Diffuse Large B Cell Lymphoma

Current Standard Care

弥漫性大B细胞淋巴瘤的标准治疗

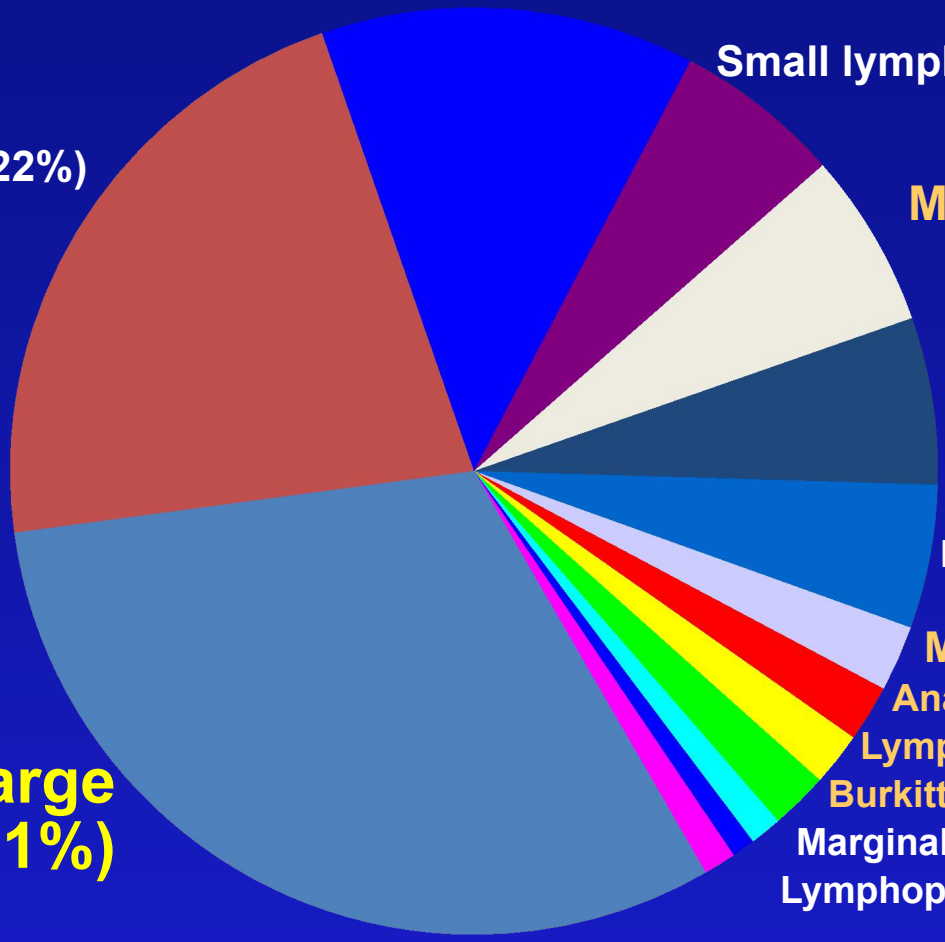
RuiRong Yuan, MD

Topics

- Introduction
- Current Standard Therapy
  - Frontline
  - Relapsed/refractory DLBCL (复发或难治性)
- Special issues in management of DLBCL
  - Double Hit Lymphoma (双重打击)
  - Transformed DLBCL

Frequency of NHL Subtypes

N = 1403



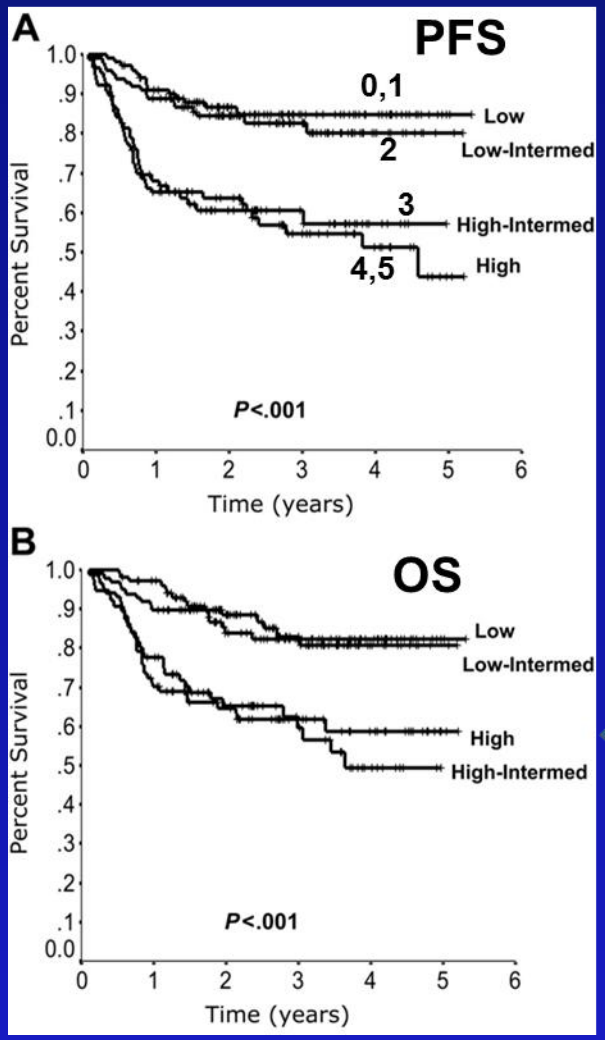
Armitage JO, et al. *J Clin Oncol*. 1998.

Risk Factors: Stage III-IV; Age > 60; PS >2; Elevated LDH; and Extranodal sites

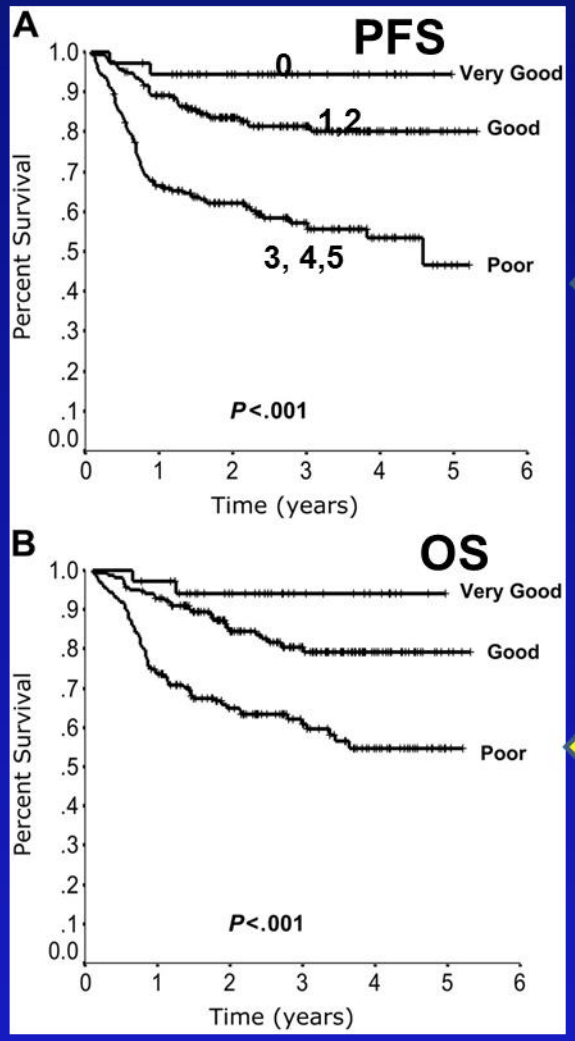
国际预后指数

鉴别经标准治疗后可能或不可能被治愈的患者

Standard IPI



Revised IPI



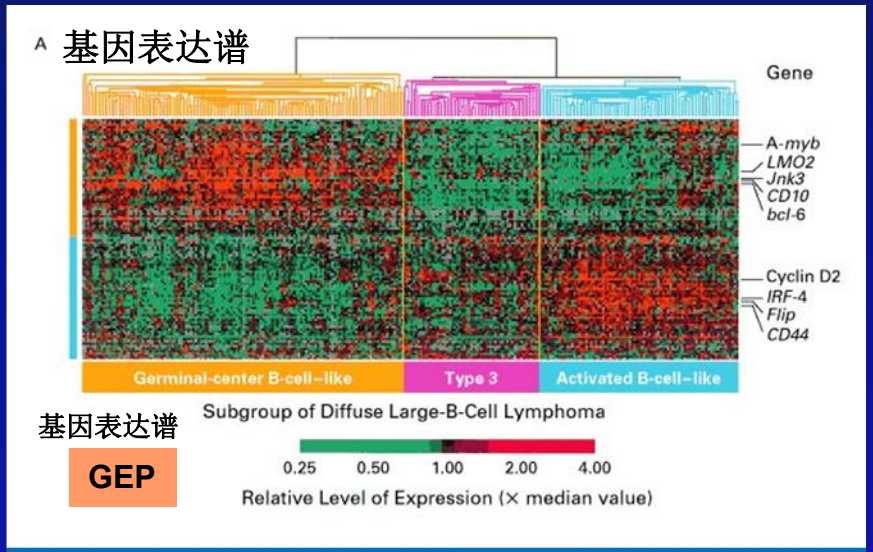
预后非常好

更好地区分出低危和高危亚组的患者

Laurie H. Sehn et al. Blood 2007;109:1857-1861

blood

Biologic prognostic factors: determining the Cell of Origin in DLBCL ABC vs GCB



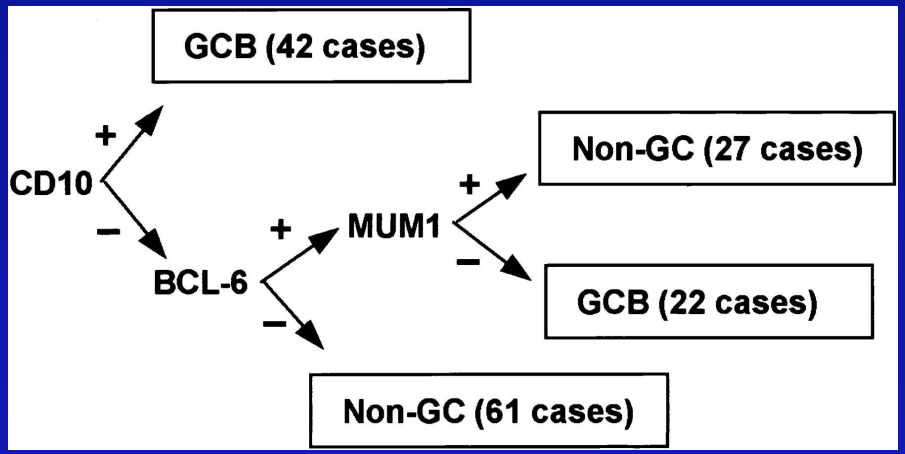
- **Gene Expression Profiling**
  - Green is relative under-expression (GCB)
  - Red is relative over-expression (ABC)

