Unraveling Treatment
Linking Patients to Optimal Therapy

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New Evidence in Oncology is a publication that provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian Perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice. In addition, the Investigator Commentary sections provide information on key clinical studies from interviews with principal investigators. New Evidence also publishes discussion and expert opinion papers on timely topics of interest to oncologists in Canada.

Our September 2014 issue presents coverage from the following key conferences: the 6th Annual Canadian Conference on Lymphoproliferative Disorders (CCOLD), the 19th Congress of the European Hematology Association (EHA), and the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO). This issue reports on key clinical trials evaluating the treatment of chronic lymphocytic leukemia, acute promyelocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma as well as lung, head and neck, and colorectal cancers. The development of new therapies, combined with a deeper understanding of disease biology, has increased the number of available treatment options and allowed patient care to become more individualized.

We would like to thank Dr. David MacDonald, Dr. Carolyn Owen, and Dr. Jeffrey Rothenstein for their Canadian Perspectives and Dr. Tom Kouroukis and Dr. Stephan Stilgenbauer for their Investigator Commentaries. We would also like to thank Dr. Dietger Niederwieser and Dr. Laurie Sehn for their Expert Commentaries and Dr. Barbara Melosky for her case study.

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

Canadian Perspectives

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

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Investigator Commentaries

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C. Tom Kouroukis, MD

Dr. Tom Kouroukis graduated from the University of Toronto and completed training in internal medicine and hematology, and M.Sc. training at McGill and McMaster Universities. He was awarded a National Cancer Institute of Canada Clinical Research Fellowship.

Dr. Kouroukis is a hematologist at the Juravinski Cancer Centre/Hamilton Health Sciences and Associate Professor in the Department of Oncology. He is the Provincial Hematology Disease Site Team Lead, Co-Chair of the Hematology Cancer Disease Site group of the Cancer Care Ontario Practice Guidelines Initiative, and Chair of the Stem Cell Transplant Committee for Cancer Care Ontario. His research interests include the care of older patients with hematological cancers, the impact and evaluation of comorbidity in older cancer patients, and practice guideline development.
Expert Commentaries

**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.

**Dietger Niederwieser, MD**

Dr. Dietger Niederwieser is the Head of the Department of Hematology and Oncology at the University Hospital of Leipzig in Germany. He completed his medical degree and postgraduate training in internal medicine and hemato-oncology at the University of Innsbruck in Austria. His research interests include leukemia, myelodysplastic syndrome, renal cell carcinoma, Hodgkin lymphoma, allogeneic stem cell transplantation, and graft versus host disease and he is currently involved in a variety of clinical trials in these areas.

Dr. Niederwieser is President of the Worldwide Network for Blood and Marrow Transplantation, past President of the European Group for Bone and Marrow Transplantation (EBMT), and a former Chair of the EBMT Chronic Leukemia Working Party. He is a member of several scientific societies, including the European Hematology Association, the American Society of Hematology, and the American Society of Clinical Oncology and he serves as an external reviewer for universities in Europe and the United States. Dr. Niederwieser is the author or co-author of numerous articles (<390) published in international peer-reviewed journals, such as The New England Journal of Medicine, Blood, the Journal of Clinical Oncology, the Journal of the American Medical Association, Nature Clinical Practice Oncology, Annals of Oncology, Leukemia, and Bone Marrow Transplantation.

Case Study

**Barbara Melosky, MD, FRCP(C)**

Dr. Barbara Melosky is a Clinical Associate Professor of Medicine at the University of British Columbia and a medical oncologist at the British Columbia Cancer Agency in Vancouver. She graduated from medical school at the University of Manitoba, and did a residency in internal medicine and an oncology fellowship at the University of British Columbia. Dr. Melosky is currently working in the fields of lung and gastrointestinal malignancies with a special interest in the side effects of targeted therapy. She sits on the Executive Committee for the Lung Disease Site NCIC Clinical Trials Group and is the annual Chair of the Canadian Lung Cancer Conference.
In the treatment of many cancers, a common concern is the development of a therapeutic regimen that will achieve high efficacy with minimal toxicities. In chronic lymphocytic leukemia (CLL), the standard therapy for young, fit patients is fludarabine, cyclophosphamide, and rituximab (FCR), which achieves high response rates in patients with CLL at the expense of significant toxicities. For this reason, FCR may not be a suitable option for unfit patients with CLL who have short response duration to initial therapy, are elderly, or are positive for high-risk prognostic factors such as del(17p). Less-aggressive treatment options for these unfit subpopulations of patients are currently available, while other up-and-coming agents have shown promising results in clinical trials.

The treatment regimen of bendamustine plus rituximab (BR) is a combination of a DNA alkylating agent and an anti-CD20 monoclonal antibody, respectively. It is increasingly being used as an alternative to FCR to treat elderly patients with CLL. A new generation of anti-CD20 antibodies (e.g., obinutuzumab, ofatumumab) along with several targeted therapies against phosphatidylinositol 3-kinase (e.g., idelalisib), Bruton’s tyrosine kinase (e.g., ibrutinib), and the anti-apoptotic protein BCL-2 (e.g., ABT-199) are currently being investigated in clinical trials, many of which were presented at the 19th Congress of the European Hematology Association (EHA) in Milan, Italy.

In acute promyelocytic leukemia (APL), the standard therapy of ATRA and an anthracycline leads to cure rates of up to 80% in patients, but hematological toxicity is a problem. Recent trials investigating ATRA in combination with arsenic trioxide (ATO) confirm its non-inferiority to standard care while patients benefit from its reduced toxicity. New treatment guidelines for APL and analysis on ATRA plus ATO treatment were among the abstracts presented at EHA 2014.

The following provides a summary of results from 17 presentations covered at the 2014 EHA Congress:

- An interim analysis on safety in the CLL10 trial, comparing FCR with BR as first-line therapy, found that severe infections occurred more frequently in CLL patients treated with FCR compared to those treated with BR.
- Retrospective analysis of the efficacy and safety of BR in real-world treatment of elderly patients with CLL revealed that this treatment had high response rates and a good safety profile in the population studied.
- Another retrospective analysis of BR in the real-world treatment of previously untreated CLL patients also found that this regimen resulted in high complete response (CR) rates and low toxicity in this population of patients.
- The Be-CeLL1st trial, which is a non-interventional trial currently assessing the efficacy and safety of bendamustine in clinical practice in Germany, has confirmed in the first interim analysis that bendamustine with or without rituximab treatment is safe and effective for patients with CLL.
- An Italian multicentre study of the safety and efficacy of BR as first- or second-line therapy in elderly patients with CLL confirmed that this regimen was effective in the selected population and hematological toxicity was manageable.
- The evaluation of bendamustine, ofatumumab, and high-dose methylprednisolone (BOMP) as salvage treatment for high-risk patients with relapsed/refractory CLL found that the overall response rate (ORR) and CR of patients was comparable to previous trials assessing bendamustine plus rituximab or ofatumumab.
• The second interim analysis of Study 116 by Coutre et al. confirmed that idelalisib plus rituximab improved the ORR and overall survival (OS) as well as progression-free survival (PFS) in patients with CLL, including those with high-risk genetic markers.

• In the first interim analysis of a randomized, double-blind, placebo-controlled trial evaluating idelalisib in combination with rituximab in the treatment of patients with relapsed CLL (Study 116), idelalisib plus rituximab demonstrated robust efficacy in high-risk CLL subpopulations harbouring del(17p) and other adverse risk factors.

• Exploratory analysis of data from Study 116 by Hillmen et al. identified a protective effect of idelalisib on infusion-related reactions (IRRs) after rituximab treatment, indicating that idelalisib can enhance safety in relation to IRRs in addition to increasing efficacy.

• Prospective analysis of Study 116 by Ghia et al. found that treatment with idelalisib plus rituximab compared to rituximab plus placebo resulted in a significant decrease in levels of the chemokines CCL3 and CCL4, whose high levels have been associated with decreased PFS in patients with CLL.

• Evaluation of the health-related quality of life (HRQoL) in patients with relapsed CLL was also performed in Study 116 and results from Eradat et al. indicate statistically and clinically significant improvements in leukemia-related symptoms and well-being after treatment with idelalisib plus rituximab.

• A phase Ib dose-escalation trial evaluating the safety profile and maximum tolerated dose of ABT-199 in combination with rituximab revealed that ABT-199 plus rituximab is well tolerated and demonstrates high anti-tumour activity in patients with CLL.

• The incidence and impact of the SF3B1 mutation in CLL patients from the Complement 1 trial was assessed, and although the mutation was associated with high white blood cell count and the absence of NOTCH1 mutations, it had no impact on response to treatment and was only a moderate prognostic factor for PFS.

• Results from a randomized phase III trial comparing ofatumumab with ibrutinib as monotherapy in patients with relapsed/refractory CLL/small lymphocytic lymphoma (SLL) showed increases in PFS, OS, and response in the ibrutinib treatment arm.

• A phase II trial evaluating the efficacy of ibrutinib in risk-stratified patients with relapsed/refractory CLL/SLL reported a significant difference in ORR between patients with and without the chromosome 17 deletion, although a lower best ORR was observed compared to previous phase II trials.

• A new algorithm for managing patients with APL was created to improve OS based on a retrospective review of charts, and its implementation was successful in decreasing the number of early induction deaths.

• In the secondary analysis of HRQoL in APL patients from the Lo-Coco et al. trial, ATRA plus ATO resulted in clinically relevant improvement in treatment-related symptoms post-induction therapy compared to ATRA plus chemotherapy.


Langerbeins P et al. EHA 2014:P237

Severe infections are more common in physically fit CLL patients with FCR-therapy compared to bendamustine plus rituximab

Background

Infections are a common complication in patients with CLL who are receiving chemoimmunotherapy, which greatly impacts the course of disease. The combination regimen of fludarabine, cyclophosphamide, and rituximab (FCR) is associated with a higher risk of infection compared to bendamustine plus rituximab (BR) as first-line therapy.1

This analysis prospectively assessed the frequency, characteristics, and risk factors of infections in physically fit CLL patients receiving FCR or BR as first-line therapy.

Study design

• This was a prospective evaluation of the data on incidence of infection gathered from the multicentre phase III CLL10 trial comparing FCR and BR as first-line therapy in patients with CLL.
• Patients in this study were physically fit, negative for del(17p), and had previously untreated, active CLL.
• Of the 561 patients enrolled in this study, 282 were randomised to the FCR arm and 279 were randomized to the BR arm.
• The protocol did not recommend routine anti-infective prophylaxis during and after chemoimmunotherapy except for PCJ-prophylaxis in long lasting neutropenia.

Key findings
• Of the 561 patients studied, 395 (70.4%) patients developed a total of 1,032 infections, with an average of 2.6 infections occurring per patient.
• High-grade (grade 3–5) infections and pneumonia occurred more frequently in the FCR arm (51.4% vs. 38.8%, \(p = 0.012\); 11.5% vs. 6.1%, \(p = 0.027\), respectively). (Table 1)
• The most frequent infections reported in all patients were:
  ◦ Fever of unknown origin (13.9%);
  ◦ Pneumonia (8.9%); and
  ◦ Urinary tract infection (4.6%).
• The causative pathogens were classified as bacterial in 15.7%, viral in 14.8%, fungal in 2.0%, and other in 2.3% of reported infections in all patients. (Table 2)
  ◦ The pathogen was unknown in 66.8% of infections.
  ◦ No significant difference in pathogen classification was observed between treatment arms.
• Of the 767 treated infections, antibiotics were administered in 76.1%, antivirals in 15.3%, and antifungals in 4.6%. (Table 3)
• Both granulocyte colony-stimulating factor (G-CSF) and red blood cell transfusion treatment were significantly more frequent in the FCR arm compared to the BR arm (6.2% vs. 2.0%, \(p = 0.001\); 4.0% vs. 1.5%, \(p = 0.017\), respectively). (Table 3)
• The median onset of infection was 4.6 months and 5.0 months in the FCR arm and BR arm, respectively.
• A total of 11 patients died from infection-related complications with no difference in the frequency of deaths observed between treatment arms.

![Study design Diagram](image)

**Study design**

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤6, creatinine clearance ≥70 mL/min)

N = 561

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 (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

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**Table 1. Infections per patient**

<table>
<thead>
<tr>
<th>AE</th>
<th>Total, n (%)</th>
<th>FCR, n (%)</th>
<th>BR, n (%)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>395 (70.4)</td>
<td>210 (74.5)</td>
<td>185 (66.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>Grades 3–5</td>
<td>179 (45.5)</td>
<td>108 (51.4)</td>
<td>71 (38.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>70 (12.6)</td>
<td>41 (14.7)</td>
<td>29 (10.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Grades 3–5</td>
<td>49 (8.8)</td>
<td>32 (11.5)</td>
<td>17 (6.1)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

\(AE = \) adverse event; \(BR = \) bendamustine, rituximab; \(FCR = \) fludarabine, cyclophosphamide, rituximab; \(n.s. = \) not significant

**Table 2. Causative pathogens**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Total, n (%)</th>
<th>FCR, n (%)</th>
<th>BR, n (%)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>162 (15.7)</td>
<td>98 (9.5)</td>
<td>64 (6.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Viral</td>
<td>153 (14.8)</td>
<td>87 (8.4)</td>
<td>66 (6.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fungal</td>
<td>21 (2.0)</td>
<td>14 (1.4)</td>
<td>7 (0.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Unknown</td>
<td>69 (6.8)</td>
<td>394 (38.1)</td>
<td>297 (28.7)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

\(BR = \) bendamustine, rituximab; \(FCR = \) fludarabine, cyclophosphamide, rituximab; \(n.s. = \) not significant
### Table 3. Management of infections

<table>
<thead>
<tr>
<th></th>
<th>Total, n (%)</th>
<th>FCR, n (%)</th>
<th>BR, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>767 (75.3)</td>
<td>459 (78.5)</td>
<td>308 (71.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>583 (76.1)</td>
<td>346 (45.2)</td>
<td>237 (30.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Antiviral</td>
<td>117 (15.3)</td>
<td>75 (9.8)</td>
<td>42 (5.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Antifungal</td>
<td>35 (4.6)</td>
<td>25 (3.3)</td>
<td>10 (1.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>125 (16.3)</td>
<td>82 (10.7)</td>
<td>43 (5.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>G-CSF</td>
<td>85 (8.3)</td>
<td>64 (6.2)</td>
<td>21 (2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>85 (8.3)</td>
<td>47 (4.6)</td>
<td>38 (3.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Red blood cell transfusion</td>
<td>56 (5.4)</td>
<td>41 (4.0)</td>
<td>15 (1.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>16 (1.6)</td>
<td>13 (1.3)</td>
<td>3 (0.3)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab; G-CSF = granulocyte colony-stimulating factor; n.s. = not significant

### Key conclusions

- Patients with CLL who are treated with either FCR or BR have an increased risk of infection, although infections were more frequent and severe when patients were treated with FCR.
- The causative pathogen of infection is rarely detected in patients.
- Anti-infective prophylaxis in neutropenic patients during first-line chemoimmunotherapy is strongly recommended.


Laurenti L et al. EHA 2014:P875

**Efficacy and safety of bendamustine in combination with rituximab for elderly patients with previously untreated B-cell CLL — an Italian, retrospective, multicentre study**

**Background**

Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) is the front-line therapy for young patients with chronic lymphocytic leukemia (CLL), but high toxicities from this treatment make it an inappropriate choice for elderly or unfit patients. Bendamustine plus rituximab (BR) has been demonstrated to be a safe and effective front-line therapy for unfit and elderly patients.1

The objective of this retrospective study was to evaluate the efficacy and tolerability of BR in elderly patients with CLL, in real-world clinical practice.

**Study design**

- This was a retrospective study evaluating elderly patients with CLL from 12 Italian centres, who received treatment between November 2000 and December 2013.
  - Data were collected from 70 patients who met the following criteria:
    - ≥65 years old;
    - Were previously untreated; and
    - Assigned up to six 28-day treatment cycles of bendamustine (90 mg/m² for 2 consecutive days) plus rituximab (375 mg/m² for cycle 1, 500 mg/m² for subsequent cycles).
  - The primary endpoints were overall response rate (ORR) and hematologic or non-hematologic adverse events (AEs).
Key findings

- A total of 47 males and 23 females with a median age of 72 years (range, 65–87 years) were included in the study.
- All patients had an Eastern Cooperative Oncology Group (ECOG) performance status <2.
- Cumulative Illness Rating Scale (CIRS) score ≥7 was identified in 8 patients.
- FISH analysis was performed in 54 out of 70 patients:
  - 27.8% had a normal karyotype;
  - 18.5% had del(13q);
  - 22.2% had +12;
  - 25.9% had del(11q); and
  - 5.6% had del(17p).
- A mean number of 5.46 courses of BR was given.
- The ORR was 88.6% (31.4% showed complete response, 57.2% showed partial response)
- Gender, age, Binet stage, fitness status, lymphocyte counts, del(11q), and IgHV status did not show any impact on response and time-dependent variables.
- Only the presence of del(17p) had a negative impact in terms of ORR ($p = 0.023$) and progression free-survival (PFS) ($p <0.001$).
- PFS and overall survival at 2 years were 79% and 89.6%, respectively.
- Findings related to patient tolerability included:
  - Identification of grade 3/4 hematologic AEs in 25 patients;
  - Identification of grade 1–3 non-hematologic AEs in 35 patients;
  - Dose reduction of bendamustine by >10% occurring in 39 patients; and
  - Hospital admission occurring in 11 patients. (Table 1)

<table>
<thead>
<tr>
<th>Table 1. Patient tolerability to BR treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>Bendamustine dose reduction &gt;10%</td>
</tr>
<tr>
<td>Grade 3/4 hematologic AEs</td>
</tr>
<tr>
<td>Grade 1–3 non-hematologic AEs</td>
</tr>
<tr>
<td>Admission to hospital</td>
</tr>
</tbody>
</table>

AEs = adverse events; BR = bendamustine, rituximab

Key conclusion

The results of this study indicate that BR as first-line therapy demonstrates high response rates and a good safety profile in this group of elderly patients with CLL.


Gentile M et al. EHA 2014:PB1503

Bendamustine in combination with rituximab as first-line therapy for patients with CLL — real-world clinical practice reviewed in an Italian, retrospective, multicentre study

Background

In recent clinical studies, the combination of bendamustine plus rituximab (BR) has produced promising results in the treatment of relapsed/refractory and previously untreated CLL. The objective of this retrospective study was to assess the real-world safety and efficacy of BR in patients with previously untreated CLL.¹

Key findings

- The median age of patients included in the analysis was 71 years (range, 43–85 years).
- Of the 118 patients included in analysis:
  - All had active disease as per National Cancer Institute-Working Group (NCI-WG) criteria;
  - 51% were male;
Key conclusion

- **Chemoimmunotherapy with BR is effective, producing high CR rates, and well-tolerated in untreated CLL patients in real-world clinical practice.**


Bruch H-R et al. EHA 2014:PB1504

**Bendamustine-based first-line therapy in CLL in routine clinical practice — interim analysis of the German non-interventional study Be-CeLL1st**

**Background**

Bendamustine is an established treatment option for chronic lymphocytic leukemia (CLL) and is frequently used in daily practice in Germany. Be-CeLL1st is a non-interventional trial that is currently being conducted to gain insight into the treatment modalities, efficacy, and safety of bendamustine-based therapy in clinical practice in Germany.¹

**Study design**

- A total of 400 patients with B-CLL are to be enrolled over a period of 43 months at approximately 70 study centres in Germany.

- Patient response was analyzed in 93 evaluable cases.
  - CR was reported in 69% of patients, PR was reported in 27%, and 4% had stable disease.

- In the analysis of clinical and biological parameters only, the following parameters were associated with achievement of CR:
  - Age <70 years ($p <0.0001$);
  - White blood cell count $<50 \times 10^9/L$ ($p = 0.038$); and
  - Creatinine clearance $>70 \text{ mL/min}$ ($p <0.0001$).

- After a median follow-up of 8 months, 2-year progression-free survival and overall survival were 87% and 80%, respectively.

- Of the 10 deaths that occurred, 5 were CLL-related (infections in four cases and disease progression in one case).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>19 (16.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>32 (27.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (16.1)</td>
</tr>
<tr>
<td>Severe infection</td>
<td>8 (6.8)</td>
</tr>
</tbody>
</table>

Table 1. Grade 3/4 adverse events

- Of the 78 cases with FISH data available, del(17p) and del(11q) were identified in 6.4% and 10.3% of patients, respectively.
- All patients received treatment on a 28-day cycle, with a dose of bendamustine given on days 1 and 2 plus a dose of rituximab given on day 1.
- The median number of treatment cycles administered per patient was four.
- Bendamustine was given at a dose of 90 mg/m² in 68% of patients, and at a dose of 70 or 80 mg/m² in 32% of patients.
- Rituximab was given at a dose of 375 mg/m² for all cycles in 59% of patients and 41% of patients received a dose of 375 mg/m² in the first cycle, followed by 500 mg/m² in subsequent cycles.
- Early discontinuation occurred in 13 patients due to serious infections ($n = 6$), persistent hematological toxicity ($n = 3$), grade 4 dermatological toxicity ($n = 2$), and withdrawal of consent ($n = 2$).
- Grade 3/4 AEs reported included:
  - Neutropenia (16.1%);
The main criteria for trial entry are:
- Indication for first-line therapy with bendamustine;
- No previous treatment with interferon or rituximab;
- Inappropriate candidate for fludarabine-based therapy; and
- Absence of contraindications.

Patient demographics, tumour characteristics, treatment modalities, side effects, and investigator-assessed response will be recorded.

Interim results of more than 200 patients were included in the current analysis.

Key findings
- A total of 264 patients were registered between October 2011 and December 2013.
- Analysis of treatment modalities and efficacy data included 202 patients who were enrolled at least 6 months before the data cut-off.
- Analysis of safety data included 253 patients with at least one treatment cycle administered.
- The median age of patients was 73 years (range, 32–90 years), with 63% of patients aged 70 years or older. (Figure 1)
- Of the patients analyzed:
  - All had an Eastern Cooperative Oncology Group performance status of 1;
  - 65% were male;
  - 26% presented with B-symptoms; and
  - 87% had a Cumulative Illness Rating Scale score ≤6.

- The tumours were staged as 21% Binet A, 44% Binet B, and 31% Binet C.
- The majority of patients were treated with a combination of bendamustine and rituximab (90%), with 3% of these patients additionally receiving steroids.
- Bendamustine monotherapy was administered to 7% of patients and 3% of patients received other combinations of therapy.
- Bendamustine was given on days 1 and 2 per cycle to 83% of patients, and 10% of patients received it only once per cycle.
- The median number of treatment cycles given for bendamustine combination therapy was 6 (bendamustine monotherapy: median 3 cycles), the median dose of bendamustine per cycle was 174 mg/m², and the median dose intensity per week was 38 mg/m².
- Therapy modification most frequently occurred due to adverse events (AEs) and comorbidities.
  - These modifications included dose modification in 36% of patients and at least one therapy delay in 45% of patients.
- A total of 313 AEs (all grades) were reported in 124 patients (49%), with neutropenia or leukopenia being the most common AEs observed (25%).
- A total of 61 grade 3/4 AEs occurred in 14% of patients, and serious adverse reactions occurred in 10% of patients, with one death occurring due to sepsis.
- The investigator-assessed overall response rate for 158 evaluable patients was 89%.
  - Complete response was 38.6%, partial response 50.6%, stable disease 7.6%, and progressive disease 3.2%. (Figure 2)
Key conclusions

- The interim data of this study demonstrates that bendamustine (± rituximab) is an effective and safe treatment for patients with B-CLL in daily clinical practice.

- Study of this non-selected patient population supports the broad applicability of bendamustine (± rituximab) as first-line therapy for patients with CLL.

- The efficacy and safety data from this analysis are in line with previous clinical trials.


Gozzetti A et al. EHA 2014:PB1529

Bendamustine plus rituximab as first- or second-line therapy in elderly patients with CLL

Background

A combination of fludarabine, cyclophosphamide, and rituximab (FCR) is the current standard therapy for young, fit patients with chronic lymphocytic leukemia (CLL), but is inappropriate for elderly patients due to unacceptable myelotoxicity and increased risk of infection.

The objective of this study was to evaluate the safety and efficacy of bendamustine plus rituximab (BR) as first- or second-line therapy in elderly patients with CLL.1

Study design

- This study analyzed elderly patients from three centres in Tuscany, Italy.
- Patients were treated with a combination of:
  - Rituximab at a dose of 375 mg/m² on day 3 of the first cycle and at 500 mg/m² on day 1 of subsequent cycles; and
  - Bendamustine at a dose of 70 mg/m² on day 1 and day 2 of the first cycle, and days 2 and 3 of subsequent cycles.
- Antibiotic prophylaxis was given on day 1 through day 10 of each cycle.
- Biological prognostic factors assessed included IgHV mutational status, ZAP-70 and CD38 levels, and presence of trisomy 12, del(11q), del(13q), and del(17p).

Key findings

- Of the 26 patients studied, nine were treated at diagnosis and 17 were treated at first relapse.
- The median age of patients was 72 years (range, 67–80 years).
- The median number of treatment cycles was 6 and the median follow-up was 18 months.
- The overall response rate was 84% with 23% achieving complete response and 61% achieving partial response.
- Median progression-free survival (PFS) was not reached in patients treated at time of diagnosis and was 17 months in patients treated at first relapse.
- Presence of del(11q), del(13q), and trisomy 12 had no impact on PFS or response.
- Patients with del(17p) or unmutated IgHV had poorer responses.
- Grade 3/4 hematologic toxicities occurred in 10 patients (38%) and grade 1/2 hematologic toxicities occurred in 7 patients (27%).
- Non-hematologic toxicities were mild and included grade 1 gastrointestinal adverse events (AEs) in 19 patients (73%) and grade 1 cutaneous AEs in 5 patients (19%).
- Four patients developed pneumonia.
**Key conclusions**

- The results of this study demonstrate that BR is an effective therapy in a selected elderly population of patients with CLL.
- Hematological toxicity is the most important toxicity observed, but is manageable with growth factors and antibiotic prophylaxis.


**Salvage treatment with bendamustine, ofatumumab, and high-dose methylprednisolone (BOMP) in high-risk relapsed/refractory CLL — interim results of the ICLL01 phase II trial**

**Background**

A number of agents have produced promising results in the treatment of poor prognosis patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL). Bendamustine in combination with rituximab (BR) and ofatumumab monotherapy have shown overall response rates (ORR) of 59% and 58%, respectively, in previous clinical trials. High doses of methylprednisolone (HDMP) have also been used in poor prognosis patients with bulky nodal involvement or p53 impairment.

Based on these results, the objective of this study was to evaluate the efficacy and toxicity of a combination of bendamustine, ofatumumab, and HDMP (BOMP) in the treatment of fit patients with R/R CLL. 1

**Study design**

- This was a planned interim analysis of the ICLL01 phase II trial evaluating the efficacy and toxicity of BOMP.
- The main inclusion criteria for patients on this study were:
  - R/R CLL with active disease as per the International Workshop for CLL 2008 criteria;
  - Previous receipt of 1–3 lines of treatment;
  - Previous receipt of at least one line of fludarabine treatment and/or presence of del(17p)/TP53 mutation; and
  - Generally fit condition (Eastern Cooperative Oncology Group performance status ≤2, Cumulative Illness Rating Scale score ≤6, creatinine clearance >40 mL/min).
  - Intravenous (iv) doses of ofatumumab (300 mg) and HDMP (100 mg/m²) were given 8 days prior to treatment with BOMP.
  - Six monthly courses of BOMP iv were to be administered, which included:
    - Bendamustine at 70 mg/m² on days 2 and 3;
    - Ofatumumab at 1,000 mg total dose on day 1 of all courses and day 15 of the first and second course only; and
    - HDMP at 1,000 mg/m² on days 1, 2, and 3 of all courses and day 15 of the first and second course only.
  - The primary objective was complete response (CR).
- Secondary objectives included:
  - ORR, partial response (PR), and minimal residual disease (MRD);
  - Progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT);
  - Safety; and
  - Exhaustive TP53 assessment.
- Statistical analysis was planned to answer the question: Does the BOMP regimen lead to a 10% improvement in CR rate compared to the results of the phase II CLL2M trial (bendamustine + rituximab) CR rate of 9%?
**Key conclusions**

- The results of this study demonstrate that BR is an effective therapy in a selected elderly population of patients with CLL.
- Hematological toxicity is the most important toxicity observed, but is manageable with growth factors and antibiotic prophylaxis.

**Key findings**

- Data from the first 55 patients enrolled, between May 2013 and July 2014, were available for analysis.
- Of the 55 evaluable patients:
  - Median age was 63.8 years;
  - Median number of previous lines of treatment received was 1 (1–3);
  - 93% had previously received an FCR (fludarabine, cyclophosphamide, rituximab)-based regimen;
  - 73% had either a high risk of relapse (<2 years post FCR treatment) and/or del(17p)/TP53 mutation;
  - Unmutated IgHV was present in 90% (48/53);
  - Del(17p) was detected in 27% (15/55);
  - Del(11q) was detected in 33% (18/55);
  - Del(13q) was detected in 64% (35/55);
  - Trisomy 12 was detected in 11% (6/55); and
  - 39% (18/46) had a complex karyotype.

- In the safety analysis of 268 cycles, the most common grade 3/4 adverse events (AEs) recorded were neutropenia (41 events), thrombocytopenia (27 events), and infections (20 events). (Table 1)
  - A total of 28 severe AEs were reported in 14 patients, including febrile neutropenia (6 events) and pneumopathy (5 events). (Table 1)
  - Death occurred in seven patients due to progressive disease (4 patients), progressive multifocal leukoencephalitis (1 patient), EBV-induced lymphoproliferation (1 patient), or sepsis (1 patient).

- After a median follow-up of 340 days, 14 cases of relapse or progression were reported, including four cases of Richter syndrome.

- Among evaluable patients, ORR was 74.5% with 20% achieving CR and 54.5% achieving PR. (Table 2)

- Stable disease and progressive disease were reported in 9.1% and 10.9% of patients, respectively.
The ORR and CR from this study, which evaluated the BOMP regimen in high-risk patients with R/R CLL, compare favourably to the CLL2M (BR) and GIMEMA (bendamustine plus ofatumumab) trials. (Table 2)

There is some concern with toxicity as two of the 28 severe AEs that were recorded were consistent with severe immune suppression.

This trial is to be continued with some modifications, including restriction of inclusion criteria for the trial to only high-risk patients with previous FCR treatment and/or del(17p)/TP53 mutations and reduction of HDMP infusions from three to two injections per cycle.

Second interim analysis of a phase III study evaluating idelalisib and rituximab for relapsed CLL

Background
The oral inhibitor of PI3Kδ, idelalisib, is highly active in heavily pretreated patients with chronic lymphocytic leukemia (CLL), either as a single agent or in combination with rituximab as demonstrated in several phase I trials.

The objective of this study was to provide a second interim analysis of a phase III study comparing idelalisib plus rituximab versus placebo plus rituximab.1

Study design
• This was a phase III, randomized, double-blind, placebo-controlled study comparing CLL patients treated with placebo plus rituximab with CLL patients treated with idelalisib (150 mg twice daily) plus rituximab.
• The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall response rate (ORR), lymph node response (LNR), and overall survival (OS).

Key findings
• Baseline characteristics of all patients on the study were similar in both arms.
• A total of 220 patients were randomized (N = 110 in each arm), with a median age of 71 years and a median number of three prior therapies (range, 1–12).

Study design
• The percentage of patients with high-risk CLL genetics was well-balanced between the two arms (idelalisib plus rituximab vs. placebo plus rituximab):
  - Del(17p)/TP53mut: 42% vs. 45%;
  - Unmutated IgHV: 83% vs. 85%.
• Median PFS was improved in patients treated with idelalisib plus rituximab compared with those who received placebo plus rituximab (not reached vs. 5.5 months, respectively; HR = 0.18, p <0.0001). (Figure 1)
  - Improved PFS was also observed in CLL patients with del(17p)/TP53mut (HR = 0.16) or unmutated IgHV (HR = 0.14) treated with idelalisib plus rituximab.
• The study showed an improved ORR (77% vs. 15%; OR [odds ratio] = 17.3; p <0.0001) and LNR (92% vs. 6%; OR = 165.5; p <0.0001) in patients treated with idelalisib plus rituximab compared with placebo plus rituximab. (Table 1)
• Improved OS was shown in patients treated with idelalisib plus rituximab (HR = 0.28, p = 0.003). (Figure 2)
• Idelalisib plus rituximab demonstrated an acceptable safety profile. (Table 2)
• The most common grade ≥3 adverse events (AEs) (idelalisib plus rituximab vs. placebo plus rituximab) were:
  - Neutropenia (37% vs. 27%);
  - Thrombocytopenia (11% vs. 18%);
  - Anemia (7% vs. 17%);
  - Pneumonia (8% vs. 9%); and
  - Alanine/aspartate aminotransferases elevated (8% vs. 1%). (Table 3)
### Table 2. Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + rituximab (N = 110)</th>
<th>Placebo + rituximab (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>106 (96)</td>
<td>106 (98)</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>70 (64)</td>
<td>56 (52)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>54 (49)</td>
<td>41 (38)</td>
</tr>
<tr>
<td>AEs leading to study drug dose reduction</td>
<td>8 (7)</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to study drug discontinuation</td>
<td>11 (10)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>3 (3)</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>

*AE = adverse event*

### Table 3. Adverse events (≥10% in either study arm) and laboratory abnormalities of interest

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Idelalisib + R (N = 110)</th>
<th>Placebo + R (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any AE</td>
<td>106 (96)</td>
<td>70 (64)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>38 (35)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28 (26)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (26)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>23 (21)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>21 (19)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>IRR</td>
<td>21 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (17)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Bleeding†</td>
<td>15 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (13)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Night sweats</td>
<td>12 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (10)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (10)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (10)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>11 (10)</td>
<td>0</td>
</tr>
<tr>
<td>URTI</td>
<td>8 (7)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

#### Laboratory abnormalities of interest

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>32 (29)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>66 (60)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (19)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>ALT/AST elevation†</td>
<td>44 (40)</td>
<td>9 (8)</td>
</tr>
</tbody>
</table>

*AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; bid = twice daily; CLL = chronic lymphocytic leukemia; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; R = rituximab; URTI = upper respiratory tract infection

†Three of five patients with colitis on idelalisib plus rituximab also reported diarrhea.

¶Includes 16 preferred terms according to a standardized MedDRA query.

‡Seven of the nine patients in the idelalisib plus rituximab arm were successfully re-challenged: three patients at 150 mg bid, four at the reduced dose of 100 mg bid. One patient's transaminase elevation was associated with CLL transformation (Richter) in the liver (progressive disease).
Table 4. Serious adverse events in ≥2 patients on idelalisib plus rituximab

<table>
<thead>
<tr>
<th>SAE, n (%)</th>
<th>Idelalisib + R (N = 110)</th>
<th>Placebo + R (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any SAE</td>
<td>54 (49)</td>
<td>41 (38)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (9)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (9)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneum. jirov. pneumonia</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Colitis</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Lung infection</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Pneum. jirov = pneumocystis jirovecii; R = rituximab; SAE = serious adverse event

Key conclusions

- In patients with heavily pretreated relapsed CLL not suitable for chemotherapy, idelalisib plus rituximab demonstrated improved PFS (including in patients with del(17p)/TP53mut or unmutated IgHV), improved ORR, and improved OS.
- Idelalisib plus rituximab demonstrated an acceptable safety profile.


Stilgenbauer S et al. EHA 2014:S1341

Efficacy of idelalisib in CLL subpopulations harbouring del(17p) and other adverse prognostic factors

Background

An unmet need exists for effective therapies in patients with chronic lymphocytic leukemia (CLL) positive for del(17p) and other adverse prognostic factors. Idelalisib is a selective inhibitor of PI3Kδ, which is critical for activation, proliferation, and survival of B cells as well as their homing and retention in lymphoid tissues. The objective of this study was to assess the efficacy of idelalisib in combination with rituximab in patients with high-risk relapsed CLL.1

Study design

- Inclusion criteria were:
  - Patients who had CLL progression in less than 24 months since completion of last therapy, and were considered unfit to receive cytotoxic therapy according to the International Workshop on Chronic Lymphocytic Leukemia;
  - Patients with ≥1 measurable nodal lesion;
  - Patients whose prior therapies included ≥1 anti-CD20 antibody-containing therapy or ≥2 prior cytotoxic therapies;
  - Patients with a Cumulative Illness Rating Scale score ≥6, creatinine clearance of <60 mL/min (≥30 mL/min), or grade 3/4 neutropenia or thrombocytopenia due to prior myelotoxicity;
  - Patients with any grade anemia, thrombocytopenia, neutropenia; and
  - Patients with a Karnofsky score ≥40.
- This was a phase III, randomized, double-blind, placebo-controlled study (Study 116/117) comparing treatment with placebo plus rituximab versus idelalisib (150 mg twice daily [bid]) plus rituximab in patients with relapsed CLL.
In Supportive Care Oncology

- The primary endpoint of the trial was progression-free survival (PFS).
- The secondary endpoints were overall response rate (ORR), lymph node response (LNR), and overall survival (OS).
- Samples were collected prospectively and tested using standard methods for: del(17p), del(11q), TP53 mutation (mut), mutated immunoglobulin heavy chain (IgHV), ZAP70 and CD38 expression, and β2-microglobulin.
- Patients were stratified based on the presence of del(17p) and/or TP53mut, and on IgHV mutational status.
- After disease progression, patients could enroll into a blinded extension study to receive idelalisib at 150 mg bid (those treated with placebo plus rituximab) or 300 mg bid (those treated with idelalisib plus rituximab).
- Interim analysis was planned at 50% and 75% of total events.
- The first interim analysis (published by Furman et al., NEJM 2014) led to the decision of early termination due to overwhelming efficacy.
- Analysis on high-risk subpopulations was performed for PFS and ORR using data from the first interim analysis.

