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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 May 2014 issue features coverage from the 55th American Society of Hematology Annual Meeting and the 36th Annual San Antonio Breast Cancer Symposium. At these conferences, investigators presented encouraging data on various combinations of chemotherapies and/or targeted agents for the treatment of acute promyelocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, and breast cancer. Based on these results, oncologists could soon be offering their patients new combination therapies that have greater safety and tolerability, and efficacy that is at least comparable to the standard of care. We would like to thank Dr. Carolyn Owen and Dr. Douglas Stewart for their Canadian Perspectives. We would also like to thank Dr. Richard Furman for his Investigator Commentary.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research.
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• Response to first-line treatment with BR or FCR in patients with CLL: first outcome data from the TLN registry. (Knauf W, et al. ASH 2013:4181)

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Contributors

Canadian Perspectives

Carolyn Owen, MD
Dr. Carolyn Owen completed postgraduate training in internal medicine and hematology at the University of Ottawa and the University of British Columbia, respectively, followed by a research fellowship in molecular genetics at Barts and the London School of Medicine and Dentistry in London, U.K. 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.

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

Richard R. Furman, MD

Dr. Furman is a member of the Lymphoma/Myeloma Service in the Division of Hematology/Oncology at the New York Weill Cornell Medical Center. He is head of the chronic lymphocytic leukemia (CLL) and Waldenstrom’s macroglobulinemia (WM) program at Weill Medical College, and focuses on identifying new and promising therapies for patients with CLL and WM. Along with collaborators at Columbia Presbyterian, Johns Hopkins, Roswell Park Cancer Institute, and Ohio State University, Dr. Furman has initiated the Waldenstrom’s Research Consortium in order to enhance treatment and understanding of WM.
Leukemias

New Treatments Maintain Efficacy but Reduce Toxicity Compared with Standard Regimens in APL and CLL

As with the majority of cancers, treatments for chronic lymphocytic leukemia (CLL) and acute promyelocytic leukemia (APL) have largely been dependent on chemotherapy-based approaches. Though some of these approaches have resulted in high response and remission rates, the price many patients pay in toxic side effects remains very high. In the case of APL, despite all-trans retinoic acid (ATRA) plus anthracycline-based approaches leading the way to cure rates as high as 80%, hematological toxicity is typical.\(^1\) The recent demonstration that arsenic trioxide (ATO) plus ATRA was noninferior to idarubicin plus ATRA in standard-risk APL patients solidified the arrival of a chemotherapy-free approach in front-line treatment of APL, with the added benefit of reduced hematological toxicity.\(^2\)

In the case of CLL, where the goal is to achieve long-lasting remissions, toxicity is a great concern given that FCR (fludarabine, cyclophosphamide, rituximab), the standard treatment for young, fit patients, can cause significant adverse events. Based on these challenges, the scientific community has tried to introduce less toxic treatment options such as BR (bendamustine, rituximab), the introduction of a new generation of anti-CD20 antibodies (obinutuzumab), and recent developments in chemotherapy-free targeted approaches that include the phosphatidylinositol-3-kinase inhibitor, idelalisib, and the antiapoptotic inhibitor, ABT-199. These exciting new developments were among many studies presented at the American Society of Hematology (ASH) 2013 Annual Meeting in New Orleans.

The following is a report on 13 presentations given at ASH 2013:

- A study on the long-term outcomes of second-line chemotherapy or ATO-based regimens in patients with relapsed APL found that salvage therapy with the ATO-based regimen allowed autologous stem cell transplantation to be performed more frequently in patients with negative bone marrow samples.
- Updated results of the European registry of Relapsed APL study, which examined ATO-based therapy in patients with relapsed APL, revealed that 50% of patients in first relapse can probably be cured with ATO-based salvage therapy.
- A Canadian analysis compared the cost-effectiveness of ATO plus ATRA vs. ATRA plus idarubicin in the treatment of newly diagnosed APL patients. This economic evaluation demonstrated that ATO plus ATRA can be considered a more cost-effective strategy than the standard therapy.
- A study examining ATO or ATRA for consolidation treatment in non-elderly, newly diagnosed patients with APL concluded that substitution of arabinoside with ATO or ATRA during consolidation cycles may be accomplished without increasing the risk of relapse, and may decrease the number of deaths in patients who experience a CR.
- In the CLL11 study, the comparison of obinutuzumab plus chlorambucil (G-Clb) vs. rituximab plus chlorambucil (R-Clb) as first-line treatment for CLL patients with comorbidities demonstrated that G-Clb had superior efficacy to R-Clb and an acceptable safety profile in this typical CLL patient population.
- An interim analysis of the CLL10 trial comparing the safety and noninferiority of BR vs. FCR for progression-free survival (PFS) in fit patients with CLL showed that no firm recommendation of one regimen over the other could be given.
- A phase I study examined monotherapy with the antiapoptotic inhibitor ABT-199 in high-risk patients with relapsed/refractory (R/R) CLL or small lymphocytic lymphoma. In addition to showing robust ABT-199 activity in patients with R/R CLL, no additional tumour lysis syndrome events were reported with a new dosing scheme.
Background
Arsenic trioxide (ATO) is currently regarded as the best treatment option in relapsed acute promyelocytic leukemia (APL).1 However, the comparison of long-term outcomes of an ATO-based or a chemotherapy-based approach to salvage therapy has not been well established.

The objective of this study was to analyze the clinical outcomes of APL patients who received second-line therapy with chemotherapy or ATO-based regimens after relapsing from front-line therapy with all-trans retinoic acid (ATRA) and anthracyclines.

Study design
• From June 1997 to May 2013, 151 patients (94 male/57 female; median age: 42 years [range: 2–81]) relapsed after front-line therapy in the Programa de Estudio y Tratamiento de las Hemopatias Malignas (PETHEMA) trials.
  ◆ Patients presented with either molecular relapse (n = 47) or hematological relapse (n = 104).
• A total of 67 patients (44%) received salvage therapy with chemotherapy-based regimens (chemotherapy group) consisting of induction with mitoxantrone plus cytarabine plus ATRA (n = 45), EMA (etoposide, methotrexate, actinomycin D; n = 7), or other regimens (n = 15).
Patients not eligible for stem cell transplantation (SCT) received consolidation with or without maintenance therapy.

From October 2003, 84 patients (56%) received salvage therapy with ATO-based regimens (ATO group) consisting of induction with ATO (0.15 mg/kg intravenously until complete response [CR], with ATRA [n = 19] or chemotherapy [n = 6]) followed by one consolidation cycle with ATO plus ATRA.

In patients whose post-consolidation bone marrow polymerase chain reaction (PCR) was negative, an autologous (auto)-SCT was recommended; in patients whose PCR was still positive an allogeneic (allo)-SCT was planned.

Patients who were not eligible for SCT received maintenance therapy with ATO plus ATRA with or without low-dose chemotherapy.

**Key findings**

- Baseline characteristics, including sex, relapse-risk at primary diagnosis, morphologic and B-cell receptor subtype, as well as age at relapse and type of relapse, were similar in both cohorts of patients.
- Although not significant, patients rescued with chemotherapy-based regimens presented more frequently with early relapses (<18 months after initial APL diagnosis; 55% vs. 43%, \(p = 0.13\)).
- The CR rates were 85% in the chemotherapy group (eight deaths and two patients experienced resistance) and 92% in the ATO group (four deaths and three patients experienced resistance) \(p = 0.11\). (Figure 1)
- Twenty-two patients in the chemotherapy group (39%) and 16 in the ATO group (21%) did not have a transplant in second CR \(p = 0.04\).

**Figure 1. Induction outcomes**

![Induction outcomes graph](image1)

**Figure 2. Post-remission therapy**

![Post-remission therapy graph](image2)

*ATO = arsenic trioxide*
• The reasons why patients in the chemotherapy and the ATO groups, respectively, did not have SCT were ineligibility (6 vs. 8 patients), early relapse before planned SCT (10 vs. 7 patients), and mobilization failure (6 vs. 1 patients).

• Overall, 34 patients underwent SCT in the chemotherapy group (auto-SCT, n = 20; allo-SCT, n = 14), and 57 underwent SCT in the ATO group (auto-SCT, n = 47; allo-SCT, n = 10). (Figure 2)

• The median follow-up in the chemotherapy group was 95 months (range: 24–167), and in the ATO group, it was 33 months (range: 3–100).

• Five-year survival rates were reported for the following patient populations:
  - All patients (chemotherapy vs. ATO):
    - Overall survival (OS): 40% vs. 56% (p = 0.01); (Figure 3)
    - Disease-free survival (DFS): 31% vs. 39% (p = 0.07);
    - Relapse-free survival (RFS): 34% vs. 48% (p = 0.09);
  - Patients not receiving SCT because of mobilization failure or ineligibility (chemotherapy vs. ATO):
    - OS: 56% vs. 19% (p = 0.11);
    - DFS: 42% vs. 19% (p = 0.49);
    - RFS: 42% vs. 29% (p = 0.63);
  - Patients receiving auto-SCT (chemotherapy vs. ATO):
    - OS: 55% vs. 80% (p = 0.04);
    - DFS: 40% vs. 54% (p = 0.06); (Figure 4)
    - RFS: 44% vs. 57% (p = 0.13);
  - Patients receiving allo-SCT (chemotherapy vs. ATO):
    - OS: 56% vs. 43% (p = 0.77);
    - DFS: 29% vs. 21% (p = 0.48); (Figure 5)
    - RFS: 31% vs. 57% (p = 0.34).
  - All but one patient underwent auto-SCT with negative PCR (this patient relapsed rapidly after auto-SCT).

• Regarding allo-SCT, seven patients were PCR positive and 17 were PCR negative before transplant (5-year DFS: 0% vs. 41%, respectively; p = 0.01).

Figure 3. Overall survival according to salvage therapy

![Figure 3](image1)

ATO = arsenic trioxide; CT = chemotherapy

Figure 4. Disease-free survival after Auto-SCT according to salvage therapy

![Figure 4](image2)

ATO = arsenic trioxide; Auto-SCT = autologous stem cell transplantation; CT = chemotherapy
Background
Arsenic trioxide (ATO) is regarded as the treatment of choice for relapsed acute promyelocytic leukemia (APL) that is PML-RARA (promyelocytic leukemia-retinoic acid receptor alpha)-positive.1 In 2008, a European registry for relapsed APL (PROMYSE) based on uniform case report forms (CRFs) was established under the auspices of the European LeukemiaNet (ELN) to gain insights into the clinical and biological characteristics of relapsed APL treated with ATO and to allow an assessment of the different options for post-consolidation therapy.

The objective of the study was to assess ATO-based salvage therapies in patients with relapsed APL.

Study design
• Eligibility criteria for prospective or retrospective registration from 2003 onwards were:
  ◦ Patients who were PML-RARA+ and who had experienced first or successive molecular or clinical relapse of APL;
  ◦ Patients who had received any treatment option for relapsed APL.
  • Recommended treatment algorithm for relapsed APL is shown in Figure 1.
  ◦ Among several options for post-consolidation treatment, the most appropriate option for the individual patient should be selected depending on patient’s age, performance status, PCR status after consolidation, type of front-line therapy, first CR duration, and donor availability.
  ◦ Central nervous system (CNS) relapses should receive methotrexate-based intrathecal therapy ± irradiation in addition to ATO.

Key conclusions
■ This study, which was performed in a large series with prolonged follow-up of APL patients who relapsed after front-line therapy with ATRA and anthracycline, showed high rates of CR with either ATO (92%) or chemotherapy regimens (85%).

■ Salvage therapy with the ATO-based regimen allowed for auto-SCT to be performed more frequently in patients with a negative PCR; this strategy resulted in an overall improvement of the five-year OS, DFS, and RFS.

Reference:

Lengfelder E, et al. ASH 2013:1406

Arsenic trioxide-based therapy of relapsed APL: updated results of the European registry of relapsed APL
Key findings

- By 30 June 2013, 198 of 220 registered cases were evaluable (172 patients in 1st relapse, 26 in ≥2nd relapse).
  - Of these, 149 patients in first relapse received ATO-based salvage therapy after standard front-line therapy based on all-trans retinoic acid (ATRA) and anthracyclines (98 patients with hematological relapses of bone marrow combined with CNS relapse in 5 patients, 40 patients with molecular relapse, and 11 patients had isolated extramedullary relapse, mainly CNS).
  - Clinical characteristics of patients included:
    - The median age at relapse was 44 years (range: 4–81);
    - 67% were males;
    - Median duration of first remission was 1.5 years (range: 105 days–7.0 years).
- Patients received either ATO monotherapy (induction: 68%; consolidation: 48%), ATRA plus ATO (induction: 32%; consolidation: 36%) or other (induction: 0; consolidation: 16%).
- Patients who experienced a CNS relapse were treated with ATO and intrathecal methotrexate ± irradiation.
- In patients with non-hematological relapses, no early deaths occurred and no major side effects associated with ATO were seen. (Tables 1 and 2)

### Table 1. Laboratory data at first relapse and adverse events during induction therapy

<table>
<thead>
<tr>
<th></th>
<th>Molecular + extramedullary relapse (n = 51)</th>
<th>Hematological relapse (n = 98)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory data at first relapse</td>
<td>Median (range)</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>WBC (x 10^9/L)</td>
<td>4.5 (1.9–9.0)</td>
<td>3.2 (0.5–112)</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelets (x 10^9/L)</td>
<td>182 (40–453)</td>
<td>58 (8–479)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.7 (8.7–16.1)</td>
<td>12.4 (5.5–16.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>6% (2/35)</td>
<td>25% (16/64)</td>
<td>0.02</td>
</tr>
<tr>
<td>Signs of bleeding</td>
<td>2% (1/44)</td>
<td>24% (20/85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adverse events during induction therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APL differentiation syndrome</td>
<td>0</td>
<td>28%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>40%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QT-prolongation</td>
<td>9%</td>
<td>10%</td>
<td>0.9</td>
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</tbody>
</table>

APL = acute promyelocytic leukemia; Hb = hemoglobin; WBC = white blood cell
• The median follow-up of the 149 patients was 2.8 years (range: 6 days–10 years).
• For patients treated with ATO, the three-year overall survival (OS) was 70% and six-year OS was 56% (95% CI: 42–70). (Figure 2)
• The three-year OS for patients with hematological, molecular, or extramedullary relapse was 69% [95% CI: 58–80], 66% [95% CI: 48–84], and 90% [95% CI: 81–99], respectively (p = 0.37).
• The three-year OS after autologous stem cell transplantation (SCT; n = 55) was 82% (95% CI: 70–94), after an allogeneic SCT (n = 32) was 75% (95% CI: 58–92), and without transplantation or transplantation after at least two relapses (n = 55) was 66% (95% CI: 48–84) (p = 0.19). (Figure 3)

<table>
<thead>
<tr>
<th>Table 2. Results after induction and consolidation</th>
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<td>Results after induction</td>
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<td></td>
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<tr>
<td>Results after consolidation</td>
</tr>
</tbody>
</table>

CR = complete response; PCR = polymerase chain reaction

Figure 2. Overall survival after first relapse treated with ATO-based salvage therapy (N = 149)
Key conclusions

■ The analysis revealed that 50% of patients in first relapse can probably be cured with ATO-based salvage therapy.

■ Induction death and adverse effects of ATO were lower in patients with non-hematological (molecular and extramedullary) relapse.

■ Patients treated in molecular relapse had a survival advantage in the first months compared to patients in hematological relapse.

■ Transplantation in second remission seemed to improve outcome.

■ Long-term survival may also be observed after transplantation in third or later remission or even without transplantation.


Lachaine J, et al. ASH 2013:1677

Cost-effectiveness of ATO plus ATRA compared with ATRA plus idarubicin in the treatment of newly diagnosed APL patients

Background

Acute promyelocytic leukemia (APL) is a distinct and rare morphological, clinical, and pathological subtype of acute myeloid leukemia (AML). Although current treatments (all-trans retinoic acid [ATRA], anthracyclines, and conventional chemotherapy) are associated with high remission rates, cytotoxic effects of chemotherapy remain a concern in the management of newly diagnosed APL. Arsenic trioxide (ATO) has been approved in several countries, including Canada, for the induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, ATRA and anthracycline chemotherapy.
The objective of this study was to assess, from a Canadian perspective, the economic impact of the combination of ATO plus ATRA in the treatment of patients with newly diagnosed APL.

**Study design**
- A time-dependent Markov model was constructed to assess the cost-effectiveness of ATO plus ATRA compared to ATRA plus idarubicin in the treatment of newly diagnosed APL.
- The Markov model comprises four health states: event-free survival (EFS), treatment failure/relapse, post-failure, and death. (Figure 1)
- The length of each Markov cycle was one month for the 48-month period of the Lo-Coco et al. study² and then of one year.
- All patients started in the EFS state and could then move to other health states.
- In the case of treatment relapse/failure, patients were subsequently treated with a salvage induction therapy composed of ATRA and conventional chemotherapy followed by autologous hematopoietic stem cell transplantation as consolidation treatment.
- The model also took into account the incidence of treatment-induced adverse events that were significantly different between both treatment arms in the Lo-Coco et al. study² (neutropenia, thrombocytopenia, fever episodes, and QTc interval prolongation).
- Utility values associated with each health state and adverse events were used to estimate the number of quality-adjusted life-years (QALYs) associated with each treatment.
- The model also allowed comparison with the combination of ATRA plus idarubicin plus cytarabine, which is also used in Canada.
- Analyses were conducted from both a Canadian Ministry of Health (MoH) and a societal perspective over a lifetime horizon.
- The costs included in the analysis from a MoH perspective were those associated with medication, treatment administration, APL disease management, and healthcare resources used to manage severe adverse effects.
- From a societal perspective, additional costs associated with loss of productivity were considered.

*APL = acute promyelocytic leukemia
*Treatment failure comprises relapse or incomplete treatment response.
Table 1. Cost-effectiveness results

<table>
<thead>
<tr>
<th>Source</th>
<th>Costs (CAD)</th>
<th>Incremental costs (CAD)</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
<th>ICER (CADS/QALY)</th>
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<tr>
<td>Ministry of Health perspective</td>
<td></td>
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</tr>
<tr>
<td>ATRA + IDA</td>
<td>73,768</td>
<td>13.24</td>
<td>13.24</td>
<td>1.44</td>
<td>50,193</td>
</tr>
<tr>
<td>ATO + ATRA</td>
<td>145,962</td>
<td>14.68</td>
<td>14.68</td>
<td>1.44</td>
<td>46,367</td>
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<td>Societal perspective</td>
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<tr>
<td>ATRA + IDA</td>
<td>101,352</td>
<td>13.24</td>
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<tr>
<td>ATO + ATRA</td>
<td>168,043</td>
<td>14.68</td>
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<td>46,367</td>
</tr>
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</table>

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CAD = Canadian; ICER = incremental cost-effectiveness ratio; IDA = idarubicin; QALY = quality-adjusted life-year

Key findings

- In the treatment of newly diagnosed APL, ATO plus ATRA was associated with incremental cost-effectiveness ratios (ICERs) of $50,193 per QALY and $46,367 per QALY from a MoH and societal perspective, respectively, when compared with ATRA plus idarubicin. (Table 1)
- According to the one-way sensitivity analysis results, the ICER of ATO plus ATRA compared to ATRA plus idarubicin varied from $23,045 per QALY to $60,759 per QALY from a MoH perspective and between $21,294 per QALY and $56,933 per QALY from a societal perspective. (Figure 2)
- Results of the probabilistic sensitivity analysis indicated that the ICER remains below $50,000 in 48.33% and 74.21% of the Monte Carlo simulations from a MoH and a societal perspective, respectively.

Key conclusions

- This economic evaluation demonstrated that from a Canadian perspective, ATO plus ATRA can be considered a cost-effective strategy over the standard therapy in APL.
- This is the first chemotherapy-free regimen that showed significant clinical benefits compared to the current standard therapy for the treatment of patients with APL.

ATO or ATRA as consolidation treatment for non-elderly patients with newly diagnosed standard-risk APL

**Background**

All-trans retinoic acid (ATRA) combined with anthracycline-based chemotherapy remains the reference treatment for newly diagnosed acute promyelocytic leukemia (APL) in most centres. However, this treatment is myelosuppressive and may be associated with long-term cardiac toxicity. Arsenic trioxide (ATO) and ATRA may allow clinicians to reduce the amount of chemotherapy used and further decrease the risk of relapse.

The objective of the APL 2006 trial was to test the role of ATO and ATRA in consolidation treatment in patients with standard-risk APL. The study compared the use of ATO, ATRA, or cytosine arabinoside (AraC) in consolidation treatment.

**Study design**

- Patients <70 years of age who were newly diagnosed with standard-risk APL (white blood cell count <10G/L) were randomized for two courses of consolidation treatment that included AraC (standard group), ATO, or ATRA.
- Patients received the following doses and treatment schedules:
  - Induction therapy: all patients received ATRA (45mg/m²/day) until complete response (CR), idarubicin (12 mg/m²/day x 3), and AraC (200 mg/m²/day x 7, starting on day 3).
  - First consolidation course: all patients received idarubicin (12 mg/m² x 3) in combination with one of:
    - AraC: 200 mg/m²/day x 7;
    - ATO: 0.15 mg/kg/day, days 1 to 25; or
    - ATRA: 45 mg/m²/day, days 1 to 15.
  - Second consolidation course: all patients received idarubicin (9 mg/m²/day x 3) in combination with one of:
    - AraC: 1 g/m² x 8;
    - ATO: 0.15 mg/kg/day, days 1 to 25; or
    - ATRA: 45 mg/m²/day, days 1 to 15.
  - Maintenance therapy: over a two-year period, all patients were given intermittent ATRA (15 days/3 months) and continuous 6-mercaptopurine plus methotrexate.
- The primary endpoint of the study was event-free survival (EFS) at two years from the achievement of CR.
- Secondary endpoints were the rates of relapse, overall survival (OS), adverse events of treatment, and the duration of patient hospitalization.
- These results are from a second interim analysis made at the reference date of January 1, 2012.
**Key findings**

- Baseline patient characteristics were well balanced between the three consolidation groups.
  - Following induction therapy, 117, 118, and 117 patients were in the AraC, ATO, and ATRA arms, respectively.
- The 2-year EFS rates in the AraC, ATO, and ATRA arms were 95.5%, 96.5%, and 95.6% \( (p = \text{not significant [NS]}) \), respectively. (Table 1)
- The 2-year OS rates in the AraC, ATO, and ATRA arms were 96.6%, 96.5%, and 97.4% \( (p = \text{NS}) \), respectively. (Table 1)
- The number of patients who relapsed in the AraC, ATO, and ATRA arms was four, none, and five, respectively.
- The number of patients who died during consolidation and maintenance therapies in the AraC, ATO, and ATRA arms was seven, four, and four, respectively.
- There were 11 early deaths that occurred during induction therapy.
- Hematological toxicity is shown in table 2.

**Table 1. Efficacy results**

<table>
<thead>
<tr>
<th></th>
<th>AraC arm ( (n = 117) )</th>
<th>ATO arm ( (n = 118) )</th>
<th>ATRA arm ( (n = 117) )</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (%)</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>—</td>
</tr>
<tr>
<td>No. of relapses</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>2-year EFS (95% CI)</td>
<td>95.5( (91.7-99.5) )</td>
<td>96.5( (93.3-99.9) )</td>
<td>95.6( (91.9-99.4) )</td>
<td>NS</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2-year OS (95% CI)</td>
<td>96.6( (93.4-99.9) )</td>
<td>96.5( (93.3-99.9) )</td>
<td>97.4( (94.5-100) )</td>
<td>NS</td>
</tr>
</tbody>
</table>

* AraC = cytosine arabinoside; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CI = confidence interval; CR = complete response; EFS = event-free survival; NS = not significant; OS = overall survival.

**Table 2. Hematological toxicity**

<table>
<thead>
<tr>
<th>Median (days)</th>
<th>AraC arm</th>
<th>ATO arm</th>
<th>ATRA arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt;1 G/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st consolidation</td>
<td>24</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>2nd consolidation</td>
<td>23</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Platelets &gt;50 G/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st consolidation</td>
<td>25</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>2nd consolidation</td>
<td>27</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st consolidation</td>
<td>32</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>2nd consolidation</td>
<td>29</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

* ANC = absolute neutrophil count; AraC = cytosine arabinoside; ATO = arsenic trioxide; ATRA = all-trans retinoic acid.

**Key conclusions**

- Current CR rates obtained in standard-risk APL are very high (97%), with very few relapses.
- The substitution of AraC with ATO or ATRA during consolidation cycles may be accomplished without increasing the risk of relapse, and may decrease the number of deaths in patients who experience CR.
- Myelosuppression was reduced in patients who received idarubicin plus ATRA consolidation courses compared with those who received idarubicin plus AraC.

For induction of remission and consolidation of APL refractory to or relapsed from retinoid and anthracycline therapy, and where APL shows the presence of the t(15;17) translocation or PML-RAR\textalpha\, gene expression.

**PART OF THE LUNDBECK ONCOLOGY PORTFOLIO**

- Overall 87% CR* rate demonstrated (n=52) (combined results of 2 open-label, single-arm studies)†

TRISENOX (arsenic trioxide) is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL), which is refractory to or has relapsed from retinoid and anthracycline therapy, and whose APL is characterized by the presence of the t(15;17) translocation or promyelocytic leukemia-retinoic-acid-receptor alpha (PML-RAR\textalpha) gene expression.

Refer to the page in the bottom-right icon for additional safety information and a web link to the Product Monograph discussing:
- Contraindications in pregnancy and nursing mothers
- Most serious warnings and precautions regarding APL differentiation syndrome, acute cardiac toxicities (rhythm disturbance) and avoiding concomitant use of drugs that prolong the QT interval or disrupt electrolyte levels
- Other relevant warnings and precautions regarding tumor lysis syndrome, carcinogenesis of arsenic trioxide, increased heart rate, hyperleukocytosis, elevated transaminases, peripheral neuropathy, fertility, embryotoxicity, teratogenicity, presence of arsenic in semen (use condom during treatment and for 3 months after stopping treatment), patients with renal or hepatic impairment, and monitoring of electrocardiograms, laboratory parameters (potassium, calcium, magnesium, glucose, hematologic, hepatic, renal, coagulation), serious arsenic toxicity in the obese, and for hypoxia and development of pulmonary infiltrates and pleural effusion in all patients
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions

In addition, the page contains the reference list and study parameters relating to this advertisement.

*CR (complete remission) was defined as cellular bone marrow aspirate with <5% blasts, peripheral blood leukocyte count \( \geq 3,000/\text{mm}^3 \) or absolute neutrophil count \( \geq 1,500/\text{mm}^3 \), and platelet count \( \geq 100,000/\text{mm}^3 \).

APL=acute promyelocytic leukemia; PML-RAR\textalpha=promyelocytic leukemia-retinoic-acid-receptor alpha

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Chronic Lymphocytic Leukemia

Goede V, et al. ASH 2013:6

Head-to-head comparison of obinutuzumab plus chlorambucil versus rituximab plus chlorambucil in patients with CLL

Background

Obinutuzumab (GA101) is a novel glycoengineered type II, anti-CD20 monoclonal antibody that has been shown to possess superior activity to rituximab in preclinical studies. The CLL11 study is a large, randomized phase III trial investigating the use of GA101 as part of chemoimmunotherapy in the first-line treatment of chronic lymphocytic leukemia (CLL) patients who have comorbidities.

The objectives of the CLL11 study are to establish chemoimmunotherapy as a treatment option in older CLL patients who have comorbidities, and to make a head-to-head comparison between GA101 and rituximab, as the standard of care.

Study design

- CLL11 (NCT01010061) is a two-stage, randomized, open-label, multicentre, international, three-arm, phase III trial:
  - Stage I: GA101 plus chlorambucil (G-Clb) vs. Clb alone and rituximab plus Clb (R-Clb) vs. Clb alone;
  - Stage II: G-Clb vs. R-Clb.

- Eligibility criteria included patients with previously untreated and documented CD20+ CLL, age ≥18 years, and a total Cumulative Illness Rating Scale (CIRS) score >6 and/or an estimated creatinine clearance (CrCl) of <70 mL/min.

- Patients were randomized in a 1:2:2 ratio to receive one of three regimens, Clb alone, G-Clb, or R-Clb, at the following dosages:
  - Clb: 0.5 mg/kg orally on days 1 and 15 of cycles 1–6, every 28 days;
  - GA101: 1,000 mg intravenously (iv) on days 1, 8, and 15 of cycle 1, 1,000 mg on day 1 of cycles 2–6, every 28 days;
  - Rituximab: 375 mg/m² iv on day 1 of cycle 1, 500 mg/m² on day 1 of cycles 2–6, every 28 days.

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

- The primary end point was investigator-assessed progression-free survival (PFS).

- The secondary end points included overall response rate (ORR), minimal residual disease (MRD), overall survival (OS), and safety.
Key findings
• Final results of the stage two analysis:
  - A total of 663 patients comprised the intent-to-treat population (G-Clb, n = 333; R-Clb, n = 330) and 657 patients comprised the safety population (G-Clb, n = 331; R-Clb, n = 326).
  - The median observation time was 18.7 months.
  - Baseline characteristics for the G-Clb and R-Clb treatment arms were well balanced, including:
    - Median age: 74 vs. 73 years;
    - Median CIRS score: 8.0 (in each arm);
    - Median CrCl: 62.5 vs. 62.6 mL/min.
  - The OR rates for patients in the G-Clb and R-Clb arms were 78% and 65%, respectively (p < 0.0001). (Table 1)
  - The frequency of MRD-negative blood samples at the end of treatment was 37.7% in the G-Clb arm and 3.3% in the R-Clb arm (p < 0.0001). (Figure 1)
  - The median PFS for patients in the G-Clb and R-Clb arms were 26.7 and 15.2 months, respectively (HR = 0.39 [95% CI: 0.31–0.49], p < 0.0001). (Figure 2)
  - The PFS benefit experienced by patients receiving G-Clb over R-Clb was supported by all pre-planned subgroup analyses (including the cytogenetic subgroups 17p–, 11q, 12+, 13q–).
  - The OS benefit for patients in the G-Clb arm compared with those in the R-Clb arm was not significant (HR = 0.66 [95% CI: 0.41–1.06], p = 0.0849).
  - The incidences of adverse events of interest were similar between the G-Clb and R-Clb arms except for grade 3/4 infusion-related reactions, which occurred more frequently in the G-Clb treatment arm and only at first infusion. (Table 2)
• Updated results of the stage one analysis:
  - The median observation time was 23 months.

### Table 1. End-of-treatment response

<table>
<thead>
<tr>
<th>Responses</th>
<th>G-Clb (n = 333)</th>
<th>R-Clb (n = 329)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>78</td>
<td>65</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>Complete response†</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Partial response‡</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Not evaluable§</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

CR = complete response; GA101 = obinutuzumab; G-Clb = GA101, chlorambucil; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; PR = partial response; R-Clb = rituximab, chlorambucil

*Assessment not reached by data cut-off in one patient in R-Clb arm; as assessed by iwCLL criteria 3 months after end of treatment.
†Confirmed by imaging and bone marrow, and includes incomplete CR.
‡Includes nodular PR.
§Due to missing data or withdrawal from study treatment prior to response assessment.

