Inside This Issue

Multiple Myeloma
New and Diverse Therapies Provide Effective Treatment Options

Lymphomas
Advances in Treatments for Lymphoma Subtypes Improve Patient Outcomes

Leukemias
Novel and Standard Treatments Benefit Hard-to-Treat Patients

Lung Cancer
Targeted Agents in Second-Line Treatment of Squamous Cell Carcinoma of the Lung

Interviews with Dr. Assouline, Dr. Berinstein, Dr. Chamakhi, Dr. Cramer, Dr. Fraser, Dr. Hirsh, Dr. Isidori, Dr. Johnson, Dr. LeBlanc, Dr. Lonial, Dr. Owen, Dr. Seftel, and Dr. Sehn

This issue includes a paper reviewing the latest available treatments for CLL
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 October 2015 issue presents coverage from the following key conferences: the 7th Annual Canadian Conference on Lymphoproliferative Disorders (CCOLD), the 2015 Annual Meeting of the American Society of Clinical Oncology (ASCO), the 20th Congress of the European Hematology Association (EHA), and the 13th International Conference on Malignant Lymphoma (ICML). This issue reports on key clinical trials evaluating the treatment of multiple myeloma, chronic lymphocytic leukemia, acute promyelocytic leukemia, lymphoma, and squamous cell carcinoma of the lung. The latest therapies — with new mechanisms of action — and optimal combination regimens are creating hope for patients who are harder to treat with conventional therapies. We would like to thank Dr. Sarit Assouline, Dr. Neil Berinstein, Dr. Ines Chamakhi, Dr. Graeme Fraser, Dr. Vera Hirsh, Dr. Nathalie Johnson, Dr. Richard LeBlanc, Dr. Matthew Seftel, and Dr. Laurie Sehn for their Canadian Perspectives and Dr. Paula Cramer, Dr. Alessandro Isidori, Dr. Sagar Lonial, Dr. Carolyn Owen, and Dr. Laurie Sehn and for their Investigator Commentaries. This issue also includes a paper reviewing the latest treatments for patients with chronic lymphocytic leukemia, with contributions from Dr. Carolyn Owen, Dr. Sarit Assouline, Dr. John Kuruvilla, Dr. David MacDonald, and Dr. Laurie Sehn.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research.
Contents

MULTIPLE MYELOMA

Treatment of Relapsed Patients: Current Challenges and Novel Agents

10
• Phase II study of daratumumab in patients with ≥3 lines of prior therapy or double-refractory MM (54767412MMY2002—Sirius). (Lonial S, et al. ASCO 2015:LBA8512)
• Multiple myeloma: practice patterns across Europe. (Raab MS, et al. EHA 2015:P647)

Investigator Commentary

18
An Interview with Dr. Sagar Lonial on the MMY2002 Study

Canadian Perspective

21
An Interview with Dr. Richard LeBlanc on the MMY2002 Study

CHRONIC LEUKEMIA

Novel Agents and New Combination Therapies in the Treatment of CLL

23

Investigator Commentary

30
An Interview with Dr. Paula Cramer on the HELIOS Study

Canadian Perspective

34
An Interview with Dr. Graeme Fraser on the HELIOS Study

• Results of a phase III trial evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL (Study 119). (Jones JA, et al. ASCO 2015:7023)

Investigator Commentary

41
An Interview with Dr. Carolyn Owen on Study 119

Canadian Perspective

45
Interviews with Dr. Laurie Sehn, Dr. Neil Berinstein, and Dr. Sarit Assouline on Study 119

• Long-term follow-up of a phase Ib trial of idelalisib in combination with chemoimmunotherapy in patients with relapsed/refractory CLL. (Barrientos JC, et al. ASCO 2015:7011)
• Adherence and dose intensity following administration of the ibrutinib 420 mg dose in patients with previously treated CLL. (Barr PM, et al. ASCO 2015:7012 & Jaeger U, et al. EHA 2015:S435)
• Phase III study of ibrutinib plus obinutuzumab versus chlorambucil


• Outcomes of anticoagulant or antiplatelet use in patients with CLL or iNHL in idelalisib trials. (Barrientos JC, et al. ASCO 2015:8563 & Stilgenbauer S, et al. EHA 2015:e1064)

• Nonmyeloablative allogeneic conditioning with bendamustine, fludarabine, and rituximab improves survival in CLL. (Khouri IF, et al. ICML 2015:056)

CCOLD Summaries

65
Fit vs. Frail Assessment Strategies in CLL: Summary of the Presentation by Dr. Alina Gerrie at CCOLD 2015

71
Frontline Management of the CLL Patient: Summary of the Presentation by Dr. Clemens Wendtner at CCOLD 2015

Review Article

78
New Treatment Perspectives in CLL: Using Disease and Patient Characteristics to Optimize Outcomes

Carolyn Owen MD, Sarit Assouline MD, John Kuruvilla MD, David MacDonald MD, Anna Christofides MSc RD, Sarah Di Clemente MSc, Laurie Sehn MD

ACUTE LEUKEMIA

Acute Promyelocytic Leukemia

Chemo-Free or Chemo-Reduced Therapy is Effective and Safe in APL for Different Risk Groups

87

• APL of all risk groups is highly curable with a chemo-free combination of attenuated arsenic trioxide and ATRA. (Burnett AK, et al. EHA 2015:LB2067)

• Safety and tolerability of ATRA plus arsenic trioxide plus gemtuzumab ozogamicin in high-risk APL: initial report of the SWOG/Alliance/ECOG S0535 trial. (Lancet JE, et al. ASCO 2015:7016)


Canadian Perspective

96
An Interview with Dr. Matthew Seftel on the AML17 Study
Advances in Single-Agent and Combination Therapies for the Treatment of Non-Hodgkin and Hodgkin Lymphomas

100
Non-Hodgkin Lymphoma


Investigator Commentary

108
An Interview with Dr. Laurie Sehn on the GADOLIN Study

Canadian Perspective

111
An Interview with Dr. Nathalie Johnson on the GADOLIN Study


• Final results of a phase I study on the use of bendamustine, rituximab, and lenalidomide in the treatment of relapsed/refractory low-grade NHL. (Nowakowski GS, et al. ASCO 2015:8540)

• Rituximab, bendamustine, and lenalidomide in patients with aggressive B-cell lymphoma ineligible for anthracycline-based first-line therapy or an intensive salvage regimen. (Hitz F, et al. ICML 2015:015)


Follicular Lymphoma

125

• Idelalisib efficacy and safety in patients with follicular lymphoma from a phase II study. (Zinzani PL, et al. EHA 2015:P689)

• Evaluation of complete response rate at 30 months as a surrogate endpoint for PFS in first-line follicular lymphoma studies: analyses of patient data from the FLASH database. (Sargent DJ, et al. ASCO 2015:8504)

• Two doses of polatuzumab vedotin in patients with relapsed/refractory follicular lymphoma: durable responses at the lower dose level. (Advani RH, et al. ASCO 2015:8503)

• A phase III study of ibrutinib in combination either with bendamustine and rituximab or with R-CHOP in patients with previously treated FL or MZL. (Fowler N, et al. ASCO 2015:TPS8601)

• Phase II study of venetoclax in combination with bendamustine and rituximab (BR) versus BR alone or venetoclax in combination with rituximab in relapsed/refractory FL. (Hiddemann W, et al. ICML 2015:OT04)

Mantle Cell Lymphoma

141

• Lenalidomide, rituximab, and bendamustine in first line for patients >65 years old with MCL: final results of the Nordic Lymphoma Group MCL4 phase I/II trial. (Albertsson-Lindblad A, et al. ICML 2015:060)

• Rituximab, lenalidomide, and bendamustine as second-line therapy for relapsed or refractory MCL: a phase II study. (Zaja F, et al. ICML 2015:014)

• Rituximab, bendamustine, and cytarabine (RBAC500) as induction therapy in elderly patients with mantle cell lymphoma: a phase II study. (Visco C, et al. ICML 2015:059)

• Results of a randomized phase II trial of R-Hyper-CVAD versus bendamustine and rituximab followed by consolidation with ASCT in previously untreated patients with MCL. (Chen R, et al. ICML 2015:062)
CCOLD Summary

155
New Developments in Mantle Cell Lymphoma: Summary of the Presentation by Dr. Mathias Rummel at CCOLD 2015

Diffuse Large B-cell Lymphoma

162
- Benda-EAM high-dose therapy prior to ASCT is effective in resistant/relapsed DLBCL: a phase II multicentre study. (Isidori A, et al. EHA 2015:P353)
- Bendamustine in combination with rituximab in elderly frail patients with newly diagnosed DLBCL. (Storti S, et al. EHA 2015:P328)

Investigator Commentary

167
An Interview with Dr. Alessandro Isidori on Preliminary Results from the Benda-EAM Study

Canadian Perspective

170
A Canadian Perspective on DLBCL Treatment by Dr. Ines Chamakhi

Waldenström Macroglobulinemia

171
- Idealalisib monotherapy results in durable responses in patients with relapsed or refractory Waldenström macroglobulinemia. (Coutre S, et al. ASCO 2015:8532)
- A phase III study of rituximab with or without ibrutinib in patients with Waldenström macroglobulinemia. (Dimopoulos MA, et al. ASCO 2015:TPS8599)

Hodgkin Lymphoma

177
- Bendamustine-containing regimen (BeGeV) as induction chemotherapy prior to ASCT for relapsed/refractory Hodgkin lymphoma. (Mazza R, et al. EHA 2015:S806)

LUNG CANCER

Squamous Cell Lung Carcinoma

Targeted Agents in Second-Line Treatment of SCC of the Lung

183
- CheckMate 017: a phase III study of nivolumab versus docetaxel in previously treated advanced or metastatic squamous cell non-small-cell lung cancer. (Spigel DR, et al. ASCO 2015:8009)

Canadian Perspective

194
An Interview with Dr. Vera Hirsh on LUX-Lung 8

General Overview

196
Contributors

Canadian Perspectives

Sarit Assouline, MD, MSc
Dr. Sarit Assouline is a hematologist at the Jewish General Hospital in Montreal, Quebec, and an Associate Professor in the Department of Medicine and Oncology at McGill University. She received her medical degree from McGill University and completed residencies at both McGill University and the University of Toronto. Dr. Assouline has a master’s degree in epidemiology and biostatistics from McGill University and completed a fellowship in drug development at the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) at Queen’s University in Kingston, Ontario. Her research interests are in the clinical development of new therapies for the treatment of leukemia and lymphoma.

Neil Berinstein, MD
Dr. Neil Berinstein earned his pre-medical degree and Medical Doctorate from the University of Manitoba and received further specialty and research training at the University of Toronto and Stanford University.

Dr. Berinstein currently holds multiple academic and professional positions, including as a Professor in the Department of Medicine at the University of Toronto, and he is on the active staff of the Hematology Oncology Site Group at the Odette Cancer Centre of the Sunnybrook Health Sciences Centre. He is currently the Director of Translational Research at the Ontario Institute for Cancer Research.

Dr. Berinstein specializes in the management and research of patients with lymphoproliferative disorders, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, Hodgkin lymphoma, and myeloma. Dr. Berinstein has received numerous grants throughout his career for his research, which focuses on the development of novel immunotherapeutic and targeted approaches for cancer and hematologic malignancies. He has published six book chapters and over 100 peer-reviewed, invited, or review papers.

Ines Chamakhi, MD, FRCPC
Dr. Ines Chamakhi is currently a hematologist and a medical oncologist at the Sacré-Coeur Hospital in Montreal and a Clinical Assistant Professor at the University of Montreal. She completed her post-graduate training in internal medicine, hematology, and medical oncology at the University of Montreal. Dr. Chamakhi also completed a clinical fellowship in malignant hematology at the Peter McCallum Cancer Centre in Melbourne, Australia. She serves as the Director of the Medical Biology Department at the Sacré-Coeur Hospital and is also a local principal investigator for several non-Hodgkin lymphoma and chronic lymphocytic leukemia trials.
Graeme Fraser, MD, MSc, FRCPC

Dr. Graeme Fraser graduated from the University of Western Ontario (UWO) and completed post-graduate training in Internal Medicine and Hematology at UWO and McMaster University, respectively. His training in malignant hematology was supported by a National Cancer Institute of Canada-Terry Fox Foundation Clinical Research Fellowship. Dr. Fraser is a hematologist at the Juravinski Cancer Centre/Hamilton Health Sciences in Hamilton, Ontario, and he is an Associate Professor in the Department of Oncology. His research interests include the care of adolescent and young adult cancer patients, clinical trials in chronic lymphocytic leukemia, lymphoma, and myeloma, and practice guideline development as a member of the Cancer Care Ontario Program in Evidence-Based Care.

Vera Hirsh, MD, FRCPC

Dr. Vera Hirsh, who currently practices in both hematology and oncology, is a Professor in the Department of Oncology at McGill University and Chief of the Hematology-Oncology Service at Santa Cabrini Hospital in Montreal. Her research at the Quebec Pulmonary Unit focuses on the treatment of lung cancer, and she continues to chair ongoing international chemotherapy trials. Dr. Hirsh chaired the Quebec Lung Cancer Committee to establish guidelines for the treatment of lung cancer. In addition, she has published many abstracts, articles, and book chapters. Dr. Hirsh is a member of advisory boards for many pharmaceutical companies and the Medical Oncology Standing Committee of the Radiation Therapy Oncology Group (RTOG).

Nathalie Johnson, MD, PhD

Dr. Nathalie Johnson completed her clinical training in Hematology and Oncology at McGill University. In 2010, she also completed a Ph.D. in Pathology at the British Columbia Cancer Agency, which focused on biomarkers associated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) resistance in diffuse large B-cell lymphoma. Dr. Johnson is currently an Assistant Professor in the Department of Medicine and Oncology at McGill University and a Clinician Scientist at the Jewish General Hospital in Montreal. She is the hematologist at the McGill Oncology Adolescent and Young Adult (AYA) clinic, where she addresses the needs of AYA patients with lymphoma. Her research focuses on investigating biomarkers for resistance and response to conventional and novel therapies in patients with relapsed or refractory lymphoma.

Richard LeBlanc, MD

Dr. Richard LeBlanc is a hematologist and medical oncologist at Hôpital Maisonneuve-Rosemont in Montreal, Quebec. He is also a Clinical Assistant Professor of Medicine at the University of Montreal. Dr. LeBlanc obtained his medical degree at Laval University and is certified in internal medicine, hematology, and medical oncology. He worked as a research fellow at the Dana Farber Cancer Institute in Boston from 2000 to 2002. Dr. LeBlanc was recruited by Hôpital Maisonneuve-Rosemont in Montreal to help improve medical care, research, and teaching in multiple myeloma.

Dr. LeBlanc is the Chair Holder of the Myeloma Canada Chair at the University of Montreal. He is the Director of the Myeloma Cell Bank at Hôpital Maisonneuve-Rosemont, affiliated with the Quebec Leukemia Cell Bank. He is also the Medical Chief of the clinical immunology laboratory at Hôpital Maisonneuve-Rosemont. Finally, Dr. LeBlanc is a member of the scientific advisory board of Myeloma Canada.
Contributors (Cont.)

Canadian Perspectives

Matthew Seftel, MD, MPH, MRCP, FRCPC

Dr. Matthew Seftel is the Department Head of Hematology and Oncology at CancerCare Manitoba and the Section of Hematology/Oncology, Department of Internal Medicine at the University of Manitoba in Winnipeg, Manitoba. He is also an Associate Professor at the University of Manitoba. Dr. Seftel’s research interests include leukemia epidemiology and clinical trials in leukemia and lymphoma (including blood and marrow transplantation). He is an investigator with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Centre for International Blood and Marrow Transplant Research (CIBMTR).

Laurie H. Sehn, MD, MPH

Dr. Laurie H. Sehn is a Clinical Assistant Professor at the BC Cancer Agency and the University of British Columbia in Vancouver. She has been a medical oncologist and clinical investigator with the Lymphoma Tumour Group since 1998. Dr. Sehn has served on the Board of Directors of Lymphoma 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.

Investigator Commentaries

Paula Cramer, MD

After Dr. Paula Cramer received her medical degree from the University of Cologne in 2008, she started her fellowship in Internal Medicine, Haematology and Oncology at the University Hospital of Cologne, Germany. During her medical studies, she joined the German CLL Study Group, chaired by Professor Dr. Michael Hallek. Since then Dr. Cramer has worked on several clinical trials for patients with chronic lymphocytic leukemia. Currently, she is responsible for several phase II protocols evaluating novel agents, such as ibrutinib, idelalisib, and ABT-199, together with an anti-CD20 antibody in sequential treatment. Dr. Cramer is also the German Principal Investigator for the Helios study, a phase III trial evaluating the addition of ibrutinib to bendamustine and rituximab. Her special interest is the evaluation of combinations of novel agents and the use of clinical and biological prognostic markers for the definition of risk groups and guidance in treatment decisions.
Alessandro Isidori, MD, PhD

Dr. Alessandro Isidori is an attending physician in the Division of Hematology and Stem Cell Transplant Centre at San Salvatore Hospital, Italy. He graduated magna cum laude from the Bologna University School of Medicine in 1999. In 2004, he obtained his specialization in Hematology and Medical Oncology at the Bologna University School of Medicine, after a seven-year internship at the Institute of Hematology and Medical Oncology “Seragnoli”. Finally, he got his Ph.D. in Experimental and Clinical Hematology in 2007 at the Bologna University School of Medicine. He is mainly involved in clinical trials for the treatment of chronic and acute leukemias, lymphomas, and stem cell mobilization and transplantation. He has worked extensively in the area of cell therapy at the Centre for Stem Cell Research of the Bologna University. He is co-author of 70 publications in peer-reviewed journals, more than 200 abstracts, and five book chapters on hematological malignancies. He is a member of the American Society for Blood and Marrow Transplantation (ASBMT), the European Hematology Association (EHA), the American Society of Hematology (ASH), and the American Association for Cancer Research (AACR). He is also a member of the editorial board of the following medical journals: *Leukemia Research and Treatment, American Journal of Blood, World Journal of Stem Cells, and World Journal of Transplantation.*

Sagar Lonial, MD

Dr. Sagar Lonial is a Professor in the Department of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University, where he is also Vice Chair of Clinical Affairs for the department and Director of the Translational Research for the B-Cell Malignancy Program. He earned his medical degree from the University of Louisville School of Medicine. He completed his internship and residency at Baylor College of Medicine in Houston, Texas, followed by a fellowship in Hematology/Oncology at Emory University School of Medicine in Atlanta, Georgia. Dr. Lonial’s clinical interests include evaluating the combination of new molecular targeted agents for B-cell tumours as well as target discovery and validation. In addition, he serves on the editorial board of the *Journal of Clinical Oncology, Leukemia,* is the myeloma editor for *Clinical Lymphoma, Myeloma, and Leukemia,* and is an invited or ad hoc reviewer for several publications, including *Blood, Haematologica, Clinical Cancer Research, The New England Journal of Medicine,* and others. Dr. Lonial has authored or co-authored over 200 publications and recently was awarded the Celgene ‘Young Investigator’ Award, the Multiple Myeloma Research Foundation ‘Top 15 Innovator’ Award, and the Multiple Myeloma Research Consortium ‘Center of the Year’ Award.

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.

Laurie H. Sehn, MD, MPH

Dr. Laurie H. Sehn is a Clinical Assistant Professor at the BC Cancer Agency and the University of British Columbia in Vancouver. She has been a medical oncologist and clinical investigator with the Lymphoma Tumour Group since 1998. Dr. Sehn has served on the Board of Directors of Lymphoma 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.
Multiple Myeloma

Treatment of Relapsed Patients: Current Challenges and Novel Agents

Multiple myeloma (MM) is the second most common hematologic malignancy in Canada, with an overall age-standardized incidence rate of 5.1 cases/100,000 people, accounting for 1.2–1.5% of all new cancers and 1.7–1.8% of deaths from cancer in 2015. Although novel therapeutic agents such as proteasome inhibitors (PIs) (e.g., bortezomib) and immunomodulatory drugs (IMiDs) (e.g., thalidomide and lenalidomide) have improved the length of survival for patients with MM, the disease remains incurable and patients will eventually relapse. In addition, many patients will become refractory to prior therapies, thus further limiting their treatment options. Options for salvage therapy may include treatment with next generation drugs (e.g., carfilzomib [PI] and pomalidomide [IMiD]) or different alkylalting agents (e.g., bendamustine). New classes of agents with different mechanisms of action are also being investigated in patients with relapsed MM, such as daratumumab, an anti-CD38 human monoclonal antibody that binds to CD38-expressing malignant cells and induces cell death through multiple pathways.

With multiple new agents available for patients with relapsed MM, and numerous different combination therapies to choose from, it is difficult for physicians to know which treatment approach will be the most suitable for individual patients based on the available evidence. Therefore, current goals in relapsed MM are to optimize combination regimens, determine the optimal sequencing of treatment, and investigate novel agents.

Here we report the results of two studies, presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting and the 20th Congress of the European Hematology Association (EHA), which are working towards these goals:

- In the international phase II MMY2002 study, single-agent daratumumab demonstrated impressive response rates in heavily pretreated and refractory patients with MM who have exhausted other therapeutic options. (Lonial S, et al. ASCO 2015:LBA8512)
- A cross-sectional and retrospective patient chart review of patients with MM in seven European countries demonstrated that the treatment regimens prescribed for patients with MM are diverse within the same country and across Europe, confirming that the optimal sequence of treatments has not been established. (Raab MS, et al. EHA 2015:P647)

In Supportive Care Oncology

**Background**

At ASCO 2015, results were presented for the MMY2002 study, which examined the efficacy and safety of single-agent daratumumab in heavily pretreated and refractory patients with multiple myeloma (MM).1

**Study design**

- This is an ongoing open-label, international, multicentre, phase II study.
- Patients were eligible for the study if they had:
  - Received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or were refractory to their most recent PI and IMiD irrespective of the number of prior lines of therapy;
  - Documented MM with disease progression on the most recent treatment;
  - Eastern Cooperative Oncology Group performance status of ≤2;
  - Absolute neutrophil count >1 x 10^9/L;
  - Hemoglobin >7.5 g/dL;
  - Platelet count ≥50 x 10^9/L; and
  - Creatinine clearance >20 mL/min/1.73 m².
- Patients were initially randomized 1:1 to receive either daratumumab at 8 mg/kg every 4 weeks or 16 mg/kg every week for 8 weeks, followed by every 2 weeks for 16 weeks, and then every 4 weeks thereafter.
- The 16 mg/kg dose was established as the recommended dose for further study.
- The primary endpoint of the study was overall response rate (ORR) as assessed by an independent review committee.
- Secondary endpoints included progression free-survival (PFS), overall survival (OS), duration of response (DOR), time to response (TTR), clinical benefit rate (ORR + minimal response [MR]), and safety.

**Key findings**

- This analysis was performed on the 106 patients treated with the 16 mg/kg dose of daratumumab, 16 (15%) of whom remained on the study at data cut-off.
- In this population, the median time since diagnosis was 4.8 years (range: 1–24) and the median number of prior lines of therapy was 5 (range: 2–14).
- Most patients were refractory to their last lines of PI and IMiD therapy (95%), 77% were refractory to alkylating agents, and 66% were refractory to three of four agents including bortezomib, lenalidomide, carfilzomib, and pomalidomide.
- Discontinuations from the study were predominantly due to disease progression (82 patients, 77%).
- The majority of patients had reductions in paraprotein from baseline; including 40 patients (38%) with reductions >50% and 17 patients (16%) with reductions >90%.
- The ORR for patients receiving 16 mg/kg of daratumumab was 29% (95% confidence interval [CI]: 21–39%). (Figure 1)
  - A stringent complete response (sCR) was achieved in 3% of patients (95% CI: 0.6–8.0%);
  - Very good partial response (VGPR) or better was achieved in 12% of patients (95% CI: 7–20%); and

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**Phase II study of daratumumab in patients with ≥3 lines of prior therapy or double-refractory multiple myeloma (54767412MMY2002—Sirius)**

**Study design**

<table>
<thead>
<tr>
<th>Randomization</th>
<th>16 mg/kg (n = 16)*</th>
<th>8 mg/kg (n = 18)*</th>
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<tr>
<td>Response evaluated</td>
<td></td>
<td>Additional 90 patients enrolled at 16 mg/kg daratumumab</td>
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<tr>
<td>16 mg/kg (n = 106)</td>
<td>Daratumumab 16 mg/kg every week for 8 weeks, followed by every 2 weeks for 16 weeks, and then every 4 weeks thereafter.</td>
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<tr>
<td>8 mg/kg (n = 18)</td>
<td>Daratumumab 8 mg/kg every 4 weeks.</td>
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Figure 1. Overall response rate

![Figure 1. Overall response rate]

ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

Figure 2. Overall response rate by subgroup

![Figure 2. Overall response rate by subgroup]

BORT = bortezomib; CARF = carfilzomib; CrCl = creatinine clearance; IMiDs = immunomodulatory drugs; LEN = lenalidomide; ORR = overall response rate; PIs = proteasome inhibitors; POM = pomalidomide

Figure 3. Progression-free and overall survival

![Figure 3. Progression-free and overall survival]

CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression-free survival
The clinical benefit rate (ORR + MR) was 34% (CI: 25–44%).

• The ORR was consistent across all clinically relevant subgroups analyzed. (Figure 2)

• At a median follow-up of 9.3 months, the median TTR among responders was 1 month and the median DOR was 7.4 months (95% CI: 5.5–not estimable [NE]).

• The initial response deepened with continued daratumumab treatment in many patients.

• The median PFS was 3.7 months (95% CI: 2.8–4.6) and the median OS has not been reached. (Figure 3)

• The estimated 1-year OS rate was 65% (95% CI: 51.2–75.5%).

• Of the 31 patients who responded, 29 patients are still alive.

• Infusion-related reactions (IRRs) were reported in 43% of patients.

• Most IRRs occurred during the first infusion (>90%) and these were predominantly grade 1 or 2 in severity, with only 5% experiencing a grade 3 IRR and no patients experiencing a grade 4 IRR.

• Seven percent of patients had an IRR at more than one infusion.

• The most common IRRs included nasal congestion (12%), throat irritation (7%), cough, dyspnea, chills, and vomiting (6% each).

• Other common treatment-emergent adverse events (TEAEs) of any grade included fatigue (40%), anemia (33%), nausea (29%), thrombocytopenia (26%), neutropenia (23%), back pain (22%), and cough (21%).

• Serious TEAEs occurred in 32 patients (30%) and 24 patients (23%) experienced grade 3/4 serious TEAEs, however, there were no discontinuations due to daratumumab-related AEs.

• Few patients required additional supportive care such as red blood cell transfusions (38%), platelet transfusions (13%), and granulocyte colony-stimulating factor (8%).

Key conclusions

■ Daratumumab has demonstrated remarkable single-agent activity in heavily pretreated and refractory MM patients who have exhausted other therapeutic options.

■ The responses to daratumumab were rapid, durable, and deepened over time and were consistent across all subgroups.

■ Daratumumab was well tolerated, with no patients having to discontinue treatment due to daratumumab-related AEs.

■ Daratumumab represents a new standard of care in this relapsed/refractory MM setting.


Raab MS, et al. EHA 2015:P647

Multiple myeloma: practice patterns across Europe

Background

At EHA 2015, results were presented from a cross-sectional patient chart review study which investigated the management of patients with symptomatic multiple myeloma (MM).1

Study design

• This study surveyed patients in seven European countries (Belgium, France, Germany, Italy, Spain, Switzerland, and the U.K.).

• Physicians completed three research components: a questionnaire, a cross-sectional patient chart review, and a retrospective patient chart review.

• The questionnaire ensured physicians met eligibility criteria (managed at least 10 patients with MM per month, had ≥3 years clinical practice experience, and were personally responsible for the initiation of treatments in MM).

• The cross-sectional patient chart review collected basic patient characteristics and current treatment in a short case report form for every patient seen during a predefined time period.

• Physicians included all patients seen during a 2–4 week observation period, regardless of the patient’s treatment status.

• Physicians with large caseloads had 2 weeks to
collect data, and physicians with smaller caseloads had 4 weeks to collect data.

- Patients were only included once during the observation period.
- The retrospective patient chart review included detailed case report forms for 12 patients (14 patients in the U.K.) seen during the previous 3 months who had completed specific lines of treatment.
- Data collected included patient characteristics at diagnosis and at the start and end of the most recently completed line of anti-tumour drug treatment.
- Quotas were defined by line of therapy to ensure sufficient sample size in later lines.
- Patient data from the cross-sectional phase were weighted by probability of inclusion in the study using the date of the next scheduled consultation in order to adjust for potential selection bias due to the frequency of a patient’s visits.
- The final pooled analysis was adjusted for country contribution size.

Key findings

- A total of 435 physicians completed 7,635 cross-sectional patient chart reviews and 4,997 retrospective patient chart reviews.
- The majority of physicians were hematologists (60%) or onco-hematologists (32%).
- The median age at diagnosis of patients diagnosed in the past 12 months was 68 years.

Cross-sectional patient chart review:

- Most patients (62%) were ≥65 years and the median time since diagnosis was 33 months.
- Patient characteristics were similar across countries except Spain, where fewer patients had International Staging System stage III MM (24%).

- Forty-seven percent (n = 3,559) of patients with symptomatic MM were undergoing anti-tumour treatment, 42% (n = 3,187) were not undergoing anti-tumour treatment but had previously received one or more lines of therapy, and 12% (n = 890) had not yet received anti-tumour therapy. (Figure 1)
- Reasons for patients not currently being treated were: in remission/stabilized (60%), completion of planned cycles (38%), drug holiday (5%), poor overall state of patient (4%), patient refusal (3%), and renal issues (1%).
- Table 1 shows the treatment received by patients in the first-line setting and beyond.
- Bortezomib-based regimens were most commonly used in the first-line setting (48%) overall, except in the U.K. where thalidomide-based regimens were more frequently used (56%).
- Lenalidomide was the most commonly used maintenance therapy.
- Lenalidomide-containing regimens were the most commonly used in second- (60%) and third-line (52%) therapy.
- Figure 2 shows treatment pathways for patients with symptomatic MM.

Retrospective patient chart review:

- In general, bortezomib was the primary treatment used in the first-line setting.
- Patients were often re-treated with bortezomib in the second (26%) and third (20%) lines. (Figure 3)
- In the third-line setting, the majority of patients who had previously received second-line bortezomib subsequently received lenalidomide (first-line bortezomib: 59%, first-line thalidomide: 80%).
- Of those who received thalidomide first-line (excluding patients receiving it as part of a bortezomib, thalidomide, dexamethasone [VTD] regimen), 76% received bortezomib and 17% received lenalidomide-based regimens in the second-line.
Figure 1. Treatment status of patients with symptomatic multiple myeloma

Table 1. Treatment received by patients: first-line and beyond

<table>
<thead>
<tr>
<th>Based regimen (%)</th>
<th>BORT</th>
<th>LEN</th>
<th>BORT-LEN</th>
<th>BORT-THAL</th>
<th>THAL</th>
<th>BENDA</th>
<th>POM</th>
<th>Other</th>
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<td>15</td>
<td>1</td>
<td>11</td>
<td>21</td>
<td>2</td>
<td>1</td>
<td>14</td>
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<tr>
<td>Induction</td>
<td>43</td>
<td>5</td>
<td>1</td>
<td>14</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Maintenance</td>
<td>17</td>
<td>44</td>
<td>1</td>
<td>3</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>11</td>
</tr>
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<td>2</td>
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</tbody>
</table>

*BENDA = bendamustine; BORT = bortezomib; LEN = lenalidomide; POM = pomalidomide; THAL = thalidomide*
Symptomatic MM patients with a confirmed diagnosis  
$n = 7,635$ (100%)

- Directly to treatment (65%)
- Watch and wait (31%)
- Directly to supportive (5%)

SCT eligible  
$n = 798$ (44%)

- SCT  
$n = 550$ (31%)

- Consolidation  
$n = 121$ (7%)

- Receive maintenance  
$n = 64$ (4%)

- Receive a 2nd line anti-tumour drug treatment (61%)

SCT ineligible  
$n = 1,004$ (56%)

- Non SCT  
$n = 1,253$ (69%)

- No consolidation  
$n = 429$ (24%)

- Receive maintenance  
$n = 148$ (8%)

- Do not receive maintenance  
$n = 1,105$ (61%)

- Receive a 3rd line anti-tumour drug treatment (38%)

- Receive a 4th line anti-tumour drug treatment (15%)

- Receive a ≥5th line anti-tumour drug treatment (1%)

**Figure 2.** Treatment pathways for patients with symptomatic multiple myeloma

**MM = multiple myeloma; SCT = stem cell transplant**
**Figure 3. Treatment sequencing for patients receiving bortezomib-based regimens in the first line (retrospective analysis)**

**Key conclusions**

- The cross-sectional study design captures a snapshot of the treatment of patients with symptomatic MM at a particular time point and is therefore likely to reflect real-world practice.
- The large sample size gathered from multiple countries supports the results’ generalizability.
- The diversity of regimens prescribed in this study confirms that the optimal sequence of available treatment options has not yet been established, and there are no standard or globally adopted treatment guidelines.
- There is a need for new agents such as carfilzomib, elotuzumab, and daratumumab for patients who have progressed in previous lines of therapy to avoid re-treating with the same agent in subsequent lines.

An Interview with Dr. Sagar Lonial on the MMY2002 Study

At the ASCO 2015 Annual Meeting, New Evidence spoke with Dr. Sagar Lonial, Professor and Executive Vice Chair in the Department of Hematology and Medical Oncology at Emory University School of Medicine and Chief Medical Officer at the Winship Cancer Institute, in Atlanta, Georgia, about the results of the phase II MMY2002 study that evaluated the efficacy and safety of daratumumab in patients with multiple myeloma who have received at least three prior therapies including a proteasome inhibitor and an immunomodulatory drug (IMiD) or were refractory to their most recent proteasome inhibitor and IMiD.

New Evidence: What are the current treatment options for patients with relapsed multiple myeloma (MM)?

Dr. Lonial: Currently we use drugs like lenalidomide, bortezomib, carfilzomib, and pomalidomide, which basically have two targets: bortezomib and carfilzomib target the proteasome, and lenalidomide and pomalidomide target the cereblon protein. Both of these targets are important for normal plasma cell survival, and consequently, both of these classes of agents are very effective in managing patients with relapsed MM. The other agent that has been developed over the last few years that is not categorized as a proteasome inhibitor or IMiD is the histone deacetylase inhibitor panobinostat. Panobinostat was approved by the U.S. Food and Drug Administration in February of this year when used in combination with bortezomib and dexamethasone, but it is not yet approved by Health Canada. We are continuing to look for new targets to broaden our selection of therapies that can induce cell death in myeloma cells.

New Evidence: What are the challenges in treating patients with relapsed/refractory MM?

Dr. Lonial: The biggest challenge in the treatment of relapsed/refractory MM is determining what the next best treatment is for patients. There are currently no simple biomarkers or tools to tell us whether a patient who had a certain drug will respond to something else. Patient age and complications from initial treatments can also be an issue when selecting a therapy. Another element to consider is how the patient’s relapse is manifesting in terms of whether it is simply a biochemical relapse or a full-blown symptomatic relapse with renal failure and hypercalcemia. All of these factors come into play when deciding on a treatment for patients with relapsed MM. If you get to a point where you’ve exhausted the proteasome inhibitors and both IMiDs, your treatment options become quite limited, and the benefit from conventional chemotherapy at that point is likely also very limited. You may be able to add panobinostat to an IMiD or proteasome inhibitor to resensitize end-stage refractory patients, but we are not sure how long that benefit will last. We clearly need new targets in the refractory population.

New Evidence: What are the potential advantages of daratumumab for the treatment of MM?

Dr. Lonial: There are a couple advantages of daratumumab in the treatment of MM. Daratumumab is a monoclonal antibody that targets CD38 and represents an immune-based approach that induces cell death through complement-dependent cytotoxicity, antibody-dependent cell-mediated phagocytosis and cytotoxicity, and direct apoptosis. As this molecule has multiple mechanisms of action that are
completely different from other drugs we have used so far, it can achieve responses in patients who may be resistant
to other agents. Another potential strength of daratumumab is that it has demonstrated efficacy not only as a single
agent, but also in combination with other classes of agents that are already used in MM. The efficacy and safety of
daratumumab has been demonstrated in preliminary studies, particularly in combination with IMiDs like lenalidomide
and pomalidomide, but also with bortezomib and other drugs used in MM therapy.

New Evidence: What have previous studies shown us about the efficacy and safety of daratumumab in patients with MM?

Dr. Lonial: The first-in-human study evaluating daratumumab in patients with MM was the GEN501 study, where
daratumumab was given at doses up to 24 mg/kg. For the 16 mg/kg dose, the response rate was approximately 35%.
Although this was in a small number of patients, it certainly gave us the sense that daratumumab could work approximately
one third of the time in patients with refractory MM. The safety results from this phase I study suggest that daratumumab
is very well tolerated overall, and other than infusion-related reactions (IRRs) that occur predominantly with the first dose,
there are few additional side effects attributed to daratumumab therapy.

New Evidence: Please describe the design of the MMY2002 study and the characteristics of this patient population.

Dr. Lonial: This was an open-label, international, multicentre study with a Simon-two-stage design, evaluating the
efficacy and safety of daratumumab in patients with MM who had received at least three prior lines of therapy includ-
ing a proteasome inhibitor and an IMiD or who were refractory to their most recent proteasome inhibitor and IMiD
regardless of the number of prior lines of therapy. The first question to be addressed in this study was: ‘what is the
optimal dose and schedule of daratumumab?’ Patients were initially randomized to receive either 8 mg/kg or 16 mg/
kg of daratumumab. After enrolment of the first 34 patients, it was pretty clear that the 16 mg/kg dose was the optimal
dose to move forward with, so an additional 90 patients were enrolled to more fully understand what the response rate
would look like in a variety of different patients.

Inclusion criteria for the hematologic parameters were more relaxed than what is typically seen in other clinical trials, which
allowed for more refractory patients to be treated, resulting in a potentially sicker population. In this trial, 82% of patients
received greater than three prior lines of therapy. The median number of prior lines of therapy was five and the average time
from diagnosis was approximately 5 years, so these patients were basically going through a line of therapy per year. Since
we know that each subsequent line of therapy is often shorter than the previous one, many of these patients probably had
short-lived remission to their last therapy, if they responded at all. Nearly all patients were double refractory to a proteasome
inhibitor and IMiD, many patients were triple refractory, and a subset of patients were even quadruple refractory, so overall
this was a very heavily pretreated, very advanced stage population.

New Evidence: Please describe the efficacy results of the study. What are your impressions of these results?

Dr. Lonial: In this study, single-agent daratumumab achieved a 29% overall response rate (ORR), and given the exposure
history and refractoriness that the patients had coming into treatment, that is a very remarkable ORR. In addition, we saw
several very good partial responses, as well as some complete responses, which again is quite striking. The other point
that I think is of interest from my perspective as a clinician is that the response rate appeared to be relatively consistent
regardless of patient characteristics or prior therapiess. That response rate can serve as a benchmark, as we will know that
in the refractory MM population, you will get roughly one third of patients responding to single-agent daratumumab.
The response rate will increase even more when you start to combine daratumumab with other drugs such as lenalidomide,
bortezomib, and pomalidomide.

The progression-free survival (PFS) in this study was 3.7 months. In a refractory population such as this one, the PFS is
often weighed down by the non-responders, so this endpoint often doesn’t tell the whole story. The average duration
of response was approximately 7.4 months, which I think is a better metric to evaluate response, and it does compare
favourably to what was seen in the carfilzomib and pomalidomide registration trials that led to their accelerated approval. It is also important to remember that many patients in this trial were refractory to pomalidomide and carfilzomib.

The overall survival data are also intriguing because the estimated 1-year survival rate, at a median follow-up of just over 9 months, was 65%; however, of the 31 patients who did respond, 29 are in fact still alive. That speaks very powerfully first of all to how sick these patients are, because if they don’t respond they have very poor outcomes. Second of all, if the patients do respond, that can actually change the natural history curve, which I think is a real step forward.

**New Evidence:** What were the main toxicities observed with daratumumab? How were these toxicities managed?

**Dr. Lonial:** Many of the adverse events (AEs) reported, including thrombocytopenia, neutropenia, anemia, fatigue, and nausea, were simply associated with the refractory MM patient population. The one AE that was unique was the IRRs. Forty-three percent of patients had an IRR associated with daratumumab, with no grade 4 IRRs reported and only 5% of these IRRs being grade 3. More than 90% of IRRs occurred with the first dose, 7% of patients experienced an IRR at more than one infusion, and no patients had to discontinue daratumumab because of IRRs. There are a number of things that can be done to manage these IRRs, such as slowing down the infusion and giving additional premedications. Most hematologists and oncologists are very familiar with the management of IRRs when treating patients with monoclonal antibodies.

**New Evidence:** Given the results of this study, in which patients would you consider using daratumumab if it were available?

**Dr. Lonial:** I think refractory MM patients, like those included in this study, would be where I would consider using daratumumab, as this is where we have the most data. With the emerging data on combination therapies, daratumumab is going to have a role in a number of different treatment settings beginning as early as newly diagnosed MM, but we need additional data to support that.

**New Evidence:** What do you see as the next step in examining daratumumab for the treatment of MM?

**Dr. Lonial:** The next step would be to perform phase III comparative trials where daratumumab is added to agents such as lenalidomide, pomalidomide, bortezomib, or carfilzomib, in various treatment settings. There are currently five phase III trials that are ongoing or have completed enrollment that are doing just that. It seems that many of these steps have already been taken, and now it is just a matter of getting data to more fully understand what the magnitude of benefit is for daratumumab in combination with the commonly used MM drugs. I think all of these combinations are promising right now. I would be surprised if daratumumab did not improve the regimen when it is combined with pretty much any drug. I think daratumumab will have a similar magnitude of benefit to what is seen when rituximab is added to a lymphoma regimen, if not better.

**New Evidence:** Where do you see daratumumab fitting in terms of sequencing of therapy?

**Dr. Lonial:** I do not believe in sequencing, I believe in combinations. If we want to cure MM and eliminate the clone, we need to hit it at any given time point with drugs that possess as many different mechanisms of action as possible. Once we have done that, the hard part will be finding a way to maintain those responses. I think daratumumab will be a great option not only as part of initial therapy, but also as part of a maintenance strategy. There are still a lot of unanswered questions, but I think there are opportunities to use daratumumab in every phase of treatment.

**New Evidence:** What is the take-home message we can draw from the results of the MMY2002 study?

**Dr. Lonial:** I think the take-home message is that we have an exciting new drug that targets something very different from the other agents used in MM so far. In patients with limited treatment options, it is a safe and well-tolerated way to induce responses. Hopefully, with time, we will move towards using daratumumab earlier in the disease course.
An Interview with Dr. Richard LeBlanc on the MMY2002 Study

Following ASCO 2015, New Evidence spoke with Dr. Richard LeBlanc, a medical oncologist at Hôpital Maisonneuve-Rosemont and Clinical Assistant Professor of Medicine at the University of Montreal, about the MMY2002 study, which examined the efficacy and safety of single-agent daratumumab in heavily pretreated and refractory patients with multiple myeloma (MM).¹

**New Evidence:** What are the standard treatment options in Canada for patients with relapsed MM?

**Dr. LeBlanc:** There are various treatment options available in Canada for patients with relapsed MM. In cases where a treatment has shown efficacy and has been well tolerated by a patient in the first-line setting, a similar therapy can be proposed in the relapsed setting, including a second autologous stem cell transplantation. In other cases, bortezomib-, lenalidomide-, or pomalidomide-based therapies can offer further options, depending on the clinician’s access to those drugs. Despite the available choices, relapse almost always occurs in MM, and patients eventually become refractory to chemotherapy regimens. As a result, alternative therapies are urgently needed.

**New Evidence:** What are the key unmet needs for patients with relapsed MM?

**Dr. LeBlanc:** At relapse, standard chemotherapy is often associated with a short duration of response (DOR), after which alternative treatments are needed. There is a lack of novel drugs with unique mechanisms of action that can be used in combination therapies in order to improve progression-free survival (PFS) and, possibly, overall survival (OS). Furthermore, once all standard therapies have been exhausted, patients with MM need new treatment options to help them control the disease and improve their quality of life.

**New Evidence:** What are the potential advantages of daratumumab for the treatment of MM?

**Dr. LeBlanc:** Daratumumab is a first-in-class human monoclonal antibody that targets CD38, a glycoprotein that is expressed on myeloma cells. It offers the advantage of a completely new mechanism of action compared with all other standard therapies in MM. Daratumumab can cause cytotoxicity in two ways after binding to myeloma cells. First, it can directly cause cell death by activating apoptosis pathways. Secondly, it can indirectly lead to immune cytotoxicity, such as antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity. Daratumumab also offers a different toxicity profile from other agents, which can be advantageous because it allows for its use in combination treatments with other standard regimens.

**New Evidence:** What have previous studies shown us about the efficacy and safety of daratumumab in patients with MM?

**Dr. LeBlanc:** Phase I/II studies have demonstrated the high activity of daratumumab as monotherapy in patients with relapsed or refractory MM. For example, in the GEN501 study presented at ASCO 2014, the use of daratumumab at 16 mg/kg led to an overall response rate (ORR) of 46%². Additionally, studies have demonstrated that daratumumab has a manageable safety profile.

**New Evidence:** Please describe the population of the MMY2002 study. Were these patients representative of those you see in clinical practice?

**Dr. LeBlanc:** The patients with MM that were included in the MMY2002 study had progressive disease after their most recent treatment regimen. They had received at least three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or were refractory to both proteasome inhibitor and immunomodulatory drug, irrespective of the number of prior lines of treatment. The enrolled patients were heavily pretreated and had received a median of five prior therapies. In addition, patients with renal insufficiency were included as long as their creatinine clearance was above 20 mL/min/1.73 m².

The patient population included in the MMY2002 study accurately represents patients with MM in the clinic, who have been exposed to standard therapies such as bortezomib, lenalidomide, and pomalidomide.

**New Evidence:** What are your impressions of the efficacy results? How do they compare to those of other treatment options in this patient population?

**Dr. LeBlanc:** A total of 106 patients with MM were treated with daratumumab at 16 mg/kg. An ORR of 29% was observed, with 9% of patients achieving very good partial response and 3% of patients achieving a stringent complete response. A clinical benefit rate of 34% was achieved, when patients with a minimal response were included. Additionally, responses were durable, with a median DOR of 7.4 months. The median PFS was 3.7 months and the median OS was not reached after a median follow-up of 9.3 months. Furthermore, the one-year
survival rate was 65%. These single-agent efficacy results are impressive given the relapsed or refractory state of the disease.

Additionally, in a recent study from the International Myeloma Working Group (IMWG) published in the *Leukemia* journal in 2012, patients with relapsed myeloma, who were refractory to bortezomib and were relapsed following, refractory to, or ineligible for an immunomodulatory drug, had a median OS and event-free survival of only nine and five months, respectively. The results of MMY2002 compare favourably to those of the 2012 IMWG study.

The results of the MMY2002 study are similar to those observed with other treatment options with comparable population such as the MM-003 study using pomalidomide-dexamethasone and PX-171-003-A1 using carfilzomib. In the MM-003 and the PX-171-003-A1 studies, the ORR was 31% and 24%, the DOR was 7 months and 7.8 months, the median PFS was 4 months and 3.7 months, and median OS was 12.7 months and 15.6 months, respectively.

**New Evidence**: Were there any safety signals of concern in the study? How might these toxicities be effectively managed in clinical practice?

**Dr. LeBlanc**: Common adverse events (AEs) included fatigue in 40% of patients (grade 3 fatigue: 3%), nausea (29%), and hematologic toxicity with anemia (33%; grade 3: 24%; red blood cell transfusions required in 38%), thrombocytopenia (26%; grade 3: 17% and grade 4: 8%; platelet transfusions required in 13%), and neutropenia (23%; grade 3: 11% and grade 4: 3%). No cases of febrile neutropenia were observed. These side effects were not of major concern, as no patients discontinued treatment due to treatment-related AEs.

The potential infusion-related reactions (IRRs), occurring in 43% of patients, were of more concern. They characteristically happen during the first infusion and are usually of grade 1 or 2. In the MMY2002 study, 5% of patients presented with grade 3 IRRs and none had grade 4 reactions. These reactions usually manifest with nasal congestion, throat irritation, cough, dyspnea, chills, and vomiting. No patients discontinued treatment due to IRRs. However, 85% of patients discontinued treatment during the study due to other reasons. The most common causes for study discontinuation were progressive disease (77%) and AEs unrelated to daratumumab (5%).

In order to help prevent IRRs, it is recommended that corticosteroids, acetaminophen, and diphenhydramine are administered prior to infusion with daratumumab. For patients with myeloma, who are at high risk of respiratory complications (such as patients with concomitant chronic obstructive pulmonary disease), post-infusion medication, such as antihistamine medication and a short-acting β2 adrenergic receptor agonist, can be considered. In the event that IRRs occur, their management would depend on the type of manifestation and the grade.

A potential disadvantage of daratumumab use is its long infusion period, particularly for the first two infusions, which depends on the weight of patients. This is something that should be addressed in future trials in order to improve ease of administration.

**New Evidence**: Given the results of this study, in which patients would you consider using daratumumab if it were available for frontline therapy and in the relapsed setting?

**Dr. LeBlanc**: Presently, there is no mature study that recommends the use of daratumumab in first-line therapy. However, if daratumumab became available in the relapsed setting, I would use it as monotherapy in patients who are refractory or intolerant to bortezomib and lenalidomide, before or after pomalidomide and carfilzomib. I would use daratumumab as such until clinical trials confirm its superiority in combination treatments.

**New Evidence**: In which combination regimens would you consider using daratumumab?

**Dr. LeBlanc**: The MMY2002 study confirmed that daratumumab is active as monotherapy. However, combination treatments with daratumumab are attractive and may help to improve outcomes of patients with myeloma. It would be interesting to combine an immunomodulatory agent, such as lenalidomide, with daratumumab. In preclinical studies, the combination of daratumumab and lenalidomide enhanced myeloma cell death *in vitro* and *in vivo*. In addition, a clinical trial presented at ASCO 2014 demonstrated that the combination of daratumumab, lenalidomide, and dexamethasone had a favourable safety profile with manageable toxicities in patients with relapsed or refractory MM, coupled with encouraging activity (ORR of 72%). Presently, phase III clinical trials are ongoing with the daratumumab, lenalidomide, and dexamethasone combination treatment in the first-line setting (MMY3008 study) and in relapsed or refractory MM (MMY3003 study). Importantly, given that the mechanism of action of daratumumab involves the immune system, one has to be cautious when using immunosuppressors, such as high doses of dexamethasone, to avoid a potential decrease in the activity of daratumumab.

**New Evidence**: How might the results of the MMY2002 study be used to change clinical practice in Canada?

**Dr. LeBlanc**: When used as monotherapy, without the use of corticosteroids (except in pre-infusion preparation),
the results of daratumumab are provocative and impressive. If daratumumab were available, clinical practice in Canada would certainly change for relapsed or refractory MM.

**New Evidence:** What do you see as the next step in examining daratumumab for the treatment of MM?

**Dr. LeBlanc:** Daratumumab is presently being studied as part of combination chemotherapy. As with other drugs available for the treatment of MM, daratumumab will be evaluated in first-line patients with myeloma, who are eligible or ineligible for transplantation. Results so far have demonstrated that daratumumab is a very promising drug in the treatment of MM.

**References:**

**Leukemias**

**Novel Agents and New Combination Therapies in the Treatment of CLL**

Over the past few decades considerable improvements have been made in the treatment of chronic lymphocytic leukemia (CLL). However, despite these therapeutic advances, the disease remains incurable and patients will invariably relapse. Thus, the goal of therapy is to control the disease and provide long, durable remissions, while minimizing treatment-related toxicities.

Fludarabine, cyclophosphamide, and rituximab (FCR) is currently the standard of care for first-line treatment of young and fit patients with CLL. However, due to its associated toxicities, FCR is not suitable for the many patients with CLL who are older and/or have multiple comorbidities. Bendamustine plus rituximab (BR) is a potential first-line treatment option for fit patients with CLL who are older than 65 years of age. In these patients, BR has demonstrated similar efficacy, and lower rates of neutropenia and infections, to FCR. For untreated, elderly CLL patients with multiple comorbidities, the novel anti-CD20 antibody obinutuzumab in combination with chlorambucil has demonstrated good efficacy and acceptable levels of toxicity, leading to Health Canada approval of this regimen for treatment-naive patients with CLL. As there are a limited number of safe and highly effective first-line treatment options for older CLL patients with comorbidities, new combination regimens continue to be investigated.

For patients with relapsed CLL, many novel agents are currently being investigated in clinical trials, two of which have been approved by Health Canada within the last year: ibrutinib and idelalisib. Ibrutinib is a Bruton’s tyrosine kinase inhibitor approved as monotherapy in CLL patients who have received at least one prior therapy, or for the front-line treatment of patients with deletion 17p [del(17p)]. Idelalisib is a phosphoinositide 3-kinase inhibitor approved in combination with rituximab for patients with relapsed CLL. Both ibrutinib and idelalisib are first-in-class,
oral inhibitors that target proteins downstream of the B-cell receptor pathway. In addition, both of these agents have demonstrated impressive efficacy in patients with relapsed CLL, including patients with high-risk factors such as del(17p)/TP53 mutations.4,5,6

Several completed and ongoing studies were presented at international conferences this past summer, which aimed to further characterize the efficacy and safety of these two agents as monotherapy, and in combination with other drugs, in the treatment of CLL. Below we report the results of studies, and one study design, presented at the 2015 Annual Meeting of the American Society of Clinical Oncology (ASCO), the 20th Congress of the European Hematology Association (EHA), and the 13th International Conference on Malignant Lymphoma (ICML):

• The addition of ibrutinib to BR resulted in significantly prolonged progression-free survival (PFS) compared with placebo plus BR in the randomized, double-blind, phase III HELIOS study in patients with CLL or small lymphocytic lymphoma (SLL). (Chanakhan A, et al. ASCO 2015:LBA7005 & Cramer P, et al. EHA 2015:LB218)

• In an open-label, phase III trial of patients with relapsed CLL (Study 119), the combination of idelalisib plus ofatumumab demonstrated significantly prolonged PFS compared to ofatumumab alone. (Jones JA, et al. ASCO 2015:7023)

• In a phase Ib trial, idelalisib in combination with chemotherapy regimens induced durable responses, and had a manageable safety profile, in patients with relapsed/refractory CLL. (Barrientos JC, et al. ASCO 2015:7011)

• An analysis of the effect of dose adherence on PFS in CLL patients from the phase III RESONATE trial highlighted the clinical importance of sustained adherence to continuous once-daily 420 mg ibrutinib dosing. (Barr PM, et al. ASCO 2015:7012 & Jaeger U, et al. EHA 2015:S435)

• The ongoing phase 3 iLLUMINATE study was initiated to evaluate the efficacy and safety of ibrutinib plus obinutuzumab compared with chlorambucil plus obinutuzumab in treatment-naive patients unfit for chemomunotherapy. The study design was presented at ASCO and ICML. (Flinn I, et al. ASCO 2015:TPS7095 & Moreno C, et al. ICML 2015:OT06)

• An integrated analysis of safety data from eight clinical trials of idelalisib in B-cell malignancies reported that patients with pneumonitis, grade ≥3 diarrhea/colitis, alanine aminotransferase/aspartate aminotransferase/aspartate aminotransferase elevations, or rash could be successfully rechallenged after dose interruption. (Coutre S, et al. ASCO 2015:e18030 & Coutre S, et al. EHA 2015:S433)

• In patients treated with idelalisib for CLL and indolent non-Hodgkin lymphoma, results from a post hoc analysis suggest that there were no specific trends with respect to the anticoagulant or antiplatelet used and the occurrence of bleeding events. (Barrientos JC, et al. ASCO 2015:8563 & Stilgenbauer S, et al. EHA 2015:e1064)

• An analysis on patients with CLL receiving allogeneic stem cell transplantation found that compared to FCR, conditioning with bendamustine, fludarabine, and rituximab (BFR) resulted in less myelosuppression, less graft versus host disease, and improved overall survival for patients. (Khoury IF, et al. ICML 2015:056)

In Supportive Care Oncology

Background

At ASCO 2015 and EHA 2015, efficacy and safety results were presented from the preplanned interim analysis of the phase III HELIOS study, which evaluated ibrutinib plus bendamustine and rituximab (BR) versus placebo plus BR in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL).1,2

Study design

• HELIOS is a randomized, placebo-controlled, double-blind, phase III study.
• Key eligibility criteria included:
  ◦ Active CLL/SLL requiring treatment according to ≥1 International Workshop on CLL criteria and age ≥18 years;
  ◦ Relapsed or refractory CLL/SLL following ≥1 prior line of systemic therapy (minimum 2 cycles);
  ◦ Eastern Cooperative Oncology Group performance status of 0–1;
  ◦ Measurable lymph node disease (>1.5 cm) by computed tomography (CT) scan;
  ◦ Adequate bone marrow, liver, and kidney functions; and
  ◦ No deletion 17p [del(17p)], defined as the presence of del(17p) in ≥20% of cells examined by fluorescence in situ hybridization.
• Patients were randomized 1:1 to receive standard BR treatment (≤6 cycles) with either ibrutinib 420 mg daily (ibrutinib + BR) or placebo (placebo + BR) until progressive disease (PD) or unacceptable toxicity.
• Patients were stratified by refractoriness to purine analog chemoimmunotherapy (i.e., failure to respond or relapse within 12 months) and the number of prior lines of therapy (i.e., 1 line vs. >1 line).
• Standard BR therapy was bendamustine 70 mg/m² intravenous on cycle 1, days 2–3 and cycles 2–6, days 1–2; and rituximab 375 mg/m² on cycle 1, day 1, and 500 mg/m² on cycles 2–6, day 1.
• Patients in the placebo + BR arm could cross over to ibrutinib treatment after Independent Review Committee (IRC)-confirmed PD.
• The primary endpoint was IRC-assessed progression-free survival (PFS).
• Secondary endpoints included:
  ◦ IRC-assessed overall response rate (ORR) (i.e., complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular partial response, and partial response) confirmed by ≥2 CT scans performed every 12 weeks;
  ◦ Overall survival (OS);
  ◦ Rate of minimal residual disease (MRD)-negative responses; and
  ◦ Safety.

