Moving Forward

Providing Safer Treatment Options

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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 2015 issue presents coverage from the 56th American Society of Hematology (ASH) Annual Meeting. This issue reports on key clinical trials evaluating treatment for hematological malignancies, including acute myelogenous leukemia, acute promyelocytic leukemia, chronic lymphocytic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma. The studies presented in this issue highlight new and existing therapies that can now benefit a larger range of patients by providing effective disease management without unacceptable levels of toxicity. We would like to thank Dr. Isabelle Bence-Bruckler, Dr. Sujaatha Narayanan, Dr. Carolyn Owen, and Dr. Cynthia Toze for their Canadian Perspectives. We would also like to thank Dr. Wolfgang Knauf, Dr. Philippe Moreau, Dr. Susan O’Brien, Dr. Uwe Platzbecker, Dr. Torben Plesner, Dr. Mathias Rummel, and Dr. Clemens-Martin Wendtner for their Investigator Commentaries.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research.
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New Drug Combinations and Novel Agents in the Treatment of Multiple Myeloma

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• Immunomodulatory drugs affect hematopoiesis via CRBN-dependent degradation of the IKZF1 protein in CD34+ cells. (Li S, et al. ASH 2014:418)

• Comparison of sequential versus alternating administration of bortezomib, melphalan, and prednisone, and lenalidomide plus dexamethasone in elderly patients with newly diagnosed multiple myeloma. (Mateos MV, et al. ASH 2014:178)

• Persistent benefit of VTD (bortezomib, thalidomide, dexamethasone) as pre-transplant induction therapy for multiple myeloma: long-term follow-up of a randomized phase III PETHEMA/GEM study. (Rosinol L, et al. ASH 2014:3457)

• Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed and refractory multiple myeloma. (Plesner T, et al. ASH 2014:84)

• An open-label, multicentre, phase 1b study of daratumumab in combination with backbone regimens in patients with multiple myeloma. (Moreau P, et al. ASH 2014:176)


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• Updated efficacy and overall safety in the phase III RESONATE™ trial of ibrutinib versus ofatumumab in previously treated CLL/SLL. (Brown JR, et al. ASH 2014:3331)

• In vivo evidence that ibrutinib deregulates chemokine receptor CXCR4 surface membrane expression and signaling, along with inhibiting B-cell antigen receptor signaling, as causes for defective homing and impaired retention of CLL cells in tissues. (Chen S-S, et al. ASH 2014:1948)

• Patterns of use of anticoagulation and/or antiplatelet agents in patients with CLL treated with single-agent ibrutinib. (Jones JA, et al. ASH 2014:1990)

• Hematologic and immunologic function and patient well-being for the phase III RESONATE™ study of ibrutinib versus ofatumumab in relapsed/refractory CLL/SLL. (Barrientos JC, et al. ASH 2014:4696)
• The addition of rituximab abrogates ibrutinib-induced lymphocytosis and promotes more rapid decrease in absolute lymphocyte counts in patients with relapsed CLL. (Kim E, et al. ASH 2014:1998)

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Canadian Perspectives

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Dr. Philippe Moreau is Head of the Hematology Department at the University Hospital of Nantes, France. He specializes in clinical hematology, with a particular focus on multiple myeloma and its treatment with high-dose therapy and novel agents. Dr. Moreau was appointed University Professor of Clinical Hematology at Nantes Faculty of Medicine in 2003.

As the lead researcher in multiple myeloma, Dr. Moreau is head of the unit for early phase I and phase II trials in clinical hematology at the University Hospital of Nantes. Additionally, he was a member of the organizing committee for the 2011 International Myeloma Workshop, in Paris. Dr. Moreau is currently a member of the administration council of the Intergroupe Francophone du Myélome (IFM), and he was chairman of the IFM from 2006 through 2009. Dr. Moreau is widely published, with more than 300 peer-reviewed articles and reviews that have appeared in high impact factor journals. He is a member of the Editorial Board of the Journal of Clinical Oncology, Blood, and Blood Cancer Journal.

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Multiple myeloma (MM) is the second most common hematologic malignancy in Canada, accounting for approximately 1% of all cancers and 2% of deaths from cancer. Although it is an incurable disease, novel therapeutic agents such as proteasome inhibitors (e.g., bortezomib) and immunomodulatory drugs (IMiDs) (e.g., thalidomide and lenalidomide) have improved the length of survival for these patients.

Generally, newly diagnosed patients with MM who are young and fit initially receive induction therapy, followed by stem cell harvest and autologous stem cell transplantation (ASCT). Various regimens are available for induction therapy, including the combination of novel agents such as bortezomib, thalidomide, and lenalidomide, with alkylating agents (e.g., cyclophosphamide) and corticosteroids (e.g., prednisone and dexamethasone).

As MM is considered a disease of the elderly, with the median age at diagnosis being older than 70 years, the majority of patients have comorbidities that make them ineligible for ASCT. For these patients, treatment with melphalan and prednisone (MP) in combination with a novel agent has been shown to be superior to MP alone. However, frail patients and those with significant comorbidities may be more vulnerable to toxicities associated with these therapies, highlighting a need to identify effective treatment regimens with good safety profiles.

Although the introduction of proteasome inhibitors and IMiDs have improved overall survival, patients will eventually relapse and many will acquire resistance to prior therapies by mechanisms that are only beginning to be discovered. Options for salvage therapy are numerous and can include treatment with next generation drugs (e.g., carfilzomib and pomalidomide), different alkylating agents (e.g., bendamustine), and the use of new class agents such as monoclonal antibodies (e.g., daratumumab).

Evaluation of a number of combination regimens and novel agents in the first-line and relapsed settings for transplant-eligible and -ineligible patients with MM are ongoing. Here we report the results of several studies, presented at the 56th Annual Meeting of the American Society of Hematology (ASH) in San Francisco, that investigated the safety, efficacy, and mechanisms of action of novel agents and drug combinations in the treatment of MM:

- In an in vitro study using relapsed/refractory MM patient samples, increased expression of the cereblon (CRBN) splice isoform lacking exon 10 was identified as a novel mechanism of IMiD resistance.
- The pathologic mechanism by which IMiDs (lenalidomide and pomalidomide) induce neutropenia in patients was studied in an in vitro cell system, where CRBN and IKZF1 were found to play an important role.
- Both sequential and alternating administration of bortezomib, melphalan, and prednisone (VMP) and lenalidomide and dexamethasone were found to be effective and tolerable in a study of elderly patients with newly diagnosed MM.
- In the 5-year follow-up of a phase III PETHEMA/GEM trial comparing pretransplant induction therapies, a combination of bortezomib, thalidomide, and dexamethasone (VTD) as induction therapy resulted in significantly longer progression-free survival.
- The anti-CD38 monoclonal antibody daratumumab, in combination with lenalidomide and dexamethasone, was tolerable and demonstrated impressive response rates in a phase I/II study of relapsed, or relapsed and refractory, patients with MM.
- Preliminary results from a phase Ib study showed that daratumumab in combination with bortezomib and dexamethasone (VD), VMP, or pomalidomide and dexamethasone (POM-D) produced promising response rates, was tolerable, and did not affect stem cell mobilization.
- An in vitro study comparing daratumumab with surrogate analogs of anti-CD38 antibodies revealed that daratumumab was able to induce high levels of complement-dependent cytotoxicity compared to other monoclonal anti-CD38 antibodies.
- Bendamustine, lenalidomide, and dexamethasone as second-line treatment was shown to be safe and effective in a phase II study of relapsed/refractory patients with MM.

References:


The cereblon splice isoform lacking exon 10 (CRBNΔ10) attenuates lenalidomide-mediated degradation of Aiolos and is upregulated in immunomodulatory drug-resistant myeloma patients

Background
Treatment with IMiDs (immunomodulatory drugs) has improved survival for patients with multiple myeloma (MM); however, many of these patients develop resistance to IMiDs over time. The cytotoxic effect of IMiDs on MM cells is mediated through direct binding to cereblon (CRBN), with several amino acids (aa) within exons 10 and 11 of CRBN being essential for this interaction (W382 and H378). CRBN is a substrate receptor of the cullin ring E3 ubiquitin ligase complex, CRL4-CRBN, which can interact with and ubiquitinate transcription factors such as Aiolos (IKZF3) upon treatment with lenalidomide or pomalidomide. Several groups have reported an association between loss of CRBN and resistance to IMiDs; however, this does not appear to be the sole mechanism of resistance in primary MM cells.

Study design
• This study investigated the expression of CRBN splice variants in MM cells and their potential contribution to IMiD resistance.
• Ribonucleic acid-sequencing (RNA-seq) analysis was performed on CD138-sorted cells from 15 paired MM patients’ samples obtained sequentially prior to initiation of lenalidomide treatment and after development of resistance.
• Transcriptome sequence data was generated by RNA-seq with a minimum of 70 x 10^6 reads per sample.
• Filtered Fastq files were processed with the splice aligner TopHat against hg19.

Key findings
• RNA-seq analysis of pre- and post-IMiDs transcriptomes identified several CRBN splice isoforms including isoforms lacking exon 10 (CRBNΔ10) (and to a lesser extent exon 8) that were present in most patients at a variable frequency.
• Splicing almost universally involved the full length of exon 10, including aa W382 and H378.
• Mutation analysis of the 30 samples using the Genome Analysis Toolkit RNA-seq pipeline did not identify any mutations within CRBN exons 10 or 11.
• Exome sequencing of CD138 cells from 10 additional lenalidomide resistant patients did not identify any CRBN single nucleotide variants or insertion/deletions, confirming the rarity of this event.
• Quantitative PCR (qPCR) confirmed that low pretreatment CRBN levels was significantly associated with shorter progression-free survival to lenalidomide (p = 0.008).
• The mRNA expression of full-length CRBN (CRBN-FL) (probe spanning exons 10-11) and CRBNΔ10 (probe spanning exons 9-11 junction) was evaluated by qPCR in 21 paired samples collected immediately pre-lenalidomide and at the time of progression post-lenalidomide.
The ratio of CRBNΔ10 to CRBN-FL (CRBNΔ10/CRBN-FL) was >1.5 (range: 1.5–54.9) in 7 of 21 paired samples.

- CRBN-FL and CRBNΔ10 transcripts were cloned and transfected into HEK293T cells and could be detected by Western blot.
- The CRBNΔ10 isoform maintained the ability to interact with the DDB1-CUL4A E3 ligase complex.

- HEK293T cells co-transfected with CRBN-FL and a plasmid expressing Aiolos resulted in a loss of Aiolos upon treatment with lenalidomide.
- This effect was attenuated upon transfection with CRBNΔ10, indicating a dominant negative effect of this splice isoform.

**Key conclusions**

- High levels of CRBN-FL mRNA or protein does not always predict response to IMiDs.
- The splice isoform CRBNΔ10 is protein coding and its expression is increased at the time of acquired resistance to IMiDs.
- CRBNΔ10 significantly diminishes the ability of IMiDs to degrade Aiolos after lenalidomide treatment, indicating a novel mechanism of IMiDs resistance by which CRBNΔ10 acts in a dominant-negative manner by blocking IMiDs binding to the CRL4 E3 ligase.

**References:**

Li S, et al. ASH 2014:418

**Immunomodulatory drugs affect hematopoiesis via CRBN-dependent degradation of the IKZF1 protein in CD34+ cells**

**Background**
Immunomodulatory drugs (IMiDs) induce high response rates in patients with multiple myeloma (MM); however, grade 3/4 neutropenia and thrombocytopenia are dose-limiting adverse effects, occurring in approximately 42% and 15% of patients, respectively.1 Previous studies observed that IMiD compounds can shift lineage commitment of CD34+ cells towards myeloid development by affecting critical transcription factors, such as GATA1 and PU.1, and concomitantly inhibiting cell maturation, which can lead to anemia and neutropenia. Nonetheless, the underlying mechanism for these hematotoxic effects is still unknown. Recently, IMiD compounds were shown to bind to cereblon (CRBN) in MM cells, which is the substrate recognition component of the cullin-RING E3 ubiquitin ligase CRL4-CRBN, and upon treatment with lenalidomide, CRL4-CRBN leads to the ubiquitination and degradation of two lymphoid transcription factors, IKZF1 and IKZF3.

**Study design**
- This study investigated the roles of CRBN, IKZF1, and IKZF3 in IMiD-induced effects on lineage commitment and maturation of CD34+ cells.