Key findings

- Baseline characteristics of high-risk patients were similar in both arms.
- In the overall high-risk patient population, idelalisib plus rituximab demonstrated high ORR (80.7%; odds ratio = 29.92), and that was comparable to the responses observed within each high-risk subpopulation. (Figure 1)
  - Patients positive for both del(17p) and TP53mut who were treated with idelalisib plus rituximab achieved an ORR of 76.5%.
  - The best percent decrease in nodal size was greater in patients treated with idelalisib plus rituximab than with placebo plus rituximab.
  - Nodal decreases were seen in patients with and without del(17p) and in patients with and without IgHV mutations.
- Overall, idelalisib plus rituximab demonstrated a more favourable PFS rate compared to placebo plus rituximab (median PFS not reached vs. 5.5 months, HR = 0.15).
  - Patients positive for both del(17p) and TP53mut who were treated with idelalisib plus rituximab achieved a median PFS that was not yet reached, with a HR of 0.13. (Figures 2 and 3)
Figure 1. Overall response rates in high-risk subpopulations

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>n</th>
<th>ORR(%)</th>
<th>Placebo + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>29.92</td>
<td>12.76, 70.11</td>
<td>88</td>
<td>80.7</td>
<td>88</td>
</tr>
<tr>
<td>Del(17p) positive*</td>
<td>NA</td>
<td>NA, NA</td>
<td>20</td>
<td>80.0</td>
<td>24</td>
</tr>
<tr>
<td>Del(17p) negative</td>
<td>21.01</td>
<td>8.46, 52.18</td>
<td>68</td>
<td>80.9</td>
<td>64</td>
</tr>
<tr>
<td>TP53 mut positive</td>
<td>41.51</td>
<td>8.12, 212.26</td>
<td>34</td>
<td>79.4</td>
<td>30</td>
</tr>
<tr>
<td>TP53 mut negative</td>
<td>23.16</td>
<td>8.57, 62.60</td>
<td>54</td>
<td>81.5</td>
<td>58</td>
</tr>
<tr>
<td>Both del(17p) and TP53 mut*</td>
<td>NA</td>
<td>NA, NA</td>
<td>17</td>
<td>76.5</td>
<td>15</td>
</tr>
<tr>
<td>Either del(17p) or TP53 mut</td>
<td>48.00</td>
<td>7.23, 318.84</td>
<td>20</td>
<td>85.0</td>
<td>24</td>
</tr>
<tr>
<td>Neither del(17p) nor TP53 mut</td>
<td>20.46</td>
<td>7.31, 57.26</td>
<td>51</td>
<td>80.4</td>
<td>49</td>
</tr>
<tr>
<td>Del(11q) positive</td>
<td>175.82</td>
<td>11.48, 2692.29</td>
<td>28</td>
<td>78.6</td>
<td>29</td>
</tr>
<tr>
<td>Del(11q) negative</td>
<td>22.03</td>
<td>8.27, 58.69</td>
<td>57</td>
<td>82.5</td>
<td>59</td>
</tr>
<tr>
<td>IgH mutated</td>
<td>62.92</td>
<td>5.79, 683.55</td>
<td>17</td>
<td>88.2</td>
<td>16</td>
</tr>
<tr>
<td>IgH unmutated</td>
<td>26.36</td>
<td>10.52, 66.06</td>
<td>71</td>
<td>78.9</td>
<td>72</td>
</tr>
<tr>
<td>ZAP70 positive</td>
<td>28.73</td>
<td>11.33, 72.85</td>
<td>77</td>
<td>79.2</td>
<td>75</td>
</tr>
<tr>
<td>ZAP70 negative</td>
<td>NA</td>
<td>NA, NA</td>
<td>8</td>
<td>100.0</td>
<td>12</td>
</tr>
<tr>
<td>CD38 positive</td>
<td>29.27</td>
<td>7.67, 111.65</td>
<td>43</td>
<td>83.7</td>
<td>34</td>
</tr>
<tr>
<td>CD38 negative</td>
<td>30.32</td>
<td>9.57, 96.09</td>
<td>44</td>
<td>77.3</td>
<td>54</td>
</tr>
<tr>
<td>β2-microglobulin ≤4 mg/L</td>
<td>21.13</td>
<td>9.24, 57.89</td>
<td>74</td>
<td>77.0</td>
<td>68</td>
</tr>
</tbody>
</table>

*No subjects in the control arm reached the overall response status of CR or PR as of the date of analysis.
†All subjects in the treatment arm reached the overall response status of CR or PR as of date of analysis.

Figure 2. Hazard ratios for progression-free survival in high-risk subpopulations

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>Median PFS (months)</th>
<th>Placebo + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.15</td>
<td>0.08, 0.28</td>
<td>110</td>
<td>NR</td>
</tr>
<tr>
<td>Del(17p) positive</td>
<td>0.14</td>
<td>0.04, 0.47</td>
<td>26</td>
<td>NR</td>
</tr>
<tr>
<td>Del(17p) negative</td>
<td>0.14</td>
<td>0.07, 0.31</td>
<td>84</td>
<td>NR</td>
</tr>
<tr>
<td>TP53 mut positive</td>
<td>0.11</td>
<td>0.04, 0.31</td>
<td>42</td>
<td>NR</td>
</tr>
<tr>
<td>TP53 mut negative</td>
<td>0.15</td>
<td>0.06, 0.37</td>
<td>68</td>
<td>NR</td>
</tr>
<tr>
<td>Both del(17p) and TP53 mut</td>
<td>0.13</td>
<td>0.04, 0.47</td>
<td>22</td>
<td>NR</td>
</tr>
<tr>
<td>Either del(17p) or TP53 mut</td>
<td>0.09</td>
<td>0.02, 0.42</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>Neither del(17p) nor TP53 mut</td>
<td>0.17</td>
<td>0.07, 0.43</td>
<td>64</td>
<td>NR</td>
</tr>
<tr>
<td>Del(11q) positive</td>
<td>0.16</td>
<td>0.05, 0.59</td>
<td>36</td>
<td>NR</td>
</tr>
<tr>
<td>Del(11q) negative</td>
<td>0.14</td>
<td>0.07, 0.31</td>
<td>71</td>
<td>NR</td>
</tr>
<tr>
<td>IgH mutated</td>
<td>0.25</td>
<td>0.07, 0.95</td>
<td>19</td>
<td>12.1</td>
</tr>
<tr>
<td>IgH unmutated</td>
<td>0.13</td>
<td>0.06, 0.27</td>
<td>91</td>
<td>NR</td>
</tr>
<tr>
<td>ZAP70 positive</td>
<td>0.13</td>
<td>0.06, 0.25</td>
<td>98</td>
<td>NR</td>
</tr>
<tr>
<td>ZAP70 negative</td>
<td>NA</td>
<td>NA, NA</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>CD38 positive</td>
<td>0.13</td>
<td>0.05, 0.34</td>
<td>62</td>
<td>NR</td>
</tr>
<tr>
<td>CD38 negative</td>
<td>0.13</td>
<td>0.05, 0.34</td>
<td>47</td>
<td>NR</td>
</tr>
<tr>
<td>β2-microglobulin ≤4 mg/L*</td>
<td>NA</td>
<td>NA, NA</td>
<td>16</td>
<td>NR</td>
</tr>
<tr>
<td>β2-microglobulin &gt;4 mg/L</td>
<td>0.14</td>
<td>0.07, 0.27</td>
<td>92</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Subjects in the treatment arm are 100% censored as of date of analysis.
Figure 3. Progression-free survival plots: high-risk subpopulations

$β2$-microglobulin levels

$β2M ≤ 4\ mg/L\ (n = 24)$

$β2M > 4\ mg/L\ (n = 81)$

$β2M > 4\ mg/L\ (n = 92)$

$β2M ≤ 4\ mg/L\ (n = 16)$

$β2M = β2$-microglobulin; del = deletion; IgHV = immunoglobulin heavy chain, variable region; mut = mutation; PFS = progression-free survival; TP53 = tumor protein p53
Key conclusions

- In high-risk, heavily pretreated patients with relapsed CLL who are not suitable for chemotherapy, idelalisib in combination with rituximab demonstrates comparable efficacy in all the high-risk subpopulations studied.

- In the highest risk patients positive for both del(17p) and TP53mut, idelalisib plus rituximab treatment achieved a 76.5% ORR and PFS HR of 0.13.

- These results identify idelalisib as a potentially important novel therapy for all patients, regardless of risk factors.


Hillmen P et al. EHA 2014: P236

Pre-treatment with idelalisib markedly reduces rituximab infusion-related reactions and infusion interruptions in patients with CLL

Background

Infusion related reactions (IRRs) during the first infusion of rituximab in patients with chronic lymphocytic leukemia (CLL) have been reported to occur frequently, presenting a significant medical burden. IRRs may be more frequent in patients with high absolute lymphocyte counts (ALCs). Idelalisib reduces cytokine production by stimulated human peripheral blood mononuclear cells and also inhibits basophil degranulation.

The objective of this study was to: 1) compare the incidence of rituximab IRRs per infusion in subjects receiving idelalisib with the incidence in those receiving placebo, 2) compare the incidence of rituximab infusion interruptions in the two groups, and 3) explore the effect of the ALC on the frequency of IRRs.

Study design

- This was a phase III double-blind study that evaluated idelalisib plus rituximab vs. placebo plus rituximab in patients with relapsed CLL who experienced progression within 24 months since completion of the last therapy and who were considered unfit to receive cytotoxic therapy. (Please see the study design for Stilgenbauer et al. and Coutre et al.)

- Rituximab was administered at 375 mg/m² (first dose) and then at 500 mg/m² every two weeks for the next four doses, followed by every four weeks for a total of eight doses.

- Infusion premedication included an antipyretic and an antihistamine; local procedures often also included corticosteroids.

- The standard morning dose of idelalisib/placebo (150 mg twice a day) was administered 30 minutes before the start of each rituximab infusion. Idelalisib was started on the same day as the first rituximab dose.

- IRRs were analyzed in two ways:
  1. MST-IRR: occurrence of at least one adverse event (AE), starting on the day of infusion, that appears on the list of the Medical Search Terms (MST) as related to IRRs;
  2. PT-IRR: occurrence of an AE that is coded with the Medical Dictionary for Regulatory Activities Preferred Term (PT) “infusion related reaction”.

- The data presented in this study are from an exploratory analysis based on an interim analysis of this phase III study.

Key findings

- In both arms, IRRs were most common after the first and second rituximab infusions. (Figures 1 and 2)
In high-risk, heavily pretreated patients with relapsed CLL who are not suitable for chemotherapy, idelalisib in combination with rituximab demonstrates comparable efficacy in all the high-risk subpopulations studied.

In the highest risk patients positive for both del(17p) and TP53mut, idelalisib plus rituximab treatment achieved a 76.5% ORR and PFS HR of 0.13.

These results identify idelalisib as a potentially important novel therapy for all patients, regardless of risk factors.

- Fewer infusion interruptions were required in the idelalisib plus rituximab arm than in the placebo plus rituximab arm (5.8% vs. 11.1% of total infusions, \( p < 0.05 \)). (Table 1)
- Patients treated with placebo plus rituximab who experienced infusion reactions after the first dose had higher ALCs than those who did not (\( p < 0.05 \)). (Table 2)
- Patients treated with idelalisib plus rituximab experienced significantly fewer (\( p < 0.05 \)) PT IRRs during the first and second infusions despite a 3.5 fold higher median ALC at the second infusion. (Figure 1)
- Grade 3 IRR AEs were reported for three infusions in three patients who received idelalisib plus rituximab, and for seven infusions in five patients who received placebo plus rituximab.

**Table 1**

<table>
<thead>
<tr>
<th>Infusion number</th>
<th>Placebo + rituximab</th>
<th>Idelalisib + rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>108</td>
</tr>
<tr>
<td>3</td>
<td>103</td>
<td>107</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>106</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>51</td>
</tr>
</tbody>
</table>

**Figure 1. PT-IRR at each rituximab infusion**

**Figure 2. MST-IRR at each rituximab infusion**
Table 1. Infusion interruptions

<table>
<thead>
<tr>
<th>Infusion Week</th>
<th>Placebo + rituximab</th>
<th>Idelalisib + rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Interruptions, n (%)</td>
<td>N Interruptions, n (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>108 38 (35.2)</td>
<td>110 37 (33.6)</td>
</tr>
<tr>
<td>1</td>
<td>0 108 32 (29.6)</td>
<td>110 27 (24.5)</td>
</tr>
<tr>
<td>2</td>
<td>2 105 12 (11.4)*</td>
<td>108 4 (3.7)*</td>
</tr>
<tr>
<td>3</td>
<td>4 103 5 (4.9)</td>
<td>107 2 (1.9)</td>
</tr>
<tr>
<td>4</td>
<td>6 96 6 (6.3)</td>
<td>106 2 (1.9)</td>
</tr>
<tr>
<td>5</td>
<td>8 90 6 (6.7)</td>
<td>94 1 (1.1)</td>
</tr>
<tr>
<td>6</td>
<td>12 71 4 (5.6)</td>
<td>81 2 (2.5)</td>
</tr>
<tr>
<td>7</td>
<td>16 47 5 (10.6)</td>
<td>65 3 (4.6)</td>
</tr>
<tr>
<td>8</td>
<td>20 37 3 (8.1)</td>
<td>51 1 (2.0)</td>
</tr>
</tbody>
</table>

73 interruptions in 657 infusions (11.1%)*
42 interruptions in 722 infusions (5.8%)*

*Nominal p <0.05

Table 2. ALC in placebo subjects with and without an IRR during the first rituximab infusion

<table>
<thead>
<tr>
<th></th>
<th>With IRR</th>
<th>Without IRR</th>
<th>Nominal p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRR per MST-IRR</td>
<td>54.5 (13.6, 110.5)</td>
<td>17.0 (2.8, 83.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IRR per PT-IRR</td>
<td>69.2 (20.9, 131.6)</td>
<td>22.2 (3.9, 86.8)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ALC = absolute lymphocyte counts; IRR = infusion-related reaction; MST = medical search terms; PT = preferred term

Key conclusions

- Idelalisib treatment given only 30 minutes before rituximab reduced the frequency of IRRs and infusion interruptions.
- Of the 108 subjects receiving their first dose of rituximab following placebo:
  - 44% experienced an IRR;
  - The median ALC in the group with a reaction was significantly higher than in the group without an infusion reaction, thus confirming previous observations.
- Despite the relationship between higher ALC and risk of IRR in the placebo group, the protective effect of idelalisib was particularly notable for the second rituximab infusion, at which time the idelalisib group had a median ALC that was 3.6 times higher than that of the placebo group.
- Thus, in addition to the demonstrated improvement in progression-free and overall survival resulting from the addition of idelalisib to rituximab in patients with relapsed CLL, this exploratory analysis has shown a benefit of enhanced safety regarding IRRs.
  - This observation will be prospectively confirmed, including measurement of plasma cytokine levels, in an upcoming trial with an anti-CD20 monoclonal antibody.


Ghia P et al. EHA 2014:P239

Effect of idelalisib plus rituximab combination treatment of relapsed CLL on the BCR signaling-related chemokines CCL3 and CCL4

Background

Idelalisib is a potent and selective inhibitor of PI3Kδ, which can modulate B-cell receptor (BCR) signaling in addition to cytokine and chemokine receptor signaling. Published data have demonstrated that idelalisib monotherapy reduces the levels of CCL3 and CCL4 (MIP-1α/β), two chemokines secreted by chronic lymphocytic leukemia (CLL) cells in response to BCR activation.1 High levels of CCL3 and CCL4 have been associated with shorter progression-free survival (PFS) in CLL and therefore have been suggested as BCR-related risk factors with cut-off levels for negative prognosis of >10 pg/mL and >60 pg/mL, respectively.

The objective of this study is to describe the effect of idelalisib plus rituximab and placebo plus rituximab treatment on CCL3 and CCL4 levels in patients with relapsed CLL.

Study design

- This was a phase III (116/117), double-blind, placebo-controlled study that evaluated idelalisib plus rituximab (n = 110) vs. placebo plus rituximab (n = 110) in patients with relapsed CLL who experienced progression within 24 months since completion of their last therapy and were considered unfit to receive cytotoxic therapy. (Please see the study design for Stilgenbauer et al. and Coutre et al.)
• Patients were stratified based on the presence of del(17p) and/or TP53 mutation (mut), IgHV mutational status, and on prior anti-CD20 therapy.
• The primary endpoint was progression free survival (PFS).
• Interim analysis was planned at 50% and 75% of total events; the Data Monitoring Committee recommended an early stop to the study after the first interim analysis due to overwhelming efficacy.
• The plasma levels of CCL3 and CCL4 were assessed at baseline and at week 4 (day 28) of treatment with idelalisib plus rituximab or placebo plus rituximab.
• CCL3 and CCL4 quantification was performed by EMD Millipore at St. Charles, MO, U.S.A., using a bead-based enzyme-linked immunosorbent assay.

Key findings
• After four weeks, treatment with idelalisib plus rituximab resulted in a prominent reduction of CCL3 and CCL4 plasma levels. (Figures 1 and 2, Table 1)
  ◦ The reduction of CCL3 and CCL4 levels at week 4 was significantly greater ($p < 0.0001$) with idelalisib plus rituximab vs. placebo plus rituximab:
    • CCL3: 80.4% vs. 24.3% mean decrease from baseline; median level of 11.8 pg/mL vs. 53.2 pg/mL;
    • CCL4: 62.2% vs. 21.4% mean decrease from baseline; median level of 35.4 pg/mL vs. 74.0 pg/mL.
• The difference in CCL3 and CCL4 reduction observed between the two treatment arms remained highly significant across all key CLL prognostic factors ($p < 0.001$).
  ◦ Sensitivity analysis was performed to confirm the difference in CCL3 and CCL4 reduction observed between the two treatment arms.
  ◦ The analysis took into consideration the other key prognostic factors measured in the study [del(17p), TP53mut, del(11q), IgHV mutational status and β2-microglobulin] as well as baseline chemokine levels.
• Importantly, 37% and 47% of patients with baseline levels above negative prognosis cut-offs for CCL3 and CCL4, respectively, reached levels below the cut-off at day 28 of idelalisib plus rituximab treatment. (Table 1)
  ◦ In comparison, only 4% and 12% of patients on placebo plus rituximab achieved such a reduction for CCL3 and CCL4, respectively.
Table 1. Summary of changes in levels of CCL3 and CCL4

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + R</th>
<th>Placebo + R</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCL3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable patients (N)</td>
<td>101</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Median level at BL (pg/mL)</td>
<td>67.7</td>
<td>71.5</td>
<td></td>
</tr>
<tr>
<td>Median level at week 4 (pg/mL)</td>
<td>11.8</td>
<td>53.2</td>
<td></td>
</tr>
<tr>
<td>Subjects with levels at BL above negative prognosis cut-off, n (%)</td>
<td>99 (98)</td>
<td>91 (96)</td>
<td></td>
</tr>
<tr>
<td>Subjects with levels at BL above and at week 4 below negative prognosis cut-off, n (%)</td>
<td>37 (37)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Mean decrease from BL at week 4, % (95% CI)</td>
<td>80.4 (76.5–83.7)</td>
<td>24.3 (8.7–37.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CCL4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable patients (N)</td>
<td>90</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Median level at BL (pg/mL)</td>
<td>81.7</td>
<td>85.0</td>
<td></td>
</tr>
<tr>
<td>Median level at week 4 (pg/mL)</td>
<td>35.4</td>
<td>74.0</td>
<td></td>
</tr>
<tr>
<td>Subjects with levels at BL above negative prognosis cut-off, n (%)</td>
<td>58 (64)</td>
<td>62 (70)</td>
<td></td>
</tr>
<tr>
<td>Subjects with levels at BL above and at week 4 below negative prognosis cut-off, n (%)</td>
<td>42 (47)</td>
<td>11 (12)</td>
<td></td>
</tr>
<tr>
<td>Mean decrease from BL at week 4, % (95% CI)</td>
<td>62.2 (55.5–67.8)</td>
<td>21.4 (7.5–33.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BL = baseline; CCL3 = chemokine (C-C motif) ligand 3; CCL4 = chemokine (C-C motif) ligand 4; CI = confidence interval; R = rituximab

Key conclusions

■ In patients with CLL, idelalisib plus rituximab rapidly and prominently reduces the levels of CCL3 and CCL4, two chemokines secreted by CLL cells in response to BCR activation.

■ Sensitivity and two-way interaction analyses demonstrated that the reduction of CCL3 and CCL4 levels remained highly statistically significant (p <0.0001) across all the evaluated key prognostic marker subpopulations.

■ Given that high levels of CCL3 and CCL4 have been suggested as BCR-related risk factors in CLL, the rapid normalization of their levels may contribute to the strong clinical benefit observed with idelalisib and other emerging novel therapies that inhibit BCR-signaling.


Eradat HA et al. EHA 2014:P252

Health-related quality of life impact of idelalisib in patients with relapsed CLL

Background

Idelalisib, an oral inhibitor of PI3Kδ, is highly active in frail, heavily pretreated patients with chronic lymphocytic leukemia (CLL) whether as single agent or in combination with rituximab. Although idelalisib has been examined in several clinical trials, the impact of these treatments on health related quality of life (HRQoL) is less studied.

The objective of this study was to use patient-reported outcomes (PROs) to evaluate HRQoL among patients with relapsed CLL treated with idelalisib plus rituximab or placebo plus rituximab.1
In Supportive Care Oncology

Key conclusions
- In patients with CLL, idelalisib plus rituximab rapidly and prominently reduces the levels of CCL3 and CCL4, two chemokines secreted by CLL cells in response to BCR activation.
- Sensitivity and two-way interaction analyses demonstrated that the reduction of CCL3 and CCL4 levels remained highly statistically significant \( (p < 0.0001) \) across all the evaluated key prognostic marker subpopulations.
- Given that high levels of CCL3 and CCL4 have been suggested as BCR-related risk factors in CLL, the rapid normalization of their levels may contribute to the strong clinical benefit observed with idelalisib and other emerging novel therapies that inhibit BCR-signaling.

Study design
- This was a randomized phase III, double-blind, placebo-controlled study comparing idelalisib plus rituximab \( (n = 110) \) with placebo plus rituximab \( (n = 110) \) in relapsed CLL patients.
- HRQoL was measured every two weeks until week 8, then every four weeks until week 24, then every six weeks until week 48, then every 12 weeks.
- It was measured using the 44-item Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) questionnaire as per the FACT scoring guideline and user manual.
- Repeated measures mixed-effects models were used to assess mean change from baseline within and between treatment arms.
- The least squares mean change from baseline was plotted over time for each arm.
- The FACT-Leu questionnaire compliance and completion rates for each study arm and at each time point were calculated.

Key findings
- Baseline patient characteristics were similar between the two arms.
- After the first interim analysis, the study showed an improved overall PFS in patients treated with idelalisib plus rituximab.
- The mean change in leukemia subscale was significantly higher in patients treated with idelalisib plus rituximab compared with placebo plus rituximab. (Figure 1)
- In the mixed-effects model analysis, the study showed significantly higher scores of physical well-being \( (WB, p = 0.015) \), functional WB \( (p = 0.014) \), trial outcome index \( (p = 0.002) \), and FACT-Leu total \( (p = 0.006) \) in patients treated with idelalisib plus rituximab compared with placebo plus rituximab. (Figures 2–4)
- Scores of emotional/social WB did not change significantly in patients treated with idelalisib plus rituximab compared with placebo plus rituximab.
- Scores of leukemia-specific concerns were significantly higher in patients treated with idelalisib plus rituximab compared with placebo plus rituximab \( (p = 0.001) \).

Figure 1. Mean change in leukemia subscale

<table>
<thead>
<tr>
<th>Patients on study, n</th>
<th>Idelalisib + rituximab</th>
<th>Placebo + rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>110</td>
<td>108</td>
</tr>
<tr>
<td>110</td>
<td>106</td>
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<td>72</td>
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<td>51</td>
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<td>39</td>
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<td>30</td>
<td>15</td>
</tr>
<tr>
<td>26</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>

\* \( p < 0.05 \) for treatment difference, time point, mixed model; \( p = 0.001 \) for overall treatment effect, longitudinal analysis.
Key conclusions

- The phase III Study 116 compared idelalisib plus rituximab with rituximab alone in elderly, frail patients with CLL with a high incidence of poor prognostic factors.

- Patients on idelalisib plus rituximab experienced statistically significant and clinically meaningful improvements in leukemia-related symptoms and in physical and functional well-being compared to patients in the comparator arm.

- Compared with patients on the comparator arm, overall HRQoL was better for patients treated with idelalisib plus rituximab.

ABT-199 combined with rituximab in patients with relapsed/refractory CLL — interim results of a phase Ib study

**Background**

ABT-199 (GDC-0199) is a selective orally bioavailable BCL-2 inhibitor that induces response rates of approximately 80% in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). In preclinical models of CD20-positive lymphoid cancers, a combination of ABT-199 and rituximab demonstrates synergy.

The objective of this study was to evaluate the safety profile and maximum tolerated dose (MTD) of ABT-199 treatment in combination with rituximab.

**Study design**

- This was a phase Ib, international, multicentre, open-label, dose-escalation trial in patients with R/R CLL/SLL.
- The primary objectives were to:
  - Assess the safety profile of ABT-199 plus rituximab; and
  - Determine the MTD, recommended phase II dose, and dosing schedule.
- Secondary objectives were to assess pharmacokinetics and preliminary efficacy.
- Exploratory objectives included identification of biomarkers, pharmacogenetics, and minimal residual disease (MRD) status.
- Inclusion criteria were:
  - Patients with R/R CLL/SLL receiving no more than 3 prior myelosuppressive regimens;
  - Eastern Cooperative Oncology Group performance status of 0 or 1; and
  - Adequate bone marrow, renal, and hepatic function.
- Exclusion criteria were:
  - Patients with prior autologous or allogeneic stem cell transplant;
  - Uncontrolled autoimmune hemolytic anemia or thrombocytopenia; and
  - History of severe allergic or anaphylactic reactions to rituximab.
- Dosing schedule for cohorts 1 and 2:
  - During weeks 1–3, patients began daily ABT-199 treatment at a dose of 50 mg, with weekly increases to a final designated cohort dose (DCD) of 200 mg and 300 mg.
  - Rituximab was given at a starting dose of 375 mg/m² on day 1, week 4, then 500 mg/m² on day 1 for weeks 5, 6, 10, 14, 18, 22, and 26 (8 doses total) with continuation of daily ABT-199 until progressive disease (PD).
  - After a fatal event of tumour lysis syndrome (TLS) on a first dose of 50 mg, modifications were made to the dosing schedule and enhanced TLS prophylaxis and monitoring were introduced in subsequent cohorts.
- Dosing schedule for cohorts 3–6:
  - Patients received a test dose of 20 mg ABT-199 on day 1 of week 1, followed by a 50 mg daily dose for the remainder of the week. This was followed by a dose increase to 100 mg and 200 mg during weeks 2 and 3, respectively, and a DCD of 400 mg, 500 mg, and 600 mg until 6 months or PD.
  - Rituximab was given at a starting dose of 375 mg/m² on day 1 of month 1, then 500 mg/m² on day 1 of months 2–6.
  - Adjustments to the dosing schedule were made if one or more electrolytes met Cairo-Bishop criteria and/or if there was ≥30% decrease in absolute lymphocyte count with the first dose.

**Key findings**

- As of April 16, 2014, 45 patients were evaluable.
- Patient characteristics were:
  - Median age was 69 years (range, 50–88);
  - 62% were male;
  - 20% were positive for del(17p);
  - 91% had prior rituximab treatment (24% refractory); and
  - 47% had prior fludarabine treatment (24% refractory).
- The median time on study was 13.3 months (range, 1.5–19.6) in cohorts 1 and 2, and 5.1 months (range, 0.03–9.2) in cohorts 3–6.
• Seven patients discontinued from the study due to PD (Richter’s transformation \(n = 4\) and progressive CLL \(n = 1\)), fatal TLS \(n = 1\), and withdrawal of consent \(n = 1\).

• A list of all adverse events (AEs) observed is presented in Table 1.

• Serious AEs reported included two cases each of febrile neutropenia, pyrexia, lung infection, and TLS.

• Dose-limiting toxicities included one case of grade 4 thrombocytopenia (300 mg ABT-199 + 375 mg/m² rituximab) and one case of hemophagocytic syndrome (300 mg ABT-199 + 500 mg/m² rituximab).

• As all doses of ABT-199 showed substantial efficacy, a dose of 400 mg was selected for safety expansion based on toxicity data. (Table 2)

• There was no difference in dose-normalized ABT-199 exposure in the presence or absence of rituximab.

• Of the 25 patients with lymphocytosis at baseline, 100% achieved lymphocyte normalization (median time of 17 days).

### Table 1. Adverse events

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>All grades (≥20% of patients)</th>
<th>Grade 3/4 (≥3 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(N = 45) n (%)</td>
<td>(N = 45) n (%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>23 (51)</td>
<td>21 (47)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>17 (38)</td>
<td>7 (16)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>15 (33)</td>
<td>6 (13)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>12 (27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>12 (27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>11 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>11 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>11 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia*</td>
<td>9 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3/4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*includes four events of autoimmune thrombocytopenia, one of which was grade 3.

†includes one event of autoimmune hemolytic anemia.
• Of the 33 patients with bulky nodes at baseline, 94% achieved ≥50% reduction in nodal masses (median time of 12 weeks). (Figure 1)

• Of the 25 patients evaluable for response:
  ◦ Overall response rate (ORR) was 84% with complete response (CR)/CRi (CR with incomplete marrow recovery) of 36% and PR of 48%;
  ◦ Six patients with CR were MRD negative; and
  ◦ Stable disease and PD each occurred in one patient (4%).
• Three patients discontinued ABT-199 treatment after CR/CRi, and they have remained in CR for 8.6, 8.8, and 11.6 months after cessation.

<table>
<thead>
<tr>
<th>Table 2. Toxicity data for phase II dose recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort dose (mg)</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>400</td>
</tr>
<tr>
<td>500</td>
</tr>
<tr>
<td>600</td>
</tr>
</tbody>
</table>

GI = gastrointestinal

Figure 1. Change in nodal mass from baseline

Key conclusions

■ The combination of ABT-199 and rituximab is well tolerated, with no new toxicities identified.
  ◦ Fatal TLS occurred in one patient following the original dosing scheme, but no further events occurred under the modified dosing scheme.

■ Preliminary pharmacokinetics results suggest no effect of rituximab on ABT-199 exposure.

■ ABT-199 plus rituximab demonstrates high antitumour activity in patients with R/R CLL, with an ORR of 84% of patients to date and an MRD negative status in 6 of 8 patients with CR/CRi.

■ A phase III trial comparing ABT-199 and rituximab versus bendamustine plus rituximab in previously treated patients with CLL is currently underway.

SF3B1 mutations and outcome in patients with CLL treated with chlorambucil alone or ofatumumab plus chlorambucil — results from the phase III study Complement 1

Background
SF3B1, a gene encoding subunit 1 of splicing factor 3b of the spliceosome machinery, has been found to be mutated in 10 to 20% of patients with chronic lymphocytic leukemia (CLL). These mutations were found to be an independent unfavourable prognostic factor for progression-free survival (PFS) and overall survival (OS) in the UK CLL4 and GCLLSG CLL8 trials.

The objective of this study was to evaluate the incidence and impact of mutated SF3B1 in the Complement 1 (OMB110911) trial.1

Study design
• The Complement 1 trial was a two-arm, phase III study comparing chlorambucil alone with ofatumumab plus chlorambucil as first-line therapy for patients with CLL who were inappropriate candidates for fludarabine treatment.
• Of the 447 patients in this study, pretreatment samples were available from 376 (84.1%) patients with informed consent.
• Illumina MiSeq amplicon-based next-generation sequencing (NGS) was performed on patient samples that included a custom gene panel for exons 14, 15, 16, and 18 of the SF3B1 gene.
• Deep sequencing (median depth 2278x) allowed for exact variant frequency calling.

Key findings
• A total of 56 mutations were detected in 53 of the 376 patients (14.1%), all of which were missense single nucleotide variants.
• Of the detected mutations, 50 had been previously reported in the Catalogue of Somatic Mutations in Cancer (COSMIC).
• The mean variant fraction for patients with one SF3B1 mutation was 0.31 and was 0.16 among the three patients with two distinct SF3B1 mutations, indicating the presence of different subclones.
• SF3B1 mutations were significantly associated with:
  ◦ Higher white blood cell (WBC) count at baseline (SF3B1mut, 129 G/L vs. SF3B1 wildtype [wt], 90 G/L; \( p = 0.012 \));
  ◦ Male sex (\( p = 0.02 \)); and
  ◦ Absence of NOTCH1mut (\( p = 0.012 \)). (Table 1)
• Trends towards the association of SF3B1 mutations with absence of +12q (\( p = 0.056 \)), or del(17p) (\( p = 0.089 \)) were also observed. (Table 1)

| Table 1. Univariate analysis for patient parameters and response |
|-----------------|-----------------|-----------------|
|                  | SF3B1wt, n (%)  | SF3B1mut, n (%) |
| Total number     | 323 (100)       | 53 (100)        |
| NOTCH1 mutation  | 54 (16.7)       | 2 (3.8)         |
| Male             | 202 (62.5)      | 42 (79.2)       |
| +12q             | 51 (12.3)       | 3 (5.8)         |
| Del(17p)         | 19 (6.1)        | 0 (0)           |
| CR rate          | 24 (7.6)        | 4 (7.5)         |
| OR rate          | 250 (79.4)      | 41 (77.3)       |

\( CR = \) complete response; \( del = \) deletion; \( mut = \) mutation; \( OR = \) overall response; \( SF3B1 = \) splicing factor 3b, subunit 1; \( wt = \) wild type
• No significant associations were observed with Binet stage, age, Eastern Cooperative Oncology Group performance status, Cumulative Illness Rating Scale score, β2-microglobulin, IgHVmut status, del(11q), or del(13q).

• SF3B1 mutations had no significant impact on overall response (OR) or complete response (CR) in either treatment arm. (Table 1)

• At a median follow-up of 29.0 months, SF3B1 mutation was associated with shorter PFS (median PFS: SF3B1mut, 13.4 months vs. SF3B1wt, 17.7 months; HR = 1.662; p = 0.003). (Figure 1)

• Multivariate analysis for PFS and OS identified several independent prognostic factors, but no significant associations with SF3B1 mutation were identified. (Tables 2 and 3)

  ○ In multivariate analysis of PFS where only common prognostic factors were included (as performed in past studies), SF3B1 mutation was identified as an adverse independent prognostic factor (HR = 1.48, p = 0.032).

**Key conclusions**

- SF3B1mut was found to be associated with high WBC count, male sex, and absence of NOTCH1mut and a trend towards absence of +12q and del(17p).

- SF3B1 mutations had no impact on response to treatment.

- SF3B1 mutation was a moderate prognostic factor for PFS in univariate analysis, but did not impact PFS in a multivariate analysis that included WBC count.

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Randomized comparison of ibrutinib versus ofatumumab in previously treated CLL/SLL: results from the phase III PCYC-1112 RESONATE trial

Background

High-risk patients with relapsed chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) have poor outcomes and limited treatment options. Ibrutinib is a first-in-class, orally administered inhibitor of Bruton's tyrosine kinase that has demonstrated a 75% progression-free rate at two years when prescribed to patients with relapsed or refractory CLL/SLL.\textsuperscript{1}

The objective of this study was to compare efficacy and safety of oral ibrutinib versus intravenous (iv) ofatumumab in patients with relapsed or refractory CLL/SLL.

Study design

- The PCYC-1112 RESONATE trial was a randomized, two-arm, phase III trial comparing:
  - Ibrutinib (n = 195): 420 mg orally once daily until progressive disease (PD) or unacceptable toxicity; vs.
  - Ofatumumab (n = 196): initial dose of 300 mg intravenously followed by 11 doses of 2,000 mg over 24 weeks.

- Inclusion criteria for patients in this study were:
  - Diagnosis of CLL/SLL;
  - Received at least one previous therapy;
  - Inappropriate candidates for treatment/retreatment with purine analogues due to:
    - A short progression-free interval (≤3 years) following combination immunotherapy;
  - Advanced age (≥70 years or 65–69 years with comorbidities); or
  - Presence of del(17p).
  - Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1;
  - Measurable lymph node disease (>1.5 cm) by computed tomography (CT) scan;
  - Absolute neutrophil count ≥750 cells/µL and platelet count ≥30,000 cells/µL;
  - Adequate liver function;
  - Creatinine clearance ≥30 mL/min; and
  - No warfarin or strong CYP3A4 inhibitors.

- Patients were stratified by high-risk baseline characteristics, such as whether their disease was refractory to purine analogs and the presence or absence of del(17p).

- The median time on the study at interim analysis was 9.4 months.

- The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per the 2008 International Workshop for CLL criteria (with 2012 clarification for treatment-related lymphocytosis).

- Secondary endpoints included overall survival (OS), safety, tolerability, and IRC/investigator-assessed overall response rate.

- Crossover to ibrutinib at 420 mg, once daily, was allowed after IRC-confirmed PD.
Key findings

- There was no difference in baseline characteristics or molecular features between arms.
  - This evaluation included: age, gender, refractory to purine analogs, ECOG PS, Rai stage, bulky disease, treatment history, β2-microglobulin level, and presence of del(11q), del(17p), and immunoglobulin heavy chain variable (IgHV) mutations.
- PFS was significantly prolonged in the ibrutinib arm (median not reached vs. 8.1 months for ofatumumab, HR = 0.215 [95% CI: 0.146-0.317], p <0.0001). (Figure 1)
  - PFS hazard ratios favoured ibrutinib across all patient characteristics and molecular subgroups.
- OS was significantly prolonged in the ibrutinib arm (HR = 0.434 [95% CI: 0.238-0.789], p = 0.0049). (Figure 2)
  - The impact of ibrutinib on OS was observed despite the crossover of 57 patients after PD was confirmed.
- Ibrutinib increased the overall response to therapy compared to ofatumumab in both IRC and investigator assessments. (Figure 3)
- Some differences in adverse events (AEs) were observed in the ibrutinib arm, such as an increased frequency of diarrhea and arthralgia and decreased frequency in infusion-related reactions. (Table 1)

Figure 1. Progression-free survival

![Progression-free survival graph]

CI = confidence interval; NR = not reached

Figure 2. Overall survival (censored at crossover)

![Overall survival graph]

CI = confidence interval; NR = not reached

Figure 3. Overall response to therapy — IRC and investigator assessments

![Overall response graph]

CR = confirmed response; CT = computed tomography; IRC = independent review committee; PD = progressive disease; PR = partial response; PR + L = partial response with lymphocytosis; SD = stable disease
*Confirmed responses by the IRC required at least two CT scans performed approximately every 12 weeks per protocol. For unknown/missing/not evaluable category: ibrutinib, 3% (5/195) for both IRC and investigator; ofatumumab, 8% (15/196) for IRC and 9% (17/196) for investigator
**Key conclusions**

- **Ibrutinib treatment** significantly improved PFS, OS, and response rates as compared to ofatumumab, and its impact was observed irrespective of high-risk baseline characteristics or molecular features such as the presence of del(17p) or purine refractoriness.