Study design

BR = bendamustine, rituximab; CLL = chronic lymphocytic leukemia; IRC = independent review committee; iv = intravenous; PD = progressive disease; SLL = small lymphocytic lymphoma

*Stratified by disease refractory to purine analog chemoimmunotherapy (failure to respond or relapse within 12 months)

†BR (similar to Fischer K, et al. J Clin Oncol 2011;29:3559–3566): bendamustine: 70 mg/m² iv on cycle 1, days 2–3 and cycles 2–6, days 1–2; rituximab: 375 mg/m² on cycle 1, day 1, and 500 mg/m² on cycles 2–6, day 1.
The study was designed to detect a hazard ratio (HR) of 0.7 for the ibrutinib + BR group relative to the placebo + BR group.

Approximately 580 patients were to be randomized to observe 342 PFS events and one interim analysis was planned after approximately 171 PFS events (50% total planned PFS events).

**Key findings**

- A total of 578 patients were randomized in this study (289 in each arm) between September 2012 and January 2014.
- Baseline characteristics were balanced between the two treatment arms.
- The median age of patients was 64 years in the ibrutinib + BR arm and 63 years in the placebo + BR arm.
- The median number of prior therapies in both arms was two.
- Six cycles of BR were completed in 81.9% and 77.4% of patients in the ibrutinib + BR and placebo + BR arms, respectively.
- The median study drug exposure (ibrutinib vs. placebo) was 14.7 months vs. 12.8 months, with 73.2% and 55.7% of patients receiving study drug treatment for ≥12 months.
- At a median follow-up of 17.02 months, IRC-assessed PFS in the intent-to-treat population was significantly longer for patients treated with ibrutinib + BR vs. placebo + BR (IRC-assessed median PFS not reached vs. 13.3 months, respectively; HR = 0.203 [95% CI: 0.150–0.276], \( p < 0.0001 \)). (Figure 1)
  - IRC-assessed PFS subgroup analysis favoured ibrutinib + BR across all patient characteristics and molecular subgroups.
- The investigator-assessed median PFS HR for ibrutinib + BR vs. placebo + BR was 0.201 (95% CI: 0.145–0.278).
- No Richter’s transformations were observed in the ibrutinib + BR arm, and three were observed in the placebo + BR arm.
- The IRC-assessed ORR was 82.7% vs. 67.8% (\( p < 0.0001 \)) in the ibrutinib + BR vs. placebo + BR arms, with CR/CRi rates of 10.4% vs. 2.8%, respectively.
- The investigator-assessed ORR was 86.2% vs. 68.9% in the ibrutinib + BR and placebo + BR arms (\( p < 0.0001 \)), with CR/CRi rates of 21.4% vs. 5.9%, respectively.
- In both treatment arms, the median OS was not reached (HR for ibrutinib + BR vs. placebo + BR = 0.628 [95% CI: 0.385–1.024], \( p = 0.0598 \)). (Figure 2)
  - Ninety patients (31%) in the placebo + BR arm with IRC-confirmed PD crossed over to receive ibrutinib 420 mg once daily, which confounded the OS results.
- MRD-negative response was higher in the ibrutinib + BR vs. placebo + BR arm (12.8% vs. 4.8%, \( p = 0.0011 \)).
- MRD status was assessed in 120 and 57 patients in the ibrutinib + BR and placebo + BR arms, respectively.
- The incidence of most treatment-emergent adverse events (AEs) and serious AEs was similar between treatment arms. (Table 1 and Table 2)
- The most common grade 3/4 AEs with ibrutinib + BR and placebo + BR were neutropenia (53.7% vs. 50.5%, respectively) and thrombocytopenia (15% each arm). (Table 1)
- Overall, serious AEs were reported more frequently in the ibrutinib + BR arm (52.6%) than the placebo + BR arm (43.6%).
- The incidence of all bleeding AEs and atrial fibrillation (AF) was higher in the ibrutinib + BR arm (Table 3), which is consistent with the single-agent ibrutinib safety profile.
  - Of the patients with a prior history of AF/atrial flutter, seven of 25 (28.0%) patients on ibrutinib + BR and two of 22 (9.1%) patients on placebo + BR had an episode of AF/atrial flutter during the study.
- The rate of other malignancies reported during treatment and follow-up was similar in each arm (8.4% for ibrutinib + BR and 8.0% for placebo + BR).
Figure 1. IRC-assessed progression-free survival in the ITT population

Figure 2. Overall survival in the ITT population
### Table 1. Treatment-emergent adverse events (>15% of patients)

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Ibrutinib + BR (N = 287)</th>
<th>Placebo + BR (N = 287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58.2</td>
<td>53.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>36.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>22.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Cough</td>
<td>19.5</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>18.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Rash</td>
<td>18.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>16.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Headache</td>
<td>14.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**AE = adverse event; BR = bendamustine, rituximab**

### Table 2. Treatment-emergent serious adverse events (>2% of patients)

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Ibrutinib + BR (N = 287)</th>
<th>Placebo + BR (N = 287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**BR = bendamustine, rituximab; SAE = serious adverse event**
Key conclusions

■ Ibrutinib + BR significantly reduced the risk of progression or death by 80% and improved ORR compared with placebo + BR.

■ The safety profile of ibrutinib + BR was consistent with the known individual safety profiles of each drug.

■ These results demonstrate that ibrutinib + BR is superior to BR in previously treated patients with CLL/SLL.

■ OS results accounting for crossover were presented at the XVI International Workshop on CLL.

■ HELIOS is the second phase III study demonstrating that ibrutinib significantly delays relapse for patients with previously treated CLL/SLL and is effective in combination with chemoimmunotherapy in relapsed, physically fit patients.

An Interview with Dr. Paula Cramer on the HELIOS Study

At the EHA 2015 Annual Congress, New Evidence spoke with Dr. Paula Cramer, member of the German CLL Study Group (GCLLSG) and physician at the Department I of Internal Medicine, University Hospital, Cologne, Germany, about the results of the phase III HELIOS study, which is evaluating the efficacy and safety of ibrutinib plus bendamustine and rituximab (BR) versus placebo plus BR in patients with relapsed chronic lymphocytic leukemia (CLL).

**New Evidence:** With the treatment options available thus far, what are the challenges in treating patients with relapsed CLL?

**Dr. Cramer:** Patients with relapsed CLL can be difficult to treat; with every relapse the treatment-free survival becomes shorter and patients often acquire cytogenetic abnormalities during the course of the disease due to clonal evolution and selection of more resistant clones during previous treatment. In addition, relapsed patients are older and may have residual toxicities from previous therapies, which is why the toxicity profile of the subsequent therapy has to be taken into account when making treatment decisions. Until recently, patients with relapsed CLL were challenging to treat, especially if they relapsed early — within 24 to 36 months after chemoimmunotherapy such as FCR (fludarabine, cyclophosphamide, rituximab) — and if high-risk cytogenetics, such as del(17p) or TP53 mutations, were present. With the currently available novel kinase inhibitors, the Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib and the phosphatidylinositol-3-kinase (PI3K) inhibitor idelalisib, we have better therapeutic options for those patients. However, there is no defined standard therapy in the relapsed setting.

**New Evidence:** What are the benefits of using bendamustine and rituximab (BR) in patients with relapsed CLL?

**Dr. Cramer:** We have often used BR in CLL patients without del(17p)/TP53 mutations who relapsed after FCR because a change in the chemotherapy backbone might be beneficial. In addition, first-line treatment with FCR may result in prolonged cytopenias, which is another reason why a less myelotoxic regimen should be used. The ESMO guidelines recommend changing the therapeutic approach in patients who have relapsed within 24–36 months after therapy. However, a meta-analysis of patients treated in GCLLSG trials has demonstrated that an intensification of treatment, such as the use of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and related regimens, FCM (fludarabine, cyclophosphamide, mitoxantrone), or other anthracycline-containing regimens, has no benefit compared with standard chemoimmunotherapies, such as FCR and BR. The novel agents, ibrutinib and idelalisib, were not included in this analysis, but cross-trial comparisons suggest that those agents are superior to all other conventional therapies in this situation.
Dr. Cramer: From other hematological diseases, such as Hodgkin’s lymphoma, we learned that by combining a variety of drugs together we can achieve higher remission rates, as well as prolong progression-free survival (PFS) and overall survival (OS). With the addition of the BTK inhibitor ibrutinib to BR, three agents with three different mechanisms of action are combined in order to achieve better outcomes in relapsed CLL patients. The combination of ibrutinib plus BR had previously been studied in a phase I/II trial where it appeared to be both effective and well tolerated. The results from this trial provided the rationale to investigate ibrutinib plus BR in a phase III, double-blind, placebo-controlled trial.

New Evidence: Please describe the design of the HELIOS trial.

Dr. Cramer: This was a phase III, international, multicentre trial with 21 participating countries. It included patients with relapsed/refractory CLL or small lymphocytic lymphoma (SLL) who required treatment according to International Workshop on CLL (iwCLL) criteria and who had at least one measurable lymph node. Patients with del(17p) were excluded from trial participation. This was a double-blind study design where patients were randomized 1:1 to receive either BR plus placebo or BR plus ibrutinib. The dosing schedule was adapted from previous trials (e.g., the GCLLSG’s CLL2M trial). As with most CLL regimens, rituximab was administered at a dose of 375 mg/m² on day 1 in the first cycle and at 500 mg/m² on day 1 in cycles 2–6. Bendamustine was given at a dose of 70 mg/m² on days 2 and 3 in the first cycle and on days 1 and 2 in cycles 2–6. Ibrutinib was given daily at a dose of 420 mg starting on day 2 of the first cycle.

New Evidence: Please describe the characteristics of the population studied.

Dr. Cramer: There were 289 patients with relapsed/refractory CLL/SLL enrolled in each treatment arm. The overall study population had received a median of two prior therapies, and a considerable number of these patients had received three or more prior therapies. Seventy percent of patients had previously been treated with an anti-CD20 antibody, 95% of patients had previously received an alkylator, 72% had previously received a purine analogue, and 26% of patients were refractory to purine analogue therapy. Although patients with del(17p) were excluded from trial participation, a considerable number of patients had other high-risk features, including 80% of patients with unmutated IGHV and 26% of patients with del(11q). In addition, more than half of the patients had bulky disease. Overall, the patient collective on the HELIOS trial was not an ultra-high risk population, but a significant proportion of these patients could be considered difficult to treat.

New Evidence: What were the PFS results for the overall population and in the different subgroups analyzed?

Dr. Cramer: PFS was the primary endpoint of the study, and the recently performed interim analysis showed an impressive improvement in PFS with the addition of ibrutinib to BR, as determined by an independent review committee (IRC). At a median follow-up time of 17 months, patients in the BR plus placebo arm had a median PFS of 13.3 months, whereas in the BR plus ibrutinib arm the median PFS was not reached; this difference was highly statistically significant ($p<0.0001$). Although the results from this study are still early, the difference between the two PFS curves is broad and the hazard ratio is impressive, with an 80% reduction in the risk of progression or death with the addition of ibrutinib to BR. Also, a significant PFS benefit was demonstrated in all subgroups of patients analyzed, including patients with unmutated IGHV status, presence of del(11q), and purine analogue refractory disease.
New Evidence: Please describe the efficacy results for the secondary endpoints of the study, including overall response rate, OS, and minimal residual disease (MRD) negativity.

Dr. Cramer: The overall response rate was 83% in the BR plus ibrutinib arm compared with 68% in the BR plus placebo arm. This improvement in response was also highly statistically significant ($p <0.0001$). Furthermore, the rates of complete remission and MRD negativity were higher in the BR plus ibrutinib arm. Regarding OS, at this early time point there is a trend towards an OS benefit with the addition of ibrutinib to BR, but the difference between the two curves is not yet statistically significant. This is certainly influenced by the fact that 31% of patients treated with BR plus placebo crossed over to receive single-agent ibrutinib after disease progression was confirmed by an IRC.

New Evidence: Please describe the safety results of the study. Were there any concerning toxicities?

Dr. Cramer: The toxicities seen in this trial were very similar to what has been previously observed with ibrutinib monotherapy and the BR regimen. No cumulative toxicities occurred with the addition of ibrutinib to BR. The incidence of hematological toxicities and the incidence of infections was similar between treatment arms. Adverse events (AEs) that were more common in the BR plus ibrutinib arm and are known AEs for ibrutinib were diarrhea and rash, which were mostly mild-to-moderate, and the rare but sometimes worrisome events of bleeding and atrial fibrillation. The latter AEs were also mostly mild-to-moderate, and only a few patients had to discontinue treatment because of them. Interestingly, in the BR plus placebo arm, infusion-related reactions (IRRs) were observed in 22.0% of patients, whereas when ibrutinib was added to BR, IRRs occurred less often (in 16.7% of patients), which is consistent with previous observations and laboratory experiments.

Regarding the toxicities related to ibrutinib, especially diarrhea, rash, bleeding events, and atrial fibrillation, it is very important to inform patients about these risks so that they can notify their treating physician early on, should any of these AEs occur.

New Evidence: How would you currently use BR and ibrutinib in patients with relapsed CLL?

Dr. Cramer: The treatment of patients with relapsed CLL is still challenging, but there are now several available therapeutic options for this situation, which not only include different chemoimmunotherapy combinations, but also the novel agents ibrutinib and idelalisib. Thus far, there is no therapeutic standard in the relapsed setting, which is why different factors such as the time between last treatment and relapse, presence of cytogenetic abnormalities, patient factors (e.g., age and comorbidities), the patient’s expectations, and the therapeutic goal should be taken into account for a treatment decision. We usually discuss the different treatment options openly with the patient.

For CLL patients without del(17p)/TP53 mutation who have experienced a long remission duration after chemoimmunotherapy with FCR or BR — which is not uncommon, especially in patients with a mutated IGHV status — repeating chemoimmunotherapy might be a good therapeutic choice, especially if the patient prefers a limited treatment period and an established regimen. In case of an earlier progression, a novel drug should be used; based on data from the HELIOS trial, the combination of BR and ibrutinib is one of the possible options. However, in patients with a very short remission duration after chemoimmuno therapy or in case of a del(17p)/TP53 mutation, the kinase inhibitor should be administered alone, as BR will not be very effective in this situation and might only increase the toxicity.

New Evidence: Do you think that this trial is a practice-changing study?

Dr. Cramer: As described, the combination of BR and ibrutinib will be beneficial in some cases, especially in cases of shorter remission duration or if the patient has a higher tumour load and a more intense treatment is needed to achieve a faster response than with kinase inhibitor monotherapy. However, this trial is clinically very important because it is the second phase III trial that has shown a clear benefit with ibrutinib in CLL patients, demonstrating improved response rates and PFS. Furthermore, the addition of ibrutinib did not lead to any cumulative toxicities.
**New Evidence:** What future treatment combinations appear promising for the treatment of relapsed CLL?

**Dr. Cramer:** Currently, the GCLLSG is conducting phase II trials on several nearly chemotherapy-free regimens that combine a novel agent with an antibody, including ibrutinib plus obinutuzumab, idelalisib plus obinutuzumab, venetoclax (ABT-199) plus obinutuzumab, and ibrutinib plus ofatumumab. In all of these trials, patients with a higher tumour load undergo debulking with 2 cycles of bendamustine at the beginning of treatment in order to achieve a faster remission and reduce the risk of IRRs and tumour lysis syndrome. Another important question we wish to investigate is whether treatment with the novel agents can be stopped in patients who achieve a complete response and MRD-negative status. Also, the combination of obinutuzumab, ibrutinib, and venetoclax will be evaluated, aiming for a faster and deeper remission.

Aside from the two licensed kinase inhibitors and the BCL2 antagonist venetoclax, several other agents, including next generation BTK and PI3K inhibitors, inhibitors of other enzymes, and new antibodies, are currently being investigated and will become available in the near future. Thus, there are many other possible drug combinations to be tested, which makes the therapeutic decisions and design of trials even more challenging. We are very fortunate at the moment to have so many effective drugs available, and with these drugs we will certainly be able to further improve the outcomes for our patients.
At the 2015 ASCO Annual Meeting, New Evidence spoke with Dr. Graeme Fraser, Associate Professor at McMaster University and Hematologist at the Juravinski Cancer Centre, about the results of the phase III HELIOS study, which evaluated the efficacy and safety of ibrutinib plus bendamustine and rituximab (BR) versus placebo plus BR in patients with relapsed chronic lymphocytic leukemia (CLL).

New Evidence: Please describe the Canadian involvement in the HELIOS study.

Dr. Fraser: Canadian centres have made a very important contribution to the HELIOS study, with patient accrual exceeding expectations. Some centres were among the highest accruing sites globally and have also been involved in numerous scientific presentations of the data.

New Evidence: What are the current challenges in treating patients with relapsed CLL?

Dr. Fraser: It is important to consider both disease and patient-related factors, which primarily influence treatment efficacy and tolerability, respectively. Disease-related factors associated with poor outcomes include the presence of high-risk cytogenetics, such as deletions of 17p [del(17p)] and 11q [del(11q)], which are more common in relapsed disease, early relapse following a standard frontline chemo-immunotherapeutic regimen, and fludarabine-refractory disease. Patients in the relapsed setting are often elderly and have a number of comorbidities that can impact management. Those patients may also be less able to tolerate chemotherapy as a consequence of advanced disease or complications from prior lines of therapy which include myelosuppression and immunosuppression.

New Evidence: What are the potential advantages of an agent such as ibrutinib for patients with relapsed or refractory CLL?

Dr. Fraser: Ibrutinib is a targeted therapy with a unique mechanism of action that is very effective at controlling CLL. Published phase II and III studies have demonstrated high overall response rates and significantly prolonged progression-free survival (PFS) and overall survival (OS) with ibrutinib therapy. Ibrutinib is also associated with reduced rates of myelosuppression and infection-related toxicities compared with fludarabine- and bendamustine-containing regimens. Although there are some unique toxicities with this agent, such as mild-to-moderate bleeding and a small increased risk of atrial fibrillation, it is generally well tolerated overall and may improve hematopoietic function over time compared with standard therapies. An additional advantage of ibrutinib is that it can be given orally, which provides a solution to some of the more practical issues we face with these patients such as chemotherapy chair time and travel to and from the cancer clinic for intravenous therapies.

New Evidence: In which CLL patients do you recommend using ibrutinib?

Dr. Fraser: Ibrutinib has been approved by Health Canada for the treatment of patients with CLL who have received at least one prior therapy, and for the frontline treatment of patients with del(17p). I believe ibrutinib is an important therapy to consider for all patients that fall into these two categories. In the relapsed or refractory setting, ibrutinib has been effective across all patient subgroups evaluated to date. Patients that have historically had limited or ineffective treatment options, such as high-risk disease or those unable to tolerate standard myelosuppressive chemotherapy, derive substantial benefit in particular from treatment with ibrutinib. Ibrutinib is therefore a very reasonable second-line treatment option for patients with CLL.

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

Dr. Fraser: The HELIOS study included patients with CLL or small lymphocytic lymphoma who had at least one prior line of therapy and a good performance status. Patients with del(17p) were excluded; however, a fairly large proportion had other cytogenetic risk factors such as del(11q) and unmutated IGHV. The study population therefore does reflect the type of patients I see in my clinic.

New Evidence: Please comment on the efficacy results of the study.

Dr. Fraser: There was a significant improvement in PFS, the primary endpoint of the study, with ibrutinib plus BR compared with placebo plus BR. This analysis was assessed by an independent review committee. Additionally, there was a fairly strong trend towards an improvement in OS in the ibrutinib plus BR group, but this did not reach statistical significance. The improvement in efficacy outcomes with ibrutinib were achieved in all subgroups, regardless of age, interphase FISH cytogenetics, early versus late stage disease, refractoriness to purine analogues, number of lines of therapy, and IGHV mutation status.

It is important to consider the effect of crossover within
this trial. Thirty-one percent of patients in the placebo arm crossed over to receive ibrutinib. Crossover to an effective agent has the potential to underestimate the benefit in the experimental arm for outcomes that occur subsequently, including survival. This potential crossover effect may account for the lack of a survival benefit with ibrutinib therapy in the HELIOS trial.

**New Evidence**: Please describe the safety results of the study. How would you manage the unique toxicities that are associated with ibrutinib?

**Dr. Fraser**: The safety data from our study reflect the known toxicities of the two regimens evaluated and were therefore not surprising. What is important to note is that there was almost no additional grade 3 or 4 neutropenia, thrombocytopenia, or anemia associated with the addition of ibrutinib. It is very reassuring that we can combine ibrutinib with BR without seeing additive myelosuppression. There was also no difference in all-grade infections or infusion-related reactions (IRRs) between study arms.

As observed consistently across previously published ibrutinib trials in the relapsed or refractory setting, there were increased rates of bleeding, atrial fibrillation, and diarrhea seen in the ibrutinib plus BR arm versus the placebo plus BR arm. From a bleeding perspective, the majority of events were grade 1 or 2; however, there was a slight increase in major hemorrhage — 3.8% compared with 1.7% in the placebo arm. Major hemorrhage in the HELIOS trial was defined as any of the following: bleeding that was grade 3 or higher, intracranial hemorrhage, or serious bleeding of any grade. Approximately 42% of patients on ibrutinib plus BR were also receiving concomitant antiplatelet or anticoagulant therapy.

In cases of mild bleeding, such as bruising, gum bleeding, or epistaxis, ibrutinib can be continued with close monitoring. When more severe bleeding occurs, ibrutinib should be withheld until the bleeding has stabilized and unrelated causes or reversible risk factors have been assessed before considering reinitiation of treatment. Whether ibrutinib dose reduction can be used as an effective management strategy is unclear, but it is a reasonable approach when restarting treatment in a patient with a prior history of bleeding on treatment. For patients who are already on antiplatelet or anticoagulant drugs, ibrutinib should still be strongly considered because most bleeding events are mild and there is increasing experience with ibrutinib.

It is not entirely clear why there is a slightly increased risk of atrial fibrillation with ibrutinib and further study of this side effect is required. In our trial, this toxicity was most commonly seen in patients with a prior history or risk factors for its development. The majority of patients with grade 3 or 4 atrial fibrillation were able to continue on therapy after temporarily withholding treatment until stabilization. In patients with a prior history of atrial fibrillation, it is important that this condition is well controlled when ibrutinib is initiated. For those without a prior history, I do not recommend screening or monitoring prior to treatment with ibrutinib since it is an uncommon complication and does not have a predictable time of onset. In severe cases where the patient is unstable, I would withhold the drug until the patient has stabilized before considering resumption of therapy.

Ibrutinib has consistently been associated with a slight increase in mild and short-lasting diarrhea. This toxicity is usually easily managed with antidiarrheals and by changing the administration time of ibrutinib to the evening. Overall, I have not found diarrhea to be a significant issue for my patients.

**New Evidence**: How would you use ibrutinib plus BR in patients with relapsed CLL?

**Dr. Fraser**: For patients with relapsed or refractory disease who would not otherwise be eligible for more aggressive regimens, we know that the single-agent tolerability of ibrutinib is excellent and it should be a standard treatment in this setting. For fitter patients eligible for BR, the addition of ibrutinib is strongly supported by the results of the HELIOS trial. However, an important question that was not addressed in HELIOS, and therefore represents an important gap in the literature, is the additional benefit BR adds to single-agent ibrutinib in relapsed and refractory CLL. BR is costly and associated with additional toxicities that need to be justified. Unfortunately, any effort to compare ibrutinib plus BR with single-agent ibrutinib through cross-trial comparisons will be limited by important differences in study populations. An additional practical issue is that BR is not widely available or funded in Canada for the management of relapsed or refractory CLL. In such cases, I would recommend the use of single-agent ibrutinib for the treatment of relapsed or refractory CLL, based on the available evidence.

**New Evidence**: What future treatment combinations appear promising for the treatment of relapsed CLL?

**Dr. Fraser**: It is an exciting time to be involved in the management and clinical investigation of CLL. In addition to ibrutinib, two other highly active agents — idelalisib and venetoclax — are in advanced clinical development. Numerous second generation Bruton’s tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K) inhibitors, new monoclonal antibodies, and cellular and small molecule immunotherapeutics are being rapidly developed and investigated in early phase trials. The challenge will be to efficiently and rationally develop clinical trials.
that can determine the optimal combinations of these novel agents and clarify the future role of established chemo-immunotherapy regimens within this rapidly evolving landscape. Finally, the incorporation of novel targeted therapy into frontline management has now begun. Many Canadian centres are participating in an NCIC-CTG sponsored frontline study in CLL patients 65 years or older that is comparing BR, ibrutinib, and ibrutinib plus rituximab.


Results of a phase III trial evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL (Study 119)

Background
At ASCO 2015, Jones and colleagues presented the efficacy and safety results from a phase III randomized, controlled study evaluating idelalisib in combination with ofatumumab vs. ofatumumab alone in patients with chronic lymphocytic leukemia (CLL).1

Study design
• This was an open-label study where patients with relapsed CLL were randomized 2:1 to receive continuous idelalisib (150 mg twice daily) in combination with ofatumumab (1,000 mg x 12 doses) or ofatumumab alone (2,000 mg x 12 doses) followed by observation, until disease progression or death from any cause.

• Patients were required to have:
  ◦ Prior allogeneic stem cell or solid organ transplantation; or
  ◦ Progression within 6 months of their last dose of ofatumumab.
  ◦ The primary endpoint was progression-free survival (PFS).

• Secondary endpoints included overall response rate (ORR), lymph node response (LNR), complete response (CR) rate, overall survival (OS), and safety.

• Patients were stratified by deletion 17p [del(17p)] and/or TP53 mutation status, immunoglobulin heavy chain variable region (IGHV) mutation status, and recurrent disease status (relapsed vs. refractory).

• Computed tomography (CT) or magnetic resonance imaging (MRI) scans were required at baseline, weeks 8, 16, and 24, and every 12 weeks thereafter.

• Response was assessed by an independent review committee based on imaging, clinical, and laboratory data.

Key findings
• Patient characteristics were balanced between the two treatment arms.

• Overall, the median age of patients was 68 years (range: 36–85 years), 51% of patients had Rai stage IV disease, 49% percent of patients had refractory disease, 39% of patients had del(17p) and/or TP53 mutations, and 79% of patients had unmutated IGHV.

• The median number of prior therapies was three (range: 1–11).
• The median duration of idelalisib exposure was 12.3 months (range: 0.2–23.9 months).

• A larger percentage of patients in the ofatumumab arm discontinued the study early (prior to PFS event) than in the idelalisib plus ofatumumab arm (39% vs. 20%, respectively).

• PFS was significantly prolonged in patients treated with idelalisib plus ofatumumab compared with ofatumumab alone (median PFS: 16.3 months vs. 8.0 months, respectively; hazard ratio [HR] = 0.27 [95% CI: 0.19–0.39], p <0.0001). (Figure 1)

• Among patients with del(17p) and/or TP53 mutations, PFS was also significantly prolonged with idelalisib plus ofatumumab treatment compared with ofatumumab treatment alone (median PFS: 13.7 months vs. 5.8 months, respectively; HR = 0.32 [95% CI: 0.18–0.57], p <0.0001). (Figure 2)

• PFS HRs favoured idelalisib plus ofatumumab across all subgroups analyzed, including disease status (relapsed/refractory), IGHV mutation status, presence of del(17p) or TP53 mutations, sex, age (<65 years/≥65 years), and race (white/non-white).

• ORR was superior in the idelalisib plus ofatumumab arm compared with the ofatumumab alone arm (75% vs. 18%, respectively; odds ratio = 15.9 [95% CI: 7.8–32.6], p <0.001).

• The ORR odds ratio favoured idelalisib plus ofatumumab in all subgroups analyzed.

• LNR was superior in the idelalisib plus ofatumumab arm compared with the ofatumumab alone arm (odds ratio = 486.96 [95% CI: 97.91–2421.85], p <0.0001).

• There was no significant difference in OS between the idelalisib plus ofatumumab and ofatumumab alone treatment.

Figure 1. Progression-free survival in all patients

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Median PFS (95% CI), months</th>
<th>Adjusted HR (95% CI)*</th>
<th>p-value†</th>
<th>Median observation, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib + ofatumumab (n = 174)</td>
<td>76 (44)</td>
<td>16.3 (13.6–17.8)</td>
<td>0.27 (0.19–0.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ofatumumab (n = 87)</td>
<td>54 (62)</td>
<td>8.0 (5.7–8.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl = confidence interval; HR = hazard ratio; PFS = progression-free survival

*Based on Cox proportional hazards with stratification factors. †Based on stratified log-rank test.
arms (median OS: 20.9 months vs. 19.4 months, respectively; HR = 0.74 [95% CI: 0.44–1.25], p = 0.27).

- Grade ≥3 adverse events (AEs) were reported in 88% of patients in the idelalisib plus ofatumumab arm and 56% of patients in the ofatumumab alone arm.

- The most frequent grade ≥3 treatment-emergent AEs (TEAEs) in the idelalisib plus ofatumumab arm were neutropenia (34%), diarrhea and/or colitis (20%), and pneumonia (13%).

- Infusion-related reactions associated with ofatumumab occurred in 1.6% (31/1,887) of total infusions in patients treated with idelalisib plus ofatumumab and 4.3% (35/822) of total infusions in patients treated with ofatumumab alone (p = 0.0001).

- Treatment-emergent laboratory abnormalities and serious AEs (SAEs) are presented in Table 2 and Table 3.

- SAEs were reported in 70% of patients in the idelalisib plus ofatumumab arm and 42% of patients in the ofatumumab alone arm.

- Fifty-three patients (31%) in the idelalisib plus ofatumumab arm discontinued treatment due to a TEAE.

- The most common TEAEs leading to treatment discontinuation included diarrhea (n = 11, 6%), pneumonia (n = 5, 3%), alanine aminotransferase elevation (n = 4, 2%), pneumonitis (n = 4, 2%), and colitis (n = 3, 2%).

- TEAEs leading to death occurred in 18 patients (10%) receiving idelalisib plus ofatumumab (exposure-adjusted rate = 0.10/year) and six patients (7%) receiving ofatumumab alone (exposure-adjusted rate = 0.18/year).

- The most frequent TEAEs leading to death were sepsis/septic shock (n = 6) and cardiogenic shock (n = 2) in patients receiving idelalisib plus ofatumumab, and pneumonia (n = 2) and progressive multifocal leukoencephalopathy (n = 2) in patients receiving ofatumumab alone.

- The incidence of Richter’s transformation and second malignancy, adjusted for exposure, was 0.03 (95% CI: 0.0094–0.0675) and 0.15 (95% CI: 0.0964–0.2240), respectively, in the idelalisib plus ofatumumab arm, and 0.12 (95% CI: 0.0333–0.3125) and 0.26 (95% CI: 0.1136–0.5183), respectively, in the ofatumumab alone arm.

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**Figure 2. Progression-free survival in patients with del(17p)/TP53 mutations**

<table>
<thead>
<tr>
<th></th>
<th>Idealalisib + ofatumumab (n = 70)</th>
<th>Ofatumumab (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>35 (50)</td>
<td>20 (61)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>13.7 (11.0–17.8)</td>
<td>5.8 (4.5–8.4)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)*</td>
<td>0.32 (0.18–0.57)</td>
<td></td>
</tr>
<tr>
<td>p-value†</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median observation, months</td>
<td>11.1</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*CI = confidence interval; HR = hazard ratio; PFS = progression-free survival
*Based on Cox proportional hazards with stratification factors.
†Based on stratified log-rank test.
### Table 1. Treatment-emergent adverse events* (≥15% in the idelalisib plus ofatumumab arm)

<table>
<thead>
<tr>
<th>Event</th>
<th>Idelalisib + ofatumumab (n = 173)</th>
<th>Ofatumumab (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any AE</td>
<td>172 (99)</td>
<td>152 (88)</td>
</tr>
<tr>
<td>Diarrhea and/or colitis</td>
<td>85 (49)</td>
<td>35 (20)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>61 (35)</td>
<td>59 (34)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>56 (32)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55 (32)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>52 (30)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>52 (30)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Rash†</td>
<td>49 (28)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>36 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>34 (20)</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Headache</td>
<td>33 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>31 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30 (17)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>30 (17)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>29 (17)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Infusion-related reaction‡</td>
<td>29 (17)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>29 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (15)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

*Using MedDRA preferred terms unless otherwise noted.
†Using Medical Search Term list. ‡IRRs associated with ofatumumab occurred in: Total infusions: 31/1,887 (1.6%) in idelalisib + ofatumumab and 35/822 (4.3%) in ofatumumab (p = 0.0001); Total patients: 23/173 (13%) in idelalisib + ofatumumab and 23/86 (27%) in ofatumumab (p = 0.01); First infusion: 19/173 (11%) in idelalisib + ofatumumab and 20/86 (23%) in ofatumumab (p = 0.016).
Key conclusions

■ Idelalisib plus ofatumumab yielded superior PFS, ORR, and LNR compared with ofatumumab alone in patients of varying fitness levels with previously treated CLL.

■ The benefit of combination therapy was shown across all risk-related stratification groups, including patients with del(17p).

■ The safety of idelalisib plus ofatumumab was manageable with a profile similar to what has been observed in previous studies of patients with relapsed CLL.

■ Patients in the ofatumumab alone arm disproportionately discontinued treatment prior to disease progression, often to receive alternative therapy; this may have contributed to the similar overall survival in the two treatment groups.

An Interview with Dr. Carolyn Owen on Study 119

New Evidence: What are the key unmet needs in the treatment of CLL?

Dr. Owen: There are two groups of patients with CLL that are still in need of effective and tolerable therapy: patients who are refractory to chemotherapy and patients with poor risk cytogenetics, such as del(17p) and, to a lesser extent, del(11q). Although these patients are doing better with novel agents, no one is cured, and they still have worse outcomes than others with relapsed CLL. Patients who are refractory to both chemotherapy and novel agents do particularly poorly and are in need of better therapies.

New Evidence: What is the mechanism of action of idelalisib?

Dr. Owen: Idelalisib is an inhibitor of the phosphatidylinositol-3-kinase (PI3K) delta isoform. PI3K is involved in the signaling pathway from the B-cell receptor (BCR), and it is also a key component of multiple signaling pathways within lymphocytes. Therefore, it is overly simplistic to classify idelalisib solely as a BCR pathway inhibitor. It is clearly an inhibitor of signaling that turns off survival signals within CLL cells, however, due to the involvement of PI3K in multiple signaling pathways, the exact mechanism of action of idelalisib is not yet clearly understood.

New Evidence: What are the potential advantages of treating CLL patients with idelalisib?

Dr. Owen: The key advantages for idelalisib are that it is an oral agent and that it specifically targets B cells. Another major benefit of idelalisib is that compared to traditional chemotherapy, idelalisib is not as myelosuppressive and, therefore, it may be advantageous to patients who cannot tolerate chemotherapy because of comorbidities or cytopenias from prior therapy. In addition, idelalisib has demonstrated efficacy in high-risk relapsed CLL patients, including patients with poor prognostic factors and high-risk disease.

New Evidence: What have previous studies shown us about the efficacy and safety of idelalisib in patients with CLL?

Dr. Owen: Idelalisib has been approved by Health Canada based on its registration trial data in combination with rituximab, which is a published, phase III study that showed that the drug is very efficacious in relapsed/refractory patients, even in those with poor-risk prognostic factors like del(17p).
or TP53 mutations or patients who are refractory to fludarabine. We also know that idelalisib is quite safe and, in general, patients tend to do very well with this agent. However, there are a few toxicities to be aware of, such as transaminitis, colitis, pneumonitis, and neutropenic infections. It is important to follow management guidelines for these adverse events (AEs), so that patients can successfully continue therapy.

**New Evidence:** Please describe the rationale and design of Study 119.

**Dr. Owen:** The rationale for initiating this randomized phase III study was that idelalisib is a novel agent that required investigation in the relapsed/refractory CLL population. In Study 119, patients experiencing CLL progression within 24 months of the completion of their last therapy were randomized 2:1 to receive either idelalisib in combination with ofatumumab or ofatumumab alone. Ofatumumab was chosen to be combined with idelalisib because it had better evidence of efficacy as monotherapy than rituximab, with phase II data showing that refractory patients could get a reasonable response rate from ofatumumab alone. Therefore, the experimental arm was being compared with a reasonable alternative, which is in fact the same monotherapy that ibrutinib was compared with in its registration trial. A key difference from the published, randomized, phase III study evaluating idelalisib in combination with rituximab was that this was an unblinded study, so that patients knew which treatment they were receiving. The study was designed this way because a higher dose of ofatumumab was used in monotherapy than when it was given in combination with idelalisib (2,000 mg vs. 1,000 mg, respectively), which resulted in the need for longer infusion times for the monotherapy arm. In the end it proved that the open-label design might not have been a good idea because there was a higher withdrawal rate in the monotherapy arm. Also, unlike the study of idelalisib in combination with rituximab, crossover into the experimental arm was not allowed in this study, which further motivated patient discontinuation from the ofatumumab monotherapy arm.

**New Evidence:** Please describe the characteristics of the population studied.

**Dr. Owen:** This study enrolled a heavily pretreated population, with a median of three prior treatments, and a larger proportion of high-risk patients than in other relapsed CLL studies. Since patients in this study had to have relapsed within 24 months after completion of their last therapy, most of them will have relapsed within 24 months from completing chemiimmunotherapy, which is recognized to be a very high-risk population. This is unlike other studies in the relapsed setting that may have included patients who were considered inappropriate for purine analog therapy for a variety of reasons, including age or comorbidities, which aren’t as clear predictors of short survival as refractory disease.

In this study, 49% of patients had refractory disease, which is much higher than the average study in relapsed CLL. Thirty-nine percent of patients had del(17p) and/or TP53 mutations, which is also high yet similar to the frequency reported in other studies with idelalisib. The frequency of patients with unmutated immunoglobulin heavy chain variable region gene status was elevated at 79%, but it is appropriate in the fact that this study included a very high-risk relapsed patient population. At 68 years, the median age of patients in this study was not that old, but this is reflective of patients who would be fit for a clinical trial after already having received numerous prior therapies.

**New Evidence:** What were the progression-free survival (PFS) results in this study and how do they compare to other studies with a similar patient population?

**Dr. Owen:** The median PFS for idelalisib plus ofatumumab was 16.3 months versus 8.0 months for ofatumumab alone. This was a statistically significant difference with a hazard ratio of 0.27 (p <0.0001). There are not that many other phase III studies that have a similar population with which to compare these results. The phase III trial comparing ibrutinib with ofatumumab in patients with relapsed CLL showed a longer PFS for ibrutinib than what was seen in this study. However, the ibrutinib study did not require patients to have relapsed within 2 years
of their last therapy. As these patient populations are different, the results from the two studies cannot be directly compared.

The other phase III study on idelalisib, which compared idelalisib plus rituximab to rituximab plus placebo in patients with relapsed CLL, had a similar high-risk population. Very similar results were reported for the group of patients with TP53 mutations or del(17p) in each of these studies, with the median PFS of 16.6 months for idelalisib plus rituximab, based on what was reported at the 2014 American Society of Hematology Annual Meeting, and 13.7 months for idelalisib plus ofatumumab, based on the results from this study. Similarly, in the overall patient group, the median PFS was 19.4 months for idelalisib plus rituximab and 16.3 months for idelalisib plus ofatumumab. Although this was not a head-to-head comparison, Study 119 does not obviously suggest that ofatumumab is a lot better than rituximab when used in combination with idelalisib. This is probably a good thing in Canada because most patients will have better access to rituximab than ofatumumab.

As a general first impression, it appears that the effects of idelalisib in combination with an anti-CD20 antibody are not as durable as ibrutinib monotherapy (comparing between studies). However, the patient populations were not exactly the same, and based on the reported characteristics, it appears that the idelalisib studies may have selected a higher risk group of patients. Overall, other than with ibrutinib, no other phase III randomized trials have shown good, durable responses in a high-risk relapsed/refractory CLL population.

**New Evidence:** Please describe the response and overall survival (OS) results of Study 119.

**Dr. Owen:** The overall response rates reported for idelalisib plus ofatumumab in this study were good. This is consistent with what is generally seen with any of the novel agents. The lymph node reductions are prompt and patients feel better quickly, which is important, but those results would not be enough motivation to use a treatment without it demonstrating reasonable disease control in terms of PFS or OS.

In this study, the median OS was the same in both arms, but this might be due to the fact that in the era of novel agents, and with other new clinical trials recruiting, patients had other novel salvage therapies available to them after going off the study, particularly in the U.S. where they would have had access to ibrutinib. As this was an unblinded study, more patients opted to leave the ofatumumab arm to seek other therapies, which makes it difficult to draw a conclusion from the OS data.

The major take-home message from these data is that idelalisib plus ofatumumab does work well for a lot of patients and it produces reasonably durable responses in a very high-risk population compared with options that were available 5 years ago; however, this is not a cure. The median OS of 20.9 months is not what we would like to see in a population with a median age of 68 years, which reminds us that there is still a long way to go in terms of maximizing outcomes for patients with CLL.

**New Evidence:** What were the most common toxicities observed with idelalisib plus ofatumumab? How were these toxicities managed?

**Dr. Owen:** The most common grade 3/4 toxicities reported in this study were neutropenia, diarrhea/colitis, and pneumonia/pneumonitis. This is consistent with the safety results reported in an integrated analysis of 8 idelalisib trials in B-cell malignancies by Coutre et al. This type of integrated analysis provides very valuable information, however, it would be helpful if the study reported the median time on therapy. It is sometimes difficult to determine the incidence of AEs for an agent like idelalisib that is given until disease progression because the drug is very efficacious, and therefore, an advantage in terms of response and survival may be seen quickly; this leads to results being presented early, when the median number of months on therapy is not that long. Diarrhea/colitis can occur very late, with a median of about 7 months on idelalisib before its onset. In a phase II study evaluating idelalisib in combination with rituximab in CLL patients 65 years or older, grade ≥3 diarrhea/colitis was reported to be 42% with a median duration of idelalisib exposure of 22.9 months. In this study, with the median duration of idelalisib exposure of 12.3 months, the reported frequency of 20% grade 3/4 diarrhea/colitis is reasonable.
With increased experience in using idelalisib, as is the case with any new agent moving from initial phase I/II studies to controlled phase III trials, strategies to manage emerging AEs have been established. A recent paper by Coutre et al. provides recommendations from an expert panel on how to manage the AEs associated with idelalisib treatment. Guidance on how to manage common AEs can also be found in the product monograph. Diarrhea/colitis can be managed with drug discontinuation and use of oral steroids such as budesonide. Diarrhea/colitis then generally resolves quickly and approximately half of patients can be successfully rechallenged with lower doses of idelalisib after drug discontinuation and treatment with steroids. I have had some patients that need to remain on steroids in order to be successfully maintained on idelalisib because the colitis returned. The recommendation for the management of pneumonitis is drug discontinuation and treatment with systemic corticosteroids such as prednisone. I would not recommend rechallenging with idelalisib after drug-induced pneumonitis.

New Evidence: Given the results of this study, in which patients would you consider using idelalisib plus ofatumumab if it were available?

Dr. Owen: I think that any high-risk relapsed/refractory patient could get clinical benefit from the combination of idelalisib and ofatumumab. That being said, at this point, combining idelalisib with ofatumumab does not seem to be better than with rituximab, so with the current Health Canada approval for idelalisib in combination with rituximab, Canadian physicians should feel comfortable with giving idelalisib in combination with rituximab in patients who are eligible to receive it.

New Evidence: Which idelalisib combination therapy do you see as most promising for the treatment of CLL?

Dr. Owen: I think it is difficult at this point to say which idelalisib combination therapy is best because there have not been any head-to-head studies. I would debate, based on results so far from this phase III trial, that there is no reason to want to choose ofatumumab in combination with idelalisib when rituximab is currently available in Canada. Ideally, I would want to use the best anti-CD20 monoclonal antibody available in combination with idelalisib, and currently, the new anti-CD20 antibody obinutuzumab appears to be more potent and has better single-agent efficacy than rituximab. However, this antibody has not been studied in combination with idelalisib for the treatment of patients with relapsed CLL, so we would need such a study to be completed to see whether the addition of obinutuzumab to idelalisib leads to better responses.
Background

Although therapies for patients with chronic lymphocytic leukemia (CLL) have significantly improved over the last few decades, there is no curative therapy and patients will invariably relapse and require additional treatment. Until recently, safe and effective treatment options were limited for many patients with relapsed CLL. In particular, there were no effective treatment options for patients with high-risk cytogenetics, such as del(17p) or TP53 mutations, as these patients do not respond to chemomunotherapy to the same degree as other CLL patients and they generally maintain shorter responses. In addition, after each line of therapy, patients become older and their performance status often declines. Therefore, patients with CLL who have already received multiple lines of therapy have markedly reduced tolerance to available chemotherapies.

Fortunately, we are now entering a new era of CLL management where we are beginning to see how the improved understanding of the molecular biology of CLL is being translated into highly effective targeted options. Two novel targeted agents for CLL that are now approved by Health Canada are the BTK inhibitor, ibrutinib, and the PI3K delta inhibitor, idelalisib (in combination with rituximab). Both of these agents have the advantage of being orally available, making them desirable options for patients and physicians. More importantly, ibrutinib and idelalisib have been shown to be highly effective in patients that are notoriously difficult to treat with chemotherapy, such as those with high-risk cytogenetics. In addition, although these new agents are not free of toxicity, they have relatively favourable toxicity profiles, and contrary to other chemotherapy regimens, elderly patients are better able to tolerate both ibrutinib and idelalisib.

Several clinical trials are further investigating the efficacy and safety of ibrutinib and idelalisib in CLL. At the ASCO Annual Meeting in Chicago this year, the final results were presented for Study 119, a phase III randomized controlled trial evaluating the efficacy and safety of idelalisib in combination with ofatumumab versus ofatumumab alone in patients with relapsed CLL. New Evidence spoke with Dr. Laurie Sehn (British Columbia [B.C.]), Dr. Neil Berinstein (Ontario), and Dr. Sarit Assouline (Quebec), who have provided their perspectives on the results of Study 119 and the safety of idelalisib in CLL.

New Evidence: What are the current treatment options available for patients with relapsed/refractory CLL in your province?

Dr. Sehn: In B.C., treatment of relapsed CLL relies mostly on chemotherapy-based regimens. The combination of fludarabine and rituximab (FR) is the preferred first-line therapy for patients with CLL in B.C., and at the time of relapse, it may be used again if the patient had a prolonged benefit from this treatment. However, a different chemotherapy backbone, such as bendamustine, CVP (cyclophosphamide, vincristine, prednisone), or chlorambucil, is typically used after treatment with FR. We are eager to introduce ibrutinib and idelalisib into the treatment algorithm in B.C.; currently, these drugs are only available through company-sponsored patient programs.

Dr. Berinstein: There are many therapeutic regimens that look exciting for the treatment of patients with relapsed CLL; however, access to those therapies in Ontario is complicated, particularly for combination regimens. In Ontario, alkylating agents (e.g., chlorambucil, bendamustine) or fludarabine, given as single agents, are the only therapies that are provincially funded for the treatment of relapsed CLL. We try to avoid using these chemotherapies in patients with del(17p) or TP53 mutations, and in those cases would apply for ibrutinib via a compassionate access program. pCODR (pan-Canadian Oncology Drug Review) made a positive recommendation for ibrutinib and for idelalisib in combination with rituximab for the treatment of relapsed CLL, conditional on the cost-effectiveness of these regimens being improved to an acceptable level. However, we do not yet know when these regimens will be funded by Cancer Care Ontario.

Dr. Assouline: In Quebec, patients with relapsed CLL have access to chemotherapy-based regimens such as FCR (fludarabine, cyclophosphamide, rituximab), FR, and chlorambucil plus rituximab. Many physicians have also been using other chemomunotherapy combinations. However, with the recent funding of ibrutinib for patients with relapsed CLL in Quebec, I am currently using much less chemotherapy in the relapsed setting than in prior years. Idelalisib plus rituximab is not yet provincially funded and is currently only available by company-sponsored patient programs.
**New Evidence**: Please describe the patient population included in Study 119.

**Dr. Sehn**: The strength of this study is that it generally targeted a higher risk, difficult-to-treat population, as enrolled patients had to have experienced CLL progression less than 24 months from completion of their last prior therapy. This was not a required inclusion criterion in other CLL studies in the relapsed setting, such as the phase III RESONATE study that evaluated ibrutinib versus ofatumumab in patients with relapsed CLL. The patients in Study 119 had a biologically poor risk profile, with approximately 40% of patients having del(17p) or TP53 mutations and 80% having unmutated immunoglobulin heavy chain variable region (IGHV) status. In addition, almost 50% of patients had refractory disease (defined as the first evidence of CLL progression less than 6 months from completing last therapy).

**Dr. Berinstein**: Study 119 allowed patients with high-risk features to be enrolled, such as del(17p) and TP53 mutations, and overall, the population appears to be heavily pretreated. This population is representative of the types of relapsed CLL patients that are currently in need of more effective therapies.

**Dr. Assouline**: The patient population investigated in this study would be considered difficult to treat, since a large number of patients had del(17p), unmutated IGHV status, and bulky disease. I think the characteristics of patients reported in this study are typical of what you would see in a relapsed CLL population.

**New Evidence**: Please describe the efficacy results of Study 119. How do these results compare to other regimens in a similar patient group?

**Dr. Sehn**: Given that entry criteria for each trial can be different, I would not compare results across different trials in CLL. Certainly the results within this trial demonstrate that idelalisib plus ofatumumab is an effective regimen. The combination of idelalisib and ofatumumab achieved superior response rates and progression-free survival (PFS) compared with ofatumumab alone, and in general, the results were favourable in terms of what we would normally expect in this type of heavily pretreated, high-risk patient population.

**Dr. Berinstein**: The overall response rate in the idelalisib plus ofatumumab arm was significantly better than in the ofatumumab monotherapy arm (75% vs. 18%, p<0.001), and this superiority was observed in all of the subgroups analyzed. The median PFS in the idelalisib plus ofatumumab arm was essentially double the length of the median PFS in the ofatumumab monotherapy arm, and this same benefit was observed in the population of patients with del(17p) or TP53 mutations. The improved PFS seen with the addition of idelalisib to ofatumumab did not translate into an overall survival (OS) advantage; however, a larger number of patients in the ofatumumab monotherapy arm discontinued the study prior to disease progression, which likely contributed to the similar OS results in the two treatment groups.

Overall, this study shows that the combination of idelalisib with an anti-CD20 antibody improves outcomes compared with the antibody alone, which is what we would expect to see. I think the strength of this study, compared with the study which evaluated idelalisib plus rituximab versus rituximab alone (Study 116/117), is that ofatumumab monotherapy has higher single-agent activity than rituximab in CLL and is therefore a more reasonable comparator.

In terms of comparing the results of this study to other studies with a similar patient group, because patient populations are so heterogeneous, the only way you can really compare regimens is through a randomized controlled trial. Even if there are some differences in characteristics, such as the frequency of patients with del(17p), this could have an effect on the results, thus making them difficult to compare.

**Dr. Assouline**: The efficacy results for idelalisib plus ofatumumab in the overall population were very good. A significantly prolonged PFS was observed for patients treated with idelalisib plus ofatumumab compared with ofatumumab alone (median PFS: 16.3 vs. 8.0 months, p <0.0001). As is seen with other novel targeted therapies, all subgroups of patients benefited from the addition of idelalisib to ofatumumab. In the phase III RESONATE trial, which evaluated ibrutinib versus ofatumumab in patients with relapsed/refractory CLL, at a median follow-up of 16 months, the median PFS reported for ibrutinib was not reached compared with 8.1 months for ofatumumab. This PFS result is a little better than what was achieved with idelalisib plus ofatumumab in Study 119, however, the patient populations in these two studies were different, making them difficult to compare.

**New Evidence**: Please describe the safety results of Study 119.

**Dr. Sehn**: Idelalisib plus ofatumumab was fairly well tolerated, although the addition of idelalisib resulted in a greater toxicity risk than ofatumumab alone. In this study, the toxicities reported were consistent with what has been previously described with idelalisib, including neutropenia, diarrhea/colitis, rash, and infections (i.e., pneumonia). In general, the majority of these toxicities were lower in grade.
Dr. Berinstein: The safety results from Study 119 showed that there is an increase in certain grade 3/4 adverse events (AEs) and serious AEs and with the addition of idelalisib to ofatumumab. These include diarrhea/colitis, neutropenia, transaminitis, and febrile neutropenia. These data show that there is a modest price to be paid, in terms of increased toxicity, for the improved response and PFS you can achieve by adding idelalisib to ofatumumab.

Dr. Assouline: I think the safety results presented are as expected based on previous idelalisib trials. Grade 3/4 diarrhea/colitis was more frequent in patients treated with idelalisib plus ofatumumab than with ofatumumab alone (20% vs. 1%). This is similar to what was reported in Study 116/117, which evaluated idelalisib plus rituximab versus rituximab alone. The most frequent grade 3/4 AE in patients treated with idelalisib plus ofatumumab was neutropenia, which occurred in 34% of patients. This is partly related to CLL rather than idelalisib treatment; although, the incidence of grade 3/4 neutropenia in the ofatumumab arm was lower (15%), indicating that idelalisib treatment does appear to cause some neutropenia. The frequency of neutropenia with idelalisib plus ofatumumab would not prevent me from using this regimen, as other CLL drugs such as ibrutinib or rituximab also lead to some neutropenia. The two AEs associated with idelalisib plus ofatumumab therapy that would need to be considered when treating patients with this regimen are diarrhea/colitis, because it might impact the long-term ability to give the drug, and infusion-related reactions, because in the short term they can bring stress to the patients and clinic.

New Evidence: Another abstract presented at ASCO 2015 reported on an integrated analysis of eight clinical trials focusing on the safety of idelalisib in B-cell malignancies. What was your impression of the results from this analysis?

Dr. Sehn: This compilation of data further solidifies our understanding of the toxicities associated with idelalisib, so that they can be identified early and managed successfully. With any new medication there is a learning curve, but as we gain more experience with idelalisib, we are now better able to look out for common toxicities and manage them if they occur.

Dr. Berinstein: I am thankful that I was able to enter patients in an idelalisib trial so I could gain experience with the drug and learn more about its toxicities. There was a learning curve, but I now feel comfortable managing the toxicities associated with idelalisib. I learned that many toxicities (transaminitis, diarrhea) are fairly responsive to temporarily holding or reducing the dose of idelalisib. I also found that if a patient develops pneumonia or pneumonitis, you need to have a high index of suspicion as to the cause of this AE. Appropriate testing is needed to determine if the cause was septic or drug-related, because if idelalisib treatment was the cause, one must be very careful about rechallenging the patient.

Dr. Assouline: Although I have not yet used idelalisib in my practice, I do not feel concerned about the toxicity profile and this would certainly not deter me from using it. Based on the literature describing the AEs related to idelalisib and the management of these events, I feel confident that most medical and hemato-oncologists could effectively treat patients with idelalisib.

New Evidence: Please describe the type(s) of CLL patients who would benefit from an idelalisib-based regimen.
Dr. Sehn: Based on its favourable toxicity profile, idelalisib should be readily administrable to most patients with CLL. The patients who will be most eager to access the drug are those with high-risk cytogenetics, because of its demonstrated efficacy in this population, as well as in patients where chemoimmunotherapy is lacking in effectiveness. Regardless of cytogenetics, patients with relapsed and refractory CLL run out of treatment options, and it is important for them to have access to novel therapies such as idelalisib.

Dr. Berinstein: Based on what we know today, I think that an idelalisib-based regimen would be an effective treatment option for a patient with recurrent CLL that had previously been treated with fludarabine and an alkylating agent such as bendamustine. It would also be a good regimen to consider for higher-risk CLL patients, as they might not have as good of a response to more standard treatment.

Dr. Assouline: Idelalisib-based regimens would not only benefit relapsed CLL patients with high-risk features, but I believe any patient with relapsed CLL could see a benefit from this type of regimen.