**Key findings**
- CRBN and IKZF1, but not IKZF3, are expressed in CD34+ cells at the protein level.
- Direct binding of IMiDs to CRBN in CD34+ cells was observed in a pull-down assay using thalidomide analog coupled beads.
- Treatment of CD34+ cells with lenalidomide and pomalidomide for 1 hour resulted in a drastic decrease in IKZF1 protein expression, but had no effect on IKZF1 messenger ribonucleic acid (mRNA) levels.
- Ubiquitination assays confirmed that lenalidomide and pomalidomide promote IKZF1 ubiquitination.
- Treatment with proteasome inhibitors (which function as cullin-dependent ubiquitin ligase inhibitors) blocked lenalidomide- and pomalidomide-induced IKZF1 degradation.
• PU.1 and GATA1 levels were down-regulated in CD34+ cells treated with IMiDs.
• Short hairpin RNA (shRNA) knockdown of IKZF1 resulted in decreased mRNA and protein expression of PU.1 and GATA1, and reversed the pomalidomide-induced lineage shift in colony-formation assays.
• Chromatin immunoprecipitation assays demonstrated that IKZF1 binds to promoter regions of PU.1 and GATA1, suggesting that these transcription factors are direct downstream targets of IKZF1 in CD34+ cells.

• shRNA knockdown of CRBN in CD34+ cells induced resistance to pomalidomide-induced IKZF1 downregulation and reversed the pomalidomide-induced lineage shift, suggesting that pomalidomide-induced degradation of IKZF1 in hematopoietic stem cells requires CRBN.
• In myeloablated NOD/SCID mice reconstituted with hematopoietic stem cells from human fetal thymus, treatment with pomalidomide (vs. DMSO) resulted in a decreased ratio of common lymphoid to myeloid progenitors and, 3 weeks later, an increased ratio of granulocyte macrophage to megakaryocyte erythrocyte progenitors.

Key conclusions

■ CRBN and IKZF1 mediate the effects of IMiD compounds on hematopoietic progenitors. (Figure 1)

• IMiDs directly bind to CRBN in CD34+ cells, leading to IKZF1 ubiquitination and degradation.
• Loss of IKZF1 decreases PU.1 and GATA1 expression in CD34+ cells, resulting in a shift to myeloid commitment with inhibition of myeloid maturation.
■ These data, for the first time, provide a pathologic mechanism of how lenalidomide and pomalidomide affect hematopoiesis and induce neutropenia, thrombocytopenia, and anemia.


Figure 1

CRL4-CRBN E3 ubiquitin ligase

CRBN = cereblon; CRL4 = cullin 4-RING ubiquitin ligase; CUL4 = cullin 4; DDB1 = damage-specific DNA binding protein 1; GATA1 = globin transcription factor 1; IKZF1/3 = Ikaros family zinc-finger 1/3; IMiDs = immunomodulatory drugs; PU.1 = transcription factor binding the PU-box; Ub = ubiquitin
Background
The combinations of bortezomib, melphalan, and prednisone (VMP) or lenalidomide and dexamethasone (Rd) are two of the most effective regimens for the treatment of newly diagnosed multiple myeloma (MM) in elderly patients. Given together, VMP and Rd may potentially improve patient outcome, but may be too toxic if given simultaneously. With the intention of minimizing the emergence of resistant clones while reducing potential toxicity, this study compared a regimen of VMP and Rd given in a sequential versus an alternating scheme.

Study design
• In this study, 240 patients older than 65 years with symptomatic, newly diagnosed MM were randomized to receive sequential (9 cycles of VMP followed by 9 cycles of Rd) or alternating (1 cycle of VMP and 1 cycle of Rd alternated up to 18 cycles) treatment schemes.
  ◦ Within each treatment scheme, 50% of the patients would start on VMP and 50% would start on Rd.
  ◦ The hypothesis of this study was that the alternating scheme would achieve higher efficacy, have lower probability of cell tumour escape, and lower cumulative toxicity.
  ◦ The VMP regimen consisted of one 6-week cycle, followed by eight 4-week cycles of:
    ◦ Bortezomib 1.3 mg/m² given weekly (except for the first cycle when it was given twice weekly for 2 weeks on, 1 week off);
    ◦ Melphalan 9 mg/m² (or 6 mg/m² if >75 years old) given on days 1–4; and
    ◦ Prednisone 60 mg/m² given on days 1–4.
  ◦ The Rd regimen consisted of nine 4-week cycles of:
    ◦ Lenalidomide 25 mg given daily on days 1–21; and
    ◦ Dexamethasone 40 mg given weekly.
  ◦ The primary objectives were to evaluate the complete response (CR) rate and to compare the safety of both treatment schemes.
  ◦ The secondary objectives were to evaluate progression-free survival (PFS) and overall survival (OS), as well as the efficacy of these schemes in patients with high-risk features.

Key findings
• In all, 233 patients were evaluable for safety and efficacy, including 118 patients in the sequential arm and 115 patients in the alternating arm.
  ◦ No significant differences in baseline characteristics were observed between arms.
  ◦ In the sequential and alternating arms respectively, the frequency of:
    ◦ Patients 75 years or older was 55% and 45%;
    ◦ Patients with International Staging System (ISS) stage III disease was 35% and 29%; and
    ◦ Patients with t(4;14), t(14;16), del(17p), and +1q was 51% and 50%.
  ◦ After 9 cycles of sequential VMP or alternating VMP/Rd, the stringent CR (sCR)/CR rates were 21% and 34% (p = 0.01), and the percentages of patients with very good partial response (VGPR) or greater were 48% and 59% (p = 0.002), respectively.
  ◦ After a median number of 18 cycles (range: 1–18), the overall response rate (ORR) in the intent-to-treat (ITT) population was 77% in the sequential arm and 80% in the alternating arm. (Table 1)
    ◦ In the sequential and alternating arms respectively, 63% and 64% of patients had VGPR or better, and 58% and 53% of patients in sCR/CR were in flow-CR.

Table 1. Response rates on ITT (n = 233)

<table>
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<tr>
<th>Response, %</th>
<th>Sequential arm (n = 118)</th>
<th>Alternating arm (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>sCR</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>CR</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>VGPR</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>PR</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DP</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>NE*</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

CR = complete response; DP = disease progression; ITT = intent-to-treat; NE = not evaluable; ORR = overall response rate; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response

*Eight patients in the sequential arm and four patients in the alternating arm were not evaluable because of early discontinuations.
• There were no significant differences in the frequency of hematological or non-hematological toxicities between treatment arms. (Table 2)

• Early discontinuations occurred in 33 patients (28%) in the sequential arm and 35 patients (30%) in the alternating arm, with 70% of all early discontinuations occurring in patients older than 75 years.

• Early deaths occurred in 5 patients (4%) and 6 patients (5%) in the sequential and alternating arms, respectively, all of which occurred in patients older than 75 years with comorbidities.

• In the ITT analysis (median follow-up of 30 months), median PFS was 32 months and 34 months, and OS at 3 years was 73% and 71%, in the sequential and alternating arms, respectively ($p = \text{not significant [NS]}$).

### Table 2. Toxicity profile (n = 233)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3/4 toxicities, n (%)</th>
<th>Sequential arm (n = 118)</th>
<th>Alternating arm (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematological toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (3)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (19)</td>
<td>26 (22)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25 (21)</td>
<td>23 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-hematological toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections $^*$</td>
<td>7 (6)</td>
<td>8 (7)</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>7 (6)</td>
<td>7 (6)</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy $^+$</td>
<td>5 (4)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>5 (3)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

$^*$Grade 1/2 infections were 22% and 17% in the sequential and alternating arms, respectively.
$^+$Grade 1/2 peripheral neuropathy was 29% and 21% in the sequential and alternating arms, respectively.
• In an analysis of patients who completed 18 cycles (n = 138), PFS at 3 years was 52% and 60%, and OS at 3 years was 91% and 95%, in sequential and alternating arms, respectively (p = NS).
• Analysis of PFS and OS were performed in patients stratified by response, age, and cytogenetic abnormalities. (Figures 1, 2, and 3).
  • PFS and OS rates at 3 years were significantly higher in patients who achieved sCR/CR vs. ≤ VGPR (PFS: 70% vs. 27%, p<0.0001; OS: 95% vs. 58%, p<0.001).
  • Median PFS and OS rates at 3 years were significantly higher in patients <75 years old vs. ≥75 years old (median PFS: 37 months vs. 27 months, p = 0.04; OS: 89% vs. 56%, p<0.0001)
  • There was no significant difference in median PFS and OS rates at 3 years in patients with high risk vs. standard risk cytogenetic abnormalities (median PFS: 24 months vs. 35 months, p = NS; OS: 72% vs. 79%, p = NS).

Figure 1. Progression-free survival and overall survival according to response on ITT analysis (n = 233)

Figure 2. Progression-free survival and overall survival according to age
Key conclusions

- Both the alternating and sequential schemes yielded similar efficacy and toxicity results.
- This total therapy approach is effective, especially in patients who are 65–75 years of age.
- The toxicity of the sequential and alternating treatment schemes was acceptable; however, patients older than 75 years may benefit from further optimization.
- These combination regimens appear to overcome the poor prognosis associated with the presence of high risk cytogenetic abnormalities.


Rosinol L, et al. ASH 2014:3457

Persistent benefit of VTD (bortezomib, thalidomide, dexamethasone) as pre-transplant induction therapy for multiple myeloma: long-term follow-up of a randomized phase III PETHEMA/GEM study

**Background**

Results from the randomized PETHEMA/GEM phase III trial GEM05menos65, published in *Blood* in 2012, demonstrated that a combination of bortezomib, thalidomide, and dexamethasone (VTD) produced significantly higher complete response (CR) rates pre- and post-transplant, as well as significantly longer progression-free survival (PFS) in patients with multiple myeloma (MM), when compared with thalidomide and dexamethasone (TD), or a combination of chemotherapy plus bortezomib.² This analysis reports the long-term results of the PETHEMA/GEM trial, five years after the last patient was included.
Study design

- This study enrolled 386 patients younger than 65 years, with newly diagnosed symptomatic MM, between April 6th, 2006 and August 5th, 2009.
- Patients were randomized to receive one of three different induction regimens lasting 24 weeks:
  - VBMCP/VBAD/B: VBMCP and VBAD chemotherapy for 4 cycles on an alternating basis, followed by 2 cycles of bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 at 3-week intervals;
  - TD: Thalidomide 200 mg daily (escalating doses in the 1st cycle) and dexamethasone 40 mg on days 1–4 and 9–12 at 4-week intervals for 6 cycles; or
  - VTD: Bortezomib 1.3 mg/m² on days 1, 4, 8, and 11, thalidomide 200 mg daily (escalating doses in the 1st cycle), and dexamethasone 40 mg days 1–4 and 9–12, at 4-week intervals for 6 cycles.
- After induction, all patients were planned to undergo autologous stem cell transplantation (ASCT) with high-dose melphalan at 200 mg/m², followed by maintenance therapy with thalidomide/bortezomib vs. thalidomide vs. alfa-2b-interferon for 3 years.

Key findings

- Patient characteristics at diagnosis and prognostic factors, such as International Staging System (ISS) stage, cytogenetics, and maintenance arm, were similarly distributed in the three arms.
- Of the 330 patients with cytogenetic studies, 70 (21%) had high-risk cytogenetics (i.e., t[4;14], t[14;16], and/or 17p deletion)
- At a median follow-up of 70.6 months:
  - The PFS was significantly longer in patients treated with VTD compared with TD and VBMCP/VBAD/B (median: 56.1 vs. 39.9 vs. 29.2 months, \( p = 0.005 \)); and
  - The estimated overall survival (OS) at 8 years was 60%, with no significant differences among treatment arms. (Figure 1)
- Overall, PFS was significantly shorter in patients with high-risk cytogenetics compared with patients with standard-risk cytogenetics (median: 15.7 vs. 44.3 months, \( p = 0.003 \)). (Figure 2)
- In the TD and VBMCP/VBAD/B arms, PFS was significantly shorter in patients with high-risk cytogenetics than in patients with standard-risk cytogenetics.
- In the VTD arm, there was no significant difference in PFS between patients with high-risk and standard-risk cytogenetics (median: 23.6 vs. 56.1 months, \( p = 0.2 \)).

ASCT = autologous stem cell transplantation; TD = thalidomide, dexamethasone; VBMCP/VBAD/B = vincristine, carmustine, cyclophosphamide, melphalan, prednisone/vincristine, carmustine, doxorubicin, dexamethasone/bortezomib; VTD = bortezomib, thalidomide, dexamethasone
TD and VTD at 4-week intervals.
* Bortezomib: 1.3 mg/m² on days 1, 4, 8, and 11.
† Thalidomide: 200 mg/day, dexamethasone: 40 mg on days 1–4 and 9–12.
Patients with high-risk cytogenetics had significantly shorter OS than those with standard-risk cytogenetics overall (median: 42.1 months vs. not reached, \( p = 0.00001 \)), as well as within each of the three treatment arms. (Figure 3)

Patients who achieved CR at the end of induction had significantly longer PFS compared with patients who achieved a lower degree of response, irrespective of the treatment arm (median: 62 vs. 28 months, \( p = 0.00001 \)).

On the intention-to-treat basis, patients who were in post-transplant CR had significantly longer PFS (\( p < 0.00001 \)) and OS (\( p < 0.00001 \)) compared with patients who did not reach CR after ASCT (\( p < 0.001 \)).

