12th Annual Hematology & Breast Cancer Update
Update in Lymphoma

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Initial Treatment of Indolent Lymphoma

- Expectant observation
- Treatment
  - Rituximab
  - Immunochemotherapy
    - R-CHOP
    - R-CVP
    - R-bendamustine

Initial Treatment of Indolent Lymphoma

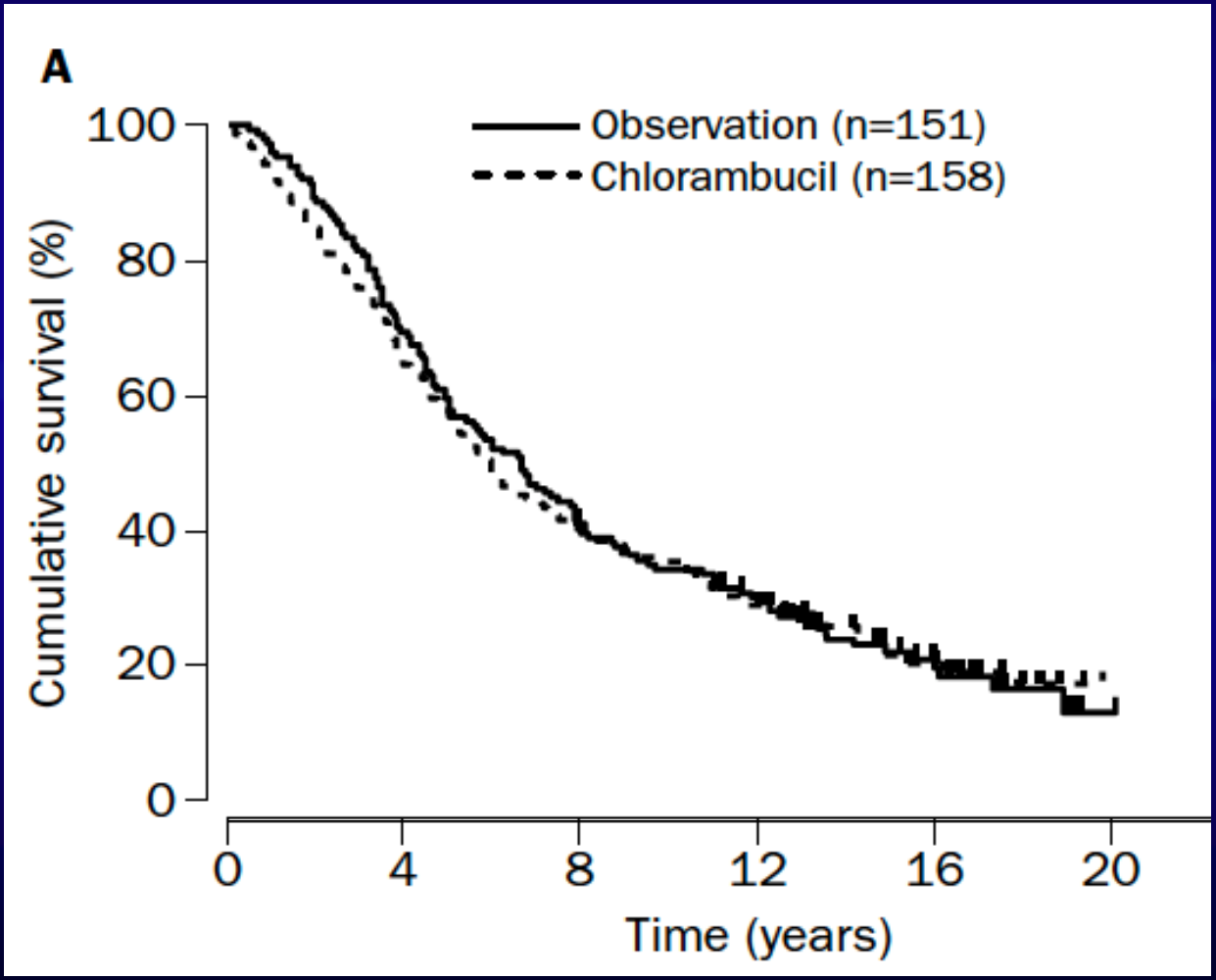
- Expectant observation
  - » Rationale
    - – Avoids treatment related toxicity
    - – No reduction in survival
      - Tx at diagnosis (advance disease) vs deferred (Horning et al NEJM 1984)

Initial Treatment of Indolent Lymphoma

- British National Lymphoma Investigation (Lancet 362:516, 2003)
  - 309 pt with asymptomatic, advanced stage low-grade Non-Hodgkin lymphoma
  - Enrolled 1981-1990
  - Tx with chlorambucil (0.2 mg/kg daily) vs observation
    - Observation arm treated with same regimen when developed symptomatic disease.
  - Median follow-up 16 years

Initial Treatment of Indolent Lymphoma

Overall Survival



British National Lymphoma Investigation (Lancet 362:516, 2003)

Initial Treatment of Indolent Lymphoma

Time to 1st treatment (obs)

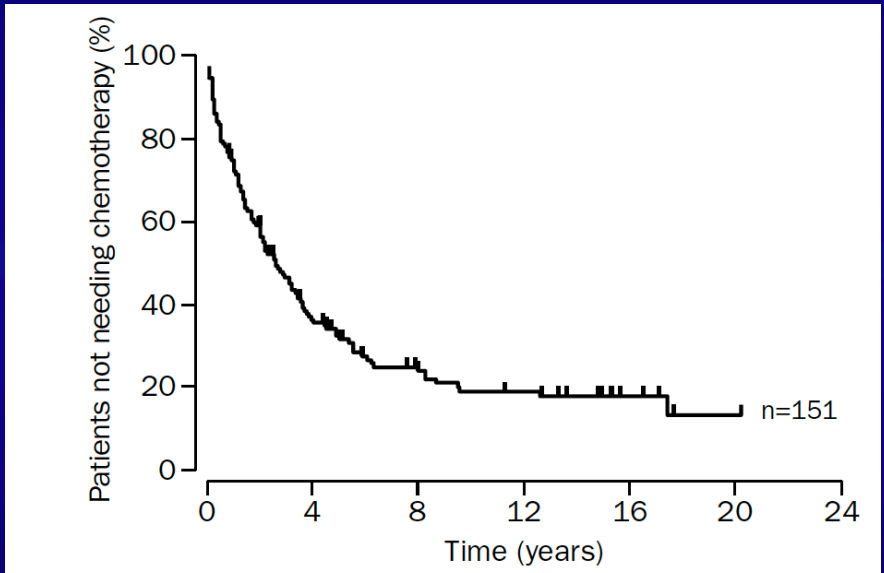


Figure 3: **Time to first systemic treatment for patients in the observation group**
At 10 years, 19% (95% CI 13–27) of patients either did not need chemotherapy or died of lymphoma (non-lymphoma deaths were censored).

