PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL)

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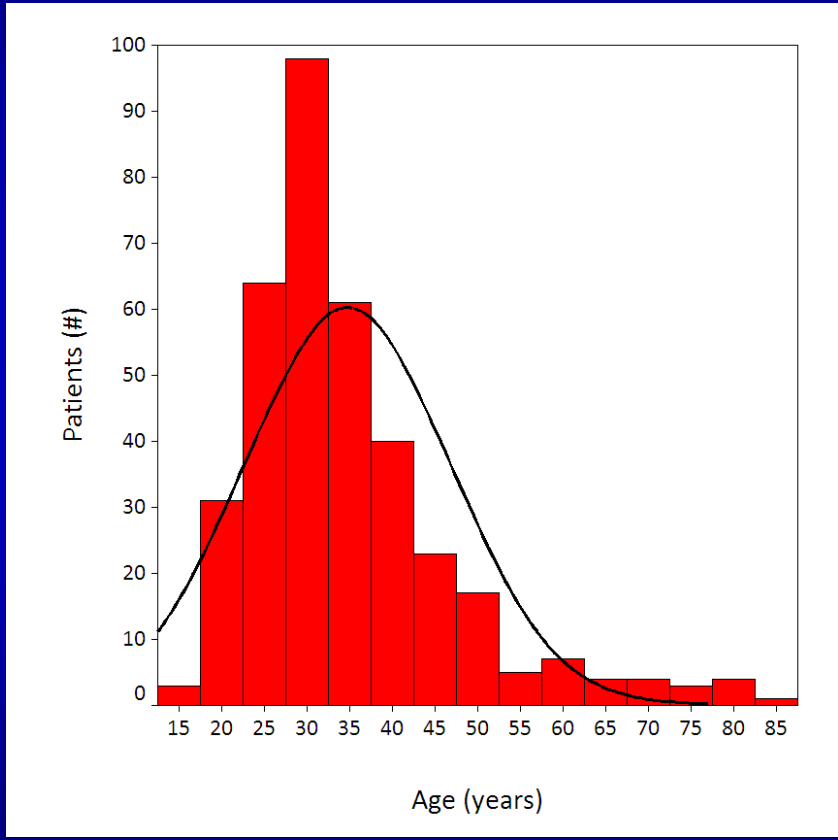
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Introduction

- 2.5% of all non-Hodgkin's lymphomas
- REAL classification (1994): Subtype of DLBCL
- WHO 2001, 2008, 2016 classifications: Separate entity
- Distinctive demographic and clinicopathologic characteristics
- Gene expression signature rather resembling to classical Hodgkin lymphoma than to DLBCL

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Demographic Characteristics

- Young adults
- Median age 30-35 years
- Female preponderance up to 2:1



Age distribution in 368 non-pediatric patients treated with R-CHOP in Greece

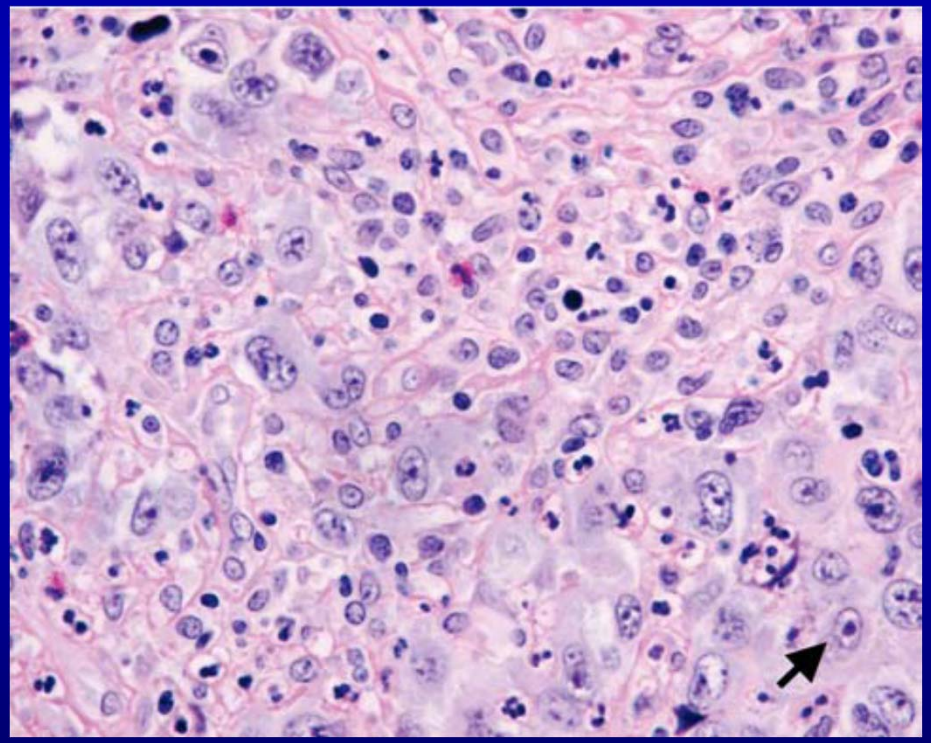
Median 32 yrs (range: 16-85), >60 yrs: only 5%

Females 65%

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Histologic Findings (I)

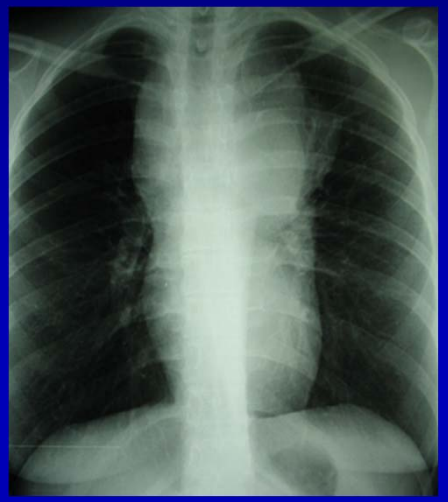
- Diffuse pattern
- Medium or large cells
- Clear cell morphology
- Fibrosis - Compartmentalization
- Extensive necrosis common
- Sometimes R-S-like cells
- Thymic remnants in 50%

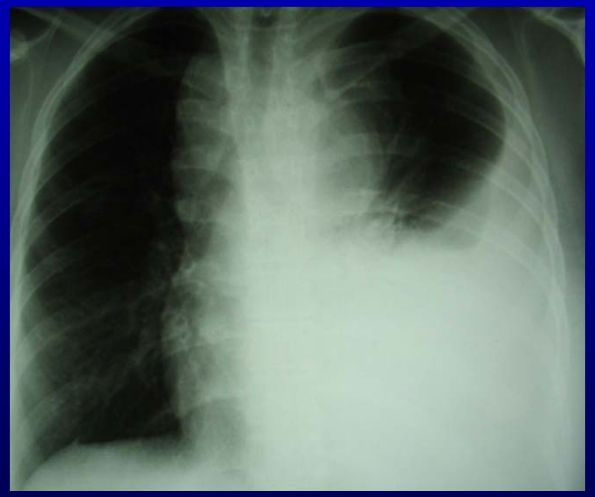


PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Clinical and Morphologic Differential Diagnosis

- Classical Hodgkin Lymphoma
- Diffuse large B-cell Lymphoma
- Gray zone Lymphomas (mediastinal)
- Epithelial neoplasms – Thymoma
- Germ cell tumors
- Lymphoblastic Lymphoma





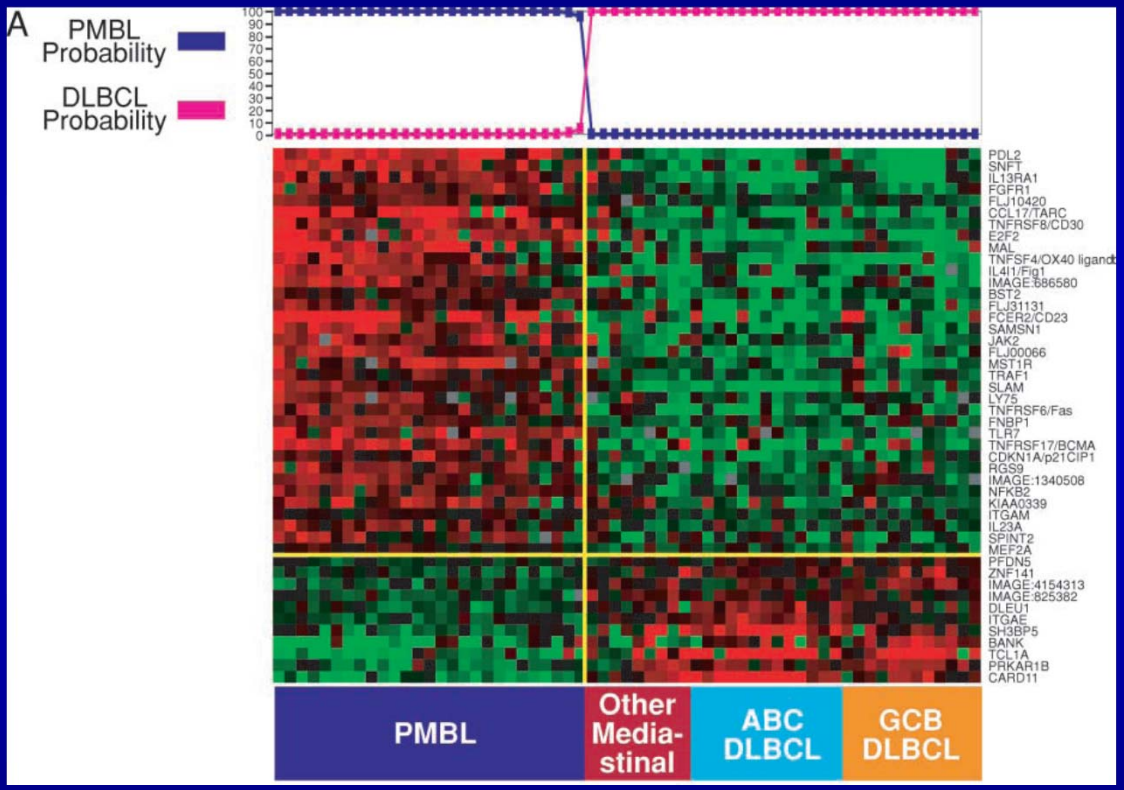
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

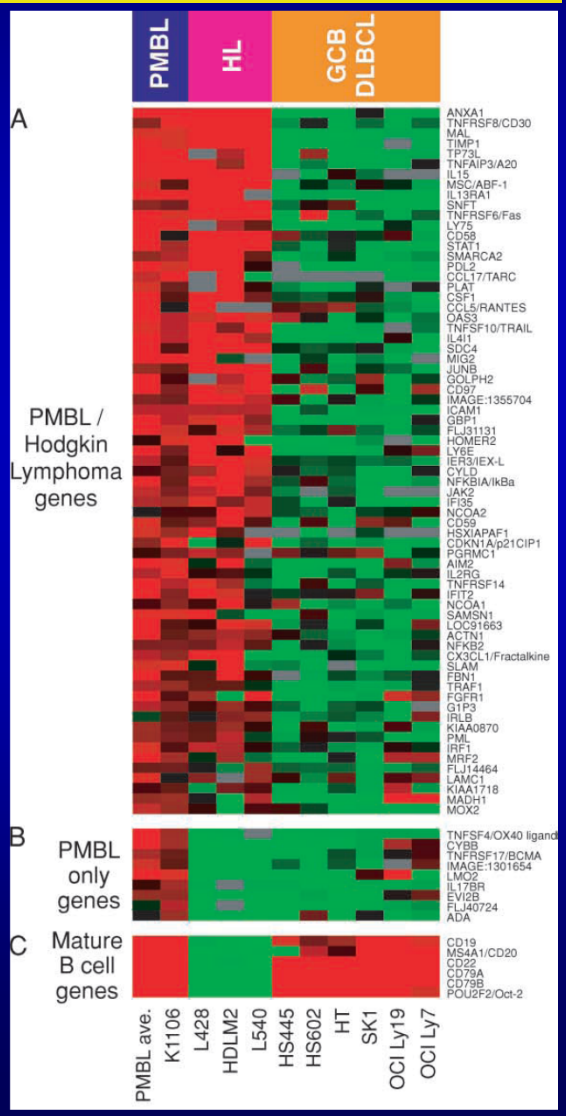
Immunohistochemistry (I)

- Pan-B markers: CD20, CD19, CD79a, PAX-5
- Ig expression absent (!!) in the majority of cases
- CD10 (-) in the majority, bcl-6 (+) >50%, MUM-1 (+) ~75%
- bcl-2 typically (+)
- CD23 typically (+)
- CD30 (+) 80% (but faint and heterogenous), but CD15 (-)

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Gene Expression Signature (I)





Rosenwald A, J Exp Med. 2003; 198: 851-862

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Molecular Findings

- 9p: JAK2, PDL-1, PDL-2
- 2p: c-Rel, bcl-11A
- X

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

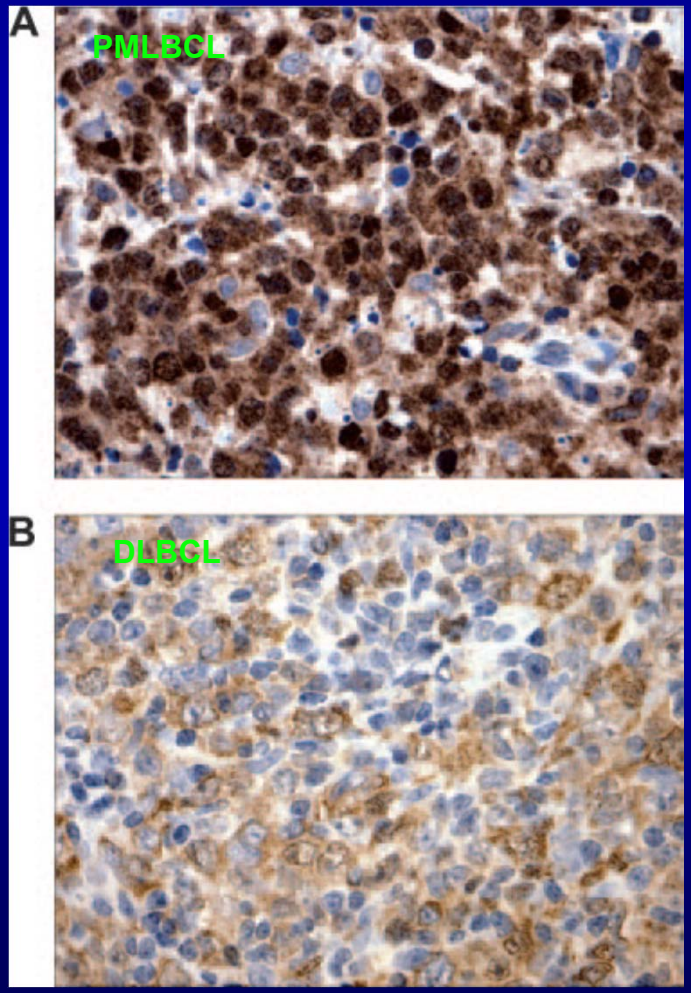
Immunohistochemistry (II) – Newer, More Specific Markers

- **CD23:** Activation marker
- **Nuclear c-Rel:** Member of NFκB family
- **TRAF-1:** Signalling molecule – target of NFκB
- **MAL:** Unclear function
- **CD200:** Membrane glycoprotein of the Ig superfamily

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Differential Diagnosis from DLBCL – Immunohistochemistry (II)

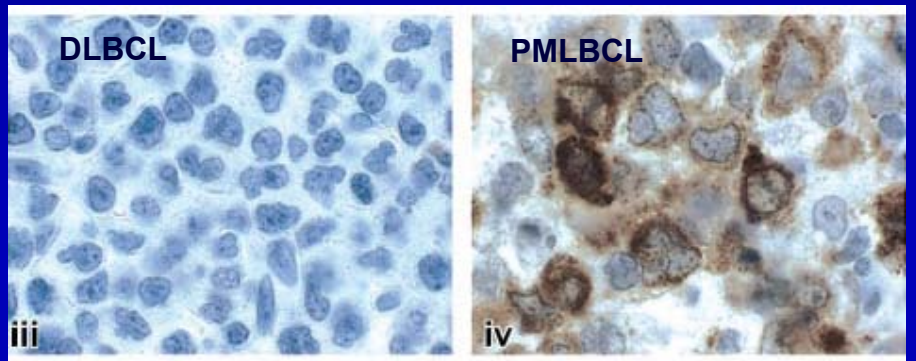
Nuclear c-Rel



Feuerhake et al, Blood 2005; 106: 1392-9

TRAF-1,

Savage et al, Blood 2003; 102: 3871-9



	PMLBCL (n=45)	DLBCL (n=156)
cRel + TRAF-1 +	53%	2%
cRel + TRAF-1 -	11%	16%
cRel - TRAF-1 +	20%	8%
cRel - TRAF-1 -	16%	74%

Rodig SJ et al, Am J Surg Pathol. 2007; 31: 106-12

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Immunohistochemistry (III)

Differential Diagnosis from DLBCL and classical Hodgkin lymphoma

	PMLBCL	DLBCL	cl. Hodgkin
CD45	+++	+++	-
CD19, CD79a	+++	+++	-/+
CD20	+++	+++	-/+
PAX-5	+++	+++	+++ (faint)
CD10	-/+	+	-
bcl-6	+/++	++	-/+
MUM-1	++	+	++/+++
CD30	++	-/+	+++
CD15	-	-	++

- : <10%, -/+ : 10-35%, + : 35-65%, ++ : 65-95%, +++ : >95% of cases

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Immunohistochemistry (IV)

Differential Diagnosis from DLBCL and classical Hodgkin lymphoma

	PMLBCL	DLBCL	cl. Hodgkin
CD23	++	- or -/+	- ή -/+
TRAF-1	+/++	- or -/+	+++
Nuclear c-Rel	+/++	- or -/+	++
TRAF-1+ / c-Rel +	+/++	-	
MAL	++	-	-/+
CD200*	++/+++ (94%)	- (7%)	++/+++ (92%)
c-Jun	-	-	+++
Galectin-1	-/+	-	+++
EBV	-	- ή -/+	-/+

- : <10%, -/+ : 10-35%, + : 35-65%, ++ : 65-95%, +++ : >95% of cases

** Dorfman DM, Mod Pathol. 2012; 25: 1637-1643*

** Dorfman DM, Am J Clin Pathol. 2010; 134: 726-733*

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Immunohistochemistry (V)

Frequency of Expression of Specific Markers in PMLBCL

 # markers expressed in PMLBCL

5 / 5	13 / 35	37%
4 / 5	15 / 35	43%
3 / 5	5 / 35	14%
2 / 5	2 / 35	6%

 # markers expressed in PMLBCL (CD200 excluded)

4 / 4	13 / 35	37%
3 / 4	16 / 35	46%
2 / 4	5 / 35	14%
1 / 4	1 / 35	3%

BUT, definitions matter !