### Figure 1. Minimal residual disease*

### Figure 2. Progression-free survival (head-to-head)*
Key conclusions

- Patients in the G-Clb arm had statistically significant and clinically meaningful prolongation of PFS, as well as higher rates of complete response and MRD negativity, compared with those in the R-Clb arm.
- Patients treated with G-Clb experienced more infusion-related reactions and neutropenia, without an increase in infections.
- Patients treated with G-Clb demonstrated a higher OS rate compared with patients receiving chlorambucil alone.
- The study demonstrated that G-Clb was superior to R-Clb and was highly active as first-line treatment of CLL patients with comorbidities, a typical CLL patient population.

Fludarabine, cyclophosphamide, and rituximab versus bendamustine and rituximab in previously untreated and physically fit patients with CLL: interim analysis of the CLL10 study

**Background**
Fludarabine, cyclophosphamide, and rituximab (FCR) is the current standard first-line treatment regimen for patients with advanced chronic lymphocytic leukemia (CLL). However, this treatment is associated with significant side effects.

The objective of this study was to test the noninferiority with respect to progression-free survival (PFS) and potentially better tolerability of bendamustine plus rituximab (BR) compared with FCR in first-line therapy of physically fit CLL patients without the del(17p) mutation.

**Study design**
- CLL10 was a phase III, noninferiority trial conducted by the German CLL Study Group.
- A total of 564 patients with previously untreated, active CLL without del(17p) and with good physical fitness (Cumulative Illness Rating Scale [CIRS] score ≤6 and creatinine clearance ≥70 mL/min) were enrolled between October 2008 and June 2011.
- Patients were randomly assigned to receive six courses of either:
  - FCR (n = 284; fludarabine: 25 mg/m² intravenously [iv], days 1–3; cyclophosphamide: 250 mg/m² iv, days 1–3; rituximab: 375 mg/m² iv, day 0 at first cycle and 500 mg/m² day 1 on all subsequent courses; every 28 days [q28d]); or
  - BR (n = 280; bendamustine: 90 mg/m² iv on days 1 and 2; rituximab: 375 mg/m² iv on day 0 at first cycle and 500 mg/m², day 1, all subsequent courses; q28d).
- The primary endpoint was noninferiority of BR vs. FCR for 24-month PFS at a hazard ratio (λBR/FCR) less than 1.388.

**Study design**

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

**Randomization**

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

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

**Noninferiority of BR in comparison to FCR for PFS:**
HR (λBR/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
Key findings

- The intent-to-treat population consisted of 561 patients.
  - 22% of the patients were classified as Binet A, 38% were classified as Binet B and 40% as Binet C.
- The median age was 62 years, and the median CIRS score was 2.
- Overall, baseline characteristics were well balanced between treatment arms except for the following:
  - There were significantly more patients with the unmutated immunoglobulin heavy chain variable region (IgHV) gene in the BR arm compared with the FCR arm (67.8% vs. 55.3%, \( p = 0.003 \)).
  - There were significantly more patients in the BR arm who were \( \geq 70 \) years old (21.5% vs. 13.8%, \( p = 0.020 \)).
- The median observation time was 27.5 months.
- Patients in the BR arm received a greater mean number of treatment cycles (5.41 vs. 5.27, \( p = 0.022 \)).
- The median PFS was not reached in the FCR arm and was 44.9 months in the BR arm (HR = 1.385; \( p = 0.041 \)). (Figure 1)
- PFS was assessed in patients <65 and \( \geq 65 \) years old. While there was a significant difference in patients <65 years old between both treatment arms (median PFS for BR was 36.5 months vs. not reached for FCR; \( p = 0.016 \)), the difference disappeared in elderly patients (median PFS [BR vs. FCR]: not reached vs. 45.6 months; \( p = 0.757 \)).
- The overall response rate was identical in both arms (97.8%, \( p = 1.0 \)). (Table 1)
- The complete response (CR) rate in the FCR arm was 47.4%, compared with 38.1% in the BR arm (\( p = 0.031 \)). (Table 1)
- A total of 74.1% of patients in the FCR arm and 62.9% in the BR arm achieved MRD levels below \( 1 \times 10^{-4} \) in the peripheral blood at final staging (\( p = 0.024 \)). (Figure 2)
- The two-year overall survival (OS) rate for the FCR arm was similar to that of the BR arm (94.2% vs. 95.8%, respectively; \( p = 0.593 \)).
- A multivariate analysis that included treatment arm, Binet stage, age, sex, comorbidity, serum TK, serum beta2-microglobulin (Beta2M), del(11q), and IgHV mutation status identified treatment arm, Beta2M, del(11q), and IgHV as independent prognostic factors for PFS. (Table 2)
- Patients treated with FCR had significantly more frequent severe, common toxicity criteria grade three to five adverse events during the observation period (90.8% vs. 78.5%; \( p < 0.001 \)). (Table 3)
- Patients in the FCR arm experienced a higher rate of severe hematotoxicity (90.0% vs. 66.9%, \( p < 0.001 \)).
- The higher rate of severe neutropenia in the FCR arm compared with the BR arm (81.7% vs. 56.8%, \( p < 0.001 \)) resulted in a significantly higher rate of severe infections in the FCR arm than the BR arm (39.0% vs. 25.4%, \( p = 0.001 \)), especially in the elderly (47.4% vs. 26.5%, \( p = 0.002 \)).
- Treatment-related mortality in the FCR arm was 3.9% (\( n = 11 \)) and in the BR arm was 2.1% (\( n = 6 \)).

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**Figure 1. Progression-free survival**

**Figure 2. Minimal residual disease**
The results of this planned interim analysis showed that the FCR regimen seemed more efficacious than BR in the first-line treatment of CLL patients who are fit; the rates of CR and PFS in the FCR arm were higher than those in the BR arm.

The advantages may be balanced by a higher rate of severe adverse events, particularly neutropenia and infections, which was associated with FCR treatment.

In light of these results, no firm recommendation of one regimen over the other can be given at the present time in first-line treatment of CLL patients with good physical fitness.

ABT-199 monotherapy shows anti-tumour activity including complete remissions in high-risk relapsed/refractory CLL and SLL

**Background**

Novel agents are needed for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who are relapsed/refractory (R/R) to standard therapies. The intrinsic apoptotic pathway is often dysregulated in relapsed CLL/SLL due to a deficiency in pro-apoptotic proteins such as tumour protein p53 (TP53) and overexpression of anti-apoptotic proteins such as Bcl-2. ABT-199 is a selective, potent, orally bioavailable, Bcl-2 inhibitor that can trigger apoptosis *in vitro*, even in del(17p) CLL cells, making it a promising agent for the treatment of patients with CLL/SLL.

The objective of this phase I study was to evaluate the safety and efficacy of ABT-199 in patients with CLL/SLL.

**Study design**

- The primary objectives of this phase I, dose-escalation study were to evaluate the safety and pharmacokinetics, determine a maximum tolerated dose, and a recommended phase II dose of ABT-199.
- The secondary objectives of the study were to assess efficacy and explore biomarkers for response.
- Eligibility criteria included:
  - Measurable disease requiring therapy;
  - Relapsed or refractory to standard fludarabine or alkylator-based regimen;
  - Eastern Cooperative Oncology Group performance status of 0 or 1;
  - Adequate bone marrow function: neutrophil count ≥1,000/µL; platelets ≥50,000/µL;
  - Adequate renal (creatinine clearance >50 mL/min) and hepatic function.
- Patients were excluded from the trial if they had:
  - A prior autologous or allogeneic stem cell transplant;
  - Active infection.
- Patients with CLL/SLL received a single dose of ABT-199 on week 1 day –3 or week 1 day –7, followed by continuous once-daily dosing from week 1 day 1 until disease progression or unacceptable toxicity.
- Modifications were made to the dose-escalation scheme as well as the tumour lysis syndrome (TLS) prophylaxis and monitoring schedule after TLS was observed in some patients.

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**Seymour JF, et al. ASH 2013:872**

ABT-199 monotherapy shows anti-tumour activity including complete remissions in high-risk relapsed/refractory CLL and SLL

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**Dose escalation scheme**

- **Day –7**: 50 mg*
- **Week 1**: Starting dose
- **Week 2**: Step-up dose
- **Week 3 and following**: DCD

---

**Lead-in to designated cohort dose — expanded safety cohort**

- **ABT-199**
  - **Week 1 Day 1**: 20 mg test
  - **Week 1 Days 2-7**: 50 mg
  - **Week 2**: 100 mg
  - **Week 3**: 200 mg
  - **Week 4**: 400 mg

*DCD = designated cohort dose

*Three patients (one each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose.

†Step-up doses range from 100 to 400 mg.
Key findings

- As of September 30, 2013, 67 patients were enrolled in cohorts at doses from 150 to 1,200 mg, with a median time on study of 10.9 months (range: 0.03–23.7).
- Baseline characteristics included the following:
  - 19 (37%) patients had del(17p);
  - 35 (52%) patients had fludarabine-refractory disease;
  - 13 of 30 (43%) patients had beta-2 microglobulin levels >3 mg/L;
  - 21 of 28 (75%) patients had IgHV unmutated status.
- The most common adverse events (AEs; all grades in ≥20% patients and grade 3/4 in ≥3 patients) and serious AEs are shown in tables 1 and 2, respectively.
- The $T_{\text{max}}$ and $T_{1/2}$ values after a single dose of ABT-199 with a low-fat meal were approximately six and 17 hours, respectively. (Figure 1)
  - ABT-199 exposure ($C_{\text{max}}$ and area under the curve) was approximately dose proportional between 150 mg and 800 mg dose levels at steady state.
- Preliminary efficacy data are summarized in the table 3.
- A total of 50/57 (88%) patients had at least a 50% reduction in the sum of the product of diameters of nodal masses, and the median time to 50% reduction was six weeks.
- Anti-tumour activity of ABT-199 was observed in all tumour compartments.
  - A total of 33/37 (89%) patients had at least a 50% reduction in bone marrow infiltrate at the week 24 assessment.
  - The median time to a 50% reduction in lymphocyte count was 15 days (range: 1–170).
- Nine of the 13 patients who had a complete response (CR) or a complete response with incomplete marrow recovery (CRi) were assessed for minimal residual disease (MRD):
  - MRD was not detectable in five patients, per bone marrow;
  - Low MRD levels were observed in four patients (0.7%, 0.75%, 1.5%, and quantification pending in one patient);
  - Of the patients who had no detectable MRD levels, one was refractory to fludarabine and had del(17p), and three were refractory to fludarabine.

### Table 1. Adverse events

<table>
<thead>
<tr>
<th>All grades</th>
<th>≥20% of patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>29 (43)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>27 (40)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>25 (37)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>22 (33)</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>22 (33)</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>15 (22)</td>
</tr>
<tr>
<td><strong>Grades 3/4</strong></td>
<td>≥3 patients n (%)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>24 (36)</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>6 (9)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>6 (9)</td>
</tr>
<tr>
<td><strong>Tumour lysis syndrome</strong></td>
<td>6 (9)</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td>5 (7)</td>
</tr>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>5 (7)</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

*TLS = tumour lysis syndrome

*TLS includes three events from cohort 1: two clinical events and one laboratory TLS occurred in cohorts 2, 4, and 8.

### Table 2. Serious adverse events possibly/probably related to ABT-199*

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Febrile neutropenia (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Tumour lysis syndrome (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Sudden death (grade 5)</strong></td>
</tr>
<tr>
<td><strong>Viral URTI (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Clostridium difficile infection (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Escherichia sepsis (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Influenza (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Pneumonia (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Sepsis (grade 3)</strong></td>
</tr>
<tr>
<td><strong>URTI (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Fluid overload (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Renal failure acute (grade 3)</strong></td>
</tr>
<tr>
<td><strong>Pulmonary embolism (grade 4)</strong></td>
</tr>
</tbody>
</table>

*URTI = upper respiratory tract infection; SAE = serious adverse event

*More than one SAE may have occurred in the same person.

†In the setting of tumour lysis syndrome.
Figure 1. Preliminary pharmacokinetics of ABT-199*

*All subjects were dosed under low-fat conditions.
†Combined data from week 1 day –3 (1st cohort) and week 1 day –7 (2nd cohort and beyond).

Table 3. Responses of patients treated with ABT-199

<table>
<thead>
<tr>
<th>Responses</th>
<th>All n = 56, n (%)</th>
<th>Del(17p)† n = 17, n (%)</th>
<th>Fludarabine refractory‡ n = 27, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>47 (84)</td>
<td>14 (82)</td>
<td>24 (89)</td>
</tr>
<tr>
<td>Complete response</td>
<td>13 (23)</td>
<td>2 (12)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Partial response*</td>
<td>34 (61)</td>
<td>12 (71)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1 (2)</td>
<td>1 (6)</td>
<td>—</td>
</tr>
<tr>
<td>Discontinued prior to first (week 6) assessment</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*Three patients had confirmatory computer tomography imaging assessments at less than an eight-week interval (5, 6, and 7 weeks).
†Ten patients were both del(17 p) and fludarabine refractory.
Key conclusions

■ ABT-199 monotherapy activity was observed in patients with R/R CLL, including those with del(17p) and fludarabine-refractory disease.
  • Responses were observed in 84% of R/R patients — 23% of these patients had a CR/CRi;
  • Patients with high-risk CLL showed similar efficacy with an overall response rate of 80%.
■ No detectable MRD was observed in several patients who achieved CR, including those with high-risk disease.
■ The risk of TLS was addressed using a titrated dosing scheme combined with aggressive prophylaxis, monitoring, and management.
  • There were no additional TLS events (clinical or laboratory) reported with the new dosing scheme as of September 30, 2013.
■ A phase II monotherapy study in patients with relapsed CLL and del(17p) and combination studies with rituximab or obinutuzumab in patients with relapsed CLL have begun enrolling patients.


Knauf W, et al. ASH 2013:4181

Response to first-line treatment with BR or FCR in patients with CLL: first outcome data from the TLN registry

Background

The standard of care for medically fit patients with untreated chronic lymphocytic leukemia (CLL) is currently fludarabine, cyclophosphamide, and rituximab (FCR). However, due to significant hematological toxicity associated with FCR, other potentially less toxic regimens are currently under investigation. Results of the phase III CLL10 study comparing FCR to bendamustine plus rituximab (BR) are eagerly awaited.

Since clinical trials are restricted to highly selected patients, the objective of this study was to investigate the effectiveness of BR and FCR in unselected patients with CLL treated by German office-based hematologists in routine clinical practice.¹

Study design

• The TLN registry (Tumor Registry of Lymphatic Neoplasia) is a longitudinal, multicentre, clinical registry on lymphoid neoplasms (NCT00889798).
• Data are collected prospectively on the treatment of patients with lymphoid B-cell neoplasms as administered by a network of German office-based hematologists.
• Patients were followed up for five years.
• A broad set of data regarding patient and tumour characteristics, comorbidities, all systemic treatments and response rates, progression-free survival (PFS), and overall survival (OS) is recorded.
  ◦ The reliability of data is ensured through automated plausibility and completeness checks, with subsequently generated queries by the electronic data capture system.
  ◦ In addition, data managers regularly check for plausibility and issue queries.
• A total of 3,383 patients from 115 sites have been recruited since May 2009.

Key findings

• Patients with CLL (N = 620) were recruited at the onset of their first-line therapy, of which 56% of patients (n = 348) received first-line BR and 22% of patients (n = 137) received FCR. These 485 patients treated with either BR or FCR were included in this analysis.
Patients included in the analysis had the following characteristics:

- A median age of 70 years (range: 21–92 years; mean: 68 years);
- 67% were male;
- 42% had Binet stage C;
- 29% presented with B symptoms;
- 13% presented with bulky disease;
- 66% presented with at least one comorbidity.

Clinical and tumour characteristics were different between patients receiving BR or FCR.

- Patients treated with BR were older (mean: 70 vs. 63 years; \( p < 0.001 \)) and presented more often with Binet stage C (44% vs. 35%) or comorbidities (68% vs. 62%).

BR was the most frequently used first-line regimen. (Figure 1)

- The objective response rate was comparable between the two regimens: 92% of patients receiving BR and 97% receiving FCR responded to first-line therapy (\( p = 0.164 \)).

- The clinical unconfirmed complete remission rate was 45% after BR treatment and 40% after FCR treatment.

- Progressive disease was observed in 2% of patients in each of the BR and FCR arms.

- The proportion of patients with stable disease in the BR and FCR arms was 6% and 2%, respectively.

- Each regimen was administered over a median of six cycles.

- In univariate analyses, none of the parameters tested (type of first-line regimen, age, sex, B symptoms, bulky disease, tumour stage, comorbidities) had a significant impact on the response rate.

- In a multivariate logistic regression model adjusted for the type of regimen (BR vs. FCR) and age, neither factor had a significant impact on the response rate.

- At this point, the small number of nonresponders (\( n = 24 \)) precluded calculation of models adjusted for more than two parameters.

- After a median observation time of 22 months (maximum 52 months), 89% of patients receiving BR survived, 84% were progression-free, and 10% had received second-line treatment. In patients receiving FCR, 92% survived, 89% were progression-free, and 8% had received second-line therapy. (Figures 2, 4)

- Overall, 5% of patients were lost to follow-up.

- Given the fact that age is a prognostic factor, PFS and OS were also analysed in age-adjusted groups receiving BR or FCR. (Figures 3, 5)

- 93% of patients who received BR (mean age = 63 years, \( n = 169 \)) and 92% of patients who received FCR (mean age = 63 years, \( n = 137 \)) survived.
Figure 4. Overall survival since start of first-line treatment with BR or FCR

Figure 5. Overall survival since start of first-line treatment with BR (age-adjusted) or FCR

Key conclusions

- This study showed that previously untreated patients with CLL receiving BR or FCR in routine practice differ, with BR preferentially administered to older patients with comorbidities.
  - Nevertheless, response rates to first-line treatment with BR or FCR are comparable, even after statistical adjustment for age at the start of therapy.
  - BR is an effective and well tolerated treatment for elderly and medically less fit patients with CLL.
- If the CLL10 trial eventually confirms these results in the future, BR may present an alternative first-line treatment to medically fit patients with CLL.


Furman R, et al. ASH 2013:LBA-6

A phase III study evaluating the efficacy and safety of idelalisib and rituximab for previously treated patients with CLL

Background

Idelalisib is a first-in-class, selective, oral inhibitor of phosphatidylinositol 3-kinase delta that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues. Phase I trials demonstrated that idelalisib is highly active as a single agent or in combination with rituximab in heavily pretreated patients with chronic lymphocytic leukemia (CLL).

The objective of this study (Study 116) was to evaluate the efficacy and safety of idelalisib plus rituximab (Idela-R) versus placebo plus rituximab (Pbo-R) in previously treated patients with CLL.²

Study design

- This was a phase III, randomized, double-blind, placebo-controlled study.
- Eligibility criteria included patients with relapsed CLL (progression <24 months since the completion of last therapy) in need of treatment per the International Workshop on CLL (iwCLL) guidelines, having measurable lymphadenopathy and Karnofsky score ≥40.
  - Patients who were unfit to receive cytotoxic therapy were defined as those with comorbidities (defined as a Cumulative Illness Rating Scale score >6), renal dysfunction (creatinine clearance <60, ≥30 mL/min), or cytopenias due to poor marrow reserve.
• All patients received rituximab at 375 mg/m^2 for the first dose, and then 500 mg/m^2 every (q) two weeks x 4, followed by q4 weeks x 3 (8 doses total) plus:
  ◦ Idelalisib: 150 mg twice daily (bid), continuously; or
  ◦ Placebo: bid continuously.

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

• Secondary endpoints were objective response rate (ORR), lymph node response (LNR; defined as ≥50% reduction in nodal SPD), and overall survival (OS).

• The response rate and progression rate in both arms were assessed by an independent review committee using standard criteria.

• Interim analyses were planned at 50% and 75% of events.

• Results were reviewed by an external Data Monitoring Committee (DMC).

**Key findings**

• Patient characteristics were balanced between the idelalisib plus rituximab (Idela-R; N = 110) vs. placebo plus rituximab (Pbo-R; N = 110) arms:
  ◦ Median age (range), years: 71 (48–90) vs. 71 (47–92);
  ◦ Rai stage III-IV, %: 64 vs. 66;
  ◦ Median number of prior therapies (range): 3 (1–12) vs. 3 (1–9);
  ◦ CLL genetics, %:
    – Unmutated IgHV: 83 vs. 85;
    – Del(17p)/TP53 mutation: 42 vs. 46.

• PFS in the Idela-R arm was superior to that in the Pbo-R arm (HR = 0.15 [95% CI: 0.08–0.28]; p <0.0001). (Figure 1)
  – The median PFS was not reached in the Idela-R arm and was 5.5 months in the Pbo-R arm.
  – PFS strongly favoured Idela-R in all patient subgroups, including those with del(17p)/TP53 or unmutated IgHV.

**Figure 1. Primary endpoint: progression-free survival**

**Figure 2. Overall survival**
• Compared with those in the control arm, patients treated with Idela-R and with ≥1 post-baseline assessment had a superior ORR (81% vs. 13% [n = 88 per arm]; odds ratio [OR] = 29.92; p < 0.0001) and a higher LNR rate (93% vs. 4% [n = 85 vs. 84]; OR = 264.46; p < 0.0001).

• Relative to the control group, patients treated with Idela-R had a significant improvement in OS (HR = 0.28 [95% CI: 0.09–0.86]; p = 0.018). (Figure 2)

• A summary of the incidence of all types of adverse events (AEs) is shown in table 1.

• Nine patients treated with Idela-R and 11 patients treated with Pbo-R were discontinued from their treatment due to AEs. (Table 1)

• AEs occurring in ≥10% of patients (any grade [Gr]/Gr ≥3 [%]) in the Idela-R vs. Pbo-R treatment arms included: (Table 2)
  - Pyrexia: 29/3 vs. 16/1;
  - Fatigue: 24/3 vs. 27/2;
  - Nausea: 24/0 vs. 22/0;
  - Chills: 22/2 vs. 16/0;
  - Infusion-related reactions: 16/0 vs. 28/4; and
  - Cough: 15/0 vs. 25/2.

• Other select AEs included diarrhea (19/4 vs. 14/0) and rash (10/2 vs. 6/0).

• Select laboratory abnormalities (any Gr/Gr 3-4 [%]) in the Idela-R vs. Pbo-R treatment arms included: (Table 2)
  - Alanine aminotransferase/aspartate aminotransferase elevation: 35/5 vs. 19/1;
  - Anemia: 25/5 vs. 30/14;
  - Neutropenia: 55/34 vs. 49/22; and
  - Thrombocytopenia: 17/10 vs. 26/16.

• The most common serious adverse events (SAEs) in patients treated with Idela-R were pneumonia (6%), pyrexia (6%), and febrile neutropenia (5%). (Table 3)

• The most common SAEs in patients treated with Pbo-R were pneumonia (8%), febrile neutropenia (6%), and dyspnea (4%). (Table 3)

• The DMC recommended stopping the study early based on an efficacy and safety review.
Table 3. Serious adverse events

<table>
<thead>
<tr>
<th>SAE, n (%)</th>
<th>Idelalisib + R (N = 110)</th>
<th>Placebo + R (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any SAE</td>
<td>44 (40)</td>
<td>37 (35)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7 (6)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (5)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Lung infection</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

R = rituximab; SAE = serious adverse event

Key conclusions

■ In heavily pretreated patients with relapsed CLL, including those not suitable for chemotherapy, Idela-R demonstrated statistically significant improvements in PFS, ORR, LNR, and OS compared with Pbo-R.

■ Idela-R demonstrated an acceptable safety profile.


Coutre S, et al. ASH 2013:1632

Clinical activity of idelalisib in CLL: effect of del(17p)/TP53 mutation, del(11q), IgHV mutation, and NOTCH1 mutation

Background

Phosphatidylinositol 3-kinase delta (PI3Kδ) is critical for the activation, proliferation, and survival of B cells and plays a role in homing and retention of B cells in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a potent and selective orally administered inhibitor of PI3Kδ with demonstrated activity in previously untreated patients in combination with rituximab and in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL), either as a single agent or in combination.

The objective of this study was to evaluate the effect of genetic risk factors (del(17p), del(11q), TP53 mutation, NOTCH1 mutation, and IgHV mutation status) on overall response rate (ORR) and duration of response (DOR) in patients with CLL who were treated with idelalisib-containing regimens.1

Study design

- Long-term results from three idelalisib studies in two groups of patients with CLL were used in this analysis:
  - Patients with R/R CLL (N = 168):
    - Study 101-02 (N = 54): phase I idelalisib monotherapy, dose escalation (50–350 mg twice daily [bid], continuously) (Brown et al. ASCO 2013);
    - Study 101-07 (N = 114): phase Ib drug combinations with idelalisib (Barrientos et al. ASCO 2013; Barrientos et al. EHA 2013; Coutre et al. EHA 2013; De Vos et al. ASH 2013). (Table 1)
  - Treatment-naïve patients with CLL/small lymphocytic lymphoma (SLL):
    - Study 101-08 (N = 64): phase II, idelalisib (150 mg bid) in combination with rituximab (375 mg/m², weekly x 8) (O’Brien et al. ASCO 2013).
  - All subjects completing the 48-week primary studies could continue idelalisib treatment indefinitely on an extension study.
### Table 1. Study 101-07 (N = 114)

<table>
<thead>
<tr>
<th>N</th>
<th>Idelalisib dosage</th>
<th>Companion therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>100 or 150 mg bid</td>
<td>Rituximab 375 mg/m² weekly x 8</td>
</tr>
<tr>
<td>18</td>
<td>100 or 150 mg bid</td>
<td>Bendamustine 70 or 90 mg/m² D1 + D2, C1–6</td>
</tr>
<tr>
<td>15</td>
<td>150 mg bid</td>
<td>Bendamustine 70 mg/m² D1 + D2, C1–6; Rituximab 375 mg/m² C1–6</td>
</tr>
<tr>
<td>21</td>
<td>150 mg bid</td>
<td>Ofatumumab 300 mg D1, then 1,000 mg weekly x 7, then 1,000 mg q4w x 4</td>
</tr>
<tr>
<td>12</td>
<td>150 mg bid</td>
<td>Fludarabine 40 mg/m² D1–5, C1–6</td>
</tr>
<tr>
<td>15</td>
<td>150 mg bid</td>
<td>Chlorambucil 10 mg/m² D1–7 q4w x 3–12 cycles</td>
</tr>
<tr>
<td>14</td>
<td>150 mg bid</td>
<td>Chlorambucil as above; Rituximab 375 mg/m² C1–6</td>
</tr>
</tbody>
</table>

**bid = twice daily; C = cycle; D = day; q4w = every four weeks**

### Table 2. Best response and DOR in previously treated subjects: studies 101-02 and 101-07

<table>
<thead>
<tr>
<th></th>
<th>Del(17p)</th>
<th>Del(17p) or TPS3 mutation</th>
<th>Del(11q)</th>
<th>IgHV unmutated</th>
<th>NOTCH1 mutation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes n = 31</td>
<td>No n = 129</td>
<td>Yes n = 46</td>
<td>No n = 114</td>
<td>Yes n = 33</td>
<td>No n = 127</td>
</tr>
<tr>
<td><strong>CR, %</strong></td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>PR, %</strong></td>
<td>58</td>
<td>77</td>
<td>61</td>
<td>78</td>
<td>82</td>
<td>71</td>
</tr>
<tr>
<td><strong>SD, %</strong></td>
<td>26</td>
<td>12</td>
<td>22</td>
<td>11</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td><strong>PD, %</strong></td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Not evaluable, %</strong></td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>ORR (PR + CR), %</strong></td>
<td>65</td>
<td>82</td>
<td>67</td>
<td>83</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td><strong>95% CI, %</strong></td>
<td>45–81</td>
<td>75–88</td>
<td>52–81</td>
<td>75–90</td>
<td>68–95</td>
<td>69–84</td>
</tr>
<tr>
<td><strong>Median DOR, months</strong></td>
<td>17</td>
<td>27</td>
<td>19</td>
<td>32</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td><strong>95% CI, %</strong></td>
<td>10–*</td>
<td>16–40</td>
<td>10–27</td>
<td>16–41</td>
<td>10–*</td>
<td>16–33</td>
</tr>
</tbody>
</table>

**CI = confidence interval; CR = complete response; DOR = duration of response; NR = not reached; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease**

*Upper bound not defined.

### Table 3. Best response in previously untreated subjects: study 101-08*

<table>
<thead>
<tr>
<th></th>
<th>Del(17p)</th>
<th>Del(17p) or TPS3 mutation</th>
<th>Del(11q)</th>
<th>IgHV unmutated</th>
<th>NOTCH1 mutation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes n = 6</td>
<td>No n = 55</td>
<td>Yes n = 9</td>
<td>No n = 52</td>
<td>Yes n = 10</td>
<td>No n = 51</td>
</tr>
<tr>
<td><strong>CR, %</strong></td>
<td>33</td>
<td>15</td>
<td>33</td>
<td>14</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td><strong>PR, %</strong></td>
<td>67</td>
<td>82</td>
<td>67</td>
<td>83</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td><strong>SD, %</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>PD, %</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Not evaluable, %</strong></td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>ORR (PR + CR), %</strong></td>
<td>100</td>
<td>96</td>
<td>100</td>
<td>96</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td><strong>95% CI, %</strong></td>
<td>54–100</td>
<td>88–100</td>
<td>66–100</td>
<td>87–100</td>
<td>69–100</td>
<td>87–100</td>
</tr>
</tbody>
</table>

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

*Median DOR not reached in any subgroup (enrollment October 2010 – April 2012).
Key findings

- Response rates in the 101-02 and 101-07 studies are shown in table 2.
  
  - Idelalisib-based treatments achieved an ORR of 65% (95% CI: 45–81) and a median DOR of 17 months (95% CI: 10–upper bound undefined) in heavily pretreated patients with R/R CLL who had del(17p13).

- Response rates in the 101-08 study are shown in table 3.
  
  - The ORR in evaluable, treatment-naïve patients with CLL treated with idelalisib plus rituximab therapy, including six with del(17p13), was 100% (95% CI: 54–100).
  
  - Median DOR was not reached in any of the patient subgroups in Study 101–08.

Key conclusions

- These data demonstrate robust activity of idelalisib-based therapy in both R/R and treatment-naïve CLL patients, including those sub-populations with adverse prognostic factors.

- Although these results are from small phase I and II studies utilizing various idelalisib-based regimens, this analysis identified idelalisib as a potentially important novel therapy for all patients with CLL, regardless of risk factors, thus fulfilling a high unmet medical need.