OS after relapse was significantly shorter in patients with high-risk vs. standard-risk cytogenetics in the overall series (median: 13.3 vs. 37.5 months, \( p = 0.001 \)), as well as in the VTD (13.3 vs. 33.9 months, \( p = 0.01 \)) and VBMCP/VBAD/B arms (8.5 vs. 38 months, \( p = 0.01 \)), but not in the TD arm (\( p = 0.1 \)). (Figure 4)

The median OS after progression was 30.5 months overall, and was not significantly different among the three treatment arms (VTD: 25.4 months, TD: 50 months, VBMCP/VBAD/B: 30.2 months, \( p = 0.4 \)).

### Figure 1. Progression-free survival and overall survival from diagnosis

- **Progression-free survival**
  - VBMCP/VBAD/B
  - TD
  - VTD

- **Overall survival**
  - VBMCP/VBAD/B
  - TD
  - VTD

\( p = 0.005 \)

\( p = \text{NS} \)

NS = not significant; TD = thalidomide, dexamethasone; VBMCP/VBAD/B = vincristine, carmustine, cyclophosphamide, melphalan, prednisone/vincristine, carmustine, doxorubicin, dexamethasone/bortezomib; VTD = bortezomib, thalidomide, dexamethasone

Median follow-up: 78.6 months.

### Figure 2. Progression-free survival in patients with standard-risk and high-risk cytogenetics

- **Overall Series**
  - Standard-risk
  - High-risk

\( p = 0.003 \)

13.7 months

44.3 months

### Figure 3. Overall survival in patients with standard-risk and high-risk cytogenetics

- **Overall Series**
  - Standard-risk
  - High-risk

\( p = 0.00001 \)

42.1 months

Not reached
Key conclusions

- Induction with VTD results in significantly longer PFS compared with TD and VBMCP/VBAD/B.
- Regardless of treatment, patients with high-risk cytogenetics had a worse outcome.
- The median PFS of 56 months achieved with VTD treatment is the longest ever reported in the first-line treatment of younger patients with MM who are eligible for ASCT, which supports the use of VTD as the standard of care for pre-transplant induction therapy.

References:

Plesner T, et al. ASH 2014:84

Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed and refractory multiple myeloma

**Background**
Daratumumab is a human monoclonal antibody that targets CD38-expressing malignant plasma cells. Given that the combination of daratumumab and lenalidomide has resulted in enhanced killing of multiple myeloma (MM) cells in vitro, it is hypothesized that this combination of agents will also lead to synergistically higher efficacy in the clinical setting.1

**Study design**
- This is an ongoing phase I/II, open-label, multi-centre trial, evaluating the safety and efficacy of daratumumab in combination with lenalidomide and dexamethasone in relapsed or relapsed and refractory (RR) patients with MM.
- In both parts of the study, lenalidomide 25 mg was given orally on days 1–21 of a 28-day cycle, and dexamethasone 40 mg was given weekly.
- In Part 1, the dose of daratumumab was increased to between 2 and 16 mg/kg, and in Part 2, daratumumab was given at a dose of 16 mg/kg.
- Patients with RR MM following 2–4 prior lines of therapy were eligible for Part 1, while in Part 2, RR MM patients with a minimum of 1 prior line of therapy were eligible.
- Other eligibility criteria included adequate organ function and measurable disease by M protein and light chain.
- Patients were excluded from the study if they were refractory or intolerant to lenalidomide.

**Key findings**
- The median age of patients was 61 years (range: 41–76).
In Supportive Care Oncology

Daratumumab infusions, 2–16 mg/kg (first infusion includes pre-dose the day before)
Lenalidomide days 1–21, 25 mg orally
Dexamethasone weekly, 40 mg

**Cycle 1**

**Part 1:** Dose-escalation study (3x3 design) — Daratumumab 2–16 mg/kg (N = 13)

**Part 2:** Expansion cohort — Daratumumab 16 mg/kg (N = 32)

**Study design**

- The median number of prior lines of therapy was 2 (range: 1–4).
  - The frequency of prior exposure to proteasome inhibitors (e.g., bortezomib), immunomodulatory drugs (e.g., lenalidomide and thalidomide), and autologous stem cell transplantation (ASCT) was 91%, 80%, and 73%, respectively.
- Three patients were lenalidomide-refractory according to the International Myeloma Working Group (IMWG) criteria.
- Data from 43 patients were evaluable for efficacy (Part 1: N = 13; Part 2: N = 30).
- In Part 1, at a mean follow-up of 12.9 months (range: 4.0–22.1), the overall response rate (ORR) was 100%, including a complete response (CR) in 31% of patients, a very good partial response (VGPR) in 46% of patients, and a partial response (PR) in 23% of patients. (Figure 1)
- In Part 2, at a median follow-up of 5.6 months (range: 2.7–7.0), ORR was 86.7%, including CR, VGPR, and PR rates of 6.7%, 43%, and 37%, respectively. (Figure 1)
  - The median time to response was 1 month, and the median time to CR was 4.9 months.
- Of the patients receiving 6 or more cycles of treatment in Part 2, 64.7% of patients achieved VGPR or better. (Figure 1)
  - Including data from Parts 1 and 2, VGPR or better was achieved in 75% of patients who were treated for at least 6 months.
- The majority of patients in Part 1 and Part 2 of the study had greater than 50% reduction in M protein levels.
- Data from 45 patients (32 men and 13 women) were evaluable for safety, with no dose-limiting toxicities reported.

**Figure 1. Overall best response**

![Overall best response](image)

**Overall best response**

- **Part 1**
  - ORR 100%
    - CR 31%
    - VGPR 46%
    - PR 23%
- **Part 2**
  - ORR 86.7%
    - CR 6.7%
    - VGPR 43%
    - PR 37%

**VGPR or better response by cycles of treatment (Part 2)**

- ≥2 cycles (N = 30)
  - CR 6.7%
  - VGPR 43.3%
- ≥4 cycles (N = 25)
  - CR 8.0%
  - VGPR 52.0%
- ≥6 cycles (N = 7)
  - CR 11.8%
  - VGPR 32.9%

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

*Mean duration of follow-up in Part 1: 12.9 (range: 4.0–22.1) months.
†Mean duration of follow-up in Part 2: 5.6 (range: 2.7–7.0) months.
Four patients discontinued treatment in Part 1 (three patients with disease progression and one patient with a cardiac disorder unrelated to daratumumab) and one patient in Part 2 discontinued treatment due to an infusion-related reaction (IRR) (laryngeal edema).

The most common adverse events included neutropenia (64%), muscle spasms (44%), and diarrhea (31%). (Table 1)

In Part 2 of the study, 21 patients received treatment on the current infusion program and 11 patients received treatment on an accelerated infusion program. The mean total number of full infusions per patient was 15.6 (standard deviation [SD]: 2.77) in the current infusion program and 10.5 (SD: 4.06) in the accelerated infusion program.

The median duration of the first, second, and subsequent infusions in the current program was 8.0, 6.5, and 5.5 hours, respectively. In the accelerated program, these infusion times were reduced to 5.4, 4.3, and 3.6 hours, respectively.

IRRs were reported in 19 patients, the majority of which were grade 1 or 2.

Of the IRRs reported, 86% occurred during the first infusion, and 18 of 19 patients recovered and were able to continue with the subsequent infusion. (Figure 2)

Seven serious adverse events (SAEs) were reported in Part 1 (all unrelated to daratumumab), and 8 SAEs were reported in Part 2, four of which were related to daratumumab (one patient each with pneumonia, neutropenia, diarrhea, and laryngeal edema).

Table 1. Most common adverse events (incidence in >10% of patients)

<table>
<thead>
<tr>
<th></th>
<th>Part 1 N = 13</th>
<th>Part 2 N = 32</th>
<th>Total N = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with AEs, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>62</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>62</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Constipation</td>
<td>54</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>62</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Bone pain</td>
<td>31</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>46</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>19</td>
<td>11</td>
</tr>
</tbody>
</table>

• The mean total number of full infusions per patient was 15.6 (standard deviation [SD]: 2.77) in the current infusion program and 10.5 (SD: 4.06) in the accelerated infusion program.
• The median duration of the first, second, and subsequent infusions in the current program was 8.0, 6.5, and 5.5 hours, respectively.
• In the accelerated program, these infusion times were reduced to 5.4, 4.3, and 3.6 hours, respectively.

Figure 2. Infusion-related reactions

The key conclusions are:

- Data from Part 1 are mature and show impressive CR rates, while the depth of response in Part 2 is expected to further improve upon longer follow-up.
- The accelerated infusion program was tolerable but associated with higher incidences of grade 1/2 adverse events; therefore, accelerated infusion will require further investigation.
- Daratumumab in combination with lenalidomide and dexamethasone demonstrated a favourable safety profile with manageable toxicities in relapsed and RR MM patients.
- Phase III clinical development of daratumumab in combination with lenalidomide and dexamethasone in RR and frontline patients is ongoing.

Background

Multiple myeloma (MM) remains an incurable disease due to complex molecular abnormalities, lower sensitivity to chemotherapy of MM cells in the bone marrow microenvironment, and the emergence of drug resistance.1 Daratumumab is a human monoclonal antibody directed against CD38 that has shown efficacy in treating patients with relapsed or refractory MM as a single agent and in combination with other agents including lenalidomide and dexamethasone.

Study design

• This is an open-label, multicentre, phase Ib trial, evaluating the safety and tolerability of daratumumab in combination with other MM backbone regimens:
  - VD: bortezomib subcutaneous (sc) and dexamethasone (newly diagnosed patients, n = 6)
  - VTD: bortezomib (sc), thalidomide, and dexamethasone (newly diagnosed patients, n = 12)
  - VMP: bortezomib (sc), melphalan, and prednisone (newly diagnosed, transplant-ineligible patients, n = 12)
  - POM-D: pomalidomide and dexamethasone (relapsed/refractory patients with greater than two previous lines of therapy including two consecutive cycles of lenalidomide and bortezomib, n = 50 subjects maximum)

• Initially, six patients in each arm were treated with daratumumab 16 mg/kg and the approved label or standard of care of each backbone treatment.

• At the end of cycles 1, 2, and 3, an independent data safety monitoring board evaluated dose-limiting toxicities (DLT).

• If a DLT was observed in ≤1 of the initial six patients, the combination was considered safe and well tolerated, and a further six patients would be enrolled in the VMP, VTD, and POM-D cohorts.

VMP + DARA

POM-D + DARA
Key findings

- Safety data was reported for six patients on each of the VD, VMP, and VTD backbone regimens and for six patients on the POM-D backbone regimen. (Table 1)
- The most common grade 3/4 adverse events (AEs) reported were hematological toxicities, including neutropenia, anemia, and thrombocytopenia. (Table 1)
- Serious AEs (SAEs) were only reported in patients on the VD and POM-D backbone regimens.
  - The only SAEs considered possibly or probably related to daratumumab were positive indirect Coombs assay (VD arm) and infectious pneumonia (POM-D arm). (Table 1)
- Overall, 17 patients experience infusion-related reactions (IRRs) (all grade 1 plus three cases of grade 2).
- Efficacy data was reported for six patients on each treatment arm.

### Table 1. Safety data

<table>
<thead>
<tr>
<th></th>
<th>VD + DARA (n = 6)</th>
<th>VMP + DARA (n = 6)</th>
<th>VTD + DARA (n = 6)</th>
<th>POM-D + DARA (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAEs</td>
<td>• Pneumonia†,‡</td>
<td>• None</td>
<td>• None</td>
<td>• Infectious pneumonia§</td>
</tr>
<tr>
<td>Grade ≥3 AEs*</td>
<td>• Neutropenia†,‡,§</td>
<td>• Neutropenia (n = 2)†</td>
<td>• Neutropenia†,§</td>
<td>• Neutropenia (n = 5)</td>
</tr>
<tr>
<td></td>
<td>• Anemia‡,**</td>
<td>• Thrombocytopenia§</td>
<td>• Anemia‡,**</td>
<td>• Anemia (n = 2)</td>
</tr>
</tbody>
</table>

AEs = adverse events; DARA = daratumumab; POM-D = pomalidomide, dexamethasone; SAEs = serious adverse events; VD = bortezomib and dexamethasone; VMP = bortezomib, melphalan, and prednisone; VTD = bortezomib, thalidomide, and dexamethasone

*All grade 3 AEs except for grade 4 neutropenia in POM-D.
†Not related to daratumumab.
‡Same subject.
§Possibly or probably related to daratumumab.
**Reported pre-dose.

