A Cross-section of Data
From ASH 2010, Orlando, FL

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

Our March 2011 issue presents coverage from the 52nd Annual Meeting of the American Society of Hematology (ASH), held in Orlando, Florida, from December 4–7, 2010. The issue reports findings from an important study comparing rituximab treatment with a watch and wait strategy in asymptomatic follicular lymphoma. New strategies and treatments for NHL and CLL are also discussed. We would like to thank Dr. Joseph Connors, Dr. Douglas Stewart, and Dr. Stephen Couban for their Canadian perspectives, and Dr. Kirit Ardeshna for his investigator commentary.

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

Joseph M. Connors, MD, FRCPC
Dr. Joseph Connors is a clinical professor in the Department of Medicine, Division of Medical Oncology, at the University of British Columbia and the Clinical Director of the BC Cancer Agency Centre for Lymphoid Cancer. He is best known for his clinical investigations into the treatment of Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, chronic lymphocytic leukemias and multiple myeloma. He serves as a member of the executive committee of the Hematology Site Group for the National Cancer Institute of Canada Clinical Trials Group, as chair of the Educational Affairs Committee of the American Society of Hematology, and on the scientific advisory boards of the Lymphoma Foundation Canada and the Lymphoma Research Foundation of the United States. Dr. Connors has published over 250 peer-reviewed scientific articles addressing various aspects of research into lymphoid cancers.

Stephen Couban, MD, FRCPC
Dr. Stephen Couban is a professor of medicine at Dalhousie University and Director of the Blood and Marrow Transplant Program at Capital District Health Authority in Halifax, Nova Scotia. He is Co-Chair of the NCIC CTG Hematology Site Group and is also active with the Canadian Blood and Marrow Transplant Group. Dr. Couban is Vice President of the Canadian Hematology Society and a past-president of the Canadian Blood and Marrow Transplant Group. His research interests have focused on allografting and in particular on exploration of different types of grafts, including GCSF-stimulated allogeneic peripheral blood allografts and GCSF-stimulated bone marrow allografts. He is actively involved in a number of clinical trials for patients with leukemia and lymphoma, as well as those undergoing blood and marrow transplantation.
Douglas A. Stewart, BMSc, MD, FRCPC

Dr. Douglas A. Stewart is currently a professor in the Departments of Oncology and Medicine, and Chief of the Division of Hematology and Hematological Malignancies at the University of Calgary. Since July 1994, he has been practising medical oncology at the Tom Baker Cancer Centre in Calgary, where he is a member of the Breast Cancer and Hematology Tumour Groups, Leader of the Hematology/Blood and Marrow Transplant Program, and Provincial Leader of the Hematology Tumour Team for the Alberta Health Services Cancer Care Program. His research interests focus on clinical trials involving hematological malignancies and hematopoietic stem cell transplantation. Dr. Stewart has authored over 80 peer-reviewed manuscripts and over 120 abstracts.

Kirit Ardeshna, MD

Dr. Kirit Ardeshna is a consultant hematologist at University College London Hospital NHS Trust in London, UK, where he is lead clinician for the clinical hematology service. He also works at the Mount Vernon Cancer Center in Northwood, UK. Dr. Ardeshna specializes in managing patients with hematological malignancies and has a particular interest in treating patients with lymphoma. His research interest is in clinical trials in lymphoma, and he has been a member of the National Cancer Research Institute Lymphoma Studies Group since 2005. A Fellow of the Royal College of Physicians and Royal College of Pathologists in the United Kingdom and a member of The British Committee for Standards in Haematology, Dr. Ardeshna is the Chief Investigator of an intergroup randomized trial comparing rituximab treatment with a watch and wait strategy in asymptomatic, non-bulky follicular lymphoma.
This issue of New Evidence in Oncology reports on findings from a number of key presentations given at the 52nd Annual Meeting of the American Society of Hematology (ASH), held in Orlando, Florida, from December 4–7, 2010. The ASH Annual Meeting is a leading international forum for current research in the diagnosis, treatment, and understanding of blood disorders and plays an important role in training the next generation of researchers and clinicians in hematology. The 2010 Meeting, attended by over 20,000 participants, featured 4,326 abstracts presented in oral or poster form.

In this report, New Evidence features a summary of preliminary data from a randomized, controlled trial comparing rituximab treatment with a watch and wait strategy in asymptomatic follicular lymphoma (FL), followed by an interview with principal investigator Dr. Kirit Ardeshna. Six-year follow-up data from the MInT study examining the addition of rituximab to a CHOP-like chemotherapy regimen in young, low-risk diffuse large B-cell lymphoma patients and updated results from the MAXIMA study of maintenance rituximab in FL administered with standard or rapid infusions are also discussed. Other articles focus on new treatment options for elderly and/or frail CLL patients and novel approaches in the treatment of relapsed/refractory NHL.
Non-Hodgkin’s Lymphoma

Rituximab for Newly Diagnosed Asymptomatic FL, R-Maintenance in FL, and Long-term Follow-up of R-chemo in DLBCL

The utilization of rituximab for the treatment of non-Hodgkin’s lymphoma (NHL), a disease that comprises a heterogeneous group of lymphoproliferative malignancies, has revolutionized the treatment of both indolent and aggressive B-cell NHL over the past decade.\(^1\)

Several large-scale prospective randomized trials have demonstrated significant clinical efficacy with rituximab in the treatment of NHL, particularly in combination with chemotherapy. Furthermore, safety data from these trials indicate a consistently safe and tolerable profile in most patients.\(^2\)

At ASH 2010, investigators presented data from studies examining the use of rituximab in NHL. This article reports on three such studies, as well as on a study comparing two different imaging systems for evaluation of patients with malignant lymphoma:

- Six-year follow-up data from MInT demonstrated that the addition of rituximab to a CHOP-like regimen leads to a significant improvement of the outcome in young patients with good-prognosis diffuse large B-cell lymphoma and that the significant survival benefit is maintained.

- An international prospective trial showed initial treatment with rituximab to significantly delay the need for new therapy in patients with newly diagnosed asymptomatic follicular lymphoma, a finding that may change the management of this group of patients.

- Updated results from the phase IIIb MAXIMA study provide additional support for utilizing rituximab maintenance every 2 months for 2 years following rituximab-containing induction therapy for patients with newly diagnosed or previously treated follicular lymphoma.

- A study comparing whole body diffusion-weighted magnetic resonance imaging (DWI-MRI) with fluorine-18 fluorodeoxyglucose (FDG-PET)/CT found that DWI-MRI combined with T2 imaging and ADC analysis appeared promising as a sensitive and therapeutic response evaluation in patients with malignant lymphoma.

Rituximab versus a watch and wait strategy in patients with stage II–IV asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a): a preliminary analysis

(Note: See the interview with Dr. Ardeshna on page 20 for his commentary on this study.)

Background

Historically, patients with asymptomatic, advanced-stage follicular lymphoma (FL) have shown no benefit from immediate chemotherapy when compared with a watch and wait approach; therefore, chemotherapy — with its attendant adverse events — has been deferred until disease progression.

Recent findings outlined in an oral presentation by Dr. Ardeshna at ASH 2010, however, demonstrated that initial treatment with rituximab can significantly delay the need for new therapy.

Study design

• In the prospective, randomized, international intergroup trial, adult patients with asymptomatic stage II, III, or IV non-bulky FL (grades 1, 2, and 3a) and adequate bone marrow reserve were randomized 1:1:1 to:
  ▪ Arm A: watch and wait;
  ▪ Arm B: rituximab 375 mg/m² weekly for 4 weeks;
  ▪ Arm C: rituximab 375 mg/m² weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years (starting at month 3 until month 25).

• The primary endpoint was time to initiation of new therapy (TTINT), either chemotherapy or radiotherapy.

• Secondary endpoints were progression-free survival (PFS), overall survival (OS), response at 25 months, frequency of spontaneous clinical remissions, safety, and the effect of prior rituximab therapy on response and response duration to subsequent new therapy.

• Responses were assessed at months 7, 13, and 25.

• CT was compulsory at months 7 and 25.

• Bone marrow was required only if there was a complete response (CR) on clinical and CT criteria.

Key findings

Baseline characteristics and disposition

• A total of 463 adult patients with asymptomatic stage II, III, or IV non-bulky FL (grades 1, 2, and 3a) and adequate bone marrow reserve were randomized to the three study arms: 187 to Arm A, 84 to Arm B, and 192 to Arm C.

• Baseline characteristics between the three arms were well balanced for age, performance status, stage, grade, and FLIPI scores. (Table 1)
Ninety-five percent (95%) of patients had low tumour burden (Groupe d’Etude des Lymphomes Folliculaires [GELF] criteria); the other 5% had raised lactic dehydrogenase (LDH), but fulfilled remaining GELF criteria.

### Efficacy and safety

- In September 2007, a decision was made to discontinue arm B as evidence of the efficacy of maintenance rituximab became clear.
- Responses at month 7, 13, and 25 are shown in Table 2.
- To date, 45 serious adverse events (AEs) have been reported: 14 in Arm A, 6 in Arm B, and 25 in Arm C.
- Fourteen serious AEs were considered possibly, probably, or definitely related to the study drug.
- There were 5 allergic reactions (2, grade 3), 7 infections, and 3 episodes of grade 3/4 neutropenia.
- At interim analysis, 93 patients (20%) had initiated new treatment — 84 of the 93 (90%) had clinically reported disease progression.
- New treatment was chemotherapy in 78 (84%), radiotherapy in 10 (11%), rituximab monotherapy in 2 (2%), surgery in 1 (1%), and currently not known in 2 (2%).

### Table 1. Baseline characteristics of the follicular lymphoma study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A watch &amp; wait (n = 187)</th>
<th>Arm B R x 4 (n = 84)</th>
<th>Arm C R x 4 + R-M (n = 194)</th>
<th>Total population (n = 463)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60 (28–82)</td>
<td>60 (33–86)</td>
<td>60 (27–87)</td>
<td>60 (27–87)</td>
</tr>
<tr>
<td>Male</td>
<td>79 (42)</td>
<td>34 (40)</td>
<td>99 (52)</td>
<td>212 (46)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FL grade 1</td>
<td>38 (20)</td>
<td>19 (23)</td>
<td>42 (22)</td>
<td>99 (21)</td>
</tr>
<tr>
<td>2</td>
<td>73 (39)</td>
<td>35 (42)</td>
<td>75 (39)</td>
<td>183 (40)</td>
</tr>
<tr>
<td>3a</td>
<td>76 (40)</td>
<td>30 (36)</td>
<td>75 (39)</td>
<td>181 (39)</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM involved</td>
<td>80 (44)</td>
<td>31 (37)</td>
<td>78 (42)</td>
<td>189 (42)</td>
</tr>
<tr>
<td>LDH &gt;normal</td>
<td>9 (5)</td>
<td>3 (4)</td>
<td>9 (5)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>B2 micro &gt;2.4</td>
<td>33 (22)</td>
<td>15 (23)</td>
<td>41 (26)</td>
<td>89 (24)</td>
</tr>
<tr>
<td>FLIPI score 0</td>
<td>16 (9)</td>
<td>6 (7)</td>
<td>19 (10)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>1</td>
<td>48 (26)</td>
<td>30 (36)</td>
<td>44 (23)</td>
<td>109 (25)</td>
</tr>
<tr>
<td>2</td>
<td>71 (38)</td>
<td>32 (39)</td>
<td>86 (45)</td>
<td>178 (41)</td>
</tr>
<tr>
<td>3</td>
<td>50 (27)</td>
<td>13 (16)</td>
<td>40 (21)</td>
<td>106 (24)</td>
</tr>
<tr>
<td>4</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td>10 (2)</td>
</tr>
</tbody>
</table>

B2 micro = beta-2 microglobulin; BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; FL = follicular lymphoma; FLIPI = follicular lymphoma international prognostic index; LDH = lactic dehydrogenase; R = rituximab; R-M = rituximab maintenance

- Estimated median time to initiation of new therapy in Arm A was 33 months, similar to a previous trial of watchful waiting published by the investigators.¹

### Table 2. Response by treatment arm over time in the follicular lymphoma study population

<table>
<thead>
<tr>
<th>Response</th>
<th>7 months n (%)</th>
<th>13 months n (%)</th>
<th>25 months n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A watch &amp; wait</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + CRu</td>
<td>3 (2)</td>
<td>6 (4)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (4)</td>
<td>7 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>ORR</td>
<td>9 (6)</td>
<td>13 (10)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Arm B rituximab induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + CRu</td>
<td>35 (45)</td>
<td>35 (45)</td>
<td>29 (40)</td>
</tr>
<tr>
<td>PR</td>
<td>25 (31)</td>
<td>22 (28)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>ORR*</td>
<td>60 (74)</td>
<td>57 (72)</td>
<td>39 (54)</td>
</tr>
<tr>
<td>Arm C rituximab induction &amp; maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + CRu</td>
<td>100 (55)</td>
<td>122 (69)</td>
<td>98 (76)</td>
</tr>
<tr>
<td>PR</td>
<td>61 (33)</td>
<td>36 (20)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>ORR*</td>
<td>161 (88)</td>
<td>158 (89)</td>
<td>110 (85)</td>
</tr>
</tbody>
</table>

χ² *p = 0.0253 *p = 0.0026 *p < 0.0001

CR = complete response; CRu = unconfirmed complete response; ORR = overall response rate; PR = partial response
• Time to initiation of new therapy was significantly longer in the rituximab arms (p-value of log-rank test < 0.001 for each of rituximab arms versus arm A, and median time not reached at 4 years). (Figure 1)

○ Not all patients who were reported to have clinically progressed (n = 142) warranted initiation of therapy (n = 84).

• Significant differences in PFS were noted between the observation and rituximab arms (p-value of log-rank test < 0.001 for each of rituximab arms versus arm A). (Figure 2)

• No difference was observed in OS among the 3 arms (p > 0.5). (Figure 3)

○ Ninety-six percent (96%) of patients remain alive.

**Key conclusions**

- Rituximab significantly improves time to initiation of new therapy and progression-free survival in patients with asymptomatic FL, when compared with watchful waiting.

- Whether overall survival will be improved with rituximab treatment is currently unclear.

- There is a need to determine the impact of prior rituximab on:
  - o response to first new treatment;
  - o response duration of first new treatment;
  - o time to second new treatment.

- While upfront rituximab may not replace watchful waiting, if quality of life is no worse with rituximab as compared to watchful waiting, then initial treatment with rituximab is likely to be an option for patients with asymptomatic, non-bulky follicular lymphoma.


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**Figure 1. Proportion of asymptomatic follicular lymphoma patients not requiring initiation of new treatment**

![Figure 1](image1)

**Figure 2. Progression-free survival in asymptomatic follicular lymphoma patients by treatment arm**

![Figure 2](image2)

**Figure 3. Overall survival in asymptomatic follicular lymphoma patients by treatment arm**

![Figure 3](image3)
First-line treatment using a CHOP-like regimen with or without rituximab for young, low-risk DLBCL patients (<61 years): six-year follow-up of the MInT study

**Background**

The MabThera International Trial (MInT) was the first study to show a survival benefit with the addition of rituximab to a CHOP-like regimen in young, good-prognosis patients with diffuse large B-cell lymphoma (DLBCL).1

This European study, which was conducted at 18 different treatment centres, enrolled patients aged 18–60 who had a low-risk international prognostic index (IPI) of 0 or 1, stage 1 or 2 bulky disease, or stage 3 and 4 disease. Patients were randomized to CHOP-like regimens (half receiving CHOP and the other half receiving CHOP plus etoposide or some other CHOP-like therapy) versus identical regimens with the addition of rituximab on the first day of each treatment cycle. Results from this very important trial provided definitive evidence that the addition of rituximab to CHOP-like regimens in younger patients works just as well as in older patients.1

At ASH 2010, Pfreundschuh and colleagues presented results from an extended 6-year follow-up of patients from the MInT study, which demonstrated maintenance of survival benefit over time and showed a definitive effect on cure rates.2

**Study design**

- Previously untreated patients (18–60 years) with low-risk DLBCL (age-adjusted IPI 0 or 1, stages II–IV, and stage I with bulky disease) were randomized to receive 6 cycles of a CHOP-like regimen (CHEMO) or the same chemotherapy plus rituximab 375 mg/m², given on day 1 of each 3-week regimen and on days 1, 22, 43, 64, 85, and 106 of the 2-week regimens, respectively (R-CHEMO).

- Radiotherapy (30–40 Gy) was planned to sites of initial bulky disease and/or extranodal involvement.

- The primary endpoint was event-free survival (EFS), with events defined as failure to achieve complete remission, progressive disease, relapse, death, or additional therapy.

**Key findings**

- Of a total of 823 patients, 396 were allocated to receive CHOP-21, 361 to CHOEP-21, 34 to MACOP-B, and 32 to PMitCEBO with or without rituximab (CHEMO = 410; R-CHEMO = 413).

- After a follow-up of 72 months, patients assigned to chemotherapy plus rituximab, compared to those assigned to chemotherapy alone, had:
  - increased 6-year EFS (74.0% [95% CI: 69.0–78.3] vs. 55.7% [95% CI: 50.3–60.8]; log-rank \( p < 0.0001 \));
  - increased 6-year progression-free survival (PFS) (79.9% [95% CI: 75.1–83.8] vs. 63.8% [95% CI: 58.2–68.8]; log-rank \( p < 0.001 \));
  - increased overall survival (OS) (89.8% [95% CI: 86.0–92.6] vs. 80.0% [95% CI: 75.3–83.9; log rank \( p = 0.001 \)). (Figures 1 and 2)

- In a multivariate analysis, EFS was affected by the addition of rituximab (hazard ratio [HR] 0.49, \( p < 0.001 \)), age-adjusted IPI (HR 1.73, \( p < 0.001 \)), and bulky disease (HR 1.43, \( p = 0.004 \)). (Table 1)

- Similar effects were observed for OS, while PFS was affected by treatment arm (HR 0.49, \( p < 0.001 \)) and age-adjusted IPI (HR 1.8, \( p < 0.001 \)).

- As a consequence, a very favourable subgroup (aIPI = 0, no bulky disease) can be distinguished from a less favourable subgroup (aIPI = 1 and/or bulky disease) among good-prognosis patients treated with rituximab.

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CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL = diffuse large B-cell lymphoma; IPI = international prognostic index
Toxicity, incidence of adverse events, and severe adverse events were not significantly different in the CHEMO and the R-CHEMO arms.

