



PROGRAM

# Indolent Lymphoma Workshop

**May 15-16, 2017**

**Bologna  
Royal Hotel Carlton**

**President**  
Pier Luigi Zinzani

**Co-President**  
Michele Cavo

**Honorary President**  
Sante Tura



## Maintenance, to be or not to be **PRIMA**

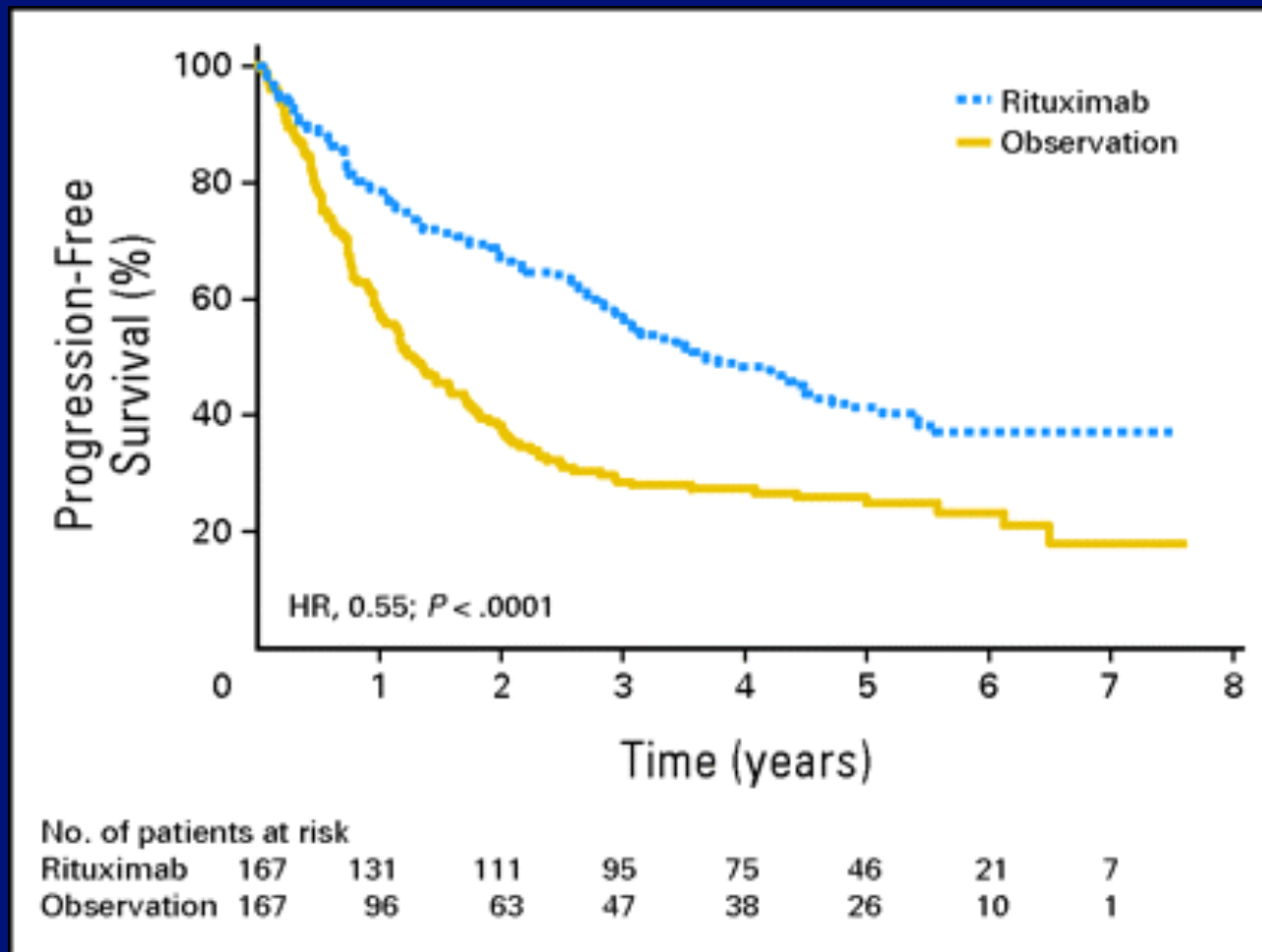
**Professeur Gilles SALLES**



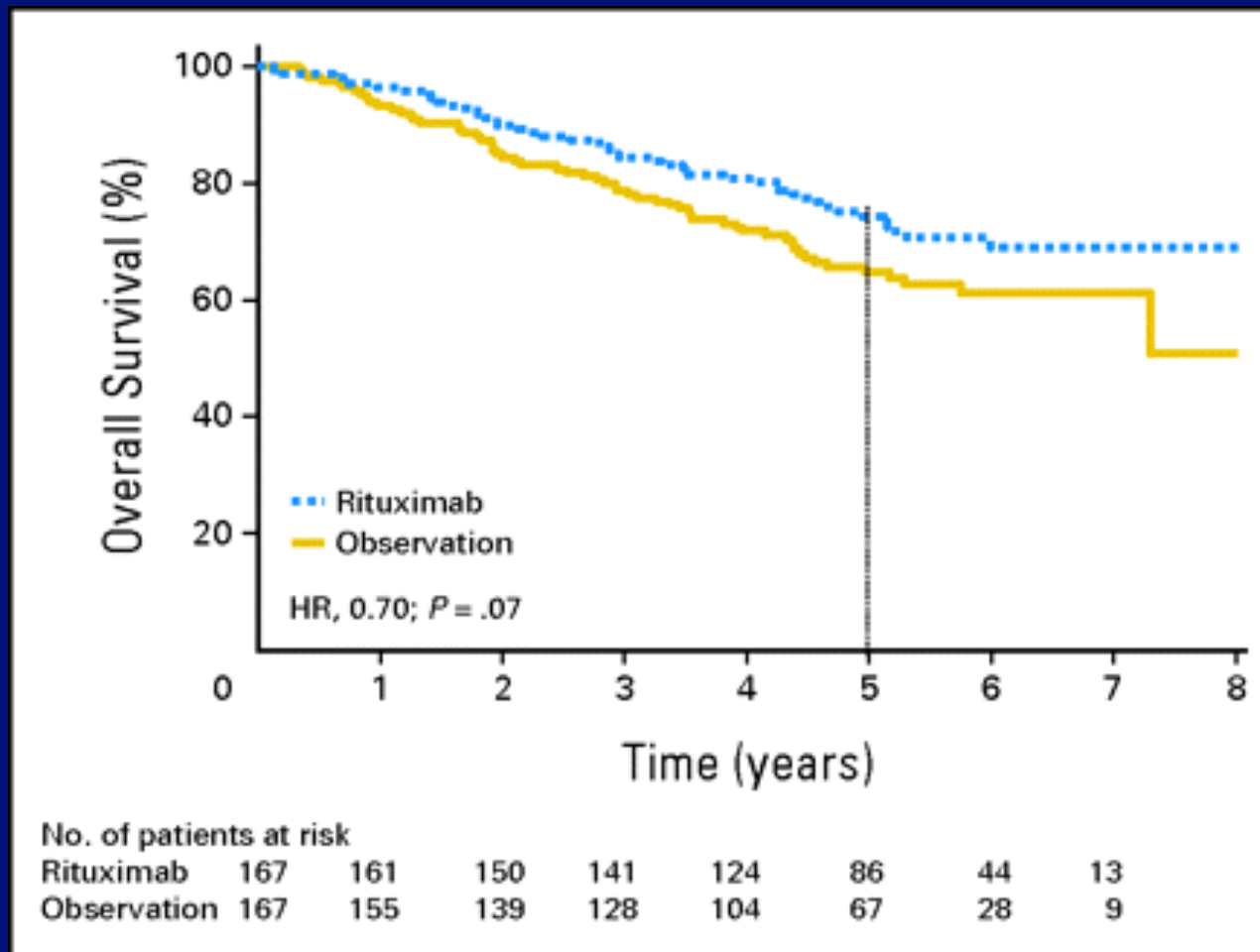
# Maintenance in the relapse setting

# EORTC 20981 Intergroup phase III trial in R/R Follicular Lymphoma patients

## PFS from 2nd randomization



# EORTC 20981 Intergroup phase III trial: 5-year Overall Survival



Maintenance in the first line setting

After R chemo ...

# PRIMA: study design

## Induction

## Maintenance

Registration

High tumor burden untreated follicular lymphoma

Immunochemotherapy  
8 x Rituximab  
+  
8 x CVP or  
6 x CHOP or  
6 x FCM

CR/CRu  
PR

Rituximab maintenance  
375 mg/m<sup>2</sup>  
every 8 weeks  
for 2 years<sup>‡</sup>