New Evidence: Are additional steps needed to better understand the efficacy and safety of idelalisib in the treatment of CLL?

Dr. Sehn: Moving forward, we need to learn more about the sequencing of all the therapeutic options available, to see where idelalisib best fits in the armamentarium of CLL treatments. Comparative trials that investigate idelalisib against other standard treatments will be useful in order to answer those questions. We are most hopeful to eventually have biomarkers that can help select the best targeted therapy for a patient based on their underlying biology. With the growing number of treatments available and new targeted agents being tested in clinical trials, we are in an exciting time for CLL research and hope that these new options will lead to improved outcomes and quality of life for patients with CLL.

Dr. Berinstein: In the era of novel agents, one of the biggest challenges is to learn how to sequence these drugs. We know that idelalisib plus ofatumumab is an effective combination in patients with relapsed/refractory CLL, so the next step should be to compare this regimen to ibrutinib in a head-to-head phase III trial. It will also be important to determine whether idelalisib plus ofatumumab will be active in patients who have relapsed while on ibrutinib therapy. Lastly, it would be interesting to see how idelalisib regimens fit into first-line therapy for unfit patients with CLL.

Dr. Assouline: An important question that remains to be answered is whether patients treated with idelalisib will regain their normal immunity so that they are at less risk of infections. In my practice, infections such as shingles and recurrent sinusitis remain a problem for patients.

Another important step is working towards finding a combination regimen that will induce a deeper (minimal residual disease [MRD] negative) response and would allow for treatment-free intervals. As seen in Study 119, treatment with idelalisib plus ofatumumab produces very few complete responses (one patient), which is also true for ibrutinib monotherapy. Combinations with other agents such ABT-199 or bendamustine might increase the number of complete responses and MRD-negative responses, which would result in a longer duration of response and the ability to stop treatment.

Long-term follow-up of a phase Ib trial of idelalisib in combination with chemoimmunotherapy in patients with relapsed/refractory CLL

**Background**
At ASCO 2015, Barrientos and colleagues presented the long-term efficacy and safety results of a phase Ib trial of idelalisib in combination with chemoimmunotherapy in patients with relapsed/refractory chronic lymphocytic leukemia (CLL).1

**Study design**
- Patients enrolled in this phase Ib trial were ≥18 years of age and had:
  - Relapsed/refractory CLL requiring treatment according to the International Workshop on CLL criteria (2008);
  - No prior bone marrow transplantation;
  - No t(11;14) or cyclin D1 overexpression;
  - Absolute neutrophil count ≥1,000/µL and platelets ≥75,000/µL (unless lower counts were related to underlying CLL);
  - Aspartate aminotransferase/alanine aminotransferase levels <2 times the upper limit of normal; and
  - No active hepatitis B or C.
- Patients were given idelalisib continuously at a dose of 100 mg or 150 mg twice daily for 48 weeks in combination with a limited number of cycles of chemoimmunotherapy: rituximab, bendamustine, bendamustine plus rituximab, ofatumumab, fludarabine, chlorambucil, or chlorambucil plus rituximab.
- The primary endpoint of the study was safety and the secondary endpoint was efficacy (i.e., overall response rate [ORR] and progression-free survival [PFS]).
- Patients could be enrolled in an idelalisib single-agent extension study after 48 weeks if they continued to benefit from idelalisib treatment.
- Grade 1, 2, and ≥3 bleeding events were reported using Medical Dictionary for Regulatory Activities and Common Terminology Criteria for Adverse Events terms.

**Key findings**
- A total of 114 patients with a median age of 65 years (range: 41–87 years) and a median of three prior therapies (range: 1–9) were enrolled in the study.
- Forty-nine percent of patients had refractory disease, 29% had deletion 17p [del(17p)] and/or TP53 mutations, 16% had del(11q), and 80% had unmutated IGHV.
- The median duration of exposure to idelalisib was 15.1 months (range: 0.3–48.6 months).
- Sixty-one patients (54%) were enrolled in the extension study and 21 patients (34%) were continuing on the extension study at the time of analysis.
- Overall, the most common reasons for drug discontinuation were progression (28 patients), adverse events (AEs) (28 patients), and death (15 patients).
- The most common AE of any grade was diarrhea (57 patients, 50%). (Table 1)
  - Grade ≥3 diarrhea occurred in 16 patients (14%).
  - Any grade and grade ≥3 colitis occurred in 12 patients (11%) and 11 patients (10%), respectively.
  - Diarrhea and colitis led to study drug discontinuation in seven patients (6%) and six patients (5%), respectively.
- Neutropenia was the most common laboratory abnormality (any grade, 70%; grade ≥3 50%). (Table 1)
- Pneumonia was the most frequent serious AE reported (n = 18, 16%). (Table 2)
- ORR was 83% overall and 70% in patients with del(17p)/TP53 mutations. (Figure 1)
- Median PFS was 26.1 months overall, 20.3 months in patients with del(17p) or TP53 mutations, and 36.8 months in patients without del(17p) or TP53 mutations. (Figure 2)
- In the overall population, the median OS had not been reached; the proportion surviving at 36 months was 73.1% (95% CI: 61.5–84.7%).
- The proportion surviving at 36 months for patients with and without del(17p) or TP53 mutations was 57.3% (95% CI: 22.6–92.1%) and 78.3% (95% CI: 66.7–89.8%), respectively.
### Study design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary (combination) Study 101–07, N = 114</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 19</td>
<td>Rituximab 375 mg/m²/wk</td>
<td>x 8 cycles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idelalisib 100 or 150 mg BID</td>
<td>Continuous therapy</td>
<td></td>
</tr>
<tr>
<td>n = 18*</td>
<td>Bendamustine 70/90 mg/m²</td>
<td>Days 1, 2 x 6 cycles</td>
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<tr>
<td></td>
<td>Idelalisib 100 or 150 mg BID</td>
<td>Continuous therapy</td>
<td></td>
</tr>
<tr>
<td>n = 15</td>
<td>Rituximab 375 mg/m²/wk</td>
<td>x 6 cycles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bendamustine 70 mg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idelalisib 150 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 21</td>
<td>Ofatumumab 1,000 mg</td>
<td>12 doses over 6 months</td>
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<tr>
<td></td>
<td>Idelalisib 150 mg BID</td>
<td>Continuous therapy</td>
<td></td>
</tr>
<tr>
<td>n = 12</td>
<td>Fludarabine (oral) 40 mg/m²</td>
<td>Days 1–5 x 6 cycles</td>
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<tr>
<td></td>
<td>Idelalisib 150 mg BID</td>
<td>Continuous therapy</td>
<td></td>
</tr>
<tr>
<td>n = 15</td>
<td>Chlorambucil 10 mg/m²</td>
<td>Days 1–7 x 12 cycles*</td>
<td></td>
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<tr>
<td></td>
<td>Idelalisib 150 mg BID</td>
<td>Continuous therapy</td>
<td></td>
</tr>
<tr>
<td>n = 14</td>
<td>Rituximab 375 mg/m²/wk</td>
<td>Day 1 x 6 cycles</td>
<td></td>
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<tr>
<td></td>
<td>Chlorambucil 10 mg/m²</td>
<td>Days 1–7 x 12 cycles*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idelalisib 150 mg BID</td>
<td>Continuous therapy</td>
<td></td>
</tr>
</tbody>
</table>

*9 patients treated with idelalisib 150 mg BID/bendamustine 70 mg/m², 5 with idelalisib 150 mg BID/bendamustine 90 mg/m², and 4 with idelalisib 100 mg BID/bendamustine 90 mg/m².

†Minimum of 3 cycles until best response up to 12 cycles.
### Table 1. Adverse events and select laboratory abnormalities

<table>
<thead>
<tr>
<th>Adverse events in &gt;10% of patients</th>
<th>All patients (N = 114)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade, n (%)</td>
<td>Grade ≥3, n (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57 (50)</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Colitis</td>
<td>12 (11)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>51 (45)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>42 (37)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (32)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (29)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>26 (23)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Constipation</td>
<td>25 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>25 (22)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Rash</td>
<td>24 (21)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chills</td>
<td>19 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>18 (16)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (13)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>15 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>13 (11)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

### Table 2. Serious adverse events in >2 patients

<table>
<thead>
<tr>
<th>SAEs in &gt;2 patients</th>
<th>All patients (N = 114) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Colitis</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>4 (4)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; SAEs = serious adverse events

ALT/AST = alanine aminotransferase/aspartate aminotransferase

*Worst grade post-baseline, primary study only.
Key conclusions

- **Idelalisib administered in combination with chemoimmunotherapy regimens:**

  - Induced responses in 83% of patients with relapsed/refractory CLL;
  - Demonstrated durable responses with an overall median PFS of 26 months;
  - Had a manageable safety profile, without increased/overlapping toxicities; and
  - Demonstrated substantial clinical activity in heavily pretreated, refractory, high-risk CLL, including in patients with del(17p)/TP53 mutations.

Adherence and dose intensity following administration of the ibrutinib 420 mg dose in patients with previously treated CLL

Background
Results from the phase III RESONATE trial demonstrated that ibrutinib prolonged progression-free survival (PFS) and overall survival (OS) compared with ofatumumab in previously treated patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).\(^1\)\(^2\) An analysis of the effect of dose adherence — to the ibrutinib 420 mg once-daily dose — on PFS in CLL patients in the RESONATE trial was presented at ASCO 2015 and EHA 2015.

Study design
• This analysis was performed using data from the interim analysis of the phase III RESONATE trial.
• In this phase III trial, patients with CLL or SLL who had received ≥1 prior therapies were randomized to receive either 420 mg ibrutinib once daily (n = 195) or intravenous ofatumumab at an initial dose of 300 mg, followed by 11 doses of 2,000 mg over 24 weeks (n = 196).
• Missed doses (≥8 days) had to be on consecutive days with ibrutinib restarting after the missed doses.
• The mean duration of missed doses was based on the sum of all missed doses for each patient.
• Dose intensity (DI) was defined as the proportion of administered vs. planned doses of the full 420 mg (3 capsules) ibrutinib dose.

Key findings
• The median age of patients in this analysis was 67 years (range: 30–86 years) and 40% of patients were ≥70 years of age.
• Other baseline characteristics included the presence of deletion 17p [del(17p)] (32%) and TP53 mutations (50%), Cumulative Illness Rating Scale score ≥6 in patients ≥65 years of age (32%), and median creatinine clearance ≤60 mL/min (33%).
• For events that led to missed doses, treatment restarted at the original dose in 73 of 79 patients (92%).
• Dose reduction of one capsule (to 280 mg) was required in 3.6% of patients.
• Dose reduction of two capsules (to 140 mg) was required in 0.5% of patients.

Study design

CLL = chronic lymphocytic leukemia; CT = computed tomography; CYP = cytochrome P450; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = Independent Review Committee; iv = intravenous; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; SLL = small lymphocytic lymphoma
Fifty percent of these patients who reduced their dose later re-escalated to ibrutinib 420 mg.

- Eight patients required a dose reduction due to an adverse event (AE).
- Diarrhea was the only AE resulting in dose reduction in >1 patient at the interim analysis.
- For patients with a missed dose, the most frequent reasons were neutropenia (13%, 10 of 79 patients) and pneumonia (11%, nine of 79 patients).
- Overall, 58 patients missed doses for ≥ 8 consecutive days.
  - The mean duration of a missed dose event was 18.7 days (range: 8–56 days).
  - The mean number of missed dose events per patient was 1.3 (range: 1–4).
- More patients missing ≥ 8 consecutive days of ibrutinib had PFS events (defined as death or non-response at 3 months) than those missing <8 days: 17/57 (30%) with PFS events vs. 17/137 (12%) with PFS events, respectively.
- PFS was shorter in patients missing ≥ 8 consecutive days of ibrutinib compared with those missing <8 days (median PFS: 10.9 months vs. not reached [NR]). (Figure 1)
- The overall mean DI was 95% (median 100%, range: 36–102%) with a median of 8.6 months of ibrutinib treatment.
- There were fewer PFS events in patients with overall DI above the mean (95%) vs. below the mean: 16/137 (11.7%) with PFS events vs. 19/58 (32.8%) with PFS events, respectively.
- PFS was longer in patients with DI above the mean vs. below the mean (median PFS: NR vs. 6.9 months, respectively; \( p = 0.0127 \)). (Figure 2)
- In patients with del(17p) and TP53 mutations, there were fewer PFS events with DI above vs. below the mean (del[17p]: 18% vs. 42%, respectively; TP53 mutations: 9% vs. 29%, respectively).
- PFS was longer in patients with del(17p) with DI above vs. below the mean: median PFS NR vs. 10.9 months, respectively.
- The following parameters describe ibrutinib exposure for 179 patients receiving ibrutinib 420 mg with pharmacokinetic assessment at weeks 1 and 4.
  - The area under the curve (AUC) was 370 ng•h/mL (steady state range: 91–1,613 ng•h/mL).
  - The median \( C_{\text{max}} \) (maximum concentration) was 74 ng/mL (steady state range: 12–316 ng/mL).
- Patients treated at the 420 mg dose experienced similar exposure regardless of weight or age.
- At the interim analysis, 8.2% of patients randomized to ibrutinib had died.
- There were fewer death events in patients with DI above (5.8%) compared with below (13.2%) the mean (i.e., 8-week mean DI compared with overall survival starting at 8-week time point). (Figure 3)

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**Figure 1. Progression-free survival by missed dose ≥ 8 consecutive days**

![Progression-free survival by missed dose ≥ 8 consecutive days](image1)

**Figure 2. Progression-free survival by mean dose intensity**

![Progression-free survival by mean dose intensity](image2)

\( NR \) = not reached; PFS = progression-free survival
Key conclusions

- The favourable tolerability profile of ibrutinib allowed for an overall high DI.
- There was no correlation between baseline weight or age and estimated steady-state AUC or Cmax.
- Higher DI was associated with improved PFS, independent of del(17p) or TP53 mutations.
- Withholding ibrutinib for more than 7 days was associated with more PFS events.
- These results demonstrate the clinical importance of sustained adherence to continuous once-daily 420 mg ibrutinib dosing in patients with previously treated CLL.

References:


Phase III study of ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in patients with treatment-naïve CLL/SLL (PCYC-1130: iLLUMINATE)

Background
The study design of a phase III trial comparing the chemotherapy-free combination of ibrutinib and obinutuzumab to chlorambucil plus obinutuzumab, in treatment-naïve patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (iLLUMINATE) was presented at ASCO 2015 and ICML 2015.12
Study design

• This multicentre, randomized, phase III study was initiated to evaluate the efficacy and safety of ibrutinib combined with obinutuzumab in treatment-naïve patients unfit for chemoimmunotherapy.

• Approximately 212 patients with treatment-naïve CLL/SLL, who are considered unsuitable for fludarabine-containing chemoimmunotherapy, will be enrolled and randomized 1:1 to receive ibrutinib in combination with obinutuzumab or chlorambucil in combination with obinutuzumab.

  ◦ Obinutuzumab will be given intravenously at 100 mg on day 1, 900 mg on day 2, and 1,000 mg on days 8 and 15 of cycle 1, followed by 1,000 mg on day 1 only for cycles 2–6.
  ◦ Oral ibrutinib (420 mg) will be given once daily continuously until progressive disease (PD) or unacceptable toxicity.
  ◦ Oral chlorambucil (0.5 mg/kg) will be given on days 1 and 15 in each of 6 cycles.

• Patients with independent review committee (IRC)-confirmed PD in the chlorambucil plus obinutuzumab arm will be allowed to cross over to receive single-agent ibrutinib therapy.

• To be included in the study, patients are required to have:
  ◦ Treatment-naïve CLL/SLL;
  ◦ Active disease requiring therapy (defined by the 2008 International Workshop on CLL criteria [iwCLL]); and
  ◦ One of the following: a Cumulative Illness Rating Scale score ≥6, an estimated creatinine clearance >30 but <70 mL/min, deletion 17p or TP53 mutation, or age ≥65 years.

• Patients will be excluded from the trial if they have evidence of central nervous system involvement or known, or suspected, history of Richter’s transformation.

• The primary endpoint of the study is progression-free survival based on IRC assessment.

• Secondary endpoints include:
  ◦ IRC-assessed overall response rate (2008 iwCLL criteria);
  ◦ Minimal residual disease-negative response rate;
  ◦ Overall survival;
  ◦ Rate of hematologic improvement;
  ◦ Patient-reported outcomes (based on European Organisation for Research and Treatment of Cancer Euro quality of life-SD-5L questionnaire); and
  ◦ Safety and tolerability.

• Exploratory endpoints include:
  ◦ Time-to-next treatment;
  ◦ Clonal evolution (new cytogenetic abnormalities);
  ◦ Predictive biomarkers of efficacy and/or disease-related mechanisms of resistance;
  ◦ Impact of ibrutinib on obinutuzumab-related infusion reactions;
  ◦ Medical resource utilization (e.g., hospitalizations, transfusions, and use of growth factors);
  ◦ Pharmacokinetic characteristics of ibrutinib; and
  ◦ Genetic and molecular prognostic markers.

• Enrollment has been initiated and is planned in 16 countries, including Canada, the United States, the European Union, and Australia.

• This study is registered on ClinicalTrials.gov (NCT02264574).

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Patient population

• Treatment-naïve CLL
• Considered unsuitable for fludarabine-containing chemoimmunotherapy

---

Oral ibrutinib 420 mg once daily continuously until PD or unacceptable toxicity

iv obinutuzumab 1,000 mg (6 cycles)*

Oral chlorambucil 0.5 mg/kg days 1 and 15 of each cycle (6 cycles)

iv obinutuzumab 1,000 mg (6 cycles)*

CLL = chronic lymphocytic leukemia; iv = intravenous; PD = progressive disease

*Cycle 1: 100 mg day 1, 900 mg day 2, 1,000 mg days 8 and 15; Cycles 2–6: 1,000 mg day only
Key conclusions

■ Additional front-line treatment options are needed for patients with CLL that are unsuitable for purine analog-based chemoimmunotherapy.

■ Ibrutinib demonstrates high response rates and durable remissions in patients with relapsed/refractory CLL and in elderly patients with treatment-naive CLL, respectively.

■ There is an ongoing phase III PCYC-115 study (RESONATE-2) evaluating single-agent ibrutinib vs. chlorambucil in treatment-naive patients age ≥65 years.

■ The phase III iLLUMINATE study was initiated to evaluate the efficacy and safety of ibrutinib combined with obinutuzumab in treatment-naive patients unfit for fludarabine-containing chemoimmunotherapy.


Safety of idelalisib in B-cell malignancies: integrated analysis of eight clinical trials

Background
At ASCO 2015 and EHA 2015, the integrated analysis of the safety data from eight clinical trials of idelalisib in B-cell malignancies was presented.1,2

Study design
• An integrated analysis of safety was conducted for 760 subjects with CLL, indolent non-Hodgkin lymphoma, or other B-cell malignancies who received idelalisib alone (50 mg twice daily [BID] to 350 mg BID) or as part of a combination regimen (idelalisib doses of 100 or 150 mg BID).
• Clinical trials included in the analysis are shown in Table 1.
• Most subjects were heavily pre-treated with relapsed disease.

Key findings
• Common adverse events (AEs) and important laboratory results in patients given idelalisib monotherapy (n = 354) and idelalisib combination therapy (n = 406) are presented in Table 2.
• Overall, grade ≥3 diarrhea occurred in 106 patients (14%) and was generally a late-onset AE. The median time to onset was 7.1 months (Q1, Q3: 3.7, 12.3). (Figure 1)
• Pneumonitis occurred in 24 patients (3%) and most AEs occurred within the first 6 months of treatment. The median time to onset was 4.2 months (Q1, Q3: 2.5, 6.6). (Figure 2)
• AEs leading to dose modification included aminotransferase/aspartate aminotransferase (ALT/AST) elevations (13%), diarrhea/colitis (11%), and rash (5%).
• Discontinuations due to these AEs were infrequent (3%, 5%, and 2%, respectively).
• Dose interruption allowed successful re-challenge in most patients. (Table 3)
Table 1. Clinical trials included in analysis

<table>
<thead>
<tr>
<th>Study number</th>
<th>N</th>
<th>Drug regimen</th>
<th>ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>101–02</td>
<td>191</td>
<td>Dose-ranging monotherapy</td>
<td>NCT00710528</td>
</tr>
<tr>
<td>101–07</td>
<td>232</td>
<td>Dose-ranging combination therapies</td>
<td>NCT01088048</td>
</tr>
<tr>
<td>101–08</td>
<td>64</td>
<td>Idelalisib 150 mg BID + rituximab</td>
<td>NCT01203930</td>
</tr>
<tr>
<td>101–09</td>
<td>125</td>
<td>Idelalisib 150 mg BID</td>
<td>NCT01282424</td>
</tr>
<tr>
<td>101–10</td>
<td>13</td>
<td>Idelalisib 150 mg BID</td>
<td>NCT01306643</td>
</tr>
<tr>
<td>101–11</td>
<td>25</td>
<td>Idelalisib 150 mg BID</td>
<td>NCT01393106</td>
</tr>
<tr>
<td>101–99</td>
<td>NA*</td>
<td>Continued idelalisib after parent study</td>
<td>NCT01090414</td>
</tr>
<tr>
<td>312–0116</td>
<td>110</td>
<td>Idelalisib 150 mg BID + rituximab</td>
<td>NCT01539512</td>
</tr>
</tbody>
</table>

*101-99 is a long-term extension study that enrolls eligible patients from studies 02, 07, 08, and 10; safety data from this study are included herein, but patients are not counted twice in the overall safety population.

BID = twice daily; NA = not applicable

Table 2. Common adverse events (≥15 % of patients) and laboratory abnormalities

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Idelalisib monotherapy (n = 354)</th>
<th>Idelalisib combination therapy (n = 406)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>96 (27)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>131 (37)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>112 (32)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>91 (26)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Cough</td>
<td>80 (22)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>60 (17)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Chills</td>
<td>49 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>47 (13)</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Constipation</td>
<td>39 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>43 (12)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40 (11)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>53 (15)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46 (13)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

Laboratory abnormality, n (%)

<table>
<thead>
<tr>
<th>Laboratory abnormality, n (%)</th>
<th>Idelalisib monotherapy (n = 354)</th>
<th>Idelalisib combination therapy (n = 406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>162 (46)</td>
<td>234 (58)</td>
</tr>
<tr>
<td>Anemia</td>
<td>102 (29)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>94 (27)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>ALT or AST increased</td>
<td>176 (50)</td>
<td>56 (16)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase
Key conclusions

■ Idelalisib has been evaluated in a range of B-cell malignancies and had a manageable safety profile in clinical trials.

■ Clinically significant AEs reported include severe diarrhea/colitis (generally later onset) and pneumonitis (occurring most often during the first 6 months of treatment).

■ Grade ≥3 ALT/AST elevations occurred in 14% of patients; most resolved with dose interruption.

■ Patients with pneumonitis, grade ≥3 diarrhea/colitis, ALT/AST elevations, or rash have been successfully rechallenged after dose interruption.

Outcomes of anticoagulant or antiplatelet use in patients with CLL or iNHL in idelalisib trials

Background
Preclinical studies indicate that idelalisib treatment results in minimal toxicity to platelets, making it a potential option for patients predisposed to bleeding events. A recent post hoc analysis characterized bleeding events, and the use and outcomes of antiplatelet (AP) and anticoagulant (AC) medication, in patients treated with idelalisib for chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin lymphoma (iNHL) in two registrational trials. The results from this analysis were presented at ASCO 2015 and EHA 2015.1,2

Study design
• This was a post hoc analysis of two clinical trials:
  ◦ A multicentre, randomized, double-blind, placebo-controlled phase III trial in 220 frail patients with CLL (study 312–116; NCT01539512); and
  ◦ A multicentre, single-group, open-label phase II trial in 125 relapsed/refractory iNHL patients (study 101–09; NCT01282424).
• Patients with CLL received either continuous idelalisib 150 mg twice daily (BID) or placebo plus 8 doses of rituximab.
• Patients with iNHL received idelalisib 150 mg BID (option for dose reductions to 100 or 75 mg) until disease progression, unacceptable toxicity, or death.
• Concomitant AC, AP, and/or thrombolytic use was permitted in both studies.
• The following patients were included in the CLL and iNHL studies:
  ◦ Patients with relapsed CLL who could not receive cytotoxic agents due to severe neutropenia or thrombocytopenia (patients with any grade of thrombocytopenia were allowed), creatinine clearance <60 mL/min, or Cumulative Illness Rating Scale score >6 for coexisting illnesses unrelated to CLL; and
  ◦ Patients ≥18 years of age with iNHL refractory to rituximab and an alkylating agent, Eastern Cooperative Oncology Group performance score of 0, 1, or 2, absolute neutrophil count ≥1.0 x 10^9/L, and platelet count ≥50 x 10^9/L.
• Data cutoffs were October 15, 2014 (CLL) and June 11, 2014 (iNHL).

• AC/AP medications were searched using Medical Dictionary for Regulatory Activities (MedDRA) coding (World Health Organization Anatomical Therapeutic Chemical antithrombotic agents and drugs containing acetylsalicylic acid).
• Grade 1, 2, and ≥3 bleeding events were summarized using MedDRA and Common Terminology Criteria for Adverse Events (CTCAE) terms.

Key findings
• The analysis included 345 patients with CLL (n = 220) or iNHL (n = 125).
• In the CLL study, 16% of patients on idelalisib plus rituximab and 28% of patients on placebo plus rituximab had grade ≥3 thrombocytopenia at baseline.
• In the iNHL study, 2% of patients had grade ≥3 thrombocytopenia at baseline.
• Concomitant AC, AP, and/or thrombolytic use was common in all treatment groups, occurring in 62.7% of patients in the idelalisib plus rituximab arm and 36.1% of patients in the idelalisib plus placebo arm of the CLL study, and in 47.2% of patients in the iNHL study.
• The most common concomitant AC/AP medications used were aspirin, enoxaparin, and heparin.
• The incidence of bleeding events was similar with idelalisib monotherapy, idelalisib plus rituximab, and placebo plus rituximab. (Figure 1)
• Grade ≥3 bleeding events occurred in one patient on idelalisib plus rituximab, one patient on placebo plus rituximab, and four patients on idelalisib monotherapy.
  ◦ The patient treated with idelalisib plus rituximab was receiving both AC and AP therapy.
  ◦ The patient treated with placebo plus rituximab received one day of AC therapy seven days before the bleeding event, and had grade 4 thrombocytopenia at baseline and at the time of the event.
  ◦ Of the patients on idelalisib monotherapy, two were receiving concomitant AC therapy and two were not receiving any AC or AP therapy.
The proportion of bleeding events by CTCAE grade was also similar between the idelalisib plus rituximab and the placebo plus rituximab treatment groups.  
- Of the 59 bleeding events that occurred overall, 40 (68%) were grade 1.  
- In patients receiving AC/AP therapy, the incidence of bleeding events was similar across treatment groups. (Figure 2)  
- Of the 30 patients receiving warfarin, seven reported bleeding events: two patients in each of the arms of the CLL study (all grade 1), and three patients in the iNHL study (grade 1, n = 2; grade 2, n = 1).  
- Bleeding events were most frequent with placebo plus rituximab in patients not receiving AC/AP therapy. (Figure 3)  
- Overall, small proportions of patients had events while on only an AC (n = 12) or only an AP (n = 6).  
- The most frequent bleeding events included epistaxis and contusions.  
- There were no intracranial or intraspinal bleeds.
Nonmyeloablative allogeneic conditioning with bendamustine, fludarabine, and rituximab improves survival in CLL

**Background**

The preliminary results of allogeneic stem cell transplantation in lymphoma or chronic lymphocytic leukemia (CLL) patients after conditioning with bendamustine, fludarabine, and rituximab (BFR) were recently reported. At ICML 2015, more mature outcomes from this investigation were reported for CLL, and safety and efficacy results were compared with those from a previous regimen using fludarabine, cyclophosphamide, and rituximab (FCR).
Study design

- This study included 89 CLL patients treated on three trials (one included consecutive FCR-BFR) at a single centre.

- Twenty-six patients (29%) received BFR and 63 patients (71%) received FCR.

- The BFR regimen consisted of bendamustine 130 mg/m² intravenously (iv) daily on days −5 to −3 prior to transplantation, as a substitute for cyclophosphamide (750 mg/m² on days –5, –4, and –3) in the FCR regimen.

- The dose and schedule of fludarabine (30 mg/m² iv daily on days –5, –4, and –3) and rituximab (375 mg/m² iv on day −13 and 1,000 mg/m² on days −6, +1, and +8) were similar in both regimens.

- Tacrolimus and methotrexate were used for graft versus host disease (GVHD) prophylaxis.

- Thymoglobulin 1 mg/kg iv was given on days −2 and −1 in patients receiving a matched unrelated donor (MUD).

Key findings

- Patient characteristics were similar in the FCR and BFR groups, including median age (57 years and 58 years, respectively), median number of prior therapies (3 in each group), refractory disease (48% and 38%, respectively), presence of deletion 17p [del(17p)] (24% and 27%, respectively), and unmutated IGHV status (92% and 90%, respectively).

- Peripheral blood was the stem cell source for 92% of patients in the BFR arm and 87% of patients in the FCR arm.

- More patients in the BFR group than in the FCR group received their transplants from unrelated donors (54% vs. 32%, respectively; p = 0.05).

- Thirty-eight percent of BFR patients vs. 3% of FCR patients did not experience an absolute neutrophil count <500 (p<0.001), and 81% vs. 63% of patients, respectively, did not experience a platelet count <20,000 (p = 0.08). (Table 1)

- The median follow-up times for patients in the BFR and FCR groups were 29 months (range: 19–60 months) and 104 months (range: 34–195 months), respectively.

- The 3-year overall survival (OS) in the BFR and FCR groups was 82% and 51%, respectively (p = 0.03). (Figure 1)

- The 3-year OS values were consistently better in the BFR group compared with the FCR group across the prognostic factors studied. (Table 2)

- Non-relapse mortality (NRM) was 8% for BFR and 23% for FCR at 2 years (p = 0.09). (Table 3)

- In patients with a Hematopoietic Stem Cell Transplantation-specific Comorbidity Index ≥3, BFR had a trend towards a lower NRM rate compared with FCR (14% vs. 28%, respectively, p = 0.4).

- The incidence of acute grade III-IV GVHD was 4% and 10% in the BFR and FCR groups, respectively, despite the higher frequency of MUD transplants in the BFR group. (Table 3)

- Grade 4 acute GVHD was not observed in either group.

- The 3-year incidence of extensive chronic GVHD in the BFR vs. FCR groups was 45% vs. 58%, respectively (p = 0.01). (Table 3)

---

### Table 1. Engraftment

<table>
<thead>
<tr>
<th>Variable</th>
<th>FCR (n = 63)</th>
<th>BFR (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD34 (x10⁶/kg)</td>
<td>4.9 (2–15)</td>
<td>5.6 (0.35–19)</td>
<td>0.3</td>
</tr>
<tr>
<td>Percentage of patients with ANC never &lt;500</td>
<td>3</td>
<td>38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of patients with platelets never &lt;20,000</td>
<td>63</td>
<td>81</td>
<td>0.08</td>
</tr>
<tr>
<td>Day 90 donor T cell</td>
<td>93 (12–100)</td>
<td>98 (47–100)</td>
<td>0.4</td>
</tr>
<tr>
<td>Day 90 donor myeloid</td>
<td>98 (46–100)</td>
<td>100 (39–100)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count; BFR = bendamustine, fludarabine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab
Table 2. Three-year overall survival by prognostic factor

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>FCR (%)</th>
<th>BFR (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched unrelated donor</td>
<td>30</td>
<td>93</td>
<td>0.02</td>
</tr>
<tr>
<td>Presence of del(17p)</td>
<td>50</td>
<td>80</td>
<td>0.3</td>
</tr>
<tr>
<td>Absence of del(17p)</td>
<td>50</td>
<td>79</td>
<td>0.05</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>50</td>
<td>79</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 3. Non-relapse mortality and graft-versus-host disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>FCR (%)</th>
<th>BFR (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>7</td>
<td>4</td>
<td>0.09</td>
</tr>
<tr>
<td>1 year</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2 year</td>
<td>23</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Acute GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II-IV</td>
<td>40</td>
<td>23</td>
<td>0.2</td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD (Extensive, 3 years)</td>
<td>58</td>
<td>45</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Key conclusions

- This is the first study to suggest that conditioning in nonmyeloablative stem cell transplant for CLL patients is important.
- Compared to FCR, BFR resulted in less myelosuppression, less GVHD, and better overall survival.

Fit vs. Frail Assessment Strategies in CLL

A Summary of the Presentation by Dr. Alina Gerrie at CCOLD 2015

At the 2015 Canadian Conference on Lymphoproliferative Disorders (CCOLD), Dr. Alina Gerrie, Clinical Assistant Professor at the University of British Columbia, Canada, presented the use of fitness assessment as a tool for identifying treatment goals for older patients with chronic lymphocytic leukemia (CLL). The presentation, summarized in this article, highlighted several criteria in fitness assessment and emphasized its incorporation in clinical trials, as age alone may be inadequate in determining treatment goals and strategies.

In 2014, the Canadian Cancer Statistics showed that Canadians over the age of 50 years represented 89% of all new cases of cancer in Canada, while nearly half (43%) of all new cases occurred in individuals aged 70 years or older. According to 2014 statistics from the National Cancer Institute in the U.S., new cases of leukemia and non-Hodgkin lymphoma were diagnosed in patients at the median age of 66 years.

CLL is commonly diagnosed in the elderly, with the median age at diagnosis being 72 years. Conventional therapies for CLL, such as orally administered chlorambucil, are generally considered to be mild. However, researchers now recognize the wide heterogeneity of the disease due to the underlying tumour biology (e.g., deletions of 17p and 11q); thus, current treatments have become more effective but also more intensive and aggressive. In the past, elderly patients have been underrepresented in clinical trials. Therefore, the focus of recent CLL studies has now been shifted toward the elderly, but the inclusion criteria for these studies remain to be addressed.

As treatment intensity increases, there is a need for reliable methods that can identify patients who may not be eligible for standard chemotherapy but would benefit from alternative therapies. Age as a criterion alone for patient selection in clinical trials or for treatment selection ignores the heterogeneity among individuals. As such, at the International Workshop for CLL in 2013, the fitness of patients with CLL was proposed to be a better determinant for patient selection and for identifying treatment goals.

The classification of fitness is necessary because it can: (i) accurately categorize a patient’s life expectancy unrelated to CLL (i.e., other health problems); (ii) determine the patient’s ability to tolerate aggressive chemotherapy, which includes the prediction of treatment modifications and discontinuation; and (iii) allow for more consistent stratification and selection of patients across clinical trials.

For fitness assessment, there are various criteria that can be used to classify patient: performance status, functional assessments, comorbidities, organ function, the Comprehensive Geriatric Assessment (CGA), and frailty assessment and biomarkers.

Performance Status

For the evaluation of performance status, the Eastern Cooperative Oncology Group (ECOG) score and the Karnofsky score are often used. In North America, the ECOG score is more commonly used than the Karnofsky score (Table 1).

Functional Assessments

Functional assessments include Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). The ADL assessment encompasses basic self-care tasks such as feeding, toileting, and bathing. The IADL assesses complex tasks that are performed to enable independent living, such as managing finances, handling transportation, and using electronic devices. It has been shown that 9% of patients who were newly diagnosed with CLL reported difficulty with ADL.

Comorbidities

In a Mayo Clinic study of 373 patients who were newly diagnosed with CLL, 89% of patients had one or more comorbidities, and 46% of these patients had at least one major comorbidity, such as coronary
artery disease, peripheral vascular disease, diabetes mellitus, or chronic obstructive pulmonary disease. There are numerous scoring systems for categorizing the severity of comorbidities in patients with CLL, such as the Cumulative Illness Rating Scale (CIRS), the Charlson Comorbidity Index, the National Cancer Institute Comorbidity Index, and the Hematopoietic Cell Transplant Comorbidity Index.

The CIRS scoring system was first proposed in 1968, and it was investigated in the elderly in 1992. The CIRS score has been validated and it has been shown to predict the life expectancy in a general geriatric population. Recently, the CLL8 trial from the German CLL Study Group (GCLLSG) included only patients with a CIRS score ≤6, and the results demonstrated that the risk of mortality was doubled for patients with a CIRS score >3 compared with those who had a CIRS score of 0–3. There are a few limitations in the CIRS scoring system. The cut-offs in CIRS are unclear and not validated. It is also difficult to determine if CIRS can predict patient survival. Moreover, CIRS may not be the best tool for predicting treatment toxicity, as various studies have shown differing results.

There are 14 domains in the CIRS scoring system and each domain represents a different physiological system. Each system can be scored from 0 to 4, ranging from ‘no problem’ to ‘extremely severe problem’, respectively (Table 2). It should be noted that many elderly patients have mild problems such as acid reflux, and thus it would be very easy to attain a total CIRS score >6.

Organ Function

Renal function has been measured extensively in patients with CLL because it has been shown to be a better predictor of toxicity with fludarabine-based therapy compared with age. Renal function is commonly estimated with the Cockcroft-Gault equation. The equation relies heavily on age, and thus it may lose precision in elderly patients. There are other equations for estimating renal function (e.g., Modification of Diet in Renal Disease formula), but they have not been studied thoroughly. There are also other biomarkers of organ function, such as liver enzymes, B-type natriuretic peptide (for heart failure), and hemoglobin A1c (HbA1c; for diabetes).

Comprehensive Geriatric Assessment

The CGA can systematically quantify functional impairments and disabilities in elderly patients. It has been demonstrated to predict treatment toxicity, treatment modification, and mortality in older patients with solid and hematologic malignancies. Standardized scales are available for the CGA. However, all of the reported studies with the CGA have been retrospective and there were heterogeneities in the patient population as well as in the geriatric assessment methodology that was used. Despite these limitations, the CGA has been incorporated into guidelines. For instance, the International Society of Geriatric Oncology has recently published a consensus statement which states that the CGA should be performed in older patients with cancer, but due to the diversity of tools and lack of detailed study, the exact set of tools remains to be defined. The National Comprehensive Cancer Network guidelines for older adult oncology have also made similar recommendations. It is foreseen that the CGA will be more commonly used in the field of geriatric oncology.
The main domains in the CGA are listed in Table 3.13,14 The CGA can be very time-consuming and resource-demanding, but it can provide detailed information for clinicians and health care providers such that the most effective treatments can be delivered to older patients with cancer.

**Frailty Assessment and Biomarkers**

For frailty assessment, simplified geriatric assessments (GAs) with self-reporting questionnaires are available, allowing for quicker and simultaneous assessment of multiple domains (e.g., Geriatric 8, Vulnerable Elders Scale).15 Some of the frailty biomarkers that have been tested and reported in clinical studies include chronic inflammatory markers (e.g., TNF-α, IL-6, PAI-1), markers of cellular senescence (e.g., telomere length), and markers of sarcopenia (e.g., muscle mass). These biomarkers have been shown to be associated with frailty and mortality, but may be altered by the malignancy itself.

**The Ideal Tool**

The ideal tool for fitness assessment would be one that can predict life expectancy (independent of CLL), risk of treatment toxicity, and risk of treatment modification and discontinuation.16 In routine clinical practice, clinical judgement remains the standard of care, but the aforementioned tools may help in forming these judgments. The advantages and disadvantages of fitness assessment tools are listed in Table 4. Figure 1 outlines how fitness assessment in patients with CLL can determine the goals of therapy.

To better demonstrate how fitness assessment can be used to determine treatment goals in patients with CLL, two clinical examples are provided.

### Table 3. The domains and corresponding tests in the Comprehensive Geriatric Assessment

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional status</td>
<td>ADL, IADL</td>
</tr>
<tr>
<td></td>
<td>Performance status</td>
</tr>
<tr>
<td></td>
<td>Falls – Timed Up and Go test (TUG)</td>
</tr>
<tr>
<td>Socioeconomic issues</td>
<td>Social support, income, housing, transport</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>CIRS, Older American Resources &amp; Services (OARS)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Dementia (MMSE, MoCA)</td>
</tr>
<tr>
<td></td>
<td>Depression (Geriatric Depression Scale, HADS)</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Mini nutritional assessment, BMI, weight loss</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Medication reconciliation, drug interactions</td>
</tr>
<tr>
<td>Geriatric syndromes</td>
<td>Delirium, incontinence, neglect, FTT, pressure ulcers, osteoporosis, fractures</td>
</tr>
</tbody>
</table>

ADL = Activities of Daily Living; BMI = body mass index; CGA = Comprehensive Geriatric Assessment; FTT = failure to thrive; HADS = Hospital Anxiety and Depression Scale; IADL = Instrumental Activities of Daily Living; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment

### Table 4. The advantages and disadvantages of various tools used in fitness assessment

<table>
<thead>
<tr>
<th>Tool</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age</td>
<td>Easiest Predicts life expectancy May predict treatment toxicity</td>
<td>Significant heterogeneity Risks undertreatment of elderly patients</td>
</tr>
<tr>
<td>Performance status</td>
<td>Easy, fast, reproducible May predict treatment toxicity (limited evidence)</td>
<td>Does not predict life expectancy Deterioration of ECOG/KI may be due to disease itself</td>
</tr>
<tr>
<td>Comorbidity scores</td>
<td>Predict life expectancy May predict treatment toxicity (inconsistent results)</td>
<td>Time-consuming Differences in methodology Cut-offs not validated</td>
</tr>
<tr>
<td>Organ function</td>
<td>Easy, reproducible within labs Predicts treatment toxicity/ modification (CrCl)</td>
<td>Other organ function not studied</td>
</tr>
<tr>
<td>CGA</td>
<td>Thorough assessment May predict toxicity and life expectancy (retrospective)</td>
<td>Very time-consuming Resource-demanding Interpretation is complex</td>
</tr>
<tr>
<td>Frailty screening</td>
<td>Simpler than CGA May predict toxicity and life expectancy (retrospective)</td>
<td>Not enough evidence thus far Biomarkers not yet ready for prime time</td>
</tr>
</tbody>
</table>

CGA = Comprehensive Geriatric Assessment; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; KI = Karnofsky Index
Clinical Case Study #1 — The Fit Patient with CLL

A 70-year-old female was diagnosed at the age of 65 with Rai stage 0 CLL with an absolute lymphocyte count (ALC) = 8. The disease has now progressed to Rai stage 4 CLL with ALC = 27, hemoglobin (Hb) = 100, platelets = 85, small palpable neck lymph nodes, and symptomatic splenomegaly (17 cm). Fluorescence in situ hybridization (FISH) testing showed an isolated deletion of 13q. She has normal test results for creatinine clearance (CrCl) and liver function. She is extremely active and involved in multiple physical activities, such as hiking and rafting. Her past medical history includes prior surgeries for carpal tunnel syndrome and left knee arthroscopy.

The GCLLSG’s CLL8 trial has established the chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab (FCR) as a standard of care for fit patients with CLL.17 In the trial, the inclusion criteria are those for a fit patient (ECOG of 0–1, CIRS ≤6, and CrCl ≥70 mL/min). The median age was 61 years (range 30–81); 31% of the patients were ≥65 years old and 11% were ≥70 years old. The study showed that there were significant improvements in progression-free survival (PFS) and overall survival (OS) for patients treated with FCR compared with those who were treated with fludarabine plus cyclophosphamide (FC), regardless of the patient’s age. However, there was an increase in grade 3/4 toxicities for patients over 65 years of age who were treated with FCR.

The GCLLSG then conducted another trial, known as CLL10, comparing FCR with bendamustine plus rituximab (BR) in fit patients (CIRS ≤6 and CrCl ≥70 mL/min).18,19 The median age was 61 years (range 33–82); 37% of the patients were ≥65 years old and 18% were ≥70 years old. The study showed that in the overall patient population, treatment with FCR resulted in a significant increase in PFS compared with BR (p < 0.001), as well as increases in complete response and minimal residual disease (MRD) negativity (Figure 2).19 For patients over 65 years of age, there was no significant difference in PFS between FCR and BR. At three years of observation, there was no significant difference in OS between the treatment arms. Patients treated with FCR showed increased severe neutropenia (87.7% for FCR vs. 67.8% for BR) and infections (39.8% for FCR vs. 25.4% for BR).

Recently, an ECOG Alliance (U.S.) phase III clinical trial is being conducted in younger patients with CLL (age ≤65 years, ECOG 0–2, CrCl >40 mL/min). The trial compares clinical outcomes from treatment with FCR versus ibrutinib plus rituximab. In this trial, comorbidity is not used as an entry criterion, but it will be evaluated and analyzed for the effect on clinical outcomes.

The female patient described in this case study has been evaluated as having a CIRS score of 1 (due to prior surgeries; +1 if prescription glasses are included; +2 if CLL is included). She is considered as having a long life expectancy unrelated to CLL and is considered fit. Based on the outline in Figure 1, she would be classified as a “Go-Go” patient. She would not be a candidate for the Alliance trial in younger patients with CLL but would be eligible for an equivalent trial (Alliance [U.S.]/National Cancer Institute of Canada [NCIC] trial) in older patients which compared the efficacy and safety of BR, ibrutinib plus rituximab, and ibrutinib alone. In the absence of a clinical trial, it is recommended that BR or FCR be used because more intensive treatments can be given to fit patients.
Clinical Case Study #2 — The Unfit Patient with CLL

A 70-year-old retired male veterinarian was diagnosed at the age of 68 with Rai stage 1 CLL (ALC = 8). The disease has now progressed to Rai stage 3 CLL with ALC = 200 with rapid lymphocyte doubling time, Hb = 105, platelets = 130, and symptomatic splenomegaly (18 cm). The patient has reported night sweats and weight loss. FISH test results are normal. He has CrCl of 35 mL/min, but he has normal liver function test results and total bilirubin. His past medical history includes hypothyroidism, atrial fibrillation (on warfarin), hypertension (on angiotensin-converting enzyme inhibitors), congestive heart failure, recurrent pneumonia, benign prostatic hypertrophy (on treatment), multiple squamous cell carcinomas, and renal cysts.

In the recently published CLL11 study, Goede et al. investigated the effects of obinutuzumab plus chlorambucil (G-Clb) in patients with CLL and coexisting conditions.20,21 In total, 780 patients with previously untreated CLL (CIRS >6 and/or CrCl <70 mL/min) were enrolled in this trial and they were randomized to receive one of three treatments: (i) G-Clb, (ii) rituximab plus chlorambucil (R-Clb), or (iii) chlorambucil alone (control). The median age of the patients was 73 years (range 39–90), with a median CrCl of 61 mL/min. The median CIRS score was 8 (i.e., decreased fitness); 82% of patients had more than three conditions, while 27% had at least one condition that was not well controlled at baseline (i.e., CIRS = 3). The results showed that G-Clb significantly improved PFS compared with R-Clb (29.2 months vs. 15.4 months; \( p <0.001 \)) (Figure 3), but there was no significant difference in OS between the two treatments.21 In addition, treatment with G-Clb resulted in MRD negativity in the bone marrow and blood in 19.5% and 37.7% of patients, respectively.20 For patients treated with G-Clb, 33% had neutropenia, 12% had infections, and 20% experienced infusion-related reactions.20

An ECOG Alliance (U.S.)/NCIC study is currently being conducted in older patients (age ≥65 years, ECOG 0–2, CrCl ≥40 mL/min, and total bilirubin <1.5 times upper limit of normal) to compare the efficacy and safety of BR vs. ibrutinib plus rituximab vs. ibrutinib alone. The optional GAs include: functional assessments (ADL, IADL, Karnofsky, number of falls every 6 months, and the Timed-Up-and-Go test), comorbidities (Older American Resources and Services evaluation), psychological state (Blessed Orientation-Memory-Concentration scale and Hospital Anxiety and Depression Scale [HADS]), social activity (Medical Outcomes Study of Social Activity), social support (Social Support Survey), and nutrition (body mass index [BMI] and weight loss in the last 6 months).

The male patient described in this case study has multiple comorbidities and would have a CIRS score of 10 (+1 if renal insufficiency is considered a hard-to-control chronic problem; +2 if CLL is included). Based on the outline in Figure 1, he would be considered a “Slow-Go” patient. He would not be eligible for the previously described Alliance (U.S.)/NCIC study due to low CrCl (<40 mL/min). However, it is suggested that chlorambucil plus an anti-CD20 monoclonal antibody (obinutuzumab, if available) would be a good treatment option based on the CLL11 study by Goede et al.20,21 BR would be an alternative for this patient but the treatment would be started at a lower dose of 70 mg/m².

Figure 3. PFS of patients with CLL treated with obinutuzumab plus chlorambucil vs. rituximab plus chlorambucil

![Image of Figure 3](image-url)
Conclusion

In conclusion, using age as the only criterion for determining treatment goals and strategies for patients with CLL is inadequate. Clinical trials should incorporate fitness assessments in order to determine the optimal treatment options. Numerous fitness assessment tools exist, but it should be noted that the cut-offs are not validated and the resulting numbers should be used collectively. In routine practice, clinical judgement remains the standard of care. More importantly, an allied health care team is crucial for the successful implementation of fitness stratification in the clinic.

17. Fischer K, Bahlo J, Fink A, et al. Extended follow up of the CLL8 protocol, a randomized phase-III trial of the German CLL Study Group (GCCLLSG) comparing fludarabine and cyclophosphamide (FC) to FC plus rituximab (FCR) for previously untreated patients with chronic lymphocytic leukemia (CLL): results on survival, progression-free survival, delayed neutropenias and secondary malignancies confirm superiority of the FCR regimen. Blood (ASH Annual Meeting Abstracts) 2012;120:435.
18. Eichhorst B, Fink AM, Busch R, et al. Chemomunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus bendamustine and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): results of a planned interim analysis of the CLL10 trial, an international, randomized study of the German CLL Study Group (GCCLLSG). Blood (ASH Annual Meeting Abstracts) 2013;122:526.
19. Eichhorst B, Fink AM, Busch R, et al. Frontline chemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (R) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): final analysis of an international, randomized study of the German CLL Study Group (GCCLLSG). Blood (ASH Annual Meeting Abstracts) 2014;124:19.
Frontline Management of the CLL Patient

A Summary of the Presentation by Dr. Clemens Wendtner at CCOLD 2015

At the 2015 Canadian Conference on Lymphoproliferative Disorders (CCOLD), Dr. Clemens Wendtner, Secretary of the German CLL Study Group (GCLLSG), Professor of Medicine at the University of Cologne, and Director of the Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine at the Klinikum Schwabing, Munich, gave a presentation on the frontline management of patients with chronic lymphocytic leukemia (CLL). This article summarizes Dr. Wendtner’s presentation.

Treatment Options Based on Fitness

There are many first-line therapies available for treating patients with CLL. For example, the National Comprehensive Cancer Network (NCCN) Guidelines give multiple suggested treatment regimens. However, recommendations such as these guidelines are usually a list of treatment options without guidance on which treatment is best for individual patients that doctors see in their clinics on a day-to-day basis.

Multiple factors, including age and fitness, impact treatment choices. For young, fit CLL patients the frontline standard of care is usually chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR). However, CLL is primarily a disease of the elderly: the median age at which patients are diagnosed is 72 years and 70% of patients with CLL are at least 65 years of age at diagnosis. These elderly patients often have comorbidities, which make them ineligible for FCR due to its high rate of toxicity. Frail patients with CLL can be treated with chlorambucil, which has a lower rate of toxicity; however, it is also less efficacious than FCR. Higher efficacy is often accompanied by higher rates of toxicity, and physicians must determine which regimen is most appropriate for each patient, balancing efficacy with toxicity.

Fit Patients

In Germany, practical guidelines for treating patients with CLL were released in 2014 (Figure 1). The German treatment guidelines give two age-dependent treatment options for fit patients with CLL without deletion 17p [del(17p)] or TP53 mutations (TP53mut): FCR and bendamustine plus rituximab (BR). The study that helped determine the German guidelines for treating fit patients with CLL was the CLL10 study. This was a phase III noninferiority trial comparing FCR with BR in first-line treatment of patients with active CLL without del(17p) and with good physical fitness (CIRS ≤6, creatinine clearance ≥70 mL/min). Patients were randomized to receive either FCR or BR. The primary endpoint was noninferiority of BR in comparison with FCR for 24-month PFS (hazard ratio less than 1.388) (Figure 2).

The complete response (CR) rate (CR + CRi) was higher for FCR compared with BR (39.7% vs. 30.8%, respectively; \( p = 0.034 \)) and the overall response rate (ORR) was similar in each group (95.4% vs. 95.7%, respectively; \( p = 1.0 \)). Overall, the median progression-free survival (PFS) was longer for FCR than BR (55.2 months vs. 41.7 months, respectively; \( p < 0.001 \)) (Figure 3). Although not powered for this subgroup analysis, for patients >65 years of age, the median PFS for BR was 48.5 months; the median PFS in this age group had not yet been reached for FCR (\( p = 0.170 \)). However, for patients ≤65 years of age, FCR had a significantly better PFS compared with BR (53.6 months vs. 38.5 months, respectively; \( p < 0.001 \)) (Figure 4). Overall, grade 3/4 infection rates were significantly higher in the FCR group compared with the BR group (39.1% vs. 26.8%, respectively; \( p < 0.001 \)). In the subgroup analysis by age, the rate of grade 3/4 infections was almost twice as high in patients >65 years of age who were treated with FCR compared with BR (47.7% vs. 20.6%, respectively; \( p < 0.001 \)). The conclusion from this study, which was included in the German treatment guidelines, was that for fit patients (i.e., go-go) with CLL without del(17p) or TP53mut who are >65 years of age, it does not make sense to use FCR, which is a more aggressive treatment; instead this group of patients should receive BR, which is less toxic. Patients who are ≤65 years of age should receive FCR.
Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min)

Randomization

**FCR**
- Fludarabine 25 mg/m² iv, days 1–3;
- Cyclophosphamide 250 mg/m², days 1–3;
- Rituximab 375 mg/m² iv day 0, cycle 1;
- Rituximab 500 mg/m² iv day 1, cycles 2–6

**BR**
- Bendamustine 90 mg/m² days 1–2;
- Rituximab 375 mg/m² iv day 0, cycle 1;
- Rituximab 500 mg/m² iv day 1, cycles 2–6

Noninferiority of BR in comparison to FCR for PFS:
HR (0.1, BR/FCR) less than 1.388

*BR = bendamustine, rituximab; CLL = chronic lymphocytic leukemia; CIRS = Cumulative Illness Rating Scale; FCR = fludarabine, cyclophosphamide, rituximab; HR = hazard ratio; PFS = progression-free survival*
Elderly, Unfit Patients

For symptomatic patients who are unfit (i.e., slow go), without del(17p) or TP53mut, the German CLL guidelines give five choices for first-line treatment: BR, chlorambucil plus rituximab (R-Clb), chlorambucil plus obinutuzumab (G-Clb), chlorambucil plus ofatumumab, and bendamustine plus ofatumumab. However, as with the NCCN guidelines, it is still difficult to advise physicians on which treatment they should choose for an individual patient.

Several studies have investigated first-line treatment for elderly, unfit patients with CLL. The CLL11 study was a phase III trial of previously untreated CLL patients with comorbidities (Cumulative Illness Rating Scale [CIRS] score >6) who were randomized to one of three treatment arms: chlorambucil alone (the previous standard of care for this patient population), R-Clb, and G-Clb (Figure 5). The primary endpoint was PFS. Patients in this trial were a median age of 73 to 74 years. The ORR was significantly higher in the G-Clb arm compared with the R-Clb arm (78.4% vs. 65.1%, respectively; \( p < 0.001 \)); the CR rate was also higher in the G-Clb arm. Minimal residual disease (MRD) negativity was higher in the G-Clb arm than in the R-Clb arm (blood: 38% vs. 3%; bone marrow: 20% vs. 3%, respectively). In this trial, achieving MRD negativity in a 79-year-old patient was not essential. However, MRD negativity can be used to predict response and survival in this trial; the chance of being MRD negative in the G-Clb arm was quite high. At the April 2014 data cut-off, the median investigator-assessed PFS for the G-Clb arm was nearly twice that of the R-Clb arm (29.2 months vs. 15.4 months, respectively) (Figure 6). There was a trend toward an overall survival (OS) advantage in the G-Clb group compared with the R-Clb group, which was not statistically significant. The incidence of infusion-related reactions (IRRs) was higher in patients treated with obinutuzumab. There are clear recommendations to split the antibody treatment; for patients with high leukocyte counts, we have started patients on chlorambucil alone and added the antibody for the second cycle of treatment.