Science 2002

生发中心 B cell（GCB）亚型（CD10+ 或BCL6+、IRF4/MUM1-）和非-GCB 亚型（CD10-、IRF4/MUM1+ 或BCL6-、IRF4/MUM1-）

Hans Algorithm

More commonly used



Hans C P et al. Blood 2004

GCB subtype is associated with a favorable outcome when treated with standard RCHOP chemotherapy

Therapy of DLBCL

Treatment of DLBCL
重要里程碑 (过去25年)

- **1993: CHOP is the standard of care**
  - **Fisher et al**
- **1997: Does rituximab add benefit to CHOP?**
  - ***2 studies started:***

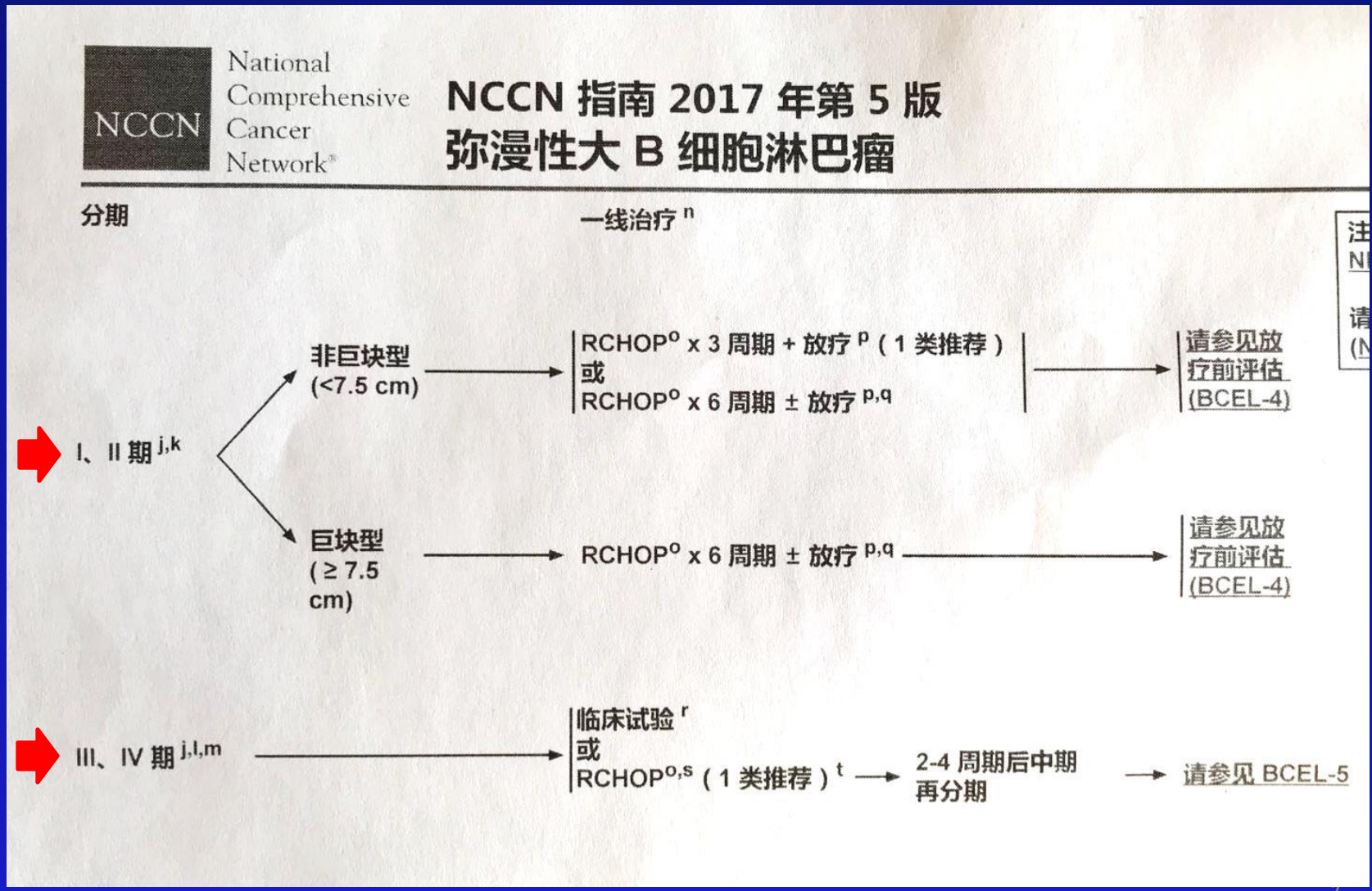
GELA	**Coffier et al**
E4494	**Habermann et al**

- **2001: Rituximab + CHOP is better than CHOP alone (GELA Trial)**

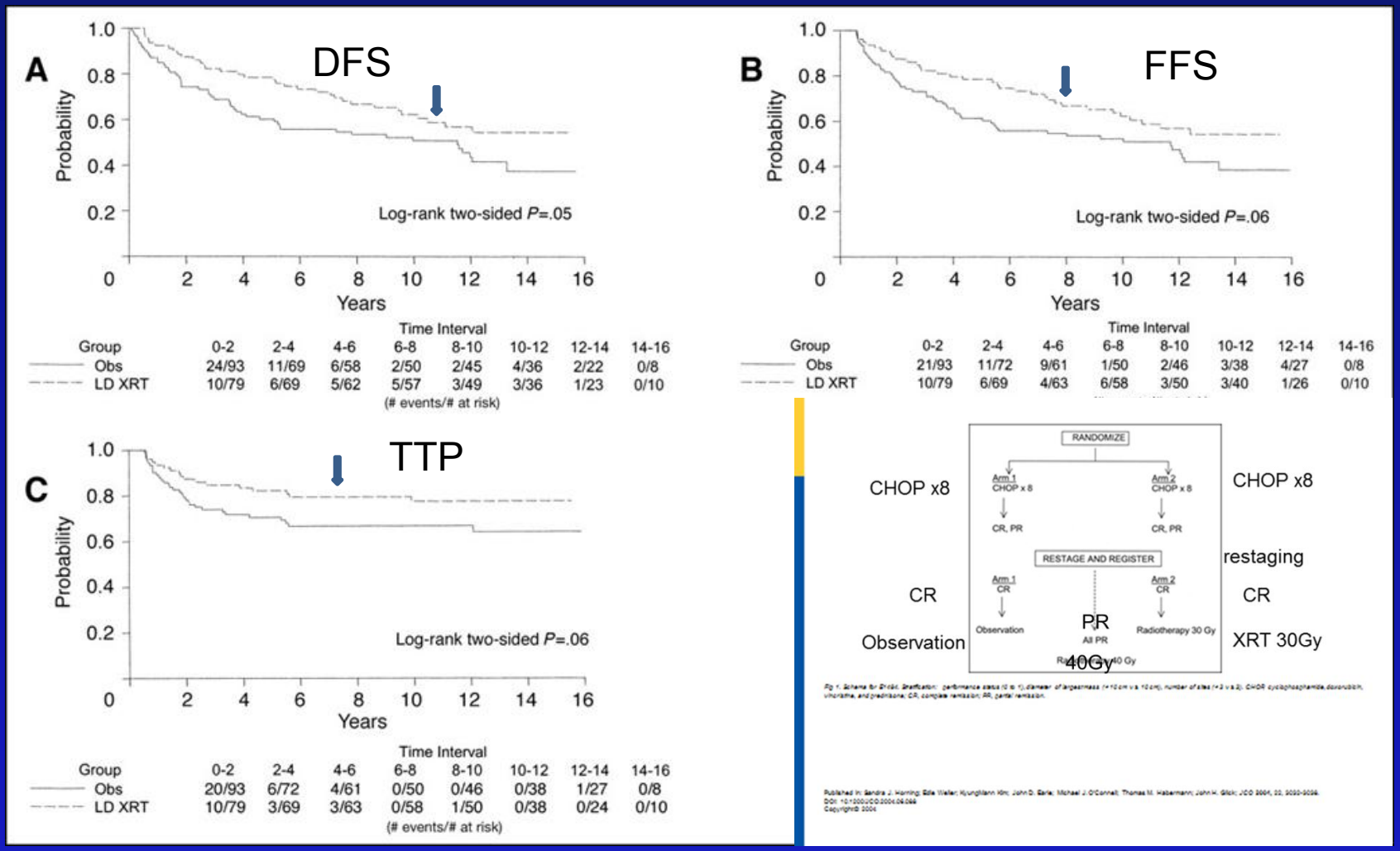
DLBCL: Current Standard of Care

- **Front line: RCHOP-21 X 6**
- **Special cases : REPOCH instead of RCHOP**
  - DH lymphoma

Therapy of DLBCL 一线治疗：Summary



Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive NHL (CHOP± radiation)



Horning et al: JCO 2004
Study conducted between 1984-1992

支持Chemo +Radiotherapy; better local control, but no OS benefit for pts with CR

Treatment of Early-stage DLBCL
(pre R-CHOP)

ECOG trial (Horning S et al)	**Stage I bulky and stage II** **• CHOP (6-8 cycles) followed by RT vs followed by observation in CR patients** **• At 10 years, DFS and TTP favored CHOP-RT, but disease specific survival was 81% in both treatment arms**
SWOG trial (Miller TP et al)	**• Stage I and II, non-bulky** **• CHOP (3 cycles) plus RT vs CHOP (8 cycles)** **• At 9 years, DFS and TTP favored CHOP-RT, with less toxicity, but OS was similar**
GELA trial (Fillet G et al)	**Elderly, IPI = 0** **• CHOP (4 cycles) plus RT vs CHOP** **• No improvement in CR, 5-year EFS, or 5-year OS**

Glick J et al. Proc Am Soc Clin Oncol. 1995:391.
Miller TP et al. N Engl J Med. 1998;339:21-26.
Horning S et al. Blood. 2001;98:724a. Abstract 3023.
Fillet G et al. Blood. 2002;100:92a. Abstract

