Traitement des lymphomes à grandes cellules B

Bertrand Coiffier

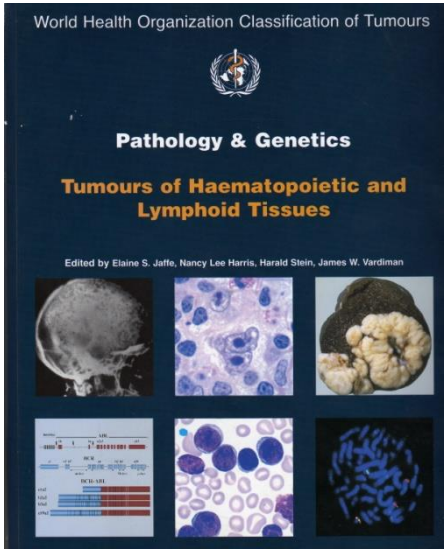
Hôpitaux de Lyon

Service d' Hématologie
Hospices Civils de Lyon

Equipe
« Pathologie des Cellules Lymphoïdes »
UMR 5239 CNRS – UCB – ENS - HCL

The Lymphoma
Study Association

DLBCL WHO Classification (2008)



Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)

- Common morphologic variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
- Molecular subgroups
  - Germinal-centre B-cell-like (GCB)
  - Activated B-cell-like (ABC)
- Immunohistochemical subgroups
  - CD5-positive DLBCL
  - Germinal-centre B-cell-like (GCB)
  - Non-germinal-centre B-cell-like (Non-GCB)

DLBCL subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- Epstein-Barr virus–positive DLBCL of the elderly

Other lymphomas of large B cells

- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive DLBCL
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma

Borderline cases

- between DLBCL and Burkitt lymphoma
- between DLBCL and classical Hodgkin lymphoma

DLBCL – Pathology (WHO)

- Some subtypes worse than others
- No indication that treatment must be different for each subtype
  - Primary CNS lymphoma
  - Intermediate Burkitt or Hodgkin
  - Plasmablastic (CD20-)
  - “Double hit” myc+ bcl2+

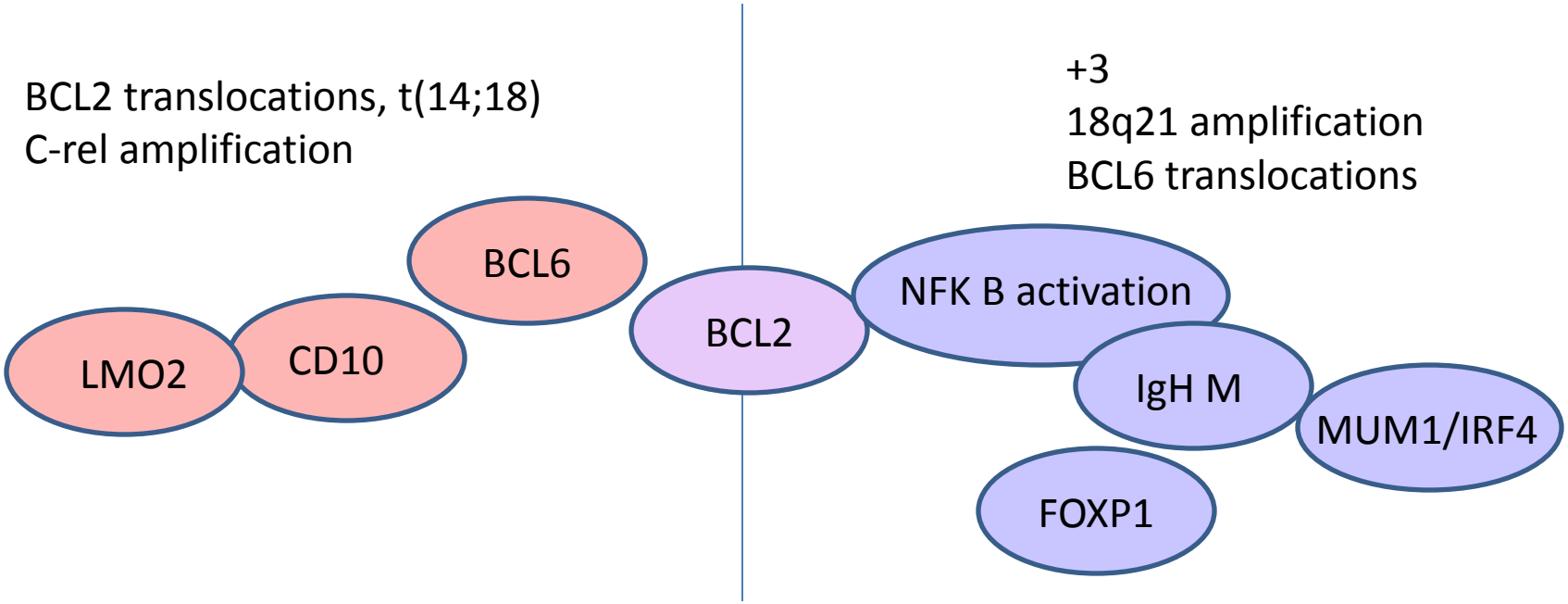
Two distinct diseases

GC B-cell like

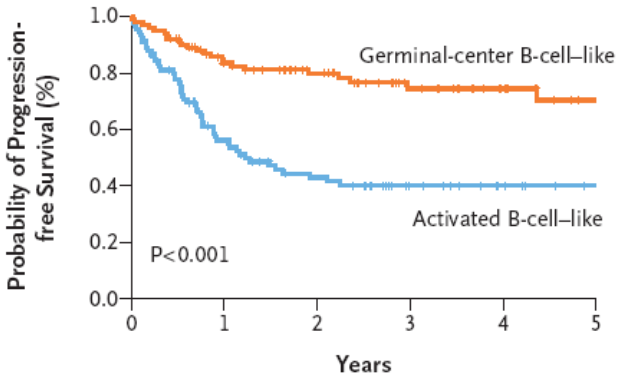
BCL2 translocations, t(14;18)
C-rel amplification

Activated B-cell like

+3
18q21 amplification
BCL6 translocations

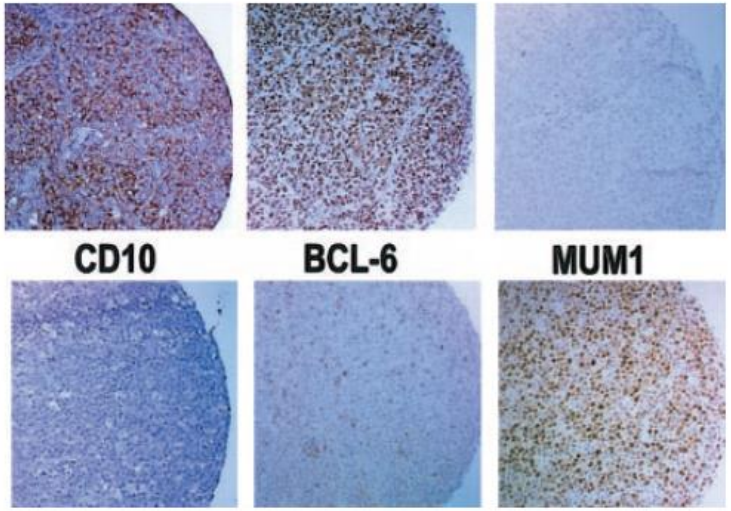


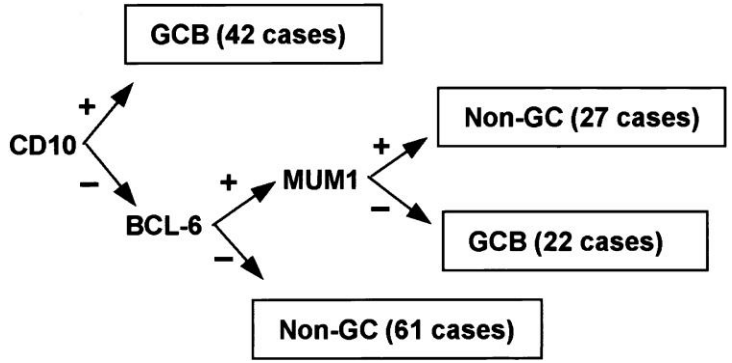
Mir-125b
Mir-17-92

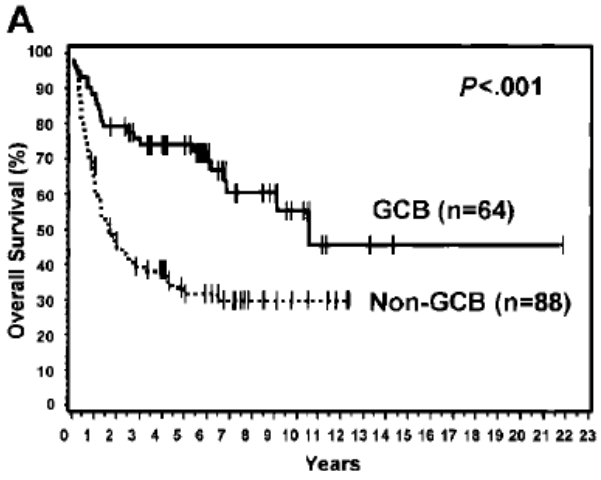


Mir-155
Mir-21
Mir-223

Immunohistochemistry as surrogate







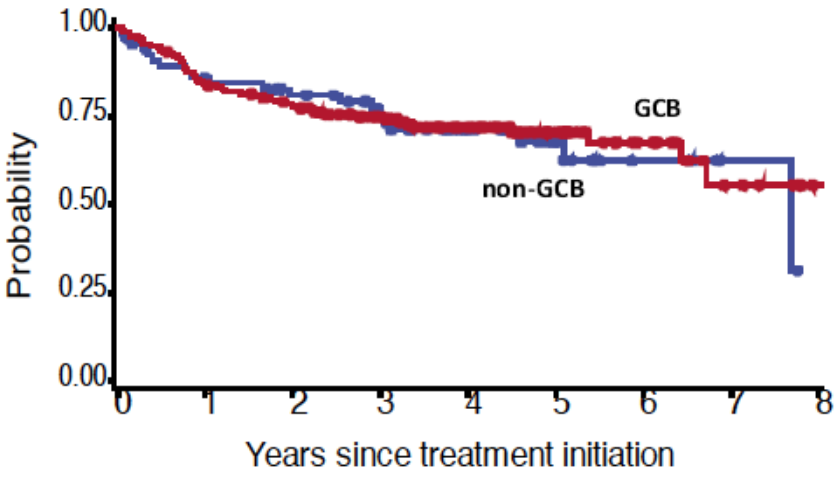
Discordances with cDNA : 20%

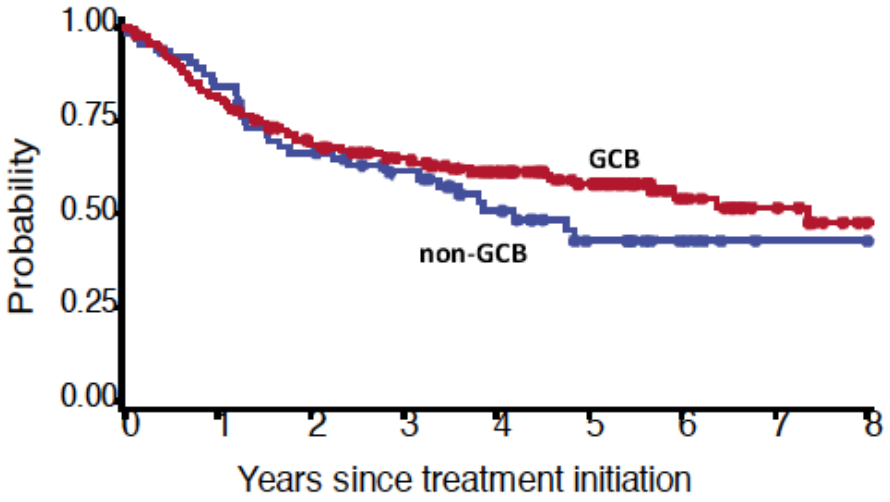
Hans CP et al. *Blood* 2004;103:275-82

Prognostic significance of immunohistochemical biomarkers in DLBCL

A study from Lunenburg Lymphoma Biomarker Consortium

2 randomized studies comparing R-CHOP to CHOP





R-CHOP
347 patients

CHOP
289 patients

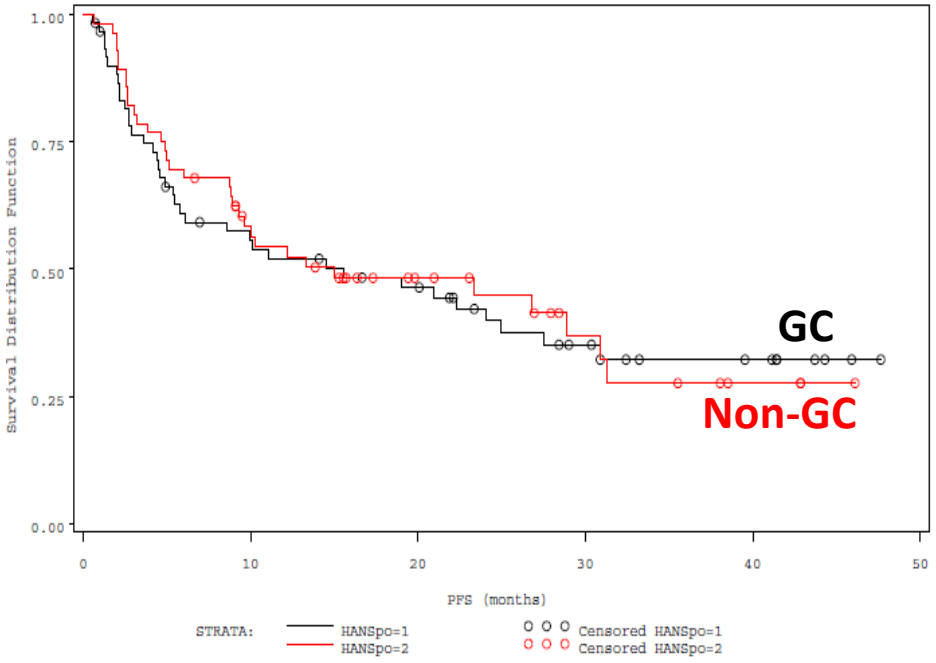
1514/2451 patients from 12 studies with TMA material

G Salles et al. Blood online 05/2011

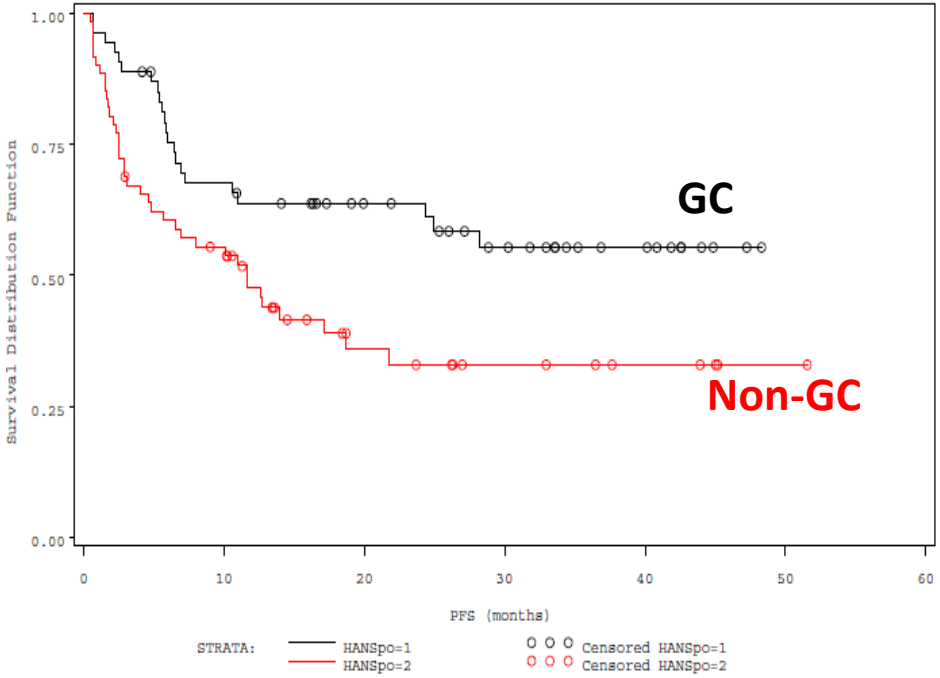
Progression-free survival

According to salvage regimen and phenotype

R-ICE



R-DHAP



Interaction test p = 0.035

Thieblemont C et al. *J Clin Oncol*. 2011;29: Sept 26

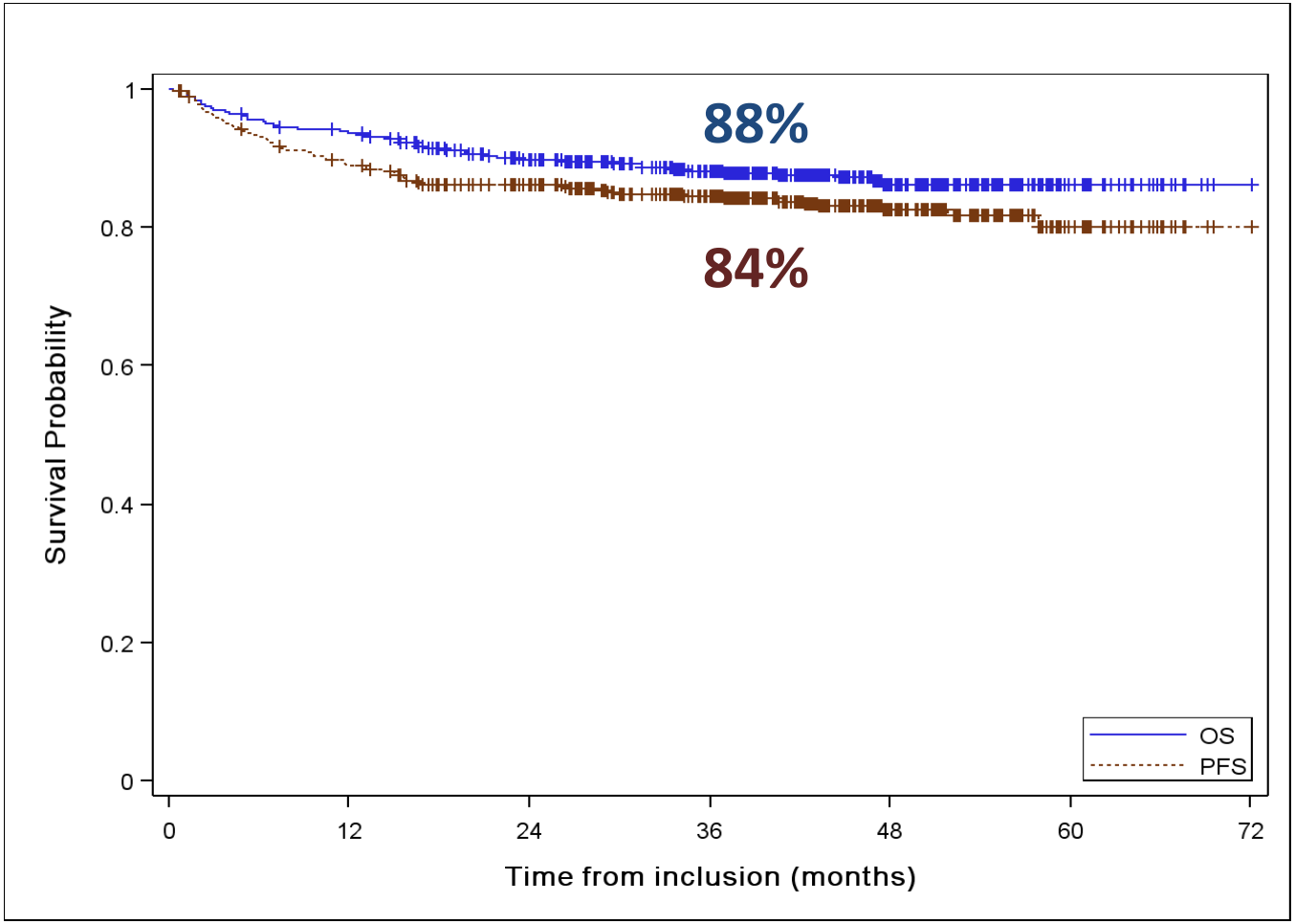
DLBCL = One Shot Cancer

- Only patients who reached a CR with the first line chemotherapy have a chance to be cured
  - Most true (with positive PET scan) PR progress
- A minority of patients who progressed responded to salvage chemotherapy and will be transplanted
  - Only 40% of transplanted patients did not relapse

