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Updates from ASH 2016

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

Our April 2017 issue presents coverage from the 58th American Society of Hematology (ASH) Annual Meeting. This issue reports on presentations and perspectives about the latest therapeutic developments in acute lymphoblastic leukemia, acute promyelocytic leukemia, chronic lymphocytic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma.

We would like to thank Dr. Neil Berinstein, Dr. Joseph Connors, Dr. Richard LeBlanc, Dr. Carolyn Owen, and Dr. Anthea Peters for their Canadian Perspectives. We would also like to thank Dr. Bruce Cheson for his Investigator Commentary.

New this year, the NE Live app was launched to provide physicians with a forum to discuss the latest clinical data presented at national and international conferences. NE Live collaborates with Key Opinion Leaders in Oncology to provide up-to-date, unbiased perspectives and commentary on the latest studies. These perspectives are presented in short videos or in written format, highlighting key takeaways and opinions. Physicians who wish to stay up-to-date with the reports are invited to visit www.newevidence.live, as well as Apple’s App Store or the Google Play store to download the NE Live app.

We also invite you to visit our website at www.newevidence.com any time for the online version of New Evidence and more reports on current research.
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A Canadian Perspective by Dr. Carolyn Owen on the Updated Analysis of the CLL10 Study that Examined Long-term Outcome of First-line BR Therapy Compared to FCR in Fit, Elderly Patients with CLL

- Updated analysis of overall survival in randomized phase III study of idelalisib in combination with BR in patients with relapsed/refractory CLL. (Zelenetz AD, et al. ASH 2016:231)


- Updated efficacy and safety from the phase III RESONATE™-2 study: Ibrutinib as a first-line treatment option in patients 65 years and older with CLL/SLL. (Barr PM, et al. ASH 2016:234)
CHRONIC LYMPHOCYTIC LEUKEMIA (con't)

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• Analysis of the randomized trial, APL2006, on whether arsenic trioxide is required in the treatment of high-risk, newly diagnosed APL. (Ades L, et al. ASH 2016:895)

• ATRA, ATO, and gemtuzumab ozogamicin are safe and highly effective in patients with previously untreated high-risk APL: Final results from SWOG/Alliance/ECOG 5055 Trial. (Lancet JE, et al. ASH 2016:896)

• Reduction of early deaths and improved survival in elderly patients (>60 years) with APL as a result of using a simplified treatment algorithm and expert support: A prospective multicentre trial. (Kota V, et al. ASH 2016:1622)

• Real-life experience with ATRA- and ATO-based regimen in APL: Updated results of the prospective German intergroup Napoleon registry. (Platzbecker U, et al. ASH 2016:2815)

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• Anti-pegaspargase, anti-calaspargase pegol, and anti-polyethylene glycol antibody incidence in high-risk ALL patients receiving pegaspargase or calaspargase pegol and associated anaphylactic or hypersensitivity reaction rates. (Schore RJ, et al. ASH 2016:3965)

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New Treatments Improve Outcomes for Patients with Lymphoma Throughout the Continuum of Care

• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs OS compared with bendamustine alone in patients with rituximab-refractory iNHL: Updated results of the GADOLIN study. (Cheson BD, et al. ASH 2016:613)

• Autologous stem cell transplantation with Benda-EAM in aggressive NHL and Hodgkin lymphoma. (Noesslinger T, et al. ASH 2016:2265)

• Obinutuzumab-based induction and maintenance prolongs PFS in patients with previously untreated FL: Primary results of the randomized phase III GALLIUM study. (Marcus R, et al. ASH 2016:6)

• Rituximab, bendamustine and cytarabine as induction therapy in elderly patients with MCL: Final results of a phase II study from the Fondazione Italiana Linfomi. (Visco C, et al. ASH 2016:472)

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Contributors

Neil Berinstein, MD, FRCPC, ABIM

Dr. Neil Berinstein earned his premedical degree and medical doctorate from the University of Manitoba and received further specialty and research training at the University of Toronto and Stanford University.

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

Dr. Berinstein specializes in the management and research of patients with lymphoproliferative disorders, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, Hodgkin lymphoma, and myeloma.

Bruce D. Cheson, MD, FACP, FAAS, FASCO

Dr. Bruce Cheson completed his internship and residency in Internal Medicine at the University of Virginia Hospitals and then a clinical and research fellowship in Hematology at New England Medical Center Hospital. He is former Editor-in-Chief of Clinical Advances in Hematology and Oncology and Clinical Lymphoma, Leukemia and Myeloma, and a former Associate Editor of the Journal of Clinical Oncology. From 2002 to 2006, he was on the Oncologic Drug Advisory Committee to the U.S. Food and Drug Administration. He is past-Chair of the Lymphoma Committee of the Cancer and Leukemia Group B/Alliance, the Scientific Advisory Board of the Lymphoma Research Foundation, and the American Joint Committee on Cancer (AJCC) Subcommittee on Lymphoma.

Currently, Dr. Cheson is Professor of Medicine, Head of Hematology, and Deputy Chief of Hematology-Oncology at Georgetown University Hospital, Lombardi Comprehensive Cancer Center. Dr. Cheson’s clinical interests focus on the development and evaluation of new therapeutic approaches for hematologic malignancies.

Joseph Connors, MD, FRCPC

Dr. Joseph Connors earned his medical degree from Yale University. He completed his residency training in Internal Medicine and chief residency at the University of North Carolina in Chapel Hill. Prior to completing his Medical Oncology Fellowship at Stanford University, he worked at the Indian Health Service in Alaska for two years. In 1981, he accepted a position in Medical Oncology at the BC Cancer Agency. He has been a member of the Faculty of Medicine at the University of British Columbia since that time, reaching the position of Clinical Professor in 1997.

At present, he is a Clinical Professor in the Department of Medicine, Division of Medical Oncology, at the University of British Columbia and the Chair of the Lymphoma Tumour Group for the BC Cancer Agency. Dr. Connors’ clinical activities and research efforts are focused in the area of lymphoid cancers. He is best known for his clinical investigations into the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma.
Richard LeBlanc, MD, FRCPC

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

Dr. LeBlanc holds the Myeloma Canada Chair at the University of Montreal. He is the Director of the Myeloma Cell Bank at Hôpital Maisonneuve-Rosemont, which is affiliated with the Quebec Leukemia Cell Bank. He is also the Medical Director of the Clinical Immunology Laboratory at Hôpital Maisonneuve-Rosemont. Finally, Dr. LeBlanc is a member of the Scientific Advisory Board of Myeloma Canada.

Carolyn Owen, MD, FRCPC

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 and Tom Baker Cancer Centre, University of Calgary, 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.

Anthea Peters, MD, FRCPC

Dr. Anthea Peters obtained her medical degree from the University of Saskatchewan in 2006. She then completed her residencies in Internal Medicine at the University of Alberta and in Hematology at the University of Calgary. Dr. Peters joined the Division of Hematology at the University of Alberta as a Clinical Scholar in July 2011. Her main area of interest is in lymphoma.
Multiple Myeloma

Improved Outcomes in Patients with Relapsed/Refractory Multiple Myeloma

A majority of patients with multiple myeloma (MM) relapse after therapy, and the duration of remission decreases with each line of therapy. Novel agents, including proteasome inhibitors (PIs) and immuno-modulatory agents (IMIDs), have improved outcomes for patients with MM. However, treatment options are limited for patients who become refractory to PIs and IMIDs. The CD38 inhibitor daratumumab has demonstrated rapid, deep, and durable responses in patients with relapsed/refractory (R/R) MM, both as a single agent and in combination with the IMID, lenalidomide, or the PI, bortezomib. Daratumumab was also well tolerated, with manageable adverse events.

The phase III POLLUX study found improved outcomes with the combination of daratumumab, lenalidomide, and dexamethasone (DRd) over lenalidomide and dexamethasone (Rd) in patients with R/R MM, while the phase III CASTOR study showed a similar benefit for daratumumab, bortezomib, and dexamethasone (DVd) over bortezomib and dexamethasone (Vd).

Daratumumab has been approved as monotherapy for patients with heavily pretreated R/R MM by the Food and Drug Administration (FDA), the European Medicines Agency, Health Canada, Mexico, and Singapore. The FDA, in part due to data from the POLLUX and CASTOR studies, has also approved daratumumab in combination with standard of care regimens in patients with R/R MM after at least one prior therapy.

New Evidence reported on the results of five studies, presented at the 2016 American Society of Hematology (ASH) Annual Meeting, which reaffirmed the efficacy and safety of daratumumab in patients with R/R MM:

- Updated results from the POLLUX study demonstrated improved outcomes with DRd over Rd in patients with R/R MM and 1–3 prior lines of treatment. Benefits with DRd were seen regardless of prior lenalidomide treatment, refractoriness to bortezomib, or cytogenetic profile. (Moreau P, et al. ASH 2016:489)
- An additional analysis of the POLLUX study found that patients who received DRd experienced deeper responses than those who received Rd, regardless of the risk status or refractoriness to prior treatment. (Usmani SZ, et al. ASH 2016:1151)
- An updated analysis of the CASTOR study reaffirmed the superiority of the combination of DVd over Vd in patients with R/R MM. The superiority of DVd over Vd was observed regardless of prior lines of therapy, with the greatest benefit observed in patients with one prior line of therapy. (Mateos MV, et al. ASH 2016:1150)
- Results from the Early Access Treatment Protocol (EAP), which provided patients with early access to daratumumab, showed that patients with R/R MM who received daratumumab experienced similar adverse events as previously reported while maintaining quality of life. (Chari A, et al. ASH 2016:2133)
- A subanalysis of the EAP provided evidence that premedication with montelukast may mitigate infusion-related reactions associated with the first infusion of daratumumab. (Chari A, et al. ASH 2016:2142)

Moreau P, et al. ASH 2016:489

Efficacy of daratumumab, lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone for R/R MM among patients with 1–3 prior lines of therapy based on previous treatment exposure: Updated analysis of POLLUX

Background
In a phase I/II study, 32 patients with relapsed or refractory (R/R) multiple myeloma (MM) were treated with daratumumab, lenalidomide, and dexamethasone (DRd), which induced rapid, deep, and durable responses with a manageable safety profile. The phase III POLLUX study compared DRd to the combination of lenalidomide and dexamethasone (Rd) in patients with R/R MM. Updated results from the POLLUX study were presented at the 2016 ASH Meeting.

Study design
- The POLLUX study was a multicentre, randomized, open-label, active-controlled, phase III study.
- Patients were stratified by number of lines of therapy, International Staging System stage at study entry, and prior lenalidomide treatment.
- The primary endpoint was progression-free survival (PFS).
- Secondary endpoints included time to progression, overall survival, overall response rate (ORR), minimal residual disease (MRD), time to response, and duration of response.
- The primary analysis included 177 PFS events.
- MRD was evaluated at three sensitivity thresholds ($10^{-4}$, $10^{-5}$, and $10^{-6}$).
- MRD-negativity rate was defined as the proportion of patients with negative MRD test results at any time during treatment.
- A stringent, unbiased MRD evaluation was applied:
  - MRD-negativity counts were evaluated against the intent-to-treat (ITT) population;
  - Any patient in the ITT population not determined to be MRD-negative was scored as MRD-positive; and
  - A minimum cell input equivalent to the given sensitivity threshold was required to determine MRD-negativity (i.e., MRD at $10^{-6}$ required that $\geq 1,000,000$ cells were evaluated).
- MRD was assessed at suspected complete response (CR) and three and six months after CR.

Key eligibility criteria
- R/R MM
- $\geq 1$ prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Creatinine clearance $\geq 30$ mL/min

Cycles: 28 days

DRd (n = 286)
- Daratumumab 16 mg/kg iv
- Qw in Cycles 1–2, q2w in Cycles 3–6, then q4w until PD
- R 25 mg po
- Days 1–21 of each cycle until PD
- d 40 mg po
- 40 mg qw until PD

Rd (n = 283)
- R 25 mg po
- Days 1–21 of each cycle until PD
- d 40 mg po
- 40 mg qw until PD

$d = \text{dexamethasone}; DRd = \text{daratumumab, lenalidomide, dexamethasone}; iv = \text{intravenous}; MM = \text{multiple myeloma}; PD = \text{progressive disease}; po = \text{oral}; qw = \text{weekly}; q2w = \text{every two weeks}; q4w = \text{every four weeks}; R = \text{lenalidomide}; Rd = \text{lenalidomide, dexamethasone}; R/R = \text{relapsed/refractory}$
Key findings

Baseline characteristics and disposition

- In the updated analysis, evaluations were performed on the subgroup of patients who had received 1–3 prior lines of therapy, which comprised 95% of the DRd arm and 93% of the Rd arm.
- Baseline demographics were similar between groups.
- Median age was 65 years in both treatment arms; 10% and 12% of patients were aged ≥75 years in the DRd and Rd groups, respectively.
- In both treatment arms, 18% of patients had received prior lenalidomide, and 21% of patients were refractory to bortezomib.
- Cytogenetic profiling was conducted on 161 patients in the DRd arm and on 150 patients in the Rd arm.
  - The majority of patients tested had standard risk cytogenetic profiles (83% in the DRd arm and 75% in the Rd arm).

Efficacy

- For patients who received 1–3 prior lines of therapy, responses continued to deepen in the DRd group with longer follow-up (median: 18.4 months). (Figure 1)
- DRd maintained treatment benefit in lenalidomide-naïve patients:
  - The 18-month PFS was 76% in the DRd arm vs. 49% in the Rd arm (HR = 0.37; 95% CI: 0.26–0.51; p <0.0001); and
  - ORR was 93% and 77% in the DRd and Rd arms, respectively (p <0.0001).
- DRd also improved outcomes in lenalidomide-exposed patients. (Figure 2)
  - A DRd treatment benefit was observed in patients who were refractory to their last line of therapy:
    - The 18-month PFS was 65% in the DRd arm vs. 37% in the Rd arm (HR = 0.45; 95% CI: 0.27–0.74; p = 0.0014); and
    - ORR was 89% and 63% in the DRd and Rd arms, respectively (p = 0.0003).
- DRd significantly improved outcomes regardless of refractoriness to bortezomib:
  - The 18-month PFS was 65% in the DRd arm vs. 40% in the Rd arm (HR = 0.51; 95% CI: 0.28–0.91; p = 0.021); and
  - ORR was 92% and 68% in the DRd and Rd arms, respectively (p = 0.0024).
- Patients achieved deeper responses, including MRD-negativity, irrespective of prior lenalidomide exposure or bortezomib refractoriness. (Figure 3)
  - MRD-negative patients (at a sensitivity of 10⁻⁵) achieved prolonged PFS in both treatment arms.
- DRd improved outcomes in both high-risk and standard-risk patients. (Figure 4)

Safety

- No new safety signals were reported in the study. (Table 1)

Figure 1. Efficacy in the patient subgroup who received 1–3 prior lines of therapy
Figure 2. Efficacy in lenalidomide-exposed patients

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Number at risk
Rd (n = 45) 45 38 35 29 26 22 4 1 0
DRd (n = 46) 46 41 38 37 37 30 8 1 0
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CI = confidence interval; CR = complete response; DRd = daratumumab, lenalidomide, dexamethasone; HR = hazard ratio; ORR = overall response rate; PFS = progression-free survival; PR = partial response; Rd = lenalidomide, dexamethasone; sCR = stringent complete response; VGPR = very good partial response

* Kaplan-Meier estimate.
† Response-evaluable population.
‡ p = 0.0001 for DRd vs. Rd.
§ p <0.0001 for DRd vs. Rd.

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Figure 3. MRD-negative rates (10⁻⁵)

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MRD-negative rate (%)
0  5  10  15  20  25  30

<table>
<thead>
<tr>
<th>DRd</th>
<th>Rd</th>
<th>DRd</th>
<th>Rd</th>
<th>DRd</th>
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<td>n = 286</td>
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```

DRd = daratumumab, lenalidomide, dexamethasone; ITT = intent to treat; MRD = minimal residual disease; Rd = lenalidomide, dexamethasone

* p <0.0001.
† p <0.01.
‡ p <0.05.
P-value calculated using likelihood-ratio chi-square test.
Figure 4. Responses and PFS by cytogenetic status

Table 1. Most common AEs in the patient subgroup who received 1–3 prior lines of therapy

<table>
<thead>
<tr>
<th>Hematologic (%)</th>
<th>DRd (n = 269)</th>
<th>Rd (n = 262)</th>
</tr>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>All grade ≥25%*</td>
<td>Grade 3/4 ≥5%*</td>
</tr>
<tr>
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<td>61</td>
<td>54</td>
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<td></td>
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<tr>
<td>Febrile neutropenia</td>
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<td>Anemia</td>
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<td>Thrombocytopenia</td>
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<td>Lymphopenia</td>
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<table>
<thead>
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<th>Non-hematologic (%)</th>
<th>DRd (n = 269)</th>
<th>Rd (n = 262)</th>
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</thead>
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<td>Diarrhea</td>
<td>48</td>
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<td>Cough</td>
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<td>Pneumonia</td>
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</tr>
</tbody>
</table>

AE = adverse event; DRd = daratumumab, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone

* Common treatment-emergent AEs listed are either ≥25% all grade OR ≥5% grade 3/4.
• DRd significantly improved outcomes for patients with R/R MM and 1–3 prior lines of treatment.
• This treatment benefit was maintained regardless of prior treatment with lenalidomide or refractoriness to bortezomib.
• Higher MRD-negative rates were observed in the DRd arm vs. the Rd arm for all subgroups.
• DRd was superior to Rd in both standard- and high-risk cytogenetic patients.
• The safety profile was unchanged between treatment arms.
• These data support the use of DRd, irrespective of prior lenalidomide treatment or bortezomib refractoriness.


Usmani SZ, et al. ASH 2016:1151

Efficacy of daratumumab, lenalidomide and dexamethasone versus lenalidomide and dexamethasone in R/R MM among patients with 1–3 prior lines of therapy: Updated analysis of POLLUX

Background
The POLLUX study has previously demonstrated deeper response with daratumumab, lenalidomide, and dexamethasone (DRd) compared to lenalidomide and dexamethasone (Rd) in patients with relapsed/refractory (R/R) multiple myeloma (MM). At the 2016 ASH Meeting, Usmani and colleagues also reported updated results from the POLLUX study.1

Study design
• The POLLUX study was a multicentre, randomized, open-label, active-controlled, phase III study that compared DRd to Rd.
• Premedication for the DRd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine.
• On daratumumab dosing days, dexamethasone 20 mg was administered as a premedication on Day 1 and Day 2.
• Patients were stratified by number of lines of therapy, International Staging System stage at study entry, and prior lenalidomide treatment.
• The primary endpoint was progression-free survival (PFS).
• Secondary endpoints included time to progression, overall survival (OS), overall response rate (ORR), minimal residual disease (MRD), time to response, and duration of response.
• The primary analysis included 177 PFS events.

Key findings
Baseline characteristics and disposition
• Baseline demographics were similar between groups.
• Median age was 65 years in both treatment arms; 10% and 12% of patients were aged ≥75 years in the DRd and Rd groups, respectively.
• A total of 28% and 27% of patients were refractory to their last line of therapy in the DRd and Rd groups, respectively.
Cytogenetic profiling was conducted on 161 patients in the DRd arm and on 150 patients in the Rd arm.

The majority of patients tested had standard risk cytogenetic profiles (83% in the DRd arm and 75% in the Rd arm).

**Efficacy**

- Responses continued to deepen in the DRd group with longer follow-up (median 17.3 months).
  - The 18-month PFS was 76% in the DRd arm vs. 49% in the Rd arm (HR = 0.37; 95% CI: 0.28–0.50; p < 0.0001); and
  - ORR was 93% and 76% in the DRd and Rd arms, respectively (p < 0.0001).
- MRD-negative rates were more than threefold higher in the DRd arm compared to the Rd arm at all thresholds for MRD. (Figure 1)
- MRD-negativity was associated with improved PFS in both treatment arms. (Figure 2)
- In terms of PFS, DRd was superior to Rd regardless of time since last therapy. (Figure 3)
- DRd also benefitted patients who were refractory to the last line of therapy. (Figure 4)
- DRd improved outcomes regardless of cytogenetic risk.
  - Among high-risk patients, median PFS was not reached in the DRd arm and was 10.2 months in the Rd arm (HR = 0.44; 95% CI: 0.19–1.03; p = 0.0475); and
  - Among standard-risk patients, PFS was not reached in the DRd arm and was 17.1 months in the Rd arm (HR = 0.30; 95% CI: 0.18–0.49; p < 0.0001); and
  - Among standard-risk patients, ORR was 95% in the DRd arm and 82% in the Rd arm (p = 0.0020).
- OS data were immature; however, preliminary data favoured DRd. (Figure 5)
  - There were 40 OS events (14%) in the DRd arm and 56 events (20%) in the Rd arm.

**Safety**

- No new safety signals were reported in the study.
**Figure 1. MRD-negative rates in the intent-to-treat population**

<table>
<thead>
<tr>
<th>Sensitivity threshold</th>
<th>DRd MRD-negative rate (%)</th>
<th>Rd MRD-negative rate (%)</th>
<th>DRd MRD-negative rate (%)</th>
<th>Rd MRD-negative rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-4}$</td>
<td>31.8</td>
<td>8.8</td>
<td>24.8</td>
<td>5.7</td>
</tr>
<tr>
<td>$10^{-5}$</td>
<td>2.5</td>
<td>11.9</td>
<td>11.9</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* $p < 0.0001$

DRd = daratumumab, lenalidomide, dexamethasone; MRD = minimal residual disease; Rd = lenalidomide, dexamethasone

P-values are calculated using likelihood-ratio chi-square test.

**Figure 2. PFS stratified by MRD status ($10^{-5}$) in the intent-to-treat population**

- **Rd MRD-negative (n = 16)**
- **DRd MRD-negative (n = 71)**
- **DRd MRD-positive (n = 215)**
- **Rd MRD-positive (n = 267)**

Number at risk

<table>
<thead>
<tr>
<th>DRd MRD-negative</th>
<th>71</th>
<th>71</th>
<th>70</th>
<th>66</th>
<th>57</th>
<th>28</th>
<th>6</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd MRD-negative</td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drd MRD-positive</td>
<td>267</td>
<td>233</td>
<td>190</td>
<td>166</td>
<td>144</td>
<td>120</td>
<td>38</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rd MRD-positive</td>
<td>215</td>
<td>195</td>
<td>178</td>
<td>167</td>
<td>161</td>
<td>137</td>
<td>54</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

DRd = daratumumab, lenalidomide, dexamethasone; MRD = minimal residual disease; PFS = progression-free survival; Rd = lenalidomide, dexamethasone
Figure 3. PFS stratified by time from last line of therapy

![Graph showing PFS stratified by time from last line of therapy.](image)

CI = confidence interval; DRd = daratumumab, lenalidomide, dexamethasone; HR = hazard ratio; PFS = progression-free survival; Rd = lenalidomide, dexamethasone

* Kaplan-Meier estimate.

