How I approach newly diagnosed Follicular Lymphoma patients with advanced stage ?

Professeur Gilles SALLES

iC-HCL Institut de Cancérologie des Hospices Civils de Lyon

Hospices Civils de Lyon Lyon University Hospital

Lyon 1

CRCL

Lysa The Lymphoma Study Association

How I Choose First Line Treatment in Follicular Lymphoma in 2017?

1. How do I take into account the heterogeneity of patients with advanced stage FL ?

2. Choosing first line therapy: standards or options ?

3. What is next in first line therapy ?

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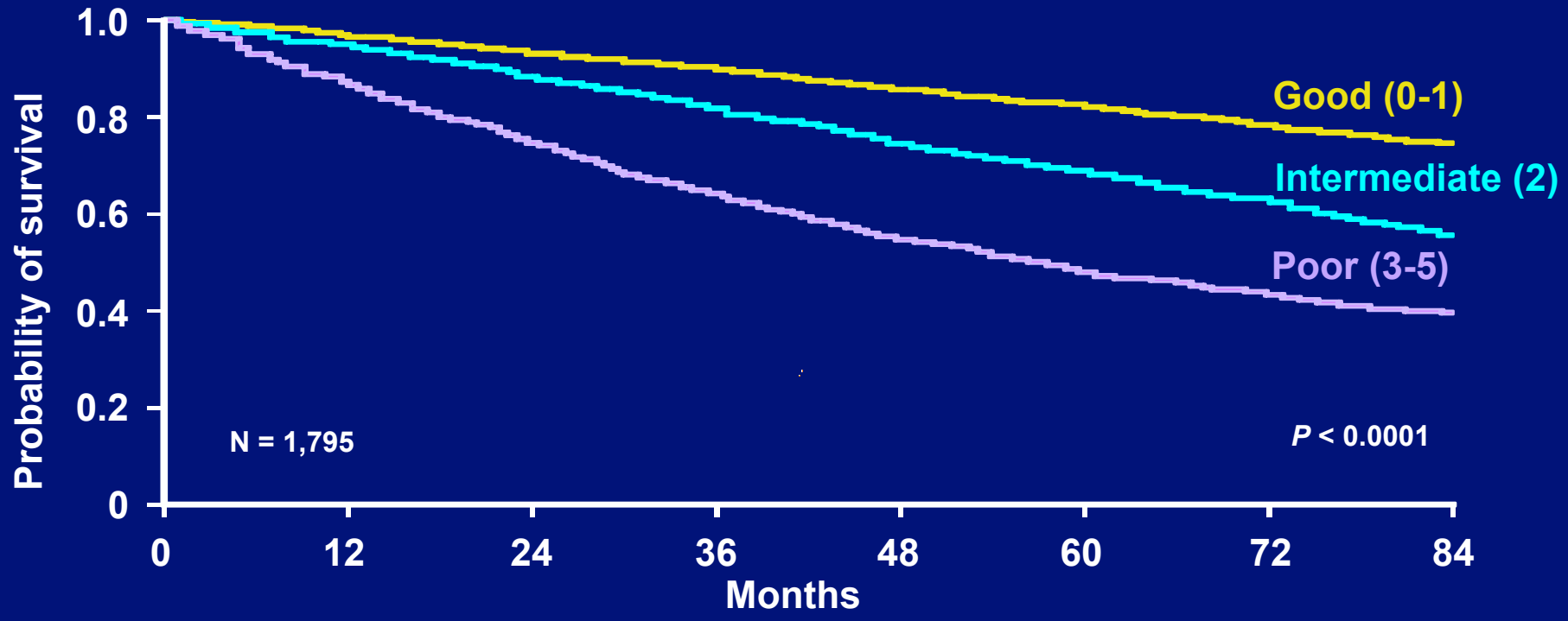
The Follicular Lymphoma International Prognostic Index (FLIPI): Overall survival

Solal-Céligny P, et al. Blood 2004; 104:1258-1265.



– Age < 60 *vs.* ≥ 60

– Hemoglobin level ≥ 12g/dL *vs.* < 12g/dL

– Serum LDH level ≤ ULN *vs.* > ULN

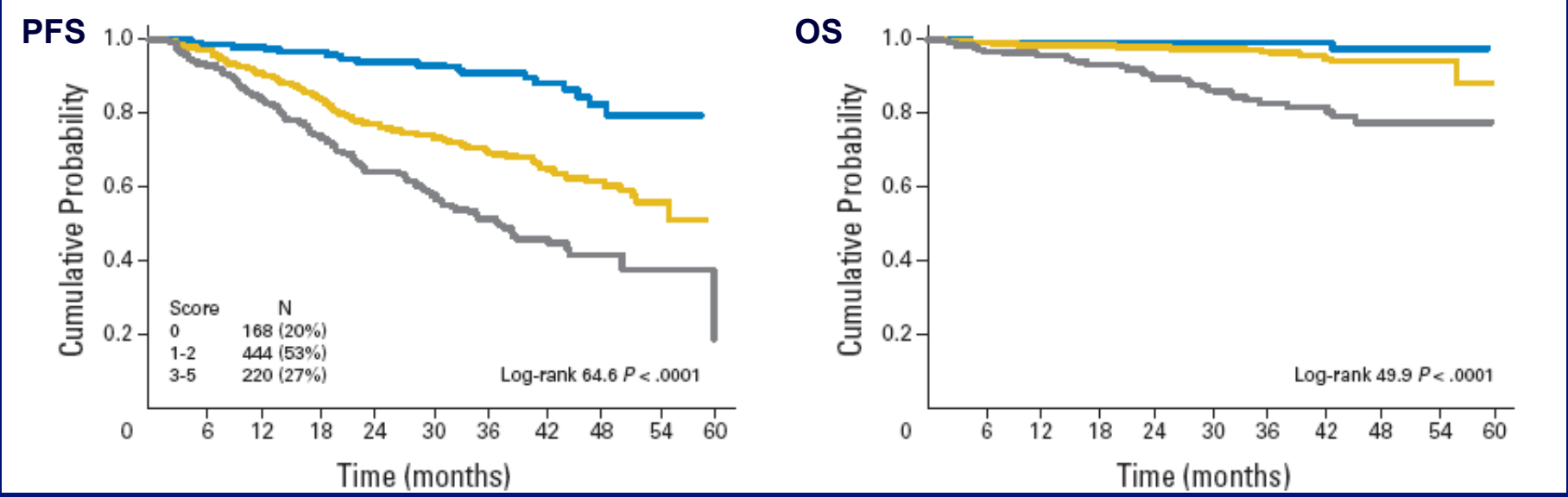
– Ann Arbor stage I – II *vs.* III – IV

– Number of nodal sites involved ≤ 4 *vs.* > 4

Improving FLIPI: may be FLIPI-2 ?

Federico M, et al. J Clin Oncol 2009; **27;4555**.

59% of patients had received rituximab ; assess both PFS and OS



Risk group	– Age ≤ 60 *vs.* > 60 – Hemoglobin level ≥ 12g/dL *vs.* < 12g/dL – β2 microglobulin ≤ ULN *vs.* > ULN – Bone marrow involvement no *vs.* yes – Largest diameter of the largest node ≤ 6 cm *vs.* > 6 cm	OS
Good		
Intermedia		
Poor		

Despite progress in understanding FL biology, clinical features still guide treatment decision

- Ann Arbor stage, symptoms, LDH and b2microglobulin
- FLIPI and FLIPI2 indexes
- Tumor burden criteria

GELA criteria

✓ High tumor bulk defined by either:
- a tumor > 7 cm
- 3 nodes in 3 distinct areas each > 3 cm
- symptomatic splenic enlargement
- organ compression
- ascites or pleural effusion

✓ Presence of systemic symptoms
✓Serum LDH or β2-microglobulin above normal values

BNLI criteria

✓ Rapid disease progression in the preceding 3 months

✓ Life threatening organ involvement
✓ Renal or liver infiltration
✓ Bone lesions

✓ Systemic symptoms or pruritus
✓ Hb<10 g/dL or WBC< 3.0×10^9/L or Plat.<100×10^9/L ; related to marrow involvement

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Choosing first line therapy in patients with advanced stage: standards or options

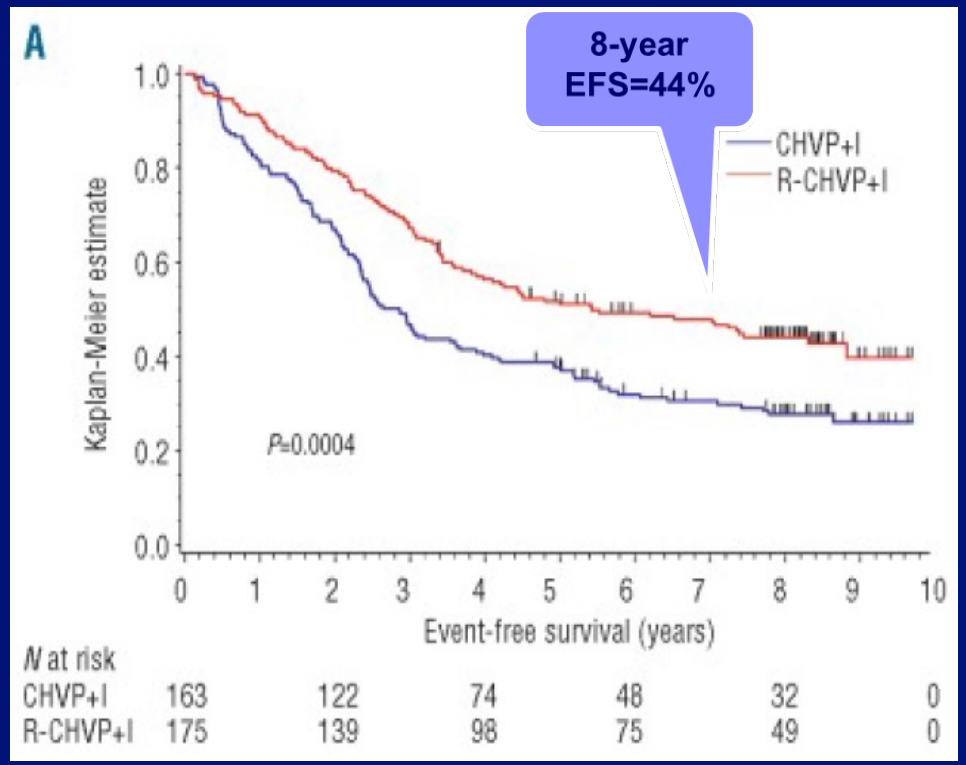
1. Rituximab plus chemotherapy represents the standard of care

