How I treat

High-risk follicular lymphoma

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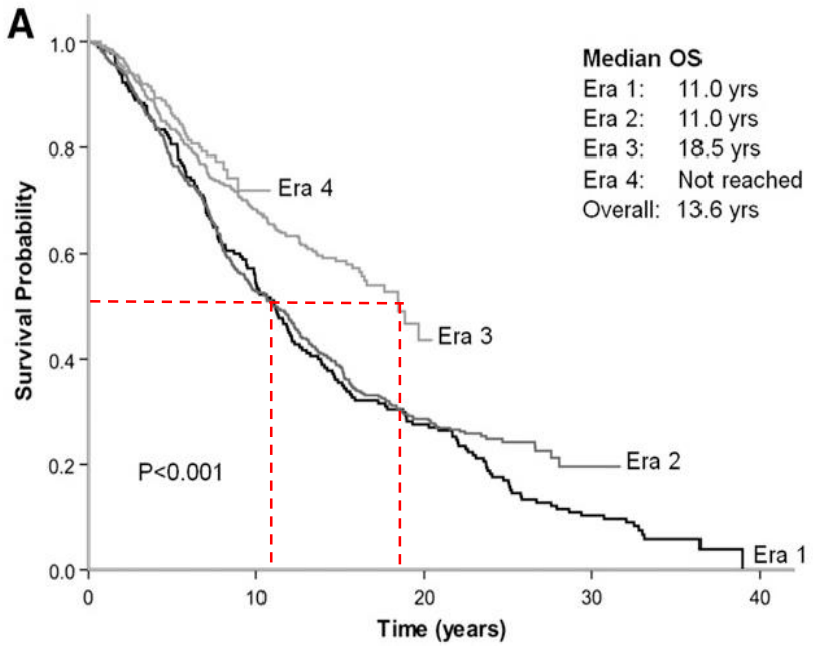
Bellinzona

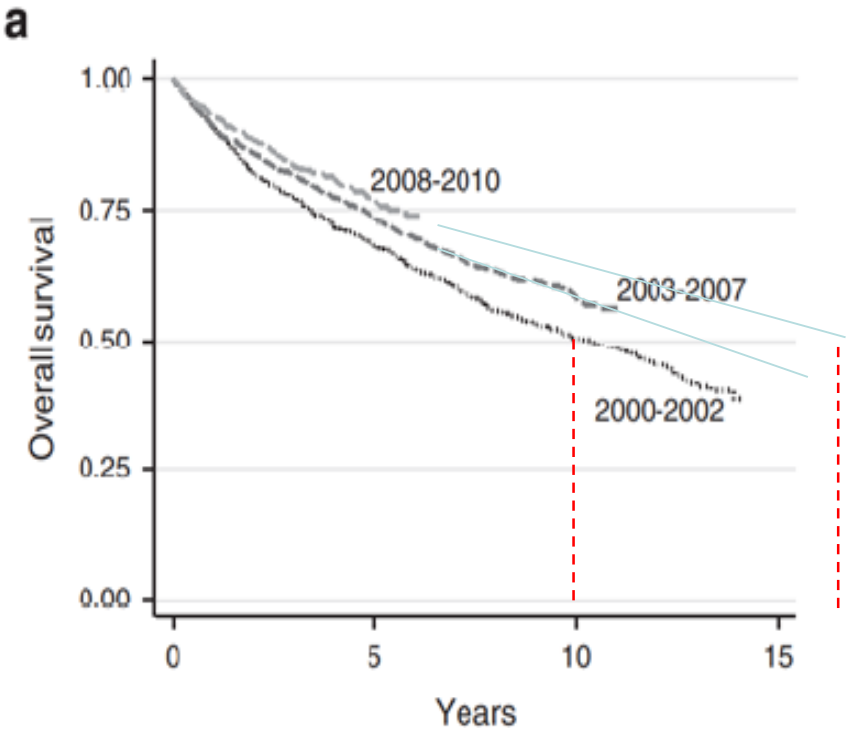
1) median OS raised from 10 to 18 y
2) advanced FL remains uncurable

Stanford, n = 1334



Tan et al. Blood 2013

Swedish registry, n = 2641



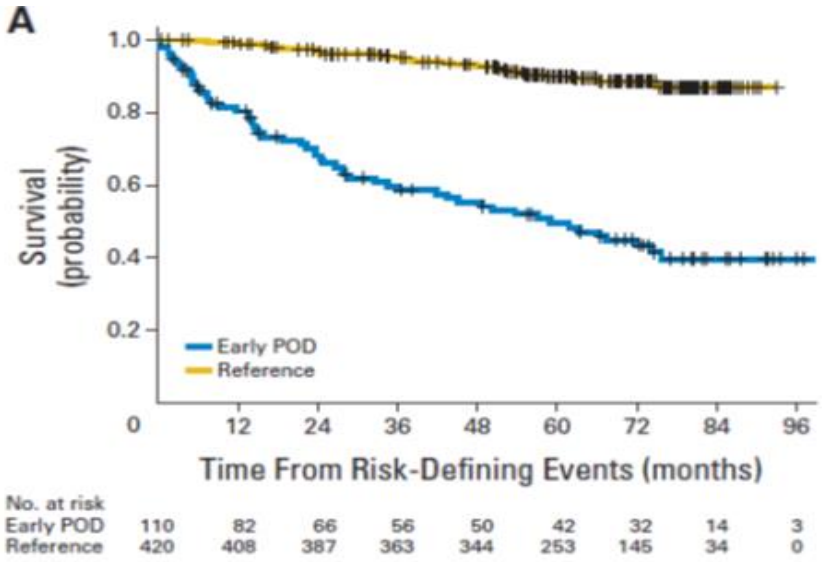
Junlén et al. Leukemia 2015

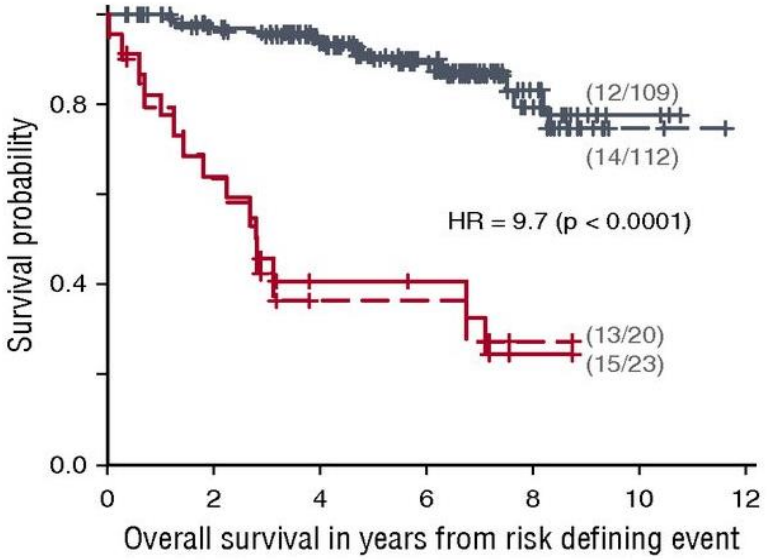
Prognostic factors for FL

Chemosensitivity	**Early relapse** **Quality of response**
Patient	**Age**
Disease	**Histological grade** **Glucose avidity (SUV)**
Combined scores	**FLIPI** **M7-FLIPI**

Prognostic value of early relapse (POD24)

Relapse within 24 months of front line chemoimmunotherapy (early progression) is associated with poor outcomes



