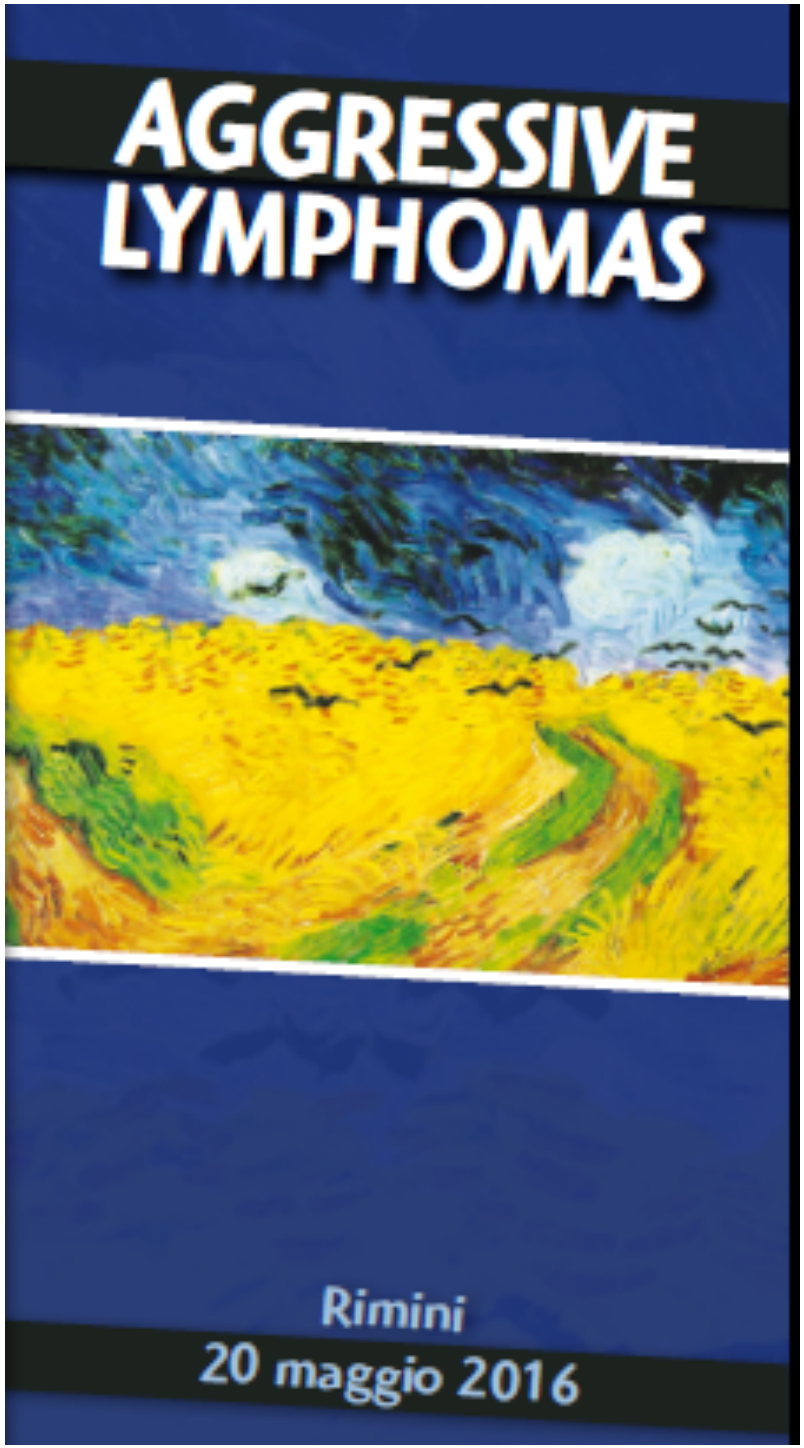

PMBCL: first line treatment and salvage therapy

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Disclosures

Research Support (institution)	**Mundipharma**
Employee	-
Major Stockholder	-
Speakers Bureau	-
Speakers Honoraria	**Celgene, Janssen, Mundipharma, Pfizer, Roche**
Scientific Advisory Board	**Celgene, Janssen, Pfizer, Roche, Teva, Servier**

MACOP-B + IFRT is an effective therapy in DLBCL with mediastinal involvement

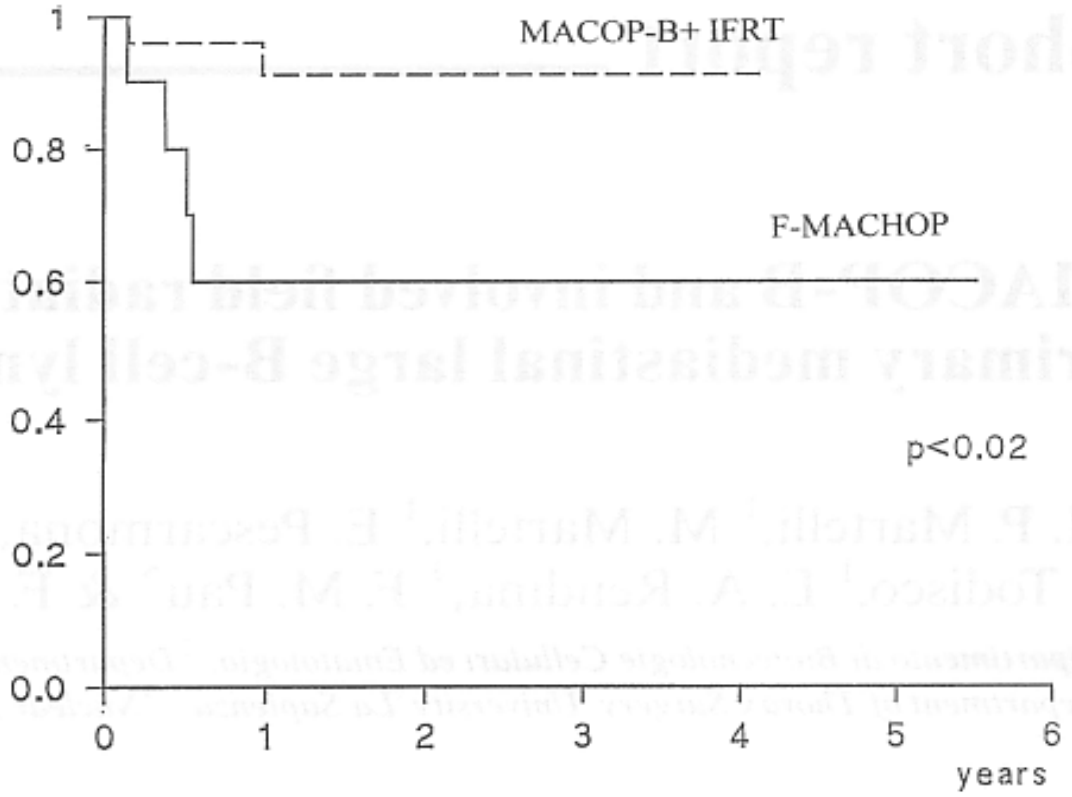


Figure 1. Primary mediastinal large B-cell lymphoma: progression-free survival (PFS) for 10 patients responsive to F-MACHOP and 26 patients responsive to MACOP-B + IFRT. PFS is 60% vs. 91% ($P < 0.02$).

Falini, Martelli et al. B.J Haematology 1995 *Martelli et al. Annals of Oncology 1996*

Is PMBCL a distinct clinico-biological entity of DLBCL that needs of a different therapeutic approach ?

Outline of discussion

- **Epidemiology**
- Pathology and molecular biology
- Clinical features
- Treatment and outcome
- Open questions

Epidemiology

- PMBCL is a relatively uncommon entity of NHL
- About 2-4% of NHL and 6-10% of DLBCL
- Over-represented in younger female patients
- Peak incidence 3-4th decade of life

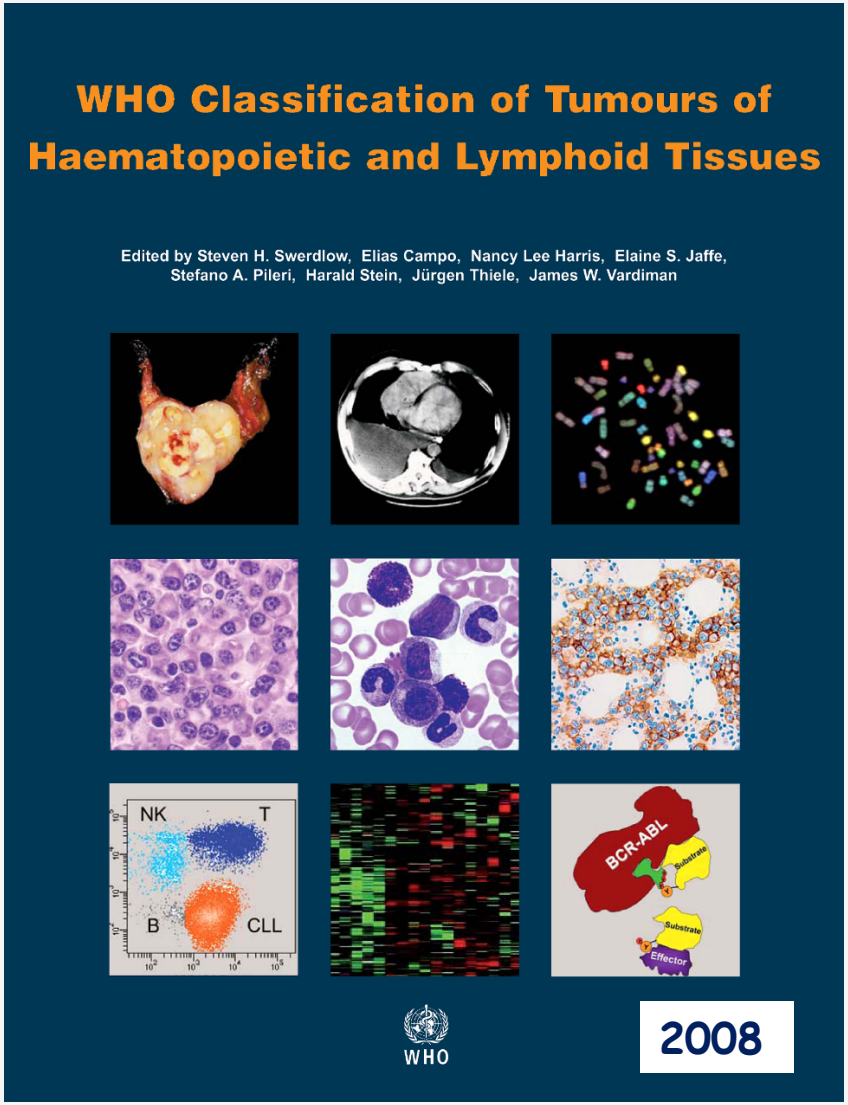
Age at diagnosis: DLBCL vs PMBCL

Age	DLBCL		PMBCL
	ABC	CGB	
median	66	61	33
<35	5%	10%	53%
35-60	29%	38%	37%
> 60	66%	52%	9%

Outline of discussion

- Epidemiology
- **Pathology and molecular biology**
- Clinical features
- Treatment and outcome
- Open questions

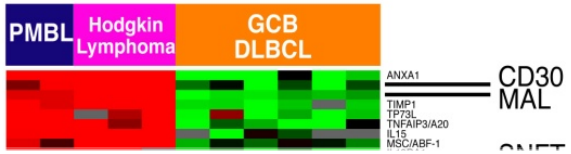
Aggressive B cell lymphomas



- Diffuse large B cell lymphoma (DLBCL)
- Primary DLBCL of CNS
- Primary DLBCL leg type
- EBV positive DLBCL of elderly
- DLBCL associated with chronic infiammation
- Plasmablastic lymphoma
- Primary mediastinal lymphoma (PMBL)
- Intravascular large B cell lymphoma
- ALK positive large B cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma,intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma,intermediate between DLBCL and classical Hodgkin's disease

Borderland between PMBCL, MGZL and cHL

Extensive Gene Expression Overlap Between Hodgkin Lymphoma and Primary Mediastinal Large B Cell Lymphoma



MGZL

HL mo

CD20

C

OCT2+

hology

15+

3 1 +

MGZL

ORIGINAL ARTICLE

(*Am J Surg Pathol* 2005;29:1411–1421)

Mediastinal Gray Zone Lymphoma

The Missing Link Between Classic Hodgkin's Lymphoma and Mediastinal Large B-Cell Lymphoma

Alexandra Traverse-Glehen, MD, Stefania Pittaluga, MD, PhD,* Philippe Gaulard, MD,† Lynn Sorbara, PhD,* Miguel A. Alonso, PhD,‡ Mark Raffeld, MD,* and Elaine S. Jaffe, MD*

PMBCL

CD20+;CD30+/- ;
CD15- ; OCT2 +;BOB.1+

MGZL

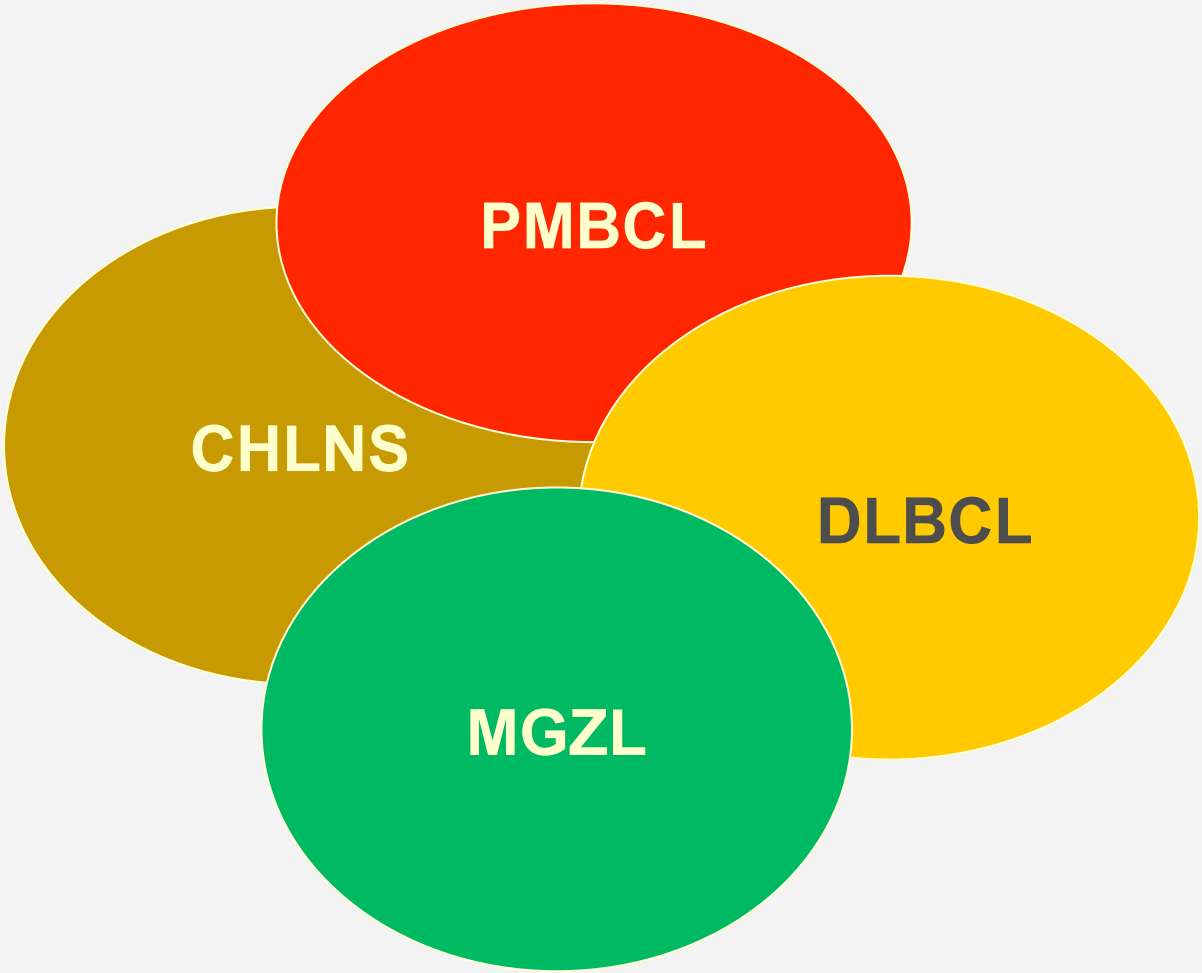
Intermediate features to fulfill the morphological and phenotypic criteria

Classical HL

CD20-/+ weak; CD30+;
CD15+; OCT2- BOB.1-

Jaffe E . Educational ASH 2010

Types of Mediastinal Lymphoma-related diseases

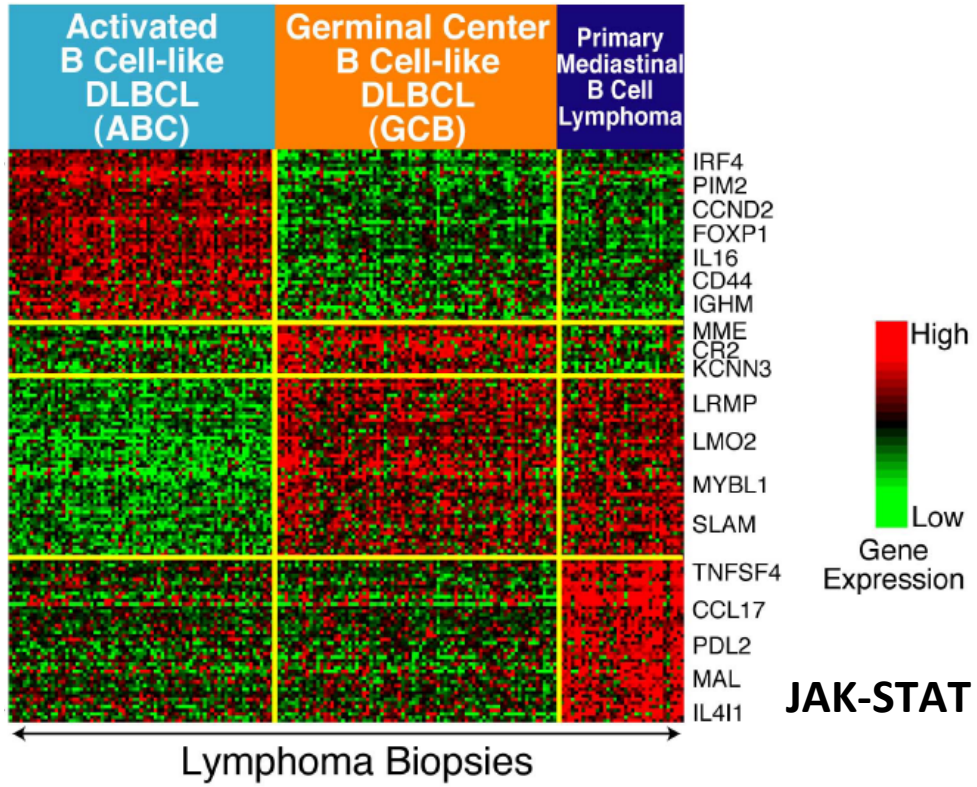


Clinical features of mediastinal lymphomas

Features	*PMBCL*	*cHL*	*DLBCL*	*MGZL*
Female/male	3:1	1:1	1:1	1:3
Median age	35	28	55	35
Stage I-II	70-80%	55%	30%	70-80%
Mediastinal invol.	100%	80%	20%	80%
Extranodal sites	uncommon	uncommon	common	uncommn
Bone marrow	2%	3%	10-15%	3%
Elevated LDH	70-80%	rare	50%	70-80%
B symptoms	< 20%	40%	50%	40%
Bulky disease	70-80%	50%	10-15%	60-70%