Time to second treatment

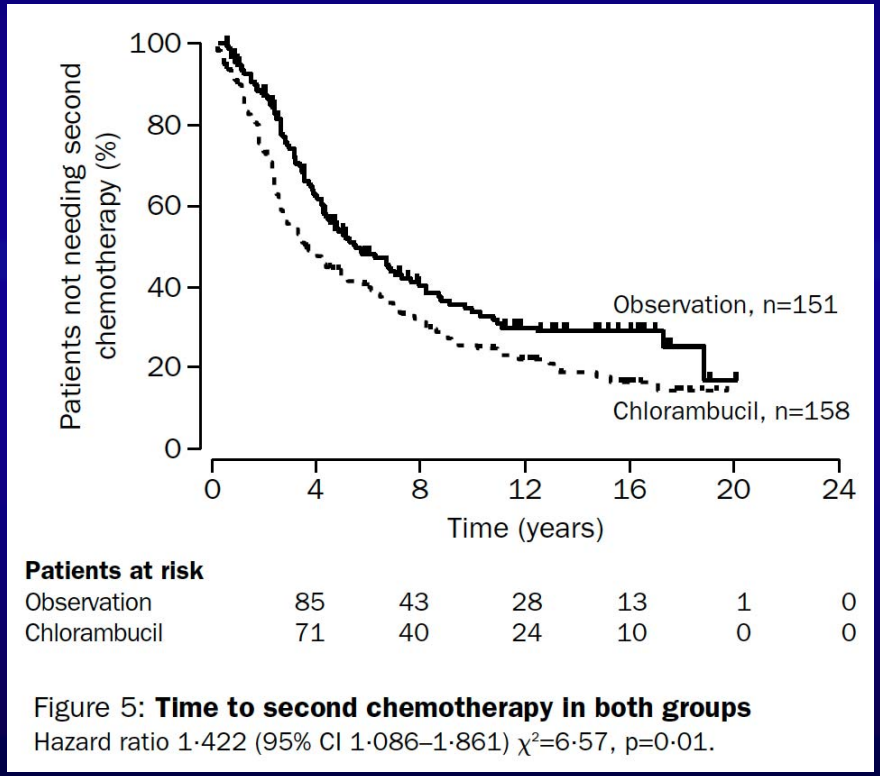


Figure 5: **Time to second chemotherapy in both groups**
Hazard ratio 1·422 (95% CI 1·086–1·861) χ^2=6·57, p=0·01.

British National Lymphoma Investigation (Lancet 362:516, 2003)

Intergroup study of rituximab vs watch and wait (Ardeshna, K *et al*)

- Expectant observation – still relevant today?
- Oral Plenary Scientific Session
- Authors: Ardeshna, Kirit et al.
- Objective
  - Does initial treatment with rituximab in patients with *asymptomatic advanced stage FL* result in a significant delay in the initiation of chemotherapy or radiotherapy when compared with a watchful waiting approach?

Thank Dr. Ardeshna for sharing his slides

Intergroup study of rituximab vs watch and wait (Ardeshna, K *et al*)

- Major Inclusion Criteria
  - » Stage II, III, IV
  - » Asymptomatic (no B symptoms or puritis)
  - » Non-bulky (<7 cm)
  - » No more than 3 nodal sites with a diameter >3 cm
  - » FL grade 1, 2, and 3a
  - » Entry within 3 months of Dx
  - » No major cytopenia

