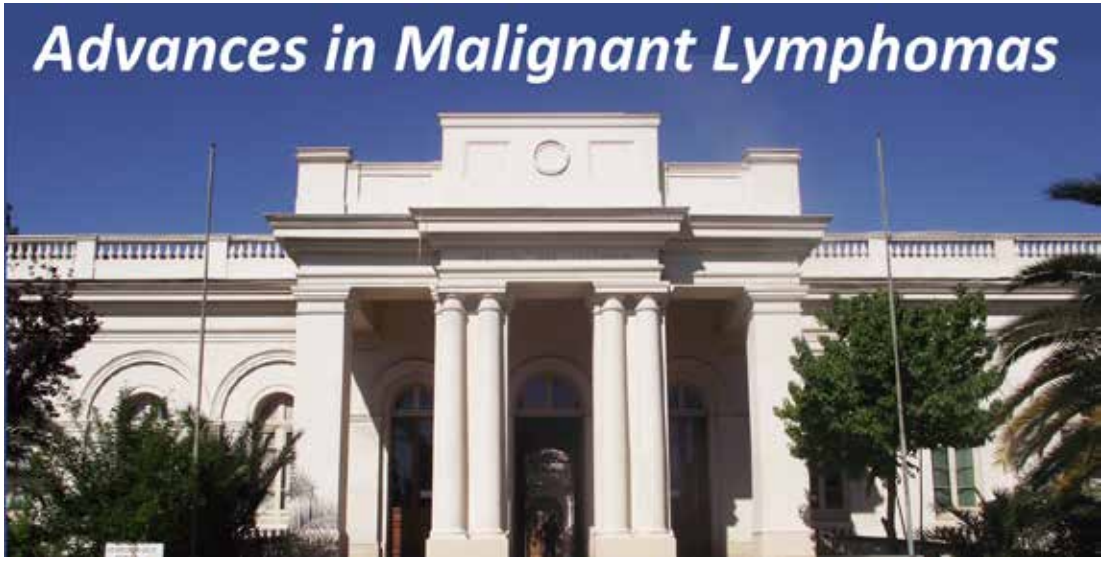


Hospital del Salvador
Santiago de Chile
April 5, 2016

Primary Testicular Lymphomas

Emanuele Zucca, M.D.
Bellinzona, Switzerland

ISTITUTO ONCOLOGICO DELLA SVIZZERA ITALIANA • ONCOLOGY INSTITUTE OF SOUTHERN SWITZERLAND
IELSG - INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP - www.ielsg.org

Talk overview

- Epidemiology, risk factors, and etiology
- Pathological and biological features
- Clinical features
- Prognostic factors and patterns of relapse
- Treatment and outcome

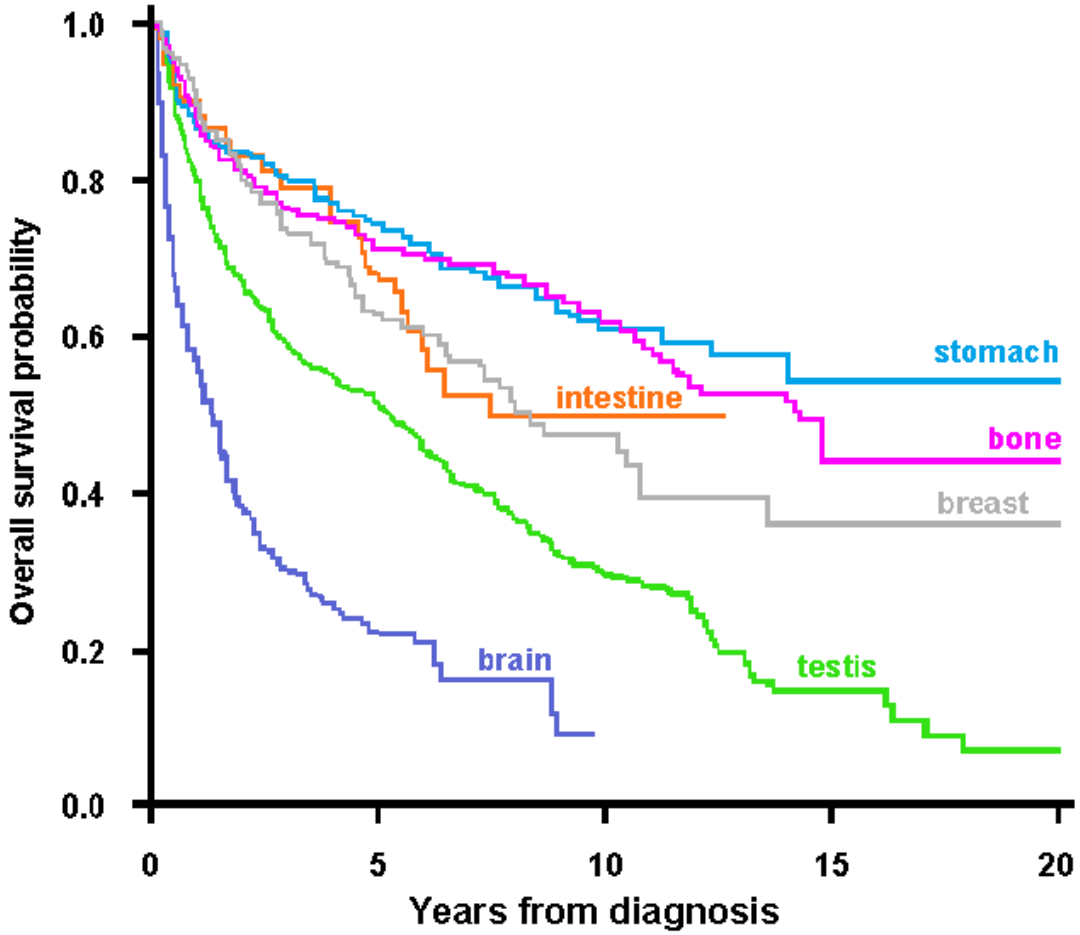
Epidemiology of primary testicular lymphoma

- incidence: 0.09 to 0.26 per100,000 person-year
- <5% of all testicular malignancies
- 1-2% of all non-Hodgkin's lymphoma
- most common testicular malignancy in men >60 years
- Most common bilateral testicular malignancy (up to 30%;)
- median age at presentation 66-68 years

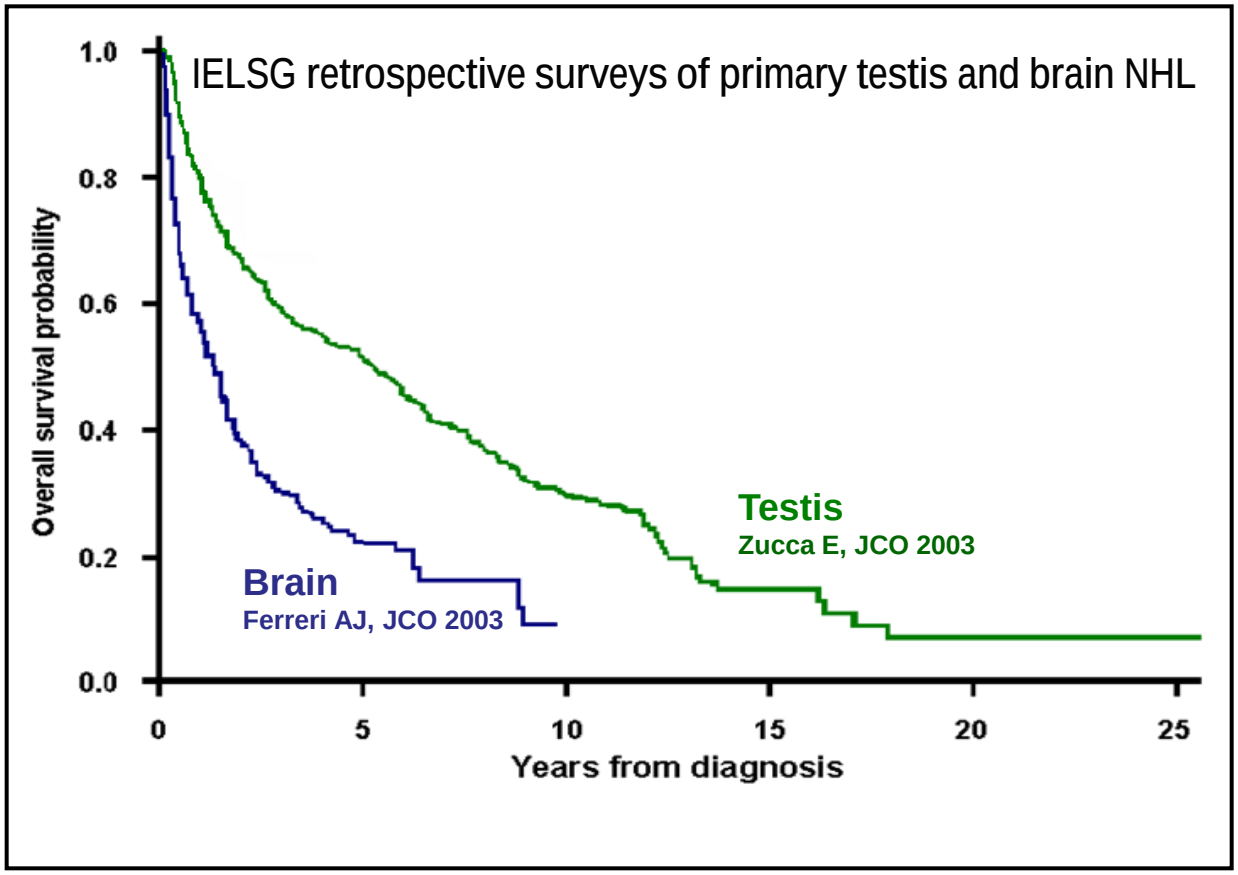
Cheah et al. Blood, 2014
Ahmad et al. Clin Oncol , 2012