Positivity defined as expression in >20% of neoplastic cells

Table 2 Summary of primary mediastinal large B cell lymphoma immunostaining results.[a]

Case no.	CD200	CD23	MAL	TRAF	REL
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
sensitivity	33/35 = 94%	24/35 = 69%	30/35 = 86%	30/35 = 86%	27/35 = 77%

Table 3 Summary of diffuse large B cell lymphoma immunostaining results[a]

Case no.	CD200	CD23	MAL	TRAF	REL
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
specificity	28/30 = 93%	28/30 = 93%	29/30 = 97%	23/30 = 77%	25/30 = 83%

[a]Dark cells: ≥20% immunoreactivity; light cells: <20% immunoreactivity.

Dorfman DM, Mod Pathol. 2012; 25: 1637-1643

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Cell of Origin

Asteroid B-cells of thymic medulla

- B-cell lymphoma developing at the anatomic site of thymus
- CD23 expression
- MAL expression

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Clinical and Laboratory Patients' Characteristics (I)

Author	Pts (n)	Gender (%)	Stage III/IV (%)	B-sympt (%)	PS≥2 (%)	LDH ↑ (%)	HI/H Risk a/aIPI (%)
Savage, 2006	153	*44*	26	*47*	40	77	*59*
Mazzarotto, 2007	53	72	*9*	30			51
Todeschini, 2004	138	54	31	41			34
De Sanctis, 2008	92	*74*		47	*42*	74	43
Hamlin, 2005	141	46	*40*	40	40	77	55
Massoud, 2008	105	61	33		14	73	*19*
Ahn, 2010	35	51	37	31	*11*	*91*	31
Zinzani, 2009	45	53	10	40		69	35
Lazzarino, 1997	106	54	14 (43)	*29*	27	*52*	25 (38)
*Vassilakopoulos, 2013**	*201*	*63*	*12*	*31*	*16*	*79*	*22*

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Clinical and Laboratory Patients' Characteristics (II)

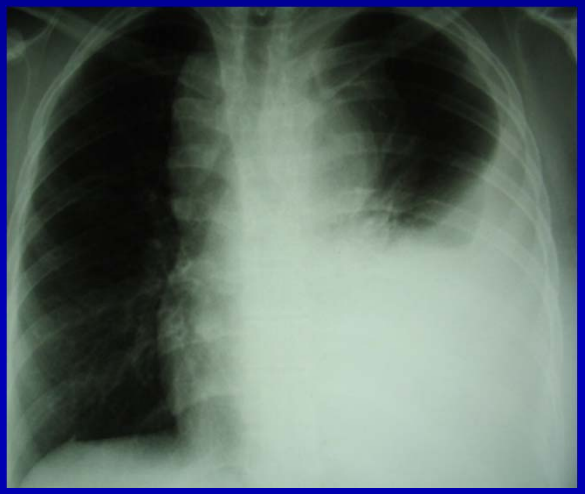
Author	Pts (n)	Bulky Disease (%)*	Pleural effusion (%)	Pericardial effusion (%)	SVCS (%)
Savage, 2006	153	75			
Mazzarotto, 2007	53	*46*	26	*9*	30
Todeschini, 2004	138	80	45	27	49
De Sanctis, 2008	92	*87*			50
Hamlin, 2005	141	75	*19*	19	
Massoud, 2008	105	80			
Ahn, 2010	35	74	*49*	*49*	*20*
Zinzani, 2009	45	95			*55*
Lazzarino, 1997	106	73	36	25	
Vassilakopoulos, 2013	*201*	*61*	*34*	*29*	

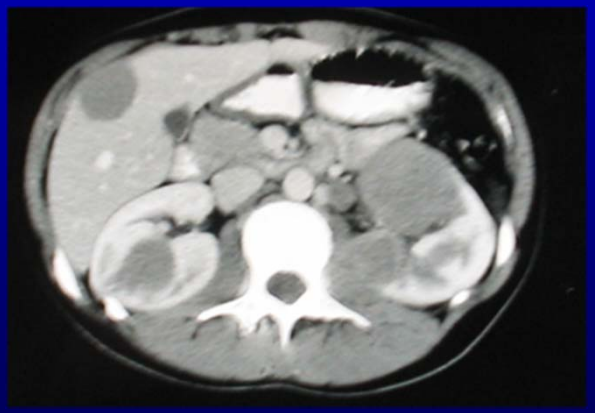
* Variable definition for bulky disease

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Localization - Staging

- Typically stage I/II (>70%) or IV
- Intrathoracic or supradiaphragmatic disease
- Frequent intrathoracic extranodal involvement (mainly lung) and serous effusions
  - Problems in stage definitions
- Infradiaphragmatic nodal disease <10% at diagnosis
- Rare extrathoracic extranodal sites at diagnosis (kidneys, liver <5%)
- No bone marrow involvement (<1-2%)
- Frequent extrathoracic, peculiar extranodal sites involved at relapse/progression
  - Kidneys, CNS, adrenals, ovaries, intestine – stomach etc





PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Laboratory Findings

- Data from Greek multicenter study (paucity of published data !!)
  - Elevated LDH in ~85% (>2x in 25-30%; up to 6x)
  - Frequent anemia (40%), neutrophilia (25%), thrombocytosis (20%)
  - Lymphocytopenia <1.0x10^9/L 45-50%
  - ESR >50 mm/h in 40% (very rarely >100 mm/h)
  - CRP typically elevated (~90%)
  - Albumin <4 g/dl in 45%
  - Usually normal β_2- microblobulin levels (~80%)

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Treatment Strategies

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Treatment Strategies

- **Rituximab – chemotherapy.** **Which regimen ?**
  - ***R-CHOP-21***
  - ***Intensified chemotherapy,*** ***e.g.*** **R-da-EPOCH, R-M(V)ACOP-B or regimens designed for Burkitt lymphoma**

- **Radiotherapy.** **Which patients ??**

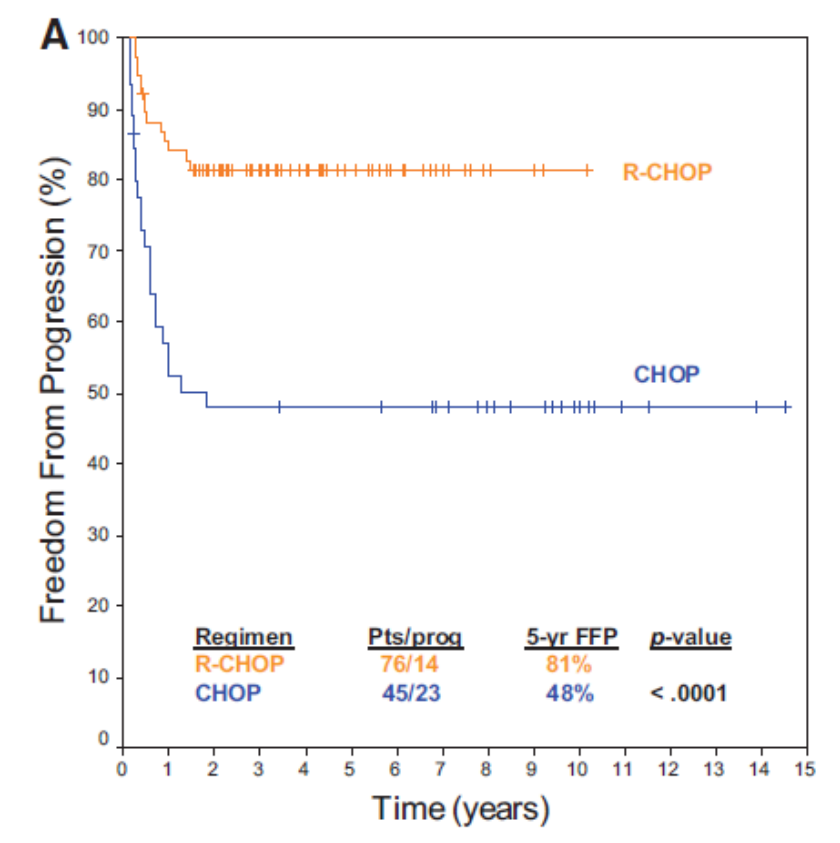
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

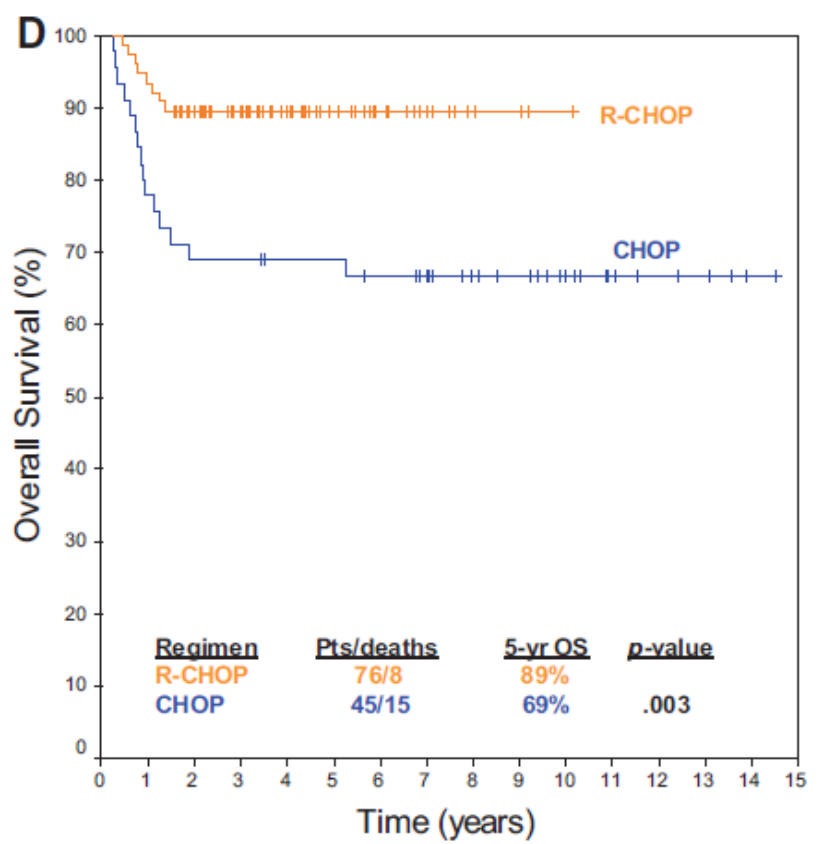
The Role of R-CHOP-21

R-CHOP-21 IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Retrospective Study in 10 Greek Centers

Freedom From Treatment Failure and Overall Survival

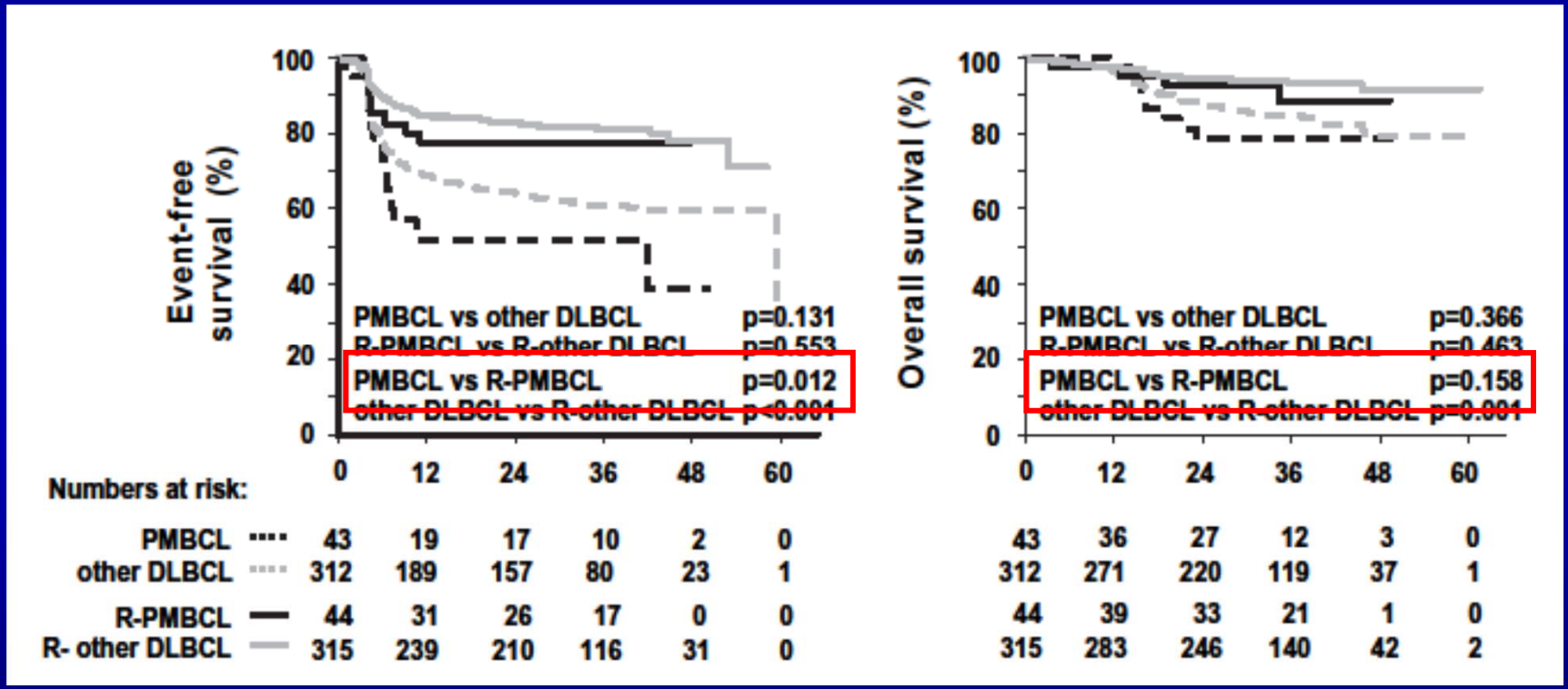




Vassilakopoulos TP et al. Oncologist. 2012; 17: 239-249.

