Primary Mediastinal Lymphoma I-II-II Generation Regimens

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CANCER RESEARCH UK

Recurrent gene alterations in PMBL

Gene	Pathway/function	Frequency %
Copy number gain		
REL	NF-κB pathway	75
PDL1/PDL2	Induction of T-cell exhaustion/apoptosis	63
JAK2	IL/JAK-STAT pathway/histone modification	63
JMJD2C	Histone modification	63
Chromosomal translocation/rearrangement		
CIITA	Transcriptional regulation of HLA class II/antigen presentation	38
Coding sequence mutation		
SOCS1	IL/JAK-STAT pathway	45
STAT6	IL/JAK-STAT pathway	36
TNFAIP3	NF-κB pathway	36
MYC	Transcriptional regulation/chromatin remodeling	25
TP53	p53 pathway	13
Promoter hypermethylation		
p16/INK	Cell-cycle progression, p53 pathway	9

Steidl C , Gascoyne R D Blood 2011;118:2659-2669

Management

- Almost all cures will come from initial therapy: we need to be certain we are doing it right
- Outcomes following recurrence are poor
- Third generation CHOP like schedules appear superior to CHOP
- The addition of rituximab enhances activity of chemotherapy
- Impressive results with DA-EPOCH-R without IFRT (small series uncontrolled)

ESMO Guideline..2010

‘Primary mediastinal large B-cell lymphoma (PMBL) is probably a distinct entity. R-CHOP 21 is not established as the definitive treatment option and radiotherapy remains controversial.’

H. Tilly, M. Dreyling and On behalf of the ESMO Guidelines Working Group. Ann Oncol (2010) 21 (suppl 5): v172-v174.

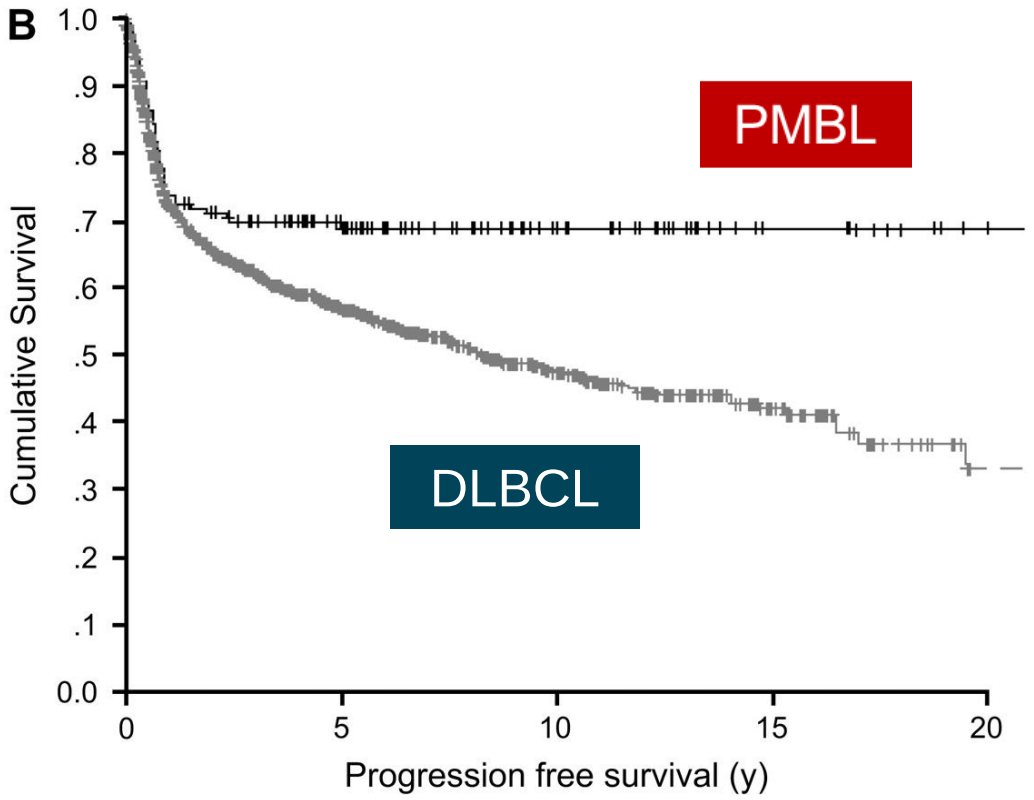
ESMO PMBL Guidelines..2016

Primary mediastinal lymphoma	Treatment	Consolidation	CNS Prophylaxis
	R-CHOP or R-V/MACOP-B or R-CHOP14 or DA-EPOCH-R	Mediastinal RT (30 Gy) in responding patients; RT could be omitted in CMR only after DA-EPOCH-R HDCT/ASCT is not recommended in CR1	: Not recommended