2. Is there an optimal chemotherapy regimen ?
   - R-CVP, R-CHOP, R-FC/FM/FCM or R-Benda..

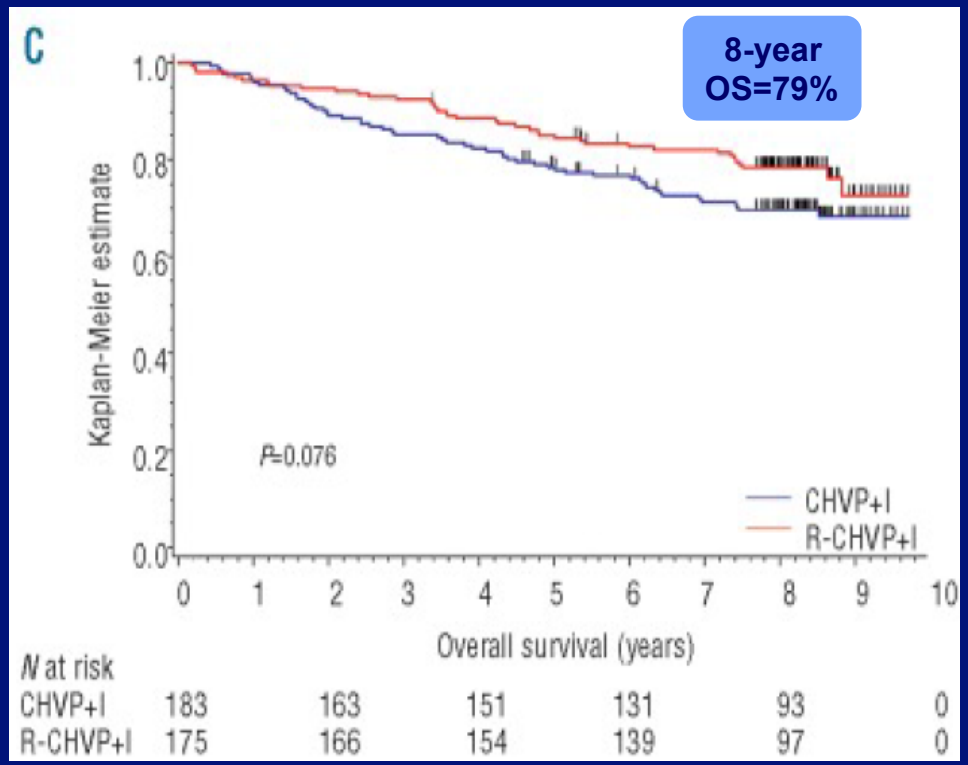
3. What is the benefit of further consolidation ?
   - radioimmunotherapy, rituximab maintenance

High tumor burden follicular lymphoma (FL2000 update)

Event free survival



Overall survival



median follow-up = 8.3 years

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Bachy et al, Haematologica 2013

Rituximab + chemotherapy has improved overall survival

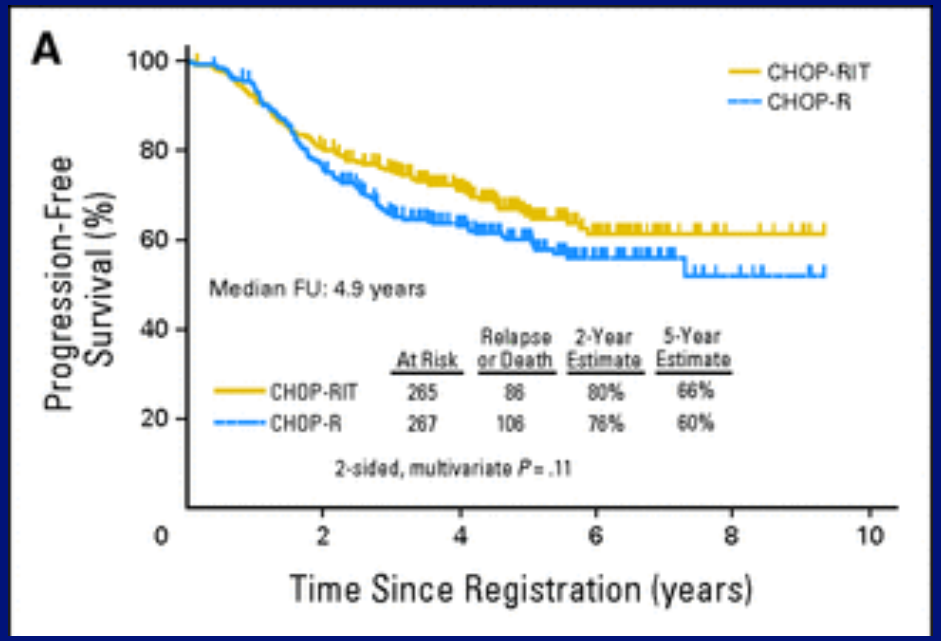
Study name and author	Follow-up	Overall survival (%)		*P*
		Control	Rituximab	
M3902; Marcus *et al.*[1]	4 years	77	83	✓
GLSG; Hiddemann *et al.*[2]	5 years	84	90	✓
M39023; Herold *et al.*[3]	4 years	75	89	✓
FL2000; Salles *et al.*[4]	8 years	79	84	✓ (high risk pts)

Cochrane analysis:
HR = 0.63 [0.51–0.79]
Schulz H et al. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003805.

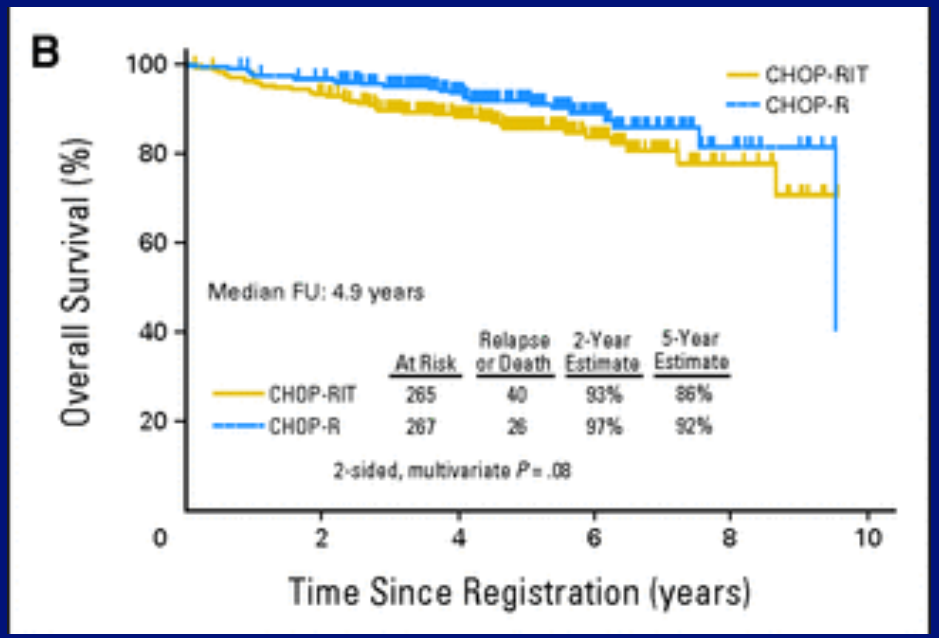
1. Marcus R, *et al. J Clin Oncol* 2008; 26:4579–4586.
2. Buske C, *et al. Blood* 2008; 112:abstract 2599.
3. Herold M, *J Clin Oncol* 2007; 25:1986–1992.
4. Salles G, *et al. Blood* 2008; Bachy E. *et al*; Haamtologica 2013

Randomized trial comparing rituximab-CHOP versus CHOP followed by ^{131}I tositumomab (CHOP-RIT) in untretated follicular lymphoma (SWOG S0016)

Progression free survival



Overall survival

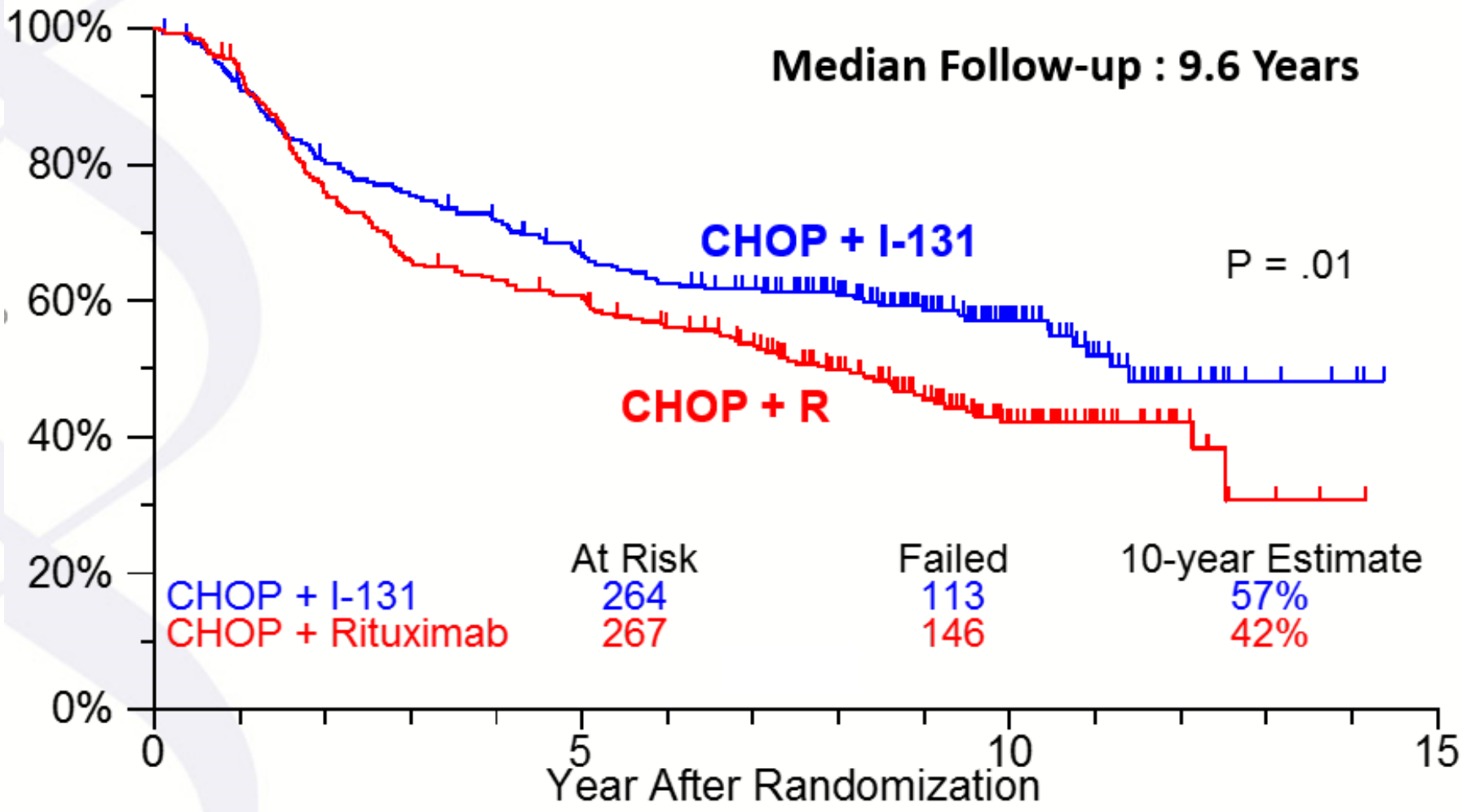


Significantly more Gr. 3 or more febrile neutropenia with R-CHOP, and more Gr. 3 thrombocytopenia with CHOP+RIT

