Newly Diagnosed and Relapsed Follicular Lymphoma: Diagnosis and Treatment

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Koç University  Hematology Department
Follicular Lymphoma

• Follicular lymphoma (FL) is the second most common form of NHL in the United States and Western Europe.
  – 35% of all NHLs and 70% of indolent lymphomas.
• Median age at diagnosis: 65 years


*Includes PMLBCL.
Follicular Lymphoma

- Despite most FL patients present with asymptomatic lymphadenopathy, the majority are diagnosed with disseminated disease.
  - Bone marrow involvement 70%.

- B symptoms < 20%, increased LDH <20%.

- Risk of transformation into an aggressive lymphoma (eg, DLBCL) 2% - 3% per year.

Pathogenesis

- FLs are malignant counterparts of normal germinal center B-cells.

- Heterogeneous group of cells (including macrophages, follicular dendritic cells, fibroblasts, endothelial cells and T lymphocytes) form a disease-specific microenvironment.

Pathogenesis

Overview of common mechanisms for the pathogenesis of follicular lymphoma

1. **Promoter**
   - 18q21
   - Translocation placing BCL-2 gene under the control of a new promoter (~90 percent)

2. **Aberrant BCL-2 expression in germinal center B cells**

3. **Encodes integral membrane protein BCL-2**

4. **Anti-apoptotic factors prevent caspase activation**

5. **Tumor microenvironment**

6. **Additional genetic lesions**

7. **Prolonged cell survival**

The molecular pathogenesis of follicular lymphoma (FL) is a complex, multistep process leading to the replication of a malignancy clone of germinal B cell origin. While some steps in this pathway have been elucidated, many remain unknown. The majority of FL tumors demonstrate translocations or mutations that result in the increased expression of the B cell lymphoma 2 (BCL-2) gene. Approximately 85 percent demonstrate a translocation between the long arm of chromosome 18 and the immunoglobulin heavy chain gene on chromosome 14, resulting in the t(14;18)(q32;q21). BCL-2 is an anti-apoptotic factor that prevents caspase activation, thereby resulting in prolonged cell survival. Overexpression of BCL-2 is not sufficient to cause FL, and additional factors, such as the tumor microenvironment and other genetic lesions, likely contribute to the pathogenesis.
Pathogenesis

• Additional genetic alterations such as gains, losses or mutations of genes such as MLL2, EPHA7, TNFRSF14, BCL6, CREBBP and EZH2 have been reported in almost all cases of FL.

Tumor Grading in FL: WHO Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤5 centroblasts/HPF</td>
</tr>
<tr>
<td>2</td>
<td>6-15 centroblasts/HPF</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;15 centroblasts/HPF; centroblasts with intermingled centrocytes</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;15 blasts/HPF; pure sheets of centroblasts</td>
</tr>
</tbody>
</table>

• Grades 1, 2 and 3A typically display an indolent clinical course.

• Grade 3B histologically resembles DLBCL, reveals different molecular characteristics and is clinically more aggressive.

Staging in FL: Revised Ann Arbor Staging System

- Stage I, II FL is commonly considered limited disease and stage III, IV advanced disease.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involved Body Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 LN region or 1 extranodal site without nodal involvement</td>
</tr>
<tr>
<td>II</td>
<td>≥ 2 LN regions on the same side of the diaphragm or ≥ 1 LN regions plus 1 extralymphatic site contiguous or proximal to affected nodal region on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>LN regions on both sides of the diaphragm or LN regions above the diaphragm with spleen involvement and/or optional extranodal site contiguous or proximal to affected nodal region</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated or diffuse extranodal organ involvement in addition to LN sites</td>
</tr>
</tbody>
</table>

FLIPI: Follicular Lymphoma International Prognostic Index

**FLIPI Criteria:** LN sites (≤ 4 vs > 4), LDH (≤ vs > ULN), age (≤ 60 vs > 60 yrs), Ann Arbor stage (I/II vs III/IV), Hb (≥ 12 vs < 12 g/dL)