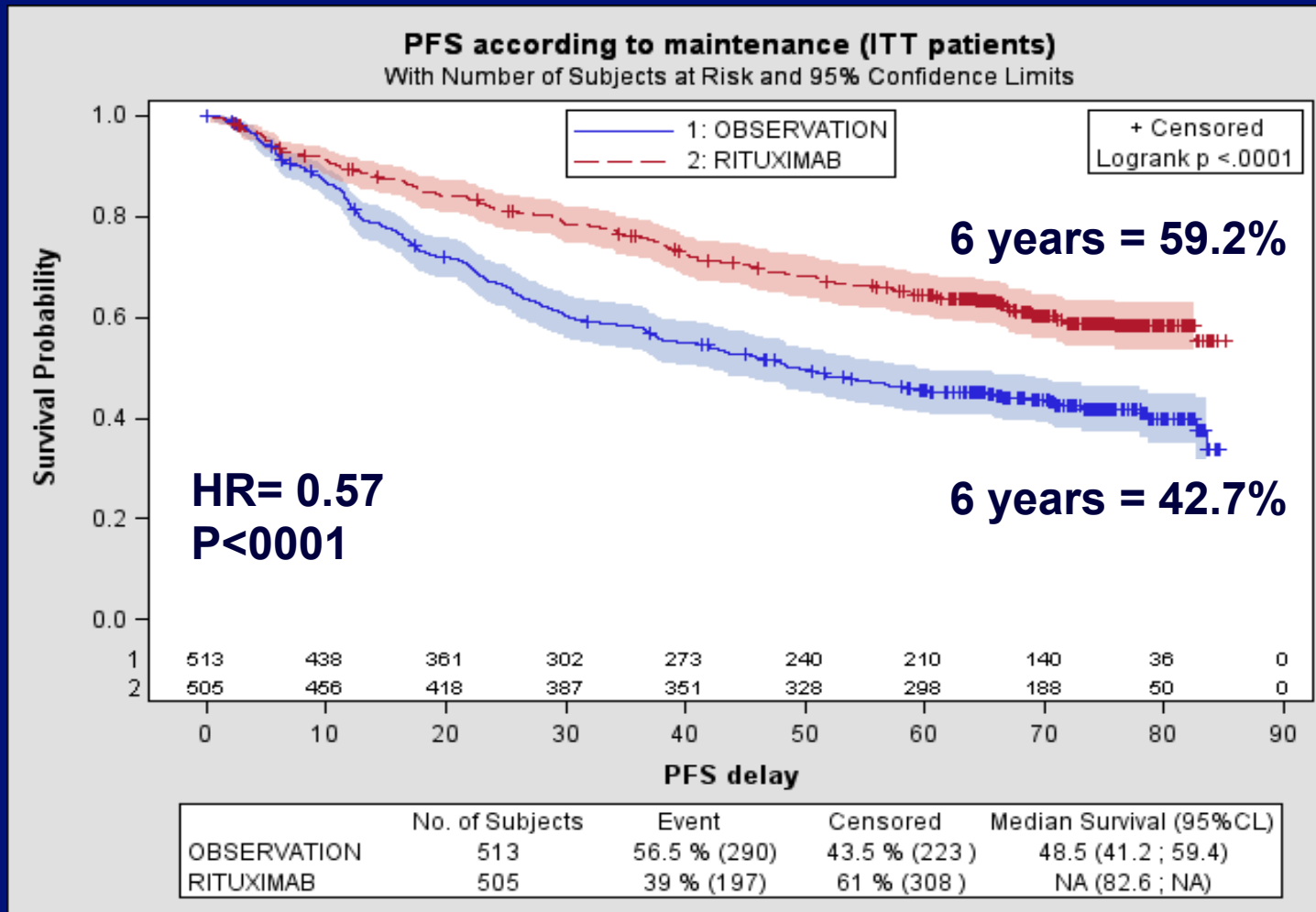
Random 1:1\*

Observation<sup>‡</sup>

PD/SD  
off study

# PRIMA 6 years follow-up

## Progression free survival from randomization



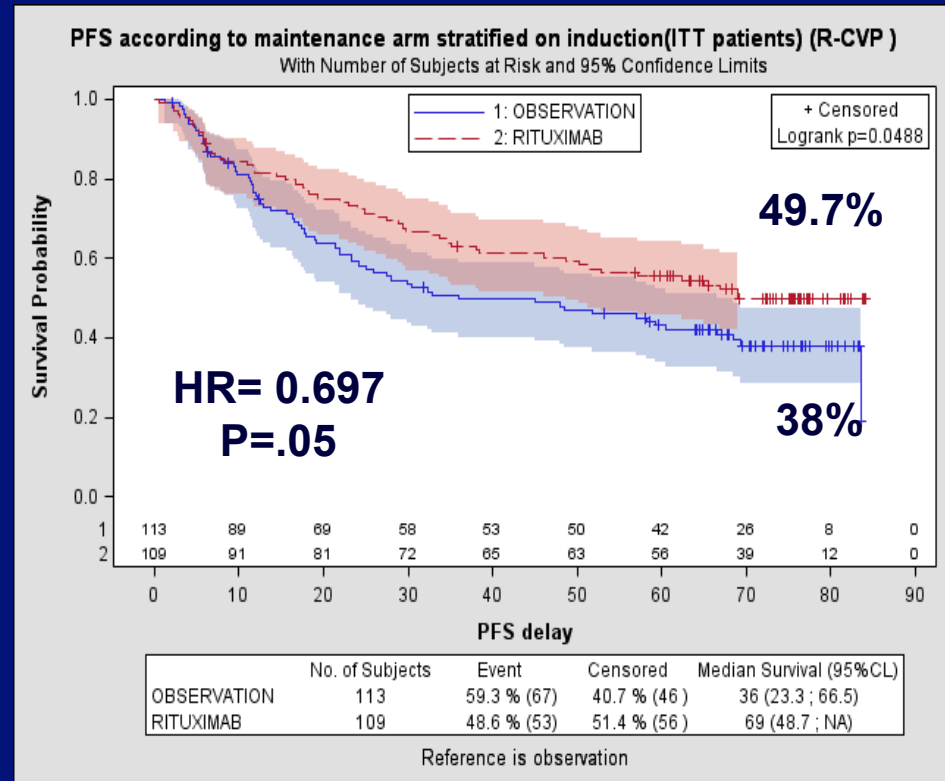
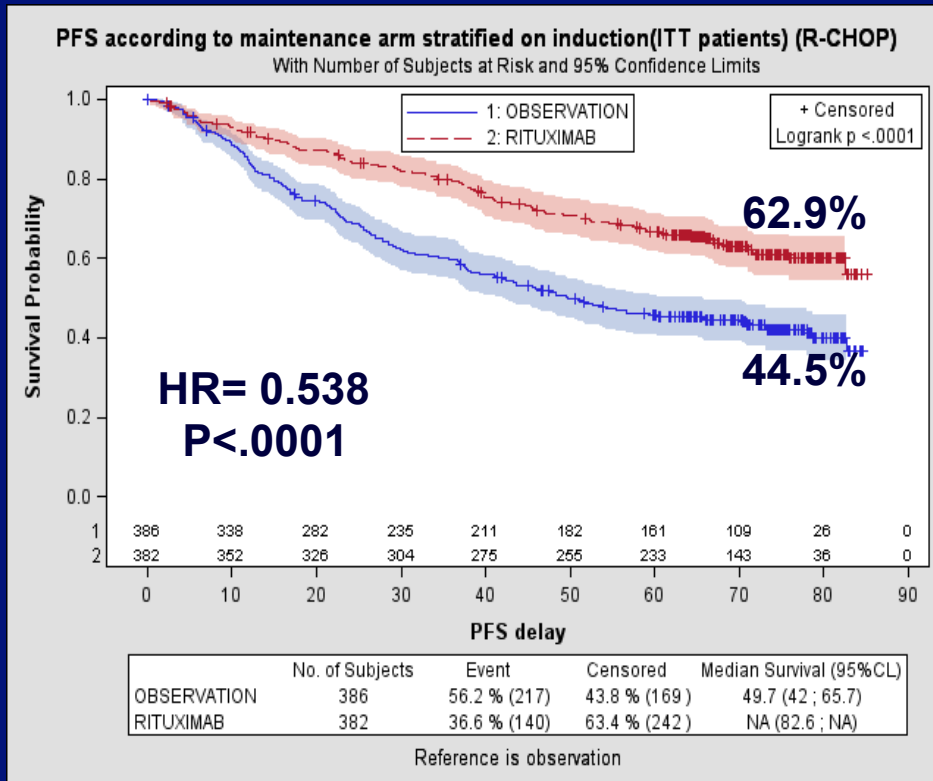
Median follow-up since randomization : 73 months