Thank Dr. Ardeshna for sharing his slides

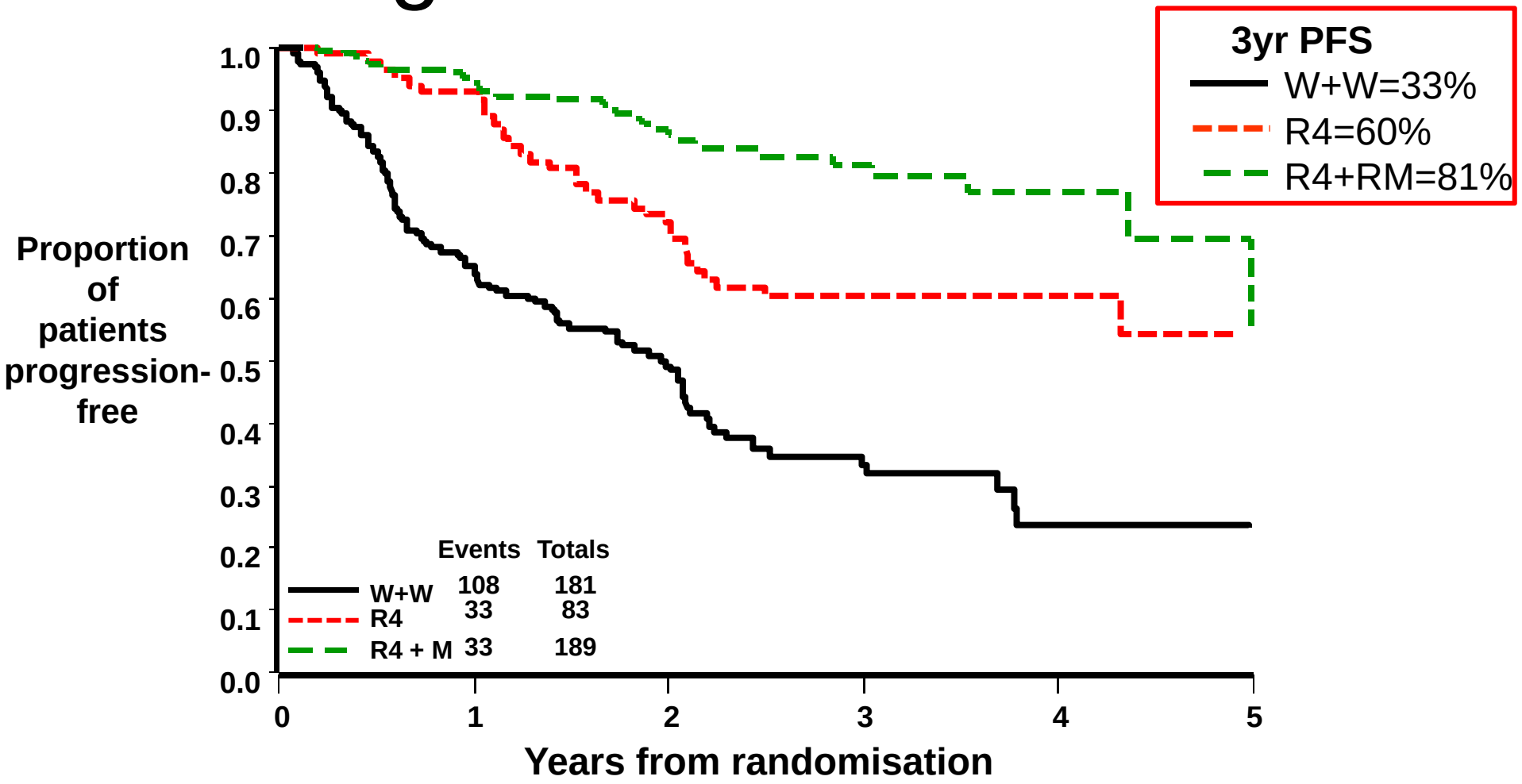
Endpoints

- Primary endpoint
  - Time to Initiation of New Therapy (TTINT)
    - New therapy=chemotherapy or radiotherapy
- Secondary endpoints
  - Progression free survival
  - Overall survival
  - Response at 25 months
  - Frequency of spontaneous clinical remissions
- Arm B closed due to perceived efficacy of maintenance

Intergroup study of rituximab vs watch and wait (Ardeshna, K et al)

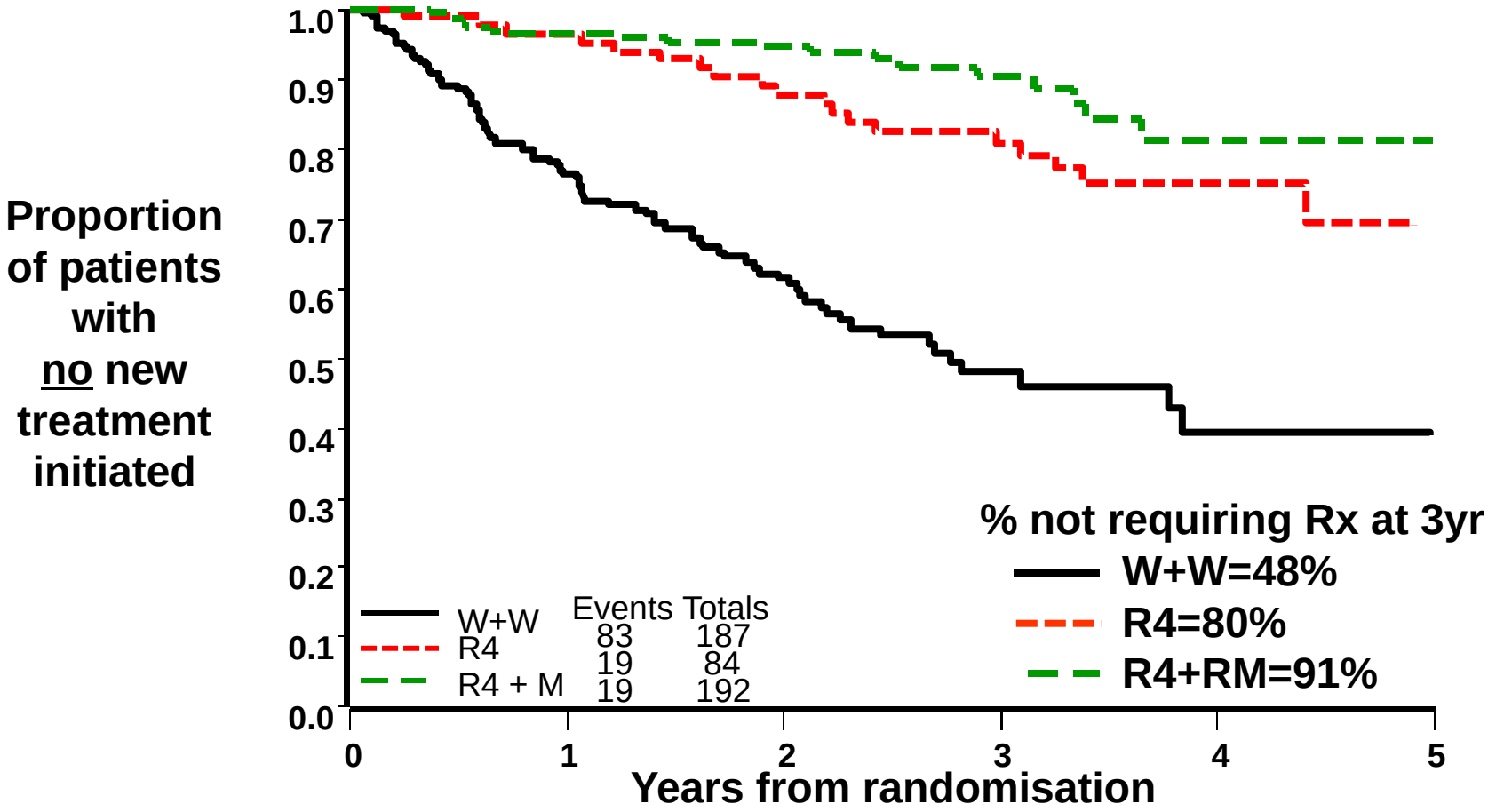
- Accrual
  - 9/2004 to 5/2009
  - 463 patients
    - A: 187, B: 84, C:192
- Analysis done on March 2010
  - Data monitoring committee concluded data regarding the TTINT was mature and recommended full analysis
- Follow up
  - Median follow up = 32 months