Furman R, et al. ASH 2013:4180

A phase I study of idelalisib in combination with rituximab or ofatumumab in patients with relapsed or refractory CLL

Background

Phosphatidylinositol 3-kinase delta (PI3Kδ) signaling is critical for the proliferation and survival as well as for homing and tissue retention of malignant B cells. Idelalisib is a first-in-class, targeted, highly selective, oral inhibitor of PI3Kδ that has shown considerable activity as monotherapy in heavily pretreated patients with chronic lymphocytic leukemia (CLL).

The objective of this phase I study was to evaluate the safety and efficacy of idelalisib in combination with an anti-CD20 antibody, ofatumumab or rituximab, in patients with relapsed/refractory (R/R) CLL.1

Study design

- This phase Ib trial had a duration of 48 weeks.
- Patients ≥18 years of age with R/R CLL requiring treatment (according to International Workshop on CLL 2008 criteria) were eligible.
- The primary endpoint of the study was safety.
- The secondary endpoints of the study were: duration of response (DOR), overall response rate (ORR), and progression free survival (PFS).
- Drug treatments:
  
  - Idelalisib plus rituximab (Idela-R) arm: idelalisib was given continuously at 100 or 150 mg twice daily (bid) in combination with rituximab (375 mg/m² weekly x 8)
  
  - Idelalisib plus ofatumumab (Idela-O) arm: idelalisib was given continuously at 150 mg bid with ofatumumab (300 mg week 1, followed by 1,000 mg weekly x 8, then 1,000 mg x 3 months).

- After 48 weeks on the study, patients on treatment were eligible to continue idelalisib monotherapy in an extension study until the end of benefit.

Key findings

Baseline characteristics and patient disposition

- A total of 40 patients (Idela-R, n = 19; Idela-O, n = 21) were enrolled in the study with the following baseline characteristics:
  
  - Sex: 12 female/28 male;
  
  - Median age (range), years: 66 (43–87);
  
  - Number of prior therapies, median (range): 2 (1–9).
  
  - The types of prior therapies included alkylating agents (78%), purine analogs (78%), and rituximab (98%).
Patients had the following disease characteristics, n (%):
- Rai Stage III/IV: 20 (50);
- Bulky lymphadenopathy: 23 (58);
- Refractory disease: 15 (38);
- Unmutated IgHV: 30 (75);
- Del(17p) and/or TP53 mutations: 11 (28);
- Del(11q): 5 (13);
- NOTCH1 mutation: 5 (13).

The median (range) treatment duration on the primary and extension studies was 18 (0–34) months.
- A total of 23 (58%) patients had completed the primary study and enrolled into the extension study.
- The most common reasons for discontinuation from the primary or extension study were disease progression (n = 11) and adverse events (AEs) (n = 11).

There were four deaths reported on the study.

Safety
- Selected treatment-emergent AEs (any grade [Gr]/Gr ≥3 [%], regardless of causality) included: (Table 1)
  - Diarrhea: 53/10;
  - Cough: 40/3;
  - Pyrexia: 40/3;
  - Dyspnea: 30/3;
  - Fatigue: 25/0;
  - Nausea: 25/0;
  - Rash: 20/0;
  - Pneumonia: 20/18; and
  - Colitis: 10/10.

### Table 1. Adverse events in ≥10% of patients

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Any grade</th>
<th>Grade ≥3</th>
<th>AE (cont’d), n (%)</th>
<th>Any grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>21 (53)</td>
<td>4 (10)</td>
<td>Abdominal pain</td>
<td>6 (15)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (40)</td>
<td>1 (3)</td>
<td>Back pain</td>
<td>6 (15)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (40)</td>
<td>1 (3)</td>
<td>Pain in extremity</td>
<td>6 (15)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (30)</td>
<td>1 (3)</td>
<td>Sinusitis</td>
<td>6 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (25)</td>
<td>0</td>
<td>Dizziness</td>
<td>5 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (25)</td>
<td>0</td>
<td>Productive cough</td>
<td>5 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (20)</td>
<td>7 (18)</td>
<td>UTI</td>
<td>5 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (20)</td>
<td>0</td>
<td>Vomiting</td>
<td>5 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (18)</td>
<td>1 (3)</td>
<td>Colitis</td>
<td>4 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Chills</td>
<td>7 (18)</td>
<td>0</td>
<td>Febrile neutropenia</td>
<td>4 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (18)</td>
<td>0</td>
<td>Infusion-related reaction</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (18)</td>
<td>0</td>
<td>Edema peripheral</td>
<td>4 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (18)</td>
<td>0</td>
<td>Oropharyngeal pain</td>
<td>4 (10)</td>
<td>0</td>
</tr>
<tr>
<td>URI</td>
<td>7 (18)</td>
<td>1 (3)</td>
<td>Upper airway cough syndrome</td>
<td>4 (10)</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event; URI = upper respiratory tract infection; UTI = urinary tract infection
Idelalisib in combination with therapeutic anti-CD20 antibodies such as rituximab or ofatumumab represent non-cytotoxic regimens with acceptable safety profiles and high activity resulting in durable tumour control in patients with heavily pretreated relapsed/refractory CLL.

Phase III trials evaluating the efficacy of idelalisib in combination with rituximab2 (NCT01539512) or ofatumumab are ongoing (NCT01659021).

Barrientos JC, et al. ASH 2013:4176

Idelalisib with bendamustine/rituximab or chlorambucil/rituximab in patients with relapsed/refractory CLL demonstrates efficacy and tolerability

**Background**

Phosphatidylinositol 3-kinase delta (PI3Kδ) signaling is critical for proliferation, survival, homing and tissue retention of malignant B cells. Idelalisib is a selective, oral inhibitor of PI3Kδ that has been previously shown to be safe and tolerable and has demonstrated considerable activity as monotherapy or in combination with other agents in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).

The objective of this study was to provide an update on the safety and efficacy of a phase I study of idelalisib with two chemo-immunotherapy regimens: bendamustine plus rituximab (BR) and chlorambucil plus rituximab (Clb-R).

**Study design**

- This phase I study evaluated the use of idelalisib in combination with chemoimmunotherapy: BR or Clb-R.
- The enrollment period for patients treated with idelalisib plus BR was from March to August 2011, and for patients treated with idelalisib plus Clb-R, it was March to August 2012.
- Key inclusion criteria were:
  - Patients with R/R CLL requiring treatment (according to International Workshop on CLL 2008 criteria);
  - Age ≥18 years;
  - World Health Organization propensity score ≤2.
- Key exclusion criteria were:
  - History of allogeneic hematopoietic stem cell transplantation;
  - Known central nervous system malignancy;
  - Bilirubin, aspartate aminotransferase/alanine aminotransferase ≥2.0 mg/dL x upper limit of normal;
  - Active hepatitis B or C.
- The primary endpoint was safety.
- The secondary endpoints were objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS).
- After completion of the study period, patients who continued to derive benefit from treatment were included in the extension study and given idelalisib monotherapy.

---

**Study design**

- Bendamustine 70 or 90 mg/m² iv, days 1 and 2, cycles 1–6
- Rituximab 375 mg/m², day 1, cycles 1–6
- Idelalisib 150 mg bid x 48 weeks

- Chlorambucil 10 mg/m², days 1–7 x 1–12 cycles
- Rituximab 375 mg/m², day 1, cycles 1–6
- Idelalisib 150 mg bid x 48 weeks

*bid = twice daily; CT = computed tomography; iv = intravenous; PD = progressive disease

*CT imaging at baseline and beginning of every third cycle.
**Key findings**

- Fifteen patients were treated with idelalisib plus BR and 14 were treated with idelalisib plus Clb-R.
- Baseline characteristics were well balanced with the following exceptions:
  - The median age (age [range]) of patients in the idelalisib plus Clb-R arm was higher than patients in the idelalisib plus BR arm (68 [41–82] vs. 63 [45–73]).
  - There was a greater percentage of patients with refractory disease in the idelalisib plus BR arm than in the idelalisib plus Clb-R arm (60% vs. 29%).

| Table 1. Treatment-emergent adverse events and select treatment-emergent lab abnormalities |
|-------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Treatment-emergent AEs (>20%)                    |                                |                                  |                                |
| Number of subjects with any TEAE                 | 15 (100)                       | 14 (100)                        | 29 (100)                       |
| Pyrexia                                          | 7 (47)                         | 0                               | 15 (52)                        |
| Diarrhea                                         | 5 (33)                         | 2 (13)                          | 7 (24)                         |
| Constipation                                     | 4 (27)                         | 0                               | 8 (28)                         |
| Fatigue                                          | 3 (20)                         | 0                               | 9 (31)                         |
| Nausea                                           | 4 (27)                         | 0                               | 9 (31)                         |
| Cough                                            | 4 (27)                         | 0                               | 8 (28)                         |
| Rash                                             | 3 (20)                         | 2 (13)                          | 5 (36)                         |
| Insomnia                                         | 4 (27)                         | 0                               | 3 (21)                         |
| Pneumonia                                        | 2 (13)                         | 1 (7)                           | 2 (14)                         |
| Neutropenia                                      | 13 (87)                        | 9 (60)                          | 22 (76)                        |
| Thrombocytopenia                                 | 4 (27)                         | 1 (7.0)                         | 10 (34)                        |
| Anemia                                           | 5 (33)                         | 2 (13)                          | 11 (38)                        |
| ALT/AST elevation                                | 4 (14)                         | 0                               | 11 (38)                        |

- Commonly reported treatment-emergent adverse events (AEs; ≥20% of all subjects) and lab abnormalities of interest, and serious AEs (in ≥2 subjects) are shown in Tables 1 and 2, respectively.

- The ORR for the two cohorts was 90.0% (95% CI: 72.6–97.8%). (Table 3)
  - Median time to response in both cohorts was 1.9 months.
- Patients treated with idelalisib plus BR had an ORR of 87% (95% CI: 59.5–98.3%; complete response [CR] = 13%, partial response [PR] = 73%).
- For patients treated with idelalisib plus R-Clb, the ORR was 93% (95% CI: 66.1–99.8%; CR = 14.0%, PR= 79.0%).
- The median DOR for combined cohorts was 21.2 months (95% CI: 11.3– not reached).
- The median PFS for combined cohorts was 23.0 months (95% CI: 13.1–not reached). (Figure 1)
Key conclusions

- The study demonstrated that the combinations of idelalisib plus BR or idelalisib plus R-Clb were safe and tolerable.
- The ability to induce responses in this particularly difficult-to-treat patient population with refractory disease, the non-overlapping toxicity with these agents, and the ease of administration make these regimens an option in this patient population.
- The results support further studies with these chemoimmunotherapy regimens in patients with CLL.
- A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with BR for previously treated CLL patients (NCT01569295) is currently recruiting subjects.


De Vos S, et al. ASH 2013:2878

Idelalisib in combination with bendamustine, fludarabine, or chlorambucil in patients with relapsed or refractory CLL

Background

Phosphatidylinositol 3-kinase delta (PI3Kδ) is critical for activation, proliferation, and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a potent and selective orally administered inhibitor of PI3Kδ with demonstrated activity in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) as a single agent and in combination with cytotoxic chemotherapies or with anti-CD20 monoclonal antibodies.

The objective of this study was to summarize the experience of idelalisib with cytotoxic chemotherapies in phase I studies.1

Study design

- This phase Ib study (101-07), with a duration of 48 weeks, evaluated multiple idelalisib combinations.
- Eligibility criteria were:
  - Age ≥18 years;
  - Patients with relapsed/refractory CLL requiring treatment (International Workshop on CLL 2008 criteria);
Absolute neutrophil count ≥1,000/μL and platelets ≥75,000/μL, unless due to bone marrow infiltration with CLL;
Aspartate aminotransferase and alanine aminotransferase <2 x upper limit of normal;
Total bilirubin <2 mg/dL;
Creatinine <2 mg/dL.

• Patients were enrolled from April 2010 through August 2012.
• The study included three cohorts: idelalisib plus bendamustine, fludarabine, or chlorambucil.
• Patients were treated with idelalisib (100 or 150 mg BID continuously) in combination with:
  - Bendamustine (B): 70 or 90 mg/m² days 1, 2 days x cycle 1–6;
  - Fludarabine (F): 40 mg/m² orally days 1–5 x cycle 1–6;
  - Chlorambucil (Clb): 10 mg/m² days 1–7 x 3–12 cycles.
• The study was initiated sequentially, with the bendamustine and fludarabine arms overlapping.
• The primary endpoint of the study was safety.
• The secondary endpoints were overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS).

• After completion of the study period, patients who continued to derive benefit from treatment were included in the extension study and given idelalisib monotherapy.

**Key findings**
• A total of 45 patients were enrolled in three treatment arms:
  - Idelalisib plus B: n = 18;
  - Idelalisib plus F: n = 12;
  - Idelalisib plus Clb: n = 15.
• Patients had the following characteristics:
  - Median age: 65 years;
  - Rai stage III/IV: 76%;
  - Median number of prior therapies: 3 (range: 1–9);
• The median exposure times to idelalisib for the bendamustine, fludarabine, and chlorambucil cohorts were 10.6 months (range: 1–38), 13.1 months (range: 2–28), and 13.3 months (range: 1–18), respectively.
• At the time of analysis, 16 (36%) subjects remained on treatment.
  - Of the 29 patients who discontinued treatment, seven were due to adverse events (AEs).
• The most common treatment-emergent AEs (>15%) and treatment-emergent lab abnormalities, and serious AEs (in ≥2 subjects) are shown in tables 1 and 2, respectively.
Table 1. Treatment-emergent adverse events and lab abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + B N = 18, (%)</th>
<th>Idelalisib + F N = 12, (%)</th>
<th>Idelalisib + Clb N = 15, (%)</th>
<th>All subjects N = 45, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>39 (21)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>61 (34)</td>
<td>11 (6)</td>
<td>42 (29)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Cough</td>
<td>28 (16)</td>
<td>0 (0)</td>
<td>50 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44 (26)</td>
<td>6 (4)</td>
<td>42 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (19)</td>
<td>0 (0)</td>
<td>33 (22)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>33 (19)</td>
<td>33 (22)</td>
<td>8 (5)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (6)</td>
<td>0 (0)</td>
<td>42 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (13)</td>
<td>0 (0)</td>
<td>17 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (10)</td>
<td>11 (6)</td>
<td>17 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>22 (13)</td>
<td>22 (13)</td>
<td>8 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>44 (26)</td>
<td>22 (13)</td>
<td>8 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>17 (10)</td>
<td>0 (0)</td>
<td>17 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (4)</td>
<td>0 (0)</td>
<td>25 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>11 (6)</td>
<td>0 (0)</td>
<td>17 (11)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Treatment-emergent lab abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + B N = 18, (%)</th>
<th>Idelalisib + F N = 12, (%)</th>
<th>Idelalisib + Clb N = 15, (%)</th>
<th>All subjects N = 45, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>78 (47)</td>
<td>67 (44)</td>
<td>75 (50)</td>
<td>58 (40)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>67 (42)</td>
<td>22 (14)</td>
<td>33 (22)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Anemia</td>
<td>67 (42)</td>
<td>28 (18)</td>
<td>33 (22)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>ALT/AST elevation</td>
<td>44 (26)</td>
<td>22 (13)</td>
<td>33 (22)</td>
<td>25 (17)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = bendamustine; Clb = chlorambucil; F = fludarabine

Table 2. Serious adverse events in ≥2 subjects

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + B N = 18, n (%)</th>
<th>Idelalisib + F N = 12, n (%)</th>
<th>Idelalisib + Clb N = 15, n (%)</th>
<th>All subjects N = 45, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>16 (89)</td>
<td>9 (75)</td>
<td>9 (60)</td>
<td>34 (76)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (17)</td>
<td>1 (8)</td>
<td>4 (27)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (22)</td>
<td>1 (8)</td>
<td>1 (7)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (22)</td>
<td>1 (8)</td>
<td>1 (7)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>2 (11)</td>
<td>1 (8)</td>
<td>2 (13)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>2 (11)</td>
<td>2 (17)</td>
<td>0 (0)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (11)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (6)</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (13)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>HHV 6 infection</td>
<td>0 (0)</td>
<td>2 (17)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (6)</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (6)</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

B = bendamustine; Clb = chlorambucil; F = fludarabine; HHV = human herpes virus; SAE = serious adverse event
• With a median exposure time of 13 months to idelalisib, the ORR was 80% (95% CI: 65–90%). (Table 3)
• The best responses observed (% partial response/% complete response) were 78/0 in patients treated with bendamustine, 83/8 in patients with fludarabine, and 60/13 in patients treated with chlorambucil.
• All non-responding subjects had stable disease.
• The PFS rate for the combined cohorts (N = 45) was 28.5 months (95% CI: 15.6–not reached [NR]). (Figure 1)
• The median duration of response for the combined cohorts was 26.6 months (95% CI: 14.8–NR).

Table 3. Best response*

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + B N = 18, (%)</th>
<th>Idelalisib + F N = 12, (%)</th>
<th>Idelalisib + Clb N = 15, (%)</th>
<th>All subjects N = 45, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>8</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>PR</td>
<td>78</td>
<td>83</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>SD</td>
<td>11</td>
<td>8</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>11</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>ORR (PR + CR)</td>
<td>78</td>
<td>92</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>52–94</td>
<td>62–100</td>
<td>45–92</td>
<td>65–90</td>
</tr>
</tbody>
</table>

*B = bendamustine; CI = confidence interval; Clb = chlorambucil; CR = complete response; F = fludarabine; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

*Median time to response 1.9 months (range: 1.4–6.0).

Figure 1. Progression-free survival — combined cohorts (N = 45)
In Supportive Care Oncology

Key conclusions

■ Idelalisib can be combined with bendamustine, fludarabine, or chlorambucil with acceptable safety.
- All combinations were well tolerated, with infrequent discontinuations due to AEs.
■ In this heavily pretreated group of patients, many of whom have refractory disease and adverse genetic markers, the high ORR (80%) and median DOR (26.6 months) are indicative of significant clinical activity.
■ This study showed that bendamustine, fludarabine, and chlorambucil are suitable for idelalisib combination trials.


Canadian Perspective by Dr. Carolyn Owen

Outside of Canada, the most widely used front-line treatments for patients with CLL today are FCR (fludarabine, cyclophosphamide, rituximab), BR (bendamustine, rituximab), and R-Clb (rituximab, chlorambucil). For fit CLL patients younger than 65 years of age, the standard front-line treatment is FCR, based on the overall survival (OS) data from the CLL8 study.1 For CLL patients older than 65 years of age with few comorbidities, a lower toxicity profile makes BR a better alternative for front-line therapy than FCR, based on the recent results of the CLL10 study.2 For patients of more advanced age or with significant comorbidities, R-Clb appears to be the most appropriate treatment currently available.

Unlike first-line treatment options, the choice for second-line treatment is less clear. There have been no studies clearly demonstrating superiority of one second-line treatment option over another, and many of the front-line treatment options are less well tolerated after prior treatment. For example, practice guidelines suggest FCR re-treatment for relapsed patients if more than a two-year remission is achieved after first-line FCR, but this often results in significant myelosuppression and slow marrow recovery. For this reason, many physicians would like access to BR as a second-line treatment, given its reduced toxicity compared to FCR. Unfortunately, randomized controlled trials have yet to examine the choice between FCR and BR in second-line treatment.

In addition to the need for clarity on the best second-line treatment option for relapsed patients with CLL, there are limited treatment options for high-risk patients, including those with 17p deletions [del(17p)] and/or those who are refractory to fludarabine. Emerging therapies such as ibrutinib and idelalisib are exciting for patients with del(17 p); however, these drugs are unavailable in Canada outside of clinical trials. These unmet needs and other important questions in the treatment of CLL were addressed in several important studies at ASH 2013.

The CLL10 study by Eichhorst et al. presented an interim analysis from the first head-to-head, non-inferiority, phase III clinical trial comparing BR with FCR in fit, previously untreated CLL patients.2 Results were reported after limited follow-up, with PFS as a primary endpoint. The analysis showed that after a median observation time of 27.5 months, the two-year PFS rate in patients treated with FCR was numerically higher than in patients treated with BR (85.0% vs. 78.2%, $p = 0.041$, $HR = 1.385$). This difference in PFS rate was not observed in patients ≥65 years.

At the same time, we should not lose sight of the fact that BR was toxic as well, with 25% of patients experiencing grade ≥3 infections. Interestingly, this is a much higher infection rate than what we observe in lymphoma patients treated with BR,
possibly related to the older age of CLL patients or to heavy bone marrow involvement at the time of treatment. These clinically significant results mean that physicians should anticipate infections in patients treated with either regimen but with a significantly higher risk of infection with FCR.

The authors concluded that FCR was more effective in young, fit patients, but that BR has a better toxicity profile and there was no advantage to FCR use in patients ≥65 years. In addition, the study justifies the use of BR in general in CLL, given the very good response rates and reasonable tolerability.

Another German study, by Knauf et al., reported on a retrospective analysis of response rates with BR versus FCR in first-line treatment of CLL patients, using the German Tumor Registry of Lymphatic Neoplasia (TLN). The study demonstrated several interesting findings, including consecutive increases in the frequency of BR administration between 2009 and 2013 and a decreasing frequency of FCR administration during the same period. The increased frequency of BR use may be related to physician’s comfort with administering bendamustine, given that it is less toxic than FCR. The decreasing frequency of FCR administration suggests that German physicians in the community prefer BR to FCR, which is likely due to toxicity concerns.

Despite the positive results for BR in this study, the authors’ conclusion that BR may represent an alternative first-line treatment for fit patients has limited strength given the retrospective nature of the analysis and lack of any randomization. However, the study did show that the BR regimen was very tolerable in real-life practice, and that there were no new safety signals. Furthermore, the efficacy of the BR regimen demonstrated in this real-life setting should encourage patient-physician discussions on this treatment option, especially if toxicity is a concern.

Improving the efficacy of FCR and BR without compromising safety is an important goal for the treatment of CLL. The generation of a novel anti-CD20 antibody, obinutuzumab, has great promise toward this end. Brown et al. reported results of a head-to-head comparison of obinutuzumab plus FC (G-FC) or obinutuzumab plus bendamustine in the first-line treatment of patients with CLL. Although the study was based on a small number of patients (N = 41), results showed a very acceptable safety profile for obinutuzumab. The high frequencies of febrile neutropenia and neutropenia observed in both groups are consistent with what was observed in the FCR and BR groups in the CLL10 study and reinforces what we already know about FC and bendamustine regimens regarding toxicities. The frequency of infusion-related reactions (IRRs) was acceptable; although it was higher with obinutuzumab than what has been observed with rituximab, IRRs are easily managed by treatment providers. Anticipating IRRs and taking necessary steps to prevent them are key steps to effective management, as discussed in more detail in the subsequent section on the Goede et al. study. Efficacy results from this study are more difficult to discuss given the small number of patients. More follow-up time is required to validate the higher response rates observed in the G-FC group, though the small patient numbers make it unlikely that any meaningful conclusions about efficacy will be possible.

The efficacy and safety of obinutuzumab in patients with CLL was more fully examined in the CLL11 trial by Goede et al. The stage 2 analysis in this head-to-head comparison investigated the efficacy and safety of obinutuzumab plus chlorambucil (G-Clb) versus rituximab plus chlorambucil (R-Clb) in CLL patients with comorbidities. The study showed that the PFS rate was statistically superior in the G-Clb group than in the R-Clb group. Even more impressive was the ten-fold higher level of MRD negativity in the G-Clb arm compared with the R-Clb arm. It is tempting to speculate that with a longer follow-up, a difference in OS might be observed because of the trend towards a difference noted in the study (p = 0.08) and the knowledge that MRD negativity is associated with a longer survival. Regardless, a PFS advantage of one year is clinically very valuable for these patients and argues that obinutuzumab should be the antibody of choice for patients with CLL.

The increase in IRRs observed in the obinutuzumab group is noteworthy, though this led to only a small percentage of patient withdrawals. The IRRs occurred only in the first cycle, with no subsequent reactions observed. Physicians have been managing IRRs due to rituximab in the clinic for years and are experienced at minimizing their frequency and severity. This experience with rituximab should also be applied to obinutuzumab. Firstly, all patients should receive antibodies in divided doses, with a smaller dose provided on day 1 of cycle 1 to reduce the chance of a reaction. Standard prophylactic medications, including acetaminophen, hydrocortisone, and diphenhydramine should also be provided. Apart from the IRRs, the safety profile of obinutuzumab was consistent with that of rituximab except for a slight increase in thrombocytopenia also occurring early in treatment.

The superior PFS rate with obinutuzumab makes a strong argument for replacing rituximab with obinutuzumab in the front-line treatment of all patients with CLL, although more studies will likely be required by funding agencies to justify this change. Personally, I would prefer to treat my patients with obinutuzumab given these striking results. One potential criticism of the study is the higher dose of obinutuzumab
compared to rituximab in the study. However, studies of dose-dense rituximab have not reported a survival advantage or a significant MRD negativity advantage. Based on the results of this study, obinutuzumab is in my opinion the best antibody available today for the treatment of patients with CLL.

While the efficacy of treatment in patients with standard-risk CLL has been steadily improving, one of the greatest remaining unmet needs is the lack of effective treatments for high-risk patients, including those who are refractory to fludarabine and/or who have del(17p). Allogeneic stem cell therapy (SCT) is the only effective option for these patients. However, most patients are not eligible for SCT or are unable to achieve disease control prior to SCT. The study by Seymour et al. investigated the very promising antiapoptotic BCL-2 inhibitor ABT-199 in high-risk patients with CLL and small lymphocytic lymphoma (SLL). The results showed very high activity with ABT-199 in patients who were fludarabine-refractory (overall response rate [ORR] = 89%) and in patients with del(17p) (ORR = 82%).

The robust activity of ABT-199 in this patient population was highlighted by the high frequency of tumour lysis syndrome (TLS) observed in the initial dosing scheme of the same trial. The rapid destruction of tumour cells in this highly resistant patient population by ABT-199 is very indicative of the potency of this drug. These TLS events necessitated a change in the dose-escalation scheme and happily there have been no fatal TLS cases reported since those changes were implemented. TLS remains a very serious risk in patients treated with this agent, especially since experience with TLS management for high-risk patients is rare. Subsequent trials will confirm whether this new dosing scheme abrogates the risk of TLS. Apart from the risk of TLS, the study presented no other warning signals and suggested that ABT-199 is the most exciting drug currently being studied in CLL.

In addition to ABT-199, the PI3-kinase inhibitor idelalisib is another new drug being investigated for CLL treatment. In the Furman et al. phase III trial, efficacy and safety of idelalisib plus rituximab were investigated in patients with previously treated CLL. The study showed that patients with relapsed CLL, including those with adverse genetic features, had statistically significant improvements in PFS, ORR, lymph node reduction, and OS compared to the group receiving placebo plus rituximab. The study also showed an acceptable safety profile for idelalisib plus rituximab. Although idelalisib showed much promise in this trial, rituximab plus placebo was not the appropriate comparator, in my opinion. Rituximab is not effective as a single agent for treatment of relapsed CLL and should not have been used as the comparator in this trial. The choice of an ineffective comparator completely undermines the value of any conclusions reported in terms of efficacy.

Idelalisib was also investigated in a study by Coutre et al., with the objective being an evaluation of its effects on patients with del(17p), 11q deletions [del(11q)], TP53 mutation, NOTCH1, and immunoglobulin heavy chain variable region (IgHV) mutations. The study concluded that idelalisib demonstrated robust activity in patients with del(11q), NOTCH1 mutations, and unmutated IgHV. Curiously, the authors failed to mention in their conclusions that idelalisib was also active in patients with del(17p)/TP53 mutation as reported in their results. Overall, the activity of idelalisib across all patient groups was very encouraging. No patient group with CLL has yet to show a lack of response towards this drug. Idelalisib is another important addition to our treatment armamentarium for CLL.

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
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- 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 and liver function, blood sugar during treatment
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions

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

Dr. Furman: Idelalisib (formerly CAL-101 or GS-1101) is a targeted and highly selective inhibitor of the PI3 Kinase Delta (PI3Kδ) isoform that is present primarily in hematopoietic cells and plays an important role in the survival of malignant lymphocytes. Although the alpha and beta forms are ubiquitously expressed, the delta and gamma forms are uniquely important in the hematopoietic system. Idelalisib is an orally bioavailable inhibitor of the PI3Kδ isoform and thereby impairs the normal tracking of CLL lymph nodes, leading to high response rates following treatment. This mechanism of action is thought to be effective due to the role of PI3Kδ in the activation, proliferation, and survival of B cells.

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

Dr. Furman: There are a large number of phase I/II studies using idelalisib. Because it is so well tolerated, it is important to test idelalisib in combination with other existing therapies such as bendamustine and rituximab. Data from phase I studies show idelalisib remains well tolerated as part of these combination regimens.

One of the important changes we needed to make in our assessment of patients treated with agents such as idelalisib is how we characterize responses. Idelalisib, being a B-cell receptor antagonist, results in a lymphocytosis which would normally qualify patients as having progressive disease, even though lymphadenopathy and blood counts have improved. In 2012, the National Cancer Institute (NCI) response criteria were modified to remove lymphocytosis alone as a measure of progressive disease for B-cell receptor acting agents.

New Evidence: Please describe the rationale of your phase III study.

Dr. Furman: The rationale for our phase III study was to determine whether idelalisib is beneficial to a group of patients that are medically unfit and not candidates for cytotoxic chemotherapy.
New Evidence: Please describe the study population in your phase III study.

**Dr. Furman:** Our study investigated patients considered to be medically unfit, as defined by a Cumulative Illness Rating Scale (CIRS) score greater than six, creatinine clearance (CrCl) less than 60 mL/min, or myelosupression from previous chemotherapy that precluded subsequent chemotherapy. Patients also needed to have progressed within 24 months of their prior treatment. The median CIRS was eight and the median CrCl was 62 mL/min. Additionally, 45% of patients had del(17p) or p53 mutations. These are patients that have a number of negative prognostic factors and are on average less fit than those typically seen in clinical practice.

New Evidence: Why was rituximab chosen as the control in your study?

**Dr. Furman:** Rituximab monotherapy is the most commonly used agent in clinical practice based on usage patterns. Typically, rituximab is used alone in this medically unfit population, as these patients would not respond to chlorambucil given that they did not respond to fludarabine. The goal is therefore to minimize toxicity in these heavily pre-treated patients.

New Evidence: Please describe the efficacy results of your study. Are these results clinically meaningful?

**Dr. Furman:** Data from our study showed an improvement in progression-free survival (PFS) of idelalisib with rituximab (not reached) versus rituximab monotherapy (5.5 months), with a hazard ratio (HR) of 0.15 ($p <0.0001$). Results also demonstrated a marked improvement in overall response rates (ORRs) of idelalisib plus rituximab (81%) versus rituximab alone (13%) ($p <0.0001$). An improvement in overall survival (OS) was also shown with a HR of 0.28 ($p = 0.018$). These data represent the unblinding of the interim analysis performed after 50% of expected events occurred. The median time on study was 3.8 months for idelalisib plus rituximab versus 2.9 months for rituximab alone. These are clinically meaningful results and represent remarkable efficacy in a group of patients with a large number of comorbidities and poor prognostic markers.