<table>
<thead>
<tr>
<th>FLIPI Risk Group</th>
<th>No. Risk Factors</th>
<th>5-Yr OS,* %</th>
<th>10-Yr OS,* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>91</td>
<td>71</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>78</td>
<td>51</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3</td>
<td>53</td>
<td>36</td>
</tr>
</tbody>
</table>

**FLIPI-2 Criteria:** age (≤ 60 vs > 60 years), Hb (≥ 12 vs < 12 g/dL), serum β-2 microglobulin (≤ vs > ULN), BM involvement (Y vs N), > 6 cm greatest diameter of largest involved LN (Y vs N)

<table>
<thead>
<tr>
<th>FLIPI-2 Risk Group</th>
<th>No. Risk Factors</th>
<th>3-Yr PFS,* %</th>
<th>5-Yr PFS,* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>High</td>
<td>3-5</td>
<td>51</td>
<td>19</td>
</tr>
</tbody>
</table>

* FLIPI survival data from pre-rituximab era.

m7 FLIPI

- FLIPI *plus*
  - Mutation status of 7 genes (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD)
  - ECOG PS

- 5-year failure – free survival
  - Positive predictive value: 72%
  - Negative predictive value: 68%

- Compared with FLIPI
  - HR 2.18, 95% CI, 1.21-3.92

For high-tumor burden FL, GELF criteria include at least 1 of the following:
- Any mass ≥ 7 cm in diameter
- Involvement of ≥ 3 LNs, each ≥ 3 cm in diameter
- Presence of B symptoms
- Splenomegaly
- Compression syndrome (ureteral, orbital, GI)
- Ascites or pleural effusion
- Elevated LDH or β-2 microglobulin
- Cytopenias
- Leukemia (> 5.0 x 10^9/L circulating malignant cells)

Initial Treatment of FL

Stage I and II
Stage I and II FL Treatment

- Stage I and II account for about 15–20% of FL and the median survival ranges up to 25 years from diagnosis.

- Radiation therapy is generally the treatment of choice for limited stage FL.
Radiotherapy

- Stage I-II, 106 patients
- %76 RT, %24 RT/CT
- 15-year overall survival 62%, median survival time 19 years

- Stage I-II, 6568 patients
- %34 were initially treated with RT
- DSS at 5 (90 vs 81%), 10 (79 vs 66%), 15 (68 vs 57%) and 20 (63 vs 51%) years were high in pts who received initial RT.

Radiotherapy

- N: 361 indolent NHL (predominantly follicular NHL and marginal zone lymphoma)
- 40-45Gy vs 24Gy
- No difference in ORR (p=0.72), PFS and OS.


- 4 Gy (315 sites) vs 24 Gy (299 sites)
- After a median follow-up of 26 months, 91 local progressions (21 in the 24 Gy group and 70 in the 4 Gy group) had been recorded.

Radiotherapy is not considered standard therapy in the majority of cases...

- 471 stage I FL (206 patients underwent rigorous staging)
- < 1/3 patients were actually treated with RT alone: R-chemo 28%, RT 27%, observation 17%, systemic therapy + RT 13%, rituximab monotherapy 12%, and other 3%.
Watch & Wait

• At a median follow-up of 7.2 years, 27 patients (63%) had not been treated.

• If significant morbidity is possible from RT based on disease location (e.g. cervical: sicca syndrome, hypothyroidism; abdominal: mucositis, myeloablative suppression) or if the patient chooses to not receive radiation, watch and wait may be a reasonable alternative (esp. for stage II pts).
Stage I and II FL Treatment

Low tumour burden

Stage I/II

Radiotherapy (involved field) 24 Gy
In selected cases, consider watchful waiting or rituximab monotherapy

Stage III/IV

Watch and wait
In selected cases, consider rituximab monotherapy
Initial Treatment of Follicular Lymphoma

Stage III and IV
Stage III and IV FL Treatment

- Majority (80%) of FL patients have advanced stage disease at diagnosis.
- Despite the improved outcome, most patients still experience disease relapse at a median time of 1.5–5 years.
- A standard first line therapy for advanced stage FL has not yet been defined.
  - When to start therapy?
  - Which regimen to choose?