**Figure 1. Efficacy results**

*DARA = daratumumab; MR = minimal response; PD = progressive disease; POM-D = pomalidomide, dexamethasone; PR = partial response; sCR = stringent complete response; VD = bortezomib, dexamethasone; VGPR = very good partial response; VMP = bortezomib, melphalan, and prednisone; VTD = bortezomib, thalidomide, dexamethasone

*One VGPR confirmed; one VGPR repeat assessment pending.
• The overall response rate (ORR) was 100% in the newly diagnosed group:
  - VMP and VTD arms: VGPR, n = 1; PR, n = 5; and
  - VD arm: VGPR, n = 3; PR, n = 3. (Figure 1)
• In the relapsed group, the ORR was 50%:
  - POM-D arm: VGPR, n = 2; stringent CR, n = 1. (Figure 1)
• The median time to first response was less than 50 days in all treatment arms. (Figure 2)
• All newly diagnosed patients (VD, VMP, and VTD arms) had a 50% or greater reduction in paraprotein levels from baseline. (Figure 3)
• The total stem cell yield of the six patients who underwent transplantation (VD arm: n = 1; VTD arm: n = 5) ranged from 2.5 x 10⁶ cells/kg to 11.44 x 10⁶ cells/kg. (Table 2)

**Figure 2. Median time to first response**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Median Time to First Response (Range), Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD + DARA (n = 6)</td>
<td>0 (25)</td>
</tr>
<tr>
<td>VMP + DARA (n = 6)</td>
<td>0 (25)</td>
</tr>
<tr>
<td>VTD + DARA (n = 6)</td>
<td>0 (25)</td>
</tr>
<tr>
<td>POM-D + DARA (n = 3)</td>
<td>0 (25)</td>
</tr>
</tbody>
</table>

**Figure 3. Maximal change in paraprotein from baseline**

| Treatment Group | Maximal Change in Paraprotein from Baseline (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VD + DARA</td>
<td>-100</td>
</tr>
<tr>
<td>VTD + DARA</td>
<td>-75</td>
</tr>
<tr>
<td>VMP + DARA</td>
<td>-25</td>
</tr>
<tr>
<td>POM-D + DARA</td>
<td>-50</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- DARA = daratumumab
- POM-D = pomalidomide, dexamethasone
- VD = bortezomib, dexamethasone
- VMP = bortezomib, melphalan, prednisone
- VTD = bortezomib, thalidomide, dexamethasone

**Legend:**
- VD + DARA
- VTD + DARA
- VMP + DARA
- POM-D + DARA

**Note:**
- Relative change in paraprotein from baseline (°C)
- Patients
Table 2. Mobilization regimen and stem cell yield of transplant patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mobilization regimen</th>
<th>Days of collection</th>
<th>Total stem cell yield ($x$ $10^6$/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD</td>
<td>Cyclophosphamide</td>
<td>4</td>
<td>3.99</td>
</tr>
<tr>
<td>VTD</td>
<td>G-CSF and Plerixafor</td>
<td>2</td>
<td>6.67</td>
</tr>
<tr>
<td>VTD</td>
<td>G-CSF</td>
<td>2</td>
<td>7.76</td>
</tr>
<tr>
<td>VTD</td>
<td>Cyclophosphamide</td>
<td>3</td>
<td>5.14</td>
</tr>
<tr>
<td>VTD</td>
<td>Cyclophosphamide</td>
<td>1</td>
<td>11.44</td>
</tr>
<tr>
<td>VTD</td>
<td>G-CSF</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

G-CSF = granulocyte colony stimulating factor; VD = bortezomib dexamethasone; VTD = bortezomib, thalidomide, dexamethasone

Key conclusions

- Addition of daratumumab 16 mg/kg to various backbone regimens was well tolerated in all evaluable patients and did not result in significant additional toxicity.
- Daratumumab in combination with VD, VMP, VTD, or POM-D resulted in promising response rates.
- Daratumumab does not appear to have a negative impact on stem cell mobilization.
- Phase III studies of daratumumab in combination with VMP (transplant ineligible) and VTD (induction therapy) are planned or ongoing.


Direct in vitro comparison of daratumumab with surrogate analogs of anti-CD38 antibodies

Background
Daratumumab is a human monoclonal antibody directed against CD38, with direct and Fc-mediated killing activity. It induces killing of multiple myeloma (MM) cells through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and programmed cell death (PCD) upon secondary cross-linking. Several other anti-CD38 monoclonal antibodies are in development that have similar mechanism of action, however, direct comparison studies have not yet been performed.

Study design
- This study evaluated the in vitro efficacy of daratumumab compared with surrogates of other anti-CD38 monoclonal antibodies currently in development, including SAR650984 (SAR), MOR03087 (MOR), and Ab79 (TAK).
  - Efficacy was evaluated by binding, CD38 ectoenzyme activity, and the induction of ADCC, ADCP, CDC, and PCD.
  - Surrogate antibodies of SAR, MOR, and TAK were generated on the basis of protein sequence, as published in their corresponding patent families, and were attached to the backbone of daratumumab.

Key findings
- Using flow cytometry to analyze CD38 antibody binding on Daudi cells, all anti-CD38 antibodies showed similar half maximal effective concentrations (EC50 ~0.1 µg/mL) and maximal binding, except MOR which showed a lower apparent affinity (EC50 ~0.3 µg/mL).
- Enzyme-linked immunosorbent assay (ELISA) analysis demonstrated reduced binding of daratumumab but not SAR, MOR, or TAK when Q272 and S274 on CD38 were mutated (Q272R and S274F), indicating that daratumumab binds a unique epitope on CD38.

- SAR produced the largest inhibition of cyclic GDP-ribose (cGDPR) production, indicating a higher modulation of CD38 cyclase activity.

- Daratumumab demonstrated superior induction of CDC in Daudi cells as determined by flow cytometry. (Figure 1)
  - Daratumumab induced more than 80% lysis at concentrations above 1 µg/mL, whereas maximum lysis induced by TAK and MOR was 50% and 20%, respectively.

- All anti-CD38 antibodies were equally potent at inducing ADCC of Daudi cells in a 51Cr-release assay using human PBMC effector cells (40–60% lysis at 0.02 µg/mL).

- Induction and effective elimination by ADCP was analyzed in Daudi cells using mouse macrophages as effector cells.
  - Daratumumab and TAK demonstrated similar levels of ADCP induction and were approximately 2-fold more potent than MOR (TAK and daratumumab: EC50 ~0.01 µg/mL; MOR: EC50 = 0.04 µg/mL). (Figure 2)

- Evaluation of Annexin V/propidium iodide (AnnV/PI) staining and caspase-3 activation showed that only SAR induced AnnV/PI+ in Ramos cells (~40%) after 48 hour exposure without Fc crosslinking, but did not activate caspase-3. (Figure 3)
  - In the presence of Fc crosslinking antibodies, all anti-CD38 antibodies induced AnnV/PI+, caspase-3 mediated PCD.
Key conclusions

- All anti-CD38 antibodies demonstrated similar binding to cells and induced similar amounts of ADCC.
- Differences in the ability to inhibit CD38 enzymatic activity, to induce CDC and ADCP, and to directly induce PCD were observed between the four CD38 antibodies investigated. (Table 1)
- Most strikingly, daratumumab induced high levels of CDC at low concentrations compared to other anti-CD38 monoclonal antibodies which were less capable of inducing CDC.
- Accordingly, CDC is believed to be the most important mechanism driving the clinical efficacy of daratumumab, although other effector functions might also contribute to the clinical efficacy in MM.

Mey UJM, et al. ASH 2014:4779

Multicentre phase II trial of bendamustine, lenalidomide, and dexamethasone as second-line therapy for multiple myeloma

**Background**

Multiple myeloma (MM) remains an incurable disease with nearly all patients relapsing after first-line therapy. Lenalidomide and dexamethasone (Rd) is considered a standard second-line regimen; however, it results in only 32.3% of patients achieving a very good partial response (VGPR) or better in second-line MM treatment. The feasibility of combining Rd with the bifunctional alkylating agent bendamustine (B-Rd) has been demonstrated in a phase I trial and was therefore evaluated in second-line MM patients in this study.

**Study design**

- This was a phase II, multicentre study evaluating the complete response (CR)/VGPR rate after completion of induction therapy, based on standard IMWG criteria.
- Induction therapy included six 4-week cycles (or until progressive disease [PD] or unacceptable toxicity) of:
  - Bendamustine 75 mg/m² intravenous (iv) on days 1 and 2;
  - Lenalidomide 25 mg orally (po) on days 1–21; and
  - Dexamethasone 40 mg (patients ≤75 years) or 20 mg (patients >75 years) po on days 1, 8, 15, and 22.
- Pegfilgrastim 6 mg subcutaneous (sc) was given on day 3 in case of severe neutropenia.
- Maintenance therapy included 12 (4-week) cycles (or until PD or unacceptable toxicity) of:
  - Lenalidomide 25 mg po on days 1–21; and
  - Dexamethasone 40 mg (patients ≤75 years) or 20 mg (patients >75 years) po on days 1, 8, 15, and 22.
- The primary endpoint was to evaluate the combined CR/VGPR rate achieved after completion of the induction treatment phase.
- A Simon’s two-stage design was used to differentiate between 20% (considered uninteresting) vs. 40% (considered promising) of high quality responses.
- Secondary objectives included:
  - Objective response rates (stringent CR [sCR], CR, VGPR, partial response [PR], and minimal response [MR]);
  - Best response (sCR, CR, VGPR, PR, MR) during study duration (including maintenance phase);
  - Time to progression;
  - Overall survival at 18 months after the last evaluable patient has been enrolled; and
  - Safety and tolerability.
Main inclusion criteria were:
- Relapsed or refractory MM, having received no more than one prior therapy;
- Measurable disease defined by serum monoclonal protein level ≥1 g/dL, urine M-protein level ≥200 mg/24 hours, or involved free light-chain (FLC) level ≥10 mg/dL (provided serum FLC ratio is abnormal);
- No prior treatment with a bendamustine-containing regimen;
- Prior treatment with lenalidomide was allowed if the treatment was completed >12 months prior to study entry and response to prior lenalidomide treatment;
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2;
- Adequate hematological values defined as absolute neutrophil count ≥1.5 x 10⁹/L, platelets ≥100 x 10⁹/L, and hemoglobin >80 g/L (unless considered to be caused by the underlying hematologic malignancy); and
- Adequate renal function (calculated creatinine clearance >50 mL/min).

Key findings
- A total of 45 patients, out of the 50 enrolled in the study, were evaluable (median age: 67 years [range: 46–84]).
- At baseline, the evaluable patients’ characteristics included:
  - 21/45 patients had International Staging System (ISS) stage II/III;
  - 20/45 had undergone prior autologous stem cell transplant; and
  - 12/37 patients with cytogenetics data had known high-risk cytogenetic aberrations (with del17p13, t[4;14], or t[14;16]).
- Prior treatment with thalidomide and bortezomib was reported in 14/45 and 38/45 patients, respectively.
- Of the 41 patients who completed induction, 23 patients received 6 cycles of the B-Rd regimen as per protocol.
- Of the 30 patients who had completed study treatment, 5 patients received 18 cycles of treatment per protocol, while 25 patients went off protocol due to toxicities (n = 15), PD (n = 2), and other reasons, such as stem cell transplantation and withdrawal of informed consent (n = 8).
- Treatment with pegfilgrastim was required in 34 patients.
- Twenty-three of the 45 evaluable patients (51.1%) achieved a best response of VGPR or better within or after completion of the induction treatment phase. (Table 1)

<table>
<thead>
<tr>
<th>Best response</th>
<th>Patients, n (%)</th>
<th>(N = 45)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/sCR</td>
<td>3 (6.7)</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>20 (44.4)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>17 (37.8)</td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>3 (6.7)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>1 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Five patients were not evaluable for response according to protocol definition: 1 due to withdrawal of consent during cycle 1, 1 due to inadequate response evaluation, 1 due to death of unknown cause within cycle 1 (judged unrelated to study treatment by investigator), 2 received less than one complete treatment cycle due to toxicity.

Study design

**Induction treatment**
(Cycles 1–6, every 4 weeks, or until PD or unacceptable toxicity)
- **Bendamustine** 75 mg/m² iv, days 1 and 2
- **Lenalidomide** 25 mg po, days 1–21
- **Dexamethasone** 40/20* mg po, days 1, 8, 15, and 22
- **Pegfilgrastim** 6 mg sc, day 3 in case of severe neutropenia (as defined in section 13.5)

**Maintenance treatment**
(Cycles 7–18, every 4 weeks, or until PD or unacceptable toxicity)
- **Lenalidomide** 25 mg po, days 1–21
- **Dexamethasone** 40/20* mg po, days 1, 8, 15, and 22

*iv = intravenous; PD = progressive disease; po = orally; sc = subcutaneous

*Dexamethasone 40 mg for patients ≤75 years of age, dexamethasone 20 mg for patients >75 years of age.
• With a median follow-up of 7.5 months (range: 1.0 – 29.4 months), the median progression-free survival has not yet been reached. (Figure 1)
• PD during follow-up occurred in three patients who had achieved a VGPR or better during induction treatment and in six patients who had initially achieved less than a VGPR.
• Of the 50 patients evaluable for safety, neutropenia (104 events), thrombocytopenia (34 events), and hyperglycemia (16 events) were the most common grade 3/4 toxicities. (Table 2)
• Only one patient developed grade 4 febrile neutropenia.
• A single grade 4 thromboembolic event was observed. This event occurred in a patient who was non-compliant with mandatory anti-thrombotic prophylaxis.

