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New Evidence in Oncology is a publication for Canadian healthcare professionals in the field of oncology. Our journal provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice.

Our March 2010 issue presents coverage from the 2009 ASH Annual Meeting held in New Orleans, Louisiana, from December 5–8, 2009. The issue reports on important data showing an overall survival benefit for FCR over FC in CLL, as well as on new treatment strategies in both CLL and NHL, including promising new agents and chemotherapy combinations. We would like to thank Dr. Stephen Couban, Dr. Laurie H. Sehn, and Dr. C. Tom Kouroukis for their Canadian perspectives; and Dr. Michael Hallek, Dr. Bertrand Coiffier, and Dr. Gilles Salles for their investigator commentaries.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research. Slide presentations on various topics are available for download.
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Canadian Perspectives

Stephen Couban, MD

Dr. Stephen Couban joined the Department of Medicine at Dalhousie University and the Capital District Health Authority in Halifax, Nova Scotia, in 1997. He is Service Chief in the Division of Hematology and Director of the Blood and Marrow Transplant Program. He is also Service Chief of the Department of Medicine Medical Teaching Unit. His research interests have focused on allografting and in particular on exploration of different types of grafts, including GCSF-stimulated allogeneic peripheral blood allografts and GCSF-stimulated bone marrow allografts. Dr. Couban is Past-President of the Canadian Blood and Marrow Transplant Group, Secretary of the Canadian Hematology Society, and Co-Chair of the Hematology Site Group of the National Cancer Institute of Canada Clinical Trials Groups.

Laurie H. Sehn, MD, MPH

Dr. Laurie H. Sehn is Clinical Assistant Professor at the BC Cancer Agency and the University of British Columbia in Vancouver. She has been a medical oncologist and clinical investigator with the Lymphoma Tumour Group since 1998. Dr. Sehn has served on the Board of Directors of the Lymphoma Foundation Canada (LFC) since 2002 and is now Director of Research Fellowships for the LFC. Her research interests include the lymphoid cancers with particular focus on the biology and treatment of large-cell lymphoma, the application of new imaging techniques such as PET scanning to lymphoma management, and innovative new approaches to treatment.

C. Tom Kouroukis, MD

Dr. C. Tom Kouroukis graduated from the University of Toronto and completed training in Internal Medicine, Hematology and MSc training at McGill and McMaster Universities. He was awarded a National Cancer Institute of Canada Clinical Research Fellowship. He is a Hematologist at the Juravinski Cancer Centre/Hamilton Health Sciences and Associate Professor in the Department of Oncology. He is Co-Chair of the Hematology Cancer Disease Site group of the Cancer Care Ontario Practice Guidelines Initiative. His research interests include the care of older patients with hematological cancers, the impact and evaluation of co-morbidity in older cancer patients, clinical trials in mantle cell lymphoma, and practice guideline development.
Bertrand Coiffier, MD

For the past 15 years, Dr. Bertrand Coiffier has been Professor and Head of the Department of Hematology in the Hospices Civils de Lyon, France, a leading centre for expertise and treatment of lymphoma patients. He is a founding member of the Groupe d’Etude des Lymphomes de l’Adulte or GELA, a cooperative group of French and Belgian physicians interested in the treatment of lymphomas. As such, he has initiated and coordinated several key randomized trials for the treatment of lymphoma patients. Dr. Coiffier is a member of the scientific committee of several scientific organizations and has participated in the organization of various international meetings on lymphoma or hematology. He is also a member of the editorial board of several journals, and has authored more than 200 original publications in the field of lymphoma and many books or chapters on lymphoma.

Gilles Salles, MD

Dr. Gilles Salles is a Professor in the Department of Hematology at the Centre Hospitalier Lyon-Sud, Lyon, France, and Head of the Research Unit Pathologie des Cellules Lymphoïdes at the University of Lyon. He served as Chairman of the Scientific Committee of GELA (Groupe d’Etude des Lymphomes de l’Adulte) until 2007 and is presently acting as vice-president of this group. He is also a member of several professional societies, including the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association. Professor Salles has been especially interested in the clinical and biological study of malignant lymphoma, and major focuses of his work include the description and validation of prognostic factors as well as clinical trials in indolent lymphomas. He has been involved as a coordinator or co-investigator in many clinical trials and studies within his field, and has published numerous articles in international peer-reviewed journals.
This issue of *New Evidence in Oncology* reports on findings from a number of key presentations given at the American Society of Hematology (ASH) Annual Meeting, which was held in New Orleans, Louisiana, from December 5–8, 2009. The ASH Annual Meeting is a leading international forum for cutting-edge research in hematology and plays an important role in training the next generation of researchers and clinicians in this field. The 2010 Meeting featured 4,097 abstracts presented in oral or poster form.

In this report, *New Evidence* examines the addition of the monoclonal antibodies rituximab and alemtuzumab to chemoimmunotherapy in chronic lymphocytic leukemia (CLL) and the combination bendamustine-rituximab in non-Hodgkin’s lymphoma (NHL). Long-term experience with R-CHOP in NHL and variations in dosing intervals are also reviewed, and rituximab maintenance therapy is discussed as a strategy in both NHL and CLL. Other articles focus on promising new agents and chemotherapy combinations in CLL and NHL, such as GA101 and PRO131921.
Improving Response to Treatment in CLL with the Addition of Rituximab and Alemtuzumab to Chemoimmunotherapy

Combinations of purine analogs, alkylating agents, and monoclonal antibodies have dramatically improved response to treatment in chronic lymphocytic leukemia (CLL), resulting in a shift in the treatment goal from symptom palliation to achieving maximal disease control. In fit patients, an improvement in overall survival (OS) balanced with health-related quality of life (HRQL) is the ultimate goal of clinical studies. However, until recently, no phase III study had shown an improvement in OS or HRQL of one regimen over another.  

At the ASH 2008 meeting, results of the German CLL Study Group’s CLL-8 study showed that the addition of rituximab to fludarabine and cyclophosphamide (FCR) produced the highest response rates observed to date. However, no improvement in OS was reported, and findings did not clearly indicate whether the efficacy of the FCR regimen balanced adequately with patient HRQL. FCR may be unsuitable in some patient groups, such as in patients with co-morbidities or high-risk disease. In frail patients, less toxic treatments such as chlorambucil may be preferable to FCR, although complete response (7%) and overall response (65%) rates are relatively low with chlorambucil. Response rates with FCR are lower in patients with high-risk features, such as those with serum Beta-2 microglobulin ($\beta_2$M) $\geq$ 4 mg/L or del(17p). Alemtuzumab, a humanized anti-CD52 monoclonal antibody that acts via a p53 independent mechanism, may be preferable to FCR in these high-risk patients. The benefit of rituximab in CLL may also extend to consolidation and maintenance therapy; this strategy is being examined in an ongoing phase II study.

This article reports on five studies presented at ASH 2009: follow-up data from the phase III CLL-8 study show a significant improvement in OS for FCR compared to FC; a second phase III study shows no difference in HRQL between first-line FCR and FC; a phase II study reports good response rates with the addition of rituximab to chlorambucil, versus historical controls; a second phase II study demonstrates that the addition of alemtuzumab to FCR (CFAR) in high-risk patients results in response rates comparable to historical FCR controls; and a final phase II study shows that consolidation and maintenance therapy with rituximab significantly prolongs response duration in patients with CLL.

Background

The CLL-8 study was a multicentre, phase III, randomized, active, comparative, placebo-controlled study designed to evaluate the efficacy of FCR (fludarabine, cyclophosphamide, rituximab) versus FC (fludarabine, cyclophosphamide) as first-line treatment in chronic lymphocytic leukemia (CLL). Hallek and colleagues presented preliminary data from the CLL-8 study at ASH 2008, which were reported in the February 2009 issue of New Evidence. At ASH 2009, the authors presented follow-up results after a longer median observation time of 37.7 months.1

Study design

- Between July 2003 and March 2006, the study enrolled 817 treatment-naïve CLL patients with good physical fitness, as defined by a Cumulative Illness Rating Scale (CIRS) score of up to 6 and a creatinine clearance (Cr Cl) ≥70 mL/min.

- Patients were randomly assigned to receive 6 courses of either:
  - FC (n = 409) – fludarabine 25 mg/m² iv on days 1–3 and cyclophosphamide 250 mg/m² iv on days 1–3; every 28 days;
  - FC plus R (n = 408) – rituximab 375 mg/m² iv on day 0 of the first cycle and 500 mg/m² iv on day 1 of all subsequent cycles; every 28 days.

- Prophylactic use of antibiotics or growth factors was not generally recommended in the protocol.

Key findings

Baseline characteristics and disposition

- As of June 2009, the median observation time was 37.7 months.
- Both treatment arms were well balanced with regard to sex, age, stage, genomic aberrations, and IgVH gene status.
- Median age was 61 years (range 30 to 81 years) and median CIRS score was 1 (range 0–8); 25.7% of patients were female in both arms.
- Binet stage of patients was as follows: 64.1% Binet B, 31% Binet C, and 4.9% Binet A.
- Incidence of cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) were del(13q) (57%), trisomy 12 (12%), del(11q) (25%), and del(17p) (8%), with no statistically significant differences in distribution between treatment arms.
- A mean number of 5.2 treatment courses were delivered in the FCR arm versus 4.8 courses in the FC arm (p = 0.006).
- Dose reductions by more than 10% in at least one treatment course were performed in 47% and 27% of patients in the FCR and FC arms, respectively (p <0.001).
- Seventy-four percent (74%) of patients in the FCR arm and 67% of patients in the FC arm received 6 cycles (p = 0.02).
Efficacy

- FCR induced a higher overall response (OR) rate than FC (95.1% versus 88.4%) and more complete responses (CR) (44.1% versus 21.8%; p < 0.01). (Table 1)

- Median PFS was 32.8 months for FC and 51.8 months for FCR patients (p < 0.001; hazard ratio [HR] 0.56; 95% CI: 0.460–0.689). (Table 1)

- In Binet C, the median PFS was 14 months for patients treated with up to 3 courses of FC, but 44 months for patients who received 4 courses or more (p < 0.001).

- Median PFS for patients treated with up to 3 cycles of FCR was 12.5 months, while for patients with 4 cycles or more, median PFS has not been reached (p < 0.001).

- The OS rate at 37.7 months was 87.2% in the FCR arm versus 82.5% in the FC arm (p = 0.012); the median OS has not been reached in either arm. (Table 1)

Table 1. Efficacy of FCR versus FC as first-line treatment of CLL (median observation time 37.7 months)

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>FC (n = 371)</th>
<th>FCR (n = 390)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rates (OR)</td>
<td>88.4</td>
<td>95.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>21.8</td>
<td>44.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>66.6</td>
<td>51.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Progression-free survival (PFS) (months)</td>
<td>32.8</td>
<td>51.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall survival (OS) (%)</td>
<td>82.5</td>
<td>87.2</td>
<td>0.012</td>
</tr>
</tbody>
</table>

- Only patients in Binet stages A and B showed a superior OS after FCR treatment (Binet A: HR 0.19, 95% CI: 0.023–1.613, p = 0.09; Binet B: HR 0.45, 95% CI: 0.296–0.689, p < 0.001; Binet C: HR 1.4, 95% CI: 0.843–2.620, p = 0.168).

- Multivariate analysis was performed to evaluate factors predicting outcome.

Safety

- As previously reported, more hematologic adverse events, particularly neutropenia, were observed with FCR treatment, but this did not result in an increased infection rate.

- More deaths have occurred in the FC arm (86 / 396, 21.7%) than in the FCR arm (65 / 404, 16.1%). (Table 2)

- Treatment-related mortality occurred in 8 (2.0%) of patients in each arm. Of these, 7 FC-treated patients and 5 FCR-treated patients died from infections related to treatment.

- In 7 patients (3 FC, 4 FCR), treatment was discontinued before the third treatment course due to fatal toxicity.

Key conclusions

- Treatment with FCR chemoimmunotherapy is more effective than FC chemotherapy.

- There was no demonstrated benefit for FCR in Binet stage C patients, which may be related to insufficient treatment intensity in these patients with higher tumour loads.

- This study is the first randomized trial to demonstrate that a specific first-line treatment for CLL results in an improved overall survival.

- Results of the study corroborate the recommendation to use FCR as standard therapy in physically fit CLL patients requiring therapy.

Background
At ASH 2009, Del Poeta and colleagues presented data from their study examining the efficacy of consolidation/maintenance rituximab after first-line treatment with fludarabine followed by rituximab in chronic lymphocytic leukemia (CLL).1

Study design
• A phase II study was performed in 120 symptomatic CLL patients treated with six monthly courses of intravenous or oral fludarabine at conventional doses and then, after a median time of 31 days, with four weekly doses (375 mg/m²) of rituximab.

• Fifty-four (54) patients with complete responses (CR) then received consolidation and maintenance therapy with four monthly cycles of rituximab at 375 mg/m² followed by twelve monthly low doses of rituximab at 150 mg/m².

• High-risk patients were defined as having a minimum of two of the following markers:
  ◦ unmutated IgVH;
  ◦ CD38 >30%;
  ◦ ZAP-70 >20%;
  ◦ intermediate/unfavorable cytogenetics including trisomy 12, del(11q), or del(17p).

• Remission status was evaluated by multicolour flow cytometry enumerating CD19+, CD5+, CD79b+/-clonal B cells in marrow.
• Minimal residual disease (MRD) was defined as CD19+, CD5+, or CD79b- B cells >1%.
• Study endpoints were:
  ◦ remission rates and response duration in all patients;
  ◦ efficacy of consolidation/maintenance immunotherapy in prolonging response duration and overall survival (OS);
  ◦ impact of a biologic high-risk profile on patient outcome.

Key findings
• Of the 120 enrolled patients, 57 were male and 63 female, with a median age of 62 years (range 37 to 79 years).
• Rai stage of patients was as follows: 14 patients with stage 0; 103 patients with stage I and II; and 3 patients with stage III and IV.
• Median follow-up duration was 50 months.
• Based on NCI criteria, 92/120 patients (77%) achieved a CR, 24/120 (20%) a partial response (PR), and 4/120 (3%) no response or progression. (Figure 1)

![Figure 1. Response to induction treatment with fludarabine versus fludarabine-rituximab*](image_url)
Key conclusions

■ The addition of rituximab to fludarabine during induction increased the complete response rate and response duration in CLL patients, with no added toxicity.

■ The addition of rituximab consolidation and maintenance significantly prolongs response duration, avoiding early relapses. Whether the addition has an impact on overall survival is not known.

■ Low-dose rituximab as maintenance therapy in CLL significantly improves the outcome of high-risk patients.

Background
At ASH 2009, Hillmen and colleagues presented data from their phase II study assessing the feasibility of adding rituximab to chlorambucil in order to improve outcomes for patients with chronic lymphocytic leukemia (CLL), particularly elderly patients or those with co-morbidities.1

Study design
• Previously untreated patients with Binet stage B or C CLL who required therapy according to the International Workshop on CLL (IWCLL) criteria were included in the study if:
  - life expectancy was >6 months;
  - Eastern Cooperative Oncology Group (ECOG) performance status was ≤2;
  - absolute neutrophil count (ANC) ≥1 x 10⁹ L;
  - platelet count ≥50 x 10⁹ L, unless due to involvement of bone marrow by CLL;
  - total bilirubin ≤2 x upper limit of normal (ULN);
  - alkaline phosphatise and transaminases ≤2 x ULN.
• Patients were excluded from the study if they had:
  - known hematological malignancy or other malignancy within two years prior to the study entry point;
  - active bacterial, viral, fungal infection requiring systemic therapy;
  - a history of severe co-morbidities;
  - transformation to aggressive B-cell malignancy.

• Patients included in the study received rituximab (day 1: 375 mg/m² iv cycle 1, 500 mg/m² cycles 2–6) plus chlorambucil (days 1–7: 10 mg/m²/day orally), repeated every 28 days for 6 cycles.
• A further 6 cycles of chlorambucil alone was permitted in patients with continuing clinical response at 6 cycles.
• Primary endpoint was the adverse event (AE) profile.
• Secondary endpoints included response rates, progression-free survival (PFS), overall survival (OS), and assessment of minimal residual disease (MRD).
• Efficacy results from this study were compared with historical data from patients in the UK LRF CLL-4 study who received chlorambucil at the same dose, but as monotherapy, between 1999 and 2004.
• Each of the 50 patients in the R-chlorambucil trial were matched to three patients from the CLL-4 trial by Binet stage (B or C), VH Mutation (mutated or unmutated), 11q FISH (deleted or not), and age.

Key findings
• Results are based on a planned interim analysis including the first 50 patients out of a total 100 patients from 12 centres.
• Of the 50 patients, 47 patients were evaluable (2 missing bone marrow data at the time of the interim analysis; 1 protocol violation where a patient with breast cancer received only 1 cycle).
Key conclusions

- Based on this planned interim analysis, the addition of rituximab to chlorambucil is a feasible combination with no unexpected adverse events.
- The combination of rituximab and chlorambucil was effective for untreated patients with CLL, producing a high clinical response rate.
- Response rates were higher with R-chlorambucil than those seen with chlorambucil alone in historical matched analysis.
- The median age of patients in this study was considerably greater than the median age of patients in other CLL studies and more representative of patients presenting with CLL in the clinic.
- Further investigation in a randomized phase III study is warranted.


Note: Remission status in this study by Hillmen, et al. was assessed in a central specialist laboratory (HMDS) with MRD assessment by flow cytometry, unlike in the UK LRF CLL-4 trial where local laboratories were used with no central review or MRD assessment. It therefore appears that the assessment of CR was more stringent in this trial evaluating R-chlorambucil than in the UK LRF CLL-4 trial.
Background
At ASH 2009, Parikh and colleagues presented data from their phase II study assessing the efficacy of adding alemtuzumab to FCR (CFAR) as front-line therapy in patients with high-risk chronic lymphocytic leukemia (CLL). 1

Study design
- Patients included in the study:
  - met the National Cancer Institute (NCI) criteria to initiate therapy;
  - were <70 years old;
  - had a Beta-2 microglobulin (\(\beta_2M\)) concentration \(\geq\) 4 mg/L.
- Patients were given front-line CFAR, consisting of cyclophosphamide (200 mg/m\(^2\) on days 3–5), fludarabine (20 mg/m\(^2\) on days 3–5); alemtuzumab (30 mg iv on days 1,3,5), and rituximab (375–500 mg/m\(^2\) on day 2).
- Courses were repeated every 28 days for a total of 6 courses.
- All patients received pegylated filgrastim at 6 mg subcutaneously with each course of therapy.
- All patients received allopurinol for tumour lysis prophylaxis and antibiotic prophylaxis.
- Cytomegalovirus (CMV) antigenemia was monitored before each course.

Key findings
- A total of 60 patients were enrolled from July 2005 through August 2008; one patient was lost to follow-up.
- Median age was 59 years (range 42–69 years).
- Forty-four (44) patients (75%) were male, and 30 patients (51%) were in Rai stage III–IV.
- Median \(\beta_2M\) was 5.1 mg/L (range 4–11.6 mg/L); hemoglobin was 11.5 g/dL (range 5.5–15.1 g/dL); platelet (PLT) concentration was 139 k/\(\mu\)L (range 41–446 k/\(\mu\)L); white blood cell (WBC) concentration was 100 k/\(\mu\)L (range 5–665 k/\(\mu\)L); and alanine aminotransferase (ALC) was 92 k/\(\mu\)L (range 4–619 k/\(\mu\)L).
- The median number of courses administered was four (range 2–6); reasons for not completing six courses included:
  - delayed recovery of counts (18 patients);
  - infection (8 patients);
  - autoimmune hemolytic anemia (AIHA) (4 patients);
  - treatment failure (3 patients);
  - patient choice (2 patients).
- A complete response (CR) was achieved in 70% of patients, nodular partial response (nPR) in 3% of patients, partial response (PR) in 18% of patients, and no response in 7% of patients. The overall response (OR) rate was 92% (Table 1).
- There was no significant correlation between CR or OR with Rai stage, IgVH mutation status, fluorescence in situ hybridization (FISH) status, ZAP-70, or CD38 expression. (Table 1)
- After a median follow-up of 24 months (range 3–49 months), 19 patients (32%) had progressive disease.
- Patients with del(17p) and unmutated IgVH had significantly shorter time-to-progression (TTP). (Table 1)
- Median overall survival (OS) for all patients has not been reached; the median TTP was 38 months.
- Eleven patients (19%) died, including:
  - four patients with disease progression after achieving CR;
  - two patients who did not respond;
  - two patients with Richter’s transformation;
  - one patient who transformed to acute myeloid leukemia (AML);
  - one patient with metastatic lung cancer;
  - one patient with severe pneumonia eight months after achieving CR.
- Grade 3/4 neutropenia and thrombocytopenia occurred in 31% of patients and in 13% of courses.

Parikh SA, et al. ASH 2009: Abstract 208

Front-line chemotherapy with fludarabine, cyclophosphamide, alemtuzumab, and rituximab (CFAR) in high-risk chronic lymphocytic leukemia
Major infections, including pneumonia and sepsis, were reported in 10 patients (17%).

Minor infectious such as bronchitis, urinary tract infections, and herpes zoster were reported in 15 patients (25%).

Infusion reactions associated with alemtuzumab occurred in 42 patients (71%).

CMV reactivation occurred in 7 patients (12%), all of whom were on valacyclovir prophylaxis.

There was one death due to CMV pneumonia; all other episodes of CMV reactivation were promptly treated with valganciclovir leading to resolution of fever and/or antigenemia.

### Table 1. Response to CFAR by patient characteristic

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Number of patients</th>
<th>Complete response (%)</th>
<th>Overall response (%)</th>
<th>Time-to-progression (months)</th>
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<tbody>
<tr>
<td>All evaluable patients</td>
<td>59</td>
<td>70</td>
<td>92</td>
<td>38</td>
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<tr>
<td>Age</td>
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<td>57</td>
<td>78</td>
<td>18†</td>
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<tr>
<td>del (11q)</td>
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<td>80</td>
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<td>27†</td>
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<td>42*</td>
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*median not reached; †p-value = 0.01; ‡p-value = 0.001

### Key conclusions

- CFAR is an active frontline regimen in high-risk patients with CLL.

- Although complete response rates in patients with other high-risk features such as del(17p) and unmutated IgVH were >50%, time-to-progression was significantly shorter for these patients than for patients without these features.

- With the current follow-up, overall survival, time-to-progression, infectious complications, and grade 3/4 hematologic toxicity are comparable to historic high-risk patients treated with FCR.

Health-related quality of life in patients receiving FCR or FC for first-line treatment of chronic lymphocytic leukemia

**Background**

At ASH 2009, Eichhorst and colleagues presented data from their study assessing the health-related quality of life (HRQL) of chronic lymphocytic leukemia (CLL) patients given FC or FCR as first-line treatment in the CLL-8 study.

**Study design**

- A total of 817 patients were enrolled between July 2003 and March 2006. (See page 9 for a report on the CLL-8 study.)
- Eligible patients had good physical fitness, as defined by a Cumulative Illness Rating Scale (CIRS) score of up to six and a creatinine clearance (Cr Cl) concentration $\geq$ 70 mL/min.
- Patients were randomly assigned to receive FC (n = 409) or FCR (n = 408).
- FC included fludarabine at 25 mg/m$^2$ iv on days 1–3 and cyclophosphamide at 250 mg/m$^2$ iv on days 1–3; FCR included FC (as described above) plus rituximab at 375 mg/m$^2$ iv on day 0 of the first cycle and 500 mg/m$^2$ iv on day 1 of all subsequent cycles.
- Cycles were given every 28 days for a total of six courses.
- European Organization for Research and Treatment of Cancer (EORTC) C30 questionnaires were sent to all patients included in Germany or Austria at baseline, after 3, 6, and 12 months, and at the yearly follow-up.
- In all other countries, questionnaires were handed out to the patients personally at the same time points during their visits in the study centre.
- Analysis of the questionnaires was performed according to the EORTC recommendations.
- The questionnaire contained:
  - a global health scale;
  - five functional scales (physical, role, cognitive, emotional, and social);
  - three symptom scales (fatigue, pain, nausea and vomiting);
  - six single items (dyspnea, appetite loss, sleep disturbances, financial impact, constipation, and diarrhea).
- Mean score values of the EORTC scales ranged between 0 and 100.
- High scores in the functional scales represent good HRQL, low scores in the symptom scales represent low symptom burden.

**Key findings**

- HRQL was evaluated in 763 patients (93%), who completed at least one questionnaire: 376 patients (49%) in the FC arm, and 387 patients (51%) in the FCR arm.
- Compliance rate was significantly higher in countries where the questionnaire was handed out personally: 92% in Germany and Austria versus 96% in other countries ($p = 0.013$).
- Patients answering >1 questionnaire including the baseline questionnaire (n = 444, 58%) had a significantly higher CIRS score (1.77 versus 1.43; $p = 0.007$) and more frequent grade 3/4 leukocytopenias (24% versus 13%; $p < 0.001$) than those with a missing baseline questionnaire or who answered ≤1 questionnaire (n = 319, 42%).
- Age, distribution of Binet stages, gender, and poor prognostic factors [del(11q), del(17p), or unmutated IgVH] were similarly distributed between both groups.
- There were no differences in the rate of other toxicities or response rates.
- A total of 482 questionnaires were available: 406 at interim staging (3 months), 454 at final staging (6 months), 496 after 12 months follow-up, 414 after 24 months follow-up, and 198 after 36 months follow-up.
- A comparison of the two treatment arms at interim or final staging showed no significant difference between arms in terms of global health status, functional scales, and symptom scales. (Figures 1–4)
- Dyspnea was scored significantly higher with FC treatment (23) in comparison to FCR (18) at interim and final staging ($p = 0.023$). (Figure 4)
• At 12, 24, and 36 months of follow-up, no significant difference was found between the FC and FCR arms in all functional, symptom, single item, and global health status scales. (Figures 1–4)

• Both treatment arms showed a slight improvement (defined as a difference of 5–10 points) in global health status at 12 months follow-up in comparison to baseline (62 versus 68 in the FC arm and 62 versus 70 in the FCR arm). (Figure 1)

Key conclusions

- Although the FCR regimen had a higher rate of hematological toxicity than the FC arm, no difference in HRQL was observed between the treatment arms.

- The superior response rates and progression-free survival in the FCR regimen did not result in an improved HRQL.

- Longer follow-up is needed to evaluate the HRQL after chemoimmunotherapy.

The CLL-8 study presented by Hallek, et al. is one of only two studies showing a survival benefit of one treatment over another in chronic lymphocytic leukemia (CLL). This overall outcome is what is most important, even though the survival benefit of FCR over FC was not seen in the Binet C subgroup. When we perform retrospective analyses on subgroups, there are always limitations. The Binet C group may have been too small, or this group of patients may just be difficult to treat with any regimen.

Several points for discussion about the CLL-8 study also come to mind. The study had a very high proportion of males to females. Although CLL is more common in men than women, the proportion of male patients in this study was unexpectedly high, which suggests that there may have been some significant selection of patients. Also important to note are the higher number of deaths observed in the FC arm: perhaps this finding represents a higher number of early disease progressions. Finally, though it is reassuring to know that the addition of rituximab to FC did not increase toxicity, both FCR and FC have significant treatment-related mortality.

In younger patients with no other co-morbidities FCR is certainly a reasonable treatment option, but I would hesitate to use this regimen in older patients or in those with other co-morbidities. The CLL-8 study has a number of implications for clinical practice. For many years we used less effective and less toxic regimens upfront and increased the intensity of treatment over time. The CLL-8 data suggest that we should consider rethinking this paradigm and use a highly effective regimen first. Although FCR is not yet approved for use in certain Canadian provinces, data from this study will likely be used to seek approval.

Traditionally, we do not use maintenance or consolidation therapy in CLL; we tend to wait until patients progress or develop symptoms before starting a second treatment. The study by Poeta, et al. is timely and of interest, since maintenance therapy with rituximab has been successful in other indolent lymphoproliferative disorders such as follicular lymphoma. Phase II studies such as the study by Poeta, et al. have limitations: the outcomes may be more a reflection of the patients themselves rather than a result of the intervention. However, the long median follow-up time of over four years in this study does suggest a benefit for long-term treatment with rituximab in CLL. Although data are insufficient to recommend using rituximab maintenance/consolidation therapy on a routine basis at present, this strategy is certainly worth exploring further in a large randomized trial.

The phase II study by Hillmen, et al. showed encouraging early data on the use of rituximab added to chlorambucil in an older, less fit population. The overall response rate for rituximab plus chlorambucil was compared to chlorambucil monotherapy using 3:1 matched controls from the CLL-4 study, with favourable results. In addition, this group of patients were able to tolerate the rituximab-chlorambucil combination without any significant or concerning side effects. A randomized prospective trial is therefore the next step in examining this combination, which may provide a valuable treatment option in older, less fit patients.

Response rates in the phase II study by Parikh, et al. are highly impressive, given that CFAR includes four major active agents. Note, however, that patients over 70 years old were not included in the study, and therefore many patients with CLL would be excluded. In addition, a substantial number of adverse events occurred, including delayed recovery of counts, infections, and hemolytic anemia, despite the administration of growth factors. In Canada, alemtuzumab is often given subcutaneously, which may reduce infusional side effects, and in this study the alemtuzumab in the CFAR regimen was given subcutaneously. However, CFAR is an intensive therapy that requires pre-medication with growth factors and monitoring for CMV. Using CFAR as first-line therapy is therefore not something that I would consider based on current data, although it might be considered for fit patients after relapse. One of the greatest challenges for hematologists today is in treating del(17p) patients, who are often unresponsive to standard treatments. Although some evidence suggests that alemtuzumab benefits del(17p) patients, whether the drug should be given as monotherapy or in combination with other agents is unclear.