Esmo Guidelines. Vitolo et al. 2016

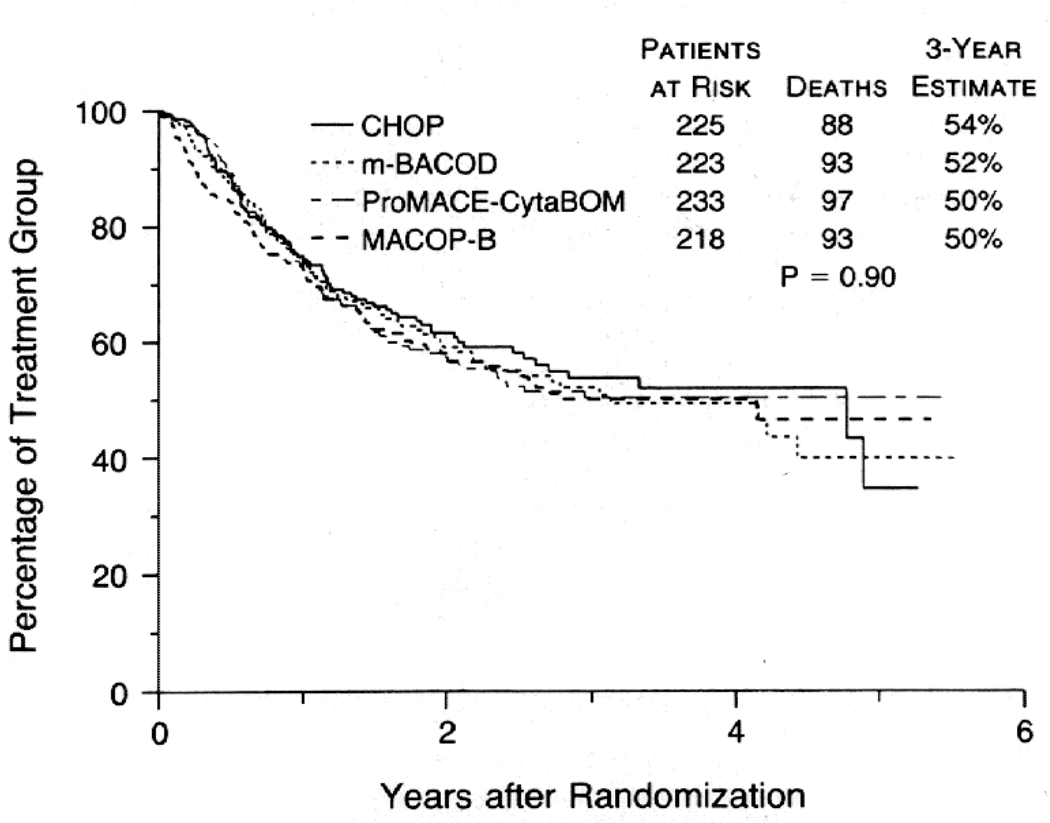
Outcomes superior to DLBCL

Almost all recurrences within first 12-18 months



Savage, K. J. et al. Ann Oncol 2006 17:123-130

Therapy…evolution of regimens



Fisher et al 1993

No difference in SWOG study for aggressive lymphomas

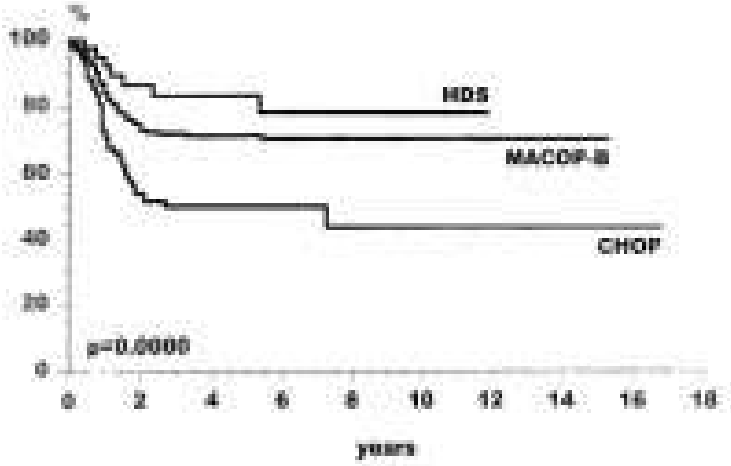
These results may mask underlying differences for PMBL as not recognised as distinct entity

But…More intensive chemotherapy may be superior in PMBL

Zinzani et al 2002

Multinational retrospective (n=426), three different chemotherapeutic approaches

10yr OS	CHOP	44%
	3rd Generation	71%
	high-dose77%	

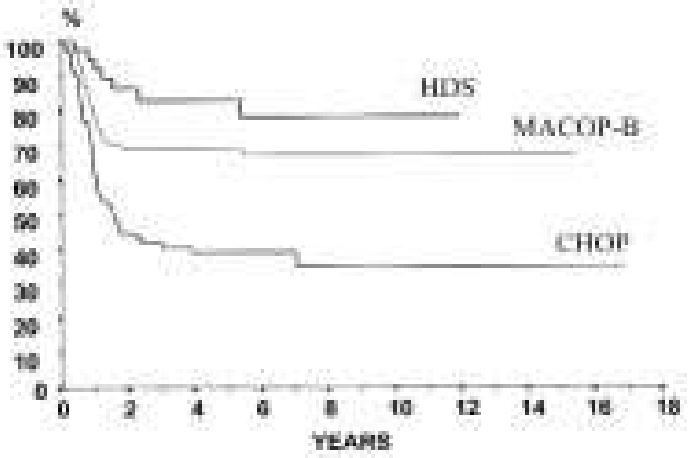


Overall survival with three different chemotherapeutic approaches

Todeschini *et al* 2004

Italian multicentre retrospective (n=138)

