New Evidence reports on presentations given at ASCO and EHA 2010

Rituximab Maintenance Therapy and New R-Chemo Combinations in the Treatment of Follicular Lymphoma
Report on ASCO and EHA 2010 presentations

- **Rituximab maintenance in patients with follicular lymphoma after response to immunochemotherapy (PRIMA)** 

- **Rituximab in relapsed/resistant FL patients as in vivo purging prior to high-dose therapy and to maintain remission following high-dose therapy** 
  (Pettengell R, et al. ASCO 2010: Abstract 8005)

- **Treatment with MCP versus MCP plus rituximab in advanced follicular lymphoma** 
  (Herold M, et al. EHA 2010: Abstract 0575)

- **Rituximab and chlorambucil as front-line treatment for follicular lymphoma** 
  (Bassi S, et al. EHA 2010: Abstract 0277)

- **Lenalidomide plus rituximab as treatment for indolent B-cell NHL** 
  (Fowler N, et al. ASCO 2010: Abstract 8036)
Rituximab maintenance in patients with follicular lymphoma after response to immunochemotherapy (PRIMA)

The PRIMA study is a Groupe d’Étude des Lymphomes de L’Adulte (GELA)-sponsored intergroup phase III study.

PRIMA investigated the efficacy of two years of rituximab maintenance treatment in patients with follicular lymphoma responding to first-line immunochemotherapy.

Salles and colleagues presented results of the PRIMA study at ASCO 2010 and EHA 2010.1,2

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Study design

- A total of 1,217 patients were enrolled in the study from 223 centers (25 countries) between December 2004 and April 2007.
- Patients received induction treatment with R-CHOP (75%), R-CVP (22%), or R-FCM (3%).
- Eligible patients responding to induction therapy (n = 1,018) were randomized (after stratification by regimen and response to induction) to:
  - observation (n = 513);
  - rituximab maintenance (R-maintenance) treatment with 375 mg/m² of rituximab every 8 weeks for 2 years (n = 505).

Study design *(cont’d)*

**INDUCTION**

- High tumour burden untreated follicular lymphoma
- Immunotherapy: 8 x rituximab + 8 x CVP (n = 272)
- 6 x CHOP (n = 769)
- 6 x FCM (n = 28)

**MAINTENANCE**

- CR/CRu or PR
- PD/SD: off study
- Rituximab maintenance†: 375 mg/m² every 8 weeks for 2 years (n = 505)
- Observation‡ (n = 513)

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*Stratified by response after induction, regimen of chemotherapy, and geographic region
†Frequency of clinical, biological, and CT-scan assessments identical in both arms
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CR = complete response; CRu = unconfirmed complete response;
CVP = cyclophosphamide, vincristine, prednisone; FCM = fludarabine, cyclophosphamide, mitoxantrone; PD = progressive disease;
PR = partial response; SD = stable disease

Study design (cont’d)

- The primary endpoint was PFS from randomization to rituximab maintenance or observation.

- Secondary endpoints included EFS, OS, TTNLT, TTNCT, response rates at the end of maintenance, safety and toxicity, and QoL using FACT-G and EORTC scales.

- Sample size was based on a 45% increase in median PFS, with a power of 80% to detect this difference.

- Interim analysis was planned after 258 events and a full analysis after 344 events.

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Inclusion and exclusion criteria

- Patients included in the study were aged >18 years with previously untreated, histologically confirmed grades 1, 2, or 3a FL and an ECOG performance status <2.