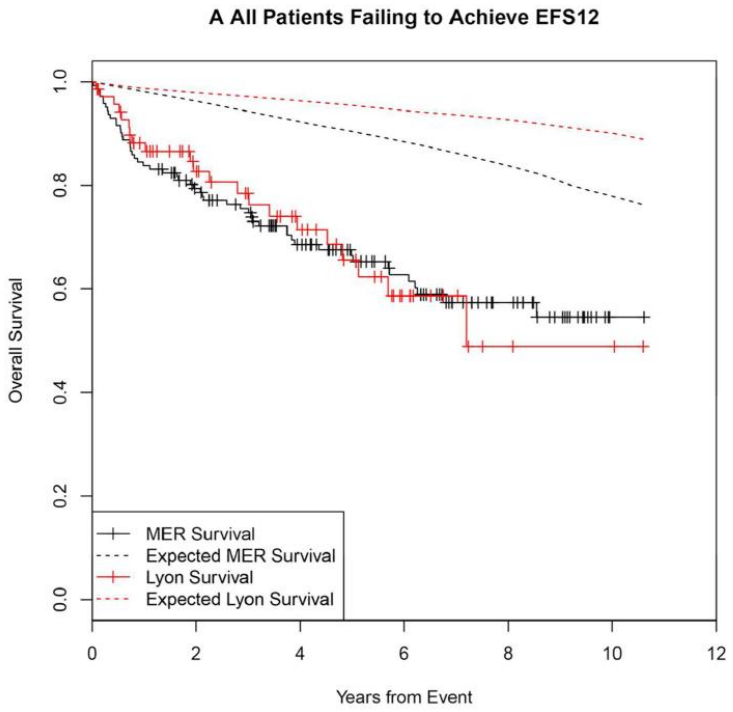


Casulo et al.
***J Clin Oncol.* 23: 2516-2522. 2015**

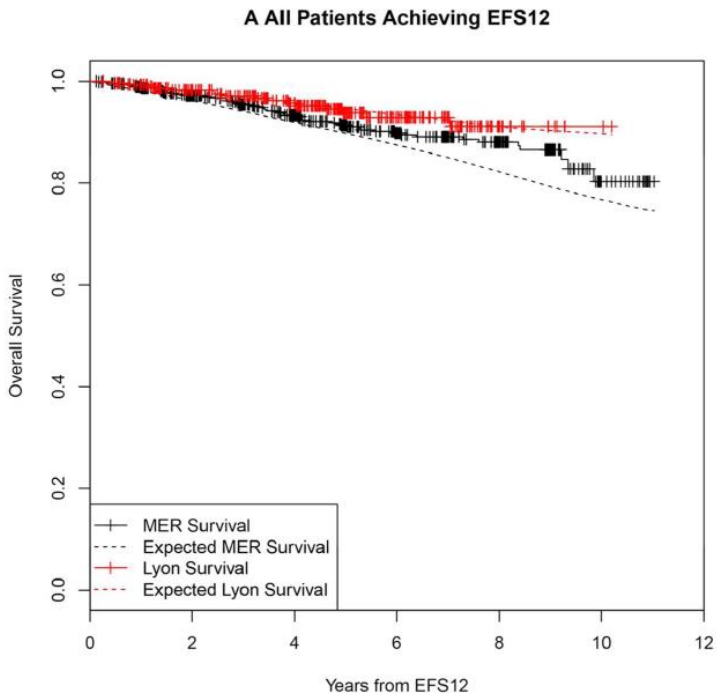
Jurinovic et al.
***Blood*. 2016; 128: 1112-1120, 2016**

Prognostic value of early relapse (POD12)

Progressing at 12 m



NOT Progressing at 12 m

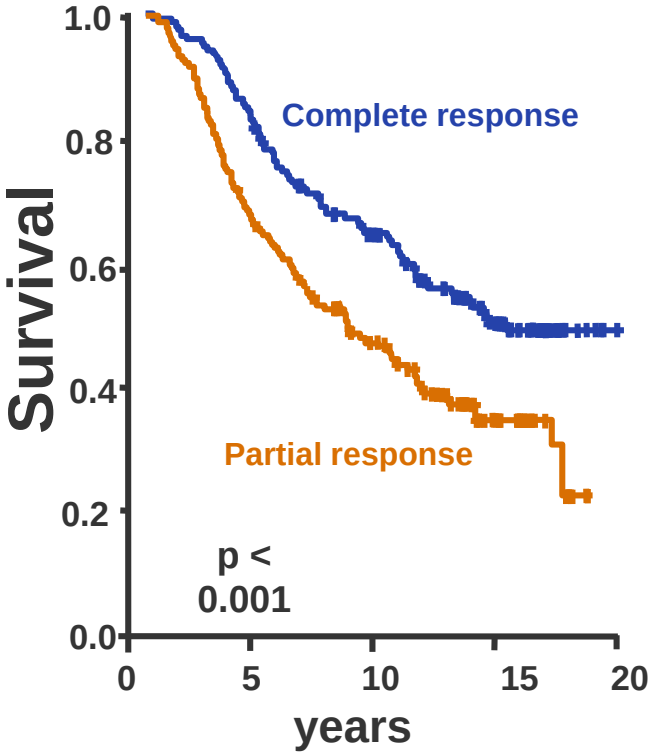


If NO early progression after treatment, the survival is same as general population!

Maurer et al. *Am J Hematol*. 2016

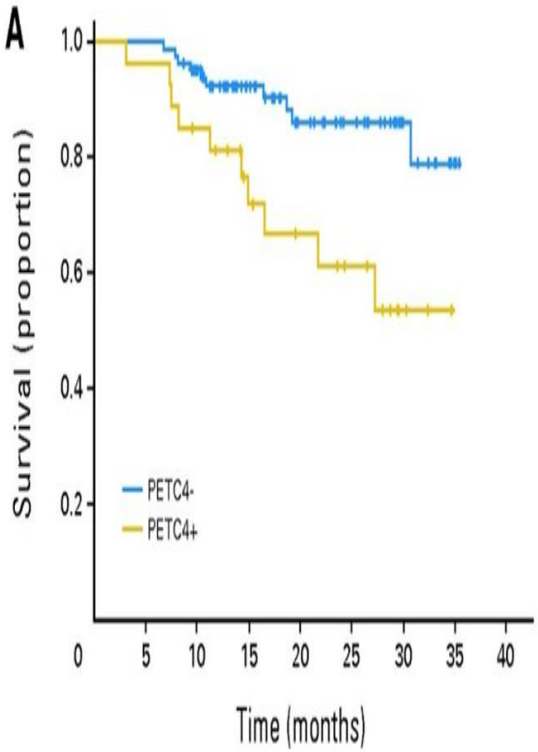
Responders (= chemosensitive FL) have a better prognosis

