RETE ONCOEMATOLOGICA DEL PIEMONTE E VALLE D'AOSTA

INCONTRO DI AGGIORNAMENTO SUI DISORDINI LINFOPROLIFERATIVI E SUI PROTOCOLLI DELLA FONDAZIONE ITALIANA LINFOMI

Torino, 25 novembre 2016

Centro Congressi Torino Incontra
Via Nino Costa, 8 - Torino

Linfomi primitivi del mediastino: terapia standard , ruolo della PET e nuove prospettive

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Dip. Biotecnologie Cellulari ed Ematologia
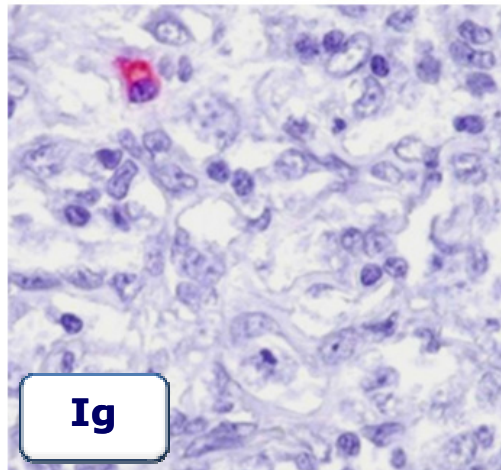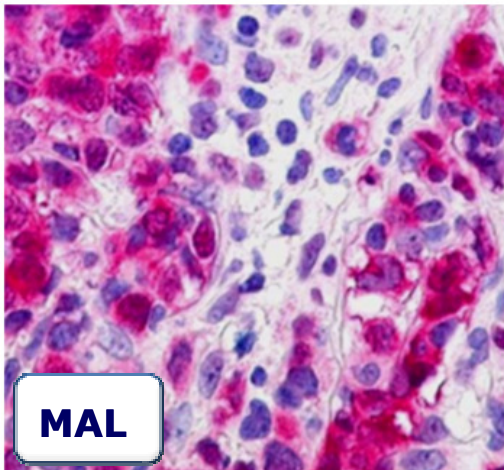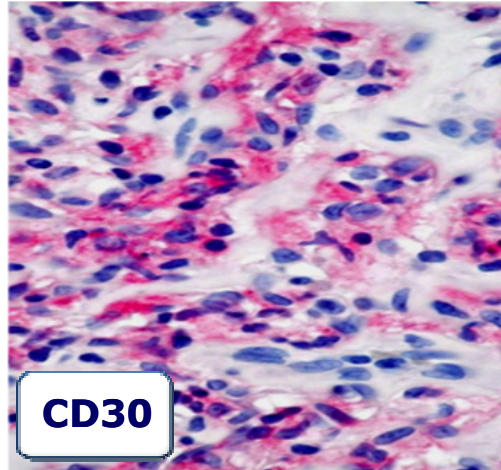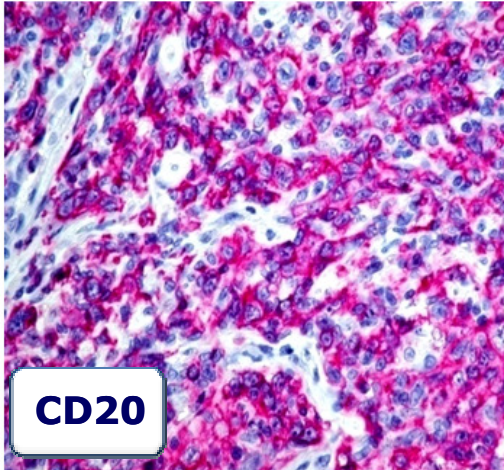**Università "Sapienza" Roma**

SAPIENZA
UNIVERSITÀ DI ROMA

Outline of discussion

▸ Pathology and molecular biology

▸ Clinical features

▸ Treatment and outcome

▸ Open questions

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PMBCL: immunohistochemical features

CD20

CD30

MAL

Ig

Courtesy of SA Pileri

High frequency of BCL-6 mutations and consistent expression of the transcription factors OCT-2, BOB.1, and PU.1 in the absence of Immunoglobulins

CD20	100%
CD30	87%
CD23	70%
CD15	---
EBV	---
Bcl-6	80%
IRF4	75%
Bcl-2	80%
Ig (ISH)	---
BOB.1/Oct-2/PU.1	80%
MAL protein	70%
CD200*	94%

Pileri SA, et al. Am J Pathol 2003;162:243–53.
*Dorfman DM et al Modern Pathology 2012

GEP defines molecularly and clinically distinct subgroups in DLBCL

Rosenwald A, et al. J Exp Med. 2003
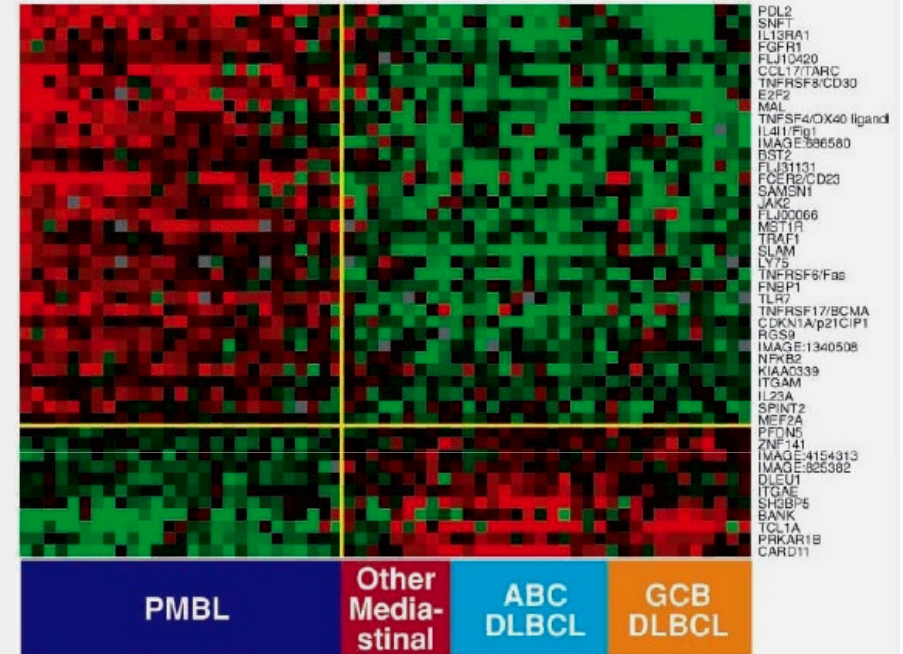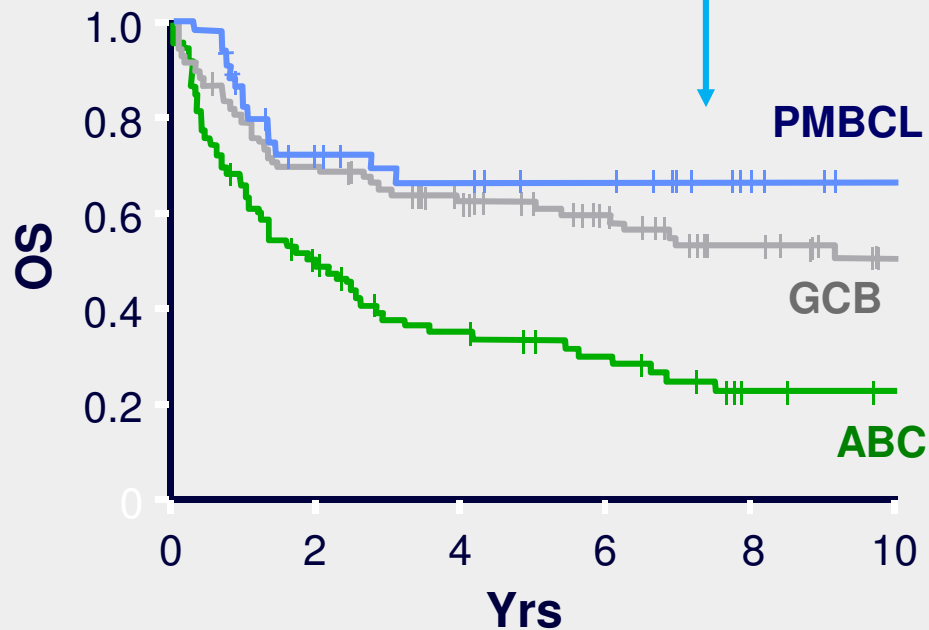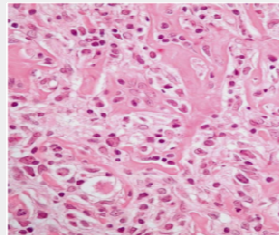
DLBCL Subgroup	5-Yr OS, %
PMBL	64
GCB DLBCL	59
ABC DLBCL	30

Borderland between PMBCL, MGZL and cHL

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

PMBL	Hodgkin Lymphoma	GCB DLBCL	
			ANXA1 — CD30 MAL
			TIMP1 TP73L TNFAIP3/A20 IL15 MSC/ABF-1
			SNFT

MGZL

HL mo...

CD20

C

OCT2+

MGZL

...hology

15+

B 1 +

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-... ...a, MD, PhD,*
Philippe Gaulard, MD, ...A. Alonso, PhD,‡
Mark Ra... ...MD

WHO Classification of Tumours of
Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe,
Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman

WHO
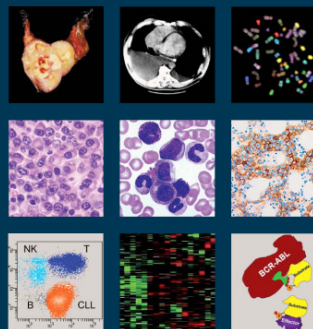
PMBCL
**CD20+;CD30+/- ;
CD15- ; OCT2 +;BOB.1+**

Inte...
fulfill t...
p...

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

Jaffe E . Educational ASH 2010

Mediastinal gray zone lymphoma (MGZL)

MGZL: immunohistochemical features

CD30 [CD45]