The CLL-8 study has shown the FCR regimen to be highly efficacious, but FCR’s effect on health-related quality of life (HRQL) remains uncertain. The study by Eichhorst, et al. is therefore important, since one would generally expect intensive regimens to reduce HRQL. It is interesting that there was no difference in HRQL between the FCR and FC arms, because it is not clear to what extent treatment toxicities or symptoms of the disease itself play a role in HRQL. The higher incidence of dyspnea in the FC group could be related to the disease itself, but may also have occurred by chance if the study was not powered to examine these comparisons. Further studies that investigate the effect of treatment regimens on HRQL would provide valuable information to assist in making treatment decisions.
An Interview with Dr. Michael Hallek on the CLL-8 Study Comparing First-line FCR to FC in CLL patients

At the ASH 2009 meeting, New Evidence spoke with Dr. Michael Hallek, Professor of Medicine, Director and Chair of the Department of Internal Medicine at the University of Cologne and Chair of the German CLL Study Group, about the CLL-8 trial. Dr. Hallek, who is the principal investigator, presented follow-up results of the study at the ASH meeting.

New Evidence: In the CLL-8 study, you used the Cumulative Illness Rating Scale (CIRS) for determining performance status as one of the selection criteria. Why did you choose this scoring system as opposed to others, such as the Eastern Cooperative Oncology Group (ECOG) Performance Status or the Charlson Comorbidity Index.

Dr. Hallek: The CIRS was developed by a geriatric oncologist in 1968 and is currently being used in the United States in that field. CIRS rates the relevant co-morbidities in a number of organ systems, helping doctors determine whether a patient is fit enough to undergo intensive therapies. We used this method for determining performance status based on advice from geriatric oncologists and because of its simplicity. CIRS is also a little more detailed than the ECOG score, taking into account a number of organ systems such as the heart and lungs. The CIRS assessment process takes only a few minutes and gives a simple, yet broad, assessment of a patient’s fitness. There are many other scoring systems for geriatric assessments, but the CIRS met the needs of our study.

New Evidence: What might explain the differences in overall response (OR) and complete response (CR) rates between the current analysis and the previous interim results?

Dr. Hallek: The differences seen in response rates between the interim results and the current findings are due to variations in the types of analyses that were used at the two points. The interim analysis involved counting the number of events two months after the final treatment, while the current analysis assessed the best response. Therefore, although response rates are slightly different, the differences are not clinically relevant. In fact, the current OR rates make more sense medically and fall within the expected range.
**New Evidence:** The greatest benefit in response after treatment with FCR was observed in Binet stage A and B patients, with lower responses seen in Binet C patients. What might explain these results?

**Dr. Hallek:** The interim analysis showed no significant benefit from FCR in the Binet C patients. However, with a median observation time of over 30 months, we now see clear trends for improved response rates and an improved progression-free survival (PFS) for Binet C patients treated with FCR. Statistically speaking, the differences are more impressive in the Binet A and B subgroups than in the Binet C subgroup, but I expect these differences to diminish over time. Reasons for the lower response rates may be due to differences in adherence and risk factors in the FCR versus the FC group in Binet C patients. Treatment delays and dose reductions were also more frequent in Binet C patients for FCR versus FC. The bottom line is that there are clear imbalances, which might explain why Binet C patients did not benefit as strongly. But the benefit of FCR is seen across all stages, and so far differences between Binet stages have diminished over time. We do currently give FCR to Binet C patients, as a benefit in response rates has been shown across all stages.

**New Evidence:** Please discuss the overall survival (OS) results seen in the current analysis.

**Dr. Hallek:** The reason we presented the data at this year’s ASH meeting was a surprising finding from an updated analysis showing a survival benefit for FCR. The OS rate at 37.7 months was 87.2% in the FCR arm versus 82.5% in the FC arm (p = 0.012). This means that there is a 5% difference over three years in the percentage of patients who are still alive. To our knowledge, this is the first randomized trial able to show a survival benefit for any initial therapy given to CLL patients. If you were to extrapolate the OS curve to four years, the difference between treatment groups would increase to around 10%–15%. In other words, we can expect that at four years there will be 10 to 15 additional patients out of 100 who are alive due to the FCR treatment, which would be a substantial improvement.

The importance of the OS finding extends beyond the benefits of FCR. For more than 40 years, we have believed that the order of treatment given in CLL is irrelevant; we thought that we could start with a milder therapy and move to a more aggressive treatment later on. This trial challenges that way of thinking, because it shows that a specific first-line treatment is altering and improving the natural course of the disease. Future research may therefore focus on giving the best treatment first, achieving optimal dosing, and improving CR rates, since these are connected to OS. As a consequence, the current paradigm of CLL treatment will change, which is very positive for patients with CLL.

**New Evidence:** Please discuss the infection rates reported in this analysis.

**Dr. Hallek:** The infection rates are what we would expect to see with treatment; they are mildly increased, but not significantly so, with the addition of FCR. It may be important to give growth factor support or prophylaxis after an infectious episode; however, we did not find this to be necessary in our study. Overall, in a first-line setting, I have found treatment with FCR to be very well tolerated.

**New Evidence:** How might cytogenetic prognostic factors, found to be associated with response in your study, be used in clinical practice?

**Dr. Hallek:** We have found that patients with certain cytogenetic abnormalities benefit particularly from FCR and should be given it as a first choice whenever possible. These patients include those with del(11q), del(13q), and trisomy 12, which include more than 70% of chromosomal aberrations. Thus far, only patients with del(17p) aberrations have shown a limited response to FCR. Three years after randomization, less than 40% of these patients will survive after treatment. For patients with del(17p), we therefore recommend eradication of the disease with FCR or alemtuzumab, followed by allogeneic transplant whenever possible.
**New Evidence:** Given the improvement in OS seen with FCR, should FCR now be considered the standard of care for the first-line treatment of CLL?

**Dr. Hallek:** To this question I profoundly believe there is only one short answer, namely “yes”. Discussions continue on the use of PCR, FR, and other regimens in healthcare systems such as in the United States. However, based on the profound and solid evidence that exists for FCR, I feel it should now be considered a standard for physically fit patients with CLL, and all other regimens should be investigated against FCR in randomized comparisons.

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**New Evidence:** Are there any patients who should not be given FCR first-line? What treatment should be given as an alternative?

**Dr. Hallek:** There is only one alternative to FCR in fit patients and that is to participate in clinical trials. I admit that this is a bit of a rigid answer — maybe reflecting a typically “German” behaviour — but if you want to give the best care to patients, stick to the standard and only deviate when absolutely necessary. I want to stress, however, that FCR is a treatment for physically fit patients. For older patients with severe co-morbidities, one should consider alternatives that are less toxic. In less fit patients, findings are not as far advanced, because clinical research has typically been done in patients who are younger and physically fit. In Europe, chlorambucil monotherapy is considered to be the best standard in this setting. We are looking for improvements to this regimen by adding monoclonal antibodies, as these are usually less toxic. There are several ongoing randomized trials combining chlorambucil with rituximab, GA101, or ofatumumab to see whether their addition will improve the outcome in the “slow-go” patient population.

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**New Evidence:** Is there any justification for using FR in patients who fall between the “slow-go” and the “go-go” categories?

**Dr. Hallek:** I would say that there are only three main patient categories: “go-go”, “slow-go”, and “no-go”. I don’t see a category that falls between “go-go” and “slow-go”. Data presented at this ASH meeting on the use of FR has been disappointing, showing a median PFS that is much lower after 10 years of follow-up than we have seen after using FCR for only 3 years. I would therefore not give FR to fit patients unless proof from a randomized comparison with FCR shows that these regimens are equally effective.

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**New Evidence:** Please describe the administration methods for FCR that are used at your centre.

**Dr. Hallek:** At our centre we use the usual administration methods for FCR. If there are concerns around high leukocyte counts, we sometimes split the dose over two days or use a slower infusion rate in the first few hours; we then observe the patient to ensure the treatment is well tolerated. With the correct pre-medication of antihistamines and steroids, we do not experience any problems in most patients.
A Canadian Perspective on the Management of Chronic Lymphocytic Leukemia

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Laurie H. Sehn, MD, MPH,3
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Medical Writer: Anna Christofides, MSc, RD, New Evidence
Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world, accounting for approximately 7% of non-Hodgkin’s lymphomas. In Canada, the median age at diagnosis is approximately 72 years, with less than 10% of cases diagnosed in patients under 50 years. Age-adjusted incidence rates are 7.5/100,000 person-years (p-yrs), with males representing approximately 57% of cases (male:female ratio = 1.3:1). The five-year relative survival is about 80% (95% CI: 73–86) in men and tends to be higher in women (85%; 95% CI: 78–92).

### Purpose of this document

There is no uniform standard of care for the treatment of CLL and at present, no national guidelines for managing CLL have been developed in Canada. In determining the optimal treatment for CLL, individual patient characteristics including performance status and disease stage must be considered. Based on these criteria, a number of patient subgroups therefore exist and should be included in treatment decisions.

Dr. Douglas Stewart, Dr. Chaim Shustik, Dr. Christine Chen, and Dr. Laurie Sehn drafted this document, which outlines a management approach to CLL. Topics addressed include initial diagnosis, staging and prognostic tests, indications for treatment, first- and second-line treatment options, new regimens, and associated management issues. The document was then reviewed by 10 Canadian hematologists who contributed further content to the document. The following paper describes a general consensus on CLL management, but does not reflect a true evidence-based guideline process with a systematic literature review. In addition, patient preference should always be considered in any treatment decision.

### Diagnosing CLL

The World Health Organization (WHO) defines CLL and small lymphocytic lymphoma (SLL) as “a neoplasm composed of monomorphic small, round to slightly irregular B lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes, admixed with prolymphocytes and paraimmunoblasts forming proliferation centers in tissue infiltrates.”

According to the International Workshop on CLL (IWCLL) 2008 guidelines, the diagnosis of CLL requires ≥5 x 10⁹ B lymphocytes/L in the peripheral blood for the duration of at least three months. In Canada, bone marrow biopsies and computed tomography (CT) scans are not routinely used in the diagnosis or management of CLL. Although CLL and SLL are considered together as similar entities, the term SLL is used to indicate neoplastic tissue infiltration in lymph nodes, spleen, or other organs associated with a circulating B lymphocyte count <5 x 10⁹/L.

As many as 12% of healthy individuals >40 years of age may have low levels (<5 x 10⁹/L) of circulating monoclonal B cells. These cells are phenotypically identical to CLL cells, but there is no evidence of tissue infiltration. This recently identified condition is referred to as monoclonal B-cell lymphocytosis (MBL). MBL progresses to CLL at a rate of 1%–2% of patients per year.

Clinical features of CLL vary in their presentation, course, and outcome. Patients are often asymptomatic at diagnosis, but fatigue, autoimmune hemolytic anemia (AIHA), infections, splenomegaly, hepatomegaly, lymphadenopathy, or extra-nodal infiltrates may be present. Some patients may also exhibit a small serum monoclonal protein, an M-component. Although in rare cases patients may not have lymphocytosis at diagnosis, peripheral blood and bone marrow are usually involved as the disease progresses. Lymph nodes, liver, and spleen are commonly infiltrated, with other extra-nodal sites becoming involved in some patients.

Although some CLL cases may have an atypical immunophenotype, the characteristic profile includes CD19/CD5/CD23/CD43 positivity with weak CD20 and CD11c positivity and dim surface immunoglobulin expression with restricted light chain expression. (Table 1)

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*Adapted from Kalil, et al. 1999; Rothel, et al. 1996.† All express pan B-cell-associated antigens (e.g., CD19, CD20) and HLA-DR class II antigens; –/+, –, +, ++, +/– symbols refer to the frequency a marker is expressed.

CLL = chronic lymphocytic leukemia; FL-L = follicular lymphoma-leukemic phase; HCL/v = hairy cell leukemia/hairy cell leukemia variant; LPL = lymphoplasmacytoid lymphoma; MCL = mantle cell lymphoma; PLL = prolymphocytic leukemia; sIg = surface immunoglobulin
Clinical staging

Two widely accepted staging methods are used at diagnosis in both patient care and clinical trials: the modified Rai and the Binet systems, with the modified Rai system being the most commonly used in Canada. (Tables 2 and 3) These staging systems are relatively simple, relying solely on physical examination and standard laboratory tests.3,5,10

Prognostic tests

A number of predictive and prognostic markers have been identified that may predict for responsiveness to chemotherapy and survival, and may contribute to decisions in the optimal management of CLL. However, these tests may not be routinely available and, with the current state of knowledge, should not determine when to initiate first-line treatment outside the setting of a clinical trial.5

Cytogenetic testing

Interphase fluorescence in situ hybridization (FISH) can be used to identify cytogenetic abnormalities in more than 80% of patients.5 The most common are del(13q) in 14%–40%, deletions and/or trisomy in chromosome 12 in 11%–18%, del(11q) in 10%–32%, del(6q) in 2%–9%, and del(17p) in 3%–27% of patients (the higher value for del(17p) occurring with disease progression and treatment).11 In general, patients with a normal karyotype or isolated del(13q) can be categorized as low risk with prolonged time-to-disease-progression and better chances of long-term survival, whereas patients with del(17p), and del(11q) are more likely to have a poor prognosis.11 Patients with trisomy 12 have a treatment advantage over those with del(17p) or del(11q), as they tend to respond better to fludarabine-based therapy. In addition, patients with del(11q) appear to benefit from the addition of cyclophosphamide to fludarabine (FC), and do particularly well with FC plus rituximab (FCR).11,12 Del(17p) leads to loss of the p53 tumour suppressor gene, which mediates cell death induced by alkylating agents and purine analogues. Hence, patients with del(17p) are typically less responsive to these agents, but may respond to agents such as alemtuzumab, flavopiridol, and lenalidomide.5,11 FISH analysis may therefore be useful in the selection of patients with high-risk disease who might benefit from allogeneic stem cell transplantation (allo-SCT). Such patients are at high risk of treatment failure and are likely to become refractory to treatment or to relapse early after fludarabine-based therapy.13 Though the prognostic value of FISH cytogenetics is best validated when performed at diagnosis, repeat analysis may be justified to identify additional genetic defects acquired with disease progression.5

Staging and prognosis of patients with CLL

### Table 2. Rai and modified Rai classification system*

<table>
<thead>
<tr>
<th>Stage (Rai)</th>
<th>Description</th>
<th>Risk status (Modified Rai)</th>
<th>Median survival (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, with lymphoid cells &gt;30% in the blood and/or bone marrow</td>
<td>Low</td>
<td>11.7</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
<td>8.3</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0–1 with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
<td>5.8</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0–II with hemoglobin &lt;110 g/L</td>
<td>High</td>
<td>1.7</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0–III with platelets &lt;100 x 10^9/L</td>
<td>High</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 IWCLL guidelines; 2008 NCI guidelines; BC Cancer Agency 2008 guidelines3,5

†These median survival estimates are based on earlier study data and do not take into account the revision of CLL diagnostic techniques and the improved efficacy of treatment. A recent retrospective study by Shanafelt, et al. examined median estimated survival times by Rai stage category in CLL patients from the Mayo Clinic patient database. Results showed that median survival times were not reached for low-risk, were approximately 10 years for intermediate-risk, and around 7 years for high-risk patients.10

### Table 3. Binet classification system†

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥100 g/L and platelets ≥100 x 10^9/L and &lt;3 involved nodal areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥100 g/L and platelets ≥100 x 10^9/L and ≥3 involved nodal areas</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt;100 g/L and or platelets &lt;100 x 10^9/L and any number of involved nodal areas</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 NCI guidelines1
†Areas of involvement considered for staging are as follows: (1) Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged), (2) Axillae (involvement of both axillae counts as one area), (3) Groins, including superficial femorals (involvement of both groins counts as one area), (4) Palpable spleen, (5) Palpable liver (clinically enlarged).
IgVH mutational status and VH3.21 gene usage
Approximately half of all CLL patients have leukemic cells with somatic hypermutations in the immunoglobulin heavy chain variable region (IgVH) genes. Patients with IgVH mutations (mutated CLL) have improved survival as compared to those with unmutated IgVH (unmutated CLL). Patients with unmutated CLL exhibit faster disease progression, atypical peripheral blood cell morphology, adverse cytogenetic features, and clonal evolution. The VH3.21 gene is an unfavourable prognostic marker, regardless of IgVH mutational status. Sequencing of the genome required to determine IgVH mutational status is expensive, time-consuming, and not readily available for clinical purposes at most sites.

ZAP-70 and CD38 expression
In the course of identifying surrogate markers for IgVH mutational status, a small number of genes were identified that allow the separation of mutated and unmutated CLL. The most specific of these genes is the one that encodes for a 70-kD zeta-associated protein (ZAP-70). The majority of mutated CLL cases are ZAP-70 negative (defined as ≤20% positive cells), whereas unmutated forms are more often ZAP-70 positive (defined as >20% positive cells). Discordance of ZAP-70 expression and IgVH mutational status is reported in about 25% of CLL patients. ZAP-70 analysis is hampered by variation in technique, leading to inconsistent results across centres.

CD38 is an ectoenzyme involved in transmembrane signalling and cell adhesion, and can correlate with unmutated IgVH status, predicting a poor prognosis. Though easy to perform through flow cytometric techniques, CD38 is discordant with IgVH mutational status in a significant proportion of cases and variability in results over time are drawbacks for its use.

Serum markers
Serum markers such as CD23, thymidine kinase (TK), and β2-microglobulin (β2M) may predict survival or progression-free survival (PFS). Even in cases of early stage disease, serum TK levels correlate with tumour mass and proliferative activity of CLL cells. In addition, high levels of CD23 are associated with diffuse bone marrow infiltration and rapid lymphocyte doubling time. Serum TK and CD23 assays are not routinely used in Canada. Alternatively, serum levels of β2M are easily available at most centres and correlate with both clinical stage and overall survival (OS).

Assessing patient fitness
Patient fitness and co-morbidities should be considered in treatment decisions to determine whether aggressive treatments can be tolerated. Several systems exist for determining patient fitness, two of the most common being the Eastern Cooperative Oncology Group (ECOG) Performance Status and the Cumulative Illness Rating Scale (CIRS). In determining whether a patient can be categorized as fit, one of these scoring systems should be used.

In 1982, ECOG developed a set of performance status criteria that categorizes patients into one of five categories from high to low levels of physical function. These categories were designed to assess how the patient’s disease affects daily living. The ECOG Performance Status categories are also commonly used within the context of CLL to assess treatment intensity and whether elderly patients could be included in specific clinical trials.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*Adapted from Oken, et al.1982
ECOG = Eastern Cooperative Oncology Group
A second system for assessing patient fitness is the Cumulative Illness Rating Scale (CIRS). The CIRS assesses co-morbidities in different organ systems by assigning points to various conditions, such as heart disease. The physician tabulates the number of points in a variety of body systems, where a low score indicates optimal health. 16 This scoring system in combination with creatinine clearance (CrCl) has been used by the German CLL Study Group to assess patient fitness for eligibility in a phase III study evaluating the efficacy of FCR (rituximab, fludarabine, cyclophosphamide) versus FC (fludarabine, cyclophosphamide). 17 See Appendix A for a detailed description of how to calculate the CIRS score. 18

Decision to treat and determining response in the management of CLL

The 2008 National Cancer Institute (NCI) guidelines support the initiation of treatment based on a combination of clinical staging, the presence of symptoms, and disease activity. These criteria are also supported by the 2008 National Comprehensive Cancer Network (NCCN) Guidelines on Non-Hodgkin’s Lymphomas. 5,19 (Table 6)

To date, no studies have demonstrated a clear benefit of early treatment for asymptomatic CLL. However, a number of ongoing studies in otherwise healthy patients with poor prognosis are being performed, examining whether early intervention improves outcomes in this group. These studies by the German CLL Study Group and several U.S. cooperative groups will address whether early intervention with chemoimmunotherapy can improve long-term survival in high-risk patient groups. Whether or not treatment is indicated at the time of assessment, patients should continue to be evaluated for possible infections and disease-related complications, as outlined in the Managing complications and supportive care in CLL section on page 35.

Determining response to treatment

In assessing the response to treatment, a thorough physical examination and blood analysis should be performed. Although useful in clinical trials, imaging studies, including CT scans, are not an essential part of general practice. 5,20 Patients in remission should be re-evaluated every 3–6 months to monitor disease status. 21,22

Based on the results of the assessment, patients may be categorized as having a complete response (CR), a partial response (PR), progressive disease (PD), or stable disease (SD). (Table 7) Patients with a clinically beneficial response include those achieving CR and PR; treatment failure includes those with SD, non-response, PD, or death from any cause. Patients experiencing treatment failure during or within six months of treatment are identified as having refractory disease. Those demonstrating PD after ≥6 months of treatment, who have previously achieved a CR or PR, are identified as having relapsed disease. 5

### Categorizing patients into fitness types

Once a fitness score has been determined based on one of the systems discussed, it is possible to group patients into a fit or frail group. (Table 5)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Fit group** | One of the following:  
  a) ECOG Performance Status 0–2  
  b) CIRS =6 and CrCl ≥70 mL/min |
| **Frail group** | One of the following:  
  a) ECOG Performance Status 3–4  
  b) CIRS >6 or CrCl <70 mL/min |

CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group

### Table 5. Patient fitness types

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Fit group** | One of the following:  
  a) ECOG Performance Status 0–2  
  b) CIRS =6 and CrCl ≥70 mL/min |
| **Frail group** | One of the following:  
  a) ECOG Performance Status 3–4  
  b) CIRS >6 or CrCl <70 mL/min |

CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group

### Table 6. NCI minimum criteria for initiating treatment*†‡

- Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia
- Massive (i.e., at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
- Massive nodes (i.e., at least 10 cm in the longest diameter), or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis, with an increase >50% over two months, or lymphocyte doubling time of <6 months (factors contributing to lymphocytosis or lymphadenopathy other than CLL such as infections should be excluded)
- Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids/standard therapy

*Adapted from the 2008 NCI guidelines*  
†Any one of the following symptoms should also be present: unintentional weight loss ≥10% within the previous six months, significant fatigue, inability to work or perform usual activities, fevers of ≥38.0°C for ≥2 weeks without other evidence of infection, or night sweats for ≥1 month without evidence of infection.  
‡Despite the availability of guidelines for the initiation of treatment, these should be viewed as minimum criteria. Good clinical judgement is always required to determine whether an individual patient will benefit from cytotoxic therapy.  
NCI = National Cancer Institute
Overall survival (OS) is defined as the interval between diagnosis and death from any cause. Until recently, no phase III studies in CLL had shown a significant improvement in OS for one therapy over another. Lack of improvements in OS may be due to ineffective therapy, but may also be due to the natural history of the disease, as well as to the success of salvage therapies and the length of follow-up needed to show a significant effect. For example, in the case of follicular lymphoma, early study results of rituximab added to chemotherapy initially showed an improvement in progression-free survival (PFS) with no OS benefit. However, with longer follow-up, an improvement in OS was observed after 48 months.

### Progression-free survival

PFS is defined as the interval between the first treatment day to the first sign of disease progression, or death from any cause. The International Workshop in CLL (IWCLL) and a publication by Chakravarty and colleagues support the use of PFS as a primary endpoint of phase III clinical trials. Chakravarty, et al. suggest that in the absence of an effect on OS, clinical practice should be guided by trials demonstrating clinically significant improvements in PFS. For example, based on studies showing an improvement in PFS with no established survival benefit, fludarabine-based therapy became a preferred first-line treatment option over chlorambucil in many Canadian provinces.

### Table 7. Criteria for identifying treatment response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response (CR)*</th>
<th>Partial response (PR)†</th>
<th>Progressive disease (PD)</th>
<th>Stable disease (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy†</td>
<td>None &gt;1.5 cm</td>
<td>Decrease ≥50%</td>
<td>Increase ≥50% or appearance of any new lesion</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Liver and/or spleen size</td>
<td>Normal size</td>
<td>Decrease ≥50%</td>
<td>Increase ≥50% or new enlargement when previously normal</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>&gt;1.5 x 10^9/L without need for exogenous growth factors</td>
<td>&gt;1.5 x 10^9/L or &gt;50% improvement over baseline without need for exogenous growth factors</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;100 x 10^9/L without need for exogenous growth factors</td>
<td>&gt;100 x 10^9/L or increase ≥50% over baseline</td>
<td>Decrease ≥50% from baseline or to &lt;100 x 10^9/L secondary to CLL</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;110 g/L (untransfused and without need for exogenous erythropoietin)</td>
<td>&gt;110 g/L or increase ≥50% over baseline</td>
<td>Decrease of &gt;20 g/L from baseline or to &lt;100 g/L secondary to CLL</td>
<td>Increase ≤110 g/L or &lt;50% over baseline, or decrease &lt;20 g/L</td>
</tr>
<tr>
<td>Marrow</td>
<td>Normocellular for age, &lt;30% lymphocytes, no B-lymphoid nodules</td>
<td>No BM requirements to document PR</td>
<td>No BM requirements to document PD</td>
<td>No BM requirements to document SD</td>
</tr>
</tbody>
</table>

*Adapted from 2008 NCI guidelines
†Assessed at least 3 months after treatment
‡At least one parameter must be documented for a minimum of 2 months to establish PR
§Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical exam or ultrasound in general practice)
BM = bone marrow; CR = complete response; CRi = complete response with incomplete marrow recovery; NCI = National Cancer Institute; PD = progressive disease; PR = partial response; SD = stable disease
Minimal residual disease (MRD) assessment in patients who have achieved a CR by standard criteria is typically performed using four-colour flow cytometry or allele-specific oligonucleotide polymerase chain reaction (PCR). With these techniques, one can identify residual CLL cells to a sensitivity of <1 CLL cell per 10^4 leukocytes.\(^5\) Recent studies have suggested that complete elimination of the CLL clone with achievement of an MRD-negative CR may be associated with an improved outcome and a longer PFS.\(^6,31\) However, whether treatments designed to eradicate MRD will improve clinical outcomes requires further clinical study. In clinical trials, the number of MRD-positive CRs is often used as an endpoint and is presumed to be a more sensitive prognostic indicator than CR alone.

First-line treatment options for CLL

Goals of therapy

The ultimate treatment goal in CLL is to achieve a long OS, while minimizing toxicities and improving quality of life (QoL). In the absence of an OS benefit, achieving a long PFS is a reasonable goal of therapy. However, for some frail patients, less aggressive treatments may be required; for others, supportive/palliative treatment may be the best course.\(^32\) Considering the patient’s preference is always important in the determination of any treatment decision.

Chlorambucil

Chlorambucil is an oral antineoplastic nitrogen mustard that acts as an alkylating agent. For over 40 years since its discovery, chlorambucil has been used as a mainstay treatment for CLL. Many different dosing schedules have been used in CLL, including intermittent dosing from 40 mg/m^2 every 28 days to 10 mg/m^2 x 7 every 28 days, or continuous daily dosing of 0.1 mg/kg/day. In clinical trials, chlorambucil leads to overall response (OR) rates of 40%–70% and complete response (CR) rates ranging from 2%–7%. (Table 8) Median time-to-progression is approximately 1–1.5 years with this treatment. A convenient oral dosing and well-established side effect profile make chlorambucil a valuable option for frail patients or for those who decline or are unsuitable for more intensive intravenous therapy.\(^33–36\)

Fludarabine

Fludarabine is a purine analogue that is typically administered intravenously, but is also available in an equally efficacious oral formulation in Canada and Europe. In patients refractory to traditional alkylating-agent therapy, fludarabine was shown to achieve OR rates of approximately 60%\(^37,38\). Following the success of second-line treatment, fludarabine monotherapy was subsequently studied in treatment-naïve patients. The superior activity of fludarabine has been confirmed in randomized comparisons to alkylating agents. Studies showed prolonged PFS (median approximately 2 years), as compared to chlorambucil. Fludarabine also demonstrated superior clinical response, with response rates of 60%–80% and CR rates of 15%–40%\(^34,36,39,40\). (Table 8) A Cochrane meta analysis of four randomized trials (Steurer, et al. 2006) supported the findings of superior PFS with fludarabine (Hazard ratio [HR] 0.70; 95% CI: 0.61–0.82).\(^30\) Recently, a long-term survival analysis of patients from a previous study by Rai, et al. (2000) has shown evidence of an OS advantage of F (63 months; 55–75 months) over chlorambucil (59 months; 51–70 months) \((p = 0.04)\).\(^23\) Despite improved efficacy, rates of neutropenia are higher with fludarabine (41%) than with chlorambucil (28%) \((p < 0.0001)\), reflecting greater hematologic toxicity.\(^26\) Fludarabine is now used in preference to chlorambucil for first-line treatment in many provinces. However, chlorambucil remains a valuable option in frail patients, given the lower rates of neutropenia.

Fludarabine-cyclophosphamide (FC)

Studies of the combination of fludarabine and cyclophosphamide (FC) for second-line treatment in CLL have demonstrated good clinical response, with acceptable toxicity.\(^41\) These promising results in refractory settings led to the examination of FC in treatment-naïve patients.

