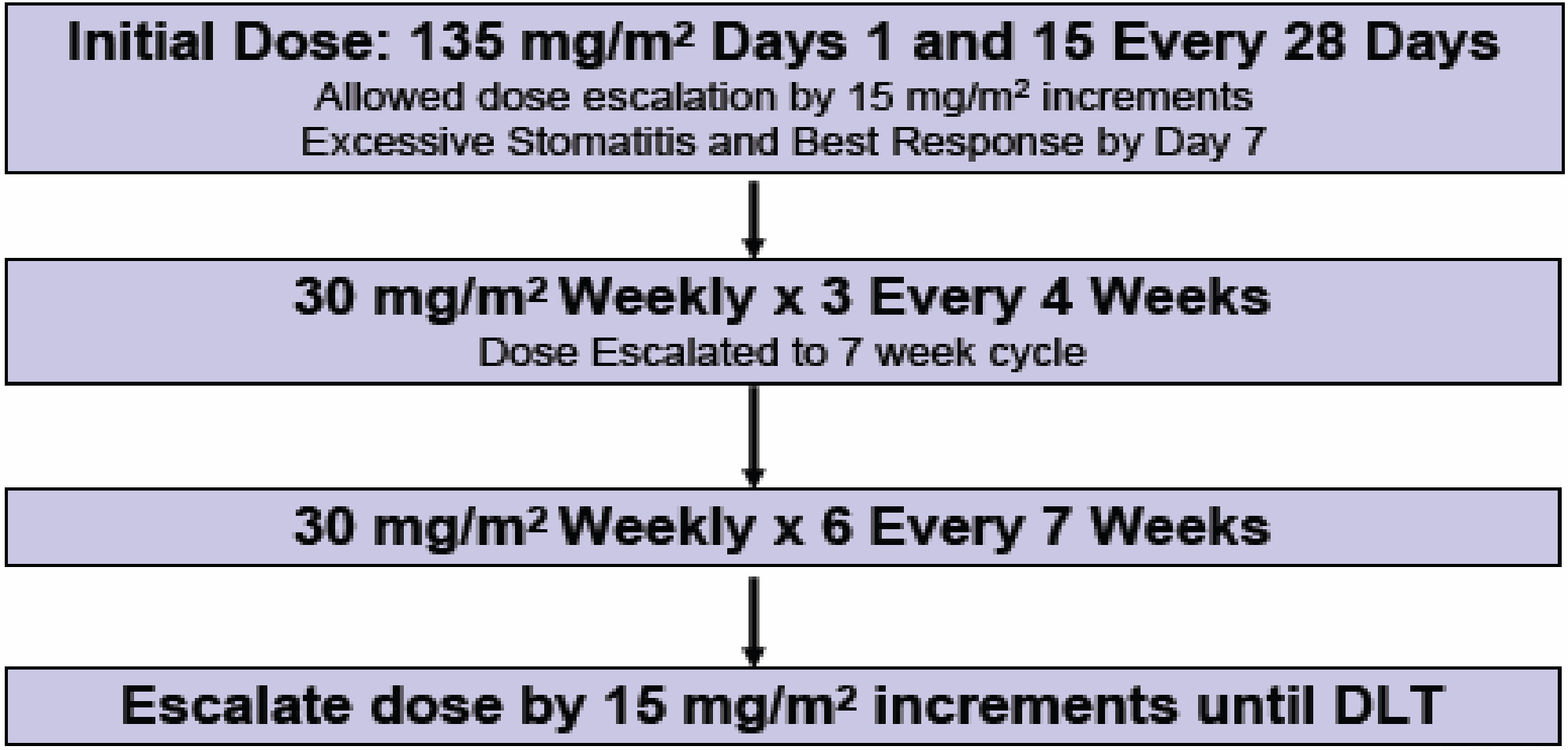
Pralatrexate - A Novel Rationally Designed Antifolate Selectively Targets Folate Metabolism



Rationally designed potent DHFR inhibitor with efficient cell entry and retention

- Efficient permeant for RFC-1 (transport)
- Effective substrate for FPGS (polyglutamation)
- PDX primarily targets DHFR (pM affinity)
  - Allmta, 5-FU and Tomudex target TS

Evolution of Pralatrexate NHL Studies
MSKCC Phase I/II Program (02-078)



Pralatrexate in B- and T-Cell Lymphomas: Response

Disease	CR/CRu	PR	ORR	POD
All Patients (n=42/54)	6	6	28%	13
B-Cell (n=20/24)	0	2	10%	3
T-Cell** (n=22/30)	6	4 3 PET (-)	45%	10

** All but one patient is on the weekly schedule.

Phase II EU and US on going

O'Connor OA, et al. Blood 2006 vol 108 Abstract 400
O'Connor OA, et al. Blood 2006 vol 108 Abstract 400