Objective of treatment: Reach a CR and prevent a relapse

PFS / OS in DLBCL, patients < 60 years

GELA studies 2003-2009, first line R-ACVBP



Gela

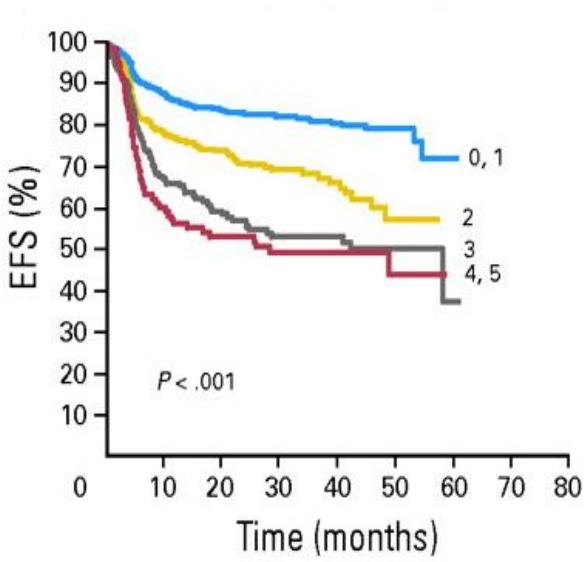
What is important to know before treating a patient with DLBCL

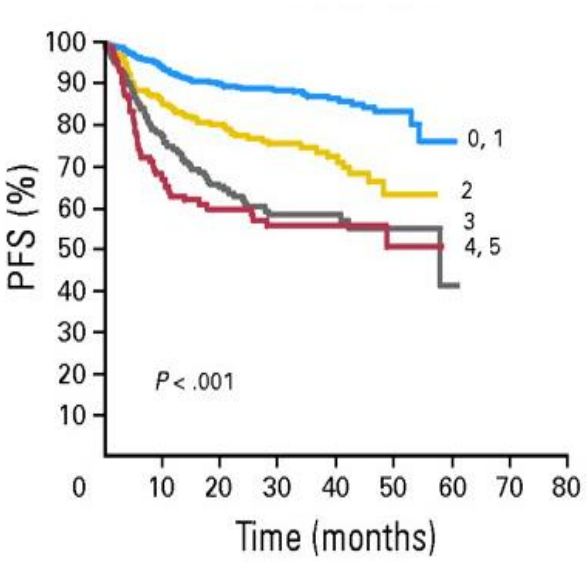
- Age
  - Young (<61 y)
  - Elderly (60-80 y)
  - Very old (>80 y)
- IPI – age-adjusted IPI
  - Score 0
  - Score 1
  - Score 2 or 3

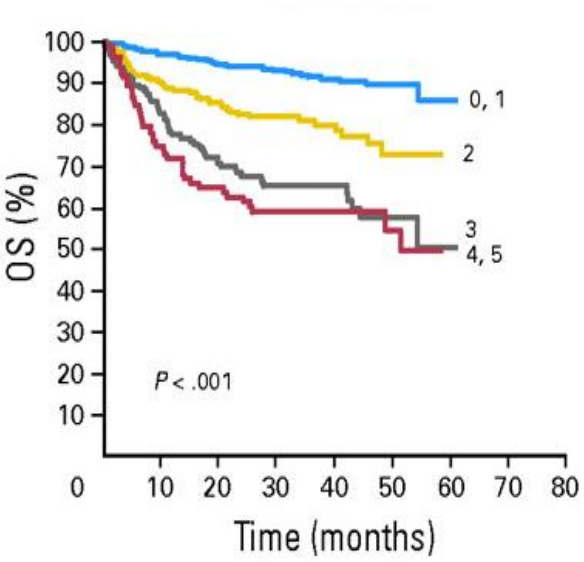
EFS, PFS, and OS, according to IPI score

MInT (≤ 60 years, age-adjusted IPI [aaIPI] 0, 1; n = 380)
MegaCHOEP trial (≤ 60 years, aaIPI 1-3; n = 72)
RICOVER-60 (> 60 years, all IPI groups; n = 610)

All trials (18 to 80 years of age, all IPI groups; n = 1,062)







Ziepert M et al. *JCO* 2010;28:2373-2380

How to chose the good treatment?

- Patient
  - Age, concomitant diseases
  - Expectations
- Lymphoma
  - Prognostic factors
    - IPI, biological parameters …
  - Cell of origin

→ No single solution for all DLBCL patients

How many subgroups?

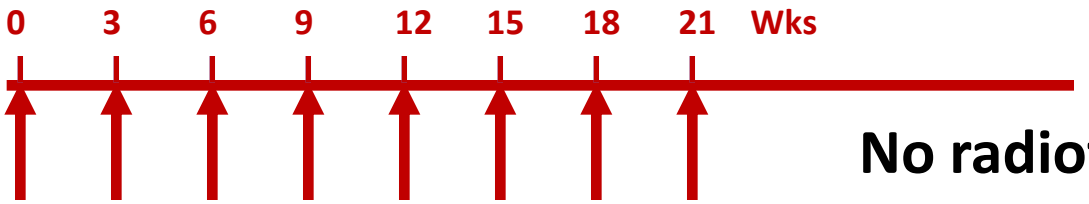
- Young (<60 or 65 y)
  - Localized: stage I or aaIPI=0
  - Standard risk: aaIPI=1
  - Poor risk: aaIPI=2 or 3
- Elderly (65 – 80 y)
  - Localized: stage I or aaIPI=0
  - aaIPI=1 to 3
- Very old (>80 y)

Gela

Standard Regimen for DLBCL patients

R-CHOP

R-CHOP 21



No radiotherapy

Usual results with R-CHOP in DLBCL

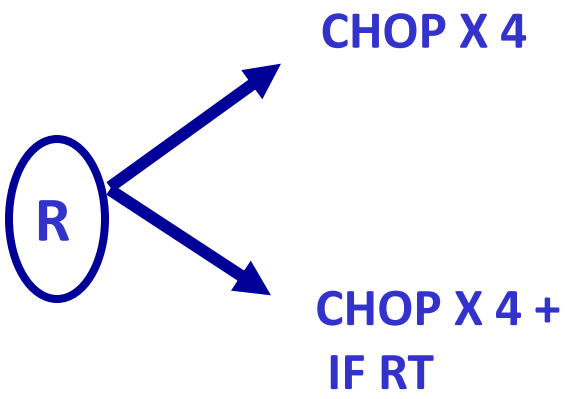
- 5-year survival according to aaIPI & age
  - aaIPI score = 0: over 85%
  - Young, aaIPI score = 1: over 80%
  - Young, aaIPI score >1: around 60%
  - Elderly, aaIPI score >0: around 50%
  - Very old: around 30%
- For 30-40% of patients, R-CHOP is not satisfactory

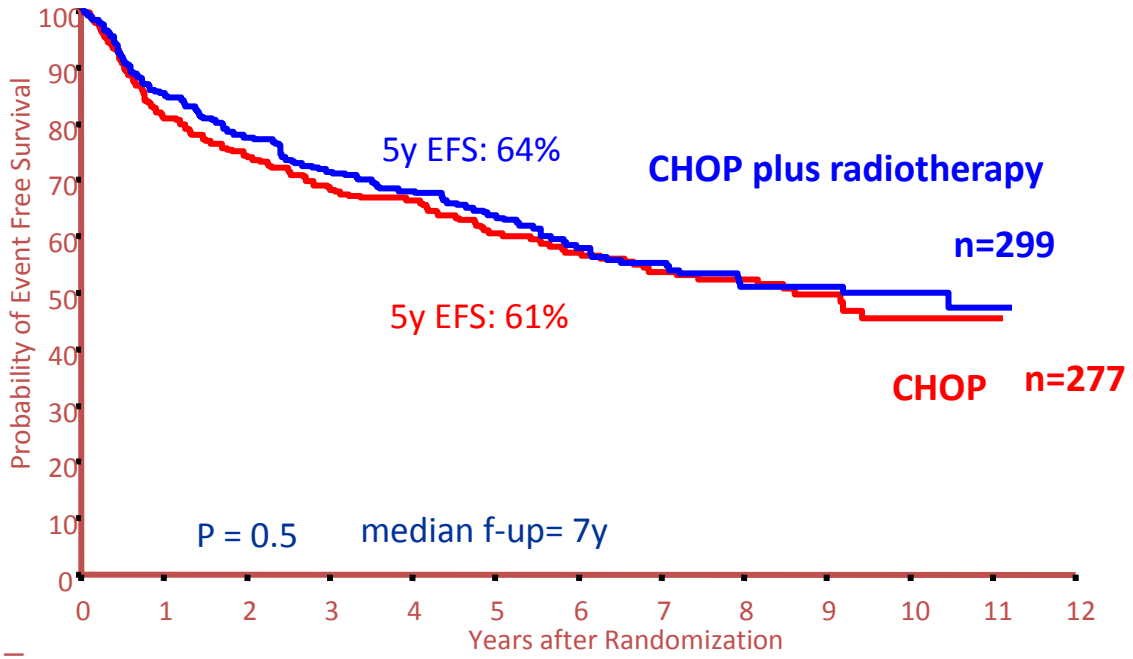
Young & elderly patient, score 0
(Localized disease)

R-CHOP x 6

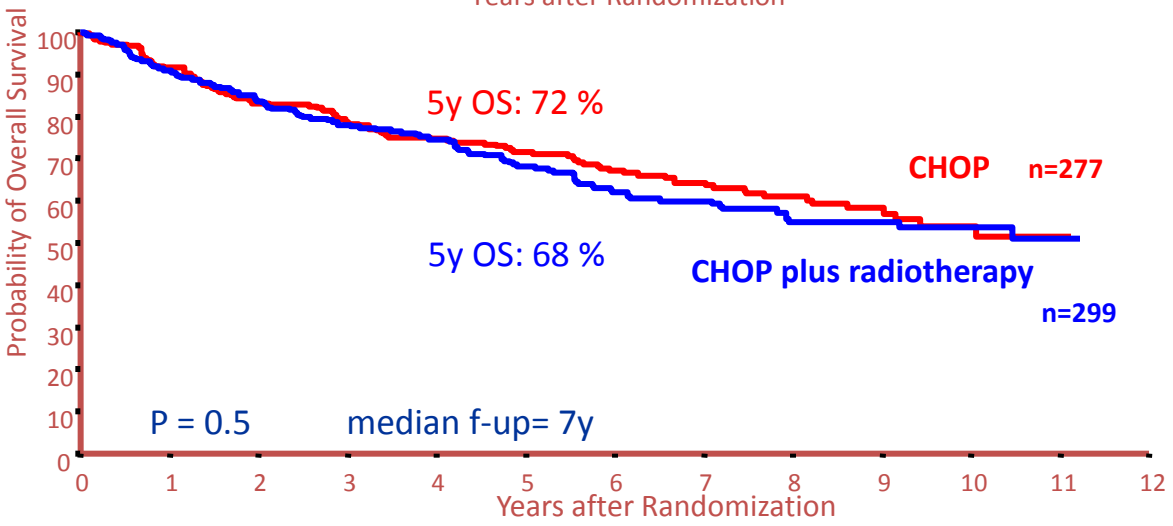
No radiation therapy
(Some do RT)

LNH 93-4 study: IPI=0; >60y



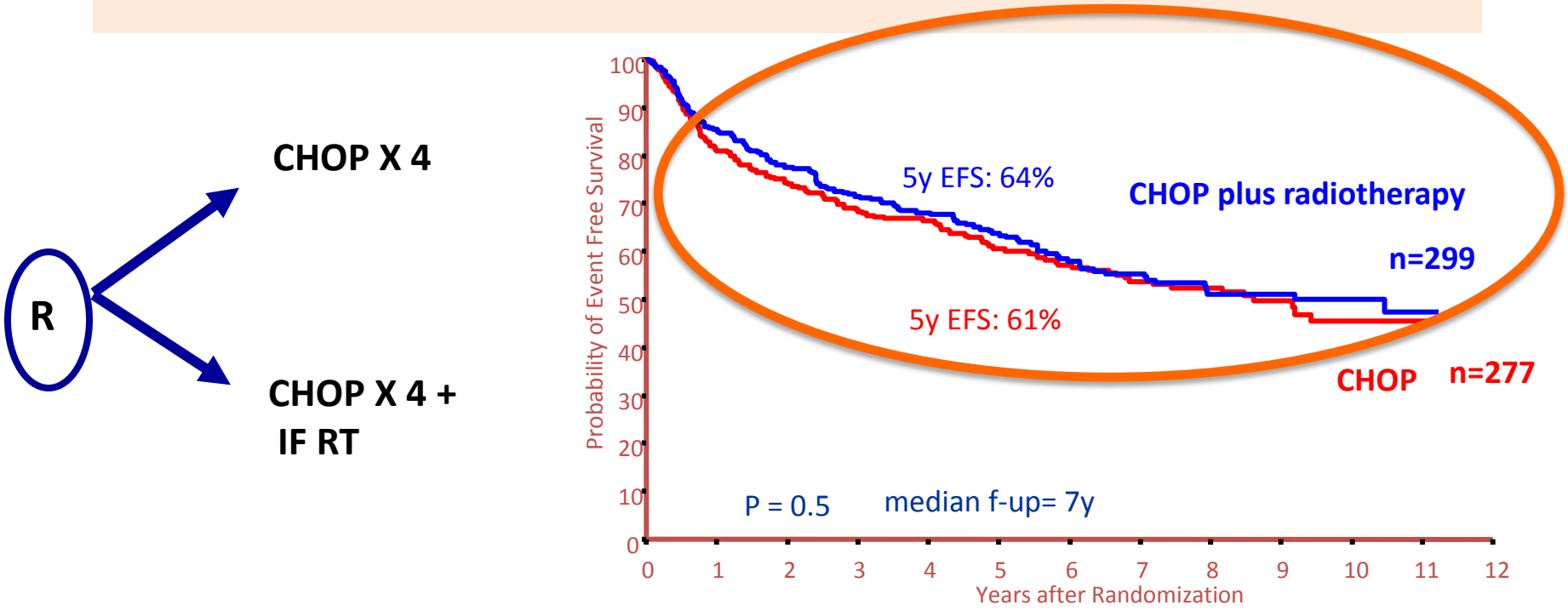


- **Identical CR rates**
- **More secondary cancers with RT**



G Fillet, JCO 2007

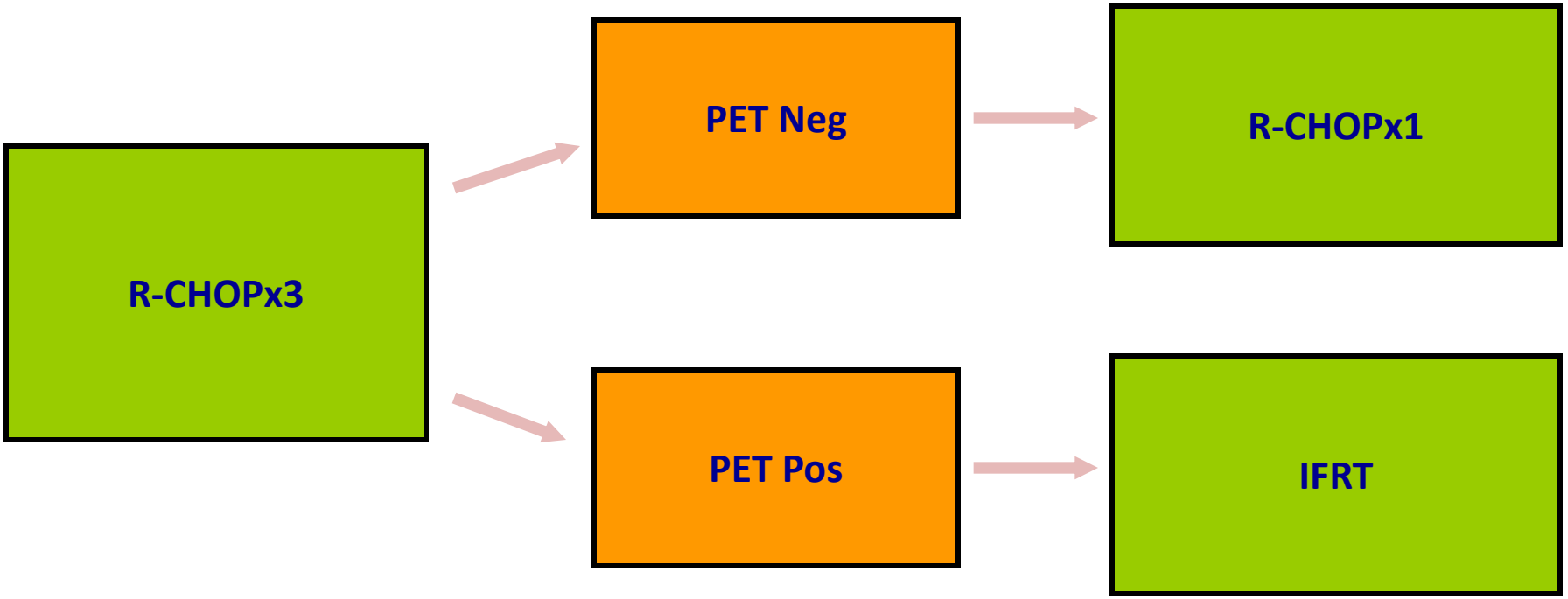
LNH 93-4 study: IPI=0; >60y



In good risk patients, 50% survival is not a satisfactory result

- Add rituximab
- Use 6 cycles of R-CHOP

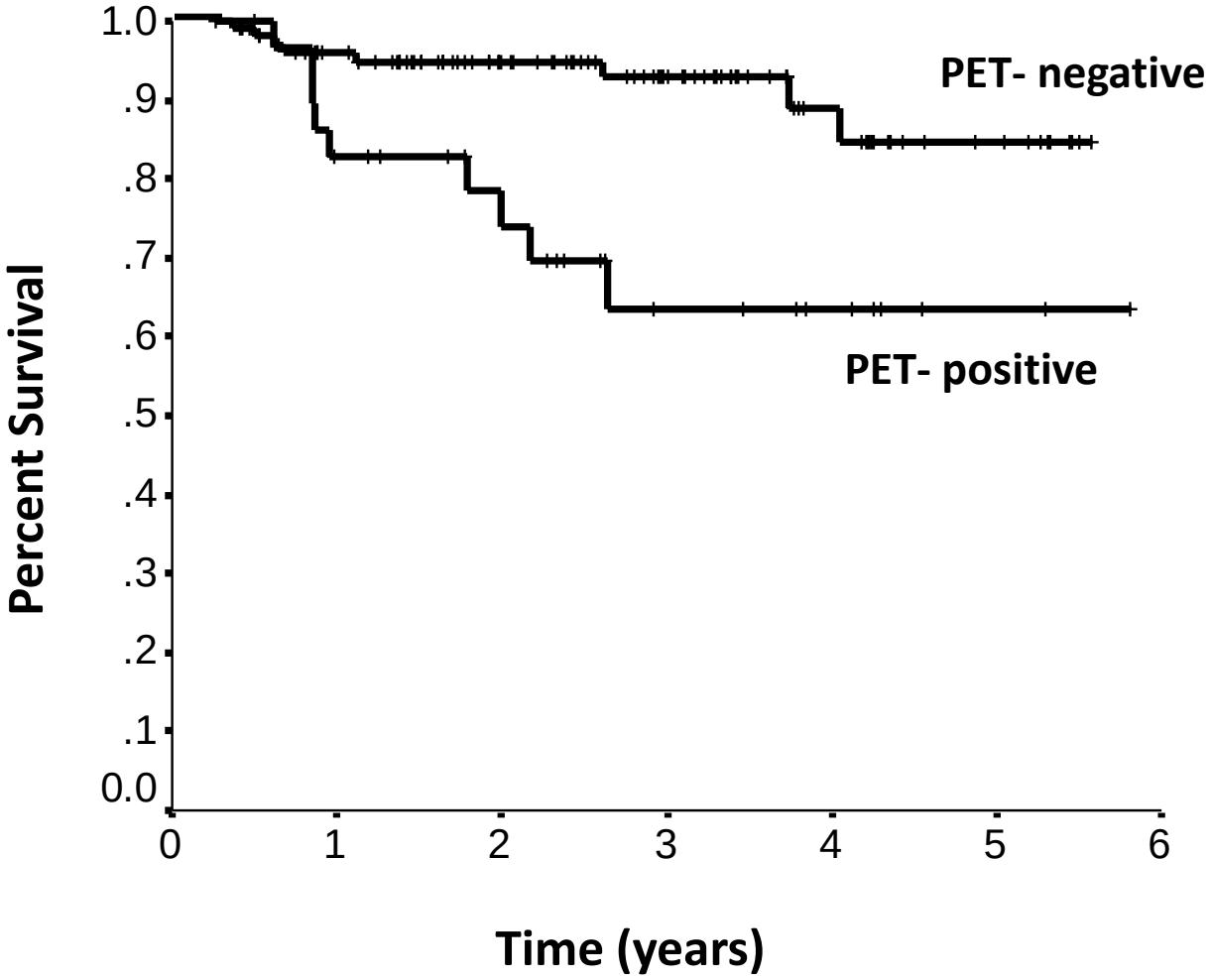
PET-Based Treatment Algorithm for Limited-Stage DLBCL