Three randomized trials comparing fludarabine (F) or FC for frontline therapy in CLL have been published. A study by Eichhorst, et al. from the German CLL Study Group randomized 375 previously untreated patients to FC or F. The OR rate (95% vs. 83%), CR rate (24% vs. 7%), median PFS (48 vs. 20 months), and treatment-free survival (37 vs. 25 months) were higher with FC versus F, with no difference in OS.\(^42\) A study by Flinn, et al. from the U.S. ECOG randomized 278 patients to F or FC. FC achieved higher OR (74% vs. 60%), CR (23% vs. 5%), and median PFS (32 vs. 19 months), with no improvement in OS.\(^43\) Finally, Catovsky, et al. in the UK CLL-4 study randomized patients to chlorambucil, fludara- buce, or FC. Patients treated with FC had better CR and OR rates than with fludarabine (CR: 38% vs. 15%, respectively; OR: 94% vs. 80%, respectively; \(p < 0.0001\) for both comparisons), which were in turn better than with chlorambucil (CR: 7%; OR: 72%; \(p < 0.006\) and 0.04, respectively). In addition, a statistically significant advantage in PFS was seen for the FC arm compared with the other arms \((36\% for FC versus 10\% for both the fludarabine and chlorambucil arms; \(p < 0.00005)\).
FC was superior in all age groups, including patients over 70 years old. However, patients with del(17p) and del(11q) had inferior CR and OR rates, irrespective of treatment group. The above trials demonstrated that FC administered intravenously is more efficacious than fludarabine or chlorambucil as monotherapy, achieving higher CR rates (25%–40%) and longer median PFS (32–48 months). (Table 8)

Despite the improved efficacy of FC versus F, the UK CLL-4 and U.S. ECOG studies found higher neutropenia rates in the FC group; however, less hemolytic anemia was observed with FC (5%) than with fludarabine (11%) or chlorambucil (12%). A second study by Eichhorst, et al. (2007) showed no difference in quality of life (QoL) between treatment groups, while the FC group had a significantly longer PFS.

FC is now considered by many CLL study groups worldwide to be a standard first-line treatment. The FC combination is not approved in most provinces in Canada; however, its use as first-line treatment has been adopted by physicians as a common treatment option. The improvement in response seen with FC as compared to fludarabine or chlorambucil monotherapy makes FC a reasonable option in fit patients who are able to tolerate more aggressive treatment. In frail patients, less aggressive treatment options may be warranted to ensure side effects can be tolerated. In cases where a patient declines intravenous treatment, oral fludarabine or chlorambucil are alternatives.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>Remission duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>40–70</td>
<td>&lt;10</td>
<td>~1 year</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>60–80</td>
<td>15–40</td>
<td>1.5–2 years</td>
</tr>
<tr>
<td>Fludarabine-cyclophosphamide (FC)</td>
<td>75–95</td>
<td>25–40</td>
<td>3–4 years</td>
</tr>
<tr>
<td>Fludarabine-cyclophosphamide-rituximab (FCR)</td>
<td>95.1</td>
<td>44.1</td>
<td>~6–7 years</td>
</tr>
</tbody>
</table>

* These regimens have not been compared in head-to-head clinical trials. CR = complete response; OR = overall response

Addition of rituximab to chemotherapy backbones

Rituximab is a chimeric monoclonal antibody that selectively targets CD20-positive B cells. Rituximab is currently indicated for use in non-Hodgkin’s lymphoma (NHL), where it is recommended as first-line treatment for CD20-positive, diffuse large B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and for untreated Stage III/IV follicular, CD20-positive, B-cell NHL in combination with CVP (cyclophosphamide, vincristine, prednisolone). Rituximab is also indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL and as maintenance therapy for patients with follicular NHL who have responded to induction therapy with either CHOP or R-CHOP.

As a single agent in CLL, rituximab has only moderate activity, perhaps because of the dim CD20 expression on B-CLL cells. However, with higher doses than are typically used in lymphoma, the activity of single-agent rituximab in CLL is greatly enhanced. In a study by Byrd, et al. examining the efficacy of rituximab (375 mg/m²) monotherapy in CLL, the OR, CR, and PR rates were 45% (95% CI: 28–64), 3%, and 42%, respectively. Rituximab has been studied in a number of clinical trials evaluating its additional impact in combination therapy. The NCCN guidelines on CLL currently recommend the use of rituximab in combination with F, FC, or PC (pentostatin, cyclophosphamide) for fit patients. In frail patients, rituximab monotherapy may be a reasonable first-line option; however, results are moderate as mentioned above.

**Fludarabine-rituximab (FR)**

Initial studies of rituximab combinations explored the addition of rituximab to fludarabine. Byrd, et al. (2003) conducted the randomized CALGB 9712 phase II study to determine the efficacy, safety, and optimal administration schedule for rituximab with fludarabine in previously untreated CLL patients. Patients were randomized to receive either six monthly courses of fludarabine concurrently with rituximab, followed two months later by four weekly doses of rituximab as consolidation therapy; or sequential fludarabine monotherapy, followed two months later by rituximab consolidation therapy. A total of 104 patients were randomized to the concurrent (n = 51) and sequential (n = 53) regimens. An OR rate of 90% and CR rate of 47% was observed in the concurrent group, as compared to an OR rate of 77% and CR rate of 28% in the sequential group.

In a subsequent retrospective analysis, Byrd, et al. (2005) compared the treatment outcome for patients given FR in the CALGB 9712 trial to patients given fludarabine monotherapy in the CALGB 9011 trial. Results showed statistically significant higher PFS and OS in patients who received fludarabine and rituximab, as compared with patients who received fludarabine alone.

Despite the lack of phase III studies, the Byrd, et al. phase II results suggest that adding rituximab to fludarabine improves PFS and OS, compared to F monotherapy. Based on the results of phase II trials, some Canadian centres have adopted the use of FR as the standard first-line treatment in both fit and frail patients. Further studies evaluating the FR regimen are currently underway, which may help to clarify its role in CLL patient subsets.
Fludarabine-cyclophosphamide-rituximab (FCR)
The successful addition of rituximab to fludarabine led to the development of other rituximab chemotherapy regimens. Phase II studies examining the addition of rituximab to FC (FCR) demonstrated a high CR and OR rate of ≈70% and ≈95%, respectively.37,49

The impressive results of phase II studies drove the design and execution of a phase III study by the German CLL Study Group (CLL-8 study) comparing the primary endpoint of PFS after treatment with FCR or FC.17 Study participants included 817 patients selected for minimal co-morbidity (CIRS <6). Patients were randomly assigned to receive 6 courses of either FC (F: 25 mg/m² iv on days 1–3 plus C: 250 mg/m² iv on days 1–3) or FC with the addition of rituximab (375 mg/m² iv on day 0 of the first cycle and 500 mg/m² on day 1 of all subsequent cycles). Prophylactic use of antibiotics or growth factors were used at the discretion of the treating physician, but were not specifically recommended in the protocol.

The median observation time was 37.7 months, at which point 761 patients were evaluable for response. The median patient age was 61 years, with a range of 30 to 81 years. Median PFS was reported as 32.8 months in the FC arm and 51.8 months in the FCR arm (HR 0.56; p < 0.0001). The PFS shown in the FC arm was similar to that shown in previous studies using FC, which have reported a range of 32 to 48 months.42,43 Statistically significant differences were observed in OS between the two treatment arms. The OS rate at 37.7 months was 87.2% in the FCR arm versus 82.5% in the FC arm (p = 0.012). In both arms, the median OS has not been reached. Only patients in Binet stages A and B showed a superior OS after FCR treatment (Binet A: HR 0.19, p = 0.09; Binet B: HR 0.45, p < 0.001; Binet C: HR 1.4, p = 0.168). Response rates were higher in the FCR group versus the FC group and are the highest rates of any chemotherapy regimen used to date. (Tables 8 and 9) Grade 3/4 hematological toxicity, neutropenia, and leukocytopenia rates were higher in the FCR versus FC arm (55.7% versus 39.6%, 33.7% versus 21.0%, and 24.0% versus 12.1%, respectively; p < 0.0001).

Based on a high level of evidence from this phase III randomized trial, FCR is currently the best option for the first-line treatment of fit patients with CLL.17 Given that the dose of rituximab used in the FCR regimen for the phase III study was cycle 1–375 mg/m² and cycles 2 to 6–500 mg/m², in combination with 25 mg/m² of fludarabine and 250 mg/m² of cyclophosphamide on days 1–3 of each cycle, it is reasonable to recommend this dose of FCR in clinical practice. However, there is a lack of evidence to show that 500 mg/m² per cycle is superior to 375 mg/m² per cycle; a study comparing the efficacy of these two doses is needed to determine the optimal dose of FCR in CLL. Despite the improved efficacy, the potential toxicity of FCR suggests that frail patients may benefit from less aggressive treatments. In balancing toxicity with efficacy, FR remains a reasonable first-line option in CLL until results from randomized studies are available. For those patients who decline intravenous treatments, oral fludarabine and chlorambucil are reasonable options.

Other rituximab combinations
The addition of rituximab to other chemotherapy backbones in first-line treatment has been explored in a number of phase II studies. These studies have shown promising results using cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR); reduced-dose FCR (FCR-Lite); pentostatin, cyclophosphamide, and rituximab (PCR); rituximab with alemtuzumab (R-A); and rituximab with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM).50–54 A study investigating R-chlorambucil in the first-line treatment of CLL is also being conducted, as well as a study comparing R-chlorambucil to R-bendamustine. The results of these and ongoing studies suggest that the benefits of adding rituximab may extend beyond FCR to other R-chemo regimens. As phase III data become available, these regimens may become valuable options for the first-line treatment of CLL.

| Table 9. Efficacy of FCR versus FC as first-line treatment of CLL (median observation time 37.7 months)* |
|--------------------------------------------------------|--------|--------|--------|
| Efficacy parameter | FC (n = 371) | FCR (n = 390) | p-value |
| Response rates (%) | | | |
| Overall response (OR) | 88.4 | 95.1 | <0.01 |
| Complete response (CR) | 21.8 | 44.1 | <0.01 |
| Partial response (PR) | 66.6 | 51.0 | <0.01 |
| Progression-free survival (PFS) (months) | 32.8 | 51.8 | <0.001 |
| Overall survival (OS) (%) | 82.5 | 87.2 | 0.012 |

*Adapted from Hallek, et al. ASH 200917
**Alemtuzumab for patients with del(17p)**

In cases where FISH analysis has been performed and reveals the presence of del(17p), standard treatments which rely on the p53 pathway for activity may be less effective. Treatments with chlorambucil, fludarabine, and rituximab have shown poor response rates in patients with this cytogenetic abnormality. Alemtuzumab, a humanized anti-CD52 monoclonal antibody that acts via a p53 independent mechanism, may have beneficial results in patients with del(17p).

Evidence of the beneficial role of alemtuzumab was first shown in the refractory setting. A study by Moreton, et al. found an overall response rate of 54% in fludarabine-refractory patients. A subsequent trial performed by Lozanski, et al. found a partial response in 40% of patients with del(17p) or p53 mutations. In the first-line setting, results of a randomized controlled trial (RCT) comparing alemtuzumab to chlorambucil were reported by Hillmen, et al. Of the 282 patients who underwent FISH cytogenetic analysis, 21 (7%) patients had del(17p). Patients with del(17p) who were treated with alemtuzumab had a PFS of 10.7 months compared to 2.2 months for patients who received chlorambucil. Although there was a trend of increased PFS in the del(17p) group treated with alemtuzumab, it did not reach statistical significance. Overall response rates for these two groups were 64% and 20%, respectively. Given the limited effectiveness of standard therapy in patients with del(17p), alemtuzumab may be considered a valuable alternative in this poor-risk group.

**Current options for the first-line treatment of CLL**

To date, only the phase III studies by Hallek, et al. comparing FCR with FC and by Rai, et al. comparing F to chlorambucil have shown evidence of improved OS with one regimen over another. The recommended regimens, as presented in Table 10, are therefore based on the results of studies also showing improvements in remission, with the understanding that the optimal sequence of treatments has not been adequately evaluated in clinical trials.

**Table 10. Recommendations for first-line treatment in CLL**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended regimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit group</td>
<td>First choice: FCR†</td>
</tr>
<tr>
<td></td>
<td>Alternative choice: FR†</td>
</tr>
<tr>
<td>Frail group</td>
<td>First choice: F, Chlorambucil</td>
</tr>
</tbody>
</table>

*In areas where rituximab is not funded for CLL or there exists a contraindication to the use of rituximab, FC may be considered as an alternative to FCR in fit patients.
†To date, there have been no data available from randomized studies examining the efficacy of FR, and no studies have compared FCR to FR. An ongoing NCI randomized study (NCIC CL.3) that includes a number of Canadian centres is currently comparing FCR, FR, and FR with lenalidomide in symptomatic patients. Therefore, in balancing toxicity with efficacy, FR remains a reasonable first-line option in CLL until results from randomized studies are available.

**Individualizing patient treatment**

In some cases, fit patients may require less aggressive therapy to minimize toxicities. In addition, certain frail patients with borderline performance status and normal organ function may be able to tolerate more aggressive therapies than F or chlorambucil. In these instances, FR may be a reasonable treatment option. For patients with del(17p), alemtuzumab may be preferable to standard options due to the poor response to standard therapies. In patients who decline intravenous therapy, oral chlorambucil or fludarabine are acceptable options, although these are associated with lower response durations.

**Treatment for relapsed or refractory CLL**

**Second-line treatment options for relapsed and refractory patients with CLL**

As defined earlier, patients experiencing treatment failure within six months of treatment are identified as having refractory disease. Those demonstrating PD after ≥6 months of treatment, who have previously achieved a CR or PR, are identified as having relapsed disease. Initiation of second-line treatment should be based on NCI criteria, as discussed in the Decision to treat and determining response in the management of CLL section on page 27.

When initial remission is long, re-treatment with the initial regimen may be a reasonable option. When initial remission is short, however, a better response may be achieved by giving a different regimen as second-line treatment. A long remission may be arbitrarily defined as one that is over 1 year, and a short remission as one that is ≤1 year. These second-line treatment options are discussed in the following section.

**Second-line options for frail patients**

Fludarabine and chlorambucil

Where patients have not previously been given fludarabine or chlorambucil, these regimens may be reasonable options for second-line treatment. As discussed earlier, in patients refractory to traditional alkylating-agent therapy, fludarabine has achieved response rates of approximately 60% and may be a good second-line option. Data on the use of chlorambucil or other alkylators as second-line treatment after fludarabine is limited, but may also be reasonable.
Fludarabine-rituximab (FR)
Where not given previously, or after a long first remission, FR may be considered as a second-line option in otherwise healthy patients with borderline performance status or in fit patients requiring less aggressive treatment, as discussed in the First-line treatment options for CLL section on page 29.

Second-line options for fit patients
Fludarabine-cyclophosphamide-rituximab (FCR)
In a phase II study by Wierda, et al. FCR was evaluated in 177 previously treated patients. Treatment consisted of fludarabine (25 mg/m² on days 2–4 of course 1 and days 1–3 of courses 2–6); cyclophosphamide (250 mg/m² on days 2–4 of course 1 and days 1–3 of courses 2–6); and rituximab (375 mg/m² on day 1 of course 1 and 500 mg/m² on day 1 of courses 2–6). Courses were repeated every 4 weeks. The overall CR rate in this study was the highest reported in previously treated patients with CLL; however, low response rates were seen in fludarabine-refractory patients. (Table 11)

In a recent phase III study conducted by the German CLL Study Group (REACH study), FCR was compared to FC in previously treated patients. A median of one prior treatment had been administered, consisting of single-agent alkylator therapy (60%), purine-analogs (16%), or combination treatments (18%). Combination treatments administered were CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), CVP (cyclophosphamide, vincristine, and prednisolone) or F-containing therapy. Patients with prior FC combination treatment or prior rituximab were not eligible. Treatment consisted of fludarabine (25 mg/m² iv/day over 3 days for 6 cycles), cyclophosphamide (250 mg/m² iv/day over 3 days for 6 cycles), and rituximab (375 mg/m² iv for cycle 1 and 500 mg/m² iv for cycles 2–6) for a total of 6 treatment cycles at intervals of 28 days. Patients with a CIRS >6, decreased kidney function, or who had previously received FC were excluded. PFS, the primary endpoint, was prolonged by a median of 10 months (a 50% improvement) in the FCR arm (30.6 months) compared with the FC arm (20.6 months) (p = 0.0002; HR 0.65 [95% CI: 0.51–0.82]). Response rates were also superior in the FCR versus the FC group. (Table 12) Median OS was not reached for FCR and was 53 months for FC (p = 0.29; HR 0.83).

<p>| Table 11. Response to FCR by prior treatment* |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>CR</th>
<th>nPR</th>
<th>PR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>177</td>
<td>25</td>
<td>16</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>25</td>
<td>28</td>
<td>12</td>
<td>36</td>
<td>76</td>
</tr>
<tr>
<td>Rituximab</td>
<td>7</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>76</td>
</tr>
<tr>
<td>FC</td>
<td>34</td>
<td>24</td>
<td>15</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>Fludarabine sensitive</td>
<td>78</td>
<td>33</td>
<td>19</td>
<td>24</td>
<td>77</td>
</tr>
<tr>
<td>Fludarabine refractory</td>
<td>33</td>
<td>6</td>
<td>9</td>
<td>42</td>
<td>58</td>
</tr>
</tbody>
</table>

*Adapted from Wierda, et al. 200559
CR = complete response; nPR = nodular partial response; OR = overall response; PR = partial response

<p>| Table 12. Efficacy of FCR versus FC as second-line treatment of CLL (median observation time 25 months)* |</p>
<table>
<thead>
<tr>
<th>Response rates (%)</th>
<th>FC (n = 276)</th>
<th>FCR (n = 276)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>13.0</td>
<td>24.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>Partial response (PR)/nodular partial response (nPR)</td>
<td>44.9</td>
<td>45.7</td>
<td>0.8642</td>
</tr>
<tr>
<td>Overall response (OR)</td>
<td>58.0</td>
<td>69.9</td>
<td>0.0034</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>22.1</td>
<td>17.0</td>
<td>n/d</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>5.4</td>
<td>2.5</td>
<td>n/d</td>
</tr>
<tr>
<td>Not evaluable†</td>
<td>14.5</td>
<td>10.5</td>
<td>n/d</td>
</tr>
</tbody>
</table>

*Adapted from Robak, et al. 200860
†Mainly patients with response that was not confirmed through a second assessment
The studies by Wierda, et al.\textsuperscript{59} and Robak, et al.\textsuperscript{60} show that FCR may be a reasonable second-line option in fit patients not previously given rituximab or FC. Re-treatment with FCR may also be reasonable in those experiencing a long remission after initial treatment. As previously discussed in the First-line treatment options for CLL section on page 29, frail patients should be given less aggressive treatments due to the potential toxicity of the FCR regimen.

Allogeneic stem cell transplantation (allo-SCT)
In the past 20 years, remarkable advances have been made in allogeneic stem cell transplantation (allo-SCT) for CLL. Traditionally, allo-SCT have been myeloablative, involving the depletion of bone marrow cells through administration of high doses of chemotherapy or radiation prior to transplantation. More recently, non-myeloablative techniques have been developed that require less intensive conditioning in an effort to reduce transplant-related mortality (TRM) rates.\textsuperscript{61}

Myeloablative allo-SCT achieved promising results in chemosensitive patients, with OS and PFS rates of approximately 80\% after 5 years.\textsuperscript{62,63} Unfortunately, the beneficial response of myeloablative procedures is tempered by high TRM rates of approximately 38\%–50\%.\textsuperscript{61,64} Registry data indicate that while one-third of patients will be cured after myeloablative allo-SCT, approximately two-thirds will not survive as a result of TRM or recurrent disease. Experimental studies using non-myeloablative allo-SCT have achieved OS and PFS rates of 60\%–72\% and 52\%–67\%, respectively, with low non-relapse mortality rates of 15\%–22\% after 2 years.\textsuperscript{65,66} However, the risk of relapse may be higher with non-myeloablative versus myeloablative techniques.\textsuperscript{67}

After the failure of first-line therapy, allo-SCT may be considered for patients <65 years with no response to therapy or early relapse (within 12 months), relapse within one year of fludarabine treatment or within two years of fludarabine-based combination therapy, or del(17p) abnormalities requiring treatment.\textsuperscript{13}

Subsequent treatment options for relapsed and refractory patients with CLL
Alemtuzumab (Campath-1H)
Alemtuzumab is a humanized monoclonal antibody against CD52, which is expressed on all CLL cells. An initial phase II study in relapsed patients achieved an OR rate of 54\% and CR rate of 36\%. In addition, approximately 20\% of relapsed patients were categorized as minimum residual disease (MRD) negative. A subsequent study showed a favourable response of approximately 40\% in patients with del(17p) abnormalities.\textsuperscript{55,57} A phase III study in previously untreated patients (CAM307) has showed a reduction in the risk of progression of 42\% with alemtuzumab versus chlorambucil (HR 0.58; \(p = 0.0001\)).OR rates (83\% versus 55\%) and CR rates (24\% versus 2\%) were higher in the alemtuzumab versus chlorambucil group.\textsuperscript{58}

As a result of promising monotherapy results, alemtuzumab has been examined as part of a number of combination regimens. A UK phase II study (UKCLL02) examined alemtuzumab monotherapy in fludarabine-refractory patients, where patients not responding to alemtuzumab could be given concurrent fludarabine. Interim results presented at ASH 2005 in 36 evaluable patients showed OR rates of 44\% in all patients combined.\textsuperscript{68} Another phase II study added alemtuzumab to FCR (R-FC) to determine if efficacy could be improved in previously treated high-risk patients. Preliminary results presented at ASH 2008 showed OR and CR rates of 94\% and 69\%, respectively.\textsuperscript{69} Currently, an ongoing NCI phase III study is comparing FCA with FCR as first-line treatment for CLL, with the primary outcome being PFS at 36 months. A second phase III study is examining the efficacy of FA versus F in previously treated patients, with PFS also the primary outcome. Alemtuzumab may be a reasonable third-line option in fit patients who are fludarabine-resistant or as a method to debulk the disease in preparation for allo-SCT.

Fludarabine-cyclophosphamide-mitoxantrone (FCM)
In a phase II study by Hendry, et al., fludarabine, cyclophosphamide and mitoxantrone (FCM) was evaluated in 24 patients with relapsed or refractory CLL. Patients were treated with mitoxantrone (5 mg/m\(^2\) iv on day 1), fludarabine (25 mg/m\(^2\) iv for 3 days or 24 mg/m\(^2\) orally for 5 days), and cyclophosphamide (250 mg/m\(^2\) iv for 3 days or 150 mg/m\(^2\) orally for 5 days). Eighteen patients had previously received fludarabine, and most were heavily pre-treated, with 40\% having \(>2\) prior treatments. Results showed an OR rate of 78.5\%, CR rate of 32\%, and PR rate of 46.5\%. Median duration of response was 19 months and median survival was 42 months.\textsuperscript{70} A second phase II study by Bosch, et al. examined FCM in 37 patients with recurrent or resistant CLL. Treatment consisted of up to six cycles of fludarabine (25 mg/m\(^2\) iv for 3 days), cyclophosphamide (200 mg/m\(^2\) iv for 3 days), and mitoxantrone (6 mg/m\(^2\) iv for 1 day). The CR rate was 50\%, with 10 cases of negative MRD. The PR rate was 28\% and the median duration of response was 19 months.\textsuperscript{70} FCM was later examined as front-line therapy in a phase II study by Bosch, et al. Sixty-nine patients <65 years received six cycles of fludarabine (25 mg/m\(^2\) iv for 3 days), cyclophosphamide (200 mg/m\(^2\) iv for 3 days), and mitoxantrone (6 mg/m\(^2\) iv for 1 day). The OR, MRD-negative CR, MRD-positive CR, nPR, and PR rates were 90\%, 26\%, 38\%, 14\%, and 12\%, respectively. Patients with del(17p) failed to attain CR.\textsuperscript{71}

Rituximab–high-dose methylprednisolone (R-HDMP)
Rituximab combined with high-dose methylprednisolone (R-HDMP) was evaluated in a phase II study by Castro, et al. in fludarabine-refractory CLL patients. Fourteen patients were treated with three cycles of rituximab (375 mg/m\(^2\) weekly for 4 weeks) in combination with HDMP (1 gm/m\(^2\) daily for 5 days). The OR and CR rates were 93\% and 36\%, respectively;
median time-to-progression was 15 months. Recently, R-HDMP was examined in a second study by Castro, et al. as first-line treatment of CLL. Twenty-eight patients received HDMP (1 g/m^2 each day for 3 days) together with rituximab and prophylactic antimicrobial therapy. The OR and CR rates were 96% and 32%, respectively.

**Other rituximab combinations**

A number of other rituximab-containing regimens have been studied as second-line treatment for CLL. Results of these studies are presented in Appendix B. Future data from phase III studies should help determine whether these regimens are potential second-line options for fit patients. Studies examining less aggressive treatments, such as R-bendamustine and R-chlorambucil, are also underway and may provide additional options in frail patients, pending phase III study results.

**Evolving therapeutic approaches for CLL**

A number of new treatments for CLL are currently being evaluated in clinical trials. Therapies such as lenalidomide and flavopiridol, as well as new monoclonal antibodies such as ofatumumab, GA101, and lumiliximab have shown promising preliminary results. Completed and ongoing clinical trials evaluating these new therapies are presented in Appendix C. As discussed earlier, numerous rituximab combination regimens have been examined in clinical trials (see the First-line treatment options in CLL section on page 29 and Appendix B). A number of ongoing studies are also exploring newer rituximab combinations for first- and second-line treatment and for maintenance treatment in CLL. These ongoing rituximab combination studies are also presented in Appendix C. Participating in ongoing and future clinical trials can help identify optimal treatment regimens for CLL, bringing us closer to reaching our treatment goals.

**Recommendations for relapsed or refractory CLL**

Recommendations for second-line treatment of CLL should consider individual factors such as co-morbidities and the length of the disease-free interval. When initial remission is greater than one year, re-treatment with the initial regimen is reasonable; in shorter remissions, treatment with a different second-line regimen is indicated. In frail patients, fludarabine and chlorambucil are reasonable second-line options where they have not been given previously, or in those experiencing a long remission from either regimen. In fit patients, FCR is an effective regimen in patients naïve to rituximab or FC; reuse of FCR may also be reasonable in patients experiencing a long remission after initial treatment. After the failure of first-line therapy, allo-SCT may be considered for patients <65 years with no response to therapy, with PD within one year of fludarabine treatment or within two years of fludarabine-based combination therapy, or with del(17p) abnormalities requiring treatment.

**Managing complications and supportive care in CLL**

**Prevention and management of infections**

Patients with CLL often have compromised immune systems due to the disease itself and/or its associated treatments. Infections are therefore common, and prophylaxis is appropriate, depending on the type of treatment given. (Table 13) The use of live vaccines in patients with CLL is not inadvisable. However, the use of inactivated vaccines such as annual influenza and pneumococcal polysaccharide (PPV) every 5 years for patients in remission for more than three months is recommended.