Another study that compared chlorambucil alone with chlorambucil combined with an anti-CD20 monoclonal antibody was the COMPLEMENT1 trial. In this trial, CLL patients who were considered ineligible for fludarabine-based therapy with an Eastern Cooperative Oncology Group status \( \leq 2 \) were randomized 1:1 to receive either chlorambucil plus ofatumumab or chlorambucil alone. Patients were treated for a minimum of three cycles, until best response or progressive disease (PD), up to a maximum of 12 cycles (no crossover was allowed). The results of this study showed that the combination of chlorambucil plus ofatumumab had a superior median PFS compared with chlorambucil alone (22.4 vs. 13.1 months, respectively; \( p < 0.001 \)) (Figure 7). It is very difficult to compare the results from the CLL11 trial with those from the COMPLEMENT1 trial. Based on my personal experience, my preference is for G-Clb; however, other physicians may choose to use ofatumumab in combination with chlorambucil.
Chlorambucil*§

1:

GA101† + chlorambucil*

Rituximab‡ + chlorambucil*

Stage Ia G-Clb vs. Clb

Stage Ib R-Clb vs. Clb

Previously untreated CLL with comorbidities
• Total CIRS score ≥6 and/or CrCl ≤30 mL/min
• Patients with CrCl <30 mL/min or inadequate liver function excluded
• Age ≥18 years

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

*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.

‡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.

§Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb.

Figure 5. CLL11 study design

Figure 6. CLL11 stage II analysis: investigator-assessed PFS (at April 2014 cut-off)
The combination of ofatumumab plus bendamustine was investigated in a multicentre, single-arm, phase II trial of 44 treatment-naïve CLL patients who were not eligible for fludarabine. While the patients were all treatment-naïve, the trial included a mixture of patients, not only slow-go patients. After a median observation time of 14 months, 98% of patients were progression-free; however, the observation time was very short, making the PFS data not very meaningful. Nonetheless, based on this simple phase II trial with only 44 patients, this combination was approved by the European Medicines Agency (EMA) for use in treatment-naïve patients who are ineligible for fludarabine; the EMA also approved the combination of ofatumumab with chlorambucil in this patient population.

Another study that investigated the combination of BR as frontline therapy was a phase II study by the GCLLSG in previously untreated CLL patients. Baseline characteristics included 68 patients (61.8%) with unmutated IGHV, and 41 patients (35.0%) with impaired renal function (i.e., creatinine clearance ≤70 mL/min) who were ineligible for FCR. Treatment with BR resulted in an ORR of 88% with a CR rate of 23%. While there was a high proportion of patients (25.6%) who were ≥70 years of age, this was not an elderly population (i.e., median age was 64 years).

Finally, in the phase III MaBLe study, CLL patients ineligible for fludarabine-based treatment regimens were randomized to receive either BR or R-Clb. This study included patients being treated in their first or second line of therapy. The median age of patients in the study was 72 years and most patients (95%) were taking concomitant medication, making it a representative group of patients. From the interim data, the overall CR rate was significantly higher for BR compared with R-Clb (24% vs. 10%, p = 0.033). For patients receiving first-line treatment, the CR rate was numerically higher in the BR arm (30%) compared with the R-Clb arm (13%) but was not yet significant (p = 0.054). Similar CR rates with R-Clb were reported by the UK and Italian groups. An update to the MaBLe trial will be presented later this year at iwCLL 2015.

In real-world practice in Germany, there is a tumour registry that has compiled patient data from 265 private practice physicians at 122 sites; these data describe how physicians use treatment drugs on a daily basis. The age distribution of patients with CLL at primary diagnosis showed a high fraction of elderly patients (70–79 years) and 74% of patients were ≥65 years at the start of treatment. From 2012 to 2014, the majority of patients (60–65%) received BR as first-line treatment, including elderly patients; a small minority of patients received chlorambucil-based regimens.

Overall, the recommended first-line treatment regimen for elderly (>65 years of age), fit patients with CLL is BR. For less fit patients, chlorambucil with an anti-CD20 monoclonal antibody is an alternative therapy.

**Treatment for High-Risk Patients**

Treatments that are effective in fit and unfit patients without del(17p) or TP53mut are not effective in high-risk CLL patients. The majority of high-risk patients are those with del(17p) and/or TP53mut; roughly 10% of patients have only a TP53mut, without del(17p). A study by Zenz et al. showed that CLL patients with TP53mut without del(17p) have similar PFS and OS outcomes compared with patients with only del(17p).
One treatment option for these patients — alemtuzumab plus dexamethasone — was studied in the CLL2O trial. Patients were generally subdivided into three cohorts: del(17p) without prior treatment, del(17p) relapsed (not refractory), and refractory to fludarabine-based (or similar) treatments. All patients were given alemtuzumab plus dexamethasone for induction therapy, and consolidation with either allogeneic stem cell transplantation or alemtuzumab maintenance was given at the discretion of the patient and physician if at least stable disease was achieved after three cycles. In patients with del(17p) receiving first-line treatment, the PFS was approximately 33 months (Figure 8). However, alemtuzumab was withdrawn from the market in 2012.

Other first-line treatment options that are approved in Europe for patients with del(17p) or TP53mut are the novel agents idelalisib (in combination with rituximab) and ibrutinib. However, the data that have been published on these two agents are minimal. The phase Ib/II 1102/1103 trial of ibrutinib included 31 treatment-naïve patients with CLL/small lymphocytic lymphoma who were >65 years of age and treated them with a fixed daily dose of ibrutinib until disease progression or unacceptable toxicity. While the published PFS and OS data looked great, although it was a short follow-up, only two patients in the treatment-naive group had del(17p). Similarly, the data showing idelalisib can be used as first-line treatment in patients with del(17p) is based on six patients. It is not incorrect to use ibrutinib or idelalisib in this patient setting; however, there is a lack of efficacy data for both of these agents in the frontline treatment of high-risk patients. Nevertheless, in the German treatment guidelines for fit (i.e., go-go) and unfit (i.e., slow-go) patients with del(17p) and/or TP53mut, the recommended treatments are ibrutinib or idelalisib plus rituximab.

New Data on Emerging First-Line Therapies

It is important that we keep trying to improve treatment and determine the efficacy of novel agents through clinical trials. In upcoming phase II trials from the GCLLSG, the treatment regimens have few chemotherapy components. In each of the trials, patients will receive two cycles of debulking treatment with bendamustine (unless contraindicated or low tumour load where debulking is not indicated), followed by induction and MRD-tailored maintenance therapy with a combination of an anti-CD20 monoclonal antibody (i.e., obinutuzumab or ofatumumab) and ibrutinib, idelalisib, or venetoclax. There are four phase II trials using this strategy: CLL2-BIG: bendamustine, ibrutinib, obinutuzumab; CLL2-BAG: bendamustine, venetoclax, obinutuzumab; CLL2-BCG: bendamustine, idelalisib, obinutuzumab; and CLL2-BIO: bendamustine, ibrutinib, ofatumumab.

There is also a fourth generation of phase III trials from the GCLLSG that are designed using chemotherapy-reduced regimens (Figure 9): CLL12, CLL13, and CLL14. The CLL13 trial is for fit patients (go-go) who will be treated in one of four arms of the study: FCR or BR, rituximab plus venetoclax, obinutuzumab plus venetoclax, or obinutuzumab plus ibrutinib and venetoclax (GIVe). The primary outcomes of this trial are PFS (chemoimmunotherapy vs. GIVe) and the MRD negativity rate in peripheral blood at month 15 (chemoimmunotherapy vs. obinutuzumab plus venetoclax). In contrast, the CLL14 trial is for less fit patients (slow-go) who will be treated with either G-Cbl or venetoclax plus obinutuzumab. The primary goal of this trial is to achieve long-term disease control with minimal adverse events. Finally, the CLL2-GIVE trial is a first-line study of patients of all fitness groups with del(17p) and/or TP53mut. The two arms of the study are GIVe versus ibrutinib as initial therapy, followed by ibrutinib in both arms as consolidation therapy, and then, in case of PD, venetoclax. The primary endpoint of the study is the 12-month PFS rate in historical comparison to FCR [del(17p) from CLL8].

Figure 8. (A) Progression-free survival and (B) overall survival by cohort in the CLL2O trial
Summary

For first-line treatment, the German CLL guidelines recommend FCR as the standard therapy for fit, young patients without del(17p) or TP53mut. For elderly (>65 years of age), fit patients without del(17p) or TP53mut, BR is recommended. BR is also an option for unfit patients without del(17p) or TP53mut; other options given in the German CLL guidelines for these patients include chlorambucil plus an anti-CD20 monoclonal antibody. For high-risk patients with CLL [i.e., del(17p) and TP53mut], ibrutinib alone or idelisib plus rituximab are now the preferred treatment options. BCL-2 inhibition (e.g., venetoclax) is another interesting principle that is currently being investigated in the frontline within clinical trials and might potentially synergize with an anti-CD20 monoclonal antibody and/or BTK/P13K inhibition.

Figure 9. Upcoming, fourth-generation, phase III trials from the GCLLSG

References
New Treatment Perspectives in CLL: Using Disease and Patient Characteristics to Optimize Outcomes

Carolyn Owen MD,* Sarit Assouline MD,† John Kuruvilla MD,‡ David MacDonald MD,§ Anna Christofides MSc RD,‖ Sarah Di Clemente MSc,‖ Laurie Sehn MD#

*Dr. Carolyn Owen, Assistant Professor, Foothills Medical Centre & Tom Baker Cancer Centre, Calgary, Alberta; †Dr. Sarit Assouline, Assistant Professor of Medicine, McGill University, Hematologist, Jewish General Hospital, Montreal, Quebec; ‡Dr. John Kuruvilla, Assistant Professor of Medicine, University of Toronto, Hematologist, Princess Margaret Hospital, Toronto, Ontario; §Dr. David MacDonald, Assistant Professor of Medicine, Dalhousie University, Hematologist, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; ‖Anna Christofides, Senior Medical Writer and Managing Director, New Evidence, Toronto, Ontario; ||Sarah Di Clemente, Medical Writer, New Evidence, Toronto, Ontario; #Dr. Laurie H. Sehn, Clinical Assistant Professor, University of British Columbia, Hematologist, British Columbia Cancer Agency, Vancouver, British Columbia.

Corresponding Author: Dr. Carolyn Owen, South Tower Room 603, Foothills Medical Centre, Calgary, AB, Canada, T2N 2T9

Abstract

Therapies for chronic lymphocytic leukemia (CLL) have evolved over the last two decades and newer treatment regimens have significantly improved patient survival. Fludarabine, cyclophosphamide, and rituximab (FCR) was the first therapy to demonstrate a survival advantage for young and fit patients with CLL, making it the gold standard treatment for these patients. However, as the CLL population is diverse in terms of patient age, fitness level, and disease characteristics, patients with CLL vary in their ability to tolerate and respond to FCR; thus highlighting the need for individualized therapy. Recently, important advances have been made in understanding CLL pathogenesis, inspiring the generation of new, targeted agents, such as ibrutinib and idelalisib, which may address the limitations of FCR. These new agents are intelligently designed to target B-cell receptor (BCR) signalling and the CLL microenvironment, resulting in alternate mechanisms of cell death that are specific to CLL cells. This review will highlight the factors currently influencing treatment decisions, the advances made in understanding CLL biology, and the novel BCR pathway inhibitors that may impact treatment decisions and patient outcomes in the future.

1. Background

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, accounting for approximately 11% of all hematologic cancers in adults.1 CLL is predominantly a disease of the elderly, with the median age being 72 years at diagnosis and approximately 75% of patients being 65 years or older.1 In 2010, the overall age-standardized incidence rate for CLL in Canada was 4.8/100,000 people; 6.6/100,000 people for males and 3.3/100,000 people for females.2

Although CLL remains an incurable disease, therapies to treat CLL have evolved over the last 50 years which have significantly improved patient outcomes. Introduction of the monoclonal antibody rituximab to treatment regimens has largely contributed to these improved outcomes. Rituximab is a targeted therapy against CD20, which is expressed on the surface of CLL cells. It induces its cytotoxic effects through complement-mediated lysis, antibody-dependent cellular cytotoxicity, and direct induction of apoptosis.3 Rituximab monotherapy demonstrates only modest response rates in patients with CLL; however, when combined with fludarabine and cyclophosphamide (FC), this regimen can achieve overall response rates (ORRs) and complete response (CR) rates of 95% and 70%, respectively.3 In addition, rituximab plus FC (FCR) demonstrated improved overall survival (OS) compared with FC alone in a randomized, phase III trial of treatment-naïve patients with CLL.4 This was the first ever demonstration of an OS advantage in a phase III trial in CLL and led to the approval of this regimen by the Food and Drug Administration.
As patients differ in their response and ability to tolerate therapy, it is apparent that CLL therapy needs to be individualized for each patient. This emphasizes the need to identify patient and disease characteristics that are indicators for selection of specific therapies, and also the need to develop new therapeutic agents that will be effective in the highest-risk patient subgroups. Recently, significant advances have been made in understanding the biology of CLL, inspiring the generation of new targeted agents that may address the limitations seen with FCR. In contrast to chemotherapies, these new agents are intelligently designed to target dysregulated pathways, resulting in alternate mechanisms of cell death that are specific to CLL cells. Thus, by understanding the biology of CLL, we are moving towards individualizing treatments for CLL patients.

Although many novel agents are currently being investigated in CLL, this review will focus on the B-cell receptor (BCR) signalling inhibitors, idelalisib and ibrutinib, which have been approved by Health Canada for the treatment of CLL. The purpose of this paper is to describe the current patient and disease characteristics that may influence treatment decisions, highlight the advances made in understanding CLL biology that led to the development of BCR signalling inhibitors, and to discuss the potential impact of these novel therapies on treatment decisions and patient outcomes in the future.

2. Factors influencing treatment decisions

2.1. Patient characteristics

As current CLL regimens vary in level of toxicity, one of the most influential factors when choosing a therapeutic regimen for an individual patient is his or her medical fitness. When evaluating fitness, a combination of factors including organ function, performance status, age, and comorbidities must be considered. Fitness assessment tools such as the Cumulative Illness Rating Scale (CIRS) for measuring comorbidities and the Eastern Cooperative Oncology Group (ECOG) system for measuring performance status are often used in clinical trials. However, in clinical practice, Canadian physicians routinely rely on personal experience and patient observation to assess fitness and make treatment decisions, as not all comorbidities are equal when it comes to predicting drug tolerability.

The German CLL Study Group (GCLLSG) has used CIRS to evaluate patient fitness in clinical trials. Using tools such as the CIRS score, the GCLLSG separates patients into the following three fitness categories: ‘go-go’, ‘slow-go’, and ‘no-go’. This classification of patient fitness is a useful aid for defining treatment goals and making treatment decisions. The ‘go-go’ group of patients are typically young and fit with a long life expectancy; therefore, deep remission would be the primary goal of therapy and treatment efficacy would be the priority when choosing a treatment regimen. In contrast, the ‘no-go’ patients are typically frail patients with multiple or severe comorbidities and a short life expectancy. For these patients, palliation is a more appropriate goal; therefore, tolerability of therapy and maintenance of quality of life would be the priority when selecting therapy for these patients. The ‘slow-go’ patients fall in the middle of this spectrum and are typically less fit, with some comorbidities and an unknown life expectancy; therefore, achieving durable remission with a tolerable regimen is the goal for these patients.

For the majority of patients who fall into the ‘slow-go’ category, a balance between efficacy and toxicity is required when choosing therapy for these patients. The relationship between efficacy and safety of CLL therapies has been described by Shanafelt et al., and is a useful perspective to consider when choosing an appropriate therapy. Generally, a strong correlation has existed between efficacy and toxicity, where historically the most effective treatments have been associated with the highest toxicities. As most patients with CLL are older, have at least one comorbidity, and are unable to tolerate highly intensive therapy such as FCR, less effective therapies with fewer toxicities have been preferable.

The patient’s preference is another important consideration when making treatment decisions. A number of factors may affect a patient’s expectations of therapy. Some patients are much more willing to accept the risks of severe toxicity in the hopes of a longer remission, while other patients prefer a less toxic regimen and are accepting of an earlier expected relapse. The need for a doctor-patient partnership when making treatment decisions is important for a disease such as CLL where there are multiple treatment options, each with different risks and benefits. As patients have to undergo treatment and accept toxicities, it is important that patient preferences are communicated and respected.
2.2. Disease characteristics

CLL is a heterogeneous disease with diverse genetic and molecular characteristics, which translates into a wide range of clinical outcomes among patients. Several recurring genetic abnormalities can be seen in CLL, with the most common chromosomal abnormalities including deletions in 13q, deletions in 11q, trisomy 12, deletions in 17p (del(17p)), and deletions in 6q. However, the only genetic marker that is currently used to guide treatment selection is the presence of del(17p).

Patients with del(17p) have the poorest prognosis among genetic subgroups identified thus far, with very low survival rates. These patients also respond poorly to fludarabine-based treatments. In the CLL8 trial, ORR in patients with del(17p) treated with FC or FCR was 34% and 68%, respectively, which was markedly lower than the ORR in the total population (80% and 90%, respectively). Moreover, a high proportion of refractory patients were positive for del(17p) (34.4%), and the PFS at 3 years in patients with del(17p) was very low (0% and 18% in the FC and FCR arms, respectively). Although not directly compared, alemtuzumab in combination with steroids appears to produce better response rates than FCR for patients with del(17p), however, median PFS was still quite short, particularly in relapsed or refractory patients. Because of its poor prognosis, del(17p) has been an indication for consideration of allogeneic stem cell transplantation. However, a recent analysis of patients with advanced CLL who received an allograft found that del(17p) may still be an independent predictor of poor PFS and OS following transplantation. This highlights the need for more effective therapies to treat CLL patients with del(17p).

The deletion of 17p results in the loss of the TP53 locus which encodes the tumour suppressor p53, a protein that plays a critical role after DNA damage by inducing cell cycle arrest and apoptosis. Fludarabine and the alkylating agents function via a p53-dependent mechanism, thus explaining the poor responses of patients with del(17p) to FCR and other chemoimmunotherapies. TP53 mutations, even in the absence of del(17p), have also been observed in a number of studies. In the CLL8 trial, the presence of TP53 mutations was associated with a lower ORR compared with patients with wild-type TP53 (62.1% vs. 95.3%, respectively), as well as a shorter median PFS (12.4 months vs. 45 months) and median OS (39.3 months vs. not reached).

As the presence of del(17p) and TP53 mutations are associated with a poor response to conventional chemotherapy-based treatment, analysis for these genetic lesions is recommended prior to treatment initiation to identify patients who require alternative therapies. The incidence of del(17p) and TP53 mutations in patients with CLL at diagnosis is approximately 4–5% and 5–10%, respectively. This incidence significantly increases at relapse through a process of acquisition of genetic aberrations called clonal evolution. Indeed, in relapsed and fludarabine-refractory patients with CLL, the incidence of del(17p) and TP53 mutations has been reported to be up to 30% and 40%, respectively. This supports the recommendation of a thorough search for TP53 mutations/deletions to be performed before each line of therapy.

3. Understanding the molecular mechanisms driving CLL

3.1. CLL microenvironment

A deeper understanding of the mechanisms of CLL pathogenesis is imperative for the development of novel therapies. At the cellular level, CLL is characterized by the accumulation of mature, non-functional, CD5+, CD19+, CD20+, and CD23+ B-lymphocytes in the blood, bone marrow, and lymphoid tissue. This accumulation of CLL cells was once thought to be strictly a result of impaired apoptosis; however, it is now recognized that an increase in cell proliferation also contributes to the expansion of the CLL clone. Proliferation of CLL cells occurs in distinct anatomical tissue sites called pseudofollicles located in the bone marrow and lymphoid tissues. Within these pseudofollicles, CLL cells interact with accessory cells, including T cells, mesenchymal stromal cells, and monocyte-derived nurse-like cells (NLCs), which, along with matrix factors, make up the CLL microenvironment. The homing and retention of CLL cells to this microenvironment play a critical role in the maintenance of the CLL clone, presenting an attractive target for therapy. The expression and function of chemokine receptors and integrins on CLL cells is essential for this homing to occur. The chemokine receptor CXCR4, which is expressed at high levels on CLL cells in the blood, mediates CLL cell chemotaxis and migration beneath bone marrow stromal cells in response to CXCL12 gradients secreted by stromal cells and NLCs. Similarly, very late antigen-4 (VLA-4) integrin expression on CLL cells, which plays a critical role in lymphocyte trafficking, adhesion, and survival in normal B cells, increases the ability of CLL cells to access protective niches by interacting with vascular cell adhesion molecule-1 (VCAM-1) and fibronectin on stromal cells.

The protective effect of the CLL microenvironment is a product of the complex interactions between CLL cells, accessory cells, and matrix factors that induce survival and proliferative pathways. CLL cell survival can be induced by engagement with the ligands B-cell activating factor of the tumour necrosis factor family (BAFF), CD40L, and a proliferation-inducing ligand (APRIL), which are expressed on the surface of accessory cells. In addition, a recent study that analyzed gene expression in blood, bone marrow, and lymphoid samples from 24 patients with CLL showed that the gene sets associated with the BCR pathway and nuclear factor κB (NF-κB) pathway had the most striking differential expression between tissues,
with significant up-regulation in the lymph nodes. This indicates the prominent role of BCR signalling within the CLL microenvironment. The details of this signalling pathway in normal and malignant B cells are described in the following section.

### 3.2. BCR signalling

Dysregulated BCR signalling has emerged as a key mechanism in CLL pathogenesis. Although the precise mechanism of BCR stimulation is unknown, the BCR has been reported to be activated by antigen binding and by antigen-independent autonomous signalling mechanisms. The BCR is composed of a ligand binding moiety, consisting of an antigen-specific membrane immunoglobulin, and a signal transduction moiety, consisting of two membrane-spanning proteins – Immunoglobulin-associated alpha (CD79A) and Immunoglobulin-associated beta (CD79B). Upon BCR activation, the SRC-family tyrosine kinase LYN is recruited to the receptor where it phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs) on the intracellular portion of CD79A and CD79B. The spleen tyrosine kinase (SYK) is subsequently recruited to phosphorylated ITAMs where it too becomes phosphorylated and activated by LYN. SYK and LYN then play an essential role in BCR signalling by initiating several pathways (Figure 1).

Figure 1. B-cell receptor signalling

AKT = v-akt murine thymoma viral oncogene homolog protein; ATF2 = activating transcription factor 2; BAD = BCL2-associated agonist of cell death; BCR = B-cell receptor; BLNK = B-cell linker protein; BTK = Bruton’s tyrosine kinase; Ca2+ = calcium ion; CD = cluster of differentiation; FOXO3a = forkhead box O3a; GSK3 = glycogen synthase kinase 3; JUN = jun proto-oncogene protein; LYN = LYN proto-oncogene, Src family tyrosine kinase protein; MAPK = mitogen-activated protein kinase; MYC = v-myc myelocytomatosis viral oncogene homolog protein; NFAT = nuclear factor of activated T-cells; NF-κB = nuclear factor of kappa light polypeptide gene enhancer in B-cells; PIP3 = phosphatidylinositol 3,4,5-triphosphate; PI3K = phosphoinositide 3-kinase; PKC = protein kinase C; PLC-γ2 = phospholipase C-γ2; SYK = spleen tyrosine kinase.
In tumour samples from CLL patients, both the levels and activation of Lyn and Syk have been shown to be up-regulated. Moreover, downstream of Lyn and Syk, the Btk and PI3K pathways have also been reported to be amplified in CLL. In addition to activating cell survival and proliferation, BCR stimulation in CLL cells can also induce the secretion of chemokines, including CCL22, CCL3, and CCL4, which can attract accessory cells, such as T cells. This indicates that CLL cells may also play an active role in creating and maintaining their own microenvironment.

4. Novel therapeutic agents targeting BCR signalling

Given the substantial role of BCR signalling in CLL pathogenesis, new therapies have been developed to target this pathway. Currently, ibrutinib (IMBRUVICA®, Janssen Inc.) and idelalisib (Zydelig®, Gilead Sciences Canada, Inc.), which inhibit Btk and PI3K-δ respectively, have demonstrated efficacy in phase III clinical trials in CLL. Although several other agents that target the BCR pathway are being investigated, the following section will focus on ibrutinib and idelalisib, which have been approved by Health Canada for use in patients with CLL.

4.1. Ibrutinib

4.1.1. Mechanism of action

Ibrutinib is the first-in-class, irreversible inhibitor of Btk that covalently binds to Cysteine-481 in the ATP binding domain of the Btk molecule. In CLL cell lines, ibrutinib initiates apoptosis via the caspase pathway and results in reduced MAPK, PI3K, and NF-κB signalling. In addition to disrupting BCR signalling pathways, ibrutinib also affects the interaction between CLL cells and their microenvironment. For example, ibrutinib has been shown to disrupt the protective effect of stromal cells by inhibiting CD40, BAFF, Toll-like receptor, and cytokine signalling. In another study, ibrutinib interfered with the homing and adhesion of CLL cells to the stroma by reducing secretion of chemokines CCL3 and CCL4 in response to BCR activation, and inhibiting CLL cell chemotaxis towards CXCL12 and CXCL13. The inhibitory actions of ibrutinib on the homing of CLL cells to their microenvironment may explain the phenomenon known as redistribution lymphocytosis, which is characteristically seen during the first months of treatment with ibrutinib or idelalisib after patients show a nodal response.

4.1.2. Clinical trials

Ibrutinib has produced promising results in several clinical trials of relapsed/refractory and high-risk patients with CLL. Early results from a pivotal phase Ib/II trial examining ibrutinib monotherapy in previously treated patients with CLL led to its accelerated approval by the FDA for patients with CLL who have received at least one previous therapy. In the published results from this trial, including 85 patients with previously treated CLL, ORR was 71% and response was independent of clinical and genomic risk factors, including the presence of del(17p). At 26 months, the estimated PFS and OS rates were 75% and 83%, respectively. A randomized, phase III study of ibrutinib versus ofatumumab (a next-generation, fully humanized anti-CD20 monoclonal antibody) was also initiated in patients with relapsed or refractory CLL (RESONATE trial). After the first interim analysis, the response rate as determined by an independent review committee was 63% for ibrutinib (including 20% partial response with lymphocytosis), compared to 4% response with ofatumumab. In addition, at a median follow-up of 9.4 months for ibrutinib, PFS was significantly prolonged in the ibrutinib arm compared with the ofatumumab arm (median PFS: not reached vs. 8.1 months, HR = 0.22 [95% CI: 0.15–0.32]; p <0.001). Importantly, this positive effect of ibrutinib was also observed in subgroups of patients with high-risk features, including del(17p) and resistance to purine analogue therapy. Based on the results from the RESONATE trial, the FDA expanded the use of ibrutinib to include patients with CLL that are positive for del(17p). Single-agent ibrutinib has also been approved by Health Canada for CLL patients who have received at least one prior therapy, or for the frontline treatment of patients with del(17p).

The safety results from these clinical trials indicate that ibrutinib is a very well-tolerated drug, with few discontinuations due to treatment-emergent adverse events (AEs) reported. Most of the AEs were grade 1 or 2, including transient diarrhea, fatigue, and upper airway infections. Grade 3/4 hematologic toxicity was infrequent and consisted mostly of neutropenia (approximately 15% incidence). In the RESONATE trial, atrial fibrillation was a serious AE reported at a higher frequency in the ibrutinib arm (ibrutinib, 10 patients; ofatumumab, 1 patient). Bleeding-related AEs of any grade also occurred more frequently in the ibrutinib arm (ibrutinib, 44%; ofatumumab, 12%).

4.2. Idelalisib

4.2.1. Mechanism of action

Idelalisib is an orally bioavailable, first-in-class, isoform-selective PI3K-δ inhibitor. PI3K has four catalytic isoforms (α, β, γ, δ); the delta isoform being highly expressed in lymphoid cells. As idelalisib is highly selective for PI3K-δ, patients do not experience elevations of serum glucose, insulin, or proinsulin C-peptide levels that are typical in patients receiving pan–PI3K inhibitors. In addition, unlike pan-PI3K inhibitors, idelalisib is not cytotoxic to normal Natural Killer cells and T cells. In vitro studies have shown that idelalisib decreases phosphorylation of AKT and extracellular signal-regulated kinase (ERK), thus disrupting BCR signalling. Idelalisib also initiates apoptosis via the caspase pathway, and this was found to be independent of genomic features such as del(11q), del(17p), and immunoglobulin heavy chain variable region
(IgHV) mutational status. Like ibrutinib, idelalisib was also found to antagonize survival signals initiated by CD40L, BAFF, TNF-α, and fibronectin; as well as inhibit BCR-induced secretion of CCL3 and CCL4 from CLL cells and migration of CLL cells towards the chemokines CXCL12 and CXCL13. 53,54

4.2.2. Clinical trials

Idelalisib has demonstrated encouraging results in combination with rituximab in a phase III, randomized controlled study of patients with CLL who had progressed within 24 months after their last treatment and were considered ineligible for chemotherapy due to comorbidities, decreased renal function, or myelosuppression. 55 The population in this study was heavily pretreated and more than 40% of patients were positive for del(17p) or TP53 mutations. The trial was stopped at the interim analysis due to the overwhelming efficacy of idelalisib plus rituximab over rituximab plus placebo. The ORRs were 81% in patients who received idelalisib plus rituximab versus 13% for rituximab plus placebo. Notably, after 12 months of follow-up, patients treated with idelalisib plus rituximab had a significantly improved PFS (HR = 0.15, \( p < 0.001 \)) and OS (HR = 0.28, \( p = 0.02 \)) compared with patients treated with rituximab plus placebo. The PFS superiority held in all subgroups analyzed, including patients with del(17p), TP53 mutations, and IgHV unmutated status. 55 Results from this study led to the FDA approval of idelalisib plus rituximab in July 2014 for patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other existing medical conditions. Health Canada has also approved idelalisib in combination with rituximab for patients with relapsed CLL.

In current clinical trials, idelalisib has demonstrated a good safety profile, and showed good tolerability in heavily pretreated patient populations. The most frequent AEs included fatigue, diarrhea, pyrexia, nausea, chills, and cough, most of which were grade 1 or 2. 51,55 The most clinically significant grade ≥3 AEs reported included pneumonia/pneumonitis, diarrhea with colitis, and alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations. 56 These AEs occur in as many as 20% of patients and are primarily observed after continued drug exposure. They are also manageable in most patients and resolve with appropriate intervention.

5. Future impact on treatment decisions

The introduction of rituximab in combination with FC has largely impacted the goals of therapy for patients with CLL. By combining targeted and non-targeted therapies with unique mechanisms of action, FCR displays additive and synergistic effects that translate to favourable response rates and prolonged PFS and OS. The new small-molecule inhibitors ibrutinib and idelalisib have been intelligently designed to target signalling pathways involved in CLL pathogenesis and are therefore expected to change the landscape of treatment for patients with CLL (Table 1). These new therapies appear to be very tolerable, even in heavily pretreated patients, suggesting that they should also be a good frontline therapy option for unfit CLL patients who are unable to tolerate

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<th>Table 1. The role of patient and disease factors on influencing treatment decisions, in the present and in the future, with the availability of new targeted agents</th>
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aggressive chemoimmunotherapies. In addition, as hematologic toxicities are infrequent, these new agents may be particularly useful in relapsed patients with residual cytopenias from prior therapies. As more experience with these agents is gathered in frailler patients, it is possible that patient fitness will adopt a lesser role in influencing treatment goals in the future.

Ibrutinib and idelalisib have several additional advantages, including the convenience of oral administration. This is an important benefit for patients, giving them flexibility in the timing and location of treatment administration. Unfortunately, these agents are also provided indefinitely (until disease progression), which may lead to issues with patient adherence.

One of the most important features of these novel targeted therapies is their ability to produce substantial responses in heavily pretreated, high-risk patients, including those with del(17p) and TP53 mutations. As patients with these genetic aberrations currently have limited treatment options, the availability of new targeted agents will significantly and positively impact these patients. Although del(17p) and TP53 mutations are the only genetic markers that currently instruct treatment decisions, these genetic aberrations can only partly explain chemotherapy resistance, as TP53 disruptions are present in only about 40% of relapsed and fludarabine-refractory CLL patients. Therefore, it will be important to continue to investigate the biology behind chemorefractoriness in order to identify additional subgroups of patients who may benefit from earlier access to targeted therapy.

6. Conclusions

Understanding CLL biology has led to a new generation of treatment options that promise to be (i) effective, even in patients with TP53 aberrations or heavily pretreated patients with refractory disease, and (ii) convenient and tolerable, even for elderly frail patients. A number of unanswered questions remain with the use of targeted therapies in the treatment of CLL, including which combination therapies are most effective, as well as their long-term efficacy and safety. Over the next few years, it will be exciting to watch how these new agents are incorporated into treatment algorithms and to see whether these new treatments will change the goals of therapy for a wider range of patients to include prolonged survival and maintenance of quality of life.

7. Acknowledgements

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8. Conflict of interest disclosures

Dr. Owen has received honoraria and has served as a consultant for Hoffmann-La Roche and Lundbeck Canada, and has received honoraria from Gilead Sciences, Inc. and Janssen. Dr. Assouline has received honoraria from Hoffmann-La Roche, Lundbeck Canada, and Janssen. Dr. Kuruvilla and Dr. MacDonald have received honoraria from Hoffmann-La Roche, Lundbeck Canada, Gilead Sciences, and Janssen. Dr. Sehn has received honoraria from Hoffmann-La Roche, Lundbeck Canada, Gilead Sciences, and Janssen.

9. References


22. Zenz T, Roth P, Busch R, et al. TP53 mutations and outcome after fludarabine and cyclophosphamide (FC) or FC plus rituximab (FCR) in the CLL8 Trial of the GCLLSG. Blood 2011;114:2854.
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 and for the treatment of patients with symptomatic chronic lymphocytic leukemia (CLL) who have received no prior treatment.

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Acute Promyelocytic Leukemia

Chemo-Free or Chemo-Reduced Therapy is Effective and Safe in APL for Different Risk Groups

The combination of all-trans retinoic acid (ATRA) and anthracycline has been regarded as the standard of care for acute promyelocytic leukemia (APL); however, this regimen is associated with significant toxicity and serious complications, such as cardiomyopathy and secondary myelodysplastic syndromes.\(^1,2\)

Arsenic trioxide (ATO) has been shown to be effective as a single agent for APL, and it has been approved in the relapsed setting in the U.K.\(^3,4\) In North America, ATO is indicated for induction of remission and consolidation in patients with APL, characterized by the PML/RAR\(\delta\) translocation t(15;17), which is refractory to or has relapsed from retinoid and anthracycline therapy.\(^5,6\) In low-risk patients (white blood cell count [WBC] $<10 \times 10^9/L$), the study by Lo-Coco et al. showed that a daily schedule of ATRA plus ATO resulted in improved event-free and overall survival (OS) when compared with ATRA plus idarubicin (AIDA), and indicated that ATRA plus ATO was at least as efficacious as chemotherapy-containing protocols.\(^7\)

APL presents a therapeutic challenge in high-risk patients (WBC $>10 \times 10^9/L$), as these patients have a significantly greater early mortality rate and higher risk of relapse compared with low-risk patients.\(^8\) CD33 is highly expressed in leukemic blast cells, which can be a therapeutic target in APL. Gemtuzumab ozogamicin (GO), an anti-CD33 antibody conjugated with a calicheamicin, has been demonstrated to be effective in monotherapy for patients with molecularly relapsed APL.\(^9,10\) A previous pilot study by Ravandi et al. showed that the combination of ATO, ATRA, and GO was efficacious as a first-line therapy in high-risk patients with APL.\(^10\)

Secondary APL (sAPL) constitutes a small proportion of all APL cases. Currently, there are no prior large population-based studies on sAPL. Previous studies have inconsistently demonstrated similar OS rates between sAPL and de novo APL, with sAPL having a higher early mortality rate than de novo APL.\(^11\)

At the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting and the European Hematology Association (EHA) Congress, investigators presented studies on ATRA plus ATO as a first-line therapy for APL patients in all risk groups, the use of GO in ATRA plus ATO therapy for high-risk patients, as well as the OS and mortality rates of patients with sAPL in a large cohort. The following is a report on three presentations from ASCO and EHA 2015:

- A study that compared the efficacy and safety of ATRA plus ATO with that of AIDA showed that ATRA plus ATO, in an attenuated schedule, resulted in a lower risk of hematological and molecular relapse compared with AIDA, especially in high-risk patients who were given GO prophylaxis. (Burnett AK, et al. EHA 2015:LB2067)
- A phase II study showed that low early mortality rate was achieved in high-risk patients with APL who received ATO, ATRA plus GO, which confirmed the efficacy and safety of this regimen. (Lancet JE, et al. ASCO 2015:7016)
- A large population-based study on sAPL demonstrated that patients with sAPL had similar OS and mortality rates to those with de novo APL. (Pathak R, et al. ASCO 2015:7046)
Burnett AK, et al. EHA 2015:LB2067

APL of all risk groups is highly curable with a chemo-free combination of attenuated arsenic trioxide and ATRA

Background
At the 2015 EHA Congress, Burnett and colleagues presented results from the U.K. National Cancer Research Institute AML17 trial, which compared the efficacy and safety of the chemotherapy-free combination of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO), in an attenuated schedule, with that of ATRA plus idarubicin (AIDA) in the treatment of patients with acute promyelocytic leukemia (APL).

Study design
• The AML17 study was a randomized, controlled, open-label, phase III trial.
• The study period was from May 2009 to October 2013, with 242 patients enrolled from 81 centres.
• A total of 235 patients met the eligibility criteria, which consisted of those 16 years of age or older with molecularly confirmed APL.
• Results were based on follow-up to January 2014, a median of 30.5 months (range: 0.2–56.1 months).
• Patients were randomized into one of the two following treatment arms:
  ▶ ATRA plus ATO (n = 116):
    – Induction treatment with ATRA 45 mg/m²/day for 60 days or until complete response (CR), plus ATO 0.3 mg/kg from days 1 to 5 in the first week, and then 0.25 mg/kg twice per week for seven weeks;
    – Four consolidation courses of ATRA plus ATO, in which ATRA 45 mg/m² was given daily as a divided oral dose for two weeks on, two weeks off, and ATO 0.3 mg/kg was given on days 1 to 5 in the first week, followed by 0.25 mg/kg twice per week for three weeks;
  ▶ AIDA (n = 119):
    – Course 1: Induction treatment with ATRA 45 mg/m²/day for 30 days or 60 days if CR was not achieved, plus idarubicin 12 mg/m² on days 2, 4, 6 and 8;
    – Courses 2–4: ATRA 45 mg/m² was given daily as a divided oral dose on days 1 to 15, plus: idarubicin 5 mg/m² on days 1 to 4 of course 2; mitoxantrone 10 mg/m² on days 1 to 4 of course 3; and idarubicin 12 mg/m² on day 1 of course 4.
• A provision was made for all high-risk patients (n = 57) to receive a single initial dose of gemtuzumab ozogamicin (GO) at 6 mg/m² within the first four days of induction.
• No maintenance therapy was required.
• Patient’s bone marrow was monitored with real-time polymerase chain reaction.

References
**ATRA plus ATO schedule:**

**Induction**

- Week 1: 0.3 mg/kg d1–5
- Weeks 2–8: 0.25 mg/kg twice per week

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<thead>
<tr>
<th>Day</th>
<th>ATO 18 mg/m² d1–5</th>
<th>ATRA 45 mg/m² as a divided oral dose daily to day 60 or CR</th>
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**Consolidation x4**

- Week 1: 0.3 mg/kg d1–5
- Weeks 2–4: 0.25 mg/kg twice per week

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**AIDA schedule:**

**Induction**

- Idarubicin 12 mg/m² d2, 4, 6, 8
- ATRA 45 mg/m² as a divided oral dose daily to day 30

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<th>Day</th>
<th>Idarubicin 12 mg/m² d2, 4, 6, 8</th>
<th>ATRA 45 mg/m² as a divided oral dose daily to day 30</th>
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**Consolidation Courses 2–4**

- Idarubicin 5 mg/m² d1–4
- ATRA 45 mg/m² as a divided oral dose d1–15

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<tr>
<th>Day</th>
<th>Idarubicin 5 mg/m² d1–4</th>
<th>ATRA 45 mg/m² as a divided oral dose d1–15</th>
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</table>

**Study design**

AIDA = ATRA plus idarubicin; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CR = complete response
Key findings

- Baseline characteristics were similar between groups:
  - Median age was 47 years (range: 16–77);
  - The number of patients >60 years of age was 25 in the ATRA plus ATO arm vs. 24 in the AIDA arm;
  - The number of high-risk patients (white blood cell count >10 x 10^9/L) was 30 in the ATRA plus ATO arm vs. 27 in the AIDA arm.

- Treatment outcomes:
  - 94% of patients entered morphological CR in the ATRA plus ATO arm vs. 89% in the AIDA arm (p = 0.18);
  - The 30-day mortality was 4% in the ATRA plus ATO arm vs. 6% in the AIDA arm (p = 0.6);
  - The 60-day mortality was 5% in the ATRA plus ATO arm vs. 9% in the AIDA arm (p = 0.2).

- Overall survival (OS) at four years was similar between treatment arms in different subgroups:
  - In all patients (N = 235), OS was 93% in the ATRA plus ATO arm vs. 89% in the AIDA arm (p = 0.2) (Figure 1);
  - In low-risk patients (n = 177), OS was 95% in the ATRA plus ATO arm vs. 90% in the AIDA arm (p = 0.17);
  - In high-risk patients (n = 56), OS was 87% in the ATRA plus ATO arm vs. 84% in the AIDA arm (p = 0.8);
  - In patients >60 years old (n = 49), OS was 80% in the ATRA plus ATO arm vs. 74% in the AIDA arm (p = 0.7).

- Event-free survival (EFS) at four years was achieved in 91% of patients in the ATRA plus ATO arm vs. 74% in the AIDA arm (HR = 0.36, 95% CI: 0.19–0.70, p = 0.003), due to the lack of relapse after complete remission.

- The frank relapse-free survival (RFS) rate at four years was 97% in the ATRA plus ATO arm vs. 83% in the AIDA arm (HR = 0.24, 95% CI: 0.09–0.63, p = 0.004):
  - In all patients (n = 213), RFS at four years was achieved in 97% of patients in the ATRA plus ATO arm vs. 78% in the AIDA arm;
  - In low-risk patients (n = 165), RFS at four years was achieved in 96% of patients in the ATRA plus ATO arm vs. 79% in the AIDA arm;
  - In high-risk patients (n = 48), RFS at four years was achieved in 100% of patients in the ATRA plus ATO arm vs. 74% in the AIDA arm.

- Molecular RFS was achieved in 98% of all patients in the ATRA plus ATO arm vs. 70% in the AIDA arm (HR = 0.17, 95% CI: 0.08–0.39, p <0.0001).

- In all patients, the cumulative incidence of frank hematological relapse was 1% in the ATRA plus ATO arm vs. 18% in the AIDA arm (HR = 0.16, 95% CI: 0.06–0.46, p = 0.0007) (Figure 2):
  - In low-risk patients, 1% had hematological relapse in the ATRA plus ATO arm vs. 5% in the AIDA arm (p = 0.03);
  - In high-risk patients, 0% had hematological relapse in the ATRA plus ATO arm vs. 26% in the AIDA arm (p = 0.008).

Figure 1. Overall survival for all-risk groups
• Among patients who achieved molecular negativity, 0% had molecular relapse in the ATRA plus ATO arm vs. 27% in the AIDA arm (HR = 0.12, 95% CI: 0.05–0.30, p < 0.0001). (Figure 3)

• Of the 30 high-risk patients in the ATRA plus ATO arm, 28 were given GO prophylaxis; the OS at four years was 89% for these patients. Of the two patients not treated with GO, one died on day 12 of treatment.

• Significantly less alopecia, as well as less grade 3/4 liver and gastrointestinal toxicity, was observed in the ATRA plus ATO arm than the AIDA arm.

• Regarding supportive care, significantly fewer blood and platelet transfusions were used with ATRA plus ATO than AIDA. Patients in the ATRA plus ATO arm spent fewer days on antibiotics and in hospital than those in the AIDA arm. (Table 1)

• The quality of life and Hospital Anxiety and Depression Scale (HADS) assessments did not differ significantly between groups. (Figure 4)

• Compared with the GIMEMA-AMLSG-SAL study, less liver toxicity was reported in this study (<10% vs. 63%).1 Also, less frequent dosing (63 vs. 140 doses) and a lower amount of ATO (1,190 mg vs. 1,470 mg for a 70-kg patient) were required in the AML17 trial, representing a cost reduction for patients.
AIDA = ATRA plus idarubicin; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CR = complete response; Exp. = expected; HR = hazard ratio; No. = number; Obs. = observed.
### Table 1. Supportive care

<table>
<thead>
<tr>
<th>Type of care</th>
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<td>Platelets (mean units)</td>
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<td>Antibiotics (mean days)</td>
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<td>Hospitalization (mean days)</td>
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AIDA = ATRA plus idarubicin; ATO = arsenic trioxide; ATRA = all-trans retinoic acid

### Key conclusions

- The combination of ATRA plus ATO resulted in a low risk of relapse in patients with APL and induced significantly better EFS than AIDA. Regarding OS, ATRA plus ATO is at least equivalent to AIDA.
- Benefit was achieved in the ATRA plus ATO arm, with significantly less liver toxicity and supportive care requirements than the AIDA arm.
- The attenuated schedule of ATRA plus ATO is safe and effective in high-risk patients who were given GO prophylaxis.
- The attenuated dosing approach used in the AML17 study is more convenient for patients and is less costly than the one used in the GIMEMA-AMLSG-SAL study.
- Unless patients are given AIDA, the low risk of relapse in the ATRA plus ATO arm negates the need for minimal residual disease monitoring.


Lancet JE, et al. ASCO 2015:7016

Safety and tolerability of ATRA plus arsenic trioxide plus gemtuzumab ozogamicin in high-risk APL: initial report of the SWOG/Alliance/ECOG S0535 trial

### Background

At the 2015 ASCO Annual Meeting, the results of a U.S. intergroup trial were presented, evaluating the safety and efficacy of all-trans retinoic acid (ATRA), arsenic trioxide (ATO), plus gemtuzumab ozogamicin (GO) in high-risk patients with acute promyelocytic leukemia (APL).

### Study design

- This is a single-group, multicentre, open-label, phase II study.
- The study period was from 2008 to 2013.
- Eligibility criteria included:
  - Age >18 years;
High-risk patients (white blood cell count ≥10,000/µL), with newly diagnosed APL.

- **Induction therapy consisted of:**
  - ATRA (45 mg/m²/day) from day 1 until complete remission (CR);
  - ATO (0.15 mg/kg/day) from day 10 until CR;
  - GO (9 mg/m²) on day 1.

- Patients in CR received consolidation therapy with: ATO for cycles 1 and 2, ATRA plus daunorubicin for cycles 3 and 4, and GO for cycles 5 and 6.

- Subsequent maintenance therapy consisted of ATRA, 6-mercaptopurine (6-MP) plus methotrexate for up to one year.

- The primary endpoints were:
  - Three-year continuous complete remission rate (target ≥70%);
  - Early (six-week) mortality rate (target ≤15%).

- The secondary endpoints were:
  - Frequency and severity of toxicities with ATRA, ATO, and GO;
  - Molecular relapse rate;
  - Overall survival.

### Key findings

- A total of 73 patients (52% female and 48% male) were enrolled and were evaluable for toxicity in the study.

- The median age of patients was 46.5 years (range: 19.2–86.4 years).

- Of the 73 patients, 62 (85%) completed induction therapy as planned and registered for consolidation therapy.

- Of these patients, 48 (66%) completed all planned consolidation cycles.

- Of the 14 withdrawals, five were due to voluntary withdrawal, four were due to adverse events (AEs), three were due to ineligibility, and two were due to unknown reasons.

- Eight patients (11%) died within six weeks of treatment initiation (95% CI: 6–21%), which supported rejection of the null hypothesis (30% early mortality rate).

- Causes of patient deaths included central nervous system hemorrhage (two patients), infection/sepsis (two patients), APL-not otherwise specified (two patients), liver/renal failure (one patient), and unknown reasons (one patient).

- A total of 41 patients were registered for maintenance therapy, and 32 completed the regimen.

- Of the nine withdrawals, four were due to AEs, two were due to voluntary withdrawal, one was due to ineligibility, one was due to death, and one was due to unknown reasons.

- The most common treatment-emergent, grade 3–4 AEs during induction included (n = 73):
  - Febrile neutropenia (34%);
  - Aspartate transaminase (AST) and alanine transaminase (ALT) elevation (12% and 11%, respectively);
  - Hypoxia/differentiation syndrome (11%);
  - Hyperglycemia (11%);
  - Headache (11%);
  - Prolonged corrected QT interval (QTc; 11%).

- Among 59 patients who received consolidation therapy, the most common treatment-emergent, grade 3–4 AEs included:
  - Febrile neutropenia (51%);
  - Headache (14%);
  - Fatigue (14%);
  - Nausea (12%).

- Among 40 patients who received maintenance therapy, the most common treatment-emergent, grade 3–4 AEs included:
  - ALT elevation (12%);
  - Headache (12%);
  - Nausea (12%).
Key conclusions

- Induction with ATRA, ATO, and GO in high-risk patients with APL was feasible and safe.
- The targeted low rate of early mortality was reached (11%).
- The rate of completion of all planned therapy (44%) was lower than expected, suggesting that consolidation or maintenance therapy may be overly toxic.
- The three-year continuous complete remission rate assessment is ongoing.


Pathak R, et al. ASCO 2015:7046

Survival of de novo and secondary APL: a propensity matched analysis of the SEER database

Background
At the 2015 ASCO Annual Meeting, Pathak et al. presented the results of their investigation into whether there are any differences in the overall survival (OS) rates between secondary acute promyelocytic leukemia (sAPL) and de novo APL.¹

Study design
- The Surveillance, Epidemiology, and End Results (SEER) 13 database and appropriate International Classification of Disease (ICD-O-3) histology codes were used to identify adult patients with sAPL and de novo APL who were diagnosed between 1992 and 2011.
- Propensity matching was performed to create a matched dataset of sAPL and de novo APL.
- Kaplan-Meier survival curves were plotted to compare survival statistics.
- Multivariate analysis was performed using the Cox proportional hazard regression model.

Key findings
- sAPL (n = 109) accounted for 5.5% of all APL cases (n = 1,964).
- The crude incidence of sAPL was 0.85 per 10,000 primary malignancies.
- Patients with sAPL had different demographic characteristics from patients with de novo APL:
  - Median age was 65 years for sAPL patients vs. 44 years for de novo APL patients (p <0.001);
  - Regarding race, 85% of sAPL patients vs. 79% of de novo APL patients were white (p = 0.003);
  - 53% of sAPL patients vs. 40% of de novo APL patients were diagnosed after the year 2005 (p = 0.008).
- The two subgroups of patients did not differ by gender (p = 0.665) and marital status (p = 0.745).
- Within the first month of diagnosis, the mortality rate was 28.9% for sAPL vs. 23.0% for de novo APL (p = 0.20);
- Overall survival (OS) rates were similar between patients with sAPL and de novo APL:
  - At one year, the OS rate was 55% for sAPL vs. 57% for de novo APL (p = 0.70);
  - At two years, the OS rate was 51% for sAPL vs. 54% for de novo APL (p = 0.79);
  - At five years, the OS rate was 42% for sAPL vs. 50% for de novo APL (p = 0.24).
- In a multivariate analysis, sAPL was not associated with a significantly worsened OS compared with de novo APL (HR = 1.11, 95% CI: 0.78–1.58, p = 0.546).
• OS was worse with older age at diagnosis, but it was improved in more recent years.
  ▷ Compared with patients <55 years of age, patients who were 55–70 years old and >70 years old were more likely to have worse OS (55–70 years old: HR = 1.86, 95% CI: 1.02–3.41, \( p = 0.043 \); >70 years old: HR = 4.64, 95% CI: 2.54–8.46, \( p <0.001 \));
  ▷ Compared with patients diagnosed before 1995, OS was better among patients who were diagnosed in recent years (between 1995 and 2005: HR = 0.46, 95% CI: 0.21–0.98, \( p = 0.046 \); after 2005: HR = 0.37, 95% CI: 0.17–0.80, \( p = 0.012 \)).

**Key conclusions**

- To date, this is the largest population-based study utilizing propensity matched cohorts of sAPL and de novo APL.
- OS was similar between patients with sAPL and de novo APL.
- Early mortality rate (i.e., within first month of diagnosis) was also similar between groups.
- The study indicates that: (i) patients with sAPL can be managed very similarly to patients with de novo APL, and (ii) patients with sAPL do not need to be excluded from clinical trials of APL.


**Canadian Perspective**

**An Interview with Dr. Matthew Seftel on the AML17 Study**

**New Evidence:** In Canada, what is the current standard of care for acute promyelocytic leukemia (APL) in low-risk patients (white blood cell count [WBC] <10 x 10^9/L)? In high-risk patients (WBC >10 x 10^9/L)?

**Dr. Seftel:** The current standard of care for non-high-risk patients with APL in Canada is a “chemotherapy-free approach”, which is the combination of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO). All provinces will have adopted the ATRA-ATO schedule that was used in the GIMEMA-AMLSSG-SAL trial for two reasons: (i) the GIMEMA-AMLSSG-SAL trial was an adequately powered, multicentre, randomized controlled trial, and (ii) the trial has been published in a peer-reviewed journal and has been reviewed by regulatory bodies for use in Canada, including the Pan-Canadian Oncology Drug Review.1,2 For high-risk patients, there is more uncertainty about the best therapy because the GIMEMA-AMLSSG-SAL trial did not include this patient group. Several Canadian centres have already adopted the combination of ATRA-ATO for high-risk patients, but exactly how to do this is variable amongst the provinces and leukemia centres. Some centres include ATRA-ATO plus an anthracycline (e.g., idarubicin) upfront in remission induction therapy, using the Australasian approach as published in a phase II trial by Iland et al.3 Other centres have adopted the treatment schedule published in the Intergroup C9710 study by Powell et al., which used ATRA, daunorubicin, and cytarabine for induction; if complete response (CR) was achieved, ATO was used for consolidation before resuming the two additional cycles of chemotherapy-based consolidation.4 Neither of these studies are chemotherapy-free. The current APL trial by Burnett et al., known as AML17, is the closest to a chemotherapy-free approach that examines the role of ATRA plus ATO in high-risk patients.5

**New Evidence:** Please describe the design of the AML17 trial by Burnett et al. Can you comment on the choice of the primary and secondary endpoints?

**Dr. Seftel:** The study by Burnett et al. is the U.K. National Cancer Research Institute (NCRI) AML17 trial.5 It is a randomized, controlled, open-label trial that examined therapy for adults with APL, in all risk groups. Patients were randomized to receive ATRA plus ATO (the experimental arm) or ATRA plus idarubicin (AIDA; the control arm) for induction and consolidation. Importantly, the study did not use maintenance therapy for either arm.
The primary endpoint was patient quality of life (QoL), a rather unconventional choice of outcome. The secondary endpoints were remission rates, overall survival (OS) rates, and relapse rates. APL patients constitute only around 10% of all acute myelogenous leukemia (AML) patients; thus, the likelihood of recruiting a large enough trial population to determine differences in survival outcomes between treatment groups would be very difficult indeed. If we assume that OS and event-free survival (EFS) outcomes will be similar between treatment groups, other endpoints would need to be considered, which includes QoL and resource utilization. These outcomes, although harder to measure, are still of great interest to patients, physicians, and funding agencies.

**New Evidence:** What are the usual endpoints measured in APL?

**Dr. Seftel:** When looking at frontline phase III trials, I would regard EFS as the most powerful endpoint, if there were enough patients to allow this endpoint to be examined. Early and late therapy-related severe adverse events (SAEs) and deaths are also very important. OS is an ideal outcome, but very difficult to power because of the low mortality rates in APL and the possibility of crossover of patients from control to experimental arms upon relapse. Endpoints measured in APL trials are changing because conventional outcomes (i.e., OS, EFS) have improved dramatically over the last 20 years; therefore, a renewed focus in the designing of clinical trials in APL is needed.

**New Evidence:** What is the significance of including high-risk APL patients in the AML17 trial?

**Dr. Seftel:** Including high-risk patients is laudable, because it allows us to make some conclusions about the role of a chemotherapy-free approach in these high-risk patients. The challenging part of the AML17 trial was the unusual administration of the monoclonal antibody-drug conjugate, gemtuzumab ozogamicin (GO), during remission induction for up to two doses in high-risk patients. The reason for using GO was to reduce the risk of leukocytosis and differentiation syndrome in high-risk patients. Strictly speaking, I do not consider the experimental arm as chemotherapy-free. Moreover, GO is not readily available in North America; therefore, I am unsure of the performance of ATRA plus ATO alone in high-risk patients, in the absence of GO. In the pivotal GIMEMA-AMLSG-SAL trial, the use of a short-term cytotoxic drug (hydroxyurea) was permitted in order to reduce WBC during induction; in the AML17 trial, they used GO for similar reasons. Whether we can equate the effect of short-term hydroxyurea to GO is unclear.

**New Evidence:** How does the proportion of high-risk patients in the AML17 trial (25%) compare with what you see in clinical practice?

**Dr. Seftel:** Compared with the AML17 trial, high-risk patients constitute around the same proportion of all patients with APL in Canada (20%), as we noted in a recent Canadian APL study by Paulson et al.* I congratulate the authors on recruiting the relatively large number of high-risk patients in the trial because these patients usually have unstable and complicated conditions at diagnosis; the fact that the authors consented and accrued these patients is impressive.