Figure 1. Progression-free survival

Table 2. Toxicity

<table>
<thead>
<tr>
<th>Toxicity**</th>
<th>Number of events(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
</tr>
<tr>
<td>Hepatobiliary disorder</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>16</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Infections (other)</td>
<td>4</td>
</tr>
<tr>
<td>Skin/rash</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>Cerebral insult</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsia</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^{a}\)Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.  
\(^{b}\)Possible, probable, or definite relations to study treatment.  
\(^{c}\)Number of events observed in a total number of 222 cycles of B-Rd treatment.

Key conclusions

■ B-Rd is a safe and efficacious regimen for the second-line treatment of relapsed/refractory patients with MM whose first line of therapy included thalidomide or bortezomib.
■ High quality responses (≥ VGPR) can be achieved in a considerable proportion of patients.
■ This study suggests that the fraction of patients achieving VGPR or better after B-Rd treatment may be substantially higher than that which is attainable with Rd alone.

An Interview with Dr. Torben Plesner on the GEN503 Study

At the ASH 2014 Annual Meeting, New Evidence spoke with Dr. Torben Plesner, Hema-
tologist in the Department of Hematology at Vejle Hospital in Denmark and Professor at
the University of Southern Denmark, about the GEN503 study that examined the safety
and tolerability of daratumumab in combination with lenalidomide and dexamethasone
for the treatment of relapsed and relapsed/refractory multiple myeloma (MM).

New Evidence: Please describe the mechanism of action of daratumumab. What are the potential advantages of this molecule for the treatment of MM?

Dr. Plesner: The mechanism of action of daratumumab is very different from other MM therapies. It works with the body’s own immune system to kill cancer cells by activation of serum factors called complement (i.e., complement-dependent cytotoxicity), antibody-dependent cell-mediated phagocytosis and cytotoxicity, and it may also kill cancer cells directly by binding to their surface and inducing programmed cell death (“apoptosis”). As this molecule has multiple and different mechanisms of action, it has the potential to work in patients who are refractory to other MM therapies, and this is what we see in the clinic.

New Evidence: What might be the advantage of a combination including daratumumab, lenalidomide, and dexamethasone?

Dr. Plesner: There is clear evidence from pre-clinical data that the combination of daratumumab, lenalidomide, and dexamethasone works well together. In vitro, the combination of daratumumab and lenalidomide enhance the killing of MM cells and this synergism is thought to be a result of the immune-boosting effects of lenalidomide, and the multiple mechanisms of action of daratumumab. Patients with MM are in need of more effective therapies as few patients receiving treatment are cured, and despite treatment, patients still die from the disease. Many patients with MM who have received multiple lines of therapy have deficient host immune systems, therefore the addition of lenalidomide may produce a better platform for the activity of daratumumab. This provided the rationale to evaluate the combination of daratumumab, lenalidomide, and dexamethasone in a clinical trial.

New Evidence: Describe the objectives and methodology of the study.

Dr. Plesner: The objective of this study was to evaluate the safety and efficacy of the combination of daratumumab, lenalidomide, and dexamethasone in relapsed or relapsed and refractory patients with MM. This phase I/II, single-arm study was designed in two parts with a dose-escalation phase (Part one) and a cohort-expansion phase (Part two). We have currently enrolled 45 patients in this trial and have completed enrolment. In both parts of the study, lenalidomide was given on a 28-day cycle at a standard dose of 25 mg for 3 weeks with 1 week off. Simultaneously, dexamethasone was given on a weekly basis
at a dose of 40 mg for younger patients and 20 mg for patients older than 75 years. In Part one of the study, the dose of daratumumab was escalated from 2 mg/kg to 4, 8, and 16 mg/kg. As no toxic dose was reached in Part one, in Part two of the study daratumumab was given at a dose of 16 mg/kg. The dosing schedule of daratumumab in this study was weekly for 8 cycles, followed by every second week for 8 cycles, and then monthly for 2 years. Currently, daratumumab is administered until disease progression, rather than ending treatment at 2 years.

**New Evidence:** Please describe the infusion times used for daratumumab in the study.

**Dr. Plesner:** In this study, the initial median durations of the first infusion, second infusion, and subsequent infusions, as determined per protocol, were 8 hours, 6.5 hours, and 5.5 hours, respectively. However, on an accelerated infusion program we have had success reducing the median duration of the first, second, and subsequent infusions to 5.4 hours, 4.3 hours, and 3.6 hours, respectively. We are now aiming to reduce the first infusion time to 5 hours, however, we are seeing infusion-related reactions (IRRs), as seen with other monoclonal antibodies. We are currently looking at optimizing the pre-medications used to create a more stable situation that will allow for reduced infusion times.

**New Evidence:** How might shortening the infusion times benefit patients and the healthcare team?

**Dr. Plesner:** As daratumumab is very well tolerated, it can be given on an outpatient basis; in fact, it is currently given in some outpatient clinics. However, in clinics that do not have a back-up facility, it is critical that patients finish their infusions within the clinic’s working hours. Therefore, shorter infusion times will not only benefit the patient as it will reduce the number of hours they will spend receiving treatment, but it also benefits the healthcare team and allows them to treat more patients within a day.

**New Evidence:** What were the main safety signals reported with the addition of daratumumab to lenalidomide and dexamethasone? Were any dose-limiting toxicities observed?

**Dr. Plesner:** The side effects we see are primarily from lenalidomide and dexamethasone, and not daratumumab. No dose-limiting toxicities for daratumumab were observed; however, the dose of lenalidomide is reduced if patients develop neutropenia. I encourage my colleagues to give granulocyte colony-stimulating factor (G-CSF) support 2 to 3 times per week in the event of neutropenia in order for patients to receive the highest possible dose of lenalidomide. This is critical, as a suboptimal dose of lenalidomide may interfere with the full synergistic response typically observed with the combination of daratumumab and lenalidomide, and therefore may potentially result in a suboptimal clinical response.

**New Evidence:** Please describe the IRRs reported with daratumumab. Were they easily managed?

**Dr. Plesner:** The IRRs reported are mainly airway symptoms, including nasal congestion, hay fever-like symptoms, asthma-like symptoms, oppression, coughing, and a general feeling of being unwell. The majority of these symptoms were mild in severity (grade 1 or 2) and easily managed.

**New Evidence:** What patient-sparing strategies might you implement in practice to prevent and manage these IRRs?

**Dr. Plesner:** The strategy for managing IRRs is to pause the infusion, give additional steroids and antihistamines, and then resume the infusion after one hour of observation when the symptoms have abated. The infusion is resumed at a decreased rate that is slowly escalated. To try to reduce IRRs, intravenous methylprednisolone or oral dexamethasone, antihistamines, and paracetamol are given prior to the start of treatment. The problem is not a major clinical issue as we are used to handling IRRs with other antibodies used in the clinic and it is largely confined to the first one or two infusions. After that we see very little or no IRRs.
**New Evidence**: Can you comment on the efficacy of daratumumab seen in this study? Were any complete responses (CRs) observed?

**Dr. Plesner**: In the dose escalation phase of the trial, the overall response rate (ORR) was 100% including 31% CR and 46% very good partial response (VGPR). Interestingly, in Part two of the study when the highest dose of 16 mg/kg of daratumumab was given, the ORR was 87% and the CR and VGPR rates were 7% and 43%, respectively. This can be explained by the duration of treatment, which was much shorter in the Part two expansion cohort. We do expect the response rates to catch up with those observed in Part one of the study as the time on treatment increases.

**New Evidence**: How do these response rates compare to other regimens used in a similar patient group? What was the duration of the response?

**Dr. Plesner**: These response rates are very high. Generally, in a relapsed/refractory population, a response rate between 30% and 40% is considered good, and in this trial the ORR was much higher. The duration of response is also important because in many relapsed situations, other agents can induce a remission for a median of 4 months, but with this treatment we have patients doing well after 2 years. We do not yet have median progression-free survival data, but my expectation is that the median will be much higher than 4 months.

**New Evidence**: How was the response to treatment measured? What was the impact of daratumumab on M protein levels?

**Dr. Plesner**: We measure the response to treatment using the IMWG criteria, which essentially looks at the drop of M protein levels in the blood, urine, and, more recently, by the free light chain assay. Interestingly, similar to what is observed with other antibody therapies, treatment with daratumumab results in the presence of an IgG kappa protein that is detected in the serum protein electrophoresis assay and cannot always easily be distinguished from the patient’s original serum M protein if this was also IgG kappa. For this reason, an assay was developed to displace the IgG attributed to daratumumab and thereby confirm the presence or absence of M-protein. This information is important to differentiate between VGPR and CR.

Although M protein levels are key to evaluating the response to treatment, it is not the only parameter used. We also examine the residual bone marrow plasma cells, which need to be reduced to below 5% in order to claim CR. To claim a more stringent CR, we have to show there are no dominant clones with kappa or lambda expression.

**New Evidence**: How long until a treatment effect was observed? How important is speed of response in managing MM disease symptoms?

**Dr. Plesner**: The response to treatment was very rapid in this study with a median time to PR of 1 month in Part two of the study and a median time to CR of approximately 5 months. In some cases, the speed of response can be critically important, such as when there is evidence of renal failure or medullary compression. Often in those situations we would give radiation and steroids, or bortezomib. Perhaps in the future daratumumab may have a place as combination therapy with dexamethasone and bortezomib in treating these patients.

**New Evidence**: Given the results of this study, what do you see as the next step in examining daratumumab for the treatment of MM?

**Dr. Plesner**: The next step would be to examine daratumumab in combination with lenalidomide and dexamethasone in a phase III trial in order to determine the exact contribution of daratumumab to the overall response. We have now initiated a phase III trial for relapsed patients with MM using a similar regimen as that used in the current trial, except all patients receive lenalidomide and dexamethasone, and then they are randomized to receive either daratumumab or no antibody.
It will also be important to move this treatment combination to the frontline setting. Since it is a well-tolerated therapy, it will be a very good fit for elderly or frail patients. It is also important to offer an effective alternate treatment that is associated with low toxicity in the first-line, as this may extend the period of time that patients will have good quality of life. We are planning to initiate a similar phase III trial in elderly patients with MM, offering lenalidomide and dexamethasone with or without daratumumab in the first-line.

It should be noted that other Phase III studies have started or are planned in 2015 to evaluate daratumumab in combination with three different bortezomib-based regimens, bortezomib plus dexamethasone in the relapsed setting; bortezomib, melphalan and prednisone in the frontline transplant ineligible population; and bortezomib, thalidomide, and dexamethasone in the frontline transplant setting. The safety of these regimens was reported at ASH by Dr. Philippe Moreau.

For younger patients with MM, it will be important to explore whether daratumumab in combination with induction therapy is safe to use before stem cell harvest. Presently, there is no reason to believe that daratumumab in combination with other agents (except prolonged exposure to lenalidomide) would negatively impact the harvesting of stem cells. Early evidence from the study led by Dr. Moreau suggests that daratumumab is safe to use before stem cell harvest.

**New Evidence:** What treatment combination do you see as the most promising for the treatment of MM?

**Dr. Plesner:** I think the combination of daratumumab, lenalidomide, and dexamethasone will be the most promising. As noted, we are also currently testing daratumumab in combination with several bortezomib regimens and results are also encouraging. However, I think the ability of lenalidomide to restore part of the immune system and to enable better efficacy of daratumumab is an important feature of this regimen.

**New Evidence:** In which patients would you consider using daratumumab if it were available?

**Dr. Plesner:** Based on the information I have today, I would use daratumumab in combination with lenalidomide and dexamethasone in elderly patients with MM in the frontline setting as well as in the relapsed setting. Even for frail elderly patients, this combination could be used successfully. Also, younger patients with MM who receive high-dose melphalan and autologous stem cell transplantation may benefit from having daratumumab added to their induction and consolidation therapy. Daratumumab could also potentially be used for prolonged maintenance of all ages of MM patients, and since it is so well tolerated, it could also be considered for treatment of patients with asymptomatic (smouldering) myeloma. A Phase II study in smouldering myeloma will start in 2015.
An Interview with Dr. Philippe Moreau on the MMY1001 Study

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

**Dr. Moreau:** The last decade has seen much progress in the treatment of MM with the advent of new agents such as carfilzomib and pomalidomide. Although survival has improved, the majority of patients relapse and eventually die as a result of their disease. New classes of agents are therefore needed to improve outcomes in these patients. One of the most promising new classes of agents used to treat MM is monoclonal antibodies. Examples of these agents in development include SLAMF7 antibodies, such as elotuzumab, and CD38 antibodies, such as daratumumab. The development of daratumumab is fairly advanced, with phase III trials underway. It is expected that daratumumab will provide a valuable new option for our patients with MM.

**New Evidence:** Describe the mechanism of action of daratumumab for the treatment of MM.

**Dr. Moreau:** Daratumumab is a monoclonal antibody that targets the cell surface glycoprotein CD38. CD38 is almost always expressed by the MM tumour cells and is therefore an excellent target. Daratumumab has multiple mechanisms of action, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, direct apoptosis, and modulation of cellular enzymatic activities associated with calcium mobilization and signaling.