- This study confirms that ibrutinib is an effective new single-agent therapy for patients with CLL/SLL.

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**Reference:**


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**A phase II study of the BTK inhibitor ibrutinib in genetic risk-stratified relapsed and refractory CLL/SLL**

**Background**

Ibrutinib, an irreversible inhibitor of Bruton’s tyrosine kinase, has demonstrated significant single-agent activity in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), independent of high-risk molecular features such as the 17p13 deletion [del(17p)]. The objective of this study was to evaluate the clinical efficacy of ibrutinib given to patients with R/R CLL or small lymphocytic lymphoma (SLL) harbouring all types of genetic risk factors.

**Study design**

- This was a phase II, single institution, non-randomized study.
- Eligibility criteria for patients in this study were:
  - ≥18 years with R/R CLL/SLL requiring treatment as per National Cancer Institute or International Workshop Group guidelines;
  - Failed at least one prior therapy;
  - Previously received ofatumumab or have a CD20 negative (<10% positive) immunophenotype;
  - Had interphase cytogenetics performed using the CLL FISH panel prior to starting and following their most recent therapy;
  - No anticoagulation with warfarin or other low molecular weight heparin; and
  - Normal organ function with:
    - Bilirubin ≤1.5X institutional upper limit of normal (ULN);
    - Aspartate transaminase or alanine transaminase ≤2.5X institutional ULN (unless it is disease related);
    - Creatinine ≤1.5X institutional ULN; and
    - Absolute neutrophil count ≥0.5 x 10^9 cells/L, platelet count ≥30 X 10^9 cells/L (unless patient has bone marrow involvement with their disease).
- All patients received oral ibrutinib at 420 mg daily.

---

**Table 1. Safety: adverse events (≥15%) regardless of attribution**

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib (n = 195)</th>
<th>Ofatumumab (n = 191)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median treatment duration</strong></td>
<td>8.6 months</td>
<td>5.3 months</td>
</tr>
<tr>
<td>Any TEAE, %</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>30</td>
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<td>Nausea</td>
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<td>18</td>
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<tr>
<td>Cough</td>
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<td>23</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>0</td>
<td>28</td>
</tr>
</tbody>
</table>

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**Maddocks K et al. EHA 2014:S1343**

- **A phase II study of the BTK inhibitor ibrutinib in genetic risk-stratified relapsed and refractory CLL/SLL**

---

- Serious AEs were more frequent in ibrutinib-treated patients.
  - Atrial fibrillation (ibrutinib n = 10, ofatumumab n = 1) occurred in patients ≥60 years old with predisposing risk factors.
  - Bleeding-related AEs of any grade occurred more frequently in the ibrutinib arm (ibrutinib = 44%, ofatumumab = 12%), but there were no differences in severe/major bleeding-related AEs (ibrutinib n = 2, ofatumumab n = 3).

---

- Toxocities associated with ibrutinib were manageable, as 86% of patients continued treatment (dose reduction occurrence 4%, treatment discontinuation 4%).
In Supportive Care Oncology

Patients were stratified into two groups based on cytogenetic risk:

- Patients with del(17p) (n = 27); or
- Patients with other interphase cytogenetics (n = 45).

The primary endpoint was two-year progression-free survival (PFS).

The secondary endpoints were best overall response rate (ORR), extended toxicity, overall survival (OS), independent evaluation of ORR and PFS in high-risk cytogenetics, effects on immunologic function, influence on cytokines, emotional distress/quality of life, and primary and secondary features of resistance.

Key findings

- The baseline characteristics of patients on this study were as follows:
  - Median age of 65 years (range, 37–85 years);
  - 74% male patients;
  - 38% with del(17p);
  - 84% with unmutated IgHV; and
  - Median number of prior therapies of 4 (range, 1–16).
- Median follow-up time was 17 months (range, 10–20 months).
- Some of the most frequent treatment-related adverse events (AEs) observed were diarrhea, infection, myalgias, bleeding, thrombocytopenia, neutropenia, and bruising. (Figure 1)

Figure 1. Treatment-related AEs occurring in ≥10% of patients

AE = adverse event; LFT = liver function test
• The most frequent grade 3/4 AEs possibly related to treatment were neutropenia, infections, and thrombocytopenia.

• High incidences of bleeding AEs were reported. (Table 1)

<table>
<thead>
<tr>
<th>Bleeding episodes</th>
<th>Number of events (99 events in 54 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contusion</td>
<td>23</td>
</tr>
<tr>
<td>Oral mucosal</td>
<td>16</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>15</td>
</tr>
<tr>
<td>Petechial</td>
<td>10</td>
</tr>
<tr>
<td>Ocular</td>
<td>7</td>
</tr>
<tr>
<td>Skin</td>
<td>7</td>
</tr>
<tr>
<td>Hematuria</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
</tr>
<tr>
<td>Hematoma</td>
<td>3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3</td>
</tr>
<tr>
<td>Post-operative</td>
<td>1</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>1</td>
</tr>
<tr>
<td>Purpura</td>
<td>1</td>
</tr>
<tr>
<td>Other (ears, vaginal, vascular access)</td>
<td>3</td>
</tr>
</tbody>
</table>

• Discontinuation of treatment occurred in 29 patients.

○ Reasons for treatment discontinuation included: death (34.48%), disease progression (27.59%), nonfatal toxicity (27.59%), and patient withdrawal (10.34%).

• The best ORR in all patients as determined by the investigator was 67%, with 55% of patients achieving partial response (PR) and 12% of patients attaining PR with lymphocytosis.

○ There was no significant difference in ORR observed between the del(17p) cohort and the other cytogenetics group. (Figure 2)

• Twelve-month estimates of PFS and OS were 70% and 74%, respectively, for the del(17p) cohort, and 78% and 84%, respectively, for the other cytogenetics cohort.

### Key conclusions

- **Ibrutinib was well tolerated in patients; toxicities were similar to what has been previously reported, with the exception of an increased incidence of bleeding complications.**

- **There was no significant difference in ORR between patients with or without del(17p).**

- **The best ORR observed was lower than what was previously reported in a phase II trial, although the 12-month PFS still remained high with responses improving over time.**

A simple and effective strategy to decrease early deaths in acute promyelocytic leukemia using a streamlined set of guidelines paired with expert support

**Background**

Induction mortality in patients with acute promyelocytic leukemia (APL) has been estimated to occur in 5–10% of patients in large multicentre trials. However, recent reports suggest that up to 30% of patients with APL die during induction treatment. Patients who survive induction have an excellent cure rate with few late relapses. Hence, decreasing early death rate is a high priority.

The objective of this study was to decrease early deaths in APL with a streamlined algorithm and expert support and to improve overall survival in APL across the general population.1

**Study design**

- The study conducted a retrospective chart review of patients with APL at Georgia Regents University Medical Center (GRU) and Emory University Hospital (EUH) between July 2005 and June 2009.
- The total number of APL patients in the study was 59 (GRU, n = 19; EUH, n = 40).
- Seven patients (high risk, n = 5; low risk, n = 2) died during induction treatment at GRU, resulting in an unusually high mortality rate of 37%.
- Nine patients died during induction treatment at EUH with two patients presenting in very late stage to EUH.
  - This resulted in an induction mortality of 17.5%, which was comparable to other single institution centres but was still higher than what has been reported in clinical trials.
- This high early death rate at GRU prompted the GRU group to evaluate the reasons for early death.
- The following steps were undertaken:
  1. Literature review;
  2. Review of all charts, specifically those of deceased patients;
  3. The issues surrounding the cases were discussed with experts; and
  4. An external consultant was recruited to review charts of deceased patients.
- The strategy to decrease early death rate comprised the following steps:
  1. A simple 1.5-page treatment algorithm;
  2. Quick diagnosis and ad hoc meetings with treating staff and nurse;
  3. Prompt initiation of therapy with all-trans retinoic acid (ATRA) on suspicion of APL;
  4. Proactive and aggressive management of coagulopathy;
  5. Prevention, early recognition, and treatment of differentiation syndrome;
  6. Prophylaxis and aggressive treatment of infections;
  7. The treatment protocol was made available to other treatment centres;
  8. All patients were treated either under direct guidance of an APL expert or comanaged by an APL expert in collaboration with the local oncologist;
  9. Oncologists who were treating patients were visited and educated about the treatment strategy;
  10. Flyers and email communications were sent out frequently to remind health care providers to seek expert advice when managing these patients; and
  11. APL experts contacted local oncologists at regular intervals during induction treatment to ensure that the patient’s clinical course was as expected.

**Key findings**

- The new algorithm was used by the GRU for managing patients and was made available to other treatment facilities.
- A total of 50 patients were treated and comanaged at 15 centres from November 2010 to March 2014.
- The age range of patients in the study was 21 to 86 years.
- There were 11 high-risk patients and 39 low-risk patients in the study.
- The median follow-up was 128 days (range, 26–1,258 days).
The study showed that after the median follow-up period, the rate of early mortality after implementation of the treatment algorithm was 4%. (Figure 1)

- In contrast, after a median follow-up of 2,176 days, the rate of early mortality in patients who did not get treated using the algorithm was 37%.

- ATRA and chemotherapy, as per the AIDA (ATRA plus idarubicin) protocol, was the preferred regimen initially.

- ATRA and arsenic trioxide induction has been the preferred regimen since June 2013 for low-risk patients.

- There were two deaths after implementing the new algorithm.

- There was one death at GRU; this patient refused transfusions for religious reasons.

- The other death was a patient who had an intracranial bleed early in her treatment phase (the patient was treated at a non-academic centre).

- There were no deaths at EUH.

![Figure 1. Survival probability before and after implementation of algorithm](image)

**Key conclusions**

- Widespread education of hematologists and oncologists about early death and the need for rapid diagnosis and treatment is needed to improve outcomes.

- The treatment process at experienced and inexperienced centres should be simplified.

- A network with leukemia experts should be developed to provide an available resource to comanage patients.

- As a result of the study, a 1.68-million-dollar grant was awarded by the Leukemia & Lymphoma Society under the Therapy Acceleration Program (TAP) to implement this protocol in the states of Georgia and South Carolina to cover 15 million people.


Efficace F et al. EHA 2014:S1330

**A randomized phase III trial of ATRA plus ATO versus ATRA plus chemotherapy in patients with APL: health-related quality of life outcomes**

**Background**

In a recent randomized clinical trial (RCT), the efficacy and toxicity of all-trans retinoic acid (ATRA) plus chemotherapy was compared with ATRA plus arsenic trioxide (ATO) in patients with newly diagnosed, low-to-intermediate risk acute promyelocytic leukemia (APL). Health-related quality of life (HRQoL) assessment was included as a secondary endpoint of this RCT because the potential clinical benefits of newer experimental treatments need to be weighed against possible burdens to the patient, and because there is a lack of published data on the impact of ATO on the patient’s symptoms and wellbeing. The objective of this study was to assess the secondary endpoint of HRQoL in patients with APL from this trial.
Widespread education of hematologists and oncologists about early death and the need for rapid diagnosis and treatment is needed to improve outcomes.

The treatment process at experienced and inexperienced centres should be simplified.

A network with leukemia experts should be developed to provide an available resource to comanage patients.

As a result of the study, a 1.68-million-dollar grant was awarded by the Leukemia & Lymphoma Society under the Therapy Acceleration Program (TAP) to implement this protocol in the states of Georgia and South Carolina to cover 15 million people.

**Study design**

- The study was a prospective, randomized, multicentre, open-label, phase III trial designed to show that ATRA plus ATO was not inferior to ATRA plus chemotherapy with respect to the event-free survival rate at two years.

- Eligible patients were newly diagnosed adults between 18 and 71 years old, had genetically confirmed, non-high-risk APL (white blood cell [WBC] ≤10 x 10^9/L), and a World Health Organization (WHO) performance status ≤2.

- Patients were randomized to receive either:
  - Arm A: Induction treatment with ATRA plus ATO (0.15 mg/kg of ATO plus 45 mg/m² ATRA daily until complete remission [CR], after which ATO was given five days/week in a cycle of four weeks on, four weeks off, for a total of four courses, while ATRA was given for two weeks on, two weeks off, for a total of seven courses);
  - Arm B: Standard induction treatment with AIDA (ATRA plus idarubicin) followed by three cycles of ATRA plus anthracycline-based chemotherapy as consolidation; ATRA was given for maintenance.

- HRQoL was a secondary endpoint of this trial.

- The EORTC QLQ-C30 was used to assess HRQoL at the end of induction and after consolidation therapy.

**Key findings**

- Out of 156 patients analyzed in the primary clinical analysis, 150 were eligible for HRQoL evaluation at the end of induction phase and 142 at the end of consolidation phase. (Figure 1)

  - Differences in baseline characteristics, including age, red blood cell count, WBC count, risk level (low and intermediate), promyelocytic leukemia-retinoic acid receptor isoform, hemoglobin counts, and any toxicity present during the induction phase (grade 3/4), between those who had HRQoL assessments after induction therapy (Yes, n = 115) and those who did not (No, n = 41) were not statistically significant, except for gender (Yes, male vs. female: 53.9% vs. 46.1%; No, male vs. female: 34.1% vs. 65.9% p = 0.03).

  - The largest difference was in fatigue severity and it was statistically significant, favouring patients treated with ATRA plus ATO. (Table 1)

  - All other symptoms, except for pain, were favouring patients treated with ATRA plus ATO. (Figure 2)

  - Similarly, except for social functioning, all functional and global HRQoL scores favoured patients treated with ATRA plus ATO. (Figure 3)

---

6MP = 6-Mercaptopurine; ATO = arsenic trioxide; ATRA = all-transretinoic acid; Chemo = chemotherapy; CR = complete response; IDA = idarubicin; MTX = methotrexate; MTZ = mitoxantrone; QoL = quality of life; R = randomized
**ATRA-Chemotherapy**

N = 150 expected
Compliance 77%

N = 142 expected
Compliance 84%

**ATRA-ATO**

N = 62

N = 61

N = 53

N = 58

*ATO = arsenic trioxide; ATRA = all-trans retinoic acid; HRQoL = health-related quality of life*

---

**Figure 1. Patients eligible for HRQoL assessment**

---

**Table 1. Estimated EORTC QLQ-C30 mean scores and standard deviations by treatment arm and QoL assessment**

<table>
<thead>
<tr>
<th>EORTC QLQ-C30 scales</th>
<th>ATRA-ATO</th>
<th>ATRA-chemotherapy</th>
<th>p-value for treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score (SD)</td>
<td>Mean score (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After induction</td>
<td>After third consolidation course</td>
<td>After induction</td>
</tr>
<tr>
<td>Functional scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>80.9 (21.5)</td>
<td>80.6 (20.6)</td>
<td>75.6 (23.5)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>68.0 (34.8)</td>
<td>72.4 (29.7)</td>
<td>62.5 (38.1)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>81.2 (21.0)</td>
<td>74.7 (24.0)</td>
<td>76.8 (23.0)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>87.2 (21.1)</td>
<td>80.8 (24.5)</td>
<td>81.4 (23.1)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>68.8 (30.2)</td>
<td>77.5 (26.5)</td>
<td>72.4 (33.1)</td>
</tr>
<tr>
<td>Global health status QoL</td>
<td>67.2 (21.8)</td>
<td>72.7 (22.4)</td>
<td>64.7 (24.1)</td>
</tr>
<tr>
<td>Symptom scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>29.1 (25.7)</td>
<td>29.8 (26.4)</td>
<td>38.4 (28.1)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>3.1 (13.9)</td>
<td>5.3 (13.1)</td>
<td>8.3 (15.2)</td>
</tr>
<tr>
<td>Pain</td>
<td>16.1 (25.3)</td>
<td>16.9 (26.3)</td>
<td>11.1 (27.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15.8 (24.8)</td>
<td>16.7 (26.6)</td>
<td>16.3 (27.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16.2 (28.7)</td>
<td>21.2 (30.0)</td>
<td>19.4 (31.4)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>5.6 (22.6)</td>
<td>5.3 (19.9)</td>
<td>12.7 (24.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.5 (30.5)</td>
<td>5.3 (27.6)</td>
<td>20.6 (33.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.6 (20.6)</td>
<td>7.8 (15.9)</td>
<td>9.5 (22.5)</td>
</tr>
</tbody>
</table>

*ATO = arsenic trioxide; ATRA = all-trans retinoic acid; EORTC = European Organization for Research and Treatment of Cancer; QLQ = quality of life questionnaire; QoL = quality of life; SD = standard deviation*
Figure 2. Functional aspects/global QoL: estimated differences in EORTC QLQ-C30 mean (95% CI) scores between ATRA plus ATO and ATRA plus chemotherapy groups

Figure 3. Symptoms: estimated differences in EORTC QLQ-C30 mean (95% CI) scores between ATRA plus ATO and ATRA plus chemotherapy groups

Key conclusions

- Overall, current QoL findings further support the use of ATRA plus ATO as the preferred first-line treatment in patients with low-to-intermediate risk APL.
  - In post-induction results, patients treated with ATRA plus ATO reported statistically significant less fatigue, and other clinically relevant better outcomes for appetite loss, nausea/vomiting, constipation, physical and cognitive functioning.
  - In post-consolidation results, QoL differences between treatment arms at the end of the third consolidation course were trivial with no major difference between treatment arms.
- More research is needed to better understand if advantages with ATRA plus ATO can be maintained over a long-term period, and if the oral administration of ATO can further increase QoL advantages over intravenous administration.

Reference:
The prognosis for patients with chronic lymphocytic leukemia (CLL) has dramatically improved with the addition of rituximab to chemotherapy combination regimens such as fludarabine plus cyclophosphamide (i.e., FCR), or to single agents such as chlorambucil. Although efficacy has improved with these new combinations, two significant challenges that remain are the high toxicities associated with the standard chemotherapy regimen FCR and the lack of effective treatments for high-risk CLL patients, including those with del(17p) and/or the unmutated immunoglobulin heavy chain variable region (IgHV) gene. With respect to toxicities, the current first-line treatment for fit patients with CLL, FCR, poses high risk of hematological toxicities. In the CLL8 trial by the German CLL Study Group (GCLLSG), 34% of patients treated with FCR experienced Common Toxicity Criteria (CTC) grade 3/4 neutropenia and 25% experienced grade 3/4 infections. Mitigating toxicity with prophylactic treatments or developing less toxic options without sacrificing efficacy are two approaches that would help address this issue. The challenge facing the treatment of high-risk CLL is even more critical. Aside from clinical trials, or hematopoietic stem cell transplantation for which many patients are not eligible, there is no effective treatment for patients with high-risk CLL. New effective agents in this group are urgently needed. Some of the abstracts at this year’s European Hematology Association Congress that addressed these issues are discussed below.

The efficacy and safety of bendamustine plus rituximab (BR) in CLL was examined in two studies. The study by Langerbeins et al. of physically fit patients with del(17p)-negative CLL compared the rate of severe infections from FCR treatment with the rate from BR treatment. Results from this interim analysis of the CLL10 trial by the GCLLSG showed that the rate of grade 3–5 infections and pneumonia were higher in the FCR arm than the BR arm (51.4% vs. 38.8%, \(p = 0.012\); 11.5% vs. 6.1%, \(p = 0.027\), respectively). The high rate of infections associated with FCR is consistent with prior reports and even higher than that reported in the CLL8 study despite added years of experience with the FCR regimen. This is in keeping with my experience with FCR in the same patient population. The difference of 12.6% in infection rate between the two arms justifies giving BR instead of FCR in a setting where the physician and the patient are concerned about toxicity issues, although these results also show that the infection rate in the BR arm was not insignificant. This means that physicians and patients should be prepared for the potential of developing infections with FCR and BR.

Another significant finding from the CLL10 study was the more frequent use of granulocyte colony-stimulating factor (G-CSF) and red blood cell (RBC) transfusions in the FCR arm compared to the BR arm (6.2% vs. 2.0%, \(p = 0.001\); 4.0% vs. 1.5%, \(p = 0.017\), respectively). The potential to receive these treatments can be a significant factor in patient decision-making because of the cost, inconvenience, and risk of these treatments. Most patients would strongly prefer a regimen that has a lower chance of resulting in the need for RBC transfusions. Furthermore, provincial coverage of G-CSF is not available in all provinces, making this an important factor for many patients. In summary, the study demonstrates that the FCR regimen is associated with a higher frequency of serious infections and other toxicities than the BR regimen. These infections would typically result in hospitalization, which adds to the quality of life impairment. However, both treatments require vigilance on the part of physicians and patients due to the significant risk of infections.

In a second study, the efficacy and safety of BR were addressed in a real-world, Italian retrospective study by Laurenti et al. This study evaluated previously untreated elderly patients with CLL (≥65 years; median age = 72 years) who received treatment between November 2000 and December 2013 in 12 Italian centres. The study reported an overall response rate (ORR) of 88.6%, and progression-free survival (PFS) and overall survival (OS) at 2 years of 79% and 89.6%, respectively. These are impressive results but should be interpreted with caution given the possible bias of physician selection inherent to such real-world reports. Real-world retrospective studies offer a picture of safety issues, thus the lack of new safety signals with BR over a 13-year period is a very reassuring finding. However, this study confirmed the results from the Langerbeins et al. study, showing that BR also poses significant risks of hematological toxicity since 25 out of the 70 patients in the study reported grade 3/4 hematologic toxicities. This should be a reminder that even though BR is associated with a significantly lower risk of hematological toxicities than FCR, this risk is still relatively high. Overall, the findings of this study should reassure physicians that BR has good efficacy and safety profiles in a real-world clinical setting.
The most exciting recent development in CLL has been the emergence of several new non-chemotherapeutic agents with promising efficacy in high-risk patients with CLL. These agents include idelalisib, a selective inhibitor of PI3Kδ, ibrutinib, an inhibitor of Bruton’s tyrosine kinase, and ABT-199, an inhibitor of the anti-apoptotic protein BCL-2. The second interim analysis of the phase III study by Coutre et al. compared the efficacy and safety of idelalisib plus rituximab with rituximab monotherapy in patients with relapsed CLL. Although the study’s use of rituximab monotherapy as a comparator is inappropriate in my opinion since this agent is not considered a standard treatment for this patient population in Canada (rituximab monotherapy is recommended by NCCN guidelines and is used in some countries), there are some take away points that are very promising. The study shows an impressive lymph node response (LNR) in 92% of patients receiving idelalisib plus rituximab. This is especially significant since this is a heavily pretreated CLL population with del(17p) and unmutated IgHV. The lack of an appropriate comparator makes it difficult to interpret other efficacy endpoints; however, the fact that the median PFS has not been reached after 16 months is very encouraging. Additionally, the study clearly demonstrated that idelalisib was associated with a very good safety profile even when compared with rituximab monotherapy. The medical community will be looking forward to more studies which compare idelalisib plus rituximab with other therapies that are more established in this treatment population. A sub-analysis by Stilgenbauer et al. of this same study clarified the effect of idelalisib on CLL subpopulations harbouring adverse prognostic factors including del(17p), del(11q), TP53 mutation, unmutated IgHV, and high levels of ZAP70 and CD38 expression. Excitingly, idelalisib in combination with rituximab demonstrated comparable efficacy in all of these high-risk subpopulations, with the highest risk patients positive for both del(17p) and TP53 mutation experiencing an ORR of 76.5% and an impressive PFS rate (median not yet reached).

In the Hillmen et al. study, the Bruton’s tyrosine kinase inhibitor ibrutinib was compared to ofatumumab in previously treated CLL/SLL patients. The anti-CD20 antibody ofatumumab has been shown previously to have efficacy in fludarabine-refractory patients with CLL and is an indicated treatment for this patient population. Therefore, the prolonged PFS observed in patients treated with ibrutinib (median PFS: not reached vs. 8.1 months for ofatumumab, \( p < 0.0001 \)) and the prolonged OS (\( p = 0.0049 \)) is impressive. Similar to idelalisib, ibrutinib seems to be effective irrespective of high-risk baseline characteristics, such as the presence of del(17p), a result that is very promising for patients in this high-risk category. The study also shows a good overall safety profile except for some differences in cardiac adverse events, which were observed in the ibrutinib arm. The study noted an increased frequency of bleeding events though these are manageable, especially with suggested drug cessation for invasive procedures. The cardiac adverse event (high rate of atrial fibrillation) was surprising and raises questions about the long-term safety of ibrutinib and the impact on the quality of life in patients who may develop such toxicity. Further studies will be important in clarifying this question. Overall, the study confirms the efficacy of ibrutinib as a new single-agent therapy for patients with relapsed CLL/SLL. An important question in the future will be whether ibrutinib shows similar or greater efficacy in front-line therapy for CLL.

Unlike idelalisib and ibrutinib, which work by inhibiting kinases involved in critical signalling pathways in cells, ABT-199 is an inhibitor of BCL-2, a potent anti-apoptotic protein whose expression is necessary for CLL cell survival. The interim results of the phase Ib study by Roberts et al. showed some very exciting results regarding the efficacy of ABT-199 plus rituximab in patients with relapsed/refractory CLL. The study showed an ORR of 84% in the 25 patients who were evaluable for response, and a ≥50% nodal mass reduction in 94% of patients who had bulky nodes at baseline. Furthermore, six out of eight patients who achieved a complete response were also negative for minimal residual disease (MRD). This is a highly significant result because MRD negativity is associated with an improvement in OS,\(^8\) and such deep responses have not been reported in the idelalisib and ibrutinib studies. In addition, it is encouraging that there have been no new tumour lysis syndrome (TLS) cases reported since the adoption of the new dose-escalation schedule. With respect to safety data, the combination of ABT-199 and rituximab seems to be well tolerated with no new toxicities identified. However, the safety of ABT-199 regarding TLS will have to be settled in future studies that have more patients and include real-world data. The upcoming phase III clinical trial comparing BR with ABT-199 plus rituximab will be eagerly awaited to reassure us that TLS is not a concern with ABT-199, and that the very exciting MRD results continue to hold.

Idelalisib, ibrutinib, and ABT-199 represent a new generation of non-chemotherapeutic, target-specific agents
that hold much promise for CLL patients, especially for those with high-risk disease for whom other effective treatments are lacking. Exactly how these agents will shape the treatment practices for CLL is difficult to predict at this early stage, especially since each agent has the capacity to transform treatment on its own and combinations of these agents could still be considered. We do not yet know how these agents will fare in the front-line setting because the data are not yet mature, but it is reasonable to expect equally encouraging results. The need for new effective agents in high-risk patients, particularly those with del(17p) and those refractory to fludarabine or chemoimmunotherapy, is dire because of the lack of other treatments for these patients. The medical community will be eagerly looking forward to the availability of these novel agents in the near future.

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.

Refer to the page in the bottom-right icon for additional safety information and a web link to the Product Monograph discussing:

- Contraindication in patients hypersensitive to mannitol
- The most serious warnings and precautions regarding myelosuppression, infections (including fatalities), second malignancies and serious infections
- Other relevant warnings and precautions regarding patients with poor tolerance to prior therapies; extravasation; cardiac disorders; ECG changes; hypertension; tumor lysis syndrome; increase in liver enzymes and bilirubin; use of live attenuated vaccines; infusion reactions and anaphylaxis; reproductive capacity; skin reactions; recommendation during pregnancy or breast-feeding; women and men of childbearing potential; use with renal impairment; use in hepatic impairment; monitor/test for complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function, electrolytes, blood pressure and hepatitis B prior to treatment; monitor/test for CBC, electrolytes, signs of infection, ECG in patients with cardiac disorders, particularly if electrolyte imbalances, renal function, liver function and blood sugar during treatment
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions
The Management of Fit, Unfit, and High-Risk CLL Patients

A summary of the presentation by Dr. Paula Cramer at the 2014 Canadian Conference on Lymphoproliferative Disorders in Whistler, B.C., Canada

Background

Significant challenges to determining appropriate treatments for patients with chronic lymphocytic leukemia (CLL) are the heterogeneity in the CLL patient population and the biology of the disease. Some prognostic factors implemented in separating different CLL patients include genetic status of TP53, del(17p), immunoglobulin heavy chain variable (IgHV), and age. Age is a significant prognostic factor because about 70% of patients with CLL are 65 years of age or older and have significant comorbidities, thus making assessment of fitness and comorbidity a critical step in treatment decisions. In determining the biological age of a patient with CLL, the German CLL Study Group (GCLLSG) employs the Cumulative Illness Rating Scale (CIRS) score in conjunction with creatinine clearance. CIRS is composed of 14 comorbidity categories with up to four points in each category. A CIRS score of six is used to differentiate between patients who are eligible for intensive chemoimmunotherapy treatments (so called go-go patients) and those who are not (slow-go).

First-line treatments for physically fit CLL patients: the CLL10 study

The CLL8 trial by Hallek et al. established fludarabine, cyclophosphamide, and rituximab (FCR) as the standard first-line treatment for fit patients with CLL. A recent CLL8 update in 2012 showed that after a median observation time of 5.9 years, 69.4% of patients who had received FCR treatment remained alive compared to 62.3% in the fludarabine, cyclophosphamide (FC) arm (hazard ratio [HR] = 0.68, 95% CI: 0.535–0.858; \( p = 0.001 \)).

The GCLLSG that conducted the CLL8 trial then conducted the CLL10 study comparing FCR to bendamustine in combination with rituximab (BR) in previously untreated patients with CLL (Figure 1). Patients included in the study had a CIRS score ≤6 and a creatinine clearance of ≥70 mL/min. Patients with del(17p) were excluded. In the interim analysis, baseline characteristics were well balanced between the two groups, except in the BR arm there was a higher percentage of patients who were 70 years of age or older (21.5% vs. 13.8%; \( p = 0.020 \)) as well as a higher number of patients with unmuted IgHV status (BR vs. FCR: 67.8% vs. 55.3%; \( p = 0.003 \)). Although the overall response rates (ORRs) were the same for both groups, more of the patients treated with FCR attained complete response (CR) and minimal residual disease (MRD) negativity than those treated with BR. The progression-free survival (PFS) rate was significantly higher in patients treated with FCR in comparison to BR (PFS rate at 24 months: 85.0% vs. 78.2%; HR = 1.385; \( p = 0.041 \) (Figure 2). However, given that the HR of 1.385 was less than the predefined criterion for non-inferiority (HR < 1.388), rejection of FCR in comparison to BR for PFS:

HR (BR/FCR) less than 1.388

Randomization

**Figure 1. CLL10 study design: FCR versus BR in front-line therapy**
In Supportive Care Oncology

In Supportive Care Oncology

the BR regimen was therefore statistically non-inferior to FCR. Although more time is needed for a proper evaluation of overall survival (OS), OS analysis revealed no difference between the two arms after a median observation time of 27.9 months (HR = 0.842; \( p = 0.593 \)) (Figure 3). With respect to adverse events (AEs), patients in the BR arm experienced fewer AEs, in particular, neutropenia (56.8% vs. 81.7%; \( p < 0.001 \)) and infections (25.4% vs. 39.0%; \( p = 0.001 \)), than patients in the FCR arm (Table 1).

**Figure 3. Overall survival from the CLL10 study (median observation time: 27.9 months)**

- FCR, median OS: not reached; OS at 24 months: 94.2%
- BR, median OS: not reached; OS at 24 months: 95.8%

HR: 0.842, \( p = 0.593 \)

BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab; HR= hazard ratio; OS = overall survival

Table 1. Adverse events* from the CLL10 study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (%)</th>
<th>BR (%)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>90.8</td>
<td>78.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematological AEs</td>
<td>90.0</td>
<td>66.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81.7</td>
<td>56.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>12.9</td>
<td>9.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Infection</td>
<td>39.0</td>
<td>25.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>3.9</td>
<td>2.1</td>
<td>0.23</td>
</tr>
</tbody>
</table>

AEs = adverse events; BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab

*Common Toxicity Criteria grade 3–5 (interval from first cycle until three months after final staging).

In conclusion, the FCR regimen is more effective than BR with respect to PFS, CR, and MRD negativity, and therefore will remain for the GCLLSG group the standard of care in front-line therapy for fit patients with CLL. However, it is important to remember that a distribution bias of unmutated IgHV status was in favour of the FCR arm. Given that patients in the BR arm experienced a lower rate of AEs, BR should be considered for patients with a higher risk of infections.

**First-line treatments for CLL patients with relevant comorbidities: the CLL11 study**

Several clinical trials have compared the use of chlorambucil as a single agent with other single agents, such as bendamustine, fludarabine, or alemtuzumab, in unfit patients with CLL. Although most of these trials demonstrated that CR and PFS rates were higher with bendamustine, fludarabine, or alemtuzumab, these treatments were accompanied with higher rates of AEs. The GCLLSG adopted single-agent chlorambucil as the standard first-line treatment for unfit CLL patients aged 65 years or older due to the published results of the CLL5 study, which compared fludarabine with chlorambucil in a similar patient population. The CLL5 study showed that the median OS for patients in the chlorambucil arm was longer than for those in the fludarabine arm.

Based on the results of the CLL5 study, chlorambucil was used as the comparator in the CLL11 study, which examined the efficacy of chlorambucil (Clb) in combination with rituximab (R-Clb) or obinutuzumab (G-Clb) in previously untreated, unfit patients with CLL. Patients included in the trial had a CIRS score \( \geq 6 \) and/or a creatinine clearance of \(<70\text{ mL/min}\) (Figure 4). The study initially compared each of the antibody-containing arms against the chlorambucil arm, and more recently made a head-to-head comparison between the two antibody-containing arms. Patients progressing on the chlorambucil arm were allowed to cross over to the G-Clb arm. Baseline characteristics were well balanced between the three arms, with a median CIRS score of 8 across all arms and a median age.
higher than typically observed in clinical trials, reflecting the
usual age at initial diagnosis (72–74 years).

The study showed that Common Toxicity Criteria (CTC) AEs
grades III–V were higher with antibody-containing regimens
(G-Clb: 70% vs. R-Clb: 55% vs. Clb: 50%) (Table 2). The differ-
ences were limited to hematological AEs and infusion-related
reactions (IRRs), as infection rates were similar across all groups.
The high rate of IRRs observed in the G-Clb arm occurred in
the first cycle (only one grade III observed), probably reflecting
the immediate efficacy of obinutuzumab. In general, IRRs were
manageable with prophylaxis and dose splitting.

Regarding efficacy in CLL11, the study showed that ORRs were
higher in the chemoimmunotherapy arms for all comparisons
(G-Clb: 77.3% vs. R-Clb: 65.7% vs. Clb: 31.4%; p <0.001). Compared to patients treated with R-Clb, more patients in
the G-Clb arm achieved a CR (22.3% vs. 7.3%; p <0.001) and
a greater proportion of patients treated with G-Clb became
MRD-negative than those treated with R-Clb (bone marrow:
19.5% vs. 2.6%; p <0.0001). Furthermore, the study showed a
significantly longer PFS for both antibody-containing arms in
comparison to the single-agent chlorambucil arm (Figure 5).
Furthermore, PFS was considerably better with G-Clb than
with R-Clb (median PFS: 26.7 vs. 15.2 months; stratified
HR = 0.39; p <0.0001). This translated into a benefit in OS
with the addition of an anti-CD20 antibody to chlorambucil;
however, extended OS was only statistically significant in pa-
Figure 4. CLL11 study design

<table>
<thead>
<tr>
<th>Stage Ia</th>
<th>G-Clb vs. Clb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ib</td>
<td>R-Clb vs. Clb</td>
</tr>
<tr>
<td>Stage II</td>
<td>G-Clb vs. R-Clb</td>
</tr>
</tbody>
</table>

Table 2. Adverse events from the CLL11 study

<table>
<thead>
<tr>
<th>Adverse events CTC III-V (% of patients)</th>
<th>G-Clb n = 336</th>
<th>R-Clb n = 321</th>
<th>Clb n = 116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological AEs CTC III-V (% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33%</td>
<td>28%</td>
<td>10%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Infections CTC III-V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>12%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Infusion-related reactions CTC III-V</td>
<td>20%</td>
<td>4%</td>
<td>-</td>
</tr>
</tbody>
</table>

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

*R-Chlorambucil administered at 0.5 mg/kg po on days 1 and 11 of cycles 1–6 q28d.
†GA101 administered at 1,000 mg iv on days 1, 8, and 15 of cycle 1, and then 1,000 mg iv on day 1 of cycles 2–6 q28d.
‡Rituximab administered at 375 mg/m² iv on day 1 of cycle 1, followed by 500 mg/m² iv on day 1 of cycles 2–6 q28d.
§Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb.
chlorambucil (Figure 6). The numerical differences in the OS rates between R-Clb and chlorambucil and in the head-to-head comparison of R-Clb and G-Clb are not yet statistically significant, but look promising.

In summary, the study demonstrated that the combinations of chlorambucil with rituximab or obinutuzumab are feasible in CLL patients with significant comorbidities. Both the R-Clb and G-Clb regimens resulted in increased ORR, CR, and PFS rates compared to chlorambucil alone, with only G-Clb improving OS. The study concluded that the combination of chlorambucil with a monoclonal anti-CD20 antibody, preferably obinutuzumab, is the newly defined standard of care in first-line treatment of CLL patients with relevant comorbidities.
Treatment of patients with high-risk CLL: CLL2O trial

Defining which patients ought to be considered high-risk remains a significant challenge in the treatment of CLL. Several important prognostic markers have been identified, including del(17p), TP53, and IgHV mutation status, as well as del(11q). CLL patients with del(17p) or TP53 mutations have worse OS outcomes compared to patients with del(11q), and the previously observed poorer outcome of patients with del(11q) seems to be overcome with the use of FCR chemoimmunotherapy.\(^1\)

With the CLL8 study data set, it could be demonstrated that a short PFS is associated with a poor OS outcome. Interestingly, only approximately 25% of patients with a PFS lasting less than 24 months have del(17p), and therefore, several other prognostic markers seem to play a role. Because of worse outcomes for patients with an early progression, the guidelines of the European Society for Medical Oncology (ESMO) recommend changing the treatment in case of a PFS lasting less than 24 months and repeating the previous treatment only in case of a later occurring relapse. This guidance is consistent with that of the European Bone Marrow Transplantation Consortiums (EBMT) which recommends an allogeneic stem cell transplantation (SCT) for patients who relapse within 24 months and for patients who have del(17p) or TP53 mutation, if eligible. Given these guidelines, bringing these patients into remission is a very important issue before proceeding with SCT.
The CLL2O phase II study was designed for patients who were refractory to previous treatments, who relapsed within six months, or who had del(17p) (Figure 7). Patients received up to 12 weeks of induction treatment with alemtuzumab (30 mg subcutaneously [sc] on days 1, 8, and 15) and dexamethasone (40 mg orally on days 1–4 and 15–18) with pegfilgrastim support, followed by allogeneic SCT or alemtuzumab maintenance therapy. Interim results in evaluable patients showed that ORR and CR rates respectively were: 70% and 5% in patients with refractory CLL; 76% and 0% in relapsed patients with del(17p); and 97% and 20% in first-line patients with del(17p). Median PFS in each of the three previously described patient populations was 8.4, 10.4, and 16.9 months, respectively. These results compare favourably to those for the small number of first-line patients with del(17p) treated with FCR in the CLL8 trial, who achieved ORR and CR rates of 68% and 5%, respectively, and a median PFS of 11.3 months (Table 3). Consequently, alemtuzumab/dexamethasone should be preferred over the FCR regimen in patients with del(17p). However, with the introduction of novel agents, more potent and less toxic therapies might be available in the near future.