134 patients, 57% stage I & 43% stage II

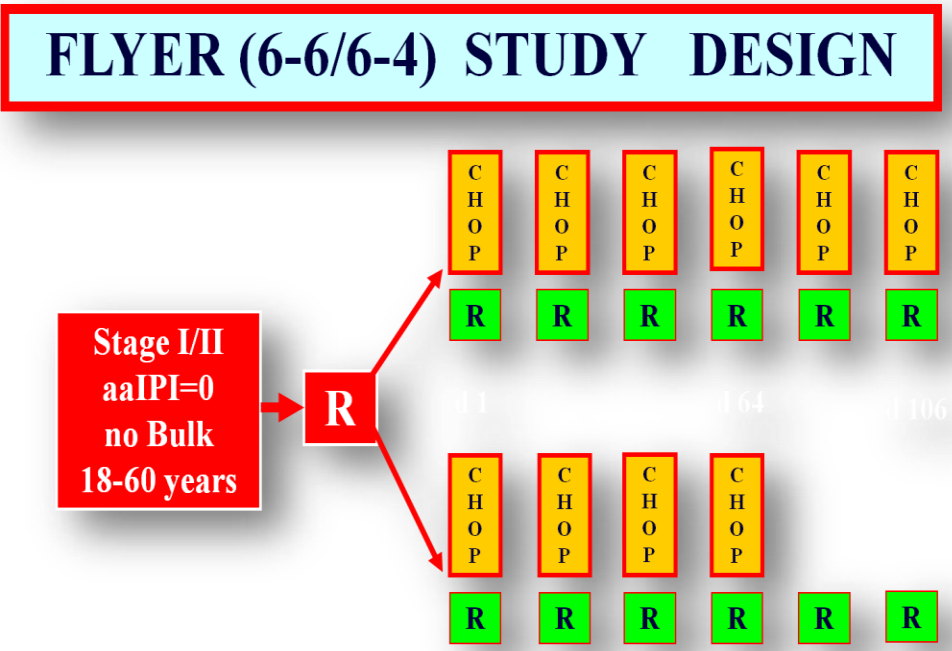
L Sehn et al. ICML 2011

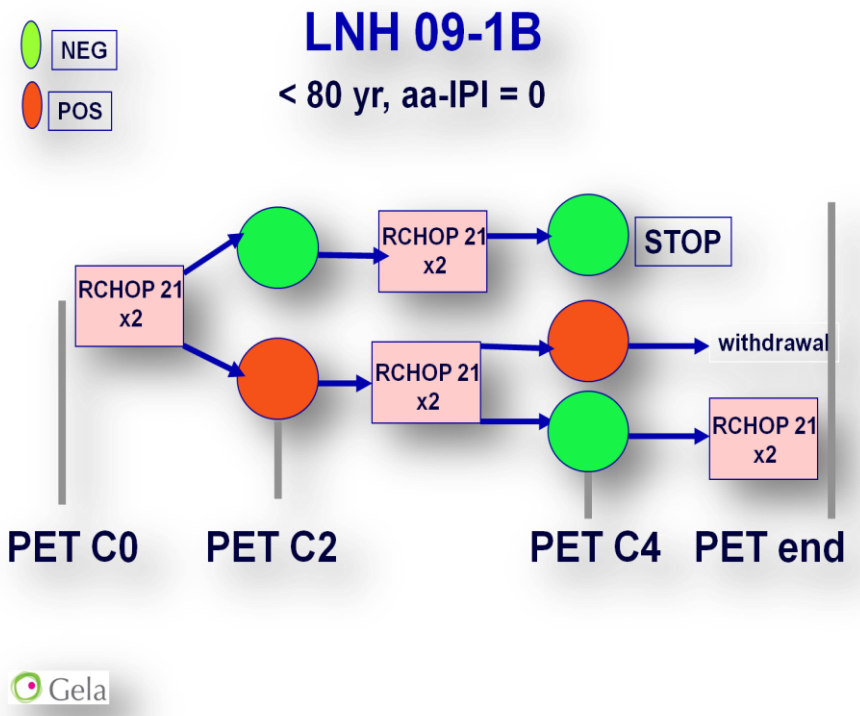
TTP According to PET Status



L Sehn et al. ICML 2011

Ongoing studies, aaIPI = 0





Elderly patient, score > 0

R-CHOP x 8

Is there something better?

GELA study: 10 years follow-up

Figure 3. Event-free survival.

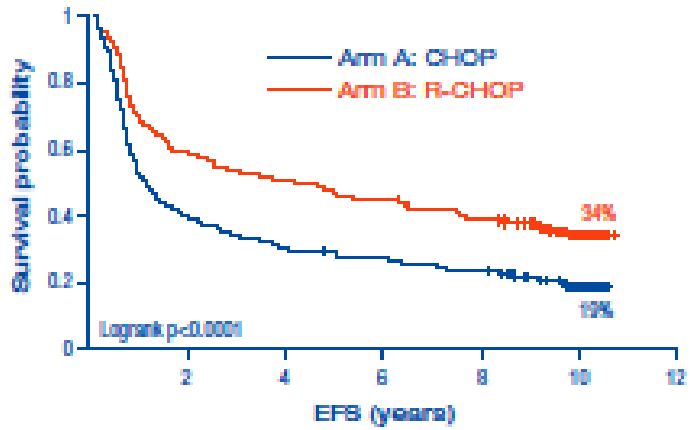


Figure 4. Progression-free survival.

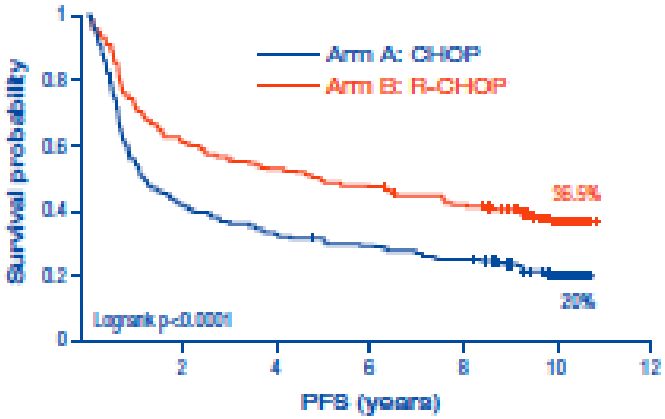


Figure 5. Disease-free survival for patients in CR.

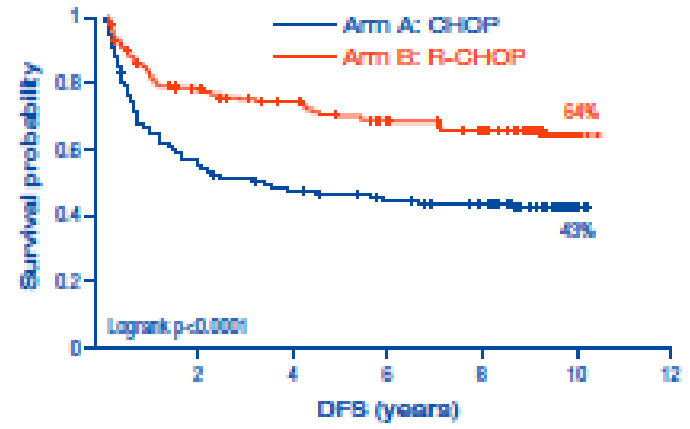
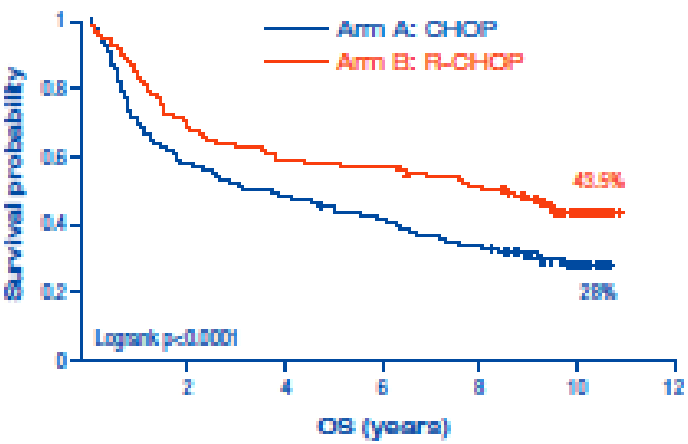


Figure 6. Overall survival.



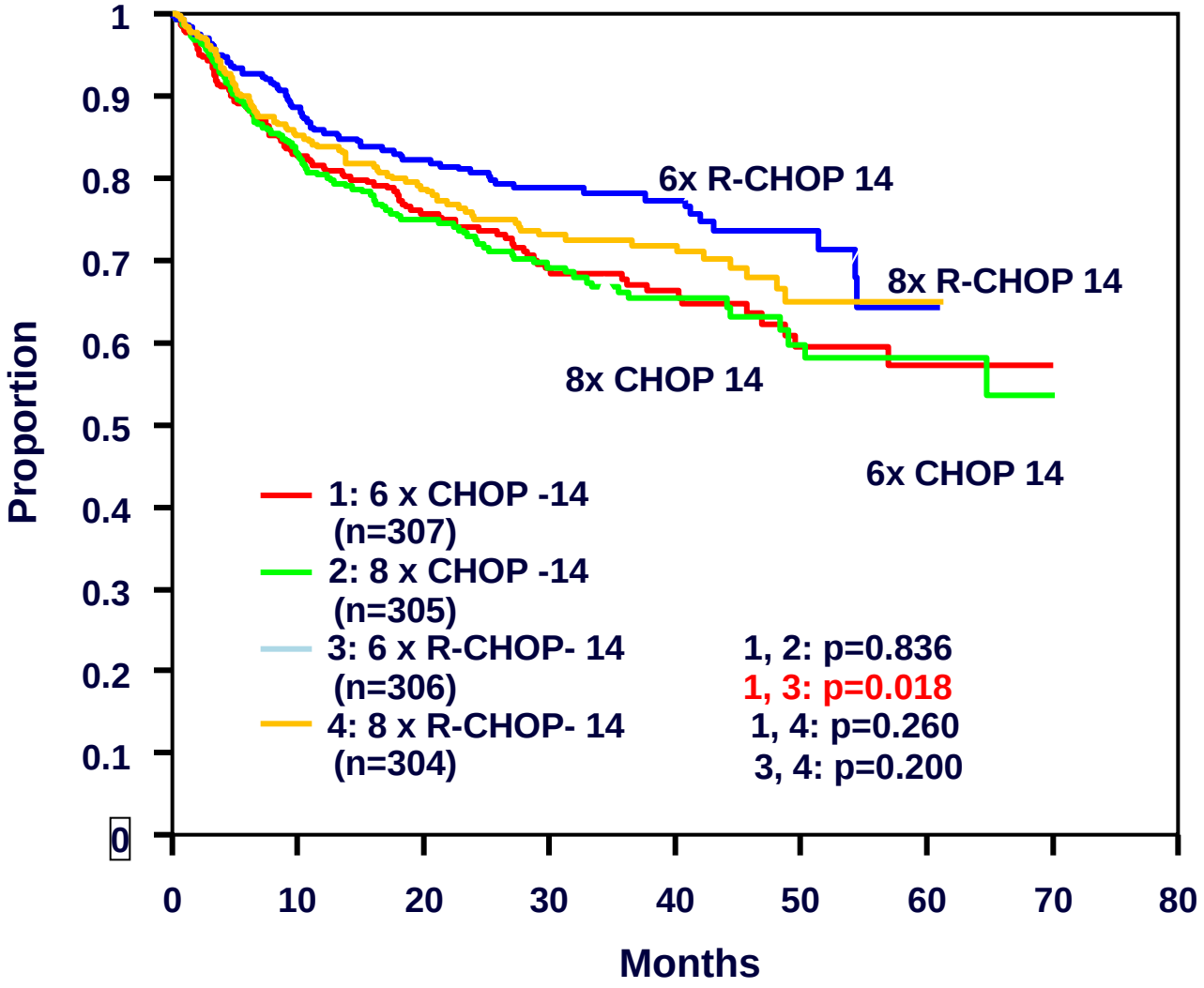
Gela

B Coiffier et al. Blood 2010;116:2040

Elderly (<80 y) - Possibilities

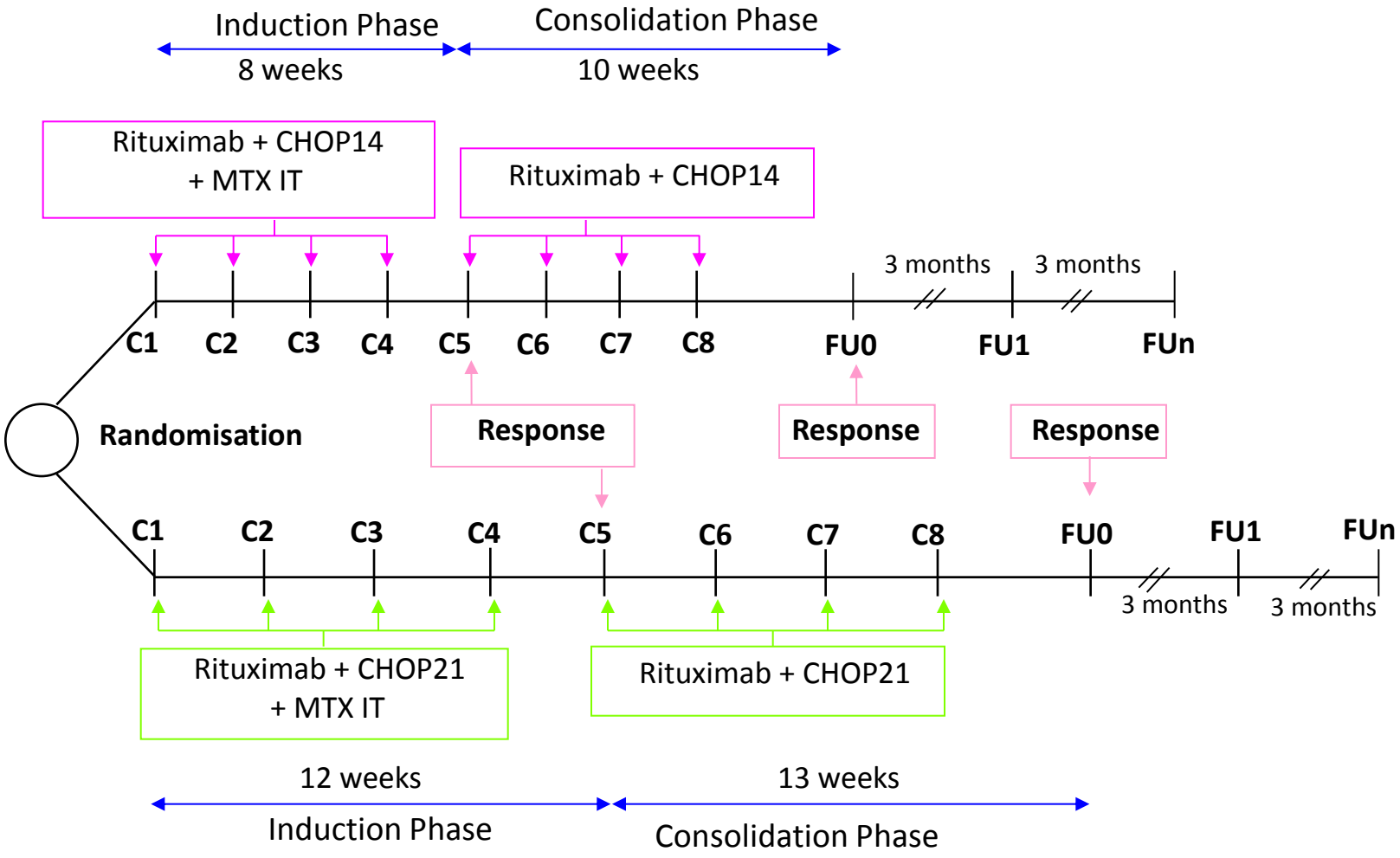
- R-CHOP-14
- Replace one component of R-CHOP by a better drug
- R-CHOP + X
- R-CHOP followed by X
- Higher dose regimens

RICOVER-60
Overall Survival



Pfreundschuh et al., Lancet Oncol. (2008)

LNH 03-6B: Study design

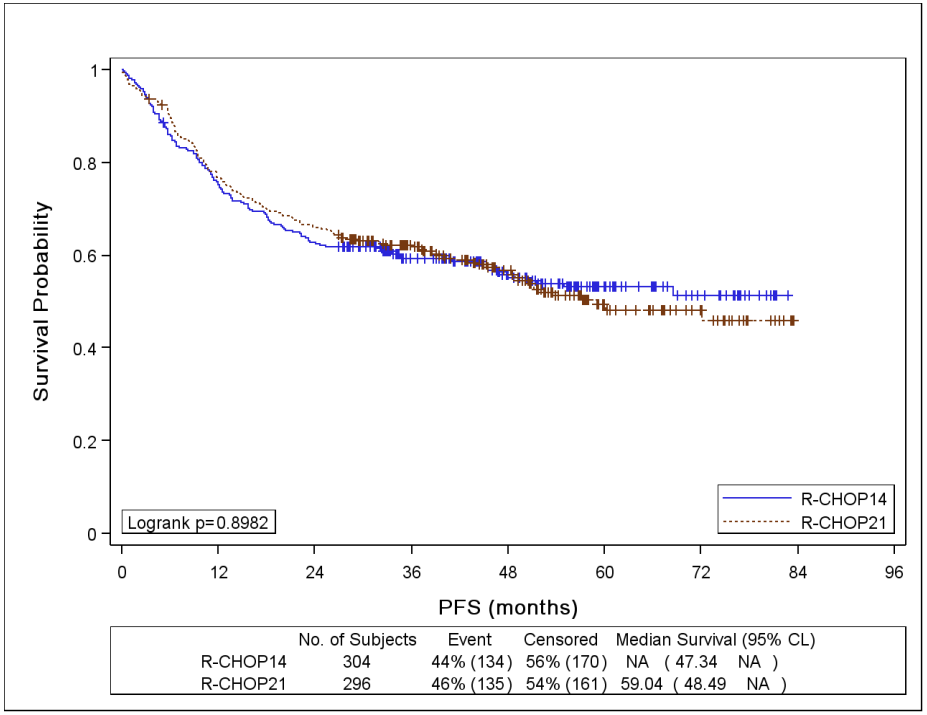


Aranesp®, one weekly subcutaneous injection in Arms A1 and B1
Filgrastim ou Pegfilgrastim according to physician decision