Figure 4. Efficacy in patients refractory to the last line of therapy

![Graph showing efficacy in patients refractory to the last line of therapy.](image)

CI = confidence interval; CR = complete response; DRd = daratumumab, lenalidomide, dexamethasone; HR = hazard ratio; ORR = overall response rate; PFS = progression-free survival; PR = partial response; Rd = lenalidomide, dexamethasone; sCR = stringent complete response; VGPR = very good partial response

* Kaplan-Meier estimate

† Response-evaluable population

‡ p <0.0001 for DRd vs. Rd

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd &gt;12</td>
<td>149</td>
<td>139</td>
<td>123</td>
<td>111</td>
<td>103</td>
<td>88</td>
<td>76</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRd &gt;12</td>
<td>140</td>
<td>133</td>
<td>127</td>
<td>122</td>
<td>118</td>
<td>109</td>
<td>98</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rd ≤12</td>
<td>134</td>
<td>110</td>
<td>83</td>
<td>70</td>
<td>56</td>
<td>44</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRd ≤12</td>
<td>146</td>
<td>133</td>
<td>122</td>
<td>115</td>
<td>109</td>
<td>85</td>
<td>38</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
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</thead>
<tbody>
<tr>
<td>Rd</td>
<td>76</td>
<td>60</td>
<td>44</td>
<td>34</td>
<td>30</td>
<td>26</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRd</td>
<td>80</td>
<td>68</td>
<td>62</td>
<td>55</td>
<td>52</td>
<td>40</td>
<td>24</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The addition of daratumumab to lenalidomide and dexamethasone (DRd) vs. lenalidomide and dexamethasone (Rd) alone was evaluated in the POLLUX trial, a randomized, open-label, multicentre, phase III study. The population of the study included 569 patients with multiple myeloma (MM), who had received at least one previous line of therapy.

DRd treatment resulted in an improved progression-free survival, response rate, and depth of response in all subgroups including patients who had a treatment-free interval ≤12 months and those with high-risk cytogenetics. Daratumumab is a relatively new drug that has already shown clinical benefit when used as monotherapy. Now it clearly demonstrates a positive effect as an addition to an immunomodulatory backbone treatment.

The impressive results of the POLLUX trial in patients with R/R MM (not refractory to lenalidomide) are among the best in this setting. It is certainly a practice-changing study that will have a significant impact on the way we are treating Canadian patients with R/R MM. The fact that lenalidomide-exposed patients (although a small group) had a similar outcome as other subgroups of patients, including lenalidomide-naïve patients, is interesting, since many relapsed patients have been previously exposed to lenalidomide but are not refractory.

Another related abstract sought to evaluate how the addition of daratumumab to Rd in the POLLUX trial promoted T-cell response. The findings certainly support an immunomodulatory effect of daratumumab as its mechanism of action. The understanding of its immunomodulating properties is of interest since daratumumab is administered in combination with dexamethasone, which is associated with immunosuppressive effects. It is theoretically plausible that dexamethasone could decrease part of the efficacy of daratumumab through its immunosuppressive effect.

Key conclusions

- DRd significantly improved outcomes for patients with MM, with a 63% reduction in risk of progression or death for DRd vs. Rd.
- More patients achieved deeper responses, including MRD-negativity, with DRd.
- DRd is superior to Rd regardless of time since last therapy, refractoriness to last line of therapy, or cytogenetic risk.
- Safety profiles remained unchanged.
- These data support the use of DRd for patients who received at least one prior therapy regardless of risk status or refractoriness to prior treatment.

Efficacy of daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in R/R MM based on prior lines of therapy: Updated analysis of CASTOR

Background
An early phase study of daratumumab in combination with bortezomib showed deep and durable responses in patients with multiple myeloma (MM). The combination was also well tolerated with manageable adverse events. The CASTOR study compared the combination of daratumumab, bortezomib, and dexamethasone (DVd) to bortezomib and dexamethasone (Vd) alone in patients with relapsed/refractory (R/R) MM. Updated results from the CASTOR study were presented at the 2016 ASH Meeting.

Study design
- The CASTOR study was a multicentre, randomized, open-label, active-controlled, phase III study that enrolled 498 patients.
- Premedication for the DVd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine.
- Patients were stratified by number of lines of therapy (1 vs. 2 or 3 vs. 3 or >3), International Staging System stage (I, II, and III), and prior bortezomib treatment (no vs. yes).
- The study planned to enrol 480 patients.
- The primary endpoint was progression-free survival (PFS).

Key findings
Baseline characteristics and disposition
- Baseline demographics were similar between groups.
- Median age was 64 years in both treatment arms; 9% and 14% of patients were aged ≥75 years in the DVd and Vd groups, respectively.
- The majority of patients had received 1–3 prior lines of therapy, which comprised 91% of the DVd arm and 89% of the Vd arm.
- Cytogenetic profiling was conducted on 167 patients in the DVd arm and 186 patients in the Vd arm.
- The majority of patients tested had standard risk cytogenetic profiles (74% in the DVd arm and 73% in the Vd arm).
Efficacy

- Responses continued to deepen in the DVd group with longer follow-up (median 13.0 months). (Figure 1)
- An additional 7% of patients in the DVd arm achieved at least a CR with longer follow-up.
- DVd was superior to Vd regardless of prior lines of therapy, with the greatest benefit observed in patients with one prior line of therapy. (Figure 2)
- In patients who received one prior line of therapy, DVd provided a treatment benefit regardless of prior bortezomib exposure.
- More patients achieved a deeper response with DVd after one prior line of treatment.
- In patients with one prior line of treatment, ORR was 91% in the DVd arm vs. 74% in the Vd arm ($p = 0.0014$); and
- In patients with 2–3 prior lines of treatment, ORR was 79% in the DVd arm vs. 58% in the Vd arm ($p = 0.0022$).
- MRD-negative rates for the DVd arm were at least threefold higher than the Vd arm across all thresholds. (Figure 3)
- MRD-negativity was associated with better PFS outcomes in both treatment arms.
- DVd improved PFS regardless of cytogenetic risk. (Figure 4)
- Overall survival (OS) data were immature; however, preliminary data favoured DVd ($HR = 0.63; 95\% CI: 0.42–0.96$).
- There were 37 OS events (15%) in the DVd arm and 58 events (24%) in the Vd arm.
- In patients who received one prior line of therapy, $HR = 0.42; 95\% CI: 0.19–0.93$.
- In patients who received 1–3 prior lines of therapy, $HR = 0.54; 95\% CI: 0.34–0.84$.

Safety

- Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 79% of patients in the DVd arm vs. 63% in the Vd arm. (Table 1)
- Discontinuations due to TEAEs occurred in 9% of patients in both treatment arms.
- No new infusion-related reactions were reported (incidence remained stable at 45% with longer follow-up).

Figure 1. Updated efficacy
Figure 2. PFS stratified by prior lines of treatment

One prior line

- 12-month PFS*
  - Median: 7.9 months
  - HR (95% CI): 0.22 (0.14–0.34); p < 0.0001

- Patients surviving without progression (%)
  - Vd
  - Dvd

2–3 prior lines

- 12-month PFS*
  - Median: 9.8 months
  - HR (95% CI): 0.51 (0.36–0.73); p = 0.0002

- Patients surviving without progression (%)
  - Vd
  - Dvd

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Vd</th>
<th>113</th>
<th>91</th>
<th>69</th>
<th>43</th>
<th>11</th>
<th>5</th>
<th>0</th>
<th>0</th>
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<tbody>
<tr>
<td>Dvd</td>
<td>122</td>
<td>109</td>
<td>104</td>
<td>99</td>
<td>59</td>
<td>19</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Vd</th>
<th>106</th>
<th>73</th>
<th>50</th>
<th>27</th>
<th>11</th>
<th>4</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dvd</td>
<td>107</td>
<td>87</td>
<td>77</td>
<td>51</td>
<td>27</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CI = confidence interval; Dvd = daratumumab, bortezomib, dexamethasone; HR = hazard ratio; PFS = progression-free survival; Vd = bortezomib, dexamethasone

* Kaplan-Meier estimate.

Figure 3. MRD rates stratified by prior lines of therapy

**ITT (N = 498)**

- **One prior line (n = 235)**

<table>
<thead>
<tr>
<th>Sensitivity threshold</th>
<th>Dvd</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>10⁻⁴</td>
<td>18.3</td>
<td>3.6</td>
</tr>
<tr>
<td>10⁻³</td>
<td>10.4</td>
<td>2.4</td>
</tr>
<tr>
<td>10⁻²</td>
<td>4.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity threshold</th>
<th>Dvd</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>10⁻⁴</td>
<td>23.0</td>
<td>3.5</td>
</tr>
<tr>
<td>10⁻³</td>
<td>12.3</td>
<td>2.7</td>
</tr>
<tr>
<td>10⁻²</td>
<td>5.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Dvd = daratumumab, bortezomib, dexamethasone; ITT = intent to treat; MRD = minimal residual disease; NS = not significant; Vd = bortezomib, dexamethasone

P-values are calculated using likelihood-ratio chi-square test.

* p < 0.0001.

† p < 0.01.
Figure 4. PFS stratified by cytogenetic risk in all evaluable patients

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Dvd (n = 44)</th>
<th>Vd (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>11.2</td>
<td>7.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.27–0.89)</td>
<td>0.31 (0.16–0.62)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0167</td>
<td>0.0001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>p-value</td>
<td>0.019</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Table 1. Most common treatment-emergent adverse events (all patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>Dvd (n = 243)</th>
<th>Vd (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (≥25%)</td>
<td>145 (60)</td>
<td>110 (45)</td>
</tr>
<tr>
<td>Thrombocytopenia (≥5%)</td>
<td>105 (44)</td>
<td>78 (33)</td>
</tr>
<tr>
<td>Anemia</td>
<td>67 (28)</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>45 (19)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>32 (13)</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Non-hematologic, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>120 (49)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>83 (34)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>72 (30)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>66 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>53 (22)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>33 (14)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (9)</td>
<td>16 (7)</td>
</tr>
</tbody>
</table>

Dvd = daratumumab, bortezomib, dexamethasone; TEAE = treatment-emergent adverse event; Vd = bortezomib, dexamethasone
* Common TEAEs listed are either ≥25% all grade or ≥5% grade 3/4.
Vd arm treated for eight cycles and Dvd arm treated until progressive disease, per protocol.
• A PFS benefit was continually maintained with DVd over time.
• DVd was superior to Vd regardless of prior lines of therapy.
• The largest magnitude of benefit with DVd was observed in patients with one prior line of therapy, who had a 78% reduction in the risk of progression or death with DVd vs. Vd.
• More patients in the DVd arm achieved deeper responses with longer follow-up, including higher CR and MRD-negative rates.
  – MRD-negativity translated into longer PFS.
• DVd was superior to Vd regardless of cytogenetic risk or time since last therapy.
• These data support the use of DVd for patients with R/R MM, with most benefit observed in patients with one prior line of therapy.


Chari A, et al. ASH 2016:2133

Results of an early access program of daratumumab in U.S. patients with R/R MM

Background
A multicentre, open-label, Early Access Treatment Protocol (EAP) was opened in June 2015 after the MMY2002 study demonstrated the efficacy and safety profile of daratumumab in patients with relapsed/refractory (R/R) multiple myeloma (MM).¹ Results from the EAP were presented at the 2016 ASH Meeting.²

Study design
• The objectives of the EAP were to provide early access to daratumumab treatment and to collect safety and patient-reported outcome data in patients with MM who had received ≥3 prior lines of therapy, including a proteasome inhibitor (PI) and an immuno-modulatory agent (IMID), or who were double refractory to a PI and an IMID.
• Additional inclusion criteria were:
  ◦ Age ≥18 years;
  ◦ Documented MM;
  ◦ Progression by International Myeloma Working Group criteria; and
  ◦ An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2.
• Exclusion criteria were:
  ◦ Known chronic obstructive pulmonary disease (COPD);
  ◦ Persistent asthma;
  ◦ Ongoing MM therapy;
  ◦ Prior exposure to anti-CD38 antibody therapy;
  ◦ Absolute neutrophil count ≤0.5 × 10⁹/L;
  ◦ Platelet count <50 × 10⁹/L; and
  ◦ Creatinine clearance ≤20 ml/min/1.73 m².
• Patients received daratumumab at a dose of 16 mg/kg intravenously (iv) every week for eight weeks, then every two weeks for 16 weeks, and then every four weeks until disease progression, unacceptable toxicity, or 60 days after U.S. approval.
• Pre- and post-infusion medications were administered as per study MMY2002:
Daratumumab 16 mg/kg iv

D = day; iv = intravenous
Cycle length = 28 days.

Key findings

Baseline characteristics and disposition

- In total, 400 patients were screened and 348 patients were enrolled and dosed.
- Patients were enrolled at 39 U.S. sites from July to November 2015.
- The median age was 65 years (range: 27–94).
- The majority of patients were male (59%), Caucasian (72%), and had an ECOG PS of 1 (58%).
- Patients received a median eight doses of daratumumab (range: 1–17), and the median treatment exposure time was 1.9 months (range: 0.03–6.0).
- Patient disposition is summarized in Figure 1.

Efficacy

- The median change from baseline in all domains of the EuroQol-five dimensions, five-level questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scales was 0 after one and two cycles, as well as at patients’ last assessment. (Table 1)

Figure 1. Patient disposition

* Remaining patient disposition: five (1.4%) discontinued due to other reasons, four (1.1%) discontinued due to physician decision, two (0.6%) discontinued due to disease relapse, and one subject (0.3%) each discontinued due to adverse event (other) and lost to follow-up.
The exception to this was the EQ-5D-5L visual analogue scale, which showed a median increase of 1 and 2 units after one and two cycles, respectively.

**Safety**
- The total number of patients who experienced an adverse event (AE) was 281 (80.7%).
- Grade ≥3 AEs were reported in 50% of patients. (Table 2)
- The total number of patients who discontinued treatment due to an AE was 13 (3.7%).
- Serious AEs (SAEs) occurred in 35% of patients, including 12% of patients with SAEs that were determined by the investigator to be drug-related.
- Grade 3/4 SAEs occurred in 29.0% of patients. (Table 3)
- A total of 195 patients (56%) experienced infusion-related reactions (IRRs) during the study, and all 195 of them experienced IRRs during their first infusion. (Table 4)
- No subjects discontinued the study due to an IRR.

---

### Table 1. Patient-reported outcomes

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean, Median (N: Min, Max)</th>
<th>Cycle 2 Day 1 Mean, Median (N: Min, Max)</th>
<th>Cycle 3 Day 1 Mean, Median (N: Min, Max)</th>
<th>Last Assessment Mean, Median (N: Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EQ-5D-5L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utility score</td>
<td>0.75, 0.79 (324: 0.1, 1.0)</td>
<td>–0.01, 0.00 (223: –0.6, 0.3)</td>
<td>0.00, 0.00 (142: –0.6, 0.3)</td>
<td>–0.02, 0.00 (269: –0.6, 0.4)</td>
</tr>
<tr>
<td>VAS</td>
<td>63.06, 66.00 (324: 9.0, 100.0)</td>
<td>0.71, 1.00 (223: –70.0, 60.0)</td>
<td>3.35, 2.00 (142: –72.0, 58.0)</td>
<td>–0.16, 0.00 (269: –80.0, 58.0)</td>
</tr>
<tr>
<td><strong>EORTC QLQ-C30</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite loss</td>
<td>19.94, 0.00 (326: 0.0, 100.0)</td>
<td>5.04, 0.00 (225: –66.7, 100.0)</td>
<td>0.93, 0.00 (144: –66.7, 100.0)</td>
<td>4.57, 0.00 (270: –66.7, 100.0)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>76.89, 83.33 (326: 0.0, 100.0)</td>
<td>0.89, 0.00 (225: –83.3, 83.3)</td>
<td>0.93, 0.00 (144: –66.7, 83.3)</td>
<td>–0.74, 0.00 (270: –66.7, 66.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15.54, 0.00 (326: 0.0, 100.0)</td>
<td>0.44, 0.00 (225: –100.0, 100.0)</td>
<td>–1.16, 0.00 (144: –100.0, 66.7)</td>
<td>–0.49, 0.00 (270: –100.0, 66.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.48, 0.00 (326: 0.0, 100.0)</td>
<td>0.44, 0.00 (225: –66.7, 100.0)</td>
<td>1.62, 0.00 (144: –66.7, 100.0)</td>
<td>1.48, 0.00 (270: –100.0, 100.0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22.60, 33.33 (326: 0.0, 100.0)</td>
<td>–0.15, 0.00 (225: –66.7, 66.7)</td>
<td>–3.01, 0.00 (144: –55.6, 66.7)</td>
<td>3.71, 0.00 (270: –66.7, 66.7)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>77.53, 83.33 (326: 0.0, 100.0)</td>
<td>1.11, 0.00 (225: –75.0, 66.7)</td>
<td>2.49, 0.00 (144: –33.3, 41.7)</td>
<td>–1.42, 0.00 (270: –66.7, 66.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42.26, 33.33 (326: 0.0, 100.0)</td>
<td>3.01, 0.00 (225: –55.6, 66.7)</td>
<td>–0.54, 0.00 (144: –55.6, 55.6)</td>
<td>2.55, 0.00 (270: –66.7, 88.9)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>24.34, 0.00 (326: 0.0, 100.0)</td>
<td>–4.74, 0.00 (225: –100.0, 66.7)</td>
<td>–0.93, 0.00 (144: –100.0, 66.7)</td>
<td>2.35, 0.00 (270: –100.0, 66.7)</td>
</tr>
<tr>
<td>Global health status</td>
<td>58.61, 58.33 (326: 0.0, 100.0)</td>
<td>1.11, 0.00 (225: –58.3, 66.7)</td>
<td>4.69, 0.00 (144: –50.0, 66.7)</td>
<td>–1.48, 0.00 (270: –58.3, 66.7)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7.31, 0.00 (326: 0.0, 83.3)</td>
<td>1.04, 0.00 (225: –50.0, 100.0)</td>
<td>0.58, 0.00 (144: –33.3, 50.0)</td>
<td>3.46, 0.00 (270: –50.0, 100.0)</td>
</tr>
<tr>
<td>Pain score</td>
<td>39.11, 33.33 (326: 0.0, 100.0)</td>
<td>–1.41, 0.00 (225: –66.7, 83.3)</td>
<td>–2.55, 0.00 (144: –66.7, 66.7)</td>
<td>0.74, 0.00 (270: –66.7, 83.3)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>68.68, 73.33 (326: 6.7, 100.0)</td>
<td>–1.73, 0.00 (225: –80.0, 40.0)</td>
<td>0.83, 0.00 (144: –46.7, 66.7)</td>
<td>–3.40, 0.00 (270: –80.0, 53.3)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>64.37, 66.67 (326: 0.0, 100.0)</td>
<td>0.07, 0.00 (225: –83.3, 66.7)</td>
<td>0.81, 0.00 (144: –83.3, 66.7)</td>
<td>–3.70, 0.00 (270: –100.0, 66.7)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>29.86, 33.33 (326: 0.0, 100.0)</td>
<td>1.48, 0.00 (225: –100.0, 100.0)</td>
<td>–1.39, 0.00 (144: –66.7, 100.0)</td>
<td>–0.12, 0.00 (270: –100.0, 100.0)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>65.13, 66.67 (326: 0.0, 100.0)</td>
<td>2.67, 0.00 (225: –50.0, 66.7)</td>
<td>1.50, 0.00 (144: –83.3, 66.7)</td>
<td>–0.99, 0.00 (270: –100.0, 66.7)</td>
</tr>
</tbody>
</table>

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQol-five dimensions, five-level questionnaire; VAS = visual analogue scale.
In previous studies, daratumumab has been shown to have anti-myeloma activity in patients refractory to lenalidomide and bortezomib, and promising activity when combined with drugs such as lenalidomide and dexamethasone in patients with recurrent myeloma.

The results from this study demonstrate that daratumumab can be safely administered in a community-type setting. Although the efficacy of daratumumab, either alone or in combination therapies, in patients with recurrent or refractory myeloma has been demonstrated in previous studies, the adverse event profile highlighted here must be considered. Treatment-related adverse events (TRAEs) of grade ≥3 were mostly of the hematologic nature and occurred in 51% of patients. Furthermore, 12% of patients had serious TRAEs. This toxicity profile may be expected for a heavily pretreated myeloma population.

Additionally, infusion-related reactions (IRRs) occurred in 56% of patients and required careful management. Relatively long infusion times were required (between 3.5 and 7.4 h). Although these IRRs occurred in over half of patients, only 8% were grade ≥3. In order to limit IRRs, premedication with steroids and bronchodilators or other interventions were used. Optimizing strategies with premedication to mitigate IRRs could potentially reduce the incidence and severity of these reactions. These IRRs may limit access, particularly in busy chemotherapy units.

Finally, a reduction of IRRs would make this treatment more attractive.
Background
Daratumumab is a CD38-directed monoclonal antibody indicated for the treatment of patients with relapsed/refractory (R/R) multiple myeloma (MM). CD38 is expressed on airway smooth muscle cells, and infusion-related reactions (IRRs) in registration studies of daratumumab were marked by symptoms similar to those of allergic rhinitis (e.g., cough, wheezing, rhinorrhea). Anecdotal reports indicated that premedication with montelukast, a leukotriene receptor antagonist, may reduce the IRR rate associated with daratumumab therapy. At the 2016 ASH Meeting, Chari et al. presented results from the Early Access Treatment Protocol (EAP) that investigated the efficacy of montelukast premedication on IRR reduction in patients with R/R MM who were treated with daratumumab.¹

Study design
• The EAP was a multicentre, open-label study.
• The objectives of this study were to provide early access to daratumumab treatment, to collect safety data (including IRRs), and to allow the use of montelukast as a premedication for daratumumab therapy.
• Inclusion criteria were:
  ○ Age ≥18 years;
  ○ Documented MM;
  ○ Progression by International Myeloma Working Group criteria following the most recent therapy;
  ○ Three or more prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMID), or disease double refractory to a PI and an IMID; and
  ○ An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2.
• Exclusion criteria were:
  ○ Known chronic obstructive pulmonary disease (COPD);
  ○ Persistent asthma;
  ○ Ongoing MM therapy;
  ○ Prior exposure to anti-CD38 antibody therapy;
  ○ Absolute neutrophil count ≤0.5 × 10⁹/L;
  ○ Platelet count <50 × 10⁹/L; and
  ○ Creatinine clearance ≤20 mL/min/1.73 m².
• Patients received daratumumab at a dose of 16 mg/kg intravenously (iv) every week for eight weeks, then every two weeks for 16 weeks, and then every four weeks until disease progression, unacceptable toxicity, or 60 days after U.S. approval.
• Pre- and post-infusion medications were administered as per study MMY2002.
• Premedications administered one hour (± 15 minutes) prior to the daratumumab infusion included:
  ○ Methylprednisolone 100 mg (or equivalent) iv for the first two infusions, and 60 mg with subsequent infusions;
  ○ Acetaminophen 25–50 mg (or equivalent antihistamine drug).
• Postmedication included a corticosteroid (methylprednisolone 20 mg or equivalent) and was given on the two consecutive days following daratumumab infusions.²
• Montelukast was not recommended but was allowed at the investigator’s discretion.