# PRIMA 6 years follow-up

## Progression free survival from randomization

### R-CHOP induction

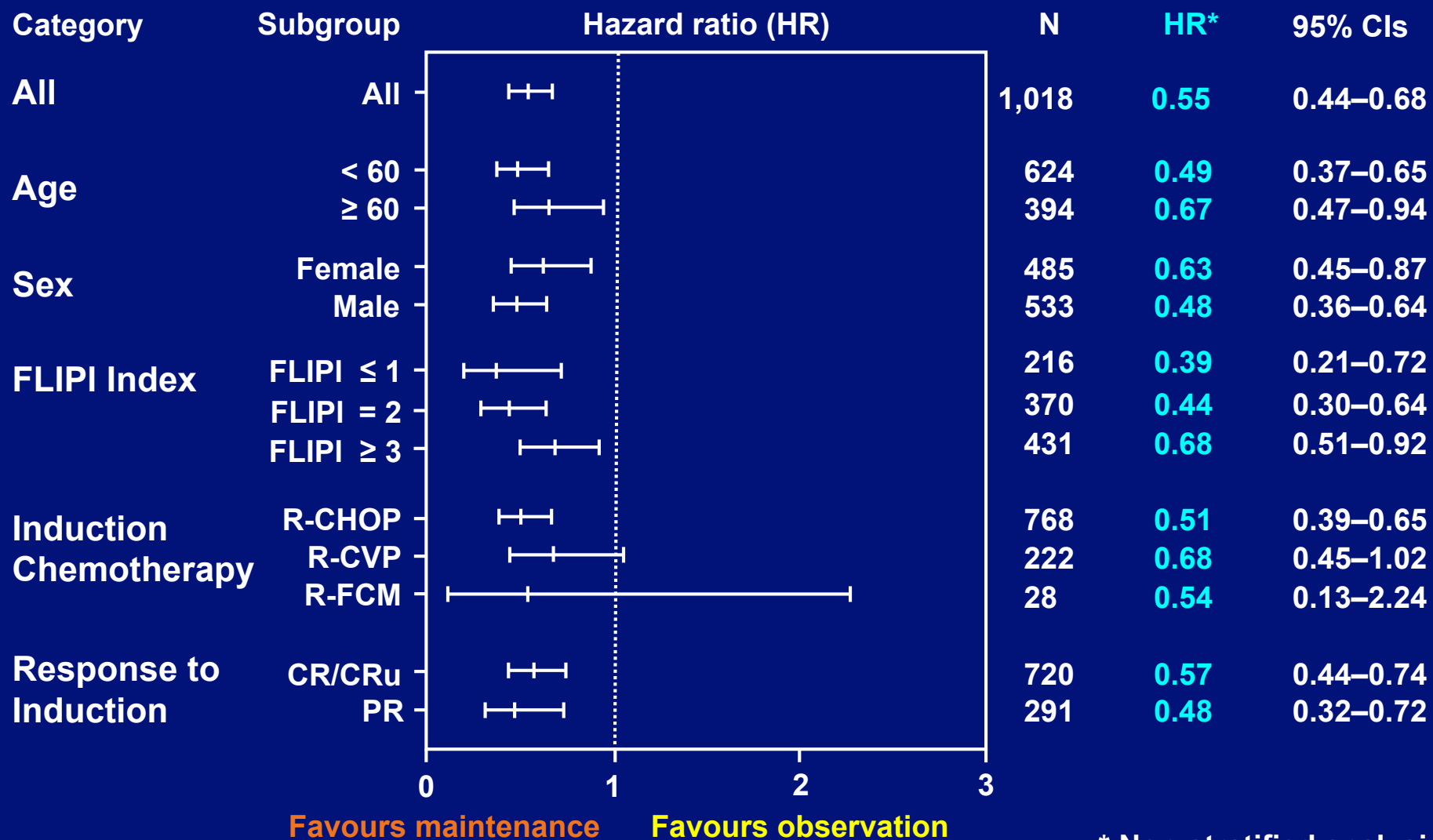
### R-CVP induction



Median follow-up since randomization : 73 months



# Consistent benefit in subgroups

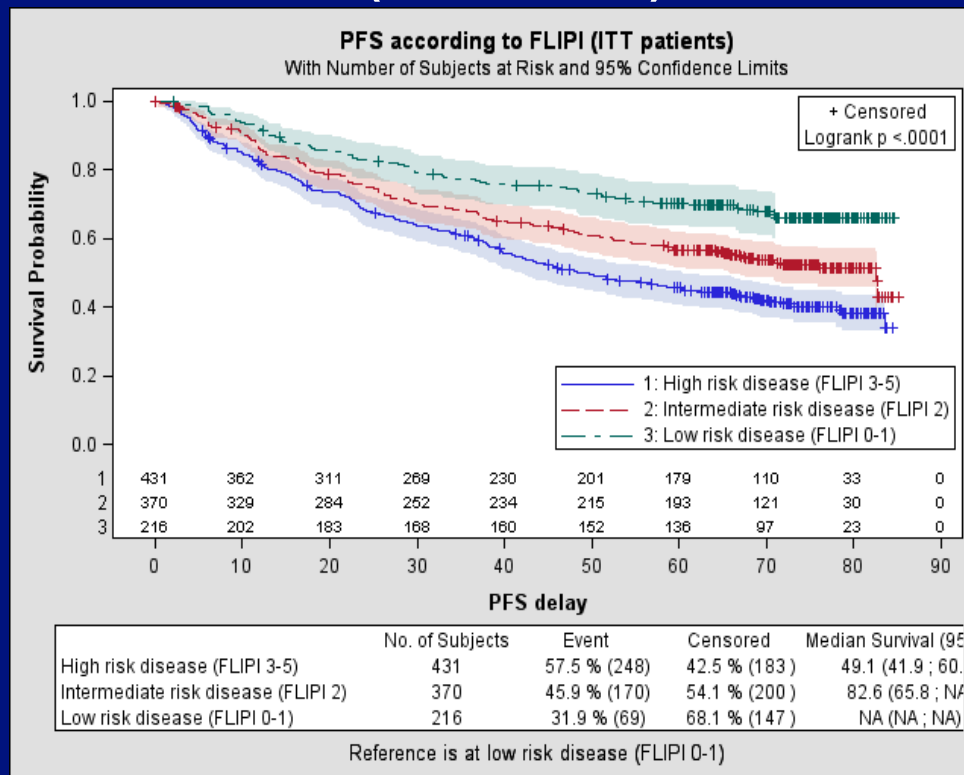


\* Non-stratified analysis.

# PRIMA 6 years follow-up

## Progression free survival from randomization

### PFS according to FLIPI (both arms)

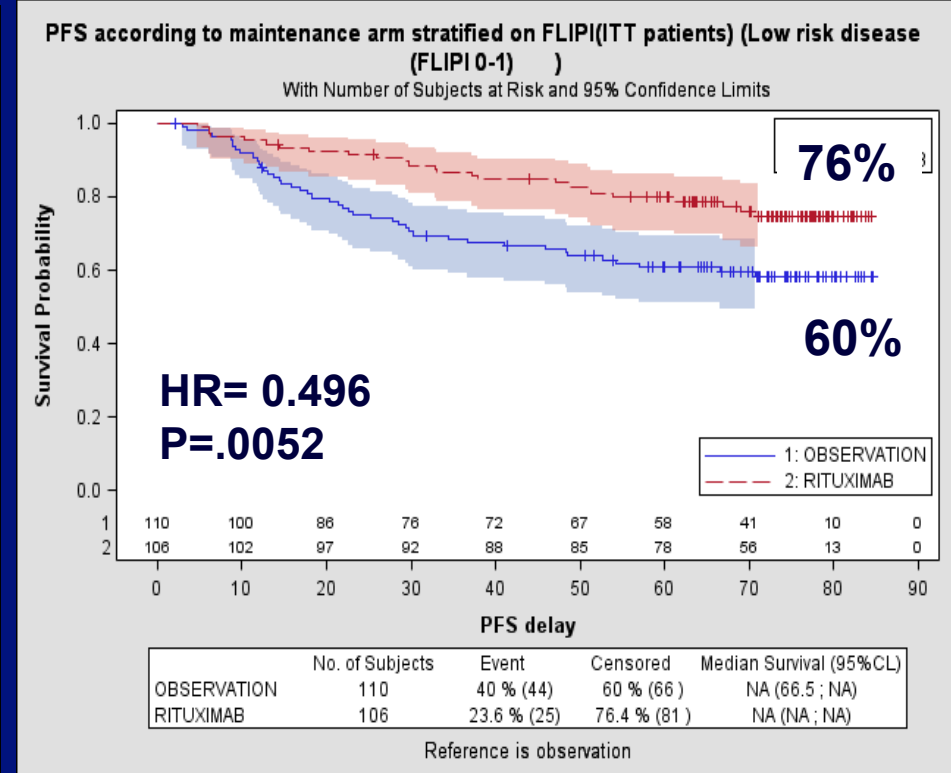
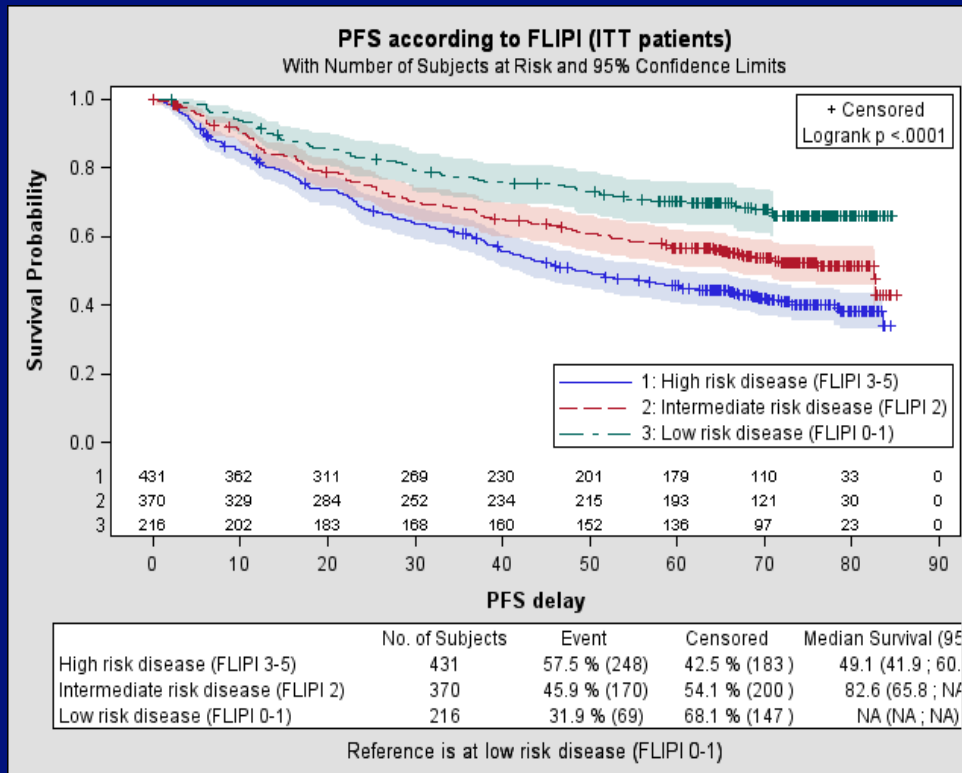


Median follow-up since randomization : 73 months

# PRIMA 6 years follow-up

## Progression free survival from randomization

### FLIPI low



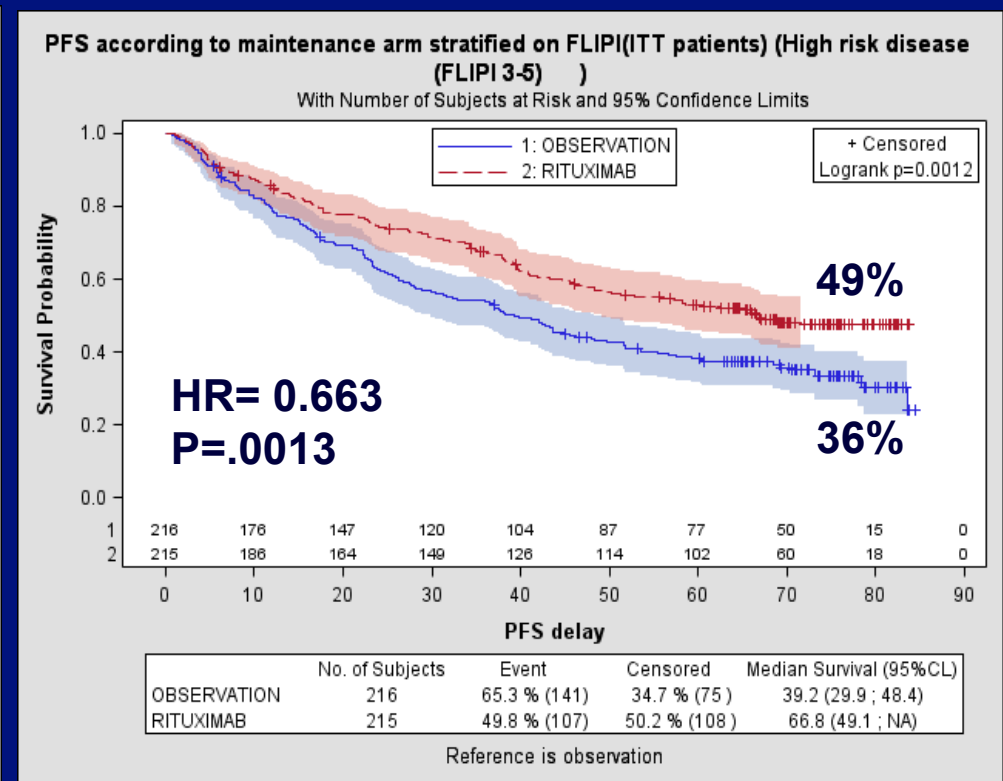
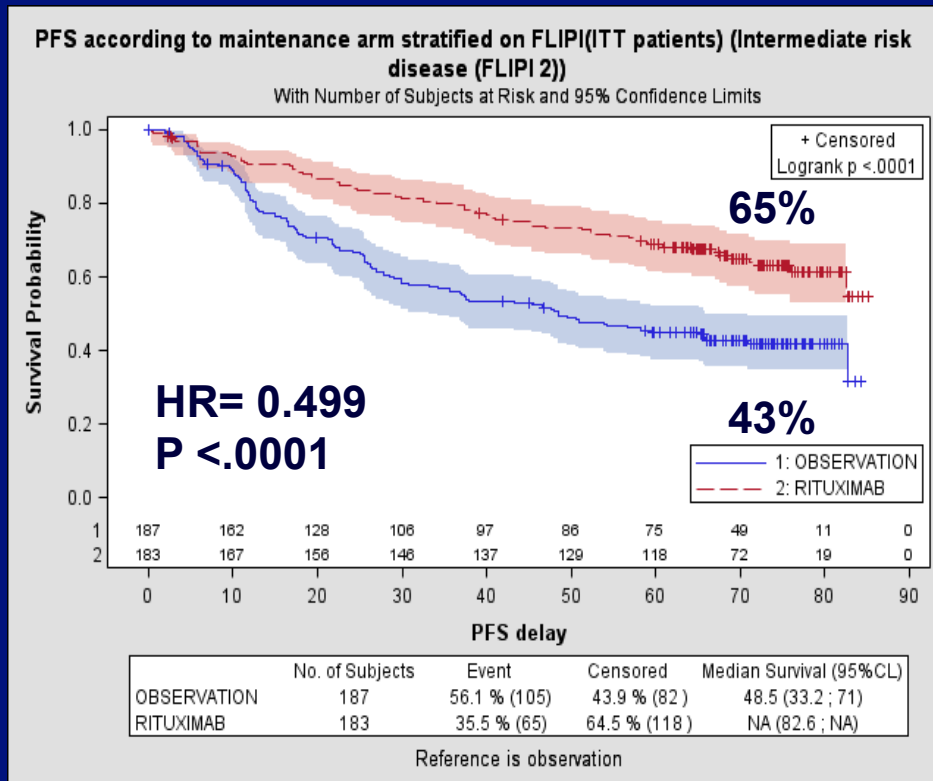
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# PRIMA 6 years follow-up

