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New Evidence in Oncology is a publication that 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. In addition, the investigator commentary sections provide information on key clinical studies from interviews with principal investigators. New Evidence also publishes discussion and expert opinion papers on timely topics of interest to oncologists in Canada.

Our April 2012 issue presents coverage from the 53rd Annual Meeting of the American Society of Hematology (ASH), held in San Diego, California, from December 10–13, 2011. The issue reports findings from key studies using new treatment combinations in patients with chronic lymphocytic leukemia who are unable to tolerate standard regimens. In addition, the results of important studies in relapsed non-Hodgkin lymphoma are discussed. We would like to thank Dr. James Johnston, Dr. Laurie Sehn, and Dr. Tom Kouroukis for their Canadian perspectives. We would also like to thank Dr. Mathias Rummel, Dr. Jennifer Woyach, and Dr. John Byrd for their investigator commentaries.

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

James Johnston, MD, FRCPC

Dr. James Johnston is a professor in the Department of Internal Medicine at the University of Manitoba and a hematologist at CancerCare Manitoba. He is primarily interested in the treatment of chronic lymphocytic leukemia (CLL) and is responsible for the CLL clinic at CancerCare Manitoba. He is also the Clinical Director of the Manitoba CLL Tumour Bank. Dr. Johnston’s research activities relate to the epidemiology of CLL and to the mechanism of action of anti-tumour agents in this disease. He is involved in a number of educational activities related to CLL and with Dr Spencer Gibson organizes the “Canadian CLL Meeting” which is held annually in Winnipeg.

Laurie H. Sehn, MD, MPH

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

C. Tom Kouroukis, MD

Dr. C. Tom Kouroukis graduated from the University of Toronto and completed training in Internal Medicine, Hematology and MSc (Health Research Methodology) training at McGill and McMaster Universities. He was awarded a National Cancer Institute of Canada Clinical Research Fellowship. He is a hematologist at the Juravinski Cancer Centre/Hamilton Health Science, Chair of the Hematology Disease Site Team, Head of the Division of Malignant Hematology, and Associate Professor in the Department of Oncology. He is Co-chair of the Hematology Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative and Chair of the Stem Cell Committee of Cancer Care Ontario. His research interests include the care of older patients with hematological cancers, the impact and evaluation of co-morbidity in older cancer patients, clinical trials, and practice guideline development.
Investigator Commentary

John C. Byrd, MD
Dr. John Byrd is the D. Warren Brown Chair of Leukemia Research and Director of the Division of Hematology at The Ohio State University, OH, USA. Dr. Byrd is an active member of the Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group B) and the CLL Research Consortium. Dr. Byrd has a long track record of preclinical and clinical drug development in chronic lymphocytic leukemia and related diseases. He has over 250 peer reviewed publications related to his work.

Jennifer A. Woyach, MD
Dr. Jennifer Woyach completed her Internal Medicine Residency and Chief Medical Residency at The Ohio State University (OSU), OH, USA and is currently in the third year of her hematology and oncology fellowship at OSU. Her clinical and research interests are in chronic lymphocytic leukemia (CLL) and lymphoma. She is also a member of the CLL Experimental Therapeutics Laboratory at OSU and is the Junior Investigator on the Leukemia Committee of the Alliance for Clinical Trials in Oncology.

Mathias J. Rummel, MD, PhD
Mathias J. Rummel is the head of the Department for Hematology at the Clinic for Hematology and Medical Oncology at the Justus-Liebig University-Hospital, Giessen, Germany. Professor Rummel studied medicine at J.W. Goethe University Hospital in Frankfurt, Germany, obtaining his licence to practice medicine in 1995. Following this, he completed his doctoral degree and residency, obtained board certification in internal medicine, and was awarded his PhD from J.W. Goethe University Hospital. Professor Rummel’s current research focuses on novel treatment approaches in hematological malignancies, most notably follicular and other indolent lymphomas as well as hairy cell leukemia and also immune thrombocytopenic purpura (ITP). He is the chair of the Study group indolent Lymphomas (StiL) and principal investigator of several on-going clinical trials in leukemias, lymphomas, and ITP. He is actively involved in a number of professional scientific societies, he is a reviewer for a number of journals, and has several published book chapters and papers to his credit.
Welcome to the *New Evidence* coverage of the 53rd American Society for Hematology (ASH) meeting held in San Diego, California from December 10th to 13th, 2011.

ASH is the world’s largest professional society concerned with the causes and treatments of blood disorders. With a commitment to research in the diagnosis, treatment, and understanding of blood disorders, ASH plays an important role in training the next generation of researchers and clinicians in the field of hematology.

Advances in the treatment of hematological malignancies such as chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) have led to the development of new and effective treatment regimens, which have redefined the standards of care in these settings. However, in patients unable to tolerate standard regimens, new treatment options are needed that are effective and better tolerated. In addition, effective treatment options are needed in the relapsed setting for patients that are refractory to first-line treatments. In this report, *New Evidence* features a summary of presentations in CLL and NHL aimed at improving the outcomes of patients in these clinical settings.

**UPSTART CROW – A gathering of the minds at ASH 2011**

At ASH 2011, New Evidence was pleased to sponsor the Lymphoma Foundation Canada (LFC) event at the Upstart Crow. The Upstart Crow was a relaxing sanctuary for hematologists to catch up with colleagues during their hectic schedule at ASH. On behalf of all the hematologists attending the Upstart Crow, New Evidence provided a $3,000 donation to the LFC. We hope you enjoyed this atmospheric venue at ASH 2011.
Pharmacology and Mechanism of Action

Getting Better Acquainted with GA101 and Bendamustine

In recent years, there have been significant improvements in the treatment options for patients with lymphoid malignancies. As research efforts have continued to focus in this area, the studies of two promising agents, obinutuzumab (GA101) and bendamustine, have demonstrated both their efficacy and safety in a number of different settings. In order to better understand these agents and use them effectively as monotherapy or in combination, it is crucial to elucidate their mechanisms of action and pharmacokinetics.

GA101 is a type II glycoengineered and humanized monoclonal anti-CD20 antibody that is currently being extensively studied in clinical trials. Anti-CD20 therapies are central to the treatment of B-cell malignancies as evidenced by the clinical utility of rituximab, which is a type I antibody that redistributes CD20 into lipid rafts and promotes complement dependent cytotoxicity (CDC).1,2 In contrast, GA101 has lower CDC activity but higher antibody-dependent cellular cytotoxicity (ADCC) and direct cell death activity.3 In preclinical studies, GA101 was superior to rituximab with respect to B-cell killing in vitro, depletion of B-cells from whole blood, and inhibition of tumour cell growth in lymphoma xenograft models.3,4,5 GA101 is currently being evaluated in phase II/III trials, including comparative studies with rituximab.

Bendamustine is a unique alkylating agent, which combines a nitrogen mustard moiety of mechlorethamine with a benzimidazole, whose clinical efficacy has been demonstrated in the treatment of chronic lymphocytic leukemia (CLL) and refractory indolent B-cell non-Hodgkin lymphoma (NHL).6,7 It has a unique mechanism of action, a reduced susceptibility to drug resistance, and a favourable safety profile, which make this agent a promising option in the management of lymphoproliferative disorders.6 Although data is limited, sex, age, mild-to-moderate renal impairment, and mild-to-moderate hepatic impairment do not appear to influence the pharmacokinetic profile of bendamustine.8 Bendamustine’s clinical benefit combined with its favourable toxicity profile may therefore have utility in older, less fit patients and this agent in combination is being studied in this setting.9 A better understanding of bendamustine’s disposition will allow for safer, more effective use in the special populations that may have impaired organ function due to age and comorbidities.

The elucidation of the pharmacokinetics and mechanisms of action of GA101 and bendamustine were the focus of selected studies that were presented at ASH 2011:

- In a phase Ib study of GA101 in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) or fludarabine and cyclophosphamide (G-FC) in patients with lymphoma it was determined that response rates correlate with serum concentrations of GA101 and that serum concentrations were higher when GA101 was administered with CHOP.
- Messenger RNA (mRNA) profiling and confocal imaging was used to investigate any differences between the effects of GA101 and rituximab on B-cell lymphoma in order to better understand the mechanism of action of GA101. This study concluded that type I and II antibodies bind to functionally distinct subpopulations of CD20 complexes, which have inherently different signaling capacities, and this may account for the differences in the mechanisms of action and antitumour activity between GA101 and rituximab.
An open-label phase I pharmacokinetic study of \[^{14}C\] bendamustine was conducted to characterize the distribution, metabolism, and elimination of bendamustine and its metabolites to assess the role of both hepatic and renal pathways in its elimination. It was revealed that bendamustine is extensively metabolized by a number of metabolic pathways and excreted in both the urine and feces suggesting that renal impairment is unlikely to have a substantial impact on the systemic exposure to bendamustine. Combined with the dosing schedule and short half-life of bendamustine, patients with hepatic impairment are not likely to experience sustained increases in bendamustine exposure either.


**Pharmacokinetics of obinutuzumab (GA101) in patients with CD20+ relapsed/refractory malignant disease receiving concomitant chemotherapy (phase Ib study BO21000)**

**Background**

The efficacy and safety of GA101 in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) or fludarabine and cyclophosphamide (G-FC) in patients with CD20-positive relapsed/refractory B-cell follicular lymphoma has been evaluated in an open-label, multicentre, randomized phase Ib study (BO21000). Response rates were similar for G-CHOP (94%) and G-FC (93%). Studies in patients with CD20+ malignancies treated with GA101 monotherapy have suggested that responding patients eliminate GA101 more slowly than non-responders. At ASH 2011, Carlile and colleagues described the results from BO21000 and explored GA101 pharmacokinetics (PK), exposure and response in patients receiving concomitant chemotherapy.²

**Study design**

- Patients received induction therapy with six to eight cycles of G-CHOP every 21 days or four to six cycles of G-FC every 28 days.
- The choice of chemotherapy and number of cycles were at the discretion of the investigator.
- After stratification by chemotherapy backbone, patients were randomized to receive one of two GA101 dose regimens:
  - 1,600 mg on days 1 and 8 of cycle 1, then 800 mg on day 1 of subsequent cycles (1,600/800 mg; G-CHOP, n = 14; G-FC, n = 14),
  - 400 mg on days 1 and 8 of cycle 1 and on day 1 of subsequent cycles (400/400 mg; G-CHOP, n = 14; G-FC, n = 14).
- Patients who achieved a response were eligible to receive maintenance therapy with GA101 at induction dose (400 mg or 800 mg) every three months for two years.
- Serum samples were taken prior to and directly after each infusion, for all treatment cycles during the induction phase, between days 1 and 21 of cycle 1 (G-CHOP), days 1 and 28 of cycle 1 (G-FC), and for up to 32 days after the final cycle.
- Serum levels of GA101 were measured by enzyme-linked immunosorbent assay (ELISA).
Key findings
• GA101 serum concentrations were higher in the 1,600/800 mg cohort compared with the 400/400 mg cohort, regardless of chemotherapy arm (Figure 1).
• In patients receiving the 1,600/800 mg dose, serum concentrations were slightly higher for those treated with G-CHOP every 21 days compared with G-FC every 28 days (Figure 1).

Maximum and minimum concentrations
• Notable differences in PK profiles were observed in the clearance of GA101 in later cycles and varied between G-CHOP and G-FC.
• For the 400/400 mg G-CHOP cohort, steady state was reached by cycle 2, with maximal plasma concentration (C_max) values of approximately 200–250 μg/ml and minimal plasma concentration (C_min) values of approximately 100 μg/ml.
• In contrast, C_max and C_min values for the 1,600/800 mg G-CHOP cohort were stable from cycles 2 to 4 (600 and 350 μg/ml, respectively), but increased slightly from cycles 5 to 7.
• For the 400/400 mg G-FC cohort, steady state was reached by cycle 2 and maintained for the rest of treatment.

• C_max values were approximately 200 μg/ml and C_min values were approximately 100 μg/ml.
• In the 1,600/800 mg G-FC cohort, steady state was reached by cycle 2; GA101 concentrations declined slightly from cycles 3 to 6.
• C_max values were approximately 600 μg/ml and C_min values declined from approximately 380 μg/ml to approximately 250 μg/ml.
• The G-CHOP and G-FC 1,600/800 mg cohorts showed similar approximate C_max values of 580 and 600 μg/ml, respectively, in cycle 3.
• By the end of treatment the C_max values were approximately 675 μg/ml (cycle 8, G-CHOP) and 400 μg/ml (cycle 6, G-FC).
• In contrast, C_max and C_min values for the 400/400 mg cohorts were similar for both treatment arms, being around 200 μg/ml and 100 μg/ml, respectively.

Correlation between response and GA101 serum concentrations
• In the 1,600/800 mg G-CHOP cohort patients who were complete responders (CRs) had higher GA101 concentrations after the second dose, with these concentrations maintained over the remaining cycles. (Figure 2)
• Patients with CR demonstrated an increase in GA101 concentration over time, whereas in patients with a partial response (PR) it remained the same from cycle 2 onwards. (Figure 2)
• Similar trends were seen for the 400/400 mg G-CHOP cohort, and for both dose levels of the G-FC cohort, with higher concentrations observed in CRs.
Key conclusions

■ GA101 serum concentrations were higher in the 1,600/800 mg cohorts compared with the 400/400 mg cohorts when dosed with either G-CHOP or G-FC.

■ Furthermore, GA101 serum concentrations appeared to be higher in the 1,600/800 mg G-CHOP cohort compared with the 1,600/800 mg G-FC cohort.

■ Response data indicated that patients with the best clinical response had higher GA101 serum concentrations and that with the higher dose, serum concentrations were maintained or increased with further treatment.

■ The data in this study are consistent with observations from monotherapy studies and may reflect the impact of shrinking tumour burden upon the clearance of GA101, which will be subject to further analyses.

■ Based on these data and those obtained from the GAUDI and GAUSS studies, a flat dose of 1,000 mg was chosen for phase III studies.


Differential patterns of gene expression and CD20 localization by GA101 compared with rituximab suggests binding to functionally distinct CD20 subpopulations on B-cell lymphoma cell lines

Background

The precise molecular mechanism(s) by which GA101 exerts its effect on B-cells has not yet been elucidated. Niederfellner and colleagues investigated the differences in direct effects of GA101 and rituximab on B-cell lymphoma by messenger RNA (mRNA) profiling and confocal imaging.1 Their results were presented at ASH 2011.

Study design

- Cell lines with varying levels of CD20 expression were used for these studies:
  - SU-DHL4: A diffuse large B-cell lymphoma (DLBCL) cell line that expresses high levels of CD20 (1,000,000 molecules/cell);
  - Oci-Ly18: A DLBCL cell line that expresses medium levels of CD20 (120,000 molecules/cell);
  - Z-138: A mantle cell lymphoma (MCL) cell line that expresses low levels of CD20 (60,000 molecules/cell).
- Antibody binding-dependent changes in patterns of gene expression were analyzed using a GeneChip Human Genome U133 Plus 2.0 Array (Affymetrix).

Key findings

- Rituximab and GA101 rapidly induced gene expression changes in SU-DHL4 and Z-138 cells, but not in the Oci-Ly18 cell line.
- Those genes that displayed an altered expression pattern included genes known to be associated with activation of B-cell receptors:
  - Transcription factors, including egr1, egr2, and nab2;
  - GPCR signaling components, including rgs1, rgs2, and gpr183;
  - The anti-apoptosis factor bcl2a1;
  - BIC, the gene locus for miRNA-155.
- Gene expression changes were detected as early as one hour after antibody addition, peaked between two and four hours, and returned to baseline levels within 24 hours.
• The effects on gene expression differed markedly between different cell lines for the same antibody and between the two antibodies on the same cell line.
• SU-DHL4 cells showed pronounced changes in the gene expression pattern to rituximab treatment, while Z-138 cells showed less pronounced changes in gene expression.
• The reverse was true for GA101, suggesting not only that the signaling mediated by CD20 differs in different cell lines, but also that in a given cell line the two types of antibodies bind CD20 molecules with different signaling capacity.
• Rituximab and GA101 were localized to different compartments on the membrane of lymphoma cells.
  ◦ Rituximab/CD20 complexes were dynamic and predominantly located outside areas associated with cell–cell contact.
  ◦ GA101/CD20 complexes were relatively static and predominantly associated with sites of cell–cell contact.

Key conclusions

■ Gene expression analysis indicated that both GA101 and rituximab rapidly induced changes in the expression of genes in SU-DHL4 and Z-138 cell lines that were involved in B-cell receptor activation, including egr2, bcl2a1, rgs1, and nab2.

■ In addition, the changes in gene expression profiles induced by GA101 or rituximab varied by both antibody and cell type.

■ These data on differences in gene expression and subcellular localization of type I and II antibodies suggest that the two classes of antibody bind to functionally distinct subpopulations of CD20 complexes, which have inherently different signaling capacities.

■ The observed variances in CD20 binding could potentially account for the differences in mechanisms of action and antitumor activity observed between the two types of antibodies.


An open-label phase I pharmacokinetic study of [14C] bendamustine in patients with relapsed or refractory malignancy

Background
Dubbelman and colleagues conducted a study to characterize the distribution, metabolism, and elimination of [14C] bendamustine and its metabolites (M3, M4, and dihydroxy-bendamustine [HP2]) and to assess the roles of renal and hepatic pathways in the drug’s metabolism and excretion. A secondary objective was to further characterize the safety profile of single-agent bendamustine. The results of this study were presented at ASH 2011.

Study design
• This open-label, phase I study enrolled adult patients with confirmed relapsed or refractory malignancy.
• The study was divided into two assessment periods:
  ◦ Period A (cycle 1, days 1–8): The mass balance and pharmacokinetics (PK) of [14C] bendamustine were investigated;
  ◦ Period B (cycle 1, day 9 to cycle 6 day 28): Non-labelled bendamustine was administered and safety continued to be assessed.
• Patients received intravenous (iv) bendamustine (120 mg/m²), containing 80-95 μCi of [14C] bendamustine, on day 1 of cycle 1 and non-labeled iv bendamustine (120 mg/m²) was used in subsequent infusions.
• Samples of blood for the quantitative determination of plasma concentrations of bendamustine, M3, M4, and HP2 and/or the measurement of plasma
and blood total radioactivity (TRA) were obtained pre-dose and at preselected time points through 168 hours after the start of the [14C] bendamustine infusion.

- PK parameters of bendamustine and metabolites M3, M4, and HP2 were calculated from plasma concentrations measured through 24 hours following administration of bendamustine on day 1.
- Samples of urine and feces for metabolic profiling (urine only), quantitative measurement of the concentrations of bendamustine, M3, M4, and HP2 (urine only), and/or the measurement of TRA were collected from each patient pre-dose and then as voided beginning with the start of infusion and lasting to 168 hours (day 8) after the start of the infusion.
- Collection of excreta could continue if ≥1% of the radiolabeled bendamustine dose was measurable in the 144- to 168-hour urine or feces collection and continued until the recovery in each 24-hour urine or feces collection was <1% of dose.

### Key findings

- Six patients (three males and three females) with a median age of 66 years (range: 48–75 years) were enrolled and completed the pharmacokinetic portion of the study.
- The mean PK parameters for bendamustine, M3, M4, and HP2 are summarized in Table 1.
- For bendamustine, the decline from peak plasma concentration was characterized by an initial rapid distribution phase, followed by a somewhat slower secondary phase. (Figure 1)
- The pharmacologically relevant half-life (t1/2; that of the secondary phase) was 39 minutes.
- The plasma concentrations of M3, M4, and HP2 were very low relative to the bendamustine concentrations, with a maximum plasma concentration (Cmax) of approximately 1/10, 1/100 and 1/100 that of bendamustine, respectively.
- While plasma concentrations of bendamustine, M3, M4, and HP2 rapidly decreased to low levels after the end of the infusion, levels of TRA in plasma were more sustained suggesting that while bendamustine has a short t1/2, biologically inactive metabolites and by-products of the alkylation process (e.g., DNA fragments and protein adducts) may circulate in the plasma for a longer period.
- Urinary excretion was shown to be a relatively minor elimination pathway for bendamustine, M3, M4, and HP2 as at 24 hours, approximately 3.3% of the dose was recovered in urine as bendamustine, <1% was recovered as M3 and M4, and <5% as HP2.
- The steady-state volume of distribution for TRA was approximately 50 L suggesting that neither bendamustine nor TRA is extensively distributed into the tissues.

### Table 1. Pharmacokinetic parameters of bendamustine, M3, M4, and HP2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bendamustine (n = 6)</th>
<th>M3 (n = 6)</th>
<th>M4 (n = 6)</th>
<th>HP2 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>5,319.1 (2,069.90)</td>
<td>685.2 (285.86)</td>
<td>58.7 (36.11)</td>
<td>54.5 (18.85)</td>
</tr>
<tr>
<td>tmax (hour)</td>
<td>1.1 (0.05)</td>
<td>1.3 (0.13)</td>
<td>1.3 (0.18)</td>
<td>1.1 (0.05)</td>
</tr>
<tr>
<td>AUCl∞ (ng-hour/ml)</td>
<td>6,397.2 (2,542.45)</td>
<td>922.2 (350.81)</td>
<td>82.5 (36.36)</td>
<td>190.2 (119.97)</td>
</tr>
<tr>
<td>AUCl∞ (ng-hour/ml)</td>
<td>6,397.8 (2,542.61)</td>
<td>924.8 (350.67)</td>
<td>83.0 (36.51)</td>
<td>189.8 (120.09)</td>
</tr>
<tr>
<td>Extrapolation (%)</td>
<td>0.01 (0.01)</td>
<td>0.3 (0.20)</td>
<td>1.0 (0.33)</td>
<td>22.1 (6.84)*</td>
</tr>
<tr>
<td>λ1 (hour⁻¹)</td>
<td>1.2 (0.34)</td>
<td>0.5 (0.23)</td>
<td>1.4 (0.26)</td>
<td>0.0 (0.01)*</td>
</tr>
<tr>
<td>t1/2 (hour)</td>
<td>0.6 (0.21)</td>
<td>1.7 (1.03)</td>
<td>0.5 (0.14)</td>
<td>17.8 (5.27)*</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>598.3 (261.83)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CLnormalised (ml/min/m²)</td>
<td>312.3 (106.17)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vss (L)</td>
<td>20.1 (7.14)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vss, normalised (L/m²)</td>
<td>10.5 (2.86)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* n = 3; the terminal phase λ1 could not be reliably estimated for three patients.