CD15

CD20

CD79a

BSAP/PAX5

BOB.1

Oct-2

Histology images courtesy Professor Pileri.
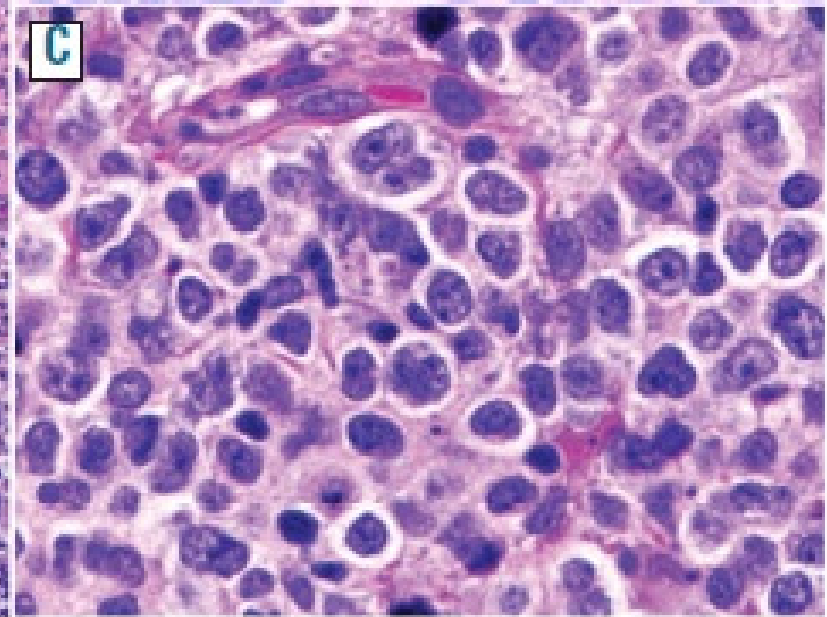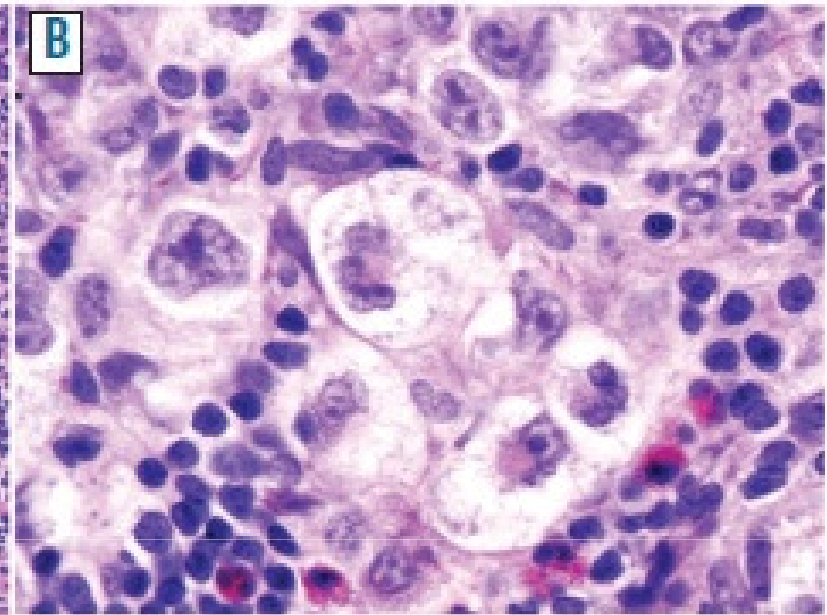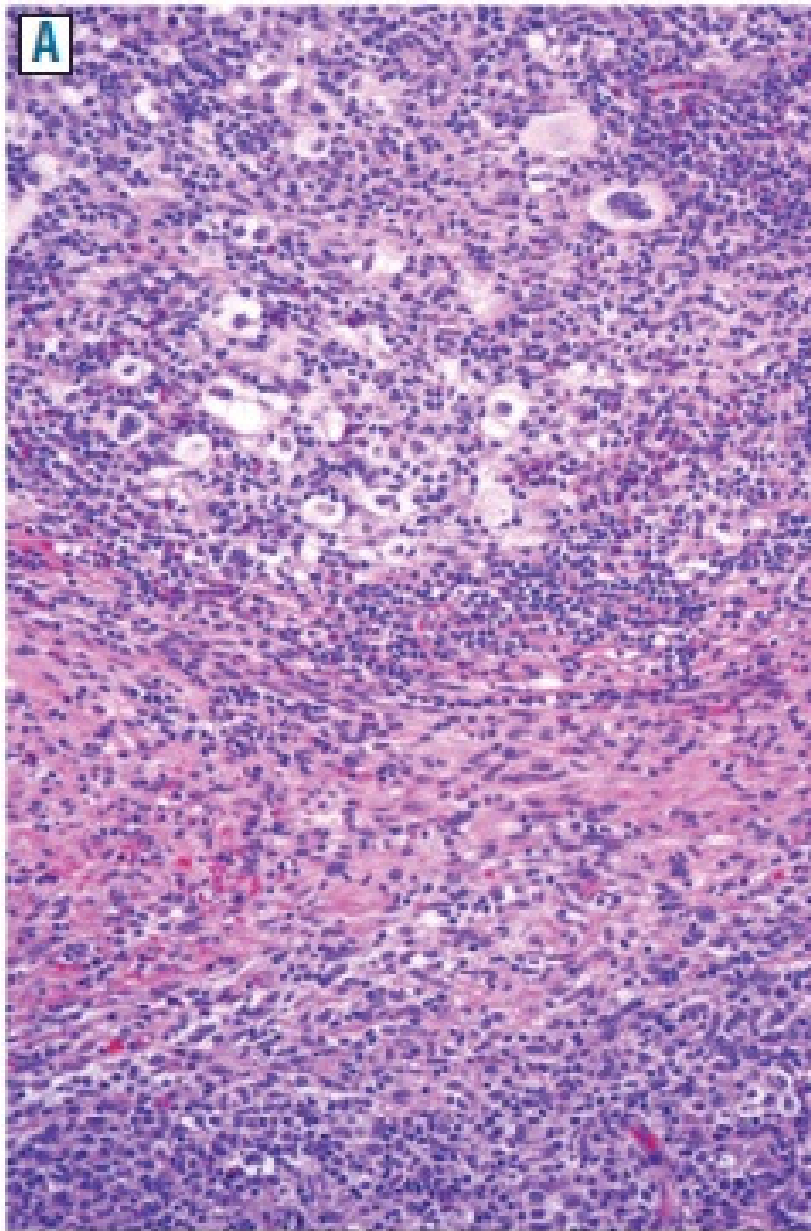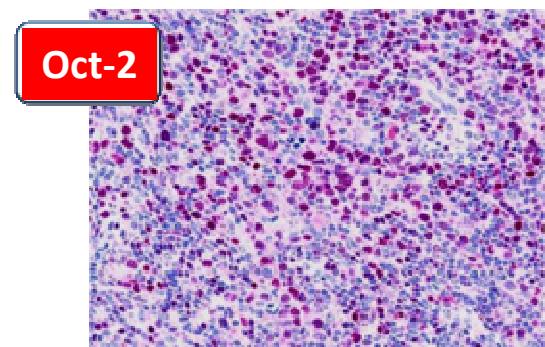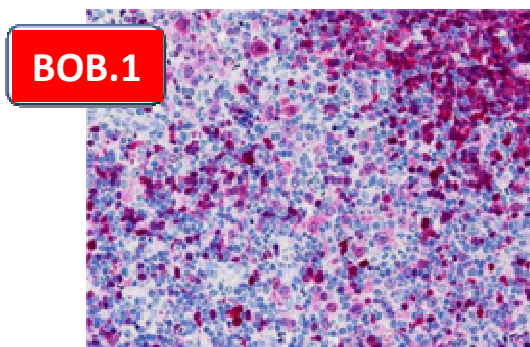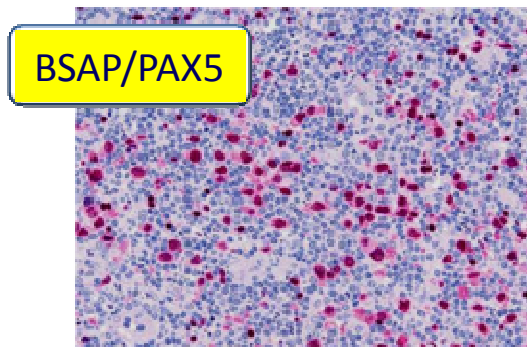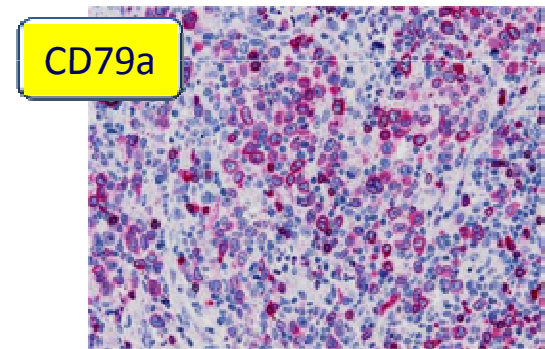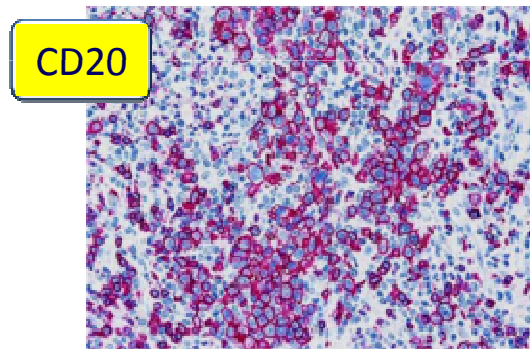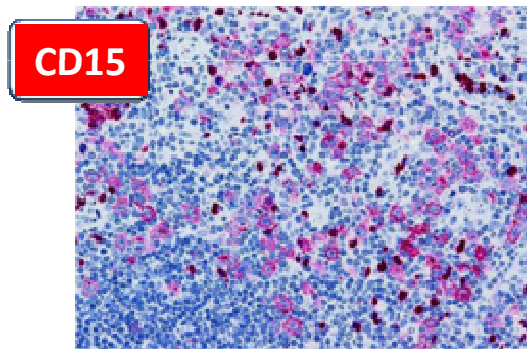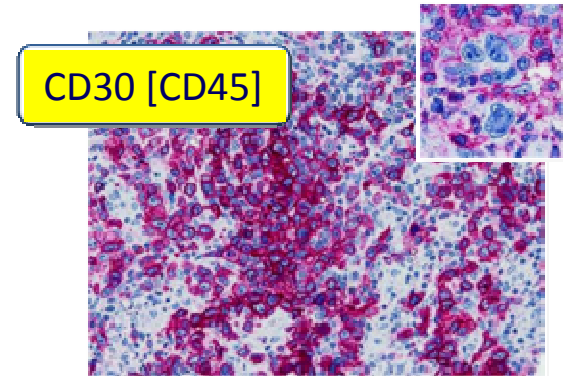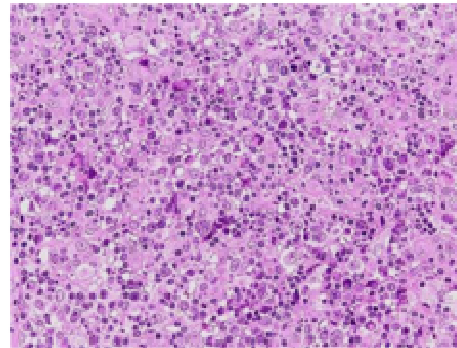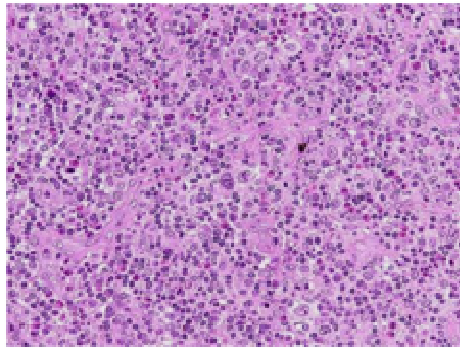
Pathological and immunophenotype features

Features	PMBL	MGZL	NSchL
Morphology	Sheets of large cells; clear cells ; no inflammatory	Sheets of pleomorphic large cells; HRS cells; rare inflammatory	Lacunar HRS cells Inflammatory
Sclerosis	70-100% (alveolar, fine bands)	Focal fibrous bands	100% (large bands)
CD30	Positive weak (70-80%)	positive	positive
CD15	negative	positive	positive
CD20	positive	positive	negative
PAX-5	positive	positive frequently	weak positive
Immun.	negative	negative	negative
BOB-1	positive	positive frequently	negative
OCT-2	positive	positive frequently	negative
MAL	60-70%	30-40%	<20%

AJH

Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort

Andrew M. Evens,[1]* Jennifer A. Kanakry,[2] Laurie H. Sehn,[3] Athena Kritharis,[1] Tatyana Feldman,[4] Aimee Kroll,[5] Randy D. Gascoyne,[3] Jeremy S. Abramson,[6] Adam M. Petrich,[7] Francisco J. Hernandez-Ilizaliturri,[8] Zeina Al-Mansour,[9] Camille Adeimy,[10] Jessica Hemminger,[11] Nancy L. Bartlett,[12] Anthony Mato,[4] Paolo F. Caimi,[13] Ranjana H. Advani,[14] Andreas K. Klein,[1] Chadi Nabhan,[15] Sonali M. Smith,[15] Jesus C. Fabregas,[16] Izidore S. Lossos,[16] Oliver W. Press,[17] Timothy S. Fenske,[18] Jonathan W. Friedberg,[19] Julie M. Vose,[20] and Kristie A. Blum[11]

HD meeting Colonia 2016
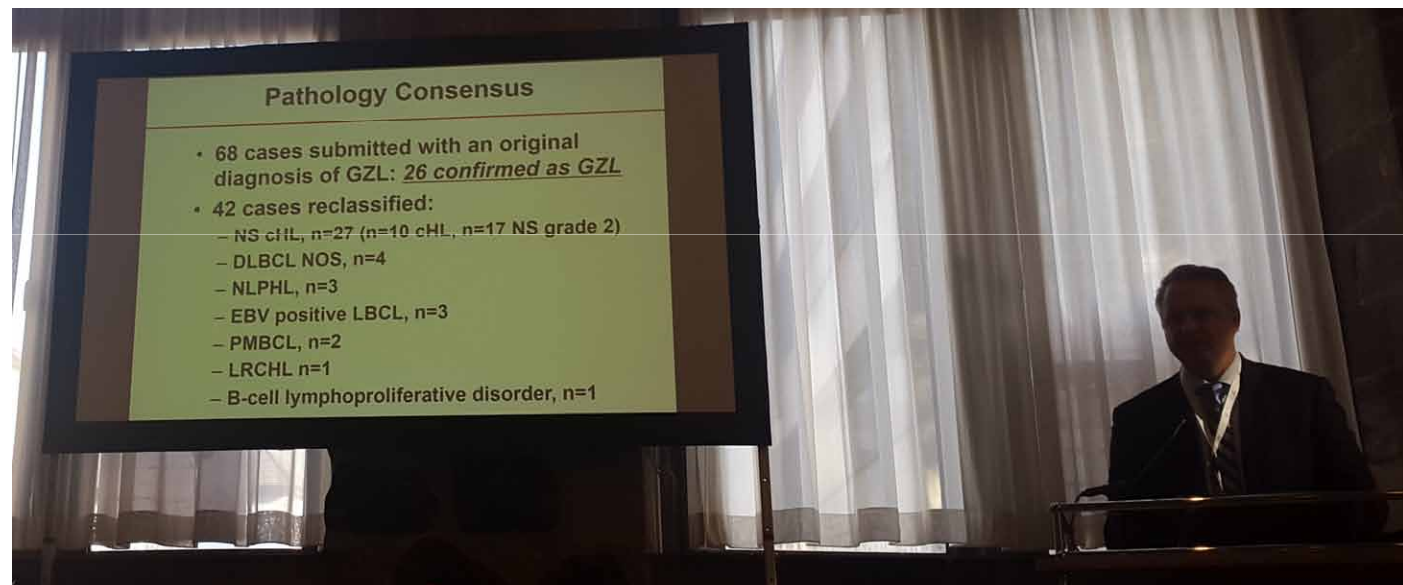
Evens et al. AJH 2015

112 GZL pts
68 cases submitted with an original diagnosis of GZL
28 confirmed
42 reclassified (60%)
(NSchL, PMBCL, DLBCL)

Clinical characteristics MGZL vs NMGZL

	MGZL	*Non MGZL*	*P*
Age > 45 years	12%	47%	0.0001
Bone marrow invol.	0	20%	0.001
Extranodal sites >1	8%	37%	0.014
Stage III vs IV	13%	81%	0.0001
Bulky disease	44%	8%	0.0001
IPI 3-5	7%	35%	0.001
IPI 4-7	6%	27%	0.002

Evens et al. AJH 2015

Genomic hybridization: amplification of JAK2, PDL1, PDL2

PMBL transcriptional signature: constitutively activated JAK2
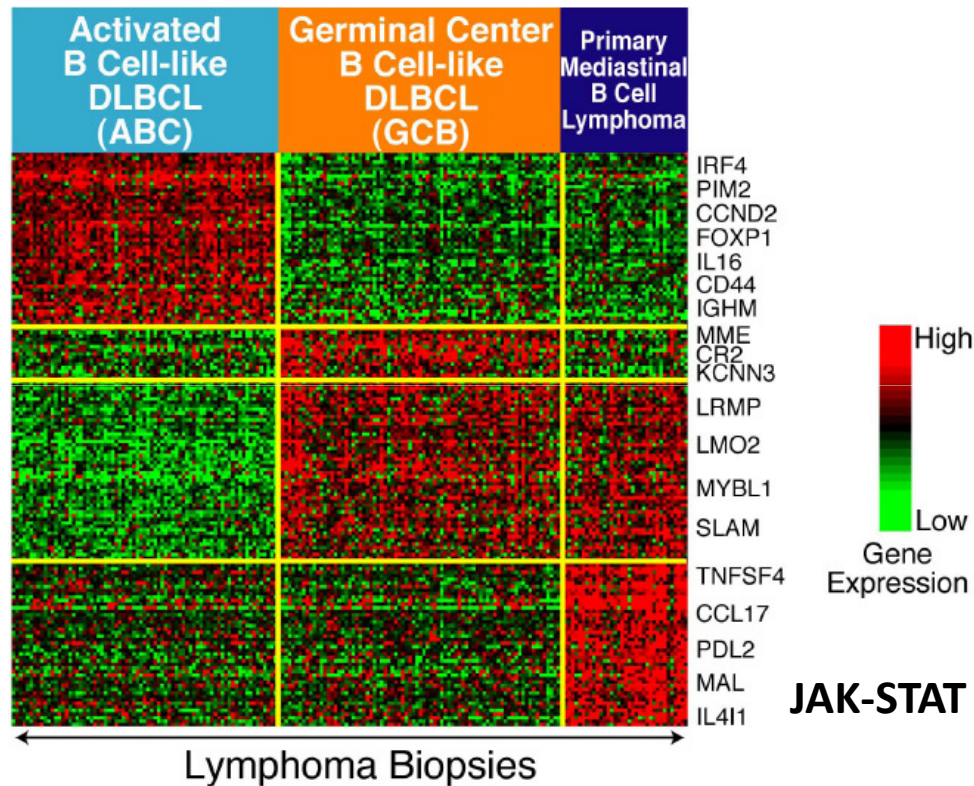
Recurrent amplification involving *JAK2* is the underlying genetic basis
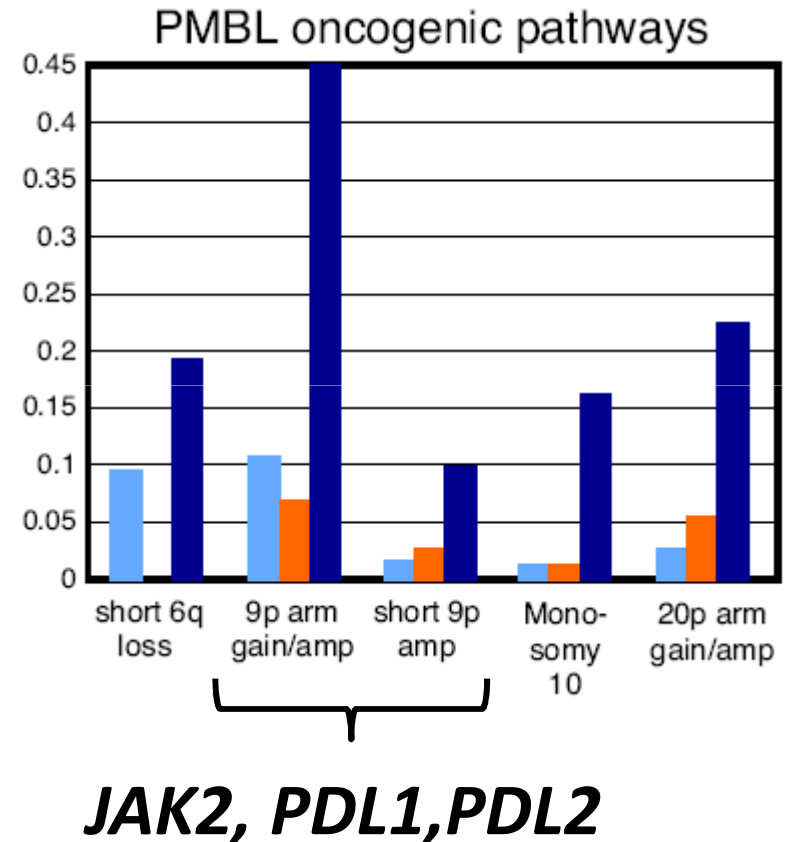
JAK-STAT

