Targeting Patient Fitness
Expanding Treatment Approaches

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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 September 2013 issue presents coverage from the following key conferences: the 2013 Annual Meeting of the Association des Médecins Hématologues et Oncologues du Québec (AMHOQ), the 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO), the 18th Congress of the European Hematology Association (EHA), and the 12th International Conference on Malignant Lymphoma (ICML). This issue reports on key studies testing novel agents that target specific molecular pathways for the treatment of leukemias and lymphomas. In addition to developing targeted therapeutics for these diseases, researchers have optimized current therapies based on the patient’s fitness level in order to meet particular treatment goals — be it to prolong survival or to increase treatment-free intervals — while balancing toxicities with the patient’s quality of life. We would like to thank Dr. Carolyn Owen, Dr. Jaroslav Prchal, and Dr. Laurie Sehn for their Canadian Perspectives, and Dr. Clemens-Martin Wendtner for his International Perspective. We would also like to thank Dr. Valentin Goede and Dr. Francesco Lo-Coco for their Investigator Commentaries.

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- A phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL. (Flinn I, et al. ASCO 2013:TPS7131)

- Obinutuzumab (GA101) or rituximab plus chlorambucil versus chlorambucil alone in patients with CLL and comorbidities: final stage I results of the CLL11 phase III trial. (Goede V, et al. EHA 2013:S567)


Canadian Perspective by Dr. Carolyn Owen
LYMPHOMAS

New and Promising Targeted Drugs are to be Tested in Combination with Standard Treatments for Non-Hodgkin Lymphoma

- A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated indolent NHL. (De Vos S, et al. ASCO 2013:TPS8618 and Czuczman MS, et al. ICML 2013:135)
- A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated indolent NHL. (Leonard J, et al. ASCO 2013:TPS8617)
- The BCL-2 inhibitor ABT-199 (GDC-0199) is active and well tolerated in patients with relapsed or refractory mantle cell lymphoma and other non-Hodgkin lymphomas. (Davids MS, et al. EHA 2013:P849)
- Time and resource savings with rituximab subcutaneous injection versus rituximab intravenous infusion: first results from a time-and-motion study. (De Cock E, et al. EHA 2013:PS07)
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- Gemcitabine, dexamethasone, cisplatin (GDP) compared with dexamethasone, cytarabine, cisplatin (DHAP) salvage chemotherapy prior to autologous stem cell transplantation for relapsed and refractory aggressive lymphomas: final results of the phase III NCIC CTG study LY12. (Crump M, et al. ICML 2013:085)

- The RELEVANCE trial: a LYSA-sponsored phase III randomized study to compare the efficacy and safety of rituximab plus lenalidomide with those of rituximab plus any chemotherapies in patients with previously untreated advanced follicular lymphoma. (Morschhauser F, et al. ICML 2013:136)
- A phase III trial comparing obinutuzumab (GA101) plus CHOP (G-CHOP) versus rituximab plus CHOP (R-CHOP) in previously untreated diffuse large B-cell lymphoma. (Mobasher M, et al. ICML 2013:131)
- Pharmacokinetics, safety, and overall response rate achieved with rituximab sc were comparable to those with rituximab iv in the first-line treatment of patients with follicular lymphoma: stage I results of the phase III SABRINA study. (Davies A, et al. ICML 2013:194)

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Canadian Perspectives

Carolyn Owen, MD

Dr. Carolyn Owen completed postgraduate training in internal medicine and hematology at the University of Ottawa and the University of British Columbia, respectively, followed by a research fellowship in molecular genetics at Barts and the London School of Medicine and Dentistry in London, UK. Her research focused on familial myelodysplasia and acute myeloid leukemia. She is currently an Assistant Professor at the Foothills Medical Centre & Tom Baker Cancer Centre, and her clinical interests are low-grade lymphoma and chronic lymphocytic leukemia. She is also the local principal investigator in Calgary for several clinical trials in these areas.

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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 Canada (LC) since 2002 and is now Director of Research Fellowships for LC. Her research interests include the lymphoid cancers with particular focus on the biology and treatment of large-cell lymphoma, the application of new imaging techniques such as PET scanning to lymphoma management, and innovative new approaches to treatment.

Jaroslav F. Prchal, MD

Dr. Jaroslav F. Prchal is an Associate Professor of Oncology and Medicine at McGill University, and Chair of the Department of Oncology at St. Mary’s Hospital Center in Montreal, Quebec, Canada. Dr. Prchal attended Charles University in Prague, receiving his Doctor of Medicine degree in 1964. He trained in Medicine at Toronto General Hospital and subsequently completed a post-graduate fellowship in Hematology at the University of Toronto and a Medical Research Council fellowship in Hematology and Marrow Transplantation in Seattle, Washington, USA. In 1979, he joined the staff at McGill University and the Royal Victoria Hospital, as well as St. Mary’s Hospital Center, where he has helped to build the Cancer Care program, serving as Chief of Oncology since 1997. Dr. Prchal’s main research interests include bone marrow disorders, specifically chronic myeloproliferative neoplasms, and his work has been published in journals such as Blood, the Journal of Clinical Investigation, Nature, and the New England Journal of Medicine.
International Perspective

Clemens-Martin Wendtner, MD

Clemens-Martin Wendtner, M.D., is Professor of Medicine and Director of the Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine at the Klinikum Schwabing, Munich — an academic hospital of the University of Munich. He completed his M.D. at the University of Münster in 1993. Thereafter, he received postdoctoral training at the Max-Planck-Institute in Martinsried, Germany and at the National Institutes of Health (NIH) in Bethesda, USA, until 1995. After a clinical fellowship at the University of Munich, he gained his German and US licence (ECFMG) in Internal Medicine before specialising as a Hematologist and Oncologist at the same institution. Dr. Wendtner received his postdoctoral lecture qualification at the University of Munich in 2002, and since 2004, he is a full professor of Internal Medicine, Hematology, and Medical Oncology at the University of Cologne. Dr. Wendtner is a member of multiple national and international societies in the field of Medicine and has won several research awards, including first prize at the 6th International Symposium Biological Therapy of Cancer in Munich, and a merit award from the American Society of Clinical Oncology. As a founding member of the German CLL Study Group (GCLLSG), he participates on the Steering Committee and is Secretary of GCLLSG. He has been principal investigator for numerous phase I-III clinical studies, and his interests focus on the development of new therapies in the field of CLL.

Valentin Goede, MD

Valentin Goede, M.D. is a Hematologist/Oncologist in the Department I of Internal Medicine at the University Hospital of Cologne, Cologne, Germany. He is also a Senior Physician and Consultant at the Department of Geriatric Medicine and Research at St. Marien Hospital, University of Cologne. After obtaining his M.D. at the University of Goettingen, Dr. Goede was trained in internal medicine at the Ammerland Clinic Westerstede. His hematology and oncology training was completed at the University Hospital Munich-Großhadern and the University Hospital of Cologne. His training in geriatric medicine was completed at the St. Marien Hospital, University of Cologne. Dr. Goede's main research interest focuses on the prediction and management of age-related vulnerability in elderly patients with leukemia, lymphoma, and other types of cancer.

Francesco Lo-Coco, MD

Dr. Francesco Lo-Coco is a full Professor of Hematology and Head of the Laboratory of Integrated Diagnosis of Oncohematologic Diseases at the Department of Biopathology, University of Rome Tor Vergata, Rome, Italy. His main research activities include genetic characterization, monitoring, and treatment of hematologic tumours, particularly acute myeloid leukemia and acute promyelocytic leukemia (APL). He has served as President of the Italian Society of Experimental Hematology, been a board member of the Italian Foundation for Cancer Research, and a member of the Committee on Health Research at the Italian Ministry of Health. He is presently chairman of the APL subcommittee of the Italian National Cooperative Group GIMEMA, chairman of the Education Committee of the European Hematology Association, and a member of the editorial board for the journals Leukemia and Haematologica.
MYELOPROLIFERATIVE NEOPLASMS, LEUKEMIAS, & LYMPHOMAS
In the clinical setting of myelofibrosis, with the exception of allogeneic stem cell transplantations, treatment has been primarily palliative. However, the discovery that patients with myelofibrosis have a dysregulation in the Janus kinase (JAK) signaling pathway led to the development of ruxolitinib, an orally bioavailable, potent, and selective inhibitor of JAK1 and JAK2. Ruxolitinib is now the first and only approved drug treatment for myelofibrosis. In clinical trials, ruxolitinib has demonstrated reductions in splenomegaly and disease-related symptoms, and improvements in quality of life compared with the best available treatment (BAT). In addition to accumulating long-term data in ongoing clinical trials, research is currently focused on optimizing ruxolitinib efficacy through the identification of markers of disease outcome or treatment efficacy, development of genetic assays for identifying ideal candidates for JAK inhibitor therapy, and determining whether ruxolitinib is capable of slowing the natural progression of other myelofibrosis-related symptoms (e.g., bone marrow fibrosis).

The latest findings in myelofibrosis were presented at the European Hematology Association (EHA) 2013 Congress. A brief summary of each of the main findings are as follows:

- Multivariate analysis of the phase III COMFORT-II trial data identified multiple cytokines that are prognostic for changes in spleen size or predictive of decreases in spleen volume with ruxolitinib therapy.
- A case study highlighted the first report of re sensitization to ruxolitinib therapy in a patient with myelofibrosis from the COMFORT-II trial.
- A preclinical study reported on a gene signature assay that may be used to identify patients with a hyperactive JAK/signal transducer and activator of transcription 5 (STAT5) signaling pathway, thereby identifying potential candidates for treatment with JAK inhibitors, including ruxolitinib.
- In a phase I/II trial, long-term therapy with ruxolitinib in patients with myelofibrosis appeared to slow the natural progression of bone marrow fibrosis, and a comparable effect was not evident with BAT.
- A three-year update of the COMFORT-II trial revealed that long-term ruxolitinib therapy continues to be well tolerated and provides rapid reductions in splenomegaly that were sustained for at least 3 years of treatment in the majority of patients with myelofibrosis. Additionally, ruxolitinib-treated patients had a longer survival over those who received BAT.

Multivariate analysis of the association of cytokine levels and reductions in spleen size in COMFORT-II, a phase III study comparing ruxolitinib to best available therapy

**Background**
Ruxolitinib is a Janus kinase (JAK)-1 and -2 inhibitor that has demonstrated rapid and durable improvements in splenomegaly, disease-related symptoms, and quality of life in two phase III COMFORT studies in patients with myelofibrosis (MF). Previously, an analysis was performed to evaluate the associations between cytokine levels and spleen size reductions in COMFORT-II. At the 2013 EHA Congress, Harrison and colleagues presented an analysis of these associations, using univariate and multivariate methodologies to determine whether any cytokines could be used to predict disease outcome or ruxolitinib efficacy.1

**Study design**
- COMFORT-II is an international, randomized, open-label phase III study (NCT00934544).
- Patients (n = 219) with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF were randomized in a 2:1 ratio and treated with ruxolitinib or best available therapy, respectively.
- Plasma samples were analyzed at baseline and weeks four, 24, and 48. Eighty-nine cytokines were measured using Rules-Based Medicine’s HumanMAP v1.6.
- Cytokines with a high proportion (≥30%) of values below the lower level of quantification were excluded. The association between the remaining 59 cytokines at baseline and percent change from baseline in spleen volume at week 48 was estimated via a multivariate linear model.
- The penalized regression Elastic Net method was used to carry out variable selection and estimate the linear model.
- Explanatory variables included in the model were baseline cytokines (standardized after a log 2 transformation), treatment arm, and interaction between the treatment and baseline cytokine levels.
- The primary objective was to assess whether levels of any cytokines were prognostic for decreases in spleen volume or predictive of decreases in spleen volume with ruxolitinib therapy.
- Prognostic: defined as providing information on the likely outcome of the disease outside of the context of therapy.
- Predictive: defined as providing information on the likely benefit of treatment.

**Study design**

![Study design diagram](image)
Key findings

- The Elastic Net model identified 10 cytokines for which the baseline level was prognostic for changes in spleen volume: alpha-fetoprotein (AFP), beta-2 microglobulin (B2M), carcinoembryonic antigen (CEA), CD40 ligand (CD40L), lymphotactin (LTN), myoglobin (MB), prostatic acid phosphatase (PAP), regulated on activation, normal T cell expressed and secreted (RANTES), thyroxine-binding globulin (TBG), and vascular cell adhesion molecule-1 (VCAM1). (Table 1)

- Insulin (INS), eotaxin (CCL11), and interleukin-18 (IL18) were identified as potentially predictive of treatment response. (Table 1)

- Of the cytokines identified in the Elastic Net model, CD40L, PAP, TBG, INS, IL18, MB, and RANTES were identified as significant when analyzed in a univariate fashion. (Table 2)

- Scatter plots and local regression (LOESS) lines showed that lower or higher levels of the following cytokines at baseline were associated with greater reductions in spleen volume:
  - Lower baseline levels of AFP, CEA, LTN, MB, and TBG; and
  - Higher baseline levels of B2M, CD40L, PAP, RANTES, and VCAM1.

- Scatter plots and LOESS regression lines identified lower baseline levels of AFP, CCL11, INS, and IL18 as potentially predictive of greater reductions in spleen volume with ruxolitinib treatment.

- The scatter plot depicted in figure 1 shows the predicted data based on the Elastic Net model vs. the observed data and was used to determine the accuracy of the model in predicting the response to treatment.

### Table 1. Cytokine biomarkers identified by the Elastic Net model

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Original scale</th>
<th>Log2 scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>AFP</td>
<td>0.54</td>
<td>0.80</td>
</tr>
<tr>
<td>B2M</td>
<td>4.70</td>
<td>5.37</td>
</tr>
<tr>
<td>CEA</td>
<td>0.68</td>
<td>0.88</td>
</tr>
<tr>
<td>CD40L</td>
<td>0.43</td>
<td>0.95</td>
</tr>
<tr>
<td>CCL11</td>
<td>224.00</td>
<td>242.02</td>
</tr>
<tr>
<td>INS</td>
<td>1.00</td>
<td>1.70</td>
</tr>
<tr>
<td>IL18</td>
<td>688.00</td>
<td>926.26</td>
</tr>
<tr>
<td>LTN</td>
<td>92.00</td>
<td>205.69</td>
</tr>
<tr>
<td>MB</td>
<td>8.80</td>
<td>10.80</td>
</tr>
<tr>
<td>PAP</td>
<td>1.20</td>
<td>1.64</td>
</tr>
<tr>
<td>RANTES</td>
<td>11.00</td>
<td>16.53</td>
</tr>
<tr>
<td>TBG</td>
<td>59.00</td>
<td>60.24</td>
</tr>
<tr>
<td>VCAM1</td>
<td>1960.00</td>
<td>2130.62</td>
</tr>
</tbody>
</table>

*AFP = alpha-fetoprotein; B2M = beta-2 microglobulin; CCL11 = eotaxin; CEA = carcinoembryonic antigen; CD40L = CD40 ligand; IL18 = interleukin-18; INS = insulin; LTN = lymphotactin; MB = myoglobin; PAP = prostatic acid phosphatase; RANTES = regulated on activation, normal T cell expressed and secreted; SD = standard deviation; TBG = thyroxine-binding globulin; VCAM1 = vascular cell adhesion molecule-1*
### Table 2. Univariate linear regressions by treatment arm*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best available therapy</th>
<th>Ruxolitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>Standard error of coefficient</td>
</tr>
<tr>
<td>C3</td>
<td>4.09</td>
<td>2.13</td>
</tr>
<tr>
<td>FABP</td>
<td>-4.54</td>
<td>2.29</td>
</tr>
<tr>
<td>FACTC2</td>
<td>3.96</td>
<td>2.15</td>
</tr>
<tr>
<td>FACTVII</td>
<td>6.68</td>
<td>3.59</td>
</tr>
<tr>
<td>FIBRINO</td>
<td>7.00</td>
<td>3.33</td>
</tr>
<tr>
<td>IL13</td>
<td>3.67</td>
<td>1.74</td>
</tr>
<tr>
<td>IL8</td>
<td>4.57</td>
<td>1.97</td>
</tr>
<tr>
<td>MCP1</td>
<td>5.39</td>
<td>2.88</td>
</tr>
<tr>
<td>MMP3</td>
<td>-6.17</td>
<td>3.47</td>
</tr>
<tr>
<td>PAP</td>
<td>-5.10</td>
<td>1.84</td>
</tr>
<tr>
<td>SHBG</td>
<td>5.44</td>
<td>2.33</td>
</tr>
<tr>
<td>TBG</td>
<td>5.86</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APOH = apolipoprotein H (beta2-glycoprotein I); C3 = complement component 3; CEA = carcinoembryonic antigen; CD40L = CD40 ligand; EGF = epidermal growth factor; FABP = fatty acid binding protein; FACTC2 = complement component C2; FACTVII = coagulation factor VII; FIBRINO = fibrinogen; IL8/13/18 = interleukin 8, 13, or 18; INS = insulin; MB = myoglobin; MCP1 = monocyte chemoattractant protein 1; MMP3 = matrix metallopeptidase 3 (stromelysin 1, progelatinase); MPO = myeloperoxidase; PAI1 = plasminogen activator inhibitor 1; PAP = prostatic acid phosphatase; RANTES = regulated on activation, normal T cell expressed and secreted; SHBG = sex hormone-binding globulin; TBG = thyroxine-binding globulin; VEGF = vascular endothelial growth factor

*Table lists only those cytokines that had estimated slopes significantly different from zero.

### Key conclusions

- This analysis identified two sets of cytokines that are either prognostic for greater reductions in spleen volume (AFP, B2M, CD40L, CEA, LTN, MB, PAP, RANTES, TBG, and VCAM1) or potentially predictive of spleen volume change upon ruxolitinib therapy (AFP, CCL11, IL18, and insulin).
- Additional validation of the multivariate model is needed to determine the utility of the identified cytokines in predicting response to treatment.
- The roles of individual cytokines identified in this study are not well defined, nor are their potential prognostic relevance in terms of changes in spleen volume or potential relevance as predictors of response to ruxolitinib.
- Future analyses will focus on the association of changes in cytokine levels over time and symptomatic end points.

A case study of resensitization to ruxolitinib, a JAK1/JAK2 inhibitor, in a patient with myelofibrosis

**Background**
Janus kinase (JAK)-2 inhibitor-resistant mutants have been generated in vitro. However, a recent report suggests that persistent JAK2 signaling despite chronic inhibition may be reversible in vitro, with cells becoming resensitized to JAK2 inhibition after a washout period. At the 2013 EHA Congress, Gisslinger and colleagues presented a case study of a patient who had a response after reinitiation with the JAK1/JAK2 inhibitor ruxolitinib while enrolled in the COMFORT-II study.

**Study design**
- COMFORT-II is a randomized, open-label, phase III study comparing ruxolitinib with best available therapy for the treatment of primary myelofibrosis (MF), postpolycythemia vera MF, and postessential thrombocythemia MF.
- Patients with intermediate-2 or high-risk MF by International Prognostic Scoring System (IPSS) criteria received ruxolitinib at 15 or 20 mg twice a day (bid) based on their platelet (PLT) count at baseline (100–200 or >200 x 10⁹/L).

**Key findings**
- This is a case report of a 59-year-old, female patient who was diagnosed with primary MF 17 years (in 1992) prior to enrolling in COMFORT-II. The patient’s bone marrow was hypercellular, with increased fibrosis, and granulopoiesis and megakaryopoiesis had typical morphology for primary MF.
- At study entry, it was determined that the patient had intermediate-2-risk MF, with two IPSS risk factors: constitutional symptoms and 2% blasts.
- Splenomegaly was 19 cm below the costal margin and the patient reported pruritus, night sweats, and occasional headache.
- Because the patient had a PLT count of 258 x 10⁹/L, ruxolitinib therapy was initiated at 20 mg bid.

**Figure 1. Patient’s timeline**

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IFN = interferon; IPSS = International Prognostic Scoring System; PMF = primary myelofibrosis
The daily dose of ruxolitinib from Sept. 10 to Dec. 10, 2012 is shown in Figure 2A.

Upon initiation of ruxolitinib treatment in Dec. 2009, spleen size reduced from 19 cm to 8 cm (58% reduction) at week 4; pruritus and night sweats resolved.

However, PLT count dropped to $90 \times 10^9/L$, so the dose was reduced to 10 mg bid.

Over the two months following dose reduction, spleen size gradually increased to approximately baseline level and night sweats (but not other symptoms) returned.

Consequently, ruxolitinib dose was increased to 15 mg bid in March 2010, and a 35% spleen volume reduction from baseline was observed at 24 weeks; night sweats resolved.

Baseline hemoglobin was 10.6 g/dL and ranged from 5.1–12.1 g/dL on study; anemia was managed with transfusions. (Figure 2D)

After three years of ruxolitinib treatment, the patient experienced a return of constitutional symptoms and severe anemia. (Figure 2D)

Ruxolitinib was tapered over a two-week period, and then discontinued after 152 weeks for unsatisfactory therapeutic effect (spleen size had increased to baseline levels). (Figures 2A and 2B)

During tapering of the ruxolitinib dose, the patient experienced a severe deterioration of her general condition, with worsening of constitutional symptoms, anemia, and an increase in spleen size to 26 cm; the patient became wheelchair bound. (Figures 2B and 2D)

After two days with no treatment, ruxolitinib was reinitiated at 10 mg bid. The patient became completely mobile again, constitutional symptoms improved, and her spleen size reduced from 26 cm to 14–16 cm. (Figure 2B)

Figure 2. Response to ruxolitinib treatment

Hb = hemoglobin; LDH = lactate dehydrogenase; PLT = platelet; WBC = white blood cell
Key conclusions

- This case study is the first report of resensitization to JAK2 inhibitor therapy in a patient with MF.
- The mechanism by which patients lose response to JAK inhibitors and become resensitized again is unknown.
  - However, preclinical evidence suggests that transactivation of JAK2 occurs through heterodimer formation with other JAKs and results in JAK-STAT (signal transducer and activator of transcription) pathway activation even in the context of JAK inhibitor therapy. This persistent JAK-STAT signaling is reversible upon removal of the JAK inhibitor.
- This finding has implications for both the treatment of patients with MF using JAK inhibitors, as well as for future trials that may examine second-line JAK inhibitor therapy in relapsed or refractory patients.


Sonkin D, et al. EHA 2013:P265

The identification of a pSTAT5 gene signature in hematologic malignancy

Background

Dysregulated Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling have been implicated in the pathogenesis of multiple human malignancies. Therefore, it is important to identify patients with an overactivated JAK-STAT pathway for possible treatment with JAK inhibitors. At the 2013 EHA Congress, Sonkin and colleagues presented a gene signature assay developed to detect overactivated JAK-STAT signaling.1

Study design

- The Cancer Cell Line Encyclopedia (CCLE) and associated gene-expression data were used to correlate the activation status of STAT5 with the induction of a set of STAT5 target genes.
- First, investigators used 28 tumour cell lines of hematologic lineage, with predetermined phosphorylated STAT5 (pSTAT5) status, to derive gene signatures for STAT5 activation.
- Next, the putative gene signatures were validated against a different set of 12 hematologic tumour cell lines.
- The STAT5 gene signature was then used to examine the pharmacodynamic response to ruxolitinib in a preclinical setting.
- Nine hematologic tumour cell lines (five positive for pSTAT5 and four negative for pSTAT5) were treated in vitro with ruxolitinib 0.2 μM or 1 μM, and samples were collected at 4 hours and 24 hours after treatment.

Each cell line had messenger RNA (mRNA) expression profile data from the Affymetrix® U133Plus2 arrays. All expression values are MAS5 normalized, with a 2% trimmed mean of 150.

The fold change and probability associated between pSTAT5-positive and pSTAT5-negative cell lines for each of the genes were calculated with the Student t test.
• Gene set activity scores were calculated by performing z-score transformations.
• Activity scores for the putative four-gene signature were also measured in different types of human hematologic malignancies. STAT5 activity in these samples is not shown.

**Key findings**
• Investigators initially identified 47 genes that were modulated by pSTAT5.
• This list of 47 genes was further enriched to include three different putative STAT5 gene signatures containing just four, six, or seven genes. (Table 1)

| Table 1. Putative STAT5 gene signatures |
| Four-gene signature | Six-gene signature | Seven-gene signature |
| PIM1 | PIM1 | PIM1 |
| CISH | CISH | CISH |
| SOCS2 | SOCS2 | SOCS2 |
| ID1 | ID1 | ID1 |
| LCN2 | LCN2 | LCN2 |
| EPOR | EPOR | EPOR |
| EGR1 | | |

\[ p = 0.015 \text{ (validation)} \]
\[ p < 0.0001 \text{ (enrichment + validation)} \]
\[ p = 0.016 \text{ (validation)} \]
\[ p < 0.0001 \text{ (enrichment + validation)} \]
\[ p < 0.0001 \text{ (enrichment + validation)} \]

\[ \text{CISH} = \text{cytokine-inducible SH2-containing protein; EGR1 = early growth response 1; EPOR = erythropoietin receptor; ID1 = inhibitor of DNA binding 1; LCN2 = lipocalin 2; PIM1 = proto-oncogene serine/threonine-protein kinase pim-1; SOCS2 = suppressor of cytokine signaling 2} \]

- The seven genes that were selected as being the most predictive of STAT5 activity were: (Table 1)
  - CISH (cytokine-inducible SH2-containing protein), EGR1 (early growth response 1), EPOR (erythropoietin receptor), ID1 (inhibitor of DNA binding 1), LCN2 (lipocalin 2), PIM1 (proto-oncogene serine/threonine-protein kinase), and SOCS2 (suppressor of cytokine signaling 2).
- The activity scores of the four-gene signature (i.e., PIM1, CISH, SOCS2, ID1) significantly correlated with STAT5 activity (i.e., pSTAT5-negative vs. pSTAT5-positive) in all 40 cell lines tested \( (p < 0.0001) \); the four-gene signature activity scores in 20 cell lines are shown in figure 1.
- The four-gene signature was further validated in nine cell lines, in which mRNA expression of these four genes appeared to correlate with STAT5 activity status. (Figure 2)
- The pharmacodynamic response to ruxolitinib treatment was tested by measuring mRNA expression of the four genes and seemed to indicate the effectiveness of ruxolitinib.
  - Expression of the four genes appeared to decrease with ruxolitinib treatment in cells with pSTAT5-positive status, both *in vitro* and *in vivo* in a tumor xenograft.
  - mRNA expression did not change with ruxolitinib treatment in a cell line with pSTAT5-negative status, where ruxolitinib would be ineffective.
- The average activity scores of the four-gene signature, which correlates with STAT5 activity, were classified by different types of human hematologic malignancies. (Figure 3)
Figure 2. Confirmation of four-gene signature with TaqMan

CT = cycle threshold; CISH = cytokine-inducible SH2-containing protein; ID1 = inhibitor of DNA binding 1; JAK2 = Janus kinase 2; PIM1 = proto-oncogene serine/threonine-protein kinase pim-1; pSTAT5 = phosphorylated signal transducer and activator of transcription 5; SOCS2 = suppressor of cytokine signaling 2

*JAK2 wildtype
†JAK2 mutant

Figure 3. Gene signature scores in human hematologic malignancies

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; CML = chronic myeloid leukemia; DLBCL = diffuse large B-cell lymphoma; MALT = mucosa-associated lymphoid tissue; MCL = mantle cell lymphoma; MF = mycosis fungoides; MM = multiple myeloma (or plasma cell myeloma); PTCL = peripheral T-cell lymphoma; SS = Sézary syndrome
Key conclusions

■ With the use of the CCLE, the investigators identified a four-gene signature that differentiates hematologic cancer cell lines based on their STAT5 activation status.

■ Expression levels of the four-gene signature correlated with pharmacodynamic response to ruxolitinib in a preclinical setting.

■ Additional studies are required to characterize the relevance of the gene signature to JAK-STAT pathway activation and inhibition in human malignancies.


Kvasnicka HM, et al. EHA 2013:S591

Long-term intervention effects on bone marrow morphology in myelofibrosis: patients treated with ruxolitinib and best available therapy

Background
Bone marrow (BM) fibrosis in patients with myelofibrosis is considered a secondary event in myeloproliferative neoplasms. Unfortunately, standard pharmacotherapy has not resulted in the improvement of BM fibrosis; however, the clinical impact of such an improvement is not fully understood. At the 2013 EHA Congress, Kvasnicka and colleagues presented evidence that the Janus kinase (JAK)-1/JAK2 inhibitor ruxolitinib improves BM morphology to a greater extent than does best available therapy.1

Study design
• This was a phase I/II, single-arm, open-label study of ruxolitinib (NCT00509899).
• Patients (n = 158) with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (Post-PV MF), or post-essential thrombocythemia myelofibrosis (Post-ET MF) were on this study for a median follow-up period of 32 months.
• The inclusion criteria were:
  ◦ Patients diagnosed with PMF, Post-ET MF, or Post-PV MF requiring therapy;
  ◦ Intermediate or high-risk status (Lille scoring);
  ◦ Splenomegaly.
• The dosing of ruxolitinib was tested at 10–50 mg twice daily or 25–200 mg once daily.2
• BM trephine biopsies were taken at baseline (BL), 24 months, and 48 months. Three hematopathologists independently reviewed all study samples in a blinded fashion for hematopoietic cellularity, World Health Organization (WHO) grade of BM fibrosis, degree of collagen deposition, and degree of osteosclerosis.
• Changes in BM fibrosis at 24 and 48 months compared to BL were characterized as improvement, stabilization, or worsening.
• In this exploratory analysis, BM biopsy data from patients in this study (68 patients had samples at both BL and 24 months; 18 patients also had samples at 48 months) were compared with BM biopsy data from patients with PMF who were treated with best available therapy (BAT).
• Patient data and BM biopsies were retrieved prospectively and analyzed at BL (160 patients), 24 months (97 patients), and 48 months (63 patients).
• Cases were matched for BM morphology at BL to the ruxolitinib cohort (p = 0.441; Cochran-Mantel-Haenszel test).

Key findings
• Baseline clinical characteristics for patients who received ruxolitinib vs. BAT were:
  ◦ Mean age: 66.8 vs. 59.3 years;
  ◦ Gender (female/ male): 44%/56% vs. 53%/47%;
  ◦ International Prognostic Scoring System (IPSS) risk status: 59% vs. 18% high risk, 28% vs. 17% intermediate-2, 13% vs. 37% intermediate-1, 0% vs. 28% low risk;
  ◦ Mean spleen size (palpable length below costal margin): 18.8 cm vs. 3.8 cm.
• After 24 months of ruxolitinib, changes in BM fibrosis for 72% of patients were characterized as improvement or stabilization, compared with improvement or stabilization for 60% of patients after 24 months of BAT. (Figure 1)

• After 48 months of ruxolitinib, 78% of patients were classified as having improvement or stabilization in BM fibrosis, whereas 48% of patients treated with BAT were classified as having improvement or stabilization in BM fibrosis after the same duration of treatment. (Figure 1)

• The odds ratio for worsening BM fibrosis at 24 months with ruxolitinib treatment was 0.40 (95% CI: 0.18–0.87), and at 48 months it was 0.11 (95% CI: 0.03–0.43). Odds ratio was calculated using the logistic regression method. (Figure 1)

• In the ruxolitinib cohort, the hazard of death over time was lower in patients with a BM fibrosis response classified as improvement or stabilization compared with those classified as worsening after 24 months of treatment, as measured by Cox regression (HR = 0.604, 95% CI: 0.151–2.415). (Figure 2)

**Key conclusions**

- Ruxolitinib may retard the natural progression of BM fibrosis seen in MF.
- A comparable effect was not seen with other long-term therapies, which was consistent with previous studies.
- Improvement or stabilization in BM fibrosis with ruxolitinib may be associated with a more favourable outcome.
- Additional research is ongoing to further expand on the potential significance of these findings in MF, including an ELN initiative with international collaboration to better define the role of fibrosis in this disease.

**References:**
Long-term outcomes from a phase III study comparing ruxolitinib with best available therapy for the treatment of myelofibrosis: a three-year update of COMFORT-II

Background
Ruxolitinib is a Janus kinase (JAK)-1/JAK2 inhibitor that has shown superiority over conventional therapies for the treatment of myelofibrosis (MF). In two phase III COMFORT studies, ruxolitinib demonstrated rapid and durable reductions in splenomegaly, improved MF-related symptoms and quality of life, and prolonged survival compared with placebo and best available therapy (BAT). The primary and key secondary end points of the COMFORT-II study were both previously met: the proportion of patients achieving a response (defined as a ≥35% reduction in spleen volume) at week 48 (ruxolitinib, 28.5%; BAT, 0%; p < 0.0001) and week 24 (ruxolinitib, 31.9% and BAT, 0%; p < 0.0001), respectively. At the 2013 EHA Congress, Vannucchi and colleagues updated the efficacy and safety findings of COMFORT-II with approximately three years of follow-up.5

Study design
- COMFORT-II is a randomized, open-label, multicentre phase III study (NCT00934544).
- Patients (n = 219) with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF were randomized in a 2:1 ratio and treated with ruxolitinib or BAT, respectively.

Key findings
- Patients were stratified based on their baseline International Prognostic Scoring System (IPSS) risk category.
- Patients were admitted to the ruxolitinib crossover or extension phase if they had a splenectomy, or progressive splenomegaly as defined by a 25% increase in spleen volume compared with the on-study nadir (including baseline).
- The primary end point was patient response, defined as a ≥35% reduction in spleen volume at week 48. The key secondary end point was a ≥35% reduction in spleen volume at week 24.