Another approach in assessing high-risk CLL involves categorizing patients after end of treatment based on the MRD levels achieved, which can predict the length of remission. Patients with an MRD level of $1 \times 10^{-2}$ or higher were shown to have a high risk of early progression. Also, patients with a MRD level between $1 \times 10^{-2}$ and $1 \times 10^{-4}$ and who have in addition a del(17p) or TP53 mutation and/or unmutated IgHV have an equally high risk of early relapse. This approach is being used in the CLLM1 trial of the GCLLSG to categorize patients into high and low risk based on the MRD level achieved after first-line treatment and the presence of risk factors. This phase III randomized, double-blind, placebo-controlled trial aims to evaluate the efficacy and safety of lenalidomide as maintenance therapy for two years in patients with a high risk of early progression after first-line therapy of the treating physician’s choice.

In conclusion, effective treatments for high-risk patients are a great unmet need in CLL. This is an area that requires novel approaches as well as novel agents to make significant headway.

**Figure 7. CLL2O study design**

<table>
<thead>
<tr>
<th>Ultra high-risk CLL</th>
<th>Alemtuzumab, Dexamethasone, Pegfilgrastim (up to 12 weeks)</th>
<th>Allogeneic SCT or alemtuzumab maintenance (up to two years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory*, 1st-line and relapsed del(17p)</td>
<td>Alemtuzumab: 30 mg sc, days 1, 8 and 15</td>
<td>Alemtuzumab: 30 mg sc days 1, 15</td>
</tr>
<tr>
<td>Dexamethasone: 40 mg p.o. day 1–4 and 15–18</td>
<td>Pegfilgrastim: 6 mg sc days 1 and 15</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Patient characteristics and response rates in CLL2O trial: alemtuzumab/dexamethasone in ultra high-risk CLL**

<table>
<thead>
<tr>
<th>ORR 70%</th>
<th>CR 5%</th>
<th>Median PFS 10.4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>97%</td>
<td>0%</td>
<td>16.9 months</td>
</tr>
<tr>
<td>68%</td>
<td>5%</td>
<td>11.3 months</td>
</tr>
</tbody>
</table>

CR = complete response; FCR = fludarabine, cyclophosphamide, rituximab; ORR = overall response rate; PFS = progression-free survival

**References:**
2. 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 (GCLLSG) 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. ASH Annual Meeting Abstracts 2012:345.
3. Eichhorst B, Fink A, Busch R, et al. Chemioimmunotherapy 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 (GCLLSG). ASH Annual Meeting Abstracts 2013:526.
An Interview with Dr. Stephan Stilgenbauer on the Use of Idelalisib in CLL

New Evidence: Please describe the rationale and patient population included in your study.

Dr. Stilgenbauer: Currently, no standard of care exists for the treatment of patients with CLL who have failed conventional treatment. In addition, new agents are needed for high risk patients with adverse prognostic factors, who are often difficult to treat using currently available options. Patients included in our study (Gilead GS-US-312-0116) had failed conventional treatment within two years, were elderly or frail, and had existing comorbidities such as poor renal function. We allowed a Karnofsky score down to as little as 40, which included frail patients in very poor condition. In addition, the vast majority of patients presented with genetic abnormalities, of which del(17p) and TP53 mutations are the most adverse prognostic markers related to conventional treatment.

New Evidence: What percentage of patients in the general population typically harbour del(17p) and TP53 mutations?

Dr. Stilgenbauer: In a population that is typical of primary treatment trials, the incidence of del(17p) and TP53 mutations is around 8–12%. Despite the fact that this is a relatively small subgroup of patients, in first-line treatment trials, these factors have shown to be the strongest prognostic factor of treatment failure. In addition, in subsequent lines of therapy, the proportion of patients with these markers is much higher, being 40–50% among refractory patients. These patients typically fail treatment earlier and therefore need subsequent treatment sooner than other patients.

New Evidence: Currently, which prognostic factors do you test for in the general population?

Dr. Stilgenbauer: In all patients requiring treatment in clinical trials, we typically test for genomic abnormalities by fluorescence in situ hybridization (FISH) and IGHV mutation status as well as the “novel CLL mutations”. In routine practice, it is recommended to test for del(17p) prior to all lines of treatment. Testing can be done within a few days and is very feasible, being a standardized test. However, other cytogenetic testing is not always done as part of routine clinical practice.
**New Evidence:** Currently, how do you treat patients with these adverse prognostic factors?

**Dr. Stilgenbauer:** It is very difficult to treat high risk patients with del(17p) with currently available treatment options. These patients typically fail first-line treatment with FCR (fludarabine, cyclophosphamide, rituximab) after a median duration of 12 months. Treatment with alemtuzumab may produce somewhat better results than FCR, but this has not been proven with randomized comparison in clinical trials. If patients are young and fit, they may be candidates for allogeneic stem cell transplantation. Otherwise, we will try to enrol them in a clinical trial investigating novel agents, given the lack of effective agents available for this population.

**New Evidence:** Please describe the mechanism of action of idelalisib.

**Dr. Stilgenbauer:** Idelalisib is a delta-specific phosphatidylinositol 3-kinase (PI3K) inhibitor that blocks cellular pathways critical for proliferation and survival of CLL, lymphoma, and other cancer cells.

**New Evidence:** What have the results of previous studies taught us about the use of idelalisib in the treatment of CLL?

**Dr. Stilgenbauer:** Initial studies demonstrated that idelalisib is efficacious in high risk patients failing conventional therapy. However, these were not randomized studies, making comparisons with other agents difficult. We therefore performed a randomized study (Gilead GS-US-312-0116) comparing rituximab plus placebo to rituximab plus idelalisib (R-idelalisib) in frail patients ineligible for more intensive treatments. Although rituximab monotherapy is not usually considered very effective in these patients, there is currently no established option available for this frail patient group. A crossover to the idelalisib group was allowed for patients failing rituximab. In addition, genetic parameters and central biobanking were included as part of the study, which will allow for additional questions to be addressed in the future.

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

**Dr. Stilgenbauer:** Results of our study (Gilead GS-US-312-0116) showed superior response rates, progression-free survival, and overall survival in the R-idelalisib versus the rituximab group. Although the superior efficacy of the R-idelalisib group was expected, the degree of the difference was remarkable, especially in this frail population characterised by a high incidence of adverse biological markers. In studies of conventional treatments, patients with del(17p) have consistently inferior outcomes. What is astonishing in this study is that the presence of del(17p) did not affect the efficacy of treatment with R-idelalisib. Results of this study therefore show R-idelalisib to be a valid treatment option for these high risk patients.

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

**Dr. Stilgenbauer:** In our study (Gilead GS-US-312-0116), R-idelalisib demonstrated a favourable safety profile with a few unique factors to consider. There did appear to be a higher rate of immunologically mediated reactions, such as colitis, that occurred at low incidences. In dealing with these reactions, we recommend stopping this regimen, doing a thorough, multidisciplinary work-up and possibly giving immunosuppressive treatment. These reactions need to be explored further as we are not used to managing them with conventional treatments. However, hematological toxicities and infections were very infrequent and appeared lower than rates shown with currently available treatments. Overall, as compared to conventional chemotherapy, the toxicity profile looked very favourable, in particular when considering the patient population under study.
**New Evidence:** Given the results of this study, in which patient population would you use R-idelalisib if available?

**Dr. Stilgenbauer:** Based on the results of this trial, R-idelalisib is a valid treatment option for patients where conventional treatment is inappropriate due either to early failure of conventional treatment or ineligibility due to poor fitness level. In addition, results of this study in the del(17p) subgroup highlight the fact that R-idelalisib could be a valid option for young and fit patients with this cytogenetic abnormality. I would still recommend FCR as the standard first-line treatment until further data become available in the frontline setting in fit patients. However, it would be, in general, preferable not to use conventional chemotherapies, as they induce hematotoxicity, cause infections, and may lead to the evolution of harmful clones with del(17p) and TP53 mutation.

Ongoing trials comparing FCR to novel agents in the first-line setting will take time to mature. In the meantime, if available, I would use R-idelalisib as an option in unfit patients not eligible for conventional chemotherapy, in young fit patients with del(17p) mutations in both the first-line and relapsed setting, as well as in those who failed conventional therapy early.

**New Evidence:** What are the next steps in evaluating idelalisib for the treatment of CLL?

**Dr. Stilgenbauer:** The next steps in evaluating idelalisib for the treatment of CLL are to examine this agent earlier in the treatment algorithm, in fit patients, and as part of other combination regimens. Ongoing trials show promise with the bendamustine, rituximab (BR) plus idelalisib combination, but more trials examining this and other regimens are needed.

**New Evidence:** What do you see as the overall benefits of idelalisib for the treatment of CLL?

**Dr. Stilgenbauer:** In patients with del(17p), the R-idelalisib regimen appears to offer the greatest margin of benefit compared to existing treatments. This is proof of concept that targeting disease biology works, and that it is possible to avoid selection of harmful subclones. In addition, if resistance occurs, it is likely to be specific to this agent and other available agents may overcome it. Therefore, from a theoretical standpoint, it may be preferable to use this agent upfront than to use chemotherapy, where mutations causing resistance (such as del(17p) and TP53 mutations) make patients more difficult to treat.
New Evidence spoke with Dr. Tom Kouroukis, from the Juravinski Cancer Centre at McMaster University in Hamilton, Ontario, Canada, about the results of the Bend-ACT study, an expanded access trial looking at the safety of bendamustine monotherapy in Canadian patients.

New Evidence: Please describe the rationale for the Bend-ACT study.

Dr. Kouroukis: The rationale for the study was two-fold: to look at the safety of bendamustine monotherapy and to give access to single-agent bendamustine to Canadian patients as indicated by Health Canada.

New Evidence: Please describe the study design.

Dr. Kouroukis: The Bend-ACT study was an expanded-access, open-label, prospective clinical trial conducted in 16 centres across Canada. Patients with indolent non-Hodgkin lymphoma (iNHL) received up to eight cycles of bendamustine (120 mg/m²) on days 1 and 2 every 21 or 28 days, where the cycle length was decided by the physician. Patients with chronic lymphocytic leukemia (CLL) were given bendamustine (100 mg/m²) on days 1 and 2 every 28 days for up to six cycles.

New Evidence: Please describe the patient population that enrolled in the study.

Dr. Kouroukis: There were two groups of patients enrolled in the trial: patients with relapsed/refractory iNHL who were previously treated with a rituximab-containing regimen and patients with CLL who had not received any prior treatment. Histologies in the iNHL group (n = 74) included follicular lymphoma grade 1 to 3A, marginal zone lymphoma, lymphoplasmacytic lymphoma, and small lymphocytic lymphoma. The mean age was 64 years (range: 40–90 years); in the CLL group, 44% of patients were 70 years of age or older. All patients were at least 18 years old, had an ECOG performance status of 0–2, and good organ function.

New Evidence: How does the patient population in the study compare to the patients that you see in your practice?

Dr. Kouroukis: Overall, the mean age of the patient population in the study was very close to what I see in practice with perhaps only the iNHL group being slightly younger. Sometimes it is challenging to enroll older patients into clinical trials but this did not appear to be an issue in this study.
New Evidence: What were the most frequently reported concomitant medications taken by patients?

Dr. Kouroukis: For patients with CLL, the most common medications used after the first dose of bendamustine were ondansetron, acetaminophen, prochlorperazine, allopurinol, dexamethasone, and granulocyte colony-stimulating factor (G-CSF). Patients with iNHL used the same medications as patients with CLL with the exception of allopurinol, which was used more frequently in the CLL group presumably due to concerns about tumour lysis syndrome.

New Evidence: What were the most common supportive medications used with bendamustine?

Dr. Kouroukis: In the study, the two most common concomitant medications used for supportive care were ondansetron and dexamethasone, which were both used to treat nausea.

New Evidence: In your practice, which concomitant and supportive medications do you typically use?

Dr. Kouroukis: For concomitant medications, I typically use anti-nausea medications. I do not generally use G-CSF; in Ontario, it is not possible to obtain G-CSF for incurable lymphoma histologies. Other provinces may have better access to it, which may be why more patients than I had expected were receiving it, to mitigate against neutropenia. For supportive care, I primarily use ondansetron. I do not routinely use a steroid unless there is an infusion reaction issue or more nausea than expected.

New Evidence: What percentage of patients with iNHL was on the 21-day cycle versus the 28-day cycle of treatment? Why?

Dr. Kouroukis: Physicians were allowed to choose which schedule to use for patients with iNHL. The majority of patients (77%) were on the 28-day cycle because this is more standard and is suggested in most of the literature. Fewer physicians started their patients on the 21-day cycle, possibly because they thought their patients had more aggressive disease. This number decreased slightly over the course of the study as patients were switched to the 28-day cycle.

New Evidence: Please describe the safety results, including the most frequent serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs) by patient group (iNHL vs. CLL).

Dr. Kouroukis: All of the patients in the Bend-ACT study experienced at least one adverse event (AE). SAEs occurred in 36.7% of patients; mortality was low (4.4%), with only one drug-related death.

For patients with iNHL, the most common SAEs were fever, febrile neutropenia, and pneumonia. The most common TEAEs of any grade were gastrointestinal (GI) effects (i.e., nausea, diarrhea, vomiting, constipation, and anorexia) and blood count abnormalities (i.e., neutropenia, anemia, and thrombocytopenia).

For patients with CLL, the most frequent SAEs were fever, febrile neutropenia, and tumour lysis syndrome. Similar to the iNHL group, the most common TEAEs of any grade were GI effects and blood count abnormalities. Fatigue was also common in both iNHL and CLL patients, but it was also quite commonly noted at baseline (just less than half of the patients had fatigue at baseline).

New Evidence: How do you typically manage these AEs in your practice?

Dr. Kouroukis: First, we maximize the use of supportive medications, in particular the use of antiemetics because many of the AEs associated with bendamustine are GI related. Second, dose reductions or delays may be necessary for some of the blood count abnormalities; typically we reduce the dose by 25%. In the case of neutropenia, G-CSF is used if available.
In Ontario, we now commonly use bendamustine plus rituximab (BR), and dose reductions occur relatively infrequently when bendamustine is used in this combination, compared with this study. One potential reason for this observation could be that we use BR upfront in iNHL, which means we have a less heavily treated population who can perhaps better tolerate the myelosuppression than those who were enrolled in the Bend-ACT study.

**New Evidence:** What were the most common causes of dose delays in the iNHL and CLL patient groups?

**Dr. Kouroukis:** Overall, 31.1% of patients had grade 3/4 TEAEs that led to dose delays. For patients with iNHL on the 21-day treatment cycle, dose delays were more frequent compared with patients on the 28-day cycle. This suggests that the three-week cycle was more difficult for patients to tolerate compared with the four-week cycle. The most common reasons for dose delays in the overall iNHL population were blood and lymphatic system disorders, including neutropenia and anemia. The most common reasons for dose delays in the CLL group were blood and lymphatic system disorders including neutropenia, thrombocytopenia, and anemia, as well as rash and hemolysis.

**New Evidence:** For patients with iNHL, can you comment on why dose delays and neutropenia were more frequent in patients on the 21-day cycle compared with the 28-day cycle?

**Dr. Kouroukis:** I suspect that it was related to bone marrow tolerance, which can be impacted by prior treatments. When bendamustine was first on the market, a number of studies used three-week treatment cycles. However, this was a challenging dosing regimen for patients with relapsed/refractory iNHL; four weeks was found to be a better tolerated schedule.

**New Evidence:** What were the most common reasons for dose reductions in the study?

**Dr. Kouroukis:** The most common reasons that led to dose reductions in patients with iNHL were neutropenia, anemia, diarrhea, and fatigue. For CLL patients, dose reductions were related to tumour lysis syndrome.

**New Evidence:** How do the safety results from this study compare with those from other studies with bendamustine?

**Dr. Kouroukis:** For the relapsed/refractory iNHL population, the safety results were comparable to the results of other studies using bendamustine. For the upfront CLL population, I would say the results were also comparable to those of other studies. However, the number of patients with CLL was small in this study and therefore, I am cautious about overgeneralizing the results for these patients.

**New Evidence:** Were the results stratified by subpopulation? Were there any differences in safety profiles between groups?

**Dr. Kouroukis:** The Bend-ACT study did not have any preplanned stratification. However, on analysis there were more SAEs in patients with CLL who were at least 70 years of age compared with patients who were under 70 years of age. The safety profiles otherwise were similar between the iNHL and CLL groups.

**New Evidence:** What were the conclusions of this study?

**Dr. Kouroukis:** The main conclusions of the study were there were no unexpected toxicities and overall, the toxicities were in line with those seen in other studies. The hematological toxicities were important regarding dose delays; SAEs primarily resulted from infection and fever.
**New Evidence:** Do the safety results from the study confirm your practical experience with bendamustine?

**Dr. Kouroukis:** Yes, they do. The deaths in the study were infrequent (<5%), which was within reasonable limits for a pretreated group of patients with iNHL. We typically see the same percentage of SAEs in practice as were seen in the study. GI AEs are also common in practice. In terms of GI AEs, what was illustrated by this study was that nausea can often linger for a few days. This is in contrast to treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, in which the nausea usually occurs early on in therapy and we prescribe anti-nauseants for a maximum of two or three days. When treating with bendamustine, we tend to prescribe anti-nauseants for a longer period of time — up to five days of ondansetron — because the nausea tends to last longer for some patients.

**New Evidence:** Do these safety results increase your confidence to use bendamustine in your practice?

**Dr. Kouroukis:** In general, they do. There were no significant safety concerns about using bendamustine in this patient population. The study did not address the benefits of bendamustine because it was largely designed as a safety study. However, bendamustine is highly efficacious based on other large prospective studies, particularly when used upfront in patients with iNHL. In Ontario, BR has evolved to be the standard of care in upfront iNHL treatment.

**New Evidence:** How will the results of the Bend-ACT study impact your clinical practice?

**Dr. Kouroukis:** The results of the study provide reassurance to health care providers (HCPs) that bendamustine has an acceptable safety profile. Adding rituximab to bendamustine is unlikely to add substantial toxicity.

Using bendamustine in the study allowed HCPs to gain experience with the drug; many centres had never used bendamustine prior to the study. When funding became available for bendamustine, because of their involvement in the study it was easier for those centres to transition to using bendamustine as part of their normal practice. For example, in our centre, because of the Bend-ACT study we had all of the pharmacy procedures in place, the nurses had been educated in the use of bendamustine, and the clinical staff had the experience and confidence to use it. From the study, we gained important practical experience with bendamustine: for example, we learned that we had to be more aggressive with the use of anti-nausea medications. We also learned that phlebitis could occur with the infusions, which led us to increase the volume of the required post-infusion flushing. Bendamustine administration was then easier to roll out once the drug became funded.

**New Evidence:** In which patients in your current practice do you use bendamustine?

**Dr. Kouroukis:** I use BR upfront for most patients with iNHL as well as for patients who have relapsed after at least one year following a prior rituximab-containing regimen. This is based on funding in Ontario. In Ontario, we are not funded to use bendamustine for patients with iNHL who are refractory, where refractory implies a patient has relapsed quickly after treatment with a rituximab-containing regimen (within one year). For patients with CLL, I can use bendamustine upfront as a single agent but not for patients with relapsed CLL, again based on funding. Other provinces may have more leeway to use bendamustine either upfront or for relapsed CLL, and in refractory iNHL.
**Lymphomas**

**Advances in Single-Agent and Combination Therapies for the Treatment of NHL**

Remarkable advances in cancer treatment have improved the prognosis and quality of life of patients with non-Hodgkin lymphoma (NHL). One of the newest treatments for NHL in Canada is bendamustine plus rituximab (BR).\(^1\) Bendamustine is a chemotherapeutic drug with structural similarities to alkylating agents and purine analogs that has demonstrated significant synergism with the anti-CD20 monoclonal antibody rituximab.\(^2\) In fact, the BRIGHT and StiL NHL trials have shown that patients with B-cell lymphoma responded very well to BR treatment, with significant improvements in progression-free survival (PFS) and complete response (CR) rates.\(^3\) More recently, treatment with idelalisib has been shown to actively induce durable responses in patients with indolent B-cell NHL. Ongoing studies show promising results for cancer treatment with idelalisib, which is a selective PI3K\(\delta\) inhibitor that blocks proliferation and induces apoptosis in many B-cell malignancies. Idelalisib reduces B-cell survival by inhibiting homing and retention of malignant B-cells in lymphoid tissues.\(^4\)

Other emerging therapies for NHL involve the addition of antibody-drug conjugates (ADC) to the repertoire of anticancer drugs. ADCs are unique combinations of cytotoxic drugs covalently linked to monoclonal antibodies that deliver the chemotherapeutic agent and release it at the tumour thus limiting systemic exposure. Among these ADCs, anti-CD22 pinatuzumab vedotin (PoV) and anti-CD79b polatuzumab vedotin (PiV) demonstrated promising results in phase II trials involving patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and indolent NHL.\(^5\)

At the 19\(^{th}\) Congress of the European Hematology Association (EHA), New Evidence covered several studies showing the latest advances in NHL treatment:

- A phase II, single-arm study evaluating patient-reported outcomes found that treatment with idelalisib resulted in stable or improved health-related quality of life (HRQoL) for patients with refractory indolent NHL.
- A single-centre, retrospective study investigating the toxicity of BR in patients with NHL who are of advanced age or who have severe comorbidities demonstrated that frail patients who are at high risk and unsuitable to receive intense chemotherapies could benefit from treatment with BR.
- An expanded access trial involving 16 centres across Canada evaluated the safety of bendamustine in the treatment of patients with indolent NHL who relapsed from a rituximab-based regimen or patients who had previously untreated chronic lymphocytic leukemia (CLL). This study found that the toxicity and safety profiles of bendamustine were consistent with previous studies. The most common adverse events included hematological toxicities, infections, and fever.
- The BrIL study evaluated the efficacy of BR as first-line chemoimmunotherapy for patients with follicular lymphoma (FL), mantle cell lymphoma, and other indolent NHL. This study demonstrated that BR is effective, with promising PFS at an acceptable level of toxicity.
- The collection and analysis of data from patients treated with bendamustine in the region of Tuscany showed that patients with indolent NHL had very high response rates following first-line treatment with bendamustine.
- An assessment of the risk of infections associated with bendamustine treatment demonstrated that bendamustine does not have a significantly different rate of infections compared with other alkylating agents or fludarabine and therefore remains a safe therapeutic option for NHL, CLL, and multiple myeloma.
The ROMULUS trial evaluated the efficacy of the ADCs PoV and PiV in combination with rituximab in the treatment of patients with relapsed/refractory DLBCL and FL. This study found that both combinations had acceptable safety profiles and pharmacokinetics, and durable responses.

The SEXIE-R-CHOP-14 trial investigating the safety and efficacy of a higher dose of rituximab in the treatment of elderly males with DLBCL found that increasing the dose by one-third did not increase the risk of toxicities in elderly males compared to females and also improved the outcome.

**Background**
Idealisib is active in inducing many durable responses in patients with refractory indolent B-cell non-Hodgkin lymphoma (NHL). The purpose of this study was to evaluate patient-reported outcomes (PRO) data in order to determine whether idealisib treatment was associated with a change in health related quality of life (HRQoL).1

**Study design**
- This was a phase II, single-arm study (n = 125) where idealisib was administered (150 mg orally, twice daily) to patients with refractory indolent NHL until disease progression.
- Patients were enrolled between April 2011 and October 2012.
- Inclusion criteria included:
  - Patients with histologically confirmed follicular lymphoma (FL), small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), or lymphoplasmacytic lymphoma (LPL);
  - Patients who had ≥1 measurable nodal lesion (≥2 cm);
  - Patients refractory to rituximab and an alkylating agent, who showed a lack of response while on therapy or progression within 6 months of completion of therapy;
  - Patients with the following bone marrow function: absolute neutrophil count >1,000/µL; hemoglobin >8 g/dL; platelets >50,000/µL;
  - Patients with creatinine <1.5 x upper limit of normal (ULN); transaminases <2.5 x ULN; and bilirubin <1.5 x ULN; and
  - Patients with a Karnofsky score ≥60 (ECOG PS >2).
- The primary endpoint of this study was the overall response rate (ORR), whereas the secondary endpoints included: duration of response, progression-free survival (PFS), overall survival, safety, and quality of life.
- Tumours were assessed at 0, 8, 16, 24, 36, and 48 weeks, and every 12 weeks thereafter.
- The Functional Assessment of Cancer Therapy for patients with Lymphoma (FACT-Lym) was scored at 0, 4, 8, 12, 16, 18, 24, 30, 36, 42, and 48 weeks, and every 12 weeks thereafter.
- The assessment endpoints of FACT-Lym considered 5 domains: lymphoma subscale (LymS), physical well-being, social/family well-being, emotional well-being, and functional well-being.
- Composite scores included the Total Outcome Index (TOI) and FACT-Lym total. (Table 1)
- The FACT-Lym was scored based on the FACIT (Functional Assessment of Chronic Illness Therapy) scoring guideline and user manual.
- Repeated measured mixed-effects models were used to assess mean change from baseline within the treatment arm.
- The primary endpoint of PFS was calculated using the Kaplan-Meier method and was compared using a stratified long-rank test. Cox model with adjustment for stratification was used to calculate the hazard ratio.
Key findings

- The baseline characteristics of enrolled patients (N = 125) included:
  - Median age of 64 years (range, 33–87);
  - 64% were male;
  - 70% with Stage IV disease; and
  - Number of prior regimens, median (range): 4 (2–12).
- With a median follow-up of 9.4 months, the ORR was 57% (95% CI: 47.6–65.6%) and the median PFS for all patients was 11.4 months.
- LymS change scores exceeded the minimum important difference for at least 90% of the patients, indicating a clinically significant improvement in lymphoma-related concerns at some point in the study. The median best change from baseline in LymS was 5.0, with a median time to improvement of 1.9 months. (Figure 1)
- Improvements were noted in the FACT-General (G), FACT-Lym, and TOI total scores during the study, progressively increasing with time. (Figures 2 and 3)
- The median best changes from baseline for the FACT-G, FACT-Lym and TOI total scores were 5.0, 8.3, and 6.0, respectively.
- In FACT-G subscales, improvements were noted by 4 weeks for EWB scores.

### Table 1. Assessment endpoints of FACT-Lym

<table>
<thead>
<tr>
<th>Domain</th>
<th>Number of items</th>
<th>Score range*</th>
<th>MID†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma Subscale (LymS)</td>
<td>15</td>
<td>0–60</td>
<td>3.5</td>
</tr>
<tr>
<td>Physical well-being (PWB)</td>
<td>7</td>
<td>0–28</td>
<td>2.3</td>
</tr>
<tr>
<td>Social/family well-being (SFWB)</td>
<td>7</td>
<td>0–28</td>
<td>2.3</td>
</tr>
<tr>
<td>Emotional well-being (EWB)</td>
<td>6</td>
<td>0–24</td>
<td>2.3</td>
</tr>
<tr>
<td>Function well-being (FWB)</td>
<td>7</td>
<td>0–28</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Composites**

| Total Outcome Index (TOI)‡   | 29              | 0–116        | 7.8  |
| FACT-Lym Total§             | 42              | 0–168        | 10–11|

*Higher scores reflect better HRQoL and lower symptom burden.
†When examining difference for groups, the lower end of the MID is unitized (Trask 2011).
‡TOI = LymS + PWB + FWB
§FACT-Lym Total = LymS + PWB + FWB + SFWB + EWB

### Study design

- **Enrolled April 2011 to October 2012**
- **Single-arm study (N = 125)**
  - Idelalisib 150 mg bid
  - Therapy maintained until progression

**Primary endpoint:**
- Overall response rate

**Secondary endpoints:**
- Duration of response
- Progression-free survival
- Overall survival
- Safety
- Quality of life

**Tumour assessments:**
- Weeks 0, 8, 16, 24, 36, 48
- Every 12 weeks thereafter

**FACT-Lym assessments:**
- Weeks 0, 4, 8, 12, 16, 18, 24, 30, 36, 42, 48
- Every 12 weeks thereafter

*bid = twice daily; FACT-Lym = Functional Assessment of Cancer Therapy for patients with Lymphoma*
Key conclusions

- Monotherapy with idelalisib induced responses in 57% of patients with double refractory indolent NHL.
- Patients on idelalisib experienced trends for clinically meaningful improvements in lymphoma-related symptoms and in physical and functional well-being.
- Improvements were most apparent in the lymphoma specific subscore.
- Overall HRQoL was stable or improved for patients on idelalisib.

Low toxicity of the bendamustine plus rituximab combination: results of a retrospective, single-centre analysis

Buquicchio C et al. EHA 2014:PB1799

Background
Recent data from clinical trials have shown the efficacy of bendamustine plus rituximab (BR) in the treatment of non-Hodgkin lymphoma (NHL). The objective of this study was to investigate if the BR combination had low toxicity and improved the quality of life of frail patients, such as the elderly or those with severe co-morbidities.1

Study design
• This was a retrospective study that included 33 patients with NHL who had been treated with bendamustine at a single Italian centre between 2011 and 2013.
• Bendamustine was administered intravenously (iv) at 70 to 90 mg/m²/day for two consecutive days in combination with rituximab (375 mg/m²) for one day every 28-day cycle for four to eight courses, for a total of 156 courses.
• Primary prophylactic granulocyte colony-stimulating factor (G-CSF) support and antimicrobial therapy were administered routinely.

Key findings
• Baseline characteristics of the 33 patients with NHL were:
  ▷ Females/males: 13/20;
  ▷ Median age of 70 years (range: 52–88), with 42% of patients older than 75 years.
  ▷ Performance status of 1-3; and
  ▷ Indolent NHL, n = 25; aggressive NHL, n = 8:
    – Patients >65 years old with relapsed/refractory NHL (n = 29); and
    – First-line patients who were <65 years old and had severe dilated cardiomyopathy (n = 4).
• The patients’ comorbidities included: hepatopathy associated with hepatitis B or C virus, hypertensive, ischemic, or dilated cardiomyopathy, chronic bronchitis, diabetes, and chronic renal impairment without dialysis.
• At a median follow-up of 12 months, 25 patients were evaluable for efficacy and safety.
• The overall response rate (ORR) was 90%, with 57% attaining complete response and 30% partial response, while 12% had stable disease and 3% early death. The latter refers to a 77-year-old patient who died from febrile neutropenia after a second episode of S. haemolyticus sepsis.
• The most common adverse event (AE) was grade 1 neutropenia, which was not associated with infectious complications, delay of therapy, or dose reductions. (Table 1)

Table 1. Adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia, grade 1</td>
<td>31</td>
<td>94</td>
</tr>
<tr>
<td>Cytopenia, grade 4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Fever infections requiring antibiotics</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Skin allergic toxicity</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal toxicity, grade 2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

• Other AEs and their treatments were:
  ▷ Grade 4 cytopenias (6%): reversible with G-CSF treatment and supported with transfusions of red blood cells and platelets;
  ▷ Fever infections (6%) requiring iv antibiotics: E. coli pneumonia in one patient and S. haemolyticus sepsis in another patient;
  ▷ Allergic skin reactions (9%): rash and pruritus were reversible in two patients after stopping concomitant treatment with cotrimoxazole and allopurinol, and grade 2 urticaria was treated with short and low doses of steroid therapy in one patient; and
  ▷ Gastrointestinal toxicity (3%): nausea and vomiting (grade 2), treated with antiemetic drugs in one patient.
• Cases of myelodysplastic syndrome, secondary neoplasms, or drug-drug interaction were not observed in this study.
• The quality of life assessment demonstrated that patients willingly accepted BR treatment and that it did not change their personal living routine.
Background

Bendamustine is widely used in the treatment of indolent non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). The purpose of this study was to evaluate additional safety data for bendamustine in up to 100 patients with indolent NHL relapsing from a rituximab regimen or CLL.1

Study design

• The Bend-ACT study was an expanded access trial conducted at sixteen centres across Canada, with patients enrolled from March 2012 to June 2013.

• Eligibility criteria included:
  ◦ Patients at least 18 years old with relapsed/refractory indolent NHL;
  ◦ Ability to provide informed consent;
  ◦ Previously treated with a rituximab-containing regimen or had previously untreated CLL;
  ◦ Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; and
  ◦ Good organ function.

• Patients with indolent NHL received up to 8 cycles of bendamustine (120 mg/m²) on days 1 and 2 every 21 or 28 days.

• Patients with CLL were given bendamustine (100 mg/m²) on days 1 and 2 every 28 days for up to 6 cycles.

• Patients were followed for up to 6 weeks after completion of treatment.

• Dose adjustments were made for toxicities.

Key findings

• A total of 90 patients with indolent NHL (n = 76) and CLL (n = 16) received treatment.

• Patients were a median age of 64 years (range: 40–90), with 44% of the CLL patients being at least 70 years old.

• For patients with indolent NHL, 77% were treated on a 28-day schedule with a median of 6 cycles of treatment (24.3% of patients received 8 cycles). The median time of treatment was 137 days (28–224 days).

• For CLL patients, the majority received at least 3 cycles of treatment and the median time on treatment was 91 days (28–168 days).

• All patients reported at least one adverse event (AE). Grade 3 or 4 toxicities resulted in dose delays in 31.1% of patients, with hematological toxicities (24.4%) being the most common reason.

• Withdrawal from treatment secondary to treatment-emergent AEs occurred in 32.2% of patients and was mainly due to rash, hematological, gastrointestinal, respiratory, and infectious reasons.

• Serious AEs were reported in 36.7% of patients. (Table 1)

• The cycle length did not result in any obvious difference in the rate of serious AEs.

• The overall mortality was 4.4%; AEs associated with death included Pneumocystis jiroveci pneumonia, cardiac arrest, respiratory failure, abdominal pain, and multi-organ failure (the only fatal AE deemed probably related to treatment).

Key conclusion

Frail patients with NHL (the elderly or those with severe comorbidities) who might be at increased risk of toxicities and who would not be suitable to receive intense chemotherapies could benefit from BR combination therapy.

Table 1. Serious adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td>6.6</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5.5</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3.3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2.2</td>
</tr>
<tr>
<td>Syncope</td>
<td>2.2</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Key conclusions

- Hematological toxicities were the most frequent reason for bendamustine dose delays.
- Infections or fever were the most common reasons for serious AEs.
- The toxicity and safety profile of single-agent bendamustine is consistent with other published studies in a similar patient population.


Hagberg H et al. EHA 2014:PB1802

Retrospective analysis of primary chemoimmunotherapy with bendamustine in combination with rituximab in patients with indolent and mantle-cell lymphomas

Background

The aim of this study was to evaluate the efficacy of bendamustine plus rituximab (BR) as first-line chemoimmunotherapy in a population-based setting for patients with follicular lymphoma (FL), mantle cell lymphoma (MCL), and other indolent non-Hodgkin lymphoma (NHL).²

Study design

- This was a retrospective, Nordic multicentre study (BRiL study).
- Eligibility criteria included:
  - Patients older than 18 years;
  - Patients with an histological diagnosis of MCL or indolent NHL, including: FL, splenic marginal zone lymphoma (SMZ), mucosa-associated lymphoid tissue (MALT) lymphoma, plasmacytic lymphoma (PL, including Waldenström’s lymphoma), and low-grade lymphoma not otherwise specified (indolent NHL NOS);
  - Patients who received at least two cycles of BR (minimum dose of 70 mg/m²) as first-line treatment.
  - Previous treatment with rituximab monotherapy and/or radiotherapy, and patients on rituximab maintenance following BR treatment were allowed.
  - Informed consent from patients was obtained according to country regulations.
- This study assessed complete remission (CR), overall response rate (ORR), progression-free survival (PFS), and toxicity.

Key findings

- This study included 116 patients (FL: n = 71; MCL: n = 15; SMZ: n = 8; MALT: n = 9; PL: n = 6; indolent NHL NOS: n = 7) with a mean age of 65.7 years and median of 67 years.
- Fifteen of these patients had previously received rituximab monotherapy.
- CR and ORR achieved after treatment with BR are summarized in Table 1.
This study confirms, at a population-based level, the efficacy and tolerability of BR as first-line chemoimmunotherapy for indolent NHL and MCL.


Rigacci L et al. EHA 2014:PB1810

Use of bendamustine as first-line treatment in a selected population of patients with NHL: Tuscany region experience

**Background**
Bendamustine was first introduced in Italy in 2008 and has been used since 2011 as an off-label drug in first-line therapy of non-Hodgkin lymphoma (NHL). The purpose of this study was to collect and summarize data from patients treated with first-line bendamustine at seven centres located in Tuscany.1

**Study design**
- Patients were enrolled between June 2011 and December 2012.
- Patients (n = 72) of various diagnoses of NHL were included in this study. (Table 1)
- Patients were administered one of the following doses of bendamustine for two days per cycle:
  - 90 mg/m²: n = 39;
  - 70 mg/m²: n = 28;
  - 120 mg/m²: n = 5.
- Bendamustine was used alone (n = 14) or in combination with rituximab or another drug (n = 56).
- During rituximab maintenance, another patient suffered from herpes encephalitis but survived.
- The estimated 3-year PFS of 70% for patients with FL without previous rituximab monotherapy (Figure 1) is similar to the PFS of a comparable group in the German study reported by Rummel et al.