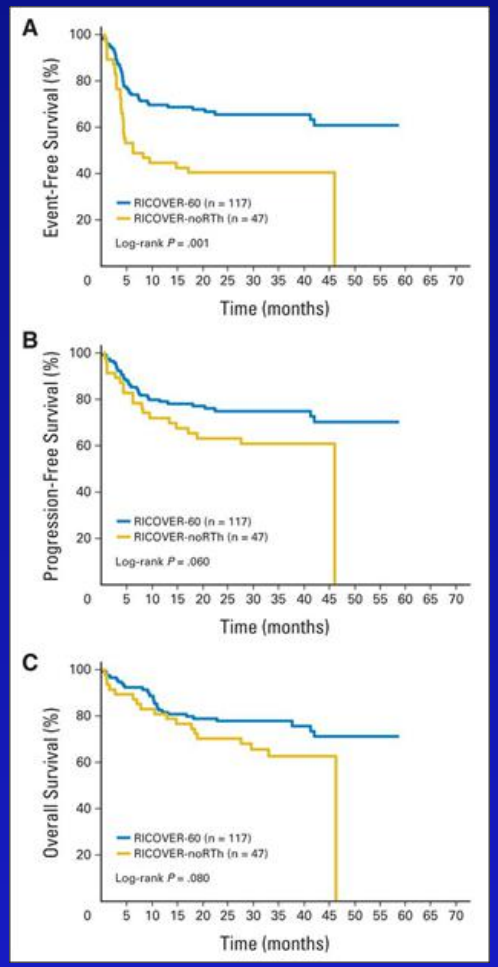
√

RICOVER 60 Sequential Cohorts with bulky (>7.5 cm) or extranodal site

RCHOP-14 X 6 +/- XRT

Any stage
Any IPI
Older than 60

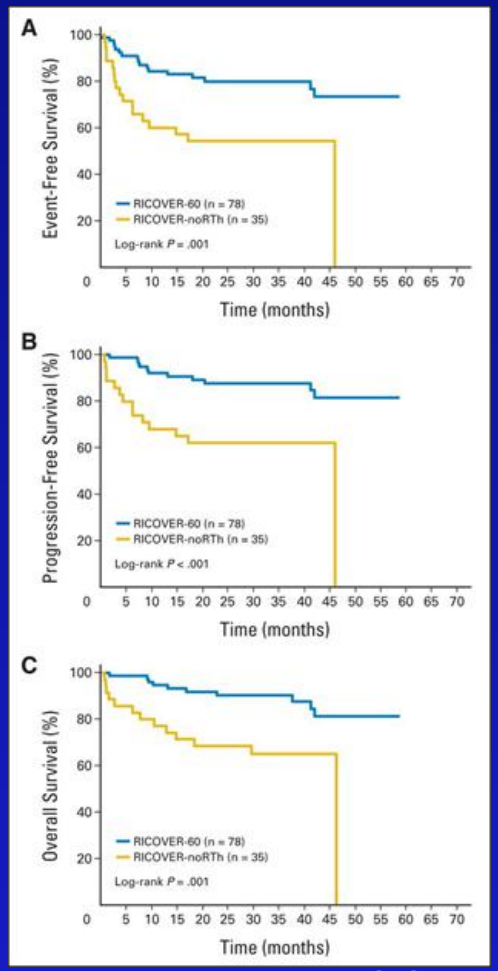
- 支持RCHOP加局部放疗



EFS

PFS

OS



Held et al, JCO 2014

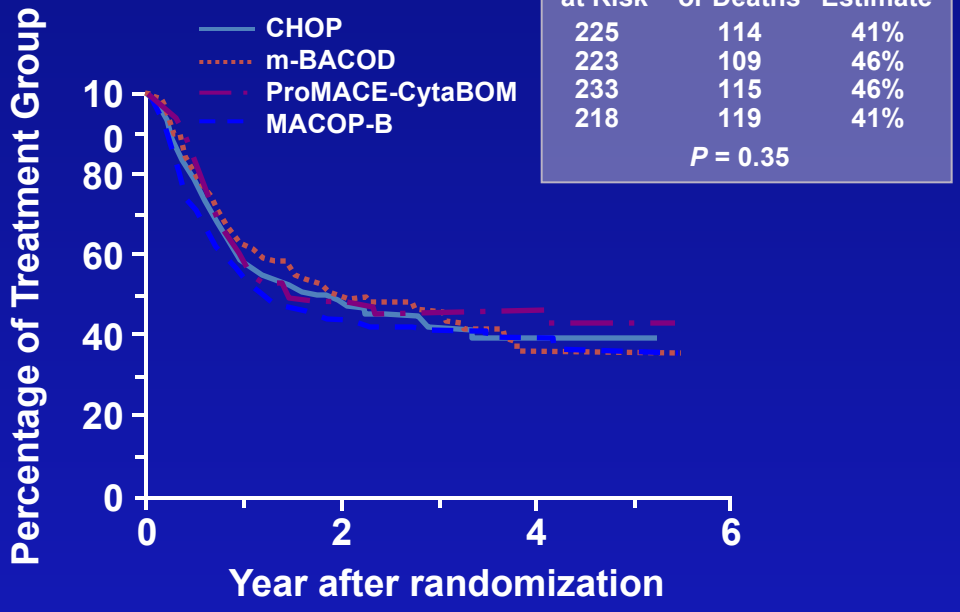
Early-stage DLBCL: RCHOP+IFRT

SWOG0014

- RCHOPx 3 cycles plus local XRT
- 短程RCHOP 联合受累野放疗，能更好地进行前期疾病的控制并且毒性更小

CHOP for Advanced-stage DLBCL: The Former Standard (before RCHOP)

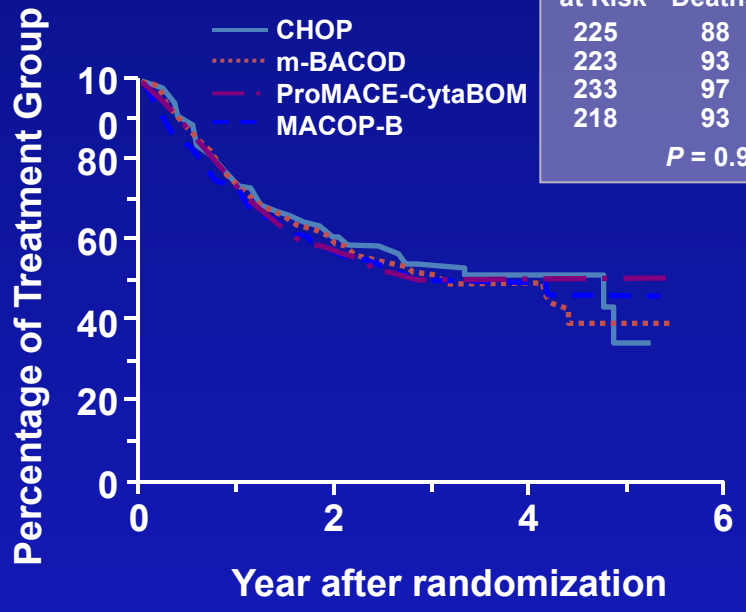
TTF



Patients at Risk	Relapses or Deaths	3-Year Estimate
225	114	41%
223	109	46%
233	115	46%
218	119	41%

P = 0.35

OS



Patients at Risk	Deaths	3-Year Estimate
225	88	54%
223	93	52%
233	97	50%
218	93	50%

P = 0.90

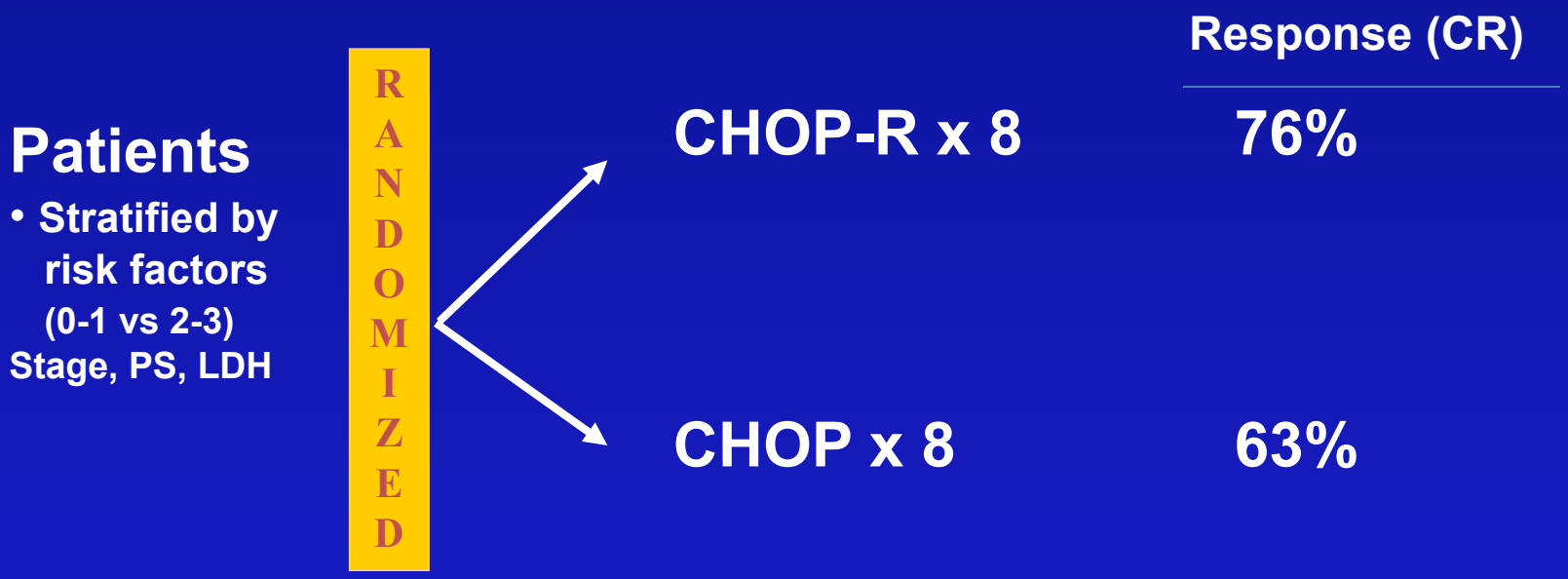
- CHOP was as effective as second- and third-generation chemotherapy regimens, with less toxicity
- **50% to 60% remained uncured**

Fisher RI et al. *N Engl J Med*. 1993;328:1002-1006.