Vannucchi AM, et al. EHA 2013:S1111
Long-term outcomes from a phase III study comparing ruxolitinib with best available therapy for the treatment of myelofibrosis: a three-year update of COMFORT-II

Patients with PMF, PPV-MF, or PET-MF with ≥2 IWG risk factors
N = 219

Ruxolitinib (INC424)
R = 2:1
n = 146

Best available therapy
n = 73

Patients with progressive splenomegaly eligible for crossover

Ruxolitinib crossover and extension phase

Patients with progressive splenomegaly eligible for extension phase

IWG = International Working Group; PET-MF = post-essential thrombocythemia myelofibrosis; PMF = primary myelofibrosis; PPV-MF = post-polycythemia vera myelofibrosis
Efficacy

- Overall, 75 (51.4%) patients treated with ruxolitinib achieved a ≥35% reduction from baseline in spleen volume, and six of these patients achieved a ≥35% reduction after the primary analysis at 48 weeks. (Figure 1)
- The median duration of spleen response for patients treated with ruxolitinib has not been reached after 151 weeks of follow-up.
- Patients treated with BAT, excluding those who crossed over, had no change in spleen size after 96 weeks of treatment (the longest time point measured). (Figure 1)

Safety

- Consistent with ruxolitinib’s mechanism of action and previous reports, the most common AEs were anemia (ruxolitinib, 50.0%; BAT, 16.4%) and thrombocytopenia (50.7%; 13.7%).
- The most common all-grade nonhematologic AEs in patients from the ruxolitinib vs. BAT randomized arms included:
  - Peripheral edema (20.0% vs. 31.4%), diarrhea (22.3% vs. 19.4%), asthenia (16.5% vs. 13.4%), dyspnea (14.1% vs. 22.4%), nasopharyngitis (15.9% vs. 14.9%), pyrexia (12.9% vs. 10.5%) and fatigue (13.5% vs. 11.9%).
  - Overall, the most frequent grade 3/4 AEs in the ruxolitinib arm during three years of treatment were anemia (18.5%) and thrombocytopenia (11.6%).
  - Overall survival appeared to be greater in the ruxolitinib group than in the BAT group, providing patients with a relative 52% reduction in the risk of death (HR = 0.48 [95% CI: 0.28–0.85]; log-rank test p = 0.009). (Figure 2)
  - The probability of survival at 144 weeks was 81% with ruxolitinib vs. 61% with BAT.

Figure 1. Mean change in spleen volume from baseline over time
Table 2. Adverse events of special interest by six-month intervals*

<table>
<thead>
<tr>
<th>Ruxolitinib Randomized + Extension, %</th>
<th>0–24 (n = 146)</th>
<th>24–48 (n = 134)</th>
<th>48–72 (n = 116)</th>
<th>72–96 (n = 101)</th>
<th>96–120 (n = 93)</th>
<th>120–144 (n = 81)</th>
<th>144–168 (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMQ Preferred term</strong></td>
<td>SMQ Preferred term</td>
<td>Percentage of patients†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>34.9 12.7 8.6 13.9 8.6 7.4 8.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43.2 22.4 15.5 12.9 10.8 12.3 2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>17.1 14.2 9.5 11.9 7.5 9.9 6.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6.8 1.5 0.9 4.0 0 1.2 1.4</td>
<td></td>
<td></td>
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<tr>
<td>Hematoma</td>
<td>5.5 4.5 3.4 1.0 0 2.5 1.4</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Infections</strong></td>
<td>50.0 35.1 37.9 25.7 43.0 33.3 25.0</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Bronchitis</td>
<td>3.4 6.7 8.6 3.0 10.8 4.9 4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5.5 3.0 0.9 1.0 2.2 1.2 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13.7 5.2 7.8 4.0 10.8 3.7 4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.8 2.2 5.2 4.0 5.4 3.7 2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>8.2 8.2 5.2 5.0 2.2 0 0</td>
<td></td>
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*AEs = adverse events; SMQ = standardized Medical Dictionary for Regulatory Activities queries

**Figure 2. Overall survival (ITT)**

**Key conclusions**

- In COMFORT-II, ruxolitinib provided rapid reductions in splenomegaly that were sustained for at least three years of treatment in the majority of patients.
- Ruxolitinib was well tolerated, with 45.2% of patients remaining on study after more than three years of therapy.
  - The rates of AEs of special interest generally decreased after the first 24 weeks of ruxolitinib treatment.
- Longer follow-up continues to suggest a survival advantage with ruxolitinib treatment compared with BAT.

Ruxolitinib is a Janus kinase-1 and -2 inhibitor that has demonstrated the ability to significantly reduce spleen size and improve well-being in patients with myelofibrosis (MF). In our clinic, we treat patients with ruxolitinib who have more advanced disease (International Working Group stage intermediate II to high) and who are expected to respond well (i.e., those with very large spleens and clinical symptoms such as fatigue and difficulty eating). Occasionally, we also treat patients with stage intermediate I MF.

In clinical trials, ruxolitinib is not recommended for patients with thrombocytopenia (platelet count <50,000). This recommendation is based on the fact that platelets may initially drop to very low levels with ruxolitinib. However, this potential issue can be effectively managed. For example, we have used an initial treatment with hydroxyurea in patients with low platelet levels. If patients have an initial response to hydroxyurea, their platelet levels may rise to the point that they are eligible for treatment. In addition, starting with very low doses of ruxolitinib (5 mg once or twice a day) may be a reasonable strategy to overcome thrombocytopenia. As spleen size decreases, platelet counts rise; therefore, starting with a very low dose of ruxolitinib and then increasing the dose as the platelet count improves may be feasible.

The mechanism by which ruxolitinib causes a decrease in spleen size still remains to be elucidated. The current hypothesis is that the improvement in symptoms is related to modified levels of cytokines, but research still needs to be done to clarify which cytokines are specifically responsible for the beneficial action of ruxolitinib. Many of these studies are already underway or have been recently reported at meetings.

At the 2013 EHA Congress, Harrison and colleagues presented one such study, which analyzed associations between cytokine levels and reductions in spleen size with either ruxolitinib or best available therapy (BAT). This analysis identified four cytokines that might be predictive of decreases in spleen volume with ruxolitinib therapy: alpha-fetoprotein (AFP), eotaxin, insulin, and interleukin (IL)-18. It was surprising that AFP and insulin were identified because the relationship between these cytokines and a decrease in spleen size is unclear. The modulation of eotaxin and IL-18 levels is less surprising because they are both associated with the inflammatory response. Even though the data were quite convincing, biomarkers such as these are not generally measured in clinical laboratories; therefore, the results are not providing any clinical guidance. Before serum cytokine levels can be used to assist with treatment decisions in patients with MF, there is a need to enlarge the study size. The number of patients in this particular study was quite small, so additional research would be very helpful.

Sonkin, et al. also examined potential predictors of ruxolitinib efficacy. In a preclinical study, the investigators identified a four-gene signature whose expression correlated with the presence of phosphorylated STAT5 (signal transducer and activator of transcription-5). The methods used by the investigators were valid, but it seems impractical for clinicians to use this signature to predict STAT5 activity or ruxolitinib effectiveness because the lab results would not be available in a reasonable amount of time. Instead, our clinic would simply use ruxolitinib and judge its effectiveness based on clinical criteria. The signature could be used in future research studies examining ruxolitinib in conditions other than MF. The important point from this study is that ruxolitinib modifies STAT5 activity; it is reassuring that ruxolitinib has a specific effect on the signalling pathway that it was intended to target.

Ruxolitinib efficacy was also investigated by Kvasnicka and colleagues who compared long-term intervention effects on bone marrow morphology in MF patients treated with ruxolitinib or BAT. The degree of bone marrow fibrosis eventually correlates with the degree of thrombocytopenia in patients with MF; so the fact that the degree of fibrosis was decreased or less increased in the ruxolitinib group compared with that in the BAT group was very clinically relevant. These data are additional evidence of the effectiveness of ruxolitinib, which has clinical relevance and provides further justification for its use.

Vannucchi, et al. reported long-term data on the efficacy and safety of ruxolitinib in the COMFORT-II study, which were quite convincing. Ruxolitinib is well tolerated; almost half of the patients in this study still continued with ruxolitinib after more than three years. Overall survival...
(OS) seemed to be increased in patients treated with ruxolitinib compared with those who received BAT. Longer-term data is preferable with OS, but there was at least a very important suggestion that survival was prolonged. Five years of follow-up will eventually be collected for this study and that will likely confirm the current data.

In the COMFORT-II study, the rate of adverse events (AEs) (approximately 15%) for patients treated with ruxolitinib was quite acceptable. The AEs are often hematological and can usually be handled by adjusting the dose of ruxolitinib, as we have done with some of our patients. Our clinic has also used erythropoietin in patients who develop anemia so that the dose of ruxolitinib does not have to be decreased. The results clearly showed that ruxolitinib was efficacious and its tolerability was quite high, which will further encourage us to use ruxolitinib for the treatment of appropriate patients in our clinic.

Gisslinger and colleagues presented a case study of one patient with MF who was resensitized to ruxolitinib after a brief washout period. The return of symptoms and increased anemia observed in this patient were not surprising; however, the fact that it was possible to restart ruxolitinib after an initial pause was very interesting. The report was an anecdotal study of one patient from which one cannot draw any definite conclusions. However, it tells us that perhaps one should not give up on ruxolitinib treatment if there appears to be an initial failure. The investigators also concluded that this finding has implications for future trials that may examine second-line ruxolitinib therapy in relapsed or refractory patients. In addition to its effectiveness as a first-line therapy, ruxolitinib has shown some benefit as a second-line therapy, so it is possible to switch patients to ruxolitinib from other treatments. Physicians will have to use their own judgment on whether or not this is needed, but clearly it is possible and effective.

Leukemias

Latest Advances in Emerging Targeted Therapies for Chronic Lymphocytic Leukemia

Many patients with chronic lymphocytic leukemia (CLL) relapse or become refractory to first-line chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR). Furthermore, since CLL is a disease of the elderly with a median age of 70 years at diagnosis, treatment with FCR is considered too aggressive, and consequently, no standard of care has been established for this population. In addition to advanced age, several other factors further complicate treatment strategies in CLL, including physical fitness, comorbidities, and genetic abnormalities. Accordingly, current research in CLL is focused on optimizing and individualizing treatment in these high-risk populations. In addition to investigating new combinations of conventional agents, an emerging understanding of the molecular pathophysiology of CLL has led to the development of novel agents directed at specific targets critical to the survival or chemoresistance of CLL B cells, including phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ), CD20, and B-cell CLL/lymphoma 2 (BCL-2). These targeted agents are currently undergoing clinical investigation and have the potential to change the future treatment of CLL.

The latest findings on the aforementioned advances in CLL were presented at the American Society of Clinical Oncology (ASCO) 2013 meeting, the European Hematology Association (EHA) 2013 congress, and the 2013 International Conference on Malignant Lymphoma (ICML). A brief summary of each of the main findings are as follows:

- Updated results from a phase I trial demonstrated that idelalisib, a first-in-class, highly selective, oral inhibitor of PI3Kδ, in combination with rituximab and/or bendamustine had a favourable safety profile and substantial clinical activity in heavily pretreated patients with relapsed or refractory CLL.

- In light of the promising findings in phase I trials, a phase III development program for idelalisib was initiated to evaluate the efficacy and safety of idelalisib in combination with bendamustine plus rituximab (BR) (study 115) or ofatumumab (study 119) for previously treated CLL.

- Final results from stage I of the phase III CLL11 trial demonstrated that the addition of obinutuzumab, a novel type II anti-CD20 monoclonal antibody, or rituximab to chlorambucil had significant clinical activity and both combination therapies appeared to be superior treatment options to chlorambucil monotherapy in elderly patients with CLL and comorbidities.

- Updated results from a phase I trial found that ABT-199, a novel, selective, potent BCL-2 inhibitor, was highly active in patients with relapsed or refractory CLL, including those with ultra high-risk disease (i.e., deletion of chromosome 17p or fludarabine-refractory CLL). However, additional dosing and scheduling modifications are being explored to minimize the risk of dose-limiting tumour lysis syndrome.

In Supportive Care Oncology

Background

Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ) signaling is critical for the activation, proliferation, and survival of B cells. It also plays an important role in the homing and retention of B cells in lymphoid tissues. In many B-cell malignancies, including chronic lymphocytic leukemia (CLL), PI3Kδ is hyperactive and promotes the proliferation and survival of malignant B cells.1 Idelalisib (GS-1101; formerly CAL-101) is a first-in-class, highly selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells.1,2 In a phase I trial, monotherapy with idelalisib resulted in substantial clinical activity and a favourable safety profile in heavily pretreated patients with relapsed or refractory CLL.3 On the basis of these findings, the safety and efficacy of idelalisib were also investigated in combination with rituximab, bendamustine, or both (BR) for relapsed or refractory CLL in the phase I setting; Barrientos and colleagues presented an update on the findings of this study at ASCO 2013.4

Study design

• In this phase I trial (NCT01088048), patients with relapsed or refractory CLL were treated continuously with idelalisib at a dose of 150 mg twice daily in combination with either:
  ◦ Rituximab (375 mg/m² intravenous [iv] on day 1 weekly for eight cycles);
  ◦ Bendamustine (70 mg/m² iv on days 1 and 2 every four weeks [q4w] for six cycles); or
  ◦ Bendamustine plus rituximab (BR) (B: 70 mg/m² on days 1 and 2 and R: 375 mg/m² iv on day 1, q4w for six cycles).
• Clinical response was evaluated according to the published criteria of the 2008 International Workshop on CLL and the 2011 Lymphoma Research Foundation Scientific Workshop.
• Patients that were still on treatment after 48 weeks were eligible to continue idelalisib on an extension study (NCT01090414).

Key findings

• A total of 52 patients (female [n = 23] and male [n = 29]) with a median age of 64 years (range: 41-87 years) were enrolled.
• The baseline characteristics of patients in this study included:
  ◦ Bulky lymphadenopathy: 62%;
  ◦ Refractory disease: 50%;
  ◦ Median number of prior therapies: 3 (range: 1-14);
  ◦ Prior therapy with rituximab: 96%;
  ◦ Prior therapy with bendamustine: 44%.
• As of January 14, 2013, the median treatment duration was 18 months (range: 1-33 months).
• For all treatment groups combined, the overall response rate was 81%, and the median time to response was 1.9 months (range: 1.5-8.3 months).
  ◦ A complete response was observed in one patient.
• At two years of follow-up, 71% of the responses were still enduring.
• The two-year progression-free survival and overall survival rates were 62% and 85%, respectively.
• There were no significant differences in outcomes between patients with <3 prior treatments (n = 21) versus those with ≥3 prior treatments (n = 31).
• The most common treatment-emergent adverse events (AEs), independent of causality, included pyrexia, diarrhea, cough, fatigue, nausea, pneumonia, and rash. (Table 1)
• In terms of laboratory-based AEs, 10% of patients experienced grade ≥3 aspartate aminotransferase/alanine aminotransferase elevations.
• At the time of this update, 60% of patients (n = 31) had been enrolled into the extension study, with 46% (n = 24) of patients continuing on idelalisib treatment.
Table 1. Treatment-emergent adverse events, according to grade

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Any grade, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Key conclusions

- A lack of overlapping toxicities allowed idelalisib to be co-administered with rituximab, bendamustine, or BR, and all three combination regimens were highly active, resulting in durable tumour control in heavily pretreated patients with relapsed or refractory CLL.
- Phase III trials evaluating the efficacy and safety of idelalisib in combination with BR and rituximab are currently ongoing (NCT01569295 and NCT01539512, respectively; see Eradat et al. on p. 26).


Eradat HA, et al. ASCO 2013:TP57133

A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously treated CLL

Background

Idelalisib is a first-in-class, highly selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ). Recent phase I trial data, which were presented at ASCO 2013 (see Barrientos et al. on p. 25), demonstrated that idelalisib, as monotherapy or in combination with either bendamustine, rituximab, or both (BR), is highly active in heavily pretreated patients with relapsed or refractory chronic lymphocytic leukemia (CLL). Based on these promising findings, a phase III development program for idelalisib was initiated and currently encompasses three ongoing trials evaluating the efficacy and safety of idelalisib in combination with BR (study 115), rituximab alone (study 116/117), or ofatumumab alone (study 119) for previously treated CLL (Figure 1). At ASCO 2013, Eradat and colleagues presented the design of study 115.1

Study design

- Study 115 is a phase III, randomized, double-blind, placebo-controlled trial (NCT01569295) evaluating the efficacy and safety of idelalisib in combination with BR vs. BR plus placebo for previously treated ‘fit’ patients with CLL.

- Investigators will enroll a total of 390 patients with previously treated CLL who meet the following inclusion criteria:
  - Measureable lymphadenopathy (i.e., presence of ≥1 measurable nodal lesion(s) as assessed by computed tomography or magnetic resonance imaging);
  - Prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody;
  - Not refractory to bendamustine;
  - No prior treatment with any therapy inhibiting B-cell receptor signaling pathways (i.e., inhibitors of AKT, BTK, JAK, mTOR, PI3K [including idelalisib], or SYK);
  - Experienced CLL progression in <36 months since completion of their last therapy;
  - Sufficiently fit to receive cytotoxic therapy:
    - No specific Cumulative Illness Rating Scale (CIRS) requirement, but a score ≤6 is preferred;
    - Karnofsky score ≥60;
    - Adequate bone marrow function (i.e., grade ≤2 anemia, neutropenia, and thrombocytopenia);
    - Adequate renal function (i.e., creatinine clearance ≥60 mL/min, which will be changed to ≥40 mL/ min in an upcoming amendment).
Patients will be randomized in a 1:1 ratio to receive either:

- Arm A (n = 195): idelalisib (150 mg orally, twice daily, continuously) plus bendamustine (70 mg/m² intravenous [iv] on days 1 and 2 every four weeks [q4w] for six cycles) and rituximab (first dose of 375 mg/m² iv and then 500 mg/m² iv q4w for six cycles);
- Arm B (n = 195): placebo plus BR (same dosing regimen as in arm A).

Patients will be stratified according to genetic and clinical factors:

- Genetic: 17p deletion and/or p53 mutation (either vs. neither) and immunoglobulin heavy chain variable (IgHV) mutation (mutated vs. unmutated);
- Clinical: recurrent disease status (refractory vs. relapsed).

The primary end point is progression-free survival (PFS).

The secondary end points include:

- Tumour response (overall response rate, lymph node response rate, complete response, and overall survival);
- Patient well-being (health-related quality-of-life questionnaire);
- Disease-related biomarkers;
- Exposure (pharmacokinetics);
- Safety (incidence of adverse events);
- Health economics (utility measure questionnaire).

This trial is an event-driven trial and the primary end point evaluation will be based on independent central review.

For the primary end point analysis, the difference in PFS between treatment arms will be assessed in the intent-to-treat analysis set.

The study was initiated in June 2012.
Key conclusion

- Study 115 is an ongoing phase III trial that will determine the safety and efficacy of idelalisib in combination with BR in patients with previously treated CLL.


Flinn I, et al. ASCO 2013:TPS7131

A phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL

Background

Ofatumumab, a fully human anti-CD20 monoclonal antibody, is approved for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. Two trials of single-agent ofatumumab have previously demonstrated encouraging efficacy in patients with relapsed or refractory CLL, despite heavy prior therapy with not only fludarabine and alemtuzumab, but also with rituximab.

Idelalisib, a novel, highly selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ), was recently shown to be highly active as monotherapy or in combination with either rituximab, bendamustine, or both (BR) in heavily pretreated patients with relapsed or refractory CLL. These phase I trial data were presented at ACSO 2013 (see Barrientos et al. on p. 25). On the basis of these promising results — particularly the combination of idelalisib with anti-CD20 targeted therapy — a phase III trial, known as study 119, was initiated in order to evaluate the efficacy and safety of combination therapy with idelalisib and ofatumumab for previously treated CLL. At ASCO 2013, Flinn and colleagues presented the study design of study 119, which is one of the three ongoing trials in the phase III development program for idelalisib (see Eradat et al. on p. 26).^1^

Study design

- Study 119 is a phase III, randomized, double-blind, placebo-controlled trial (NCT01659021) evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL.
- This study will enroll a total of 210 patients with previously treated CLL who meet the following inclusion criteria:
  - Measureable lymphadenopathy (i.e., presence of ≥1 measurable nodal lesion(s) ≥2 cm as assessed by computed tomography or magnetic resonance imaging);
  - Prior therapy containing two cycles of a purine analog or two cycles of bendamustine;
  - Not refractory to ofatumumab;
  - No prior treatment with any therapy inhibiting B-cell receptor signaling pathways (i.e., inhibitors of AKT, BTK, JAK, mTOR, PI3K [including idelalisib], or SYK);
  - Experienced CLL progression in <24 months since completion of their last therapy;
  - Fit or unfit to receive cytotoxic therapy:
    - No specific Cumulative Illness Rating Scale requirement;
    - Karnofsky score ≥60;
    - Any bone marrow function permitted;
    - Creatinine clearance ≥30 mL/min.
  - Patients will be randomized in a 2:1 ratio to receive either:
    - Arm A (n = 140): idelalisib (150 mg orally, twice daily, continuously) plus ofatumumab (300 mg intravenous [iv] on day 1 of cycle 1, and then 1,000 mg iv weekly [q1w] for seven cycles, followed by every four weeks [q4w] for four cycles);
    - Arm B (n = 70): placebo plus ofatumumab (300 mg iv on day 1 of cycle 1, and then 2,000 mg iv q1w for seven cycles, followed by q4w for four cycles).
- Patients will be stratified according to genetic and clinical factors:
  - Genetic: 17p deletion and/or p53 mutation (either vs. neither) and immunoglobulin heavy chain variable (IgHV) mutation (mutated vs. unmutated);
  - Clinical: recurrent disease status (refractory vs. relapsed).
• The primary end point is progression-free survival (PFS).
• The secondary end points include:
  ◦ Overall response rate;
  ◦ Lymph node response rate;
  ◦ Complete response rate;
  ◦ Overall survival;
  ◦ Safety (incidence of adverse events).
• The tertiary end points include:
  ◦ Patient reported outcomes (the Functional Assessment of Cancer Therapy–Leukemia and European Quality of Life–5 Dimensions questionnaires);
  ◦ Pharmacokinetics;
  ◦ Biomarkers.
• This trial is an event-driven trial and the primary end point evaluation will be based on independent central review.
• For primary end point analysis, the difference in PFS between treatment arms will be assessed in the intent-to-treat analysis set.
• The study opened for enrollment in December 2012.

Study 119 design

**Randomized combination therapy**
- Arm A (n = 140)
- Arm B (n = 70)

**Continuing single-agent therapy**
- Ofatumumab* (6 months)
- Idelalisib (150 mg po bid)
- Placebo (po bid)
- Ofatumumab† (6 months)

**Post-study therapy**
- Investigator’s choice

**Disease progression**

*Ofatumumab administered at 300 mg iv on day 1 of cycle 1, and then 1,000 mg/m² iv q1w × 7 cycles, followed by q4w × 4 cycles.
†Ofatumumab administered at 300 mg iv on day 1 of cycle 1, and then 2,000 mg/m² iv q1w × 7 cycles, followed by q4w × 4 cycles.

**bid = twice daily; iv = intravenous; po = oral; q1w = weekly; q4w = every 4 weeks**

Key conclusion

- **Study 119** is an ongoing phase III trial that will determine the safety and efficacy of idelalisib in combination with ofatumumab in patients with previously treated CLL.


Goede V, et al. EHA 2013:S567

**Obinutuzumab (GA101) or rituximab plus chlorambucil versus chlorambucil alone in patients with CLL and comorbidities: final stage I results of the CLL11 phase III trial**

**Background**

Chemoinmunotherapy with fludarabine, cyclophosphamide, and rituximab is the standard first-line treatment in younger and physically fit patients with chronic lymphocytic leukemia (CLL). Unfortunately, no standard of care has been established for older and physically less fit patients with CLL, a population underrepresented in clinical trials and characterized by an increased burden of comorbidity. Encouraging phase II data on chemoimmunotherapy with chlorambucil and rituximab (R-Clb) in elderly patients with CLL support the use of chlorambucil in combination with an anti-CD20 monoclonal antibody in this population.
Obinutuzumab (GA101), a novel type II anti-CD20 monoclonal antibody, demonstrated superior activity compared to type I antibodies (e.g., rituximab) in preclinical studies. Additionally, in phase I and II studies, GA101 monotherapy was found to be safe and have promising activity in patients with relapsed or refractory CLL. Accordingly, CLL11, a two-stage, phase III trial, was initiated to study the efficacy and safety of GA101 in combination with chlorambucil (G-Clb) as compared with R-Clb or chlorambucil (Clb) alone in patients with previously untreated CLL and comorbidities. The final stage I results of CLL11 were presented at EHA 2013.

Study design

- CLL11 (NCT01010061) is a two-stage, randomized, open-label, multicentre, international, phase III trial of G-Clb vs. Clb alone (stage I) or R-Clb (stage II) in patients with previously untreated CLL and comorbidities.
- Eligibility criteria included age ≥18 years, and a total Cumulative Illness Rating Scale (CIRS) score >6 and/or an estimated creatinine clearance (CrCl) of <70 mL/min.
- Patients were randomized in a 1:2:2 ratio to receive either:
  - Clb (n = 118);
  - G-Clb (n = 238);
  - R-Clb (n = 233).
- The primary end point was investigator-assessed progression-free survival (PFS).
- The secondary end points included overall response rate (ORR), minimal residual disease (MRD), overall survival (OS), and safety.
- G-Clb vs. Clb were compared in the stage Ia analysis and R-Clb vs. Clb were compared in the stage Ib analysis.

Key findings

Baseline characteristics and disposition

- Of the 589 randomized patients, 582 received treatment (Clb: n = 116; G-Clb: n = 236; R-Clb: n = 230).
- Baseline characteristics were well balanced between study arms, including median:
  - Age: 73 years for both stage Ia and Ib;
  - CIRS score: 8 for both stage Ia and Ib;
  - Eastern Cooperative Oncology Group Performance Status: 1 for both stage Ia and Ib;
  - CrCl: 61.1 mL/min for stage Ia and 62.1 mL/min for stage Ib. (Table 1)
- The median observation times at data cut-offs in the stage Ia (July 11, 2012) and stage Ib (August 10, 2012) analyses were similar between the treatment arms (stage Ia: 13.6 and 14.5 months for Clb and G-Clb, respectively; stage Ib: 14.2 and 15.3 months for Clb and R-Clb, respectively).

Efficacy

- At the end of treatment, ORRs were 75.5% in the G-Clb arm and 30.2% in the Clb arm for the stage Ia analysis, and 65.9% in the R-Clb arm and 30.0% in the Clb arm for the stage Ib analysis. (Table 2)
- None of the patients treated with Clb alone had a complete response (CR), whereas 22.2% and 8.3% of patients receiving G-Clb and R-Clb, respectively, achieved a CR. (Table 2)
- MRD negativity in peripheral blood and bone marrow were achieved in a higher proportion of patients treated with G-Clb (31.1% and 17.0%, respectively) compared with those in patients treated with Clb (0% and 0%, respectively). In the R-Clb arm, 2.0% and 2.8% of patients achieved MRD negativity in peripheral blood and bone marrow, respectively. (Table 2)

Study design of the CLL11 phase III trial

The study design of the CLL11 phase III trial is illustrated as follows:

Previous untreated CLL with comorbidities
- Total CIRS score >6 and/or CrCl <70 mL/min
- Age ≥18 years

Randomize

Stage I, n = 590

Additional 190 patients to complete stage II

Chlorambucil

GA101 + chlorambucil

Rituximab + chlorambucil

Stage Ia G-Clb vs. Clb

Stage Ib R-Clb vs. Clb

Stage II G-Clb vs. R-Clb

CIRS = Cumulative Illness Rating Scale; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; GA101 = obinutuzumab; G-Clb = GA101, chlorambucil; iv = intravenous; po = oral; q28d = every 28 days; R-Clb = rituximab, chlorambucil

*Chlorambucil administered at 0.5 mg/kg po on days 1 and 15 of cycles 1–6 q28d.
†GA101 administered at 1,000 mg iv on days 1, 8, and 15 of cycle 1, and then 1,000 mg iv on day 1 of cycles 2–6 q28d.
‡Rituximab administered at 375 mg/m2 iv on day 1 of cycle 1, followed by 500 mg/m2 iv on day 1 of cycles 2–6 q28d.
### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Stage Ia</th>
<th></th>
<th>Stage Ib</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clb (n = 118)</td>
<td>G-Clb (n = 238)</td>
<td>Clb (n = 118)</td>
<td>R-Clb (n = 233)</td>
</tr>
<tr>
<td>Male, %</td>
<td>64</td>
<td>59</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>72 (43–87)</td>
<td>74 (39–88)</td>
<td>72 (43–87)</td>
<td>73 (40–90)</td>
</tr>
<tr>
<td>≥65 years, %</td>
<td>78</td>
<td>82</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td>≥75 years, %</td>
<td>37</td>
<td>45</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>Median CIRS score</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>CIRS score ≥6, %</td>
<td>78</td>
<td>75</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>Median ECOG PS</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Median CrCl, mL/min*</td>
<td>64</td>
<td>61</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>CrCl &lt;70 mL/min, %</td>
<td>61</td>
<td>68</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>CrCl &lt;50 mL/min, %</td>
<td>21</td>
<td>29</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Lymphocyte count, %</td>
<td>84</td>
<td>76</td>
<td>84</td>
<td>71</td>
</tr>
<tr>
<td>≥25 × 10^9/L</td>
<td>37</td>
<td>24</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>≥100 × 10^9/L</td>
<td>20</td>
<td>23</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Binet stage, %</td>
<td>20</td>
<td>23</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>A</td>
<td>42</td>
<td>41</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>B</td>
<td>37</td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Cyto genetics, %</td>
<td>17p</td>
<td>10</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>11q</td>
<td>15</td>
<td>16</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Tri12</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>13q</td>
<td>33</td>
<td>29</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Other abnormality</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>16</td>
<td>24</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>IgHV status, %</td>
<td>62</td>
<td>61</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Unmutated</td>
<td>59</td>
<td>61</td>
<td>58</td>
<td>62</td>
</tr>
</tbody>
</table>

CIRS = Cumulative Illness Rating Scale; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GA101 = obinutuzumab; G-Clb = GA101, chlorambucil; IgHV = immunoglobulin heavy chain variable; R-Clb = rituximab, chlorambucil

*CrCl data available for 117/118 patients in the Clb arms.

†Circulating lymphocyte counts available for 116/118 patients in the Clb arms, 237/238 in the G-Clb arm, and 231/233 patients in the R-Clb arm.

### Table 2. End-of-treatment response rates

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Stage Ia</th>
<th></th>
<th>Stage Ib</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clb (n = 106)</td>
<td>G-Clb (n = 212)</td>
<td>Clb (n = 110)</td>
<td>R-Clb (n = 217)</td>
</tr>
<tr>
<td>Response rate*, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>30.2</td>
<td>75.5</td>
<td>30.0</td>
<td>65.9</td>
</tr>
<tr>
<td>CR†</td>
<td>0</td>
<td>22.2</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>PR‡</td>
<td>30.2</td>
<td>53.3</td>
<td>30.0</td>
<td>57.6</td>
</tr>
<tr>
<td>SD</td>
<td>21.7</td>
<td>4.7</td>
<td>20.9</td>
<td>13.4</td>
</tr>
<tr>
<td>PD</td>
<td>25.5</td>
<td>3.8</td>
<td>28.2</td>
<td>11.5</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>22.6</td>
<td>16.0</td>
<td>20.9</td>
<td>9.2</td>
</tr>
<tr>
<td>MRD-negative§, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0 (0/80)</td>
<td>31.1 (41/132)</td>
<td>0 (0/82)</td>
<td>2.0 (3/150)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0 (0/30)</td>
<td>17.0 (15/88)</td>
<td>0 (0/32)</td>
<td>2.8 (2/72)</td>
</tr>
</tbody>
</table>

Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; GA101 = obinutuzumab; G-Clb = GA101, chlorambucil; MRD = minimal residual disease; ORR = overall response rate; PD = progressive disease; PR = partial response; R-Clb = rituximab, chlorambucil; SD = stable disease

*Not reached by cut-off in 12 patients in stage Ia Clb arm, 26 patients in G-Clb arm, eight patients in stage Ib Clb arm, and 16 patients in the R-Clb arm, as assessed by International Workshop on CLL criteria.

†Includes CR with incomplete hematologic recovery.

‡Includes nodular PR.

§As measured by central laboratory assessment (ASO-RQ-PCR); bone marrow samples were usually only taken from patients thought to be in CR.
Compared with Clb monotherapy, chemoimmunotherapy with either G-Clb or R-Clb significantly prolonged PFS by 12.1 and 4.9 months, respectively:

- G-Clb vs. Clb: 23.0 vs. 10.9 median months, HR = 0.14 [95% CI: 0.09–0.21]; p < 0.0001; and
- R-Clb vs. Clb: 15.7 vs. 10.8 median months, HR = 0.32 [95% CI: 0.24–0.44]; p < 0.0001. (Figure 1)

Subgroup analyses of PFS according to age, sex, Binet stage at baseline, CIRS score at baseline, CrCl, IgHV mutational status, and chromosomal abnormalities at baseline revealed that both G-Clb and R-Clb were better treatment options than Clb for every subgroup. (Figure 2)

- The OS rates at the time of data cut-off were:
  - Stage Ia: 94.5% for G-Clb and 92.4% for Clb;
  - Stage Ib: 92.3% for R-Clb and 89.8% for Clb.