JAK2, PDL1,PDL2

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

Outline of discussion

▸ Pathology and molecular biology

▸ Clinical features

▸ Treatment and outcome

▸ Open questions

Types of mediastinal Lymphoma
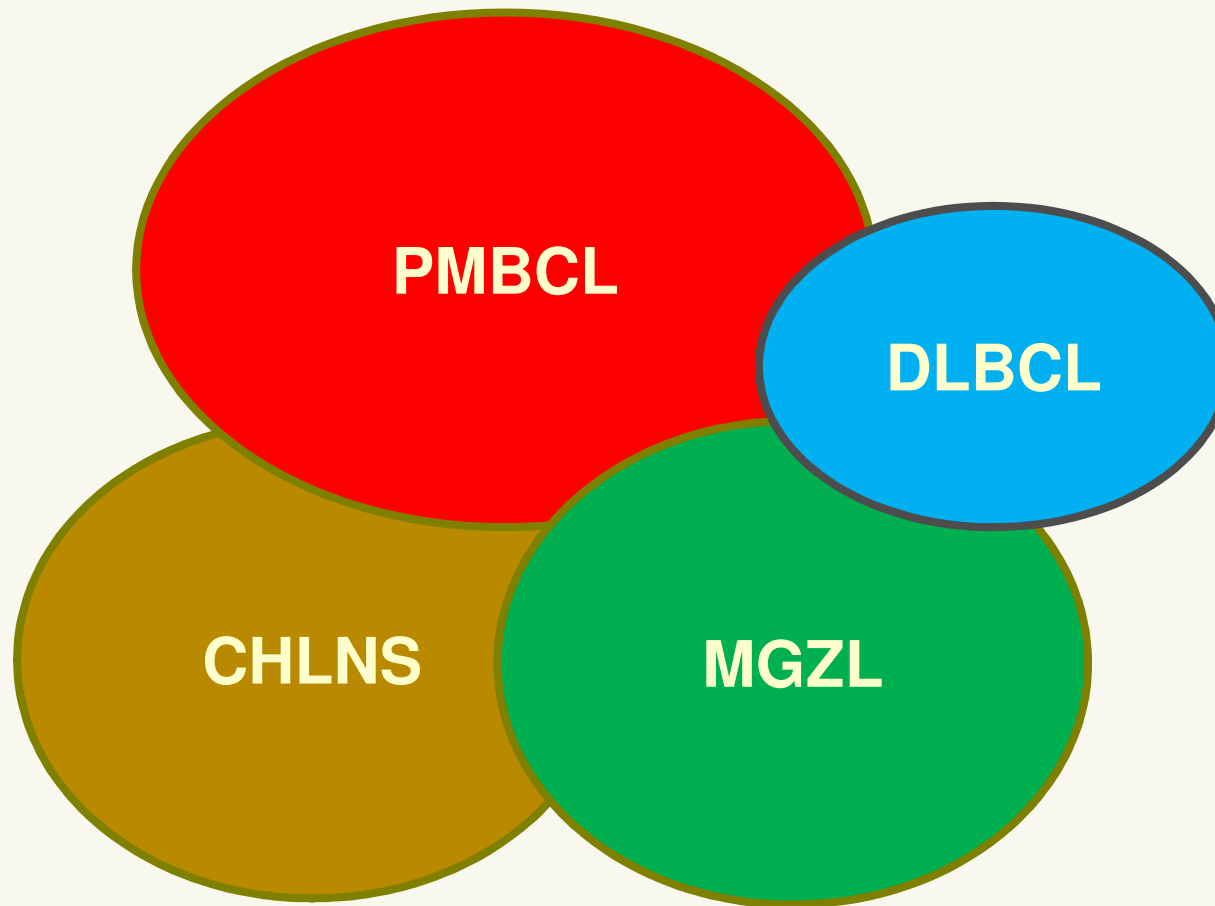
Clinical features

- 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

Clinical features of mediastinal lymphomas

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

Outline of discussion

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Induction chemotherapy strategies in PMBCL: A multinational retrospective study on 426 untreated patients
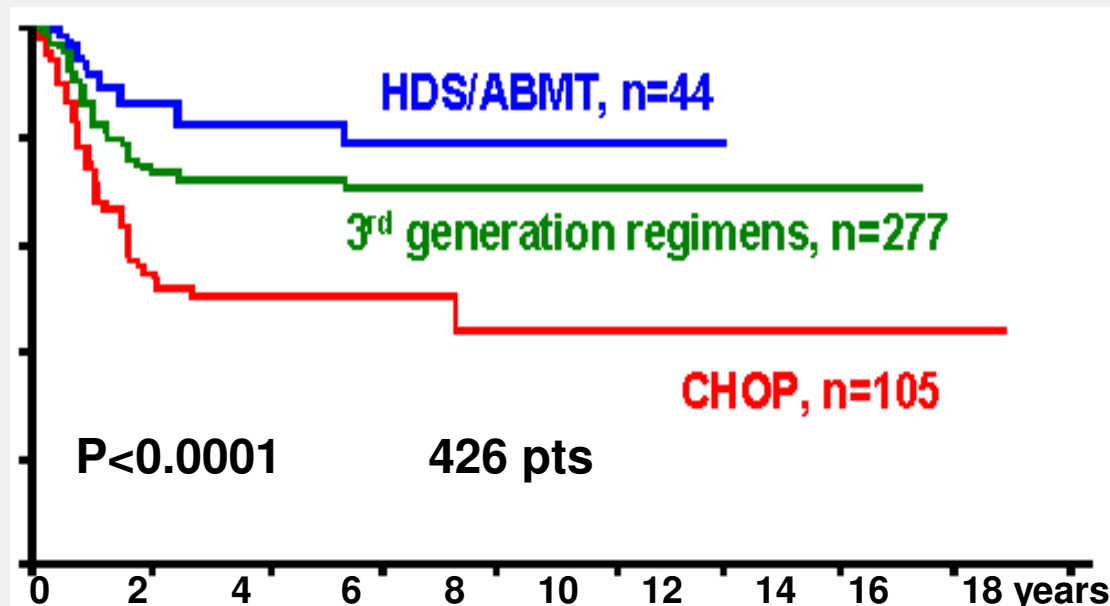
	CHOP	3rd generation	HDS / ABMT
CR after CT	49%	51%	53%
CR after CT+RT	61%	79%	75%
10-year OS	44%	71%	77%
Follow-up	52 mos	55 mos	36 mos

Zinzani, Martelli, Bertini

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

87.7%

R-CHEMO (n=44)

64.1%

CHEMO (n=43)

p = 0.0058

PFS

88.5% R-CHEMO (n=44)

78.2% CHEMO (n=43)

p = 0.1582

OS
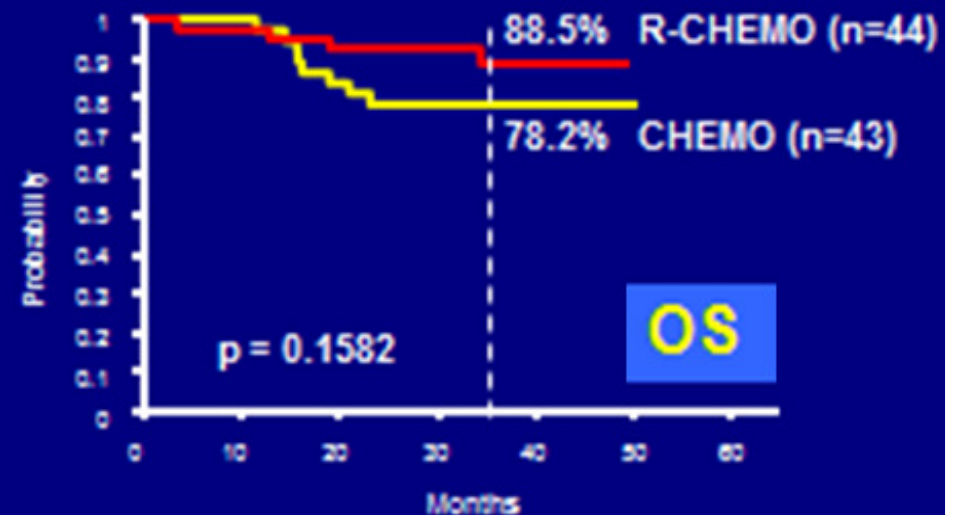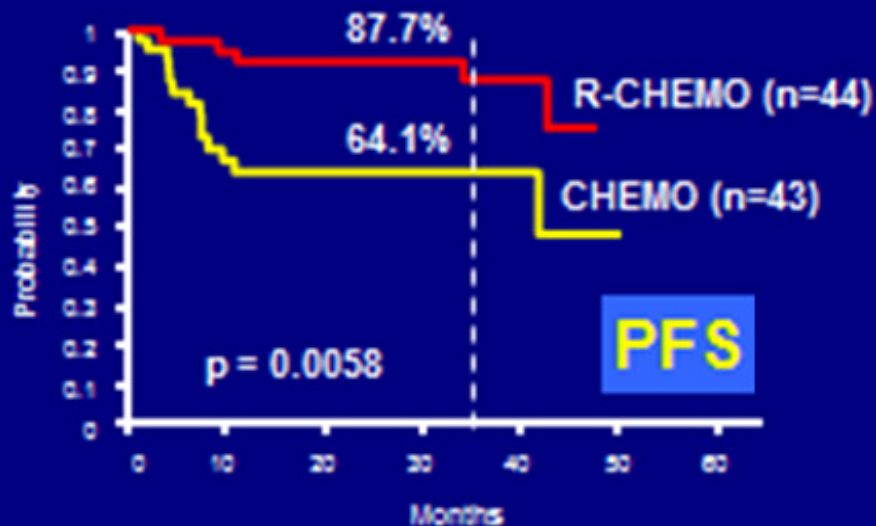
M. Rieger et al, Ann Oncol; 2010

M / VACOP-B + mediastinal RT
PFS in pre / post Rituximab era
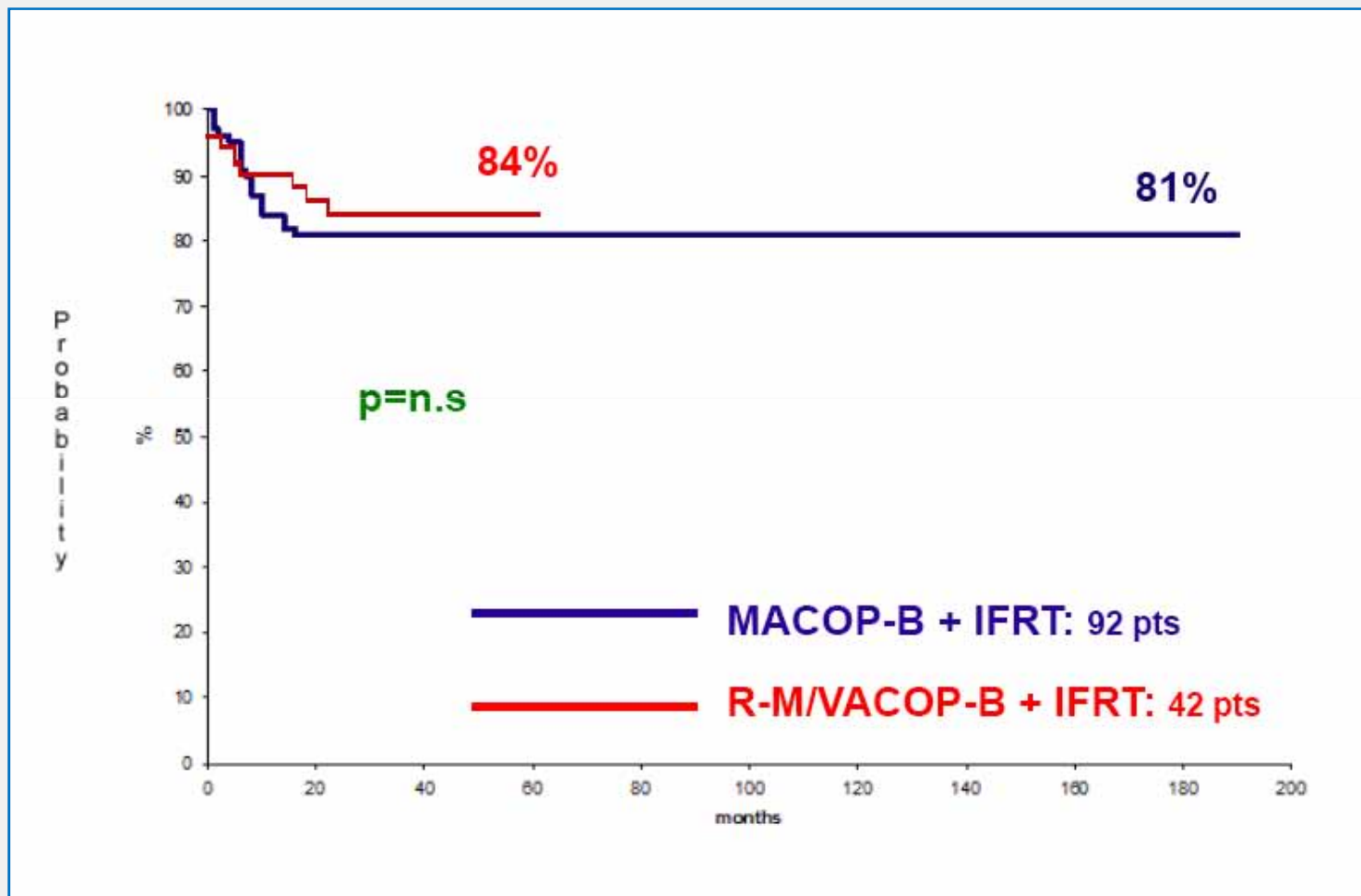
De Sanctis V, Martelli M et al. Int J Rad Oncol Biol Phys 2008;
Zinzani PL, Martelli M et al. Clinical Lymph and Myeloma 2009