**Key conclusion**
- CR was lower in patients who had previously received rituximab monotherapy (40%) compared with those who had not (60%).
- Stem cells were harvested from four patients and all of them had >2 x 10⁶/kg CD34+ cells.
- At the end of the study, 89% of patients were alive.
- The incidence of adverse events was similar to previously reported trials with BR.
- Thirteen patients died, but only two of the deaths were related to treatment: one patient died during treatment with BR due to sepsis, and one patient experienced progressive multifocal leukoencephalopathy and died during rituximab maintenance.
- The remaining patients died from: progressive lymphoma (n = 6), secondary malignancy (n = 2), cardiac arrest (n = 1), and other causes (n = 2).

**Table 1. CR and ORR after treatment with bendamustine plus rituximab**

<table>
<thead>
<tr>
<th></th>
<th>ORR (%)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>85.3</td>
<td>56.9</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>87.3</td>
<td>57.7</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>66.7</td>
<td>46.7</td>
</tr>
</tbody>
</table>

ORR = overall response rate; CR = complete remission

**Figure 1. Product-limit survival estimates**

During rituximab maintenance, another patient suffered from herpes encephalitis but survived.

The estimated 3-year PFS of 70% for patients with FL without previous rituximab monotherapy (Figure 1) is similar to the PFS of a comparable group in the German study reported by Rummel et al.
Key conclusion

Bendamustine treatment showed a very high response rate in patients with indolent NHL and also in more aggressive forms of the disease.


Gafter-Gvili A et al. EHA 2014:P439

Bendamustine is not associated with an increase in infections: A systematic review and meta-analysis of randomized controlled trials

Background

Bendamustine is a chemotherapeutic drug with structural similarities to both alkylating agents and purine analogues. Based on its nucleoside-like properties, bendamustine might be associated with infections. Since there are currently limited data regarding the infection-related adverse events of bendamustine-containing regimens, the purpose of this study was to assess the risk of infections associated with bendamustine treatment.1

Study design

• This study was a systematic review and meta-analysis of all randomized controlled trials comparing bendamustine-containing regimens (alone or combined with other chemotherapeutic agents and/or rituximab) to any other regimens in patients with lymphoproliferative disorders or plasma cell dyscrasias.
A comprehensive literature review was conducted, searching The Cochrane Library, MEDLINE, and conference proceedings and references until February 2014.

Two reviewers independently inspected relevant studies, applied inclusion and exclusion criteria, extracted the data, and appraised the quality of the trials.

The outcomes assessed were:
- Any infections;
- Any grade 3-4 infections;
- Fatal infections;
- Grade 3-4 neutropenia; and
- Grade 3-4 lymphopenia.

The relative risks (RR) with 95% confidence intervals (CI) were estimated and pooled for dichotomous data.

The data were pooled using the fixed effect model unless there was significant data heterogeneity, in which case the random effects model was used.

**Key findings**
- This study included nine trials conducted between 2006 and 2013, with a total of 2,586 randomized patients.
- Trials included in the meta-analysis:
  - Four trials of patients with chronic lymphocytic leukemia (CLL): Knauf et al. 2009, Niederle et al. 2013, Leblond et al. 2013, and Eichhorst et al. 2013 (CLL10); and
  - One trial of patients with multiple myeloma (MM): Ponisch 2006.
- The bendamustine arm included the following regimens:
  - Bendamustine alone: two trials;
  - Bendamustine, rituximab (BR): five trials;
  - Bendamustine, vincristine, prednisone (BOP): one trial; and
  - Bendamustine, prednisone (BP): one trial.
- The comparator arms in six of the trials included other alkylating agents:
  - Chlorambucil;
  - R-chlorambucil;
  - R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in two trials;
  - R-COP (rituximab, cyclophosphamide, vincristine, prednisone);
  - COP (cyclophosphamide, vincristine, prednisone); and
  - MP (melphalan, prednisone).
- The comparator arm in three of the trials included fludarabine alone or with rituximab (with or without cyclophosphamide).
- Bendamustine did not have a statistically significant effect on:
  - The rate of any type of infection (RR = 1.06 [95% CI: 0.83–1.34]; six trials);
  - The rate of grade 3-4 infections (RR = 1.11 [95% CI: 0.65–1.91]; seven trials); or
  - The rate of fatal infections (RR = 0.69 [95% CI: 0.30–1.58]; three trials).
- The rate of infections was similar between trials that administered bendamustine as first line and trials that administered it for relapse.
- Patients in the bendamustine arm showed no increase in the rate of grade 3–4 neutropenia compared to those on other regimens (RR = 0.82 [95% CI: 0.61-1.11]; seven trials).
- When the comparator was fludarabine-containing regimens, there was even a decrease in neutropenia (RR = 1.02 [95% CI: 0.54-1.91]; two trials).
- This study found a significant increase in grade 3-4 lymphopenia with bendamustine-containing regimens compared to regimens containing other alkylating agents (RR = 1.95 [95% CI: 1.54–2.47]).

**Key conclusions**
- This systematic review demonstrated that bendamustine treatment had no effect on the rate of infections when compared to other regimens, despite an increase in lymphopenia.
- Bendamustine remains a safe therapeutic option for NHL, CLL, and MM.
- The main drawback of this meta-analysis was the heterogeneity between malignancies and treatments.

Preliminary results of a phase II randomized study (ROMULUS) of polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed/refractory NHL

Background

Polatuzumab vedotin (PoV) and pinatuzumab vedotin (PiV), antibody drug conjugates (ADC) that contain the antimitotic MMAE (monomethyl auristatin E) and target CD79b (PoV) and CD22 (PiV), respectively, showed clinical activity in phase I studies of patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and indolent non-Hodgkin lymphoma (NHL).

The objective of this study was to compare PoV and PiV, each in combination with rituximab, in the treatment of R/R DLBCL and follicular lymphoma (FL).

Study design

• A total of 41 patients with FL and 81 patients with DLBCL were randomized to receive treatment with rituximab plus PoV (R + CD79b ADC) or rituximab plus PiV (R + CD22 ADC) at a dose of 2.4 mg/kg for the ADCs plus rituximab at 375 mg/m² every 21 days until disease progression or unacceptable toxicity, for a maximum of one year.

• Tumours were assessed every 3 months using the revised International Working Group (IWG) criteria.

• Treatment emergent adverse events (AEs) were graded per NCI CTCAE v.4.0.

• Anti-tumour activity was evaluated per revised IWG criteria (Cheson et al., 2007) every three months; PET scans were performed at the discretion of the investigator.

• Pharmacokinetic and pharmacodynamic evaluations included: total antibody, conjugate (antibody-conjugated cytotoxic agent MMAE), and unconjugated MMAE.

• Data from crossover patients was not included in this presentation.

Key findings

• The median number of prior systemic therapies was balanced between the two treatment arms for both disease types.

• The details of therapy delivered in this study are shown in Table 1.

• Overall safety profiles of both regimens were similar. The treatment-emergent AEs found in more than 25% of patients were: fatigue (52%), diarrhea (42%), nausea (37%), peripheral neuropathy (32%), and constipation (26%).
• Grade ≥3 AEs in over 3% of patients were:
  ◦ Neutropenia: 21%;
  ◦ Diarrhea: 6%;
  ◦ Dyspnea: 4%;
  ◦ Febrile neutropenia: 4%;
  ◦ Hyperglycemia: 4%; and
  ◦ Peripheral neuropathy: 4%.
• Neutropenia and peripheral neuropathy were considered the principal toxicities.
• Neutropenia was the most common grade 3–4 treatment-emergent AE, occurring primarily as a laboratory abnormality with few clinically significant sequelae.

  • Only one patient discontinued study treatment due to neutropenia.
  • Febrile neutropenia was reported in 4% of all patients.
  • Treatment was discontinued due to AEs in 45% of patients (n = 55). (Table 1)
  ◦ Peripheral neuropathy was the most common AE leading to discontinuation of study treatment. The protocol-defined mitigation for new or worsening grade 2 peripheral neuropathy was to dose delay ADC until improvement to grade 1 or baseline grade, followed by dose reduction to 1.8 mg/kg.
  • Pharmacokinetics (PK) profiles were similar for both ADCs across DLBCL and FL, showing no accumulation of free MMAE. (Figure 1)

### Table 1. Details of therapy delivered

<table>
<thead>
<tr>
<th></th>
<th>DLBCL R + CD22 ADC (N = 42)</th>
<th>DLBCL R + CD79b ADC (N = 39)</th>
<th>FL R + CD22 ADC (N = 21)</th>
<th>FL R + CD79b ADC (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of follow-up, months (range)</td>
<td>8.5 (0.5–14.8)</td>
<td>8.1 (0.6–13.8)</td>
<td>10.2 (0.2–13.2)</td>
<td>11.3 (6.7–15.0)</td>
</tr>
<tr>
<td>Median cycles received, (range)</td>
<td>7 (1–15)</td>
<td>6 (1–16)</td>
<td>7 (1–14)</td>
<td>10 (3–17)</td>
</tr>
<tr>
<td>Median time on study treatment, months (range)</td>
<td>4.1 (0.03–11.3)</td>
<td>3.4 (0.03–13.1)</td>
<td>4.4 (0.03–11.7)</td>
<td>6.9 (1.7–11.6)</td>
</tr>
<tr>
<td>Treatment modifications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuations for AEs</td>
<td>16 (38)</td>
<td>12 (31)</td>
<td>15 (71)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>7 (17)</td>
<td>8 (21)</td>
<td>6 (29)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Treatment delays</td>
<td>13 (31)</td>
<td>12 (31)</td>
<td>6 (29)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

AEs = adverse events; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; R + CD22 ADC = rituximab plus anti-CD22 antibody-drug conjugate; R + CD79b ADC = rituximab plus anti-CD79b antibody-drug conjugate

### Figure 1. Cycle 1 mean pharmacokinetics profile

![Figure 1. Cycle 1 mean pharmacokinetics profile](image-url)
• Compared to phase I single-agent data and based on population PK analysis, combination treatment with rituximab did not have a clinically meaningful impact on the PK of either ADC in the R/R NHL population.

• The investigator-assessed best responses in treated patients are summarized in Table 2.

• Anti-tumour responses observed by lymphoma subtypes and refractoriness to last prior therapy were similar in both arms. (Figure 2)

• In DLBCL patients, the median progression-free survival (PFS) was 5.4 months (95% CI: 2.8–8.4 months) and 5.2 months (95% CI: 4.1 months–not reached) for those treated with R + CD22 ADC and R + CD79b ADC, respectively. (Figure 3)

• The median PFS for patients with FL was not reported due to insufficient duration of follow-up.

### Table 2. Investigator-assessed best responses in treated patients*

<table>
<thead>
<tr>
<th></th>
<th>DLBCL</th>
<th>FL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R + CD22 ADC (N = 42)</td>
<td>R + CD79b ADC (N = 39)</td>
</tr>
<tr>
<td>Objective response, n (%)</td>
<td>24 (57)</td>
<td>22 (56)</td>
</tr>
<tr>
<td>Complete response</td>
<td>10 (24)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[12–39%]</td>
<td>[6–31%]</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (33)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[20–50%]</td>
<td>[26–58%]</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>3 (7)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>7 (21)</td>
<td>11 (30)</td>
</tr>
<tr>
<td>Unable to evaluate, n (%)</td>
<td>8 (19)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Median duration of response, months [95% CI]</td>
<td>6.0 [2.9–12.2]</td>
<td>NR [2.6–NR]</td>
</tr>
</tbody>
</table>

ADC = antibody-drug conjugate; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; NR = not reached; R + CD22 ADC = rituximab plus anti-CD22 antibody-drug conjugate; R + CD79b = rituximab plus anti-CD79b antibody-drug conjugate

*Patients who received ≥1 dose of study treatment; patients unable to evaluate did not have a post-baseline tumour assessment.

Figure 2. Anti-tumour responses by lymphoma subtypes and refractoriness to last prior therapy.
Figure 3. Progression-free survival

Key conclusions

■ Both the R + CD22 ADC and R + CD79b ADC had similar and generally acceptable safety profiles, with most AEs being grade 1–2.

■ Both ADCs had acceptable pharmacokinetics.
  • Rituximab combination had no clinically meaningful impact on ADC PK in the R/R NHL population.

■ Durable responses were observed in both DLBCL and FL, including in tumours refractory to last prior treatment.

■ Treatment with R + CD79b ADC showed a higher complete response rate, suggesting greater clinical activity in R/R FL.

■ Combination studies of the CD79b ADC with chemotherapy and strategies to evaluate and reduce peripheral neuropathy are ongoing or being planned.

Increased rituximab doses eliminate increased risk and improve outcomes for elderly male patients with aggressive CD20+ B-cell lymphomas: the SEXIE-R-CHOP-14 trial

**Background**

In previous trials involving patients with diffuse large B-cell lymphoma (DLBCL), elderly male patients demonstrated significantly lower rituximab serum levels, shorter exposure times, and worse outcomes than those in elderly female patients. The objective of this study was to investigate whether increasing the dose of rituximab in elderly males with DLBCL reduces their hazard compared to elderly females.¹

**Study design**

• The SEXIE-R-CHOP-14 trial was designed to test the administration of increased doses of rituximab in elderly male patients with CD20+ DLBCL: male patients received 500 mg/m² instead of the standard 375 mg/m² dose of rituximab.

• As a randomized phase II study with a factorial design, this trial also investigated the administration of six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone for 14 days per cycle (CHOP-14) in combination with either:
  - Eight doses of rituximab every two weeks; or
  - Eight upfront dose-dense applications of rituximab on days –1, 0, 3, 7, 14, 21, 28, and 42.

• In total, 271 patients were randomized and 268 patients were evaluable.

• Male patients (n = 148) received rituximab at 500 mg/m² and female patients (n = 120) received rituximab at 375 mg/m².

**Key findings**

• Protocol adherence was excellent, with median relative doses of rituximab and myelosuppressive drugs greater than 98%.

• The increased rituximab dose in males resulted in slightly higher trough serum levels than in females. However, rituximab levels dropped faster in males compared to females, resulting in very similar serum levels thereafter and a marginally longer rituximab exposure time in males. (Figure 1)

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**DLCL** = diffuse large B-cell lymphoma; **R** = randomization
• The increased rituximab dose was not associated with increased grade 3-4 toxicities. (Figure 2)

Figure 2. Toxicity (grades 3 & 4)

• The rates of progression-free survival (PFS) after a period of 3 years were 74% in males and 68% in females ($p = 0.396$). (Figure 3)

Figure 3. Progression-free survival according to sex

• The 3-year overall survival (OS) rates were 82% in males and 72% in females ($p = 0.111$). (Figure 4)

Figure 4. Overall survival according to sex

• In a historical comparison with a previous trial by multivariable analysis, adjusting for International Prognosis Index (IPI) risk factors and age over 70 years, the increased rituximab dose in male patients (vs. female patients) in this trial was associated with a reduced risk of an event in PFS and in OS. (Table 1)
### Table 1. Sex as a risk factor in elderly patients with DLBCL

<table>
<thead>
<tr>
<th></th>
<th>Event-free survival</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95% CI]</td>
<td>HR [95% CI]</td>
<td>HR [95% CI]</td>
</tr>
<tr>
<td>RICOVER (n = 610)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1.8 (p &lt;0.001)</td>
<td>1.7 (p = 0.170)</td>
<td>2.2 (p &lt;0.001)</td>
</tr>
<tr>
<td>ECOG &gt;1</td>
<td>1.8 (p = 0.001)</td>
<td>1.1 (p = 0.873)</td>
<td>1.7 (p = 0.004)</td>
</tr>
<tr>
<td>Stages III &amp; IV</td>
<td>1.5 (p = 0.011)</td>
<td>1.2 (p = 0.755)</td>
<td>1.5 (p = 0.045)</td>
</tr>
<tr>
<td>&gt;1 Extra-lympatic site</td>
<td>1.0 (p = 0.937)</td>
<td>1.9 (p = 0.121)</td>
<td>1.1 (p = 0.937)</td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>1.4 (p = 0.016)</td>
<td>0.9 (p = 0.708)</td>
<td>1.6 (p = 0.004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8 (p = 0.613)</td>
</tr>
</tbody>
</table>

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDH = lactate dehydrogenase

### Key conclusions

- Increasing the rituximab dose by one-third, from 375 mg/m² to 500 mg/m², eliminates the increased risk in elderly males compared to females.

- An increase in rituximab dose significantly improved the outcome in elderly male patients and in young male and female patients who have rituximab pharmacokinetics similar to elderly males, but these results should be confirmed in a larger randomized study.

- It remains unclear whether the rituximab dose of 375 mg/m² for elderly females is optimal.

The addition of rituximab to chemotherapy regimens, such as fludarabine, cyclophosphamide (FCR) in chronic lymphocytic leukemia (CLL), and to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and cyclophosphamide, vincristine, prednisolone (R-CVP) in indolent B-cell non-Hodgkin lymphoma (iNHL), marked a major improvement in the efficacy of these treatments. However, the increased efficacy observed with these regimens remains associated with high toxicity, especially in the case of R-CHOP and FCR. Two approaches aimed at addressing this issue have been to provide effective alternative chemo-immunotherapeutic options with better toxicity profiles and to develop new non-chemotherapeutic agents. Examples of these approaches include the alkylator bendamustine and the phosphatidylinositol 3-kinase delta (PI3Kδ) kinase inhibitor idelalisib, respectively.

The safety and efficacy of bendamustine monotherapy and bendamustine in combination with rituximab (BR) have been investigated in several phase III trials in iNHL and CLL. As a result, BR is now both a first- and second-line treatment option in iNHL and mantle cell lymphoma, and bendamustine monotherapy is a first-line treatment option in CLL. In fact, 90% of patients in my clinic now receive BR in first-line treatment of iNHL, and the remaining 10% receive BR second-line. The lack of funding for bendamustine in combination with rituximab in CLL makes bendamustine-based treatment in this setting much less frequent, with about 20% of patients receiving bendamustine in first-line and a little more in second-line.

Bendamustine has advantages and disadvantages over the standard alternative treatments in both settings. In iNHL, consensus on available data suggests that BR is associated with higher progression-free survival (PFS) and lower toxicity than R-CHOP, but probably has a similar toxicity profile to R-CVP. In CLL, a randomized comparison of bendamustine to chlorambucil suggested that bendamustine is more effective but is also more toxic, with a higher frequency of myelosuppression, infections, and rashes. The efficacy of BR compared with FCR is currently being investigated in the CLL10 trial by the German CLL Study Group. Recent interim results from that study suggest that BR is non-inferior to FCR and is associated with less hematological toxicities. Therefore, it would appear that the efficacy and toxicity profiles of BR are intermediate between the less toxic R-Clb or R-CVP and the more toxic FCR or R-CHOP.

Data on the safety of bendamustine in CLL and iNHL continues to accumulate. Kouroukis et al. reported safety results from Bendamustine Expanded Access Trial (Bend-ACT) on bendamustine monotherapy in patients with untreated CLL or relapsed iNHL. This trial was conducted at sixteen centres across Canada from March 2012 to June 2013. The study concluded that the toxicity and safety profile of bendamustine monotherapy was consistent with other published studies. Of the 90 patients, 31.1% experienced dose delays due to grade 3–4 toxicities, with the most common reason for delays being hematological toxicities (24.4%). Furthermore, treatment emergent adverse events (AEs) led to treatment withdrawal in 32.2% of patients. These were not surprising results and are consistent with the medical literature as well as my experience with bendamustine in real-life practice. Also significant was the absence of new safety signals; the most common reasons for withdrawal due to treatment emergent AEs were rash and hematological, gastrointestinal, respiratory, and infectious AEs. Together these results confirm previous results of the Bend-ACT trial, which was conducted in Canada on a small number of patients and at a time when bendamustine was not available. Those initial trials gave Canadian physicians their first experience with bendamustine, and it is reassuring that the toxicity profile observed in small early studies in Canada are consistent with these new results.

A more specific look at the safety of bendamustine came from the systematic review and meta-analysis by Gafter-Gvili et al., which investigated the risk of developing infections after bendamustine treatment. Using the Cochrane Library, MEDLINE, conference proceedings and references, the review included all trials evaluating bendamustine for any lymphoproliferative or plasma cell disorders up until February 2014. The study concluded that, compared with either alkylating agents or fludarabine, bendamustine treatment had no effect on the rate of grade 3–4 infections, fatal infections, grade 3–4 neutropenia, or grade 3–4 lymphopenia. These results are consistent with the safety results of other studies, and with our experience with bendamustine in real-life
practice. The analysis also revealed an intriguing finding: when compared with alkylating agent-containing regimens, bendamustine led to an increase in lymphopenia without an increase in opportunistic infections. The significance of this finding remains unclear, and requires further study. Also interesting was the observation that there was no effect on the rate of infections in trials that used bendamustine in the first-line setting compared with those that used bendamustine in relapsed settings. This would be a great finding if confirmed in subsequent studies. However, the risk of infections is generally expected to increase in the relapsed setting compared to first-line, likely due to cumulative marrow toxicities and mucosal damage. Therefore, the absence of this observation from this analysis was surprising. Overall, the study provides assurance that bendamustine is not associated with high toxicity and, therefore, remains a safe option.

With respect to idelalisib, this new agent shows early promise in efficacy and safety, especially in patients with high-risk CLL harbouring del(17p) or p53 mutations. Most early studies on idelalisib have been focused on safety and efficacy, so the analysis on health-related quality of life (HRQoL) is significant. Salles et al. analyzed patient-reported outcomes from a phase II study in which patients with iNHL who were refractory to rituximab and an alkylating agent were treated with idelalisib monotherapy. Previous analysis from this study had shown that after a median follow-up of 9.4 months idelalisib monotherapy resulted in an overall response rate (ORR) of 57%, an impressive result given that the expected ORR with monotherapy in this patient population is typically 20–30%. Also reported was a median PFS of 11.4 months. The impact of idelalisib on HRQoL was subsequently addressed in this analysis using the Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) tool, which is an assessment of five domains: sub-scale (LymS), and physical, social/family, emotional, and functional well-being. The study concluded that HRQoL results were stable or improved for patients on idelalisib. However, it was not clear if the LymS change from baseline scores exceeded the minimum important difference (MID) of 3–5 for ≥90% of the patients because the scores seemed to stay below the MID for a significant amount of the study period. Furthermore, it was unclear if the spike in scores observed towards the end of the study period reflected improvements due to treatment or reflected patient death which would in turn cause the remaining healthier patients to contribute to higher scores. Overall, the study suggests that idelalisib monotherapy in this patient population is not only effective but also leads to steady or improved HRQoL scores.

HRQoL is an increasingly important endpoint in clinical trials because new or improved treatments have significantly increased overall survival in leukemia patients. This means that physicians are increasingly asking whether patients would feel better from second- or third-line treatments when treatments do not promise a long-lasting remission. In such cases, response rates become less important and symptomatic aspects take on more significance. Thus, showing that a second- or third-line treatment improves HRQoL is a strong argument in favour of using a proposed treatment. In addition to helping us understand the impact of treatments on patients’ lives, the more frequent employment of HRQoL analysis in clinical trials will help the research and medical community improve the interpretation of this tool. For example, it is very difficult to see how FACT-Lym differentiates between HRQoL improvements due to efficacy and those due to toxicity.

New Developments in Follicular Lymphoma

Summary of the Presentation by Dr. Nathan Fowler at CCOLD 2014

At the 2014 Canadian Conference on Lymphoproliferative Disorders (CCOLD), Dr. Nathan Fowler, Lead, New Drug Development and Co-Director of Clinical and Translational Research in the Department of Lymphoma/Myeloma at MD Anderson Cancer Center, Houston, Texas, presented a summary of new therapeutic options in follicular lymphoma (FL).

Challenges to Progress

Survival outcomes of patients with indolent B-cell lymphoma at the MD Anderson Cancer Center have improved significantly over the past 60 years. Overall survival (OS) after 60 months was 29.3% for the period of 1944 to 1954, but increased to 82.7% for the period of 1995 to 2004. This improvement can be attributed to multiple factors, including introduction of rituximab, earlier diagnosis, and advances in supportive care.

However, despite aggressive therapy and newer agents, most patients with indolent lymphomas relapse within the first five years of initiating therapy. Therapies for relapsed patients are therefore an unmet need and an active area of research.

Multiple factors have contributed to the difficulty in designing clinical trials and making continued progress in the development of improved treatments for patients with indolent lymphomas. Firstly, since there is currently no consensus on the accepted standard of care, patients receive different therapies at different treatment centres, making it difficult to compare outcomes. Secondly, frontline therapies have tended to result in very heterogeneous outcomes, further complicating interpretation of data. Thirdly, although it is favourable that patients with indolent lymphomas have prolonged remission and survival, the costs associated with designing clinical trials in which primary outcomes occur after many years of treatment frequently discourage initiation of trials for low-grade lymphomas. Lastly, understanding of the biological processes that underlie lymphoma development has been undergoing a rapid evolution in recent years. These advances are raising hopes that novel drugs based on key new insights are poised to lead to dramatic improvements in the treatment of indolent lymphomas.

Improvements to Standard Regimens

The current standard of care for advanced indolent non-Hodgkin lymphoma (NHL) consists of rituximab (R) plus chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisone (CVP). However, many patients eventually become refractory to these regimens and require new therapies.

Bendamustine

Bendamustine is a cytotoxic alkylating drug that has recently gained approval in Canada for use in indolent NHL and chronic lymphocytic leukemia (CLL), although it has been approved for use in Germany for more than 20 years. Incorporation of bendamustine into standard treatment regimens for indolent NHL has demonstrated promising clinical activity.

Several studies have investigated the efficacy of bendamustine in indolent lymphomas. The German Study Group for Indolent Lymphomas (StiL) conducted a noninferiority trial, with progression-free survival (PFS) as the primary endpoint, to compare bendamustine plus rituximab (BR) versus rituximab plus CHOP (R-CHOP) in previously untreated patients with indolent lymphoma. More than half of the patients in this trial had FL (279 out of 514 patients analyzed). Patients in the BR treatment group received bendamustine administered intravenously (iv) at 90 mg/m² on days 1 and 2 of a 4-week cycle for up to six cycles. Patients randomized to receive R-CHOP were given cycles every 3 weeks of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (up to a maximum dose of 2 mg) on day 1, and prednisone 100 mg per day for 5 days, up to a maximum of six cycles. All patients additionally received rituximab 375 mg/m² on day 1 of each cycle.

PFS was significantly prolonged in the BR group compared to the R-CHOP group (69.5 vs. 31.2 months; HR: 0.58 [95% CI: 0.44–0.74]; p <0.0001). For the subgroup of patients with FL in this study, median PFS was not reached with BR and was 40.9 months with R-CHOP.
In Supportive Care Oncology

In Supportive Care Oncology

In Supportive Care Oncology

In Supportive Care Oncology

(HR: 0.61 [95% CI: 0.42–0.87]; p = 0.0072). BR was associated with fewer adverse events (AEs) compared with R-CHOP, including alopecia (0% vs. 100%; p <0.0001), hematological toxicity (30% vs. 68%; p <0.0001), infections (37% vs. 50%; p = 0.0025), paresthesia (7% vs. 29%; p <0.0001), and stomatitis (6% vs. 19%; p <0.0001). In contrast, erythematous skin reactions occurred at greater frequency in patients treated with BR than with R-CHOP (16% vs. 9%; p = 0.024). However, there was no significant difference in 5-year OS between the two treatment groups (80% for BR vs. 78% for R-CHOP).

Flinn et al. also investigated the efficacy and safety of bendamustine versus standard chemotherapy in the global, phase III BRIGHT study. The primary objective of the study was to determine whether BR was noninferior to standard chemotherapy, as assessed by the complete response (CR) rate. Patients with treatment-naïve indolent NHL or mantle cell lymphoma (MCL) were randomized to receive treatment with BR or immunochemotherapy consisting of either R-CHOP or R-CVP. Patients treated with BR received rituximab iv at 375 mg/m² on day 1 followed by bendamustine iv at 90 mg/m² on days 1 and 2. Cycles of BR were repeated every 28 days for six cycles, up to a maximum eight cycles at the discretion of the investigator. Patients treated with standard therapy received rituximab iv at 375 mg/m² on day 1, cyclophosphamide iv at 750 mg/m² on day 1 (up to 1,000 mg/m² if treated with R-CVP), vincristine iv at 1.4 mg/m² (up to 2 mg) on day 1, and prednisone orally at 100 mg/day on days 1 to 5. Patients receiving R-CHOP were additionally given doxorubicin iv at 50 mg/m² on day 1. Cycles of R-CHOP or R-CVP were repeated every 21 days.

Out of 419 evaluable patients, there were 297 patients who had FL. In the overall study population, the CR rate was 31% for patients treated with BR and 25% for patients treated with standard therapy. The CR-rate ratio between BR and R-CHOP/R-CVP was noninferior (CR-rate ratio 1.26; p = 0.0225 for noninferiority) but not statistically superior (p = 0.1269). The overall response rate (ORR) was 97% for patients treated with BR and 91% for patients treated with standard chemotherapy, which was statistically superior for the BR treatment group (p = 0.0102). In the subset of patients with FL, the CR rate was 30% for patients treated with BR and 25% for patients treated with standard therapy, and noninferiority approached significance (CR-rate ratio: 1.27 [95% CI: 0.87–1.84]; p = 0.0569) (Table 1). The ORR was >99% for patients treated with BR and 94% for patients treated with R-CHOP/R-CVP.

Although CR and partial response (PR) were similar between the two arms of the study, differences in toxicity were seen between the regimens. R-CHOP and R-CVP were associated with higher reports of all-grade peripheral neuropathy and alopecia, and grade 3/4 neutropenia, whereas BR treatment resulted in higher levels of all-grade drug hypersensitivity and vomiting, and grade 3/4 lymphopenia. The BRIGHT study is ongoing and will evaluate the secondary endpoints of PFS and OS after the required minimum 5 years of follow-up is completed.

In light of at least comparable efficacy of BR and R-CHOP/R-CVP observed to date and the lower toxicity of BR compared to standard chemotherapy, the combination of bendamustine and rituximab can be considered as an alternative first-line treatment for FL.

### Table 1. Independent review committee assessment of response to treatment with BR vs. R-CHOP or R-CVP (evaluable analysis)

<table>
<thead>
<tr>
<th>Efficacy in follicular lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BR, n/N (%)</strong></td>
</tr>
<tr>
<td><strong>CR</strong></td>
</tr>
<tr>
<td><strong>CR + PR</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most common adverse events in all histologic subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preselected for R-CHOP</strong></td>
</tr>
<tr>
<td><strong>BR (%)</strong></td>
</tr>
<tr>
<td>Lymphopenia (grade ≥3)</td>
</tr>
<tr>
<td>Neutropenia (grade ≥3)</td>
</tr>
<tr>
<td>Vomiting (all grades)</td>
</tr>
<tr>
<td>Rash/urticaria (all grades)</td>
</tr>
<tr>
<td>Infections (grade ≥3)</td>
</tr>
<tr>
<td>Peripheral neuropathy/paresthesia (all grades)</td>
</tr>
<tr>
<td>Alopecia (all grades)</td>
</tr>
</tbody>
</table>


BR = bendamustine, rituximab; CR = complete response; FL = follicular lymphoma; ns = not significant; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone
Emerging Therapy for Follicular Lymphoma

Kinase Inhibitors

Research into the factors that drive proliferation, growth, and survival of normal and malignant B cells has uncovered the importance of signaling pathways downstream of the B-cell receptor (BCR). Constitutive activation of signaling from the BCR is likely to play a central role in the pathogenesis of B-cell malignancies, and drugs that target these pathways are an area of rapid development. Inhibitors of key proximal kinases in the BCR pathway are among recent promising therapeutic approaches for B-cell lymphomas.

Ibrutinib

Ibrutinib is a potent small molecule kinase inhibitor that selectively forms an irreversible bond with the Cys481 residue in the active site of Btk, an essential kinase in B-cell development. A number of studies have investigated the possibility of using ibrutinib to treat B-cell lymphomas.

In a phase I clinical trial by Fowler et al., the efficacy and safety of ibrutinib was examined in 47 patients with various relapsed or refractory B-cell malignancies, 15 of which were FL. Patients were treated with escalating doses of ibrutinib in six cohorts, beginning with 1.25 mg/kg/day and progressing to 2.5, 5.0, 8.3, 8.3 continuous dosing, and 12.5 mg/kg/day. Overall response (OR) was achieved in four patients with FL (26.7%), all of which were PR. Treatment-related grade ≥3 AEs occurred in nine out of 47 patients (19%), and included neutropenia lasting >7 days, hypersensitivity reaction, small bowel obstruction, and exacerbation of chronic obstructive pulmonary disease. There was no evidence of cumulative hematologic toxicity.

Another phase I study to examine the efficacy and safety of ibrutinib treated 56 patients with relapsed or refractory B-cell NHL, CLL, or Waldenström macroglobulinemia with escalated dosing of the drug. Patients received ibrutinib either orally once daily at 1.25, 2.5, 5, 8.3, or 12.5 mg/kg/day on a 28 days on, 7 days off schedule, or as continuous daily dosing of 8.3 mg/kg or 560 mg fixed dose until disease progression, unacceptable toxicity, or decision by patient or investigator to discontinue treatment. An objective response (CR or PR) was achieved by 60% of evaluable patients in the study, including CR of 16%. Out of 16 patients with FL, six showed an overall response, three of which were CR. Median PFS in all patients studied was 13.6 months. Most AEs were grade 1 or 2 in the overall study group, with grade ≥3 hematologic toxicities including neutropenia (12.5%), thrombocytopenia (7.2%), and anemia (7.1%). As in the study by Fowler et al., no cumulative hematologic or nonhematologic toxicity was apparent with prolonged dosing.

Based on the positive preliminary data indicating that ibrutinib is well tolerated and active, phase II clinical trials have been launched. ORR will be evaluated in patients with refractory FL whose disease has relapsed from at least two prior therapies, including at least one rituximab combination chemotherapy regimen (NCT01779791). An additional phase II study is evaluating the efficacy of ibrutinib and rituximab combination therapy as assessed by ORR in previously untreated patients with FL (NCT01980654).

Idelalisib

Phosphatidylinositol-4,5 bisphosphate 3-kinase (PI3K) is a lipid kinase consisting of a catalytic subunit with four different isoforms. The delta isoform of PI3K is primarily expressed in leukocytes and is a key regulator of B-cell function. PI3K-delta is hyperactive in many B-cell malignancies. The small molecule inhibitor idelalisib is highly selective for the PI3K-delta isoform and is being investigated as a therapeutic option for patients with B-cell lymphomas.

A phase I study by Benson et al. evaluated continuous idelalisib monotherapy in 64 patients with relapsed or refractory indolent NHL, 38 of whom had FL. Doses of idelalisib ranged from 50 to 350 mg once or twice per day. ORR in the entire study group was 48%, with one patient showing CR. Median duration of response (DOR) was 18.4 months and median PFS was 7.6 months. In the subgroup of patients with FL, the ORR was 45%. Idelalisib displayed a favourable safety profile in this study. The most common grade ≥3 AEs included alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations (25%), pneumonia (16%), diarrhea (8%), rash (3%), fatigue (3%), pyrexia (3%), cough (2%), and nausea (2%).

Leonard et al. evaluated idelalisib in combination with rituximab and/or bendamustine for the treatment of patients with relapsed or refractory indolent NHL. In this phase I study, patients were randomized to receive continuous (48 weeks) idelalisib (Idela) at 100 or 150 mg twice a day in combination with: rituximab (R) (375 mg/m² weekly x 8 doses) (Idela+R), bendamustine (B) (90 mg/m² x 2, for 6 cycles) (Idela+B), or both R (375 mg/m² monthly x 6) and B (90 mg/m² x 2), for 6 cycles (Idela+BR). The study group consisted of 78 patients, 36% of whom were patients with FL with high Follicular Lymphoma International Prognostic Index scores. The ORR/CR for patients treated with Idela+R was 77%/20%, with Idela+B was 85%/29%, and with Idela+BR was 79%/43%. At 20 months of follow-up, PFS for the overall study group was 66%. Similar to the study by Benson et al., the most common grade ≥3 AEs included ALT/AST elevations (17%), pneumonia (15%), diarrhea (8%), rash (8%), fatigue (4%), and pyrexia (4%).

A clinical trial by Gopal et al. addressed the unmet need of treating patients with indolent NHL who had become refractory to both rituximab and an alkylating agent. This single-group, phase II study administered idelalisib orally at 150 mg twice per day to 125 patients, 72 of whom (58%) had FL. Out of 122 evaluable patients, 110 (90%) had a reduction in tumour size. The ORR was 57% (95% CI: 48%–66%) for the entire study group, and 54% (95% CI: 42%–66%) for the subgroup of...
patients with FL. In the entire study group, median DOR was 12.5 months and median PFS was 11.0 months (Figure 1). At the time of data cutoff, median OS was 20.3 months, and OS at 1 year was estimated to be 80%. Incidence of AEs was low, with the most common grade ≥3 AEs including neutropenia (27%), thrombocytopenia (6%), anemia (2%), diarrhea (13%), pneumonia (7%), dyspnea (3%), increased ALT (13%), and increased AST (8%). Discontinuation of treatment due to AEs occurred in 25 patients.

Figure 1. Progression-free survival after treatment with idelalisib (intention-to-treat population)

Apoposis Regulators
Disruption of apoptosis regulatory pathways can contribute to malignancy by promoting cancer cell survival and increasing resistance to chemotherapy drugs. For example, the anti-apoptotic protein BCL2 is frequently overexpressed in B-cell lymphomas. Therefore, BCL2 is a potential therapeutic target since its inhibition may restore sensitivity to pro-apoptotic signals and lead to the programmed death of malignant cells.

ABT-199
Among the new therapies being investigated for B-cell lymphomas is ABT-199, a small molecule inhibitor of BCL2. Davids et al. undertook a phase I dose-escalation study to evaluate safety and pharmacokinetics and to determine the maximum tolerated dose (MTD) of ABT-199. Patients with relapsed or refractory NHL received ABT-199 on Week 1 Day -7 (W1D-7) followed by continuous, once-daily dosing from W1D1. Treatment continued until progressive disease or unacceptable toxicity. A 2 to 3 week lead-in period with stepwise escalation of ABT-199 was started from lower doses to final cohort doses of 200, 300, 400, 600, and 900 mg. At the time of reporting, 32 patients had been enrolled, 11 of whom (34%) had FL. The most common grade ≥3AEs in the overall group were anemia (15%), neutropenia (13%), and thrombocytopenia (13%). Patients demonstrated an ORR of 53%, with 2 CR (6%) and 15 PR (47%). In the subgroup of patients with FL, ORR was 27%, all of which were PR. SD occurred in the remaining FL patients (73%). The responses reported for all FL patients occurred at doses of ≥600 mg. This study is ongoing and dose escalation is continuing to determine the MTD.