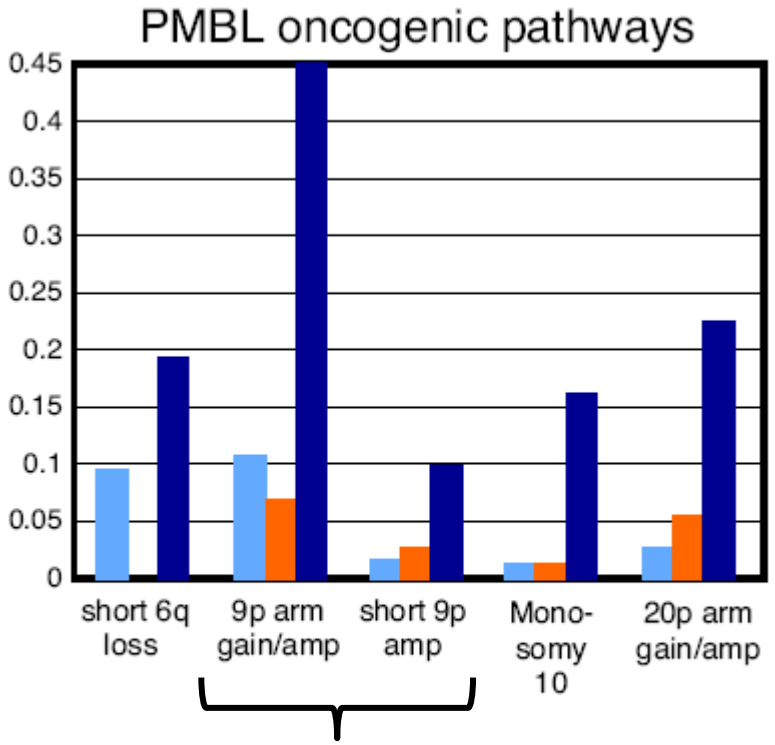
Genomic hybridization: amplification of JAK2, PDL1, PDL2

PMBL transcriptional signature: constitutively activated JAK2



JAK-STAT

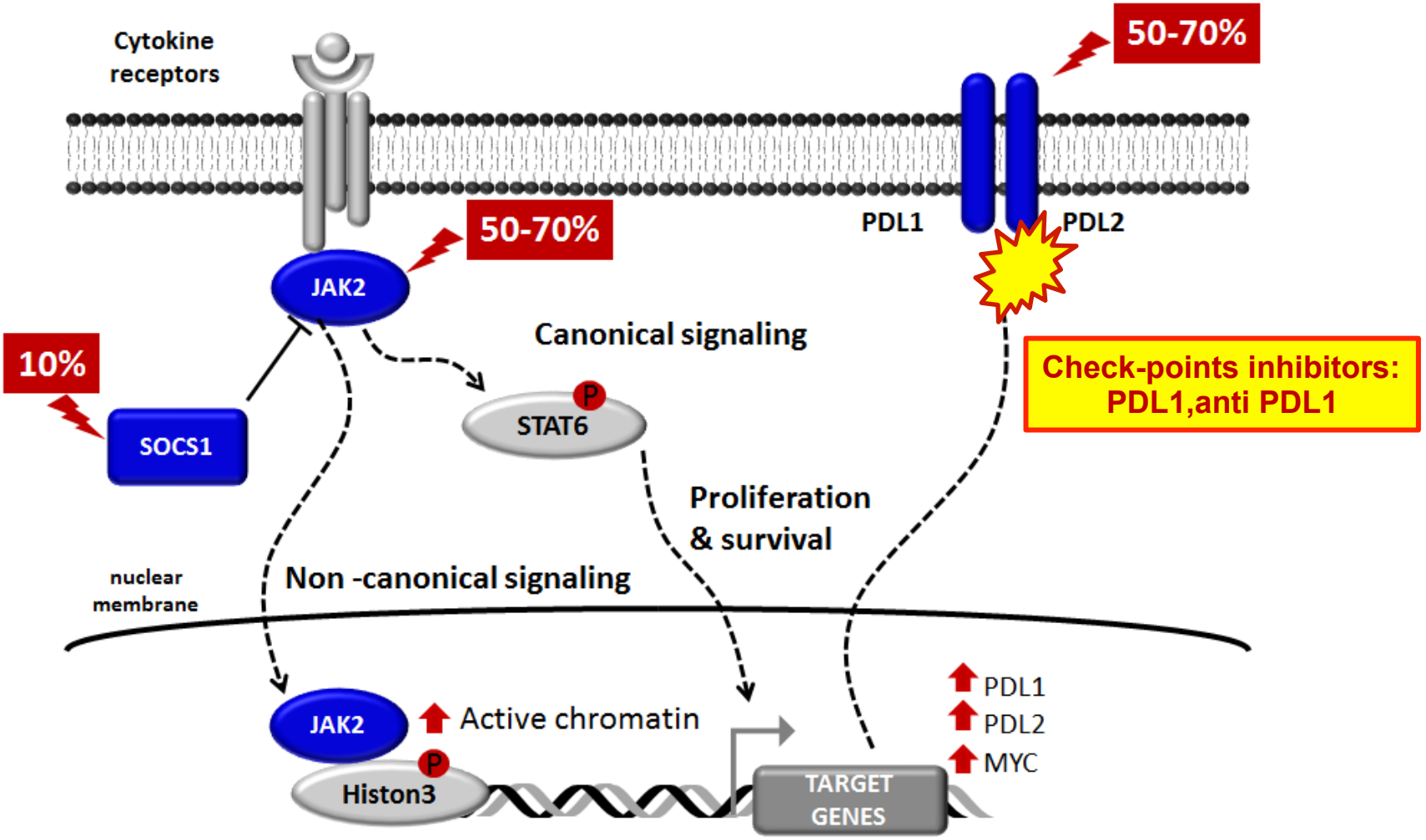
Recurrent amplification involving *JAK2* is the underlying genetic basis



JAK2, PDL1,PDL2

Rosenwald et al. JEM, 2003, Lenz et al, PNAS 2008

JAK-STAT pathway deregulation is the hallmark of PMBCL and positively regulate the expression of PDL1 and PDL2



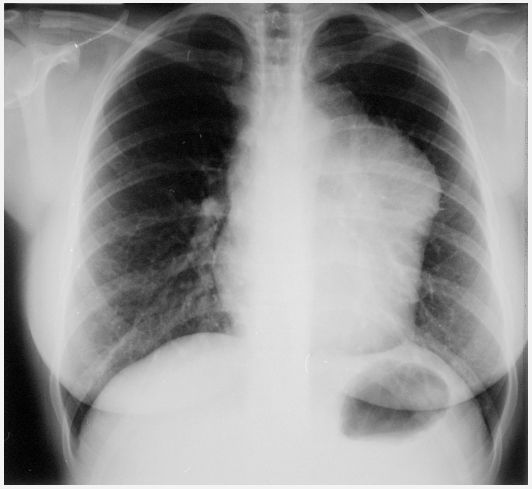
Rosenwald et al. JEM, 2003, Lenz et al, PNAS 2008, Steidl et al. Nature 2011

Outline of discussion

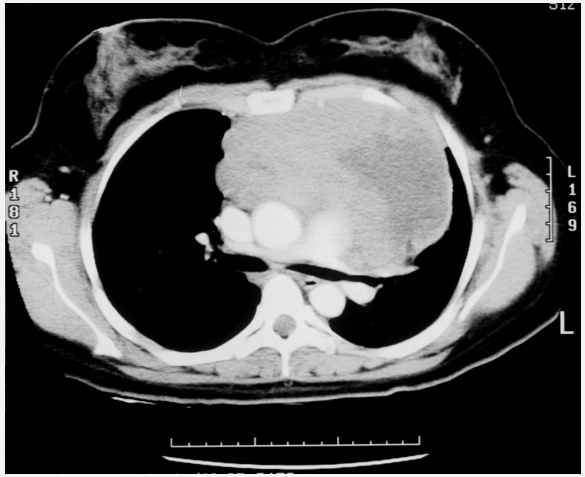
- Eidemiology
- Pathology and biology
- **Clinical and prognostic features**
- Treatment and outcome
- Open questions

Clinical features

- Bulky anterior mediastinal mass
- Local typically extension
  - *Pleuro-pericardial effusions*
  - *Vena Cava Syndrome (VCS)*
  - *Dyspnoea, cough*
  - *Dysphagia*



- Usually stage I/II (bulky mass)
- No infradiaphragmatic lymph node
- No marrow involvement
- Tipical extranodal sites (kidney, ovary, pancreas) more common at relapse



VCS (50%) may be a clinical emergency

Prognostic factors

IPI and aaIPI are less useful

- LDH elevated and age over 40 years *
- Male gender and B symptoms at diagnosis **

- ***Presence of extranodal disease at diagnosis***
- ***Inadequate response to initial therapy***

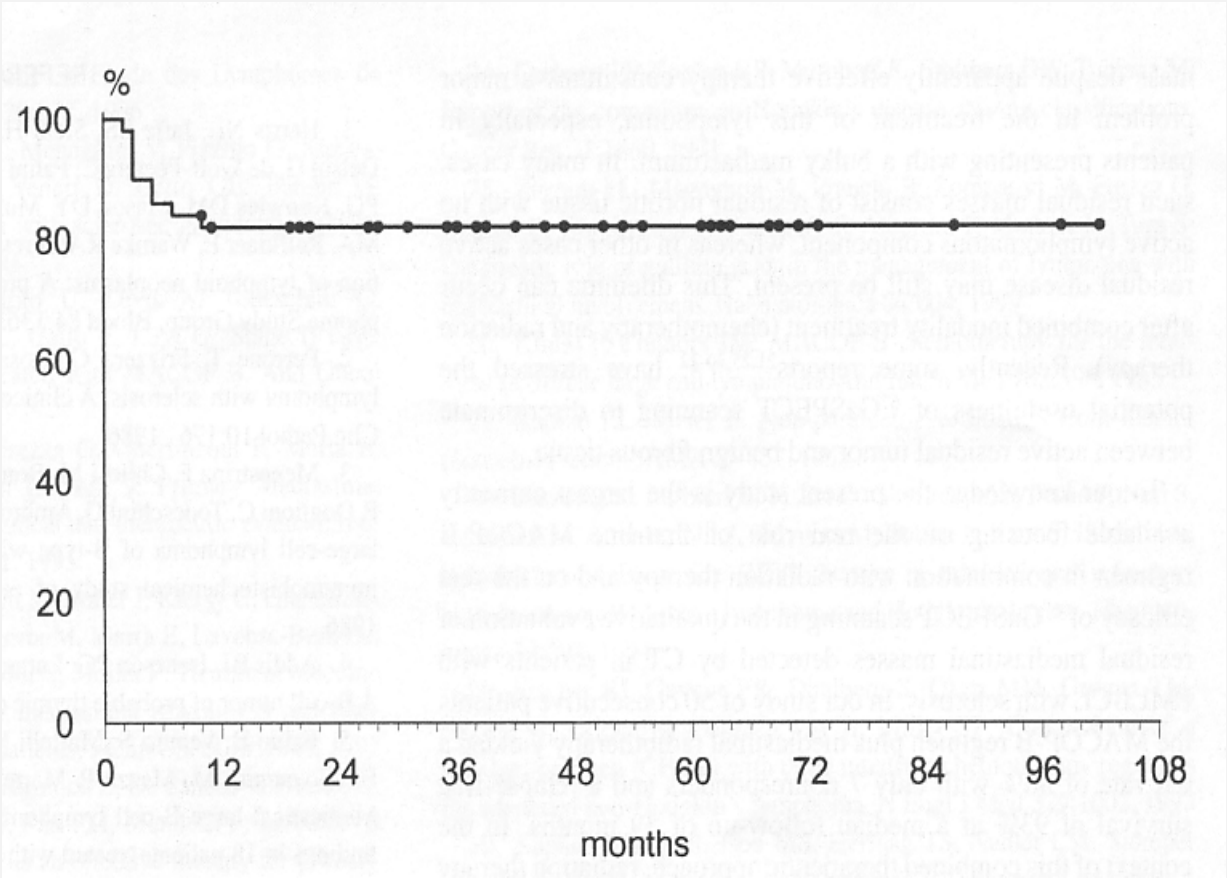
*Zinzani P.L et al. Haematologica, 2002*** *Savage et al Ann. Oncol 2006**

Outline of discussion

- Epidemiology
- Pathology and biology
- Clinical features
- **Treatment and outcome**
- Open questions

PMBCL : MACOP-B + mediastinal IFRT in 50 pts

Relapse Free Survival



Zinzani P.L, Martelli M, Magagnoli M, et al. Blood, 1999

A multicenter italian prospective study on 89 untreated patients treated with MACOP-B plus IFRT

Overall survival

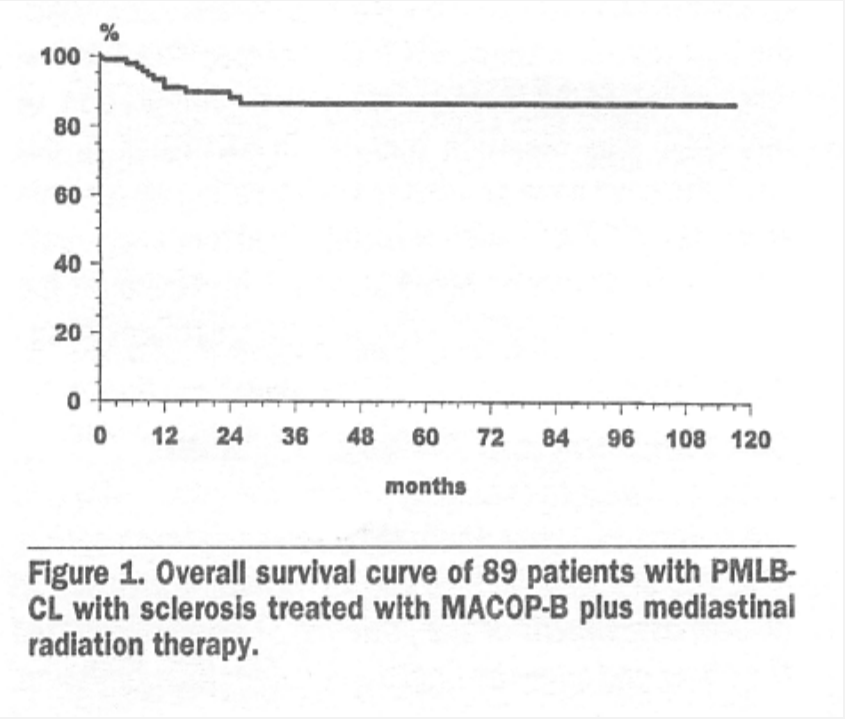


Figure 1. Overall survival curve of 89 patients with PMLB-CL with sclerosis treated with MACOP-B plus mediastinal radiation therapy.

Relapse Free Survival

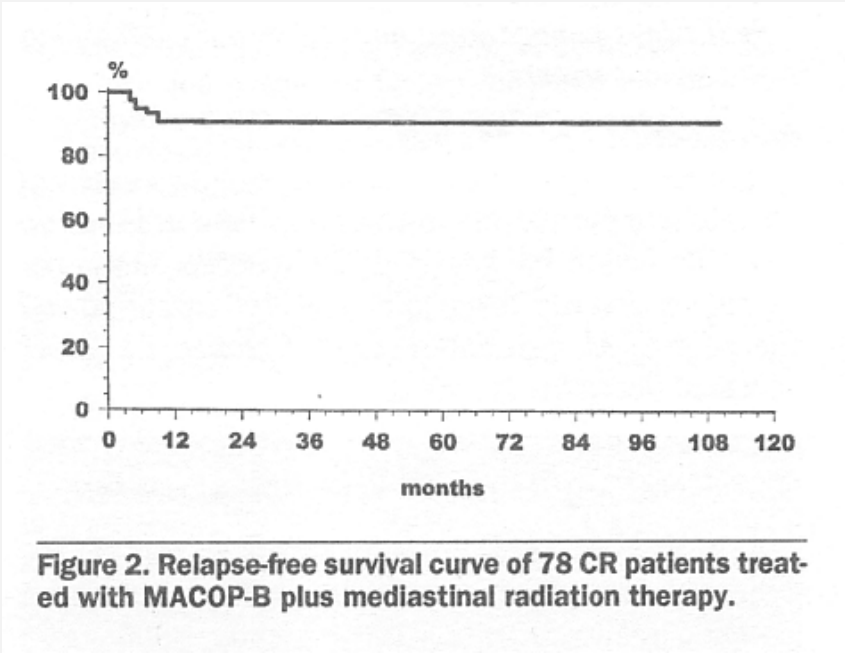
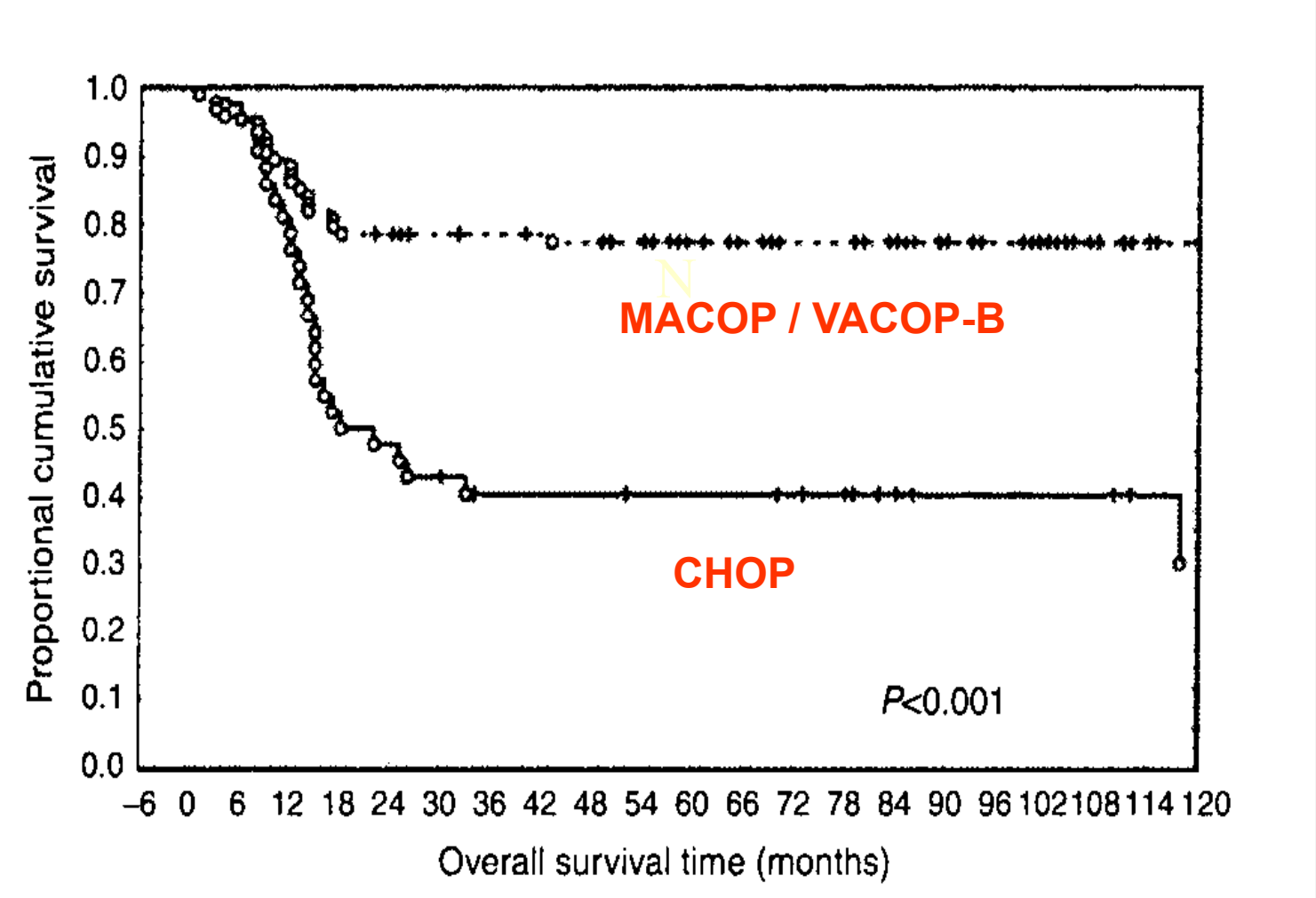


Figure 2. Relapse-free survival curve of 78 CR patients treated with MACOP-B plus mediastinal radiation therapy.