AUC = area under the curve; AUCl∞ = AUCl from time 0 to infinity; AUCl∞ = time 0 to the time of the last measurable concentration; AUCl∞ = time 0 to 24 hours; CL = apparent total plasma clearance; Cmax = maximum observed plasma drug concentration; λ1 = apparent plasma terminal elimination rate constant; NA = not applicable; SD = standard deviation; t1/2 = apparent terminal elimination half-life; tmax = time to maximum observed plasma concentration; Vss = steady state volume of distribution.
• Of the TRA dose administered, 45.5% of the dose was recovered in the urine and 25.2% of the dose was recovered in the feces. (Figure 2)

• The mean recovery of TRA in excreta was 70.6% of the radiochemical dose at 168 hours.

• Collection continued after 168 hours for five of six patients for a cumulative TRA recovery of approximately 76% of the radiochemical dose.

• Total recovery was incomplete due to continued slow excretion of TRA at the end of the collection period.

• All six patients withdrew prior to completion of period B due to disease progression (n = 4), an adverse event (n = 1), or refusal to continue treatment (n = 1).

• Bendamustine was well tolerated when administered at a dosage of 120 mg/m² for 2–3 cycles.

• The most frequent treatment-related adverse events were fatigue (50%) and vomiting (50%).

• A grade 3/4 absolute lymphocyte count decrease occurred in all patients at some point during the study.

• There were no other grade 3/4 hematologic adverse events.

**Key conclusions**

- Bendamustine was extensively metabolized via multiple metabolic pathways, with subsequent excretion in both urine and feces.

- A small fraction of bendamustine was excreted unchanged in the urine, supporting the belief that urinary excretion plays a relatively minor role in bendamustine elimination; thus, renal impairment is unlikely to have a substantial impact on the systemic exposure to bendamustine.

- Although urinary metabolite profiling indicates that bendamustine is extensively metabolized via multiple pathways, the dosing schedule and short half-life of bendamustine suggests that patients with hepatic impairment are not likely to experience sustained increases in bendamustine exposure.

- Adverse events and hematologic changes were consistent with the known safety profile of bendamustine and the drug is well tolerated.

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Effective and Better Tolerated Treatment Options for CLL

The treatment of chronic lymphocytic leukemia (CLL) has rapidly evolved over the last two decades. Until the early 1990s alkylating agents were the only available option but since then the range of therapeutic choices has expanded. Currently, chemoimmunotherapy consisting of the purine analogue fludarabine, the alkylating agent cyclophosphamide, and the CD20 antibody rituximab (FCR) is the standard of care for first-line therapy. Novel agents such as bendamustine, alemtuzumab, lenalidomide, and others have shown activity in second-line therapy for relapsed disease.1

CLL is a disease that primarily affects older adults with the median age at diagnosis of 72 years and more than 40% of patients are older than 75 years. Treatment and management of CLL in this older population is a key challenge. However, the data that favoured some of these newer therapies were derived from trials in which the elderly demographic was underrepresented. It is therefore difficult to generalize whether these treatments are appropriate for the elderly patients who may not be able to tolerate FCR.1 In addition to age, comorbid conditions, reduced organ function, and performance status are also important considerations in selecting therapies.2 Recognizing this gap in solid evidence on appropriate treatment options for the elderly and frail patients with CLL, research efforts have been focused on this subgroup. A number of options are being investigated including chlorambucil with rituximab, bendamustine with or without rituximab, the use of novel CD20 antibodies, and reduced dose versions of fludarabine-based regimens.

Data from studies evaluating effective and less toxic treatment options for elderly and unfit patients with CLL were presented at ASH 2011:

- An analysis of the outcomes of initial therapy in patients older and younger than 70 years with CLL and the impact of adding rituximab or alemtuzumab to chemotherapy demonstrated that chlorambucil is an appropriate treatment for elderly patients with CLL and that the addition of rituximab to fludarabine-containing regimens significantly improves outcomes in younger and older patients.1
- A microarray analysis to determine baseline characteristics of elderly CLL patients undergoing first-line therapy with rituximab plus chlorambucil revealed that gene expression profiling is useful in predicting which patients will respond to therapy.
- In a retrospective real-world study of the efficacy of bendamustine with or without rituximab in CLL patients older than 70 years it was concluded that bendamustine-based therapies are generally well tolerated and provide clinically meaningful improvements in progression-free survival (PFS) in both previously untreated and treated patients.
- An evaluation of the second-line therapies used in patients who were initially treated with FCR or fludarabine cyclophosphamide (FC) in the CLL8 study revealed that second-line therapies were very heterogeneous; however, the data support retreatment with chemoimmunotherapies such as FCR or bendamustine and rituximab in cases of relapse >24 months after initial treatment.

Impact of age on outcomes following initial therapy with various chemotherapy and chemoimmunotherapy regimens in patients with CLL: results of CALGB studies

**Background**
In order to determine the current optimal standard therapy for older patients with chronic lymphocytic leukemia (CLL) Woyach and colleagues reviewed data on all patients enrolled in the successive phase II and III CALGB CLL trials for previously untreated CLL. The objectives of their study were to determine whether outcomes after initial therapy for CLL differ in patients older than 70 years compared with those younger than 70 years; to determine the ideal chemotherapy choice for older CLL patients; and to determine the impact on treatment outcomes of adding rituximab or alemtuzumab to chemotherapy. Their findings were presented at ASH 2011.

**Study design**
- A total of 663 patients with previously untreated CLL enrolled in four CALGB first-line studies were evaluated.
  - 515 patients were younger than 70 years and 148 were 70 years old or older.
- The treatment regimens evaluated in the CALGB studies were as follows:
  - CALGB 9011: chlorambucil (n = 193) vs. fludarabine (n = 179);
  - CALGB 9712: fludarabine plus rituximab (FR; n = 104);
  - CALGB 19901: fludarabine with consolidation alemtuzumab (F; n = 85);
  - CALGB 10101: fludarabine plus rituximab with consolidation alemtuzumab (FRA; n = 102).
- Multivariable analyses were conducted for progression-free survival (PFS) and overall survival (OS) as a function of treatment regimen, age (younger or older than 70 years), Rai stage, white blood cell (WBC) count, and gender.

**Key findings**
- The baseline characteristics for the patients enrolled in the four studies were similar.
- The median follow-up was 91 months (range: 16–236 months).
- The overall response rates (ORR) varied significantly amongst the treatment regimens (p < 0.0001). (Table 1)
  - The lowest response rate was observed in patients treated with chlorambucil.
  - The ORR improved in patients treated with fludarabine and improved further with FR treatment.
  - Response rates were not significantly higher with alemtuzumab consolidation when compared to the ORR achieved with similar regimens without alemtuzumab consolidation.
- In a multivariable analysis there was no significant difference in ORR between younger and older patients (p = 0.78) and there was no significant treatment by age interaction (p = 0.77).

<table>
<thead>
<tr>
<th>Table 1. Overall response rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Regimen</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Fludarabine (F)</td>
</tr>
<tr>
<td>Fludarabine + rituximab (FR)</td>
</tr>
<tr>
<td>Fludarabine + consolidation alemtuzumab (FA)</td>
</tr>
<tr>
<td>Fludarabine + rituximab + alemtuzumab (FRA)</td>
</tr>
</tbody>
</table>

CI = confidence interval
• Among all patients, fludarabine improved PFS when compared to chlorambucil ($p = 0.0001$), although there was a moderate interaction with age ($p = 0.07$).
  - In patients younger than 70, fludarabine significantly improved PFS when compared to chlorambucil.
  - For patients aged 70 or older, there was no difference in PFS between the two regimens. (Figure 1)
• A significant treatment by age interaction effect was also observed for OS when comparing fludarabine to chlorambucil ($p = 0.01$).
  - OS was improved for patients younger than 70 years treated with fludarabine vs. chlorambucil.
  - However, this benefit did not hold for patients 70 years or older and trended toward favoring chlorambucil. (Figure 2)
• The addition of rituximab to fludarabine improved both PFS (Figure 3) and OS (Figure 4) over fludarabine alone in all patients, with no significant differences in benefit between younger and older patients ($p = 0.51$ for PFS and $p = 0.74$ for OS).
• Consolidation with alemtuzumab did not improve PFS (FA vs. F: $p = 0.77$ and FRA vs. FR: $p = 0.94$) or OS (FA vs. F: $p = 0.26$ and FRA vs. FR: $p = 0.68$), irrespective of age.

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**Figure 1. Progression-free survival: chlorambucil vs. fludarabine**

![Figure 1](image1.png)

**Figure 2. Overall survival: chlorambucil vs. fludarabine**

![Figure 2](image2.png)

**Figure 3. Progression-free survival: fludarabine + rituximab vs. fludarabine**

![Figure 3](image3.png)
**Background**

Fludarabine-containing regimens may be difficult for elderly and unfit chronic lymphocytic leukemia (CLL) patients to tolerate, so chlorambucil-based treatments are frequently used for these patients despite the fact that clinical benefits are limited. There is a need for well-tolerated and more effective treatment regimens for elderly CLL patients.

Foa and colleagues studied the combination of rituximab plus chlorambucil (R-chlorambucil) as first-line treatment for elderly CLL patients who were ineligible to receive fludarabine, cyclophosphamide, rituximab (FCR).1 They evaluated the effects of baseline biological characteristics and gene expression patterns on response to treatment. These results were presented at ASH 2011.

**Study design**

- Patients older than 65 years (or between the ages of 60 and 65 who were ineligible for fludarabine) were treated with eight 28-day cycles of chlorambucil (8 mg/m²/day on days 1 to 7) with rituximab administered on day 1 of cycle 3 (375 mg/m²) and cycles 4 to 8 (500 mg/m²).
- At the end of the induction period, patients with a response were randomized to rituximab maintenance therapy (375 mg/m² every 8 weeks for two years) or observation.

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**Key conclusions**

- The data from this analysis demonstrate that chlorambucil is an acceptable treatment for CLL patients aged 70 years or older and it should be considered as an appropriate chemotherapeutic backbone for future trials.

- The addition of rituximab to fludarabine-containing regimens significantly improves both PFS and OS in younger and older patients, confirming the importance of this agent in current front-line CLL regimens.

- The addition of consolidation alemtuzumab did not improve ORR, PFS, or OS regardless of age, compared to similar regimens that did not include alemtuzumab consolidation; however, these data are less mature compared with those derived from the older studies.

- Collectively, these data suggest that future clinical trials for older CLL patients should incorporate rituximab or other anti-CD20 antibodies with similar or improved efficacy; however, fludarabine and alemtuzumab do not appear to play an important role in improving outcomes in elderly CLL patients.

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• To further investigate possible factors influencing response, pre-treatment patterns of gene expression were analyzed in different patient subgroups after the completion of induction therapy.

• mRNA expression was examined using Affymetrix® Human Genome U133 microarrays.

**Key findings**

• At the time of presentation, the induction phase of this study was complete while the maintenance phase was still ongoing.

• The overall response rate (ORR) in 85 patients who received at least one dose of rituximab during induction was 81.2% (n = 69) with 16.5% (n = 14) achieving a complete response (CR) and 2.4% (n = 2) a CR with incomplete bone marrow recovery (CRi). (Table 1)

  - ORR was similar across the different Binet stages. (Figure 1)
  - ORR was also similar across different age categories. (Figure 1)
  - Two of four patients older than 80 years responded to induction treatment.

• Logistic regression analysis revealed no correlation between known biological prognostic factors (including CD38, cytogenetics, IgVH mutational status, ZAP-70, thymidine kinase, soluble CD23, and β-2 microglobulin) and response to treatment.

• Induction therapy was well tolerated with 75.2% of patients completing all cycles of the induction phase.

  - Chlorambucil dose reductions were required in 7.8% of cycles and due to toxicity in 5.9% of cycles.
  - There were a total of 20 serious adverse events (SAEs) reported, eight of which were treatment related. (Table 2)

• Maintenance therapy was also very well tolerated.

  - Rituximab administration was delayed in 4.6% of cycles administered and due to toxicity in 0.6% of cycles.
  - Rituximab was withheld entirely in 2.6% of cycles.
  - There were four SAEs in the rituximab arm, one of which was treatment related.
  - There were three SAEs in the observation arm none of which were treatment related. (Table 3)

• A total of 73 patients completed induction and material was available for 72 patients for the exploratory mRNA expression analysis. The patients’ responses to induction therapy were as follows:

  - CR/CRi: n = 16
  - Partial response (PR): n = 41
  - Stable disease (SD): n = 2
  - Progressive disease (PD): n = 3.
Key conclusions

- R-chlorambucil is an active and well tolerated first-line therapy for elderly CLL patients.
- There does not appear to be a correlation between biological prognostic factors and response to R-chlorambucil.
- However, gene expression profiling may be useful in predicting response to R-chlorambucil as complete responders and non-responders have different gene expression signatures.


Demographics, treatment patterns, safety, and real-world effectiveness in patients ≥70 years of age with CLL receiving bendamustine with or without rituximab

Background

Bendamustine is a unique, well-established alkylating agent with a multifaceted mechanism of action that results in cancer cell death in several hematologic malignancies. In a phase III trial in treatment-naïve patients with chronic lymphocytic leukemia (CLL), overall response rates (ORR) and progression-free survival (PFS) were significantly superior in patients treated with bendamustine compared with patients treated with chlorambucil.1 In vitro studies have demonstrated that the cytotoxic activity of bendamustine against CLL-derived cell lines is synergized by rituximab.2 Bendamustine-rituximab has a favourable toxicity profile and the National Comprehensive Cancer Network (NCCN) consensus guidelines recommend it as the preferred chemoimmunotherapy regimen for the elderly and for patients with co-morbidities. It is also a recommended regimen for younger patients. Despite this, published clinical data on bendamustine-rituximab are scarce.

In this retrospective study Kolibaba and colleagues sought to characterize a population of CLL patients older than 70 years who received bendamustine with or without rituximab.3 Additional objectives of the study included describing patterns of care, assessing data on real-world effectiveness outside of the controlled environment of clinical trials, and assessing safety of this regimen. Their findings were presented at ASH 2011.
**Study design**

- Records were extracted from U.S. Oncology iKnowMed (iKM) record databases for all outpatients older than 70 years with CLL (but no other tumour), more than one visit recorded (but not enrolled in clinical trials), and who received bendamustine between March 2008 and May 2010.

- Patients were classified as treatment-naïve or relapsed, which included patients receiving second-line or higher lines of therapy.

- To ascertain mortality, the iKM data were supplemented with vital-status data from the Social Security Administration Death Index.

- The ORR included complete response (CR), nodal partial response (nPR), and partial response (PR).

- PFS was time from first bendamustine dose to progressive disease (change in line of therapy), relapse, or death from any cause.

- Data from patients were censored if they did not die, had no progression, or were lost to follow-up.

**Key findings**

- A total of 91 patients met the criteria for inclusion in this analysis.
  - 16 patients were treatment naïve.
    - Of these, 10 patients received bendamustine monotherapy and six received bendamustine-rituximab.
  - 75 patients were relapsed or receiving second-line or higher lines of treatment.
    - Of these, 20 had received bendamustine monotherapy and 55 received bendamustine-rituximab.

- The mean initial age at beginning of first therapy was 77.4 years (standard deviation = 5.6 years), the age at diagnosis was 70.3 years (standard deviation = 6.5 years), and 63.7% were male.

**Treatment efficacy**

- The observed ORR for treatment-naïve patients was 56.3% (n = 9; 18.8% CR, 37.5% PR, and 0% nPR); 6.3% had progressive disease. (Table 1)

- For relapsed patients, the ORR was 58.7% (n = 44; 13.3% CR, 44.0% PR, and 1.3% nPR); 24.0% had progressive disease (PD). (Table 1)

- Among the 89 patients with data, median PFS for the 16 treatment-naïve patients had not yet been reached (median follow-up 15.1 months); while for the 73 relapsed patients, the median PFS was 18.4 months. (Figure 1)

**Patterns of treatment**

- All patients received a median of three cycles of treatment except for treatment-naïve patients receiving bendamustine monotherapy, who received a median of two cycles of treatment.

- Bendamustine doses administered varied among the treatment groups.
  - Of the 16 treatment-naïve patients, 10 received a median dose of 97.9 mg/m² of bendamustine monotherapy and six received a median of 76.1 mg/m² of bendamustine combined with rituximab.
  - Of the 75 relapsed patients, 20 received a median dose of 98.1 mg/m² of bendamustine monotherapy and 55 received a median of 82.0 mg/m² of bendamustine combined with rituximab.

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### Table 1. Response rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment-naïve</th>
<th>Relapsed or ≥ second-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 91)</td>
<td>Bendamustine monotherapy (n = 10)</td>
</tr>
<tr>
<td>ORR*</td>
<td>53 (58.2)</td>
<td>5 (50.0) [18.7–81.3]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[47.4–68.5]</td>
<td>[10.0] [0.25–44.5]</td>
</tr>
<tr>
<td>CR</td>
<td>13 (14.3)</td>
<td>1 [0.05–144.5]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[7.8–23.2]</td>
<td>[4.0] [12.1–73.7]</td>
</tr>
<tr>
<td>PR</td>
<td>39 (42.9)</td>
<td>4 (40.0) [12.1–73.7]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[32.5–53.6]</td>
<td>[0.0] [0.05–144.5]</td>
</tr>
<tr>
<td>nPR</td>
<td>1 (1.1)</td>
<td>0 [0.05–144.5]</td>
</tr>
<tr>
<td>SD</td>
<td>14 (15.4)</td>
<td>2 (20.0) [0.05–144.5]</td>
</tr>
<tr>
<td>PD</td>
<td>19 (20.9)</td>
<td>1 (10.0) [0.05–144.5]</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (5.5)</td>
<td>2 (20.0) [0.05–144.5]</td>
</tr>
</tbody>
</table>

*ORR = CR + PR + nPR
CI = confidence interval; CR = complete response; nPR = nodular partial response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease
Key conclusions

- In this real-world retrospective chart review of CLL patients 70 years or older, bendamustine, either alone or with rituximab, provided meaningful response rates,
  - Among all patients, the ORR was greater than 58%.
  - For the total patient population, the median PFS was longer than 1.5 years; however, the median had not been reached among the subgroups of treatment-naïve patients or those receiving combination therapy.
- The length of PFS of both treatment-naïve and relapsed patients was clinically meaningful.
- Bendamustine-based therapies are generally well tolerated.

Second-line therapies after treatment with fludarabine, cyclophosphamide, and rituximab (FCR) or fludarabine and cyclophosphamide alone (FC) for CLL within the CLL8 protocol of the German CLL Study Group (GCLLSG)

Background

The CLL8 trial of physically fit, treatment-naïve chronic lymphocytic leukemia (CLL) patients was the first study to show not only an increase in complete remission (CR) rates and progression-free survival (PFS), but also an improved overall survival (OS) following treatment with fludarabine cyclophosphamide rituximab (FCR)-chemoimmunotherapy compared with fludarabine cyclophosphamide (FC) alone.1 Despite this remarkable progress, CLL remains an incurable disease and virtually all patients will eventually relapse. However, to date, little is known about the efficacy of second-line therapies in these patients. Cramer and colleagues followed the patients enrolled in CLL8 and reviewed their outcomes following second-line therapies.2 Results of this study were presented at ASH 2011.

Study design

- Between July 2003 and March 2006, 817 patient in good physical fitness, as defined by a cumulative illness rating scale (CIRS) score of ≤6 and creatinine clearance ≥70 ml/min, were randomized within the CLL8 trial (first-line treatment).
  - 409 patients received six courses FC (F: 25mg/m² iv and C: 250 mg/m² iv on days 1–3 every 28 days).
  - 408 patients received the same FC regimen with rituximab (375 mg/m² iv on day 0 of cycle 1 and 500 mg/m² on day 1 of all subsequent cycles every 28 days).

Key findings

- As of March 2009, 65% of the patients who received FCR were free of progression compared with 45% of those who were treated with FC (p <0.0001).1
- The median PFS for the FCR arm was 57.9 months and for FC it was 32.9 months (p <0.0001).1
- Until July 2010, 232 patients were treated for relapsed CLL.
  - 91 of these patients were initially treated with FCR (22% of the 408 in this treatment arm).
  - 141 of these patients were initially treated with FC (35% or the 409 in this treatment arm).