Extranodal DLBCL survival by anatomic site

in the IELSG retrospective series of pre-rituximab era



DLBCL at immuno-privileged sites



Brain and testis DLBCL share many clinicopathological and biological features, suggesting that lymphomas arising at immuno-privileged sites may represent a separate entity

Booman M, *et al*. J Pathol 2008

Peculiar biological features of primary testis lymphoma

- Somatic hypermutation of IgH genes, T-cell infiltrate, plasmacytoid differentiation
  (Hyland et al, 1998)
  - à **antigen-driven stimulation?**
- Altered expression of adhesion molecules
  (Horstmann & Timens,1996)
  - à **easy dissemination?**
- Alterations (loss of expression) of HLA class I and II regions associated with downregulation of other immune regulatory genes perhaps also in tumor environment *(Riemersma et al, 2000; Jordanova et al, 2003, Booman et al, 2006)*
  - à **immune escape?**

Dissemination patterns of DLBCL at immuno-privileged sites: the dangerous liaisons between testis and the brain

- Most testis DLBCL relapses involve contralateral testis and/or CNS
  - 15% of testicular DLBCL relapse to the CNS *(Zucca, JCO 2003)*
- Pattern of recurrences in PCNSL *(Jahnke, J Neurooncol 2006)* :
  - isolated CNS, 85%
  - isolated testis relapses, 6%
  - isolated relapses at others sites, 6%
  - 10-20% of PCNSL relapse to eye
- Additional reports of PCNSL relapsing in the testis
  (Booman, Haematologica 2007; Silvani, J Neurooncol 2007)
- 15% of isolated CNS relapses had initial testis involvement
  (Doolittle, Blood 2008)

Hypothetical explanations for the growth and dissemination patterns of lymphoma arising at immuno-privileged sites

- immune sanctuary theory: balance between tolerant vs. cytotoxic immune response
- lymphoma cell survival possibly facilitated by:
  - ongoing modulation of idiotype
  - loss of HLA class II and I expression
  - additional acquired genetic alterations affecting immune modulation and apoptosis
- lymphocyte traffic and homing regulation mechanisms

Site-specific aberrations in CNS and testis DLBCL suggesting deregulation of apoptosis and immune response pathways

	CNS DLBCL ($n = 9$)	Testicular DLBCL ($n = 16$)	Nodal DLBCL ($n = 15$)	Significantly higher frequency in:	Candidate genes
Loss					
6p21.32–p25.2	5 (56%)	11 (69%)	2 (13%)	IP-DLBCL	
Gain					
2p16.1–p25.3	0 (0%)	0 (0%)	4 (27%)	Nodal DLBCL	*SUPT7L, BIRC6, BRE*
12q15–q21.1	5 (56%)	3 (19%)	2 (13%)	CNS DLBCL	*MDM2, YEATS4*
12q24.32–q24.33	5 (56%)	3 (19%)	2 (13%)	CNS DLBCL	—
19q13.12–q13.43	2 (22%)	11 (69%)	0 (0%)	Testicular DLBCl	*LILRA3, SPIB, BCL2L12, PAK4, PPP5C*

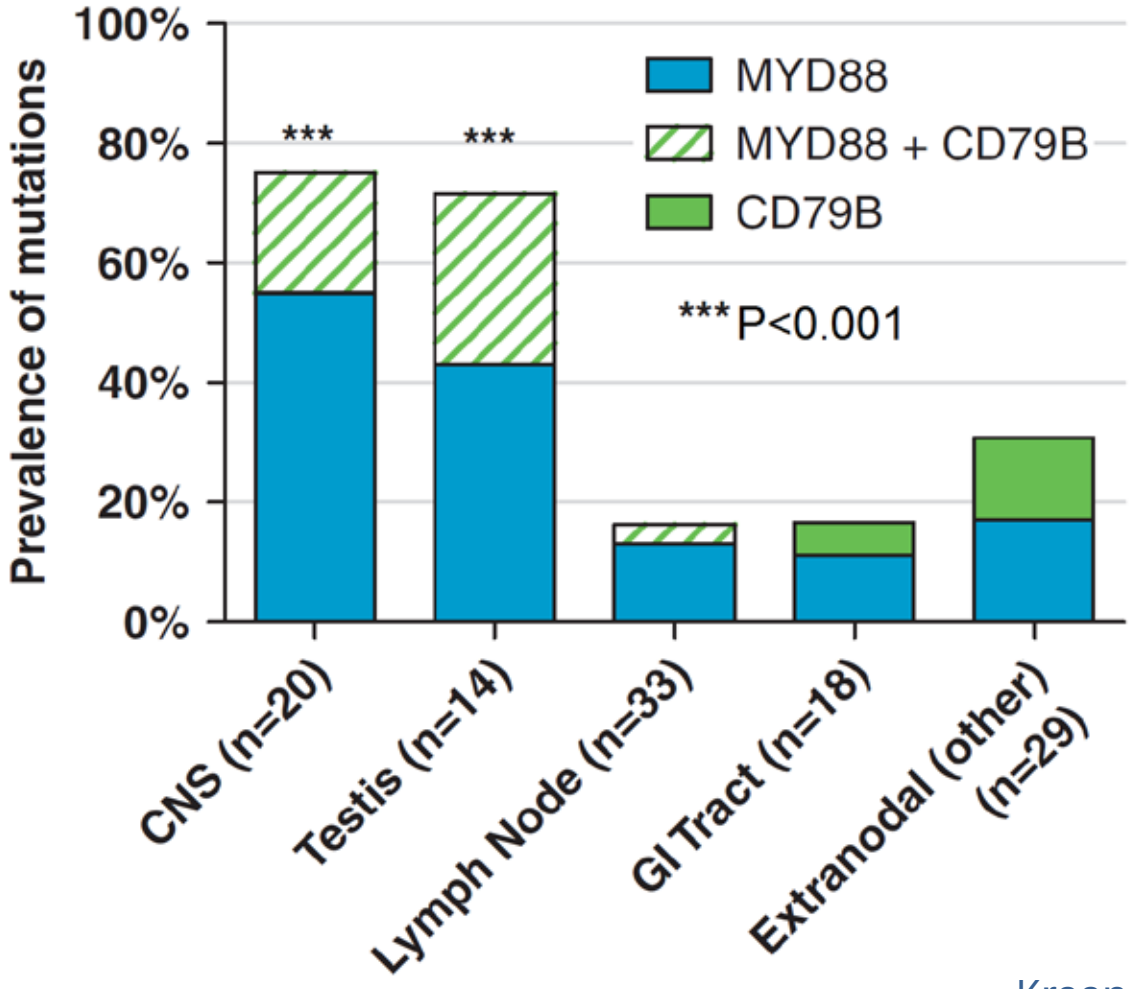
Loss of HLA class I and II (gene) expression associated with 6p21.3 deletions in 50% of IP-DLBCL

The presence of both common and site-specific alterations supports the concept of IP-DLBCL but also suggests that CNS and testis DLBCL are separate entities

Several candidate genes have a role in inhibition of apoptosis

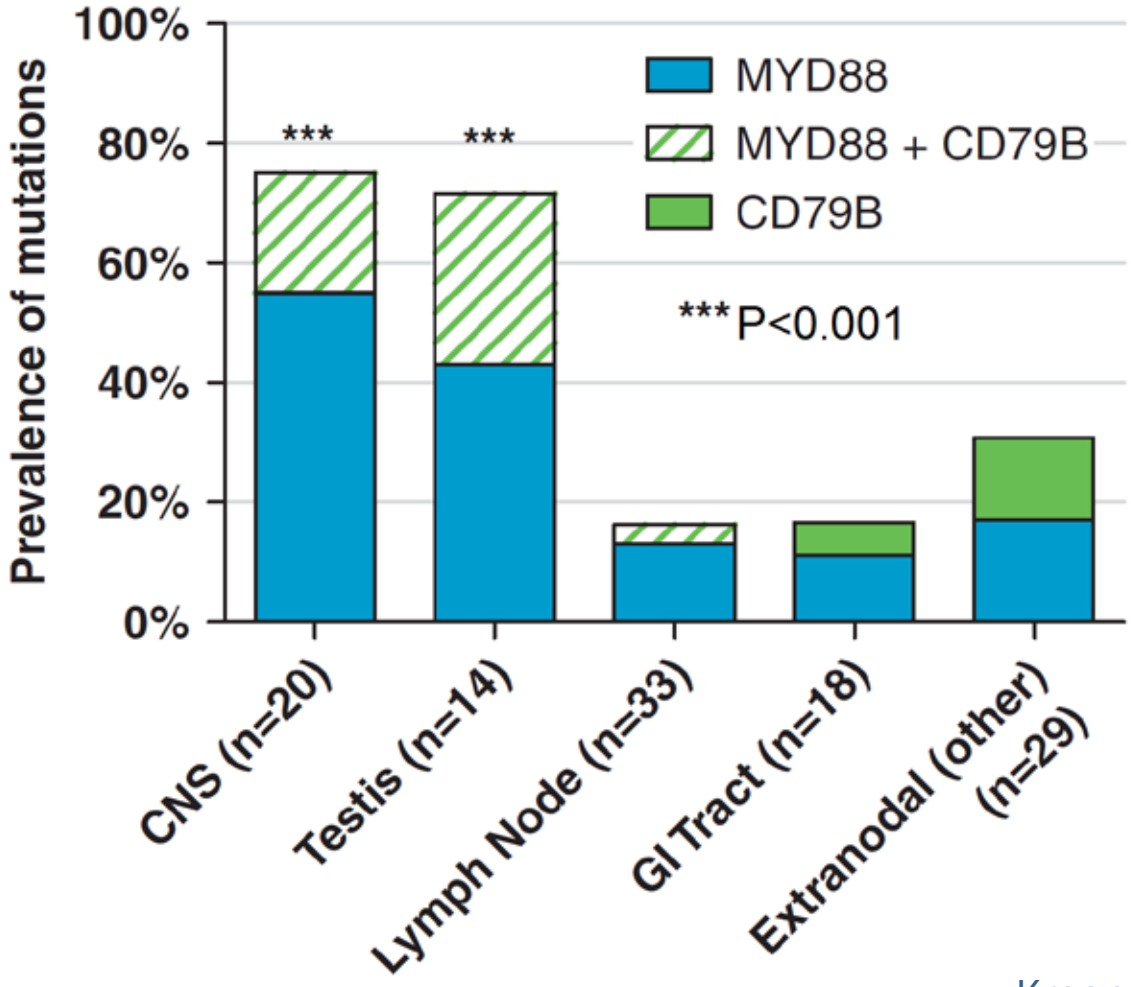
Booman M, et al. J Pathol 2008

Prevalence of mutations in MYD88 and CD79B in ABC DLBCL at different anatomical sites



Kraan et al. Blood Cancer J , 2013

Prevalence of mutations in MYD88 and CD79B in ABC DLBCL at different anatomical sites



Role for therapies targeting MYD88 signaling components?