Ten (10) late (>60 months) events occurred after CHEMO (61.4 to 96.1 months), including 4 in the very favourable subgroup; all 8 late events (67.5 to 105.7 months) after R-CHEMO occurred in the less favourable subgroup only, and none occurred in the very favourable subgroup.

**Key conclusions**

- Addition of rituximab to a CHOP-like regimen leads to a significant improvement of the outcome in young patients with good-prognosis diffuse large B-cell lymphoma, with significant survival benefit maintained during a 6-year follow-up.

- Except in the very favourable subgroup after R-CHEMO, late relapses after 5 years occur. While reduction of treatment in a randomized study like the FLYER trial (NCT00278421) of the German High Grade Non-Hodgkin’s Lymphoma Study Group (DSH-NHL) is justified, further progress, such as dose densification (UNFOLDER trial [NCT00278408]) of the DSH-NHL and/or dose escalation, is still warranted for the less favourable subgroup.

Maintenance rituximab every two months for two years is effective and well tolerated in patients with follicular lymphoma, using standard or rapid infusion: updated results from MAXIMA

**Background**

Data from the PRIMA and MAXIMA maintenance trials have added to the growing body of evidence to support induction and maintenance with rituximab as an important strategy for the management of follicular lymphoma (FL). Results from the PRIMA trial demonstrated that 2 years of rituximab maintenance therapy after immunochemistry as first-line treatment for follicular lymphoma significantly improves progression-free survival.\(^1\)

Data from the phase IIIb MAXIMA study provides additional support for the use of rituximab maintenance every 2 months for 2 years following rituximab-containing induction therapy for patients with newly diagnosed or previously treated FL. The MAXIMA study also evaluates the safety of standard versus rapid infusion rate. At ASH 2010, Foà and colleagues presented updated results at a median follow-up of 28.8 months from the MAXIMA study.\(^2\)

**Study design**

- MAXIMA is a phase IIIb study evaluating the safety of rituximab maintenance therapy given at either a standard infusion rate or as a rapid infusion in patients with treatment-naïve or previously treated FL responding to induction treatment.
- The study also aims at confirming the effectiveness of rituximab maintenance therapy with respect to improvement of progression-free survival (PFS) and overall survival (OS), and the rate of conversion from partial response (PR) to complete response/unconfirmed complete response (CR/CRu) while on maintenance therapy.
- Patients with FL who had completed adequate induction therapy as part of first-line treatment or at relapse (≥8 cycles of rituximab alone or with chemotherapy) were eligible for inclusion.
- Patients who had confirmation of CR/CRu or PR to induction therapy up to 8 weeks prior to study entry were enrolled.
- Patients received maintenance treatment with rituximab (375 mg/m\(^2\)) every 2 months for a maximum of 2 years.
- Rituximab could be administered at a standard infusion rate (>90 minutes duration) or as a rapid infusion (≤90 minutes) according to the standard practice at each centre.

**Key findings**

- A total of 545 patients from 211 centres in 24 countries who achieved a CR/CRu or PR following induction therapy with 8 cycles of a rituximab-containing regimen received maintenance treatment with rituximab (375 mg/m\(^2\)) every 2 months for a maximum of 2 years.
- Median age was 57 years (range: 29–86 years), with 11.7% over the age of 70 years.
- The majority of patients (72.5%) were previously untreated.
- Of the 545 patients, 381 patients (69.9%) entered the study in CR/CRu after induction and 164 (30.1%) in PR.
- Of 381 patients with post-induction CR/CRu, 353 (92.6%) remained in CR/CRu during maintenance (progressive disease 7.1%; missing 0.3%).

**MAXIMA study design**

- First-line/relapsed FL
- Various induction regimens
  - ≥8 cycles of rituximab-based induction
- CR/CRu/PR*
- Rituximab every 2 months for 2 years

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* Measured by CT, PET, or MRI scan within 8 weeks of study entry
CR = complete response; CRu = unconfirmed complete response; CT = computerized tomography;
FL = follicular lymphoma; MRI = magnetic resonance imaging; PET = positron emission tomography; PR = partial response
• Of 164 patients achieving PR during induction, 11 patients (6.7%) converted to CR/CRu during maintenance. (Figure 1)

The full course of maintenance therapy was completed by 74.7% patients (n = 407).

○ For those who did not complete rituximab maintenance (n = 137), reasons for premature discontinuation were disease progression (n = 58), treatment toxicity (n = 16), voluntary withdrawal (n = 11), death (n = 5), and other reasons (n = 47).

• In the safety population (n=534), 52 infusion-related adverse events (AEs) occurred in 5.8% of patients (n = 31), the majority of which were grade 1.

• The most commonly reported AEs were hypotension (n = 5), pyrexia (n = 3), hypertension (n = 3), headaches (n = 3), insomnia (n = 3), and erythema (n = 3).

• No clinically meaningful differences in the incidence of infusion-related AEs were observed by infusion schedule; AEs occurred with 0.9% of standard infusions and 0.5% of rapid infusions.

• Other AEs were observed in 62.9% of patients (336 of 534 patients), the majority of which were grade 1/2; grade 3, 4, and 5 AEs occurred in 16.1% (n = 86), 5.6% (n = 30) and 1.7% (n = 9) of patients, respectively.

• Rituximab-related AEs were rare, occurring in 10.7% of patients (n = 57) and accounting for only 6.1% (105/1721) of all AEs.

• The most common rituximab-related AEs were infections, occurring in 22 patients (4.1%); two grade 5 rituximab-related AEs were reported: 1 liver disorder and 1 cerebral hemorrhage.

• A total of 141 serious adverse events (SAEs) occurred in 104 patients; of these, only 19 events in 15 patients were deemed to be related to rituximab. The most common rituximab-related SAE was pneumonia, with 3 events reported.

### Key conclusions

- The majority of patients entering the study in CR/CRu or PR maintained their response throughout maintenance therapy.

- Maintenance treatment was associated with few infusion-related AEs, and a rapid infusion schedule did not appear to affect tolerability.

- Updated results from the phase IIIb MAXIMA study provide additional support for utilizing rituximab maintenance every 2 months for 2 years following rituximab-containing induction therapy for patients with newly diagnosed or previously treated follicular lymphoma.

Whole-body diffusion-weighted magnetic resonance imaging: a new sensitive non-invasive method for staging and monitoring chemotherapy response in malignant lymphoma

Background

Positron emission tomography with fluorine-18 fluorodeoxyglucose (FDG-PET) is an established functional imaging modality for the evaluation of human disease. FDG-PET is a useful imaging producer for tumour staging and therapy monitoring that can visualize active tumour tissue, including malignant lymphoma. However, the spatial resolution of FDG-PET is limited, and low accuracy rates in patients with low grade lymphoma have been reported.

Diffusion-weighted magnetic resonance imaging (DWI-MRI) is rapidly emerging as a promising functional whole-body imaging modality that can be used to evaluate oncological and non-oncological lesions throughout the body. DWI-MRI provides functional information and is able to highlight oncological lesions. The usefulness of this technique has not been established as yet in malignant lymphoma, especially for monitoring therapeutic response.

Studies on the correlation and comparison between FDG-PET and DWI-MRI are still scarce, and most of these studies suffer from several methodological shortcomings. At ASH 2010, Kishi and colleagues presented a poster on the utility of DWI-MRI with T2 imaging and apparent diffusion coefficient (ADC) for staging and monitoring therapeutic responses in patients with malignant lymphoma compared with that of FDG-PET/CT.

Study design

- Twenty-eight (28) newly diagnosed patients with malignant lymphoma on biopsy underwent both MRI and FDG-PET examination before treatment (n = 28), after 2 courses of chemotherapy (n = 25), and one month after the end of chemotherapy (n = 9). (Table 1)

Table 1. Description of patient population

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td>16</td>
</tr>
<tr>
<td>Follicular lymphoma (FL)*</td>
<td>7</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma (ATLL)</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma (ALCL)</td>
<td>1</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma (AITL)</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma (HL)</td>
<td>2</td>
</tr>
<tr>
<td>M/F: 19/9; Age: 33–76 years (median 61 years)</td>
<td></td>
</tr>
</tbody>
</table>

*One diabetic patient was included

Figure 1. Diffusion-weighted imaging

[Diagram showing lymphoma, chemotherapy, and changes in DWI]
While MRI examination was performed with a 3-Tesla MR system (Signa Excite, General Electrics), whole-body DWI-MRI was performed with an echo planar imaging sequence with short T1 inversion recovery (STIR) fat suppression.

ADC measurement was performed based on the region of interest (ROI) method.

ROI was placed on the lesion showing the highest standardized uptake value (SUV) on FDG-PET/CT scanner (Discovery LS, General Electrics) in each patient.

The crucial parameters of the ADC and SUV were compared using t-tests.

**Key findings**

- Comparison between FDG-PET and DWI-MRI at diagnosis:
  - For diagnosis, evaluation by DWI-MRI tended to be underestimated, whereas the findings combined with T2 imaging increased the match with PET/CT.
  - DWI-MRI could detect the lymphoma lesion more accurately than PET/CT in patients with indolent lymphoma such as FL. (Table 2)

- Chemotherapy response:
  - For chemotherapy response, a high concordance rate with PET/CT was demonstrated.
  - During early response to chemotherapy, 19 of 25 patients (76%) were considered to show complete response (CR) on PET/CT. DWI-MRI findings matched PET/CT in 23 patients (92%).
  - During final response to chemotherapy, 7 of 9 patients (78%) were considered to show CR on PET/CT. DWI-MRI findings matched PET/CT in 8 of the 9 patients (89%).
  - Of these nine patients, one patient with diffuse large B-cell lymphoma (DLBCL) who did not show a match was false positive on PET/CT.

**Key conclusion**

- Whole body DWI-MRI combined with T2 imaging and ADC analysis appears promising as a sensitive method for staging and therapeutic response evaluation in patients with malignant lymphoma.

The study by Ardeshna, et al. addresses a very important question about the appropriateness of watchful waiting (WW) as a treatment strategy in follicular lymphoma (FL). Approximately 90% of the time, patients with FL present with widely metastatic disease and are generally regarded as incurable. However, around 30%–40% of these patients are asymptomatic and are not threatened by their disease. After 2–3 years of WW, 50% of patients will have developed the need for treatment, and by 5 years this percentage will have risen to 80%. WW is therefore most appropriate in patients with other co-morbidities or in frail patients who are not likely to live past 5 years. For these patients, delaying therapy as long as possible to avoid treatment-related toxicities is reasonable. Note, however, that WW requires patients to be constantly monitored to ensure they are treated at the first signs of threatening disease. As studies have shown no advantage to treating asymptomatic patients with aggressive chemotherapy, it seems sensible to reserve treatment until patients develop symptoms or cosmetic changes, such as bulky visible lymphadenopathy. In Canada, WW has become the standard of care.

The study by Ardeshna, et al. is a well designed randomized trial with an observation-only control group. Patients included in the study closely mimic those seen in clinical practice, and results are therefore generalizeable to these patients. One of the most difficult things to control in this type of study is the variation among physicians in factors influencing treatment initiation. To minimize variation, the authors defined standard conditions for treatment initiation, which are similar to those used in clinical practice.

At three years, the percentage of patients not requiring treatment with chemotherapy was significantly greater in the rituximab maintenance (91%) and induction-only (80%) arms, compared to the WW arm (48%) ($p < 0.001$). The WW arm had the outcome we would expect, with 50% of patients needing treatment at 2.5 years. These results suggest that rituximab has a substantial impact on the natural history of the disease.

A number of studies have demonstrated that the rate at which recurrence occurs decreases with time. If we assume that the same pattern will occur in this study, extrapolated results imply that the median time to intervention will be a decade or longer. This extended time would provide substantial freedom from treatment for patients given early rituximab to delay more aggressive treatment and would justify a change in clinical practice. Although some might argue that we should not make this assumption, I am comfortable with doing so, based on the results of previous studies.

A limitation of this study is that investigators closed the induction-only arm, which included 4 doses of rituximab with no maintenance treatment. The justification for closing this arm was the assumption that rituximab maintenance would become standard practice, negating the usefulness of the induction-only arm. However, results of the study showed that the two intervention arms were statistically indistinguishable and that the curves drew closer together over time. More adverse events (AEs) were reported in the induction plus maintenance arm, compared to the induction-only arm. Although safety results with either arm gave no reason for alarm and are in line with those shown in other studies using rituximab in a larger number of patients, the lower number of AEs in the induction-only arm is an important factor to consider. Given the savings in cost and treatment toxicity of giving rituximab for a shorter duration, closing this treatment arm was a mistake.

Based on the Ardeshna, et al. study, I believe it is reasonable to give rituximab using the shorter 4 dose intervention. Using this strategy, a substantial portion of patients will be spared the need to take more aggressive treatments for close to 8–10 years. With the possible investment of around $12,000 for 4 doses of rituximab, one might quite considerably defer the need to spend $50,000 on more aggressive treatments. Based on these calculations, we would anticipate that in British Columbia this strategy would amount to a savings of 1–2 million dollars per year for the next ten years.

The next step in addressing the issue of early treatment with rituximab versus WW is to duplicate this study. The Eastern Cooperative Oncology Group (ECOG) is currently conducting a study to investigate early versus delayed
introduction of rituximab in patients eligible for WW. Several unanswered questions also need further investigation, such as establishing whether the benefit of rituximab comes mainly from the first 4 doses and determining how often and for how long rituximab should be given.

A Groupe d’Étude des Lymphomes de l’Adulte (GELA) study by Coiffier, et al. (2002) was the pivotal study in diffuse large B-cell lymphoma (DLBCL) showing that the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) improves response rates and overall survival (OS) in elderly patients. At the time of this GELA study, a separate protocol was recruiting patients <60 years, and the Coiffier study was only able to include patients 60–80 years of age. It was therefore not clear whether the benefits of adding rituximab to CHOP (R-CHOP) could be extrapolated to patients <60 years.

The Mabthera International Trial (MInT) group study by Pfreundschuh, et al. (2006) was conducted to examine the addition of rituximab to CHOP in younger patients, and results showed that R-CHOP also improved OS in DLBCL patients 18–60 years of age. The usefulness of adding rituximab to front-line chemotherapy has now been demonstrated in a number of studies and is a well-accepted treatment strategy. However, the six-year follow-up of the MInT study presented by Pfreundschuh, et al. at ASH 2010 is useful, because it solidifies earlier findings and shows us that the favourable response seen with R-CHOP is sustained over time.

The MInT study gave 6 cycles of R-CHOP to all patients, regardless of disease stage. However, in patients with limited stage (stage I or II) and no bulky disease, many physicians in Canada give R-CHOP for a shorter duration of 3 cycles, followed by radiation therapy. Although this study demonstrates that adding rituximab to CHOP is favourable for younger patients with advanced stage disease, it does not address the issue of whether patients with limited stage disease need to be given 6 cycles of treatment.

The MInT study also corroborates findings from other studies, which showed that although relapse rates decline over time, some late relapses do occur. Therefore, the addition of rituximab to CHOP does not completely eliminate late relapses, especially in patients with bulky disease.

The study by Foà, et al., which examines maintenance rituximab in FL using standard or rapid infusion protocols, adds to the growing body of knowledge showing that rapid infusion of rituximab is safe. Our centre in British Columbia pioneered the use of rapid infusions, and this administration is now used by most institutions across Canada. At our institution, we have not seen any greater level of toxicity with the rapid protocol than we would have anticipated with prolonged infusions. Given the reduction in healthcare provider time and patient burden, the study by Foa, et al. provides further evidence that rapid infusion of rituximab can remain the standard of care across Canada.

New Evidence: What was the rationale for your study?

Dr. Ardeshna: Previous studies in patients with asymptomatic follicular lymphoma (FL) have shown that early initiation of chemotherapy does not improve survival. The current standard of care is to wait for patients to develop symptoms before starting chemotherapy. This approach is designed to spare the patient from unnecessary side effects, hospital visits, and blood tests and to improve their overall quality of life (QoL). However, once diagnosed, some patients feel anxious when told they need to wait for symptoms to develop before being treated. Asymptomatic patients may therefore benefit from early treatment with less aggressive agents that can delay the initiation of toxic chemotherapies.

Currently, rituximab is the only treatment option proven to be efficacious in a maintenance setting and to have a relatively favourable safety profile. If rituximab is effective in delaying time to treatment, patients may be spared toxicities related to standard chemotherapy. Our study was designed to determine whether early treatment with rituximab can reduce the time until treatment with chemotherapy or radiation.

New Evidence: Please describe the design of your study.

Dr. Ardeshna: Our study was a randomized controlled trial (RCT) that included patients from the United Kingdom, Turkey, Poland, and Australasia. Patients were randomized into three arms:

- watch and wait – patients were given no treatment;
- induction rituximab – four infusions of rituximab over four weeks;
- maintenance rituximab – induction rituximab plus maintenance rituximab given every two months over two years.

Since the study was accruing more slowly than anticipated and given that other studies were showing the benefits of maintenance rituximab, the rituximab induction arm was stopped midway through the study.
New Evidence: What was the justification for using time until treatment initiation as the primary endpoint of the study?

Dr. Ardeshna: Disease progression can mean different things for different patients and is therefore a less clinically meaningful outcome than the time until treatment initiation. To enhance consistency across centres, standard criteria were suggested to determine when treatment should be initiated, but this was not mandated. Criteria for initiating treatment included bulky disease, disease transformation to a high grade, symptomatic nodes, cytopenias, and critical organ involvement.

New Evidence: Please describe the safety results of your study.

Dr. Ardeshna: Side effects in the combined rituximab arms were minimal. Overall, there were seven infections, only four of which resulted in grade 3 infections requiring IV antibiotics. There were also five allergic reactions, two of which were grade 3. Finally, there were four cases of neutropenia, most of which improved without the use of growth factor.

In general, safety results of this study appear to be superior to those of studies examining patients given maintenance rituximab after chemotherapy. Should final results confirm this positive safety profile, I would feel very comfortable using maintenance rituximab in asymptomatic patients with FL.

New Evidence: Please describe the differences in efficacy results across study arms.

Dr. Ardeshna: At three years, the percentage of patients not requiring treatment with chemotherapy was significantly greater in the rituximab maintenance (91%) and induction (80%) arms, compared to the watch and wait arm (48%) ($p < 0.001$). Progression-free survival (PFS) was also significantly greater in the rituximab arms versus the watch and wait arm ($p < 0.001$). The magnitude of the difference in efficacy between the rituximab and the watch and wait arms suggests a strong benefit of rituximab in these patients.