R Delarue et al. ICML 2011

R-CHOP 14/21 Study

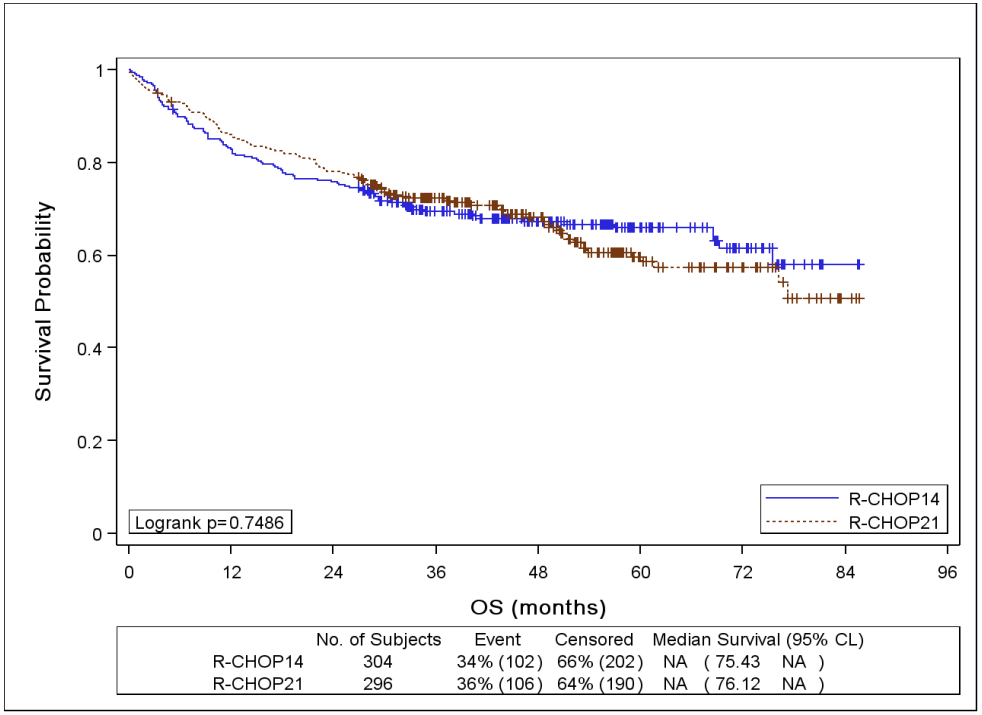
PFS



3y-PFS : 60% vs 62%

HR: 0.99 (95%CI: 0.78-1.26); p=0.94

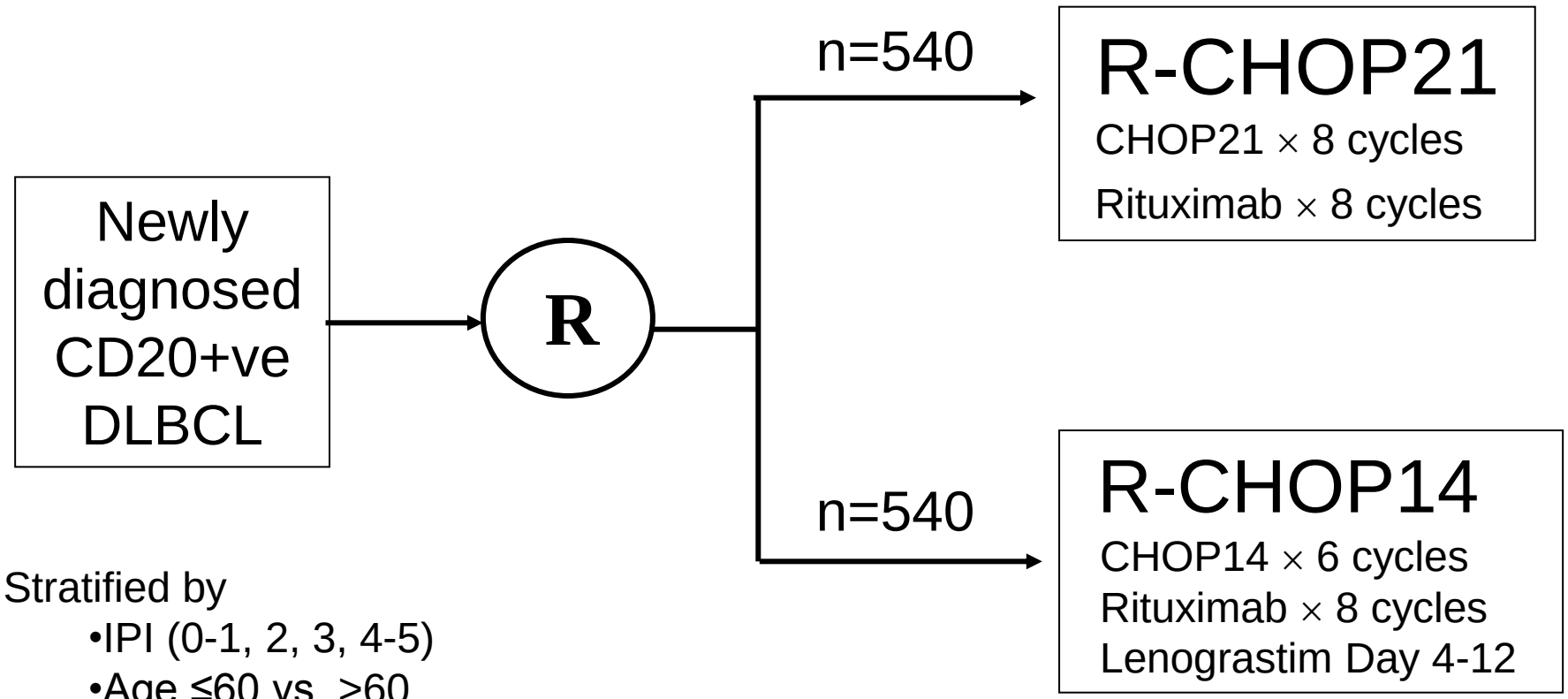
OS



3y-OS : 69% vs 72%

HR: 0.93 (95%CI: 0.76-1.26); p=0.76

Trial design: R-CHOP14 vs. 21



Stratified by

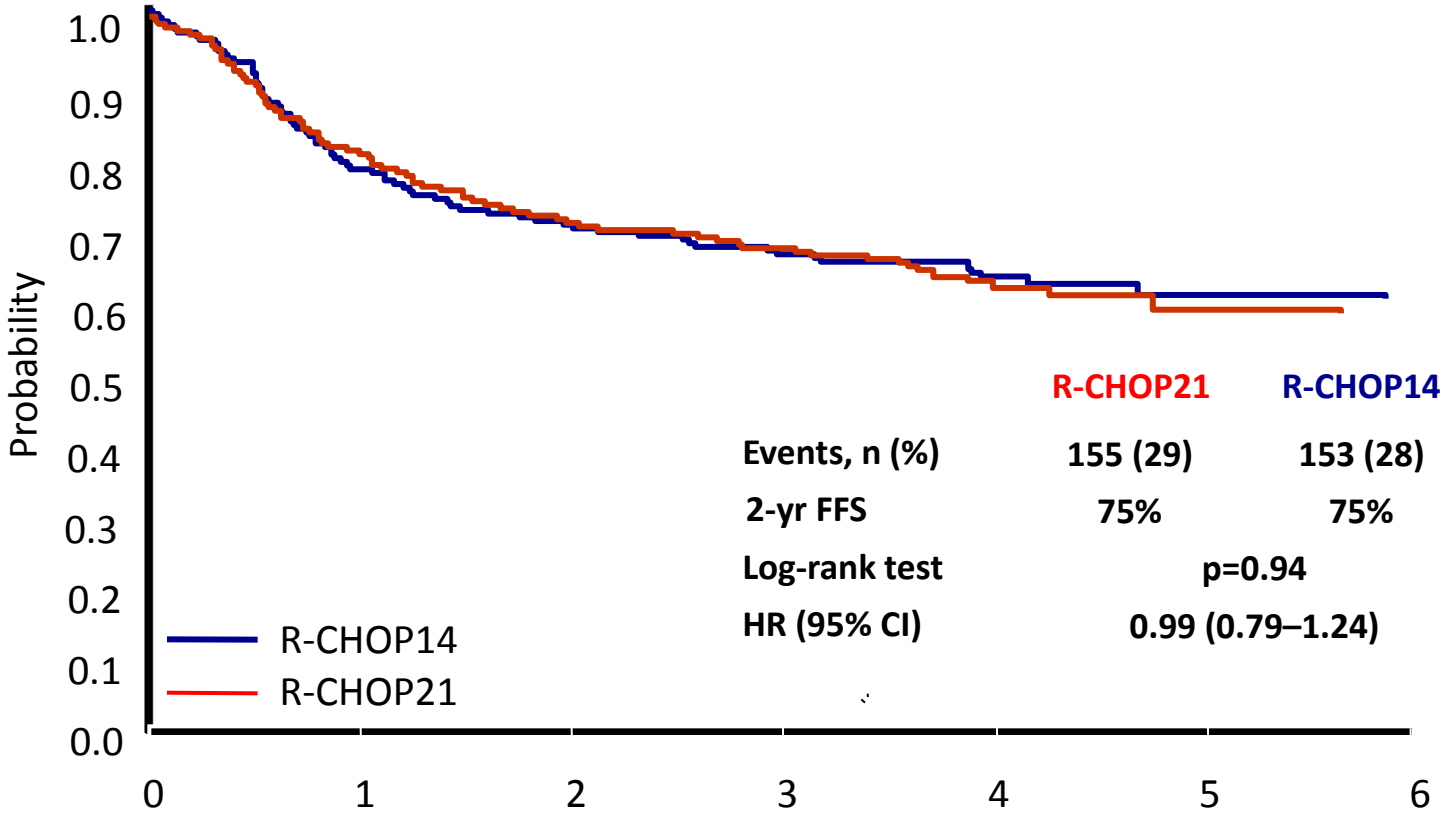
- IPI (0-1, 2, 3, 4-5)
- Age ≤60 vs. >60
- Treatment centre

1080 patients; 119 sites

Recruitment March 2005 - Nov 2008

D Cunningham et al. ASCO 2011

Failure-free survival



Patients at Risk

R-CHOP21	534	429	358	216	116	25	1
R-CHOP14	533	438	355	224	102	25	1

D Cunningham et al. ASCO 2011

Young patient, score 1

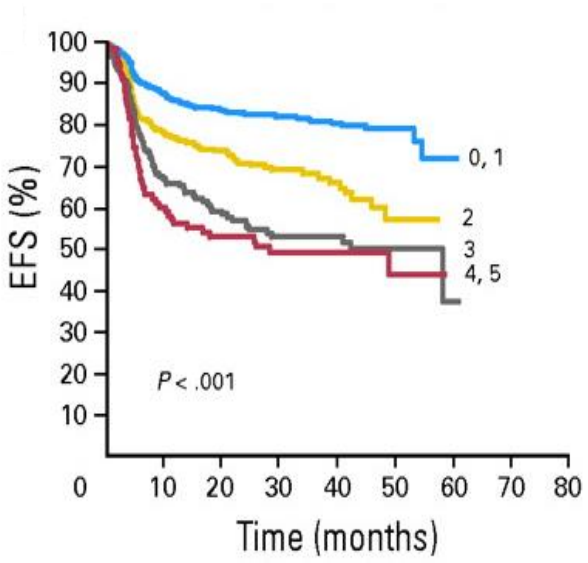
R-CHOP 14 vs. 21

R-ACVBP

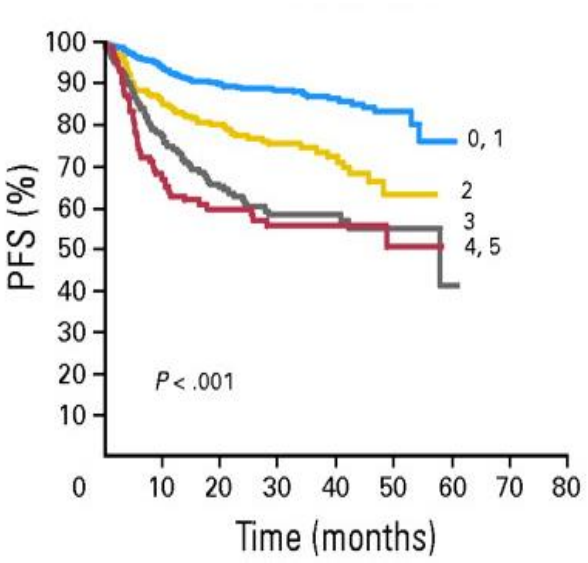
EFS, PFS, and OS, according to IPI score

MInT (≤ 60 years, age-adjusted IPI [aaIPI] 0, 1; n = 380)
MegaCHOEP trial (≤ 60 years, aaIPI 1-3; n = 72)
RICOVER-60 (> 60 years, all IPI groups; n = 610)

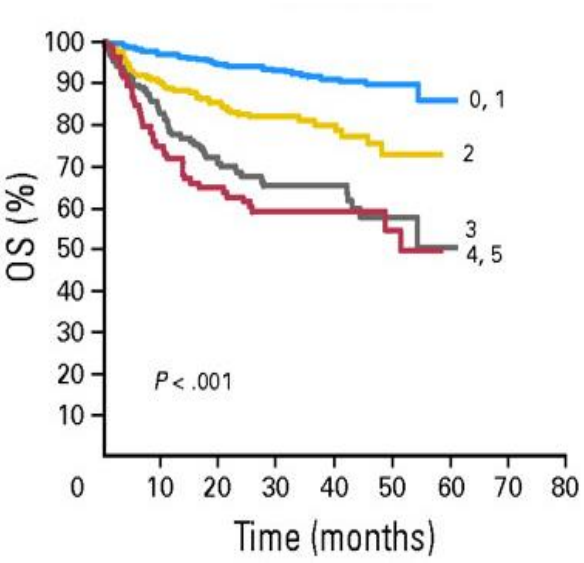
All trials (18 to 80 years of age, all IPI groups; n = 1,062)