R-CHO(E)P-21 IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Unplanned Analysis of the MInT Trial based on 87 patients with PMLBCL



Rieger M et al., Ann Oncol. 2011; 22: 664-670

<60 years and Age-adjusted IPI 0-1

(low or low/intermediate)

CHOP; 47%

CHOEP; 45% **RT; 71%**

MACOP-B; 7%

PMitCEBO; 1%

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Summary of retrospective studies of R-CHOP and similar regimens

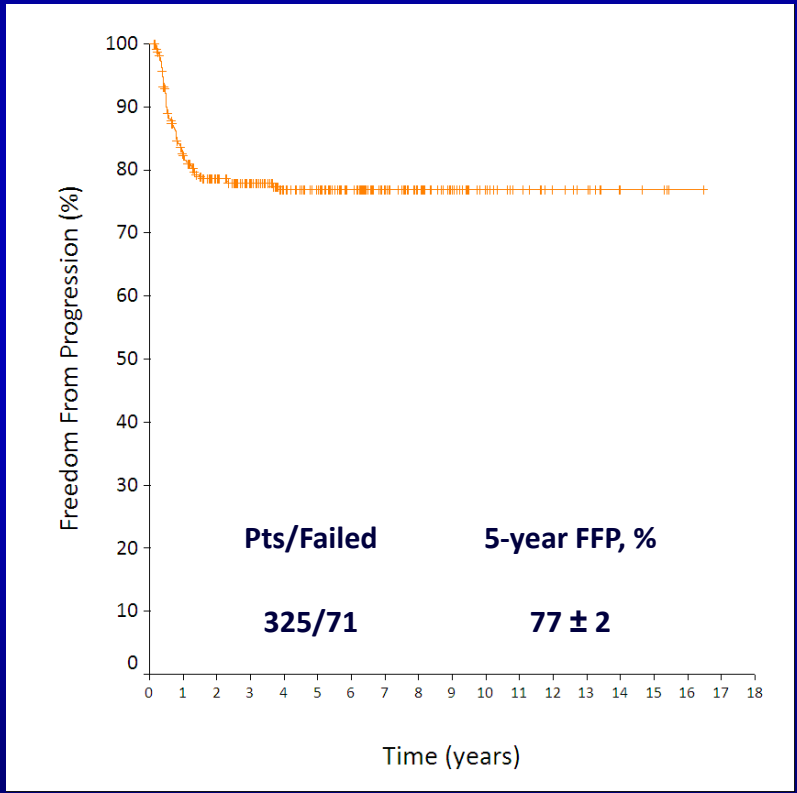
Regimen, Author	Pts (#)	RT	3-year FFP	3-year OS
Vassilakopoulos et al, Oncologist 2012 (updated 2013)	201	++	76%	89%
Savage et al, ASH 2012, abstr. #303	96	++	78%	88%
Rieger et al (MinT, aa IPI 0-1), Ann Oncol 2011; ASH 2012	44	++	90%	90%
Soumerai et al, Leuk Lymphoma 2013	63	+++	68% (5y)	79% (5y)
Xu et al, Leuk Lymphoma 2012	39	+++	77%	84%
Tai et al, Leuk Lymphoma 2013	27	+++	88%	87%
Schneider et al, ASH 2010	23	+++	91%	96%
Ahn et al, Int J Hematol 2010	21	++	79%	83%
Novoselac et al, Commun Oncol 2007	10	++	100%	100%
ALL PATIENTS (except of Rieger et al)	480		77.5%	87.3%

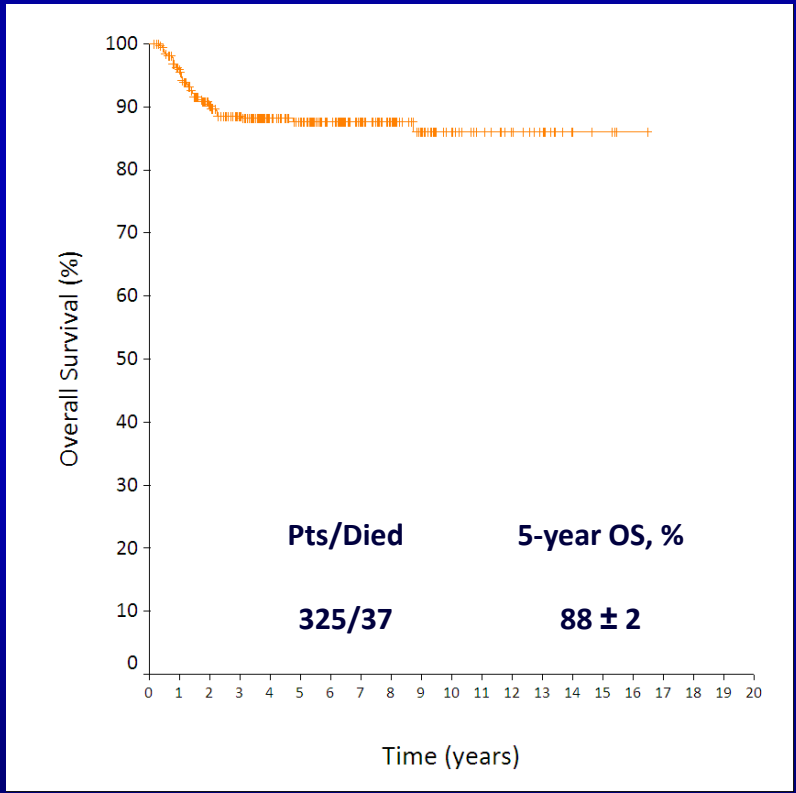
-/+: <10%, +: 10-50%, ++: 50-75%, +++: >75%.

R-CHOP-21 IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Retrospective Study in 20 Greek Centers

Freedom From Treatment Failure and Overall Survival





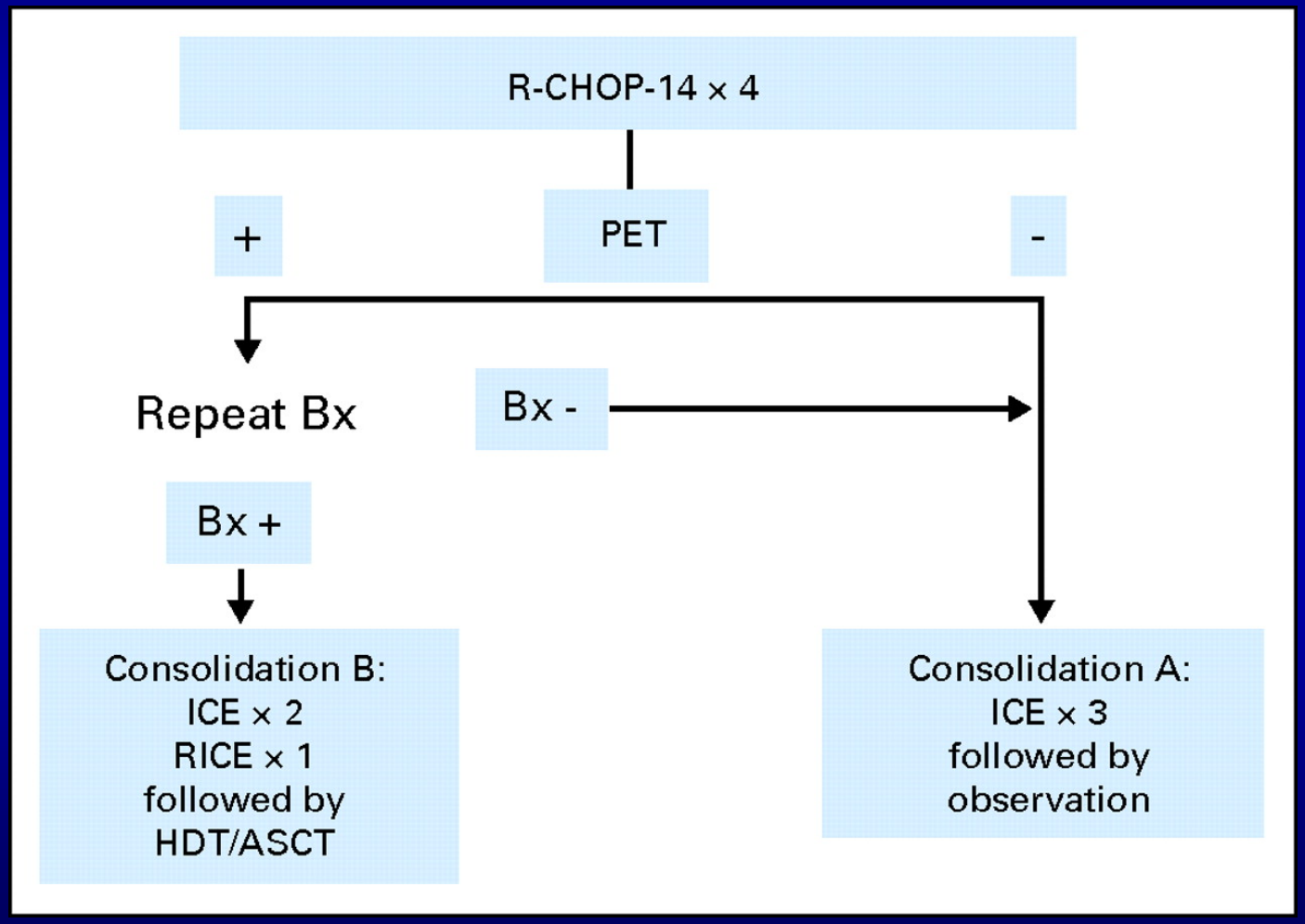
TREATMENT OF PRIMARY MEDISTINAL LARGE B-CELL LYMPHOMA

Interim Conclusion I

- When the majority of responding patients receive RT, R-CHOP-21 results to similar or better outcomes compared to more intensive regimens without Rituximab
- The data are derived from retrospective, *non-randomized* studies
- Can further benefit be obtained with the addition of Rituximab to more intensive chemotherapy regimens ?

PET-SCAN IN AGGRESSIVE B-CELL LYMPHOMAS

Early, interim PET-driven Treatment Modification in Aggressive B-Cell Lymphomas



Moskowitz CH et al. J Clin Oncol. 28:1896-1903, 2010

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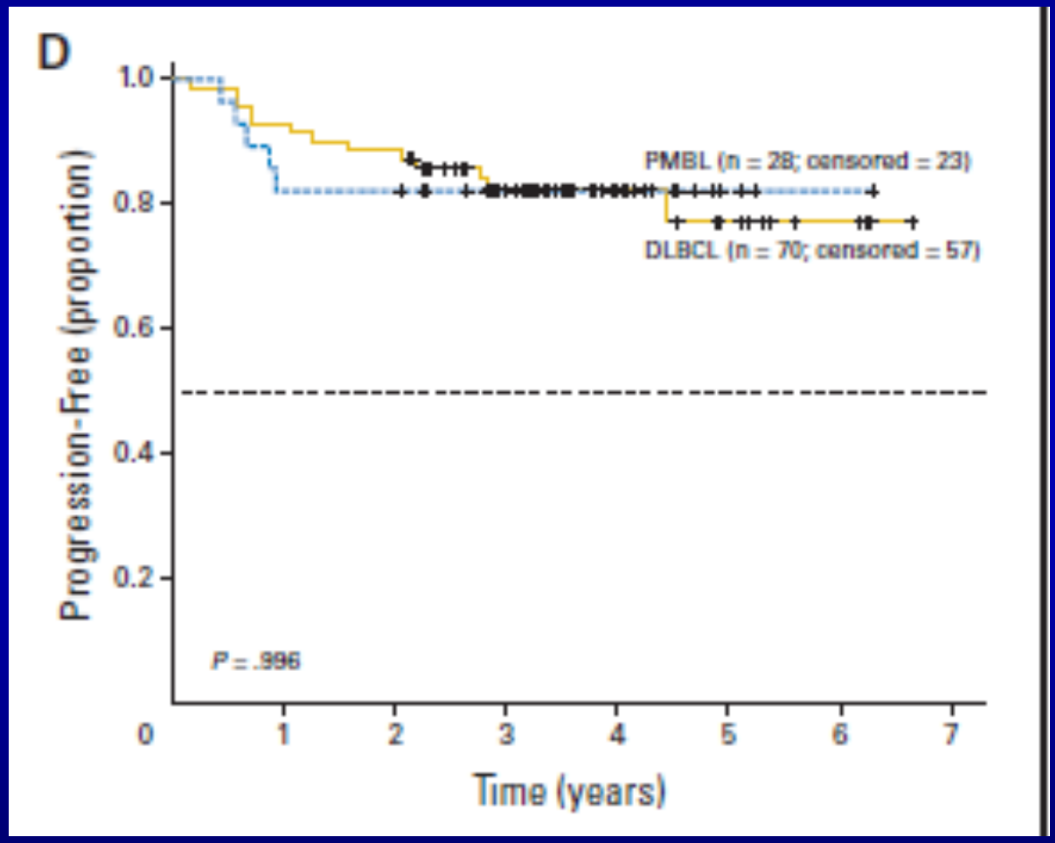
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Intensification of Immunochemotherapy I

Intensified R-C_{1000}HOP-14 and early, interim PET-driven, Treatment modification without RT



Moskowitz CH et al. J Clin Oncol. 28:1896-1903, 2010

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Intensification of Immunochemotherapy I

The impressive results of NCI
with the R-DA-EPOCH regimen in 96-hr Infusion
(Almost universal omission of RT)

Dunleavy K et al. N Engl J Med. 2013; 368: 1408-1416

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Intensification of Immunochemotherapy I

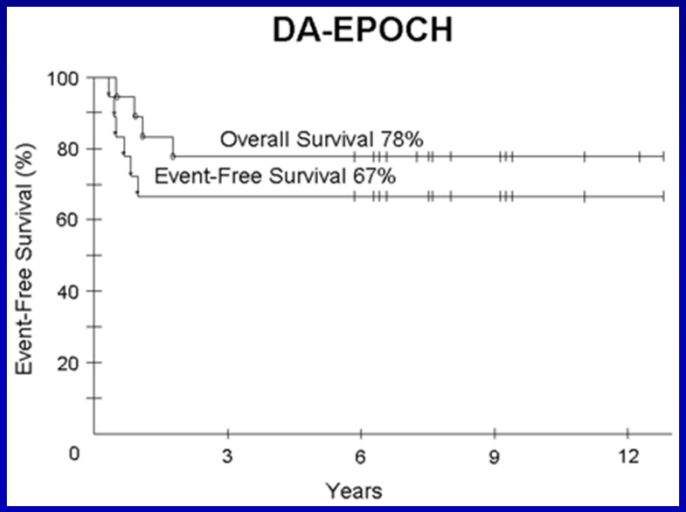
R-DA-EPOCH in 96-hr Infusion (Almost universal omission of RT)

Characteristic	Total Cohort (N=93)	Evaluable EOT FDG-PET (N=80)	Prospective NCI Cohort (N=59)	Retrospective Stanford Cohort (N=34)
Female sex- no. (%)	55 (59)	44 (55)	35 (59)	20 (59)
Age- yr.				
Median	31	31	30	32.5
Range	18-68	18-68	19-54	18-68
Bulky tumor, > 10 cm				
Patients- no. (%)	54 (59)[a]	52 (66)[b,d]	36 (61)	18 (55)[c]
Maximal diameter- Median (Range), cm	10.7 (4-18.9)	10.9 (5.5-18.9)[e]	10.9 (4-18.9)	10 (4.9-18.3)
Stage IV disease- no. (%)	18 (19)	14 (18)	14 (24)	4 (12)
International prognostic index (IPI)- no. (%)				
Low (0-1)	60 (65)	53 (66)	37 (63)	23 (68)
Low-intermediate (2)	22 (24)	18 (23)	15 (25)	7 (21)
Intermediate-high (3)	8 (9)	7 (9)	6 (10)	2 (6)
High (4-5)	3 (3)	2 (3)	1 (2)	2 (6)
ECOG- no. (%)				
0-1	81 (87)	69 (86)	57 (97)	24 (71)
2-3	12 (13)	11 (14)	2 (3)[f]	10 (29)
Elevated LDH- no. (%)	68 (74)[a]	59 (75)[b]	46 (78)	22 (65)[c]
Extranodal site- no. (%)				
0-1	80 (86)	69 (86)	50 (85)	30 (88)
≥ 2	13 (14)	11 (14)	9 (15)	4 (12)
Any	38 (41)	30 (38)	27 (46)	11 (32)
Pleural effusion- no. (%)	45 (48)	40 (50)	27 (46)	18 (53)
Pericardial effusion- no. (%)	38 (41)	35 (44)	21 (36)	17 (50)

[a]N = 92 patients; [b]N = 79 patients; [c]N = 33 patients; [d]P=0.0013 comparing patients with and without evaluable EOT FDG-PET scans; [e]P= 0.0009 comparing patients with and without evaluable EOT FDG-PET scans; [f]P=0.00058 comparing patients treated at NCI *vs.* Stanford; ECOG: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; EOT FDG-PE: end-of-treatment; ^{18}F-fluorodeoxyglucose-positron-emission tomography; NCI: National Cancer Institute.