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 (52 patients)

A Event-free Survival (NCI Patients) — 93%

B Overall Survival (NCI Patients) — 97%

Mediastinal-RT in 2/51 (4%)

C Event-free Survival (Stanford Patients) — 100%

D Overall Survival (Stanford Patients)
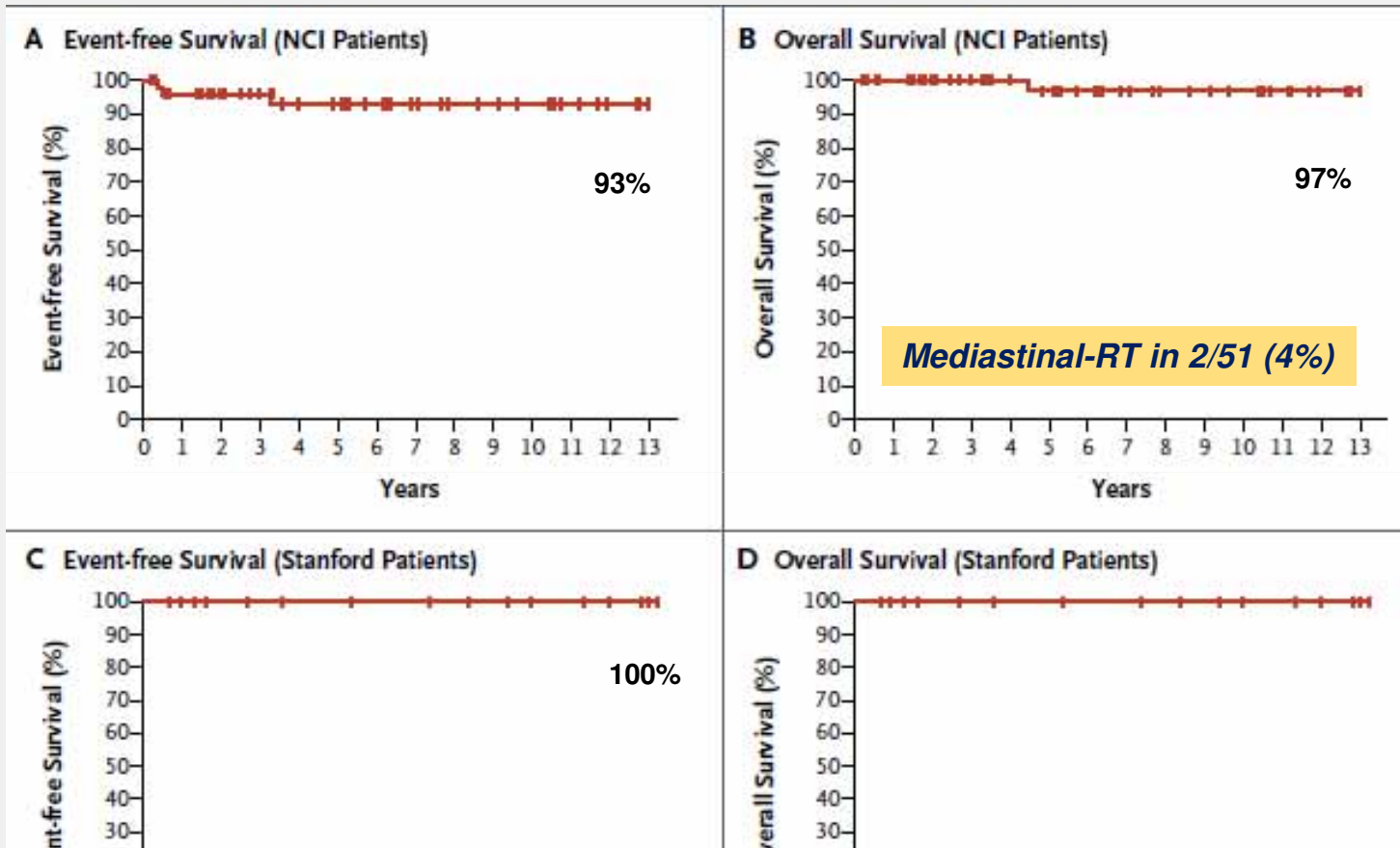
Therapy with DA-EPOCH-R had an high cure rate and obviated the need of a mediastinal radiotherapy

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

MDACC retrospective PMBCL series

Progression-Free Survival According to Chemotherapy

PFS probability (%) vs Time (months)

P=.3507

Type of Chemotherapy
- R-CHOP
- R-HCVAD
- R-EPOCH
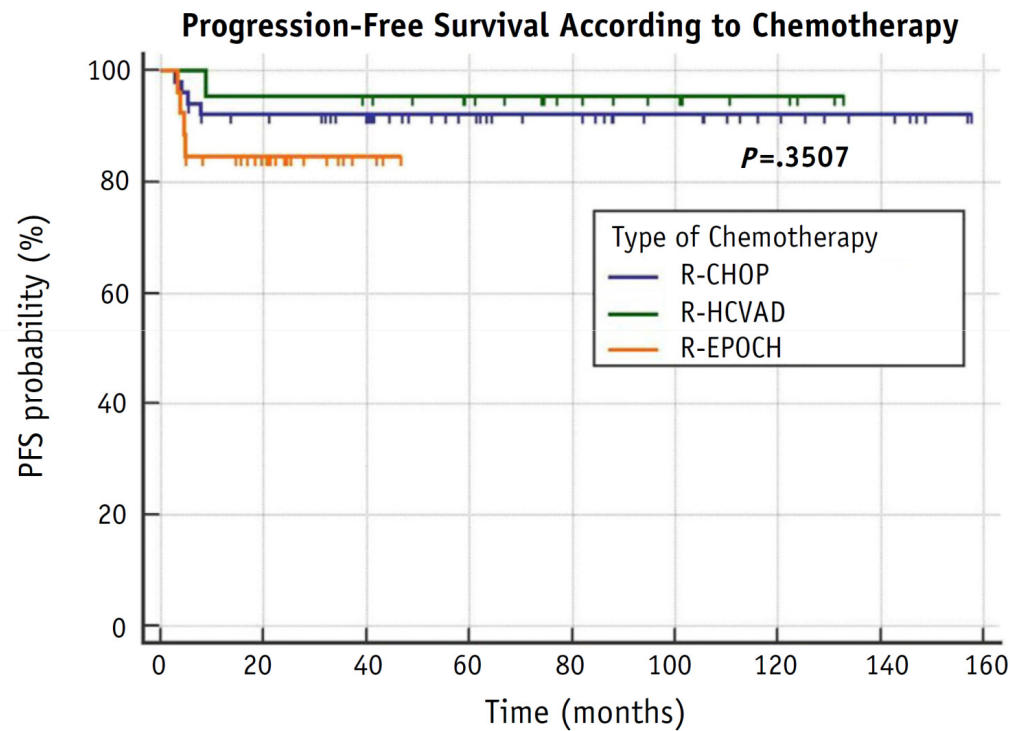
Characteristic	Treatment characteristics		
	R-CHOP (n=50)	R-HCVAD (n=22)	R-EPOCH (n=25)
No. of cycles			
Median	6	6	6
Range	5-8	5-8	4-7
Radiation therapy			
Consolidative (presumed CR)	42 (84%)	17 (77.2%)	5 (20%)
Salvage	3 (6%)	1 (4.5%)	4 (16%)
No radiation	5 (10%)	4 (18.2%)	16 (64%)
Radiation dose			
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

Prospective study of DA-EPOCH-R IN MGZL AND PMBL

Central review pathology

MGZL=24 pts　　　　　　　　　　　**PMBL=51 pts)**
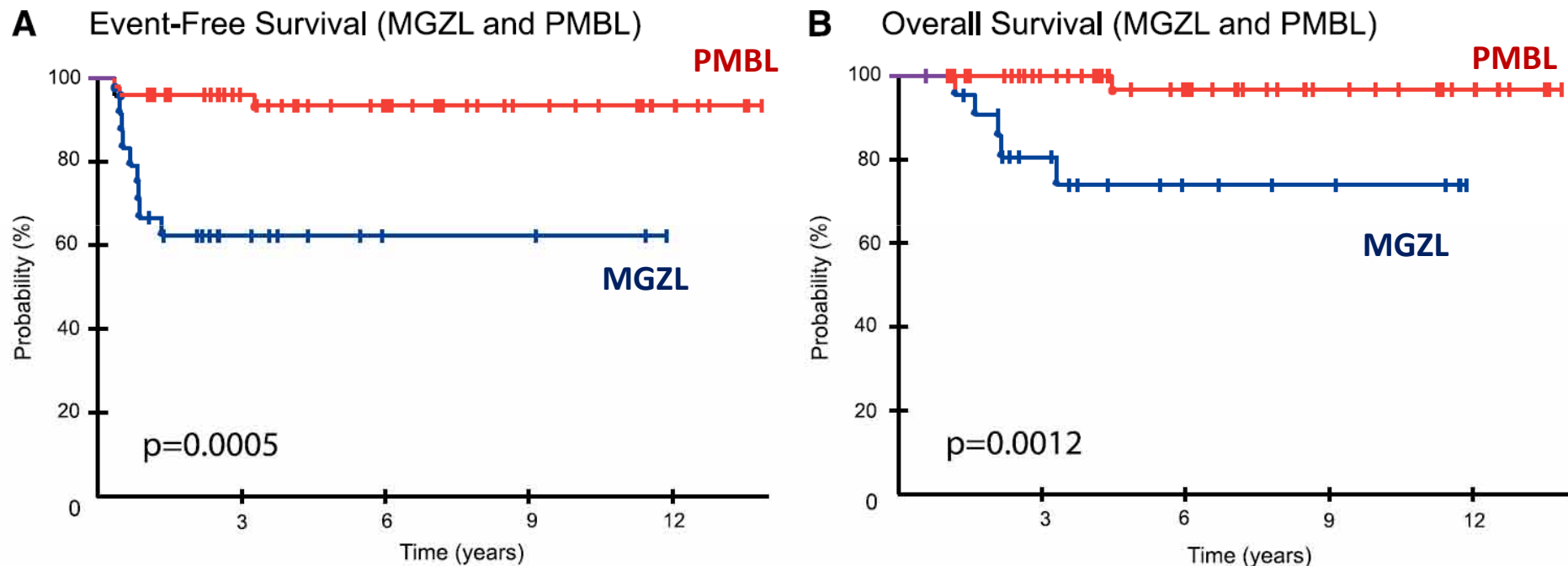
Figure 3. Kaplan-Meier plots of EFS and OS of MGZL and PMBL. (A) EFS was 62% (95% CI, 42% to 79%) for MGZL (blue curve) compared with 93% (95% CI, 81% to 98%) for PMBL (red curve) at 5 years (*P* = .0005). (B) OS was 74% (95% CI, 51% to 89%) for MGZL (blue curve) compared with 97% (95% CI, 83% to 99%) for PMBL (red curve) at 5 years (*P* = .0012).