- Patients were excluded if they had:
  - transformed to high-grade lymphoma or grade 3b FL;
  - regular corticosteroid use during the last four weeks (>20 mg/day prednisone);
  - prior or concomitant malignancies;
  - serious underlying medical conditions, poor renal, or poor hepatic function;
  - HIV infection, active HBV, or HCV infection;
  - sensitivity or allergy to murine products.
Key findings

- The primary endpoint of PFS was met at the planned interim analysis (ITT: 513 observation, 505 rituximab maintenance).
- Median follow-up was 25 months from randomization (31 months from study entry).
- Median age of patients was 56 years (range 22–87 years), and 52% were male.
- Baseline characteristics and response to induction treatment were comparable across R-maintenance and observation groups.
- A significant improvement in PFS for R-maintenance was observed (two-year PFS 82%; 95% CI: 78–86 versus 66%; 95% CI: 61–70; \( p < 0.0001 \)).
Figure 1. Progression-free survival after rituximab maintenance versus observation in FL patients


FL = follicular lymphoma
Key findings (cont’d)

- Benefits of R-maintenance were shown in all subgroups including age (<60 versus ≥60 years), FLIPI score, induction treatment, and response to induction treatment.

- A significant improvement in TNLT for R-maintenance was observed (HR 0.61; \( p = 0.0003 \)).

- Improvements in response rates for R-maintenance were observed.

- Consistent improvements in other secondary endpoints were also found, including EFS and TNCT rates.

EFS = event-free survival
FLIPI = follicular lymphoma international prognostic index
HR = hazard ratio; R= rituximab
TTNCT = time to next chemotherapy
TTNL = time to next anti-lymphoma treatment

Figure 2. Progression-free survival in age, FLIPI score, induction chemotherapy, and response to induction subgroups after rituximab maintenance versus observation

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>Hazard ratio (HR)</th>
<th>N</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td></td>
<td>1018</td>
<td>0.49</td>
<td>0.38–0.64</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60</td>
<td></td>
<td>624</td>
<td>0.45</td>
<td>0.33–0.62</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td></td>
<td>394</td>
<td>0.59</td>
<td>0.39–0.90</td>
</tr>
<tr>
<td>FLIPI score</td>
<td>≤1</td>
<td></td>
<td>216</td>
<td>0.38</td>
<td>0.19–0.77</td>
</tr>
<tr>
<td></td>
<td>= 2</td>
<td></td>
<td>370</td>
<td>0.39</td>
<td>0.25–0.61</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td></td>
<td>431</td>
<td>0.61</td>
<td>0.43–0.67</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>R-CHOP</td>
<td></td>
<td>768</td>
<td>0.43</td>
<td>0.31–0.59</td>
</tr>
<tr>
<td></td>
<td>R-CVP</td>
<td></td>
<td>222</td>
<td>0.69</td>
<td>0.44–1.08</td>
</tr>
<tr>
<td></td>
<td>R-FCM</td>
<td></td>
<td>28</td>
<td>0.51</td>
<td>0.13–2.07</td>
</tr>
<tr>
<td>Response to induction</td>
<td>CR/CReu</td>
<td></td>
<td>721</td>
<td>0.52</td>
<td>0.38–0.70</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td></td>
<td>290</td>
<td>0.45</td>
<td>0.29–0.72</td>
</tr>
</tbody>
</table>

*Non-stratified analysis
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CI = confidence interval;
CR = complete response; CReu = unconfirmed complete response; CVP = cyclophosphamide, vincristine, prednisone; FCM = fludarabine, cyclophosphamide, mitoxantrone;
FLIPI = follicular lymphoma international prognostic index; PR = partial response; R = rituximab

Figure 3. Time to next anti-lymphoma treatment after rituximab maintenance versus observation in FL patients


FL = follicular lymphoma
Table 1. Response status after rituximab maintenance versus observation in FL patients

<table>
<thead>
<tr>
<th></th>
<th>Rituximab maintenance (n = 389)* n (%)</th>
<th>Observation (n = 398)* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease (PD)</td>
<td>79 (20.3)</td>
<td>162 (40.7)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>28 (7.2)</td>
<td>29 (7.3)</td>
</tr>
<tr>
<td>Complete response (CR/CRu)</td>
<td>260 (66.8)</td>
<td>190 (47.7)</td>
</tr>
<tr>
<td>Remaining in CR/CRu</td>
<td>209 (75)†</td>
<td>153 (56)</td>
</tr>
<tr>
<td>Converting from PR/SD to CR/CRu</td>
<td>49 (45)</td>
<td>37 (30)</td>
</tr>
</tbody>
</table>