CHOP (n=43)	CR 51%
MACOP-B (n=95)	CR 80%



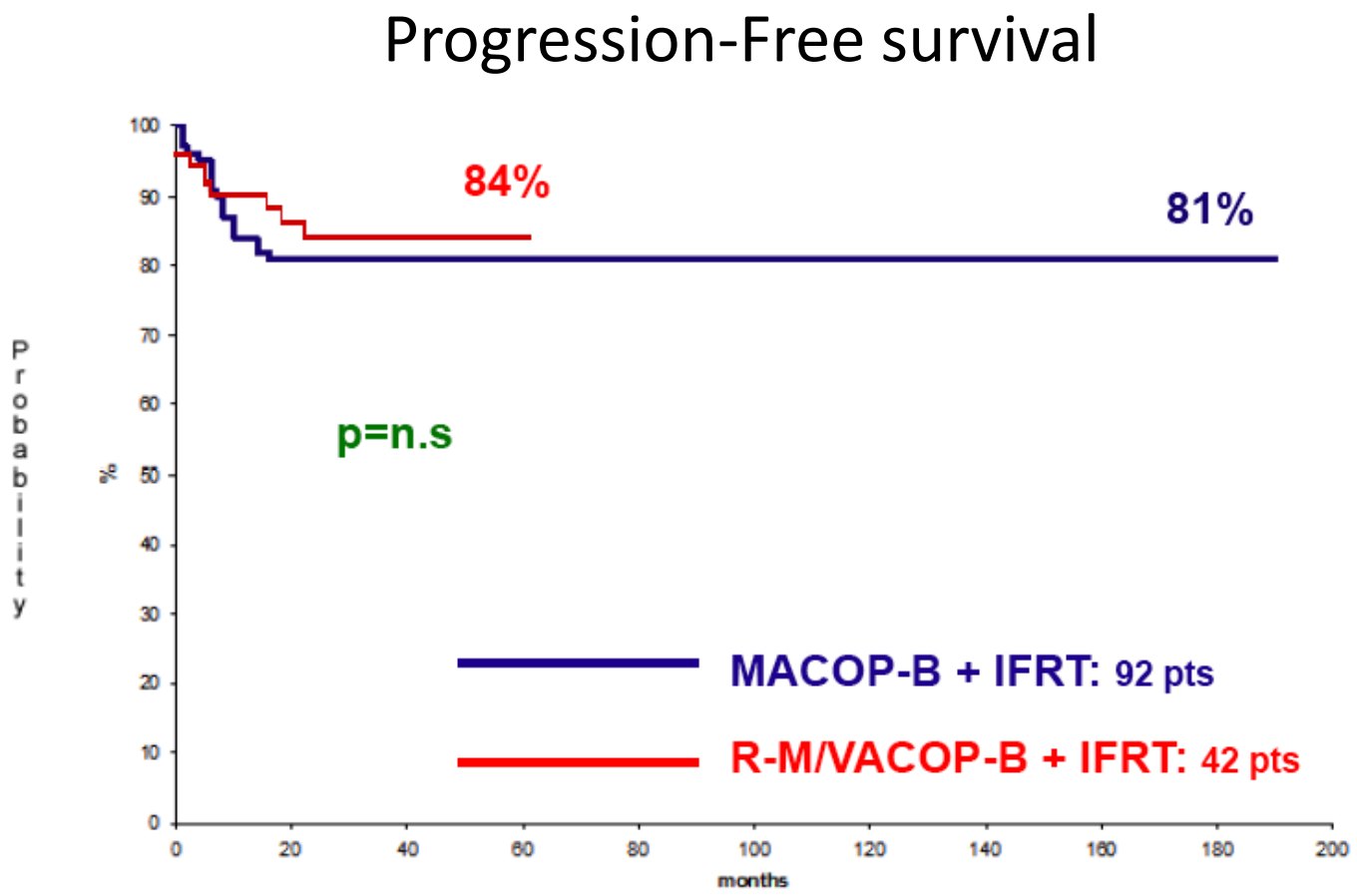
Progression free survival with three different chemotherapeutic approaches

Zinzani et al 2002

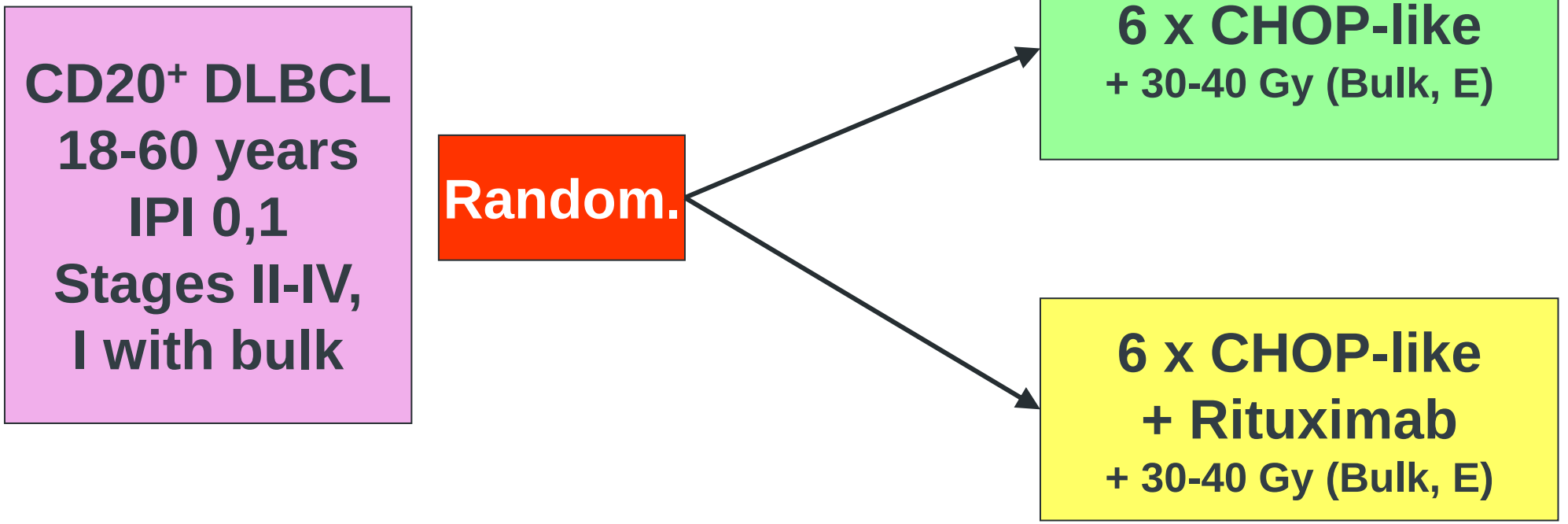
What is the role of rituximab?