Wilson et al., Blood 2015 -

Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort

MGZL= 48

GZL= 112

Non MGZL= 64
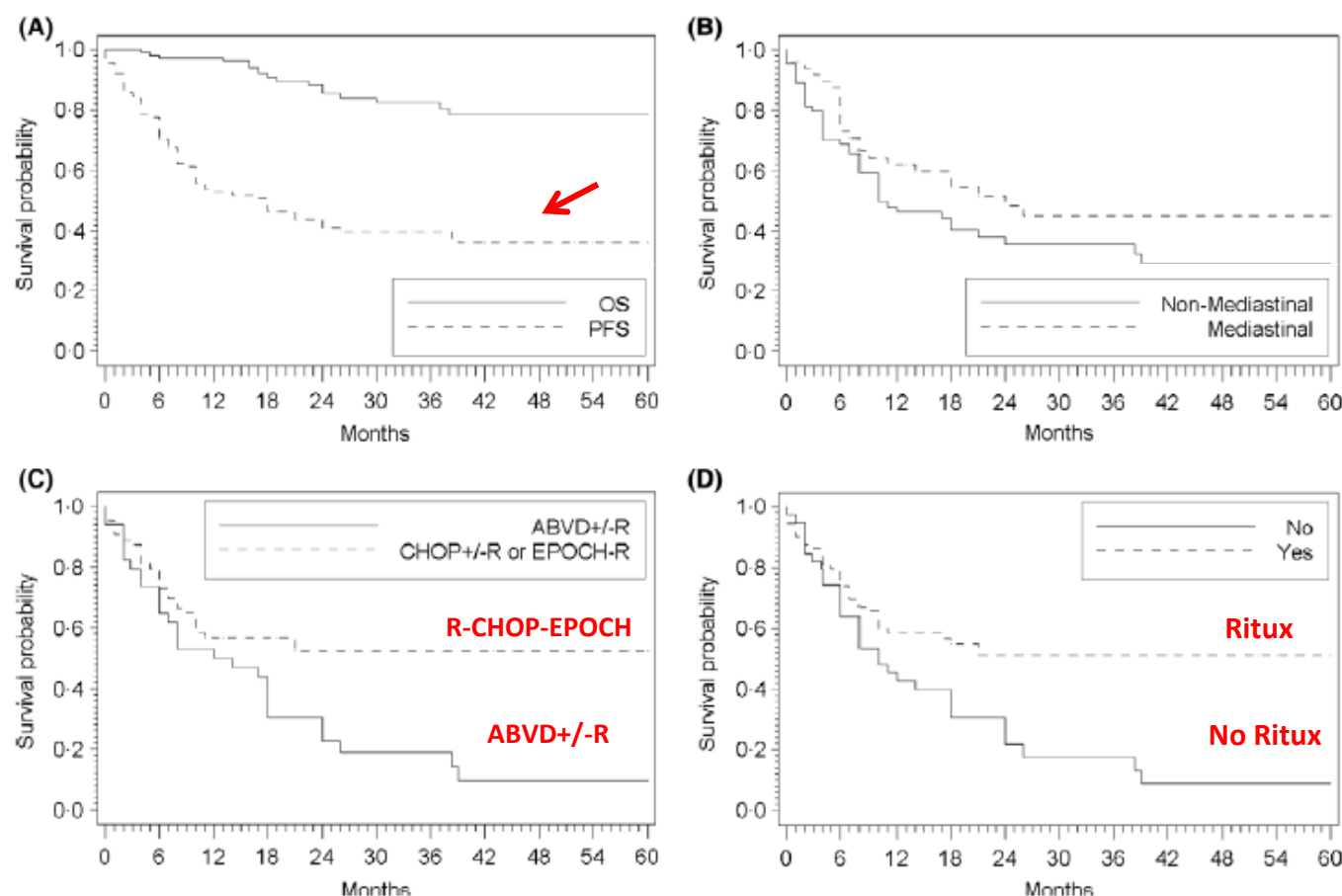
Evens et al .AJM 2015

Retrospective study of 89 MGZL

CENTRAL PATHOLOGY REVIEW
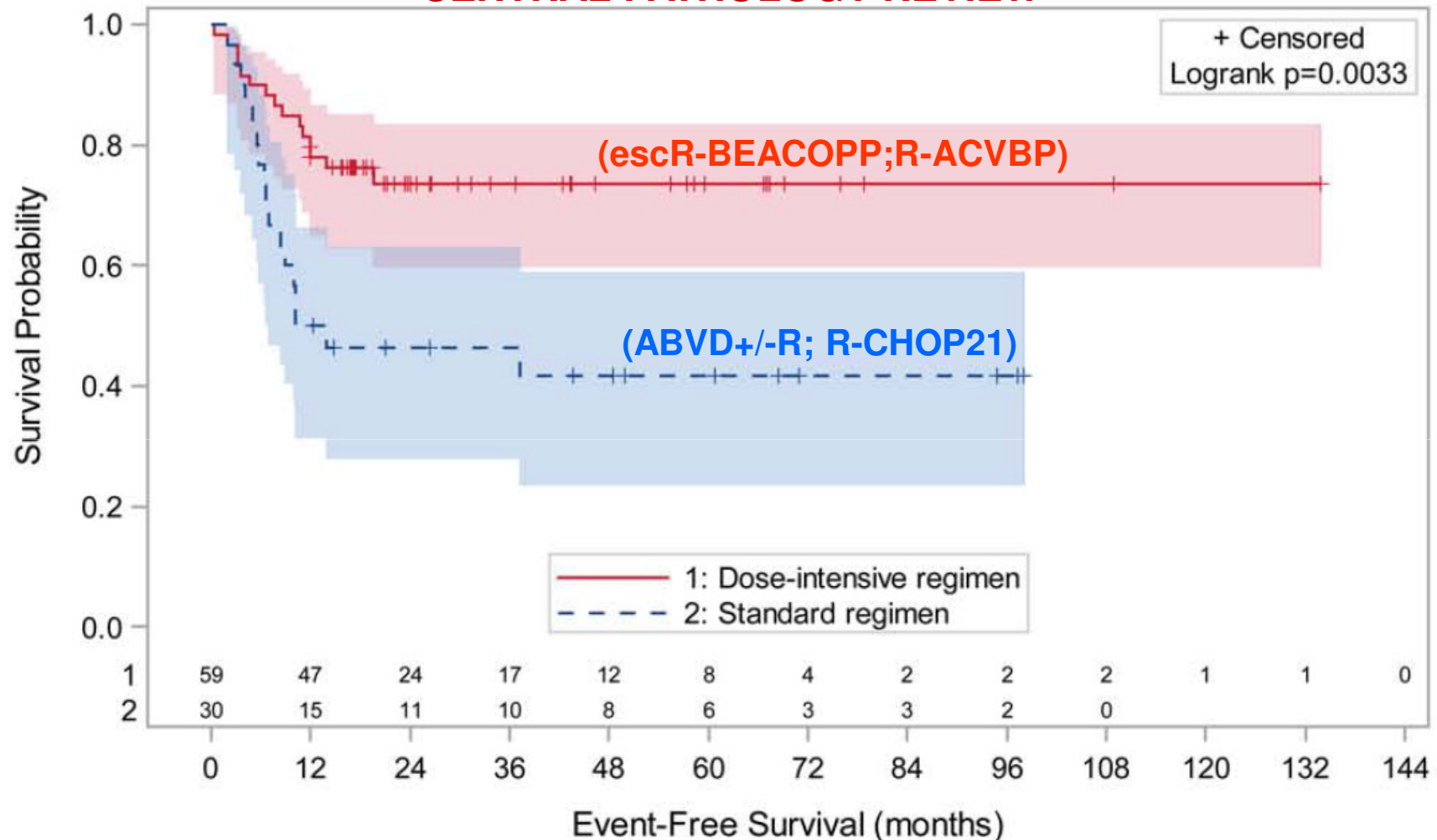
Sarkozy et al., Haematologica 2016

PMBCL Treatment: take home messages

- ❖ PMBCL has better outcome than others DLBCL

- ❖ R-CHOP,**R-CHOP14**,V/MACOP-B with mediastinal IFRT may be considered the standard treatment

- ❖ DA-EPOCH-R without mediastinal IFRT has shown very promising results in a prospective phase II trial.

- ❖ DA-EPOCH-R therapeutic advance for PMBCL need to be confirmed in further prospective trials.

Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in the management of primary mediastinal B-cell lymphoma: a subgroup analysis of the UK NCRI R-CHOP 14 versus 21 trial

PMBCL 50 pts (R-CHOP21= 28 R-CHOP14= 22)

(C) Proportion alive vs Time from randomisation (years). R-CHOP 14, R-CHOP 21. HR = 0·14 (95% CI: 0·02-1·08, P = 0·06)

(D) Proportion progression-free vs Time from randomisation (years). R-CHOP 14, R-CHOP 21. HR = 0·28 (95% CI: 0·06-1·31, P = 0·10)
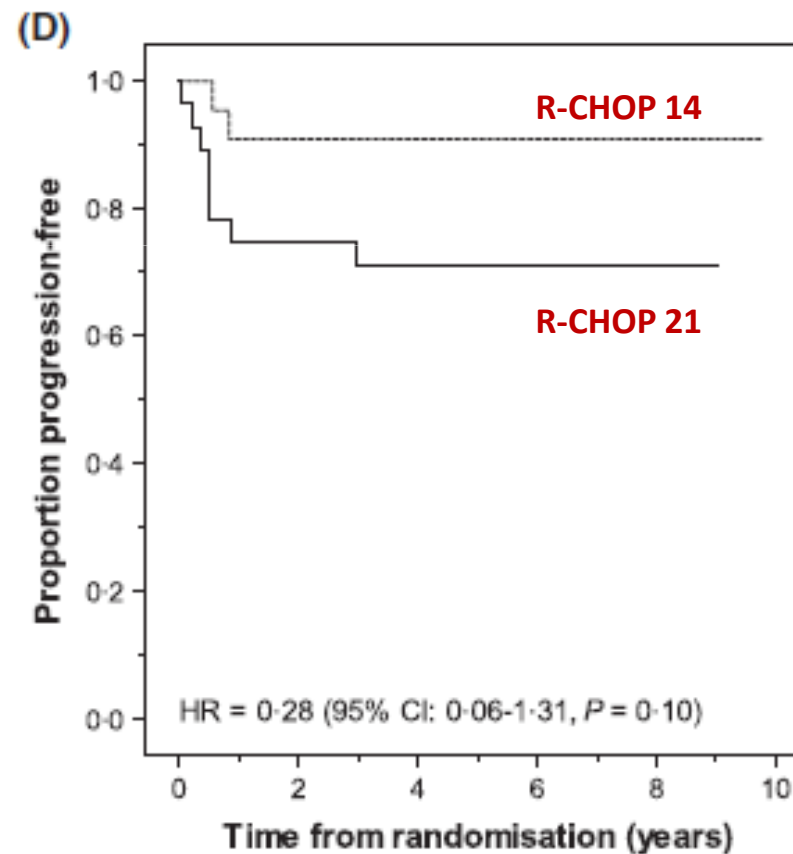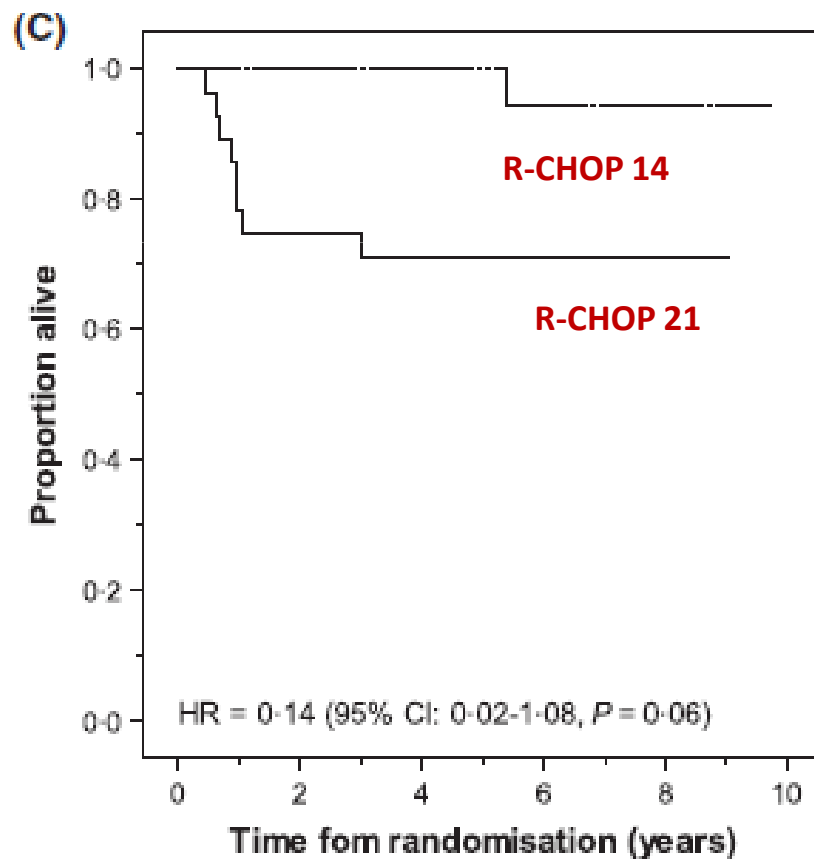
Gleeson M et al B. J Med. 2016

MGZL treatment: take home messages

❖ **_MGZL_** have a more aggressive clinical course and poorer outcome than PMBCL

❖ Need of an expert hematopatholigist to recognize it

❖ There is no consensus in the optimum treatment of MGZL

❖ MGZL outcomes seem superior when treated with Rituximab based DLBCL regimen (R-CHOP14, R-ACVBP, DA-EPOCH-R)

❖ MGZL requires more likely mediastinal RT .

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▸ Pathology and molecular biology

▸ Clinical features

▸ Treatment and outcome

▸ Open questions

Open questions in PMBCL and MGZL

- Is a negative PET/CT a reliable indicator of cure following R-CHOP chemotherapy alone making mediastinal RT unnecessary in PET negative patients?

- PET-CT scan parameters may help us to identify patients with at increased risk for whom more intensive therapy should be proposed.

Study background

➢ The incidence of a ***post therapy PET-positive in PMBCL is higher (53%)*** than in others DLBCL using the ***MBP cut-point***

➢ ***Negative post-therapy PET/CT scan*** after R-CHT is significantly ***associated with a longer PFS.***

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

Martelli M et al. J.Clin.Oncol. May 5, 2014

PET/CT response : results

Post R-chemo PET interpretation - <u>blind central review</u>
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 - <u>blind central review</u>
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

Study background:
PFS better defined by liver cut-point

IELSG-26 study: Kaplan-Meier estimates of progression-free survival in PMLBCL, according to the PET response defined using the liver uptake cut-off, at 3-4 weeks after immunochemotherapy
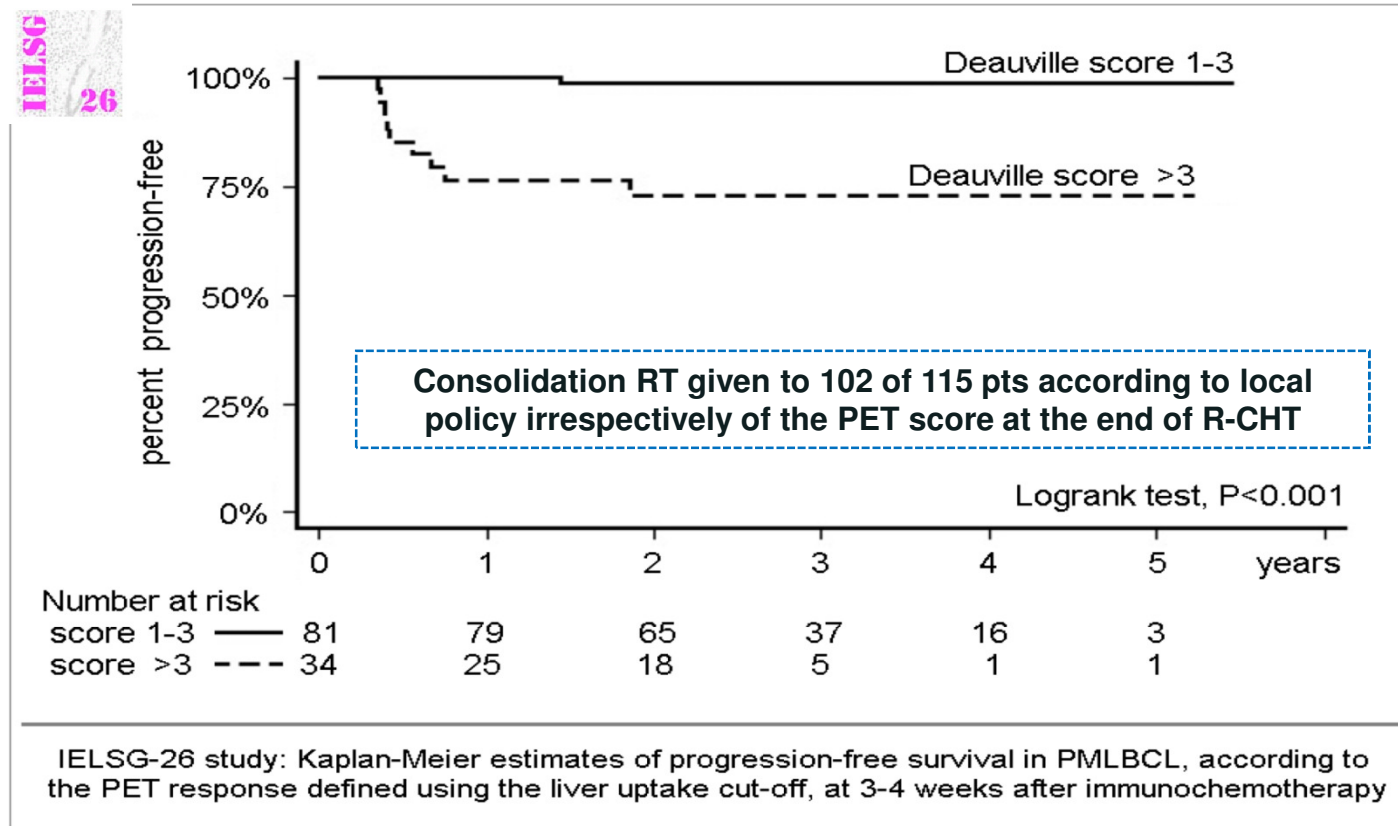
However the IELSG-26 study did not answer the question about the role of mediastinal RT.

Martelli M et al. J.Clin.Oncol. May 5, 2014

PMBCL: RT PET+ residual area

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

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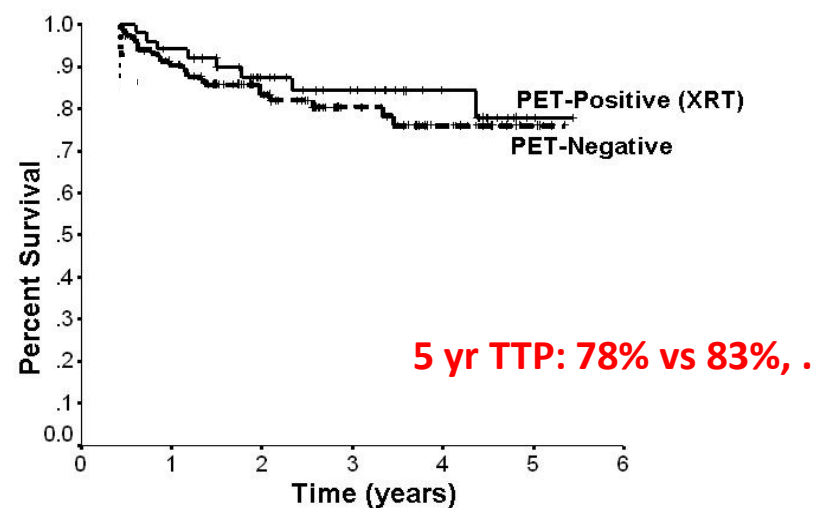
NEG =   35 (59%): *No RT* (regardless of initial bulk)
POS=   24 (41%) : *23 /24 XRT*

5 yr TTP: 78% vs 83%, .