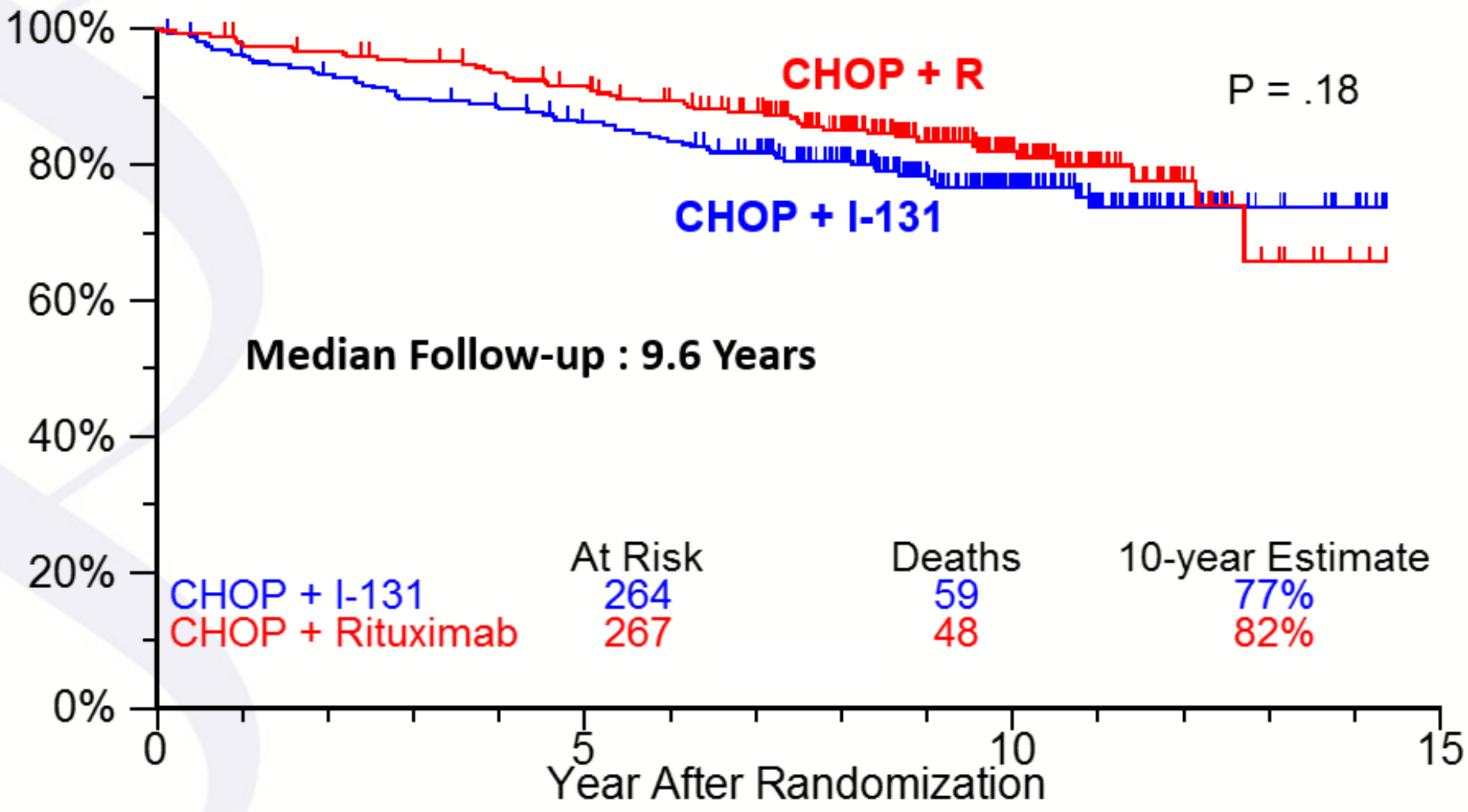
AML/MDS: 3 cases of with R-CHOP and 8 cases in CHOP-RIT (non significant)

Press O et al, *JCO January 20, 2013 vol. 31 no. 3 314-32*

Progression-Free Survival



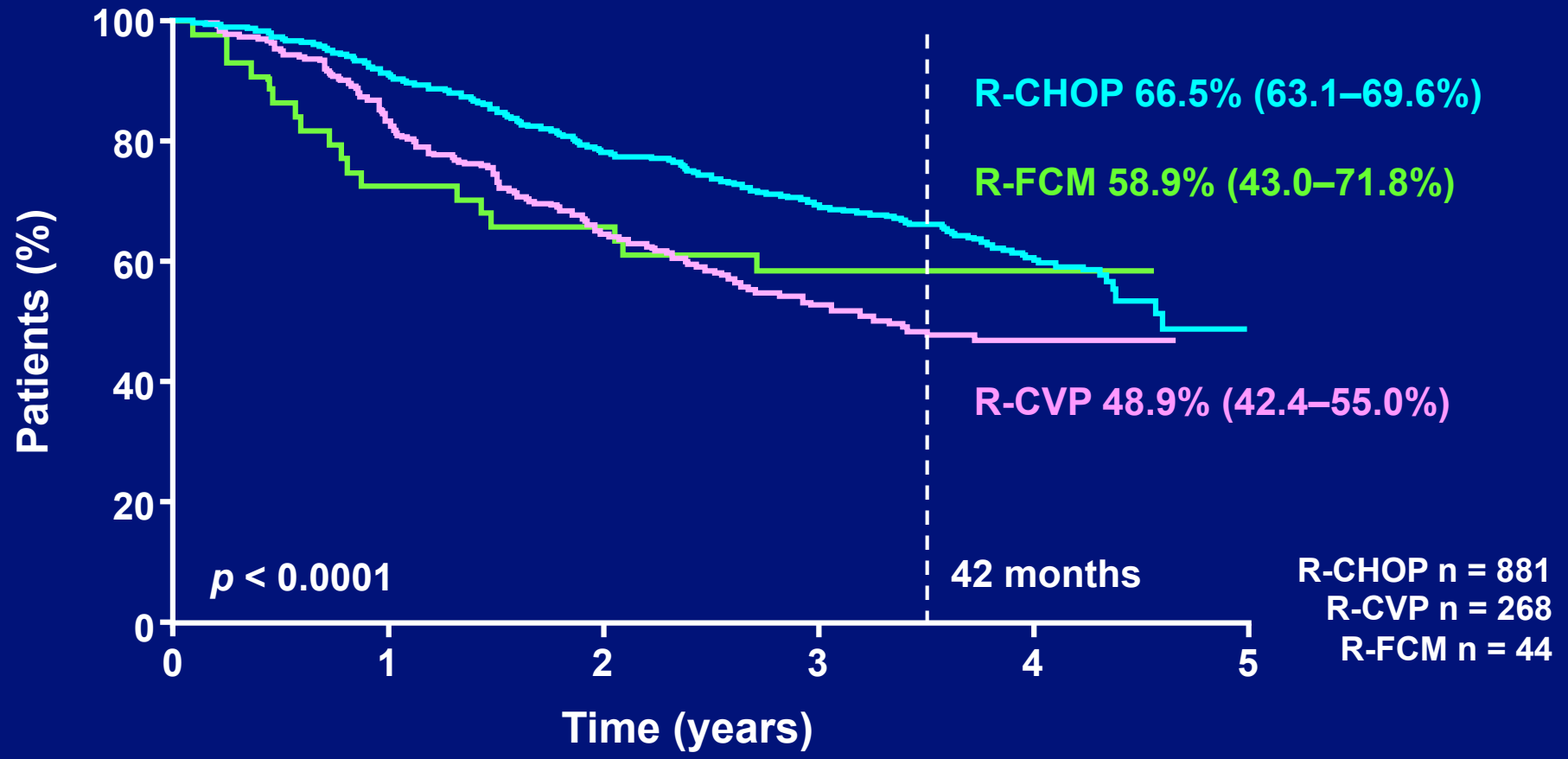
Overall Survival



All chemo regimen are not equal:

PRIMA study :

PFS from registration by induction regimen



Morschhauser et al., ICML 2011

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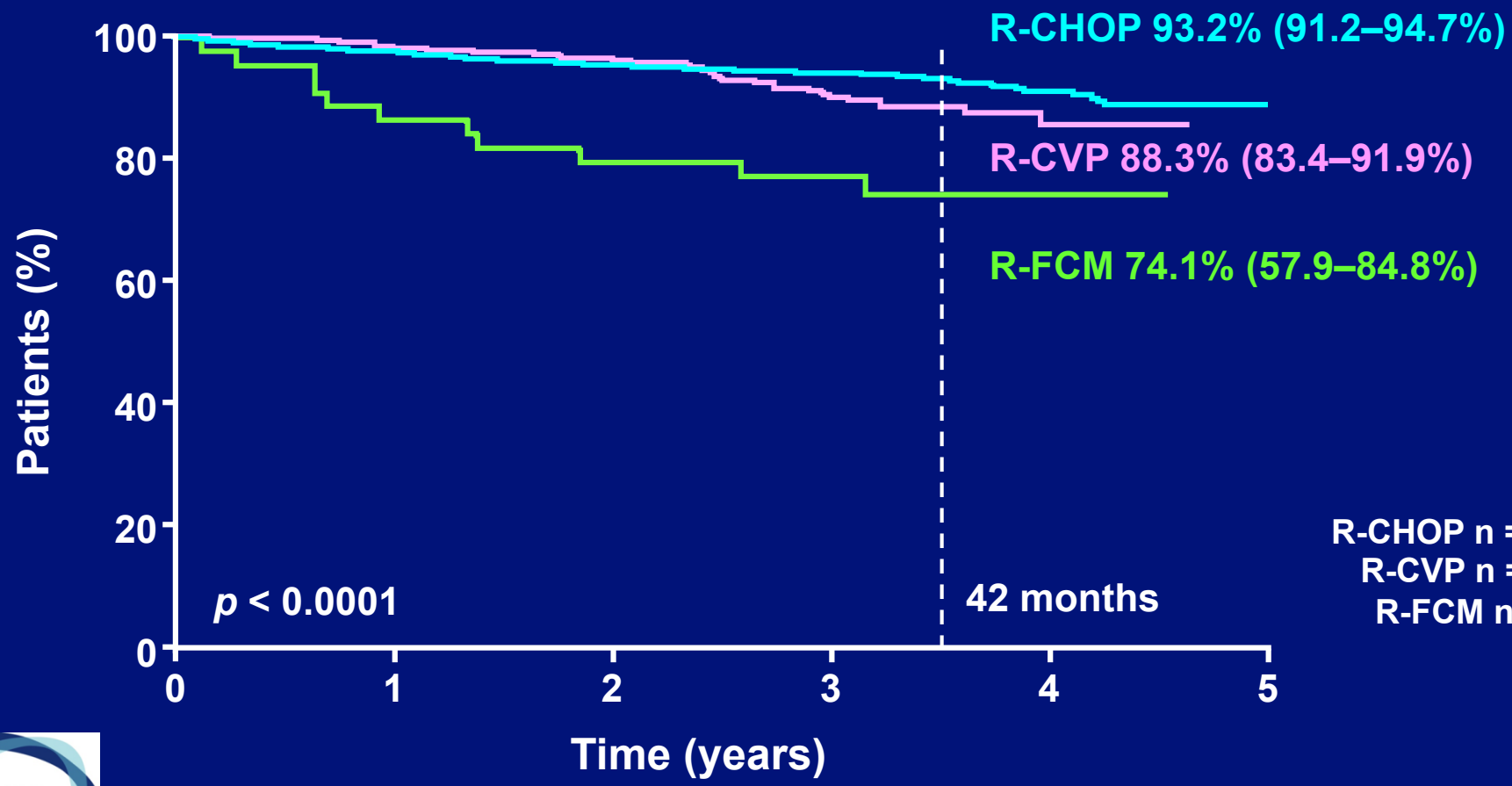