New Evidence: Are there any concerns with giving rituximab to asymptomatic patients?

Dr. Ardeshna: One concern with giving rituximab early is that it may become less effective when given in combination with chemotherapy (R-chemo) after patients have progressed. This issue is something we plan to monitor closely.

New Evidence: What are the next steps in examining the use of rituximab in asymptomatic patients with FL?

Dr. Ardeshna: The next step in our study will be to analyze QoL data to determine whether rituximab is a reasonable treatment option in these patients. It is possible that side effects from rituximab and the burden of undergoing treatment will reduce QoL. However, it is also possible that QoL will improve by delaying more toxic treatments, such as standard chemotherapy, and by improving disease burden. If patient QoL is the same or better with rituximab, offering rituximab maintenance as a treatment option to patients with asymptomatic FL would be reasonable.

To determine whether R-chemo is effective in patients given prior rituximab, we will be examining the duration of response after R-chemo and time to second treatment. These results should confirm whether asymptomatic patients in the rituximab and watch and wait arms benefit equally from R-chemo after disease progression.

New Evidence: How might this study change clinical practice?

Dr. Ardeshna: In the US, some oncology centres administer rituximab to asymptomatic patients; however, this practice is uncommon in the UK and Canada. If follow-up results confirm interim safety results and QoL is reasonable, rituximab maintenance may become a standard option in patients with asymptomatic FL. With the advent of new antibodies, other treatment options may become available that could also be tested in this setting.
The management of chronic lymphocytic leukemia (CLL), the most common adult lymphoid malignant disease in western countries, is rapidly changing as treatment goals shift from symptom palliation to maximum disease control with the advent of purine analogs and monoclonal antibodies. Since the presentation of overall survival data from the CLL-8 trial, the chemoimmunotherapy combination of fludarabine, cyclophosphamide, and rituximab (FCR) has become the standard first-line treatment for young, fit patients with CLL. The REACH study has established FCR in relapsed CLL.

Despite the advances, however, a significant proportion of patients are not suitable for intensive therapy due to age and/or co-morbidity, and almost all patients with CLL will eventually relapse. Research is ongoing to explore novel agents and new therapy combinations, identify prognostic biomarkers that may result in personalized therapy, and improve current treatment options, including allogeneic hematopoietic stem cell transplantation (alloHSCT). Though it offers the possibility of a definite cure, alloHSCT is currently only feasible in a minority of CLL patients.

At ASH 2010, various studies were presented that highlighted the ongoing clinical advances in CLL. This article reports on four of these studies.

- Interim analysis data from a study by the Australasian Leukaemia and Lymphoma Group (ALLG) and the CLL Australian Research Consortium (CLLARC) found that oral F(C)R therapy appeared generally safe and well tolerated in CLL patients aged ≥65 years who required first-line treatment.

- Final response analysis data from a phase II study conducted by the UK National Cancer Research Institute (NCRI) CLL subgroup confirmed that in previously untreated CLL patients who are unable to tolerate a more intensive chemotherapy regimen such as FCR, the combination of rituximab and chlorambucil is well tolerated with acceptable toxicity (slightly more neutropenia) and appears to result in a higher overall response rate than chlorambucil monotherapy.

- Data from a pooled analysis of first-line clinical trials conducted by the German CLL Study Group revealed a differential influence of immunoglobulin heavy chain variable (IGHV) gene mutation status and gene usage in the different genomic subgroups, which may hint at different biological behaviour apart from postulated mechanisms like B-cell receptor–mediated antigen drive and could also be reflected by differences in clinical disease course.

- A study examining the use of combination chemotherapy as pre-transplant targeted lymphocyte depletion (TLD) showed that the use of TLD resulted in a rapid conversion to full donor T-lymphocyte chimerism without incidence of engraftment failure after reduced intensity conditioning alloHSCT in patients with CLL. In this study, rapid donor engraftment (by 14 days) was associated with lower rates of minimal residual disease positivity, better disease control, and higher incidence of acute graft-versus-host disease, but did not appear to alter overall survival.

Background
Combination immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) in the treatment of chronic lymphocytic leukemia (CLL) demonstrated superior progression-free and overall survival compared to FC in the German CLL-8 study. As a result, FCR has become the standard first-line treatment in younger, fit CLL patients.1

The median age in the CLL-8 trial was 61 years compared to a median age for overall CLL patients of 72 years. Consequently, an ongoing debate is taking place regarding the tolerability and safety of FCR in elderly patients. Arbitrary dose reductions are common practice, and oral FC is thought to be more convenient for many older patients.2

Entering into this debate, Mulligan and colleagues presented data at ASH 2010 from an interim analysis of a phase II, multicentre, randomized, dose intensification study conducted by the Australasian Leukaemia and Lymphoma Group (ALLG) and the CLL Australian Research Consortium (CLLARC). The study is investigating the safety and tolerability of oral fludarabine with or without cyclophosphamide and rituximab therapy in previously untreated, elderly (≥65 years) CLL patients.2

Study design
• Previously untreated patients with progressive CLL aged ≥65 were randomized to one of three treatment regimens, FR5, FCR3, and FCR5, all given at monthly intervals for an intended 6 cycles, as follows:
  - FR5: oral fludarabine 24 mg/m² on days 1–5 plus i.v. rituximab 375 mg/m² on day 0 of cycle 1 and 500 mg/m² on day 1 of cycles 2–6;
  - FCR3: oral fludarabine 24 mg/m² and oral cyclophosphamide 150 mg/m² on days 1–3 plus i.v. rituximab 375 mg/m² on day 0 of cycle 1 and 500 mg/m² on day 1 of cycles 2–6;
  - FCR5: oral fludarabine 24 mg/m² plus oral cyclophosphamide 150 mg/m² on days 1–5 plus i.v. rituximab 375 mg/m² on day 0 of cycle 1 and 500 mg/m² on day 1 of cycles 2–6.


Safety and tolerability of oral fludarabine, with or without oral cyclophosphamide and rituximab therapy, in previously untreated CLL patients ≥65 years
The dosage of FCR5 is equivalent to standard intravenous FCR in the CLL-8 study.

Patients were administered their therapy arm with no dose reduction.

Fludarabine dosing was reduced according to renal function by calculated glomerular filtration rate (GFR).

Therapy was delayed by 2 weeks if any grade 3/4 toxicity occurred. If toxicity resolved to grade 2 or less after 2 weeks, therapy proceeded; if toxicity was unresolved, patients were taken off study and treated according to physician discretion.

Planned enrollment was 120 patients in total, 40 to each arm of the study.

Interim staging was planned to take place at 3–4 months, post-cycle 3/prior to cycle 4; initial response assessment was planned for post-cycle 6, with final staging at 2 months post-cycle 6 and follow-up 12 months later.

Primary endpoint was the completion of 6 treatment cycles.

Secondary endpoints were the rate of treatment-related adverse events (AEs), overall response (OR) rate, including complete response (CR) and partial response (PR), quality of life (QoL), and duration of remission/response.

Key findings

At the time of the interim analysis (August 1, 2010), over half the planned patients (65 of 120) had been enrolled from 21 centres in Australia and New Zealand and were randomized 1:1:1 to the three study arms: FR5 (n = 22), FCR3 (n = 22), FCR5 (n = 21).

Median age was 72 years (range: 65–85 years).

Binet stage at registration was as follows:
- progressive A – 11 patients (16.9%);
- B – 32 patients (49.2%);
- C – 22 patients (33.8%).

Fluorescence in situ hybridization (FISH) data was available for 56 patients: 24 patients (42%) with del(13q), 11 patients (20%) with trisomy 12, 5 patients (9%) with del(11q), and 6 patients (10.7%) with del(17p).

PS3 functional analysis was available for 13 patients.

Interim reasons for cessation of treatment included completion of the protocol 6 cycles, unresolved grade 3/4 toxicity, and intercurrent illness. (Table 1)

Cessations for reasons other than toxicity occurred in 7 patients: intercurrent illness (n = 2) with acute myocardial infarction (AMI) and recurrent episodes of amnesia, and other reasons (n = 5), including patient choice and ineligibility.

Interim dose delays during treatment occurred at a frequency of 30 (61.2%).

Interim clinical response after 3 cycles showed 30% of patients in CR; initial clinical response after 6 cycles showed 59% of patients in CR; overall response rate for the total patient cohort at final staging (2 months after completion of treatment) was 92.8%. (Table 2)

Deaths were recorded for 2 patients due to infection and AMI.

To date, no analysis by treatment arm is available.

### Table 1. Interim reasons for cessation of treatment (all patients)

<table>
<thead>
<tr>
<th>Reason for cessation</th>
<th>Frequency</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of protocol 6 cycles</td>
<td>13</td>
<td>46.4</td>
</tr>
<tr>
<td>Unresolved grade 3/4 toxicity &gt;2 weeks</td>
<td>8</td>
<td>28.6</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>Other/social/non-toxicity reasons</td>
<td>5</td>
<td>17.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

25%

### Table 2. Response at interim time points (all patients)

<table>
<thead>
<tr>
<th>Response</th>
<th>Interim clinical response (3 cycles)</th>
<th>Initial clinical response (6 cycles)</th>
<th>Final staging (2 months after completion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>13 (30)</td>
<td>19 (59)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Nodular partial response (nPR)</td>
<td>1</td>
<td>1</td>
<td>5 (17.8)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>27</td>
<td>9</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>2</td>
<td>3</td>
<td>2 (7.2)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>43</strong></td>
<td><strong>32</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

ORR = overall response rate

92.8%


**Key conclusions**

- Oral F(C)R therapy appears generally safe and well tolerated at interim analysis in CLL patients aged ≥65 years requiring first-line treatment.

- Using stringent stopping criteria, with a delay of 2 weeks for recovery of grade 3/4 toxicity but no dose reduction, about half the patients will stop early due to toxicity, intercurrent illness, or other issues.

- Nevertheless, response rates are high and accrual is ongoing.

**References:**


Hillmen P, et al. ASH 2010: Abstract 697

**Rituximab plus chlorambucil in patients with CD20-positive B-cell chronic lymphocytic leukemia**

**Background**

Despite the increasing use of combination therapy with rituximab, fludarabine, and cyclophosphamide (FCR) for chronic lymphocytic leukemia (CLL), a significant proportion of patients are not suitable or eligible for such intensive chemotherapy due to co-morbidity and/or age. In patients considered unfit for FCR, chlorambucil remains a widely used first-line therapy. However, overall response (OR) rates with chlorambucil are relatively modest, with very few complete remissions, and therefore more effective treatment options are required for this patient group.1

Hillmen and colleagues, on behalf of the UK National Cancer Research Institute (NCRI) CLL subgroup, conducted an open-label, multicentre, phase II study (CLL-208) to evaluate the toxicity and tolerability of adding rituximab to chlorambucil (R-chlorambucil) in the treatment of a representative population of patients with CLL and to assess response rates compared to single-agent chlorambucil in matched patients from the LRF CLL-4 trial.2 Data from a final response analysis of the Hillman, et al. CLL-208 trial were presented at ASH 2010.1

**Study design**

- One hundred (100) previously untreated CLL patients requiring therapy received rituximab (375 mg/m² i.v. on day 1 of cycle 1, 500 mg/m² on day 1 of cycles 2–6) plus chlorambucil (10 mg/m²/day orally on days 1–7) every 28 days for 6 cycles.

- A further 6 cycles of chlorambucil alone were permitted in patients with continuing clinical response (but not in complete remission) at 6 cycles.

- Efficacy data were compared to matched historic data from the UK LRF CLL-4 trial,3 which treated patients between 1999 and 2004 with chlorambucil monotherapy at the same dose as was used in this study.

- Each patient in this study was matched to two patients treated with chlorambucil in the LRF CLL-4 study according to age, Binet stage, VH mutational status, and 11q deletion status by fluorescence in situ hybridization (FISH) assessment. (Table 1)

- Note that the CLL-4 data were from 1999–2005, while the R-chlorambucil responses were from 2008. Over this time, any improvements in patient response may be due to factors such as better care, improved knowledge, and different concomitant medications, rather than to treatment used.

- Median age of patients in LRF CLL-4 was significantly lower than those treated with R-chlorambucil (66.5 years compared with 70 years).

- Primary endpoint was safety; secondary endpoints were response (including minimal residual disease [MRD]), progression-free survival (PFS), and overall survival (OS).
Key findings

Baseline characteristics and disposition
• A total of 100 patients from 12 UK centres were enrolled between November 2007 and November 2009; all patients who had completed treatment were included in the analysis.
• Median age was 70 years (range: 43–86), and 66% were male. (Table 1)
• Forty-four percent (44%) of patients were Binet stage B, and 56% were Binet stage C. (Table 1)
• Thirty percent (30%) of patients showed an IgVH mutation; 45% had a 13q deletion. (Table 1)

Safety
• Ninety-two patients (92%) had reported an adverse event (AE) by the end of treatment; most AEs reported were grade 1/2.
• The most common grade 3/4 AEs were neutropenia (68 events in 41 patients), leukopenia (28 events in 22 patients), anemia (22 events in 19 patients), and thrombocytopenia (22 events in 18 patients).
• Infusion-related reactions occurred in 7 patients.
• A total of 57 serious AEs (SAEs) occurred in 39 patients. (Table 2)
  ◦ The most common SAEs were febrile neutropenia (5 patients) and neutropenic sepsis (4 patients).

Table 1. Baseline characteristics of the R-chlorambucil–treated CLL study population and the chlorambucil–treated matched control population*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R-chlorambucil (n = 100)</th>
<th>Chlorambucil* (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female, %</td>
<td>66 / 34</td>
<td>78.5 / 21.5</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>70 (43–86)</td>
<td>66.5 (43–85)</td>
</tr>
<tr>
<td>Binet stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>44</td>
<td>46.5</td>
</tr>
<tr>
<td>C</td>
<td>56</td>
<td>50.5</td>
</tr>
<tr>
<td>IGVH mutation status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>30</td>
<td>32.5</td>
</tr>
<tr>
<td>Unmutated</td>
<td>49</td>
<td>50.5</td>
</tr>
<tr>
<td>Cytogenetics, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13q deletion</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>12q trisomy</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>11q deletion</td>
<td>14</td>
<td>19</td>
</tr>
</tbody>
</table>

* Matched historical control population data from the UK LRF CLL-4 trial.2

CLL = chronic lymphocytic leukemia; R = rituximab

Table 2. Serious adverse events reported in 39/100 R-chlorambucil–treated CLL patients

<table>
<thead>
<tr>
<th>Serious adverse event (SAE)</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>4</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>32</td>
</tr>
<tr>
<td>Total serious adverse events</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 3. Response rates for the R-chlorambucil–treated CLL study population compared with the chlorambucil–treated matched control population*

<table>
<thead>
<tr>
<th>Trial / Treatment regimen</th>
<th>N</th>
<th>OR rate (%)</th>
<th>CR (%)</th>
<th>SD/PD (%)</th>
<th>Not evaluable (%)</th>
<th>95% CI (for % of patients achieving at least a PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-208 R-chlorambucil</td>
<td>100</td>
<td>80</td>
<td>12</td>
<td>17</td>
<td>3</td>
<td>70.8–87.3</td>
</tr>
<tr>
<td>CLL-4 Chlorambucil monotherapy</td>
<td>200</td>
<td>66</td>
<td>6</td>
<td>30</td>
<td>4</td>
<td>59.0–72.5</td>
</tr>
</tbody>
</table>

* Matched historical control population data from the UK LRF CLL-4 trial.2
CI = confidence interval; CLL = chronic lymphocytic leukemia; CR = complete response; N = number of patients; OR = overall response; PD = progressive disease; PR = partial response; R = rituximab; SD = stable disease

To date, 87 patients remain alive and 13 patients have died, 11 due to progressive disease and 2 considered to be treatment-related (neutropenic sepsis and cerebrovascular accident [CVA]).

Efficacy
• Overall response (OR) rate was 80% (95% CI: 70.8–87.3), with 12% of patients achieving a complete response (CR), 68% of patients showing partial response (PR), and 17% of patients with stable disease (SD) or progressive disease (PD); no patients had an MRD negative remission.
• OR rate in this study for patients treated with R-chlorambucil was 14% higher than in the matched subset of chlorambucil-treated patients from the CLL-4 study, suggesting improved responses for R-chlorambucil compared with chlorambucil alone. (Table 3)
• Median PFS to date is 23.9 months, compared with 18 months for the chlorambucil monotherapy matched pairs from CLL-4. (Figure 1)
Key conclusions

- Compared with CLL-4 and other large trials, the median age of patients in this study was more representative of the typical age of CLL patients in the clinic.

- These data confirm that in previously untreated CLL patients who are unable to tolerate a more intensive chemotherapy regimen such as FCR, the combination of rituximab and chlorambucil is well tolerated with acceptable toxicity (slightly more neutropenia) and appears to result in a higher OR rate than chlorambucil monotherapy; remissions are not as good as those reported for FCR.

- The combination of rituximab with chlorambucil is current under study in a randomized phase III trial (German CLL Study Group CLL-11 trial) in elderly/unfit patients with CLL.

References:


Bühler A, et al. ASH 2010: Abstract 3609

IGHV-mutation status, IGHV-gene usage, and chromosomal aberrations in CLL: pooled analysis from first-line clinical trials of the German CLL Study Group

Background

Immunoglobulin heavy chain variable (IGHV) mutation status and genomic aberrations are of independent prognostic importance in chronic lymphocytic leukemia (CLL). Furthermore, IGHV-gene usage showed prognostic value for distinct subgroups, such as IGHV3-21. While the introduction of chemoimmunotherapy, such as the combination fludarabine-cyclophosphamide-rituximab (FCR) regimen, has led to remarkable improvement of outcome in CLL, it remains unclear which of the known genetic markers retain their prognostic value after standard first-line treatment.