Progression-free survival



HR (Rituximab vs W+W) = 0.46, 95%CI = 0.33, 0.65, p<0.001
HR (Rituximab + M vs W+W) = 0.21, 95%CI = 0.15, 0.29, p<0.001
HR (Rituximab + M vs Rituximab) = 0.43, 95%CI = 0.24, 0.72, p=0.001

Time to Initiation of New Therapy (TTINT)



HR (Rituximab vs W+W) = 0.37, 95%CI = 0.25, 0.56, p<0.001
HR (Rituximab + M vs W+W) = 0.20, 95% CI = 0.13, 0.29, p <0.001
HR (Rituximab + M vs Rituximab) = 0.57, 95% CI = 0.29, 1.12, p =0.10

Conclusions (Ardeshna et al)

- Rituximab significantly improves TTINT and PFS in patients with asymptomatic FL when compared with watchful waiting.
- If QoL no worse in rituximab arms then
  - initial treatment with rituximab is likely to prove a popular option with patients and their doctors and may become the standard of care
- Whether overall survival will be improved is currently unclear
  - Need to determine the impact of prior rituximab on
    - Response to 1st new treatment
    - Response duration of 1st new treatment and
    - Time to 2nd new treatment

Intergroup study of rituximab vs watch and wait (Ardeshna, K et al)

- Comparing “apples to oranges”
  - Not fair to look at time to “new” treatment between no treatment and rituximab
- More interesting questions to possibly come from the study
  - Overall survival
  - Time to second treatment
  - Transformation rate
  - Response to initial treatment
- Still open question if asymptomatic FL patients benefit from treatment -> expectant observation is still appropriate management.

405 Bendamustine Plus Rituximab Is Superior in Respect of Progression Free Survival and CR Rate When Compared to CHOP Plus Rituximab as First-Line Treatment of Patients with Advanced Follicular, Indolent, and Mantle Cell Lymphomas: Final Results of a Randomized Phase III Study of the StiL (Study Group Indolent Lymphomas, Germany)

- Presented ASH 2009
- Median observation 32 months

	Bendamustine-R	**CHOP-R**
Overall Response rate	93.8%	93.5%
Complete Response	40.1%	30.8%
PFS (months)	54.8	34.8
EFS (months)	54	31
Median TTNT (months)	Not reached	40.7
Overall Survival	No difference	

B-R Is Superior with better PSF and CR Compared to CHOP-R as First-Line Treatment of Advanced Follicular, Indolent, and Mantle Cell Lymphomas: Randomized Phase III Study of the StiL

	Bendamustine-R	CHOP-R
Neutropenia	10.7%	46.5
Infection	95 pt	121 pt
Neuropathy	18 pt	73 pt
Alopecia	15%	62%
Rash	42 pt	23 pt

- Cost: 1 cycle
  - » bendamustine ~$8,000
  - » CHOP ~ $1,500

R-CVP followed by Maintenance for initial therapy of FL

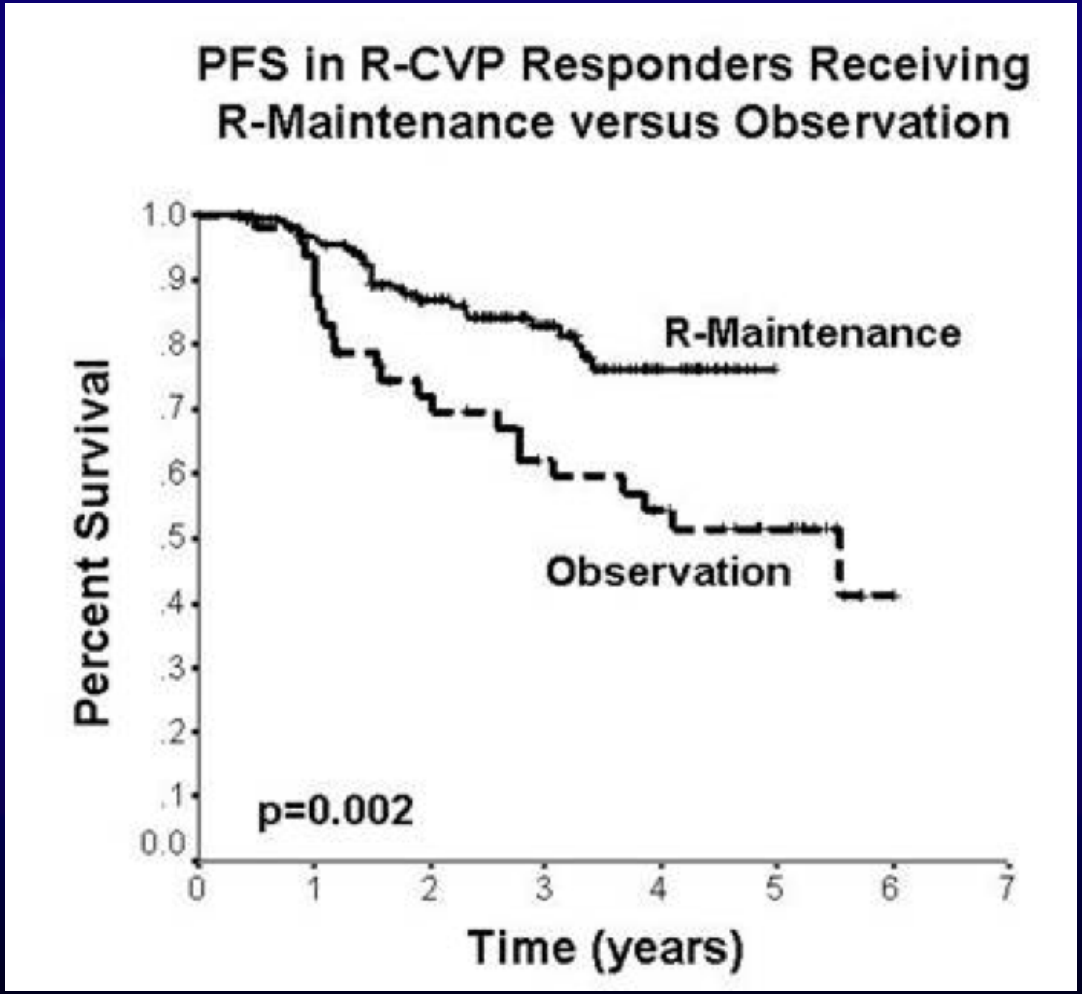
- "Front-Line Therapy with Rituximab, Cyclophosphamide, Vincristine, and Prednisone (R-CVP) Followed by 2 Years of Rituximab Maintenance for Follicular Lymphoma (FL) Is Associated with Excellent Outcomes and Improved Progression-Free Survival (PFS) In Comparison to No Maintenance"
- Moccia AA *et al.* British Columbia Cancer Agency
- Retrospective review of FL patient treated in British Columbia
  - Tx between 3/2004 and 1/2010
  - R-CVP vs R-CVP with maintenance (policy since 2006)