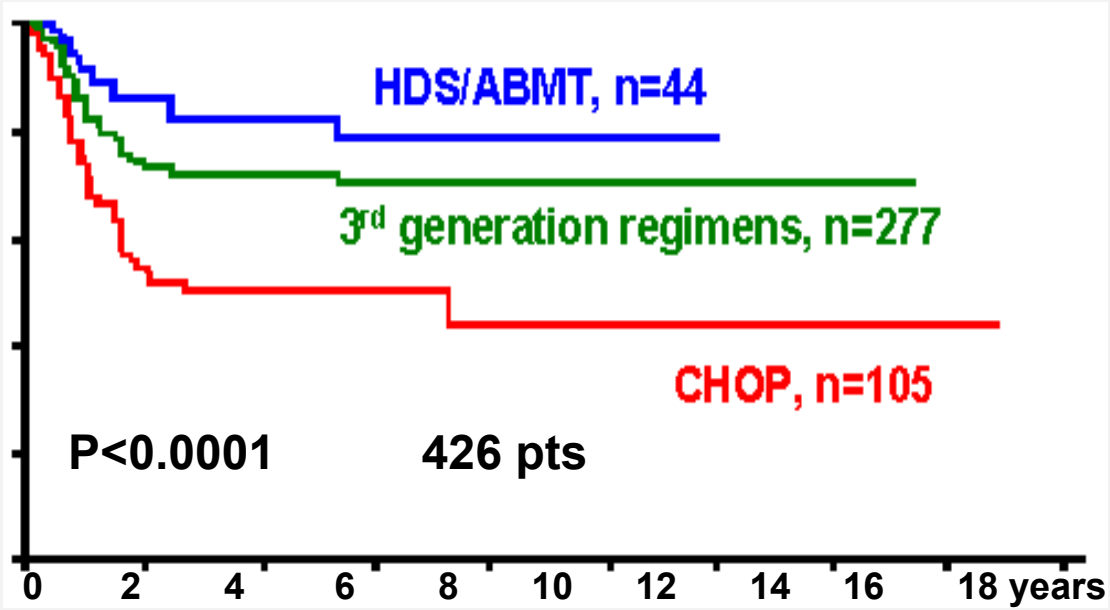
Zinzani P.L, Martelli M, De Renzo A, et al. Haematologica, 2001

PMBCL: retrospective multicentre italian study



Todeschini et al B.J.Cancer 2004

Induction chemotherapy strategies in PMBCL: A multinational retrospective study on 426 untreated patients



	CHOP	3rd generation	HDS / ABMT
CR after CT	49%	51%	53%
CR after CT+RT	61%	79%	75%
10-year OS	44%	71%	77%
Follow-up	52 mos	55 mos	36 mos

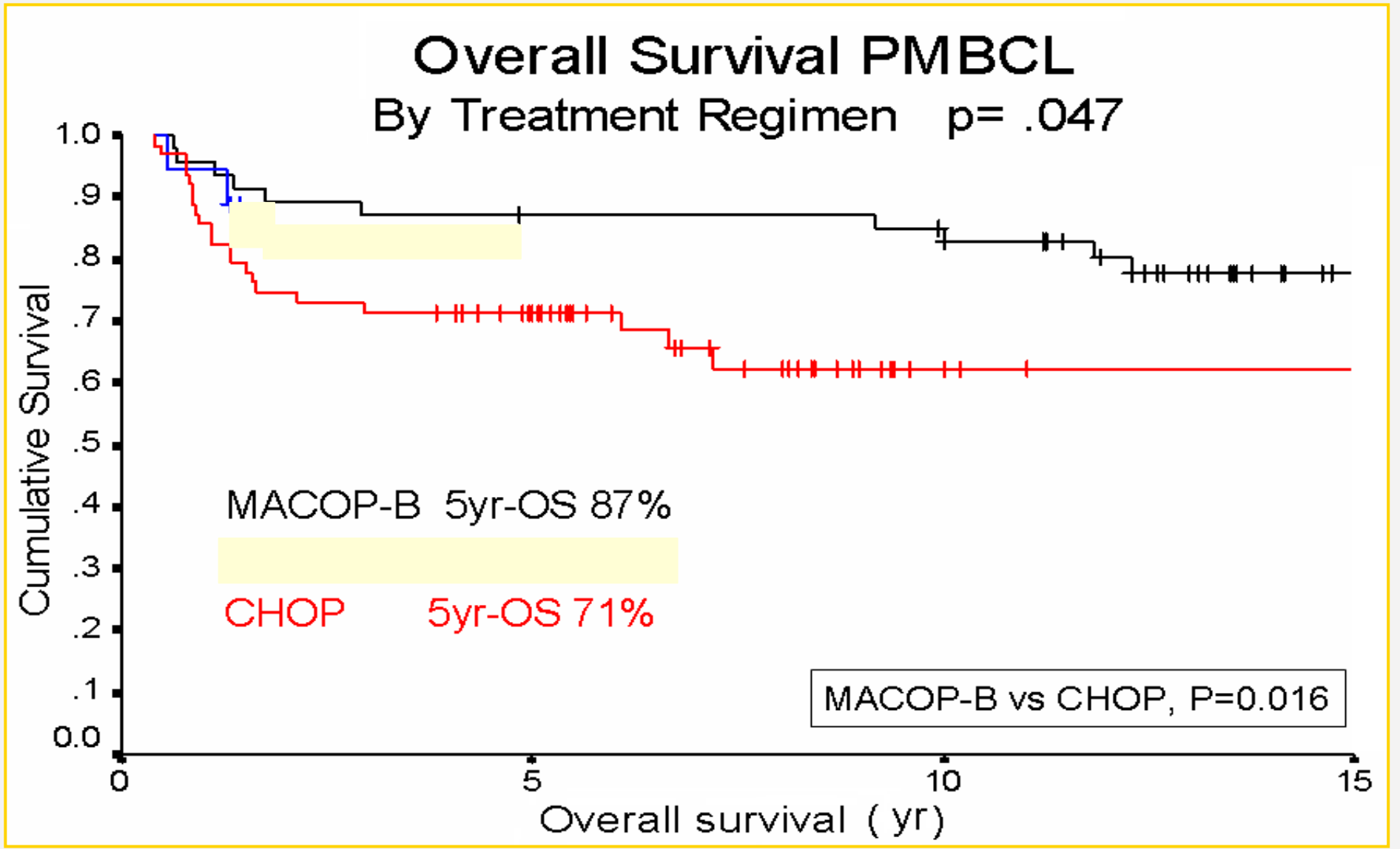
Zinzani, Martelli, Bertini

haematologica 2002; 87:1258-1264

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

The Vancouver Experience

Savage et al. Annals of Oncology 2006



BC Cancer Agency
CARE & RESEARCH
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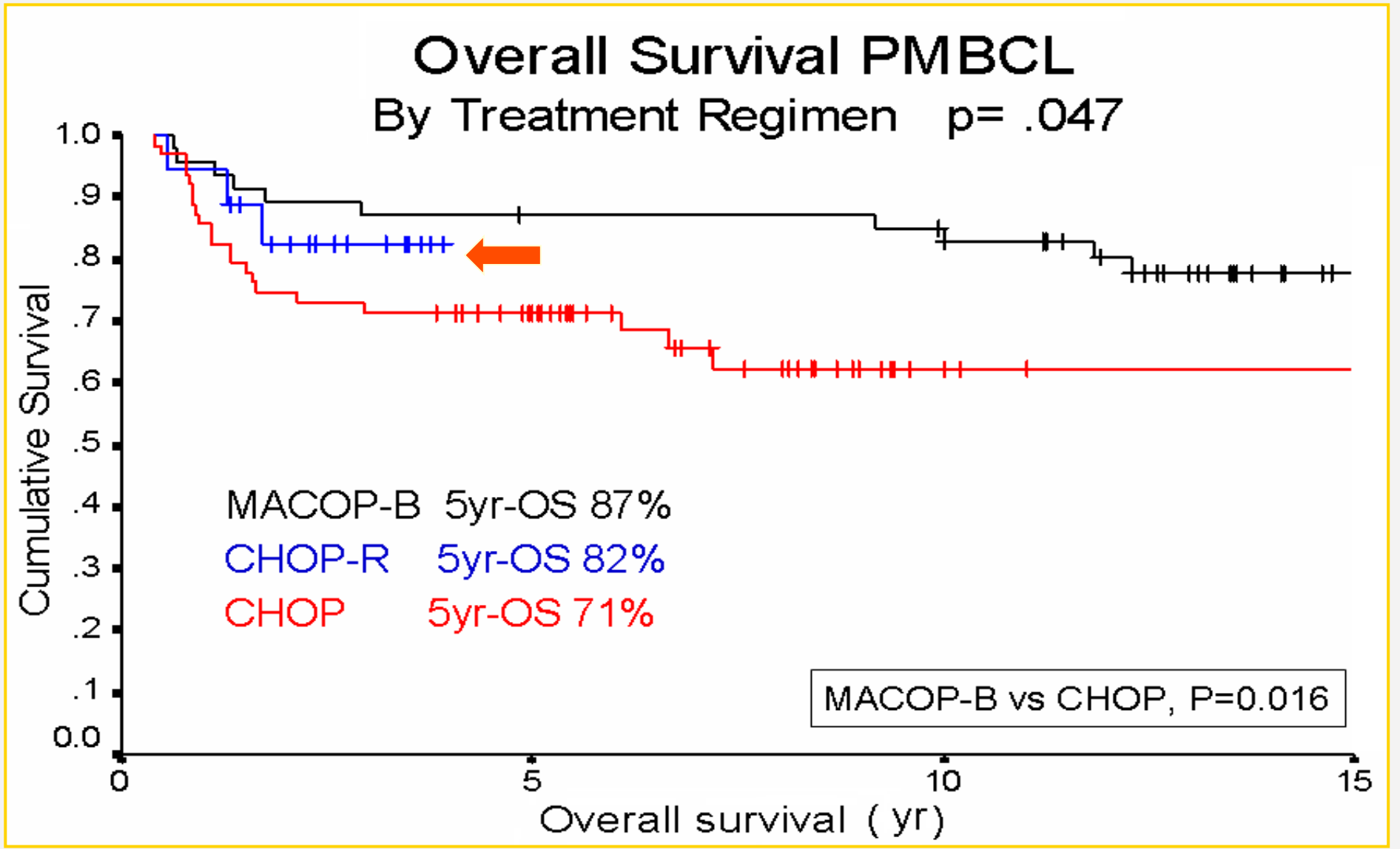
The Vancouver Experience

Savage et al. Annals of Oncology 2006

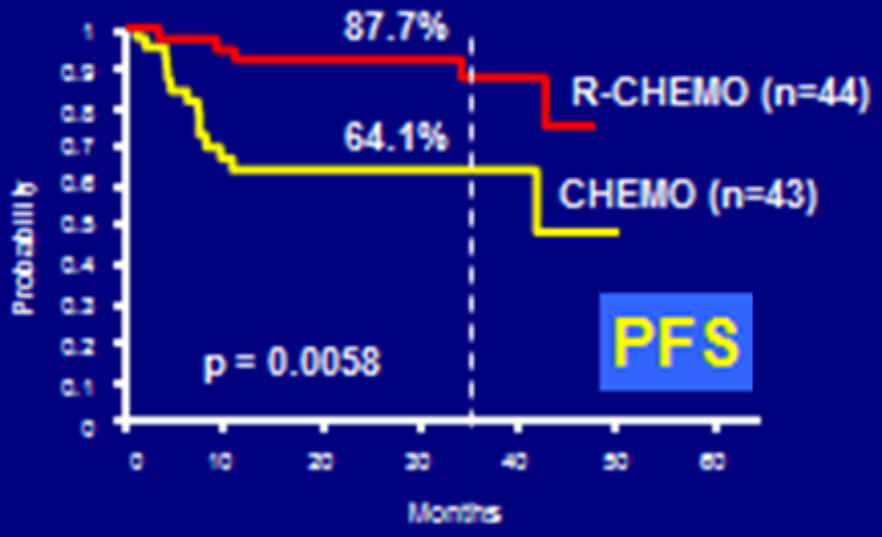


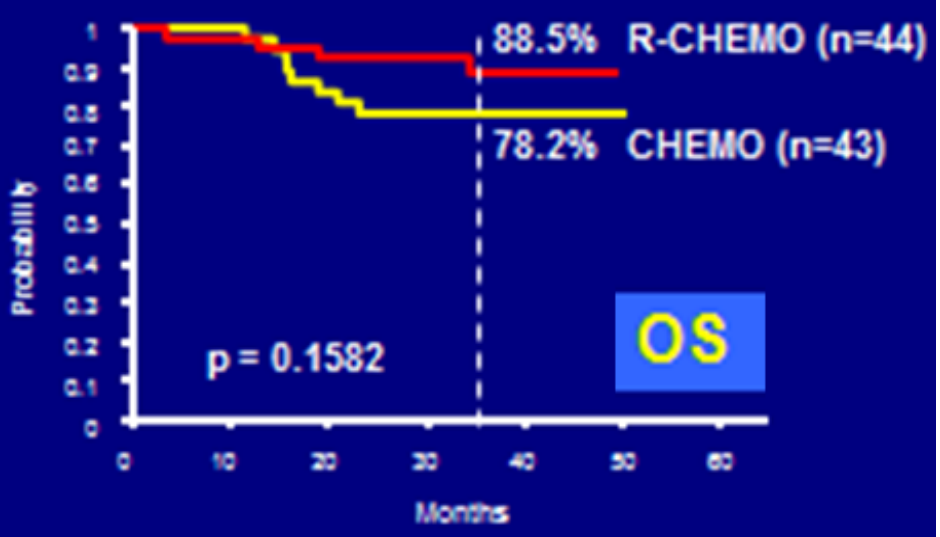
MInT

PMBCL: Chemo vs R-Chemo

aa IPI= 0-1 only

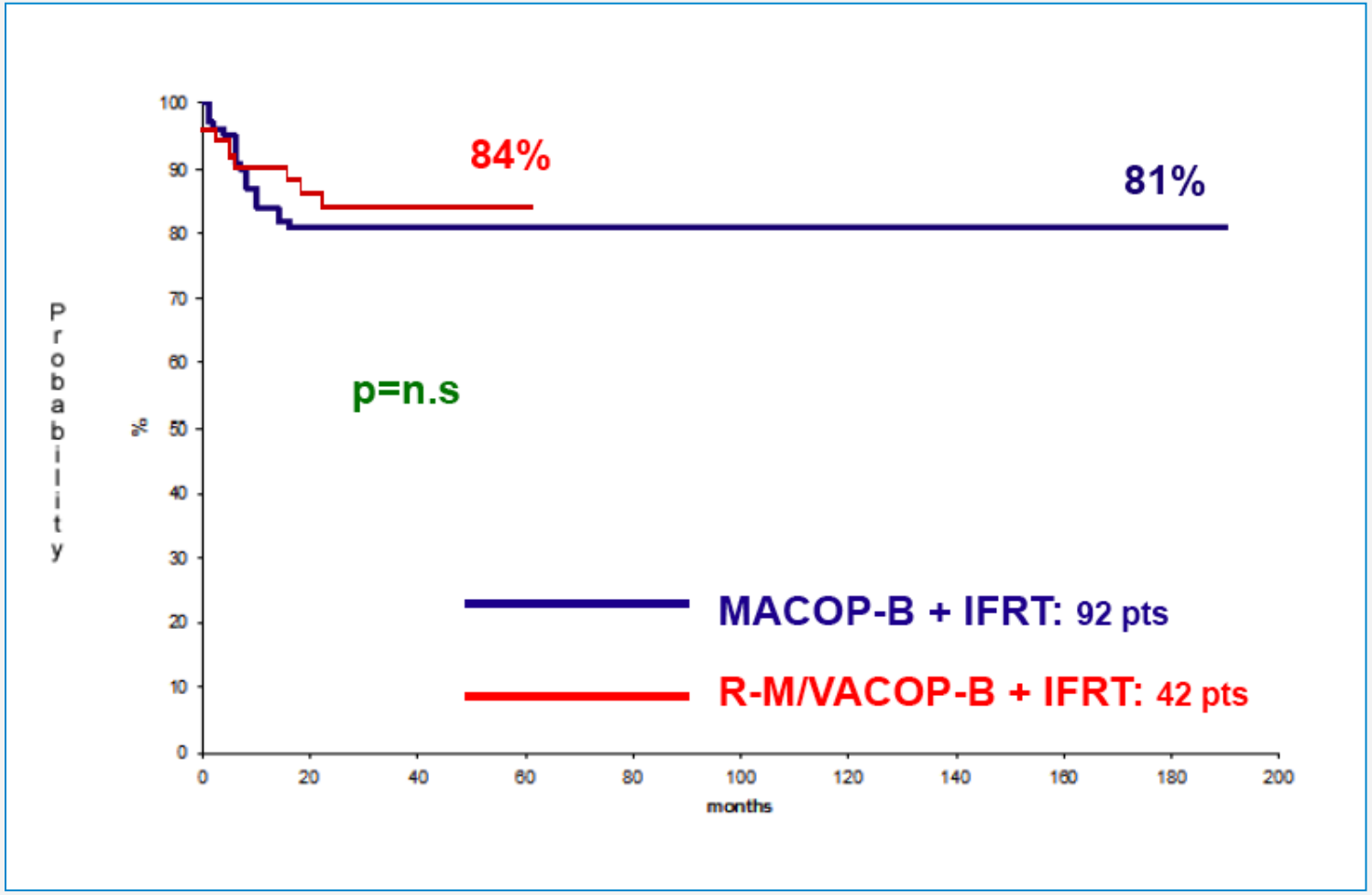
- **87 /714 (10.5%) of DLBCL were PMBCL**
- **median follow-up, 37 months**
- **R-chemo CR = 80% vs Chemo alone 54% (p= 0.03)**
- **R virtually eliminated PD in PMBCL (2.5% vs 24%; p = .006)**
- **Mediastinal IFRT 74% of patients**