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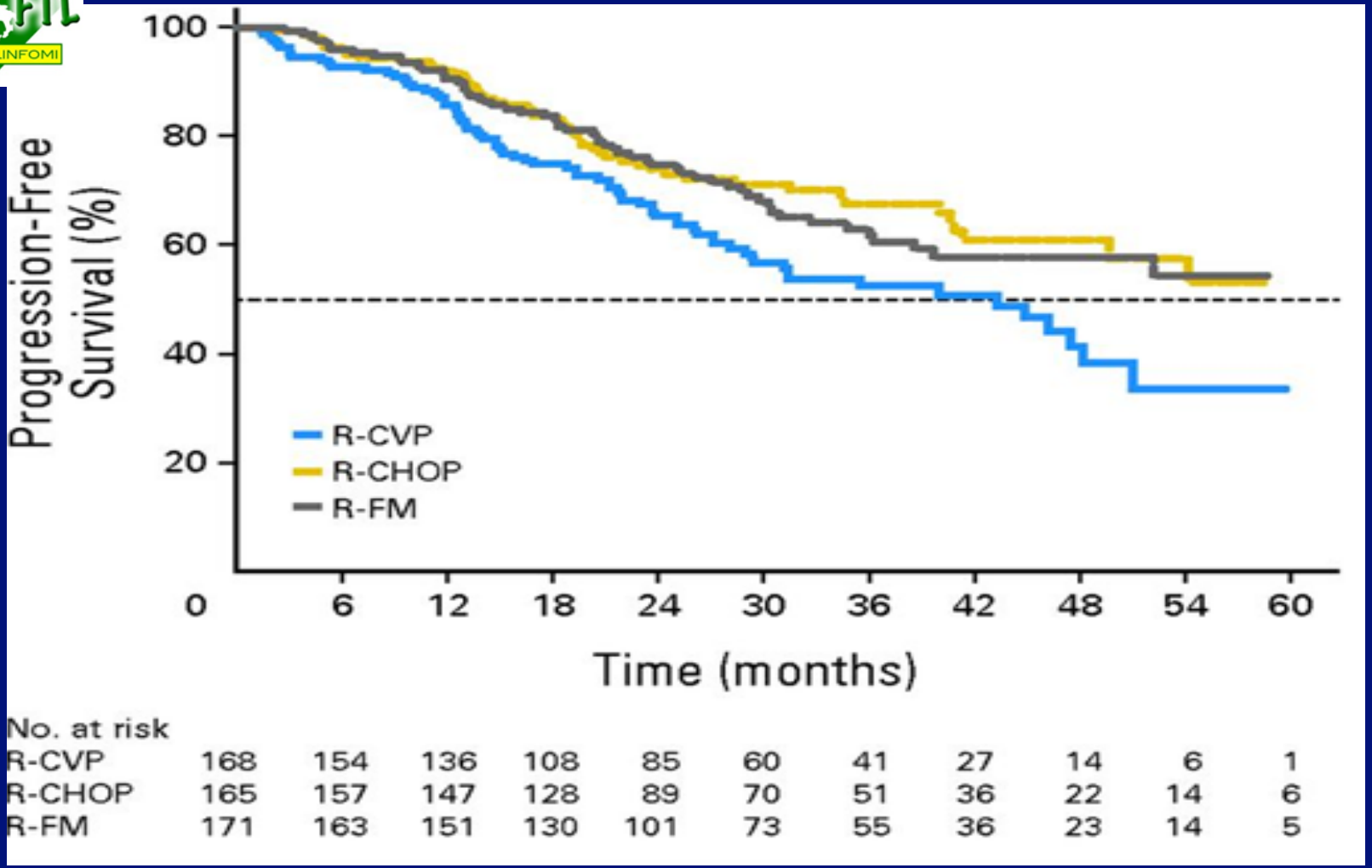
Morschhauser et al., ICML 2011

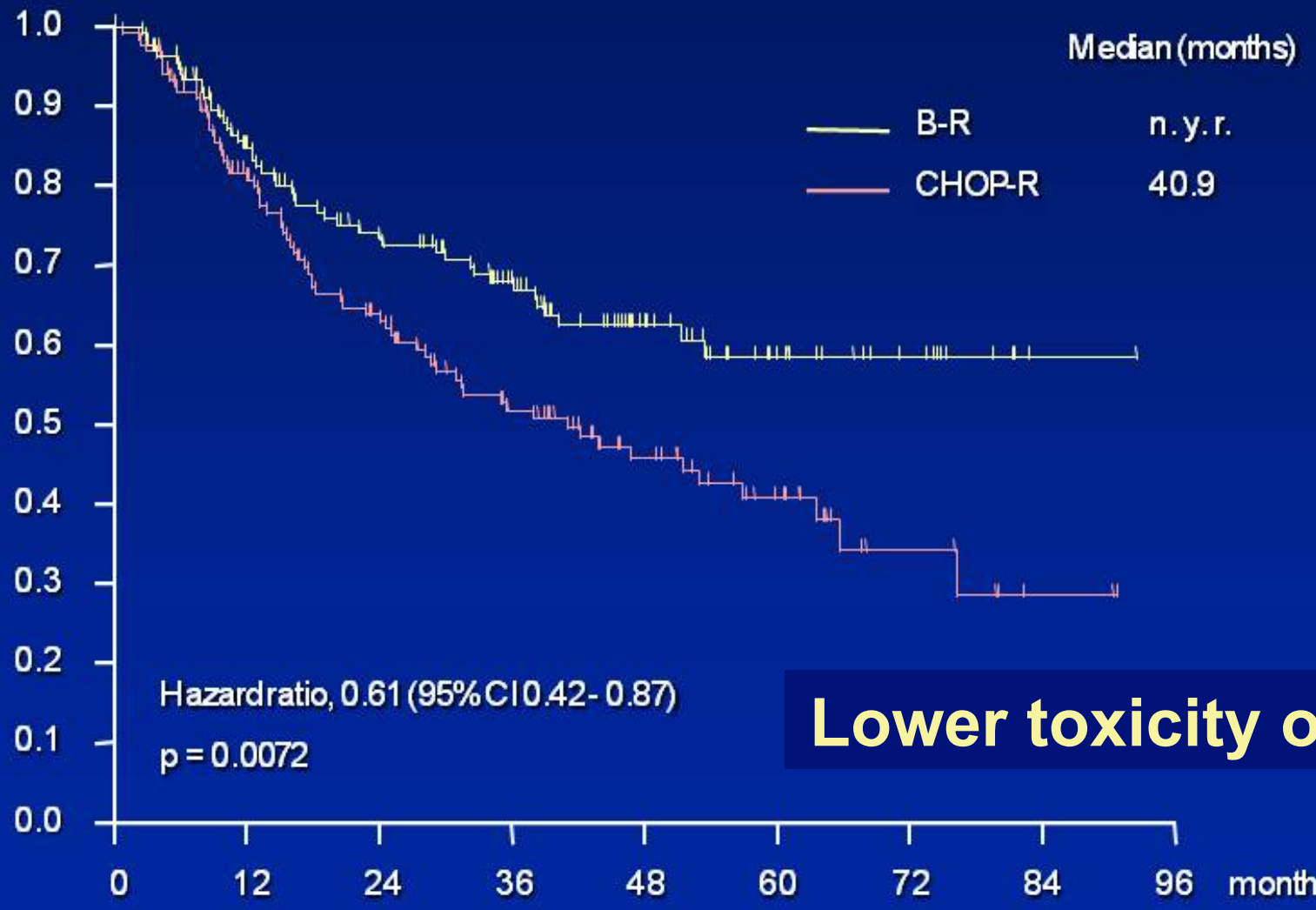
Italian FIL foll05 study: PFS by arm (N=504)



Federico M et al. J Clin Oncol. 2013 Apr 20;31(12):1506-1

R-Bendamustine versus R-CHOP

Progression free survival follicular lymphoma (n=279 pts)



Lower toxicity of B-R

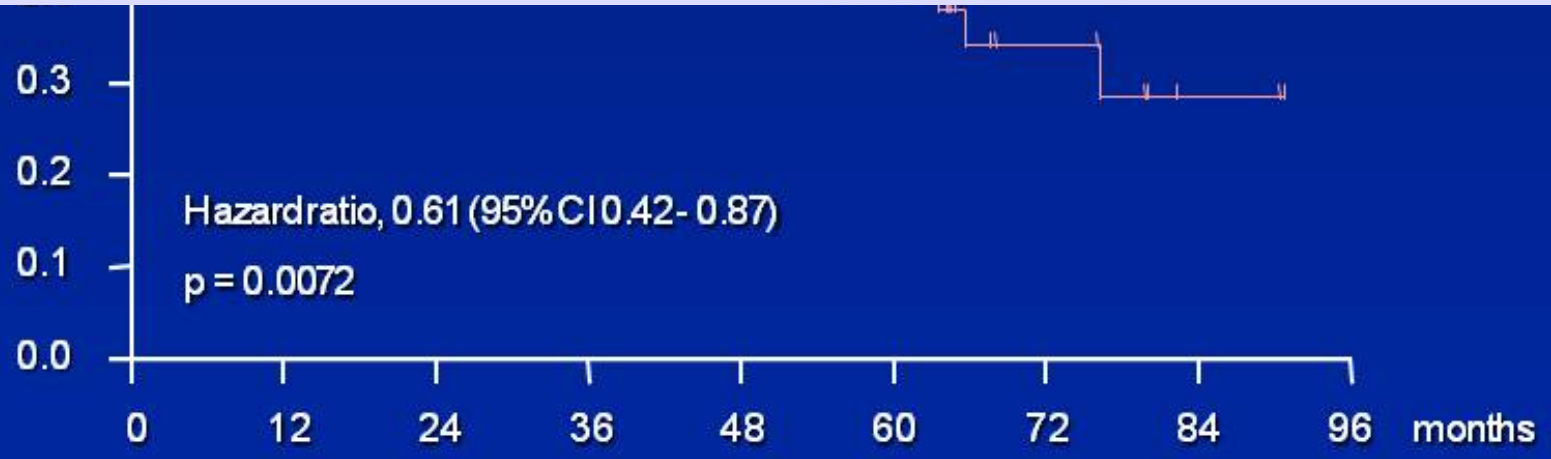
Rummel et Al, Lancet 2013 MJR

R-Bendamustine versus R-CHOP

Progression free survival follicular lymphoma (n=279 pts)

Some questions:

- Only grade 1-2 FL in the trial
- Poor results of the R-CHOP arm ?
- Early results reported at ASH 2007 ?
- Long term toxicity of benda ??
- Lack of OS benefit