Stage III and IV FL Treatment

Low Tumor Burden
‘Observation’ vs ‘Immediate Treatment’

- **Observation vs ProMACE-MOPP**
  - 89 patients
  - Young, 1988

- **Observation vs Prednimustine**
  - 130 patients
  - Brice, 1997

- **Observation vs Chlorambucil**
  - 309 patients
  - Ardeshna, 2003
Can rituximab change this approach in early treatment in asymptomatic patients?
Stage III and IV FL: Low Tumor Burden

Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial

Kirit M Ardesna, Wendi Qian, Paul Smith, Nivette Braganca, Lisa Lowry, Pip Patrick, June Warden, Lindsey Stevens, Christopher FE Pocock, Fiona Miall, David Cunningham, John Davies, Andrew Jack, Richard Stephens, Ian Walewski, Burhan Ferhanoglu, Ken Bradstock, David CLinch

Patients with asymptomatic stage II, III, IV FL with low tumor burden (N = 463)

- Stratified by age, grade, stage, and institution
- Mo 3
  - Rituximab 375 mg/m² wkly for 4 wks (n = 192)
- Mo 7 CT scan*
  - Rituximab 375 mg/m² every 2 mos for 2 yrs
- Mo 13 CT scan if clinical CR*
  - Regular clinic visits
- Mo 25 CT scan*
  - Continued follow up

*If CT shows CR, bone marrow biopsied for restaging.
‘Rituximab’ vs ‘Watch and Wait’

Figure 3: Kaplan-Meier curves for the 252 patients randomly assigned in the initial three-arm study
(A) Time to start of new treatment, (B) progression-free survival, (C) overall survival, and (D) time to histological transformation. HR = hazard ratio.
QoL Results: Rituximab Induction Can be Delivered Without a Reduction in QoL

- Patients in the maintenance rituximab group;
  - felt more in control of their disease (Mental Adjustment to Cancer scale score) \( (p=0.0004) \)
  - were less anxious about interacting with the medical team (Illness Coping Style score) \( (p=0.0012) \)
  - were less worried about needing treatment \( (p=0.0037) \).

Rituximab monotherapy should be considered as a treatment option for patients with asymptomatic, advanced-stage, low-tumour-burden FL.
Stage III and IV FL: Low Tumor Burden

In low–tumor burden FL, a re-treatment strategy uses less R while providing disease control comparable to that achieved with a maintenance strategy.
Stage III and IV FL Treatment: Low Tumor Burden

Low tumour burden

Stage I/II
- Radiotherapy (involved field) 24 Gy
- In selected cases, consider watchful waiting or rituximab monotherapy

Stage III/IV
- Watch and wait
- In selected cases, consider rituximab monotherapy
Stage III-IV FL Treatment

High Tumor Burden
Rituksimab has changed the outcome of FL patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus</td>
<td>CVP vs CVP-R</td>
<td>Improved</td>
</tr>
<tr>
<td>Hiddeman</td>
<td>CHOP vs CHOP-R</td>
<td>Improved</td>
</tr>
<tr>
<td>Herold</td>
<td>MCP vs MCP-R</td>
<td>Improved</td>
</tr>
<tr>
<td>Salles</td>
<td>CHVP vs CHVP-R (+ interferon)</td>
<td>Improved (High 3-5 FLIPI)</td>
</tr>
</tbody>
</table>

Hiddeman W. Blood 2005; 106.
Salles G. Blood 2008; 112.
StiL NHL 1-2003: BR vs R-CHOP in Newly Diagnosed FL

- Randomized, open-label phase III noninferiority trial

**Stratified by histological subtype**

Treatment-naive patients with MCL or indolent CD20-positive lymphoma, including FL (N = 549)

- BR (n = 274*)
- R-CHOP (n = 275†)

* median follow up: 45 mos

BR: bendamustine 90 mg/m² on Days 1-2; rituximab 375 mg/m² on Day 1; 4-wk cycles for 6 cycles max.

R-CHOP: cyclophosphamide 750 mg/m² on Day 1; doxorubicin 50 mg/m² on Day 1; vincristine 1.4 mg/m² on Day 1; prednisone 100 mg on Days 1-5; rituximab 375 mg/m² on Day 1; 3-wk cycles for 6 cycles max. No maintenance or consolidation treatment given.