EFS



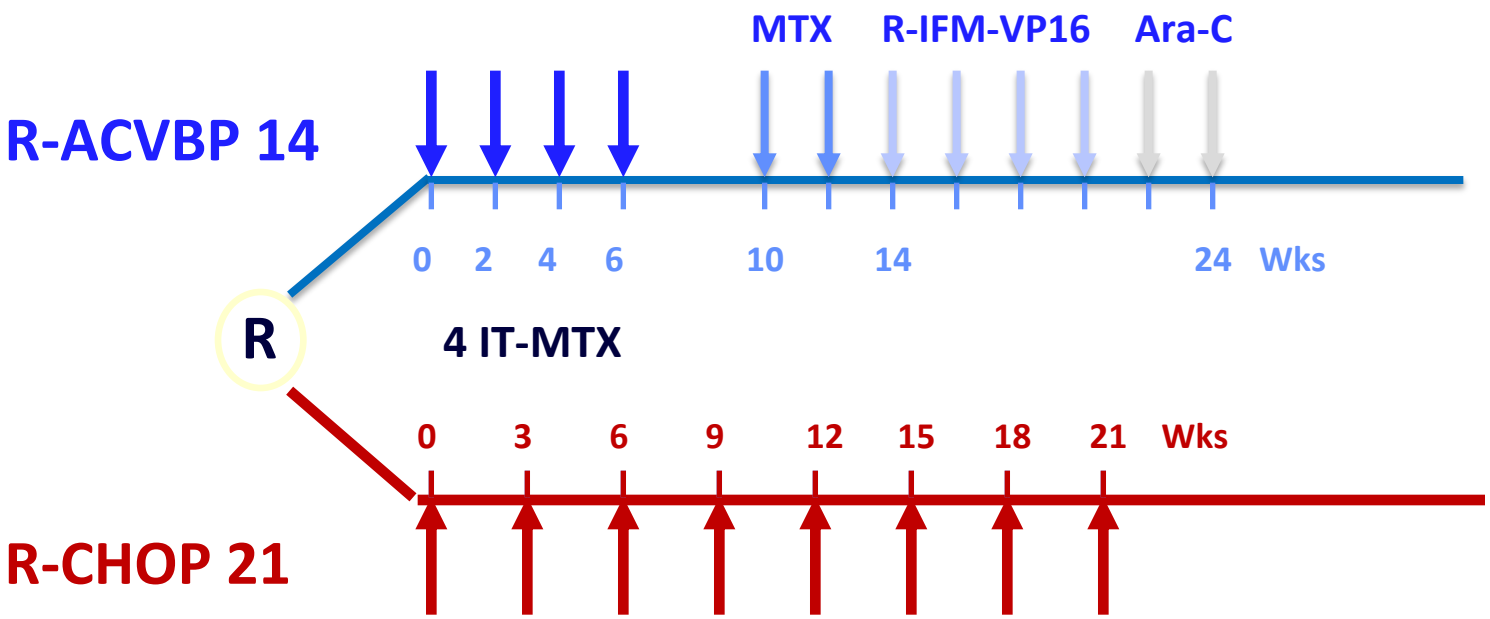
PFS



OS

Ziepert M et al. *JCO* 2010;28:2373-2380

LNH 03-2B study

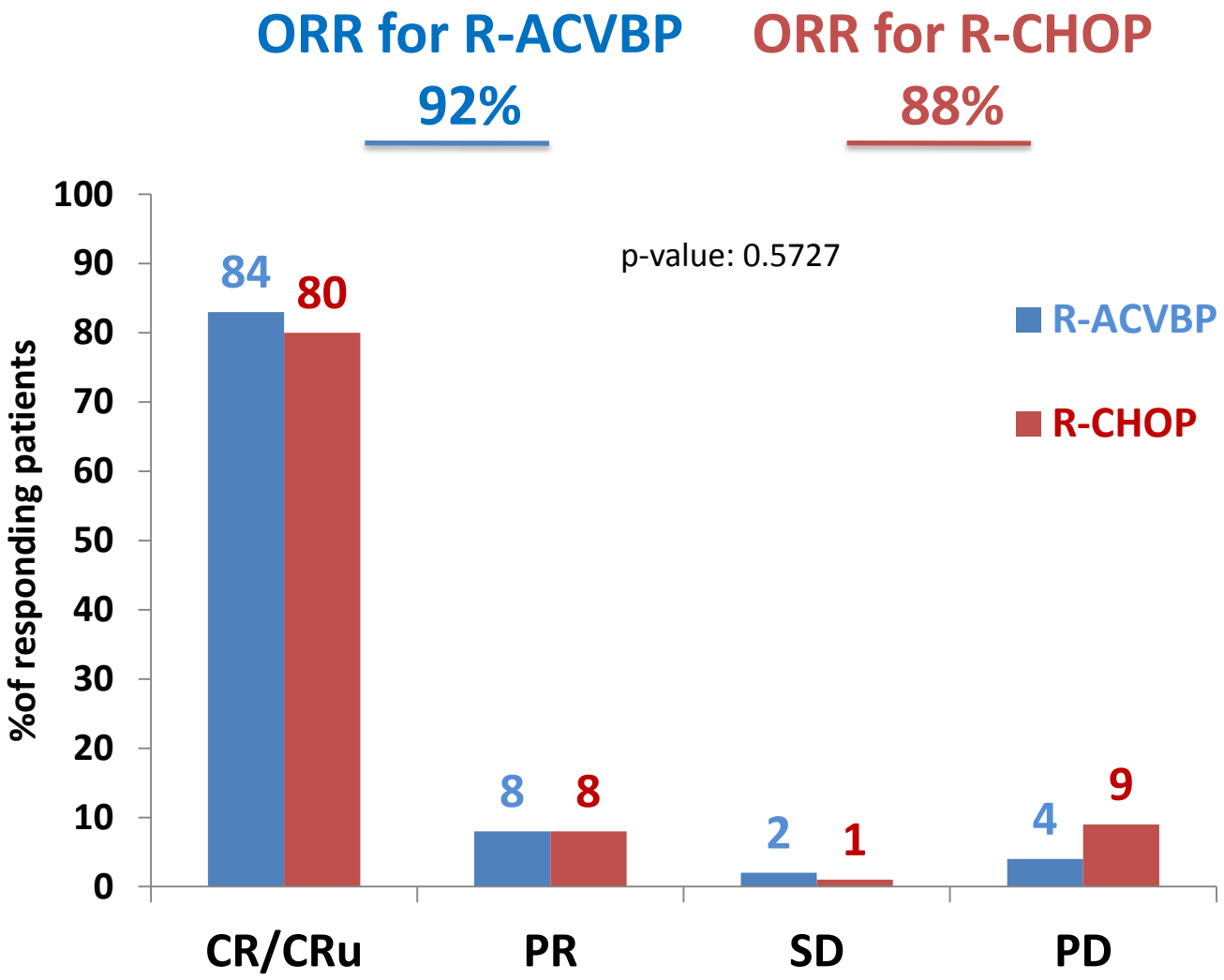


***No radiotherapy in both arms**

Gela

C Rechert et al. Lancet 2011;378:1858

Response at the end of treatment

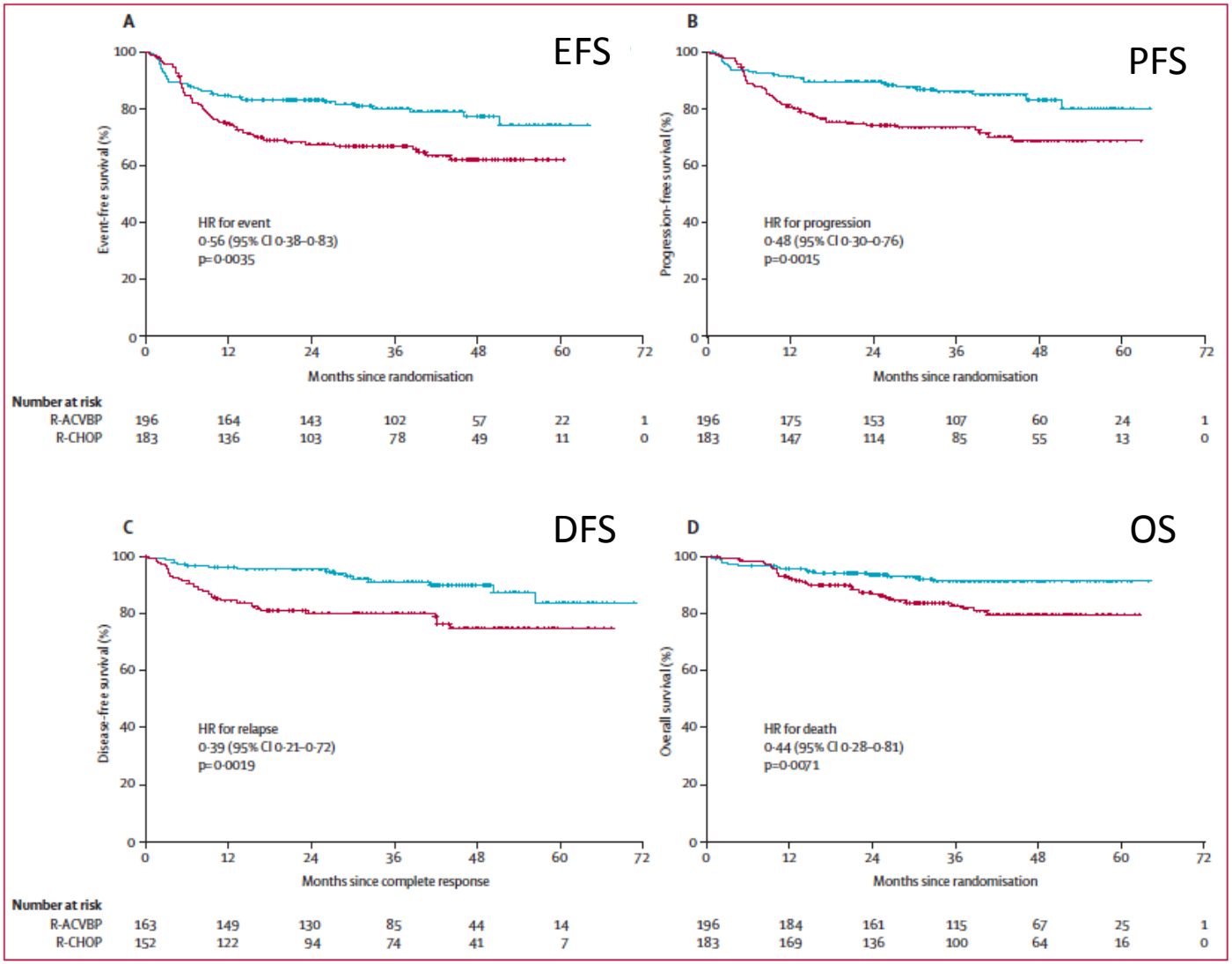


Gela

C Rechert et al. Lancet 2011;378:1858

LNH 03-2B study

R-ACVBP
R-CHOP

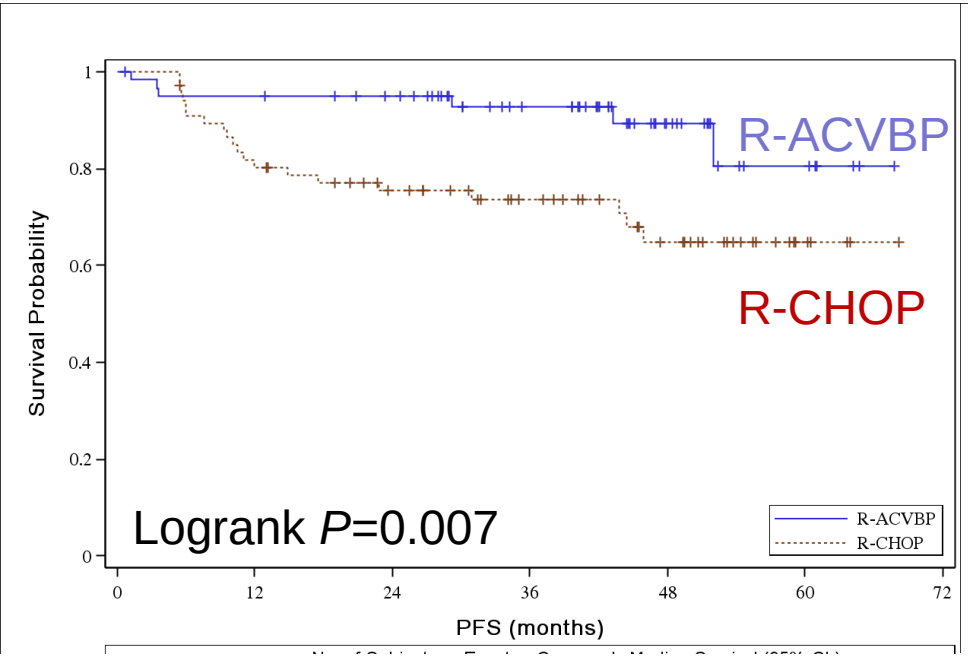


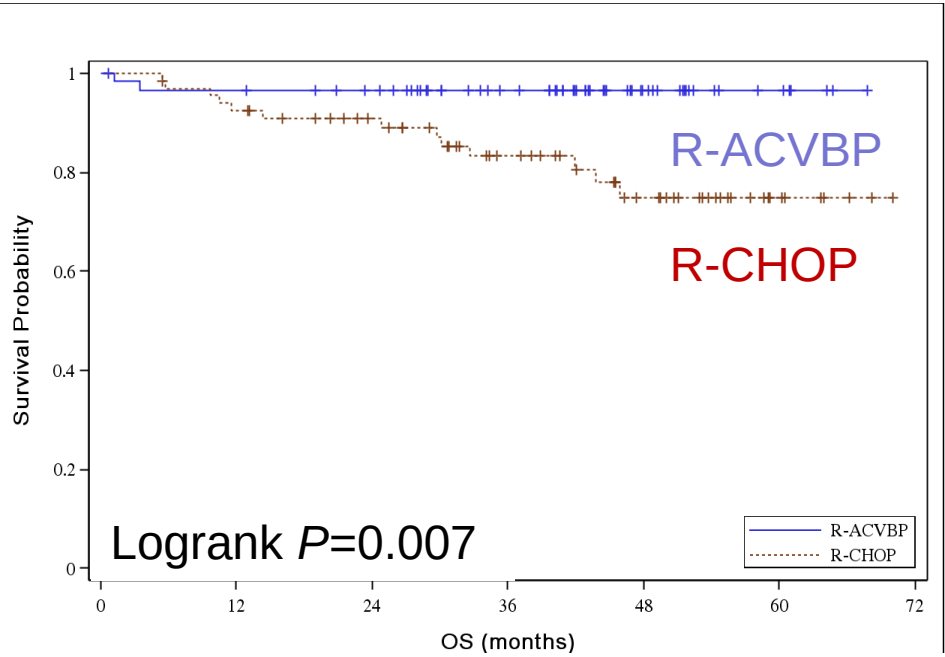
Gela

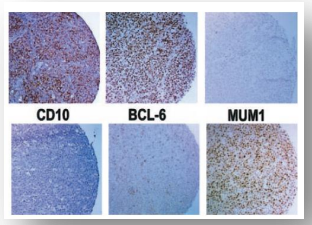
C Rechert et al. Lancet 2011;378:1858

03 2B trial : PFS and OS according to treatment arm in patients with non GC phenotype

PFS non-GC tumors OS



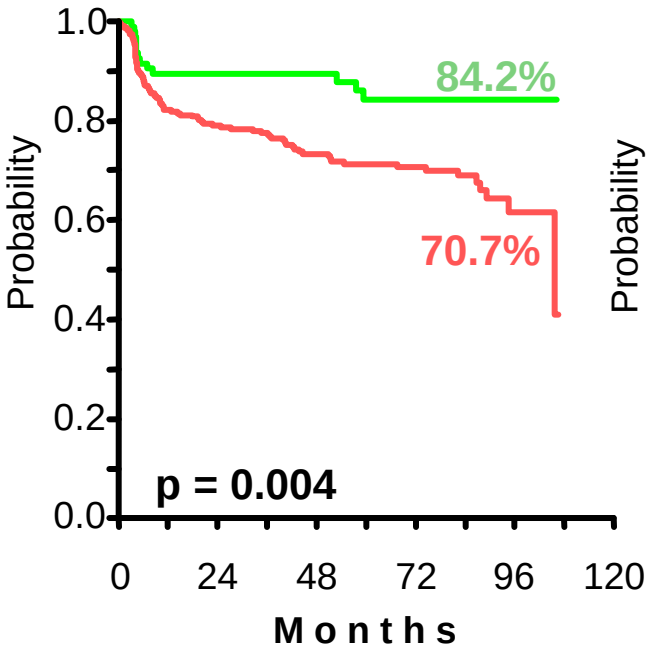




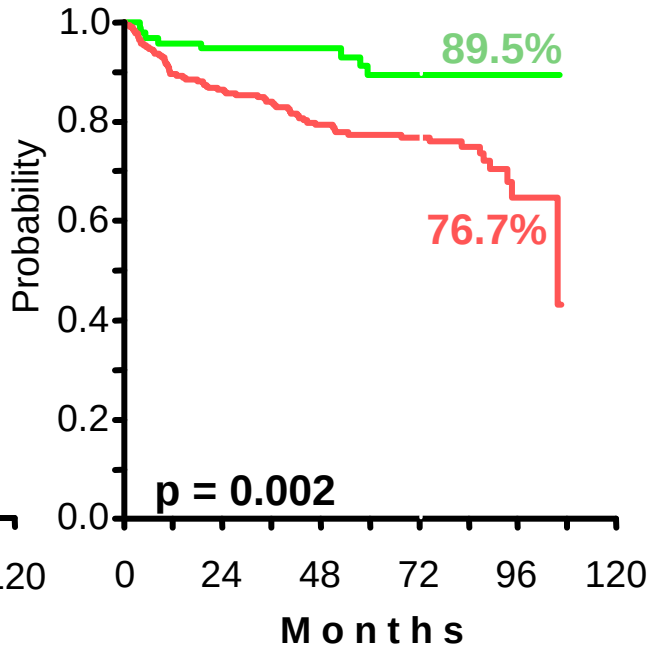
aaIPI score 1 DLBCL patients (18-59) with non-GC DLBCL benefit from Intensified chemotherapy with R-ACVBP compared to RCHOP

Prognostic Groups in the Rituximab Era: Favourable vs. Unfavourable

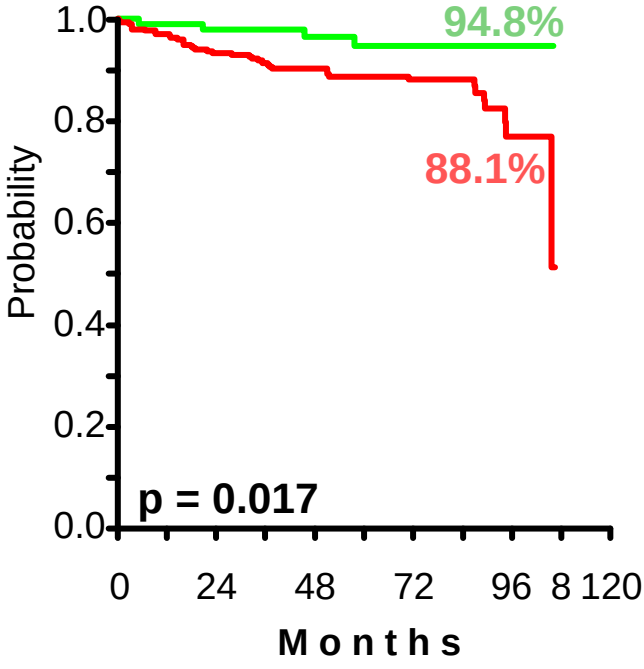
EFS



PFS



OS



Favourable: IPI=0 / ∅ bulk

Unfavourable: IPI=1 and / or bulk

R-ACVBP or R-CHOP?

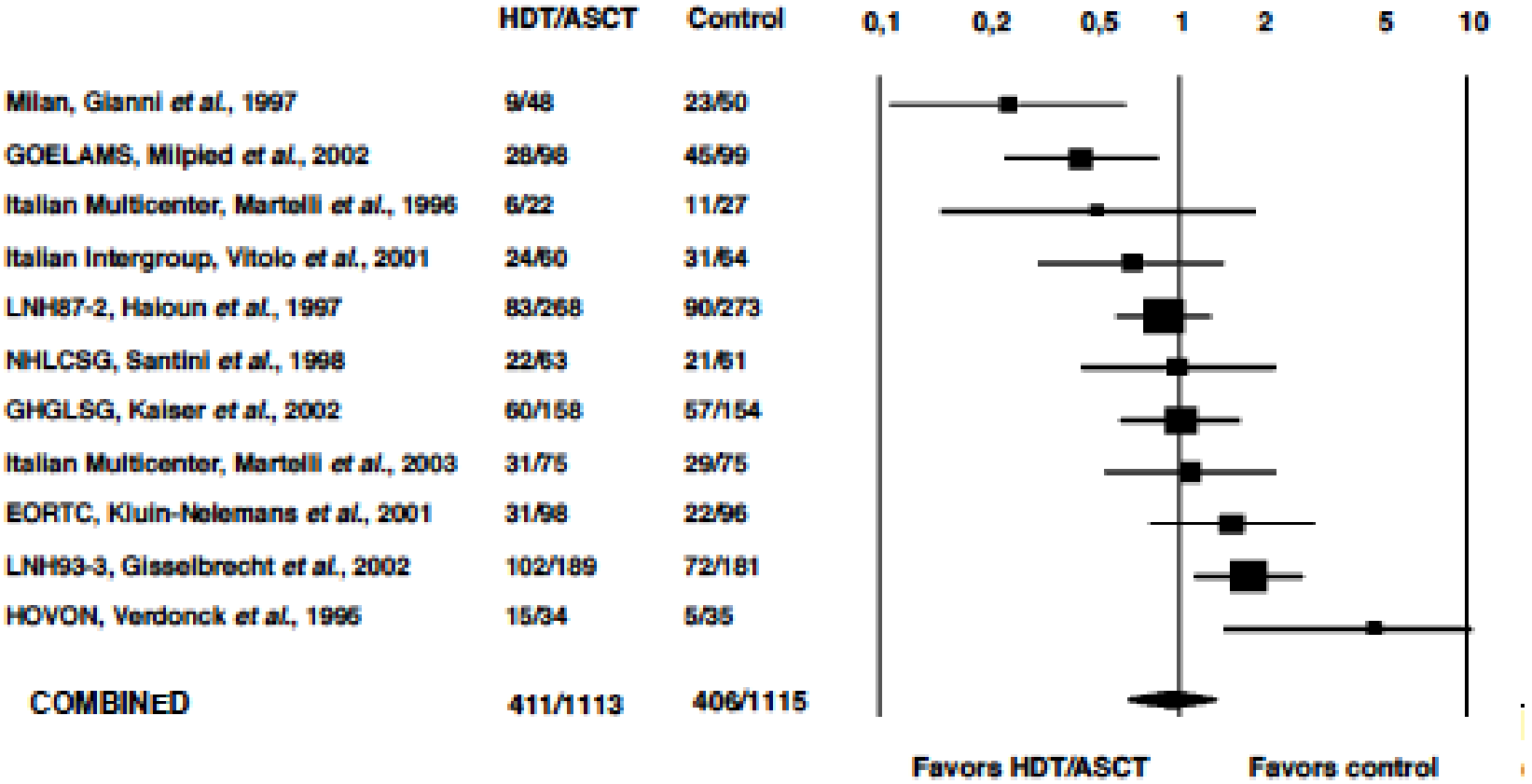
- R-CHOP is easier for patients and physicians
- R-CHOP is a good but significantly inferior to R-ACVBP
- Solution:
  - Find prognostic parameters before treatment
  - R-CHOP for good risk patients
  - R-ACVBP for poor risk patients
  - ? R-CHOP + radiation therapy?

Young patient, score 2/3

R-ACVBP
(or other high-dose regimen)

Any role for HDT and autologous transplant?

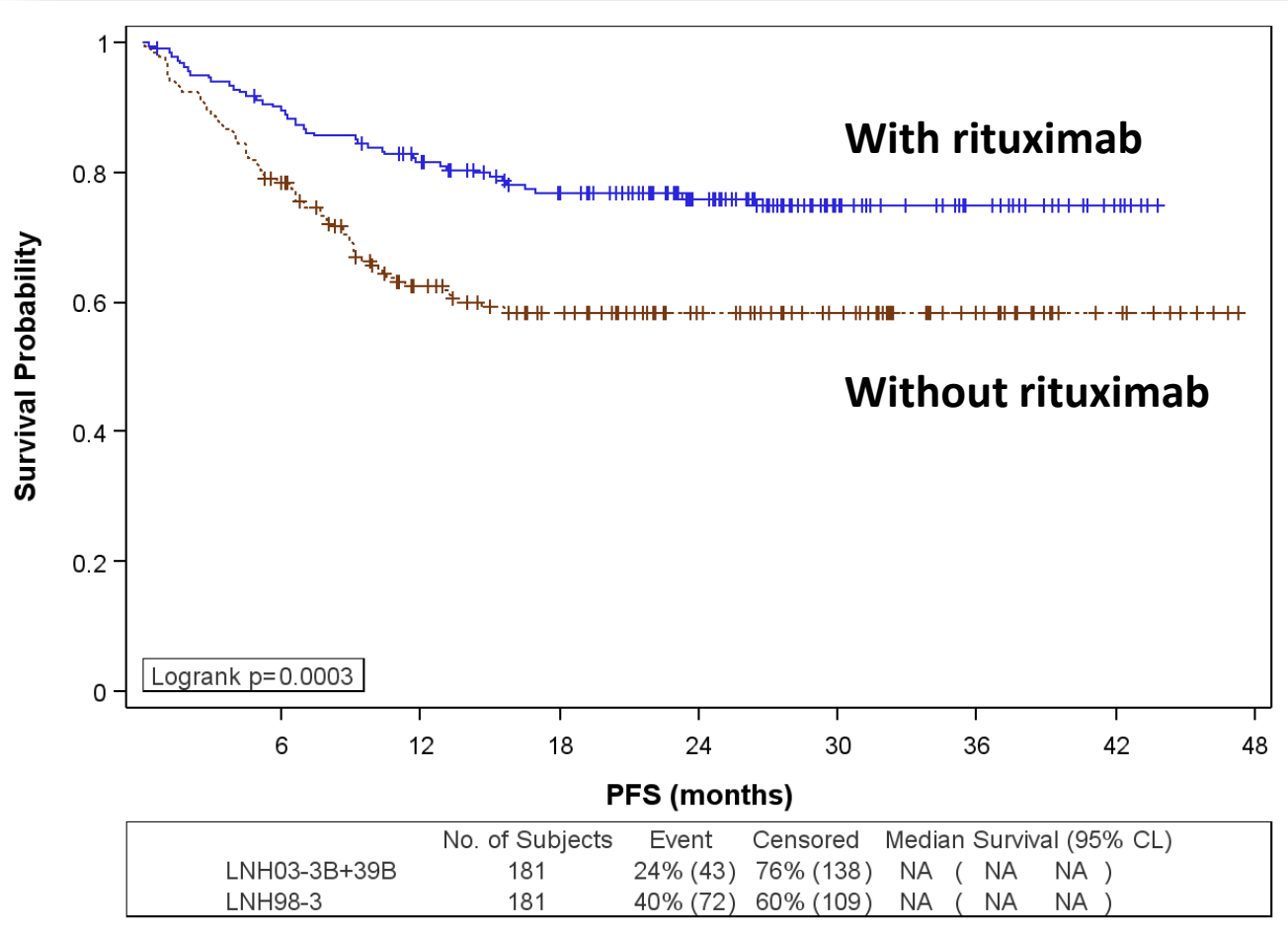
Meta-analysis of High Dose Chemotherapy +ASCT as first-line therapy in aggressive NHL