**New Evidence:** The study was designed and powered to recruit 600 patients; however, only 242 patients were recruited and 235 were randomized. How does the reduction in patient number affect the validity of results?

**Dr. Seftel:** Clinical trials require a pre-defined sample size to meet primary outcomes. Based on the sub-optimal sample size of 242 patients, all presented results of the study remain exploratory. This limits the applicability of the available results.

**New Evidence:** Please comment on the efficacy results of the study. In your opinion, has this study met its objectives?

**Dr. Seftel:** Despite the small sample size, the outcomes reported in the study remain clinically important because the reported relapse and OS rates suggest that ATRA plus ATO alone was at least as good as the AIDA approach, for all APL risk groups. OS for both treatment groups was excellent, which is testament to the power of modern therapy of APL as well as the rigour of supportive care in the U.K. NCRI AML17 trial. The results from this study strengthen the conclusions from the GIMEMA-AMLSG-SAL trial. It would now be interesting if a meta-analysis could be done using both trials. Overall, I think the data from the AML17 trial further justify the use of ATRA plus ATO for low- and intermediate-risk APL, but there is still uncertainty for high-risk patients.

**New Evidence:** Please comment on the efficacy findings in different subgroups of patients.

**Dr. Seftel:** I was impressed by the excellent OS results for high-risk patients in both arms. Also, the study included a large proportion of patients over the age of 60 (~20%). The outcomes for older patients is substantially poorer than those for other subgroups, and the current study shows that survival in older patients was better in the ATRA plus ATO arm compared with the AIDA arm. Even though statistical significance was not reached, most of the key outcomes had numerical differences between arms in favour of the ATRA-ATO approach.
**New Evidence:** Cumulative incidence of relapse was notably lower in the ATRA plus ATO versus AIDA arms, especially for high-risk patients. What is the significance of these results?

**Dr. Seftel:** Any hematological or molecular relapse is very undesirable, even if it can be salvaged with subsequent therapy. Relapse complicates treatment planning and it implies that bone marrow transplantation may be needed for these patients. The fact that the cumulative incidence of frank hematological relapse for ATRA plus ATO was only 1% (versus 18% for AIDA) is outstanding. Encouragingly, the cumulative incidence of molecular relapse in those patients who had already achieved molecular negativity was 0% in the ATRA plus ATO arm (versus 27% in the AIDA arm).

**New Evidence:** Based on the AML17 trial, would you recommend GO prophylaxis be added to the ATRA-ATO therapy for high-risk patients?

**Dr. Seftel:** Since the number of high-risk patients receiving GO was small in the AML17 trial, it is difficult to make any conclusions on the effect of GO. If GO was licensed and available in Canada for high-risk patients, I would recommend that short-term GO be added to the ATRA-ATO therapy for this subgroup.

**New Evidence:** In this study, ATO was given to patients in an attenuated schedule. In the GIMEMA-AMLSG-SAL trial, ATO was given to patients daily at a slightly lower dose than that used in this study. What is the advantage of using an attenuated dosing approach?

**Dr. Seftel:** Since ATO is a key drug, the cost and toxicity of ATO are very important. It is impossible to compare the effect of these dosing and schedule differences on clinical outcomes between trials (i.e., Italian-German group vs. British group).

**New Evidence:** There was no maintenance therapy in the AML17 trial whereas the GIMEMA-AMLSG-SAL trial included one. Do you use maintenance therapy in your routine practice?

**Dr. Seftel:** In regular practice, the use of maintenance therapy remains controversial. In low- and intermediate-risk patients who have received ATO as part of the treatment, I would not recommend maintenance therapy because it carries some risks and financial burden without any clear benefit. In high-risk patients, if we use ATO-based therapy as a first-line treatment, then maintenance therapy is questionable and probably not necessary. In my practice with high-risk APL patients, I would discuss the risks and benefits of maintenance therapy with patients, and I would still monitor patients for molecular relapse whether maintenance therapy was used or not.

**New Evidence:** Can you comment on the toxicity profile reported for both arms in the AML17 trial?

**Dr. Seftel:** The ATRA plus ATO arm was associated with fewer incidences of hepatic and gastrointestinal toxicity, as well as alopecia. Importantly, fewer blood transfusions were required in the ATRA plus ATO arm. There appeared to be greater early cardiotoxicity in the ATRA-ATO arm. I am interested in the details behind the cardiotoxicity with ATRA plus ATO, and wonder whether this was restricted to QT prolongation or extended to other serious cardiac conditions. I am also interested in any reports of myelodysplastic syndrome and secondary AML in the longer-term follow-up of this study.

**New Evidence:** In the AML17 trial, SAEs were not defined as per the Good Clinical Practice European Directive. Can you comment on the modalities of reporting adverse events in the AML17 trial?

**Dr. Seftel:** The key to a successful clinical trial is to make the trial as simple to conduct as possible, while retaining high measures of safety and ethical conduct. Since patients with APL tend to have significant medical issues at onset, and the drugs that were used in the AML17 trial have predictable toxicities, I believe there was a decision in the trial design to avoid the need of reporting certain SAEs that were expected in the course of treating APL.

**New Evidence:** The approved dosage of ATO is 0.15 mg/kg/day, with electrocardiogram monitoring twice a week. Given the attenuated dosing schedule for ATO in this study, how would you monitor for cardiotoxicity?

**Dr. Seftel:** Based on the approved dose for ATO, I am concerned with the possible cardiotoxicity associated with the higher dose of ATO used in the AML17 trial; I am reluctant to adopt the new schedule that was used in this study. Until the study is published and the exact details of cardiotoxicity are known, it is difficult to decide on a schedule change beyond current practice norms.

**New Evidence:** In terms of cost, how does the AML17 trial compare with the GIMEMA-AMLSG-SAL trial? If a capped dose of 10 mg/dose was used, the cost of ATO in the GIMEMA-AMLSG-SAL trial would be less than that reported for this study. Do you cap ATO doses in your centre for all patients?
**Dr. Seftel:** The fact that the AML17 trial used less frequent dosing and required a lower total amount of ATO than the GIMEMA-AMLSG-SAL trial is very attractive because of lower cost. Nevertheless, clinical practice would be hard to change if results from the study were not published in detail. At our centre, we do not cap doses of ATO.

**New Evidence:** How will the results of this study impact the use of ATO, in combination with ATRA, in patients with APL in clinical practice?

**Dr. Seftel:** The results are reassuring and support those from the GIMEMA-AMLSG-SAL trial. Clinicians will still most likely continue to adopt the approach used in the GIMEMA-AMLSG-SAL trial. The study does have implications for high-risk patients in that ATRA plus ATO is effective and safe in this subgroup. In terms of the attenuated ATO dosing schedule, results of the study will not change the treatment schedule clinically until the study is published and the toxicities associated with the new schedule are explained.

**New Evidence:** What do the findings from the AML17 trial mean for different subgroups of patients with APL?

**Dr. Seftel:** For non-high-risk patients, the results of the study are practice-affirming, and they build well on the GIMEMA-AMLSG-SAL trial. For high-risk patients, the study gives us more confidence in the chemotherapy-free approach, but we still have to wait for the availability of GO in Canada. Results for the elderly patients are very reassuring.

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**References**

Lymphomas

Advances in Single-Agent and Combination Therapies for the Treatment of Non-Hodgkin and Hodgkin Lymphomas

The standard treatment for indolent non-Hodgkin lymphoma (NHL) is bendamustine in combination with rituximab (BR). BR has shown to be more efficacious and more tolerable compared with previously used treatments such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone).\(^2\) The advantages of BR over R-CHOP, in terms of reduced toxicity, are especially apparent in elderly patients (i.e., >70 years old).\(^4\)

Despite these results, indolent NHL remains incurable and many patients relapse or become refractory to treatments. Patients with indolent NHL refractory to rituximab-containing therapy have limited treatment choices. Therefore, there remains a clear need for new therapies.

Obinutuzumab, a monoclonal antibody, has shown promise as a single agent and in combination with chemotherapy, resulting in high response rates in patients with refractory or relapsed (R/R) indolent NHL.\(^5\)-\(^7\) As a result, studies using obinutuzumab-based combination treatments against indolent NHL are currently ongoing.

Another potential option is idelalisib, a first-in-class, oral, selective phosphatidylinositol 3-kinase delta (PI3K\(\delta\)) inhibitor. Idelalisib showed antitumour activity and manageable tolerability as a single agent in a phase II open-label study in indolent NHL refractory to rituximab and an alkylating agent.\(^8\)

Venetoclax, a BCL2 selective inhibitor, is another potential treatment option for patients with R/R FL. BCL2 is a protein that is often overexpressed in follicular lymphoma (FL), contributing to resistance to chemoinmunotherapy. Venetoclax has shown antitumour activity in patients with NHL as a single agent and has the potential for higher response rates as part of combination regimens.

Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy, most often diagnosed in elderly patients. While multiple treatment options with promising response rates exist, there is currently no standard therapy. Patients almost always relapse after chemotherapy, with each relapse typically being more difficult to treat. R-Hyper-CVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) or R-CHOP, followed by autologous stem cell transplantation (ASCT) are effective treatments. However, their use in frail patients is limited due to the high occurrence of hematological toxicities.\(^9\)-\(^10\) BR is a less toxic, yet effective alternative against MCL, currently making it the most viable option for elderly patients.\(^1\)

Lenalidomide, an immunomodulatory drug, has also demonstrated efficacy as a salvage therapy in patients with R/R MCL.\(^11\) Furthermore, lenalidomide has shown significant synergy when combined with rituximab-containing therapies. Phase I, II, and III clinical trials have also determined the efficacy and safety of lenalidomide in various other NHL subtypes, including FL and diffuse large B-cell lymphoma (DLBCL).\(^12\)

DLBCL is the most common subtype of NHL. Traditionally, the standard treatment for patients with DLBCL has been R-CHOP. BR has only recently been investigated in the treatment of DLBCL, demonstrating modest activity and an acceptable toxicity profile.\(^13\) Nevertheless, treatments for patients with DLBCL, especially for the elderly and for those with chemorefractory disease, remain limited.

Waldenström macroglobulinemia (WM) is a rare form of B-cell lymphoma, making up 1% to 2% of all NHL
cases, and is currently considered to be an incurable disease. Although there is no standard treatment for WM, rituximab is commonly used as monotherapy or in combination with chemotherapy. Novel agents that target the B-cell receptor signalling pathway, such as idelalisib, a PI3Kδ inhibitor, and ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, have each shown promising single-agent activity in patients with R/R WM.8,14 Confirmatory randomized trials are underway for each of these agents: idelalisib in combination with chemoimmunotherapy and ibrutinib in combination with rituximab.

Patients with R/R Hodgkin lymphoma (HL) often undergo salvage chemotherapy if they relapse or progress after frontline treatment and ASCT. Brentuximab vedotin and bendamustine have shown promise as highly active agents in patients with R/R HL, and have been associated with an acceptable toxicity profile.15–17 Early stage studies are underway to evaluate the safety of combining these two therapeutic agents.

At the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, the 2015 Congress of the European Hematology Association (EHA), and the 2015 International Conference on Malignant Lymphoma (ICML), New Evidence covered several studies on these topics. The following abstracts are summarized in this section:

**NHL**

- Primary results from the phase III, international GADOLIN study demonstrated that obinutuzumab with bendamustine followed by obinutuzumab maintenance improved progression-free survival (PFS) compared with bendamustine alone in patients with rituximab-refractory indolent NHL. (Sehn LH, et al. ASCO 2015:LBA8052, Sehn LH, et al. EHA 2015:LB691, & Cheson BD, et al. ICML 2015:123)
- Interim results from a phase I study demonstrated that venetoclax in combination with BR had a tolerable safety profile and was associated with early and long-lasting responses in patients with R/R NHL. (de Vos S, et al. EHA 2015:S109)
- A phase I study on the use of bendamustine, rituximab, and lenalidomide in the treatment of R/R indolent NHL found this combination therapy to be safe and well-tolerated by patients. (Nowakowski GS, et al. ASCO 2015:8540)
- A phase II trial showed that rituximab, bendamustine, and lenalidomide combination therapy had activity in elderly, comorbid patients with aggressive B-cell lymphomas who were ineligible for anthracycline-based first line or intensive salvage treatment. The combination therapy was also associated with acceptable toxicities. (Hitz F, et al. ICML 2015:015)
- A meta-analysis of data from clinical studies on the efficacy and safety of rituximab maintenance therapy in FL, DLBCL, and MCL found that it offered a significant PFS benefit in FL, DLBCL, and MCL and a significant overall survival (OS) benefit in FL. (Wang Y, et al. ASCO 2015:8551)

**FL**

- The post hoc analysis of a phase II study evaluating the efficacy and safety of idelalisib in highly pretreated patients with R/R FL showed that idelalisib was a superior oral therapy in terms of efficacy and safety for this patient population when compared with their previous therapy. (Zinzani PL, et al. EHA 2015:P689)
- A meta-analytic surrogacy evaluation found that the complete response (CR) rate at 30 months can be an appropriate surrogate endpoint for PFS, which could speed up clinical trials and access to treatments for first-line FL patients. (Sargent Df, et al. ASCO 2015:8504)
- Pooled data from two clinical trials of NHL patients found that the antitumour activity of polatuzumab vedotin (PoV) was similar for two doses (1.8 mg/kg and 2.4 mg/kg), but the tolerability of PoV could be improved by prescribing the lower dose for a fixed duration of eight cycles or less. (Advani RH, et al. ASCO 2015:8503)
- A phase III study (SELENE) was designed to evaluate whether the addition of ibrutinib to BR or R-CHOP would prolong PFS in patients with indolent NHL, while also assessing OS and the safety of the treatment. (Fowler N, et al. ASCO 2015:TPS8601)
- An ongoing phase II study (CONTRALTO) aims to determine the safety and efficacy of venetoclax in combination with rituximab or BR versus BR alone in patients with R/R FL. (Hiddemann W, et al. ICML 2015:OT04)

**MCL**

- A phase I/II study demonstrated that lenalidomide with BR was an effective first-line treatment in elderly patients with MCL, leading to high CR and molecular remission rates. However, it was associated with higher than expected toxicity, suggesting that it may not be the optimal treatment for this patient population. (Albertsson-Lindblad A, et al. ICML 2015:060)
- A phase II study demonstrated that the combination treatment of bendamustine, lenalidomide, and rituximab as a second-line therapy led to high response rates in patients with R/R MCL. These results compared well with other salvage treatments in this patient population. (Zaja F, et al. ICML 2015:014)
A phase II study demonstrated that R-BAC500 (rituximab, bendamustine, and cytarabine combination therapy) was a highly effective and safe treatment for younger (i.e., <65 years old) patients with MCL. Hematological toxicities were reduced when cytarabine was used at 500 mg/m² compared with 800 mg/m² in previous trials. (Visco C, et al. ICML 2015:059)

A phase II study showed that both R-Hyper-CVAD and BR were effective regimens for younger (i.e., <65 years old) patients with MCL, exhibiting high response rates and PFS at two years. However, the R-Hyper-CVAD regimen demonstrated significantly higher toxicities and was associated with a higher percentage of patients with inadequate stem cell mobilization, suggesting that it is not an ideal treatment regimen for future clinical trials. (Chen R, et al. ICML 2015:062)

DLBCL

A phase II multicentre study confirmed the safety and efficacy of the Benda-EAM regimen followed by ASCT in a heavily pretreated patient population with DLBCL. The treatment led to a low mortality rate and high CR rates, even though a high proportion of patients had progressive disease. (Isidori A, et al. EHA 2015:P353)

A phase II, open-label study demonstrated that treatment with BR had a low toxicity profile and led to promising response rates in newly diagnosed elderly patients with DLBCL. (Storti S, et al. EHA 2015:P328)

WM

A phase I/II study demonstrated that idealisib therapy was associated with a clinical benefit in most patients with R/R WM, and a manageable safety profile, with no disease-specific safety signals. (Coutre S, et al. ASCO 2015:8532 & Coutre S, et al. EHA 2015:P690)

An ongoing phase III study aims to evaluate the effect of the addition of ibrutinib to rituximab on the progression-free survival of patients with WM. (Dimopoulos MA, et al. ASCO 2015:TPS8599)

HL

A phase II multicentre study found that the BeGeV (bendamustine, gemcitabine, vinorelbine) regimen was a very effective second-line chemotherapy regimen in patients with R/R HL, with a tolerable and manageable toxicity profile. (Mazza R, et al. EHA 2015:S806)

A phase I trial demonstrated that the combination of brentuximab vedotin and bendamustine represented an effective and tolerable regimen in a heavily pretreated population of HL and anaplastic large T-cell lymphoma. (Kuruvilla J, et al. ICML 2015:090)

Non-Hodgkin Lymphoma


Primary results from GADOLIN: a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent NHL

Background
At ASCO, EHA, and ICML 2015, the primary results from the GADOLIN study were presented, which investigated whether obinutuzumab, a novel anti-CD20 monoclonal antibody, in combination with bendamustine for induction, followed by obinutuzumab maintenance, could improve outcomes in patients with rituximab-refractory indolent non-Hodgkin lymphoma (iNHL) when compared with bendamustine alone.1-3

Study design
• In the international, open-label, phase III GADOLIN study, a total of 413 rituximab-refractory, CD20-positive (CD20+) patients with iNHL were randomized 1:1 to receive:
  ◦ Obinutuzumab (1,000 mg intravenously [iv] on days 1, 8, and 15 for cycle one and day 1 for cycles 2–6 [28-day cycles]) plus bendamustine (90 mg/m²/day iv on days 1 and 2 for cycles 1–6), and after complete response, partial response, or stable disease, patients received obinutuzumab maintenance (1,000 mg iv every two months for two years or until progression); or
  ◦ Bendamustine (120 mg/m²/day iv on days 1 and 2 for cycles 1–6).

• Key eligibility criteria included:
  ◦ Patients who had no exposure to:
    – Bendamustine in the last two years; and
    – Monoclonal antibodies (except rituximab) in the last three months or any exposure to obinutuzumab.
  ◦ Rituximab-refractory was defined as:
    ◦ Patients who did not respond to rituximab as monotherapy or rituximab in combination with chemotherapy; or
    ◦ Patients who progressed within six months of completion of the last dose of a rituximab-containing regimen (after at least four doses of monotherapy or four cycles of rituximab plus chemotherapy).
  ◦ Response was monitored by computerized tomography scan post-induction, then every three months for two years, and then every six months.
  ◦ The primary endpoint was progression-free survival (PFS) as measured by an independent radiology facility (IRF).
  ◦ The secondary endpoints included PFS as assessed by investigator, overall survival (OS), end-of-induction response, best overall response (OR), and safety.

Rituximab-refractory
CD20+ iNHL
(incl. FL, MZL, and SLL)
(N = 413)

Stratification factors:
• NHL subtype (FL vs. other)
• Prior therapies (≤2 vs. >2)
• Refractory type (R-mono vs. R-chemo)
• Geographic region

CR/PR/SD
G-B
G-maintenance

Obinutuzumab
1,000 mg iv days 1, 8, and 15,
cycle 1; day 1, cycles 2–6 (28-day cycles)

Bendamustine
90 mg/m²/day iv days 1 and 2,
cycles 1–6 (28-day cycles)

Obinutuzumab
1,000 mg iv every 2 months for
2 years or until progression

B = bendamustine; CR = complete response; FL = follicular lymphoma; G = obinutuzumab; G-B = obinutuzumab, bendamustine;
iNHL = indolent non-Hodgkin lymphoma; IV = intravenous; MZL = marginal zone lymphoma; PR = partial response; R = rituximab;
SD = stable disease; SLL = small lymphocytic lymphoma
Key findings

Baseline characteristics and disposition

- The study enrolled a total of 194 patients in the obinutuzumab-bendamustine (G-B) arm and 202 patients in the bendamustine arm. (Figure 1)
  - A total of 156 patients from the G-B arm and 129 patients from the bendamustine arm completed induction;
  - A total of 35 patients from the G-B arm completed obinutuzumab maintenance.
- The median age of patients in both study arms was 63 years.
- There were no significant differences in baseline patient characteristics between the two treatment arms.
- Of the 194 rituximab-refractory patients in the G-B arm, 80.4% had received rituximab plus chemotherapy while 19.6% had received rituximab monotherapy.
- Of the 202 rituximab-refractory patients in the bendamustine arm, 77.7% had received rituximab plus chemotherapy while 22.3% had received rituximab monotherapy.
- The proportion of patients by lymphoma subtype was similar between the G-B and bendamustine arms, with the most common subtypes being follicular lymphoma (79.9% vs. 82.2%, respectively), marginal zone lymphoma (13.9% vs. 9.4%), and small lymphocytic lymphoma (6.2% vs. 7.9%).
- Median follow-up was 21 months. (Figure 1)

Efficacy

- As assessed by the IRF:
  - The median PFS in months for patients receiving G-B was not reached (NR; 95% CI: 22.5–NR);
  - The median PFS for patients receiving bendamustine alone was 14.9 months (95% CI: 12.8–16.6);
  - The stratified hazard ratio (HR) was 0.55 (95% CI: 0.40–0.74); \( p = 0.0001 \). (Figure 2)
- As assessed by the investigator:
  - The median PFS for patients receiving G-B was 29.2 months (95% CI: 20.2–NR);
  - The median PFS for patients receiving bendamustine alone was 14.0 months (95% CI: 11.7–16.0);
  - The stratified HR was 0.52 (95% CI: 0.39–0.70); \( p <0.0001 \).
- Median OS was not reached for either study arm (HR = 0.82; 95% CI: 0.52–1.30; \( p = 0.4017 \);
- In the G-B arm 18% of patients died, while in the bendamustine arm 20% of patients died.
- End-of-induction OR was achieved in 69.2% of the patients in the G-B arm and 63.0% of the patients in the bendamustine arm. (Figure 3)
- The best OR was achieved in 78.7% of patients in the G-B arm and 76.7% of patients in the bendamustine arm. (Figure 3)

Figure 1. Patient disposition in the GADOLIN trial

![Diagram showing patient disposition in the GADOLIN trial](image-url)

- **Enrolled and randomized**
  - G-B (n = 194)
  - B (n = 202)
- **Started induction**
  - G-B (n = 194)
  - B (n = 198)
- **Completed induction**
  - G-B (n = 156)
  - B (n = 129)
- **Started maintenance**
  - G (n = 143)
- **Completed maintenance**
  - G (n = 35)

**Data analysis cut-off:** September 1, 2014
**Median follow-up:** 21 months
**Patients still on study:** G-B, n = 149; B, n = 141

AE = adverse event; B = bendamustine; G-B = obinutuzumab-bendamustine; PD = progressive disease

*Withdrawal of both drugs. Eleven additional patients stopped one drug (B, n = 10; G, n = 1).
†One additional patient received all G maintenance but was considered as withdrawn due to PD; overall, 36 patients were recorded as having received all 12 doses.
At time of analysis, 19 patients were still in induction, six from the G-B arm and 13 from the bendamustine arm.

Safety
- The adverse event (AE) profiles of the two study arms were similar, with no new safety signals observed. (Figure 4)
- The most significant grade 3-4 AEs were: (Table 1)
  - Neutropenia: 33.0% of G-B patients and 26.3% of bendamustine patients;
  - Thrombocytopenia: 10.8% of G-B patients and 16.2% of bendamustine patients;
  - Infusion-related reactions: 10.8% of G-B patients and 5.6% of bendamustine patients.
- The most significant serious AEs were: (Table 2)
  - Febrile neutropenia: 4.1% of G-B patients and 3.0% of bendamustine patients;
  - Pneumonia: 2.6% of G-B patients and 5.1% of bendamustine patients.

### Figure 2. Progression-free survival as assessed by an independent radiology facility

<table>
<thead>
<tr>
<th>G-B (n = 194)</th>
<th>B (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%): 71 (37%)</td>
<td>104 (51%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI): NR (22.5–NR)</td>
<td>14.9 (12.8–16.6)</td>
</tr>
<tr>
<td>Stratified HR (95% CI): 0.55 (0.40–0.74)</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value: 0.0001</td>
<td></td>
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</tbody>
</table>

No. at risk: G-B 194 B 202

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>G-B</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>194</td>
<td>202</td>
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<tr>
<td>6–12</td>
<td>157</td>
<td>149</td>
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<td>12–18</td>
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<td>7</td>
<td>4</td>
</tr>
<tr>
<td>60–72</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**PFS (probability)**
- Median follow-up: 21 months
- IRF-assessed PFS: G-B (n = 194) B (n = 202)
- Events, n (%): 71 (37%) 104 (51%)
- Median PFS, months (95% CI): NR (22.5–NR) 14.9 (12.8–16.6)
- Stratified HR (95% CI): 0.55 (0.40–0.74)
- Log-rank p-value: 0.0001

End-of-induction response (IRF)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>G-B (n = 188*)</th>
<th>B (n = 192†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>11.2</td>
<td>16.7</td>
</tr>
<tr>
<td>PR</td>
<td>58.0</td>
<td>62.0</td>
</tr>
<tr>
<td>SD</td>
<td>10.1</td>
<td>4.7</td>
</tr>
<tr>
<td>PD</td>
<td>11.7</td>
<td>10.9</td>
</tr>
<tr>
<td>PD</td>
<td>18.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**B = bendamustine; CR = complete response; G-B = obinutuzumab-bendamustine; IRF = independent radiology facility; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease**

*Patients ongoing in induction therapy are excluded from analysis. Patients with end-of-induction response assessment performed >60 days after last induction dose shown as missing.

†Best overall response excludes ongoing patients who have not yet reached the first response assessment.

Best overall response to 12 months (IRF)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>G-B (n = 192*)</th>
<th>B (n = 197†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>16.7</td>
<td>17.3</td>
</tr>
<tr>
<td>PR</td>
<td>78.7</td>
<td>59.4</td>
</tr>
<tr>
<td>SD</td>
<td>4.7</td>
<td>5.7</td>
</tr>
<tr>
<td>PD</td>
<td>11.7</td>
<td>11.7</td>
</tr>
<tr>
<td>NE/missing</td>
<td>4.1</td>
<td>7.6</td>
</tr>
</tbody>
</table>

**B = bendamustine; CR = complete response; G-B = obinutuzumab-bendamustine; IRF = independent radiology facility; NE = not evaluable**
Figure 4. Overview of adverse events

$\geq 1$ AE

$\geq 1$ SAE

$\geq 1$ AE leading to withdrawal of any treatment

$\geq 1$ AE leading to dose modification

$\geq 1$ grade 3/4 AE

AE leading to death

$\geq 1$ AE

$\geq 1$ SAE

$\geq 1$ AE leading to withdrawal of any treatment

$\geq 1$ AE leading to dose modification

$\geq 1$ grade 3/4 AE

AE leading to death

$\geq 1$ AE

$\geq 1$ SAE

$\geq 1$ AE leading to withdrawal of any treatment

$\geq 1$ AE leading to dose modification

$\geq 1$ grade 3/4 AE

AE leading to death

AE = adverse event; B = bendamustine; G-B = obinutuzumab-bendamustine; SAE = serious adverse event

Table 1. Grade 3–4 adverse events

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>G-B (n = 194)</th>
<th>B (n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>64 (33.0)</td>
<td>52 (26.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (10.8)</td>
<td>32 (16.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>15 (7.7)</td>
<td>20 (10.1)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9 (4.6)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Non-hematological AEs†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR‡</td>
<td>21 (10.8)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (2.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (1.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.5)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1.0)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1.0)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>

*Multiple occurrences of the same AE in an individual were only counted once.
†AEs occurring during or within 24 hours after an infusion and considered to be related to any study drug.
Key conclusions

- G-B followed by obinutuzumab maintenance resulted in a statistically significant and clinically meaningful PFS benefit compared with bendamustine monotherapy;
  - IRF-assessed median PFS was not reached in the G-B arm and was 14.9 months in the bendamustine arm (HR = 0.55);
  - PFS data were consistent across the majority of subgroups tested.
- No significant differences were found in response rates between the two treatment arms even though bendamustine was given at a higher dose in the monotherapy arm than the G-B arm.
- The AE profile was similar in the two study arms and no new safety signals were observed.
- G-B followed by obinutuzumab maintenance is an effective treatment option for patients with relapsed/rituximab-refractory iNHL.

An Interview with Dr. Laurie Sehn on the GADOLIN Study

At the ASCO 2015 Annual Meeting, New Evidence spoke with Dr. Laurie Sehn, Medical Oncologist at the BC Cancer Agency and Clinical Assistant Professor at the University of British Columbia, Vancouver, British Columbia, about the results of the phase III GADOLIN study, which is comparing the efficacy and safety of obinutuzumab plus bendamustine induction, followed by obinutuzumab maintenance, with bendamustine induction alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma (iNHL).

**New Evidence:** What are the advantages of the new anti-CD20 antibody obinutuzumab over rituximab?

**Dr. Sehn:** Obinutuzumab is a novel agent that has been engineered to be potentially better than rituximab. It is a type II anti-CD20 monoclonal antibody and has a different mechanism of action from rituximab, a type I monoclonal antibody. Compared with rituximab, obinutuzumab has increased affinity for the FcγRIII receptors and therefore has enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. Obinutuzumab has also been shown to induce a higher degree of direct cell death, but lower complement activation, compared with rituximab.

**New Evidence:** Please describe the treatments that are currently available for patients with rituximab-refractory iNHL? What key unmet needs remain for these patients?

**Dr. Sehn:** Patients with rituximab-refractory iNHL have been shown to have relatively poor outcomes with limited treatment options. In this setting, most physicians would likely be using standard single-agent chemotherapy or chemotherapy combinations, or they would be looking to see whether they could access novel agents or clinical trials. In B.C., we frequently use single-agent chemotherapy, which is usually an alkylator, such as bendamustine, or a purine analogue; the choice depends on which therapies the patients have previously received. There continues to be a need for more effective therapies with lesser toxicities for patients with rituximab-refractory iNHL.

**New Evidence:** Please describe the design of the GADOLIN study. What was the rationale for the chosen doses of bendamustine and obinutuzumab?

**Dr. Sehn:** The GADOLIN study was a multicentre, international, randomized, phase III trial evaluating obinutuzumab plus bendamustine versus bendamustine alone in patients with rituximab-refractory iNHL. The Canadian participation was excellent in this study; multiple sites were open across Canada, and the Canadian sites were some of the highest recruiting sites within the study overall.

As this was intended as a registration trial, the comparator arm had to be considered the standard of care for patients with rituximab-refractory iNHL at the approved doses. For this reason, single-agent bendamustine, which is considered to be a standard management option for these patients, was chosen for the control arm and was given at the regulatory-approved dose of 120 mg/m² on days 1 and 2 of a 28-day cycle. The study arm combined obinutuzumab to the backbone of bendamustine, followed by extended dosing with maintenance obinutuzumab, which is in keeping with the standard approach used with rituximab.
combined with obinutuzumab, bendamustine was given at 90 mg/m² on days 1 and 2 of a 28-day cycle, as this is the standard dosage with immunotherapy.

Obinutuzumab was administered according to the dosing scheme developed in prior phase I and II studies, whereby a flat 1,000 mg dose was given on days 1, 8, and 15 of the first 28-day cycle, and then on day 1 in subsequent cycles. The maintenance therapy schedule comprised the administration of obinutuzumab at a dose of 1,000 mg every 2 months for up to 2 years, as this was demonstrated to be optimal in phase I and II trials.

New Evidence: Please describe the efficacy results of this study.

Dr. Sehn: At the time of a planned interim analysis, the study was recommended to be stopped because it met its primary endpoint of progression-free survival (PFS) as assessed by an independent radiology facility. At a median follow-up of 21 months, the median PFS as assessed by an independent radiology facility was not reached for obinutuzumab plus bendamustine versus 14.9 months for single-agent bendamustine. This was a statistically significant and clinically meaningful improvement in PFS for the obinutuzumab plus bendamustine arm (hazard ratio = 0.55; \( p = 0.0001 \)). PFS as assessed by the investigator was similar, where obinutuzumab plus bendamustine also achieved a statistically significant improvement in median PFS compared with bendamustine alone (29.2 months vs. 14.0 months, respectively; \( p < 0.0001 \)). Essentially, a doubling in median PFS was observed. I think it is fair to say that these results are impressive. In terms of the degree of benefit, it is highly comparable to what was observed in the initial studies that examined the addition of rituximab to chemotherapy, and now we are seeing similar improvements in a rituximab-refractory subgroup with the addition of a novel anti-CD20 antibody to bendamustine.

At the time of analysis there was no significant difference in overall survival (OS), but relatively few events have been observed, so longer follow-up will be necessary to assess the impact on OS. Some patients were still actively receiving treatment at the time of this interim analysis, so an updated analysis will be valuable.

There was also no difference in overall response rates between treatment arms, which may be in part due to the difference in bendamustine dose, as the single-agent arm received a higher dose of bendamustine. However, PFS is the more clinically relevant endpoint, and based on the results of this analysis, it was significantly improved by the combination of obinutuzumab plus bendamustine.

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

Dr. Sehn: Overall, the observed toxicities accorded with what was anticipated for the individual agents used, and no new safety signals were noted. Tolerability in both arms was quite comparable. There was no difference in the rates of adverse events (AEs), serious AEs, grade 3/4 AEs, AEs leading to death, or AEs leading to withdrawals between treatment arms. The most commonly observed non-hematologic AEs were primarily infusion-related reactions (IRRs), which occurred in 64% of patients in the obinutuzumab plus bendamustine arm and 58% of patients in the bendamustine alone arm. Nausea, fatigue, and diarrhea were also common. Neutropenia and thrombocytopenia were the primary hematologic AEs.

New Evidence: How were treatment-related toxicities managed? In your practice, are there any prophylactic measures you would take prior to treatment with obinutuzumab plus bendamustine?

Dr. Sehn: There were no unexpected toxicities observed in this trial. Most toxicities were managed as indicated, based on prior experience with other regimens of chemoimmunotherapy. Although it is recognized that there is a higher rate of IRRs, including grade 3/4 IRRs, with obinutuzumab compared to rituximab, in general these are quite manageable and prophylaxis is similar to what is recommended for rituximab, which includes acetaminophen and diphenhydramine. Routine prophylaxis with corticosteroids is not required.
New Evidence: Given the results of this study, in which patients would you currently recommend giving obinutuzumab plus bendamustine followed by obinutuzumab maintenance?

Dr. Sehn: Bendamustine is a commonly used treatment for patients with relapsed/refractory iNHL and is associated with a favourable toxicity profile. For that reason, the majority of patients with relapsed/refractory iNHL could be considered for bendamustine therapy. I think this trial has demonstrated that the combination approach of obinutuzumab plus bendamustine results in a significant clinical benefit in terms of prolonged PFS and would therefore be a good therapy choice for those patients. The addition of obinutuzumab does not add significant toxicity, so patients who are candidates for bendamustine should be appropriate for this combination.

New Evidence: Where do you see the regimen of obinutuzumab plus bendamustine best fitting in the sequence of iNHL treatments?

Dr. Sehn: There are other clinical trials ongoing, including a trial that is evaluating the use of obinutuzumab in a head-to-head comparison with rituximab in patients with follicular lymphoma in the frontline setting. So, we will have data from other clinical trials assessing whether or not obinutuzumab should be moved to the frontline setting in the management of iNHL. The GADOLIN study is the first randomized trial that has assessed the value of a novel monoclonal antibody in patients who are rituximab-refractory. I think this is a key study and demonstrates that in patients who are no longer considered candidates for rituximab, there is a substantial benefit from the addition of obinutuzumab to bendamustine. This raises the question of whether this benefit can be extrapolated to other chemotherapy platforms. In previous rituximab trials, the benefit of rituximab was seen regardless of the chemotherapy backbone used, and it is certainly conceivable that obinutuzumab may have added value with other backbones as well.

New Evidence: In which cases would you choose to give a patient obinutuzumab over rituximab?

Dr. Sehn: Based on the results of this trial, in patients who are refractory to rituximab, obinutuzumab plus chemotherapy would be the treatment of choice. In order to assess the utility of obinutuzumab in other subsets of patients, additional information from the ongoing clinical trials will be required.

New Evidence: Do you think that obinutuzumab plus bendamustine will fill the current unmet need for patients with rituximab-refractory iNHL? Will the results from this study change the standard of care for patients in this setting?

Dr. Sehn: I think this regimen certainly offers a significant improvement over what is currently available for this population with unmet need. The trial results are impressive, demonstrating a clinically meaningful improvement in PFS with the addition of a well-tolerated monoclonal antibody to bendamustine for patients with rituximab-refractory iNHL. For this reason, I think obinutuzumab plus bendamustine should be considered the standard of care for rituximab-refractory patients.
At the 2015 International Conference on Malignant Lymphoma (ICML), *New Evidence* spoke with Dr. Nathalie Johnson, Hematologist at the Jewish General Hospital and Assistant Professor in the Division of Medicine, Hematology, and Oncology at McGill University, about the results of the phase III GADOLIN study that is evaluating the efficacy and safety of obinutuzumab plus bendamustine induction followed by obinutuzumab maintenance compared with bendamustine induction monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (iNHL).

**New Evidence:** What key unmet needs remain for the management of patients with relapsed iNHL?

**Dr. Johnson:** There are two important unmet needs that remain for the treatment of patients with relapsed iNHL. Firstly, there is a need for more treatment options, which include effective and well-tolerated drugs that can easily be combined with chemotherapy if needed. Drugs that use novel mechanisms of action to kill cancer cells have the most potential to overcome the therapeutic resistance that is often seen in patients with relapsed or refractory lymphoma. Secondly, it is important that we are able to identify high-risk patients who do not achieve adequate remissions from standard chemotherapy; these patients may benefit from the addition of novel agents as part of their induction regimen. Research into biomarkers that can better identify these patients is ongoing and will likely optimize treatment approaches.

**New Evidence:** In Quebec, what treatment options are available for the management of relapsed iNHL?

**Dr. Johnson:** In the relapsed setting, conventional chemotherapy, including alkylating agents and purine analogues, as well as stem cell transplantation (SCT) are available in Quebec. Bendamustine in combination with rituximab (BR) would be the first choice of treatment among physicians, based on the superior efficacy of BR versus fludarabine and rituximab (FR) that was demonstrated by the Study Group of Indolent Lymphomas’ (STiL) NHL2 study. However, while there is funding for this regimen in the majority of Canadian provinces, it is not funded in Quebec and consequently not available to all patients.

**New Evidence:** How do you manage patients who relapse early following first-line treatment?

**Dr. Johnson:** For patients experiencing an early relapse, most physicians would give an alternative chemotherapy regimen followed by autologous SCT in suitable patients. In Quebec, bendamustine monotherapy would be an option in this setting. I consider enrolling many of these patients into clinical trials that incorporate bendamustine with novel agents, as these regimens often offer the best available treatment options that would otherwise not be available to them.

**New Evidence:** Please comment on the design and the choice of bendamustine monotherapy as a comparator used in the GADOLIN study.

**Dr. Johnson:** Patients included in the GADOLIN study had rituximab-refractory CD20+ indolent lymphoma, which was defined as a lack of response or progression within six months of a rituximab-based regimen or rituximab monotherapy. Patients had no exposure to bendamustine in the last 2 years and no exposure to other monoclonal antibodies within the last 3 months. These patients were randomized to receive obinutuzumab in combination with bendamustine (G-B) followed by obinutuzumab maintenance every 2 months for 2 years, or bendamustine monotherapy without maintenance. The choice of bendamustine monotherapy as a comparator was reasonable given that it has very good response rates as a single agent in this setting. The low toxicity profile of bendamustine also makes it easy to combine with other agents such as obinutuzumab in the treatment arm. Finally, most patients had no prior exposure to bendamustine and would not have developed resistance to the drug.

**New Evidence:** Please comment on the efficacy results of the GADOLIN study.

**Dr. Johnson:** The GADOLIN study demonstrated excellent response rates that were similar in both arms following induction treatment. The best overall response at 12 months was 79% [complete response (CR) 17%, partial response (PR) 62%] for the combination G-B arm compared to 77% (CR 17%, PR 59%) for the bendamustine monotherapy arm. The dose of bendamustine was lower in the combination arm (90 mg/m²) compared to the monotherapy arm (120mg/m²), which may in part explain the lack of difference between groups in the induction phase.
The difference between arms became apparent during the maintenance phase of the study, where the group that received G-B followed by obinutuzumab maintenance had a longer remission than the bendamustine monotherapy group. My interpretation of these results is that bendamustine is a good induction regimen, and that obinutuzumab maintenance can prolong remission by achieving a longer progression-free survival (PFS) compared with observation alone (PFS of 29 months for obinutuzumab maintenance versus 14 months for no maintenance, \( p < 0.0001 \)). These results are supported by other randomized studies that have demonstrated a prolonged PFS, but no difference in overall survival, with rituximab maintenance.

**New Evidence:** In which patients would you give bendamustine monotherapy if all other options were available to you?

**Dr. Johnson:** There is only a small group of patients where I would consider using bendamustine monotherapy, which mainly includes patients who have severe reactions to antibody therapy. However, for the majority of patients, obinutuzumab can be added with minimal additional toxicity, consisting of slightly higher rates of neutropenia and infusion-related reactions.

**New Evidence:** In which patients would you give obinutuzumab plus bendamustine if it were available?

**Dr. Johnson:** I would consider giving G-B, followed by obinutuzumab maintenance to any patient who has relapsed or refractory follicular lymphoma (FL) that has progressed within 6 months of their last rituximab-based chemotherapy regimen and has had no recent exposure to bendamustine. These are the patients that benefited the most from the combination treatment. If the regimen of G-B followed by obinutuzumab maintenance is approved to include all patients with relapsed or refractory FL, regardless of their last rituximab dose, then this could significantly improve the treatment options for patients with relapsed FL in Quebec, given that BR is not funded in this setting.

**New Evidence:** How might the results of the GADOLIN trial benefit patients in Canada and in Quebec specifically?

**Dr. Johnson:** Overall, the GADOLIN study has the potential to help patients living in Canada if the combination of G-B is funded in the relapse setting. We hope that the GADOLIN study will convince funding bodies to provide access to this combination, which would be especially useful for those patients in Quebec who would not have been previously treated with BR and who have limited access to BR.

I have been working with patient advocacy groups for the past 2 years to get BR approved for patients in Quebec, which has been an ongoing challenge. Given that GADOLIN is a registration trial, G-B should be submitted to Health Canada for approval as an official combination regimen. The Institut National d’Excellence en Santé et en Services Sociaux (INESSS) would then be able to evaluate the GADOLIN study and make a decision, based on efficacy and cost, to approve G-B followed by obinutuzumab maintenance for patients with relapsed or refractory FL, which would be a big step forward for patients living in Quebec. I am hopeful that funding agencies will acknowledge the injustice that patients are not treated equally across Canada and will recognize G-B as a valid regimen for these patients.

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A dose-escalation study of the BCL2 inhibitor, venetoclax, plus bendamustine and rituximab in patients with relapsed or refractory NHL

**Background**
Preclinical studies have suggested that venetoclax enhances the efficacy of bendamustine and rituximab (BR) combination therapy. De Vos and colleagues designed this phase I, open-label, multi-centre study to evaluate venetoclax in combination with BR in patients with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL). Interim results were presented at both EHA 2015 and ASCO 2015.1,2

**Study design**
- In the dose-escalation portion of the study, patients were treated on a 28-day cycle with daily venetoclax ranging from 50 mg to 400 mg, following three dosing schedules.
  - Rituximab was given at 375 mg/m² as a single intravenous (iv) infusion on day 1 of all six cycles.
  - Bendamustine was given at 90 mg/m² as an iv infusion on two consecutive days of all six cycles.
- Upon completion of the BR portion of the regimen, patients could have continued venetoclax mono-therapy for up to two years with continued tolerability in the absence of disease progression.
  - During monotherapy, dosing with venetoclax may have been escalated to the highest dose level based on another single-agent study of venetoclax.
- The criteria for patient inclusion were:
  - Age ≥18 years;
  - Histologically documented diagnosis of R/R NHL;
  - Eastern Cooperative Oncology Group (ECOG) performance score of ≤1; and
  - Adequate bone marrow independent of growth factor support.
- Patients with diffuse large B-cell lymphoma (DLBCL) must have received first-line therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or a similar rituximab-containing chemoimmunotherapy regimen.
- The exclusion criteria included:
  - Post-transplant lymphoproliferative disease,
Burkitt’s or Burkitt-like lymphoma, lymphoblastic lymphoma/leukemia, chronic lymphocytic leukemia, small lymphocytic lymphoma, or mantle cell lymphoma;
- Refractory DLBCL that has not responded to or progressed during or within three months of completion of first-line therapy with R-CHOP or equivalent, or progressed during or within two months of their last course of subsequent chemotherapy.

- The primary objectives of the study were:
  - To evaluate the safety and characterize the pharmacokinetics of the therapy; and
  - To determine the maximum tolerated dose (MTD) and recommended phase II dose.
- The secondary objectives of the study were to evaluate preliminary efficacy data, including progression-free survival (PFS), objective response rate, time to tumour progression, overall survival, and duration of overall response.
- An exploratory objective was biomarker analysis correlating response to BCL2 family member expression and will be reported at a later time.
- Dose-limiting toxicities (DLTs) were assessed during cycle 1.
- Adverse events (AEs) were graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE).
- Pharmacokinetic parameters were assessed for venetoclax and bendamustine for each patient at each dose level.
- Responses were assessed by International Working Group criteria on day 1 of cycles 3, 5, 7, 11, 14, 17, and 23, and every six cycles thereafter.
- Following cohort 5, a protocol amendment was filed to strongly encourage granulocyte-colony stimulating factor (G-CSF) prophylaxis during venetoclax administration, particularly in heavily pretreated patients, and to revise the DLT definition to better distinguish between toxicities due to the combination and those commonly observed with the BR backbone regimen.

**Key findings**

**Baseline characteristics**
- As of April 2015, 35 patients were enrolled in nine dose escalation cohorts, with a median age: 62 years (range: 29–90).
- The majority of patients were male (63%) and had follicular lymphoma (60%) or DLBCL (31%).
- The median number of prior therapies in the patient population was three (range: 1–8).
- Overall, 94% of patients had received rituximab-based chemotherapy, and 23% had received bendamustine or BR therapy.

**Safety**
- AEs of any grade were observed in 97% of patients.
  - The most common AEs were nausea (60%), thrombocytopenia (51%), anemia (46%), and diarrhea (46%).
- Grade 3/4 AEs were observed in 77% of patients.
  - The most common grade 3/4 AEs were lymphocyte count decreased (34%) and neutropenia (31%).
- Serious AEs (SAEs) were observed in 37% of patients.
  - These SAEs included febrile neutropenia (9%), malignant neoplasm progression (6%), syncope (6%), and dyspnea (6%).
- No grade 5 AEs were observed.
- Three DLTs were observed during cycle 1, which included:
  - One case of thrombocytopenia and one case of febrile neutropenia were observed in Cohort 5 (200 mg [28/28d]); and
  - One case of Stevens-Johnson Syndrome in Cohort 8 (400 mg [28/28d]); the primary reasonable possibility due to allopurinol (patient discontinued).

**Pharmacokinetics**
- The concentrations of venetoclax in the presence (cycle 1 day 2) or absence (cycle 2 day 1) of bendamustine were comparable.

**Preliminary treatment efficacy**
- The current status of evaluable patients is summarized in Table 1.
- Most patients responded to treatment prior to first assessment on day 1 of cycle 3.
- The median time on study was 4.9 months (range: 0.1–32.5). (Figure 1)
- Of the 35 patients, 66% had an objective response, 11% had stable disease, and 17% had progressive disease. (Table 2)
- Out of 32 patients who underwent post-baseline tumour assessment, 26 achieved a reduction in nodal size. (Figure 2)
### Table 1. Current status of evaluable patients

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 35), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active at time of analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Completed BR induction regimen</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Elected to continue venetoclax monotherapy</td>
<td>15 (43)</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td>14 (40)</td>
</tr>
<tr>
<td>Prior to completion of BR induction regimen(^1)</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Following completion of BR induction regimen</td>
<td>15 (43)</td>
</tr>
<tr>
<td>During venetoclax monotherapy(^2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Dose reductions of venetoclax during cycle 1–6 of BR induction regimen(^3)</strong></td>
<td>3 (9)</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td>19 (54)</td>
</tr>
<tr>
<td>Prior to completion of BR induction regimen(^1)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Following completion of BR induction regimen</td>
<td>1 (3)</td>
</tr>
<tr>
<td>During venetoclax monotherapy(^2)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

**AE** = adverse event; **BR** = bendamustine, rituximab; **PD** = progressive disease

\(^1\)11/14 (78%) are still active on venetoclax monotherapy maintenance.

\(^2\)11 due to PD, 2 due to AEs, 1 withdrew consent, 1 non-compliance.

\(^3\)2 due to PD, 1 due to an unrelated AE of lung adenocarcinoma.

\(^4\)In cohort 5, cycle 1; 1 in cohort 8, cycle 2.

### Table 2. Summary of response rate by histology

<table>
<thead>
<tr>
<th></th>
<th>FL (N = 21) n (%)</th>
<th>DLBCL (N = 11) n (%)</th>
<th>MZL (N = 3) n (%)</th>
<th>Total (N = 35) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>15 (71)</td>
<td>5 (45)</td>
<td>3 (100)</td>
<td>23 (66)</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (29)</td>
<td>1 (9)</td>
<td>1 (33)</td>
<td>8 (23)</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>9 (43)</td>
<td>4 (36)</td>
<td>2 (67)</td>
<td>15 (43)</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>2 (10)</td>
<td>2 (18)</td>
<td>0 (0)</td>
<td>4 (11)</td>
</tr>
<tr>
<td><strong>Discontinued without response assessment</strong></td>
<td>2 (10)</td>
<td>4 (36)</td>
<td>0 (0)</td>
<td>6 (17)</td>
</tr>
</tbody>
</table>

**DLBCL** = diffuse large B-cell lymphoma, **FL** = follicular lymphoma, **MZL** = marginal zone lymphoma
Figure 1. Summary of responses by cohort and histology

<table>
<thead>
<tr>
<th>Dose level</th>
<th>FL</th>
<th>MZL</th>
<th>DLBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg (3/28d)</td>
<td>FL</td>
<td>FL</td>
<td>FL</td>
</tr>
<tr>
<td>100 mg (3/28d)</td>
<td>FL</td>
<td>MZL</td>
<td>DLBCL</td>
</tr>
<tr>
<td>100 mg (7/28d)</td>
<td>DLBCL</td>
<td>FL</td>
<td>FL</td>
</tr>
<tr>
<td>100 mg (28/28d)</td>
<td>FL</td>
<td>DLBCL</td>
<td>FL</td>
</tr>
<tr>
<td>200 mg (28/28d)</td>
<td>FL</td>
<td>DLBCL</td>
<td>FL</td>
</tr>
<tr>
<td>200 mg (7/28d)</td>
<td>FL</td>
<td>FL</td>
<td>FL</td>
</tr>
<tr>
<td>400 mg (7/28d)</td>
<td>FL</td>
<td>MZL</td>
<td>FL</td>
</tr>
<tr>
<td>400 mg (28/28d)</td>
<td>FL</td>
<td>DLBCL</td>
<td>FL</td>
</tr>
</tbody>
</table>

Active, Time to first assessment, CR, PR, PD, SD, Discontinued without assessment

CR = complete response; DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, MZL = marginal zone lymphoma; PD = progressive disease; PR = partial response; SD = stable disease

Figure 2. Best percent change from baseline in nodal size*

*kn = 3 did not have a post-baseline tumour sample.

DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, MZL = marginal zone lymphoma
Key conclusions

- Venetoclax in combination with BR had a tolerable safety profile, as demonstrated by preliminary data.
- Early and long-lasting responses were observed across all dose cohorts in a heavily pretreated population.
- Bendamustine did not affect venetoclax exposure.
- Dose escalation is still ongoing and the MTD was not reached.

References:

Nowakowski GS, et al. ASCO 2015:8540

Final results of a phase I study on the use of bendamustine, rituximab, and lenalidomide in the treatment of relapsed/refractory low-grade NHL

Background
In this phase I study, presented at ASCO 2015, Nowakowski and colleagues aimed to establish the maximum tolerated dose (MTD), safety and feasibility of bendamustine, rituximab, and lenalidomide (BRR) combination treatment in patients with relapsed or refractory (R/R) low-grade non-Hodgkin lymphoma (NHL).1

Study design
- In this phase I study, a 3+3 dose escalation method was used.
  - Dose levels and schedules are shown in Table 1.
  - Pegfilgrastim was given on day 3 of the cycle.
- Eligibility criteria included patients who had R/R low-grade NHL and had received at least one prior treatment.
- A dose-limiting toxicity (DLT) was defined as lack of hematological recovery before day 28 or grade ≥3 non-hematological toxicity.

Key findings
- A total of 15 patients were enrolled on the study.
- The median age of the patients was 59 years (range: 47–79).
- The majority of patients were male (66%).
- Among all patients, 47% had a performance status (PS) of 0, 47% had a PS of 1, and 6% had a PS of 2.
- The majority of patients had Ann Arbor Stage IV disease (80%).
- No DLTs were observed in any of the patients.
- A summary of adverse events (AEs) by grade is shown in Figure 1:
  - The most common grade 1 AEs were thrombocytopenia and neutropenia;
  - The most common grade 2 AE was fatigue;
  - The only grade 3 AEs were urticaria and neutropenia; and
  - No grade 4 AEs were observed.
- Out of the 15 patients in the study, four achieved a complete response and 11 achieved a partial response. (Figure 2)
- No dose escalation above 25 mg daily of lenalidomide was performed, since 25 mg is considered a biologically effective dose.
- All patients remain alive with median follow-up of 17 months (range: 6–28);
  - One patient had disease progression at 12 months.
Table 1. Dose levels and DLTs

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Lenalidomide (days 1–10)</th>
<th>Bendamustine (days 1,2)</th>
<th>Rituximab (day 1)</th>
<th>Number of DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 mg</td>
<td>70 mg/m²</td>
<td>375 mg/m²</td>
<td>0/3</td>
</tr>
<tr>
<td>2</td>
<td>20 mg</td>
<td>70 mg/m²</td>
<td>375 mg/m²</td>
<td>0/3</td>
</tr>
<tr>
<td>3</td>
<td>20 mg</td>
<td>90 mg/m²</td>
<td>375 mg/m²</td>
<td>0/3</td>
</tr>
<tr>
<td>4</td>
<td>25 mg</td>
<td>90 mg/m²</td>
<td>375 mg/m²</td>
<td>0/6</td>
</tr>
</tbody>
</table>

DLTs = dose-limiting toxicities

Figure 1. Summary of adverse events: highest grade per patient for each toxicity (N = 15)

Figure 2. Complete and partial response rates

Key conclusions

- Lenalidomide at 25 mg/day for days 1–10 of a 28-day cycle can be safely combined with the standard dose of bendamustine (70 mg/m² or 90 mg/m²) and rituximab (375 mg/m²) and is well tolerated.

- Other research groups have reported similar results for this combination of agents with different schedules of lenalidomide.

- Given the positive results of this study, the BRR regimen should be further evaluated in larger clinical trials.

Rituximab, bendamustine, and lenalidomide in patients with aggressive B-cell lymphoma ineligible for anthracycline-based first-line therapy or an intensive salvage regimen

Background
In this phase II trial, Hitz and colleagues evaluated the efficacy and safety of rituximab, bendamustine, and lenalidomide combination treatment in patients with relapsed or refractory (R/R) B-cell lymphoma and in those not suitable for first-line anthracycline-based therapy. The results were presented at ICML 2015.¹

Study design
- Using doses established in phase I results, patients with aggressive B-cell lymphoma were treated with the following, for six 28-day cycles:
  - Rituximab 375 mg/m² on day 1;
  - Bendamustine 70 mg/m² on days 1 and 2; and
  - Lenalidomide 10 mg on days 1–21.
- The main inclusion criteria were:
  - Histologically confirmed aggressive B-cell lymphomas:
    - Diffuse large B-cell lymphoma;
    - Transformed follicular lymphoma; or
    - Follicular lymphoma, grade 3b;
  - Ineligible for anthracycline-based first-line therapy or an intensive salvage regimen according to local guidelines;
  - World Health Organization performance status: 0–3;
  - Ejection fraction >40%;
  - Adequate renal and liver function;
  - No central nervous system involvement;
  - No more than 25% bone marrow involvement; and
  - Measureable lesions with computerized tomography.
- The primary endpoint was overall response rate (ORR; complete response [CR]/complete response, unconfirmed [CRu] + partial response [PR]).
- The secondary endpoints were: CR/CRu, progression-free survival (PFS), event-free survival (EFS), response duration, time to progression (TTP), overall survival (OS), and adverse events (AEs).