Chari A, et al. ASH 2016:2142

Use of montelukast to reduce infusion reactions in an early access program of daratumumab in U.S. patients with R/R MM
Study design

Daratumumab 16 mg/kg iv

D1 D8 D15 D22 D1 D15 D1

Cycle 1–2 Cycle 3–6 Cycle 7+ Follow-up

$D = \text{day}; \text{iv} = \text{intravenous}$

Cycle length = 28 days.

- Patients received a median eight doses of daratumumab (range: 1–17), and the median treatment exposure time was 1.9 months (range: 0.03–6.0).

Safety
- A total of 195 patients (56%) experienced IRRs during the study, and all 195 of them experienced IRRs during their first infusion. (Table 1)
- The most common IRRs were respiratory or thoracic symptoms, which occurred in 31% of patients.
- Sixty patients received montelukast during therapy, including 50 patients who received montelukast 10 mg given >30 minutes prior to the first infusion. (Table 2)
- Median time for the first infusion was 6.7 and 7.6 hours for patients who did or did not receive montelukast, respectively, while times for subsequent infusions were similar in both groups.
- A total of 24 patients experienced IRRs that were considered serious adverse events, but no patient discontinued the study due to an IRR.

Key findings

Baseline characteristics and disposition

- In total, 400 patients were screened and 348 patients were enrolled and dosed.
- Patients were enrolled at 39 U.S. sites from July to November 2015.
- The median age was 65 years (range: 27–94).
- The majority of patients were male (59%), Caucasian (72%), and had an ECOG PS of 1 (58%).

- For subjects with a higher risk of respiratory complications (predicted % forced expiratory volume in one minute <75%), the following post-infusion medications were considered:
  - Diphenhydramine (25–50 mg) or equivalent on the two days following all daratumumab infusions;
  - Short-acting $\beta_2$ adrenergic receptor agonists such as salbutamol aerosol;
  - Inhaled corticosteroids ± long-acting $\beta_2$ adrenergic receptor agonists for subjects with asthma; and
  - Long-acting bronchodilators such as tiotropium or salbutamol ± inhaled corticosteroids for subjects with COPD.

Table 1. Infusion-related reactions

<table>
<thead>
<tr>
<th>IRRs (%)</th>
<th>N = 348</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade &gt;3 IRRs</td>
<td>8</td>
</tr>
<tr>
<td>Percentage of patients with IRRs</td>
<td></td>
</tr>
<tr>
<td>First infusion</td>
<td>56</td>
</tr>
<tr>
<td>Second infusion</td>
<td>2</td>
</tr>
<tr>
<td>All subsequent infusions</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory or thoracic symptoms</td>
<td>31</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>6</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>5</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>2</td>
</tr>
</tbody>
</table>

IRR = infusion-related reaction
The findings of the EAP study were similar to those observed in the MMY2002 registration study conducted on the same patient population.

The observed IRR rate during the first daratumumab infusion was one-third lower in patients who received 10 mg of montelukast >30 minutes prior to the first infusion vs. patients who did not receive montelukast.

- Respiratory and gastrointestinal symptoms were lower in patients who received montelukast, while chills were observed at a similar rate in both groups.

The median time for the first infusion was 0.9 hours shorter in patients who received montelukast.

Because the use of montelukast was limited to a small number of centres, the role of montelukast in reducing IRRs cannot be determined from these uncontrolled observations.

Additional studies to determine if montelukast mitigates the IRRs associated with the first infusion of daratumumab are needed.

### Key conclusions

- The findings of the EAP study were similar to those observed in the MMY2002 registration study conducted on the same patient population.²

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### Table 2. Observed IRRs in patients with or without montelukast therapy

<table>
<thead>
<tr>
<th></th>
<th>Montelukast 10 mg as pre-infusion (n = 50)</th>
<th>No montelukast given as pre-infusion (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRR rate at first infusion, %</td>
<td>38.0</td>
<td>58.5</td>
</tr>
<tr>
<td>Respiratory symptoms, %</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>Gastrointestinal symptoms, %</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Chills, %</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Median time for first infusion, hours</td>
<td>6.7</td>
<td>7.6</td>
</tr>
</tbody>
</table>

IRR = infusion-related reaction

This study sought to evaluate how infusion-related reactions (IRRs) related to treatment with daratumumab were affected by premedication with montelukast, a leukotriene receptor antagonist. The rationale for this stems from the high incidence of IRRs (up to 71% of patients in one phase I trial) and the requirement for relatively long infusion times (over 7 h for the first infusion).

A total of 348 patients were enrolled in an Early Access Program. Pre- and post-infusion systemic corticosteroids and post-infusion inhaled corticosteroids and bronchodilators were prescribed. Montelukast was used randomly in 50 patients based on investigator discretion.

The results of this study showed that the use of montelukast resulted in an IRR rate of 38% vs. 58.5% for those who did not receive montelukast for the first infusion. The rate of respiratory IRRs decreased from 32% to 20% and the rate of gastrointestinal IRRs decreased from 11% to 4%. In addition, the median duration time of IRRs was reduced from 7.6 to 6.7 h with the use of montelukast. The authors concluded that further studies to evaluate montelukast would be useful, suggesting perhaps a randomized trial.

The major limitation of this study is in the design, as patients were not randomized to receive or not receive montelukast. It is unclear why some patients were offered montelukast while others were not; there was likely some bias for its use. Furthermore, it was not clear whether the patients who received montelukast had all received the same other premedications.

Finally, the objective of making daratumumab infusions more tolerable and quicker warrants further investigation, and perhaps this abstract can give us some clues on how to approach it.

### Dr. Neil Berinstein: Insights on the Use of Montelukast in Patients with R/R Multiple Myeloma Receiving Daratumumab

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The findings of the EAP study were similar to those observed in the MMY2002 registration study conducted on the same patient population.

The observed IRR rate during the first daratumumab infusion was one-third lower in patients who received 10 mg of montelukast >30 minutes prior to the first infusion vs. patients who did not receive montelukast. Respiratory and gastrointestinal symptoms were lower in patients who received montelukast, while chills were observed at a similar rate in both groups.

The median time for the first infusion was 0.9 hours shorter in patients who received montelukast.

Because the use of montelukast was limited to a small number of centers, the role of montelukast in reducing IRRs cannot be determined from these uncontrolled observations.

Additional studies to determine if montelukast mitigates the IRRs associated with the first infusion of daratumumab are needed.

Key conclusions

We will change what a cancer diagnosis means. Together.

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Chronic Lymphocytic Leukemia

Long-term Studies Provide Reassurance on Efficacy and Safety of Treatments in Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is considered incurable with conventional therapies. However, with the emergence of novel agents and combination therapies, many clinical trial programs have been established and demonstrated significant improvement in patient survival. The favourable study results have prompted investigation on the long-term efficacy and safety profiles for these treatments, and a majority of patients enrolled in these trials continued on their treatment for an extended period of time.

One such clinical trial is the CLL10 study, conducted by the German CLL Study Group, which aimed to show the noninferiority of bendamustine plus rituximab (BR) compared to fludarabine, cyclophosphamide, and rituximab (FCR) in fit, elderly patients. For patients with CLL who are young and fit, FCR is the gold-standard therapy; however, due to the significant toxicities associated with FCR, it is an unsuitable treatment for older patients with CLL, who often have multiple comorbidities. As the median age of patients with CLL is 72 years, many patients with CLL are unable to tolerate FCR therapy and require alternative treatment. In the CLL10 study, at a median follow-up of 37.1 months, BR showed comparable efficacy and reduced toxicity in fit patients older than 65 years when compared with FCR, indicating that BR is a suitable alternative to FCR in this patient population.

For patients with CLL who are young and fit, FCR is the gold-standard therapy; however, due to the significant toxicities associated with FCR, it is an unsuitable treatment for older patients with CLL, who often have multiple comorbidities. As the median age of patients with CLL is 72 years, many patients with CLL are unable to tolerate FCR therapy and require alternative treatment. In the CLL10 study, at a median follow-up of 37.1 months, BR showed comparable efficacy and reduced toxicity in fit patients older than 65 years when compared with FCR, indicating that BR is a suitable alternative to FCR in this patient population. Based on these data, long-term follow-up has been initiated to confirm that results are consistent.

Aside from the CLL10 study, long-term efficacy and safety have also been examined for novel targeted agents in patients with treatment naïve (TN) or relapsed/refractory (R/R) CLL/small lymphocytic lymphoma (SLL). Studies have shown that these targeted agents have tolerable safety profiles, which make them suitable for physically unfit and elderly patients, and they are efficacious in patients with cytogenetic abnormalities such as deletion of 17p (del[17p]) or 11q (del[11q]), who typically respond poorly to chemoimmunotherapy.

Among these targeted agents is ibrutinib, a first-in-class, oral, covalent inhibitor of Bruton’s tyrosine kinase. Ibrutinib has been approved by Health Canada for patients with CLL/SLL who received ≥1 prior therapy or those with del(17p). This approval was based on data from the phase III RESONATE™ trial, which showed a 78% and 57% reduction in the risk of progression and death, respectively, in patients with R/R CLL treated with ibrutinib compared with ofatumumab. In the RESONATE™-2 study, ibrutinib has also demonstrated reduced risk of progression or death (by 84%) compared to chlorambucil in elderly patients with TN CLL/SLL. In addition, ibrutinib has also shown encouraging results in the phase Ib/II PCYC-1102 study in patients with TN and R/R CLL/SLL. The promising short-term efficacy and safety profile for ibrutinib shown in these studies urges researchers to perform longer term follow-ups.

Another targeted agent that is being examined in longer term follow-up is idelalisib. Idelalisib is a first-in-class, oral inhibitor which selectively targets phosphatidylinositol 3-kinase (PI3K) delta; it has been approved by Health Canada in combination with rituximab for the treatment of patients with relapsed CLL. In a phase III study, idelalisib in combination with BR has been shown to improve progression-free survival in patients with R/R CLL when compared with BR alone after a median follow-up of 12 months, which prompted further analysis of overall survival in a longer observation time.

At the 2016 American Society of Hematology (ASH) Annual Meeting, long-term efficacy and safety of the aforementioned therapies in CLL were reported:

- In an updated analysis of the CLL10 study, BR continued to show comparable efficacy with a favourable toxicity profile compared to FCR in fit, elderly patients with CLL. (Eichhorst BF, et al. ASH 2016:4382)
• After a longer observation period, overall survival was in favour of idelalisib plus BR compared to BR alone in patients with R/R CLL, regardless of high-risk features, and the combination had a manageable safety profile. (Zelenetz AD, et al. ASH 2016:231)

• The extension study of PCYC-1102, which is the longest experience to date for ibrutinib-treated patients, confirmed ibrutinib’s durable responses and tolerable safety profile in patients with TN or R/R CLL/SLL, including those with cytogenetic abnormalities. (O’Brien SM, et al. ASH 2016:233)

• In the long-term follow-up of the RESONATE™-2 study, ibrutinib continued to demonstrate substantial efficacy and reduction in risk of progression or death in elderly patients with TN CLL/SLL when compared with chlorambucil. (Barr PM, et al. ASH 2016:234)

• The integrated safety analysis of RESONATE™ and RESONATE™-2, and the long-term safety analysis of PCYC-1102/1103 supported the manageable safety profile of prolonged ibrutinib treatment in patients with TN and R/R CLL/SLL. (Coutre S, et al. ASH 2016:4383)


Eichhorst BF, et al. ASH 2016:4382

Favourable toxicity profile and long-term outcome of elderly, physically fit CLL patients receiving first-line BR chemoimmunotherapy in comparison to FCR in advanced CLL: Update analysis of the CLL10 study

Background
Fludarabine, cyclophosphamide, and rituximab (FCR) is the standard frontline regimen for physically fit patients with chronic lymphocytic leukemia (CLL) without tumour protein 53 (TP53) alteration. The CLL10 study, conducted by the German CLL Study Group (GCLLSG), has previously demonstrated the noninferiority of bendamustine plus rituximab (BR) compared to FCR in this population.1 At the 2016 ASH Meeting, Eichhorst and colleagues presented an updated analysis of the study, which evaluated the long-term outcome and toxicity.2

Study design
• The CLL10 study was an international, phase III, multicentre trial that evaluated the noninferiority of BR compared to FCR for progression-free survival (PFS) in frontline therapy of physically fit patients with CLL.

• Trial inclusion criteria allowed enrolment of patients with untreated active CLL, without significant comorbidity (Cumulative Illness Rating Score ≤6 and normal creatinine clearance), and without the deletion of 17p (del[17p]).

• A total of 688 patients were screened and 561 patients were randomized to receive FCR (n = 282) or BR (n = 279).

• Patients were followed every three months for two years and every six months for three years, then annually until progressive disease (PD).

• After PD, annual visits were documented either within the study or within the GCLLSG registry.

• Health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer questionnaire (EORTC C30), which was completed at baseline, after Month 3, 6, and 12, and then annually until Year 5.

• The median observation time was 58.2 months.
**Study design**

- Patients with untreated active CLL, without significant comorbidity (CIRS ≤ 6 and normal creatinine clearance), and without del(17p)

---

**6 x FCR**
- Fludarabine 25 mg/m² iv, Days 1–3
- Cyclophosphamide 250 mg/m² iv, Days 1–3
- Rituximab 375 mg/m² iv Day 0, Cycle 1
- Rituximab 500 mg/m² iv Day 1, Cycles 2–6; q28d

**6 x BR**
- Bendamustine 90 mg/m² iv, Days 1–2
- Rituximab 375 mg/m² iv Day 0, Cycle 1
- Rituximab 500 mg/m² iv Day 1, Cycles 2–6; q28d

Follow-up until PD = long-term observation within the GCLLSG registry

---

**Key findings**

- The median age was 61.5 years.
- There were 86 and 108 patients who were >65 years in the FCR and BR arms, respectively.
- The median PFS for FCR was 57.6 months, compared to 42.3 months for the BR arm (HR = 1.593; 95% CI: 1.271–1.996; p < 0.0001). (Figure 1)
- While the median PFS for FCR vs. BR was significantly different in younger patients with age ≤65 years (57.6 months vs. 38.2 months; p < 0.0001), the difference between arms was not statistically significant in elderly patients with age >65 years (57.9 months vs. 48.5 months; p = 0.134). (Figure 2)
- The difference in overall survival (OS) for younger patients and elderly patients was not statistically significant between both arms. For younger patients, the OS at 5 years was 85.6% for FCR and 81.1% for BR; for elderly patients, the OS at 5 years was 70.9% for FCR and 78.8% for BR.
- A total of 51 patients (18.1%) died in the FCR arm and 54 patients (19.4%) died in the BR arm. The main causes of death are outlined in Table 1.

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**Figure 1. Progression-free survival**

![Progression-free survival](image1)

**Figure 2. PFS according to treatment and age**

![Progression-free survival according to treatment and age](image2)

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**Secondary malignancies were documented in 49 patients (17%) in the FCR arm and 35 patients (13%) in the BR arm. (Table 2)**

- Secondary myelodysplastic syndrome and/or acute myeloid leukemia occurred more frequently after FCR therapy, particularly in elderly patients.
- Following frontline treatment, 77 patients (27.3%) in the FCR arm and 108 patients (38.7%) in the BR arm received at least one subsequent therapy. Second-line treatments are outlined in Table 3.
- A total of 540 patients (96.3%) were evaluable for HRQoL analysis, with 272 patients in the FCR arm and 268 patients in the BR arm.

- No differences were detected between arms with respect to global health status or any functional or symptom scale.
- Compared to an age- and sex-matched normal population, functional scale values were impaired mostly during treatment phase, and symptom scale values were affected during follow-up.
• Long-term follow-up of the CLL10 study confirms the superiority of the FCR regimen in young and fit patients with CLL.

• BR is an alternative frontline treatment option in fit elderly patients with CLL.

**Table 1. Main causes of death**

<table>
<thead>
<tr>
<th></th>
<th>FCR n (%)</th>
<th>BR n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPM</td>
<td>14 (5.0)</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>CLL/RT</td>
<td>11 (3.9)</td>
<td>15 (5.4)</td>
</tr>
<tr>
<td>Infections</td>
<td>7 (2.5)</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td>6 (2.1)</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>Other*</td>
<td>13 (4.6)</td>
<td>7 (2.5)</td>
</tr>
</tbody>
</table>

*BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, rituximab; RT = Richter’s transformation; SPM = secondary primary malignancy

**Table 2. Secondary primary malignancies**

<table>
<thead>
<tr>
<th></th>
<th>FCR (n = 279) n (%)</th>
<th>BR (n = 278) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPM</td>
<td>49 (17)</td>
<td>35 (13)</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>28 (10)</td>
<td>25 (9)</td>
</tr>
<tr>
<td>Skin tumour</td>
<td>9 (4)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>All</td>
<td>9 (3)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>6 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>RT</td>
<td>5 (2)</td>
<td>8 (3)</td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia; BR = bendamustine plus rituximab; FCR = fludarabine, cyclophosphamide, rituximab; MDS = myelodysplastic syndrome; RT = Richter’s transformation; SPM = secondary primary malignancies

**Table 3. Second-line treatment**

<table>
<thead>
<tr>
<th></th>
<th>FCR (n = 77)</th>
<th>BR (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>BR</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Antibody alone</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ibrutinib or idelalisib + rituximab</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>24</td>
</tr>
</tbody>
</table>

*BR = bendamustine plus rituximab; FCR = fludarabine, cyclophosphamide, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine

Canadian Perspective by Dr. Carolyn Owen on the Updated Analysis of the CLL10 Study that Examined Long-term Outcome of First-line BR Therapy Compared to FCR in Fit, Elderly Patients with CLL

In the treatment of chronic lymphocytic leukemia (CLL), a key challenge is patient tolerability of the most effective treatment, which is often accompanied by toxicities that are difficult to manage. In Canada, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) is the standard of care for first-line, fit, and young patients with CLL. FCR has demonstrated an overall survival (OS) advantage when compared to fludarabine and cyclophosphamide, and it has been shown to induce long remission durations in patients with CLL. However, it is associated with significant toxicities such as prolonged cytopenias, increased risk of infections, and secondary malignancies, which may be intolerable for unfit or older patients. Since the median age of patients with CLL at diagnosis is 72 years², and the average age of patients receiving treatment would be older than that because less than half of those patients require treatment upon first diagnosis, most treated CLL patients have multiple comorbidities and require alternative treatment options.

For older patients who are relatively fit or any patient who can tolerate treatments that are more aggressive than chlorambucil-based therapies, one treatment option is bendamustine plus rituximab (BR), which is available in many provinces. For unfit, elderly patients with CLL, most centres have adopted the regimen from the CLL11 study conducted by the German CLL Study Group (GCLLSG) and use the combination of chlorambucil and obinutuzumab.³

In the treatment of chronic lymphocytic leukemia (CLL), a key challenge is patient tolerability of the most effective treatment, which is often accompanied by toxicities that are difficult to manage. In Canada, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) is the standard of care for first-line, fit, and young patients with CLL. FCR has demonstrated an overall survival (OS) advantage when compared to fludarabine and cyclophosphamide, and it has been shown to induce long remission durations in patients with CLL. However, it is associated with significant toxicities such as prolonged cytopenias, increased risk of infections, and secondary malignancies, which may be intolerable for unfit or older patients. Since the median age of patients with CLL at diagnosis is 72 years², and the average age of patients receiving treatment would be older than that because less than half of those patients require treatment upon first diagnosis, most treated CLL patients have multiple comorbidities and require alternative treatment options.

For older patients who are relatively fit or any patient who can tolerate treatments that are more aggressive than chlorambucil-based therapies, one treatment option is bendamustine plus rituximab (BR), which is available in many provinces. For unfit, elderly patients with CLL, most centres have adopted the regimen from the CLL11 study conducted by the German CLL Study Group (GCLLSG) and use the combination of chlorambucil and obinutuzumab.³

**Key conclusions**

• Long-term follow-up of the CLL10 study confirms the superiority of the FCR regimen in young and fit patients with CLL.

• BR is an alternative frontline treatment option in fit elderly patients with CLL.

When determining patient fitness, I would mostly consider kidney function, comorbidities, and the number of concomitant medications. I worry about drug clearance in those with reduced renal function because it can greatly affect treatment outcome due to tolerability. Since liver failure or significant liver dysfunction is uncommon in patients with CLL, poor kidney function is the most important problem that usually leads to treatment modification. For a full assessment of comorbidities, I tend to use the Cumulative Illness Rating Score (CIRS) because this was an inclusion criteria in the GCLLSG CLL8 and CLL11 practice-changing studies. However, most physicians do not look at the CIRS score; rather, they base their assessment of fitness on age and functional ability.

The CLL10 study conducted by the GCLLSG aimed to show the noninferiority of BR compared to FCR based on progression-free survival (PFS) in fit patients with CLL. Overall, the rationale and design of the CLL10 study were excellent. It was a properly conducted, randomized, phase III study in a large population. In terms of patient selection, patients with CIRS ≤6 and normal creatinine clearance were included. This patient population is less reflective of the general CLL population because many real-world patients have either CIRS >6 or reduced renal function upon their first treatment and are not as fit as those included in this study. Moreover, the median age was 61.5 years, which is younger than that of an average patient with CLL. These differences cause difficulty in extrapolating results from this study to a broader CLL population.

At the 2016 ASH Meeting, the long-term follow-up of the CLL10 study was presented, which confirmed the superiority of FCR in young and fit patients with CLL (age ≤65 years), and supported the recommendation of using BR in fit, elderly patients with age >65 years. The median PFS for young patients was 57.6 months for FCR compared to 38.2 months for BR (p <0.0001), while the median PFS for patients with age >65 years was not significantly different between treatment groups. For young and fit patients, the data continue to indicate that FCR is a more effective therapy than BR and that it produces longer remissions. However, FCR was associated with more frequent adverse events (AEs), particularly infectious toxicity, compared to BR. For fit, elderly patients, the data justified using BR as an alternative frontline treatment because FCR and BR had similar efficacy in this patient subgroup and FCR treatment resulted in a significant excess of AEs. In addition, this long-term follow-up data continues to show no difference in OS, which reassures clinicians in their choice of FCR or BR.

The original CLL10 presentation supported the use of BR in fit, elderly patients, and its results led to a change in our practice where BR was then used in many CLL patients. This longer-term follow-up gives us similar information as the published data and does not change our interpretation; thus, it does not influence our practice. It would be more interesting to see longer follow-ups in patients who are treated more recently because treatment options in CLL have changed significantly since this study was started (e.g., availability of novel agents at relapse). Moreover, a more in-depth, longer-term safety analysis is desired because the current follow-up only reported deaths and frequency of secondary malignancies after a relatively short period. There are still a lot of questions about secondary malignancies and the length of the current follow-up is too short to make any conclusions about this adverse event.

Based on the CLL10 study and its long-term follow-up, I would recommend BR as first-line treatment to fit, elderly patients with age >65 years. Since elderly patients tolerated FCR poorly, we would extrapolate that younger, less fit patients would be similar. Thus, many clinicians would assume that BR is safer than FCR in young unfit patients, though the CLL10 study did not include such patients and such a study has not been conducted.

Overall, since a minority of the total CLL patient population can tolerate FCR well, the CLL10 study and its long-term follow-up support using BR in a relatively large percentage of first-line patients. In many centres, physicians prefer to give a stronger treatment, such as BR, rather than a chlorambucil-based therapy as first-line treatment in younger unfit patients, though a study of BR versus chlorambucil plus obinutuzumab has not been performed.