J Strehl et al. Haematologica 2003;88:1304

ACVBP vs R-ACVBP + PSCT

LNH98-3/LNH03-3B aaIPI=2,3



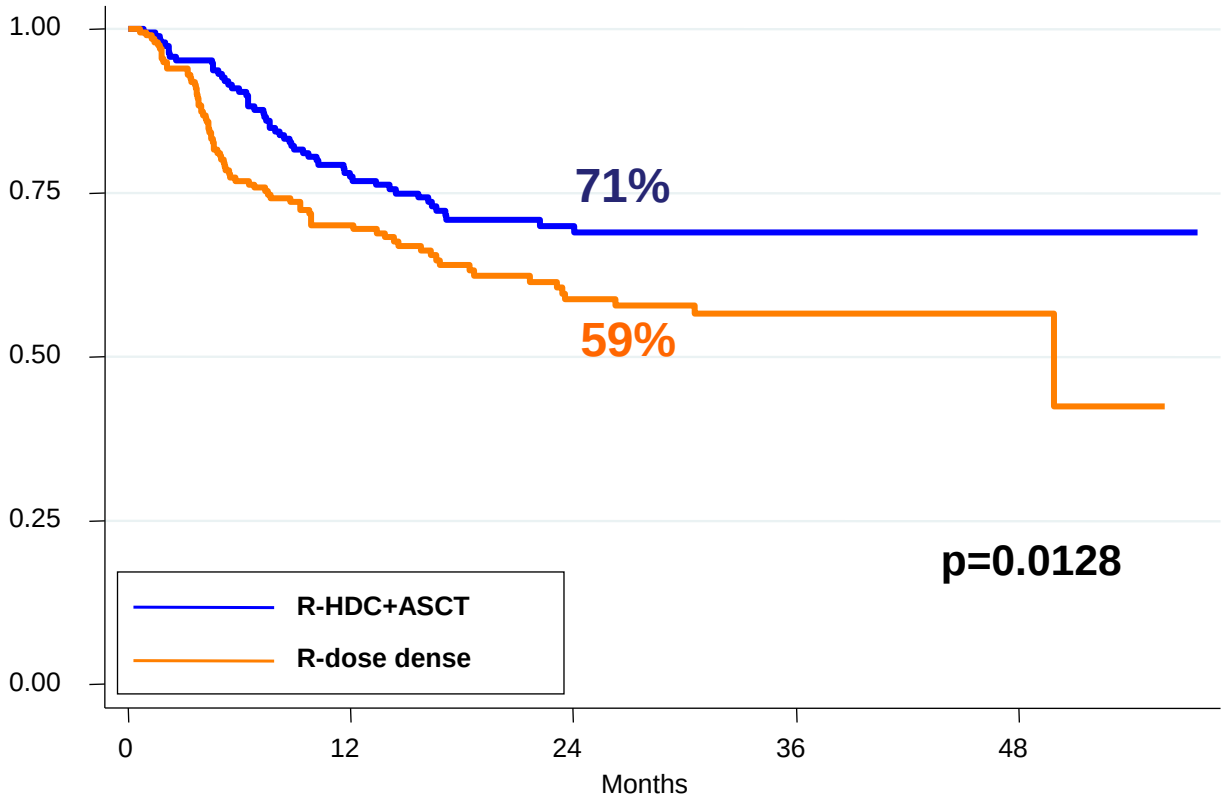
	No. of Subjects	Event	Censored	Median Survival (95% CL)
LNH03-3B+39B	181	24% (43)	76% (138)	NA (NA NA)
LNH98-3	181	40% (72)	60% (109)	NA (NA NA)

Fitoussi O et al. *Hematologica* 2011;96:1136

Gela

2-year PFS: R-HDC+ASCT vs R-CHOP/R-MegaCHOP median follow-up 24 months

aaIPI=2/3



At risk:									
R-HDC+ASCT	192	166	124	99	74	60	49	32	14
R-dose dense	200	143	115	77	63	46	30	19	5

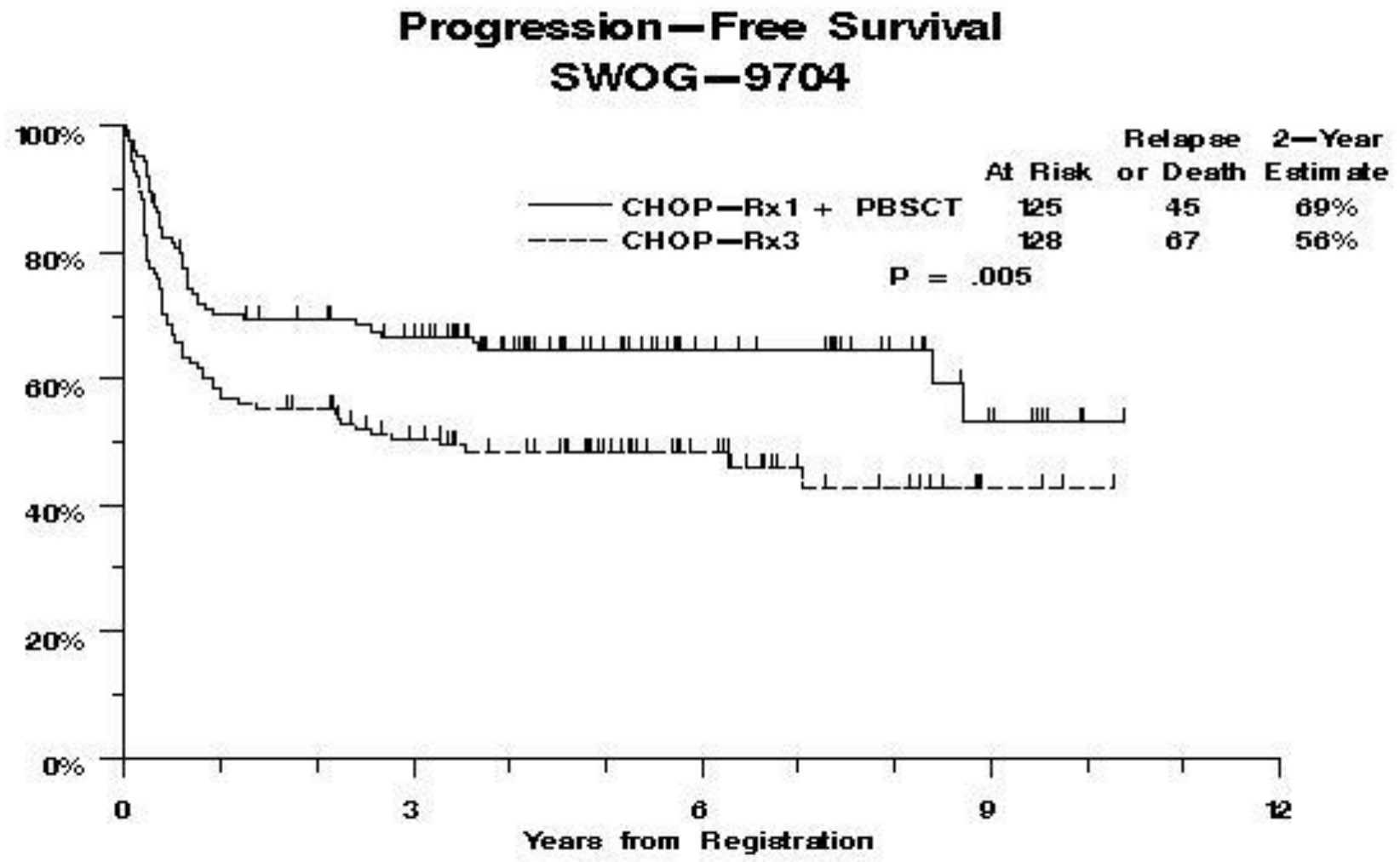
Umberto Vitolo

Randomized phase III US / Canadian Intergroup trial (SWOG S9704) comparing CHOP±R x 8 vs CHOP±R x 6 followed by high dose therapy and auto transplant for patients with diffuse aggressive non-Hodgkin's lymphoma (NHL) in high-intermediate (H-Int) or high IPI risk groups.

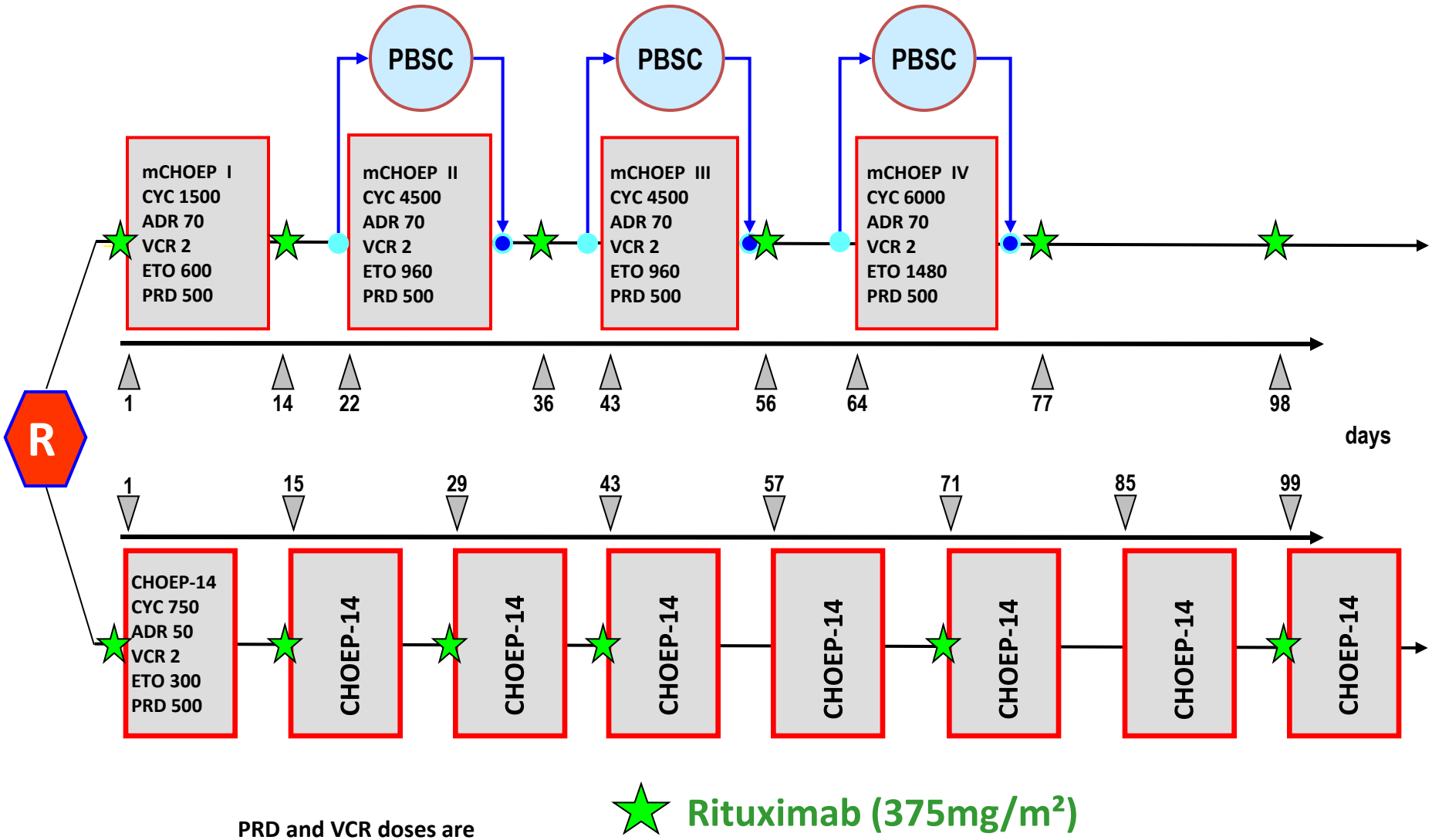
P.J. Stiff[1], J.M. Unger[2] J.R. Cook[3], L.S. Constine[4], S. Couban[5], T.C. Shea[6], J.N. Winter[7], T.P. Miller[8], R.R. Tubbs[3], D.C. Marcellus[9], J. Friedberg[4], K. Barton[1], G. Mills[10], M. LeBlanc[2], L. Rimsza[8], S.J. Forman[11], R.I. Fisher[4]

[1]Loyola University Medical Center, Maywood, IL; [2]SWOG Statistical Center, Seattle, WA; [3]Cleveland Clinic Foundation, Cleveland, OH; [4]University of Rochester, Rochester, NY; [5]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, CAN; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC; [7]Northwestern University, Chicago, IL; [8]University of Arizona, Tucson, AZ; [9]Margaret and Charles Juravinski Cancer Centre, Hamilton, Ontario, CAN; [10]Louisiana State University Medical Center, Shreveport, LA; [11]City of Hope Medical Center, Duarte, CA

Overall Outcome : PFS



DSHNHL 2002-1 -- R-MegaCHOEP vs R-CHOEP-14
Age 18-60, aa-IPI=2-3

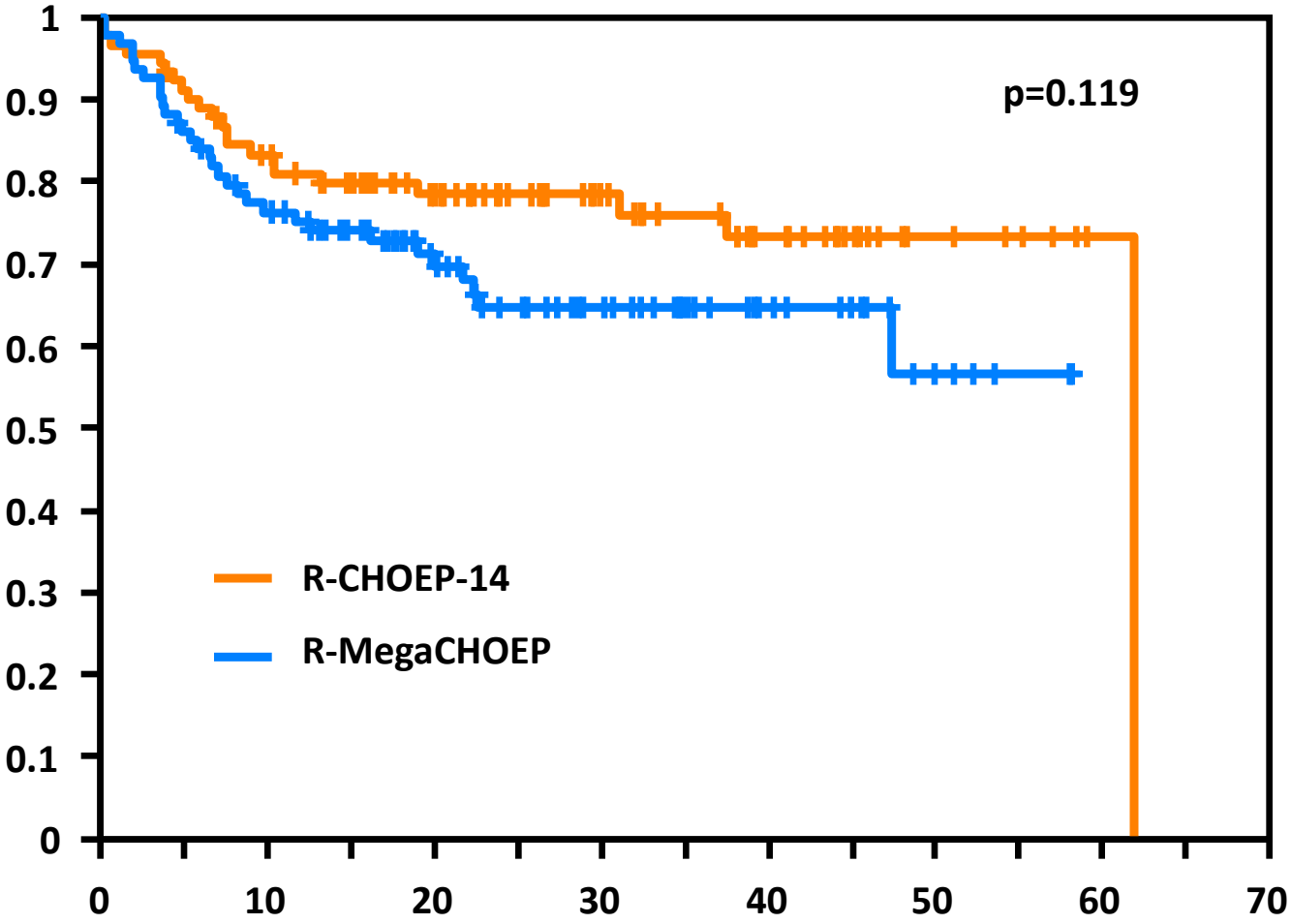


Rituximab (375mg/m²)

PRD and VCR doses are absolute, all others are per m²

Schmitz N et al. ASH 2009

DSHNHL 2002-1 -- MegaCHOEP
Progression-free survival



Schmitz N et al. ASH 2009

Which patients to intensify?

- True PR (PET+ or pathology +)
- All young patients with aaIPI >1
- All young patients with high risk
- Slow responding patients (interim PET)

?

Very old patients

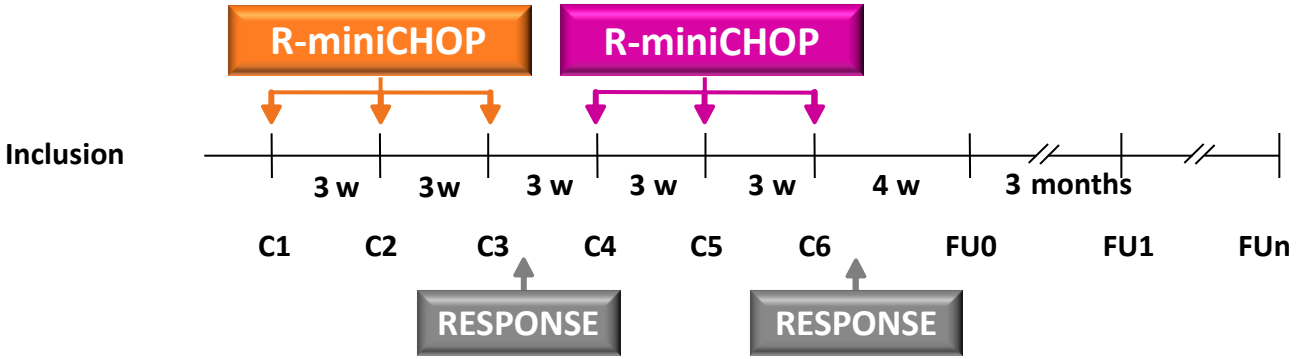
Fit patients: R-mCHOP

Non-fit patients: R-Chemo

Patients aged >80

- CD20+ Diffuse large B-cell lymphoma histologically proven
- Age > 80 years
- Non pretreated patient
- aaIPI 0, 1, 2 or 3
- Ann Arbor Stages I bulky to IV
- Perfomance status 0 to 2
- Bone marrow biopsy, lumbar punction and TEP-TDM were non mandatory

R-miniCHOP	Dose	D1	D2	D3	D4	D5
Prednisone	40 mg/m²	X	X	X	X	X
Rituximab	375 mg/m²	X				
Doxorubicin	25 mg/m²	X				
Cyclophosphamide	400 mg/m²	X				
Vincristine	1 mg DT	X				