- Primary endpoint: noninferiority of BR vs R-CHOP for PFS (decrease < 10% at 3 yrs)
- Secondary endpoints: response rate, time to next treatment, EFS, OS, safety

StiL NHL 1-2003: PFS in FL

- No OS difference between treatment arms (for both, median OS: NR)

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-CHOP</td>
<td>B-R</td>
<td>R-CHOP</td>
<td>B-R</td>
<td>R-CHOP</td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>13 (5%)</td>
<td>52 (19%)</td>
<td>39 (15%)</td>
<td>80 (30%)</td>
<td>110 (44%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (2%)</td>
<td>30 (11%)</td>
<td>19 (8%)</td>
<td>61 (23%)</td>
<td>70 (28%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>12 (5%)</td>
<td>14 (5%)</td>
<td>72 (29%)</td>
<td>38 (14%)</td>
<td>87 (35%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>115 (46%)</td>
<td>102 (38%)</td>
<td>84 (33%)</td>
<td>44 (16%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>89 (35%)</td>
<td>104 (39%)</td>
<td>20 (8%)</td>
<td>19 (7%)</td>
<td>11 (4%)</td>
</tr>
</tbody>
</table>

B-R = bendamustine plus rituximab. R-CHOP = CHOP plus rituximab. *p<0.0001 between groups.

Table 3: Haematological toxic events in patients receiving at least one dose of study treatment
BRIGHT: BR vs R-CHOP or R-CVP in Newly Diagnosed FL

- Open-label, randomized phase III noninferiority study

Stratified by preassigned tx, lymphoma type

Treatment-naïve patients with MCL or iNHL, including FL (N = 447)

- Primary endpoint: CR rate
- Secondary endpoints: PFS, EFS, DoR, OS

BRIGHT 5-Yr Follow Up: PFS in iNHL

### BRIGHT 5-Yr Follow Up: Patient Mortality

<table>
<thead>
<tr>
<th>Reported Cause of Mortality, n</th>
<th>BR (n = 224)</th>
<th>R-CHOP/R-CVP (n = 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>• PD</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>• Other,* reason not reported</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>• Cardiovascular</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>• Respiratory</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>• Infection</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>• Secondary malignancy†</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Deaths within 100 d of last dose</td>
<td>4†</td>
<td>3§</td>
</tr>
</tbody>
</table>

*Stem cell transplant complications. †Excluding transformed NHL. ‡Pneumonia, n = 2; cardiac arrest, n = 1; respiratory failure, n = 1. §Septic shock, n = 1; PD, n = 2.

- Incidence of secondary malignancies was found to be higher with BR (19%) than R-CHOP/R-CVP (11%) (P= 0.022).

FOLL05: R-CVP vs R-CHOP vs R-FM in Newly Diagnosed Advanced-Stage FL

- Prospective, multicenter, randomized, open-label phase III trial

  Stratified by FLIPI (0-2 vs 3-5)

  Adult patients with untreated Ann Arbor stage II-IV FL, ECOG PS 0-2, and no CNS involvement or prior malignancy (N = 534)

  R-CVP (n = 178)

  R-CHOP (n = 178)

  R-FM (n = 178)

  Follow up: 84 mos (1-119 mos)

  Rituximab 375 mg/m² Day 1 x 8 cycles; CVP x 8, CHOP x 6, FM x 6.
  No maintenance allowed.

- Primary endpoint: TTF
- Secondary endpoints: PFS, OS, cause-specific mortality, cumulative incidence of second malignancies, late AEs

FOLL05: Outcomes

- Grade 3/4 neutropenia: 64% with R-FM, 50% with R-CHOP, and 28% with R-CVP
- 23 second malignancies were registered during follow-up: four in R-CVP, five in R-CHOP, and 14 in R-FM.