- Second-line therapy following FCR or FC, most frequently included the following agents either alone or in combination:
  - Rituximab: 52%.
  - Fludarabine: 21%.
  - Bendamustine: 21%.
  - Alemtuzumab: 12%.
- Cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab (R-CHOP) was the most common treatment combination used in 35 patients (15%) mainly in cases with a relapse ≤24 months after FC/FCR.
- FCR or bendamustine and rituximab (BR) were administered predominantly in case of relapse >24 months (32 and 27 patients, 14% and 12%, respectively).
- Other prevalent second-line therapies were:
  - Single agent alemtuzumab in 20 patients;
  - Single agent bendamustine in 17 patients;
  - CHOP in 11 patients;
  - FC in 11 patients;
  - Chlorambucil in nine patients;
  - Rituximab monotherapy in seven patients;
  - Stem cell transplantations in nine patients.
- Second-line therapies with FC with or without rituximab and bendamustine with or without rituximab were found to be more effective with respect to treatment-free survival (TFS, time to second relapse) and OS when compared to alemtuzumab or R-CHOP and CHOP-like chemotherapies. (Figure 1)
- The outcome of second-line therapies seemed to be influenced by the first-line treatment.
  - In patients initially treated with FC, FCR was found to be the most effective second-line therapy (TFS: 23 months, OS: not reached),
  - In patients initially treated with FCR, a substitution of the chemotherapeutic agents FC by bendamustine seemed justified, as TFS was superior after second-line treatment with bendamustine with or without rituximab (16 and 18 months, respectively) when compared to FC with or without rituximab (11 and 8 months, respectively).
Furthermore, in patients who had received FCR in first-line, chemotherapy with FC or bendamustine was found to be at least equally or even more effective in prolonging OS than FCR or bendamustine and rituximab (OS calculated from beginning of second-line therapy (FC: not reached, bendamustine: 45 months, FCR: 19 months, and bendamustine and rituximab 18 months). (Figure 1)

Figure 1. Outcomes of most prevalent second line therapies

<table>
<thead>
<tr>
<th>Second-line therapies</th>
<th>Median TFS in FC/FCR patients</th>
<th>Median OS in FC/FCR patients</th>
<th>Median OS in FC patients</th>
<th>Median OS in FCR patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>14.9 months (n = 11)</td>
<td>not reached (n = 21)</td>
<td>not reached (n = 7)</td>
<td>not reached (n = 4)</td>
</tr>
<tr>
<td>FC R</td>
<td>16.1 months (n = 24)</td>
<td>69.2 months (n = 27)</td>
<td>40.5 months (n = 15)</td>
<td>37.0 months (n = 10)</td>
</tr>
<tr>
<td>B</td>
<td>17.7 months (n = 17)</td>
<td>64.9 months (n = 17)</td>
<td>51.6 months (n = 25)</td>
<td>34.3 months (n = 3)</td>
</tr>
<tr>
<td>A</td>
<td>12.7 months (n = 20)</td>
<td>42.3 months (n = 20)</td>
<td>44.3 months (n = 9)</td>
<td>42.2 months (n = 11)</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>15.3 months (n = 33)</td>
<td>40.5 months (n = 35)</td>
<td>40.5 months (n = 25)</td>
<td>37.0 months (n = 10)</td>
</tr>
<tr>
<td>CHOP</td>
<td>13.0 months (n = 11)</td>
<td>51.6 months (n = 11)</td>
<td>51.6 months (n = 8)</td>
<td>34.3 months (n = 3)</td>
</tr>
<tr>
<td>A</td>
<td>12.7 months (n = 20)</td>
<td>42.3 months (n = 20)</td>
<td>44.3 months (n = 9)</td>
<td>42.2 months (n = 11)</td>
</tr>
</tbody>
</table>

A = alemtuzumab; B = bendamustine; BR = bendamustine and rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; FC = fludarabine and cyclophosphamide; FCR = fludarabine cyclophosphamide, and rituximab; R-CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab; OS = overall survival; TFS = treatment-free survival
Key conclusions

- Second-line therapies of patients with a relapse after FC or FCR were found to be surprisingly heterogeneous even though the patient population studied was comparatively homogenous due to the inclusion/exclusion criteria of the CLL8 trial.

- As the majority of CLL8 patients are still in remission and have not yet received a second-line treatment, the therapies captured in this analysis are predominantly second-line therapies for earlier relapses.

- As a result of the short follow-up time, these results should be considered as preliminary and descriptive of trends.

- The worse outcome of CHOP-like regimen and alemtuzumab-based therapies in comparison to more established CLL-therapies such as FC with or without rituximab and bendamustine with or without rituximab might be related to the fact that these therapies were administered more often in case of an early relapse after FC or FCR, which is known to be related to other poor prognostic factors.3

- The observation of favourable TFS and OS times after second-line treatment with FC with or without rituximab and bendamustine with or without rituximab supports the recommendation to repeat chemoimmunotherapy in case of a relapse >24 months after first-line treatment.

- Further analyses are needed to confirm the observation that chemotherapy (FC or bendamustine) without rituximab might be sufficient for second-line treatment after FCR.

References:


Canadian perspective by Dr. James Johnston

The selection of treatment for patients with chronic lymphocytic leukemia (CLL) is influenced by a number of important factors. Although CLL is a disease that primarily affects the elderly, performance status, comorbidities, and renal function are more important factors to consider than age in making treatment decisions. Our clinic in Winnipeg is run by three physicians and offers standard treatment to patients with CLL. First-line treatment with the standard of care, fludarabine, cyclophosphamide, and rituximab (FCR), requires that patients meet eligibility criteria including good performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] score of 0–1), a cumulative illness rating score (CIRS) of six or less, and adequate renal function. According to these criteria, approximately one-third of patients are eligible for FCR at our clinic.

Patients at our clinic who do not meet the criteria for FCR are treated with fludarabine and rituximab (FR), or rituximab, cyclophosphamide, and dexamethasone (RCD; also given to patients with immune cytopenias). In addition, we tend to give chlorambucil to patients who are very frail. For patients who relapse following initial therapy, the length of time since initial therapy, age, and fitness are used to determine the course of action for second-line therapy. Patients younger than 65 years of age who relapse less than two years following FCR are generally given alemtuzumab and considered for a non-myeloablative marrow stem-cell transplant (BMT). Older patients or those ineligible for BMT may be treated with FR, RCD, alemtuzumab, or ofatumumab. Those who are progression-free for longer than two years are retreated with FCR or FR.
Although the elderly comprise a significant portion of patients with CLL, few studies have focused on treatment in these patients. There has long been a misconception that elderly patients with CLL will die with their disease rather than from their disease, but growing evidence indicates that CLL patients of all ages die from progressive CLL, or due to the effects of immune suppression (e.g., infections or secondary malignancies). Elderly patients over the age of 80 years are the only group of patients with CLL where we have not seen a significant improvement in relative survival over the last 20 years. The cause for this is unclear, but may reflect a referral bias where older CLL patients are not being referred for therapy, or may be due to the fact that CLL in the elderly is intrinsically more resistant to therapy. Given the significant number of elderly patients with CLL and their unique treatment needs, further research is needed to identify more effective and tolerable treatments in this patient group.

A number of treatment approaches are currently being used in the elderly, such as FR or PCR (pentostatin, cyclophosphamide, and rituximab) instead of FCR. For patients who have had extensive prior chemotherapy and for whom there is concern over bone marrow function, cyclophosphamide-based regimens should be considered. A number of promising new agents, including ofatumumab and bendamustine are well tolerated by the elderly and frailer patients and will soon be available in Canada. Bendamustine is of particular interest because pharmacokinetics do not appear to be dependent on mild renal or hepatic impairment, which may be common in the elderly. Results of ongoing studies will more clearly define the efficacy of these newer agents in elderly patients with CLL.

The goal of treatment for patients with CLL is to achieve the longest remission possible, and hopefully also improve survival. Optimizing remission duration means increasing the time before patients require additional therapy, which may in turn improve survival. Although poorly understood, elderly patients with CLL appear to have worse outcomes than younger patients, which may be due to more aggressive disease or dose-reduced treatments. The study by Woyach, et al. evaluated the impact of age on outcomes following treatment with chemotherapy and chemoimmunotherapy regimens in patients with CLL entered in four Cancer and Leukemia Group B (CALGB) studies. A key finding of the study was that the addition of rituximab to fludarabine improved outcomes for all age groups; however, this improvement was not as dramatic for older patients as for younger patients. In addition, when comparing fludarabine and chlorambucil, both drugs appeared to have equal efficacy in patients older than 70 years whereas both progression-free survival (PFS) and overall survival (OS) were increased in younger patients treated with fludarabine. However, it should be emphasized that the dose of chlorambucil in this study was relatively low at 40 mg/m² administered monthly.

A number of ongoing studies are examining new treatment combinations in the elderly. Adding rituximab to chlorambucil (R-chlorambucil) is expected to improve the efficacy of chlorambucil, particularly in unfit and elderly CLL patients. This treatment combination is currently being studied by the German CLL Study Group (GCLLSG) in the CLL11 study, where R-chlorambucil is being compared with chlorambucil alone or GA101-chlorambucil in patients not fit enough to receive first-line FCR. A number of Canadian centres are participating in the trial and while accrual for the trial is very good, it is too early to speculate about the benefits of the different treatment combinations. While rituximab is a chimeric antibody against CD20, GA101 is a humanized antibody against CD20, which has been modified to enhance cell killing. Similarly, ofatumumab is another humanized monoclonal antibody against CD20, which is being extensively evaluated alone or with other agents in CLL. Based on these studies, it is expected that CD20 antibodies will play a very prominent role in the treatment and management of unfit CLL patients.

The study by Foa and colleagues employed a gene expression approach to predict response of elderly CLL patients treated with rituximab and chlorambucil, followed by maintenance therapy with rituximab or observation. This was a very interesting approach to predict response and resistance to rituximab-containing therapy and presents a new avenue for identifying prognostic markers. An interesting observation was that none of the standard prognostic markers correlated with outcomes in this study. This may be accounted for by the fact that this was an elderly population, unlike those of other studies. In order to gain a better understanding of the cause of resistance to rituximab, it would have been interesting to compare gene expression patterns in patients treated with chlorambucil versus those treated with rituximab and chlorambucil.

While the addition of rituximab to chlorambucil is expected to improve efficacy, chlorambucil alone is a good agent when used at the appropriate dose. Many physicians continue to use chlorambucil as monotherapy in the elderly and in unfit CLL patients because it is so well tolerated. In the study by Foa, et al. rituximab was administered at a dose of...
375 mg/m² for the first three cycles of induction. This dose was likely selected because of high tumour load and the risk of inducing a tumour lysis reaction. In the subsequent five cycles of induction, rituximab was given at 500 mg/m² as there would have been less circulating tumour cells and a lower risk of tumour lysis.

The rationale for studying maintenance rituximab in CLL patients is based on its efficacy in follicular lymphoma. The real question is whether rituximab maintenance will be effective in CLL since initial studies with rituximab as a single agent did not show much activity in this disease. A major barrier to the use of maintenance rituximab in CLL will also be cost. Therefore, very strong and solid data will be required in order to pursue and accept this treatment approach.

In a real world practice study, Kolibaba, et al. evaluated the treatment patterns, safety, and efficacy of bendamustine or bendamustine with rituximab (BR) in elderly patients with CLL. The fact that the study was conducted in a real-life setting provides valuable information; however, given that the data was not collected in a controlled setting, its robustness is uncertain. A variety of bendamustine-based treatments were included in this study – both first- and second-line as well as with and without rituximab. Bendamustine appears to be a very promising agent for CLL patients given that it has demonstrated promising efficacy and is well tolerated.

Studies are still needed to determine where in the treatment algorithm bendamustine will be used. It is expected that upon licensing it will be used first-line as a mono-therapy; however, as further clinical trials evolve it may be used in combination with rituximab. To date, studies have shown that bendamustine is well tolerated in the elderly in both the first- and second-line settings but that better outcomes are observed in patients treated first-line. One key advantage of bendamustine is that dose adjustments in patients with mildly compromised renal and hepatic function, which may be common in the elderly, are not necessary; however, because it can suppress the bone marrow, it should be used with caution in patients with compromised bone marrow. A very important study in this patient population is the head-to-head comparison of FCR with BR. These results will be very interesting and are eagerly anticipated.

Cramer and colleagues have attempted to delineate what happened to the patients in the CLL8 trial originally treated with either fludarabine and cyclophosphamide (FC) or FCR. They demonstrated that second-line therapies following FC or FCR were very heterogeneous. This heterogeneity underscores the lack of consistency in the approach to treatment of patients who relapse following first-line therapy in CLL. This varied approach to second-line therapy in CLL is also evident in Canada. While it is reasonable to expect longer remissions with FCR than with FC, some patients on FCR do relapse early and second-line treatments tend to depend on the duration of response. Thus, if a patient relapses 24 or more months following initial therapy with FCR, a reasonable approach is to retreat with FCR. However, for patients who relapse earlier, the optimal treatment approach is unclear. Patients younger than 65 years are frequently considered for an allogeneic BMT if a further response can be obtained with chemotherapy or alemtuzumab. Some Canadian provinces use FR instead of FCR. Longer remissions are expected with FCR but FR is less myelosuppressive and may carry a lower risk of inducing myelodysplasia. The value of FCR over FR is unclear and the subject of an ongoing research trial. This study by Cramer, et al. demonstrates the need for guidelines for treating CLL patients in the second-line setting in addition to those that exist in the first-line setting. Further studies will provide insight into how patients should be treated after relapse.

CLL is a disease that primarily affects the elderly and we must continue to optimize therapy with effective and tolerable treatments that minimize the impact on quality of life. A number of new and encouraging approaches include new antibodies such as ofatumumab, new chemotherapeutic agents such as bendamustine, and new combinations of these, as well as existing, agents. While these new approaches continue to be evaluated in phase III clinical trials, it is equally important to develop guidelines for the most appropriate therapeutic options for CLL patients in the second-line setting.
New Evidence: What outcomes are the most important to consider in elderly patients with chronic lymphocytic leukemia (CLL)?

**Dr. Byrd and Dr. Woyach:** Overall survival (OS) is an important outcome in measuring the efficacy of treatment in CLL. However, OS is confounded by age and comorbidities, suggesting that it is not the best endpoint in trials with elderly patients. Therefore, progression-free survival (PFS) may be a more appropriate surrogate outcome in this patient population.

In addition, toxicities related to treatment can contribute significantly to negative outcomes, as the elderly are more affected by complications that can impede their independence. Once their independence has been lost, it is very difficult for them to regain it, making them more vulnerable to negative outcomes. Because of this, quality of life indicators are also important in the older population.

New Evidence: What treatment options do you recommend for elderly or unfit patients with CLL?

**Dr. Byrd and Dr. Woyach:** The standard treatment for elderly or unfit patients with CLL is chlorambucil. However, the addition of rituximab to chemotherapy backbones has improved outcomes in patients with CLL and may justify the addition of rituximab to chlorambucil. There have been two phase II trials which have investigated this regimen. One study conducted in the UK was presented at the ASH 2010 annual meeting and showed improved response rates and PFS over historical controls of chlorambucil-only treated patients. Additionally, preliminary results of a phase II study presented at the ASH 2011 meeting by Foa, et al. demonstrate that the addition of rituximab to chlorambucil improves PFS, with very little additional toxicity in elderly patients with CLL.1

New Evidence: What is the evidence for the role of anti-CD20 antibodies in unfit patients with CLL?

**Dr. Byrd and Dr. Woyach:** A study by Hainsworth, et al. examining rituximab monotherapy followed by maintenance therapy, included a large number of elderly patients and showed no difference in outcomes in the elderly subgroup.2 However, we do not have any published studies that examine the use of rituximab-based regimens in unfit patients. Currently, all the data we have on the use of rituximab-based regimens comes from combination studies that include nucleoside analogues. These studies generally required fairly good performance status and did not include large numbers of older patients. The German CLL8 study showed that there is a survival advantage to the addition of rituximab to chemotherapy in fit patients. Similarly, our analysis showed a PFS and OS benefit of the addition of rituximab to fludarabine.
A number of ongoing studies are examining the addition of rituximab to chlorambucil in CLL. An ongoing phase III study (NCT01283386) in patients aged >60 years with a cumulative illness rating score (CIRS) ≥7 is examining the efficacy and safety of rituximab plus chlorambucil compared to rituximab plus fludarabine and cyclophosphamide (FCR). In addition, the MaBLe study (NCT01056510) is examining the efficacy and safety of rituximab added to bendamustine or chlorambucil in patients with CLL. A third ongoing study (NCT01010061) is examining the efficacy and safety of chlorambucil plus GA101 compared to chlorambucil plus rituximab and chlorambucil monotherapy in patients with untreated CLL.

**New Evidence:** Other than age, what other factors should be considered in making treatment decisions for unfit patients with CLL?

**Dr. Byrd and Dr. Woyach:** Although in the United States we do not use as stringent scoring methods as used by German physicians; however we do consider age, organ status, co-morbidities, and general performance status when making treatment decisions. It is also important to consider genetic factors associated with the disease, such as deletions of 17p (del[17p]) and 11q (del[11q]). In patients with del(11q), treatment with alkylators such as cyclophosphamide is recommended based on the benefits of their use shown in clinical trials. It is very difficult to treat older patients in these high-risk genetic groups because of the toxicities associated with fludarabine-based chemoimmunotherapy.

**New Evidence:** Describe the use of fludarabine in elderly patients with CLL.

**Dr. Byrd and Dr. Woyach:** Results of our study show that there is no difference in PFS and OS between patients older than 70 years given fludarabine and those given chlorambucil (hazard ratio [HR] = 0.9; 95% CI: 0.6–1.5; HR = 1.3; 95% CI: 0.8–2.0). Although this was a retrospective analysis, the purpose was to independently verify data from the CLL5 phase III study by the German CLL Study Group (GCLLSG) that compared fludarabine to chlorambucil in elderly patients with CLL. Results from our study support the data from the CLL5 study. In addition, our study results suggest that fludarabine is not the best therapy for elderly patients with CLL and that chlorambucil is a good option in these patients.

**New Evidence:** Can elderly patients who have a good performance status benefit from more aggressive treatments?

**Dr. Byrd and Dr. Woyach:** The use of comorbidity indices in making treatment decisions is important within the context of clinical trials, as they allow for easy comparison of results across studies. However, in practice, there is a good correlation between these comorbidity indices scores and chronological age. Therefore, it is reasonable to use age instead of these indices when making treatment decisions. Since fludarabine treatment in patients older than 70 years of age has shown no benefit, we do not use fludarabine-based chemoimmunotherapy regimens in elderly patients with CLL.

**New Evidence:** What do you see as the future for the treatment of CLL?

**Dr. Byrd and Dr. Woyach:** In the future, we anticipate that the treatment of CLL patients will involve less toxic, non-chemotherapeutic agents such as monoclonal antibodies, kinase inhibitors, and cell cycle inhibitors. Responses in patients treated with some of the new kinase inhibitors, such as CAL-101 and PCI32765, have been very promising with excellent response rates and remission durations. Previous studies have shown that adding rituximab to chemotherapy improves outcomes with little additional toxicity. Future studies may also show that adding antibodies to these newer agents also improve outcomes.

**References:**
New Evidence: Please describe bendamustine’s unique mechanism of action.

Dr. Rummel: Bendamustine is a bifunctional alkylating agent comprised of three structural elements: a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain. Although classified as an alkylator, bendamustine appears to have additional properties that make it effective in patients who are refractory to other alkylators. The additional properties of bendamustine may be attributable to its benzimidazole ring.

CLL:

New Evidence: What are the advantages of bendamustine as a treatment for chronic lymphocytic leukemia (CLL)?

Dr. Rummel: Based on registry data in Germany, bendamustine is the front-line treatment that is used the most often for the treatment of CLL. The advantage of bendamustine is that it appears to be as effective and has a safety profile that is superior to that of standard treatment using fludarabine, cyclophosphamide, and rituximab (FCR). Given that the typical patient with CLL is elderly and may also have renal insufficiency, bendamustine is preferable to fludarabine in this patient population. Therefore, in Germany, bendamustine plus rituximab (BR) is used in preference to fludarabine-based regimens as first-line treatment for CLL. An ongoing study by the German CLL Study Group (GCLLSG) is comparing treatment with FCR to BR in untreated patients with CLL and should confirm whether BR is preferable to FCR as standard therapy for CLL.

New Evidence: What dose and what regimen of bendamustine do you recommend for the treatment of CLL?

Dr. Rummel: For the first-line treatment of CLL, we follow the dosing recommended by Cheson, et al., which suggests a dose of 90 mg/m² of bendamustine on days 1 and 2 given every four weeks when combined with rituximab.¹ For the first-line treatment of CLL, we always combine bendamustine with rituximab based on the evidence from previous studies demonstrating that the addition of rituximab to chemotherapy improves outcomes.

New Evidence: Which CLL patients do you treat with bendamustine?

Dr. Rummel: At the Justus-Liebig University Hospital, I treat almost all CLL patients with BR. In my opinion, any patient who can tolerate rituximab can also tolerate bendamustine. In the small proportion of patients with 17p deletions (17p[del]), I do not give BR and consider other more appropriate options such as high-dose therapy, followed by transplant. I also believe bendamustine should be used in patients that are refractory to fludarabine, given that it has shown to be highly effective in these patients.
New Evidence: In your opinion, and based on the results from studies to date, how should bendamustine be used in CLL?

Dr. Rummel: I believe bendamustine should be used in combination with rituximab. We know that bendamustine monotherapy is highly effective, and it is not clear the extent that adding rituximab may improve progression-free survival (PFS). However, based on data from the CLL8 study by the GCLLSG, we know that adding rituximab to chemotherapy improves overall survival (OS), without significantly increasing toxicity.2 I would therefore assume that the addition of rituximab to bendamustine improves outcomes in CLL.

iNHL & MCL:

New Evidence: What are the advantages of bendamustine as a treatment for indolent non-Hodgkin lymphoma (NHL) and mantle cell lymphoma (MCL)?

Dr. Rummel: The advantage of bendamustine for the treatment of indolent NHL and MCL has been shown in our study, which demonstrated that BR improves PFS and is less toxic than rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).3 In addition, patients do not lose their hair when treated with bendamustine, which means a lot more than we acknowledge as physicians. These patients are able to go out into society without being recognized as cancer patients. Although survival is more important as an endpoint than quality of life (QoL), given the improved PFS and tolerability with bendamustine compared to R-CHOP, the additional improvements in QoL are important to consider.

New Evidence: In which patients with NHL do you use bendamustine?

Dr. Rummel: Currently, I give BR to all patients with indolent NHL who are in need of treatment. I also treat patients with small lymphocytic leukemia (SLL) with this regimen. In patients with aggressive disease, I may preferentially treat with R-CHOP instead of BR, but this is decided on a case by case basis. I even give BR to older patients with a poorer performance status, as I have found it to be well tolerated in this population. In addition, more than 50% of elderly patients will demonstrate an extended benefit of treatment with BR. Conversely, R-CHOP appears to show more early relapses than BR, as demonstrated in my study. The median PFS with BR is around five years and can be longer if combined with rituximab maintenance. At present, we have some patients who have an ongoing remission after BR for up to eight years without relapse.

New Evidence: What dose and regimen of bendamustine do you recommend using in iNHL and MCL?