## Progression free survival from randomization

### FLIPI intermediate

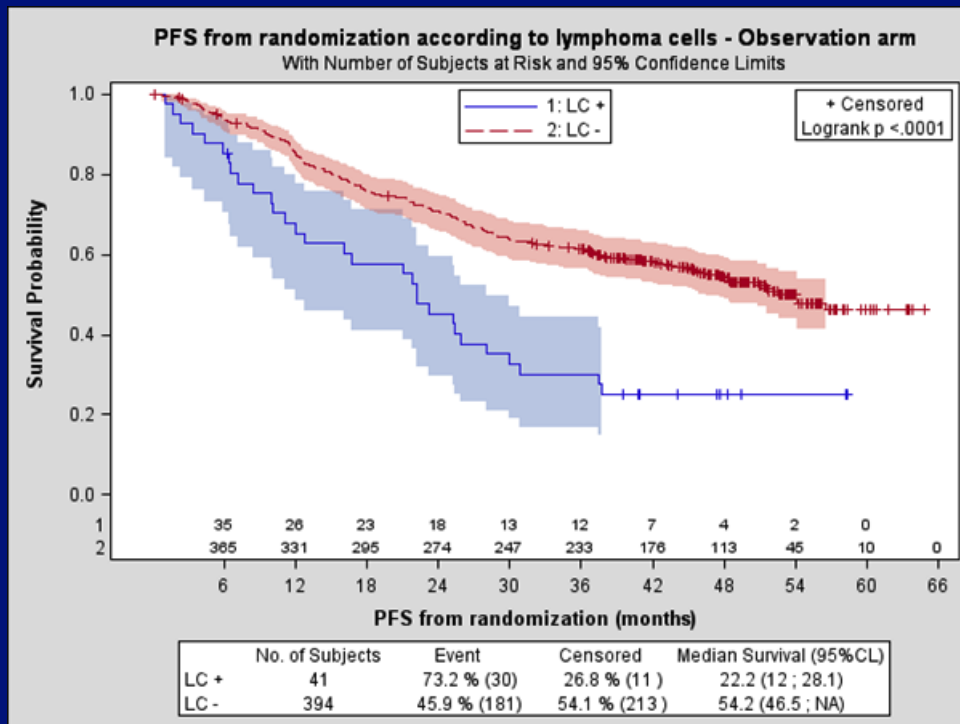
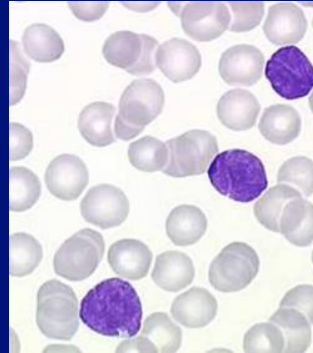
### FLIPI high



Median follow-up since randomization : 73 months

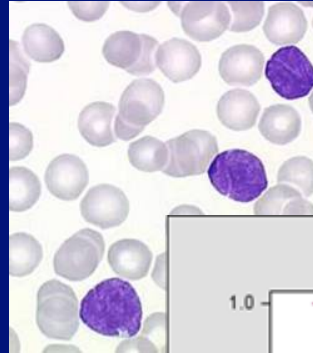
# Rituximab maintenance obviates the adverse outcome associated with lymphoma circulating cells

observation

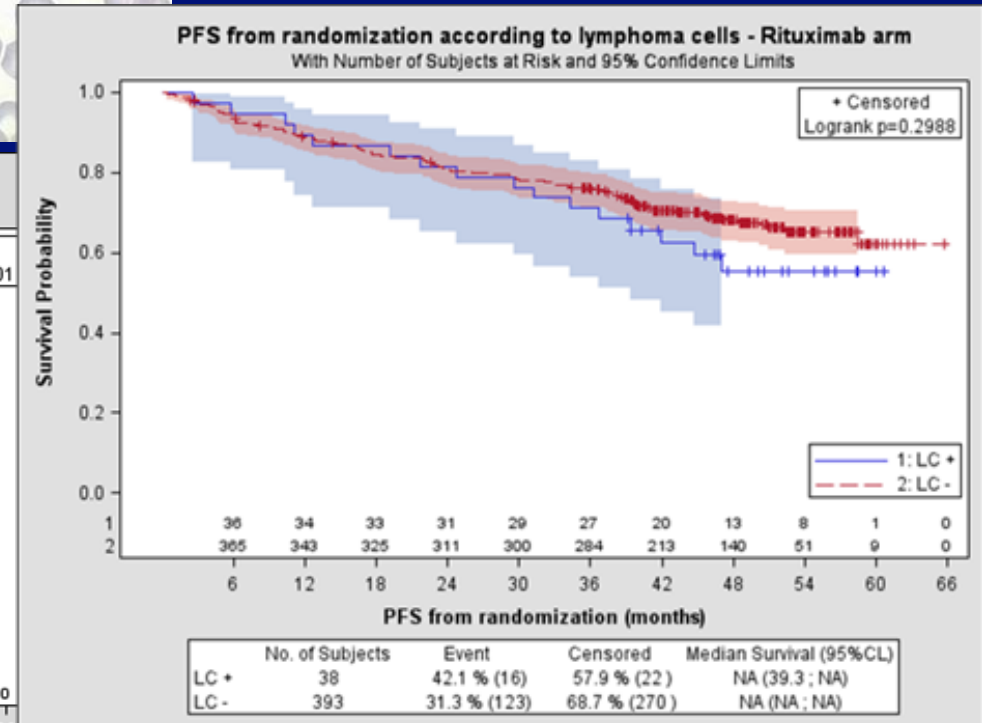
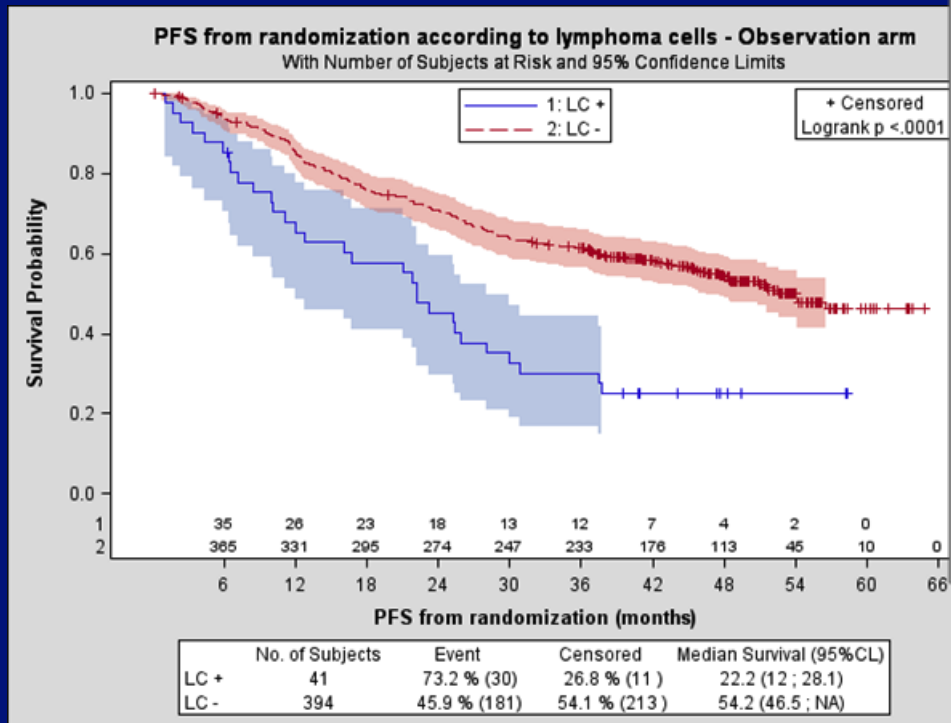