**Figure 1. Investigator-assessed progression-free survival**

**Figure 2. Stage Ia and Ib: progression free-survival subgroup analysis**
**Safety**

- Overall, grade ≥3 adverse events (AEs) were reported in 66.7%, 45.8%, and 41.4% of patients treated with G-Clb, R-Clb, and Clb, respectively. (Table 3)

- The most common grade ≥3 AE in all arms was neutropenia, which was experienced by more patients in both the G-Clb and R-Clb arms compared with those in the Clb arm (34.2% and 25.3%, respectively, vs. 14.7%). (Table 3)

- Grade ≥3 infusion-related reactions (IRR) were experienced by more patients treated with G-Clb vs. R-Clb (21.3% vs. 4.0%); however, these occurred at first infusion only. (Table 3)

- AEs leading to study withdrawal were reported in 19.6%, 13.8%, and 14.7% of patients treated with G-Clb, R-Clb, and Clb, respectively. (Table 3)

- Fewer patients treated with either G-Clb or R-Clb had AEs leading to death compared with those treated with Clb (2.1% and 1.8%, respectively, vs. 5.2%). (Table 3)

**Table 3. Relevant adverse events during treatment**

<table>
<thead>
<tr>
<th>Safety</th>
<th>Stage Ia</th>
<th></th>
<th>Stage Ib</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clb</td>
<td>G-Clb*</td>
<td>Clb</td>
<td>R-Clb</td>
</tr>
<tr>
<td></td>
<td>(n = 116)</td>
<td>(n = 240)</td>
<td>(n = 116)</td>
<td>(n = 225)</td>
</tr>
<tr>
<td>Any AE grade ≥3, %</td>
<td>41.4</td>
<td>66.7</td>
<td>41.4</td>
<td>45.8</td>
</tr>
<tr>
<td>IRR, %</td>
<td>-</td>
<td>21.3</td>
<td>-</td>
<td>4.0</td>
</tr>
<tr>
<td>Neutropenia, %</td>
<td>14.7</td>
<td>34.2</td>
<td>14.7</td>
<td>25.3</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>5.2</td>
<td>3.8</td>
<td>5.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>3.4</td>
<td>10.8</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Infection, %</td>
<td>11.2</td>
<td>6.3</td>
<td>11.2</td>
<td>8.4</td>
</tr>
<tr>
<td>AE leading to withdrawal from study medication, %</td>
<td>14.7</td>
<td>19.6</td>
<td>14.7</td>
<td>13.8</td>
</tr>
<tr>
<td>AE leading to death, %</td>
<td>5.2</td>
<td>2.1</td>
<td>5.2</td>
<td>1.8</td>
</tr>
<tr>
<td>AE new malignancy, %</td>
<td>0.9</td>
<td>2.5</td>
<td>0.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

AE = adverse event; Clb = chlorambucil; GA101 = obinutuzumab; G-Clb = GA101, chlorambucil; IRR = infusion-related reaction; R-Clb = rituximab, chlorambucil

*Safety population for G-Clb includes four patients randomized to R-Clb who received one infusion of GA101 by mistake.

**Key conclusions**

- **CLL11** is the first and largest phase III trial directly comparing the efficacy and safety of Clb with Clb plus anti-CD20 monoclonal antibodies for treating elderly patients with CLL and comorbidities.

- The addition of either GA101 or rituximab to Clb was found to have significant clinical activity and appears to be a superior treatment option to Clb monotherapy in this population.
  - G-Clb and R-Clb significantly prolonged PFS and achieved higher ORRs compared to Clb monotherapy.
  - A higher proportion of patients treated with G-Clb achieved MRD negativity in peripheral blood and bone marrow.

- Both G-Clb and R-Clb had acceptable safety profiles, with IRR and neutropenia being the most important AEs.

- G-Clb and R-Clb will be compared in stage II analysis, which will include an additional 190 patients and more follow-up data.

**References:**
Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed or refractory CLL

Background
In patients with chronic lymphocytic leukemia (CLL), overexpression of B-cell CLL/lymphoma 2 (BCL-2) and failure to activate upstream pro-apoptotic pathways (i.e., BH3-only proteins) lead to chemoresistance.1-3 These observations suggest that targeting BCL-2 may be a promising strategy for treating CLL. Additionally, patients with CLL and deletions of chromosome 17p (del[17p]) or those with fludarabine-refractory disease are considered to have ultra high-risk CLL, as their median life expectancy is less than two to three years with standard therapy.3 Accordingly, novel agents are urgently needed to improve outcomes in this population.3

Navitoclax, a first-generation BCL-2 inhibitor, achieved clinical efficacy in patients with relapsed or refractory CLL; however, concomitant BCL-XL inhibition resulted in dose-limiting thrombocytopenia.1,3 In preclinical studies, ABT-199, a selective, potent, orally bioavailable BCL-2 inhibitor, was found to have >500-fold higher affinity for BCL-2 than BCL-XL, as well as activity in a wide range of BCL-2–expressing hematologic malignancies.1-3 Based on these findings, a phase I trial of ABT-199 was initiated in patients with relapsed or refractory CLL/small lymphocytic lymphoma (SLL) and non-Hodgkin lymphoma (NHL).1,3 The updated findings from the CLL/SLL arm of this ongoing phase I trial, also known as M12-175, were presented at both ICML 2013 and EHA 2013.1,3

Study design
- M12-175 (NCT 01328626) is a first-in-human, open-label, dose-escalation, multicentre, international, phase I trial evaluating the safety and pharmacokinetics profile of ABT-199 (GDC-0199) in patients with relapsed or refractory CLL/SLL and NHL.
- The inclusion criteria were:
  - Measureable disease requiring therapy;
  - Relapsed after, or refractory to, standard fludarabine or alkylator-based regimen;
  - Eastern Cooperative Oncology Group Performance Status 0 or 1;
  - Adequate bone marrow function (neutrophil count ≥1,000/μL; platelets ≥50,000/μL);
  - Adequate renal (creatinine clearance >50 mL/min) and hepatic function.
- The exclusion criteria were:
  - Prior autologous or allogeneic stem cell transplant;
  - Active infection.
- Eligible patients received an initial single oral dose of ABT-199 (cohort 1: 200 mg; cohorts 2–8: 50 mg), which was followed by a 3-day (cohort 1) or 7-day (cohorts 2–8) off-drug period, and then, continuous once daily dosing until disease progression or unacceptable toxicity.
- After cohort 1, the initial dose was reduced and daily dosing was modified to include a two- or three-step weekly dose escalation to the target dose for each cohort (150–1,200 mg).
- The coprimary end points were to:
  - Assess safety and pharmacokinetics;
  - Determine the maximum tolerated dose and recommended phase II dose.
- The secondary end points included objective response rate (ORR), duration of response, time to tumour progression, progression-free survival, overall survival, biomarkers, and pharmacogenetics.
- In this update, the investigators sought to determine if patients with ultra-high risk CLL have similar response rates to the overall study population.

Key findings
- As of April 14, 2013, 56 patients were enrolled, of which 30% (n = 17) had del(17p) CLL and 32% (n = 18) had fludarabine-refractory CLL.
- The baseline characteristics of the overall study population, as well as patients with del(17p) or fludarabine-refractory CLL were:
  - Age, median (range): 67 years (36–86), 69 years (47–80), and 66 years (36–78), respectively;
  - Male: 73%, 71%, and 67%, respectively;
  - Diagnosis of CLL/SLL: 88%/12%, 100%/0%, and 94%/6%, respectively;
Lymphocyte count >5.0 × 10^9/L: 59%, 71%, and 56%, respectively;
Bulky nodes ≥5 cm/≥10 cm: 50%/14%, 35%/0%, 56%/22%, respectively;
Prior therapies, median (range): 4 (1–10), 4 (2–9), and 5 (1–10), respectively;
Prior fludarabine treatment: 61%, 94%, and 100%, respectively.

• The median time on study in each group of patients was:
  All patients with CLL: 7.7 months (range: 0–17.8);
  Patients with del(17p) CLL: 6.5 months (range: 1.1–16.3);
  Patients with fludarabine-refractory CLL: 8.1 months (range: 0–17.5).

Safety
• The most common nonhematological all-grade adverse events (AEs) occurring in >15% of patients were diarrhea (41%), nausea (38%), fatigue (29%), upper respiratory tract infection (27%), cough (23%), and headache (16%). (Table 1)
• The most common grade 3/4 AEs occurring in >10% of patients were neutropenia (38%), thrombocytopenia (11%), and tumour lysis syndrome (TLS; 11%). (Table 1)
• The major dose-limiting toxicity (DLT) was TLS, which occurred in all patients in cohort 1 (n = 3) and in two patients with the modified dosing schedule (i.e., cohorts 4 and 8).
• One fatal AE involved a patient with clinical TLS (renal or other organ dysfunction), which occurred within 48 hours of dose escalation to the highest target dose of 1,200 mg.
• The other DLTs that occurred were muscle spasms and vomiting (one patient in cohort 5), and neutropenia (one patient in cohort 6).

• A total of 16 patients discontinued the study due to progressive disease (n = 9), AEs (n = 5), or other (n = 2).

Pharmacokinetics
• Following a single dose of ABT-199 with a low-fat meal, T_{max} and T_{1/2} were approximately 7 and 17 hours, respectively, supporting daily dosing.

Preliminary efficacy
• Of the 55 evaluable patients, 11% achieved a complete response (CR), 7% achieved a CR with incomplete marrow recovery, and 65% achieved a partial response (PR) for an ORR of 84%. (Table 2)
• Patients with ultra-high risk CLL had ORRs comparable to that of the entire study population (del[17p] CLL: 81%; fludarabine-refractory CLL: 78%). (Table 2)
• Computed tomography scan assessments revealed the best percent change from baseline in nodal size, with similar median times to 50% reduction for:
  All patients with CLL: 1.4 months (range: 0.7–13.7);
  Patients with del(17p) CLL: 1.4 months (range: 1.1–2.7); and
  Patients with fludarabine-refractory CLL: 1.4 months (range: 0.7–2.9). (Figure 1)
• Antitumour activity (i.e., percent change from baseline) of ABT-199 was observed in all tumour compartments, as demonstrated by the median times to 50% reduction in lymphocyte count (0.5 months [range: 0.1–1.4]) and bone marrow infiltrate (5.6 months [range: 1.9–17.4]). (Figure 2)
• Median times to 50% reduction in lymphocyte count for patients with del(17p) (0.3 months [range: 0.1–0.9]) and fludarabine-refractory (0.4 months [range: 0.1–1.4]) CLL were comparable to that of the entire study population.
Table 1. Adverse events in the overall study population

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades (&gt;10% of patients), n (%)</th>
<th>Grades 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>23 (41)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (39)</td>
<td>21 (38)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (38)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (29)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15 (27)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (23)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>10 (18)</td>
<td>6 (11)†</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (16)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (14)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (13)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>7 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>Tumour lysis syndrome§</td>
<td>6 (11)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6 (11)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>6 (11)</td>
<td></td>
</tr>
</tbody>
</table>

*Responses assessed by 2008 International Workshop on CLL criteria.

†Includes patients with autoimmune thrombocytopenia (n = 3), grade 3/4 (n = 2).

‡Patients (n = 6) had pre-existing thrombocytopenia; one in the setting of PD and one in TLS.

§TLS also includes three events from cohort 1; two clinical events and one laboratory TLS occurred with the new dosing schedule.

Table 2. Response assessment

<table>
<thead>
<tr>
<th>Best response</th>
<th>All CLL† n (%)</th>
<th>del (17p)§ n (%)</th>
<th>Fludarabine-refractory¶ n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>46 (84)</td>
<td>13 (81)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>CR</td>
<td>6 (11)</td>
<td>1 (6)</td>
<td>–</td>
</tr>
<tr>
<td>CR with incomplete marrow recovery</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>PR</td>
<td>36 (65)</td>
<td>11 (69)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2)</td>
<td>1 (6)</td>
<td>–</td>
</tr>
</tbody>
</table>

†CLL = chronic lymphocytic leukemia; CR = complete response; del(17p) = deletion of chromosome 17p; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

§One patient has not reached week 6 for evaluation by scan; four patients discontinued prior to week 6 assessment.

¶16 patients were evaluable; one patient has not reached week 6 for evaluation by scan.

††18 patients were evaluable; three patients discontinued prior to week 6 assessment.
Key conclusions

- As monotherapy, ABT-199 is highly active in patients with relapsed or refractory CLL, achieving an ORR of 84%, as well as in ultra high-risk CLL patients, achieving comparable ORRs of 81% in patients with del(17p) CLL and 78% in patients with fludarabine-refractory CLL.

- Treatment with ABT-199 resulted in some cases of dose-limiting TLS; additional dosing and scheduling modifications are being explored to minimize the risk of TLS.
  - A titrated dosing scheme combined with more aggressive prophylaxis, monitoring, and management may provide adequate protection for patients.

- A phase II single-agent study in patients with del(17p) CLL and phase III combination therapy study in patients with relapsed or refractory CLL are planned to start in late 2013 to early 2014.

References:
While the fludarabine, cyclophosphamide, and rituximab (FCR) combination is the first-line treatment option for chronic lymphocytic leukemia (CLL), a majority of patients with CLL are elderly, have pre-existing comorbidities, become refractory to treatment, or have genetic abnormalities, and thereby cannot tolerate this aggressive treatment due to the high risk of toxicity. Given that these special patient populations are heavily underrepresented in clinical trials, there is a lack of evidence supporting which treatments are not only most effective, but also tolerable. Consequently, there is no true standard of care for the treatment of CLL in elderly or unfit patients, or in those with high-risk CLL (e.g., deletion of chromosome 17p [del(17p)] and fludarabine-refractory disease). In Canada, treatment algorithms for CLL vary across the country and access and funding for newer agents is limited, further complicating treatment of these patients.

At the Foothills Medical Centre in Calgary, our standard approach for treating elderly and unfit patients is based on the following two factors. First, we believe in the findings of the German CLL5 phase III trial, which reported that chlorambucil was as clinically beneficial as fludarabine to elderly and unfit patients. Second, unlike in other provinces, in Alberta, we have been fortunate to have access to rituximab. Since we find rituximab to be very tolerable and an effective agent for use in combination with chemotherapy, we have been using it in elderly and unfit patients despite a lack of evidence from clinical trials. It was only recently that our approach was validated by the German CLL11 study, which confirmed that anti-CD20 monoclonal antibodies are beneficial in this subpopulation. Thus, our standard approach for elderly and unfit patients with CLL is either a combination of chlorambucil plus rituximab or fludarabine plus rituximab, with the latter being in line with the treatment strategy used in British Columbia. Our experience with bendamustine is very limited given that we only recently acquired funding for use in patients unfit for FCR. Several other challenges in treating these patients remain, including difficulty in tolerating treatment due to pre-existing comorbidities, polypharmacy and risk of drug interactions, and patient resistance to intravenous (iv) therapy or multiple visits.

For high-risk patients with del(17p) and those with fludarabine-refractory CLL, alemtuzumab, high-dose corticosteroids, or allogeneic stem cell transplantation are considered reasonable treatment options. Due to previous limited access in Alberta, we do not have a lot of experience with alemtuzumab at our centre. Additionally, despite having good reported activity, there is fear associated with using alemtuzumab because it significantly increases the risk for opportunistic infections. In particular, there is a risk of cytomegalovirus (CMV) reactivation, which requires regular monitoring during therapy, and if CMV reactivation is confirmed, there are issues in obtaining funding for valganoclovir or ganciclovir. Thus, in my opinion, treatment with alemtuzumab is more difficult to administer than many other agents available for CLL. Accordingly, for high-risk patients, we have tried high-dose corticosteroids alone or in combination with rituximab, and encourage allogeneic stem cell transplantation in those who are eligible. However, in our experience, these high-risk patients are difficult to treat and tend to do quite poorly.

While many different treatments are currently being used in elderly, unfit, and high-risk patients with CLL, there is often no strong evidence to support the use of any one of these treatment options, and thereby, an unmet need exists for the development of effective agents with favourable tolerability in these particular patient populations. Currently, there are several emerging targeted therapies being clinically investigated that appear to be very promising, some of which will be discussed in this perspective. These novel agents target critical molecular pathways or cell surface markers involved in the survival or chemoresistance of B cells in CLL. I believe that these novel agents may soon overshadow the excitement surrounding the bendamustine and rituximab (BR) combination and change the future therapeutic landscape of CLL. If these agents become available, we may be looking at a significant shift in the entire approach to treating CLL; patients would receive chronic oral therapy until progression rather than episodic therapy at symptomatic progression with periods of treatment-free intervals. Additionally, if these agents continue to be as efficacious and tolerable as they have been in early phase clinical trials, I can foresee them entering front-line therapy, as well as in the relapsed or refractory CLL (R/R CLL) setting, and ideally used in combination with other agents that are better tolerated by older, unfit, and/or high-risk patients, such as rituximab or other anti-CD20 monoclonal antibodies. Indeed, if such a combination could be a really effective regimen per se, then we would question whether any patient would ever need a conventional cytotoxic agent.

One of the novel targeted therapies being investigated for R/R CLL is idelalisib, a highly selective inhibitor of...
the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ). Barrientos and colleagues recently presented the updated findings of the phase I trial assessing the combination of idelalisib with rituximab and/or bendamustine. The results of this study appear to be extremely promising, as the overall response rate (ORR) was 81% with 71% of these responses maintaining durability over a 2-year period. Indeed, at a glance, idelalisib appears to be significantly more effective than any other agent approved for CLL, as the ORR and durability of responses achieved were very dramatic and unprecedented. In addition to having substantial clinical activity, this combination demonstrated a favourable safety profile, with pneumonia and diarrhea being the two most notable adverse events (AEs). Pneumonia is, unfortunately, a very common problem in the R/R CLL population and I do not believe that the incidence is significantly greater than what might be expected; however, future placebo-controlled phase III trials will clarify this issue. Diarrhea, on the other hand, is a more notable AE, as this is not a common complaint among this population. In fact, many patients complain of constipation with chemotherapy, and therefore, I believe that diarrhea is a clear treatment-related AE. Fortunately, diarrhea is not a treatment ending concern for most patients and they can be easily informed about its management.

Another interesting observation made by the investigators is that there were no differences in the outcomes of patients with fewer than three prior therapies versus those with at least three prior therapies. The lack of differences between these two groups is really encouraging, as patients who are heavily pretreated tend to not respond to other therapies at all. This observation suggests that idelalisib is clinically effective even when other treatments have failed. However, I would not put too much focus on this observation, as there was a fairly small number of patients in this study. Moreover, instead of separating patients by the number of prior treatments, I would have been more interested in the differences between refractory versus relapsed patients.

Being a phase I trial, there are a number of limitations and questions that remain unanswered. Aside from the obvious limitations of phase I trials (e.g., small number of patients), there are two major limitations worth mentioning. First, the study population included patients treated with mixed combinations of idelalisib with either rituximab, bendamustine, or both, which makes it difficult to determine the best combination to use with idelalisib. Second, the investigators did not use standard doses of rituximab in the CLL setting and it is not entirely clear as to why this treatment approach was chosen. In summary, the findings of this phase I trial are very encouraging and have motivated the development of phase III trials for idelalisib; however, the following questions remain unanswered: (1) What is the best combination therapy with idelalisib? (2) Who are the patients who are not doing well with idelalisib and may respond better with other novel agents?

In light of the promising findings in phase I trials, the safety and efficacy of idelalisib is currently being investigated through a phase III development program for idelalisib, which includes three separate trials evaluating idelalisib in combination with BR (study 115), rituximab alone (study 116/117), and ofatumumab alone (study 119) in previously treated patients with CLL. This program will help answer many of the remaining questions, including how we can best use idelalisib in the CLL setting. However, since there is no strong evidence to support rituximab monotherapy for R/R CLL, I am less excited and interested in the findings of study 116/117. It would have been more reasonable to compare idelalisib alone versus idelalisib plus rituximab, particularly if the goal was to determine whether rituximab adds to the efficacy of idelalisib. Conversely, it is noteworthy to mention that the use of ofatumumab monotherapy as an active control in study 119 is completely justified, as it previously demonstrated single-agent activity and is approved for fludarabine- and alemtuzumab-refractory CLL.

At ASCO 2013, Eradat et al. and Flinn et al. presented on the study design of study 115 and study 119, respectively. Both studies are phase III, randomized, double-blind, placebo-controlled trials. Overall, these trials appear to be well designed and reasonable, and the end points are clinically relevant. However, it should be noted that the inclusion of patients with measurable lymphadenopathy is a limitation because many patients without lymphadenopathy can present with marked cytopenias and require CLL treatment. Although the most obvious reason for including lymphadenopathy as part of the eligibility criteria is to get around the issue of lymphocytosis, which would ultimately make it difficult to determine response rates from hematological parameters, it is still a considerable flaw in the generalizability of these studies to all CLL patients. Despite this limitation, study 115 will still help determine whether treatment with idelalisib plus BR versus BR alone is more effective in the CLL setting. Furthermore, the findings of study 119 will answer the important questions of whether combination therapy with a PI3K inhibitor and an anti-CD20 antibody is an attractive option for the majority of patients and if treatment with conventional cytotoxic agents, such as bendamustine, is necessary.

Another emerging targeted therapy that is currently being investigated is obinutuzumab (GA101), a novel type II anti-CD20 monoclonal antibody. Goede and colleagues presented the final stage I results of the CLL11 phase III trial on the efficacy and safety of GA101 or rituximab in combination with chlorambucil as compared with those of chlorambucili...
alone in elderly patients with previously untreated CLL and comorbidities. It was found that the addition of an anti-CD20 monoclonal antibody to chlorambucil significantly prolonged progression-free survival compared to chlorambucil monotherapy. The findings of this study are not only clinically meaningful, but also potentially practice-changing because this is the first study to show that anti-CD20 monoclonal antibodies are effective in older and frailler patients. Indeed, the addition of anti-CD20 monoclonal antibodies to chlorambucil may eventually become the standard of care for elderly and unfit patients.

While the findings appear promising, it is important to be aware of the high-grade infusion-related reactions associated with GA101 therapy, particularly at first infusion. As with rituximab, one solution for this issue is to divide the initial dose. In fact, due to our centre’s first-hand experience with GA101 (i.e., through our participation in this trial), we feel very comfortable in using this drug in elderly and unfit patients, as we did not find it any less tolerable than rituximab when the first dose was divided (as was our standard practice). We also believe that the AEs associated with GA101 would not deter us from using it, especially if it proved to be significantly more effective than rituximab. A disadvantage of GA101 is its iv route of administration compared to chlorambucil, which is taken orally and used in an outpatient manner. However, I think that most patients would still prefer the extra months of remission in exchange for the inconvenience of iv therapy.

Currently, it is an exciting period for GA101 and due to its longer follow-up, stage II of the CLL11 trial may answer a number of remaining questions, including: (1) Which anti-CD20 monoclonal antibody is more effective? and (2) Does the addition of an anti-CD20 monoclonal antibody to chlorambucil provide an overall survival advantage? If the stage II results of this study clearly demonstrate that GA101 is superior to rituximab, then I would consider prescribing it instead of rituximab.

By far the most interesting findings on any emerging targeted therapy or, for that matter, within the CLL field, were with ABT-199, a potent BCL-2 inhibitor. Seymour et al. and Roberts et al. reported on a phase I trial evaluating the safety and pharmacokinetics profile of ABT-199 in patients with R/R CLL. ABT-199 was found to be highly active not only in patients with R/R CLL (ORR of 84%), but also in ultra high-risk patients with del(17p) or fludarabine-refractory CLL (ORRs of 81% and 78%, respectively). It is surprising and extremely encouraging to see such dramatic activity in ultra high-risk patients who do not normally respond to conventional treatments, fare extremely poorly, and have very short survival. In fact, it appears that ABT-199 may be too effective, as the major dose-limiting toxicity and barrier to treatment is tumour lysis syndrome. However, since the investigators are already introducing dosing and scheduling modifications into the study, I am very optimistic that they will figure out a way of making this treatment more tolerable in the near future.

In conclusion, the world of CLL has changed dramatically in just a few years, making it a very exciting time. Currently, there are a number of novel agents undergoing clinical investigation that may completely revolutionize the treatment of CLL. This is really encouraging because there are so many patients with this disease who can benefit from all of these new therapies. Unfortunately, even if the findings of future studies are positive, I do not think that they will affect clinical practice until these novel agents become more accessible and funded, which is the sad reality of the healthcare system. For example, we do not yet have full access to BR for front-line therapy of CLL across Canada, as we are still waiting on the findings of the German CLL10 trial. In fact, realistically, it may be quite some time before we have ready access to these novel agents.

Lastly, while more evidence is warranted before we can determine which of the emerging targeted therapies are the most promising, I predict that the most ideal combination for the majority of patients with CLL is an anti-CD20 monoclonal antibody with one of the novel agents. For young and fit patients, a combination of bendamustine, an anti-CD20 monoclonal antibody, and one of the novel agents may be suitable, as they can better tolerate the cytotoxic effects of bendamustine than older and frailer patients. Also, future studies that allow for the inclusion of patients who have undergone allogeneic stem cell transplantation or the combination of novel agents with transplantation may potentially lead to the development of more curable options for CLL.

An Interview with Dr. Clemens-Martin Wendtner on the Treatment of Less Fit Patients with Chronic Lymphocytic Leukemia

At the 2013 EHA Congress, New Evidence spoke with Dr. Clemens-Martin Wendtner, Professor of Medicine and Director of the Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine at Klinikum Schwabing, Munich, and secretary of the German chronic lymphocytic leukemia (CLL) Study Group (GCLLSG) about the treatment of less fit patients with CLL.

**New Evidence:** What criteria do you use to determine whether a patient is able to tolerate standard treatments for CLL?

**Dr. Wendtner:** The most important consideration in determining a patient’s fitness for aggressive treatments is the use of clinical judgement. In addition, a simple tool can be used to calculate creatinine clearance, which is based on a straightforward formula. The Cumulative Illness Rating Scale (CIRS) can also be helpful; however, we know the scoring system should be interpreted with caution given that organ dysfunction is not weighted in a meaningful way. For example, a dysfunction with a patient’s heart would be weighted in the same way as one with a patient’s eyes. A combination of strategies are therefore used in clinical practice to determine a patient’s fitness for treatment.

**New Evidence:** New data are suggesting there are patients who are not fit enough to receive standard aggressive treatments, but can tolerate more than supportive care. Please describe these patients.

**Dr. Wendtner:** Originally, we described three categories of patients: the “no-go” patients, who should be given best supportive care; the “slow-go” patients, who do not qualify for standard aggressive treatments but can tolerate something marginally less toxic; and the “go-go” patients, who qualify for standard aggressive therapies. We have now discovered that some of these “slow-go” patients can tolerate somewhat more aggressive treatments, while others fall closer to the “no-go” patients. In these less fit patients, we have therefore created two categories: the “slow-go” patients, where a durable remission is the goal; and the “not so slow-go” patients, where improving complete response (CR) or progression-free survival (PFS) is the aim of treatment. (Figure 1)

Approximately 10% of patients will fall into the fit or “go-go” category, 30% will fall into the unfit or “slow-go” category, and the majority of 50% to 60% will fall into the less fit categories. There is therefore a need to find effective treatment options for the less fit population that meet the individual treatment goals of these patients.

**New Evidence:** What are your standard treatments in less fit patients with CLL?

**Dr. Wendtner:** Currently, we still give monotherapy as chlorambucil or bendamustine to the more “slow-go” patients, as they may not tolerate the addition of rituximab. In Germany, we prefer to give bendamustine, as chlorambucil is given orally and involves taking a large number of pills, making it difficult to monitor the dosage given to patients. In addition, data from the study by Knauf, et al. showed an efficacy advantage of bendamustine over chlorambucil, suggesting that bendamustine is the better treatment choice in these patients. For “slow-go” patients, we usually reduce the dose of bendamustine to 70 mg/m² and in the “not so slow-go” category, we give the standard 90 mg/m² dose and add rituximab.
New Evidence: What studies have been done in less fit CLL patients that support the use of particular regimens in these patients?

Dr. Wendtner: The MABLE study is a phase III study comparing rituximab plus chlorambucil (R-Clb) to bendamustine plus rituximab (BR). In the results of an interim analysis, BR appears superior to R-Clb with respect to response rates. Based on these results, I would tend to use BR over R-Clb in less fit patients with CLL.

In addition, the CLL11 study is comparing GA-101 plus chlorambucil (G-Clb) or R-Clb versus chlorambucil mono-therapy using a phase III, randomized design. The study has shown good rates of minimal residual disease (MRD) negativity with the addition of either rituximab or GA-101 to chlorambucil. In practice, we are currently able to give R-Clb, but once data on the head-to-head comparison of R-Clb versus G-Clb becomes available, we may be able to give G-Clb to these patients. In my practice, I will still prefer to give BR over G-Clb, even if data shows an advantage of this regimen over R-Clb, as I am more familiar with BR and there is no data comparing the two regimens.

The next logical step would be to examine GA-101 plus bendamustine in the front-line setting. The GCLLSG is currently looking at this combination in a two-arm phase II trial in the relapsed setting (CLLR3) of FC plus GA-101 versus bendamustine plus GA-101, followed by maintenance with GA-101. The study is planned to open in October 2013. In addition, an American study is examining this combination in a phase I/II study; results will most likely be presented at the American Society of Hematology (ASH) meeting in December 2013.

Newer agents may also provide promising therapies for these less fit patients. For example, idelalisib (GS-1101) is currently being examined in a number of trials, including a phase III trial comparing rituximab plus idelalisib versus rituximab plus placebo in “slow-go” patients. Another phase III study in the relapsed setting is examining ibrutinib plus BR versus BR plus placebo (CLLR1) and includes patients with inferior creatinine clearance (CrCl ≥ 40 ml/min). There is also an ongoing phase I/II trial using ABT-199 in the relapsed setting and includes both fit and less fit patients. Based on the results of this phase I/II trial, another trial is planned adding ABT-199 to BR and comparing that with BR alone. Other ongoing phase III trials are comparing ofatumumab plus chlorambucil versus ofatumumab plus bendamustine (RIALTO), and lenalidomide monotherapy compared to chlorambucil monotherapy. Results of these studies using newer agents may provide additional treatment options for these patients. Future combinations worth examining include idelalisib plus GA-101, ibrutinib plus GA-101, and ABT-199 plus GA-101.
New Evidence: What criteria do you use to determine whether a patient is able to tolerate standard treatments for CLL?

Dr. Goede: There are currently no standardized criteria to assess the fitness of a patient that can be used to determine whether a patient can receive standard treatment. The German CLL study group (GCLLSG) is currently using the Cumulative Illness Rating Scale (CIRS) in combination with the assessment of renal function to assess the comorbidity burden of patients in clinical trials. Although we use the CIRS and creatinine clearance to stratify patients in our trials, in clinical practice, it is important to consider the individual experience of the treating physician, as these tools are not fully validated in this setting. For elderly patients, other factors other than comorbidity also need to be considered such as cognitive function, mobility, nutritional status, and functioning in terms of disabilities and dependency. These factors are not fully covered by the CIRS and should therefore be considered in decisions regarding treatment. Given the need for better fitness scores for elderly patients, the scientific community is currently undertaking an international initiative under the leadership of the International Workshop for CLL (iwCLL) to develop a scoring system appropriate for use in clinical practice and in clinical trials.

New Evidence: What percentage of your patients are not eligible for standard treatments?

Dr. Goede: In academic centres, we primarily see younger and fitter patients who are able to travel to these centres for treatment. The percentage of fit patients in these centres is therefore higher than that found in private practices. In academic centres, approximately 20% to 25% of patients are not eligible for standard treatments, whereas in private practice this percentage may be closer to 50%. Of the patients included in our CLL11 trial, none of them would have been eligible for a recent landmark trial exploring aggressive CLL treatments.

New Evidence: What treatment options do you give less fit patients with CLL who are unable to tolerate standard treatments?

Dr. Goede: There is no broadly accepted standard treatment for less fit patients with CLL. Until recently, there has been no conclusive proof from phase III trials that any existing treatments are superior to chlorambucil monotherapy. Nevertheless, several phase II trials have shown promising results using treatments such as low-dose FCR, bendamustine plus rituximab (BR), chlorambucil plus rituximab (R-Clb), or experimental approaches with the tyrosine kinase inhibitors, ibrutinib and idelalisib, and the immunomodulator, lenalidomide. However, none of these regimens have proved superior to chlorambucil in a phase III study; we therefore still need to consider chlorambucil monotherapy for these patients. With recent data from the CLL11 study, this view is changing since it has been recently shown that adding a CD20 antibody improves the efficacy of treatment with chlorambucil. Therefore, we now need to consider the addition of a CD20 antibody to treatment.
New Evidence: What are the most convincing studies that have been done in less fit CLL patients to support the use of particular regimens in these patients?

Dr. Goede: Data from phase II studies in elderly patients have shown promising results with several regimens. As already said, low-dose FCR, BR, ibrutinib or idelalisib plus rituximab, and lenalidomide are among those; however, there are very few data from phase III studies. One phase III study, the CLL5 study, compared chlorambucil monotherapy versus fludarabine monotherapy. This study did not show any advantage of fludarabine over chlorambucil in these patients. In addition, interim results of a study comparing R-Clb versus BR in elderly patients showed superiority of BR over R-Clb for complete remission (CR). However, these are very early results and we need to wait for progression-free survival (PFS) data and longer follow-up in a larger number of patients. To date, the largest phase III trial providing convincing results is the CLL11 trial.