PET-Positive (XRT)
PET-Negative

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

MACOP-B plus RT: 5-yr DFS 91%
MACOP-B: 5-yr DFS 90%

p= 0.8544
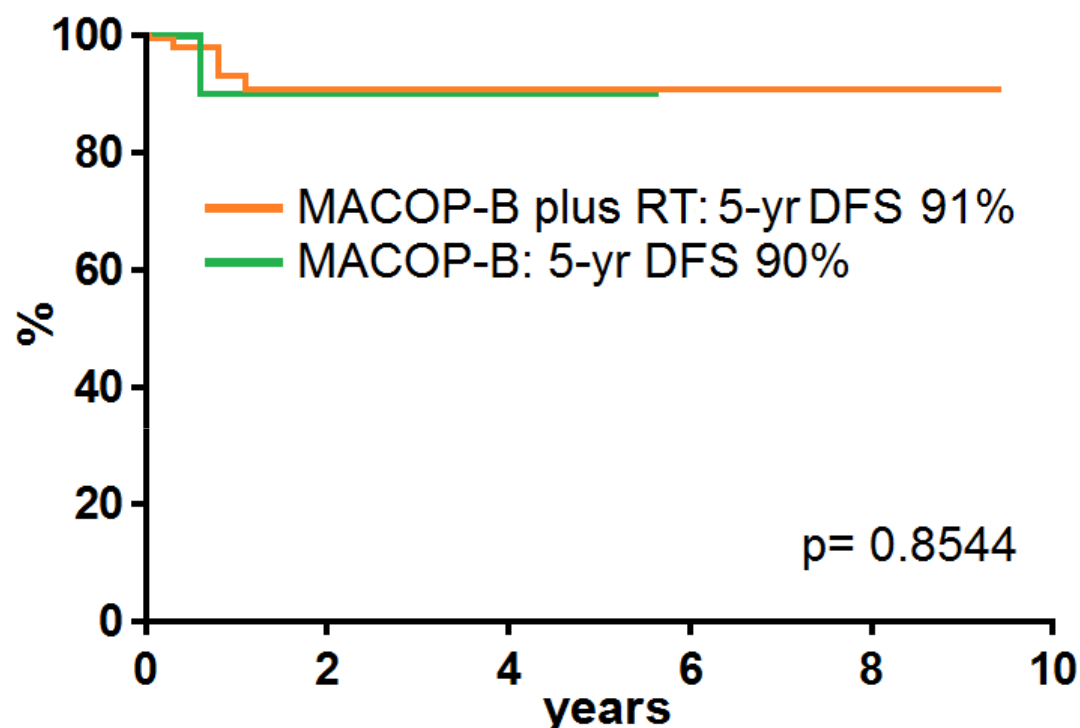
- *A PET-guided RT approach after MACOP-B plus rituximab may allow a patient tailored treatment*

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

IELSG 37 trial design

Registration
PET-CT 0

Standard therapy
R-Chemo

*RCHOP 14-21; R-V/MACOP-B
DA-EPOCH-R; R-ACVBP;
R-CHO(E)P like

PET-CT 1
Central review

5-6 wks after R-Chemo

Positive not randomised pts will be followed for PFS and OS analysis and for response to the **chosen salvage strategy** .

Positive

Negative

Randomize 1:1

8 wks after R-Chemo

**Primary end-point:
2-yrs PFS**

**Mediastinal RT
30Gy**

Observation

Central PET-CT review workflow

Local PET centre uploads PET images on Widen

PET-0 + PET-1

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

Reviewer 1 | Reviewer 2 | Reviewer3 | Reviewer4 | Reviewer5 | Reviewer6 | Reviewer 7

PET evaluation within 3-4 working days

Pos/neg   **Pos/neg**   **Pos/neg**

Complete agreement between the first three reviewer

PET-1 positive or negative

Clinical Centre   **Randomization**
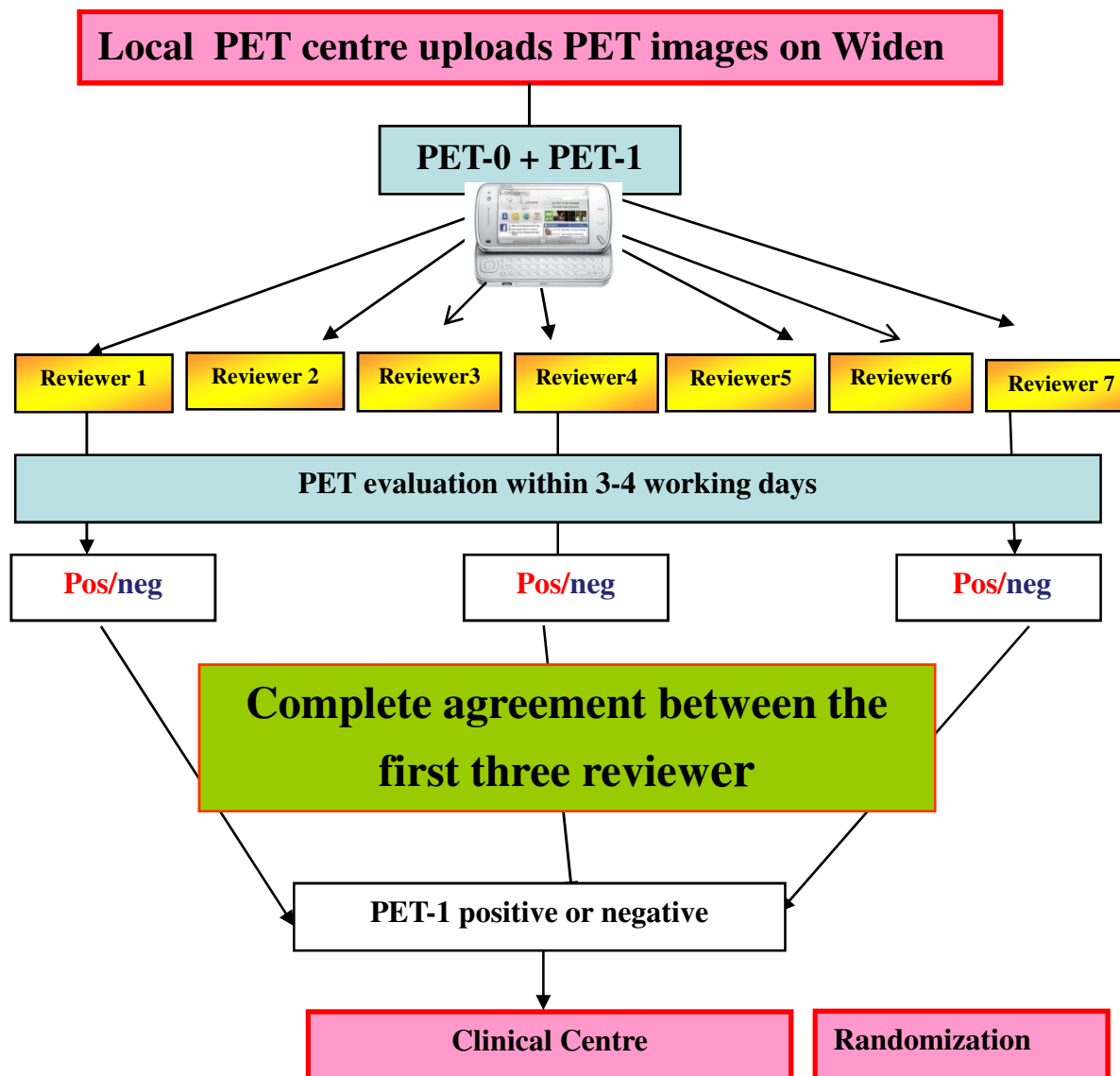
Enrolled patients by sites
(November 16, 2016)

In Brief	
Total number of patients enrolled	**291**
Countries enrolling	9
Centres with at least 1 patient	57

Country	Center	Patients
Italy	**FIL**	**209**
UK	Southamptom	24
Ukraine	Kiev	21
Canada	Toronto	6
Norway	Oslo	4
	Trondheim	2
Sweden	Lund	4
Poland	Warsaw	6
Switzerland	Bern	6
	St. Gallen	2
	Bellinzona	3
	Olten	1
USA	Lousiville	1

Enrolled patients by italian sites
(November 16, 2016)

Country	Center	Patients
Italy	Alessandria	4
	Ancona	6
	Aviano	7
	Bari Istituto Oncologico	5
	Bologna	1
	Brescia	13
	Brindisi	1
	Cagliari	8
	Firenze	7
	Catania	4
	Meldola	3
	Lecce	4
	Milano HSR	7
	Milano IEO	5
	Milano Niguarda	12
	Modena	1
	Palermo Cervello	3
	Parma	6

Country	Center	Patients
Italy	Pavia	8
	Perugia	4
	Pescara	4
	Piacenza	2
	Ravenna	4
	Reggio Calabria	10
	Reggio Emilia	7
	Roma La Sapienza	20
	Roma Regina Elena IFO	3
	Roma S. Andrea	2
	Rozzano Humanitas	10
	Siena	3
	Terni	1
	Torino Molinette	17
	Torino Università	4
	Udine	7
	FIL tot	**209**

Central PET Review After Chemoterapy
(November 16, 2016)

PET REVIEWED	PET NEGATIVE	PET POSITIVE
236	112 (47%)	124 (53%)
107 (MBP neg score 1-2)	37 (35%)	70 (65%)
129 (Liver neg score 1-2-3)	75 (58%)	54 (42%)

*The average and median review time was 69 h and 46 h, respectively*
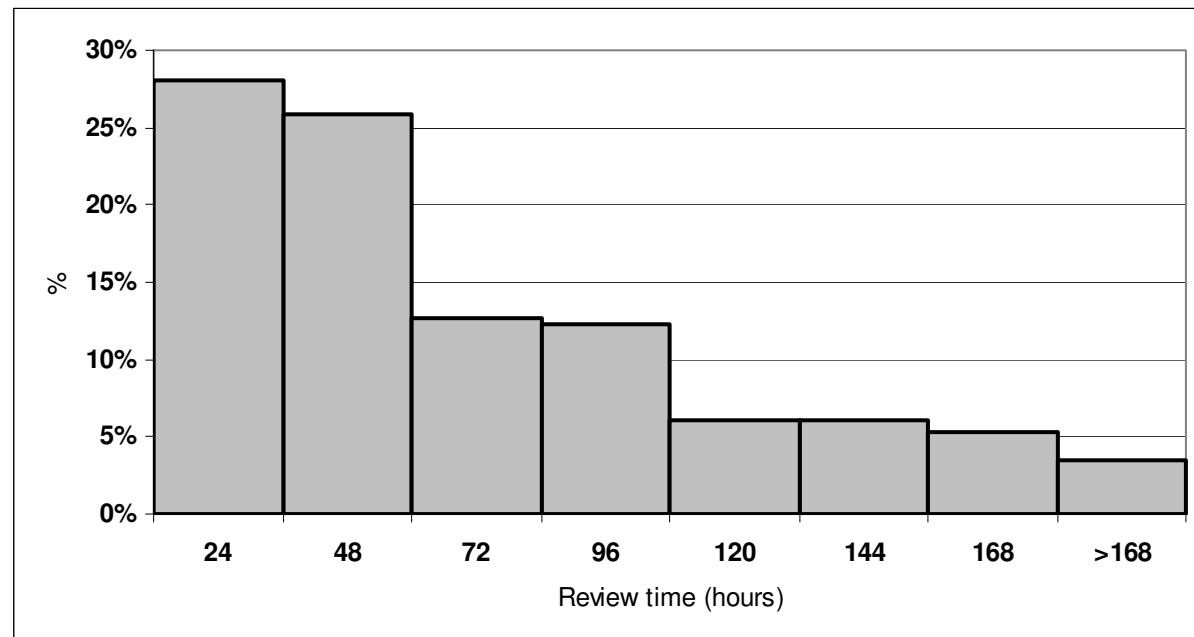
Open questions in PMBCL and MGZL

- Is a negative PET/CT a reliable indicator of cure following R-CHOP chemotherapy alone making mediastinal RT unnecessary in PET negative patients?

- PET-CT scan parameters may help us to identify patients with at increased risk for whom more intensive therapy should be proposed.