**References:**
Updated analysis of overall survival in randomized phase III study of idelalisib in combination with BR in patients with relapsed/refractory CLL

Background
Idelalisib in combination with bendamustine and rituximab (BR) has been shown to improve progression-free survival (PFS) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) when compared with BR alone after a median follow-up of 12 months. At the 2016 ASH Meeting, Zelenetz and colleagues presented the updated data on overall survival (OS) in this study.²

Study design
- This was a phase III, randomized, placebo-controlled study, which was unblinded by the independent data monitoring committee at the first interim analysis for efficacy.
- Between June 2012 and August 2014, patients with R/R CLL were enrolled in the study across 19 countries. Key eligibility criteria included:
  - Age ≥ 18 years;
  - R/R CLL requiring treatment;
  - CLL progression within 36 months from the last prior therapy;
  - Measurable disease;
  - No history of transformation of CLL;
  - No progression within six months from the last bendamustine treatment; and
  - No prior treatments with inhibitors of the B-cell pathway.
- Patients were randomized to BR for six four-week cycles and idelalisib (arm A) or placebo (arm B).
- Stratification was based on the presence of deletion of 17p (del[17p]) and/or tumour protein 53 (TP53) mutation, immunoglobulin heavy chain variant (IGHV) mutation status, and disease status (refractory vs. relapsed CLL).
- Pre-specified interim analysis was performed at 67% of the total number of planned events of CLL progression.
- There was an improvement in median PFS from 15 months to 22.5 months due to the addition of idelalisib to BR (HR = 0.67).
- The primary endpoint was PFS, assessed by independent review committee (IRC).
- Secondary endpoints included OS, overall response rate (ORR), nodal response, and complete response (CR).

Study design

![Double-blind initial combination therapy](image)

**Arm A**
- n = 207
- **B (70 mg/m² D1, D2 of each four-week cycle, C1–C6)**
- **R (375 mg/m² C1, 500 mg/m² C2–C6)**
- **Idelalisib (150 mg bid)**

**Arm B**
- n = 209
- **B (70 mg/m² D1, D2 of each four-week cycle, C1–C6)**
- **R (375 mg/m² C1, 500 mg/m² C2–C6)**
- **Placebo (bid)**

**Post-study therapy**
- Investigator’s choice (standard of care or investigational)

*B = bendamustine; bid = twice daily; C = cycle; D = day; PD = disease progression; R = rituximab*
Key findings

Baseline characteristics and disposition

- A total of 416 patients were enrolled in the study (n = 207 for idelalisib plus BR, n = 209 for placebo plus BR).
- The percentage of male patients was similar between arms (77% for idelalisib plus BR, 75% for placebo).
- The median age of patients was 62 years (range: 38–83) in the idelalisib plus BR arm and 64 years (range: 32–82) in the placebo arm.
- A total of 48% of patients in the idelalisib plus BR arm and 42% of patients in the placebo arm had Rai stage III/IV disease.
- The median number of prior therapies was two for both arms.
- In both arms, 33% of patients had del(17p) and/or TP53 mutation.
- There were 84% and 83% of patients with unmutated IGHV in the idelalisib plus BR and control arms, respectively.
- There were 34% and 33% of patients with refractory disease in the idelalisib plus BR and control arms, respectively.
- Data cutoff of the current analysis was in May 2016, representing a median follow-up of 21 months (range: 0.1–43.3).

Efficacy

- In the intent-to-treat population, the median OS for idelalisib plus BR was not reached, compared to 40.6 months for placebo plus BR (HR = 0.67; 95% CI: 0.47–0.96; p = 0.04). (Figure 1)
- In patients without del(17p) or TP53, the median OS was not reached in the idelalisib plus BR arm, compared to 40.6 months in the control arm (HR = 0.67; 95% CI: 0.4–1.12; p = 0.12).
- The median IRC-assessed PFS of idelalisib plus BR vs. placebo was 23 vs. 11.1 months (HR = 0.67; 95% CI: 0.24–0.41; p <0.0001). (Figure 2)
- In all the subgroups analyzed, OS favoured idelalisib plus BR.

Safety

- In the idelalisib plus BR arm, 64 patients discontinued the study; 44 patients discontinued the study in the control arm. Reasons for discontinuation include adverse events (AEs), physician decision, consent withdrawal, and other.
- There were 35% and 68% of patients in the idelalisib plus BR and control arms, respectively, who were off study due to disease progression or death.
- AE summary is outlined in Table 1.
  - Serious AEs (SAEs) occurred in 147 patients (71%) in the idelalisib plus BR arm and 94 patients (45%) in the control arm.
  - The most common all-grade AEs with idelalisib plus BR were neutropenia (64%) and pyrexia (44%); with placebo plus BR, they were neutropenia (55%) and nausea (35%).

Figure 1. OS in intent-to-treat population

<table>
<thead>
<tr>
<th>At risk (events)</th>
<th>Median OS, months</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib + BR</td>
<td>NR</td>
<td>0.67</td>
<td>0.47–0.96</td>
<td>0.04 (stratified)</td>
</tr>
<tr>
<td>Placebo + BR</td>
<td>40.6</td>
<td></td>
<td></td>
<td>0.06 (unstratified)</td>
</tr>
</tbody>
</table>

BR = bendamustine plus rituximab; CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival
The most common grade ≥3 AEs with idelalisib plus BR were neutropenia (60%) and febrile neutropenia (24%); with placebo plus BR, they were neutropenia (47%) and anemia (13%).

Grade ≥3 diarrhea occurred in 12% of patients treated with idelalisib plus BR and in 2% of patients treated with placebo plus BR.

Transaminase abnormalities were observed more frequently in the idelalisib plus BR vs. placebo plus BR arms.

- Alanine transaminase (ALT) elevation of any grade was observed in 63% and 32% of patients in the idelalisib plus BR and placebo plus BR arms, respectively.
- Grade ≥3 ALT elevation was observed in 21% and 3% of patients in the idelalisib plus BR and placebo plus BR arms, respectively.
- Aspartate transaminase (AST) elevation of any grade was observed in 54% and 29% of patients in the idelalisib plus BR and placebo plus BR arms, respectively.
- Grade ≥3 AST elevation was observed in 16% and 3% of patients in the idelalisib plus BR and placebo plus BR arms, respectively.

Infections and infestations occurred in 73% and 60% of patients in the idelalisib plus BR and placebo plus BR arms, respectively.

- The total number of patients with opportunistic infections (*Pneumocystis jirovecii* pneumonia/cytomegalovirus) was 5/13 in the idelalisib plus BR arm vs. 0/3 in the placebo arm.

**Figure 2. IRC-assessed PFS**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>PFS probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 1. Adverse event summary**

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + BR (n = 207)</th>
<th>Placebo + BR (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>207 (100)</td>
<td>203 (97)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>196 (95)</td>
<td>163 (78)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>147 (71)</td>
<td>94 (45)</td>
</tr>
<tr>
<td>AE leading to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug dose reduction</td>
<td>34 (16)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Study drug discontinuation</td>
<td>68 (33)</td>
<td>31 (15)</td>
</tr>
<tr>
<td>Death</td>
<td>25 (12)</td>
<td>19 (9)</td>
</tr>
</tbody>
</table>

AE = adverse event; BR = bendamustine plus rituximab; SAE = serious AE
The combination of idelalisib and BR was superior to BR alone with regards to OS in patients with R/R CLL.

The efficacy results were consistent across patients with or without high-risk features, such as del(17p)/TP53 mutations, unmutated IGHV, and refractory disease.

The safety profile was manageable.

Opportunistic infections and SAEs were more frequent with idelalisib plus BR.

Idelalisib plus BR represents an important option for patients with R/R CLL.

Key conclusions


Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory CLL/SLL

Background

The PCYC-1102 trial has demonstrated the efficacy and tolerability of single-agent ibrutinib in patients with treatment naïve (TN) or relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).1,2 At the 2016 ASH Meeting, O’Brien and colleagues reported the efficacy and safety of ibrutinib in a five-year follow-up study (PCYC-1103), which is the longest experience to date for ibrutinib-treated patients.3

Study design

- The PCYC-1103 study is an extension of the phase II PCYC-1102 study.

- Patients with CLL/SLL received 420 mg or 840 mg of oral ibrutinib once daily.

- Overall response rate (ORR), including partial response (PR) with lymphocytosis (PR-L), was assessed using the updated International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria.

- Responses were assessed by risk groups: unmutilated immunoglobulin heavy chain variant (IGHV), complex karyotype (≥3 unrelated chromosomal abnormalities by stimulated cytogenetics, assessed by a reference lab), and in hierarchical order for deletion of 17p (del[17p]) then deletion of 11q (del[11q]).

- Grade ≥3 adverse events (AEs), serious AEs (SAEs), and AEs requiring dose reduction or discontinuation were recorded.
Key findings

Baseline characteristics and disposition

- There were 31 patients who were TN and 101 patients with R/R CLL/SLL.
- The median age of TN patients was 71 years (range: 65–84) and the median age of patients with R/R disease was 64 years (range: 37–82).
  - There were 74% of TN patients and 34% of patients with R/R CLL/SLL who were ≥70 years.
  - There were 55% of TN patients and 57% of patients with R/R CLL/SLL with Rai stage III/IV disease.
- Patient’s cytogenetic abnormalities and IGHV mutation are summarized in Table 1.

Efficacy

- The median time on study for TN patients was 62 months (range: 1–67) and 49 months (range: 1–67) for patients with R/R disease.
- After five years of follow-up, 65% of TN patients and 30% of patients with R/R disease remained on ibrutinib therapy.
- Primary reasons for discontinuation include progressive disease, AE, consent withdrawal, investigator decision, and lost to follow-up.

Table 1. Patients’ cytogenetic abnormalities and IGHV mutation

<table>
<thead>
<tr>
<th>Cytogenetic abnormalities, %</th>
<th>TN (n = 31)</th>
<th>R/R (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(17p)</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Del(13q)</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>Unmutated IGHV, %</td>
<td>48</td>
<td>78</td>
</tr>
</tbody>
</table>

Figure 1. ORR in all treated patients

Figure 2. ORR in patients with R/R disease and high-risk abnormalities

Key conclusions
• Median overall survival (OS) was not reached for all treated patients, with five-year OS rates of 92% for TN patients and 57% for patients with R/R disease.

• In patients with R/R disease, the median PFS was 63 months for patients with mutated IGHV and 43 months for patients with unmutated IGHV, with five-year PFS rates of 53% and 38%, respectively.

• The PFS outcomes sorted by chromosomal abnormalities in patients with R/R disease are shown in Figure 4.
  - There were two TN patients with chromosomal abnormalities who showed progressive disease or death.
  - Median PFS was 33 months for patients with complex karyotype and it was not reached for patients without complex karyotype.
  - The majority of patients (90%) with complex karyotype had R/R disease, with a median of 4 prior therapies.

• Median PFS was not reached for patients with no prior therapies, 63 months for those with 1–2 prior therapies, 59 months for those with 3 prior therapies, and 39 months for those with 4 prior therapies.

• Multivariate analysis identified del(17p) as a significant predictor of PFS and OS.

Safety

• Among all-treated patients, the onset of grade ≥3 treatment-emergent AEs was highest in the first year and decreased during subsequent years.

• With five years of follow-up, the most frequent grade ≥3 AEs were hypertension (26%), pneumonia (22%), neutropenia (17%), and atrial fibrillation (9%).

Key conclusions

• At five years of follow-up, single-agent ibrutinib continues to show durable responses in patients with TN or R/R CLL/SLL, including those with del(17p), del(11q), or unmutated IGHV.

• Survival outcomes for patients with complex karyotype or del(17p) were less robust compared to those in the lower risk genetic groups.

• Ibrutinib was well tolerated, and the manageable safety profile allows for extended dosing.

Background
The RESONATE™-2 trial had previously shown that ibrutinib significantly reduced the risk of progression or death by 84% in older patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). The current extension study provides updated efficacy and safety results of ibrutinib versus chlorambucil for RESONATE™-2.

Study design
• RESONATE™-2 (PCYC-1115) was a randomized, phase III, open-label, multicentre, international study.
• Treatment-naïve patients with CLL/SLL who were 65 years of age or older were randomized 1:1 to receive ibrutinib or chlorambucil.
• Patients with deletion of 17p (del[17p]) were excluded.
• Primary endpoint was progression-free survival (PFS), as evaluated by the independent review committee (as per the 2008 International Workshop on CLL criteria).
• Secondary endpoints included overall survival (OS), overall response rate (ORR), rate of hematologic improvement, and safety.

Key findings
• A total of 269 patients were enrolled in the study (n = 136 for the ibrutinib arm, n = 133 for the chlorambucil arm).
• Baseline characteristics were balanced between treatment arms:
  o The median age was 73 years, with 70% of patients aged over 70 years; and
  o Approximately 45% of patients had advanced Rai stage disease, 20% had deletion of 11q (del[11q]), and 69% had comorbidities at baseline, including a Cumulative Illness Rating Scale (CIRS) score >6, reduced creatinine clearance, or an Eastern Cooperative Oncology Group (ECOG) performance status of 2.
• The median follow-up was 29 months.
• Median PFS was not reached in the ibrutinib arm compared to 15 months in the chlorambucil arm, demonstrating that there was an 88% reduction in the risk of progression or death for patients who received ibrutinib. (Figure 1)
• Subgroup analysis of PFS revealed that the effect of ibrutinib was preserved across all subgroups.
• There was a 99% reduction in the risk of progression or death for patients with del(11q) who received ibrutinib, and a 82% reduction in those without del(11q). (Figure 2)
• The two-year OS was estimated to be 95% and 84% in the ibrutinib and chlorambucil arms, respectively.
• The investigator-assessed ORR was 92% and 36% in the ibrutinib and chlorambucil arms, respectively.
• Overall, 4/135 patients discontinued ibrutinib due to progressive disease.
• One case of Richter’s transformation was observed in each arm.
• In the ibrutinib arm, grade ≥3 AEs occurring in ≥5% of patients included neutropenia (12%), pneumonia (7%), anemia (7%), and hypertension (5%).
• AEs led to dose reductions in 13% of patients.
• Major hemorrhage occurred in 7% of patients and atrial fibrillation occurred in 10% of patients in the ibrutinib arm.
Figure 1. PFS of ibrutinib vs. chlorambucil

![Graph showing PFS of ibrutinib vs. chlorambucil with time in months on the x-axis and PFS (%) on the y-axis.]

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>24-month PFS, %</td>
<td>89</td>
<td>34</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.121 (0.074–0.198)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

Figure 2. PFS in patients with del(11q)

![Graph showing PFS in patients with del(11q) with time in months on the x-axis and PFS (%) on the y-axis.]

<table>
<thead>
<tr>
<th></th>
<th>Del(11q)</th>
<th>No del(11q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.014 (0.002–0.108)</td>
<td>0.180 (0.106–0.303)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; del(11q) = deletion of 11q; HR = hazard ratio; PFS = progression-free survival

Key conclusion

- **Ibrutinib continued to have substantial efficacy compared to chlorambucil in elderly patients with CLL/SLL.**

References:
Abstracts #233 and #234 presented at ASH 2016 are best appreciated together. Both address the long-term outcomes using ibrutinib for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). In the first abstract, Dr. Susan O’Brien describes the long-term follow-up of patients treated with ibrutinib. In the second abstract, Dr. Paul Barr describes the outcome on the experimental arm of RESONATE™-2 where patients received ibrutinib. Results are largely consistent across both studies; ibrutinib has been proven to be a remarkably effective and well tolerated treatment. The responses to the treatment have also proven durable, with the two studies showing a 5-year progression-free survival (PFS) of 92% (O’Brien) and a 2-year PFS of 89% (Barr), respectively. Both studies used daily oral ibrutinib and patients tolerated it very well, with very modest levels of grade 3/4 toxicities.

Finally, oral ibrutinib was able to overcome the adverse effect associated with major prognostic factors. Patients with 11q deletion and patients with unmutated Immunoglobulin Heavy Chain Variable gene responded equally well compared to those without these adverse factors, an achievement never seen with a well-tolerated agent for CLL in the past.

The B-cell response pathway inhibitors, led by the first widely-tested agent, ibrutinib, are transforming the management of CLL. The updates of these two experiences verify that this agent is remarkably effective, well tolerated even over years of administration, and able to overcome previously resistant types of CLL in the majority of patients. Keep your eye on them!

Dr. Paul Barr presented updated results of RESONATE™-2, a large phase III trial that randomized elderly treatment-naïve patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), with few comorbidities, to receive ibrutinib or chlorambucil. Preliminary results published in 2015 (Burger et al., N Engl J Med 2015;373:2425) demonstrated a substantial advantage in both progression-free survival (PFS) and overall survival (OS) in the ibrutinib arm. With extended median follow-up from 18 to 29 months, PFS remained significantly superior for the ibrutinib arm (89% vs. 34% at 24 months). OS was also superior in the ibrutinib arm despite a crossover rate of 41%.

This study confirms an unquestionable advantage of single-agent ibrutinib over chlorambucil in the treatment-naïve setting, lending credence to a chemotherapy-free approach in CLL/SLL and expanding valuable data on ibrutinib in treatment-naïve patients. However, the comparator arm of chlorambucil is no longer relevant because a survival advantage, by combining it with anti-CD20 antibody obinutuzumab in elderly patients with comorbidities, has been previously shown (Goede et al., N Engl J Med 2014;370:1101). Furthermore, the cost and duration of therapy is substantially greater for ibrutinib, which is particularly relevant in publicly-funded jurisdictions. For these reasons, caution should be exercised before widely adopting front-line ibrutinib in elderly patients with CLL until definitive evidence of its superiority to chemoimmunotherapy emerges.

Dr. Joseph Connors: Insights on Ibrutinib Treatment for Patients with CLL/SLL

Dr. Anthea Peters: Commentary on Updated Efficacy and Safety from the RESONATE™-2 Study
Integrated and long-term safety analysis of ibrutinib in patients with CLL/SLL

**Background**
At the 2016 ASH Meeting, Coutre and colleagues reported results from the integrated and long-term safety analysis of ibrutinib in patients with treatment-naïve (TN) or relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).\(^1\)

**Study design**
- In this integrated safety analysis, data from the ibrutinib-treated patients from the RESONATE\(^\text{TM}\) and RESONATE\(^\text{TM}\)-2 trials were pooled.
  - RESONATE\(^\text{TM}\) study:
    - Patients were randomized to receive ibrutinib or ofatumumab.
    - The inclusion criteria were CLL/SLL diagnosis, \(\geq 1\) prior therapy, and ineligibility for treatment or retreatment with purine analogs.
    - In the ofatumumab arm, 132 patients crossed over to ibrutinib following progressive disease (PD).
  - RESONATE\(^\text{TM}\)-2 study:
    - Patients were randomized to receive ibrutinib or chlorambucil.
    - The inclusion criteria were TN CLL/SLL, age \(\geq 65\) years, and comorbidity that precludes fludarabine, cyclophosphamide, and rituximab for patients with age 65–69 years.
    - Patients with deletion of 17p were excluded.
    - In the extension study (PCYC-1116), 55 patients in the chlorambucil arm crossed over to ibrutinib.
- Long-term safety data from the phase Ib/II PCYC-1102 study were also examined.
  - Patients could continue receiving ibrutinib in the long-term extension study PCYC-1103, where adverse event (AE) collection was limited to grade \(\geq 3\) AEs, major hemorrhage, or AEs leading to dose modification.
  - Only data from patients treated with 420 mg/day ibrutinib were examined.

---

**Study design**

<table>
<thead>
<tr>
<th>RESONATE(^\text{TM}) study</th>
<th>RESONATE(^\text{TM})-2 study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ibrutinib (420 mg once daily) until PD or unacceptable toxicity (n = 195)</td>
<td>Ofatumumab iv (initial dose of 300 mg followed by 2,000 mg x 11 doses) over 24 weeks (n = 196)</td>
</tr>
<tr>
<td>Ofatumumab iv (initial dose of 300 mg followed by 2,000 mg x 11 doses) over 24 weeks (n = 196)</td>
<td>In ofatumumab arm, 132 patients crossed over to ibrutinib following PD</td>
</tr>
<tr>
<td>Ibrutinib 420 mg once daily until PD or unacceptable toxicity (n = 136)</td>
<td>ICRC-confirmed progression</td>
</tr>
<tr>
<td>Ibrutinib 420 mg once daily until PD or unacceptable toxicity (n = 136)</td>
<td>PCYC-1116 Extension Study</td>
</tr>
<tr>
<td>Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) on Days 1 and 15 of 28-day cycle for up to 12 cycles (n = 133)</td>
<td>In chlorambucil arm, 55 patients crossed over to ibrutinib</td>
</tr>
</tbody>
</table>

IRC = independent review committee; iv = intravenous; PD = progressive disease
Key findings

Integrated safety analysis

- In the RESONATE™ trial, 391 patients were enrolled, with 195 patients in the ibrutinib arm and 196 patients in the ofatumumab arm.

- In the RESONATE™-2 trial, 269 patients were enrolled, with 136 patients in the ibrutinib arm and 133 patients in the chlorambucil arm.

- The integrated analysis included 330 ibrutinib-treated patients, with 66% being male, 51% having Rai stage III/IV disease, 54% having bulky disease \( \geq 5 \) cm, and 37% having reduced creatinine clearance.

- Patients received a median of 29 months of ibrutinib.

- A total of 124 patients (38%) discontinued ibrutinib, mostly due to PD or AEs.
  - Of these 124 patients, 29.8% discontinued due to AEs.
  - Discontinuation due to AEs occurred primarily during the first year of treatment and declined over time.

- Dose reduction occurred in 41 patients (12%) due to AEs, which occurred primarily during the first year of treatment.

- Concomitant medications of interest included CYP3 inhibitors (53%), antiplatelet agents (50%), anticoagulants (28%), packed red blood cell transfusions (6%), granulocyte growth factors (3%), and intravenous immunoglobulin (2%).

- The most common all-grade AEs were diarrhea (53%) and fatigue (36%), and the most common grade 3/4 AEs were neutropenia (18%) and pneumonia (12%). (Figure 1)

Figure 1. Most common AEs (>15% all grade or >2% grade 3/4)
A total of 29 patients (9%) died, most commonly due to PD and pneumonia/lung infection.

Select AEs of clinical relevance (diarrhea, arthralgia, hypertension, rash, bleeding/bruising, fatigue, and atrial fibrillation) were primarily grade 1/2 and infrequently led to ibrutinib dose adjustments or discontinuation.

- Most AEs were resolved in most patients, with the exception of hypertension.
- Hypertension and arthralgia were frequently managed with concomitant medications.
- Atrial fibrillation was resolved in over half of the patients, and was often short lived (median duration of 3 days).

Rates of diarrhea, fatigue, grade ≥3 infections, and rash were highest during the first year of treatment.

Prevalence of hypertension increased over time, with most events ongoing or recurrent after 12 months.

Prevalence of atrial fibrillation was similar across time periods, with many events ongoing or recurrent after 12 months.