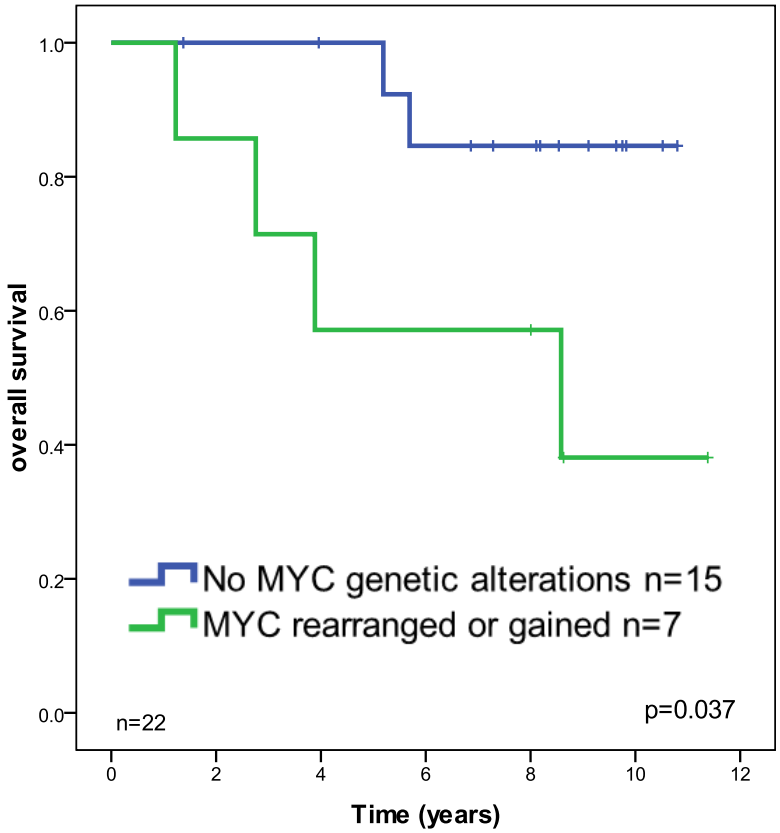
à IRAK kinase inhibitors, either alone or in combination with drugs blocking key mediators of BCR signaling such as BTK

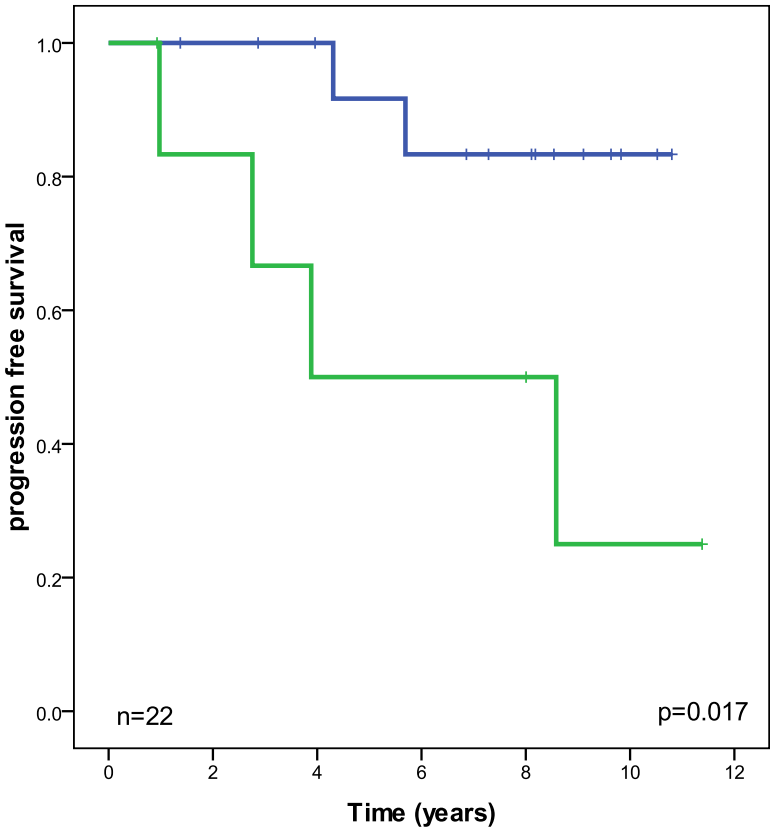
Kraan et al. Blood Cancer J , 2013

MYC genetic alterations link to worse prognosis

but not MYC expression nor MYD88L265P mutation

- MYD88^{L265P} correlates with an older age of the patients (p=0.009)
- *MYC* genetic alterations: the sole predictor of unfavorable outcome