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

**Dr. Furman:** Early studies have demonstrated possible drug-related toxicities with idelalisib such as transaminitis and diarrhea occurring between weeks 6 to 12. In this study, transaminitis was seen in six patients, with four patients being successfully rechallenged and continuing on drug; one patient currently being rechallenged, and one patient not being rechallenged due to progressive disease. Transaminitis is managed by withholding the drug and is generally reversible and asymptomatic without hyperbilirubinemia. Diarrhea was not increased in the idelalisib plus rituximab group. Additionally there was a decrease in the number of infusion related reactions (IRRs) in patients treated with idelalisib, most likely due to inhibition of cytokine release.

New Evidence: Given the results of this study, in which patient population would you use idelalisib plus rituximab if available?

**Dr. Furman:** Given the results of this study, I would use idelalisib plus rituximab in preference to rituximab alone in this medically unfit population. I believe avoiding chemotherapy is of prime importance for our patients and I therefore plan to quickly utilise these novel agents wherever possible.

Currently, if available, I would give either idelalisib or ibrutinib to all patients with CLL. My preferred regimen would be to combine idelalisib or ibrutinib with GA101, if GA101 were also available. To minimize toxicity, I would delay giving GA101 until six to nine months of treatment to decrease disease bulk and lymphocytosis. In general, I believe that ibrutinib or idelalisib should be used in all patients, regardless of fitness. However, I would be concerned about using idelalisib in patients that show other signs of T-cell autoimmunity such as inflammatory bowel syndrome, and psoriasis. The implications of this research are that we have a highly effective and well tolerated treatment that does not include chemotherapy. It is my hope and belief that idelalisib will eventually be used for all patients in order avoid the toxicities associated with chemotherapy.
**New Evidence**: What are the next steps in evaluating idelalisib for the treatment of CLL?

**Dr. Furman**: As more effective agents such as idelalisib and ibrutinib are developed, they will require more extensive follow-up in order to measure outcomes such as PFS. For example, the FLAIR study is examining ibrutinib plus rituximab versus fludarabine, cyclophosphamide, rituximab (FCR), with PFS being the primary outcome. However, given that the median PFS of FCR is around 50 months and that in untreated patients receiving ibrutinib we have only seen one patient that has progressed after 28 months, it is expected that the follow-up time needed to observe a difference in PFS between groups will be very long. It does not seem reasonable or ethical to wait for these data and to subject patients to these trials. European groups have to do these studies because of government rules and regulations; however, this results in a huge expenditure in resources.

In addition, a lot of investigators, due to financial restrictions, are forced to perform discontinuation studies, where patients are treated until they are minimal residual disease (MRD) negative, after which the drug is discontinued. It may seem more reasonable to examine outcomes such as MRD negativity; however, ibrutinib and idelalisib push cells out of lymph nodes, which may result in MRD positivity. Therefore, MRD negativity for these types of drugs has a much higher bar and may take longer to achieve.

Studies of interest include those in high risk patients that examine whether less toxic therapies such as idelalisib should be moved earlier in the treatment paradigm. Since these drugs work in high risk patients and are well tolerated, they may provide benefits in long term disease control.

**New Evidence**: What idelalisib treatment combinations show the most promise?

**Dr. Furman**: Ultimately, an agent such as ABT-199, which works through a different molecular pathway than idelalisib and shows minimal toxicity, would be interesting to combine with idelalisib. In patients who have gotten six months of idelalisib and had reduced tumour burden, ABT-199 could be used safely. We are currently examining idelalisib in combination with lenalidomide as well as with GA101.

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

**Dr. Furman**: The main benefit of idelalisib is the provision of a highly effective therapy without the toxicity of chemotherapy. The hope is that putting a patient into remission and continuing therapy will result in continuous control of the CLL clone, leading to long term remissions. This is a very exciting time to be in CLL research. The availability of these new agents will change the lives of CLL patients forever.
New Combinations of Targeted and Chemotherapeutic Agents Form Well-Tolerated Regimens That Can More Effectively Treat Patients with Non-Hodgkin Lymphomas

The current standard treatment for indolent non-Hodgkin lymphoma (iNHL) in Canada is R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), or bendamustine plus rituximab (BR). BR was shown to have superior efficacy and reduced toxicity compared with R-CHOP in patients with indolent lymphoma and mantle cell lymphoma. The type II anti-CD20 monoclonal antibody obinutuzumab (GA101) has shown excellent activity when compared with rituximab in patients with iNHL. Another molecule that is showing promise in this area is idelalisib, an inhibitor of phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit delta, which has shown good activity in phase I studies of relapsed/refractory patients with iNHL.

Stem cell transplantation is another treatment that is beneficial for relapsed/refractory patients. Myeloablative conditioning prior to transplantation results in lower relapse rates, but it is also associated with high toxicity. Investigators are now attempting to create reduced-intensity conditioning regimens, including BeEAM (bendamustine, etoposide, cytarabine, and melphalan) and BFR (bendamustine, fludarabine, rituximab), to overcome this increased toxicity.

At the 2013 American Society of Hematology (ASH) Annual Meeting, New Evidence covered many studies that provided new information on these topics. The following abstracts are covered in this issue:

- An update of the PRIMA study, investigating the benefits of two years of rituximab maintenance after first-line immunochemotherapy in patients with follicular lymphoma (FL), found that the efficacy benefit of rituximab maintenance was durable for six years.
- A study determined that the BeEAM conditioning regimen prior to autologous stem cell transplantation is safe, effective, and results in long-term remission in patients with Hodgkin or non-Hodgkin lymphomas.
- A study sought to determine the safety and efficacy of BR in the first-line treatment of patients with indolent nonfollicular B-cell lymphomas. The results showed that BR is active and well tolerated, with response rates that compare favourably with current therapies.
- The Lysa trial tested the efficacy of the RiBVD regimen (rituximab, bendamustine, bortezomib, dexamethasone) in patients with mantle cell lymphoma. Preliminary results showed that RiBVD is effective, with acceptable toxicity.
• A phase II trial examined the conditioning regimen of BFR, which induces immunosuppression without myelo-suppression, prior to allogeneic stem cell transplantation. The authors found that BFR is safe, with low incidences of mortality and graft versus host disease.

• Data from a German prospective registry compared the use of BR and R-CHOP in previously untreated patients with iNHL in a real-world setting. The data showed that while patients receiving BR and R-CHOP differ (with BR preferentially administered to less fit patients), response rates to first-line treatment are similar.

• A study investigating the efficacy of idelalisib in patients with iNHL that is refractory to rituximab and alkylating agents found that idelalisib demonstrated high, durable response rates with an acceptable safety profile.

References:

Salles GA, et al. ASH 2013:509

Updated six-year follow-up of the PRIMA study confirms the benefit of two-year rituximab maintenance in follicular lymphoma patients responding to front-line immunochemotherapy

Background
The PRIMA study investigated the potential benefit of two years of rituximab maintenance following first-line chemotherapy plus rituximab in patients with follicular lymphoma (FL) and found that three-year progression-free survival (PFS) was improved with two years of rituximab maintenance. At ASH 2013, Salles et al. updated the original analyses with an additional three years of follow-up data, for a total of six years of follow-up.1

Study design
• Patients with previously untreated FL were registered in the PRIMA study from December 2004 until April 2007 (27 months).
• Induction therapy was nonrandomized and consisted of one of the three following first-line regimens (% of patients):
  ◦ R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone): 75%;
  ◦ R-CVP (rituximab, cyclophosphamide, vincristine, prednisone): 22%;
  ◦ R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone): 3%.
• Patients whose induction therapy resulted in a complete response (including unconfirmed CR) or partial response (PR) were stratified based on their geographic region, immunochemotherapy regimen, and response to induction, and randomized to observation or rituximab maintenance therapy (one 375 mg/m² infusion every 8 weeks for 2 years).
• Data from a total of 1,018 randomized patients were analyzed according to the intention-to-treat principle (observation: n = 513; rituximab maintenance: n = 505).
• The clinical cutoff for this analysis was January 31, 2013, with a median follow-up of 73 months from randomization.
• The outcomes measured after six years of follow-up included:
  ◦ PFS, including overall PFS and PFS stratified by: induction therapy, response to induction therapy, and disease severity;
  ◦ Time to next lymphoma treatment (TNLT);
  ◦ Overall survival (OS);
  ◦ Response rates;
  ◦ Histological transformation rate;
  ◦ Causes of death.
**Key findings**

- All initial pre-treatment patient characteristics were well balanced between arms and the response status at the time of randomization was CR: 39%, CRu: 32%, PR: 28%, and others: 1%.
- The six-year PFS estimate was significantly higher in the group that received two years of rituximab maintenance than in the observation group (59.2% vs. 42.7%, respectively; HR = 0.57, \( p < 0.0001 \)). (Figure 1)

- At six years from randomization, the improvement in PFS with rituximab maintenance over observation was consistent, regardless of the disease severity at baseline, the induction therapy used, or the response to induction therapy (rituximab maintenance vs. observation):
  - Disease severity (as measured by the Follicular Lymphoma International Prognostic Index):
    - Low risk: 76% vs. 60%; HR = 0.496, \( p = 0.0052 \);
    - Intermediate risk: 65% vs. 43%; HR = 0.499, \( p < 0.0001 \);
    - High risk: 49% vs. 36%; HR = 0.663, \( p = 0.0013 \);

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**Figure 1. Progression-free survival from randomization**

- HR = hazard ratio; PFS = progression-free survival

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CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CR = complete response; CRu = unconfirmed complete response; CT = computerized tomography; CVP = cyclophosphamide, vincristine, prednisone; FCM = fludarabine, cyclophosphamide, mitoxantrone; PD = progressive disease; PR = partial response; SD = stable disease

*Stratified by response after induction, regimen of chemotherapy, and geographic region.

†Frequency of clinical, biological, and CT-scan assessments were identical in both arms.

‡Five additional years of follow-up.
Induction therapy:
- R-CHOP: 62.9% vs. 44.5%; HR = 0.538, \( p < 0.0001 \);
- R-CVP: 49.7% vs. 38%; HR = 0.697, \( p = 0.05 \);

Response to induction therapy:
- CR: 64.9% vs. 51%; HR = 0.520 (95% CI: 0.363–0.744);
- CRu: 57.4% vs. 43.4%; HR = 0.635 (95% CI: 0.446–0.905);
- PR: 56.2% vs. 34.2%; HR = 0.449 (95% CI: 0.298–0.676).

- The TNLT estimate at 70 months was higher in the group that received two years of rituximab maintenance than in the observation group (63.5% vs. 51.0%, respectively; HR = 0.625, \( p < 0.0001 \)). (Figure 2)
- The six-year OS estimates were not different between the rituximab maintenance and observation groups (87.4% vs. 88.7%, respectively; HR = 1.027, \( p = 0.885 \)). (Figure 3)

In the rituximab maintenance group, 186 patients (36.8%) progressed; of the 117 patients treated at the time of progression, 39 (33%) received second-line treatment without rituximab.

In the observation group, 278 patients (54%) progressed; of the 170 patients treated at the time of progression, 27 (16%) received second-line treatment without rituximab.

- The responses to second-line treatment, as reported by the investigators, were not different between the groups. (Figure 4)
- The rate of histological transformation was not different between the groups (rituximab maintenance vs. observation: 20% vs. 21%).
- Relevant causes of death were similar between groups. (Table 1)
Figure 4. Response to second-line treatment

![Response to second-line treatment graph]

Table 1. Relevant causes of death

<table>
<thead>
<tr>
<th></th>
<th>Observation (N = 518)</th>
<th>Rituximab maintenance (N = 505)</th>
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<tbody>
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<td>Total number of relevant causes of death</td>
<td>58</td>
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<td>Lymphoma</td>
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<tr>
<td>Second malignancies (MDS/AML)</td>
<td>19 (5)</td>
<td>6 (2)</td>
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<tr>
<td>Infections*</td>
<td>4 (5)</td>
<td>7</td>
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<tr>
<td>Others</td>
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<td>18</td>
</tr>
</tbody>
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Key conclusions

- The benefit of rituximab maintenance, in terms of PFS and TNLT for patients with FL, was durable and consistent among those with differing disease severity, chemotherapy used during induction, and response to induction therapy.
- No new safety signals were detected.
- No survival benefit was observed, with similar numbers of patients dying from lymphoma in both arms.
- Response to second-line therapy needs to be improved in both study arms.
- With approximately 60% of patients without disease progression at six years of follow-up, updated results of the PRIMA study challenge the view that all patients with FL will ultimately relapse.
- This treatment strategy should be considered as a standard of care for patients with FL requiring cytotoxic therapy.

Bendamustine, etoposide, cytarabine, and melphalan (BeEAM) followed by autologous stem cell transplantation produce a three-year PFS of 75% in patients with heavily pretreated Hodgkin and non-Hodgkin lymphomas

**Background**

The conditioning regimen of bendamustine, etoposide, cytarabine, and melphalan (BeEAM) prior to autologous stem cell transplant (ASCT) has been shown to have acceptable safety and significant anti-lymphoma activity in patients with resistant/relapsed lymphoma. The objective of this study was to evaluate the long-term efficacy of the BeEAM regimen in terms of progression-free survival (PFS) and overall survival (OS) in this patient population.¹

**Study design**

- A total of 43 patients with relapsed/refractory Hodgkin lymphoma (HL; n = 15) or non-Hodgkin lymphoma (NHL; n = 28) were treated with the BeEAM regimen for seven days prior to ASCT.
- The primary objective was the PFS rate at 36 months.
- The lowest acceptable rate was set at 40%; a successful rate was defined as 60%

**Key findings**

- The patients’ baseline characteristics were as follows:
  - Median age, years (range): 47 (18–70);
  - Patients with primary refractory disease, n (%): 21 (49);
  - Patients with relapsed disease, n (%): 22 (51);
  - Status at time of transplant, n (%):
    - Complete response: 14 (34);
    - Partial response: 22 (50);
    - Progressive disease: 7 (16).

- After a median follow-up of 41 months after transplant:
  - 72% of patients were in complete remission (as measured by computerized tomography and positron emission tomography);
  - 23% of patients relapsed (n = 10; five deaths were reported).
- Among patients who relapsed, the median disease-free survival was 7.5 months.
- Among patients with NHL, six of 28 patients (21%) were resistant/relapsed after treatment; three deaths occurred.
- Among patients with HL, six of 15 patients (40%) were resistant/relapsed after treatment; four deaths occurred.
- Two patients out of the entire population were refractory to treatment and rapidly died.
- One patient developed myelodysplasia; no other late effects have been reported at this time.

**Study design**

**Bendamustine 200 mg/m²**
**Etoposide 200 mg/m²**
**Cytarabine 400 mg/m²**
**Melphalan 140 mg/m²**

ASCT = autologous stem cell transplant
Key conclusions

- The BeEAM regimen met the primary endpoint of the study and confirmed its safety for patients with HL and NHL.
- After 41 months of follow-up, 72% of patients remained in complete remission following BeEAM and ASCT treatments.
- Interestingly, there was no significant difference between patients with HL and those with NHL in terms of both PFS and OS, as the BeEAM regimen followed by ASCT demonstrated high efficacy in both populations.


Luminari S, et al. ASH 2013:3049

Bendamustine and rituximab combination in untreated indolent nonfollicular B-cell non-Hodgkin lymphomas: a phase II study from the Fondazione Italiana Linfomi

Background

Indolent nonfollicular B-cell lymphomas (INFL) are a heterogeneous group of lymphomas that include small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphomas (LPL), and marginal zone lymphomas (MZL). Combination chemoimmunotherapy regimens are used in the majority of patients with advanced stage INFL who require treatment. Bendamustine is approved for the treatment of relapsed indolent B-cell non-Hodgkin lymphomas, and when administered with an anti-CD20 monoclonal antibody, the combination has been shown to be highly active and well tolerated.

The purpose of this phase II, multicentre study was to determine the activity and safety of bendamustine, rituximab (BR) in first-line treatment of patients with INFL.¹

Study design

- The main inclusion criteria for the study were:
  - Untreated patients with SLL, nodal MZL, or LPL;
  - Stage II–IV disease;
  - Presence of at least one of the following criteria for the definition of active disease:
    - Systemic symptoms;
    - Hemoglobin <10 g/dL;
    - Platelets <100 x 10⁹/L;
    - Diffuse bone marrow infiltrate;
    - Lymphocyte doubling time <12 months;
    - Bulky disease.
Patients were scheduled to receive six cycles of bendamustine (90 mg/m² on days 1 and 2 every 28 days) and eight rituximab doses (375 mg/m² on day 8 of cycle 1, and on day 1 of subsequent cycles).

The primary endpoint was the complete remission rate (CRR) based on the 2007 International Working Group criteria.

The secondary endpoints were the rate of adverse events (AEs), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS).

The sample size was defined at 67 patients evaluable for response assuming a CRR of 60%, a power of 80%, and a p value of 5%.

Key findings

Baseline characteristics and patient disposition

Among 20 centres in Italy, 72 patients were enrolled and three patients were excluded due to a major violation.

Baseline characteristics of the patients were as follows:
- Median age, years (range): 65 (45–75);
- Male, n (%): 45 (65);
- Lactate dehydrogenase > upper limit of normal (ULN), n (%): 10 (14);
- β2-microglobulin > ULN, n (%): 43 (62);
- Stage III–IV, n (%): 68 (99);
- Bone marrow-positive, n (%): 64 (93);
- B symptoms, n (%): 11 (16);
- Serum monoclonal antibody, n (%): 45 (66);
- Follicular Lymphoma International Prognostic Index, n (%):
  - 0–1: 3 (4);
  - 2: 19 (28);
  - 3–5: 47 (68).

Based on local pathology reports, 17 patients had SLL, 20 had nodal MZL, and 32 had LPL.

Of the 69 patients who received treatment, 59 patients (85.5%) received at least six cycles of BR.

Efficacy

Based on the intention-to-treat analysis and on local assessment of response, ORR was 84%, including 39 patients (57%) in complete remission (CR) and 19 (27%) in partial remission (PR). (Figure 1)

After centralized review, response was changed from CR to PR in 6/39 patients due to persistence of serum monoclonal component. Revised CR and ORR rates were 48% and 86%, respectively. (Figure 1)

At the time of the current analysis and with a median follow-up of 15.6 months (range: 1–25 months), seven disease progressions and one death (due to lymphoma) were observed.

Two-year PFS was 88% (95% CI: 77–94%). (Figure 2)

Two-year OS was 96% (95% CI: 87–98%).

Safety

Safety analysis was available for all 69 patients and for 472 cycles of BR.

One patient died during treatment due to a severe infection after cycle 2.

Hematological and non-hematological events are shown in Table 1.

Figure 1. Patients’ flow and response per treatment cycle (N = 69)

CR = complete remission; EOT = end of treatment; NA = not available; PD = progressive disease; PR = partial remission; SD = stable disease
Key conclusions

- **BR** is active and well tolerated in patients with previously untreated INFL.
- The **ORR** of 84% and **CRR** of 57% compare favourably with previously reported response rates observed in patients with indolent lymphoma.


Gressin R, et al. ASH 2013:370

The **RiBVD** regimen offers a high complete response rate in elderly patients with untreated mantle cell lymphoma: preliminary results of the Lysa trial “Lymphome du Manteau 2010 SA”

**Background**

Efforts are currently being made to improve the efficacy and safety of first-line rituximab plus chemotherapy in the treatment of mantle cell lymphoma (MCL); for example, the regimen of bendamustine plus rituximab (BR) has been found to be superior to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. Many studies are currently investigating the efficacy of adding drugs to the BR regimen. In the study presented by Gressin et al. at ASH 2013, the efficacy and safety of the RiBVD (rituximab, bendamustine, bortezomib, dexamethasone) regimen was investigated in patients with MCL.1

**Study design**

- Inclusion criteria for the study were:
  - MCL, as defined by the World Health Organization 2008 criteria;
  - No prior chemotherapy;
• Patients >65 years old without limits, or patients <65 years old who refused or could not receive an autotransplant;
• Ann Arbor stage II–IV;
• Performance score of 0–2;
• No other neoplasm, or in complete remission from a previous neoplasm for three years;
• Biological limits except if organ involvement:
  – Absolute neutrophil count ≥1 g/L;
  – Platelets ≥50 g/L;
  – Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤4x normal;
  – Bilirubin ≤3x normal;
  – Creatinine clearance ≥20 mL/min;
• The ability to undergo regular monitoring;
• Written informed consent.

• Exclusion criteria were as follows:
• Other types of lymphoma;
• Patients in relapse, except for those with irradiated, localized stage or who were splenectomized;
• Central nervous system involvement;
• Human immunodeficiency virus-positive;
• Active hepatitis B or C;
• Neuropathy ≥2, according to the National Cancer Institute scale;
• Non-stabilized cardiomyopathy or diabetes;
• No feasible hyperhydration if necessary to prevent tumour lysis syndrome.

• Patients were treated with RiBVD for six 28-day cycles:
  • Rituximab: 375 mg/m² intravenously (iv) on day 1;
  • Bendamustine: 90 mg/m² iv on days 1 and 2;
  • Bortezomib: 1.3 mg/m² subcutaneously on days 1, 4, 8, and 11;
  • Dexamethasone: 40 mg iv on day 2.
• Valacyclovir was administered to prevent viral infections, but there was no recommendation for bacterial prevention.
  • The primary endpoint was progression-free survival (PFS). The Fleming one-step method was used, with α = 5% and β = 20%.
  • Secondary endpoints included:
    ▪ Toxicity and response after four and six cycles;
    ▪ Overall survival;
    ▪ Prognostic indicators of survival (MCL International Prognostic Index [MIPI], Goelams index, and positron emission tomography [PET] scan).
  • This interim report focused on the toxicity and response data after four cycles.

Key findings

Baseline characteristics and patient disposition

• A total of 76 patients were enrolled between November 2011 and December 2012.
• The results of this interim analysis include data for 70 evaluable patients:
  • One patient missed inclusion (hepatitis B-positive);
  • Five patients were missing data.
• The patients’ baseline characteristics were as follows:
  • Male/Female, n: 49/21;
  • Median age, years (range): 72 (64–83);
  • Ann Arbor stage II/III–IV, n: 5/65;

<table>
<thead>
<tr>
<th>Study design</th>
<th>D1</th>
<th>D2</th>
<th>D4</th>
<th>D8</th>
<th>D11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab: 375 mg/m²</td>
<td>iv</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendamustine: 90 mg/m²</td>
<td>iv</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib: 1.3 mg/m²</td>
<td>sc</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dexamethasone: 40 mg</td>
<td>iv</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prevention: viral infection YES (valacyclovir) — pneumocystosis NO

C1 C2 C3 C4 Interim evaluation C5 C6 Final evaluation 1 2 3

C = cycle; D = day; iv = intravenous; MRD = minimal residual disease; PET = positron emission tomography; sc = subcutaneous
Eastern Cooperative Oncology Group performance score 0–1/2, n: 59/11; MIPI score, n (%):
- Low: 3 (4);
- Intermediate: 19 (27);
- High: 48 (69).

A total of 271 out of a planned 280 cycles of RiBVD were administered (97%). Seven patients stopped treatment prematurely:
- Three patients died;
- One patient stopped for toxicity;
- Three patients had disease progression.

In the 271 cycles completed:
- 99% of rituximab doses were administered;
- 94.5% of bortezomib doses were administered;
  - 46 patients stopped because of hematotoxicity;
  - 10 patients stopped because of neurotoxicity;
- 99.8% of bendamustine doses were administered.

Efficacy

Response rates were assessed using the 2007 International Workshop criteria.

Overall response rate (ORR) was 87%, with a complete response (CR) and unconfirmed CR (CRu) rate of 60% and a partial response rate of 27%. (Table 1)

PET scans were performed on 69 patients; when response was analyzed this way, ORR was 87%, CR was 57%, and PR was 30%. (Table 1)

Minimal residual disease (MRD) was measured as an indicator of molecular response. MRD in the blood was 85.3%, and MRD in the bone marrow was 84.6%. (Figure 1)

Table 1. Clinical response (IWC 2007)

<table>
<thead>
<tr>
<th></th>
<th>no PET</th>
<th>with PET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>70</td>
<td>69*</td>
</tr>
<tr>
<td>ORR</td>
<td>61 (87%)</td>
<td>61 (87%)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>42 (60%)</td>
<td>39 (57%)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (27%)</td>
<td>21 (30%)</td>
</tr>
</tbody>
</table>

CR = complete response; CRu = unconfirmed complete response; IWC = International Workshop criteria; ORR = overall response rate; PET = positron emission tomography; PR = partial response

*No PET for nine patients: eight no response, one forgotten (patient in CRu).

MRD analysis method: allele-specific oligonucleotide VDJ quantitative polymerase chain reaction and EURO-MRD guidelines (Gimenez E et al., Brit J Haematol 2012).
Safety
- Grade 3/4 adverse events were as follows (grade 3 %/grade 4%): (Figure 2)
  - Neutropenia (23/23);
  - Febrile neutropenia (4/3);
  - Thrombopenia (25/10);
  - Anemia (7/0);
  - Fatigue (11/3);
  - Gastrointestinal (4/0);
  - Liver (4/0);
  - Neuropathy (13/0);
  - Fever (6/3);
  - Rash (4/0);
  - Lung (3/1);
  - Cardiac (7/1);
  - Glycemia (4/0).
- Grade 2/3 neuropathies occurred in 16 patients, 14 of which were observed after cycle 3. There was no correlation of neuropathy with age, and neuropathy was reversible in 11 of 16 patients. (Figure 2)
- No cases of pneumocystosis, CMV reactivation, alopecia, and visual or ear toxicities were observed.
- Four deaths occurred during the study, one of which was determined to be related to RiBVD (progressive multifocal leukoencephalopathy during cycle 3, related to rituximab). (Table 2)

Figure 2. Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>23</td>
<td>23</td>
<td></td>
<td></td>
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<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombopenia</td>
<td></td>
<td>25</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Neuropathy*</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
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<tr>
<td>Cardiac</td>
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<td>Glycemia</td>
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<tr>
<td>Creatinine</td>
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<tr>
<td>Injection site reaction</td>
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</tbody>
</table>

*16 patients grade 2 or 3; 14 after cycle 3; no correlation with age; mainly reversible (11/16).
† No pneumocystosis or cytomegalovirus reactivation, alopecia, visual, or ear toxicities.

Table 2. Causes of death

<table>
<thead>
<tr>
<th>Cause</th>
<th>Cycle (age in years)</th>
<th>Related to RiBVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PML</td>
<td>C3 (65)</td>
<td>Rituximab</td>
</tr>
<tr>
<td>2 cardiac arrests</td>
<td>C2 and C4 (71 and 71)</td>
<td>No</td>
</tr>
<tr>
<td>1 pneumonia</td>
<td>C1 (77)</td>
<td>No</td>
</tr>
</tbody>
</table>

C = cycle; PML = progressive multifocal leukoencephalopathy; RiBVD = rituximab, bendamustine, bortezomib, dexamethasone

Key conclusions
- RiBVD is effective for untreated elderly MCL patients, with a high CR rate of 60% after 4 cycles of treatment, and an MRD negativity rate of 85%.
  - The final PFS results will be available in six months.
- Toxicity appears acceptable, with only one treatment-related death reported.
  - Subcutaneous bortezomib caused neurotoxicity in 13% of patients, which is similar to reports in previous studies.

Nonmyeloablative allogeneic conditioning with bendamustine, fludarabine, rituximab: a novel regimen inducing immunosuppression without myelosuppression

**Background**
The authors of this study previously reported the use of bendamustine, fludarabine, rituximab (BFR) in a phase I trial of escalating daily doses of bendamustine for three days prior to allogeneic stem cell transplantation (alloSCT) without dose-limiting toxicity. In the current study, the authors reported results of an expanded phase II trial.1

**Study design**
- **Inclusion criteria** for the study were as follows:
  - Relapsed non-Hodgkin lymphoma or chronic lymphocytic leukemia;
  - Acceptable organ function;
  - A human leukocyte antigen-matched donor;
  - Age 18 to 70 years.
- **Exclusion criteria** were as follows:
  - Active central nervous system disease;
  - Active major infection;
  - Performance status >2;
  - Prior refractoriness to bendamustine.
- The BFR regimen was administered as follows:
  - Rituximab 375 mg/m² on day –13 (prior to transplantation), then 1,000 mg/m² on days –6, +1, and +8;
  - Fludarabine 30 mg/m² and bendamustine 70–130 mg/m² on days –5, –4, and –3.
  - Methotrexate was also administered at a dose of 5 mg/m² on days 1, 3, and 6 (and day 11 for those with matched unrelated donors [MUDs]).
  - Patients with MUDs also received thymoglobulin at a dose of 1 mg/kg on days –2 and –1.

**Key findings**
- The analysis included all 56 patients who received BFR.
- The patient characteristics were:
  - Median age, years (range): 56 (39–70);
  - Histology, n:
    - Chronic lymphocytic leukemia (CLL): 15 (3 with 17p–, 2 with Richter's transformation);
    - Follicular lymphoma: 13;
    - Mantle cell lymphoma: 16;
    - Diffuse large B-cell lymphoma/T-cell lymphoma: 9/3;

**Study design**

```
<table>
<thead>
<tr>
<th>Patients with relapsed disease</th>
<th>MTX</th>
<th>MTX</th>
<th>MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>-13</td>
<td></td>
<td></td>
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<tr>
<td>-6</td>
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<td>-5</td>
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<td>-4</td>
<td></td>
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<td>0</td>
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<tr>
<td>+1</td>
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<tr>
<td>+8</td>
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</table>

Tacrolimus until day +180
```

- Rituximab 375 mg/m² (dose 1), then 1,000 mg/m² (doses 2–4)
- Fludarabine 30 mg/m², Bendamustine 70–130 mg/m²
- MTX Methotrexate 5 mg/m² days 1, 3, 6 (and day 11 for patients with MUDs)
- Thymoglobulin 1 mg/kg days –2, –1 for patients with MUDs

MTX = methotrexate; MUD = matched unrelated donor
Number of prior regimens, median (range): 3 (1–7);
Prior transplant, n (%): 7 (12);
Disease status, n (%):
  – Complete response/unconfirmed complete response: 27 (48);
  – Partial response: 23 (41);
  – Refractory: 6 (11);
Donor (related/MUD): 30/26 (54/46).

• Patients were administered one of the following doses of bendamustine:
  70 mg/m²: n = 2;
  90 mg/m²: n = 3;
  110 mg/m²: n = 3;
  130 mg/m²: n = 48.

• A median 5.58 x 10⁶ CD34+ cells/kg were infused during the transplantation.

• One transplant rejection occurred, in a patient who received a transplant from a MUD and a low stem cell dose.