Key findings

Baseline characteristics and disposition
- A total of 41 patients were enrolled, the majority of whom were males (59%).
- The median age of the patients was 75 years (range: 40–94).
- The majority of the patients were Ann Arbor stage III–IV (63%).
- Of the 41 patients, 32% were ineligible for anthracycline-based standard treatment.
- Of the patients ineligible for a salvage regimen, 44% had relapsed after R-CHOP-like treatment, 10% had relapsed after autologous stem cell transplantation, and 15% were refractory to anthracycline-based chemotherapy.
- The six cycles of treatment were completed by 14 patients.
- Trial treatment was discontinued by 27 patients, due to:
  - Progressive disease (PD) (n = 13);
  - Unacceptable toxicity (n = 8);
  - Patient refusal (n = 2);
  - Death (n = 3); and
  - Abdominal pain with suspicion of clinical PD (n = 1).
**Efficacy**

- The ORR in the whole patient population was 61% (25/41), including 37% of patients with CR/CRu and 24% with PR. (Figure 1)
  - In patients who were ineligible for anthracycline-based first-line chemotherapy, the ORR was 77% (10/13).
  - In patients with refractory or relapsed disease, the ORR was 54% (15/28).
- At a median follow-up time of 25.9 months (range: 0.2–37.9) for secondary endpoints:
  - Median PFS was 4.8 months (95% CI: 2.4–6.7);
  - Median EFS was 3.7 months (95% CI: 1.8–5.2);
  - Median response duration was 6.8 months (95% CI: 3.4–12.3);
  - Median TTP was 6.4 months (95% CI: 2.4–8.6); and
  - Median OS was 14.4 months (95% CI: 4.9–21.6). (Figure 2)

**Safety**

- Hematologic AEs (59%) were the most common grade ≥3 AEs. (Table 1)
- Death occurred in 22% of patients. (Table 1)

---

**Figure 1. Response rates to treatment**

![Response rates to treatment graph](image1.png)

**Figure 2. Overall survival**

![Overall survival graph](image2.png)
Key conclusions

- Rituximab, bendamustine, and lenalidomide combination therapy showed activity in elderly patients with aggressive B-cell lymphoma and comorbidities, who were ineligible for anthracycline-based first-line therapy or an intensive salvage regimen.
  - The combination therapy had acceptable toxicities.

- Although many progressed during treatment, one third of the patients enrolled in the study were still alive after two years.

- The treatment of comorbid patients with aggressive lymphoma remains challenging.


Table 1. Grade ≥3 adverse events

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Skin toxicity (rash)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Constitutional (fatigue)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Neurology</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (22)</td>
</tr>
</tbody>
</table>
  - Disease progression     | 4               |
  - Decrease of general condition | 1       |
  - Death of unknown cause  | 1               |
  - Sudden death            | 1               |
  - Subdural hematoma       | 1               |
  - Pneumonitis             | 1               |

Wang Y, et al. ASCO 2015:8551

Rituximab maintenance therapy in B-cell lymphoma: a meta-analysis

Background

Wang and colleagues reviewed data from clinical studies and conducted a meta-analysis to evaluate the efficacy and safety of rituximab maintenance therapy in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). Their findings were presented at ASCO 2015.1

Study design

- PubMed, American Society of Clinical Oncology (ASCO), and American Society of Hematology (ASH) databases were searched for eligible clinical studies.

- For inclusion, the studies had to have used rituximab as maintenance therapy in FL, DLBCL, or MCL, and investigated the following:
  - Survival outcomes: overall survival (OS), progression-free survival (PFS), event-free survival (EFS) and/or time to progression (TTP); and
  - Adverse events (AEs).

- Comprehensive MetaAnalysis (version 2) was used to calculate pooled hazard ratios (HRs) for survival outcomes and risk ratios (RRs) for dichotomous AE data with 95% confidence intervals (CIs).

Key findings

- A total of 132 potential relevant studies were identified from the databases, 22 clinical studies of 6,785
patients, including 15 randomized controlled trials (RCTs) enrolling 5,029 patients, were included in the meta-analysis. (Figure 1)

- The Forest plot in Figure 2 summarizes the HRs for PFS in the rituximab maintenance arm vs. the control arm in the randomized controlled trials (RCTs).

- The overall HRs for PFS by disease subgroup were as follows:
  - FL: $HR = 0.51$ (95% CI: 0.42–0.64; $p <0.001$);
  - DLBCL: $HR = 0.70$ (95% CI: 0.57–0.86; $p <0.001$);
  - MCL: $HR = 0.55$ (95% CI: 0.41–0.73; $p <0.001$).
- In the RCTs alone: (Table 1)
  - The combined HR for PFS was 0.56 (95% CI: 0.48–0.65; $p <0.001$);
  - The combined HR for OS was 0.79 (95% CI: 0.67–0.93; $p = 0.005$).
- For all trials included in the final analysis: (Table 1)
  - The combined HR for PFS was 0.57 (95% CI: 0.49–0.67; $p <0.001$);
  - The combined HR for OS was 0.76 (95% CI: 0.66–0.88; $p <0.001$).
- Significant PFS benefit was seen with rituximab maintenance therapy in all types of lymphomas.
- Significant OS benefit with rituximab maintenance therapy was only seen in FL.
- The most prevalent grade 3-4 AE was neutropenia, which occurred in 164/2,285 patients receiving rituximab as maintenance therapy vs. 93/2,287 patients in the control arm in 17 trials (RR = 1.82; 95% CI: 1.40–2.37; $p <0.001$); (Table 2)
- The next most prevalent grade 3-4 AE was infection, which occurred in 72/1,685 patients receiving rituximab as maintenance therapy vs. 29/1,828 patients in the control arm in 13 trials (RR = 2.49; 95% CI: 1.61–3.85; $p <0.001$). (Table 2)

---

**Figure 1. Screening and selection of eligible studies**

- Potentially relevant studies identified through database searching: $n = 132$
  - Excluded: $n = 93$
    - Basic searches
    - Review articles
    - Not involving maintenance therapy with rituximab
  - Trials retrieved for further assessment: $n = 39$
    - Excluded: $n = 17$
      - Not on patients with FL/MCL/DLBCL
      - Single arm trials
      - Data not adequate to determine pooled HR for PFS/OS
      - Duplicate reports
  - Trials included for analysis: $n = 22$

**Notes:**
- DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HR = hazard ratio; MCL = mantle cell lymphoma; OS = overall survival; PFS = progression-free survival
Figure 2. Forest plot of HR for PFS of rituximab maintenance arms versus control arms in RCTs

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup</th>
<th>Statistics for each study</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forstpointner (2006)</td>
<td>FL</td>
<td></td>
<td>0.66</td>
<td>0.44</td>
<td>0.99</td>
<td>0.045</td>
</tr>
<tr>
<td>Hochster (2009)</td>
<td>FL</td>
<td></td>
<td>0.43</td>
<td>0.29</td>
<td>0.64</td>
<td>0.000</td>
</tr>
<tr>
<td>Martinelli (2010)</td>
<td>FL</td>
<td></td>
<td>0.55</td>
<td>0.39</td>
<td>0.78</td>
<td>0.001</td>
</tr>
<tr>
<td>van Oers (2010)</td>
<td>FL</td>
<td></td>
<td>0.54</td>
<td>0.41</td>
<td>0.71</td>
<td>0.000</td>
</tr>
<tr>
<td>Salies (2011)</td>
<td>FL</td>
<td></td>
<td>0.55</td>
<td>0.44</td>
<td>0.68</td>
<td>0.000</td>
</tr>
<tr>
<td>Pettingell (2013)</td>
<td>FL</td>
<td></td>
<td>0.66</td>
<td>0.47</td>
<td>0.92</td>
<td>0.014</td>
</tr>
<tr>
<td>Vitolo (2013)</td>
<td>FL</td>
<td></td>
<td>0.71</td>
<td>0.43</td>
<td>1.17</td>
<td>0.180</td>
</tr>
<tr>
<td>Ardeshna (2014)</td>
<td>FL</td>
<td></td>
<td>0.23</td>
<td>0.16</td>
<td>0.33</td>
<td>0.000</td>
</tr>
<tr>
<td>Kahl (2014)</td>
<td>FL</td>
<td></td>
<td>0.54</td>
<td>0.34</td>
<td>0.86</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>FL</td>
<td></td>
<td><strong>0.51</strong></td>
<td><strong>0.42</strong></td>
<td><strong>0.64</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Habermann (2006)</td>
<td>DLBCL</td>
<td></td>
<td>0.63</td>
<td>0.44</td>
<td>0.90</td>
<td>0.011</td>
</tr>
<tr>
<td>Haioun (2009)</td>
<td>DLBCL</td>
<td></td>
<td>0.66</td>
<td>0.37</td>
<td>1.17</td>
<td>0.157</td>
</tr>
<tr>
<td>Gisselbrecht (2012)</td>
<td>DLBCL</td>
<td></td>
<td>0.92</td>
<td>0.63</td>
<td>1.34</td>
<td>0.665</td>
</tr>
<tr>
<td>Jaeger (2013)</td>
<td>DLBCL</td>
<td></td>
<td>0.62</td>
<td>0.43</td>
<td>0.90</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>DLBCL</td>
<td></td>
<td><strong>0.70</strong></td>
<td><strong>0.57</strong></td>
<td><strong>0.86</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Ghielmini (2005)</td>
<td>MCL</td>
<td></td>
<td>0.69</td>
<td>0.32</td>
<td>1.50</td>
<td>0.349</td>
</tr>
<tr>
<td>Forstpointner (2006)</td>
<td>MCL</td>
<td></td>
<td>0.50</td>
<td>0.32</td>
<td>0.78</td>
<td>0.002</td>
</tr>
<tr>
<td>Kluin-Nelemans (2012)</td>
<td>MCL</td>
<td></td>
<td>0.55</td>
<td>0.35</td>
<td>0.86</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>MCL</td>
<td></td>
<td><strong>0.55</strong></td>
<td><strong>0.41</strong></td>
<td><strong>0.73</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td><strong>0.56</strong></td>
<td><strong>0.48</strong></td>
<td><strong>0.65</strong></td>
<td><strong>0.000</strong></td>
</tr>
</tbody>
</table>

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HR = hazard ratio; MCL = mantle cell lymphoma; PFS = progression-free survival; RCTs = randomized controlled trials
Key conclusions

- Rituximab maintenance therapy improved PFS in FL, DLBCL, and MCL, and it improved OS in FL.
- Further studies are required to evaluate whether rituximab maintenance therapy can improve OS in DLBCL and MCL.

Follicular Lymphoma


Idelalisib efficacy and safety in patients with follicular lymphoma from a phase II study

**Background**
Idelalisib has previously shown antitumour activity and acceptable tolerability as monotherapy against indolent non-Hodgkin lymphomas (iNHL) refractory to rituximab and an alkylating agent. At EHA 2015 and ASCO 2015, Zinzani and colleagues presented a post hoc analysis on the efficacy and safety of idelalisib in highly pretreated patients with relapsed or refractory (R/R) follicular lymphoma (FL).1,2

**Study design**
- In this post hoc subgroup analysis of a phase II, multicentre, single-group, open-label study, patients with double refractory FL received oral idelalisib 150 mg twice daily until progressive disease (PD), unacceptable toxicity, or death.
- Dose modification was allowed in patients with adverse events (AEs).
- The inclusion criteria were:
  - Age ≥18 years with iNHL (FL grade 1, 2, or 3a);
  - Treated with ≥2 prior systemic therapies and refractory to rituximab and an alkylating agent;
  - Eastern Cooperative Oncology Group (ECOG) performance score of 0–2; and
  - Absolute neutrophil count ≥1.0 x 10^9/L and platelet count ≥50 x 10^9/L.
- The exclusion criteria were histologic transformation, central nervous system lymphoma, hepatic dysfunction, or active systemic infection.
- Tumour assessments were performed at: screening; weeks 8, 16, and 24; and every 12 weeks thereafter.
- Response was evaluated by an independent review committee.
- The primary outcome was overall response rate (ORR).
- The secondary outcomes were lymph node response rate (≥50% decrease in the sum of products [SPD] of the diameters of index lesions), duration of response (DOR), progression-free survival (PFS), time to response (TTR), overall survival (OS), and health-related quality of life (HRQoL; Functional Assessment of Cancer Therapy: Lymphoma [FACT-Lym]).
- PFS, OS, and time to symptom improvement for FACT-Lym were summarized using the Kaplan-Meier (KM) method.

**Key findings**

**Baseline characteristics and disposition**
- A total of 72 patients with FL were enrolled, with a median age of 62 years (range: 33–84).
- The majority of patients were male (54.2%) and had grade 2 FL (54.2%).
- Of the total patient population, 83.3% had stage III or IV disease.
- The most common prior therapies were bendamustine (69.4%) and anthracycline (72.2%).
- The median duration of treatment was 6.5 months (range: 0.6–31.0), and median follow-up was 19.4 months (range: 0.7–35.6).
- At data cut-off, 7 (9.7%) patients were still on treatment and 65 (90.3%) had discontinued therapy.
  - The most frequent reasons for discontinuation were PD (52.8%) and AEs (20.8%).

**Efficacy**
- A ≥50% SPD reduction in lymph node size was shown in 57% of patients.
- The ORR was 55.6% (n = 40/72; 95% CI: 43.4–67.3%; p <0.001) in all patients and 66.7% (n = 8/12; 95% CI: 34.9–90.1%) in patients with FL grade 3a. (Figure 1)
  - Complete response (CR) was achieved in 13.9% of all patients;
  - The disease control rate (CR + partial response + stable disease) was 87.5%;
  - At the time of first analysis, ORR and CR were 54.2% and 8.3%, respectively.
• Median TTR was 2.6 months (range: 1.6–11.0) and median DOR was 10.8 months (range: 0–26.9).

• Median PFS for the overall patient population was 11.0 months; 44.7% of patients were progression-free at one year. (Figure 2)

• Median KM-estimated OS was not reached; OS was 88.1% at 12 months, 74.2% at 18 months, and 69.8% at 24 months. (Figure 3)

• The median best change from baseline in FACT-Lym score showed clinically meaningful improvement at least once during follow-up for:
  ◦ Emotional well-being;
  ◦ Functional well-being;
  ◦ Additional concerns;
  ◦ Trial outcome index score; and
  ◦ FACT: general total score subscales.

Safety
• AEs reported in at least 10% of patients are shown in Table 1.

• The most common AEs resulting in study discontinuation in more than one patient (n = 2 each) were diarrhea, pneumonitis, and alanine aminotransferase/aspartate aminotransferase elevation.

• Serious AEs occurred in 48.6% (35/72) of patients:
  ◦ The most common AEs were pyrexia (12.5%), diarrhea (6.9%), pneumonia (5.6%), and colitis (4.2%).

Figure 1. Best overall response in relapsed/refractory patients (n = 72)

Figure 2. Comparison of progression-free survival with previous line of therapy before study inclusion
Key conclusions

■ In this post hoc analysis evaluating the efficacy and safety of idelalisib in highly pretreated patients with relapsed or refractory FL, idelalisib monotherapy produced a high rate of OR.

- Among all patients, the OR was 55.6%.
- Among patients with FL grade 3a, OR was 66.7%.

■ Median PFS (11 months) and median OS (not reached) were impressive in this heavily pretreated population.

■ PFS was approximately doubled in patients who received idelalisib compared with their most recent regimen before study entry.

■ Idelalisib therapy had a manageable safety profile in this aging and frail patient population with relapsed or refractory disease.

■ Patients treated with idelalisib maintained or improved HRQoL outcomes over time and showed clinically meaningful improvement in QoL.

■ Results from this analysis confirm that idelalisib is beneficial as an oral, chemotherapy-free option for the treatment of heavily pretreated relapsed or refractory patients with FL.


Table 1. Adverse events reported in ≥10% of patients

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Any grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>71 (98.6)</td>
<td>47 (65.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (51.4)</td>
<td>10 (13.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>23 (31.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (29.2)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (27.8)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (27.8)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (19.4)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (19.4)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (18.1)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (16.7)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>11 (15.3)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11 (15.3)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>11 (15.3)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (13.9)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (13.9)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>9 (12.5)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (11.1)</td>
<td>5 (6.9)</td>
</tr>
</tbody>
</table>

AE = adverse event
Evaluation of complete response rate at 30 months as a surrogate endpoint for PFS in first-line follicular lymphoma studies: analyses of patient data from the FLASH database

Background
Sargent and colleagues set out to establish a surrogate endpoint for progression-free survival (PFS) in first-line follicular lymphoma (FL) in order to speed up the duration of clinical trials and to expedite patient access to effective new treatments. The Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) group conducted a meta-analysis to evaluate whether treatment effects on complete response rate at 30 months (30mCR), an earlier endpoint, could accurately predict treatment effects on PFS. The investigators analyzed individual patient data from previous randomized trials in FL by using a prospectively designed meta-analytic surrogacy evaluation. The data were presented at ASCO 2015.1

Study design
• A total of 348 references were identified via a September 2011 Medline database search for publications and conference abstracts using the search terms “follicular lymphoma” AND “randomized”, “indolent lymphoma” AND “randomized”, and “low-grade lymphoma” AND “randomized”. The references were subsequently evaluated for inclusion.
  ◦ Patient data from studies included in the final analysis was compiled into the FLASH database.
  ◦ All studies that were included had to:
    ◦ Be randomized and multicentre studies;
    ◦ Be conducted on previously untreated patients with FL;
    ◦ Contain >100 total or >50 patients with FL; and
    ◦ Be published after 1990.
  ◦ Studies evaluating induction vs. observation therapy and studies containing uncertain or insufficient data were excluded.
  ◦ The principal surrogacy candidate used was 30mCR after trial enrollment.
    ◦ The Cheson criteria published in 1999 were used to evaluate 30mCR (No CR unconfirmed). Positron emission tomography was not used;
    ◦ 30mCR was chosen as it captures both induction and maintenance treatment effects and may allow for earlier completion of clinical trials;
  ◦ Preliminary clinical data showed that durable CR was associated with prolonged PFS.

Surrogacy evaluation methods
• The primary evaluation method was trial-level surrogacy, which measured how precisely the observed treatment effect on the surrogate endpoint could be used to predict the treatment effect on the true endpoint.
  ◦ Two measurements were used: $R^2_{WLS}$ (weighted least squares) and $R^2_{Copula}$; the closer each value was to 1.0, the stronger the surrogacy.
  ◦ For surrogacy qualification:
    – Either $R^2_{WLS}$ or $R^2_{Copula}$ had to be ≥0.80;
    – Neither value could be <0.7; and
    – The lower bound 95% confidence interval (CI) had to be >0.6.
  ◦ The supplemental measures that were used were:
    ◦ Surrogate threshold effect (STE), which was used to evaluate suitability for future trials; and
    ◦ Concordance of significance (CoS), which was used to assess how often the same conclusion is reached if both the surrogate and the true measurement are used.
  ◦ Sensitivity analyses were conducted.
    ◦ The coefficient of determination (R2) was re-estimated by excluding one trial at a time to ensure that no one trial was overly influential.
  ◦ Finally, investigators evaluated individual-patient-level surrogacy.
    ◦ Supplemental or supportive evaluation was conducted.
    ◦ Correlation between true and surrogate endpoint at individual patient level was assessed using the global odds ratio (OR).

Key findings
Baseline characteristics and disposition
• A total of 13 studies were included in the final analysis. (Table 1)
  ◦ Study disposition is outlined in Figure 1;
A total of 3,837 patients over 26 treatment arms were identified.
• Of the 13 studies, nine contained at least one arm with rituximab, while the other four did not involve rituximab.
• Eight of the trials involved induction therapy and five involved maintenance therapy.
• The median age of patients was 55.7 years in the control arms and 56.5 years in the experimental arm ($p = 0.031$).
• There were no other significant differences in baseline characteristics between the two groups.

Results
• The log of the OR for 30mCR was plotted against the log of the hazard ratio (HR) for PFS. (Figure 2)
• The log values compared the experimental arm to the control arm in terms of 30mCR and PFS for each of the studies.
• A strongly linear relationship was seen between log(OR) and log(HR).
• 30mCR met the prespecified surrogacy qualification criteria for PFS.
  - $R^2_{WLS}$ was $0.88$ (95% CI: 0.77–0.96) and $R^2_{Copula}$ was $0.86$ (95% CI: 0.72–1.00).
• Surrogacy criteria were met even when data was stratified into rituximab vs. non-rituximab trials and induction versus maintenance trials.
  - This indicated that the association between log(OR) and log(HR) was consistent between all types of trials.
• Supplemental evaluations also supported surrogacy.
• The CoS was 92%; 12 of the 13 trials gave the same conclusion ($p < 0.05$).
• The STE had an estimated OR of 1.56.
  - This implied that, in future trials, an observed OR of ≥1.56 (corresponding to an improvement in 30mCR from a control rate of 50% to an experimental rate of 61%) would reliably predict a non-zero treatment effect on PFS in an ongoing trial.
• Sensitivity evaluation showed that regardless of which of the 13 trials were left out, the surrogacy measures ($R^2_{WLS}$ and $R^2_{Copula}$) all exceeded the threshold of 0.8 and excluded the lower confidence bound of 0.6. (Figure 3)
• Surrogacy was very strong at the individual level.
  - The global OR for all 13 trials combined was 11.84 (95% CI: 10.03–13.65), indicating that patients who have a 30mCR status have a greatly reduced odds of having progression at any time in the follow-up of the study.
  - Global ORs for trials by type are presented in Table 2.

Future Implications
• Surrogacy evaluations are limited to the specific patient population (in this study, previously untreated FL) and are only valid for similar types of treatments (in this study, cytotoxic treatments, with or without rituximab).
• The FLASH database that was assembled during this study provides a rich repository to explore the biology and treatment of FL in the future.
  - Multiple additional analyses based on this database are being considered by the investigators.
  - The FLASH project demonstrates the importance of international collaboration and data sharing.
Table 1. The 13 included studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Reference</th>
<th>Line of Treatment</th>
<th>n</th>
<th>Treatment</th>
<th>n</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 7951</td>
<td>Peterson 2003</td>
<td>Induction</td>
<td>86</td>
<td>Cyclophosphamide</td>
<td>103</td>
<td>CHOP-B</td>
</tr>
<tr>
<td>ECOG 1496</td>
<td>Hochster 2009</td>
<td>Maintenance</td>
<td>113</td>
<td>CVP/observation</td>
<td>115</td>
<td>CVP/R maintenance</td>
</tr>
<tr>
<td>EORTC 20921</td>
<td>Hagenbeek 2006</td>
<td>Induction</td>
<td>117</td>
<td>CVP</td>
<td>114</td>
<td>Fludarabine</td>
</tr>
<tr>
<td>Favld 06</td>
<td>Freedman 2009</td>
<td>Maintenance</td>
<td>130</td>
<td>Rituximab/placebo</td>
<td>127</td>
<td>Rituximab/idiotype vaccine</td>
</tr>
<tr>
<td>GOELAMS 064</td>
<td>Gyan 2009 Deconinck 2005</td>
<td>Induction</td>
<td>81</td>
<td>CHVP/CHVP-IFN-α</td>
<td>85</td>
<td>VCAP/ASCT</td>
</tr>
<tr>
<td>M39021</td>
<td>Marcus 2008</td>
<td>Induction</td>
<td>160</td>
<td>CVP</td>
<td>162</td>
<td>R-CVP</td>
</tr>
<tr>
<td>M39023/OSSHO-39</td>
<td>Herold 2007</td>
<td>Induction</td>
<td>96</td>
<td>MCP/IFN-α</td>
<td>105</td>
<td>R-MCP/IFN-α</td>
</tr>
<tr>
<td>ML 16865/NLG</td>
<td>Kimby 2015</td>
<td>Induction</td>
<td>117</td>
<td>Rituximab</td>
<td>111</td>
<td>Rituximab + IFN-α</td>
</tr>
<tr>
<td>ML 17638/FIL</td>
<td>Vitolo 2013</td>
<td>Maintenance</td>
<td>101</td>
<td>R-FND/observation</td>
<td>101</td>
<td>R-FND/R maintenance</td>
</tr>
<tr>
<td>PRIMA</td>
<td>Salles 2010</td>
<td>Maintenance</td>
<td>513</td>
<td>R-chemo/observation</td>
<td>505</td>
<td>R-chemotherapy/R maintenance</td>
</tr>
<tr>
<td>SAKK 35/98</td>
<td>Ghelmini 2004 Martinelli 2010</td>
<td>Maintenance</td>
<td>23</td>
<td>Rituximab/observation</td>
<td>22</td>
<td>Rituximab/R maintenance</td>
</tr>
<tr>
<td>STUDY 1/GLSG</td>
<td>Nickenig 2006</td>
<td>Induction</td>
<td>362</td>
<td>CHOP/ASCT, IFN-α</td>
<td>146</td>
<td>MCP/ASCT, IFN-α</td>
</tr>
<tr>
<td>STUDY A/GLSG</td>
<td>Hiddemann 2005</td>
<td>Induction</td>
<td>290</td>
<td>CHOP/ASCT, IFN-α</td>
<td>292</td>
<td>R-CHOP/ASCT, IFN-α</td>
</tr>
</tbody>
</table>

ASCT = autologous stem cell transplantation, B = bendamustine; CHVP = cyclophosphamide, doxorubicin, vincristine, prednisolone; CHOP = cyclophosphamide, doxorubicin, etoposide, prednisone; CVP = cyclophosphamide, vincristine, prednisone; FND = fludarabine, mitoxantrone, dexamethasone; IFN-α = interferon alpha; MCP = mitoxantrone, chlorambucil, prednisolone; R = rituximab; VCAP = vincristine, cyclophosphamide, doxorubicin, prednisone

Figure 2. Primary surrogacy evaluation: Log(OR) on 30mCR vs. Log(HR) on PFS

30mCR = complete response at 30 months; CR = complete response; HR = hazard ratio; OR = odds ratio; PFS = progression-free survival
Object size is proportional to sample size.
Table 2. Global odds ratios by type of trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of trials</th>
<th>Global odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>13</td>
<td>11.84 (10.03–13.65)</td>
</tr>
<tr>
<td>Rituximab trials</td>
<td>9</td>
<td>11.08 (9.13–13.03)</td>
</tr>
<tr>
<td>Non-rituximab trials</td>
<td>4</td>
<td>14.40 (9.96–18.84)</td>
</tr>
<tr>
<td>Induction trials</td>
<td>8</td>
<td>10.34 (8.27–12.41)</td>
</tr>
<tr>
<td>Maintenance trials</td>
<td>5</td>
<td>14.14 (10.82–17.46)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Key conclusions

- The principal candidate, 30mCR, met the surrogacy qualification criteria for PFS.
- The conclusions were supported by the highly consistent supplemental surrogacy evaluations and sensitivity analyses.
- 30mCR may be considered an appropriate primary endpoint in future first-line FL studies.

Two doses of polatuzumab vedotin in patients with relapsed/refractory follicular lymphoma: durable responses at the lower dose level

Background
Polatuzumab vedotin is an antibody-drug conjugate composed of an anti-CD79b monoclonal antibody linked to the potent microtubule inhibitor monomethyl auristatin E. Two dose levels of polatuzumab vedotin, 1.8 mg/kg and 2.4 mg/kg, were assessed in patients with relapsed or refractory follicular lymphoma (FL) in phase I and II clinical trials. Advani and colleagues pooled data from these two trials and evaluated treatment-related adverse events (AEs) and anti-tumour activity of polatuzumab vedotin. The data were presented at ASCO 2015 and EHA 2015.1,2

Study design
• The study aimed to compare:
  ◦ The safety and efficacy of polatuzumab vedotin, at 1.8 mg/kg vs. 2.4 mg/kg dose levels, plus rituximab (375 mg/m²); and
  ◦ The safety and efficacy after eight cycles vs. end of treatment (EOT).
• Data were pooled from prior phase I and II trials on patients with FL. (Figure 1)
• Treatment-emergent AEs were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
• Antitumour activity was evaluated based on revised International Working Group criteria (Cheson et al. 2007) every 3 months.

Key findings
Patient characteristics and treatment details
• A total of 20 and 25 patients were given 1.8 mg/kg and 2.4 mg/kg of polatuzumab vedotin, respectively.
• The median age was 62 years (range: 42–77) for patients who received 1.8 mg/kg of polatuzumab vedotin and 67 years (range: 46–87) for those who received 2.4 mg/kg.
• The median number of treatment cycles and median treatment duration were as follows: (Table 1)
  ◦ For the 1.8 mg/kg arm: 13.5 cycles (range: 2–17) and 9.4 months (range: 1–12), respectively;
  ◦ For the 2.4 mg/kg arm: 10 cycles (range: 3–17) and 7.6 months (range: 2–13) respectively.

Safety
• Grade 1/2 toxicities were not clinically significant between the two doses through eight cycles of treatment as well as through treatment completion.

Figure 1. Design of clinical trials from which data was extracted

Phase I
R/R FL (n = 5) ≥ PoV (2.4 mg/kg) + RTX

Phase II (ROMULUS)
R/R FL (n = 20) ≥ PoV (2.4 mg/kg) + RTX
R/R FL (n = 20) ≥ PoV (1.8 mg/kg) + RTX

PoV + RTX 375 mg/m² administered in q21d cycles until progressive disease or unacceptable toxicity
Study amended to evaluate lower dose

FL = follicular lymphoma; PoV = polatuzumab vedotin; q21d = every 21 days; R/R = relapsed or refractory; RTX = rituximab
In Supportive Care Oncology

The most common grade 3/4 toxicity was neutropenia, which was seen with both doses, through eight cycles of treatment and through treatment completion.

Grade 1/2 peripheral neuropathy occurred in 80% of the 1.8 mg/kg dose and 88% of the 2.4 mg/kg dose. (Table 2)

Grade 3 peripheral neuropathy occurred in only one patient at each of the dose levels.

The median time to any serious AEs was 2.4 months (range: 1–9.6) in the 1.8 mg/kg arm and 2.1 months (0.26–19.1) in the 2.4 mg/kg arm.

The median time to AEs leading to study drug discontinuation was 5.4 months (range: 4.6–11.0) at each of the dose levels, respectively:
- Median times to grade ≥2 peripheral neuropathy (6.7 months for the 1.8 mg/kg dose and 2.4 mg/kg dose), and drug discontinuation suggested that capping treatment at eight cycles (~5.5 months) may alleviate treatment-related toxicities.
- The incidences of grade ≥3 neutropenia were the same through cycle 8 and at EOT, and were comparable between the two dose levels. (Table 3)

Lower incidences of grade ≥2 peripheral neuropathy were observed through cycle 8 compared with EOT, and in the 1.8 mg/kg arm compared with the 2.4 mg/kg arm. (Table 3)

Fewer AEs leading to discontinuation were observed through cycle 8 compared with EOT. (Table 3)

Treatment response

Higher response rates were observed at the higher polatuzumab vedotin dose level and with longer treatment duration. (Table 4)

The median time to first response was 2.8 months at each of the polatuzumab vedotin dose levels and the median times to best response were 5.4 months and 5.3 months at the 1.8 mg/kg and 2.4 mg/kg dose levels, respectively.

Median duration of response (DOR) was not estimable (NE) for the 1.8 mg/kg dose level (95% CI: 5.6–NE months) and 10 months (95% CI: 5.8–NE) for the 2.4 mg/kg dose.

PFS was similar for both study doses: (Figure 2)
- The 12-month estimated PFS was 61.1% for the 1.8 mg/kg dose and 66.8% for the 2.4 mg/kg dose.
### Table 2. Occurrence of peripheral neuropathy

<table>
<thead>
<tr>
<th></th>
<th>PoV 1.8 mg/kg + RTX (n = 20)</th>
<th>PoV 2.4 mg/kg + RTX (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with prior treatment with vinca alkaloids, n (%)</td>
<td>14 (70)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Patients with PN, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>6 (30)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10 (50)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Time to Grade ≥ 2 PN (months), median (IQR)</td>
<td>6.7 (4.9–10.4)</td>
<td>5.5 (4.4–7.4)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; PN = peripheral neuropathy; PoV = polatuzumab vedotin; RTX = rituximab

### Table 3. Comparison of safety between cycle 8 and end of treatment

<table>
<thead>
<tr>
<th></th>
<th>Through Cycle 8</th>
<th>Through EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>PoV 1.8 mg/kg + RTX (n = 20)</td>
<td>PoV 2.4 mg/kg + RTX (n = 25)</td>
</tr>
<tr>
<td>Deaths (unrelated)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Grade ≥ 3 neutropenia</td>
<td>7 (35)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Grade ≥ 2 PN</td>
<td>5 (25)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>6 (30)</td>
<td>6 (24)</td>
</tr>
</tbody>
</table>

AE = adverse event; EOT = end of treatment; PN = peripheral neuropathy; PoV = polatuzumab vedotin; RTX = rituximab
Table 4. Antitumour response rates with polatuzumab vedotin and rituximab

<table>
<thead>
<tr>
<th></th>
<th>Through Cycle 8</th>
<th></th>
<th>Through EOT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PoV 1.8 mg/kg + RTX (n = 20)</td>
<td>PoV 2.4 mg/kg + RTX (n = 25)</td>
<td>PoV 1.8 mg/kg + RTX (n = 20)</td>
<td>PoV 2.4 mg/kg + RTX (n = 25)</td>
</tr>
<tr>
<td>Overall response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>8 (40)</td>
<td>15 (60)</td>
<td>14 (70)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.9–63.9</td>
<td>38.7–77.8</td>
<td>46.7–86.0</td>
<td>56.9–89.0</td>
</tr>
<tr>
<td>Complete response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>2 (10)</td>
<td>7 (28)</td>
<td>4 (20)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.8–31.5</td>
<td>12.1–47.5</td>
<td>7.1–41.1</td>
<td>24.4–65.1</td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>6 (30)</td>
<td>8 (32)</td>
<td>10 (50)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>95% CI</td>
<td>14.0–53.3</td>
<td>16.1–52.5</td>
<td>29.3–70.7</td>
<td>16.1–52.5</td>
</tr>
</tbody>
</table>

CI = confidence interval; EOT = end of treatment; PoV = polatuzumab vedotin; RTX = rituximab
Figure 2. Progression-free survival with polatuzumab vedotin and rituximab

![Graph showing progression-free survival with polatuzumab vedotin and rituximab](image)

**Key conclusions**

- **Tolerability of polatuzumab vedotin may be improved by prescribing a dose of 1.8 mg/kg with a fixed duration of treatment of ≤8 cycles; this could lead to:**
  - A lower rate of and lower median time to grade ≥2 peripheral neuropathy;
  - Longer treatment duration; and
  - Fewer AEs leading to treatment discontinuation.

- **Efficacy of polatuzumab vedotin is observed at both dose levels, with:**
  - Similar objective response rates;
  - Similar median time to onset of first and best response; and
  - Similar PFS and DOR despite higher number of complete responses observed at 2.4 mg/kg.

- **Polatuzumab vedotin may represent a clinically meaningful treatment option for patients with non-Hodgkin lymphoma at 1.8 mg/kg with a fixed duration of ≤8 cycles.**
  - Studies of polatuzumab vedotin at this dosing schedule in combination with immunochemotherapy in diffuse large B-cell lymphoma and FL are ongoing.

A phase III study of ibrutinib in combination either with bendamustine and rituximab or with R-CHOP in patients with previously treated FL or MZL

**Background**

Completed and ongoing studies have demonstrated that ibrutinib can be safely combined with either bendamustine and rituximab (BR) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). At ASCO 2015, Fowler et al. presented the ongoing phase III SELENE study, designed to evaluate whether the addition of ibrutinib to BR or R-CHOP will prolong progression-free survival (PFS) in patients with indolent non-Hodgkin lymphoma (iNHL).1

**Study design**

- SELENE is a randomized, double-blind, placebo-controlled, multicentre phase III trial.
  - Ibrutinib will be combined with either BR or R-CHOP in patients with previously treated follicular lymphoma (FL) or marginal zone lymphoma (MZL).
  - Subjects will be stratified by:
    - Background chemoimmunotherapy treatment;
    - Refractory versus relapsed disease;
    - iNHL histology; and
    - Number of prior lines of therapy.
  - Patients will receive six cycles of BR or R-CHOP (based on prior treatment), and either:
    - A daily oral dose of 560 mg ibrutinib; or
    - Placebo; until disease progression.

**Patient population**

- The following are the inclusion criteria for the study:
  - Age ≥18 years;
  - Histologically confirmed B-cell iNHL, with subtypes FL grade 1, 2, or 3a, or MZL (splenic, nodal, or extranodal);
  - Disease that has relapsed or was refractory after prior chemoimmunotherapy;
  - At least one prior therapy with an anti-CD20 antibody and chemotherapy combination regimen;
  - At least one measurable site of disease; and
  - Eastern Oncology Group performance status of 0 or 1.

- The study will aim to enroll 400 patients from approximately 145 sites in Europe, Asia, Australia, the United States, and South America.

- To date, a total of 267 patients have been randomized, 45% of whom are from Europe, 42% are from the Asia-Pacific region, and 13% are from the Americas. (Figure 1)

**Study endpoints**

- The primary endpoint of the study is progression-free survival (PFS).
- The secondary endpoints are overall survival, complete response rate, overall response rate, patient-reported lymphoma symptoms, and safety.
- Exploratory endpoints include the minimal residual disease-negative rate in patients with FL, patient-reported outcomes related to general health status, and pharmacokinetics of ibrutinib.

---

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

*Continued until disease progression or unacceptable toxicity.
SELENE is an ongoing phase III study aiming to evaluate whether the addition of ibrutinib to BR or R-CHOP will prolong PFS in patients with iNHL.


Hiddemann W, et al. ICML 2015:OT04

Phase II study of venetoclax in combination with bendamustine and rituximab (BR) versus BR alone or venetoclax in combination with rituximab in relapsed/refractory FL

Background
In this phase II study, presented at ICML 2015, Hiddemann and colleagues aim to evaluate the safety and efficacy of venetoclax in combination with rituximab, and in combination with BR versus BR alone in patients with refractory or relapsed (R/R) follicular lymphoma (FL). 1

Study design
• This is an open-label, international multicentre, phase II study (CONTRALTO) that aims to evaluate the safety and efficacy of venetoclax in combination
In Supportive Care Oncology

Key conclusion

■ SELENE is an ongoing phase III study aiming to evaluate whether the addition of ibrutinib to BR or R-CHOP will prolong PFS in patients with iNHL.

• The CONTRALTO study will enrol an estimated 156 patients, from eight countries, who meet the following inclusion criteria:

  ♦ Aged >18 years;
  ♦ Histologically confirmed FL of grade 1, 2, or 3a;
  ♦ At least one prior therapy for FL;
  ♦ Minimum of one bi-dimensionally measurable lesion on imaging scan;
  ♦ Eastern Cooperative Oncology Group performance status of 0–2;
  ♦ Adequate hematologic function;
  ♦ Patients who are to receive chemotherapy must have had a response longer than one year to prior bendamustine treatment.

• The exclusion criteria for the study are:

  ♦ Severe allergic or anaphylactic reaction to monoclonal antibodies;
  ♦ Sensitivity or allergy to murine products;
  ♦ Ongoing prednisone use of >30 mg/day, or on a stable dose for ≥4 weeks if taking ≤30 mg/day; and
  ♦ Contraindication to rituximab, or if patients are to receive chemotherapy, contraindication to bendamustine.

• Patients will be divided between a chemotherapy group and a non-chemotherapy group at the investigator’s discretion.

• In Arm A, patients in the chemotherapy-free group will receive, in 28-day cycles:

  ♦ Venetoclax: 800 mg/day for one year; and
  ♦ Rituximab: 375 mg/m² on days 1, 8, 15, and 22 of cycle 1, and on day 1 of cycles 4, 6, 8, 10, and 12.

• The chemotherapy group will undergo a safety run-in, in 28-day cycles, composed of:

  ♦ Venetoclax: 600 mg/day for one year;
  ♦ Rituximab: 375 mg/m² on day 1 of cycles 1–6; and
  ♦ Bendamustine: 90 mg/m² on days 1 and 2 of cycles 1–6.

• The chemotherapy group will then be randomized into:

  ♦ Arm B:
    - Venetoclax: at the defined daily dose for one year;
    - Rituximab: 375 mg/m² on day 1 of cycles 1–6; and
    - Bendamustine: 90 mg/m² on days 1 and 2 of cycles 1–6.
  ♦ Arm C:
    - Rituximab: 375 mg/m² on day 1 of cycles 1–6; and
    - Bendamustine: 90 mg/m² on days 1 and 2 of cycles 1–6.

• The primary study endpoint will be complete response (CR) by positron emission tomography (PET), using the Lugano Classification: Revised Criteria for Response Assessment.

• The secondary endpoints will be:

  ♦ CR rate by PET;
  ♦ CR rate by computerized tomography;
  ♦ Objective response rate;
  ♦ Duration of response;
  ♦ Event-free survival;
  ♦ Progression-free survival;
  ♦ Overall survival; and
  ♦ Incidence of adverse events.

• Three response assessments will be conducted:

  ♦ Interim assessment: during days 22–28 of cycle 3;
  ♦ Primary assessment: 6–8 weeks after day 1 of cycle 6; and
  ♦ One-year assessment: at 52 weeks (± 4 weeks).

• Safety analyses will be conducted on Arm A and Arm B.

  ♦ For Arm A, the safety of venetoclax plus rituximab will be evaluated.
  ♦ For Arm B safety run-in (6 patients), the tolerability of the 600 mg/day dose of venetoclax in combination with BR will be established, and the 800 mg/day dose will be explored if appropriate after randomization.
  ♦ The safety of venetoclax with BR will be compared with BR alone during the randomization phase.

• Pharmacokinetic analysis will be conducted on venetoclax plus rituximab or BR, and exploratory analysis with higher doses of venetoclax will be conducted on venetoclax plus BR.

• Other exploratory analyses will also be conducted, including:

  ♦ Potential biomarkers to predict disease response or resistance;
  ♦ Conversion rate of partial response (PR) or stable disease to PR or PR/CR after extended therapy or observation; and
  ♦ Evaluation of minimal residual disease (MRD) negativity and risk of progression, assayed through baseline levels and changes of Bcl2, immunoglobulin heavy chain (IgH) rearrangements, and other MRD markers.
Key conclusion

**CONTRALTO** is an ongoing phase II study that will determine the safety and efficacy of venetoclax in combination with rituximab or BR versus BR alone in patients with R/R FL.

Mantle Cell Lymphoma


Lenalidomide, rituximab, and bendamustine in the first line for patients >65 years old with MCL: final results of the Nordic Lymphoma Group MCL4 phase I/II trial

**Background**
In this phase I/II study, presented at ICML 2015, Albertsson-Lindblad and colleagues evaluated the addition of lenalidomide to bendamustine and rituximab (BR), followed by seven months of lenalidomide maintenance in previously untreated elderly patients (i.e., >65 years) with mantle cell lymphoma (MCL).¹

**Study design**
- The inclusion criteria for this study were:
  - Age >65 years, or ≤65 years and unable to tolerate high-dose chemotherapy including autologous stem cell transplantation (ASCT);
  - Histologically confirmed diagnosis of stage II–IV MCL;
  - World Health Organization performance status 0–3;
  - Treatment required due to at least one of the following symptoms: bulky disease, B-symptoms, elevated serum lactate dehydrogenase, involvement of ≥3 nodal sites, symptomatic splenic enlargement, and compressive syndrome or pleural/peritoneal effusion; and
  - No previous treatment, except for one cycle of chemotherapy and/or radiotherapy.
- During the phase I study, patients were divided among three cohorts, each treated with:
  - Bendamustine: 90 mg/m² on days 1 and 2 of all six cycles;
  - Rituximab: 375 mg/m² on day 1 of all six cycles; and
  - Lenalidomide: 5 mg, 10 mg, or 15 mg on days 1–21, for six cycles of 28 days each.
- After amendment, lenalidomide was only given on days 1–14, in cycles 2–6 at maximum tolerated dose (MTD).
- During the phase II study, patients were treated with the following:
  - Bendamustine: 90 mg/m² on days 1 and 2 of all six cycles;
  - Rituximab: 375 mg/m² on day 1 of all six cycles; and
  - Lenalidomide: at MTD on days 1–14 of cycles 2–6.

**Study design**

**Treatment schedule**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Induction phase</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LBR</td>
<td>L</td>
</tr>
<tr>
<td>5</td>
<td>LBR</td>
<td>L</td>
</tr>
<tr>
<td>9</td>
<td>LBR</td>
<td>L</td>
</tr>
<tr>
<td>13</td>
<td>LBR</td>
<td>L</td>
</tr>
<tr>
<td>17</td>
<td>LBR</td>
<td>L</td>
</tr>
<tr>
<td>21</td>
<td>LBR</td>
<td>L</td>
</tr>
<tr>
<td>25</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>29</td>
<td>L</td>
<td>L</td>
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<tr>
<td>33</td>
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<td>45</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>49</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

**Induction phase**
- Bendamustine: 90 mg/m² on days 1 and 2
- Rituximab: 375 mg/m² on day 1
- Lenalidomide: at MTD, initially on days 1–21, and after amendment on days 1–14

**Maintenance**
- Lenalidomide: at MTD on days 1–21

BM = bone marrow; CT = computerized tomography; L = lenalidomide; L-BR = lenalidomide, bendamustine, rituximab; MRD = minimal residual disease; MTD = maximum tolerated dose; PB = peripheral blood; PET = positron emission tomography
Prednisolone (20 mg) was given twice a day, on days 1–14 starting on cycle 2 during both phases I and II of the study.

For the maintenance phase, lenalidomide was given at 10 mg on days 1–21 of cycles 7–8, and at 15 mg on days 1–21 of cycles 9–13.

Cotrimoxazole was recommended as prophylaxis against pneumonia jiroveci (PCP).

The primary endpoints were:
- Phase I: MTD of lenalidomide in combination with BR.
- Phase II: progression-free survival (PFS).

The secondary endpoints were:
- Overall response rate (ORR) and complete response (CR) rate to lenalidomide with BR (L-BR), evaluated with/without positron emission tomography;
- Molecular remission rate by polymerase chain reaction (PCR);
- Health-related quality of life;
- Overall survival (OS); and
- Safety.

**Key findings**

**Baseline characteristics and disposition**
- A total of 51 patients were enrolled in the study, with a median age of 71 years (range: 62–84); 50 patients were evaluable.
- The majority of the patients were male (n = 37).
- Four patients had received one cycle of prior therapy for MCL: one was treated with R-AraC (rituximab, cytarabine), one with BR, and two with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).
- The majority of the patients (n = 28) were high risk, according to the MCL International Prognostic Index (MIPI), while 19 were intermediate risk, and two were low risk.

During phase I of the study, 12 patients were divided among the three lenalidomide cohorts: 5 mg (n = 3), 10 mg (n = 3), and 15 mg (n = 6).
- A total of 16 patients were enrolled at amendment of lenalidomide.
- The median follow-up time was 31 months.
- A total of 36 patients completed all six L-BR induction cycles, while 12 patients completed all 13 cycles (L-BR induction and lenalidomide maintenance). (Figure 1)
- The median number of cycles completed was seven.
- The main causes of treatment discontinuation were:
  - Adverse events (AEs): 26 patients;
  - Progressive disease (PD): 8 patients;
  - Secondary primary malignancy: 3 patients; and
  - Withdrawn consent: 1 patient.

**Efficacy**
- The CR rates were 53% at three months, 73% at six months, and 78% at one and a half months after the completion of therapy. (Figure 2)
- The levels of minimal residual disease (MRD) in the bone marrow, as assessed by PCR, were as follows: (Figure 2)
  - At three months, 50% of patients were MRD-negative;
  - At six months, 56% of patients were MRD-negative; and
  - At one and a half months post-completion of therapy, 64% of patients were MRD-negative.
- The median PFS was 42 months (95% CI: 31–53), and the PFS at three years was 63%. (Figure 3)
- The median OS was 53 months, and the OS at three years was 74%. (Figure 3)
- A total of 14 deaths occurred, with the main causes being: PD (n = 6), toxicity (n = 3), second primary malignancy (n = 3), and other (n = 2).

**Figure 1. Patient disposition**
Safety

- The most common grade 3 AEs were infection, neutropenia, thrombocytopenia, and cutaneous. (Figure 4)
- The most common grade 4 AEs were neutropenia and infection. (Figure 4)
- Infection was the only grade 5 AE. (Figure 4)
- Nine patients (18%) developed new primary malignancies: hematological malignancies (n = 3), non-melanoma skin cancer (n = 2), kidney cancer Fuhrman grade 2 (n = 1), squamous epithelial lung cancer (n = 1), adenocarcinoma of the liver (n = 1), and prostate cancer (n = 1).
Figure 4. Grade 3–5 adverse events*

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Thrombocytopenia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Infection</td>
<td>Cutaneous</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Tumour lysis syndrome</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Mucositis/esophagitis</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Anorexia</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

*Grade 3–5 adverse events occurring in more than one patient.

Key conclusions

- L-BR may be a feasible regimen in first-line elderly patients with MCL, if lenalidomide is given from the second cycle onwards with concomitant corticosteroids and PCP prophylaxis.
  - A high CR rate of 78% and molecular remission rate of 64% were achieved with the L-BR regimen.
- The PFS of patients using L-BR appeared to be longer than that previously reported with BR alone (42 vs. 35 months).
- Toxicity was higher than expected, with 42% of patients developing grade 3–5 infections, and 26 patients stopping treatment due to toxicity.
- Lenalidomide may not be an optimal partner with BR, and the L-BR treatment may not be a standard option for elderly patients.

Reference:

Zaja F, et al. ICML 2015:014

Rituximab, lenalidomide, and bendamustine as second-line therapy for relapsed or refractory MCL: a phase II study

Background
At ICML 2015, Zaja et al. presented the results of a phase II study evaluating the efficacy of bendamustine, lenalidomide and rituximab (R2-B) combination treatment as second-line therapy for patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL).¹

Study design
- The inclusion criteria for this phase II study were:
  - Age ≥18 years;
Key conclusions

- L-BR may be a feasible regimen in first-line elderly patients with MCL, if lenalidomide is given from the second cycle onwards with concomitant corticosteroids and PCP prophylaxis.
- A high CR rate of 78% and molecular remission rate of 64% were achieved with the L-BR regimen.
- The PFS of patients using L-BR appeared to be longer than that previously reported with BR alone (42 vs. 35 months).
- Toxicity was higher than expected, with 42% of patients developing grade 3–5 infections, and 26 patients stopping treatment due to toxicity.
- Lenalidomide may not be an optimal partner with BR, and the L-BR treatment may not be a standard option for elderly patients.

Baseline characteristics and disposition

- A total of 42 patients were enrolled, with a median age of 70 years (range: 45–86).
- The majority of the patients were male (74%).

Key findings

Efficacy

- At induction phase completion (after four cycles), 43% of patients achieved both a CR and a PR for an ORR of 86%.

Study design

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Rituximab</th>
<th>Lenalidomide</th>
<th>Bendamustine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction phase</td>
<td>375 mg/m²</td>
<td>10 mg, days 1–14</td>
<td>70 mg/m², days 2–3</td>
</tr>
<tr>
<td></td>
<td>15 mg, days 1–21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consolidation phase</td>
<td>375 mg/m², day 1</td>
<td>15 mg, days 1–21</td>
<td></td>
</tr>
<tr>
<td>Maintenance phase</td>
<td>15 mg, days 1–21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; R2 = rituximab, lenalidomide; R2-B = rituximab, lenalidomide, bendamustine; SD = stable disease

- Of the Ki-67-positive patients (n = 19), 58% had high Ki-67 levels (>30%).
- The majority of the patients had a World Health Organization performance status of 0–1 (95%) and Ann Arbor stage III/IV disease (93%).
- The majority of the patients had a low MCL International Prognostic Index (MIPI) score (43%).
- Previous treatments included:
  - R-CHOP-like (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), or R-VNCOP (rituximab, etoposide, mitoxantrone, cyclophosphamide, vincristine, and prednisolone) in 64% of patients;
  - R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) in 5%;
  - R-AraC (rituximab and cytarabine) based therapy in 26%;
  - R-FC (rituximab, fludarabine, and cyclophosphamide) in 5%; and
  - First-line autologous stem cell transplantation in 24%.

- In response to previous first-line therapy, 71% of patients achieved a CR, 19% achieved a partial response (PR), 5% had stable disease (SD), and 5% had progressive disease (PD).
- The median duration of response to previous first-line therapy was 19 months (range: 2–85), with 10% of the patients being primary refractory.
- Response durations to previous first-line therapy were as follows:
  - Less than 12 months: 26%;
  - More than 12 months, but less than 24 months: 31%; and
  - More than 24 months: 33%.

Baseline characteristics and disposition

- A total of 42 patients were enrolled, with a median age of 70 years (range: 45–86).
- The majority of the patients were male (74%).

- Eastern Cooperative Oncology Group performance status ≤2;
- MCL relapsed after a single previous treatment or refractory to frontline treatment; and
- Adequate cardiac, hepatic, and renal function.

- The exclusion criteria were:
  - Central nervous system involvement;
  - Human immunodeficiency virus and other active infections; and
  - Active malignancy other than lymphoma.

- In this study, patients were treated as follows:
  - Induction phase: four cycles (28 days/cycle) of rituximab (375 mg/m² on day 1), lenalidomide (10 mg on days 1–14), and bendamustine (70 mg/m² on days 2–3);
  - Consolidation phase: two cycles (28 days/cycle) of rituximab (375 mg/m² on day 1) and lenalidomide (15 mg on days 1–21);
  - Maintenance phase: 18 months of lenalidomide (15 mg on days 1–21 of every 28-day cycle).

- The primary endpoint was complete response (CR), as defined by Cheson et al. 2007.
  - Assuming a 20% improvement in CR (from 40% to 60%) with significance level α = 0.05 and power = 80%, 42 patients would be required, with 23 of them achieving CR for primary endpoint to be reached.

- The secondary endpoints were overall response rate (ORR), minimal residual disease (MRD) after induction and consolidation and during maintenance, safety/toxicity profile, progression-free survival (PFS), overall survival (OS), and correlation with cereblon (CRBN) expression.
• At induction phase completion, 3% of patients had SD and 12% had PD.

• At consolidation phase completion (after six cycles), 55% of patients achieved a CR and 24% achieved a PR for an ORR of 79%. (Table 1)

• At consolidation phase completion, 2% of patients had SD and 19% had PD.

• After a median follow-up of 24 months (21–31), the PFS was (Figure 1):
  - At 12 months: 64% (95% CI: 0.48–0.77);
  - At 18 months: 59% (95% CI: 0.43–0.72); and
  - At 24 months: 48% (95% CI: 0.32–0.62),

• After a median follow-up of 20 months (10–27), the OS was 83% at 12 months and 66% at 24 months.

• None of the predictors of response (age, gender, Ki-67, MIPI, AraC vs. non-AraC containing first-line therapy, and duration of response of first-line therapy) showed a relationship with ORR, CR, or PFS.

• The median CRBN scores for the 29 samples stained were:
  - Cytoplasm: 120 (range: 70–300);
  - Nucleus: 40 (range: 0–190); and
  - Total score: 190 (range: 100–490).

• The proportions of MRD-negative samples were as follows:
  - Post-induction: 45% (samples = 29);
  - Post-consolidation: 39% (samples = 28);
  - After 12 months of maintenance: 48% (samples = 21); and
  - After 18 months of maintenance: 40% (samples = 15).

• The MRD levels, as detected by Droplet Digital™ polymerase chain reaction, in bone marrow and peripheral blood over the course of treatment are shown in Figure 2.

Safety
• Neutropenia was the most prevalent grade 3/4 toxicity during the induction and consolidation phase, as well as the maintenance phase. (Table 2)

• Thrombocytopenia was the next most common grade 3 toxicity during the induction and consolidation phase. (Table 2)

### Table 1. Response rates

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of cycle 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Induction phase, n (%)</td>
<td>36</td>
<td>18</td>
<td>18</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(86)</td>
<td>(43)</td>
<td>(43)</td>
<td>(3)</td>
<td>(12)</td>
</tr>
<tr>
<td>End of cycle 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consolidation phase, n (%)</td>
<td>33</td>
<td>23</td>
<td>10</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(79)</td>
<td>(55)</td>
<td>(24)</td>
<td>(2)</td>
<td>(19)</td>
</tr>
</tbody>
</table>

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

Figure 1. Progression-free survival

![Figure 1](image_url)
Figure 2. Minimal residual disease in bone marrow and peripheral blood

<table>
<thead>
<tr>
<th>Time points</th>
<th>MRD in BM</th>
<th>Time points</th>
<th>MRD in PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9</td>
<td>Baseline</td>
<td>19</td>
</tr>
<tr>
<td>Ind</td>
<td>18</td>
<td>Ind</td>
<td>18</td>
</tr>
<tr>
<td>Cons</td>
<td>9</td>
<td>Cons</td>
<td>16</td>
</tr>
<tr>
<td>Maint1</td>
<td>8</td>
<td>Maint2</td>
<td>8</td>
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<tr>
<td>Maint2</td>
<td>9</td>
<td>Maint3</td>
<td>12</td>
</tr>
<tr>
<td>Maint3</td>
<td>8</td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>

Note: 7 relapsing patients

BM = bone marrow; Cons = consolidation; ddPCR = droplet digital polymerase chain reaction; Ind = induction; Maint = maintenance; MRD = minimal residual disease; Neg = negative; PB = peripheral blood; PNQ = positive not quantifiable

Table 2. Treatment toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Induction + consolidation (n = 42)</th>
<th>Maintenance (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3, n (%)</td>
<td>Grade 4, n (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 (29)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>6 (14)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Key conclusions

- The combination of bendamustine, lenalidomide, and rituximab induced responses in 79% of patients with relapsed or refractory MCL, and compared well with other salvage treatments.
- The treatment led to a CR being achieved by 55% of patients and PFS of 64% and 48% at 12 and 24 months, respectively.
- Almost half of the responding patients achieved MRD negativity after induction.
- Grade 3/4 neutropenia was the most significant toxicity, and non-hematological toxicities were low.
- Investigators were unable to identify predictors of response, possibly due to the low number of patients.