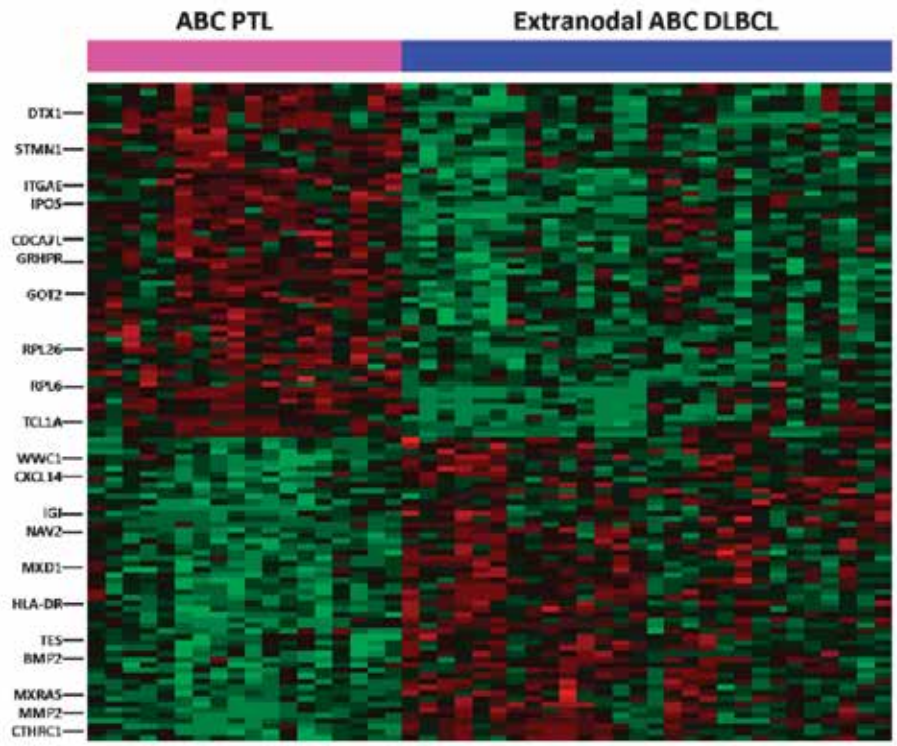


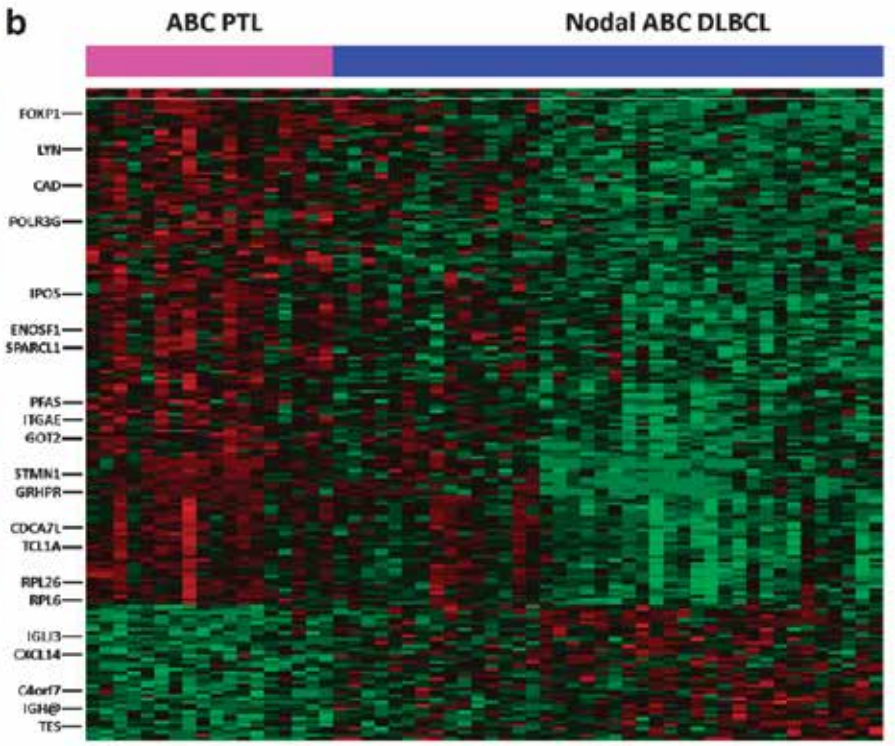


A Valera et al ICML 2015

Unique GEP in testicular ABC-DLBCL

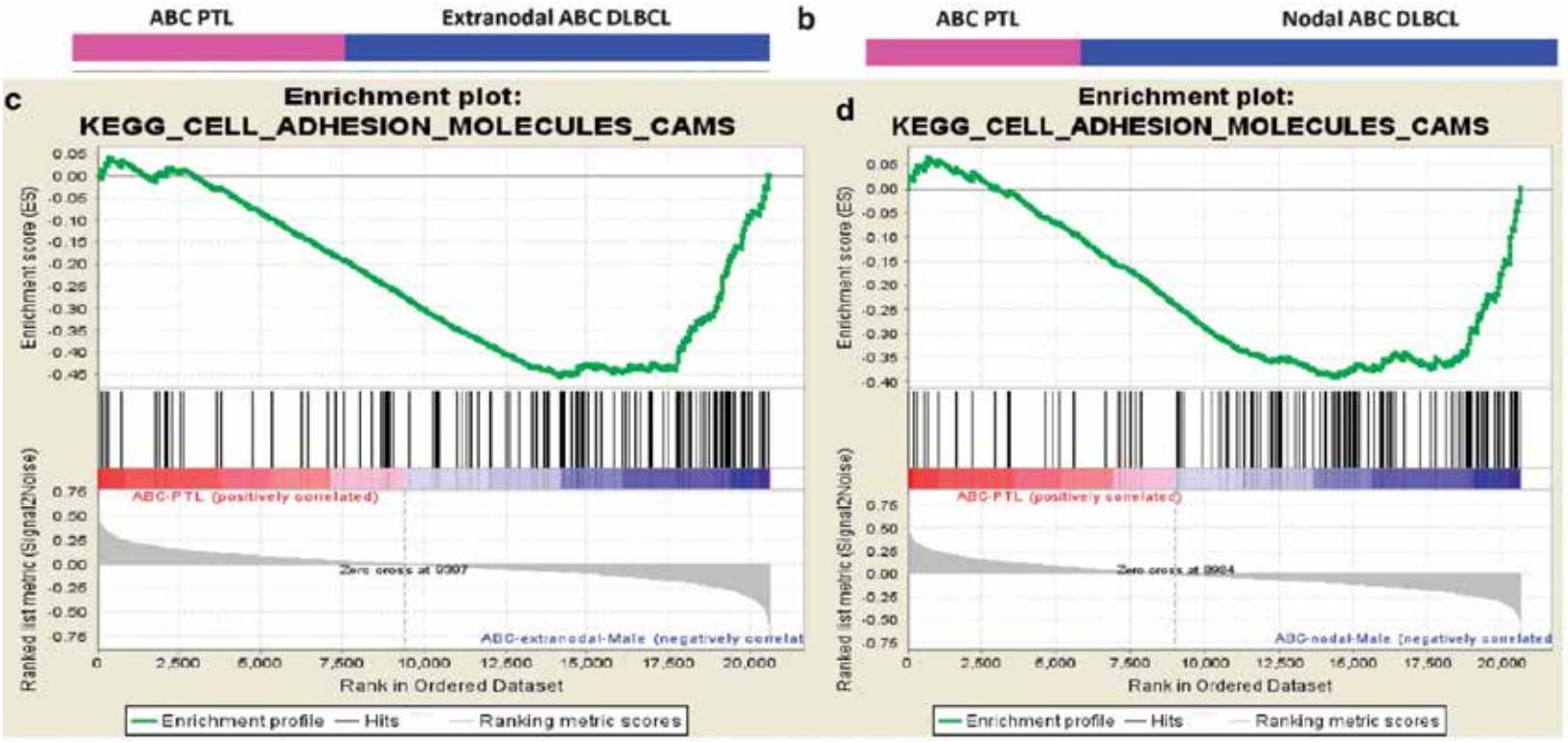
compared with extranodal and nodal ABC-DLBCL





Deng et al. Leukemia, 2016

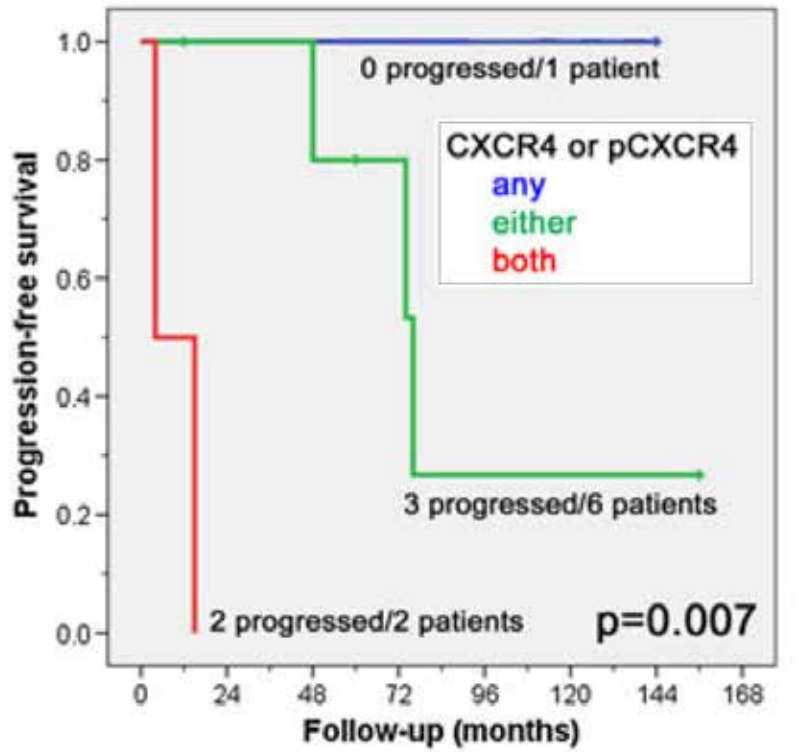
Different expression of cell adhesion molecules
compared with extranodal and nodal ABC-DLBCL



GSEA validated differentially expressed genes of cell adhesion molecules in ABC PTL. A pattern that may be associated with the tendency to disseminate to extranodal sites

Deng et al. Leukemia, 2016

Effect of c expression of chemokine (C-X-C motif) receptor 4 (CXCR4) in primary testicular DLBCL



Kaplan–Meier survival curves of testicular diffuse large B-cell lymphomas according to the expression of CXCR4 and pCXCR4

N= 45 testicular DLBCL

- ü low levels of p53 expression
- ü high levels of pSTAT3
- ü overexpression of pCXCR4
- ü upregulation of NF-kB
- ü expression of both CXCR4 and pCXCR4 was predictive of inferiorPFS (p .007)
- ü overexpression of CXCR4 may favor extranodal relapse

Menter et al. Hematol Oncol, 2013.

Targetable genetic features of primary testicular and primary CNS lymphomas

	DLBCL		PTL	EBV⁻ PCNSL	PMBL
	All	ABC-type			
Genomic instability					
CDKN2A^{loss}	24% (43/180)[a]	35% (19/55)[a]	88% (44/50)[c]	71% (15/21)[k]	0% (0/11)
bi-alleic	19% (8/43)[a]	26% (5/19)[a]	77% (34/44)	73% (11/15)	0% (0/11)
CNAs of additional p53/cell cycle components	multiple[a,b]	multiple[a,b]	no	rare[d]	no
Total CNAs	high	high	high	high	low
Oncogenic TLR and BCR Signaling					
MYD88^{L265P}	12% (6/49)[e]	29% (45/155)[f]	78% (38/49)[g]	60% (33/55)[l]	NA
NFKBIZ^{gain}	9% (16/180)[a]	20% (11/55)[a]	42% (21/50)[h]	45% (28/62)[m]	0% (0/11)
NFKBIZ^{gain} and/or *MYD88*^{L265P}	NA	NA	92% (45/49)	83% (44/53)[n]	NA
CD79B^{Y196mut}					
Total	16% (8/49)[e]	23% (35/155)[f]	49% (22/45)[i]	38% (19/50)[o]	NA
Concurrent with *MYD88*^{L265P}	38% (3/8)[e]	43% (15/35)[f]	91% (20/22)	89% (17/19)	NA
PD-1 Ligand Deregulation					
9p24.1/*PD-L1*^{gain} and/or *PD-L2*^{gain}	6% (11/180)[a]	7% (4/55)[a]	54% (26/50)[h]	52% (33/63)[p]	55% (6/11)
PD-L1 or *PDL-2* translocation	NA	NA	4% (2/50)[j]	6% (4/66)[q]	20% (25/125)[r]

