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ASH 2008
Spanning 50 years of ground-breaking research
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 February 2009 issue presents coverage from the 2008 ASH Annual Meeting held in San Francisco, California, from December 6–9, 2008. The content examines the latest chronic lymphocytic leukemia (CLL) research: results from the landmark CLL-8 and REACH trials, and a discussion on the use of rituximab in the treatment of CLL. Other articles include a look at rituximab maintenance treatment for follicular lymphoma and a report on GA101, a new monoclonal antibody currently in development.

We would like to thank Dr. Joseph Connors for his 50th anniversary tribute to ASH; Dr. Chaim Shustik, Dr. Laurie Sehn, and Dr. John Kuruvilla for their Canadian perspectives; and Dr. Michael Hallek and Dr. Tadeusz Robak 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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Contributors

50th Anniversary Tribute to ASH

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Dr. Joseph M. Connors is Clinical Professor at the University of British Columbia; and Clinical Director of the Centre for Lymphoid Cancer, Chair of the Lymphoma Tumour Group, and Chair of the Research Ethics Board at the BC Cancer Agency. He is best known for his clinical investigations into the treatment of Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and multiple myeloma. He has served as the chairman of the Hematology Site Committee for the National Cancer Institute of Canada Clinical Trials Group, as a liaison member between the American Society of Clinical Oncology and the American College of Radiology, and as a vice-chairman of the ASH Educational Committee. Dr. Connors is a founding member and coordinator of the Scientific Advisory Board for the Lymphoma Foundation Canada.

Investigator Commentary

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Dr. Michael Hallek is Professor of Medicine, and Director and Chair of the Department of Internal Medicine I at the University of Cologne in Cologne, Germany, where he oversees internal medicine, hematology, hemostaseology, oncology, intensive care, infectious diseases, and immunology. From 1994–2005, Dr. Hallek was head of the Gene Therapy Program at the Gene Center of the University of Munich and of the Clinical Cooperation Group for Gene Therapy at the National Centre for Research on Environment and Health (GSF) in Munich. In 2007, Dr. Hallek was appointed Director of the Center of Integrated Oncology (CIO), the joint comprehensive cancer centre of the Universities of Cologne and Bonn. Since 1994, he has been Chair of the German CLL Study Group. Dr. Hallek is the principal investigator for the CLL-8 clinical trial.

Tadeusz Robak, MD, PhD
Dr. Tadeusz Robak is Professor of Hematology at the Medical University of Lodz and Chief of the Department of Hematology at the Copernicus Memorial Hospital in Lodz, Poland. In 1996–2002, Professor Robak was Vice-rector and Rector of the Medical University of Lodz. Professor Robak is also editor-in-chief of Acta Haematologica Polonica and vice-president of the Polish Leukemia Study Group (PALG). His particular research emphasis has been on the application of purine analogs and monoclonal antibodies in the treatment of leukemia and lymphoma. Professor Robak has published more than 500 journal articles, 350 abstracts, and 15 books or chapters. He is the principal investigator for the REACH clinical trial.
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.

Chaim Shustik, MD, FRCP(C)

Dr. Chaim Shustik is a McGill Professor of Medicine and a staff physician in the Division of Hematology at the Royal Victoria Hospital in Montreal. His primary area of interest is in the treatment of hematologic malignancies. Dr. Shustik holds the Louis Lowenstein Chair in Hematology and Oncology. He is a member of the Scientific Advisory Board of the International Myeloma Foundation.

John Kuruvilla, MD

Dr. John Kuruvilla is Assistant Professor of Medicine at the University of Toronto and a clinical investigator in the Department of Medical Oncology at Princess Margaret Hospital in Toronto. He is a hematologist and member of the Lymphoma Program and the Autologous and Allogeneic Stem Cell Programs. His research interests include novel drug development in lymphoid malignancies and the study of stem cell transplant strategies, and clinical trials in these disorders.
On December 6–9, 2008, the American Society of Hematology (ASH) held its Annual Meeting in San Francisco, a culmination of the year-long celebration of the society’s 50th anniversary.

The origins of ASH are rooted in the history of the science of hematology, which stems from a fascination with blood and the circulatory system, and a recognition of the central role that the hematopoietic system plays in human health and disease. Blood’s vital role in the body has been recognized since ancient times. The circulation of blood was first described by William Harvey in his thesis, *Exercitatio Anatomica de Moto Cordi et Sanguinis in Animalibus*, in 1628. Since then, the study of blood has led to deep insight into basic molecular biology and human disease processes.

The first national and regional organizations dedicated to hematology were developed in the early twentieth century. The New York Society for the Study of Blood was organized in 1945 and is considered to be the oldest “blood club” in the United States. By 1946, the International Society of Hematology (ISH) was founded.

In 1956, Dr. William Dameshek, Professor of Medicine at Tufts University School of Medicine and president of ISH, began the work to create an American Society of Hematology. ASH was founded in 1958 and held its first Annual Meeting in Atlantic City, New Jersey, on April 26–27, 1958, with Dr. James L. Tullis, Professor of Medicine at the Harvard School of Medicine and Chairman of Medicine at the Deaconess Hospital, presiding.

Over the past fifty years, ASH has grown from a few hundred members to more than 15,000. The ASH Annual Meeting, consisting of just 33 invited scientific papers in 1958, now includes approximately 800 oral presentations and over 2,500 poster presentations chosen from more than 6000 submissions. In half a century, ASH has become the major international forum for cutting-edge research in hematology, and plays an important role in training the next generation of researchers and clinicians in the study and treatment of blood and blood-related disease.

Over the past 20 years I have had the privilege of participating in ASH educational and scientific programs, presenting original research, acting as moderator of educational and scientific sessions, serving on various committees, and working closely with ASH to develop its extensive program of large and small meetings. In all instances I have found ASH to be an exemplary professional organization, always placing excellent patient care and promotion of world class research at the head of its priorities. As ASH continues to meet its responsibility to promote the best possible understanding of hematologic diseases and their treatment around the world, I would like to extend my congratulations on its first 50 years of outstanding achievement.

Joseph M. Connors, MD  
Vancouver, BC  
February 16, 2009
Improving Patient Response to Treatment with the Addition of Rituximab to Fludarabine-Cyclophosphamide

Progress in the treatment of chronic lymphocytic leukemia (CLL) has been marked by an improvement in response rates following the introduction of fludarabine. An improvement in response duration has also been observed with the use of purine nucleoside analogues over alkylating agent therapy.

While curative therapy may be the ultimate goal in a select group of patients, stepwise improvements in CLL therapy have led to the consideration of more active regimens. The combination of fludarabine with cyclophosphamide (FC) has resulted in superior complete response (CR) rates compared with fludarabine, the most active single agent. These higher levels of response have been associated with the prolongation of progression-free survival (PFS). These advances have expanded the therapeutic options for a disease with a variable clinical course determined by different prognostic variables and affecting patients in a wide age range.

Rituximab, a monoclonal anti-CD20 antibody, has been shown to have a broad spectrum of activity in indolent and aggressive B-cell lymphoproliferative disorders. Despite limited single-agent activity in CLL, a dose response has been demonstrated. However, the therapeutic potential of rituximab in CLL is more evident in combination regimens. The concurrent administration of rituximab with fludarabine in a randomized phase II study demonstrated an advantage over sequential administration. The addition of rituximab to FC at the M. D. Anderson Cancer Center resulted in the highest CR rates observed in a single institution experience, with unprecedented levels of minimal residual disease (MRD) status achieved.

The results of two widely anticipated randomized phase III clinical trials were reported at the ASH 2008 meeting, which confirm the therapeutic benefit of rituximab in CLL. CLL-8, conducted by the German CLL Study Group, investigated the role of rituximab added to FC in previously untreated patients, while REACH, a multicentre international study, examined the same combination in patients with relapsed CLL.

In this article, New Evidence reports on data presented at the ASH 2008 meeting for these pivotal studies, including a UK-based cost-benefit analysis of the R-FC regimen in the CLL-8 trial.

Immunotherapy with R-FC versus FC improves response rates and progression-free survival of previously untreated patients with advanced chronic lymphocytic leukemia

**Background**

Single institution phase II studies have suggested that adding rituximab to the fludarabine-cyclophosphamide (FC) regimen (R-FC) for first-line treatment of chronic lymphocytic leukemia (CLL) improves response. The German CLL Study Group initiated a multicentre phase III trial, CLL-8, to evaluate the efficacy and safety of R-FC compared with FC for untreated patients with CLL requiring therapy. Results from the CLL-8 study were presented at the 2008 ASH meeting.

**Study design**

- The study enrolled 817 patients with good physical fitness, as defined by a Cumulative Illness Rating Scale (CIRS) score of up to 6 and a creatinine clearance ($\geq 70$ mL/min), between July 2003 and March 2006.
- Patients were randomly assigned to receive 6 courses of either:
  - FC ($n = 409$) – fludarabine $25$ mg/m$^2$ iv on days 1–3 and cyclophosphamide $250$ mg/m$^2$ iv on days 1–3; every 28 days or
  - FC plus R ($n = 408$) – rituximab $375$ mg/m$^2$ iv on day 0 of the first cycle and $500$ mg/m$^2$ iv on day 1 of all subsequent cycles; every 28 days.
- Prophylactic use of antibiotics or growth factors was not generally recommended in the protocol.

**Key findings**

- A total of 409 patients were randomized to the FC treatment arm, and 408 patients were randomized to the R-FC arm.
- Both treatment arms were well balanced with regard to age, stage, genomic aberrations, and IgVH status.
- Binet stage of patients was as follows: 64% Binet B, 32% Binet C, and 5% Binet A.
- Median age was 61 years (range 30 to 81 years) and the median CIRS score was 1 (range 0–8).
- Incidence of cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) were del 13q (57%), trisomy 12 (12%), del 11q23 (25%), and del 17p13 (8%), with no statistically significant differences in distribution between treatment arms.
- A mean number of 5.2 courses was given in the R-FC arm versus 4.8 courses in the FC arm ($p = 0.006$). 74% (R-FC) and 67% (FC) of patients received 6 cycles.
- Dose was reduced by more than 10% in at least one treatment course in 43% (R-FC) and 30% (FC) of patients, and in 21% (R-FC) and 17% (FC) of all treatment courses given.
• Seventeen patients did not receive any study medication: 10 due to violation of enrolment criteria (4 decreased renal function, 2 active secondary malignancies, 2 active infections, 1 autoimmune thrombocytopenia, 1 not requiring treatment), 3 due to withdrawal of consent, 2 due to worsened concomitant diseases. Two patients were lost before the start of treatment.

• Fifty-six patients were not evaluable for response: 17 did not receive any study medication, 16 withdrew consent before interim staging, 7 violated enrolment criteria, 4 discontinued treatment due to toxicity, and 12 due to early death (caused by toxicity, progression, or secondary malignancy).

• Median observation time was 25.5 months at the time of analysis in June 2008.

• A total of 761 patients (R-FC 390; FC 371) were evaluable for response; 787 patients (R-FC 400; FC 387) were evaluable for progression-free survival (PFS); and all were evaluable for overall survival (OS).

**Efficacy**

• Overall response (OR) rate was 95% (370/390) in the R-FC arm compared with 88% (328/371) in the FC arm (p = 0.001). (Table 1)

<table>
<thead>
<tr>
<th>Response</th>
<th>FC n = 371</th>
<th>R-FC n = 390</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>22.9%</td>
<td>44.5%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRu</td>
<td>5.1%</td>
<td>3.3%</td>
<td>0.22</td>
</tr>
<tr>
<td>CRI</td>
<td>1.9%</td>
<td>2.6%</td>
<td>0.52</td>
</tr>
<tr>
<td>nPR</td>
<td>4.9%</td>
<td>2.8%</td>
<td>0.15</td>
</tr>
<tr>
<td>PR</td>
<td>50.4%</td>
<td>39.6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SD</td>
<td>6.7%</td>
<td>3.9%</td>
<td>0.08</td>
</tr>
<tr>
<td>PD</td>
<td>8.1%</td>
<td>3.3%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*CR = complete response; CRI = complete response with incomplete marrow recovery; CRu = unconfirmed complete response; nPR = nodular partial response; PD = progressive disease; PR = partial response; SD = stable disease*

• Exploratory analysis of subgroups showed that the PFS benefit of R-FC was seen across almost all subgroups where there were sufficient numbers to draw meaningful conclusions (Binet A: p = 0.01, Binet B: p <0.0001). One exception was the Binet C subgroup, where the PFS was not statistically significant. Further analysis showed that this result could be explained by the imbalance of the prognostic factors between arms in the Binet C subgroup.

• Study showed a trend toward an increased OS rate in the R-FC arm (91% versus 88% at 2 years, HR = 0.76; p = 0.18). (Figure 2)
• Multivariate analyses were performed to evaluate factors predicting outcome. Age, sex, Binet stage, CIRS score, and renal function (cr cl <70 mL/min) were independent prognostic factors predicting OS or PFS.

Safety
• R-FC treatment was more frequently associated with grade 3 and 4 adverse events (AEs) (R-FC 77.5% versus FC 62.6%). (Table 2)
• Severe hematologic toxicity was higher with R-FC treatment (R-FC = 55.7%, FC = 39.4%).
• Significant differences were observed for neutropenia (R-FC 33.7% versus FC 21.0%; \( p = 0.0001 \)) and leuko-
cytopenia (R-FC 24% versus FC 12.1%; \( p <0.0001 \)), but not for thrombocytopenia (R-FC 7.4% versus FC 10.9%; \( p = 0.09 \)) and anemia (R-FC 5.4% versus FC 6.8%; \( p = 0.42 \)).
• Incidence of grade 3 or 4 infections was not significantly increased in the R-FC arm (18.8% versus 14.9% in the FC arm, \( p = 0.14 \)).
• Tumour lysis syndrome (R-FC 0.2% versus FC 0.5%) and cytokine release syndrome (R-FC 0.25% versus FC 0.0%) were rarely observed in both arms.
• Treatment-related mortality occurred in 2.0% in the R-FC and 1.5% in the FC arm.

### Table 2. CTC grade 3/4 adverse events in R-FC and FC treatment groups

<table>
<thead>
<tr>
<th>Event type</th>
<th>FC % (n = 371)</th>
<th>R-FC % (n = 390)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological toxicity</td>
<td>39.4</td>
<td>55.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21.0</td>
<td>33.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>12.1</td>
<td>24.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.9</td>
<td>7.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Anemia</td>
<td>6.8</td>
<td>5.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Infection</td>
<td>14.9</td>
<td>18.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>0.5</td>
<td>0.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>0.0</td>
<td>0.25</td>
<td>0.32</td>
</tr>
<tr>
<td>Total patients with ≥1 grade 3/4 event n (%)</td>
<td>248 (62.6)</td>
<td>309 (77.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CTC = Common Terminology Criteria

Key conclusions

- Treatment with R-FC results in superior complete and overall response rates and an improvement in progression-free survival in comparison with FC.

- R-FC is relatively safe: although it results in a higher rate of neutropenia as compared with FC, it does not cause more infections or other severe side effects.

- R-FC is well tolerated in physically fit patients, even those >65 or 70 years.

- R-FC might become the new standard first-line treatment for physically fit CLL patients.

Quantitative minimal residual disease assessments predict progression-free survival in CLL patients treated with FC with or without rituximab: a prospective analysis in 471 patients from the CLL-8 trial

**Background**
Data correlating clinical outcome with achievement of minimal residual disease (MRD) are of interest as increased complete response (CR) rates are achieved with advances in treatment. At the 2008 ASH meeting, Boettcher and colleagues presented a subset analysis examining the relationship between MRD and progression-free survival (PFS) in the CLL-8 trial.

**Study design**
- MRD was assessed by four-colour flow cytometry in patients accrued to the CLL-8 trial, who were randomized to receive 6 cycles of fludarabine and cyclophosphamide (FC) or FC plus rituximab (R-FC).
- MRD was assessed before therapy, after 3 cycles (interim staging, IS), 1 month after therapy (initial response assessment, IRA) and 2 months after IRA (final restaging, FR).
- 1,402 samples from 471 patients who had received at least 3 cycles of therapy were included in the analysis (1,162 peripheral blood, PB; 240 bone marrow, BM samples).
- MRD results were separated into 5 cohorts (<10^{-4}, \geq 10^{-4} to <10^{-3}, \geq 10^{-3} to <10^{-2}, \geq 10^{-2} to <10^{-1}, and >10^{-1}) in order to assess the prognostic significance of MRD for PFS.

**Key findings**
- While initial disease levels were identical between the treatment arms, median PB MRD levels were significantly lower within the R-FC arm at all time points of analysis (FC versus R-FC at IS: 5.8 x 10^{-3} versus 5.8 x 10^{-4}; IRA: 3.6 x 10^{-3} versus 0; FR: 4.4 x 10^{-4} versus 0; all \(p < 0.0001\)).
- Median BM infiltration was higher after FC than after R-FC at FR (8.1 x 10^{-4} versus 1.2 x 10^{-4}; \(p < 0.0001\)).
- Proportion of PB samples with MRD levels below 10^{-4} was significantly higher in the R-FC arm than in the FC arm (34% versus 6% at IS; 66% versus 37% at IRA; 66% versus 34% at FR; all \(p < 0.0001\)). (Figure 1)
- BM samples with MRD levels below 10^{-4} at FR accounted for 47.6% and 27.3% of samples from the R-FC and FC arms, respectively (\(p = 0.005\)).

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**Figure 1. Percentage of minimal residual disease–negative patients in R-FC and FC treatment groups**

*\(p < 0.0001\)
- Significant differences in median PFS were obtained when PB MRD levels at IS were grouped into <10^{-2} (70.2% of patients, PFS 44 months), ≥10^{-2} to <10^{-1} (19.7% of patients, PFS 27 months), and >10^{-1} (10.1% of patients, PFS 11 months).
- PFS of all patients who experienced an MRD reduction below 10^{-2} was similar, regardless of the exact level.
- Considering PB MRD levels at FR, clear-cut differences in median PFS were observed between patients demonstrating levels <10^{-4} (49.6% of patients, PFS not reached), ≥10^{-4} and <10^{-3} (36.8% of patients, 34 months) and ≥10^{-3} (13.6% of patients, 15 months). (Figure 2)
- Further subdivisions within those three cohorts resulted in very similar Kaplan-Meier estimates.
- BM MRD levels at FR were best classified into two groups, comprising patients with MRD levels of at least 10^{-2} and below 10^{-2}, respectively. Patients from the former group (11.9% of patients) experienced a median PFS of 15 months, compared with a median PFS of 43 months in the latter group (88.1% of patients).
- When MRD levels and treatment regimens were analyzed simultaneously for prognostic significance, only MRD levels were identified as prognostic parameters for PFS using Cox regression in this model. Prognostic significance was also tested for PB at IS, as well as for PB and for BM at FR.
- Patients who received R-FC achieved significantly lower MRD levels up to FR and were more often MRD-negative. However, once low-level MRD was achieved, it had the same prognostic significance in both treatment arms.
- MRD levels at IS were also associated with the achievement of CR. Only 14.7% of patients with an MRD level of at least 10^{-2} achieved a CR after therapy compared with 49.4% of patients with an MRD level below that threshold (p <0.0001).

**Figure 2. Relationship between minimal residual disease and progression-free survival in R-FC and FC treatment groups**

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>n</th>
<th>Events</th>
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<tbody>
<tr>
<td>&lt;10^{-4}</td>
<td>49</td>
<td>7</td>
</tr>
<tr>
<td>10^{-4}−10^{-3}</td>
<td>72</td>
<td>27</td>
</tr>
<tr>
<td>&gt;10^{-3}</td>
<td>24</td>
<td>20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>n</th>
<th>Events</th>
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</thead>
<tbody>
<tr>
<td>&lt;10^{-4}</td>
<td>90</td>
<td>22</td>
</tr>
<tr>
<td>10^{-4}−10^{-3}</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>&gt;10^{-3}</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

**Key conclusions**

- Lower MRD levels are significantly associated with improved PFS, regardless of therapy, sample material, or sampling time point.
- Identical MRD levels predict similar PFS in patients treated with R-FC or FC.
- Superior efficacy of the R-FC regimen is demonstrated by significantly lower median MRD levels as compared with the FC regimen.