M. Rieger et al, Ann Oncol; 2010

M / VACOP-B + mediastinal RT
PFS in pre / post Rituximab era



De Sanctis V, Martelli M et al. Int J Rad Oncol Biol Phys 2008;
Zinzani PL, Martelli M et al. Clinical Lymph and Myeloma 2009

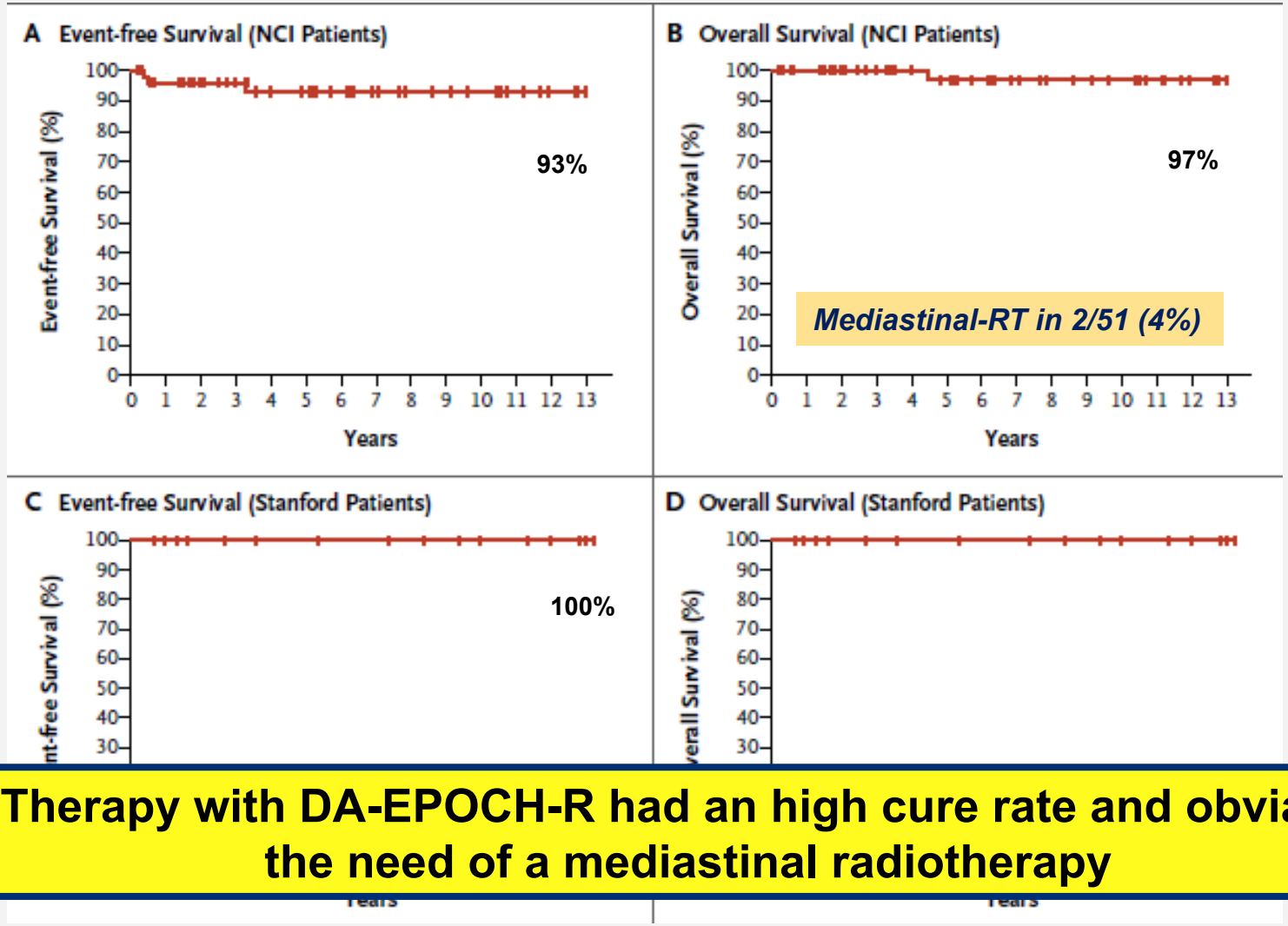
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Lauren S. Maeda, M.D., Ranjana Advani, M.D., Clara C. Chen, M.D., Julie Hessler, R.N., Seth M. Steinberg, Ph.D., Cliona Grant, M.D., George Wright, Ph.D., Gaurav Varma, M.S.P.H., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., and Wyndham H. Wilson, M.D., Ph.D.

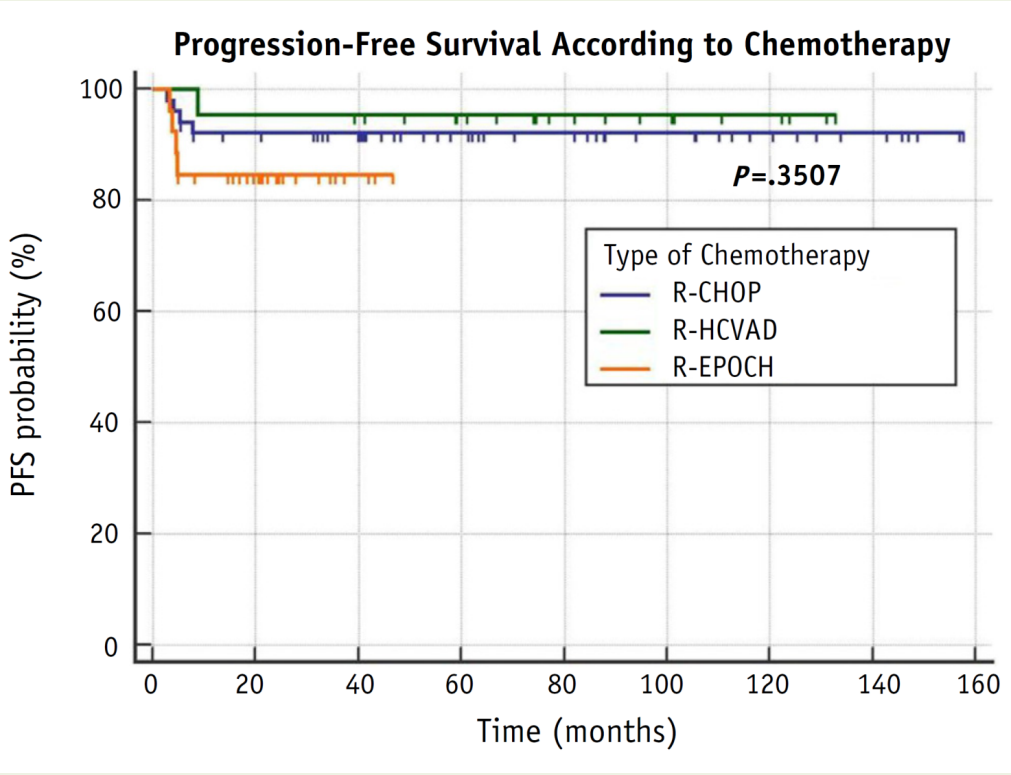
DA-EPOCH Rituximab: NCI results (51 patients)



Therapy with DA-EPOCH-R had an high cure rate and obviated the need of a mediastinal radiotherapy

Dunleavy K et al N.Engl. J. Med 2013

MDACC retrospective PMBCL series



Characteristic	Treatment characteristics R-CHOP (n=50)	R-HCVAD (n=22)	R-EPOCH (n=25)
No. of cycles			
Median	6	6	6
Range	5-8	5-8	4-7
Radiation therapy			
Consolidative (presumed CR)	42 (84%)	17 (77.2%)	5 (20%)
Salvage	3 (6%)	1 (4.5%)	4 (16%)
No radiation	5 (10%)	4 (18.2%)	16 (64%)
Radiation dose			
Median, Gy	39.6	39.6	39.6
Range, Gy	30-45	16.2-45	30.6-43.2
Radiation technique			
3D	36 (80%)	16 (88.9%)	1 (11.1%)
IMRT	6 (13.3%)	1 (5.6%)	7 (77.8%)
Protons	3 (6.7%)	1 (5.6%)	1 (11.1%)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

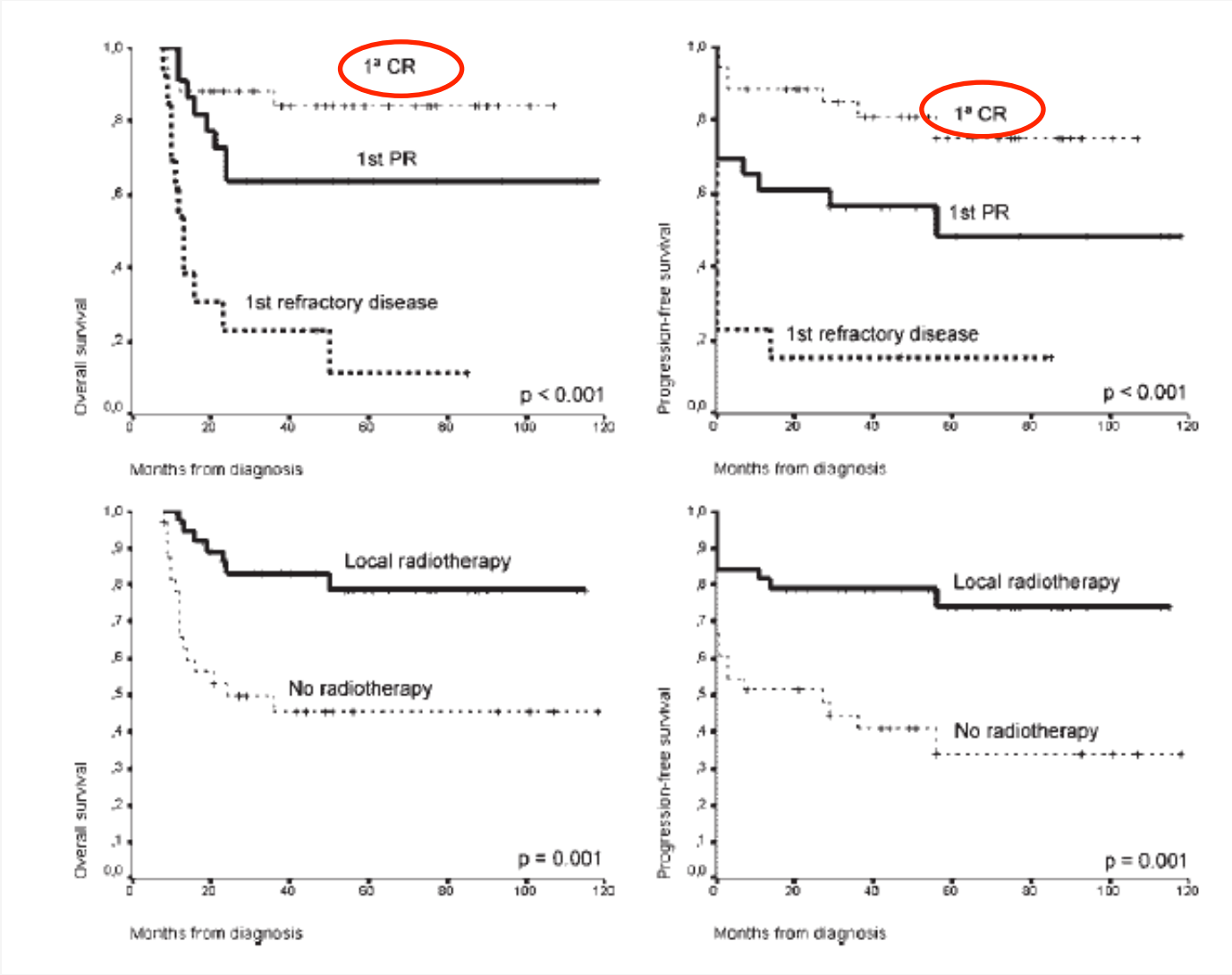
Pinnix CC et al. Int J Radiat Oncol Biol Phys. 2015; 92:113-121

PMBCL and MGZL comparison in clinical outcome following DA-EPOCH-R

Characteristics	PMBCL (n=40)	MGZL(n=16)	P-value
Male sex	38%	75%	0.017
Age	32 (19-52)	30(14-51)	ns
Stage III/IV	30%	12%	ns
Extranodal sites	57%	25%	0.039
Pleural effusion	52%	12%	0.007
EFS	95%	45%	0.0002
OS	100%	75%	0.0036

Dunleavy K. et al 11 ICML 2011; 150

ASCT in PMBCL: GELTAMO experience



Rodriguez et al Hematological Oncology 2008

PMBCL: take home messages (1)

- PMBCL has better outcome than others DLBCL
- Third generation regimens (M/VACOP-B) superior to CHOP regimen in the pre-Rituximab era
- Rituximab combination with CHOP/CHOP like regimens removes the differences with more intensive third generation regimens
- ***R-CHOP-V/MACOP-B with mediastinal IFRT*** may be considered the standard treatment ***(5-yrs EFS=80-85%)***
- ***DA-EPOCH-R without mediastinal IFRT*** *has shown very promising* results in a single prospective phase II trial but ***need to be confirmed*** in further prospective trials.

PMBCL: take home messages (2)

- There are no evidences to support ASCT as first line consolidation therapy in PMBCL and should be reserved only for patients who achieve a not complete response
- ***MGZL*** have a more aggressive clinical course and poorer outcome than PMBCL
- ***DA-EPOCH-R*** in a recent prospective series of ***MGZL*** have reported a significantly lower EFS and OS if compared to PMBCL.
- There is no consensus in the optimum treatment of ***MGZL***
- ***MGZL*** requires more likely mediastinal RT than PMBCL .

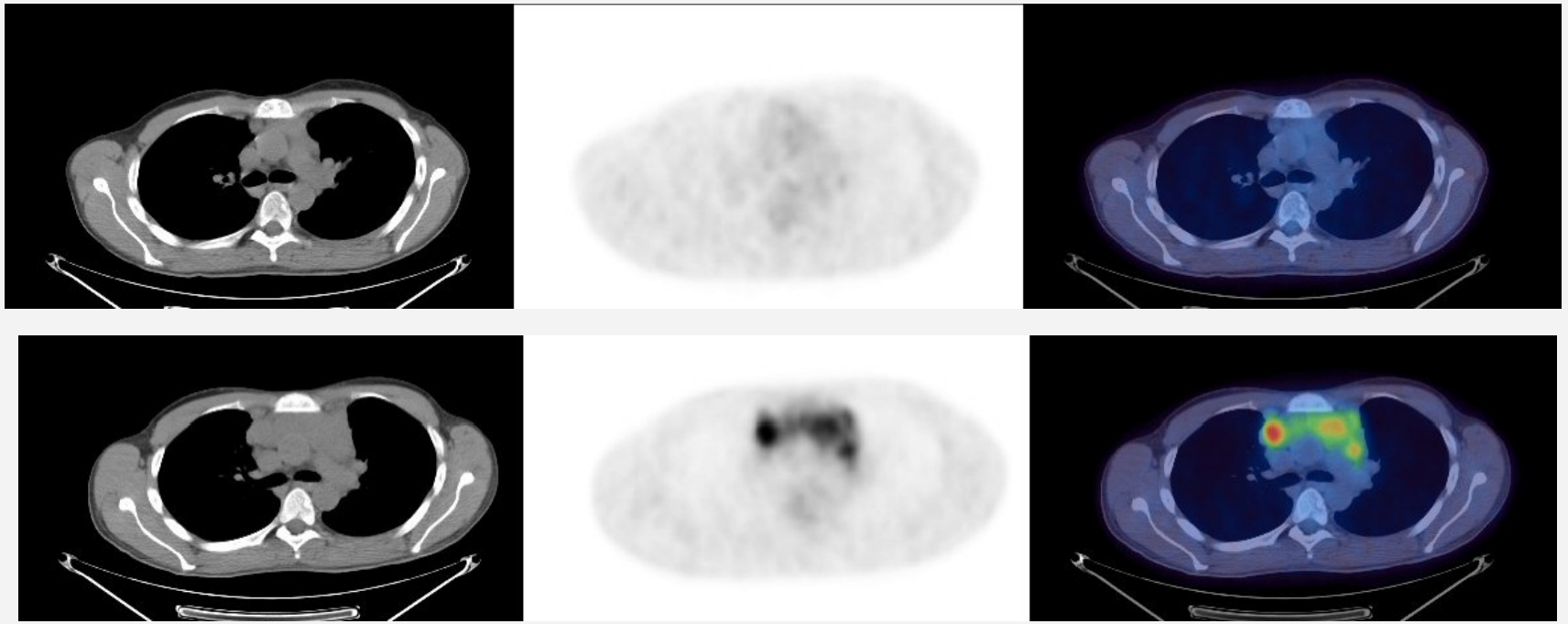
Outline of discussion

- Epidemiology
- Pathology and biology
- Diagnostic criteria and clinical features
- Treatment and outcome
- **Open questions**

Open questions

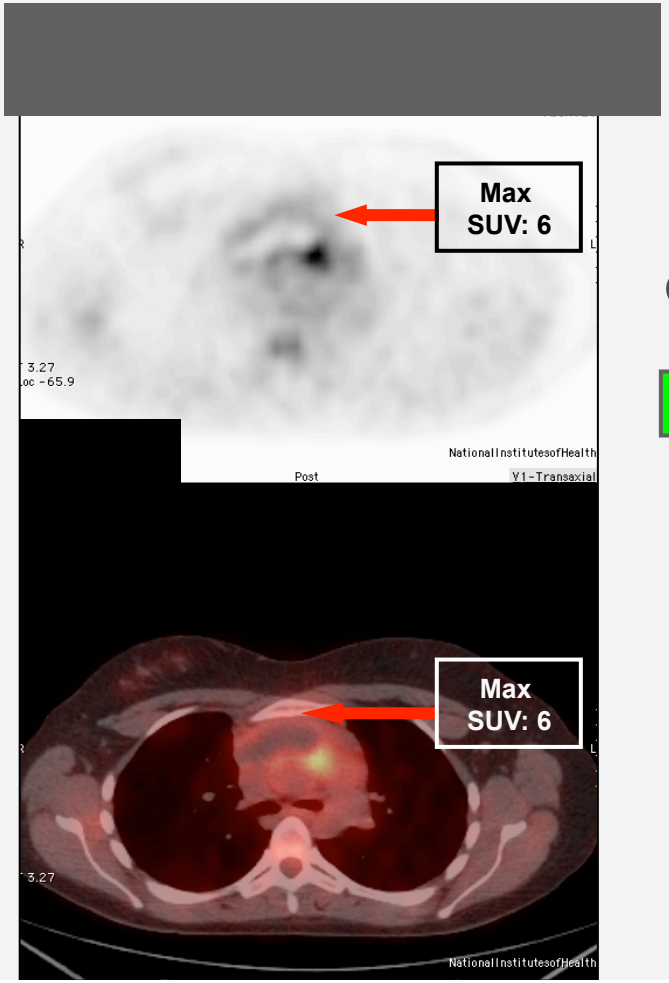
- What is the role of PET scan in the response evaluation after chemo-immunotherapy?
- Can mediastinal radiotherapy be removed in selected patients and if the PET scan can drive this selection?
- Should new quantitative functional PET parameters (QPM), identify very high risk patients to candidate for more intensive regimens as DA-EPOCH-R ?