CT-scan



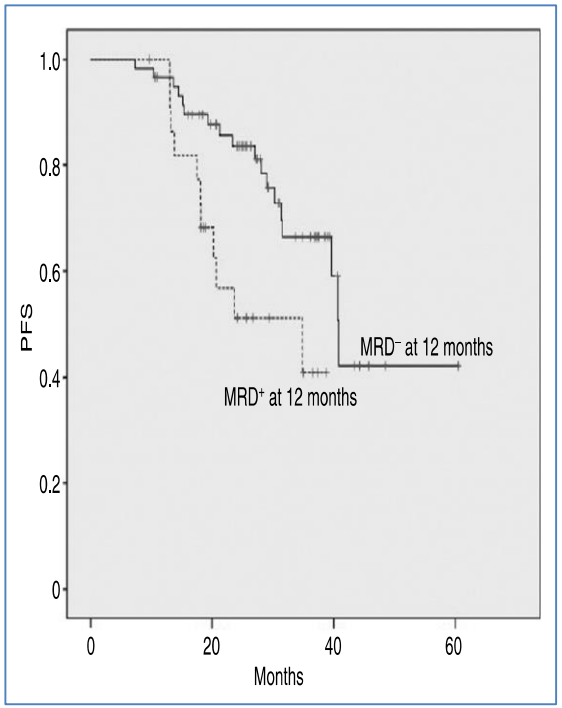
Bachy , J Clin Oncol 2010

PET-scan



Barrington, JCO 2015

MRD

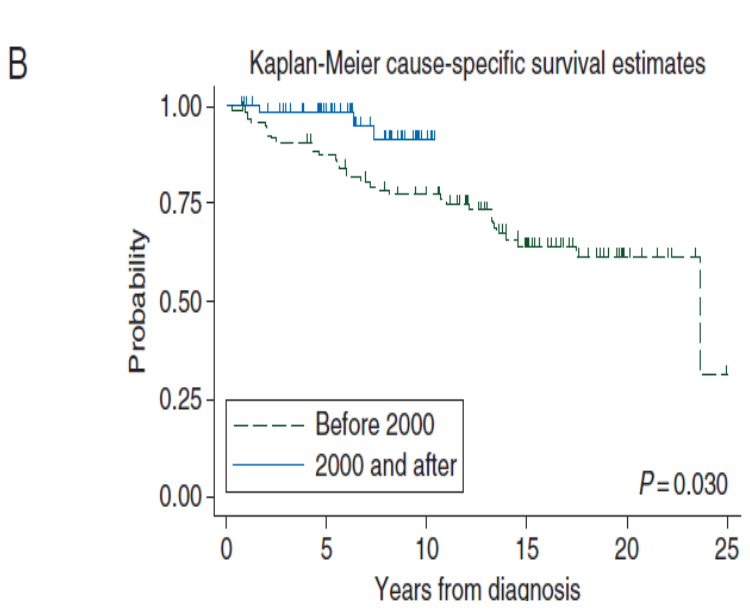


Galimberti, Clin Cancer Res 2014

90% of FL aged <40 are alive at 10 years

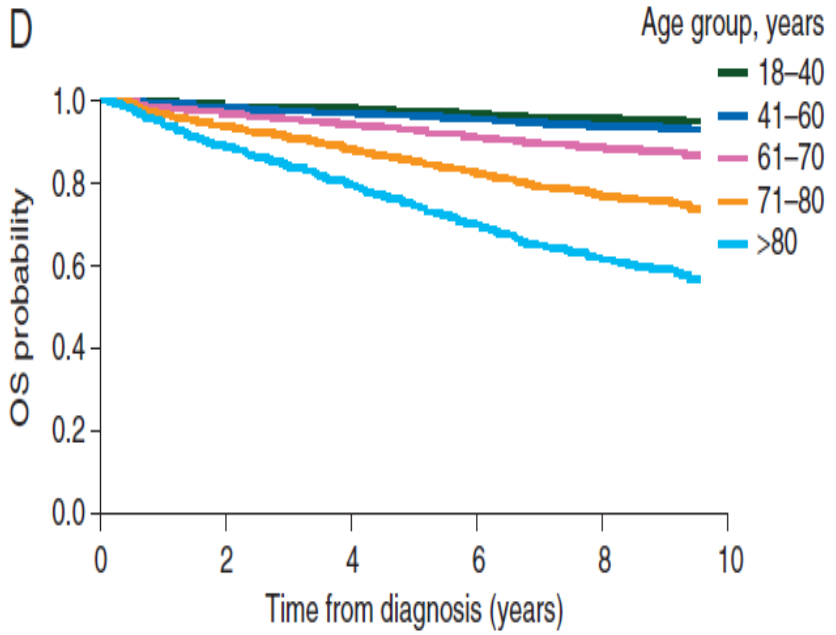
The median survival of FL patients aged < 40 is expected to be ≥ 30 years!

N= 155/1002, 4 EU centres
(Bellinzona, Novara, Barcelona, London)