At ASH 2010, Bühler and colleagues presented findings from their pooled analysis evaluating genetic markers in a large, well-characterized cohort of first-line–treated CLL patients from three prospective German CLL Study Group (GCLLSG) clinical trials.
**Study design**

- The study evaluated data of first-line–treated CLL patients from three GCLLSG trials:
  - CLL-2B (rituximab-bendamustine);
  - CLL-4 (fludarabine versus fludarabine-cyclophosphamide [FC]);
  - CLL-8 (FC versus FCR).
- Genetic characterization was performed in a central laboratory (Ulm).
- IGHV data was available for 1,063 patients (388 IGHV-mutated and 675 IGHV-unmutated patients).
- Fluorescence in situ hybridization (FISH)/genomic aberrations were available for 1,053 patients.
- The impact of IGHV mutation status on progression-free survival (PFS) and overall survival (OS) was investigated within the hierarchical model of genomic abnormalities:
  - del(13q) single (n = 353);
  - trisomy 12 (n = 115);
  - del(11q) (n = 229);
  - del(17p) (n = 73).
- Median follow-up was 48.6 months.
- The prognostic influence of certain IGHV-genes (IGHV3-21, unmutated IGHV1-69, mutated IGHV3-23) was evaluated; analyses of IGHV1-69 and IGHV3-23 were available only for the CLL-2M and CLL-8 cohorts (n = 732).

**Key findings**

**Chromosomal aberrations and IGHV mutation status**

- Of the del(13q) patients, 56% carried a mutated IGHV gene and 44% an unmutated IGHV gene.
  - A significant difference in PFS and OS was observed between the del(13q) IGHV-mutated and del(13q) IGHV-unmutated subgroups (PFS: p = 0.002, HR: 1.596; OS: p = 0.002, HR: 2.15; median PFS: mutated 70.5 months versus unmutated 41.5 months). (Figure 1)
- In the trisomy 12 subgroup, 35% of patients showed a mutated IGHV gene, whereas 65% showed an unmutated IGHV gene.
  - For the trisomy 12 IGHV-unmutated subgroup, a trend towards a shorter PFS and OS was detected compared to the trisomy 12 IGHV-mutated subgroup, but this trend was not statistically significant (PFS: p = 0.059, HR: 1.784; OS: p = 0.079, HR: 3.05; median PFS not reached versus 36.8 months).
- In the del(11q) subgroup, 17% were IGHV mutated, and 83% were unmutated.
  - No significant difference for PFS and OS could be detected between the del(11q) IGHV-mutated subgroup and the del(11q) IGHV-unmutated subgroup (PFS: p = 0.451; OS: p = 0.64; median PFS: 32.7 months for both subgroups).
- Of the del(17p) patients, 23% carried an IGHV-mutated gene and 77% an IGHV-unmutated gene.
  - No difference in PFS or OS was found between the IGHV-mutated or unmutated subgroups (PFS: p = 0.995, HR: 0.998; OS: p = 0.584, HR: 0.80; median PFS: 8.8 months versus 9.6 months). (Figure 1)

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Figure 1. Overall survival in first-line–treated, medically fit CLL patients: del(17p) and del(13q) single subgroups
**Key conclusions**

- The current data from pooled subgroup analyses revealed a differential influence of IGHV-mutation status and gene usage in the different genomic subgroups.
- This finding might hint at different biological behaviour apart from postulated mechanisms like B-cell receptor-mediated antigen drive and could also be reflected by differences in clinical course.
- The impact of IGHV3-21 usage and potentially other IGHV genes appears to be less pronounced in this cohort.
- The prognostic role of distinct IGHV genes must be further evaluated in different clinical situations also considering stereotyped B-cell receptors.


Shaffer BC, et al. ASH 2010: Abstract 3476

**Combination chemotherapy as pre-transplant targeted lymphocyte depletion in CLL patients undergoing allogeneic hematopoietic transplantation**

**Background**

The development of reduced intensity conditioning (RIC) regimens has increased the use of allogeneic hematopoietic stem cell transplantation (alloHCT) in patients with chronic lymphocytic leukemia (CLL). Despite decreased rates of transplant-related mortality, RIC regimens confer slower rates of donor engraftment and increased relapse post-transplant. A study by Brown, et al. reported that faster rates of conversion to donor chimerism after RIC alloHSCT result in lower rates of CLL relapse.¹

Shaffer and colleagues hypothesized that systematic targeted host T-lymphocyte depletion (TLD) to a target level by serial administration of standard chemotherapy prior to RIC alloHSCT would result in more rapid donor engraftment and full donor chimerism, thereby enhancing graft versus leukemia activity. Results of their study evaluating the effects of TLD on host CD4 lymphocyte depletion, disease response, and toxicity, as well as on donor engraftment, non-relapse mortality, and disease control in CLL patients undergoing RIC alloHSCT was presented at ASH 2010.²
Study design

- The study evaluated 27 patients undergoing RIC alloHSCT for CLL from 1999 to 2010.
- All patients underwent TLD receiving 1–3 cycles of EPOCH-F±R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, fludarabine ± rituximab) prior to RIC (fludarabine/cyclophosphamide) and matched-related (n = 17) or unrelated (n = 10) donor transplantation, followed by calcineurin inhibitor-based graft-versus-host disease (GVHD) prophylaxis.
- The number of cycles administered (maximum of three cycles) was titrated to achieve an absolute CD4 count ≤100 cells/µL prior to RIC.
- Bone marrow chimerism was evaluated on days 14, 28, 60, 100, 180, and 360; restaging was done on days 28, 60, 100, 180, 360, and then yearly.

Key findings

- Median age of patients was 56 years (range: 37–71 years); 21 patients (78%) were male, 16 patients (59%) had Rai stage 3/4 disease, and 14 (52%) were refractory to their last treatment.
- The median number of EPOCH-F±R cycles given was 2.
- The overall response rate to EPOCH-F±R was 50% (9% complete response [CR], 41% partial response [PR]), including 44% of patients who were refractory to their last treatment. (Table 1)
- The median time to full myeloid engraftment was 21 days.
- The median time to full lymphoid engraftment was 28 days.
- Engraftment failure was 0%.
- The incidence of acute GVHD was 55%.
- The incidence of chronic GVHD was 44%.
- The rate of non-relapse mortality was 30% (2 years).
- Median event-free survival (EFS) was 3.75 years, and median overall survival (OS) was 5.99 years (95% CI: 2.11–not reached).
- The rate of complete remission was 54%, and the rate of minimal residual disease negativity after transplantation as assessed by multicolor flow cytometry was 55%.
- The incidence of disease progression after transplant was 33%.
- No patients failed to engraft.
- Incidence of acute (grade 2–4) and chronic GVHD were 55% and 44%, respectively.
- Non-relapse-related mortality at two years was 30%.
- The number of cycles administered (maximum of three cycles) was titrated to achieve an absolute CD4 count ≤100 cells/µL prior to RIC.
- The median time to full myeloid engraftment was 21 days.
- The median time to full lymphoid engraftment was 28 days.
- Engraftment failure was 0%.
- The incidence of acute GVHD was 55%.
- The incidence of chronic GVHD was 44%.
- Non-relapse mortality was 30% (2 years).
- Median event-free survival (EFS) was 3.75 years, and median overall survival (OS) was 5.99 years (95% CI: 2.11–not reached).
- The rate of complete remission was 54%, and the rate of minimal residual disease negativity after transplantation as assessed by multicolor flow cytometry was 55%.
- The incidence of disease progression after transplant was 33%.
- The effect of targeted lymphocyte depletion on lymphocyte subsets is shown in Figure 1.
- Development of full lymphoid chimerism by day 14 (first evaluation point) versus day 28 or greater trended towards association with development of acute GVHD (90% vs. 35%, \( p = 0.014 \)), but not chronic GVHD (50% vs. 41%, \( p = 0.71 \)). (Figure 2)
- Achievement of full lymphoid chimerism on day 14 as compared to day 28 or greater trended towards association with decreased CLL cells identified in the bone marrow by multicolor flow cytometry at day 100 (median 0% vs. 8.5%, \( p = 0.016 \)), but was not associated with improved OS (\( p = 0.077 \)). (Figure 3)
- There was no association between rates of development of full myeloid chimerism and acute or chronic GVHD or disease control.

Table 1. Clinical outcomes using EPOCH-F±R as targeted lymphocyte depletion for RIC allogeneic transplantation

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response to TLD</td>
<td>50%</td>
</tr>
<tr>
<td>Grade ≥3 non-hematological toxicity</td>
<td>72%</td>
</tr>
<tr>
<td>Median time to full myeloid engraftment</td>
<td>21 days</td>
</tr>
<tr>
<td>Median time to full lymphoid engraftment</td>
<td>28 days</td>
</tr>
<tr>
<td>Engraftment failure</td>
<td>0%</td>
</tr>
<tr>
<td>Incidence of acute GVHD</td>
<td>55%</td>
</tr>
<tr>
<td>Incidence of chronic GVHD</td>
<td>44%</td>
</tr>
<tr>
<td>Non-relapse mortality</td>
<td>30% (2 years)</td>
</tr>
<tr>
<td>Event-free survival (median)</td>
<td>3.75 years</td>
</tr>
<tr>
<td>Overall survival (median)</td>
<td>5.99 years</td>
</tr>
</tbody>
</table>

EPOCH-F = etoposide, doxorubicin, vincristine, cytoxan, prednisone, fludarabine; 
GVHD = graft-versus-host disease; R = rituximab; RIC = reduced intensity conditioning; 
TLD = targeted lymphocyte depletion
Key conclusions

- The use of targeted lymphocyte depletion resulted in a rapid conversion to full donor T-lymphocyte chimerism without incidence of engraftment failure after RIC alloHSCT in patients with CLL.

- Rapid donor engraftment (by 14 days) was associated with lower rates of minimal residual disease positivity, better disease control, and higher incidence of acute GVHD, but did not appear to alter overall survival.

Mulligan and colleagues studied an oral FCR (fludarabine, cyclophosphamide, rituximab) regimen for the treatment of chronic lymphocytic leukemia (CLL) in elderly patients. The study by Mulligan et al. is very relevant for physicians in Canada, because we prefer to use oral chemotherapy to free up chair time in treatment clinics and to increase patient convenience. Even though the authors report that a bioequivalent dose of fludarabine was used, the oral fludarabine dose appears to have been relatively lower than that used in IV FCR studies. Drawing any major conclusions from the study is difficult, because the study was primarily a safety and tolerability study, and the design did not include a comparison group. Nonetheless, the study is still important for Canada, where oral FCR might be used for older as well as younger CLL patients.

The study by Hillmen et al., evaluating the safety and tolerability of adding rituximab to chlorambucil (R-chlorambucil) and comparing R-chlorambucil to single-agent chlorambucil, is a promising study. Chlorambucil has been the standard of care in CLL, especially for those patients who are elderly and unlikely to tolerate the FCR regimen. The results of the Hillmen et al. study show that patients treated with R-chlorambucil had higher response rates and better outcomes than patients treated with chlorambucil alone. R-chlorambucil also seemed to be fairly well tolerated. These results are encouraging indeed, and R-chlorambucil is now the subject of a phase III trial by the German CLL study group.

Hoffmann La Roche is studying a subcutaneous formulation of rituximab. Once this becomes available, oral chemotherapy such as chlorambucil or FC will become even more convenient for patients and less labour-intensive for nursing staff and pharmacists.

In the study by Buhler et al., the authors examined immunoglobulin heavy chain variable (IGHV) mutation status and chromosomal abnormalities by fluorescence in situ hybridization (FISH). We know that the natural history of CLL is influenced by genetic heterogeneity. Some of these molecular factors influence treatment in CLL. For example, 11q– CLL requires treatment with an alkylator in addition to fludarabine and rituximab (i.e., FCR rather than just FR). For other subgroups, it’s not clear whether FCR is more efficacious than FR. Comparing these two regimens is the focus of the NCIC-CTG CL.3 study. At relapse, patients with 17p– (p53) do not respond well to standard chemotherapy. Outcomes are better with alemtuzumab and much better with allogeneic transplantation.

At the present time, IGHV mutation status has no implications for treatment, but there may be an option in the future for targeted therapy based on what genetics are driving the tumours. For now, as clinicians, we are generally more interested in studies of predictive markers that inform treatment decisions, than studies of prognostic markers.
Rafat Faraawi, MD, FRCP(C);1 Mark Brown, PharmD, BCPS;2 Janet Pope, MD, FRCP(C);3 Roy Lee, BSc, PhM, RPh;4 Kelly Roth, RN5

1Division of Rheumatology, McMaster University, Hamilton, Ontario, and St. Mary’s Hospital, K-W Musculoskeletal Research, Kitchener, Ontario; 2Hamilton Health Sciences, Juravinski Hospital and Cancer Centre, Hamilton, Ontario; 3Division of Rheumatology, University of Western Ontario, St. Joseph’s Health Care, London, Ontario; 4Princess Margaret Hospital, University Health Network, Toronto, Ontario; 5K-W Musculoskeletal Research, Kitchener, Ontario

Medical Writer: Anna Christofides MSc, RD, New Evidence
Rituximab is a human/murine immunoglobulin G1 chimeric monoclonal antibody that binds to the B-cell CD20 antigen, causing rapid and targeted B-cell depletion.1,2 In Canada, rituximab is approved by Health Canada for the treatment of patients with non-Hodgkin’s lymphoma (NHL) and B-cell chronic lymphocytic leukemia (CLL). Rituximab is also indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies. Rituximab in combination with methotrexate (MTX) has been shown to reduce the rate of progression of joint damage as measured by X-ray in the RA setting.3

The addition of rituximab to standard chemotherapy has been shown to improve outcomes in patients with NHL, CLL, and RA. In patients with NHL and untreated CLL, rituximab improves both progression-free survival (PFS) and overall survival (OS); maintenance and second-line rituximab also delays progression in these patients.4–7

Rituximab is a good treatment alternative to patients with RA who have failed TNF inhibitors and has proven to be as or more effective than a second TNF inhibitor in this setting.8,9 Results of clinical trials in RA patients show that a significant number achieve ACR50 and low disease activity levels after treatment with rituximab.10 Ongoing clinical trials are also examining the use of rituximab in vasculitis, multiple sclerosis, refractory thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and epidermolysis bullosa acquista.

Although generally well tolerated, biologic treatments, including rituximab, are associated with infusion-related reactions. To minimize these reactions, the standard administration of rituximab has a long infusion time, resulting in a significant drain on health resources and patient time. For this reason, shorter infusion protocols have been tested in oncology settings and have proven to be safe and practical. Similarly, routine use of rapid infusion protocols in the RA setting should provide further benefits for these patients and their healthcare providers.

Standard administration protocol

One barrier to effective treatment with rituximab is its lengthy administration protocol, resulting in a time- and labour-intensive process.3,11,12 (Figures 1 and 2) The standard administration protocol for rituximab takes approximately three or four hours for the first infusion and two or three hours for subsequent infusions in the oncology and RA settings, respectively. These long infusion times place a significant strain on health resources.

Patients are expected to arrive at the clinic early and wait afterwards to ensure there are no adverse reactions. A total of around four to six hours of patient time is therefore needed to complete one rituximab infusion, including waiting time.11,12 Because of the long infusion time, patients need to plan for a full day of treatment at the clinic, with a negative impact on their quality of life.

The burden of the standard infusion protocol to the healthcare system is also significant. Long infusion protocols increase required patient chair time, thus decreasing the ability to treat other patients. This results in increased nursing and administration staff workload, longer wait times for treatment, and less efficient delivery of services. The financial cost in terms of healthcare provider time and use of resources is also a concern. Ultimately, the burden of long infusion times may result in a lack of adherence or discontinuation of treatment, potentially reducing treatment efficacy. For these reasons, rapid infusion protocols have been developed in some infusion centres.
Figure 1. Standard administration of rituximab: initial infusion

Adapted from Hoffmann-La Roche Ltd. RITUXAN® Product Monograph, 2010.
Note: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, the infusion rate may be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Figure 2. Standard administration of rituximab: subsequent infusions

Adapted from Hoffmann-La Roche Ltd. RITUXAN® Product Monograph, 2010.
Note: Subsequent infusions of rituximab can be administered at an initial rate of 100 mg/hr and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr as tolerated.
Infusion-related reactions

Rituximab is generally well tolerated in both the oncology and rheumatology settings. However, infusion-related reactions may occur and typically manifest 30 to 120 minutes after rituximab administration. Although the mechanism is poorly understood, symptoms may develop as a result of the binding of rituximab to tumour cells and normal B cells, causing the release of inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) and/or other chemical mediators.1–3,11

Usually, symptoms of infusion reactions are less severe in the RA setting than in the oncology setting. Symptoms are generally mild to moderate in nature and may include fever, rash, and cardiovascular or respiratory insufficiency. Rarely, severe symptoms occur, which may result in urticaria, hypotension, angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock.2,3,11

Infusion reactions are more frequent in the oncology than the RA setting due to the higher B-cell burden of these patients. In the oncology setting, older patients and those with increased tumour bulk are at highest risk.2,13,14 Typically, the risk of infusion-related toxicity is greatest with the first infusion, occurring in 77% and 29% of patients with NHL and RA, respectively.2,10 Infusion reaction rates decrease substantially after the first infusion, with approximately 30% of NHL patients and 12% of RA patients reporting reactions after subsequent infusions.10,11 A similar trend is observed for severe (grade 3/4) reactions, which occur in around 7% of patients with NHL after the first infusion and decrease to 2% after the fourth infusion; severe reactions in RA patients are rare and occur in <1% of patients.2,3,11

The risk for infusion reactions associated with the use of rituximab should be kept in perspective with the risk of reactions associated with other agents. In general, the incidence of infusion reactions associated with rituximab in the oncology setting is similar to that associated with other biologics, taxanes, and platinum agents.14 In the RA setting, the incidence of infusion reactions is similar to that of other biologics and some TNF inhibitors, such as infliximab.15 Discontinuation of rituximab rarely occurs as a result, and the majority of reactions are resolved by slowing or interrupting the infusion and giving supportive care.14 In addition, the clinical benefit of rituximab clearly outweighs the risk, with a favourable risk:benefit profile.

Rapid infusion protocols in clinical trials

Oncology setting

Routine use of rapid infusion protocols can result in significant reductions in healthcare costs and resources. Accelerated infusions of rituximab were first used in the oncology setting in patients diagnosed with NHL or CLL. A preliminary study by O’Brien, et al. (2001) in patients with CLL found that dose escalations of rituximab up to 2,250 mg/m² given at infusion rates up to 400 mg/hr did not increase the rate of infusion reactions.16 Subsequently, 60- and 90-minute infusion protocols were developed and tested in a number of studies in the oncology setting; these protocols were found to be well tolerated with no increase in the rate of infusion-related reactions. (Appendix A) However, the standard infusion rate was given for the first infusion of all courses in both protocols to assess patient tolerability.

