Updated 6 Year Follow-Up Of The PRIMA Study Confirms The Benefit Of 2-Year Rituximab Maintenance In Follicular Lymphoma Patients Responding To Frontline Immunochemotherapy


From: France, Australia, Belgium, Spain, Czech Republic, Denmark, Finland, the Netherlands, Thailand, Portugal, UK, Argentina and others PRIMA investigators

An intergroup study coordinated by Lysa
PRIMA: study design

**INDUCTION**

- 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
- PD/SD
- off study

**MAINTENANCE**

- Rituximab maintenance 375 mg/m² every 8 weeks for 2 years
- Random 1:1
- Observation

* 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
Patient disposition

Induction

Patients registered: N = 1217

Patients evaluable (N = 1202)*

R-CHOP
N = 885
Randomized
N = 769

R-CVP
N = 272
Randomized
N = 222

R-FCM
N = 45
Randomized
N = 28

Maintenance

Patients randomized: N = 1018‡

Observation
N = 513

Rituximab
N = 505

* 15 pts in 3 sites closed prematurely

† 9 pts did not receive chemo

‡ 147 pts withdrew during or at the end of induction (failure to respond; toxicity)

‡ 28 pts failed to be randomized

† 1 pt died during the randomization process
PRIMA: Primary endpoint (PFS): 3 years

Stratified HR = 0.55
95% CI: 0.44–0.68
p < 0.0001

Patients at risk

<table>
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<tr>
<th>Time (months)</th>
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<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
<th>60</th>
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<td>472</td>
<td>445</td>
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<td>387</td>
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<tr>
<td>6</td>
<td>513</td>
<td>469</td>
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Salles et al., Lancet 2011
Aim of the updated analysis

• Is the initial benefit achieved with rituximab maintenance for PFS and time to next treatment (TNLT) extended with 3 additional years of follow-up?

• How do initial patients characteristics and induction treatment impact on PFS?

• Is there an overall survival benefit with prolonged follow-up?

• What is the response rate to second line treatment after progression?

• What is the incidence of histological transformation at relapse?
Methodology

• All centers participated to this follow-up

• Pattern of relapses, information about biopsy, initiation of new treatment, regimen used, … were all collected on CRF and monitored.

• Patients were registered in PRIMA from Dec 2004 until April 2007 (27 months):
  – Clinical cut-off for this analysis = 31st January 2013
  – Median time from randomization = 73 months
PRIMA 6 years follow-up
Progression free survival from randomization

PFS according to maintenance (ITT patients)
With Number of Subjects at Risk and 95% Confidence Limits

- Censored
Logrank p = 0.001

HR = 0.57
P < 0.001

6 years = 59.2%
6 years = 42.7%

<table>
<thead>
<tr>
<th>PFS delay</th>
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<tbody>
<tr>
<td>513</td>
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<tr>
<td>458</td>
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<tr>
<td>416</td>
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<tr>
<td>397</td>
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<td>351</td>
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<tr>
<td>328</td>
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<tr>
<td>300</td>
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<tr>
<td>188</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>HR</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.57</td>
<td>56.5% (290)</td>
<td>43.5% (223)</td>
<td>48.5 (41.2 : 59.4)</td>
</tr>
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</tr>
</tbody>
</table>

Median follow-up since randomization: 73 months
PRIMA 6 years follow-up
Time to next treatment

TTNT according to maintenance (ITT patients)
With Number of Subjects at Risk and 95% Confidence Limits

HR= 0.625
P<.0001

Median follow-up since randomization: 73 months
PRIMA 6 years follow-up
Overall survival

OS according to maintenance (ITT patients)
With Number of Subjects at Risk and 95% Confidence Limits

6 years = 88.7%
6 years = 87.4%

HR= 1.027
P= .885

Median follow-up since randomization: 73 months
PRIMA 6 years follow-up
Progression free survival from randomization

R-CHOP induction

HR = 0.538
P < .0001

R-CVP induction

HR = 0.697
P = .05

Median follow-up since randomization: 73 months
PRIMA 6 years follow-up
Progression free survival from randomization

**FLIPI low**

- **PFS according to FLIPI (ITT patients)** with number of subjects at risk and 95% Confidence Limits
- **PFS according to maintenance arm stratified on FLIPI (ITT patients) Low risk disease (FLIPI 0-1)** With number of subjects at risk and 95% Confidence Limits