StiL
Studiengruppe indolente Lymphome

MJR

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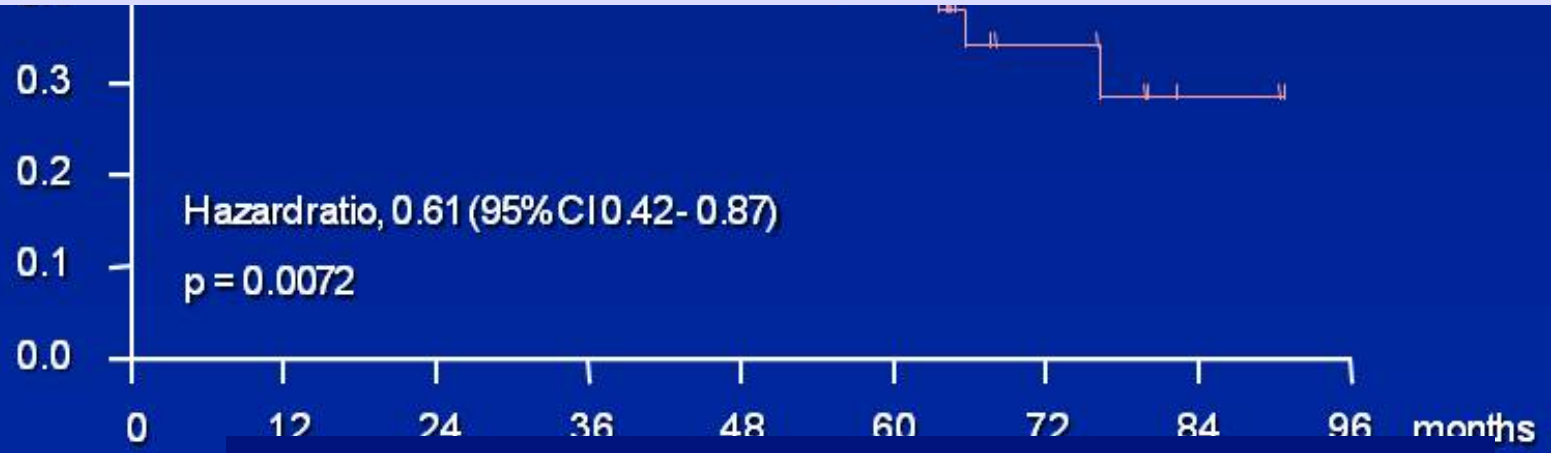
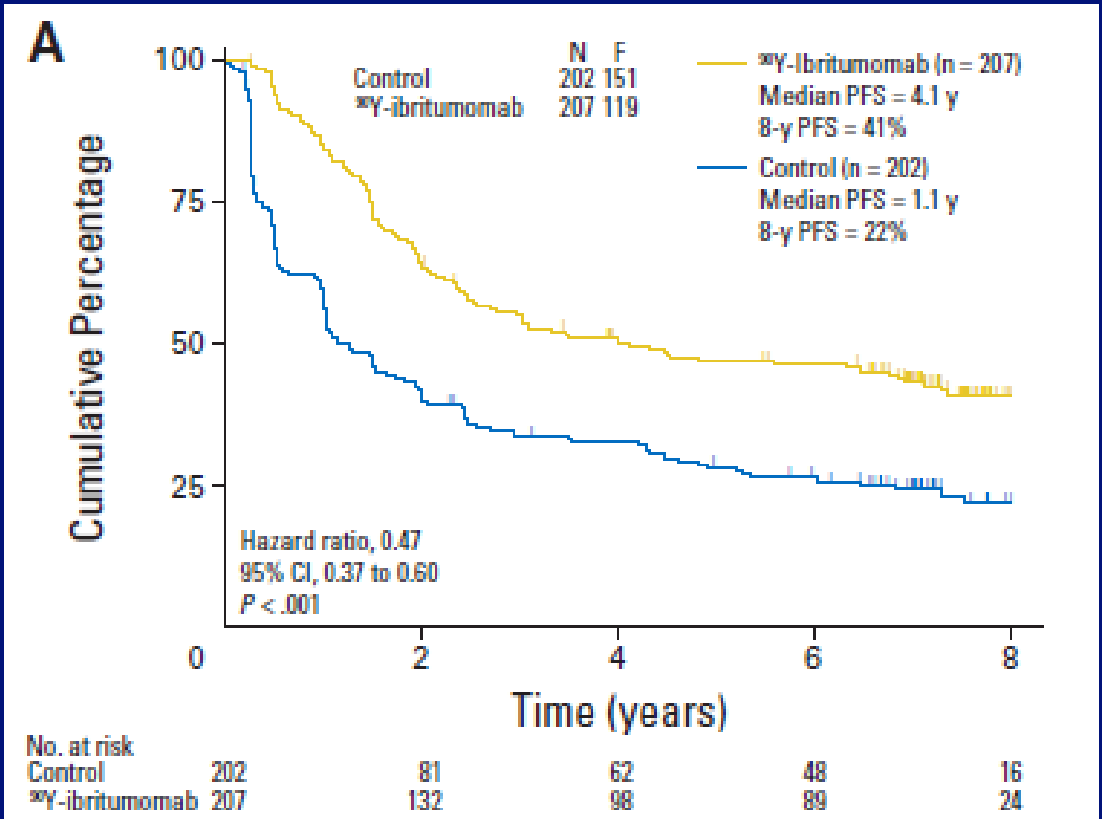


Will be updated at ASCO 2017…

MJR

^{90}Y Ibritumomab tiutexan (RIT) consolidation in FL patients after chemotherapy (FIT trial)
Progression free survival in all patients



- Very high complete response rates after RIT

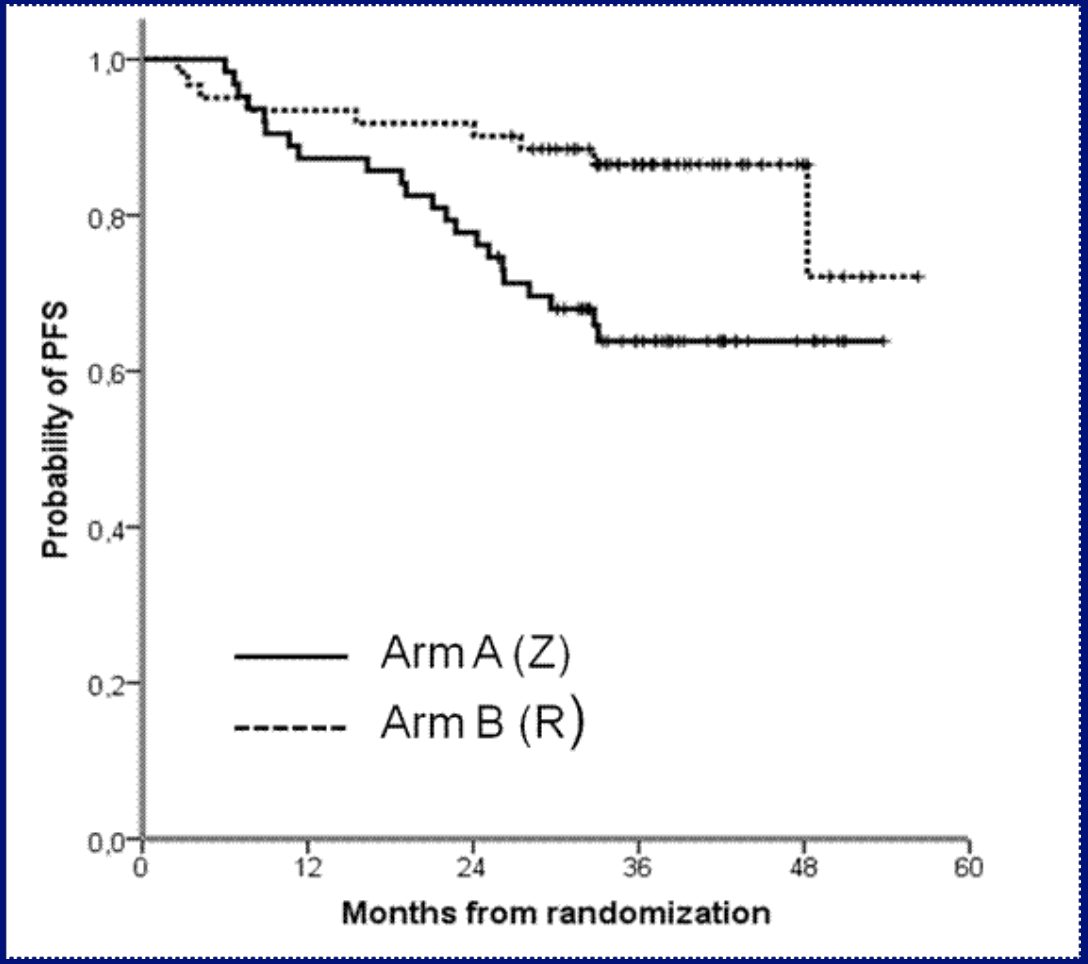
- But few patients had received Rituximab - chemo as induction

- Secondary malignancies 26 after RIT vs. 14 without (including 7 vs. 1 MDS/AML)

Morchhauser et al, J Clin Oncol, 2013 Apr 1. [Epub ahead of print]

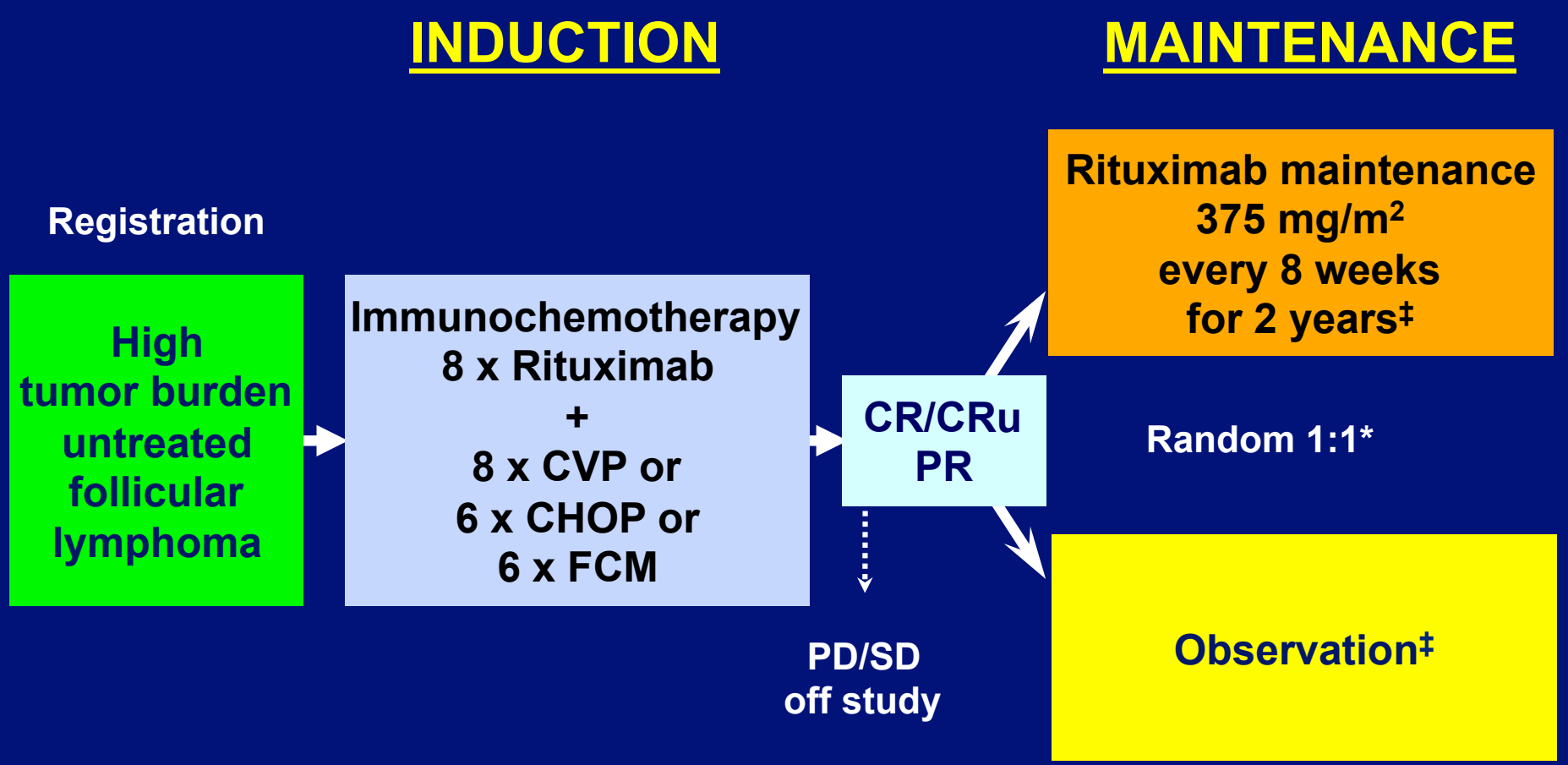
In patients responding to R-CHOP,

is radio-immunotherapy better than rituximab maintenance ?