---

**Table 13. Antibiotic prophylaxis in patients with CLL**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Possible infection</th>
<th>Antibiotic prophylaxis</th>
<th>Vaccine</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>Encapsulated bacteria</td>
<td>Penicillin</td>
<td>Pneumococcal, Hemophilus, and Meningococcal prior to splenectomy</td>
<td>CMV monitoring by PCR every 1–2 weeks</td>
</tr>
<tr>
<td>Alemtuzumab or allo-SCT</td>
<td>CMV</td>
<td>Valgancyclovir pre-emptive therapy for increased PCR</td>
<td>n/a</td>
<td>CMV monitoring by PCR every 1–2 weeks</td>
</tr>
<tr>
<td>Alemtuzumab, fludarabine, or rituximab</td>
<td>Hepatitis B</td>
<td>Lamivudine 100 mg/day orally for the entire duration of chemotherapy and for six months afterwards</td>
<td>n/a</td>
<td>Avoid in patients with known prior hepatitis B</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Varicella Zoster</td>
<td>Acyclovir or equivalent</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Fludarabine-based treatment</td>
<td>PJP</td>
<td>Bactrim or equivalent may be considered</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; n/a = not applicable; PJP = pneumocystis juroveci pneumonia; PCR = polymerase chain reaction; SCT = stem cell transplant
When infections occur, they should be diagnosed, treated, and reported. The etiology of any infection should be identified as bacterial, viral, or fungal, and the severity should be quantified as minor (requiring either oral antimicrobial therapy or symptomatic care alone), major (requiring hospitalization and systemic antimicrobial therapy), or fatal (death as a result of the infection). Where patients experience recurrent infections that require intravenous antibiotics or hospitalization, antimicrobials should be given as needed. In patients with recurrent infections and where serum IgG is <5 g/L, monthly intravenous immunoglobulins should be given at 0.3–0.5 g/kg; dose and interval should be adjusted to maintain a nadir level of more than 5–7 g/L.19

Autoimmune cytopenias

Patients with CLL are at increased risk of developing autoimmune cytopenias, such as autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenia purpura (ITP), and pure red cell aplasia (PRCA). AIHA will develop in approximately 11% of advanced-stage CLL patients.29 AIHA is diagnosed by the presence of at least one marker of hemolysis (increased indirect bilirubin not due to liver disease, increased lactate dehydrogenase without alternative etiology, increased absolute reticulocyte count, or increased bone marrow erythropoiesis in the absence of bleeding) with direct or indirect evidence of an autoimmune mechanism (positive direct antiglobulin for either IgG or C3d, cold agglutinins, or at least two markers of hemolysis in the absence of evidence of bleeding or hypersplenism).80 ITP is less common, occurring in 2%–3% of CLL patients at diagnosis or during early stage disease.79 ITP can be identified where platelet counts are ≤100 × 10^9/L with no evidence of hypersplenism, no evidence of increased platelet consumption due to other causes, and normal or increased megakaryocytes on bone marrow examination.80 PRCA is present in 6% of CLL patients who are tested.79 PRCA can be diagnosed when hemoglobin concentration is ≤120 g/L with reticulocytopenia and isolated absence of erythrocyte precursors in the bone marrow. Parvovirus infection must be ruled out, which can be done by using blood polymerase chain reaction (PCR) assay.80

ITP and AIHA, as a single abnormality caused by CLL, should be treated initially using glucocorticoids. Second-line options for AIHA include splenectomy, intravenous immunoglobulins, and/or immunosuppressive therapy with cyclosporine A, azathioprine, or low-dose cyclophosphamide. Good responses have also been obtained using rituximab or alemtuzumab.3 Most patients with PRCA will respond to treatment with corticosteroids, but prolonged high doses are usually needed; steroid-sparing agents such as cyclophosphamide may therefore be required. Rituximab may be an additional option for the treatment of PRCA, but success rates are lower than those seen for AIHA or ITP.80

Richter’s syndrome

The majority of Richter syndrome (RS) cases involve the transformation of CLL to an aggressive lymphoma, diffuse large B-cell lymphoma (DLBCL). The morphology of DLBCL consists of sheets of large neoplastic B lymphocytes clearly distinguishable from small lymphocytes, with sparse cytoplasm and clumped chromatin typical of CLL. Diagnosis of RS requires the pathologic identification of CLL transformation to aggressive lymphoma. Ideally, this should be determined by histology using a biopsy of the index lesion.81

Based on existing data, RS may be treated with cytoreductive chemotherapy appropriate for DLBCL, such as R-CHOP, with the goal of achieving a response. The role of consolidation therapies previously tested for CLL or DLBCL in patients responding to initial therapy, as well as the impact of new first-line therapies, may aid in the development of an ideal treatment approach in these patients.81

Tumour lysis syndrome

Tumour lysis syndrome (TLS) occurs when the release of large amounts of intracellular components of lysed malignant cells leads to a number of metabolic imbalances. Resulting hyperuricemia, hyperkalemia, hypocalcemia, and hyperphosphatemia may then lead to renal failure and cardiac arrhythmias. TLS usually occurs within 2–3 days after the initiation of therapy, with rare cases occurring after second-line treatment. Major risk factors include high tumour burden, high rate of proliferation, and disease that is highly responsive to therapy.82

Before the initiation of treatment, hospitalization should be considered for patients with white blood cell counts (WBC) >50,000/mm^3 to ensure adequate hydration and monitoring. In patients with previous episodes of TLS, consultation with a nephrologist should be considered. Where overt uremic symptoms are present, dialysis may be necessary in order to prevent acute renal failure. In outpatients, frequent monitoring of serum electrolytes and uric acid is recommended as a preventative measure.82 Prophylactic allopurinol (300 mg/day orally) is necessary when a rapid lysis of large numbers of lymphocytes is anticipated (initial WBC >200 × 10^9/L). Allopurinol should also be given to patients with significant renal dysfunction or chronic hyperuricemia.3 In the advent of TLS, it may be necessary to interrupt treatment until symptoms are resolved. In hospitalized patients, cardiac activity should be monitored continuously and frequent monitoring of electrolyte levels is recommended.82

Blood product support

Transfusion-related graft-versus-host disease has been described in patients actively receiving fludarabine or alemtuzumab. The Canadian Blood Service recommends that patients on fludarabine or alemtuzumab should receive irradiated and CMV negative blood products.76,77
Over the last decade, the management of CLL has evolved considerably, with the introduction of treatments that extend progression-free survival (PFS) and dramatically improve response rates. The recent phase III study comparing FCR to FC is one of the first to show an improvement in overall survival (OS) of one regimen (FCR) over another (FC). These findings, as well as results showing the highest response rates to date in a phase III study, make FCR the best first-line option for fit patients. Another reasonable option for the initial treatment of CLL is fludarabine-rituximab (FR), which may result in a more favourable safety profile. A randomized study comparing FR to FCR and FR with lenalidomide is underway and will provide further insight into the balance between efficacy and toxicity of the FR regimen. In frail patients, less aggressive treatments such as fludarabine and chlorambucil remain valuable options for the initial treatment of CLL.

When initial remission is long (over one year), re-treatment with the initial regimen is a reasonable option; in shorter remissions, a different second-line regimen may yield a superior response. In frail patients, fludarabine and chlorambucil are reasonable second-line options where they have not been given previously, or in those experiencing a long remission from either regimen. In fit patients, results of a phase III study demonstrating a 50% improvement in PFS over FC show that FCR is an effective treatment choice in patients naïve to rituximab or FC; FCR may also be reasonable in those experiencing a long initial remission. After the failure of first-line therapy, allo-SCT may be considered for patients under 65 years with no response to therapy or early relapse (within 12 months), with progressive disease within a year of fludarabine treatment or within two years of fludarabine-based combination therapy, or with del(17p) abnormalities requiring treatment.

Subsequent treatment with alemtuzumab, FCM, R-HDMP, and other rituximab combinations may be reasonable options based on results of preliminary phase II studies. Future studies on these and evolving new treatments such as lenalidomide, flavopiridol, ofatumumab, GA101, and lumiliximab may provide additional options for the treatment of patients with CLL.

Variability in patient characteristics such as performance status, disease progression, and individual preference should be considered in the development of treatment goals. In addition, the development of prognostic factors aiding in the stratification of patients into high- and low-risk groups may aid in decisions concerning optimal treatment strategies. Positive developments in the treatment of CLL and recent findings from a number of phase III studies move us closer to the creation of a Canadian guideline for its management.
APPENDIX A: Calculating the fourteen-system modified Cumulative Index Rating Scale (CIRS)*

<table>
<thead>
<tr>
<th>Systems</th>
<th>Description</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>- Any cardiac problem (angina, myocardial infarction, arrhythmia, valve problems)?</td>
<td>0</td>
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<tr>
<td></td>
<td>- If affirmative, any medication taken for these problems?</td>
<td>1</td>
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<tr>
<td></td>
<td>- Any heart surgery in the past?</td>
<td>2</td>
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<tr>
<td>Vascular</td>
<td>- Any circulatory problem (includes peripheral atherosclerotic disease, aneurysm of the abdominal aorta...), hypertension, or cholesterol problem?</td>
<td>3</td>
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<td></td>
<td>- If affirmative, any medication taken for these problems?</td>
<td>4</td>
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<tr>
<td></td>
<td>- Any vascular surgery in the past (bypass graft surgery of lower limbs, carotid endarterectomy...)?</td>
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<tr>
<td>Hematological</td>
<td>- Any blood problem (anemia, leukemia, hypercoagulability or any other problem affecting the blood, the blood cells, the spleen or the lymphatic system)?</td>
<td>0</td>
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<tr>
<td></td>
<td>- If affirmative, any medication taken for these problems (such as iron)?</td>
<td>1</td>
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<tr>
<td></td>
<td>Note: Patients taking anticoagulants belong to this system if the main problem is hypercoagulability (thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in Cardiac.</td>
<td>2</td>
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<tr>
<td>Respiratory</td>
<td>- Any respiratory problem (asthma, emphysema, bronchitis, pulmonary embolism)?</td>
<td>3</td>
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<td></td>
<td>- If affirmative, any medication taken for these problems (such as pressurized aerosols)?</td>
<td>4</td>
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<td></td>
<td>- Any lung surgery?</td>
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<td></td>
<td>- Cigarette smoking? How many packs per day? For how long?</td>
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<td>Pack years = number of packs per day x the number of years smoked (example: 1 pack per day for 20 years = 20 pack years)</td>
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<td></td>
<td>Smoker up to 20 pack years: Rated 1</td>
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<td></td>
<td>Smoker from 21 to 40 pack years: Rated 2</td>
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<td></td>
<td>Smoker over 40 pack years: Rated 3</td>
<td></td>
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<tr>
<td>Ophthalmological and otorhinolaryngology</td>
<td>- Any problem with eyes (glaucoma, cataract, important lost of vision), ears (includes important hearing impairment), nose, throat, voice?</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>- Any medication taken for these problems (such as eye drops)?</td>
<td>1</td>
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<tr>
<td></td>
<td>Note: Vertigo and dizziness are included in this section, unless they are of neurological origin.</td>
<td>2</td>
</tr>
<tr>
<td>Systems</td>
<td>Description</td>
<td>Scores</td>
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<tr>
<td><strong>Upper gastrointestinal</strong></td>
<td>- Any problem with stomach or digestion (includes the esophagus, the stomach, and the duodenum)?&lt;br&gt;- If affirmative, any medication taken for these problems?&lt;br&gt;- Any surgery for the stomach or the esophagus?</td>
<td></td>
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<tr>
<td><strong>Lower gastrointestinal</strong></td>
<td>- Any intestinal problem (includes intestinal hernias, constipation, anal problems, incontinence...)?&lt;br&gt;- If affirmative, any medication taken for these problems?&lt;br&gt;- Any surgery for the abdomen?</td>
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<tr>
<td><strong>Hepatic and pancreatic</strong></td>
<td>- Any problem in the liver or the pancreas?&lt;br&gt;- Any medication taken for these problems?&lt;br&gt;- Any surgery for the liver or the pancreas?</td>
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<td></td>
<td>Note: Cholecystectomy is rated in this section.</td>
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<tr>
<td><strong>Renal</strong></td>
<td>- Any problem in the kidneys (impairment in function, infection...)?&lt;br&gt;- If affirmative, any medication taken for these problems?&lt;br&gt;- Any surgery for the kidneys?</td>
<td></td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td>- Any urinary problem (lithiasis, incontinence...)?&lt;br&gt;- If affirmative, any medication taken for these problems?&lt;br&gt;- Any surgery for the urinary bladder, for renal lithiasis?</td>
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<tr>
<td><strong>Musculoskeletal and tegumental</strong></td>
<td>- Any problem in the skin, the joints, the bones, the muscles (includes arthrosis, osteoporosis, carpal tunnel, and any other skin or musculoskeletal problem)?&lt;br&gt;- Any medication, anti-inflammatory drugs? Infiltrations? Creams prescribed by a doctor?&lt;br&gt;Note: Fibromyalgia is rated in this section, but it may also be rated in Psychiatric if necessary.</td>
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<tr>
<td><strong>Neurological</strong></td>
<td>- Any neurological problem (cerebrovascular accident, peripheral neuropathy, headaches...)?&lt;br&gt;- If affirmative, any medication taken for these problems?&lt;br&gt;- Any surgery for these problems?</td>
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<tr>
<td><strong>Endocrine, metabolic, breast</strong></td>
<td>- Any problem of the thyroid gland, obesity, diabetes, or any other hormonal problem?&lt;br&gt;- For obesity:&lt;br&gt;Body mass index (BMI) ≥30: Rated 1&lt;br&gt;BMI ≥30 + medication or moderate disability: Rated 2&lt;br&gt;BMI ≥45: Rated 3&lt;br&gt;- Any medication? Surgery for any of these problems?&lt;br&gt;- Any problem with breasts (dysplasia, cancer....)?&lt;br&gt;- Surgery for these problems?&lt;br&gt;- Menopause (or andropause in men)? Any hormone (the same for men in andropause)?&lt;br&gt;Menopause or andropause: Without hormonotherapy or symptoms: Rated 0&lt;br&gt;Symptomatic or with hormonotherapy: Rated 1</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td>- Any problem of depression, anxiety, alcohol, drug abuse, or other problems?&lt;br&gt;- Any medication taken for these problems?&lt;br&gt;Note: Personality problems are rated in this section, but the patient’s chart should be checked.</td>
<td></td>
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</tbody>
</table>

*Adapted from the Abbreviated guidelines for scoring the Cumulative Illness Rating Scale (CIRS) in family practice. J Clin Epidemiol 2007*.
## APPENDIX B: Studies evaluating rituximab-based regimens for second-line treatment in CLL

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>Treatment arms</th>
<th>Primary/Secondary endpoints</th>
<th>Dose</th>
<th>Patient characteristics</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>German CLL Study Group (GCLLSG) REACH ASH 2008 Abstract: Iba-1</td>
<td>III</td>
<td>Rituximab-fludarabine-cyclophosphamide (FCR) vs. fludarabine-cyclophosphamide (FC) (n = 552, none with previous rituximab or FC treatment)</td>
<td>-OR -CR -PR -PFS</td>
<td>R: 375 mg/m² iv on day 0 of cycle 1; 500 mg/m² iv on day 1 of cycles 2-6 F: 25 mg/m² iv on days 1-3 C: 250 mg/m² iv on days 1-3</td>
<td>-CIRS score &lt;6 -Creatinine clearance ≥70 mL/min</td>
<td>Efficacy: -OR: FCR = 70%, FC = 58% (p = 0.0034) -CR: FCR = 42%, FC = 13% (p = 0.0007) -PR/nPR: FCR = 46%, FC = 45% (p = 0.86) -PFS: FCR = 30.6 months, FC = 20.6 months (10 months difference, p = 0.0002, HR = 0.65) Safety: -AEs (grade 3/4): FCR = 80%, FC = 74% -SAEs: FCR = 50%, FC = 48% -Neutropenia (grade 3/4): FCR = 42%, FC = 40% -Thrombocytopenia (grade 3/4): FCR = 11%, FC = 9% -Infections (grade 3/4): FCR = 18%, FC = 19% -Anemia (grade 3/4): FCR = 2%, FC = 5% Fatal AEs: FCR = 13%, FC = 10%</td>
</tr>
<tr>
<td>Wierda, et al. 2005 J Clin Oncol 2005;23(18):4070–4078</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (FCR) (n = 177)</td>
<td>-OR -CR -PR -nPR</td>
<td>R: 375 mg/m² iv on day 1 of course 1 and 500 mg/m² iv on day 1 of courses 2-6 F: 25 mg/m²/day iv on days 2-4 of course 1 and days 1-3 of courses 2-6 C: 250 mg/m²/day iv on days 2-4 of course 1 and days 1-3 of courses 2-6</td>
<td>-Performance status ≤3 -Adequate kidney and liver function</td>
<td>Efficacy: -OR: 73% -CR: 25% -PR: 32% -nPR: 16% Safety: First infusion: 63% adverse events, but all grade 1/2 Neutropenia:15% (grade 3), 66% (grade 4) Thrombocytopenia:16% (grade 3), 18% (grade 4) Anemia (grade 3/4): 24% Major infections: 16% Minor infections: 18%</td>
</tr>
<tr>
<td>Hillmen, et al. ASH 2007 Abstract: 752 Blood (ASH Annual Meeting Abstracts) 2007;110(11):752</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide-alemtuzumab (CFAR) (n = 60 high-risk patients; 48 evaluable)</td>
<td>-OR -CR -PR -nPR</td>
<td>C: 200 mg/m² on days 3-5 F: 20 mg/m² on days 3-5 A: 30 mg iv on days 1, 3, 5 R: 375-500 mg/m² iv on day 2</td>
<td>Not available</td>
<td>Efficacy: -OR: 94% -CR: 69% Safety: -Myelosupression an issue vs. historical FCR control -No difference in infection vs. historical FCR control</td>
</tr>
<tr>
<td>Castro, et al. 2008 Leukemia 2008;22(11):2048–2053</td>
<td>II</td>
<td>Rituximab-methylprednisolone (R-M) (n = 14)</td>
<td>-OR -CR</td>
<td>R: 375 mg/m² iv weekly for 4 weeks High-dose methylprednisolone: 1 gm/m² daily for 5 days</td>
<td>F-refractory</td>
<td>Efficacy: -OR: 93% -CR: 36% -Median time-to-progression: 15 months -Median time-to-next-treatment: 22 months</td>
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<tr>
<td>Authors</td>
<td>Phase</td>
<td>Treatment arms</td>
<td>Dose</td>
<td>Patient characteristics</td>
<td>Main results</td>
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<tr>
<td>Tsimberidou, et al.</td>
<td>I–II</td>
<td>Rituximab-oxaliplatin-cytarabine (OFAR) (n = 50)</td>
<td>R: 375 mg/m² iv on day 3 of cycle 1 and day 1 of subsequent cycles</td>
<td>-Confirmed Richter’s transformation or F-refractory CLL</td>
<td><strong>Efficacy (CLL patients):</strong></td>
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<td>(CLL: n = 30; RT: n = 20)</td>
<td>Oxaliplatin: 17.5, 20, or 25 mg/m²/day on days 1–4</td>
<td>-Adequate kidney and liver function</td>
<td>• OR: 33%</td>
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<td></td>
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<td></td>
<td>F: 30 mg/m² on days 2, 3</td>
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<td>• Responses achieved: 33% of patients with 17p deletion, 20% of patients</td>
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<td>Cytarabine: 1 g/m² on days 2, 3</td>
<td>with 11q deletion, 0% of patients with trisomy 12, and</td>
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<td>Pegfilgrastim: 6 mg on day 6, every 4 weeks for a maximum of 6 courses</td>
<td>33% of patients with 13q deletion</td>
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<td>-Median response duration: 10 months</td>
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<td><strong>Safety:</strong></td>
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<td>• Mainly hematologic: OFAR caused</td>
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<td>grade 3/4 neutropenia and/or thrombocytopenia in the</td>
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<td>majority of patients</td>
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<td>• Prolonged myelosuppression was not observed</td>
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<td><strong>Efficacy:</strong></td>
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<td>• OR: 65.2%</td>
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<td>• CR: 13.0%</td>
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<td>• PR: 52.2%</td>
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<td><strong>Safety (% of courses):</strong></td>
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<td></td>
<td>• Anemia (grade 3/4): 6.3%</td>
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<td></td>
<td>• Leukopenia/neutropenia (grade 3/4): 10.8%</td>
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<td>• Thrombocytopenia (grade 3/4): 11.9%</td>
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<td>• CTC grade 3/4 infections: 6 episodes</td>
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<td><strong>Efficacy:</strong></td>
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<td></td>
<td>• OR: 70% in all patients; 69% in F-refractory patients</td>
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<td>-No CR documented</td>
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<td><strong>Safety (% of courses):</strong></td>
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<td>• Myelosuppression: 59%</td>
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<td></td>
<td>• Anemia: 32%</td>
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<td>• Thrombocytopenia: 29%</td>
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<td></td>
<td>• Leukocytopenia: 26%</td>
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<td>• Nausea and vomiting: 26%</td>
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<td>• Infections: 22%</td>
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<td>• CTC grade 3/4 infections: 6 episodes</td>
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<td><strong>Safety:</strong></td>
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<td>• Infections in 52% of patients</td>
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<td><strong>Efficacy:</strong></td>
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<td>• OR: 52%</td>
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<td>• CR: 8%</td>
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<td>• PR: 40%</td>
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<td>• nPR: 4%</td>
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<td>• Median time-to-progression: 6 months</td>
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<td><strong>Safety:</strong></td>
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<td></td>
<td>• Neutropenia (grade 3/4): 53%</td>
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<td></td>
<td>• Anemia (grade 3/4): 9%</td>
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<td></td>
<td>• Thrombocytopenia (grade 3/4): 16%</td>
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<td></td>
<td>• Infections (grade 3/4): 28%</td>
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<tr>
<td>Fischer, et al.</td>
<td>II</td>
<td>Rituximab-bendamustine (n = 81; 31 data available)</td>
<td>B: 70 mg/m² on days 1, 2</td>
<td>Included F-refractory patients, patients with AIHA, and patients with RT</td>
<td><strong>Efficacy:</strong></td>
<td></td>
</tr>
<tr>
<td>ASH 2007</td>
<td></td>
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<td>R: 375 mg/m² iv for the first cycle and 500 mg/m² iv for</td>
<td>• OR: 70% in all patients; 69% in F-refractory patients</td>
<td>• OR: 70%</td>
<td></td>
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<tr>
<td>Blood (ASH Annual</td>
<td></td>
<td></td>
<td>subsequent cycles, every 28 days for a maximum of 6 courses</td>
<td>• CR: 13.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting Abstracts)</td>
<td></td>
<td></td>
<td></td>
<td>• PR: 52.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007;110(11):3107</td>
<td></td>
<td></td>
<td></td>
<td>• Myelosuppression: 59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Anemia: 32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Thrombocytopenia: 29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Leukocytopenia: 26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Nausea and vomiting: 26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Infections: 22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• CTC grade 3/4 infections: 6 episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eichhorst, et al.</td>
<td>II</td>
<td>Rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone (R-CHOP)</td>
<td>C: 750 mg/m² iv Doxorubicin: 50 mg/m² iv Vincristine: 1.4 mg/m² iv on</td>
<td>Included F-refractory patients, patients with AIHA, and patients with RT</td>
<td><strong>Safety (% of courses):</strong></td>
<td></td>
</tr>
<tr>
<td>ASH 2005</td>
<td></td>
<td>(n = 34; 25 data available)</td>
<td>day 1 Prednisolone: 100 mg/m² po for 5 days R: 375 mg/m² iv on day 0</td>
<td>-Performance status &lt;3</td>
<td>• Anemia (grade 3/4): 6.3%</td>
<td></td>
</tr>
<tr>
<td>Blood (ASH Annual</td>
<td></td>
<td></td>
<td>from the second treatment course</td>
<td>• Adequate kidney and liver function</td>
<td>• Leukopenia/neutropenia (grade 3/4): 10.8%</td>
<td></td>
</tr>
<tr>
<td>Meeting Abstracts)</td>
<td>II</td>
<td></td>
<td></td>
<td>• Thrombocytopenia (grade 3/4): 11.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005;106(11):2126</td>
<td></td>
<td></td>
<td></td>
<td>• CTC grade 3/4 infections: 6 episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faderl, et al. 2003</td>
<td>II</td>
<td>Rituximab-alemtuzumab (R-A)</td>
<td>A: 3 mg, 10 mg, and 30 mg on 3 consecutive days followed by 30 mg</td>
<td>Included F-refractory patients, patients with AIHA, and patients with RT</td>
<td><strong>Efficacy:</strong></td>
<td></td>
</tr>
<tr>
<td>Blood 2003;101(9):</td>
<td></td>
<td>(n = 48)</td>
<td>on days 3 and 5 of weeks 2–4</td>
<td>• OR: 70% in all patients; 69% in F-refractory patients</td>
<td>• OR: 70%</td>
<td></td>
</tr>
<tr>
<td>3413–3415</td>
<td></td>
<td></td>
<td>R: 375 mg/m² iv weekly for 4 weeks</td>
<td>• CR: 13.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamanna, et al. 2006</td>
<td>II</td>
<td>Rituximab-pentostatin-cyclophosphamide (PCR)</td>
<td>-OR P: 4 mg/m² iv C: 600 mg/m² iv R: 375 mg/m² iv except cycle 1</td>
<td>-Performance status &lt;3</td>
<td>• OR: 70%</td>
<td></td>
</tr>
<tr>
<td>J Clin Oncol 2006;24(10)</td>
<td>II</td>
<td></td>
<td>-All for 6 cycles at 3-week intervals</td>
<td>• Adequate kidney and liver function</td>
<td>• CR: 25%</td>
<td></td>
</tr>
<tr>
<td>1575–1581</td>
<td></td>
<td></td>
<td></td>
<td>• nPR: 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PR: 47%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE = adverse event; AIHA = autoimmune hemolytic anemia; CIRS = Cumulative Illness Rating Scale; CR = complete response; CRI = complete response with incomplete marrow recovery; EFS = event-free survival; HR = hazard ratio; MRD = minimal residual disease; nPR = nodular partial response; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; RT = Richter’s transformation; SAE = serious adverse event
## APPENDIX C. Completed and ongoing studies evaluating new treatment regimens in CLL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors/Patient setting</th>
<th>Dose</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Lenalidomide (Revlimid)    | Chanan-Khan, et al. 2006/Relapsed setting (n = 45)          | 25 mg on days 1–21 of a 28 day cycle                                  | OR: 47%  
CR: 9%                                                             |
|                            | Ferrajoli, et al. 2008/Relapsed setting (n = 45)            | 10 mg daily with dose escalation up to 25 mg daily                   | OR: 32% and 25% in F-refractory patients  
CR: 7%                                                             |
|                            | Chen, et al. ASH 2008/Previously untreated CLL (n = 25)     | 10 mg daily with dose escalation up to 25 mg daily                   | PR: 65%  
SD: 35%                                                             |
|                            | RV-CLL-PI-0099: University Health Network (UHN) Ongoing/Previously untreated CLL (n = 27) | 2.5 mg/day for 3 weeks escalating to 10 mg/day for 3 weeks, followed by 1 week off therapy on a 28 day cycle | Not available |
|                            | RV-CLL-PI-0188: German CLL Study Group (GCLLSSG) Ongoing/Previously untreated CLL (n = 60) | 5 mg daily for 28 days | Not available |
|                            | CC 5013-CLL-008: National Cancer Institute (NCI) Ongoing/Relapsed setting (n = 70) | Arm 1: Lenalidomide – 5 mg daily on days 1–28 of cycle 1; 10 mg daily on days 1–28 of cycle 2; 15 mg daily for remainder  
Arm 2: Chlorambucil – 0.8 mg/kg on days 1 and 15 of each 28-day cycle | Not available |
| Flavopiridol (Alvocidib)   | Lin, et al. 2009/Relapsed high-risk setting (n = 64)        | 30 mg/m² iv bolus + 30 mg/m² iv continuous for dose 1, with escalation to 30 mg/m² iv bolus + 50 mg/m² iv continuous at dose 2 and all subsequent treatments | OR: 53%  
PR: 47%  
CR: 1.6%  
Median PFS: 10–12 months |
|                            | CLLRC-OSU-0491: National Cancer Institute (NCI) Ongoing/Relapsed setting (n = 42) | Infusion (iv) over 30 minutes followed by a 4-hour infusion on days 1, 8, 15, and 22 | Not available |
|                            | EFC6663: Sanofi-Aventis Ongoing/Relapsed setting (n = 165)  | Flavopiridol given weekly                                             | Not available |
| Ofatumumab (HuMax-CD20)    | Coiffier, et al. 2008/Relapsed setting (n = 33)             | Three cohorts: A) 100 mg and three 500 mg doses; B) 300 mg and three 1000 mg doses; C) 500 mg and three 2000 mg doses | Response in largest dose combination (cohort C):  
OR: 50%  
PR: 46%                                                             |
|                            | Osterborg, et al. ASH 2008/Relapsed setting (failed fludarabine; failed/eligible for alemtuzumab) (n = 138) | 8 weekly infusions followed by 4 monthly infusions (dose 1: 300 mg; doses 2–12: 2000 mg) | Response in double-refractory cohort:  
OR: 51%  
Time-to-next-therapy:  
9.0 months  
OS: 13.7 months |
|                            | OMB110911: GlaxoSmithKline Ongoing/Previously untreated CLL (n = 444) | Arm 1: Ofatumumab – 300 mg on day 1 and 1000 mg on day 8 of cycle 1; subsequent cycles, 1000 mg on day 1 every 28 days; Chlorambucil – 10 mg/m² on days 1–7 every 28 days  
Arm 2: Chlorambucil – 10 mg/m² on days 1–7 every 28 days | Not available |
|                            | OMB110913: GlaxoSmithKline Ongoing/Relapsed setting (n = 352) | Arm 1: Fludarabine – 25 mg/m² on days 1–3 for 6 cycles; Cyclophosphamide – 250 mg/m² on days 1–3 for 6 cycles  
Arm 2: Ofatumumab – 300 mg on day 1 and 1000 mg on day 8 of cycle 1; 1000 mg on day 1 of cycles 2–6; FC as above | Not available |
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors/Patient setting</th>
<th>Dose</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA101</td>
<td>Salles, et al. ASH 2008/ Relapsed setting (n = 24)</td>
<td>Escalating doses from 50 mg to 2000 mg iv as a flat dose on days 1, 8, and 22, and subsequently every 3 weeks for a total of 9 infusions</td>
<td>Data for first 12 patients: OR: 58%; CR: 25%; PR: 33%</td>
</tr>
</tbody>
</table>
| BO21004 (CLL11): Hoffman-La Roche Ongoing/ Previously untreated CLL (n = 786) | Arm 1: Chlorambucil – 0.5 mg/kg on days 1 and 15 of cycles 1–6
Arm 2: Rituximab – 375 mg/m² on day 1 of cycle 1; 500 mg/m² for cycles 2–6; Chlorambucil as above
Arm 3: GA101–1000 mg on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2–6; Chlorambucil as above | OR: 65%; CR: 52%; PR: 13%; Median PFS: 19.3 months |
| Lumiliximab | Byrd, et al. ASCO 2008/ Relapsed setting (n = 31) | Either 375 mg/m² or 500 mg/m² of lumiliximab + FCR for up to six 28-day cycles | Not available |
| Veltuzumab | Immunomedics Ongoing/ Patients with previously treated or untreated NHL and CLL (n = 72) | Subcutaneous administration at different doses | Not available |
| Rituximab-bendamustine | German CLL Study Group (GCLLSG) Ongoing/ Previously untreated CLL (n = 550) | Arm 1: FC – iv on days 1–3; Rituximab – iv on day 0 of course 1 and on day 1 of courses 2–6
Arm 2: Bendamustine – iv on days 1 and 2; Rituximab – as in arm 1 | Not available |
| Rituximab-pentostatin-cyclophosphamide | U.S. Oncology Research Ongoing/Previously untreated or treated CLL (n = 280) | Arm 1: Fludarabine-cyclophosphamide-rituximab; doses not given
Arm 2: Rituximab-pentostatin-cyclophosphamide; doses not given | Not available |
| Fludarabine-cyclophosphamide-rituximab-lumiliximab | 152CL201: Biogen Idec Ongoing/ (n = 627) | Arm 1: Fludarabine – 25 mg/m² daily, every 4 weeks for 21 weeks; Cyclophosphamide – 250 mg/m² daily, every 4 weeks for 21 weeks; Rituximab – 50 mg/m² on day 1 and 325 mg/m² on day 3 for the first week, then single doses of 500 mg/m² every four weeks for 21 weeks
Arm 2: Lumiliximab – 50 mg/m² on day 2 and 450 mg/m² on day 4 for the first week, then single doses of 500 mg/m² every four weeks, for 21 weeks; FCR as above | Not available |
| Fludarabine-rituximab-lenalidomide | CL.3 CALGB 10404: Cancer and Leukemia Group B; National Cancer Institute of Canada (NCIC) Ongoing/ (n = 405) | Arm 1 (remission-induction [RI] therapy with FR): Rituximab iv on days 1, 3, and 5 of course 1 and on day 1 of all subsequent courses; Fludarabine phosphate iv or orally on days 1–5; treatment repeats every 28 days for up to 6 courses
Arm 2 (RI therapy with FR followed by remission-consolidation [RC] therapy with lenalidomide): RI therapy as in Arm 1; patients with a CR, PR, or SD proceed to RC therapy beginning approximately 4 months after completion of RI, comprising oral lenalidomide once daily on days 1–21; treatment repeats every 28 days for 3–6 courses
Arm 3 (RI therapy with FCR): Rituximab iv on days 1 and 3 of course 1 and on day 1 of all subsequent courses; Fludarabine phosphate iv or orally on days 1–3; Cyclophosphamide iv on days 1–3; treatment repeats every 28 days for up to 6 courses
Arm 4 [del(11q22.3)-positive] (RI therapy with FCR followed by RC therapy with lenalidomide): First course of RI therapy as in Arm 1 or 2; Rituximab iv on day 1 of all subsequent courses; Fludarabine iv and Cyclophosphamide iv on day 1 on days 1–3; treatment repeats every 28 days for up to 6 courses; beginning approximately 4 months after completion of RI therapy, patients receive RC therapy comprising oral lenalidomide as in Arm 2. | Not available |
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors/Patient setting</th>
<th>Dose</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab-chlorambucil</td>
<td>Hoffman-La Roche Global Ongoing/ (n = 100)</td>
<td>Rituximab: 375 mg/m² iv in cycle 1 and 500 mg/m² iv subsequently Chlorambucil: 10 mg/m² oral on days 1–7 of each cycle</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Hoffman-La Roche Global Ongoing/ (n = 300)</td>
<td>Arm 1: Rituximab-chlorambucil; doses not given Arm 2: Rituximab-bendamustine; doses not given</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab-lenalidomide</td>
<td>CLL Research Consortium Ongoing/ Previously untreated CLL (n = 80)</td>
<td>Rituximab: 375 mg/m² iv weekly for cycle 2, then every 4 weeks for subsequent cycles Lenalidomide at increasing doses orally</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>German CLL Study Group (GCLLSG) Ongoing/ Relapsed setting (n = 36)</td>
<td>Rituximab: 375 mg/m² iv on days 1, 8, 15, 22, then continued once every 4 weeks during cycles 3–12 (not given in cycle 2) Lenalidomide: 10 mg orally starting day 9 of cycle 1</td>
<td>Not available</td>
</tr>
<tr>
<td>Rituximab-lenalidomide-pentostatin-cyclophosphamide</td>
<td>National Cancer Institute (NCI) Ongoing/ Previously untreated CLL (n = 45)</td>
<td>Rituximab: iv on days 1 and 2 for course 1, and on day 1 subsequently PC: iv on day 1 Lenalidomide: 2 months after completion of induction therapy, once daily orally on days 1–28</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Del Poeta, et al. 2007 (n = 28)</td>
<td>Arm 1: Consolidation with rituximab – 375 mg/m² for 4 monthly doses, followed by 150 mg/m² for 12 monthly doses, in patients with a clinical response to FR Arm 2: Observation</td>
<td>Patients receiving rituximab consolidation had a significantly longer response duration than those without consolidation therapy (87% versus 32%, p = 0.001)</td>
</tr>
<tr>
<td></td>
<td>ML19514: Hoffman-La Roche Global/ Previously untreated CLL (n = 85)</td>
<td>Maintenance with rituximab: 375 mg/m² every 3 months for 2 years after a clinical response to R-FCM</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>National Cancer Institute (NCI) Ongoing/ (n = not given)</td>
<td>Arm 1: Maintenance with rituximab every 2 months in patients with a clinical response to FCR Arm 2: Observation</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>ML21283 Hoffman-La Roche Global Ongoing/ (n = 218)</td>
<td>Arm 1: Maintenance with rituximab at 375 mg/m² in patients with a clinical response to rituximab-cladribine-cyclophosphamide Arm 2: Observation</td>
<td>Not available</td>
</tr>
</tbody>
</table>