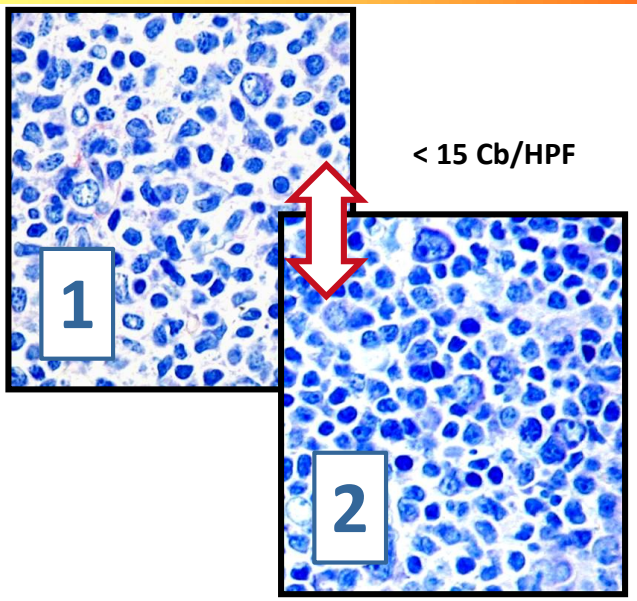
Conconi et al. Ann Oncol 2015

N= 164/2652, Lymphocare

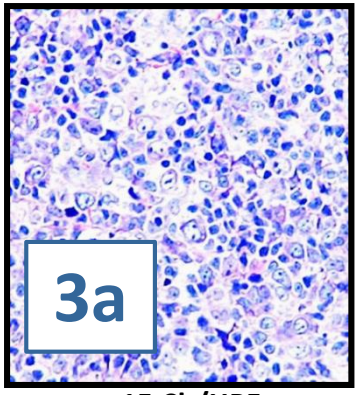


Casulo et al. Ann Oncol 2015

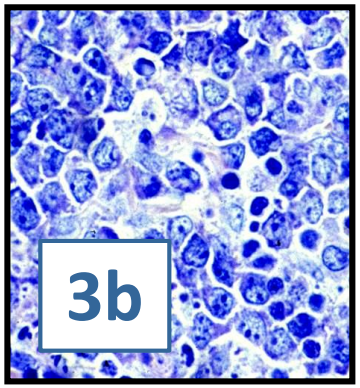
FL Grading



< 15 Cb/HPF

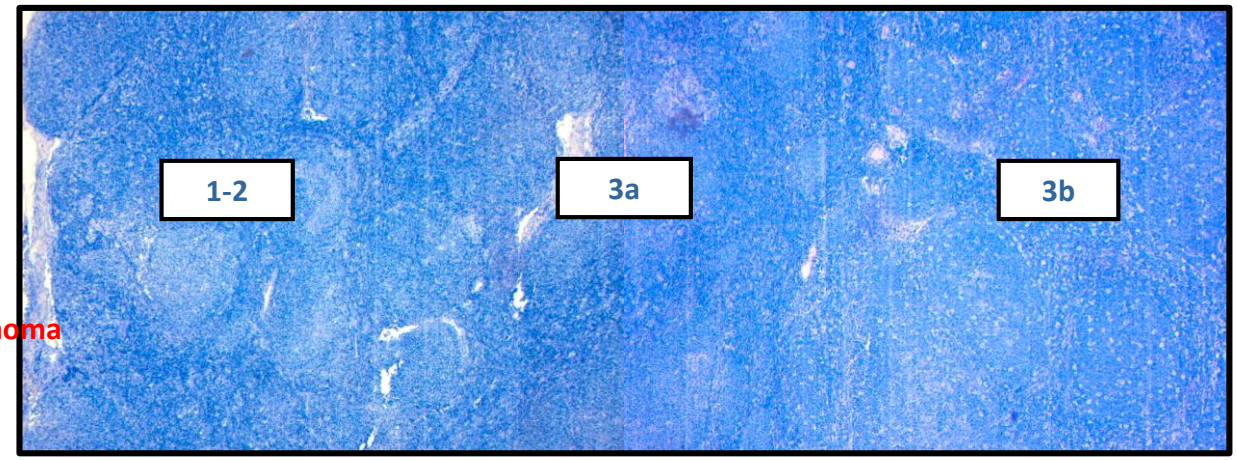


> 15 Cb/HPF



All Cb/follicular

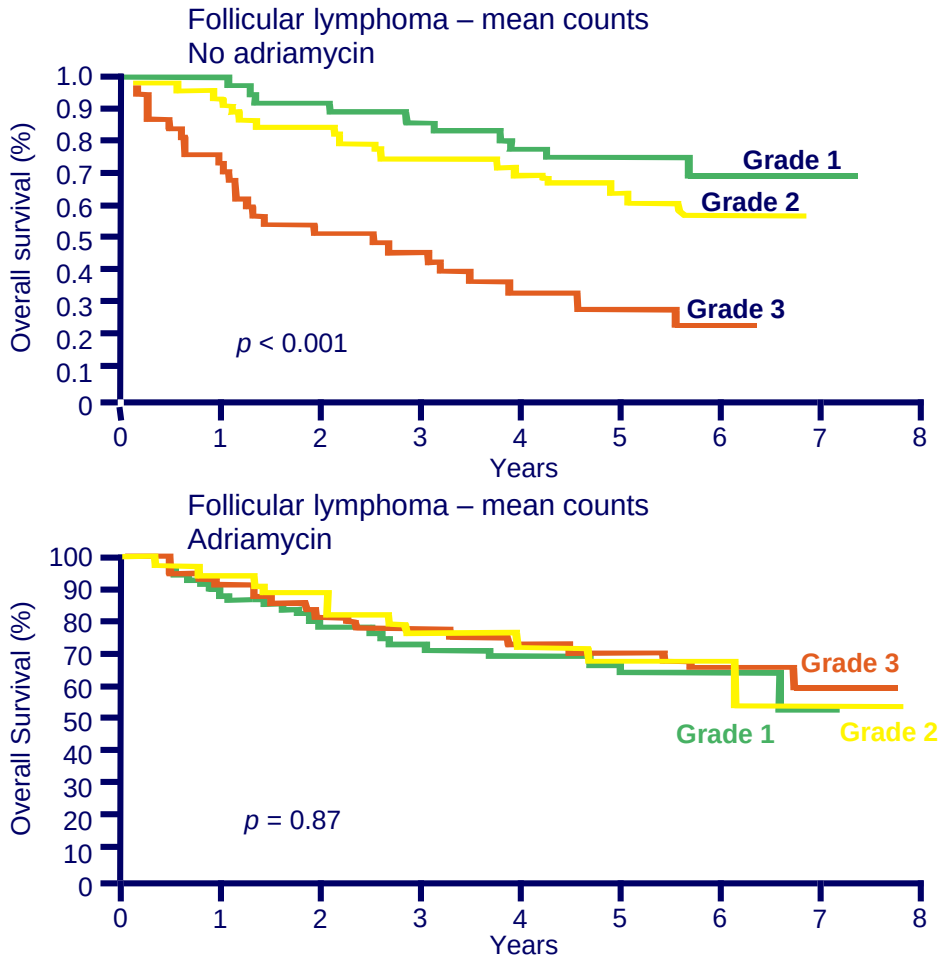
LBCL/follicular



LBCL = large B-cell lymphoma

Images courtesy of Stefano A Pileri, MD

Grade is not a prognostic but a *predictive* factor: Omaha

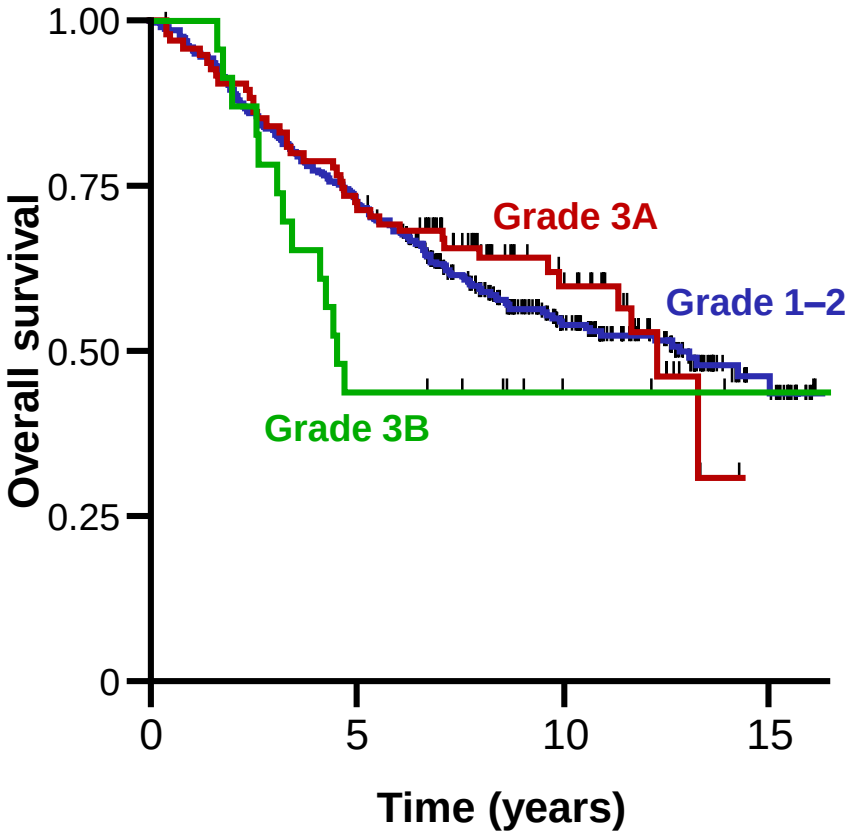


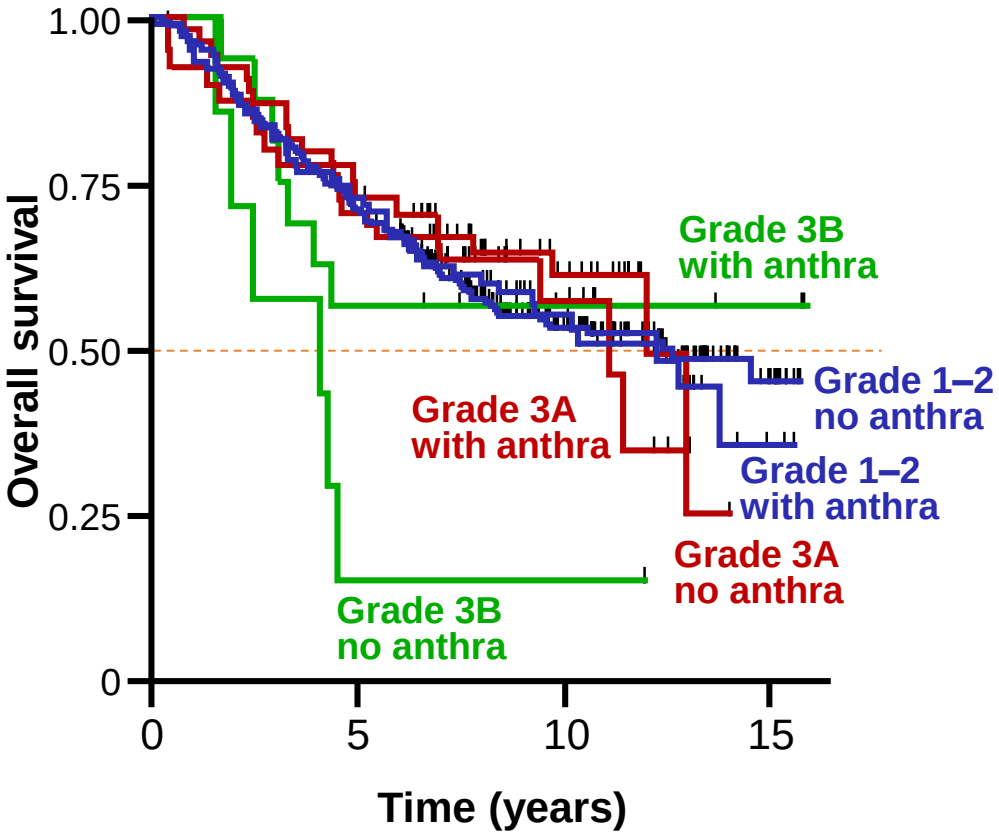
Grade 3 FL must be treated with an anthracycline-containing regimen

Nathwani BN, *et al.* Follicular lymphoma. In *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissue*. Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds). IARC Press: Lyon 2001.

Grade 3A vs 3B is not a prognostic but a *predictive* factor: Nordic group

Overall survival





Wahlin BE, *et al. Br J Haemtaol* 2012; 156:225–233.

To be on the safe side...

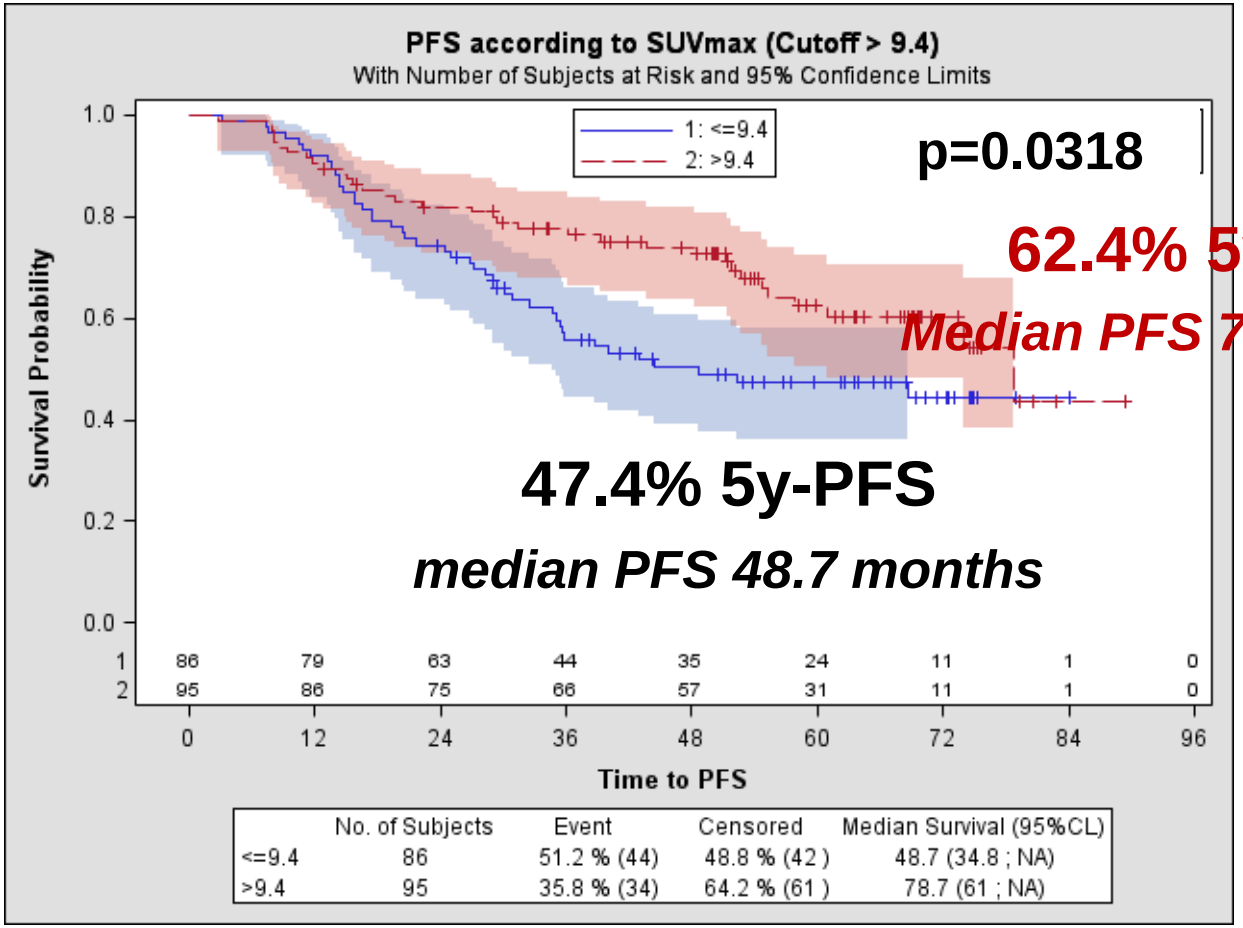
Theoretically: give R-CHOP only to grade 3B

