

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

Liat Vidal<sup>1,2</sup>, Anat Gaffer-Gvili<sup>1,2</sup>, Gilles Salles<sup>3</sup>, Sami Bousseta<sup>4</sup>, Bernice Oberman<sup>5</sup>, Carmit Rubin<sup>5</sup>, Marinus H.J. van Oers<sup>6</sup>, Catherine Fortpied<sup>7</sup>, Ruth Pettengell<sup>8</sup>, Peter Dreger<sup>9</sup>, Mathias Witzens-Harig<sup>10</sup>, Umberto Vitolo<sup>11</sup>, Andrea Evangelista<sup>11</sup>, Maria Gomes da Silva<sup>12</sup>, Hailun Li<sup>13</sup>, Laurence Freedman<sup>5</sup>, Thomas M Habermann<sup>14</sup>, Ofer Shpilberg<sup>15</sup>

<sup>1</sup>Sackler Faculty of Medicine, Tel Aviv University, Israel; <sup>2</sup>Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Israel; <sup>3</sup>Centre Hospitalier Lyon-Sud, Pierre-Benite, France; <sup>4</sup>Biostatistics department, LYSARC, Pierre-Benite, France; <sup>5</sup>Sheba Medical Center, Gertner Institute for Epidemiology and Health Policy Research, Israel; <sup>6</sup>EORTC Lymphoma Group/ HOVON, Academic Medical Center, Amsterdam, Netherlands; <sup>7</sup>EORTC, Brussels, Belgium; <sup>8</sup>Department of Haematology, St. George's University of London, United Kingdom; <sup>9</sup>Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; <sup>10</sup>Department of Hematology, University of Heidelberg Hospital, Heidelberg, Germany; <sup>11</sup>Città della Salute e della Scienza Hospital and University, on behalf of FIL, Turin, Italy; <sup>12</sup>Portuguese Institute of Oncology, Lisbon, Portugal; <sup>13</sup>Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MS; <sup>14</sup>Division of Hematology, Mayo Clinic, Rochester, MN; <sup>15</sup>Assuta Medical Center, Tel Aviv, Israel

## OBJECTIVES

In a previous systematic review and meta-analysis of summary (aggregate) data we demonstrated an overall survival (OS) benefit of MR for patients with relapsed or refractory FL and an improved progression free survival (PFS) in all FL patients. To identify sub-groups who may benefit from MR and to evaluate factors that interact with the effect of MR we conducted an international IPD (raw data) meta-analysis of MR for patients with FL.

## METHODS

A systematic review and meta-analysis of RCTs that compared MR to no treatment or other treatment, for patients with FL. In 2012 we searched *The Cochrane Library*, MEDLINE, conference proceedings, and databases of ongoing trials for eligible trials with an update in June 2014.

The investigators of 11 trials that fulfilled inclusion criteria were invited to cooperate. Seven study groups participated in this collaborative project and contributed IPD.