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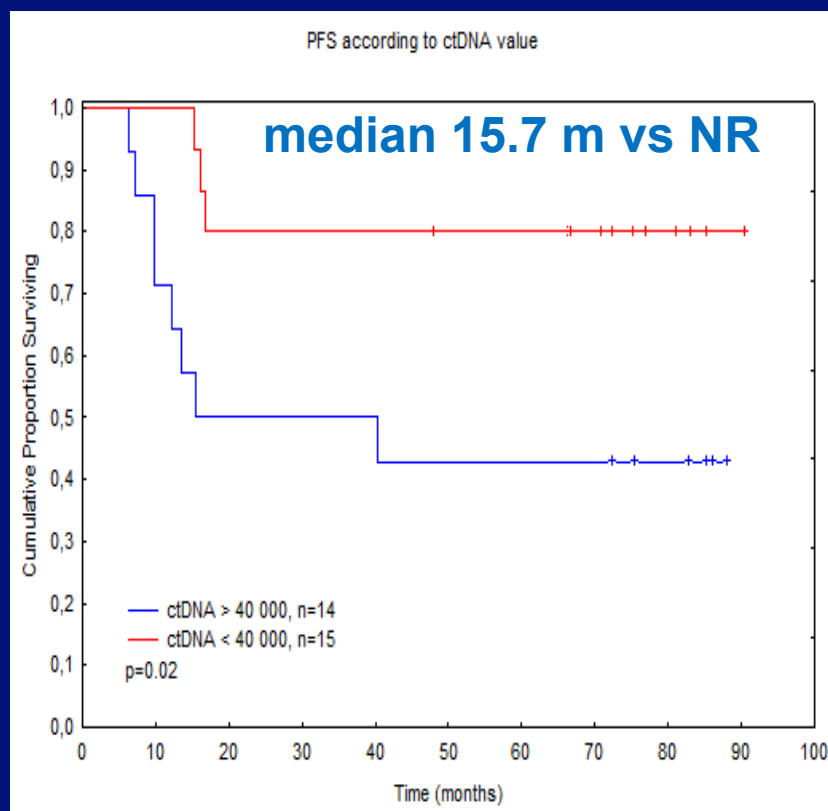


maintenance



# Prognostic value of ctDNA levels in PRIMA patients

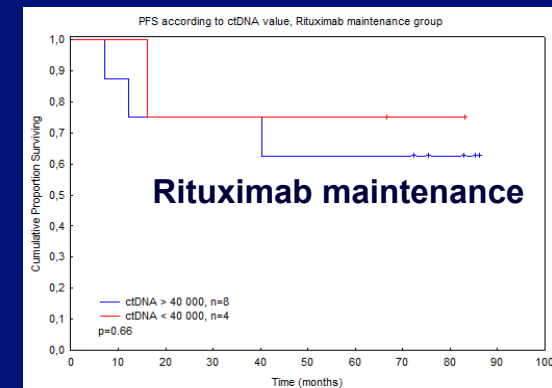
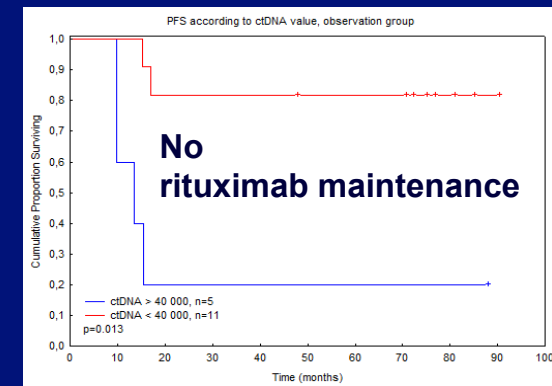
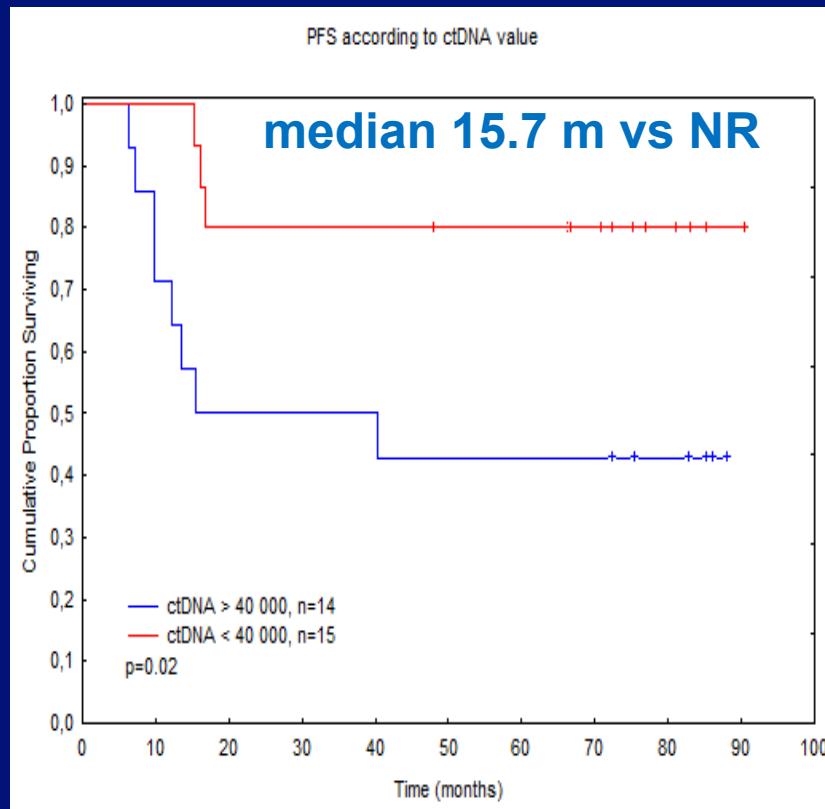
Using Lymphosight® technology, in serum at diagnosis



In multivariate analysis (FLIPI, bulk,  $\beta$ 2-m and ctDNA), ctDNA was the only significant parameter (HR 4.2, IC 95 (1.1-17) P=.039)

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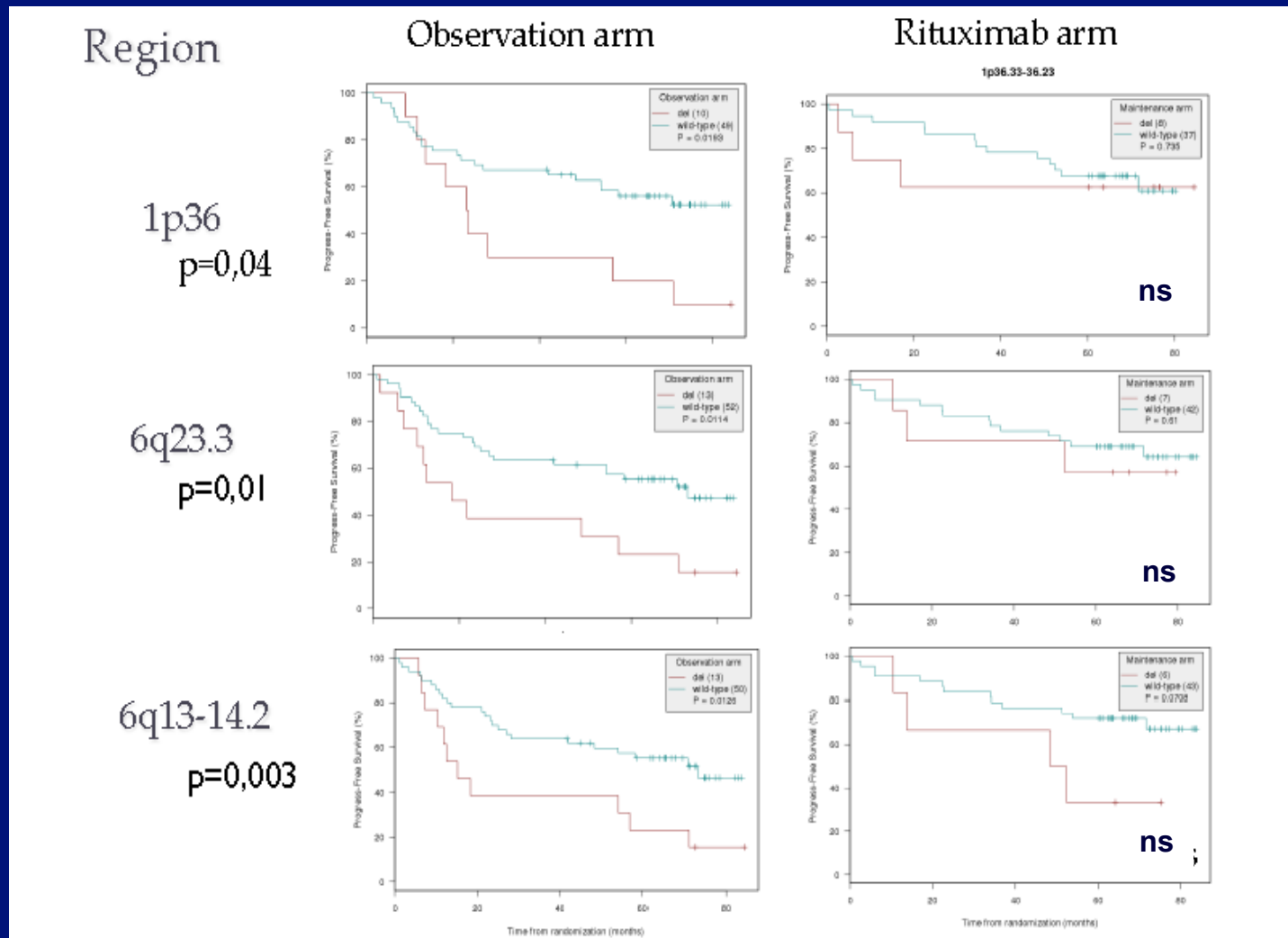
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# R-maintenance may also abrogate some adverse genetic prognostic features



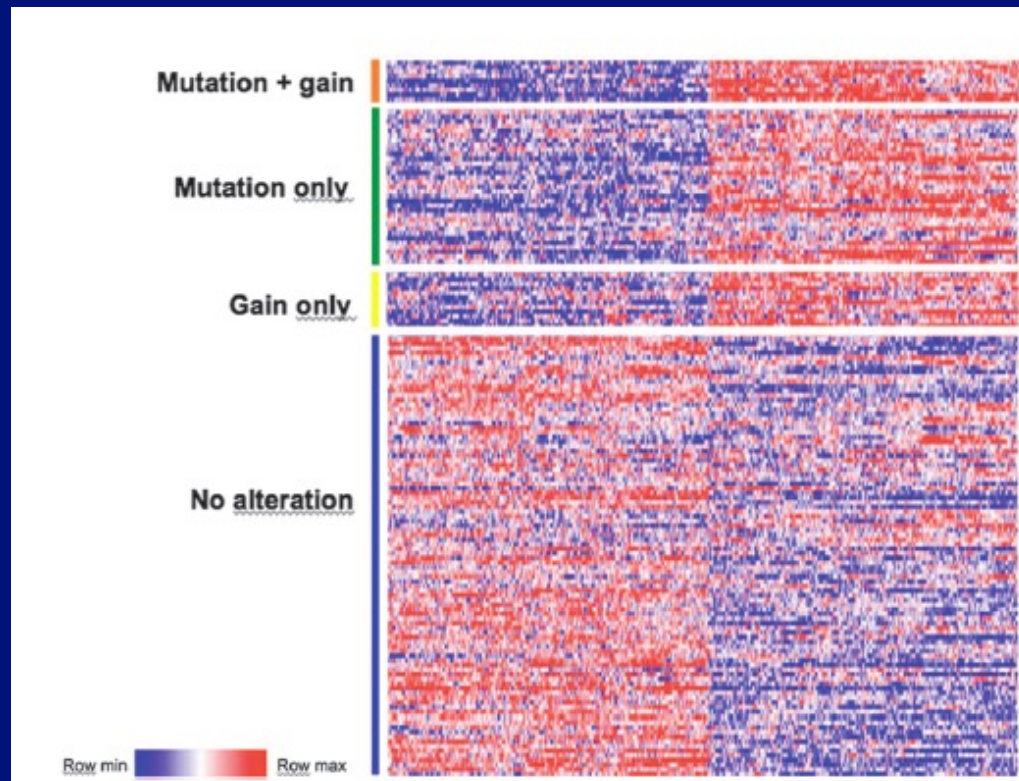
# R-maintenance may also improves the outcome of genetically defined groups with favorable prognostic features !