*Sixteen (16) patients were not evaluated, and 22 patients had missing data.
†Two patients were not evaluated in the rituximab maintenance arm.
Key findings (cont’d)

- Adverse events (AEs) were reported in 35% (observation) and 52% (R-maintenance) of patients.
- The most common AEs were infections (22% observation, 37% R-maintenance).
- Grade 3/4 AEs were reported in 16% (observation) and 23% (R-maintenance) of patients (neutropenia <1% versus 4%; infections <1% versus 4% in observation and R-maintenance groups, respectively).
- At the time of analysis, few patients withdrew for toxicity-related reasons during maintenance (1 patient in the observation arm, 10 patients in the R-maintenance arm).
- Most deaths occurring throughout the study were related to lymphoma (12/18 observation, 10/13 R-maintenance).

Key conclusions

- The PRIMA study demonstrates that two years of rituximab maintenance therapy after induction immunochemotherapy in previously untreated FL patients significantly improves PFS with little additional toxicity.

- Further follow-up will allow evaluation of a possible effect on overall survival.

- R-chemo followed by two years of rituximab maintenance:
  - represents a new standard of care for FL patients in need of treatment;
  - constitutes a new platform to further develop more efficient and well-tolerated strategies.

FL = follicular lymphoma
PFS = progression-free survival
R= rituximab

Rituximab in relapsed/resistant FL patients as in vivo purging prior to high-dose therapy and to maintain remission following high-dose therapy

Background

- Pettengell and colleagues conducted a study evaluating the effects of in vivo purging with rituximab and maintenance rituximab in patients with relapsed FL undergoing high-dose therapy with BEAM conditioning.

- Results of the study were presented at ASCO 2010.

ASCO = American Society of Clinical Oncology
BEAM = carmustine, etoposide, cytosine arabinoside, melphalan
FL = follicular lymphoma
Study design

- From October 1999 to April 2006, 280 of a planned 420 patients with relapsed FL were included in the study.

- Patients in first (n = 16), second (n = 222), or third remission (n = 41) who achieved either a CR (n = 83) or a very good PR (n = 196) to induction chemotherapy were included.

- Patients underwent a single randomization in a 2 x 2 design to rituximab purging (375 mg/m$^2$ weekly x 4; n = 72) and/or maintenance rituximab (375 mg/m$^2$ every 3 months for 2 years; n = 69), or no rituximab (n = 70).

- The primary objective was to evaluate the effects of in vivo purging with rituximab and maintenance rituximab on time to disease progression.

- Secondary outcomes included RRs, OS, and safety.

CR = complete response; FL = follicular lymphoma
OS = overall survival; PR = partial response
RR = response rates
Study design (cont’d)

*BEAM = carmustine, etoposide, cytosine arabinoside, melphalan; NHL = non-Hodgkin’s lymphoma; PBPC = peripheral blood progenitor cell*

Inclusion and exclusion criteria

- Patients with the following characteristics were included in the study:
  - rituximab-naïve patients with relapsed follicular NHL;
  - limited bone marrow infiltration (<25% B-lymphocytes);
  - one to two prior chemotherapy regimens;
  - CD20-positive disease;
  - CR or good PR following re-induction of chemotherapy;
  - good performance status;
  - pathological material for review and PCR;
  - no histological transformation, previous transplant, or extensive prior radiotherapy.

CR = complete response; NHL = non-Hodgkin’s lymphoma
PCR = polymerase chain reaction; PR = partial response
Key findings

Baseline characteristics and disposition

- No differences in baseline characteristics were found between treatment groups.
- A total of 87 patients withdrew from the study:
  - fifty-seven (57) patients as a result of failure to mobilize;
  - five patients due to SAEs;
  - nine patients due to lack of compliance;
  - four patients due to withdrawal of consent;
  - one patient due to withdrawal by physician;
  - nine patients for other reasons.

SAE = serious adverse event

Key findings (cont’d)

**Efficacy**

- Progression-free survival (PFS) at 5 years was 54.1% versus 48% for in vivo rituximab purging versus none (log rank PFS; \( p >0.20 \); HR 0.81, 95% CI: 0.58–1.13).