Functional and quantitative PET parameters

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

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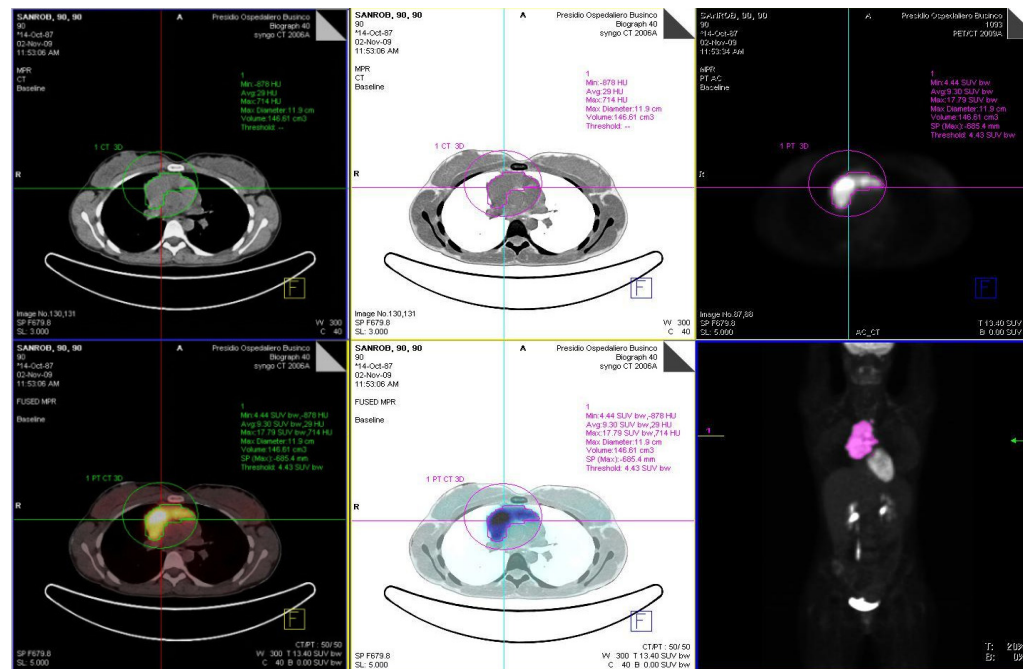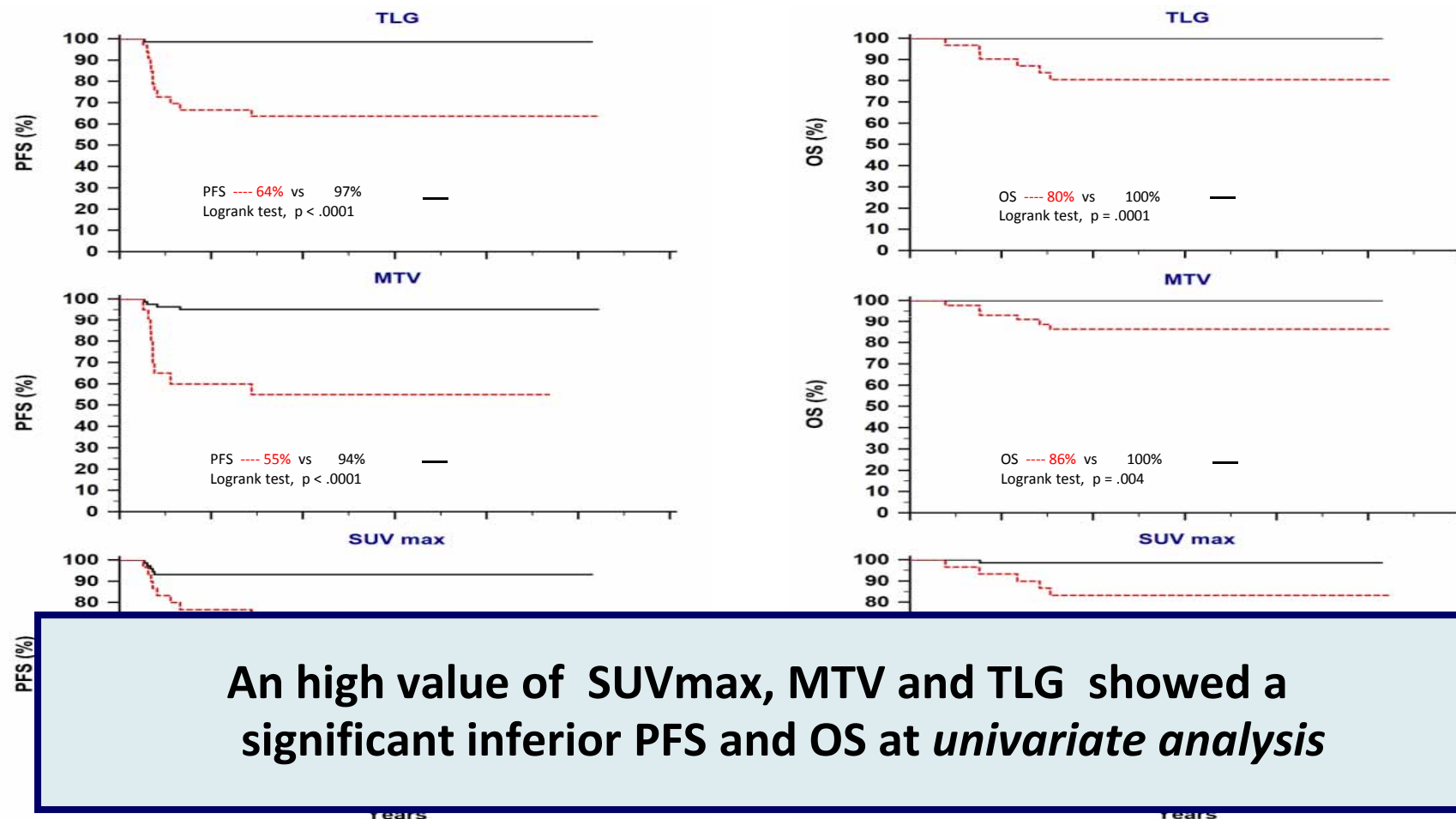
Regular Article

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

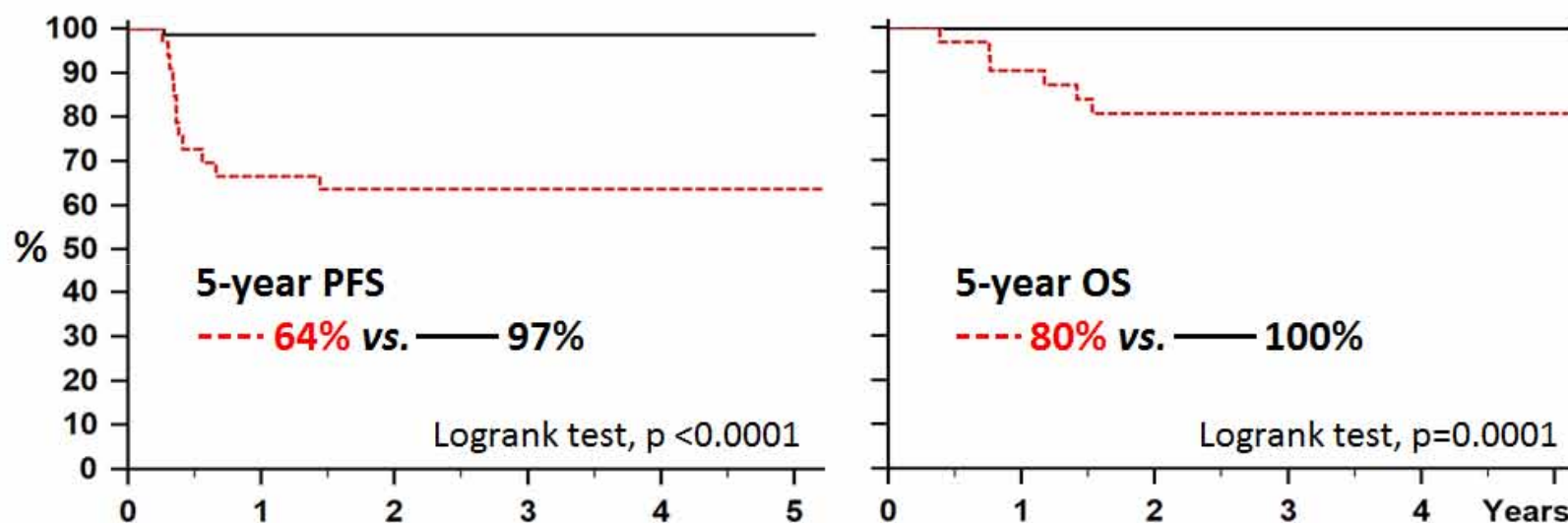# Prognostic value of baseline functional 18-FDG parameters in the IELSG 26 study in PMBCL

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

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

5-year PFS
- - - - 64% *vs.* ——— 97%

Logrank test, p <0.0001

5-year OS
- - - - 80% *vs.* ——— 100%

Logrank test, p=0.0001

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

PET/CT response : results

Post R-chemo PET interpretation - <u>blind central review</u>
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

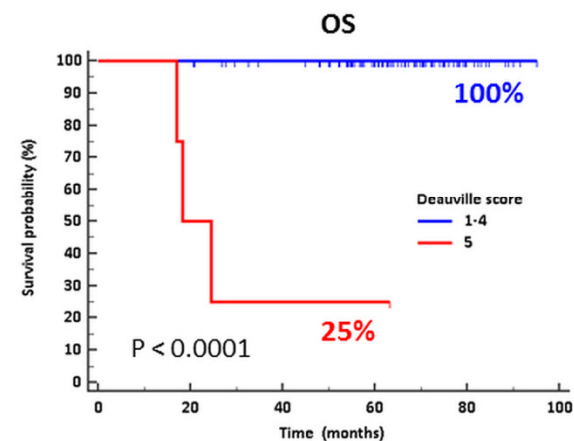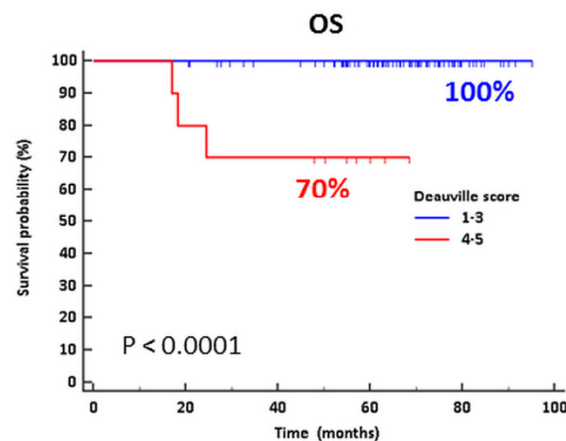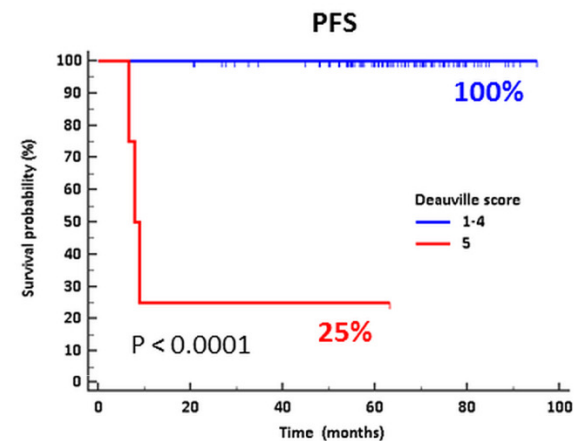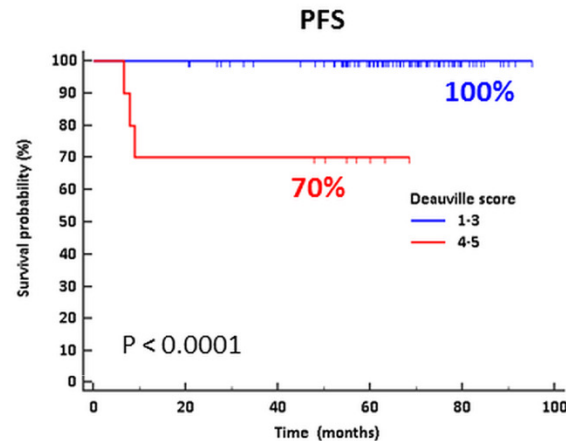*Liver cut-off*   **21%**   **60%**

PET/CT assessment after immunochemotherapy and RT using the Lugano Classification criteria in the IELSG-26 study of PMLBCL

125 pts prospectively enrolled in IELSG 26

88 received **mediastinal IFRT** and elegible for PET-CT central review

PET-TC scan > 2 months after IFRT

Ceriani , Martelli , Ricardi et al. Int J Radiat Oncol Biol Phys 2016, in press

Outcome after mediastinal IFRT
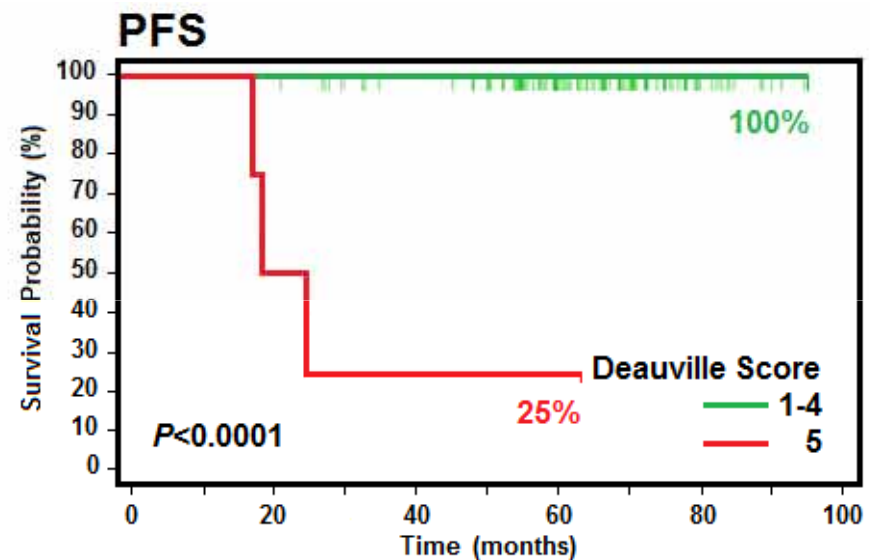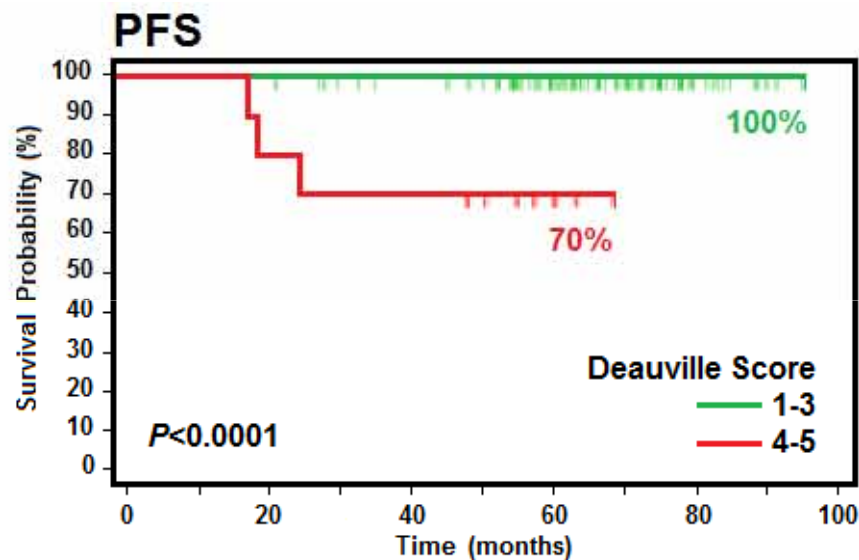
- Patients with **DS-4** do not necessarily require additional chemotherapy, but only IFRT . The residual FDG uptake may be due to an inflammatory reaction

- Those with a **DS-5** appear at high risk of progression and death and might be candidates for an intensified programs

Ceriani , Martelli , Ricardi et al. Int J Radiat Oncol Biol Phys 2016, in press

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.

- **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.

- 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

Take home messages (4)

- Deauville Score (DS) 5 after R-CHT should identify patients with a significant poor outcome.