Rituximab, bendamustine, and cytarabine (RBAC500) as induction therapy in elderly patients with mantle cell lymphoma: a phase II study

Background
Visco and colleagues assessed the efficacy and safety of rituximab, bendamustine, and cytarabine combination therapy (R-BAC500) in patients with mantle cell lymphoma (MCL) and presented the results at ICML 2015.1

Study design
• In this phase II, single-arm, two-stage, multicentre trial, previously untreated patients with MCL were treated with R-BAC500 for up to six cycles, as follows:
  ○ Rituximab: 375 mg/m² intravenously (iv) on day 1;
  ○ Bendamustine: 70 mg/m² iv on days 2 and 3; and
  ○ Cytarabine: 500 mg/m² iv on days 2–4.
• The inclusion criteria were:
  ○ Age >65 years or 60–65 years and unfit;
  ○ Newly diagnosed MCL; and
  ○ Ineligible for autologous stem cell transplantation.
• The Bryant and Day two-stage design was adopted to calculate the sample size.
  ○ The first stage would stop if complete response (CR) was achieved in less than eight patients or if toxicity was unacceptable in more than seven patients.
• The primary endpoints were the CR rate (according to Cheson 2007 criteria, as measured by positron emission tomography) and the safety profile of R-BAC500.
• The secondary endpoints were the rate of molecular response, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).
• Minimal residual disease (MRD) assessment, a comprehensive geriatric assessment (CGA), and a central pathology revision were conducted.

Key findings
Baseline characteristics and disposition
• A total of 57 patients from 29 centres were enrolled between May 2012 and February 2014.
• The median age of patients was 71 years (range: 61–79).
• The majority of patients were male (75%).
• The majority of patients had a performance status of 0–1 (94%) and Ann Arbor stage III/IV disease (91%).
• Mantle Cell International Prognostic Index (MIPI) was low in 16% of patients, intermediate in 40%, high in 44%, and 9% had the blastoid variant.

CR = complete response; MRD = minimal residual disease; PD = progressive disease; PET = positron emission tomography; PR = partial response; R-BAC500 = rituximab, bendamustine, cytarabine (cytarabine at 500 mg/m²); SD = stable disease
• All 57 patients completed at least two cycles of R-BAC500, after which four patients discontinued due to toxicities.
• Fifty-three patients (93%) completed at least four cycles, after which 11 patients discontinued due to toxicities, one patient discontinued due to progressive disease (PD), and five patients discontinued due to their own or their physician’s decision.
• Thirty-six patients completed six cycles (63%).
• A total of 21 patients (37%) discontinued the study.

**Efficacy**
• An overall response rate (ORR) of 100% was achieved after two cycles (CR = 37% and partial response [PR] = 63%).
• An ORR of 96% and a CR of 93% were achieved at the end of treatment.
• At the end of treatment, 4% of patients had PD.
• At a median follow-up of 22 months (range: 15–38): (Figure 1)
  • The two-year PFS was 80 ± 5%; and
  • The two-year OS was 89 ± 4%.
• The MIPI score (high vs. low/intermediate), blastoid variant vs. classical, and the failure of achieving MRD-negativity on bone marrow samples were the only statistically significant adverse prognostic factors for PFS.
• Bcl1 or IgH markers were detected in 81% (n = 46) of patients enrolled.
• At various timepoints, the proportions of patients with MRD-negative bone marrow/peripheral blood samples respectively were:
  • After cycle 2 (n = 44): 55%/63%;
  • At the end of therapy (n = 39): 51%/77%;
  • After six months (n = 29): 59%/76%.

**Safety**
• Grade 3/4 neutropenia, leukopenia, and thrombocytopenia were observed in about half of the administered cycles, and febrile neutropenia occurred in 6% of cycles. (Table 1)
  • Febrile neutropenia lasted a median duration of 3.4 days (range: 1–10).
  • Platelet transfusion was required in 49% of patients and in 29% of the cycles compared with 62% of the cycles in a previous study where cytarabine was administered at a higher dose of 800 mg/m².
• Grade 3/4 non-hematological toxicities were relatively uncommon. (Table 2)
  • Fatigue (25%), nausea/vomiting (21%), and infusion-related toxicities (21%) were the most common non-hematological toxicities overall.

Figure 1. Kaplan-Meier cumulative survival plots for progression-free survival and overall survival

OS = overall survival; PFS = progression-free survival
Median follow-up: 22 months (range: 15–38)
Table 1. Hematological toxicities (% of delivered cycles)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Overall* Delivered cycles: 303</th>
<th>R-BAC study (JCO 2013)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 1 2 3 4 Grade 4</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>— 30% 26% 17% 27% 28%</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>— 15% 36% 14% 35% 17%</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>— — — 5% 1% 4%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>— 14% 34% 16% 36% 64%</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>21% 24% 43% 12% &lt;1% 12%</td>
<td></td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>89/303 cycles (29%)</td>
<td>62%</td>
</tr>
</tbody>
</table>

*Values are given as percentages of delivered cycles (n = 303).
†R-BAC study conducted in 2013, with cytarabine administered at 800 mg/m².
JCO = Journal of Clinical Oncology; R-BAC = rituximab, bendamustine, cytarabine

Table 2. Non-hematological toxicities occurring in more than one patient

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades, n (%)</th>
<th>Grade 3, n (%)</th>
<th>Grade 4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>12 (21)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation/diarrhea</td>
<td>6 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infusion related/TLS</td>
<td>12 (21)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (25)</td>
<td>1 (2)</td>
<td>NA</td>
</tr>
<tr>
<td>Documented infections</td>
<td>5 (9)</td>
<td>5 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>g-GT/GOT-GPT elevation</td>
<td>7 (12)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>5 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

g-GT = gamma-glutamyl-transpeptidase; GOT = glutamate oxaloacetate transaminase; GPT = glutamic-pyruvic transaminase; NA = not applicable; TLS = tumour lysis syndrome
*HZV reactivation, infection of the surgical wound, CMV reactivation (n = 2), fungal infection.
†Pseudomonas Aeruginosa and Gram− sepsis.
‡Atrial fibrillation, chest pain.
§Myocardial infarction with cerebral ischemia.

Key conclusions

■ R-BAC500 is a safe treatment that can be administered as first-line therapy to elderly patients with MCL.

■ Hematological toxicity is substantially reduced compared with previous studies, where cytarabine was administered at the higher 800 mg/m² dose.

■ R-BAC500 is a highly effective treatment for elderly patients with MCL, given that it produced:
  • A PET-negative CR in 93% of patients;
  • Negative nested-PCR in bone marrow samples from 51% of patients tested; and
  • A median two-year PFS of 80% without maintenance therapy.

Chen R, et al. ICML 2015:062

Results of a randomized phase II trial of R-Hyper-CVAD versus bendamustine and rituximab followed by consolidation with ASCT in previously untreated patients with MCL

Background
In this randomized, phase II study, Chen and colleagues compared the efficacy and safety of R-Hyper-CVAD (rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) with bendamustine and rituximab (R-bendamustine) in previously untreated patients ≤65 years of age with mantle cell lymphoma (MCL). The results were presented at ICML 2015.1

Study design
• A total of 160 patients were expected to be enrolled and randomized 1:1 between R-bendamustine and R-Hyper-CVAD induction.
• The inclusion criteria for the first registration, before induction therapy, were:
  ◦ Patients aged ≥18 and ≤65;
  ◦ Previously untreated stage III, IV, or bulky stage II MCL;
  ◦ CD19+ or CD20+;
  ◦ Cyclin D1 presence as assayed by immunohistochemistry, or t(11;14);
  ◦ Bidimensional measurable disease; and
  ◦ Adequate organ function.
• The inclusion criterion for the second registration, prior to autologous stem cell transplantation (ASCT), was:
  ◦ Collection of 1.5 x 10⁶ CD34+ cells.
• For induction therapy, one study arm received R-Hyper-CVAD in cycle 1 and R-MTX/AraC (rituximab, methotrexate, cytarabine) in cycle 2.
  ◦ Following restaging, patients achieving partial response (PR) or greater received another cycle of R-Hyper-CVAD, followed by stem cell collection and another cycle of R-MTX/AraC.
• The second study arm received four cycles of R-bendamustine.
  ◦ Following restaging, patients achieving ≥PR received a further two cycles of R-bendamustine, followed by one cycle of rituximab in combination with cyclophosphamide (3 g/m²) and stem cell collection.
  ◦ After a second restaging, prior to ASCT, patients received the following regimens, based on their age:
    ◦ If <61 years of age: BCV (carmustine, cyclophosphamide, and etoposide), BEAM (carmustine, etoposide, cytarabine, and melphalan), or TBI/VP16/Cy (total body irradiation, etoposide, and cyclophosphamide); or
    ◦ If 61–65 years of age: BCV or BEAM.
• The primary endpoint was two-year progression-free survival (PFS).
• The secondary endpoints were:
  ◦ Overall response rate (ORR);
  ◦ Overall survival (OS);
  ◦ Toxicity and tolerability; and
  ◦ Prognostic value of minimal residual disease (MRD) monitoring in peripheral blood.
• The targeted two-year PFS was at least 75%.
  ◦ If neither arm met PFS of 75%, none would be selected.
  ◦ If both arms met PFS of 75%, R-bendamustine would be selected due to lower expected toxicity, unless the hazard ratio (HR) >1.2 was in favour of R-Hyper-CVAD.
• If stem cell collection failure was ≥10%, neither arm would be acceptable.
  ◦ If stem cell collection failed in 4 out of 20 patients on either arm, then the arm would close.

Key findings
Baseline characteristics and disposition
• This study was closed after 53 patients were accrued. A total of 51 patients were evaluable, 16 in the R-Hyper-CVAD arm and 35 in the R-bendamustine arm.
• The baseline characteristics were well balanced between the two study arms, except for an imbalance in patient sex, with more females in the R-Hyper-CVAD arm than the R-bendamustine arm (44% vs. 9%, respectively).
• A total of 8 patients (50%) from the R-Hyper-CVAD arm, and 17 patients (49%) from the R-bendamustine arm were able to undergo ASCT. (Table 1)
### Study design

1. **First registration**
   - Randomize for Induction
   - **R-Hyper-CVAD, cycle 1**
   - **R-MTX/AraC, cycle 2**
   - **Restaging**
     - <PR> Off study
       - Follow for survival
     - ≥PR
       - R-Hyper-CVAD, cycle 3
         - Stem cell collection
       - **R-MTX/AraC, cycle 4**
   - Second registration
     - **Restaging**
     - ≥PR
     - <PR> R-Bendamustine for cycle 2
   - **Stem cell transplant**
     - <61 years: BCV, BEAM, or TBI/VP16/Cy
     - 61–65 years: BCV or BEAM
     - R-Hyper-CVAD, cycle 3
     - Stem cell collection
     - R-MTX/AraC, cycle 4
   - Off study
   - Follow for survival

**BCV = carmustine, cyclophosphamide, etoposide; BEAM = carmustine, etoposide, cytarabine, melphalan; Cy = cyclophosphamide; PR = partial response; R-Hyper-CVAD = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; R-MTX/AraC = rituximab, methotrexate, cytarabine; TBI = total body irradiation; VP16 = etoposide**

### Table 1. Reasons for treatment termination

<table>
<thead>
<tr>
<th>Reasons for going off treatment or not continuing to ASCT</th>
<th>R-Hyper-CVAD (12/16)</th>
<th>R-Bendamustine (14/35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to collect stem cells</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Patient choice</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Allergy</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Seizure</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Insurance denial</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Off protocol ASCT</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total undergoing ASCT</strong></td>
<td><strong>8 (50%)</strong></td>
<td><strong>17 (49%)</strong></td>
</tr>
</tbody>
</table>

**ASCT = autologous stem cell transplantation; R-Hyper-CVAD = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone**
**Efficacy**

- The median follow-up was 30 months (range: 7.8–36.5) for the R-Hyper-CVAD arm and 26 months (range: 1–39.5) for the R-bendamustine arm.
- The two-year PFS rates for the R-Hyper-CVAD and the R-bendamustine arms were 87% (95% CI: 58.1%–96.7%) and 88% (95% CI: 70.0%–95.1%), respectively. (Figure 1 and Table 2)
- The ORR for the R-Hyper-CVAD and the R-bendamustine arms were 93.8% (95% CI: 69.8%–99.8%) and 85.7% (95% CI: 69.7%–95.2%), respectively. (Table 2)
- The two-year OS rates for the R-Hyper-CVAD and the R-bendamustine arms were 86% (95% CI: 57.3%–96.6%) and 87% (95% CI: 68.5%–94.9%), respectively. (Figure 2 and Table 2)

**Safety**

- Grade 3/4 hematological and non-hematological toxicities were much more prevalent in the R-Hyper-CVAD arm than the R-bendamustine arm. (Table 3)
- The most common grade 3/4 toxicities were hematological in both study arms (R-Hyper-CVAD vs. R-bendamustine), which included thrombocytopenia (69% vs. 17%, respectively), neutropenia (63% vs. 34.3%), anemia (56% vs. 8.6%), and febrile neutropenia (31% vs. 14%).

---

**Figure 1. Progression-free survival**

![Progression-free survival](image)

*At risk 35 Failed 5 2-year PFS estimate 88%
At risk 16 Failed 2 2-year PFS estimate 87%

**Figure 2. Overall survival**

![Overall survival](image)

*At risk 35 Deaths 4 2-year OS estimate 87%
At risk 16 Deaths 2 2-year OS estimate 86%
### Table 2. Response and survival rates

<table>
<thead>
<tr>
<th>Evaluable patients (N = 51)</th>
<th>R-Hyper-CVAD (n = 16)</th>
<th>R-Bendamustine (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>93.8 (69.8–99.8)</td>
<td>85.7 (69.7–95.2)</td>
</tr>
<tr>
<td>CR</td>
<td>31</td>
<td>43</td>
</tr>
<tr>
<td>PR</td>
<td>63</td>
<td>43</td>
</tr>
<tr>
<td>Inadequate</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td><strong>Median follow-up (months)</strong></td>
<td>30 (7.8–36.5)</td>
<td>26 (1–39.5)</td>
</tr>
<tr>
<td><strong>Survival, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year PFS</td>
<td>94 (65.0–99.2)</td>
<td>88 (70.0–95.1)</td>
</tr>
<tr>
<td>1-year OS</td>
<td>93 (63.2–99.1)</td>
<td>91 (73.7–96.9)</td>
</tr>
<tr>
<td>2-year PFS</td>
<td>87 (58.1–96.7)</td>
<td>88 (70.0–95.1)</td>
</tr>
<tr>
<td>2-year OS</td>
<td>86 (57.3–96.6)</td>
<td>87 (68.5–94.9)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CR = complete response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; R-Hyper-CVAD = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone

### Table 3. Grade 3/4 adverse events

<table>
<thead>
<tr>
<th>Grade 3/4 adverse events</th>
<th>R-Hyper-CVAD (N = 16), %</th>
<th>R-Bendamustine (N = 35), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological toxicities (Induction phase only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>56</td>
<td>8.6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63</td>
<td>34.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69</td>
<td>17</td>
</tr>
<tr>
<td>ALT increased</td>
<td>6.3</td>
<td>—</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>AST increased</td>
<td>6.3</td>
<td>—</td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>6.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Dehydration</td>
<td>6.3</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.3</td>
<td>—</td>
</tr>
<tr>
<td>Enterocolitis infection</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12.5</td>
<td>—</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>25</td>
<td>5.7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>25</td>
<td>2.9</td>
</tr>
<tr>
<td>Infection</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.3</td>
<td>—</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Rash</td>
<td>6.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Sore throat</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Tumour pain</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>UTI</td>
<td>—</td>
<td>2.9</td>
</tr>
<tr>
<td>Vascular access complication</td>
<td>—</td>
<td>2.9</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; R-Hyper-CVAD = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; UTI = urinary tract infection
New Developments in Mantle Cell Lymphoma

A Summary of the Presentation by Dr. Mathias Rummel at CCOLD 2015

At the 2015 Canadian Conference on Lymphoproliferative Disorders (CCOLD), Dr. Mathias Rummel, Head of the Department of Hematology at the Clinic for Hematology and Medical Oncology at the Justus-Liebig University Hospital, Giessen, Germany, presented an update on new therapeutic developments for mantle cell lymphoma (MCL). His presentation, summarized in this article, highlighted the efficacy and safety of single agents and combination therapies for younger and elderly patients with previously untreated or relapsed/refractory MCL.

Considerable advances have been made in the treatment and management of MCL during the past decade. The National Comprehensive Cancer Network (NCCN) Guidelines for MCL (Version 1.2015) provides a list of suggested treatment regimens that can be used depending on the patient’s characteristics, including age and prior treatment history. Although the approaches to treatment differ between younger (≤65 years of age) and elderly patients (>65 years of age), chemoimmunotherapy remains the first line of defence. In younger patients, the standard chemotherapy approach involves high-dose therapy with cytarabine, combined with rituximab, followed by autologous stem cell transplantation (ASCT). In elderly patients, chemoimmunotherapy includes the less aggressive agent bendamustine in combination with rituximab (BR), with or without cytarabine.

Rituximab, an anti-CD20 antibody, is used in targeted therapy approaches in combination with other drugs or as a single agent in maintenance therapy after initial treatment. Other targeted therapy agents include lenalidomide, a drug targeting the tumour microenvironment, as well as bortezomib and temsirolimus, which respectively target the proteasome and the mTOR pathway. Some of the newer compounds that are being used in clinical trials include idelalisib, a phosphatidylinositol-3-kinase (PI3K) inhibitor, and ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor.

Aggressive Treatment in Younger Patients with MCL

Studies have shown that cytarabine plays a highly relevant role in the treatment of MCL in younger patients. In a study by the European MCL Network, previously untreated patients younger than 65 years of age were randomized between two kinds of treatment regimens in order to assess the efficacy and safety of adding cytarabine. The first regimen comprised two rounds of three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin,
vincristine, prednisone) followed by ASCT. The second regimen consisted of alternating treatments of three cycles of R-CHOP and three cycles of R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin), followed by a conditioning regimen that included four rounds of cytarabine at 1.5 g/m², and then ASCT. There was an increased possibility of achieving minimal residual disease eradication in the R-DHAP group versus the R-CHOP group, which translated into an improved time to treatment failure (TTF) for the R-DHAP group (median TTF: not reached vs. 49 months; HR = 0.68, p = 0.0382) (Figure 1).

Another study by the European MCL Network, published in 2005, aimed to address the role of ASCT in the treatment of MCL. Patients were given six cycles of CHOP-like induction chemotherapy, after which they were randomized to either two cycles of consolidation followed by interferon-α (IFNα) maintenance or DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan) treatment followed by ASCT. In the intent-to-treat population, ASCT was found to be superior to IFNα, as shown by a prolonged median TTF of 2.6 years compared with 1.4 years in the IFNα group (p = 0.0001) (Figure 2), as well as an improved median overall survival (OS) of 7.0 years compared with 5.3 years in the IFNα group (p = 0.0308) (Figure 3).² Combined, the data from these studies are in support of the use of high-dose therapy.

The Nordic Lymphoma Group published a study in 2008 called the MCL2 trial, which aimed to determine the long-term progression-free survival (PFS) in patients with MCL following intensive chemoimmunotherapy coupled with in vivo purged ASCT. This study built upon a previous one by the same group, the MCL1 trial, which treated patients with CHOP followed by ASCT. In the MCL2 trial, rituximab and high-dose cytarabine were added to the protocol, and data from MCL1 was used as an historic control because the patients’ characteristics were similar in both trials. Cytarabine was given as four infusions of 3 g/m² to patients ≤60 years old and four infusions of 2 g/m² to patients >60 years old.³

The Nordic study showed a significant improvement in 6-year event-free survival (EFS) and OS in patients from the MCL2 trial (56% and 75%, respectively) compared with the MCL1 trial (8% and 41%, respectively) (Figure 4). A follow-up study, published in 2012, indicated that late relapses occurred in patients from the MCL2 trial; however, after 10 years, the median for OS and remission duration had not yet been reached.
indicating positive results with the rituximab and high-dose cytarabine approach (Figure 5).4

Rituximab as Maintenance Therapy

Rituximab, in combination with chemotherapy, has been shown to be efficacious as induction therapy for patients with MCL, but its efficacy as a maintenance drug is uncertain. A large European study on elderly patients newly diagnosed with MCL was conducted between 2004 and 2010. Patients were randomized between two groups: one receiving eight rounds of R-CHOP and the other receiving six rounds of FCR (fludarabine, cyclophosphamide, rituximab). After the initial treatment, the patients were randomized once more into two maintenance therapy groups: one receiving IFNα (or pegylated IFN) and the other receiving rituximab. The OS was prolonged in patients treated with R-CHOP compared with those who received FCR (median OS: 77 vs. 43 months, respectively; \(p = 0.0023\)) (Figure 6).5 Interestingly, compared with maintenance therapy with IFNα, rituximab maintenance led to improved OS in patients who had previously been treated with R-CHOP (\(p = 0.0058\)) and had no significant effect on OS for patients previously treated with FCR (\(p = 0.5\)) (Figure 7). These results indicate that rituximab maintenance therapy can be efficacious, but perhaps only in patients who have received specific induction regimens.

The Use of Bendamustine in Elderly and Relapsed Patients with MCL

Under the NCCN Guidelines for MCL, bendamustine is categorized as a less aggressive treatment, making it an ideal treatment for elderly patients with MCL. Bendamustine has shown positive results when used in combination with rituximab, with or
without cytarabine. In a small subgroup of patients with MCL from the StiL NHL 1-2003 trial, the PFS was improved in those treated with BR compared with R-CHOP (35.4 vs. 22.1 months, respectively; HR = 0.50, p = 0.0061) (Figure 8).6

The North American BRIGHT trial, published in 2014, further supported those results. In that study, patients with indolent non-Hodgkin lymphoma or MCL were randomized between three groups: BR, R-CHOP, and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone). In the subgroup of patients with MCL, BR showed a significantly higher complete response (CR) rate (51%) compared with those of the R-CHOP (30%) and R-CVP (14%) groups (Table 1).7 Together with data collected from other studies, R-CHOP has become an unfavourable regimen for elderly patients with MCL among many investigators, with BR offering more positive outcomes.

A 2013 study by Visco et al. investigated the efficacy and safety of R-BAC (rituximab, bendamustine [70 mg/m2], low-dose cytarabine [800 mg/m2]) in elderly patients with previously untreated or relapsed/refractory (R/R) MCL.8 The doses of cytarabine and bendamustine were reduced because these patients were ineligible for intensive treatments. Overall, R-BAC was well tolerated by patients. Thrombocytopenia was the most significant grade 3/4 adverse event (AE), observed in 76% of all cycles; this was mainly attributed to the use of cytarabine. Toxicity was higher in R/R patients than in those who were previously untreated.

The efficacy of R-BAC was assessed in terms of overall response rate (ORR), CR, PFS, and OS. Responses were evaluated by computerized tomography scan, bone marrow biopsy, and positron emission tomography scan, using Cheson et al. 2007 criteria.
criteria. The ORR and CR rates were 100% and 95%, respectively, in previously untreated patients, and 80% and 70% in R/R patients. The PFS and OS of both previously untreated and R/R patients receiving R-BAC treatment were very promising even though the observation period was relatively short. In ongoing R-BAC studies, cytarabine is being used at 500 mg/m² in an attempt to reduce its toxicity.

Bendamustine is currently being used in combination with other agents, such as rituximab, bortezomib, cytarabine, lenalidomide, and ibrutinib, in various ongoing clinical trials around the world. An ongoing trial in Germany, StiL NHL 7-2008, is comparing the combination of BR with or without two years of rituximab maintenance in 168 patients with MCL who are ineligible for high-dose cytarabine and ASCT. Additionally, a randomized phase II trial is being conducted on previously untreated elderly patients with MCL who are ineligible for ASCT. This study is testing the effects of BR in the presence or absence of bortezomib, followed by rituximab alone, or rituximab in combination with lenalidomide.

**Efficacy of Bortezomib in Previously Untreated Patients with MCL**

Bortezomib is another agent that is found under less aggressive treatments in the NCCN Guidelines for MCL. In a recently published study (LYM-3002), bortezomib was used in place of vincristine as part of the R-CHOP protocol for newly diagnosed patients with MCL. The results showed an improved median PFS in patients undergoing the modified R-CHOP treatment with bortezomib (called VR-CAP) compared with the standard R-CHOP protocol (24.7 vs. 14.4 months; HR = 0.63, p <0.001) (Figure 9). The ORR was similar between the R-CHOP and VR-CAP groups (90% and 92%, respectively; p = 0.275); but, the CR rate in the VR-CAP group was higher than in the R-CHOP group (53% vs. 42%; p = 0.007). Furthermore, the median duration of response (DOR) was significantly improved in the VR-CAP group (36.5 months) compared with the R-CHOP group (15.1 months). These findings outline the importance of studies not only focusing on CR rates, but also paying attention to long-term disease control.

Notably, the improved median DOR in the VR-CAP group came at the cost of a significantly higher occurrence of grade ≥3 thrombocytopenia (6% in R-CHOP versus 57% in VR-CAP), which led to an increase in the use of platelet transfusions in VR-CAP patients (23%), a procedure that was quite uncommon during R-CHOP treatment (3%). The incidences of neutropenia and infections were also elevated with the bortezomib-containing regimen.

**Efficacy of Lenalidomide**

Lenalidomide is an agent that has been used on its own or as part of a combination regimen. It can safely be given continuously and, as a result, could play an important role in maintenance therapy. The use of lenalidomide has shown single-agent activity in some small studies of patients with MCL, producing ORRs of 53% and 43%. In other trials, lenalidomide was combined with rituximab in the treatment of patients with R/R or previously untreated MCL, resulting in ORRs of 57% and 77%, respectively. Lenalidomide in combination with dexamethasone resulted in an ORR of 52% for patients with R/R MCL.

Figure 9. Progression-free survival by IRC of patients with MCL receiving R-CHOP or VR-CAP

<table>
<thead>
<tr>
<th>Events, n</th>
<th>R-CHOP</th>
<th>VR-CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>165</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>14.4 (12.0–16.9)</td>
<td>24.7 (19.8–31.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.50–0.79)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IRC = independent review committee; MCL = mantle cell lymphoma; PFS = progression-free survival;
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone

Two important lenalidomide trials in patients with MCL are currently ongoing. Firstly, MCL-002/SPRINT is a multicentre, phase II, randomized trial focused on comparing the efficacy of lenalidomide to other drugs of the investigator’s choice in patients with R/R MCL. Secondly, MCL R2 Elderly is a phase III, randomized study that is evaluating whether the combination of lenalidomide and rituximab as maintenance therapy improves PFS in elderly patients (≥60 years of age) compared with standard rituximab maintenance, after those patients have received initial induction treatment with either R-CHOP combined with R-HAD (rituximab, cytarabine, dexamethasone) or R-CHOP alone.

Promising Early Results Using Idelalisib

Idelalisib has shown some activity as a single agent in the treatment of MCL. During one study, idelalisib resulted in tumour shrinkage in the majority of patients with MCL, as measured in percent change of lymph node area (Figure 10). Studies are ongoing and more data on idelalisib, as a single agent and in combination regimens, will be reported at the American Society of Hematology (ASH) Annual Meeting later this year.

Efficacy of Ibrutinib as a Single Agent or in Combination Therapy

Ibrutinib is a drug that is approved for use as a single agent in the U.S. and in Europe. A trial was conducted on 111 patients with MCL (45% refractory to last treatment) to assess the efficacy of a 560 mg daily dose of ibrutinib. Patients responded well to the treatment with an ORR of 68%, a median PFS of 13.9 months, and a median DOR of 17.5 months. Notably, the response was independent of prior use of bortezomib.

Because of the promising results demonstrated by ibrutinib as a single agent, preliminary studies are being conducted using ibrutinib in combination with other established drugs for MCL. The results from an ongoing trial of ibrutinib in combination with rituximab were presented at ASH 2014. A total of 45 patients with relapsed MCL were split into two categories: those with a Ki-67 index <50% and those with Ki-67 index ≥50%. Patients with Ki-67 <50% had a 100% ORR with a CR of 48%, whereas the Ki-67 ≥50% group had an ORR of 50% and a CR of 8% (Table 2). DOR and PFS data are currently unavailable because the study is in its early stages.

![Figure 10. Best on-treatment change in tumour sizes in patients with MCL treated with idelalisib](image-url)

**Table 2. Preliminary results with the ibrutinib and rituximab combination for patients with MCL**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Ki-67 &lt;50%</th>
<th>Ki-67 ≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluated patients, n</td>
<td>45</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>39 (87)</td>
<td>33 (100)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>17 (38)</td>
<td>16 (48)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>22 (49)</td>
<td>17 (52)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>2 (4)</td>
<td>0</td>
<td>2 (17)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>4 (9)</td>
<td>0</td>
<td>4 (33)</td>
</tr>
<tr>
<td>DOR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PFS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

CR = complete response; DOR = duration of response; MCL = mantle cell lymphoma; NR = not reached; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

Adapted from Wang M, et al. ASH Annual Meeting Abstracts 2014-627

*MCL = mantle cell lymphoma

**Criterion for response (Cheson 2007, Hallek 2008).†Two patients have not had any tumour assessments recorded.
Adapted from Kahl B, et al. Blood 2014*
Summary and Conclusions

Although MCL is still considered to be an incurable disease, patient survival has almost doubled in the past 30 years thanks to the development of new therapeutic agents and the use of existing drugs in certain combination regimens. Progress has also been achieved through the intensification of therapy (e.g., the use of high-dose cytarabine), the advances in stem cell transplantation, and the novel use of agents (e.g., rituximab) for maintenance therapy. Furthermore, new efficacious targeted agents, such as bortezomib, lenalidomide, and ibrutinib, have been approved by the U.S. Food and Drug Administration and the European Medicines Agency and are now available in some parts of the world for the treatment of relapsed MCL, with ibrutinib providing the most hope in recent studies. Lastly, ongoing trials are investigating the efficacy and safety of targeted agents, which have already demonstrated single-agent activity, in combination regimens.

References


**Diffuse Large B-cell Lymphoma**

Isidori A, et al. EHA 2015:P353

**Benda-EAM high-dose therapy prior to ASCT is effective in resistant/relapsed DLBCL: a phase II multicentre study**

**Background**
Bendamustine, etoposide, cytarabine, and melphalan in combination with autologous stem cell transplantation (Benda-EAM/ASCT) has shown long lastinganti-lymphoma activity, with a three-year progression-free survival (PFS) of 75%. Isidori and colleagues evaluated the efficacy of Benda-EAM/ASCT in patients with resistant/relapsed (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL) and presented their data at EHA 2015.1

**Study design**
- This was an open-label, multicentre, single-arm, phase II study in patients with R/R aggressive B-cell NHL.
  - It was designed according to Fleming’s Method ($P_0 = 55\%$, $P_1 = 70\%$, $\alpha = 0.05$, $1-\beta = 0.90$).
- Patients received the following:
  - Bendamustine 200 mg/m² on days –7 and –6;
  - Cytarabine 400 mg/m² and etoposide 200 mg/m² from day –5 to –2; and
  - Melphalan 140 mg/m² on day –1, before ASCT.
- The primary objectives of the study were to assess the 1-year complete remission (CR) rate, the safety of the regimen, PFS, and overall survival (OS).

**Key findings**

**Baseline characteristics and disposition**
- In total, 48 patients were evaluable with a median age of 53 years (range: 19–69).
  - The majority of the patients (79%) had diffuse large B-cell lymphoma (DLBCL), while 21% of them had grade IIIb follicular NHL.
  - Of the total patient population, 25% had stage I–II disease, while 75% had stage III–IV disease.
  - Fifteen patients were primary refractory and 33 had relapsed after a median of two lines of therapy (range: 1–3).
  - Twenty-two patients had a secondary or subsequent CR after salvage therapy, 19 had a partial response (PR), and three had progressive disease.
  - Twenty-two patients had a secondary or subsequent CR after salvage therapy, 19 had a partial response (PR), and three had progressive disease.
- The majority of the patients (65%) had received R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) or R-DHAOX (rituximab, dexamethasone, oxaliplatin, cytarabine) prior to study initiation.

**Efficacy**
- A CR was achieved by 83% of the patients, as assessed by computerized tomography and positron emission tomography scans.
- PR was achieved by 6% of the patients.
- A lack of response to therapy was observed in 8% of the patients.
- Thirty-seven responding patients (77%) were still in remission after a median follow-up from ASCT of 10 months (range: 1–37).
- After a median time of 8 months (range: 3–11), 21% of patients had relapsed or were resistant to treatment.
- The median number of CD34+ cells engrafted was 5.75 x 10⁶/kg (range: 2.80–9.42 x 10⁶).

**Study design**

<table>
<thead>
<tr>
<th>Bendamustine 200 mg/m² days –7, –6</th>
<th>Cytarabine 400 mg/m² days –5 to –2</th>
<th>Etoposide 200 mg/m² days –5 to –2</th>
<th>Melphalan 140 mg/m² day –1</th>
<th>ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>–7</td>
<td>–6</td>
<td>–5</td>
<td>–3</td>
<td>–2</td>
</tr>
<tr>
<td>–1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The median time to absolute neutrophil count >0.5 x 10^9/L was 10 days.
- The median time to platelet (PLT) count >20 x 10^9/L was 12 days.
- The median time to PLT count >50 x 10^9/L was 18 days.
- Median PFS and OS have not yet been reached. (Figure 1)

**Safety**
- Gastrointestinal toxicity was the most common grade 1/2 (45% of patients) and grade 3 (34% of patients) toxicity. (Table 1)
- No grade 4/5 non-hematological toxicities were observed.
- Transplant-related mortality (TRM) occurred in 2% of patients.

**Figure 1. Progression-free survival and overall survival**

![Graph showing progression-free survival and overall survival](image)

**Table 1. Occurrence of toxicities of treatment**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hematological toxicity</td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>7 (16)</td>
</tr>
<tr>
<td>GI toxicity</td>
<td>20 (45)</td>
</tr>
<tr>
<td>Metabolic toxicity</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>6 (13)</td>
</tr>
</tbody>
</table>

**Key conclusions**
- The Benda-EAM regimen was confirmed to be safe in a setting of heavily pretreated patients.
  - The TRM was only 2%.
  - No grade 4/5 non-hematological toxicities were observed.
- Preliminary results confirmed the efficacy of Benda-EAM.
  - Thirty-five patients achieving CR (73%) were still in remission at the time of the presentation of these results.
  - Results are encouraging, given that 50% of patients had a PR or were in progression before starting this bendamustine-based conditioning regimen.

Background
Recent studies have suggested that bendamustine plus rituximab (BR) is superior to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in effectiveness and tolerability in the treatment of indolent and mantle cell lymphomas. At EHA 2015, Storti and colleagues reported the safe and effective use of BR in elderly patients with diffuse large B-cell lymphoma (DLBCL).1

Study design
• In this phase II, open-label, non-randomized study, elderly patients with newly diagnosed DLBCL received:
  ◦ Bendamustine (90 mg/m² daily on days 1 and 2 of each 28-day cycle); and
  ◦ Rituximab (on day 1 for up to six cycles).
• Patients with International Prognostic Index equal to 0 and limited stage of disease (stage I-II, non-bulky) received four cycles of bendamustine and six cycles of rituximab.
• All other patients received six cycles of bendamustine and eight cycles of rituximab, with or without radiotherapy at physician’s discretion based on the policy of the study centre and/or the results from the positron emission tomography scan after six cycles, if performed.
• The eligibility criteria included patients who were:
  ◦ Age >70 years;
  ◦ Newly diagnosed DLBCL, unsuitable for R-CHOP-based chemotherapy;
  ◦ Categorized as frail, after being evaluated by Comprehensive Geriatric Assessment (CGA) according to Activities of Daily Living (ADL), Instrumental ADL (IADL), and CIRS-G:
    – Aged between 70–80 years with ADL ≤4, or IADL ≤5, or one grade 3 comorbidity, or more than eight grade 2 comorbidities; or
    – Aged >80 years with ADL >5, or IADL >6, or 5–8 grade 2 comorbidities.
• The primary objectives of the study were:
  ◦ To evaluate the activity of BR in terms of complete response (CR) rate; and
  ◦ To evaluate the safety and tolerability of BR in terms of the occurrence of adverse events (AEs).
• The secondary objectives of the study were:
  ◦ To evaluate progression-free survival (PFS); and
  ◦ To evaluate overall survival (OS).

Key findings
Baseline characteristics and disposition
• A total of 49 patients were enrolled in 24 Italian centres between February 2012 and February 2014.
• The median age was 82 years (range: 72–89), with 83% of patients being ≥80 years old.
• The majority of the patients had an Eastern Cooperative Oncology Group performance status of 0–1 (63%) and stage III–IV disease (59%).
• The CGA showed that the majority of patients had unfavourable 3 criteria (68%).
• The most frequent comorbidities were cardiovascular (37%), metabolic (11%), and respiratory diseases (7%).
• Of the 49 patients enrolled, 25 completed all planned cycles of chemotherapy, and 24 discontinued the treatment (12 due to progressive disease [PD], 8 due to AEs, and 4 due to death). (Figure 1)

Safety
• The AEs that led to treatment discontinuation were:
  ◦ Persistent cytopenia (n = 3);
  ◦ Worsening general condition (n = 2);
  ◦ Coronary acute syndrome (n = 1);
Second tumour (n = 1); and
Febrile neutropenia associated with infection (n = 1).

Based on National Cancer Institute’s Common Terminology
Criteria for Adverse Events (NCI-CTCAE) version 4.03, grade
3/4 toxicities were documented in 24 (53%) patients.

Efficacy

At the last analysis, the median follow-up time was 8 months
(range: 1–29).

Of the four patients not receiving at least two courses of BR,
two progressed.

A total of 47 patients remained evaluable.

The overall response rate was 64%, with 26 (55%) patients
achieving a CR. (Table 1)

A total of 13 patients had PD and four patients relapsed.

The two-year PFS was 43% and the two-year OS was 59%.
(Figure 2)

By the time of last analysis, 16 deaths had occurred: 10 due
to PD, one during sleep, and one each due to relapse, second
tumour, cardiac failure, pneumonia, and worsening general
condition.

Figure 1. Patient responses

![Patient responses](image)

**Table 1. Response rates**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Uncompleted treatment</th>
<th>Completed treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>26</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Partial response</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14</td>
<td>12</td>
<td>2*</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>22</td>
<td>25</td>
</tr>
</tbody>
</table>

*Two patients had progressive disease or stable disease
**Figure 2. Progression-free survival and overall survival**

Median follow-up: 13 months (range: 1–31)

No. of OS events = 15
Two-year OS (95% CI): 59% (39–75)

No. of PFS events = 23
Two-year PFS (95% CI): 44% (26–61)

Median PFS = 14 months (95% CI: 7–NR)

CI = confidence interval; NR = not reached; OS = overall survival; PFS = progression-free survival

**Key conclusions**

- Combination therapy with BR showed a low toxicity profile in this high-risk population.
- These promising results of BR activity could convince clinicians to consider BR as an alternative treatment in frail, elderly patients with DLBCL who are ineligible for R-CHOP.

Reference:
An Interview with Dr. Alessandro Isidori on the Benda-EAM/ASCT Study

**New Evidence**: What is the current approach in the management of patients with resistant or relapsed DLBCL? What are the key challenges and unmet needs in treating these patients?

**Dr. Isidori**: At present, the standard treatment for patients with relapsed, chemosensitive aggressive non-Hodgkin lymphoma (NHL) is high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT), based on the results of the PARMA and CORAL studies. Over the years, various HDTs have led to improvements in disease-free survival (ranging from 34% to 60%) and overall survival (OS) (ranging from 26% to 46%) compared with salvage chemotherapy alone in this patient population. However, very few comparative randomized trials have been performed and no HDT regimen has demonstrated superiority to another. Although clinicians have access to these promising therapies, they are still curing very few patients with aggressive forms of NHL. Patients who are chemoresistant after undergoing salvage therapy are unlikely to achieve a long-lasting response and long OS. Therefore, there is a clear need for a new agent to improve the outcomes and reduce toxicity in these patients.

**New Evidence**: What are the possible advantages of the Benda-EAM regimen versus other conditioning regimens for ASCT, such as the carmustine-based one?

**Dr. Isidori**: We showed in our first Benda-EAM study that bendamustine was able to potentiate the effects of cytarabine and melphalan better than carmustine. Furthermore, the addition of bendamustine to etoposide, cytarabine, and melphalan induced a higher rate of complete remission (CR) in patients with refractory or relapsed lymphoma than carmustine; a follow-up study three years later showed that 72% of the patients were still progression-free. In addition to this preliminary efficacy, bendamustine had reduced toxicity compared with carmustine. Last but not least, there were no treatment-related mortalities (TRM) in the first study and only 2% of the patients died due to treatment in the latest trial. When comparing the bendamustine-based regimen with other HDTs, which have shown TRM as high as 15%, one can clearly see the advantages of using bendamustine over carmustine. Lastly, bendamustine is not only more readily available than carmustine, but it is also less expensive.

**New Evidence**: Please describe the rationale and design of the Benda-EAM/ASCT study. Why was this specific conditioning regimen selected for the study?

**Dr. Isidori**: Bendamustine was first synthesized in the early 1960s. It combines the alkylating activity of the mustard group with the antimetabolite activity of the purine analog structure. Early *in vitro* data showed that bendamustine had a different pharmacologic profile than other alkylating agents. Further *in vitro*
studies were performed in two lymphoma cell lines, MEC-1 and JEKO-1, with increasing doses of bendamustine or carmustine in combination with etoposide, cytarabine, and melphalan. Bendamustine was able to potentiate the in vitro activity of these three agents much more strongly than carmustine. We also looked at clinical data and other studies at the time, which demonstrated high activity with bendamustine against low-grade indolent lymphoma, and its efficacy in combination with other drugs against refractory or relapsed lymphomas. Finally, bendamustine demonstrated a manageable toxicity profile in various studies, including our first Benda-EAM/ASCT study, highlighted by a lack of cardiotoxicity in patients. Given these promising results, as well as the safety profile of bendamustine, we decided to treat patients with the maximum tolerated dosage of bendamustine. In this open-label, multicentre, single arm, phase II study, patients were treated with 200 mg/m$^2$ of bendamustine on days –7 and –6, 200 mg/m$^2$ of etoposide and 400 mg/m$^2$ of cytarabine on days –5 to –2, and 140 mg/m$^2$ of melphalan on day –1, followed by ASCT. All patients received granulocyte-colony stimulating factor (G-CSF) two days after transplantation and were actively treated for any infections.

**New Evidence:** What were the inclusion criteria and the main characteristics of the patient population in this study?

**Dr. Isidori:** While in our 2011 Benda-EAM/ASCT study we enrolled patients with resistant or relapsed NHL or Hodgkin’s disease (HD), this time we decided to enroll only patients with very aggressive tumours, including DLBCL and stage IIIb follicular lymphoma (FL). The patients had to be 18–70 years of age with a Karnofsky score of >70%. Furthermore, patients had to have an adequate renal, pulmonary, and hepatic function, as well as no uncontrolled infections or secondary malignancies. Overall, 79% of the patients had DLBCL, 21% had grade IIIb FL, 75% had stage III or IV disease, and 31% were primary refractory. Based on these criteria, all our real-world patients with DLBCL or stage IIIb FL who have relapsed after initial treatment would be eligible for this study. Our clinical trial was designed to closely resemble real-world treatment for these patients. During the study, we transplanted a similar proportion of the patients that would have received ASCT in a real-world scenario.

**New Evidence:** Please describe the efficacy results for the Benda-EAM/ASCT therapy in terms of response rates, rates of remission, and engraftment times.

**Dr. Isidori:** At present, 64 patients are enrolled. I will discuss only the data we presented at the 2015 EHA Congress. A total of 48 patients were evaluable. So far, CR has been achieved by 40 patients, while three patients achieved partial response and four patients did not respond to treatment. After a follow-up period of ten months, 35/48 (73%) patients were still in CR. All patients were engrafted successfully, with a median of 5.75 x 10$^6$ CD34+ cells per kilogram. The median time to an absolute neutrophil count of >0.5 x 10$^9$/L was 10 days and the median times to achieve a platelet counts of >20 x 10$^9$/L and >50 x 10$^9$/L were 12 and 18 days, respectively. We believe these data are especially impressive, considering that our patient population had very aggressive forms of lymphoma. An update of these results will be provided at the 2015 ASH Annual Meeting.

**New Evidence:** How does Benda-EAM/ASCT therapy compare to other conditioning regimens used for refractory or relapsed DLBCL in terms of efficacy?

**Dr. Isidori:** We have seen an improvement in CR rates compared with other conditioning regimens, such as carmustine. Given the design of our study using Fleming’s Method, a CR rate higher than 70% would have been enough to indicate a significant improvement. As previously noted, our patients achieved CR rates of over 80%, which was well above the set threshold. Looking at our population, 30% of patients were primary refractory to treatment. Given the aggressiveness of the disease in these patients, you would normally expect a low rate of CR and progression-free survival (PFS). Our patients had a PFS and OS of almost 80% at a median follow-up time of three years. While we cannot make sound comparisons without head-to-head trials, results from previous studies using HDT regimens have not been as encouraging as ours, which is especially significant given that their patient populations were not as refractory as ours.

**New Evidence:** How do the safety results of the study, specifically the mortality rate of only 2%, compare to other conditioning regimens that could have been used in this patient population?

**Dr. Isidori:** Our regimen demonstrated a relatively manageable safety profile. Unfortunately, one of our patients died as a result of an incomplete hematological recovery; we consider this to be a very low mortality rate, especially when compared to other
HDT approaches, which have demonstrated TRM rates as high as 23%. This improvement can be attributed to the relatively quick engraftment, good management of infections and renal complications, and the exclusive use of peripheral blood in our ASCT. Additionally, our HDT did not lead to any grade 4/5 non-hematological toxicities. Importantly, some patients who have taken bendamustine in the past have experienced dehydration and renal toxicity during treatment. We were proactive at managing these side effects by hyper hydrating our patients and putting them on dopamine at renal dose for up to seven days during HDT, to help them hydrate before treatment began. Small increases in fever and infection rates were observed in our study compared with other HDTs, with 23% of patients presenting with a fever of unknown origin and 47% of patients having clinically documented infections. However, these were treated with early antibiotic therapy and G-CSF after ASCT, which led to reduced times of fever and similar hospitalization times compared with other HDT regimens.

New Evidence: Could you please comment on the main conclusions of the study and the strength of the results given the patient population involved (i.e., 50% in progression at study start)?

Dr. Isidori: As we first showed in vitro several years ago, bendamustine is a great partner for etoposide, cytarabine, and melphalan. This combination of drugs was able to induce a high CR rate in a population that did not have an opportunity of being cured with other therapies. Furthermore, we are confident that this regimen would be superior to others in head-to-head randomized clinical trials. Given that 50% of patients were in progression, with few options available to them, the results of this study are even more impressive. Therefore, this therapy can give hope to patients with refractory disease and an abysmal prognosis.

New Evidence: How might these study results impact clinical practice?

Dr. Isidori: Our study showed that bendamustine can provide high-efficacy treatment with a very manageable side effect profile. In our opinion, bendamustine, as part of an HDT regimen prior to ASCT, should become the gold standard for patients with DLBCL worldwide. It would be informative to see, through retrospective studies, whether similar results have been obtained in other parts of the world using this regimen.

New Evidence: What are the plans for future clinical trials using the Benda-EAM/ASCT conditioning regimen?

Dr. Isidori: We have demonstrated that bendamustine has high activity as part of an HDT conditioning regimen prior to ASCT in Hodgkin, aggressive, and indolent lymphomas. Further efforts will be put towards studying bendamustine in these disease states. In the meantime, it would be beneficial to collect data from several countries on the use of bendamustine in conditioning regimens prior to ASCT and conduct retrospective analysis. In addition, we have been implementing screening in order to identify genetic markers that could help us better predict prognosis for our patients. Through the identification of various polymorphisms in genes involved in DNA repair, we are able to recognize patients who could benefit from bendamustine and those who have a higher chance of failing our treatment.

New Evidence: If this conditioning regimen were available to you, in which patient population would you choose to use it in clinical practice?

Dr. Isidori: We currently use this regimen in patients with HD, relapsed FL, relapsed marginal zone lymphoma, and relapsed mantle cell lymphoma. Importantly, we have seen positive results in all of these disease states. Our latest findings have afforded us the confidence to use this regimen in all relapsed lymphoma patients. Finally, given that it is difficult for cells to become resistant to bendamustine, we can use this treatment in patients that have already received bendamustine on its own or as part of another regimen.

Despite significant improvements in the treatment of diffuse large B-cell lymphoma (DLBCL), a significant proportion of patients develop relapsed or refractory disease, which remains a major cause of morbidity and mortality. Presently, our first step in the treatment of relapsed or refractory DLBCL is a salvage chemotherapy regimen, such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin), R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), or R-GDP (rituximab, gemcitabine, cisplatin, dexamethasone). Only once patients demonstrate chemosensitivity do they undergo a conditioning regimen consisting of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), with curative intent.

The key challenge in DLBCL remains chemoresistance, which occurs in a significant proportion of these patients. Results from the CORAL and PARMA studies suggest that patients who are refractory to rituximab-containing regimens have inferior outcomes with ASCT.\(^2\) Although there have been improvements in ASCT techniques, they have a limited impact, since many patients with DLBCL are ineligible for ASCT due to refractory disease, old age, or comorbidities. Further attempts of salvage treatments in the DLBCL population generally fail. As a result, there remains a large group of patients who have incurable disease and require new targeted agents.

Carmustine is an old agent that has traditionally been used in high-dose conditioning regimens prior to ASCT. Alternatively, bendamustine is a relatively newer addition to conditioning regimens. Bendamustine has a very unique mechanism of action, and it has already shown activity in various types of lymphoma. As such, bendamustine represents a novel agent, which patients with relapsed or refractory DLBCL have not been exposed to before. The timing of its emergence is very interesting, given that not many new agents against DLBCL have appeared in the past five years. A study by Visani and colleagues showed that the addition of bendamustine to etoposide, cytarabine, and melphalan led to higher complete response (CR) rates and reduced toxicity, when compared with the use of carmustine in a similar regimen, in patients with resistant or relapsed lymphoma.\(^3\) These promising findings led the investigators to perform the larger Benda-EAM (bendamustine, etoposide, cytarabine, melphalan) trial in patients with DLBCL.\(^4\)

The results of the Benda-EAM study, even though preliminary, are quite impressive. The CR rate of 83% (40 out of 48 patients) is very encouraging, especially given that half the patients were chemoresistant at the beginning of the study and many patients had a very aggressive form of DLBCL. The fact that 73% (35/48) of patients are still in remission after a median follow-up of 10 months post ASCT further strengthens these efficacy results. It will be very interesting to look at the mature data, but at the present time the findings certainly look positive.

Many clinicians were wary of the possible toxicities presented by the use of bendamustine. However, the Benda-EAM study demonstrated a relatively manageable safety profile. The treatment mortality rate (TMR) of 2% is very reassuring, given that previous conditioning regimens have led to much higher TMR. We usually aim for a TMR of less than 5%, and often achieve 2% to 3% in our centres. Importantly, although it is still early, the investigators of the Benda-EAM study have not seen any late toxicity effects of the regimen. Given our standards of safety and the results so far, Benda-EAM should be considered a very safe regimen.

While current results are promising, it is difficult to make head-to-head comparisons of the results of the Benda-EAM study with those for other conditioning regimens used in relapsed or refractory DLBCL. One reason for this is that older regimens were evaluated using outdated methods. Unlike now, positron emission tomography was not used in the past; instead, clinicians relied on computerized tomography for patient assessments. Furthermore, the baseline characteristics of the patient population in the Benda-EAM study are different from previous trials, further impeding suitable comparisons. As a result, it is unlikely that head-to-head assessments will be made between Benda-EAM and other conditioning regimens.

The data so far are strong enough that the choice should depend solely on efficacy and toxicity results. Although final results of the study will be instrumental, it is clear that, all things being equal, the Benda-EAM regimen is at least as efficacious as, if not more efficacious than, prior treatments in patients with DLBCL. These results suggest that Benda-EAM will very soon be the conditioning regimen of choice for patients with DLBCL in Canada. This is quite an achievement, given that we have not seen much progress in terms of new therapies in chemoresistant patients in quite some time. Importantly, a few centres in Quebec, including our own, have already started using Benda-EAM in the DLBCL population, based on the results from the 2011 Benda-EAM study.\(^5\) The current trial further supports our decision. Finally, it is important to note that we currently also use Benda-EAM in...
patients with non-Hodgkin lymphoma and Hodgkin lymphoma (HL). The regimen has yielded very good results in these disease states, coupled with low toxicity profiles. Patients with HL are especially responsive to the regimen.

In conclusion, based on the efficacy and safety results presented at the 2015 EHA Congress, Benda-EAM should certainly be the first choice of conditioning regimens in Canada for patients with relapsed or refractory DLBCL, especially those who are chemoresistant.


Waldenström Macroglobulinemia

Coutre S, et al. ASCO 2015:8532

Idelalisib monotherapy results in durable responses in patients with relapsed or refractory Waldenström macroglobulinemia

Background

In this phase I/II study, Coutre and colleagues investigated the safety of idelalisib in patients with relapsed or refractory (R/R) hematologic malignancies (phase I) and evaluated the efficacy and safety of idelalisib in patients with R/R B-cell non-Hodgkin lymphoma (NHL) (phase II). The results were presented at ASCO 2015, EHA 2015, and ICML 2015.1-3

Study design

• For the phase I, single-arm idelalisib monotherapy study (Study 02), patients with Waldenström macroglobulinemia (WM)/lymphoplasmacytic lymphoma were given continuous therapy with idelalisib (50–350 mg twice a day [BID]) in 28-day cycles.
  • Tumour assessments were done at days 28, 56, 112, 168, 224, 280, and 336.
  • Patients benefiting from treatment after 48 weeks continued their dose of idelalisib until disease progression.
  • The primary endpoint was safety and the secondary endpoint was overall response rate (ORR).

• For the phase II, single-arm idelalisib monotherapy study (Study 09), patients with WM were given continuous therapy with idelalisib (150 mg BID).
  • Tumour assessments were done at weeks 0, 8, 16, 24, 36, and 48, and every 12 weeks thereafter by an independent review committee (IRC).
  • Patients benefiting from treatment after 48 weeks continued receiving idelalisib 150 mg BID until disease progression.
  • The primary endpoint was ORR and the secondary endpoints were duration of response (DOR), progression-free survival (PFS), and safety.
  • The eligibility criteria for the studies are outlined in Table 1.

Key findings

Baseline characteristics and disposition

• A total of nine patients were enrolled in Study 02 and 10 patients were enrolled in Study 09.
• Primary accrual for Study 02 was completed in January 2012 and the extension study is ongoing.
• Primary accrual for Study 09 was completed in October 2012.
Table 1. Key eligibility criteria

<table>
<thead>
<tr>
<th></th>
<th>Study 02</th>
<th>Study 09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>• Previously treated</td>
<td>• Previously untreated</td>
</tr>
<tr>
<td>Performance status</td>
<td>• World Health Organization performance status ≤ 2</td>
<td>• Eastern Cooperative Oncology Group score 0–2</td>
</tr>
<tr>
<td></td>
<td>• Eastern Cooperative Oncology Group score 0–2</td>
<td>• Karnofsky score &gt;60</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>• Refractory to or relapsed after ≥ 1 prior chemotherapy regimen and received rituximab as single agent or combined with other therapies</td>
<td>• Refractory to rituximab and alkylating agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progression within 6 months of completing therapy</td>
</tr>
<tr>
<td>Measurable disease minimum requirement</td>
<td>• &gt;2 cm lymph-node enlargement or symptomatic disease needing treatment and measurable serum monoclonal IgM</td>
<td>• &gt;2 cm lymph-node enlargement</td>
</tr>
<tr>
<td>Organ function</td>
<td>• Serum ALT/AST &lt; 2 x ULN</td>
<td>• Neutrophils &gt; 1,000 cells/μL</td>
</tr>
<tr>
<td></td>
<td>• Serum bilirubin &lt; 2 mg/dL</td>
<td>• Hemoglobin &gt; 8 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Serum creatinine &lt; 2 mg/dL</td>
<td>• Platelets &gt; 50,000 μL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serum ALT/AST &lt; 2.5 x ULN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serum bilirubin &lt; 1.5 x ULN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serum creatinine &lt; 1.5 x ULN</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IgM = immunoglobulin M; ULN = upper limit of normal

- The median age of patients in Study 02 was 63 years (range: 42–83) and for Study 09, it was 60 years (range: 49–73).
- The majority of the patients in both studies were male (78% for Study 02 and 80% for Study 09).
- In Study 02, 44% of patients were refractory and 56% were relapsed, while 100% of patients in Study 09 were refractory.
- Patients in both studies had received a median number of four prior therapies.
- In Study 02, the doses of idelalisib administered were as follows:
  - One patient received 50 mg BID;
  - Three patients received 150 mg every day;
  - One patient received 100 mg BID;
  - One patient received 150 mg BID; and
  - Three patients received 200 mg BID.
- In Study 09, all 10 patients received idelalisib 150 mg BID.
- The median exposure to idelalisib was 9 months (range: 1–11) in Study 02, and 13 months (range: 1–26) in Study 09.
- In Study 02:
  - Four (44%) patients completed the primary study; and
  - Five (56%) patients were enrolled and no patients are ongoing in the extension study.
- Seven (70%) patients are ongoing in Study 09.