CR = complete response; FC = fludarabine-cyclophosphamide; FCR = fludarabine-cyclophosphamide-rituximab; FR = fludarabine-rituximab; OR = overall response; OS = overall survival; PC = pentostatin-cyclophosphamide; PFS = progression-free survival; PR = partial response; R-FCM = rituximab-fludarabine-cyclophosphamide-mitoxantrone; RC = remission-consolidation; RI = remission-induction; SD = stable disease
References:


In Canada, non-Hodgkin’s lymphomas (NHL) represent approximately 4% of all cancers. The Canadian Cancer Society estimates that about 7,200 new cases of NHL were diagnosed in Canada in 2009, and approximately 3,200 deaths occurred in the 29,619 patients with NHL.1

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of NHL, accounting for approximately 31% of NHL cases.2 More than 50% of DLBCL patients are over 60 years of age, bringing challenges such as age and concomitant disease into play in making treatment decisions.3 Previously, the standard of care for aggressive lymphomas was CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); however, prognosis was poor, and intensification of chemotherapy was not well tolerated in this group. Results from the Groupe d’Étude des Lymphomes de l’Adulte (GELA) LNH98.5 study, which added rituximab to CHOP (R-CHOP), changed the paradigm for the treatment of elderly DLBCL patients: R-CHOP has now become the standard of care in this setting, and studies are currently underway to determine optimal dosing.4

Follicular lymphoma (FL) is the second most common type of NHL at 22% of cases; FL is relatively more frequent in North American and Western Europe, and less frequent in Asia. Other lymphomas, such as mantle cell lymphoma (MCL), account for between 5% and 10% each of NHL cases.2 The standard of care for aggressive FL is combined immunochemotherapy with rituximab (R-chemo). A 2007 meta-analysis conducted by Schultz and colleagues demonstrated that R-chemo is also superior in patients with indolent or mantle cell lymphoma, as compared to chemotherapy alone.5 In the search for new and more efficacious treatments in this setting, the combination of rituximab and bendamustine, a novel agent consisting of a mechlorethamine (nitrogen mustard) group, a benzimidazole ring, and a butyric acid side chain, is currently under examination.6

Because of the high relapse rate that characterizes the clinical course of FL, new strategies to extend the duration of remission, without significantly increasing toxicity, are needed. Rituximab maintenance therapy is one such strategy that has been the subject of several key clinical trials and has demonstrated clear benefits. Ongoing trials are in progress to determine the safety and efficacy of rituximab maintenance in FL.7

To explore the topics mentioned above, this article reports on four studies in NHL patients presented at ASH 2009. The first study demonstrates that R-CHOP is more efficacious than CHOP in elderly patients with DLBCL after ten-years of follow-up. Interim results of the second study show a trend of higher efficacy and lower toxicity of R-CHOP-21 over R-CHOP-14 in DLBCL. A third study demonstrates superior progression-free survival and complete response for first-line bendamustine plus rituximab (B-R) over R-CHOP in follicular, indolent, and mantle cell lymphomas. Finally, early results of the fourth study suggest that rituximab maintenance therapy for follicular lymphoma patients is safe and well tolerated, even when administered with a rapid infusion protocol.

Background

The Groupe d’Étude des Lymphomes de l’Adulte (GELA) LNH98.5 study compared CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) to CHOP with rituximab (R-CHOP) for the treatment of patients with diffuse large B-cell lymphoma (DLBCL). Follow-up results of the this study at 2, 4, and 7 years have been previously published.1–3

At ASH 2009, Coiffier and colleagues presented data from the ten-year follow-up of the LNH98.5 study, comparing long-term outcomes in DLBCL patients who received either CHOP or R-CHOP.4

Study design

- Patients, aged 60 to 80 years (median age 69 years), were eligible for the study if they had:
  - untreated DLBCL diagnosed according to the Revised European-American Lymphoma or the World Health Organization (WHO) classifications;
  - Stage II, III, or IV disease;
  - Eastern Clinical Oncology Group (ECOG) performance status 0 to 2.
- Patients were excluded if they had:
  - T-cell lymphoma;
  - a history of indolent lymphoma;
  - central nervous system involvement;
  - any serious active concomitant disease;
  - a cardiac contraindication to doxorubicin therapy or a neurological contraindication to vincristine;
  - a positive serologic test for human immunodeficiency virus (HIV);
  - unresolved hepatitis B virus infection.
- At total of 399 patients with untreated DLBCL were randomized to receive:
  - CHOP (n = 197);
  - R-CHOP (n = 202).
- Treatments were administered every three weeks over eight cycles in the following dosages:
  - cyclophosphamide: 750 mg/m² on day 1;
  - doxorubicin: 50 mg/m² on day 1;
  - vincristine: 1.4 mg/m² (up to 2 mg/m²) on day 1;
  - prednisolone: 40 mg/m²/day on days 1–5;
  - rituximab: 375 mg/m² on day 1.
- Sixty percent (60%) of patients had poor risk lymphoma according to International Prognostic Index (IPI) criteria.

Key findings

- Original response rates reported after 2 years of follow-up1 were as follows ($p = 0.005$):
  - R-CHOP – CR: 75%; PR: 7%; no response: 18%.
- After a median follow-up of 7.1 years, events such as progressive disease (PD) during treatment, new treatment, PD after stable disease (SD) or PR, relapse, and death during treatment or following CR were reported for 76% of patients in the CHOP arm versus 58% in the R-CHOP arm.
- After a median follow-up of 10 years, the percentage of events had increased to 80.0% and 64.5% for the CHOP and R-CHOP arms, respectively. (Table 1)

<table>
<thead>
<tr>
<th>Event</th>
<th>CHOP (%)</th>
<th>R-CHOP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD during treatment</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>New treatment</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PD after SD</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>PD after PR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Relapse</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Death during treatment</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Death in CR</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>All events</td>
<td>80</td>
<td>64.5</td>
</tr>
</tbody>
</table>

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

- No events were observed in 105/399 patients: 37 (19%) in the CHOP arm and 68 (34%) in the R-CHOP arm.
- Relapse was observed in 74 (59%) and 51 (34%) of CR patients in the CHOP and R-CHOP arms, respectively.
During the last 3 years of follow-up, 10 additional patients relapsed, 4 in the CHOP arm and 6 in the R-CHOP arm, representing 4% of CR patients.

Causes of death in patients who died when in CR are presented in Table 2.

There were 109 deaths after progression in the CHOP arm (out of 124 patients with progression) compared with 66 in the R-CHOP arm (out of 80 patients with progression).

Twenty-two (22) patients in the CHOP arm and 21 in the R-CHOP arm developed another cancer after study entry.

The most frequent secondary cancers were colon and lung cancer. Two cases of myelodysplastic syndrome (MDS) were observed in the CHOP arm, and one case of acute myelogenous leukemia (AML) was seen in the R-CHOP arm. One patient receiving CHOP presented a multiple myeloma 10 years after DLBCL.

Median overall survival (OS) was much longer in the R-CHOP arm as compared to the CHOP arm (8.4 years versus 3.5 years).

At ten years, event-free survival (EFS) was 34% versus 19%, progression-free survival (PFS) was 36.5% versus 20%, disease-free survival (DFS) was 64% versus 43%, and OS was 43.5% versus 28% for patients treated with R-CHOP versus CHOP, respectively. (Figures 1, 2, 3)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHOP n (%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>90 (64)</td>
</tr>
<tr>
<td>Treatment toxicity</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Infection due to neutropenia</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Another cancer</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Toxicity of additional treatment</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Toxicity of progression-treatment</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Unknown but related to lymphoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Major alteration of general status</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Digestive hemorrhagia</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>140 (100)</td>
</tr>
</tbody>
</table>

Figure 1. Event-free survival in DLBCL patients receiving CHOP or R-CHOP (ten-year median follow-up)

Figure 2. Progression-free survival in DLBCL patients receiving CHOP or R-CHOP (ten-year median follow-up)
Figure 3. Overall survival in DLBCL patients receiving CHOP or R-CHOP (ten-year median follow-up)

Key conclusions

- Results of the ten-year follow-up analysis of the GELA LNH98.5 study show that the benefit induced with the addition of rituximab to CHOP continues over the long term.

- Late relapses (after 5 years) were observed in approximately 4% of patients in both arms, representing 3.5% of all patients, 2% of patients in CR, and 7% of all relapses.

- Outcome after progression is poor with a five-year survival of 25% and 15% in the R-CHOP and CHOP arms, respectively.

- The number of secondary cancers is nearly identical in both arms: 23 secondary cancers overall in 21 (R-CHOP) and 22 (CHOP) patients.

References:

Interim analysis of the LNH03-6B GELA study: R-CHOP-14 compared to R-CHOP-21 in elderly patients with diffuse large B-cell lymphoma

Background
At ASH 2009, Delarue and colleagues presented the results of a planned interim analysis of the LNH03-6B trial, a multicentre, phase III, open-label, randomized trial evaluating the efficacy of R-CHOP given every 14 days (R-CHOP-14) compared to R-CHOP given every 21 days (R-CHOP-21). The analysis was carried out after the inclusion of the first 202 patients, with a median follow-up of 24 months.  

Study design
- Patients aged between 60 and 80 years with DLBCL and age-adjusted International Prognostic Index (aaIPI) ≥1 were eligible for the study.
- Patients were randomized to eight cycles of:
  - R-CHOP-14 (rituximab plus CHOP every 2 weeks);
  - R-CHOP-21 (rituximab plus CHOP every 3 weeks).
- Patients were subsequently randomized between a prophylactic treatment with darbepoetin alfa and a conventional treatment of chemotherapy-induced anemia.
- Granulocyte colony-stimulating factor (GCSF) was given according to physician decision.
- The primary objective was to evaluate the efficacy of R-CHOP-14 compared to R-CHOP-21 as measured by event-free survival (EFS). Events were defined as death from any cause, relapse for complete responders and unconfirmed complete responders, progression during or after treatment, and changes of therapy during allocated treatment.
- Secondary objectives were overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), response rate, and analysis of dose-intensity and toxicity.
• According to previous LNH98-5 protocol, sample size was calculated to demonstrate an improvement of two-year EFS from 55% to 65% with R-CHOP-14.

• Six-hundred (600) patients, randomized 1:1 between the two treatment groups, recruited over four years, and followed for a minimum of one year, will provide 80% power at the overall 5% (two-sided) significance level to detect the expected difference.

Key findings
• In this planned interim analysis, 202 patients were randomized, and 201 received study treatment: 103 with R-CHOP-14 and 98 with R-CHOP-21.

• Median age of patients was 72 years.

• Patients’ characteristics were similar in both groups with a slightly higher proportion of patients with aaIPI 2–3 in the R-CHOP-14 group (67% versus 59%).

• A higher proportion of patients in the R-CHOP-21 group presented with B symptoms (43% versus 37%).

• The median interval between cycles was 15 days in the R-CHOP-14 group and 21 days in the R-CHOP-21 group.

• Seventy-three (73) patients (71%) in the R-CHOP-14 group and 74 patients (76%) in the R-CHOP-21 group completed 8 cycles without progression.

• In the R-CHOP-14 group, the increase of dose-intensity at the end of treatment, calculated according to a three-week interval as a reference, was 125% for cyclophosphamide and doxorubicin.

• Ninety percent (90%) of patients treated with R-CHOP-14 received GCSF versus 66% in the R-CHOP-21 group.

• Response rates for complete response (CR) and unconfirmed complete response (CRu) are shown in Table 1.

• The two-year EFS was 48% in the R-CHOP-14 group compared with 61% in the R-CHOP-21 group ($p = \text{ns}$). (Table 1)

• A similar trend was observed for two-year PFS (49% versus 63%), two-year DFS (57% versus 70%), and two-year OS (67% versus 70%) in the R-CHOP-14 versus the R-CHOP-21 group, respectively ($p = \text{ns}$ for all). (Table 1)

• Grade 3/4 hematological toxicity was more frequent in the R-CHOP-14 group, with a higher proportion of patients receiving red cell or platelet transfusions and/or experiencing febrile neutropenia, which resulted in a higher proportion of patients hospitalized for adverse events.

• No difference was seen for extra-hematological grade 3/4 toxicities.

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>R-CHOP-14 n = 103 (%)</th>
<th>R-CHOP-21 n = 98 (%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response including unconfirmed complete response (CR + CRu)</td>
<td>67</td>
<td>75</td>
<td>$p = \text{ns}$</td>
</tr>
<tr>
<td>Event-free survival (EFS)</td>
<td>48</td>
<td>61</td>
<td>$p = \text{ns}$</td>
</tr>
<tr>
<td>Progression-free survival (PFS)</td>
<td>49</td>
<td>63</td>
<td>$p = \text{ns}$</td>
</tr>
<tr>
<td>Disease-free survival (DFS)</td>
<td>57</td>
<td>70</td>
<td>$p = \text{ns}$</td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td>67</td>
<td>70</td>
<td>$p = \text{ns}$</td>
</tr>
</tbody>
</table>

$\text{ns} = \text{not significant}$

Key conclusions

■ Results of this two-year interim analysis of the LNH03-6B trial do not support data from a previous study that show R-CHOP-14 is superior to R-CHOP-21, given the observed trend to higher efficacy and lower toxicity of the R-CHOP-21 regimen.

■ These results await the final analysis planned for 2010, which will include all 602 patients.

Background
Promising results have been observed in two phase II studies evaluating the combination of bendamustine and rituximab (B-R) in patients with relapsed/refractory indolent or mantle cell lymphomas.1,2

In October 2003, Rummel and colleagues of the German Study Group on Indolent Lymphomas (StiL) initiated a multicentre, randomized, phase III study to compare the efficacy and safety of B-R versus R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) as first-line therapy for patients with follicular (FL), indolent, and mantle cell lymphomas (MCL). Final results of this StiL trial were presented at ASH 2009.3

Study design
- A total of 549 lymphoma patients were randomized to receive a maximum of six cycles of:
  - B-R: rituximab (375 mg/m² on day 1) plus bendamustine (90 mg/m² on days 1 and 2) every 28 days;
  - R-CHOP: rituximab (375 mg/m² on day 1) plus standard CHOP regimen every 21 days.
- The primary endpoint was progression-free survival (PFS).
- Patient characteristics, including age, stage, lactic dehydrogenase (LDH), International Prognostic Index (IPI) score, Follicular Lymphoma International Prognostic Index (FLIPI) score, bone marrow infiltration, and extranodal involvement, showed no statistically significant differences between the two arms of the study.
- Median patient age was 64 years (range 31–83 years).
- Most patients were in Stage IV (B-R: 76.9%; R-CHOP: 77.5%) and Stage III (B-R: 19.2%; R-CHOP: 18.6%).
- Histologies were distributed equally between the B-R and R-CHOP arms: FL: 55% and 56%; MCL: 18% and 19%; and other indolent lymphomas: 27% and 24%, respectively.
- Prophylactic use of antibiotics or growth factors was not generally recommended in this protocol.

Key findings
- A total of 513 randomized patients were evaluable for the final analysis:
  - B-R: 260 patients;
  - R-CHOP: 253 patients.
- Of these, nine patients were not evaluable for response:
  - four patients (three from the R-CHOP arm and one from the B-R arm) due to early death from neutropenic sepsis;
  - three patients due to a subsequent change of therapy after severe toxicity in the first cycle of R-CHOP;
  - one patient in the B-R arm due to progress of disease;
  - one patient in the B-R arm due to early death.
- All patients were counted for evaluation of PFS, overall survival (OS), event-free survival (EFS), and time-to-next treatment (TTNT).
- An event was defined as a response less than a partial response, disease progression, relapse, or death from any cause.
- A median number of six cycles was given in both treatment arms: 82% of B-R patients and 86% of R-CHOP patients received six cycles.
- Median observation time was 32 months at the time of analysis (August 2009).
- Overall response (OR) rate for patients treated with B-R was similar to that of the R-CHOP group. (Table 1)
- Complete response (CR) rate was significantly higher with B-R, compared to R-CHOP ($p = 0.0323$). (Table 1)
- Median PFS, EFS, and TTNT were significantly longer after B-R treatment compared to R-CHOP treatment ($p = 0.0002$). (Table 1)
- OS did not differ between the treatment groups.
- At the time of analysis, 67 deaths had occurred (B-R: 34; R-CHOP: 33).
• R-CHOP treatment was more frequently associated with serious adverse events (SAEs), than treatment with B-R. (Table 2)

• Hematologic toxicities, such as grade 3/4 neutropenia and leukocytopenia, were significantly lower for B-R as compared to R-CHOP ($p < 0.0001$). (Table 2)

• GCSF was used more often in R-CHOP-treated patients (20.0% of all cycles) than in B-R-treated patients (4.0% of all cycles) ($p < 0.0001$).

• The B-R regimen was better tolerated than the R-CHOP regimen, as evidenced by a lower rate of alopecia, a lower number of infectious complications, a lower incidence of peripheral neuropathy, and fewer episodes of stomatitis. (Table 2)

• Drug-associated erythematous skin reaction (urticaria, rash) was seen more often with B-R than with R-CHOP ($p = 0.01$). (Table 2)

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### Table 1. Efficacy of R-B versus R-CHOP in the treatment of patients with advanced follicular, indolent, and mantle cell lymphomas (median observation time 32 months)

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>R-B n = 260 (%)</th>
<th>R-CHOP n = 253 (%)</th>
<th>$p$-value</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (OR)</td>
<td>93.8</td>
<td>93.5</td>
<td>n/a</td>
<td>–</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>40.1</td>
<td>30.8</td>
<td>$p = 0.0323$</td>
<td>–</td>
</tr>
<tr>
<td>Progression-free survival (PFS) (months)</td>
<td>54.8</td>
<td>34.8</td>
<td>$p = 0.0002$</td>
<td>0.58 (0.43–0.77)</td>
</tr>
<tr>
<td>Event-free survival (EFS) (months)</td>
<td>54</td>
<td>31</td>
<td>$p = 0.0002$</td>
<td>0.60 (0.45–0.78)</td>
</tr>
<tr>
<td>Time-to-next-treatment (TTNT)</td>
<td>median not yet reached</td>
<td>40.7</td>
<td>$p = 0.0002$</td>
<td>0.54 (0.39–0.75)</td>
</tr>
</tbody>
</table>

CI = confidence interval; n/a = not available

### Table 2. Adverse events seen in R-B versus R-CHOP treatment groups (median observation time 32 months)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>R-B n = 260 (%)</th>
<th>R-CHOP n = 253 (%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>49 (18.8)</td>
<td>74 (29.2)</td>
<td>n/a</td>
</tr>
<tr>
<td>Hematologic toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neutropenia (grade 3/4)</td>
<td>28 (10.7)</td>
<td>118 (46.5)</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>leukocytopenia (grade 3/4)</td>
<td>31.5 (12.1)</td>
<td>97 (38.2)</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>Alopecia (grade 1 only)</td>
<td>39 (15)</td>
<td>157 (62)</td>
<td>n/a</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>95 (36.5)</td>
<td>121 (47.8)</td>
<td>$p = 0.04$</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>18 (6.9)</td>
<td>73 (28.8)</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16 (6.2)</td>
<td>47 (18.6)</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>Drug-associated erythematous skin reaction</td>
<td>42 (16.2)</td>
<td>23 (9.1)</td>
<td>$p = 0.01$</td>
</tr>
</tbody>
</table>

### Key conclusions

- This final analysis shows that the combination of rituximab plus bendamustine (B-R) improves progression-free survival and complete response rates, with a better tolerability profile than R-CHOP.

- These promising results suggest that B-R has the potential to become a new standard first-line treatment option for patients with FL, MCL, and other indolent lymphomas.

References:
Background
At ASH 2009, Witzens-Harig and colleagues presented early results of the ongoing phase IIIb MAintenance rituximab In follicular lymphoma (MAXIMA) study, designed to evaluate safety and efficacy of rituximab maintenance therapy in first-line patients and patients with relapsed follicular lymphoma (FL).1

Study design
- The MAXIMA study is an ongoing phase IIIb study initiated in August 2006, involving 23 countries.
- The study planned to recruit approximately 500 patients with FL who had responded to induction therapy, including those with a complete response (CR), unconfirmed complete response (CRu), or partial response (PR).
- The goal of the study was to evaluate a broad population of first-line and relapsed patients in the daily clinical practice setting (i.e., varying induction regimens).
- Patients with first-line or relapsed/refractory FL who achieved a response after eight cycles of rituximab-containing induction therapy were eligible to receive rituximab maintenance therapy at the standard dose for FL (375 mg/m²) every eight weeks for a maximum of two years.
- Rituximab was administered as a rapid infusion in centres which use this schedule of administration as standard.
- Primary endpoint was to evaluate safety: adverse events (AEs), serious adverse events (SAEs), lab tests, and vitals.
- Secondary endpoints were to assess the efficacy (PR to CR/CRu) conversion rates, progression-free survival (PFS), event-free survival (EFS), time-to-next-lymphoma-therapy (TNLT), and overall survival (OS).
- The study also examined safety variables associated with the rapid infusion of rituximab.

Main inclusion criteria
- Patients included in the study had histologically confirmed, CD20-positive, grade 1–III A follicular non-Hodgkin's lymphoma (NHL).
- Patients had received adequate induction therapy as first-line treatment or as treatment for relapsed disease.
- Adequate induction therapy was defined as treatment with ≥8 cycles of rituximab (375 mg/m² body surface area), either as monotherapy or combined with chemotherapy.
- Type and number of cycles of chemotherapy added to rituximab were determined according to the investigator's judgment (e.g., 6 cycles of CVP [cyclophosphamide, vincristine, prednisone] combined with 8 cycles of rituximab was considered adequate).
- Patients included in the study had documented complete, unconfirmed complete, or partial response with induction therapy as measured by computed tomography scan, positron emission tomography, or magnetic resonance imaging.
- Response assessment was made within six weeks of study entry.

Key findings
- Recruitment was completed in March 2008, and 545 patients with FL were enrolled in the study.
- Median observation time at clinical cut-off in September 2009 was 20.2 months; at that time 533 patients (97.8%) had completed their first infusion visit.
- Median age of patients was 57 years (range 29–86 years), with 11.6% of patients older than 70 years; 57.2% of patients were female.
- Of the recruited patients, 72.8% had been treated first-line, while the remaining 27.2% had ≥1 previous treatment; 65.1% of patients had an induction with eight cycles of rituximab in combination with CHOP.
Follicular Lymphoma International Prognostic Index (FLIPI) scores were available for 514/545 patients (94%) before induction and 523/545 patients (96%) after induction. FLIPI scores (before/after induction) were: FLIPI 0 (41/228), FLIPI 1 (111/186), FLIPI 2 (195/73), FLIPI 3 (120/27), FLIPI 4 (38/8), and FLIPI 5 (9/1).

Two-thirds (69.7%) of patients entered the study in CR/CRu, and the remaining patients had a PR as a result of their most recent treatment.

Data on a total of 5367 infusions are available, 4000 of standard speed and 1367 of fast infusion.

Median infusion time was 3.26 hours for the standard speed arm and 1.63 hours for the rapid infusion arm.

### Efficacy

- Relapses occurred in 63 of 545 patients (11.6%).
- Only 10.1% of relapses occurred in first-line patients. First-line patients had a lower incidence and later onset of relapse compared to patients who had >1 lines of prior therapy. (Table 1)

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Median time (months)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>7.6</td>
<td>10.1</td>
</tr>
<tr>
<td>&gt;1 line</td>
<td>5.3</td>
<td>15.4</td>
</tr>
</tbody>
</table>

- Patients with a high risk profile (defined as FLIPI >3 before induction therapy) were observed to be at higher risk of relapse. (Table 2)

<table>
<thead>
<tr>
<th>FLIPI score at trial entry</th>
<th>Number of patients</th>
<th>Relapse (n)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLIPI 0, 1</td>
<td>152</td>
<td>11</td>
<td>7.2</td>
</tr>
<tr>
<td>FLIPI 2</td>
<td>195</td>
<td>19</td>
<td>19.7</td>
</tr>
<tr>
<td>FLIPI 3–5</td>
<td>167</td>
<td>31</td>
<td>18.6</td>
</tr>
</tbody>
</table>

- Relapses were seen in only 6.4% of patients who entered maintenance therapy already in CR. (Table 3)
- Of the patients with CRu at study entry, 1.9% improved to CR due to maintenance therapy, while 6.7% of patients with PR at study entry improved towards CRu or CR. (Table 3)

### Safety

- A total of 130 SAEs were reported in 94 patients (17.6% of all treated patients); 16 were considered related to rituximab.
- Grade 3/4 neutropenia occurred in four patients, with two resulting in febrile neutropenia; 21 patients (3.9%) had grade 3/4 infections, with three cases of pneumonia.
- Except for one patient who received rituximab at standard infusion speed and suffered a stroke, no SAEs were recorded within 24 hours of the maintenance infusion, including those patients who received rituximab via a rapid infusion protocol.
- AEs occurred in 0.9% of rapid infusions (12/1367) and 0.8% of standard infusions (32/3980).
- Three laboratory SAEs occurred: increases in alanine transaminase (ALT), aspartate transaminase (AST), and lactic dehydrogenase (LDH) (grade 4).
- Twenty (20) deaths (3.7%) were reported: 6 from lymphoma, 7 from concurrent illness, 2 from other cancer, and 5 others, including 1 from refractory idiopathic thrombocytopenia purpura (ITP), 1 from myocarditis, 1 from secondary leukemia, and 1 from gastrointestinal bleeding.