Overall, clinical studies in the oncology setting show that adverse events (AEs) with rapid infusions are rare and manageable, the majority being mild in nature (grade 1/2). The largest study to date included 206 patients receiving the 90-minute protocol and reported no serious infusion reactions and no increase in mild infusion reactions. After follow-up of more than 1,200 patients, only one patient experienced a more serious (grade 3) reaction.11 Based on the results of clinical trials, rapid infusion protocols are now routinely used in the majority of oncology centres across Canada.
Prevention of infusion-related reactions

Identification of patients at increased risk is of key importance in preventing infusion-related reactions. Prior to rituximab administration, individual patient risk factors for infusion reactions should be assessed. (Table 1) Other factors, such as whether rituximab is to be administered in combination or as a single agent and which (if any) other concomitant therapies will be used may also influence the risk of infusion reactions. Of particular importance is any history of previous allergic reactions. A detailed patient history, including baseline assessments of vital signs and cognition, is therefore an important first step before initiating treatment with rituximab.14

In the oncology setting, pre-medication consisting of oral acetaminophen (1,000 mg), oral diphenhydramine (50 mg), and IV methylprednisolone (100 mg). Only one mild (grade 1) AE was reported, which resolved during the infusion. Overall, the rapid infusion protocol was well tolerated, and patients reported being satisfied with this administration method. Several other studies support the use of accelerated rituximab infusions in RA patients. Further studies examining rapid infusions in the rheumatology setting should aid in determining its use in clinical practice.

Rapid infusion protocols in clinical practice

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Table 1. Patient risk factors for hypersensitivity reactions

<table>
<thead>
<tr>
<th>Female gender</th>
<th>Pre-existing cardiac or pulmonary dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher than standard drug doses</td>
<td>Previous exposure to the drug</td>
</tr>
<tr>
<td>Iodine or seafood allergies</td>
<td>Asthma diagnosis</td>
</tr>
<tr>
<td>Newly diagnosed, untreated patients</td>
<td>Atopic patients (i.e., patients who tend to react to specific allergens, such as hay fever, skin irritations, and asthma)</td>
</tr>
<tr>
<td>Older age</td>
<td>Circulating lymphocyte counts of 25,000 mm³ or higher</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>Concomitant β-adrenergic blocker therapy</td>
</tr>
<tr>
<td>Personal history of significant drug allergy or previous immediate reaction to a medication</td>
<td>Concurrent autoimmune disease</td>
</tr>
</tbody>
</table>

Adapted from Vogel, et al. 2010.
Stepwise or fractionated dosing, for example administering a 100 mg dose in 1,000 mL of normal saline on day 1 and the remainder on day 2, may also be considered in these high-risk patients. At Princess Margaret Hospital (PMH) in Toronto, Ontario, fractionated dosing is given to CLL patients with high white blood cell (WBC) counts. A similar approach is employed at the Juravinski Hospital and Cancer Centre (JHCC) in Hamilton, Ontario, where physicians may elect to give 50 mg/m² on day 1 and the remaining 325 mg/m² on day 2 for the first cycle. For high-risk patients, hospitalization may be necessary when stringent monitoring is required.

Many patients with RA are not given pre-medications, and the use of corticosteroids is not required before rituximab administration. However, in a study by Emery, et al. (2006), use of glucocorticoids reduced infusion reactions and did not alter the response to rituximab in patients with RA.

Prior to rituximab administration, patients should be educated about the potential for infusion reactions and instructed to report any adverse reactions immediately. Healthcare practitioners should reassure patients that appropriate measures will be taken to prevent infusion reactions. Patients should also be advised that these reactions are generally mild to moderate and are easily managed.

**Administration of the rapid infusion protocol**

In the oncology setting, it is recommended that rituximab infusions be administered in an environment with full resuscitation facilities and under the close supervision of professionals capable of dealing with severe reactions. During infusions, healthcare practitioners should monitor patient vital signs, watching for any sign of infusion reactions. Constant visual observation is important during the first infusion, when patients are at the greatest risk; however, monitoring should continue with every subsequent infusion. The first infusion of rituximab should be delivered at the standard infusion rate to assess patient tolerability. If the first infusion is well tolerated, subsequent infusions may be given at an accelerated infusion rate over approximately 90 to 120 minutes in the oncology setting or 120 minutes in the RA setting. (Figure 3)

**Figure 3. Rapid administration of rituximab**

<table>
<thead>
<tr>
<th>Rate</th>
<th>Time</th>
<th>Quantity of rituximab</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg/hr</td>
<td>0–30 min</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>400 mg/hr</td>
<td>30–60 min</td>
<td>200 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>600 mg/hr</td>
<td>60–90 min</td>
<td>300 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>800 mg/hr</td>
<td>90–120 min</td>
<td>400 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

Note: The rituximab solution for infusion should be administered intravenously at an initial rate of 200 mg/hr. If hypersensitivity or infusion-related events do not occur, the infusion rate may be escalated in 200 mg/hr increments every 30 minutes, to a maximum of 800 mg/hr.
In the oncology setting, rapid infusion of rituximab has become the standard in the majority of centres across Canada. PMH began using the rapid infusion protocol shortly after data from the Sehn, et al. (2007) study in the NHL setting was released. The standard protocol at PMH therefore recommends administering 375 mg/m² at the 90-minute infusion rate if the patient tolerates the first infusion or has only a mild-to-moderate reaction. If there are significant pulmonary symptoms after the first infusion, the second infusion may be given using the standard infusion rate before moving to the rapid protocol. When patients show more severe reactions (grade 3/4), treatment may be stopped; however, severe reactions rarely occur.

The adoption of a rapid infusion protocol at PMH means that a total of 8 to 10 patients can be seen per day, compared to only 5 patients with the standard protocol. Patients are often able to concurrently book lab and infusion time on the same day, thereby reducing the number of days spent in the clinic. A detailed description of the rapid infusion protocol at PMH is presented in Appendix B.

Recent funding approval in Ontario for the use of rituximab in combination with fludarabine-based treatment for previously untreated CLL has required a slightly different approach to the management of rituximab infusions. First, CLL patients tend to have higher grade 1 and 2 reactions than patients with other lymphocytic subtypes. As previously mentioned, this risk is managed by optional fractionated first dosing. Second, the rituximab dose in cycles 2–6 for CLL is 500 mg/m². Early pharmacokinetic and dose-escalation studies observed that rituximab at standard 375 mg/m² was less effective in CLL than in other lymphoma subtypes. Reasons for this finding include generally lower CD20 expression and a shorter rituximab half-life in CLL, which can be overcome with higher doses.

The current practice at JHCC for rituximab infusions in CLL follows the PMH processes previously described, with cycle 1 at 375 mg/m² (with optional fractionation) and cycle 2 at 500 mg/m² at standard infusion rates. Assuming no clinically significant reactions are observed, cycles 3–6 are given at 500 mg/m² over approximately 90 minutes.

Given the success of rapid infusion protocols in the oncology setting and the growing evidence of their safety in patients with RA, the accelerated protocol should become the standard of care in the RA setting across Canada.

**Conclusion**

Rituximab has proven to be an invaluable treatment option, dramatically improving the outcome of patients with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. Despite the clear benefits of rituximab in the oncology and rheumatology settings, its standard administration is time consuming, resulting in a significant burden for patients and health-care providers.

Studies using accelerated infusion protocols for rituximab in both oncology and RA settings have shown rapid administration to be safe and practical. Rapid infusion of rituximab can reduce healthcare costs, improve resource utilisation, and increase patient satisfaction and quality of life. Based on the positive results of studies in the oncology and RA settings, rapid infusion of rituximab should be recommended in all infusion clinics across Canada.
## Appendix A. Rapid infusion protocols used in clinical trials

<table>
<thead>
<tr>
<th>Study/Patient population</th>
<th>Rapid infusion protocol</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byrd JC, et al.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| (CLL, SLL; R-monotherapy)| • 100 mg administered over 4 hours (25 mg/h) for first infusion  
• 375 mg/m² using standard infusion rate for second infusion  
• 375 mg/m² for infusions 3 to 12 administered at 50 mg/h rate for 15 minutes, then increased to administer entire dose over 60 minutes | • Rapid infusion data from cohort III of study: 23/33 patients  
• No IRRs noted beyond the second infusion in the 23 patients using rapid infusion on the third and subsequent infusions  
• No SAEs with rapid infusions |
| Pre-medication: diphenhydramine (50 mg IV), acetaminophen (650 mg orally) | | |
| Aurran Scleinitz T, et al. | • 375 mg/m² using standard infusion rate for first infusion  
• In cases where patients had circulating malignant CD20+ cells, first infusion administered over 2 days  
• Subsequent infusions given at 100 mg/h for 15 minutes, then at 500 mL/h for a total of 60 minutes | • Data from 69 patients for a total of 115 courses, including 21 first cycles  
• No grade 3/4 toxicity noted  
• During the first infusion, two patients developed grade 2 reactions and three developed grade 1 reactions  
• One CLL patient had a grade 1 reaction after the second cycle |
| *ASH 2005: Abstract 4759* (NHL, CLL; 67 R-chemo; 2 R-monotherapy) | Pre-medication: 1 mg/kg dose of steroids, diphenhydramine, acetaminophen given 20 minutes before | |
| Middleton HJ, et al. | • 375 mg/m² using standard infusion rate for first infusion  
• Subsequent infusions using rapid infusions  
• In first four patients, infusion was administered at 100 mg/h, increasing to 400 mg/h after 15 minutes in the absence of reaction  
• All subsequent patients commenced the infusion at 400 mg/h | • Data from 23 patients and 62 infusions (median 3 infusions per patient)  
• Median infusion time was 1 hour and 55 minutes; 76% of infusions completed within 2 hours  
• Two AEs with no grade 3/4 IRRs |
| *ASH 2005: Abstract 4777* (NHL, CLL; R-chemo, R-monotherapy) | Pre-medication: acetaminophen, promethazine, hydrocortisone | |
| Salar A, et al. | • 375 mg/m² using standard infusion rate for first infusion  
• Subsequent infusions over 90 minutes (20% of the dose in the first 30 minutes, the remaining 80% over 60 minutes) | • Data from 70 patients and 319 rapid infusions  
• No grade 3/4 AEs  
• Three patients developed symptoms, all were grade 1  
• Rapid infusion was well tolerated, both in patients who received steroids and in patients who did not |
| *Eur J Haematol* 2006 (CD20+ disease; R-chemo with or without steroids) | Pre-medication: acetaminophen, diphenhydramine, methylprednisolone given only to patients receiving steroid-containing chemotherapy | |
| Provencio M, et al. | • 375 mg/m² using standard infusion rate for first course  
• Subsequent courses using constant infusion rate over 60 minutes | • Data on 40 patients given a total of 233 infusions  
• IRRs reported included fever (n = 1), chills (n = 2), and limited cutaneous reaction with rash (n = 2), all grade 1  
• Voluminous mass and advanced age was not associated with increased toxicity  
• Rituximab was well tolerated with no additional toxicity when added to CHOP |
| *Ann Oncol* 2006 (DLBCL, low-grade lymphoma, Hodgkin’s lymphoma; R-chemo[R-CHOP, n = 27], R-monotherapy) | **Pre-medication:** acetaminophen, 1g IV, dexchlorpheniramine (5 mg orally), steroids recommended by each therapeutic protocol | |
| Sehn LH, et al. | • 375 mg/m² using standard infusion rate for first course  
• Subsequent courses over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes) | • Data from 150 patients receiving rituximab as a component of corticosteroid-containing chemotherapy and 56 patients receiving R-maintenance therapy  
• No grade 3/4 reactions  
• No increase in minor IRRs  
• Rituximab was well tolerated when added to chemotherapy or as maintenance therapy |
<p>| <em>Blood</em> 2007 (DLBCL, FL, other NHL; R-chemo, R-maintenance) | <strong>Pre-medication:</strong> corticosteroids for R-chemo and no pre-medication for R-maintenance | |</p>
<table>
<thead>
<tr>
<th>Study/Patient population</th>
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<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology setting</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
| Gibbs S, et al. EHA 2007 Abstract 0708 (DLBCL; R-CHOP) | - 375 mg/m² using standard infusion rate for first infusion  
  - Subsequent courses over 90 minutes  
  **Pre-medication:** chlorphenamine (8 mg), prednisolone (100 mg), acetaminophen (1 g), and tropisetron (5 mg) | - Data from 61 patients given 250 rapid infusions  
  - One patient had a grade 1 reaction during initial standard-rate infusion; all patients progressed to the accelerated protocol  
  - All rapid infusions were well tolerated with no IRRs |
| Milone J, et al. ASH 2007 Abstract 4503 (NHL, CLL; R-CHOP or R-maintenance) | - All patients had previously received rituximab at standard infusion rate for ≥1 infusion without grade 3/4 toxicity  
  - Subsequent courses over 90 minutes (20% of dose over first 30 minutes, remaining 80% over 60 minutes)  
  **Pre-medication:** oral acetaminophen, hydrocortisone (IV), diphenhydramine | - Data from 31 patients and 67 rapid infusions  
  - Four patients had grade 1 AEs and one patient developed a grade 3 AE and withdrew from rapid protocol  
  - Rapid infusion was safe and well tolerated |
| El-Agnaf MR, et al. Leuk Lymphoma 2007 (DLBCL, FL; R-CHOP, R-CVP) | - 375 mg/m² using standard infusion rate for first infusion  
  - Subsequent infusions over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes)  
  **Pre-medication:** chlorphenamine (10 mg IV), corticosteroids (hydrocortisone, 100 mg IV), acetaminophen (1 g) 30 minutes prior | - Data from 17 patients and 73 rapid infusions  
  - No AEs reported  
  - Rapid infusion was safe and well tolerated |
| Siano M, et al. ASH 2007 Abstract 3411 (DLBCL, FL, indolent and aggressive NHL; most R-chemo) | - 375 mg/m² at an initial infusion rate of 200 mg/h in the first cohort and increased by 100 mg/h in each subsequent cohort  
  - Rate increased by 100 mg/h every 30 minutes within each cycle to the prescribed total dose  
  - In each subsequent infusion, initial rate increased by 100 mg/h to a maximal rate of 700 mg/h  
  **Pre-medication:** Standard antihistamines and acetaminophen | - Data from 32 patients and 128 cycles  
  - All patients tolerated the increased infusion rate without major side effects  
  - Concluded that rituximab could be administered safely as a one-hour infusion without steroid pre-medication in patients with normal cardiac function who had already received at least one rituximab dose in the previous three months |
  - 82.5% of patients used standard infusion rate for the first maintenance infusion  
  - At one year, 54% patients were receiving rapid infusion | - Data from 545 patients and 5,579 combined standard and rapid infusions  
  - One SAE with standard infusion, but otherwise no SAEs within 24 hours of the maintenance infusion, including those receiving rapid infusion  
  - 141 SAEs recorded in 104 patients who received at least 1 infusion (all but 19 considered unrelated)  
  - Rapid infusion protocol was well tolerated as maintenance therapy |
| Al Zahrani A, et al. J Oncol Pharm Pract 2009 (NHL; R-chemo) | - 375 mg/m² using standard infusion rate for first course  
  - Subsequent courses over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes) | - Data from 21 patients and 126 infusions  
  - Rapid infusion was well tolerated with no grade 3/4 IRRs |
<table>
<thead>
<tr>
<th>Study/Patient population</th>
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<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peinert S, et al.</td>
<td>• Standard infusion rate for first infusion</td>
<td>• Data from 2 cohorts totalling 108 patients and 284 rapid infusions</td>
</tr>
<tr>
<td>EHA 2009: Abstract 0424</td>
<td>• Subsequent infusions over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes)</td>
<td>• No grade 3/4 AEs</td>
</tr>
<tr>
<td>(DLBCL, FL, CLL, indolent NHL; most R-chemo)</td>
<td><strong>Pre-medication:</strong> Standard including corticosteroids</td>
<td>• Only 2/284 (0.7%) administrations associated with IRRs, which were resolved with interruption for 30 minutes and additional antihistamine and corticosteroids</td>
</tr>
<tr>
<td>Provencio M, et al.</td>
<td>• See Provencio M, et al. 2006</td>
<td>• Liberated resources as a result of reduced infusion times were used for 15 additional treatments</td>
</tr>
<tr>
<td>Leuk Lymphoma 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NHL; R-chemo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 375 mg/m² using standard infusion rate for first infusion</td>
<td>• Data from 54 patients and 105 rapid infusions</td>
<td></td>
</tr>
<tr>
<td>• Subsequent infusions given over 60 minutes</td>
<td>• No significant IRRs were noted</td>
<td></td>
</tr>
<tr>
<td><strong>Rheumatology setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farawi R, Roth K</td>
<td>• First infusion of first course using standard infusion rate</td>
<td>• Survey of 20 major cancer centres in the UK showed that 70% of centres were using rapid 90-minute infusion protocol</td>
</tr>
<tr>
<td>EULAR 2010: Abstract FRI0203</td>
<td>• All subsequent infusions in all courses over 2 hours, with an increase in dose every 30 minutes, for a total of 1000 mg per infusion</td>
<td>• Data suggest that rapid infusion does not cause relevant cardiac toxicity; however, there was a high percentage of reductions in LVEF &gt;10%</td>
</tr>
<tr>
<td><strong>Pre-medications:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acetyaminophen (1000 mg IV), diphenhydramine (50 mg orally), methylprednisolone (100 mg IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bukh G, et al.</td>
<td>• Initial infusion rate for the first cycle was 50 mL/h, increased by 50 mL/h every 30 minutes up to 200 mL/h (3.25 hours in total)</td>
<td>• One patient reported minor IRR, which was resolved during the infusion</td>
</tr>
<tr>
<td>ACR 2008: Abstract 1885</td>
<td>• Next cycle was given initially at 200 mL/h, increased by 200 mL/h after 30 minutes up to 400 mL/h (1.5 hours in total).</td>
<td>• Rapid infusion protocol was safe and well tolerated in this community setting</td>
</tr>
<tr>
<td><strong>Pre-medications:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acetyaminophen (1 g orally), methylprednisolone (100 mg IV), clemastine (1 mg IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoeffel DA, et al.</td>
<td>• First infusion of each course using standard infusion rate</td>
<td>• Data from 13 patients and 14 treatment courses</td>
</tr>
<tr>
<td>EULAR 2008: Abstract FRI0161</td>
<td>• Second infusion of each course over 67 minutes (range: 37–150 minutes)</td>
<td>• One patient experienced a grade 1 AE and one patient had to stop treatment after one hour due to IRRs</td>
</tr>
<tr>
<td><strong>R-chemo</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; AE = adverse event; SAR = serious adverse event; ASH = American Society of Hematology; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; EHA = European Hematology Association; EULAR = European League Against Rheumatism; FL = follicular lymphoma; IRR = infusion-related reaction; ITP = idiopathic thrombocytopenic purpura; IV = intravenous; LVEF = left ventricular ejection fraction; NHL = non-Hodgkin’s lymphoma; R = rituximab; R-chemo = rituximab plus chemotherapy; R-maintenance = rituximab maintenance; R-monotherapy = rituximab as single agent; SLL = small lymphocytic leukemia
Appendix B. Rituximab infusion protocol at Princess Margaret Hospital