We know that daratumumab is effective as a single agent in very advanced patients. The advantage of this agent is that it is not toxic; in fact, the safety profile of daratumumab has proven to be excellent. In addition, daratumumab shows synergistic activity when combined with other drugs.

**New Evidence:** What have previous studies using daratumumab as monotherapy and in combination with other backbones told us about its activity and safety for the treatment of MM?

**Dr. Moreau:** Phase I of the MMY1001 study examined the efficacy of daratumumab in advanced patients. The goal of this phase was to establish an optimal dose of daratumumab. Although the study is not yet published, results suggest the optimal dose to be 16 mg/kg. A second ongoing study (GEN503) was described at the ASH 2014 Annual Meeting. The study combined daratumumab plus lenalidomide and dexamethasone in the relapsed setting, as lenalidomide plus dexamethasone is considered to be the standard of care.

These ongoing studies have shown daratumumab has strong activity in MM, with a 35% response rate at the 16 mg/kg dose in very advanced patients in the MMY1001 study. This response is quite high and few agents have produced such strong outcomes in this setting, especially as single agents. In addition, the lenalidomide-dexamethasone-daratumumab combination achieved a very good partial response in more than 75% of patients, which is also very promising.
**New Evidence:** What was the rationale and design of the MMY1001 study?

**Dr. Moreau:** The rationale of the MMY1001 study was to combine daratumumab with other drugs, with the idea that daratumumab may act synergistically to increase response when combined with a number of backbone agents. Our study was a phase 1b study with four arms: bortezomib, dexamethosone (VD); bortezomib, thalidomide, dexamethasone (VTD); bortezomib, melphalan, prednisone (VMP); and pomalidomide, dexamethasone (POM-D), all in combination with daratumumab (16 mg/kg). All arms were given upfront with the exception of the POM-D arm, which was given in the relapsed/refractory setting and included at least two consecutive cycles of lenalidomide and bortezomib. Patients in the POM-D arm were heavily pre-treated and were previously exposed to other immunomodulatory drugs, bortezomib, and lenalidomide. The aim of the study was to examine the tolerability of daratumumab when added to a number of backbone agents.

**New Evidence:** What was the rationale for using a 16 mg/kg dose of daratumumab?

**Dr. Moreau:** The 16 mg/kg dose was defined in the phase I dose-escalation study, which found this dose to be optimal in terms of pharmacokinetics and activity, without undue toxicity. Results of phase I demonstrated that the CD38 target was well covered by the drug at the 16 mg/kg dose.

**New Evidence:** Please describe the infusion times used for daratumumab in the MMY1001 study.

**Dr. Moreau:** When daratumumab is used as a single agent, infusion times are currently 6 to 8 hours for the first dose and 3 to 4 hours for subsequent doses. However, when combined with other agents, daratumumab is usually given at a volume of 500 mL over a three-hour infusion. Ongoing trials are determining the optimal duration and volume of infusion. These trials will establish whether shortening the infusion time can be done safely and effectively for these patients. It will be interesting therefore to see whether infusion time of daratumumab can be reduced, as was seen previously with rituximab. We know that rituximab is moving towards subcutaneous administration; it is unclear whether daratumumab may be given subcutaneously in the future.

**New Evidence:** What were the main safety signals reported with the addition of daratumumab?

**Dr. Moreau:** The addition of daratumumab did not result in any additional toxicity in our study. There were 17 infusion-related reactions (IRRs) reported for all cycles evaluated. These IRRs were mild and easily managed. IRRs are common with all monoclonal antibodies and can be easily prevented and managed with the use of premedications such as low-dose steroids and paracetamol. Our study confirms the results of previous studies showing daratumumab is highly tolerable.

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

**Dr. Moreau:** It is too early to comment on the efficacy of our study given the short follow-up, small number of patients per arm, and the fact that there is a median of only four cycles of treatment thus far. Therefore, we need longer follow-up before evaluating the efficacy of these daratumumab combinations. We also need to demonstrate the efficacy of daratumumab in phase III trials before we can draw conclusions as to how daratumumab should be optimally used in clinical practice.

**New Evidence:** What treatment combination including daratumumab do you see as the most promising for the treatment of MM?

**Dr. Moreau:** The addition of daratumumab to lenalidomide or pomalidomide is very exciting. However, it is important to examine daratumumab with all the potential combinations we have so we do not limit our treatment options. We want to succeed with MM as we have done previously with non-Hodgkin lymphoma, where the addition of rituximab to CHOP created a new standard of care. We are hoping that by examining daratumumab with these various treatment regimens, we will find a new and effective standard treatment for MM.
New Therapies Provide Tolerable and Efficacious Options for CLL Patients Ineligible for Standard Treatment Regimens

For patients with chronic lymphocytic leukemia (CLL), the primary unmet need is a lack of a cure. Without a cure, treatment goals are to provide the maximum efficacy with the lowest toxicity, while maintaining or improving quality of life.1 When considering which treatment option is appropriate for patients with CLL, age and fitness play key roles in the decision-making process.

For first-line treatment, the standard of care for fit, young (<65 years old) patients remains fludarabine, cyclophosphamide, and rituximab (FCR). However, in North America, the median age of CLL patients at diagnosis is between 67 and 72 years.2 Elderly patients also typically present with other comorbidities making them unsuitable candidates for FCR. For patients who cannot tolerate FCR, there are several less aggressive treatment options available. One of these options is bendamustine plus rituximab (BR), an efficacious chemoimmunotherapy regimen that is less toxic and more tolerable than FCR; the results of the CLL10 trial showed that BR can also be considered as an alternative to FCR in fit elderly patients.3 BR has also proven to be effective in routine clinical practice. In a recently published prospective registry study from Germany, BR was the most frequently used first-line treatment for CLL by office-based hematologists, even more so than FCR, helping patients to achieve an objective response rate of 92%, which includes a 45% complete response rate.4

Even though first-line regimens are effective, CLL remains incurable, and patients will likely relapse or even become refractory to treatment.3 In the relapsed/refractory setting, there is no standard treatment regimen, as the criteria for selecting subsequent therapy include response to previous treatments, patient fitness and comorbidities, and genetic status. However, ongoing studies are examining a number of treatment options including BR, ibrutinib, and obinutuzumab (a new-generation anti-CD20 antibody) with or without chemotherapy.

FCR is ineffective in a subset of patients who present with CLL that harbor deletion 17p [del(17p)], a high-risk genetic marker associated with poor outcomes. The incidence of del(17p) in patients with CLL is approximately 5-8% at diagnosis, but its incidence significantly increases to up to 30% in relapsed and refractory patients.2,6 For patients with del(17p), alternate therapeutic regimens are being explored, including ongoing studies with ibrutinib, a Bruton’s tyrosine kinase inhibitor. To date, ibrutinib has been shown to be highly efficacious in patients with del(17p) and was recently approved in Canada for first-line treatment, and for subsequent lines of therapy, in this CLL patient subgroup.7

At the American Society of Hematology (ASH) 2014 Annual Meeting, clinical trials investigating these agents continued to make progress toward optimizing therapy for patients with CLL. The following 13 presentations from ASH 2014 reported interesting results of clinical trials in the CLL setting:

• The final analysis of the CLL10 study by the German CLL Study Group found that BR was inferior to FCR as first-line chemoimmunotherapy for physically fit patients with advanced CLL. However, BR may be considered as an alternative treatment in fit elderly patients.

• The interim analysis of the Russian NORMA trial showed outstanding clinical efficacy of BR in first-line treatment of CLL. Response rates were not inferior in patients with advanced age, disease stage, or high comorbidity burden.

• A 2014 survey of U.S.-based hematology-oncology physicians found BR remained the most common first-line prescribing preference for patients with a new diagnosis of CLL. For patients with del(17p), the prescribing preference was toward ibrutinib as first-line therapy.
Eichhorst B, et al. ASH 2014:19

Frontline chemoimmunotherapy with FCR shows superior efficacy in comparison to BR in previously untreated and physically fit patients with advanced CLL: final analysis of the CLL10 study from the German CLL Study Group

**Background**

Fludarabine, cyclophosphamide, and rituximab (FCR) is the standard frontline therapy for physically fit patients with chronic lymphocytic leukemia (CLL) that have a low comorbidity burden. The CLL10 study evaluated the efficacy and tolerability of bendamustine and rituximab (BR) compared with FCR as frontline therapy in physically fit patients with CLL without deletion 17p (del(17p)).

**Study design**

- The CLL10 study was a phase III, international, multicentre trial that evaluated the non-inferiority of BR compared with FCR for progression-free survival (PFS) in frontline therapy of physically fit patients with CLL without del(17p).

References:
3. Eichhorst B, Fink AM, Busch R, et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study). ASH Annual Meeting Abstracts 2014:19.
Patients enrolled in the study required a Cumulative Illness Rating Scale (CIRS) score ≤6 and creatinine clearance ≥70 mL/min.

Eligible patients were randomized to receive:

- **FCR**: fludarabine 25 mg/m² iv, days 1–3; cyclophosphamide 250 mg/m² days 1–3; rituximab 375 mg/m² iv day 0, cycle 1; rituximab 500 mg/m² iv day 1, cycles 2–6
- **BR**: bendamustine 90 mg/m² days 1–2; rituximab 375 mg/m² iv day 0, cycle 1; rituximab 500 mg/m² iv day 1, cycles 2–6

The primary endpoint was the non-inferiority of BR compared with FCR for PFS, defined as hazard ratio (HR) $\lambda_{BR/FCR} < 1.388$.

### Key findings

- A total of 688 patients were screened centrally for immunophenotype, genomic aberrations, immunoglobulin heavy chain variant (IGHV) sequencing, CIRS score, and glomerular filtration rate.
- Of these patients, 564 were randomized 1:1 to receive either FCR (n = 284) or BR (n = 280).
- The intent-to-treat (ITT) population, consisting of 282 patients in the FCR treatment group and 279 patients in the BR treatment group, was used for safety and efficacy evaluation.
- The median observation time was 37.1 months (range: 0–59.9 months).
- The median age of patients in the FCR and BR groups was 61.0 years and 62.1 years, respectively ($p = 0.131$).
- The percentage of patients over 65 years of age was 30.5% in the FCR group and 38.7% in the BR group ($p = 0.042$).
- There were no statistically significant differences between treatment groups in the following baseline patient characteristics: sex, median time since diagnosis, Eastern Cooperative Oncology Group performance status of zero, median CIRS score, and mean number of cycles administered.
- Baseline prognostic factors included Binet stage, IGHV mutation status, genomic aberrations (11q deletion, trisomy 12, and 13q deletion), thymidine kinase levels >10 U/L, and beta-2-microglobulin levels >3.5 mg/L:
  - IGHV mutation status was the only prognostic factor at baseline that was significantly imbalanced between treatment groups, with more patients with unmutated IGHV in the BR vs. FCR group (FCR, 55.3%; BR, 67.8%; $p = 0.003$).
- In the ITT population, complete response (CR), defined as CR plus CR with incomplete marrow recovery (CRi), was achieved by 39.7% of the FCR group compared with 30.8% of patients in the BR group ($p = 0.034$). (Table 1)
- At final restaging, minimal residual disease (MRD) negativity in the bone marrow was 26.6% in the FCR group and 11.1% in the BR group, and in the peripheral blood it was 48.6% in the FCR arm and 38.4% in the BR arm. (Table 2)
- MRD negativity in the peripheral blood was 19.7% in the FCR group and 9.0% in the BR group at 12 months after final restaging, decreasing to 18.0% and 8.5%, respectively, at 18 months after final restaging. (Table 2)
In the ITT population, the median PFS was 55.2 months and 41.7 months in the FCR and BR groups, respectively, and the HR was >1.388, indicating FCR was superior to BR in terms of PFS (HR = 1.626; \( p < 0.001 \)). (Figure 1)

- Median PFS was significantly longer in the FCR group compared with the BR group in patients with unmutated IGHV (42.7 vs. 33.6 months, respectively; \( p = 0.017 \)), but not in patients with mutated IGHV (not reached vs. 52.0 months, respectively; \( p = 0.153 \)). (Figure 2)

- In patients ≤65 years of age, median PFS was significantly longer in the FCR group compared with the BR group (53.6 vs. 38.5 months, respectively; \( p < 0.001 \)); there was no significant difference in median PFS for patients >65 years old (not reached vs. 48.5 months, respectively; \( p = 0.170 \)). (Figure 3)

- The PFS of patients in the FCR group was also superior to that of patients in the BR group in an analysis of the IGHV-matched population (n = 398): Median PFS was not reached in the FCR group compared with 43.1 months in the BR group (HR = 1.565; \( p = 0.005 \)).

- The overall survival at 36 months was not statistically different between the FCR group and the BR group (90.6% vs. 92.2%, respectively; \( p = 0.897 \)).