Stilgenbauer S, et al. ASH 2008: Abstract 781

Genomic aberrations, VH mutation status, and relationship to response after treatment with fludarabine and cyclophosphamide (FC) or FC plus rituximab (R-FC) in the CLL-8 trial

Background
At the 2008 ASH meeting, Stilgenbauer and colleagues presented results from a study examining the relationship between genetic aberrations and VH mutation status, and their effect on response in chronic lymphocytic leukemia (CLL) patients who participated in the CLL-8 trial.

Study design
- Fluorescence in situ hybridization (FISH) analyses of genomic aberrations and DNA sequencing of VH mutation status were performed for a subset of countries at a central reference laboratory.
- Samples were available for 648 patients (79%) and representative of the full CLL-8 trial population in terms of other baseline prognostic factors and demographics.
- Outcomes were analyzed for subgroups defined by genetic parameters in univariate analyses.
- Treatment results for R-FC and FC were compared in subgroups defined by genetic parameters to identify prognostic and predictive markers.
- Multivariate analysis was performed by Cox regression with backward selection including age, sex, stage, treatment arm, VH status, and genomic aberrations as parameters.

Key findings
- Incidences of the most common genomic aberrations were 56.7% in 13q−, 36.4% in 13q− single, 24.6% in 11q−, 12.0% in +12q, and 8.2% in 17p−. No aberration was found for these regions in 22.4% of samples. VH was unmutated in 63.4% and V3-21 was re-arranged in 4.9% of samples.
- Distributions of genetic parameters were not significantly different between treatment arms.
- Genomic aberrations according to the hierarchical model were correlated with differences in complete response (CR), CR + partial response (PR), progression-free survival (PFS), and overall survival (OS) in both treatment arms combined and individually (all p <0.001).
- Particularly poor outcomes were observed in patients with del 17p in both FC and R-FC arms: CR (4.5% and 19.0%), CR + PR (45.5% and 71.4%), PFS (at 24 months: 0.0% and 29.6%), and OS (at 24 months: 41.0% and 53.3%), respectively.
- Unmutated VH status was correlated with shorter PFS in both arms combined and individually (all p <0.001), shorter OS in the FC arm (p = 0.006), and a trend towards shorter OS in the R-FC arm (p = 0.092).
- While R-FC improved outcome, the effect was different in specific genetic subgroups. (Figures 1–4)

**Figure 1: Complete response rates of 11q− single patients in R-FC versus FC treatment groups**

- For PFS, independent prognostic factors were del 17p (HR = 6.76; p <0.001), unmutated VH (HR = 1.97; p <0.001), R-FC (HR = 0.51; p <0.001) and trisomy12 (HR = 0.58; p = 0.020).
- For OS, only del 17p (HR = 7.47; p <0.001) and unmutated VH (HR = 2.09; p = 0.018) were identified as significant independent factors, while a trend for OS was observed for R-FC (HR = 0.66, p = 0.085).
Figure 2: Progression-free survival of 11q– single patients in R-FC versus FC treatment groups

![Progression-free survival of 11q– single patients in R-FC versus FC treatment groups](image)

Figure 3. Overall survival of 11q– single patients in R-FC versus FC treatment groups

![Overall survival of 11q– single patients in R-FC versus FC treatment groups](image)

Figure 4. Progression-free survival in R-FC versus FC treatment groups by IgVH mutation status

![Progression-free survival in R-FC versus FC treatment groups by IgVH mutation status](image)

Key conclusions

- Improved outcomes were seen with R-FC as compared with FC in most cytogenetic subgroups.
- The overall improvements seen with R-FC result from specific treatment effects in distinct genetic subgroups, and 11q– appears to benefit particularly. However, 17p– and unmutated VH status remain predictors for shorter PFS and OS, independent of the overall improvement with R-FC.

Reference: 1. Stilgenbauer S, Zenz T, Winkler D, et al. Genomic aberrations, VH mutation status and outcome after fludarabine and cyclophosphamide (FC) or FC plus rituximab (FCR) in the CLL-8 trial. Program and abstracts of the 50th American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California; Abstract 781.
R-FC prolongs progression-free survival in relapsed or refractory chronic lymphocytic leukemia compared with FC alone: final results from the phase III REACH trial

**Background**

The R-FC regimen has demonstrated particularly high rates of overall response (OR), complete response (CR), progression-free survival (PFS), and overall survival (OS) in relapsed/refractory chronic lymphocytic leukemia (CLL). At the 2008 ASH meeting, Robak and colleagues presented results from the phase III REACH study comparing the R-FC and FC regimens in relapsed/refractory CLL.

**Study design**

- **REACH** was an open-label, multicentre, randomized, phase III study to evaluate the efficacy and tolerability of R-FC versus FC in relapsed or refractory patients with CD20-positive CLL.
- The primary endpoint for analysis of the study was PFS.
- Five hundred and fifty-two patients from 17 countries were randomized (1:1) to receive either R-FC or FC.
- Rituximab was administered intravenously before the FC infusion for a total of 6 treatment cycles at intervals of 28 days (cycle 1: 375 mg/m² iv; cycles 2–6: 500 mg/m² iv).
- Fludarabine (25 mg/m² iv/day) and cyclophosphamide (250 mg/m² iv/day) were administered over 3 days for 6 cycles.
- Baseline demographics, disease characteristics, and prognostic factors were well balanced between the two arms.

**Key findings**

**Efficacy**

- OR rate was higher for R-FC versus FC (70% versus 58%, \(p = 0.0034\)), with superior CR rates (24% versus 13%; \(p = 0.0007\)). (Table 1)
- The primary endpoint, PFS, was significantly prolonged by a median of 10 months in the R-FC arm (30.6 months) compared with the FC arm (20.6 months; \(p = 0.0002\); HR = 0.65 [95% CI: 0.51, 0.82]). (Figure 1)
- Secondary endpoints of event-free survival (EFS), time-to-new treatment (TTNT), and duration of response (DR) showed similar results.
- Multiple subgroups were analyzed applying a Cox regression model: all Binet stages experienced similar incremental benefits in PFS (HR = 0.75 for Binet A, HR = 0.65 for Binet B, HR = 0.61 for Binet C).

---

**R-FC Q4W X 3**

**FC Q4W X 3**

**CR, PR**

**SD may continue treatment**

**PD off study**

**CR** = complete response; **ECOG** = Eastern Cooperative Oncology Group; **PD** = progressive disease; **PR** = partial response; **PS** = performance status; **Q4W** = every 4 weeks; **SD** = stable disease

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**Study design**

- CLL
- Binet A, B, or C
- Relapsed disease, excluding fludarabine refractory
- ECOG PS 0–1
- \(n = 552\)

Rituximab

- Cycle 1: 375 mg/m² iv
- Cycles 2-6: 500 mg/m² iv

Fludarabine

- 25 mg/m² iv, days 1–3

Cyclophosphamide

- 250 mg/m² iv, days 1–3
Mutational status and cytogenetic subgroups remained prognostic and benefited from the addition of rituximab to FC (HR: IgVH unmutated = 0.62; IgVH mutated = 0.7; del 17p positive = 0.75; del 17p negative = 0.63; del 13q positive = 0.56; del 13q negative = 0.77).

Median OS was not reached for R-FC and was 51.9 months for FC ($p = 0.29; \text{HR} = 0.83$). (Figure 2)

Of 47 patients who relapsed and were treated in the R-FC arm, 30% received rituximab again. Sixty-nine patients were treated at relapse in the FC arm, and 49% received rituximab.

**Safety**

- Grade 3/4 adverse events (AEs) were higher in the R-FC arm (65%) versus the FC arm (60%), but serious adverse events (SAEs) were similar (50% versus 48%, respectively). (Table 2)
- Grade 3/4 neutropenia and febrile neutropenia were only slightly higher for R-FC (42% and 15%) versus FC (40% and 12%), respectively, and for grade 3/4 thrombocytopenia (R-FC 11% versus FC 9%).
- Grade 3/4 infections (R-FC 17% versus FC 19%) were similar, and there was no difference in bacterial, viral, or fungal infections between the two arms.
- Grade 3/4 anemia was slightly increased in the FC arm (R-FC 2% versus FC 5%).
- Slightly higher fatal AEs were seen with R-FC (13%) versus FC (10%). Fatal SAEs were mainly due to infections, secondary neoplasms, and cardiac disorders.

Figure 1. Progression-free survival in R-FC versus FC treatment groups (median follow-up of 25.3 months)

| Table 1. Response rates in R-FC versus FC treatment groups |
|---|---|---|
| Response | FC (n = 276) % | R-FC (n = 276) % | $p$-value |
| Complete response | 13.0 | 24.3 | 0.0007 |
| Partial response / nodal partial response | 44.9 | 45.7 | 0.8642 |
| Overall response rate | 58.0 | 69.9 | 0.0034 |
| Stable disease | 22.1 | 17.0 | n/d |
| Progressive disease | 5.4 | 2.5 | n/d |
| Not evaluable* | 14.5 | 10.5 | n/d |

* Mainly patients with response that was not confirmed through a second assessment

| Table 2. CTC grade 3/4 adverse events in R-FC and FC treatment groups |
|---|---|---|
| Event type | FC (n = 272) % | R-FC (n = 274) % |
| All events | 60 | 65 |
| Infusion-related (days 1–2 of first cycle) | 4 | 6 |
| Tumour lysis syndrome | 3 | 2 |
| Neutropenia | 40 | 42 |
| Febrile neutropenia | 12 | 15 |
| Thrombocytopenia | 9 | 11 |
| AIHA | 12 | 5 |
| Infections | 19 | 17 |
| Hepatitis B | — | 2 |
| Benign or malignant neoplasms | 3 | 7 |

AIHA = autoimmune hemolytic anemia; CTC = Common Terminology Criteria
Key conclusions

- Rituximab plus FC is significantly superior to FC alone in relapsed/refractory CLL patients.
- Results were consistent in all subgroups, including adverse prognostic groups Binet C, 11q–, unmutated IgVH, and ZAP-70 positivity.
- R-FC showed a favorable risk-benefit profile with no unexpected safety findings.

References:
2. Robak T, Moiseev S, Dmoszynska M, et al. Rituximab, fludarabine, and cyclophosphamide prolongs progression-free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized phase III REACH trial. Program and abstracts of the 50th American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California; Abstract 15742.

Papadakis K, et al. ASH 2008: Abstract 2392

A UK cost-effectiveness analysis comparing first-line treatment with R-FC versus FC in chronic lymphocytic leukemia patients

**Background**

At the 2008 ASH Annual Meeting, Papadakis and colleagues presented results from a UK cost-effectiveness study comparing the R-FC and FC regimens as first-line treatment for previously untreated chronic lymphocytic leukemia (CLL) patients using data from the CLL-8 trial.1,2

**Study design**

- A cost-effectiveness model was developed to evaluate the lifetime health outcomes and direct costs of R-FC compared with FC as first-line treatment for CLL patients in the UK.
- Patients were modelled to be in one of three health states: progression-free survival (PFS), progressed, or death.
- The best parametric fit (Weibull) was used to extrapolate PFS beyond the end of the CLL-8 trial follow-up period to a 15-year lifetime horizon.
- The number of patients in each treatment arm who died while in PFS was based on the maximum of either the observed rate of death or background mortality.
- Because median overall survival (OS) had not been reached in CLL-8, a Markov process was used to model the transition from the progressed health state to death.
• Given the non-significant difference in post-progression survival by treatment (R-FC or FC), patients transitioning from progression to death were modelled as a single population with mean time-to-death (Kaplan-Meier) converted to a monthly probability of dying.

• This Markovian approach is conservative in that treatment benefit is exclusively a function of time spent in PFS.

• Predicted time in each health state was weighted using CLL utility scores to account for patient quality of life (QoL) and to estimate the quality adjusted life-years (QALYs).

• Drug administration, patient monitoring, and pharmacy costs were taken from the UK National Health Service (NHS) schedule of reference costs for 2006 and the published literature.

• Blood transfusions, bone marrow transplants, stem cell therapy, and second-line CLL treatments collected prospectively in CLL-8 were included in monitoring costs.

• The cost of treatment-related grade 3 or 4 infections were not included in the analysis as the incidence between the two treatment arms was comparable.

• Both costs and outcomes were discounted by 3.5%.

Key findings

• R-FC improved mean life expectancy by 1.073 years compared with FC alone. (Table 1)

• The incremental cost-effectiveness ratios (ICERs) were estimated to be £10,825 per life-year gained with R-FC.

• When health-related QoL was taken into account, the ICER was £13,189 per QALY gained for R-FC, well below commonly accepted thresholds in the UK.

• Although there is uncertainty associated with the progression of CLL and relapse treatment costs, the ICER did not exceed £22,458 per QALY, despite a wide variation in each parameter value used in the probabilistic sensitivity analysis.

• The cost-effectiveness acceptability curve for R-FC versus FC is presented in Figure 1.

Figure 1. Cost-effectiveness acceptability curve in the R-FC versus FC treatment groups

Table 1. Cost-utility results in the R-FC versus FC treatment groups

<table>
<thead>
<tr>
<th>Cost-utility results</th>
<th>R-FC</th>
<th>FC</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean life-years</td>
<td>5.73</td>
<td>4.65</td>
<td>1.07</td>
</tr>
<tr>
<td>Mean QALYs</td>
<td>4.26</td>
<td>3.38</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean total cost</td>
<td>£25,595</td>
<td>£13,978</td>
<td>£11,617</td>
</tr>
<tr>
<td>Cost per life-year gained (£)</td>
<td>£10,825</td>
<td>£13,006</td>
<td></td>
</tr>
<tr>
<td>Cost/QALY gained (£) – iv FC</td>
<td>£13,006</td>
<td>£13,189</td>
<td></td>
</tr>
</tbody>
</table>

QALY = quality adjusted life-year

• After adjusting for QoL, the incremental quality-adjusted life expectancy estimated was 0.881 years.

• Improvements in health outcomes were attributed to an increase in the time R-FC patients spent in the PFS health state (1.185 years).

• Total direct costs were higher for R-FC by £11,617 per patient; however, this was partially offset by a reduction in medication and monitoring costs incurred in the progressed health state.

• Based on the significant prolongation of PFS demonstrated in the CLL-8 trial, first-line R-FC significantly increases quality-adjusted life expectancy.

• R-FC is well within the UK threshold of cost-effectiveness of £20,000 per QALY.

• The sensitivity analysis performed provides adequate reassurance that the cost-effectiveness of R-FC held under most plausible scenarios.

References: 1. Hallek M, Fingerle-Rowson G, Fink A, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). Program and abstracts of the 50th American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California; Abstract 325. 2. Papadakis K, Oscier D, Carr E., et al. A UK cost-effectiveness analysis comparing first-line treatment with rituximab in combination with fludarabine and cyclophosphamide versus fludarabine and cyclophosphamide alone in chronic lymphocytic leukemia (CLL) patients. Program and abstracts of the 50th American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California; Abstract 2392.
Canadian perspective by Dr. Chaim Shustik

The German CLL-8 trial reported by Hallek et al. is a timely study evaluating a treatment regimen which is under consideration by many physicians in Canada. The stepwise improvement in treatment outcome, particularly in complete response (CR) rates and the prolongation of progression-free survival (PFS) observed in randomized trials with fludarabine and cyclophosphamide (FC), has prompted physicians to use the most effective regimen in first-line treatment — particularly in fit patients. The addition of rituximab to the FC regimen has thus far been reported as a single institution experience; the German study confirms the observations in a randomized trial in a multicentre setting.

The study population in the CLL-8 trial is fairly representative of patients with this disease. However, the Cumulative Illness Rating Scale (CIRS) used in the study to exclude patients with co-morbidities is not widely used in CLL studies, and questions regarding exclusion of patients with a high score not necessarily related to significant medical co-morbidities may be raised. Most clinical trials have used impaired performance status as an exclusionary criterion. The median age and age range in the study reflect the usual experience in CLL, but the percentage of patients in this study over age 70 is rather low (7%). Consequently, extrapolating these results to an older population warrants caution.

In both the CLL-8 and the REACH studies, the primary endpoint for analysis was progression-free survival (PFS). PFS is a useful outcome measure, but with limitations as it affects the patient. Disease progression may be clinically apparent if characterized by a progressive lymphocytosis, as compared to a more accelerated tempo of progression with enlarging adenopathy or worsening hematologic parameters requiring treatment. Improvement in overall survival (OS) may be difficult to demonstrate in a disease such as CLL, in which the impact of salvage therapies at relapse must be considered. In studies of first-line therapy in low-grade lymphoproliferative disorders, PFS may be the best available outcome measure to assess efficacy. The hazard ratio (HR) for PFS is helpful in appreciating differences between treatment groups.

In the CLL-8 and REACH trials, no significant difference in OS was seen between the R-FC and FC regimens. However, the median follow-up times were too short, and it is possible that survival differences will be seen with longer follow-up. Also the success of salvage therapies may influence results and minimize differences between treatment groups.

The impact of minimal residual disease (MRD) on PFS was analyzed in the CLL-8 study. Although methodology for MRD analysis in CLL is not standardized, the ability to reduce tumour burden below a level defined as CR has been an important therapeutic step in other hematologic malignancies, notably chronic myelogenous leukemia (CML), and remains a more exacting measure of the efficacy of a particular treatment.

In conceiving a potentially curative strategy in this disease, achievement of MRD would seem to be a required initial endpoint. However, the unequivocal relation between MRD, as defined by four-colour flow cytometry (with a threshold of detection at 1/10^4 CLL cells), and PFS in CLL is shown in the CLL-8 study for both treatment arms, although a higher rate of MRD negativity was observed in the R-FC arm at completion of therapy. The caveat concerning MRD as detected in peripheral blood or bone marrow is the possible persistence of disease in other compartments, such as lymph nodes or spleen, which cannot be assessed.

Analysis of outcomes according to cytogenetic abnormality also demonstrated an improvement in PFS for R-FC compared with FC in most subgroups, although stratification by cytogenetic abnormality was not specified in the study. Even though the treatment arms were balanced for each cytogenetic abnormality, complex abnormalities were not reported, and this remains a retrospective subgroup analysis with its limitations.

The cost-effectiveness study performed by Papadakis is interesting from a UK perspective, but an analysis with costs in the Canadian healthcare system is critical for generating applicable data. Because of the higher incidence of grade 3 and 4 neutropenia with the R-FC regimen, cost-effectiveness studies comparing R-FC to FC will need to factor the utilization of granulocyte colony-stimulating factor (G-CSF). The impact on quality of life may be minimal if febrile neutropenia rates are low and do not result in an increase in hospital admissions.
An Interview with Dr. Michael Hallek

At the ASH 2008 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 implications of the CLL-8 trial. Dr. Hallek was the principal investigator of the CLL-8 study.

New Evidence: Given the selection criteria used in the CLL-8 study and the age distribution of the participants, what can we say about the generalizability of the results?

Dr. Hallek: The CLL-8 study is a trial that has involved many community and private practitioners, so it is a study that is relevant for private practice. The selection criteria that we used to include patients in the trial are important. For the first time in CLL research and maybe even in cancer research, we used a score for the inclusion of patients in a trial — the Cumulative Illness Rating Scale (CIRS), developed by Balducci and Extermann. If patients had a score of less than or equal to 6, they would be considered sufficiently fit and could be included in the trial. In this way, we were able to include patients over 80 years who were sufficiently fit into the protocol. One of the major messages from the CLL-8 trial is that when you are able to define “good fitness,” even R-FC, a triple-combination therapy, can be given relatively safely. This is a finding that is somewhat against expectations. Former trials at M.D. Anderson Cancer Center have shown that patients >70 years have problems with this regimen. This shows that our selection process was good and that we were able to select the right patients.