Dunleavy K et al. N Engl J Med. 2013; 368: 1408-1416; Updated in Melani C et al. Haematologica/THJ. 2018; 103: 1337-1344

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Intensification of Immunochemotherapy II
R-DA-EPOCH in 96-hr Infusion (Almost universal omission of RT)

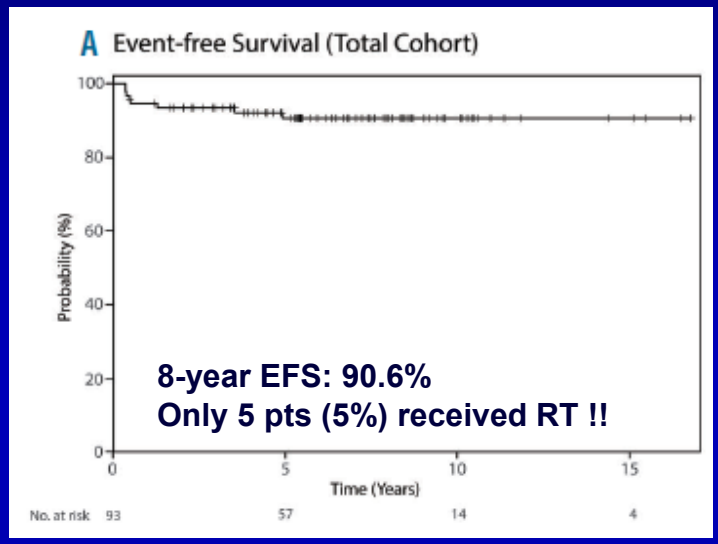


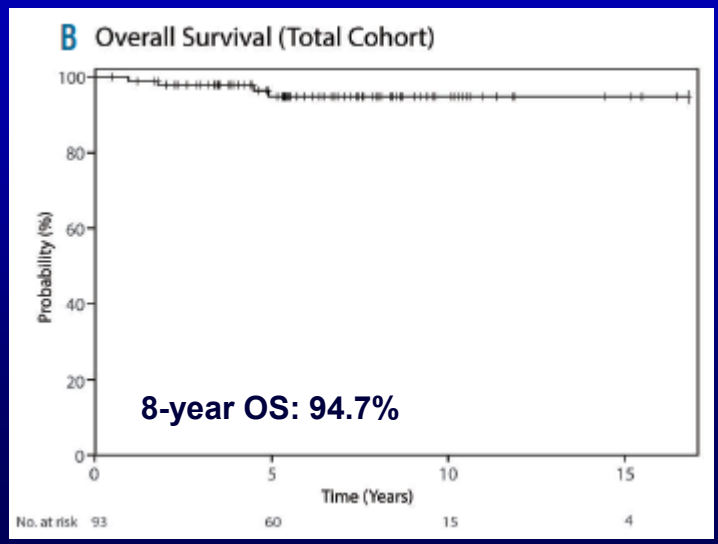
Dunleavy K et al. Blood. 108:abstract #209, 2006
Updated in Lugano Meeting: Ann Oncol. 19 (S4): abstract 043: 208

R-DA-EPOCH: 93 patients

RT: Only 2/51 based on PET

Dunleavy K et al. N Engl J Med. 2013; 368: 1408-1416
Updated in Melani C et al. Haematologica/THJ. 2018; 103: 1337-1344





PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Intensification of Immunochemotherapy I

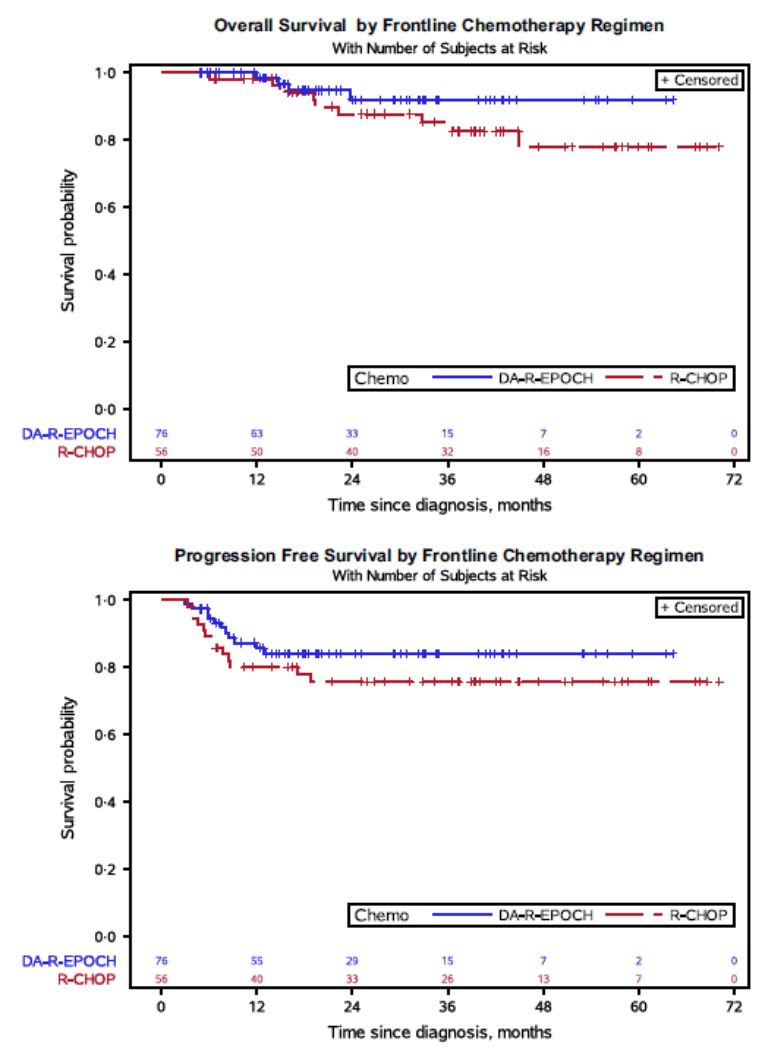
Is R-DA-EPOCH really better than R-CHOP ?

Difficult to estimate in the absence of randomized trials

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Intensification of Immunochemotherapy I

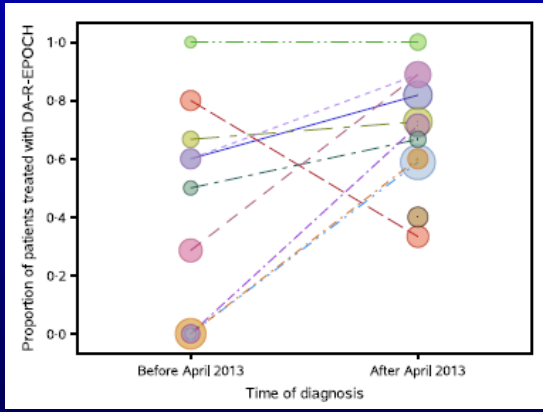
Is R-DA-EPOCH really better than R-CHOP ?



Adjusted Analysis

	Survival estimate	95% confidence interval	*P*-value
PFS at 24 months for R-CHOP	0·76	0·64–0·88	0·28
PFS at 24 months for DA-R-EPOCH	0·85	0·75–0·94	
OS at 24 months for R-CHOP	0·89	0·80–0·99	0·83
OS at 24 months for DA-R-EPOCH	0·91	0·82–0·99	

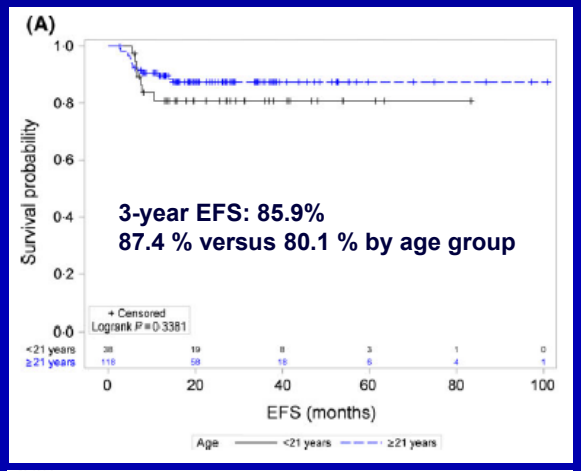
	Parameter	Estimate	95% confidence interval	*P*-value
OS, months	HR	0·63	0·19–2·15	0·46
PFS, months	HR	0·62	0·27–1·47	0·28
Infection	OR	1·16	1·01–1·33	0·04
Neutropenic fever	OR	1·19	1·03–1·38	0·02
Hospitalizations	OR	1·22	1·11–1·34	<0·01
Complete response	OR	1·19	1·06–1·34	<0·01



Shah NN et al. Br J Haematol, 180: 534-544, 2018

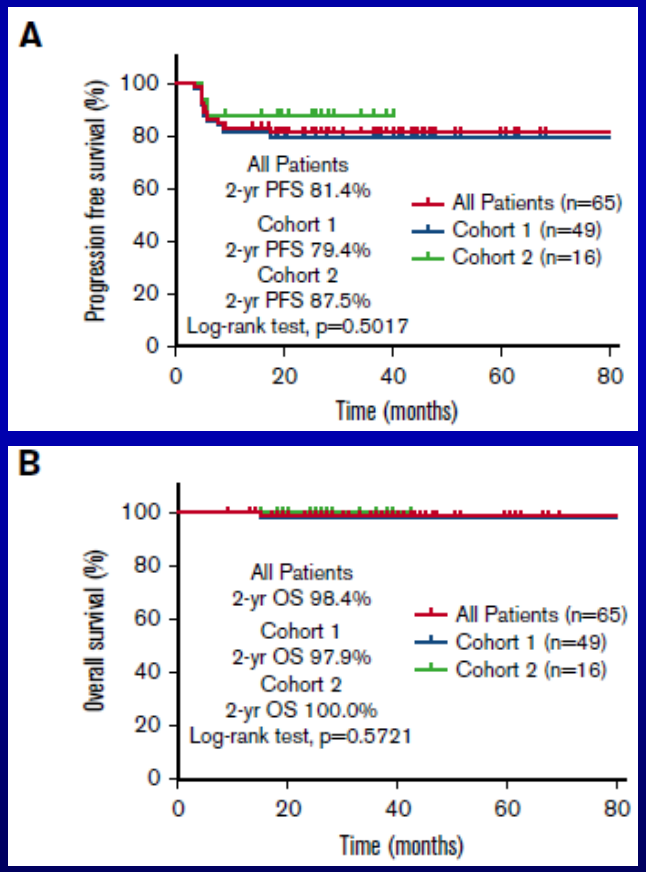
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Intensification of Immunochemotherapy I
Real life data with R-DA-EPOCH

24 US/Canadian Academic Centers, 2005-2015, 156 pts; 15% RT



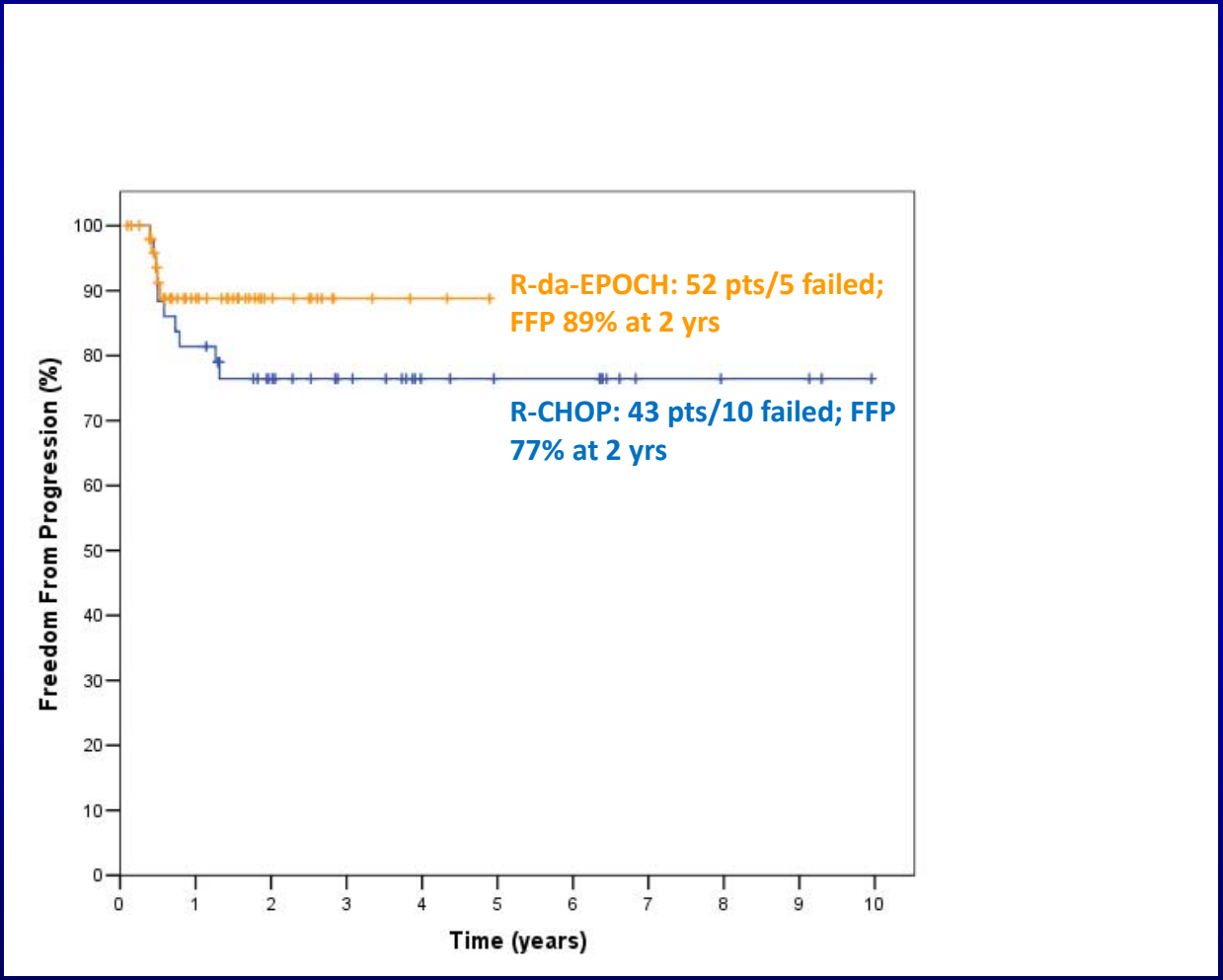
Giulino-Roth L et al. Br J Haematol, 179: 739-747, 2017

MD Anderson / Dana-Farber: 65 pts; 20% RT (5% consolidative – 15% salvage)



Pinnix C et al. Blood Adv, 11: 1334-1343, 2018

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
R-da-EPOCH vs R-CHOP Historical Controls in Greece



Vassilakopoulos TP et al, Poster Presentation, EHA 2019

Current status of the Collaborative Study

- Patients collected or to be collected
  - Greece ~65
  - Israel ~40
  - Turkey ~35
  - Total ~140 (ongoing)
- Expected failures: ~15-20

Aims of the Collabnorative Study I

To collect a large multicenter series of PMLBCL patients <65 years old, treated with R-da-EPOCH in Greece, Israel and Turkey

To assess the PFS and OS of this series, which represents a real life situation

To assess:

- The compliance with the strict R-da-EPOCH protocol in the real life
- The effect of protocol violations on the outcome
- The long-term toxicity of R-da-EPOCH

To assess:

- The utility of PET/CT in R-da-EPOCH patients with PMLBCL
- The use of RT in this population in relation to PET findings

To search for potential prognostic factors and/or validate or prognostic model (LDH plus extranodal sites) under R-da-EPOCH

Aims of the Collaborative Study II

If it is possible, to expand the strict historical control comparison of R-da-EPOCH with R-CHOP, which has been already performed in Greek patients. This should include Centers fulfilling the following:

Have used exclusively R-CHOP in consecutive patients for a given time period

Have subsequently adopted R-da-EPOCH as sole therapy in patients <65 (or <60) years old at a certain time point and have not violated this strategy

- If very few patients have been treated with R-CHOP within the R-da-EPOCH era, they might be included in an era-by-era comparison, counted as R-da-EPOCH treated (worst case scenario)

The eligibility of each Center will be evaluated separately on the basis of the above

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Intensification of Immunochemotherapy III
R-M(V)ACOP-B with or without RT

Regimen, Author	Pts (#)	RT	3-year FFP / EFS	3-year OS
R-MACOP-B Zinzani PL et al. Clin Lymphoma Myeloma 2009; 9: 381-385	45	71%	84%	80%
R-VACOP-B Avigdor A et al. Blood 2007; 110: 1283 (abstract)	21	no	84%	~96%

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Intensification of Immunochemotherapy IV
R-GMALL 2002 with or without RT

Table I: Patient characteristics

	PMBL	BL
Patients (f/m)	15 (7/8)	28 (8/20)
Age (years), median (range)	36 (22-60)	48 (22-70)
>55 years (%)	20	39.3
Stage III–IV (%)	33.3	76.9
ECOG ≥2 (%)	13.3	18.5
IPI		
low risk	26.6	17.9
low-intermediate risk	40.0	28.6
high-intermediate risk	26.7	32.1
high risk	6.7	21.4
Elevated LDH (>ULN), n (%)	14 (93.3)	24 (88.9)
range in µmol/L	229-1973	227-7661
Pericardial effusion (%)	46.7	0
Pleural effusion (%)	26.7	14.3
B symptoms (%)	33.3	28.6
Extranodal sites (%)		
0	26.7	7.7
1	53.3	26.9
≥2	20.0	65.4

PMBL: primary mediastinal B-cell lymphoma; BL: Burkitt's lymphoma; f: female; m: male; IPI: international prognostic index; LDH: Lactate dehydrogenase; ULN: upper limit of normal