- PFS at 5 years was 59.4% versus 42.0% in patients receiving maintenance rituximab versus none (log rank PFS; \( p = 0.01 \); HR 0.65, 95% CI: 0.46–0.90).

- PFS in the ITT population is presented in Figure 1.

- The success of salvage therapy is reflected in an OS at 5 years of 80.0% (95% CI: 0.54–1.45).

- OS in the ITT population is presented in Figure 2.

CI = confidence interval; HR = hazard ratio
ITT = intent to treat; OS = overall survival
PFS = progression-free survival

Figure 1. Effect of purging and maintenance rituximab on progression-free survival in patients with relapsed follicular lymphoma


CI = confidence interval; HR = hazard ratio
Figure 2. Effect of purging and maintenance rituximab on overall survival in patients with relapsed follicular lymphoma

Key findings (cont’d)

Safety

- In total, there were 39 deaths, three of which were due to infection.

- Six SAEs occurred post-rituximab.

- Hematological values in patients receiving maintenance rituximab were lower at three months.

- No late neutropenia was reported.

SAE = serious adverse event

Table 1. Cause of death in 37 transplanted patients with relapsed follicular lymphoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NHL</th>
<th>Treatment complication</th>
<th>Second malignancy</th>
<th>Other (GvHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No purging or maintenance</td>
<td>4</td>
<td>0</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Purging/no maintenance</td>
<td>6</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>2</td>
</tr>
<tr>
<td>Maintenance/no purging</td>
<td>5</td>
<td>(1)</td>
<td>–</td>
<td>(1)</td>
</tr>
<tr>
<td>Purging and maintenance</td>
<td>3</td>
<td>1 (1)</td>
<td>(3)</td>
<td>(1)</td>
</tr>
<tr>
<td>Total</td>
<td>18  (8.9%)</td>
<td>6  (3.0%)</td>
<td>8  (3.9%)</td>
<td>7  (3.4%)</td>
</tr>
</tbody>
</table>

GvHD = graft-versus-host disease; NHL = non-Hodgkin's lymphoma
Key conclusions

- This study shows that peri-autograft, rituximab in vivo purging, and two-year maintenance rituximab post-autograft gives a superior PFS compared to no rituximab.

- To date, there appears to be no plateau on the survival curve with rituximab maintenance treatment.

- Engraftment and hematopoietic recovery were not compromised; maintenance rituximab appeared to be safe in this setting.


PFS = progression-free survival
Treatment with MCP versus MCP plus rituximab in advanced FL

Background

- A phase III study examining the efficacy and safety of MCP versus MCP plus rituximab (R-MCP) in indolent NHL and MCL patients was conducted by Herold and colleagues.

- The authors reported the sixty-month (five-year) results for the study at EHA 2010.


EHA = European Hematology Association
MCL = mantle cell lymphoma
MCP = mitoxantrone, chlorambucil, prednisolone
NHL = non-Hodgkin’s lymphoma
Study design

- Previously untreated patients with advanced stage, symptomatic CD20-positive indolent NHL and MCL (n = 358) were included in the original study.

- Only patients with FL (n = 201) were included in this analysis.

- Patients were randomized to receive either:
  - MCP (n = 96): mitoxantrone (8 mg/m^2 on days 3 and 4), chlorambucil (3 x 3 mg/m^2 on days 3–7), and prednisolone (25 mg/m^2 on days 3–7) every four weeks;
  - R-MCP (n = 105): MCP (as above) plus rituximab (375 mg/m^2 on day 1), followed by interferon maintenance treatment (3 x 4.5 million IU per week) for patients achieving a CR or PR.

CR = complete response; FL = follicular lymphoma
MCL = mantle cell lymphoma
MCP = mitoxantrone, chlorambucil, prednisolone
NHL = non-Hodgkin’s lymphoma
PR = partial response; R= rituximab

Study design (cont’d)

- Study endpoints included OR and CR rates, PFS, EFS, TTNT, OS, and toxicities.