New Evidence: Do you feel that age should be used as a selection criterion?

Dr. Hallek: Age is not a reliable marker. You can find some very sick patients with co-morbidities around the age of 50 or 60 and some very physically fit patients at the age of 80. What is important is to consider the patient’s fitness and co-morbidities.

New Evidence: What about patients who are not physically fit?

Dr. Hallek: In the German CLL Study Group, we run a different protocol with monotherapies in those patients who are less fit. In our protocol, we call the physically fit patients the “go-go” patients, the less fit the “slow-go” patients, and the really frail patients the “no-go” patients. The “slow-go” population, the ones with a CIRS score >6, usually receive a monotherapy, because the treatment goal is different. In the less fit patients, you just want to control the symptoms and are not as concerned with long-term remissions.
**New Evidence:** Considering the results of the CLL-8 trial and the results from phase II studies adding rituximab to chemotherapy backbones, should we add rituximab to milder chemotherapy regimens in less fit patients?

**Dr. Hallek:** This is exactly what we are doing right now. We are currently designing a trial in less fit patients that will compare chlorambucil, which is the old gold standard N-alkylator, to a combination of chlorambucil and rituximab. We may even add the new drug GA101 as a third treatment arm. The objective will be to test whether rituximab plus a mild chemotherapy can help the less fit “slow-go” patients.

**New Evidence:** Do you think that progression-free survival (PFS) is an acceptable outcome, as compared to overall survival (OS) and other indicators, in making decisions for clinical practice?

**Dr. Hallek:** In recurrent diseases like indolent lymphomas, including follicular lymphoma and CLL, the only measure of an advantage for a drug is PFS and the quality of remission. Salvage treatments that are given when the disease recurs destroy initial treatment effects. Therefore, to see a difference in OS, you need an extremely high sample size. In a couple of years we may see some survival effects, but so far we have not. I am not disappointed, because it is not possible to show a significant difference with these patient numbers. PFS is therefore the best endpoint that we can possibly get. There is one other thing that I would use as an argument. If you look at the responders and at the minimal residual disease (MRD) data presented by Dr. Sebastian Boettcher, all patients who have a good response, complete response (CR) or even MRD-negative CR, have a longer survival time. This shows that if you achieve more CRs, there will most likely be a survival advantage. Adding rituximab to FC improves its efficacy, but the difference in OS may not be seen until we have a longer follow-up.

**New Evidence:** In choosing the best patient population to receive treatment with R-FC, what factors would you consider?

**Dr. Hallek:** We have not seen more toxicity with R-FC as compared with FC. R-FC was surprisingly well tolerated, and therefore I would imagine that patients in CR must experience a better quality of life. I have seen this from my own experience. Our first attempt is to identify the treatment target. Many CLL patients want to achieve CRs and have long remissions. Because they are around 60 years old, they are often still working and don’t want to get treated every year. They want to be free of disease and to survive longer. For those patients, a better and longer response is important. In an educated conversation with the patient, you have to make it clear that there are options. One option is that you get a single drug, and after a year you re-treat. The patient will be under control but will need to be re-treated all the time. The other option is a more aggressive treatment that gives the patient time to do what he or she wants for five to seven years without any treatment. For younger, physically fit patients, it is clear what the best option is. They want to be free of disease and gain some time until we have developed novel treatments. Seven years from now we may have novel therapies which are even more efficacious.

**New Evidence:** Is the higher neutropenia rate seen with the R-FC regimen of any concern?

**Dr. Hallek:** It is definitely important to watch those patients with neutropenia. One thing I did not mention in my presentation is that there was more growth factor used with R-FC. However, we did not see more infections and other side effects in the R-FC arm, as compared with the FC arm. There’s clearly more neutropenia in the R-FC-treated patients, but R-FC did not have any other additional side effects as you might expect.
**New Evidence:** How do you rate MRD as an outcome measure?

**Dr. Hallek:** The advantage of an MRD assessment is that it’s objective and relatively simple to perform. I think one of the most important outcomes of this study is that the MRD assessment predicts PFS. I am almost certain MRD will also predict OS. We have not done the latter analysis yet because there are not enough events, but I am relatively sure that we are going to see survival differences. It may well be that if you have an MRD-negative status after three courses, the duration and quality of the response will be much better.

**New Evidence:** How do you feel results of the REACH trial in relapsed/refractory patients with CLL will influence practice?

**Dr. Hallek:** The REACH results give us a second-line option if the patient has not previously received rituximab. Results from the REACH trial also confirm data from the CLL-8 study. The doubling of the response rates and the 10-month increase in PFS is in line with results from the CLL-8 trial. The overall response (OR) rates in the REACH trial are lower than in the CLL-8 trial, as is expected in second-line treatment. Having said this, I am expecting that from now on CLL patients will be treated first-line with R-FC. The question then becomes: can you still use R-FC as second-line treatment? A very simple rule in CLL treatment is that if you have remission for approximately seven years, you can repeat the same treatment. For all the other patients, it may be best to change the regimen.

**New Evidence:** In the UK, a cost-effectiveness study was done to measure the benefit of the R-FC regimen as compared with the FC regimen. What is your opinion of using cost-effectiveness studies to make regulatory decisions about drug funding?

**Dr. Hallek:** It is very difficult to calculate the value of a human life; I actually don’t think that is possible. If we use common sense, a two-month difference in PFS is probably not sufficient to justify funding. However, a gain of a year or more may be worthwhile. If the patient can gain years of freedom from treatment, it is substantial progress. Everything appears to indicate that this will be the case. The results of the CLL-8 study show a gain of a year. With a longer maturation of the trial and based on the phase II evidence, there may be a much larger impact to come. The next point to stress is that we double the rate of CRs, and the patients in CR survive much longer than the others. I believe this will translate one day to a substantial benefit. Our society should be evaluated by the way this prolongation of life is offered to patients, regardless of income and other factors. However, we will need to identify the populations that benefit the most and those that don’t benefit as much or at all.
New Evidence: Given the selection criteria and treatment protocol used in the REACH study, what can we say about the generalizability of the results?

Dr. Robak: Patients in the REACH trial were not heavily pre-treated. They received only one previous treatment, mainly an alkylating agent. If they were treated with a purine analog, it was a single agent like oral cladribine and was not used in combination with other cytotoxic drugs such as cyclophosphamide. Therefore, this was a very homogeneous population, despite the fact that the patients were pre-treated. Also, patients who received rituximab earlier or were refractory to purine analogs were excluded. Possibly some of the latter patients could respond to R-FC, because this regimen includes three drugs, which will produce a different effect than monotherapy. The REACH study also excluded patients with neutropenia, thrombocytopenia, heart insufficiency, and renal insufficiency.

New Evidence: Do you feel that age should be used as a selection criterion when choosing the best treatment option?

Dr. Robak: Biological age and calendar age are not the same. You can have older patients without organ insufficiencies who are fit enough to receive all of the more aggressive treatment options we are discussing. You can also have younger patients with co-morbidities, diabetes, and myocardial infarctions. In the latter patients, you should be careful when choosing more aggressive treatments. Age is therefore important, but it is biological age and the existence of co-morbidities, not calendar age, that should be considered when making treatment decisions.

New Evidence: Do you feel it is important to show a significant improvement in overall survival (OS) when justifying the use of new treatment regimens?

Dr. Robak: To date there are no randomized trials confirming that one treatment regimen is significantly better than another when it comes to OS. There are 10 to 15 recent, well-designed randomized studies published in the past 10 years, which have found higher complete response (CR) and overall response (OR) rates, and longer progression-free survival (PFS); however, none of these trials have shown an advantage in terms of OS. The reason for this lack of OS advantage is quite simple. Patients are treated with several drugs in their life. If they relapse after the initial treatment, studies frequently cross over by offering these patients other treatments. This sequence of treatments leads to an improvement in OS, not one specific treatment regimen. One drug leads to a temporary improvement, but if the patient still has the disease, he or she will eventually relapse. Some other treatment should then be found for that patient. It should therefore not be necessary to show an OS advantage to justify the use of a specific treatment regimen.
**New Evidence:** Do you think that PFS and response rates are acceptable outcomes in making decisions for clinical practice?

**Dr. Robak:** These are very important parameters that should be evaluated, because there is a close relationship between CR, PFS, and MRD negativity with OS. Therefore, we should try to obtain the best results to prolong OS. Although there is no evidence from randomized trials to show a relationship between PFS or response rate outcomes and OS, there is evidence from historical control groups. This relationship has been demonstrated at the M.D. Anderson Cancer Center in a recent study, where patients treated with R-FC survived significantly longer than patients treated with FC (fludarabine and cyclophosphamide) or fludarabine given alone.

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**New Evidence:** What sequence of treatments would you suggest using in the treatment of CLL?

**Dr. Robak:** It is important for the physician to present different treatment options and sequences to the patient, explaining the advantages and disadvantages of each. In contrast to many other hematologists, my feeling is that we should use the less efficacious combinations first, saving better regimens for later in the treatment protocol. The REACH study does not address the issue of the optimal sequence of treatments. However, we do know that we have a very powerful method of treatment confirmed in a randomized study, and sooner or later the patient should be treated with R-FC. This is, I think, the main conclusion to be drawn from the REACH and CLL-8 studies.

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**New Evidence:** Are there any toxicity concerns with R-FC that became apparent from the REACH study?

**Dr. Robak:** In our study, there were no differences found in the number of severe adverse events (SAEs) and the rate of infections in the R-FC versus the FC treatment groups. If there is no difference in SAEs and infection rates, relative toxicity should not be considered a significant problem.

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**New Evidence:** How does rituximab compare to other treatments for CLL in terms of its toxicity?

**Dr. Robak:** Rituximab is a highly selective drug, targeting B-cells only. Alemtuzumab kills all lymphocytes and can lead to many opportunistic infections, CMV reactivations, and complications as a result of the deep immunosuppression. However, alemtuzumab may help a patient where other treatments do not. It is therefore not always easy to choose the most effective and safest treatment for a given patient.

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**New Evidence:** In the UK, a cost-effectiveness study was done to measure the benefit of the R-FC regimen, as compared with the FC regimen. What is your opinion of using cost-effectiveness studies to make regulatory decisions about drug funding?

**Dr. Robak:** Especially in poorer countries, but also in rich countries, we should consider the cost of the treatment. The new modern drugs are very expensive, particularly in hematology. No country can cover all the costs of treatment for everybody. Therefore, in my opinion, cost-effectiveness studies are a very important part of research and decision-making. I think that the UK is a good example; the government examines the options and then selects the cheaper treatments. The government and agencies take the decision-making responsibility. In my opinion, it is not good when the responsibility for the cost is taken by the doctor; it is better when patients understand that it is the decision of their government and that these decisions are based on the safety and effectiveness of the treatment.
A Canadian Perspective for the Use of Rituximab in the Treatment of Chronic Lymphocytic Leukemia

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Background

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world, with an incidence in Canada of 4.64/100,000. The incidence is higher in males (6.18/100,000) than females (3.38/100,000). The disease is rare in persons less than 30 years of age, and its incidence increases after age 40. In 50- to 54-year-olds, rates are lower at 4.43/100,000, but increase to 32.89/100,000 in 75- to 79-year-olds.  

Data from the National Cancer Institute (NCI) has shown that in the United States the median age at diagnosis is approximately 72 years, with the median age of death being 79 years. 

CLL is an indolent disease of neoplastic B cells and is often grouped with small lymphocytic lymphoma (SLL), which is histologically, immunophenotypically, and cytogenetically the same disease. Management of CLL and SLL is comparable.

Purpose of this document

Treatment patterns for the management of CLL vary considerably in Canada, and no uniformly accepted standard of care exists. Access to newer agents with activity in CLL is also widely disparate within the country. However, these regional differences may be eliminated (or may change) over time as new data from clinical trials in CLL become available.

Addition of rituximab to cyclophosphamide, vincristine, and prednisolone (R-CVP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improves complete response (CR) rates and progression-free survival (PFS), with acceptable safety profiles, in follicular lymphoma. Randomized phase III trials have shown improved overall survival and consistent safety profiles with rituximab-based regimens. Recently, in CLL, two randomized phase III trials have shown promising results using R-FC in first- and second-line settings. Results of these trials suggest a need for continued discussion of the use of rituximab in this patient population.

To address the need for a standard treatment approach for CLL, a Canadian steering committee was formed and met in November, 2008. The committee consisted of four CLL experts from four Canadian provinces: Dr. Laurie Sehn from the British Columbia Cancer Agency, Vancouver; Dr. Douglas Stewart from the Tom Baker Cancer Centre, Calgary; Dr. Michael Crump from Princess Margaret Hospital, Toronto; and Dr. Chaim Shustik from Royal Victoria Hospital, Montreal. The objective of the steering committee meeting was to discuss the use of rituximab in the management of CLL. This document incorporates their perspectives and has been reviewed by eight additional Canadian hematologists. Topics addressed include the initiation of treatment, the development of first-line treatment options, new research in relapsed or refractory disease, and rituximab dosing considerations.

Decision to treat in the management of CLL

Goals of therapy

Traditionally, the treatment goal for CLL has been disease control and extending life. For all patients, achieving a long progression-free survival (PFS) or overall survival (OS) is often the goal. However, for older patients with reduced organ function and the presence of co-morbidities, palliation and minimizing side effects of treatment often become the focus.

For patients with asymptomatic indolent disease, a policy of observation until disease progression has usually been adopted. The decision of when to treat is therefore a difficult one.
Clinical staging

Two widely accepted staging methods are used in both patient care and clinical trials: the modified Rai and the Binet systems. (Tables 1 and 2). The original Rai classification has been modified to reduce the number of prognostic groups from five to three. These staging systems are simple and inexpensive, relying solely on physical examination and standard laboratory tests. They do not require ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

Indications for treatment

The 2008 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.1,11

The NCI guidelines outline the following criteria for initiating treatment:

- Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia;
- Massive, progressive, or symptomatic splenomegaly;
- Massive nodes or progressive, or symptomatic lymphadenopathy;
- Progressive lymphocytosis with an increase >50% over 2 months or lymphocyte doubling time of <6 months (factors contributing to lymphocytosis or lymphadenopathy other than CLL should be excluded);
- Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids/standard therapy.

Any one of the following symptoms should also be present: unintentional weight loss ≥10% within the previous 6 months, significant fatigue, inability to work or perform usual activities, fevers of >100.5°F/38.0°C for ≥2 weeks without other evidence of infection, or night sweats for >1 month without evidence of infection.3

Factors guiding choice of treatment

A number of factors may be considered in determining optimal treatment regimens. The 2008 NCI guidelines recommend testing for co-morbidities and physical functioning for inclusion in clinical trials, especially in the elderly. Such factors may affect the ability of patients to cope with the toxicities of treatment. In addition, where patients are not mobile, they may not be eligible for intravenous regimens. A review article on the management of CLL by Shanafelt and Kay (2007)10 suggests that optimal therapy for an individual patient should consider the therapy itself, molecular characteristics of the patient’s disease (cytogenetic abnormalities, IgVH status), clinical features of the patient’s disease (disease bulk and presence of autoimmune cytopenias), and characteristics of the patient (age, organ function, and co-morbid conditions).

<table>
<thead>
<tr>
<th>Table 1. Rai classification system*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 NCI guidelines; BC Cancer Agency 2008 guidelines.3,4

<table>
<thead>
<tr>
<th>Table 2. Binet classification system*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 NCI guidelines.†

†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).
Calendar age may not be as important as physiological age in making treatment decisions. For example, elderly patients who are mobile with a good performance status may benefit from more aggressive intravenous treatments. However, those with reduced ability to visit a clinic, either because of mobility or distance, may require oral regimens. Determining the patient's Eastern Cooperative Oncology Group (ECOG) performance status is also important, as those with an ECOG of 2–4 are often excluded from aggressive treatment protocols. Patients’ preferences and their expectations should be considered when choosing treatments, as well as individual differences in goals for survival and health-related quality of life (QoL).3

Establishing appropriate response criteria
With the absence of curative treatment in CLL, treatment goals often focus on improving survival and quality of life. According to the 2008 NCI guidelines, the optimal treatment endpoint may depend on the patient’s fitness. For example, if the primary consideration in choosing therapy is to minimize side effects, QoL outcomes may be most appropriate. However, for patients who have a better performance status, optimal outcomes may include improving OS and the number of minimal residual disease (MRD)-negative complete responses (defined as blood or marrow with <1 CLL cell per 10,000 leukocytes).3

To date, no randomized controlled trials in CLL have shown a significant improvement in OS for one therapy over another.12 This result may be due to the natural history of the disease, as well as to the success of salvage therapies and the length of follow-up that may be needed to show a significant effect. In the case of follicular lymphoma, early study results of rituximab added to chemotherapy initially showed only an increase in PFS. However, with longer follow-up (>2 years), an improvement in OS was observed.5,7,14–15

Progression-free survival is a common endpoint used in clinical trials. PFS is defined in the 2008 NCI guidelines as the interval between the first treatment day to the first sign of disease progression.1 The International Workshop in CLL (IWCLL) and a publication by Chakravarty and colleagues16 support the use of PFS as the primary endpoint of phase III clinical trials. They also suggest that clinical practice should be guided by trials demonstrating clinically significant improvements in PFS. PFS may also be related to QoL.

Response rates including complete response (CR), partial response (PR), and disease progression are also commonly used as endpoints of clinical trials. NCI criteria for CR, PR, and disease progression are presented in Tables 3 and 4.3

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**Table 3. Criteria for identifying complete response (CR) or partial response (PR)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response (CR)</th>
<th>Partial response (PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy†</td>
<td>None above 1.5 cm</td>
<td>Decrease ≥50%</td>
</tr>
<tr>
<td>Liver and/or spleen size</td>
<td>Normal size</td>
<td>Decrease ≥50%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>&gt;1.5 × 10⁹/L (1,500/µL)</td>
<td>&gt;1.5 × 10⁹/L (1,500/µL) or &gt;50% improvement over baseline</td>
</tr>
<tr>
<td>Circulating clonal B-lymphocytes</td>
<td>None</td>
<td>Decrease ≥50% over baseline</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;100 × 10⁹/L (100,000/µL)</td>
<td>&gt;100 × 10⁹/L (100,000/µL) or increase ≥50% over baseline</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;110 g/L (11.0 g/dL) (untransfused and without erythropoietin)</td>
<td>&gt;11.0 g/dL or increase ≥50% over baseline</td>
</tr>
<tr>
<td>Marrow</td>
<td>Normocellular, &lt;30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines complete response with incomplete blood count recovery (CRi)</td>
<td>≥30% lymphocytes, or B-lymphoid nodules, or not done</td>
</tr>
</tbody>
</table>

*Adapted from 2008 NCI guidelines
†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).
CR: complete remission, all of the criteria have to be met; PR: partial remission, at least one of the criteria has to be met
**Table 4. Criteria for identifying disease progression***

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Disease progression</th>
</tr>
</thead>
</table>
| Lymphadenopathy    | (1) Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates  
                      (2) An increase by ≥50% in greatest determined diameter of any previous site  
                      (3) An increase of ≥50% in the sum of the product of diameters of multiple nodes  |
| Liver and/or spleen size | An increase in the liver or spleen size by ≥50% or the de novo appearance of hepatomegaly or splenomegaly |
| Blood lymphocytes    | An increase in the number of blood lymphocytes by ≥50% or with at least 5,000 B lymphocytes per microliter |
| Histology           | Transformation to a more aggressive histology (e.g., Richter syndrome); whenever possible, this diagnosis should be established by lymph node biopsy |
| Cytopenia:          | Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL |
| Platelet count      | Decrease by >50% or to <100 x 10^9/L (100,000/ul), which occurs at least 3 months after treatment |
| Hemoglobin          | Decrease by >20 g/L (2 g/dL) or to <100 g/L (10 g/dL) occurring at least 3 months after treatment |
| Marrow              | Demonstrates an infiltrate of clonal CLL cells |

*Adapted from 2008 NCI guidelines*

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**Options in first-line treatment for CLL**

**Evolution of chemotherapy backbones in CLL**

**First-line monotherapy trials**

For more than 40 years, the standard treatment for CLL was monotherapy with the alkylating agent chlorambucil. Using doses between 40 mg/m² every 28 days and 10 mg/m² x 7 every 28 days in previously untreated patients, an overall response (OR) of 40%–70% was achieved. However, CR rates ranged between 2%–8%. Median time-to-progression has been approximately 1–1.5 years with this treatment. In some Canadian provinces, chlorambucil is currently one of the recommended first-line options for the treatment of CLL, especially in older, less fit patients.5,17–19

Fludarabine was the first effective new agent to be extensively evaluated in CLL, achieving response rates of 50%–60% in patients who had failed traditional alkylating-agent therapy.20,21 Fludarabine monotherapy was subsequently studied as first-line treatment. In randomized comparisons to alkylating agents, the superior activity of fludarabine was confirmed. With fludarabine, remission rates of 60%–80% and CR rates of 15%–20% were achieved. PFS was also prolonged (median approximately 2 years) when compared to chlorambucil.19,22

A Cochrane meta analysis of four randomized trials (Steurer, et al. 2006) reinforced the finding that purine analog monotherapy versus alkylators showed a significant improvement in PFS (HR 0.70, p <0.00001), but not in OS (HR 0.89, p = 0.07).23 Based on the improvement in PFS, even without an increase in OS, fludarabine is now being used as an initial option in many provinces.