OPEN

Citation: Blood Cancer Journal (2017) 7, e555; doi:10.1038/bcj.2017.32  
www.nature.com/bcj

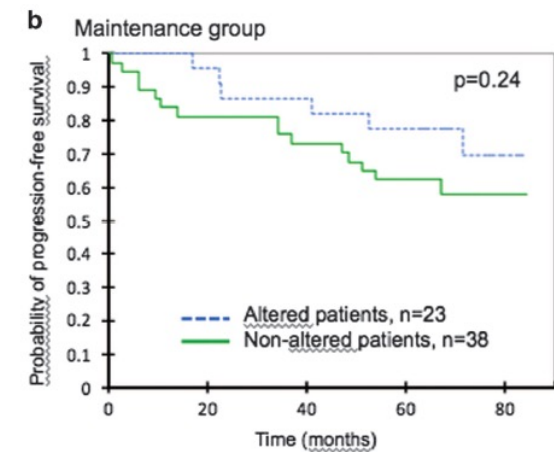
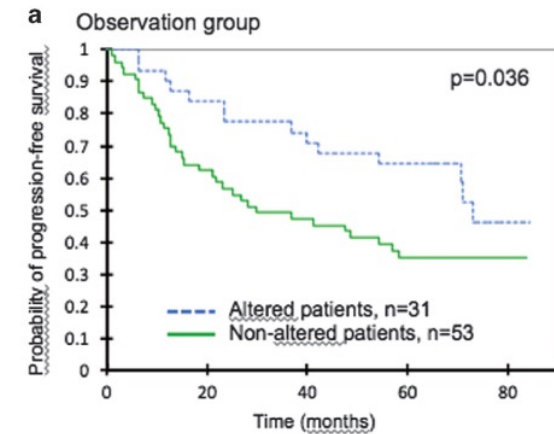
ORIGINAL ARTICLE

*EZH2* alterations in follicular lymphoma: biological and clinical correlations



Role of *EZH2* alterations in follicular lymphoma  
S Huet et al

6

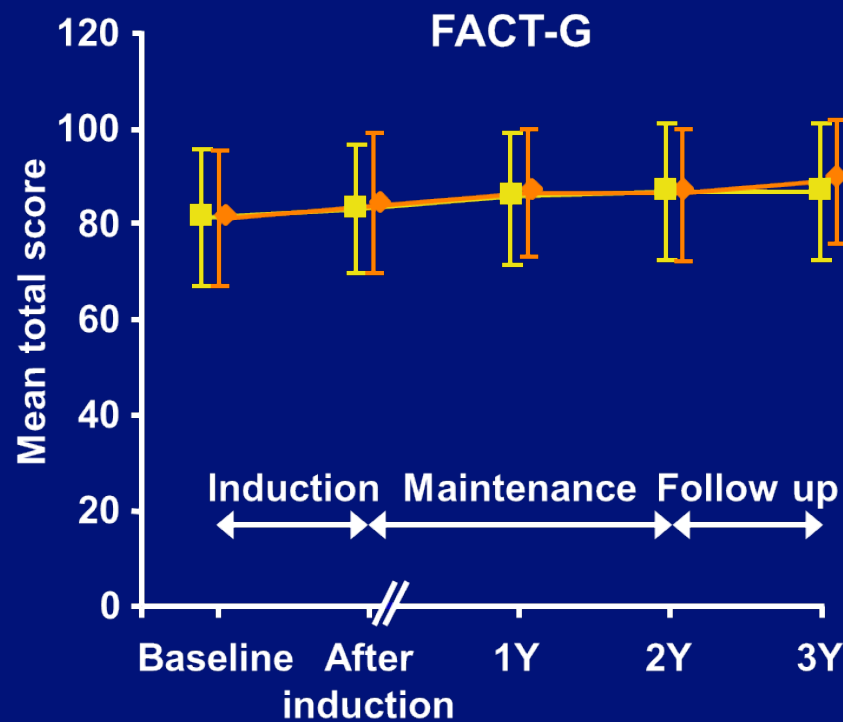


Maintenance in FL  
unanswered questions

# Maintenance in FL unanswered questions ?

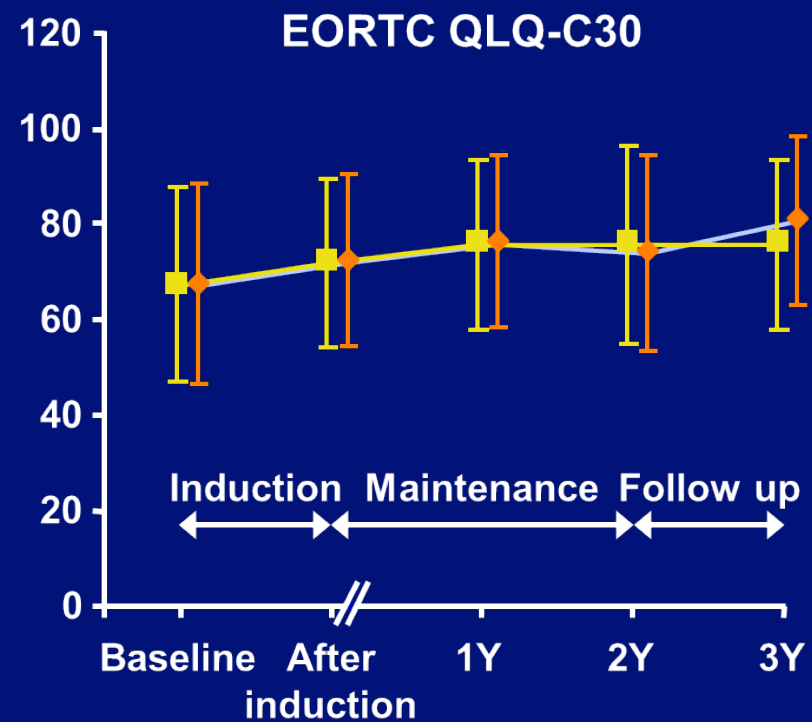
- Safety during maintenance
- Long term side effects
- Efficacy of subsequent treatment(s)
- Maintenance and induction regimens
- Overall survival data

# Quality of life during Rituximab maintenance



|         |     |     |     |    |
|---------|-----|-----|-----|----|
| n = 384 | 334 | 213 | 219 | 96 |
| n = 375 | 331 | 168 | 160 | 54 |

— Rituximab maintenance



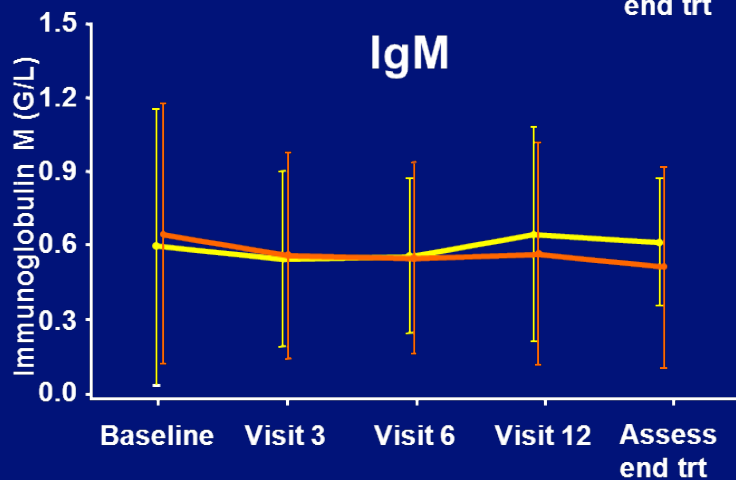
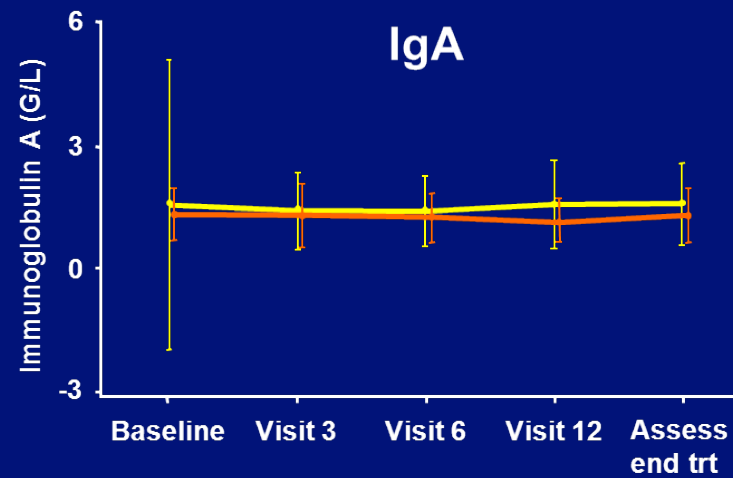
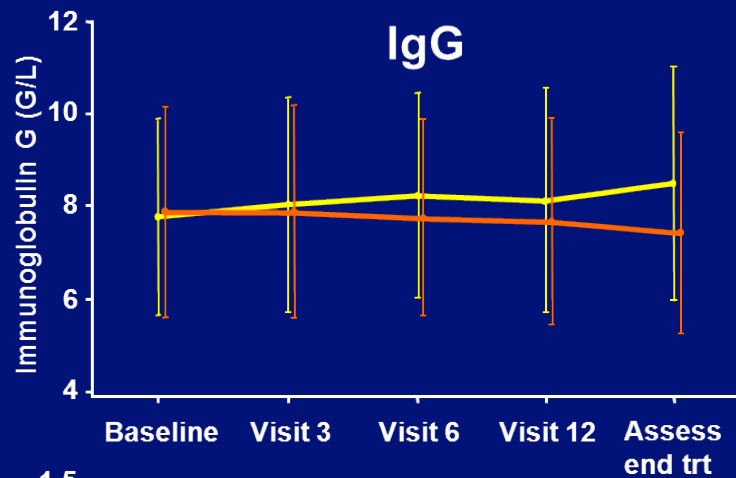
|         |     |     |     |    |
|---------|-----|-----|-----|----|
| n = 394 | 343 | 217 | 224 | 93 |
| n = 374 | 341 | 166 | 158 | 56 |