Dr. Rummel: Currently we use 90 mg/m² of bendamustine on two consecutive days, combined with rituximab. In my study it was an arbitrary decision to use this dose, but results show it is effective. Although the recommended dose for monotherapy is higher than 90 mg/m², I feel the lower dose is the correct one.

New Evidence: In your opinion and based on the results from studies, how should bendamustine be used in patients with NHL and in which patients?

Dr. Rummel: For the treatment of indolent NHL, we always use bendamustine in combination with rituximab. The majority of physicians in Germany give BR instead of R-CHOP based on internal data from registries. We do also give BR to elderly patients with diffuse large B-cell lymphoma (DLBCL) if they relapse after R-CHOP and are not eligible for high-dose therapy with autologous stem cell support. Some colleagues also use BR in patients with aggressive lymphoma who have low cardiac ejection fraction, but I prefer to use R-CHOP in these patients whenever applicable. In young patients with MCL, we recommend giving chemotherapy with high-dose cytarabine (ARA-C) and consolidation with stem cell transplant. In older patients with MCL, we give BR instead of R-CHOP.

New Evidence: Based on the results of studies in the relapsed setting, how do you see bendamustine being used in these patients?
**Dr. Rummel:** Most likely, BR will eventually be recommended as first-line treatment in patients with indolent NHL. However, where patients have been given a different regimen as first-line treatment, BR can be given in the relapsed setting. In our study in the relapsed setting, BR was shown to be highly effective as salvage treatment. In patients given BR as first-line treatment, I would re-treat with BR where there is a long response duration. Otherwise I would change to a CHOP- or fludarabine-based treatment.

**Safety:**

**New Evidence:** How should potential hematologic toxicity and infections be effectively managed with the use of bendamustine?

**Dr. Rummel:** If prolonged cytopenias are observed with bendamustine, I recommend stopping treatment or increasing the interval time between treatments. In some cases, it is also possible to reduce the dose of bendamustine. In general, infections are not a major concern with the use of bendamustine.

**New Evidence:** Could you comment on the risk of second malignant neoplasms among patients treated with bendamustine?

**Dr. Rummel:** Results from our study comparing BR to R-CHOP demonstrated a total of 20 malignancies with BR, compared to 23 malignancies after R-CHOP. This data suggests there is no increased risk of secondary neoplasms with the use of bendamustine. However, the observation period is too short and the number of patients is too small to draw strong conclusions.

**New Evidence:** How would you compare the toxicity of fludarabine versus bendamustine?

**Dr. Rummel:** In our study in the relapsed setting comparing BR to FR, the toxicity of fludarabine and bendamustine appeared to be similar. However, the risk of secondary malignancies appears higher with fludarabine, but strong conclusions cannot be made without longer follow-up data on bendamustine.

**New Evidence:** What is your biggest safety challenge when using bendamustine?

**Dr. Rummel:** Bendamustine commonly induces nausea, which should be treated with anti-emetic agents. Some patients also experience hematologic toxicities; however, these are usually easily managed. In addition, there have been some reports of skin reactions, which should be treated with prednisone and anti-histamines. In physicians routinely treating with prednisone, skin reactions are rarely reported and this has never been a dose-limiting toxicity.

**New Directions:**

**New Evidence:** What new combinations of bendamustine are being investigated?

**Dr. Rummel:** In a number of ongoing studies, bendamustine is being combined with other agents such as bortezombib, GA101, lenalidomide, CAL-101, and new kinase inhibitors. Thus far, it is unclear whether any of these combinations are superior to BR. To date, BR is the best combination regimen available and it appears to be difficult to combine bendamustine with other cytostatic drugs or fludarabine. One combination that shows some promise is the rituximab, bendamustine, and cytarabine (R-BAC) regimen used in MCL. Given the success of the BR combination, I do see bendamustine being used as a backbone chemotherapy. Although there are currently only a few studies available using other bendamustine combinations, there is a high motivation to use bendamustine given the successful clinical experience with this agent.

Optimizing Treatment Strategies for Indolent Non-Hodgkin Lymphoma

CD20 is an important target for the treatment of B-cell malignancies, including non-Hodgkin lymphoma (NHL). B-cell depletion therapy using monoclonal antibodies against CD20, such as rituximab, has revolutionized the treatment of these disorders by greatly improving response rates, progression-free survival (PFS), and overall survival (OS).<sup>1,2</sup> However, the typical approach to the treatment of newly diagnosed, asymptomatic patients with indolent disease, including follicular lymphoma (FL), has been to delay treatment and follow a watchful waiting strategy unless they have symptomatic nodal disease, compromised end organ function, B symptoms, symptomatic extranodal disease, or cytopenias. Ongoing studies are exploring strategies of early treatment with rituximab monotherapy in asymptomatic patients.<sup>3</sup>

Following initial therapy, relapse is an expected and common occurrence in NHL and thus, there remains a need for treatments that delay the onset of relapse. Various approaches are being explored, including new chemotherapies, small molecules, antibody-drug conjugates, and the use of alternative B-cell targets.<sup>1</sup> GA101 is the first type II glycoengineered CD20 monoclonal antibody in phase II/III clinical trials for NHL and chronic lymphocytic leukemia (CLL). In preclinical models, GA101 mediated enhanced direct cell death and increased antibody-dependent cellular cytotoxicity (ADCC) compared with other anti-CD20 antibodies.<sup>4</sup> The body of evidence supporting its clinical utility in patients with relapsed/refractory NHL and CLL is continually growing and demonstrating that this agent is efficacious and well tolerated.

Bendamustine is a bi-functional chemotherapeutic agent that combines the properties of an alkylating agent and a purine analogue. Bendamustine-containing regimens have shown high response rates and long lasting remissions in relapsed/refractory indolent B-cell malignancies. It has a favourable side-effect profile and the presently available clinical data strongly suggests that bendamustine is a valuable addition to the treatment armamentarium for patients with indolent lymphomas.<sup>5</sup>

Data from studies examining GA101, bendamustine, and new rituximab treatment strategies in indolent lymphomas were presented at ASH 2011:

- In a phase I/II study (BO20999) of a heavily pretreated group of relapsed/refractory indolent NHL patients, GA101 monotherapy showed encouraging efficacy with an acceptable safety profile. Two dose levels were evaluated and a dose response relationship was observed with a higher response observed at a higher dose of GA101 and a response rate of 50% was observed in rituximab-refractory patients.<sup>5</sup>

- In the first head-to-head study of GA101 vs. rituximab in relapsed indolent NHL patients, the phase II GAUSS study demonstrated that GA101 was well tolerated and associated with higher response rates compared with rituximab while PFS was similar.

- The final results of the phase I GAUDI study (BO21000), which evaluated GA101 with fludarabine and cyclophosphamide (FC) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with relapsed or refractory follicular lymphoma, demonstrated that GA101 can be combined safely and effectively with chemotherapy regimens used in the treatment of relapsed/refractory follicular lymphoma.

- A substudy of the Primary Rituximab and Maintenance (PRIMA) trial concluded that the rituximab maintenance did not negatively impact disease- or treatment-related symptoms and was generally comparable to no treatment. In addition, the low rates of adverse events caused by chemotherapy induction improved during the rituximab maintenance/observation phase.
• Retreatment of patients with relapsed/refractory lymphomas with bendamustine-containing regimens was found to be tolerable and associated with high response rates.

• An observational study aimed to delineate differences in the management strategies for newly diagnosed follicular lymphoma patients by comparing the outcomes and safety of common treatments including watchful waiting and the initiation of active therapy with rituximab upon diagnosis. It was concluded that rituximab monotherapy prolonged the time to first chemotherapy among patients with stage III/IV disease when compared with watchful waiting.

• In the phase III RESORT study comparing two different dosing strategies for low tumour burden follicular lymphoma patients, it was determined that rituximab retreatment was as effective as rituximab maintenance with respect to time to treatment failure.


Efficacy and safety of obinutuzumab (GA101) monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma: results from a phase I/II study (GAUGUIN, BO20999)

Background
The efficacy of GA101 monotherapy in patients with relapsed/refractory indolent non-Hodgkin lymphoma (iNHL) is currently under investigation in the phase I/II GAUGIN (BO20999) study. At ASH 2011, Salles and colleagues reported their updated results following a median observation time of 32 months for the phase I portion of the GAUGIN study and 23 months for the phase II portion.1

Study design
• The phase I portion of the GAUGIN study was a non-randomized dose-escalating study with a 3 + 3 design (n = 21) of GA101 monotherapy (50-2,000 mg) on days 1 and 8 of cycle 1, and on day 1 of cycles 2–8 (21-day cycles). (Study design – phase I)
• The primary objective of phase I of this study was to determine the safety and pharmacokinetics of GA101 in patients with NHL.

Study design – phase I

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IRR = infusion related reaction; NHL = non-Hodgkin lymphoma
• In phase II, patients with iNHL were randomized to receive GA101 at one of two doses:
  ◦ 1,600 mg on days 1 and 8 of cycle 1 and then 800 mg on day 1 of cycles 2–8 (1,600/800 mg; n = 22);
  ◦ 400 mg on days 1 and 8 of cycle 1 and on day 1 of cycles 2–8 (400/400 mg; n = 18). (Study design – phase II)
• The primary efficacy endpoint of the phase II portion of the study was end of treatment response, assessed four weeks after the last infusion.
• Secondary endpoints included safety, pharmacokinetics, best overall response (BOR), and progression-free survival (PFS).

**Study design – phase II**

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**Key findings**

• In iNHL patients that were enrolled in phase I (n = 16), response was observed in nine patients (56%), with a complete response (CR) in five patients (31%) and a partial response (PR) in four patients (25%).
• Responses were observed across all dose levels and there was no clear dose-response relationship.
• The median duration of response for the phase I portion was 32 months (range: 3–36 months).
• In phase II, baseline patient characteristics were similar for each of the two dose cohorts with respect to age, disease histology and stage, and prior therapies.
• Most patients enrolled had follicular lymphoma (FL).
• For all patients in the phase II portion, the end of treatment responses were as follows:
  ◦ Objective response rate (ORR): three patients (17%) and 12 patients (55%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
  ◦ Complete response/unconfirmed complete response (CR/CRu): no patients and two patients (9%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
  ◦ Partial response (PR): three patients (17%) and 10 patients (45%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
• The median duration of response for the phase II portion was 17 months (range: 1–20 months).
• In the subset of 12 and 10 patients in the 400/400 mg and 1,600/800 mg dose groups who were rituximab refractory, objective responses were also observed at the following rates:
  ◦ ORR: one patient (8%) and five patients (50%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
  ◦ CR/CRu: no patients and one patient (10%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
  ◦ PR: one patient (8%) and four patients (40%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
• When evaluating the FL subpopulation, 14 patients were treated with 400/400 mg and 20 patients were treated with 1,600/800 mg. Responses were observed at the following rates:
  ◦ BOR: five patients (36%) and 12 patients (60%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
  ◦ CR/CRu: one patient (7%) and four patients (20%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
  ◦ PR: four patients (29%) and eight patients (40%) in the 400/400 mg and 1,600/800 mg dose groups, respectively.
• After a median observation time of 23.1 months, median PFS for patients with FL was 11.8 months (range: 1.8–22.8 months) for the 1,600/800 mg cohort and 6.0 months (range: 1.0–23.0 months) for the 400/400 mg cohort (hazard ratio [HR]: 0.77 [95% CI: 0.34–1.77]). (Figure 1)

**Figure 1. GAUGUIN iNHL phase II study: progression-free survival in FL patients**

![Progression-free survival graph](image)

**In the phase II study, GA101 was well tolerated at both dose levels.**
• Infusion-related reactions (IRRs) were the most common adverse event (AE).
Grade 3/4 AEs were more common in the 1,600/800 mg cohort than in the 400/400 mg cohort and that occurred in more than 5% of patients included infections and infestations, neutropenia and IRRs. (Table 1).

**Table 1. GAUGUIN iNHL phase II: All grade 3/4 events**

<table>
<thead>
<tr>
<th></th>
<th>400/400 mg (n = 18)</th>
<th>1,600/800 mg (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total AEs, n</strong></td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>–</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia, n (%)</td>
<td>–</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Lymphopenia, n (%)</td>
<td>1 (6)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Neutropenia, n (%)</td>
<td>–</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Febrile neutropenia, n (%)</td>
<td>–</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Infections and infestations, n (%)</td>
<td>1 (6)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Infusion-related reaction, n (%)</td>
<td>–</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Asthenia, n (%)</td>
<td>–</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pleural effusion, n (%)</td>
<td>1 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>1 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Cytolytic hepatitis, n (%)</td>
<td>–</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Suicide attempt, n (%)</td>
<td>–</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>1 (6)</td>
<td>–</td>
</tr>
</tbody>
</table>

– indicates that no events were observed

AEs = adverse events; iNHL = indolent non-Hodgkin lymphoma

**Key conclusions**

- GA101 monotherapy shows encouraging efficacy in this group of heavily pretreated relapsed/refractory iNHL patients.
- In the phase II study, a higher response was observed at a higher dose of GA101 (1,600/800 mg vs. 400/400 mg) and a response rate of 50% was observed in rituximab-refractory patients.
- Promising PFS and response duration for monotherapy with a CD20 antibody is reported.
- GA101 demonstrated an acceptable safety profile at both dose levels in the phase II study.
- Based on these data and pharmacokinetic studies, a 1,000 mg flat dose of GA101 was taken forward to subsequent studies.
- Phase III trials are ongoing in GA101 in combination with chemotherapy for first-line treatment of patients with advanced iNHL.


Sehn LH, et al. ASH 2011: Abstract 269

**Randomized phase II trial comparing GA101 (obinutuzumab) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: preliminary analysis of the GAUSS study**

**Background**

Single-arm clinical studies of GA101 have demonstrated responses in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL), but to date there have been no direct comparisons with rituximab. The aim of this randomized phase II trial (GAUSS) conducted by Sehn and colleagues was to compare efficacy and safety of monotherapy with GA101 compared with rituximab in patients with relapsed indolent NHL (iNHL). Their findings were presented at ASH 2011.

**Study design**

- Patients with relapsed iNHL requiring therapy who had demonstrated a prior response (complete response/unconfirmed complete response [CR/CRu] or partial response [PR] to a rituximab-containing regimen lasting longer than six months were eligible for the GAUSS trial.
• Patients stratified by histology (follicular lymphoma [FL] or non-follicular iNHL) were randomized 1:1 to receive induction therapy that consisted of four weekly infusions (on days 1, 8, 15, and 22) of either GA101 (1,000 mg; n = 87) or rituximab (375 mg/m²; n = 88).

• The end of treatment response was assessed between 28 and 42 days after the last induction dose.

• Patients without evidence of disease progression following induction therapy received ongoing maintenance treatment with GA101 or rituximab every two months for up to two years at the same dose. (Study design)

• The primary endpoint was overall response rate (ORR) to induction therapy in the FL patients.

• Secondary endpoints included CR/CRu to induction therapy, best ORR achieved during induction or maintenance, safety and toxicity, progression-free survival (PFS), event-free survival (EFS), duration of response, pharmacokinetics, pharmacodynamics, and pharmacogenetics.

**Key findings**

• A total of 175 patients (149 FL and 26 non-follicular iNHL) were enrolled.

• Treatment arms were well balanced for standard prognostic features including age, Eastern Cooperative Oncology Group performance status (ECOG PS), Ann Arbor stage, follicular lymphoma international prognostic index (FLIPI) risk score at initial diagnosis, lactate dehydrogenase (LDH), and prior treatment characteristics.

• Patients in both arms had received a median of two prior lines of therapy (range: 1–7 in the GA101 arm and 1–6 in the rituximab arm) and 99% had received prior rituximab.

• At baseline, patients in the GA101 cohort had a larger volume of disease based on the median sum of product diameters (SPD).

• The primary efficacy analysis was conducted in the FL patients at the end of induction.

• Based on investigator assessment, ORR for GA101 was 44.6% (33/74) vs. 33.3% (25/75) for rituximab.

• The difference in response rates was 11.3% (95% CI: −5.1–27.6; \( p = 0.08 \)).

• The CR/CRu rate in the GA101 arm was 12.2% vs. 5.3% for rituximab.

• At the time of analysis 28/149 patients had progressed; 15/74 on GA101 and 13/75 on rituximab.

• A central blinded independent radiology review (IRF) was performed to independently assess response. In FL patients the IRF determined that:

  • The ORR for GA101 was 44.6% (33/74) and for rituximab it was 26.7% (20/75).

  • The difference in response rates by the IRF was 17.9% (95% CI: −2.0–33.8; \( p = 0.01 \)).

  • In the overall population (FL and non-follicular iNHL), the ORR as assessed by investigators was 44.3% (39/88) vs. 31.0% (27/87) and by the IRF was 44.3% (39/88) vs. 23.0% (20/87) for GA101 and rituximab, respectively.

---

**Study design**

- **Randomization**
  - Relapsed CD20-positive iNHL
  - Prior response ≥6 months to last rituximab regimen

- **Induction**
  - Rituximab 375 mg/m² iv weekly x 4

- **End of Induction visit**
  - GA101 1,000 mg iv weekly x 4

- **Maintenance**
  - Rituximab 375 mg/m² iv every 2 months x 12
  - GA101 1,000 mg iv every 2 months x 12

- **End of maintenance visit**

**Stratified by histology and country**

CT scans continue every six months for two years after the completion of maintenance based upon the International Working Group criteria (Cheson BD, et al. J Clin Oncol. 1999;17(4):1244.)

CT = computed tomography; iNHL = indolent non-Hodgkin lymphoma; iv = intravenous; PD = progressive disease
The PFS in FL patients, as assessed by the investigators, had a hazard ratio of 1.1 (95% CI: 0.6–1.8). (Figure 1)

The investigator-assessed EFS in FL patients was 17.3 months in the GA101 group and 17.4 months in the rituximab group.

Safety was analyzed in the overall population and includes the induction and maintenance periods as well as 28 days following the last dose of study drug.

No new safety signals were observed in either the GA101 or rituximab arms.

Table 1. Safety summary for overall population

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Rituximab (n = 86)</th>
<th>GA101 (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one AE</td>
<td>70 (81)</td>
<td>81 (93)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6 (7)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Patient with AE leading to death within 28 days of last dose</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patient with AE leading to withdrawal from treatment</td>
<td>9 (10)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Patients with at least one SAE</td>
<td>12 (14)</td>
<td>12 (14)</td>
</tr>
</tbody>
</table>

Includes treatment period (induction and maintenance) plus 28 days after last dose

AE = adverse event; SAE = serious adverse event

More patients in the GA101 arm reported infusion-related reactions (IRRs) (GA101 vs. rituximab: any grade, 74% vs. 51%; grade 3/4, 11% vs. 6%).

IRRs were primarily seen during the first infusion and decreased in both frequency and severity with subsequent infusions.

Other AEs (any grade) that occurred at a rate greater than 5% and with higher incidence in the GA101 group included fatigue (25% vs. 20%), cough (21% vs. 6%), back pain (8% vs. 2%), decreased appetite (9% vs. 3%), and bronchitis (7% vs. 3%).

There were no notable differences in rates of AEs between the induction and maintenance phases of the study. (Figure 2)
Key conclusions

■ The phase II GAUSS study is the first head-to-head study of GA101 vs. rituximab in relapsed iNHL.
■ Treatment with GA101 resulted in higher response rates compared with rituximab as assessed by both investigators and the IRF.
■ PFS was similar for both GA101 and rituximab.
■ GA101 was well tolerated and had a similar safety profile to rituximab, with the exception of higher rates of IRRs and cough in patients treated with GA101 but this did not result in significant differences in treatment discontinuation.
■ GA101 is currently under study in phase III trials in combination with chemotherapy.


Radford J, et al. ASH 2011: Abstract 270

Obinutuzumab (GA101) in combination with FC or CHOP in patients with relapsed or refractory follicular lymphoma: final results of the phase I GAUDI study (BO21000)

Background
To date no studies have examined the safety and activity of GA101 in combination with chemotherapy, or compared GA101 dose levels in large cohorts. In the GAUDI (BO21000) study Radford and colleagues evaluated the feasibility, safety, and efficacy of GA101 in combination with standard chemotherapy regimens for FL at two different doses of GA101. Their findings were presented at ASH 2011.

Study design
• The GAUDI study is a phase I study in which patients with relapsed or refractory FL (n = 56) were stratified by chemotherapy regimen based upon prior treatment history:
  ◦ CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) – six to eight 21-day cycles (n = 28);
  ◦ FC (fludarabine and cyclophosphamide) – four to six 28 day cycles (n = 28).
• Patients were then randomized to have GA101 added to their chemotherapy regimen at one of two dose levels:
  ◦ 1,600 mg on days 1 and 8 of cycle 1 followed by 800 mg for subsequent cycles (1,600/800 mg);
  ◦ 400 mg in all cycles (400/400 mg).
• The resulting treatment groups were G-CHOP (GA101 + CHOP) or G-FC (GA101 + FC).
• These regimens represent a range of active doses in indolent lymphoma, based upon phase I and II trials in which there were no dose-limiting toxicities (DLTs).
• Responding patients were offered maintenance treatment for two years or until progression.
• The primary objective of this study was safety and the evaluation of response rates was a secondary objective.
• Response was assessed at the end of induction using International Working Group response criteria, which were modified to classify unconfirmed complete response (CRu) as partial response (PR).

Key findings
• Baseline characteristics were similar for both groups (G-CHOP and G-FC, respectively):
  ◦ Median age 62.5 and 61.0 years;
  ◦ Patients with a low-risk FLIPI of 29% in both groups;
  ◦ Median prior treatments 1 (range: 1–3) and 2 (range: 1–6);
  ◦ Bone marrow involvement 25% and 26%;
  ◦ Ann Arbor stage III/IV at study entry 64% and 82%.
• All patients (28/28) in the G-CHOP arm and 22/28 patients in the G-FC arm completed treatment.

• Reasons for withdrawal (G-FC arm) were:
  ◦ Neutropenia (n = 3);
  ◦ Rash (n = 1);
  ◦ Infection (n = 1);
  ◦ Insufficient response (n = 1).