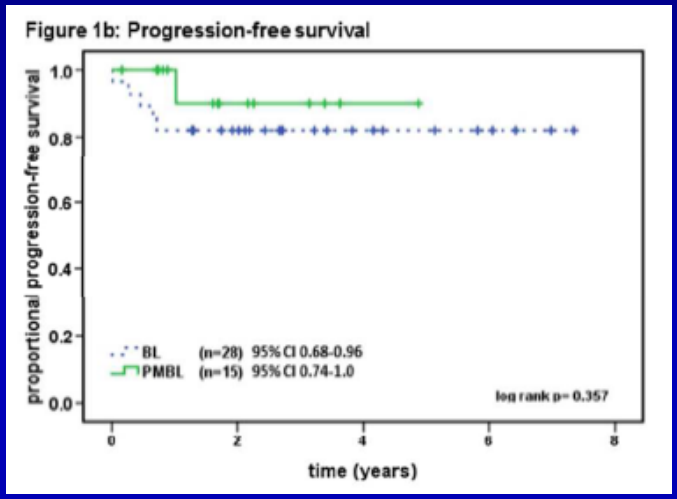
Table IIa: Treatment protocol, patients 18-55 years

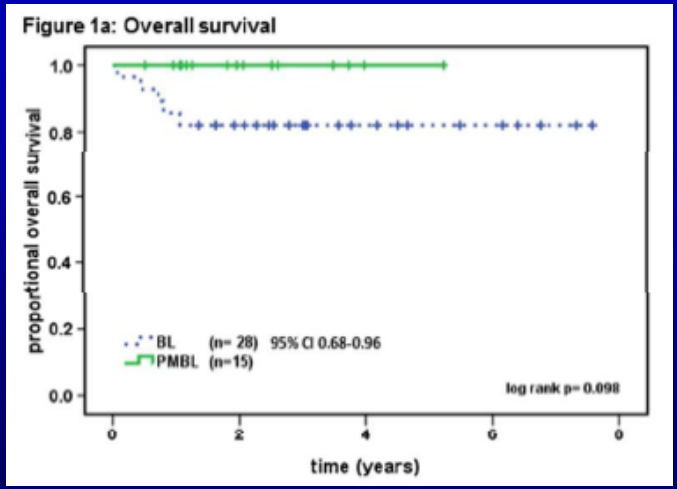
Block A	
rituximab	375 mg/m², d1
dexamethasone	10 mg/m², d2-6
vincristine	2 mg, d2
ifosfamide	800 mg/m², d2-6
HD-methotrexate	1500 mg/m², over 24 hours, d2
etoposide	100 mg/m², d5-6
cytarabine	2x 150 mg/m², d5-6
intrathecal triple therapy	cytarabine 40 mg, methotrexate 15 mg, dexamethasone 4 mg; d2+6
Block B	
rituximab	375 mg/m², d1
dexamethasone	10 mg/m², d2-6
vincristine	2 mg, d2
cyclophosphamide	200 mg/m², d2-6
HD-methotrexate	1500 mg/m², over 24 hours, d2
adriamycin	25 mg/m², d5-6
intrathecal triple therapy	cytarabine 40 mg, methotrexate 15 mg, dexamethasone 4 mg; d2+6
Block C	
rituximab	375 mg/m², d1
dexamethasone	10 mg/m², d2-6
vindesine	3 mg/m², max 5 mg, d2
HD-methotrexate	1500 mg/m², over 24 hours, d2
etoposide	250 mg/m², d5-6
HD-cytarabine	2x 2000 mg/m², d6

HD: high-dose; d: day

Condolidation
RT: 67%

Prophylactic
i.t.: 93%





Pohlen M et al. Am J Hematol. 2011; 86: E61-64.

TREATMENT OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Interim Conclusion II

- Rituximab combined with more intensive chemotherapy:
  - May be superior to R-CHOP-21 with respect to disease control
  - Overall survival comparison much more obscure
  - Limits the need of additional RT ???
- Data derived from non-randomized comparisons. Urgent need for randomized trials.
  - All patients or only high risk ?
  - If only in high risk patients, who are they ?
- Is there a role for PET-Scan ?

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
PET and the role of Radiotherapy

How does PET work in PMLBCL ?

Is this depended on the chemo regimen?

PET/CT after R-CHOP in PMLBCL

Leukemia (2015), 1–5

www.nature.com/leu

LETTER TO THE EDITOR

PET/CT in primary mediastinal large B-cell lymphoma responding to rituximab-CHOP: An analysis of 106 patients regarding prognostic significance and implications for subsequent radiotherapy

Leukemia accepted article preview 14 May 2015; doi:10.1038/leu.2015.120

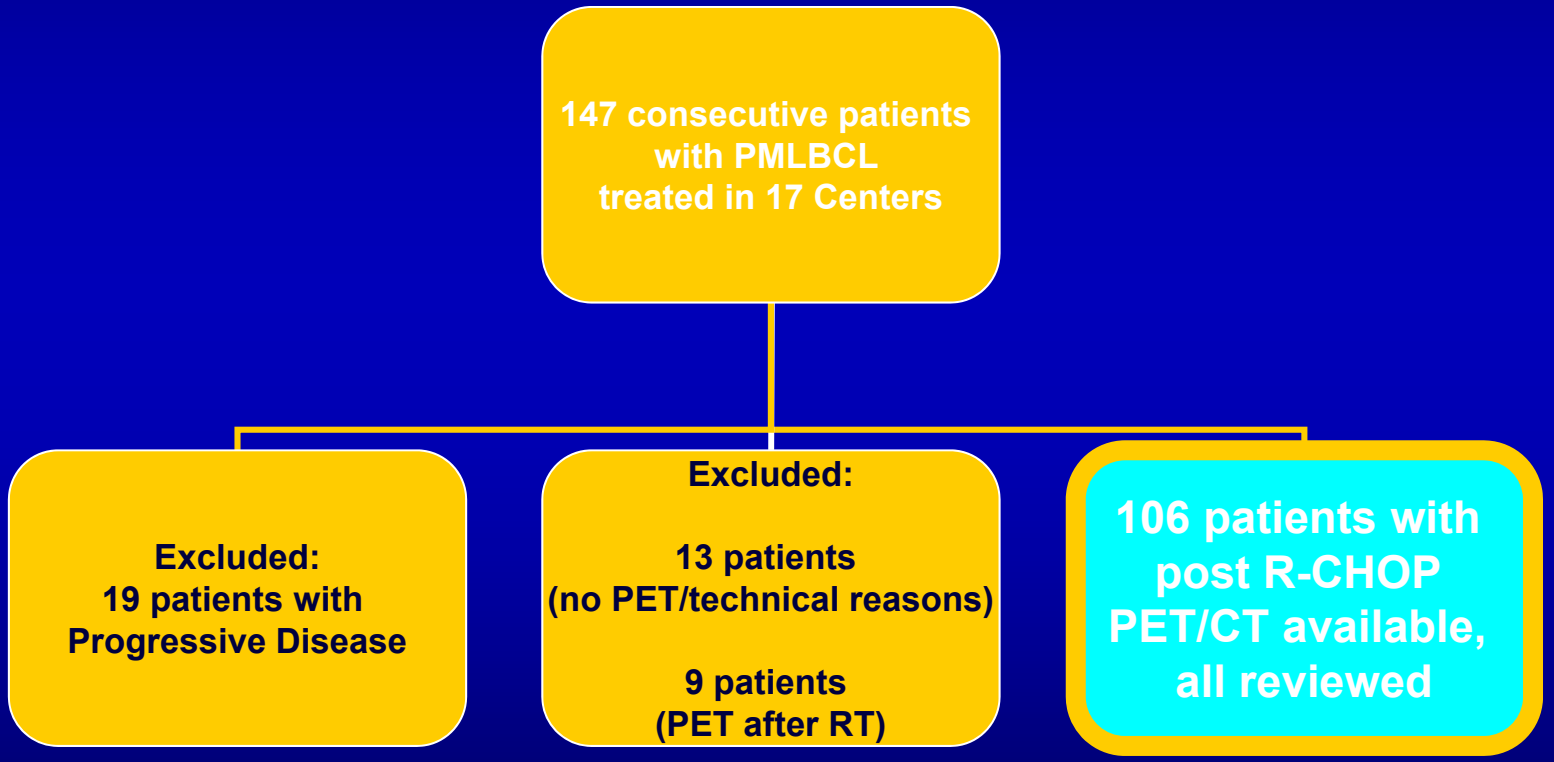
according to the Deauville criteria (Deauville 5-point scale; D5PS),[11] without the knowledge of patients' clinical outcomes. The degree

TP Vassilakopoulos[1], GA Pangalis[2], S Chatziioannou[3], S Papageorgiou[4], MK Angelopoulou[1], Z Galani[5], G Kourti[6], V Prassopoulos[7], T Leonidopoulou[8], E Terpos[9], MN Dimopoulou[1], S Sachanas[2], C Kalpadakis[10], P Konstantinidou[11], D Boutsis[12], E Stefanoudaki[13], L Kyriazopoulou[14], MP Siakantaris[15], M-C Kyrtsonis[16], E Variami[15], I Kotsianidis[17], A Symeonidis[18], E Michali[19], I Katodritou[11], G Kokkini[8], C Tsatalas[17], H Papadaki[10], M-A Dimopoulos[9], V Sotiropoulos[20], V Pappa[4], T Karmiris[6], J Meletis[1], J Apostolidis[6], I Datseris[21], P Panayiotidis[16], K Konstantopoulos[1], P Roussou[5] and P Rondogianni[21]

Vassilakopoulos TP et al. Leukemia, 30: 238-242, 2016

PET/CT ΣΤΟ ΠΡΩΤΟΠΑΘΕΣ ΛΕΜΦΩΜΑ ΜΕΣΟΘΩΡΑΚΙΟΥ

Αξιολόγηση Υπολειμματικών Μαζών και Ανταπόκρισης στη Θεραπεία



Median follow-up

42 months

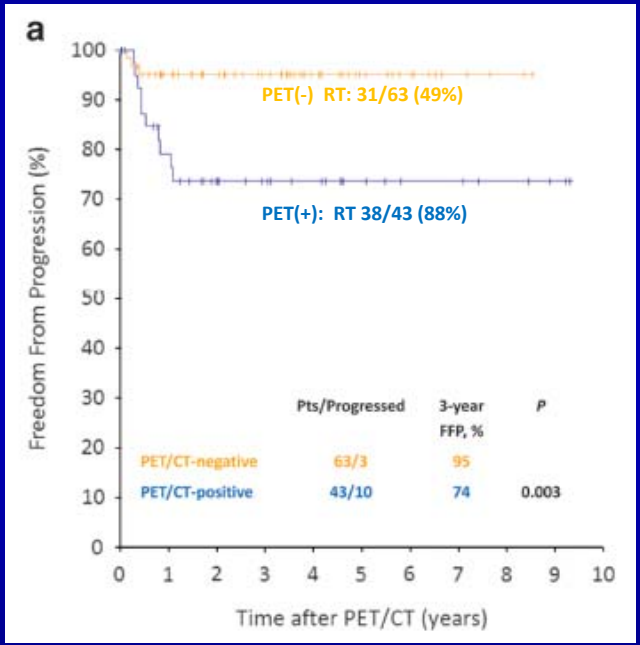
Vassilakopoulos TP et al. Leukemia, 30: 238-242, 2016

PET/CT ΣΤΟ ΠΡΩΤΟΠΑΘΕΣ ΛΕΜΦΩΜΑ ΜΕΣΟΘΩΡΑΚΙΟΥ

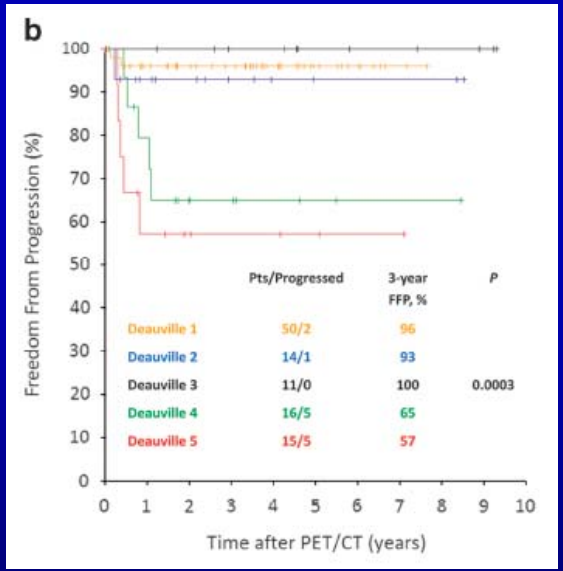
Αξιολόγηση Υπολειμματικών Μαζών και Ανταπόκρισης στη Θεραπεία

Επιβίωση Ελεύθερη Εξέλιξης Νόσου Αναλόγως του PET μετά το R-CHOP

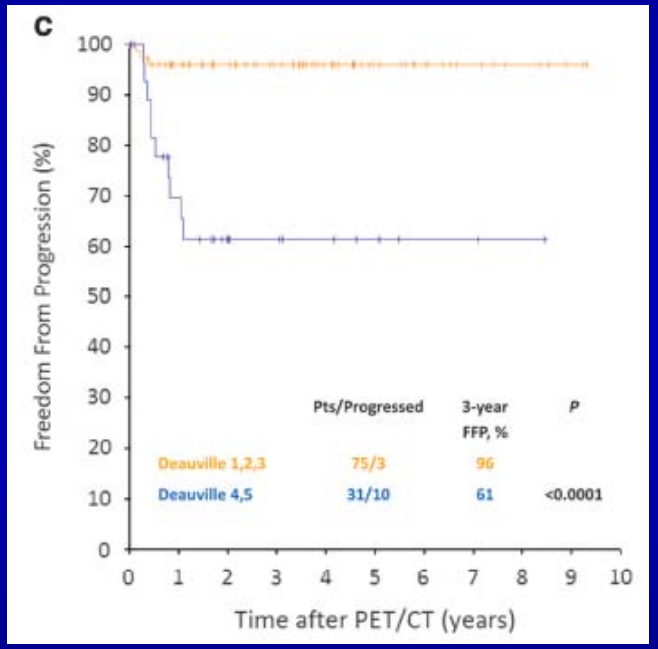
IHP Criteria



Deauville Criteria



Deauville Criteria, grouped



43/106 (41%) των ανταποκριθέντων στο R-CHOP παρέμειναν PET/CT θετικοί

Vassilakopoulos TP et al. Leukemia, 30: 238-242, 2016

PET/CT ΣΤΟ ΠΡΩΤΟΠΑΘΕΣ ΛΕΜΦΩΜΑ ΜΕΣΟΘΩΡΑΚΙΟΥ

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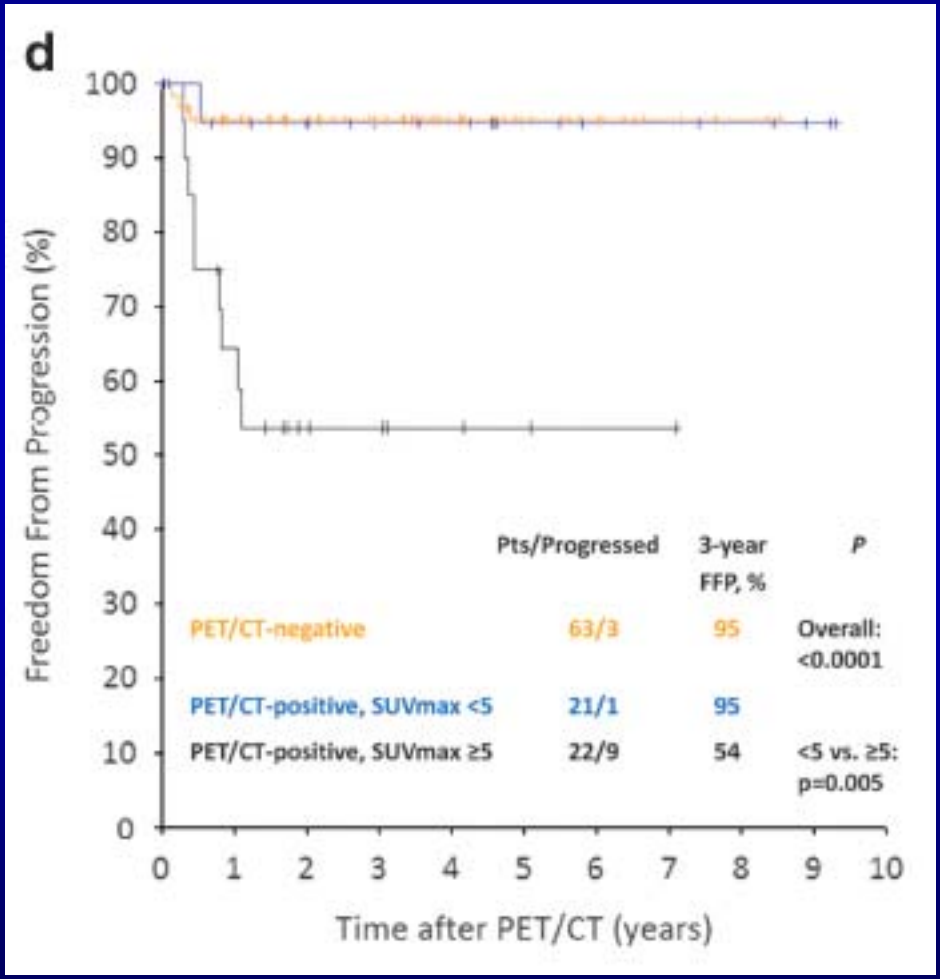
Επιβίωση Ελεύθερη Εξέλιξης Νόσου