Obinutuzumab is a type II anti-CD20 mAb

- Specific properties in comparison with rituximab\textsuperscript{1,2}
  - glycoengineered type II anti-CD20 mAb
  - enhanced direct cell killing
  - enhanced antibody-dependent cellular phagocytosis
  - enhanced antibody-dependent cellular cytotoxicity

mAb, monoclonal antibody

GALLIUM: Frontline Obinutuzumab-Based vs Rituximab-Based Chemoimmunotherapy

- International randomized, open-label phase III study

**Induction**

- Obinutuzumab\(^1\) + CHOP, CVP, or Bendamustine\(^\text{II}\) (n = 601)
- Rituximab\(^1\) + CHOP, CVP, or Bendamustine\(^\text{II}\) (n = 601)

**Maintenance**

- Obinutuzumab\(^\text{I}\) (n = 593)
- Rituximab\(^\text{I}\) (n = 527)

**For 2 yrs or until PD**

- Median f/u: 34.5 mos (range: 0-54.5)

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**Stratified by chemotherapy, FLIPI, and geographic region**

- Adult patients with untreated CD20+ iNHL (grade 1-3a)\*; stage III/IV or stage II bulky disease (≥ 7 cm); ECOG PS 0-2 (N = 1202)

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*All data presented for patients with FL, although study also enrolled MZL patients (randomized separately). \(^1\)Obinutuzumab: 1000 mg IV, Days 1, 8, 15 of cycle 1 and Day 1 of cycles 2-8 (Q3W) or cycles 2-6 (Q4W). \(^\text{II}\)Rituximab: 375 mg/m\(^2\) IV on Day 1 of cycles 1-8 (Q3W) or cycles 1-6 (Q4W). \(^\text{II}\)Obinutuzumab: 1000 mg IV every 2 mos. \(^\text{III}\)Rituximab: 375 mg/m\(^2\) IV every 2 mos. \(^\text{IV}\)CHOP: Q3W, 6 cycles; CVP: Q3W, 8 cycles; bendamustine: Q4W, 6 cycles. \(^\text{V}\)Patients with SD at EOI followed up to 2 yrs for PD.

- Primary endpoint: investigator-assessed PFS in FL patients
- Secondary endpoints: IRC-assessed PFS (confirmatory), OS, EFS, DFS, DoR, TTNT, CR/ORR at EOI (± FDG-PET), safety

GALLIUM: Investigator-Assessed PFS

- No significant difference in ORR at end of induction ($P = .33$) or OS (HR for death: 0.75; 95% CI: 0.49-1.17; $P = .21$) between arms

## GALLIUM: Adverse Events

<table>
<thead>
<tr>
<th>AE, %</th>
<th><strong>Obinutuzumab + CT</strong> (n = 595)</th>
<th><strong>Rituximab + CT</strong> (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>99.5</td>
<td>98.3</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>74.6</td>
<td>67.8</td>
</tr>
<tr>
<td>Serious</td>
<td>46.1</td>
<td>39.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infusion-related reaction</th>
<th><strong>Obinutuzumab + CT</strong> (n = 595)</th>
<th><strong>Rituximab + CT</strong> (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>68.2</td>
<td>58.5</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>12.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Serious</td>
<td>5.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibody-related reaction</th>
<th><strong>Obinutuzumab + CT</strong> (n = 595)</th>
<th><strong>Rituximab + CT</strong> (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>59.3</td>
<td>48.9</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>10.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Serious</td>
<td>4.7</td>
<td>2.0</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>AE, %</th>
<th><strong>Obinutuzumab + CT</strong> (n = 595)</th>
<th><strong>Rituximab + CT</strong> (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>50.6</td>
<td>45.1</td>
</tr>
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<td>Grade 3-5</td>
<td>45.9</td>
<td>39.5</td>
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<tr>
<td>Serious</td>
<td>8.4</td>
<td>7.4</td>
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<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th><strong>Obinutuzumab + CT</strong> (n = 595)</th>
<th><strong>Rituximab + CT</strong> (n = 597)</th>
</tr>
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<tbody>
<tr>
<td>Any grade</td>
<td>11.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>6.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Serious</td>
<td>0.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second neoplasm</th>
<th><strong>Obinutuzumab + CT</strong> (n = 595)</th>
<th><strong>Rituximab + CT</strong> (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>7.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>4.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Serious</td>
<td>5.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>
GALLIUM: Nonrelapse-Related Fatal AEs