• Granulocyte colony-stimulating factor (G-CSF) was not required in 13 patients (23%).

• The average number of G-CSF doses required was 1.5 (range: 0–8).

• Absolute neutrophil counts recovered to >0.5 x 10⁹/L in a median of 6 days (range: 0–16) after transplantation.

• The percentage of patients with neutrophil counts ≥0.5 x 10⁹/L dropped to approximately 70% six days after transplantation, and recovered to 100% by day 14.

• A total of 45 patients (87%) required platelet transfusions.

• Among patients with normal platelet counts at study entry, the percentage of those with platelet counts ≥20 x 10⁹/L did not drop below 90% at any point in the first 30 days following transplantation.

• After 30 days, donor M and T chimerism was 85% and 97%, respectively. Both reached 100% by day 90.

• After a median follow-up of 2.2 years (range: 0.5–4.2), the probability of overall survival (OS) was approximately 0.8. (Figure 1)

• There was no difference in OS when patients were stratified by histology (p = 0.635).

• Event-free survival was also not significantly different among patients stratified by disease histology (p = 0.747). (Figure 2)

• OS was unaffected by the donor type (p = 0.61). (Figure 3)

• The rate of acute grade 2–4 GVHD was also unaffected by the donor type (p = 0.27).

• Chronic graft versus host disease (GVHD) occurred at a rate of approximately 30%. (Figure 4)

• The same group presented a different study at ASH 2013 (abstract 3349) that showed patients with CLL who were conditioned with BFR had a lower risk of progression two years post alloSCT than those who were conditioned with fludarabine, cyclophosphamide, rituximab (p = 0.04). (Figure 5).
**Figure 3. Overall survival by donor type**

![Graph](image)

**Figure 4. Chronic graft vs. host disease**

![Graph](image)

**Figure 5. Risk of progression (two-year): BFR vs. FCR conditioning in allogeneic SCT for patients with CLL**

![Graph](image)

**Key conclusions**

- Bendamustine at 130 mg/m² per day for three days in combination with fludarabine and rituximab is a safe nonmyeloablative conditioning regimen, which provides immunosuppression without myelosuppression.
- The incidences of treatment-related mortality and GVHD were low.
- BFR can be used as a platform for outpatient allogeneic transplantation.

**References:**
Response to first-line treatment with BR or R-CHOP in patients with indolent non-Hodgkin lymphoma: first outcome data from the German prospective TLN registry

Background
Recent data from phase III clinical trials have shown that in previously untreated patients with indolent non-Hodgkin lymphoma (iNHL), bendamustine plus rituximab (BR) resulted in superior progression-free survival (PFS) and noninferior response rates compared to rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). Since clinical trials are restricted to highly selected patients, Knauf et al. investigated the effectiveness of BR and R-CHOP in unselected patients treated in routine practice by German office-based hematologists.1

Study design
• This open, longitudinal, multicentre, clinical registry on lymphoid neoplasms (NCT00889798) prospectively collects data on the treatment of patients with lymphoid B-cell neoplasms as administered by a network of German office-based hematologists.
• Data regarding patient and tumour characteristics, comorbidities, systemic treatments and response rates, PFS, and overall survival are recorded; patients are followed up for five years.
• Automated plausibility and completeness checks with subsequently generated queries by the electronic data capture system ensure data reliability. In addition, data managers regularly check for plausibility and issue queries.
• Since May 2009, 115 sites (259 hematologists) have recruited a total of 3,383 patients.

Key findings
• A total of 947 patients with iNHL were recruited at the onset of first-line therapy. The choice of therapy was at the discretion of the treating physician in accordance with the patient’s informed consent.
• The most frequently used regimens were BR (n = 640, 68%) and R-CHOP (n = 145, 15%).
• Since 2009, BR has been used more frequently while the use of R-CHOP has decreased. (Figure 1)

Figure 1. Frequency of first-line treatment with BR or R-CHOP over time

BR = bendamustine, rituximab ± prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
• The following analysis is based on 785 patients with iNHL (53% follicular, 17% marginal zone [including MALT], 13% mantle cell lymphoma, and 13% immunocytoma) treated with either BR or R-CHOP.

• Clinical and tumour characteristics differed between patients receiving BR and R-CHOP. Patients treated with BR were (BR vs. R-CHOP):
  - Older (mean age: 67 vs. 62 years, \( p < 0.001 \));
  - Presented more often with stage IV disease (56% vs. 41%, \( p = 0.021 \));
  - Presented more often with comorbidities (65% vs. 55%, \( p = 0.022 \)).

• Patients treated with R-CHOP were (R-CHOP vs. BR):
  - More often diagnosed with follicular lymphoma (72% vs. 49%, \( p < 0.001 \));
  - Presented more frequently with bulky disease (36% vs. 21%, \( p < 0.001 \)).

• Objective response rates (ORR), as assessed by the local site, were similar between the two regimens (90% BR vs. 93% R-CHOP, \( p = 0.817 \)). (Figure 2)

• On average, patients received five cycles of BR or six cycles of R-CHOP. Both groups received a mean six cycles of rituximab.

• In univariate analyses, young age, male sex, follicular subtype, and absence of comorbidities were significantly associated with an objective clinical response to the first-line regimen.

• In a multiple logistic regression analysis adjusted for the type of first-line regimen and the age at the onset of therapy, the likelihood for response was lower for older patients (odds ratio \([OR] = 0.97, p = 0.015 \)), and the type of first-line regimen had no effect (\(OR = 1.28, p = 0.537 \)).

• After a median follow-up of 22 months, 92% of patients who received BR are alive, while 91% of patients who received R-CHOP are alive. (Figure 3)

• PFS was 89% for BR and 90% for R-CHOP. (Figure 4)

• The percentage of patients who received second-line therapy was 8% and 10% for BR and R-CHOP, respectively.

• Overall, 5% of patients have been lost to follow-up.

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**Figure 2. Best response in first-line treatment with BR or R-CHOP**

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*BR = bendamustine, rituximab ± prednisone; CRu = unconfirmed complete response; PD = progressive disease; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SD = stable disease*
**Key conclusions**

- Previously untreated patients with iNHL receiving BR or R-CHOP in routine practice differ, with BR preferentially administered to patients with a less favourable prognostic profile.

- Response rates to first-line treatment with BR or R-CHOP are similar.

- These results, from unselected patients treated in routine practice, favourably support response data from clinical trials.²³

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Mature response data from a phase II study of the PI3K-delta inhibitor idelalisib in patients with double (rituximab and alkylating agent)-refractory indolent B-cell non-Hodgkin lymphoma

Background
Idelalisib is a selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ) that inhibits proliferation and induces apoptosis in many B-cell malignancies. It also inhibits homing and retention of malignant B cells in lymphoid tissues, thereby reducing B-cell survival. Patients with indolent non-Hodgkin lymphoma (iNHL) who are refractory to rituximab and alkylating agents have few viable treatment options; idelalisib could be efficacious in these patients. The aim of this study was to investigate the efficacy of idelalisib in patients with double refractory iNHL.1

Study design
• Key eligibility criteria included:
  ◆ Previously treated iNHL;
  ◆ Refractory to both rituximab and an alkylating agent (defined as less than a partial response on therapy, or progression within six months of completion of therapy), with refractoriness documented radiologically;
  ◆ Measurable disease (>2 cm lymph node diameter);
  ◆ Eastern Cooperative Oncology Group performance status 0–2 or Karnofsky performance status ≥60;
  ◆ Organ function:
    – Neutrophil count ≥1,000 cells/μL;
    – Hemoglobin ≥8 g/dL;
    – Platelet count ≥50,000/μL;
    – Serum transaminases ≤2.5x upper limit of normal (ULN);
    – Bilirubin ≤1.5x ULN;
    – Serum creatinine <1.5x ULN.

• Patients were enrolled in this single-arm study between April 2011 and October 2012 (N = 125).
• Idelalisib was administered at a dose of 150 mg twice a day; therapy was maintained until progression.
• Disease assessments were performed using Cheson and Waldenström macroglobulinemia (WM) criteria at weeks 0, 8, 16, 24, and every 12 weeks thereafter.
  ◆ An independent review committee of two radiologists evaluated the assessments, with adjudication by a third if needed.
  ◆ Clinical reviews were performed by a hematologist/oncologist.

• The primary endpoint was overall response rate (ORR).
• Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and quality of life.

Key findings
• Baseline characteristics and patient disposition
  ◆ The patients’ baseline characteristics were as follows:
    ◆ Sex (male/female), n (%): 80/45 (64/36);
    ◆ Median age, years (range): 64 (33–87);
    ◆ Disease type, n (%):
      – Follicular lymphoma: 72 (58);
      – Small lymphocytic lymphoma: 28 (22);
      – Lymphoplasmacytic lymphoma/WM: 10 (8);
      – Marginal zone lymphoma: 15 (12);
    ◆ Lactate dehydrogenase > upper limit of normal, n (%): 38 (30);
Bulky disease (≥5 cm), n (%): 59 (47);
Bulky disease (≥7 cm), n (%): 33 (26).

• Prior therapy exposures included:
  • Number of prior regimens, median (range): 4 (2–12);
  • Prior therapies, n (%):
    – Rituximab: 125 (100);
    – Alkylating agent: 125 (100);
    – Bendamustine: 81 (65);
    – Anthracycline: 80 (64);
    – Purine analog: 42 (33);
    – Stem cell transplantation: 14 (11);
  • Median time from last regimen to study entry: 3.9 months.

• Patients were previously refractory to the following regimens, n (%):
  – Rituximab: 125/125 (100);
  – Alkylating agent: 124/125 (99);
  – Rituximab, alkylation: 108/114 (96);
    – Rituximab, bendamustine: 47/60 (78);
    – Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone: 40/56 (71);
    – Rituximab, cyclophosphamide, vincristine, prednisone: 29/36 (81);
  – The number of patients who were refractory to ≥2 regimens was 99 (79%).
  – The number of patients who were refractory to their last regimen was 112 (90%).

• Patient disposition was as follows:
  – Forty patients (32%) remain on treatment;
  – Eighty-five patients (68%) discontinued for the following reasons, n (%):
    – Disease progression: 41 (32);
    – Adverse event (AE): 25 (20);
    – Death: 8 (6.4);
    – Investigator request: 7 (5.6) (three patients were referred for transplant);
    – Withdrew consent: 4 (3.2).

• Idelalisib was administered for a mean 8.1 months (standard deviation: 5.7) and a median 6.6 months, with a range of 0.6–23.9 months.

Efficacy

• The ORR was 57% (71/125 patients):
  – Complete response: 6% (n = 7);
  – Partial response: 50% (n = 63);
  – Minor response: 1% (n = 1).

• Stable disease was achieved in 42 patients (34%), progressive disease occurred in 10 patients (8%), and two patients were not evaluated.

• The median time to response was 1.9 months (interquartile range: 1.8–3.7).

• As measured by the best percent change in lymph node response, 90% of patients had improvement in lymphadenopathy, and 57% had a ≥50% decrease from baseline.

(Figure 1)
• ORR was similar across patients, regardless of disease type, prior therapies, or response to prior therapies. (Figure 2)
• Median DOR was 12.5 months. (Figure 3)
• Median PFS was 11 months. (Figure 4)

Safety
• AEs that occurred in >10% of patients included (any grade %/grade ≥3 %):
  ◦ Diarrhea: 43/13;
  ◦ Fatigue: 30/2;
  ◦ Nausea: 30/2;
  ◦ Cough: 29/0;
  ◦ Pyrexia: 28/2;
  ◦ Dyspnea: 18/3;
  ◦ Decreased appetite: 18/1;
  ◦ Abdominal pain: 16/2;
  ◦ Vomiting: 15/2;
  ◦ Upper respiratory tract infection: 14/0;
  ◦ Decreased weight: 13/0;
  ◦ Rash: 13/2;
  ◦ Asthenia: 11/2;
  ◦ Night sweats: 11/0;
  ◦ Pneumonia: 11/7.
• Serious AEs are summarized in Table 1.

Baseline hematologic abnormalities included (any grade %/grade ≥3 %):
  ◦ Decreased neutrophils: 24/5;
  ◦ Decreased hemoglobin: 51/1;
  ◦ Decreased platelets: 34/3.

On-study hematologic abnormalities included (any grade %/grade ≥3 %):
  ◦ Decreased neutrophils: 56/27;
  ◦ Decreased hemoglobin: 28/2;
  ◦ Decreased platelets: 26/6.

Alanine or aspartate transaminase levels were elevated in the following numbers of patients:
  ◦ Any grade: 60 (48%);
    – Grade 1–2: 44 (35%);
    – Grade 3: 13 (10%);
    – Grade 4: 3 (2%).

Grade 1–2 transaminase elevations resolved with continued idelalisib treatment, while grade ≥3 elevations were reversible with drug interruption.

Out of the 16 patients who experienced grade ≥3 transaminase elevations, 14 were rechallenged with idelalisib; 10 had no recurrence of transaminase elevations, and four had a recurrence of grade ≥3 elevations.

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Figure 2. Forest plot of overall response rate

<table>
<thead>
<tr>
<th>Overall (N = 125)</th>
<th>FL (n = 72)</th>
<th>SLL (n = 28)</th>
<th>MZL (n = 15)</th>
<th>LPL/WM (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulky disease: No (lymph diameter &lt;7 cm) (n = 92)</td>
<td>0.57 (0.48–0.66)</td>
<td>0.54 (0.42–0.66)</td>
<td>0.61 (0.41–0.79)</td>
<td>0.47 (0.21–0.73)</td>
</tr>
<tr>
<td>Yes (lymph diameter ≥7 cm) (n = 33)</td>
<td>0.57 (0.46–0.67)</td>
<td>0.58 (0.39–0.75)</td>
<td>0.57 (0.46–0.67)</td>
<td>0.58 (0.39–0.75)</td>
</tr>
<tr>
<td>Number of prior therapies: &lt;4 (n = 52)</td>
<td>0.50 (0.36–0.64)</td>
<td>0.62 (0.50–0.73)</td>
<td>0.50 (0.36–0.64)</td>
<td>0.62 (0.50–0.73)</td>
</tr>
<tr>
<td>≥4 (n = 73)</td>
<td>0.57 (0.41–0.72)</td>
<td>0.57 (0.45–0.68)</td>
<td>0.57 (0.41–0.72)</td>
<td>0.57 (0.45–0.68)</td>
</tr>
<tr>
<td>Prior bendamustine: No (n = 44)</td>
<td>0.50 (0.27–0.73)</td>
<td>0.59 (0.46–0.71)</td>
<td>0.50 (0.27–0.73)</td>
<td>0.59 (0.46–0.71)</td>
</tr>
<tr>
<td>Yes (n = 81)</td>
<td>0.69 (0.39–0.91)</td>
<td>0.55 (0.46–0.65)</td>
<td>0.69 (0.39–0.91)</td>
<td>0.55 (0.46–0.65)</td>
</tr>
</tbody>
</table>

ORR (95% CI)

CI = confidence interval; FL = follicular lymphoma; LPL = lymphoplasmacytic lymphoma; MZL = marginal zone lymphoma; ORR = overall response rate; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia

*Dotted line: null hypothesis <20% response rate.
CR = complete response; DOR = duration of response; IRC = independent review committee; LPL = lymphoplasmacytic lymphoma; MR = minor response; PR = partial response; WM = Waldenström macroglobulinemia

*Analysis includes subjects who achieved a CR or PR (or MR for LPL/WM patients) according to IRC assessments.

### Table 1. Serious adverse events

<table>
<thead>
<tr>
<th>Serious adverse event*</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>13 (10.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9 (7.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (7.2)</td>
</tr>
<tr>
<td>Colitis</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Fever/neutropenia</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

*Serious adverse event occurring in more than two subjects.

### Key conclusions

- **Idelalisib demonstrates high response rates in double refractory iNHL.**
- **Responses were independent of number of prior treatments, degree of refractoriness, and histologic subtype.**
- **Response durations were prolonged (median 12.5 months), and the safety profile was acceptable and manageable.**
- **Idelalisib may provide meaningful disease control in iNHL patients refractory to rituximab and alkylating agents.**

Obinutuzumab is a novel anti-CD20 antibody that has recently been approved by the FDA for use in combination with chlorambucil for untreated chronic lymphocytic leukemia. Although obinutuzumab has not yet been approved for use in patients with lymphoma, ongoing phase III randomized controlled trials are currently investigating obinutuzumab in combination with bendamustine in patients with follicular lymphoma (FL), and in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in patients with diffuse large B-cell lymphoma (DLBCL). If the results of these randomized controlled trials are positive, I would consider replacing rituximab with obinutuzumab for CD20 positive B-cell malignancies in my practice. However, a major scientific criticism of these trials is the fact that they all gave higher and more frequent doses of obinutuzumab than rituximab. To be certain that obinutuzumab is more effective than rituximab, a phase III trial comparing these agents at an equivalent dose and schedule is needed. It is unclear if such a study will ever be done.

The combination of bendamustine and rituximab (BR) is used as initial therapy for indolent lymphomas requiring systemic therapy, and in patients with mantle cell lymphoma (MCL) who are ineligible for transplant. BR is also used in patients with relapsed MCL if they did not receive BR as initial therapy. The main evidence for these indications comes from the StiL study that compared BR to rituximab plus CHOP (R-CHOP) in patients with indolent lymphoma or MCL, and showed significantly increased PFS and less toxicity with BR. There is no reason why I would not give BR to patients with indolent non-Hodgkin lymphoma (iNHL) unless they received it and did not tolerate it; however, this is a rare occurrence.

At the 2013 ASH Annual Meeting, new information was presented about both obinutuzumab and BR in patients with lymphoma. Davies et al. presented data from the maintenance period of the phase Ib GAUDI study, which investigated obinutuzumab in combination with either CHOP or fludarabine plus cyclophosphamide in patients with relapsed/refractory FL, followed by a maintenance period of obinutuzumab monotherapy. The patient population from this study was fairly typical for those with relapsed/refractory FL — the population was not heavily pretreated, with 75% presenting with advanced stage disease and a median age of 62. The safety profile of obinutuzumab monotherapy was similar to that which has been previously observed with rituximab monotherapy, with no obvious increase in toxicity with obinutuzumab.

Complete response (CR) rates increased between the end of the induction period and the end of the maintenance period in the Davies et al. study. This is not an unexpected finding and could have occurred for two reasons. The first is that the maintenance antibody treatment led to an ongoing further response. The second is that over a longer period of time, initial partial responses converted to CRs. In my practice, I would not yet consider giving obinutuzumab over rituximab as a maintenance regimen — there is not enough evidence to support it, and I would want to see long-term results from prospective randomized trials before making this change. From this study, we can conclude that obinutuzumab monotherapy seems relatively safe and effective, and the results support the need for large phase III trials to further define the role of obinutuzumab relative to rituximab in lymphoma.

Zelenetz et al. also investigated the efficacy and safety of obinutuzumab in combination with CHOP (G-CHOP) in the first-line therapy of patients with DLBCL. This phase II study utilized a typical population of advanced stage (stage II-IV or bulky disease), previously untreated patients with DLBCL. After a successful first course of obinutuzumab, patients were given the option of a short duration infusion of obinutuzumab, which lasted either 90 minutes or 120 minutes. Infusion-related adverse events (AEs) were neither common nor severe with the short infusion, suggesting that the short infusion is safe for these patients. It is of interest that G-CHOP is well tolerated when given as a short infusion, as this shorter infusion time would be beneficial for patients.

A total of 77.5% of patients had an AE related to obinutuzumab in the Zelenetz et al. study; however, the majority of these AEs were mild to moderate and occurred during the first infusion. This information is concerning, and is important to know for nurses giving treatment. However, these data alone would not affect my decision to use obinutuzumab with my patients. If obinutuzumab were not associated with improved outcomes compared to rituximab however, the AEs would be a reason not to use obinutuzumab. More efficacy data from phase III randomized controlled trials are needed in order to make this determination.
The overall response rate (ORR) data from this study are what one would expect from a front-line trial with chemotherapy in patients with DLBCL. However, it is difficult to draw conclusions from response rate data, and I would not base treatment decisions on an ORR endpoint; progression-free survival (PFS) is a much more important endpoint from a clinical perspective. This study also stratified ORR by cell of origin and found that ORR was similar between the two subtypes. However, most Canadian centres do not test patients for cell of origin, and those that do determine cell of origin do not base treatment decisions on their findings. Therefore, these data are not very important for most Canadian physicians. We can conclude that G-CHOP seems relatively safe and effective in this phase II trial. However, this will not impact clinical decisions in Canada. The most important trial that needs to be done in this area is a phase III prospective randomized trial comparing G-CHOP and R-CHOP.

Luminari et al. presented a phase II study that examined BR in untreated indolent nonfollicular B-cell non-Hodgkin lymphomas. This patient population is interesting because it included patients with iNHL but not FL; most studies of iNHL use predominantly patients with FL. An ORR of 86% and a CR rate of 48% were observed in this study, which are excellent response rates and are similar to other studies of BR in patients with iNHL. The median follow-up time in this study was 15.6 months, which is quite short. A longer follow-up is preferable because PFS is a more important endpoint than response rates, and 15.6 months is too short of a time to assess PFS. A five-year follow-up would be ideal, but three years of follow-up is the minimum that I would like to see in this type of study. A breakdown of ORR by disease type would also have been informative.

Overall, the BR regimen was quite well tolerated in the Luminari et al. study, with the main issues being gastrointestinal toxicity and skin rash (20% incidence, 1% severe). Infections were rare in this study (1%), and the main grade 3/4 AE reported was neutropenia (43%). The conclusion that can be made from this study is that in non-FL patients with iNHL, BR is well tolerated and gives high response rates. This supports the available phase III data for patients with iNHL.

Gressin et al. also presented data about BR, but in combination with bortezomib and dexamethasone (the RiBVD regimen). I have occasionally combined bortezomib and bendamustine with my patients who have MCL. There are reports of cytarabine being used in combination with BR, but there are no phase III trials as of yet. New investigational agents have also been added to BR, including ibrutinib and idelalisib. The addition of these agents to BR appear to be safe and effective, but we would need to see results from phase III trials comparing these combinations to BR alone before I would consider using them in my practice.

The patient population of the study by Gressin et al. included patients with MCL who were ineligible for transplant and at an advanced stage of disease. In addition to typical exclusion criteria, patients were excluded if they had peripheral neuropathy of grade ≥2 or a lack of diabetic control. The ORR was 87%, with a CR of 60%. These are very encouraging response data; the CR is quite high for this patient population. Minimal residual disease (MRD) negativity was also high (85% in blood and bone marrow), which is an excellent result. However, MRD is not part of standard clinical practice and not something we would measure. Some studies have suggested that MRD correlates with PFS, but the assessment of MRD has not been standardized, so it is not possible to compare results between centres.

Bortezomib caused neurotoxicity at a rate of 13% in the above study. This is concerning, since grade 3 peripheral neuropathy impacts the patient’s quality of life. This finding would not prevent me from using the RiBVD regimen in my practice, but I would monitor my patients closely and consider dose reductions if necessary. It would be interesting to perform another study with weekly doses of intravenous or subcutaneous bortezomib to see if similar efficacy rates can be achieved with lower toxicity. Based on the results, we can conclude that the RiBVD regimen seems relatively effective and feasible, but before it could be adopted as a standard of care it would need to be compared to BR alone in a prospective randomized phase III trial.

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.

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

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

GIOTRIF (afatinib) demonstrated a reduction in risk of tumour progression or death of 53%.

The first irreversible TKI to block ErbB Family signalling

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

References:
2. GIOTRIF® Product Monograph, Boehringer Ingelheim Canada Ltd., December 2013.

* LUX-Lung 3 is a large (N = 345), multinational, prospective, randomized, open-label, phase III trial of treatment-naïve patients with EGFR M+ stage IIIB/IV lung adenocarcinoma and ECOG 0 or 1. Patients were randomized to receive either GIOTRIF (40 mg oral, once daily until tumour progression) or pemetrexed/cisplatin (500 mg/m² / 75 mg/m² IV every 3 weeks for up to 6 cycles). PFS was the primary end point.

† Comparative clinical significance unknown.

CI = confidence interval; Del19 = exon 19 deletions; 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.
Myelomas

Three-Drug Combination Therapies Improve Outcomes for Elderly Patients with Multiple Myeloma

Multiple myeloma (MM) makes up 1.3% of all new cancer cases in Canada, 1.8% of all cancer deaths, and is the second most common blood cancer after non-Hodgkin lymphoma. On average, Canadian men are diagnosed with MM at age 62 and women at age 61, with only 4% of cases diagnosed in patients under 45. At present, it is estimated that the global median survival is approximately five years for elderly, fit patients (significantly less if patients are frail) and approaching ten years for younger patients who are eligible for autologous stem cell transplant and newer treatments. While MM remains incurable, new advances in research and treatment have favourably impacted patient outcomes.

The latest results of clinical trials using bendamustine-based regimens in the treatment of patients with MM were presented at the American Society for Hematology (ASH) 2013 Annual Meeting:

- In an elderly patient population (median age of 75 years) with MM who were not candidates for high-dose chemotherapy, the combination of bendamustine, bortezomib, and dexamethasone was feasible and efficacious.
- In patients with newly diagnosed MM who were candidates for high-dose therapy-autologous stem cell transplantation, treatment with bendamustine, bortezomib, and prednisone gave response rates comparable to other three-drug, bortezomib-based combinations, both before and after transplant.
- Peripheral blood stem cell mobilization following the combination of bendamustine, etoposide, and dexamethasone demonstrated a 100% success rate in mobilization of CD34+ cells sufficient for tandem autologous stem cell transplants.
- The addition of bendamustine to bortezomib plus dexamethasone in the Intergroupe Francophone du Myelome 2009-01 trial improved the outcome of relapsed and refractory MM without significantly increasing toxicity in elderly patients previously untreated with proteasome inhibitors.
- The combination of bendamustine, bortezomib, and dexamethasone was an effective treatment regimen for patients with relapsed/refractory MM and was well-tolerated provided that adapted therapy and adequate antibiotic prophylaxis were employed in patients older than 70 years of age.

Bendamustine, bortezomib, and dexamethasone as first-line treatment for patients with multiple myeloma who are not candidates for high-dose chemotherapy

Background
Despite significant advances, multiple myeloma (MM) is an incurable plasma cell disorder with an eventually fatal outcome. In newly diagnosed MM, combinations of bortezomib, steroids, and alkylating agents, such as melphalan or prednisone, have achieved response rates in excess of 70% and have been established as a standard of care in patients who are ineligible for high-dose chemotherapy. In this study, the efficacy and feasibility of the combination of bendamustine, bortezomib, and dexamethasone (BVD) was evaluated as first-line therapy for patients with MM.

Study design
• Patients newly diagnosed with MM who were not candidates for high-dose chemotherapy and who met the standard eligibility criteria with regard to renal, hepatic, and hematologic function were enrolled in this study.
• The original BVD treatment regimen consisted of:
  ◦ Bendamustine: 80 mg/m² intravenous (iv) on days 1 and 4;
  ◦ Bortezomib: 1.3 mg/m² iv on days 1, 4, 8, and 11; and
  ◦ Dexamethasone: 40 mg on days 1, 2, 3, and 4, with cycles repeating every 28 days.
  ◦ Patients had the option to continue treatment up to eight cycles or two cycles beyond confirmed complete response (CR).
• An interim analysis found this combination to be efficacious but relatively toxic. As a result, the BVD treatment regimen was modified to the following:
  ◦ Bendamustine: 80 mg/m² iv on days 1 and 2;
  ◦ Bortezomib: 1.3 mg/m² iv on days 1, 8, and 15; and
  ◦ Dexamethasone: 20 mg on days 1, 8, 9, 15, and 16, every 28 days for a total of eight cycles or two cycles beyond documented CR, whichever occurred first.
• Patients achieving at least stable disease (SD) continued on to maintenance therapy.
• Acyclovir or equivalent viral prophylaxis was originally recommended and became required on the modified treatment regimen.
• The primary objectives were to evaluate the CR rate and to assess the tolerability and toxicity of BVD as first-line treatment of MM.
• The secondary objectives were to evaluate the overall response rate (ORR; ≥ partial response [PR]), progression-free survival (PFS), and overall survival (OS).

Key findings
• A total of 48 patients have been enrolled in the study; 18 on the original treatment regimen and 30 on the modified regimen.
  ◦ In total, 38% (n = 18) of patients were over 75 years of age; 11% (n = 5) on the original treatment regimen and 27% (n = 13) on the modified regimen.
• The majority of patients had MM that was classified as International Staging System (ISS) stage I (46%) or ISS stage II (32%).
• At the time of analysis, 12 (25%) patients were on active treatment and seven (15%) patients were on maintenance treatment, all on the modified schema.
• The median follow-up time was 13.8 (range: 1.2–39.8) months.
• The ORR among all evaluable patients (N = 44) was 87%: 7% with a CR, 5% with an unconfirmed CR (CRu), 48% with a very good PR (VGPR), and 27% with a PR. The remaining patients had SD (14%). (Table 1)
  ◦ Evaluable patients on the modified treatment regimen (N = 27) had an ORR of 85% (11% CR, 7% CRu, 41% VGPR, and 26% PR).
  ◦ For evaluable patients >75 years old (N = 16), the ORR was 94% (0% CR/CRu, 63% VGPR, and 31% PR).
**Study design**

**Original treatment regimen**

Cycles 1–8 (28-day cycle)*
- Bendamustine: 90 mg/m² iv (days 1 and 4)
- Bortezomib: 1.3 mg/m² iv (days 1, 4, 8, and 11)
- Dexamethasone: 40 mg po (days 1, 2, 3, and 4)

Response evaluation every 4 weeks
(CR, PR, SD)

Continue until a total of 8 cycles or CR + 2 cycles
(Assuming SD or better and no intolerable toxicity)

**Modified treatment regimen**

Cycles 1–8 (28-day cycle)
- Bendamustine: 80 mg/m² iv (days 1 and 2)
- Bortezomib: 1.3 mg/m² iv (days 1, 8, and 15)
- Dexamethasone‡: 20 mg po (days 1, 2, 8, 9, 15, and 16)

Response evaluation every 4 weeks
(CR, PR, SD)

Continue until a total of 8 cycles or CR + 2 cycles
(Assuming SD or better and no intolerable toxicity)

**Maintenance therapy**
- Bortezomib: 1.3 mg/m² iv (days 1, 8, and 15)
- Dexamethasone‡: 20 mg po (days 1, 2, 8, 9, 15, and 16)

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**Table 1. Response to treatment (N = 44*)**

<table>
<thead>
<tr>
<th>Response</th>
<th>All patients (N = 44)</th>
<th>Patients &gt;75 years of age (N = 16)</th>
<th>Original treatment regimen (N = 17)</th>
<th>Modified treatment regimen (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>38 (87)</td>
<td>15 (94)</td>
<td>15 (88)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (7)</td>
<td>0</td>
<td>0</td>
<td>3 (11)</td>
</tr>
<tr>
<td>CRu</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>VGPR</td>
<td>21 (48)</td>
<td>10 (63)</td>
<td>10 (59)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (27)</td>
<td>5 (31)</td>
<td>5 (29)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>MR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>6 (14)</td>
<td>1 (6)</td>
<td>2 (12)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
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</tr>
</tbody>
</table>

Median follow-up in months (range): 13.8 (1.2–39.8)

CR = complete response; CRu = unconfirmed complete response; MR = minor response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response

*Four patients were not evaluable for response due to the following: two patients died on study prior to evaluation; one patient withdrew consent prior to evaluation; and one patient has not yet reached first evaluation.
• The one-year PFS probability was 0.83 in patients >75 years of age and 0.60 in the total population. (Figure 1)
  > The median PFS was 17.7 (95% CI: 13.3–not reached) months in patients >75 years of age and 14.2 (95% CI: 8.7–18.1) months in the total population.
• The one-year OS probability was 0.83 in patients >75 years of age and 0.78 in the total population. The median OS has not been reached in either patient population. (Figure 2)
• The most common grade 3 hematologic adverse events (AEs) were leukopenia (17%) and neutropenia (8%). The only grade 4 hematologic AEs were neutropenia (6%) and anemia (2%).
• The most common nonhematologic grade 3 AEs were fatigue, peripheral neuropathy, and pneumonia, each observed in 6% of patients. There were no treatment-related grade 4 nonhematologic AEs.