R-CVP followed by Maintenance for initial therapy of FL

- Identified 251
  - Median follow-up 36 m
  - Response to R-CVP 89%
    - CR/CRu 44%
    - PR 37%
  - Post initial treatment
    - 59 pt observed 59 pt
    - 167 pt received R-maintenance (q 3 m)
      - 23% pt converted from PR to CR/CRu

R-CVP followed by Maintenance for initial therapy of FL

- 3 y PFS
  - » Rituximab 83%
  - » Observation 62%
- Overall survival same (93%)
- R-CVP followed by R maintenance gives good results



Rituximab Maintenance x 2 years (PRIMA)

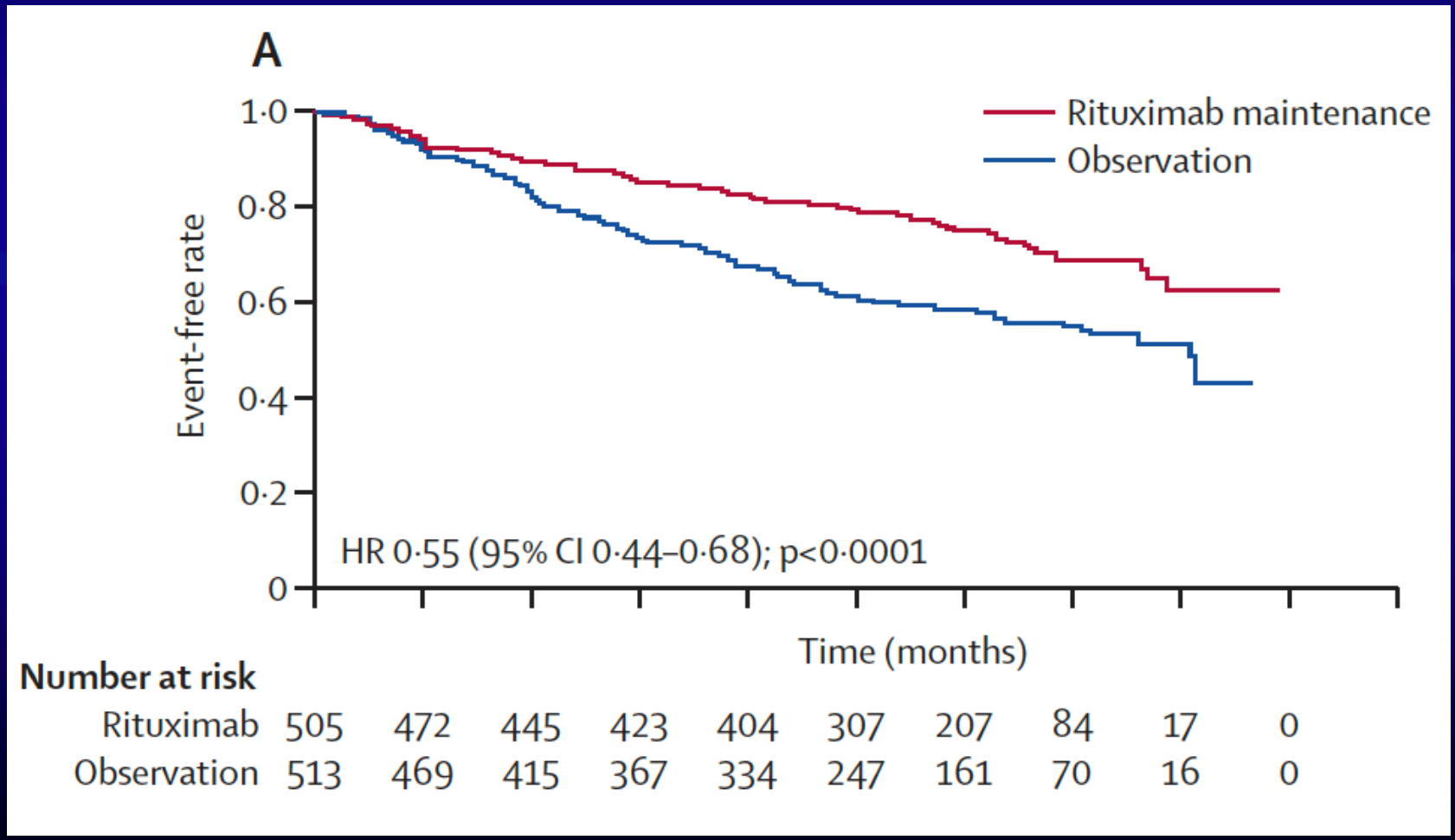
- Study design
  - » Randomized, open label
  - » 223 centers in 25 countries
  - » 1217 patients
  - » Untreated follicular lymphoma
  - » Symptomatic
- Rituximab maintenance 375 mg/m2 every 8 weeks)
- Median follow-up of 36 months
- Published (Lancet 2010; 377:42-51)