Italian Series comparing weekly +/- Rituximab

De Sanctis et al. Int J Radiation Oncology Biology Physics 2008; 72:1154-60
Martelli et al. Ann Oncol. 2008 Jun;19 Suppl 4



MInT

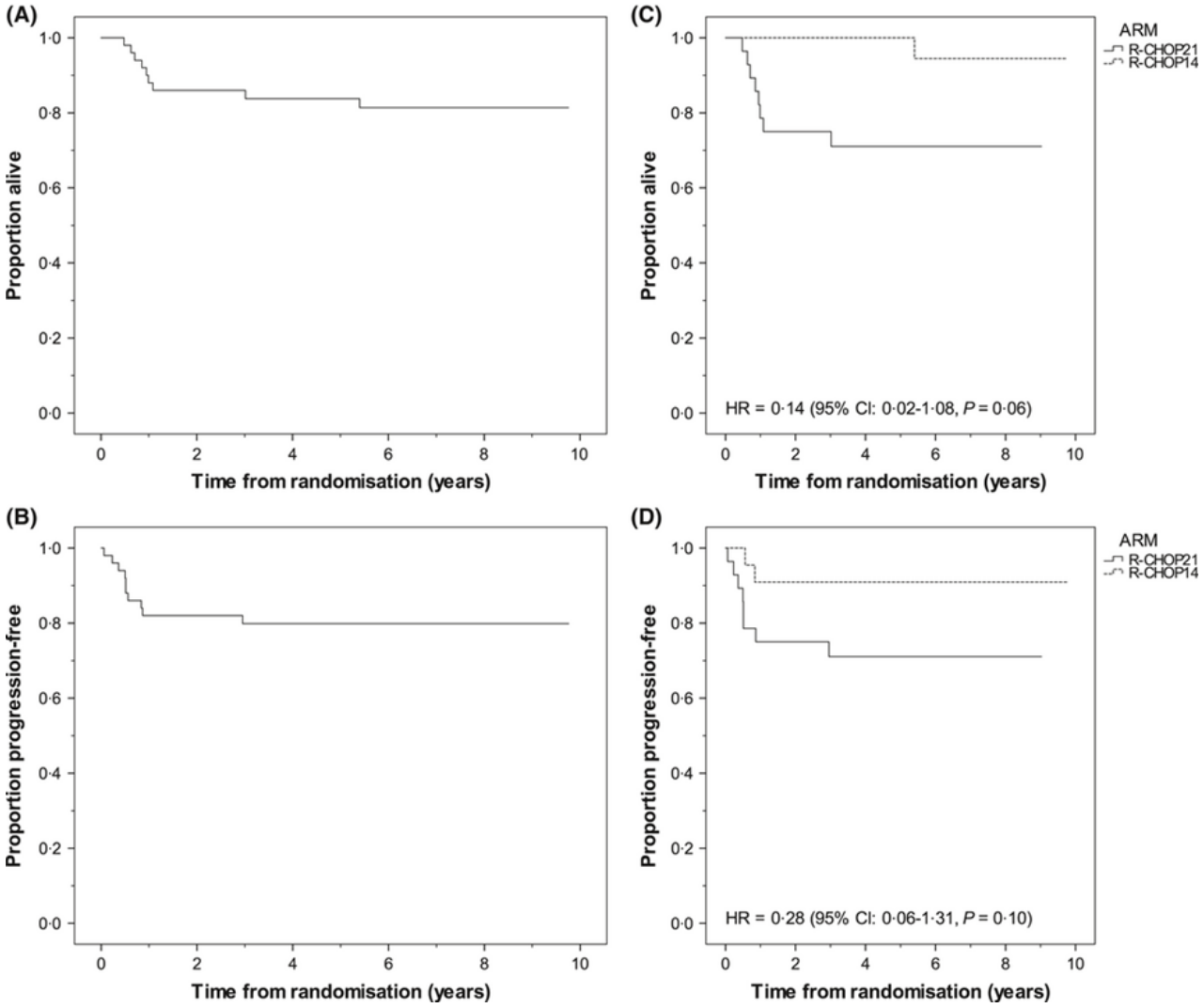


Rieger M et al. Ann Oncol 2011;22:664-670

R-CHOP 14/21: PMBL sub-group analysis

Subgroup analysis of R-CHOP 14-21
n=50

- R-CHOP is very effective
- Observation that less events in R-CHOP-14 : biology?
- Mutli-centre and older population
- Results lie in 95% CI of DA-EPOCH-R
- RT in 58%