**Purine analog combination treatment**

Combinations of purine analogs and alkylating agents have been evaluated in a number of clinical studies. Of these, the most widely studied combination is fludarabine and cyclophosphamide (FC).24,25

These trials, described in the following paragraphs, demonstrated that FC may be more efficacious than fludarabine or chlorambucil as monotherapy, achieving significantly better PFS, and CR and OR rates. The combination of FC is not approved in Canada; however, its use as first-line treatment has been adopted by physicians as a common treatment option.

The UK CLL-4 trial was a phase III randomized, three-arm, first-line trial assessing the efficacy and safety of FC versus fludarabine versus chlorambucil alone.17 The results showed no statistically significant difference in OS, but demonstrated a statistically significant advantage in PFS for the FC arm compared with the two other arms (36% for FC versus 10% for both the fludarabine and chlorambucil arms; p <0.00005). CR and OR rates were also better with the FC arm than with the fludarabine arm (CR: 38% versus 15%, respectively; OR: 94% versus 80%, respectively; p <0.0001 for both comparisons), which were in turn better than the chlorambucil arm (CR: 7%; OR: 72%; p <0.006 and 0.04, respectively). FC was
the best comparator for all ages, including patients >70 years of age, and for prognostic groups defined by immunoglobulin heavy chain gene mutation status and cytogenetics. Patients had more neutropenia in the FC arm compared with the fludarabine and chlorambucil arms, but less hemolytic anemia was observed with FC (5%) than with fludarabine (11%) or chlorambucil (12%).

Superiority of FC over fludarabine alone was also reported by the German CLL Study Group trial, a large-scale, multi-centre, randomized trial comparing a three-day schedule of combined FC versus fludarabine alone as initial therapy for CLL. This study also found superior CR rates and remission durations in favour of FC.26

Overall, treatment with FC can induce remissions in up to 95% of previously untreated CLL patients achieving high CR rates (25%–40%) and longer median PFS (32–48 months). (Table 5). FC is now considered by many CLL study groups worldwide as a standard treatment for previously untreated patients and is prescribed first-line in several Canadian provinces.

There is greater toxicity with the FC regimen versus F monotherapy, specifically, an increase in neutropenia. The study by Eichorst, et al.27 showed that despite this increase in toxicity, the QoL was no different in patients given F or FC. The QoL improved by the end of treatment in both treatment groups, with the FC group having a significantly longer PFS.

**Addition of rituximab to chemotherapy backbones**

Exploring the use of rituximab, a novel monoclonal antibody, has led to an exciting array of novel treatment approaches in CLL. 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, and prednisone) and for untreated Stage III/IV follicular, CD20-positive, B-cell NHL in combination with CVP (cyclophosphamide, vincristine, and 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 CHOP or CHOP plus rituximab.11,29

**Rituximab-fludarabine (R-F) regimen**

The development of rituximab combinations began by exploring the addition of rituximab to fludarabine. Byrd, et al. (2003)30 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 a significantly higher CR rate of 47% were observed in the concurrent group as compared with the 77% OR and 28% CR rates in the sequential group.

In a subsequent retrospective analysis, Byrd, et al. (2005)12 compared the treatment outcome for patients given R-F in the CALGB 9712 trial to patients given fludarabine alone 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. Even though the study by Byrd, et al. (2005) was a historical comparison study, the strong suggestion of a benefit in PFS and OS may justify the addition of rituximab.4

**Rituximab-fludarabine-cyclophosphamide (R-FC) regimen**

In 2005, Keating, et al.20 initiated a phase II trial to determine if CR rates in previously untreated CLL patients could be increased to 50% or more with the addition of rituximab to chemotherapy. The single-arm study of R-FC as initial therapy

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### Table 5. Evolution of chemotherapy regimens in CLL

<table>
<thead>
<tr>
<th>Chemotherapeutic approach</th>
<th>Typical example</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>Remission duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agent</td>
<td>Chlorambucil</td>
<td>40–60</td>
<td>&lt;10</td>
<td>~1 year</td>
</tr>
<tr>
<td>Purine analog</td>
<td>Fludarabine</td>
<td>60–80</td>
<td>10–20</td>
<td>1.5–2 years</td>
</tr>
<tr>
<td>Purine analog and alkylating agent</td>
<td>Fludarabine, Cyclophosphamide (FC)</td>
<td>80–95</td>
<td>20–40</td>
<td>3–4 years</td>
</tr>
<tr>
<td></td>
<td>Fludarabine, Cyclophosphamide, Rituximab (R-FC)</td>
<td>95</td>
<td>52</td>
<td>~6–7 years</td>
</tr>
</tbody>
</table>

CR = complete response; OR = overall response
was conducted in 224 patients with progressive or advanced
CLL. Patients enrolled in a previous regimen that utilized FC
served as historical controls. The CR rate, proportion of pa-
tients achieving an MRD state (less than 1% CD5 and CD19
cells in bone marrow assessed by flow cytometry), time-to-
treatment-failure, time-to-progression, and survival appeared
significantly better with R-FC than with FC. CR was achieved
in 70% and OR was achieved in 95% of R-FC–treated patients.
In patients evaluated for MRD, a molecular CR rate of 67%
(138/207) was observed. These patients had less than 1% CD5
and CD19 co-expressing cells. This was the highest response
rate reported for any regimen in previously untreated patients
with CLL. The time-to-treatment-failure analysis showed that
69% of patients treated with the R-FC regimen were projected
to be failure-free at four years.

In an update to this study, Tam, et al. (2008)28 presented the
long-term outcome of the R-FC regimen at a medium follow-
up of six years. The investigators reported an OR rate of 95%,
with CR in 72% of patients. The six-year OS and failure-free
survival (FFS) were 77% and 51%, respectively. Among patients
with a PR or better, median time-to-progression was 80 months,
with a six-year projected PFS of 60%. Post-treatment bone mar-
row was negative for MRD by flow cytometry and polymerase
chain reaction in 82% and 42% of patients in CR, 39% and
36% of patients in nPR, and 55% and 31% of patients in PRi
(partial response due to incomplete recovery), respectively.
Patients in CR had the most favourable time-to-progression
(median 85 months) and survival (88% at 6 years), followed
by patients in nPR who had a shorter time-to-progression
(median 71 months, \( p = 0.03 \)), but similar survival (77% at
6 years, \( p = 0.12 \)). Compared with nPR, patients in PRi had
similar time-to-progression (median 50 months, \( p = 0.28 \)), but
experienced shorter survival (42% at 5 years, \( p = 0.01 \)).

A recent study conducted by the German CLL Study Group8
(CLl-8 study) investigated R-FC versus FC as first-line treatment
in 817 previously untreated patients with CLL. The study was an
open-label, multicentre, two-arm, randomized, phase III trial;
the primary study objective was PFS. Study participants included
only those with a good performance status and excluded those
with significant co-morbidities according to a Cumulative Illness
Rating Score (CIRS) >6. Prophylactic use of antibiotics or growth
factors was not specifically recommended in the protocol.

The median observation time was 25.5 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 32.3 months in the FC arm and 42.8 months in the
R-FC arm (HR = 0.59; \( p <0.0001 \)). (Table 6) The PFS shown in
the FC arm was similar to that shown in previous studies using
FC, which have reported a range of 32–48 months.26

The addition of rituximab to FC led to lower median MRD
levels, assessed by four-color flow cytometry, compared with
FC alone.31 The improvement in PFS was also associated with
a decrease in MRD.

Figure 1 shows the PFS over time in the FC and R-FC groups
using Kaplan-Meier curves. Results of the CLL-8 trial provide
strong evidence that R-FC is effective in prolonging PFS in previ-
ously untreated patients with CLL. R-FC was well tolerated and
no new safety signals were detected (see Safety on page 35).

**Table 6. Efficacy of R-FC versus FC as first-line treat-
ment of CLL (median observation time 25.5 months)**

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>FC (n = 371)</th>
<th>R-FC (n = 390)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rates (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response (OR)</td>
<td>88</td>
<td>95</td>
<td>0.001</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>22.9</td>
<td>44.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>50.4</td>
<td>39.6</td>
<td></td>
</tr>
<tr>
<td>Progression-free survival (PFS) (months)</td>
<td>32.3</td>
<td>42.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall survival (OS) (%)</td>
<td>91</td>
<td>88</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Adapted from Hallek, et al. ASH 2008*8

**Figure 1. Kaplan-Meier curve showing progression-free
survival in the R-FC versus the FC group**

*Adapted from Hallek, et al. ASH 2008*8
Other rituximab combinations

The addition of rituximab to chemotherapy backbones in first-line treatment has been explored in a number of phase II studies. These studies examined the efficacy and safety of rituximab, fludarabine, cyclophosphamide, and alemtuzumab (R-FCA), reduced-dose R-FC (R-FC Lite), rituximab, pentostatin, and cyclophosphamide (R-FC), and rituximab with alemtuzumab (R-A). 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.10 (Appendix A)

Implications of study results

Recent clinical trials using rituximab in combination with standard chemotherapy regimens have shown positive results, with implications for treatment recommendations. The improved efficacy and minimal additional toxicity from adding rituximab suggest an advantage for rituximab-based regimens. Changes in the standard of care for the treatment of CLL, as for other indolent lymphomas, have occasionally been based on improvements in PFS, without an observed increase in OS.

In the CLL-8 trial, the risk of progression was reduced by 41% in the R-FC group (median PFS 42.8 months) versus the FC group (median PFS 32.3 months) (HR = 0.59, p <0.0001). This provides compelling evidence to justify the addition of rituximab to FC in first-line CLL. Although HRs demonstrate the outcome superiority of one treatment over another statistically, the absolute improvement in outcome, along with toxicity and cost data, may be the factors that influence decision-makers when considering whether a new treatment should be used or funded. From this perspective, the ten-month improvement in PFS may be more important than the PFS hazard ratio.31

FC regimens do not appear to reduce QoL, despite the relative increase in toxicity as compared with fludarabine.27 As has been the case in follicular lymphoma, longer follow-up studies may demonstrate an increase in OS. Until these results are available in CLL, the statistically significant PFS results support the use of R-FC as a first-line option for the treatment of CLL.

As patients in the CLL-8 study had a good initial performance status and patients with significant co-morbidities were excluded, caution should be exercised in extrapolating results to patients with a worse initial performance status. Where the goal of therapy is to minimize toxicity, for example in patients with low levels of fitness, R-F may be an option. Based on the findings of the CLL-8 study and previous experience adding rituximab to other chemotherapies, it may be appropriate to assume that rituximab added to any chemotherapy backbone could improve results. The study by Byrd, et al. (2005)12 and other studies adding rituximab to chemotherapy backbones have consistently shown improved PFS and CR, strengthening the argument that rituximab is a valuable addition to regimens for the first-line treatment of CLL.

In cases where patients are not able to receive intravenous treatment (reduced mobility or long distance to cancer centres), chlorambucil or oral fludarabine monotherapy may remain a reasonable option. However, elderly patients who are mobile and have a good performance status may tolerate R-F or other rituximab-based combinations. Patient preferences should always be considered in making treatment decisions.

Options in second-line treatment for CLL

Distinguishing between relapsed and refractory disease

The NCI guidelines define refractory disease as treatment failure or disease progression within six months of the last anti-leukemic therapy. Relapse is defined as a patient who has previously achieved the criteria for CR or PR, but after a period of six or more months, demonstrates evidence of disease progression. See Tables 3 and 4 for NCI criteria for CR, PR, and disease progression.3

Studies assessing rituximab-based second-line options

Historically, and for ethical reasons, new regimens tend to be tested in second-line patients as a first step in the development of new treatment options. Until recently, there have been no randomized trials comparing second-line treatment options. A number of phase II studies have examined the use of rituximab added to chemotherapy backbones for second-line treatment of CLL. (Appendix A) In some cases, such as that of R-FC, these studies have been followed by first-line studies, which may lead to new first-line treatment options.

R-FC regimen

In 2005, Wierda, et al.24 evaluated the R-FC regimen in 177 previously treated CLL patients to see if CR for previously treated patients could be improved. CR was achieved in 25% of 177 patients, and nPR and PR were achieved in 16% and 32% of patients, respectively. The OR rate was 73%. Thirty-two percent of the 37 CRs tested achieved molecular remission in bone marrow. The CR rate in this study was the highest reported in previously treated patients with CLL; however, response varied according to initial regimen. (Table 7)
A recent study conducted by the German CLL Study Group (REACH study) examined R-FC versus FC in previously treated patients with CLL. REACH was an open-label, multicentre, randomized, phase III study to evaluate the efficacy and tolerability of R-FC versus FC in relapsed or refractory patients with CD20-positive CLL. The primary endpoint of the study was PFS.

Five hundred and fifty-two patients from 17 countries were randomized (1:1) to receive either R-FC or FC. Rituximab was administered using standard dosing (cycle 1: 375 mg/m² iv; cycles 2–6: 500 mg/m² iv). Fludarabine (25 mg/m²/day iv) and cyclophosphamide (250 mg/m²/day iv) were administered over three days for six cycles. A median of one prior treatment had been administered, consisting of single-agent alkylator therapy (66%), purine analogs (16%), or combination treatments (CHOP, COP [cyclophosphamide, vincristine sulfate, prednisone], F-containing, 18%). Patients who were previously treated with FC or rituximab were not eligible.

Median observation time was 25.3 months. PFS, the primary endpoint, was prolonged by a median of 10 months (50% improvement) in the R-FC arm (30.6 months) compared with the FC arm (20.6 months) \( (p = 0.0002, \text{HR} \ 0.65 \ [95\% \ CI: \ 0.51, \ 0.82]). \) (Figure 2) Secondary endpoints such as event-free survival showed similar results.

OR was higher for R-FC versus FC \( (p = 0.0034) \) due to superior CR rates \( (p = 0.0007). \) (Table 8) Median OS was not reached for R-FC and was 51.9 months for FC \( (p = 0.29, \text{HR} \ 0.83). \) Of 47 patients who relapsed after receiving R-FC, 30% received rituximab again. Of 69 patients who relapsed after receiving FC, 49% received rituximab again.

In this large randomized trial in relapsed or refractory CLL, R-FC demonstrated statistically significant and clinically meaningful superiority to FC in the primary analysis, achieving 10 months improvement in PFS and a doubling of CR rates. The addition of rituximab to FC in REACH showed a very favourable risk-benefit profile and did not reveal any new or unexpected safety concerns (see Safety on page 35). Where previous therapy has not included rituximab or fludarabine-cyclophosphamide, R-FC is a reasonable option for the second-line treatment of CLL.

---

**Table 7. Response to R-FC by prior treatment***

<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>
</tbody>
</table>

**Prior treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FC (n = 276)</th>
<th>R-FC (n = 276)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>13.0</td>
<td>24.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>PR/nPR</td>
<td>44.9</td>
<td>45.7</td>
<td>0.8642</td>
</tr>
<tr>
<td>OR</td>
<td>58.0</td>
<td>69.9</td>
<td>0.0034</td>
</tr>
<tr>
<td>SD</td>
<td>22.1</td>
<td>17.0</td>
<td>n/d</td>
</tr>
<tr>
<td>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 Wierda, et al. 2005

| CR = complete response; nPR = nodal partial response; OR = overall response; PR = partial response

---

*Adapted from Robak, et al. ASH 2008

**Table 8. Efficacy of R-FC versus FC as second-line treatment of CLL (median observation time 25 months)**

<table>
<thead>
<tr>
<th>CR</th>
<th>FC (n = 276)</th>
<th>R-FC (n = 276)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.0</td>
<td>24.3</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>44.9</td>
<td>45.7</td>
<td>0.8642</td>
<td></td>
</tr>
<tr>
<td>58.0</td>
<td>69.9</td>
<td>0.0034</td>
<td></td>
</tr>
<tr>
<td>22.1</td>
<td>17.0</td>
<td>n/d</td>
<td></td>
</tr>
<tr>
<td>5.4</td>
<td>2.5</td>
<td>n/d</td>
<td></td>
</tr>
<tr>
<td>14.5</td>
<td>10.5</td>
<td>n/d</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Robak, et al. ASH 2008

†Mainly patients with response that was not confirmed through a second assessment

CR = complete response; n/d = not determined; nPR = nodal partial response; OR = overall response; PD = progressive disease; PR = partial response, SD = stable disease

In this large randomized trial in relapsed or refractory CLL, R-FC demonstrated statistically significant and clinically meaningful superiority to FC in the primary analysis, achieving 10 months improvement in PFS and a doubling of CR rates. The addition of rituximab to FC in REACH showed a very favourable risk-benefit profile and did not reveal any new or unexpected safety concerns (see Safety on page 35). Where previous therapy has not included rituximab or fludarabine-cyclophosphamide, R-FC is a reasonable option for the second-line treatment of CLL.
Dosing rationale for the R-FC regimen

The dose of R-FC used in clinical trials investigating the efficacy and safety of rituximab was as follows: cycle 1–375 mg/m² iv and cycles 2 to 6–500 mg/m² iv, in combination with 25 mg/m² iv of fludarabine and 250 mg/m² iv of cyclophosphamide on days 1–3 of each cycle.8,20,28 The dose of other regimens used in clinical trials are presented in Appendix A.

The rationale behind increasing the dose of rituximab from 375 mg/m² iv to 500 mg/m² iv after the first treatment cycle is to compensate for the relatively low CD20 expression on B cells in CLL, compared with NHL, which could limit the effectiveness of rituximab at doses shown to be effective in NHL.30,32 Pharmacokinetic studies indicating that post-infusion levels of rituximab are lower in CLL suggest that the standard dose of rituximab is inadequate to saturate the large tumour mass.33 There is a dose response effect with escalating rituximab doses in CLL, as shown in the study by O’Brien and colleagues.33 However, as with many monoclonal antibodies, the optimal dose for rituximab has not been established. Since the standard dosing from the R-FC regimen was used in the CLL-8, REACH, and other studies demonstrating efficacy, this dosing, based on available data, is justifiable at this time.