New Evidence: Please describe the rationale and design of the CLL11 study.

Dr. Goede: The rationale of the CLL11 study can be divided into two parts. Firstly, CLL is a disease of elderly patients, many of whom have comorbidities and are therefore not able to tolerate aggressive treatments. There is therefore an unmet treatment need in these patients. Secondly, chlorambucil has a relatively safe toxicity profile and it makes sense to combine it with an anti-CD20 antibody. In pre-clinical models, GA101 has been shown to be superior to rituximab and there is therefore a need to explore the potential superiority of this agent over rituximab. We therefore want to improve treatment in elderly patients by adding CD20 antibodies to chlorambucil and also to test the new monoclonal antibody, GA101, in this setting.

New Evidence: Please describe the patient population included in this study. How does this patient population compare to those you see in clinical practice?

Dr. Goede: The median age in our study population was 73 years, 10 to 15 years older than those in previous studies including the CLL8 trial. In addition, almost half of patients were 75 years of age or older. The median CIRS score was 8, meaning that patients had at least three comorbidities of clinical significance or many mild comorbidities. Typical comorbidities were hypertension, coronary heart disease, heart failure, diabetes, musculoskeletal problems, and renal impairment. The median creatinine clearance at baseline was 60 mL/min. If we consider all of these factors, the patient population in our study reflects typical patients treated by private practitioners.

New Evidence: Please describe the key efficacy results of the CLL11 study.

Dr. Goede: Currently, we have analyzed data comparing R-Clb versus chlorambucil monotherapy and GA101 plus chlorambucil (G-Clb) versus chlorambucil monotherapy. Results comparing R-Clb to G-Clb will be available at a later date and will most likely be presented at the American Society of Hematology (ASH) 2013 meeting.

In comparing G-Clb with chlorambucil monotherapy, the overall response rate (ORR) was higher in the G-Clb arm (22% G-Clb versus 0% Clb). Among patients assessed for minimal residual disease (MRD), there were no MRD negative patients in the control arm and in the G-Clb arm, one third of patients evaluated had MRD negativity in the blood and 17% had MRD negativity in the bone marrow. The hazard ratio (HR) for PFS was 0.14 for G-Clb (median 23 months) versus chlorambucil monotherapy (median 11 months), which is perhaps the lowest HR I have seen so far in a phase III hematology study. The PFS in the G-Clb arm is still immature and it is likely to improve significantly with longer follow-up. Currently there is no significant difference in overall survival (OS), but we also hope to see this with a longer follow-up.

For the comparison between R-Clb versus chlorambucil monotherapy, 8% of patients achieved a CR in the R-Clb arm versus 0% in the chlorambucil monotherapy arm. There were no MRD-negative patients in the control arm and in the R-Clb arm, 2% of evaluable patients had MRD negativity in the blood and 3% had MRD negativity in the bone marrow. The HR for PFS was 0.32 for the comparison between groups, with a median PFS of 11 months in the control arm and 16 months in the rituximab arm. Thus far, there is no significant difference in OS.
New Evidence: Please describe the safety results of the study.

Dr. Goede: There were more toxicities in the G-Clb arm compared with those in the chlorambucil monotherapy arm. Around one fifth of patients in the G-Clb arm experienced infusion-related reactions (IRRs) of grade 3 or greater. These IRRs were all seen during the first infusion of GA101 and not during subsequent infusions. Therefore, monitoring of patients during the first infusion is crucial; however, even if an IRR occurs, it is unlikely that patients will experience a subsequent IRR. In the majority of cases, IRRs were manageable and completely resolved and there were no deaths due to these toxicities. However, we do want to communicate the importance of monitoring for IRRs during the first infusion. In addition, there were more neutropenias in the G-Clb arm; however, fewer infections were reported, most likely because of better disease control with G-Clb.

There were also more toxicities in the R-Clb arm compared with those in the control arm. Around 4% of patients had IRRs grade 3 and greater in the R-Clb arm and there were also more neutropenias, but again, fewer infections in this treatment group. Therefore, it appears that GA101 produces a greater number of IRRs than rituximab, which may be due to the faster and superior killing of CLL cells by GA101 during and immediately after the first infusion. This finding needs to be studied further, but it may reflect superior efficacy of GA101.

New Evidence: Based on these results, what treatment regimen would you recommend for less fit patients with CLL?

Dr. Goede: Chlorambucil combined with a CD20 antibody is an effective and safe regimen for these less fit patients. Although other treatment options exist, these should be compared to R-Clb instead of chlorambucil monotherapy. My general recommendation is to put all of these less fit patients into clinical trials to further improve treatment. There is a strong movement to replace chlorambucil with other, stronger options, such as bendamustine, which is being examined in ongoing studies. In addition, newer options such as BCL2 inhibitors (ABT-199) and tyrosine kinase inhibitors (ibrutinib and idelalisib) could replace chlorambucil and give us a chemotherapy-free regimen. First results from ongoing phase II studies are now available examining some of these options and results also look promising in elderly patients.

Given the data to date, I would clearly choose to enroll elderly patients into clinical trials; however, if this was not possible, I would give R-Clb as first-line treatment, since rituximab is currently the only approved antibody for this indication. Once GA101 is licensed, I would not hesitate to use this newer antibody in combination with chlorambucil.

New Evidence: How might the results of this study influence clinical practice?

Dr. Goede: The CLL11 study has immediate impact on clinical practice, since results show that patients given chlorambucil should also be given a CD20 antibody in combination. In addition, future studies need to use combination treatment as a control arm, since chlorambucil monotherapy has now shown to be inferior to combination treatment in at least one phase III trial. With upcoming results of the head-to-head comparison between G-Clb and R-Clb, I hope we will be prompted to use a more effective antibody such as GA101 to treat patients with CLL.
Presentation Summary

Advances in the Management of Acute Promyelocytic Leukemia: Summary of the Presentation by Dr. Lo-Coco at AMHOQ

Background

Epidemiology
Acute promyelocytic leukemia (APL) is a very rare disease with an annual incidence in Italy estimated at 0.6 in 1,000,000.1 APL represents 10% to 15% of acute myeloid leukemia (AML) cases, with approximately 100 to 150 cases of APL reported yearly in Italy and Germany. Of these cases, approximately 20 relapses are expected. In Canada, the age adjusted incidence of APL is 0.073 cases per 100,000.2 The median age of patients diagnosed with APL is much younger than those diagnosed with AML (40 vs. 70 years), and the incidence in males is the same as in females. Therapy-related cases in APL and AML are likely to increase due to an increase in the number of cancer survivors and an aging population. Therefore, one can expect secondary or therapy-related AML cases to become as high as 20%.

Prognosis
The prognosis for patients with APL has dramatically improved since its first description in 1957. However, since patients are at high risk of death from internal hemorrhaging within a few hours after presenting at the clinic, this improvement is critically dependent on prompt patient diagnosis followed by the immediate provision of antileukemic and supportive transfusion therapies. Owing to the high risk of early death, treatment initiation may be considered the first prognostic factor. Without treatment, APL is the most malignant form of AML, with a median survival of less than one month after diagnosis. With modern therapy, however, APL is associated with very high curative rates.

For patients receiving the current standard of care, all-trans retinoic acid (ATRA) plus anthracyclines, the main prognostic marker for relapse is the white blood cell count (WBC). Patients at a high risk of relapse are defined as those with a WBC of >10 x 10^9/L. These patients also have a higher risk of fatal hemorrhaging at presentation and during the first days following diagnosis.

Diagnosis
Most APL cases can be diagnosed morphologically as hypergranulated promyelocytes (± Auer rods).2 However, in about 20% of cases, cells are microgranular or agranular requiring confirmation through molecular biology techniques. Patients with APL may have one of several presenting features: 1) weakness, mucocutaneous hemorrhage (epistaxis, ecchymoses), severe bleeding (cranial, pulmonary); 2) dysplastic promyelocytes in the bone marrow with low counts in the peripheral blood; and 3) an abrupt onset with rapid coagulopathy that develops into a medical emergency. Patients typically feel normal a few weeks or days before symptoms appear. Although the presenting features of APL are very well known, it is important for nonspecialists to be aware that patients presenting with the disease may either have normal or abnormal blood counts (i.e., decreased platelets, high WBCs, or low hemoglobin).
Diagnostic work-up on patients suspected of having APL involves several steps.\(^4,5\) Given the rapid progression of APL, an important first step is to view the disease as a medical emergency. Treatment with ATRA and supportive care should be initiated following morphological diagnosis and this should be followed by confirming the presence of the promyelocytic leukemia (PML)/retinoic acid receptor (RAR)\(\alpha\) translocation, t(15;17). This can be accomplished rapidly through fluorescence in situ hybridization or staining for PML, a vital step to determine a patient’s eligibility for ATRA or arsenic trioxide (ATO)-based protocols. PML detection is a rapid procedure that can be completed in as little as two hours by immunofluorescence. Cells that are positive for PML/RAR\(\alpha\) display a bespeckled or microgranular pattern, while PML/RAR\(\alpha\)-negative cells display the nuclear body pattern. In addition to these steps, a patient’s sample should then be sent to a reference laboratory to determine baseline ribonucleic acid (RNA) expression of PML/RAR\(\alpha\) by reverse transcriptase–polymerase chain reaction (RT-PCR), which is necessary for successive monitoring of patients through the duration of treatment.

**Significance of the PML/RAR\(\alpha\) fusion protein**

The PML/RAR\(\alpha\) fusion protein is significant in the diagnosis and management of APL for several reasons. In addition to being the hallmark of this disease, it is unique to APL as no other leukemias have this translocation. The PML/RAR\(\alpha\) fusion protein is also strongly associated with the pathogenesis of APL. Both ATRA and ATO target and degrade PML/RAR\(\alpha\). Once the translocation has been detected, physicians can predict the response to ATRA or ATO in all cases. The prediction is so strong that if patients who have been diagnosed with APL have a primary resistance to ATRA or ATO, a wrong diagnosis may be concluded, i.e., it is safe to assume the patient does not have APL. Finally, the fusion protein is useful to monitor minimal residual disease in patients with APL during treatment.

**History of progress in APL**

The history of APL is one of the most fascinating stories in medicine (Figure 1). Advances in its treatment have made APL highly curable. In 1957 by the Norwegian hematologist Dr. Leaf Hillestad,\(^6\) who accurately identified APL as a distinctive subtype of AML, and one that is aggressive and rapidly fatal if not correctly diagnosed and treated immediately. Approximately a decade later after its discovery, the prognosis of APL began to change dramatically. In 1973, Professor Jean Bernard in France published a seminal paper showing APL to be highly responsive to the anthracycline daunorubicin.\(^7\) Similar findings were later replicated by our Italian multicentre GIMEMA (Gruppo Italiano Malattie Ematologiche Maligne dell’Aduloto) group with idarubicin, another anthracycline.\(^8\) These findings revealed a unique feature of APL. Unlike other leukemias, APL was highly sensitive to single anthracycline agents such as daunorubicin and idarubicin. The reason for this extreme sensitivity remains unclear and one that is an interesting area for investigation. Following the discovery of this sensitivity to anthracyclines was the identification of the translocation between chromosomes 15 and 17 [t(15;17)] by Dr. Janet Rowley in Chicago.\(^9\)

Nearly a decade later, Chinese scientists made the revolutionary discovery that APL was responsive to ATRA.\(^10\) The discovery was inspired partly by emerging data from Europe that cancer could be treated by differentiating agents, and partly by the philosophical thinking of the famous Chinese philosopher Confucius who taught that there was a greater benefit to society if criminals were rehabilitated instead of punished.\(^11\) The investigators, Dr. Zhu Chen and his mentor Professor Zhen-Yi Wang, believed that perhaps malignant cells, like criminals, could be converted into normal cells. The result of their success tore down the long held dogma that cancer is an irreversible condition.

![Figure 1. History of APL](New Evidence in Oncology | September 2013)

Although ATRA converts APL cells into differentiated, nonmalignant cells, patients receiving ATRA alone are destined to relapse. We and others therefore investigated the efficacy of ATRA plus chemotherapy in the treatment of APL. The AIDA (ATRA plus idarubicin) study, begun by the GIMEMA group in 1993, observed patients who had received ATRA plus idarubicin over 12 years. Among other findings, this study revealed an overall survival (OS) rate of at least 75%, an observation later confirmed by other international studies.

In 1996, the same institution in Shanghai that discovered the effects of ATRA on APL cells also discovered that the ancient Chinese remedy ATO was extremely active in APL.\(^9\) More than a decade later in 2001, the efficacy of ATO as a single agent in patients with APL was established with the publication of the U.S. multicentre ATO trial in patients with...
relapsed APL.12 This study showed that patients who received the single agent ATO achieved molecular remission in 78% of cases after two cycles of treatment. The success of this trial suggested that the prospect of a cure in the relapsed state was significant, and led to the registration and licencing of ATO for the treatment of patients with relapsed APL.

The pioneering work of Eli Estey et al. from the MD Anderson Cancer Center further established the role of ATO in a chemotherapy-free approach for APL, showing that patients with $<10 \times 10^9/L$ (low risk) or $>10 \times 10^9/L$ (high risk) WBC at diagnosis, and who had received ATRA plus ATO, had a greater rate of event-free survival (EFS) than that of patients who received idarubicin plus ATRA over a five-year period. The fact that patients in this trial did not receive chemotherapy was highly significant. A minor exception was the administration of one or two doses of the anti-CD3 chemotherapy agent gemtuzumab ozogamicin to patients who had $>10 \times 10^9/L$ leukocytes.

Although the mechanism of action of ATO on APL cells is not fully understood, it is now known that ATO has at least two different modes of action. Similar to ATRA, ATO targets and degrades the PML/RAR$\alpha$ fusion protein leading to activation of repressed genes. Unlike ATRA, however, ATO also leads to activation of apoptosis.

The current recommendation for patients with relapsed APL after receiving ATRA plus chemotherapy is ATO with or without ATRA. Treatment approaches for patients who achieve remission remain a matter of debate. Different strategies such as autologeneic versus allogeneic remission are difficult to compare due to the absence of randomized trials. Important factors to consider when making a decision for consolidation of second remission in patients with APL include: the age and performance status of the patient, the length of first remission, the type of first-line treatment, the availability of a human leukocyte antigen (HLA)-identical donor, and the achievement of molecular remission. With respect to molecular remission, the consensus is that patients who do not achieve PCR negativity of PML/RAR expression should not be approved for an autologous transplantation. Patients who show persistent molecular positivity after re-induction should receive an allogeneic transplant instead.

**Challenges with modern APL treatment**

**Early death in APL and its reduction**

The risk of early death in patients with APL is a critical issue in APL management. Clinical trials report a wide range of early death frequency ($2\%–25\%$) which is most likely due to a patient selection bias.1 For example, 15/792 patients with cranial hemorrhaging and four patients with pulmonary hemorrhaging were excluded from the PETHEMA (Programa de Estudio y Tratamiento de las Hemopatías Malignas) trials.13 In addition, 14/792 patients were deemed unfit for chemotherapy and were excluded from the same trial.

Population-based studies have reported a high frequency of early death (<30 days after treatment initiation), ranging from 17% in the Surveillance, Epidemiology, and End Results database (SEER)14 to 29% in a study based on a Swedish registry.15 The percent of early death occurrence before patients receive therapy remains unknown and, in my opinion, is likely to be around 20% to 30%.

Reducing the frequency of early death in patients with APL is of paramount importance in its management. Although APL is a very rare condition, promoting education and awareness of this disease in emergency units is critical to reducing early death in these patients. Physicians in emergency units need to know of the existence of APL, and that patients, even young patients, may present with sudden bleeding without clear signs of leukemia (i.e., patients may have nonleukemic blood counts). Other recommended measures to lower the rate of early death include fostering registry studies, referring patients to highly specialized centres, improving early diagnosis and ATRA availability, as well as more studies to understand factors that can predict sudden hemorrhages and coagulopathy. In APL, supportive treatments are at least as important as antileukemic treatments. Supportive measures recommended by an international panel of experts include platelet infusion to maintain platelet levels $>30–50 \times 10^9/L$, and fresh frozen plasma to maintain fibrinogen levels $>150 \text{mg/dL}$.4 The use of heparin and antifibrinolytics was not recommended by the panel.

**ATO plus chemotherapy toxicity**

In an effort to manage the toxicity of ATRA and chemotherapy, we and other investigators developed risk-adapted treatments in which patients received different intensities of postinduction treatment.16 In Italy for example, AIDA induction was followed by more or less intensified treatment based on the assigned risk of patients (low or high risk). This approach led to a significant improvement in the rate of disease-free survival (DFS) among patients who received the new risk-adapted AIDA protocol (AIDA 2000) compared with those who received the old AIDA protocol (0493).16

**Breaking new ground**

**ATO plus ATO as first-line treatment: rationale and study**

Despite the high cure rates with ATRA plus chemotherapy, there are several challenges to overcome. These include a high rate of patient death during induction and remission,16 death from toxicity during consolidation therapy,15 and death from the development of therapy-related secondary tumours (myelodysplastic syndrome/AML) in about 2% of patients treated with ATRA plus chemotherapy.18 Given the high potential to cure patients with APL, these are, in my opinion, unacceptable statistics.
In an effort to overcome these challenges, we investigated the chemotherapy-free approach to APL treatment. Unlike studies examining ATRA plus ATO, several multicentre studies examining ATRA plus chemotherapy in patients with APL have demonstrated a high cure rate of at least 75%, and a similarly high nonrelapse rate, as determined during the observation of thousands of patients. In contrast, the quantity and quality of studies on ATRA plus ATO have been limited. These studies show that ATRA plus ATO is effective with low toxicity. However, they were also single-centre studies involving a small number of patients with a relatively short follow-up.

In 2006, we began a phase III, long-term follow-up study on patients not at high risk (low- and intermediate risk patients) with APL comparing the AIDA protocol (ATRA plus chemotherapy plus two years of maintenance therapy) with the Eli Estey protocol (ATRA plus ATO for induction and consolidation) (Figure 2).\(^1\) The trial was designed to assess noninferiority between the two groups at a margin difference of 5%. Patients were recruited from the GIMEMA (40 centres) and SAL-AMLSG (27 centres) groups, and observed for a median of 34.3 months. Patients in both groups had similar baseline clinical and biological characteristics.

The study — presented at the American Society of Hematology in December 2012 and recently published in the NEJM in July 2013 — revealed several important findings. Induction outcome between both groups was not statistically significant (complete response [CR] = 100% in ATRA plus ATO; CR = 95% in ATRA plus chemotherapy). However, there were four deaths in the ATRA plus chemotherapy group and none in the ATRA plus ATO group. The frequency of differentiation syndrome was similar between the two groups (all patients received prophylactic prednisone 0.5 mg/kg/day until CR). However, there were significant differences in toxicities between the groups. As expected, hematological toxicity increased in patients receiving ATRA plus chemotherapy during induction and consolidation phases (Figure 3). On the other hand, patients in the ATRA plus ATO group experienced a greater frequency of QTc prolongation (13% vs. 0%, \(p = 0.0005\)), a greater frequency of grade 3/4 hepatic toxicity (57% vs. 5%; \(p <0.0001\)), and increased leukocytosis (>10 x 10^9/L; 47% vs. 24%; \(p = 0.007\)). These were expected from previous experiences with ATO plus ATRA, and were managed with temporary discontinuation and dose modifications of ATO, which were already written into the protocol. Out the 13 patients experiencing these toxicities, there was one permanent drug discontinuation. Patients experiencing leukocytosis were managed with hydroxyurea (500 mg four times a day (qid) if WBC ≤50 x 10^9 and 1 g qid if >50 x 10^9). No significant differences in DFS or cumulative incidence of relapse were observed between the two groups (Figure 4, Figure 5).

The primary endpoint of the study, EFS, was significantly greater in the ATO plus ATRA group than in the ATRA plus chemotherapy group (Figure 6). Similarly, patients in the ATO plus ATRA group had a slight but significant increase in OS compared with the ATRA plus chemotherapy group (Figure 7). Since this trial was designed to test noninferiority only, we concluded that ATRA plus ATO was at least not inferior to ATRA plus chemotherapy when comparing EFS after two years in patients with low- or high-risk APL. The study also showed that while ATO and ATRA was associated with less hematological toxicity, it was associated with more hepatic toxicity and QTc prolongation, both of which were effectively managed by dose adjustments. It is our belief that this regimen may emerge as a new standard of care for patients with APL who are at low or intermediate risk.

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**Figure 2: Study design**

![Study design diagram](image-url)

(ATR = 6-Mercaptopurine; ATO = arsenic trioxide; ATRA = all-transretinoic acid; Chemo = chemotherapy; CR = complete response; IDA = idarubicin; MTX = methotrexate; MTZ = mitoxantrone; R = randomized)
**Figure 3. Hematologic toxicity**

Grade 3/4 thrombocytopenia >15 d

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Grade 3/4 neutropenia >15 d

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ATO = arsenic trioxide; ATRA = all-trans-retinoic acid; Chemo = chemotherapy; CONS = consolidation; d = days; IND = induction

**Figure 4. Disease-free survival**

Disease-free survival probability (%) over time from CR

- ATRA + ATO
- ATRA + chemo

- p = 0.14

**Figure 5. Cumulative incidence of relapse**

Relapse probability (%) over time from CR

- ATRA + ATO
- ATRA + chemo

- p = 0.28

**Figure 6. Event-free survival**

Event-free survival probability (%) over time from diagnosis

- ATRA + ATO
- ATRA + chemo

- p = 0.02

**Figure 7. Overall survival**

Overall survival probability (%) over time from diagnosis

- ATRA + ATO
- ATRA + chemo

- p = 0.02

ATO = arsenic trioxide; ATRA = all-trans-retinoic acid; Chemo = chemotherapy; CR = complete response
Summary

Tremendous amounts of progress have been made in the treatment of APL since its first description over five decades ago. This progress has highlighted several important lessons including 1) the observation that cancer may in fact be reversed and, therefore, killing cancer cells is not the only necessary strategy to combat this disease, 2) targeted treatment is a highly successful strategy to eradicate leukemia cells, and finally, 3) eradication of leukemia stem cells leading to a cure can be achieved without chemotherapy.

† Phase-3, multicentre, randomized, open-label, parallel-group study in previously-untreated patients with Binet Stage B or C (Rai Stages I-IV) CLL requiring PR=partial response; PFS=progression-free survival

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2. WU et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia.

Kahl BS et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: ORR=overall response rate; CI=confidence interval; DR=duration of response; CR=complete response; Cru=complete response unconfirmed; M

Patients treated with TREANDA are likely to experience myelosuppression. If this occurs, monitor leukocytes, platelets, hemoglobin and neutrophils closely. Prior to the start of treatment, complete blood counts (CBC), renal (creatinine) and liver function tests, electrolytes, blood pressure and hepatitis B testing should be performed and/or measured. During treatment, CBC and liver function tests should also be performed periodically.

Serious Warnings and Precautions:

The following are clinically significant adverse events: myelosuppression, infections (including fatalities) and second malignancies.

TREANDA is not recommended for use in patients with serious infections, including HIV. CMV testing should be considered in patients with fever of unknown origin. TREANDA should be used with caution in patients with infections and should be used in patients with serious infections. TREANDA should be administered under the supervision of a qualified health professional who is familiar with the use of antineoplastic drugs. Cardiac disorders and hypertension are rare, and no major adverse vascular events have been reported. 

Effectiveness of TREANDA in patients with indolent B-cell NHL is based on results from a multicenter study. Efficacy relative to first-line therapies other than chlorambucil has not been established.

Bendamustine is an active alkylating agent and the risk of second malignancies is increased in all patients receiving chemotherapy. All patients must be informed of the increased risk of second malignancies. 

Patients with compromised liver function should be treated cautiously. Prior to treatment, complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function tests, electrolytes, blood pressure and hepatitis B testing should be performed and/or measured. During treatment, CBC and liver function tests should also be performed periodically. 

Patients with mild hepatic impairment and should not be used in patients with moderate or severe hepatic impairment. Prior to treatment, complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function tests, electrolytes, blood pressure and hepatitis B testing should be performed and/or measured. During treatment, CBC and liver function tests should also be performed periodically.

Female patients of childbearing potential must practice effective contraception from 2 weeks before receiving TREANDA until at least 4 weeks after the last dose. TREANDA is not recommended during pregnancy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Cardiac disorders and hypertension are rare, and no major adverse vascular events have been reported. 

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A NEW OPTION IN THE ATTACK AGAINST RELAPSED
INDOLENT NON-HODGKIN LYMPHOMA | iNHL AND
CHRONIC LYMPHOCYTIC LEUKEMIA | CLL:

TREANDA®

TREANDA is indicated for treatment of patients with relapsed indolent B-cell non-Hodgkin lymphoma (NHL) who did not respond to or progressed during or shortly following treatment with a rituximab regimen. Effectiveness of TREANDA in patients with indolent B-cell NHL is based on overall response rate and duration of response data from a single-arm pivotal study of TREANDA monotherapy in patients who had prior chemotherapy and did not respond to or progressed during or within 6 months of treatment with rituximab or a rituximab-based regimen.

TREANDA is indicated for treatment of patients with symptomatic chronic lymphocytic leukemia (CLL) who have received no prior treatment. Approval of TREANDA in CLL is based on a progression-free survival and overall response rate advantage of TREANDA over chlorambucil in a single randomized controlled trial. Prolongation of overall survival or improvement in quality of life was not demonstrated for TREANDA in this study. Efficacy relative to first-line therapies other than chlorambucil has not been established.

TREANDA is contraindicated in patients who are hypersensitive to bendamustine or to any ingredient in the formulation, including mannitol, or component of the container.

Serious Warnings and Precautions: The following are clinically significant adverse events: myelosuppression, infections (including fatalities) and second malignancies. TREANDA should not be used in patients with serious infections. TREANDA should be administered under the supervision of a qualified health professional who is experienced in oncology.

Patients treated with TREANDA are likely to experience myelosuppression. If this occurs, monitor leukocytes, platelets, hemoglobin and neutrophils closely. Prior to the initiation of the next cycle of therapy, the absolute neutrophil count (ANC) should be ≥1 x 10^9/L and the platelet count should be ≥75 x 10^9/L. In the NHL study, 98% of patients had Grade 3 or 4 myelosuppression. Three patients (2%) died from myelosuppression-related adverse reactions. Infusion reactions to TREANDA have occurred commonly in clinical trials. Severe anaphylactic reactions have rarely occurred. Tumor lysis syndrome has been reported and may lead to acute renal failure and death. Hold or discontinue TREANDA for severe or progressive skin reactions. Take precautions to avoid extravasation. Women or men of childbearing potential should be advised to use effective contraception from 2 weeks before receiving TREANDA until at least 4 weeks after the last dose. TREANDA is not recommended during pregnancy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Cardiac disorders and hypokalemia have been reported in patients receiving bendamustine. Serum potassium levels should be closely monitored in patients with cardiac disorders and ECG measurements should be performed where indicated. Hypertension should be well-controlled prior to administration of TREANDA. TREANDA should not be administered to patients with serious infections, including HIV. CMV testing should be considered in patients with fever of unknown origin. TREANDA should be used with caution in patients with creatinine clearance (CrCl) between 40-80 mL/min and should not be used in patients with CrCl < 40 mL/min. TREANDA should be used with caution in patients with mild hepatic impairment and should not be used in patients with moderate or severe hepatic impairment. Prior to treatment, complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function tests, electrolytes, blood pressure and hepatitis B testing should be performed and/or measured. During treatment, CBC and electrolytes should be measured at regular intervals and CBC more frequently in patients who develop cytopenias. Patients and physicians should closely monitor for signs of infection. Monitoring of liver and renal functions, blood pressure and blood sugar should also be performed periodically.

The most common adverse reactions occurring in the single-arm NHL pivotal trial (n=100) were: Non-hematologic: nausea (77%), fatigue (64%), diaphoresis (42%), vomiting (40%), pyrexia (36%) and constipation (31%); Hematologic: neutropenia (45%), anemia (37%) thrombocytopenia (36%) and leukopenia (16%).

The most common adverse reactions in the CLL clinical trial (n=161) were: Non-hematologic: pyrexia (25%), nausea (19%) and vomiting (16%); Hematologic: neutropenia (27%), thrombocytopenia (23%), anemia (19%), leukopenia (17%) and lymphopenia (6%).

ORR=overall response rate; CI=confidence interval; DR=duration of response; CR=complete response; Cru=complete response unconfirmed; PR=partial response; PFS=progression-free survival

For more information, please refer to the complete TREANDA Product Monograph.

References:
New Evidence: Please describe the typical patient who presents with APL.

Dr. Lo-Coco: The median age of patients with APL is around 40 years and varies from that of other acute myeloid leukemias (AMLs), where the typical age is closer to 70 years. As with other leukemias, the performance status of patients with APL varies; however, patients usually have a short duration of symptoms leading to diagnosis.

The typical patient with APL may have only minor cutaneous hemorrhage, presenting with hematomas or other minor forms of hemorrhage. In addition, women may report prolonged menstruation. Patients frequently have decreased blood cell counts with low platelet numbers and fatigue together with signs of cutaneous hemorrhage. However, in some patients there is an abrupt and dramatic presentation and severe hemorrhage may result. In these cases, pulmonary or cranial hemorrhage may occur, leading to early death. APL therefore has an early death rate of 20% to 30% according to registry based studies.

New Evidence: Describe the importance of early treatment of this disease.

Dr. Lo-Coco: Acute Leukemia is a disease that requires early diagnosis and treatment; this is of utmost importance in the setting of APL. Firstly, the risk of early death due to coagulopathy means early treatment is crucial. Secondly, early institutional supportive care and anti-leukemic treatment can correct the coagulopathy, resulting in a high cure rate of up to 90%. Finally, the rate of early death of 20-30% is much greater than that in relapsed disease, which is around 10–15%. Therefore, APL should be considered a medical emergency in which prompt action can dramatically reverse the disease, rendering a highly fatal and aggressive disease course to a highly curable one.
New Evidence: What are the steps taken when APL is suspected?

Dr. Lo-Coco: Based on the National Comprehensive Cancer Network (NCCN) and Medical Research Council (MRC) guidelines, a number of steps must be taken immediately if APL is suspected. Retinoic acid should be started to correct for coagulopathy and supportive transfusions should be given to maintain a platelet level above 30–50 x 10^9/L and a fibrinogen level above 150 mg/dL. A marrow sample should simultaneously be sent to a reference laboratory. More than 70% of samples are leukopenic, with no blasts in the peripheral blood. Genetic confirmation of diagnosis should then be obtained; however, we recommend starting treatment while waiting for the results of molecular studies.

New Evidence: Please describe the current standard of care for the first-line treatment of low/intermediate and high-risk APL.

Dr. Lo-Coco: Based on the results of international studies in thousands of patients conducted by large cooperative groups in the United States, Europe, Japan, and China, the current consensus is to give an anthracycline plus ATRA as first-line treatment to patients with low/intermediate APL. This should be followed by two to three cycles of consolidation, including simultaneous ATRA plus anthracycline-containing chemotherapy. However, it is understood that cytarabine should be added at least in consolidation for high-risk patients with APL. In French protocols, cytarabine is given both in induction and during consolidation, while in Italian and Spanish protocols, cytarabine is only given during consolidation for high-risk patients.

New Evidence: Is a maintenance regimen recommended after first-line treatment for APL?

Dr. Lo-Coco: The accepted maintenance regimen for APL following front-line treatment is intermittent ATRA given every three months for 15 days or given for two weeks on followed by two weeks off for a period of two years. A second accepted maintenance regimen is low-dose chemotherapy with mercaptopurine and methotrexate with intermittent ATRA given for 15 days every three months. However, whether we should give maintenance treatment to patients with APL following front-line treatment remains unclear.

A study by the Italian GIMEMMA group and a second study by a Japanese multicentered group suggested that there is no clear benefit of maintenance treatment. In addition, 98% of patients achieve molecular remission (negative PML RARA signal) at the end of consolidation. However, in high-risk patients, a recently presented study from Japan showed a benefit from maintenance treatment following front-line therapy. Therefore, in high-risk patients, maintenance treatment may be beneficial.

New Evidence: How effective is the current standard first-line treatment? Describe the toxicities associated with this treatment.

Dr. Lo-Coco: The standard treatment for APL, ATRA plus chemotherapy (ATRA+chemo) followed by consolidation, is very effective and there is no more than a 10–15% chance of relapse. However, the problem with standard treatment is that it can be fairly toxic. In elderly patients, the death rate during remission can be as high as 25%. In addition, hematological toxicities, such as prolonged neutropenia and thrombocytopenia, combined with serious infections are experienced by many patients during chemotherapy treatment. Finally, secondary malignancies due to chemotherapy occur in around 2% of patients and are typically very serious, resulting in death. Given that APL is highly curable, the toxicity of standard treatment with ATRA+chemo needs to be improved.

New Evidence: Do you feel there remains an unmet need in the treatment of this disease?