Αναλόγως της Έντασης Θετικότητος του PET μετά το R-CHOP

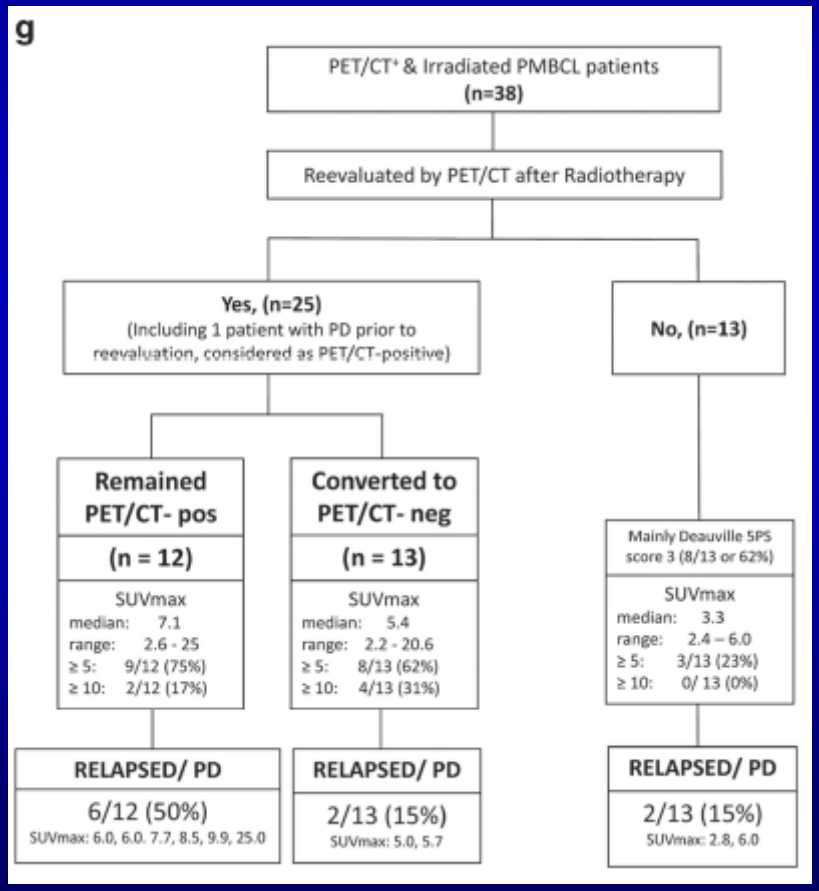


Vassilakopoulos TP et al. Leukemia, 30: 238-242, 2016

PET/CT ΣΤΟ ΠΡΩΤΟΠΑΘΕΣ ΛΕΜΦΩΜΑ ΜΕΣΟΘΩΡΑΚΙΟΥ

Αξιολόγηση Υπολειμματικών Μαζών και Ανταπόκρισης στη Θεραπεία

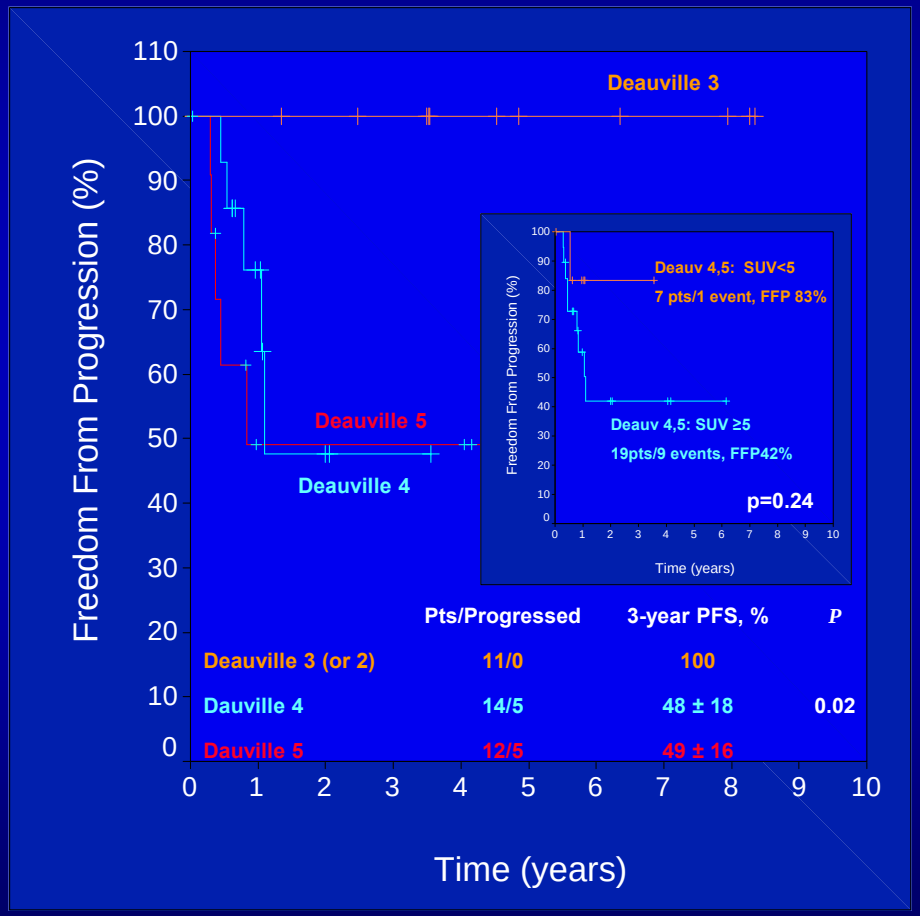
Έκβαση αναλόγως του PET μετά την Ακτινοθεραπεία (μετά το R-CHOP)

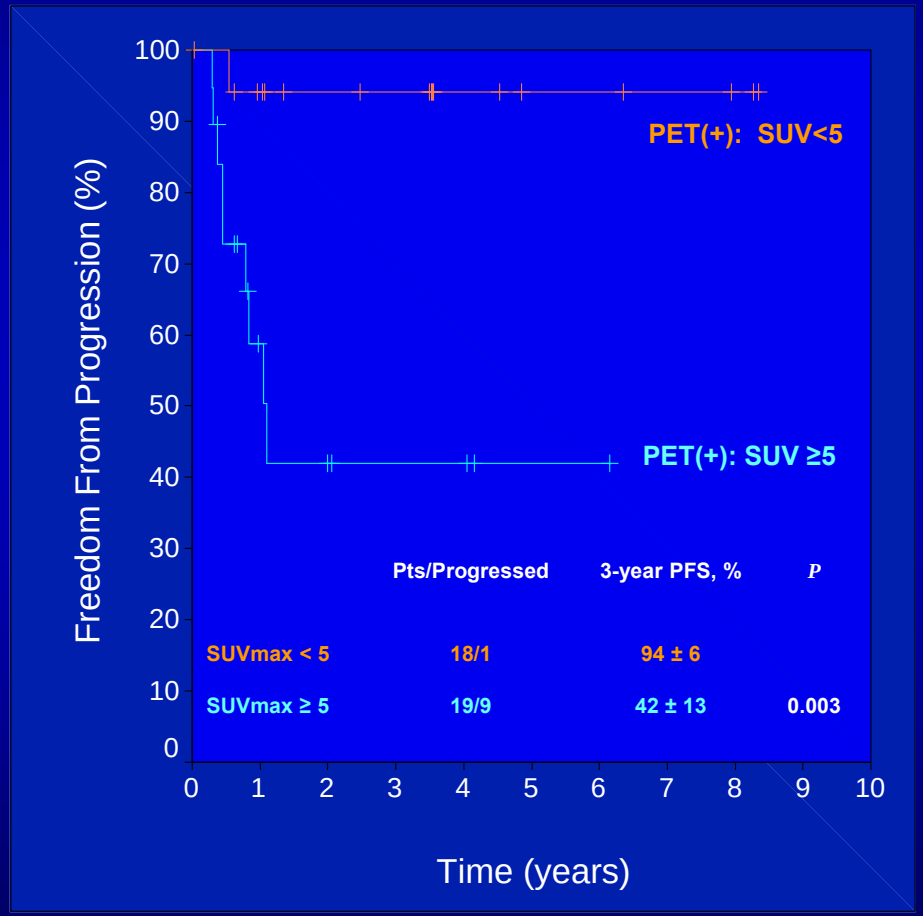


Vassilakopoulos TP et al. Leukemia, 30: 238-242, 2016

PET/CT after R-CHOP x 6-8 in PMLBCL

Freedom From Progression in PET-pos Patients by Deauville Criteria or SUVmax



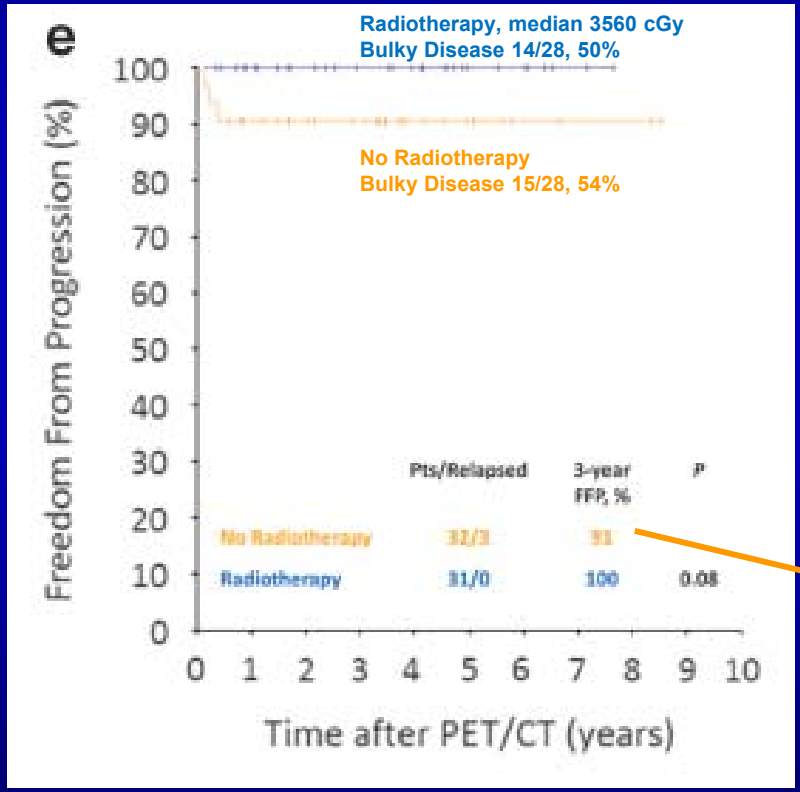


PET/CT ΣΤΟ ΠΡΩΤΟΠΑΘΕΣ ΛΕΜΦΩΜΑ ΜΕΣΟΘΩΡΑΚΙΟΥ

Αξιολόγηση Υπολειμματικών Μαζών και Ανταπόκρισης στη Θεραπεία

Επιβίωση Ελεύθερη Εξέλιξης Νόσου

Αναλόγως της Επακόλουθης Ακτινοβόλησης στους PET(-) ασθενείς



* 97% if 2 patients with isolated CNS relapses were censored, p=0.32

Vassilakopoulos TP et al. Leukemia, 30: 238-242, 2016

PET/CT after R-MACOP-B in PMLBCL

Επιβίωση Ελεύθερη Εξέλιξης Νόσου Αναλόγως του PET μετά από R-M(V)ACOP-B (ή R-CHOP)

Martelli M et al.

J Clin Oncol.

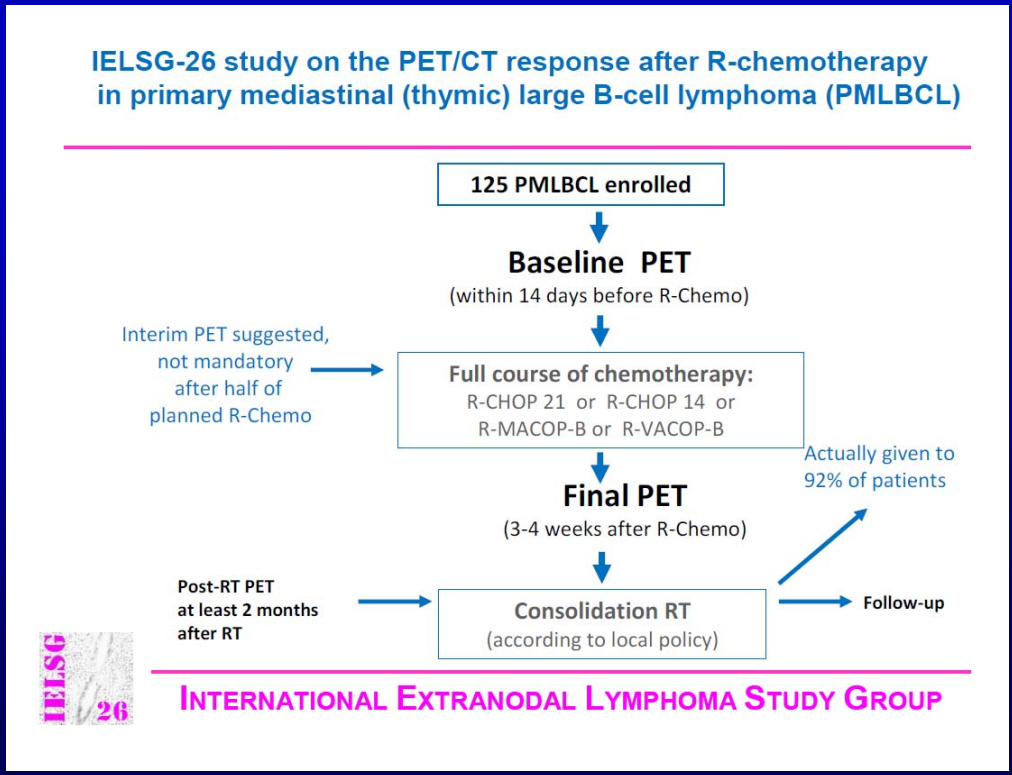
2014; 32: 1769-1775

Published Ahead of Print on May 5, 2014 as 10.1200/JCO.2013.51.7524
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.7524

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

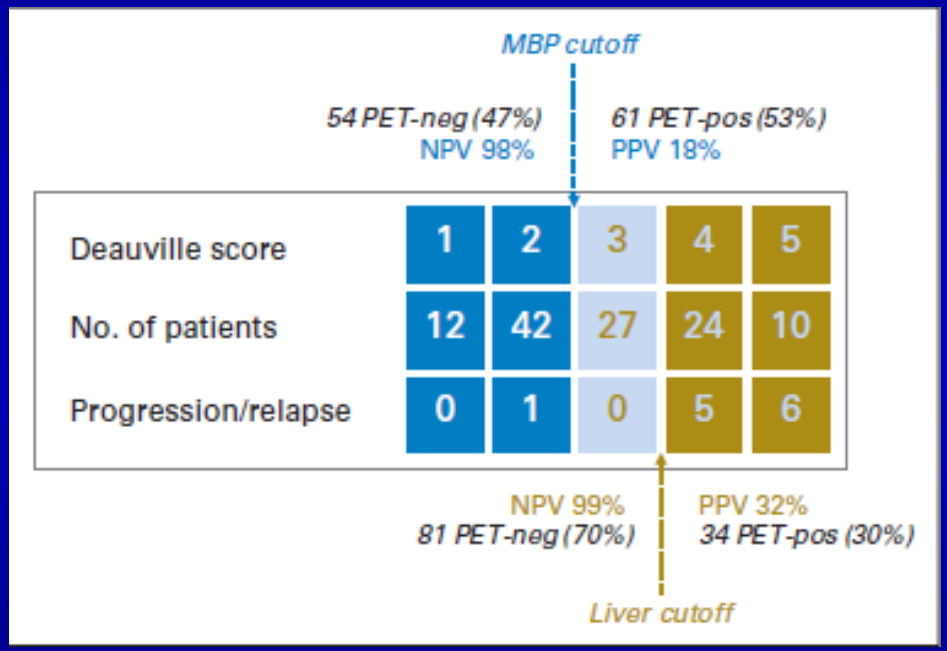
[^{18}F]Fluorodeoxyglucose Positron Emission Tomography Predicts Survival After Chemoimmunotherapy for Primary Mediastinal Large B-Cell Lymphoma: Results of the International Extranodal Lymphoma Study Group IELSG-26 Study