### Long-term safety analysis of PCYC-1102/1103

- The median follow-up was 47.9 months (range: 0.3–67.4).
- The most frequent grade 3/4 AEs were similar to those reported in the integrated analysis, with hypertension as the most commonly reported AE (30%). (Table 1)

- Given the approximately additional 19 months of median treatment, prevalence of some AEs was increased compared to the integrated analysis.

- The most frequent malignancies of other types included basal cell carcinoma, squamous cell carcinoma, and myelodysplastic syndromes; malignancy was diagnosed in 7 of 15 patients during the first year.

- Kaplan-Meier analysis showed that:
  - For TN patients, overall survival (OS) was 95% at 2 years in the RESONATE™-2 study and 91% at 5 years in the PCYC-1102/1103 studies.
  - For patients with R/R disease, OS was 74% at 3 years in the RESONATE™ study and 62% at 5 years in the PCYC-1102/1103 studies.

### Key conclusion

- The integrated and long-term analyses showed that AEs were primarily grade 1/2 and manageable, allowing the majority of older patients to have prolonged treatment with ibrutinib.

### Table 1. Most common grade 3/4 (>3%) AEs in PCYC-1102/1103 studies

<table>
<thead>
<tr>
<th>Ibrutinib (N = 94)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic AEs</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Decreased lymphocyte count</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Increased lymphocyte count</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>3 (3)</td>
</tr>
<tr>
<td><strong>Non-hematologic AEs</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Syncope</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

AE = adverse event

The integrated and long-term analyses showed that AEs were primarily grade 1/2 and manageable, allowing the majority of older patients to have prolonged treatment with ibrutinib.

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.

Please consult the product monograph at http://www.lundbeck.com/upload/ca/en/files/pdf/pm/Treanda.pdf for important information about:

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

The product monograph is also available by calling us at 514-844-8515 or 1-800-586-2325.

* Since international launch in 1971 to January 6, 2016, the cumulative exposure from marketing experience is estimated to be 297,494 patients.
† Clinical significance is unknown.

Acute Leukemias

Current Insights and Challenges in the Treatment of APL and ALL

The standard of care for acute promyelocytic leukemia (APL) has traditionally been all-trans retinoic acid (ATRA) and chemotherapy; however, newer regimens are showing improved outcomes. One recent addition to APL treatment is arsenic trioxide (ATO), which has demonstrated efficacy as a single agent in the treatment of acute promyelocytic leukemia (APL). In North America, ATO is indicated for induction of remission and consolidation in patients with APL characterized by the PML/RARα (promyelocytic leukemia/retinoic acid receptor alpha) gene translocation t(15;17), who are refractory to or have relapsed from retinoid and anthracycline therapy.

In low-risk patients (white blood cell count [WBC] <10 x 10^9/L), a daily schedule of all-trans retinoic acid (ATRA) plus ATO led to improved event-free and overall survival (OS) when compared with ATRA plus idarubicin (AIDA). These results indicated that ATRA plus ATO was at least as efficacious as chemotherapy-containing protocols.

However, APL presents a therapeutic challenge in high-risk patients (WBC >10 x 10^9/L), with significantly greater early mortality rates and higher risk of relapse when compared with low-risk patients. Cluster of differentiation 33 (CD33) is a therapeutic target in APL and is highly expressed in leukemic blast cells. Gemtuzumab ozogamicin (GO), an anti-CD33 antibody, has demonstrated efficacy in monotherapy for patients with molecularly relapsed APL. The combination of ATO, ATRA, and GO was efficacious as first-line therapy in high-risk patients with APL. Studies are ongoing to confirm the role of ATO in this treatment regimen.

Acute lymphoblastic leukemia (ALL), a common type of cancer in children, has seen remarkable progress in treatment over the past few decades. Once considered fatal, it is now a cancer with a cure rate of almost 90%. This is in part due to optimal use of antileukemic agents, improved supportive care, and precise risk assessment.

L-asparaginase is an important component of ALL treatment. A pegylated form of L-asparaginase, called pegaspargase (SS-PEG), is commonly used in frontline therapy. Calaspargase pegol (SC-PEG) is a novel form of L-asparaginase. It has a longer half-life than SS-PEG because it possesses a different linker molecule, rendering it more hydrolytically stable. The longevity of L-asparaginase in the human body is of special importance, given that antibodies to either form of it have been associated with its rapid clearance. Studies are ongoing to determine the more effective form of L-asparaginase in the treatment of ALL.

Here we report the results of six studies that investigated these agents, presented at the 2016 American Society of Hematology (ASH) Annual Meeting:

- In a randomized study, APL2006, the addition of ATO to and the removal of cytarabine from chemotherapy reduced myelosuppression in patients with high-risk APL. (Ades L, et al. ASH 2016:895)
- Final results from a randomized trial showed that the combination of ATRA, ATO, and GO is safe and highly effective in patients with previously untreated high-risk APL. (Lancet JE, et al. ASH 2016:896)
- A prospective multicentre trial demonstrated that using a simplified treatment algorithm and expert support can lead to a reduction of early deaths and improved survival in elderly patients with APL. (Kota V, et al. ASH 2016:1622)
- Updated results of the prospective German intergroup Napoleon registry provided further evidence for the efficacy and safety of ATRA plus ATO in low-and intermediate-risk APL. (Platzbecker U, et al. ASH 2016:2815)
• A randomized study found that a single dose of SC-PEG during induction led to a more sustained therapeutic effect when compared with SS-PEG in pediatric patients with newly diagnosed ALL or lymphoblastic lymphoma. (Silverman LB, et al. ASH 2016:175)

• Preliminary analysis from COG AALL07P4 showed that patients with ALL receiving SC-PEG have numerically less antibody formation and anaphylactic or hypersensitivity reactions than patients receiving SS-PEG. (Schore RJ, et al. ASH 2016:3965)


Ades L, et al. ASH 2016:895

Analysis of the randomized trial, APL2006, on whether arsenic trioxide is required in the treatment of high-risk, newly diagnosed APL

Background

While acute promyelocytic leukemia (APL) is predominantly associated with low white blood cell count (WBC), 25% of cases have a WBC of >10 x 10^9/L and a higher rate of relapse (considered high-risk APL). In patients with high-risk APL, it is still unclear if chemotherapy can be avoided or greatly reduced. However, the addition of arsenic trioxide (ATO) to all-trans retinoic acid (ATRA) plus chemotherapy reduces relapses in patients.1 Ades and colleagues evaluated the addition of ATO to chemotherapy during consolidation in a randomized trial (APL2006) in high-risk patients with APL, who received ATRA plus chemotherapy during induction. The findings were presented at ASH 2016.2

Study design

• Newly diagnosed patients with high-risk APL, who had received induction of ATRA with idarubicin and cytarabine until complete remission (CR), were randomized for consolidation between chemotherapy and chemotherapy plus ATO.

• After a first interim analysis in September 2010 of 81 patients, cytarabine was removed from the consolidation cycles of the chemotherapy plus ATO group.

• The inclusion criteria were:
  ◦ Newly diagnosed patients with APL (subsequently confirmed by conventional cytogenetics and/or presence of promyelocytic leukemia/retinoic acid receptor alpha transcript);
  ◦ Aged <70 years;
  ◦ WBC count of >10 x 10^9/L; and
  ◦ No contraindication to induction and consolidation chemotherapy or ATO.

• The primary endpoint was event-free survival (EFS) from the time of CR achievement.

Key findings

Baseline characteristics and disposition

• Analysis was conducted on a total of 219 patients over 48 centres.
  ◦ A total of 193 patients were randomized for consolidation, 97 in the chemotherapy arm and 96 in the chemotherapy plus ATO arm.
• The median follow-up was 55 months.
• The median age was 39.2 years (range: 29.6–54.2) in the chemotherapy arm and 45.0 years (range: 34.2–58.9) in the chemotherapy plus ATO arm.
• The median WBC was 23.7 x 10^9/L (range: 14.9–40.5) in the chemotherapy arm and 19.7 x 10^9/L (range: 13.0–33.9) in the chemotherapy plus ATO arm.
• Pre-treatment characteristics were well balanced between the two groups.
  ◦ Seven patients (three in the chemotherapy arm and four in the chemotherapy plus ATO arm) had relapsed.
  ◦ The 2-year cumulative incidence of relapse (CIR) was 3.7% vs. 3.9% for the chemotherapy arm and chemotherapy plus ATO arm, respectively (p = 0.69).
  ◦ Nine patients had died in CR: seven (7.8%) in the chemotherapy arm and two (5.1%) in the chemotherapy including cytarabine and ATO arm.
• The 5-year CIR was 3.7% for the chemotherapy arm, 5.3% for the chemotherapy plus cytarabine and ATO arm, and 3.3% for the chemotherapy plus ATO without cytarabine arm (p = 0.62).

Efficacy
• Prior to consolidation, 95.7% of patients achieved CR and 1% had resistant leukemia.
• The 2-year EFS rate was 93.0% in the chemotherapy arm and 94.5% in the chemotherapy plus ATO arm (p = 0.63). (Figure 1)
• The 2-year overall survival rate was 95.0% in the chemotherapy arm and 96.0% in the chemotherapy plus ATO arm (p = 0.77). (Figure 2)

Safety
• Median days with antibiotics, median number of red blood cell transfusions, median time to absolute neutrophil count >1 x 10^9/L, and median time to platelet count >50 x 10^9/L were all significantly improved in the chemotherapy plus ATO arm after September 2010 vs. prior to September 2010. (Table 1)
**Figure 1. Event-free survival**

![Event-free survival graph](image)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Chemotherapy Arm</th>
<th>Chemotherapy + ATO Arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
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<td>24</td>
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<td>84</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
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<td></td>
</tr>
</tbody>
</table>

**Number of events**
- Chemotherapy Arm: 10
- Chemotherapy + ATO Arm: 8

**Two-year EFS, % (95% CI)**
- Chemotherapy Arm: 93.0 (87.8–98.6)
- Chemotherapy + ATO Arm: 94.5 (90.0–99.3)

**p-value**: 0.63

---

**Figure 2. Overall Survival**

![Overall survival graph](image)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Chemotherapy Arm</th>
<th>Chemotherapy + ATO Arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>6</td>
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</tr>
<tr>
<td>96</td>
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</tr>
</tbody>
</table>

**Number of deaths**
- Chemotherapy Arm: 7
- Chemotherapy + ATO Arm: 6

**Two-year OS, % (95% CI)**
- Chemotherapy Arm: 95.0 (91.0–99.9)
- Chemotherapy + ATO Arm: 96.0 (91.7–99.9)

**p-value**: 0.77

---

ATO = arsenic trioxide; CI = confidence interval; EFS = event-free survival; OS = overall survival
The addition of ATO to the ATRA plus chemotherapy regimen did not reduce the number of relapses, but added some myelosuppression. If ATO was added and cytarabine was omitted from consolidation cycles, relapses were not increased, while myelosuppression and deaths in CR were reduced. Therefore, ATO appears to be useful in patients with high-risk APL.

**Key conclusions**

- The addition of ATO to the ATRA plus chemotherapy regimen did not reduce the number of relapses, but added some myelosuppression.
- If ATO was added and cytarabine was omitted from consolidation cycles, relapses were not increased, while myelosuppression and deaths in CR were reduced.
- Therefore, ATO appears to be useful in patients with high-risk APL.


**ATRA, ATO, and gemtuzumab ozogamicin are safe and highly effective in patients with previously untreated high-risk APL: Final results from the SWOG/Alliance/ECOG S0535 trial**

**Background**

Cluster of differentiation 33 (CD33) is highly expressed in acute promyelocytic leukemia (APL), representing a viable therapeutic target in the disease. Gemtuzumab ozogamicin (GO) (anti-CD33 plus calicheamicin) has demonstrated single-agent activity in APL. The efficacy of combined arsenic trioxide (ATO), all-trans retinoic acid (ATRA), and GO in a subset of high-risk APL has been shown. Final results from a trial combining the three agents in patients with untreated high-risk APL were presented at ASH 2016.3

**Study design**

- ATRA, ATO, and GO were given as induction until complete remission (CR).
- Consolidation 1 and 2 consisted of ATO, consolidation 3 and 4 consisted of daunorubicin and ATRA, and consolidation 5 and 6 consisted of GO.
- One-year maintenance was done with ATRA, mercaptopurine, and methotrexate.
- The primary objectives of the trial were three-year continuous CR rate and six-week mortality rate.

**Table 1. Hematological toxicities**

<table>
<thead>
<tr>
<th>Median</th>
<th>Chemotherapy Arm (before September 2010)</th>
<th>Chemotherapy + ATO Arm (after September 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days with antibiotics</td>
<td>15.0</td>
<td>18.0</td>
</tr>
<tr>
<td>1st Consolidation</td>
<td>10.0</td>
<td>14.5</td>
</tr>
<tr>
<td>2nd Consolidation</td>
<td></td>
<td>10.0*</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>1st Consolidation</td>
<td>4.0</td>
<td>2*</td>
</tr>
<tr>
<td>2nd Consolidation</td>
<td></td>
<td>1.0*</td>
</tr>
<tr>
<td>Time to ANC &gt;1 x 10^9/L</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Time to platelet &gt;50 x 10^9/L</td>
<td>24</td>
<td>26</td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count; ATO = arsenic trioxide; RBC = red blood cell
* p <0.001 vs. chemotherapy + ATO before September 2010.

ANC = absolute neutrophil count; ATO = arsenic trioxide; RBC = red blood cell
* p <0.001 vs. chemotherapy + ATO before September 2010.
The secondary objectives were frequency and severity of toxicities with ATRA, ATO, and GO, as well as molecular response rate.

Key eligibility criteria were:
- Patients aged ≥18;
- Confirmed diagnosis of APL;
- White blood cell count (WBC) of >10,000/μL; and
- Corrected QT interval ≤0.47 seconds.

Key findings
Baseline characteristics and disposition
- The median age was 46.5 years, with 53% of patients being female.
- The majority of patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 (70%).
- The median WBC was 27,700/μL and the median platelet count was 27,000/μL.

Induction
- After induction, a total of 60 patients (86%) had a CR.
- Of the nonresponding patients, six (9%) died, three (4%) had an inadequate assessment (two of which had an early death), and one (1%) had resistant disease.
- The median overall survival (OS) was not reached, while the estimated three-year OS was 86%. (Figure 1)
- The estimated three-year event-free survival rate was 78%.
- The median relapse-free survival (RFS) was not reached, while the estimated three-year RFS was 91%.
- One relapse occurred within three years of registration.

Study design

<table>
<thead>
<tr>
<th>Induction</th>
<th>CR</th>
<th>Consolidation 1 &amp; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA – 45 mg/m²/day (Day 1–CR)</td>
<td></td>
<td>ATO – 0.15 mg/kg/day x 25 days</td>
</tr>
<tr>
<td>ATO – 0.15 mg/kg/day (Day 10–CR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GO – 9 mg/m² (Day 1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consolidation 5 &amp; 6</th>
<th></th>
<th>Consolidation 3 &amp; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO – 9 mg/m² (Day 1)</td>
<td></td>
<td>Daunorubicin – 50 mg/m² (Day 1–3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATRA – 45 mg/m²/day (Day 1–7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance (1 year)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA – 45 mg/m²/day x 7 days (every 14 days)</td>
<td></td>
</tr>
<tr>
<td>Mercaptopurine – 60 mg/m²/day</td>
<td></td>
</tr>
<tr>
<td>MTX – 20 mg/m² (once per week)</td>
<td></td>
</tr>
</tbody>
</table>

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CR = complete remission; GO = gemtuzumab ozogamicin; MTX = methotrexate
**Postinduction**
- Sixty-two patients registered for consolidation.
  - Three patients were ineligible, five withdrew voluntarily, three experienced adverse events (AEs), and two were not registered due to other reasons.
- Forty-nine patients completed consolidation as planned.
- Forty-eight patients registered for maintenance.
  - Two patients were ineligible, two withdrew voluntarily, four experienced AEs, one died, and two were not registered due to other reasons.
- Thirty-seven patients completed maintenance as planned.

**Safety**
- The most common grade 3–5 AE after induction was febrile neutropenia (34%). (Table 1)
  - Eight patients died within six weeks: four due to hemorrhage, two due to sepsis or infection, one due to hepatic failure, and one due to other reasons.
- The most common grade 3–5 AEs after consolidation were febrile neutropenia (53%), fatigue (14%), and headache (14%). (Table 2)
- The grade 3–5 AEs experienced in ≥5% of patients during maintenance were nausea (11%), headache (11%), elevated alanine aminotransferase (11%), fatigue (9%), and elevated bilirubin (9%).
- During induction therapy, five patients (7%) experienced retinoic acid syndrome of Common Terminology Criteria for Adverse Events (CTCAE) grade 1/2, while one patient (1%) experienced retinoic acid syndrome of CTCAE grade 3/4.

**Table 1. Induction grade 3–5 AEs in ≥5% of patients (n = 70)**

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>24 (34)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>8 (11)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (10)</td>
</tr>
<tr>
<td>QTc prolonged</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; QTc = corrected QT interval

**Table 2. Consolidation grade 3–5 AEs in ≥5% of patients (n = 59)**

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>31 (53)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (12)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Blood infection</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (7)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Lung infection</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (5)</td>
</tr>
<tr>
<td>QTc prolonged</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; QTc = corrected QT interval
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Key conclusions

• This was the largest reported experience of ATO, ATRA, and GO combination therapy in high-risk APL.
  – The treatment led to durable responses, low rates of early mortality, and compared favourably with chemotherapy-based induction regimens.
• The ATO, ATRA, and GO combination regimen should be considered as a therapeutic option for patients with high-risk APL in the future.
• Results on molecular response are pending and will be evaluated for effect on outcomes.
• High failure rate of completion of all planned therapy raises questions about the benefit of extended consolidation and maintenance.


Kota V, et al. ASH 2016:1622

Reduction of early deaths and improved survival in elderly patients (>60 years) with APL as a result of using a simplified treatment algorithm and expert support: A prospective multicentre trial

Background
In large multicentre trials, induction mortality occurs in only 5%–10% of patients with acute promyelocytic leukemia (APL); however, it is higher outside clinical trials. Patients who survive induction show excellent cure rates with few late relapses. Therefore, reducing the number of early deaths (EDs) is a high priority in this highly curable disease. Specifically, there is a need for significant improvement in the outcomes of elderly patients (>60 years old). At ASH 2016, Kota and colleagues presented outcomes from a prospective trial of elderly patients with APL, using a set of simplified treatment guidelines along with support from APL experts.1

Study design
• Elderly patients with APL were prospectively enrolled in the trial from July 2013 to June 2016 (newer group [NG]).

• Outcomes were compared with prior institutional experience among elderly patients (early group [EG]) taken from January 2007 to June 2013.
• The protocol consisted of a simplified treatment algorithm with emphasis on preventing the most common causes of ED: bleeding, infection, and differentiation syndrome (DS).

Key findings
• A total of 70 elderly patients with APL were treated or co-managed between 2007 and 2016.
  ◦ Twenty-three of these patients were in the EG, while 47 were in the NG.
  ◦ All EG patients were treated in the authors’ institution.
  ◦ Thirteen NG patients were treated in the authors’ institution, while the remaining 34 were managed in 18 other centres.
• The median age was 66 years in the EG and 69 years in the NG.
Clinical characteristics are outlined in Table 1.

In the EG, induction consisted of:
- All-trans retinoic acid (ATRA) alone (n = 5; 21%);
- ATRA with arsenic trioxide (ATO) (n = 5; 21%); and
- ATRA with anthracyclines (n = 13; 56%).

In the NG, induction consisted of:
- ATRA alone (n = 2; 4%);
- ATRA with ATO (n = 43; 91%); and
- ATRA with chemotherapy (n = 2; 4%).

In the NG, doses of ATRA and/or ATO were reduced in a majority of the patients.

Bleeding at presentation occurred in four (17%) EG vs. five (11%) NG patients.

The median follow-up was 2,165 days (range: 1–3,540) in EG and 267 days (1–960) in NG.

Complications during induction for the EG vs. NG were as follows:
- Infection in 13 (56%) vs. 10 (22%) patients; and
- Differentiation syndrome in 13 (56%) vs. 18 (40%) patients.

In the EG, 12 patients (52%) died during induction.

NG had eight induction deaths.
- One death was due to refusal of transfusions and one was due to multi-organ failure, after failing to consult the investigators for 12 days.

The induction mortality rate in the NG was 6/45 (13.3%).
- Four patients in the NG experienced late deaths from a secondary cancer (n = 1), relapse (n = 1), and non-APL related deaths (n = 2).

With a median follow-up of 267 days in the NG, overall survival was 77.8% when compared with 42% in the EG. (Figure 1)

Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Early group</th>
<th>Newer group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>66 (61–80)</td>
<td>69 (61–83)</td>
</tr>
<tr>
<td>Median WBC/mm³</td>
<td>1.9 (0.3–132)</td>
<td>2.3 (0.3–38)</td>
</tr>
<tr>
<td>Male to female ratio</td>
<td>1:2</td>
<td>1:1</td>
</tr>
<tr>
<td>Low risk (WBC &lt;10,000/mm³), %</td>
<td>73</td>
<td>93</td>
</tr>
<tr>
<td>Treatment centre (large &gt;3 patients/year vs. small hospital)</td>
<td>100% large hospital</td>
<td>42.5% large/57.5% small hospitals</td>
</tr>
</tbody>
</table>

WBC = white blood cell count

Key conclusions

- Elderly patients tolerate full doses of ATRA and ATO poorly during induction.
- ATRA and ATO are better tolerated at reduced doses.
- Use of a simplified treatment algorithm with expert support has the potential to decrease induction mortality (13.3%) and improve population-wide survival (77.8%).
- APL treatment should be simplified and standardized in all large and experienced institutions.
- To improve outcomes in this patient population, education of hematologists and oncologists about EDs and rapid diagnosis and treatment is needed.
- A network of leukemia experts who can co-manage patients during treatment might help improve outcomes in elderly patients.
- Arsenic-based induction was used more frequently in the NG.
  - Improvised treatment protocols based on age and comorbidities might help improve outcomes.

Real-life experience with ATRA- and ATO-based regimen in APL: Updated results of the prospective German intergroup Napoleon registry

Background
The combination of all-trans retinoic acid (ATRA) and chemotherapy is the standard therapy for acute promyelocytic leukemia (APL). The introduction of arsenic trioxide (ATO) in APL treatment has allowed achievement of similarly high remission and survival rates coupled with significantly reduced myelosuppression. Recent results of the APL0406 trial by the GIMEMA-AML-SG-SAL study groups showed that the combination of ATRA and ATO is superior to standard ATRA and chemotherapy in frontline therapy of low- and intermediate-risk APL.\(^1\) An APL registry, Napoleon, was recently initiated in order to provide evidence of the clinical reality of APL patient care in Germany. The first analysis of patients prospectively enrolled in the registry was presented at ASH 2016.\(^2\)

Study design
- The eligibility criteria were adults of at least 18 years of age, with newly diagnosed or relapsed APL within their first year of diagnosis or relapse.
- The aims of the registry are:
  - To document epidemiologic data, treatment, long-term outcomes, and quality of life of patients with APL;
  - To obtain real-world data on APL demographics, as well as use of various therapies and adherence to therapeutic guidelines;
  - To collect samples from patients for biobanking and further translational studies;
  - To improve access to the current treatment approaches and assist in the development of best practice guidelines; and
  - To examine the implementation of existing diagnostic and therapeutic guidelines.