PET-CT assessment for PMBCL



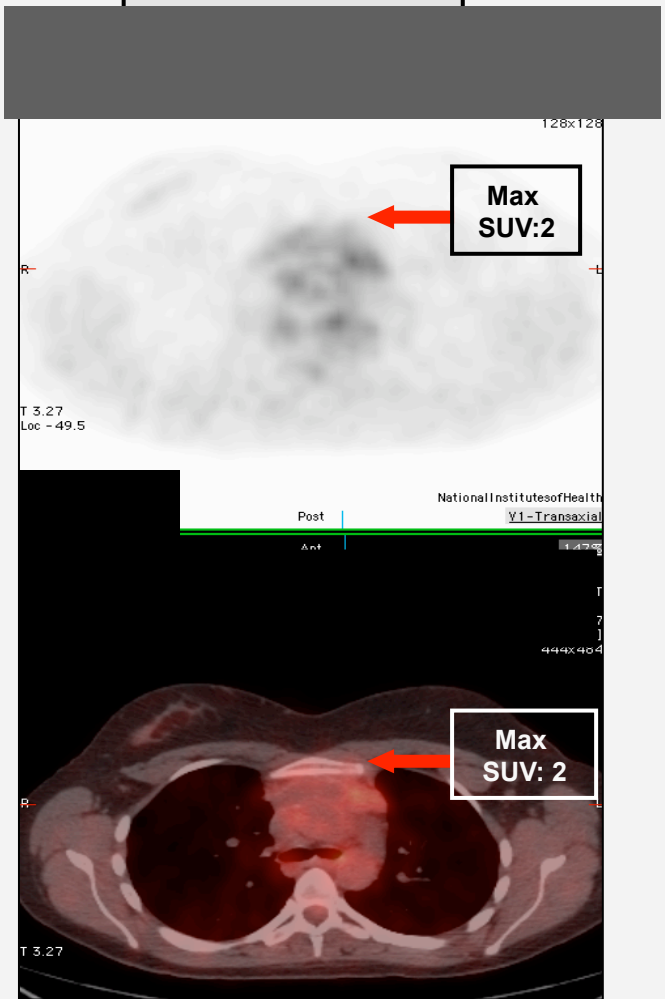
FDG-PET Post R-CHT
The problem of false positive results

2weeks end of chemoimmunotherapy

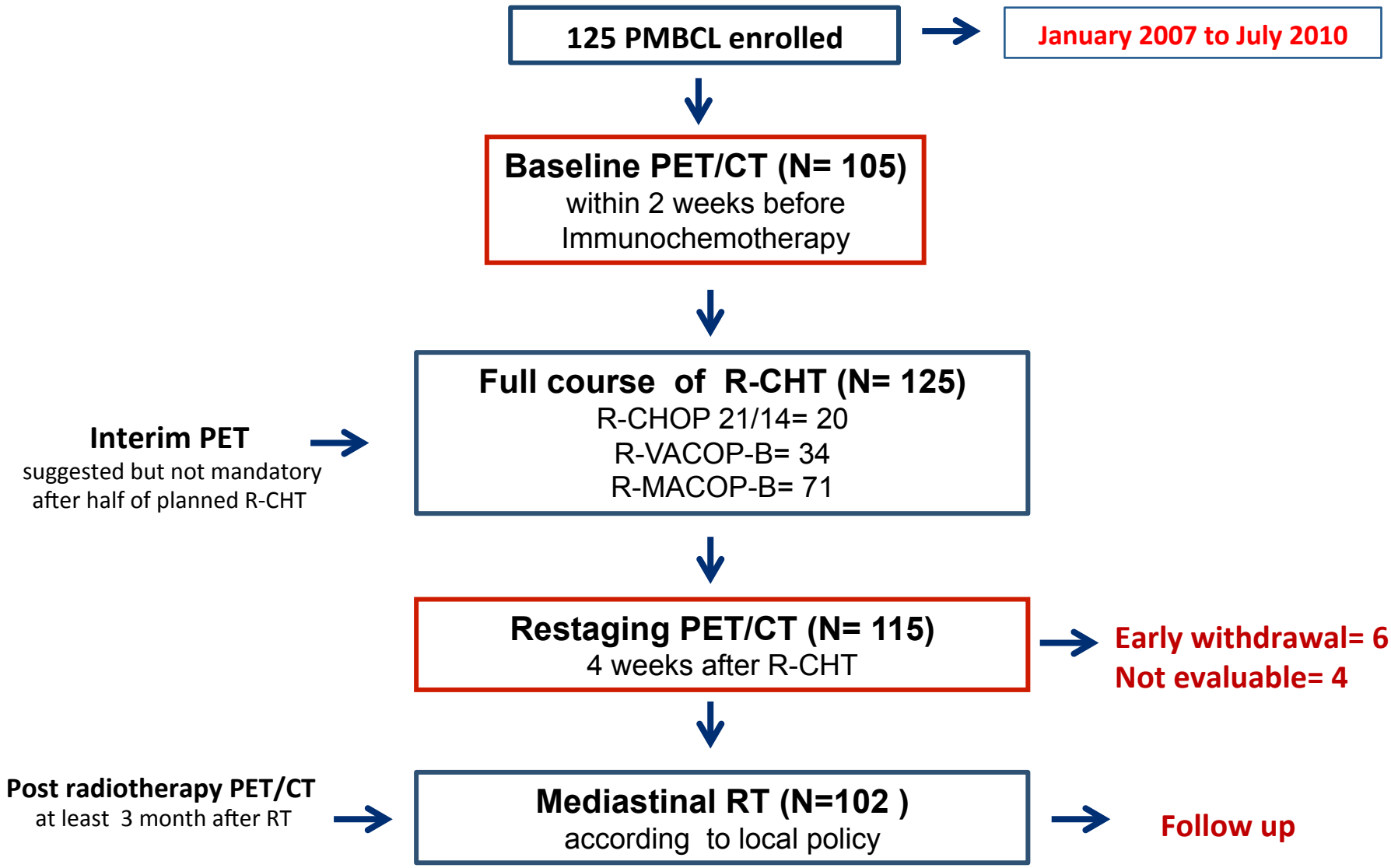


Observe

6 weeks later



IELSG-26 study design



JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

[^{18}F]Fluorodeoxyglucose Positron Emission Tomography Predicts Survival Following Chemoimmunotherapy for Primary Mediastinal Large B-Cell Lymphoma: Results of the International Extranodal Lymphoma Study Group IELSG-26 Study

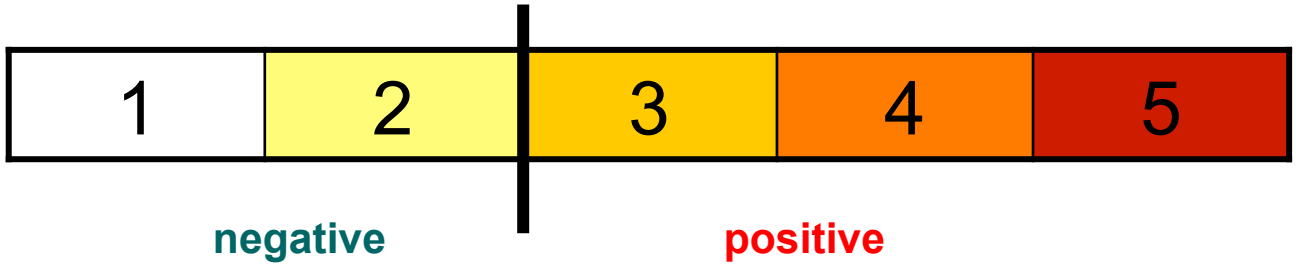
Maurizio Martelli, Luca Ceriani, Emanuele Zucca, Pierluigi Zinzani, Andrés J.M. Ferreri, Umberto Vitolo, Caterina Stelitano, Ercole Brusamolino, Maria Giuseppina Cabras, Luigi Rigacci, Monica Balzarotti, Flavia Salvi, Silvia Montoto, Armando Lopez-Guillermo, Erica Finolezzi, Stefano A. Pileri, Andrew Davies, Franco Cavalli, Luca Giovanella, and Peter W.M. Johnson

Published Ahead of Print on May 5, 2014

PET/CT response criteria (4 weeks after R-CHT)

* *Deauville criteria [5-point visual analysis scale] (Leuk Lymphoma 2009)*

1. **No uptake.**
2. **Uptake ≤ mediastinum.**
3. **Uptake > mediastinum but ≤ liver.**
4. **Uptake moderately more than liver uptake, at any site.**
5. **Markedly increased uptake at any site and new disease sites**



Patients achieving a metabolic CR (mCR) according the IHP criteria are designated by score 1-2 in the Deauville criteria

PET/CT response : results

Post R-chemo PET interpretation - blind central review
115 /125 studies reviewed

115 PET/CT

	54 (47%) PET-neg		***61 (53%) PET-pos***		
	NPV= 98%		**PPV=18%**		
Deauville score	1	2	3	4	5
Nr. of patients	**12**	**42**	**27**	**24**	**10**
PD or relapse	**-**	**1**	**-**	**5**	**6**
	negative		**positive**		

MBP cut-off

PET/CT response : results

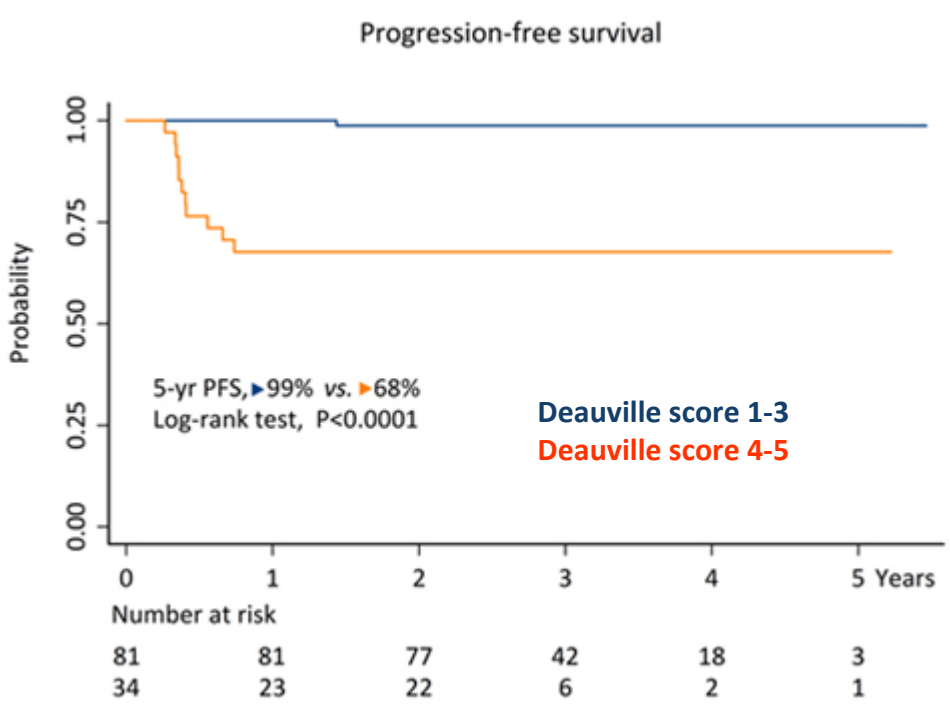
Post R-chemo PET interpretation - blind central review
115 /125 studies reviewed

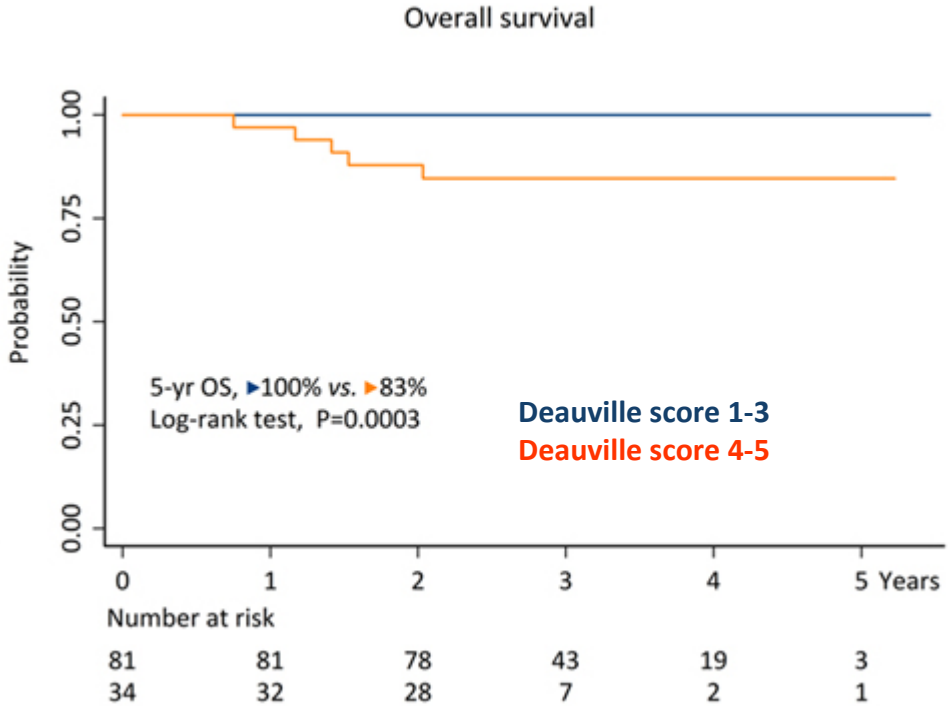
115 PET/CT

	81 (70%) PET-neg			*34 (30%) PET-pos*	
	NPV= 99%			**PPV=32%**	
Deauville score	1	2	3	4	5
Nr. of patients	**12**	**42**	**27**	**24**	**10**
PD or relapse	**-**	**1**	**-**	**5**	**6**
	negative			**positive**	

Liver cut-off

PET response defined by the *liver uptake cut-point*





Martelli et al. J.Clin.Oncol 2014

Take home messages (3)

- The incidence of PET-positive rate after R-CHT in PMBCL was higher (53%) than in DLBCL using the MBP cut-point. However approximately 90% of patients are projected to be alive and 5-yrs PFS after treatment.

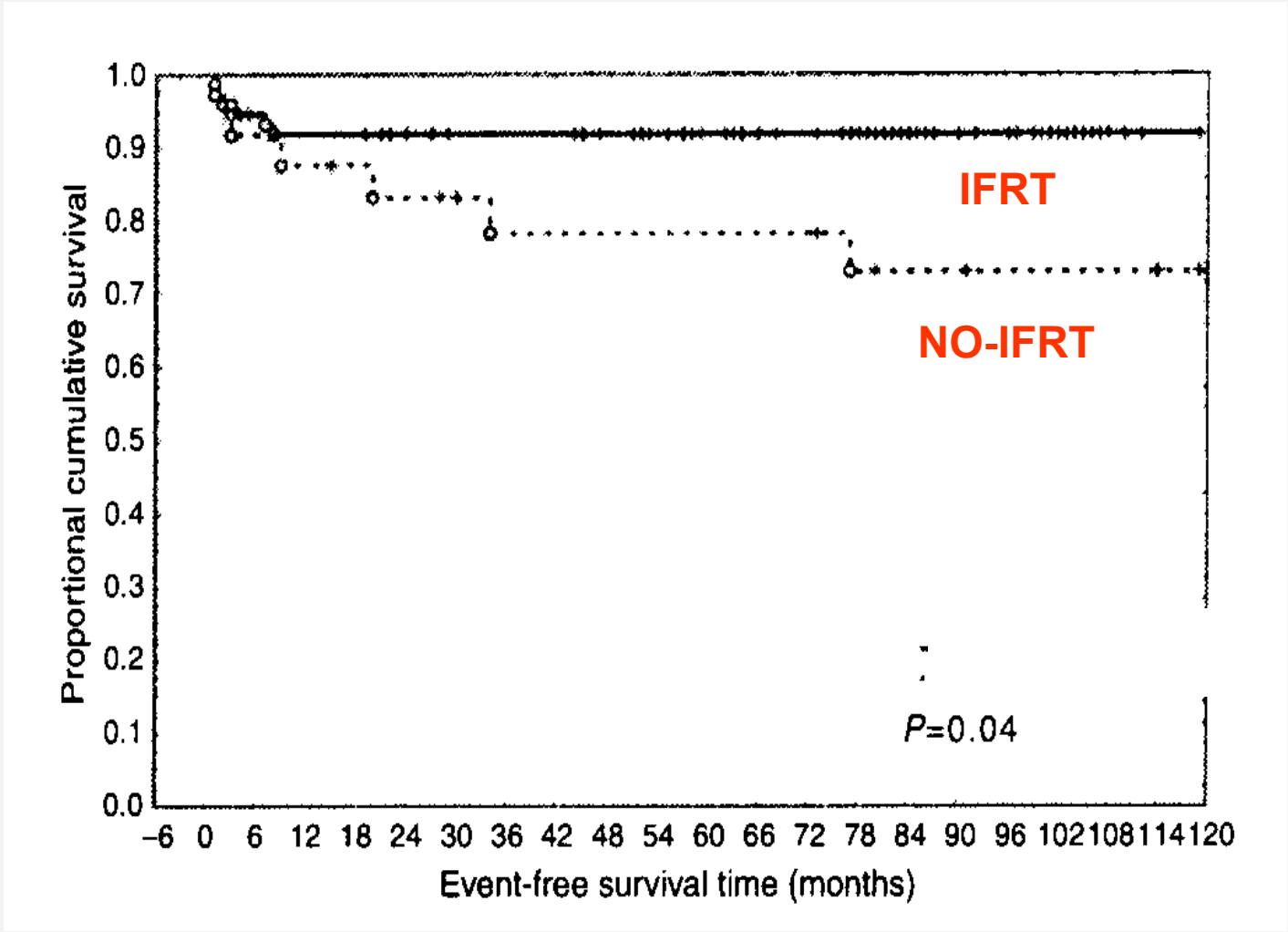
- Post-treatment negative PET/CT after R-CHT is significantly associated with a longer PFS.

- ***Liver uptake*** may represent a more appropriate cut-point than MBP to identify those patients with a significant increased risk of relapse or progressive disease.