### Key conclusions

- No notable safety issues were observed with rituximab maintenance therapy administered every two months in either first-line FL patients or patients with relapsed FL.
- Maintenance treatment delivered via a rapid infusion protocol appeared to be safe and well tolerated in this observational study.

The addition of rituximab to CHOP is one of the most important advances in the treatment of diffuse large B-cell lymphoma (DLBCL) in the past decade and has changed the natural history of the disease. Long-term results of the study by Coiffier et al. clearly show that the benefits of R-CHOP are sustained over time, because the ten-year follow-up data from the study remain relatively unchanged from previous analyses. The study found that approximately 4% of patients relapsed after five years, which is to be expected in this population. The significant long-term improvement in overall survival with R-CHOP solidifies this regimen’s position as the standard treatment in DLBCL outside of a clinical trial.

The study by Delarue, et al. comparing R-CHOP-14 to R-CHOP-21 in DLBCL demonstrates that a shorter interval of treatment is feasible, but requires a greater proportion of patients be supported with growth factor. Previous data have suggested that CHOP-14 may be superior to CHOP-21, but this has not yet been studied when combined with rituximab. The Delarue study reports a trend towards improved efficacy and safety for R-CHOP-21 over R-CHOP-14. Based on this interim analysis, the use of R-CHOP-14 outside of clinical trials would be difficult to justify, given the apparent lower toxicity and decreased growth factor requirement with R-CHOP-21. Final results of this study should clarify the relevance of treatment interval in the management strategy of DLBCL.

The combination of bendamustine and rituximab (B-R) in indolent or mantle cell lymphoma (MCL) has shown promise in several phase II studies. These favourable results were confirmed in a randomized phase III trial reported by Rummel, et al. that compared B-R to R-CHOP in a mixed histology population, including patients with indolent and MCL. Overall response rates were similar in both arms of the study; however, a higher complete response rate was seen in the B-R cohort. Notably, progression-free survival was significantly longer for patients receiving B-R compared with R-CHOP. Treatment with B-R was also associated with fewer adverse events, including lower rates of alopecia, leukopenia, peripheral neuropathy, stomatitis, and infectious complications. Bendamustine is not yet approved for use in Canada, but when available will provide an additional therapeutic option for these patients. Ongoing studies should further clarify the role of B-R in the treatment of follicular lymphoma (FL), MCL, and other indolent lymphomas.

The study by Witzens-Harig et al. provides further data on the safety of rituximab maintenance in both front-line and pre-treated FL. Interim results show that rituximab maintenance given as rapid infusion appears to be safe, with minimal toxicities. Given the observational design and short follow-up of this study, the efficacy of maintenance rituximab cannot be assessed. Based on previous reports demonstrating a benefit of maintenance rituximab, B.C. Cancer Agency guidelines recommend the use of rituximab maintenance administered as a 90-minute infusion for patients with newly diagnosed or relapsed indolent lymphoma who achieve a response following induction therapy.

An Interview with Dr. Bertrand Coiffier on Ten-year Follow-up Results of the GELA Study Comparing R-CHOP to CHOP in DLBCL patients

At the ASH 2009 meeting, New Evidence spoke with Dr. Bertrand Coiffier, Head of the Department of Hematology at Hospices Civils de Lyon and Professor at the University Claude Bernard, Lyon, France, about the GELA study. Dr. Coiffier, who is the principal investigator, presented ten-year follow-up results of the study at the ASH meeting.

New Evidence: The results of the Groupe d’Étude des Lymphomes de l’Adulte (GELA) LNH98.5 study were last presented after seven years of follow-up. Please describe the differences between the seven- and ten-year follow-up data.

Dr. Coiffier: After seven years, 76% of patients in the CHOP arm had reported an event, including progressive disease, a new treatment, relapse, or death, compared with 58% in the R-CHOP arm. At ten years, the percentages had increased to 80.0% and 64.5% in the CHOP and R-CHOP arms, respectively.

The main difference seen with the data at ten years is that late relapses occurred in both arms. We noticed that relapses happened between five and ten years after treatment in approximately 4% of patients. We have another paper on late relapses in our centre, which has shown that approximately 5% of patients relapse after five years.

Although it is difficult to prove, these relapsed patients may have had a second lymphoma. Some patients who had germinal centre B-cell-like (GCB) lymphoma at diagnosis had non-GCB lymphoma at the time of relapse. This finding intrigued us, because no trials have ever shown that the phenotype of a lymphoma could change over time. We saw a greater number of overall relapses in the CHOP arm, but if you count only the late relapses that happened after five years, the numbers are almost the same in both arms. It is therefore unlikely that the relapses occurred as a result of the type of treatment given.
**New Evidence:** Please discuss the causes of death in each group.

**Dr. Coiffier:** The causes of death recorded in this study vary greatly, mainly because these patients were older and had a number of concomitant diseases. Deaths were not necessarily related to lymphoma or to the toxicity of the treatment. A few more deaths occurred in the R-CHOP arm. However, fewer relapses were seen in this group, and the average age at death was nearly 80 years; therefore there were more unrelated deaths. We did not see any cardiac- or cancer-related deaths.

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**New Evidence:** Please discuss the survival data in the R-CHOP versus the CHOP arm.

**Dr. Coiffier:** The overall median survival was much longer in the R-CHOP arm than in the CHOP arm: 8.4 versus 3.5 years, respectively. These numbers have not changed much from earlier analyses, since median survival was reached after five years of follow-up.

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**New Evidence:** Please discuss the secondary cancers that were found in each study arm.

**Dr. Coiffier:** The number of secondary cancers was nearly identical in each arm: 21 cancers in the R-CHOP arm and 22 cancers in the CHOP arm. The most frequent cancers found in both groups were colon and lung cancer.

---

**New Evidence:** Please discuss the outcome of patients who had progressive disease in this study.

**Dr. Coiffier:** Five-year survival was 25% in the R-CHOP arm and 15% in the CHOP arm. Approximately 70% of patients died within one year of progression. In addition, around 20% of patients were late responders, and some were given salvage therapy with autologous stem cell transplant.

---

**New Evidence:** How does this study add to the knowledge on the use of R-CHOP in diffuse large B-cell lymphoma (DLBCL)?

**Dr. Coiffier:** There are several conclusions to be drawn from this study. First, R-CHOP improves survival, as compared to CHOP — we reached this conclusion some time ago. Second, R-CHOP has radically changed treatment for elderly patients. We used to believe that elderly patients could not be given intensive therapy or should only receive smaller doses. Clearly, this paradigm has changed, because we now know that patients up to 80 years old can be treated with R-CHOP if they are able to tolerate it. This paradigm shift is the main message of the study. Other important findings are the observation of late relapses and R-CHOP’s low toxicity.

---

**New Evidence:** Please describe the previous experience with R-CHOP in DLBCL.

**Dr. Coiffier:** Before this study, a phase II study in approximately 35 patients, which was reported by Dr. Rose, showed that treatment with R-CHOP was feasible and did not appear to have increased toxicity.

---

**New Evidence:** What are your overall impressions of R-CHOP in DLBCL?

**Dr. Coiffier:** I think that R-CHOP is currently the best treatment for almost all patients with B-cell lymphoma. Before the use of R-CHOP, approximately 30%–35% of patients were refractory to treatment. After R-CHOP became available, this number decreased to approximately 18% of patients. Improvements in treatment have therefore been made, but we need to continue seeking ways to better treat patients who do not respond to R-CHOP. R-CHOP’s advantage is that it is simple to administer and not very toxic. Some neutropenia may occur, but if a granulocyte colony-stimulating factor (GCSF) is used in elderly patients, problems with infections can be minimized. R-CHOP is therefore a good, efficacious treatment that is well tolerated.
New Evidence: What is your experience with R-CHOP-14 (every 2 weeks) versus R-CHOP-21 (every 3 weeks)?

Dr. Coiffier: We now have two studies that compare R-CHOP-14 with R-CHOP-21. A study presented this year by the UK group did not show any difference in response rates between the groups. A higher rate of neutropenia was reported in the R-CHOP-21 group, but GCSF was only used in the R-CHOP-14 group and not in the R-CHOP-21 group, which could explain this finding. We have found similar results in response rates in an ongoing study at our centre. Reasons for the lack of a significant difference may be that the difference in the amount of R-CHOP given is not sufficient to demonstrate a benefit.

New Evidence: What is your experience with rituximab maintenance treatment in DLBCL?

Dr. Coiffier: Very few studies have been published examining the efficacy of rituximab maintenance treatment in DLBCL. The few studies that have been completed show no benefit for this treatment strategy. Approximately 5% of patients with a partial response (PR) will respond to rituximab alone, while approximately 50% of patients with a complete response (CR) will not benefit from rituximab since they have already been “cured.” Of the approximately 25% of patients with a CR who have subsequently relapsed, only 10% will benefit. This means that a total of around 15% of patients will benefit from rituximab maintenance therapy; a large sample size would therefore be needed to show any benefit.

New Evidence: What are the advantages of adding other treatment regimens to R-CHOP?

Dr. Coiffier: Adding other regimens to R-CHOP may be a useful strategy in refractory patients. Ongoing studies examining the efficacy of adding bevacizumab or lenalidomide to R-CHOP are currently underway, but results are not yet available. Bevacizumab monotherapy does not appear to have much effect in DLBCL, but lenalidomide has shown more activity in these patients. However, when added to R-CHOP, these regimens may show an added benefit.

New Evidence: What salvage treatments do you recommend in DLBCL?

Dr. Coiffier: Dihydroxyacetone phosphate (DHAP) is a good salvage treatment, but should not be used in elderly patients due to its toxicity. Ifosfamide, carboplatin, and etoposide (ICE) may be a better choice in older patients. Rituximab should not be used once patients are refractory to R-CHOP. However, if relapses occur more than 6 months after treatment, rituximab-containing regimens such as R-DHAP may be a good option. New combinations may provide additional options for these patients.

In our centre we transplant all patients who relapse and respond to chemotherapy with R-DHAP or DHAP. We usually choose R-DHAP, because we want a chemotherapy that will give a good response before transplant, and it is often difficult to know if patients are refractory to rituximab.

New Evidence: What do you consider is the standard of care in DLBCL?

Dr. Coiffier: R-CHOP is the chemotherapy of choice for the majority of patients. The difficult decision is whether to give 6 x R-CHOP or 8 x R-CHOP. Toxicity is not usually greater with the larger dose, but it is not clear whether or not the larger dose is necessary. We use 8 x R-CHOP in our centre, since this dosage is based on evidence from our study.
Pfizer: Targeting cancer’s many pathways

Pfizer is dedicated to the field of oncology and to improving the lives of patients with cancer through innovative research. Our mission is to bring discovery to life for every person touched by common cancers such as in the breast, colon or lung and less common cancers such as in the pancreas, thyroid or kidney.¹

Pfizer is uncovering the ways in which cancer cells survive and grow in the following four areas of cancer research:

**Angiogenesis**
- Tumours rely on new blood vessels to feed them the nutrients they need to grow.²
- Pfizer is researching ways of blocking the growth of new blood vessels.²

**Immunology**
- The immune system is a group of organs and cells in the body that helps defend it from infections and diseases.²
- Pfizer is striving to understand the role the immune system plays in cancer.²
- This process is called biological response modification.²

**Signal Transduction**
- Signal transduction is the process in which a signal is passed from one molecule to another inside a cell.²
- Signals can be used to activate or block many processes in the cell, such as cell division. In patients with cancer, this signalling process is activated even when it should not be.²
- Pfizer is researching the ways in which these signals interact with cancer cells.²

**Repair and Replication**
- Cancer cells have weaknesses that stop them from repairing themselves or replicating.²
- Pfizer is striving to understand the weaknesses of these cancer cells.

References:
New Agents in the Treatment of Chronic Lymphocytic Leukemia

An increase in knowledge of the key pathways governing cell survival, disease pathogenesis, and the microenvironment in chronic lymphocytic leukemia (CLL) has led to the identification of new targets for drug development. Of the several new agents currently under investigation in clinical trials, some show promising response as monotherapies, while others perform better in combination with existing regimens.1 Three new agents discussed at the ASH 2009 Meeting include GA101 (RO5072759), lenalidomide, and bendamustine.

GA101 (RO5072759) is the first humanized glycoengineered type II anti-CD20 monoclonal antibody to enter clinical trials. Compared to rituximab, GA101 has demonstrated superior antibody-dependent cytotoxicity (ADCC) and direct cell death in vitro. Depletion of B-cells is also greater with GA101, which has shown over 95% decrease in B-cell numbers in lymph nodes. Based on this data, GA101 may be a promising new treatment for CLL.2

Lenalidomide is an immunomodulatory agent that has clinical activity in CLL. In patients with relapsed/refractory CLL, treatment with single agent lenalidomide induces an overall response (OR) rate of 32%–47%. In patients with CLL who have progressed while on lenalidomide monotherapy, the addition of rituximab results in a clinical response in some patients. The combination of rituximab and lenalidomide may therefore improve response in CLL.3

Bendamustine is a purine analog/alkylator hybrid agent that has shown good clinical efficacy and acceptable tolerability in patients with various hematological malignancies. Based on a study showing higher response rates with bendamustine over chlorambucil, with no increase in toxicity (aside from slightly higher myelosupression), the U.S. Food and Drug Administration (FDA) has approved bendamustine for the treatment of CLL. Bendamustine may therefore be a good alternative to chlorambucil in frail patients requiring less aggressive treatments.4

This article reports on four studies presented at ASH 2009: one phase I study indicates that GA101 has promising efficacy and a safety profile similar to rituximab in heavily pre-treated patients; a second phase I study demonstrates GA101 has a similar safety profile in CLL to that observed in non-Hodgkin’s lymphoma (NHL), but with an increased incidence of transient neutropenia; a phase II study shows that lenalidomide in combination with rituximab has superior efficacy to lenalidomide monotherapy in relapsed/refractory CLL, with no increase in toxicity; and a phase III study demonstrates that first-line bendamustine achieves significantly higher response rates and longer remissions than chlorambucil, and is well tolerated in CLL.

Results of a phase I study of GA101 monotherapy followed by maintenance in patients with multiple relapsed/refractory CD20-positive malignant disease

Background
At ASH 2009, Sehn and colleagues presented results of a phase I study investigating the pharmacokinetics, safety, and tolerability of GA101 administered on a weekly x 4 schedule, followed by maintenance therapy.1

Study design
• Patients with relapsed/refractory CD20-positive malignant disease for whom no therapy of higher priority was available were treated with GA101 monotherapy.
• GA101 was administered as a flat dose on days 1, 8, 15, and 22, with the first infusion administered at 50% of the cohort dose.
• Cohort doses were escalated based on safety in a 3 + 3 design.
• Tumour response was assessed at three months.
• Patients achieving a complete response (CR) or partial response (PR) were eligible to receive three-monthly maintenance GA101 for 2 years.
• Select patients with stable disease (SD) and major clinical benefit were also permitted to receive maintenance therapy.

Key findings
Baseline characteristics and disposition
• Since January 2008, 22 patients from five Canadian sites have been treated with GA101 at doses ranging from 100 mg to 2000 mg.
• Safety data were available on all patients, 20 of whom were evaluable for response following induction.
• Median age was 59 years (range 47–77 years).
• Histologies included:
  ▪ ten patients with follicular lymphoma (FL);
  ▪ five patients with chronic lymphocytic leukemia (CLL);
  ▪ three patients with diffuse large B-cell lymphoma (DLBCL);
  ▪ two patients with small lymphocytic lymphoma (SLL);
  ▪ one patients with mantle cell lymphoma (MCL);
  ▪ one patients with marginal zone lymphoma (MZL) with high-grade transformation.
• Patients were highly pre-treated, having received a median of four (range 1–7) prior therapies.
• Nineteen (19) of the 22 patients (86%) had been treated with rituximab at least once.
• Median number of previous treatments was two (range 1–4 treatments).
• Eleven (11) of the 22 patients (50%) were refractory to rituximab.

Pharmacokinetics
• Measurement of plasma cytokines during and immediately after the first infusion showed an increase in interleukin (IL)-6 and IL-8 with a smaller increase in IL-10 and tumour necrosis factor (TNF), a pattern of change that is broadly similar to other anti-CD20 antibodies.
• Minimal change in complement fractions was observed, which is in keeping with the known pre-clinical profile of GA101.
• GA101 pharmacokinetics in this study was characterized by two clearance components, one linear and one saturable, consistent with target-mediated disposition.
• Peak serum concentration levels were achieved by the third dose, with significant inter-patient variability in peak levels noted.

Efficacy
• Overall response (OR) rate was 25% (5 patients), all with PRs; 13 patients had SD; and two patients had progressive disease.
• Of those patients with SD, 6/13 had objective evidence of tumour shrinkage, with one consolidating to a PR with maintenance treatment.
• Clinical benefit was seen across all dosing cohorts, including rituximab-refractory patients.
• Overall (best) response rate in patients with lymphoma was 38% (six PRs).
• In all, eight patients have continued on to maintenance treatment following induction, three of whom have subsequently progressed.
• Patients who progressed included two patients with aggressive lymphoma and one patient with CLL.
• Five patients remain on maintenance therapy: four in remission, with durations ranging from 73 to 258 days, and one with SD.

Safety
• GA101 was well tolerated, with no dose-limiting toxicities observed across the escalating dose cohorts.
• The most common adverse events were grade 1/2 infusion-related reactions (IRRs), characterized by fever, chills, hypo/hypertension, nausea, and vomiting.
• IRRs were mainly associated with the first infusion (16 events), with decreased frequency in subsequent infusions (8 events for all subsequent infusions). (Table 1)
• Four grade 3 IRRs were reported, one associated with tumour lysis syndrome, and one grade 4 IRR, which led to the only permanent discontinuation from the protocol.
• To date, eight serious adverse events have been reported in seven patients, two of which were IRRs. (Table 1)

Table 1. Adverse events in 22 patients following induction treatment with GA101

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reactions (IRRs)</td>
<td>24</td>
</tr>
<tr>
<td>Total IRRs</td>
<td>24</td>
</tr>
<tr>
<td>IRRs (grade 3/4)</td>
<td>5</td>
</tr>
<tr>
<td>Minor infections</td>
<td>6</td>
</tr>
<tr>
<td>Neutropenia (grade 3/4)</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia (grade 3/4)</td>
<td>1</td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>8</td>
</tr>
</tbody>
</table>

Key conclusions

■ GA101 is a novel type II anti-CD20 monoclonal antibody that appears to have a safety profile similar to rituximab, with promising efficacy in a clinically heterogeneous, heavily pre-treated, end-stage patient population.

■ Following review of pharmacokinetic and efficacy data, a dose of 1000 mg has been selected for ongoing phase II trials.


Morschhauser F, et al. ASH 2009: Abstract 884

Results of a phase I study of GA101 in relapsed/refractory chronic lymphocytic leukemia

(Note: See the interview with Dr. Gilles Salles on page 82 for his commentary on this study.)

Background
At ASH 2009, Morschhauser and colleagues presented data from their phase I study examining the safety, tolerability, dose-limiting toxicity (DLT), and pharmacokinetics of GA101 monotherapy in relapsed/refractory chronic lymphocytic leukemia (CLL).1

Study design
• A flat, intravenous dose of GA101 ranging from 400 mg to 2000 mg was given in a safety-driven, dose escalating, 3 x 3 design.

• Two patients have died, one with DLBCL who completed induction but progressed and died prior to efficacy assessment, and one with follicular lymphoma who progressed and died on day 133.

• GA101 was given on days 1, 8, and 22, and subsequently every 3 weeks, for a total of nine infusions.
• Data from 13 CLL patients were analyzed. Of these patients:
  ▪ thirty-three percent (33%) had high-risk cytogenetics [del(17p) or del(11q)];
  ▪ seventy percent (70%) displayed unmutated IgVH status.
• Patients received a median of three (range 1–8) prior regimens, including fludarabine (13/13) and rituximab-containing therapy (8/13).
Key findings

Baseline characteristics and disposition

- Baseline median hematology parameters included:
  - Hemoglobin 12.6 g/dL (range 9.4–14.9 g/dL);
  - White blood cell (WBC) concentration 51.8 x 10^9/L (range 10–124 x 10^9/L);
  - Platelets 191 x 10^9/L (range 48–404 x 10^9/L);
  - Lymphocytes 47.4 x 10^9/L (range 7.0–119.3 x 10^9/L).

Pharmacokinetics

- No significant changes to baseline immunoglobulin levels were observed.
- Measurement of plasma cytokines during and immediately after the first infusion showed a transient increase in interleukin (IL)-6 and IL-8, with smaller increases in IL-10, interferon (IFN)-γ, and tumour necrosis factor (TNF) α.
- Activation of complement was not observed (C3a, C4a, C5a).
- Concurrent to cytokine increase was a decrease in T-cell subsets and natural killer (NK) cell counts (peripheral blood) after the first infusion.
- At the end of treatment, CD3 and CD8 counts had recovered, while median CD4 and CD16/56 counts remained just below the normal range, with no clinical sequelae observed.
- Immunologic monitoring is ongoing.
- B-cell (CD19+) depletion was almost complete for all 13 patients and sustained following the first infusion.
- GA101 pharmacokinetics was characterized by one linear and one time-dependent saturable clearance component, consistent with target-mediated disposition, which is also observed with rituximab.
- While the plasma concentrations demonstrated a dose-dependent increase, there was significant inter- and intra-patient variability.
- Time-dependent clearance was consistent with a reduction in target-mediated antibody clearance with increasing duration of treatment.
- With the same doses of GA101, clearance is faster in CLL patients than in non-Hodgkin’s lymphoma (NHL) patients.

Efficacy

- Best overall response (OR) rate according to the International Workshop on CLL (IWCLL) criteria was 62% (8/13), with one complete response with incomplete hematologic recovery (CRI), seven partial responses (PRs), and five with stable disease (SD), observed across all Fc γIIαA (158F/V polymorphism) genotypes. (Table 1)
- No clear dose relationships were found.
- Responses are ongoing with durations ranging from 3.5 to 8 months.
- End-of-treatment minimal residual disease (MRD) from 7/11 evaluable patients was detectable for six patients (median reduction of 2 log; range 2–4 log) and negative for one (despite an SD, as assessed by CT-scan). (Table 1)

<table>
<thead>
<tr>
<th>Table 1. Response rates following treatment with GA101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
</tr>
<tr>
<td>Best overall response (OR) (n = 13)</td>
</tr>
<tr>
<td>Complete response with incomplete hematologic recovery (CRI) (n = 13)</td>
</tr>
<tr>
<td>Partial response (PR) (n = 13)</td>
</tr>
<tr>
<td>Stable disease (SD) (n = 13)</td>
</tr>
<tr>
<td>MRD positive (n = 7)</td>
</tr>
<tr>
<td>MRD negative (n = 7)</td>
</tr>
</tbody>
</table>

MRD = minimal residual disease

Safety

- GA101 was well tolerated with no dose-limiting toxicities and no dose reductions.
- The most common adverse events were grade 1/2 infusion-related reactions, which were essentially limited to the first infusion.
- GA101-related grade 3/4 hematological toxicities included transient neutropenia (9 events), febrile neutropenia (1 event) and transient thrombocytopenia (1 event). (Table 2)
- Neutropenia recovered spontaneously or with granulocyte colony-stimulating factor (GCSF).
- Serious adverse events were reported in three patients (febrile neutropenia, thrombocytopenia, bronchitis, gingivitis, neutropenia, and tumour lysis syndrome). (Table 2)
- Ten patients had infections (17 episodes with only three of them grade 3). (Table 2)

<table>
<thead>
<tr>
<th>Table 2. Adverse events in 13 patients following treatment with GA101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
</tr>
<tr>
<td>Transient neutropenia (grade 3/4)</td>
</tr>
<tr>
<td>Febrile neutropenia (grade 3/4)</td>
</tr>
<tr>
<td>Transient thrombocytopenia (grade 3/4)</td>
</tr>
<tr>
<td>Infections</td>
</tr>
</tbody>
</table>
Key conclusions

- Phase I results of this study indicate that GA101 has promising activity when given as a single agent to heavily pre-treated CLL patients and has a similar safety profile to that observed in NHL patients, with an increased incidence of transient neutropenia in CLL.

- GA101 is also being explored as a single agent in a phase II study in relapsed/refractory CLL and indolent/aggressive NHL, and in a second phase Ib study in combination with chemotherapy.


Evaluating combination therapy with lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia

Background
At ASH 2009, Ferrajoli and colleagues presented data from their phase II study evaluating the combination of lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL).1

Study design
- Patients with active CLL were eligible if they had received prior purine analog therapy.
- Standard inclusion criteria included:
  - good organ function and performance status;
  - good absolute neutrophil and platelet counts.
- All patients received rituximab (375 mg/m²) intravenously on days 1, 8, 15, and 22 of cycle 1, and then once every four weeks during cycles 3–12.
- Lenalidomide was given orally at a dose of 10 mg/day starting on day 9 of cycle 1 and continuing daily for 12 cycles.
- Each cycle consisted of 28 days of treatment.
- During the first two weeks of therapy, allopurinol was prescribed at a dose of 300 mg as prophylaxis for tumour lysis syndrome.
- Sixty (60) patients were accrued between October 2008 and July 2009.
- Thirty-seven (37) patients received treatment for at least 6 cycles and were evaluable for response and toxicity.

Key findings

Baseline characteristics and disposition
- Median age was 59 years (range 44–83 years), and 15 patients (41%) had Rai stage III–IV disease.
- Median beta-2 microglobulin level was 3.6 mg/dL (range 1.5–9 mg/dL).
- Median number of prior treatments was 2 (range 1–9); nine patients (24%) were refractory to fludarabine, and all patients had received prior rituximab.
- Twenty-six (26) patients (70%) had unmutated IgVH, nine patients (24%) had del(17p) and ten patients (37%) had del(11q) by fluorescent in situ hybridization (FISH) analysis.

Efficacy
- After six cycles of treatment, 25 patients achieved a response:
  - six patients (16%) achieved nodular partial response (nPR);
  - nineteen (19) patients (51%) achieved partial response (PR); for an overall response (OR) of 68%.
- Six patients (16%) attained stable disease (SD) or clinical improvement and are continuing on treatment.
Six patients (16%) failed to respond, including one death that occurred on day 34 owing to infectious complications.

Response rates stratified by individual patient characteristics are presented in Table 1.

**Safety**

- The most common grade 3/4 treatment-related adverse events were:
  - neutropenia in sixteen patients (43%);
  - fatigue in six patients (16%);
  - thrombocytopenia in four patients (11%).
- One patient (3%) developed grade 3 tumour lysis syndrome, and one patient (3%) had grade 3 joint pain.

- Infectious complications occurred in nine patients (24%), including:
  - neutropenic fever in six patients;
  - pneumonia in two patients;
  - urosepsis in one patient.
- Lenalidomide-associated tumour flare reaction was limited to grade 1 in eight patients (22%) and grade 2 in one patient (3%).
- When compared to the baseline, there were significant decreases in the percentage of CD19+, and CD20+ B cells, along with significant increases in the percentages of CD4+, CD8+, CD4+CD25hiCD127- regulatory T, and CD3-CD16+CD56+ natural killer (NK) cells after three cycles of therapy.

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<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total n</th>
<th>nPR n (%)</th>
<th>PR n (%)</th>
<th>OR n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0-65 years</td>
<td>23</td>
<td>4 (17)</td>
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<td>15 (65)</td>
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<td>&gt;65 years</td>
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<td>2 (14)</td>
<td>8 (57)</td>
<td>10 (71)</td>
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<td>Rai stage</td>
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<td>5 (23)</td>
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<td>16 (73)</td>
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<tr>
<td>1–2</td>
<td>22</td>
<td>4 (18)</td>
<td>11 (50)</td>
<td>15 (68)</td>
</tr>
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<td>3–9</td>
<td>15</td>
<td>2 (13)</td>
<td>8 (53)</td>
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<td>FISH</td>
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<tr>
<td>del(17)p</td>
<td>9</td>
<td>3 (33)</td>
<td>3 (33)</td>
<td>6 (67)</td>
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<td>del(11)q</td>
<td>10</td>
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<td>6 (60)</td>
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<td>7</td>
<td>2 (29)</td>
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<td>4 (57)</td>
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<td>Mutated</td>
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<td>Unmutated</td>
<td>26</td>
<td>6 (23)</td>
<td>12 (46)</td>
<td>18 (69)</td>
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<tr>
<td>ß-2M</td>
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<tr>
<td>0–4 mg/L</td>
<td>20</td>
<td>3 (15)</td>
<td>11 (55)</td>
<td>14 (70)</td>
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<tr>
<td>&gt;4 mg/L</td>
<td>16</td>
<td>3 (19)</td>
<td>8 (50)</td>
<td>11 (69)</td>
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<tr>
<td>All patients</td>
<td>37</td>
<td>6 (16)</td>
<td>19 (51)</td>
<td>25 (68)</td>
</tr>
</tbody>
</table>

β-2M = beta-2 microglobulin; FISH = fluorescent in situ hybridization; nPR = nodule partial response; OR = overall response; PR = partial response

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**Key conclusions**

- Results suggest that the combination of lenalidomide and rituximab is superior to single agent lenalidomide, despite all patients having received prior rituximab.