GELA Phase III Trial (LNH98-5): CHOP +/- Rituximab (利妥昔单抗)

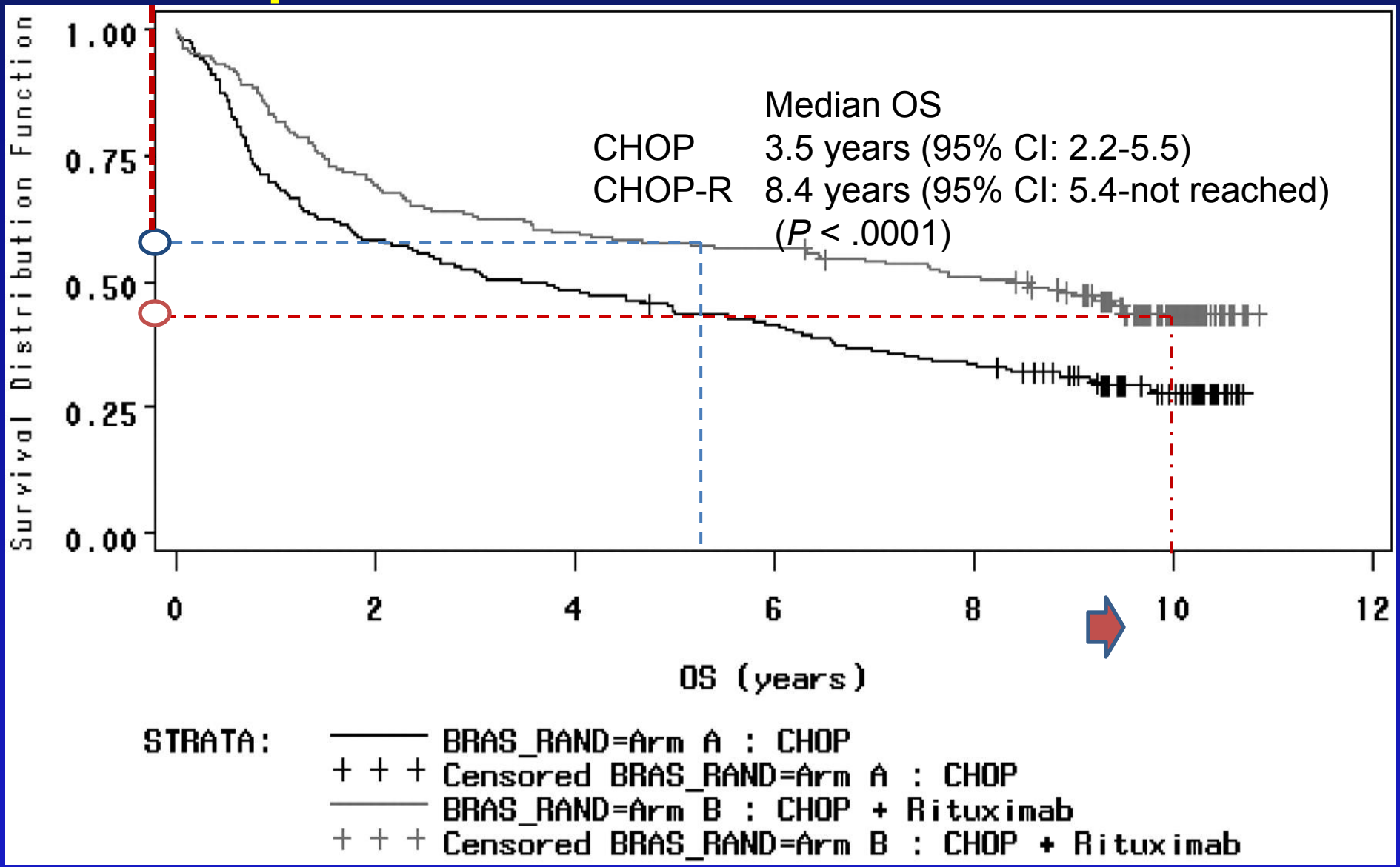
Study Design: To evaluate the efficacy of combining rituximab with CHOP in previously untreated patients age 60-80 with DLBCL

- 1st endpoint: event-free survival (EFS)
- 2nd endpoints: OS, ORR and toxicity



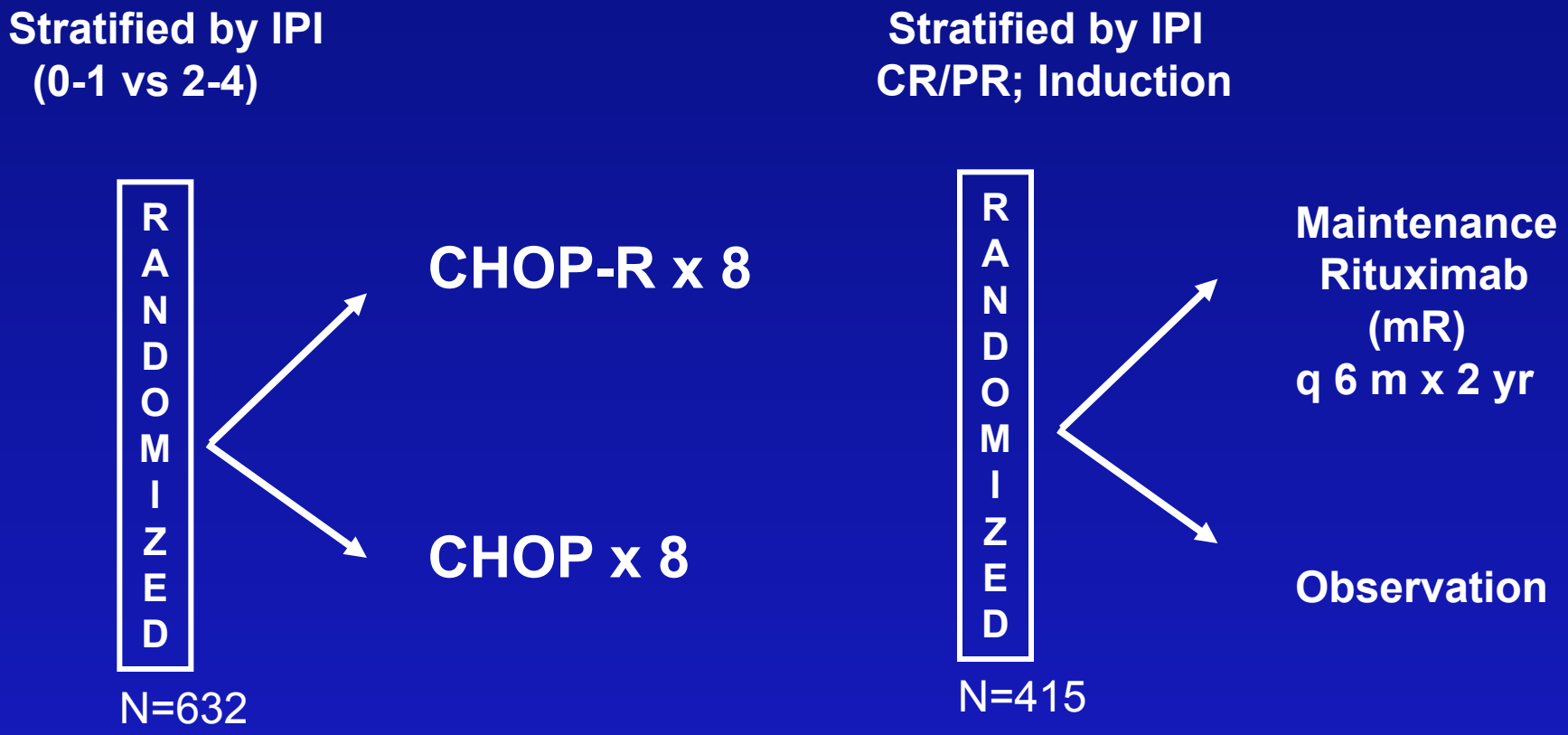
Coiffier et al. *N Engl J Med*. 2002.

GELA LNH 98-5 Trial: 10 year Follow-up
OS in patients treated with CHOP and R-CHOP