BUT

- 30–50% of pathologists do not agree on grade

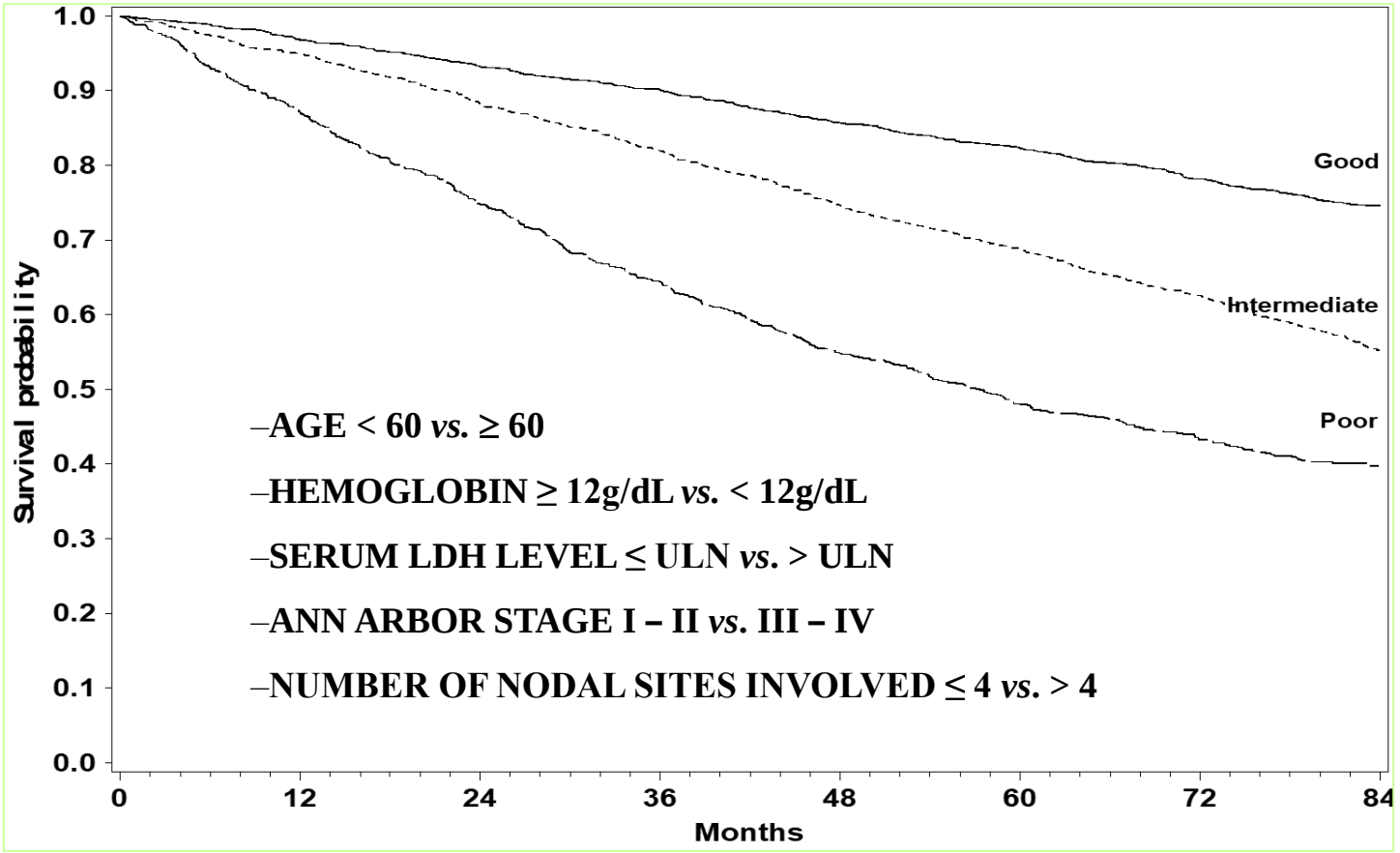
Practically: R-CHOP to all grade 3?