- No increase in toxicity was reported.

- Lenalidomide-associated tumour flare reaction was less frequent and less severe with rituximab and lenalidomide, as compared to single agent lenalidomide.

Background
At ASH 2009, Knauf and colleagues presented data from their phase III study comparing the efficacy and tolerability of first-line bendamustine to chlorambucil monotherapy in chronic lymphocytic leukemia (CLL).1

Study design
- The study was a randomized, open-label, parallel-group, phase III trial conducted at 45 centres in Austria, Bulgaria, France, Germany, Italy, Spain, Sweden, and the United Kingdom.
- Patients were randomized in a 1:1 ratio to receive bendamustine or chlorambucil with stratification by centre and Binet stage.
- Bendamustine was given by intravenous infusion over 30 minutes at a dose of 100 mg/m²/day on days 1–2, every 4 weeks.
- Chlorambucil was given orally at a dose of 0.8 mg/kg (Broca's normal weight) on days 1 and 15 (or as divided doses on days 1–2 and 15–16) every 4 weeks.
- Patients were assessed for response after three cycles of treatment.
- Two additional cycles were recommended for patients with complete response (CR) or partial response (PR), up to a maximum limit of six cycles in total.
- Patients up to 75 years of age with symptomatic Binet stage B or C CLL were eligible for the study if they met the need-to-treat criteria for CLL and had not previously received treatment.
- All patients were required to have a World Health Organization (WHO) performance status of 0–2 and a life expectancy of at least three months.
- Women of childbearing potential were required to use adequate contraception for at least six months after treatment.
- Patients were required to have adequate renal and hepatic function, and good general health status to be included in the study.
- Bone marrow biopsy (histology and cytology) was performed to confirm a CR at least eight weeks after a CR had been clinically assumed.
- Patient status was assessed after each cycle, with a follow-up of three monthly intervals after completion of therapy.

Key findings
- A total of 319 patients were randomized (162 bendamustine; 157 chlorambucil); all patients were evaluable for efficacy, and 312 were evaluable for safety.
- Median age was 64 years (range 35–78 years).
- Median number of treatment cycles was six in both study arms, regardless of age above or below 65 years.
- Median observation time was 35 months.
- Overall response rate was significantly higher with bendamustine than with chlorambucil (68% versus 31%, \( p < 0.0001 \)).
- Median progression-free survival (PFS) was 21.6 months with bendamustine and 8.3 months with chlorambucil (\( p < 0.0001 \)).
- So far, there is no difference in overall survival (median not reached with bendamustine versus 65.4 months with chlorambucil; \( p = 0.16 \)).
- No significant difference in remission rates became apparent when comparing patients below and above the age of 65 years. (Table 1)

Table 1. Quality of response to bendamustine and chlorambucil by age category

<table>
<thead>
<tr>
<th>Quality of response</th>
<th>Bendamustine</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;65 years n (%)</td>
<td>≥65 years n (%)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>31 (35.2)</td>
<td>19 (25.7)</td>
</tr>
<tr>
<td>Nodular partial response (nPR)</td>
<td>12 (13.6)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>20 (22.7)</td>
<td>23 (31.1)</td>
</tr>
<tr>
<td>Overall response (OR)</td>
<td>63 (71.6)</td>
<td>47 (63.5)</td>
</tr>
</tbody>
</table>
• PFS was not influenced by age category, stage of disease (Binet stage B versus C), or elevated lactate dehydrogenase (LDH). (Figures 1–3)

• Patients without B symptoms had a longer median PFS with bendamustine than those patients with B symptoms (30.4 months versus 17.7 months; \( p < 0.0001 \)); whereas median PFS was not affected by the presence of B symptoms in patients with chlorambucil (8.9 months in both patient groups).

• The most common grade 3/4 treatment-related adverse events included blood and lymphatic disorders, pneumonia, and rash. (Table 2)
Table 2. Grade 3/4 adverse events reported in >5% of patients by age category

<table>
<thead>
<tr>
<th>Organ class</th>
<th>Bendamustine &lt;65 years n (%)</th>
<th>≥65 years n (%)</th>
<th>Chlorambucil &lt;65 years n (%)</th>
<th>≥65 years n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14 (16.1)</td>
<td>9 (12.2)</td>
<td>1 (1.4)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Lymphopenia/ granulocytopenia</td>
<td>6 (6.9)</td>
<td>4 (5.4)</td>
<td>0 (0.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23 (26.4)</td>
<td>14 (18.9)</td>
<td>5 (7.1)</td>
<td>9 (11.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (12.6)</td>
<td>8 (10.8)</td>
<td>4 (5.7)</td>
<td>8 (9.9)</td>
</tr>
<tr>
<td>Infections</td>
<td>2 (2.3)</td>
<td>1 (1.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0.0)</td>
<td>4 (5.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Skin disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>0 (0.0)</td>
<td>4 (5.4)</td>
<td>2 (2.9)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Key conclusions

- Bendamustine achieved significantly higher response rates and longer remissions than chlorambucil when used as first-line therapy in patients with CLL, and showed superiority over chlorambucil in the elderly (≥65 years) and across major clinical risk groups.

- Bendamustine was generally well tolerated in this study; hematotoxicity due to bendamustine was not pronounced in the elderly, as compared to younger patients.

- The presence of B symptoms shortened progression-free survival in bendamustine-treated patients; B symptoms may therefore define a subgroup of patients who could especially benefit from bendamustine-based combinations.

A number of ongoing studies are investigating the efficacy of GA101, a new monoclonal antibody, for the treatment of chronic lymphocytic leukemia (CLL). The study by Sehn, et al. examines monotherapy and maintenance treatment with GA101 in relapsed/refractory disease; patients with potentially poor outcomes, such as those with mantle cell lymphoma and diffuse large B-cell lymphoma are included. Despite this high-risk patient population, results thus far appear favourable, with overall response (OR) rates of 25%. In addition, eight patients went on to receive maintenance treatment, half of whom are in remission. Safety results are also reassuring, given that some neutropenia is to be expected in this high-risk population.

A second ongoing study by Morschhauser, et al. investigates GA101 monotherapy in relapsed CLL. In this study, the pharmacokinetic data appears similar to what has been shown using other anti-CD20 antibodies, such as rituximab. Although transient neutropenia was observed in some patients, this side effect is also not uncommon with rituximab and is not of great concern.

Overall, data from both the Sehn, et al. and the Morschhauser, et al. studies suggest GA101 may be a useful treatment option in previously treated patients. However, maintenance therapy with GA101 needs to be explored further, as maintenance treatment is not routinely used in CLL.

The next step in the assessment of GA101 in CLL is to conduct a larger phase II study using a higher dose. The optimal dose of GA101 is still uncertain, so comparing the efficacy results across doses in both studies would help to determine the best dose moving forward. A similar avenue of research could be used for GA101 as was implemented with rituximab, where various chemotherapy combinations were explored. Investigating the efficacy of GA101 added to fludarabine or to FC would be particularly interesting and timely. In all cases, these regimens would need to be compared to FCR in a phase III randomized trial, since FCR is now emerging as a standard treatment in CLL.

Ferrajoli, et al. presented an exciting study that examined the efficacy of lenalidomide plus rituximab in relapsed CLL. Although the study was small, an OR rate of 69% is promising, given that the OR rate in the FCR group from the REACH study was 70%. These efficacy results are especially favourable, because the study population were high-risk patients who had previously been given rituximab, unlike in the REACH study where patients were rituximab-naïve. Results also appear to be consistent across FISH and IVgH prognostic subgroups. However, additional data with outcomes such as progression-free survival, disease-free survival, or response duration are needed in order to gain a complete picture. Safety results are also comparable to those seen in the REACH study, with no unusual or concerning signals at this time. Further studies are required before rituximab-lenalidomide could be considered as a treatment option in CLL; however, access to another oral agent such as lenalidomide when oral FC is not available would be useful, and both are useful options in terms of avoiding intravenous access and chemotherapy chair time.

In older patients, or in those with reduced performance status, chlorambucil is often given as standard treatment in CLL; however, treatment options are limited in these patients. In the study by Knauf, et al., response rates with bendamustine were superior to those with chlorambucil in patients older than 65 years. Bendamustine also appeared to be well tolerated in these older patients, with neutropenia rates of 5%–20%. Bendamustine may therefore be a reasonable alternative to chlorambucil in patients over 65 years. The disadvantage of this study is that all age groups were included, requiring a subgroup analysis to examine the efficacy in patients over 65 years. In addition, patients had a good performance status and were reasonably fit. Whether bendamustine would be tolerable from a toxicity perspective in less fit patients remains unclear. As a next step, a randomized study that compares bendamustine to fludarabine or FR in older patients or to chlorambucil in older and frailer patients needs to be conducted.

New Evidence in Oncology | March 2010

New Agents in the Treatment of Non-Hodgkin’s Lymphoma

Treatment of B-cell non-Hodgkin’s lymphoma (NHL) has progressed significantly in past years, resulting in superior outcomes in the majority of patients. Despite the advances in treatment, a substantial proportion of patients relapse. Increasing knowledge of the cellular and molecular pathogenesis of B-cell NHL subtypes has spurred the development of novel targeted therapies. These new therapies aim to increase anti-tumour activity with fewer side effects. A number of these agents are being examined in clinical trials, both as monotherapy and in combination with existing combination regimens. Three new agents discussed at the ASH 2009 meeting are veltuzumab, PRO131921, and bortezomib.

Veltuzumab is a second generation anti-CD20 humanized monoclonal antibody that triggers complement-dependent cell lysis (CDCL) and antibody-dependent cell-mediated cytotoxicity (ADCC) following binding. Initial clinical studies using low doses of veltuzumab in NHL have demonstrated good safety and efficacy outcomes. Studies have also shown infusion times using all doses are shorter than with rituximab. Based on these initial studies, subcutaneous injection is now being examined in NHL. Subcutaneous injection may circumvent the need for lengthy intravenous administration and dedicated infusion sites.

PRO131921 is a third-generation, humanized anti-CD20 monoclonal antibody, engineered to have superior ADCC and complement-dependent cytotoxicity (CDC) than rituximab. In preclinical in vivo lymphoma studies, PRO131921 has demonstrated superior anti-tumour efficacy, as compared to rituximab. PRO131921 is now being examined in a phase I/II trial in NHL.

Bortezomib was the first proteosome inhibitor (PI) to be evaluated in human studies and is now approved by Health Canada in refractory/relapsed plasma cell myeloma and mantle cell lymphoma (MCL). Although results in patients with small lymphocytic lymphoma (SLL) are disappointing, better outcomes have been reported in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL). The role of bortezomib in combination with rituximab and conventional therapies, such as R-CVP, is now being explored in FL and MZL. Bortezomib has limited single agent activity in diffuse large B-cell lymphoma (DLBCL); hence, it is being examined in combination with standard chemotherapy (CHOP) in this NHL subtype.

This article reports on four studies presented at ASH 2009: one phase I/II study shows that subcutaneous administration of veltuzumab is well tolerated, pharmacologically active, and achieves comparable response rates to intravenous dosing in untreated or relapsed indolent NHL; a second phase I study demonstrates that PRO131921 has good clinical activity, with a reasonable safety profile in relapsed/refractory indolent NHL; a phase II study shows that first-line treatment with bortezomib added to dose-dense CHOP has promising activity, but reports a number of grade 3/4 toxicities in DLBCL; and a second phase II study demonstrates that first-line treatment with bortezomib added to standard dose R-CVP in advanced FL is feasible and well tolerated, with favorable response rates compared to historical controls given R-CVP.

References:
Subcutaneous low-dose veltuzumab in indolent B-cell malignancies

**Background**
At ASH 2009, Negrea and colleagues presented results from their study examining the efficacy and safety of subcutaneous low doses of veltuzumab for the treatment of patients with indolent B-cell malignancies.1

**Study design**
- A multicentre, phase I/II study was conducted to evaluate the safety, tolerability, and preliminary efficacy of subcutaneous veltuzumab in previously untreated or relapsed CD20-positive indolent non-Hodgkin’s lymphoma (NHL) or chronic lymphocytic leukemia (CLL).
- All patients received four subcutaneous injections of veltuzumab, two weeks apart at dose levels of 80, 160, or 320 mg.
- In the phase I section of the study, a dose escalation (3 + 3) design was used; NHL and CLL were escalated separately.
- In the phase II section of the study, additional patients were enrolled to confirm data.
- A twelve-week post-treatment evaluation period was also carried out.
- Efficacy was assessed by CT-based IWG criteria for NHL or hematology-based NCI/IWCLL criteria for CLL at 4 and 12 weeks, with responding patients continuing follow-up.
- Other evaluations included adverse events (AEs), safety, B-cell blood levels (CD19), serum veltuzumab levels, and human anti-veltuzumab antibody (HAHA) titers.

**Key findings**
- Twenty-eight patients (11 male/17 female, median age 64) were enrolled, including:
  - seventeen (17) NHL patients (14 follicular lymphoma, 1 marginal zone lymphoma, 2 small lymphocytic lymphoma; 5 treatment naïve), most with Stage III or IV disease (12/17);
  - eleven (11) CLL patients (four treatment naïve), most with Rai stage II or III disease.
- Patients received subcutaneous veltuzumab at one of three doses:
  - 80 mg (3 NHL, 3 CLL);
  - 160 mg (9 NHL, 3 CLL);
  - 320 mg (5 NHL, 5 CLL).
- Pre-treatment with antihistamines or steroids was not required.
- Subcutaneous veltuzumab was well tolerated with only mild, transient injection-site reactions and tenderness, and no other safety issues.
- To date, all HAHA response results have been negative.
- In NHL patients, subcutaneous veltuzumab demonstrated good bio-availability, with a slow release pattern over several days, and a median Cmax of 21, 20 and 72 µg/mL at 80, 160, and 320 mg dose levels, respectively.
- Depletion of circulating B cells was observed starting after the first injection.
- In the 15 evaluable NHL patients, the overall response (OR) rate was 53% (8/15), with a complete response (CR) rate of 27% (4/15). (Table 1)
- Most ORs (7/8) are currently in remission up to six months after treatment. (Table 1)
- The 11 CLL patients presented with mean white blood cell levels of 55K/µL (maximum 122K/µL) and achieved much lower serum veltuzumab levels, with median Cmax values of 2, 5, and 31 µg/mL at the 80, 160, and 320 mg dose levels, respectively.
- No ORs were seen in the CLL patients; 5/9 patients (56%) with available response assessments showed stable disease, with >50% decreases in B-cell levels for up to 12 weeks. (Table 2)
Key conclusions

- Subcutaneous administration of veltuzumab is well tolerated, achieves slow but efficient delivery into the blood, and is pharmacologically active when given every two weeks for a total of four doses.
- Low subcutaneous doses achieved sustained serum levels in NHL, with overall response rates comparable to those seen with higher intravenous doses.
- More frequent and prolonged dosing is likely required in CLL, which has high levels of circulating leukemic cells.


### Table 1. Efficacy of subcutaneous injections of low-dose veltuzumab in the treatment of patients with NHL

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Overall response (PR + CR + CRu) n (%)</th>
<th>Complete response (CRu/CR) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable NHL patients (n = 15)</td>
<td>8 (53)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Follicular lymphoma (n = 12)*</td>
<td>7 (58)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Non-follicular lymphoma (n = 3)*</td>
<td>1 (33)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Dose level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg (n = 3)</td>
<td>2 (67)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>160 mg (n = 9)</td>
<td>4 (44)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>320 mg (n = 3)</td>
<td>2 (67)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prior treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 10)</td>
<td>6 (60)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>No (n = 5)</td>
<td>2 (40)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Prior rituximab:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 6)</td>
<td>4 (67)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>No (n = 9)</td>
<td>4 (44)</td>
<td>2 (30)</td>
</tr>
<tr>
<td>IPI score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 (n = 11)</td>
<td>6 (55)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>3–5 (n = 4)</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

* Of the 12 FL patients: 2 patients with POD activity at 4 weeks, 1 patient with CR lasting 24 weeks, 6 others with OR, and 3 with SD still ongoing, including 4 now ≥6 months
* Of the 2 SLL patients and 1 MZL patient: one POD at 12 weeks, 1 SD ongoing at 12 weeks, and 1 SLL patient with CR still ongoing at 18 weeks
CR = complete response; CRu = unconfirmed complete response; FL = follicular lymphoma; IPI = International Prognostic Index; MZL = marginal zone lymphoma; OR = overall response; POD = peroxidase; PR = partial response; SD = stable disease; SLL = small lymphocytic lymphoma

### Table 2. Efficacy of subcutaneous injections of low-dose veltuzumab in the treatment of CLL

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable CLL patients (n = 9)</td>
<td>No overall responses (ORs), but 5 patients (56%) had stable disease (SD) ≥12 weeks*</td>
</tr>
<tr>
<td>Dose level:</td>
<td></td>
</tr>
<tr>
<td>80 mg (n = 3)</td>
<td>3 patients with SD, all ongoing at 4 weeks, 12 weeks, 12 months</td>
</tr>
<tr>
<td>160 mg (n = 3)</td>
<td>2 patients with peroxidase (POD) activity, but 1 patient with SD ongoing at 12 weeks</td>
</tr>
<tr>
<td>320 mg (n = 3)</td>
<td>2 patients with SD, all ongoing at 8 weeks, 12 weeks, 6 months</td>
</tr>
</tbody>
</table>

* SD by criteria, with most B-cell decreases >50%, but no lymph node (LN) reduction >50%
Background

At ASH 2009, Friedberg and colleagues presented data from their phase I study examining the safety and tolerability of PRO131921 in relapsed/refractory patients with indolent non-Hodgkin's lymphoma (NHL). 1

Study design

- The primary objectives of the study were to:
  - evaluate the safety and tolerability of escalating intravenous (iv) doses of PRO131921 in patients with CD20-positive indolent NHL who have relapsed or progressed after a prior rituximab-containing regimen;
  - define the maximum tolerated dose (MTD) for the first infusion of PRO131921 based on the incidence and nature of reversible, infusion-related dose-limiting toxicities (DLTs) occurring with the first infusion;
  - define the MTD for subsequent weekly infusions of PRO131921 based on the incidence and nature of DLTs.
- Secondary objectives were to:
  - characterize the pharmacokinetics (PK) of PRO131921 in patients with relapsed or refractory CD20-positive indolent NHL;
  - obtain preliminary data on the anti-lymphoma activity of PRO131921.

Patients (n = 24) with CD20-positive relapsed/refractory NHL (follicular, small lymphocytic lymphoma [SLL], and marginal zone lymphoma [MZL]) were enrolled.

Patients were treated with PRO131921 by weekly iv infusion for four weeks on days 1, 8, 15, and 22.

Premedication with acetaminophen and anti-histamines was given.

The dose of the first infusion was approximately 50% that of subsequent infusions.

The dose was escalated based on safety in a 3 + 3 design.

PK samples were obtained pre- and post-infusion on days 1, 8, 15, and 22; once each on days 2, 23, 29, 50, and 78; and at later time points for up to a year.

Inclusion/exclusion criteria

- Patients with the following criteria were included:
  - age ≥18 years;
  - histologically confirmed CD20-positive indolent NHL that either had relapsed after a response of ≥6 months to a rituximab-containing regimen or was refractory to a previous rituximab-containing regimen;
  - bi-dimensionally measurable disease with at least one lesion >1.5 centimeters;
  - absolute B cell count greater or equal to the lower limit of normal (LLN).

### Study design: phase I dose-escalation cohorts for PRO131921 trial*

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Week 1 (mg/m²)</th>
<th>Week 2 (mg/m²)</th>
<th>Week 3 (mg/m²)</th>
<th>Week 4 (mg/m²)</th>
<th>Total dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: 25/25 mg/m²</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>B: 25/50 mg/m²</td>
<td>25</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>175</td>
</tr>
<tr>
<td>C: 50/100 mg/m²</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>350</td>
</tr>
<tr>
<td>D: 100/200 mg/m²</td>
<td>100</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>700</td>
</tr>
<tr>
<td>E: 200/400 mg/m²</td>
<td>200</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>1400</td>
</tr>
<tr>
<td>F: 400/800 mg/m²</td>
<td>300</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>2700</td>
</tr>
</tbody>
</table>

*Patients in each cohort (n = 3–6) received four weekly doses of PRO131921 at the dose levels shown
• Patients were excluded if they had:
  - prior use of anti-CD20 monoclonal antibody therapy (other than rituximab or radioimmunotherapy);
  - prior use of any non-CD20 targeted monoclonal antibody therapy within six months;
  - current or recent lymphoma treatment within four weeks (including corticosteroids);
  - history of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies;
  - evidence of significant uncontrolled concomitant diseases;
  - evidence of myelodysplasia or myelodysplastic changes.

**Key findings**

• Best investigator-assessed responses to treatment in the 22 evaluable patients by day 78 or later were 6 patients with partial response (PR), 13 with stable disease (SD), and 3 with progressive disease (PD); 5/10 patients in the two highest dose cohorts responded. (Table 1)

• PRO131921 was generally well tolerated and no MTD was reached in the study.

• The most common adverse events (AEs) were grade 1 or 2 chills, flushing, itching, fatigue, fever, nausea, dizziness, diarrhea, and hypotension, most of which were part of infusion-related reactions generally limited to the first infusion.

• Grade 1 or 2 AEs responded well to slowing or interruption of the infusion and symptomatic treatment (including steroids).

• Two patients did not receive all four doses of therapy due to DLTs. (Table 1)

• One DLT was observed in the 200/400 mg/m² dose cohort due to a significant infusion reaction.

• A second DLT was observed in the 300/800 mg/m² dose cohort due to grade 3 joint pain and fatigue after two infusions.

• Serious adverse events (SAEs) are presented in Table 2.

• PK studies of PRO131921 in all patients were broadly similar to rituximab with dose-dependent increase in exposure, but with significant inter- and intra-patients variability.

• PK data demonstrated a correlation between higher normalized drug exposure (normalized area under the curve [AUC]) and both tumour shrinkage ($p = 0.049$) and clinical response ($p = 0.034$), consistent with the hypothesis that rapid drug clearance may result in reduced clinical efficacy.

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**Table 1. Response to PRO131921 by treatment cohort**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Diagnosis</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: 25/25 mg/m²²</td>
<td>fNHL (n = 3)</td>
<td>−</td>
<td>−</td>
<td>2</td>
<td>1</td>
<td>−</td>
</tr>
<tr>
<td>B: 25/50 mg/m²²</td>
<td>fNHL (n = 3), SLL (n = 1)</td>
<td>−</td>
<td>−</td>
<td>3</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>C: 50/100 mg/m²²</td>
<td>fNHL (n = 3)</td>
<td>−</td>
<td>1</td>
<td>2</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>D: 100/200 mg/m²²</td>
<td>fNHL (n = 2), SLL (n = 1)</td>
<td>−</td>
<td>−</td>
<td>3</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>E: 200/400 mg/m²²</td>
<td>fNHL (n = 5)*, MZL (n = 1)</td>
<td>−</td>
<td>2</td>
<td>2*</td>
<td>1</td>
<td>(MZL) 1</td>
</tr>
<tr>
<td>F: 300/800 mg/m²²</td>
<td>fNHL (n = 5), SLL (n = 1)</td>
<td>−</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>(SLL) 1</td>
</tr>
</tbody>
</table>

*One fNHL patient was refractory to prior R-CHOP

CR = complete response; DLT = dose-limiting toxicity; fNHL = follicular non-Hodgkin’s lymphoma; MZL = marginal zone lymphoma; PD = progressive disease; PR = partial response; SD = stable disease; SLL = small lymphocytic leukemia

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**Table 2. Serious adverse events by treatment cohort in the PRO131921 trial**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>NHL subtype</th>
<th>Serious adverse event</th>
<th>Related to PRO131921*</th>
<th>Resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>E: 200/400 mg/m²²</td>
<td>follicular</td>
<td>Hypoxia (grade 3)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>B: 25/50 mg/m²²</td>
<td>follicular</td>
<td>Pneumonia (grade 3)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>C: 50/100 mg/m²²</td>
<td>follicular</td>
<td>Pulmonary embolism (grade 4)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>E: 200/400 mg/m²²</td>
<td>follicular</td>
<td>Deep-vein thrombosis (grade 3)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*As assessed by the investigator
Key conclusions

■ PRO131921 has shown clinical activity with an acceptable safety profile in indolent NHL patients with prior rituximab exposure.

■ The observation that higher normalized area AUC may be associated with improved clinical responses suggests that the dosing regimen of an antibody therapeutic may influence clinical outcomes, depending upon its ability to saturate tumour burden and achieve sustained drug levels and improved exposure.

■ Data from this trial have potential implications for future trials of monoclonal antibody-based therapies and emphasize the importance of PK studies to optimize antibody efficacy.


Assessing the efficacy and toxicity of bortezomib added to dose-dense CHOP in previously untreated diffuse large B-cell lymphoma

Background
Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and dose-dense CHOP therapy have improved the outcome for diffuse large B-cell lymphoma (DLBCL) patients. Nevertheless, a substantial number of patients progress or relapse. New treatments are therefore needed to improve outcomes in these DLBCL patients. At ASH 2009, Kim and colleagues presented interim data from their phase II study assessing the efficacy and toxicity of bortezomib in combination with dose-dense CHOP in untreated DLBCL patients.1

Study design
- Patients included in the study had the following characteristics:
  - histologically confirmed DLBCL;
  - Eastern Cooperative Oncology Group (ECOG) 0–2 performance status;
  - aged 70 years or less;
  - previously untreated advanced DLBC (Stage III, IV, or non-contiguous Stage II).
- Thirty-five (35) patients were enrolled from March 2007 to March 2009.

- Patients were treated with cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (CHOP) on day 1.
- Oral prednisolone 100 mg was given on days 1–5.
- Granulocyte colony-stimulating factor (GCSF) was given at a dose of 5µg/kg from days 4–13, every 2 weeks.
- Bortezomib was administered at a dose of 1.6 mg/m² on days 1 and 4 of each cycle, as recommended by the previous phase I trial.
- Toxicity was assessed on day 1 of each cycle.
- Response assessment was completed on days 10–14 of the third and sixth cycle.

Key findings
- A total of 188 cycles of treatment were given to 35 patients.
- Twenty-six (26) patients finished six cycles of treatment.
- Nine (9) patients could not continue all planned treatment due to treatment-related toxicities.
- One patient experienced disease progression after five cycles of treatment.
• After 6 cycles, twenty-four (24) patients (92.4%) had a complete response (CR), one patient (3.8%) had a partial response (PR), and one patient (3.8%) had progressive disease (PD). (Table 1)

• As of June 30, 2009, eight patients had progressive disease.

• Grade 3 and 4 hematologic toxicities are presented in Table 2.

Table 1. Response rates after 3 and 6 cycles of dose-dense CHOP

<table>
<thead>
<tr>
<th>Response</th>
<th>After 3 cycles n (%)</th>
<th>After 6 cycles n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>17 (65.4)</td>
<td>24 (92.4)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>9 (34.6)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>0 (0.0)</td>
<td>1 (3.8)</td>
</tr>
</tbody>
</table>

Table 2. Grade 3 and 4 adverse events after treatment with bortezomib added to dose-dense CHOP

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (10.7)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (2.1)</td>
<td>11 (5.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (3.2)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (11.4)</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.9)</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (5.7)</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (8.6)</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>–</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (8.6)</td>
<td>–</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>7 (20.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

Key conclusions

- This interim analysis shows that first-line treatment with bortezomib plus dose-dense CHOP given every two weeks has promising activity in DLBCL patients; however, a significant proportion of patients had grade 3 and 4 toxicities.

- Further accrual will be continued until the planned patient enrollment goal has been reached for phase II results.


Evaluating the safety and efficacy of first-line bortezomib added to R-CVP in previously untreated advanced stage follicular lymphoma

Background

At ASH 2009, Sehn and colleagues presented early results from their phase II study examining the safety and efficacy of first-line bortezomib added to R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) in patients with advanced follicular lymphoma (FL).¹

Study design

- The study by Sehn and colleagues is a phase II, multicentre, open-label trial in patients with newly diagnosed Stage III/IV FL.

- Patients were given bortezomib (1.3 mg/m² days 1 and 8) added to standard dose R-CVP: cyclophosphamide (750 mg/m²); vincristine (1.4 mg/m², capped at 2 mg); prednisone (40 mg/m² x 5); and rituximab (375 mg/m²). Up to eight cycles were given.

- Response was assessed following four and eight cycles.

- The two primary endpoints were complete response/unconfirmed complete response (CR/CRu) and incidence of grade 3/4 neurotoxicity.

- Following the final response assessment, patients were permitted to receive maintenance rituximab at the discretion of the treating physician.

Key findings

Baseline characteristics

- Between March 2007 and February 2009, 95 patients were enrolled.

- Median age was 56.6 years (range 29.5–83.6 years).

- Forty-eight percent (48%) of patients were male and 63% had Stage IV disease.