**Figure 1. Progression-free survival: all patients vs. patients >75 years old**

<table>
<thead>
<tr>
<th></th>
<th>Patients &gt;75 years</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>18</td>
<td>48</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>17.7 (13.3–NR)</td>
<td>14.2 (8.7–18.1)</td>
</tr>
<tr>
<td>12-month PFS probability (95% CI)</td>
<td>0.83 (0.56–0.94)</td>
<td>0.60 (0.41–0.75)</td>
</tr>
</tbody>
</table>

CI = confidence interval; NR = not reached; PFS = progression-free survival

**Figure 2. Overall survival: all patients vs. patients >75 years old**

<table>
<thead>
<tr>
<th></th>
<th>Patients &gt;75 years</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>18</td>
<td>48</td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>NR</td>
<td>NR (23.4–NR)</td>
</tr>
<tr>
<td>12-month OS probability (95% CI)</td>
<td>0.83 (0.56–0.94)</td>
<td>0.78 (0.61–0.89)</td>
</tr>
</tbody>
</table>

CI = confidence interval; NR = not reached; OS = overall survival
• There were a total of 16 treatment-related serious AEs (SAEs) that occurred in 14 patients, the two most frequent SAEs being grade 3 pneumonia (n = 3) and sepsis (n = 2).
  ○ The two treatment-related grade 4 SAEs reported were atrial fibrillation and thrombocytopenia. One treatment-related death was reported (CHF).

• Peripheral neuropathy of all grades occurred in 58% of all patients and in 50% of patients on the modified regimen. (Table 2)

• Herpes zoster of all grades was seen in 19% of the patients, all of whom were on the original treatment regimen. (Table 2)

| Table 2. Incidences of Herpes zoster and peripheral neuropathy: all patients vs. modified regimen |
|-----------------------------------------------|-----------------------------------------------|
| All patients (N = 48)                        | Modified regimen (N = 30)                      |
| n (%)                                        |                                              |
| Herpes zoster                               | Peripheral neuropathy                         |
|      | Herpes zoster | Peripheral neuropathy | Herpes zoster | Peripheral neuropathy |
| Grade 1 | 4 (8)         | 14 (29) | 0 | 11 (37) |
| Grade 2 | 4 (8)         | 11 (23) | 0 | 4 (13)  |
| Grade 3 | 1 (2)         | 3 (6)   | 0 |       |
| Grade 4 | 0             | 0       | 0 | 0      |
| Total  | 9 (19)        | 28 (58) | 0 | 15 (50) |

**Key conclusions**

■ In this elderly patient population with a median age of 75 years, the combination of bendamustine, bortezomib, and dexamethasone was feasible and efficacious.

■ The modified treatment regimen appeared to be better tolerated, which should translate into longer treatment duration and may ultimately lead to improved responses and survival, as seen in other studies.

■ Enrollment on the modified treatment regimen is ongoing.


**Phase II study of bendamustine, bortezomib, and prednisone treatment for patients newly diagnosed with multiple myeloma**

**Background**

Bortezomib-based combinations, including alkylating agents or immunomodulatory drugs, are widely used treatment regimens in patients with newly diagnosed multiple myeloma (MM). Bendamustine is a bifunctional alkylating agent that is effective in treating patients with relapsed and/or refractory MM, and is approved in Europe in combination with prednisone for elderly patients with newly diagnosed MM. Bendamustine may be more efficient than other alkylators, therefore, the objective of this study was to investigate bendamustine in combination with bortezomib and prednisone (BVP) as treatment for patients newly diagnosed with MM, both in transplant and nontransplant candidates. ¹

**Study design**

• Patients with newly diagnosed MM were included in the trial.
  ○ The first cycle of BVP therapy consisted of:
    ○ Bendamustine: 90 mg/m² intravenous (iv) on days 1 and 4;
Bortezomib: 1.3 mg/m² iv on days 1, 4, 8, 11, 22, 25, 29, and 32; and
Prednisone: 60 mg/m² orally on days 1–4.

In the following cycles, bendamustine was given on days 1 and 8, bortezomib on days 1, 8, 15, and 22 (weekly schedule), and prednisone as it was given in the first cycle.

Patients younger than 65 years proceeded to peripheral blood stem cell collection using growth factors alone after four cycles;
High-dose therapy-autologous stem cell transplantation (HDT-ASCT) was performed after six cycles.

Patients older than 65 years received up to nine 28-day cycles.

Key findings

Enrollment of 60 patients was completed between May 2011 and July 2012.

Patients enrolled in the study had the following baseline characteristics:
The median age was 61 years (range: 38–82 years) with 18 patients ≥65 years old;
The majority (67%) were International Staging System stage II/III; and
The majority (67%) had unfavourable cytogenetics: t(4;14), t(14;16), del 17p, or 1q gains by fluorescence in-situ hybridization.

After a median of six cycles (range: 2–9 cycles), 75% of patients achieved at least a partial response (PR), including 16% with a stringent complete response (sCR), 9% with a complete response (CR), and 28% with a very good PR.

There was a trend toward a higher CR rate in the group of patients <65 years (31%) compared with elderly patients (11%), although the difference was not statistically significant.

Forty patients proceeded to stem cell collection after a median of four cycles of BVP.

With granulocyte-colony stimulating factor (G-CSF) alone, 14 patients (35%) failed to collect a minimum of 2 x 10⁶ CD34+ cells/kg.

An amendment to the treatment regimen recommended plerixafor for poor mobilizers (i.e., a peripheral CD34 cell count inferior to 10/μL on day 4).

With G-CSF plus plerixafor, all patients except two achieved the minimum CD34+ cells required to proceed to ASCT.

The remaining two patients successfully collected CD34+ cells using chemotherapy, G-CSF, and plerixafor.

Of the 31 patients who received HDT-ASCT, sCR and CR rates before transplant were 18% and 13%, respectively; after transplant the rates were 39% sCR and 13% CR.

Seven patients (22%) achieved immunophenotypic CR.

After a median follow-up of 12 months (range: 5–25 months), eight patients had progressed, resulting in a 15-month time to progression (TTP) of 85%.

At 15 months:
For overall survival (OS), 89% of patients remained alive;
No patients achieving sCR and CR had progressed and all were alive at this time point.

Comparing the standard risk and high-risk cytogenetic subgroups:
No differences were observed in overall response rates and CR rates;
No significant differences were observed for 15-month OS (100% vs. 92%, respectively);
In the standard risk group, one patient progressed compared with five patients in the high-risk cytogenetic subgroup, resulting in a 15-month TTP of 93% vs. 85%, respectively.

Hematologic toxicities included grade 3/4 anemia (11%), neutropenia (23%), and thrombocytopenia (14%).

The most common grade 3/4 nonhematologic toxicities were asthenia (10%), infections (9%), and peripheral neuropathy (4%).

Key conclusions

In patients who were candidates for HDT-ASCT, response rates obtained before and after transplant were comparable to other three-drug, bortezomib-based combinations, such as bortezomib, thalidomide, plus dexamethasone or cyclophosphamide, bortezomib, plus dexamethasone.

Growth factors alone for stem cell collection after four cycles of BVP as induction therapy resulted in 35% of patients being poor mobilizers, who were rescued with plerixafor.

In the elderly population, although the number of patients included was small, BVP seems not to be superior to bortezomib, melphalan, plus prednisone in response rates.

Green DJ, et al. ASH 2013:2033

**Bendamustine-based regimens are effective in mobilizing peripheral blood hematopoietic stem cells for autologous stem cell transplantation**

**Background**
High-dose chemotherapy as conditioning for autologous stem cell transplantation (ASCT) is a standard of care for patients with multiple myeloma (MM) and advanced or treatment-refractory non-Hodgkin lymphoma (NHL). Stem cell proliferation and mobilization can be enhanced by the addition of myelosuppressive chemotherapy prior to granulocyte colony-stimulating factor (G-CSF) administration. Prior to ASCT, chemotherapeutic agents not cross-resistant to prior therapies may support peripheral blood stem cell collection and simultaneously improve patient outcomes through a more potent, direct, antitumour effect. Bendamustine has structural similarities to both purine analogs and alkylating agents, without significant cross-resistance to other compounds in either drug class. In addition, it is well tolerated, appears to have low stem cell toxicity in vitro, and has activity against MM and NHL. The objective of this study was to estimate the frequency of successful stem cell mobilization following bendamustine combined with G-CSF and dexamethasone.1

**Study design**

- Patients received one cycle of bendamustine, etoposide, dexamethasone (BED) therapy as outpatients:
  - Bendamustine: 120 mg/m² intravenous [iv] days 1 and 2;
  - Etoposide: 200 mg/m² iv days 1–3; and
  - Dexamethasone: 40 mg orally days 1–4.

- This was followed by filgrastim at a starting dose of 10 µg/kg/day on day 5 through to the end of collection.
- Apheresis was initiated when peripheral blood CD34 counts were >5/µL.
- Patients were eligible for this study if they had relapsed or refractory MM, B-cell or T-cell NHL, and were candidates for ASCT.
- Other eligibility criteria included: age ≥18 years, absolute neutrophil count ≥1,500/mm³, platelets ≥100,000/mm³, adequate renal and hepatic function, and Eastern Cooperative Oncology Group performance status <2.
- The primary objective was to estimate the frequency of successful stem cell mobilization (as determined by collecting a minimum of 2 x 10⁶ CD34+ cells/kg) following bendamustine combined with G-CSF and dexamethasone.
- The secondary objectives were:
  - To examine the number of apheresis cycles required to collect a minimum of 2 x 10⁶ CD34+ cells/kg and, ideally, >5 x 10⁶ CD34+ cells/kg; and
  - To evaluate the response rate to bendamustine using established disease-specific response criteria.
- Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events v. 4.0.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bendamustine 120 mg/m²</td>
<td>X</td>
</tr>
<tr>
<td>Etoposide 200 mg/m²</td>
<td>X</td>
</tr>
<tr>
<td>Dexamethasone 40 mg</td>
<td>X</td>
</tr>
<tr>
<td>Filgrastim (GCSF) ≥10 µg/kg/day sc</td>
<td></td>
</tr>
</tbody>
</table>

*GCSF = granulocyte colony-stimulating factor; sc = subcutaneous*
**Key findings**

- Forty patients (34 with MM, five with B-cell NHL, and one with natural killer (NK)/T-cell NHL) with a median age of 60 years (range: 43–70 years) were enrolled in the study.
- The mean number of prior therapies was one (range: 1–3) for patients with MM and two (range 1–3) for patients with NHL.
- All patients were successfully mobilized.
- Two patients were given plerixafor for mobilization, one on day 20 and the other on day 12 (second day of collection), and therefore, as per the protocol, both patients were deemed nonevaluable.
  - However, these patients collected 7 x 10^6 and 13.45 x 10^6 CD34+ cells over two and three days, respectively.
- The median number of CD34+ cells collected was 18.17 x 10^6 (mean: 21.90 x 10^6 cells; range: 4.35–55.5 x 10^6 cells [n = 38]).

*Figure 1. Total CD34+ cells collected*

- In two patients, the G-CSF dose was increased to 16 μg/kg, twice a day.
- All MM patients collected >10 x 10^6 CD34+ cells/kg (sufficient for tandem ASCT).
- The median time from the start of BED mobilization therapy to the first day of CD34 stem cell collection was 12 days (mean: 11.8 days; range: 9–15 days [n = 38]).
- Apheresis was started in 95% of patients between days 9 and 13. The median number of days of apheresis was one (mean: 1.3 days; range: 1–4 days [n = 38]).
- To date, 33 patients have undergone ASCT with BED mobilized cells and 100% have engrafted.
  - The median time to unsupported neutrophil counts ≥500/μL and platelet counts >20,000/μL post stem cell reinfusion was 15 days (mean: 14.8 days; range: 7–19 days [n = 33]) and 11 days (mean: 10.7 days; range: 8–15 days [n = 28]), respectively.
- In 33 patients, responses included a complete response in four patients, a partial response (PR) in two patients, stable disease in 23 patients, and progressive disease in four patients. (Table 1)
  - As expected, almost all patients experienced grade 3 or 4 thrombocytopenia, leukopenia, and lymphopenia.
  - Six serious AEs (SAEs) that were considered treatment-related occurred in five patients:
    - Grade 3: infection (n = 1), tumour lysis syndrome (n = 1), hypotension (n = 1), and neutropenic fever (n = 1);
    - Grade 2: atrial fibrillation (n = 1);
    - Grade 1: renal insufficiency (n = 1).
  - One patient died due to disease progression. This patient accounted for two of the six SAEs, the aspartate transaminase and bilirubin elevations, and was one of the two patients who required plerixafor for mobilization.
  - The original protocol of bendamustine, dexamethasone, and G-CSF (BDG) was modified after three patients were enrolled to include etoposide because BDG did not yield a predictable pattern of leukocyte nadir and recovery (median time to collection: 22 days). The first three patients were censored from the analysis; however, all three were successfully mobilized and collected.

<table>
<thead>
<tr>
<th>Responses</th>
<th>CR</th>
<th>VGPR (MM only)</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 33</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>23</td>
<td>4</td>
</tr>
</tbody>
</table>

CR = complete response; MM = multiple myeloma; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response
Key conclusions

■ Peripheral blood stem cell mobilization after BED:
  • Was safe and effective;
  • Did not impair platelet or neutrophil engraftment after ASCT;
  • Yielded predictable mobilization kinetics, while BDG did not;
  • Resulted in short collection durations;
  • Demonstrated a 100% success rate in mobilization of CD34+ cells sufficient for tandem ASCTs in all MM patients who met the enrollment eligibility criteria; and
  • Improved response in 18% of patients (≥PR).

■ Based on the results of this study, this regimen warrants further investigation.


Rodon P, et al. ASH 2013:1971

Bendamustine, bortezomib, and dexamethasone in elderly patients with multiple myeloma in first relapse: final analysis of the Intergroupe Francophone du Myelome 2009-01 trial

Background
Prognosis of relapses remains severe in elderly patients with multiple myeloma (MM). The Intergroupe Francophone du Myelome (IFM) 2009-01 trial evaluated the combination of bendamustine, bortezomib, and dexamethasone (BVD) in elderly patients with progressive MM on or after first-line treatment.1

Study design
• Patients with symptomatic MM in the phase II IFM 2009-01 trial were older than 65 years and either in first relapse or refractory to first-line treatment.
• Inclusion criteria included measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, serum creatinine level ≤ 250 mmol/L, aspartate aminotransferase and alanine aminotransferase ≤ 3 x upper limit of normal.
• Patients with any prior exposure to bortezomib or bendamustine were excluded.
• The BVD treatment regimen was given at the following dosing schedule:
  ◦ Bendamustine: 70 mg/m² intravenous (iv) on days 1 and 8;
  ◦ Bortezomib: 1.3 mg/m² iv on days 1, 8, 15, and 22; and
  ◦ Dexamethasone: 20 mg on days 1, 8, 15, and 22, every 28 days.
• Six cycles were administered. Responders were assigned to receive maintenance treatment with six additional cycles administered every two months.
• The primary objective was response rate. Response was evaluated according to IMWG criteria.
• The secondary objectives were time to best response, progression-free survival (PFS), overall survival (OS), and toxicity.

Key findings
• From March 2010 to July 2011, 83 patients were screened in 27 IFM centres. Of those screened, there were five screening failures, four patients with co-morbidities who did not receive treatment, and one patient who did not fulfill the inclusion criteria, leaving 73 patients who were analyzed.
The median time from diagnosis to inclusion was 29 months (range: 5–88 months).

The median age was 75.8 years (range: 66–86 years).

All patients received only one prior line of therapy: melphalan-prednisone (MP) (n = 12), MP-thalidomide (n = 42), lenalidomide-dexamethasone (n = 14), other regimens (n = 5).

The median number of treatment cycles administered was seven (range: 1–12).

The overall response rate was 69.8% (75.3% including minor responses). (Table 1)

Unfavourable predictive factors for response included:
- By univariate analysis, an ECOG PS of 2 (p = 0.004) or del(17p) (p = 0.03);
- By multivariate regression, an ECOG PS of 2 was identified as a discriminating factor for lower response rate (HR = 0.306 [95% CI: 0.16–0.59], p = 0.0004).

The median PFS was 10.8 months (95% CI: 7.0–18.2 months) and the median OS was 23 months (95% CI: 15.4–27.5 months).

At the time of data cutoff, 37 patients (50.6%) had died from MM (n = 31), sepsis (n = 5), and renal failure (n = 1).

Grade 3-4 adverse events are shown in Table 2, with the most common being sepsis (23.2%), neutropenia (20.5%), and thrombocytopenia (9.5%).

 Peripheral neuropathy grade >1 occurred in 16 patients, grade 2 occurred in 12 patients (preexisting in two), and grade 3 occurred in four patients.

Table 1. Response to treatment

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>10</td>
<td>13.6</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>12</td>
<td>16.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>29</td>
<td>39.7</td>
</tr>
<tr>
<td>Minor response</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>6.8</td>
</tr>
<tr>
<td>Progression</td>
<td>13</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Table 2. Adverse events grade 3-4

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>15</td>
<td>20.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
<td>9.5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>17</td>
<td>23.2</td>
</tr>
<tr>
<td>Heart diseases</td>
<td>4</td>
<td>5.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>5.4</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>3</td>
<td>4.1</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3</td>
<td>4.1</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>2</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Key conclusions

- The results of the IFM 2009-01 trial suggest that the addition of bendamustine to bortezomib plus dexamethasone improves the outcome of relapsed and refractory MM in elderly patients previously untreated with proteasome inhibitors, without inducing a significant increase in toxicity.

- This regimen could be the basis of future trials in this patient population.


Bendamustine, bortezomib, and dexamethasone shows substantial activity and manageable toxicity in patients with relapsed/refractory multiple myeloma

Background

In patients with multiple myeloma (MM), several studies have demonstrated the efficacy and tolerability of bendamustine either as monotherapy or in combination with new drugs. In particular, bortezomib has been shown to enhance the in vitro sensitivity of MM cells to bendamustine. At ASH 2013, Offidani and colleagues presented the results of their study in patients with relapsed/refractory MM treated with bendamustine, bortezomib, and dexamethasone (BVD).¹

Study design

- This was a prospective, single-arm, open-label, phase II study conducted in 21 Italian centres.
- Eligibility criteria included:
  - Patients of any age with relapsed/refractory MM;
  - Adequate cardiac, liver, and hematological function;
  - Not refractory to bortezomib;
  - Previously treated with no more than four lines of therapy.
- Patients were given the BVD regimen at the following dosing schedule:
  - Bendamustine: 70 mg/m², days 1 and 8 for cycles 1–4;
  - Bortezomib: 1.3 mg/m², days 1, 3, 8, and 11 in cycles 1 and 2, and on days 1, 8, 15, and 22 in cycles 3 and 4;
  - Dexamethasone: 20 mg, days 1, 2, 4, 5, 8, 9, 11, and 12 in cycles 1 and 2, and on days 1, 8, 15, and 22 in cycles 3 and 4.
- Patients achieving less than a partial response (PR) were taken off study. Patients obtaining at least a PR received two additional cycles (every 28 days) of induction therapy and consolidation with six cycles every 56 days.
- The primary endpoint was overall response rate (ORR; ≥PR) after four cycles of treatment.
- The secondary endpoints were toxicity, best response in responding patients following additional treatment cycles, time to progression (TTP), progression-free survival, overall survival (OS), time to next treatment, complete response (CR), very good partial response (VGPR), and time to response.

Key findings

- From March 2011 to June 2012, 75 patients were included in the study.
- A total of 36 patients were on protocol and 39 patients were off protocol (due to: no response [n = 15], disease progression [n = 11], death [n = 9], adverse events [AEs; n = 2], autologous stem cell transplantation [ASCT; n = 1], and withdrawn consent [n = 1]).
- Patients were a median age of 68 years (range: 41–85 years), 26.5% were International Staging System (ISS) stage III, 20% had IgA myeloma, and 9% had renal failure.
Patients had received a median of one prior line of therapy (range: 1–4), including alkylators (69%) and ASCT (44%).

All patients had received prior treatment with new drugs, including targeted agents such as thalidomide (57%), lenalidomide (54.5%), or bortezomib (46.5%). The ORR (≥PR) after four cycles was 71.5% (n = 50), including 11 (16%) patients with a CR, 13 (18.5%) with a VGPR, and 26 (37%) with a PR. (Table 1)

Also, 14 patients (20%) had stable disease while six (8.5%) had progressive disease.

At a median follow-up of 12 months:
- The median TTP was 16.5 months; (Figure 1)
- The median OS had not been reached; 78% of patients were alive at one year.

Patients who had received prior therapy with bortezomib plus lenalidomide had significantly reduced TTP compared with those who had not previously received either agent (9 vs. 17 months; p ≤0.001).

**Table 1. Response to therapy**

<table>
<thead>
<tr>
<th>Response</th>
<th>After 4 cycles n (%)</th>
<th>Best response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>11 (16)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>13 (18.5)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (37)</td>
<td>26 (37)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>14 (20)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (8.5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Overall response rate (≥PR)</td>
<td>50 (71.5)</td>
<td>54 (77)</td>
</tr>
</tbody>
</table>

PR = partial response

**Figure 1. Time to progression**

- The median OS had not been reached; 78% of patients were alive at one year.

- The median OS had not been reached; 78% of patients were alive at one year.
• TTP was similar between patients ≤70 vs. >70 years of age (16.5 vs. 16 months, respectively; \( p = 0.803 \)), whereas according to renal function, TTP was longer in patients without renal failure than in those with renal failure (17 vs. 4.5 months, respectively; \( p = 0.002 \)). (Figure 2)

• AEs led to therapy reduction in 15 (20%) patients (neuropathy, \( n = 8 \); thrombocytopenia, \( n = 7 \)) and to protocol discontinuation in eight (10.5%) patients (thrombocytopenia, \( n = 3 \); infection, \( n = 3 \); neuropathy, \( n = 1 \); and heart failure, \( n = 1 \)).

• The most frequent grade 3-4 AEs were thrombocytopenia (30.5%), neutropenia (18.5%), and anemia (12%).

• Grade 5 AEs of infection (\( n = 3 \)) and cardiac toxicity (\( n = 2 \)) were reported.

• Compared with patients ≤70 years of age, patients aged >70 years had a higher incidence of grade 3-4 thrombocytopenia (37% vs. 22%; \( p = 0.042 \)), severe infections (19% vs. 7%; \( p = 0.047 \)), and consequently a higher rate of dose reduction (34% vs. 9%; \( p = 0.007 \)) and therapy discontinuation (15% vs. 7%; \( p = 0.043 \)).

**Key conclusions**

- BVD is an effective regimen in relapsed/refractory MM patients because it elicits rapid, high (>70%), and good quality responses (i.e., more than a third of patients achieved CR + VGPR).

- BVD is a feasible and well-tolerated regimen provided that adapted therapy and adequate antibiotic prophylaxis are employed in patients older than 70 years of age.

Breast Cancer

Targeted Therapies Have Acceptable Safety Profiles and Improve Response Rates in Patients with Different Molecular Subtypes of Primary or Advanced Breast Cancer

The decision of which treatment strategy to use for patients with breast cancer is based on multiple factors, including tumour surface markers and clinical factors. Molecular techniques, including gene expression profiling, have helped to refine the classification of breast cancer, and to assess response to therapy and prognosis.¹ One molecular determinant of therapy is whether or not the tumour is human epidermal growth factor receptor 2-positive (HER2+).² A number of HER2-targeted therapies have been developed for patients with HER2+ tumours, including monoclonal antibodies (e.g., trastuzumab and pertuzumab), the monoclonal antibody-drug conjugate trastuzumab emtansine, and tyrosine kinase inhibitors (e.g., lapatinib and afatinib).

For patients with recurrent or metastatic breast cancer that is hormone receptor-positive (HR+), antiestrogen first-line treatment regimens, including the steroidal aromatase inhibitor exemestane, have shown significant disease control with better-tolerated toxicity than standard chemotherapy.³

The latest results from clinical trials investigating treatment for HER2+, and HR+/HER2-negative (HER2−) breast cancer, as well as a cost analysis of treatment, were presented at the 2013 San Antonio Breast Cancer Symposium (SABCS).

- The dual HER2 blockade of lapatinib plus trastuzumab appears to provide superior benefit (i.e., pathological complete response, event-free survival, and overall survival) than either agent alone in patients with HER2+/HR-negative tumours.
- The combination of pertuzumab, trastuzumab, and vinorelbine as first-line treatment of HER2+ locally advanced or metastatic breast cancer showed an acceptable safety profile with no new safety signals observed.
- The combination of everolimus plus exemestane in the BOLERO-2 trial significantly improved the overall response rate compared with placebo plus exemestane in patients with HR+, HER2− advanced breast cancer who had progressed during or after nonsteroidal aromatase inhibitor therapy.
- The benefit-risk profile of the combination of pertuzumab, trastuzumab, and docetaxel supports this regimen as the preferred therapy for patients with HER2+, first-line metastatic breast cancer from Asia and all other geographic regions.
- In a phase II trial, the combination of eribulin plus trastuzumab as first-line therapy for locally recurrent or metastatic HER2+ breast cancer resulted in an objective response rate of 71.2%, a median progression-free survival of 11.6 months, and an acceptable safety profile.
- A cost analysis of managing treatment-related adverse events from the perspective of Canadian public payers demonstrated that using trastuzumab emtansine for the treatment of HER2+ breast cancer resulted in considerable cost savings due to the improved safety profile compared with capecitabine plus lapatinib and trastuzumab plus docetaxel.
- The combination of afatinib (40 mg/day) plus vinorelbine (25 mg/m²/week) showed early signs of clinical activity in Japanese patients with confirmed refractory advanced/metastatic solid tumours.

The survival follow-up analysis of the NeoALTTO study: neoadjuvant lapatinib, trastuzumab, or their combination in HER2-positive breast cancer

Background
The NeoALTTO study demonstrated a significantly higher breast pathological complete response (pCR) rate with dual human epidermal growth factor receptor 2 (HER2) blockade using lapatinib and trastuzumab compared with single HER2 blockade using either lapatinib or trastuzumab (51.3% vs. 24.7% vs. 29.5%, respectively; \( p < 0.01 \) for both) in HER2-positive (HER2+) primary breast cancer (BC).

The survival follow-up analysis of the NeoALTTO study, including event-free survival (EFS) and overall survival (OS), was presented at SABCS 2013.\(^1\)

Study design
- From January 2008 to December 2009, 455 patients were randomized from 99 participating sites in 23 countries.
- Patients were randomized to receive one of the following for a total of 6 weeks:
  - Lapatinib 1,500 mg/day (n = 154);
  - Trastuzumab 4 mg/kg intravenous (iv) loading dose followed by 2 mg/kg iv weekly (n = 149); or
  - Lapatinib 1,000 mg/day plus trastuzumab as above (n = 152).
- After this biological window, patients continued on the same targeted therapy plus weekly paclitaxel 80 mg/m\(^2\) for a further 12 weeks, until definitive surgery (i.e., a total neoadjuvant therapy duration of 18 weeks).
- After surgery, patients received three cycles of adjuvant fluorouracil, epirubicin, and cyclophosphamide, followed by the same targeted therapy as in the biological window of the neoadjuvant phase for a further 34 weeks (i.e., to complete 52 weeks of anti-HER2 therapy), with ongoing follow-up planned until 10 years after the last randomized patient.
- Secondary objectives included EFS and OS, following a protocol amendment:
  - Amendments were made to the protocol secondary objectives (released in May 2013):
    - Disease-free survival was replaced by EFS from randomization;
    - OS from surgery was correspondingly replaced with OS from randomization; and
    - Examination of the association between these survival endpoints and locoregional pCR (pT0/is pN0) was added as a secondary objective.
- The analyses of EFS and OS by treatment arm are underpowered and are intended to be descriptive.
  - Assuming a hazard ratio of 0.78 for the combination group, the study has a power of approximately 20%.
  - Analysis was adjusted for stratification factors (hormone receptor [HR] status, tumour size, lymph node status, and breast conservation).
- The clinical cutoff date for the first planned analysis of these secondary objectives was on May 26, 2013 (with a database freeze on November 13, 2013), three years after the date of the last breast cancer surgery.