CR = complete response; EFS = event-free survival
OR = overall response; OS = overall survival
PFS = progression-free survival; TTNT = time to next treatment

Key findings

Baseline characteristics and disposition

- Median age of patients was 60 years (range 33–78 years) in the R-MCP group and 57 years (range 31–76 years) in the MCP group.

- In the R-MCP group, 50.5% (53/105) of patients were male; in the MCP group, 38% (36/96) of patients were male.

- FLIPI subgroups included 14, 75, and 112 patients in low-, medium-, and high-risk groups, respectively.

- Baseline characteristics were comparable between groups.

FLIPI = follicular lymphoma international prognostic index
MCP = mitoxantrone, chlorambucil, prednisolone; R= rituximab

Key findings (cont’d)

**Efficacy**

- OR and CR rates were higher in the R-MCP group (OR: 92.4%; CR: 49.5%) than in the MCP group (OR: 75%; CR: 25%) ($p < 0.001$).

- PFS was 65% (median 86 months) in the R-MCP group versus 33% (median 35 months) in the MCP group ($p < 0.0001$).

- In the FLIPI intermediate-risk subgroup (FLIPI 2), PFS was 70% (median PFS not reached) in the R-MCP group versus 36% (median 37 months) in the MCP group ($p = 0.0017$).

- In the FLIPI high-risk subgroup (FLIPI 3), PFS was 63% (median 86 months) in the R-MCP group versus 30% (median 29 months) in the MCP group ($p = 0.0001$).


CR = complete response
FLIPI = follicular lymphoma international prognostic index
MCP = mitoxantrone, chlorambucil, prednisolone
OR = overall response; PFS = progression-free survival
R = rituximab
Figure 1. Progression-free survival after treatment with MCP or R-MCP in follicular lymphoma patients (median follow-up 60 months)

Key findings (cont’d)

- EFS was 62% (median 86 months) in the R-MCP group versus 30% (median 27 months) in the MCP group ($p < 0.0001$).

- In the FLIPI intermediate-risk subgroup (FLIPI 2), EFS was 69% (median not reached) in the R-MCP group versus 33% (median 29 months) in the MCP group ($p = 0.0001$).

- OS was 86% (median not reached) in the R-MCP group versus 74% (median 108 months) in the MCP group ($p = 0.028$).

- In the FLIPI intermediate-risk subgroup (FLIPI 2), OS was 93% (median not reached) in the R-MCP group versus 91% (median 89 months) in the MCP group ($p = 0.21$).

- In the FLIPI high-risk subgroup (FLIPI 3), OS was 74% (median not reached) in the R-MCP group versus 57% (median 108 months) in the MCP group ($p = 0.071$).

EFS = event-free survival
FLIPI = follicular lymphoma international prognostic index
MCP = mitoxantrone, chlorambucil, prednisolone
OS = overall survival; R = rituximab
Figure 2. Overall survival after treatment with MCP or R-MCP in follicular lymphoma patients (median follow-up 60 months)

Key conclusions

- Rituximab plus MCP was significantly superior to MCP alone in all endpoints.

- Further research is needed to determine the best rituximab-chemotherapy combination in the treatment of follicular lymphoma.

Rituximab and chlorambucil as front-line treatment for follicular lymphoma

Bassi S, et al. EHA 2010: Abstract 0277
Background

- At EHA 2010, Bassi and colleagues presented results of their study examining the combination of rituximab and chlorambucil (R-chlorambucil) in untreated follicular lymphoma (FL) patients.
Study design

- Since November 2001, 58 patients (28 male and 30 female) with FL received R-chlorambucil as first-line treatment.
- Patients were given the following treatment protocol:
  - **Induction phase**: four weekly infusions of rituximab at 375 mg/m² and six consecutive weeks of chlorambucil at 6 mg/m² daily;
  - **Restaging phase**: patients were restaged at 8–10 weeks from beginning of treatment;
  - **Maintenance phase**: if there was no progressive disease, patients were given four monthly infusions of rituximab and 14 days of chlorambucil each month for four consecutive months.