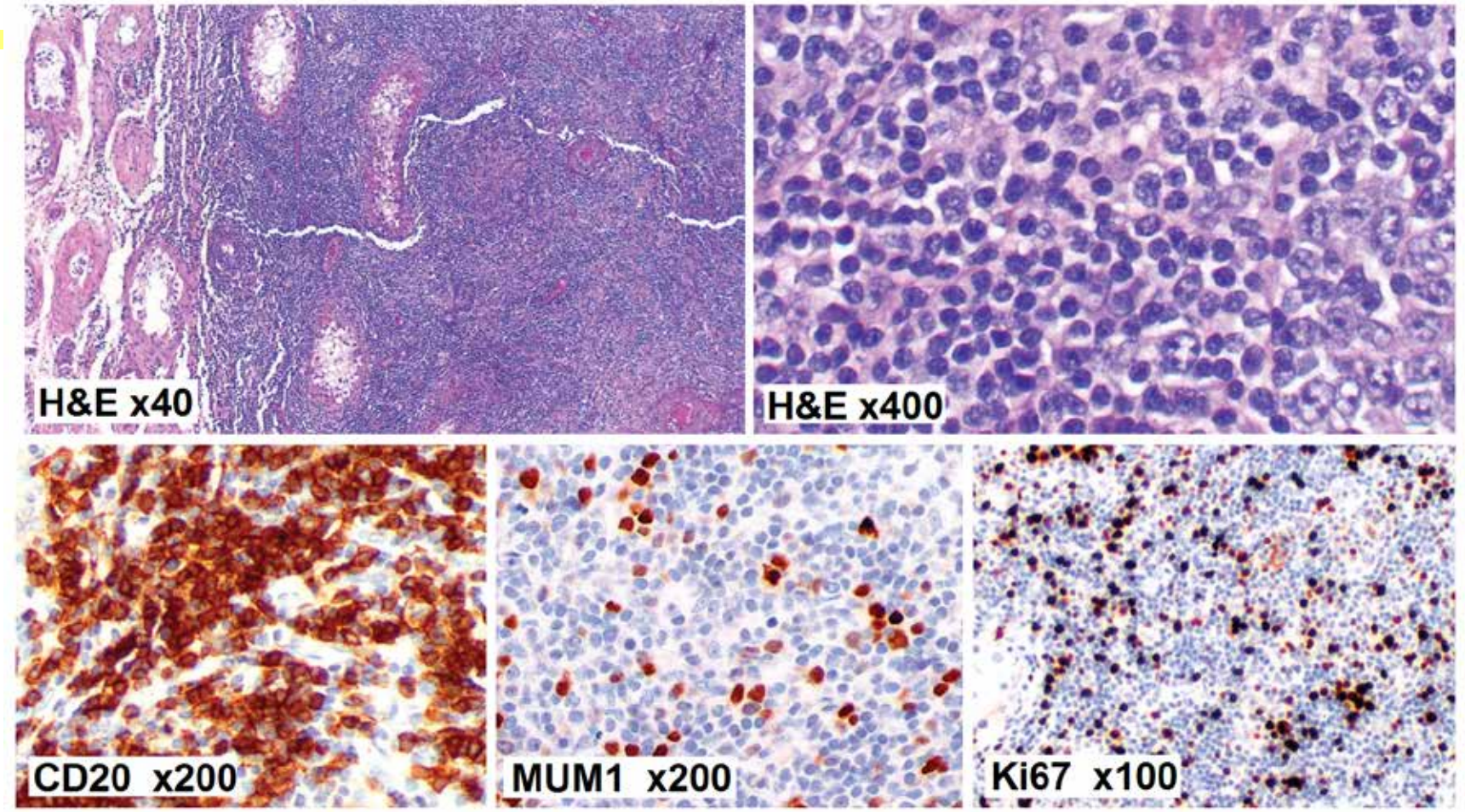
Chapuy et al. Blood, 2016

Testicular Lymphoma Histology

- ABC- DLBCL 90%
  (with plasmacytoid differentiation in ~50%)
- Burkitt and Burkitt-like: 10-20% (mainly HIV+)
- Follicular: rare (in children)
- T-cell: very rare

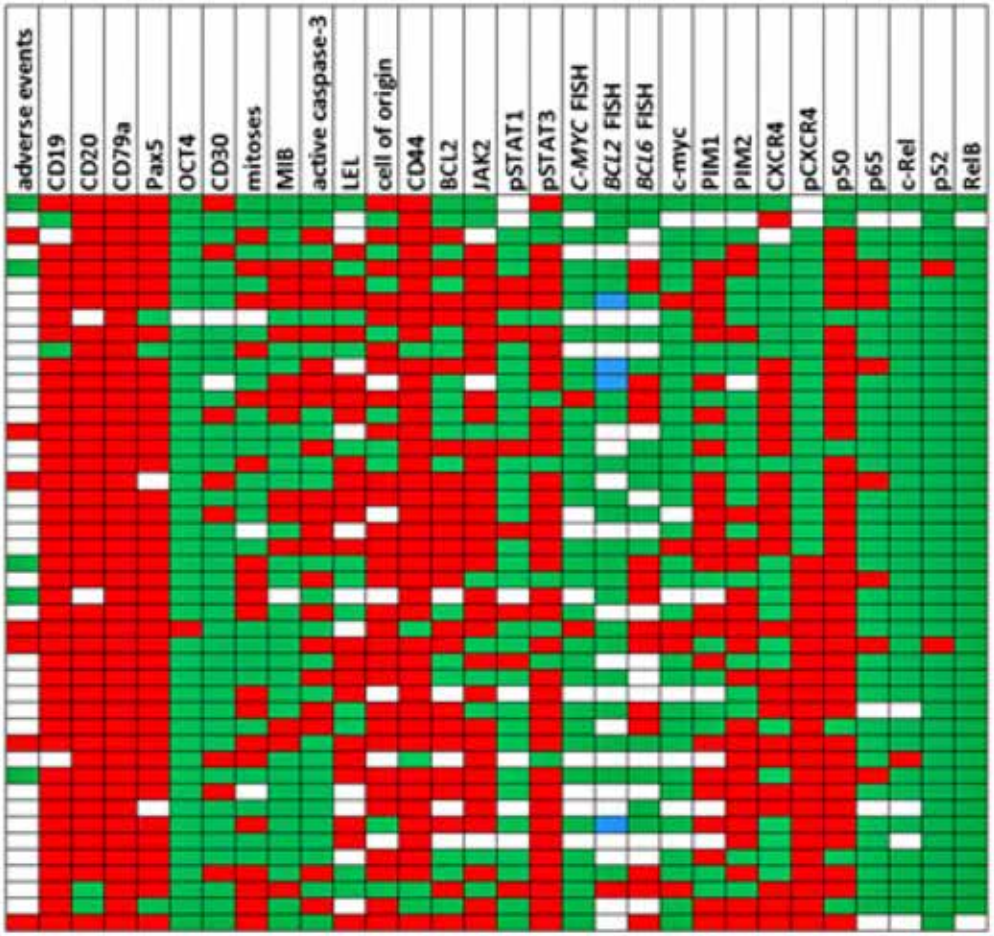
Shahab & Doll 1999; Booman et al 2006

Histopathology of primary DLBCL of the testis

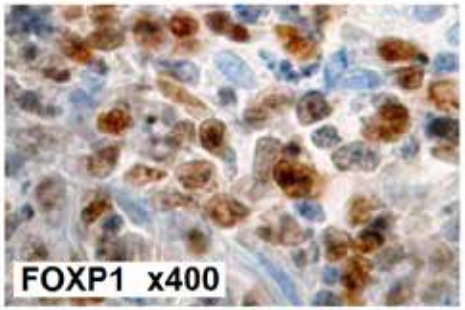


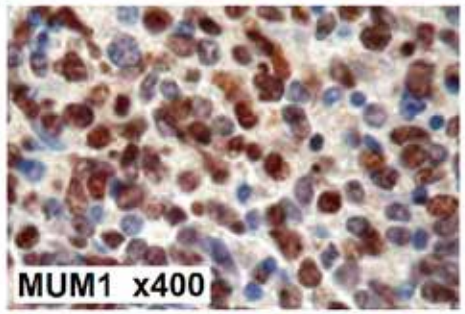
Horne & Adeniran. Arch Pathol Lab Med, 2011

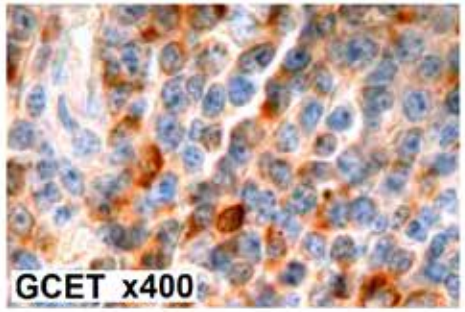
Most DLBCL of the testis are non-GCB



Heatmap like summary of the immunohistochemical results







Booman et al. J Pathol 2006

enter et al. Hematol Oncol, 2014

Testicular Lymphoma

Outcome of stage I-II patients (historical series)

- most patients relapse within 2 years after orchiectomy alone
- ~70% distant nodal or extranodal relapses after radiotherapy alone (in-field failures only if dose <35 Gy)
- aggressive chemotherapy appears beneficial:

  relapse rate 15 % (vs 64%) if adjuvant chemotherapy is given (Danish Lymphoma Study Group Survey, 1994)

Shahab & Doll 1999

IELSG-5 Testis DLBCL Study

Zucca et al. J Clin Oncol, 2003

- 373 pts from 23 centres, median age 66 yrs (range: 19-91)

Patients characteristics

- Stage (n=373)

I	214 pts	} 79%
II	81 pts	
III	7 pts	
IV	71 pts	

- IPI (n=302)

Low	82 pts	} 81%
Low-Int	25 pts	
Int-High	26 pts	
High	19 pts	

- B symptoms 33 pts (9%)
- PS (ECOG) >1 50 pts (13%)
- Additional extranodal sites 69 pts (18%)
- Synchronous contralateral testis (2%)

IELSG-5 Testis DLBCL Study

Zucca et al. J Clin Oncol, 2003

Patterns of relapse

- Stage I Relapsed: 102/214 pts (48%)
- Total Relapsed: 195/373 pts (52%)
- Extranodal relapse 140/195 pts (72%)
  - CNS relapse 56 pts (15%)
  - Testis relapse 43 pts (11%)

IELSG-5 Testis DLBCL Study

Zucca et al. J Clin Oncol, 2003

	stage I	***overall***
Total CNS Relapses	27	56
à Brain	16	30
à Meninges	3	13
à Brain+Meninges	3	6
à Unspecified	5	7
Isolated CNS Relapses	17	34
à Brain	11	19
à Meninges	1	6
à Brain+Meninges	3	5
à Unspecified	2	4