Safety

The safety of rituximab has been well documented in the treatment of NHL, where the recommended dosage for use with CHOP or CVP is 375 mg/m² iv given for 8 cycles (21 days per cycle), administered as an intravenous infusion on day 1 of each cycle.29

The safety of the cycle 1–375 mg/m² iv; cycles 2 to 6–500 mg/m² iv dosing regimen in CLL has been assessed in several studies and was well tolerated. Safety endpoints of these studies are highlighted in Appendix A.

Historically, there has been some concern regarding toxicities associated with the first infusion of rituximab. The very first dose of rituximab was not increased, because the high number of circulating malignant cells characteristic of CLL might increase the risk of severe infusion-related reactions. However, Keating, et al.20 showed that grade 3/4 first-infusion reactions were rare in patients given R-FC based on standard dosing. Grade 1/2 reactions were noted in some patients, but these were usually responsive to meperidine or hydrocortisone. (Table 9) Adverse reactions to rituximab in courses 2–6 were noted in only three out of 224 patients.

**CLL-8 study safety results**

In the CLL-8 study, the safety population consisted of 761 evaluable patients. Overall, R-FC was well tolerated and no new safety signals were detected. More patients in the R-FC group experienced at least one grade 3/4 AE: 77.5% of patients in the R-FC arm compared with 62.6% of patients in the FC arm (Table 10). The difference was mainly due to a higher rate of hematologic toxicity, including neutropenia and leukocytopenia. However, the incidence of grade 3/4 infections was not significantly higher in the R-FC arm (18.8% in the R-FC arm versus 14.9% in the FC arm, p = 0.14). Treatment-related mortality occurred in 2.0% of patients in the R-FC arm versus 1.5% of patients in the FC arm.8

**REACH study safety results**

In the REACH study, slightly higher rates of grade 3/4 AEs were noted in the R-FC arm (65%) versus FC (60%). (Table 11) Grade 3/4 infections were similar, and there was no difference in bacterial, viral, or fungal infections between the two arms.8

### Table 9. Toxicities associated with the first infusion*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1/2 n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and chills</td>
<td>94 (42)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>22 (10)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>28 (13)</td>
<td>None</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 (11)</td>
<td>None</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (5)</td>
<td>None</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (3)</td>
<td>None</td>
</tr>
<tr>
<td>Urticaria</td>
<td>7 (3)</td>
<td>None</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2)</td>
<td>None</td>
</tr>
</tbody>
</table>

*Adapted from Keating, et al. 2005*

### Table 10. Grade 3/4 adverse events in R-FC and FC regimens*

<table>
<thead>
<tr>
<th>Event type</th>
<th>FC (n = 371) %</th>
<th>R-FC (n = 390) %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>62.6</td>
<td>77.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hematological toxicity</td>
<td>39.4</td>
<td>55.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21.0</td>
<td>33.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>12.1</td>
<td>24.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.9</td>
<td>7.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Anemia</td>
<td>6.8</td>
<td>5.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Infection</td>
<td>14.9</td>
<td>18.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>0.5</td>
<td>0.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>0.0</td>
<td>0.3</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Adapted from Hallek, et al. ASH 2008*
Table 11. Grade 3/4 adverse events in R-FC and FC regimens*

<table>
<thead>
<tr>
<th>Event type</th>
<th>FC n = 272 %</th>
<th>R-FC n = 274 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Infusion-related (days 1–2 of first cycle)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Infections</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Benign or malignant neoplasms</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

*Adapted from Robak, et al. ASH 2008

Conclusions

Prescribing patterns and access to drugs vary widely in Canada, and there is currently no universally accepted standard of care for the treatment of CLL. These regional differences may change or be eliminated over time as new data from clinical trials in CLL become available.

As CLL has traditionally been approached with a watch and wait attitude, the decision of when and how aggressively to treat needs to be addressed. The 2008 NCI guidelines provide criteria for the initiation of treatment. Because a large proportion of CLL patients are elderly, patient factors to consider in the choice of initial therapy are: number of co-morbidities, ECOG performance status, and ability to reach cancer clinics. In choosing treatment for elderly CLL patients, calendar age may be of secondary importance to physiologic age when determining the patient’s ability to tolerate more aggressive treatment options. Of course, patient preferences and expectations of treatment should always be considered in choosing an optimal regimen. For immobile patients or those without access to cancer centres, chlorambucil or oral fludarabine may remain the most appropriate options.

Phase II studies in CLL investigating the addition of rituximab to accepted chemotherapy regimens have shown promising results in the treatment of CLL. New data from the randomized phase III CLL-8 study comparing R-FC to FC show significant increases in PFS and CR with the addition of rituximab to the FC regimen. However, results have not led to an improvement of OS in CLL. Longer-term follow-up is needed to confirm whether there will be an overall survival advantage in using the R-FC regimen.

Until longer follow-up results are available in CLL, the significant PFS results from the CLL-8 trial support R-FC as a reasonable first-line option in patients with a good performance status. In cases where the toxicities of cyclophosphamide are a concern, R-F may be an option.

In the refractory and relapsed setting, emerging data from the REACH trial showed that R-FC improved PFS by 10 months and doubled the CR rates, as compared with FC. The REACH trial suggests that in patients who were not previously given rituximab or fludarabine-cyclophosphamide, R-FC is a reasonable second-line option.

Finally, the dose for R-FC used in clinical trials to date was as follows: rituximab (cycle 1–375 mg/m² iv, cycles 2 to 6–500 mg/m² iv) in combination with fludarabine (25 mg/m² iv) and cyclophosphamide (250 mg/m² iv) on days 1–3 of each cycle. This dosing was used in the pivotal CLL-8 study, the REACH study, and in previous R-FC studies by Keating, et al. and Tam, et al. However, the optimal dose for rituximab has not been established. Unless comparative dose studies are performed, the use of a dose established in previous studies is justifiable.

The objective of this document was to create a perspective on the use of rituximab by examining data from the CLL-8 and REACH trials and to suggest a standardized approach for adding rituximab to chemotherapy backbones. Future studies with extended follow-up may show an improvement in OS for the R-FC regimen. The document will have reached its goal if it serves to facilitate the development of a Canadian consensus for the use of rituximab in the first- and second-line treatment of CLL.
## APPENDIX A: Studies evaluating rituximab-based regimens

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>Treatment arms</th>
<th>Dose</th>
<th>Patient characteristics</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrd, et al.</td>
<td>II</td>
<td>Rituximab-fludarabine (R-F) consolidated or sequentially (n = 104)</td>
<td>R: 375 mg/m² iv on days 1 + 4 of cycle 1 and on day 1 of cycles 2–6&lt;br&gt;F: 25 mg/m² iv on days 1–5 of cycles 1–6</td>
<td>• CALGB performance status ≤3&lt;br&gt;• No reduced kidney function, no negative direct antiglobulin test</td>
<td>Efficacy:&lt;br&gt;• OR: concurrent = 90% (95% CI, 82%–98%), sequential = 77% (95% CI, 66%–89%)&lt;br&gt;• CR: concurrent = 47% (95% CI, 33%–61%), sequential = 28% (95% CI, 16%–40%)&lt;br&gt;• PR: concurrent = 43%, sequential = 49%&lt;br&gt;&lt;br&gt;Safety:&lt;br&gt;• Grade 3/4 neutropenia: concurrent = 74% vs. sequential = 41%&lt;br&gt;• Grade 3/4 infusion-related toxicity: concurrent = 20% vs. sequential = 0%&lt;br&gt;• All other toxicities were similar in the 2 arms</td>
</tr>
<tr>
<td>Byrd, et al.</td>
<td>II</td>
<td>Rituximab-fludarabine (R-F) vs. fludarabine (F) (n = 104 for R-F and 178 for F)</td>
<td>R: 375 mg/m² iv weekly for 4 weeks&lt;br&gt;F: 25 mg/m² iv on days 1–5 of each cycle</td>
<td>• Performance status = 0–3 in R-F vs. 0–2 in F group&lt;br&gt;• All other eligibility criteria were the same between groups&lt;br&gt;• No discussion of exclusion based on co-morbidities except creatinine levels</td>
<td>Efficacy:&lt;br&gt;• OR: R-F = 0.84, F = 0.63 (p = 0.003)&lt;br&gt;• CR: R-F = 0.38, F = 0.2 (p = 0.002)&lt;br&gt;• PFS: higher in R-F group (p &lt;0.0001) with 2-year PFS probability of 0.67 in R-F vs. 0.45 in F&lt;br&gt;• PFS hazard ratio = 2.89&lt;br&gt;• OS: higher in R-F group (p = 0.003) with 2-year OS probability of 0.93 in R-F vs. 0.81 in F&lt;br&gt;• OS hazard ratio = 2.59&lt;br&gt;&lt;br&gt;Safety:&lt;br&gt;• Neutropenia (0.61 vs. 0.21), dyspnea (0.14 vs. 0.03), hypotension (0.05 vs. 0.01) rates more common in R-F vs. F&lt;br&gt;• No difference in thrombocytopenia or infections</td>
</tr>
<tr>
<td>Keating, et al.</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC) (n = 224)</td>
<td>R: 375 mg/m² iv on day 1, 500 mg/m² iv for remaining cycles&lt;br&gt;F: 25 mg/m² iv on days 1–3 of each cycle&lt;br&gt;C: 250 mg/m² iv on days 1–3 of each cycle</td>
<td>• Zubrud performance status 0–2&lt;br&gt;• Co-morbidities excluded: reduced kidney and liver function</td>
<td>Efficacy:&lt;br&gt;• OR: 95% (95% CI, 92%–98%).&lt;br&gt;• CR: 70% (95% CI, 63%–76%)&lt;br&gt;• PR: 15%&lt;br&gt;• nPR: 10%&lt;br&gt;&lt;br&gt;Safety:&lt;br&gt;• Grade 3/4 infusion reactions rare in first infusion (under 5%)&lt;br&gt;• Grade 3/4 neutropenia: 52% of courses&lt;br&gt;• Major infections: 2.6% of courses&lt;br&gt;• Minor infections: 10% of courses</td>
</tr>
</tbody>
</table>

AE = adverse event; AIHA = autoimmune hemolytic anemia; CR = complete response; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CRi = complete response with incomplete marrow recovery; DFS = disease-free survival; EFS = event-free survival; FFS = failure-free survival; 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; TTP = time-to-progression
<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>Treatment arms</th>
<th>Dose</th>
<th>Patient characteristics</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tam, et al. 2008 (Long-term follow-up of Keating, et al. 2005)</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC) (n = 300)</td>
<td>R: 375 mg/m² iv on day 1, 500 mg/m² iv for remaining cycles F: 25 mg/m² iv on days 1-3 of each cycle C: 250 mg/m² iv on days 1-3 of each cycle</td>
<td>• Zubrud performance status 0-2 • Co-morbidities excluded: reduced kidney and liver function</td>
<td>Efficacy:                                                                 • OR: 95% • CR: 72% • PR (cytopenia): 7% • PR (residual disease): 6% • nPR: 10% • OS (6 years): 77% • median PFS: 80 months Safety: • Persistent cytopenia (&gt;3 months): 19% • Recurrent late cytopenia: 69 of 245 (28%) patients • Risk of serious infection (≥grade 3): 10% in first year and 4% in second year</td>
</tr>
<tr>
<td>Wierda, et al. ASH 2007 Abstract: 628</td>
<td>II</td>
<td>Rituximab-fludarabine-alemtuzumab (R-FCA) (n = 40)</td>
<td>R: 375–500 mg/m² iv on day 2 C: 200 mg/m² iv on days 3-5 F: 20 mg/m² iv on days 3-5 A: 30 mg iv on days 1, 3, 5</td>
<td>Not available</td>
<td>Efficacy:                                                                 • CR: 71% • PR: 19% • nPR: 5% Safety: • Grade 3/4 neutropenia: 27% of courses • Grade 3/4 thrombocytopenia: 7% of courses • Major infections: 2% of courses • Minor infections: 8% of courses</td>
</tr>
<tr>
<td>Tarhini, et al. ASH 2006 Abstract: 2844</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC Lite) (n = 28)</td>
<td>R: 500 mg/m² iv on days 1, 14 for 4 weeks F: 20 mg/m² iv on days 1-3 for 4 weeks C: 150 mg/m² iv on days 1-3 for 4 weeks</td>
<td>Not available</td>
<td>Efficacy:                                                                 • OR: 100% • CR: 86% • PR: 14% Safety: • Grade 3/4 neutropenia: 12 (8%) of courses • Grade 3/4 thrombocytopenia: 4 (3%) of courses • Grade 3 anemia: 2 (1%) of courses</td>
</tr>
<tr>
<td>Kay, et al. 2007</td>
<td>II</td>
<td>Rituximab-pentostatin-cyclophosphamide (R-PC) (n = 65)</td>
<td>R: 375 mg/m² iv on day 1 with reduced dose in first week P: 2 mg/m² iv on day 1 C: 600 mg/m² iv on day 1</td>
<td>• ECOG 0–3 • Adequate kidney and liver function</td>
<td>Efficacy:                                                                 • OR: 91% (95% CI, 81%-96%) • CR: 26 patients, 41% (95% CI, 29%-54%) • PR: 18 patients, 28% • nPR: 14 patients, 22% • Equally effective in young vs. old (&gt;70 yrs) Safety: • Grade 3/4 neutropenia: 26 patients (41%) • Grade 3/4 thrombocytopenia: 13 patients (21%) • Most common ≥ grade 3 non-hematologic toxicities included nausea (n = 6), infection (n = 6), vomiting (n = 4), and fever without neutropenia (n = 4)</td>
</tr>
</tbody>
</table>
## Studies evaluating rituximab-based regimens as first-line treatment

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>Treatment arms</th>
<th>Dose</th>
<th>Patient characteristics</th>
<th>Main results</th>
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</thead>
<tbody>
<tr>
<td>Zent, et al. 2008</td>
<td>II</td>
<td>Rituximab-alemtuzumab (R-A) (n = 30)</td>
<td>R: 375 mg/m² iv each week for 4 weeks</td>
<td>Not available</td>
<td>• OR: 27 patients, 90%</td>
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<td>A: initial dose escalation followed by 30 mg 3 days/week for 4 weeks</td>
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<td>• CR: 11 patients 37%</td>
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<td>• 17% of those with CR had no MRD</td>
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<td></td>
<td>• Median response duration: 14.4 months</td>
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<tr>
<td>German CLL Study Group (GCLLSG)</td>
<td>III</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC) vs. fludarabine-cyclophosphamide (FC) (n = 817)</td>
<td>R: 375 mg/m² iv on day 0 of cycle 1; 500 mg/m² iv on day 1 of cycles 2–6</td>
<td>• CIRS score ≤6</td>
<td>Efficacy:</td>
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<tr>
<td>ASH 2008 Abstract: 325</td>
<td></td>
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<td>F: 25 mg/m² iv on days 1–3</td>
<td></td>
<td>• OR: R-FC = 95%, FC = 88% (p = 0.001)</td>
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<td></td>
<td>C: 250 mg/m² iv on days 1–3</td>
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<td>• CR: R-FC = 44.5%, FC = 22.9% (p &lt; 0.01)</td>
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<td></td>
<td>• PR: R-FC = 39.6%, FC = 50.4% (p &lt; 0.01)</td>
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<td></td>
<td>• PFS: R-FC = 42.8 months, FC = 32.3 months (p &lt; 0.0001; Hazard ratio = 0.59)</td>
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<td>• OS: trend showing it was higher in R-FC but not significant</td>
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<td>Safety:</td>
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<td>• Grade 3/4 AEs:</td>
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<td></td>
<td>• Hematological: R-FC = 55.7%, FC = 39.4% (p &lt; 0.0001)</td>
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<td></td>
<td>• Neutropenia: R-FC = 33.7%, FC = 21.0% (p &lt; 0.0001)</td>
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<td></td>
<td>• Leukocytopenia: R-FC = 24.0%, FC = 12.1% (p &lt; 0.0001)</td>
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<td>• Thrombocytopenia: R-FC = 7.4%, FC = 10.9% (p = 0.09)</td>
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<td>• Infections: R-FC = 18.8%, FC = 14.9% (p = 0.14)</td>
</tr>
<tr>
<td>Wierda, et al. 2005</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC) (n = 177)</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</td>
<td>• Performance status ≤3</td>
<td>Efficacy:</td>
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<td>F: 25 mg/m²/d iv on days 2–4 of course 1 and days 1–3 of courses 2–6</td>
<td>• Adequate kidney and liver function</td>
<td>• OR: 73%</td>
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<td>C: 250 mg/m² iv on days 2–4 of course 1 and days 1–3 of courses 2–6</td>
<td></td>
<td>• CR: 25%</td>
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<td></td>
<td>• PR: 32%</td>
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<td></td>
<td>• nPR: 16%</td>
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<td>Safety:</td>
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<td>• First infusion: 63% adverse events, but all grade 1/2</td>
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<td>• Neutropenia: 15% grade 3, 66% grade 4</td>
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<td></td>
<td></td>
<td></td>
<td>• Thrombocytopenia: 16% grade 3, 18% grade 4</td>
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<td></td>
<td>• Anemia: 24%</td>
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<td></td>
<td>• Major infections: 16%</td>
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<td>• Minor infections: 18%</td>
</tr>
</tbody>
</table>

AE = adverse event; AIHA = autoimmune hemolytic anemia; CR = complete response; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CRi = complete response with incomplete marrow recovery; DFS = disease-free survival; EFS = event-free survival; FFS = failure-free survival; 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; TTP = time-to-progression
<table>
<thead>
<tr>
<th>Authors</th>
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<th>Dose</th>
<th>Patient characteristics</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Wierda, et al. ASH 2006 | II    | Rituximab-fludarabine-cyclophosphamide-alemtuzumab (R-FCA) (n = 79)             | C: 250 mg/m² on days 3–5  
F: 25 mg/m² on days 3–5  
A: 30 mg iv on days 1, 3, 5  
R: 375–500 mg/m² iv on day 2 | Not available            | Efficacy:  
• OR: 48 patients, 65%  
• CR: 18 patients, 24%  
• PR: 28 patients, 38%  
• nPR: 2 patients, 3%  
Safety:  
• Neutropenia: grade 3 = 20%, grade 4 = 39% of 231 courses  
• Thrombocytopenia: grade 3 = 17%, grade 4 = 15% of 231 courses |
| Hillmen, et al. ASH 2007 | II    | Rituximab-fludarabine-cyclophosphamide-mitoxantrone (R-FCM) vs. fludarabine-  
                                                      cyclophosphamide-mitoxantrone (FCM) (n = 52)               | F: 24 mg/m² oral for 5 days  
C: 150 mg/m² for 5 days  
M: 6 mg/m² iv on day 1 of each cycle  
R: 375 mg/m² iv cycle 1; 500 mg/m² iv cycles 2–6 | Not available           | Efficacy:  
• OR: R-FCM = 16 patients, 70%  
• FCM = 13 patients, 57%  
• CR + CRi: R-FCM = 43%, FCM = 13%  
• MRD negativity: R-FCM = 5 patients, FCM = 2 patients  
Safety:  
• No difference in the number of patients with SAE’s between the arms |
| Castro, et al. 2008     | II    | Rituximab-methylprednisolone (n = 14)                                            | R: 375 mg/m² iv weekly for 4 weeks  
High-dose methylprednisolone: 1 gm/m² daily for 5 days | • F refractory         | Efficacy:  
• OR: 93%  
• CR: 36%  
• Median time-to-progression: 15 months  
• Median time-to-next-treatment: 22 months |
| Tsimberidou, et al. 2008| II    | Rituximab-oxaliplatin-cytarabine (R-OFA) (n = 30 with CLL)                       | R: 375 mg/m² iv on day 3 of cycle 1 and day 1 of subsequent cycles  
Oxaliplatin: 17.5, 20, or 25 mg/m²/d on days 1–4  
F: 30 mg/m² on days 2,3  
Cytarabine: 1 g/m² on days 2,3  
Pegfilgrastim: 6 mg on day 6, every 4 weeks for a maximum of 6 courses | Not available           | Efficacy:  
• OR: 33%  
• Responses achieved: 35% of patients with 17p deletion, 29% of patients with 11q deletion, 100% patients with trisomy 12, and 40% of patients with 13q deletion  
• Median response duration: 10 months  
Safety:  
• Mainly hematologic; prolonged myelosuppression was not observed |