HR = 0.496
P = .0052

60% vs 76%

**Median follow-up since randomization:** 73 months
PRIMA 6 years follow-up
Progression free survival from randomization

FLIPI intermediate

PFS according to maintenance arm stratified on FLIPI(ITT patients) (Intermediate risk disease (FLIPI 2))
With Number of Subjects at Risk and 95% Confidence Limits

Survival Probability

HR = 0.499
P < .0001

65%

43%

Median follow-up since randomization: 73 months

FLIPI high

PFS according to maintenance arm stratified on FLIPI(ITT patients) (High risk disease (FLIPI >3.0))
With Number of Subjects at Risk and 95% Confidence Limits

Survival Probability

HR = 0.663
P = .0013

49%

36%

Reference is observation
**PRIMA 6 years follow-up**  
Progression free survival from randomization

Effect of rituximab maintenance according to the response status after induction

<table>
<thead>
<tr>
<th>Response status at the end of induction</th>
<th>Observation</th>
<th>Rituximab Maintenance</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>51%</td>
<td>64.9%</td>
<td>0.520 0.363-0.744</td>
</tr>
<tr>
<td>Unconfirmed CR</td>
<td>43.4%</td>
<td>57.4%</td>
<td>0.635 0.446-0.905</td>
</tr>
<tr>
<td>Partial Response</td>
<td>34.2%</td>
<td>56.2%</td>
<td>0.449 0.298-0.676</td>
</tr>
</tbody>
</table>

Median follow-up since randomization: 73 months
### PRIMA 6 years follow-up
Second line treatment

<table>
<thead>
<tr>
<th></th>
<th>Observation 518 pts</th>
<th>Rituximab 505 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts with progression</strong></td>
<td>278     54%</td>
<td>186     36.8%</td>
</tr>
<tr>
<td><strong>Treated at time of progression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- - - With rituximab</td>
<td>170     61%</td>
<td>117     63%</td>
</tr>
<tr>
<td>- - - Without rituximab</td>
<td>143     84%</td>
<td>78      67%</td>
</tr>
<tr>
<td>- - - Without rituximab</td>
<td>27      16%</td>
<td>39      33%</td>
</tr>
</tbody>
</table>

Detailed treatments are being further analyzed
PRIMA 6 years follow-up
Response to second line treatment

Responses reported by the investigators (percentage)
PRIMA = 6 years follow-up
Rate of histological transformation

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Rituximab Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>278</td>
<td>186</td>
</tr>
<tr>
<td>With pathology</td>
<td>114</td>
<td>80</td>
</tr>
<tr>
<td>documentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transformed histology</td>
<td>24 (21%)</td>
<td>16 (20%)</td>
</tr>
</tbody>
</table>
PRIMA = 6 years follow-up
Relevant causes of death

<table>
<thead>
<tr>
<th></th>
<th>OBSERVATION 58 / 518</th>
<th>RITUXIMAB MAINTENANCE 59 / 505</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>2nd malignancies</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>(MDS / AML)</td>
<td>(5)</td>
<td>(2)</td>
</tr>
<tr>
<td>Infections *</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>18</td>
</tr>
</tbody>
</table>

* 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 aspergilosis in the observation arm.
Summary

- Durability of rituximab maintenance benefit for PFS and TNLT; consistent across patients with different FLIPI scores, chemo induction, and response to chemo induction;
- No new safety signals were detected;
- No survival benefit was observed, with similar nb of patients dying from lymphoma in both arms;
- Response to second line therapy needs to be improved in both study arms.

With ~ 60% of patients without disease progression at 6 years, PRIMA updated results “challenge the view that all patients will ultimately relapse”¹ and comfort this strategy as a standard of care for patients with FL in need of cytotoxic therapy.

1. Press O et al., JCO 2012
Acknowledgements

- All the investigators and their staff from 223 centers in 25 countries

- Other cooperative groups in Australia/New Zealand, Spain, Czech Republic, UK and the Netherlands and several key investigators in various countries that made this study possible

- The GELA/LYSA and GELARC/LYSARC teams for organization, monitoring, data cleaning and statistics

- Pathology review: L Xerri, N Brousse, D Canioni, F Charlotte, C Chassagne-Clément, P Dartigues, B Fabiani, L Deleval, E Campos, D DeJong

- DMSC members: J Armitage, D Hasenclever, M Ghielmini

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