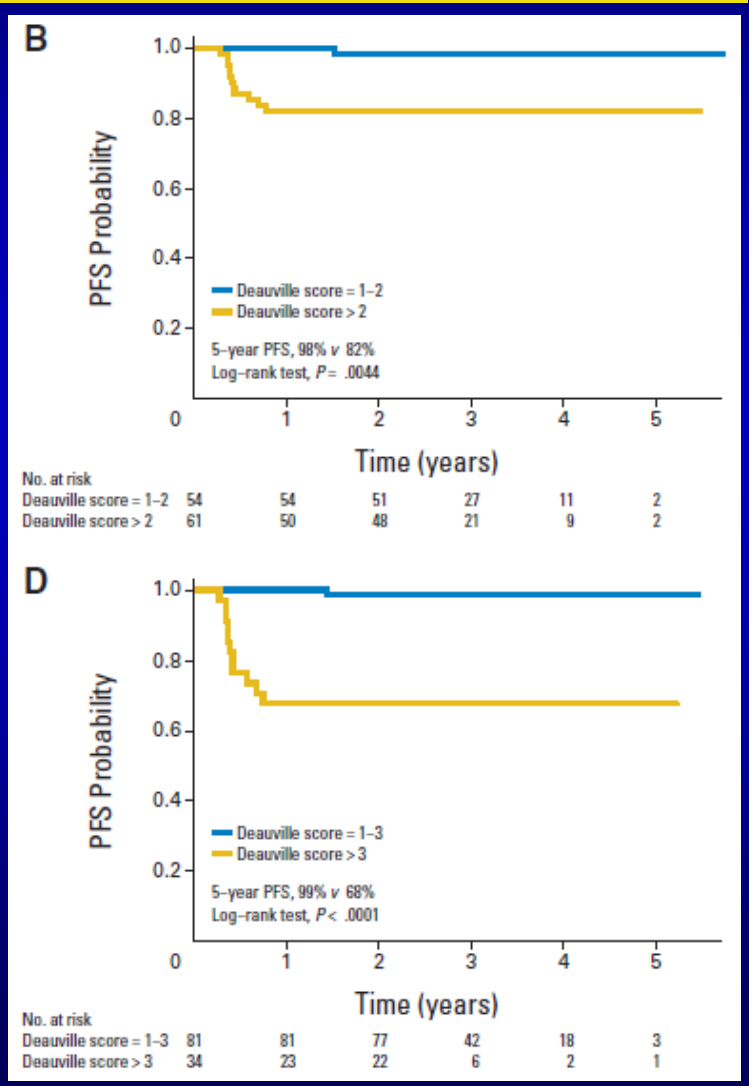
Maurizio Martelli, Luca Ceriani, Emanuele Zucca, Pier Luigi Zinzani, Andrés J.M. Ferreri, Umberto Vitolo, Caterina Stelitano, Ercole Brusamolino, Maria Giuseppina Cabras, Luigi Rigacci, Monica Balzarotti, Flavia Salvi, Silvia Montoto, Armando Lopez-Guillermo, Erica Finolezzi, Stefano A. Pileri, Andrew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



PET/CT after R-MACOP-B in PMLBCL

Επιβίωση Ελεύθερη Εξέλιξης Νόσου Αναλόγως του PET μετά από R-M(V)ACOP-B (ή R-CHOP)





Martelli Met al. J Clin Oncol. 2014; 32: 1769-1775

PET/CT after R-DA-EPOCH in PMLBCL

Significance of PET/CT Findings – no RT given

Table 2. FDG-PET-CT Findings after DA-EPOCH-R Therapy in the Prospective NCI Cohort.*

Lymphoma Status	Maximum Standardized Uptake Value				FDG-PET-CT Performance
	≤Value in Mediastinal Blood Pool (N=18)	>Value in Mediastinal Blood Pool (N=18)			
		total	value <5	value ≥5	
					percent
No disease (no. of patients)	18	15	12	3	
Disease recurrence (no. of patients)	0	3	0	3	
Sensitivity					100
Specificity					54
Positive predictive value					17
Negative predictive value					100

* Shown are values for 36 patients with residual mediastinal masses in the prospective NCI study after treatment. The maximum standardized uptake value is the amount of ^{18}F-fluorodeoxyglucose that is taken up by tumor tissue as seen on positron-emission tomography–computed tomography (FDG-PET-CT). Mediastinal blood pool activity was defined as the maximum standardized uptake value over the great vessels and ranged from 1.5 to 2.5 in the study population. A maximum standardized uptake value that is lower than the value in the mediastinal blood pool typically indicates the likelihood of no disease, and a value that is higher typically indicates the likelihood of disease. The three patients who were found to have actual residual disease had maximum standardized uptake values of 5.9, 10.2, and 14.5.

Dunleavy K et al. N Engl J Med. 2013; 368: 1408-1416

PET/CT after R-DA-EPOCH in PMLBCL

Significance of PET/CT Findings – no RT given

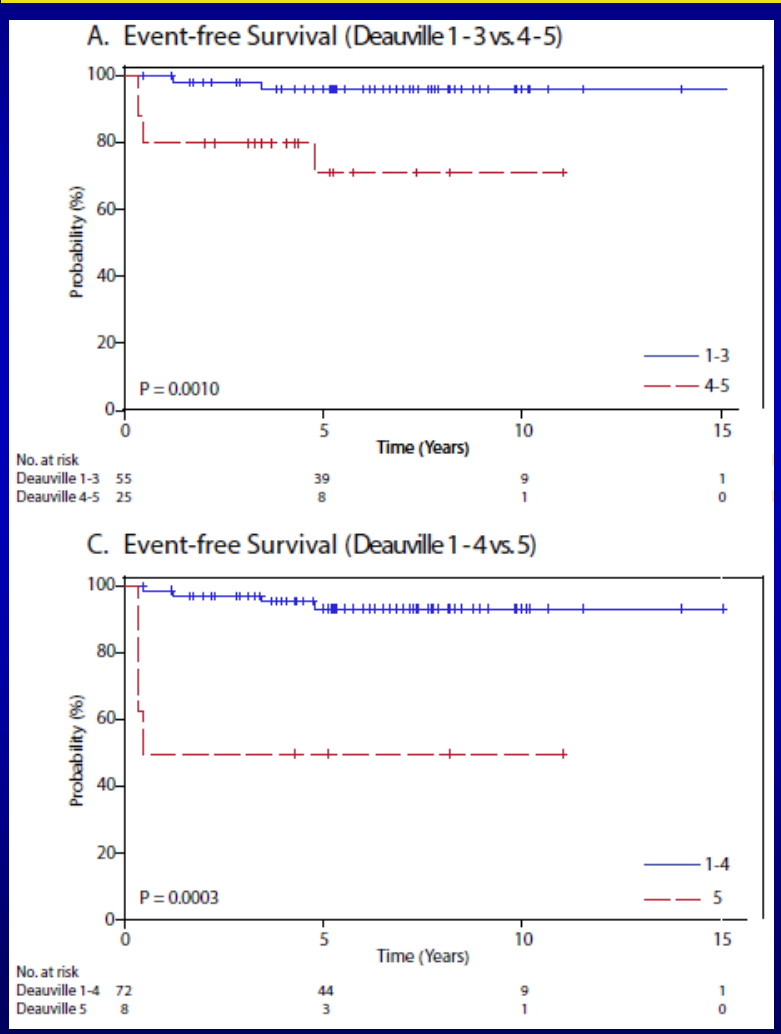


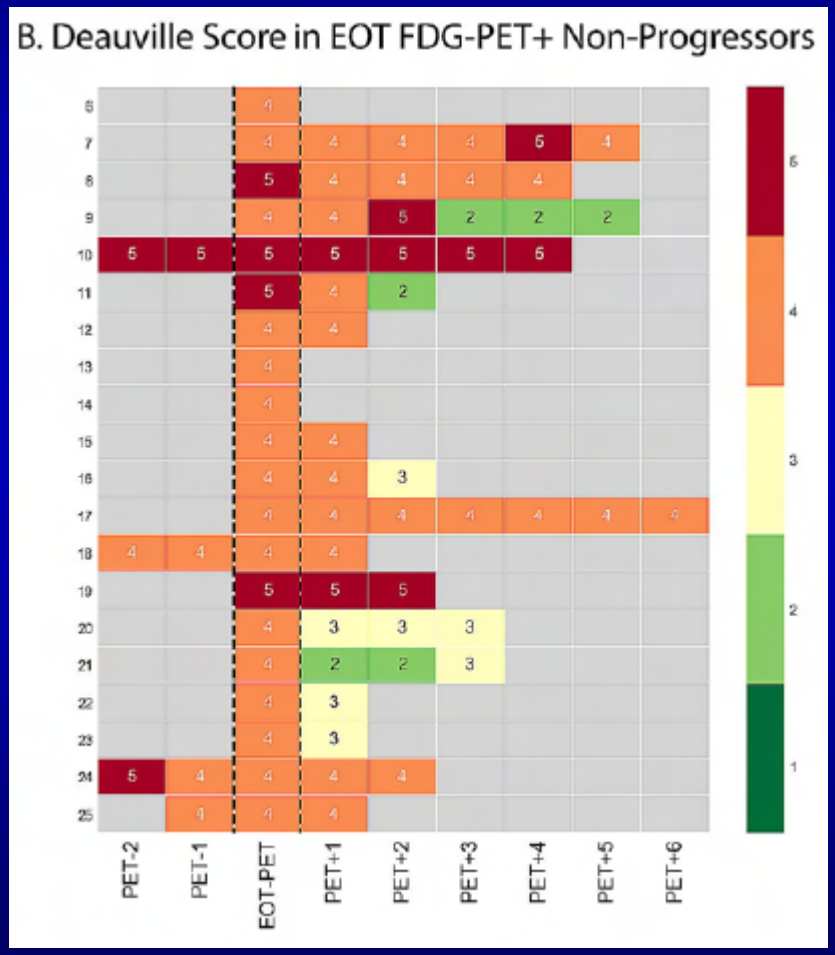
Table 2. EOT FDG-PET Response Following DA-EPOCH-R Therapy

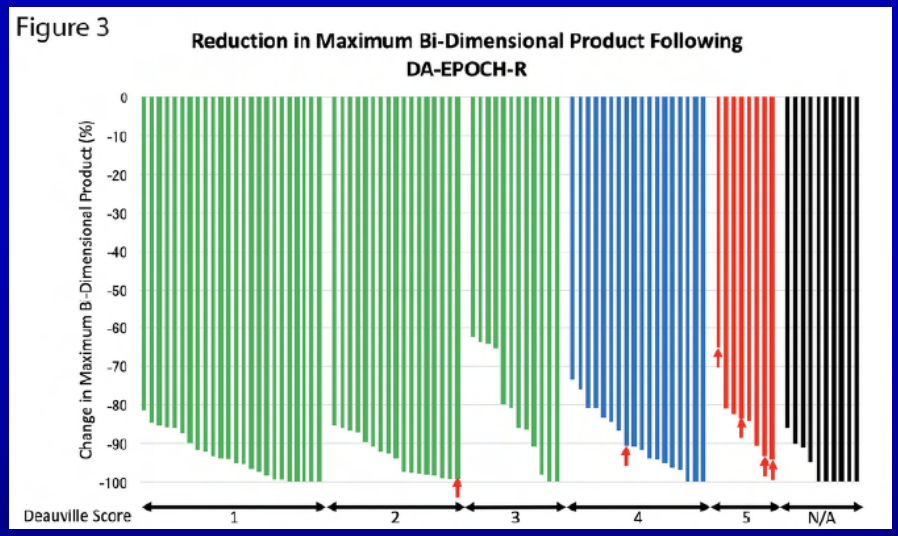
Lymphoma Status	Deauville Score				
(N=80 total with EOT FDG-PET)	Negative (55/80, 69%)			Positive (25/80, 31%)	
	1 (30%)	2 (24%)	3 (15%)	4 (21%)	5 (10%)
No treatment failure- no. patients	24*	18	12	16*	4
Treatment failure- no. patients	0	1	0	1	4

Melani C et al. Haematologica/THJ. 2018; 103: 1337-1344

PET/CT after R-DA-EPOCH in PMLBCL

Serial PET findings without RT / Anatomic response and PET





Melani C et al. Haematologica/THJ. 2018; 103: 1337-1344

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Prognostic Factors

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Prognostic Factors

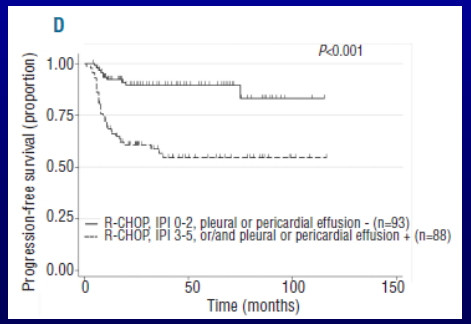
- Mainly studied in the pre-Rituximab era
- Age-adjusted IPI: Statistically significant in certain, but not all studies in the pre-Rituximab era. Problems:
  - Reproducibility of age-adjusted IPI
  - Heterogeneity in staging
  - Reproducibility of PS
- Paucity of studies of clinically relevant prognostic factor studies in the Rituximab era

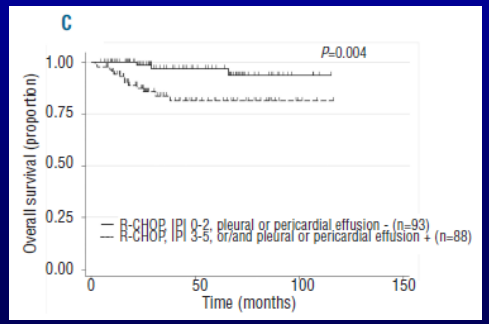
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Prognostic Factors in the Rituximab Era

Author	Reference	Patients (#)	aaIPI	Serous Effusions	B-symptoms	Age
Savage KJ, 2012	ASH 2012, abstract #303	96 R-CHOP±RT		●	●	●
Aoki T, 2014	Haematologica. 2014; 99: 1817-1825	123 (187)* R-CHOP without RT	●	●		

*** Selected among a broad series of patients, who had received various chemotherapy regimens at physician's discretion**





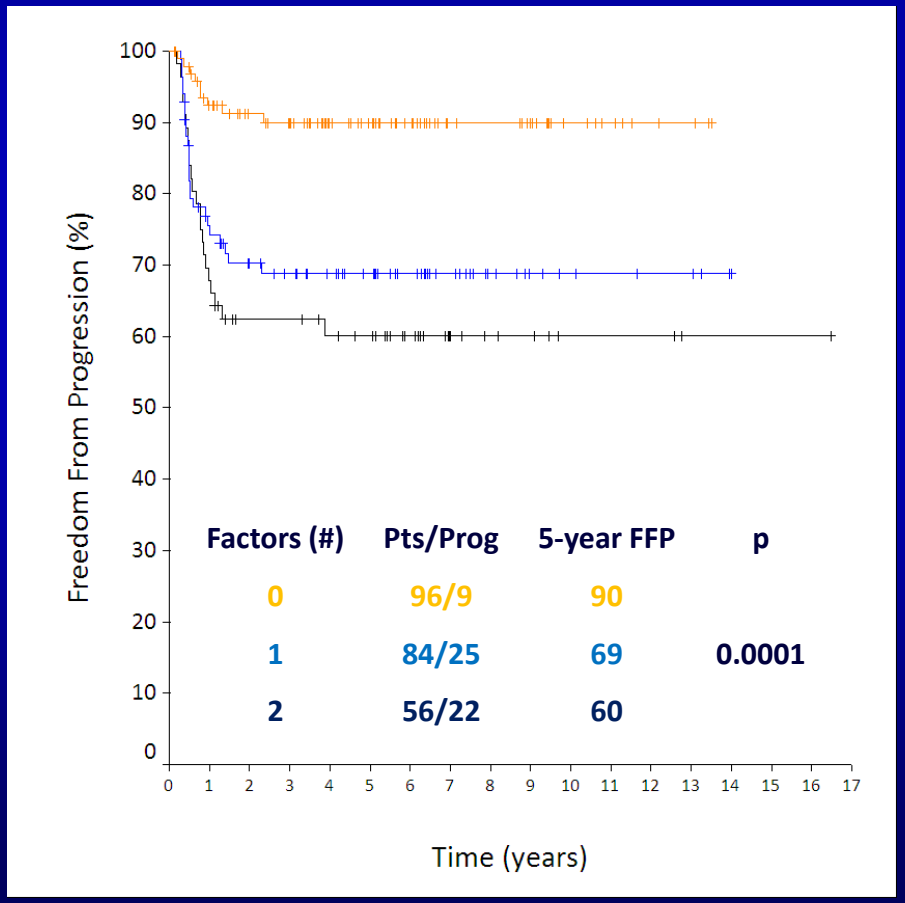
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Prognostic Factors under Rituximab-CHOP with or without Radiotherapy