AE = adverse event; AIHA = autoimmune hemolytic anemia; CR = complete response; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CRi = complete response with incomplete marrow recovery; DFS = disease-free survival; EFS = event-free survival; FFS = failure-free survival; 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; TTP = time-to-progression
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<th>Patient characteristics</th>
<th>Main results</th>
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<tbody>
<tr>
<td>Fischer, et al. ASH 2007 Abstract: 3107</td>
<td>II</td>
<td>Rituximab-bendamustine (n = 81; 31 data currently available)</td>
<td>Bendamustine: 70 mg/m² on days 1,2 R: 375 mg/m² iv for the first cycle and 500 mg/m² iv for subsequent cycles</td>
<td>Not available</td>
<td>Efficacy:</td>
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<td></td>
<td>• OR: 65.2%</td>
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<td>• CR: 13%</td>
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<td></td>
<td>• PR: 52.2%</td>
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<td>Safety:</td>
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<td>• Grade 3/4 anemia: 6.3% of courses</td>
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<td>• Grade 3/4 leukopenia/neutropenia: 10.8% of courses</td>
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<td>• Grade 3/4 thrombocytopenia: 11.9% of courses</td>
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<td>• CTC Grade 3/4 infections: 6 episodes</td>
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<td>Safety (% of courses):</td>
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<td>• Myelosuppression: 59% of courses</td>
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<td>• Anemia: 32% of courses</td>
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<td></td>
<td>• Thrombocytopenia: 26% of courses</td>
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<td>• Leukocytopenia: 25% of courses</td>
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<td>• Nausea and vomiting: 26% of courses</td>
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<td></td>
<td>• Infections: 22% of courses</td>
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<td>• CTC Grade 3/4 infections: 4 episodes</td>
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<tr>
<td>Eichorst, et al. ASH 2005 Abstract: 2126</td>
<td>II</td>
<td>Rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone (R-CHOP) (n = 34)</td>
<td>C: 750 mg/m² iv R: 375 mg/m² iv on day 2 from the second treatment course</td>
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<td>Efficacy:</td>
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<td>• OR: 69% in F refractory patients</td>
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<td>• No CR documented</td>
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<td>Safety (% of courses):</td>
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<td>• Myelosuppression: 59% of courses</td>
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<td>• Anemia: 32% of courses</td>
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<td>• Thrombocytopenia: 26% of courses</td>
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<td>• Leukocytopenia: 25% of courses</td>
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<td>• Nausea and vomiting: 26% of courses</td>
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<td>• Infections: 22% of courses</td>
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<td>• CTC Grade 3/4 infections: 4 episodes</td>
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<tr>
<td>German CLL Study Group REACH ASH 2008 Abstract: 15742</td>
<td>III</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC) vs. fludarabine-cyclophosphamide (FC) (n = 552, none with previous rituximab or FC treatment)</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 ≤6 * Creatinine clearance ≥70 mL/min</td>
<td>Efficacy:</td>
</tr>
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<td></td>
<td>• OR: R-FC = 70%, FC = 58%</td>
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<td>(p = 0.0034)</td>
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<td>• CR: R-FC = 24%, FC = 13%</td>
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<td>(p = 0.0007)</td>
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<td>• PR/nPR: R-FC = 46%, FC = 45%</td>
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<td>(p = 0.86)</td>
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<td>• PFS: R-FC = 30.6 months, FC = 20.6 months (10 months difference, p = 0.0002, HR = 0.65)</td>
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<td>Safety (% of courses):</td>
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<td>• Grade 3/4 AEs: R-FC = 65%, FC = 60%</td>
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<td></td>
<td>• SAEs: R-FC=50%, FC=48%</td>
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<td>• Grade 3/4 neutropenia:</td>
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<td>• R-FC = 42%, FC = 40%</td>
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<td>• Grade 3/4 thrombocytopenia:</td>
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<td>• R-FC = 11%, FC = 9%</td>
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<td>• Grade 3/4 infections:</td>
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<td></td>
<td>• R-FC = 17%, FC = 19%</td>
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<td>• Grade 3/4 anemia: R-FC = 2%, FC = 5%</td>
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<td></td>
<td>• Fatal AEs: R-FC = 13%, FC = 10%</td>
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<td>AE = adverse event; AIHA = autoimmune hemolytic anemia; CR = complete response; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CRi = complete response with incomplete marrow recovery; DFS = disease-free survival; EFS = event-free survival; FFS = failure-free survival; 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; TTP = time-to-progression</td>
</tr>
</tbody>
</table>
### Ongoing studies evaluating rituximab as a first- or second-line treatment

<table>
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<tr>
<th>Authors</th>
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<th>Patient characteristics</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche Global</td>
<td>II</td>
<td>Rituximab-chlorambucil (target n = 100)</td>
<td>R: 375 mg/m² iv in cycle 1; 500 mg/m² iv subsequently \nChlorambucil: 10 mg/m² oral on days 1–7/cycle</td>
<td>≥18 yrs \n• ECOG ≤2</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Roche Global</td>
<td>II</td>
<td>Rituximab-chlorambucil vs. rituximab-bendamustine (target n = 300)</td>
<td>To be determined</td>
<td>To be determined</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CLC.1 (NCIC/ CALGB)</td>
<td>III</td>
<td>Rituximab-fludarabine (R-F) vs. Observation (n = 100 asymptomatic patients)</td>
<td>To be determined</td>
<td>To be determined</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CL.3 (NCIC/ CALGB)</td>
<td>II</td>
<td>Rituximab-fludarabine (RF) vs rituximab-fludarabine (R-F) + lenalidomide consolidation vs. rituximab-fludarabine-cyclophosphamide (R-FC)</td>
<td>To be determined</td>
<td>To be determined</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CLL-7</td>
<td>II</td>
<td>Rituximab-fludarabine-cyclophosphamide (R-FC)(n = 150 Binet A patients)</td>
<td>To be determined</td>
<td>To be determined</td>
<td>Ongoing</td>
</tr>
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AE = adverse event; AIHA = autoimmune hemolytic anemia; CR = complete response; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CRi = complete response with incomplete marrow recovery; DFS = disease-free survival; EFS = event-free survival; FFS = failure-free survival; 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; TTP = time-to-progression

### References:
8. Hallek M, Fingerle-Rowson G, Fink A, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludara- 
bine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic 
lymphocytic leukemia (CLL). Program and abstracts of the 50th American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, 
California; Abstract 325.

9. Robak T, Moiseev S, Dmoszynska M, et al. Rituximab, fludarabine, and cyclophosphamide prolongs progression-free survival in relapsed or refractory chronic 
lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized phase III REACH trial. Program and abstracts of the 50th 
American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California; Abstract 15742.


13. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after 
salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (RF-CM) in patients with recurring and refractory 
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Long-term Outcome and Safety of Rituximab Maintenance Treatment for Follicular Lymphoma

Follicular lymphoma (FL), an indolent B-cell non-Hodgkin’s lymphoma (NHL), is one of the most common types of lymphoma seen in Canada, making up >25% of new lymphoma cases with an annual incidence of >1,500 and a prevalence of >20,000. FL is presently considered to be incurable; median survival is approximately 10 years.1–3

Although FL generally responds well to induction therapy, the disease follows a pattern of remissions and relapses. The goal of therapy for FL is to achieve longer disease-free intervals and to decrease the frequency of relapse, while considering patient quality of life. Achieving treatment goals therefore involves using effective treatments that are relatively non-toxic.3,4

The addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy backbones such as CVP (cyclophosphamide, vincristine, and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) has become a standard for first- and second-line treatment of FL. R-CVP and R-CHOP have demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS), and have a reasonable safety profile.4,5

Maintenance therapy with rituximab, given after an initial response to induction therapy, is an increasingly attractive approach for prolonging remission duration in FL. It has shown promising results with improved efficacy, low toxicity, and a long half-life that allows for infrequent administration. To date, several randomized, phase III clinical trials have demonstrated both increased PFS and improved OS with rituximab maintenance, regardless of whether the patients had been treated with chemotherapy alone, single-agent rituximab, or chemoimmunotherapy. In these studies, rituximab was well tolerated with no additional significant toxicities. However, follow-up times are still relatively short to evaluate the full impact of rituximab maintenance therapy on OS in FL patients and to confirm long-term safety.4,6

At ASH 2008, van Oers and colleagues presented data from the six-year follow-up to a phase III Intergroup clinical trial that examined treatment of relapsed FL with R-CHOP versus CHOP, followed by rituximab maintenance therapy. Witzens-Harig and colleagues presented preliminary data from the phase IIIb MAXIMA trial designed to extend the safety database for rituximab maintenance therapy and to compare the safety of standard versus rapid infusion administration. This article reports and discusses the data from both of these presentations.

Background
Several recent randomized, phase II/III clinical trials in the treatment of follicular lymphoma (FL) have compared rituximab maintenance therapy with observation or with re-treatment at progression. Results from these studies have shown significantly improved progression-free survival (PFS). In two of the six studies, an improvement in overall survival (OS) was also observed.1-6

In 2005, Van Oers and colleagues analyzed the results of the prospective, randomized phase III EORTC 20981 Intergroup trial, evaluating the role of rituximab in both remission induction and maintenance treatment of 465 relapsed/resistant FL patients.6

The analysis showed that the addition of rituximab to CHOP (R-CHOP) induction yielded increased overall response (OR) and complete response (CR) rates, and that rituximab maintenance strongly improved median PFS and OS, both after induction with CHOP and with R-CHOP. Median follow-up was 39 months for the induction phase and 33 months for the maintenance phase at the time of the first analysis.6

At ASH 2008, Van Oers and colleagues presented a report on the long-term outcome of maintenance treatment, with a median follow-up of 6 years from start of maintenance.7

Study design
- Patients (n = 465) with Stages III or IV FL at initial diagnosis, who relapsed after or were resistant to a maximum of two non-anthracycline-containing systemic chemotherapy regimens, were randomized to remission induction with either:
  - CHOP (n = 231) – 6 cycles of standard CHOP (once every 3 weeks) or
  - R-CHOP (n = 234) – 375 mg/m² rituximab at day 1 of each cycle of CHOP.
- Patients (n = 334) with a CR or PR after 6 cycles of therapy underwent a second randomization to either:
  - observation (n = 167) – no further treatment or
  - maintenance treatment with rituximab (n = 167) – 375 mg/m² once every 3 months – until relapse or for a maximum period of two years.
- Primary endpoints were response to treatment for the induction phase and progression-free survival for the maintenance phase.

*375 mg/m² every 3 months for 2 years or until relapse
CR = complete response; FL = follicular lymphoma; PR = partial response
Key findings

- CHOP and R-CHOP induction yielded similar partial response (PR) rates (57% versus 56%), but significantly different CR rates (16% versus 29%; \( p = 0.0001 \)).
- Rituximab maintenance resulted in a highly significant improvement in PFS: median 3.7 years versus 1.3 years in the observation arm (\( p < 0.0001 \); hazard ratio [HR] 0.55). (Figure 1)
- The advantage of rituximab maintenance was observed both after CHOP induction (\( p < 0.0001 \); HR 0.37) and after R-CHOP induction (\( p = 0.043 \); HR 0.69), and in both the CR (\( n = 97; p = 0.003 \)) and the PR (\( n = 237; p = 0.0006 \)) subgroups.
- Five-year overall survival (OS) was 74% in the rituximab maintenance arm versus 65% in the observation arm (\( p = 0.070 \)). (Figure 2)

The highly improved PFS after rituximab maintenance did not translate into a significant OS advantage; this finding might partially be explained because 41% of progressing patients received rituximab as salvage therapy. The percentage of patients receiving rituximab salvage therapy was 59% in those receiving CHOP followed by observation and 26% in those receiving R-CHOP followed by rituximab maintenance.

- Rituximab maintenance was associated with a significant increase in grade 3/4 infections: 9.7% versus 2.4% in the observation arm (\( p = 0.01 \)).
- Seven of the 167 patients had to discontinue rituximab maintenance because of toxicity, mostly recurrent infection.

Key conclusions

- Long term follow-up data show the superiority of rituximab maintenance for PFS, the primary endpoint of the analysis, in all patients and in all subgroups (after treatment with CHOP or R-CHOP, and in CR and PR subgroups).
- Improvement of OS was not statistically significant, probably due to rituximab salvage therapy.

References:
Safety in patients receiving maintenance rituximab for follicular lymphoma: results from the phase IIIb MAXIMA trial

Background
Rituximab has a well established safety profile. The main adverse events (AEs) have been infusion-related reactions, usually occurring after the first infusion. To date, several randomized phase II and III clinical trials using rituximab as maintenance therapy in follicular lymphoma (FL) have not shown any significant increase in toxicity or infections. However, further trials are needed to evaluate safety in the long term.1-7

In August 2006, Witzens-Harig and colleagues initiated the MAXIMA study in 23 countries. By March 2008, recruitment was completed with 545 FL patients enrolled who had had a complete response (CR), an unconfirmed complete response (CRu), or a partial response (PR) to induction therapy, as measured by computed tomography (CT) scan or magnetic resonance imaging (MRI) within 6 weeks of study entry.8

The primary objective of the ongoing phase IIIb MAXIMA trial is to extend the safety database for rituximab maintenance following a wide range of induction therapies. The study also examines the safety profile associated with rapid infusion of rituximab. At ASH 2008, the authors of the MAXIMA study presented data from an initial sample of patients.8

Study design
• Sample size of the single-arm MAXIMA trial was calculated to detect at least one rare event with a true incidence of 0.32% with 80% power.
• Patients (n = 545) with first-line or relapsed/refractory FL achieving a response after adequate rituximab-containing induction therapy were eligible to receive rituximab at the standard dose for FL of 375 mg/m² every eight weeks for a maximum of two years.
• Median age of patients was 57 years, ranging from 29 to 86 years; 57.2% were female.
• Two-thirds of patients were in CR or CRu, and the remaining patients had a PR as a result of their most recent treatment.
• The primary study endpoint was safety (adverse events, serious adverse events, lab tests and vitals). Secondary endpoints were progression-free survival (PFS), event-free survival (EFS), time-to-new-lymphoma (TTNL), and overall survival (OS).
• Median observation time at clinical cut-off in October 2008 was 10.4 months; at that time, 531 patients (95.3%) had had their first infusion visit.

Key findings

Safety
• Adverse events (AEs) occurred in 0.8% of rapid infusions (7/913) and 0.7% of standard infusions (19/2,583). (Figure 1)

One patient who received rituximab at standard infusion speed suffered from a stroke; no other serious adverse events (SAEs) were recorded within 24 hours of the maintenance infusion at either speed.

A total of 71 SAEs were recorded in 59 patients (11.1% of all treated patients). Only 4 of the SAEs were rituximab-related.

One (0.2%) laboratory SAE was reported as a decreased neutrophil count (grade 4).

Grade 3/4 neutropenia occurred in 10 patients, with one resulting in febrile neutropenia.

Twelve patients (2.3%) developed grade 2–4 infections.

Twelve deaths were reported: three from lymphoma, four from concurrent illness, one from cancer, four from other causes.

Figure 1. Percentage of patients with adverse events in the rapid infusion and standard infusion groups
Efficacy

- Relapses occurred in 42 patients (7.7%).
- Relapses in patients treated after first-line induction were less frequent and occurred later than in patients receiving more than two lines of therapy (first-line: 5.9 months and 6.8% of patients; second-line: 3.6 months and 10.1% of patients).
- Relapses differed by response to the most recent treatment:
  - CR patients – 5.1%
  - CRu patients – 15.6%
  - PR patients – 13.0%


Canadian perspective by Dr. Laurie Sehn

The study by Van Oers, et al. assessing the utility of rituximab maintenance therapy in relapsed follicular lymphoma has had a huge impact on clinical practice in Canada. The update presented at ASH 2008 reports a median progression-free survival (PFS) of 3.7 years for patients receiving rituximab maintenance therapy, compared with 1.3 years for those in the observation only group. This is a clinically relevant improvement in the length of time until disease progression and provides a compelling argument for the use of rituximab as maintenance therapy.

In this long-term follow-up analysis, a trend in improved overall survival (OS) with maintenance rituximab was also reported; however, this did not reach statistical significance. The lack of a statistically significant difference in OS may in part be explained by the high prevalence of rituximab use for salvage therapy. Downstream options are often highly effective and may influence survival outcomes.

The goal of maintenance therapy in follicular lymphoma is to keep patients symptom-free and extend the durability of disease control. The documented safety profile in the Van Oers study demonstrated that rituximab maintenance was associated with minimal toxicity. However, a higher rate of grade 3/4 infections was seen in the rituximab maintenance arm, which should be considered when monitoring patients in routine practice. This increase in infection rate was generally not life-threatening, as death rates were not increased. The overall benefit of rituximab maintenance therapy in improving PFS may therefore outweigh the reported safety risks.

The study by Witzens-Harig, et al. serves to further characterize the safety profile of maintenance rituximab. Initial results from this ongoing study corroborate data from previous studies demonstrating rituximab maintenance to be relatively non-toxic with a low adverse event rate.

In British Columbia, rituximab induction and maintenance is administered as a rapid infusion given over 90 minutes (following the initial cycle). To date, there has been no reported increase in infusion reactions or other toxicities with the rapid administration. This is corroborated in the study by Witzens-Harig, et al., which shows no difference in adverse events between the rapid and standard infusion groups. However, full interpretation of these results will only be possible once further details from this ongoing study become available.

Results of clinical studies have shown rituximab maintenance therapy to be relatively non-toxic and to significantly improve PFS in patients who achieve a partial response or complete response following induction therapy. These results solidify rituximab as standard of care in relapsed follicular lymphoma. Until further data becomes available, extrapolation of results to the first-line setting may also be justifiable.

Key conclusions

- Based on the initial sample with FL, no apparent significant safety issues were associated with rituximab maintenance therapy administered every two months.
- Speed of the rituximab infusion did not influence the safety profile.
- Efficacy data for rituximab are in line with previously published randomized clinical trials.
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New Treatment Modalities

GA101 Improves Tumour Growth Inhibition in Mice and Exhibits a Promising Safety Profile in Patients with CD20+ Malignant Disease

Since the development of monoclonal antibodies in the 1980s, biologic therapy has transformed the treatment of cancer. In 1997, rituximab, a type I chimeric monoclonal antibody (mAb) that targets the CD20 antigen, became the first mAb approved specifically for cancer.¹,²

Researchers are currently developing a range of second and third generation anti-CD20 mAbs as well as mAbs specific for other targets. GA101 (RO5072759) is the first humanized, glycoengineered, type II anti-CD20 mAb to enter clinical trials. Glycoengineering results in a significantly increased antibody-dependent cellular cytotoxicity (ADCC) compared with rituximab. The increased ADCC of GA101 has been established in pre-clinical in vivo lymphoma models, where GA101 has also exhibited direct cell-death induction, reduced complement-dependent cytotoxicity (CDC), and superior B-cell depletion in whole blood assays, as compared with rituximab. These in vitro findings have also been confirmed by in vivo efficacy studies in Cynomolgus monkeys and huCD20 transgenic mice.³,⁴

At the ASH 2008 meeting, Dalle and colleagues presented data from a study comparing the anti-tumour efficacy of GA101 versus rituximab in severe combined immune deficient (SCID) mice. Salles and colleagues reported results from a phase I/II clinical trial testing the safety and tolerability of GA101 in 21 patients with CD20-positive malignant disease. In this article, New Evidence reports on data from these two studies.