Rituximab (Rituxan®) Infusion Rate Guidelines and Hypersensitivity Reaction Algorithm

First infusion: Rituximab in normal saline (1 mg/mL) – Infuse 50 mL/hr) for first hour, then increase by 50 mg/hour every 30 minutes to a maximum of 400 mg/hr

Patient reacts

Assess patient for hypersensitivity reaction
See below for toxicity grading

Patient tolerates

Continue with infusion schedule

Grade 1 or 2 reactions
May continue with rituximab infusion
Administer PRN medications appropriate to reactions
- Diphenhydramine (Benadryl®) 50 mg iv x 1 for flushing, rash, urticaria
- Acetaminophen (Tylenol®) 650 mg po x 1 for fever
- Meperidine (Demerol®) 25–50 mg iv x 1 for rigors/chills
- Dimenhydrinate (Gravol®) 50 mg iv x 1 for nausea and/or vomiting
- Normal saline bolus 500–1000 mL iv for hypotension
- Famotidine (Pepcid®) 20 mg iv x 1 for additional histamine blocker
- O2, 2–4L nasal prongs
- Ventolin inhaler 2 puffs x 1 for wheezing

Grade 3 or 4 reactions – STOP infusion
Give PRN medications appropriate for reactions. If no resolution of symptoms, add hydrocortisone sodium succinate (SoluCortef®) 100 mg iv x 1 over 5 minutes. If still no improvement, page physician STAT

If symptoms improve, restart rituximab infusion at 50% of the iv rate at which the reaction occurred and continue with the escalation schedule

If patient reacts a 2nd time, restart after the clearance of symptoms at one infusion rate lower and continue at the rate without further escalation

For subsequent rituximab infusion, if patient experienced:
No reactions: Proceed with the accelerated rituximab infusion (90 minutes)*
Grade 1 or 2 reaction: Proceed with the accelerated rituximab infusion (90 minutes)*
Grade 3 or 4 reaction: Consult with physician to determine rate for subsequent infusion

*Accelerated rituximab infusion rate (90 minutes)
Rituximab in 250 mL of normal saline – Infuse 50 mL of the dose over 30 minutes (100 mL/hr), then infuse the remaining 200 mL over 60 minutes (200 mL/hr)

Toxicity grading

Grade 1 and 2
- Fever of 38°C up to and including 40°C
- Mild to moderate rigors/chills
- Intense and wide spread itching or pruritis
- Rash, flushing, and urticaria (duration is less than 24 hours)
- Hypoxia – decreased O2 saturation with activity and requires intermittent oxygen treatment
- Symptomatic cough (may require narcotic medication, such as codeine)
- Dizziness that is not interfering with activity
- Wheezing and/or bronchospasm that is not interfering with activity
- Hypertension with or without symptoms (greater than 20 mmHg from baseline) - drug intervention may be required
- Hypotension with or without symptoms (less than 20 mmHg from baseline), that responds to intravenous fluid

Based on assessment finding, RN may treat patient’s symptoms accordingly with PRN medications

Grade 3 and 4
- Fever greater than 40°C
- Severe rigors/chills that are not responding to narcotics
- Urticaria and rash that lasts longer than 24 hours
- Symptomatic cough that is interfering with sleep or activity of daily living (ADL)
- Dizziness that is not interfering with ADL
- Wheezing, bronchospasm that are interfering with activity
- Hypoxia – O2 saturation is less than 88% at rest and requires continuous oxygen treatment
- Uncontrolled hypertension that requires more than one drug intervention
- Sustained hypotension that is equal to or lasting longer than 24 hours

Notify physician and respiratory therapist STAT if patient experiencing acute respiratory distress
References:
New Treatment Modalities

Novel Approaches in the Treatment of Relapsed/Refractory NHL

A number of exciting presentations on novel approaches for the treatment of patients with relapsed/refractory non-Hodgkin’s lymphoma (NHL) were given at ASH this year. This article presents highlights from four of these presentations.

• GA101, the first type II, glycoengineered and humanized monoclonal anti-CD20 antibody, demonstrates promising efficacy with very encouraging progression-free survival data and tolerability in heavily pre-treated relapsed and refractory patients with indolent NHL.

• Subcutaneous rituximab is safe, can be delivered quickly, and provides serum exposure comparable to the approved intravenous rituximab formulation in patients with follicular lymphoma during maintenance treatment.

• The combination of bendamustine plus rituximab provides superior progression-free survival in patients with relapsed follicular, other indolent, or mantle cell lymphoma as compared to combined fludarabine and rituximab.

• In high-risk patients with relapsed, rituximab-naïve or rituximab-sensitive follicular lymphoma, bortezomib in combination with rituximab provides significantly longer progression-free survival as compared to rituximab treatment alone.


Encouraging progression-free survival data with GA101 from a phase II study in patients with relapsed/refractory indolent NHL

Background
GA101 is the first type II, glycoengineered, humanized monoclonal anti-CD20 antibody with promising phase I and phase II results in non-Hodgkin’s lymphoma (NHL). At ASH 2010, Salles and colleagues presented new and encouraging progression-free survival (PFS) data from their open-label, multicentre, randomized study with single-agent GA101.

Study design
Forty (40) eligible patients with CD20+ indolent NHL, including 34 patients with follicular lymphoma (FL), 3 with marginal zone lymphoma, and one each with Waldenstrom’s macroglobulinemia, lymphocytic lymphoma, and lymphoplasmacytic lymphoma, were randomized to receive GA101 in a low-dose (LD, n = 18) or a high dose (HD, n = 22) cohort.

• GA101 was given on days 1, 8, and 22, and then every 21 days for a total of 9 infusions.

○ In the LD cohort, 400 mg GA101 was given at all infusions (total dose of 3600 mg).

○ In the HD cohort, 1600 mg GA101 was given on days 1 and 8, and 800 mg for subsequent infusions (total dose 8800 mg).

• Primary endpoint was end of treatment response (EOR), assessed 4 weeks after last infusion (28 weeks after treatment start).

• Secondary objectives were safety, pharmacokinetics, and PFS.
Key findings

- There were no significant differences in demographics and baseline tumour burden between the two cohorts.
  - 78% of patients completed all scheduled 9 infusions.
- Patients were heavily pre-treated (median 3 prior therapies), with 55% of patients not responding to or relapsing within six months after a previous rituximab-containing regimen (rituximab refractory).
- Median observation time was 13.9 months (range: 2–17.2 months).
- EOR was 17% in the LD cohort and 55% in the HD cohort. (Table 1)
  - Of note, 6 of 22 rituximab-refractory patients (5 HD, 1 LD) responded, with an EOR response of 50% in rituximab-refractory patients in the HD cohort (5/10).

- Responding patients from both LD and HD groups appeared to have higher GA101 plasma concentrations compared to non-responding patients.
- Median PFS was 6 months (range: 1.1–16.9+ months) and 11.3 months (range: 1.8–14.2+ months) for the LD and HD cohorts, respectively (HR: 0.55, 95% CI: 0.24–1.27). (Figure 1)
- Of 15 responding patients at EOR (complete response [CR] and partial response [PR]), 9 have an ongoing response in follow-up (LD = 2, HD = 7), with 2 patients with PR converting to CR (LD = 1, HD = 1) and another PR (HD) to unconfirmed complete response (CRu).
- Two (2) patients (LD = 1, HD = 1) in follow-up converted from EOR stable disease (SD) to PR: one patient with an ongoing response and the other subsequently relapsing; therefore, 10 patients currently have an ongoing response.

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Table 1. Response data in patients with indolent NHL

<table>
<thead>
<tr>
<th>GA101 cohort</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Unknown</th>
<th>OR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment response* by dose cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low-dose (n = 18)</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>0</td>
<td>17%</td>
</tr>
<tr>
<td>High-dose (n = 22)</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>55%</td>
</tr>
<tr>
<td>End of treatment response in rituximab-refractory† patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose (n = 13)</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>High-dose (n = 21)</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>50%</td>
</tr>
</tbody>
</table>

* End of treatment response is defined as 28 days from the last GA101 infusion using Cheson 1999 response criteria.
† Rituximab-refractory patients are defined as those patients who have had no response or a response of <6 months to a rituximab-containing regimen (rituximab monotherapy or in combination with chemotherapy) at any time point in their treatment history.

CR = complete response; NHL = non-Hodgkin’s lymphoma; OR = overall response; PD = progressive disease; PR = partial response; SD = stable disease
• GA101 was well tolerated in both cohorts with the most common adverse events (AEs) being infusion-related reactions (LD 72%, HD 73% of patients), mostly grade 1/2.
• During treatment, related grade 3/4 hematological AEs were transient neutropenia (n = 3 in HD), febrile neutropenia (n = 1 in HD), and thrombocytopenia (n = 1 in HD).
• Nine (9) patients experienced a total of 12 severe adverse events (SAEs) during the treatment period, with 4 related to GA101 (HD, n = 4: herpes zoster, febrile neutropenia, pancreatitis, neutropenia), and 2 patients in the additional follow-up period, with SAEs of pyrexia (LD) and bacteremia (HD), both unrelated to GA101.
• Even though no B-cell recovery has been observed to date, no serious infections have been reported.

Key conclusion

- As a single agent, GA101 has promising efficacy with very encouraging PFS data and is well tolerated in heavily pre-treated relapsed and refractory indolent NHL patients, indicating a survival advantage for those patients in the HD cohort (1600/800 mg).

References:


Subcutaneous rituximab in patients with follicular lymphoma as part of maintenance treatment

Background

Rituximab-containing regimens have demonstrated significant clinical efficacy and have extended overall survival in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).1–3 Currently, rituximab is administered as an intravenous (IV) infusion over several hours, with infusion times ranging from 90 minutes to 6 hours.

Long infusion times are often inconvenient for patients and occupy a large amount of ambulatory chair time, resulting in increased economic costs for both healthcare providers and patients. Switching to a subcutaneous (SC) administration for other monoclonal antibodies has resulted in improved tolerability, with fewer infusion-related reactions, shorter administration times, increased patient convenience, and improved cost-effectiveness.

Preclinical experiments in cynomolgus monkeys have suggested that an SC dosing route does not influence the efficacy of rituximab.4 SC administration of rituximab could significantly simplify treatment, shortening administration to less than 10 minutes, and ameliorate patient experience. Recombinant human hyaluronidase (rHuPH20) has been developed and approved to better dispersion and absorption of co-administered drugs.5,6 When combined with rituximab, rHuPH20 allows for injection of volumes larger than 10 mL to be safely and comfortably administered subcutaneously.
Salar and colleagues are currently conducting clinical trial BP22333 (NCT00930514), a two-stage, randomized, open-label, multicentre phase Ib study of a new SC rituximab formulation with rHuPH20 in patients with FL. Objectives of the study are to determine the SC rituximab dose giving comparable exposure to that of standard IV rituximab and to assess the safety and tolerability of SC rituximab in FL patients during maintenance treatment. Stage 1 results of the study were presented at ASH 2010.

**Study design**

- Eligible patients with previously treated or untreated FL (grade 1, 2 or 3a) who had responded to a rituximab-containing induction regimen and had received at least one dose of rituximab IV (375 mg/m²) in the maintenance setting were included in the study.

- Inclusion criteria were as follows:
  - adult patients, ≥18 years of age;
  - CD20-positive follicular non-Hodgkin’s lymphoma (NHL);

- partial or complete response (PR or CR) at the end of induction treatment with rituximab;
- must have completed induction treatment and received ≥1 dose of IV rituximab maintenance treatment;
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

- Exclusion criteria were as follows:
  - histological evidence of NHL transformation or types of NHL other than FL;
  - presence or history of central nervous system (CNS) disease;
  - history of malignancy other than follicular NHL, which could affect compliance with protocol or interpretation of results;
  - recent major surgery (within 4 weeks prior to screening, excluding lymph node biopsy).

- Baseline characteristics of patients in the study population (n = 124) are shown in Table 1.

### Table 1. Baseline characteristics of follicular lymphoma study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rituximab cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>375 mg/m² IV (n = 16)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>57.0 (35–82)</td>
</tr>
<tr>
<td>Regimen q2m, n (%)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Regimen q3m, n (%)</td>
<td>7 (44)</td>
</tr>
</tbody>
</table>

*IV = intravenous; q2m = every 2 months; q3m = every 3 months; SC = subcutaneous*
Patients were randomized to one of four rituximab maintenance treatment groups and received a single dose of rituximab:
- 375 mg/m² IV (n = 16)
- 375 mg/m² SC (n = 34)
- 625 mg/m² SC (n = 34)
- 800 mg/m² SC (n = 40)

After this single dose, all patients received maintenance rituximab IV every 2 or 3 months for a further year.

Once the final fixed SC dose had been determined, patients in the SC cohorts who had completed one year of maintenance therapy could choose to either switch to rituximab SC or continue rituximab IV until completion of the 2-year maintenance period.

**Key findings**

- Safety data from a total of 124 patients demonstrated that rituximab SC was generally well tolerated.
- No clinically significant observations or treatment-related serious adverse events (SAEs) were reported.
- A total of 157 adverse events (AEs) were reported in 65 patients (52.4%).
- The most commonly documented AE was administration-associated reaction (AAR), including rash, erythema, and mild discomfort, in 30 patients.
- AARs were reversible, predominantly mild in intensity, and only 1 event necessitated any treatment (metoclopramide for nausea).
- Overall, the AE profile was not significantly different from that expected in patients treated with IV rituximab; after AAR, the most frequent AEs were gastrointestinal disorders (n = 17) and mild infections (n = 18).
- Four SAEs were observed in 4 separate patients, all reported as unrelated to study medication.
- There were no AEs leading to death, withdrawal, or treatment discontinuation.
- The incidence and severity of AEs appeared balanced between cohorts.
- There was no apparent difference in frequency of AEs reported in patients receiving only IV rituximab and those receiving 1 dose of SC rituximab.
- No apparent dose-related increase in the frequency and severity of AEs was seen within the cohorts receiving SC rituximab.
- The total volume administered SC in each patient ranged between 4.4 –15.0 mL.
- The average injection duration was 1.9 mL/min (range: 0.4–3.8).
- Rituximab maximum serum concentrations in the SC cohorts occurred between day 2 and day 8 (48 h and 168 h). (Figure 1)
- Pharmacokinetic parameters were linear with respect to dose over the range of SC doses administered (375, 625, and 800 mg/m²).

![Figure 1. Mean (± SD) serum concentration of rituximab over time by administration schedule](image-url)
- Rituximab concentrations on day 28 and the extent of serum exposure (AUC0–57) in patients administered 625 mg/m² SC rituximab were comparable to those in patients administered the standard IV rituximab dose of 375 mg/m². (Table 2).

- Simulations of mean C_{trough} values based on body surface area data from 54 patients predicted that a fixed dose of SC rituximab of 1400 mg would be non-inferior to the IV rituximab dose of 375 mg/m².

### Table 2. Pharmacokinetic parameters by study cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Regimen</th>
<th>C_{trough} (µg/mL)</th>
<th>C_{max} (µg/mL)</th>
<th>AUC_{0-57} (day* µg/mL)</th>
<th>AUC_{0-85} (day* µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>375 mg/m² IV mean±SD (n)</td>
<td>q2m</td>
<td>45.2±32.5 (8)</td>
<td>243±58.6 (9)</td>
<td>4830±1550 (9)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>q3m</td>
<td>14.6±6.76 (5)</td>
<td>238±50.9 (7)</td>
<td>–</td>
<td>4300±946 (7)</td>
</tr>
<tr>
<td>375 mg/m² SC mean±SD (n)</td>
<td>q2m</td>
<td>19.1±11.7 (15)</td>
<td>70.2±21.6 (17)</td>
<td>2380±944 (17)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>q3m</td>
<td>13.8±10.0 (11)</td>
<td>68.0±22.4 (17)</td>
<td>–</td>
<td>2880±1240 (16)</td>
</tr>
<tr>
<td>625 mg/m² SC mean±SD (n)</td>
<td>q2m</td>
<td>42.5±18.0 (15)</td>
<td>130±33.6 (18)</td>
<td>4530±1580 (18)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>q3m</td>
<td>15.6±9.76 (9)</td>
<td>105±38.8 (15)</td>
<td>–</td>
<td>4130±1700 (15)</td>
</tr>
<tr>
<td>800 mg/m² SC mean±SD (n)</td>
<td>q2m</td>
<td>52.1±21.0 (16)</td>
<td>144±42.9 (22)</td>
<td>5120±2010 (20)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>q3m</td>
<td>19.9±11.8 (7)</td>
<td>156±33.9 (18)</td>
<td>–</td>
<td>5740±1710 (18)</td>
</tr>
</tbody>
</table>

*AUC = area under the curve; IV = intravenous; q2m = every 2 months; q3m = every 3 months; SC = subcutaneous; SD = standard deviation*

### Key conclusions

- Subcutaneous rituximab can be delivered quickly, comfortably, and safely, while achieving serum exposure comparable to the approved intravenous rituximab formulation in FL patients during maintenance treatment.

- These results support further testing of subcutaneous rituximab, and a fixed dose of 1400 mg SC rituximab has been selected for formal C_{trough} non-inferiority testing in stage 2 of the trial.