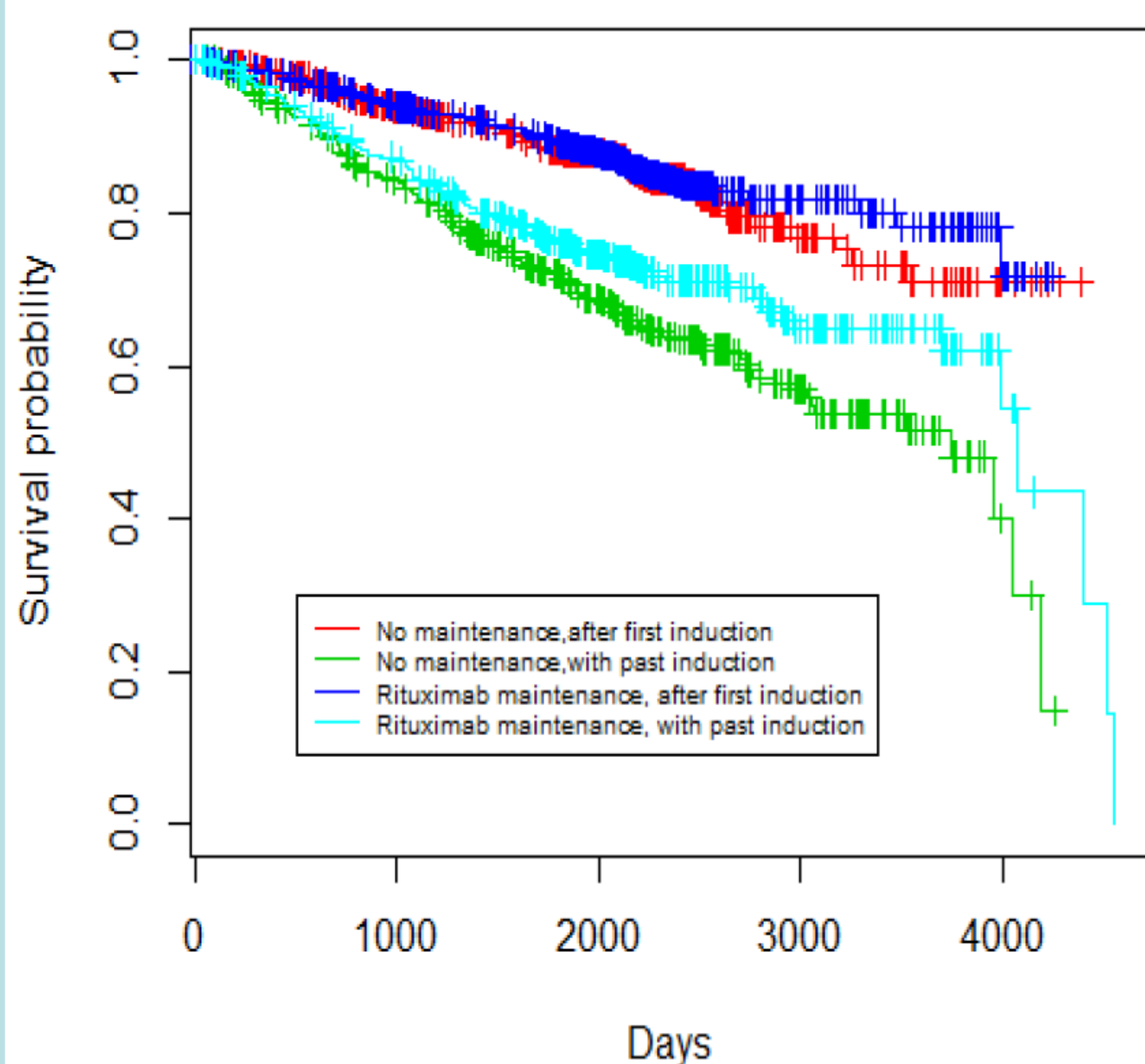
We examined the effect of MR on OS, adjusting for patients, disease and treatment characteristics in a series of Cox regression analyses stratified by trial. Sub-analyses on different groups of patients were also performed.

## RESULTS

2317 patients randomized in 7 trials of MR were included in the analysis. Patients treated with MR had an improved PFS compared to the observation group (HR 0.57, 95% CI 0.51-0.64). Being female and achieving complete response (CR) were associated with a lower risk of progression or death, whereas a higher FLIPI, CVP and a past induction were associated with a higher risk.