SUVmax and PFS



Cotterau et al, ASH 2016, Abstract 1101

FLIPI = Follicular Lymphoma International Prognostic Index



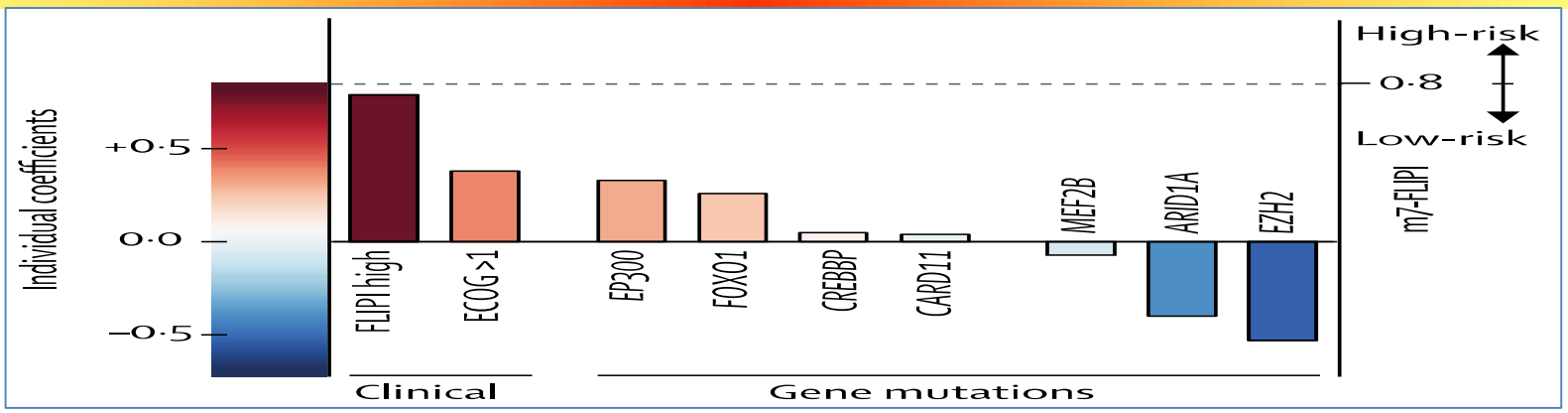
0-1 factor

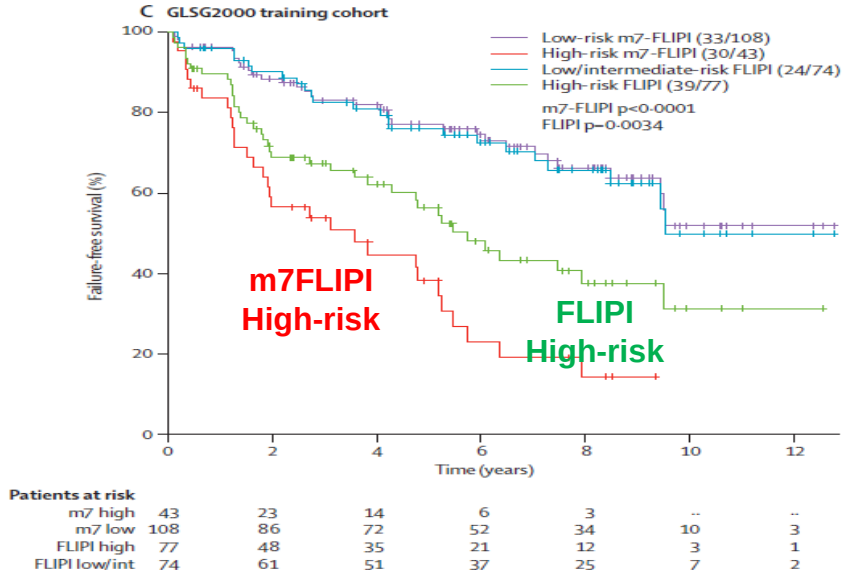
2 factors

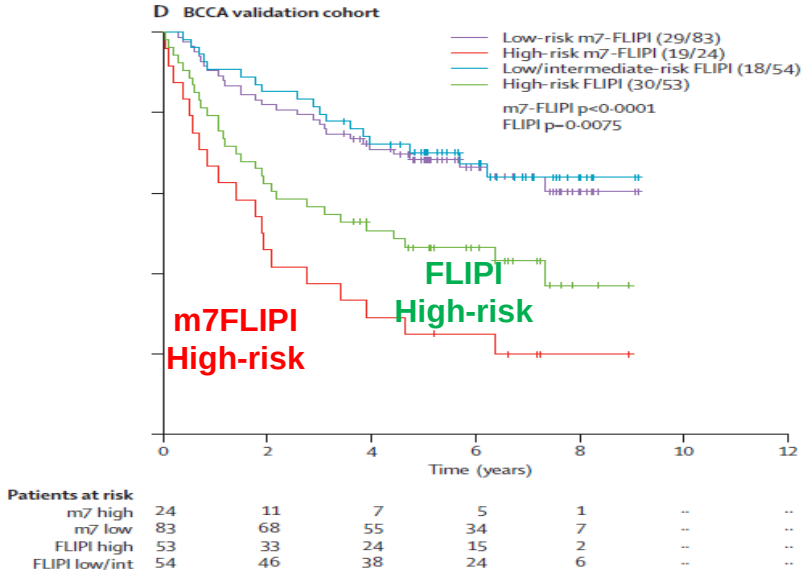
3-5 factors

Solal-Celigny, Blood 2004

The clinicogenetic risk model m7-FLIPI



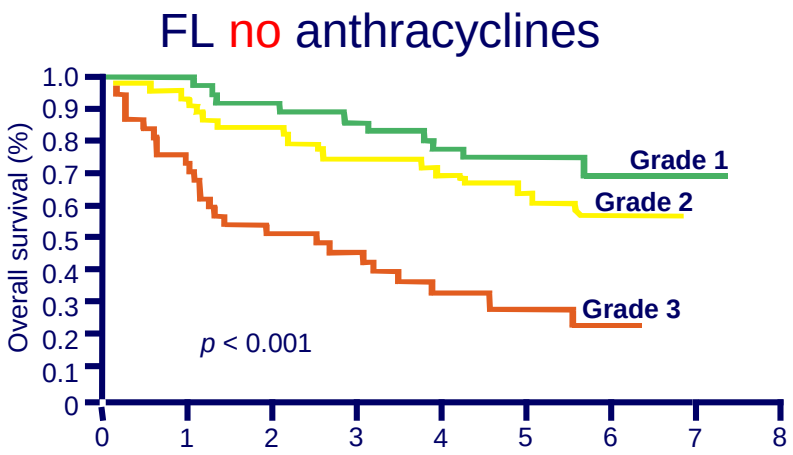


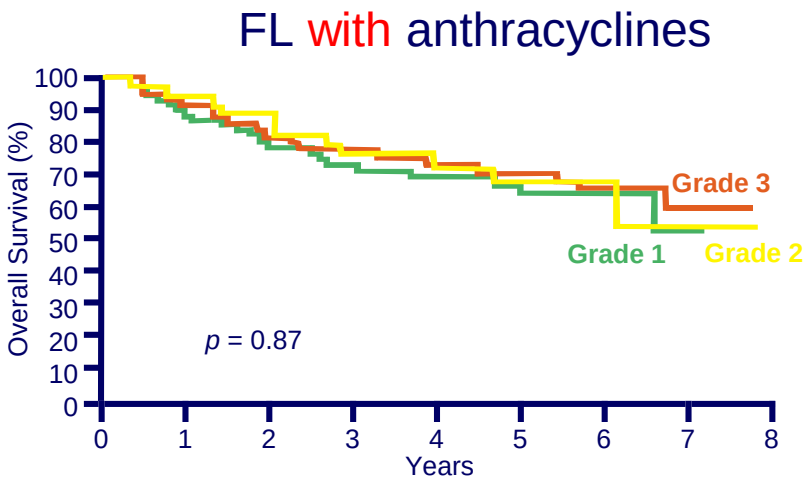


Pastore et al., Lancet Oncol., 2015

The ideal treatment for high-risk pts

A treatment which gives high-risk cases the same prognosis as low-risk cases





Nathwani BN, *et al.* Follicular lymphoma. In WHO classification 2001

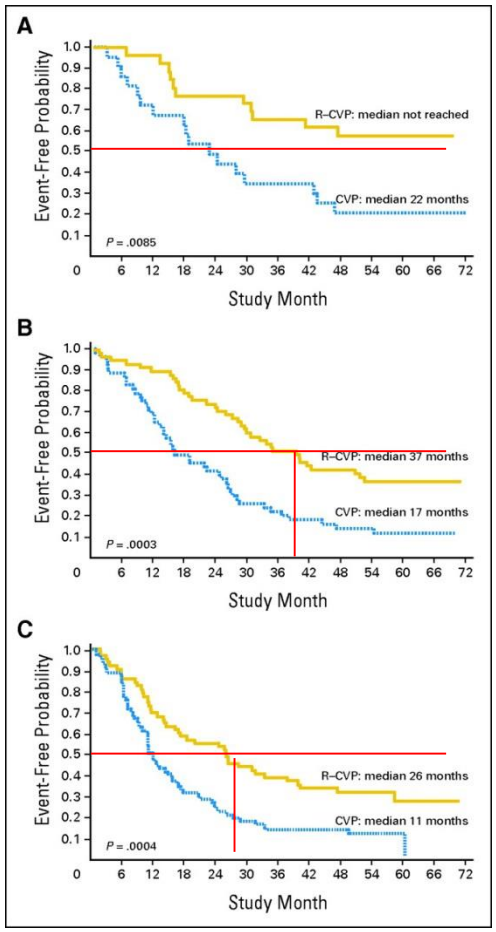
R-chemo (CVP) by FLIPI

EFS

FLIPI 0-1
Median EFS: NR

FLIPI 2
Median EFS: 40m

FLIPI 3-5
Median EFS: 27m



311 first line FL

CVP vs R-CVP

R gives the smallest benefit in FLIPI high-risk

High-risk worse prognosis despite of R

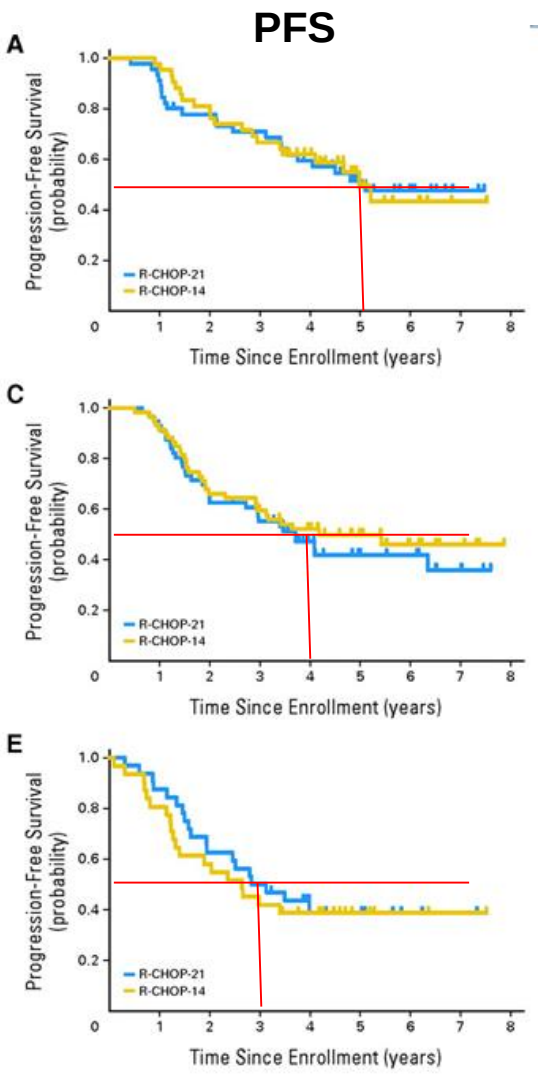
Marcus et al.; *JCO* 2008, 26, 4579-4586.