Key findings
- A total of 106 patients were included in the registry.
- As of August 2016, 88 patients were included in this study with a median age of 57 years (range: 22–87).
- All patients had newly diagnosed APL with 58 (66%) being of low/intermediate risk according to the Sanz score.
- Out of those patients, 44 (76%) received an ATO and ATRA-based induction regimen followed by a median of four courses of consolidation (according to the APL0406 study).
- The characteristics of these patients are outlined in Table 1.
- Of the 41 patients evaluable for response to induction, 40 (98%) patients achieved complete remission with the ATRA-ATO regimen.
- Early death rate within 30 days of therapy was 2% (one of 44 patients).
- After a median follow-up of 12 months, the event-free survival, cumulative incidence of relapse, and overall survival at 12 months were 97%, 0%, and 97%, respectively.
- Therapy was well tolerated with no new safety signals.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA + ATO (n = 44)</td>
</tr>
<tr>
<td>Age, median (range)</td>
</tr>
<tr>
<td>WBC 10^9/L, median (range)</td>
</tr>
<tr>
<td>Sanz risk Low/intermediate, n (%)</td>
</tr>
<tr>
<td>FLT3-ITD, n mutated/n total (%)</td>
</tr>
</tbody>
</table>

\(^{ATO} = \text{arsenic trioxide}; \ ATRA = \text{all-trans retinoic acid}; \ FLT3-ITD = \text{FMS-like tyrosine kinase-internal tandem duplication}; \ WBC = \text{white blood cell count}\)

Key conclusions
- The real-life data from this prospective German registry provide further evidence for the safety and sustained anti-leukemic efficacy of ATRA-ATO in low- and intermediate-risk APL.
- The results presented here further support ATRA-ATO as the new standard of care in this clinical setting.

Background
Pegaspargase (SS-PEG) is commonly used as frontline therapy in childhood acute lymphoblastic leukemia (ALL). Calaspargase pegol (SC-PEG) is a novel formulation that uses the same asparaginase enzyme and PEG moiety as SS-PEG but a different linker molecule. Patients typically receive a single dose of SS-PEG during induction, followed by 15 doses every two weeks post induction in order to maintain therapeutic serum asparaginase activity (SAA), defined as ≥0.1 IU/mL, for 30 consecutive weeks. The investigators hypothesized that SC-PEG could be administered less frequently than SS-PEG during post-induction therapy with a similar SAA and toxicity profile. Findings were presented at ASH 2016.¹

Study design
- Between 2012 and 2015, patients were randomized at study entry to receive either SS-PEG or SC-PEG.
- Both groups received a single dose during multi-agent remission induction.
- Post induction, patients assigned to SS-PEG received 15 doses every two weeks, while those assigned to SC-PEG received 10 doses every three weeks along with other risk-stratified chemotherapy.
- The endpoints of the study were:
  - SAA;
  - Asparaginase-related toxicities (hypersensitivity, pancreatitis, clots, hyperbilirubinemia, and infection);
  - End-induction minimal residual disease (MRD); and
  - Event-free survival (EFS).
- Serum samples were obtained at 4, 11, 18, and 25 days after the induction dose to determine SAA prior to each post-induction dose to determine nadir SAA (NSAA) by a validated biochemical assay.
- Patients were switched to Erwinia asparaginase for grade 2 or higher allergy or for silent inactivation (defined as two consecutive non-detectable NSAA).
- Asparaginase was permanently discontinued for pancreatitis and held for thrombosis (but restarted once the clot improved).
- End-induction MRD was assessed in patients with ALL by immunoglobulin heavy chain/T-cell receptor polymerase chain reaction assay, with low MRD defined as <0.001 and high MRD defined as ≥0.001.

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Silverman LB, et al. ASH 2016:175

Results from a randomized study of pegaspargase and calaspargase pegol in pediatric patients with newly diagnosed acute lymphoblastic leukemia or lymphoblastic lymphoma

<table>
<thead>
<tr>
<th>Study design</th>
<th>Asparaginase type</th>
<th>Remission induction</th>
<th>Postinduction (Week 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>SC-PEG 2,500 IU/m²</td>
<td>1 dose (Day 7)</td>
<td>10 doses every three weeks (30 weeks total)</td>
</tr>
<tr>
<td>Arm B</td>
<td>SS-PEG 2,500 IU/m²</td>
<td>1 dose (Day 7)</td>
<td>15 doses every two weeks (30 weeks total)</td>
</tr>
</tbody>
</table>

SC-PEG = calaspargase pegol; SS-PEG = pegaspargase
To be eligible for inclusion, patients had to be between 1 and 21 years of age and newly diagnosed with ALL or lymphoblastic lymphoma (LL).

Two patients in the SC-PEG arm (1.7%) and none in the SS-PEG arm met criteria for silent inactivation.

Key findings
- A total of 239 patients were enrolled (230 patients with ALL and 9 with LL).
- A total of 119 patients received SC-PEG and 120 received SS-PEG.
- There were no significant differences in presenting characteristics between the two groups.
- The SAA was higher for patients on SC-PEG when compared with those on SS-PEG (median 0.298 IU/mL vs. 0.056 IU/mL). (Figure 1)
  - Twenty-five days after dose, 88% of patients on SC-PEG had SAA ≥0.1 IU/mL vs. 15% of patients on SS-PEG (p <0.001).
- Post-induction NSAA was similar between arms, with median NSAA ≥1.0 IU/mL at 7, 13, 19, and 25 weeks after beginning the 30-week post-induction asparaginase treatment.
  - NSAA was ≥0.1 IU/mL in ≥98% of patients on both arms at each time point.
- There were no significant differences in rates of asparaginase-related toxicities between the two arms. (Table 1)
- There were no differences in rates of complete remission between the two arms (95% for the SC-PEG arm and 99% for the SS-PEG arm; p = 0.12).
- There were no differences in end-induction MRD.
  - Low MRD was 91% in the SC-PEG arm vs. 90% in the SS-PEG arm.
  - High MRD was 9% in the SC-PEG arm vs. 10% in the SS-PEG arm.
- EFS awaits longer follow-up.

![Figure 1. Median SAA by asparaginase type](image1)

Table 1. Induction adverse events

<table>
<thead>
<tr>
<th>Adverse event (%)</th>
<th>SC-PEG (n = 119)</th>
<th>SS-PEG (n = 120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparaginase allergy (grade ≥2)</td>
<td>0</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Pancreatitis (grade ≥3)</td>
<td>3</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3</td>
<td>7</td>
<td>0.22</td>
</tr>
<tr>
<td>Elevated bilirubin (grade ≥3)</td>
<td>8</td>
<td>12</td>
<td>0.40</td>
</tr>
<tr>
<td>Insulin-requiring hyperglycemia</td>
<td>1</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>Infection: bacterial (grade ≥3)</td>
<td>13</td>
<td>10</td>
<td>0.55</td>
</tr>
<tr>
<td>Infection: fungal (grade ≥3)</td>
<td>4</td>
<td>5</td>
<td>1.00</td>
</tr>
</tbody>
</table>

SC-PEG = calaspargase pegol; SS-PEG = pegaspargase

Key conclusions
- Single dose of SC-PEG during induction led to a more sustained therapeutic effect when compared with SS-PEG.
  - SC-PEG may be given less frequently than SS-PEG.
  - Substitution of SC-PEG may lead to more prolonged asparagine depletion.
- SC-PEG and SS-PEG showed similar toxicity.
- There were no differences in end-induction MRD between SC-PEG and SS-PEG.
- Both SC-PEG and SS-PEG might be given at a reduced dose and/or with a longer interval.

Anti-pegaspargase, anti-calaspargase pegol, and anti-polyethylene glycol antibody incidence in high-risk ALL patients receiving pegaspargase or calaspargase pegol and associated anaphylactic or hypersensitivity reaction rates

Background
Both pegaspargase (SS-PEG) and calaspargase pegol (SC-PEG) consist of L-asparaginase and antibodies to either asparaginase or polyethylene glycol (PEG) and have been associated with rapid clearance of asparaginase. The Children Oncology Group (COG) AALL07P4 study evaluated the pharmacokinetic (PK) and pharmacodynamic comparability of SS-PEG and SC-PEG as part of an augmented Berlin-Frankfurt-Munster chemotherapy regimen for the treatment of newly diagnosed, National Cancer Institute high-risk, B-precursor acute lymphoblastic leukemia (ALL). Results from COG AALL07P4 were presented at ASH 2016.1

Study design
- A total of 166 patients were randomized.
  - Fifty-four patients were randomized to SS-PEG at 2,500 IU/m², 43 to SC-PEG at 2,500 IU/m², and 69 to SC-PEG at 2,100 IU/m².
  - One patient was not evaluable.
  - Both SC-PEG treatment groups were pooled for this report.
- Blinded analyses of anti-SS-PEG and anti-SC-PEG antibodies were performed on samples obtained prior to asparaginase administration and at protocol-specified time points through the second cycle of maintenance therapy in patients with adequate samples (50 and 111 patients in the SS-PEG and SC-PEG treatment groups, respectively).

AALL07P4 Study enrolment

Patients randomized to receive treatment with SC-PEG or SS-PEG

Arm A
SC-PEG
Induction
RER
Consolidation
Interim maintenance 1
Delayed intensification 1
Maintenance

Arm B
SS-PEG
Induction
SER
Consolidation
Interim maintenance 1
Delayed intensification 1
Interim maintenance 2
Delayed intensification 2
Maintenance

MRD = minimal residual disease; RER = rapid early responders; SC-PEG = calaspargase pegol; SER = slow early responders; SS-PEG = pegaspargase
• Immunogenicity assessment included the detection of binding anti-SS-PEG or anti-SC-PEG antibodies by a validated direct enzyme-linked immunosorbent assay (ELISA).

• All detected antibodies were analyzed in a neutralizing anti-SS-PEG/anti-SC-PEG antibody assay for their neutralizing capacity using a validated enzymatic coupled activity assay.

• Analysis of anti-PEG antibodies using ELISA was assessed retrospectively in a subset of patients who had available specimens (26 and 42 patients in the SS-PEG and SC-PEG treatment groups, respectively), including all patients with anti-SS-PEG/anti-SC-PEG antibody positive samples.

• All grades of anaphylactic reactions and hypersensitivity were reported according to the Common Terminology Criteria for Adverse Events v3.0 prior to July 2011 and converted into v4.0 codes with subsequent adverse events (AEs) collected in v4.0.

Key findings
• The analysis showed fewer anti-SC-PEG antibodies (2.7% [3 of 111 patients]) than anti-SS-PEG antibodies (10.0% [5 of 50 patients]).
  ◦ The majority of positive post-treatment antibodies were transient and not detectable at subsequent visits.
  ◦ Three patients (one in the SC-PEG and two in the SS-PEG treatment group) showed positive results for binding antibodies at the last tested time point.
  ◦ It is unknown whether these antibodies are of transient or persistent nature.

• Only one patient in the SC-PEG treatment group tested positive for neutralizing antibodies at one time point with negative results at subsequent time points.

• Focusing on the subset of patients who had available anti-PEG antibody data, eight of 45 (17.8%) in the SC-PEG treatment group had detectable anti-PEG antibodies vs. six of 26 (23.1%) in the SS-PEG treatment group.

• Full analyses of antibody incidence are presented in Table 1.

  • Among 111 patients treated with SC-PEG, 30 (27.0%) developed an anaphylactic and/or hypersensitivity reaction and two of them (6.7%) had anti-SC-PEG present at the time of reaction.

  • Among 50 patients treated with SS-PEG, 12 (24%) developed an anaphylactic and/or hypersensitivity reaction and two of them (16.7%) had anti-SS-PEG present at the time of reaction.

  • In the patients who had anaphylactic and hypersensitivity reactions, two out of 10 (20%) patients treated with SC-PEG had either anti-SC-PEG or anti-PEG antibodies vs. five out of eight (62.5%) patients treated with SS-PEG, who had either anti-SS-PEG or anti-PEG antibodies.

• Full analyses of anaphylactic or hypersensitivity reaction rates are presented in Table 2.

• Observed differences in antibody responses were not statistically significant.

• As previously reported, many patients with clinical anaphylactic and hypersensitivity reactions did not have antibodies detected.

Table 1. Antibody incidence in patients with ALL receiving SC-PEG or SS-PEG

<table>
<thead>
<tr>
<th></th>
<th>SC-PEG</th>
<th>SS-PEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with post-baseline anti-SC-PEG/anti-SS-PEG assessments (n = 161)</td>
<td>n (111)</td>
<td>n (50)</td>
</tr>
<tr>
<td>Positive post-baseline anti-SC-PEG/anti-SS-PEG</td>
<td>n (%) 3 (2.7) 95% CI 0.6–7.7</td>
<td>n (%) 5 (10.0) 95% CI 3.3–21.8</td>
</tr>
<tr>
<td>Patients with post-baseline anti-SC-PEG/anti-SS-PEG and anti-PEG assessments (n = 71)</td>
<td>n (45)</td>
<td>n (26)</td>
</tr>
<tr>
<td>Anti-SC-PEG/anti-SS-PEG and/or anti-PEG*</td>
<td>n (%) 8 (17.8) 95% CI 8.0–32.1</td>
<td>n (%) 9 (34.6) 95% CI 17.2–55.7</td>
</tr>
<tr>
<td>Anti-SC-PEG/anti-SS-PEG</td>
<td>n (%) 3 (6.7) 95% CI 1.4–18.3</td>
<td>n (%) 5 (19.2) 95% CI 6.6–39.4</td>
</tr>
<tr>
<td>Anti-PEG</td>
<td>n (%) 8 (17.8) 95% CI 8.0–32.1</td>
<td>n (%) 6 (23.1) 95% CI 9.0–43.6</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; CI = confidence interval; PEG = polyethylene glycol; SC-PEG = calaspargase pegol; SS-PEG = pegaspargase

* Positive antibodies were counted if anti-SC-PEG/anti-SS-PEG or anti-PEG antibodies were positive.
In this preliminary analysis of COG AALL07P4, patients receiving SC-PEG have numerically less antibody formation to both asparaginase and PEG than patients receiving SS-PEG.

Fewer patients with anaphylactic and hypersensitivity reactions to SC-PEG had detectable antibodies as compared to those who received SS-PEG.

Since these antibodies may be associated with rapid clearance of asparaginase, further evaluation of PK and immunogenicity is ongoing.

Additional investigation is warranted to better understand the clinical significance of these findings.

UNMET NEEDS REQUIRE UNMATCHED COMMITMENT.

Our purpose is clear: to make a difference in the lives of those living with and affected by rare diseases and highly specialized conditions.

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Lymphomas

New Treatments Improve Outcomes for Patients with Lymphoma Throughout the Continuum of Care

Outcomes for patients with lymphoma have improved steadily over time; between 2001 and 2015, mortality rates for non-Hodgkin lymphomas (NHL) declined by more than 2% per year in Canada. Despite these improvements, unmet needs remain in the treatment of lymphomas.

The combination of bendamustine and rituximab (BR) recently became the standard of care in the first line for indolent NHL, due to improvements in efficacy and tolerability over the previous standard (the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Even with improved regimens, many patients eventually relapse or become refractory to these treatments. New agents (such as obinutuzumab) and regimens (such as the combination of bendamustine, rituximab, and cytarabine [R-BAC]) are being investigated to further improve response durability in the first line.

In aggressive lymphomas and relapsed/refractory (R/R) Hodgkin lymphoma (HL), autologous stem cell transplant (ASCT) is the standard of care, with five-year progression-free survival (PFS) rates of approximately 50%. New regimens are continuing to be developed in an effort to reduce the toxicities associated with conditioning for ASCT; one such example is the combination of bendamustine, etoposide, cytarabine, and melphalan (Benda-EAM).

Following transplants, chronic graft versus host disease (cGVHD) is a common cause of morbidity, with incidence rates of cGVHD post allogeneic transplant reaching 37%. Currently, there are no treatment options for cGVHD if patients do not respond to corticosteroids; the Bruton’s tyrosine kinase inhibitor ibrutinib is being investigated as an option for these patients.

For patients with R/R disease who are ineligible for ASCT, treatment options are limited. Immunotherapies such as BR have become standard treatments for this patient population; obinutuzumab is being studied as a replacement for rituximab in such regimens.

At the 2016 American Society of Hematology (ASH) Annual Meeting, New Evidence covered several studies highlighting improvements in patient outcomes throughout the continuum of care. The following abstracts are summarized in this section:

- Updated results of the GADOLIN study confirmed that induction with obinutuzumab plus bendamustine followed by bendamustine maintenance significantly reduced risk of disease progression or death relative to bendamustine alone in patients with R/R FL. (Cheson BD, et al. ASH 2016:615)

- A retrospective analysis of patients with aggressive NHL and HL who received Benda-EAM conditioning before ASCT reported promising outcomes and an acceptable toxicity profile. (Noesslinger T, et al. ASH 2016:2265)

- Primary results from the phase III GALLIUM study demonstrated clinically meaningful improvements in PFS with obinutuzumab-based regimens compared to rituximab-based regimens in patients with previously untreated follicular lymphoma (FL). (Marcus R, et al. ASH 2016:6)

- A single arm, phase II, multicentre trial supported the use of dose-reduced R-BAC in elderly patients...
with previously untreated mantle cell lymphoma, demonstrating durable responses with manageable toxicities. (Visco C, et al. ASH 2016:472)

- A direct, real-world comparison between BR and the combination of dexamethasone, rituximab, and cyclophosphamide demonstrated a trend towards superior PFS with BR in patients with either treatment-naïve or R/R Waldenström Macroglobulinemia. (Paludo J, et al. ASH 2016:2968)

- A study investigating the efficacy and safety of ibrutinib in patients with cGVHD who had failed frontline therapy found that ibrutinib treatment resulted in clinically meaningful and sustained responses. (Miklos D, et al. ASH 2016:LBA-3)


Cheson BD, et al. ASH 2016:615

Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs OS compared with bendamustine alone in patients with rituximab-refractory iNHL: Updated results of the GADOLIN study

Background

Treatment options for patients with relapsed or refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) are limited. The GADOLIN study compared the efficacy and safety of obinutuzumab plus bendamustine induction followed by obinutuzumab maintenance (G-B arm) with bendamustine induction alone (B arm), in patients with rituximab-refractory iNHL. In the primary analysis, median independent review committee-assessed progression-free survival (PFS) was not reached in the G-B arm and was 14.9 months in the B arm, a 45% reduction in risk of progression or death (HR = 0.55, 95% CI: 0.40–0.74; p = 0.0001).1 Seventeen additional patients were enrolled after the data cutoff for the primary analysis. At the ASH 2016 Meeting, Cheson and colleagues reported updated time-to-event and safety results from a planned analysis of all GADOLIN patients using a data cutoff of April 1, 2016.2

Study design

- The GADOLIN study was an open-label, multicentre, randomized, phase III study in patients with rituximab-refractory iNHL.
- Rituximab-refractory was defined as failure to respond to or progression during any prior rituximab-containing regimen, or progression within six months of the last rituximab dose, in the induction or maintenance settings.
- Endpoints considered in the following analysis included investigator-assessed PFS, overall survival (OS), time to next treatment (TTNT), and safety.

Key findings

Baseline characteristics and disposition

- A total of 204 patients were randomized to the G-B arm, while 209 patients were randomized to the B arm.
- In the G-B arm, 189 patients (93%) started follow-up; 192 patients (92%) started follow-up in the B arm.
- Two patients crossed over from the B arm to G-B maintenance at the end of induction.
In the randomized population, 80.4% of the patients in the G-B arm (n = 164) and 81.8% of the patients in the B arm (n = 171) had a follicular lymphoma (FL) diagnosis. Baseline characteristics of the FL population were similar to the overall iNHL population.

In the iNHL population, baseline characteristics were similar between treatment arms:
- Median age was 62.0 years (range: 34–87) in the G-B arm and 61.9 years (range: 21–87) in the B arm;
- The majority of patients were male (56.9% in the G-B arm and 58.4% in the B arm) and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 (95.6% in the G-B arm and 95.1% in the B arm).

Patients had received a median number of two prior regimens in both treatment arms (range: 1–7 in the G-B arm and 1–10 in the B arm); the median time since completion of the last regimen was 3.9 months in both treatment arms (range: 0.1–128.4 in the G-B arm and 0.5–64.0 in the B arm).

The majority of patients were refractory to their last regimen (92.2% in the G-B arm and 92.3% in the B arm) and were refractory to both rituximab and an alkylating agent (77.5% in the G-B arm and 81.3% in the B arm).

Treatment history was similar in the FL population.

**Efficacy**
- After a median follow-up of 31.8 months in the iNHL population and 31.2 months in the FL population, median PFS was significantly higher in the G-B arm compared to the B arm. (Figure 1)
- When PFS was stratified by baseline characteristics, nearly every subgroup favoured G-B over B (with the exception of patients with an ECOG PS of 2).
- Results were similar in the FL population.
- Median TTNT was numerically higher in the G-B arm compared to the B arm in both the iNHL and FL populations:
  - iNHL population: 40.8 months in the G-B arm vs. 19.4 months in the B arm (HR = 0.59; 95% CI: 0.45–0.77).
  - FL population: 33.6 months in the G-B arm vs. 18.0 months in the B arm (HR = 0.57; 95% CI: 0.43–0.75).
- OS was significantly higher in the G-B arm compared to the B arm in both the iNHL and FL populations. (Figure 2)

**Safety**
- Incidences of adverse events (AEs) were similar between treatment arms. (Table 1)
- Grade 3–5 AEs of interest are summarized in Table 2.
- Grade 5 AEs were as follows:
  - G-B arm: infections and infestations (n = 6), neoplasms benign, malignant, and unspecified (n = 5), blood and lymphatic system disorders (n = 1), cardiac disorders (n = 1), immune system disorders (n = 1), injury, poisoning, and procedural complications (n = 1), and renal and urinary disorders (n = 1).
  - B arm: infections and infestations (n = 7), neoplasms benign, malignant, and unspecified (n = 3), nervous system disorders (n = 2), and metabolism and nutrition disorders (n = 1).
Figure 1. Investigator-assessed progression-free survival

### iNHL population

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>B (n = 209)</th>
<th>G-B (n = 204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>209</td>
<td>204</td>
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<tr>
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<table>
<thead>
<tr>
<th>Patients with event, n (%)</th>
<th>G-B (n = 204)</th>
<th>B (n = 209)</th>
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</thead>
<tbody>
<tr>
<td>115 (56.4)</td>
<td>146 (69.9)</td>
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<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
<th>G-B (n = 204)</th>
<th>B (n = 209)</th>
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</thead>
<tbody>
<tr>
<td>25.8 (19.5–41.1)</td>
<td>14.1 (12.6–16.0)</td>
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<table>
<thead>
<tr>
<th>HR (95% CI), p-value*</th>
<th>G-B (n = 204)</th>
<th>B (n = 209)</th>
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</thead>
<tbody>
<tr>
<td>0.57 (0.44–0.73), p &lt;0.0001</td>
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### FL population

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>B (n = 171)</th>
<th>G-B (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
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</table>

<table>
<thead>
<tr>
<th>Patients with event, n (%)</th>
<th>G-B (n = 164)</th>
<th>B (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>93 (56.7)</td>
<td>125 (73.1)</td>
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<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
<th>G-B (n = 164)</th>
<th>B (n = 171)</th>
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<tbody>
<tr>
<td>25.3 (17.4–36.0)</td>
<td>14.0 (11.3–15.3)</td>
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</table>

<table>
<thead>
<tr>
<th>HR (95% CI), p-value†</th>
<th>G-B (n = 164)</th>
<th>B (n = 171)</th>
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</thead>
<tbody>
<tr>
<td>0.52 (0.39–0.69), p &lt;0.0001</td>
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</table>

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*B = bendamustine; CI = confidence interval; FL = follicular lymphoma; G-B = obinutuzumab plus bendamustine; HR = hazard ratio; iNHL = indolent non-Hodgkin lymphoma; PFS = progression-free survival

* Stratified analysis; stratification factors: iNHL subtype, prior therapies, refractory type, geographical region.