- Follicular Lymphoma International Prognostic Index (FLIPI) scores at study entry were as follows: low 11%, intermediate 43%, and high 46%.
Safety

- Safety data was available for all patients. (Table 1)
- Overall, the combination of bortezomib and R-CVP was extremely well tolerated.
- No patients developed grade 4 neurotoxicity and only 6/95 (6.3%) developed grade 3 neurotoxicity (five sensory neuropathy and one neuropathic pain).
- The incidence of grade 1 and 2 neuropathy was 65.3% and 36.8%, respectively; neurotoxicity was largely reversible.
- Five patients discontinued therapy prematurely (three patients refused further treatment, one patient was found to have Hodgkin's lymphoma as well as FL, and one patient was removed from the study for non-compliance).
- Eighty-four percent (84%) of planned bortezomib treatments and 85% of vincristine treatments were administered without dose reduction.
- Five patients experienced grade 3/4 anemia and three patients experienced grade 3/4 thrombocytopenia.
- Only four episodes of febrile neutropenia occurred; two grade 3 infections were reported.
- No grade 4 infections and no serious adverse events (SAEs) were reported.
- One patient died due to progressive disease.

Efficacy

- At the time of evaluation, 78/95 patients were evaluable for response.
- Overall response (OR) rate was 84.6% (95% CI: 76.6–96.6): (Table 2)
  - a total of 37/78 patients (47%) achieved a CR/CRu (95% CI: 36.4–58.5);
  - a total of 29/78 of patients (37%) achieved a partial response (PR).
- An additional 5/78 patients had stable disease (SD), while 7/78 progressed on therapy. (Table 2)
- Complete efficacy data as well as information on quality of life will be available at the next analysis.
- Forty-one (41) of 70 patients (58.6%) with available follow-up information went on to receive maintenance rituximab.

Table 1. Adverse events after first-line treatment with bortezomib added to R-CVP

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients (n = 95)</th>
<th>Percentage of patients (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6</td>
<td>6.3</td>
</tr>
<tr>
<td>Grade 2 (neuropathy)</td>
<td>35</td>
<td>36.8</td>
</tr>
<tr>
<td>Grade 1 (neuropathy)</td>
<td>62</td>
<td>65.3</td>
</tr>
<tr>
<td>Anemia (grade 3/4)</td>
<td>5</td>
<td>5.3</td>
</tr>
<tr>
<td>Thrombocytopenia (grade 3/4)</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4 episodes</td>
<td>–</td>
</tr>
<tr>
<td>Infections (grade 3)</td>
<td>2 infections</td>
<td>–</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Response rates after first-line treatment with bortezomib added to R-CVP

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of evaluable patients (n = 78)</th>
<th>Percentage of evaluable patients (n = 78)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (OR)</td>
<td>66</td>
<td>84.6</td>
<td>76.6–96.6</td>
</tr>
<tr>
<td>Complete response/ unconfirmed complete response (CR/CRu)</td>
<td>37</td>
<td>47.4</td>
<td>36.4–58.5</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>29</td>
<td>37.2</td>
<td>n/a</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>5</td>
<td>6.4</td>
<td>n/a</td>
</tr>
<tr>
<td>Progressed on therapy</td>
<td>7</td>
<td>9.0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a = not available

Key conclusions

- The addition of bortezomib to standard dose R-CVP is feasible and well tolerated, with minimal associated toxicity.
- Neurotoxicity was primarily low grade and reversible, and did not limit the delivery of bortezomib or vincristine.
- The complete response rate in this high-risk population compares favourably to historical results of patients receiving R-CVP.
- Based on these encouraging results, a phase III trial of R-CVP with or without bortezomib is currently being planned.

In non-Hodgkin’s lymphoma (NHL), the advantages of subcutaneous over intravenous chemotherapy are clear. Subcutaneous formulations may reduce patient chemotherapy chair time and enable the reduction or elimination of pre-medications as well as the need for intravenous access.

The study by Negrea, et al. examining the efficacy of low-dose subcutaneous veltuzumab included a small number of patients. However, approximately half (53%) of patients had a response, and nearly a third (27%) achieved a complete response (CR); some patients remained in remission for up to 6 months. Response rates in this study are similar to those shown in the phase II study by McLaughlin, et al., which reported a response rate of 49% with rituximab monotherapy.¹ Unlike the McLaughlin, et al. study, however, patients in the Negrea, et al. study were pre-treated with rituximab, and more rapid infusion times of veltuzumab were used, making results more relevant.

Lower responses with veltuzumab in the chronic lymphocytic leukemia (CLL) subgroup are not surprising. The reduced response is similar to what we have seen with rituximab monotherapy and may be due to the number of circulating cells, the expression of CD20 on the surface of the cells, and the possibility of free circulating CD20 antigen, all of which could decrease the effectiveness of the circulating anti-CD20 antibody. Nevertheless, safety data is reassuring, and the advantages of the subcutaneous formulation make veltuzumab a potentially useful treatment option. The next step is to perform larger phase I-II studies and to examine the efficacy of veltuzumab in CLL separately from other NHLs.

The study by Friedberg, et al. assessing the efficacy and safety of PRO131921 in indolent NHL showed favourable responses in approximately 50% of heavily pre-treated patients. The overall response rate is encouraging, given it is comparable to that found with rituximab in the phase II study by McLaughlin, et al.¹ Safety results were also reassuring; the grade 3 hypoxia observed with PRO131921 is not uncommon within the spectrum of reactions to monoclonal antibodies and is not of great concern. An agent such as PRO131921 may be useful in patients who are refractory to rituximab-based treatments. Looking at the number of rituximab-refractory patients who responded might provide some insight, although numbers would be small and difficult to interpret. Disadvantages of PRO131921 may include that it is administered intravenously, requires pre-medications, and results in some infusion reactions. These disadvantages are similar to those we experience with rituximab, but are not insurmountable. As a next step, I believe that the higher dose of PRO131921 (300/800 mg/m²) should be further investigated, because it showed the highest rate of response, with no substantial increase in toxicity.

The standard treatment for diffuse large B-cell lymphoma (DLBCL) in Canada is R-CHOP on a 21 day schedule, so it is disappointing that the study by Kim, et al. added bortezomib to dose-dense CHOP instead of to R-CHOP. However, efficacy results were promising in this study and do compare favourably to what we have seen historically with both R-CHOP and dose-dense CHOP. The grade 3 neuropathy rate was 20% in this study, which is more than what we would expect to see with dose-dense CHOP. Neuropathy may therefore be a concern with the addition of bortezomib. A logical eventual step would be to compare R-CHOP to bortezomib-R-CHOP in a randomized phase III study to gain a better understanding of the efficacy and safety of this regimen.

The study by Sehn, et al. examining the addition of bortezomib to R-CVP in untreated advanced follicular lymphoma (FL) achieved a response in 84% of patients. This overall response rate is similar to that found with R-CVP in the study by Marcus, et al.² Possible increased neurotoxicity is a potential concern with the addition of bortezomib, but grade 3 or 4 neurotoxicity was only seen in 6% of patients, which is encouraging. The advantage of adding bortezomib to R-CVP is that it may improve response rates, but further studies are needed to determine whether neurotoxicity is an issue. The next step in examining the efficacy and safety of bortezomib-R-CVP is to compare it to R-CVP in a randomized phase III study.

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CAT can be tamed.

FRAGMIN. The only low molecular weight heparin indicated to treat Cancer-Associated Thrombosis (CAT) in Canada.

FRAGMIN is indicated for the extended treatment of symptomatic VTE to prevent recurrence of VTE in patients with cancer.

Venous thromboembolism (VTE) is a frequent medical complication in patients with cancer, occurring in 4% to 20% of cases.

FRAGMIN Achieved A Statistically Significant 52% Relative-Risk Reduction In Recurrent VTE vs. Oral Anticoagulant Therapy.*

(27%/33% vs. 53%/33%; p=0.002)

Adverse Events: Clinically significant adverse reactions with FRAGMIN and other LMWHs include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions. In clinical trials with hospitalized patients with severely restricted mobility, the incidence of thrombocytopenia was <5% at days 14 and 21. Injection site hematomas are a common side effect with FRAGMIN, occurring at a frequency of <5% with lower (prophylaxis) doses and <10% with higher (treatment) doses.

FRAGMIN should be used with care in patients with hepatic insufficiency, renal insufficiency or a history of gastrointestinal ulceration. Please consult the Prescribing Information for complete dosing instructions, warnings and precautions, and adverse events.

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal “gasping syndrome” in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

FRAGMIN should not be administered intramuscularly.

FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACTIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWH) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-XA AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

Contraindications: FRAGMIN should not be used in patients who have hypersensitivity to FRAGMIN or any of its components, including benzyl alcohol (when using the 25,000 IU multi-dose vial) or to other low molecular weight heparins and/or heparin or any product; history of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an intravascular platelet aggregation test in the presence of FRAGMIN is positive; septic endocarditis (endocarditis infecta); subacute endocarditis; uncontrollable active bleeding; major blood clotting disorders, acute gastrointestinal ulcer; cerebral hemorrhage; severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy; other conditions or diseases involving an increased risk of hemorrhage; injuries to and operations on the central nervous system, eyes and ears; spinal/spinalidural anesthesia is contraindicated unless repeated high doses of FRAGMIN (100–125 IU/kg given intravenously every 24 hours) are required, due to an increased risk of bleeding.

FRAGMIN is not to be used during pregnancy or breastfeeding. It is not known whether FRAGMIN is excreted in breast milk.

See prescribing summary on page 85.
An Interview with Dr. Gilles Salles on a Phase I Study of GA101 in Relapsed/Refractory CLL

At the ASH 2009 meeting, New Evidence spoke with Dr. Gilles Salles, Professor of Hematology at the Centre Hospitalier Lyon-Sud in Lyon, France, about the results of his study examining the safety, tolerability, dose-limiting toxicity, and pharmacokinetics of GA101 given as a single agent to patients with CLL.

New Evidence: Please describe the design of the study.

Dr. Salles: Our study was a phase I study conducted in Europe; at ASH 2009, we presented results from 13 CLL patients. The study used a 3 x 3 dose-escalating design: the first infusion of GA101 was given at half the target level and the full dose by day 8, with an upper limit of 2000 mg. A second arm received a flat dose of 1000 mg.

To date, we only have phase I data on the use of GA101 in CLL, and the optimal dose is unknown. We are currently studying GA101 in 40 aggressive lymphoma, 40 follicular lymphoma, and 20 CLL patients. So far, the dose-related toxicity seems to be minimal, justifying the upper level of 2000 mg. In addition, pharmacokinetic data suggests that non-Hodgkin’s lymphoma (NHL) patients with a large tumour burden may require a higher dose of GA101.

New Evidence: Please describe the patient population that was included in the study.

Dr. Salles: The patients included in our study had been heavily pre-treated; all patients had previously received fludarabine, and two-thirds of patients had received rituximab, with a median of three previous treatments. There were also a substantial number of patients with adverse cytogenetics. Out of 10 patients analyzed for IgVH mutations, 7 had unmutated disease. These data suggest that the study population was a high-risk group of patients in a late disease state.
**New Evidence:** How do the infusion reactions seen in this study compare with rituximab and other treatments?

**Dr. Salles:** The infusion reactions observed in this study are comparable to those seen with rituximab. When the infusion rate was controlled, most patients were able to complete their infusions within 4–6 hours, suggesting that GA101 was well tolerated.

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**New Evidence:** Please discuss the transient neutropenia rates seen in this study.

**Dr. Salles:** We were surprised to see a relatively high rate of neutropenia after the second or third cycle of GA101, with an incidence of 9/13 patients. Some patients who were at an early stage of neutropenia were able to recover easily; four patients in cycle one recovered without the use of granulocyte colony-stimulating factor (GCSF), while seven experienced later stage neutropenia and required treatment with GCSF.

If we look back at our experience in NHL, we see only one event related to neutropenia. We do not yet understand why the neutropenia rates were higher in CLL, but I think it may be related to the mobilization of cytokines. We need to wait for the results of phase II studies to see whether neutropenia is a concern with the use of GA101 in CLL. However, results of this study show that only one patient had febrile neutropenia as a serious adverse event, and only three patients experienced a serious infection. Therefore, although the neutropenia rate was relatively high, it was mainly asymptomatic and did not translate into a high rate of febrile neutropenia or infection.

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**New Evidence:** Please describe the overall response (OR) rate achieved in this study. How does this compare with other treatments for CLL?

**Dr. Salles:** The best overall response rate according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria was 62% (8/13), with no clear dose relationship established. In our study, the clearance of lymphoid cells was rapid in all patients, which appears to be significant and sustained over time. When this finding is translated into response rates, results are very impressive. This is especially the case given the high-risk population used in this study and the stringency of the IWCLL criteria, which require a response on the lymph nodes as determined by CT scans. The high response rates with GA101 in this study suggest it is an important drug in this setting.

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**New Evidence:** Please describe any other significant findings from this study.

**Dr. Salles:** GA101 is engineered to have limited if any complement activation in vitro. In our study, we did not find any complement activation in vivo, clearly showing that depleting B cells from the circulating blood does not need activation by a complement.

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**New Evidence:** Please describe the results of other ongoing studies using GA101.

**Dr. Salles:** Last year we presented promising phase I results from a study using GA101 monotherapy in NHL; we now have updated data demonstrating a prolonged response. Follow-up findings are particularly impressive in follicular lymphoma patients, with an OR rate of 69% (9/13) and a CR rate of 38%. If we take all lymphoma patients into account (n = 21), the OR rate is 45% and CR rate is 25%. We even had one patient initially considered to have stable disease who responded six months after the first infusion. In early studies using rituximab as a single agent, the OR rate was approximately 50%; however, only 10%–15% achieved a CR. Results using GA101 as a single agent are therefore encouraging, especially given these patients have been extensively pre-treated.
We are also performing a phase II study using GA101 in 20 CLL patients. In this study, we are administering GA101 as a flat dose, with a total of ten infusions, three of which are given early on. So far there have been no important safety signals, and we are awaiting results in order to determine response rates.

GA101 is also being studied in combination with other agents for the treatment of CLL. For example, a current randomized study in CLL patients comparing chlorambucil alone, chlorambucil with rituximab, and chlorambucil with GA101 is a key study that will evaluate the benefit of adding an anti-CD20 to chlorambucil.

In follicular lymphoma, a study comparing rituximab to GA101 in relapsed patients will help determine whether GA101 is superior to rituximab in this setting. In addition, an ongoing trial that adds GA101 to CHOP or FC is being conducted in lymphoma patients and will give us further data on GA101 used in combination with other agents.

**New Evidence:** Based on results to date, what are your impressions of GA101 for the treatment of CLL?

**Dr. Salles:** Results of studies to date suggest that GA101 has impressive activity in CLL patients. The durability of B-cell depletion indicates that this antibody may be a good treatment option in CLL. However, results need to be confirmed in phase II studies. Findings from future trials will also determine whether GA101 should be used as a single agent or in combination with other agents such as fludarabine or chlorambucil.
INDICATIONS AND CLINICAL USE

FRAGMIN® (dalteparin sodium injection) is indicated for:

- Thromboprophylaxis in conjunction with surgery.
- Treatment of acute deep venous thrombosis.
- Unstable coronary artery disease (UCAJD), i.e., unstable angina and non-Q-wave myocardial infarction.
- Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency.
- Extended treatment of symptomatic venous thromboembolism to prevent recurrence of venous thromboembolism in patients with cancer.
- Reduction of deep vein thrombosis (DVT) in hospitalized patients with severely restricted mobility during acute illness. Decreased mortality due to thromboembolic events and complications has not been demonstrated.

CONTRAINDICATIONS

FRAGMIN should not be used in patients who have the following:

- Hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) (see WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS, Pregnant Women).
- To other low molecular weight heparins and/or heparin or pork products.
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an in vitro platelet-aggregation test in the presence of FRAGMIN is positive.
- Severe endocarditis (endocarditis lenta, subacute endocarditis).
- Uncontrollable active bleeding.
- Major bleeding disorders.
- Acute gastrointestinal ulcer.
- Cerebral hemorrhage.
- Severe uncontrolled hypertension.
- Diabetic or hemorrhagic retinopathy.
- Other conditions or diseases involving an increased risk of hemorrhage.
- Injuries to and operations on the central nervous system, eyes and ears.
- Spinal/epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100-120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding.

SPECIAL POPULATIONS

Pregnant Women:
The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Cases of Gasping Syndrome have been reported in neonates when benzyl alcohol has been administered in amounts of 99-404 mg/kg/day. Manifestations of the disease include: metabolic acidosis, respiratory distress, gasping respirations, central nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

There are also postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves who were receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

Teratogenic Effects: As with other low molecular weight heparins (LMWH), FRAGMIN should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic Effects: There have been postmarketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including FRAGMIN, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving FRAGMIN should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if FRAGMIN is administered during pregnancy.

Nursing Women:
It is not known whether FRAGMIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to nursing women.

Pediatrics:
The safety and effectiveness of FRAGMIN in children have not been established.

Geriatics:
Elderly patients receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing intervals and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (e.g., <45 kg) and those predisposed to decreased renal function is recommended.

Patients with Extreme Body Weight:
Safety and efficacy of low molecular weight heparins in high weight (e.g., >120 kg) and low weight (e.g., <46 kg) patients have not been fully determined. Individualized clinical and laboratory monitoring are recommended in these patients.

Safety Information

WARNINGS AND PRECAUTIONS

Special Warnings and Precautions
The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see Special Populations, Pregnant Women).
General
FRAGMIN should NOT be administered intra-muscularly.
FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACtionATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

Cardiovascular
Use in Patients with Prosthetic Heart Valves: Cases of prosthetic valve thrombosis have been reported in these patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see WARNINGS AND PRECAUTIONS, Patient Selection Criteria, SPECIAL POPULATION, Pregnant Women).

Use in Unstable Coronary Artery Disease: When thrombolytic treatment is considered appropriate in patients with unstable angina and non-Q-wave myocardial infarction, concomitant use of an anticoagulant such as FRAGMIN may increase the risk of bleeding.

Gastrointestinal
FRAGMIN should be used with caution in patients with a history of gastrointestinal ulceration.

Hematologic
Hemorrhage: Bleeding may occur in conjunction with unfractionated heparin or low molecular weight heparin as used. As with other anticoagulants, FRAGMIN should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Platelets/Thrombocytopenia: Platelet counts should be determined prior to the start of treatment with FRAGMIN and, subsequently, twice weekly for the duration of treatment. Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. Its incidence is unknown at present.

Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia or platelet defects.

During FRAGMIN administration, special caution is necessary in rapidly-developing thrombocytopenia and severe thrombocytopenia (≤100 000/µl). A positive or unknown result obtained from in vitro tests for antiplatelet antibody in the presence of FRAGMIN or other low molecular weight heparins and/or heparins would contraindicate FRAGMIN.

Hepatic
FRAGMIN should be used with caution in patients with hepatic insufficiency, as these patients may have potentially higher risk of hemorrhage.

Peri-Operative Considerations
Spinal/Epidural Hematomas:
When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see CONTRAINDICATIONS and ADVERSE REACTIONS).

When a higher dose (5000 IU s.c.) of FRAGMIN is administered for thromboprophylaxis in conjunction with surgery, no spinal/e epidural invasion should be performed for at least 12 hours following the last dose of FRAGMIN and the next dose should be held until at least 12 hours after the anesthetic procedure. Alternatively, when a lower dose (2500 IU s.c.) of FRAGMIN is administered, the dose can be initiated 1 - 2 hours prior to surgery. FRAGMIN injection should be given after spinal/epidural anesthesia and only if the anaesthesiologist considers the spinal/epidural puncture as uncomplicated. Indwelling catheters should not be removed or manipulated for at least 10 - 12 hours following the last dose of FRAGMIN.

Use in Knee Surgery: The risk of bleeding in knee surgery patients receiving low molecular weight heparins may be greater than in other orthopedic surgical procedures. It should be noted that hemorrhaxis is a serious complication of knee surgery. The frequency of bleeding events observed with FRAGMIN in orthopedic surgery patients is derived from clinical trials in hip replacement surgery patients. The physician should weigh the potential risks with the potential benefits to the patient in determining whether to administer a low molecular weight heparin in this patient population.

Selection of General Surgery Patients: Risk factors associated with postoperative venous thrombembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, and age 60 years or above.

Renal
FRAGMIN should be used with caution in patients with renal insufficiency.

Patients with impaired renal function should be carefully monitored because the half-life for anti-Xa activity after administration of low molecular weight heparin may be prolonged in this patient population. Dose reduction should be considered in patients with severe renal impairment.

ADVERSE REACTIONS
Adverse Drug Reaction Overview
Clinically significant adverse reactions observed with use of FRAGMIN and other low molecular weight heparins include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions.

Post-Marketing Adverse Reactions
In post-marketing experience, the following undesirable effects have been reported:

Bleeding: Intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hemorrhage have been reported occasionally leading to fatalty

Blood and Lymphatic System: thrombocytopenia, thrombocytopenia

Skin and Subcutaneous Tissue Disorders: skin necrosis, alopecia, rash

Immune System Disorders: immunologically-mediated heparin-induced thrombocytopenia (type I, with or without associated thrombotic complications), anaphylactic reactions

Injury, Poisoning and Procedural Complications: spinal or epidural hematoma

DRUG INTERACTIONS
Drug-Drug Interactions
FRAGMIN should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, non-steroidal anti-inflammatories and thrombolytic agents because of increased risk of bleeding. Acetylsalicylic acid (ASA), unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarctions.

Drug-Food Interactions
Interactions with food have not been established.
Drug-herb Interactions
Interactions with herbs have not been established.

Drug-lab tests Interactions
Interactions with lab tests have not been established.

Drug-lifestyle Interactions
Interactions with lifestyle have not been established.

To report an adverse event, please contact your physician, pharmacist or Pfizer Medical Information: 1-800-465-6001.

Administration

DOSAGE AND ADMINISTRATION

FRAGMIN may be given by subcutaneous (s.c.) injection or by intermittent or continuous intravenous (i.v.) infusion, depending upon the circumstances. FRAGMIN must NOT be administered intramuscularly. Clinical trials conducted in support of clinical uses outlined below generally used subcutaneous dosing.

Dosing

Thromboprophylaxis in Conjunction with Surgery
The dose of FRAGMIN required for adequate prophylaxis without substantially increasing bleeding risk varies depending on patient risk factors.

General surgery with associated risk of thromboembolic complications: 2500 IU s.c. administered 1 - 2 hours before the operation, and thereafter 2500 IU s.c. each morning until the patient is mobilized, in general 5 - 7 days or longer.

General surgery associated with other risk factors: 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5 - 7 days or longer.

As an alternative, 2500 IU s.c. is given 1 - 2 hours before the operation, with 2500 IU s.c. given again no sooner than 4 hours after surgery, but at least 8 hours after the previous dose, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5 - 7 days or longer.

Elective hip surgery: 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5 - 7 days or longer.

As an alternative 2500 IU s.c. is given 1 - 2 hours before the operation and 2500 IU s.c. 4 - 8 hours after surgery, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5 - 7 days or longer.

The pre-operative dose may be omitted and an initial dose of 2500 IU s.c. administered 4 - 8 hours after the operation, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5 - 7 days or longer. Omission of the pre-operative dose may reduce risk of peri-operative bleeding, however increased risk of venous thromboembolic events is possible. This option is based on the results of the North American Fragmin Trial (NAFT), which excluded patients at high risk of bleeding, i.e., documented cerebral or gastrointestinal bleeding within 3 months prior to surgery, defective hemostasis, e.g., thrombocytopenia (<100 x 10^9/L), ongoing anticoagulant treatment.

Treatment of Acute Deep Vein Thrombosis

The following dosage is recommended: 200 IU/kg body weight given s.c. once daily. The expected plasma anti-Xa levels during subcutaneous treatment would be <0.3 IU anti-Xa/mL before injection and <1.7 IU anti-Xa/mL 3 - 4 hours after injection. In order to individualize the dose, a functional anti-Xa assay should be performed 3 - 4 hours post-injection. The single daily dose should not exceed 18 000 IU.

The following weight intervals are recommended to be adapted to the single-dose prefilled syringes as in the table below.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
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<tbody>
<tr>
<td>46-56</td>
<td>10 000</td>
</tr>
<tr>
<td>57-68</td>
<td>12 500</td>
</tr>
<tr>
<td>69-82</td>
<td>15 000</td>
</tr>
<tr>
<td>83 and above</td>
<td>18 000</td>
</tr>
</tbody>
</table>

For patients with increased risk of bleeding, a dose of 100 IU/kg body weight given s.c. twice daily or 100 IU/kg body weight administered over a period of 12 hours as continuous i.v. infusion, can be used. The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.0 IU anti-Xa/mL 3 - 4 hours after injection.

Normally concomitant treatment with vitamin-K antagonists is started immediately. Treatment with FRAGMIN should be continued until the levels of the prothrombin complex factors (FII, FVII, FIX, FX) have decreased to a therapeutic level, in general for approximately 5 days.

Extended Treatment of Symptomatic Venous Thromboembolism (VTE) to Prevent Recurrence of VTE in Patients with Cancer

Month 1: 200 IU/kg body weight given s.c. once daily for the first 30 days of treatment. The total daily dose should not exceed 18 000 IU daily.

Months 2 - 6: Approximately 150 IU/kg given s.c. once daily using the table shown below.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤66</td>
<td>7 500</td>
</tr>
<tr>
<td>67-78</td>
<td>10 000</td>
</tr>
<tr>
<td>79-99</td>
<td>15 000</td>
</tr>
<tr>
<td>&gt;99</td>
<td>18 000</td>
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</tbody>
</table>

Dose reductions for chemotherapy-induced thrombocytopenia: In the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm^3, FRAGMIN should be interrupted until the platelet count recovers above 50,000/mm^3. For platelet counts between 50,000 and 100,000/mm^3, FRAGMIN should be reduced by 17% to 33% of the initial dose (allowing for dosage adjustment using the pre-filled syringes), depending on the patient’s weight (table below). Once the platelet count recovers to ≥100,000/mm^3, FRAGMIN should be re-instituted at full dose.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Scheduled Dose (IU)</th>
<th>Reduced Dose (IU)</th>
<th>Mean Dose Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤66</td>
<td>7 500</td>
<td>5 000</td>
<td>33</td>
</tr>
<tr>
<td>67-78</td>
<td>10 000</td>
<td>7 500</td>
<td>25</td>
</tr>
<tr>
<td>79-99</td>
<td>15 000</td>
<td>12 500</td>
<td>17</td>
</tr>
<tr>
<td>&gt;99</td>
<td>18 000</td>
<td>15 000</td>
<td>17</td>
</tr>
</tbody>
</table>

Unstable Coronary Artery Disease (Unstable Angina and Non-Q-Wave Myocardial Infarction)

120 IU/kg body weight given s.c. twice daily with a maximum dose of 10 000 IU/12 hours. The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.6 IU anti-Xa/mL 3 - 4 hours after injection. These levels were obtained from another patient population. Treatment should be continued for up to 6 days. Concomitant therapy with ASA is recommended.

Deep Vein Thrombosis in Hospitalized Patients with Severely-Restricted Mobility

In hospitalized patients with severely-restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.
Use in Patients with Renal Impairment

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully.

Administration of low molecular weight heparins to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (creatinine clearance <30 ml/min), which may lead to an increased risk of bleeding. This effect has not yet been determined for FRAGMIN. Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

Anticoagulation for Hemodialysis and Hemofiltration

Chronic renal failure, patients with no other known bleeding risk: Hemodialysis and hemofiltration for a maximum of 4 hours: dose as below, or only i.v. bolus injection of 5000 IU. Hemodialysis and hemofiltration for more than 4 hours: i.v. bolus injection of 30 - 40 IU/kg body weight followed by i.v. infusion of 10 - 15 IU/kg body weight per hour. This dose normally produces plasma levels lying within the range of 0.5 - 1.0 IU anti-Xa/ml.

Acute renal failure, patients with high bleeding risk: i.v. bolus injection of 5 - 10 IU/kg body weight, followed by i.v. infusion of 4 - 5 IU/kg body weight per hour. Plasma level should lie within the range of 0.2 - 0.4 IU anti-Xa/ml.

Dilution

FRAGMIN solution for injection may be mixed with isotonic sodium chloride or isotonic glucose infusion solutions in glass infusion bottles and plastic containers. Post-dilution concentration: 20 IU/ml.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration, whenever solution and container permit.

<table>
<thead>
<tr>
<th>1 mL 10 000 IU</th>
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<tbody>
<tr>
<td>Isotonic NaCl Infusion (5 mg/mL) 500 mL</td>
</tr>
<tr>
<td>or Isotonic Glucose Infusion (50 mg/mL) 500 mL</td>
</tr>
</tbody>
</table>

The infusion rate is 10 mL/hour. The solution should be used within 24 hours.

Study References


SUPPLEMENTAL PRODUCT INFORMATION

Overdosage

Accidental overdosage following administration of FRAGMIN may lead to hemorrhagic complications. FRAGMIN should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of FRAGMIN is inhibited by protamine. This effect may be largely neutralized by slow intravenous injection of protamine sulphate. The dose of protamine to be given should be 1 mg protamine per 100 anti-Xa IU of FRAGMIN administered. A second infusion of 0.5 mg protamine per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-Xa activity is never completely neutralized (maximum about 60%).

Particular care should be taken to avoid overdosage with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulphate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available. Refer to the protamine sulphate Product Monograph for further directions for use.

Product Monograph available on request.

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