Adverse Events

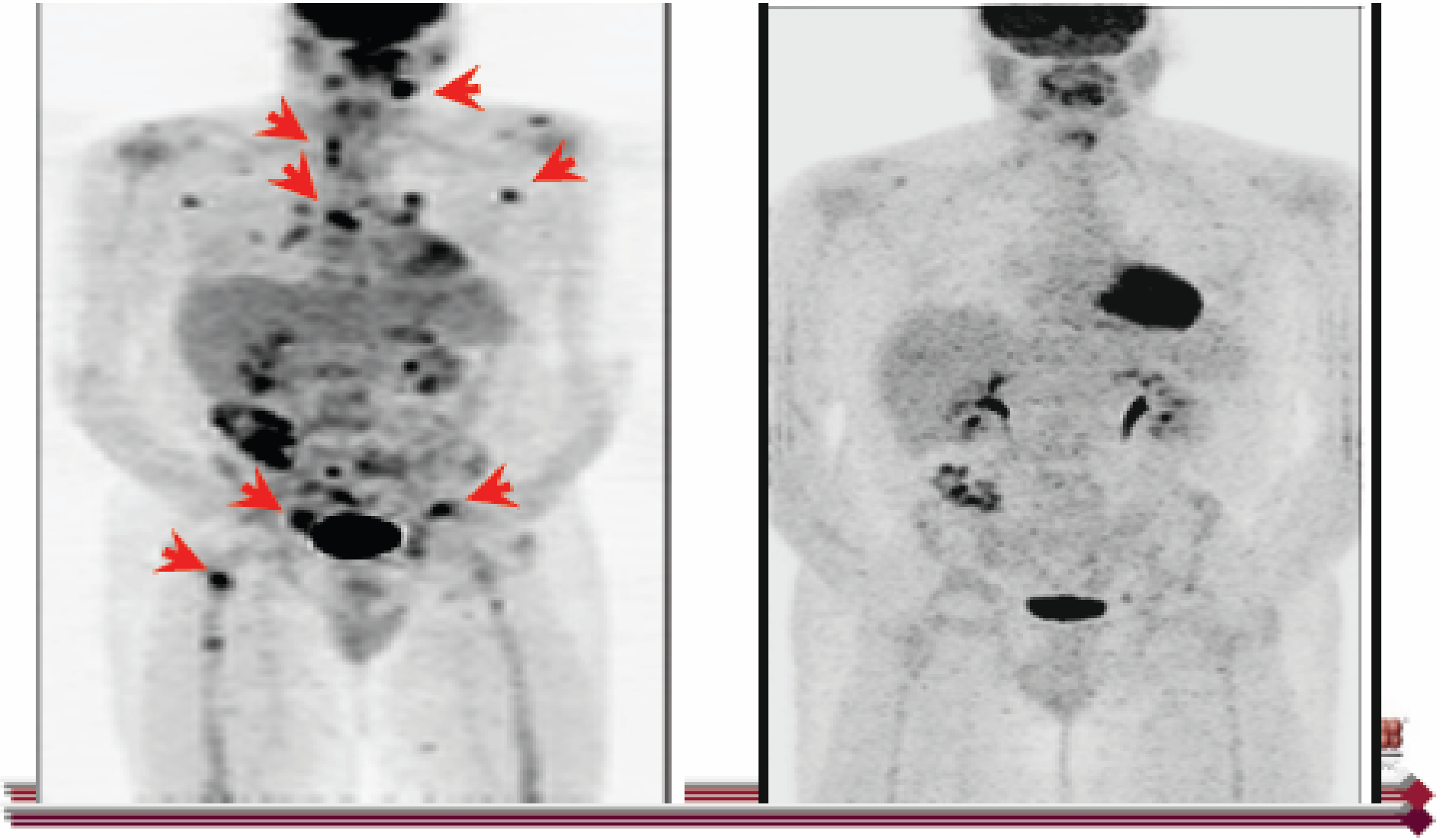
	Phase 2 QOW (N=17)		Phase 1 QW (N=17)		Phase 2 QW (N=17)	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Feb. Neutro.	2 (13%)	0	1 (6%)	0	0	0
Neutropenia	9 (56%)	6 (38%)	5 (29%)	7 (41%)	6 (35%)	2 (12%)
Anemia	9 (56%)	3 (19%)	8 (47%)	1 (6%)	6 (35%)	3 (18%)
Thrombocyt.	9 (56%)	2 (13%)	12 (71%)	3 (18%)	7 (41%)	1 (6%)
Leukopenia	11 (69%)	5 (31%)	8 (47%)	4 (24%)	4 (24%)	2 (12%)
Lymphopenia	12 (75%)	0	12 (71%)	0	12 (71%)	0
ALT/AST	2 (12%)	0	4 (24%)	0	2 (12%)	0

O'Connor OA, et al. Blood 2006 vol 108 Abstract 400

Refractory Peripheral T-Cell Lymphoma
Complete Remission Following PDX at 135 mg/m^2 x 1 dose