- A significantly higher proportion of patients in the FCR group compared with the BR group reported grade 3/4 neutropenia (84.2% vs. 59.0%, respectively; \( p < 0.001 \)) and thrombocytopenia (21.5% vs. 14.4%, respectively; \( p = 0.03 \)). (Table 3)
Figure 2. Progression-free survival by IGHV status

![Graph showing progression-free survival by IGHV status]

Unmutated IGHV: \( p = 0.017 \)
- FCR: 42.7 months
- BR: 33.6 months

Mutated IGHV: \( p = 0.153 \)
- FCR: NR
- BR: 52.0 months

BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab; IGHV = immunoglobulin heavy chain variable; NR = not reached; PFS = progression-free survival

Figure 3. Progression-free survival by age group

![Graph showing progression-free survival by age group]

Patients ≤65 years: \( p < 0.001 \)
- FCR: 53.6 months
- BR: 38.5 months

Patients >65 years: \( p = 0.170 \)
- FCR: NR
- BR: 48.5 months

BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab; NR = not reached; PFS = progression-free survival

- Infections were also reported at a significantly higher frequency in the FCR group compared with the BR group (39.1% vs. 26.8%, respectively; \( p < 0.001 \)). (Table 3)
- Of these infections, 22.6% and 17.3% were reported during therapy only in the FCR group and BR group, respectively (\( p = 0.1 \)), and 11.8% and 3.6% were reported during the first five months after therapy in the FCR group and BR group, respectively (\( p < 0.001 \)).
- The frequency of infections in patients over 65 years of age was also significantly higher in the FCR group compared with the BR group (47.7% vs. 20.6%, respectively; \( p < 0.001 \)).
Table 3. Adverse events CTC grade 3/4 (first cycle until end of study)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (%) N = 279</th>
<th>BR (%) N = 278</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>84.2</td>
<td>59.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.6</td>
<td>10.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Infection</td>
<td>39.1</td>
<td>26.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary neoplasm*</td>
<td>6.1</td>
<td>2.6</td>
<td>0.244</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>4.6</td>
<td>2.1</td>
<td>0.107</td>
</tr>
<tr>
<td>Infections</td>
<td>2.5</td>
<td>2.1</td>
<td>—</td>
</tr>
<tr>
<td>Secondary neoplasm</td>
<td>1.1</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AML/MDS: FCR, n = 6; BR, n = 1

BR = bendamustine, rituximab; CTC = Common Toxicity Criteria; FCR = fludarabine, cyclophosphamide, rituximab; sAML/MDS = secondary acute myeloid leukemia/myelodysplastic syndrome

Key conclusions

- The final analysis of the CLL10 trial showed that BR is inferior to FCR with regard to PFS and CR rate.
- BR is associated with lower rates of neutropenia and severe infections in elderly patients.
- FCR remains the standard therapy in fit patients with CLL. However, BR may be considered as an alternative treatment in fit, elderly patients.

Reference: 1. Eichhorst B, Fink AM, Busch R, et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study). ASH Annual Meeting Abstracts 2014:19.

Stadnik E, et al. ASH 2014:3332

First-line treatment with bendamustine and rituximab in chronic lymphocytic leukemia patients: interim results of the Russian NORMA trial

Background

As many patients with chronic lymphocytic leukemia (CLL) are elderly and have high comorbidity burden, they are ineligible for intensive chemotherapy regimens such as fludarabine, cyclophosphamide, and rituximab (FCR). As the CLL10 trial demonstrated, bendamustine in combination with rituximab (BR) is a good treatment alternative to FCR for slow-go patients with CLL, particularly those with advanced, chronic kidney disease.1

Study design

- This was a Russian prospective, multicentre, observational, non-interventional study of BR use in previously untreated CLL patients in routine clinical practice (NORMA), initiated in February 2012.
- There were no strict inclusion/exclusion criteria allowing for an unbiased analysis of efficacy and toxicity in real-world conditions.
- Rituximab and bendamustine were given in standard doses of 375/500 mg/m² and 90 mg/m², respectively.
- Bone marrow (BM) minimal residual disease (MRD) evaluation was performed after three cycles and at least two months after the last cycle.
- MRD was evaluated by flow cytometry according to the European Research Initiative on CLL (ERIC) recommendations.
- Remissions were confirmed by computed tomography (CT) as per the International Workshop on CLL (ERIC) recommendations.
- Data was entered to an electronic case report form (VIEDOC) by investigators and centrally analyzed.

Key findings

- By October 2014, 138 patients had been included by 32 participating centres.
- Of these patients, 75 have completed therapy, 23 have completed at least 3 cycles of therapy, and 63 are continuing treatment.
• The median duration of observation was 15 months.
• At baseline, the median age of patients was 59 years (range: 39–77 years), with 70 male patients and 41 female patients.
• The following patient characteristics were described at baseline (n):
  ◦ Binet stage A/B/C: 14/75/21;
  ◦ Eastern Cooperative Oncology Group performance status 0/1/2/3: 32/58/14/6;
  ◦ Cumulative Illness Rating Scale score <6/≥6: 86/21;
  ◦ CD38 level <30%/≥30%: 57/21;
  ◦ Immunoglobulin heavy chain variant (IGHV) mutated/unmutated: 40/76;
  ◦ Creatinine clearance <70 mL/min/≥70 mL/min: 43/62;
  ◦ Chronic kidney disease stage 0/I–II: 17/56;
  ◦ Time to treatment <2 years/≥2 years: 88/21;
  ◦ Enlarged abdominal lymph nodes: 56 (N = 107);
  ◦ Bulky lymph nodes: 15 (N = 107).
• Of the 112 patients with fluorescence in situ hybridization (FISH) data, 42% had del(13q), 34.8% had del(11q), 8% had del(17p), and 16% had trisomy 12.
• Two FISH abnormalities were detected in 22 patients, three abnormalities were detected in three patients, and four abnormalities were detected in one patient.
• NOTCH1 mutations were detected in six of 37 patients tested (16%) and IGHV stereotypy was found in 18% of analyzed cases. (Figure 1)
• Data on response after three cycles was available for 77 patients:
  ◦ Complete response (CR) in 26 patients;
  ◦ Partial response (PR) in 46 patients;
  ◦ Progressive disease (PD) in two patients;
  ◦ No response in three patients. (Figure 2)
• All refractory patients had del(17p) and/or unmutated IGHV.
• Data on response after completing six cycles was available for 58 patients:
  ◦ CR in 41 patients and PR in 11 patients (overall response rate of 89.7%);
  ◦ PD in four patients;
  ◦ No response in three patients. (Figure 2)
• There was no statistically significant difference in response rates among patients younger and older than 60, those with CIRS ≥6 and <6, those with early (A) and advanced (B and C) disease stage, and those with (glomerular filtration rate [GFR] <70 mL/min) and without (GFR ≥70 mL/min) meaningful renal dysfunction.

• MRD levels after three and six cycles are shown in Table 1 and MRD dynamics for 33 patients with known MRD at three and six cycles are shown in Figure 3.

◦ BM MRD levels after three cycles (measured by flow cytometry) correlated well with further response to therapy (p = 0.0001).

• There were four cases of grade 2/3 anemia, three cases of grade 2/3 thrombocytopenia, and 50 cases of grade 3/4 neutropenia.

• Other adverse events reported were 14 cases of infections requiring systemic antibacterial or antiviral treatment, four patients had hepatic toxicity, and nine patients had mild to moderate skin reactions.

Table 1. MRD levels after three and six cycles

<table>
<thead>
<tr>
<th>MRD levels</th>
<th>&lt;10^-4</th>
<th>≥10^-4 to &lt;10^-2</th>
<th>≥10^-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 3 cycles, n</td>
<td>7</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>After 6 cycles, n</td>
<td>16</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

MRD = minimal residual disease

Figure 3. MRD dynamics for 33 patients with known MRD at three and six cycles

Key conclusions

■ Preliminary results show outstanding clinical efficacy of BR in first-line treatment of CLL.

■ Response rates were not inferior in patients with advanced age, disease stage, or high comorbidity burden.

■ All refractory patients had known adverse prognostic factors such as del(17p) and/or unmutated IGHV genes.

■ Reported toxicity was low and patients with renal dysfunction showed good tolerability to BR.

■ MRD level <10^-2 as early as after three cycles of therapy was a robust predictor for MRD negativity after treatment completion.

First-line prescribing preferences of U.S. hematology-oncology physicians for patients with chronic lymphocytic leukemia: the impact of novel agents

Background
Within the past year, three new agents (ofatumumab plus chlorambucil, obinutuzumab plus chlorambucil, and ibrutinib) have received approval in the United States for the first-line treatment of chronic lymphocytic leukemia (CLL), creating additional therapy options for these patients. Prescribing preferences for patients with CLL may be influenced by multiple factors including patient characteristics, clinical trial data, ease of access, cost, physician familiarity, and practice setting (e.g., academic vs. community). The objective of this study was to assess the impact of specific patient features, such as age, comorbid conditions, and chromosomal abnormalities, on prescribing preferences.¹

Study design
• U.S.-based hematology-oncology physicians were surveyed using a validated, proprietary, live, case-based market research tool (Challenging Cases®) to assess prescribing preferences.
• Data were acquired using blinded audience response system technology.
  ◦ All sources of research support were blinded.
• All responses were obtained contemporaneously, prior to any display of respondent selections or data presentation.
• Research assessments took place at four live Challenging Cases® research events between March 8, 2014 and October 18, 2014.
  ◦ Patient preferences were assessed in a format analogous to a tumour conference.
  ◦ Relevant patient history, physical exam, lab, and cytogenetic data were provided.
  ◦ Up to 10 choices were offered per research query.
• Data from 359 total respondents were included.
  ◦ Not every respondent addressed every research query; therefore, the individual sizes of the response groups are shown for each query.
• Participants self-selected to attend; air and hotel expenses were paid, and no honoraria were provided.
• A core case scenario describing a newly diagnosed patient with lower-risk CLL and three variant scenarios were utilized to evoke physician prescribing preferences:
  ◦ Core Scenario (CS):
    – A 63-year-old male presents with recent fatigue and low-grade fevers;
    – He had 1 to 2 cm diffuse adenopathy and a palpable spleen tip 3 cm below the left costal margin;
    – His white blood cell count (WBC) was 36,000 with 79% mature lymphocytes, and an absolute neutrophil count (ANC) of 2800;
    – The patient’s hemoglobin level was 10.2 g/dL with no evidence of hemolysis;
    – The patient’s platelet count was 150,000;
    – He had a CD38 expression level of 12%, no FISH abnormalities, and no relevant comorbidities; ECOG performance status (PS) is 1.
  ◦ Variant Scenario 1 (VS1): Identical to CS except with deletion 17p [del(17p)] and a CD38 expression level of 42%.
  ◦ Variant Scenario 2 (VS2): Identical to CS, except with comorbidities of medication-controlled hypertension, type 2 diabetes, and mild chronic obstructive pulmonary disease.
  ◦ Variant Scenario 3 (VS3): Identical to VS2, except aged 73 years.
• At each research assessment, the scenarios were displayed and also read aloud by the moderator. Participants were then asked, “What would you recommend as first-line therapy for the patient described?” A list of possible therapy options, including no current therapy, was also read and participants then selected their prescribing preferences for that scenario.
Key findings

- Distribution of hematology-oncology physicians by geographic region:
  - West: 23%;
  - Southwest: 14%;
  - Central: 15%;
  - Southeast: 21%;
  - Northeast: 27%.

- Distribution of hematology-oncology physicians by practice setting (N = 357):
  - Academic faculty: 12%;
  - Hospital-based employee: 11%;
  - Community practitioner at a hospital-owned practice: 23%;
  - Community practitioner at a physician-owned practice: 54%.

- Hematology-oncology physicians’ assessment of the volume of new CLL patients seen per year (N = 357):
  - Zero to one: 5%;
  - Two to four: 27%;
  - Five to seven: 36%;
  - Eight to 10: 19%;
  - More than 10: 13%.

- A summary of the first-line prescribing preferences across all four scenarios is given in Table 1.

- In the CS, no changes in first-line prescribing preferences were observed over time.

- The preference for ibrutinib was most striking in the case of the previously untreated patient with del(17p).

- For patients with comorbid conditions, a strong prescribing preference for bendamustine with or without rituximab was seen, regardless of patient age.

- The prescribing preference for the newly approved combination of chlorambucil plus obinutuzumab remained limited, even for the older patient with comorbid conditions.

- Throughout 2014, prescribing preference for ibrutinib as a first-line therapy for the patient presenting with a del(17p) chromosomal abnormality has been increasing. (Figure 1)

- The prescribing preferences for the various ibrutinib-based treatment options are shown in Table 2 (i.e., ibrutinib single-agent, ibrutinib plus an anti-CD20 antibody, and ibrutinib plus bendamustine and rituximab [BR]).