Coiffier, B. et al. Blood 2010

ECOG 4494 Phase III Trial: R-CHOP vs CHOP +/- mR

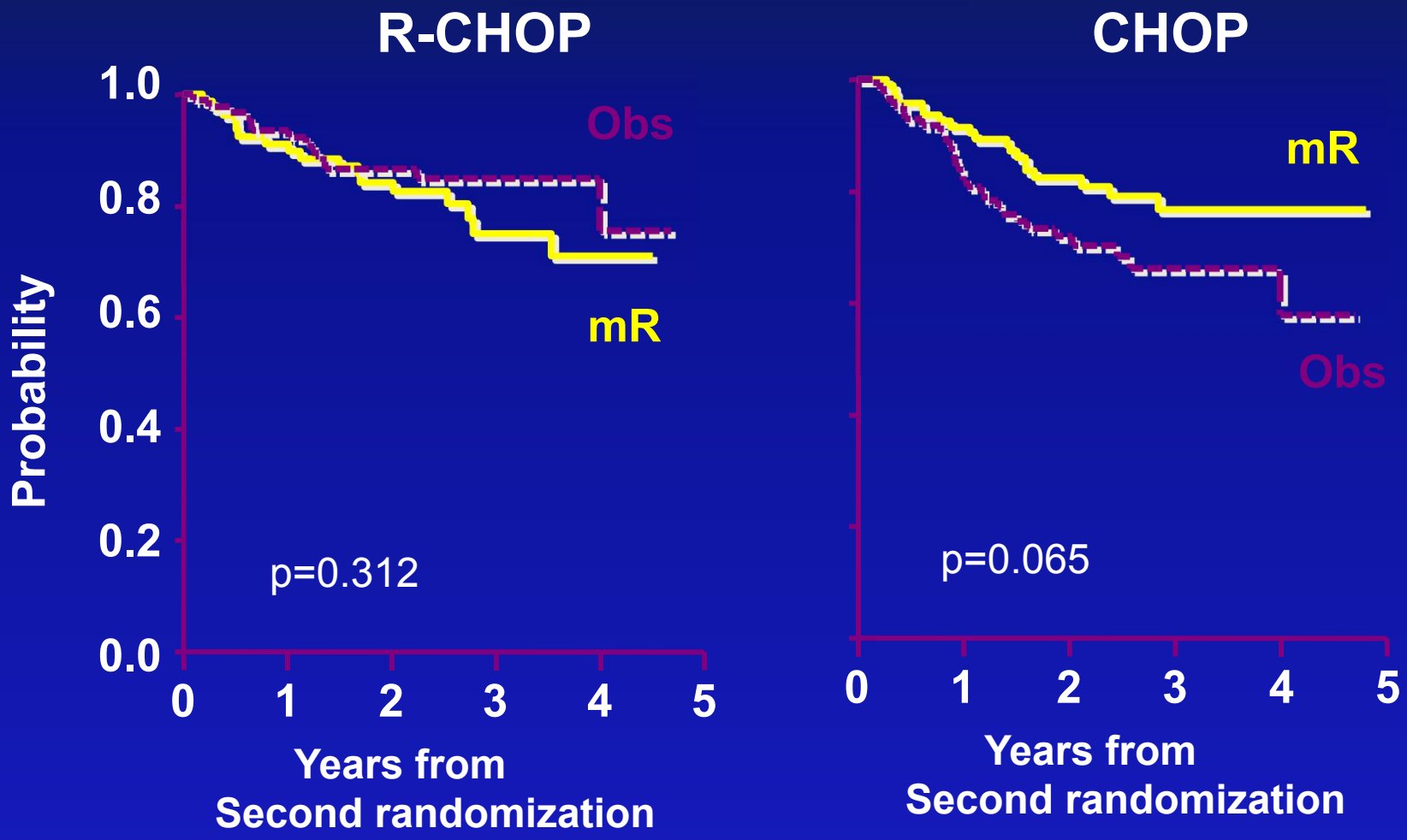


- 1° endpoint: TTF
- 2° endpoints: OS, ORR, toxicity

- 1° endpoint: TTF
- 2° endpoints: OS

Habermann et al. J Clin Oncol 2006

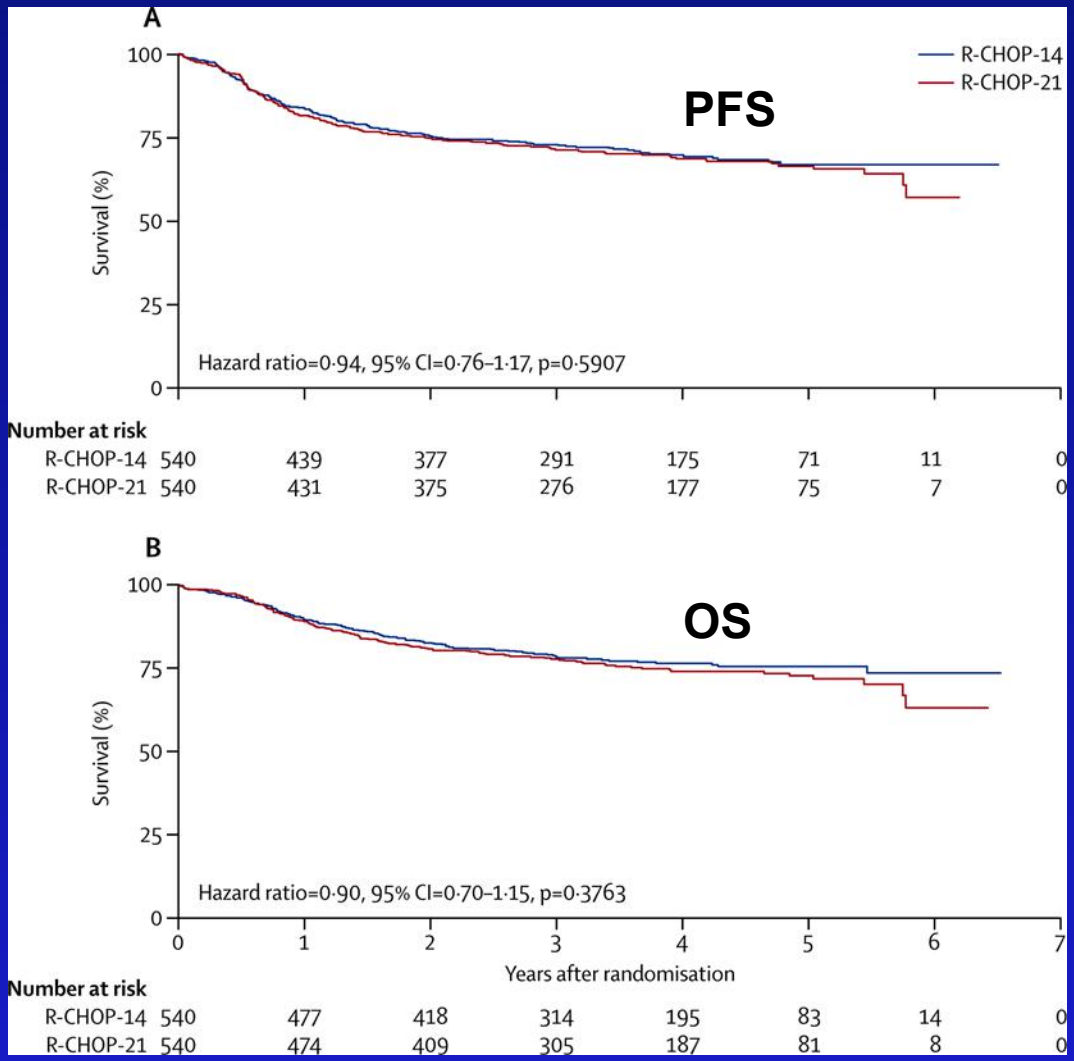
Four Arm Analysis: OS



No benefit from Rituxan Maintenance in CHOP-R arm.

Habermann et al. J Clin Oncol 2006

DLBCL: RCHOP21 vs RCHOP14



RCHOP21

Cunningham et al, The Lancet 2013

Randomized Phase III Clinical Trials: CHOP vs R-CHOP in untreated patients with DLBCL

Trial Median F/U Treatment	Patients	EFS (%)	p value	OS (%)	p value
GELA (n=399) 7 years	60-80 y All IPI				
CHOP		25	p< .0001	36	p< .0004
R-CHOP		42		53	
ECOG (3 years	>60 y All IPI				
CHOP		39	p= .003	58	p= .05
R-CHOP		52		67	
MinT (n=824) 3 years	<60 y IPI: 0-1				
CHOP-like		59	p< .0001	84	p< .0001
R-CHOP-like		79		93	
RICOVER 3 years	61-80 y All IPI				
6xCHOP-14		47	p< .001	68	p= .003
6xR-CHOP-14		66		78	
8xCHOP-14		52		66	
8xR-CHOP-14		63		72	

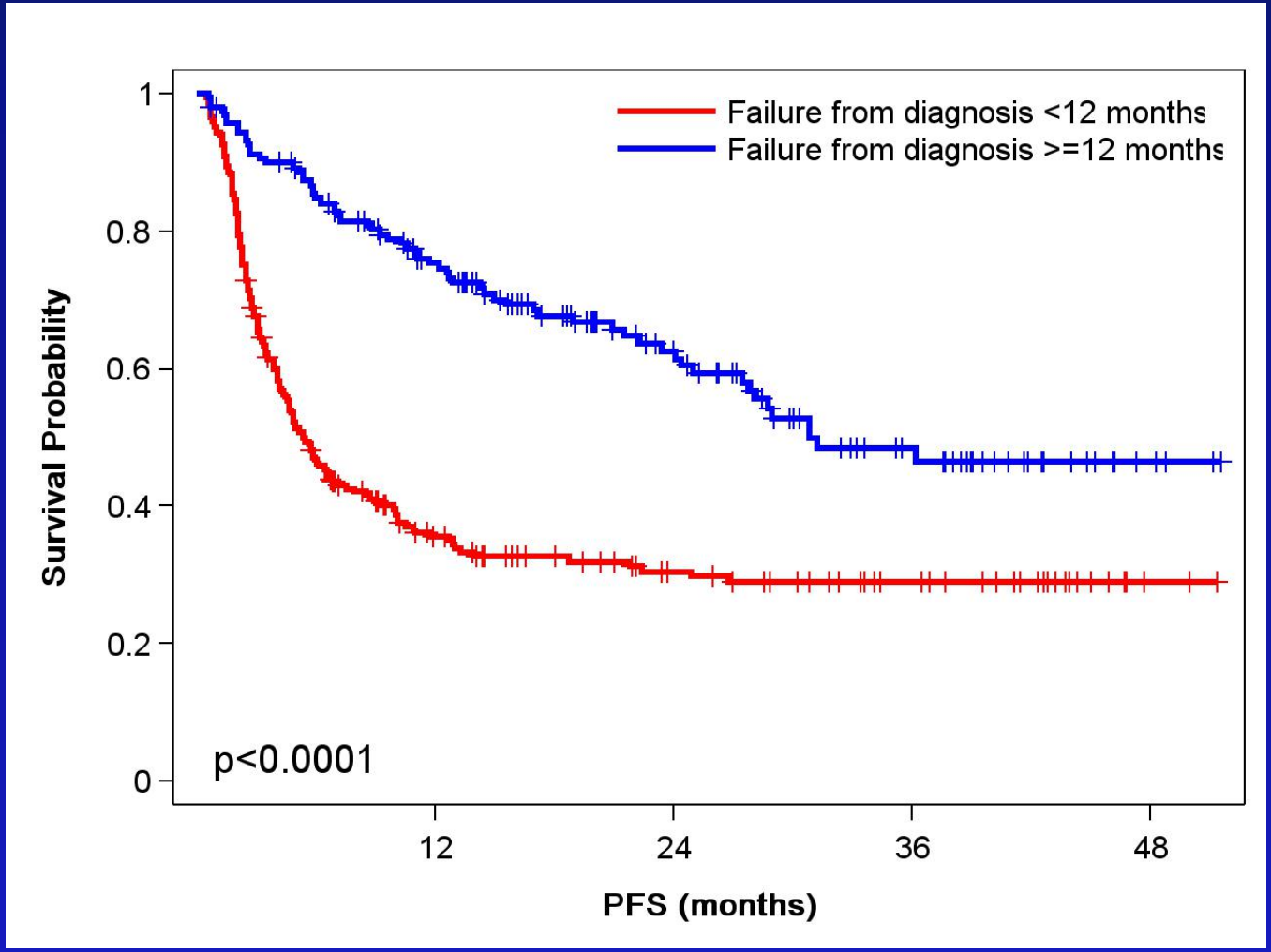
R-CHOP x6

Failed Strategies to Improve on Standard RCHOP in DLBCL

- **Dose/intensity**
  - CHOP/RCHO + ASCT
  - Mega-R-CHOEP
  - RCHOP-14 x6
- **R-CHOP => maintenance drug x**
  - RCHOP => ± enzastaurin
  - RCHOP => ± everolimus
  - RCHOP =>± Lenalidomide
- **R-CHOP + drug x**
  - R-CHOP +Bortezomib
  - G-CHOP vs R-CHOP

Canada –Fly fishing

DLBCL patients who recur post R-CHOP-21 do not do well



Gisselbrecht C, et al. *J Clin Oncol* 2009; 27(15s): Abstract 8509.