• The most common AEs in both groups were infusion-related reactions (IRRs), which occurred mostly during the first infusion at the following rates:
  ◦ All grades: 64% in patients treated with G-CHOP and 79% of patients treated with G-FC;
  ◦ Grade 3/4: 7% in G-CHOP and 7% in G-FC.

• Grade 3 or 4 neutropenia was reported in 39% of G-CHOP patients and 50% of G-FC patients.

• Of 190 cycles of G-CHOP delivered, 11 cycles (6%) were delayed in eight patients for neutropenia or infection (six cycles delayed by one week and five cycles delayed by two weeks).

• The dose of any CHOP component was reduced in 29% of patients: in five patients for neuropathy and in one patient each because of neutropenia, infection, and allergic rhinitis.

• In the G-FC group, 14 of 135 delivered cycles (10%) were delayed in 10 patients for hematologic toxicity or infections (10 cycles delayed by one week; four cycles delayed by two weeks).

• Nine of these patients also had a dose reduction in both cytostatic components of the regimen with one additional patient having a dose reduction in only one component, for an overall dose reduction in 36% of patients.

• Three deaths were reported following G-FC induction treatment (progressive disease [n = 1]; underlying Parkinson’s disease [n = 1]; and chronic obstructive pulmonary disease during maintenance [n = 1]), with none considered to be treatment-related.

• There was no evidence for increased toxicity with the 1,600/800 mg dose compared with the 400/400 mg dose of GA101.

• The overall response rates (ORR) at the end of induction were:
  ◦ G-CHOP: 96.4% (39.3% CR);
  ◦ G-FC: 92.9% (50.0% CR). (Table 1)

<table>
<thead>
<tr>
<th>Response</th>
<th>G-CHOP (n = 28)</th>
<th>G-FC (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>27 (96.4)</td>
<td>26 (92.9)</td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (39.3)</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (57.1)</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>No response assessment</td>
<td>0</td>
<td>1 (3.6)</td>
</tr>
</tbody>
</table>

G-CHOP = GA101, cyclophosphamide, doxorubicin, vincristine, prednisone; G-FC = GA101, fludarabine, cyclophosphamide

• Data from the G-CHOP cohort were compared in a matched-pair analysis to the rituximab plus CHOP (R-CHOP) arm from study M39022 (EORTC 20981) in a similar patient population.

• Response rates to G-CHOP compared favourably with response rates to R-CHOP. (Table 2)
Key conclusions

- GA101 can be combined safely with chemotherapy regimens used in the treatment of relapsed/refractory FL and demonstrates a high level of activity.

- G-CHOP could be delivered at the protocol specified three-weekly interval in most patients.

- G-FC in a more heavily pretreated population showed worse tolerability.

- Across both the G-CHOP and G-FC cohorts, there was no evidence for an increased incidence of neutropenia at the higher doses of GA101.

- GA101 demonstrated a high level of activity when combined with CHOP and FC.

- The GAUDI study has now been extended to include first-line FL patients treated with G-CHOP and G-bendamustine.

- Following these promising results, GA101 will be studied in combination with CHOP and other chemotherapies in a randomized phase III study against the standard of care, R-CHOP.


Zhou X, et al. ASH 2011: Abstract 3661

Symptoms and toxicity of rituximab maintenance versus observation following rituximab plus chemotherapy in patients with follicular lymphoma

Background
The Primary Rituximab and Maintenance (PRIMA) study demonstrated that two years of rituximab maintenance therapy following immunochemotherapy as first-line treatment of follicular lymphoma reduced the risk of disease progression compared with observation only.1 Per-protocol analyses showed that rituximab maintenance did not adversely affect patient-reported quality of life (QoL). In this substudy of the PRIMA study presented at ASH 2011, Zhou and colleagues report detailed analyses on symptom burden and toxicity.2

Study design
- PRIMA was an international, multicentre, phase III, open-label, randomized study of patients with previously untreated, advanced follicular lymphoma (FL).
- In the induction phase, patients received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP); rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP); or rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM).
- The treatment was selected according to the investigator’s routine practice.
- Patients who received eight infusions of rituximab in combination with chemotherapy and achieved a complete response (CR) or partial response (PR) at the end of induction treatment (n = 1,018) were randomized to either rituximab maintenance or observation.
- After randomization, patients in the rituximab group were treated with 375 mg/m² every eight weeks for two years or until disease progression.
- The objectives of this study were to describe the changes in patient symptoms from the end of induction to the end of maintenance and analyze the difference in symptom improvement between the rituximab maintenance and observation arms.
- The timing and frequency of toxicity were also analyzed during the maintenance/observation phase.
- Symptoms were assessed using the 12 symptom items in the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 items (QLQ-C30) at baseline, end of induction, one year of maintenance treatment, and end of two years of maintenance treatment.
Safety data were collected for all patients using a checklist with Common Terminology Criteria for Adverse Events (CTCAE), which were reported for each cycle of chemotherapy during induction and each eight-week period during the maintenance/observation period.

**Key findings**
- The sample consisted of all patients entered into the maintenance phase who completed at least one observation or treatment (n = 1,009).
- The assessment at the end of induction was considered baseline.
- At baseline, being tired (72%), need to rest (71%), feeling weak (61%), and trouble sleeping (57%) were the most frequently reported symptoms.
- These symptoms were followed by shortness of breath (39%), pain (34%), pain interfering with daily activities (31%), constipation (28%), and lack of appetite (24%).
- The least frequently reported symptoms were vomiting (4%), diarrhea (17%), and nausea (18%). (Table 1)
- None of the symptom changes were statistically significantly different between the rituximab maintenance and observation groups (p >0.10).
- By the end of the maintenance/observation phase, more patients had better symptom scores than worse symptom scores.
- Notable improvement (percentage of patients with improved symptoms minus percentage with worsened symptoms of 5% or greater) was seen for fatigue symptoms, trouble sleeping, shortness of breath, lack of appetite, and nausea.
- No symptom was observed to have worsened from baseline (i.e., the percentage worsened minus percentage improved was no more than 3%).
- Exploratory analyses suggests that those in the rituximab maintenance group had almost twice the odds of improvement in pain as those in the observation group (odds ratio [OR] = 1.97; 95% CI: 1.03–3.79; p = 0.04) after adjusting for time and pain severity at baseline.
- No significant difference in the likelihood of improvement was seen for any other symptom between maintenance and observation (p >0.05).
- In general, those who reported more severe symptoms at maintenance baseline were more likely to experience improved symptoms and there was no difference between the end of the first year after induction and the end of the second year in experiencing symptom improvement.
- Hematologic toxicity was the most frequently reported toxicity at the beginning of maintenance (>20% of patients had leukocytosis) and it gradually decreased over time in both the rituximab maintenance and observation groups.
- The frequency of other toxicities is summarized in Table 2.

**Table 1. Symptom score at maintenance baseline**

<table>
<thead>
<tr>
<th>Symptom, n (%)</th>
<th>Symptom score</th>
<th>1 (Not at all)</th>
<th>2 (A little)</th>
<th>3 (Quite a bit)</th>
<th>4 (Very much)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>N 310</td>
<td>206 (66)</td>
<td>80 (26)</td>
<td>16 (5)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Pain interfering with daily activities</td>
<td>296</td>
<td>205 (69)</td>
<td>60 (20)</td>
<td>23 (8)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Need to rest</td>
<td>311</td>
<td>90 (29)</td>
<td>153 (49)</td>
<td>54 (17)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Feeling weak</td>
<td>311</td>
<td>120 (39)</td>
<td>129 (41)</td>
<td>52 (17)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Being tired</td>
<td>307</td>
<td>86 (28)</td>
<td>147 (48)</td>
<td>52 (17)</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>314</td>
<td>192 (61)</td>
<td>81 (26)</td>
<td>33 (11)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>313</td>
<td>134 (43)</td>
<td>114 (36)</td>
<td>43 (14)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>315</td>
<td>240 (76)</td>
<td>54 (17)</td>
<td>17 (5)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>314</td>
<td>257 (82)</td>
<td>43 (14)</td>
<td>9 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>315</td>
<td>302 (96)</td>
<td>12 (4)</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>310</td>
<td>222 (72)</td>
<td>71 (23)</td>
<td>13 (4)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>307</td>
<td>256 (83)</td>
<td>38 (12)</td>
<td>9 (3)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

Data are for patients with symptoms scores at both maintenance baseline and end of treatment.
Key conclusions

- These results suggested rituximab maintenance did not negatively impact disease- or treatment-related symptoms and was generally comparable to no treatment.
- The rate of adverse events was low and hematologic toxicity induced during chemotherapy treatment improved in the maintenance/observation phase.


Retherapy with bendamustine-containing regimens in patients with relapsed/refractory CLL and indolent lymphomas achieves high response rates

Table 2. Toxicity in maintenance/observation phase

<table>
<thead>
<tr>
<th>Toxicity (CTCAE grade 1 or higher) %</th>
<th>Observation</th>
<th>Rituximab Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal hemoglobin</td>
<td>3–9</td>
<td>6–16</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>3–21</td>
<td>8–25</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2–13</td>
<td>5–15</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>4–8</td>
<td>5–9</td>
</tr>
<tr>
<td>Infection with a normal neutrophil count</td>
<td>4–9</td>
<td>7–11</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>4–12</td>
<td>8–17</td>
</tr>
<tr>
<td>Gastric symptoms</td>
<td>2–8</td>
<td>5–10</td>
</tr>
<tr>
<td>Elevated AST or ALT</td>
<td>6–10</td>
<td>8–11</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>1–4</td>
<td>3–6</td>
</tr>
<tr>
<td>Neurologic toxicity</td>
<td>5–14</td>
<td>5–14</td>
</tr>
</tbody>
</table>

Adverse event rate was calculated at each visit for each treatment arm. The ranges (min–max) of adverse event rate reported over the 12 visits are presented in the table.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events.
BM: bendamustine (90 mg/m\textsuperscript{2} on days 1 and 2) plus mitoxantrone (6–10 mg/m\textsuperscript{2} on day 1) every 29 days for up to four cycles;
BR: bendamustine (90 mg/m\textsuperscript{2} on days 1 and 2) plus rituximab (375 mg/m\textsuperscript{2} on day 1) every 29 days for up to six cycles;
BMR: bendamustine (90 mg/m\textsuperscript{2} on days 1 and 2) plus mitoxantrone (6 mg/m\textsuperscript{2} on day 1) plus rituximab (375 mg/m\textsuperscript{2} on days 8, 15, 22, and 29) with BM being repeated on day 36 for up to three cycles every four weeks.

- Patients who were treated between the years 2000 and 2010 were analyzed retrospectively following data collection from patient files.

**Key findings**
- 88 patients (57 with CLL and 31 with iNHL) received a bendamustine-based retreatment regimen.
- The median age at the first bendamustine retreatment was 72 years (range: 50–88 years).
- The mean number of prior therapies per patient was 6.4 and the mean number of bendamustine-containing therapies was 1.9.
- The overall response rate (ORR) for bendamustine retreatment was 76% (7% complete response [CR], 69% partial response [PR]).
- ORR rates decreased as the line of retreatment increased. (Figure 1)
- The main toxicity was grade 3 or 4 hematotoxicity in 42% of retreatments.
- Patients with iNHL experienced a slightly higher rate of hematotoxicity than those with CLL. (Figure 2)
- The overall survival (OS) since start of bendamustine-containing retreatment was 28 months (range: 2–129+ months). (Figure 3)

### Figure 1. Response rate of bendamustine-containing retherapies

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bendamustine-containing retherapies (N = 164)</td>
<td>7%</td>
<td>69%</td>
<td>76%</td>
</tr>
<tr>
<td>First retherapy (n = 88)</td>
<td>8%</td>
<td>70%</td>
<td>79%</td>
</tr>
<tr>
<td>Second retherapy (n = 88)</td>
<td>8%</td>
<td>64%</td>
<td>72%</td>
</tr>
<tr>
<td>Third to ninth retherapy (n = 37)</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
</tr>
</tbody>
</table>

CR = complete response; ORR = overall response rate; PR = partial response

### Figure 2. Hematotoxicity (WHO grade 3/4)

<table>
<thead>
<tr>
<th></th>
<th>Hematotoxicities</th>
<th>No hematotoxicities</th>
<th>Not evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>42%</td>
<td>55%</td>
<td>3%</td>
</tr>
<tr>
<td>Bendamustine-containing therapies (n = 252)</td>
<td>38%</td>
<td>58%</td>
<td>5%</td>
</tr>
<tr>
<td>Other therapies (n = 307)</td>
<td>21%</td>
<td>66%</td>
<td>12%</td>
</tr>
<tr>
<td>CLL</td>
<td>38%</td>
<td>58%</td>
<td>5%</td>
</tr>
<tr>
<td>Bendamustine-containing therapies (n = 172)</td>
<td>21%</td>
<td>66%</td>
<td>12%</td>
</tr>
<tr>
<td>Other therapies (n = 170)</td>
<td>21%</td>
<td>66%</td>
<td>12%</td>
</tr>
<tr>
<td>NHL</td>
<td>50%</td>
<td>50%</td>
<td>9%</td>
</tr>
<tr>
<td>Bendamustine-containing therapies (n = 80)</td>
<td>50%</td>
<td>50%</td>
<td>9%</td>
</tr>
<tr>
<td>Other therapies (n = 137)</td>
<td>24%</td>
<td>67%</td>
<td>9%</td>
</tr>
</tbody>
</table>

CLL = chronic lymphocytic lymphoma; NHL = non-Hodgkin lymphoma; WHO = World Health Organization
Key conclusions

■ Bendamustine-containing retreatment regimens resulted in high response rates in patients with relapsed/refractory CLL and iNHL.

■ Bendamustine retreatment is tolerable with hematotoxicity being observed at a relevant rate but it was reversible.


Examining the outcomes of watchful waiting among U.S. patients with advanced stage follicular lymphoma

Background
Watchful waiting has been an initial strategy for asymptomatic advanced stage low grade follicular lymphoma (FL) because randomized trials have shown no clear benefit for immediate initiation of therapy with single agent alkylators when compared with deferring therapy.1,2 However, a recent randomized trial in asymptomatic patients raises questions about watchful waiting in the era of rituximab-based frontline therapies since it showed that immediate treatment with rituximab monotherapy delayed time to initiation of new treatment and improved progression-free survival (PFS).3

In the National LymphoCare Study (NLCS) presented at ASH 2011, Sinha and colleagues aimed to delineate differences in the management strategies for newly diagnosed FL patients by comparing the outcomes and safety of common treatments.4

Study design
• The NLCS is a prospective, multicentre, observational study that collected data on 2,727 newly diagnosed FL patients from 2004 to 2007 at 265 U.S. sites (80% of which were non-academic).
• Initial management decisions were made by the treating physician and had no influence from the study. These decisions were categorized as:
  ◦ Watchful waiting: for patients who did not receive therapy in the 90-day period following diagnosis;
  ◦ Active therapy: included rituximab monotherapy, rituximab-chemotherapy, or other.
• Safety data were limited to treatment-related toxicity as measured by death and early treatment discontinuation.
• The objectives of the study were to compare the characteristics and outcomes of patients who receive active treatment to those who receive a watchful waiting approach as an initial management strategy for FL and to examine whether initial treatment with rituximab monotherapy is associated with a longer time to initiation of chemotherapy when compared with watchful waiting.
• All time to event analyses were calculated from the 90-day period following diagnosis to allow enrollment in watchful waiting, and PFS was calculated from the starting point to the clinician’s recording of progressive disease (PD) or death.
• The primary endpoint was overall survival (OS).
• Secondary endpoints included PFS, time to next treatment (TTNT), time to first chemotherapy (comparing watchful waiting and rituximab monotherapy), PFS after first active treatment and PFS after second management strategy. (Figure 1)

Key findings
• Among 1,822 patients presenting with stage III/IV FL in the analysis population, 270 underwent watchful waiting and 1,462 received active therapy immediately following diagnosis including:
  ◊ 232 patients were treated with rituximab monotherapy;
  ◊ 1,019 patients were with rituximab-chemotherapy;
  ◊ 211 patients were treated with other therapies including 129 patients treated with investigational therapy, 48 with chemotherapy and 34 with radiation, bone marrow transplant, or another form of therapy.
• Multivariable logistic regression demonstrated that the following patient characteristics were predictive of selection of watchful waiting rather than initial active therapy: age >60 years, no B-symptoms, FL grade 1 or 2, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, one or more extranodal sites involved, and lactate dehydrogenase (LDH) greater than upper limit of normal (ULN) (all \( p < 0.05 \)).
• With a median follow-up of 58 months, 18% of watchful waiting patients and 20% of active therapy patients have died, with no significant difference in OS between the two groups.
• Median PFS was longer for the active therapy patients than for those in watchful waiting.

• Compared with watchful waiting, rituximab-chemotherapy improved PFS (adjusted hazard ratio [HR] = 0.41; \( p < 0.0001 \)). (Figure 2)

Figure 2. PFS outcome for active therapy compared with watchful waiting

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.65</td>
<td>0.0015</td>
</tr>
<tr>
<td>PFS-Active</td>
<td>0.41</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for sex, treatment setting (academic/community), histology grade, and FLIPI components (age, number nodal sites, LDH, hemoglobin) at diagnosis.

FLIPI = follicular lymphoma international prognostic index; HR = hazard ratio; LDH = lactate dehydrogenase; PD = progressive disease; PFS = progression-free survival

---

**Figure 1. Endpoints for analysis**

• Primary endpoint – Overall survival (OS)

• Secondary endpoints
  ◊ Progression-free survival (PFS)
  ◊ Time to next treatment (TTNT)*
  ◊ Time to first chemotherapy (TTchemo; comparing watchful waiting and rituximab-monotherapy)
• Progression-free survival after first active treatment (PFS-active)
• Progression-free survival after second management strategy (PFS2)

*For the watchful waiting strategy, this is time to first active treatment

AT = active therapy; PD = progressive disease
Key conclusions

- In this observational study, there were notable differences in patient characteristics, including disease histology, grade, and FLIPI, between watchful waiting and active therapy groups.
- There were no significant differences in OS between watchful waiting patients and those who initiated active therapy upon diagnosis at a median follow-up of five years.
- The findings of this study were consistent with other studies that showed an improvement in PFS and TTNT with active therapy vs. watchful waiting.
- Rituximab monotherapy prolonged the time to first chemotherapy among patients with stage III/IV FL when compared with watchful waiting after adjusting for key characteristics including sex, treatment setting, histology, grade, and FLIPI components at diagnosis.

Table 1. Reasons for initiation of second management strategy*

<table>
<thead>
<tr>
<th>Patient status, %</th>
<th>Watchful waiting (n = 270)</th>
<th>Rituximab-monotherapy (n = 232)</th>
<th>Rituximab-chemotherapy (n = 1,019)</th>
<th>Other (n = 211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New treatment initiated</td>
<td>63</td>
<td>47</td>
<td>36</td>
<td>49</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>70</td>
<td>72</td>
<td>64</td>
<td>54</td>
</tr>
<tr>
<td>Toxicity</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Patient decision</td>
<td>13</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Maintain previous response</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Multiple reasons/other reasons</td>
<td>10</td>
<td>16</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

*Second management strategy = first active therapy for watchful waiting patients or second active therapy for actively treated patients

References:
Results of Eastern Cooperative Oncology Group Protocol E4402 (RESORT): a randomized phase III study comparing two different rituximab dosing strategies for low tumour burden follicular lymphoma

Background
The optimal management for low tumour burden follicular lymphoma (FL) in the rituximab era is uncertain. Historical data with watchful waiting approaches are associated with a mean of three years to the initiation of chemotherapy but rituximab monotherapy has been shown to be active and well tolerated in frontline low tumour burden FL and it may provide a low-risk treatment strategy which could delay the time to first chemotherapy.

Kahl and colleagues hypothesized that after initial therapy, rituximab maintenance (with an extended scheduled dosing) will prolong disease control compared with rituximab retreatment upon disease progression. Previously untreated, low tumour burden FL is an ideal patient population in which to test this hypothesis. E4402 is a randomized phase III study that compares rituximab maintenance with rituximab retreatment in patients with previously untreated low tumour burden FL. The results of this study were presented at ASH 2011.1

Study design
• Patients with low tumour burden FL received rituximab at a dose of 375 mg/m² weekly for four weeks.
• Responders were randomized to rituximab maintenance which consisted of a single 375 mg/m² dose every three months or to rituximab retreatment at progression which consisted of weekly doses of 375 mg/m² for four weeks.
• Each strategy was continued until treatment failure.

(Study design)
• The primary endpoint, time to treatment failure (TTTF), was defined as progression within six months of the last rituximab dose, no response to rituximab retreatment, initiations of alternative therapy, or inability to complete protocol therapy.
• Secondary endpoints included time to first cytotoxic therapy, quality of life (QoL), and toxicity.

Key findings
• From November 2003 to September 2008, 384 patients with FL were enrolled.
• Complete or partial response to induction therapy was achieved by 274 patients (71%), who were then randomized to rituximab maintenance (n = 140) or rituximab retreatment (n = 134).
• Baseline patient demographics at randomization were similar in the two arms:
  o Median age 59 years;
  o Performance status of 0–1 in all patients;
  o FLIPI low-risk (14.9% vs. 16.4%), intermediate-risk (46.3% vs. 42.9%) and high-risk (38.8% vs. 40.7%) for rituximab retreatment or rituximab maintenance, respectively.

Study design

*Continue until treatment failure
No response to retreatment or PD within 6 months of rituximab
Initiation of cytotoxic therapy or inability to complete treatment

CR = complete response; PD = progressive disease; PR = partial response
• With a median follow-up of 3.8 years, TTTF was 3.9 years for rituximab maintenance vs. 3.6 years for rituximab retreatment ($p = 0.8$). (Figure 1)

**Figure 1. Primary endpoint: time to treatment failure**

![Graph showing time to treatment failure](image)

- At three years, 95% of rituximab maintenance vs. 86% of rituximab retreatment patients ($p = 0.03$) remained free of cytotoxic therapy. (Figure 2)

**Figure 2. Time to first cytotoxic therapy**

![Graph showing time to first cytotoxic therapy](image)

• At one year after randomization, there was no discernible difference in health related QoL and anxiety between the two arms.