Study design

\[ \begin{align*}
&\text{Lapatinib} & 1,500 \text{ mg/d} & \text{Paclitaxel} & 80 \text{ mg/m}^2 \\
&\text{Trastuzumab} & 4 \text{ mg/kg} & \rightarrow & 2 \text{ mg/kg} & \text{Paclitaxel} & 80 \text{ mg/m}^2 \\
&\text{Lapatinib} & 1,000 \text{ mg/d}* & \text{Paclitaxel} & 80 \text{ mg/m}^2 \\
&\text{Trastuzumab} & 4 \text{ mg/kg} & \rightarrow & 2 \text{ mg/kg} & \\
\end{align*} \]

\[ \begin{align*}
&\text{Lapatinib} & 1,500 \text{ mg/d} & \\
&\text{Trastuzumab} & 8 \text{ mg/kg} & \rightarrow & 6 \text{ mg/kg} \\
&\text{Lapatinib} & 1,000 \text{ mg/d} & \\
&\text{Trastuzumab} & 8 \text{ mg/kg} & \rightarrow & 6 \text{ mg/kg} \\
\end{align*} \]

\[ d = \text{day} \quad \text{FEC} = \text{ fluorouracil, epirubicin, cyclophosphamide} \]

*Amendment: October 2, 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel; 54/152 had protocol-driven reduction.
Key findings

- Median clinical follow-up was 3.77 years (95% CI: 3.72–3.98 years), and median survival follow-up was 3.84 years (95% CI: 3.77–3.98 years).
- Stratification factors were well balanced between the treatment arms.
- Lapatinib completion in the lapatinib-containing arms of the study:
  - Approximately two thirds of patients were able to complete lapatinib treatment in the neoadjuvant or adjuvant phases;
  - Discontinuation in the neoadjuvant and the adjuvant phases were primarily due to adverse events, not progression or recurrence.
- Trastuzumab completion in the trastuzumab-containing arms of the study:
  - At least 90% of patients completed treatment in the neoadjuvant phase and approximately 80% of patients completed it in the adjuvant phase.
- Results of the EFS analyses by treatment arm showed: (Figure 1)
  - For all patients, the hazard ratios comparing either lapatinib plus trastuzumab or lapatinib alone with trastuzumab alone were 0.78 ($p = 0.33$) and 1.06 ($p = 0.81$), respectively;
  - For all patients, the three-year EFS rate in the lapatinib plus trastuzumab arm was 84%, compared with 78% and 76% in the lapatinib and trastuzumab arms, respectively;
  - There was little difference between treatment arms in the EFS curves for patients with HR-positive (HR+) BC. However, the combination of lapatinib plus trastuzumab showed a potential advantage over lapatinib or trastuzumab alone in patients with HR-negative (HR–) BC.

![Figure 1. Event-free survival analysis](image)

CI = confidence interval; EFS = event-free survival; HR = hormone receptor; yr = year
Results of the OS analyses by treatment arm are shown in Figure 2.

- The three-year OS rate for all patients in the lapatinib plus trastuzumab arm was 95%, compared with 93% and 90% in the lapatinib and trastuzumab arms, respectively.
- At this time, there was little difference between treatment arms in the OS curves for patients with HR+ or HR- BC.
- Results of the EFS and OS analyses by pCR status, independent of treatment arm, showed:
  - Patients who had a pCR had much improved EFS and OS than patients who did not experience a pCR (EFS: hazard ratio = 0.38, \( p = 0.0003 \); OS: hazard ratio = 0.35, \( p = 0.005 \)) (Figures 3 and 4);
  - For patients who had a pCR (vs. no pCR), there was a larger divergence towards improvement in the EFS and OS curves for those with HR- BC than for those with HR+ BC (EFS for HR- BC by pCR: hazard ratio = 0.34, \( p = 0.001 \); OS: hazard ratio = 0.29, \( p = 0.003 \)).
- By treatment arm, patients who experienced a pCR had improved EFS and OS compared with patients who did not experience a pCR, in all three treatment groups.
- The main differences in adverse events (AEs) by treatment arm were (lapatinib vs. trastuzumab vs. lapatinib plus trastuzumab, %):
  - Diarrhea: 83 vs. 35 vs. 87 (severe AEs: 25 vs. 3 vs. 26);
  - Hepatobiliary AEs: 50 vs. 28 vs. 48 (severe AEs: 22 vs. 7 vs. 11); and
  - Rash: 70 vs. 36 vs. 68 (severe AEs: 5 vs. <1 vs. 5).
- Very few cardiac events were recorded; primary cardiac events (i.e., severe congestive heart failure) occurred in 0%, 0.68%, and 1.34% of patients in the lapatinib, trastuzumab, and combination of lapatinib plus trastuzumab arms, respectively.

Figure 2. Overall survival analysis

CI = confidence interval; HR = hormone receptor; OS = overall survival; yr = year

*Tests for interaction according to HR status: lapatinib + trastuzumab vs. lapatinib, \( p = 0.19 \); lapatinib vs. trastuzumab, \( p = 0.65 \); trastuzumab vs. lapatinib + trastuzumab, \( p = 0.30 \).
Key conclusions

- Patients who achieved pCR had significantly better EFS and OS compared with no pCR from the landmark, irrespective of treatment arm.

- The NeoALTTO trial was powered to detect pCR differences but underpowered to detect moderate differences in EFS and OS.

- The ALTTO trial will provide a robust answer on the effect of dual HER2 blockade on long-term outcome.

- At approximately four years (median follow-up), and in line with previous observations, dual HER2 blockade appears to provide superior benefit (pCR, EFS, OS) in patients with HER2+/HR– tumours. A follow-up analysis is planned in 2.5 years.

- This trial provides further evidence that HER2+/HR– and HER2+/HR+ subgroups are two different diseases.

- AEs were consistent with known safety profiles of lapatinib and/or trastuzumab.

Safety of pertuzumab plus trastuzumab plus vinorelbine for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer

**Background**

Human epidermal growth factor receptor 2 (HER2) over-expression or amplification occurs in approximately 20% of breast cancers and is associated with poorer prognosis compared with HER2-normal/nonamplified breast cancer. Trastuzumab and pertuzumab are humanized monoclonal antibodies that bind to different HER2 subdomains, inhibiting HER2 signaling. In a previous study (HERNATA1), first-line treatment of patients with HER2-positive (HER2+) metastatic breast cancer (MBC) with vinorelbine plus trastuzumab had similar efficacy results to treatment with docetaxel plus trastuzumab, but with fewer adverse events (AEs). In a recent study (CLEOPATRA2), pertuzumab plus trastuzumab and docetaxel significantly improved progression-free survival (PFS) and overall survival (OS) compared with trastuzumab plus docetaxel in patients with HER2+ first-line MBC.

The objective of the VELVET study was to investigate the efficacy and safety of pertuzumab plus trastuzumab and vinorelbine for first-line treatment of HER2+ MBC. At SABCS 2013, Perez and colleagues presented the interim safety data for cohort 1.³

**Study design**

- VELVET is a multicentre, open-label, single-arm, two-cohort, phase II study.
- The key eligibility criteria for patients in this study were:
  - HER2+ MBC or locally advanced breast cancer (LABC);
  - Eastern Cooperative Oncology Group performance status of 0 or 1;
  - Left ventricular ejection fraction (LVEF) of ≥55% at baseline;
  - No prior systemic nonhormonal anticancer therapy in the metastatic setting;
  - No prior breast cancer treatment with anti-HER2 agents, except trastuzumab and/or lapatinib in the (neo)adjuvant setting (but no disease progression while on treatment);
  - Disease-free interval ≥6 months from completion of (neo)adjuvant nonhormonal therapy to disease recurrence.
- Patients received one of two treatment regimens:
  - Patients in cohort 1 received pertuzumab, trastuzumab, and vinorelbine from separate infusion bags; or
  - Patients in cohort 2, from cycle 2 onwards, received pertuzumab and trastuzumab from a single infusion bag, followed by vinorelbine.
- Study drugs for cohort 1 were administered as follows:
  - Pertuzumab: initial dose of 840 mg on day 1 of cycle 1, followed by 420 mg on day 1 of each subsequent cycle, every three weeks (q3w);
  - Trastuzumab: initial dose of 8 mg/kg on day 2 of cycle 1, followed by 6 mg/kg on day 1 or 2 of each subsequent cycle, q3w;
  - Vinorelbine: initial dose of 25 mg/m² on day 2 and day 9 of cycle 1, followed by 30–35 mg/m² on day 1 or 2 and day 8 or 9 of each subsequent cycle, q3w.
- Patients received all study drugs until disease progression or unacceptable toxicity. At the discretion of the investigator, pertuzumab/trastuzumab, and/or vinorelbine, could be stopped early.
- The interim safety data from cohort 1 were presented, which had a data cutoff point of September 10, 2013.
- The primary endpoint of the study was objective response rate, assessed by best overall response.
- The secondary endpoints were PFS, time to progression, OS, time to response, duration of response, safety and tolerability, and health-related quality of life.

**Key findings**

- Patients in cohort 1 (N = 106) had the following baseline characteristics:
  - Median age (range), years: 56 (30–82);
  - Median interval (range) between initial diagnosis of breast cancer and enrollment, years: 2.6 (0–24);
  - Disease stage III/IV at initial diagnosis, %: 29.2/33.0;
  - Disease stage at advanced BC diagnosis (LABC/MBC), %: 13.2/86.8;
  - Prior systemic cancer therapy, %: 61.3
  - Prior trastuzumab therapy (neoadjuvant/adjuvant), % 10.4/34.0.
• At the time of data cutoff, treatment was ongoing for 51 patients, and 55 patients had discontinued all three drugs, 49 of whom were still in follow-up.

• A median number of 12.0 cycles of pertuzumab and trastuzumab, and 9.0 cycles of vinorelbine were received. Four patients completed less than three cycles of study treatment.

  - The median dose intensity of vinorelbine during the first six treatment cycles was 14.99 (6.4–23.1) mg/m²/week.

• The proportion of patients that had discontinued pertuzumab, trastuzumab, and vinorelbine due to an adverse event (AE)/unacceptable toxicity was 7.5%, 5.7%, and 21.7%, respectively.

• The proportion of patients that had discontinued pertuzumab/trastuzumab and vinorelbine due to disease progression was 33.0% and 27.4%, respectively.

• The incidences of all-grade AEs and grade ≥3 AEs are presented in Table 1 and Table 2, respectively.

• Thirty patients (28.3%) experienced serious AEs. Serious AEs that occurred in ≥2 patients were: febrile neutropenia, hypersensitivity, abdominal pain, drug hypersensitivity (i.e., only when both AE and drug were reported), and pyrexia.

• The incidence of febrile neutropenia at each of the first 17 cycles, plus concomitant granulocyte-colony stimulating factor administration, is shown in Figure 1.

• There was no overall decrease in mean LVEF from baseline. (Figure 2A)

• The proportion of patients with LVEF declines to <50% at cycles 3, 6, 9, 12, and 15 was 1.1%, 2.5%, 2.8%, 3.8%, and 6.7%, respectively; the profile over time of these patients is shown in Figure 2B.

• At the time of data cutoff, two patients had died due to an AE: one had a myocardial infarction and one had septic shock; neither event was considered to be study-drug related.

• A cross-study comparison of the incidence of selected AEs suggests that the safety profile to date in VELVET compares favourably with those seen previously in CLEOPATRA and HERNATA, although it is difficult to compare results from different clinical trials. (Table 3)

### Table 1. Adverse events (all grades) in ≥20% of patients

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>All grades (N = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with ≥1 event</td>
<td>105 (99.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52 (49.1)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>50 (47.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>45 (42.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>34 (32.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (31.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>32 (30.2)</td>
</tr>
<tr>
<td>Chills</td>
<td>29 (27.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (27.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>28 (26.4)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>23 (21.7)</td>
</tr>
</tbody>
</table>

*Pooled ‘neutropenia’ and ‘neutrophil count decreased’ preferred terms.

### Table 2. Adverse events (grade ≥3) in ≥3 patients

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>All grades (N = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with ≥1 event</td>
<td>56 (52.8)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td>Leukopenia†</td>
<td>9 (8.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.8)</td>
</tr>
</tbody>
</table>

*Pooled ‘neutropenia’ and ‘neutrophil count decreased’ preferred terms.
†Pooled ‘leukopenia’ and ‘white blood cell count decreased’ preferred terms.
Figure 1. Incidences of febrile neutropenia and concomitant G-CSF administration

![Graph showing the incidences of febrile neutropenia and concomitant G-CSF administration.]

*G-CSF = granulocyte-colony stimulating factor

Figure 2. (A) Change in mean LVEF (%), 95% CI from baseline at each treatment cycle (B) LVEF (%) at each treatment cycle for patients with LVEF declines to <50%

![Graphs showing the change in mean LVEF and LVEF at each treatment cycle.]

BL = baseline; LVEF = left ventricular ejection fraction; UNS = unscheduled assessment

*Dotted line denotes baseline in A and 50% threshold in B

Table 3. Cross-study comparison of the VELVET, CLEOPATRA, and HERNATA trials

<table>
<thead>
<tr>
<th></th>
<th>VELVET</th>
<th>CLEOPATRA*</th>
<th>HERNATA†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of chemotherapy cycles, median (range)</td>
<td>9 (0–21)</td>
<td>8 (1–35)</td>
<td>10.5 (2–42)</td>
</tr>
<tr>
<td>Chemotherapy dose intensity, median (mg/m²/week)</td>
<td>14.99‡</td>
<td>24.6</td>
<td>NR</td>
</tr>
<tr>
<td>Incidence of selected AEs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49.1</td>
<td>66.8</td>
<td>11.6†</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23.6</td>
<td>60.9</td>
<td>NR</td>
</tr>
<tr>
<td>Neutropenia (grade ≥3)</td>
<td>23.6**</td>
<td>48.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5.7</td>
<td>13.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Leukopenia (grade ≥3)</td>
<td>8.5⁰</td>
<td>12.3</td>
<td>21</td>
</tr>
</tbody>
</table>

AEs = adverse events; NR = not reported
*Pertuzumab, trastuzumab, and docetaxel arm; †Trastuzumab and vinorelbine arm; ‡First six cycles only; ††Grade 2–4 only, grade 1 toxicities NR; **Pooled ‘neutropenia’ and ‘neutrophil count decreased’ preferred terms; ‰Pooled ‘leukopenia’ and ‘white blood cell count decreased’ preferred terms.
Key conclusions

- There was an acceptable safety profile with the combination of pertuzumab, trastuzumab, and vinorelbine, and no new safety signals were observed.
- The incidences of alopecia and of grade ≥3 hematologic AEs are currently lower than those observed previously with trastuzumab plus vinorelbine\(^1\) or with pertuzumab plus trastuzumab plus docetaxel.\(^2\)
- Based on encouraging interim safety data, enrollment into cohort 2 began in April 2013 and completed in September 2013. Final efficacy data from both cohorts are expected in 2015.


Burris H, et al. SABCS 2013:P2-16-17

Characterization of response to everolimus in BOLERO-2: a phase III trial of everolimus plus exemestane in postmenopausal women with HR-positive, HER2-negative advanced breast cancer

**Background**

The BOLERO-2 trial evaluated the oral mammalian target of rapamycin inhibitor, everolimus (EVE), in combination with the steroidal aromatase inhibitor, exemestane (EXE), in postmenopausal women with hormone-receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) whose disease relapsed or progressed following a nonsteroidal aromatase inhibitor (NSAI). The results demonstrated that combining EVE + EXE more than doubled median progression-free survival (PFS) compared with placebo plus exemestane (PBO + EXE) without compromising patients’ quality of life. Patients also achieved responses per Response Evaluation Criteria in Solid Tumors (RECIST) during treatment with EVE + EXE. At SABCS 2013, Burris and colleagues presented the analysis of the secondary endpoints from the BOLERO-2 trial.\(^1\)

**Study design**

- BOLERO-2 was a multicentre, international, double-blind, randomized, phase III trial.
- Inclusion criteria allowed:
  - Disease recurrence during or ≤12 months after completing adjuvant endocrine therapy;
  - One line of prior chemotherapy for advanced BC;
  - Disease progression within one month after treatment for advanced BC.
- Patients received open-label EXE 10 mg/day and were randomly assigned 2:1 to either EVE 25 mg/day or PBO.
- Randomization was stratified according to the presence of visceral metastasis (yes vs. no) and sensitivity to previous hormonal therapy (yes vs. no).
- Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal.
- No crossover was allowed after disease progression.
- The primary endpoint was PFS by local assessment, defined as the time from randomization to first documented progression or death from any cause.
- Secondary endpoints included:
  - Overall response rate (ORR; complete response [CR] or partial response [PR]);
  - Clinical benefit rate (best response of CR, PR, or stable disease ≥24 weeks);
  - Time to response (TTR; from date of randomization until first documented response); and
  - Duration of overall response (DOR) for patients with a CR or PR (from documented response to documented progression or disease-related death).

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In addition, best percentage change from baseline in the sum of the longest diameters of target lesions was assessed.

Tumours were evaluated by RECIST version 1.0 based on investigator assessment (local radiologic assessment) and supported by independent radiology committee (central radiologic assessment).

Adverse events (AEs) were monitored continuously throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

**Key findings**

- Patient characteristics at baseline were well balanced between the two treatment groups.
  - A broad range of the HR+ advanced BC disease spectrum was represented.
  - The majority of patients had ≥2 metastatic sites.
  - The objective response rate by local tumour assessment at the 18-month median follow-up was significantly higher in the EVE + EXE group compared with the PBO + EXE group (12.6% [n = 61] vs. 1.7% [n = 4], respectively; p <0.0001). (Figure 1)
  - The objective response rate was confirmed by central radiology review (12.6% [n = 61] vs. 2.1% [n = 5], respectively).
  - The median DOR by Kaplan-Meier estimate was 10.5 months (95% CI: 8.2–21.9 months) for the EVE + EXE group and 6.9 months (95% CI: 4.2–6.9 months) for the PBO + EXE group. (Figure 2)
  - Median DOR was approximately 3.6 months longer in the EVE + EXE group than in the PBO + EXE group.

**Figure 1. Best overall tumour response by local assessment (ITT population)**

- EVE + EXE (n = 485)
- PBO + EXE (n = 239)

CBR = clinical benefit rate; CR = complete response; EVE = everolimus; EXE = exemestane; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ORR = objective response rate; OS = overall survival; PBO = placebo; PFS = progression-free survival; PK = pharmacokinetics; QoL = quality of life
• The overall median TTR could not be calculated using the Kaplan-Meier method in the overall population because the proportion of patients who had a tumour response in each treatment group was low. (Figure 3)
  - Among the subgroup of patients with a CR or PR, the median TTR was 2.8 months (range, 1.2–19.4 months) in the EVE + EXE group and 5.0 months (range, 1.3–12.2 months) in the PBO + EXE group.
• Decreases from baseline in the sum of the longest target lesion diameters by local assessment were shown among the following subgroups of patients:
  - Patients with measurable disease: 71% of evaluable patients in the EVE + EXE group (n = 318 patients with valid data) and 30% of evaluable patients in the PBO + EXE group (n = 155 patients with valid data) had tumour reduction. (Table 1)
  - Patients with baseline visceral disease: 69% of these patients in the EVE + EXE group (n/N = 224/271 patients with valid data) and 27% of these patients in the PBO + EXE group (n/N = 107/135 patients with valid data) had tumour reduction.
  - Patients who had neoadjuvant and/or adjuvant treatment as last prior therapy: 79% of these patients in the EVE + EXE group (n/N = 62/100 patients with valid data) and 30% of these patients in the PBO + EXE group (n/N = 23/37 patients with valid data) had tumour reduction.
Table 1. Best percentage change from baseline in the sum of the longest target lesion diameters by local assessment

<table>
<thead>
<tr>
<th>Best percentage change</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVE + EXE (n = 318)</td>
</tr>
<tr>
<td>Decrease from baseline</td>
<td>225 (70.8)</td>
</tr>
<tr>
<td>No change from baseline</td>
<td>27 (8.5)</td>
</tr>
<tr>
<td>Increase from baseline</td>
<td>40 (12.6)</td>
</tr>
<tr>
<td>Change from baseline; contradicts overall lesion response of PD</td>
<td>26 (8.2)</td>
</tr>
</tbody>
</table>

EVE = everolimus; EXE = exemestane; PBO = placebo; PD = progressive disease

Key conclusions

- The combination of EVE + EXE significantly improved the ORR compared with PBO + EXE in patients with HR+, HER2– advanced BC progressing during or after NSAI therapy.

  - Greater than two-thirds of patients treated with EVE + EXE experienced tumour shrinkage during treatment.
  - Tumour shrinkage was also observed with EVE + EXE treatment in subsets of patients with visceral metastases at baseline or patients who had neoadjuvant and/or adjuvant therapy as their last treatment before study entry.

- Median DOR was longer in patients treated with EVE + EXE (10.5 months) compared with PBO + EXE (6.9 months). However, only four patients responded in the PBO + EXE group.

- These results support combining EVE + EXE to elicit objective response and improve clinical outcomes in HR+, HER2– advanced BC recurring/progressing on or after NSAI therapy.


Swain SM, et al. SABCS 2013:P4-12-10

Safety of pertuzumab with trastuzumab and docetaxel in patients from Asia with HER2-positive metastatic breast cancer: results from the phase III trial CLEOPATRA

Background

In the phase III trial CLEOPATRA, patients with human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) were treated with pertuzumab, trastuzumab, and docetaxel, resulting in significant improvements in progression-free survival (PFS) and overall survival (OS) compared with placebo plus trastuzumab plus docetaxel. Adverse events (AEs) were generally balanced between groups. However, the incidence of febrile neutropenia was almost doubled in patients treated in the pertuzumab arm compared with the placebo arm. An analysis of febrile neutropenia by geographic region showed that, among patients from Asia, 12% in the placebo arm and 26% in the pertuzumab arm experienced febrile neutropenia, whereas in all other geographic regions the incidence was no more than 10% in either treatment arm. The objective of this study was to investigate the safety profile of the study combinations and the exposure to docetaxel in patients from Asia compared with patients from all other geographic regions.1
Study design

- CLEOPATRA was a double-blind, placebo-controlled, international phase III study.
- Patient eligibility criteria included the following:
  - HER2+ locally recurrent, unresectable, or MBC;
  - No prior chemotherapy or biologic therapy for metastatic disease;
  - One hormonal treatment regimen for MBC before randomization allowed;
  - Eastern Cooperative Oncology Group performance status 0 or 1;
  - Left ventricular ejection fraction ≥ 50% at baseline.
- Patients were randomized to receive either:
  - Placebo arm: placebo, trastuzumab, and docetaxel; or
  - Pertuzumab arm: pertuzumab, trastuzumab, and docetaxel.
- Study drugs were administered intravenously on a 3-weekly schedule.
  - Pertuzumab/placebo: 840 mg initial dose, 420 mg subsequent doses.
  - Trastuzumab: 8 mg/kg initial dose, 6 mg/kg subsequent doses.
- Treatment with pertuzumab/placebo and trastuzumab was given until disease progression or unacceptable toxicity.
- Docetaxel: initiated at 75 mg/m².
  - Dose escalation to 100 mg/m² was allowed if tolerated.
  - Two dose reductions by 25% to 75 mg/m² and 55 mg/m² were allowed to manage toxicities.
- Use of granulocyte-colony-stimulating factors (G-CSFs) was allowed for the treatment of febrile neutropenia and as prophylaxis as per the American Society of Clinical Oncology guidelines. Docetaxel dose reductions were the preferred measure for prevention of febrile neutropenia in subsequent cycles.
- At least six cycles of docetaxel were recommended; fewer cycles were allowed for disease progression or unacceptable toxicity, more cycles were allowed at the discretion of the investigator.
- The primary endpoint was PFS by independent assessment.
- Secondary endpoints included OS, PFS by investigator assessment, objective response rate, and safety.
- AEs were monitored continuously and graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0.
- Tumour assessments were performed every nine weeks by the investigator and an independent review facility.
- Data cutoff was in May 2011 except for the OS analysis with a data cutoff in May 2012.

Key findings

- Patients (N = 808) were enrolled from 25 countries in Asia, Europe, North America, and South America (Europe, North America, and South America are referred to as “other regions”). Participating countries from Asia were China (including Hong Kong), Japan, Korea, the Philippines, Singapore, and Thailand.
• A total of 128 and 125 patients in the placebo and pertuzumab arms, respectively, were from Asia.

• The median time on study treatment was 11.8 months for patients in the placebo arm and 18.1 months for patients in the pertuzumab arm.

• The proportion of patients who underwent a docetaxel dose escalation to 100 mg/m² was 2.4% of those from Asia vs. 18.7% of those from other regions. (Table 1)

• Docetaxel dose reductions below 75 mg/m² were carried out in 47.0% of patients from Asia compared with 13.4% of patients from other regions.

• AEs (all grades) that were reported with an incidence of at least 25% in patients from Asia and the incidences of febrile neutropenia and left ventricular systolic dysfunction are presented in Table 2.

• The incidence of febrile neutropenia was 11.7% in the placebo arm vs. 25.6% in the pertuzumab arm in patients from Asia.

• Similarly, the incidence of mucosal inflammation was doubled in the pertuzumab arm (36.8%) compared with the placebo arm (18.0%) in patients from Asia.

• To analyze whether the incidence of febrile neutropenia was associated with patient weight and height, the rates of febrile neutropenia were compared by weight, body surface area, and body mass index quartiles (data not shown).

• There was no trend for patients in the lower quartiles, irrespective of geographic region and treatment received, to be more likely to experience febrile neutropenia than patients in the upper quartiles.

• Exploratory analyses of PFS and OS by region supported the results for the whole intention-to-treat population with hazard ratios being similar. (Figure 1)

---

Table 1. Exposure to docetaxel

<table>
<thead>
<tr>
<th></th>
<th>Other regions</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo arm</td>
<td>Pertuzumab arm</td>
</tr>
<tr>
<td></td>
<td>(n = 269)</td>
<td>(n = 282)</td>
</tr>
<tr>
<td>Median number of all study treatment cycles (range)</td>
<td>15.0 (1–50)</td>
<td>18.0 (1–56)</td>
</tr>
<tr>
<td>Median number of docetaxel cycles (range)</td>
<td>8.0 (1–27)</td>
<td>7.0 (1–35)</td>
</tr>
<tr>
<td>Median docetaxel dose intensity, mg/m²/week</td>
<td>25.0</td>
<td>24.7</td>
</tr>
<tr>
<td>Docetaxel dose escalation to 100 mg/m², n (%)</td>
<td>56 (20.8)</td>
<td>47 (16.7)</td>
</tr>
<tr>
<td>Docetaxel dose reduction to &lt;75 mg/m², n (%)</td>
<td>32 (11.9)</td>
<td>42 (14.9)</td>
</tr>
<tr>
<td>1 dose reduction to &lt;75 mg/m²</td>
<td>31 (11.5)</td>
<td>39 (13.8)</td>
</tr>
<tr>
<td>2 dose reductions to &lt;75 mg/m²*</td>
<td>1 (0.4)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Docetaxel permanently discontinued, n (%)</td>
<td>97 (36.1)</td>
<td>78 (27.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>172 (63.9)</td>
<td>204 (72.3)</td>
</tr>
<tr>
<td>≥6 cycles of docetaxel completed, n/N (%)</td>
<td>166/172 (96.5)</td>
<td>194/204 (95.1)</td>
</tr>
<tr>
<td>Reason for discontinuation, n/N (%)</td>
<td>125/172 (72.7)</td>
<td>144/204 (70.6)</td>
</tr>
<tr>
<td>Standard practice</td>
<td>37/172 (21.5)</td>
<td>47/204 (23.0)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>2/172 (1.2)</td>
<td>4/204 (2.0)</td>
</tr>
<tr>
<td>Refused treatment</td>
<td>8/172 (4.7)</td>
<td>9/204 (4.4)</td>
</tr>
</tbody>
</table>

*Includes patients with initial docetaxel dose escalation to 100 mg/m² followed by two subsequent dose reductions.
Table 2. AEs (all grades) reported in ≥25% of patients from Asia plus AEs of special interest

<table>
<thead>
<tr>
<th>Number of patients with event, n (%)</th>
<th>Other regions</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo arm  (n = 269)</td>
<td>Pertuzumab arm (n = 282)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>AEs all grades</td>
<td>264 (98.1)</td>
<td>281 (99.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>118 (43.9)</td>
<td>179 (63.5)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>156 (58.0)</td>
<td>175 (62.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>123 (45.7)</td>
<td>141 (50.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>53 (19.7)</td>
<td>52 (18.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>42 (15.6)</td>
<td>79 (28.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>110 (40.9)</td>
<td>120 (42.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42 (15.6)</td>
<td>39 (13.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>89 (33.1)</td>
<td>104 (36.9)</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>39 (14.5)</td>
<td>44 (15.6)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>76 (28.3)</td>
<td>54 (19.1)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>38 (14.1)</td>
<td>50 (17.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>56 (20.8)</td>
<td>29 (10.3)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>56 (20.8)</td>
<td>67 (23.8)</td>
</tr>
<tr>
<td>Edema</td>
<td>17 (6.3)</td>
<td>13 (4.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>62 (23.0)</td>
<td>66 (23.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24 (8.9)</td>
<td>32 (11.3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15 (5.6)</td>
<td>24 (8.5)</td>
</tr>
<tr>
<td>LVSD</td>
<td>27 (10.0)</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td>Use of G-CSF to treat febrile neutropenia, n/N (%)</td>
<td>8/15 (53.3)</td>
<td>11/24 (45.8)</td>
</tr>
<tr>
<td>Subsequent G-CSF prophylaxis in patients with febrile neutropenia, n/N (%)</td>
<td>6/15 (40.0)</td>
<td>3/24 (12.5)</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>194 (72.1)</td>
<td>199 (70.6)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>69 (25.7)</td>
<td>82 (29.1)</td>
</tr>
<tr>
<td>AEs resulting in death</td>
<td>9 (3.3)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>AEs resulting in dose modification/interruption</td>
<td>127 (47.2)</td>
<td>147 (52.1)</td>
</tr>
<tr>
<td>AEs resulting in discontinuation of all study treatment*</td>
<td>15 (5.6)</td>
<td>21 (7.4)</td>
</tr>
</tbody>
</table>

Adverse events highlighted in beige were reported with an incidence at least twice as high in patients from Asia compared with patients from other regions.

*Pertuzumab/placebo plus trastuzumab plus docetaxel or pertuzumab/placebo plus trastuzumab.

AEs = adverse events; G-CSF = granulocyte colony-stimulating factor; LVSD = left ventricular systolic dysfunction

**Figure 1. Independently-assessed progression-free survival and overall survival**

<table>
<thead>
<tr>
<th>Progression-free survival</th>
<th>n</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>808</td>
<td>0.63</td>
<td>0.52–0.76</td>
</tr>
<tr>
<td>Asia</td>
<td>253</td>
<td>0.68</td>
<td>0.48–0.95</td>
</tr>
<tr>
<td>Other regions</td>
<td>555</td>
<td>0.61</td>
<td>0.48–0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival*</th>
<th>n</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>808</td>
<td>0.66</td>
<td>0.52–0.84</td>
</tr>
<tr>
<td>Asia</td>
<td>253</td>
<td>0.64</td>
<td>0.41–1.00</td>
</tr>
<tr>
<td>Other regions</td>
<td>555</td>
<td>0.66</td>
<td>0.50–0.89</td>
</tr>
</tbody>
</table>

The analyses of progression-free and overall survival were unstratified.

*Data cutoff for the overall survival analyses was in May 2012.

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat
Key conclusions

■ The higher overall incidence of AEs in patients from Asia did not result in a higher study treatment discontinuation rate due to AEs (Asia: 4.0%; other regions: 6.5%).
  • This suggests that dosing guidelines and support measures were successfully applied.
■ The median number of all study treatment and docetaxel cycles was not reduced in patients from Asia; at least 95% of patients received a minimum of six cycles of docetaxel.
■ Docetaxel dose reductions below 75 mg/m² occurred in 47% of patients from Asia compared with 13% of patients from other regions. However, this did not adversely affect efficacy in patients from Asia, with PFS and OS being comparable with that of patients from other regions.
  • A reduction in the docetaxel starting dose should be considered in patients from Asia.
■ Overall, the benefit-risk profile of pertuzumab plus trastuzumab plus docetaxel supports this regimen as the preferred therapy for patients with HER2+ first-line MBC from Asia and all other geographic regions.