Relapsed/refractory DLBCL

Salvage

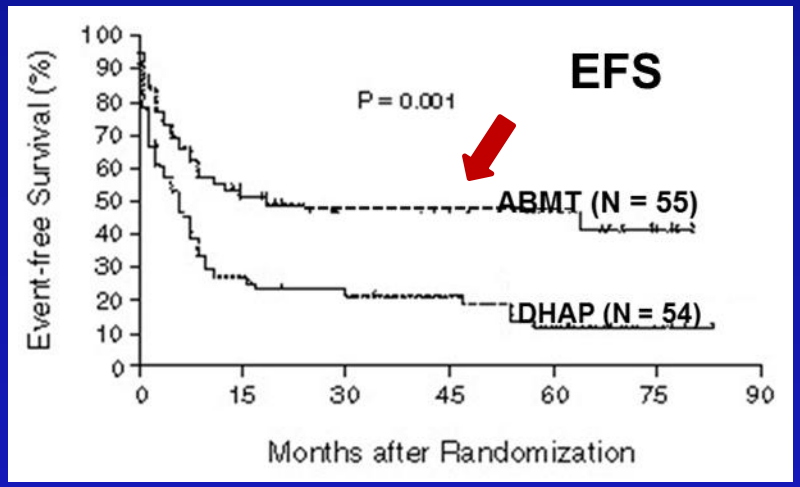
R-DHAP
or RICE

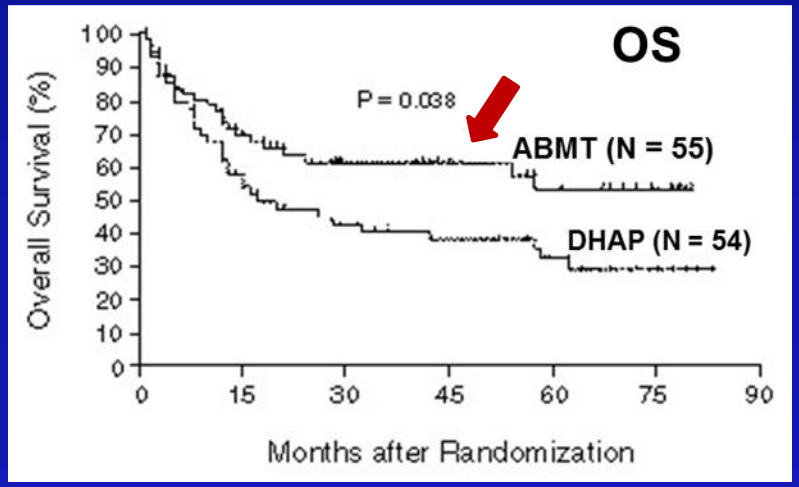
followed by
autologous stem cell transplantation (ASCT)

DHAP: dexamethasone, cisplatin, and cytarabine
RICE: rituximab, ifosfamide, carboplatin, etoposide

Parma Trial: EFS and OS

215 pts relapsed NHL; treated with 2 courses of dexamethasone, cisplatin, and cytarabine (DHAP).
109 pts who had a response to chemo were randomly assigned to receive 4 courses of chemotherapy plus radiotherapy (54 patients) or radiotherapy plus intensive chemo and autologous bone marrow transplantation (55 patients)





ABMT conditional chemo: carmustine, etoposide, cytarabine, cyclophosphamide, and mesna (BEAC)

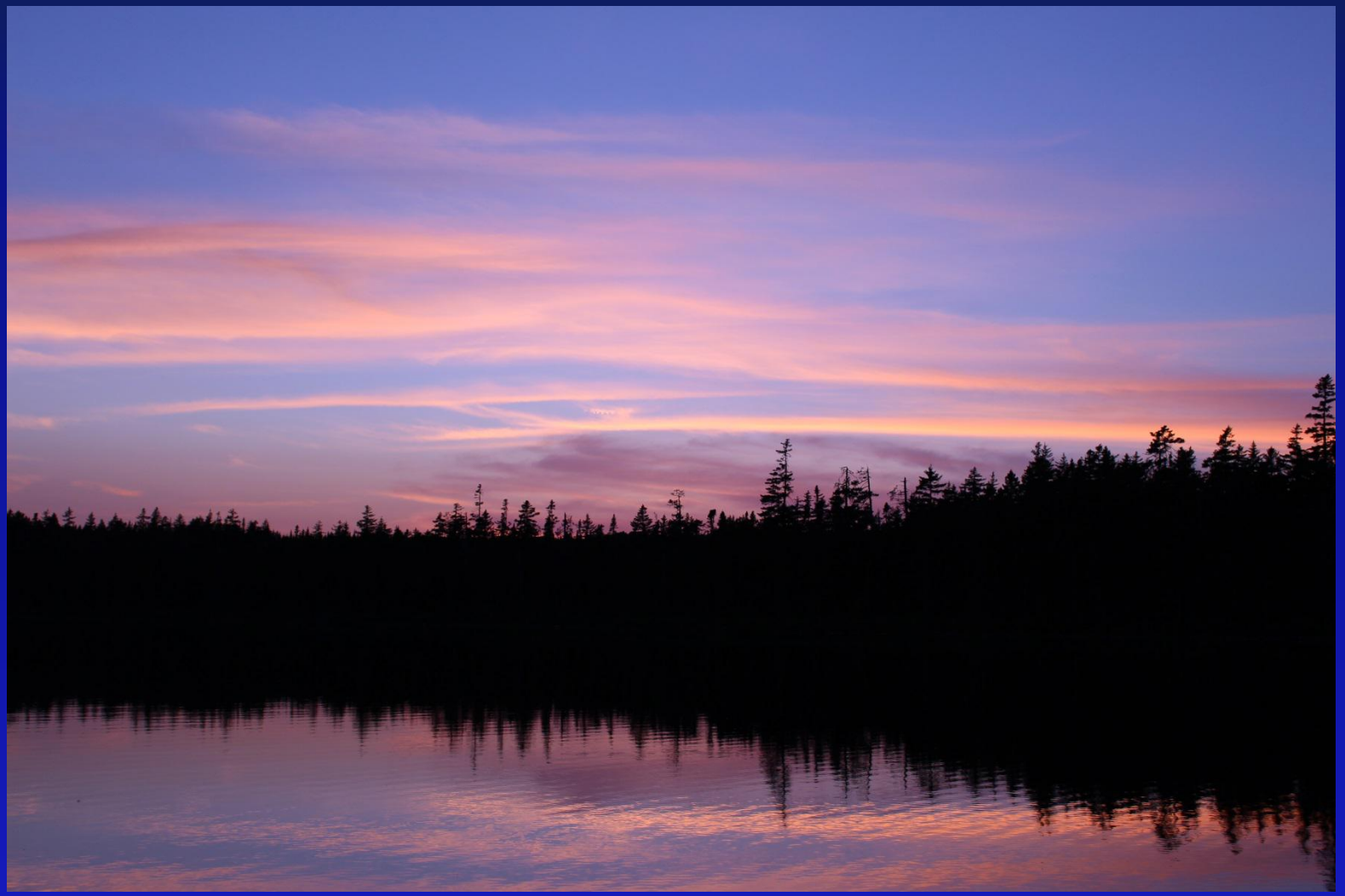
Philip et al. N Engl J Med. 1995;333:1540-1545.

Phase 3 trials evaluating salvage regimens in relapsed/refractory DLBCL

Study	1st Author	n	Regimen	% ORR	% ASCT	EFS (3-4 yrs)	OS (3-4 yrs)
Coral	Gisselbrecht	396	R-DHAP vs R-ICE	63%	54%	35%	51%
				64	50	26	47
NCIC-CTG	Crup	619	R-DHAP vs R-GDP	44	49	26	39
				45	52	26	39

Coral study C. Gisselbrecht , et al. J Clin Oncol. 2010 Sep 20;28(27):4184-90

GDP: gemcitabine, dexamethasone, and cisplatin
* both the CORAL and NCIC-CTG trials did not demonstrate a benefit for the use of maintenance rituximab after ASCT.



Canada –Fly fishing

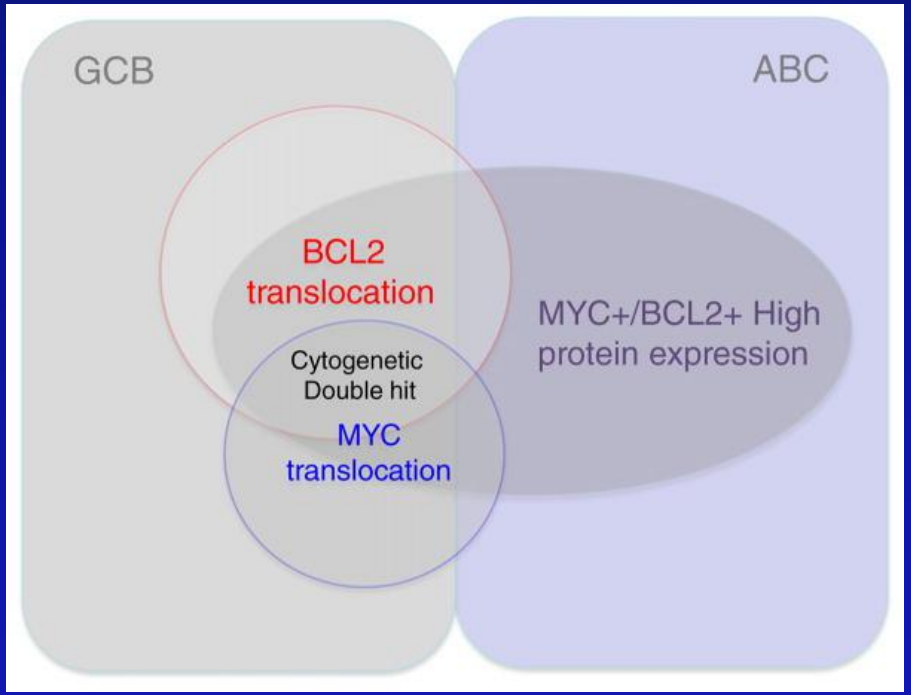
Topics

- Introduction
- Current Standard Therapy
  - Frontline
  - Relapsed/refractory DLBCL

- Special issues in management of DLBCL
  - Double Hit Lymphoma
  - Transformed DLBCL

Myc+/Bcl2+ Expressing DLBC

- BCL2+/MYC+ most common
- poor prognosis
- Can also have “triple hit”
- Recommend CNS prophylaxis