Gleeson et al. BJH 2016

Table 2
Summary of the published experience with primary mediastinal B-cell lymphoma patients with chemoimmunotherapy combinations

Author, Year	Treatment	Patients	CR, %	PFS or RFS, %
Savage et al,[7] 2006	R-CHOP ± RT	18	n.r.	82 (60 mo)[a]
Zinzani et al,[27] 2009	R-M(V)ACOP-B	45	80	88 (60 mo)
Moskowitz et al,[40] 2010	R-CHOP/ICE	54	n.r.	78 (36 mo)
Rieger et al,[24] 2011	R-CHOP	44	52	78 (78 mo)
Vassilakopoulos et al,[25] 2012	CHOP ± RT	45	n.r.	47 (60 mo)
	R-CHOP ± RT	76	n.r.	80 (60 mo)
Dunleavy et al,[29] 2013	DA-EPOCH-R	51	96	93 (60 mo)
Soumerai et al,[26] 2014	R-CHOP	63	71	68 (60 mo)
Savage et al,[43] 2012	R-CHOP ± RT	59	—	—
	• R-CHOP[b]	33	n.r.	78% (60 mo)
	• R-CHOP + RT[c]	26	n.r.	83% (60 mo)
Zinzani et al,[44] 2015	R-MACOP-B ± RT	74	82	91 (113 mo)
	• R-MACOP-B[b]	23	100	90 (68 mo)
	• R-MACOP-B + RT[c]	51	75	91 (113 mo)
Martelli et al,[41] 2014	R-CHOP/M(V)ACOP-B ± RT	115	—	—
	• Negative PET[d]		100	98 (60 mo)
	• PET > Deauville 2		82	82 (60 mo)
	• PET > Deauville 3		68	68 (60 mo)

Zinzani and Brocoli 2016

Is consolidation radiotherapy required?

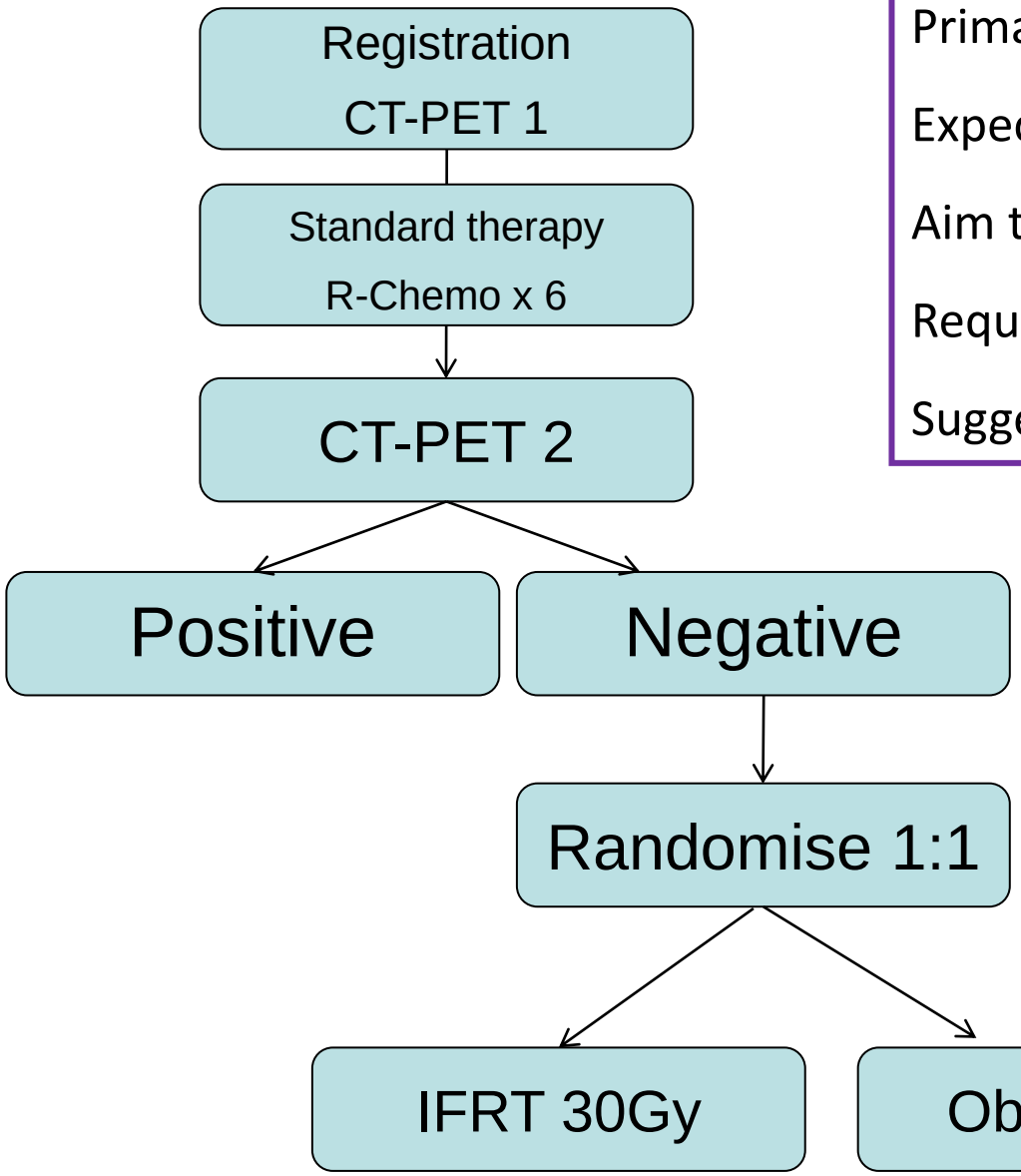
Radiotherapy may improve the quality of response