Open questions

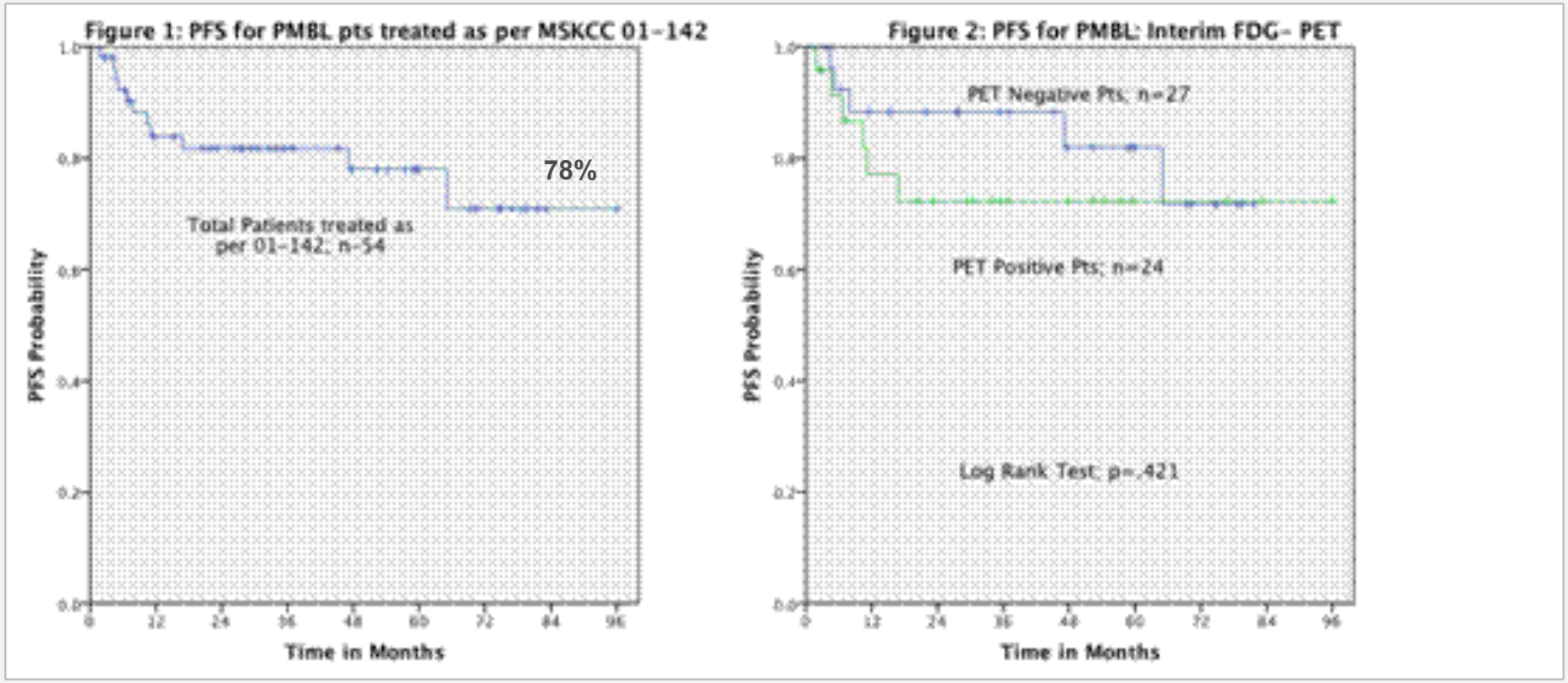
- What is the role of PET scan in the response evaluation after chemo-immunotherapy?
- Can mediastinal radiotherapy be removed in selected patients and if the PET scan can drive this selection?
- Should new quantitative functional PET parameters (QPM), identify very high risk patients to candidate for more intensive regimens as DA-EPOCH-R ?

Mediastinal RT in a retrospective Italian study



Todeschini et al B.J.Cancer 2004

Sequential R-CHOP 14 followed by ICE consolidation without consolidation IFRT for patients with PMBL
MSKCC Protocol

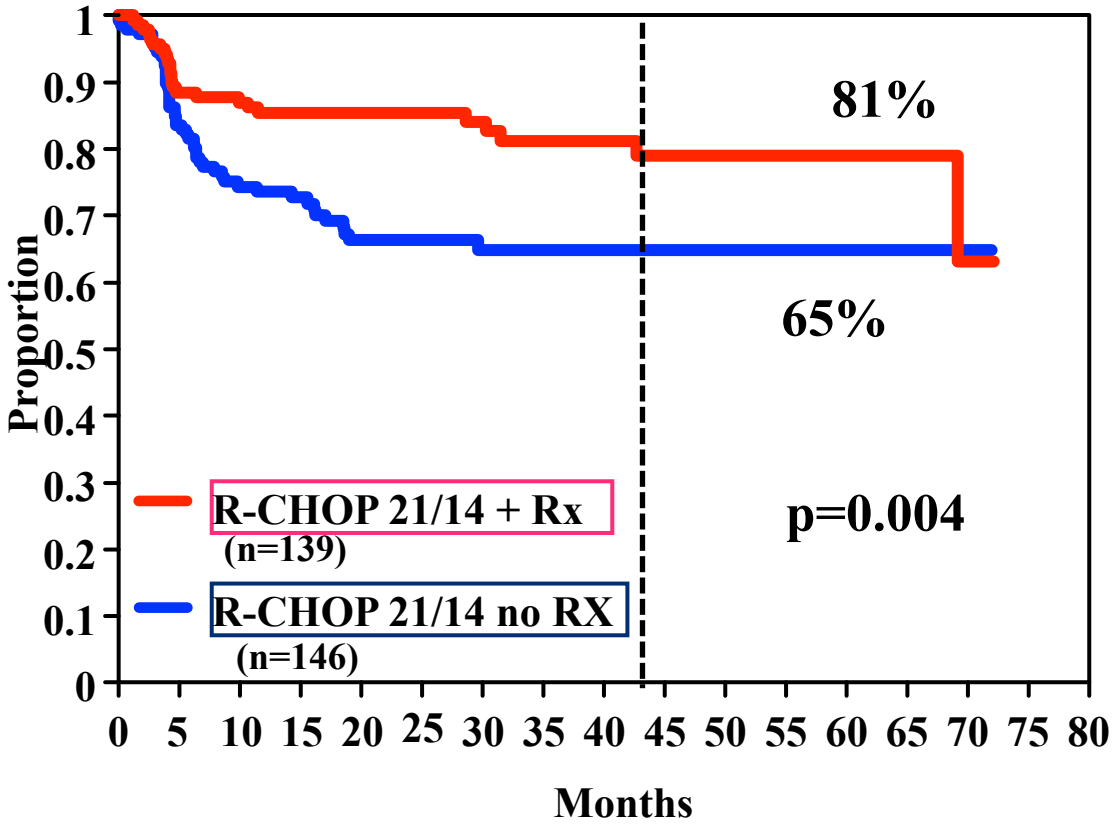


Moskowitz G. et al ASH 2010 abst 420

UNFOLDER phase 3 study: preliminary results

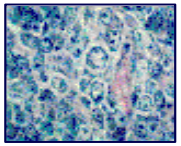
Patients 18- 60 years, aaIPI=0 with bulk or aaIPI=1, ITT (n=443)

Patients randomised to 4 arms (n=285)



GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)

www.lymphome.de/en/Groups/DSHNHL



~20% PMBCL

Patients randomized to receive or not IFRT irrespectively of PET response

Discontinuation of the no RT arms due to evident benefit for IFRT in bulky disease

DSHNHL 01.07.12

Courtesy of *M. Pfreundschuh , personal communication*

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

PMBCL: RT PET+ residual area

176 PMBCL
80 CHOP
96 R-CHOP

↓

RCHOP –21 x 6-8
RT era 96
PET era 50
PET self 9

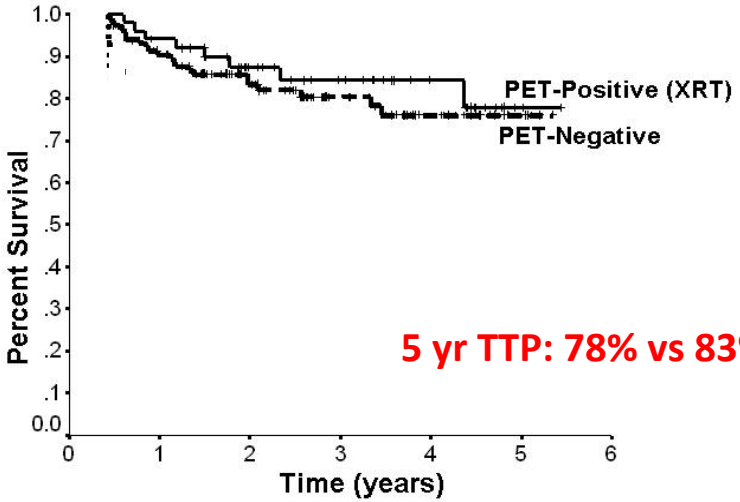
↓

CT abnormalities
≥ 2 cm

↓

R-CHOP+PET = 59

→ **NEG = 35 (59%):** *No RT* (regardless of initial bulk)
→ **POS= 24 (41%)** : *23 /24 XRT*



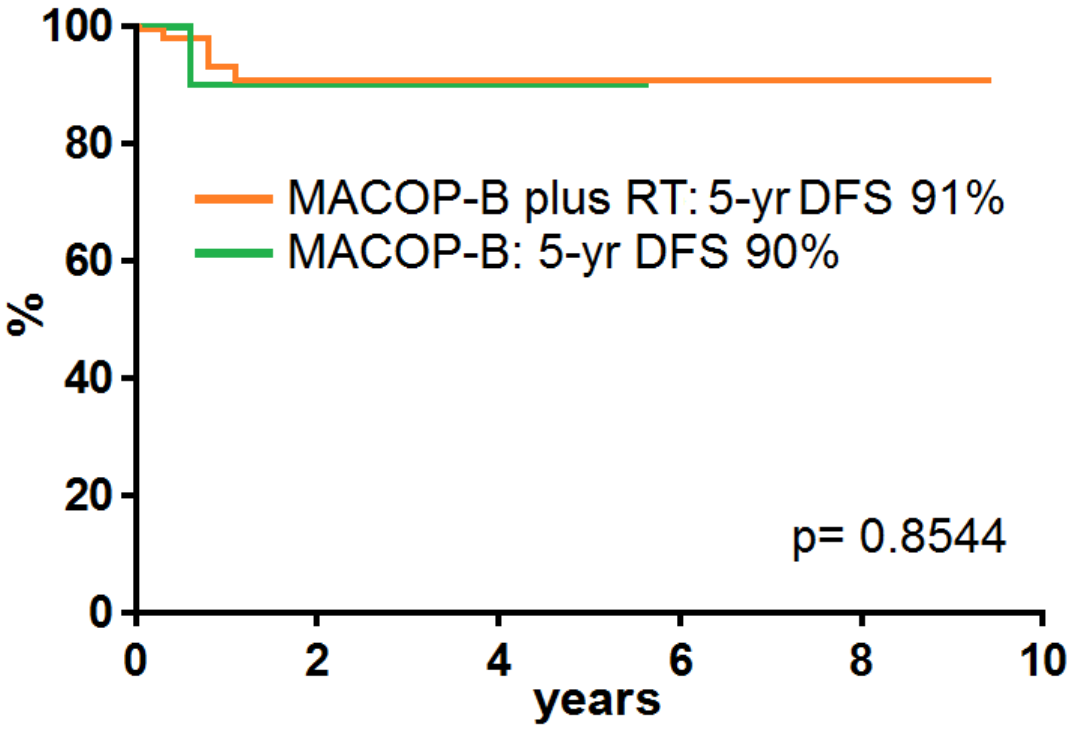
5 yr TTP: 78% vs 83%, .

Savage et al ASH 2012 abs 623

PET-guided RT after R-MACOP-B in PMBCL

MACOP-B-R ± RT		
Response	N	%
CR	61/74	82.4
PR	5/74	6.8
PD	8/74	10.8

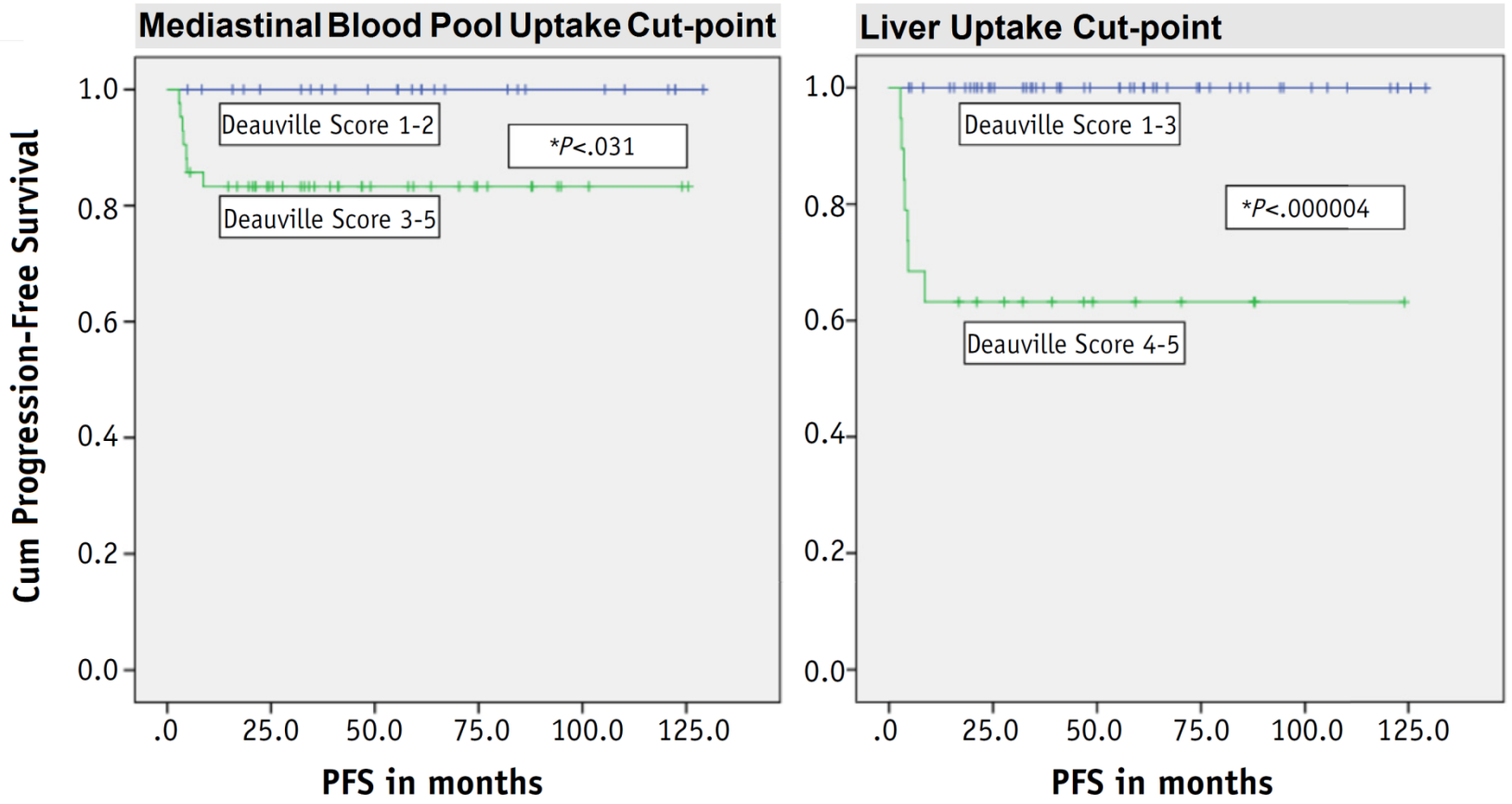
post-chemotherapy PET EVALUATION			
RESULT	N	%	
PET- POSITIVE	51	68.9	⟹ RT
PET-NEGATIVE	23	31.1	



- ***A PET-guided RT approach after MACOP-B plus rituximab may allow a patient tailored treatment***

P. Zinzani, 12-ICML, Hematol Oncol 2013. 31(suppl 1):128. Abs 097

MDACC retrospective PMBCL series:
PFS according to the DS at the end of immunochemotherapy



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

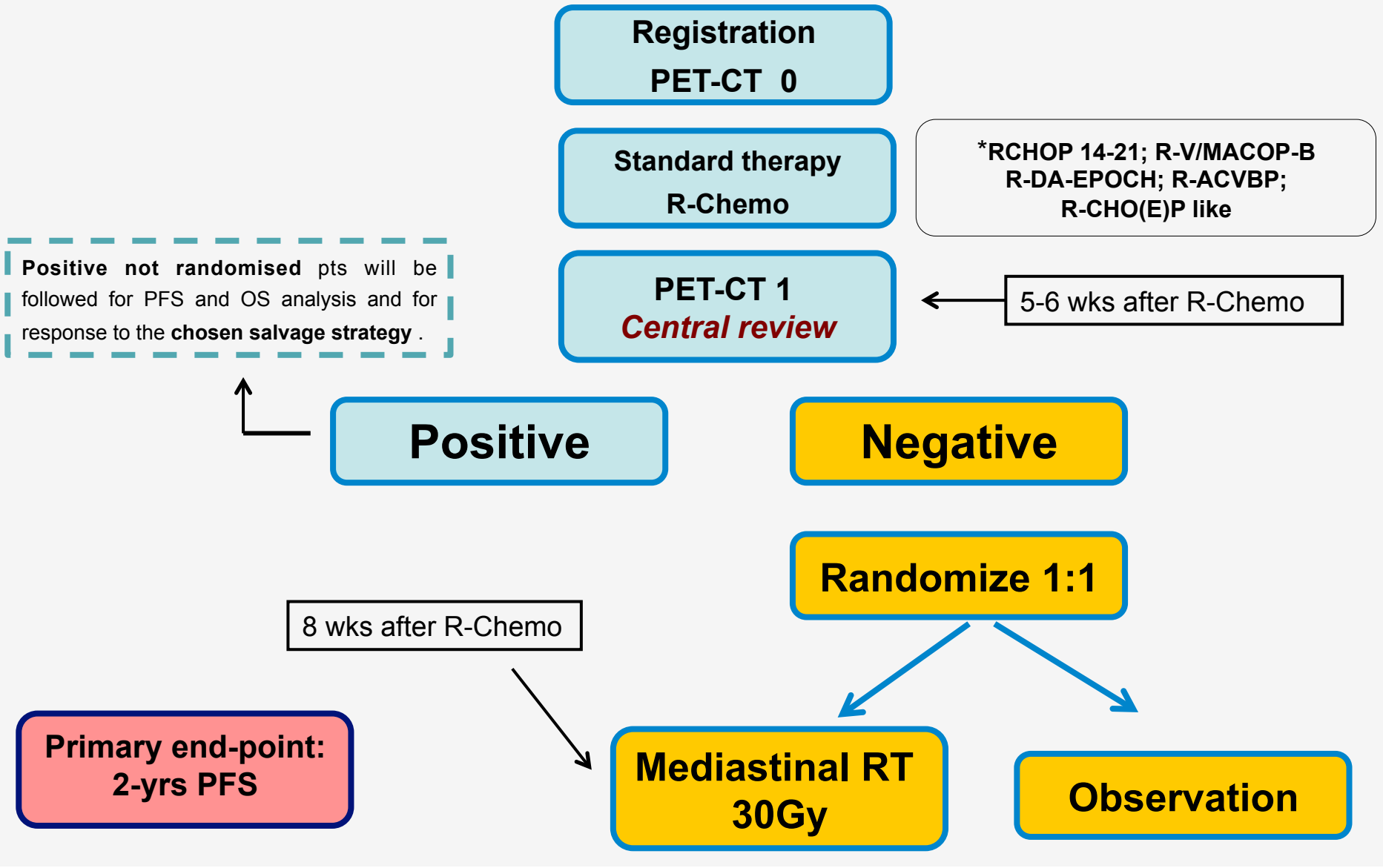
Pinnix CC et al. Int J Radiat Oncol Biol Phys. 2015; 92:113-121

IELSG 37 study

A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of involved mediastinal radiotherapy in Primary Mediastinal Large B-Cell Lymphoma (PMBCL).