Dr. Lo-Coco: A key unmet need in the management of APL is to reduce the early death rate. Given the high probability of a cure, education needs to become a priority to improve awareness in emergency and intensive care units. In addition, investigation into the predictive factors leading to severe hemorrhage and coagulopathy is needed to reduce the early death rate. Finally, it is important to focus on the ideal treatment of patients who are excluded from clinical trials due to poor performance status.
**New Evidence:** Describe the rationale and design of your study.

**Dr. Lo-Coco:** Given concerns with the number of deaths in remission following ATRA+chemo and the proven efficacy of arsenic trioxide (ATO) in the relapsed setting, pilot studies completed by the MD Anderson clinic examined the efficacy and safety of front-line ATO. Results of these studies showed promising activity and a favourable toxicity profile of this agent. Given the long follow up and large patient populations in studies examining ATRA plus idarubicin (AIDA) protocols, larger studies examining the safety and efficacy of ATO are needed. Therefore, we designed a randomized comparison of ATRA+chemo versus ATO+ATRA in low and intermediate risk APL. The trial was coordinated in Italy by the GIMEMMA group and joined by two German multicenter groups including the Study Alliance Leukemia (SAL) group and the AML Study Group (AMLSG).

**New Evidence:** Why were patients with high-risk APL not included in the study?

**Dr. Lo-Coco:** We excluded high-risk patients in the study design, as results from the MD Anderson pilot studies showed that needs to become a priority was particularly favourable for patients without high-risk APL. Results from the pilot studies showed that high risk patients did not have outcomes as positive as those shown in previous studies using the AIDA protocol, where these patients were also given cytarabine. The other reason for excluding high-risk patients was the concern for an increase in differentiation syndrome, which can be fatal and may be more frequent in patients with elevated white blood cell (WBC) counts.

**New Evidence:** Describe the efficacy endpoints of the study.

**Dr. Lo-Coco:** APL is a disease with very high chances of being cured, even after initial relapse. Therefore, we may not detect a difference between groups in overall survival (OS). We therefore chose event-free survival (EFS) as the primary endpoint of our study, as it accounts for all types of events from the first day of treatment and includes death from any cause, death in remission, and the number of relapses. Using EFS can give us a more complete picture of the efficacy of the treatment.

**New Evidence:** Please describe the efficacy results of your study.

**Dr. Lo-Coco:** The efficacy results of our study demonstrated that ATO+ATRA was noninferior to ATRA+chemo. Complete response (CR) rates, disease-free survival (DFS), and cumulative incidence of relapse (CIR) were not significantly different between groups, with a trend for improved outcomes in the ATO+ATRA arm. The CIR outcome is important, as it takes into accounts all possible competing events and gives an estimate of the real effect of treatment on the biology of the disease, while eliminating confounding factors such as death in remission. Although we need to follow these patients for longer, there are currently two relapses in the ATO+ATRA arm and five in the ATRA+chemo arm. Because the number of relapses is small in both arms, it is difficult to compare the groups, but we can say that both treatments are highly effective.

Although the difference in CR, DFS, and CIR was not significant, there was a significant improvement in OS (98.7% vs 91.1%; \(p = 0.02\)) and EFS (97.1% vs 85.6%; \(p = 0.02\)) in the ATO+ATRA group. However, because the study was designed as a noninferiority study, we cannot claim superiority of the ATO+ATRA group.

**New Evidence:** Please describe the safety results of your study. How did the two treatment groups compare?

**Dr. Lo-Coco:** Results of our study demonstrated considerably greater hematological toxicities in the ATRA+chemo arm after induction and after each consolidation treatment. In addition, there were three deaths during remission in the ATRA+chemo arm, compared to only one in the ATO+ATRA arm. The cause of death for the one patient who died in the ATO+ATRA arm was pneumonia associated with the H1N1 virus; the death was therefore unrelated to treatment.
Although the overall safety profile of the ATO+ATRA arm was better than that of the ATRA+chemo arm, QTc prolongation, an increase in liver enzymes, and the development of leukocytosis during induction were greater in the ATO+ATRA arm. These adverse effects were effectively managed by reducing the dose or temporarily suspending treatment.

For patients with leukocytosis, hydroxyurea was given at 500 mg four times per day if WBC counts were ≤50,000 and at 1g four times per day if WBC counts were >50,000. For patients with QTc prolongation, treatment was temporarily suspended and electrolytes such as magnesium and potassium were monitored. Treatment could be resumed at 50% of the recommended dose and gradually increased as tolerated.

**New Evidence:** Please describe the rate of differentiation syndrome in each group. How might you manage this complication?

**Dr. Lo-Coco:** There was no difference in the rates of moderate and severe differentiation between treatment arms; moderate and severe differentiation rates were 13% and 7% in the ATO+ATRA arm and 10% and 6% in the ATRA+chemo arm. Prednisone was given as prophylaxis to all patients for the entire duration of induction. The low rate of differentiation syndrome may be explained by giving prophylaxis and excluding high-risk patients. The duration of prednisone treatment is debatable and 15 days of prophylaxis, as given by Spanish groups may be sufficient.

**New Evidence:** What future analyses are planned for your study?

**Dr. Lo-Coco:** We have expanded our study to include a second series of 276 patients and will provide data on this larger number of patients with a prolonged follow-up of four years. We will also be analyzing the kinetics of residual disease based on a nonsignificant difference in the log reduction of transcript of PML RARA after consolidation. However, the 34 months of follow-up in the current analysis is relatively mature and we would expect to have seen any relapses within a two-year period.

We have also included self-assessment forms in the expanded study to analyze quality of life (QoL) outcomes. These results will be presented at the APL conference in Rome at the end of September 2013.

In the future, it would be interesting to perform a superiority study and to include high-risk patients as well as children in the study population. It is also interesting to examine how these treatments modulate coagulopathy — we will be collecting samples from our study to assess this in the laboratory.

**New Evidence:** Please comment on the cost-to-benefit ratio of choosing ATO+ATRA over ATRA+chemo.

**Dr. Lo-Coco:** Although we are still analyzing the data from our study, it is clearly more convenient to give ATO+ATRA than ATRA+chemo. In addition, given there are fewer infectious complications with ATO compared to chemotherapy, hospitalization time would likely be greater in patients given ATRA+chemo, raising the cost of treatment. We are planning to assess the cost versus benefit of the ATO+ATRA regimen in our study, but we are hypothesizing that the benefit of this regimen will outweigh its costs. In the future, an oral formulation of ATO would greatly improve patient QoL by allowing patients to remain out patients during treatment.

**New Evidence:** Do the results of your study justify using ATO+ATRA over the current standard in clinical practice?

**Dr. Lo-Coco:** I do feel the results of our study justify changing the current standard of care in the treatment of APL. Even though our study did not include a large number of patients, it was a multicentered randomized study. In addition, the efficacy outcomes in the control arm were very strong and were similar to those shown historically with ATRA+chemo. Although our study was not designed to show superiority, there was a clear trend for superiority in the ATO+ATRA arm compared with the ATRA+chemo arm. The results of our study therefore justify using ATO+ATRA as the new standard of care for the treatment of APL.
New Evidence: What else is needed to change the standard first-line treatment in clinical practice?

Dr. Lo-Coco: There is currently a National Cancer Research Institute (NCRI) study underway in England with the same design as our study, but including a separate protocol for high-risk patients and using QoL as the primary outcome. Given that there are so few relapses with standard treatment for APL, the goal of therapy is now changing to improving QoL. Results of the English study will most likely be presented at the APL conference in Rome in September 2013. Once we have results from these two independent randomized multicentered studies, there should be more than sufficient evidence to change the standard of care to ATO+ATRA.

New Evidence: What is the current standard of care for relapsed patients?

Dr. Lo-Coco: The current standard of care for patients relapsing after ATRA+chemo is ATO; this should be given for at least two cycles with or without retinoic acid. However, if patients are given ATO+ATRA as first-line therapy, they should be given ATRA+chemo after relapse. It is important to consider treating patients at molecular relapse instead of waiting for the development of blasts; this can reduce the rate of differentiation syndrome after treatment.

The difficulty is determining the best treatment option in patients relapsing after second-line treatment. If the patient achieved a second molecular remission, and assuming that the duration of first remission was at least two years, autologous transplantation should be considered. In patients not eligible for transplant due to increased age or inadequate performance status, prolonged treatment with ATO+ATRA may be the best option. Patients with a shorter remission and more aggressive disease may be candidates for allogeneic transplant if they are younger and have an identical sibling.

New Evidence: Are there differences in the safety profile of ATO+ATRA in the relapsed setting compared to the first-line setting?

Dr. Lo-Coco: The toxicity profile of ATO+ATRA used in the first-line setting appears to be similar to that seen in relapsed disease. We have a lot of experience giving ATO in the relapsed setting and therefore included a number of guidelines to manage potential complications when given as first-line treatment. In our study protocol, we included prednisone prophylaxis for preventing differentiation syndrome, hydroxyurea to manage increased leukocyte counts, and guidelines for dosing adjustments or temporary withdrawal to manage toxicities.
Lymphomas

New and Promising Targeted Drugs are to be Tested in Combination with Standard Treatments for Non-Hodgkin Lymphoma

The current standard of care for first-line patients with indolent non-Hodgkin lymphoma (NHL) or mantle cell lymphoma (MCL) is immunochemotherapy consisting of the anti-CD20 monoclonal antibody rituximab (R) in combination with a bendamustine (BR) or a chemotherapy regimen, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or cyclophosphamide, vincristine, and prednisone (R-CVP). The published results from a randomized, phase III, noninferiority trial by Rummel et al. have shown that BR can be considered the preferred first-line treatment option compared with R-CHOP for patients with indolent NHL or MCL because it significantly prolonged progression-free survival (PFS) and had fewer toxic adverse events. However, therapies for indolent NHL and MCL are noncurative and have short-term and long-term toxicities. This highlights the need for new drugs with different mechanisms of action that can control symptoms, prolong overall survival, and can be combined with current and emerging treatment options, all while having an acceptable safety profile. Clinical trials have been initiated to test BR in combination with new targeted agents, such as idelalisib, a highly selective oral inhibitor of the catalytic delta subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3Kδ), and ibrutinib, an inhibitor of Bruton’s tyrosine kinase (BTK). The BCL-2 (B-cell CLL/lymphoma 2) inhibitor ABT-199 is another new drug that is showing promise as a single agent early on in its development, particularly in the treatment of MCL.

Since rituximab has become a standard component of first-line and maintenance therapies for NHL, the development of a subcutaneous (sc) formulation of this drug is demonstrating its potential to offer invaluable time and resource savings to healthcare professionals and patients compared with its intravenous (iv) delivery. The SABRINA trial has preliminarily confirmed rituximab sc to be comparable with rituximab iv in terms of safety, pharmacokinetics, and response rates for the first-line treatment of patients with follicular lymphoma (FL).

The latest results from these and other clinical trials in lymphoma were presented at the 2013 annual meetings of the American Society of Clinical Oncology (ASCO) and the European Hematology Association (EHA), as well as at the 2013 biennial International Conference on Malignant Lymphoma (ICML). The following provides a brief summary of each study in lymphoma covered in this issue:

• The open-label, randomized BRIGHT study of patients with indolent NHL and MCL met its primary objective of demonstrating noninferior complete response (CR) rates with first-line BR as compared with R-CHOP and R-CVP. The study also established distinct toxicity profiles for all three study regimens.

• Two phase III, randomized, double-blind, placebo-controlled studies will be evaluating the efficacy and safety of idelalisib (GS-1101) in combination with either BR or rituximab alone for patients with previously treated indolent NHL.

• The noninterventional Be-1st study of advanced indolent NHL confirmed that, in addition to experiences from interventional trials, first-line therapy with bendamustine plus rituximab has favourable efficacy and toxicity profiles in clinical practice.

• The multicentre, randomized phase III AGMT NHL13 trial of rituximab as maintenance treatment versus observation alone in patients with diffuse large B-cell lymphoma (DLBCL) or grade 3B FL was unable to demonstrate that rituximab could significantly prolong event-free survival.
• The BCL-2 inhibitor ABT-199 (GDC-0199) was well tolerated and had antitumour activity in a phase I study of patients with relapsed or refractory NHL of different histologies, including a best response rate of 100% in patients with MCL.

• The first results of a time-and-motion study revealed that rituximab sc injections could potentially provide time and resource savings to healthcare professionals and patients when compared with rituximab iv infusions.

• The first results of an infectious disease project on the MAINTAIN study showed that immunochemotherapy with BR as induction therapy for indolent lymphomas resulted in severe lymphopenia with low CD4+ and CD8+ counts without an increase in atypical infections.

• Response rates with (rituximab), gemcitabine, dexamethasone, cisplatin ([R]-GDP) were not inferior compared with those of the standard salvage therapy of (rituximab), dexamethasone, cytarabine, cisplatin ([R]-DHAP) prior to autologous stem cell transplantation for patients with relapsed and refractory aggressive lymphomas in the phase III NCIC CTG study LY12. GDP also had significantly less toxicity and was better tolerated than DHAP.

• A new LYSAsponsored phase III randomized study called RELEVANCE is set to compare the efficacy and safety of induction and maintenance therapies of rituximab plus lenalidomide with those of rituximab plus any chemotherapy in subjects with previously untreated and advanced FL.

• A new phase III study is underway to investigate the combination of ibrutinib with BR in elderly patients with newly diagnosed MCL.

• The phase III GOYA study, which is the largest clinical trial ever conducted in patients with DLBCL, will assess the safety and efficacy of induction therapy with obinutuzumab (GA101) + CHOP (G-CHOP) vs. R-CHOP in previously untreated patients.

• Stage I results of the phase III SABRINA study showed that the pharmacokinetics, safety, and overall response rate achieved with subcutaneous rituximab plus chemotherapy were comparable to those with intravenous administration in the first-line treatment of patients with follicular lymphoma: Stage I results of the phase III SABRINA study (BO22334). ICML Abstracts 2013:194.


MacDonald D, et al. ASCO 2013:8565 and Flinn IW, et al. ICML 2013:084

The BRIGHT study of first-line bendamustine plus rituximab or R-CHOP/R-CVP in advanced indolent non-Hodgkin lymphoma or mantle cell lymphoma

Background

The BRIGHT (Bendamustine Rituximab Investigational non-Hodgkin’s Trial) study demonstrated that first-line bendamustine-rituximab (BR) was noninferior to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) in terms of complete remission (CR) rates in indolent non-Hodgkin lymphoma (NHL) and mantle cell lymphoma (MCL). At ASCO 2013, MacDonald and colleagues presented a detailed analysis of the safety and tolerability of the study regimens, while Flinn and colleagues reported efficacy and safety results from this study at ICML 2013.1,2

Study design

- Patients included in the study were ≥18 years with histologically confirmed indolent NHL or MCL, had not received prior treatment, and met the need-to-treat criteria. Additional inclusion criteria were:
  - Eastern Cooperative Oncology Group (ECOG) performance status 0–2;
  - Ann Arbor stage ≥I;
  - CD20+ biopsy or pathology sample;
  - Bidimensionally measurable disease;
  - Adequate hematologic, renal, and hepatic function (and left ventricular ejection fraction ≥50%, if pre-selected for R-CHOP).
Patients with central nervous system involvement or leptomeningeal lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, or grade 3 follicular lymphoma were excluded from the study.

Patients were preselected by the investigator for R-CHOP or R-CVP on the basis of their performance status, comorbidities, and cardiac risk factors, and then randomized 1:1 to either six to eight cycles of BR (B: 90 mg/m²/day on days 1 and 2, rituximab 375 mg/m² on day 1 of a 28-day cycle) or the preselected standard regimen of R-CHOP or R-CVP (standard dosing on 21-day cycles).

The primary objective was to determine whether BR was noninferior to standard treatment (R-CHOP/R-CVP) in terms of complete response (CR) rates as first-line treatment for indolent NHL or MCL.

The evaluable patient population was considered primary for the noninferiority (NI) test. If NI was established, then superiority (Sup) testing was done.

The NI margins were calculated as 0.78 for M1 (using 95% CI) and 0.88 for M2 (two-sided using $\alpha = 0.05$).

Secondary objectives included overall response rate (ORR), safety, and tolerability of BR and R-CHOP/R-CVP.

Tumour response was determined by a blinded independent review committee (IRC) using 2007 International Working Group revised response criteria for malignant lymphoma. Investigator assessments were compared with those of the IRC.

Adverse events (AEs) were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and were coded using the Medical Dictionary for Regulatory Activities version 15.0.

To better understand the total event burden and the time of onset of selected AEs, frequency analyses were performed (grades 1–4).

Supportive therapy (e.g., antiemetics and immunostimulants) was permitted, but not required, and was given per local standards.

**Key findings**

**Baseline characteristics and disposition**

The characteristics of the randomized groups (BR vs. R-CHOP/R-CVP) were well matched:

- Median age (range): 60 years (28–84) vs. 58 years (25–86);
- Male: 61% vs. 59%;
- ECOG status: $0 = 64\%$, $1 = 31\%$, and $2 = 4\%$ for both groups;
- Lymphoma type: indolent NHL = 83% for both groups, MCL = 16% vs. 17%;
- Ann Arbor stage IV: 69% vs. 68%.

Out of the 447 randomized patients in this study:

- 436 patients received at least one treatment (BR: $n = 221$; R-CHOP/R-CVP: $n = 215$) and were evaluable for safety;
- 419 patients were evaluable for efficacy (BR: $n = 213$; R-CHOP/R-CVP: $n = 206$); 17 patients were excluded from the evaluable analysis population due to a missing postbaseline assessment, a protocol violation, or disease progression.

The majority of patients received treatment for the planned six cycles: 92% of patients in the BR group, 95% of patients in the R-CHOP group, and 88% of patients in the R-CVP group.
Efficacy

- Among patients with evaluable efficacy, the IRC-assessed CR rate was numerically higher for BR than R-CHOP/R-CVP (31% vs. 25%), and statistically noninferior (p = 0.0225); however, it was not considered superior (p = 0.1269). (Table 1)
- The OR rate was higher for BR compared with that for R-CHOP/R-CVP (97% [95% CI: 93.3–98.7%] vs. 91% [95% CI: 86.0–94.4%]). (Table 1)
- In the randomized group of patients with indolent NHL, the CR rate ratio between BR and R-CHOP/R-CVP, as assessed by the IRC, was 1.16 (NI; p = 0.129). (Figure 1)
- In the randomized group of patients with MCL, the CR rate ratio of 1.95 significantly favoured BR over R-CHOP/R-CVP and was statistically noninferior (p = 0.017) and superior (p = 0.018). (Figure 1)
- The CR rate ratios were also separated and analyzed by pre-assigned treatment groups. (Figure 2)
  - Among the IRC-assessed evaluable patients, the CR rate ratios were:
    - BR vs. R-CHOP (1.18; NI [p = 0.197]); and
    - BR vs. R-CVP (1.34; NI [p = 0.054]).
  - Among the investigator-assessed evaluable patients, the CR rate ratios were:
    - BR vs. R-CHOP (1.55; NI [p = 0.007]; Sup [p = 0.033]); and
    - BR vs. R-CVP (1.41; NI [p = 0.119]).

Safety

- The overall AE profile was distinct for the three treatment regimens, as assessed by the incidence of all-grade AEs in the safety analysis. (Table 2)
- Nausea was reported at a significantly higher incidence in BR vs. R-CVP (63% vs. 39%), but was not significantly different between BR and R-CHOP (63% vs. 58%).
- The incidences of vomiting (BR vs. R-CHOP: 29% vs. 13%; BR vs. R-CVP: 25% vs. 13%) and drug hypersensitivity were reported at a significantly higher incidence in the standard treatment regimens vs. BR.
- Peripheral neuropathy (BR vs. R-CHOP: 9% vs. 44%; BR vs. R-CVP: 14% vs. 47%) and alopecia (BR vs. R-CHOP: 4% vs. 51%; BR vs. R-CVP: 3% vs. 21%) were reported at a significantly higher incidence in the standard treatment regimens vs. BR.
- Constipation was reported at a significantly higher incidence in the group who received R-CVP vs. BR (44% vs. 27%).
- The rates of infection (BR vs. R-CHOP: 55% vs. 57%; BR vs. R-CVP: 53% vs. 50%) were not statistically different across treatment groups. (Table 2)
- The incidences of any grade 3/4 nonhematologic AEs were not statistically different among groups: (Table 3)
  - Preselected for R-CHOP: 69% for R-CHOP vs. 59% for BR;
  - Preselected for R-CVP: 51% for R-CVP vs. 58% for BR.

- Grade 3/4 nausea, vomiting, drug hypersensitivity, and neuropathy (not shown) were infrequent in any group. (Table 3)
  - The frequency of nausea across the study period was higher in the R-CHOP and BR treatment groups than in the R-CVP treatment group. (Figure 3)
  - Vomiting associated with the start of the second cycle was evident for the BR groups in both preselection arms and there was some indication of a cumulative effect in the patients preselected for R-CHOP who were given BR. (Figure 4)
  - The use of 5HT3 antagonists was high and similar for all treatment groups.
    - However, aprepitant was more commonly used in addition to 5HT3 antagonists with R-CHOP than with the other regimens, particularly in the early cycles.
  - The frequency analysis of peripheral neuropathy showed a delayed onset in patients receiving either R-CHOP or R-CVP, with lower levels in patients receiving BR. (Figure 5)

<table>
<thead>
<tr>
<th>Table 1. Primary end point: complete response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable: IRC</td>
</tr>
<tr>
<td>CR (95% CI)</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>OR (95% CI)</td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; CI = confidence interval; CR = complete response; IRC = independent review committee; n = number of patients; NI = noninferior; OR = overall response; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; Sup = superior
**Figure 1. Complete response rate ratios**

<table>
<thead>
<tr>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable: IRC</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
<tr>
<td><strong>Evaluable: Investigator</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
<tr>
<td><strong>Indolent NHL</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
</tbody>
</table>

CI = confidence interval; IRC = independent review committee; NHL = non-Hodgkin lymphoma; NI = noninferior; MCL = mantle cell lymphoma; Sup = superior

**Figure 2. Complete response rate ratios by treatment group**

<table>
<thead>
<tr>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable: IRC</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
<tr>
<td><strong>Evaluable: Investigator</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
<tr>
<td><strong>Evaluable: Investigator</strong></td>
</tr>
<tr>
<td><strong>Randomized: IRC</strong></td>
</tr>
<tr>
<td><strong>BR vs. R-CHOP</strong></td>
</tr>
<tr>
<td><strong>BR vs. R-CVP</strong></td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; CI = confidence interval; IRC = independent review committee; NI = noninferior; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; Sup = superior
### Table 2. Selected nonhematologic adverse events by chemotherapy regimen (all grades)

<table>
<thead>
<tr>
<th>AEs (all grades)</th>
<th>Preselected for R-CHOP (%)</th>
<th>Preselected for R-CVP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BR (n = 103)</td>
<td>R-CHOP (n = 98)</td>
</tr>
<tr>
<td>Nausea</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>13†</td>
</tr>
<tr>
<td>Constipation</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Chills</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Drug hypersensitivity*</td>
<td>17</td>
<td>6†</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Infection*</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Opportunistic infection*</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Opportunistic infection*</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Peripheral neuropathy/paresthesia*</td>
<td>9</td>
<td>44†</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Rash/urticaria*</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4</td>
<td>51†</td>
</tr>
</tbody>
</table>

AEs = adverse events; BR = bendamustine, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

*Composite event composed of multiple preferred terms; †p <0.05

- The grade 3/4 hematology laboratory data revealed a greater percentage of patients with lymphopenia in the BR groups compared with those in the R-CHOP or R-CVP groups (BR vs. R-CHOP: 61% vs. 33%; BR vs. R-CVP: 63% vs. 28%). (Table 4)
- Conversely, neutropenia was greater in the R-CHOP and R-CVP groups than those in the BR groups (BR vs. R-CHOP: 39% vs. 87%; BR vs. R-CVP: 49% vs. 56%). (Table 4)
- The incidence of colony-stimulating factor use was about two-fold higher in patients receiving R-CHOP (61%) than that in patients in the other treatment groups. (Table 5)
- Erythropoiesis-stimulating agents were used most frequently in patients receiving R-CHOP. (Table 5)
- Overall, dose delays and dose reductions were infrequent in all treatment groups. (Table 5)
Figure 3. Frequency of nausea by preselected treatment group

Figure 4. Frequency of vomiting by preselected treatment group
Figure 5. Frequency of peripheral neuropathy by preselected treatment group

Table 3. Grade ≥3 nonhematologic adverse events by chemotherapy regimen occurring in ≥3% of patients

<table>
<thead>
<tr>
<th>AEs (Grade ≥3)</th>
<th>Preselected for R-CHOP (%)</th>
<th>Preselected for R-CVP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR (n = 103)</td>
<td>R-CHOP (n = 98)</td>
<td>BR (n = 118)</td>
</tr>
<tr>
<td>Patients with one or more event</td>
<td>59</td>
<td>69</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Infection*</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

AEs = adverse events; BR = bendamustine, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

*Composite event composed of multiple preferred terms.
Table 4. Grade 3/4 hematologic adverse events (laboratory data)

<table>
<thead>
<tr>
<th>Hematology test</th>
<th>Preselected for R-CHOP (%)</th>
<th>Preselected for R-CVP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BR (n = 103)</td>
<td>R-CHOP (n = 98)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>32</td>
<td>72</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>39</td>
<td>87</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>61</td>
<td>33</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Platelet count</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

AEs = adverse events; BR = bendamustine, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Table 5. Management of myelosuppression

<table>
<thead>
<tr>
<th></th>
<th>Preselected for R-CHOP (%)</th>
<th>Preselected for R-CVP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BR (n = 103)</td>
<td>R-CHOP (n = 98)</td>
</tr>
<tr>
<td>Cycles delayed (% of cycles)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dose reductions (% of cycles)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Colony-stimulating factors* (% of patients)</td>
<td>27</td>
<td>611</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents† (% of patients)</td>
<td>&lt;1</td>
<td>71†</td>
</tr>
<tr>
<td>Transfusions (% of patients)</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

*Colony-stimulating factors: pegfilgrastim, filgrastim, lenograstim; †Erythropoiesis-stimulating agents: epoetin alfa, darbepoetin alfa; 'p <0.05

Key conclusions

■ The CR rate of the BR regimen was statistically noninferior to that of R-CHOP/R-CVP.

■ The ORRs were high for both BR and R-CHOP/R-CVP treatment groups.

■ BR, R-CHOP, and R-CVP have significantly distinct AE profiles.
  • More nausea, vomiting, and drug hypersensitivity (all primarily grade 1 or 2) occurred with BR.
  • More constipation, neuropathy, and alopecia occurred with R-CHOP or R-CVP.
  • Neutropenia was more common with the R-CHOP and R-CVP regimens, whereas lymphopenia was more common with BR.

■ A review of antiemetic use in the BRIGHT study indicated that aprepitant was used more commonly as a supplement to SHT3 antagonists in patients receiving R-CHOP, particularly in cycle 1 in the United States.
  • This may have led to the observation of more nausea and vomiting in the BR group. Thus, management of nausea and vomiting might be improved in the BR regimen by similar early use of aprepitant.

A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated indolent NHL

Background
Current therapies (e.g., rituximab plus chemotherapy) for indolent non-Hodgkin lymphoma (NHL) are not curative, have short-term and long-term toxicities, and lose activity with repeated administration. Drugs with new mechanisms of action are needed in order to effectively treat relapsed or refractory disease. Idelalisib is a first-in-class, selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ) that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues. The rationale for and design of a new, ongoing phase III trial (study 125) of idelalisib in combination with bendamustine and rituximab (BR) in previously treated patients with indolent NHL were described at ASCO 2013 by De Vos et al. and at ICML 2013 by Czuczman et al.1,2

Study design
Rationale
• The rationale for study 125 is derived from the activity of idelalisib in combination with rituximab, bendamustine, or BR in a phase Ib study (101-07) of 79 patients with relapsed or refractory indolent NHL.2,3
• High response rates were observed across all drug combinations with an overall response (OR) rate of 78%, which included a complete response (CR) rate of 26%.
• These responses were durable with progression-free survival (PFS) of 62% and duration of response of 69% at 24 months.

Design
• The key inclusion criteria for this study are:
  • Histologically confirmed diagnosis of B-cell indolent NHL:
    – Follicular lymphoma grade 1, 2, or 3a;
    – Small lymphocytic lymphoma with absolute lymphocyte count <5 x 10^9/L;
    – Marginal zone lymphoma (splenic, nodal, or extranodal); or
    – Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia.
  • Relapsed, radiographically measurable nodal or extranodal indolent NHL:
    – Defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest diameter and ≥1.0 cm in the longest perpendicular diameter, as assessed by computed tomography (CT) or magnetic resonance imaging (MRI).
  • Have received prior treatment with:
    – ≥1 regimen containing a therapeutic anti-CD20 antibody administered for ≥2 doses; and
    – ≥1 regimen containing chemotherapy (e.g., alkylating agent) administered for ≥2 cycles of treatment.
  • Patients are stratified and randomized (in a 2:1 ratio) into Arm A or B.
    • In both arms, patients receive rituximab at 375 mg/m^2 on day 1 plus bendamustine at 90 mg/m^2 on days 1 and 2 of each 28-day cycle for four to six cycles;
    • In Arm A, patients also receive idelalisib at 150 mg twice per day (BID) continuously;
    • In Arm B, patients receive placebo BID continuously instead of idelalisib.
  • Stratification factors include tumor type (follicular lymphoma vs. others), tumor burden (high vs. low), and time since completion of last prior therapy for indolent NHL (<18 months vs. >18 months).
  • Radiology assessments (CT or MRI) are scheduled for every 12 weeks.
  • The study (NCT01732926) opened for enrollment in December 2012.

End points and analysis
• The primary end point is PFS.
• Key secondary end points include CR and OR rates, lymph node response rate, and overall survival.
• For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the intent-to-treat analysis set using Kaplan-Meier methods and the stratified log-rank test.
• An independent review committee will determine disease response and progression for the protocol-specified outcomes.
• A data management committee is also in place to examine accumulated safety, efficacy, and other relevant data during the course of the study.
• The key parameters and their expected values for the study are: (Table 1)

“Table 1. Study parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Expected values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>450 total (Arm A: N = 300; Arm B: N = 150)</td>
</tr>
<tr>
<td>Assumed PFS (median)</td>
<td>Comparator: 20 months</td>
</tr>
<tr>
<td></td>
<td>Treatment: 30 months</td>
</tr>
<tr>
<td>Benefit/hazard ratio</td>
<td>1.5/0.67</td>
</tr>
<tr>
<td>Planned accrual period</td>
<td>21 months</td>
</tr>
<tr>
<td>Study duration</td>
<td>51 months</td>
</tr>
<tr>
<td>Interim analysis</td>
<td>Safety: ~6 months</td>
</tr>
<tr>
<td></td>
<td>Efficacy: After ~177 events</td>
</tr>
<tr>
<td>Final analysis</td>
<td>After 267 events</td>
</tr>
</tbody>
</table>

PFS = progression-free survival
Key conclusions

- Phase I data demonstrated that idelalisib has significant activity as a monotherapeutic agent and in combination with chemo/immunotherapy in heavily pretreated patients with indolent NHL.

- The phase III development program for idelalisib in previously treated indolent NHL currently encompasses two ongoing global trials evaluating combination therapy of BR ± idelalisib (study 125) or rituximab ± idelalisib (study 124), with no results to report at this time.

References:

Leonard J, et al. ASCO 2013:TPS8617

A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated indolent NHL

Background
Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ) is critical for activation, proliferation, and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues. Phase I trials demonstrated that idelalisib is highly active in patients with heavily pretreated indolent non-Hodgkin lymphoma (NHL): patients experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit with an acceptable safety profile. At ASCO 2013, Leonard and colleagues presented the study design for a new phase III trial of idelalisib in combination with rituximab for previously treated patients with indolent NHL.

Study design

Design

- The key inclusion criteria for this study are:
  - Diagnosis of B-cell indolent NHL: follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia;
  - Relapsed, radiographically measurable nodal or extranodal indolent NHL (≥1 lesion that measures ≥2.0 cm);
  - Have received ≥1 prior therapy containing an anti-CD20 antibody (but disease was not refractory to rituximab) administered for ≥2 doses.

- Patients are stratified and randomized (in a 2:1 ratio) into Arm A or B.
  - In both arms, patients receive rituximab at 375 mg/m² once weekly for four weeks and then once every eight weeks repeated four times;
  - In Arm A, patients also receive idelalisib at 150 mg twice per day (BID) continuously;
  - In Arm B, patients receive placebo BID continuously instead of idelalisib.

- Stratification factors include tumor type (follicular lymphoma vs. others), tumor burden (high vs. low), and time since completion of last prior therapy for indolent NHL (<18 months vs. >18 months).

- Radiology assessments (CT or MRI) are scheduled once every 12 weeks.

- The study (NCT01732913) opened for enrollment in December 2012.
In Supportive Care Oncology

Key conclusions

■ Phase I data demonstrated that idelalisib has significant activity as a monotherapeutic agent and in combination with chemo/immunotherapy in heavily pretreated patients with indolent NHL.

■ The phase III development program for idelalisib in previously treated indolent NHL currently encompasses two ongoing global trials evaluating combination therapy of BR ± idelalisib (study 125) or rituximab ± idelalisib (study 124), with no results to report at this time.