References:
Background

A number of newer agents and combinations are under investigation in patients with indolent lymphoma. New agents of interest include bendamustine, lenalidomide, and bortezomib. Bendamustine plus rituximab have been shown in preclinical studies to be synergistic and to have non-overlapping toxicities; this combination has previously demonstrated its activity in patients with relapsed indolent and mantle cell lymphoma.1,2

At ASH 2009, Rummel and colleagues presented results from their previous phase III German Study Group Indolent Lymphomas (StiL) study comparing bendamustine plus rituximab to rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). The combination of bendamustine and rituximab improved progression-free (PFS) and complete response (CR) rates, while showing a better tolerability profile, when compared with R-CHOP as first-line treatment for patients with advanced follicular, other indolent, and mantle cell lymphomas. Median PFS improved by 20 months with the bendamustine-rituximab combination, and the CR rate improved by approximately one third.3

At ASH 2010, Rummel and colleagues, on behalf of StiL, presented final results from another phase III study (NHL-2-2003) that compared the combination of bendamustine plus rituximab (R-bendamustine) to fludarabine plus rituximab (FR) in relapsed follicular, other indolent, and mantle cell lymphomas.4

Study design

- A total of 219 patients with relapsed stage II (bulky disease 7.5 cm), III, or IV follicular, indolent, or mantle cell lymphoma were randomized to rituximab 375 mg/m² (day 1) plus either bendamustine 90 mg/m² (days 1 and 2) or fludarabine 25 mg/m² (days 1–3) every 28 days for a maximum of 6 cycles.
- Prophylactic use of antibiotics or granulocyte-colony stimulating factor (GCSF) was not generally recommended; however in cases of severe granulocytopenia, GCSF use was permitted.
- Primary endpoint was progression-free survival (PFS) with the objective of proving non-inferiority of R-bendamustine versus FR, defined as a difference of less than 15% in PFS after 1 year (α = 5%, β = 20%).
- Secondary endpoints included response rates, time to next treatment, event-free survival (EFS), overall survival (OS), and safety (acute and late toxicities, infectious complications).
- The protocol was amended in 2006 to allow rituximab maintenance therapy (rituximab 375 mg/m² every 3 months for up to 2 years) in both arms, following regulatory approvals in this setting.
- Eleven (11) patients were not evaluable due to protocol violations, and were not followed further; a total of 208 patients were evaluable for the final analysis (109 R-bendamustine; 99 FR).
- There were no significant differences between arms for patient characteristics, including age, stage, lactic dehydrogenase (LDH), international prognostic index (IPI), follicular IPI (FLIPI), bone marrow infiltration, and extranodal involvement.
- Most patients had stage IV (71.6% R-bendamustine; 60.6% FR) or stage III disease (21.1% R-bendamustine and 25.3% FR).
- Median patient age was 68 years (range: 38–87 years).
- Patients had received a median of 1 prior therapy (range: 1–7).
- Histological subtypes were distributed equally between the R-bendamustine and FR arms: follicular 45.9% and 47.5%, respectively; Waldenström’s macroglobulinemia 11.9% and 11.1%; mantle cell 20.2% and 21.2%; other indolent lymphomas 23% and 20.2%.

Study design of StiL NHL 2-2003 trial*

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*Bendamustine-Rituximab + 2 years rituximab maintenance
Fludarabine-Rituximab + 2 years rituximab maintenance

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Follicular
Waldenström’s
Malignant lymphoma
Small lymphocytic
Mantle cell

*Protocol amended in July 2008 to allow rituximab maintenance following regulatory approval in this setting.
Key findings

• A median number of 6 cycles were given in both treatment arms, with 75.2% of R-bendamustine patients and 53.4% of FR patients receiving 6 cycles, respectively. At the time of this analysis (June 2010), the median observation time was 33 months.

• The overall response rate was significantly higher with R-bendamustine than with FR (82% vs. 49%, respectively; p < 0.0001). (Table 1)

• The CR rate with R-bendamustine was also significantly higher than that with FR (39% vs. 16%; p = 0.0004).

• Median PFS was significantly prolonged with R-bendamustine compared with FR (30.4 months vs. 11.2 months; hazard ratio [HR] 0.50, 95% CI: 0.34–0.68; p <0.0001). (Figure 1)

• OS did not differ significantly between arms, with 42 and 46 deaths documented in the R-bendamustine and FR arms, respectively. (Figure 2)

• There were no significant differences in the rates of alopecia, stomatitis, erythema, allergic reactions, peripheral neuropathy, or infectious episodes between groups.

Table 1. Response rates in NHL patients treated with R-bendamustine versus FR

<table>
<thead>
<tr>
<th>Response</th>
<th>R-bendamustine (%)</th>
<th>FR (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>82</td>
<td>49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete response</td>
<td>39</td>
<td>16</td>
<td>0.0004</td>
</tr>
<tr>
<td>Partial response</td>
<td>43</td>
<td>33</td>
<td>–</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6</td>
<td>16</td>
<td>–</td>
</tr>
<tr>
<td>Progression</td>
<td>7</td>
<td>30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>5</td>
<td>4</td>
<td>–</td>
</tr>
</tbody>
</table>

FR = fludarabine plus rituximab; R = rituximab

Figure 1. Progression-free survival* in NHL patients treated with R-bendamustine versus FR

*Median observation period was 33 months.

CI = confidence interval; HR = hazard ratio; FR = fludarabine plus rituximab; R = rituximab

• Hematologic toxicities were also similar between arms: 8.9% grade 3/4 neutropenia with R-bendamustine vs. 9.1% with FR; 11.8% grade 3/4 leukocytopenia with R-bendamustine vs. 12.4% with FR.

• The overall incidence of serious adverse events was similar for the R-bendamustine and FR groups (17.4% and 22.2%, respectively).

• An unplanned sub-analysis of the small group of 40 patients who received rituximab maintenance therapy (23 R-bendamustine, 17 FR), compared with those who did not, showed that R-maintenance significantly prolonged OS (median not reached vs. 59.3 months [HR 0.29, 95% CI: 0.22–0.82; p = 0.0104]) and PFS (median 56.0 months vs. 24.7 months [HR 0.37, 95% CI: 0.30–0.74; p <0.0013]).

Key conclusions

■ R-bendamustine was more effective than FR in patients with relapsed follicular, other indolent, or mantle cell lymphoma, demonstrating higher response rates and longer PFS.

■ This study confirmed the high anti-lymphoma activity of R-bendamustine.

References:
Bortezomib plus rituximab is more effective than rituximab alone in patients with relapsed, rituximab-naïve or rituximab-sensitive follicular lymphoma

Background

Bortezomib and rituximab have demonstrated additive activity in preclinical models,1,2 and the combination has been shown to be active and well tolerated in a phase II study in patients with follicular lymphoma (FL).3 At ASH 2010, Coiffier and colleagues presented results from a randomized, open-label, multicentre, international, phase III clinical trial (LYM3001) that compared the efficacy and safety of bortezomib plus rituximab (R-bortezomib) versus rituximab (R) alone in patients with relapsed or refractory, rituximab-naïve or rituximab-sensitive FL.4

Study design

• Between April 2006 and August 2008, a total of 676 intent-to-treat (ITT) patients with FL were enrolled in the randomized, open-label, multicentre, international LYM3001 phase III clinical trial, which was conducted in 164 centres in 29 countries across Europe, the Americas, and the Asia-Pacific.

• Inclusion criteria were as follows:
  ◦ grade 1/2 FL with ≥ 1 measurable lesion;
  ◦ documented relapse or progression following prior therapy;
  ◦ rituximab-naïve or sensitive (response to and TTP of ≥ 6 months for prior rituximab-containing therapy);
  ◦ Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;
  ◦ adequate hematologic, renal, and hepatic function.

• Exclusion criteria were as follows:
  ◦ grade ≥ 2 peripheral neuropathy or neuropathic pain;
  ◦ clinical evidence of a transformation to an aggressive lymphoma.

• Patients were randomized to two study arms:
  ◦ R-bortezomib (n = 336): bortezomib 1.6 mg/m² on days 1, 8, 15, and 22 every 5 weeks for 5 cycles; rituximab 375 mg/m² on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 2–5;
  ◦ R alone (n = 340): rituximab 375 mg/m² on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 2–5.

• Treatment duration was 25 weeks, with 8 doses of rituximab in each arm.

• The study population was stratified by follicular lymphoma international prognostic index (FLIPI) score, prior rituximab treatment, time since last therapy, and geographical region.

• Baseline characteristics for age, region, previous lines of therapy, and prior rituximab treatment were balanced between the two arms; baseline disease characteristics are described in Table 1.

• Primary endpoint was progression-free survival (PFS).

• Secondary endpoints included overall response (OR) rate, complete response (CR), duration of response (DOR), time to progression (TTP), time to next treatment, 1-year overall survival (OS), safety/tolerability, and quality of life (QoL) measured by EORTC OLQ-C30.

• Response/progression was assessed by independent radiology committee (IRC) using modified International Workshop Response Criteria.

• Clinical data cut-off was June 15, 2010.
Key findings

- Treatment completion rates were similar between arms.
  - Median number of cycles was 5 (range: 1–5) in both arms.
  - Seventy-one percent (71%) and 72% of patients completed all 5 cycles in the R-bortezomib arm and the R alone arm, respectively.
  - Twenty-eight percent (28%) and 29% of patients discontinued prematurely in the R-bortezomib arm and the R alone arm, respectively.
  - Reasons for discontinuation varied by arm.
  - R-bortezomib was found to be associated with superior response rates and durability of response versus R alone. (Table 2)
  - R-bortezomib was also associated with significant improvement in PFS (primary endpoint) versus R alone. (Figure 1)

Table 1. Baseline disease characteristics in the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rituximab (n = 340)</th>
<th>R-bortezomib (n = 336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0</td>
<td>177 (52)</td>
<td>162 (48)</td>
</tr>
<tr>
<td>1</td>
<td>141 (41)</td>
<td>153 (46)</td>
</tr>
<tr>
<td>2</td>
<td>22 (7)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>FLIPI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>81 (24)</td>
<td>77 (23)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>119 (35)</td>
<td>120 (36)</td>
</tr>
<tr>
<td>High</td>
<td>140 (41)</td>
<td>139 (41)</td>
</tr>
<tr>
<td>High tumour burden (modified GELF criteria)</td>
<td>179 (53)</td>
<td>185 (55)</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21 (6)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>II</td>
<td>40 (12)</td>
<td>35 (11)</td>
</tr>
<tr>
<td>III</td>
<td>135 (40)</td>
<td>115 (34)</td>
</tr>
<tr>
<td>IV</td>
<td>144 (42)</td>
<td>168 (50)</td>
</tr>
</tbody>
</table>

Table 2. Response rates and durability of response in response-evaluable population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rituximab (n = 324)</th>
<th>R-bortezomib (n = 315)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR rate</td>
<td>160 (49)</td>
<td>199 (63)</td>
<td>0.569 (0.415–0.780)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>59 (18)</td>
<td>79 (25)</td>
<td>0.665 (0.455–0.973)</td>
<td>0.035</td>
</tr>
<tr>
<td>PR</td>
<td>101 (31)</td>
<td>120 (38)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stable disease</td>
<td>120 (37)</td>
<td>78 (25)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>44 (14)</td>
<td>38 (12)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Durable response (&gt;6 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall durable response</td>
<td>124 (38)</td>
<td>159 (50)</td>
<td>0.608 (0.444–0.833)</td>
<td>0.002</td>
</tr>
<tr>
<td>Durable CR</td>
<td>54 (17)</td>
<td>76 (24)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Key conclusions

- Significant PFS benefit with R-bortezomib was observed in high-risk patients who had high FLIPI scores or high tumour burden (according to modified Groupe d’Etude des Lymphomes Folliculaires [GELF] criteria). (Figure 2)

- While median time to next treatment (TTNT) was significantly delayed in the combined treatment arm, median OS was not reached in either arm (HR 0.971, 95% CI: 0.712–1.325; \( p = 0.8535 \)).

- R-bortezomib was associated with excess risk of grade ≥3 diarrhea, neutropenia, and infections versus rituximab alone.

- Peripheral neuropathy of any grade developed in 17% of patients receiving R-bortezomib versus 1% of patients receiving R alone.

- Most peripheral neuropathy events in bortezomib-treated patients were reversible: 71% of events were completely resolved and 78% either resolved or improved.

- Median time to improvement or resolution was 58 days.

- Median time to resolution was 109 days.

- While QoL improved after treatment in both arms, no clinically significant difference in QoL between the two arms was seen.

References:

Intravenous (IV) rituximab has proven to be a very effective therapy for the treatment of lymphoma — aggressive as well as indolent. There is no question that physicians would prefer to administer the drug more easily if this were possible. Therefore, I found the phase Ib study by Salar, et al. of a new subcutaneous (SC) rituximab formulation with recombinant human hyaluronidase (rHuPH20) an interesting and intriguing, albeit complicated, study. Patients were randomized to four treatment groups, and a complicated methodology was used to calculate the subcutaneous dose that was equivalent to established intravenous doses. Notwithstanding these complexities, the study is important.

One of our main concerns as clinicians is toxicity, so I find it reassuring to note that no treatment-related adverse events were observed in this study. However, four serious AEs were reported. Although the investigators did not feel that these AEs were related to treatment, it would have been reassuring to have more information about the nature of these events.

IV rituximab has been studied in many thousands of patients, and we know of its established efficacy. While preliminary work suggests that SC rituximab may be as safe as IV rituximab, we will need more studies in larger patient populations to demonstrate that this formulation is as effective as IV rituximab. The Salar et al. study is an important first step in this direction.

Bendamustine, part alkylator and part purine analogue, is arguably the most exciting new agent for the treatment of follicular lymphoma in some years and has generated a lot of interest in Canada and elsewhere. Most in the hematologic oncology field are very impressed with the results of studies using bendamustine in indolent lymphomas. The study by Rummel et al., comparing the novel combination of bendamustine and rituximab (R-bendamustine) with fludarabine-rituximab (FR) in relapsed follicular, other indolent, and mantle cell lymphoma, is therefore one of the most important studies to be presented at the ASH meeting this year.

From a Canadian perspective, there are several difficulties with the information presented by the investigators. First, it is not clear if all patients in the study were symptomatic or if fludarabine was given intravenously or orally. The latter is important information for Canadian physicians, because oral fludarabine is available in Canada, unlike in the US. Second, no information was provided about the frequency of granulocyte-colony stimulating factor (GCSF) use. Third, Canadian hemato-oncologists do not generally group follicular lymphoma and other indolent lymphomas with mantle cell lymphoma as the investigators have done in this study. Also, since the central nervous system (CNS) may be involved in patients with mantle cell lymphoma, information about the rates of CNS disease and CNS progression in the treatment arms would have been helpful.

Another consideration is that only 75% of patients in the R-bendamustine arm and only 50% in the standard FR arm received all 6 cycles of treatment. It would have been useful to know whether the reason was because patients progressed or because of toxicities like cytopenias and infections.

Notwithstanding these potential caveats, the study results are very impressive. Patients in the R-bendamustine arm showed a much higher overall response rate and greatly improved progression-free survival, compared to those in the FR arm.
New Treatment Modalities

Novel Therapies in CLL for Elderly Patients with Co-morbidities and Fludarabine-refractory Patients

Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) has been established as the treatment of choice in younger, physically fit patients with chronic lymphocytic leukemia (CLL). However, the majority of CLL patients are of advanced age (≥65 years), often with co-morbidities, and may not be able to tolerate this aggressive therapy. No standard treatment has yet been established for these patients or for other subsets of CLL patients, such as those with high-risk cytogenetic markers and bulky disease. However, several strategies are currently under investigation for these CLL populations, including reduced dosing of existing regimens, combining new agents with traditional therapies, and new monotherapies that show promising results, such as GA101.

In the elderly CLL population, a low-dose variation of FC/FCR regimens may have some efficacy. The alkylating drug chlorambucil also remains a valuable treatment option. The addition of CD20 antibodies (including the novel type II antibody GA101) to chlorambucil may enhance cytotoxicity and improve alkylator-based therapy in CLL. The efficacy of such regimens in elderly CLL patients with co-morbidity remains to be examined.

Alvocidib (flavopiridol), a cyclin-dependent kinase inhibitor, has demonstrated clinical activity in fludarabine-refractory CLL patients, particularly those with high-risk cytogenetic markers and bulky lymphadenopathy. Strategies employing monotherapy with alvocidib in this patient subset may therefore improve response and survival outcomes in CLL.

GA101 is a glycoengineered, type II anti-CD20 monoclonal antibody that has been shown to induce cytotoxicity in B-CLL cells through apoptosis and antibody-dependent cellular cytotoxicity (ADCC). In vitro studies have demonstrated improved efficacy over rituximab, while phase I trials have demonstrated favourable safety and toxicity profiles in patients with relapsed/refractory CLL. Further understanding of the mechanism of action of GA101 may result in promising new treatments strategies for CLL patients.

This article reports on four studies evaluating new treatments strategies and agents in CLL presented at ASH 2010:

- Results from a safety run-in phase of the CLL-11 trial indicate tolerability of chlorambucil plus GA101 in elderly/co-morbid CLL patients.
- A phase II trial demonstrated that low-dose FC/FCR regimens may be promising for elderly/co-morbid CLL patients.
- Interim data from a second phase II trial showed that monotherapy with alvocidib has stable clinical activity in a subset of CLL patients refractory to fludarabine.
- A preclinical study demonstrated that GA101 has superior overall activity to rituximab and ofatumumab.

References:
Chemoimmunotherapy with chlorambucil and GA101 in CLL patients with co-morbidities: results of the CLL-11 safety run-in phase

**Background**

The addition of CD-20 antibodies, including the glycoengineered type II antibody GA101, to chlorambucil (CLB) regimens to improve the efficacy of alkylator-based therapy in elderly patients with chronic lymphocytic leukemia (CLL) and co-morbidities has yet to be evaluated.\(^1\),\(^2\)

At ASH 2010, Goede and colleagues presented data from six patients in a run-in safety phase from the multicentre, international, three-arm CLL-11 trial initiated by the German CLL Study Group (GCLLSG). The trial will compare the efficacy of CLB alone, CLB plus rituximab (R-CLB) or CLB plus GA101 (G-CLB) in co-morbid CLL patients.\(^2\)

**Study design**

- Prior to opening randomization to the three study arms, a safety run-in phase including six patients with previously untreated CLL was initiated.
- Inclusion criteria were defined as a cumulative illness rating scale (CIRS) total score >6 and/or a creatinine clearance (CrCl) <70 mL/min; patients were enrolled to receive six cycles of G-CLB during the run-in phase.
- Patients received 6 cycles of G-CLB on the following treatment schedule:
  - CLB orally at 0.5 mg/kg of body weight on day 1 and day 15 of each cycle;
  - GA101 intravenously on day 1, day 8, and day 15 of cycle 1 and day 1 of cycles 2–6.
  - Each cycle consisted of 28 days.
- Stopping criteria was defined as one treatment-related death, or three episodes of febrile neutropenia or infections requiring antibiotic therapy during the first cycle.