Pre- PDX

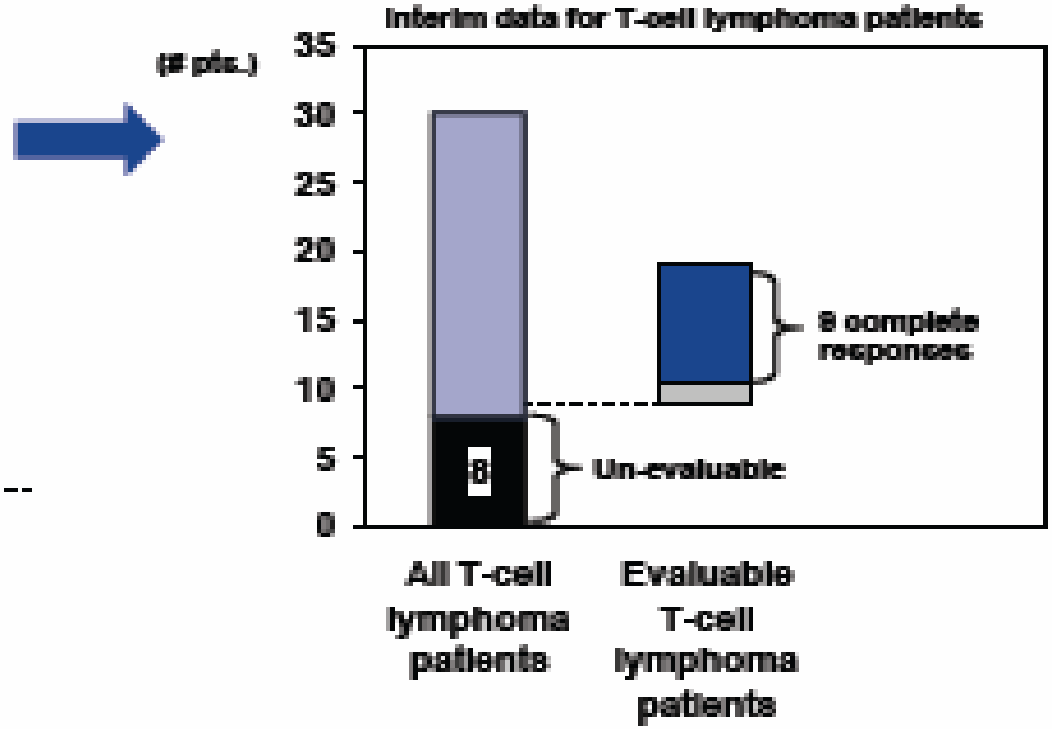
Post-PDX



PDX Achieves Durable Complete Responses in Heavily Pre-Treated Patients (O'Connor)
2006 ASH Meeting

Summary of interim Phase 1/2 results

- Favorable activity observed in heavily pre-treated T-cell lymphoma patients
  - 45% of evaluable patients (10 of 22) achieved a response with PDX
  - 6 of 10 remain in remission up to 21 months
- Vitamin supplementation mitigated stomatitis
- Recommended Phase 2 dose is 30 mg/m^2 weekly x 6



Source: O'Connor et al. American Society of Hematology 2006 Annual Meeting

PROPEL: Pivotal Phase 2 Study in PTCL

Study Design	Single arm, open label, multi-center; 2-stage Simon
Target Population	Adult patients with relapsed or refractory PTCL
Number of Patients	100 evaluable patients at up to 35 sites in US, Canada, EU
Treatment	• 30 mg/m^2 of pralatrexate weekly x 6 followed by 1 week rest • 1 mg vitamin B_{12} intramuscular every 8 – 10 weeks and 1 mg folic acid by mouth once a day
Primary Endpoint	Response Rate
Secondary Endpoints	• Duration of response • Progression-free survival • Overall survival

- Achieved agreement with FDA for a SPA in August 2006
- Received FDA's fast track designation in October 2006

PDX-009: PDX+Gemcitabine in Relapsed/Refractory NHL

Study Design	Phase 1, Single arm, non-randomized, open label, dose-escalation, multi-center, US
Target Population	Adult patients with relapsed or refractory NHL
Number of Patients	3-6 patients per cohort at 3 sites in US
Treatment	• Initial dose: 15 mg/m² of pralatrexate (Day 1) and 400 mg/m² gemcitabine (Day 2) weekly x 3 followed by 1 week rest • 1 mg vitamin B_{12} intramuscular every 8 – 10 weeks and 1 mg folic acid by mouth once a day
Primary Endpoint	• Determine MTD and Phase 2 dose
Secondary Endpoints	• Safety/Tolerability • Pharmacokinetics • Preliminary efficacy in relapsed/refractory PTCL

•Potential confirmatory trial in PTCL and 1st line for PTCL

Allos THERAPEUTICS, INC.

It's time to take care of

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