- 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 and MGZL

Brentuximab vedotin (SGN-35)

CD30

SGN-35 Antibody-toxin conjugate

SGN-35 Binds CD30

Endocytosis

ADC traffics to lysosome

Enzymatic cleavage releases MMAE from ADC

Binds tubulin

G2/M cell Cycle arrest and apoptosis
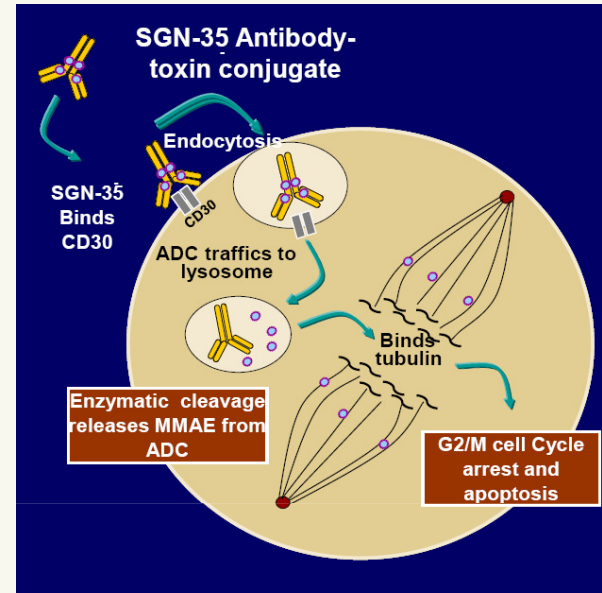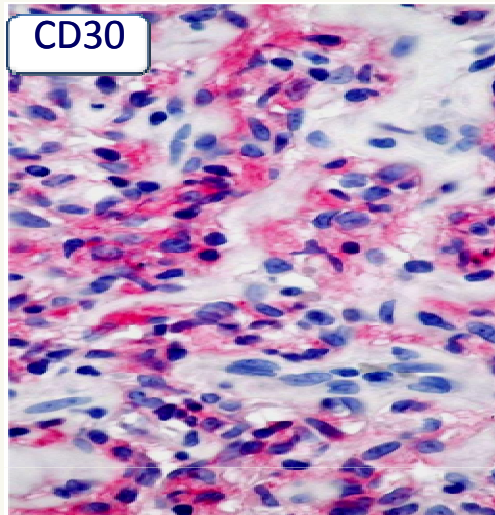
SGN-35 antibody-drug conjugate

✓ **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

PD-1 Pathway and Immune Surveillance
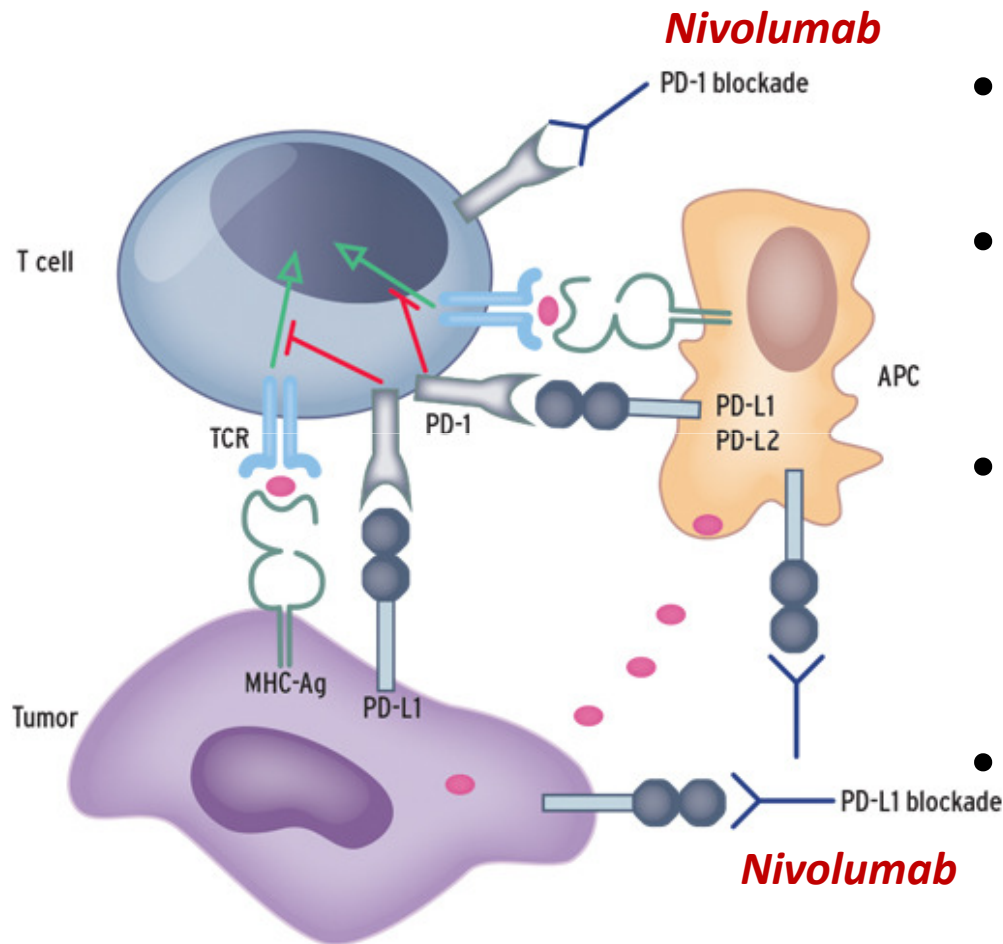
- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells (PMBCL,HD)
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response
- PD1 blockade trough MoAb therapy can restore effective anti tumor immunity

New biological drugs for PMBCL and MGZL

Clinical Protocol CA209436

A Phase I/ II Study to Evaluate the Safety and Preliminary Efficacy of Nivolumab in Combination with Brentuximab Vedotin in Subjects with Relapsed Refractory Non Hodgkin Lymphomas with CD30 Expression CheckMate 436: CHECKpoint pathway and nivolumab clinical Trail Evaluation
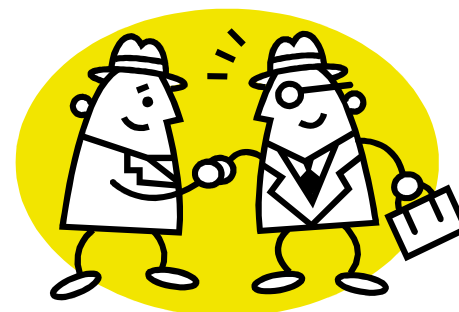
Amendment 1

- **Primary Mediastinal B Lymphoma (PMBL), *>15 years***
- **Mediastinal Gray Zone Lymphoma (MGZL) >15 years**

Courtesy of Carmelo Carlo Stella
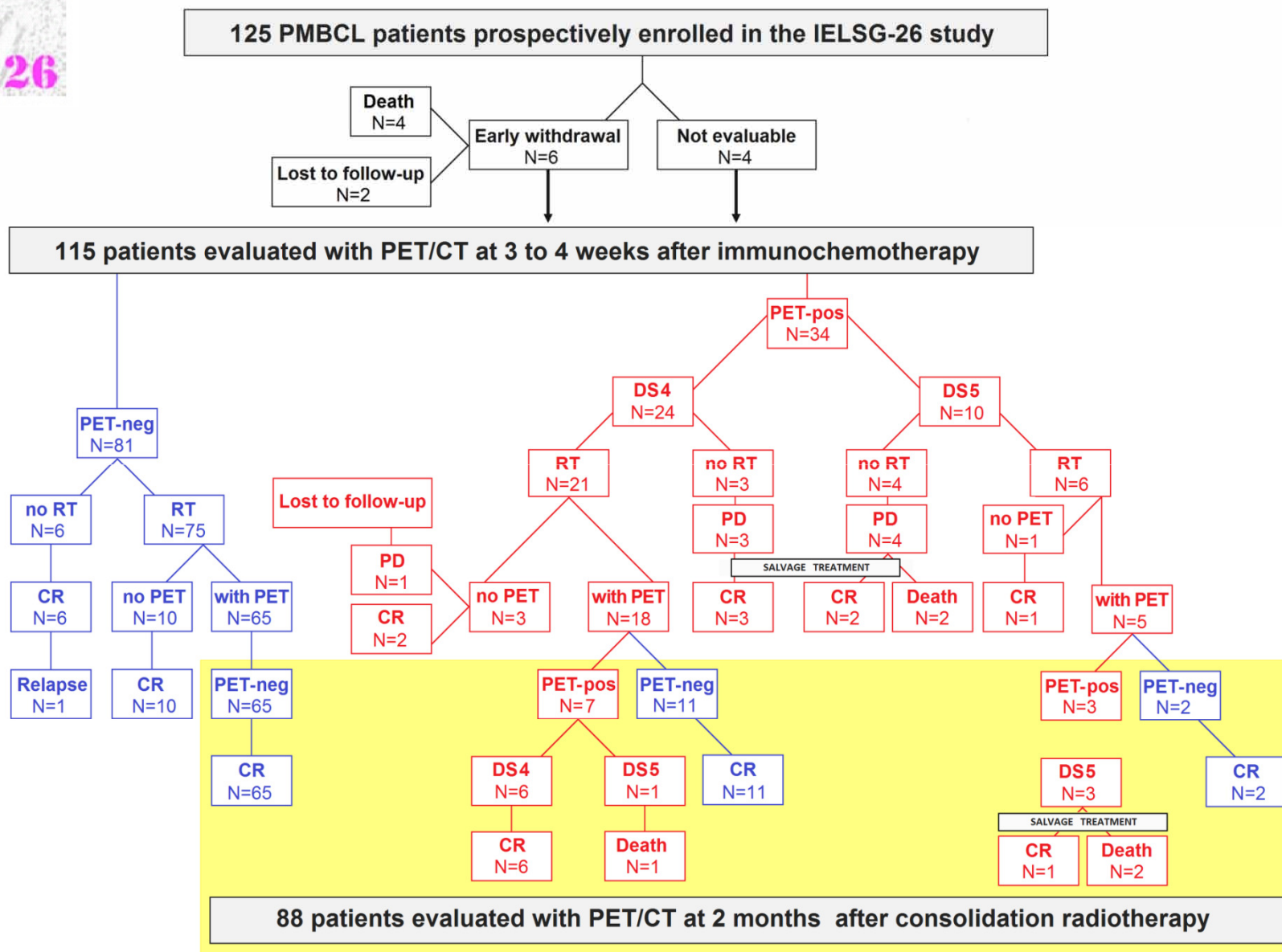
Ringraziamenti

SAPIENZA
UNIVERSITÀ DI ROMA

Alice Di Rocco
Federico De Angelis
Clara Minotti
Michela Ansuinelli
Luigi Petrucci

Robin Foà

FONDAZIONE
FIL
ITALIANA LINFOMI

Grazie per l'attenzione ……

125 PMBCL patients prospectively enrolled in the IELSG-26 study

Death
N=4

Lost to follow-up
N=2

Early withdrawal
N=6

Not evaluable
N=4

115 patients evaluated with PET/CT at 3 to 4 weeks after immunochemotherapy

PET-pos
N=34

PET-neg
N=81

DS4
N=24

DS5
N=10

no RT
N=6

RT
N=75

RT
N=21

no RT
N=3

no RT
N=4

RT
N=6

CR
N=6

no PET
N=10

with PET
N=65

Lost to follow-up

PD
N=3

PD
N=4

no PET
N=1

Relapse
N=1

CR
N=10

PET-neg
N=65

PD
N=1

CR
N=2

no PET
N=3

with PET
N=18

SALVAGE TREATMENT

CR
N=3

CR
N=3

CR
N=2

Death
N=2

CR
N=1

with PET
N=5

CR
N=65

PET-pos
N=7

PET-neg
N=11

PET-pos
N=3

PET-neg
N=2

DS4
N=6

DS5
N=1

CR
N=11

DS5
N=3

CR
N=2

CR
N=6

Death
N=1

SALVAGE TREATMENT

CR
N=1

Death
N=2

88 patients evaluated with PET/CT at 2 months after consolidation radiotherapy

*Ceriani et al. Int J Radiat Oncol Biol Phys 2016, in press*

Pathology

- Arising in thymus
- Sheets of medium to large polymorphic cells proliferation
- Cytoplasm either clear or slightly basophilic
- Alveolar fibrosis in the majority of cases
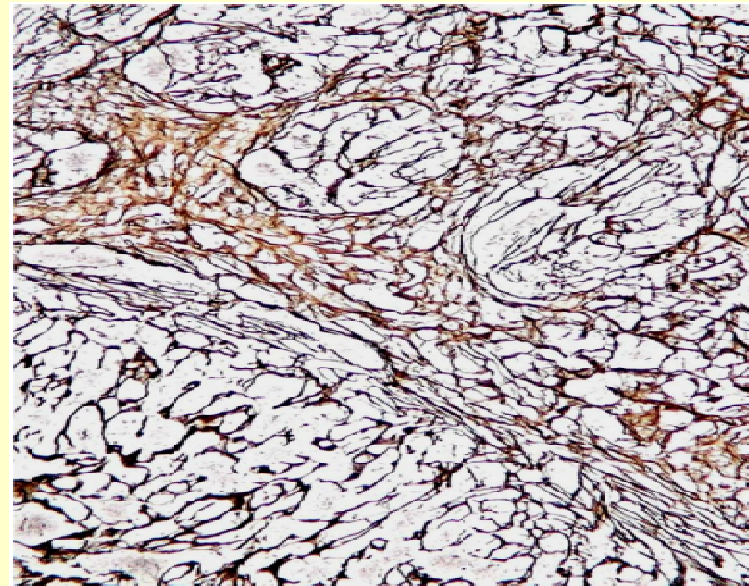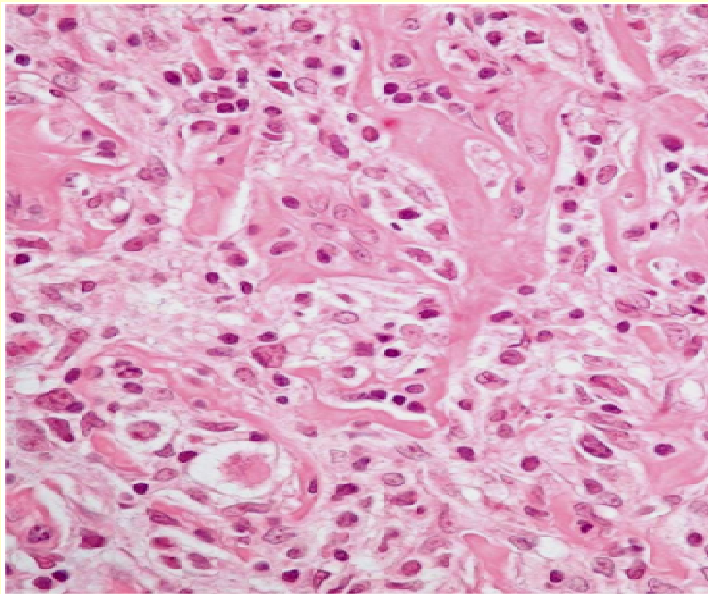
PET/CT response criteria
(4 weeks after R-CHT)

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* *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**

1	2	3	4	5

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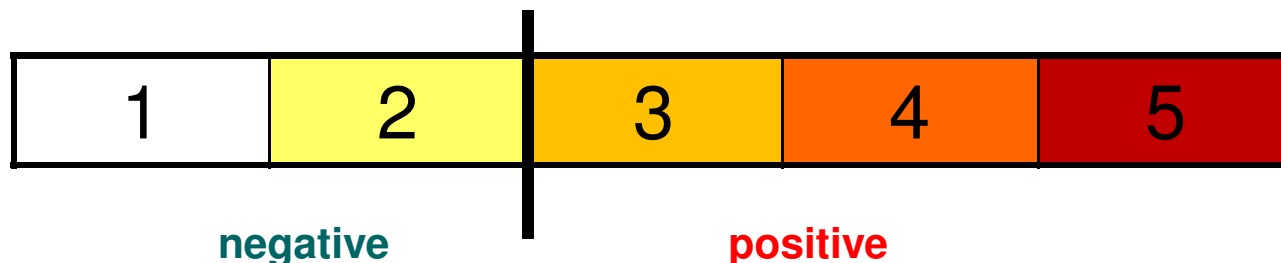
Patients achieving a metabolic CR (mCR) according the IHP criteria are designated by score 1-2 in the Deauville criteria