† Stratified analysis; stratification factors: prior therapies, refractory type, geographical region.
Figure 2. Overall survival

<table>
<thead>
<tr>
<th></th>
<th>G-B (n = 204)</th>
<th>B (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>52 (25.5)</td>
<td>73 (34.9)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NR-NR)</td>
<td>NR (48.2–NR)</td>
</tr>
<tr>
<td>HR (95% CI), p-value*</td>
<td>0.67 (0.47–0.96), p = 0.0269</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>G-B (n = 164)</th>
<th>B (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>39 (23.8)</td>
<td>64 (37.4)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NR-NR)</td>
<td>53.9 (40.9–NR)</td>
</tr>
<tr>
<td>HR (95% CI), p-value†</td>
<td>0.58 (0.39–0.86), p = 0.0061</td>
<td></td>
</tr>
</tbody>
</table>

B = bendamustine; CI = confidence interval; FL = follicular lymphoma; G-B = obinutuzumab plus bendamustine; HR = hazard ratio; iNHL = indolent non-Hodgkin lymphoma; NR = not reached; OS = overall survival

* Stratified analysis; stratification factors: iNHL subtype, prior therapies, refractory type, geographical region.
† Stratified analysis; stratification factors: prior therapies, refractory type.
The updated analysis of GADOLIN:
- Confirms that G-B induction plus obinutuzumab maintenance significantly reduces risk of disease progression or death relative to bendamustine induction alone in patients with rituximab-refractory FL;
- Demonstrates a significant improvement in OS in the G-B arm; and
- Confirms the comparable safety profile observed in the primary analysis.

Collectively, these data establish G-B induction plus obinutuzumab maintenance as a new standard of care for patients with rituximab-refractory FL.

Key conclusions

Table 1. Adverse events in the iNHL population

<table>
<thead>
<tr>
<th>% (n)</th>
<th>G-B (n = 204)</th>
<th>B (n = 203)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>99.0 (202)</td>
<td>98.5 (200)</td>
</tr>
<tr>
<td>Grade 3–5 AE</td>
<td>72.5 (148)</td>
<td>65.5 (133)</td>
</tr>
<tr>
<td>Grade 5 (fatal) AE</td>
<td>7.8 (16)</td>
<td>6.4 (13)</td>
</tr>
<tr>
<td>SAE</td>
<td>43.6 (89)</td>
<td>36.9 (75)</td>
</tr>
<tr>
<td>AE leading to withdrawal from any study treatment</td>
<td>20.1 (41)</td>
<td>17.2 (35)</td>
</tr>
<tr>
<td>AE leading to dose modification†</td>
<td>50.0 (102)</td>
<td>42.4 (86)</td>
</tr>
</tbody>
</table>

AE = adverse event; B = bendamustine; G-B = obinutuzumab plus bendamustine; iNHL = indolent non-Hodgkin lymphoma; SAE = serious adverse event

* Two patients who crossed over from the B arm to the G-B arm during maintenance are excluded.
† Decrease or delay.

Table 2. Grade 3–5 adverse events in the iNHL population

<table>
<thead>
<tr>
<th>% (n)</th>
<th>G-B (n = 204)</th>
<th>B (n = 205)*</th>
<th>G-B (n = 158)†</th>
<th>G-B (n = 204)</th>
<th>B (n = 203)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia‡</td>
<td>27.5 (56)</td>
<td>26.8 (55)</td>
<td>27.1 (55)</td>
<td>10.8 (17)</td>
<td>34.8 (71)</td>
</tr>
<tr>
<td>Thrombocytopenia‡</td>
<td>10.3 (21)</td>
<td>15.6 (32)</td>
<td>15.8 (32)</td>
<td>1.3 (2)</td>
<td>10.8 (22)</td>
</tr>
<tr>
<td>Infections and infestations§</td>
<td>7.8 (16)</td>
<td>12.2 (25)</td>
<td>22.5 (46)</td>
<td>1.16 (2)</td>
<td>2.5 (4)</td>
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<tr>
<td>Infusion-related reactions‡</td>
<td>8.8 (18)</td>
<td>3.4 (7)</td>
<td>9.3 (19)</td>
<td>0.6 (1)</td>
<td>3.4 (7)</td>
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<tr>
<td>Neoplasms**</td>
<td>1.0 (2)</td>
<td>1.0 (2)</td>
<td>5.9 (12)</td>
<td>2.5 (4)</td>
<td>5.4 (11)</td>
</tr>
<tr>
<td>Cardiac disorders††</td>
<td>2.5 (5)</td>
<td>1.0 (2)</td>
<td>4.4 (9)</td>
<td>1.9 (3)</td>
<td>1.5 (3)</td>
</tr>
</tbody>
</table>

B = bendamustine; G-B = obinutuzumab plus bendamustine; iNHL = indolent non-Hodgkin lymphoma; PT = Preferred Term; SOC = System Organ Class

* Two patients who crossed over from the B arm to the G-B arm during maintenance are included.
† Two patients who crossed over from the B arm to the G-B arm during maintenance are excluded.
‡ By PT.
§ By SOC.
** By SOC. Benign, malignant, and unspecified (including cysts and polyps).
†† By SOC. Eight of 12 patients with a history of cardiac disease.

At the 2016 ASH Annual Meeting, New Evidence spoke with Dr. Bruce Cheson, Head of Hematology and Deputy Chief of Hematology-Oncology at Georgetown University Hospital and Lombardi Comprehensive Cancer Center in Washington, D.C., U.S., about the updated results of the GADOLIN study. The study compared the efficacy and safety of obinutuzumab plus bendamustine induction followed by obinutuzumab maintenance (G-B arm) with bendamustine induction alone (B arm) in patients with rituximab-refractory indolent non-Hodgkin lymphoma (iNHL).

**New Evidence:** What advantages does obinutuzumab offer over rituximab?

**Dr. Cheson:** Obinutuzumab offers a number of advantages over rituximab. Obinutuzumab has greater antibody-dependent cellular cytotoxicity and greater direct cell death of cluster of differentiation 20 (CD20)-positive tumour cells compared to rituximab.1–3 Also, in preclinical models, obinutuzumab in combination with bendamustine was more active than the combination of bendamustine and rituximab.4

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

**Dr. Cheson:** There are a couple of treatment options available for patients with relapsed/refractory (R/R) follicular lymphoma (FL) and iNHL. The frontline therapy that the patient received will, to some extent, determine the appropriate second-line therapy. For example, if the patient received the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as frontline therapy, then the combination of bendamustine and rituximab (BR) is a reasonable alternative. However, there are not a lot of data to support the efficacy of R-CHOP in the second line if a patient received BR in the first line.

For these patients, there are two drugs currently on the U.S. market: 

- **90Y ibritumomab tiuxetan** (which is not often used) and
- **idelalisib.** While idelalisib is very active, with response rates of 50%–60%, it has been associated with a number of unpleasant adverse effects.5 There is a need in this space for newer, more effective, well-tolerated therapies.

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

**Dr. Cheson:** The GADOLIN study was a randomized phase III trial. In the G-B arm, the dose of bendamustine was 90 mg/m², which is the standard dose when bendamustine is given in combination with an anti-CD20 monoclonal antibody. In this arm, induction therapy was followed by maintenance for two years. In the B arm, bendamustine was given as a single agent at a dose of 120 mg/m², which is the approved single-agent dose of bendamustine. Even though this was a randomized trial, the doses were a bit different in each treatment arm. However, the addition of the antibody to a lower dose of bendamustine created a very interesting, effective combination.

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

**Dr. Cheson:** The overall response and complete response rates were the same in both arms. Nevertheless, the important time-dependent endpoints were quite different. There was a significantly longer progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) in the G-B arm compared to the B arm. Despite the use of a lower dose of the traditional cytotoxic agent in the G-B arm, the addition of the antibody made a more effective combination approach.

**New Evidence:** Please summarize and comment on the safety results of the GADOLIN study.

**Dr. Cheson:** Even though a combination therapy was compared to a single drug, there were no major safety signals in the study. There were more infusion-related reactions with obinutuzumab, which was expected. There was also a slightly higher incidence of neutropenia in the G-B arm compared to the B arm, although there was no difference in the incidence of neutropenic fevers or infections. There was more thrombocytopenia in the B arm compared to the G-B arm. All other observed toxicities were reasonably comparable between arms. Adverse events (AEs) were managed in a typical fashion. If patients had infections, they were treated appropriately. The most common AEs were cytopenias and infections. There were no major safety signals that had to be addressed. The increased efficacy observed in the G-B arm was not complicated by a large difference in the toxicity profile.
**New Evidence:** What kind of prophylactic measures do you take prior to treatment with G-B?

**Dr. Cheson:** There is no need for prophylactic antimicrobial therapy because the risk of infections (bacterial, fungal, and viral) is so low that it would not be appropriate.

**New Evidence:** In which patients would you currently recommend giving G-B?

**Dr. Cheson:** The population in the GADOLIN study included patients with rituximab-refractory low-grade FL, yet the FDA approval of G-B is for all patients with R/R FL following a rituximab-containing regimen. I think the G-B regimen is a reasonable treatment for all patients in this setting who have not previously received bendamustine. There were only three patients in the GADOLIN study who had previously received bendamustine, so the efficacy of the regimen in this context is unknown. No subset of patients in the G-B arm experienced reduced efficacy compared to the entire study population (age, sex, FL International Prognostic Index score, etc.).

**New Evidence:** Where do you see the G-B regimen fitting best in the sequence of iNHL treatments?

**Dr. Cheson:** I think this regimen is excellent for patients who have previously received rituximab (as a single agent, in combination with chemotherapy, or during maintenance) because G-B was advantageous in all of these prior treatment groups. In the U.S., the majority of patients receive BR as frontline therapy. We do not yet know if G-B is beneficial for this population. However, we are starting to use more targeted approaches, including in the first line. Because of this, I think there will be opportunities to use G-B in patients who failed R-CHOP, rituximab, or some other biological non-cytotoxic therapy.

**New Evidence:** Do you think that G-B will fill the current unmet need for patients with rituximab-refractory iNHL?

**Dr. Cheson:** In the foreseeable future, this regimen will fulfill the niche for patients with rituximab-refractory FL and low-grade lymphoma. When you look at the data in PFS, TTNT, and OS, G-B was superior not only in patients with FL, but also in the entire study population.

**New Evidence:** Will the results from this study change the standard of care for patients in this setting?

**Dr. Cheson:** I think the results of this study should clearly change practice, and G-B should become the standard of care for patients who are rituximab-refractory to frontline therapy.

**New Evidence:** Where do you see the treatment of rituximab-refractory iNHL heading in the future?

**Dr. Cheson:** We are currently in an era where we are moving away from traditional cytotoxic therapies (e.g., chemotherapy, chemoinmunotherapy) to more targeted, individualized, and personalized approaches. We have countless new agents that target the cell surface (e.g., monoclonal antibodies, antibody-drug conjugates), intracellular pathways (e.g., phosphoinositide 3-kinase, Bruton’s tyrosine kinase, spleen tyrosine kinase, or B-cell lymphoma 2 inhibitors), or the microenvironment (e.g., lenalidomide and the checkpoint inhibitors). Various combinations of these drugs are widely in development in clinical trials.

It is highly likely that in the next few years we will see a change in frontline therapy. One regimen that may alter our approach is the R-squared regimen (rituximab plus lenalidomide). We initially developed R-squared over a decade ago. Data in relapsed patients and in the frontline setting stimulated interest in the RELEVANCE trial, which compares R-squared to rituximab plus chemotherapy in patients with previously untreated FL. If this trial is positive, I think it will completely change how we treat FL in the first line. We are also still going to need novel approaches in the relapsed setting. For now, G-B is a great therapy for rituximab-refractory patients. However, we are developing newer non-chemotherapy approaches and I think this is the future of treatment in FL and low-grade lymphoma.

**References:**
Background

Autologous stem cell transplantation (ASCT) is the standard of care for patients with relapsed diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma (HL), and other aggressive non-Hodgkin lymphomas (NHL). The combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) is a standard conditioning regimen, but it is associated with increased risk of interstitial pneumonia and secondary tumours after ASCT. The following study, presented at ASH 2016, reported promising results with bendamustine replacing carmustine in the BEAM regimen, first described as Benda-EAM in 2011.1,2

Study design

• This study was a retrospective analysis of patients with aggressive NHL and HL who received Benda-EAM conditioning before ASCT.

• Endpoints included engraftment, safety, and response.

Key findings

Baseline characteristics and disposition

• Forty-one patients were treated as of July 1, 2016 (27 males and 14 females).

• The median age was 52 years (range: 22–71).

• A total of 29% of patients were more than 60 years of age.

• The median line of treatments was 2 (range: 1–4).

• Thirty-two patients had NHL:
  • Eleven patients had DLBCL in the second to fourth lines of treatment (two of which had double-hit lymphoma);
  • Ten patients had mantle cell lymphoma (MCL), nine of whom were in the first line of treatment;
  • Six patients had follicular lymphoma (FL) in the second to third lines of treatment;
  • Three patients had T-cell lymphoma (TCL) in the first line of treatment; and
  • Two patients had grey zone lymphoma (GZL) in the first and third lines of treatment.

Study design

<table>
<thead>
<tr>
<th>Bendamustine</th>
<th>Cytarabine Etoposide</th>
<th>Melphalan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>–8</td>
<td>–7</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>200 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>400 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>200 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>140 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

ASCT = autologous stem cell transplantation
Nine patients had HL in the second to third lines of treatment.

Salvage treatment/mobilization regimens that patients received are summarized in Table 1.

At the time of transplant, 34 patients (83%) were in complete remission and seven patients (17%) were in partial remission.

Details of engraftment are summarized in Table 2.

### Efficacy

- After ASCT, 22 patients (56%) achieved a complete response and eight patients (17%) had disease progression.
- No patients had a partial response after ASCT.
- There were 11 deaths after ASCT:
  - Three patients with HL;
  - Two patients with MCL; and
  - One patient each with GZL, TCL, and FL.
- All deaths were due to progressive disease, and all patients had complete remission before ASCT.
- After a median follow-up of 37 months (range: 19–56), 44% of patients had experienced relapse or progression.
- Median time to progression was seven months (range: 2–29).
- One- and two-year progression-free survival rates were 73.2% and 57.9%, respectively. (Figure 1)
- One- and two-year overall survival rates were 85.4% and 77.6%, respectively. (Figure 2)

### Safety

- Grade 3/4 toxicities are summarized in Table 3.
- No pulmonary toxicities were observed.
- No treatment-related mortality (TRM) was observed.

---

**Table 1. Salvage treatment/mobilization regimes**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 x R-DHAP</td>
<td></td>
</tr>
<tr>
<td>10 x (R)-mini Benda-EAM</td>
<td></td>
</tr>
<tr>
<td>10 x (R)-CHOP like</td>
<td></td>
</tr>
<tr>
<td>3 x BR or R-BAC</td>
<td></td>
</tr>
<tr>
<td>2 x R-ICE</td>
<td></td>
</tr>
<tr>
<td>1 x DA-EPOCH-R, 1 x BEACOPP esc</td>
<td></td>
</tr>
</tbody>
</table>

BEACOPP esc = dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; Benda-EAM = bendamustine, etoposide, cytarabine, melphalan; BR = bendamustine, rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; DA-EPOCH-R = dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R = rituximab; R-BAC = rituximab, bendamustine, cytarabine; R-DHAP = rituximab, desmethylcyclophosphamide, cytarabine, cisplatin; R-ICE = rituximab, ifosfamide, carboplatin, etoposide

---

**Table 2. Engraftment**

<table>
<thead>
<tr>
<th>Engraftment Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD34+ cells/kg body weight infused, n (range)</td>
<td>4.2 × 10⁶ (1.6–13.3 × 10⁶)</td>
</tr>
<tr>
<td>Median time of ANC &lt;1 × 10⁹/L, days (range)</td>
<td>10 (8–13)</td>
</tr>
<tr>
<td>Median time to platelets &gt;20 × 10⁹/L, days (range)</td>
<td>12 (7–110)</td>
</tr>
<tr>
<td>Median time of fever, days (range)</td>
<td>5 (0–15)</td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count; CD34 = cluster of differentiation 34

---

**Figure 1. Progression-free survival**

**Figure 2. Overall survival**
Table 3. Grade 3/4 toxicities (CTC 4.0)

<table>
<thead>
<tr>
<th>Toxicity (%)</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Cardiologic (7)</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal (34)</td>
<td>11</td>
</tr>
<tr>
<td>Oral mucositis (15)</td>
<td>6</td>
</tr>
<tr>
<td>Febrile neutropenia (14)</td>
<td>5</td>
</tr>
<tr>
<td>Infections (22)</td>
<td>6</td>
</tr>
</tbody>
</table>

CTC = common toxicity criteria

Key conclusions

- Benda-EAM seems to be a feasible treatment with a promising outcome.
- Rapid trilineage engraftment was observed.
- There was acceptable toxicity with no TRM.
- A randomized, international, phase II trial comparing BEAM with Benda-EAM is currently recruiting; first results are expected for 2018.


Marcus R, et al. ASH 2016:6

Obinutuzumab-based induction and maintenance prolongs PFS in patients with previously untreated FL: Primary results of the randomized phase III GALLIUM study

Background

There is a significant benefit of rituximab-based induction and maintenance therapy in patients with previously untreated, advanced-stage, symptomatic follicular lymphoma (FL), with reported progression-free survival (PFS) rates of more than six years. Obinutuzumab has greater preclinical activity than rituximab and prolonged PFS when combined with bendamustine in patients with indolent non-Hodgkin lymphoma (iNHL) who were refractory to rituximab. The GALLIUM study compared the efficacy and safety of obinutuzumab-based and rituximab-based regimens in patients with previously untreated iNHL; primary results for the subset of patients with FL were presented at ASH 2016.

Study design

- The GALLIUM study was an international, open-label, randomized phase III trial.
- Patients with previously untreated, CD20-positive FL or splenic/nodal/extranodal marginal zone lymphoma (MZL) were included in the study.
- Along with either obinutuzumab or rituximab, patients received one of the following chemotherapy regimens during induction:
  - Bendamustine (n = 827);
  - Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (n = 433); or
  - Cyclophosphamide, vincristine, prednisone (CVP) (n = 141).
- The primary endpoint was investigator-assessed PFS in patients with FL.
• A randomized, international, phase II trial comparing BEAM with Benda-EAM is currently recruiting;
• There was acceptable toxicity with no TRM.
• Rapid trilineage engraftment was observed.
• Benda-EAM seems to be a feasible treatment with a promising outcome.
  
  first results are expected for 2018.

---

**Key findings**

**Baseline characteristics and disposition**

• A total of 1,202 patients with FL were enrolled and randomized to treatment (intent to treat population).
• Median follow-up was 34.5 months; maintenance is ongoing in 114 patients (n = 54 in the rituximab arm and n = 60 in the obinutuzumab arm).
• The safety population was comprised of 1,192 patients.
• Baseline patient and disease characteristics were similar between the obinutuzumab and rituximab arms.
• The median age was 58 years in the rituximab arm and 60 years in the obinutuzumab arm.
• A large number of patients had an FL International Prognostic Index (FLIPI) score ≥3 (42.1% in the rituximab arm and 41.4% in the obinutuzumab arm) and bulky disease (45.2% in the rituximab arm and 42.5% in the obinutuzumab arm).
• The median time from diagnosis to randomization was 1.4 months in the rituximab arm and 1.5 months in the obinutuzumab arm.

**Efficacy**

• At the end of induction, ORR was 86.9% in the rituximab arm and 88.5% in the obinutuzumab arm.

• CR was achieved in 23.8% of patients in the rituximab arm and in 19.5% of patients in the obinutuzumab arm.

• The three-year investigator-assessed PFS was 80.0% in the obinutuzumab arm and 73.3% in the rituximab arm (HR = 0.66; 95% CI: 0.51–0.85; p = 0.0012). (Figure 1)

• PFS was stratified by chemotherapy regimen; however, post hoc analysis determined that the study was not powered to detect differences between chemotherapy regimens in either treatment arm.

• IRC-assessed PFS was 81.9% in the obinutuzumab arm and 77.9% in the rituximab arm (HR = 0.71; 95% CI: 0.54–0.93; p = 0.0138).

• Three-year TTNT was 87.1% in the obinutuzumab arm and 81.2% in the rituximab arm (HR = 0.68; 95% CI: 0.51–0.91; p = 0.0094).

• Three-year OS was 94.0% in the obinutuzumab arm and 92.1% in the rituximab arm (HR = 0.75; 95% CI: 0.49–1.17; p = 0.21). (Figure 2)

**Safety**

• The incidence of adverse events (AEs) was higher in the obinutuzumab arm than in the rituximab arm, particularly for infusion-related reactions (IRRs), cytopenias, and infections. (Table 1)

• Grade 5 AEs occurred more frequently in patients receiving bendamustine, regardless of treatment arm.

• There were 34 deaths in the group who received bendamustine, regardless of treatment arm.

• There were seven deaths in the group who received CHOP (three in the obinutuzumab arm and four in the rituximab arm).

• There were two deaths in the group who received CVP (one in each arm).
### Figure 1. Investigator-assessed progression-free survival (FL population)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Table 1. Progression-free survival endpoints

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (n = 601)</th>
<th>Obinutuzumab (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>144 (24.0)</td>
<td>101 (16.8)</td>
</tr>
<tr>
<td>3-year PFS, % (95% CI)</td>
<td>73.3 (68.8–77.2)</td>
<td>80.0 (75.9–83.6)</td>
</tr>
<tr>
<td>HR (95% CI), p-value*</td>
<td>0.66 (0.51–0.85), p = 0.0012</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; HR = hazard ratio; PFS = progression-free survival

* Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region.