IELSG-5 Testis DLBCL Study

Zucca et al. J Clin Oncol, 2003

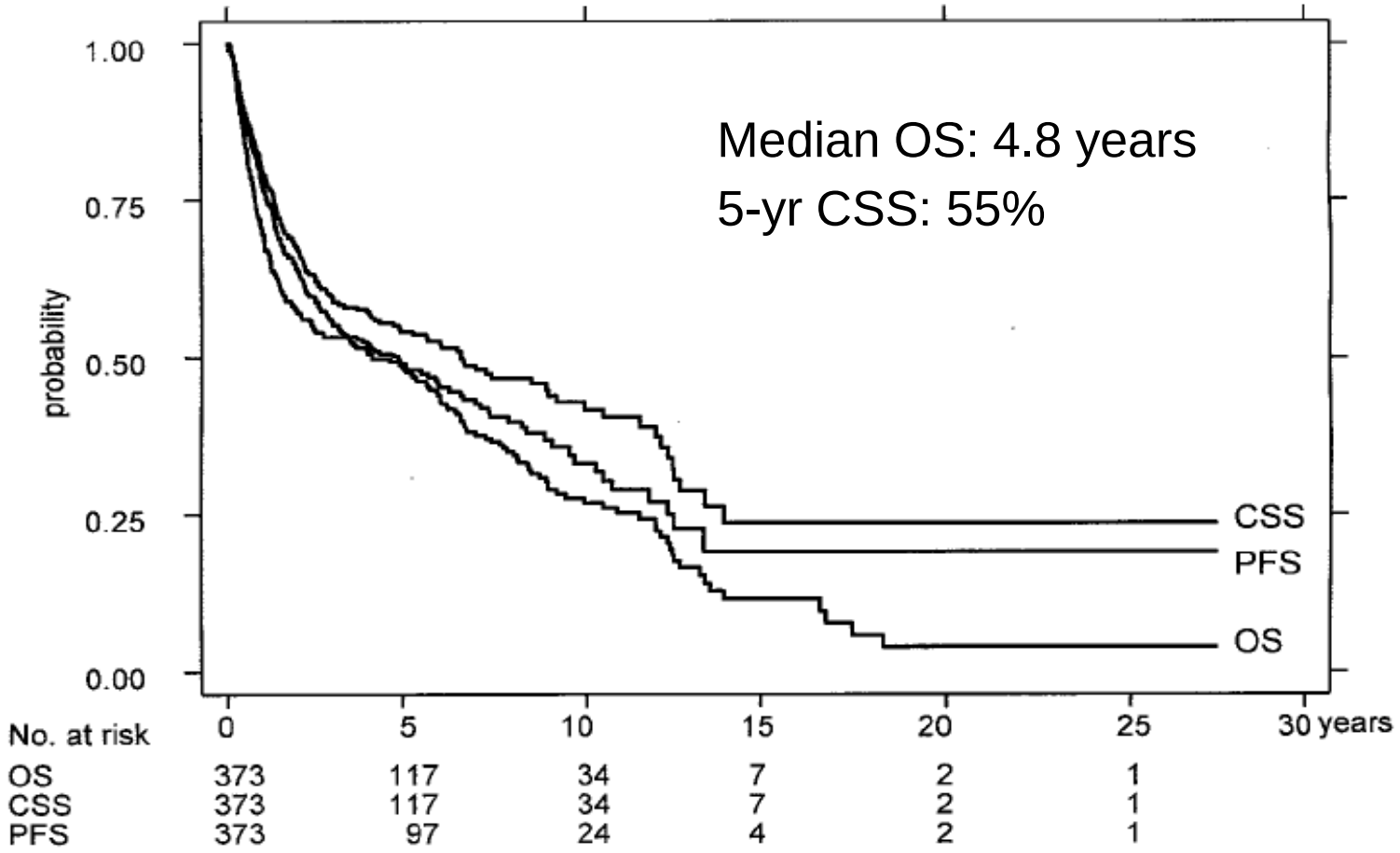
CNS prophylaxis

- 73 of 373 pts had intrathecal MTX à 20%
  - à 5 therapeutic
  - à 68 prophylactic

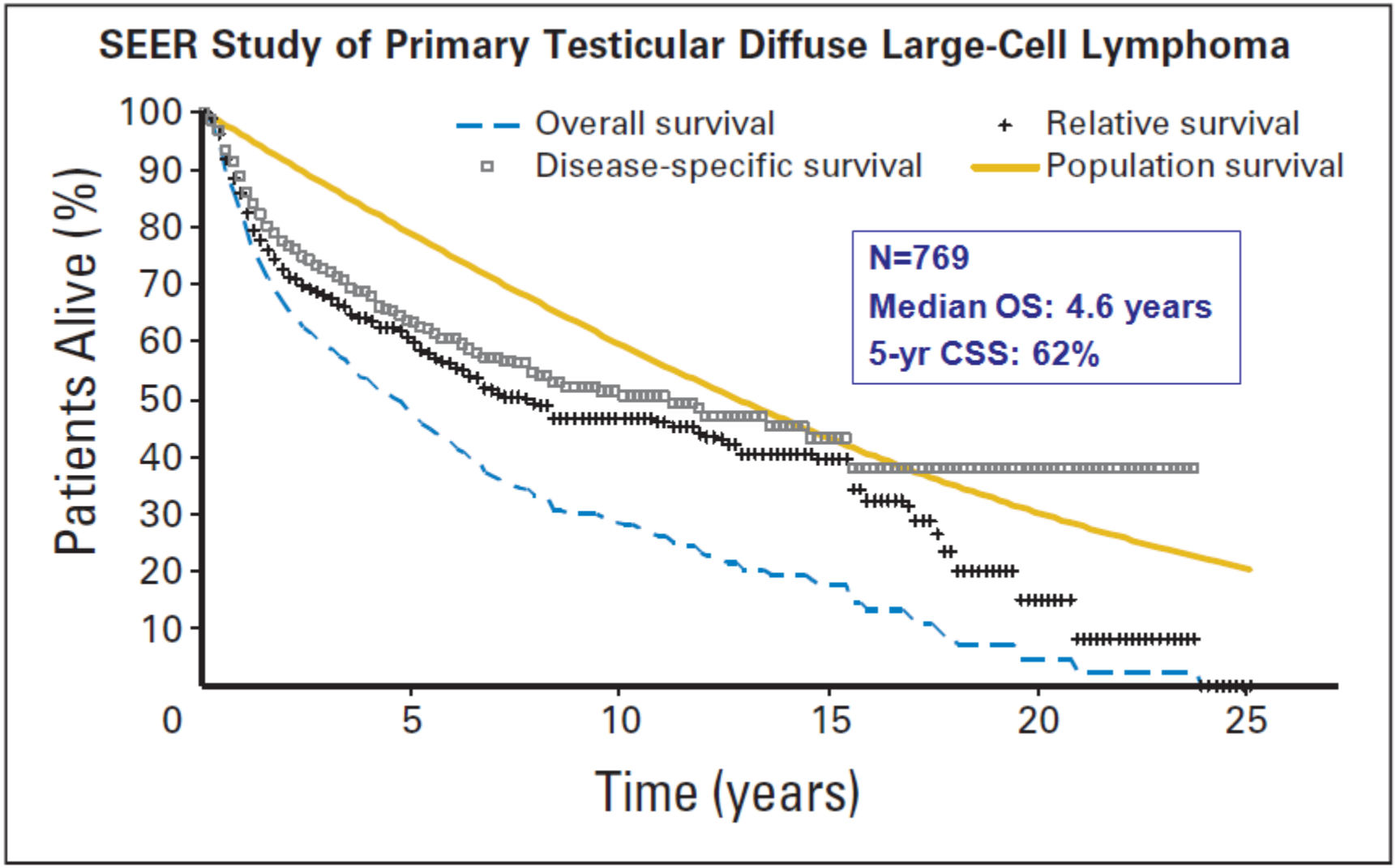
- 29 of 373 pts had intravenous HD-MTX à 8%
  - à 2 therapeutic
  - à 10 in addition to intrathecal