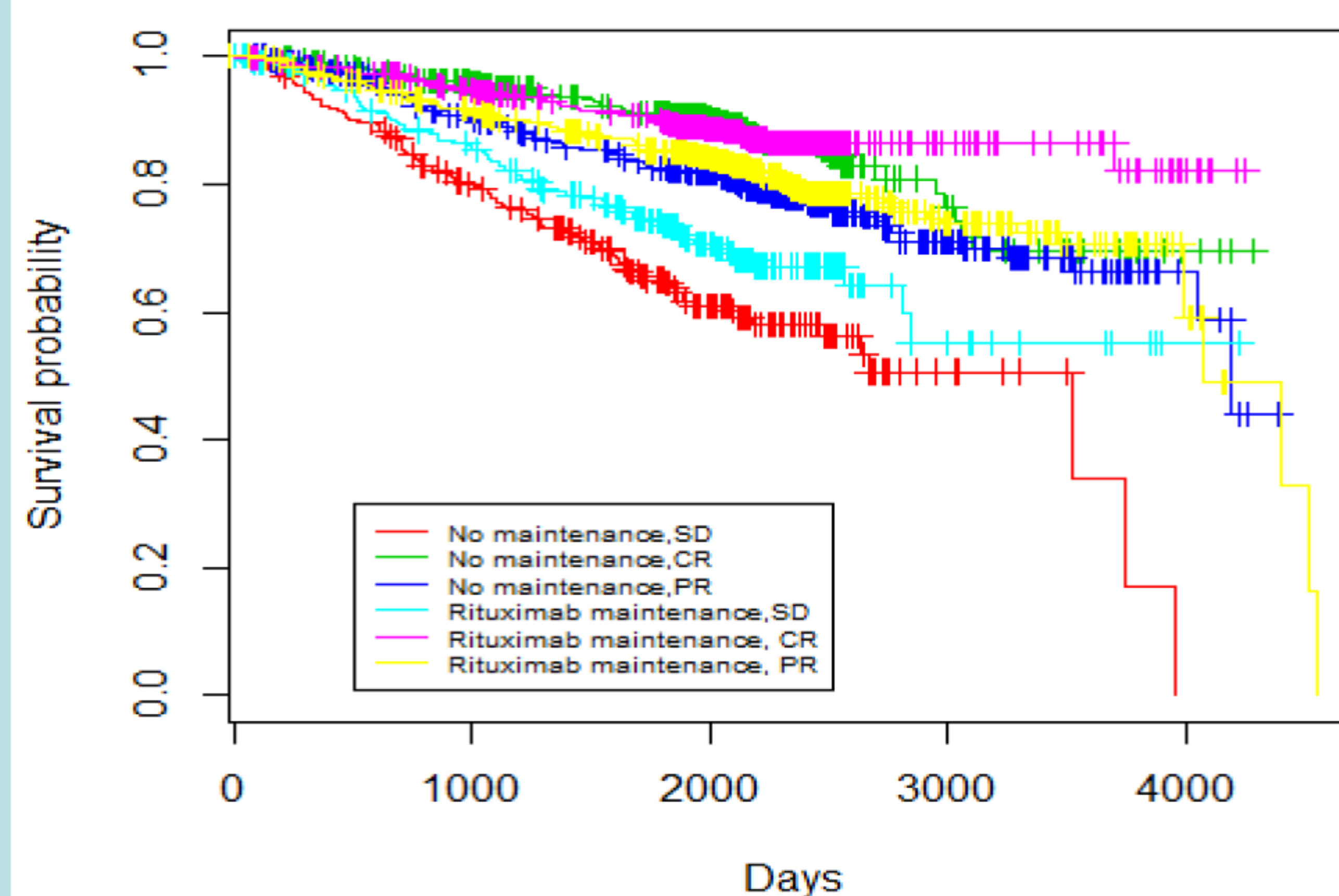
For OS, the HR for MR was 0.79 (95% CI 0.66-0.96). The MR effect remained statistically significant after adjusting for sex, age, past induction, type of chemotherapy and response.

**No significant interaction between any variable and the effect of MR was found.**



Kaplan-Meier curve of OS with and without rituximab maintenance by treatment line

OS with and without rituximab maintenance by depth of response



### Multivariate model

Variable	HR	95% CI	P-value
Female vs. male	0.73	0.61-0.99	0.0012
Age >=60 vs. younger	1.99	1.65-2.42	<0.0001
After ≥2 vs. first induction	1.48	0.79-2.77	0.22
Rituximab maintenance vs. no maintenance	0.79	0.66-0.96	0.017

No interaction between number of inductions and MR

## CONCLUSIONS

Based on individual patient data an improved PFS and OS with MR therapy for patients with FL was shown. This effect was robust for important disease and patient's characteristics including treatment line, the chemotherapy regimen, and response.