End points and analysis

- The primary end point is progression-free survival (PFS).
- Key secondary end points include tumour control, patient well-being, biomarkers, exposure, safety, and health economics.
- For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the intent-to-treat analysis set using Kaplan-Meier methods and the stratified log-rank test.
- An independent review committee will determine disease response and progression for the protocol-specified outcomes.
- Cheson (2007) criteria will be used to determine response and progression.
- The key parameters and their expected values for the study are:
  - Total number of patients: 375 (Arm A: 250 and Arm B: 125);
  - Planned accrual period: 18 months;
  - Study duration: 36 months;
  - Interim analysis: safety (at approximately six months) and efficacy (after approximately 165 events);
  - Final analysis: after 246 events.

### Table 1. Study parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Expected values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>375 total (Arm A: N = 250; Arm B: N = 125)</td>
</tr>
<tr>
<td>Assumed PFS (median)</td>
<td>Comparator 12 months</td>
</tr>
<tr>
<td></td>
<td>Treatment 18 months</td>
</tr>
<tr>
<td>Benefit/hazard ratio</td>
<td>1.5/0.67</td>
</tr>
<tr>
<td>Planned accrual period</td>
<td>18 months</td>
</tr>
<tr>
<td>Study duration</td>
<td>36 months</td>
</tr>
<tr>
<td>Power (with 2-sided $\alpha \leq 0.05$)</td>
<td>$-0.90$</td>
</tr>
<tr>
<td>Interim analysis</td>
<td>Safety $-6$ months</td>
</tr>
<tr>
<td></td>
<td>Efficacy After $-165$ events</td>
</tr>
<tr>
<td>Final analysis</td>
<td>After 246 events</td>
</tr>
</tbody>
</table>

*PFS = progression-free survival*
Background

Bendamustine has become a standard agent for treatment of indolent non-Hodgkin lymphoma (NHL). Results of the NHL1-2003 trial showed better efficacy and lower toxicity for bendamustine and rituximab (BR) compared with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). The noninterventional study Be-1st, presented by Becker and colleagues at EHA 2013, revealed the outcomes for patients with indolent NHL who were treated with first-line bendamustine in daily practice in Germany between 2010 and 2011.1

Study design

• From April 2010 until October 2011, 324 patients were enrolled at 57 study centres in Germany.
• The major inclusion criteria for patients were:
  ◦ Advanced indolent NHL according to the World Health Organization classification;
  ◦ Required first-line treatment;
  ◦ No previous chemotherapy and no pre-treatment with interferon or rituximab.
• Treatment modalities were electronically recorded for six months, up until the end of December 2011.
• Data sets included demographic information, treatment regimen, efficacy, and safety.
• Different outcome sets were necessary to assess treatment duration (n = 277) and response rates (n = 281) as the observation period for some patients was not completed at study end. (Figure 1)

Key findings

• Patient characteristics in this study included:
  ◦ Median age: 70.5 years (range, 27–92);
    – Distribution of age at therapy onset: <50 years (7.8%), 50–59 years (14.0%), 60–69 years (26.7%), 70–79 years (35.2%), and ≥80 years (16.3%).
  ◦ Percentage with at least one comorbidity: 62.5%.
    – Most frequent comorbidities: hypertension (34%), other tumour disease (10%), diabetes mellitus (9%), chronic lung disease (5%), cardiac infarction (4%), cardiac insufficiency (4%), chronic gastrointestinal disorders (4%), and kidney disease (4%).
  ◦ Median time to treatment after primary diagnosis: 8.6 weeks.
  ◦ Disease classification: follicular lymphoma (50%), marginal zone lymphoma (17%), immunocytoma (15%), mantle cell lymphoma (12%), other (6%).
  ◦ Ann Arbor tumour stage: no grade (4.6%), stage I (5.2%), stage II (13.7%), stage III (23.8%), stage IV (52.8%).
• The combination of BR was the most common therapy; applied to a total of 94.1% (n = 289) of patients.
  ◦ In 11% (n = 33) of these patients, BR was supplemented by dexamethasone or prednisone.
• Bendamustine monotherapy was chosen for 4.6% (n = 14) of patients, while four patients (1.3%) received other combinations.

Key conclusions

■ Previous data demonstrated that idelalisib has significant activity as a monotherapeutic agent and in combination with chemo/immunotherapy in heavily pretreated patients with indolent NHL.
■ The phase III development program for idelalisib in indolent NHL currently encompasses two trials evaluating combination therapy, providing enrollment options for the full spectrum of relapsed patients with indolent NHL.

Key conclusions

■ Previous data demonstrated that idelalisib has significant activity as a monotherapeutic agent and in combination with chemo/immunotherapy in heavily pretreated patients with indolent NHL.

■ The phase III development program for idelalisib in indolent NHL currently encompasses two trials evaluating combination therapy, providing enrollment options for the full spectrum of relapsed patients with indolent NHL.

Treatment was mostly administered on days 1 and 2 at four-week intervals with a median dose of bendamustine of 88.4 mg/m² (177 mg/m² per cycle).

The median treatment duration was six cycles.

The overall response rate (ORR) of patients who completed treatment was 85.1%.

The best responses to treatment were: (Figure 2)

- Complete response (CR) (42.7%), partial response (43.1%), stable disease (6.0%), progressive disease (3.6%), and not evaluable (4.6%).

In the safety population, 161 of 323 patients (49.8%) experienced a total of 429 bendamustine-related adverse events (AEs). (Figure 3)

The most frequent AE was hematotoxicity: all-grade and grade 3/4 occurred in 35.3% and 13% of patients, respectively. (Figure 3)

Two grade 5 AEs were documented; one death was associated with thrombocytopenia and the cause of the second death was unknown.

A total of 10 serious adverse drug reactions were documented for nine patients according to the following categories: constitutional symptoms (n = 3), blood/bone marrow (n = 2), infection (n = 2), cardiac arrhythmia (n = 1), gastrointestinal (n = 1), and death (not categorized, n = 1).

AEs = adverse events; GI = gastrointestinal

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease
Background
The standard of care in patients with diffuse large B-cell lymphoma (DLBCL) is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). However, the clinical impact of rituximab maintenance after intensive induction therapy in these patients remains unclear. At EHA 2013, Jäger et al. presented results of the AGMT (Austrian Study Group) NHL13 trial, which investigated the value of rituximab maintenance in an unrestricted population of patients with DLBCL or grade 3b follicular lymphoma (FL) who were in complete response (CR) or unconfirmed CR (CRu) after induction with R-CHOP–like therapy. 1

Study design
- Inclusion criteria were designed to capture a broad spectrum of adult patients with histologically confirmed, CD20-positive DLBCL or grade 3b FL at the time of diagnosis (i.e., prior to induction therapy), irrespective of age, disease stage, or International Prognostic Index (IPI) risk group.
- Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, have a known IPI score, and be in CR/CRu after induction with four to eight cycles of R-CHOP–like therapy.
- The R-CHOP–like induction regimen that was used was stipulated by the treating physician and varied by disease stage and local practice.
- Induction therapy had to have been completed with the final cycle of chemotherapy or immunotherapy administered 4–12 weeks before trial treatment began.
- Patients were excluded if they exhibited transformed lymphoma, secondary malignancy, evidence of central nervous system involvement, significant cardiac disease, creatinine >2.0 mg/dL, human immunodeficiency virus, or hepatitis.
- Patients were randomized (1:1) to either rituximab maintenance (375 mg/m² every two months for two years [12 total maintenance infusions]) or observation.
- The primary end point was event-free survival (EFS), defined as the time from diagnosis to first event (e.g., relapse, death, start of new therapy, malignancy, or toxicity).
- Secondary outcome measures were progression-free survival (PFS), overall survival (OS), and safety.

Key findings
- A total of 683 patients with previously untreated DLBCL (n = 662) or grade 3b FL (n = 21) were recruited from 27 countries (163 sites) between June 2004 and September 2007.
- A total of 338 patients were randomized to rituximab maintenance and 345 patients were randomized to observation.

Key conclusions
- This trial demonstrated that, in addition to experiences from interventional trials, bendamustine has favourable efficacy and toxicity profiles in clinical practice.
- The response rates were in line with expectations based on existing, published data.
  - The achieved CR rate met reported values by Rummel et al. for BR in first-line treatment (42.7% vs. 39.6%, respectively).
  - The ORR was slightly lower than that reported in the study by Rummel et al. (85.1% vs. 92.7%, respectively), which may be attributed to a different patient population treated in clinical practice.
- The safety results reflected the well-known safety profile of bendamustine.

**Key conclusions**

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- The safety results reflected the well-known safety profile of bendamustine.

**Eligible (CR, CRu)**

- The rituximab maintenance and observation arms were well balanced with respect to age, sex, clinical presentation, and prognostic indices at diagnosis.
- Both treatment arms were also well balanced with respect to induction treatment at the time of randomization (rituximab maintenance vs. observation):
  - The majority of patients in both treatment arms received six (41.1% vs. 43.5%) or eight (52.7% vs. 50.7%) cycles of chemotherapy.
  - All but four patients in the rituximab arm and two patients in the observation arm received all eight planned infusions of induction rituximab.
  - Most patients were administered R-CHOP on a 21-day (74.0% vs. 77.7%) vs. a 14-day (12.1% vs. 11.3%) cycle.
- Study participants were exposed to rituximab maintenance for a median of 20.5 months, with 70.2% receiving all 12 planned maintenance infusions. (Table 1)
- No major safety signals were seen in either of the two preplanned interim analyses. (Table 1)
  - The percentages of patients who experienced ≥1 adverse event (AE) were similar in the rituximab maintenance (68.6%) and observation arms (66.9%).
  - Grade 3 or 4 AEs occurred in 17.2% and 16.3% of patients in the rituximab maintenance and observation arms, respectively.
  - A total of 11.2% of patients in the rituximab maintenance arm experienced an AE that led to dose adjustment or interruption.

**Table 1. Treatment exposure and safety**

<table>
<thead>
<tr>
<th></th>
<th>Rituximab maintenance (n = 338)</th>
<th>Observation (n = 345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median observation time, mos</td>
<td>45.0</td>
<td>44.9</td>
</tr>
<tr>
<td>Median exposure to study medication, mos</td>
<td>20.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Number of rituximab cycles, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>236 (70.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>7–11</td>
<td>28 (8.3)</td>
<td>N/A</td>
</tr>
<tr>
<td>1–6</td>
<td>72 (21.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with ≥1 AE, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>232 (68.6)</td>
<td>230 (66.9)</td>
</tr>
<tr>
<td></td>
<td>58 (17.2)</td>
<td>56 (16.3)</td>
</tr>
<tr>
<td>Patients with ≥1 related AE, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>86 (25.4)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>22 (6.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with an AE leading to dose adjustment/ interruption, n (%)</td>
<td>38 (11.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with infection, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>74 (21.9)</td>
<td>65 (18.9)</td>
</tr>
<tr>
<td></td>
<td>12 (3.6)</td>
<td>4 (1.2)</td>
</tr>
</tbody>
</table>

*AE = adverse event; mos = months; N/A = not applicable*
• At a median follow-up of 45 months, in the rituximab maintenance vs. observation arms:
  ○ Three-year EFS was 80.1% vs. 76.5% (HR = 0.78 [95% CI: 0.57–1.08]; \( p = 0.067 \)); (Figure 1)
  ○ Three-year PFS was 86.3% vs. 79.0% (HR = 0.62 [95% CI: 0.43–0.90]);
  ○ Three-year OS was 92.0% vs. 90.3% (HR = 0.78 [95% CI: 0.49–1.34]).

• In the patient subgroups stratified by treatment arm and IPI risk group (\( \leq 1 \) vs. \( \geq 2 \)), EFS was significantly longer in those patients with an IPI risk score \( \leq 1 \) and was longer for rituximab maintenance vs. observation (HR = 1.67 [95% CI: 1.18–2.35]; \( p = 0.012 \)).

• A total of 10.7% of patients in the maintenance arm and 18.7% of patients in the observation arm experienced a relapse event. (Table 2)
  ○ The difference in incidences of bone marrow relapse between the observation arm (\( n = 6 \)) and the rituximab maintenance arm (\( n = 0 \)) was significant (\( p = 0.03 \)).

• The cumulative progression rate was greater in the observation arm than in the rituximab maintenance arm. (Figure 2)

---

**Figure 1. Event-free survival (intent-to-treat population)**

![Event-free survival graph]

*CI = confidence interval; HR = hazard ratio*

**Figure 2. Cumulative progression rate (intent-to-treat population)**

![Cumulative progression rate graph]
Table 2. Number and types of relapses

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 683)</th>
<th>Rituximab maintenance (n = 338)</th>
<th>Observation (n = 345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses, n (%)*</td>
<td>100 (14.7)</td>
<td>36 (10.7)</td>
<td>64 (18.7)</td>
</tr>
<tr>
<td>Histologic/cytologic</td>
<td>62</td>
<td>19</td>
<td>43</td>
</tr>
<tr>
<td>confirmation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphatic relapse</td>
<td>60</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>Extralymphatic relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>40</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Bone marrow†</td>
<td>12</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Gastric</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>(Sub)cutaneous</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Testis</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Spinal canal</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CNS = central nervous system
*All relapses (not only those that were event-defining); †Fisher’s exact test: p = 0.03

Key conclusions

- In the total cohort, rituximab maintenance did not significantly prolong EFS, PFS, or OS.
- There was, however, a trend in favour of rituximab maintenance for prolonging EFS and PFS.
- A significant prolongation in EFS was seen among patients stratified by IPI score, with patients with an IPI score ≤1 who were administered rituximab maintenance experiencing the longest duration of EFS.
- This significant clinical effect warrants further subgroup analyses.
- Relative to the observation arm, rituximab maintenance reduced the three-year relapse rate by 45%.
- These findings are applicable to standard clinical practice because this analysis focused on an unselected patient population.
- This study will help to improve the design of future clinical trials exploring the use of anti-CD20 antibodies in the treatment of DLBCL.


Davids MS, et al. EHA 2013:P849

The BCL-2 inhibitor ABT-199 (GDC-0199) is active and well tolerated in patients with relapsed or refractory mantle cell lymphoma and other non-Hodgkin lymphomas

Background

The BCL-2 (B-cell CLL/lymphoma 2) protein is an important therapeutic target that contributes to the ability of hematologic malignancies to evade apoptosis. ABT-199 is a selective, potent, and orally bioavailable small molecule inhibitor of BCL-2 that has shown preclinical activity as a single agent in a wide range of hematologic malignancies. At the 18th Congress of the EHA, Davids and colleagues presented the results from this first-in-human, phase I trial testing the safety and tolerability of ABT-199 in patients with relapsed or refractory non-Hodgkin lymphomas (NHL).1

Study design

- This study followed a modified Fibonacci dose-escalation design, with planned escalation of ABT-199 in 100 mg increments per cohort and a single initial dose for pharmacokinetics on day –3.
- Some key inclusion criteria were:
  - Histologically confirmed diagnosis of NHL requiring therapy;
  - Relapse after or refractory to standard treatments;
  - ECOG performance status 0 or 1;
  - Adequate bone marrow, kidney, and renal function.
- The primary objectives of this study were to:
  - Assess safety;
  - Determine the maximum tolerated dose and recommended phase II dose;
  - Assess pharmacokinetics.
The secondary objectives were to determine preliminary efficacy (i.e., objective response rate, duration of response, time to tumour progression, progression-free survival, and overall survival) and analyze biomarkers and pharmacogenetics.

Key findings

- As of April 4, 2013, 32 patients with a median age of 68 years (range, 35–85) were enrolled into one of six dose escalation cohorts, ranging from a final dose of 200 to 900 mg. (Table 1)
- Patients were diagnosed with the following types of NHL (subdivided as non-MCL [n = 23] or MCL [n = 8]):
  - Follicular lymphoma (n = 11), mantle cell lymphoma (n = 8), diffuse large B-cell lymphoma (n = 8), marginal zone lymphoma (n = 1), Waldenström macroglobulinemia (n = 3), or multiple myeloma (n = 1).
- The median time on study for all patients was 5.6 months (range, 0.5–14.7).

- The primary reasons for discontinuation were: progressive disease (n = 17), bone marrow transplant (n = 2), and an adverse event (AE) (rheumatoid arthritis, n = 1).
- The best percent change from baseline in nodal size by computed tomography scan is shown in Figure 1.

### Table 1. Patient dose escalation cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients enrolled (N = 32)</th>
<th>ABT-199 doses (mg) by weekly escalations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>50 100 150 200 300 400 600</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>100 200 300 400 600 800 1000</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>200 300 400 600 800 1000 1200</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>200 300 400 600 800 1000 1200</td>
</tr>
<tr>
<td>5†</td>
<td>10</td>
<td>300 600</td>
</tr>
<tr>
<td>6‡</td>
<td>4</td>
<td>400 900</td>
</tr>
</tbody>
</table>

MCL = mantle cell lymphoma; MM = multiple myeloma
*Designated final cohort doses are underlined.
†Cohort 5 includes one patient with MM who started at 50 mg.
‡Cohort 6 includes one patient with MCL who started at 200 mg.

Figure 1. Best percent change from baseline in nodal size by computed tomography scan
• The median times to 50% reduction in nodal size were:
  ○ All NHL: 1.4 months (range, 1.2–3.7);
  ○ Non-MCL: 2.5 months (range, 1.3–3.7);
  ○ MCL: 1.4 months (range, 1.2–3.7).
• The best overall response rates (ORR) for all patients and for the MCL subset were 53% (17/32) and 100% (8/8), respectively. (Table 2)
• After a single dose of ABT-199 with a high-fat meal: \( T_{\text{max}} \approx 8 \) hours and \( t_{1/2} \approx 15 \) hours. (Figure 2)
• Taking ABT-199 with food increased the area under the curve (AUC) by 3–4 fold. (Figure 2)
• The plasma concentration of ABT-199 is approximately dose proportional between 200 mg and 900 mg dose levels at steady state. (Figure 2)
• There were two incidences of dose-limiting toxicities (DLTs) in cohort 5 (one grade 4 neutropenia and one grade 3 febrile neutropenia), which had a target dose of 600 mg.
• Dose-limiting thrombocytopenia was not observed.
• The most frequent grade 3/4 AEs were neutropenia (13%), thrombocytopenia (13%), and anemia (13%). (Table 3)
• One patient with MCL (initial dose 200 mg) experienced a nonserious AE of laboratory tumour lysis syndrome.

### Table 2. Best responses in ABT-199–treated patients with non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Evaluable for response</th>
<th>CR, n (%)</th>
<th>PR, n (%)</th>
<th>SD, n (%)</th>
<th>PD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL (n = 8)</td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>1 (13)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>FL (n = 11)</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>8 (73)</td>
<td>–</td>
</tr>
<tr>
<td>MCL (n = 8)</td>
<td>–</td>
<td>8 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WM (n = 3)</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MZL (n = 1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (100)</td>
</tr>
<tr>
<td>MM (n = 1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total (n = 32)</td>
<td>3 (9)</td>
<td>14 (44)</td>
<td>9 (28)</td>
<td>6* (19)</td>
</tr>
</tbody>
</table>

CR = complete remission; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MM = multiple myeloma; MZL = marginal zone lymphoma; PD = progressive disease; PR = partial remission; SD = stable disease; WM = Waldenström macroglobulinemia

*Two patients discontinued due to PD prior to first response assessment (MZL [n = 1] and DLBCL [n = 1]).
Table 3. Adverse events in ABT-199–treated patients

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>All grades (&gt;10% of patients), n (%)</th>
<th>Grades 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>13 (41)</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (28)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (19)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (19)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (19)</td>
<td>–</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (16)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (16)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5 (16)</td>
<td>–</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>5 (16)</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (13)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (13)</td>
<td>–</td>
</tr>
</tbody>
</table>

Key conclusions

- ABT-199 had a tolerable safety profile in NHL, with febrile neutropenia and neutropenia identified as the DLTs to date in this study.
- ABT-199 had a pharmacokinetic profile that supports once-daily oral dosing.
- ABT-199 had anti-tumour activity in multiple NHL histologies, including a best response rate of 100% in patients with MCL.
- ABT-199 warrants further clinical study in multiple NHL histologies.


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De Cock E, et al. EHA 2013:P507

**Time and resource savings with rituximab subcutaneous injection versus rituximab intravenous infusion: first results from a time-and-motion study**

**Background**
A multinational, prospective, observational time-and-motion study was undertaken in order to compare the time and resource utilization associated with the subcutaneous (sc) versus the intravenous (iv) routes of rituximab administration in the treatment of patients with indolent non-Hodgkin lymphoma (NHL). 1

**Study design**
- The aims of this study were to:
  - Quantify resource utilization for each method of administration in terms of active healthcare professional (HCP) time (i.e., time actively dedicated to a patient).
  - Quantify patient chair time related to each method of administration.
  - Estimate the potential time savings associated with a switch to rituximab sc from rituximab iv.
  - Data relating to rituximab sc injections are being collected alongside the MabCute (MO25455) trial.
  - Data relating to the iv administration of rituximab are being collected from real-world practice during the same period.
  - Trained observers use a stopwatch to measure active time taken by HCPs to complete tasks associated with rituximab administration.
  - Case report forms for iv, sc, and pharmacy processes have been tailored to reflect local clinical site practices and ‘start’ and ‘stop’ descriptions for prespecified tasks have been defined to ensure accurate and unbiased data collection.
  - Infusion chair time is calculated from the time of day the patient entered and exited the chair for rituximab iv infusion or rituximab sc injection.
  - Estimated time for a single rituximab sc vs. rituximab iv process per country (pooled across sites) is calculated as the sum of individual mean task times.
  - The following preliminary results for HCP time in the treatment room and patient chair time are from nine sites in four countries (Italy [ITA], Russia [RUS], Slovenia [SVN], and the United Kingdom [GBR]). Data collection is ongoing and final results are expected in the third quarter of 2013.
Key findings

- In the treatment room, rituximab sc was associated with reductions in active HCP time in all countries when compared with rituximab iv. (Figure 1)
- In the pharmacy, rituximab sc was also associated with reductions in active HCP time ranging from 37% in SVN to 65% in RUS (data only available for ITA, RUS, and SVN).
- Excluding GBR, where no iv pharmacy preparation data were available, time savings in the treatment room accounted for a greater proportion (82% [RUS] to 86% [ITA]) of overall time savings with rituximab sc compared with time savings in the pharmacy.
- Mean patient chair time was lower with rituximab sc compared with rituximab iv in all countries. (Figure 2)
- Simulating these findings for a hypothetical centre treating 50 patients for nine sessions annually (six induction and three maintenance) resulted in total chair time savings with rituximab sc of between 109 (SVN) to 219 (RUS) 8-hour days.

Figure 1. Active healthcare professional time by country for rituximab sc versus rituximab iv

*In Italy, active HCP time associated with rituximab administration was relatively high compared with other countries. This was due to active monitoring (at patient bedside) both during and after administration of rituximab (41% and 33% of total time for rituximab iv and sc, respectively).

HCP = healthcare professional; iv = intravenous; sc = subcutaneous

Rituximab sc data collection

- Induction: 7x rituximab sc (1,400 mg fixed dose) q3–4wk + chemotherapy or monotherapy
- Maintenance: 12x rituximab sc monotherapy (1,400 mg fixed dose) q2m for 2 years

Rituximab iv data collection

- Induction: rituximab iv q3m
- Maintenance: rituximab iv q3–4wk

Sample size: 20–40 observations per process per site†

T & M study

27 countries
330 centres
N = 700 patients

Active HCP time (minutes)

Italy* 39.8
Russia 23.4
Slovenia 9.4
United Kingdom 14.2

Rituximab iv data collection

Induction: rituximab iv q3m
Maintenance: rituximab iv q3–4wk

Study start

Patients with previously untreated indolent NHL or relapsed/refractory indolent NHL

Observation q2m

Rituximab sc q2m until PD

12–14 months study duration

R & M study

Active HCP time (minutes)

Italy* 39.8
Russia 23.4
Slovenia 9.4
United Kingdom 14.2

Rituximab iv
Rituximab sc

Δ = 16.3
(−41%)
Δ = 17.1
(−65%)
Δ = 7.3
(−49%)
Δ = 11.8
(−45%)
**Figure 2. Patient chair time by country for rituximab sc versus rituximab iv**

- **Italy**: 339 minutes reduction, 225 minutes (–66%)
- **Russia**: 278 minutes reduction, 15 minutes (–94%)
- **Slovenia**: 201 minutes reduction, 70 minutes (–65%)
- **United Kingdom**: 195 minutes reduction, 19 minutes (–90%)

*In Italy, chair time associated with rituximab sc was longer compared with other countries because patients may have received other chemotherapy prior to rituximab, a physician may have visited the patient while in the chair, or because of increased waiting time. Current data suggest that actual chair time is closer to 1 hour.*

**iv = intravenous; sc = subcutaneous**

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**Key conclusions**

- These preliminary results suggest that a switch from rituximab iv to rituximab sc may lead to substantial reductions in administration chair time and active HCP time.

- Time freed up could be invested in other patient care activities or used to increase the number of patients treated, hence increasing the treatment centre’s overall efficiency.


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**Burchardt CA, et al. ICML 2013:032**

**In the MAINTAIN trial, induction therapy with bendamustine plus rituximab for indolent lymphomas results in severe lymphopenia, with low CD4+ and CD8+ counts, without an increase in atypical infections**

**Background**

Bendamustine-rituximab (BR) is a National Comprehensive Cancer Network recommended first-line treatment for indolent lymphomas, but the impact of this regimen on immunological and infectious disease parameters is not well described.

The MAINTAIN trial of BR induction followed by rituximab maintenance or observation includes a prospective investigation of infectious disease parameters. At ICML 2013, Burchardt and colleagues presented the first data for patients who completed BR induction therapy.
Study design

- Patients received a maximum of six cycles of BR as induction therapy plus two additional courses of rituximab.
- Immunological and infectious disease parameters including complete blood counts, CD4+ and CD8+ cell counts, immunoglobulin levels, antibody (Ab) titers to pneumococci and tetanus, and hepatitis B virus (HBV) serology (and HBV polymerase chain reaction, if necessary) were measured in samples taken from patients before and after induction therapy with BR. These same parameters will also be monitored during the rituximab maintenance period, but are not reported here.

Key findings

- From April 2009 to July 2012, a total of 1,060 patients had completed six cycles of BR as induction therapy at 132 active study sites in Germany and Austria.
- Of those patients who completed induction therapy, the following were evaluable for immunological parameters:
  - A total of 947 (89%) patients for white blood cell counts;
  - A total of 742 (70%) patients for immunoglobulin levels;
  - A total of 359 (34%) patients for tetanus Ab titers;
  - A total of 417 (34%) patients for pneumococci Ab titers.
- Characteristics of the patients included in this study were:
  - A total of 947 evaluable patients: 429 were female and 518 were male;
  - Median age for all patients: 67 years;
  - Median age for patients with mantle cell lymphoma (MCL): 73 years;
  - The histologies of disease included:
    - A total of 503 (53.1%) patients with follicular lymphoma;
    - A total of 136 (14.4%) patients with Waldenström macroglobulinemia;
    - A total of 135 (14.2%) patients with MCL;
    - A total of 118 (12.5%) patients with marginal zone lymphoma;
    - A total of 55 (5.8%) patients with small lymphocytic lymphoma.
- The median leukocyte count dropped from 6,600 to 3,800 cells/μL after induction therapy. (Table 1)
- Following induction therapy, the median granulocyte count declined moderately from 3,900 to 2,400 cells/μL, whereas lymphocytes decreased substantially from a median of 1,500 to 500 cells/μL. (Table 1)
- Median pre-treatment counts of CD4+ and CD8+ cells were 555 and 316 cells/μL, respectively. After induction therapy, median counts of CD4+ and CD8+ cells were 118 and 198 cells/μL, respectively. (Table 1)
- The CD4+/CD8+ ratio changed from 1.76 to an inverse ratio of 0.6 after induction. (Table 1)
- Immunoglobulin levels before and after induction therapy were:
  - IgG: 8.77 to 7.5 g/L;
  - IgM: 0.76 to 0.42 g/L;
  - IgA: 1.51 to 1.13 g/L. (Table 2)

### Table 1. White blood cell counts before and after induction therapy

<table>
<thead>
<tr>
<th>WBC counts (n = 947)</th>
<th>Before BR (cells/μL)</th>
<th>After BR (cells/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>6,600</td>
<td>3,800</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>3,900</td>
<td>2,400</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1,500</td>
<td>500</td>
</tr>
<tr>
<td>CD4+ cells</td>
<td>555</td>
<td>118</td>
</tr>
<tr>
<td>CD8+ cells</td>
<td>316</td>
<td>198</td>
</tr>
<tr>
<td>CD4+/CD8+ ratio</td>
<td>1.76</td>
<td>0.6</td>
</tr>
</tbody>
</table>

### Table 2. Immunoglobulin concentrations before and after induction therapy

<table>
<thead>
<tr>
<th>Immunoglobulins (n = 742)</th>
<th>Before BR Median (g/L)</th>
<th>After BR Median (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>8.77</td>
<td>7.5</td>
</tr>
<tr>
<td>IgM*</td>
<td>0.76</td>
<td>0.42</td>
</tr>
<tr>
<td>IgA</td>
<td>1.51</td>
<td>1.13</td>
</tr>
</tbody>
</table>

*BR = bendamustine, rituximab; FL = follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PBSCT = peripheral blood stem cell transplantation; q2m = every two months; R = randomize; WM = Waldenström macroglobulinemia

*MCL not eligible for PBSCT.

BR = bendamustine, rituximab; FL = follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PBSCT = peripheral blood stem cell transplantation; q2m = every two months; R = randomize; WM = Waldenström macroglobulinemia

*Patients with Waldenström macroglobulinemia were not included.
• For the majority of patients, pneumococci (48.0 to 40.1 mg/L) and tetanus (1.26 to 1.14 IU/mL) Ab titers remained stable after treatment with BR. (Table 3)

○ However, two patients completely lost their immunity to pneumococci and tetanus Ab titers dropped to less than 0.11 IU/mL in 13 patients.

• A total of 16 (1.5%) secondary malignancies were observed: lung (n = 4), colorectal (n = 3), gallbladder/ ductus choledochus (n = 2), prostate (n = 2), astrocytoma (n = 1), oropharynx (n = 1), breast (n = 1), myeloma (n = 1), and myelodysplastic syndrome (n = 1).

• Infections were documented in 252 patients, for an overall infection rate of 24%. The most frequent types of infectious disease complications that occurred were from fever of unknown origin (n = 94), pneumonia (n = 46), and sepsis (n = 22). (Table 4)

• Six of the cases of pneumonia were as a result of pneumocystis jiroveci infections. (Table 4)

• Additionally, 78 patients experienced other infectious complications, which included sinusitis, bronchitis, and those that affected the gastrointestinal or urinary tracts. (Table 4)

• A total of 17 patients (1.6%) died due to infectious disease complications: nine from sepsis, four (three proven, one probable) from progressive multifocal leukoencephalopathy (PML), three from pneumonia, and one from reactivated HBV. (Table 4)

<table>
<thead>
<tr>
<th>Antibody Titer before and after induction therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Titer</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Pneumococci (n = 359)</td>
</tr>
<tr>
<td>Tetanus (n = 417)</td>
</tr>
</tbody>
</table>

*BR = bendamustine, rituximab; IU = International Units

Table 4. Documented infections (serious adverse events)

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of patients (n = 252)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever of unknown origin</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>46 (3*)</td>
<td>Median age = 70 years</td>
</tr>
<tr>
<td>PcP</td>
<td>6</td>
<td>Radiological</td>
</tr>
<tr>
<td>Atypical</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>22 (9*)</td>
<td>Median age at death = 69 years</td>
</tr>
<tr>
<td>VZV</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>1</td>
<td>Reactivation</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 (1*)</td>
<td>No prophylaxis given</td>
</tr>
<tr>
<td>PML (3 confirmed, 1 probable)*</td>
<td>4 (4*)</td>
<td>1 WM, 1 MZL, 2 SLL</td>
</tr>
<tr>
<td>Other infectious complications (GI, sinusitis, bronchitis, urinary, etc.)</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; GI = gastrointestinal; HSV = herpes simplex virus; MZL = marginal zone lymphoma; PcP = pneumocystis jiroveci pneumonia; PML = progressive multifocal leukoencephalopathy; SLL = small lymphocytic lymphoma; VZV = varicella zoster virus; WM = Waldenström macroglobulinemia

*No further PML during follow-up including rituximab maintenance, up to date; †Number of patient deaths.

Key conclusions

- The results showed substantial changes in CD4+ and CD8+ cell counts following BR, with moderate decreases in neutrophils, and changes in IgG levels and Ab titers.
- During treatment, close monitoring of infectious disease complications is essential and supportive treatments such as the substitution of immunoglobulins, the use of growth factors, pneumocystis jiroveci pneumonia prophylaxis, and prophylaxis of HBV reactivation should be used as needed.
- Revaccination for tetanus and pneumococci should be taken into consideration if no protective titer exists after completing BR therapy.
- Neurologic symptoms should be monitored carefully and specific JC virus diagnostics should be conducted to detect PML.