Intensification (R-CHOP-14) by FLIPI

FLIPI 0-1
Median PFS: 5y

FLIPI 2
Median PFS: 4y

FLIPI 3-5
Median PFS: 3y



300 first line FL

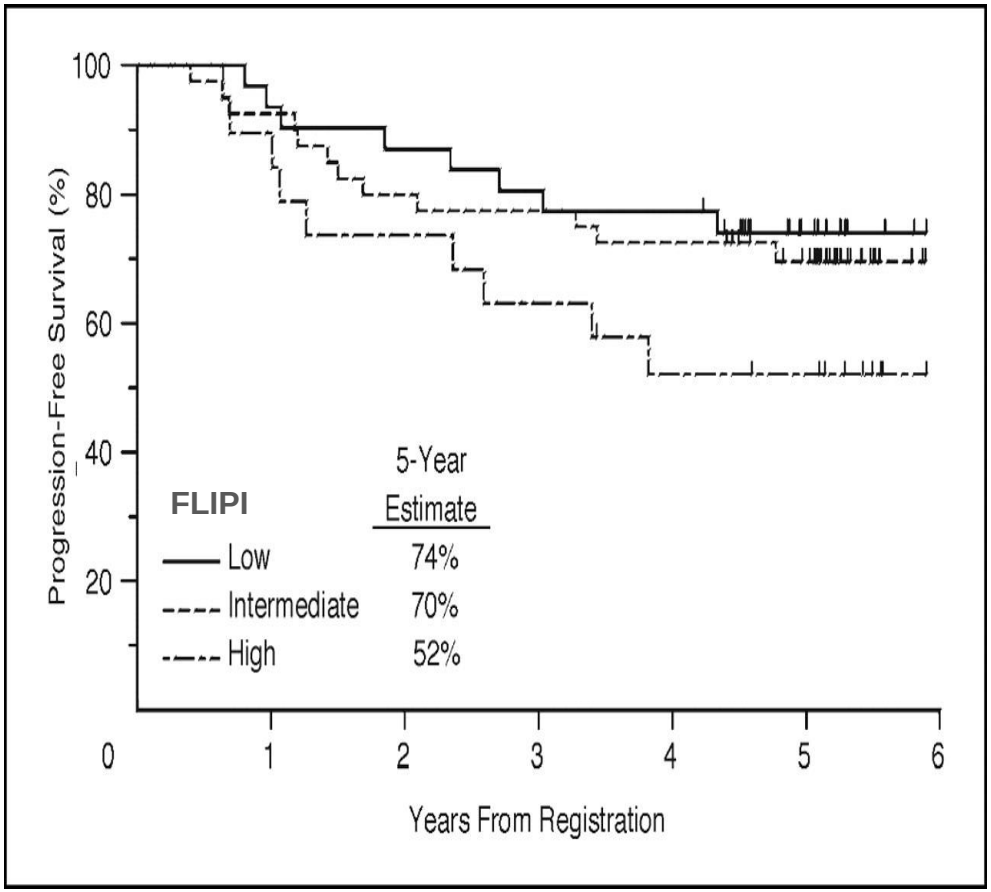
R-CHOP21 vs R-CHOP14

No benefit of intensification for all FLIPI groups

High-risk worse prognosis despite of intensification

Watanabe et al.; *JCO* 2011, 29, 3990-3998.

Radio-immunotherapy (Zevalin) consolidation by FLIPI



90 first line FL

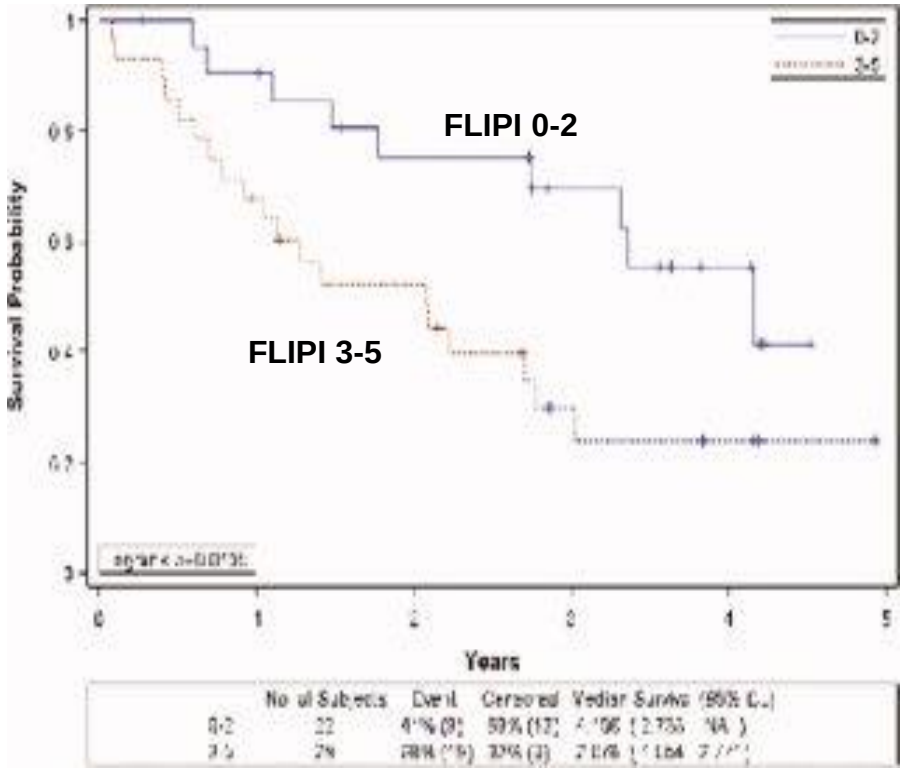
CHOP x 6 + Zevalin consolidation

High-risk FLIPI not better
Despite of zevalin consolidation

Press et al.; *JCO* 2006, 24, 4143-4149

R-FM at relapse by FLIPI

PFS



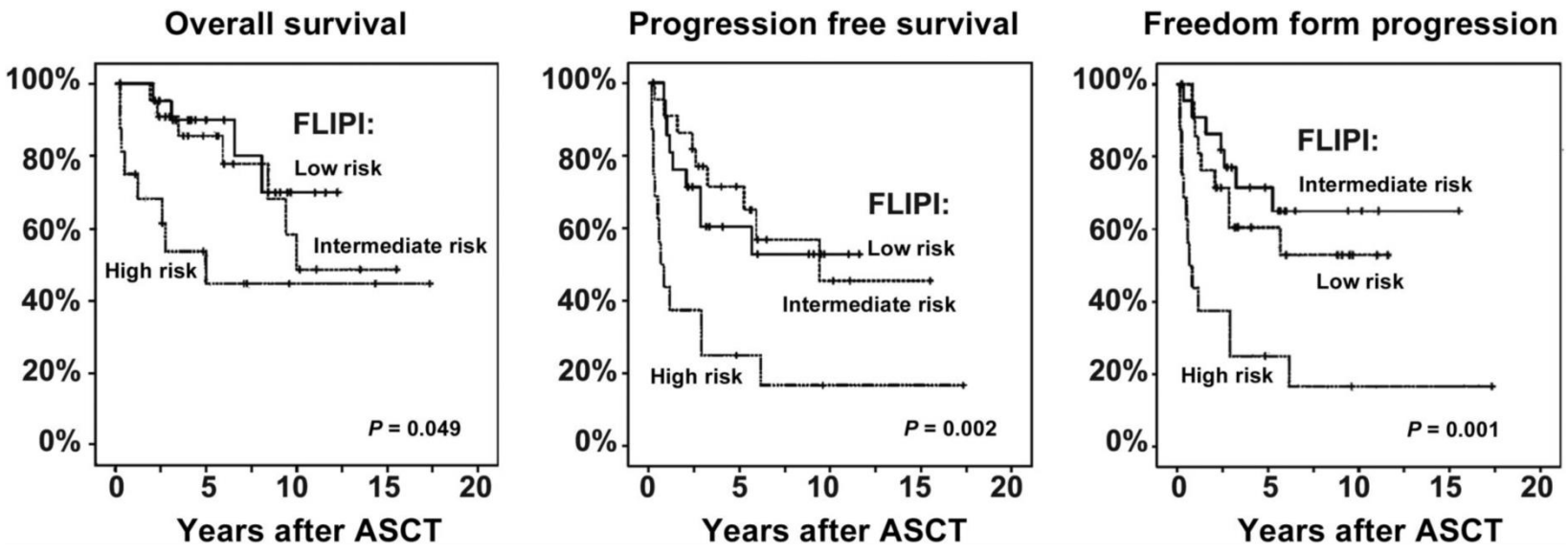
50 R-naive relapsed FL

Despite of R-FM high-risk FL has worse prognosis

Morschhauser et al., Cancer, 2010

HDCT by FLIPI at diagnosis or at relapse

18 first line FL and 34 second line FL



High-risk FLIPI worse prognosis despite of HDCT

Metzner et al. ; Ann Oncol. 2013;24(6):1609-1615.