Role of the Microenvironment
In addition to the roles that deregulated signaling proteins play in pathogenesis, the influence of the surrounding tumour microenvironment in sustaining B-cell lymphomas is becoming increasingly recognized. The stromal environment provides survival and growth signals to malignant B cells. In a complex interplay, malignant B cells also manipulate their microenvironment to promote immunosuppressive conditions favourable to their development. Analysis of these interactions is leading to identification of potential therapeutic approaches in this area.

Lenalidomide
Lenalidomide is a drug with multiple mechanisms of action, including many within the microenvironment. An immunomodulatory drug with effects on T-, B-, and natural killer cells, lenalidomide also alters cytokine profiles in the microenvironment, inhibits angiogenesis, and abrogates stromal support for cells in the bone marrow. Investigation of the activity of lenalidomide in B-cell lymphomas, as monotherapy as well as in combination trials, is underway.

In a phase II, single-arm study, patients with untreated, advanced-stage indolent NHL were given 20 mg/day of lenalidomide on days 1 to 21 and rituximab 375 mg/m² on day 1 of each 28-day cycle for 6 cycles. Patients could continue treatment for up to 12 cycles if there was evidence of a tumour response. Out of 103 patients evaluable for response in the study, 46 patients had FL. The ORR for the FL group was 98%, with the majority (87%) showing CR. Estimated PFS at 2 years was 83% for all patients and 89% for patients with FL (Figure 2). Treatment-related grade ≥3 AEs in the overall study group included neutropenia (40%) and thrombocytopenia (4%).

A phase II trial by Tilley et al. investigated the combination of lenalidomide with R-CHOP in patients with high tumour burden FL. Treatment consisted of six cycles of lenalidomide and R CHOP every 3 weeks (25 mg oral lenalidomide on days 1 to 14) followed by two additional rituximab infusions. The dose of lenalidomide was adjusted according to toxicities. Patients who responded to induction therapy received rituximab maintenance every 8 weeks for 2 years. Out of 80 patients enrolled in the study, 68 (85%) received the complete induction regimen. The CR/CRI rate was 74% (95% CI: 63%–83%) and ORR was 94% (95% CI: 86%–98%). Treatment-related AEs were similar to those typically observed with R-CHOP treatment, which included 65% grade 4 neutropenia, 12.5% grade 4 thrombocytopenia, and 7.5% febrile neutropenia. Grade 3 neuropathy was reported in one patient and grade 3 reversible skin toxicity occurred in two patients. The study concluded
that a treatment regimen combining lenalidomide with R-CHOP is well tolerated and results in high rates of complete remission in patients with high tumour burden FL.

The Rituximab and Lenalidomide versus Any Chemotherapy (RELEVANCE) study has launched and includes several Canadian investigators (NCT01650701, NCT01476787). This phase III clinical trial will enroll 1,000 patients and compare rituximab and lenalidomide versus the investigator’s choice of R-CHOP, R-CVP, or BR. The primary endpoint is PFS, which is expected to be reached in 10 years.

Summary

Advances in the understanding of the molecular pathogenesis of B-cell lymphomas have resulted in a new era of rationally designed therapy using targeted agents. Emerging drugs with activities directed at the relevant signaling molecules that underlie disease have the potential to drive a breakthrough in the treatment of indolent lymphomas and improve failure-free survival of patients. Ongoing and planned clinical trials will investigate if treatment regimens for FL that combine multiple therapeutic agents with different mechanisms of action yield the best results in patients.

References:

An Interview with Dr. Laurie Sehn on New Developments in the Management of CLL and FL in Canada

At the CCOLD 2014 Annual Meeting, New Evidence spoke with Dr. Laurie Sehn, Clinical Assistant Professor at the BC Cancer Agency and the University of British Columbia, Vancouver, British Columbia (B.C.).

Chronic Lymphocytic Leukemia

New Evidence: What are the key unmet needs in the treatment of chronic lymphocytic leukemia (CLL)?

Dr. Sehn: It is important to remember that CLL remains an incurable disease; we therefore have a lot of work to do in improving the efficacy of treatment. In addition, many of the standard treatments are toxic and cannot be used in all patients, especially the elderly and those with comorbidities. Finally, it remains a challenge to manage high-risk patients with varying biology, such as those with del(17p).

New Evidence: What are the factors you consider in determining patient fitness?

Dr. Sehn: There is some variability between provinces as well as between institutions in determining patient fitness. However, age and the presence of comorbidities are the key factors considered in determining the optimal treatment for patients. The Cumulative Illness Rating Scale (CIRS) is a reasonable guide for FCR eligibility given the design of the CLL8 study. However, in B.C., our primary treatment is fludarabine plus rituximab (FR) and we therefore do not use a lot of FCR (fludarabine, cyclophosphamide, rituximab). For treatment with FR, we consider a compilation of clinical factors and make decisions based on the ability for individual patients to tolerate treatment. If a patient is too frail, given comorbidities such as renal insufficiency, we will consider alternative treatment.

New Evidence: In clinical practice, what percentage of patients is eligible for standard treatments?

Dr. Sehn: When considering patient fitness, it is important to consider that this concept is relative to the toxicity of the treatment you are giving. For patients below age 65 and without serious comorbidities, FCR may be a reasonable treatment option. Based on these criteria, approximately one third of patients would be eligible for treatment with FCR. Conversely, FR is better tolerated and is appropriate in approximately 90% of patients.
**New Evidence:** What currently available treatment options would you recommend for less fit patients?

**Dr. Sehn:** In patients unable to tolerate FR, we would consider giving rituximab plus chlorambucil (R-Clb) or bendamustine plus rituximab (BR). We have been using chlorambucil for decades and it is still very effective and well tolerated, especially in elderly patients. Based on the evidence that adding rituximab to chlorambucil improves efficacy, it is reasonable to give R-Clb in patients unable to tolerate FR.2

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**New Evidence:** Are there any patients that you would not give rituximab?

**Dr. Sehn:** Based on the improved response and duration of response to treatment with the addition of rituximab, there are very few circumstances where we would not add it to chemotherapy.2 Very rarely, there may be a patient who is unable to receive intravenous treatment and we would not be able give rituximab.

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**New Evidence:** What are the advantages of eliminating fludarabine-based regimens for the treatment of CLL?

**Dr. Sehn:** Fludarabine is a very effective treatment for CLL and it is unlikely that we will entirely eliminate it in the near future. It is true that fludarabine is not appropriate for patients with renal insufficiency and is associated with significant cytopenias and increased risk of infection in certain patients. However, our goal is to find the most effective therapy with the least amount of toxicity and one that will not limit future treatment options. Moving forward there may be targeted treatments available that are less toxic, but for now, fludarabine is an integral part of therapy.

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**New Evidence:** What new treatment agents appear the most promising?

**Dr. Sehn:** One of the most exciting new agent is ibrutinib, which is a targeted therapy shown to be highly effective in CLL, including patients with del(17p). A key attraction of ibrutinib is that it is an oral therapy and comes with a reasonable toxicity profile. Ibrutinib is currently available in the U.S. and will soon be available in Canada. Once ibrutinib is available in Canada, it will offer an alternative for patients who are not eligible for FR. A second novel agent is idelalisib, which is also a targeted oral therapy with a favourable toxicity profile. Finally, ABT-199 is a BCL-2 inhibitor that is also showing significant efficacy in the treatment of CLL. Further studies are needed to compare these agents and to examine them as combination therapy. Although none of these novel agents have been compared in head-to-head studies, they all show significant efficacy. As a next step, it would be helpful to determine the predictive factors that identify which patients will most likely benefit from these novel treatments in order to determine the optimal treatment for individual patients. Given that these agents have targeted mechanisms of action, individual patients may have specific pathways that are dominant in terms of the oncogenesis of their CLL.

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**New Evidence:** If available, in which patients would you give obinutuzumab?

**Dr. Sehn:** The head-to-head comparison of R-Clb versus obinutuzumab plus chlorambucil (G-Clb) clearly demonstrated the improved efficacy of obinutuzumab compared to rituximab.2 The clinically significant improvements in progression-free survival (PFS), induction of remission, and rate of minimal residual disease (MRD) were very impressive and unexpected. Based on this study, I think it is reasonable to replace rituximab with obinutuzumab as the preferred antibody in the treatment of CLL when using chlorambucil. It is not unreasonable to anticipate that this benefit may also be extrapolated to other chemotherapy backbones. I would therefore use obinutuzumab with chlorambucil in preference to R-Clb in clinical practice. I also think that replacing rituximab with obinutuzumab can be considered when using it in combination with other chemotherapy backbones.

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**New Evidence:** In your opinion, what is the most exciting new development in CLL?

**Dr. Sehn:** The most important development in the treatment of CLL is the creation of novel targeted agents. We are now seeing the evolution of studies demonstrating the benefits of these agents in a variety of patients. We are also able to effectively treat higher risk patients in clinical trials that are also benefitting from these new drugs.
**Follicular Lymphoma**

**New Evidence:** What are the key unmet needs in the treatment of follicular lymphoma (FL)?

**Dr. Sehn:** Given that FL remains an incurable disease, improving the efficacy of treatment is a clear unmet need. There is also a need for less toxic therapies for the treatment of this disease. Finally, we are also looking for therapies that result in more durable remissions and minimize the amount of time that patients remain on treatment.

**New Evidence:** What first-line treatment do you give to patients with FL?

**Dr. Sehn:** Currently, the preferred first-line treatment for FL in B.C. is BR, based on results of the StiL trial, which compared BR to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and demonstrated an improvement in PFS and lower toxicity with BR. Our previous standard treatment was R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), and given that R-CHOP has been shown to be more effective than R-CVP with respect to time-to-treatment failure, our expectation is that BR would offer an even greater advantage over R-CVP. Our second-line therapy following BR is R-CVP, which remains a well-tolerated and effective regimen.

I believe the tolerability and safety of BR is comparable to R-CVP, although the toxicity profile appears to be different. BR is associated with greater lymphopenia and may induce a more prolonged immunosuppression, but it is associated with less neutropenia than R-CVP. We therefore need to monitor for a different range of infections with the use of BR.

**New Evidence:** Do the results of the BRIGHT study reinforce your choice of first-line therapy for patients with FL?

**Dr. Sehn:** The BRIGHT study compared BR to R-CHOP/R-CVP, with the primary outcome being response rate. We therefore do not have information on the difference in PFS between arms. However, results of the study demonstrate that BR has at least comparable efficacy to R-CHOP/R-CVP with respect to response induction, with a more favourable toxicity profile.

**New Evidence:** Would you treat elderly patients with FL differently than younger patients?

**Dr. Sehn:** It is important to consider the comorbidities of elderly patients with FL when making treatment decisions. BR is appropriate in around 90% of patients, but there are some very frail patients who may not tolerate this regimen. In these patients, R-Cib is a good treatment alternative.

**References:**
Multiple Myeloma

New Drug Options for the Treatment of Multiple Myeloma

Multiple myeloma (MM) is the second most common hematologic malignancy in Canada, accounting for approximately 1% of all cancers and 2% of deaths from cancer. In 2014, an estimated 2,600 Canadians will be diagnosed with MM, with 1,400 expected to die from the disease. Median age at diagnosis for MM is 71 and less than 1% of cases are diagnosed in patients under the age of 40. Since MM is primarily a disease of the elderly, treatment strategies need to take into consideration age-related patient characteristics, comorbidities, and expected toxicity profiles of the chosen regimens.

A better understanding of the biology of MM combined with the availability of drugs with different mechanisms of action, such as proteasome inhibitors (e.g., bortezomib) and immunomodulatory drugs (e.g., lenalidomide), have led to improved survival of patients in recent years. However, single-agent therapy with these drugs is only effective in a subset of patients and insight into the factors that determine responsiveness is lacking. Moreover, the majority of responding patients eventually develop resistance to therapy by mechanisms that remain unclear.

Combination therapy for patients with MM has yielded some success in the clinic, but concerns persist that patients with refractory disease are unable to tolerate a more aggressive course of treatment. Identification of treatment regimens with favourable toxicity profiles is an active area of investigation in MM.

In this article, we report results of studies presented at the EHA 2014 Congress that evaluated new drug therapies for patients with MM:

- Combination therapy consisting of bendamustine, prednisone, and bortezomib was effective and well-tolerated in patients with newly diagnosed/untreated MM and normal or impaired renal function.
- Bendamustine showed promising results as salvage therapy in heavily pretreated patients with double-refractory MM.


Bendamustine, prednisone, and bortezomib combination therapy in patients with newly diagnosed/untreated multiple myeloma

Background

Bortezomib is a proteasome inhibitor that has been shown to have clinical efficacy as monotherapy and in combination with other agents in patients with multiple myeloma (MM). At EHA 2014, Poenisch and colleagues presented results from a clinical trial that assessed efficacy and toxicity of the combination of bortezomib with bendamustine and prednisone (BPV) in patients with newly diagnosed/untreated MM. Poenisch W et al. EHA 2014:P961
Study design

- Between June 2006 and October 2013, 49 patients with newly diagnosed/untreated MM were treated with the BPV combination regimen, consisting of:
  - Bendamustine: 60 mg/m² on days 1 and 2;
  - Prednisone: 100 mg on days 1, 2, 4, 8, and 11; and
  - Bortezomib: 1.3 mg/m² on days 1, 4, 8, and 11.
- Patients were divided into three groups:
  - Group A (n = 19): Patients with normal renal function or mild dysfunction (estimated glomerular filtration rate [eGFR] ≥60 mL/min);
  - Group B (n = 15): Patients with moderate or severe renal dysfunction (eGFR 15–59 mL/min);
  - Group C (n = 15): Patients with renal failure/dialysis (eGFR <15 mL/min).

Key findings

- A median number of three (range 1–5) BPV treatment cycles were administered to all patients.
- The majority of patients (n = 40, 82%) responded after a median of two (range 1–4) cycles of BPV treatment. Responses included: (Figure 1)
  - 5 (10%) stringent complete responses (sCR);
  - 9 (18%) near complete responses (nCR);
  - 12 (24%) very good partial responses (VGPR);
  - 14 (29%) partial responses (PR).

- No significant difference in overall response rate (ORR) was observed between group A (n = 15, 79%), group B (n = 13, 87%), and group C (n = 12, 80%). (Table 1)
- The median time to first hematological response (≥PR) was 14 days, and the median time to best response was 42 days.
  - The rapidity of response in patients with normal renal function or mild renal dysfunction (group A) was not different from that of patients with moderate or severe renal dysfunction (group B) or those with renal failure/dialysis (group C).

Figure 1. Cumulative hematological response after each cycle of BPV treatment

Table 1. Best confirmed response

<table>
<thead>
<tr>
<th>Best confirmed response</th>
<th>Group A, n (%) eGFR ≥60 mL/min (n = 19)</th>
<th>Group B, n (%) eGFR 15–59 mL/min (n = 15)</th>
<th>Group C, n (%) eGFR &lt;15 mL/min (n = 15)</th>
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<tbody>
<tr>
<td>CR</td>
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</tr>
<tr>
<td>nCR</td>
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<tr>
<td>VGPR</td>
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<td>PR</td>
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</tr>
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</table>

CR = complete response; eGFR = estimated glomerular filtration rate; MR = minor response; nCR = near complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response
• Treatment was continued until the maximum response was achieved in 13 out of 49 patients (27%; 3 sCR, 3 nCR, 4 VGPR, 3 PR).

• Discontinuation of treatment occurred in 29 patients (59%; 2 sCR, 6 nCR, 8 VGPR, 9 PR, 3 MR, 1 stable disease) after a median of two cycles of BPV treatment (range 1–5) to receive autologous or autologous/allogeneic stem cell transplantation (SCT).

♦ One patient with initially diagnosed plasma cell leukemia and del(17p) discontinued treatment to receive primary allogeneic SCT.

• Median observation time of surviving patients was 13 months.

♦ Progression-free survival (PFS) at 12 months in patients with normal or mild renal dysfunction vs. patients with moderate or severe renal dysfunction was 92% vs. 83%, respectively. (Figure 2)

− PFS was better in these patients compared to patients with renal failure/dialysis (66%), although the difference was not statistically significant ($p = 0.08$).

♦ Overall survival (OS) in patients with normal or mild renal dysfunction vs. patients with moderate or severe renal dysfunction was 94% vs. 93%, respectively. (Figure 3)

− OS was better in these patients compared to patients with renal failure/dialysis (73%), although the difference was not statistically significant ($p = 0.05$).

• The BPV combination therapy regimen was well tolerated with few significant adverse events. (Table 2)

♦ The most common grade 3/4 hematological toxicities were leukocytopenia, thrombocytopenia, anemia, and neutropenia.

♦ There was a moderate difference in leukocytopenia ($p = 0.09$) and neutropenia ($p < 0.01$) between group A/B and group C, with a greater occurrence of moderate to severe infections observed in group C ($p < 0.01$).
Table 2. Adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Group A, n (%) eGFR ≥60 mL/min (n = 19)</th>
<th>Group B, n (%) eGFR 15–59 mL/min (n = 15)</th>
<th>Group C, n (%) eGFR &lt;15 mL/min (n = 15)</th>
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<td></td>
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<td>Group A, n (%) eGFR ≥60 mL/min (n = 19)</td>
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<td>Group C, n (%) eGFR &lt;15 mL/min (n = 15)</td>
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<td>Hematological</td>
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<td>Group B, n (%) eGFR 15–59 mL/min (n = 15)</td>
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<td>Infection</td>
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<td>Neuropathy (newly diagnosed)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>grade 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>grade 3</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis and embolism</td>
<td>grade 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>grade 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin rash</td>
<td>grade 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>grade 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate

Key conclusions

■ BPV combination therapy is an effective and well-tolerated treatment protocol in patients with newly diagnosed/untreated MM and normal or restricted renal function.

■ Hematological and renal responses were very rapid and occurred within six weeks in the majority of patients.

■ The high efficacy and favourable toxicity profile of BPV therapy warrant further evaluation in clinical trials.


Caers J, et al. EHA 2014:PB1667

Durable responses to bendamustine therapy in responding patients with double refractory multiple myeloma

**Background**

Bendamustine has been shown to have activity in untreated as well as relapsed/refractory patients with multiple myeloma (MM). Caers and colleagues reported the results of bendamustine therapy in patients with MM who had relapsed after both bortezomib and lenalidomide treatment.¹

**Study design**

- From February to December 2012, the Belgian Hematological Society (BHS) MM study group enrolled...
20 patients with MM with a prior history of relapse after both bortezomib and lenalidomide treatment.

- Patients were heavily pretreated, with a mean number of five prior regimens (range of 3–8 prior regimens).
- Median patient age was 69 years (range of 52–83 years).
- Inclusion criteria included:
  - Absence of end-stage renal disease;
  - Correct residual marrow function;
  - Absence of plasma cell leukemia.
- Patients received bendamustine until disease progression.
  - The median number of bendamustine cycles infused was four (range of 1–8 cycles).
- Eleven patients received at least one autologous stem cell transplantation (ASCT).
- Responses were assessed by the treating physician.

**Key findings**

- Overall response rate (according to European Society for Blood and Marrow Transplantation criteria) was 45%.
  - Investigators recorded one very good partial response, eight partial responses, two minor responses, three patients with stable disease, and six patients with disease progression. (Table 1)
- Progression-free survival (PFS) for the whole population was 90 days.
  - PFS in responding vs. non-responding patients was 133 days vs. 60 days ($p = 0.001$), respectively.
- Overall survival of responding vs. non-responding patients was 350 days vs. 137 days ($p = 0.0006$), respectively. (Figure 1)
- Toxicity was mainly hematological, with grade III-IV cytopenia recorded in 50% of patients.
- One patient presented with septicemia, while cytomegalovirus infection occurred in another patient.

**Table 1. Response rates**

<table>
<thead>
<tr>
<th>Response (according to EBMT criteria), n (%)</th>
<th>(N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>9 (45)</td>
</tr>
<tr>
<td>VGPR</td>
<td>1 (5)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (40)</td>
</tr>
<tr>
<td>MR</td>
<td>2 (10)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (15)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

EBMT = European Society for Blood and Marrow Transplantation; MR = minor response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response

**Figure 1. Overall survival of responding vs. non-responding patients**

- Survival (%)
- Time (days)
- OS = overall survival

**Key conclusions**

- Survival rates for the heavily pretreated patients in this study who responded to bendamustine salvage therapy were encouraging.

- Further prospective clinical trials are needed to investigate whether well-selected double refractory patients with MM might benefit from bendamustine as salvage therapy.

An Interview with Dr. Dietger Niederwieser on the Use of Bendamustine in Multiple Myeloma

New Evidence: What are the key unmet medical needs in the treatment of multiple myeloma (MM)?

Dr. Niederwieser: Our ultimate goal for the treatment of MM is to move beyond maintaining a non-progressive state to finding a cure for the disease. There are currently a number of new drugs that show promise in inducing a complete response (CR), but a cure remains elusive. Unfortunately, the varying genetic mutations that exist in MM make treating this disease more difficult than treating diseases such as chronic myeloid leukemia and other hematological cancers. As we gain a greater understanding of the pathways involved in the pathogenesis of MM, we may find ways to block these pathways to more effectively treat the disease.

One area of disease management that needs improvement is early diagnosis. Given the heterogeneity of the disease, which varies in its presentation, age of onset, and symptoms, patients are often misdiagnosed and treated for back pain or given dialysis without suspecting MM. Earlier detection and screening are therefore vital in the treatment of the disease.

New Evidence: How do you currently manage untreated MM in your practice?

Dr. Niederwieser: For fit patients, SCT is our treatment of choice. Although we used to give vincristine, doxorubicin, and dexamethasone (VAD) as initial treatment, it results in fewer CRs than with other regimens that include newer agents. PAD (bortezomib, adriamycin, dexamethasone) and BPV (bendamustine, prednisone, bortezomib) are frequent combinations in use today. Following this induction therapy, patients undergo an autologous-allogeneic SCT, which has been shown to be superior to autologous-autologous SCT. Maintenance is also playing a key role in treatment, especially for patients with residual disease. Generally, given recent advances in induction therapies and conditioning regimens, we prefer to enrol patients in clinical trials.

The treatment of MM varies depending on patient age and comorbidities. In patients ineligible for stem cell transplantation (SCT), such as the elderly and those with renal impairment, bendamustine plays a key treatment role. Although bendamustine has existed for over 50 years, it has not been investigated in detail for the treatment of MM. Our previous phase III study comparing bendamustine plus prednisone (BP) to melphalan plus prednisone (MP) showed superior outcomes with BP in patients ineligible for SCT. Following this study, BP became the standard of care for patients with MM ineligible for transplant. The main advantage of BP is that it is better tolerated, has superior efficacy, and has less renal toxicity than other available treatments. Therefore, in patients who were ineligible for SCT, we gave BP as first-line treatment until a few years ago. Currently, a combination of bendamustine with new drugs like thalidomide, lenalidomide and/or bortezomib is frequently given. In the future, newer agents such as pomalidomide or monoclonal antibodies may provide additional treatment options.
**New Evidence:** What are the possible advantages of an agent like bendamustine as part of induction prior to stem cell transplant?

**Dr. Niederwieser:** Bendamustine offers many advantages as part of induction regimens in MM. Because it has less renal toxicity than other treatments, it can be used in patients with renal insufficiency and is also suitable for older patients with comorbidities. In patients with renal insufficiency it is important to give fast-acting regimens to improve kidney function. However, there is some concern as to whether bendamustine may be toxic to stem cells. Although we are currently examining this issue in a clinical trial, we have not seen any indication that this is a concern in our practice.

**New Evidence:** Please describe the rationale of your study examining the use of BPV in untreated MM.

**Dr. Niederwieser:** There is growing experience with the use of BP for the treatment of MM. However, CR rates remain low. With the aim of increasing CR rates, we examined the BPV regimen in untreated patients with MM. The patient population included those with mild-to-moderate renal impairment, but were otherwise relatively fit for treatment.

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

**Dr. Niederwieser:** After at least one cycle of BPV, 82% of patients responded with 10% achieving CRs, 18% achieving near CRs, 24% achieving very good partial responses, and 29% achieving a partial response. In addition, there was no difference in overall response rates between patients with normal versus mild-to-moderate renal impairment. These results are exciting, as it is very difficult to treat patients with renal dysfunction. In addition, compared to historical controls, the efficacy of this regimen appears promising and should be confirmed in future studies.

**New Evidence:** Were there any major safety concerns in your study?

**Dr. Niederwieser:** Because only a minor portion of bendamustine is secreted through the kidneys (the rest through the liver), it is an ideal agent for patients with renal dysfunction. Although rates of anemia, infections, and nausea and vomiting were numerically higher in patients with renal dysfunction, the regimen was fairly well tolerated in this group of patients. In addition, the hematological and renal responses were rapid and occurred within six weeks of treatment initiation in the majority of patients.

**New Evidence:** In what patients might you use BPV if it were available outside of clinical trials?

**Dr. Niederwieser:** Given the results of this and other studies, I would give BPV to all patients unless I felt we could increase CR rates further with other combinations. However, investigation on the effects of bendamustine on stem cells needs to be conducted to ensure this agent can be used safely in patients prior to mobilization. If enrolment in clinical trials were not an option, I would currently give BPV to patients at diagnosis and especially to those with renal dysfunction. In the future, we might achieve even higher CR rates by adding newer agents. Obtaining a CR is a very important step in treating the disease, even if one or two SCTs are planned. Today we can perform SCTs in patients up to 75 years old with the goal of curing the disease.

**New Evidence:** How do you manage patients with relapsed/refractory MM?

**Dr. Niederwieser:** Given that there is no cross-resistance of bendamustine with other drugs, it is an essential agent for the treatment of relapsed and refractory disease. In addition, results showing the superiority of bortezomib, thalidomide, and dexamethasone over the dual combination of thalidomide and dexamethasone after autologous SCT have been published by Garderet et al. In patients without a previous transplant, I would therefore give BPV
and perform a transplant if feasible. In less fit patients, I would use BP; but if they were not responding I might try lenalidomide and low-dose dexamethasone (RD). For patients relapsing after allogeneic transplant, I would give donor lymphocyte infusion with or without maintenance therapy. Newer agents, such as new proteasome inhibitors, are currently being examined and may prove useful in the relapsed setting.

**New Evidence:** What are your impressions of the study by Caers et al. (ABSSUB-5374) examining bendamustine in double-refractory MM?

**Dr. Niederwieser:** The study by Caers et al. included heavily pre-treated patients with a prior history of relapse after treatment with both bortezomib and lenalidomide. Patients were given bendamustine; however, it was not clear whether this agent was given alone or in combination with other agents. Considering the number of previous treatments, efficacy results appear excellent. In addition, safety findings show hematological toxicity as the main concern, which corroborates the results of our study. Because there is no cross-resistance with bendamustine, this agent could be a useful agent in this relapsed setting.

**New Evidence:** Please describe the results of ongoing studies using bendamustine, bortezomib and dexamethasone (BVD) in patients with relapsed/refractory MM.

**Dr. Niederwieser:** An ongoing study (IFM 2009-01) by Rodon et al., presented at ASH 2013, examined BVD in relapsed elderly patients with MM. The median age was 75 years, which is 10 years older than the median age of patients in the general population. However, patients had only received one line of therapy. Response to BVD was reasonable in this group and the regimen demonstrated manageable toxicity that compared favourably with low-dose dexamethasone or bortezomib and dexamethasone (VD). Although some infections and cytopenias were reported, rates were not beyond those expected in this population.

A second ongoing study by Cerchione et al. (ABSSUB-5828), presented at the EHA 2014 meeting, examined the use of BVD in heavily pre-treated patients. Unlike the previous study, the median age was 66 years; however, patients had been given a median of 6.3 previous treatments. In addition, the dose of bendamustine varied from 120–180 mg/m² and was therefore a higher dose than is usually given. Efficacy was promising and the regimen demonstrated a reasonable safety profile.

**New Evidence:** What are the next steps in examining bendamustine and bendamustine-based combinations in the treatment of MM?

**Dr. Niederwieser:** One important next step in evaluating bendamustine as a treatment for MM is to examine the effect of this agent on stem cells, given the frequent need for SCT in these patients. In addition, increasing the dose of bendamustine alone or in combinations for conditioning therapy pre-transplant is another area of research that needs to be explored further. Combinations with the different drugs available today need to be tested in detail; it is therefore essential to enter patients in clinical trials.

Lung Cancer

Targeted Therapy for EGFR-Mutated and ALK-Rearranged Non-Small Cell Lung Cancer

In Canada, lung cancer accounts for 13.7% and 13.3% of new cancer cases in men and women, respectively, and is the leading cause of cancer deaths for both sexes.¹ Lung cancers are classified histologically as non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma, with NSCLC representing the majority of cases.² Approximately 30–40% of patients with NSCLC are diagnosed at an advanced stage and have poor prognosis.³

Recent advances in the understanding of the molecular mechanisms underlying NSCLC have led to classification of the disease into distinct subtypes that are defined by specific driver oncogenes. Currently, the best characterized subtypes of NSCLC involve epidermal growth factor receptor (EGFR)-activating mutations and anaplastic lymphoma kinase (ALK)-activating translocations. Treatment with reversible small molecule tyrosine kinase inhibitors (TKIs) that target these mutant proteins have resulted in improved patient response. However, seemingly inevitable resistance to these drugs, erlotinib and gefitinib in the case of EGFR-mutated NSCLC and crizotinib in ALK-rearranged NSCLC, has been a major challenge to continued therapeutic benefit.

Second-generation EGFR and ALK inhibitors have been developed and are undergoing clinical trials. Afatinib covalently binds to EGFR and other ErbB family receptors and irreversibly inhibits their tyrosine kinase activity.⁴ Ceritinib has potent antitumour activity in ALK-rearranged NSCLC, including in patients with ALK mutations that confer resistance to crizotinib.⁵ Studies with both of these drugs have yielded promising results, both as first-line therapy and for refractory malignancy. In this article, we report results presented at the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting that investigated the efficacy and safety of afatinib and ceritinib for the treatment of NSCLC:

- Overall survival results from the analysis of pooled data from LUX-Lung 3 and LUX-Lung 6 showed that first-line treatment with afatinib significantly improved overall survival versus chemotherapy in patients with NSCLC characterized by EGFR Del19 mutations.
- Continuous blockade of EGFR signalling with afatinib in addition to treatment with paclitaxel in heavily pretreated patients with NSCLC who had acquired resistance to EGFR TKIs resulted in improved progression-free survival (PFS) and overall response rates versus chemotherapy alone.
- Pooled data from multiple clinical trials did not reveal any differences in treatment-related cardiac dysfunction between patients with NSCLC treated with afatinib versus chemotherapy.
- The NSCLC Working Group at the Critical Path Institute presented the results of cognitive testing of a new patient-reported outcome measure that has been developed in order to better assess treatment benefit in advanced NSCLC clinical trials.
- Investigators from the first phase I trial of ceritinib (ASCEND-1) reported durable responses and prolonged PFS with manageable toxicity in patients with NSCLC, as well as in a subset of patients with brain metastases at baseline. Subgroup analysis indicated no significant difference in response to ceritinib in Asian versus Caucasian patients.

Yang JC-H et al. ASCO 2014:8004

Overall survival of patients with advanced NSCLC with common EGFR mutations (Del19/L858R) treated with afatinib versus chemotherapy: analysis of pooled data from LUX-Lung 3 and LUX-Lung 6

**Background**

Patients with epidermal growth factor receptor (EGFR) mutation-positive (EGFR M+) non-small cell lung cancer (NSCLC) comprise a distinct subgroup that is unique in its sensitivity to EGFR tyrosine kinase inhibitors (TKIs). The most common EGFR mutations, Del19 and L858R, are found in more than 90% of cases. Current standard first-line treatment for EGFR M+ patients consists of reversible EGFR TKI. However, despite improved progression-free survival (PFS) and overall response rates (ORR) seen with reversible EGFR TKI treatment versus platinum-doublet chemotherapy, no difference in overall survival (OS) has been observed.

The activity of afatinib, an irreversible inhibitor of ErbB family signalling, in EGFR M+ patients with NSCLC has been investigated in two sister studies of nearly identical set-up. LUX-Lung 3 (LL3) compared afatinib with cisplatin/pemetrexed in 345 patients recruited globally, whereas LUX-Lung 6 (LL6) compared afatinib with cisplatin/gemcitabine in 364 patients in Asia. As previously reported, the median time of PFS was significantly prolonged for patients with NSCLC harbouring common EGFR mutations (Del19/L858R) who were treated with afatinib compared with cisplatin/pemetrexed in LL3 (13.6 vs. 6.9; hazard ratio [HR] = 0.47, p < 0.0001) or cisplatin/gemcitabine in LL6 (11.0 vs. 5.6; HR = 0.25, p < 0.0001). Activity of afatinib was additionally observed in some types of uncommon mutations (L861Q, G719X, S768I). In both studies, treatment with afatinib improved symptom control and delayed the worsening of cancer-related cough and dyspnea. At ASCO 2014, Yang and colleagues presented mature OS results based on pooled data from the LL3 and LL6 studies.1

**Study design**

- LL3 and LL6 are randomized, open-label, phase III studies of 345 global patients and 364 Asian patients, respectively.
- Patients with treatment-naive stage IIIB/IV metastatic lung adenocarcinoma harbouring EGFR mutations were randomized 2:1 to receive afatinib or either cisplatin/pemetrexed (LL3) or cisplatin gemcitabine (LL6).
- The dosages for each drug were:
  - Afatinib: 40 mg orally once daily
  - Cisplatin/pemetrexed: (cisplatin: 75 mg/m²; pemetrexed: 500 mg/m² intravenously [iv] once every 21 days, up to six cycles);
  - Cisplatin/gemcitabine: (cisplatin: 75 mg/m² on day 1; gemcitabine: 1000 mg/m² on day 1 and 8 iv once every 21 days, up to six cycles).
- Patients were stratified by EGFR mutation type (Del19/L858R/other) and by race (LL3 only; Asian/non-Asian).
- The primary endpoint for both LL3 and LL6 was PFS.
- Secondary endpoints for both trials included ORR, disease control rate (DCR), OS, patient-reported outcomes (PRO), and safety.
- The pooled analysis included 631 patients with common EGFR mutations who had been randomized into LL3 and LL6:
  - EGFR Del19 mutations were found in 355 patients, and 276 patients had the L858R mutation;
  - Afatinib was given to 419 patients, while 212 patients received chemotherapy.

**Randomization**

<table>
<thead>
<tr>
<th>Stratification by EGFR mutation type: Del19/L858R/other and by race (LUX-Lung 3 only): Asian/non-Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib 40 mg orally once daily</td>
</tr>
<tr>
<td>LUX-Lung 3: Cisplatin + pemetrexed up to 6 cycles</td>
</tr>
<tr>
<td>LUX-Lung 6: Cisplatin + gemcitabine up to 6 cycles</td>
</tr>
</tbody>
</table>

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A, and G719C (or G719X, S768I).**


DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; PS = performance status.

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Key findings
- Median follow-up for OS in the LL3 and LL6 trials was 41 months and 33 months, respectively.
- At the time of analysis (January 2014), 404 (64%) patients had died.
- In the individual LL3 and LL6 studies:
  - The OS of patients in the overall study population who were treated with afatinib was not significantly different compared to those treated with chemotherapy:
    - Median OS in LL3 was 28.2 vs. 28.2 months (HR = 0.88, p = 0.3850);
    - Median OS in LL6 was 23.1 vs. 23.5 months (HR = 0.93, p = 0.6137).
  - The OS of patients with common EGFR mutations (Del19/L858R) who were treated with afatinib was not significantly different compared to those treated with chemotherapy: (Figure 1)
    - Median OS in LL3 was 31.6 vs. 28.2 months (HR = 0.78 [95% CI: 0.58–1.06]; p = 0.1090);
    - Median OS in LL6 was 23.1 vs. 23.5 months (HR = 0.83 [95% CI: 0.62–1.09]; p = 0.1756).
- In order to further investigate factors that affect OS outcome, data from all patients with common mutations from both LL3 and LL6 (n = 631) were combined and OS was compared between patients treated with afatinib versus chemotherapy: (Figure 2)
  - Median OS in LL3 was 33.3 vs. 21.1 months (HR = 0.54 [95% CI: 0.44–0.94]; p = 0.0229).

Figure 1. Overall survival of patients with common EGFR mutations

![Figure 1](image1.png)

Figure 2. Overall survival in the EGFR Del19 subgroup

![Figure 2](image2.png)

CI = confidence interval; gem/cis = gemcitabine, cisplatin; HR = hazard ratio; OS = overall survival; pem/cis = pemetrexed, cisplatin
treated with afatinib compared to chemotherapy (27.3 vs. 24.3 months [HR = 0.81, 95% CI: 0.66–0.99]; p = 0.0374). (Figure 3)

**Figure 3.** Overall survival of patients with common EGFR mutations — pooled data (n = 631)

Only EGFR Del19 mutation was associated with a difference in OS between the two treatment arms, with results favouring afatinib over chemotherapy. (Figure 4)

Median OS was significantly prolonged in the combined population of patients with EGFR Del19 mutation who were treated with afatinib compared to chemotherapy (31.7 vs. 20.7 months [HR = 0.59, 95% CI: 0.45–0.77]; p = 0.0001). (Figure 5)

- Treatment beyond the first line was the most important confounding factor affecting OS outcomes in this study: (Table 1)
  - In LL3, 71% of patients with common EGFR mutations who received afatinib were subsequently treated with chemotherapy, and 75% of patients who received chemotherapy were subsequently treated with an EGFR TKI.
  - In LL6, 59% of patients with common EGFR mutations who received afatinib were subsequently treated with chemotherapy, and 56% of patients who received chemotherapy were subsequently treated with an EGFR TKI.

- Treatment crossover rates varied depending on the reimbursement policies in different regions of the world: (Table 2)
  - In countries where treatment with both afatinib and chemotherapy are reimbursed, 91% of patients initially treated with chemotherapy subsequently crossed over to an EGFR TKI, and 81% of patients initially treated with afatinib subsequently crossed over to chemotherapy.