### Figure 2. Overall survival (FL population)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Table 2. Overall survival endpoints

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (n = 601)</th>
<th>Obinutuzumab (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>46 (7.7)</td>
<td>35 (5.8)</td>
</tr>
<tr>
<td>3-year OS, % (95% CI)</td>
<td>92.1 (89.5–94.1)</td>
<td>94.0 (91.6–95.7)</td>
</tr>
<tr>
<td>HR (95% CI), p-value*</td>
<td>0.75 (0.49–1.17), p = 0.21</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; HR = hazard ratio; OS = overall survival

* Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region.
### Table 1. Safety summary (FL population)

<table>
<thead>
<tr>
<th>% (n)</th>
<th>Rituximab arm (n = 597)</th>
<th>Obinutuzumab arm (n = 595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>98.3 (587)</td>
<td>99.5 (592)</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs (≥5% in either arm)</td>
<td>67.8 (405)</td>
<td>74.6 (444)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37.9 (226)</td>
<td>43.9 (261)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>8.4 (50)</td>
<td>8.6 (51)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.9 (29)</td>
<td>6.9 (41)</td>
</tr>
<tr>
<td>IRRs*</td>
<td>3.7 (22)</td>
<td>6.7 (40)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.7 (16)</td>
<td>6.1 (36)</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs of special interest by category (selected)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections†</td>
<td>15.6 (93)</td>
<td>20.0 (119)</td>
</tr>
<tr>
<td>IRRs‡</td>
<td>6.7 (40)</td>
<td>12.4 (74)</td>
</tr>
<tr>
<td>Second neoplasms§</td>
<td>2.7 (16)</td>
<td>4.7 (28)</td>
</tr>
<tr>
<td>SAEs</td>
<td>39.9 (238)</td>
<td>46.1 (274)</td>
</tr>
<tr>
<td>AEs causing treatment discontinuation</td>
<td>14.2 (85)</td>
<td>16.3 (97)</td>
</tr>
<tr>
<td>Grade 5 (fatal) AEs</td>
<td>3.4 (20)</td>
<td>4.0 (24)**</td>
</tr>
<tr>
<td>Median (range) change from baseline in IgG levels at end of induction, g/L††</td>
<td>−1.46 (−16.4 to 9.1)‡‡</td>
<td>−1.50 (−22.3 to 6.5)§§</td>
</tr>
</tbody>
</table>

AE = adverse event; EOI = end of induction; FL = follicular lymphoma; IgG = immunoglobulin G; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

* As MedDRA preferred term.
† All events in MedDRA System Organ Class ‘Infections and Infestations’.
‡ Any AE occurring during or within 24 hours of infusion of obinutuzumab or rituximab and considered drug-related.
§ Standardized MedDRA query for malignant or unspecified tumours starting six months after treatment start.
** Includes patient who died after clinical cut-off date from AE starting before cut-off date.
†† Immunoglobulin levels were measured during screening, at EOI, at end of maintenance, and during follow-up.
‡‡ n = 472.
§§ n = 462.

### Key conclusions

- Obinutuzumab plus chemotherapy and maintenance was superior to rituximab plus chemotherapy and maintenance in untreated patients with advanced FL.
- There was a clinically meaningful improvement in PFS that was supported by other time-to-event endpoints.
- Nonfatal AEs were higher in the obinutuzumab arm, particularly in IRRs, cytopenias, and infections.
- Fatal AEs were more common in patients on bendamustine in both arms.
- Obinutuzumab-based therapy significantly improves outcomes compared with rituximab-based therapy and should now be considered as a first-line treatment for FL.

### References

Rituximab, bendamustine and cytarabine as induction therapy in elderly patients with MCL: Final results of a phase II study from the Fondazione Italiana Linfomi

Background
The combination of bendamustine and rituximab is an effective frontline treatment for elderly patients with mantle cell lymphoma (MCL). Cytarabine is highly beneficial in younger patients with MCL, and the combination of bendamustine, rituximab, and cytarabine (R-BAC) is strongly synergistic when cultured consecutively on MCL cell lines. At ASH 2016, Visco and colleagues presented the results of a phase II trial that investigated the efficacy and safety of R-BAC in elderly patients with MCL.

Study design
- The study was a single arm, phase II, multicentre trial that used the Bryant and Day two-stage design. Stage I was designed to recruit 19 patients; the study would stop if fewer than eight patients achieved a complete response (CR) or if more than seven patients experienced toxicity. Stage II was designed to recruit 38 patients; the results would be considered positive if more than 28 patients achieved CR and fewer than 18 patients experienced toxicity.
- The dose of cytarabine in this study was reduced to 500 mg/m² (R-BAC500).
- Inclusion criteria were:
  - Previously untreated patients with MCL aged >65 years, or age 60–65 and unfit for autologous stem cell transplantation; and
  - No history of indolent disease (non-nodal leukemic disease).
- Patients were recruited between May 2, 2012 and February 25, 2014.
- The primary objectives were CR rate (according to 2007 International Working Group criteria) and safety.
- Secondary objectives included the rate of molecular response, progression-free survival (PFS), overall survival (OS), and duration of response (DoR).

CR = complete response; MRD = minimal residual disease; PD = progressive disease; PET = positron emission tomography; PR = partial response; R-BAC500 = rituximab, bendamustine, cytarabine (cytarabine at 500 mg/m²); SD = stable disease
Key findings

**Baseline characteristics and disposition**

- A total of 57 patients were enrolled from 29 centres; 304 cycles of R-BAC500 were delivered.
- The median age was 71 years (range: 61–79).
- The majority of patients were male (75%) with a performance status of 0–1 (94%), bone marrow involvement (63%), and classical histology (75%).
- Elevated Ki-67 expression (≥30%) was found in 31% of patients.
- No patients were excluded based on pathology review.
- Three patients discontinued due to toxicity/adverse event (AE) after at least two cycles of treatment.

- After at least four cycles, a further 16 patients discontinued treatment:
  - Eleven patients discontinued due to toxicity/AE;
  - One patient discontinued due to progressive disease (PD); and
  - Four patients discontinued due to doctor/patient decision.
- A total of 38 patients completed six cycles of treatment (67%).

**Efficacy**

- At the end of treatment, CR rate and overall response rate were both 91%.

Figure 1. Survival curves

![Survival curves](image-url)

*CI = confidence interval; DoR = duration of response; OS = overall survival; PFS = progression-free survival*
Forty-five patients were assessed for minimal residual disease (MRD).

- By the end of treatment, 55% of these patients had achieved MRD in bone marrow, and 79% had achieved MRD in peripheral blood.
- Twelve months after the end of treatment, 57% of 28 patients analyzed maintained MRD in the bone marrow, and 75% maintained MRD in peripheral blood.
- After a median follow-up of 35 months, two-year OS was 86%, two-year PFS was 81%, and two-year DoR was 90%. (Figure 1)

High MCL International Prognostic Index (MIPI) score, blastoid morphology, and elevated Ki-67 expression were associated with inferior PFS. (Figure 2)

**Safety**
- Twenty-three patients (40%) had at least one episode of hematological ‘relevant toxicity’, which exceeded the predefined safety boundaries. (Table 1)
- However, the incidence of grade 4 hematological toxicities was lower than previously reported.\(^5\)
- Forty-one patients (72%) had at least one dose reduction over treatment courses.
- Non-hematological toxicities are summarized in Table 2.

---

**Figure 2. Univariate analysis for PFS**

<table>
<thead>
<tr>
<th>Grouping variable: MIPI</th>
<th>Probability of PFS</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIPI Low-Intermediate</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>MIPI High</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

\(p = 0.03\)

<table>
<thead>
<tr>
<th>Grouping variable: Ki-67</th>
<th>Probability of PFS</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67 &lt;30%</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ki-67 ≥30%</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
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<tr>
<td></td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

\(p < 0.0001\)

<table>
<thead>
<tr>
<th>Grouping variable: Morphology</th>
<th>Probability of PFS</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Pleomorphic</td>
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</tr>
</tbody>
</table>

\(p < 0.0001\)

**HR = high risk; LR = low risk; MIPI = Mantle Cell Lymphoma International Prognostic Index; PFS = progression-free survival**
### Table 1. Hematological toxicities (% of delivered cycles)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Overall Delivered cycles: 304</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>30%</td>
<td>26%</td>
<td>17%</td>
<td>27%</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15%</td>
<td>36%</td>
<td>14%</td>
<td>35%</td>
<td>17%</td>
<td>26%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14%</td>
<td>34%</td>
<td>16%</td>
<td>36%</td>
<td>64%</td>
<td>34%</td>
</tr>
<tr>
<td>Anemia</td>
<td>21%</td>
<td>24%</td>
<td>43%</td>
<td>12%</td>
<td>&lt;1%</td>
<td>24%</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5%</td>
<td>29%</td>
</tr>
</tbody>
</table>

| Delivered cycles: 304       |         |         |         |         |         |                               |
| R-BAC study (JCO 2013)⁵     |         |         |         |         |         |                               |

| Grade 4                     |         |         |         |         |         |                               |
| Leukopenia                  |         | 26%     | 17%     | 27%     | 28%     |                               |
| Neutropenia                 |         |         | 14%     | 35%     | 17%     |                               |
| Febrile neutropenia         |         |         |         | 5%      | 1%      |                               |
| Thrombocytopenia            |         | 14%     | 34%     | 16%     | 36%     |                               |
| Anemia                      |         | 21%     | 24%     | 43%     | 12%     |                               |
| Platelet transfusion        |         | —       | —       | —       | 5%      |                               |

JCO = Journal of Clinical Oncology; R-BAC = rituximab, bendamustine, cytarabine

### Table 2. Non-hematological toxicities occurring in more than one patient

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades, n (%)</th>
<th>Grade 3, n (%)</th>
<th>Grade 4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>12 (21)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation/diarrhea</td>
<td>6 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infusion related/TLS</td>
<td>12 (21)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (25)</td>
<td>1 (2)</td>
<td>NA</td>
</tr>
<tr>
<td>Documented infections</td>
<td>5 (9)</td>
<td>5* (9)</td>
<td>2† (4)</td>
</tr>
<tr>
<td>g-GT/GOT-GPT elevation</td>
<td>7 (12)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>5 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3 (5)</td>
<td>2† (3)</td>
<td>1§ (2)</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; g-GT = gamma-glutamyl-transpeptidase; GOT = glutamate oxaloacetate transaminase; GPT = glutamic-pyruvic transaminase; HZV = herpes zoster virus; NA = not applicable; TLS = tumour lysis syndrome

*HZV reactivation, infection of the surgical wound, CMV reactivation (n = 2), fungal infection.
†Pseudomonas Aeruginosa and Gram+ sepsis.
‡Atrial fibrillation, chest pain.
§Myocardial infarction with cerebral ischemia.

### Key conclusions

- The results support the use of R-BAC500 in elderly patients with MCL, and the regimen could be considered as an inexpensive and short-term option.
- Hematological toxicity exceeded the prespecified safety boundaries, but was manageable with dose reduction and reduced compared to previous experience.
- Responses were durable without the use of maintenance therapy, and PFS compared favourably with previously reported regimens, including the combination of bendamustine and rituximab.

### References:
Background
Bendamustine plus rituximab (BR) and dexamethasone, rituximab, and cyclophosphamide (DRC) combination therapies are frequently used for the treatment of Waldenström Macroglobulinemia (WM), both in the frontline and relapsed/refractory (R/R) settings. No direct comparison between BR and DRC has been reported. At the 2016 ASH Meeting, Paludo and colleagues reported outcomes of patients receiving either BR or DRC in R/R and treatment-naïve (TN) patients with WM in the real-world setting.1

Study design
• Records of all patients with WM treated at the Mayo Clinic from January 2007 to December 2014 were reviewed.
• Myeloid differentiation primary response gene-88 (MYD88) L265P point mutation (MYD88L265P) status was recorded when available.
• Analyses were performed on patients treated with up to six cycles of either:
  ♦ BR (bendamustine 90 mg/m\(^2\) intravenous [iv] on Day 1 and 2, and rituximab 375 mg/m\(^2\) iv on Day 1); or
  ♦ DRC (dexamethasone 20 mg iv followed by rituximab 375 mg/m\(^2\) iv on Day 1, and cyclophosphamide 100 mg/m\(^2\) oral, twice a day on Days 1–5).
• Response criteria from the International WM Workshop VI were utilized.
• Time-to-event analyses were performed from BR or DRC initiation date, using the Kaplan-Meier method.

Key findings
Baseline characteristics and disposition
• Sixty patients received BR (73% in the R/R setting), and 100 patients received DRC (50% in the R/R setting, \(p = 0.004\) vs. BR).

Efficacy
• In the frontline setting:
  ◦ Median immunoglobulin M (IgM) levels decreased from 3,785 mg/dL to 724 mg/dL (\(p = 0.0001\)) at best response with BR, and from 4,130 mg/dL to 1,250 mg/dL (\(p = 0.001\)) with DRC.
  ◦ The overall response rate (ORR) was 93% for BR and 96% for DRC. (Figure 1)
  ◦ Median follow-up was 30 months for both groups.

• In the R/R population, BR was the second-line therapy (range: 2–11) in 47% of patients, while DRC was the second-line therapy (range: 2–8) in 58% of patients.

• Rituximab monotherapy was the only prior line of therapy in eight (20%) patients in the BR group and 20 (40%) patients in the DRC group (\(p = 0.66\)).

• Apart from the number of patients in the R/R setting, baseline characteristics were similar in both treatment groups. (Table 1)

Bendamustine and rituximab versus dexamethasone, rituximab, and cyclophosphamide in patients with Waldenström Macroglobulinemia

Paludo J, et al. ASH 2016:2968
The median time to best response was 7 months with both BR (range: 1–39) and DRC (range: 0.5–28) ($p = 0.77$).

- ORR was 95% for BR and 87% for DRC. (Figure 1)
- Median follow-up was 32 months for BR and 51 months for DRC ($p = 0.24$).
- The two-year PFS was 66% and 53% in the BR and DRC groups, respectively ($p = 0.08$). (Figure 2)
- The two-year TTNT was 75% and 68% in the BR and DRC groups, respectively ($p = 0.24$). (Figure 2)
- The median DSS in the BR group was 69 months (95% CI: 65–69) and NR in the DRC group ($p = 0.57$).

- In a bivariate analysis of the entire cohort for PFS, incorporating the disease setting (TN vs. R/R) and the regimen involved (BR vs. DRC), the type of regimen emerged as a significant factor (HR = 0.52, $p = 0.019$) for PFS in favour of BR.
- Time-to-event outcomes and response rates were similar in patients with the MYD88$^{L265P}$ and MYD88$^{wild-type}$ genotypes.

### Safety
- Grade ≥3 adverse events were comparable in the BR and DRC cohorts. (Table 2)

---

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter, median (range)*</th>
<th>BR (n = 60)</th>
<th>DRC (n = 100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62 (30–85)</td>
<td>65 (37–95)</td>
<td>0.39</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>41 (68)</td>
<td>58 (58)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.1 (5–15)</td>
<td>10.7 (5–15)</td>
<td>0.33</td>
</tr>
<tr>
<td>Platelet count, × 10⁹/L</td>
<td>206 (33–533)</td>
<td>213 (28–664)</td>
<td>0.74</td>
</tr>
<tr>
<td>B2 microglobulin, mcg/mL</td>
<td>3.2 (1.6–11)</td>
<td>2.8 (1.3–8)</td>
<td>0.10</td>
</tr>
<tr>
<td>IgM, mg/dL</td>
<td>3,345 (545–11,600)</td>
<td>3,208 (817–12,400)</td>
<td>0.93</td>
</tr>
<tr>
<td>BM involvement, % (range)</td>
<td>55 (5–99)</td>
<td>50 (5–90)</td>
<td>0.51</td>
</tr>
<tr>
<td>MYD88$^{L265P}$, n (%)</td>
<td>14 (74)</td>
<td>24 (83)</td>
<td>0.48</td>
</tr>
<tr>
<td>Relapsed/refractory, n (%)</td>
<td>44 (73)</td>
<td>50 (50)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Time to event, median (95% CI)†**

<table>
<thead>
<tr>
<th></th>
<th>BR (n = 60)</th>
<th>DRC (n = 100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td>58 (45–NR)</td>
<td>34 (23–51)</td>
<td>0.04</td>
</tr>
<tr>
<td>TTNT, months</td>
<td>60 (45–NR)</td>
<td>53 (38–62)</td>
<td>0.23</td>
</tr>
<tr>
<td>DSS, months</td>
<td>NR (136–NR)</td>
<td>166 (111–NR)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Bm = bone marrow; BR = bendamustine, rituximab; CI = confidence interval; DRC = dexamethasone, rituximab, cyclophosphamide; DSS = disease-specific survival; IgM = immunoglobulin M; MYD88$^{L265P}$ = myeloid differentiation primary response gene-88 L265P point mutation; NR = not reached; PFS = progression-free survival; R/R = relapsed/refractory; TN = treatment-naïve; TTNT = time to next therapy

* Unless specified otherwise.
† Combined TN and R/R patients.
**Figure 1. Best response rates**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BR</th>
<th>DRC</th>
<th>BR</th>
<th>DRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients (%)</td>
<td>29%</td>
<td>70%</td>
<td>38%</td>
<td>64%</td>
</tr>
<tr>
<td>57%</td>
<td>41%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7%</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- CR = complete response
- VGPR = very good partial response
- PR = partial response
- MR = minor response
- SD = stable disease
- PD = progressive disease

**Figure 2. Progression-free survival and time to next therapy**

**Legend:**
- BR = bendamustine, rituximab
- DRC = dexamethasone, rituximab, cyclophosphamide
- PFS = progression-free survival
- TTNT = time to next therapy
Table 2. Adverse events

<table>
<thead>
<tr>
<th>Toxicity, %</th>
<th>BR</th>
<th>DRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grade ≥3</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Fever/Chills</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Infections</td>
<td>19</td>
<td>15</td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; DRC = dexamethasone, rituximab, cyclophosphamide

Key conclusions

- Although both DRC and BR regimens show activity and comparable toxicities, the BR regimen shows a trend towards a superior PFS in patients with WM, both in the TN and the R/R settings.
- MYD88L265P mutation status does not appear to impact the activity of BR or DRC.


Miklos D, et al. ASH 2016:LBA-3

Multicentre open-label phase II study of ibrutinib in chronic graft versus host disease after failure of corticosteroids

Background
Chronic graft versus host disease (cGVHD) is the most common cause of morbidity after allogeneic transplant. There are no approved therapies for patients with cGVHD who fail corticosteroids. In preclinical models, ibrutinib reduced the severity of cGVHD, meriting its further study as a potential therapy for this disease. The following study, presented at ASH 2016, investigated the efficacy and safety of ibrutinib in patients with cGVHD who had failed frontline therapy.

Study design
- A total of 42 patients were enrolled in the study.
- The primary endpoint was cGVHD response per National Institute of Health 2005 response criteria.
- Secondary endpoints included rate of sustained response, change in Lee cGVHD symptom scale, change in corticosteroid requirement over time, safety, and the effect of lymphoid and myeloid signalling pathways, plasma cytokines, and plasma chemokines.

Key findings

Baseline characteristics and disposition
- The median age was 56 years (range: 19–74), and 52% of patients were male.

- The median time from allogeneic transplant to diagnosis of cGVHD was 7.6 months (range: 1.5–76.0) and the median time from diagnosis to ibrutinib treatment was 13.7 months (range: 1.1–63.2).
- The majority of patients had cGVHD symptoms in the mouth (86%) or skin (81%).
- The majority of patients received nonmyeloablative transplants (57%).
- The majority of patients received peripheral stem cell transplants (88%).
- The indications for transplant were as follows: acute lymphoblastic leukemia (n = 9), acute myelogenous leukemia (n = 8), chronic lymphocytic leukemia (n = 7), chronic myelogenous leukemia (n = 3), myelofibrosis (n = 3), myelodysplastic syndrome (n = 3), Hodgkin lymphoma (n = 3), aplastic anemia (n = 2), T-cell prolymphocytic leukemia (n = 1), T-cell-type acute leukemia (n = 1), diffuse large B-cell lymphoma (n = 1), and acute promyelocoid leukemia (n = 1).
- Patients received a median of two prior regimens for cGVHD (range: 1–3).
- The median dose of prednisone at enrolment was 0.3 mg/kg/day (range: 0.1–1.3).
• All patients had previously received corticosteroids as therapy for cGVHD.
• After a median follow-up of 14 months, 12 patients (29%) remained on ibrutinib.
  ◦ Reasons for ibrutinib discontinuation included adverse events (AEs) (33%), patient decision (14%), progression of cGVHD (12%), investigator decision (5%), recurrence or progression of original malignancy (5%), and noncompliance with study drug (2%).

**Efficacy**

• Ibrutinib produced a high rate of response that was sustained. (Figure 1)
  ◦ One third of responders had a complete response, 79% of whom had responded at the time of first response assessment.
  ◦ Of the 28 responders, 71% had a sustained cGVHD response of at least five months.
• A total of 80% of patients with two or more involved organs at baseline responded in at least two organs. (Figure 2)
  ◦ Out of nine patients with three or more involved organs at baseline, five (56%) responded in at least three organs.
• Overall, 26 patients (62%) achieved corticosteroid doses <0.15 mg/kg/day while on ibrutinib. (Figure 3)
  ◦ Five responders were able to discontinue all corticosteroid treatment.
• Ibrutinib produced a clinically meaningful improvement in Lee symptom scale score among responders. (Figure 4)
  ◦ Consistent with improvement in cGVHD symptoms, clinician-assessed and patient-reported reductions in overall cGVHD severity were also reported.
• Soluble plasma factors related to inflammation, fibrosis, and cGVHD decreased with ibrutinib.
• Functional blockade of Bruton’s tyrosine kinase and interleukin-2-inducible T-cell kinase was observed with ibrutinib.

**Safety**

• The AE profile showed largely low-grade events consistent with those reported for B-cell malignancies treated with ibrutinib and those observed in cGVHD patients on corticosteroids. (Figure 5)
• Serious AEs occurred in 22 patients (52%) including pneumonia (n = 6), septic shock (n = 2), and pyrexia (n = 2).
• Two fatal events occurred (multilobular pneumonia and bronchopulmonary aspergillosis).
**Figure 1. Best of cGVHD response**

- **N = 42***
- **ORR = 67%**

**Figure 2. Response by organ**

- **Skin (n = 24)**
  - 88% response

- **Mouth (n = 24)**
  - 88% response

- **GI (n = 11)**
  - 91% response

- **Liver (n = 3)**
  - 67% response

* Five patients had no response assessment during the study but were included in the denominator.

**Figure 3. Corticosteroid doses during ibrutinib treatment**

- **Median weekly average of daily corticosteroid dose (mg/kg/day)**

* cGVHD = chronic graft versus host disease; CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

* Five patients had no response assessment during the study but were included in the denominator.

**CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease**
Figure 4. Improvement in Lee symptom scale score among responders

Figure 5. Treatment-emergent adverse events occurring in >15% of patients

Key conclusions

• Ibrutinib resulted in clinically meaningful and sustained responses in patients who had failed at least one prior treatment for cGVHD.

• Patients experienced reductions in corticosteroid doses while on ibrutinib.

• Biomarker changes supported a beneficial effect of ibrutinib on cGVHD-related immune cell subsets.

• AEs were consistent with those previously reported for ibrutinib, and with those observed in patients with cGVHD on concomitant corticosteroids.

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