— Observation

# PRIMA : Infections during maintenance or observation

- **The most common adverse events reported were grade 2–4 infections in 197 (39%) and 123 (24%) patients, respectively (estimated difference 15.1%; 95% CI 9.4–20.8%, P<0.0001).**
- Grades 3-4 infections in respectively 5 (1%) and 22 (4%) patients
- **The five most common infections** reported in the rituximab and observation arms were
  - bronchitis, )
  - upper respiratory tract infections, ) in aggregate 114 and 61 cases
  - sinusitis, ) respectively
  - nasopharyngitis )
  - and urinary tract infections (14 and 9, respectively)
- The cumulative number of Herpes viruses-related infections were 19 and 12, respectively

# Immunoglobulin levels during maintenance / observation



# PRIMA = 6 years follow-up

## Relevant causes of death

|   | OBSERVATION<br>58 / 518 | RITUXIMAB<br>MAINTENANCE<br>59 / 505 |
|---|-------------------------|--------------------------------------|
| Lymphoma                                    | 28                      | 28                                   |
| 2 <sup>nd</sup> malignancies<br>(MDS / AML) | 19<br>(5)               | 6<br>(2)                             |
| Infections *                                | 4                       | 7                                    |
| Others                                      | 7                       | 18                                   |

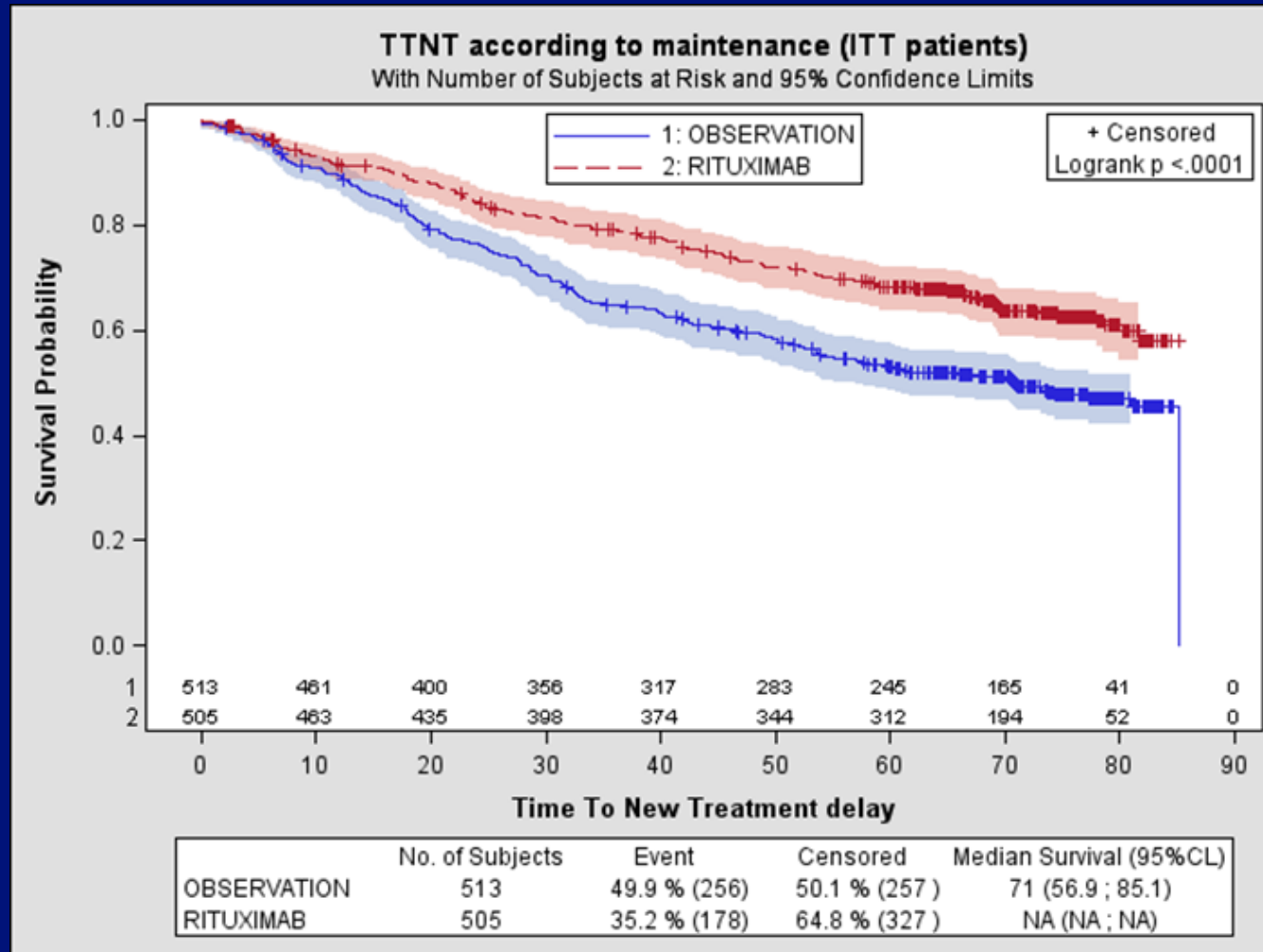
\* Infections include 1 case of PML in each arm and one case of hepatitis B in R-maintenance (both reported in 2011) and one case of aspergillosis in the observation arm.





# PRIMA 6 years follow-up

## Time to next treatment



Median follow-up since randomization : 73 months

# PRIMA 6 years follow-up

## Second line treatment

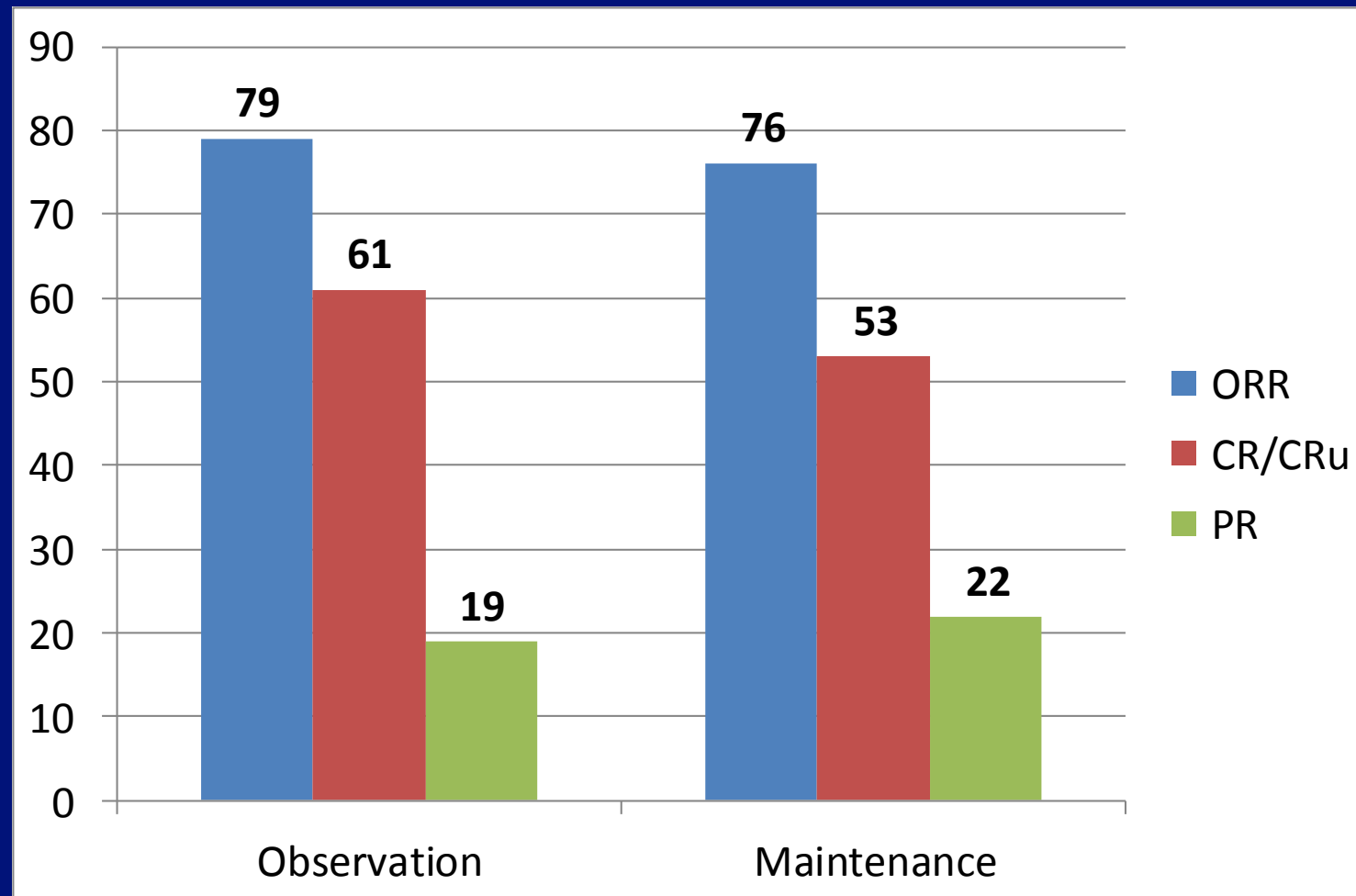
|                                       | Observation<br>518 pts |            | Rituximab<br>505 pts |              |
|---------------------------------------|------------------------|------------|----------------------|--------------|
| <b>Pts with progression</b>           | <b>278</b>             | <b>54%</b> | <b>186</b>           | <b>36.8%</b> |
| <b>Treated at time of progression</b> | <b>170</b>             | <b>61%</b> | <b>117</b>           | <b>63%</b>   |
| <b>- - - With rituximab</b>           | <b>143</b>             | <b>84%</b> | <b>78</b>            | <b>67%</b>   |
| <b>- - - Without rituximab</b>        | <b>27</b>              | <b>16%</b> | <b>39</b>            | <b>33%</b>   |