Addition of bortezomib in high-risk FL

Randomised study in 1° line HR FL (n= 257)

BR + R-maintenance
BR-Bortezomib + R-maintenance

} Same PFS and OS

Evens et al, ASH 2017, Abst. 482

Randomised study in 1° line HR FL (n= 135)

OfaB + Ofa-maintenance
OfaB-Bortezomib + Ofa-bortezomib maintenance

} Same PFS and OS

Blum et al, ASH 2017, abst 485

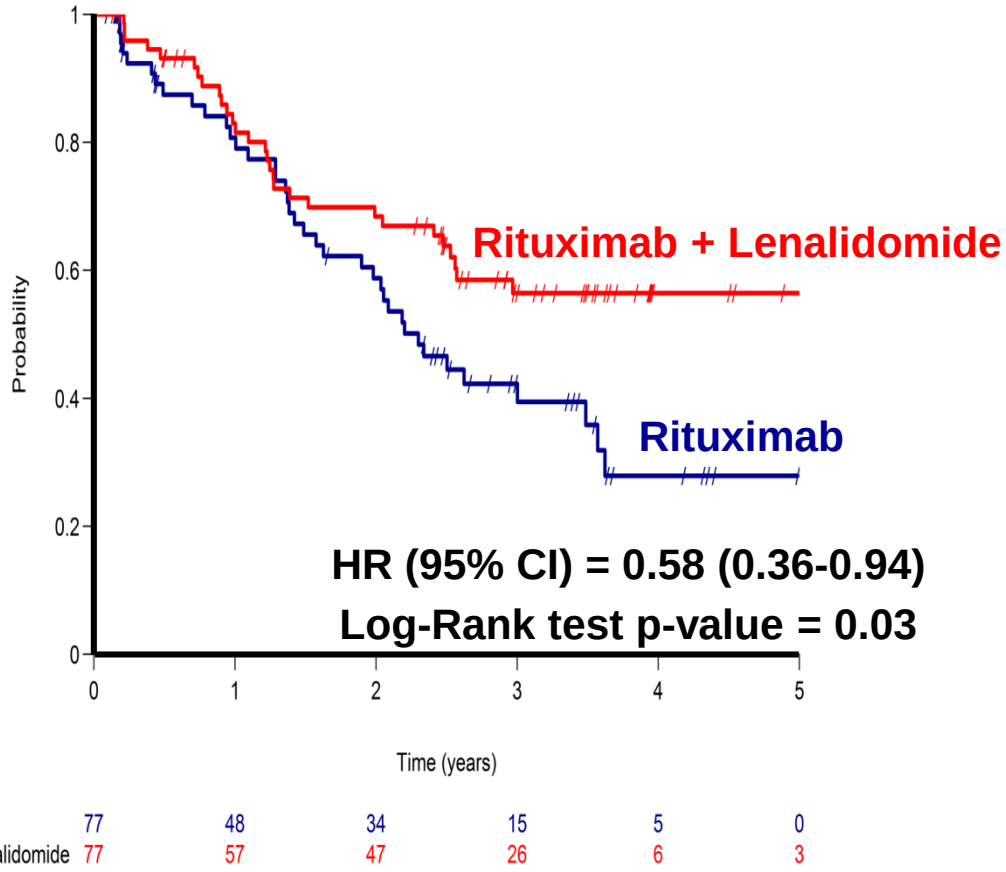
So, unfortunately ….

- **No chemotherapy has shown to improve the prognosis of bad-risk FL patients**
- **More agressive treatment does not work better than a milder treatment**
- **What about biologics?**

SAKK 35/10: R vs R2
Progression-free survival

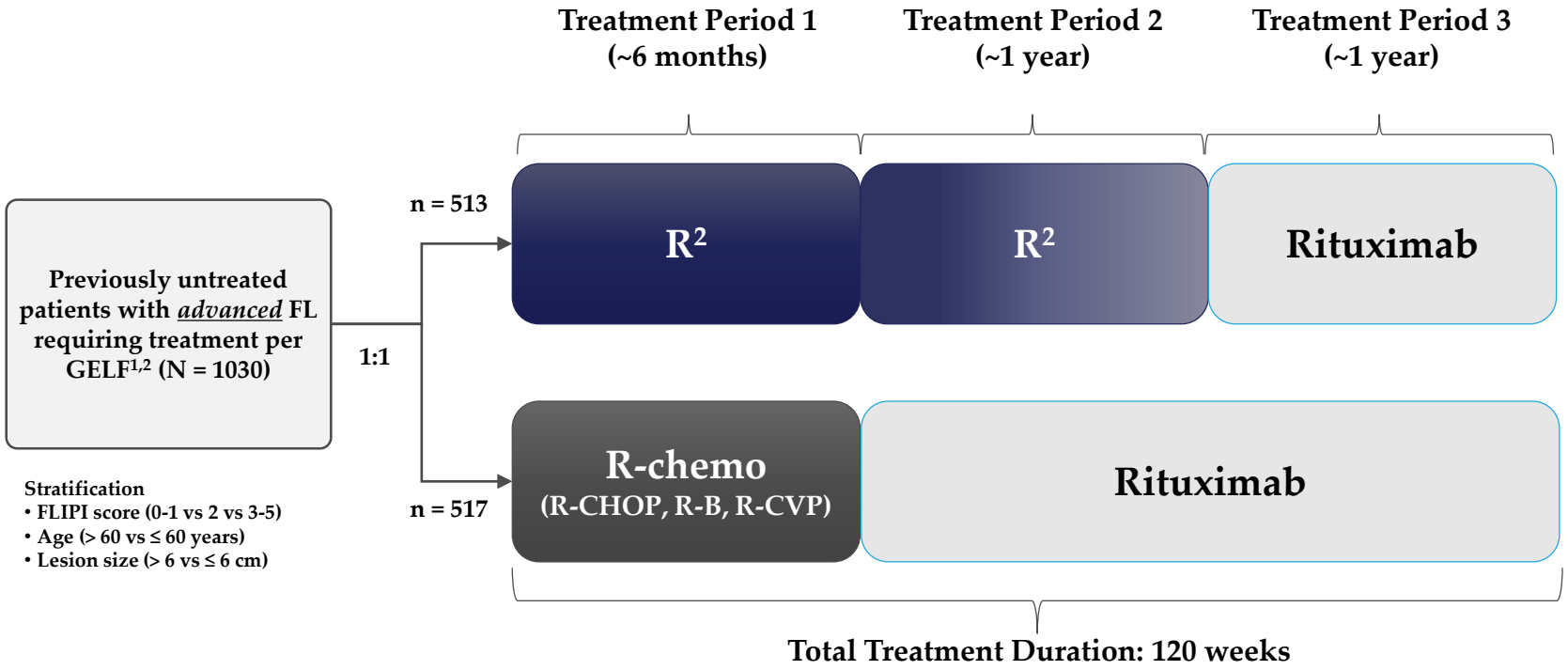
154 FL in need of treatment

	R (%)	R2 (%)
RR	75	82
CR30	19	42
G 3-4 tox	13	50
Fatigue	1	3
Neutropenia	6	23
Rash	0	5



Kimby et al, ASH 2016

RELEVANCE trial: Study Design



Potentially actionable oncogenic alterations in FL

Biomarker	Function	Agent
Biologic pathways		
BCR	B cell survival and proliferation	PI3K and BTK inhibitors
JAK/STAT	Cytokine signaling	JAK2 inhibitors
Gene mutations		
CREBBP/EP300	Histone acetylation	HDAC inhibitors
EZH2	Histone (H3K27) methylation	EZH2 inhibitors
Oncogenic proteins		
BCL2	Anti-apoptotic factor	BH3 mimetics
BCL6	Regulates B-cell differentiation	BCL6 inhibitors

Conclusions 1

- 20% of FL have a bad prognosis: the m7FLIPI is the best prognostic index for identifying them
- It is not wrong to treat all G3 FL (A + B) with R-CHOP
- For all the others, no evidence that higher risk should be treated with more aggressive chemotherapy
- Possibly high-risk FL are intrinsically chemoresistant
  - They might do better if biologicals are added (not lenalidomide)
  - They should be included in clinical trials when possible

Conclusions 2

In the future

Treatment should be determined based on predictive and NOT on prognostic factors