October 2012

Trial design



Central PET-CT review workflow

Widen send automatically e-mail and SMS to reviewers

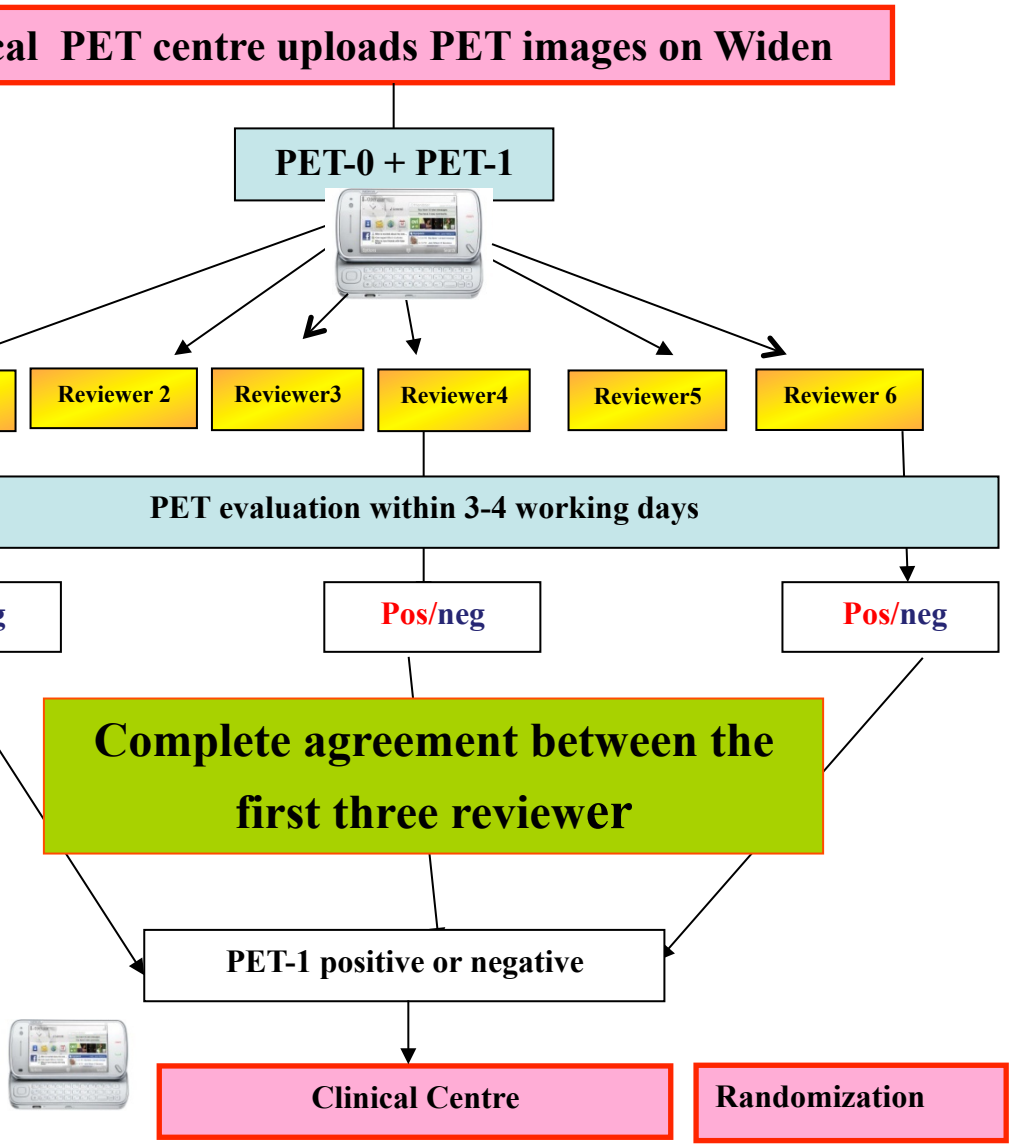
reviewers download images from Widen

reviewers evaluate images

reviewers post results to Widen

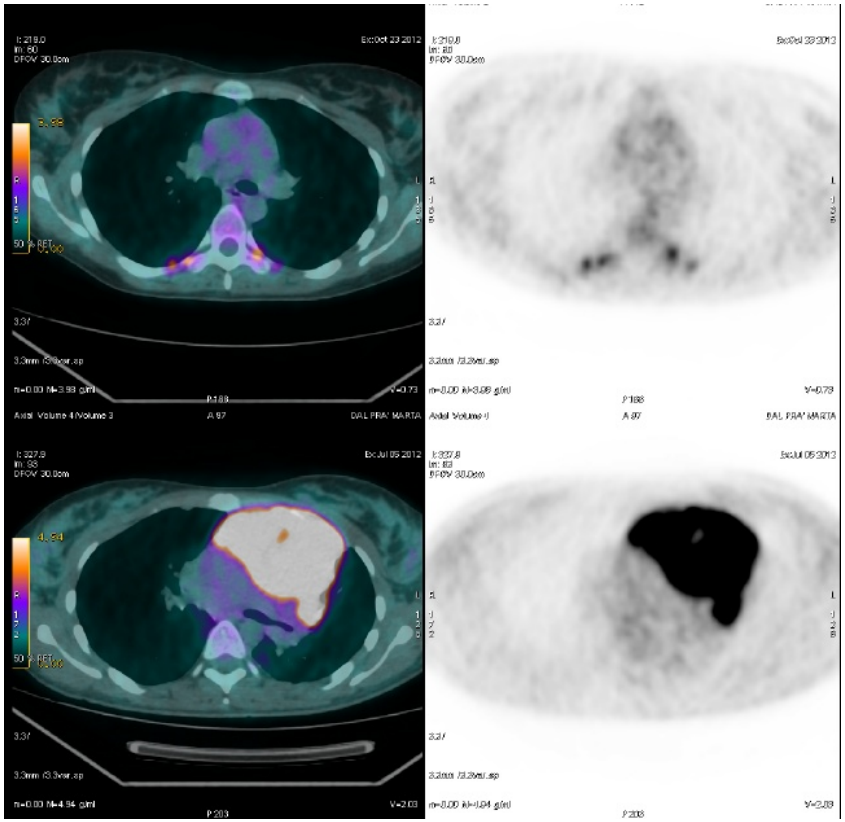
Widen combine reviews

Widen send results to Clinical Centre



PET-CT post chemotherapy PET/CT evaluation according visual assessment

Post-CHT PET

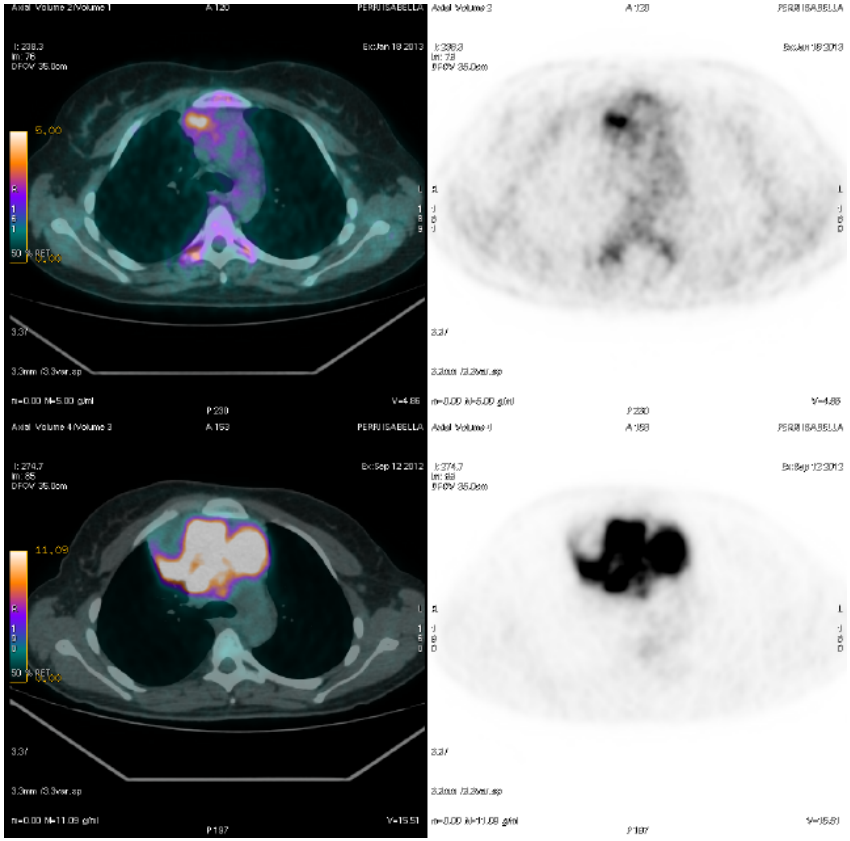


PET-0

Deauville score 2

Central review: negative

Post-CHT PET



PET-0

Deauville score 4

Central review: positive

Enrolled patients by sites (March, 2016)

Total number of patients	240
Countries enrolling	9
Centres with at least 1 patient	52

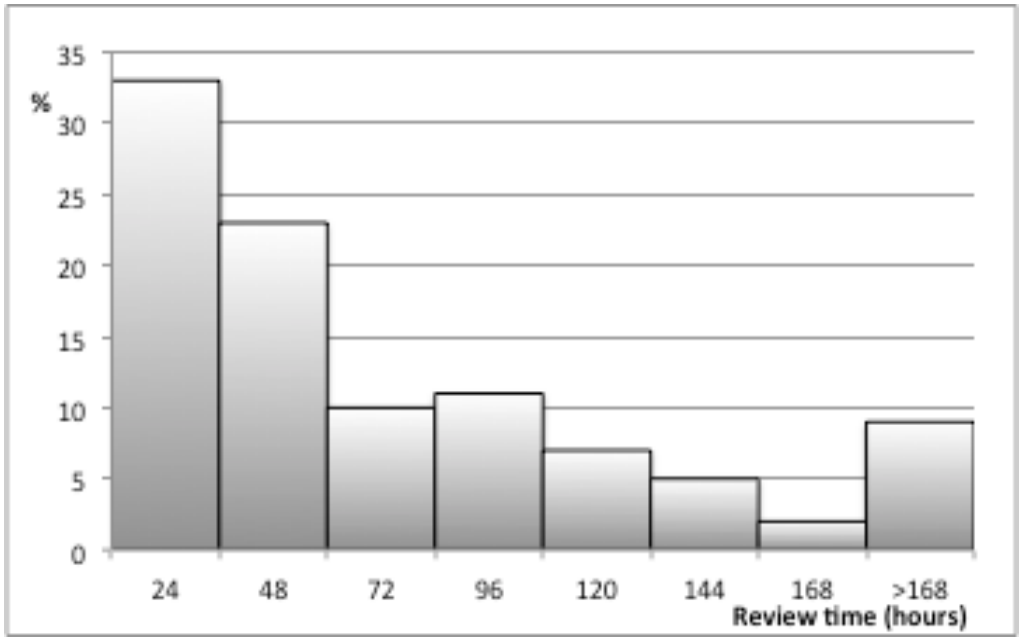
Country	Center	Patients
Italy	FIL	172
Ukraine	Kiev	21
Canada	Toronto	3
Norway	Oslo	4
	Trondheim	2
Sweden	Lund	3
Switzerland	Bern	5
	St. Gallen	2
	Bellinzona	3
UK	Glasgow	3
	Leeds St. James	1
	London Guy's & St. Thomas	2
	London UCLH	2
	Southampton	4
	Manchester	2
	Newcastle	1
	Norfolk	1
	Nottingham	2
USA	Louisville	1

Central PET Review After Chemoterapy

(March, 2016)

PET REVIEWED	PET NEGATIVE	PET POSITIVE
190	85 (45%)	105 (55%)
102 (MBP neg score 1-2)	35 (34%)	67 (66%)
88 (Liver neg score 1-3)	50 (57%)	38 (43%)

The average and median review time was 70 h and 46 h, respectively



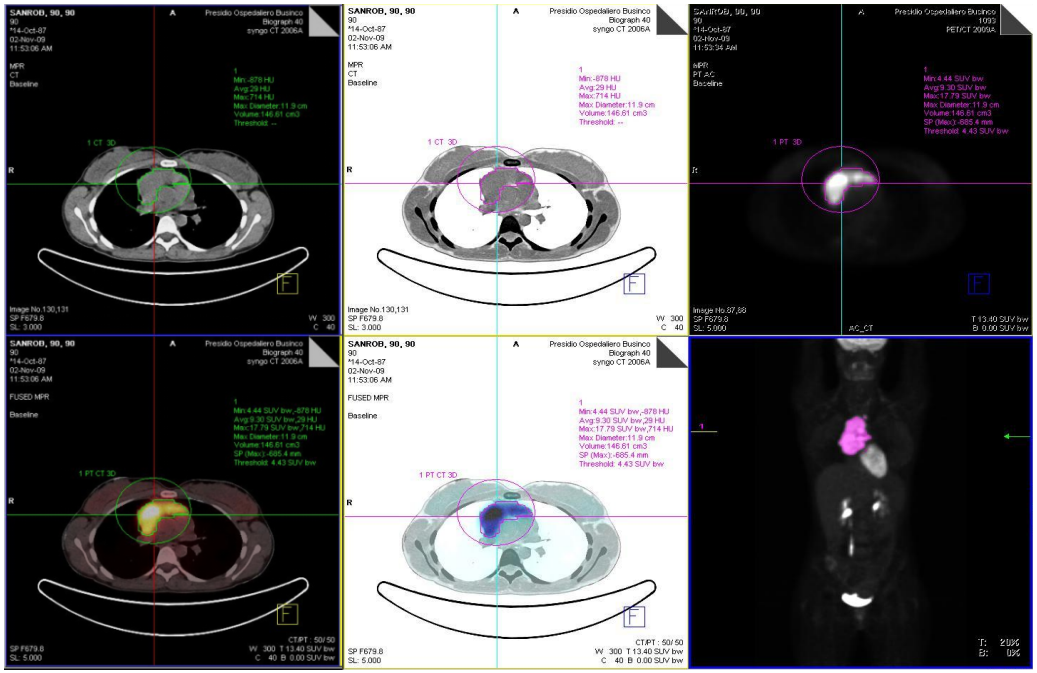
Open questions

- What is the role of PET scan in the response evaluation after chemo-immunotherapy?
- Can mediastinal radiotherapy be removed in selected patients and if the PET scan can drive this selection?
- Should new quantitative functional PET parameters (QPM), identify very high risk patients to candidate for more intensive regimens as DA-EPOCH-R ?

Functional and quantitative PET parameters

- Assessment of the prognostic value of
  - maximum Standard Uptake Value (**SUVmax**)
  - metabolic tumor volume (**MTV**)
  - total lesion glycolysis (**TLG**)

  - **SUV max, MTV** and **TLG** were measured following a standard protocol **on basal PET**



Prognostic value of the baseline functional PET parameters in PMBCL

125 PMLBCL enrolled

Baseline PET
(within 14 days before R-Chemo)

105 pts – 103 studies analyzed

Full course of chemotherapy:
R-CHOP 21 /14 or
R-MACOP-B or R-VACOP-B

Final PET
(3-4 weeks after R-Chemo)

Consolidation RT
(according to local policy)

93 patients

Follow-up

Regular Article

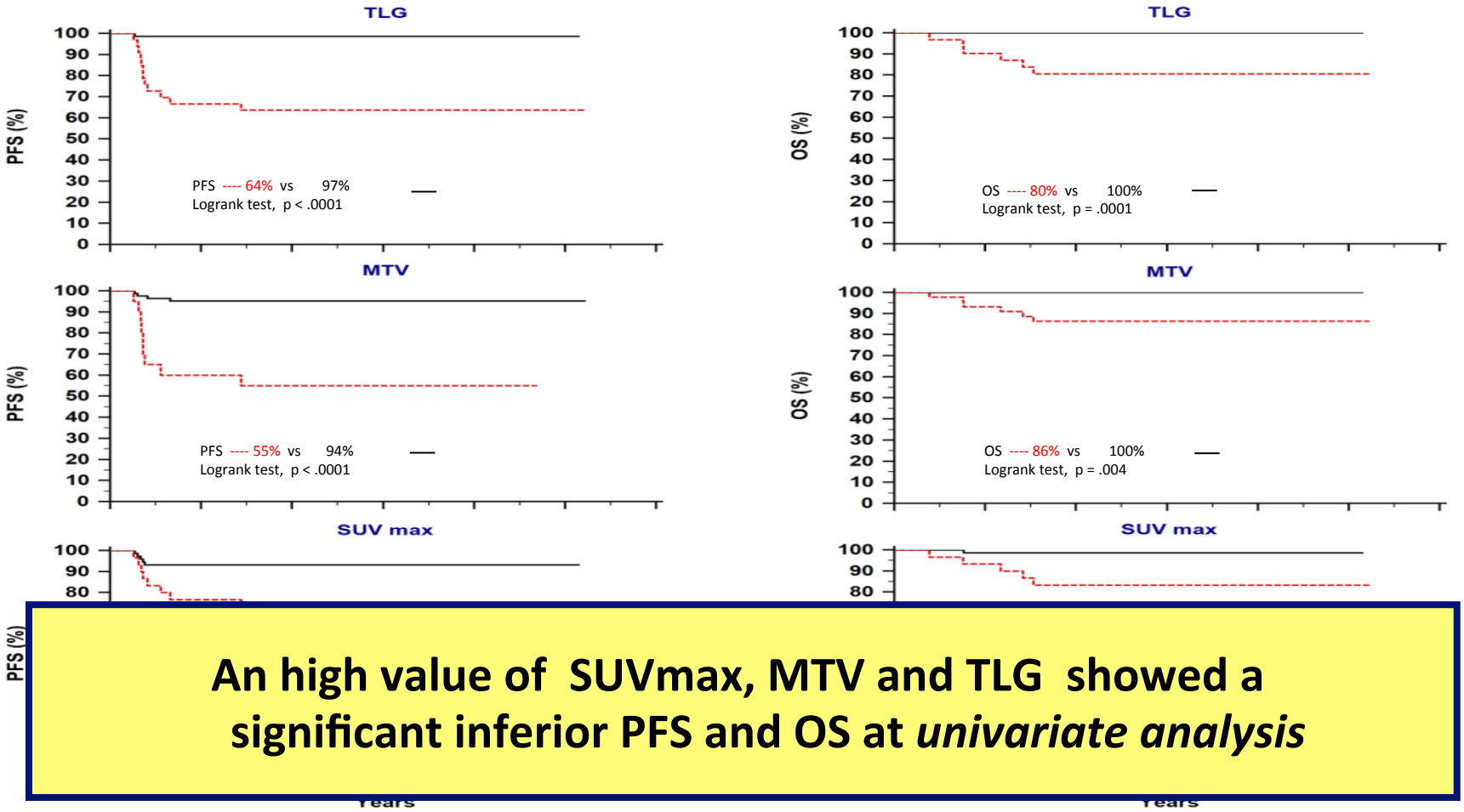
CLINICAL TRIALS AND OBSERVATIONS

Utility of baseline 18FDG-PET/CT functional parameters in defining prognosis of primary mediastinal (thymic) large B-cell lymphoma