• Grade 3/4 hematologic and non-hematologic toxicities occurred in less than 5% of patients. (Table 1)

• The median number of rituximab doses/patient (including the four induction doses) was 15.5 (range: 5–31 doses) for rituximab maintenance and 4 (range: 4–16 doses) for rituximab retreatment.

<table>
<thead>
<tr>
<th>Table 1. Toxicity</th>
<th>Rituximab retreatment grade 3</th>
<th>Rituximab retreatment grade 4</th>
<th>Rituximab maintenance grade 3</th>
<th>Rituximab maintenance grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Platelets</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fever without neutropenia</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Infection</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>–</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Insomnia</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Larynx pain</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Totals</td>
<td>4</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**Key conclusions**

- In previously untreated, low tumour burden FL patients, rituximab retreatment was as effective as rituximab maintenance with respect to TTTF.

- Notably, the time to initiation of cytotoxic therapy was delayed in both arms compared to historical watchful waiting strategies with similarly defined low tumour burden FL populations.

- Rituximab maintenance was slightly superior than rituximab retreatment for delaying time to cytotoxic therapy but the cost was 3.5 times as high.

- Maintenance rituximab did not improve QoL or anxiety.

- In summary, rituximab retreatment produces outcomes comparable to rituximab maintenance in this patient population.

New Agents for DLBCL and MCL

Aggressive non-Hodgkin lymphoma (NHL) encompasses a heterogeneous group of cancers of which the most common is diffuse large B-cell lymphoma (DLBCL). Other types of aggressive NHL include mantle cell lymphoma (MCL), HIV/AIDS-related NHL and Burkitt’s lymphoma. Cure of the disease is the primary treatment goal for newly diagnosed aggressive NHL patients. For patients with relapsed disease the goal is to achieve complete response (CR) and extend the duration of remission thereby increasing the chance of a cure.1 Ongoing research efforts aim to achieve these treatment goals with new treatment combinations that are associated with equal or superior efficacy and reduced toxicity.

New agents under investigation for the treatment of DLBCL and MCL include bendamustine, temsirolimus, and GA101 either alone or in combination. Additionally, a better understanding of the role rituximab plays in the treatment of these B-cell malignancies is needed. Data from studies evaluating these agents in clinical trials were presented at ASH 2011:

- A prospective safety/efficacy phase II study of cyclophosphamide with bendamustine and rituximab (R-BAC) in previously untreated MCL patients older than 65 years and in relapsed or refractory patients demonstrated that high rates of CR are achievable and that the treatment is well tolerated with mainly hematological toxicities observed.
- A phase I/II study of temsirolimus with bendamustine and rituximab in patients with relapsed MCL and follicular lymphoma demonstrated that this combination was feasible with mainly hematologic toxicity observed. The preliminary analysis suggests encouraging response.
- BO20999, a phase I/II study of GA101 monotherapy in patients with relapsed/refractory aNHL, indicates that GA101 is well tolerated and shows encouraging single-agent efficacy in heavily pretreated patients with relapsed/refractory DLBCL or MCL, including those patients who were refractory to rituximab.
- A phase II trial of high dose sequential therapy with rituximab, dose-intensive cyclophosphamide, etoposide, and cisplatin (RDICEP) then rituximab, carmustine (BCNU), etoposide, cytarabine (Ara-C), and melphalan (RBEAM)/autologous stem cell transplantation (ASCT) for patients who have unfavourable interim restaging 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scans after two cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) showed that the addition of rituximab to DICEP-BEAM may slightly decrease relapse for poor prognosis DLCBL patients but that it did not improve progression-free survival (PFS).
- The addition of rituximab to fludarabine and cyclophosphamide chemotherapy in the phase III NCRI trial of MCL patients indicates that this treatment combination leads to a significant improvement in both PFS and overall survival (OS) with an acceptable level of additional toxicity.

Rituximab, bendamustine and cytarabine (R-BAC) is a very active regimen in mantle cell lymphoma patients not eligible for intensive chemotherapy or autologous transplant

**Background**

Bendamustine and rituximab in combination have relevant clinical activity in mantle cell lymphoma (MCL), and a favorable toxicity profile. It has been recently demonstrated that bendamustine and cytarabine, a key drug in the treatment of younger patients with MCL, are strongly synergistic in *in vitro* studies.

Visco and colleagues studied the combination of cytarabine with bendamustine and rituximab (R-BAC) in previously untreated MCL patients 65 years and older and in patients relapsed or refractory to one previous line of immunochemotherapy. Their findings were presented at ASH 2011.

**Study design**

- This prospective safety/efficacy phase II study was divided into two parts:
  - The dose-finding part that aimed to establish the maximum tolerated dose (MTD) of cytarabine to be administered with fixed doses of rituximab (375 mg/m²) and bendamustine (70 mg/m²).
  - After the first six patients (3 + 3) were enrolled and completed treatment, the first dose level of cytarabine (800 mg/m²) was validated as the MTD for the extension part of the study.
- All subsequent patients received four to six cycles of rituximab 375 mg/m² on day 1, bendamustine 70 mg/m² on days 2 and 3 and cytarabine 800 mg/m² on days 2, 3, and 4.
- Treatment cycles were administered every four weeks.
- The primary objectives of the study were to assess the safety of R-BAC, and determine overall and complete response (OR and CR) rates.

**Key findings**

- Six patients discontinued treatment: three due to serious adverse events (SAEs), two because of disease progression or lack of response, and one because of the patient’s decision.
- Baseline characteristics of the study cohort are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients (n = 40)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>54–82</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>AAS</td>
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<td></td>
</tr>
<tr>
<td>I–II</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>III–IV</td>
<td>37</td>
<td>93</td>
</tr>
<tr>
<td>Bulky mass</td>
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<tr>
<td>Yes</td>
<td>17</td>
<td>41</td>
</tr>
<tr>
<td>No</td>
<td>23</td>
<td>59</td>
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<td>WHO performance status</td>
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<tr>
<td>0–1</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td>Patient status</td>
<td></td>
<td></td>
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<tr>
<td>Previously untreated</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td>20</td>
<td>50</td>
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<tr>
<td>Prior chemotherapy</td>
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<tr>
<td>R-CHOP</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td>R-HyperCVAD ± autotransplant</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>R-CVP/chlorambucil</td>
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<td>21</td>
</tr>
<tr>
<td>R-FCM</td>
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<td>5</td>
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<tr>
<td>Refractory</td>
<td>7</td>
<td>36</td>
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<tr>
<td>Histology/grading</td>
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<td></td>
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<tr>
<td>Classic MCL</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>Blastoid variant</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Ki-67, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26% (5–65)</td>
<td></td>
<td></td>
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<tr>
<td>IPI risk category</td>
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<td></td>
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<tr>
<td>Intermediate high/high</td>
<td>19</td>
<td>47</td>
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<td>MIPI risk category</td>
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<td></td>
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<tr>
<td>High</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

AAS = Ann Arbor stage; CVP = cyclophosphamide, vincristine, prednisone; CVAD = cyclophosphamide, vincristine, adriamycin, dexamethasone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; FCM = fludarabine, cyclophosphamide, mitoxantrone; IPI = international prognostic index; MCL = mantle cell lymphoma; MIPI = mantle cell lymphoma international prognostic index; R = rituximab; WHO = World Health Organization
• The median follow-up for survivors was 16 months (range: 2–30 months).

• Overall, R-BAC was very well tolerated.

• Toxicity was primarily hematological and was significantly more frequent in previously treated patients than in those who were treatment naive. (Table 2)

• Platelet transfusion was required in 75% of delivered cycles and the median duration of grade 3/4 neutropenia was two days (range: 0–5 days).

• Of the non-hematological toxicities, those most commonly observed were grade 1–3 fatigue in 36% of patients and gamma-GT elevation in 42% of patients.

• According to the recently revised position emission tomography (PET)-including response criteria, the overall response rate (ORR) was 95% for treatment-naïve patients and 82% for relapsed and refractory patients.

• The CR rates were 85% for previously untreated patients and 76% for relapsed and refractory patients. (Table 3)

• At a median follow-up from the start of therapy of 16 months the progression-free survival (PFS), overall survival (OS) and duration of response (DOR) are shown in Figure 1.

Table 2. Hematological toxicity according to therapy line

<table>
<thead>
<tr>
<th>Grade 3/4 event</th>
<th>Overall (n = 173)</th>
<th>Untreated (n = 96)</th>
<th>Relapsed/refractory (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cycles</td>
<td>%</td>
<td>Number of cycles</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>83</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>132</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>Anemia</td>
<td>85</td>
<td>49</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 3. Response rates

<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Number of patients</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>PD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>20</td>
<td>95</td>
<td>85</td>
<td>10</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td>17</td>
<td>82</td>
<td>76</td>
<td>6</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

CR = complete response; NR = no response; ORR = overall response rate; PD = progressive disease; PR = partial response

Figure 1. Overall survival, progression-free survival and duration of response following R-BAC

DOR = duration of response; OS = overall survival; PFS = progression-free survival; R-BAC = rituximab, bendamustine, cytarabine on day 31, and 375 mg/m2 on day 33

Key conclusions

■ The R-BAC combination induces high rates of PET-negative CR in both treatment-naïve and relapsed and refractory MCL patients.

■ R-BAC is well tolerated even in older patients with MCL with mainly hematological toxicities observed.

■ The duration of response appears to be promising but a longer follow-up period is required.

Temsrolimus in combination with bendamustine and rituximab for the treatment of relapsed mantle cell and follicular lymphoma: an ongoing phase I/II trial

**Background**

mTOR inhibition has been shown to be effective in various subtypes of malignant lymphomas. Based on a phase III trial in relapsed mantle cell lymphoma (MCL), which proved the superiority of temsirolimus, an mTOR inhibitor, over standard options, the drug was approved for this indication in Europe. Additionally, promising response rates have been observed in patients with follicular and diffuse large B-cell lymphoma (FL and DLBCL) who were treated with temsirolimus. Combining temsirolimus with rituximab seems feasible and has improved efficacy. However, limited information exists on the feasibility and efficacy of temsirolimus in combination with a chemotherapeutic agent such as bendamustine, which has been shown to be effective in indolent lymphoma and has a beneficial side effect profile.

Hess and colleagues initiated a phase I/II trial to evaluate the potential of the combination of temsirolimus with bendamustine and rituximab in patients with relapsed MCL and FL. Their findings were presented at ASH 2011.

**Study design**

- This was a non-randomized, multicentre, prospective trial in FL and MCL patients with two phases.
- The objective of the first phase was to define the maximum tolerated dose (MTD) and safety of a regimen containing bendamustine, rituximab, and temsirolimus; dose-limiting toxicities (DLTs) were evaluated after two cycles of therapy.
- The objective of the second phase was to evaluate the objective response rate (ORR) of this treatment regimen following four cycles of therapy.
- Treatment consisted of bendamustine 90mg/m² day 1 and 2, rituximab 375mg/m² day 1, and temsirolimus at escalating doses on days 2, 8, and 15 of a 28 day cycle.
- A total of four cycles was planned with interim staging after two cycles.
- In the ongoing first phase of the study the following dose cohorts for temsirolimus were planned:
  - Cohort A: 25mg;
  - Cohort B: 50mg;
  - Cohort C: 75mg.
- An independent data safety monitoring board decided on the escalation to the next dose level following evaluation of DLTs.

**Key findings**

- To date, 13 patients have been enrolled and 11 were evaluable (six patients were enrolled in cohort A, three patients were enrolled in cohort B and four were enrolled in cohort C, which is continuing accrual).
- Baseline characteristics include:
  - Median age: 74 years (range: 51–75 years);
  - Sex: two females and nine males;
  - Histology: two FL and nine MCL;
  - Median number of previous treatments: 2 (range: 1–3).
- The treatment was well tolerated overall.
- The predominant toxicity was hematologic with mostly lymphocytopenia, neutropenia, leukopenia, and thrombocytopenia observed. (Figures 1 and 2)
- Other notable grade 3/4 toxicities included two cases of angioneurotic edema (potentially related to ACE-inhibitor intake) and one case each of cerebral insult and hypertensive crisis.
- One incident of grade 2 transient parasthesia occurred during the study phase.
- Apart from the incidence of hypertension, all of these events occurred several days after the last application of study drug and were considered not to be associated to the study treatment.
- As the episode of hypertension led to hospital admission, it was considered to be a potential DLT; however, cohort A accrued a total of six patients with no further DLTs.
- Six patients have completed the entire treatment.
- At interim staging nine patients were evaluable for response.
  - The ORR was 100% (all patients achieved PR).
- After completion of the entire treatment ORR was 100% with one complete remission (CR) and eight partial remissions (PR) in nine evaluable patients. (Figure 3)
Figure 1. Lab adverse events during cycles 1 and 2

Figure 2. Lab adverse events during cycles 3 and 4

Figure 3. Best response in nine evaluable patients

ANC = absolute neutrophil count; CRP = C-reactive protein

CR= complete remission; ORR = objective response rate; PR = partial remission
Key conclusions

■ In this ongoing phase I/II trial the combination of temsirolimus with bendamustine and rituximab was feasible.
■ Temsirolimus doses of up to 50 mg weekly for three weeks could be administered in 28-day cycles.
■ The evaluation of the 75 mg dose level of temsirolimus is currently underway.
■ Toxicity was primarily hematologic and two cases of angioneurotic edema were noted in patients taking angiotensin-converting enzyme (ACE)-Inhibitors, which should strongly be discouraged.
■ To date, promising response rates have been observed with most patients achieving a PR.
■ The longest remission observed on this study is ongoing for more than one year.
■ Recruitment for the second phase of this study is expected to begin in the first quarter of 2012 and 30 patients with FL and 30 patients with MCL will be recruited.


Morschhauser F, et al. ASH 2011: Abstract 3655

Encouraging activity of obinutuzumab (GA101) monotherapy in relapsed/refractory aggressive non-Hodgkin lymphoma: results from a phase II study (BO20999)

Background

Obinutuzumab (GA101) is a type II glycoengineered, humanized anti-CD20 monoclonal antibody that has increased antibody-dependent cellular cytotoxicity (ADCC) and direct cell death activity but lower complement-dependent cytotoxicity (CDC) compared with type I anti-CD20 antibodies such as rituximab and ofatumumab. GA101 is in clinical development for the treatment of lymphoma and chronic lymphocytic leukemia (CLL). The phase I/II study BO20999 evaluated the efficacy and safety of GA101 monotherapy in patients with relapsed/refractory aggressive non-Hodgkin lymphoma (aNHL).

In this study, Morschhauser and colleagues evaluated the updated phase II results of BO20999 including progression-free survival (PFS) and best overall response (BOR). They reported their results at ASH 2011.

Study design

• Patients with relapsed/refractory aNHL were randomized to receive GA101 (on days 1, 8 and 22 and then every 21 days thereafter) for a total of nine infusions.
• GA101 was administered as a flat dose, not adjusted for body weight.
• Two dose cohorts were included in this study:
  ○ Arm 1: GA101 at a dose of 400 mg on days 1 and 8 of cycle 1 and 400 mg on day 1 of cycles 2–8.
  ○ Arm 2: GA101 at a dose of 1,600 mg on days 1 and 8 of cycle 1 and 800 mg on day 1 of cycles 2–8.
• The primary endpoint was end of treatment response, assessed four weeks after the last infusion (planned 25 weeks after treatment initiation).
• Secondary endpoints included safety, pharmacokinetics, BOR, and PFS.
Key findings

- A total of 40 patients were enrolled in this study.
- Baseline patient characteristics were similar for both cohorts.
  - The median age of the entire study group was 71 years (range: 22–85 years).
  - More patients in the 1,600/800 mg treatment group have diffuse large B-cell lymphoma (DLBCL) and had received prior stem cell therapy compared with patients in the 400/400 mg treatment group.
- The median observation time for all patients was 9.5 months (range: 0.3–26.1 months).

Efficacy

- BOR rates are summarized in Table 1.
- BOR rates according to diagnosis were:
  - DLBCL: eight of 25 patients (32%) responded (80% CI: 20–47).
  - MCL: four of 15 patients (27%) responded (80% CI: 12–46).
- BOR rates according to GA101 dosages were:
  - 400/400 mg: five of 21 patients (23.8%) responded (80% CI: 12.1–39.7).
  - 1,600/800 mg: seven of 19 patients (36.8%) responded (80% CI: 21.8–54.1).
- Among the patients with rituximab-refractory disease:
  - Partial response (PR) was observed in one of 13 patients (7.7%) in the 400/400 mg cohort.
  - Four of 12 patients (33.3%) treated in the 1,600/800 mg cohort responded.
  - Three patients had DLBCL and all achieved a complete response (CR).
  - One of the patients had MCL and this patient achieved PR.
  - The median PFS for patients with DLBCL was 1.9 months (range: 0.3–15.7 months) for the 400/400 mg cohort and 2.7 months (range: 0.2–22.3 months) for the 1,600/800 mg cohort (hazard ratio: 0.70; 95% CI: 0.30–1.66). (Figure 1)

<table>
<thead>
<tr>
<th>Table 1. Best overall response according to diagnosis and cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, n (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>CRu</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>No response assessment</td>
</tr>
</tbody>
</table>

CR = complete response; CRu = unconfirmed complete response; DLBCL = diffuse large B-cell lymphoma; MCL = mantel cell lymphoma; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Figure 1. Progression-free survival for patients with diffuse large B-cell lymphoma
Key conclusions

- For the DLBCL subgroup, the duration of response was 3.1, 5.8, and 19.5 months for three of the five responders in the 1,600/800 mg cohort and response was ongoing for the other two responders (at 3.1 and 16.5 months).
- For the three DLBCL responders in the 400/400 mg cohort, the duration of response was 6.3, 8.6, and 9.8 months.
- For the MCL group, the PFS and median duration of response were not calculated as only four patients were available for this analysis; however, individual response data indicated that two MCL patients had an ongoing response for 20.0 and 20.4 months and the two remaining responders responded for 11.2 and 5.5 months.
- Of the patients who were refractory to rituximab, three patients in the 1,600/800 mg group and one in the 400/400 mg group had a response duration greater than nine months.

Pharmacokinetics

- Pharmacokinetic studies indicated that GA101 plasma concentrations were higher in the 1,600/800 mg group compared with the 400/400 mg group in both DLBCL and MCL patients.
- Data from other phase I and phase II studies suggest that MCL patients showed lower GA101 serum concentrations compared with DLBCL patients, which could be due to the tumour burden but the data set and high inter-patient variability in this study precluded drawing similar conclusions.

Safety

- GA101 was well tolerated in both cohorts.
- Infusion-related reactions (IRRs; all grades) were the most common adverse event (AE), occurring in 81% of patients in the 400/400 mg cohort and 68% of patients in the 1,600/800 mg cohort.
- Grade 3/4 AEs occurring in more than 5% of patients across both cohorts included IRRs, tumour lysis syndrome, cardiac failure (not treatment-related), anemia, and thrombocytopenia.
- The rates of these AEs in each of the cohorts are summarized in Table 2.

Table 2. Grade 3/4 adverse events occurring in more than 5% of patients across both treatment arms

<table>
<thead>
<tr>
<th>Grade 3/4 AE, n (%)</th>
<th>400/400 mg (n = 21)</th>
<th>1,600/800 mg (n = 19)</th>
<th>All (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRR*</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Tumour lysis syndrome†</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cardiac failure‡</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (14)</td>
<td>1 (5)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Thrombocytopenia§</td>
<td>3 (14)</td>
<td>0 (0)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

* IRRs were transient; two events resolved on day 1 and one event lasted for three days.
† The reported grade 3/4 IRRs did not result in discontinuation of treatment.
‡ Both events were reported by MCL patients.
§ All events were reported by MCL patients. Two of three patients had a low baseline count (48,000 and 81,000) and the third patient was in the normal range (count of 170,000).

AE = adverse event; IRR = infusion-related reaction

**Background**

Approximately 55% of patients with stage 3 or 4 diffuse large B-cell lymphoma (DLBCL) and elevated serum lactate dehydrogenase (LDH) achieve long-term progression-free survival (PFS) following rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy.

Stewart and colleagues designed a prospective, multicentre, phase II clinical trial to evaluate the use of high dose sequential therapy with rituximab, dose-intensive cyclophosphamide, etoposide, and cisplatin (RDICEP) then rituximab, carmustine (BCNU), etoposide, cytarabine (Ara-C), and melphalan (RBEAM)/autologous stem cell transplantation (ASCT) for patients who have unfavourable interim restaging 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scans after two cycles of R-CHOP. The trial was designed to minimize false positive interim restaging PET scans by only enrolling poor prognosis patients, and modifying response interpretation criteria such that unfavourable PET response required more than one site with uptake more intense than background liver. The hypothesis was that interim PET response would stratify patients into good R-CHOP responders who should avoid upfront ASCT, and poor R-CHOP responders who may benefit from upfront ASCT, resulting in an overall PFS rate of 80%. Their findings were presented at ASH 2011.

**Study design**

- Patients with stage 3 or 4 DLBCL and elevated serum LDH were eligible for this study.
- Treatment was initiated with R-CHOP and an FDG-PET/CT scan was performed 10 to 15 days following the second cycle of R-CHOP.
- Patients who had a favourable interim PET response were treated with four additional cycles of R-CHOP.
- Patients with unfavourable PET response received:
  - One cycle of RDICEP (consisting of rituximab 375mg/m² on days 1 and 8; cyclophosphamide 1.75g/m² on days 2 to 4; etoposide 350mg/m² on days 2 to 4; cisplatin 35mg/m² on days 2 to 4, granulocyte colony stimulating factor (G-CSF) on days 15 to 21 and autologous blood stem cell collection on days 21 or 22).
  - This was followed by one cycle of RBEAM/ASCT (rituximab 375mg/m² six days prior to transplant and 14 days following transplant; BCNU 300mg/m² six days prior to transplant, etoposide 200mg/m² five and two days prior to transplant; Ara-C 400mg/m² five and two days prior to transplant; and melphalan 140mg/m² one day before the transplant).
- Both groups could receive intrathecal (IT) chemotherapy or involved field radiation therapy (IFRT) to a single site of disease at physician discretion.
- The objectives of this study were to prospectively study a new definition of unfavourable interim PET/CT response in two centres and to determine if PET-guided RDICEP-RBEAM/ASCT is a feasible treatment approach with acceptable toxicity and a three year PFS of 80%.