6 cycles of R-miniCHOP, 3 weeks interval

Peyrade F, et al. *Lancet Oncol*; 2011 12(5):460-8

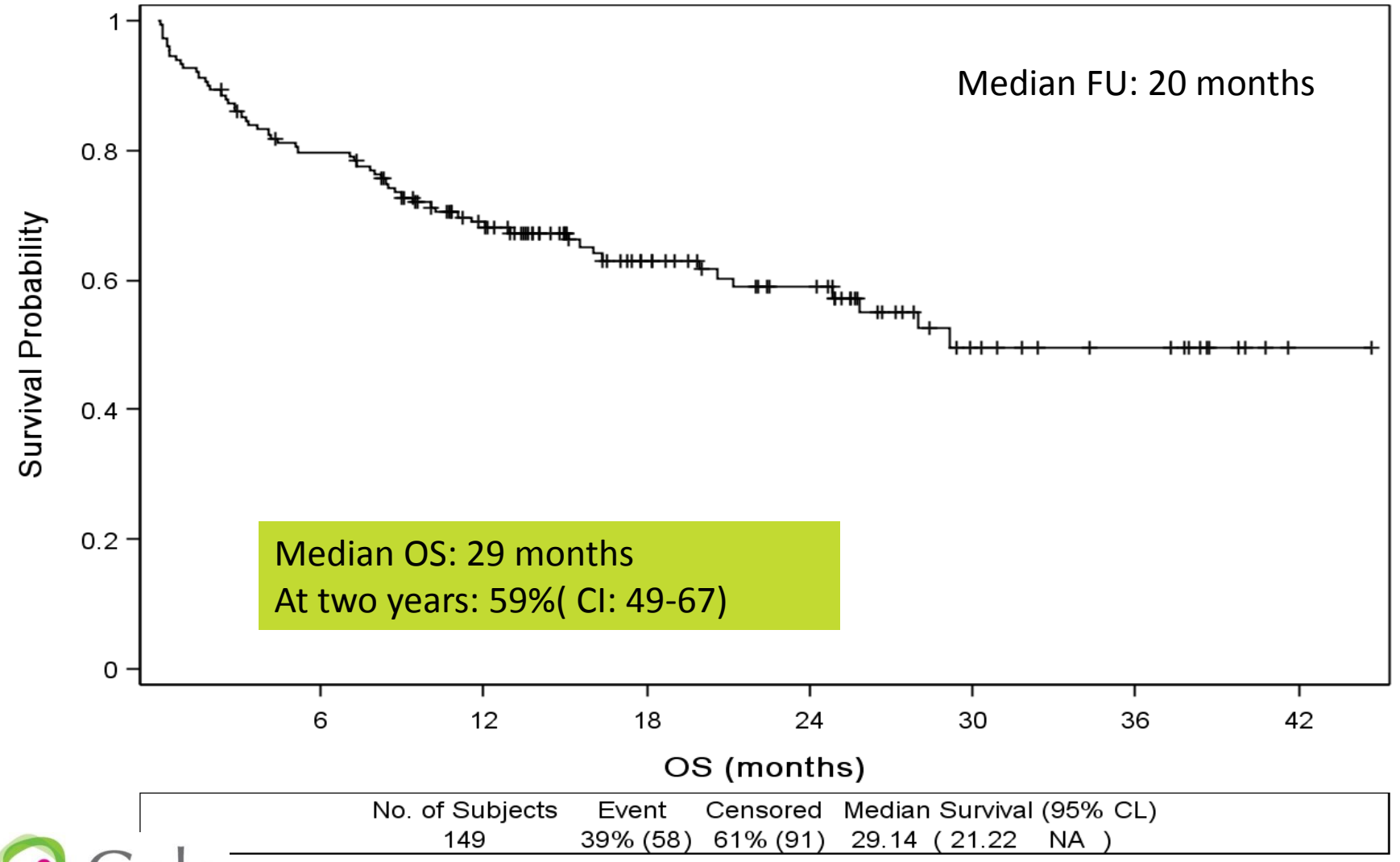
Causes of death

	Toxicity	Lymphoma progression	Others		Total
Treatment Period	12 *(including 5 during the first cycle)*	8	7	1 bleeding 2 chest pain 1 poor general condition 1 pneumopathy 2 unknow causes	27
Follow-up Period	0	25	6	1 stroke 1 acute renal insufficiency 1 poor general condition 3 unknown	31
Total	12	33	13		58

F Peyrade et al. Lancet Oncol 2011;12:460

Primary endpoint: Overall survival

Intent-to-treat population



Gela

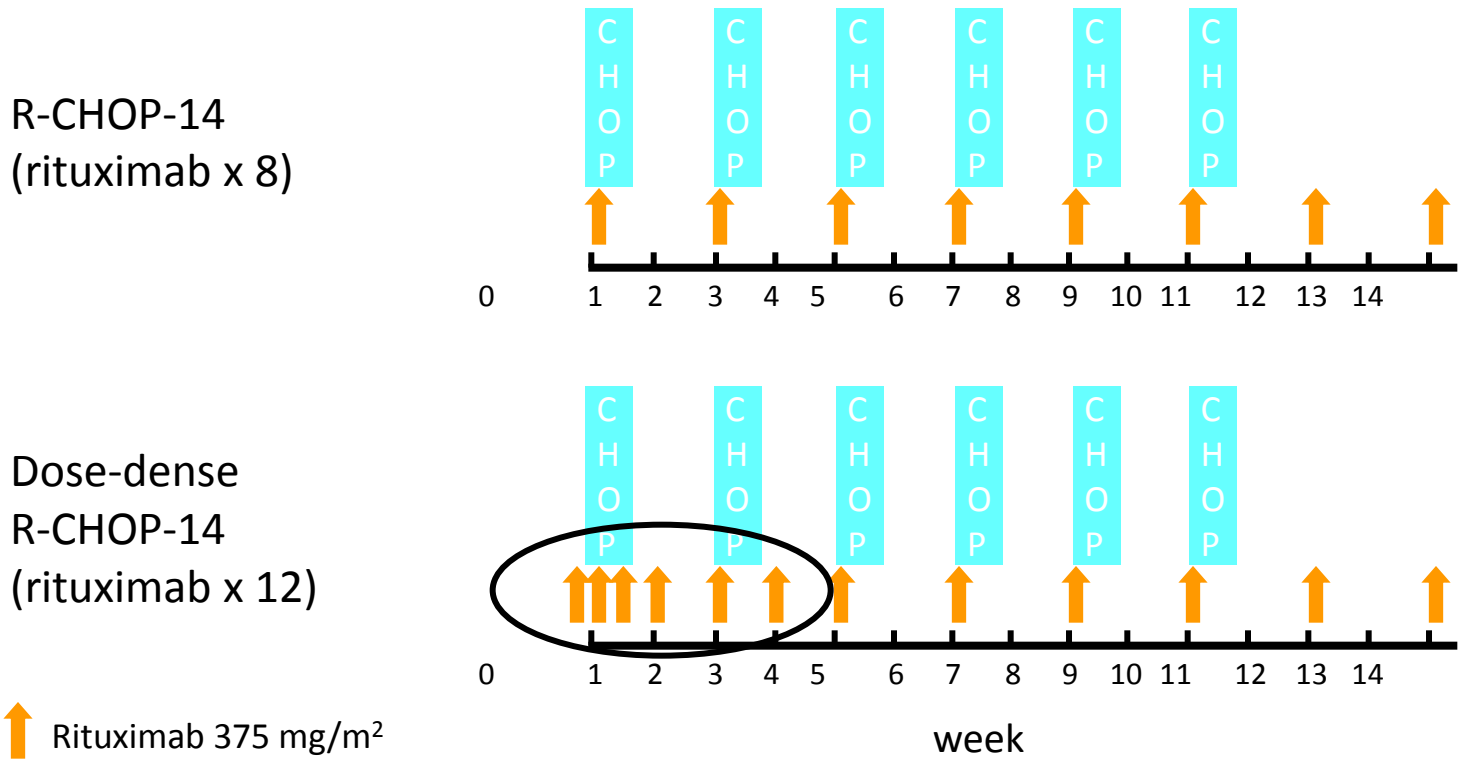
F Peyrade et al. Lancet Oncol 2011;12:460

R-CHOP

- Rituximab: better anti-CD20?
- Cyclophosphamide
- Doxorubicin: analogs
- Vincristine: other tubulin binders
- prednisone

DENSE-R-CHOP-14 for elderly patients with DLBCL: treatment schedule

- 6 cycles biweekly CHOP-14 with 12 doses of rituximab 375 mg/m^2



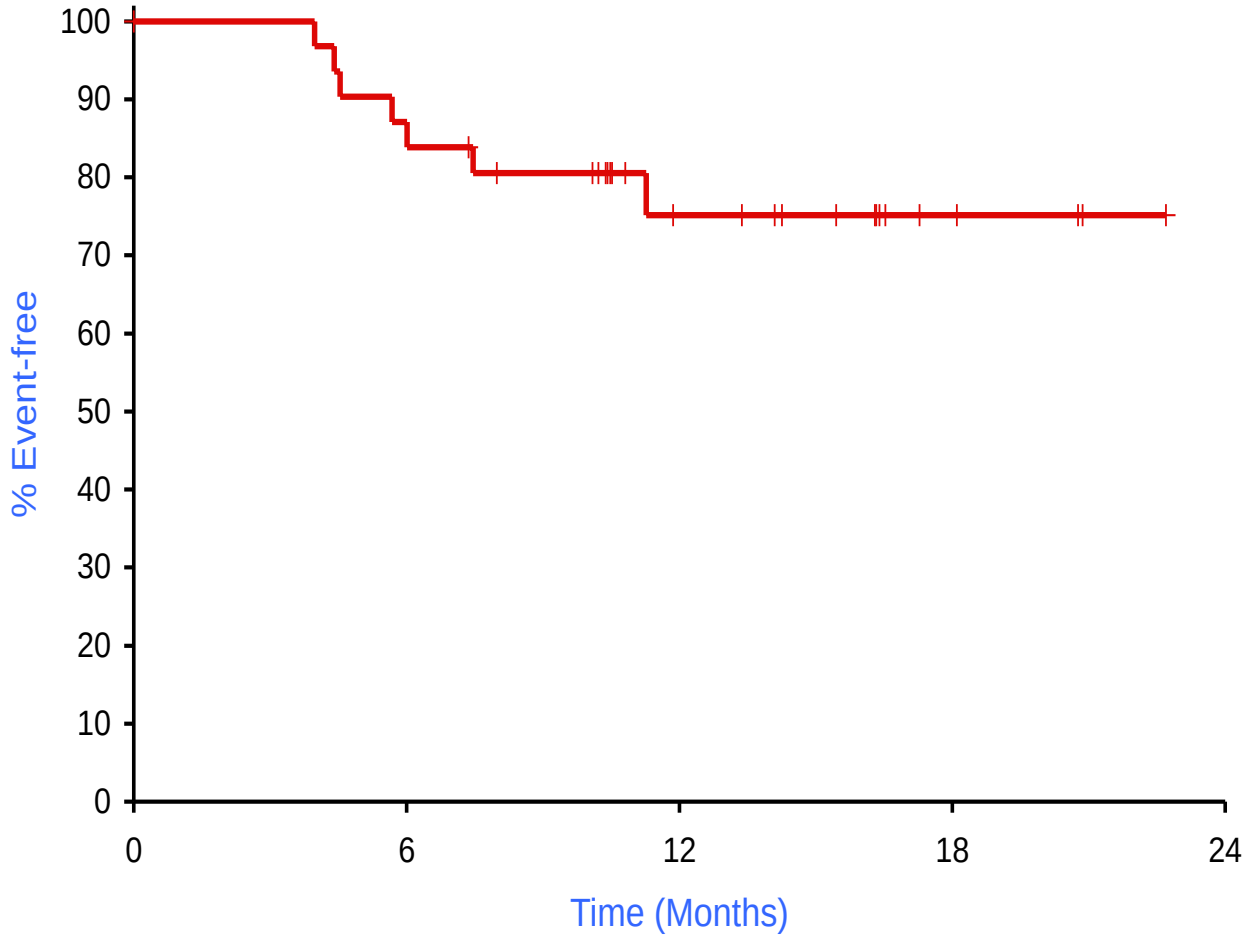
Pfreundschuh M, *et al. Blood* 2007;110: Abstract 789

R-CHOP + X

- RA-CHOP: stopped because of Avastin toxicity
- R2-CHOP: lenalidomide
  - Only phase II, no demonstration of superiority
- R-CHOP + bortezomib
- R-CHOP + enzastaurin
- R-CHOP + ibrutinib
- R-CHOP + idelalisib

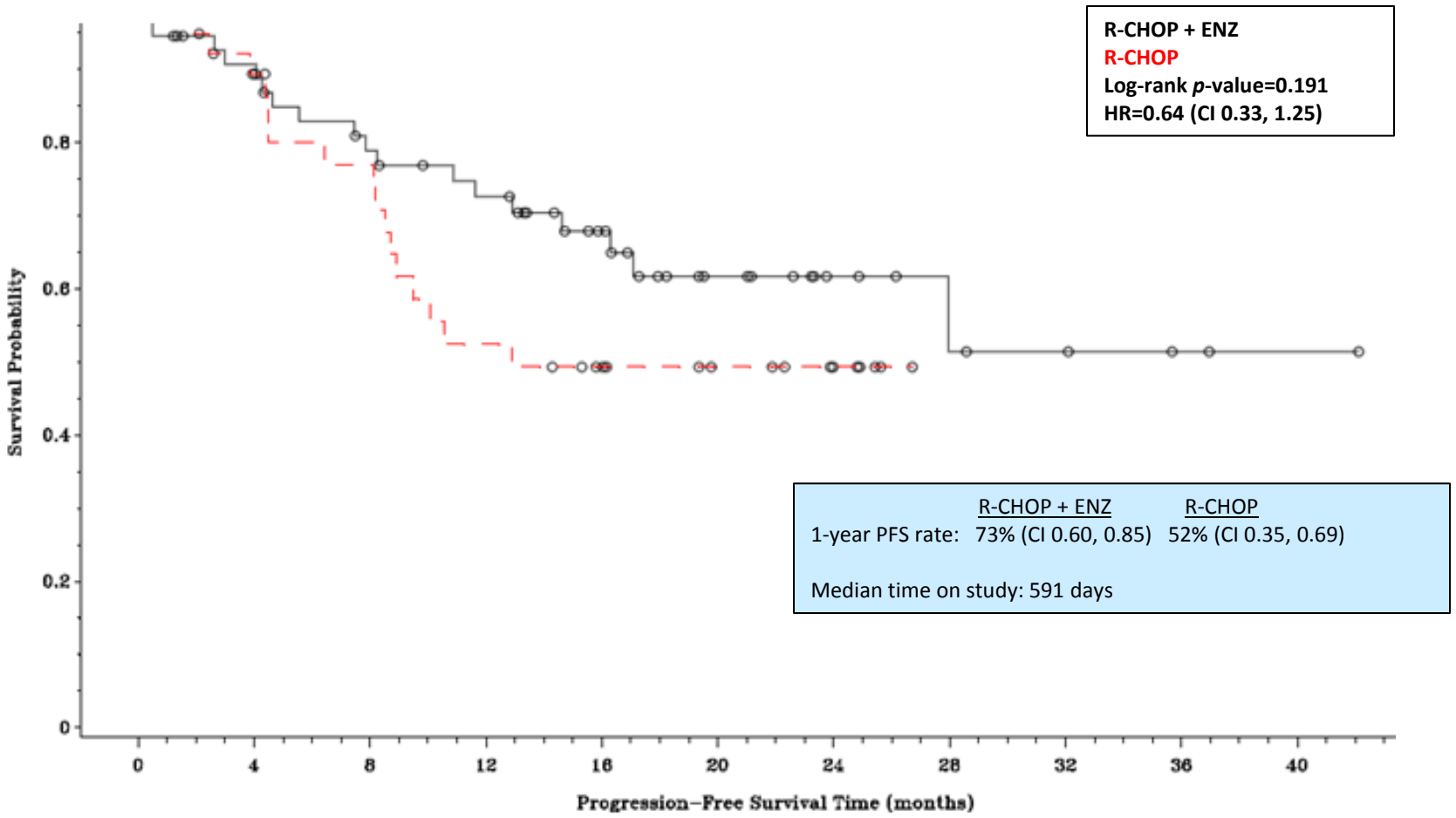
R2CHOP – Event-free Survival

Phase 2 part (N=32)



- Intend to treat analysis
- 30 patients evaluable
  - CR rate 83%
- Of 8 events,
  - 7 relapses
  - 1 death without disease from unrelated causes

Progression-free Survival (R-CHOP + ENZ Versus R-CHOP)



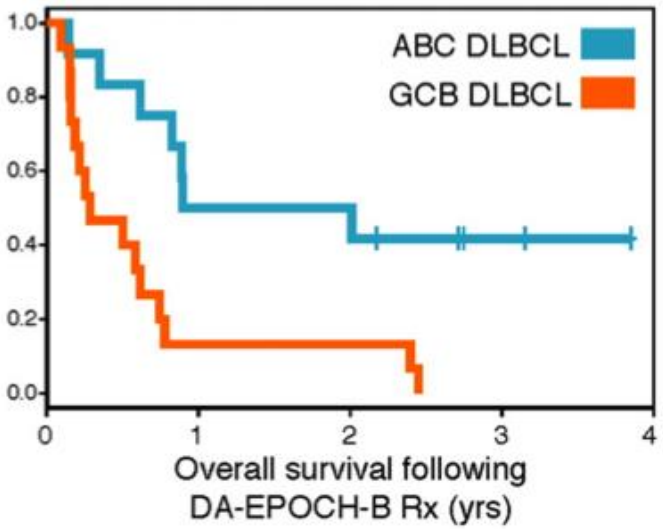
	R-CHOP + ENZ	R-CHOP
1-year PFS rate:	73% (CI 0.60, 0.85)	52% (CI 0.35, 0.69)

Median time on study: 591 days

Abbreviations: HR=hazard ratio; CI=confidence interval

J Hainsworth ICML 2011

Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of DLBCL



Dunleavy, K. et al. Blood 2009;113:6069-6076

Trial Outline:

Patient with DLBCL requiring full course chemoimmunotherapy

Consent

Biopsy material forwarded to HMDS for Expression Profiling

R-CHOP 1 cycle

Randomisation, stratified for molecular phenotype

Initially all cases with molecular phenotype randomised

Two interim analyses of GCB Group receiving R-CHOP+B

R-CHOP+Bortezomib 5 cycles

R-CHOP 5 cycles

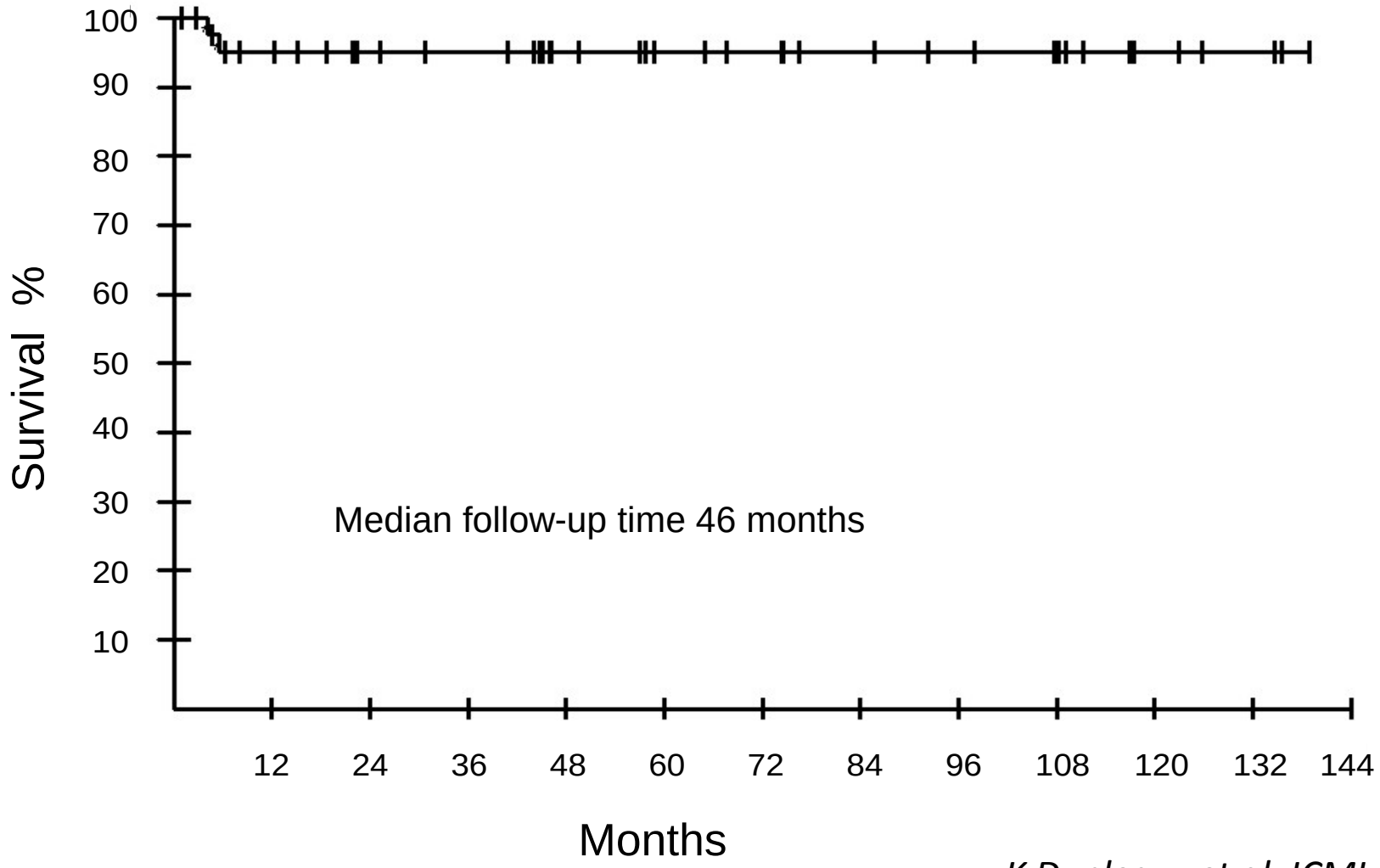
Follow up

REMoDL-B

DA-EPOCH-R

- Mostly used in NCI
- No randomized comparison
- Only phase II or retrospective analyses
- Most of them is more aggressive subgroups
- Currently tested in a phase III against R-CHOP