Rosenthal & Younes, Blood Rev 2016

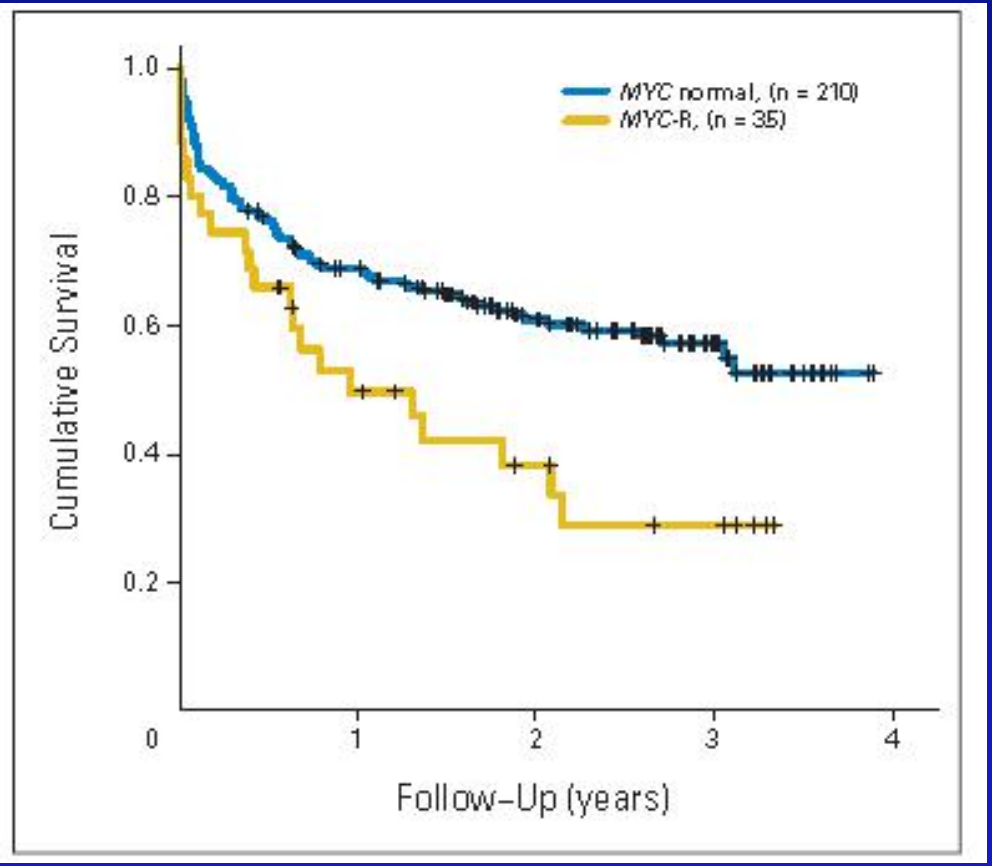
Relationship among cell of origin in DLBCL in terms of MYC/ BCL2 protein expression and genetic translocations

双重打击（双重重排）：
除 **BCL2** 和/ 或 **BCL6** 外还有 **MYC** 重排（按照 **FISH** 或标准细胞遗传学检测）的 **DLBCL** 或 **HGB-NOS**（介于 **DLBCL** 和 **BL** 之间）被称为“双重打击”淋巴瘤（如果所有这三种均重排，则称为“三重打击”淋巴瘤）。
绝大多数是生发中心 **B** 细胞样淋巴瘤

R-CHOP and MYC rearranged DLBCL

Poor prognosis

EFS



35 (14%) with MYC rearrangements

19 also had t(14;18)

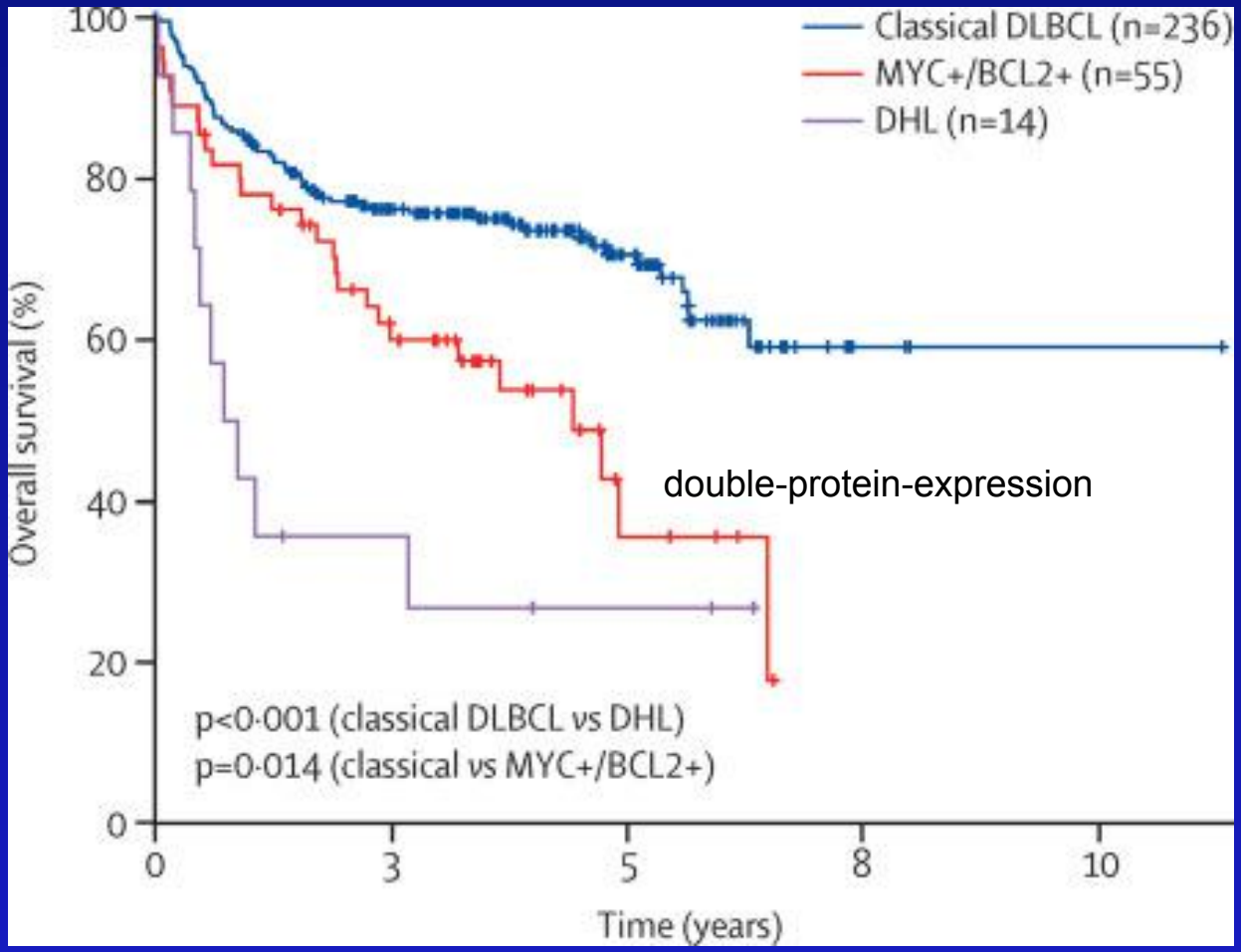
3 also had BCL6

7 "triple hit"

Therefore most "MYC+" are "double" or "triple" hit

Barrans et al, JCO 2010

Double-protein-expression lymphoma has an intermediate outcome between DHL and classical DLBCL