Luca Ceriani,[1] Maurizio Martelli,[2] Pier Luigi Zinzani,[3] Andrés J. M. Ferreri,[4] Barbara Botto,[5] Caterina Stelitano,[6] Manuel Gotti,[7] Maria Giuseppina Cabras,[8] Luigi Rigacci,[9] Livio Gargantini,[10] Francesco Merli,[11] Graziella Pinotti,[12] Donato Mannina,[13] Stefano Luminari,[14] Anastasios Stathis,[1] Eleonora Russo,[2] Franco Cavalli,[1] Luca Giovanella,[1] Peter W. M. Johnson,[15] and Emanuele Zucca[1]

[1]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [2]Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy; [3]Institute of Hematology and Medical Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy; [4]Department of Oncology, Unit of Lymphoid Malignancies, San Raffaele Scientific Institute, Milan, Italy; [5]Hematology, Azienda Ospedaliera Città della Salute e della Scienza, Turin, Italy; [6]Hematology, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; [7]Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [8]Hematology, Ospedale Businco, Cagliari, Italy; [9]Hematology, Policlinico Careggi, Florence, Italy; [10]Department of Hematology, Niguarda Ca' Granda Hospital, Milan, Italy; [11]Hematology Unit, Department of Oncology, Azienda Ospedaliera ASMN IRCCS Reggio Emilia, Italy; [12]Medical Oncology Unit, Ospedale di Circolo Fondazione Macchi, Varese, Italy; [13]Department of Hematology, Azienda Ospedaliera Papardo, Messina, Italy; [14]Onco-Hematology Department, Modena University, Modena, Italy; and [15]Cancer Research UK Centre, University of Southampton, Southampton, United Kingdom

Prognostic value of baseline functional 18-FDG parameters in the IELSG 26 study in PMBCL



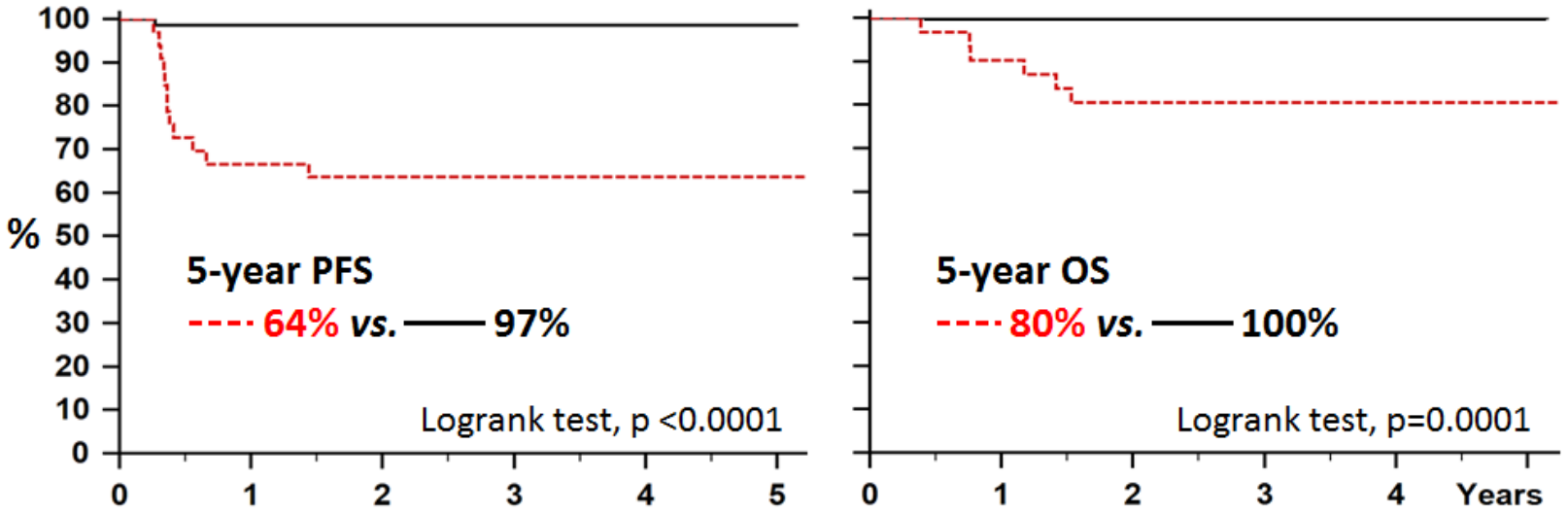
An high value of SUVmax, MTV and TLG showed a significant inferior PFS and OS at *univariate analysis*

Ceriani L, Martelli M, Zinzani PL et al Blood 2015

Prognostic value of baseline functional 18-FDG parameters in the IELSG 26 study in PMBCL

TLG retained statistical significance for both OS and PFS at multivariate analysis

Elevated *vs.* **non-Elevated TLG** (cut-off defined by ROC curve)



Ceriani L, Martelli M, Zinzani PL et al Blood 2015

Take home messages (4)

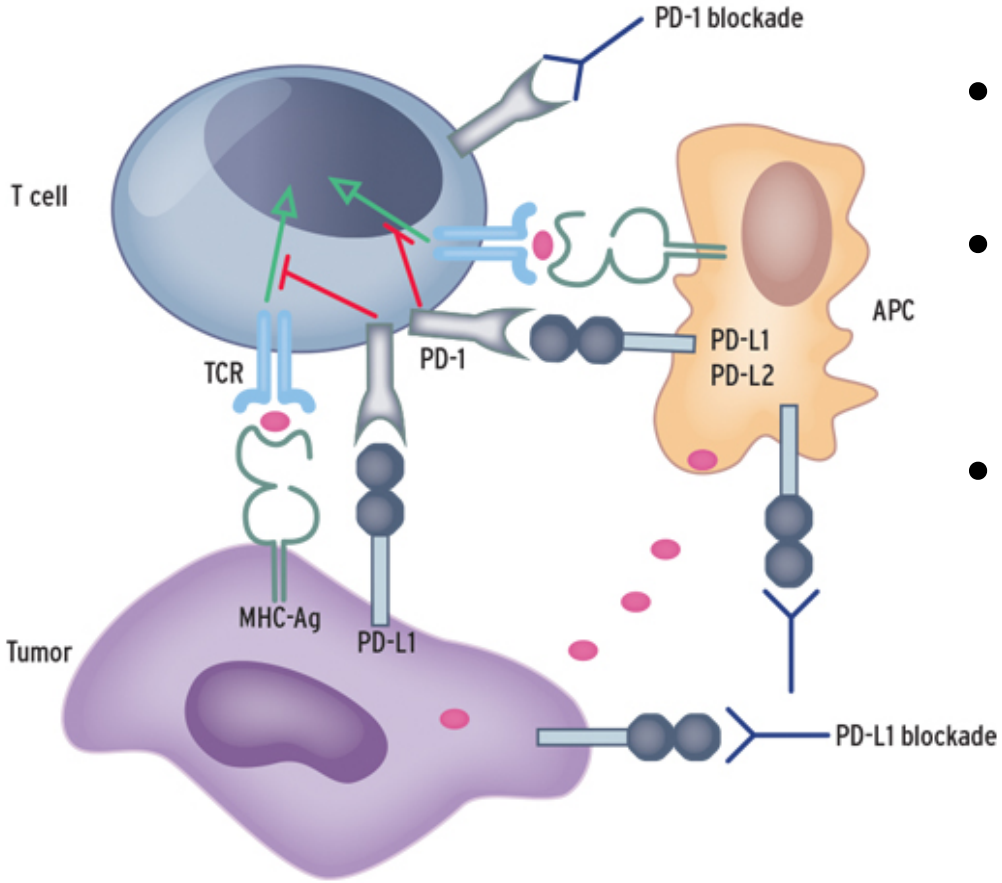
- Randomized phase IIII trial (ongoing IELSG 37 trial) will asses whether RT can be safely omitted in PMBCL with a negative PET-CT after R-Chemotherapy

- Baseline functional PET parameters (SUV,TLG,MTV) should be a powerful predictors of PMBCL outcome and in future should help us to stratify those patients with a significant increased risk of relapse/progression.

- New biological drugs for selective pathways, should be also explored in the future treatment of PMBCL

PD-1 Pathway as target therapy of PMBCL

Checkpoints inhibitors:
nivolumab,pidilizumab

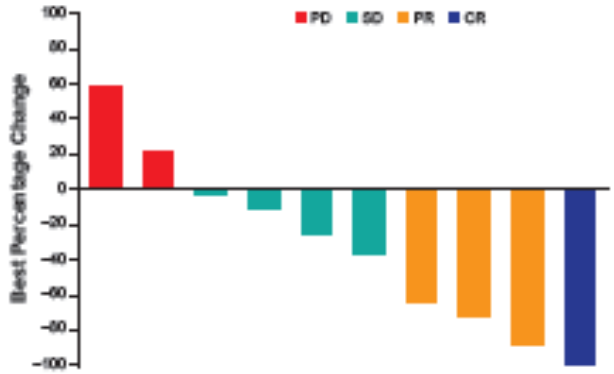


- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells ***(PMBCL, LH)***
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

Phase 1b Study of PD-1 Blockade With Pembrolizumab in Patients With Relapsed/Refractory PMBCL

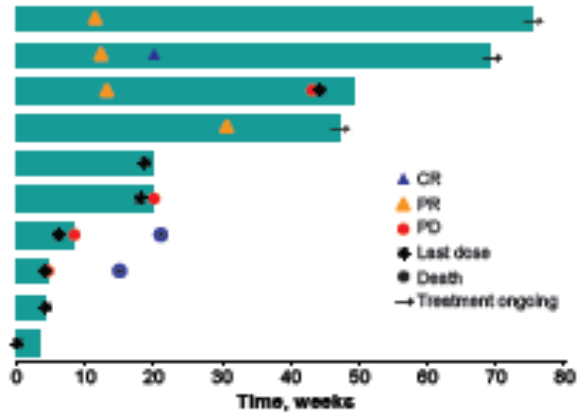
Characteristic	n = 11
Sex, n (%)	
Female	8 (73)
Male	3 (27)
Age, median (range), years	31 (23-62)
Race, n (%)	
White	10 (91)
Asian	1 (9)
ECOG PS, n (%)	
0	5 (45)
1	5 (45)
4	1 (9)
Bulky lymphadenopathy, n (%)	
Yes	7 (64)
No	4 (36)
Disease manifestation, n (%)	
Anemia	1 (9)
Bone marrow involvement	0 (0)
CNS involvement	0 (0)
Hepatomegaly	0 (0)
Lymphadenopathy	7 (64)
Splenomegaly	0 (0)
Thrombocytopenia	0 (0)
Other	1 (9)
Prior lines of therapy, n (%)	
2	4 (36)
3	1 (9)
≥4	6 (55)
Autologous stem cell transplantation, n (%)	3 (27)
Prior radiation, n (%)	7 (64)
Prior rituximab, n (%)	11 (100)

Figure 2. Change from baseline in tumor size.



CR = complete remission; PD = progressive disease; PR = partial remission; SD = stable disease.

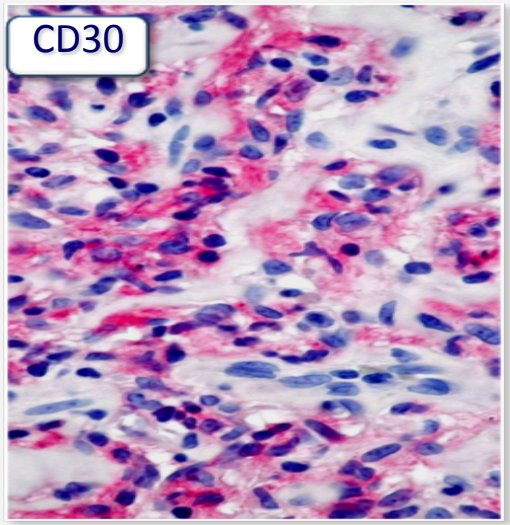
Figure 3. Time since initiation of treatment.

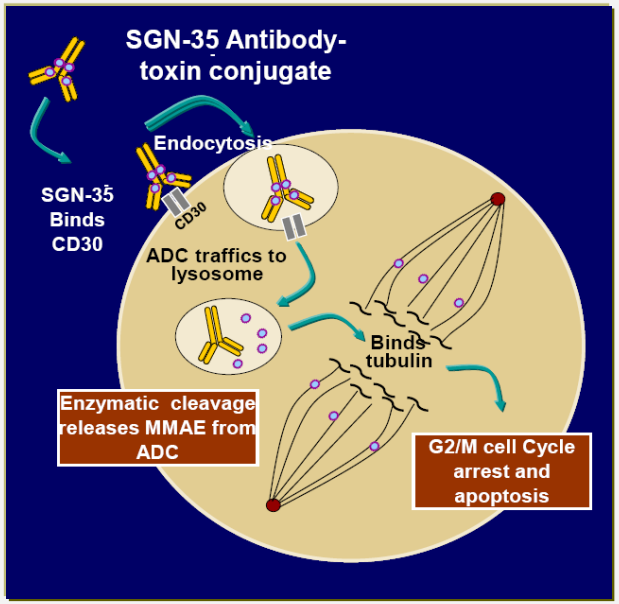


CR = complete remission; PD = progressive disease; PR = partial remission.

Zinzani PL et al.ASH 2015 Abstract 3986.

Brentuximab vedotin (SGN-35)





SGN-35 antibody-drug conjugate

✓ CD30-target antibody conjugated to an auristatin (MMAE), an anti-tubulin agent

✓**CD30 is present in more than 80% of PMBCL usually weak and heterogeneous**

Brentuximab vedotin phase II study for relapsed/ refractory PMBCL

Principal investigator PL Zinzani

Ringraziamenti

Alice Di Rocco
Federico De Angelis
Michela Ansuinelli
Vitaliana De Sanctis
Lavinia Grapulin

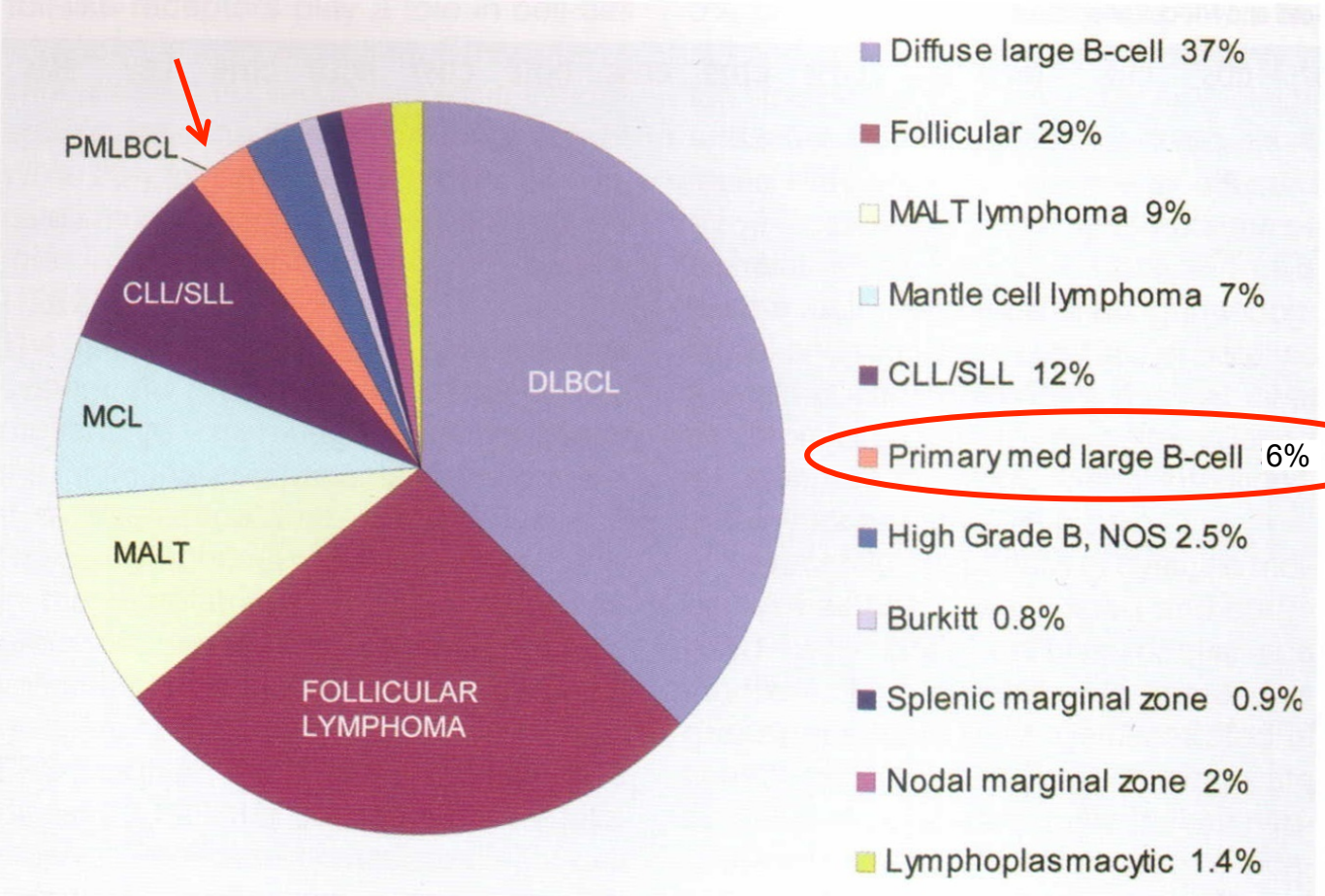
Emanuele Zucca
Luca Ceriani
Franco Cavalli

Robin Foà

INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

Thank you for the attention

Incidence of B cell NHL in adults



IELSG 37

Randomization (March, 2016)

RANDOMIZED Patients	ARM A (Radiotherapy)	ARM B (Observation)
85	43	42

Clinical Trial Coordinators	
M. Martelli	Roma (Italy)
A.J. Davis	Southampton (UK)
E. Zucca	Bellinzona (Switzerland)

Radiotherapy Coordinators	
M. Gospodarowicz	Toronto (Canada)
U. Ricardi	Torino (Italy)
N.C. Azinwi	Bellinzona (Switzerland)
Statistician	
G. Ciccone	Torino (Italy)
Medical Physicist	
S. Chauvie	Cuneo (Italy)

PET Trial Panel	
S. Barrington	London (UK)
A.Biggi	Cuneo (Italy)
L. Ceriani	Bellinzona (Switzerland)
A. Versari	Reggio Emilia (Italy)
B. Malkowski	Bydgoszcz (Poland)
U. Metser	Toronto (Canada)

INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

Back- up