**Key findings**

- All patients had previously untreated CD20-positive CLL and active disease according to NCI/IWCLL criteria.
- Median age was 76 years (range: 71–79 years); four of the six patients were male.
- Within this patient subset, median CrCl was 51 mL/min (range: 38–83 mL/min) and median CIRS total score was 8 (range: 5–9).

CLB = chlorambucil; CLL = chronic lymphocytic leukemia; G-CLB = chlorambucil plus GA101; R-CLB = chlorambucil plus rituximab
All six patients completed treatment, but two patients had significant dosing delays: one patient due to a mechanical ileus unrelated to treatment that required surgical intervention and prolonged neutropenia, and one patient due to a psychotic disorder and prolonged neutropenia.

Infusion-related reactions (IRRs) occurred in 5 patients, but all were mild (grade 1/2); all IRRs occurred at the first infusion with one exception.

Grade 3/4 afebrile neutropenias were seen in 5 of the 6 patients, with 10 episodes in total; 4 patients received granulocyte colony-stimulating factor (GCSF) with immediate response.

One patient had grade 3/4 thrombocytopenia with no patients developing grade 3/4 anemia.

There were five grade 1/2 infections during and after treatment, and no grade 3/4 infections. No febrile neutropenias or infections in the presence of neutropenia requiring antibiotic therapy were observed.

All six patients showed rapid clearing of lymphocytes from their peripheral blood within a few days of first dosing with G-CLB (response rates will be reported at the end of treatment).

After 3 cycles of treatment, palpable lymphadenopathy and hepatosplenomegaly at baseline disappeared in all six patients.

All patients responded to treatment. Data collection is on-going.

Key conclusions

- Chemoimmunotherapy with CLB plus GA101 appears to be feasible in CLL patients of advanced age (>70 years) with a high burden of co-morbidity.
- None of the stopping criteria defined for the CLL-11 run-in phase were met. The CLL-11 trial was therefore opened for randomization in April 2010.

References:

Smolej L, et al. ASH 2010: Abstract 2466

Low-dose FCR in the treatment of elderly/co-morbid patients with CLL/SLL: preliminary results of Project Q-Lite

Background
The combination of fludarabine, cyclophosphamide, and rituximab (FCR) is considered the treatment of choice in physically fit and previously treated patients with chronic lymphocytic leukemia (CLL). However, many patients cannot tolerate this aggressive treatment, either because of advanced age and/or serious co-morbid conditions. Fludarabine monotherapy has not been shown to be beneficial in elderly patients when compared to chlorambucil (CLB). For these patients, CLB has remained the standard of treatment in Europe and in many parts of Canada. However, low-dose fludarabine-based regimens have recently demonstrated promising results in small studies.

At ASH 2010, Smolej and colleagues presented preliminary data from Project Q-Lite by the Czech CLL Study Group. This study assessed the efficacy and safety of low-dose FC or FCR in patients with CLL or small lymphocytic lymphoma (SLL) deemed unfit for full-dose FCR due to advanced age and/or co-morbidities.

Study design
- Between March 2009 and December 2010, 102 patients with active CLL/SLL (first line and relapsed disease) were enrolled across 14 centres.
- The choice of regimen (FCR versus FC) was at the discretion of the attending physician.
Key findings

Baseline characteristics and disposition

• Of the 102 patients enrolled, 74 patients with active disease were treated, the majority with CLL (n = 70) and the remaining with SLL (n = 4); 37 patients were previously untreated.

• Median age of patients was 70 years (range: 58–83 years); 57% of patients were male.

• Patients had a median cumulative illness rating score (CIRS) of 4 (range: 0–10).

• Forty-two (42) patients (57%) had Rai stage III/IV disease, and 29 patients (39%) had bulky disease.

• IgVH genes were unmutated in 55 patients (74%); according to hierarchical model, 24 patients (32%) had del(11q) and 6 patients (8%) had del(17p).

• The low-dose FCR regimen was used in 72 patients, while the FC regimen was only used in 2 patients; 34 patients are still on treatment.

Efficacy

• Based on the intention-to-treat principle, the overall response (OR) rate was 70%; the complete response (CR) rate (including clinical CR and CR with incomplete marrow recovery) was 35%.

• Stable disease was noted in 11% of patients, while progression was observed in 9%; 11% of patients were not evaluable.

• Data for progression-free survival (PFS) or overall survival (OS) are not yet available.

Safety

• The most common grade 3/4 adverse events were neutropenia (51%), thrombocytopenia (13%), and anemia (10%).

• Serious infections (grade 3/4) occurred in 13% of patients.

• Four patients died on study, all after failure of treatment:
  • Two patients died of pneumonia.
  • One patient died of pulmonary embolism.
  • One patient died due to septic shock.

Key conclusions

• Treatment of elderly/co-morbid CLL patients with low-dose FC/FCR regimens has demonstrated very promising results.

• Toxicity was acceptable and manageable.

• Longer follow-up is needed for the assessment of quality of life, PFS, and OS.

Background

Patients with chronic lymphocytic leukemia (CLL) who are refractory to fludarabine have poor outcomes, with an anticipated survival of 12 to 18 months. Novel therapies are needed for this group of high-risk patients. Alvocidib (flavopiridol, HMR1275) is a broad cyclin-dependent kinase (CDK) inhibitor that mediates apoptosis independent of p53 function. Previous studies have shown that alvocidib has significant activity in patients with fludarabine-refractory CLL, including those with bulky lymphadenopathy or cytogenetic markers.

At ASH 2010, Lanasa and colleagues presented interim data from a multicentre, international, phase II clinical trial (EFC6663) examining the efficacy and safety of alvocidib monotherapy in patients with fludarabine-refractory CLL or prolymphocytic leukemia (B-PLL) arising from CLL.

Study design

- Eligible patients had fludarabine-refractory CLL or B-PLL arising from CLL and had received prior alkylator therapy. Adequate renal and liver functions were required, while cytopenias were not an exclusion factor.
- Alvocidib was administered on day 1 on a pharmacologically derived schedule, with a bolus dose of 30 mg/m² given over 30 minutes followed by a continuous infusion of 30 mg/m² over four hours.
- If no tumour lysis syndrome occurred with the first dose, subsequent doses were administered on days 8, 15, and 22 with a bolus dose of 30 mg/m² given over 30 minutes followed by a continuous infusion of 50 mg/m² over four hours (total dose 80 mg/m²).
- Alvocidib was administered once weekly for four weeks, followed by a two week break, for up to six cycles (24 total doses).
- Primary objective was to examine overall response (OR) rate. OR comprised both complete response (CR) and partial response (PR), including nodular partial response (nPR).
- Secondary objectives included examining toxicity using CTCAE criteria, progression-free survival (PFS), overall survival (OS), duration of response (DR), and pharmacokinetics.
- Responses were assessed using both NCI-96 and hybrid criteria, which incorporated nodal response as measured by CT scans with NCI 96 criteria.

Key findings

Baseline characteristics and disposition

- At the preplanned interim analysis, 113 patients were enrolled in the intent-to-treat (ITT) population; 108 patients received treatment and comprised the as-treated (AT) population.
- The evaluable patient (EP) population (n = 68) was defined as patients receiving at least two cycles of therapy. The most common reasons for discontinuing treatment before completing two cycles included adverse events (15%) and disease progression (10%).
- The ITT population had the following baseline characteristics:
  - Median age of patients was 60 years; 78% of patients were male. (Table 1)
  - Eight-one percent (81%) of patients had Rai stage III/IV disease, and 65% had bulky lymphadenopathy (≥5cm). (Table 1)
  - Median number of prior treatments was 4 (range: 1–12) and 106 patients (94%) were fludarabine-refractory.
  - Among 86 patients in the ITT population with cytogenetic data available, 31 patients (36%) had del(11q) and 26 patients (30%) had del(17p). (Table 1)

Efficacy

- In the EP population (n = 68), OR was 31% using NCI-96 criteria and 25% using the hybrid criteria. All responses were partial, including nPR. (Table 2)
- Six patients (9%) had disease progression by NCI-96 criteria. (Table 2)
Using NCI-96 criteria in the EP population, the OR rate was 30% in patients with del(11q), 25% in patients with del(17p), and 39% in patients with bulky lymphadenopathy. Using hybrid criteria, the OR rates were 20%, 19%, and 32%, respectively. (Table 2)

Among the responding patients assessed (n = 24), the median duration of response was 12.2 months (95% CI: 7.4–15.0).

In the AT population, median OS was 16.7 months (95% CI: 10.2–not reached) and median PFS was 5.7 months (95% CI: 4.1–9.5).

### Safety

- In a safety analysis of the AT population (n = 108), the most frequent adverse events (grade ≥3) were tumour lysis syndrome (19%), diarrhea (17%), fatigue (16%), febrile neutropenia (14%), and pneumonia (7%). (Table 3)
- The most common hematological toxicities (grade ≥3) were neutropenia (87%), thrombocytopenia (57%), and leukopenia (35%). (Table 3)
- Of the 40 patients treated and discontinued before completion of 2 cycles of therapy, the majority were due to adverse events (43%) and disease progression (28%).
- Within the AT population, 43 deaths (40%) have occurred, 34 of which were due to disease progression. Eight deaths (7%) occurred within 30 days of last study treatment.

### Table 1. Baseline demographics and disease characteristics in the ITT population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 years</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>88 (78)</td>
</tr>
<tr>
<td>Rai stage (n = 100)</td>
<td></td>
</tr>
<tr>
<td>0/I/II</td>
<td>19 (19)</td>
</tr>
<tr>
<td>III/IV</td>
<td>81 (81)</td>
</tr>
<tr>
<td>Binet stage (n = 69)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1 (14)</td>
</tr>
<tr>
<td>B/C</td>
<td>68 (99)</td>
</tr>
<tr>
<td>ECOG performance status (n = 108)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (37)</td>
</tr>
<tr>
<td>1</td>
<td>58 (54)</td>
</tr>
<tr>
<td>2</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Bulky lymphadenopathy (≥5 cm; n = 112)</td>
<td>73 (65)</td>
</tr>
<tr>
<td>Cytogenetics (n = 86)</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>31 (36)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>26 (30)</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat

### Table 2. Response status after treatment with alvocidib in fludarabine-refractory CLL and B-PLL patients

<table>
<thead>
<tr>
<th>Response</th>
<th>ITT population (n = 113)</th>
<th>Evaluateable population (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCI-96 n (%)</td>
<td>Hybrid n (%)</td>
</tr>
<tr>
<td>Overall response rate (CR, PR)</td>
<td>26 (23)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (including nPR)</td>
<td>25 (22)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Pending partial response (including nPR)</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>47 (42)</td>
<td>41 (36)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>15 (13)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>21 (19)</td>
<td>38 (34)</td>
</tr>
<tr>
<td>Bulky lymphadenopathy</td>
<td>20/73 (27)</td>
<td>15/73 (21)</td>
</tr>
<tr>
<td>del(11q)</td>
<td>7/31 (23)</td>
<td>4/31 (13)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>4/26 (15)</td>
<td>3/26 (12)</td>
</tr>
<tr>
<td>Double refractory</td>
<td>6/35 (17)</td>
<td>3/35 (9)</td>
</tr>
</tbody>
</table>

B-PLL = prolymphocytic leukemia arising from CLL; CLL = chronic lymphocytic leukemia; CR = complete response; ITT = intent to treat; NCI = National Cancer Institute; nPR = nodular partial response; PR = partial response
Key conclusions

- Data from this study suggest that alvocidib has stable clinical activity in a subset of fludarabine-refractory CLL patients, including those with bulky lymphadenopathy and adverse risk cytogenetics.

- With careful monitoring, alvocidib could be safely administered in the context of a multi-site international clinical trial.

- Future directions include investigating CLL settings and combinations to minimize the risk of tumour lysis syndrome and characterizing predictive biomarkers to improve patient selection and clinical benefit.

References:

Herter S, et al. ASH 2010: Abstract 3925

Efficacy of the type II CD20 antibody GA101 versus the type I CD20 antibodies rituximab and ofatumumab

Background

In combination with chemotherapy, rituximab is the standard of care for non-Hodgkin’s lymphoma (NHL) and B-cell chronic lymphocytic leukemia (B-CLL). In preclinical studies, GA101, a type II glycoengineered CD20 monoclonal antibody, has been shown to mediate superior in vitro and in vivo activity compared to the type I CD20 antibody rituximab. Epitope mapping and crystallography have shown that GA101 recognizes CD20 in a unique way that is different from type I CD20 antibodies. It is proposed that this unique way of recognizing CD20 may be the basis for the type II character of GA101.

At ASH 2010, Herter and colleagues presented data from an in vitro and in vivo study comparing the efficacy of GA101 with both rituximab and the type I CD20 antibody ofatumumab, which has recently been approved for the treatment of B-CLL in patients refractory to fludarabine and alemtuzumab.

Study design

- The three anti-CD20 antibodies were compared using the following assays:
  - binding to NHL cell lines Z138 and SU-DHL4 assessed by fluorescence-activated cell sorting (FACS);
  - cell death induction detected by annexin V/propidium iodide (AxV/PI) staining and FACS, on a panel of NHL cell lines;
antibody-dependent cellular cytotoxicity (ADCC) mediated by peripheral blood mononuclear cells (PBMNCs) as effector, and Z138 and SU-DHL4 as target cells (ADCC and lactate dehydrogenase [LDH] release assay);
- complement-dependent cytotoxicity (CDC) with Z138 and SU-DHL4 as target cells (CDC and LDH release assay);
- B-cell depletion assessed by FACS in whole blood from healthy donors;
- dose-dependent anti-tumoral activity assessed in an s.c. SU-DHL4 NHL xenograft model in Scid beige mice.

**Key findings**

**Binding properties**
- Binding studies confirmed that GA101 shows half-maximal binding to NHL cells relative to rituximab and ofatumumab, a known property of type II CD20 antibodies.
- EC50 values of binding were comparable, indicating that GA101, rituximab, and ofatumumab have apparent binding affinities in the low nanomolar range, independent of the level of CD20 expression.

**Direct cell death**
- GA101 mediated superior direct cell death induction compared with rituximab and ofatumumab on a panel of NHL cell lines of different origins.

**Antibody-dependent cellular cytotoxicity (ADCC)**
- GA101 was found to exhibit up to 100-fold higher ADCC potency than rituximab and ofatumumab on Z138 and SU-DHL4 cells. (Figure 1)

**Complement-dependent cytotoxicity (CDC)**
- GA101, as expected for a type II CD20 antibody, was around 10 to 1,000 times less potent at inducing CDC than the type I antibodies rituximab and ofatumumab. (Figure 2)

**Whole blood B-cell depletion**
- GA101 was more potent in terms of EC50 values and more efficacious in terms of absolute B-cell depletion when compared with either rituximab or ofatumumab. (Figure 3)

**Anti-tumour activity**
- In the SU-DHL4 NHL xenograft model, GA101 induced a dose-dependent anti-tumoral effect that was superior to both rituximab and ofatumumab at saturating antibody doses.
- Complete tumour remission was achieved in 10/10 mice after treatment with 30 mg/kg GA101; 4/10 and 5/9 animals were tumour free in the rituximab and ofatumumab groups, respectively. (Figure 4)

**Figure 1. Antibody-dependent cellular cytotoxicity in target cells after treatment with GA101, rituximab, or ofatumumab**
Figure 2. Complement-dependent cytotoxicity in target cells after treatment with GA101, rituximab, or ofatumumab

Figure 3. Whole blood B-cell depletion in an integrated assay of ADCC, CDC, and direct cell death mechanisms
Key conclusions

- Further clinical investigation is supported by preclinical data demonstrating that GA101 has superior overall activity to rituximab and ofatumumab.

- In contrast to previous publications, the preclinical activity of ofatumumab in this series of assays was not superior to rituximab.

References:
Canadian perspective by Dr. Stephen Couban

Geode and colleagues, on behalf of the German CLL Study Group (GCLLSG), presented data from the run-in safety phase of a planned multicentre, three-arm trial examining the efficacy of a novel combination of oral chlorambucil and an intravenous monoclonal anti-CD20 antibody (both type I rituximab and type II GA101) for the treatment of chronic lymphocytic leukemia (CLL) in elderly patients with multiple co-morbidities. From a Canadian perspective, the use of chlorambucil with a monoclonal antibody is relatively novel. Chlorambucil remains an attractive option in patients with CLL, especially elderly, frail patients, since it can be given orally and taken at home. However, if chlorambucil is to be combined with an antibody that must be given in a hospital setting, some of its appeal is lessened.

Data from the safety phase was based on a very small sample of only 6 patients, and the dose of chlorambucil used was fairly high (0.5 mg/kg of body weight on days 1 and 15). The incidence of cytopenias and infections in the study appeared quite high. However, the combination of an oral alkylator and a monoclonal anti-CD20 antibody is intriguing and warrants further study. I would definitely be interested in subsequent data about this combination from the GCLLSG, which is highly regarded as a very productive group looking at new therapies in CLL.

Older patients with CLL often fare worse than their younger counterparts, in part because they have a higher susceptibility to the toxicities of therapy, but also because of greater disease resistance. Our interest in exploring the use of reduced intensity regimens should keep these issues in mind. The study presented by Smolej, et al., which investigated low-dose FC and FCR in the treatment of elderly CLL patients with co-morbidities, is one such study examining a reduced intensity treatment regimen. In terms of design, the study included a modest number of patients, both previously untreated and relapsed. Although the study design indicates that physicians chose between FC and FCR regimens, most patients (72/74) received the FCR regimen.

As in many phase II studies, the dose-reduced FCR regimen demonstrated a promising level of activity in terms of response rate. However, in the absence of a historical or contemporaneous control group, it is difficult to know how these particular patients would have fared with full dose FCR. While intriguing, the study would have been strengthened by the inclusion of a control group who received standard FCR.
A Cross-section of Data
From ASH 2010, Orlando, FL

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