Rituximab Maintenance x 2 years

	Patients who received induction treatment (n=1193)	Randomised patients	
		Observation (n=513)	Rituximab maintenance (n=505)
FLIPI score†			
Low (0–1 risk factors)	254 (21%)	110 (21%)	106 (21%)
Intermediate (2 risk factors)	423 (36%)	187 (36%)	183 (36%)
High (3–5 risk factors)	514 (43%)	216 (42%)	215 (43%)
Initial local diagnosis of FL (other than grade 3B)	1188 (100%)	512 (100%)	504 (100%)
Central pathological review done	1115 (93%)	487 (95%)	467 (92%)
Confirmed FL (other than grade 3B)	994 (84%)	433 (84%)	425 (84%)
Diagnosis of other lymphoma subtype‡	56 (5%)	28 (5%)	16 (3%)
Unclassifiable or not assessable for technical reasons	65 (6%)	26 (5%)	26 (5%)
Induction immunochemotherapy regimen			
R-CHOP	885 (74%)	386 (75%)	382 (76%)
R-CVP	272 (23 %)	113 (22%)	109 (22%)
R-FCM	45 (4%)	14 (3%)	14 (3%)
Response to induction			
Complete response	..	195 (38%)	205 (41%)
Unconfirmed complete response	..	165 (32%)	155 (31%)
Partial response	..	152 (30%)	139 (28%)
Other§	..	1 (≤1%)	6 (1%)