	CR after Chemo	PR to CR with RT	Global CR
First generation	49%	67%	61%
Third generation (*eg* MACOP-B)	51%	84%	79%
High-dose	53%	77%	75%
Overall	51%	81%	74%

Zinzani et al 2002

- The impact on cure rates is unclear, although several older series suggest that this is favourable
- Concerns regarding long term toxicity (cardiovascular and second malignancy)

The new IELSG 37 trial



Primary endpoint 3 yr PFS

Expected PFS 85%

Aim to exclude 10% reduction from omitting RT

Require 378 randomised for 80% power, p=0.05

Suggests 740 registered patients if 50% PET-ve

DAEPOCHR 50303:
Limited real life escalation

		R-CHOP	DA-EPOCH-R	P-value
Completed per protocol*		85.9%	79%	0.037
PD during treatment		2.7%	1.5%	0.361
Early discontinuation due to AE		1.5%	6.5%	0.004
Max DA-EPOCH-R Dose level				
1			28%	
2	20% ↑		20%	
3	44% ↑		23%	
4	73% ↑		17%	
5	107% ↑		9%	
6	149% ↑		2%	
7	200% ↑		<1%	

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Wilson et al. ASH 2016

50303 Grade 3-5 Toxicities

Event	R-CHOP	DA-EPOCH-R	P-value
Treatment related deaths*	2%	2%	0.975
ALL Gr 3-4	76.3%	96.5%	<0.001
Hematologic	73.1%	97.7%	<0.001
Non-Hematologic	41.3%	70.9%	<0.001
ANC	68%	96%	<0.001
Platelets	11%	65%	<0.001
Febrile neutropenia	17%	35%	<0.001
Infection	**11%**	**14%**	**0.169**
Mucositis	2%	6%	0.011
Neuropathy - sensory	2%	14%	<0.001
Neuropathy - motor	1%	8%	<0.001

* Treatment related deaths (10 total, 5 in each arm)

- R-CHOP – CHF (1), CNS bleed (1), infection (1), F/N (1), unknown (1)
- DA-EPOCH R – infection (2), MI (1), unknown (2)

Wilson et al. ASH 2016

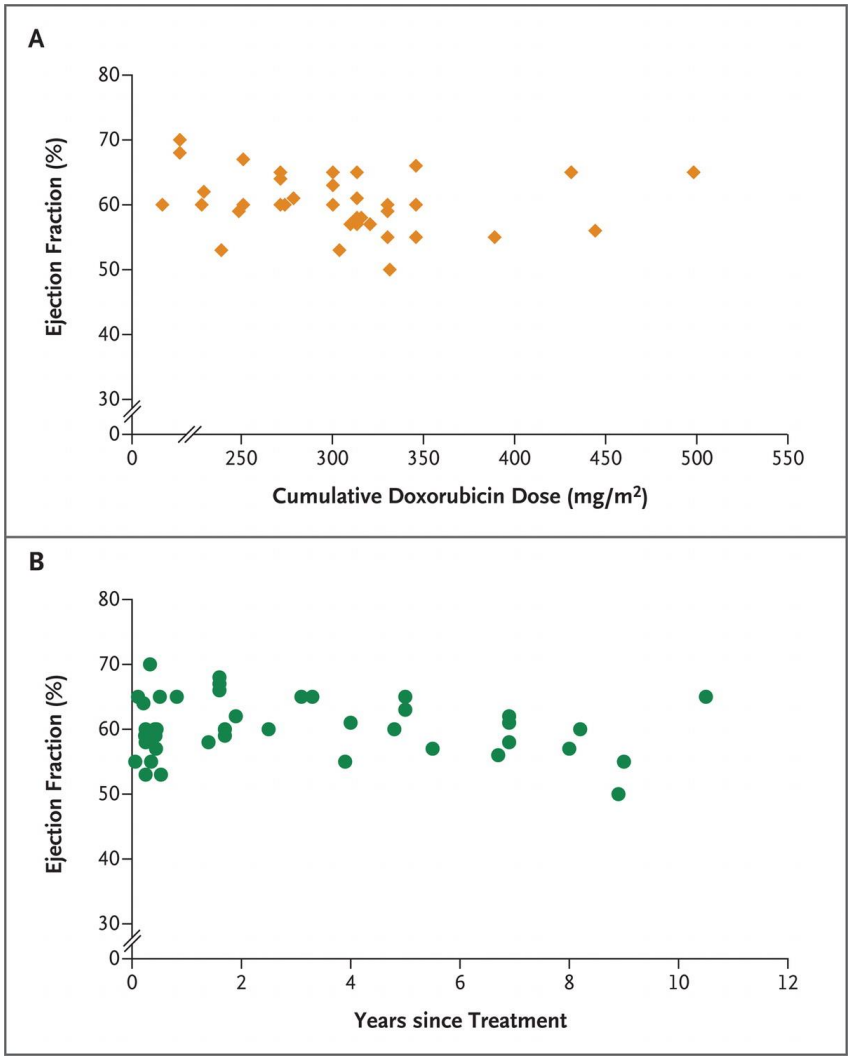
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Fertility

- Impact uncertain
- No doubt escalated cyclophosphamide dosing associated with impaired gonadal function
- From NCI cohort. Of 23 patients, 75% returned to mestruration with 6/20 pts having healthy deliveries. In 6 pts >40 yrs all premature menopause (Dunleavy Blood 2013; 122: 1779)

Cardiac function

- What is long-term impact of escalated doxorubicin dosing on cardiac function?