Safety
- The most common adverse events (AEs) of any grade for Study 02 were diarrhea and nausea. (Figure 1)
- The most common AEs of any grade for Study 09 were diarrhea, fatigue, cough, upper respiratory tract infection, nausea, abdominal pain, and weight decrease. (Figure 1)
- The occurrence of select laboratory abnormalities is outlined in Figure 2.
• One grade 3 alanine aminotransferase elevation and one grade 3 diarrhea resulted in study discontinuation.

**Efficacy**

• The ORR was 56% (95% CI: 21–86%) for Study 02 and 80% (95% CI: 44–98%) for Study 09. (Figure 3)
• Median time to minor or first response was 2 months, and most responses continued to improve over 6 months or longer.
• Median DOR was 32.8 months for Study 02 and was not yet reached for Study 09.

• In Study 09, 67% of patients had continued response at two years.
• Median PFS was 33.3 months in Study 02 and 22.1 months in Study 09. (Figure 4)
• Transient elevations in IgM levels were noted in a few responding patients in both studies.
• Improvements of >3 g/dL in hemoglobin were noted in 5/9 patients (Study 02) and 7/10 patients (Study 09) over a 3–6 month timeframe.

**Figure 1. Adverse events**

*Excluding laboratory abnormalities. AE = adverse event*
**Figure 2. Select laboratory abnormalities**

*Worst grade post-baseline.

ALT = alanine aminotransferase; AST = aspartate aminotransferase

**Figure 3. Best response rates**

CI = confidence interval; ORR = overall response rate

**Figure 4. Progression-free survival**

CI = confidence interval; ORR = overall response rate
**Key conclusions**

- *Idelalisib therapy was associated with clinical benefit in the majority of patients with R/R WM.*
- *Idelalisib was well tolerated and the safety profile was as expected in patients with R/R WM.*
- *Various phase III confirmatory randomized trials of idelalisib in combination with chemoimmunotherapy are underway in patients with WM.*


**Dimopoulos MA, et al. ASCO 2015:TPS8599**

**A phase III study of rituximab with or without ibrutinib in patients with Waldenström macroglobulinemia**

**Background**

Dimopoulos and colleagues have planned a phase III study to evaluate the effect of the addition of ibrutinib to rituximab on progression-free survival (PFS) in patients with Waldenström macroglobulinemia (WM). An update on the status of the study was presented at ASCO 2015.¹

**Study design**

- In this international, multicentre, double-blind, phase III study, patients with WM will be randomized in a 1:1 ratio between the following arms:
  - Arm A patients will be given ibrutinib (420 mg once daily, orally, until progressive disease [PD]) and rituximab (375 mg/m² iv on day 1 of weeks 1–4 and weeks 17–20);
  - Arm B patients will be given placebo (three matching placebo capsules until PD) and rituximab (375 mg/m² iv on day 1 of weeks 1–4 and weeks 17–20).
- Following independent review committee (IRC)-confirmed PD and disease requiring treatment, patients who were treated with placebo will be allowed to cross over and receive single-agent ibrutinib as their next-line therapy.
- Patients refractory to the last rituximab-containing therapy excluded from the randomized study are eligible for Arm C, an open-label, nonrandomized, single-agent substudy, where they will be given ibrutinib (420 mg once daily, orally, until PD).
  - The randomized study aims to enroll approximately 150 patients with centrally confirmed clinicopathological diagnosis of WM.
  - The nonrandomized open-label study aims to enroll approximately 30 patients.
  - The investigators plan to conduct the study at approximately 64 sites worldwide.
  - Key inclusion criteria for Arms A and B are:
    - Diagnosis of WM;
    - Untreated WM, or previously treated WM with documented PD or no response to last treatment;
    - Symptomatic disease requiring treatment per the Second International Workshop on WM;
    - Measurable disease defined as serum monoclonal IgM >0.5 g/dL;
    - Eastern Cooperative Oncology Group performance status of 0–2; and
    - Adequate hematologic, hepatic, and renal function.
  - The key exclusion criteria for Arms A and B are:
    - Central nervous system involvement and clinically significant cardiovascular disease;
    - Disease that is refractory to the last prior rituximab-containing therapy defined as relapse after <12 months since last rituximab dose or
failure to achieve at least a minor response after the last rituximab-containing therapy;
- Known anaphylaxis or IgE-mediated hypersensitivity to rituximab;
- Previous therapy for WM received \( \leq \) 30 days prior to first administration of study treatment; and
- History of infection with hepatitis C or B virus.

**Key inclusion criteria for Arm C are either:**
- Disease that is refractory to the last prior rituximab-containing treatment defined as relapse after <12 months since last rituximab dose; or
- Failure to achieve at least a minor response after the last rituximab-containing therapy.

- The exclusion criteria for Arm C are identical to those of Arms A and B, except for the criteria related to prior rituximab use that do not apply to Arm C.

- The primary endpoint is PFS as assessed by IRC per the modified Consensus Response Criteria from the Sixth International Workshop on WM.

- The secondary endpoints are:
  - Overall response rate as assessed by IRC;
  - PFS as assessed by IRC in patients with previously treated WM;
  - Hematologic improvement as measured by hemoglobin levels;
  - Time to next treatment;
  - Overall survival; and
  - Safety.

- Key exploratory endpoints include:
  - Patient-reported outcomes and disease-related symptoms according to Functional Assessment of Cancer Therapy-Anemia and Euro QoL 5 dimension questionnaire (EQ-5D-5L);
  - Evaluation of medical resource utilization;
  - Mutation analysis of prognostic and predictive biomarkers (e.g., MYD88 and CXCR4) relative to treatment outcomes.

**Current status**
- This ongoing study is registered at ClinicalTrials.gov (NCT02165397) and currently has 56 active sites, including active Canadian sites.
- Enrollment began in July 2014.
- A total of 81 patients have been enrolled across all treatment arms.
- As of April 24, 2015, recruitment is complete for Arm C.
- Recruitment is anticipated to last until the first quarter of 2016.

Hodgkin Lymphoma

Mazza R, et al. EHA 2015:S806

Bendamustine-containing regimen (BeGeV) as induction chemotherapy prior to ASCT for relapsed/refractory Hodgkin lymphoma

**Background**
Mazza and colleagues investigated the efficacy and toxicity of the combination of bendamustine, gemcitabine, and vinorelbine (BeGeV) in patients with relapsed or refractory (R/R) Hodgkin lymphoma (HL). The results of the study were presented at EHA 2015.1

**Study design**
- In this Fleming’s single-stage, phase II multicentre study, patients with R/R HL were treated with the BeGeV regimen prior to autologous stem cell transplantation (ASCT), for four 21-day cycles, as follows:
  - Gemcitabine 800 mg/m² intravenously (iv) on days 1 and 4;
  - Vinorelbine 20 mg/m² iv on day 1; and
  - Bendamustine 90 mg/m² iv on days 2 and 3.
- The key inclusion criteria were:
  - Patients with R/R HL, who had received first-line chemotherapy;
  - Eastern Cooperative Oncology Group performance status of ≤2;
  - At least one site of measurable disease (>1.5 cm in the long axis);
  - Hemoglobin ≥9.0 g/dL, absolute neutrophil count (ANC) ≥1,500/µL, and platelet count (PLT) ≥75,000/µL; and
  - Written informed consent.
- The key exclusion criteria were:
  - Active bacterial or mycotic infections;
  - Anticancer chemotherapy or radiotherapy during study or within four weeks of study entry;
  - The following laboratory values:
    - Serum creatinine ≥1.5 x upper limit of normal (ULN);
    - Serum bilirubin ≥1.5 x ULN;
    - Alanine aminotransferase and/or aspartate aminotransferase ≥2.5 x ULN.
  - Active Hepatitis B or C.

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**ASCT** = autologous stem cell transplantation; **BeGeV** = bendamustine, gemtuzumab, vinorelbine; **CR** = complete response; **CT** = computerized tomography; **PD** = progressive disease; **PET** = positron emission tomography; **PR** = partial response; **SD** = stable disease; **Tx** = treatment
The primary endpoint was complete response (CR) rate as assessed by computerized tomography or positron emission tomography scan after four cycles of BeGeV.

The secondary endpoints included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), CD34+ cell mobilization, and safety.

Assuming a 15% improvement in CR (50% to 65%), with a 10% rejection error and a power of 85%, a minimum of 35 out of the 59 patients enrolled had to achieve a CR in order to recommend BeGeV for further study.

**Key findings**

**Baseline characteristics**

- Between August 2011 and July 2014, 59 consecutive patients with relapsed (54%) or refractory (46%) HL in response to primary therapy were enrolled.
- Fifty-two percent of the patients were male.
- The median age was 33 years (range: 18–68).
- Prior to enrollment, 69% of the patients with relapsed disease had previously achieved CR for a duration of less than one year, and 31% had previously achieved CR for more than one year.
- B symptoms were observed in 46% of the patients.
- Among all patients, 15% had received prior radiotherapy, 95% had received prior chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), and 5% had received prior BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone).
- The Ann Arbor disease stage proportions were as follows: IA (2% of patients), IB (2%), IIA (17%), IIB (14%), IIIA (17%), IIIB (12%), IVA (19%), and IVB (19%).

**Efficacy**

- Upon completion of four cycles of BeGeV, 73% (43/59) of patients achieved CR and 10% (6/59) achieved partial response (PR), for an ORR of 83%. (Figure 1)
- Of the remaining 10 (17%) patients, one (2%) had stable disease, eight (13%) had progressive disease, and one (2%) dropped out of the study due to toxicity. (Figure 1)
- Of the 49 responsive patients, 43 (88%) proceeded to ASCT (38/43 of those who achieved a CR, and 5/6 of those who achieved a PR).
  - The remaining six patients did not progress to ASCT due to:
    - Failed mobilization (n = 2);
    - Physician’s decision (n = 2);
    - Early relapse (n = 1); and
    - Patient refusal (n = 1).

**Figure 1. Response rates**

<table>
<thead>
<tr>
<th>Disease status at study entry</th>
<th>ORR (CR + PR)</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>30 (94%)</td>
<td>1  (3%)</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>Refractory</td>
<td>19 (70%)</td>
<td>—</td>
<td>8  (30%)</td>
</tr>
</tbody>
</table>

CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease
With a median follow-up of 16 months for the overall population: (Figure 2)

- PFS at two years was 51% and median PFS was 26 months; and
- OS at two years was 69%, and median OS was not reached.

- No significant differences in PFS and OS were found between relapsed and refractory patients.

- The two-year PFS for the 49 responsive patients was 61% for those who achieved CR and 63% for those who achieved an overall response (CR + PR).

- The two-year OS was 86% for patients who achieved a CR or PR, and 14% for patients with induction failures ($p < 0.0001$).

- The median number of white blood cells (WBCs) was 20,000 cells/µL (range: 5,000–87,000), and the median number of CD34+ cells was 89 cells/µL (range: 1–763).

- The median number of total harvested CD34+ cells was 8.8 x $10^6$ cells/kg, and the median number of harvested CD34+ per leukapheresis (LK) was 6.3 x $10^6$ cells/kg/LK.

- The median number of days to ANC ≥500/µL was 11 days (range: 9–21), and the median number of days to PLT ≥20,000/µL was 12 days (range: 9–26).

**Safety**

- The occurrence rate of adverse events (AEs) was acceptable. (Table 1)

- The most common grade 1/2 AEs were nausea (17% of patients) and infections (15%), while the most common grade 3/4 AEs were neutropenia (14%), thrombocytopenia (14%), and febrile neutropenia (12%).

- Out of a total of 223 cycles administered, the grade 1/2 AEs occurring in the greatest number of cycles were nausea (13% of cycles), anemia (8%), and infections (7%), while the grade 3/4 AEs occurring in the greatest number of cycles were neutropenia (7%), thrombocytopenia (6%), and febrile neutropenia (5%). (Table 1)

- Only one patient stopped therapy due to toxicity, and no deaths occurred due to toxicity.
### Table 1. Adverse events in study population by patients and cycles

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number (%) of patients</th>
<th>Number (%) of cycles*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2 Grade 3/4</td>
<td>Grade 1/2 Grade 3/4</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (5) 2 (3)</td>
<td>19 (8) 2 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (2) 8 (14)</td>
<td>5 (2) 15 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 (–) 8 (14)</td>
<td>9 (4) 14 (6)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (8) 7 (12)</td>
<td>13 (6) 11 (5)</td>
</tr>
<tr>
<td>Infections</td>
<td>9 (15) 4 (7)</td>
<td>15 (7) 6 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (17) 4 (7)</td>
<td>28 (13) 5 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (8) 0 (–)</td>
<td>8 (4) 0 (–)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>6 (10) 0 (–)</td>
<td>8 (4) 0 (–)</td>
</tr>
<tr>
<td>AST/ALT increase</td>
<td>7 (12) 2 (3)</td>
<td>11 (5) 2 (1)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase

*Total number of administered cycles: 223

### Key conclusions

- The BeGeV regimen was a very effective second-line chemotherapy regimen, achieving a CR of 73% and an ORR of 83%.
- The toxicity profile of BeGeV was tolerable and manageable.
- The treatment led to excellent stem cell mobilization activity, given that only two mobilization failures were observed.
- ASCT was performed in 88% of the responding patients and 73% of the total patient population.
- The data provide strong support for further development of BeGeV.


Kuruvilla J, et al. ICML 2015:090

A phase I study of brentuximab vedotin and bendamustine in relapsed or refractory Hodgkin lymphoma and anaplastic large T-cell lymphoma

### Background

Kuruvilla and colleagues designed a phase I/II trial to evaluate the activity and safety of the brentuximab vedotin (BV) and bendamustine combination regimen in patients with Hodgkin lymphoma (HL) or anaplastic large T-cell lymphoma (ALCL). The findings for phase I of this trial were presented at ICML 2015.  

### Study design

- The eligibility criteria for this study included patients with:
  - Relapsed or refractory HL or ALCL;
  - Platelet count ≥50,000/µL; and
  - Absolute neutrophil count ≥1,000/µL.
- Patients were accrued from three centres between August 2012 and June 2014.
- In the phase I portion of this study, the patients were assigned to five dose cohorts. Accrual followed a classic Fibonacci dose escalation, with three patients being treated at each of the following dose levels:
1. BV at 1.2 mg/kg and bendamustine at 70 mg/m²;
2. BV at 1.2 mg/kg and bendamustine at 80 mg/m²;
3. BV at 1.8 mg/kg and bendamustine at 80 mg/m²;
4. BV at 1.8 mg/kg and bendamustine at 90 mg/m²; and
5. BV at 1.8 mg/kg and bendamustine at 100 mg/m².

- The primary goal of the study was to determine dose-limiting toxicities (DLTs).
- A DLT was defined as any CTCAE (Common Terminology Criteria for Adverse Events) version 4 grade 3/4 toxicity, except for:
  - Grade 3 febrile neutropenia;
  - Grade 4 thrombocytopenia or neutropenia lasting >7 days; or
  - Any modifications for gastrointestinal toxicity, alopecia, and fatigue.
- The identification of a DLT led to expansion of the dose cohort.

Key findings
Baseline characteristics and disposition
- A total of 28 patients were enrolled in the phase I trial, with a median age of 38 years (range: 27–50), and 27 patients were evaluable.
- The majority of the patients were male (65%) and had HL (96%; 4% with ALCL).
- Patients had received a median of five (range: 2–15) prior systemic therapies.
- Seventeen patients had prior autologous stem cell transplantation and 11 had prior radiation.

Efficacy
- The overall response rate was 63% (17/27 patients) as measured by computerized tomography. (Table 1)
  - Of the 27 evaluable patients, three (11%) achieved a complete response, 14 (52%) achieved a partial response (PR), and six (22%) had stable disease (SD).
  - Among the nine patients who had prior BV therapy, four (44%) responded to treatment, all with a PR. The five remaining patients had SD (n = 2) and progressive disease (PD; n = 3).
  - Among the four patients who had received prior bendamustine treatment, two (50%) responded to treatment with a PR. The two remaining patients had SD (n = 1) and PD (n = 1).
- A total of 25 patients achieved disease reduction.
  - Two of these patients achieved disease reduction while developing a new lesion.

Safety
- The most common grade 3 and 4 toxicities were anemia (22%) and neutropenia (22%), respectively. (Table 2)
- Only the first four dose levels were used.
  - DLT was not reached at dose level 4.
  - Investigators decided not to explore dose level 5, so as to not exceed the standard dose of BV and the combination dose of bendamustine.
- One DLT was observed in three of the four dose levels. (Table 3)
- The maximum tolerated dose (MTD) was 1.8 mg/m² of BV and 90 mg/m² of bendamustine.

Table 1. Response rates for phase I cohort

<table>
<thead>
<tr>
<th></th>
<th>All, n = 27 n (%)</th>
<th>Prior BV, n = 9 n (%)</th>
<th>Prior Benda, n = 4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>14 (52)</td>
<td>4 (44)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (22)</td>
<td>2 (22)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>ORR</td>
<td>17 (63)</td>
<td>4 (44)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

Benda = bendamustine; BV = brentuximab vedotin; CR = complete response; CT = computed tomography; FDG-PET = fluorodeoxyglucose-positron emission tomography; ORR = overall response rate; PR = partial response; SD = stable disease

Data are for CT imaging, not FDG-PET response.
Key conclusions

- The combination of BV and bendamustine represents an effective and tolerable regimen in this heavily pretreated patient population with HL and ALCL.
- Phase II of the study is currently accruing an additional 37 patients.
  - In addition, plasma and serum biomarkers are being prospectively collected for correlation with toxicity and response.

Squamous Cell Lung Carcinoma
Targeted Agents in Second-Line Treatment of SCC of the Lung

Squamous cell carcinoma (SCC) of the lung, a type of non-small-cell lung cancer (NSCLC), is a disease with a high unmet medical need. After first-line chemotherapy, NSCLC patients with squamous histology have limited therapeutic options and worse prognosis compared with patients with non-squamous histology. However, three targeted therapies have recently completed phase III clinical trials in second-line for patients with SCC of the lung. The first targeted agent is afatinib — an irreversible epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR TKI). The other two targeted agents are monoclonal antibodies: nivolumab — a programmed cell death-1 (PD-1) antibody — and ramucirumab — an antibody directed against vascular endothelial growth factor receptor 2 (VEGFR2).

At the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, the following four presentations reported on phase III clinical trials with targeted therapies in second-line treatment of patients with SCC of the lung:

• In the LUX-Lung 8 trial, the largest phase III trial comparing two established EGFR TKIs in the second-line treatment of SCC of the lung, afatinib showed a significant reduction in the risk of death and disease progression when compared with erlotinib, and an advantage in median overall survival and progression-free survival. (Soria J-C, et al. ASCO 2015:8002)
• Patient-reported outcomes from the LUX-Lung 8 trial showed improvements with afatinib compared with erlotinib in several parameters, including quality of life and key lung cancer-associated symptoms. (Gadgeel SM, et al. ASCO 2015:8100)
• Efficacy results from the CheckMate 017 trial showed a survival benefit with nivolumab compared with docetaxel (the standard of care) in previously treated patients with advanced squamous NSCLC. (Spigel DR, et al. ASCO 2015:8009)
• A general overview of the results from the LUX-Lung 8, CheckMate 017, and REVEL trials summarized the key findings from these trials and their significance in second-line treatment.

Afatinib versus erlotinib as second-line therapy for advanced SCC of the lung: overall survival analysis from LUX-Lung 8

**Background**
LUX-Lung 8 was a second-line, head-to-head trial of afatinib and erlotinib in patients with squamous cell carcinoma (SCC) of the lung. Preliminary results from this trial were presented at ESMO 2014. At ASCO 2015, Soria and colleagues presented the updated progression-free survival (PFS) results and the overall survival (OS) data.1

**Study design**
- LUX-Lung 8 was a global, phase III, randomized trial of patients with stage III/IV SCC of the lung who had progressed after ≥4 cycles of a first-line platinum doublet.
- Patients (n = 795) were randomized 1:1 to receive either afatinib (40 mg daily; n = 398) or erlotinib (150 mg daily; n = 397).
- The primary endpoint of the study was PFS by independent review.
- Secondary endpoints were OS (key secondary endpoint), overall response rate (ORR), disease control rate (DCR), tumour shrinkage, patient-reported outcomes, and safety.

**Key findings**
- At the time of analysis, of the 398 patients randomized to the afatinib arm, 392 were treated, 307 died, and six were still on treatment; in the erlotinib arm, 395 of the 397 randomized patients were treated, 325 died, and three were still on treatment.
- Demographic and baseline characteristics were well balanced between the afatinib and erlotinib arms.
- Median OS was significantly longer in the afatinib group compared with the erlotinib group (7.9 vs. 6.8 months, respectively; p = 0.0077) at a median follow-up of 18.4 months. (Figure 1)
- The OS subgroup analysis is shown in Figure 2.

---

*Soria J-C, et al. ASCO 2015:8002
Afatinib versus erlotinib as second-line therapy for advanced SCC of the lung: overall survival analysis from LUX-Lung 8

**Study design**

![Stratified by east Asian vs. non-east Asian](image)

**Key secondary endpoint**
- Overall survival
- Other secondary endpoints:
  - ORR, DCR, tumour shrinkage, PRO, safety

**Stratified by east Asian vs. non-east Asian**
- SCC of the lung (Stage III/IV)*
- Progressed after ≥4 cycles of a first-line platinum doublet
- ECOG PS 0–1
- Adequate organ function
- 1:1
- Afatinib 40 mg† qd
- Primary endpoint
- PFS by independent review§
- Erlotinib 150 mg‡ qd

---

†Dose escalation to 50 mg and dose reduction to 30 or 20 mg permitted.
‡Dose reduction to 100 or 50 mg permitted.
§Tumour assessment at baseline, weeks 8, 12, 16; every 8 weeks thereafter.

DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; qd = every day; PS = performance status; SCC = squamous cell carcinoma
• Post-progression therapies included subsequent systemic treatment and chemotherapy, with a minority of patients who received erlotinib or afatinib.

• Median PFS was significantly prolonged in the afatinib group vs. the erlotinib group (2.6 vs. 1.9 months, respectively; \( p = 0.0103 \)) at a data cut-off of February 2, 2015. (Figure 3)

• The duration of response was 7.29 months for afatinib and 3.71 months for erlotinib.

• The disease control rate was significantly higher in the afatinib arm compared with the erlotinib arm (50.5% vs. 39.5%, respectively; \( p = 0.002 \)).

• The objective response rate was numerically higher for the afatinib arm vs. the erlotinib arm (5.5% vs. 2.8%, respectively; \( p = 0.055 \)).

• Quality of life (QoL) measures and symptom relief favoured afatinib.

• Almost all patients in the afatinib and erlotinib arms experienced adverse events (AEs) (99.5% vs. 97.5%, respectively) with serious AEs occurring in 44.1% of patients in each arm.

• AEs leading to dose reduction occurred in 26.5% of patients in the afatinib arm compared with 14.2% of patients in the erlotinib arm; AEs leading to discontinuations occurred in 20.2% and 17.0% of patients, respectively.

• Drug-related AEs included diarrhea, rash/ acne, and stomatitis. (Table 1)

• Drug-related fatal AEs occurred in 1.5% and 1.3% of patients in the afatinib and erlotinib arms, respectively.

• Epidermal growth factor receptor (EGFR) mutations were infrequent and balanced between arms, with no correlation with PFS or OS.

  ▶ There were 14 EGFR mutation-positive patients, not concentrated in East Asian patients.

---

**Figure 1. Primary analysis of overall survival (n = 795)**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n = 398)</th>
<th>Erlotinib (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>7.9</td>
<td>6.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.2–8.7</td>
<td>5.9–7.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.69–0.95)</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

Median follow-up time: 18.4 months

---

\( CI = \text{confidence interval}; \text{HR = hazard ratio}; \text{OS = overall survival} \)
Figure 2. Overall survival subgroup analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>795</td>
<td>0.81 (0.69–0.95)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>399</td>
<td>0.68 (0.55–0.85)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>396</td>
<td>0.95 (0.76–1.19)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>666</td>
<td>0.82 (0.69–0.97)</td>
</tr>
<tr>
<td>Female</td>
<td>129</td>
<td>0.77 (0.51–1.14)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-east Asian</td>
<td>623</td>
<td>0.87 (0.73–1.03)</td>
</tr>
<tr>
<td>East Asian</td>
<td>172</td>
<td>0.62 (0.44–0.88)</td>
</tr>
<tr>
<td>ECOG at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>260</td>
<td>0.76 (0.58–1.01)</td>
</tr>
<tr>
<td>1</td>
<td>531</td>
<td>0.80 (0.66–0.97)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>44</td>
<td>0.77 (0.37–1.57)</td>
</tr>
<tr>
<td>Light ex-smoker</td>
<td>23</td>
<td>0.43 (0.16–1.12)</td>
</tr>
<tr>
<td>Current and other ex-smoker</td>
<td>728</td>
<td>0.81 (0.69–0.96)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>763</td>
<td>0.82 (0.70–0.96)</td>
</tr>
<tr>
<td>Mixed</td>
<td>32</td>
<td>0.55 (0.26–1.17)</td>
</tr>
<tr>
<td>Best response to first-line chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>371</td>
<td>0.91 (0.72–1.15)</td>
</tr>
<tr>
<td>SD</td>
<td>328</td>
<td>0.71 (0.56–0.90)</td>
</tr>
<tr>
<td>Unknown</td>
<td>89</td>
<td>0.72 (0.44–1.17)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PR = partial response; SD = stable disease

Figure 3. PFS by independent review

<table>
<thead>
<tr>
<th></th>
<th>Afatinib n = 398</th>
<th>Erlotinib n = 397</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>2.6</td>
<td>1.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.0–2.9</td>
<td>1.9–2.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.69–0.96)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0103</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival
Table 1. Drug-related adverse events

<table>
<thead>
<tr>
<th>AE category, %</th>
<th>Afatinib n = 392</th>
<th>Erlotinib n = 395</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>Rash/acne*</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Paronychia*</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Grouped terms.
AE = adverse event

Key conclusions

- LUX-Lung 8 was the largest phase III trial comparing two established EGFR tyrosine-kinase inhibitors in the second-line treatment of SCC of the lung.
- Afatinib showed a significant reduction (19%) in the risk of death and disease progression when compared with erlotinib, and had a consistent advantage across all endpoints and subgroups.
- Overall symptom relief and QoL measures favoured afatinib.
- The pattern of AEs was consistent with EGFR inhibition in both arms with similar rates of severe, serious, and fatal AEs.
- Afatinib should be the tyrosine-kinase inhibitor of choice in second-line treatment of patients with SCC of the lung.

Afatinib versus erlotinib as second-line therapy for advanced SCC of the lung: patient-reported outcome data from LUX-Lung 8

Background
Prespecified patient-reported outcome (PRO) endpoints were included in the phase III LUX-Lung 8 trial, which compared afatinib and erlotinib in patients with squamous cell carcinoma (SCC) of the lung following failure of platinum-based chemotherapy. The PRO results were presented at ASCO 2015.  

Study design
- LUX-Lung 8 was an open-label, prospective, global, randomized study.
- Patients (n = 795) were randomized 1:1 to receive either afatinib (40 mg, once daily; n = 398) or erlotinib (150 mg, once daily; n = 397).
- Key eligibility criteria included stage IIIIB/IV non-small cell lung cancer with squamous histology, progression after ≥4 cycles of a first-line platinum doublet chemotherapy, an Eastern Cooperative Oncology Group performance status of 0–1, and adequate organ function.
- The primary endpoint was progression-free survival (PFS).
- Secondary endpoints were overall survival (OS; key endpoint), overall response rate (ORR), disease control rate (DCR), tumour shrinkage, PROs, and safety.
- PROs were assessed at the first visit of each treatment course and at the end of treatment using the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and the lung cancer specific module (QLQ-LC13).
  - Scores were converted to a 0–100 scale and analyzed in line with EORTC scoring algorithms.
  - Prespecified symptoms relevant to lung cancer were considered: cough, dyspnea, pain, and global health status (GHS)/QoL.

Key findings
- Baseline characteristics were generally well balanced between the two arms.
- Afatinib improved median OS compared with erlotinib (7.9 vs. 6.8 months, respectively; p = 0.008).
- Mean (standard deviation [SD]) baseline symptom scores were low in the afatinib and erlotinib arms for:  

Stage IIIB/IV NSCLC with squamous histology
- Progressed after ≥4 cycles of a first-line platinum doublet
- ECOG PS 0–1
- Adequate organ function

EORTC QLQ-C30 and QLQ-LC13 completed once every cycle and at end of treatment
- Status change, TTD, and change in scores over time assessed for prespecified symptoms: cough, dyspnea, pain

DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC = European Organisation for Research and Treatment of Cancer; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; qd = once daily; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-LC13 = Quality of Life Questionnaire-Lung Cancer 13; TTD = time to deterioration
Cough (Q1 from QLQ-LC13): 39.7 (29.5) vs. 37.8 (26.3), respectively; 
Dyspnea (Q3–Q5 from QLQ-LC13): 28.8 (23.5) vs. 29.7 (23.5); and 
Pain (Q9, Q19 from QLQ-C30): 26.9 (29.2) vs. 29.7 (28.5).

Mean (SD) baseline score for GHS/QoL for afatinib was 60.8 (21.0) and for erlotinib was 60.2 (21.6), where higher scores reflect better status.

Completion rates for the EORTC questionnaire were high throughout treatment for afatinib (range: 77.3%–99.0%) and erlotinib (range: 68.7%–99.0%).

Afatinib significantly delayed time to deterioration (TTD) of dyspnea compared with erlotinib (median 2.6 vs. 1.9 months; hazard ratio = 0.79, 95% CI: 0.66–0.94; p = 0.008).

There was a trend towards delayed TTD of cough with afatinib vs. erlotinib (4.5 vs. 3.7 months).

TTD was similar for pain across both treatment arms (2.5 vs. 2.4 months).

TTD was consistent across subcategories of dyspnea and pain. (Figure 1)

The number of patients reporting improved GHS/QoL and cough was significantly higher with afatinib than erlotinib. (Figure 2)

More patients reported improved dyspnea with afatinib compared with erlotinib; however, the difference was not statistically significant as the effect was primarily concentrated in those reporting improvement in ‘dyspnea walked’ (34.6% vs. 26.5%; p = 0.022).

Improvement in pain was similar across both treatment arms.

Changes in mean scores over time significantly favoured afatinib compared with erlotinib for cough (p = 0.0091), dyspnea (p = 0.0024), and pain (p = 0.0384). (Figure 3)

There were no significant differences between afatinib and erlotinib for changes in GHS/QoL over time; however, with the exception of social functioning, changes in functional scales over time significantly favoured afatinib.

---

**Figure 1. Time to deterioration of symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing (Q1 from QLQ-LC13)</td>
<td>793</td>
<td>0.89 (0.72–1.09)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea (Q3–Q5 from QLQ-LC13)</td>
<td>793</td>
<td>0.79 (0.66–0.94)</td>
</tr>
<tr>
<td>Dyspnea rested (Q3 from QLQ-LC13)</td>
<td>793</td>
<td>0.82 (0.66–1.01)</td>
</tr>
<tr>
<td>Dyspnea walked (Q4 from QLQ-LC13)</td>
<td>793</td>
<td>0.83 (0.68–1.01)</td>
</tr>
<tr>
<td>Dyspnea climbed stairs (Q5 from QLQ-LC13)</td>
<td>793</td>
<td>0.80 (0.65–0.98)</td>
</tr>
<tr>
<td>Short of breath (Q8 from QLQ-C30)</td>
<td>793</td>
<td>0.91 (0.75–1.12)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (Q9, Q19 from QLQ-C30)</td>
<td>793</td>
<td>0.99 (0.82–1.18)</td>
</tr>
<tr>
<td>Have pain (Q9 from QLQ-C30)</td>
<td>793</td>
<td>0.96 (0.80–1.17)</td>
</tr>
<tr>
<td>Pain affecting daily activities (Q19 from QLQ-C30)</td>
<td>793</td>
<td>0.95 (0.79–1.16)</td>
</tr>
<tr>
<td>Pain in chest (Q10 from QLQ-LC13)</td>
<td>793</td>
<td>0.81 (0.65–1.00)</td>
</tr>
<tr>
<td>Pain in arm or shoulder (Q11 from QLQ-LC13)</td>
<td>793</td>
<td>0.94 (0.76–1.17)</td>
</tr>
<tr>
<td>Pain in other parts (Q12 from QLQ-LC13)</td>
<td>793</td>
<td>0.94 (0.77–1.16)</td>
</tr>
<tr>
<td>GHS/QoL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHS/Qol. (Q29–Q30 from QLQ-C30)</td>
<td>793</td>
<td>0.93 (0.78–1.12)</td>
</tr>
<tr>
<td>Functional scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning (Q1–Q5 from QLQ-C30)</td>
<td>793</td>
<td>0.86 (0.71–1.03)</td>
</tr>
<tr>
<td>Role functioning (Q6–Q7 from QLQ-C30)</td>
<td>793</td>
<td>0.88 (0.73–1.05)</td>
</tr>
<tr>
<td>Cognitive functioning (Q20, Q23 from QLQ-C30)</td>
<td>793</td>
<td>0.95 (0.78–1.14)</td>
</tr>
<tr>
<td>Emotional functioning (Q21–Q24 from QLQ-C30)</td>
<td>793</td>
<td>0.85 (0.69–1.03)</td>
</tr>
<tr>
<td>Social functioning (Q26–Q27 from QLQ-C30)</td>
<td>793</td>
<td>0.96 (0.80–1.15)</td>
</tr>
</tbody>
</table>

CI = confidence interval; GHS = global health status; HR = hazard ratio; Q = question; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-LC13 = Quality of Life Questionnaire-Lung Cancer 13; QoL = quality of life.
Figure 2. Proportion of patients with improvements in symptoms

![Bar chart showing proportions of patients improved in symptoms](chart.png)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Afatinib</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>43.4</td>
<td>35.2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>51.3</td>
<td>44.1</td>
</tr>
<tr>
<td>Pain</td>
<td>40.2</td>
<td>39.2</td>
</tr>
<tr>
<td>GHS/QoL</td>
<td>35.7</td>
<td>28.3</td>
</tr>
</tbody>
</table>

OR = 1.41  
\( p = 0.029 \)

OR = 1.33  
\( p = 0.061 \)

OR = 1.05  
\( p = 0.775 \)

OR = 1.40  
\( p = 0.041 \)

GHS = global health status; OR = odds ratio afatinib vs. erlotinib; QoL = quality of life

Figure 3. Difference in mean scores over time

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients</th>
<th>Adjusted mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing (Q1 from QLQ-LC13)</td>
<td>604</td>
<td>−3.5</td>
</tr>
<tr>
<td>Dyspnea (Q3–Q5 from QLQ-LC13)</td>
<td>603</td>
<td>−3.5</td>
</tr>
<tr>
<td>Pain (Q9, Q19 from QLQ-C30)</td>
<td>609</td>
<td>−2.7</td>
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<tr>
<td>GHS/QoL (Q29–Q30 from QLQ-C30)</td>
<td>602</td>
<td>−1.6</td>
</tr>
</tbody>
</table>

GHS = global health status; Q = question; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-LC13 = Quality of Life Questionnaire-Lung Cancer 13; QoL = quality of life

Key conclusions

■ In second-line treatment of SCC, significant improvements in OS and PFS were achieved with afatinib compared with erlotinib, complemented by improvements in PROs.

■ Improvements in several PRO parameters, including GHS/QoL and key lung cancer-associated symptoms, were observed across three key analyses.

■ These analyses confirmed the clinical meaningfulness of the improvements observed for PFS, OS, and tumour response with afatinib compared with erlotinib.

■ With better efficacy and PROs over erlotinib and a manageable adverse event profile, afatinib should be considered the tyrosine kinase inhibitor of choice for second-line treatment of SCC of the lung.

CheckMate 017: a phase III study of nivolumab versus docetaxel in previously treated advanced or metastatic squamous cell non-small-cell lung cancer

**Background**
CheckMate 017 was a randomized, global, phase III trial that compared the efficacy and safety of nivolumab with docetaxel in patients with advanced squamous cell non-small-cell lung cancer (NSCLC) after failure of platinum-based chemotherapy. The results of this trial were presented at ASCO 2015.1

**Study design**
- Patients with stage IIIb/IV squamous cell NSCLC who had received one prior platinum doublet-based chemotherapy were randomized 1:1 to receive either nivolumab (n = 135) or docetaxel (n = 137).
  - Patients were stratified by region and prior paclitaxel use.
- Treatment in each arm was given until progressive disease or unacceptable toxicity:
  - Nivolumab: 3 mg/kg intravenously (iv) every two weeks;
  - Docetaxel: 75 mg/m² iv every three weeks.
- The primary endpoint was overall survival (OS).
- Additional endpoints included investigator-assessed overall response rate (ORR) and progression-free survival (PFS), correlation between programmed death ligand-1 (PD-L1) expression and efficacy, safety, and quality of life (QoL) using the lung cancer symptom scale (LCSS).

**Key findings**
- The median age (range) of patients at baseline was 62 (39–85) years in the nivolumab group vs. 64 (39–85) years in the docetaxel group, with 8% vs. 13% of patients being at least 75 years of age.
- The majority of patients were male (82% vs. 71% in the nivolumab and docetaxel arms, respectively), with stage IV cancer (78% vs. 82%), and performance status 1 (79% vs. 73%).
- PD-L1 expression was quantifiable in 83% (225/272) of patients.
- The median OS (95% CI) was 9.2 (7.3–13.3) months in the nivolumab arm vs. 6.0 (5.1–7.3) months in the docetaxel arm (HR = 0.59; \( p = 0.00025 \)). (Figure 1)
  - The one-year OS rate was 42% in the nivolumab arm vs. 24% in the docetaxel arm.
- The median PFS (95% CI) was 3.5 (2.1–4.9) months in the nivolumab arm vs. 2.8 (2.1–3.5) months in the docetaxel arm (HR = 0.62; \( p = 0.0004 \)). (Figure 2)
  - The one-year PFS rate was 21% in the nivolumab arm vs. 6.4% in the docetaxel arm.
- The survival benefit (OS and PFS) with nivolumab was independent of PD-L1 expression level.
- The ORRs (95% CI) were 20% (14–28%) vs. 9% (5–15%) in the nivolumab vs. docetaxel arms, respectively (\( p = 0.0083 \)). (Table 1)
  - ORR was independent of PD-L1 expression and consistently higher for nivolumab vs. docetaxel.
• Treatment-related grade 3–5 adverse events (AEs) occurred in 7% vs. 57% of patients in the nivolumab vs. docetaxel arms, respectively.
  o No grade 5 events occurred in the nivolumab arm.
• The most frequent treatment-related grade 3/4 AEs in the nivolumab arm were fatigue (1%) and decreased appetite (1%); in the docetaxel arm they were neutropenia (30%), febrile neutropenia (10%), and fatigue (8%).
• There were no treatment-related deaths in the nivolumab arm compared with 2% of patients in the docetaxel arm.

**Figure 1. Overall survival**

![ Overall survival graph with data table and survival rate annotations. ]

**Figure 2. Investigator-assessed progression-free survival**

![ Progression-free survival graph with data table and survival rate annotations. ]
### Table 1. Objective response rate

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab n = 135</th>
<th>Docetaxel n = 137</th>
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<tr>
<td>ORR (95% CI), %</td>
<td>20 (14–28)</td>
<td>9 (5–15)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.0083</td>
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<td>Best overall response, %</td>
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<td>Complete response</td>
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<tr>
<td>Partial response</td>
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<tr>
<td>Stable disease</td>
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<td>34</td>
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<tr>
<td>Progressive disease</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Median DOR‡ (range), months</td>
<td>NR (2.9–21+)</td>
<td>8.4 (1.4+–15+)</td>
</tr>
<tr>
<td>Median time to response† (range), months</td>
<td>2.2 (1.6–12)</td>
<td>2.1 (1.8–9.5)</td>
</tr>
</tbody>
</table>

*Based on two-sided stratified Cochran-Mantel-Haenszel test on estimated odds ratio of 2.6 (95% CI: 1.3–5.5).
†One patient experienced complete response.
‡Values are for all confirmed responders per RECIST v.1.1 (nivolumab, n = 27; docetaxel, n = 12).
The symbol ‘+’ indicates a censored value.
In the nivolumab arm, 28 patients were treated beyond RECIST v.1.1-defined progression. Non-conventional benefit was observed in nine patients (not included in ORR).
CI = confidence interval; DOR = duration of response; NR = not reached; ORR = overall response rate; RECIST = Response Evaluation Criteria In Solid Tumors

### Key conclusions

- **Nivolumab** is the first PD-1 inhibitor to show a survival benefit vs. docetaxel (the standard of care) in previously treated patients with advanced squamous cell NSCLC.
- **Nivolumab** demonstrated superiority over docetaxel across all secondary efficacy endpoints.
- **The benefit of nivolumab** was independent of PD-L1 expression.
- **The safety profile of nivolumab** was favourable compared with docetaxel and consistent with prior studies.

**New Evidence:** What is the current standard of care for patients with advanced squamous cell carcinoma (SCC) of the lung?

**Dr. Hirsh:** For first-line treatment of metastatic squamous cell lung cancer, patients are usually treated with gemcitabine plus platinum chemotherapy, although some practitioners still give carboplatin plus paclitaxel. In second-line therapy, until recently, patients were treated with docetaxel because it was shown to have better progression-free survival (PFS) than erlotinib in patients with non-adenocarcinoma histology.\(^1\) However, with the approval of nivolumab — an anti-PD-1 monoclonal antibody — patients will now receive this agent, which has been shown in the CheckMate 017 trial to be superior to docetaxel in previously treated patients with lung SCC.\(^2\) In the second line of therapy, some patients prefer an oral agent, such as afatinib, because it is more convenient (i.e., taken orally, frequency of visits is lower, toxicity is manageable). Afatinib — an irreversible, ErbB family blocker — has been approved by Health Canada for the treatment of epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR-TKI) naïve patients with metastatic adenocarcinoma of the lung who are EGFR-mutation positive. While afatinib is reimbursed in most provinces, it is not yet reimbursed in Quebec. Once afatinib is approved by Health Canada for second-line treatment of SCC of the lung, and it is reimbursed in Quebec, we would consider using it for some patients with SCC of the lung in second-line.

**New Evidence:** Please briefly describe the LUX-Lung 8 study.

**Dr. Hirsh:** LUX-Lung 8 was a phase III trial of patients with metastatic SCC of the lung who had progressed after at least four cycles of first-line platinum doublet chemotherapy. Patients were randomized to receive either afatinib (40 mg) or erlotinib (150 mg) daily as second-line therapy. The primary outcome was PFS by independent review and the secondary outcomes included overall survival (OS), overall response rate (ORR), disease control rate (DCR), quality of life (QoL), and patient-reported outcomes (PROs).

**New Evidence:** Why was erlotinib chosen as the comparator instead of docetaxel?

**Dr. Hirsh:** Comparing afatinib to erlotinib — both EGFR-TKIs — made sense in this setting. Erlotinib — a reversible EGFR-TKI — has been frequently used in second-line treatment of squamous cell lung cancer. We know from previous clinical trials (e.g., the BR.21 trial)\(^3\) that erlotinib is effective in SCC and mutation-negative non-small-cell lung cancer (NSCLC), and it is a good alternative to docetaxel for patients with performance status 2 or 3 because docetaxel can be a difficult treatment for these patients.

**New Evidence:** Why was the LUX-Lung 8 study important for this patient population?

**Dr. Hirsh:** There are many ongoing first- and second-line trials for non-squamous NSCLC and progress has been made in treatment options for this patient population, particularly in the area of targeting biomarkers. However, we are really lagging behind in treatment advances for SCC of the lung, which is why this study was so important.

Afatinib has been shown to be effective in first-line treatment of lung adenocarcinoma patients who are EGFR-mutation positive.\(^4\) In addition, EGFR-mutation-negative patients treated with afatinib in the third or fourth line had a numerically higher PFS compared with placebo.\(^5\) Therefore, it was important to investigate afatinib for second-line treatment of SCC of the lung, where EGFR mutations are typically not present. In addition, erlotinib has been used in second-line treatment of SCC of the lung, therefore, given afatinib’s mechanism of action (i.e., ErbB family blocker, irreversible binding, etc.) it was also important to investigate whether afatinib had superior efficacy compared with erlotinib.

**New Evidence:** The median OS and PFS were both significantly higher in the afatinib group vs. the erlotinib group (OS: 7.9 vs. 6.8 months; \(p = 0.0077\) and PFS: 2.6 vs. 1.9 months; \(p = 0.0103\)). Can you please comment on the significance of these results? How do these results compare with those of other treatment regimens for this patient population?

**Dr. Hirsh:** In first-line, wild-type patients typically have a median OS of approximately 1 year. However, in second-line, it is not unusual to have a median OS of 6–8 months. The OS values in LUX-Lung 8 are not as high as they are in first-line, but they are significantly better for afatinib compared with erlotinib. Similarly, a PFS of 2–3 months is typical for second-line therapy. It is important to remember that this is the first trial that has been done in second-line with only SCC patients, making it difficult.
to compare these results with those of previous trials. In the BR.21 trial of erlotinib versus placebo in previously treated patients with NSCLC, the PFS values were similar to those of LUX-Lung 8; however, the BR.21 trial included patients with adenocarcinoma, SCC, and other pathology subtypes, not just patients with SCC.

**New Evidence:** Can you comment on any significant differences between afatinib and erlotinib in the OS subgroup analysis?

**Dr. Hirsh:** The results of the OS subgroup analysis showed an advantage toward afatinib regardless of the subgroup (i.e., age, gender, performance status, response to first-line therapies, etc.). These results show that afatinib has an OS advantage for all patients with SCC of the lung, not just a select subgroup.

**New Evidence:** The duration of response was almost twice as long in the afatinib arm compared with the erlotinib arm (7.29 vs. 3.71 months, respectively). Can you please comment on this result and the impact it would have on patients?

**Dr. Hirsh:** The duration of response in the afatinib group was almost double that of the erlotinib group. This result is very important because if you do not have deterioration of symptoms, then that helps improve QoL, which is very important for these palliative patients.

**New Evidence:** The objective response rate was 5.5% for afatinib and 2.8% for erlotinib, numerically higher for afatinib but not statistically significant. How do these response rates compare with those of other treatments given to this patient population?

**Dr. Hirsh:** These results are lower than we would expect for the whole group of NSCLC patients (i.e., squamous and non-squamous histologies). I do not recall any prior data on ORR for only squamous histology. However, even a minor response, or stable disease, can indicate tumour shrinkage, which can be important in terms of the patient's symptoms.

**New Evidence:** Were there any adverse events (AEs) of concern?

**Dr. Hirsh:** The AEs seen in LUX-Lung 8 were typical of those seen with EGFR-TKIs, mainly rash, diarrhea, mucositis, and paronychia. Patients on afatinib had slightly more diarrhea compared with patients on erlotinib, who had slightly more grade 3 rash. Rash and diarrhea are both manageable with patient education and early, aggressive intervention.

In the first six weeks of treatment, you must be very proactive in managing toxicities. If you get them under control early, then patients generally do not have any problems during the rest of their treatment. A mistake inexperienced oncologists make is to wait too long before treating AEs; for example, allowing a rash to become grade 3 or 4 before treating it. Afatinib is an easy treatment to give if patients and oncologists are educated and proactive in treating the AEs.

In LUX-Lung 8, it is very important to point out that even with a slightly higher incidence of grade 3 diarrhea, QoL was better on afatinib.

**New Evidence:** Baseline symptom scores for cough, dyspnea, and pain were low in both arms of the study and mean baseline GHS/QoL scores were approximately 60. Are these baseline scores typical of patients that you see in your practice?

**Dr. Hirsh:** When baseline symptom scores are low, as they were in LUX-Lung 8, the patients are in really good shape. Sometimes we see patients in our practice with baseline scores similar to those in LUX-Lung 8; however, these scores are not typical of those in our practice. Low scores in clinical trials are generally due to the eligibility criteria requiring good performance status. In our practice, patients with a poorer performance status who do not go into clinical trials might have higher baseline symptom scores yet still want to be treated. If a patient is very frail, then you may not want to use afatinib. However, if a patient has some cough, dyspnea, and pain, it is important to give them an effective drug that will improve their symptoms. From the results of the LUX-Lung 8 trial, symptom improvement was better on afatinib than erlotinib.

**New Evidence:** What were the strengths and weaknesses of this study?

**Dr. Hirsh:** LUX-Lung 8 was the largest prospective, randomized, second-line trial of patients with SCC of the lung. It had an independent review, PFS is reliable as the primary endpoint, and the results showed significance in both PFS and OS, in spite of other lines of treatment and the use of different EGFR-TKIs after the trial. Another strength of the trial was the improved QoL results for patients on afatinib compared with those on erlotinib. These results support the benefits of PFS and time to progression because better efficacy caused better QoL for patients in the afatinib arm, which is very important for these patients.

One weakness of the study was in the evaluation of pain. Improvement in pain symptoms was similar in the two treatment arms. However, the consumption of analgesics was not reported in the study results, making it difficult to
know if patients in one arm increased their consumption during the trial compared with the other arm.

**New Evidence:** Will the results of this study impact your clinical practice and the practice of other oncologists in Canada?

**Dr. Hirsh:** I believe the results of this study will impact practice. Afatinib had an efficacy advantage over erlotinib, and, once afatinib is reimbursed in Quebec, it should be used instead of erlotinib in second-line treatment of patients with lung SCC, as long as the patient does not have a history of intestinal problems or diarrhea. In second-line, afatinib does have competition from nivolumab, although the eligibility criteria are different for immunotherapy (e.g., no colitis, no autoimmune disease, etc.). In addition, some patients want an oral agent in second-line rather than another intravenous therapy. It is important to make the decision of which agent to use in second-line based on what is best for each patient.

Eventually, I think nivolumab will be used in first-line therapy in this patient population; first-line trials are ongoing. When patients progress after nivolumab, then afatinib would be the treatment of choice in the second line, making it even more important in the treatment of lung SCC in the future.

**New Evidence:** In your opinion, where do you think treatment of SCC of the lung is headed in the coming years in Canada?

**Dr. Hirsh:** We need phase III trials that combine immunotherapy with targeted agents, such as an EGFR-TKI, to increase response rates, PFS, and OS. I think the future will be in those treatment combinations.

References:

**General Overview**

**Targeting the target: second-line treatment of SCC of the lung**

Squamous cell carcinoma (SCC) makes up approximately one quarter of all cases of non-small-cell lung cancer (NSCLC). While most of the progress in the treatment of NSCLC has been made in nonsquamous histology — particularly in adenocarcinoma — recent advances have been made in the treatment of SCC of the lung. For second-line treatment in this patient population, results from three phase III trials have recently been presented. One trial investigated the use of epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR TKIs) and the other two trials investigated therapy with monoclonal antibodies.

The LUX-Lung 8 trial compared two EGFR TKIs: erlotinib and afatinib. Erlotinib is a reversible, EGFR inhibitor, whereas afatinib is an irreversible, ErbB family blocker. Compared with erlotinib, afatinib was clearly the more effective EGFR TKI in squamous cell carcinoma: median progression-free survival (PFS), median overall survival (OS), and overall response rate (ORR) were all higher in the afatinib arm (Table 1).
Of note, the drug-related fatal adverse events in the afatinib arm were a smaller fraction of the ORR compared with the erlotinib arm (1.5% and 5.5% vs. 1.3% and 2.8%, respectively). Appropriately, the author’s key conclusion from this study was that afatinib should be the EGFR TKI of choice in second-line treatment of patients with SCC of the lung. The question is: should the drug of choice for patients with squamous cell lung cancers be an EGFR TKI?

An alternative to EGFR TKIs is immunotherapy, which has also been investigated for the second-line treatment of SCC of the lung. Results of two phase III clinical trials have been recently presented: CheckMate 017 and REVEL. The CheckMate 017 trial compared nivolumab — a monoclonal antibody against the programmed cell death protein-1 (PD-1) — with the current second-line standard of care, docetaxel. The REVEL trial investigated the use of ramucirumab — a monoclonal antibody that targets the extracellular domain of VEGFR-2 — in combination with docetaxel compared with docetaxel monotherapy. The REVEL trial included patients with either squamous or nonsquamous NSCLC.

The results of the CheckMate 017 trial showed a higher response rate and longer median PFS and OS in patients treated with nivolumab compared with those treated with docetaxel (Table 1). Similarly, for patients with squamous histology in the REVEL trial, immunotherapy was more effective than docetaxel in response rate, median PFS, and median OS (Table 1).

Looking at the data from all three clinical trials, the EGFR TKIs had inferior results for treatment of SCC of the lung (Table 1). While afatinib may be the EGFR TKI of choice for patients with squamous histology, an EGFR TKI is not necessarily the drug of choice for this patient population.

**Table 1. Results from recent phase III trials in squamous cell lung cancer**

<table>
<thead>
<tr>
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<th>Response rate (%)</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
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<tr>
<td>LUX-Lung 8*</td>
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<td></td>
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<tr>
<td>Afatinib</td>
<td>6</td>
<td>2.7</td>
<td>7.9</td>
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<tr>
<td>Erlotinib</td>
<td>3</td>
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<tr>
<td>CheckMate 017†</td>
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<tr>
<td>Nivolumab</td>
<td>20</td>
<td>3.5</td>
<td>9.2</td>
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<td>Docetaxel</td>
<td>9</td>
<td>2.8</td>
<td>6.0</td>
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<tr>
<td>REVEL‡ (squamous only)</td>
<td></td>
<td></td>
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<tr>
<td>Ramucirumab + Docetaxel</td>
<td>27</td>
<td>4.2</td>
<td>9.5</td>
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<tr>
<td>Docetaxel</td>
<td>11</td>
<td>2.7</td>
<td>8.2</td>
</tr>
</tbody>
</table>

mOS = median overall survival; mPFS = median progression-free survival

† Spigel DR, et al. ASCO 2015:8009.

Indications and clinical use:

- 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.

Safety and effectiveness in patients <18 years of age have not been established.

Contraindications:

- TREANDA is contraindicated in patients who are hypersensitive to mannitol.

Most serious warnings and precautions:

- Myelosuppression: Patients treated with TREANDA are likely to experience myelosuppression. In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb) and neutrophils closely

- Infections, including fatalities: TREANDA should not be used in patients with serious infections, including patients with HIV. CMV testing should be considered in patients with fever of unknown origin

- Second malignancies: Pre-malignant and malignant diseases have developed in patients treated with TREANDA including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma.

Other relevant warnings and precautions:

- TREANDA is not recommended for a subset of relapsed indolent NHL patients with poor tolerance to prior therapies as they would not be expected to tolerate the 120 mg/m² dose on days 1 and 2 of a 21-day cycle.

- Risk of extravasation

- Cardiac disorders have been reported

- Risk of ECG changes, including QTc prolongation

- Risk of hypertension

- Risk of tumor lysis syndrome

- Risk of increase in liver enzymes and bilirubin levels

- The use of live attenuated vaccines should be avoided

- Risk of infusion reactions and anaphylaxis

- Potential risk to reproductive capacity

- Risk of skin reactions. One case of toxic epidermal necrolysis (TEN) was reported when TREANDA 90 mg/m² was used with rituximab. Cases of Stevens-Johnson syndrome (SJS) and TEN have been reported when TREANDA was administered with allopurinol

- Not recommended during pregnancy or breast-feeding

- Women and men of childbearing potential should use effective contraception from 2 weeks before and until at least 4 weeks after the last dose of TREANDA

- Use with caution in patients with CrCl of 40-80 mL/min; do not use when CrCl < 40 mL/min

- Use with caution in patients with mild hepatic impairment, do not use if hepatic impairment is moderate or severe

- Monitor/test for complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function, electrolytes, blood pressure and hepatitis B virus prior to treatment

- Monitor/test for CBC, electrolytes, signs of infection, ECG in patients with cardiac disorders, particularly if electrolyte imbalances, renal and liver function, and blood sugar during treatment

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