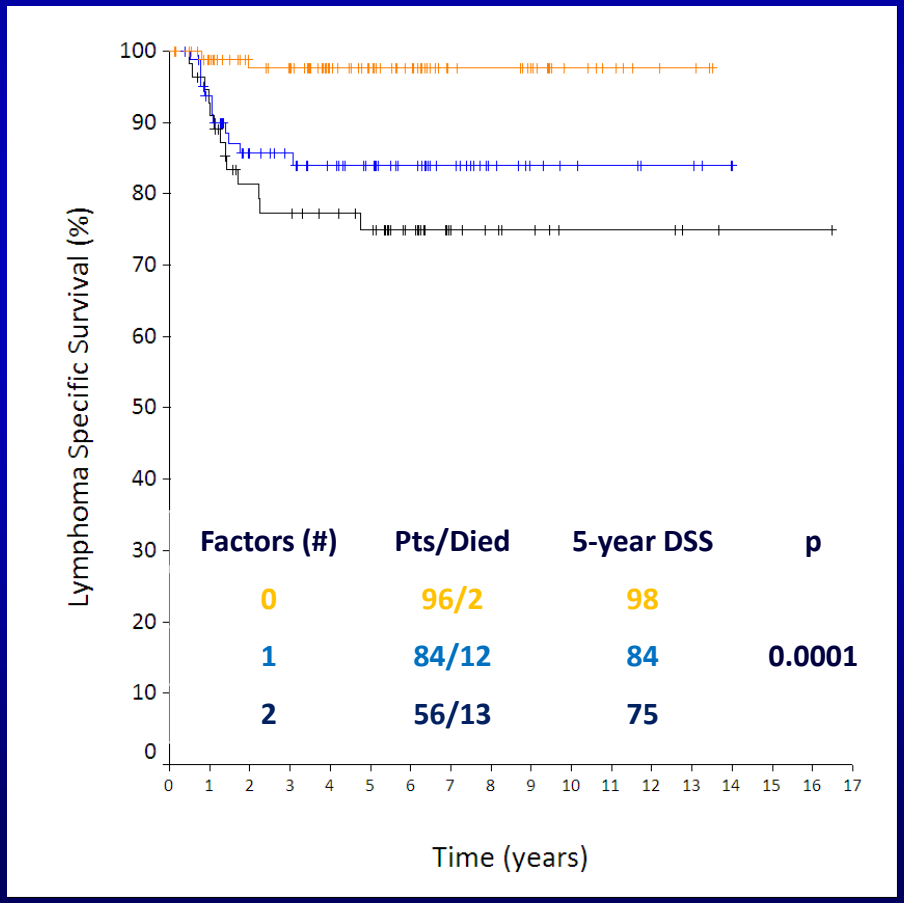
Prognostic Model

Risk Factors: (Stage IV or E) AND (any serositis) OR

(Stage IV or E) AND (LDH >2x)



Factors (#)	Pts/Prog	5-year FFP	p
0	96/9	90	
1	84/25	69	0.0001
2	56/22	60	



Factors (#)	Pts/Died	5-year DSS	p
0	96/2	98	
1	84/12	84	0.0001
2	56/13	75	

PET-Scan στο PMLBCL

Νέοι Προγνωστικοί Παράγοντες ;
Total Lesion Glycolysis (TLG)

Η συνολική γλυκολυτική δραστηριότητα των βλαβών (TLG) είχε προγνωστική αξία

σε 103 ασθενείς με PMLBCL της Μελέτης IELSG-26 μετά από R-M(V)ACOP-B (84%) ή R-CHOP (16%)

Parameter			ROC curve for PFS					ROC curve for OS				
	median	*Interquartile range*	*AUC (95% CI)*	*P value*	*Cut-off*	*Sensitivity (95% CI)*	*Specificity (95% CI)*	*AUC (95% CI)*	*P value*	*Cut-off*	*Sensitivity (95% CI)*	*Specificity (95% CI)*
SUVmax	18.8	15.5-23	.647 (.476 -.819)	.09	22.2	61.5% (31.6 - 86.1)	75.6% (65.4 – 84.0)	.711 (.488 -.935)	.06	22.2	83.3% (35.9 – 99.6)	74.2% (64.3 – 92.6)
MTV	406	267-641	.814 (.681 -.946)	.0001	703	69% (38.6 – 90.9)	87.8% (79.2 – 93.7)	.812 (.661 -.941)	.0001	490	100% (54.1 – 100)	60.8% (50.4 – 70.6)
TLG	4261	2363-6398	.867 (.746 – 1.0)	.0001	5814	92.1% (64.0 – 99.8)	77.7% (66.6 – 84.9)	.921 (.841 -1.0)	.0001	6031	100% (54.1 – 100)	74.2% (64.3 – 82.6)

SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CI, confidence interval.

	Parameter	HR	95% CI	P-value
Multivariate analysis of PFS				
Number of subjects=103				
Number of events=13				
	Bulky disease (< 10 cm vs ≥10 cm)	1.73	0.31-9.52	0.526
	MTV (increments of 10^2 ml)	1.03	0.80-1.33	0.812
	TLG (increments of 10^3)	1.36	1.16-1.58	<0.001

	Parameter	HR	95% CI	P-value
Multivariate analysis of OS				
Number of subjects=103				
Number of deaths=6				
	MTV (increments of 10^2 ml)	.96	0.66-1.40	0.833
	TLG (increments of 10^3)	1.49	1.18-1.89	0.001

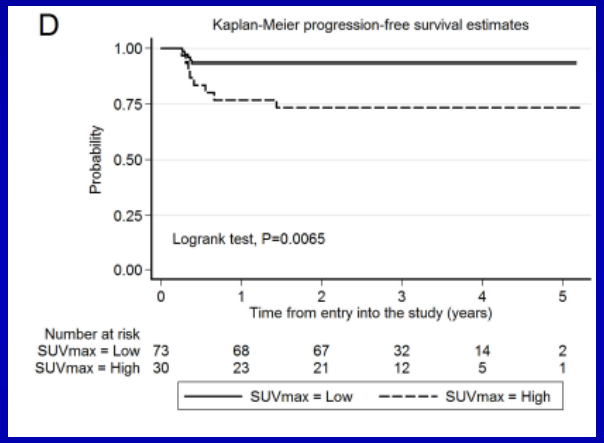
Ceriani L et al, Blood. 2015 (in press); doi: 10.1182/blood-2014-12-616474

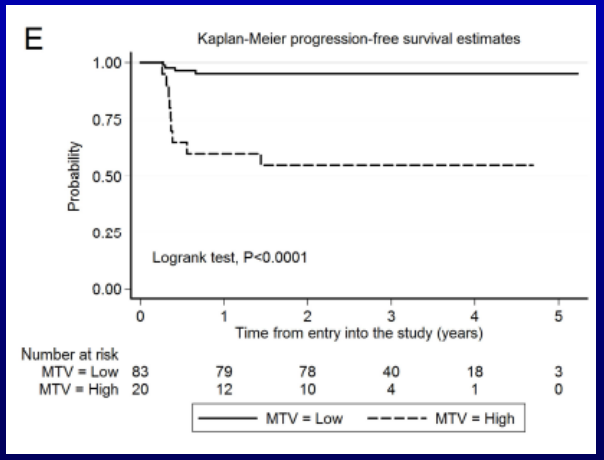
PET-Scan στο PMLBCL

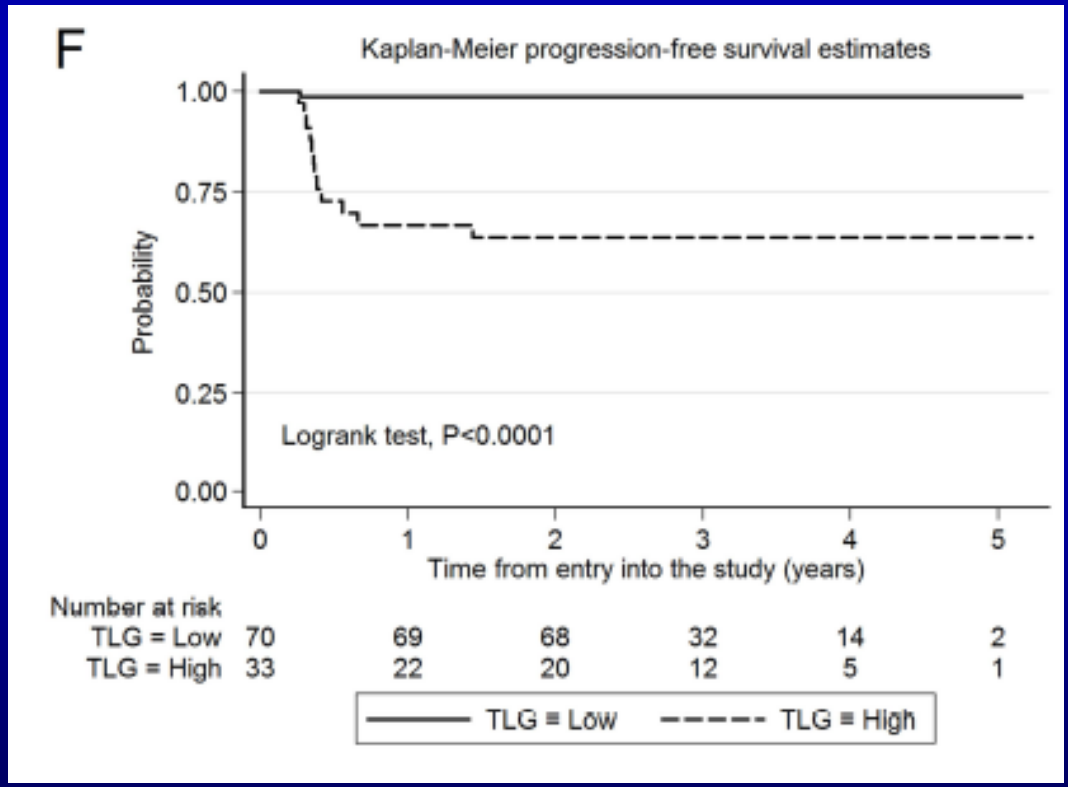
Νέοι Προγνωστικοί Παράγοντες ;
Total Lesion Glycolysis (TLG)

Η συνολική γλυκολυτική δραστηριότητα των βλαβών (TLG) είχε προγνωστική αξία

σε 103 ασθενείς με PMLBCL της Μελέτης IELSG-26 μετά από R-M(V)ACOP-B (84%) ή R-CHOP (16%)







Ceriani L et al, Blood. 2015 (in press); doi: 10.1182/blood-2014-12-616474

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Conclusions on Prognostic Factors – Future Perspectives

- The sizeable very low risk subgroup (absence of both factors) might not benefit from any treatment intensification, such as R-da-EPOCH (except probably from omission of RT)
- Need for more reproducible prognostic factors
  - Substitution of age-adjusted IPI variables (stage, PS) by factors that can be measured more objectively
- Baseline PET parameters may provide important prognostic information but may not be available in many patients (emergency presentation)
- Biological prognostic factors have not been adequately studied – small size of biopsies and issues of reproducibility limit their value

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Prognostic Factors – Interim PET

- After R-C_{1000}HOP-14 x 4 (28 pts, subsequent Tx ICE x 3):
  - PET (-): 11 pts / 2 failures (18%)
  - PET (+): 17 pts / 3 failures (18%), *17/17 biopsies negative !!*
- After R-VACOP-B interim PET (16 pts):
  - PET (-): 8 pts / 3-year FFP 86%
  - PET (+): 8 pts / 3-year FFP 75%, p=0.48
- Conclusion: Under intensive chemotherapy, >50% of pts have a positive interim PET: *In marked contrast to excellent final treatment results*
- No studies regarding PET-2 under R-CHOP-21!!

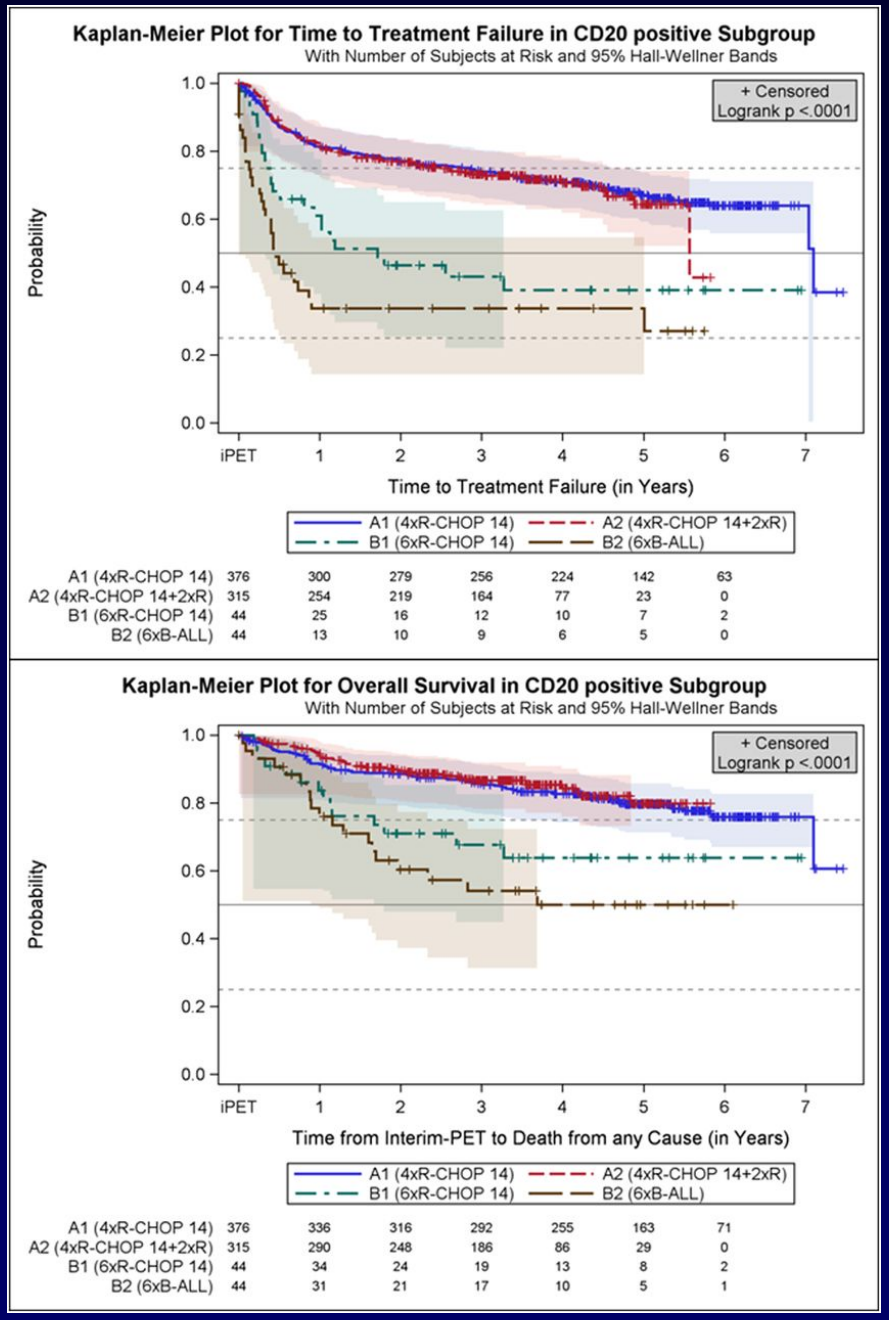
	CD20+ lymphomas	DLBCL	PMBCL	FL3
Total no. of pts.	779	606	42	42
Pts. with a favorable iPET	88.7 %	89.6 %	88.1 %	83.3 %
2-yr TTTF				
iPET favorable	77 %	76 %	89 %	91 %
iPET unfavorable	40 %[1]	41 %[1]	40 %[2]	43 %[3]
2-yr OS				
iPET favorable	89 %	88 %	97 %	100 %
iPET unfavorable	66 %[1]	57 %[1]	100 %	100 %

[1] p<0.0001; [2] p=0049; [3] p=0.0109 (compared to iPET favorable)

Positron Emission Tomography (PET) Guided Therapy of Aggressive Lymphomas - Interim PET-Based Outcome Prediction and Treatment Changes in Patients with B Cell Lymphomas Participating in the PETAL Trial

Duehrsen U et al

Blood. 2016; 128: 1857



PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
Conclusions I

- PMLBCL is a rapidly growing tumor with special demographic and clinicopathologic features

- R-CHOP-21 ± RT is the most commonly used treatment approach. In comparison to CHOP-21 + RT:
  - Greatly reduces the incidence of primary refractory disease (from 25% σε <10%)
  - Greatly reduces the rate of treatment failure (from 50% to <25%)
  - Reduces disease-related mortality to ~10-15%

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Conclusions II

- More intensive chemotherapy is not necessary in the majority of the patients in the Rituximab era. However,
  - may be needed in high-risk subgroups (which ??)
  - may obviate the need for RT; the major reason to use R-da-EPOCH
- Which patients will need RT after R-CHOP-21 ? Needs to be clarified
  - precise role of end-of-treatment PET to be accurately defined
- Reliable prognostic factors in the Rituximab era
  - highly desirable – but very difficult
  - clinical ? – PET? - biological ?
- Role of interim PET – at most questionnable

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Collaborators

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