Event-Free Survival : DA-EPOCH-R - PMBL

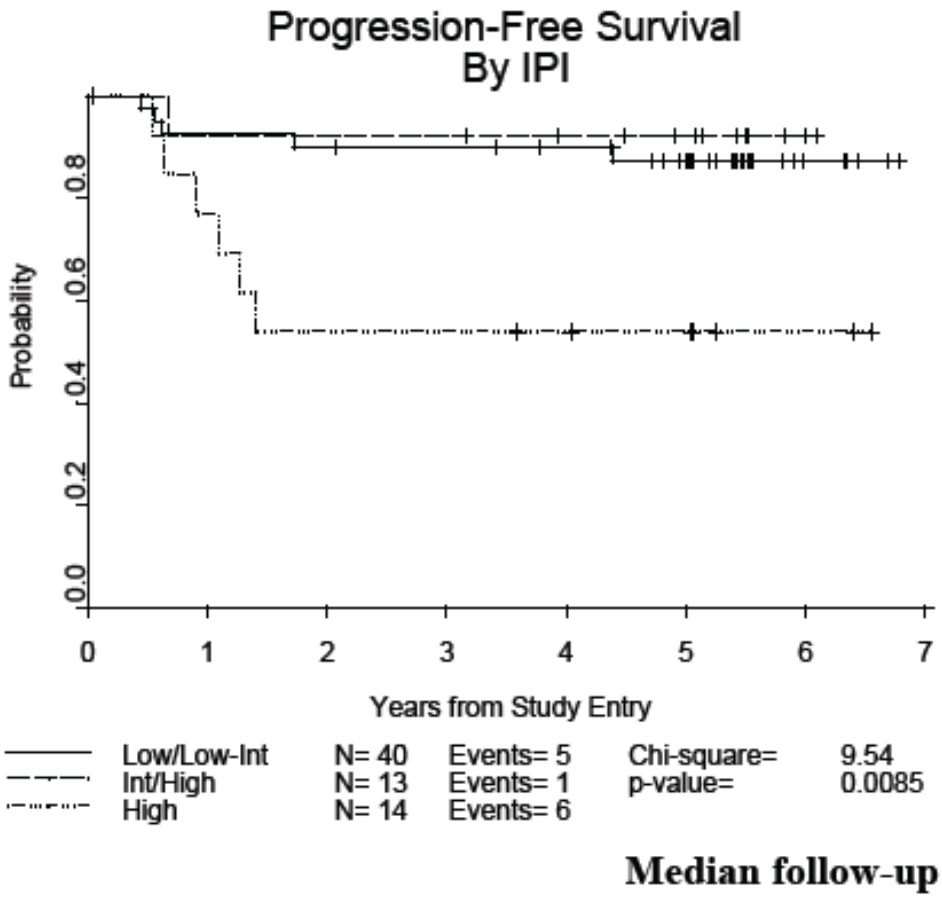


K Dunleavy et al. ICML 2011

CALGB Phase II

DA-EPOCH-R

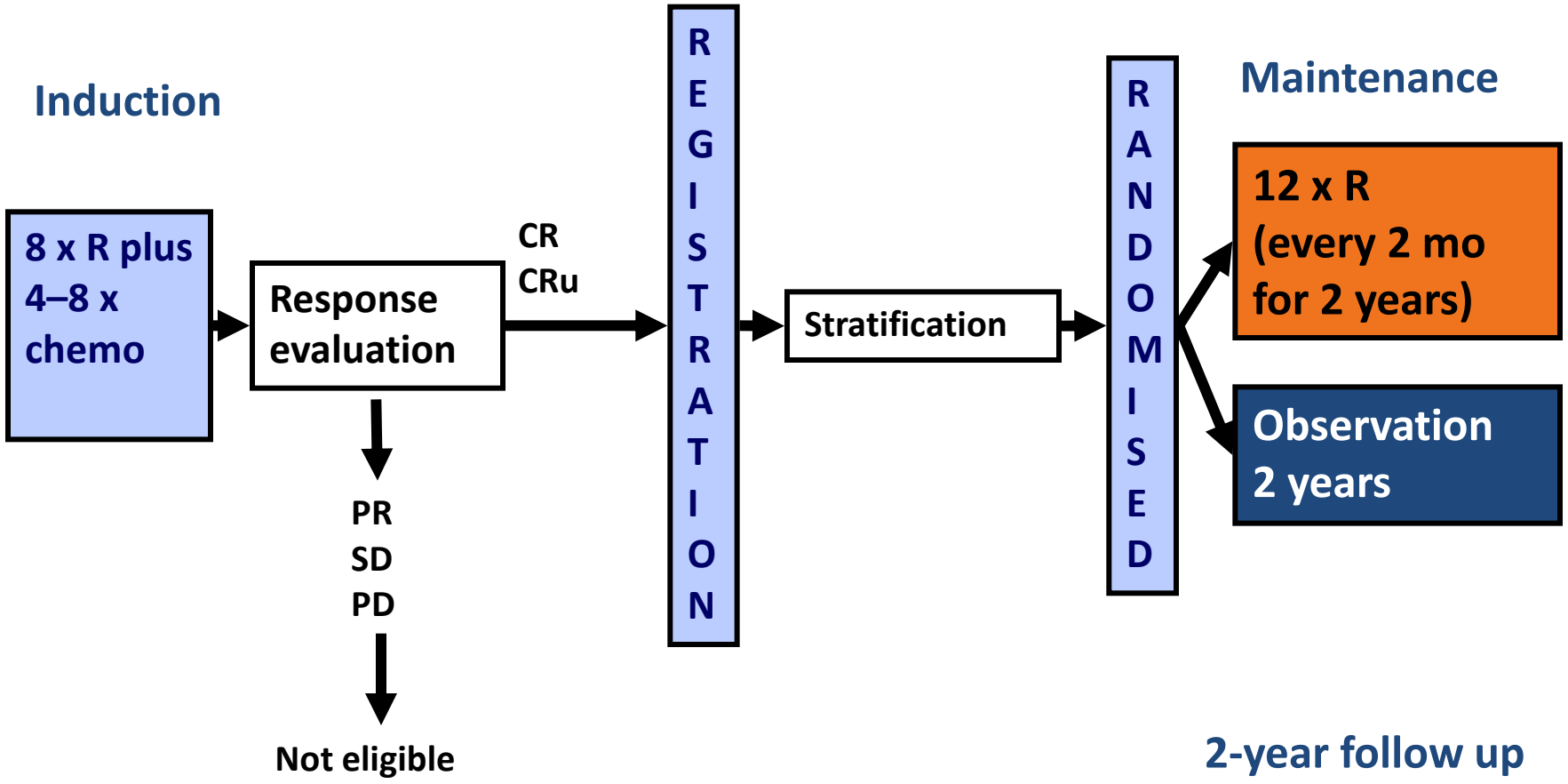
R Fisher Bologna 2010



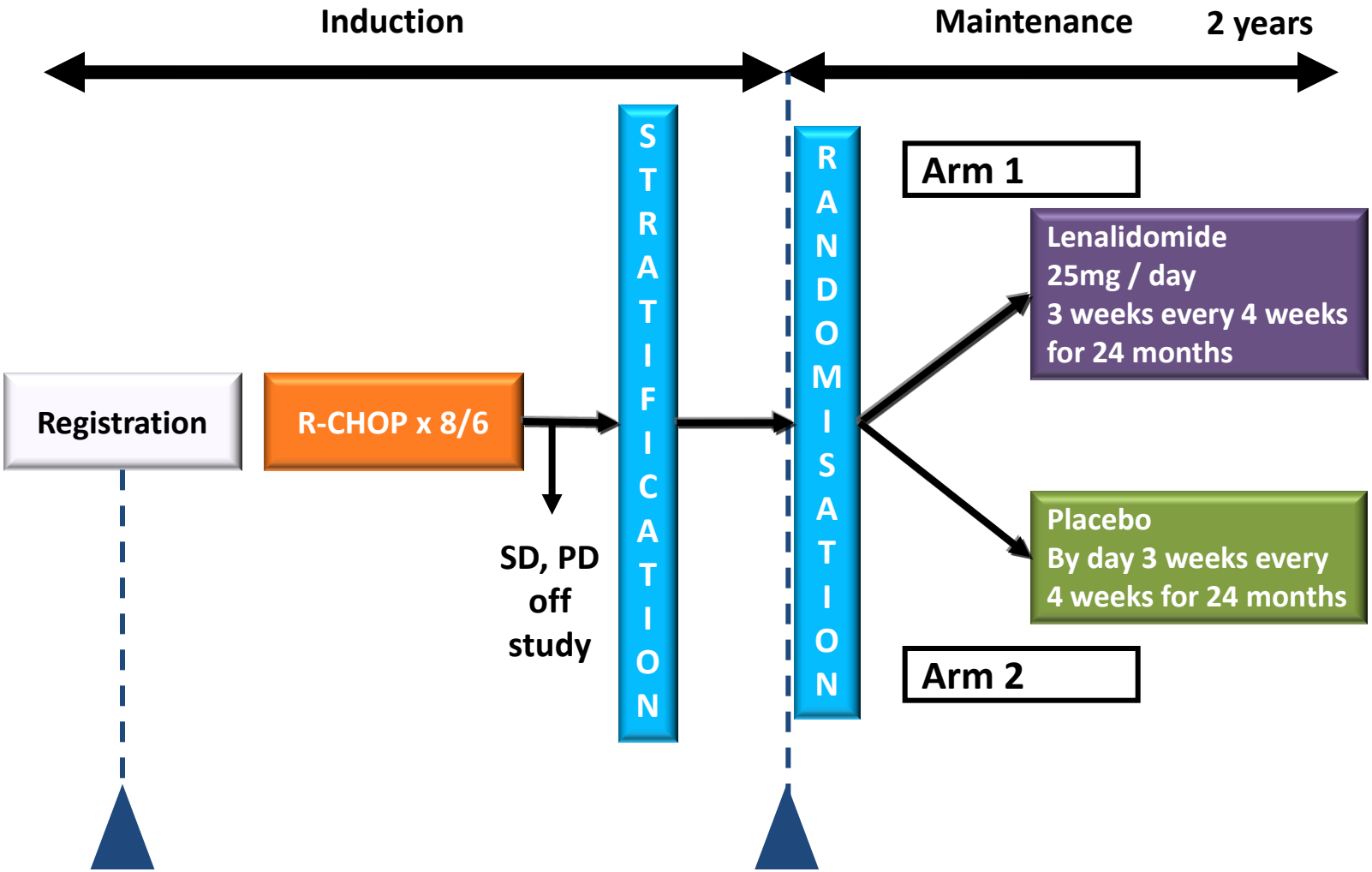
R-CHOP followed by X

- May only decrease relapse rate but not increase CR rate
- Rituximab:
  - No proof of activity in DLBCL
  - NHL-13 not yet reported
- Lenalidomide
  - Studies ongoing
- Others?

Rituximab maintenance therapy in DLBCL or follicular NHL grade 3b: NHL-13 trial



ReMaRC study: Design



ClinicalTrials.gov NCT01122472

Important small points

- Double hit DLBCL
- CNS prophylaxis
- Transformed DLBCL
- Primary CNS lymphoma
- Primary cutaneous lymphoma
- Helicobacter *pylori*-related gastric DLBCL

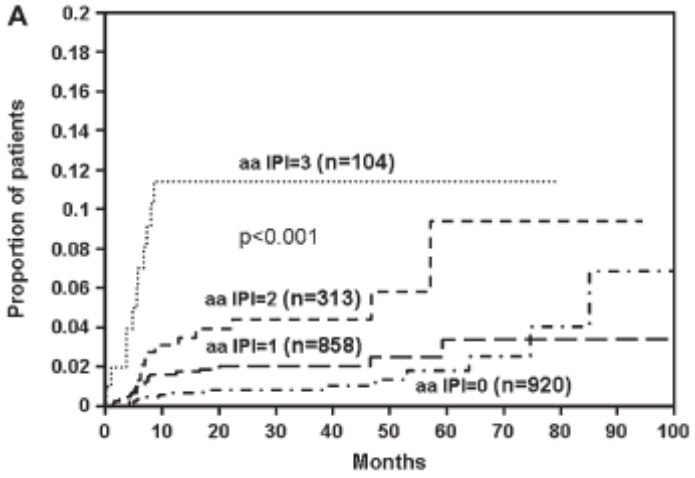
Double hit DLBCL

- Concurrent BCL2 and MYC translocation or hyperexpression
- Rare, in GCB subtype
  - Incidence <10% in primary DLBCL
  - Around 20% in transformed DLBCL
- Associated to poor response to chemotherapy and short survival
- Outcome related to other genetic abnormalities

RC Lindsey et al. Cur Op Hematol 2012;19:299. S Li et al. Mod Pathol 2012;25:145

CNS prophylaxis

- Incidence of CNS relapse is related to initial picture
- No change with rituximab-containing regimens
- Question on the value of IT methotrexate
  - DSHNHL: 2210 patients with DLBCL, 620 with prophylaxis
  - Low risk (aaIPI 0/1): 0 to 0.5%
  - High risk (aaIPI 2/3): 4% to 10%
    - No difference if prophylaxis
- Benefit of HD methotrexate?
- Poor outcome

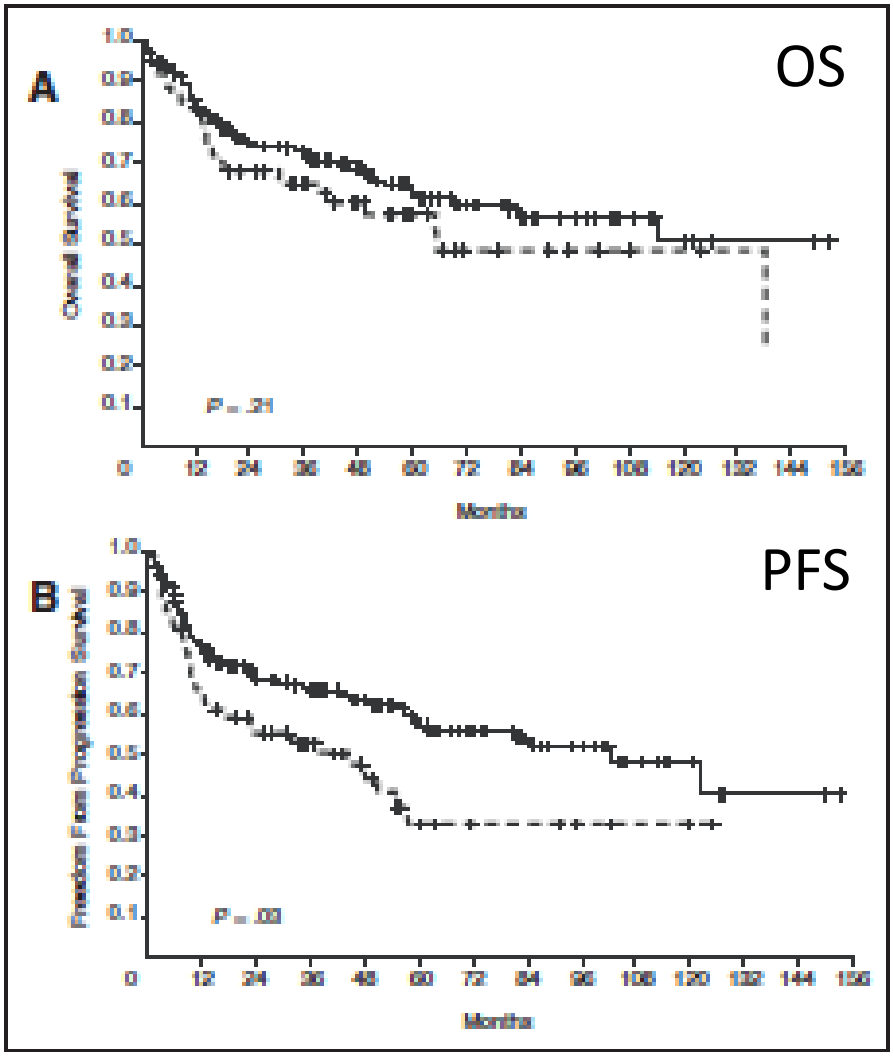


N Scmitz et al. Ann Oncol 2012;23:1267

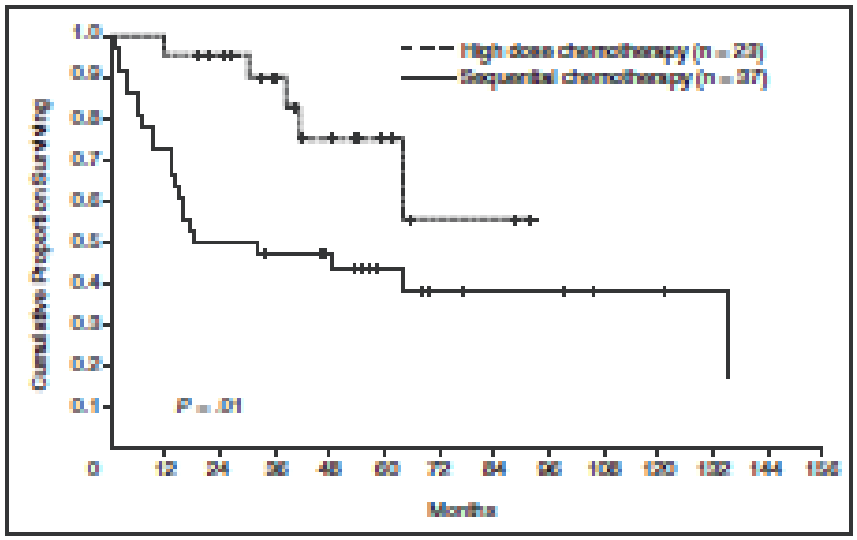
Transformed indolent L at diagnosis

- Frequent situation, undiagnosed
- To be treated like DLBCL
  - HDT with autologous transplant in first CR?
- More frequent (late) relapses
  - Indolent lymphoma (one third)
  - DLBCL
- Poorer outcome than primary DLBCL

Transformed DLBCL



HDT and autologous transplant
in first CR



H Ghesquières et al. J Clin Oncol 2006;24:5234

Primary CNS lymphoma

- Uncommon but associated with poor outcome
- Most are localized to CNS
- HD methotrexate-containing regimen is the standard treatment
  - Best regimen not yet described
- Dose and timing of whole brain radiation therapy still unclear

Primary cutaneous BLBCL

- Elderly women patients
- Few large reports
- Most frequent in legs (leg-type)
- Radiation therapy
  - High response rate but high relapse rate
- Standard chemotherapy (R-CHOP) is the recommended choice

Helicobacter *pylori*-related gastric DLBCL

- Retrospective analysis of 50 stage I/II patients
- Previously untreated
- Antibiotic treatment: 69% CR
  - 11/16 pure DLBCL in CR
  - 18/32 DLBCL (MALT) in CR
- Median follow-up of 7.7 years: All CR patients alive and free of disease*
- Same experience by A Ferreri (personal communication)

* Except one lung cancer

Kuo et al. Blood 2012;119:4838

Conclusion

- The addition of rituximab to CHOP has dramatically changed the outcome of these patients
- If R-CHOP is the standard for the majority of patients, more intensive regimens are needed for subgroups of patients
- New targeted drug will be add in the future to cure more patients