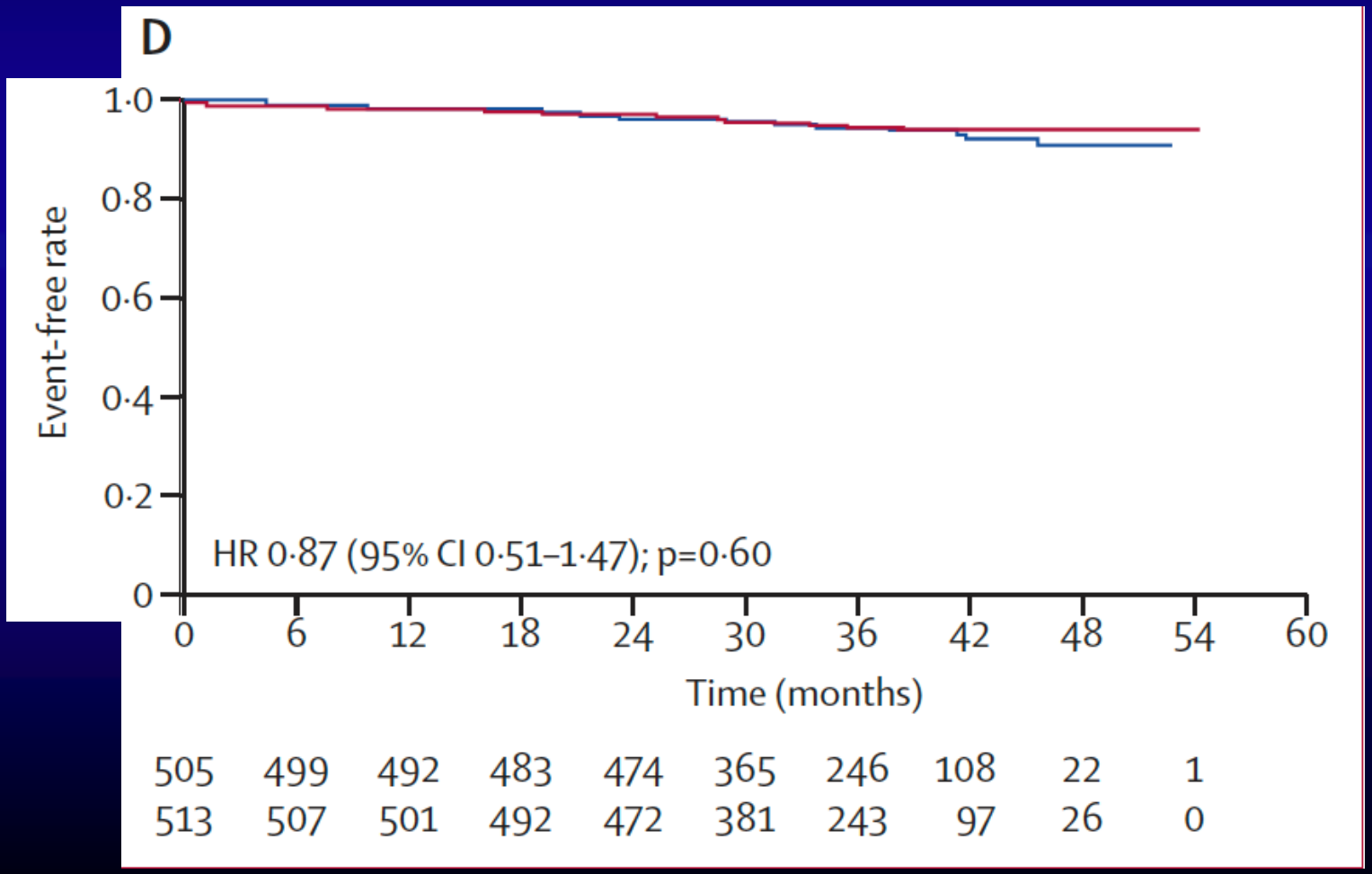
Rituximab Maintenance x 2 years

- Progression free survival



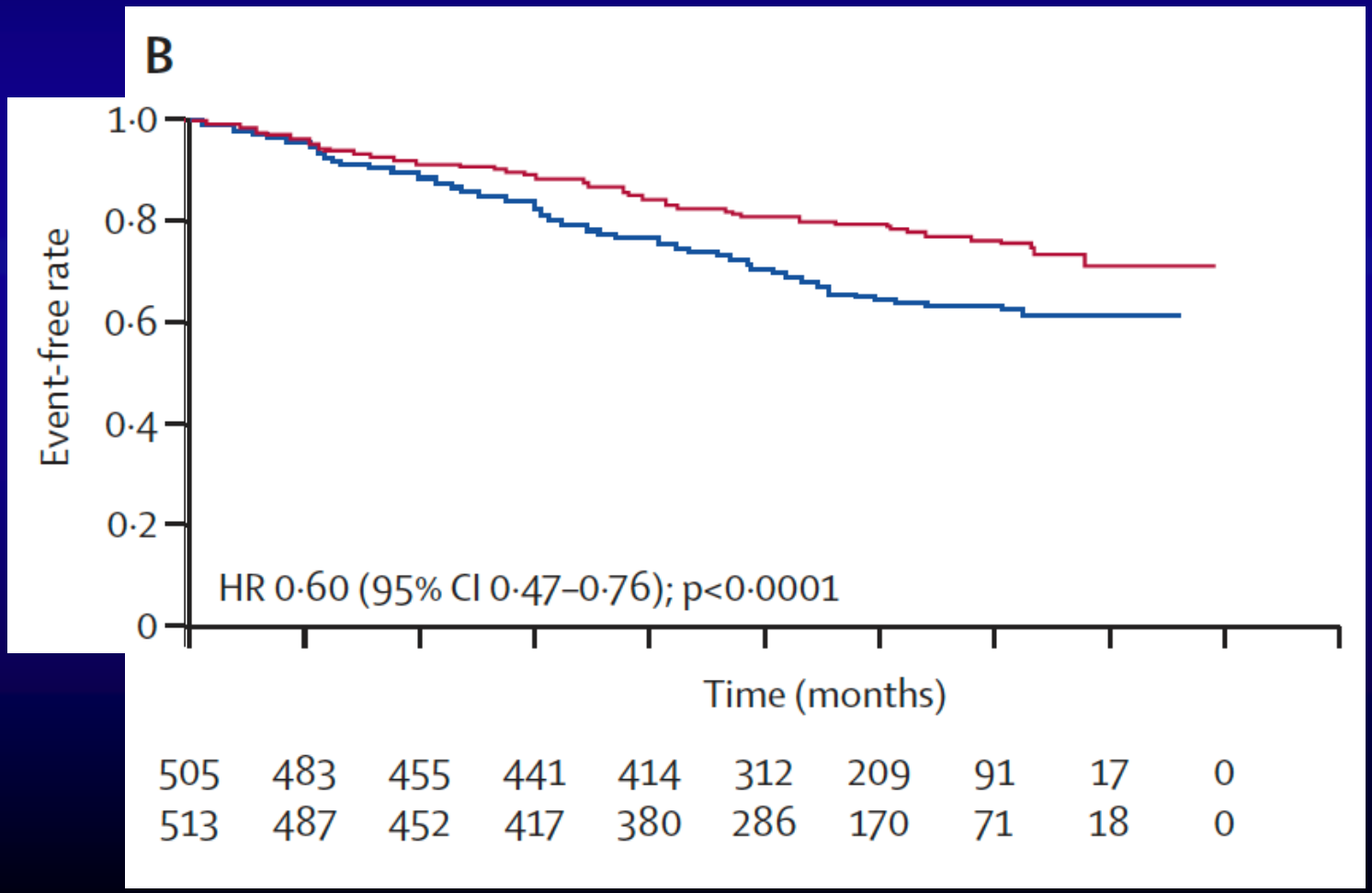
Rituximab Maintenance x 2 years

- Overall survival

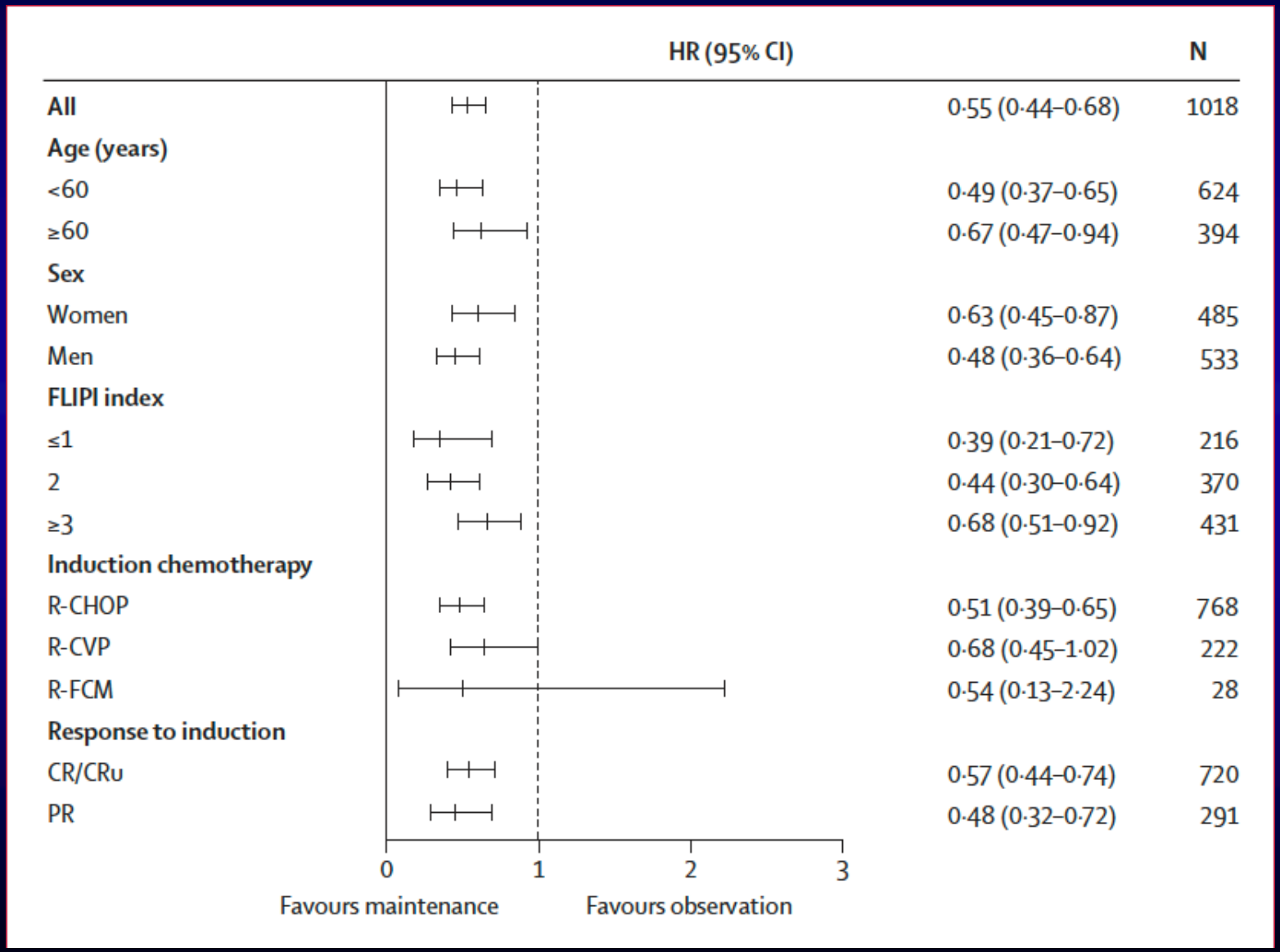


Rituximab Maintenance x 2 years

- Time to next treatment



Benefit in all prespecified subgroups



Similar safety

	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)
Pregnancy	NA	2 (<1%)	NA	3 (1%)