- Nonrelapse-related fatal AEs more common in recipients of bendamustine vs CHOP or CVP

SAKK 35/98 Trial: Single Agent Rituximab in FL

*FL pre-treated and untreated in need of treatment*

- **n = 202**
  - FL
    - (n = 151)
      - Randomizasyon
      - 375 mg/m²/wk x 4
      - SD, PR, CR
        - (n = 151)
      - PD excluded
  - 375 mg/m²/2month x 4
- **Standard treatment**
- **Prolonged treatment**
SAKK 35/98 Trial: Single Agent Rituximab in FL

- At a median follow-up of 9.5 years, median event-free survival (EFS) was 13 months for the observation and 24 months for the prolonged R maintenance arm (P < .001).
- At 8 years, 45% were still in remission with the additional R maintenance.
PRIMA: Rituximab Maintenance vs Observation in Patients With FL

- Randomized controlled phase III trial

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Untreated patients with high-tumor burden FL → Chemoimmunotherapy with R-CHOP or R-CVP or R-FCM × 8 cycles → Responders+ (N = 1019) → 10-yr follow up

Stratified by response to induction, chemotherapy regimen, geographic location

Rituximab maintenance 375 mg/m² Q8W for 2 yrs (n = 505)

Observation (n = 513)

*Only patients with CR/CRu/PR randomized to maintenance therapy; 1 pt died during randomization.
```

- Primary endpoint: PFS (ITT)

PRIMA: 10-Yr OS

- 10-yr OS estimates similar for both arms

Despite the lack of OS benefit, it is noteworthy that more than half of the patients in the R arm remain free of disease progression and have not required new anti-lymphoma treatment beyond 10 years.

Non-chemo/Immunotherapy Combination
• International, open-label, randomized phase III study
  – Lenalidomide: immunomodulatory agent with MOA complementary to rituximab

Stratified by FLIPI score (0-1 vs 2 vs 3-5), age (> 60 vs ≤ 60 yrs), lesion size (> 6 vs ≤ 6 cm)

Previously untreated patients with advanced FL requiring treatment per GELF criteria (N = 1030)

• Co-primary endpoints (superiority): CR/CRu at 120 wks, PFS

*Lenalidomide dose reduced to 10 mg QD in patients who achieved CR/CRu at cycle 6, 9, or 12. †Standard dosing in slidenotes.


- Interim PFS at median follow up of 37.9 mos was similar in both arms
- PFS benefit observed across prespecified subgroups
• Secondary primary malignancies were similar between arms (7% vs 10%, respectively)
• 1 patient per arm died due to study drug

Stage III and IV FL Treatment: High Tumor Burden

High tumour burden

Stage III/IV (<65 years)
- Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP)
  - In selected cases, rituximab monotherapy
- CR/PR: Recommend rituximab maintenance (every 2 months, up to 2 years)

Stage III/IV (>65 years)
- Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) or brief chemoimmunotherapy
  - In selected cases, rituximab-chlorambucil or rituximab monotherapy
- CR/PR: Recommend rituximab maintenance (every 2 months, up to 2 years)
Relapsed FL Treatment
Relapsed FL Treatment

• New biopsy is strongly recommended to exclude transformation into an aggressive lymphoma.
  – PET/CT scan should be used to direct a biopsy to enhance the diagnostic yield.
Relapsed FL Treatment

- **Low tumour burden**
  - Watchful waiting (asymptomatic patients)
  - Rituximab monotherapy (symptomatic patients)

- **High tumour burden, second-line therapy options**
  - Bendamustine-based regimens (single agent or with rituximab or obinutuzumab)
  - Fludarabine-based regimens (with rituximab or FCM-R)
  - Radioimmunotherapy (90yttrium–ibritumomab–tiuxetan) (esp in elderly patients with comorbidities)
GADOLIN Study

<table>
<thead>
<tr>
<th>Bendamustine doses prescribed were as high as recommended for anti-CD20 combination therapy and monotherapy, respectively(^1)</th>
</tr>
</thead>
</table>

*bAt the first data analysis cut-off (1 Sept 2014) 396 patients were enrolled and randomised; 17 additional patients were enrolled after the cut-off and therefore were not included in the original analysis* 