Detailed treatments are being further analyzed

# PRIMA 6 years follow-up

## Response to second line treatment

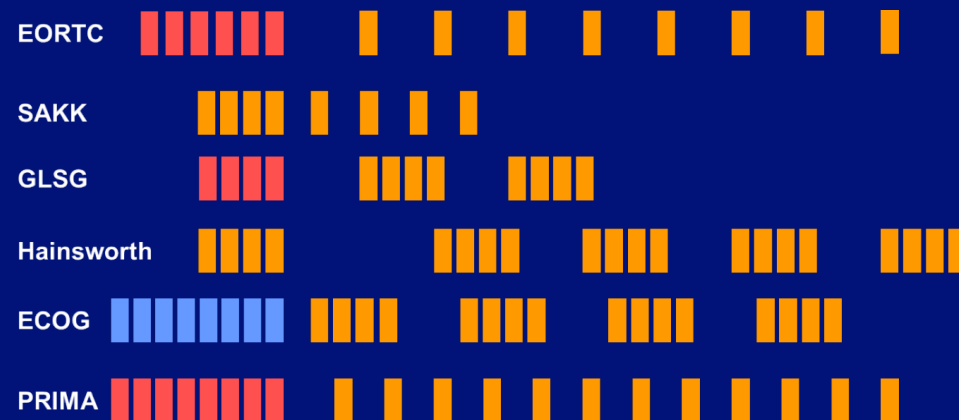


Responses reported by the investigators (percentage)



# Maintenance in FL unanswered questions ?

## Is any schedule better ?



- PK data may support the scheme with one administration every 2 months
- Comparaision about side effects ?
  - ... reflects how safety data were collected

# Rituximab maintenance after Bendamustine ?



Last updated December 17, 2014. Please note that this site represents the latest program changes and differs from the print version in some details.

3052 Bendamustine Plus Rituximab Followed By Rituximab Maintenance for Patients with Untreated Advanced Follicular Lymphomas. Results from the StiL NHL 7-2008 Trial (MAINTAIN trial) (ClinicalTrials.gov Identifier: NCT00877214)

Program: Oral and Poster Abstracts

Session: 623. Lymphoma: Chemotherapy, excluding Pre-Clinical Models: Poster II

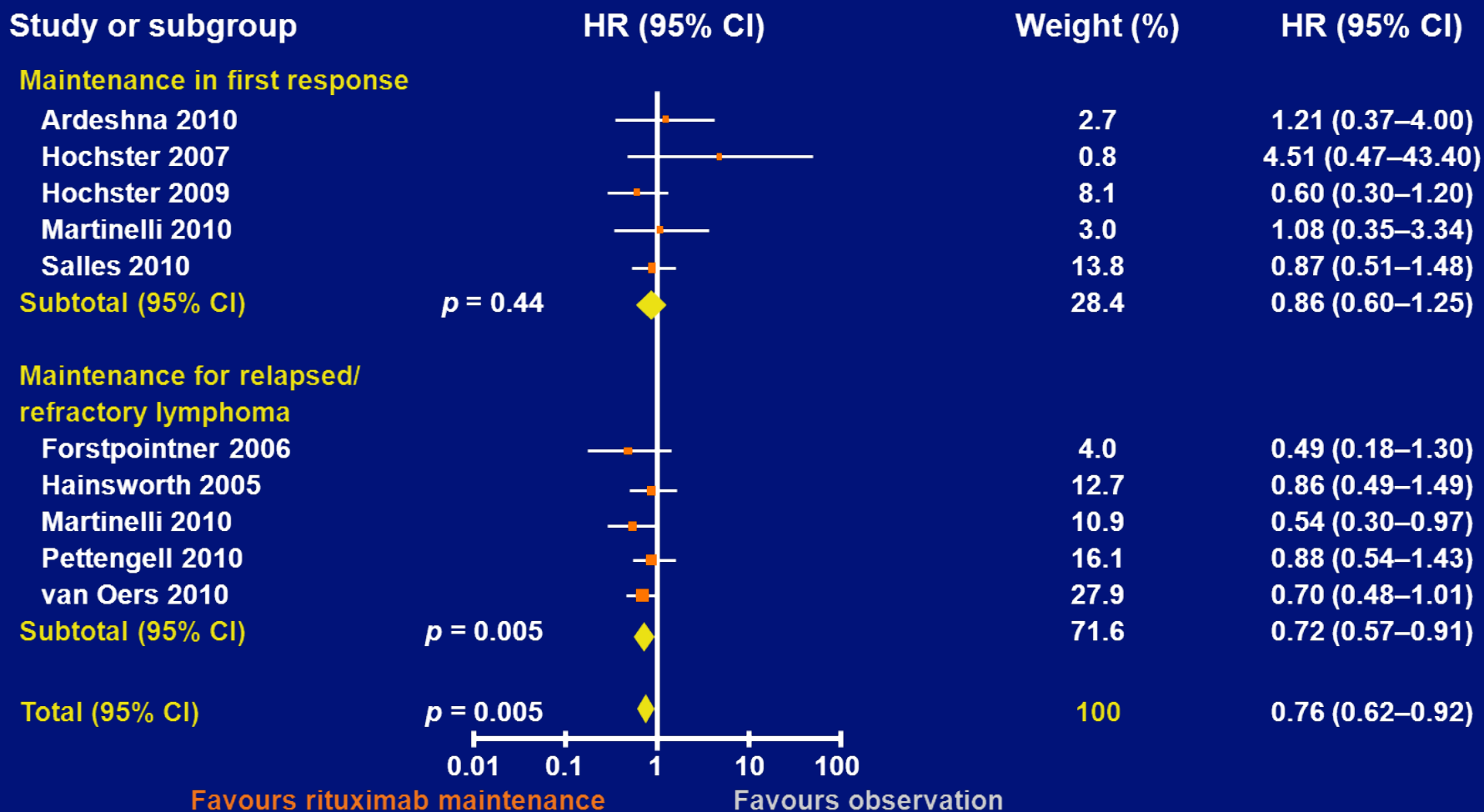
*Sunday, December 7, 2014, 6:00 PM-8:00 PM*

*West Building, Level 1 (Moscone Center)*

## GALLIUM study

- similar outcome of R-CHOP / R-benda followed by maintenance eventually suggest that R maintenance improves R-benda alone
- but higher toxicities during induction and maintenance of R/G-benda arms

# Overall Survival: Meta-analysis R maintenance in FL patients

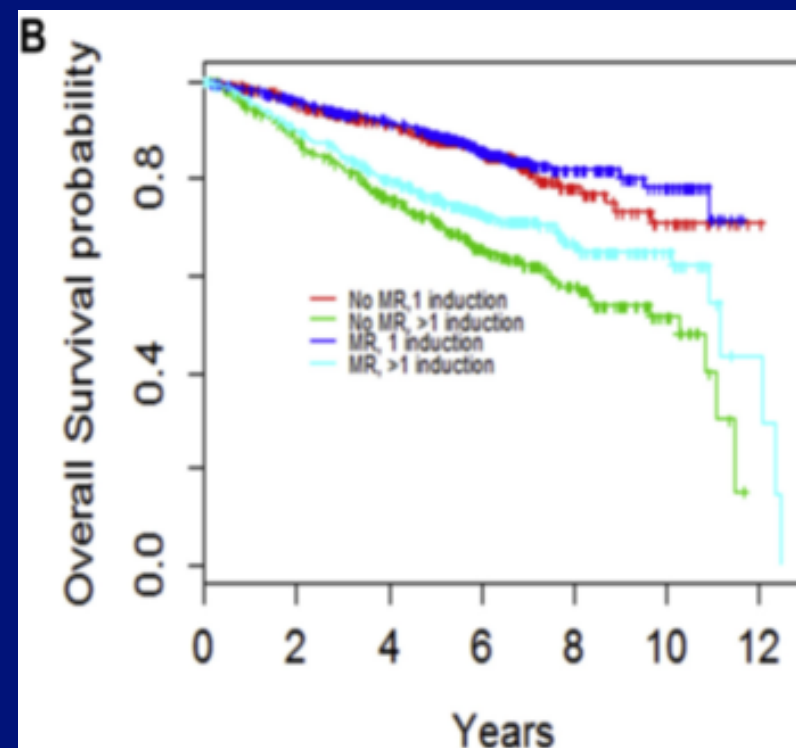


# Rituximab Maintenance (MR) for Patients with Follicular Lymphoma (FL) : Individual Patient Data (IPD) Meta-Analysis of Randomized Controlled Trials (RCTs)

## Multivariate model

| Variable                           | HR   | 95% CI    | P –value  |
|------------------------------------|------|-----------|-----------|
| Female vs. male                    | 0.73 | 0.61-0.99 | 0.0012    |
| Age $\geq 60$ vs. younger          | 1.99 | 1.65-2.42 | $<0.0001$ |
| After $\geq 2$ vs. first induction | 1.48 | 0.79—2.77 | 0.22      |
| R-maintenance vs. no maintenance   | 0.79 | 0.66-0.96 | 0.017     |

No interaction between number of inductions and MR



# Risk of histological transformation ?

## PRIMA

In pts receiving R- maintenance : lower number of progression but same proportion of transformed cases

- 708 pts without HT: 382 (54%) had received RM

- 40 pts with HT : 16 (40%) had received RM

*(Sarkozy et al. JCO 2016)*

## ARISTOTLE

ICML Abstract 105: The Risk Of Transformation Of Follicular Lymphoma Transformed By Rituximab. The Aristotle Study Promoted By The European Lymphoma Institute

*(M. Federico, Modena (Italy) – Lugano – Friday 2:00 PM)*



# The major differences between PRIMA and RESORT

|                                   | <b>RESORT</b>         | <b>PRIMA</b> |
|-----------------------------------|-----------------------|--------------|
| Tumor burden                      | Low                   | High         |
| Chemotherapy                      | No                    | Yes          |
| Depth of response after induction | +                     | +++          |
| Median F-up                       | 4 years               | 6 years      |
| Treatment at progression          | Rituximab, then chemo | chemo (80%)  |

# Maintenance and our treatment goals in follicular lymphoma

- Using R-maintenance, a significant benefit has been achieved to prolong PFS
- OS benefit is suggested from the meta-analysis data
- More than 60% of the patients remain free of disease and treatment
  - 6.5 years after diagnosis
  - 4 years after the end of maintenance

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  - OS benefit is suggested from the meta-analysis data
  - More than 60% of the patients remain free of disease and treatment
    - 6.5 years after diagnosis
    - 4 years after the end of maintenance
- > results of the 10-year update ...