Background
The response to second-line chemotherapy is an important requirement for and a predictor of outcome after autologous stem cell transplantation (ASCT) in patients with relapsed or refractory aggressive non-Hodgkin lymphomas (NHL). Second-line chemotherapy is associated with significant toxicity. Crump and colleagues previously established the safety and efficacy of outpatient treatment with GDP (gemcitabine, dexamethasone, cisplatin) in a phase II study, leading to this phase III trial, which tested the hypothesis that GDP is noninferior to and less toxic than standard DHAP (dexamethasone, cytarabine, cisplatin).1

Study design
- The population in this study included patients with aggressive B-cell or T-cell NHL, relapsed after or progressing on primary anthracycline-containing therapy.
  - Patients with transformed disease were allowed (≤3 prior regimens) in the study.
- Patients also had to be appropriate for SCT (i.e., ECOG performance status 0–3 and no formal upper age restriction) and have adequate organ function.
- Patients with active CNS lymphoma or known HIV infection were excluded.
- Randomization was stratified by treatment centre, International Prognostic Index (IPI) score at relapse, immunophenotype (B cell vs. T/Natural Killer cells), duration of response to primary therapy, and prior treatment with rituximab.
- The following regimens were administered for two to three 21-day cycles:
  - (R)-GDP: gemcitabine 1,000 mg/m² days 1 and 8, dexamethasone 40 mg days 1–4, cisplatin 75 mg/m² day 1;
  - (R)-DHAP: dexamethasone 40 mg days 1–4, cytarabine 2 g/m² every 12 hours x 2 on day 2, cisplatin 100 mg/m²/24 hours on day 1.
- The protocol was amended in November 2005 to include rituximab (R) (375 mg/m² day 1) with GDP and DHAP for patients with CD20+ lymphoma.
- Patients with a complete response (CR), partial response (PR), or <PR, as per institutional policy, proceeded to peripheral blood stem cell (PBSC) collection and ASCT.
- The study was designed to determine if the response rate (RR) to GDP was noninferior to DHAP and if the transplantation rate after GDP was superior to that after DHAP.
- Using a noninferiority (NI) design, the study was powered to set the margin at 10% difference in RRs and to detect an 11.4% difference in the transplantation rates between arms.
- Other end points included event-free survival (EFS), overall survival (OS), adverse events (AEs), quality of life (QoL), and an economic analysis.
- The FACT-G (functional assessment of cancer therapy-general) questionnaire was used to assess QoL.

Key findings
- From August 2003 to November 2011, 619 patients ([R]-GDP: n = 310 and [R]-DHAP: n = 309) were enrolled.
- All baseline characteristics were balanced between treatment arms ([R]-GDP vs. [R]-DHAP), including:
  - Relapse IPI: 0, 1: 38% per arm, 2: 29% per arm; ≥3: 33% vs. 32%;
  - Prior rituximab treatment: 67% per arm;
  - Refractory to initial therapy: 31% vs. 30%.
In the intention-to-treat (ITT) population, RR were similar in both arms:
- (R)-GDP: 45.2% vs. (R)-DHAP: 44.0%. (Table 1)

• The upper boundary of the one-sided 95.6% confidence interval for the difference in RR was 5.67%, which did not cross the prespecified 10% NI boundary, meaning (R)-GDP was noninferior to (R)-DHAP ($p = 0.005$).

• The transplantation rates were similar for (R)-GDP vs. (R)-DHAP (per protocol analysis; 51.8% vs. 49.3%, $p = 0.49$).

• Similar rates of successful stem cell mobilization ($\geq 2 \times 10^6$ CD34$^+$ cells/kg) were detected in the (R)-GDP (87.9%) vs. (R)-DHAP (82.2%) arms ($p = 0.14$).

• At a median follow-up of 53 months, patients in the (R)-GDP and (R)-DHAP arms had comparable four-year survival rates:
  - EFS: 26% per arm; HR = 0.99 (95% CI: 0.82–1.21), $p = 0.95$;
  - OS: 39% per arm; HR = 1.03 (95% CI: 0.83–1.28), $p = 0.78$.

• Patients receiving (R)-GDP experienced less grade 3/4 toxicity (47% vs. 61%), including febrile neutropenia (9% vs. 23%), fewer platelet transfusions during the first two treatment cycles (18% vs. 32%), fewer AEs requiring hospitalization (18% vs. 30%), and less hospitalization overall (46% vs. 99%). (Table 2)

According to analyses of the FACT-G total scores, superior mean and greater-than-minimally-important QoL change scores were recorded after two treatment cycles vs. baseline in patients who received (R)-GDP compared with (R)-DHAP. (Figures 1 and 2)

### Table 1. Response rates in ITT population

<table>
<thead>
<tr>
<th></th>
<th>(R)-GDP (N = 310), %</th>
<th>(R)-DHAP (N = 309), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4.5</td>
<td>5.2</td>
</tr>
<tr>
<td>CRu</td>
<td>9.0</td>
<td>9.1</td>
</tr>
<tr>
<td>PR</td>
<td>31.6</td>
<td>29.8</td>
</tr>
<tr>
<td>RR</td>
<td>45.2</td>
<td>44.0</td>
</tr>
</tbody>
</table>

CR = complete response; CRu = complete response, unconfirmed; (R)-DHAP = (rituximab), dexamethasone, cytarabine, cisplatin; (R)-GDP = (rituximab), gemcitabine, dexamethasone, cisplatin; ITT = intent to treat; RR = response rate; PR = partial response

### Table 2. Adverse events during salvage therapy

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>(R)-GDP (n = 306), %</th>
<th>(R)-DHAP (n = 304), %</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4* toxicity</td>
<td>47</td>
<td>61</td>
<td>0.0003</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9</td>
<td>23</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Platelet transfusion (cycles 1 and 2)</td>
<td>18</td>
<td>32</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Hospitalization for AE/illness</td>
<td>18</td>
<td>30</td>
<td>0.0005</td>
</tr>
<tr>
<td>Any hospitalization</td>
<td>46</td>
<td>99</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

AE = adverse event; (R)-DHAP = (rituximab), dexamethasone, cytarabine, cisplatin; (R)-GDP = (rituximab), gemcitabine, dexamethasone, cisplatin

*Common Terminology Criteria for AEs version 2.0.

**Figure 1. Quality of life results: means of FACT-G total**

**Figure 2. Quality of life results: FACT-G Total change in minimally important difference**

n = number of patients; (R)-DHAP = (rituximab), dexamethasone, cytarabine, cisplatin; (R)-GDP = (rituximab), gemcitabine, dexamethasone, cisplatin

*10% change in maximum score; baseline to mid cycle 2.
Key conclusions

- Salvage chemotherapy with (R)-GDP is not inferior to standard (R)-DHAP prior to ASCT.
- (R)-GDP results in significantly less toxicity (e.g., less febrile neutropenia, fewer platelet transfusions, fewer days in hospital) and is better tolerated as shown by superior QoL scores.
- (R)-GDP represents a new standard in practice for second-line chemotherapy and could form the basis of regimens incorporating novel agents into salvage therapy.


Morschhauser F, et al. ICML 2013:136

The RELEVANCE trial: a LYSA-sponsored phase III randomized study to compare the efficacy and safety of rituximab plus lenalidomide with those of rituximab plus any chemotherapy in patients with previously untreated advanced follicular lymphoma

**Background**

Rituximab plus chemotherapy is the standard of care for follicular lymphoma (FL) with high tumour burden. Multiple genetic defects are induced by non-Hodgkin lymphoma (NHL) cells, resulting in the impairment of actin polymerization, immune synapse formation, cytotoxicity, cytokine production, motility, and altered chemokine production. Lenalidomide reverses the FL inhibitory effect on immune effector cells, restores immune synapse, improves antibody-dependent cellular cytotoxicity, and has activity as a single agent making it a natural partner for anti-CD20 monoclonal antibodies in the treatment of NHL. Currently, the major challenge in phase III studies in first-line FL is that median PFS is approaching seven years. Therefore, it might take eight to 10 years or more to complete a phase III trial using the conventional end points of PFS or OS, highlighting the need for a surrogate end point for PFS. At ICML 2013, Morschhauser and colleagues presented the design of the RELEVANCE (Rituximab Lenalidomide Versus Any Chemotherapy) trial, an ongoing phase III study in previously untreated patients with FL.

**Study design**

**Design**

- This randomized phase III study involving first-line patients with FL will compare the induction and maintenance therapies of rituximab plus lenalidomide ($R^2$) with rituximab plus chemotherapy ($R$-chemo), which is composed of an investigator’s choice of R-CHOP, R-CVP, or BR.

**Study design**

- **Patients with first-line FL (N = 1,000)**
- **$R^2$ (lenalidomide + rituximab)**
- **$R^2$ maintenance (lenalidomide 1 yr + rituximab 2 yrs)**
- **R-chemo (Investigator’s choice of R-CHOP, R-CVP, or BR)**
- **Rituximab maintenance (2 yrs)**

**Abbreviations:**
- $R$ = bendamustine, rituximab; $R^2$ = complete response; CRu = complete response, unconfirmed; FL = follicular lymphoma; PR = partial response; $R =$ randomize; $R^2$ = lenalidomide, rituximab; $R$-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; $R$-CVP = rituximab, cyclophosphamide, vincristine, prednisone
The main inclusion criteria are:
- Histologically confirmed CD20+ FL grade 1, 2, or 3a
- Stage II, III, or IV disease
- In need of treatment as evidenced by at least one of the following criteria:
  - Bulky disease: a nodal or extranodal (except spleen) mass >7 cm in diameter or involvement of at least three nodal or extranodal sites each with a diameter >3cm;
  - Symptomatic splenomegaly;
  - B symptoms;
  - Lactate dehydrogenase or beta-2-microglobulin greater than the upper limit of normal;
  - Compression syndrome (e.g., ureteral, orbital, gastrointestinal);
  - Pleural or peritoneal serous effusion.

The main exclusion criteria are:
- Clinical evidence of transformed lymphoma by investigator assessment;
- Patients taking corticosteroids during the last four weeks (unless dose ≤10 mg/day);
- Prior history of malignancies, unless subject has been free of the disease for ≥10 years. Exceptions include a history of previously treated localized nonmelanoma skin cancer and carcinoma in situ of the cervix;
- Presence or history of central nervous system involvement by lymphoma;
- Any serious medical condition, laboratory abnormality, or psychiatric illness.

This is an international study with two sponsors looking to recruit a total of 1,000 patients:
- The Lymphoma Academic Research Organisation (LYSARC) in Europe, Australia, and Canada (up to 750 patients);
- Celgene in the U.S. (up to 250 patients).

Stratification factors include Follicular Lymphoma International Prognostic Index scores (0–1 vs. 2 vs. 3–5), age (>60 vs. ≤60 years), and diameter of the largest node (>6 cm vs. ≤6 cm).

There will be one clinical database, one Data and Safety Monitoring Committee, and one Independent Review Committee.

The central review of diagnostics will be performed by The Lymphoma Study Association-Pathology platform (LYSA-P).

The central review of computed tomography and positron emission tomography (PET) scans will be performed by Keosys.

Response assessments are scheduled for 12 weeks (off study if lesions decrease by <25%), 24 weeks (off study if response is less than a partial response), and 120 weeks.

End points and analysis
- The coprimary end points of this study and their expected values are:
  - Complete response (CR) and CRu (unconfirmed) rate at 120 weeks:
    - Increase of 12%: 60% (control) vs. 72% (experimental);
    - 644 patients, $\alpha = 0.05$ (two-sided), power = 90%.
  - Progression-free survival (PFS):
    - Hazard ratio = 1.3 (increase of 30%);
    - Median: 83 months (control) vs. 108 months (experimental);
    - 456 events, $\alpha = 0.05$ (two-sided), power = 80%.
- If both coprimary end points are fulfilled, then the experimental arm ($R^2$) is superior to the control arm ($R$-chemo).
- The secondary end points are event-free survival, overall survival, time to next anti-lymphoma treatment, and safety.
- Exploratory end points are:
  - CR and PFS by International Working Group (IWG) 2007 criteria incorporating fluorodeoxyglucose-PET;
  - Overall response rate (ORR) by IWG 1999 criteria;
  - Time to treatment failure;
  - Time to next chemotherapy treatment;
  - Health-related quality of life, as measured by the EORTC QLQ-C30.
- As of June 20, 2013, a total of 336 patients have been recruited to the study: 208 patients in France, 107 patients in the U.S., and 21 patients in Belgium.

Key conclusions
- There will be two interim analyses for futility:
  - The first interim analysis will evaluate the CR rate at six months of treatment for the first 200 patients (second quarter of 2014).
  - The second interim analysis will evaluate the CR rate at 120 weeks for the first 200 patients (second quarter of 2016).
- Surrogate end point results are expected in 2016.
- PFS end point results are expected in 2024.

A phase III study of ibrutinib in combination with bendamustine plus rituximab in elderly patients with newly diagnosed mantle cell lymphoma: the SHINE study

Background
Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma (NHL) accounting for approximately 6% of NHL diagnoses. First-line therapy has typically involved chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) combined with the anti-CD20 monoclonal antibody rituximab (R), but a constant relapse pattern is still often observed. Ibrutinib, an oral Bruton’s tyrosine kinase (BTK) inhibitor, has demonstrated promising single-agent activity in a phase II study of patients with relapsed or refractory MCL. The overall response rate (ORR) was 68%, with 46% of patients achieving partial response (PR) and 22% achieving complete remission (CR). Ibrutinib can be safely combined with BR (bendamustine, rituximab), as demonstrated in a phase I combination study of relapsed or refractory NHL where it enhanced BR’s clinical activity with an ORR of 100% (80% CR, 20% PR) in 5 evaluable MCL patients. These data suggest that combining ibrutinib with BR will improve the outcomes for patients with MCL. The design and status of this ongoing phase III study, known as SHINE, were described by Dreyling and colleagues at ICML 2013.

Study design

Design
• The SHINE study is a phase III, double-blind, placebo-controlled study of ibrutinib in combination with BR for the treatment of patients with newly diagnosed MCL.
• All patients will receive BR (B: 90 mg/m² intravenous (iv) days 1–2 and R: 375 mg/m² day 1) for six cycles.
  ▪ Patients achieving a CR or PR will receive rituximab maintenance (375 mg/m² iv) every two cycles for two years.
• In addition to BR induction and rituximab maintenance, all patients will receive an oral daily dose of either 560 mg ibrutinib or placebo concomitant with the chemotherapy and ongoing as a single agent until disease progression or unacceptable toxicity.

Study design

Phase III, randomized, double-blind, placebo-controlled study (SHINE study)

<table>
<thead>
<tr>
<th>Arm A*</th>
<th>Arm B*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background therapy (6 cycles):</strong></td>
<td></td>
</tr>
<tr>
<td>Bendamustine (90 mg/m² iv days 1–2)</td>
<td></td>
</tr>
<tr>
<td>Rituximab (375 mg/m² day 1)</td>
<td></td>
</tr>
<tr>
<td>CR/PR ➔</td>
<td></td>
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<tr>
<td>Rituximab 375 mg/m²</td>
<td></td>
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<tr>
<td>(every 2 cycles for 2 years)</td>
<td></td>
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<tr>
<td><strong>Study drug:</strong></td>
<td></td>
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<tr>
<td>Oral placebo</td>
<td></td>
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<tr>
<td>(starting on cycle 1, day 1)</td>
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<td>until PD or unacceptable toxicity</td>
<td></td>
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<tr>
<td><strong>Background therapy (6 cycles):</strong></td>
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<td>Bendamustine (90 mg/m² iv days 1–2)</td>
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<td></td>
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<tr>
<td>(every 2 cycles for 2 years)</td>
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<tr>
<td><strong>Study drug:</strong></td>
<td></td>
</tr>
<tr>
<td>Oral ibrutinib 560 mg</td>
<td></td>
</tr>
<tr>
<td>(starting on cycle 1, day 1)</td>
<td></td>
</tr>
<tr>
<td>until PD or unacceptable toxicity</td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; iv = intravenous; PD = progressive disease; PR = partial response
*A cycle is defined as 28 days.
• The study aims to enrol 520 patients (approximately 260 patients per arm). Approximately 200 sites globally will enrol patients. Enrolment began in the first quarter of 2013.

• This study will enrol patients according to the following inclusion criteria:
  - Age ≥65 years;
  - Confirmed diagnosis of MCL:
    - Local diagnosis is sufficient to initiate treatment; however, tumour block or slides must be sent to central laboratory for confirmation;
  - Clinical stage II, III, or IV disease;
  - At least one measurable site of disease;
  - No prior therapies for MCL;
  - ECOG performance status grade 0 or 1;
  - Hematology values within 14 days before randomization as follows:
    - Absolute neutrophil count ≥1,000/mm³, independent of growth factor support;
    - Platelets ≥100,000/mm³ or ≥50,000/mm³ if bone marrow involvement;
  - Biochemical values within 14 days before randomization as follows:
    - Alanine transaminase and aspartate aminotransferase ≤3 times the upper limit of normal (ULN);
    - Total bilirubin ≤1.5 times ULN;
    - Serum creatinine ≤2 times ULN or glomerular filtration rate ≥40 mL/min/1.73m².

• Some key exclusion criteria include history of stroke or intracranial hemorrhage within six months prior to randomization, requiring anticoagulation treatment with warfarin or equivalent vitamin K antagonists, and treatment with strong CYP3A4/5 inhibitors.

**End points**
- The primary objective is to evaluate if the addition of ibrutinib to BR will result in the prolongation of progression-free survival.
- Secondary objectives are the evaluation of overall survival, CR rate, ORR (CR + PR), duration of response, and safety.

**Key finding**
- As of May 13, 2013, 11 sites in five countries are actively recruiting patients and three subjects have been screened. (Table 1)

**Table 1. Current status of study recruitment**

<table>
<thead>
<tr>
<th>Country</th>
<th>Open sites (n)</th>
<th>Subjects screened (n)</th>
<th>Subjects randomized (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hungary</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Israel</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sweden</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>United States</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Key conclusion**
- No results were reported at this time, as this is an ongoing phase III trial that is currently in the process of actively recruiting patients.

A phase III trial comparing obinutuzumab (GA101) plus CHOP (G-CHOP) versus rituximab plus CHOP (R-CHOP) in previously untreated diffuse large B-cell lymphoma

**Background**
Progress has been made in treating diffuse large B-cell lymphoma (DLBCL) with the addition of rituximab—a B-cell-depleting, anti-CD20 monoclonal antibody (mAb)—to standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. Yet, a significant number of patients remain incurable. Therefore, in the first-line setting where rituximab plus CHOP (R-CHOP) is the current standard of care, an unmet need exists to further improve outcomes by developing therapies with higher cure rates. GA101, also known as obinutuzumab, is the first glycoengineered, type II anti-CD20 mAb. It has increased direct cell death and antibody-dependent cellular cytotoxicity, as well as decreased complement dependent cytotoxicity compared with nonglycoengineered, type I mAbs. Mobasher and colleagues described the rationale and design of an ongoing phase III trial known as GOYA, in which GA101 plus CHOP (G-CHOP) will be compared with R-CHOP in previously untreated DLBCL.1

**Study design**

**Rationale**
- GA101 has exhibited promising clinical activity, including in patients pretreated with rituximab and multiple lines of chemotherapy, and has been shown to have an acceptable safety profile relative to rituximab.
- Phase I and II studies have shown that:
  - GA101 monotherapy is effective in patients with relapsed or refractory DLBCL, with an overall response rate (ORR) of 32.0%.
  - GA101 can be added to CHOP without compromising dose intensity in patients with indolent non-Hodgkin lymphoma (NHL). The ORRs for GA101 combination therapies were:
    - Relapsed/refractory setting: 96.4% for G-CHOP and 92.9% for G-FC (GA101, fludarabine, cyclophosphamide);
    - First-line setting: 95.0% for G-CHOP and 92.7% for G-bendamustine.

**Design**
- The GOYA study aims to enrol 1,400 patients with DLBCL.
- Key inclusion criteria are:
  - Adults ≥18 years with previously untreated CD20-positive DLBCL;
  - Low-intermediate, intermediate-high, or high-risk International Prognostic Index (IPI) score and some low-risk;
  - One or more bidimensionally measurable lesions (>1.5 cm);
  - Eastern Cooperative Oncology Group performance status of 0–2;
  - Adequate hematologic function.
- Key exclusion criteria are:
  - Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation;
  - Central nervous system lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, plasmablastic lymphoma, primary cutaneous DLBCL, transformed lymphoma, and follicular lymphoma (grade 3b);
  - Prior treatment with cytotoxic drugs or rituximab for another condition, prior use of an anti-CD20 antibody, prior use of any mAb within three months of the start of the first cycle;
  - Ongoing corticosteroid use of >30 mg/day of prednisone or equivalent;
  - Significant, uncontrolled comorbidities;
  - Life expectancy <12 months;
  - Positive for active hepatitis B, hepatitis C, human immunodeficiency virus, or human T-lymphotropic virus type I.
- Patients are stratified based on the number of planned CHOP cycles (6 or 8), IPI score, and the region of study conduct.
- Patients are randomized 1:1 between G-CHOP and R-CHOP, given at the following doses and schedules:
  - CHOP: standard dose and schedule;
  - GA101: 1,000 mg on days 1, 8, and 15 of cycle one; on day 1 of cycles two to eight, every 21 days;
Rituximab: 375 mg/m² on day 1 of cycles one to eight, every 21 days.

**Study design**

- An independent data monitoring committee (IDMC) has been implemented for intensive review of safety.
- Early termination or modification is allowed for safety or futility concerns on the advice of the IDMC.

**End points**

- Enrollment began in July 2011. This study is scheduled to end in approximately 78 months after the first patient is enrolled.
- The primary end point is progression-free survival, based on investigator assessment.
- Secondary end points include overall survival, ORR, complete response (CR) rate, event-free survival, disease-free survival, duration of response, safety, quality of life, and medical resource utilization.

**Key finding**

- An interim futility analysis based on CR led to the addition of more sites and countries on the study.

**Key conclusions**

- On the basis of data from single-arm studies of GA101 in aggressive and indolent NHL, the phase III GOYA study, which is the largest clinical trial ever conducted in patients with DLBCL, will assess the safety and efficacy of induction therapy with G-CHOP vs. R-CHOP in previously untreated patients.
- Clinical trials in other histologies (e.g., chronic lymphocytic leukemia and NHL) are also underway.


Davies A, et al. ICML 2013:194

**Pharmacokinetics, safety, and overall response rate achieved with rituximab sc were comparable to those with rituximab iv in the first-line treatment of patients with follicular lymphoma: stage I results of the phase III SABRINA study**

**Background**

SABRINA is a two-stage phase III study of subcutaneous (sc) rituximab compared with intravenous (iv) rituximab combined with chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] or CVP [cyclophosphamide, vincristine, prednisone]) followed by rituximab sc or iv maintenance in patients with previously untreated follicular lymphoma (FL). At ICML 2013, Davies and colleagues reported the pharmacokinetics, safety, and efficacy outcomes from stage one of this study.1

**Study design**

- SABRINA (BO22334) is a two-stage international, randomized, controlled, open-label study.
- Eligible patients were ≥18 years with previously untreated, histologically confirmed CD20+ grade 1, 2, or 3a FL, an Eastern Cooperative Oncology Group performance status of 0–2, bidimensionally measurable disease (computed tomography or magnetic resonance imaging), signed informed consent forms, and had an indication for treatment.
• Patients with the presence or history of central nervous system disease, transformation to a high-grade lymphoma other than FL, or a history of malignancies other than FL were excluded.

• In stage one of the trial, patients were randomized 1:1 to standard chemotherapy (either CHOP or CVP as chosen by the treating physician) plus either 375 mg/m² rituximab iv or 1,400 mg rituximab sc.

• Patients were stratified by the Follicular Lymphoma International Prognostic Index score, chemotherapy, and region.

• In the first induction cycle, patients received rituximab iv regardless of their randomization treatment group.

• Up to eight cycles of chemotherapy were administered for patients treated with CHOP plus rituximab or CVP plus rituximab.

• Patients received eight cycles of rituximab regardless of the number of chemotherapy cycles received.

• After induction immunochemotherapy, patients with a complete response (CR), unconfirmed CR (CRu), or partial response (PR) continued to receive rituximab by the same route as in induction treatment and at the same dose every eight weeks for up to two years.

• The primary end point for stage one was the $C_{\text{IV}}/C_{\text{SC}}$ ratio at day 21 of induction cycle seven. The noninferiority limit was 0.8.

• The stage 1 secondary objectives included comparing:

  - Rituximab serum concentration area under the plasma concentration-time curve (AUC) for sc and iv administration during induction treatment given every three weeks;

  - Overall response rates (ORRs) of rituximab sc and rituximab iv given in combination with CHOP or CVP induction at the end of induction treatment.

• Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.

• An administration-related reaction (ARR) was defined as any event that occurred during or within 24 hours of treatment that was considered by the study investigator to be related to rituximab.

• All responses were assessed by the study investigators and an independent review committee.

**Key findings**

**Baseline characteristics and disposition**

- Patients were randomized to receive rituximab iv (n = 64) or to receive rituximab sc (n = 63) (intent-to-treat population).

- One patient randomized to the rituximab sc arm discontinued treatment shortly after the first rituximab iv infusion and was analyzed as part of the rituximab iv arm in the safety population (65 patients in rituximab iv arm; 62 patients in rituximab sc arm).

- Evaluable $C_{\text{IV}}/C_{\text{SC}}$ data were available for 48 and 54 patients in the rituximab iv and rituximab sc arms, respectively.

- Baseline demographics and disease characteristics were similar between the rituximab iv and rituximab sc arms including:

  - Median age: 57 years in the iv arm; 54 years in the sc arm;

  - Patients in the iv and sc arms, respectively, had FL that was classified as grade 1 (27% and 35%), grade 2 (55% and 38%), grade 3 (3% and 5%), or grade 3a (16% and 22%);

  - As first-line chemotherapy in both rituximab arms combined, 63% of patients received CHOP and 37% of patients received CVP.

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![Study design diagram](image-url)
Pharmacokinetics

- Median rituximab $C_{\text{trough}}$ levels were higher in the rituximab sc arm than those in the rituximab iv arm at each treatment cycle. (Figure 1)
- The geometric means for the rituximab $C_{\text{trough}}$ levels in the sc (n = 48) and iv (n = 54) arms at the end of induction cycle 7 were 134.6 μg/mL and 83.1 μg/mL, respectively, for a rituximab sc:iv $C_{\text{trough}}$ ratio of 1.62 (90% CI: 1.36–1.94), thereby demonstrating the noninferiority of rituximab sc.
- The geometric mean ratio of AUC_sc:AUC_iv (1.38 [90% CI: 1.24–1.53]) indicates an exposure to rituximab sc at least as high as after iv administration.

Safety

- Two patients in each study arm discontinued treatment during induction or maintenance for safety reasons.
- At a median follow-up of 8.74 months (range, 4.4–14.8) in the rituximab iv arm and 8.84 months (range, 1.0–14.5) in the rituximab sc arm, similar percentages of patients in each treatment arm had experienced adverse events (AEs) of any grade, grade $\geq 3$ AEs, and serious AEs. (Table 1)
- The only grade 3 or 4 AE occurring in $>10\%$ of patients was neutropenia (22% in rituximab iv; 26% in rituximab sc). This was not associated with an increased infection rate.
- Grade 3 or 4 infections and infestations were reported in 9% of patients in the rituximab iv arm and 5% in the rituximab sc arm.

- There were no treatment-related deaths.
- The incidence of ARRs was higher in the rituximab sc arm. The majority of these (97.8% rituximab iv; 94.5% rituximab sc) were grade 1 or 2; no grade 4 ARRs occurred.
- Any-grade ARRs occurring in $\geq 5\%$ of patients in the rituximab iv and rituximab sc arms, respectively, were erythema (3% vs. 8%), pruritus (3% vs. 6%), chills (6% vs. 3%), injection-site erythema (0% vs. 10%), and vomiting (6% vs. 3%).

Table 1. Adverse events by treatment arm

<table>
<thead>
<tr>
<th>Patients with events*, n (%)</th>
<th>Rituximab iv + CT (n = 65)$^1$</th>
<th>Rituximab sc + CT (n = 62)$^1$</th>
<th>Total (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade adverse event</td>
<td>57 (88)</td>
<td>57 (92)</td>
<td>114 (90)</td>
</tr>
<tr>
<td>Any-grade treatment-related adverse event</td>
<td>30 (46)</td>
<td>45 (73)</td>
<td>75 (59)</td>
</tr>
<tr>
<td>Administration-related adverse event</td>
<td>21 (32)</td>
<td>31 (50)</td>
<td>52 (41)</td>
</tr>
<tr>
<td>Grade $\geq 3$ adverse event</td>
<td>30 (46)</td>
<td>29 (47)</td>
<td>58 (46)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>14 (22)</td>
<td>14 (23)</td>
<td>28 (22)</td>
</tr>
</tbody>
</table>

CT = chemotherapy; iv = intravenous; n = number of patients; sc = subcutaneous
*Numbers of patients experiencing at least one adverse event.
$^1$One patient randomized to the rituximab sc arm discontinued treatment shortly after the first rituximab iv infusion but was analyzed as part of the rituximab iv arm in the safety population.

Figure 1. Rituximab $C_{\text{trough}}$ serum levels by treatment cycle

![Figure 1. Rituximab C_{trough} serum levels by treatment cycle](image-url)
• Exploratory subgroup analysis showed that patients with the lowest body surface area (BSA) and the highest exposure following rituximab sc administration did not experience a higher incidence of AEs than the corresponding rituximab iv population. (Table 2)

Response rates
• Investigator-assessed ORRs (CR, CRu, or PR) at the end of induction were 84.4% and 90.5% in the rituximab iv and rituximab sc arms, respectively. The corresponding ORRs by independent review were 87.5% (18.8% CR or CRu) and 85.7% (27.0% CR or CRu), respectively. (Table 3)

Exploratory subgroup analysis found comparable OR and CR rates among patients with high BSA, indicating that clinical benefits in these patients when treated with rituximab sc 1,400 mg fixed dose were comparable with those of high BSA patients treated with rituximab iv. (Table 4)

Table 2. Exploratory subgroup analysis of adverse events*

<table>
<thead>
<tr>
<th>Population†, n (%)</th>
<th>Grade ≥3 adverse events</th>
<th>Serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab iv + CT arm</td>
<td>Rituximab sc + CT arm</td>
</tr>
<tr>
<td>Overall</td>
<td>30/65 (46)</td>
<td>29/62 (47)</td>
</tr>
<tr>
<td>Low BSA‡</td>
<td>8/16 (50)</td>
<td>15/26 (58)</td>
</tr>
<tr>
<td>Medium BSA‡</td>
<td>15/27 (56)</td>
<td>7/15 (47)</td>
</tr>
<tr>
<td>High BSA‡</td>
<td>7/21 (33)</td>
<td>7/21 (33)</td>
</tr>
</tbody>
</table>

BSA = body surface area; CT = chemotherapy; iv = intravenous; n = number of patients; sc = subcutaneous

*Subgroup analyses are observational by nature and should be interpreted with caution due to limitations in sample size and statistical power.
†One patient randomized to the rituximab sc arm discontinued treatment shortly after the first rituximab iv infusion but was analyzed as part of the rituximab iv arm in the safety population.
‡For BSA, patients were grouped into low (≤33rd percentile), medium (between 33rd [1.7 m²] and 66th [1.9 m²] percentile), and high (≥66th percentile).

Table 3. Tumour response rates at the end of induction

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Investigator Assessment</th>
<th>Independent review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab iv + CT (n = 64)</td>
<td>Rituximab sc + CT (n = 63)</td>
</tr>
<tr>
<td>Overall response</td>
<td>54 (84.4)</td>
<td>57 (90.5)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>19 (29.7)</td>
<td>29 (46.0)</td>
</tr>
<tr>
<td>PR</td>
<td>35 (54.7)</td>
<td>28 (44.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (4.7)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Missing, invalid, or not evaluated*</td>
<td>6 (9.4)</td>
<td>4 (6.3)</td>
</tr>
</tbody>
</table>

CR = complete response; CRu = complete response, unconfirmed; CT = chemotherapy; iv = intravenous; n = number of patients; PR = partial response; sc = subcutaneous

*Patients with nonevaluated, invalid, or missing response assessments were classified as nonresponders. A response was classified as invalid if the response assessment was >56 days after the last rituximab intake, after the first rituximab iv infusion, or after the start of new antilymphoma treatment.

Table 4. Exploratory subgroup analysis of tumour response rates at the end of induction

<table>
<thead>
<tr>
<th>Population, n (%)</th>
<th>Overall response</th>
<th>CR/CRu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab iv + CT arm</td>
<td>Rituximab sc + CT arm</td>
</tr>
<tr>
<td>Overall</td>
<td>54/64 (84.4)</td>
<td>57/63 (90.5)</td>
</tr>
<tr>
<td>Low BSA‡</td>
<td>15/16 (93.8)</td>
<td>22/26 (84.6)</td>
</tr>
<tr>
<td>Medium BSA‡</td>
<td>20/26 (76.9)</td>
<td>15/16 (93.8)</td>
</tr>
<tr>
<td>High BSA‡</td>
<td>18/21 (85.7)</td>
<td>20/21 (95.2)</td>
</tr>
<tr>
<td>CHOP</td>
<td>34/40 (85.0)</td>
<td>37/40 (92.5)</td>
</tr>
<tr>
<td>CVP</td>
<td>20/24 (83.3)</td>
<td>20/23 (87.0)</td>
</tr>
</tbody>
</table>

BSA = body surface area; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CR = complete response; CRu = complete response, unconfirmed; CT = chemotherapy; CVP = cyclophosphamide, vincristine, prednisone; iv = intravenous; n = number of patients; sc = subcutaneous

*Subgroup analyses are observational by nature and should be interpreted with caution due to limitations in sample size and statistical power.
‡For BSA, patients were grouped into low (≤33rd percentile), medium (between 33rd [1.7 m²] and 66th [1.9 m²] percentile), and high (≥66th percentile).
Key conclusions

- Following cycle seven, the observed $C_{\text{trough sc}} : C_{\text{trough iv}}$ ratio was 1.62 (90% CI: 1.36–1.94), demonstrating noninferiority for rituximab sc dosing when given every three weeks.