Bassi S, et al. EHA 2010; Abstract 0277
Key findings

Baseline characteristics and disposition

- Median age at diagnosis was 56 years (range 29–79 years).
- Ann Arbor stage was advanced (stage III–IV) in 44 patients (76%), and 16 patients (27%) presented an extra-nodal localization; only 9 patients (15%) were symptomatic.
- Histological grading was available for 52 patients (grade 1 in 13 patients, grade 2 in 33 patients, and grade 3 in 6 patients).
- FLIPI score was evaluable in 55 patients, and 31 patients (53%) were at low risk.
Key findings (cont’d)

Efficacy

- After the induction phase, OR rate was 98%, with 15 patients achieving a CR and 42 a PR.
- After the consolidation phase, 46 patients achieved a CR and 11 achieved a PR; one patient remained in stable disease.
- With a median observation time of 32 months (range 7–103 months) from diagnosis, 43 patients (74%) have maintained their response; 40 patients (69%) are still in CR.
- Thirteen (13) patients (22%) relapsed, with a median TTNT of 21 months (range 6–66 months).
- Three patients died during treatment (1 patient of lymphoma at 42 months from diagnosis; 2 patients due to other causes).
### Table 1. Response rates after first-line treatment with rituximab and chlorambucil in 58 patients with follicular lymphoma

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>42</td>
<td>72</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Overall response (OR) rate</td>
<td>57</td>
<td>98</td>
</tr>
<tr>
<td><strong>Maintenance phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>46</td>
<td>79</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>Overall response (OR) rate</td>
<td>57</td>
<td>98</td>
</tr>
</tbody>
</table>

*Subsequently underwent high-dose and peripheral blood stem cell (PBSC) re-infusion*
Key findings (cont’d)

**Safety**

- All except one patient completed all planned treatments.
- The mean daily dose of chlorambucil received during the induction phase was 10 mg, while in the prolonged treatment was 8 mg.
- Chlorambucil dose was reduced in 25 patients (43%) mainly in the prolonged phase because of neutropenia.
- Chlorambucil treatment was stopped in only one patient for persistent grade 3 neutropenia after the first consolidation cycle.
- One HBsAg-positive patient did not conclude the treatment because of AST/ALT elevation.
- No late toxicity has been observed.

ALT = alanine transaminase
AST = aspartate aminotransferase
HBsAg = hepatitis B surface antigen
Key conclusions

- Preliminary results showed rituximab plus chlorambucil to be a safe and feasible combination in untreated FL patients.

- In terms of efficacy, clinical results were similar to those obtained with more aggressive therapy, but with a lower toxicity and an easier management.

- Combination with rituximab and chlorambucil may be considered a valid first-line therapy, especially in FL patients not eligible for more aggressive chemotherapy regimens.
Lenalidomide plus rituximab as treatment for indolent B-cell NHL

Background

- Preclinical models have shown that lenalidomide in combination with rituximab in the treatment of indolent NHL results in enhanced cell death relative to treatment with either agent alone.\(^1\,^2\)

- At ASCO 2010, Fowler and colleagues presented results of their phase II study evaluating the efficacy and safety of lenalidomide plus rituximab in patients with untreated, stage III/IV, indolent NHL.\(^3\)


ASCO = American Society of Clinical Oncology
NHL = non-Hodgkin’s lymphoma
Study design

- The study is a phase II, open-label, single-arm trial designed to enroll 110 patients in three cohorts: 50 FL patients, 30 MZL patients, and 30 CLL/SLL patients.

- Patients (>18 years) with the following criteria were included:
  - measurable (>1.5 cm) untreated indolent NHL (stage III or IV);
  - ECOG performance status <2;
  - ANC $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L;
  - adequate hepatic and renal function;
  - no prior exposure to lenalidomide, no known hypersensitivity to thalidomide, and no HIV or active hepatitis infection.