Dalle S, et al. ASH 2008: Abstract 1585

Compared anti-tumour activity of GA101 and rituximab against the human RL follicular lymphoma xenografts in SCID beige mice

Background
At the ASH 2008 meeting, Dalle and colleagues presented data from a study comparing the anti-tumour efficacy of GA101 and rituximab used as single agents in established RL human lymphoma xenografts in SCID mice.¹

Study design
- One million exponentially growing RL cells were injected subcutaneously into mice, yielding fast-growing xenografts.
- The study was divided into two parts:
  - Part I: GA101 was administered intravenously twice weekly at 3 dosages (10 mg/kg, 30 mg/kg, and 100 mg/kg); rituximab was given at a fixed dose of 30 mg/kg twice weekly.
  - Part II: rituximab (30 mg/kg) and GA101 (30 mg/kg) were administered once weekly intravenously for 4 weeks, either with or without cyclophosphamide (50 mg/kg), administered once weekly intraperitoneally for 4 weeks.
• Both GA101 and rituximab were administered as intravenous injections, for a total of 5 injections in part I.
• Tumor growth inhibition (TGI) was calculated using the National Cancer Institute (NCI) formula at day 34 for part I and day 42 for part II.

**Key findings**

**Part I**
• TGI showed values of 25%, 75%, and 85% for the 10 mg/kg, 30 mg/kg, and 100 mg/kg doses of GA101, respectively. The 30 mg/kg dose of rituximab induced a TGI of 43%. (Figure 1)
• Higher doses of GA101 (30 mg/kg and 100 mg/kg) significantly inhibited the growth of RL tumors and resulted in some complete tumor remissions (10%–30%).
• Anti-tumour activity of rituximab against RL xenografts was inferior to an equivalent dosing of GA101.
• GA101 was well tolerated with no toxic deaths and no significant modification of body weight.

**Part II**
• TGI values at day 42 were 79% for GA101, 35% for rituximab, and 93% for cyclophosphamide administered as single agents when compared with untreated controls.
• Groups receiving combination therapy were compared to the groups receiving the corresponding single agent antibody. Cyclophosphamide increased anti-tumour efficacy, with TGI values of 83% at day 42 and 55% at day 66 for rituximab and 94% at day 42 and 88% at day 66 for GA101, respectively. (Figure 2)

**Key conclusions**
• Results show that GA101 is more active than rituximab on RL xenografts at similar doses, both administered as a single agent or in combination with cyclophosphamide.
• Data show that the type II anti-CD20 antibody GA101 is superior to the type I antibody rituximab as both a single agent and in combination with chemotherapy.
• In the SCID mice model, a major contribution to anti-tumour efficacy is not expected to come from ADCC via the interaction of the glycoengineered mAb with murine FcgRIV receptors.
• Complementary experiments with cobra venom factor, which is used for in vivo complement inhibition, suggest that rituximab’s anti-tumour effect was strongly dependent on complement-dependent cytotoxicity, while GA101 remained active when the complement was depleted.

Background
In an open-label, multicentre, phase I/II study conducted by Salles and colleagues, GA101 was administered as a single agent to 21 non-Hodgkin’s lymphoma (NHL) patients with CD20-positive malignant disease for whom no therapy of higher priority was available. The objective of the study was to determine safety and tolerability, dose-limiting toxicity (DLT), and the pharmacokinetics (PK) of GA101, as well as to establish the recommended phase II dose. At the ASH 2008 meeting, Salles and colleagues presented preliminary data from this study.1

Study design
• Since September 2007, 21 NHL patients have been treated with GA101.
• Patients (9 male, 12 female) had the following lymphoma malignancies:
  ◦ follicular lymphoma (FL): 15 patients
  ◦ mantle cell lymphoma (MCL): 3 patients
  ◦ diffuse large B-cell lymphoma (DLBCL): 1 patient
  ◦ lymphocytic/lymphoplasmacytoid lymphoma: 1 patient
  ◦ Waldenström macroglobulinemia (WM): 1 patient.
• Median hemoglobin concentration was 12.9 g/dL (range 7.5–16.0 g/dL), median white blood count was 5.9 x 10^9/L (range 3.3–80), and median platelet count was 191 x 10^9/L (range 89–363).
• Most patients (95%) had been previously treated with rituximab and had received a median of 3 (range 1–7) prior regimens. About half the patients (52%) had a prior autologous stem cell transplant (ASCT).
• The median duration of response to last treatment was 12 months (range 3–112).
• GA101 treatment was administered according to the rituximab administration guidelines and was given at escalating doses from 50 mg to 2000 mg in 7 cohort groups.
• Treatments were given by intravenous infusion (premedication with acetaminophen and anti-histamines) and administered for a total of 9 infusions.
• Dose of the first infusion was 50% that of subsequent infusions; the dose was escalated based on the safety in a 3 + 3 design.

Key findings
• The majority of toxicities were grade 1/2; there were no grade 4 toxicities.
• The most common adverse events (AEs) were grade 1/2 infusion-related reactions, which included hypotension, nausea, pyrexia, vomiting, chills, hyperthermia, arthralgia, and diarrhea. These AEs occurred mostly after the first infusion.
• Infusion-related reactions responded well to slowing or interruption of the infusion or to steroids.
• Four serious adverse events (SAEs) were observed; only one of them was drug-related and was completely reversible (tumour lysis with thrombocytopenia and neutropenia).
• Only 6 minor infections (4 upper respiratory tract, 1 urinary tract, and 1 oral herpes) have been observed to date.
• Measurement of plasma cytokines and complement during and immediately after the first infusion showed an increase in interleukin (IL)6 and IL8 with a smaller increase in IL10 and tumour necrosis factor (TNF)-α.

• No change in complement fractions (C3, C3a, C4a, C5, C5a, Bb) was observed.

• Concurrent to cytokine increase, an apparent decrease was seen in T-cell subsets (CD3, CD4, and CD8 subsets) and natural killer (NK) cell counts in the peripheral blood.

• Both the decrease in T-cell subsets and NK cell counts, and the cytokine increase were transient; levels were at or near baseline by day 8.

• In the majority of patients, no similar changes were seen with subsequent infusions.

• Circulating B-cell (CD19) depletion occurred rapidly and was sustained.

• Pharmacokinetics of GA101 were broadly similar to those of rituximab and showed a dose-dependent increase in exposure, but with significant inter- and intra-patient variability.

• Time-dependent clearance was noted, which is consistent with a reduction in target-mediated antibody clearance that accompanies increasing duration of treatment.

• Four patients (19%) had a complete response (CR) and five (24%) had a partial response (PR). Overall response (OR) rate was 43%. (Table 1 and Figure 1)

<table>
<thead>
<tr>
<th>NHL sub-types</th>
<th>Best response (%)</th>
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<tbody>
<tr>
<td>21 patients</td>
<td></td>
</tr>
<tr>
<td>15 FL</td>
<td>4 CR, 5 PR (43%)</td>
</tr>
<tr>
<td>1 lymphocytic lymphoma</td>
<td></td>
</tr>
<tr>
<td>1 WM</td>
<td></td>
</tr>
<tr>
<td>1 DLBCL</td>
<td></td>
</tr>
<tr>
<td>3 MCL</td>
<td></td>
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</table>

• 8 of 9 responses still ongoing
• ORR = 47% when only indolent lymphoma (n = 17) are considered

CR = complete response; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; NHL = non-Hodgkin’s lymphoma; ORR = overall response rate; PR = partial response; WM = Waldenström macroglobulinemia

• One patient had stable disease (SD) at 8 months, and three patients had progressive disease (PD), two of whom have since died; one patient died from an event unrelated to treatment (cerebrovascular accident).

• Responses occurred at all dose levels.

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Figure 1. Best tumour response (18 patients) after treatment with GA101*
**Key conclusions**

- GA101 was well tolerated with no dose-limiting toxicities; it showed a similar safety profile to rituximab.
- Preliminary pharmacokinetic data suggest that baseline tumour burden is an important co-variate.
- An encouraging efficacy for GA101 was observed in relapsed/refractory NHL patients.


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**Canadian perspective by Dr. John Kuruvilla**

In the study by Dalle, et al., there was a positive dose response relationship between GA101 given at 10 mg/kg, 30 mg/kg, or 100 mg/kg and the percentage of mice with tumour growth inhibition (TGI) and complete tumour remissions (CTRs). The percentage of mice with TGI and CTRs was also higher in the GA101 30 mg/kg group, as compared with a similar dose of rituximab. When combined with cyclophosphamide, similar results were seen. Therefore, at least in the setting of a mouse model, the findings show a good dose response with GA101 for TGI. This is exactly the sort of pre-clinical data we like to see. One issue with antibodies is determining the right dose to use. Ideally, you would see a dose response in this setting and would like that to translate to the clinic. You would then try higher safe doses, ideally in phase I or II studies, to see if this translates into patient response.

The introduction of a cobra venom for complement inhibition showed that rituximab was dependent on the complement for cytotoxicity, whereas GA101 was not. As GA101 remained active when the complement was inhibited, it falls under the category of antibody-dependent cellular cytotoxicity (ADCC), and proves that you can develop an ADCC antibody. An ADCC antibody has some advantages. In cases where the complement has been depleted, such as when the immune system is disrupted for some reason, an ADCC antibody should remain effective.

The study by Salles, et al. showed a relatively good safety profile for GA101 in relapsed/refractory CD20-positive disease. The most common adverse events (AEs) were grades 1 or 2 infusion-related reactions, limited to the first infusion. In terms of AEs of more concern, infection rates were low, with only 6 minor infections reported by the time of analysis. Therefore, safety results seem promising thus far and similar to those of studies using rituximab.

In the 21 non-Hodgkin’s lymphoma (NHL) patients in the Salles, et al. study, the overall response (OR) was 43%, and 8 of 9 responses are ongoing. Phase I studies start at low doses of agents, and thus a response rate of 43% in this study appears promising. In addition, the majority of patients had indolent lymphoma (n = 17), and the OR rate was 47% in that subset of patients.

We also hope to see phase II studies in specific lymphoma histologies (follicular or diffuse large B-cell lymphoma) and in treatment groups such as rituximab-refractory or rituximab-naïve patients. It will be interesting to watch the development of this antibody and see whether it becomes a successor to rituximab.
Treatment with Bendamustine Plus Rituximab Shows Promising Results in CLL and in Follicular, Indolent, and Mantle Cell Lymphomas

In just over a decade, therapy with the monoclonal antibody rituximab has dramatically improved the treatment and management of patients with B-cell malignancies. The addition of rituximab to standard chemotherapy regimens is recommended by the 2009 National Comprehensive Cancer Network (NCCN) non-Hodgkin’s lymphomas (NHL) treatment guidelines and is approved by Health Canada.1,2 In chronic lymphocytic leukemia (CLL), phase II studies examining the benefits of adding rituximab to a number of chemotherapy agents have shown positive results.3,4 As reported at the ASH 2008 meeting, results from phase II studies in CLL have recently been confirmed by the phase III studies CLL-8 and REACH.

One of the strategies to further improve the success of rituximab combinations in both NHL and CLL has been to examine less-toxic combinations. Bendamustine, an alkylating agent with additional properties of a purine analogue, has shown considerable activity as monotherapy for solid and lymphoid malignancies, including CLL. Encouraging clinical results have been obtained using the bendamustine plus rituximab (R-B) combination treatment in relapsed/refractory and previously untreated NHL. In addition, in vitro studies have demonstrated synergistic pro-apoptotic effects between bendamustine and rituximab in primary CLL cells.5

At the ASH 2008 meeting, Fischer and colleagues presented data on the efficacy and toxicity of R-B in patients with relapsed or refractory CLL. Rummel and colleagues reported the results of a second interim analysis of a phase III study comparing R-B with CHOP plus rituximab (R-CHOP) as first-line therapy for follicular, indolent, and mantle cell lymphomas. In this article, New Evidence reports on data from these two studies.


Fischer K, et al. ASH 2008: Abstract 330

Bendamustine in combination with rituximab for patients with relapsed CLL: a multicentre phase II trial of the German CLL Study Group

Background

At the ASH 2008 meeting, Fischer and colleagues presented data from a phase II clinical trial evaluating the efficacy and toxicity of bendamustine in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL).1

Study design

• A total of 81 patients (mean age 66.7 years) with a median number of 2 (range 1–3) pre-treatments were enrolled between March 2006 and June 2007.

• Patients received 70 mg/m² bendamustine on days 1 and 2 combined with 375 mg/m² rituximab for the first cycle and 500 mg/m² for the second and subsequent cycles.

• Rituximab-bendamustine (R-B) treatment was administered every 28 days for up to 6 courses.

• Blood samples were taken for molecular cytogenetics by fluorescence in situ hybridization (FISH) and for analysis of the immunoglobulin heavy chain (IgVH) mutational status prior to the first treatment course.
• Assessment for minimal residual disease (MRD) was performed by four-colour flow cytometry of peripheral blood and bone marrow.

• The primary endpoint of the trial was the overall response (OR) rate. Secondary endpoints included toxicity, duration of response, event-free survival (EFS), MRD response rate, and OR rate in biological defined risk groups.

**Key findings**

• A total of 328 treatment cycles with a mean number of 4.5 courses were administered to 81 patients.

• Data for response assessment were available for 62 patients; 19 patients were not evaluable for response due to withdrawal or lack of consent, violation of enrolment criteria, or early discontinuation of therapy.

• OR rate was 77.4%, with complete response (CR) in 9 patients (14.5%) and partial response (PR) in 39 patients (62.9%).

• No patients achieved MRD negativity in bone marrow (n = 2 evaluable patients).

• Stable disease (SD) was achieved in 11 patients (17.7%), while 3 patients (4.8%) had progressive disease (PD).

• Differences in response were observed amongst genetic subgroups:
  - Of the 13 patients with 11q–, 12 achieved a remission, with 11 PR and 1 CR (OR: 92.3%).
  - All 8 of the 8 patients with +12 responded (7 PR, 1 CR).
  - In the high-risk group with 17p–, 4 of 9 patients showed a PR (OR: 44.4%).

• Of the 39 patients with unmutated IgVH status, 29 were responsive to R-B (OR: 74.4%).

• In total, 123 grade 3–5 adverse events (AEs) were reported, the most frequent being myelosuppression and infections.

• Grade 3/4 anemia occurred in 6.1% of all given courses; grade 3/4 leukopenia/neutropenia and thrombocytopenia occurred in 11.9% and 9.1% of all given courses, respectively. (Table 2)

• Sixteen episodes (4.9%) of grade ≥3 infections were documented; most of them were successfully managed.

• Treatment-related mortality occurred in 3.7% of patients: three patients died due to severe infections associated with treatment-related neutropenia (one fatal pneumonia, one sepsis after diagnosis of Richter’s syndrome, and one urosepsis).

### Table 1. Response rates in 62 patients after treatment with bendamustine plus rituximab (R-B)

<table>
<thead>
<tr>
<th>Response type</th>
<th>Patients (%) (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>77.4</td>
</tr>
<tr>
<td>Complete response</td>
<td>14.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>62.9</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4.8</td>
</tr>
</tbody>
</table>

### Table 2. Grade 3/4 adverse events after treatment with bendamustine plus rituximab (R-B)

<table>
<thead>
<tr>
<th>Event type</th>
<th>Courses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>6.1</td>
</tr>
<tr>
<td>Leukopenia/neutropenia</td>
<td>11.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9.1</td>
</tr>
<tr>
<td>Infections</td>
<td>4.9</td>
</tr>
</tbody>
</table>

**Key conclusions**

- **Bendamustine plus rituximab (R-B)** is an effective treatment regimen for patients with relapsed and/or refractory CLL and has notable activity in high-risk CLL disease.

- **Major treatment toxicities** were myelosuppression and infections; however, these were reported to be tolerable.

- **Ongoing trial follow-up analysis** will define response duration and long-term safety.

- **In a forthcoming trial, the German CLL Study Group** will investigate the efficacy of R-B in comparison to fludarabine-based immunochemotherapy (R-FC) for first-line treatment of CLL.

Bendamustine plus rituximab (R-B) versus R-CHOP in the first-line treatment of patients with follicular, indolent, and mantle cell lymphomas: second interim analysis of a phase III study of the Study Group Indolent Lymphomas (StiL)

Background

An open label, multicentre, phase II clinical trial initiated in 2000 by Rummel and colleagues evaluated the combination of bendamustine plus rituximab (R-B) in patients with relapsed/refractory indolent or mantle cell lymphomas. This study showed promising results, reporting an overall response (OR) rate of 90% and a complete response (CR) rate of 60%. In October 2003, Rummel and colleagues began a multicentre, randomized phase III clinical trial to compare the efficacy and safety of R-B versus R-CHOP as first-line therapy for follicular, indolent, and mantle cell lymphomas. Data from a second interim analysis of this phase III study were presented at the ASH 2008 meeting.

Study design

- The primary objective of the study was to show the non-inferiority of R-B compared with R-CHOP in the first-line treatment of patients with follicular, indolent, and mantle cell lymphomas.
- Inferiority was defined as a difference of less than 10% in progression-free survival (PFS) after 3 years.
- Secondary objectives were to compare R-B and R-CHOP in terms of:
  - response rates, relapse-free survival, and overall survival (OS)
  - acute and late toxicities and infectious complications
  - stem cell mobilization capacity in young patients eligible for autologous peripheral blood stem cell transplantation (APBSCT) in a later relapsed disease situation.
- Patients included in the study had one of the following CD20-positive lymphomas: follicular (grade 1 or 2), lymphoplasmacytic/immunocytoma, small lymphocytic lymphoma, nodular and generalized marginal zone, or mantle cell.
- Patients had no previous treatment with chemotherapy, interferon, or rituximab and had a WHO performance status of 0–2.

Study design

<table>
<thead>
<tr>
<th>Day</th>
<th>R-B</th>
<th>R-B</th>
<th>R-B</th>
<th>R-B</th>
<th>R-B</th>
<th>R-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>B</td>
<td>R</td>
<td>29</td>
<td>57</td>
<td>85</td>
<td>113</td>
</tr>
<tr>
<td>2</td>
<td>375 mg/m² day</td>
<td>90 mg/m² day</td>
<td>29</td>
<td>57</td>
<td>85</td>
<td>113</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day</th>
<th>CHOP</th>
<th>R-CHOP</th>
<th>R-CHOP</th>
<th>R-CHOP</th>
<th>R-CHOP</th>
<th>R-CHOP</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>CHOP</td>
<td>R-CHOP</td>
<td>R-CHOP</td>
<td>R-CHOP</td>
<td>R-CHOP</td>
<td>R-CHOP</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>375 mg/m² day</td>
<td>90 mg/m² day</td>
<td>22</td>
<td>43</td>
<td>64</td>
<td>85</td>
<td>106</td>
</tr>
</tbody>
</table>

R = bendamustine
B = rituximab

Randomization

n = 546
• A total of 549 patients were included in the study. At the time of this second interim analysis, 462 patients were evaluable for response (R-B: n = 235; R-CHOP: n = 227; median age 64 years).

• Patients were randomized to receive rituximab 375 mg/m² (day 1) plus either bendamustine 90 mg/m² (days 1 and 2) every 28 days or the standard CHOP regimen every 21 days for a maximum of 6 cycles.

• There was an equal percentage of patients with follicular (53%), mantle cell (19%), and other indolent lymphomas (28%) in each treatment group.

• The study is now closed according to the planned recruitment schedule.

Key findings
• OR rate for patients treated with R-B was similar to that reported with R-CHOP (94% versus 93%, respectively). (Table 1)

• CR was also similar to that reported with R-CHOP at 41% for R-B compared with 32% for R-CHOP.

• Median follow-up time for both groups was 27 months.

• Response rates by disease entity between the two groups were also similar. (Table 2)

• To date, a total of 53 deaths have been observed (R-B: 26; R-CHOP: 27).

• Progressive or relapsed disease (PD) was documented during the follow-up period: 63 in patients treated with R-B and 89 in the R-CHOP group.