BOR, best overall response; CR, complete response; DFS, disease-free survival; DOR, duration of response; DSMB, data safety monitoring board; EFS, event-free survival; INHL, indolent non-Hodgkin lymphoma; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PKs, pharmacokinetics; PROs, patient-reported outcomes; R, rituximab; TTNT, time to next therapy

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**Primary endpoint** | PFS as assessed by an IRC
---|---
**Secondary endpoints** | PFS as assessed by investigator, OS, BOR, ORR, CR rate, DOR, EFS, DFS, safety, PKs, pharmacoeconomics, PROs, TTNT (exploratory endpoint) MRD response (exploratory endpoint)
**Safety plan** | Early safety interim analysis conducted by a DSMB after 20 patients received Cycle 1 to evaluate for overt excess toxicity resulting in protocol modifications, to be considered

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GAZYVA: 1000mg on Days 1, 8 and 15 of Cycle 1, Day 1 of Cycles 2–6 and every 2 months for up to 2 years

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Bendamustine: 120mg/m\(^2\)/day or 90mg/m\(^2\)/day on Days 1 and 2 of 6 x 28-day cycles

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GADOLIN Study

P < 0.001

P = 0.0061

Relapsed FL Treatment

• After second-line therapy, optional maintenance treatment with rituximab (375mg/m2 every 3 months for 2 years) can be recommended for patients in remission.
  – However, the clinical benefit of a second-line maintenance is likely very minimal if a patient progressed during or within 6 months of first-line rituximab maintenance.
PI3K Inhibitors

- ORR: 57%
- Median DOR: 12.5 months
Relapsed FL Treatment

• High-dose chemotherapy/ASCT
  – For patients with early treatment failure (progressing within 24 months of initial chemoimmunotherapy)
  – For patients with second or third remission

• Allogeneic SCT
  – For selected younger patients with later relapses of high-risk profile
  – For patients with relapse after ASCT
Positron Emission Tomography (PET)
• 2y-PFS : PET (-) vs PET (+) patients
  – Interim : 86% vs 61% (p=.0046)
  – Final : 87% vs 51% (p< .001)
• 2y-OS: PET(-) vs PET (+) patients
  – Final : 100% vs 88% (p= .0128)
Complete metabolic response status assessed by Lugano 2014 criteria

- End of induction PET results; PET(-) vs PET (+) patients
  - 2.5 y-PFS (87.8% vs 72.0%; p<0.0001) and –OS (96.9% vs 90.6%; p=0.011)(IHP 2007 criteria)
  - 2.5 y-OS (87.4% vs 54.9%; p<0.0001) and –OS (96.6% vs 84%; p<0.0001)(Lugano 2014 criteria)

Assessment of MRD
Minimal Residual Disease

LYMPHOID NEOPLASIA

Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a rituximab-intensive program

Follow-up

<table>
<thead>
<tr>
<th>Examination</th>
<th>Details</th>
<th>Year 1–2</th>
<th>Year 3–5</th>
<th>Year &gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>B symptoms</td>
<td>Every 3–4 months</td>
<td>Twice annually</td>
<td>Annually</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Particular: peripheral lymph nodes, liver, spleen</td>
<td>Every 3–4 months</td>
<td>Twice annually</td>
<td>Annually</td>
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<tr>
<td>Laboratory work-up</td>
<td>Blood and differential count</td>
<td>Every 3–4 months</td>
<td>Twice annually</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>LDH</td>
<td>Every 3–4 months</td>
<td>Twice annually</td>
<td>If progress suspected</td>
</tr>
<tr>
<td>Imaging</td>
<td>Abdominal ultrasound</td>
<td>Twice annually</td>
<td>Every 12 months</td>
<td>If progress suspected</td>
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<tr>
<td></td>
<td>CT neck, chest, abdomen, pelvis</td>
<td>Optional: 6–12 months</td>
<td>Optional: 12–24 months</td>
<td>If progress suspected</td>
</tr>
</tbody>
</table>

PET scans are not recommended for routine surveillance in patients who have achieved a CR after treatment.
Thanks for your attention