ANC = absolute neutrophil count; CLL = chronic lymphocytic lymphoma; ECOG = European Clinical Oncology Group; FL = follicular lymphoma; HIV = human immunodeficiency virus; MZL = marginal zone lymphoma; NHL = non-Hodgkin's lymphoma; SLL = small lymphocytic lymphoma
Study design (cont’d)

- Patients received lenalidomide (20 mg/day) on days 1–21 and rituximab (375 mg/m²) on day 1 of each 28 day cycle for up to 6 cycles.

- SLL patients received lenalidomide in escalating doses: 10 mg/day in cycle 1, 15 mg/day in cycle 2, and 20 mg/day in cycle 3.

- Primary objective was to evaluate the OR rate.

- Secondary objectives included CR and PR rates, PFS, and toxicity.

- Response was assessed after 3 and 6 cycles using the International Workshop for Lymphoma Response Criteria methodology.

CR = complete response; OR = overall response; PFS = progression-free survival; PR = partial response; SLL = small lymphocytic lymphoma
Key findings

**Baseline characteristics and disposition**

- Currently, 74 patients have been enrolled in the study, of which 48 have completed 6 cycles of treatment and are included in the analysis of toxicity and efficacy.

- To date, histologies include 13 MZL patients (27%), 5 SLL patients (10%), and 30 FL patients (63%).

- Median age of patients was 57 years (range 36–77 years); 54% of patients were male.

- Of the 30 patients for whom FLIPI scores were available, 87% were classified as either intermediate or high risk.


FL = follicular lymphoma
FLIPI = follicular lymphoma international prognostic index
MZL = marginal zone lymphoma
SLL = small lymphocytic lymphoma
**Key findings (cont’d)**

**Efficacy**

- OR rate of the ITT population was 83%, with 69% of patients achieving a CR or CRu.

- OR rate was highest in the FL patients (93%), compared with 80% in SLL patients and 62% in MZL patients.

- CR was achieved by 25/30 FL patients (83%), 2/5 SLL patients (40%), and 6/13 MZL patients (46%).

- At 12 months, one patient had progressed.

- Estimated PFS at 20 months is 91%.
Table 1. Response rates in 48 indolent NHL patients treated with lenalidomide plus rituximab

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>NE (n)</th>
<th>SD (n)</th>
<th>PR (n)</th>
<th>CR/CRu (n)</th>
<th>OR rate % (CR/CRu %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>25</td>
<td>97 (86)</td>
</tr>
<tr>
<td>SLL</td>
<td>5</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>80 (40)</td>
</tr>
<tr>
<td>MZL</td>
<td>13</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>73 (55)</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>33</td>
<td>89 (73)</td>
</tr>
</tbody>
</table>

OR rate % (CR/CRu %) for Evaluable (n = 45) and ITT (n = 48)

*Patients were evaluable if they had at least one post-baseline assessment.

CR = complete response; CRu = unconfirmed complete response; FL = follicular lymphoma; ITT = intent to treat; MZL = marginal zone lymphoma; NE = not evaluable; NHL = non-Hodgkin’s lymphoma; OR = overall response; PR = partial response; SD = stable disease; SLL = small lymphocytic lymphoma
Key findings (cont’d)

Safety

- The most common grade 3/4 AEs were neutropenia (21%), thrombocytopenia (13%), and rash (13%).
- No patients developed tumour lysis syndrome, and only one patient experienced grade 3/4 neuropathy.
- Rash (all grades) was seen in 22 patients (46%), but was generally self limited and did not occur on re-exposure to the drug.
- The most common grade 1/2 AEs were fatigue, myalgia, and leukopenia, which were mild and transient.
- Three patients were removed from treatment due to AEs (severe reaction to rituximab, leukocytoclastic vasculitis, and arterial thrombosis, respectively).


AE = adverse event
Table 2. Grade 3/4 adverse events in 48 indolent NHL patients treated with lenalidomide plus rituximab

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infection (sinus)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

*NHL = non-Hodgkin’s lymphoma*
Key conclusions

- The biologic combination of lenalidomide and rituximab in patients with untreated indolent B-cell NHL produces good overall and complete response rates.

- Toxicity profile of this combination regimen is mild, with manageable hematological adverse events.

- Further randomized trials using lenalidomide and rituximab are planned.