• There was an observed trend of greater PFS in the R-B group, as compared with the R-CHOP group; however, the difference was not significant (p = 0.09) (Figure 1)

• Alopecia (0% R-B versus 91% R-CHOP) and infectious complications (31% R-B versus 41% R-CHOP) were lower with R-B than with R-CHOP. (Table 3)

• WHO grade 3/4 leukocytopenia was reported in 38% R-CHOP–treated patients compared with 14% of patients treated with R-B.

• Granulocyte colony-stimulating factor (G-CSF) was used more frequently in the R-CHOP group (21% versus 5%).

### Table 1. Response rates in R-B and R-CHOP treatment groups (median observation period 27 months)

<table>
<thead>
<tr>
<th></th>
<th>R-B (n = 232)</th>
<th>R-CHOP (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>94%</td>
<td>93%</td>
</tr>
<tr>
<td>CR</td>
<td>41%</td>
<td>32%</td>
</tr>
<tr>
<td>SD</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>PD / relapse</td>
<td>n = 63</td>
<td>n = 89</td>
</tr>
<tr>
<td>Deaths</td>
<td>n = 26</td>
<td>n = 27</td>
</tr>
</tbody>
</table>

**CR** = complete response; **ORR** = overall response rate; **PD** = progressive disease; **SD** = stable disease

### Table 2. Response rates in R-B and R-CHOP treatment groups by disease entity

<table>
<thead>
<tr>
<th>Disease Entity</th>
<th>R-B</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follicular (no.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (no.)</td>
<td>121</td>
<td>124</td>
</tr>
<tr>
<td>CR (no.)</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Mantle cell (no.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (no.)</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>CR (no.)</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>89%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>IC / SLL (no.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (no.)</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>CR (no.)</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>n/e</td>
<td>n/e</td>
</tr>
<tr>
<td><strong>Marginal (no.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (no.)</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>CR (no.)</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>52%</td>
<td>36%</td>
</tr>
</tbody>
</table>

**CR** = complete response; **IC** = immunocytic (lymphoma); **n/e** = not evaluable; **ORR** = overall response rate; **PD** = progressive disease; **SLL** = small lymphocytic lymphoma

*Figure 1. Progression-free survival in R-B and R-CHOP treatment groups*
Table 3. Adverse events in R-B and R-CHOP treatment groups

<table>
<thead>
<tr>
<th></th>
<th>R-B (n = 235)</th>
<th>R-CHOP (n = 227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>Leukocytopenia (grade 3/4)</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>G-CSF used</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Peripheral neuropathy (any grade)</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

G-CSF = granulocyte colony-stimulating factor

Key conclusions

- This second interim analysis of 462 randomized patients confirmed the non-inferiority of rituximab plus bendamustine (R-B) as compared with R-CHOP for efficacy and lower toxicity.

- Final results, with a longer observation period of up to 36 months and a full analysis of all randomized patients (n = 549), will further define the role of R-B in the treatment algorithm of patients with indolent and mantle cell lymphoma.


Canadian perspective by Dr. John Kuruvilla

In the study by Fischer, et al. evaluating the efficacy and safety of rituximab-bendamustine (R-B) for relapsed chronic lymphocytic leukemia (CLL), the response rates appear fairly promising; however, the trial originally involved 81 patients, but only 62 were available for response assessment. This is close to a 25% loss of patients to follow-up, making it difficult to interpret the results.

The genetic subgroup analysis in this study is interesting in that the high-risk 17p– subgroup showed a high level of response, with an overall response (OR) rate of 44%. However, there were only a small number of patients in each subgroup, so it is difficult to come to any strong conclusions about the results. It would also have been useful to know the response duration in this group.

The hematologic toxicity of R-B appears reasonable for a trial involving second-line therapy for CLL. The grade ≥3 infection rate is also fairly good, being under 5%. But a treatment-related mortality of 3.7%, which occurred as a consequence of severe infections, is a concern. This percentage is high for patients receiving only two types of chemotherapy, especially as one is an antibody.

R-B appears promising as a second-line regimen. The next step to develop the R-B regimen will be to conduct a randomized trial to determine if R-B is superior to standard first-line therapies with respect to progression-free or overall survival, as well as toxicity.

The hypothesis of the study by Rummel, et al. is that CHOP is more toxic than bendamustine in the treatment of follicular, other indolent, and mantle cell lymphomas. Rummel, et al. report on a study designed to demonstrate non-inferiority with regard to the efficacy of R-B and an improved toxicity profile when compared to R-CHOP. A reasonable question to ask, therefore, is not whether R-B is more effective than R-CHOP, but whether both regimens have the same effectiveness.

Based on the response rates reported in the study, the OR and CR rates appear to be similar in the two treatment groups. Adverse events such as alopecia, leukopenia, and infectious complications appeared to be more common in the patients receiving R-CHOP than in those receiving R-B.

In Canada, R-CVP remains our standard therapy for newly diagnosed symptomatic follicular lymphoma. We have continued to use R-CVP as older data failed to demonstrate an improvement in survival for patients receiving an anthracycline-containing regimen such as CHOP. Thus, the relevant trial of R-B for Canadians would be a comparison with R-CVP. As R-CVP is felt to be less toxic than R-CHOP, it would be interesting to see how R-B would compare to a less toxic standard regimen. As CVP is an inexpensive regimen, any future studies comparing these regimens should include economic analyses.
For patients with cancer...

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\(^1\).\(^2\)\(^,\)\(^3\)\(^,\)\(^4\)

(27/336 vs. 53/336; \(p=0.002\))

![Graph showing probability of recurrent VTE (%) vs. days after randomization](image)


No Significant Difference In The Incidence Of Bleeding Between FRAGMIN And Oral Anticoagulant Therapy (OAC) Was Demonstrated\(^1\),\(^3\),\(^4\)

<table>
<thead>
<tr>
<th></th>
<th>FRAGMIN</th>
<th>OAC</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Bleeding</td>
<td>8%</td>
<td>15%</td>
<td>n/a</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>6%</td>
<td>4%</td>
<td>0.27</td>
</tr>
<tr>
<td>All Bleeding</td>
<td>14%</td>
<td>19%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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 0.54% 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 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 “Gassing 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 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.

Contraindications: FRAGMIN should not be used in patients who have: hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) or to other low-molecular-weight heparins and/or heparin; 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; septic endocarditis (endocarditis lenta, subacute endocarditis); uncontrollable active bleeding; major blood-clotting disorders; acute gasto-duodenal 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; or 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.

\(p\) Platelet counts should be determined prior to the start of treatment with FRAGMIN and subsequently, twice weekly for the duration of treatment. Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia, or platelet defects. Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered in patients at higher risk of bleeding and receiving FRAGMIN, such as the elderly, patients with renal impairment or the extremes of body weight, during pregnancy, or for children.
Cancer-Associated Thrombosis

Assessing VTE Risk and Prophylaxis in Cancer Patients

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Thrombosis can develop in any vein, but most thrombi occur in the veins of the leg. When DVT in the leg embolizes and moves to the lungs, pulmonary embolism may result.1

VTE is a common complication of cancer and is strongly associated with early all-cause mortality during the course of chemotherapy.2 Consequences of thrombosis include chemotherapy interruption, hospitalization, morbidity, and death.3 Despite the existence of VTE management guidelines in cancer patients, oncologists in North America administer thromboprophylaxis routinely in less than 5% of patients.3

Although the risk of VTE is elevated in cancer, individual risk factors cannot identify a sufficiently high-risk group of outpatients who should be given thromboprophylaxis.4

Recently, Khorana and colleagues developed a model that can identify cancer patients with an elevated risk of VTE.4 At the ASH 2008 meeting, Kuderer and colleagues presented data from their study examining the relationship between VTE and disease outcomes using this VTE risk model.

Low molecular weight heparin (LMWH) is currently recommended for the prevention of VTE after surgery (except in minor surgery where patient risk is low), during immobilization of the lower limb, and during acute hospitalization for congestive heart failure, respiratory insufficiency, infection, rheumatology problems, or inflammatory bowel disease.5 LMWH therapy has also been shown to increase survival of patients with advanced malignancies and a life expectancy greater than 6 months.6 To date, the effectiveness of LMWH for the prevention of VTE in cancer patients remains unknown. At the ASH 2008 meeting, Agnelli and colleagues presented results from their study evaluating the efficacy of nadroparin, a LMWH, for the prophylaxis of thromboembolic events in cancer patients receiving chemotherapy.

Given the large percentage of VTE events related to cancer, extensive screening for malignancies after diagnosis with VTE may be of value. At the ASH 2008 meeting, Carrier and colleagues presented the results of a literature review examining the period prevalence of previously undiagnosed malignancy after VTE diagnosis and quantifying the additional value of an extensive malignancy screening strategy.

In this article, New Evidence reports on data from the studies by Kuderer et al., Agnelli et al., and Carrier et al.

Background

A clinical model for predicting the risk of venous thromboembolism (VTE) in cancer patients initiating chemotherapy has been recently developed and validated in a study by Khorana and colleagues. Results of the study showed the risk of VTE in low (group I), intermediate (group II), and high (group III) risk patients to be 0.8%, 1.8%, and 7.1%, respectively. At the ASH 2008 meeting, Kuderer and colleagues presented results of a study evaluating the ability of the VTE risk model to predict disease progression and early all-cause mortality.

Study design

- A prospective study of 4,458 adult cancer patients with solid tumours or malignant lymphoma initiating a new chemotherapy regimen was conducted between 2002 and 2006 at 115 randomly selected practice sites throughout the U.S.
- Demographic, clinical, and treatment-related information was captured prospectively at baseline and during the first four cycles of chemotherapy.
- Information on rates of documented VTE, disease recurrence, and deaths from all causes was also captured during the first four cycles.
- Progression-free survival (PFS) and overall survival (OS) were estimated within 4 months of starting chemotherapy by the Kaplan-Meier method.
- Adjusted hazard ratios (HR ± 95% CI) were estimated by a Cox regression model, incorporating VTE as a time-dependent covariate.

Key findings

Baseline characteristics and disposition

- Patient age ranged from 18–97 with a mean of 60 years.

Efficacy

- VTE occurred in 3% of patients by 4 months, with a median of 38 days following initiation of chemotherapy.
- The HR for VTE occurrence among risk score groups II and III, compared with group I, were 3.07 (1.39–6.77) and 11.73 (5.22–16.37), (p <0.0001) respectively.
- Within 4 months, disease progression occurred in 298 patients, and 137 patients died.
- Death or disease progression was reported in 7%, 18%, and 28% of risk score groups I, II, and III, respectively.
- The HR for reduced PFS among risk groups II and III compared with group I were 2.77 (1.97–3.87) and 4.27 (2.90–6.27), respectively (p <0.0001).
- Death from all causes within 4 months of treatment initiation was reported in 1.2%, 5.9%, and 12.7% patients for risk groups I, II, and III.
- HR estimates for mortality among groups II and III were 3.56 (1.91–6.66) and 6.89 (3.50–13.57), respectively (p <0.0001).
- In multivariate analysis, the risk score and VTE occurrence were both significant independent predictors for early mortality and reduced PFS after adjusting for major prognostic factors including: age, stage, cancer type, ECOG performance status, Charlson co-morbidity index, body mass index, relative dose intensity, and year of enrolment.

Key conclusions

- VTE is strongly associated with increased early all-cause mortality during the course of cancer chemotherapy.
- A recently validated risk score is not only predictive of VTE occurrence, but also of progression-free and overall survival, demonstrating a strong association with prognostic factors for disease progression and mortality.

References:
A randomized, placebo-controlled study on nadroparin for prophylaxis of thromboembolic events in cancer patients receiving chemotherapy: the PROTECHT study

Background
At the ASH 2008 meeting, Agnelli and colleagues presented data from a randomized, placebo-controlled, double-blind, multicentre, clinical outcome–based study (PROTECHT) designed to evaluate the efficacy of the low molecular weight heparin (LMWH) nadroparin for prophylaxis of thromboembolic events in cancer patients receiving chemotherapy.1

Study design
- Patients with metastatic or locally advanced lung, breast, gastrointestinal (stomach, colon, rectum, pancreas), ovary, or head and neck cancer with an ECOG performance status ≥2 were included in the study.
- Patients on adjuvant or neo-adjuvant chemotherapy were excluded from the study.
- Eligible patients were randomized in a 2:1 ratio to receive subcutaneous injections of nadroparin, 3,800 anti-Xa IU once daily, or placebo.
- Treatment was started on the day of initiation of chemotherapy (the first cycle or a new course) and planned for the overall duration of chemotherapy or up to a maximum of 4 months.
- The primary study endpoint was the composite of clinically overt venous or arterial thromboembolic events (deep vein thrombosis of the lower and upper limbs, visceral and cerebral venous thrombosis, pulmonary embolism, acute myocardial infarction, ischemic stroke, acute peripheral arterial thromboembolism, unexplained death of possible thromboembolic origin).
- Major bleeding was the main safety outcome measure.
- All study outcome events were evaluated by an independent adjudication committee unaware of treatment allocation.
- The results of one interim analysis of efficacy and two interim analyses of safety were reviewed by an independent Data and Safety Board.
- In the primary efficacy analysis, the p-value was adjusted for the interim analysis of efficacy.

Key findings
Baseline characteristics and disposition
- The two treatment study groups were well balanced for demographic characteristics, cancer site and staging, chemotherapy regimen, and thromboembolic risk factors.
- The average study treatment duration was 90.3 ± 41.2 days and 93.9 ± 39.8 days in the nadroparin and placebo groups, respectively.
- Overall, 1,166 patients were randomized and 1,150 received at least one dose of the study treatment (primary efficacy analysis and safety population).
- Cancer distribution of patients was as follows: lung 279 (24.3%), colon 235 (20.4%), breast 165 (14.3%), ovary 143 (12.4%), stomach 98 (8.5%), rectum 87 (7.6%), pancreas 53 (4.6%), head and neck 36 (3.1%), and other 54 (4.7%).

Efficacy
- Sixteen of the 769 patients treated with nadroparin (2.1%) and 15 of the 381 patients treated with placebo (3.9%) had a thromboembolic event (interim-adjusted p = 0.033, relative risk reduction 47.2%, number needed to treat [NNT] = 53.8).
- Venous thromboembolism accounted for 11 events in both the nadroparin and placebo patients.
- Fifteen of the thromboembolic events occurred in patients with lung cancer (4.0% and 8.8% in nadroparin and placebo patients, respectively; NNT = 22.7).
- Pancreatic cancer was associated with an overall rate of thromboembolic events of 7.5%.

Safety
- More patients in the nadroparin group than in the placebo group suffered major bleeding (p = 0.177, number needed to harm (NNH) = 153.8). The incidence of minor bleeding was similar in the two treatment groups. (Table 1)

| Table 1. Number of patients experiencing bleeding after treatment with nadroparin or placebo |
|---------------------------------|-----------------|-----------------|
|                                 | Nadroparin (n = 769) | Placebo (n = 381) |
| Major bleeding n (%)          | 5 (0.7)          | 0 (0.0)         |
| Minor bleeding n (%)           | 57 (7.4)         | 30 (7.9)        |
Key conclusions

- Nadroparin reduces the incidence of thromboembolic events in cancer patients receiving chemotherapy.
- Future confirmatory studies should be focused on patients at high thromboembolic risk, such as those with lung and pancreatic cancer.


Carrier M, et al. ASH 2008: Abstract 403

Screening for malignancy in patients with venous thromboembolism: a systematic review and meta-analysis

Background
Identifying previously undiagnosed malignancy in patients with newly diagnosed venous thromboembolism (VTE) can potentially diagnose more cancers and at an earlier stage, thereby preventing malignancy-associated morbidity and perhaps death. At the ASH 2008 meeting, Carrier and colleagues presented results from their study summarizing the period prevalence of previously undiagnosed malignancy after VTE diagnosis and quantifying the additional value of an extensive malignancy screening strategy.¹

Study design
- A systematic literature search strategy was conducted using MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and all EBM Reviews.
- Thirty-six studies were selected that reported the prevalence of undiagnosed malignancies at baseline, 6 months, and 12 months.
- Fourteen articles and one abstract also met inclusion criteria for the assessment of extensive versus limited malignancy screening.
- Two reviewers independently extracted data onto standardized forms.
- The period prevalence of previously undiagnosed malignancy at baseline (within 1 month of VTE diagnosis), 6 months, and 12 months following VTE was determined.
- An extensive malignancy screening strategy (using computed tomography of the abdomen/pelvis) was compared to a more limited screening (history, physical exam, and simple widely available tests) at baseline.

Key findings
- The period prevalence of previously undiagnosed malignancy in patients with unprovoked VTE was found to be 6.1% (95% CI: 5.0–7.1) at baseline and 10.0% (95% CI: 8.6–11.3) from baseline to 12 months.
- An extensive malignancy screening strategy was found to significantly increase the proportion of previously undiagnosed malignancy after VTE diagnosis alone to 69.7% (95% CI: 61.1–77.8) using extensive screening.
- Complication rates, cost-effectiveness, and difference in morbidity and mortality associated with extensive screening strategies were not determined.

Key conclusions
- Previously undiagnosed malignancies are frequent in patients with unprovoked VTE.
- Malignancy screening using an extensive screening strategy detects more malignancies compared to a limited screening strategy.
- Computed tomography of the abdomen/pelvis should be considered in the diagnostic work-up of previously undiagnosed malignancy in patients with unprovoked VTE.

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, hypothermia, 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 while 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 fatal 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.

Geriatrics:
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 “Gassing 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 use. 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/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 anaesthetic 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 hemarthrosis 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 thromboembolism 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 the 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, retropertioneal hemorrhage have been reported occasionally leading to fatalty

**Blood and Lymphatic System:** thrombocytopenia, thrombocytopenia

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

**Immunological System Disorders:** immunologically-mediated heparin-induced thrombocytopenia (type II, 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-inflammatory drugs, 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: 1-800-463-6001.

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**General surgery with associated risk of thromboembolic complications:** 2500 IU s.c. administered 1 - 2 hours before the operation, and there after 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 (NACT), 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>
</tr>
</thead>
<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 (II, VII, IX, X) 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>≤56</td>
<td>7 500</td>
</tr>
<tr>
<td>57-68</td>
<td>10 000</td>
</tr>
<tr>
<td>69-82</td>
<td>12 500</td>
</tr>
<tr>
<td>83-98</td>
<td>15 000</td>
</tr>
<tr>
<td>≥99</td>
<td>18 000</td>
</tr>
</tbody>
</table>

Dose reductions for chemotherapy-induced thrombocytopenia: In the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm³, FRAGMIN should be interrupted until the platelet count recovers above 50,000/mm³. For platelet counts between 50,000 and 100,000/mm³, 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/mm³, 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>≤56</td>
<td>7 500</td>
<td>5 000</td>
<td>33</td>
</tr>
<tr>
<td>57-68</td>
<td>10 000</td>
<td>7 500</td>
<td>25</td>
</tr>
<tr>
<td>69-82</td>
<td>12 500</td>
<td>10 000</td>
<td>20</td>
</tr>
<tr>
<td>83-98</td>
<td>15 000</td>
<td>12 500</td>
<td>17</td>
</tr>
<tr>
<td>≥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, discolouration and leakage prior to administration, whenever solution and container permit.

1 mL 10 000 IU

- Isotonic NaCl Infusion (9 mg/mL) 500 mL
- Isotonic Glucose Infusion (50 mg/mL) 500 mL

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

**Study References**

1 month, followed by a daily dose of approximately 150 IU/kg for 5 months. The primary efficacy outcome was the first episode of objectively documented, symptomatic, recurrent deep-vein thrombosis, pulmonary embolism, or both during the 6-month study period. Secondary outcome events included clinically overt bleeding (both major bleeding and any bleeding) and death.


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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Kirkland, Quebec
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