**Key findings**

- The target accrual of 70 patients was achieved between May 2007 and July 2011 and all 70 patients have undergone interim PET/CT restaging following two cycles R-CHOP.
  - 34 patients had a favourable PET result.
  - 36 patients had an unfavourable PET result.
- Baseline characteristics included:
  - Median age of 54 years (range: 19–65 years) with 16 (23%) patients older than 60 years.
  - Median international prognostic indicator (IPI) score was 3 (range: 2–5)
- The median follow-up time was 28 months (range: 4–55 months).
• All patients in the favourable PET group completed therapy and 33/36 (92%) of the patients in the unfavourable PET group completed therapy.
  - IFRT was used for eight and seven patients in the unfavourable and favourable PET response groups, respectively.
  - IT chemotherapy was used for zero and three patients in the unfavourable and favourable PET response groups, respectively. (Table 1)
• Of the 36 unfavourable PET patients, three refused the assigned RDICEP-RBEAM/ASCT treatment, nine (25%) relapsed, and three (8%) experienced non-relapse mortality (NRM), which consisted of sepsis five days following ASCT, idiopathic pneumonia 14 months after ASCT, and bronchietasis and congestive heart failure 32 months after ASCT.
• Of the 34 favourable PET patients, 12 (35.3%) relapsed, nine of which were in patients with completely negative PET scans. (Table 1)

The two-year PFS rates were:
- PET unfavourable: 67% (95%CI: 48.3–80.3);
- PET favourable: 55.7% (95%CI: 35.0–71.9). (Figure 1)

The two-year overall survival (OS) rates were:
- PET unfavourable: 70.2% (95%CI: 51.2–82.4);
- PET favourable: 74.6% (95%CI: 51.7–86.8). (Figure 2)

### Table 1. Patient disposition*

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>All patients (n = 70)</th>
<th>PET-negative (n = 34)</th>
<th>PET-positive (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed therapy</td>
<td>67 (96)</td>
<td>34 (100)</td>
<td>33 (92)†</td>
</tr>
<tr>
<td>IFRT</td>
<td>15 (21)</td>
<td>7 (21)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>NRM</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>3 (8)‡</td>
</tr>
<tr>
<td>Relapse</td>
<td>21 (30)</td>
<td>12 (35.3)</td>
<td>9 (25)</td>
</tr>
</tbody>
</table>

* median follow-up of 28 months (range: 4–55 months)
† three patients refused RDICEP-RBEAM
‡ includes sepsis 5 days post ASCT, idiopathic pneumonia 14 months post ASCT, bronchietasis and CHF 32 months post ASCT
CHF = congestive heart failure; IT = intrathecal; PET = positron emission tomography; IFRT = involved field radiation therapy; NRM = non-relapse mortality; RBEAM = rituximab, carmustine (BCNU), etoposide, cytarabine (Ara-C), melphalan; RDICEP = rituximab, dose-intensive cyclophosphamide, etoposide, cisplatin

### Key conclusions

- A favourable interim PET/CT response, as defined in this study following two cycles of R-CHOP, does not identify good prognosis DLBCL patients.
- The addition of rituximab to DICEP-BEAM may slightly decrease relapse for poor prognosis DLBCL patients with unfavourable PET response but it did not improve PFS.
- RDICEP-RBEAM/ASCT may be associated with risks of early and delayed NRM from infection.
- A phase III trial evaluating this PET-guided RDICEP-RBEAM/ASCT approach compared to standard R-CHOP alone is probably not warranted based on the PFS results not approaching the 80% target.

References:
Background
Rituximab is widely used in combination with chemotherapy for treating B-cell lymphoproliferative disorders. In patients with mantle cell lymphoma (MCL), two prior randomized trials explored the addition of rituximab to standard initial therapy. Neither trial demonstrated a significant improvement in either progression-free survival (PFS) or overall survival (OS) although it does improve response rates.

In 2002 the National Cancer Research Network (NCRN) initiated a phase II randomized trial of fludarabine cyclophosphamide (FC) chemotherapy with or without rituximab to evaluate response rates in newly diagnosed MCL patients. In 2006 this trial was extended to a phase III study with OS as the primary end point. At ASH 2011, Rule and colleagues reported on the findings of the phase III trial.1

Study design
• Newly diagnosed patients with MCL requiring therapy were randomized to receive up to eight cycles of:
  ◦ FC: fludarabine 40mg/m² and cyclophosphamide 250mg/m² both daily for three days per cycle every four weeks for up to eight cycles or
  ◦ FCR: FC plus rituximab 375mg/m² on day 1 of each cycle.
• There was no age limit to the study, no risk stratification, and no consolidation of responses with transplantation or maintenance therapy.
• The primary endpoint of the phase III study was OS and secondary endpoints included PFS, toxicity, and response.

Key findings
• 370 patients MCL were randomized.
• The median age of the entire study group was 66 years (range: 36–88 years) and 79% were male.
• The two treatment arms were well balanced by mantle cell international prognostic index (MIPI); 73% in the FC arm and 78% in the FCR arm were in the intermediate or high risk groups.
• 81.7% and 74.6% respectively received four or more cycles of FCR and FC, respectively.
• At the end of treatment the objective response rate (ORR) was 78.2% in the FC arm and 87.5% in the FCR arm (p = 0.02) with complete response plus unconfirmed (CR + CRu) rates of 45.3% and 62.5% (p = 0.002) respectively. (Table 1)

Table 1. Response rates

<table>
<thead>
<tr>
<th>Response, % (n)</th>
<th>FC (n)</th>
<th>FCR (n)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>38.2 (65)</td>
<td>54.2 (91)</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>CRu</td>
<td>7.1 (12)</td>
<td>8.3 (14)</td>
<td></td>
</tr>
<tr>
<td>CR + CRu</td>
<td>45.3 (77)</td>
<td>62.5 (105)</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>PR</td>
<td>32.9 (56)</td>
<td>25.0 (42)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>78.2 (114)</td>
<td>87.5 (147)</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>SD</td>
<td>6.5 (11)</td>
<td>3.0 (5)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>15.3 (26)</td>
<td>9.5 (16)</td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; CRu = complete response unconfirmed; FC = fludarabine cyclophosphamide; FCR = fludarabine cyclophosphamide plus rituximab; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease


The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomized UK National Cancer Research Institute (NCRI) trial
Patients in the FCR arm had longer PFS and OS.
- The median follow-up time was 47.6 months.
- The median PFS for the FC group was 15.9 months vs. 29.8 months for the FCR group (HR = 0.64; 95% CI: 0.42–0.60, p <0.001). (Figure 1)
- The median OS for the FC group was 37.4 months vs. 45.7 months for the FCR group (HR = 0.73; 95% CI: 0.54–0.97, p = 0.03). (Figure 2)
- The majority of toxicities were hematological.

Significantly more patients in the FCR arm experienced grade 3 or 4 leukopenia and thrombocytopenia; however, the numbers of grade 4 events were not significantly different.
- 10.7% of patients in the FC arm and 12.9% of patients in the FCR arm had significant infections.
- Lymphoma was the most common cause of death, but 23% of patients in the FC arm and 28.6% in the FCR arm died of other causes, of which half were infection related.
- An additional 12 patients died of a second malignancy, four of whom had acute myeloid leukemia (AML).

Key conclusions

- The addition of rituximab to FC chemotherapy leads to a significant improvement in both PFS and OS with an acceptable level of additional toxicity.
- A significant number of patients treated with FC-based chemotherapy die while in remission of non-lymphoma related causes.

The CD20 antigen is widely recognized as a key target in the treatment of indolent and aggressive non-Hodgkin lymphoma (NHL). This is evidenced by the clinical importance of rituximab, a type I chimeric monoclonal antibody against CD20, which has become a pillar in the management of these diseases. Despite the success of adding rituximab to cytotoxic induction regimens, a subgroup of patients will eventually relapse and/or become refractory to these regimens. Strategies for using rituximab monotherapy earlier in the treatment algorithm may delay the need for cytotoxic therapy. In addition, novel agents that can be used in the relapsed setting are of key importance in improving outcomes in NHL. Of these new agents, bendamustine and GA101 have demonstrated safety and efficacy in the relapsed setting.

Rituximab continues to play a central role in the treatment of NHL and CLL and efforts are being focused on further optimizing its use. The study by Kahl, et al. (RESORT) examined the benefit of a defined maintenance schedule of rituximab versus retreatment with rituximab when necessary following standard rituximab induction monotherapy in patients with asymptomatic low tumour burden follicular lymphoma (FL). This study was conducted, in patients who typically undergo watchful waiting. The RESORT study complements and builds on the data presented by Ardeshna, et al. at last year’s ASH meeting.1 In the trial by Ardeshna, et al., patients were randomized to receive watchful waiting versus early initiation of rituximab. Patients who received initial rituximab, had a significant delay in time to initiation of cytotoxic therapy. The data provided by Ardeshna and colleagues have greatly influenced clinical practice. In British Columbia, asymptomatic low tumour burden FL patients who would previously have been followed with watchful waiting are now offered four weekly doses of rituximab monotherapy upfront. While associated with an initial cost, this treatment strategy may be more cost effective by delaying the costs associated with cytotoxic chemotherapy.

In the RESORT trial, the optimal schedule of rituximab delivery is further explored. Patients were randomized to either rituximab retreatment when necessary or planned maintenance therapy every three months following standard rituximab induction. Results demonstrate that retreatment (with four additional weekly doses of rituximab) when necessary for asymptomatic FL patients results in a similar time to treatment failure as planned maintenance every three months. Based on the RESORT study, retreatment as necessary is a more favourable strategy than planned maintenance, due to the lower costs and exposure to rituximab associated with this approach.

Bendamustine is a unique cytotoxic agent with a favourable toxicity profile that is approved for the treatment of various hematological malignancies in the United States, Europe, Singapore, Japan, and Hong Kong. Available data provide ample evidence to support the use of bendamustine in the treatment of indolent NHL and mantle cell lymphoma (MCL). While approval in Canada is pending, further studies are examining the use of bendamustine as monotherapy or in combination with other agents in the relapsed setting.

In a retrospective analysis, Weide, et al. evaluated the outcomes of patients with relapsed/refractory CLL and indolent NHL who were retreated with bendamustine. Limited data evaluating the benefit of retreatment with bendamustine are currently available. The study by Weide, et al. suggests that retreatment with bendamustine is effective and well tolerated. While this study is of interest, a number of limitations make definitive conclusions difficult. The study includes a mixed histology patient population (including indolent NHL subtypes and CLL), and patients were retreated with either bendamustine monotherapy or various bendamustine combination regimens. The study does not provide a breakdown of outcomes based on the type of therapy received (monotherapy or combination) or by histologic subgroups. Further data will be required to determine the effectiveness of bendamustine retreatment in individual patient settings.

Visco, et al. evaluated the combination of rituximab, bendamustine and cytarabine (R-BAC) in a phase I/II study in a mixed population of previously untreated and relapsed/refractory elderly patients with MCL. While the R-BAC combination demonstrated favourable overall and complete response rates, this treatment combination appears to be associated with significant toxicity. In particular, the rate of cytopenias was of concern. In 75% of administered treatment cycles, platelet transfusions were required. Studies comparing the R-BAC regimen to recognized standard treatments such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and bendamustine and rituximab (BR) will be required to determine whether there is an efficacy advantage of this novel regimen in this setting.

In another phase I/II trial, Hess, et al. explored the feasibility of combining temsirolimus, bendamustine, and rituximab for the treatment of relapsed MCL and FL. An early analysis of this ongoing trial was presented at ASH 2011. While this
is a novel combination that aims to take advantage of the additive or synergistic benefit of these agents, only a small number of patients were evaluable at the time of presentation. Further data will be needed before we can assess the efficacy and feasibility of this regimen in the setting of relapsed MCL and FL.

Based on available data to date, bendamustine is an effective agent for the management of CLL and indolent NHL. In patients who are not known to be refractory to rituximab, bendamustine and rituximab would likely be the preferred option in settings where combination therapy is typically used. With demonstrated efficacy in both the upfront and relapsed/refractory settings, once available in Canada, it will offer an additional and important new therapeutic option for patients in these settings.

GA101 is a type II, glycoengineered, humanized anti-CD20 monoclonal antibody that has been developed to be more effective in terms of direct cell death and antibody-dependent cellular cytotoxicity (ADCC) than rituximab. To date, available phase I and II data demonstrate GA101 to be generally tolerable, with a similar safety profile to rituximab. In a phase I/II study of GA101 in relapsed/refractory indolent NHL, Salles and colleagues demonstrated a dose-response relationship for GA101, where the larger dose evaluated (1,600/800 mg) resulted in higher and more durable response rates than the lower dose (400/400 mg), although it should be noted that the number of patients enrolled in this study was relatively small. The primary toxicity with GA101 was infusion-related reactions (IRR), which were largely manageable with supportive measures.

Morschhauser, et al. evaluated the activity and safety of GA101 in a phase II study in relapsed/refractory aggressive NHL including patients with diffuse large B-cell lymphoma (DLBCL) and MCL. GA101 was well tolerated in this setting, again demonstrating a similar safety profile to rituximab and to GA101 in other studies. What is most encouraging about the findings of this trial is that GA101 was shown to be effective in a number of rituximab-refractory patients. This suggests that there may be some utility of GA101 in rituximab-refractory patients, which is worthy of further exploration.

Our study (Sehn, et al.) was the first attempt to directly compare GA101 and rituximab. This is a phase II trial which is not powered to provide conclusive results; however, the study provides an initial look at the comparative safety and efficacy of the two agents. Further evidence to support GA101’s favourable safety profile was provided by this study. While there were no unexpected toxicities compared with rituximab, there was a slightly higher rate of IRRs with GA101, the majority of which were low grade and easily managed with supportive measures. Additionally, GA101 was associated with a slightly higher rate of cough than rituximab. In most instances the cough was low grade and was related to IRRs, attributable to respiratory infections, or was non-specific in nature. This study also demonstrated that treatment with GA101 was associated with higher response rates, suggesting better efficacy compared with rituximab. However, it is important to note that results from this phase II comparison will need to fully evaluated in the context of phase III trials.

Initial studies have established the safety and efficacy of GA101 monotherapy. Additional trials are necessary to evaluate whether it can be administered with chemotherapy. The phase I study by Radford and colleagues evaluated the safety and tolerability of GA101 in combination with standard chemotherapy regimens used in the treatment of lymphomas including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and fludarabine and cyclophosphamide (FC). While this early phase study enrolled a limited number of patients, no new safety signals were identified. The toxicities that were observed appeared similar to those expected with rituximab, and it appears that GA101 can be safely delivered with standard chemotherapy regimens.

The dose of GA101 evaluated in the phase II comparative trial by Sehn and colleagues was a flat dose of 1,000 mg (rather than a dose based on body surface area, as is typically used for rituximab). Both pharmacokinetic and efficacy data from initial phase I and II trials have been used to determine the optimal dose of this novel agent. Rituximab and GA101 are unique molecules and dosing cannot be extrapolated from one molecule to the other. GA101 administered at the optimized dose of 1,000 mg will be compared against the standard approved dose of rituximab in ongoing phase III trials.

To date, phase I and II studies of GA101 have yielded encouraging results; however, phase III trials will be required to fully establish the utility of this agent. Phase III studies are currently underway in patients with rituximab refractory NHL, and in untreated patients with CLL, FL, and DLBCL. While data from these key studies are still several years away, they will be necessary in order to confirm the promising efficacy of GA101 that has been observed in the preclinical and early phase trials. The outcome of these phase III trials will serve to establish the role of GA101 and to determine its appropriate position within treatment algorithms for lymphoid malignancies.

New Agents in the Treatment of Lymphoproliferative Disorders

An improvement in the understanding of molecular pathways that dictate the pathogenesis of lymphoproliferative disorders has enabled the identification of new therapeutic options. The discovery of new molecular targets fuels a search for novel agents that can be developed against them. One of the goals of developing new agents is to improve the anti-tumour activity of existing therapies without increasing toxicity. Two such agents discussed at the ASH 2011 meeting were navitoclax and GS-1101.

Navitoclax (ABT-263) is a novel, orally bioavailable, small molecule that promotes apoptosis by binding to Bcl-2, Bcl-XL, and Bcl-w with high affinity. *In vitro*, navitoclax shows potent targeted cytotoxicity against Bcl-2 overexpressing T- and B-cell lymphoid malignancies. Based on phase I trial data, oral navitoclax monotherapy was well-tolerated and had anti-tumour activity in patients with chronic lymphocytic leukemia (CLL). A phase II study showed that combining bendamustine and rituximab (BR) had efficacy in relapsed or refractory CLL1 and phase III studies demonstrated improved outcomes in CLL patients treated with fludarabine, cyclophosphamide, and rituximab (FCR)2,3 and in preclinical models of B-cell lymphoma, navitoclax enhanced the efficacy of rituximab when used alone or in combination with chemotherapy. Therefore, it is hypothesized that adding navitoclax to rituximab-containing regimens could help overcome chemotherapy resistance.

GS-1101 (CAL-101) is an orally bioavailable, small-molecule, highly selective inhibitor of phosphatidylinositol 3-kinase-delta (PI3Kδ). PI3Kδ is expressed in cells of hematopoietic origin where it plays a role in regulating survival and proliferation of normal and malignant B-cells.4 A previous phase I study established 150 mg twice daily as an appropriate single-agent starting dose for GS-1101 and demonstrated that GS-1101 monotherapy is associated with substantial clinical activity in patients with hematologic malignancies. Based on this preliminary evidence, GS-1101 is being further investigated in relapsed or refractory CLL as well as previously treated, indolent non-Hodgkin lymphoma (NHL) as monotherapy and in combination with standard chemoinmunotherapies.

Data from studies evaluating single agent and combination therapy with navitoclax and GS-1101 were presented at ASH 2011:

- In a phase I dose escalation study of navitoclax in combination with bendamustine and rituximab (BR) as well as fludarabine, cyclophosphamide, and rituximab (FCR)1-3 and in preclinical models of B-cell lymphoma, navitoclax enhanced the efficacy of rituximab when used alone or in combination with chemotherapy. Therefore, it is hypothesized that adding navitoclax to rituximab-containing regimens could help overcome chemotherapy resistance.

- A phase I study of GS-1101 in combination with bendamustine and/or rituximab-based regimens in relapsed/refractory CLL demonstrated durable safety and efficacy data in a difficult to treat population.

- Similarly, GS-1101 was evaluated alone and in combination with chemoimmunotherapies in previously treated indolent NHL patients. In this setting, GS-1101 was well tolerated, had no overlapping toxicities, and was able to be administered for extended periods of time with a resulting durable clinical benefit.

Navitoclax (ABT-263) plus fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR): a phase I study in patients with relapsed/refractory CLL

**Background**

Kipps and colleagues examined whether navitoclax could be used safely in combination with fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR) for treatment of patients with relapsed/refractory chronic lymphocytic leukemia (CLL). The primary objectives of this phase I dose escalation study included assessing the safety and pharmacokinetics (PK) of navitoclax in combination with FCR and BR. Secondary objectives included the evaluation of progression-free survival (PFS), objective response rate (ORR), time to tumour progression (TTP), overall survival (OS), and duration of response. Their results were presented at ASH 2011.

**Study design**

- This study is an ongoing, international phase I, open-label, dose-escalation trial that consists of two parts:
  - The first part evaluated the safety and PK of navitoclax plus FCR (arm A) or navitoclax plus BR (arm B) with the objective of defining dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD). The FCR and BR doses remained fixed while the starting dose for navitoclax was 110 mg/day.
  - The second part of the study expanded the safety cohorts to evaluate navitoclax at the recommended phase II dose defined in the first part of the study, in combination with either FCR or BR in a cohort of 12 patients.
- Patients were assigned to arm A or arm B based on physician preference, each consisting of 28-day cycles.
- In both arms, the dose of rituximab was 375 mg/m² on day 1 of cycle 1 and 500 mg/m² on day 2 of cycle 2 and on day 1 of subsequent 28-day cycles.
- In arm A, the fludarabine dose was 25 mg/m² and the cyclophosphamide dose was 175 mg/m² administered on days 2–4 in cycles 1 and 2, and on days 1–3 in subsequent cycles.
- In arm B, the bendamustine dose was 70 mg/m² administered on days 2 and 3 of cycles 1 and 2, and on days 1 and 2 in subsequent cycles.
- Oral navitoclax was administered once daily (starting dose of 110 mg) pre-chemotherapy on days 3–5 of cycle 1 and days 1–3 of subsequent cycles.
- Patients were able to continue navitoclax monotherapy up to the recommended phase II dose of 250 mg daily for up to one year or until progressive disease or intolerable toxicity.

**Key findings**

- As of October 2011, 31 patients (median age 58 years [range: 39–80 years]) have been enrolled in this study.
  - Five patients were treated in arm A (FCR plus navitoclax; 110 mg).
  - 26 patients were treated in arm B (BR plus navitoclax).
    - Seven patients were treated with 110 mg of navitoclax, eight were treated with 200 mg and eight were treated with 250 mg.
    - Three patients have been enrolled in the 250 mg expanded safety cohort.
    - The median number of prior therapies was 2 (range: 1–13).

**Pharmacokinetics**

- For patients treated in arm B, navitoclax PK results were available for 21 patients and bendamustine PK results were available in 14 patients.
- No PK data were available for arm A at the time of this presentation.
- Preliminary PK data suggest that there is no apparent PK interaction between navitoclax and bendamustine.