Dunleavy et al NEJM 2013

R-DA-EPOCH for PMBL

- How representative was the NIH data?
- Does it translate into the ‘real-world’?
- Can we be confident in their RT strategy?
- Is it actually any better than R-CHOP?

Patient Characteristics

Where they special 'NCI' patients or the usual Friday evening special?

Pretty representative

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Prospective NCI Cohort (N=51)	Retrospective Stanford Cohort (N=16)	P Value between Study Cohorts
Female sex — no. (%)	30 (59)	9 (56)	1.00
Age — yr			0.04
Median	30	33	
Range	19–52	23–68	
Bulky tumor, ≥10 cm			0.57
Patients — no. (%)	33 (65)	9 (56)	
Maximal diameter range — cm	5–18	7–18	
Stage IV disease — no. (%)	15 (29)	7 (44)	0.36
Elevated lactate dehydrogenase level — no. (%)	40 (78)	11 (69)	0.51
Extranodal site — no. (%)	27 (53)	3 (19)	0.02
Pleural effusion — no. (%)	24 (47)	10 (62)	0.39
CD20+ malignant cells — no. (%)	51 (100)	16 (100)	1.00
BCL6+ malignant cells — no. (%)	33/37 (89)	ND	ND

* BCL6 denotes the B-cell lymphoma 6 protein, NCI National Cancer Institute, and ND not done.

Dunleavy et al NEJM 2013

One shot: Difficult to rescue

(Kurivillla et al. 2008)

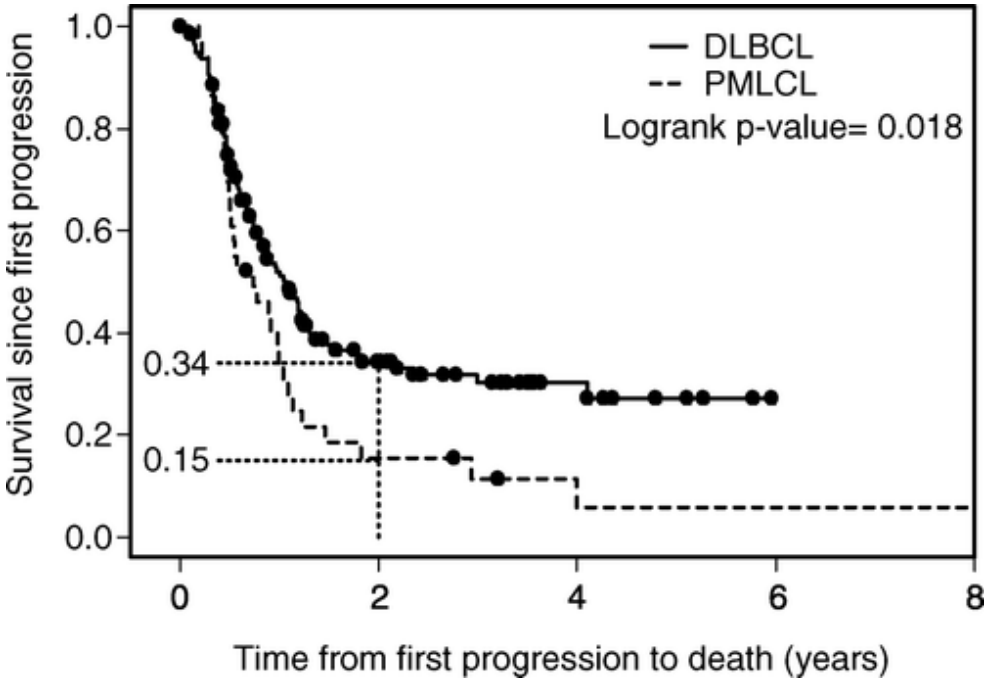
Retrospective of 37 PMBL patients and 143 DLBCL patients:

ORR to salvage

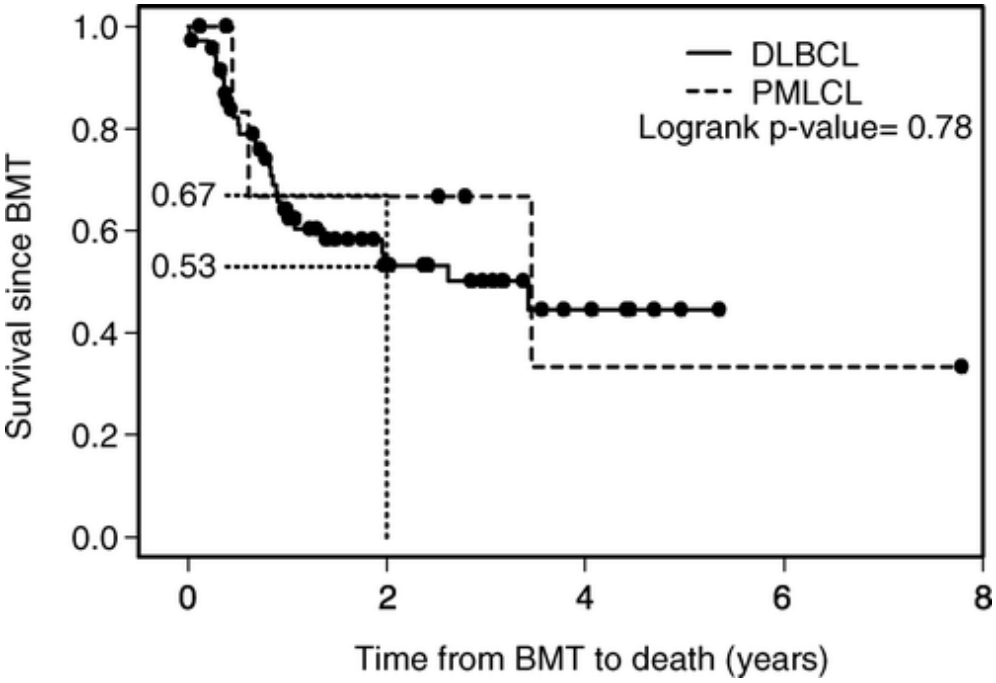
PMBL 25%

DLBCL 48%

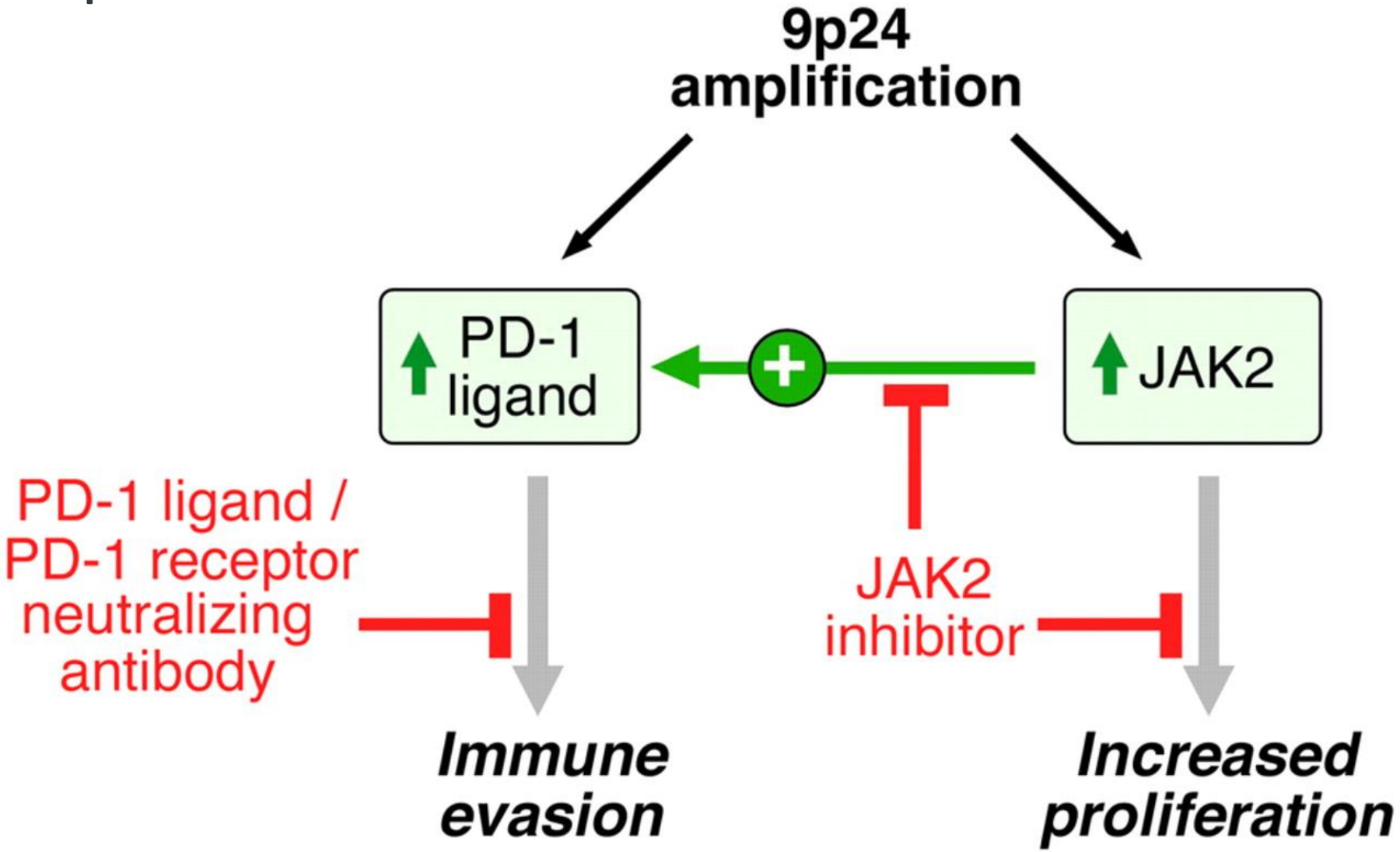
OS All Patients



OS from Auto



Consequences of 9p24 amplicon…..



Role for brentuximab?

Green M R et al. Blood 2010;116:3268-3277

Summary: PMBL

- Thymic post-GC B-cell malignancy
- Good prognosis (>80% survival) with
  - R-CHOP
  - R-MACOP-B
  - DA-EPOCH-R
- Role of radiotherapy still controversial:
  - Excellent results in series with RT
  - Excellent results in a few series without
- Randomised trials are difficult. New avenues exciting