IELSG-5 Testis DLBCL Study

Zucca et al. J Clin Oncol, 2003



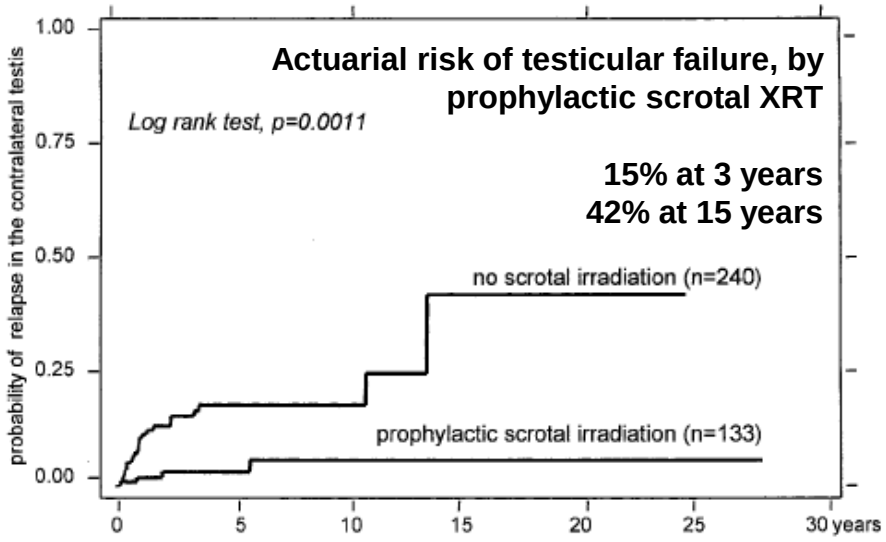
US Population-Based Survey 1980-2005

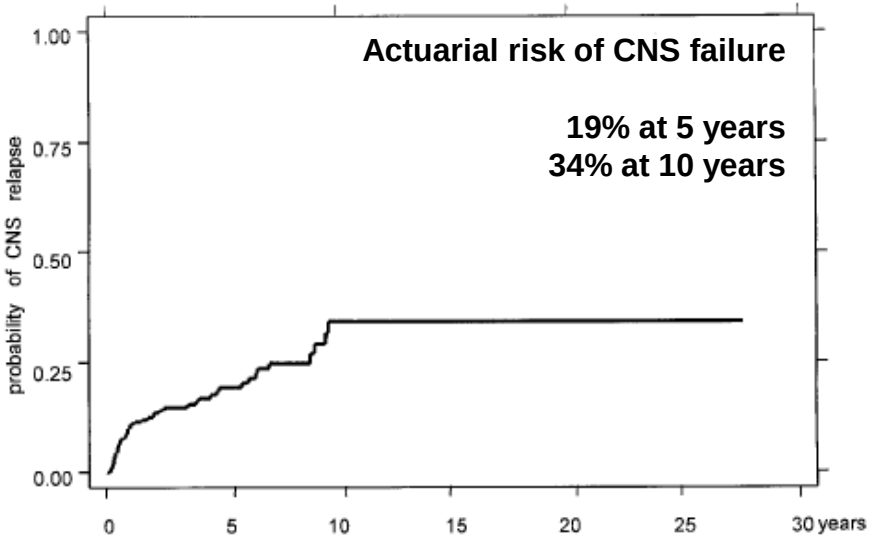


Gundrum et al. JCO 2009

Challenges in the treatment of primary testis lymphoma

- High risk of extranodal relapses
- High risk of controlateral testicular failure
- High risk of CNS recurrence