Data are number (%). NA=not applicable. *Safety during maintenance was assessed for patients who undertook at least one visit (rituximab treatment or observation) after randomisation. All adverse events, defined as any adverse change from the patient's baseline condition, whether considered related to treatment or not, were collected and graded according to the Common Terminology Criteria for Adverse Events 3.0 grading system.[18] All grade 3 and 4 events plus grade 2 infections were recorded in detail during maintenance or observation and 6 months thereafter. †Other events leading to treatment discontinuation were pyrexia, fulminant hepatitis, hypersensitivity, post-procedural fistula, and lung disorder (one case each).

Table 2: **Grade 3 and 4 adverse events* experienced by 2% or more of patients and adverse events leading to treatment discontinuation, after randomisation to rituximab maintenance or observation**

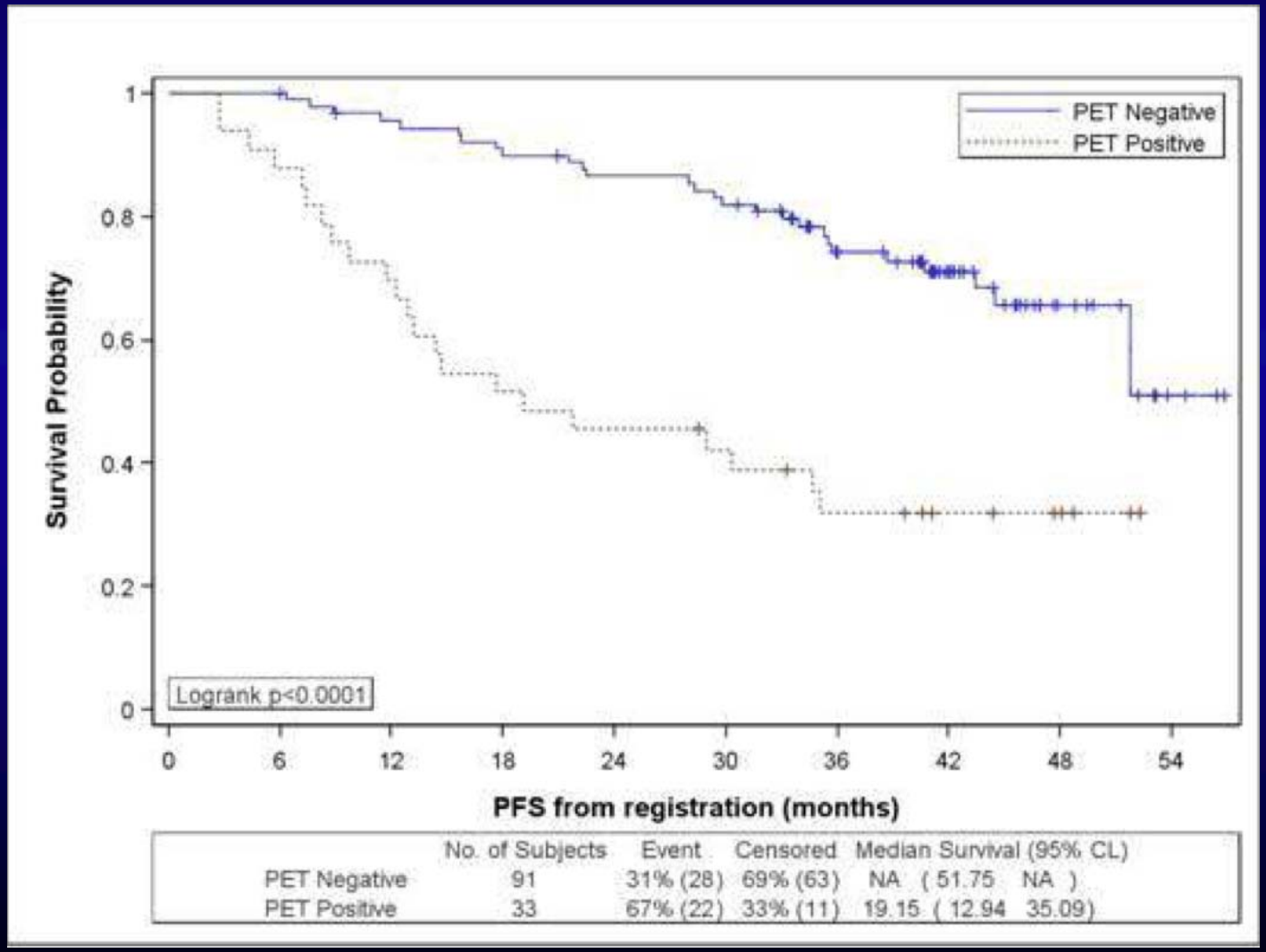
FDG PET-CT after immunochemotherapy

- Abs#855: Result of FDG PET-CT Imaging After Immunochemotherapy Induction Is a Powerful and Independent Prognostic Indicator of Outcome for Patients with Follicular Lymphoma: An Analysis From the PRIMA Study
- Authors: Trotman, J et al
- Subset of patients treated on the PRIMA study
  - » 124 patients from 40 centers had a PET-CT scan at end of treatment
  - » Decision to obtain PET at discretion of PI

FDG PET-CT after immunochemotherapy

- Comparison to CT criteria (PET+)
  - 4/50 (8%) CR
  - 12/39 (31%) CRu
  - 11/37 (41%) PR
  - 2/3 (67%) SD
  - 4/5 (80%) PD
- 73/91 of PET- patients were CR/CRu

FDG PET-CT after immunochemotherapy



FDG PET-CT after immunochemotherapy

- PET had better predictive value compared to conventional response
- In the PET + group, no difference between the CR/CRu and PR
- In patients receiving rituximab maintenance, the PET + remained predictive for 3y PFS
  - PET+ 27%
  - PET- 69%