**Efficacy**

- Preliminary tumour response data were available for 22 patients.
- Four out of five patients were assessed in arm A: two achieved a partial response (PR) and two had stable disease (SD). (Table 1)
- 18 out of 26 patients were assessed in arm B: six achieved a complete response (CR), seven achieved PR, four had SD, and one had progressive disease (PD). (Table 1)
The ORR for arm A was 50% (2/4) and for arm B it was 72% (13/18). (Figure 1)

In arm B, five patients had 17p deletion – two of whom achieved CR and three achieved PR.

Safety
- In arm A, one patient had a DLT of febrile neutropenia (110 mg).
- In arm B, five patients had DLTs:
  - One had elevated liver enzymes (110 mg);
  - One had grade 4 afebrile neutropenia (200 mg);
  - Three had grade 4 thrombocytopenia (250 mg).
- The most common navitoclax-related AEs of any grade in arm B are summarized in Table 2.
- There were no deaths related to navitoclax.

Table 1. Summary of preliminary best responses

<table>
<thead>
<tr>
<th>Objective Tumour Response, n (%)</th>
<th>110 mg; Arm A n = 5</th>
<th>110 mg; Arm B n = 7</th>
<th>200 mg; Arm B n = 8</th>
<th>250 mg; Arm B n = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0 (0)</td>
<td>4 (57)</td>
<td>2 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (40)</td>
<td>1 (14)</td>
<td>3 (38)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (40)</td>
<td>2 (29)</td>
<td>1 (13)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Incomplete data</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>2 (25)</td>
<td>6 (55)</td>
</tr>
</tbody>
</table>

Arm B best responses: seven PR and six CR in 18 evaluable subjects; 72%
Arm A best responses: two PR in four evaluable subjects; 50%
CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Table 2. Treatment-emergent adverse events in Arm B occurring in ≥10% of patients (n = 26)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>25 (96)</td>
<td>17 (65)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (77)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 (46.1)</td>
<td>10 (38.4)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>2 (7.7)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (42)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (31)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (31)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (31)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (27)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (15.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>4 (15.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (15.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>3 (11.5)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Figure 1. Best tumour response percent change from baseline

Tumour response either by physical exam (*) or CT scan
Tumour size was measured as the SPD of the largest lymph node from each nodal site
BR = bendamustine, rituximab; CT = computed tomography; FCR = fludarabine, cyclophosphamide, rituximab;
SPD = sum of the product of greatest diameter
Key conclusions

- The preliminary results evaluating the combination of navitoclax with BR are encouraging as this combination appears to be well tolerated and shows evidence of anti-tumour activity.
- Data for the combination of navitoclax and FCR are limited for this study.
- Preliminary PK evaluations indicated that there was no clinically significant pharmacokinetic interaction between navitoclax and bendamustine.
- The MTD of navitoclax has been reached at 250 mg for arm B, and escalation continues for arm A.
- To date, unacceptable myelotoxicity has not been observed when ravitoclax was used in combination with standard cytotoxic chemoimmunotherapy regimens for the treatment of patients with CLL.

Reference:

Sharman J, et al. ASH 2011: Abstract 1787

A phase I study of the selective phosphatidylinositol 3-kinase-delta (PI3Kδ) inhibitor, CAL-101 (GS-1101), in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL

Background

At ASH 2011 Sharman and colleagues presented the findings of their study evaluating the safety and activity of GS-1101 alone or in combination with rituximab and/or bendamustine as well as fludarabine in patients with previously treated chronic lymphocytic leukemia (CLL).1

Study design

- This was a phase I/II study dose-ranging study that evaluated the safety and efficacy of repeated 28-day cycles of GS-1101 alone or in combination with rituximab and/or bendamustine as well as fludarabine in patients with previously treated chronic lymphocytic leukemia (CLL).1
- The objectives of the study were to evaluate the safety and activity of GS-1101 monotherapy or that of GS-1101 in the following combination regimens:
  - **GR regimen**: GS-1101 was administered starting on day 1 of cycle 1 with rituximab (375 mg/m² on days 1 and 2 of each cycle for six cycles);
  - **GF regimen**: GS-1101 was administered starting on day 1 of cycle 1 with fludarabine (40 mg/m² days 1 to 5 of each cycle for six cycles);
  - **GB regimen**: GS-1101 was administered starting on day 1 of cycle 1 with bendamustine (70 or 90 mg/m² on days 1 and 2 of each cycle for six cycles);
  - **GRB regimen**: GS-1101 was administered starting on day 1 of cycle 1 with rituximab (375 mg/m² on day 1 of each cycle for six cycles) and bendamustine (70 or 90 mg/m² days 1 and 2 of each cycle for six cycles).
- In the monotherapy portion of the study, a wide range of GS-1101 doses were explored (50 to 350 mg BID) and in the combination portion of the study GS-1101 at 100 mg or 150 mg BID was investigated.
  - Initial cohorts of patients received GS-1101 at a dose of 100 mg/dose BID in the GR or GB regimens.
  - Thereafter, all patients received GS-1101 at a dose of 150 mg/dose BID in the GR, GB, or GRB regimens.
- After 48 weeks, patients who continued to benefit were eligible to continue GS-1101 monotherapy on an extension study.
- The endpoints of interest of interest were the selection of a recommended dosing regimen, safety, and anti-tumour activity.
**Key findings**

- Data were available for 55 patients on the GS-1101 monotherapy arm and 54 patients on GS-1101 combination therapies.
- In all groups, the majority of patients were >60 years of age, had bulky adenopathy, and had undergone extensive prior therapy. (Table 1)
- Patients remained on therapy for long periods of time with some continuing on beyond the 12 cycles (48 weeks) for up to two years.

**Safety**

- Grade ≥3 adverse events (AEs) were largely associated with background events from pre-existing disease, toxicity from prior therapy, or intercurrent illness.
- There were no obvious GS-1101-related dose-limiting toxicities (DLTs).
- The AE profile of each of the combination regimens is generally consistent with the known safety profile of each of the agents.
- Patients who experienced elevations in liver transaminases were able to resume GS-1101 therapy after a drug holiday without further abnormalities.

**Efficacy**

- During monotherapy or combination therapy, almost all patients experienced substantial reductions in nodal size resulting in a more than 50% decrease in lymph node area in greater than 75% of patients on all regimens.
- Lymph node shrinkage occurred in two phases: a steep initial reduction followed by a persistent continuing decline. The same pattern was observed in all treatment groups. (Figure 1)
- GS-1101 monotherapy resulted in lymphocyte mobilization which is expected with PI3Kδ inhibition but combination therapy with rituximab or fludarabine resulted in a shorter duration of lymphocytosis and combination with bendamustine almost completely eliminated the increase in absolute lymphocyte count. (Figure 2)
- The nodal response rates, characterized by a greater than 50% decrease on the nodal sum of the product of greatest diameter (SPD), were high and comparable amongst all treatment groups; however, combination therapies substantially increased overall response rates (ORR) compared with GS-1101 monotherapy. (Figure 3a and 3b)
- GS-1101 mono- and combination therapy was associated with durable tumour control.
- The median progression free survival (PFS) for monotherapy was longer than 12 months and the median PFS for the combination therapies has not yet been reached.
- Disease-associated chemokines and cytokines (CXCL13, CCL3, CCL4, and TNFα) that were commonly elevated at baseline were significantly reduced by GS-1101 treatment.

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**Table 1. Chronic lymphocytic leukemia patient characteristics**

<table>
<thead>
<tr>
<th>CLL patient characteristics</th>
<th>Monotherapy</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GS-1101 (n = 55)</td>
<td>GR (n = 19)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>63 (37–82)</td>
<td>66 (54–87)</td>
</tr>
<tr>
<td>Gender, males, %</td>
<td>82</td>
<td>68</td>
</tr>
<tr>
<td>Patients with bulky adenopathy*</td>
<td>82</td>
<td>63</td>
</tr>
<tr>
<td>Relapsed/refractory disease¹, %</td>
<td>29/71</td>
<td>63/37</td>
</tr>
<tr>
<td>Prior therapies, median (range), n</td>
<td>5 (2–15)</td>
<td>2 (1–8)</td>
</tr>
<tr>
<td>Prior therapy type, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purine analog</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>Rituximab</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>87</td>
<td>68</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>33</td>
<td>5</td>
</tr>
</tbody>
</table>

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* Bulky: presence of ≥1 node with diameter ≥5 cm
  ¹ Refractory: progression within 6 months of last therapy
  B = bendamustine; CLL = chronic lymphocytic leukemia; F = fludarabine; G = GS-1101; R = rituximab
Figure 1. Change in lymph node size following treatment

![Graph showing change in lymph node size](image)

GS-1101 Monotherapy

GR
GF
GRB

Cycle, 4 weeks (n)

B = bendamustine; F = fludarabine; G = GS-1101; R = rituximab; SEM = standard error of the mean

Figure 2. Lymphocyte mobilization following treatment

![Graph showing lymphocyte mobilization](image)

GS-1101 Monotherapy

GR
GF
GRB

Cycle, 4 weeks (n)

ALC = absolute lymphocyte count; B = bendamustine; F = fludarabine; G = GS-1101; R = rituximab; SEM = standard error of the mean
Figure 3a. Lymph node and overall response rates for the individual treatments and combinations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LNR*</th>
<th>OR†</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-1101 monotherapy (n = 55)</td>
<td>84%</td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR (n = 19)</td>
<td>84%</td>
<td></td>
<td>84%</td>
<td></td>
<td>84%</td>
<td></td>
<td>71%</td>
<td></td>
<td>79%</td>
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</tr>
<tr>
<td>GF (n = 7)</td>
<td>71%</td>
<td></td>
<td>71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GB (n = 14)</td>
<td>79%</td>
<td></td>
<td>79%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRB (n = 14)</td>
<td>84%</td>
<td></td>
<td>86%</td>
<td></td>
<td>86%</td>
<td></td>
<td>71%</td>
<td></td>
<td>79%</td>
<td></td>
</tr>
</tbody>
</table>

*Decrease by ≥50% in the nodal SPD
†Response by IWCLL criteria (Hallek M. Ann Oncol. 2008;19 Suppl 4:iS1-3.)

B = bendamustine; CI = confidence interval; F = fludarabine; G = GS-1101; ITT = intention-to-treat; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; LNR = lymph node response; OR = overall response; R = rituximab; SPD = sum of the product of greatest diameter

Figure 3b. Lymph node and overall response rates for the GS-1101 monotherapy vs. GS-1101 combination therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LNR*</th>
<th>OR†</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-1101 monotherapy (n = 55)</td>
<td>84%</td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-1101 combination (n = 54)</td>
<td>81%</td>
<td></td>
<td>81%</td>
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*Decrease by ≥50% in the nodal SPD
CI = confidence interval; ITT = intention-to-treat; LNR = lymph node response; OR = overall response

Key conclusions

- A favourable safety profile and lack of overlapping toxicities allows GS-1101 to be delivered at the full single-agent starting dose (150 mg BID) when co-administered with chemoimmunotherapies (rituximab, fludarabine, or bendamustine) in heavily pretreated CLL patients
- GS-1101 is well tolerated for extended periods of exposure which now exceed two years.
- The majority of these hard-to-treat patients experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit.
- The lymphocytosis induced by PI3Kδ inhibition is cleared rapidly when GS-1101 is used in combination with other agents suggesting that GS-1101 mobilization of CLL cells from sanctuary sites may make them more susceptible to combination therapy cell killing.
- The data from this trial will be used to design phase III combination studies of GS-1101 in patients with CLL.

**Phase I study of the selective phosphatidylinositol 3-kinase-delta (PI3Kδ) inhibitor, CAL-101 (GS-1101), in combination with rituximab and/or bendamustine in patients with previously treated, indolent NHL**

**Background**

In this study, de Vos and colleagues evaluated the safety and activity of the phosphatidylinositol 3-kinase-delta (PI3Kδ) inhibitor CAL-101 (GS-1101) when used as a monotherapy or in combination with rituximab and/or bendamustine in patients with previously treated indolent non-Hodgkin lymphoma (iNHL). The results of their study were reported at ASH 2011.

**Study design**

- This phase I/II dose-ranging trial evaluated the safety and efficacy of repeated 28-day cycles of GS-1101 alone or in combination with rituximab and/or bendamustine in patients with previously treated iNHL.

- The objectives of the study were to evaluate the safety and activity of GS-1101 used as a monotherapy or in the following combination regimens:
  - **GR regimen**: GS-1101 was administered starting on day 1 of cycle 1 with rituximab (375 mg/m² weekly for cycles 1 and 2);
  - **GB regimen**: GS-1101 was administered starting on day 1 of cycle 1 with bendamustine (70 or 90 mg/m² on days 1 and 2 of each cycle for six cycles);
  - **GRB regimen**: GS-1101 was administered starting on day 1 of cycle 1 with rituximab (375 mg/m², on day 1 of each cycle for six cycles) and bendamustine (90 mg/m² days 1 and 2 of each cycle for six cycles).

- In the monotherapy portion of the study, a wide range of GS-1101 doses were explored (50 to 350 mg BID) and in the combination portion of the study GS-1101 of 100 mg or 150 mg BID were investigated.

- Initial cohorts of patients received GS-1101 at a dose of 100 mg/dose BID in the GR or GB regimens.

- Thereafter, all patients received GS-1101 at a dose of 150 mg/dose BID in the GR, GB, or GRB regimens.

- After 48 weeks, patients who continued to benefit were eligible to continue GS-1101 monotherapy on an extension study.

- The endpoints of interest were the selection of a recommended dosing regimen, safety, and anti-tumour activity.

**Key findings**

- Data were available for 63 iNHL patients on the GS-1101 monotherapy arm and 52 patients on GS-1101 combination therapies.

- Types of iNHL represented in this study included follicular lymphoma, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and marginal zone lymphoma.

- Follicular lymphoma was the most common type of iNHL in all treatment arms.

- In all groups, a significant proportion of patients had adverse prognostic characteristics including older age (older than 60 years), bulky adenopathy, and refractory disease. (Table 1).

- All patients had received more than one prior treatment regimen and some had received as many as 10, which included rituximab and bendamustine that are the companion drugs to GS-1101 in this study. (Table 1)

- Patients remained on therapy for long periods of time with some continuing on therapy beyond the 12 cycles (48 weeks) and up to two years.

**Safety**

- Grade ≥3 adverse events (AEs) were largely associated with background events from pre-existing disease, toxicity from prior therapy, or intercurrent illness.

- There were no obvious GS-1101-related dose-limiting toxicities (DLTs).

- The AE profile of each of the combination regimens is generally consistent with the known safety profile of each of the agents.

- Patients who experienced elevations in liver transaminases were able to resume GS-1101 therapy after a drug holiday without further abnormalities.

**Efficacy**

- Most patients receiving GS-1101 monotherapy and almost all patients receiving GS-1101 combination therapy experienced substantial tumour regression.
• Single-agent GS-1101 at doses of 100 mg BID or more and all of the combination regimens resulted in high response rates. (Figure 1)

• The overall response rate (ORR) was 83% in patients treated with combination therapies and the complete remission (CR) rate was 19% in the combination therapy group.

• The CR rate ranged from 15% to 25% for the individual GS-1101-based combination therapies. (Figure 1)

• GS-1101 mono- and combination therapy was associated with durable tumour control.

• The median progression free survival (PFS) for monotherapy at doses of 100 mg BID or more was longer than 12 months and the median PFS for the combination therapies has not yet been reached. (Figure 2)

• Disease-associated chemokines and cytokines (CCL17, CCL22, CXCL13, and TNFα) that were commonly elevated at baseline were significantly reduced by GS-1101 treatment.

**Table 1. Non-Hodgkin lymphoma patient characteristics**

<table>
<thead>
<tr>
<th>NHL patient characteristics</th>
<th>Monotherapy</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-1101 (n = 63)</td>
<td>GR (n = 19)</td>
<td>GB (n = 20)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>63 (32–91)</td>
<td>65 (40–83)</td>
</tr>
<tr>
<td>Gender, males, %</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>Patients with bulky adenopathy*</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Relapsed/refractory disease†, %</td>
<td>43/57</td>
<td>58/42</td>
</tr>
<tr>
<td>Prior therapies, median (range), n</td>
<td>4 (1–10)</td>
<td>4 (1–9)</td>
</tr>
<tr>
<td>Prior therapy type, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>Anthracycline/anthracendelone</td>
<td>51</td>
<td>58</td>
</tr>
<tr>
<td>Purine analog</td>
<td>43</td>
<td>26</td>
</tr>
</tbody>
</table>

*Bulky: presence of ≥ 1 node with diameter ≥ 5 cm
†Refractory: progression within six months of last therapy
B = bendamustine; G = GS1101; NHL = non-Hodgkin lymphoma; R = rituximab

**Figure 1. Response rates**

*Cheson 2007 criteria
R = bendamustine; BID = twice a day; CI = confidence interval; CR = complete response;
G = GS-1101; ITT = intent-to-treat; R = rituximab
Key conclusions

■ GS-1101 is well tolerated for extended periods of exposure, which now exceed two years.

■ A favourable and safety profile and lack of overlapping toxicities allows GS-1101 to be delivered at the full single-agent starting dose (150 mg BID) when co-administered with chemoimmunotherapies (rituximab and/or bendamustine) in previously-treated iNHL patients.

■ The majority of these hard-to-treat patients experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit.

■ The data from this trial will be used to design phase III combination studies of GS-1101 in patients with iNHL.


Canadian perspective by Dr. Tom Kouroukis

While significant advances have been made in the treatment of lymphoma, there is still a need to develop efficacious and tolerable newer agents. Two such agents in development are navitoclax – an apoptosis inducing agent and GS-1101 – a phosphatidylinositol 3-kinase-delta (PI3Kδ) inhibitor. Both seem to be active in low-grade lymphomas and chronic lymphocytic leukemia (CLL) and preliminary studies indicate they are tolerable and combine well with traditional chemotherapy agents without introducing significant excess toxicity. In addition, these are oral agents and thus their administration will be facilitated. Novel treatment options for CLL, in particular, are needed. Current standards are fludarabine-based regimens with rituximab and bendamustine will soon be available offering an alternate therapeutic approach but once patients fail these standard regimens, options are limited.

In a phase I study, Kipps and colleagues evaluated the safety and efficacy of adding navitoclax to fludarabine, cyclophosphamide, rituximab (FCR) or bendamustine rituximab (BR) in relapsed/refractory CLL patients. This
was a well-designed dose-finding and safety study with two conventional treatment arms that offered a glimpse at the clinical efficacy of navitoclax. The inclusion of an expansion phase allowed further evaluation of the safety and efficacy of the selected phase II dose. From a mechanistic and toxicity perspective the combination of navitoclax with FCR or BR seems reasonable and is a rational treatment approach. Early efficacy results are encouraging for both arms but in particular for the BR arm where more patients had been enrolled and could be evaluated at the time of this presentation. The high objective response rate (ORR) of 72% for the BR arm of the study was very encouraging. Furthermore, responses were observed in five patients with 17p deletions which is normally a negative prognostic marker. Duration of response might have been a useful endpoint in this study to more clearly demonstrate how well navitoclax might perform but the median follow up may not have been long enough at the time of the data presentation. No significant toxicities were revealed by the addition of navitoclax although some easily managed grade 1 or 2 gastrointestinal toxicities were observed which is to be expected with an oral agent. Neutropenia was observed which is not unexpected in advanced CLL and may not have been caused by the addition of navitoclax to the treatment regimen. The dose-limiting toxicities (DLTs) of elevated liver enzymes, afebrile neutropenia, and thrombocytopenia were reasonable, manageable and not unexpected. Collectively these data demonstrate that navitoclax is a tolerable, novel, oral agent with encouraging and promising results in relapsed/refractory CLL in particular in combination with BR. Based on this study there is enough encouraging evidence to move forward to phase III studies.

In the two phase I studies (Sharman, et al. and de Vos, et al.) the phosphatidylinositol 3-kinase-delta (PI3Kδ) inhibitor GS-1101 was evaluated in combination with rituximab, fludarabine and bendamustine-based regimens in relapsed/refractory CLL and previously treated indolent non-Hodgkin lymphoma (iNHL). GS-1101 is on oral agent with a new mechanism of action and these data demonstrate that it can be combined with traditional cytotoxic agents, monoclonal antibodies and purine analogues. Both of these studies enrolled fairly large numbers of patients which allowed for the generation of robust data. GS-1101 demonstrated activity in a broad spectrum of low-grade lymphoproliferative disorders which could potentially translate into wide range of uses in the clinical setting. As a monotherapy, the response rate in this pre-treated group of patients hovered around a very respectable 40% for an oral agent. The response rates for the various combination therapies were similar (70–90%) and included complete responses (CRs) suggesting that GS-1101 has a broad synergy with existing chemotherapeutics. While determining response rates is important for low grade lymphomas, progression-free survival (PFS) and duration of response (DOR) were considered more important endpoints in these studies as responses can be transient. The DOR was longer than one year and median PFS has not been reached which is very promising. GS-1101 was very well tolerated in both patient groups. While there was a slight change in liver enzymes, this was easily managed and there were no DLTs and no added toxicity when compared with chemo-immune therapy.

With the observation of good responses rates with good DOR, particularly when combining GS-1101 with other treatment regimens, one might speculate that these combinations could have utility in the difficult to treat patients with poor performance status and comorbidities. Since GS-1101 seemed to result in similar benefit when combined with rituximab, fludarabine and bendamustine, it may be reasonable to treat elderly and frail patients with GS-1101 and rituximab. Based on these two studies, there is more than enough information to proceed to phase III studies and this agent has great potential to influence clinical practice in the future. All of the signals for potential success are present including respectable activity a single agent in heavily pretreated patients. In fact the single agent response rates are very reminiscent of rituximab in its early phases of clinical study.

Navitoclax and GS-1101 have unique mechanisms of action that provide physicians new molecular targets in the treatment of low-grade lymphomas and CLL. These new targets enable these agents to be combined with traditional cytotoxic agents with non-overlapping toxicity and the significant advantage of being administered orally. As these new agents continue to be developed, they may initially be used in the relapsed/refractory CLL and third-line iNHL. However, once the phase III trials are completed, they may very well move up to a place of higher priority in the various treatment algorithms.
Building Momentum
New findings at ASH 2011

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