**Figure 4.** Overall survival subgroup analysis of patients with common EGFR mutations — pooled data

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>631</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>214</td>
</tr>
<tr>
<td>Female</td>
<td>417</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>435</td>
</tr>
<tr>
<td>≥65</td>
<td>196</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Non-Asian</td>
<td>83</td>
</tr>
<tr>
<td>Asian</td>
<td>548</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
</tr>
<tr>
<td>Del19</td>
<td>355</td>
</tr>
<tr>
<td>L858R</td>
<td>276</td>
</tr>
<tr>
<td>Baseline ECOG score</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>193</td>
</tr>
<tr>
<td>1</td>
<td>437</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>461</td>
</tr>
<tr>
<td>&lt;15 pack years and stopped</td>
<td>40</td>
</tr>
<tr>
<td>≥1 year ago</td>
<td>130</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio
In countries without universal reimbursement policies, 52% of patients initially treated with chemotherapy subsequently crossed over to an EGFR TKI, and 57% of patients initially treated with afatinib subsequently crossed over to chemotherapy.

- The authors of this study examined whether differences in regional reimbursement policies, and hence differences in crossover rates, affected hazard ratio values: (Table 3)

- Regardless of reimbursement policy, HR was lower for patients with EGFR Del19 mutations than for patients with EGFR L858R mutations.
  - For patients with EGFR Del19 mutations, the HR in countries with universal reimbursement policies and high rates of crossover to EGFR TKI (91%) was not different from the HR in countries without universal reimbursement policies and lower rates of crossover to EGFR TKI (52%) (0.50 vs. 0.59).
  - For patients with EGFR Del19 mutations, HR was lowest in Japan (0.34), a country where 100% of patients received an EGFR TKI after first-line chemotherapy.

**Figure 5. Overall survival analysis according to mutation categories — pooled data**

**Table 1. Treatment beyond first line in patients with common EGFR mutations**

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 3</th>
<th>LUX-Lung 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afatinib</td>
<td>Pem/cis</td>
</tr>
<tr>
<td></td>
<td>(n = 203)</td>
<td>(n = 104)</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>184 (100)</td>
<td>104 (100)</td>
</tr>
<tr>
<td>Subsequent systemic therapy¹</td>
<td>144 (78)</td>
<td>88 (85)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>131 (71)</td>
<td>49 (47)</td>
</tr>
<tr>
<td>EGFR TKI therapy</td>
<td>81 (44)</td>
<td>78 (75)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>61 (33)</td>
<td>46 (42)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>28 (15)</td>
<td>44 (42)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>2 (1)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>AZD9291</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>—</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Icotinib</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EGFR TKI combinations</td>
<td>5 (3)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Other systemic therapy*</td>
<td>5 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>32 (17)</td>
<td>21 (20)</td>
</tr>
</tbody>
</table>

*Collection of data on subsequent therapies is still ongoing.
¹Includes investigational agents, monoclonal antibodies, non-EGFR–targeting protein kinase inhibitors, etc.

EGFR = epidermal growth factor receptor; gem/cis = gemcitabine, cisplatin; pem/cis = pemetrexed, cisplatin; TKI = tyrosine kinase inhibitor
Table 2. Treatment beyond first line in patients with common EGFR mutations by EGFR TKI reimbursement policy in country of residence

<table>
<thead>
<tr>
<th>Countries with universal reimbursement policies†</th>
<th>Countries without universal reimbursement policies‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) Afatinib (n = 144) Chemotherapy (n = 75)</td>
<td>n (%) Afatinib (n = 275) Chemotherapy (n = 137)</td>
</tr>
<tr>
<td>Discontinued treatment 127 (100) 75 (100)</td>
<td>251 (100) 137 (100)</td>
</tr>
<tr>
<td>Subsequent systemic therapy 112 (88) 69 (92)</td>
<td>158 (63) 89 (65)</td>
</tr>
<tr>
<td>Chemotherapy 103 (81) 35 (47)</td>
<td>142 (57) 43 (31)</td>
</tr>
<tr>
<td>EGFR TKI therapy 76 (60) 68 (91)</td>
<td>55 (22) 71 (52)</td>
</tr>
<tr>
<td>Other 5 (4) 2 (3)</td>
<td>3 (1) 4 (3)</td>
</tr>
<tr>
<td>Radiotherapy 27 (22) 18 (24)</td>
<td>9 (4) 3 (2)</td>
</tr>
</tbody>
</table>

* Determined by presence or absence of a national reimbursement policy in effect throughout the period of trial conduct.
† Main countries contributing: Japan, Taiwan, Korea, Germany, France, Australia, UK, Belgium, Ireland.
‡ Main countries contributing: China, Thailand, Russia, the Philippines, Malaysia.
EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor

Table 3. Impact of subsequent EGFR TKI therapy on overall survival — exploratory analyses by reimbursement policy in country of residence

<table>
<thead>
<tr>
<th>Population</th>
<th>Received TKI after first-line chemotherapy, %</th>
<th>HR (95% CI) Common EGFR mutations</th>
<th>HR (95% CI) Del19</th>
<th>HR (95% CI) L858R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined LL3 and LL6 (n = 631)</td>
<td>66%</td>
<td>0.81 (0.66–0.99)</td>
<td>0.59 (0.45–0.77)</td>
<td>1.25 (0.92–1.71)</td>
</tr>
<tr>
<td>Countries with universal reimbursement policies† (n = 219)</td>
<td>91%</td>
<td>0.71 (0.49–1.02)</td>
<td>0.50 (0.31–0.81)</td>
<td>1.14 (0.64–2.03)</td>
</tr>
<tr>
<td>Countries without universal reimbursement policies‡ (n = 412)</td>
<td>52%</td>
<td>0.85 (0.66–1.08)</td>
<td>0.59 (0.42–0.82)</td>
<td>1.32 (0.91–1.92)</td>
</tr>
<tr>
<td>Japan (n = 77)</td>
<td>100%</td>
<td>0.57 (0.29–1.12)</td>
<td>0.34 (0.13–0.87)</td>
<td>1.13 (0.40–3.21)</td>
</tr>
</tbody>
</table>

* Determined by presence or absence of a national reimbursement policy in effect throughout the period of trial conduct.
† Main countries contributing: Japan, Taiwan, Korea, Germany, France, Australia, UK, Belgium, Ireland.
‡ Main countries contributing: China, Thailand, Russia, the Philippines, Malaysia.
CI = confidence interval; HR = hazard ratio; LL3 = LUX-Lung 3; LL6 = LUX-Lung 6; TKI = tyrosine kinase inhibitor

Key conclusions

■ First-line afatinib significantly improved OS versus chemotherapy in patients with EGFR Del19 mutations in two randomized trials, LL3 and LL6.
■ Median OS was significantly prolonged in the combined population of patients with EGFR Del19 mutation who were treated with afatinib compared to chemotherapy.
■ There was no significant difference in OS of patients with EGFR L858R mutation treated with afatinib compared to chemotherapy, individually or in pooled data.
  • Benefits of afatinib versus chemotherapy in PFS, ORR, and PRO were previously shown.
■ Patients with EGFR Del19 and L858R mutations are two distinct populations and should be studied separately in the future.
■ An OS benefit was found with afatinib in patients with common EGFR mutations (Del19/L858R) in the exploratory combined analysis.
■ First-line afatinib should be the standard of care for patients with EGFR Del19 mutations and remains a treatment option for patients with EGFR L858R mutations.

Background

Despite initial response to treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), patients with non-small cell lung cancer (NSCLC) eventually develop resistance with subsequent disease progression. Retrospective/non-randomized studies suggest that continued EGFR inhibition beyond progression could lead to improved disease control, but this has not yet been evaluated in a prospective, randomized trial. Afatinib, an irreversible ErbB family TKI, has first-line efficacy in patients with activating EGFR mutations and also has activity in patients with acquired resistance to reversible EGFR TKIs. A previous phase I study showed that the combination of afatinib and paclitaxel demonstrated promising activity and manageable toxicity. At ASCO 2014, Schuler and colleagues presented results from the LUX-Lung 5 trial, which compared efficacy and safety of afatinib plus paclitaxel versus the investigator’s choice of single-agent chemotherapy in patients with NSCLC who had failed erlotinib/gefitinib and afatinib.1

Study design

- LUX-Lung 5 is a randomized, global, open-label, two-stage, phase III trial across 115 centres in 23 countries.
- This study consists of a two-part treatment regimen:
  - In Part A, patients with NSCLC who had failed ≥1 line of chemotherapy (including platinum/pemetrexed) and erlotinib/gefitinib after ≥12 weeks of treatment (n = 1,154) were treated with afatinib (50 mg/day).
  - In Part B, patients who had been treated with afatinib for ≥12 weeks followed by disease progression after part A of the study were eligible to be randomized 2:1 to afatinib (40 mg/day) plus paclitaxel (80 mg/m²/week) or investigator’s choice of single agent chemotherapy.
- The primary endpoint for this trial was progression-free survival (PFS).
- Secondary endpoints included objective response rate (ORR), overall survival (OS), and safety.

Key findings

- Patients were recruited into the non-randomized Part A of the study from April 2010 to May 2011. Results were reported previously.2
- In Part B of the study, 202 patients were randomized (afatinib + paclitaxel, n = 134; chemotherapy, n = 68).
- Out of the 60 patients that were ultimately treated with chemotherapy, 37% received paclitaxel, 29% pemetrexed, 15% docetaxel, and 19% other regimens.
• A statistically significant improvement in PFS was observed in the group treated with afatinib plus paclitaxel versus the chemotherapy group (5.6 vs. 2.8 months, hazard ratio [HR] = 0.60 [95% CI: 0.43–0.85]; \( p = 0.0031 \)). (Figure 1)

• In all patient subgroups, the HR for PFS was numerically lower, favouring the group treated with afatinib plus paclitaxel versus those treated with chemotherapy. (Figure 2)
  - The PFS advantage in patients treated with afatinib plus paclitaxel was not at the detriment of quality of life as determined by patient-reported outcome analysis (to be reported separately).

• ORR was significantly higher in the afatinib plus paclitaxel arm vs. the chemotherapy arm (32.1% vs. 13.2%; odds ratio = 3.1, \( p = 0.0049 \)); the same was true for the disease control rate (74.6% vs. 45.6%; odds ratio = 3.4, \( p < 0.0001 \)). (Figure 3)

• OS was similar in both arms of the study (12.2 vs. 12.2 months, HR = 1.0 [95% CI: 0.70–1.43; \( p = 0.994 \)]). (Figure 4)

• The most common treatment-related adverse events (AEs) with afatinib plus paclitaxel vs. chemotherapy were diarrhea (53.8% vs. 6.7%), alopecia (32.6% vs. 15.0%), and asthenia (27.3% vs. 28.3%). (Table 1)
Figure 4. Overall survival and post-progression therapy

![Graph showing overall survival and post-progression therapy]

*Beyond ≥ 1 line of chemotherapy, erlotinib/gefitinib, afatinib, and afatinib + paclitaxel.

HR = hazard ratio; OS = overall survival

Table 1. Drug-related adverse events (≥10% in either arm)

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>Part B (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afatinib plus paclitaxel (n = 134)</td>
</tr>
<tr>
<td></td>
<td>Single agent chemotherapy (n = 68)</td>
</tr>
<tr>
<td>Median on-treatment time, days</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>51</td>
</tr>
<tr>
<td>Patients with any drug-related AE</td>
<td>88.6</td>
</tr>
<tr>
<td></td>
<td>70.0</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53.8</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>32.6</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>28.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>16.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
</tr>
<tr>
<td>Rash</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>13.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>16.7</td>
</tr>
<tr>
<td>Paronychia</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>11.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>11.7</td>
</tr>
</tbody>
</table>

AE = adverse event

Key conclusions

- The LUX-Lung 5 trial demonstrated that continued ErbB family blockade with afatinib in addition to treatment with paclitaxel resulted in superior PFS and ORR vs. chemotherapy alone in heavily pretreated patients with acquired resistance to erlotinib/gefitinib and disease progression on afatinib monotherapy.
- Afatinib plus paclitaxel had a manageable safety profile.
- Global health status and quality of life was maintained over time in patients treated with afatinib plus paclitaxel.
- LUX-Lung 5 is the first and largest prospectively designed randomized trial demonstrating the benefit of continuous EGFR blockade (“treatment beyond progression”) with afatinib in patients with NSCLC who were previously treated with EGFR TKIs.
- Trial data support the hypothesis that tumours progressing on erlotinib/gefitinib and afatinib continue to depend on signalling through the receptors of the ErbB family and can benefit from continuous ErbB family blockade with afatinib.

References:
Cardiac safety of afatinib: analysis of data from multiple clinical trials

**Background**
Afatinib is an oral, irreversible ErbB family tyrosine kinase inhibitor (TKI) that is approved for treatment of patients with non-small cell lung cancer (NSCLC) with common epidermal growth factor receptor (EGFR) mutations (Del19/L858R). Cardiac dysfunction has been associated with therapies targeting HER2, an ErbB family member. Ewer and colleagues reported cardiac events from two phase III trials of afatinib and a pooled analysis of additional trials.

**Study design**
- Cardiac data were analyzed from the following sources:
  - LUX-Lung 3 (LL3): afatinib 40 mg in previously untreated patients with EGFR mutation-positive NSCLC (n = 229 afatinib, n = 111 chemotherapy);
  - LUX-Lung 1 (LL1): afatinib 50 mg in EGFR TKI-pretreated patients with NSCLC (n = 390 afatinib, n = 195 placebo);
- Additional data from 49 trials (pooled; n = 3,865 afatinib) was included.
- When feasible, left ventricular ejection fraction (LVEF) was assessed at baseline, every 12 weeks, and at the end of treatment.
- Cardiac failure adverse events (CF-AEs) including cardiac failure and depressed LVEF per multigated acquisition (MUGA) scan or echocardiogram were analyzed. (Table 1)
- Time at risk adjusted CF-AE rates were used to compare treatment arms in LL1 and LL3 due to large differences in treatment exposure.
- Clinically significant LVEF reductions were examined using established criteria: LVEF <50% and ≥10% decrease from baseline or LVEF ≥50% and ≥15% decrease from baseline.

**Key findings**
- Time at risk adjusted CF-AE rates (events/100 patient-years) were similar for afatinib versus placebo in LL1 (2.40 vs. 2.23) and versus chemotherapy in LL3 (2.28 vs. 2.92).
- The pooled afatinib CF-AE rate (2.88 per 100 patient-years) was consistent with that for LL1 and LL3.
- The frequency of clinically significant LVEF reductions was higher for chemotherapy in LL3 (chemotherapy 2/15 [13.3%], afatinib 13/208 [6.3%]) and similar to placebo in LL1 (placebo 5/122 [4.1%], afatinib 14/304 [4.6%]).
- No patients in LL3 discontinued treatment due to a CF-AE; one afatinib patient and no placebo patients discontinued treatment due to a CF-AE in LL1.

**Key conclusion**
Afatinib was not associated with cardiac failure or reductions in LVEF in patients in this clinical trial program.

Interim report from the Patient-Reported Outcome (PRO) Consortium’s Non-Small Cell Lung Cancer (NSCLC) Working Group: development of a PRO measure for assessing NSCLC symptoms in clinical trials

Background
The NSCLC Working Group at the Critical Path Institute – PRO Consortium is developing a new PRO measure in collaboration with the U.S. Food and Drug Administration (FDA). The measure will be used to assess treatment benefit in advanced NSCLC clinical trials and to support label claims. Campbell and colleagues presented the results of cognitive testing of the new PRO measure of NSCLC symptoms.1

Study design
• Symptoms relevant to patients with NSCLC were identified in the literature.
• Interviews were conducted with patients with NSCLC at six U.S. sites.
• Transcripts were coded using Atlas.ti software.
• Patient-elicited concepts were grouped by similar content and then reviewed by the Working Group and an expert panel to identify symptoms most relevant for assessing treatment benefit.
• Items were generated and combined into a draft measure for cognitive testing of patients with NSCLC.

Key findings
• The 51 patients interviewed had the following characteristics:
  ○ Mean age 64.8 years (range 46–86);
  ○ Female: 51%; males: 49%;
  ○ NSCLC Stage I (12%), III (37%), and IV (51%);
  ○ Treatment-naïve (29%), first-line (43%), or second/third-line (27%).
• The most commonly expressed symptom was fatigue, described by patients as tiredness, lack of energy, tires easily, and weakness.
• Other symptom concepts expressed included general pain, chest pain, cough, shortness of breath, difficulty breathing, appetite change, and coughing up blood.
• Items were drafted to assess either symptom frequency or severity for nine distinct symptoms using a 7-day recall period.
• During cognitive interviews, an 11-point numerical rating scale and a 5-point verbal rating scale were tested.
  ○ Preliminary cognitive testing indicates that the 5-point verbal scale is better understood by patients.

Key conclusions
• Patient-elicited NSCLC symptoms, across varied disease stages and treatments, were concordant with the pathophysiology of disease.
• A new PRO measure of NSCLC symptoms has been developed in accordance with the FDA’s PRO Guidance.
  • The content of the measure is supported by a review of existing literature, patient-reported experience, and expert opinion.
• The draft measure is currently in cognitive testing, with quantitative testing planned in 2014. Once complete, the measure and supporting evidence will be submitted to the FDA for qualification as an endpoint to quantify treatment benefit for product labeling.

ASCEND-1: ceritinib in advanced anaplastic lymphoma kinase-rearranged non-small cell lung cancer

**Background**

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is activated by chromosomal rearrangement in 3–7% of patients with non-small cell lung cancer (NSCLC). Crizotinib is an ALK inhibitor (ALKi) that displays high efficacy in patients with ALK-rearranged (ALK+) NSCLC. However, acquired resistance to crizotinib is common. Ceritinib (LDK378) is a potent and selective oral ALKi that has shown anti-tumour activity against ALKi-naive tumours as well as tumours that have progressed on crizotinib. In previously reported results, the ASCEND-1 study established a maximum tolerated dose (MTD) of 750 mg per day of ceritinib. At ASCO 2014, Kim and colleagues presented results from the expansion phase of ASCEND-1, in which the efficacy and safety of ceritinib were assessed in patients with ALK+ NSCLC.1

**Study design**

- ASCEND-1 is a global, open-label, dose-escalation, phase I study.
- Adult patients with advanced ALK+ cancers received oral ceritinib at the recommended dose (750 mg per day).
- Out of the 255 patients studied, 246 patients had ALK+ NSCLC tumours.
- After MTD determination, patients were enrolled in the following expansion groups:
  - ALKi-pretreated NSCLC
  - ALKi-naïve NSCLC
  - Non-NSCLC diseases.

The objectives of the expansion phase of ASCEND-1 were to determine anti-tumour efficacy and safety of ceritinib.

**Key findings**

- The disease characteristics of patients with NSCLC are summarized in Table 1.
- At least two prior anticancer therapies had been received by 67% of patients.

**Table 1. Disease characteristics of patients with ALK+ NSCLC**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ALKi-treated (N = 163)</th>
<th>ALKi-naïve (N = 83)</th>
<th>All (N = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour histology/cytology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>152 (93.3)</td>
<td>76 (91.6)</td>
<td>228 (92.7)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3 (1.8)</td>
<td>0</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Other/missing</td>
<td>8 (4.9)</td>
<td>7 (8.4)</td>
<td>15 (6.1)</td>
</tr>
<tr>
<td>Number of prior treatment regimens, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>16 (19.3)</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>1</td>
<td>26 (16.0)</td>
<td>38 (45.8)</td>
<td>64 (26.0)</td>
</tr>
<tr>
<td>2</td>
<td>45 (27.6)</td>
<td>16 (19.3)</td>
<td>61 (24.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>92 (56.4)</td>
<td>13 (15.6)</td>
<td>105 (42.7)</td>
</tr>
<tr>
<td>Median time from initial diagnosis to first dose, months (range)</td>
<td>21.2 (2.4–174.2)</td>
<td>8.1 (1.0–109.3)</td>
<td>18.0 (1.0–174.2)</td>
</tr>
</tbody>
</table>

Of patients who had received prior ALKi therapy, 91% had progressive disease during prior ALKi therapy (≥2 weeks from last dose) and 77% had received ALKi as last prior therapy.

ALK = anaplastic lymphoma kinase; ALKi = anaplastic lymphoma kinase inhibitor; NSCLC = non-small cell lung cancer
• The disposition of patients with NSCLC studied in this trial is summarized in Table 2.

• Overall response rate (ORR) was >50% in patients who were both ALKi-treated and ALKi-naïve. (Table 3)

• Median duration of response (DOR) in patients with ALK+ NSCLC with confirmed complete response (CR) or partial response (PR) was not estimable in ALKi-naïve patients versus 7.39 months in ALKi-treated patients. (Figure 1)

• Of all 255 patients treated with ceritinib, the most common adverse events (AEs) of all grades were diarrhea (86%), nausea (80%), vomiting (60%), abdominal pain (54%), and fatigue (52%).

• The most common grade 3/4 AEs were increased alanine transaminase (27%), increased aspartate transaminase (13%), increased glucose (13%), and increased lipase (10%).

• At least one dose reduction was made in 59% (150/255) of patients.

• Discontinuation of treatment due to AEs occurred in 9.4% (24/255) of patients.

• Interstitial lung disease/pneumonitis developed in 3.9% (10/255) of patients.

• Efficacy of ceritinib in a subset of 124 patients with ALK+ NSCLC who also had clinically and neurologically stable brain metastases at baseline was measured.

• In this subset of patients, 26 patients were ALKI-naïve while 98 patients had received prior ALKi treatment.

• The ORRs in the ALKI-treated and ALKI-naïve patients were 50.0% (95% CI: 39.7, 60.3) and 69.2% (95% CI: 48.2, 85.7), respectively.

• Median DOR in ALKI-treated patients was 6.93 months (95% CI: 4.80, 8.54) vs. non-estimable (NE) (95% CI: 5.52, NE) in ALKI-naïve patients.

• Median PFS in ALKI-treated patients was 6.70 months (95% CI: 4.86, 8.38) vs. 8.31 months (95% CI: 4.63, NE) in ALKI-naïve patients.

• Overall intracranial response rate for patients with measurable brain metastases at baseline was 40.0% (95% CI: 12.2, 73.8) for ALKI-treated patients and 75.0% (95% CI: 19.4, 99.4) for ALKI-naïve patients.

### Table 2. Disposition of patients with ALK+ NSCLC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ALKi-treated (N = 163)</th>
<th>ALKi-naïve (N = 83)</th>
<th>All (N = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of follow-up, months (range)</td>
<td>6.9 (0.1–19.1)</td>
<td>7.6 (0.4–17.6)</td>
<td>7.0 (0.1–19.1)</td>
</tr>
<tr>
<td>Patients ongoing at cut-off, n (%)</td>
<td>74 (45.4)</td>
<td>54 (65.1)</td>
<td>128 (52)</td>
</tr>
<tr>
<td>Primary reason for end of treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>17 (10.4)</td>
<td>7 (8.4)</td>
<td>24 (9.8)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>59 (36.2)</td>
<td>18 (21.7)</td>
<td>77 (31.3)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (1.8)</td>
<td>3 (3.6)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>10 (6.1)</td>
<td>1 (1.2)</td>
<td>11 (4.5)</td>
</tr>
</tbody>
</table>

ALK = anaplastic lymphoma kinase; ALKi = anaplastic lymphoma kinase inhibitor; NSCLC = non-small cell lung cancer

### Table 3. Overall response rate in patients with ALK+ NSCLC treated with ceritinib (750 mg daily)

<table>
<thead>
<tr>
<th>Efficacy parameter (RECIST 1.0), n (%)</th>
<th>ALKi-treated (N = 163)</th>
<th>ALKi-naïve (N = 83)</th>
<th>All (N = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (1.2)</td>
<td>1 (1.2)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>PR</td>
<td>87 (53.4)</td>
<td>54 (65.1)</td>
<td>141 (57.3)</td>
</tr>
<tr>
<td>SD</td>
<td>32 (19.6)</td>
<td>19 (22.9)</td>
<td>51 (20.7)</td>
</tr>
<tr>
<td>PD</td>
<td>16 (9.8)</td>
<td>0</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>26 (16.0)</td>
<td>9 (10.8)</td>
<td>35 (14.2)</td>
</tr>
<tr>
<td>ORR [95% CI]</td>
<td>89 (54.6) [46.6, 62.4]</td>
<td>55 (66.3) [55.1, 76.3]</td>
<td>144 (58.5) [52.1, 64.8]</td>
</tr>
</tbody>
</table>

*No post-baseline assessment done, or the post-baseline assessment had overall response that was not CR, PR, SD, or PD.

ALK = anaplastic lymphoma kinase; ALKi = anaplastic lymphoma kinase inhibitor; CI = confidence interval; CR = complete response; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease
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Key conclusions

- A high rate of durable responses and prolonged PFS were seen in both ALKi-treated and ALKi-naïve patients.
  - In ALKi-naïve patients, the median DOR and PFS have not been reached.
- In all patients, the most common AEs were nausea, vomiting, and diarrhea. Most AEs were grade 1 or 2.
- In the subset of patients with baseline brain metastases, ceritinib also demonstrated a high rate of durable response and prolonged PFS in both ALKi-treated and ALKi-naïve patients.
- Ceritinib treatment showed anti-tumour activity in patients with brain metastases.

Background
Rearrangement of ALK is observed in approximately 2–7% of patients with non-small cell lung cancer (NSCLC). Although treatment with crizotinib, an ALK inhibitor, has shown promising results in patients with ALK mutation-positive (ALK+) NSCLC, the majority of patients go on to develop resistance to crizotinib. In cell lines established from biopsies of crizotinib-naïve and crizotinib-resistant patients with NSCLC, potent and selective inhibition of ALK has been observed with ceritinib (LDK378), an orally-available tyrosine kinase inhibitor of ALK. The first-in-human phase I study of ceritinib (ASCEND-1) demonstrated high activity of ceritinib in crizotinib-naïve and crizotinib-resistant patients with ALK mutation-positive NSCLC, and established 750 mg/day as maximum tolerated dose. Since treatment response varies in different ethnic groups, Tan and colleagues presented a subgroup analysis of the ASCEND-1 trial, comparing treatment results in Asian versus Caucasian patients receiving ceritinib at 750 mg/day.1

Study design
ASCEND-1 is a global, open-label, dose-escalation, phase I study.

Key inclusion criteria for this trial were:
- Adult patients with locally advanced or metastatic cancer harboring genetic alterations in ALK;
- In patients with NSCLC, ALK rearrangement in ≥15% of tumour cells needed to be demonstrated by fluorescence in situ hybridization assay, with the use of break-apart probes;
- Eastern Cooperative Oncology Group (ECOG) score of ≤2;
- Asymptomatic untreated or treated central nervous system metastases and prior treatment with ≥1 ALK inhibitor were permitted.
- Patients received oral ceritinib 750 mg once daily.
- Investigator assessment of efficacy was presented for patients who received a first dose of ceritinib ≥18 weeks prior to the cut-off date (August 2, 2013).

Key findings
- Baseline characteristics between Asian and Caucasian patients were similar, but ALK inhibitor pretreatment had been received by 47 (57.3%) and 108 (69.2%) patients, respectively.

Expansion phase
- Evaluate 750 mg recommended dose
- N = 255 patients with ALK+ tumours
- N = 246 patients with ALK+ NSCLC tumours
- N = 9 ALK+ tumours other than NSCLC

ALK inhibitor treated (N = 163)
ALK inhibitor naïve (N = 83)

Key Objectives:
To determine anti-tumour efficacy and safety of ceritinib

ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer

Ceritinib in Asian versus Caucasian patients with advanced ALK-rearranged NSCLC: subgroup analysis of the ASCEND-1 trial
• At least two prior anticancer therapies had been received by 67% of patients.
• A total of 255 patients were treated with ceritinib at a dose of 750 mg/day, with median follow-up for overall survival (OS) of 7 months (95% CI: 0.1, 19.1).
• Of the 246 patients with ALK+ NSCLC, 82 were Asian, 156 were Caucasian and 8 were of other race.
• The treatment discontinuation rate was higher in Caucasian patients (53.8%) than Asian patients (39.0%). (Figure 1)
  ◦ Of the four Asian patients who discontinued treatment due to adverse events (AEs), two had AEs considered related to study treatment: grade 3 pneumonitis; grade 3 renal failure.
  ◦ Both of the discontinuations due to death in the Asian cohort were considered unrelated to treatment (pneumonia and progressive disease).
• Of the 20 Caucasian patients who discontinued treatment due to AEs:
  ◦ Seven had AEs considered related to study treatment: grade 3 aspartate aminotransferase, alanine aminotransferase, cholestasis and grade 2 blood alkaline phosphatase increased; grade 3 pneumonitis; grade 3 anorexia; grade 3 corneal infiltrates; grade 4 interstitial lung disease — fatal; grade 2 pleural effusion; grade 1 nausea.
  ◦ All four of the discontinuations due to death in the Caucasian cohort were considered unrelated to study treatment: gastric bleeding (n = 1), pneumonia (n = 1), and progressive disease (n = 2).
• The median duration of ceritinib exposure was similar in Asian and Caucasian groups (28.5 weeks vs. 25.3 weeks). (Table 1)

Figure 1. Disposition of patients with ALK+ NSCLC treated with ceritinib (750 mg daily)

Table 1. Exposure to ceritinib (750 mg/day) in patients with NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Asian (N = 82)</th>
<th>Caucasian (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of exposure (range), weeks</td>
<td>28.5 (2.0–75.4)</td>
<td>25.3 (0.4–82.3)</td>
</tr>
<tr>
<td>Dose reduction, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose reduction</td>
<td>29 (35.4)</td>
<td>70 (44.9)</td>
</tr>
<tr>
<td>At least one dose reduction</td>
<td>53 (64.6)</td>
<td>86 (55.1)</td>
</tr>
<tr>
<td>One dose reduction</td>
<td>27 (32.9)</td>
<td>65 (41.7)</td>
</tr>
<tr>
<td>Two dose reductions</td>
<td>21 (25.6)</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Patients with at least one dose interruption, n (%)</td>
<td>53 (64.6)</td>
<td>108 (69.2)</td>
</tr>
<tr>
<td>Median duration of dose interruptions (range), days</td>
<td>7 (1–20)</td>
<td>8 (1–90)</td>
</tr>
</tbody>
</table>

ALK = anaplastic lymphoma kinase; NSCLC = non-small-cell lung cancer

Note: % calculated based on number of patients.
• No marked difference (<15%) in the pharmacokinetic parameters area under the curve from 0 to 24 hours sampling time (AUC0-24h) and maximum plasma concentration (Cmax) at steady-state (Cycle 2 Day 1) was observed in Asian patients compared with non-Asian patients. (Table 2)

• The ceritinib plasma concentration-time profile and steady-state trough concentration of ceritinib were similar for Asian and non-Asian patients.

• All patients in both Asian and Caucasian groups reported ≥1 AE.

• Grade 3/4 AEs were reported in 50 (61.0%) and 123 (78.8%) patients in the Asian and Caucasian groups, respectively.

• The most common AEs are shown in Table 3.

• Response rates were high and durable for both Asian and Caucasian patients.

• Although differences were observed in the point estimates between Asians and Caucasians for overall response rate, median duration of response, and median progression-free survival, the associated confidence intervals (CIs) have a substantial overlap for Asian and Caucasian patients. (Tables 4 and 5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asian</th>
<th>Non-Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24h (ng*h/mL)</td>
<td>24,100 (6,530)</td>
<td>23,600 (7,780)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1,200 (308)</td>
<td>1,050 (487)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>5.95 (0–8.0)</td>
<td>6.0 (0–22.6)</td>
</tr>
<tr>
<td>CLss/F (L/h)</td>
<td>34.6 (15.5)</td>
<td>36.6 (17.4)</td>
</tr>
</tbody>
</table>

*All patients were Caucasian. The denominator for AUC0-24h and CLss/F is smaller than the denominator for Cmax and Tmax since a 24-hour sample was collected at cycle 2 day 1 only for some patients enrolled in the expansion phase.
†87 patients were Caucasian.

AUC0-24h = area under curve from 0 to 24 hours sampling time; Cmax = maximum plasma concentration; Tmax = time at which maximum plasma concentration is achieved; CLss/F = apparent clearance at steady-state

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Asian (N = 82)</th>
<th>Caucasian (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade, n (%)</td>
<td>Grade 3/4, n (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79 (96.3)</td>
<td>5 (6.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>65 (79.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>60 (73.2)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>42 (51.2)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31 (37.8)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>31 (37.8)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>31 (37.8)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (37.8)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>30 (36.6)</td>
<td>23 (28.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (28.0)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>21 (25.6)</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>13 (15.9)</td>
<td>6 (7.3)</td>
</tr>
</tbody>
</table>
Table 4. Best overall response based on investigator assessment

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Asian (N = 82)</th>
<th>Caucasian (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (1.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>PR</td>
<td>55 (67.1)</td>
<td>83 (53.2)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (18.3)</td>
<td>34 (21.8)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (7.3)</td>
<td>10 (6.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (6.1)</td>
<td>28 (17.9)</td>
</tr>
<tr>
<td>ORR [95% CI]</td>
<td>56 (68.3) [57.1, 78.1]</td>
<td>84 (53.8) [45.7, 61.8]</td>
</tr>
</tbody>
</table>

CI = confidence interval; CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Table 5. Duration of response and progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Asian</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with CR/PR</td>
<td>56</td>
<td>84</td>
</tr>
<tr>
<td>Number of patients censored, n (%)</td>
<td>38 (67.9)</td>
<td>46 (54.8)</td>
</tr>
<tr>
<td>Kaplan-Meier estimate of DOR rate at 12 months, % [95% CI]</td>
<td>45.8 [24.4, 64.9]</td>
<td>23.8 [8.7, 43.0]</td>
</tr>
<tr>
<td>Median DOR [95% CI], months</td>
<td>10.12 [7.29, NE]</td>
<td>7.85 [5.39, 11.07]</td>
</tr>
</tbody>
</table>

| PFS              |       |           |
| Number of patients analyzed | 82    | 156       |
| Number of patients censored, n (%) | 47 (57.3) | 77 (49.4) |
| Kaplan-Meier estimate of PFS rate at 12 months, % [95% CI] | 42.6 [27.2, 57.2] | 35.7 [26.0, 45.5] |
| Median PFS [95% CI], months | 11.07 [6.9, NE] | 6.80 [5.55, 9.03] |

CI = confidence interval; CR = complete response; DOR = duration of response; NE = not estimable; PFS = progression-free survival; PR = partial response

Key conclusions

- Ceritinib 750 mg/day resulted in high and durable anti-tumor activity and manageable tolerability in both Asian and Caucasian patients with ALK+ NSCLC.
- Discontinuation rates due to AEs were lower for Asian patients than Caucasian patients; however, the median duration of exposure was similar for both groups and there were no marked differences in steady-state $\text{AUC}_{0-24h}$ and $\text{C}_{\text{max}}$ observed in Asian patients compared with Caucasian patients.
- Although the point estimates for efficacy endpoints were higher for Asian than Caucasian patients, there is substantial overlap in the associated CIs and these differences are not considered to be significant. Furthermore, pharmacokinetic data suggests that the effect of ceritinib on Asian vs. non-Asian patients is not markedly different.
- Ongoing and planned clinical trials for ceritinib in Japanese (NCT01634763) and Chinese (NCT02040870) patients with ALK+ NSCLC, as well as the randomized global phase 3 trials (NCT01828099 and NCT01828112) should provide further information on the effect of ceritinib on Asian patients.

With the introduction of maintenance chemotherapy and targeted agents, the median overall survival (OS) of patients with advanced non-small cell lung cancer (NSCLC) has improved dramatically. Left untreated, patients with advanced NSCLC have a median OS of four to five months; when treated with platinum doublet chemotherapy, survival increases to a median of approximately eight months. In the recently published PARAMOUNT study, patients with advanced nonsquamous NSCLC were treated with cisplatin plus pemetrexed induction therapy. If they did not progress, they received continuation maintenance therapy with cisplatin plus pemetrexed or placebo. The median OS was 13.9 months in the maintenance pemetrexed arm compared with 11.0 months in the placebo arm, an improvement of almost three months. However, for NSCLC patients with an epidermal growth factor receptor (EGFR) mutation, multiple studies comparing EGFR-tyrosine kinase inhibitors (EGFR-TKIs) with chemotherapy have shown significant improvement in median progression-free survival (PFS) in patients treated with EGFR-TKIs. In addition, the Lung Cancer Mutation Consortium recently showed that patients with NSCLC with an oncogenic driver who were treated with a corresponding targeted agent lived longer than similar patients who were not (median survival: 3.49 years vs. 2.38 years, respectively). Patients with an EGFR-sensitizing mutation had a median survival that was even longer at 3.97 years. Clearly, the targetable groups did quite well in this study compared with the standard platinum doublet chemotherapy.

In Canada, for first-line treatment of patients with NSCLC that is EGFR-mutation positive, we have approval from Health Canada to use three EGFR-TKIs: gefitinib, erlotinib, and afatinib. Gefitinib and erlotinib are reversible EGFR-TKIs that bind reversibly to the adenosine triphosphate (ATP) binding site of the tyrosine kinase, blocking the EGFR signaling pathways associated with the proliferation and survival of cancer cells. Afatinib is an irreversible EGFR-TKI that potentially has increased effectiveness because it binds more permanently to the ATP binding site. In addition, afatinib is a pan-HER inhibitor that can inhibit multiple EGFR family receptors, which may have potential benefits.

In Canada, which of the EGFR-TKIs is used in practice can vary depending on provincial coverage. The standard first-line treatment that has approval and coverage across all provinces is gefitinib, making it the default drug of choice. In my practice, I usually treat patients with gefitinib. On occasion I have used erlotinib: for example, I have used it in a very young patient because erlotinib is a better inhibitor at the dose level given, acknowledging that there are no data to support a substantial difference in efficacy in this setting.

Testing patients for EGFR mutations varies across Canada; in many places, mutation testing is only for common mutations — a deletion in exon 19 (Del19) and a point mutation in exon 21 (L858R) — not uncommon mutations. In most cases, we do not know upfront if a patient’s tumour harbours an uncommon mutation. Testing for uncommon mutations is done in some research protocols and it can take a couple of months to find out the results; although, I expect the testing process to evolve over the coming years. In a Western population such as Canada, there are probably 10–15% of patients with NSCLC who have a common mutation, with variability across the provinces. For example, in British Columbia there is a larger population of Asian patients who have a higher frequency of EGFR mutations. In reality, the number of patients with EGFR mutations in Canada is probably similar to the United States and Europe, and a lot lower than in Asia.

The LUX-Lung 3 and LUX-Lung 6 randomized, phase III clinical trials compared platinum doublet chemotherapy (cisplatin plus pemetrexed and cisplatin plus gemcitabine, respectively) with afatinib in treatment-naïve patients with metastatic lung adenocarcinoma and EGFR mutations. The pooled analysis included 631 patients with common mutations. Patients treated with afatinib had a significantly prolonged median PFS compared with patients treated with chemotherapy. At the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting, the OS data were presented for each study and in a combined analysis.