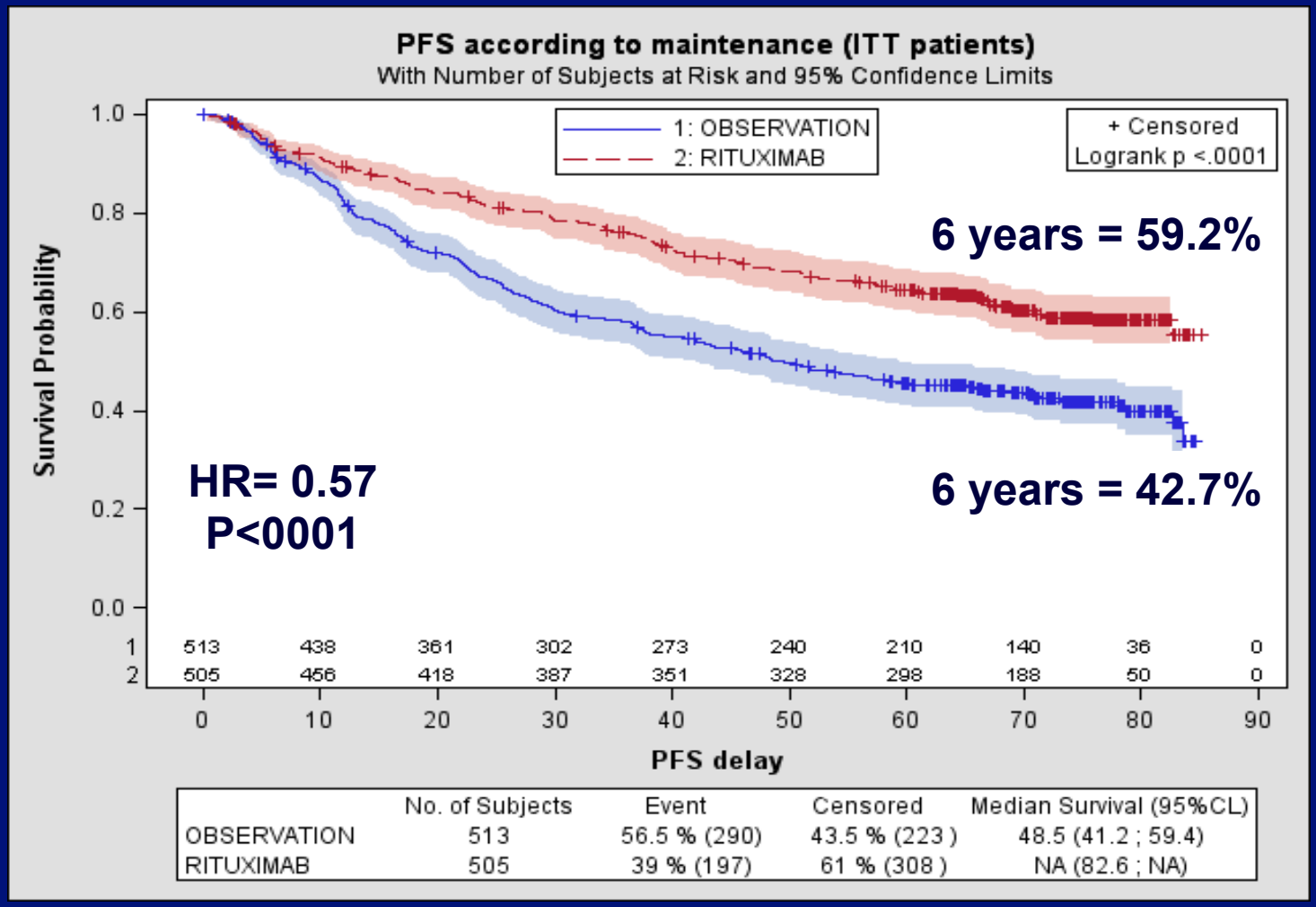
Lopez Guillermo et Al, ASH 2013, abstract 369

PRIMA: study design



* Stratified by response after induction, regimen of chemo, and geographic region
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms
Five additional years of follow-up

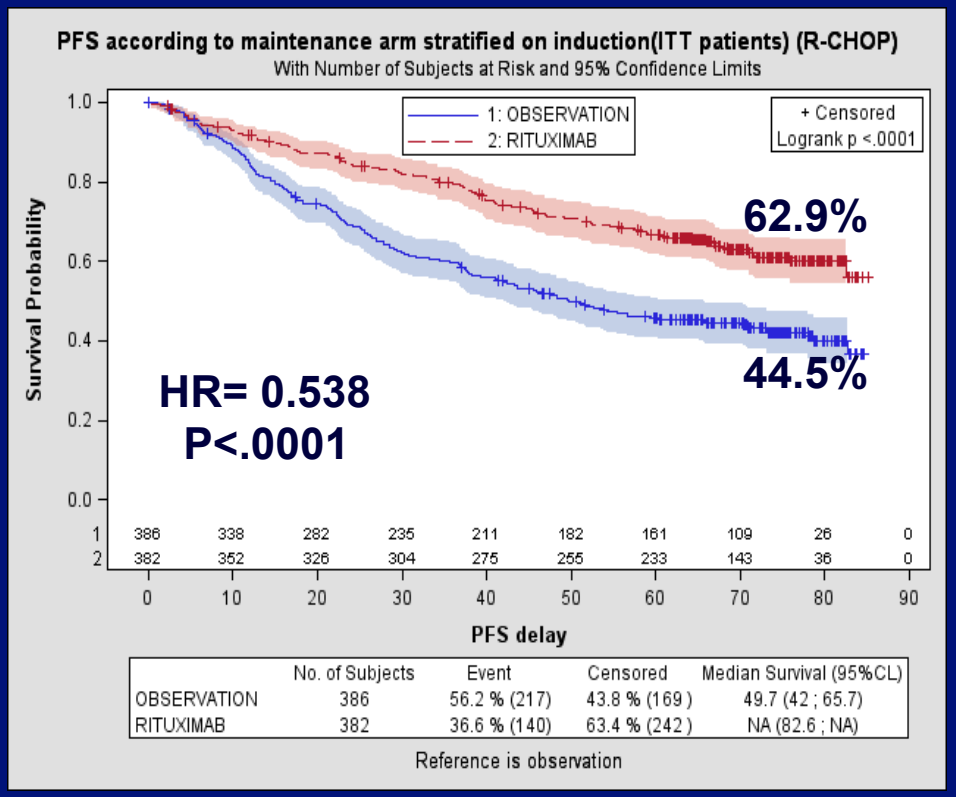
PRIMA 6 years follow-up
Progression free survival from randomization



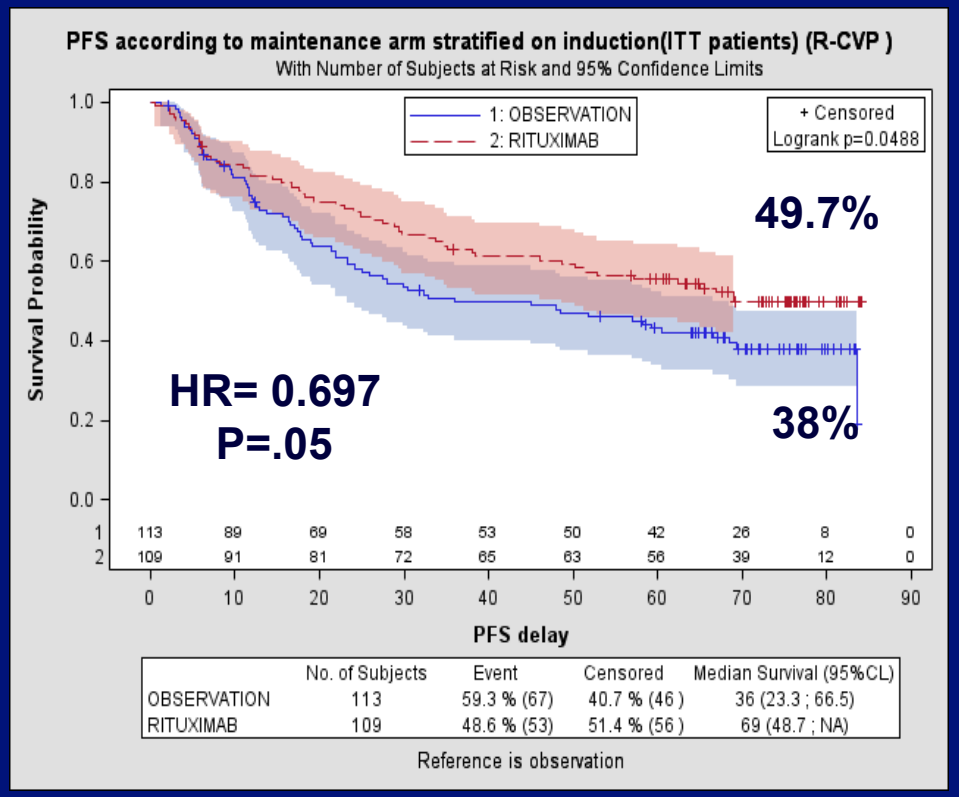
Median follow-up since randomization : 73 months

PRIMA 6 years follow-up
Progression free survival from randomization

R-CHOP induction

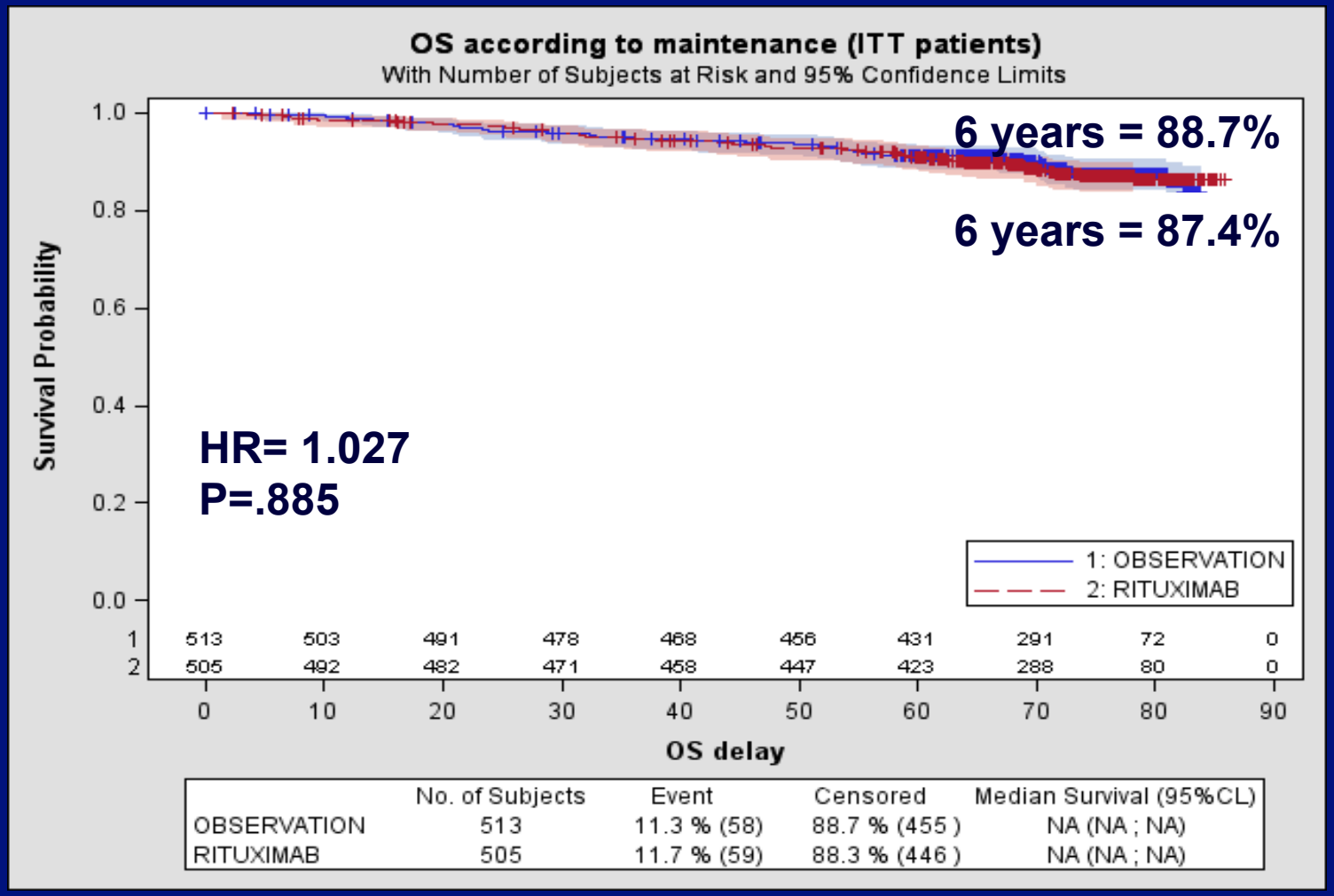


R-CVP induction



Median follow-up since randomization : 73 months

PRIMA 6 years follow-up
Overall survival



Median follow-up since randomization : 73 months

My choices in high tumor burden patients

1. **Most cases**
   - R-CHOP followed by R maintenance

2. **If contra-indication to anthracycline**
   - B-R +/- maintenance
   - Rituximab single agent ?