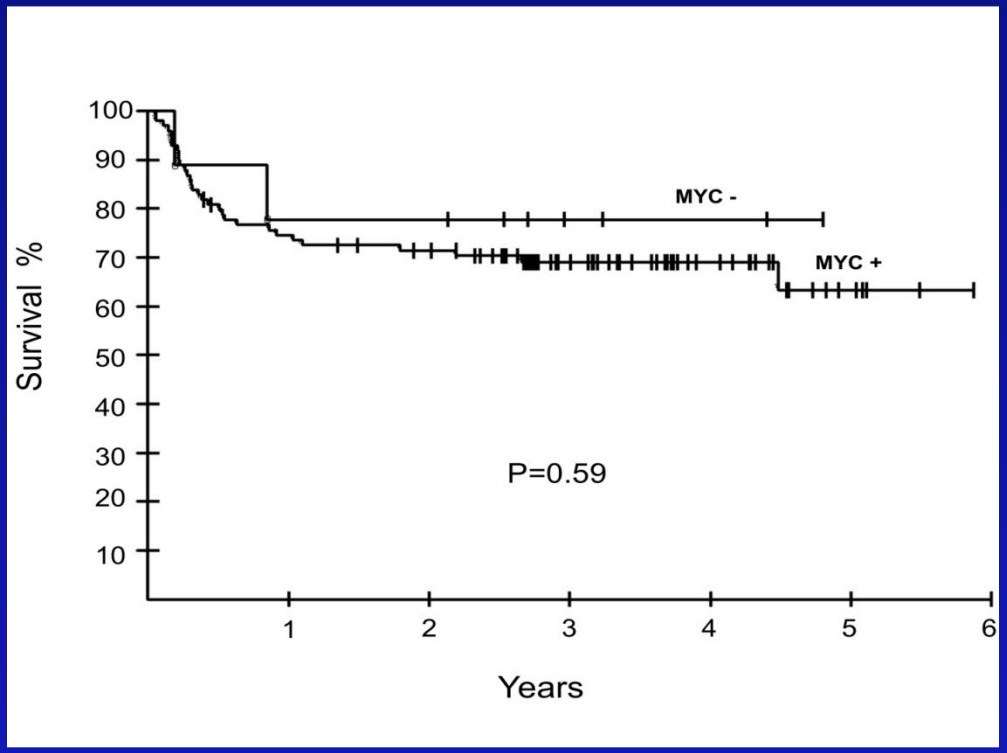


increased risk of CNS involvement
prophylaxis is recommended

Sarkozy C and Coiffier B, Lancet Oncol. 2015

DA-R-EPOCH and MYC+ DLBCL

EFS



9 MYC+ DLBCL

99 MYC- DLBCL

Similar risk by IPI

High RR/PFS in BL

Dunleavy et al, Lugano 2011

治疗

• 推荐参加临床试验。

• 虽然尚未确立标准治疗方案，但 NCCN 成员机构已采用以下方案：

DA-EPOCH-R

RHyperCVAD（环磷酰胺、长春新碱、多柔比星、地塞米松与大剂量甲氨喋呤和阿糖胞苷交替）+ 利妥昔单抗

R-CODOX-M/R-IVAC（环磷酰胺、长春新碱、多柔比星联合甲氨喋呤/ 异环磷酰胺、依托泊苷和阿糖胞苷）

• RCHOP 常伴不良结局。

• 考虑以大剂量化疗联合自体干细胞解救来巩固治疗。虽然其作用尚未确定，但已在一些 NCCN 成员机构得到采用。

• 这些患者的中枢神经系统 (CNS) 受累的风险较高（请参见 BCEL-A 2/2）；根据机构标准考虑 CNS 预防。

Outcome of chemotherapeutic regimen for DHL and DPL in retrospective series

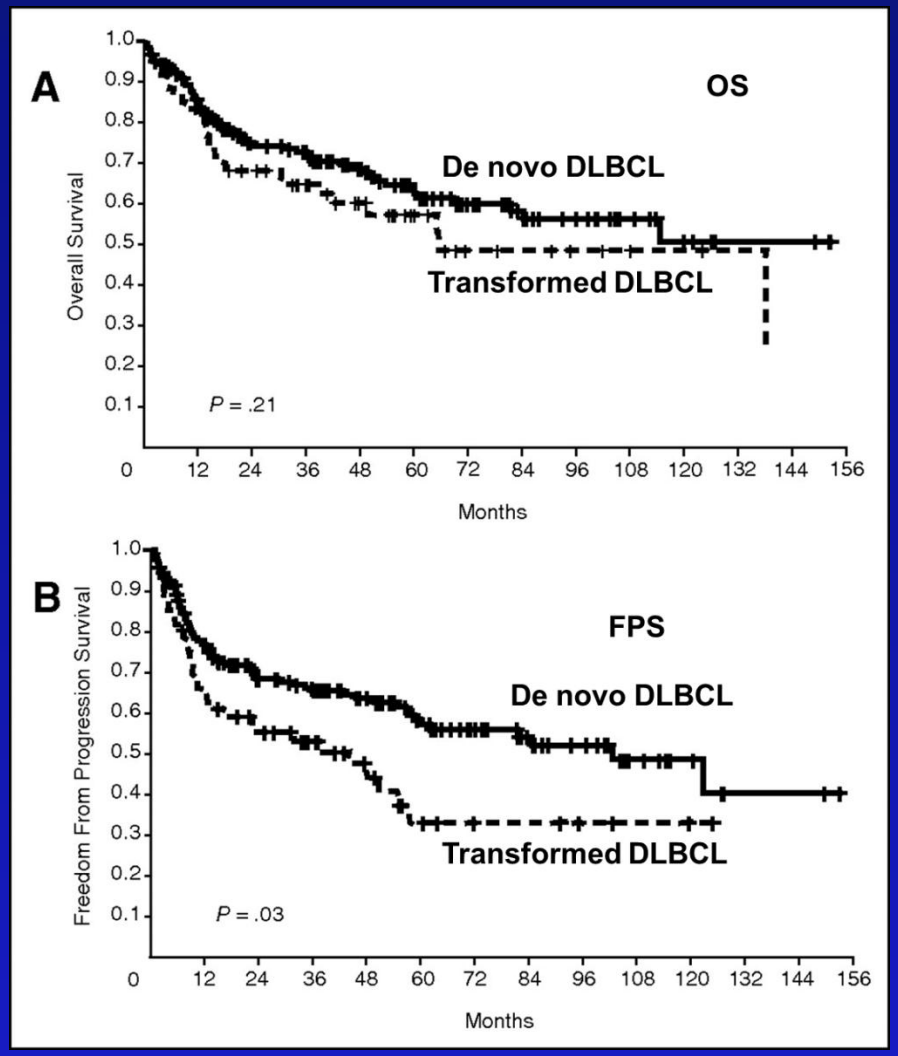
➡ *DA-EPOCH-R*

	DPL or DHL	Regimen	N (%)*	Median OS or PFS
Le Gouill et al3	DHL	R-CHOP, COPADM, ASCT, ALLO	16 (NA)	OS 5 months for all patients
Tomita et al44	DHL	CHOP, CODOX-M/IVAC, or hyperCVAD with or without rituximab	27† (NA)	OS 6 months
		High-dose chemotherapy		OS 1·4 years with rituximab
Johnson et al16	DHL	CHOP, R-CHOP	54 (4%)	0·4 years without rituximab
Li et al37	DHL	R-CHOP	57 (NA)	OS 18·6 months
	DHL			3-year EFS 15·6%;
Horn et al30	DPL	R-CHOP	21 (4·7%)	3-year OS 41·6%
Oki et al22	DHL	R-CHOP, R-hyperCVAD, DA-EPOCH-R	129 (NA)	3-year EFS 33%; OS 4%
		R-CHOP, R-hyperCVAD, DA-EPOCH-R		PFS 10·9 months<comma>OS 21·9
Petrich et al36	DHL	R-CODOX-M/IVAC	311 (NA)	months for all regimens
Sun et al48	DHL	R-CODOX-M/IVAC	32 (NA)	2-year PFS 41%; 2-year OS 53%
		R-CHOP, DA-EPOCH-R, R-HyperCVAD		
Cohen et al45	DHL	R-CODOXM/R-IVAC	29 (NA)	PFS 8 months; OS 12·5 months
	DHL	R-CHOP (81%)	23 (10%)	1-year OS 60%
Johnson et al29	DPL	R-CHOP	55 (19%)	5-year OS 36%
	DHL		14 (5%)	5-year PFS 27%
Green et al8	DPL	R-CHOP	54 (21%)	OS 24 months
	DHL		11 (6%)	OS 13 months
Valera et al15	DPL	R-CHOP	32 (15%)	PFS 18 months; OS roughly 30 months
Friedberg et al56	DPL	R-CHOP + iodine-131 tositumomab	13 (20%)	2-year PFS 58%
Perry et al57	DPL	NA	47 (44%)	2-year OS 58%; EFS roughly 52%
Hu et al33	DPL	R-CHOP	55 (18%)	5-year OS 30%PFS 27%

Sarkozy C and Coiffier B, Lancet Oncol. 2015

CTX, VCR, doxorubicin, MTX, ifosfamide, VP-16, Ara-C, and rituximab (CODOX-M/ IVAC)

Treatment Outcomes of DLBCL: *Transformed vs de novo*



Ghesquières H et al. JCO 2006

treated as de novo

Chemotherapy

CHOP:cyclophosphamide, doxorubicin, vincristine, and prednisone

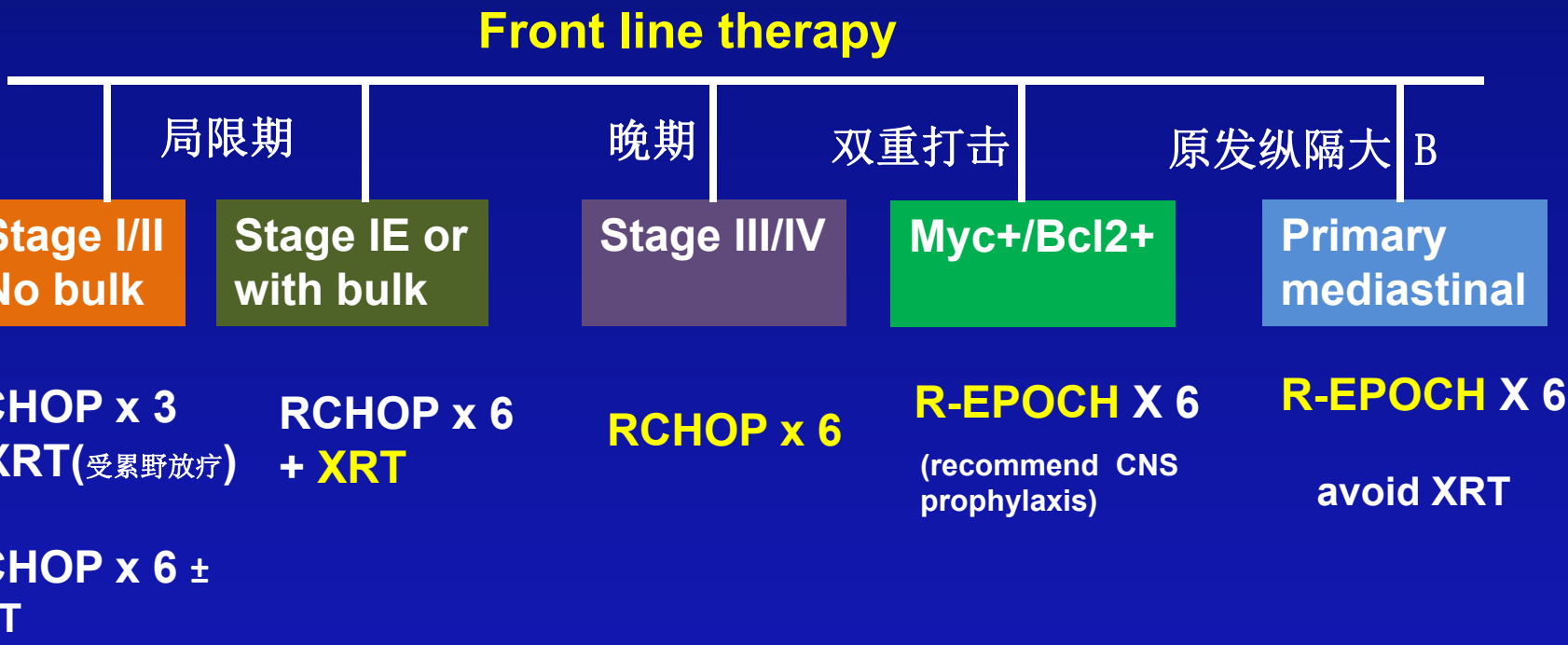
Or

ACVBP: doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone

DLBCL: CNS Prophylaxis Whom, When and What?

- Incidence of CNS involvement: 5—6% in general. Low risk group <3%, high risk 11%.
- Risk factors
- CNS prophylaxis agents and administration
  - IT-MTX, or Ara-C
  - HD MTX

Therapy of DLBCL - Summary



Relapsed/refractory DLBCL

- **Salvage:** R-DHAP,RICE,RESHAP followed by autologous stem cell transplantation
- CART
- Clinical trials

Topics and Conclusions

- Introduction
- Current Standard Therapy
  - Frontline: R-CHOP x 6
  - Relapsed/refractory DLBCL: Salvage or clinical trial
- Special issues in management of DLBCL
  - Double Hit Lymphoma: DA-REPOCH
  - Transformed DLBCL: treated as de novo

Thanks

Phase 3 trials evaluating alternative regimens to R-CHOP or evaluating high-dose therapy approaches

Study	Patients	Regimens	Outcome	*P* value
Recher et al	380	R-ACVBP	3-year PFS 87% vs 73%	.002
		vs R-CHOP	3-year OS 92% vs 84%	.007
Cunningham et al	1080	R-CHOP-14	2-year PFS 75% vs 75%	NS
		vs R-CHOP	2-year OS 83% vs 81%	NS
Delarue et al	602	R-CHOP-14	3-year EFS 56% vs 60%	NS
		vs R-CHOP	3-year OS 69% vs 72%	NS
Le Gouill et al	340	R-HDT + ASCT	3-year PFS 76%[*]	NS
		vs R-CHOP-14	3-year OS 83%	NS
Schmitz et al	275	R-Mega-CHOEP	3-year EFS 61% vs 70%	NS
		vs R-CHOEP-14	3-year OS 77% vs 85%	.08
Vitolo et al	399	R-HDT + ASCT	3-year PFS 70% vs 59%	.01
		vs R-dose dense CT	3-year OS 81% vs 78%	NS
Stiff et al	253	(R)-CHOP × 6 + ASCT	2-year PFS 69% vs 55%	.005
		vs (R)-CHOP × 8[†]	2-year OS 74% vs 71%	NS

Sehn LH and Gascoyne RD, Blood, 2015