- Overall safety profiles for rituximab sc and rituximab iv were generally similar. However, there were more ARRs in the 1,400 mg rituximab sc arm, with the majority of these events being mild or moderate injection-site reactions, reflecting the expected change of the ARR profile after the switch to the sc route of rituximab administration.

- OR rates (CR, CRu, PR) and CR rates (CR, CRu) assessed by the investigator and independent review committee indicate that the sc route of administration does not impair the antilymphoma activity of rituximab.

- Stage one patients are continuing to receive maintenance treatment with rituximab iv or sc, while an additional 280 patients are being randomized (1:1) into stage two of the study to receive rituximab sc (1,400 mg) or rituximab iv (375 mg/m²).

Reference: 1. Davies A, Merli F, Mišaljević B, et al. Pharmacokinetics, safety, and overall response rate achieved with subcutaneous rituximab plus chemotherapy were comparable to those with intravenous administration in the first-line treatment of patients with follicular lymphoma: stage I results of the phase III SABRINA study (BO22334). ICML 2013:194.

Canadian Perspective by Dr. Laurie Sehn

Until recently, the standard of care in the U.S. and Canada for first-line patients with indolent non-Hodgkin lymphoma (NHL) or mantle cell lymphoma (MCL) was immunochemotherapy consisting of the anti-CD20 monoclonal antibody rituximab in combination with the chemotherapy regimen of either cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or cyclophosphamide, vincristine, and prednisone (R-CVP). However, a published study by Rummel et al. has now shown that, compared with R-CHOP, bendamustine plus rituximab (BR) has a more favourable safety profile and prolongs progression-free survival (PFS) in patients with indolent NHL or MCL.

The BRIGHT study asked a similar question to that in the study by Rummel et al. but, in the BRIGHT study, the standard immunochemotherapy arm was composed of an investigator’s choice of either R-CHOP or R-CVP, on a per patient basis. The rationale for giving the investigator a choice of comparator regimens was to allow the investigator to select the most suitable option for the patient, since not all patients are candidates for R-CHOP due to cardiac comorbidities or age-related issues. R-CVP is a less intensive chemotherapeutic regimen and has been widely used in Canada as the preferred regimen, until recently. Presumably, this study wanted to capture a more representative group of patients.

One major difference between these two studies was that the BRIGHT trial used complete response (CR) rate as the primary end point, while the study by Rummel et al. looked at PFS, which is a more clinically relevant end point. Nonetheless, Flinn et al. reported a noninferior CR rate for evaluable patients who received BR (31%; 95% CI: 25.3–38.2%) compared with the CR rate for those who received R-CHOP or R-CVP (25%; 95% CI: 19.5–31.7%).

Investigators on the BRIGHT study also found that there are distinct differences in the safety profiles of the three regimens. Overall, BR appeared to have the most
In Supportive Care Oncology

favoured safety profile; fewer patients given BR experienced neutropenia, peripheral neuropathy, and alopecia compared with those who received R-CVP or R-CHOP. The fact that BR was associated with more nausea and vomiting suggests that we might need to modify supportive care practices to use more effective antiemetics with this regimen.

In my practice, we have recently switched over to using BR as our standard first-line treatment for both indolent NHL and MCL. BR has been accessible as of June 1st in British Columbia for the first-line treatment of these lymphomas, based on the results of the study by Rummel et al.5 It is likely that many other provinces will also switch over to using BR in the near future.

The MAINTAIN study is an ongoing trial evaluating induction therapy with BR followed by the standard two-year rituximab maintenance schedule versus a more prolonged rituximab maintenance schedule of four years for patients with follicular lymphoma (FL). In the design of previous trials, rituximab maintenance therapy was arbitrarily stopped at two years. The rationale for stopping maintenance therapy was to provide clinical benefit without increasing the risk of infectious complications related to prolonged immunosuppression. Now that the benefit of two years of rituximab maintenance has been established, the next logical step is to see if prolonging maintenance can offer patients even further benefit.

The results from the MAINTAIN study evaluating the utility of prolonged rituximab maintenance are eagerly awaited but, Burchardt et al. presented interesting preliminary results from this trial providing a better understanding of the immunosuppressive effects of BR during induction therapy.6 The investigators found that BR induction therapy resulted in substantial decreases in lymphocytes, both CD4+ and CD8+ cell counts, as well as more moderate decreases in neutrophils and immunoglobulin levels.

In this large study population, there were 252 serious adverse events (AEs) documented involving infections.6 Among these infectious events, the incidence of pneumocystis jiroveci pneumonia (n = 6) and the incidence of patients with progressive multifocal leukoencephalopathy (n = 4; three confirmed, one probable) were noteworthy. This study does highlight the need to carefully monitor patients on BR for risk of infection in the setting of immunosuppression. However, final results of this trial, as well as additional studies, will likely be required to assess whether routine infection prophylaxis should be considered.

To date, there are no data available from randomized trials evaluating the safety of rituximab maintenance following BR induction. The MAINTAIN trial will assess the safety of rituximab maintenance following BR, as well as help to answer whether there is utility in prolonging maintenance beyond two years of therapy. The intensive monitoring of infectious complications throughout this trial will provide valuable information on the feasibility of a prolonged schedule of maintenance rituximab, and whether prolonging immunosuppression will lead to an increase in the risk of infection.

As previously mentioned, rituximab maintenance therapy is routinely used for patients with indolent NHL including those with FL, where it has been shown to significantly prolong PFS,7 and in patients with transplant-ineligible MCL, where it has been associated with improved OS after initial treatment with R-CHOP.8 However, there have not been any studies to date supporting the use of rituximab maintenance therapy in DLBCL. A previous American Intergroup trial failed to demonstrate a benefit for maintenance rituximab administered as standard monotherapy (four weekly doses) every six months for two years following R-CHOP.9 The trial by Jäger et al. evaluated rituximab maintenance in the first-line setting for DLBCL using the standard dosing schedule of rituximab every two months for two years.10

Unfortunately, the overall results of this trial were negative. For the entire cohort, the trial did not meet its primary end point of improved event-free survival (EFS). Also, there were no significant differences demonstrated for any of the secondary end points when rituximab maintenance was compared with observation. At this point in time, the trial does not support the use of maintenance rituximab in patients with DLBCL. In the subgroup analysis of patients with low-risk versus high-risk Internal National Prognostic Index scores, there was a suggestion that rituximab maintenance may provide greater EFS benefit to low-risk patients but, this can only be hypothesis-generating rather than definitive evidence of its benefit.

Given that rituximab, which is currently administered as an intravenous (iv) infusion, has become a standard component of first-line and maintenance therapies for NHL, the development of a subcutaneous (sc) formulation of this drug has the potential to offer invaluable time and resource savings to healthcare providers and patients alike. De Cock et al. conducted a study that carefully assessed and compared the amount of time taken to administer rituximab sc versus rituximab iv.11 We already knew what the answer was going to be, so I am not at all surprised by the results showing...
the significant decreases in active healthcare provider time and patient chair time achieved with rituximab sc.

If rituximab sc were available in Canada, it would significantly diminish the amount of time dedicated to administration of this antibody; particularly in terms of nursing time, which is always a limited resource. Consequently, this would also allow us to reduce the wait times for patients who need to be scheduled for chemotherapy and free up more nursing time for other agents that need to be given intravenously.

Implementing the use of rituximab sc would certainly be a time-saving manoeuvre for my institution, allowing us to streamline patients through chemotherapy and enabling healthcare provider resources to be used in other areas. In addition, an abbreviation in the time needed to administer rituximab would conceivably amount to financial savings to the healthcare system.

I also see a huge advantage for patients. Given the option, I think most patients would prefer to have treatment delivered in a much shorter period of time. All of the data that has emerged to date suggests that rituximab sc appears to be safe and that the pharmacokinetic parameters are similar between rituximab sc and iv. However, I think it is still very important to await data evaluating the clinical equivalency of rituximab sc with respect to relevant clinical end points, such as response rates and PFS. Results from ongoing head-to-head clinical trials comparing the safety and efficacy of rituximab sc with rituximab iv will be important to establish whether the two rituximab formulations are indeed equivalent. Clinicians are unlikely to feel comfortable making the switch from rituximab iv to sc until this is confirmed. Once physicians feel confident that rituximab sc is comparable to rituximab iv, it will likely become widely utilized for the majority of patients.

Although much progress has been made over the years, therapies for indolent NHL and MCL are still considered noncurative. ABT-199 is a novel targeted agent that inhibits the anti-apoptotic protein BCL-2, which is an important mediator in the evasion of cell death for B-cell NHL. Compared to available drugs currently used to treat NHL, ABT-199 acts on a new and highly relevant target that will directly affect the malignant cell’s ability to survive and proliferate.

The response rates reported by Davids et al. in a phase I trial of ABT-199 in patients with relapsed or refractory NHL are highly encouraging. Even though a first-in-human trial like this one only includes a small number of patients and focuses on safety rather than efficacy, they found that most NHL subtypes responded well to ABT-199 as a single agent, including the MCL cohort in particular, where 100% (8/8) of patients achieved partial remission. This level of response was certainly remarkable given the heavily pretreated patient population, which is always difficult to treat. The recorded AEs primarily involved myelosuppression and were tolerable and manageable for the majority of patients. This preliminary experience with ABT-199 seems to indicate that it is an agent with a good safety profile and huge potential for efficacy.

While it is encouraging that ABT-199 seems to have efficacy as a single agent, I think this molecular inhibitor will likely have even greater efficacy when combined with standard cytotoxic drugs. Based on the mechanism of action of ABT-199, blocking BCL-2 should diminish the required threshold to promote apoptosis. Therefore, future trials that combine this drug with a cytotoxic agent that directly induces cell death should enable an enhanced apoptotic effect in malignant cells.


Canadian Guideline Needed for the Treatment of Follicular Lymphoma

Russell Sabio, Lymphoma Canada

When Robb Fisher learned he had follicular lymphoma (FL), he went silent. For six weeks, he kept secret the reason for his barking cough, shortness of breath, mild fever, and fatigue. He didn’t tell his family or friends and would only give in to emotion while standing in the shower.

“I simply had a ‘dirty little secret’ that I needed to protect everyone from. I needed to isolate my feelings and process them independently,” says Fisher, aged 52 years. “I could not even entertain the notion of saying the word cancer…saying that word made it real. And real meant a whole bunch of things that I was not prepared for.”

Fisher’s story is indicative of many patients with lymphoma and is not limited to any particular stage of the disease. A life-changing moment becomes more complicated with lack of knowledge and without support. This is a problem that Lymphoma Canada tries to mitigate and is one reason why the organization is advocating for national treatment guideline for FL.

**Need for national treatment guidelines**

“(The national guideline) would mean that patients would have comfort in knowing they are getting the best treatment options recommended by Canadian key opinion leaders,” says Sue Robson, Executive Director of Lymphoma Canada.

A national treatment guideline would lay out the best possible treatment strategy for a patient with FL based on research and evidence. It would remove variances in treatment guidelines between provinces and would consider newer treatment options. The objective is to support follicular patients in Canada so they have confidence in knowing they are receiving the best care supported by meticulous thought.

**No national standard of care**

Effective treatments are available for FL, but there is currently no national standard of care and guidelines differ across provinces making it more difficult for patients to know what the best treatment option is. If a particular therapy is the first treatment option used in one province, but not in another, it is hard for a patient to be fully knowledgeable with such discrepancies.

Promising new treatment options also need to be evaluated and possibly implemented in an up-to-date treatment guideline. New studies with favourable results are regularly emerging. However, it is up to a national group of experts to determine what the best evidence-based guideline would look like.

To facilitate the development of this treatment guideline, a group of medical experts including Dr. Joseph Connors from British Columbia, Dr. Michael Crump from Ontario, Dr. David Macdonald from Nova Scotia, Dr. Douglas Stewart from Alberta, and Dr. Jean-Francois Larouche from Quebec, would partner with a medical writer. The goal is to eventually attain the best for patients with FL in Canada.

**Challenges with national collaboration**

Even with the expertise and determination to see this project through, Lymphoma Canada has several roadblocks to overcome. The logistics of national collaboration are no easy task and, of course, the cost of such a project is very high. But in spite of the challenges, this is something Lymphoma Canada believes must be done.

**Lymphoma Canada’s role in helping patients**

Robb Fisher is currently on watch-and-wait and is researching his diagnosis. He goes online and tries to filter all the information available to him. The night he learned he had FL, he spent four hours on a Google search and was “completely overwhelmed,” he says.

Lymphoma Canada believes that the implementation of an FL treatment guideline is a necessary step in patient support—just another way of helping patients like Fisher.

“Our objective is to support the standardization of information for follicular treatment options. With an FL treatment guideline in place, we believe that FL patients will feel comfortable in knowing that they are getting the best treatment nationally,” Robson says.
**TREANDA®**
(bendamustine HCl)
for Injection

**Prescribing Summary**

**Therapeutic Classification**
Antineoplastic agent

**Indications and Clinical Use**
TREANDA is indicated for treatment of patients with:

- Relapsed indolent B-cell non-Hodgkin lymphoma (NHL) with prior response to or progression during or shortly following treatment with a rituximab regimen.

**Effectiveness**

- The effectiveness of TREANDA in patients with indolent B-cell NHL is based on overall response rate and duration of response data from a single-arm pivotal study of TREANDA monotherapy in patients who had prior chemotherapy and did not respond to or progressed during or within 6 months of treatment with rituximab or a rituximab-based regimen (see Clinical Trials).

**Symptomatic chronic lymphocytic leukemia (CLL) who have received no prior treatment.**
- Approval of TREANDA in CLL is based on a progression-free survival and overall response rate advantage of TREANDA over chlorambucil in a single randomized controlled trial. Prolongation of overall survival or improvement in quality of life was not demonstrated for TREANDA in this study. Efficacy relative to first-line therapies other than chlorambucil has not been established.

**Geriatrics**

- In the NHL and CLL populations, there were no clinically significant differences in efficacy and in the adverse reaction profile between geriatric (≥65 years of age) and younger patients.

**Pediatrics**

- The safety and effectiveness of TREANDA in pediatric patients has not been established.

**Contraindications**

- **TREANDA is contraindicated in patients who are hypersensitive to bendamustine or to any ingredient in the formulation, including mannitol, or component of the container. For a complete listing, see Dosage Forms, Composition and Packaging section of the product monograph.**

**Special Populations**

- For use in special populations, see Warnings and Precautions, Special Populations.

**Warnings and Precautions**

**General**

- **TREANDA is not recommended for a subset of relapsed indolent NHL patients with poor tolerance to prior therapies (including other alkylating agents) as they would not be expected to tolerate the 120 mg/m² dose administered on days 1 and 2 of a 21-day cycle. The efficacy and safety of other dosing regimens for these patients has not been established.**

**Extravasation**

- There are post-marketing reports of bendamustine extravasations resulting in hospitalizations from erythema, maculopapular and pain. Precautions should be taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA.

**Carcinogenesis and Mutagenesis**

- Pre-malignant and malignant diseases have developed in patients treated with TREANDA including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. Bendamustine is mutagenic, genotoxic and carcinogenic with cancers reported following subcutaneous and oral delivery of the drug to mice (see Toxicology).

**Cardiovascular**

- Cardiac failure, myocardial infarctions, palpitations, anginal pectoris, arrhythmias, pericardial effusion and tachycardia have been reported in patients receiving bendamustine. Hypokalemia has also been reported in clinical trials. An increase in the excretion fraction of potassium and other electrolytes has been reported in non-clinical studies (see Detailed Pharmacology. Safety Pharmacology).

**Cardiac disorders**

- Serum potassium levels should be closely monitored in patients with cardiac disorders and ECG measurements should be performed where indicated (see Monitoring and Laboratory Tests).

**ECG Changes, including QTc prolongation**

- The potential for TREANDA to cause QTc prolongation has not been studied. Isolated cases of ECG changes have been observed in patients administered TREANDA at a dose higher than recommended for NHL and CLL patients (see Dosage and Administration. Overdose).

**Infections**

- In preclinical and in vitro cardiac safety studies, TREANDA inhibited HER2-1 tail current amplitude but had no effect on the cardiac action potential in isolated canine Purkinje fibers (see Detailed Pharmacology. Safety Pharmacology).

**Hypertension**

- In the Phase-III CLL study, there were 8 reports (5%) of grade 3 or 4 hypertension (3 reported as hypertensive crisis) in the TREANDA treatment group compared to 2 (1%) events (0 reported as hypertensive crisis) in the chlorambucil control arm (see Adverse Reactions. Clinical Trial Adverse Drug Reactions). Hypertension should be well-controlled prior to administration of TREANDA.

**Endocrine and Metabolism**

**Hepatic**

- Grade 3 or 4 elevations in bilirubin occurred in 3% of TREANDA-treated patients in the CLL study. Grade 3 or 4 increases in aspartate transaminase [AST] and alanine transaminase [ALT] occurred in 3% and 5% of CLL patients in the TREANDA treatment arm, respectively. One patient in the TREANDA arm of the study discontinued due to hepatotoxicity. If abnormalities are detected, liver function tests should be continued to ensure that significant deterioration does not occur (see Monitoring and Laboratory Tests).

**Immune**

**Infections**

- **TREANDA should not be administered to patients with serious infections, including patients with HIV. Infections, including pneumonia and sepsis, have been reported in patients in clinical trials and in post-marketing reports. Infections have been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections and should be advised to contact a physician if they have symptoms or signs of infection.**

**Cytomegalovirus (CMV) infections** were reported in 5% of patients in the NHL study (Grade 3: 4%; Grade 4; 0%). Patients should be informed about early signs and symptoms of CMV infection, including fever of unknown origin. The use of live attenuated vaccines should be avoided.

**Hepatic**

- **Zoster and should seek treatment as early as possible.**

**Sensitivity/Resistance**

**Infusion Reactions and Anaphylaxis**

- Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy.

**Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.**

**Sexual Function and Reproduction**

- Impaired spermatogenesis, azoospermia, and total seminal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances, spermatogenesis may return in patients in remission, but this will occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.
Skin
A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when TRENANDA was given in combination with other anticancer agents.

In a study of TRENANDA (90 mg/m²) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TRENANDA was administered with allopurinol and there may be an increased risk of severe skin toxicity when the two agents are administered concomitantly.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, TRENANDA should be withheld or discontinued.

Special Populations

Pregnant Women: TRENANDA can cause fetal harm when administered to a pregnant woman. Toxicology studies in mice and rats demonstrated that bendamustine is embryotoxic and teratogenic (see TOXICOLOGY). There are no adequate and well-controlled studies in pregnant women. TRENANDA is not recommended during pregnancy. If this drug is being used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Women or Men of Childbearing Potential: Women or men of childbearing potential should be advised to start using an effective method of contraception 2 weeks before receiving TRENANDA until at least 4 weeks after the last dose of the study medication.

Pediatrics (< 18 years of age): The safety and effectiveness of TRENANDA in pediatric patients have not been established.

Geriatrics (> 65 years of age): In CLL and NHL studies, there were no clinically significant differences in the adverse reaction profile between geriatric (> 65 years of age) and younger patients.

Renal Impairment: No studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. TRENANDA should be used with caution in patients with mild hepatic impairment total bilirubin > ULN - 1.5 x ULN or AST or ALT or ALP > ULN - 2.5 x ULN. TRENANDA should not be used in patients with moderate or severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations in Product Monograph). Patients with non-clinically significant elevations of bilirubin due to Gilbert's disease were eligible for clinical studies with TRENANDA.

Effect of Gender: No clinically significant differences between genders were seen in the overall incidences of adverse reactions in either CLL or NHL studies.

Monitoring and Laboratory Tests
Prior to initiating treatment with TRENANDA, complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function tests, electrolytes, blood pressure and hepatitis B testing should be performed and/or measured.

During treatment with TRENANDA, CBC and electrolytes should be measured at regular intervals and CBC more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). Patients and physicians should closely monitor for signs of infection and, in the case of fever of unknown origin, CMV testing should be performed. Signs of tumor lysis syndrome should be monitored where warranted. Periodic ECG monitoring should be performed in patients with cardiac disorders, particularly in the event of electrolyte imbalances. Monitoring of liver and renal functions, blood pressure and blood sugar should also be performed periodically.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Patients with B-cell indolent NHL received a higher and more frequent dose of bendamustine compared to CLL patients in the pivotal clinical trials. The adverse event profile for indolent B-cell lymphoma patients follows administration of a 120 mg/m² dose of bendamustine on days 1 and 2 of a 21-day cycle for up to a total of 8 cycles. Patients with CLL were administered a 100 mg/m² dose of bendamustine on days 1 and 2 of a 28-day cycle for a maximum of 6 cycles. Patients with small lymphocytic lymphoma (SLL) were enrolled into both the NHL and CLL clinical trials.

In the NHL study, the median total dose was 1410 mg/m² with a median duration of treatment of 107 days (range 2-233). In the CLL study, the median total dose was 1,010 mg/m² with a median duration of treatment of 142 days (range 2-231). Twenty-one of the 100 treated patients (21%) in the NHL study had SLL while 10 of 161 patients (6.2%) in the CLL study had SLL. There were 4 on-treatment deaths in the SLL subpopulation in the NHL study compared to none for the SLL subpopulation of the CLL study.

Hematologic laboratory abnormalities (see Tables 2 and 4) were more commonly identified as adverse events following administration of bendamustine in the NHL study compared to the CLL trial (see Tables 1 and 3). In both trials the most common hematological adverse events were neutropenia, thrombocytopenia, anemia and leucopekaemia.

The most common non-hematologic adverse events (> 30%) occurring in the NHL study were: nausea (77%), fatigue (64%), diarrhea (42%), vomiting (40%), pyrexia (36%) and constipation (31%). The most common non-hematologic Grade 3 or 4 adverse events (> 5%) were: fatigue (14%), febrile neutropenia (6%), anemia, pneumonia, hypokalaemia, diarrhea and dehydration, each reported in 5% of patients. Antiemetics were concomitantly administered to 96% of patients.

Serious adverse events, regardless of causality, were reported in 39% of NHL patients receiving TRENANDA. The most common serious adverse events occurring in > 5% of patients were febrile neutropenia and pneumonia. Other important serious adverse events reported were acute renal failure, cardiac failure, hypereosinophilia, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

Non-hematologic adverse events in the CLL study that occurred with a frequency of > 15% in the TRENANDA group were: nausea (25%), vomiting (19%), and constipation (19%). Antiemetics were taken concomitantly by 57% of patients in the bendamustine treatment group compared to only 4% in the chlorambucil control group.

The most common Grade 3 or 4 non-hematologic adverse events reported for the bendamustine treatment group in CLL were: pyrexia, pneumonia, infection, hyperuricemia, rash, hypertensive crisis (all each 2%) and hypertension (3%).

Clinical Trial Adverse Drug Reactions: See Supplemental Product Information for complete information

Non-Hodgkin Lymphoma (NHL)
The data described below reflect exposure to TRENANDA in 100 patients with indolent B-cell NHL treated in a single-arm pivotal study. These patients received TRENANDA at a dose of 120 mg/m² intravenously (i.v.) over 60 minutes on Days 1 and 2 for up to 8 21-day cycles.

Sixty-eight patients (68%) had adverse events causing dose reduction, interruption or discontinuation. The most common reason for dose delay was neutropenia. Thirty-one patients had adverse events with reported outcomes of discontinuance of study drug treatment. The most common events with this outcome were thrombocytopenia (9%), fatigue (6%) and neutropenia (4%). The treatment-emergent adverse events occurring in at least 5% of the NHL patients, regardless of severity and causality, are shown in Table 1.

Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA). The following clinically relevant adverse events were reported in < 5% of the patients treated with TRENANDA:

- Cardiac disorders: myocardial infarction (3%), cardiopericardial arrest (2%), sinus tachycardia (2%)
- General disorders and administration site conditions: infusion-related reaction (2%)
- Infections and infestations: cytomegalovirus infection (2%), sepsis/septic shock (2%)
- Metabolism and nutrition disorders: hyperkalemia (2%), hypoglycemia (3%), hypotension (3%)
- Neoplasms benign, malignant and unspecified: tumour lysis syndrome (2%), myelodysplastic syndrome (1%), anaplastic large T-cell lymphoma (1%), squamous cell carcinoma (1%)
- Renal and urinary disorders: acute renal failure (1%)
- Respiratory, thoracic and mediastinal disorders: respiratory failure (2%)
- Chronic Lymphocytic Leukemia (CLL)
The data described below reflect exposure to TRENANDA in 161 patients. TRENANDA was studied in an active-controlled trial. All patients started the study at a dose of 100 mg/m² intravenously over 30 minutes on Days 1 and 2 for up to 6 28-day cycles.

Table 2 contains the treatment emergent adverse events, regardless of attribution, that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA). Worsening hypertension was reported in 4 patients treated with TRENANDA in the randomized CLL clinical study and none treated with chlorambucil. Three of these 4 adverse events were described as a hypertensive crisis and were managed with oral medications and resolved. The most frequent adverse events leading to study withdrawal for patients receiving TRENANDA were hypersensitivity (2%), pyrexia (1%) and rash (1%).

The following clinically relevant adverse events were reported in < 5% of the patients treated with TRENANDA in the Phase-III randomized controlled trial:

- Cardiac disorders: myocardial infarction (< 1%), supraventricular arrhythmia (< 1%)
- Hepatobiliary disorders: hepatotoxicity (2%) Infections and infestations: sepsis/pseudomonal sepsis (1%)
- Investigations: bilirubin increased (2%)
- Metabolism and nutrition disorders: hyperglycemia (< 1%), hyperkalemia (< 1%), hypokalemia (< 1%)
- Neoplasms benign, malignant and unspecified: tumour lysis syndrome (1%), bronchial carcinoma (< 1%), lung neoplasm (< 1%)
Renal and urinary disorders: renal impairment (1%), acute renal failure (< 1%)

Respiratory, thoracic and mediastinal disorders: dyspnoea (2%), respiratory failure (< 1%)

Vascular disorders: hypertension (3%), hypertensive crisis (2%)

Post-Market Adverse Drug Reactions

The following adverse events have been identified during post-approval use of TREANDA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency; acute respiratory distress syndrome, anaphylaxis, and injection or infusion site reactions including phlebitis, pruritus, infiltration, pain, and swelling. Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications. (See WARNINGS AND PRECAUTIONS.)

Drug Interactions

Overview

No clinical assessments of pharmacokinetic drug-drug interactions between TREANDA and other drugs have been conducted. Bendamustine’s active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-beta-hydroxy bendamustine (M4) are formed via cytochrome P450 CYP1A2. There is a potential for CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin or inducers (e.g., omeprazole, smoking) to affect the circulating levels of bendamustine and its active metabolites. However, it is unknown if this will significantly impact the activity of bendamustine in patients. Caution should be used, or alternative treat-agents considered, if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

The role of active transport systems in bendamustine distribution such as P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and other transporters has not been evaluated. In vitro data suggest that bendamustine may be a substrate for P-glycoprotein. Based on in vivo data, bendamustine is not likely to inhibit metabolism via human CYP isoenzymes CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Administration

Dosage and Administration

Dosing Considerations

TREANDA administration should be delayed in the event that non-hematologic toxicity has recovered to Grade 2 non-hematologic toxicity. Once non-hematologic Toxicity is discovered, TREANDA can be restarted at the discretion of the treating physician when any non-hematologic toxicity, including phlebitis, pruritus, infiltration, pain, and swelling. Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications. (See WARNINGS AND PRECAUTIONS.)

Recommended Dose and Dosage Adjustment

Dosing Instructions for NHL

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture can be used within 24 hours when stored refrigerated (2-8°C) or within 3 hours when stored room temperature (15-30°C) and room light. Administration of TREANDA must be completed within this period.

Oversdosage

Across all clinical experience, the reported maximum single dose received was 280 mg/m². Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients. No specific antidote for TREANDA overdosage is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

For management of a suspected drug overdosage, contact your regional Poison Control Centre.

Study Reference

Supplemental Product Information

Clinical Trial Adverse Drug Reactions

Non-Hodgkin Lymphoma (NHL)

TABLE 1: Adverse Events Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Number (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3/4</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic systems disorders</td>
<td>Neutropenia</td>
<td>45 (45)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>37 (37)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>42 (42)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>40 (40)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>31 (31)</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>21 (21)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14 (14)</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>14 (14)</td>
</tr>
<tr>
<td></td>
<td>Gastrooesophageal reflux disease</td>
<td>11 (11)</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>9 (9)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>5 (5)</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>36 (36)</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>14 (14)</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>14 (14)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>13 (13)</td>
</tr>
<tr>
<td></td>
<td>Infusion site pain</td>
<td>7 (7)</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>9 (9)</td>
</tr>
<tr>
<td></td>
<td>Thirst</td>
<td>6 (6)</td>
</tr>
<tr>
<td></td>
<td>Catheter site pain</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>
TABLE 1 (cont’d): Adverse Events Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Number (%) of patients*</th>
<th>TREANDA (N=161)</th>
<th>Chlorambucil (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Herpes zoster</td>
<td>12 (12)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>11 (11)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>9 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>9 (9)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>9 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>8 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngolaryngeal pain</td>
<td>10 (10)</td>
<td>1 (&lt; 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>16 (16)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Anxiety</td>
<td>8 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>13 (13)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>15 (15)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>15 (15)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td>16 (16)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>17 (17)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>16 (16)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngolaryngeal pain</td>
<td>10 (10)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal congestion</td>
<td>5 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>15 (15)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
<td>7 (7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>6 (6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperhidrosis</td>
<td>5 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td>8 (8)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients may have reported more than 1 adverse event.

NOTE: Patients counted only once in each preferred term category and once in each system organ class category.

Chronic Lymphocytic Leukemia (CLL)

Table 2: Adverse Events Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Number (%) of patients*</th>
<th>TREANDA (N=161)</th>
<th>Chlorambucil (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Total number of patients with at least 1 adverse event</td>
<td>143 (89)</td>
<td>88 (55)</td>
<td>123 (81)</td>
<td>49 (32)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>44 (27)</td>
<td>21 (14)</td>
<td>14 (9)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>37 (23)</td>
<td>19 (13)</td>
<td>12 (8)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>30 (19)</td>
<td>4 (2)</td>
<td>19 (13)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>28 (17)</td>
<td>5 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>10 (6)</td>
<td>1 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>31 (19)</td>
<td>1 (&lt; 1)</td>
<td>21 (14)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>25 (16)</td>
<td>2 (1)</td>
<td>10 (7)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>16 (10)</td>
<td>2 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>40 (25)</td>
<td>2 (1)</td>
<td>8 (5)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>14 (9)</td>
<td>0</td>
<td>8 (5)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>13 (8)</td>
<td>0</td>
<td>6 (4)</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>9 (6)</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hyperreactivity</td>
<td>8 (5)</td>
<td>2 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>Infections and infestations</td>
<td>11 (7)</td>
<td>0</td>
<td>12 (8)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>10 (6)</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>5 (3)</td>
<td>0</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>10 (6)</td>
<td>0</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>12 (7)</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
<td>12 (7)</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>10 (6)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>15 (9)</td>
<td>4 (2)</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>8 (5)</td>
<td>0</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

TABLE 3: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA in the NHL Study

<table>
<thead>
<tr>
<th>Hematology variable</th>
<th>Number (%) of patients*</th>
<th>TREANDA (N=161)</th>
<th>Chlorambucil (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>96</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Leukocytes decreased</td>
<td>92</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>94</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>83</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>88</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Chronic Lymphocytic Leukemia (CLL)

The Grade 3 and 4 hematologic laboratory test values by treatment group in the randomized CLL clinical study are described in Table 4.

These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

TABLE 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA or Chlorambucil in the Randomized CLL Clinical Study

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TREANDA (N=158)</th>
<th>Chlorambucil (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>141 (89)</td>
<td>21 (13)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>122 (77)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Leukocytes decreased</td>
<td>98 (62)</td>
<td>44 (28)</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>109 (69)</td>
<td>77 (49)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>119 (75)</td>
<td>67 (42)</td>
</tr>
</tbody>
</table>

In the randomized CLL clinical study, 34% of TREANDA-treated patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels.

STORAGE AND STABILITY

TREANDA may be stored at 2-25°C, with excursions permitted up to 30°C. Retain in original package until time of use to protect from light.

SPECIAL HANDLING INSTRUCTIONS

As with other toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TREANDA contains 25 mg or 100 mg benzamidine hydrochloride. Non-medicinal ingredient: mannitol.

TREANDA is supplied as a sterile lyophilized powder for injection as 25 mg in 8 mL amber single-use vials and 100 mg in 20 mL amber single-use vials.

Product Monograph available at www.lundbeck.ca
In Supportive Care Oncology

CAnAdiAn Vision for onCology

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LYMPHOMAS
Combining New Targeted Therapies with Standard Treatments for NHL
Lymphoma Canada: Canadian Guideline Needed for the Treatment of FL

Targeting Patient Fitness Expanding Treatment Approaches

INSIDE THIS ISSUE

Interviews with Dr. Goede, Dr. Lo-Coco, Dr. Owen, Dr. Prchal, Dr. Schin, and Dr. Wendtner