Reference:

Wilks S, et al. SABCS 2013:P4-12-12

Phase II, multicentre, single-arm study of eribulin mesylate plus trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer

Background
Eribulin mesylate is a nontaxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs. It has demonstrated a survival benefit relative to commonly used agents in women with metastatic breast cancer (MBC) who have previously received at least two chemotherapeutic regimens for metastatic disease. At SABCS 2013, Swain and colleagues presented final data from a phase II study that evaluated efficacy and safety of eribulin plus trastuzumab as first-line therapy for patients with locally advanced or metastatic human epidermal growth factor receptor 2-positive (HER2+) breast cancer.1

Study design
• This was a multicentre, single-arm, phase II trial of eribulin in combination with trastuzumab in women with HER2+ MBC.
• Patients received six cycles of eribulin mesylate 1.4 mg/m² intravenous (iv) infusion over 2 to 5 minutes on days 1 and 8 of each 21-day cycle and trastuzumab 8 mg/kg iv over 90 minutes on day 1 of cycle 1. Thereafter, trastuzumab 6 mg/kg was infused over 30 minutes on day 1 of each subsequent 21-day cycle.
  • Dose reductions for eribulin, but not for trastuzumab, were permitted; eribulin could be continued as monotherapy if trastuzumab was discontinued.
• The primary endpoint was objective response rate (ORR), defined as the proportion of subjects who achieved a complete response (CR) plus those who achieved a partial response (PR), based on Response Evaluation Criteria in Solid Tumours version 1.1.
• Secondary endpoints included safety and tolerability, time to first response (TTR) and duration of response (DOR) for patients whose best overall response was CR or PR, and progression-free survival (PFS). Quality of life (QoL) was also assessed.
• All efficacy analyses were based primarily on the full analysis set (i.e., patients who received ≥1 dose of study treatment).
Key findings

- A total of 52 patients entered the study; 45 patients completed the treatment phase (six cycles of treatment) and nine discontinued due to treatment-emergent adverse events (TEAEs) (n = 3), progressive disease (PD) (n = 3), or other reasons (n = 3).
- There were eight patients still in the extension phase of treatment at the time of clinical data cutoff.
- At baseline, the mean age of patients was 59.5 years, with metastatic disease reported in 98.1% of patients (48.1%, 46.2%, and 36.5% with liver, lung, and bone metastases, respectively).
- Prior treatment with a taxane and/or anthracycline was reported by 48.1% of patients and prior treatment with trastuzumab or lapatinib was reported by 42.3% of patients.
- The median number of cycles received per patient was 10.0 (range, 0–38) for eribulin and 11.0 (range, 1–37) for trastuzumab.
- The ORR was 71.2% (95% CI: 56.9–82.9%), the disease control rate was 96.2% (95% CI: 86.8–99.5%), and the clinical benefit rate was 84.6% (95% CI: 71.9–93.1%). (Table 1)
- Investigator assessments indicated CR and PR in 5.8% and 65.4% of patients, respectively.
- The median percentage change from baseline in the total sum of target lesion diameters was −62.4%.

Table 1. Best tumour responses

<table>
<thead>
<tr>
<th>Response category, n (%)</th>
<th>Eribulin/Trastuzumab (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>37 (71.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>56.9–82.9</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>34 (65.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (25.0)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Clinical benefit rate*</td>
<td>44 (84.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>71.9–93.1</td>
</tr>
<tr>
<td>Disease control rate†</td>
<td>50 (96.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>86.8–99.5</td>
</tr>
</tbody>
</table>

*CR = PR + stable disease (≥6 months).
†CR = PR + stable disease.
CI = confidence interval; CR = complete response; PR = partial response

- The median PFS was 11.6 months (95% CI: 9.1–13.9 months; N = 52), and Kaplan-Meier estimates for the 3-, 6-, 9-, and 12-month PFS rates were 96%, 82%, 67%, and 49%, respectively. (Figure 1)
- For all patients, median TTR (patients with CR or PR) was 1.3 months (95% CI: 1.2–1.4 months; N = 37) and median DOR was 11.1 months (95% CI: 6.7–17.8 months; N = 37).
• All patients reported TEAEs, which were considered to be related to either eribulin or trastuzumab. TEAEs with a Common Terminology Criteria for Adverse Events (CTCAE version 4) of grade ≥3 were reported in 71.2% of patients. (Table 2)
• TEAEs led to dose adjustment of eribulin, trastuzumab, or both, in 36 patients (69.2% of patients):
  ◦ Dose reduction, interruption, or discontinuation occurred in 21 (40.4%), 22 (42.3%), and 11 (21.2%) patients, respectively;
  ◦ Peripheral neuropathy led to discontinuations, dose reduction, and interruption in 13.5%, 19.2%, and 9.6% of patients, respectively.

• Neutropenia led to dose reductions in 11.5% of patients and dose interruptions in 21.2% of patients, but did not lead to any discontinuations.
• Serious TEAEs occurred in 15 patients (28.8%). Neutropenia occurred in 8 patients (15.4%), febrile neutropenia in 4 patients (7.7%), peripheral neuropathy in 3 patients (5.8%), and vomiting in 3 patients (5.8%).
• One death occurred during the study, which was considered to be possibly related to the study drug. A 59-year-old patient died due to chronic heart failure 15 days after her last dose of study treatment, a total treatment duration of 274 days.

Key conclusions

■ The combination of eribulin plus trastuzumab as first-line therapy for locally recurrent or metastatic HER2+ breast cancer resulted in an ORR of 71.2% with a median PFS of 11.6 months and an acceptable safety profile.

■ Safety was consistent with known profiles for eribulin and trastuzumab.
  • Alopecia, fatigue, peripheral neuropathy, neutropenia, nausea, and diarrhea were the most frequent TEAEs (all grades; occurring in >30% of patients).
  • The most common grade 3/4 TEAE was neutropenia, occurring in 20 patients (38.5%).

Safety profile and costs of related adverse events of trastuzumab emtansine compared with other regimens in the Canadian health care system

**Background**
Trastuzumab emtansine, approved in Canada on September 11, 2013, is an antibody-drug conjugate whose efficacy and safety have been reported previously in the EMILIA\(^1\) and TDM4450g\(^2\) studies. Trastuzumab emtansine, as a single agent, is indicated for the treatment of patients with human epidermal growth factor receptor 2-positive (HER2\(^+\)) metastatic breast cancer (MBC) who have received both prior treatment with trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.

The objective of this study was to estimate and compare the costs of managing treatment-related adverse events (AEs) of trastuzumab emtansine, capecitabine plus lapatinib, and trastuzumab plus docetaxel, as reported in the EMILIA and TDM4450g trials, from the perspective of Canadian public payers.\(^3\)

**Study design**
- This analysis considered treatment-related grade ≥3 AEs as well as grade 2 AEs that occurred in ≥5% of patients in either arm of either study. (Table 1)
- To identify studies reporting on the Canadian costs associated with managing the relevant treatment-related AEs, two researchers independently conducted literature searches on the Medline and Embase databases.
- Missing costing information from the literature was complemented by a survey with Canadian clinical experts. If experts were unable to report a cost for an AE, the cost was assumed to be $0.
- An Excel-based spreadsheet model was utilized to calculate the average cost, reported in 2012 Canadian dollars (CAD), of managing the treatment-related AEs.
- Based on clinical expert opinion, management of grade 2 AEs was assumed to cost the same as grade ≥3 AEs.
- For the sensitivity analysis, management of grade 2 AEs was assumed to cost only 50% of grade ≥3 AEs.
- The number of occurrences of each AE was obtained from the two trials for each treatment arm.
- Unit costs for resources were obtained from standard Canadian costing sources, such as the Ontario Drug Benefit Formulary.
- The number of occurrences of each AE was multiplied by the average cost per occurrence to calculate the total cost of each AE. All costs were summed to calculate the total cost of all AEs for each treatment arm. The calculated total costs of all AEs were divided by the number of patients in each arm to calculate the cost of AEs per patient in each arm.
- Study limitations included:
  - Costs were assigned for each AE, despite the fact that in the trials, the AEs could have been managed by dose reductions alone;
  - Less than half of the included references stated the degree of severity of the AEs that were costed (was tested in sensitivity analyses).
- Due to the different regimens studied, the results from the EMILIA and TDM4450g trials were not directly comparable and were, therefore, analyzed separately.

**Key findings**
- The average costs of treatment-related grade 2 and grade ≥3 AEs that occurred in either arm of the EMILIA and TDM4450g studies are shown in Table 2.
- In the EMILIA trial, the management of treatment-related AEs resulted in higher per patient average costs for capecitabine plus lapatinib of $6,780 compared with $1,919 for trastuzumab emtansine. This resulted in a cost difference per patient of $4,861. (Figure 1)
- In the TDM4450g trial, the management of treatment-related AEs resulted in higher per patient average costs for trastuzumab plus docetaxel of $16,370 compared with $1,507 for trastuzumab emtansine. This resulted in an average cost difference of $14,864. (Figure 1)
The results of the sensitivity analysis showed:

- In the EMILIA trial, the management of treatment-related AEs would result in higher per patient costs for capecitabine plus lapatinib of $2,776 ($723–$4,829), when compared with trastuzumab emtansine.

- In the TDM4450g trial, the management of treatment-related AEs would result in higher per patient costs for trastuzumab plus docetaxel of $14,219 ($4,008–$24,271), when compared with trastuzumab emtansine.

The results were robust in various sensitivity analyses (results to be presented in future publications).

The main cost drivers in this analysis were the management of treatment-related neutropenia, thrombocytopenia, vomiting, and diarrhea. These AEs are costly as they may require hospital admissions, emergency room and doctor visits, intravenous fluids, expensive medications, medical procedures, and increased caregiver time.

### Table 1. Treatment-related adverse events reported in the trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>EMILIA</th>
<th>TDM4450g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Data cutoff: January 2012</td>
<td>Data cutoff: November 2010</td>
</tr>
<tr>
<td>Capcitabine plus lapatinib (n = 488)</td>
<td>Trastuzumab emtansine (n = 490)</td>
<td>Trastuzumab plus docetaxel (n = 70)</td>
</tr>
<tr>
<td>Grade 2 adverse events in ≥5% of patients in each arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Asthenia</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>37</td>
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<tr>
<td>Diarrhea</td>
<td>313</td>
<td>20</td>
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<tr>
<td>Fatigue</td>
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<td>67</td>
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<td>Hand-foot syndrome</td>
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<tr>
<td>Nausea</td>
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<td>48</td>
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<tr>
<td>Neutropenia</td>
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</tr>
<tr>
<td>Vomiting</td>
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<td>Grade ≥3 adverse events</td>
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</tr>
<tr>
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<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>126</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>15</td>
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<tr>
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<tr>
<td>Fever</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Hand-foot syndrome</td>
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<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
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<td>8</td>
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<tr>
<td>Increased ALT</td>
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<td>15</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>11</td>
<td>6</td>
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<td>2</td>
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<td>17</td>
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<tr>
<td>Pneumonitis</td>
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<td>NA</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>129</td>
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<tr>
<td>Vomiting</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

ALT = alanine transaminase; AST = aspartate aminotransferase; NA = not applicable
### Table 2. Average per patient costs of managing treatment-related adverse events

<table>
<thead>
<tr>
<th>Grade 2 adverse events in ≥5% of patients in each arm</th>
<th>EMILIA</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>TDM4450g</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Capecitabine plus lapatinib (n = 488)</td>
<td>Trastuzumab emtansine (n = 490)</td>
<td>Cost difference</td>
<td>Trastuzumab plus docetaxel (n = 70)</td>
<td>Trastuzumab emtansine (n = 67)</td>
<td>Cost difference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>157</td>
<td>258</td>
<td>101</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4,038</td>
<td>257</td>
<td>(3,781)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
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</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>10</td>
<td>4</td>
<td>(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>16</td>
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<td>NA</td>
<td>NA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>22</td>
<td>(24)</td>
<td>38</td>
<td>27</td>
<td>(12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
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<td>NA</td>
<td>NA</td>
<td>2,107</td>
<td>734</td>
<td>(1,373)</td>
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<tr>
<td>Vomiting</td>
<td>582</td>
<td>234</td>
<td>(348)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade ≥3 adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Anemia</td>
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<td>29</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Diarrhea</td>
<td>1,625</td>
<td>64</td>
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<td>90</td>
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<td>(90)</td>
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</tr>
<tr>
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<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>(1)</td>
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<tr>
<td>Febrile neutropenia</td>
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<td>702</td>
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<td>(702)</td>
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<td>Fever</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>5</td>
<td>0</td>
<td>(5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tr>
<tr>
<td>Hypokalemia</td>
<td>5</td>
<td>4</td>
<td>(1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<td></td>
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<tr>
<td>Leukopenia</td>
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<td>NA</td>
<td>NA</td>
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<td>0</td>
<td>(1,795)</td>
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<td>Mucosal inflammation</td>
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<td>4</td>
<td>(3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nausea</td>
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<td>7</td>
<td>7</td>
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<tr>
<td>Neutropenia</td>
<td>201</td>
<td>190</td>
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<td>11,315</td>
<td>163</td>
<td>(11,152)</td>
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<tr>
<td>Pneumonitis</td>
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<td>NA</td>
<td>NA</td>
<td>93</td>
<td>0</td>
<td>(93)</td>
<td></td>
<td></td>
<td></td>
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<td>Thrombocytopenia</td>
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<td>1,095</td>
<td>1,078</td>
<td>59</td>
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<td>251</td>
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<tr>
<td>Vomiting</td>
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<td>9</td>
<td>(169)</td>
<td>NA</td>
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<tr>
<td>Average cost per patient</td>
<td>6,780</td>
<td>1,919</td>
<td>(4,861)</td>
<td>16,370</td>
<td>1,507</td>
<td>(14,864)</td>
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</tbody>
</table>

ALT = alanine transaminase; AST = aspartate aminotransferase; NA = not applicable
Figure 1. Average per patient savings in managing treatment-related adverse events

Key conclusion

- This analysis demonstrated that utilizing trastuzumab emtansine for the management of HER2+ breast cancer results in considerable cost savings of treatment-related AE management due to the improved safety profile compared with capecitabine plus lapatinib and with trastuzumab plus docetaxel.

References:

Masuda N, et al. SABCS 2013:P4-16-11

Phase I trial of afatinib plus vinorelbine in Japanese patients with advanced solid tumours including breast cancer

Background
Afatinib is a potent and selective, irreversible ErbB family blocker that blocks signaling from all homo- and hetero-dimers formed by the ErbB family members epidermal growth factor receptor (EGFR; ErbB1), human epidermal growth factor receptor 2 (HER2; ErbB2), ErbB3, and ErbB4. Afatinib has shown clinical activity in several tumour types and efficacy in non-small cell lung cancer with EGFR activating mutations. In preclinical studies in comparison with lapatinib, afatinib showed superior antitumour activity in trastuzumab-resistant HER2-positive (SUM190) xenografts and the activity of afatinib was enhanced by the addition of vinorelbine. A phase I afatinib/vinorelbine combination trial, in Caucasian patients, demonstrated that the recommended dose of 40 mg afatinib once daily in combination with 25 mg/m² weekly vinorelbine had a manageable safety profile. The present phase I trial was conducted to assess if afatinib (40 mg/day) in combination with vinorelbine (25 mg/m² intravenous [iv] weekly) could be safely administered to Japanese patients with advanced solid tumours, including breast cancer.1

Study design
- This phase I trial was conducted in a modified 3 + 3 dose-escalation design with a 28-day cycle duration. The trial protocol was amended to introduce dose levels 2a and 3.
- Male or female patients between 20 and 74 years of age with a histologically or cytologically confirmed diagnosis of advanced malignancy and for whom standard therapies were not effective were eligible for the trial.
- Patients also had to have an Eastern Cooperative Oncology Group performance status score of 0 or 1 at screening, and adequate organ function at study entry.
- The primary endpoint was to determine the maximum tolerated dose (MTD), based on dose-limiting toxicities (DLTs) in cycle 1.
- Secondary endpoints were to characterize the pharmacokinetics of afatinib and vinorelbine, and to evaluate the preliminary efficacy of afatinib in combination with vinorelbine.
- Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events version 3.0.
In Supportive Care Oncology

• The MTD of afatinib in combination with vinorelbine was defined as the dose level at which ≤1 in 6 evaluable patients in a dosing cohort experienced the following DLTs during the first 28-day treatment cycle:
  - Grade 4 leukopenia or neutropenia lasting >7 days, despite appropriate management (without fever ≥38.5°C);
  - Febrile neutropenia;
  - Grade 3 or 4 thrombocytopenia associated with bleeding requiring transfusion;
  - Worsening of renal function by two grades;
  - Grade ≥2 cardiac left ventricular function;
  - Grade ≥2 diarrhea persisting for >48 hours, despite appropriate management;
  - Any other grade 4 hematologic toxicity or grade ≥3 nonhematologic toxicity except for any laboratory abnormality not considered clinically significant;
  - AEs related to afatinib resulting in the inability to resume afatinib within 14 days of interruption;
  - Treatment-related AEs resulting in vinorelbine dose delays of >14 days between injections contributed to the delay.

• For pharmacokinetic (PK) analysis, venous blood (2–4 mL aliquots) was collected at prespecified timepoints on days 1, 2, 8, or 9 and day 22 or 23. If day 8 vinorelbine dosing was missed, sampling was done on day 15 or 16. If day 15 dosing was missed, samples were taken on day 22 or 23.

• Afatinib plasma and vinorelbine blood concentrations were determined by validated high-performance liquid chromatography-tandem mass spectrometry assays.

• Efficacy was assessed by Response Evaluation Criteria in Solid Tumors version 1.1 at 8 weeks and at 8-week intervals thereafter.

• Overall response was determined as best overall response occurring at any time from the date of first administration of the trial drug until disease progression.

Key findings

• Between October 2010 and October 2012, 22 patients were screened and 17 patients were recruited.

• The median number of treatment cycles was two at every dose level. The mean number of cycles was 2.3 at dose levels 1 and 3, and 5.2 and 6.3 at dose levels 2 and 2a, respectively. The maximum treatment cycles for a patient across all dose levels was 20 cycles.

• The HER2 status in breast cancer patients (n = 9) was as follows: one patient (11%) was HER2-negative by immunohistochemistry (IHC), three (33%) were HER2 IHC2+, four (44%) were IHC3+, and IHC status was unknown for one patient (11%). The majority of patients with breast cancer (78%) had received HER2-targeted therapy.

• Patients in dose levels 2a and 3 were all females with breast cancer, the majority of whom had Eastern Cooperative Oncology Group (ECOG) scores of 0, compared with patients in dose levels 1 and 2 who were predominantly male with ECOG scores of 1.

• The number of patients with DLTs was assessed at each dose level to determine the MTD/dosing feasibility of the recommended phase II/III dose for this combination. (Table 1)

• Tolerability at dose level 2a was confirmed with no DLTs observed.

• At dose level 3, 7/24 planned doses of vinorelbine were missed owing to grade 2 and 3 neutropenia, not qualifying as DLTs.

• All patients experienced at least one treatment-related AE.

• Overall, the most frequent treatment-related AEs were leukopenia (100%), neutropenia (100%), diarrhea (94.1%), anemia (70.6%), stomatitis (64.7%), and rash (41.2%). (Table 2)

• All nine patients with breast cancer treated at dose levels 2a and 3 experienced diarrhea, leukopenia, and neutropenia.

Study design

Original protocol

<table>
<thead>
<tr>
<th>Start: Level 1 (n = 3–6)</th>
<th>Intermediate Level (n = 3–6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib 20 mg qd + vinorelbine 25 mg/m2/week</td>
<td>Afatinib 30 mg qd + vinorelbine 25 mg/m2/week</td>
</tr>
<tr>
<td>If DLT in 0 of 3 patients, dose escalate to level 2</td>
<td>If DLT in 0 of 6 patients, dose escalate to an intermediate level</td>
</tr>
</tbody>
</table>

Intermediate Level (n = 3–6)

<table>
<thead>
<tr>
<th>Level 2 (n = 3–6)</th>
<th>Level 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib 40 mg qd + vinorelbine 25 mg/m2/week</td>
<td>Afatinib 20 mg qd + vinorelbine 25 mg/m2/week</td>
</tr>
<tr>
<td>If DLT in 0 of 3 patients or 1 of 6 patients, dose escalate to level 2</td>
<td>If DLT in 0 of 3 patients, dose escalate to level 2</td>
</tr>
</tbody>
</table>

Protocol amendment

<table>
<thead>
<tr>
<th>Level 2a*</th>
<th>Level 3*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib 40 mg qd + vinorelbine 20 mg/m2/week</td>
<td>Afatinib 40 mg qd + vinorelbine 25 mg/m2/week</td>
</tr>
<tr>
<td>If DLT in 0 of 3 patients or 1 of 6 patients, dose re-escalate to level 3</td>
<td>If DLT in 1 of 6 patients, dose escalate to an intermediate level</td>
</tr>
</tbody>
</table>

*At level 2a and 3, vinorelbine dose skipping allowed for absolute neutrophil count <1,500/mm3. Compared with dose level 2, dose level 3 allowed dose modifications as used in clinical practice.

†Level 3 evaluated to establish the safety, dosing feasibility, and pharmacokinetics of recommended phase III dose in Japanese patients.

DLT = dose-limiting toxicity; qd = once daily
• Administration of vinorelbine did not markedly affect the PK of afatinib, nor did afatinib affect the PK of vinorelbine, suggesting there were no drug-drug interactions. (Table 3)
• Changes in tumour target lesions following treatment with afatinib plus vinorelbine are shown in Figure 1.

![Table 1. Dose-limiting toxicities by dose level](image)

![Table 2. Treatment-related adverse events (all dose levels, all treatment courses)*](image)

*Only AEs that occurred in ≥3 patients across dose levels and treatment courses are listed; there were no grade 5 treatment-related AEs; †One patient with increased blood creatine phosphokinase.

AEs = adverse events
Table 3. Pharmacokinetic parameters of afatinib with or without vinorelbine

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>2–3†</th>
<th>3</th>
<th>4</th>
<th>2</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK parameter (afatinib)</td>
<td>gMean</td>
<td>gCV (%)</td>
<td>gMean</td>
<td>gCV (%)</td>
<td>gMean</td>
<td>gCV (%)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;ss&lt;/sub&gt; (ng•h/mL)</td>
<td>329</td>
<td>79.5</td>
<td>404</td>
<td>63.9</td>
<td>965</td>
<td>62.3</td>
</tr>
<tr>
<td>C&lt;sub&gt;max,ss&lt;/sub&gt; (ng/mL)</td>
<td>28.8</td>
<td>87.3</td>
<td>19.6</td>
<td>50.6</td>
<td>57.8</td>
<td>50.3</td>
</tr>
<tr>
<td>T&lt;sub&gt;max,ss&lt;/sub&gt; (h)*</td>
<td>4.00</td>
<td>3.00–6.00</td>
<td>3.00</td>
<td>2.97–7.00</td>
<td>2.98</td>
<td>2.97–4.00</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>3</th>
<th>3</th>
<th>3–4‡</th>
<th>3</th>
<th>5–6§</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK parameter (vinorelbine)</td>
<td>gMean</td>
<td>gCV (%)</td>
<td>gMean</td>
<td>gCV (%)</td>
<td>gMean</td>
<td>gCV (%)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (ng•h/mL)</td>
<td>867</td>
<td>9.1</td>
<td>830</td>
<td>20.5</td>
<td>647</td>
<td>24.8</td>
</tr>
<tr>
<td>C&lt;sub&gt;max,ss&lt;/sub&gt; (ng/mL)</td>
<td>1,220</td>
<td>12.1</td>
<td>1,170</td>
<td>12.5</td>
<td>1,120</td>
<td>23.0</td>
</tr>
<tr>
<td>T&lt;sub&gt;max,ss&lt;/sub&gt; (h)*</td>
<td>0.200</td>
<td>0.167–0.217</td>
<td>0.200</td>
<td>0.200–0.217</td>
<td>0.159</td>
<td>0.150–0.200</td>
</tr>
</tbody>
</table>

AUC = area under the curve; C<sub>max</sub> = peak plasma concentration; gCV = geometric coefficient of variation; gMean = geometric mean; max = maximum; PK = pharmacokinetic; qd = once daily; SS = steady state; t = time between drug dose administrations; T<sub>max</sub> = time to reach C<sub>max</sub>.

*Median and range.
†n = 2 for AUC values and n = 3 for C<sub>max</sub> and T<sub>max</sub> values.
‡n = 3 for AUC values and n = 4 for C<sub>max</sub> and T<sub>max</sub> values.
§n = 5 for AUC values and n = 6 for C<sub>max</sub> and T<sub>max</sub> values.
**Figure 1. Maximum change in tumour size from baseline (all dose levels)**

**Key conclusions**

- The recommended phase II/III dose in this trial was dose level 3, afatinib 40 mg once daily in combination with weekly vinorelbine (25 mg/m²).
- DLTs were primarily due to neutropenia and infections at this level.
- The combination of afatinib and vinorelbine had a manageable safety profile through dose modification of both drugs.
- No pharmacokinetic drug-drug interactions between afatinib and vinorelbine were apparent.
- The combination of afatinib (40 mg/day) plus vinorelbine (25 mg/m²/week) showed early signs of clinical activity in Japanese patients with confirmed refractory advanced/metastatic solid tumours.

At Roche, we’ve had HER2-positive breast cancer in our sights for years. As with any cancer, when it metastasizes, this aggressive form of the disease can pose an even greater challenge. For these reasons, and for all the people this condition affects, Roche is committed to research in HER2-positive metastatic breast cancer.

Indications and clinical use:

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

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

Contraindications:

- **TREANDA is contraindicated in patients who are hypersensitive to mannitol.**

Most serious warnings and precautions:

- **Myelosuppression:** Patients treated with TREANDA are likely to experience myelosuppression. In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb) and neutrophils closely.

- **Infections, including fatalities:** TREANDA should not be used in patients with serious infections, including patients with HIV. CMV testing should be considered in patients with fever of unknown origin.

- **Second malignancies:** Pre-malignant and malignant diseases have developed in patients treated with TREANDA including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma.

Other relevant warnings and precautions:

- **TREANDA is not recommended for a subset of relapsed indolent NHL patients with poor tolerance to prior therapies as they would not be expected to tolerate the 120 mg/m² dose on days 1 and 2 of a 21-day cycle.**

- **Risk of extravasation**

- **Cardiac disorders have been reported**

- **Risk of ECG changes, including QTc prolongation**

- **Risk of hypertension**

- **Risk of tumor lysis syndrome**

- **Risk of increase in liver enzymes and bilirubin levels**

- **The use of live attenuated vaccines should be avoided**

- **Risk of infusion reactions and anaphylaxis**

- **Potential risk to reproductive capacity**

- **Risk of skin reactions. One case of toxic epidermal necrolysis (TEN) was reported when TREANDA 90 mg/m² was used with rituximab. Cases of Stevens-Johnson syndrome (SJS) and TEN have been reported when TREANDA was administered with allopurinol.**

- **Not recommended during pregnancy or breast-feeding**

- **Women and men of childbearing potential should use effective contraception from 2 weeks before and until at least 4 weeks after the last dose of TREANDA**

- **Use with caution in patients with CrCl of 40-80 mL/min; do not use when CrCl < 40 mL/min**

- **Use with caution in patients with mild hepatic impairment, do not use if hepatic impairment is moderate or severe**

- **Monitor/test for complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function, electrolytes, blood pressure and hepatitis B 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**

For more information:

Please consult the product monograph at [http://www.lundbeck.com/upload/ca/en/files/pdf/pm/Treanda.pdf](http://www.lundbeck.com/upload/ca/en/files/pdf/pm/Treanda.pdf) for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this advertisement. The product monograph is also available by calling us at 514-844-8515 or 1-800-586-2325.
Clinical use not discussed elsewhere in the piece: A validated test is required to identify EGFR mutation status. Clinical effectiveness was based on progression-free survival and objective response. No overall survival benefit was demonstrated. Safety and efficacy of GIOTRIF have not been established in patients with EGFR mutations other than exon 19 deletions and the exon 21 L858R point mutation. Close monitoring and proactive management of diarrhea is essential for successful GIOTRIF treatment. In clinical trials, more grade 3 adverse events were reported for patients ≥65 years than <65 years. Treatment of children or adolescents with GIOTRIF is not recommended.

Most serious warnings and precautions:

EGFR mutation status: EGFR mutation-positive status must be confirmed with a well-validated and robust methodology prior to starting GIOTRIF monotherapy.

Diarrhea: Diarrhea, including severe diarrhea, has been reported with GIOTRIF treatment. Close monitoring and proactive management of diarrhea, including adequate hydration combined with anti-diarrheal agents, is essential for successful GIOTRIF treatment. GIOTRIF is not recommended for patients with significant or recent gastrointestinal disorders with diarrhea as a major symptom.

Severe skin toxicities: Grade ≥3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions were rare. Patients should be advised to avoid sun exposure or wear sun protection, as certain reactions (e.g., rash) may occur or worsen in areas exposed to sun. Discontinue if patient develops severe bullous, blistering, or exfoliating conditions.

Interstitial lung disease (ILD): ILD or ILD-like events, including fatalities, were reported with GIOTRIF treatment. Assess all patients with an acute onset and/or unexplained worsening of pulmonary symptoms, and discontinue if ILD is diagnosed. GIOTRIF is not recommended for patients with a history of ILD.

Hepatotoxicity: Hepatic failure, including fatalities, was reported with GIOTRIF. Periodic liver function testing should be performed for all patients. Discontinue if patient develops severe hepatic impairment.

Other relevant warnings and precautions:

• Patients diagnosed with ulcerative keratitis
• History of keratitis, ulcerative keratitis, or severe dry eyes
• Patients who develop relevant cardiac signs/symptoms or low ejection fraction
• Cardiac risk factors and/or conditions that can affect left ventricular ejection fraction
• Patients with paronychia
• Nursing women
• Female patients
• Patients with a low body weight
• Patients with an underlying renal impairment
• Not recommended for use in patients with severe renal impairment
• Potential for allergic, immune-based adverse reactions
• Potential for ocular adverse reactions. Contact lens use is a risk factor for keratitis and ulceration
• Interactions with strong P-glycoprotein inhibitors
• Do not use in pregnant women
• Use of contraception in women of childbearing potential during therapy and at least 2 weeks after the last dose
• Elderly patients should be closely monitored for drug-related toxicities

For more information:

Please consult the product Monograph at www.giotrif.ca/pm_english.pdf for important information relating to adverse reactions, drug interactions, and dosing information that had not been discussed in this piece. The Product Monograph is also available by calling 1-800-263-5103 x 84633.
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