The study reported a significant difference in OS for patients with Del19 mutations but not in patients with L858R mutations. This difference was not subtle — the numbers were robust — and there was nothing that accounted for the difference except for the Del19 mutation. As oncologists, we have worked with the idea that if a patient has an EGFR mutation, as long as they get the targeted therapy at some point in the sequence of treatments then they will achieve the same OS. However, considering the results of this analysis, the actual sequence may be important in terms of OS benefit. The other question that is raised is whether we should consider treating patients with Del19 mutations differently than patients with L858R mutations.

One possibility that comes up in terms of explaining the survival benefit is exposure to EGFR-TKIs in this population of patients. If a patient starts on an EGFR-TKI, they have a good chance of crossing over to chemotherapy and then...
crossing over to a second EGFR-TKI if they respond well. This treatment strategy gives more exposure to the EGFR-TKIs compared with patients who started with chemotherapy then crossed over to an EGFR-TKI and are less likely to respond to a second, sequential EGFR-TKI. The reason for the survival benefit compared with other studies is unclear, including the role of EGFR-TKI exposure.

Common mutations were a preplanned endpoint of the clinical trial. From the analysis, it appeared that the benefit in OS seen with the Del19 patients raised the average OS for all common mutations. In fact, the lower OS of patients with an L858R mutation obscured the degree of benefit in OS for patients with a Del19 mutation. Also of interest, at the time the trial was designed there was no maintenance chemotherapy built into the study regimen, which could potentially have reduced the OS benefit of afatinib. However, the use of cisplatin plus pemetrexed chemotherapy as a comparator arm in the LUX-Lung 3 trial, which from a Canadian point of view is considered the state of the art platinum doublet, was an important choice because I think the standard of care should always be the comparator in this type of trial.

For patients with L858R mutations there was a trend toward longer OS with chemotherapy. This result bothers the oncology community because there is no good explanation for it and we know these patients respond to, and can do well on, EGFR-TKIs. While we know that these patients probably do not do quite as well as the Del19 patients, this trend toward chemotherapy being of greater benefit to these patients is still puzzling. It is not intuitive. This may have been an anomaly, but it is something that I think should be pursued further with analysis of the gefitinib and erlotinib studies to see if there are similar trends.

For patients with an L858R mutation, we generally use an EGFR-TKI as first-line treatment; in Canada, the most commonly used EGFR-TKI is gefitinib. Data from the LUX-Lung studies are raising questions as to whether this is the right approach. Will these data change our practice for these patients? I do not think there is enough high-quality, level-one evidence to say that afatinib is the best EGFR-TKI and there are currently no data from a head-to-head study to compare the EGFR-TKIs. The data from the LUX-Lung 7 trial will be available in the near future, comparing gefitinib to afatinib. Many oncologists are deferring judgement until then. The LUX-Lung 7 trial is a noninferiority study, so the best we will be able to say is that the efficacy of afatinib is similar to gefitinib. However, this trial could show trends that make afatinib look like the better agent (e.g., a trend toward improved survival over gefitinib); it will help show differences between the drugs in terms of toxicity, and it will be another opportunity to look at differences between patients with Del19 and L858R mutations.

The results of a second study looking at afatinib treatment were presented at ASCO 2014: the LUX-Lung 5 trial. This was a randomized, open-label, phase III trial of patients who had previously been treated with at least one line of chemotherapy and had progressed on erlotinib/gefitinib and afatinib. These patients were subsequently treated with either afatinib plus paclitaxel or the investigator’s choice of single-agent chemotherapy. The primary endpoint of the trial was PFS. When one considers the characteristics of the patients in this trial, they were a very select group. They were clinically selected based on a treatment duration of 12 weeks on afatinib (EGFR mutation testing was not routinely available at the time of the trial), were heavily pretreated (for many this was their fourth line of therapy), and they still had a good performance status (ECOG PS 0-1). While not necessarily the “average” patient, we see this type of patient in practice and we are faced with choosing the optimal treatment for these motivated patients. In EGFR-mutation positive patients, the standard treatment approach in Canada is a first-line EGFR-TKI followed by second-line platinum doublet chemotherapy with or without pemetrexed. In the third line, the patient would receive another round of chemotherapy, for example, docetaxel, unless they had private funding. With private funding, patients could be rechallenged with a second EGFR-
Canadian Perspective by Dr. Jeffrey Rothenstein

TKI (depending on the amount of time the patient has been off the EGFR-TKI), continue the EGFR-TKI combined with chemotherapy, or use afatinib post progression (off-label). The third generation EGFR-TKIs are now in clinical trials; getting this type of patient into one of these clinical trials could be the next best option for treatment if they have a T790M resistance mutation.

The results of the LUX-Lung 5 study showed a superior PFS and overall response rate (ORR) in patients who continued afatinib treatment with paclitaxel compared with those given single-agent chemotherapy, but there was no difference in OS. In the group given single-agent chemotherapy, there were a lot more patients who had two or more subsequent lines of therapy compared with the afatinib plus chemotherapy arm. The OS benefit may have been negated by the post-progression treatment approach, where there was an imbalance between the two groups.

The most common treatment-related AEs reported with afatinib plus paclitaxel were diarrhea, alopecia, and asthenia. The percentage of patients with diarrhea was higher in the afatinib plus paclitaxel group compared with the chemotherapy alone group. This result makes sense because afatinib has a risk of diarrhea, which would increase when combined with chemotherapy. The higher rates of alopecia and asthenia seen in this group are attributable to the paclitaxel chemotherapy, not to afatinib.

Treating the AEs in the afatinib plus paclitaxel group is similar to treating AEs encountered with afatinib alone. For diarrhea, we are very proactive with management, including having loperamide available for use at the first sign of diarrhea and having dieticians involved in patient care. For paronychia, topical steroids with a higher potency are possibly the best treatment option.

The design of this study has been criticized a bit because it included a clinically selected population, not necessarily an EGFR-mutation positive population, with a lot of variables, including the choice of single-agent chemotherapy. In spite of that, this is the first prospective analysis that shows maintaining an EGFR-TKI beyond progression is of value, which I think is a good proof of concept.

It is a bit unclear how to apply the study results to practice and how to apply them to earlier lines of therapy. Some oncologists might ask if there was no OS benefit in this refractory group of patients and there was more toxicity, why should I use this regimen? From my perspective, quality of life (QoL) data, which I think is coming, will be very helpful.

In terms of applying this earlier in practice, if I have a patient on a first-line EGFR-TKI and they are progressing, do I stop the EGFR-TKI and put them on chemotherapy? Do I continue the EGFR-TKI and add chemotherapy? Do I stop the EGFR-TKI, give them chemotherapy, and then put them back on the EGFR-TKI? Those are unanswered questions and multiple trials are ongoing to try to define optimal management.

I can think of two scenarios where this regimen would be of value in this refractory fourth-line population. The first scenario is a symptomatic patient: if you could get a good response with this treatment — the ORR was impressive in the trial — it would help alleviate their symptoms and pain. There may not be an OS benefit, but a good response in a short period of time would give the patient a better QoL for five months of PFS. The second scenario may be a patient who has very bulky or extensive disease. From this trial, we know that there is a good PFS with this combination approach. If there is a clinical trial of a third generation EGFR-TKI opening up, but it is not open yet, then afatinib plus chemotherapy treatment could bridge the patient to get them to the study.

This field is evolving quickly and, again, this study provides the first piece of data showing chemotherapy plus a targeted agent is of value post progression. Funding for this regimen is an issue because afatinib is not approved by Health Canada for use in later lines of therapy, and currently in Ontario we do not have public funding for repeat treatment with an EGFR-TKI. If a patient has private funding for an EGFR-TKI in the third-line setting, then we could consider using afatinib and combining it with chemotherapy. Third generation EGFR-TKIs are also showing promise, which will give us more treatment options. However, right now there are still more questions than answers around the use of the LUX-Lung 5 regimen.

**Established efficacy in the first-line setting**

for EGFR M+ metastatic lung adenocarcinoma

GIOTRIF demonstrated superior PFS vs. pemetrexed/cisplatin in the first-line setting in LUX-Lung 3, the largest, open-label, phase III trial in EGFR M+ metastatic lung adenocarcinoma.1,2

PFS in patients with common EGFR mutations (Del19/L858R; ~90% of all mutations)

GIOTRIF (n = 204) vs. Pemetrexed/cisplatin (n = 104)

- Hazard ratio 0.47 (95% CI, 0.34–0.65)
- P<0.001

GIOTRIF (afatinib) is indicated as monotherapy for the treatment of Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor naïve patients with metastatic lung adenocarcinoma of the lung with activating EGFR mutation(s).2

The first irreversible TKI to block ErbB Family signalling

GIOTRIF (afatinib) demonstrated superior PFS vs. pemetrexed/cisplatin in the first-line setting in LUX-Lung 3, the largest, open-label, phase III trial in EGFR M+ metastatic lung adenocarcinoma.1,2

### References


2. GIOTRIF® Product Monograph, Boehringer Ingelheim (Canada) Ltd., November 2, 2013.

* Comparative clinical significance unknown.

CI = confidence interval; Del19 = exon 19 deletions; EAP = Exceptional Access Program; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; IV = intravenous; L858R = exon 21 L858R point mutations; M+ = mutation-positive; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

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Burlington, Ontario L7L 5H4
Case Study

First-Line Treatment of a Patient with EGFR M+ Non-Small Cell Lung Adenocarcinoma

Physician:
Barbara Melosky, MD, FRCPC
British Columbia Cancer Agency, Vancouver, British Columbia

Presentation:
52-year-old Caucasian female.
Cough for 4 months.
Abnormal chest X-ray showed a right middle lobe mass of 8 cm.
CT scan showed innumerable pulmonary nodules on both lungs.
PET scan showed disease: right lung lit up, multiple pulmonary nodules bilaterally lit up, and left adrenal gland lit up.
Patient has a history of light smoking: she smoked from 20 to 26 years of age, approximately 10 cigarettes per day.

Laboratory and Clinical Findings:

Laboratory:
CBC and differential: normal
Liver function test: normal
CEA: high at 22 mcg/L

Clinical:
Decreased air entry to right base.
Performance status: 2
Bronchoscopy biopsy: adenocarcinoma (TTF1 positive)

Pathology:
Molecular mutation testing: ALK M–; EGFR M+ exon 19 deletion

Diagnosis:
Stage 4 non-small cell adenocarcinoma of lung.
EGFR M+

Treatment:
Afatinib 40 mg/day (initial dose)
Patient is still on treatment 7 months later with no dose adjustments over that time period.

CT scan at baseline

CT scan at 4 weeks
**Outcome:**
Clinical response within 3 weeks of starting afatinib, with improvement in cough. Chest X-ray showed improvement by 4 weeks. Performance status improved to 1. CT scan at 8 weeks showed partial response with reduction of mass in right middle lobe and disappearance of approximately 50% of pulmonary nodules. Partial response continued to 7 months. Treatment is ongoing.

**AE Management:**
- **Diarrhea (grade 2):** Developed at 2 weeks. Treated with Imodium® (loperamide). Well controlled; used on and off for 7 months.
- **Mucositis (grade 2):** Tingling of tongue and cracking of outside corners of lips at approximately 4 weeks. Treated with Kenalog® (triamcinolone acetonide) in Orabase® (benzocaine) 0.1%. Patient has used this very successfully and is using it on a periodic basis.
- **Skin rash (grade 1):** Developed at 6 weeks. Treated with topical steroid cream applied (hydrocortisone 1% with clindamycin 2%). Patient has found this beneficial.
- **Pruritis (grade 1):** Developed on fingertips at 6 months. Treated with a high-dose steroid (betamethasone valerate) applied to nailbeds. Patient has relief of symptoms.

**Conclusion:**
Treatment with afatinib is ongoing in 52-year-old female with partial response and improvement in performance status (1) and QoL.

ALK = anaplastic lymphoma kinase; CBC = complete blood count; CEA = carcinoembryonic antigen; CT = computerized tomography; EGFR = epidermal growth factor receptor; M+ = mutation-positive; M– = mutation-negative; PET = positron emission tomography; QoL = quality of life; TTF = thyroid transcription factor
Cancers of the head and neck comprise a heterogeneous group of diseases, with head and neck squamous cell carcinoma (HNSCC) representing 90% of cases worldwide. Underscoring the need for improved diagnostics, almost half of patients with HNSCC present with metastatic disease. Although there have been improvements in patient survival for other types of cancer, the 5-year survival rate for HNSCC has remained at around 50% for the past several decades.1

Increased expression of epidermal growth factor receptor (EGFR) is observed in as many as 90% of HNSCC tumours.2 EGFR pathway activation has been linked to increased tumour size, decreased radiation sensitivity, increased risk of recurrence, and decreased overall survival.3 Improved outcomes have been achieved in patients with HNSCC that have undergone EGFR-targeted therapies. However, resistance of some patients to EGFR inhibitors has presented a challenge, and the importance of therapeutic decisions based on molecular characterization of tumours has become evident. Consequently, increasing effort has been made to identify biomarkers that can assess efficacy of therapy, help predict treatment outcome, and guide selection of the therapy that is most likely to be effective.

In this article, we describe studies presented at the ASCO 2014 Annual Meeting that sought to improve clinical management of head and neck cancers by evaluating the utility of biomarkers in guiding treatment decisions, as well as by developing patient surveys that are better able to capture key symptoms:

- Investigators outlined the rationale and design of PREDICTOR, a phase II study whose goal is to identify predictive and pharmacodynamic biomarkers to assess the efficacy of anti-EGFR treatment with afatinib in patients with untreated nonmetastatic HNSCC.
- The nCounter nanoString platform was used to identify a set of gene expression biomarkers that may predict outcome of treatment with inhibitors of EGFR and COX-2 in patients with premalignant head and neck cancer lesions.
- Preliminary testing of the Vanderbilt Head and Neck Symptom Survey – Recurrent/Metastatic (VHNSS-RM), a patient-response outcome measure designed to assess symptom burden and enable improved palliation, demonstrated that the tool is feasible and helps to identify actionable problems in patients with advanced disease.

**Background**

Several trials have investigated the therapeutic potential of targeting epidermal growth factor receptor (EGFR) in patients with head and neck squamous cell carcinoma (HNSCC). However, identification of predictive biomarkers in order to assess efficacy of therapy has been a challenge. Correlation of potential predictive and pharmacodynamic biomarkers with treatment outcome was reported in a trial in which expression analysis of sequential biopsies from patients with recurrent/metastatic HNSCC who were treated with erlotinib was performed. At ASCO 2014, Le Tourneau and colleagues presented an overview of the rationale and design of PREDICTOR, a phase II study in its early stages of enrollment whose goal is to identify potential predictive biomarkers of afatinib therapy in patients with untreated nonmetastatic HNSCC.²

**Study design**

- **PREDICTOR** is a multicentre, randomized, phase II study.
- **Inclusion criteria** for this trial include:
  - Age > 18 years;
  - Histologically or cytologically confirmed HNSCC of the oral cavity, paranasal sinus and nasal cavity, oropharynx, larynx or hypopharynx, previously untreated, amenable to curative treatment with surgery;
  - T2-4N0-2 tumours (except T2N0 endolaryngeal tumours);
  - Absence of metastases determined by positron emission tomography computerized tomography (PET CT) scan;
  - Planned date of surgery allowing the patient to receive between 14 and 28 days of afatinib treatment;
  - Eastern Cooperative Oncology Group (ECOG) performance status ≤2;
  - Adequate hematological, liver, renal, and cardiac function.
- **Exclusion criteria** for this trial include:
  - Primary site of head and neck carcinoma in nasopharynx, or skin;
  - Patients receiving other anticancer medication or other anticancer nondrug therapies;
  - Patients with uncontrolled infection;
  - Patients with other concurrent severe and/or uncontrolled medical disease;
  - Clinically relevant cardiovascular abnormalities;
  - Significant or recent acute gastrointestinal disorders with diarrhea as a major symptom or National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTC-AE) grade >1 diarrhea of any etiology;
  - Known pre-existing interstitial lung disease.
- The trial plans to recruit 60 patients with untreated nonmetastatic HNSCC.
- Patients will be randomized 2:1, with 40 patients in the treatment group and 20 patients in the control arm.
- In the treatment group, afatinib will be administered orally at 40 mg/day on a continuous schedule for 14 to 28 days, depending on the date of surgery. Surgery will be performed within a week of the end of treatment, if possible.
- In the control arm, no preoperative treatment will be administered.
- Randomization will be stratified on the site of primary tumour (oropharynx vs. non-oropharynx).
- Dose adjustments will be permitted according to the occurrence of drug-related adverse events (reduction to 30 mg/day).
Key findings

- The primary objective of this study is to identify predictive and pharmacodynamic biomarkers of afatinib biological and clinical activity in patients with untreated nonmetastatic HNSCC by exploring the correlation between potential biomarkers at baseline (at biopsy, prior to afatinib treatment) and at surgery (following afatinib treatment).

- An initial tumour biopsy will be collected during diagnostic pan-endoscopy and a tumour specimen will be collected during surgery.

- Specimens will be analyzed by the following methods for the markers as listed:
  - Immunohistochemistry: expression of EGFRvIII, HER2, Ki67, BCL-2, ERCC1, TP53, and PTEN;
  - High throughput protein analysis using the reverse phase protein array platform: EGFR, phosphorylated-(p-) EGFR, HER2, p-HER2, HER3, p-HER3, HER4, p-HER4, ERK, p-ERK, MEK, p-MEK, STAT3, p-STAT3, AKT, p-AKT;
  - Fluorescence in-situ hybridization (FISH): EGFR, HER2, CCND1 gene copy number;
  - Polymerase chain reaction (PCR) sequencing: EGFR, HER2, PI3KCA mutations;
  - Quantitative reverse transcriptase PCR (RT-PCR): EGFR, EGFRvIII, HER2, HER3, HER4, and c-MET;
  - PCR: human papilloma virus (HPV) expression.

- Secondary endpoints of this trial are:
  - To identify potential pharmacodynamic biomarkers of efficacy, where efficacy is defined as tumour size reduction between baseline and surgery (end of treatment);
  - To evaluate the efficacy of afatinib in the preoperative setting in untreated nonmetastatic HNSCC;
  - To assess safety and tolerability of afatinib, using criteria defined in the NCI CTC-AE version 4.0;
  - To assess pathological response to afatinib, as measured by presence or absence of invasive tumour in the surgical specimen and in the lymph nodes at the time of surgery;
  - To assess metabolic response to afatinib as measured by fluorodeoxyglucose positron emission tomography (FDG-PET) according to Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST) criteria.

- As of April 2014:
  - 13 centres have been opened to enrollment;
  - 41 patients have been randomized by 6 sites. (Figures 1, 2)
**Key conclusions**

- **PREDICTOR** is a multicentre, randomized, phase II trial designed to identify potential predictive and pharmacodynamic biomarkers of afatinib activity in patients with untreated nonmetastatic HNSCC. The main characteristics of this study are:
  - The pre-operative setting in untreated patients: advantage of having specimens collected before treatment (biopsy) and after surgery (surgical specimen); and
  - Randomization versus no treatment: the only way to be able to draw robust conclusions regarding the potential predictive and pharmacodynamics value of the biomarkers under evaluation.

Identification of potential gene expression signatures to predict outcome of chemoprevention with EGFR and COX-2 inhibitors in patients with premalignant head and neck lesions

Background
Preclinical studies have demonstrated that treatment with inhibitors of epidermal growth factor receptor (EGFR) and cyclooxygenase 2 (COX-2) results in synergistic inhibition of head and neck squamous cell carcinoma (HNSCC) tumourigenesis. Saba and colleagues employed the nCounter nanoString platform to analyze expression data in baseline and post-therapy samples in order to identify genomic signatures that may help to predict treatment outcome in patients with premalignant head and neck lesions.1

Study design
• A preassembled gene expression panel provided by nCounter nanoString and consisting of 236 cancer-related and internal reference genes was used to perform gene expression analysis.
• Baseline and post therapy samples from two patients who had been treated with celecoxib and erlotinib on a phase I chemoprevention trial were compared:
  • One patient was a responder who had severe dysplasia at baseline that was reduced to mild dysplasia 3 months after treatment, with no diagnosis of HNSCC as of 1 year after treatment;
  • The second patient was a nonresponder who had moderate dysplasia at baseline and 3 months after treatment, with diagnosis of HNSCC as of 1 year after treatment.

• For both patients, the baseline expression of a subset of 28 genes was compared between a biopsy versus a cytobrush sample.

Key findings
• In the responder patient, gene profiles at baseline versus 3 months post treatment showed differential increased expression of CDC2, ATM, NTRK3, BRCA2, and IGFBP6 genes.
  • In the nonresponder patient, gene profiles at baseline versus 3 months post treatment showed significantly decreased expression of the same genes.
• In the responder patient, gene profiles at baseline versus 3 months post treatment showed decreased expression of NOTCH1, TGFβ, ETS1, FGFR1, HCK, CDH1, and TNSF10.
  • In the nonresponder patient, gene profiles at baseline versus 3 months post treatment showed significantly increased expression of the same genes.
• A significant, positive correlation was observed between baseline expression of the subset of 28 genes in biopsied and cytobrush specimens in the responder (r = 0.454, p = 0.015) and nonresponder (r = 0.52, p = 0.004) patients.

Key conclusions
■ A potential set of gene expression biomarkers that differentiates between patients with premalignant lesions of the head and neck who respond to treatment with inhibitors of EGFR and COX-2 versus patients who do not respond was identified.
■ An association in gene expression profiles in biopsy and cytobrush samples was observed using nanoString technology.
■ Gene expression profiling has potential value as a predictive tool for assessing response in chemoprevention trials.

Preliminary testing of a patient-reported outcome measure for assessing recurrent or metastatic head and neck cancer

Background
Symptom burden in patients with recurrent-metastatic head and neck cancer (RMHNC) is poorly described. Currently available patient-reported outcomes (PROs) do not incorporate measures that are specific to RMHNC and instead focus on acute and late effects of primary therapy. At ASCO 2014, Jackson and colleagues described the development and preliminary testing of the Vanderbilt Head and Neck Symptom Survey – Recurrent/Metastatic (VHNSS-RM), a tool designed to assess RMHNC-related symptoms, residual toxicity from prior therapy, and side effects from current therapy.1

Study design
• The objective of this study is to develop and perform preliminary testing of a PRO specifically designed to identify symptom burden and functional issues in RMHNC.
• A list of items to include in the assessment was generated.
  - Investigators conducted 17 one-on-one interviews with patients with RMHNC.
  - A focus group consisting of 14 experts in the care of patients with head and neck cancer compiled a list of 104 symptoms and 63 psychosocial items.
  - Importance of items was rated by the experts and similar measures were combined.
  - A condensed list of 46 symptoms and 13 psychosocial issues was reviewed by 20 patients, who endorsed the items and ranked them by severity. (Table 1)
  - To develop the VHNSS-RM, investigators assembled a set of questions based on high-impact symptoms and symptoms that occurred at high frequency (endorsed by ≥35% of patients).
  - The VHNSS-RM contains 35 physical symptoms and 12 psychosocial issues that are scored on a scale from 0 to 10 (from none to severe).
  - Items included in the VHNSS-RM were compared to items in existing tools: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module and Head and Neck Module (EORTC QLQ-C30 and QLQ-H&N35), Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N), MD Anderson Symptom Inventory-Head & Neck (MDASI-HN), VHNSS v2.0, and the University of Washington Quality of Life (UWQOL).
• Pilot testing of the VHNSS-RM was completed by 50 consecutive patients with non-curable RMHNC.
  - The tool was administered online to patients during clinic visits.

Table 1. Categories of items included in VHNSS-RM

<table>
<thead>
<tr>
<th>Conceptual cluster</th>
<th>Number of items</th>
<th>Cronbach’s alpha</th>
<th>Scores Moderate/Severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition and swallowing</td>
<td>10</td>
<td>0.90</td>
<td>32</td>
</tr>
<tr>
<td>Speech/communication</td>
<td>5</td>
<td>0.85</td>
<td>32</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>5</td>
<td>0.87</td>
<td>28</td>
</tr>
<tr>
<td>Secretions</td>
<td>2</td>
<td>0.80</td>
<td>44</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>1</td>
<td>–</td>
<td>56</td>
</tr>
<tr>
<td>Wound</td>
<td>4</td>
<td>0.69</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory and nasal</td>
<td>4</td>
<td>0.75</td>
<td>14</td>
</tr>
<tr>
<td>Laceration</td>
<td>1</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>Frequent headaches</td>
<td>1</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>–</td>
<td>44</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5</td>
<td>0.88</td>
<td>16</td>
</tr>
<tr>
<td>Systemic</td>
<td>7</td>
<td>0.94</td>
<td>30</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>12</td>
<td>0.94</td>
<td>20</td>
</tr>
</tbody>
</table>

VHNSS-RM = Vanderbilt Head and Neck Symptom Survey-Recurrent/Metastatic
Key findings

- Patients testing the VHNSS-RM found the tool to be highly feasible and readable.
  - Investigators did not note any barriers to completion of the tool via computer interface.
  - In 92.4% of patients, the time required to complete the VHNSS-RM was ≤15 minutes.
  - A full range of scores was noted for 46 out of 47 questions.
- The VHNSS-RM includes 12 novel symptom questions and 7 novel psychosocial issues. (Table 2)
- Symptom burden was assessed as high in the pilot test.
  - Moderate to severe symptoms (VHNSS-RM ≥5) were identified in >30% of patients for 33 out of 47 questions (70.2%); of those, severe symptoms (VHNSS-RM ≥7) were found in 48.5% of patients.

Table 2. Novel physical symptoms and psychosocial items included in VHNSS-RM

<table>
<thead>
<tr>
<th>VHNSS-RM questions</th>
<th>Moderate-severe burden (≥5), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unique physical symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Change in diet due to swelling in mouth</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>Tongue movement affecting swallowing / speech</td>
<td>21 (42.0) / 20 (40.0)</td>
</tr>
<tr>
<td>Swelling in face or neck</td>
<td>21 (42.8)</td>
</tr>
<tr>
<td>Cramping in neck / jaw</td>
<td>11 (22.0) / 9 (18.0)</td>
</tr>
<tr>
<td>Bad breath</td>
<td>15 (30.0)</td>
</tr>
<tr>
<td>Drooling</td>
<td>18 (36.0)</td>
</tr>
<tr>
<td>Wound drainage / pain / odour</td>
<td>3 (6) / 5 (10) / 4 (8)</td>
</tr>
<tr>
<td>Nasal stuffiness, congestion / sinus drainage</td>
<td>14 (28.0) / 15 (30.0)</td>
</tr>
<tr>
<td>Eyes watering</td>
<td>11 (22.0)</td>
</tr>
<tr>
<td>Frequent headaches</td>
<td>13 (26.0)</td>
</tr>
<tr>
<td>Numbness of face / tongue / ear / scalp</td>
<td>18 (36.0) / 15 (30.0) / 9 (18.3) / 8 (16.3)</td>
</tr>
<tr>
<td>Confusion</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td><strong>Unique psychosocial items</strong></td>
<td></td>
</tr>
<tr>
<td>Perception of burden to family or friends</td>
<td>13 (26.0)</td>
</tr>
<tr>
<td>Feeling of lost independence</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>Fearfulness</td>
<td>14 (28.0)</td>
</tr>
<tr>
<td>Mood swings</td>
<td>19 (38.0)</td>
</tr>
<tr>
<td>Stress</td>
<td>18 (36.0)</td>
</tr>
<tr>
<td>Boredom</td>
<td>19 (38.7)</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>14 (28.0)</td>
</tr>
</tbody>
</table>

Key conclusions

- The VHNSS-RM is a feasible tool that can be completed in a timely manner.
- The VHNSS-RM is able to:
  - Better identify actionable problems;
  - Allow for improved palliation in this cohort of patients;
  - Assess treatment response;
  - Assess treatment impact on overall symptom burden.
- Since symptoms experienced by patients with RMHNC often differ at initial presentation and during primary treatment, the 19 novel questions included in the PRO may help to improve palliation in these patients.
- The need for a directed assessment tool for symptoms and function deficits secondary to recurrent or metastatic disease was identified.
- Studies to validate the VHNSS-RM and analyze its role in assessment of treatment response and impact on overall symptom burden are ongoing.

Colorectal Cancer

Latest Advances in Therapeutic and Prognostic Strategies for Colorectal Cancer

It is projected that 24,400 Canadians will be diagnosed with colorectal cancer (CRC) in 2014, representing 13% of all new cancer cases. Although death rates have been declining over the past decade, the 5-year survival rate is approximately 65% and an estimated 12% of all cancer deaths in Canada in 2014 will be due to CRC.¹

As with many other types of cancer, survival rates for CRC are greatly dependent on the stage of disease at diagnosis. Efforts have focused on identification of molecular markers to assist in screening for CRC, particularly at early stages of disease when physical signs and symptoms are not apparent. A major challenge has been that considerable heterogeneity exists in CRC, with only a small number of genes (e.g., APC, p53, KRAS) currently known to be associated with significant numbers of patients with CRC.²

Molecularly targeted therapy has been investigated as a therapeutic strategy for metastatic CRC (mCRC) in recent years. For example, cetuximab and panitumumab are anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, while bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody. Promising results have been observed in patients treated with these agents.³ However, treatment selection for mCRC needs to be highly individualized, taking into consideration disease and patient characteristics. For example, clinical benefit with cetuximab and panitumumab is apparent only in patients with wildtype (wt) KRAS tumours, since activation of the Ras/Raf/MAPK pathway is a key downstream event following activation of EGFR.⁴ Identification of predictive biomarkers in addition to KRAS is a priority for determination of optimal treatments and improved outcomes for patients with mCRC.

In this article, we describe studies presented at the ASCO 2014 Annual Meeting that examined new developments in CRC research:

- Investigators outlined the rationale and design of UCGI 25, a phase II, randomized trial to examine the clinical benefit of dual targeting of EGFR using cetuximab and afatinib in patients with wtKRAS mCRC who are refractory to chemotherapy.
- High expression of BUBR1 and mutation of the p53 gene were shown to be cooperatively associated with chromosomal instability in colorectal cancer and may influence the development of malignancy.
- Body mass index (BMI) is a potential prognostic measure for disease outcome in patients with mCRC, with low BMI being linked to worse patient outcomes.

UCGI 25: cetuximab plus afatinib versus cetuximab for chemotherapy-refractory wtKRAS metastatic colorectal cancer — A multicentre randomized phase II trial evaluating dual targeting of the EGFR

**Background**
Cetuximab is a recombinant, chimeric, monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR). Monotherapy with cetuximab improves overall survival (OS) and progression-free survival (PFS) in patients with wild type (wt) KRAS metastatic colorectal cancer (mCRC). When combined with the reversible EGFR inhibitor erlotinib, treatment with cetuximab yielded encouraging results in overall response rate (ORR) and PFS in chemo-refractory wtKRAS mCRC. The combination of cetuximab and the irreversible EGFR family tyrosine kinase inhibitor afatinib has been investigated in non-small cell lung cancer. The regimen was shown to be well-tolerated by patients who had acquired resistance to erlotinib or gefitinib. At ASCO 2014, Senellart and colleagues presented an overview of the rationale and design of UNICANCER GI (UCGI) 25, a phase II study in its early stages of enrollment that will investigate the combination of cetuximab and afatinib in patients with wtKRAS mCRC who have failed treatment with oxaliplatin and irinotecan.1

**Study design**
- UCGI 25 is a multicentre, randomized, phase II study.
- This trial plans to recruit 75 patients from 13 centres with wtKRAS mCRC who have failed after treatment with oxaliplatin and irinotecan.
- As of May 31, 2014, 30 patients have been enrolled.
- The inclusion period will last two years, and there will be a two-year follow-up period.
- Eligibility criteria for this trial include:
  - mCRC with wt KRAS/NRAS status;
  - Eastern Cooperative Oncology Group (ECOG) status 0 or 1;
  - No disease progression with previous anti-EGFR targeted therapy;
  - Failure with a prior regimen containing irinotecan or oxaliplatin for metastatic disease;
  - Must have previously received a thymidylate synthase inhibitor (e.g., fluorouracil, capcitabine, raltitrexed, or fluorouracil-uracil) at any point for treatment of colorectal cancer (CRC).

**Key findings**
- The primary endpoint of this study is 6-month PFS rate, as measured by the percentage of patients without disease progression at 6 months with 95% CI.
- Secondary endpoints of this trial are ORR, median PFS, OS, safety, tolerability, and quality of life.
- PFS and OS will be estimated using the Kaplan-Meier method.
- Survival estimates at one and two years will be calculated with their associated 95% CIs.
- This trial will also aim to identify predictive factors for tumour response in an ancillary translational study.

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1 Senellart H, et al. ASCO 2014: TPS3666

Senellart H, et al. ASCO 2014:TPS3666
**Key conclusion**

**UCGI 25** is a multicentre, randomized, phase II trial designed to investigate the benefit of dual targeting of the EGFR protein using the combination of cetuximab and afatinib in patients with wtKRAS mCRC who are refractory to chemotherapy.


**Ando K et al. ASCO 2014:e14578**

**Aberrations in expression of BUBR1 and TP53 in human colorectal cancer**

**Background**

Defects in mitotic checkpoint and p53-dependent pathways are associated with chromosomal instability. The spindle assembly checkpoint protein BUBR1 and p53 are known to play important roles in maintaining chromosomal homeostasis. Although functional interactions between BUBR1 and p53 have been observed, details of the interplay between these molecules and how they influence genetic instability have not been well studied. Ando and colleagues evaluated BUBR1 expression and TP53 gene status to clarify the association between these two molecules in colorectal cancer (CRC).¹
Study design
- In 139 cases of CRC, the following analyses were performed:
  - Expression of BUBR1 was evaluated by immunohistochemistry;
  - The TP53 gene was directly sequenced;
  - DNA ploidy was studied by laser scanning cytometry;
  - Microsatellite instability was examined by dual fluorescent-based fragment analysis.

Key findings
- In 64.7% of CRC cases examined, aberrantly high expression of BUBR1 was detected.
- High BUBR1 expression was associated with TP53 mutation ($p = 0.017$).
- High BUBR1 expression and TP53 mutation were associated with DNA aneuploidy ($p = 0.05$, $p = 0.011$, respectively), and were inversely associated with microsatellite instability ($p = 0.09$, $p = 0.0005$).
- Potential correlations of BUBR1 and TP53 gene with genetic instability were examined.
  - Cases were categorized into three groups according to the status of BUBR1 and TP53 gene.
    - Both high BUBR1 expression and TP53 gene mutation were found in 28.1% of cases (“Both” group).
    - Either BUBR1 or TP53 gene aberration was confirmed in 25.2% of cases (“Either” group).
    - The remaining 46.8% of cases showed neither of the aberrations (“Neither” group).
  - The “Both” group had a more profound chromosomal instability phenotype compared to the “Neither” group ($p = 0.005$).
  - The “Either” group had a moderate aneuploidy ratio.
  - The “Neither” group showed a higher microsatellite instability (+) ratio (26.1%) than the “Either” (5.7%) or “Both” group (2.5%) ($p = 0.027$ and $p <0.001$, respectively).

Key conclusions
- Results indicated that interplay between BUBR1 and p53 exists in CRC.
- Altered expression of BUBR1 and p53 is cooperatively associated with chromosomal instability, which may influence cancer development.

Reference:

Renfro LA et al. ASCO 2014:3537

Body mass index as a prognostic measure in metastatic colorectal cancer

Background
Recent retrospective analyses of clinical trials in patients with early colorectal cancer (CRC) have revealed that low and high body mass index (BMI) are associated with worse patient outcomes. However, there is limited data on the use of BMI as a prognostic measure for outcomes in metastatic colorectal cancer (mCRC). Renfro and colleagues examined pooled data in the Aide et Recherche en Cancérologie Digestive (ARCAD) trial database to investigate the influence of BMI on patient outcomes.1

Study design
- Data from the ARCAD trial database, which included 20,078 patients with mCRC from 23 first-line trials, were pooled.
- Cox models (stratified by treatment arm within the study) were used to assess the prognostic influence of baseline BMI on overall survival (OS) and progression-free survival (PFS).
- Adjustments for and interactions with age, sex, and performance status (PS) were considered.
- Possible differences in BMI effect in patients treated with anti-EGFR and anti-angiogenesis therapy were tested.
- BMI effect was treated as possibly nonlinear.
- Clinically relevant effects with $p <0.05$ were deemed significant.

Key findings
- BMI was prognostic for OS ($p <0.0001$) and PFS ($p <0.0001$) with L-shaped risk.
- Risk was highest for patients with BMI near 15, decreased as BMI increased to approximately 28, and then plateaued for higher BMI. (Figure 1)
  - BMI effect was significant after adjustment for age, sex, and PS.
- Low BMI was associated with poorer OS for males than females. (Figure 2)
- High BMI was associated with improved OS for males versus females ($p < 0.001$). (Figure 2)
- Other interactions (age, PS, and therapy type) were not significant.
- Relative to obese patients, patients with the lowest BMIs were associated with:
  - 62% increased risk of death (95% CI: 48%–77%);
  - 35% increased risk of progression or death (95% CI: 24%–46%).

Limitations to the analysis in this study include:
- BMI relationships (particularly for the increased risk observed for low BMI patients) may be related to disease;
- Although BMI is likely related to the dose received by the patient, there is no formal way to incorporate dose effect in the modeling process;
- Investigators were unable to adjust for potential confounding factors such as affluence and nutrition.

Figure 1. Overall survival and progression-free survival of all patients according to BMI

![Graph showing overall survival and progression-free survival of all patients according to BMI.]

Figure 2. Overall survival of male and female patients according to BMI

![Graph showing overall survival of male and female patients according to BMI.]

**Key conclusions**

- **BMI is prognostic for both OS and PFS.**
  - Low BMI, but not high BMI, is associated with increased risk of progression or death among the patients with mCRC who were studied.
  - The increased risk that is associated with low BMI is greater for males than females.
  - Further studies are warranted, including investigations into the possibility that molecular pathways are involved in the impact of BMI on disease outcome.

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. Effective treatment with 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

• Myelosuppression: Patients treated with TREANDA may experience myelosuppression. In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb) and neutrophils closely

Other relevant warnings and precautions:

• Use with caution in patients with CrCl < 40 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 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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