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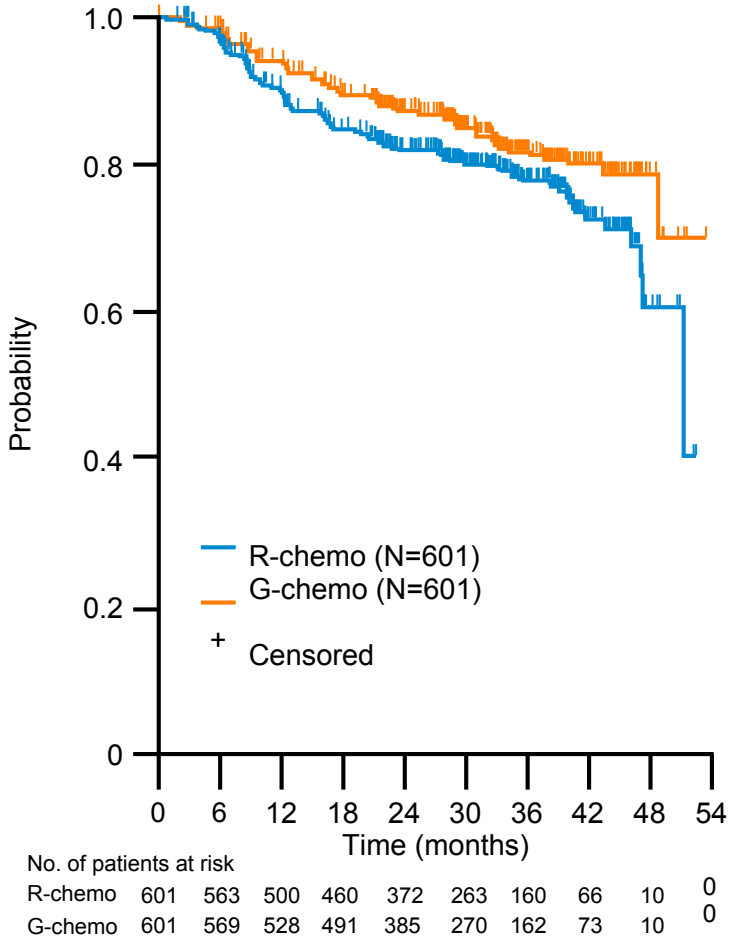
GALLIUM : Obinutuzumab in 1st line ttt
R-chemo versus G-chemo - IRC-assessed PFS (FL)



	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	125 (20.8)	93 (15.5)
3-yr PFS, % (95% CI)	77.9 (73.8, 81.4)	81.9 (77.9, 85.2)
HR (95% CI), p-value*	**0.71 (0.54, 0.93), p=0.0138**	

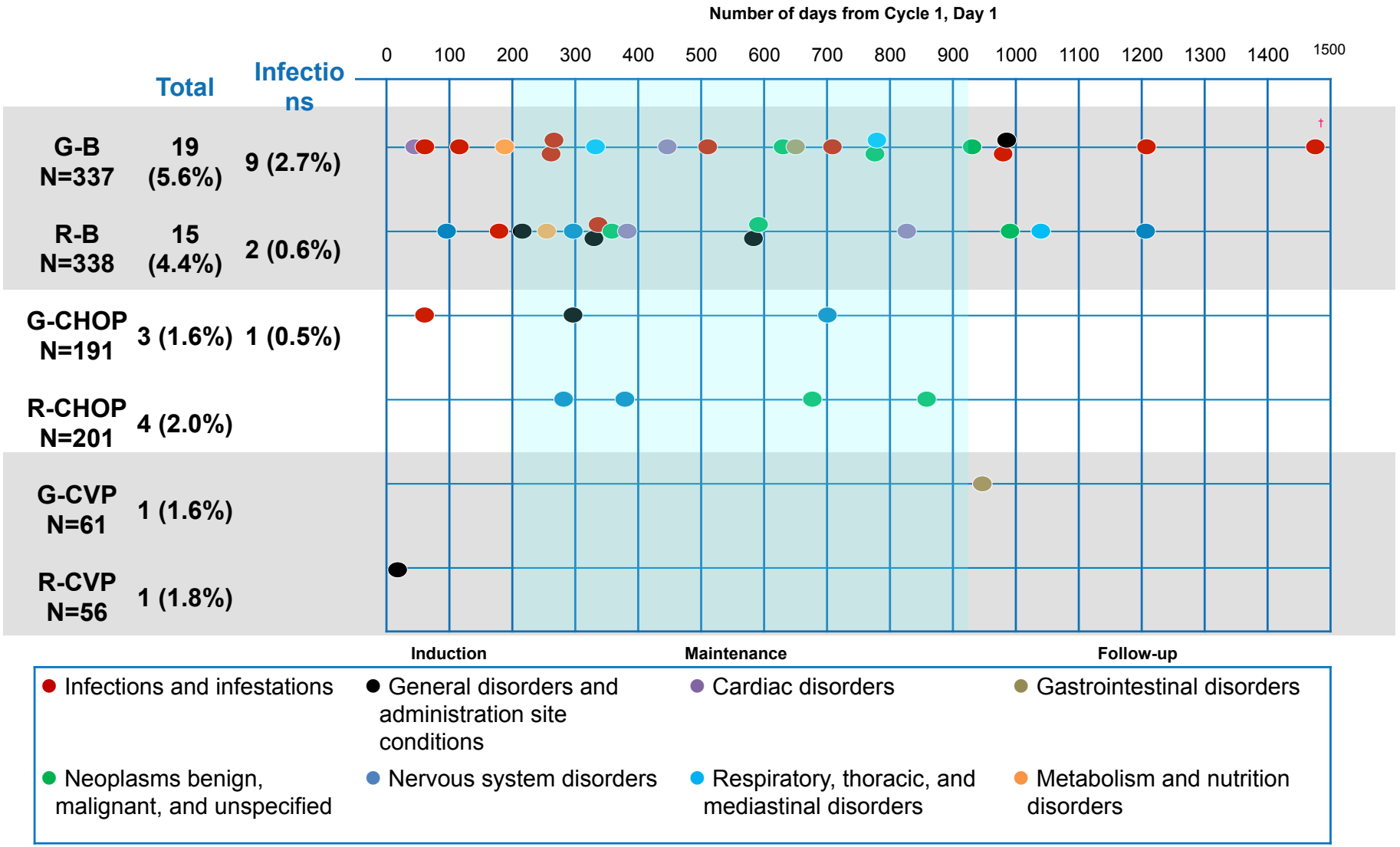
Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

Marcus RE et al, ASH 2016, Abstract 6

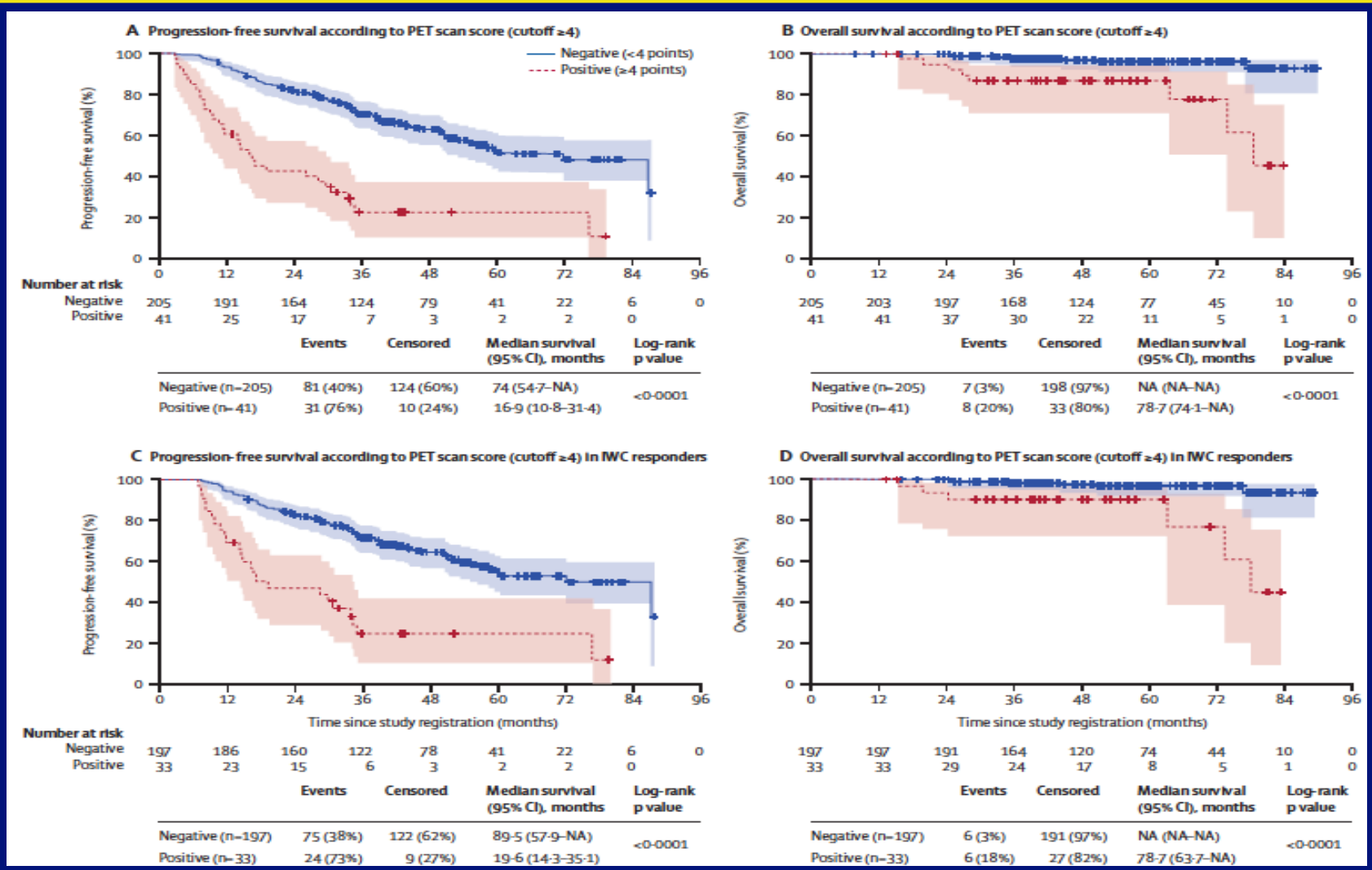
GALLIUM: toxicities according to treatment arms