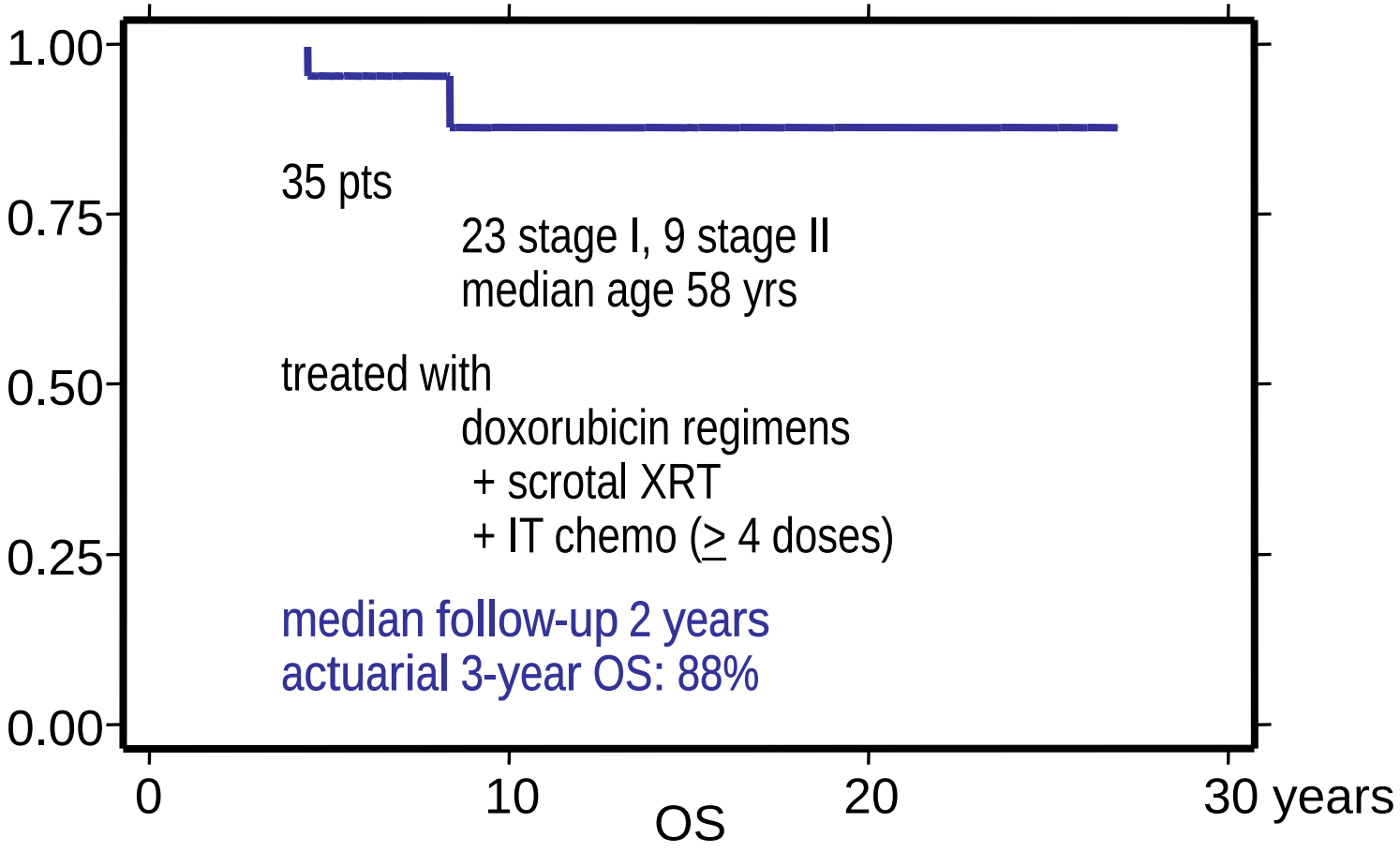




Zucca et al. JCO 2003

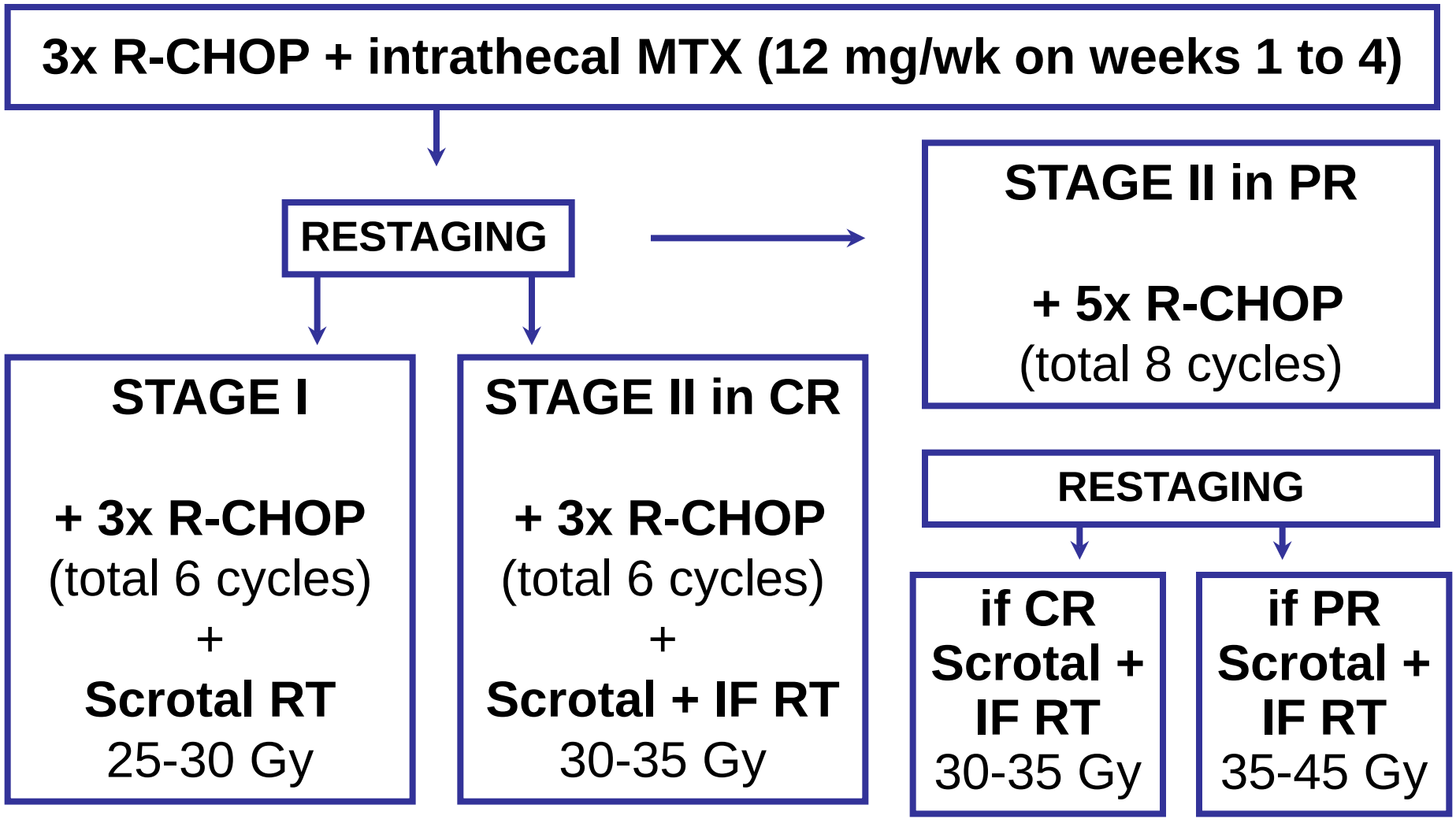
IELSG-5 Testis DLBCL Study

Zucca et al. J Clin Oncol, 2003



IELSG-10 Study Design

Prospective therapeutic clinical trial in testis DLBCL



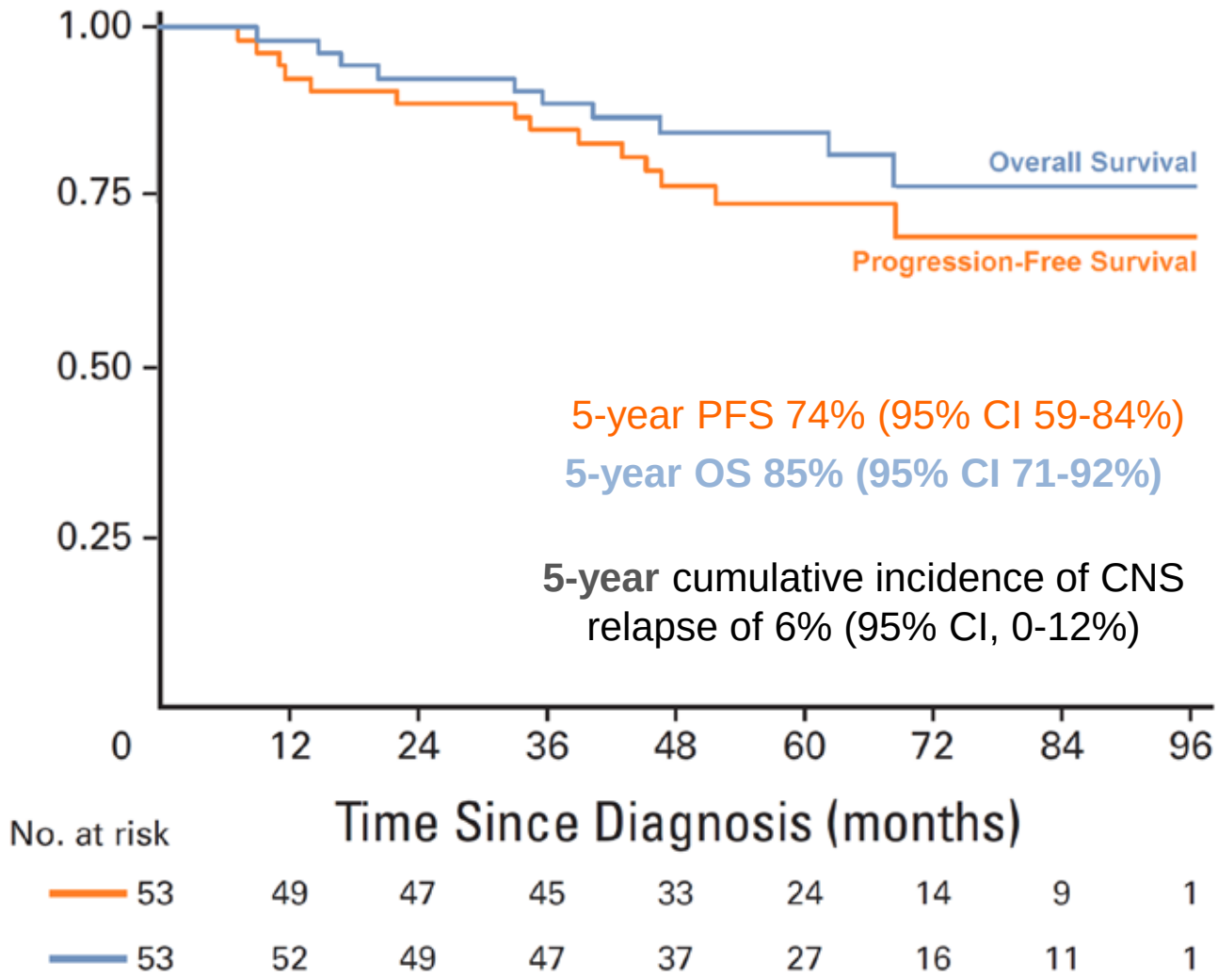
IELSG 10 study results

Median f-up, 5.5 yrs

10 relapse or PD
2 nodal, 8 extranodal
including 3 in the CNS,

No contralateral relapses

10 deaths
6 from NHL, 2 AML, 1 cardiac and 1 gastric cancer



Vitolo et al. JCO 2011

IELSG 10 long-term results

	IELSG-10 Vitolo et al. JCO 2011	IELSG-10 UPDATE- EHA 2014
OS	85%	75%
PFS	74%	67%
TTP	18%	27%
CNS relapses	6%	6%
DEATHS	10 pts died: 6 PD 2 AML 1 heart failure 1 gastric cancer	14 pts died: 8 PD 2 AML 1 heart failure 1 gastric cancer 1 hepatocarcinoma 1 matastatic melanoma

Vitolo et al. EHA 2014

Contralateral testis relapse in the pre-rituximab era

Testicular relapse rates in large published series of primary testicular lymphoma

Yr	Author	*N*	Testicular relapse among those who received radiation	Median follow up (months)	Time to relapse (months)
2000	Fonseca *et al.*	62	1of 5 (20%)	103	120
2001	Visco *et al.*	43	2 of 20 (10%)	49	24, 72
2001	Seymour *et al.*	25	0 of 6 (0%)	36	NA
2003	Zucca *et al.*	373	4 of 45 (8.9%)	91	All <60
2007	Park *et al.*	45	0 of 10 (0%)	32	NA
Pooled analysis			7 of 86 (8.1%)		Up to 120

Conrad & Go. Eur J Hematol , 2009

Contralateral testis relapse in the rituximab era

Reference	*n*	Testicular relapse among those who received radiation
[1]	373	4 of 45 (8.9%)
[10]	62	1 of 5 (20%)
[26]	72	2 of 45 (4%)
[27]	25	0 of 6 (0%)
[34]*	53	0 of 47 (0%)
[38]	43	2 of 20 (10%)
[43]*	38	0 of 33 (0%)
[44]	45	0 of 10 (0%)
[45]	35	0 of 12 (0%)
Pooled analysis		9 of 223 (4%)

Ahmad et a. Clinn Oncol, 2009

IELSG-10 study conclusions

Proper treatment improves the outcome!

- **CNS prophylaxis is mandatory in testis DLBCL**
- **R-CHOP + i.t. MTX + Scrotal RT** is feasible with acceptable toxicity and it may be regarded as the present standard
- ***Site-specific* treatment is needed**
  - contralateral testis relapses have been eliminated
  - CNS recurrence seems to be reduced
- **Different strategies to reduce CNS relapses should be further investigated**

Strategies to reduce CNS relapses

- **intrathecal depot liposomal Ara-C**

  MJ Glantz et al, J Clin Oncol. 1999;17:3110-6.

  MJ Glantz et al, Clin Cancer Res. 1999;5:3394-402.

- **systemic intermediate to high-dose MTX**

  JF Seymour et al, Clin Lymphoma. 2001;2:109-15

IELSG-30

R-CHOP with intensive CNS prophylaxis and scrotal RT

- **weeks 1-15**

6x R-CHOP 21
(Rituximab on day 0 or day 1)

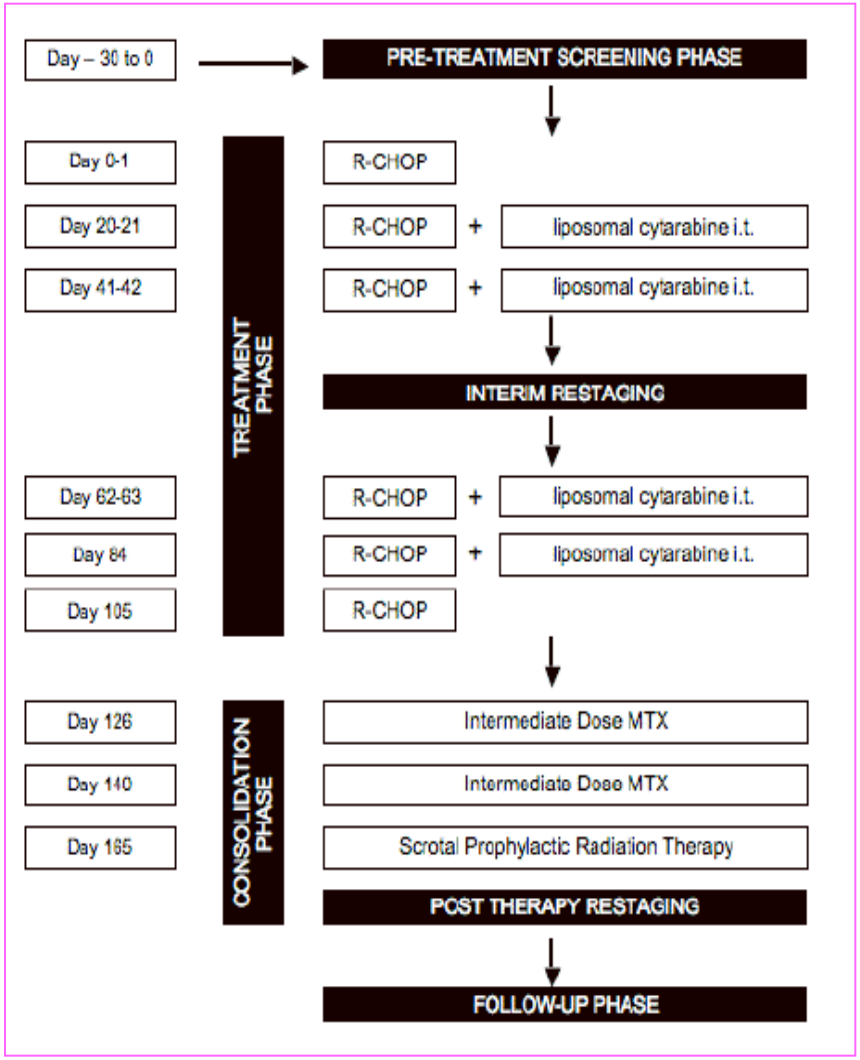
IT prophylaxis with 4x Depocyte
(50 mg on day of cycles 2-5)

- **weeks 18-22**

Methotrexate 1.5 g/m2 q 14 days x2

- **from week 24**

Scrotal prophylactic radiotherapy



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