Grade 5 (fatal) AEs by treatment (FL)*



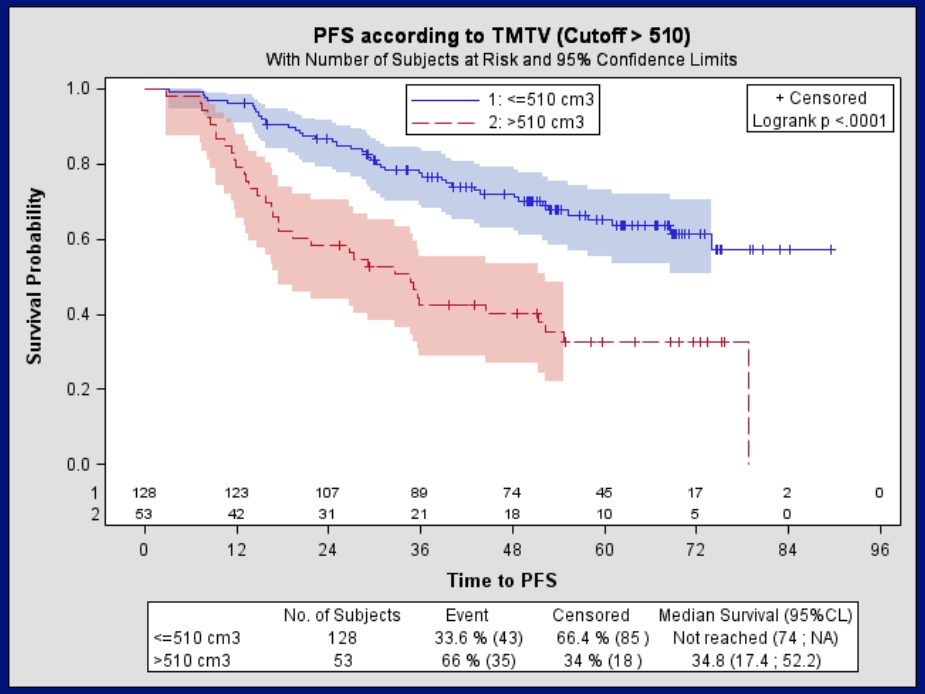
*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (*Clostridium difficile* colitis, prostate cancer, and myelodysplastic syndrome); *Clostridium difficile* colitis was the most acute, so the patient has been assigned to the 'Infections and infestations' category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3

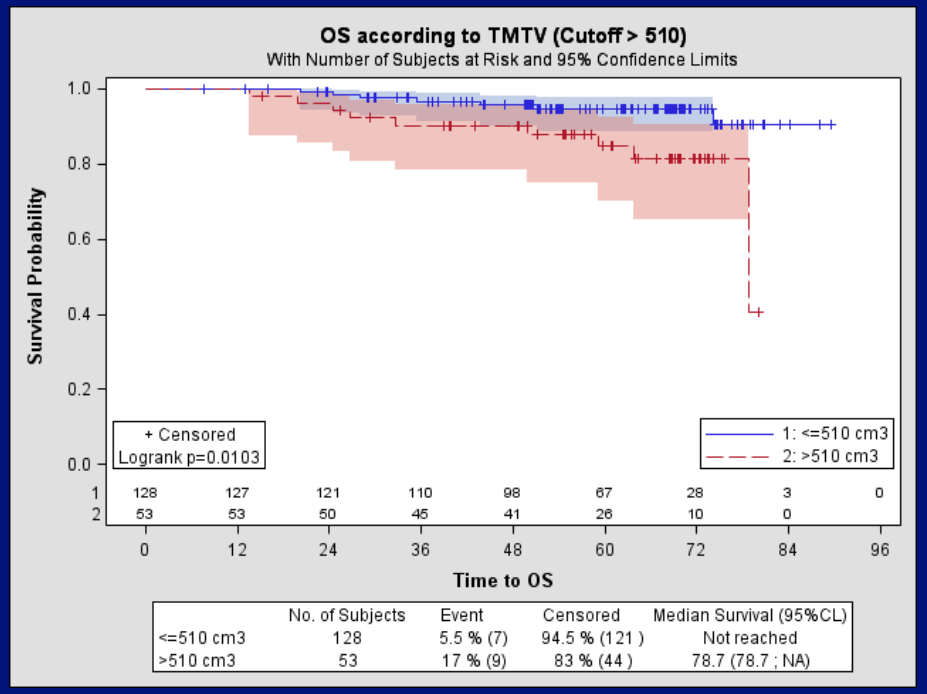
Prognostic Value of PET-CT After Frontline Therapy in FL



Trotman et al. *Lancet Haem*. 2014. epub.

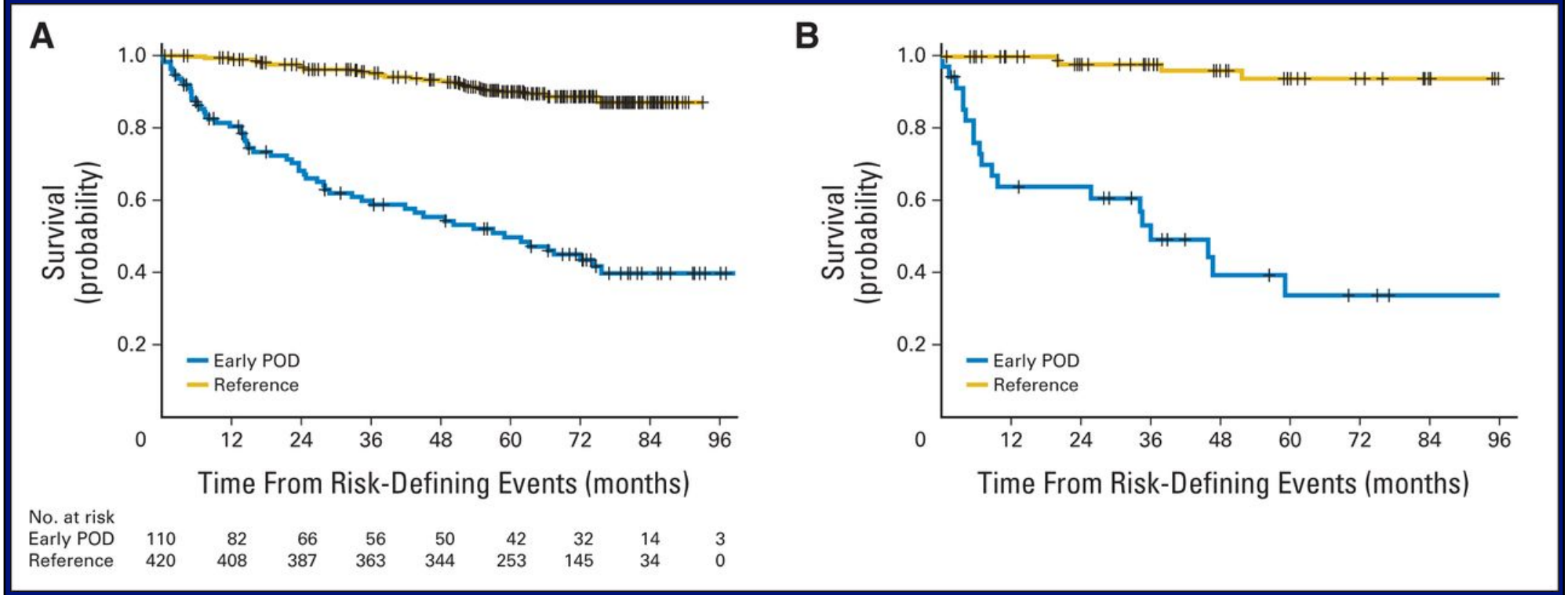
Total Metabolic Tumor Volum (TMTV) at diagnosis accurately predicts outcome





Meignan et al., JCO 2016

(A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group.

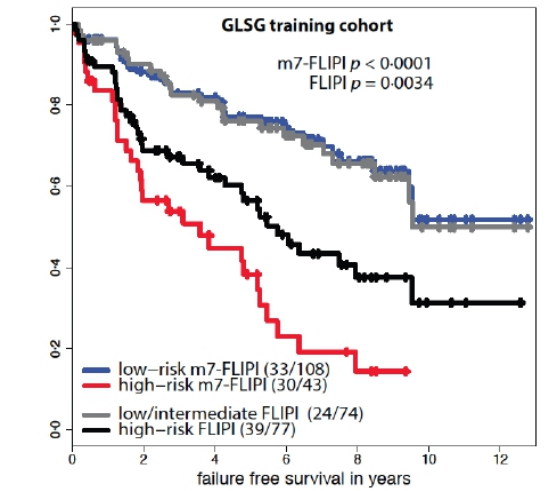


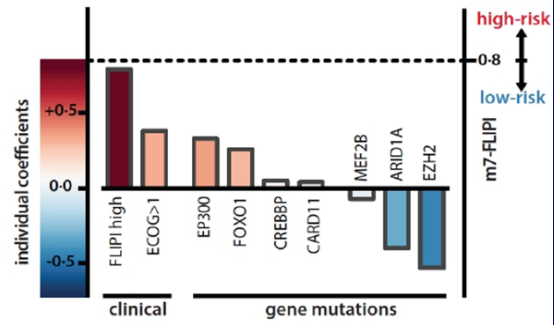
Carla Casulo et al. JCO 2015;33:2516-2522

JOURNAL OF CLINICAL ONCOLOGY ASCO

Improving clinical indexes with mutations or GEP ?

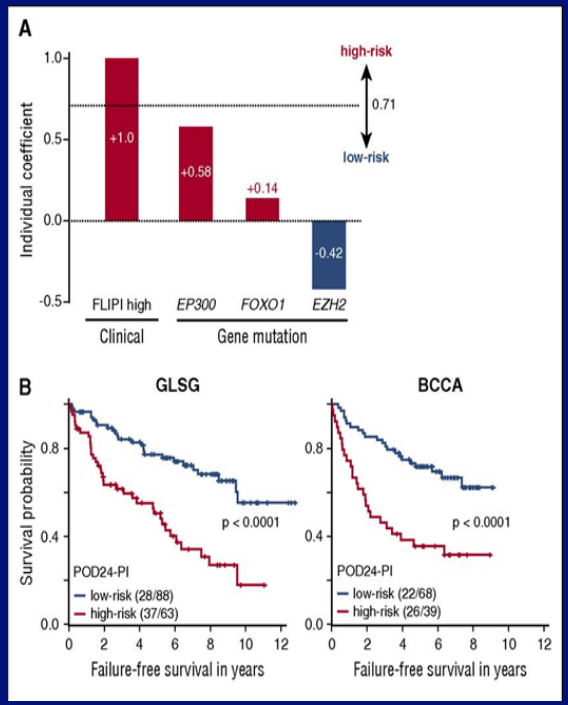
m7-FLIPI





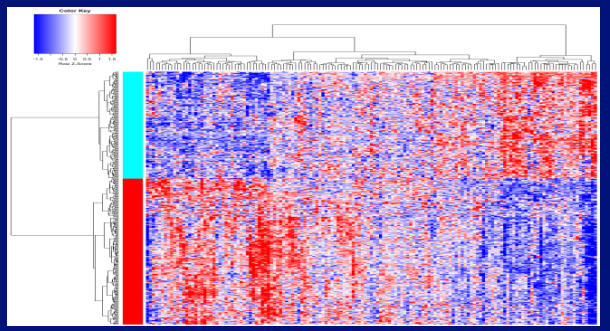
Pastore et al. Lancet Oncol 2015 16:1111-1121

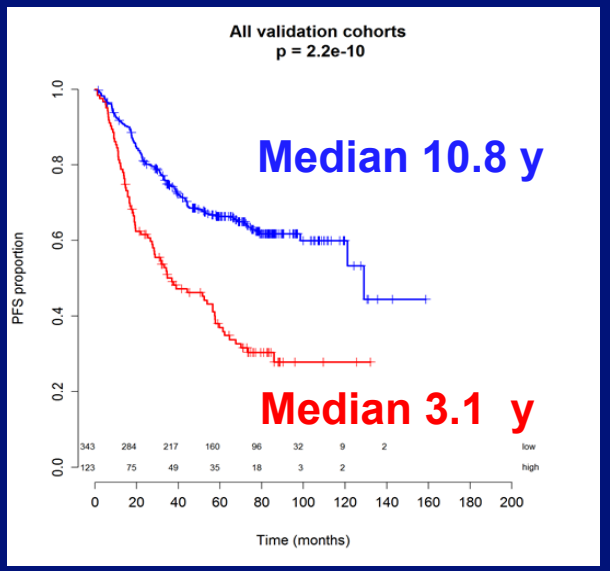
POD24-PI



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

23-gene score





Huet et al. Submitted

The increase in patients survival implies new challenges

Important endpoints for future/ongoing studies evaluating therapeutic strategies in FL :

- **Quality of response**
- **Surrogate for PFS ?**
- **Quality of life**
- **Ability to deliver second line treatments**
- **Long term toxicities**

… and Overall Survival