- The first-line prescribing preferences for VS1 by volume of new CLL patients per year are shown in Figure 2.

| Table 1. Summary of prescribing preferences across all four scenarios |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Patient age, years          | 63              | 63              | 63              | 73              |
| FISH abnormalities           | None            | 17p deletion    | None            | None            |
| CD38 expression level, %     | 12              | 42              | 12              | 12              |
| Comorbidities                | None            | None            | Present         | Present         |
| Prescribing preference, %    | CS N = 354      | VS1 N = 357     | VS2 N = 354     | VS3 N = 359     |
| Bendamustine ± rituximab     | 58              | 43              | 67              | 66              |
| Bendamustine + obinutuzumab  | 1               | 4               | 1               | 2               |
| Chlorambucil + obinutuzumab  | 2               | 2               | 5               | 12              |
| Chlorambucil + ofatumumab    | n/a             | 1               | 1               | 1               |
| Fludarabine, cyclophosphamide, rituximab | 21 | 23 | 7 | 2 |
| Ibrutinib ± additional agent(s) | 2 | 22 | 8 | 6 |
| Other                        | 2               | 2               | 1               | 0               |
| Observe                      | 14              | 3               | 10              | 11              |

CD38 = cluster of differentiation 38; CS = core scenario; FISH = fluorescence in situ hybridization; VS = variant scenario
### Table 2. Detailed first-line prescribing preferences by event in del(17p) patients (VS1)

<table>
<thead>
<tr>
<th>Prescribing preference, %</th>
<th>March 8, 2014 N = 95</th>
<th>April 26, 2014 N = 95</th>
<th>August 2, 2014 N = 78</th>
<th>October 18, 2014 N = 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine ± rituximab</td>
<td>53</td>
<td>53</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>Bendamustine + obinutuzumab</td>
<td>2</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Chlorambucil + obinutuzumab</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Chlorambucil + ofatumumab</td>
<td>n/a</td>
<td>n/a</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Fludarabine, cyclophosphamide, rituximab</td>
<td>25</td>
<td>19</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Ibrutinib ± additional agent(s)</td>
<td>11</td>
<td>14</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>Ibrutinib single agent</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Ibrutinib + anti-CD20 antibody</td>
<td>7</td>
<td>9</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Ibrutinib + bendamustine + rituximab</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>8</td>
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<tr>
<td>Other</td>
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<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Observe</td>
<td>3</td>
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<td>3</td>
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</tr>
</tbody>
</table>

*VS = variant scenario*
Key conclusions

- Across the 2014 interval studied, BR remained the most common first-line prescribing preference among U.S.-based hematology-oncology physicians for patients presenting with a new diagnosis of CLL, though there was some shift in specific patient scenarios with the approval of new treatment options for the first-line treatment of CLL.

- The presence of a del(17p) chromosomal abnormality appeared to be driving prescribing preferences toward the use of ibrutinib as a first-line therapy.

- For patients with comorbid conditions, the adoption of chlorambucil plus obinutuzumab was low (2% to 7% in the 63-year-old patient scenario and 8% to 17% in the 73-year-old patient scenario).

- In 2014, prescribing preferences for first-line therapy in the newly diagnosed CLL patient with del(17p) revealed that hematology-oncology physicians seeing the largest volume of CLL patients were the most likely to be early adopters of ibrutinib for this patient population.

Value of minimal residual disease-negative status at response evaluation in CLL: combined analysis of two phase III studies of the German CLL Study Group

Background
The detection of minimal residual disease (MRD) in patients with chronic lymphocytic leukemia (CLL), which was recommended for clinical trials in the 2008 guidelines by the International Workhop on CLL but not formally included in the definition of response, is gaining increasing importance.1 Both MRD negativity (with a threshold of <10^-4 leukemic cells per leukocytes) and the occurrence of a complete response (CR) predict long progression-free survival (PFS). In order to investigate the value of MRD with respect to clinical response, the MRD status was explored in patients with CR and partial remission (PR) in two phase III trials of the German CLL Study Group (GCLLSG).2 Furthermore, the relevance of residual splenomegaly, lymphadenopathy, or bone marrow involvement in MRD-negative patients with clinical PR was also evaluated.

Study design
• Patients (n = 1378) were randomized within the CLL8 trial (fludarabine, cyclophosphamide [FC] vs. fludarabine, cyclophosphamide, rituximab [FCR]) and the CLL10 trial (FCR vs. bendamustine, rituximab [BR]).
• Non-target population (n = 823):
  - Patients without MRD from peripheral blood (PB) at end of treatment (EOT) (n = 733);
  - Non-responders at EOT (n = 18);
  - Unconfirmed CRs at EOT (n = 46);
  - PR patients with insufficiently evaluated response (missing lymph node, spleen measurement, or lymphocyte count) at EOT (n = 26).
• The target population was patients with definitive CR or CR with incomplete marrow recovery CR(i), or PR and MRD measurement from PB at EOT (n = 555):
  - MRD-negative (−) CR group (n = 186);
  - MRD-positive (+) CR group (n = 39);
  - MRD− PR group (n = 161);
  - MRD+ PR group (n = 169).
• The aims of the study were:
  - To evaluate the relevance of MRD testing from PB in correlation to clinical response;
  - To evaluate the clinical relevance of residual splenomegaly, lymph node enlargement, and bone marrow involvement at response evaluation in MRD− PR patients;
  - To confirm that splenomegaly has no impact on PFS in patients with MRD− PR using different cut-offs for normal spleen size on radiological examination.

Key findings
• The following are baseline characteristics and prognostic factors of the target population:
  - Treatment, %:
    - FC: 21.8;
    - FCR: 53.0;
    - BR: 25.2;
  - Median age (range), years: 61 (33–81);
  - Male, %: 77.1;
  - Median Eastern Cooperative Oncology Group performance status (range): 0 (0–2);
  - Median Cumulative Illness Rating Scale score (range): 2 (0–7);
  - Binet stage A/B/C, %: 13.7/51.3/35.0;
  - Genetic aberrations by fluorescence in situ hybridization, %:
    - Del(17p): 1.5;
    - Del(11q): 25.0;
  - Immunoglobulin heavy chain variant (IGHV) unmutated, %: 62.1.
• Median observation time was 45.4 months.
• The median PFS grouped by MRD and clinical response at EOT was 68.9 months for the MRD− CR group, 44.4 months for the MRD+ CR group, 61.7 months for the MRD− PR group, and 28.1 months for the MRD+ PR group. (Figure 1)
  - Compared with the MRD− CR group, the PFS was significantly different for the MRD+ CR group (p = 0.004) and the MRD+ PR group (p <0.001).
In Supportive Care Oncology

- The median overall survival (OS) was not reached in the MRD– CR or PR groups, or in the MRD+ CR group. (Figure 2)
  - The median OS in the MRD+ PR group was 79.1 months, which was significantly different than the MRD– CR group ($p = 0.001$).
- Using multivariate analysis, the impact of MRD and clinical response on PFS was assessed:
  - MRD+ vs. –: HR = 3.487 (95% CI: 2.678–4.541; $p < 0.001$);
  - Clinical PR vs. CR: HR = 1.420 (95% CI: 1.075–1.876; $p = 0.014$);
  - Del(17p) vs. no del(17p): HR = 9.082 (95% CI: 4.325–19.072; $p < 0.001$);
  - IGHV unmutated vs. mutated: HR = 2.582 (95% CI: 1.930–3.455; $p < 0.001$).
- In the MRD– PR group, 25 patients had only lymphadenopathy, 18 had only bone marrow involvement, 78 had only splenomegaly, and 40 had more than one involvement.
- Median PFS, with $p$ values compared with the MRD– CR group, were assessed in the following MRD– PR subgroups (Figure 3):
  - With splenomegaly: 72.0 months ($p = 0.331$);
  - With lymphadenopathy: 38.7 months ($p < 0.001$);
- With bone marrow involvement: 56.8 months ($p = 0.420$);
- With more than one involvement: 51.8 months ($p = 0.202$).
- The median OS was reached in the MRD– PR subgroup of patients that had bone marrow involvement (76.3 months), which was not significantly different from the median OS of the MRD– CR group.
- Median OS was not reached in the other three subgroups of the MRD– PR group and they were not significantly different from the median OS of the MRD– CR group.
- For the exploratory analysis of splenomegaly and its impact on PFS, there were 359 patients with exact spleen measurements and a definitive CR(i) or PR at EOT:
  - MRD– CR group ($n = 84$);
  - MRD+ CR group ($n = 14$);
  - MRD– PR group ($n = 134$);
  - MRD+ PR group ($n = 127$).
- For patients in the exploratory analysis, with the cut-off for splenomegaly >14 cm, median PFS was significantly different from the MRD– CR group in the MRD+ CR group (35.8 months; $p < 0.001$), the MRD+ PR group (28.8 months; $p < 0.001$), and the MRD– PR subgroup with more than one involvement (42.5 months; $p = 0.028$). (Figure 4)
**Figure 2.** Overall survival grouped by MRD and clinical response at EOT

CR = complete response; EOT = end of treatment; MRD = minimal residual disease; NR = not reached; OS = overall survival; PR = partial remission

<table>
<thead>
<tr>
<th>MRD– CRs</th>
<th>MRD+ CRs</th>
<th>MRD– PRs</th>
<th>MRD+ PRs</th>
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<tr>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>—</td>
<td>0.915</td>
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MRD– PRs vs. MRD+ CRs, p = 0.870

**Figure 3.** PFS grouped by MRD and clinical response (including MRD– PR subgroups) at EOT

BM = bone marrow; CR = complete response; EOT = end of treatment; MRD = minimal residual disease; PFS = progression-free survival; PR = partial remission

<table>
<thead>
<tr>
<th>MRD– CRs</th>
<th>MRD+ CRs</th>
<th>MRD– PRs: with splenomegaly</th>
<th>MRD– PRs: with lymphadenopathy</th>
<th>MRD– PRs: with BM involvement</th>
<th>MRD– PRs: with &gt;1 involvement</th>
<th>MRD+ CRs</th>
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<tr>
<td>68.9</td>
<td>—</td>
<td>72.0</td>
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<tr>
<th>Median PFS (months)</th>
<th>p value (compared to MRD– CRs)</th>
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<tr>
<td>—</td>
<td>0.331</td>
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<tr>
<td>0.420</td>
<td>0.202</td>
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<td>0.004</td>
<td>&lt;0.001</td>
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<td>0.004</td>
<td>&lt;0.001</td>
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</tbody>
</table>
Key conclusions

- MRD and clinical response were both strong predictors of PFS.
- MRD in combination with clinical response predicted PFS more accurately than clinical response alone.
- Single splenomegaly as the sole abnormality at EOT had no impact on PFS in MRD– PR patients.

References:

Bosch F, et al. ASH 2014:3345

Preliminary safety results from the GREEN study of obinutuzumab (GA101) alone or in combination with chemotherapy for previously untreated or relapsed/refractory CLL

Background

Obinutuzumab (GA101) has shown superior efficacy to chlorambucil monotherapy and to chlorambucil plus rituximab, and an acceptable safety profile in patients with chronic lymphocytic leukemia (CLL). However, increased frequency and severity of infusion-related reactions (IRRs) — defined as a treatment-related adverse event (AE) occurring during or within 24 hours of obinutuzumab infusion — have been observed in cycle 1 with obinutuzumab plus chlorambucil compared with chlorambucil plus rituximab. The goal of the GREEN study was to evaluate the safety and tolerability of obinutuzumab with or without chemotherapy.\(^1\)
**Study design**

- **GREEN** is an ongoing, phase IIIb, multicentre, open-label trial investigating the safety and efficacy of obinutuzumab with or without chemotherapy in untreated or relapsed/refractory CLL.
- Subjects enrolled were ≥18 years of age with documented CLL, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hematologic function.
- Treatment included:
  - Single-agent obinutuzumab (G-mono) for six cycles (n = 59);
  - Obinutuzumab plus fludarabine and cyclophosphamide (G-FC), six cycles for fit patients (Cumulative Illness Rating Scale [CIRS] ≤6 and creatinine clearance [CrCl] ≥70 mL/min) (n = 91);
  - Obinutuzumab plus chlorambucil (G-Clb), six cycles for unfit patients (CIRS >6 and/or CrCl <70 mL/min) (n = 37);
  - Obinutuzumab plus bendamustine (G-B), six cycles for fit/unfit patients (n = 326).
- Standard obinutuzumab (1,000 mg) infusions were administered on day 1/day 2 (split over two consecutive days), day 8, and day 15 of cycle 1, and on day 1 of cycles 2–6, with 28-day cycles.
- The regulatory approved cycle 1, day 1/day 2 regimen was 100 mg at 25 mg/hour plus 900 mg at 50 mg/hour on day 2.
- The GREEN cohort 1 investigated whether a lower obinutuzumab dose (25 mg) and slower infusion rate (12.5 mg/hour) on day 1 was able to reduce the incidence and/or severity of IRRs.
- The primary endpoints were safety and tolerability of obinutuzumab with or without chemotherapy.
- The secondary endpoints were efficacy of obinutuzumab with or without chemotherapy, as measured by minimal residual disease (three months after the last study dose), overall response rate, progression-free survival, time to response, event-free survival, best overall response, overall survival, time to new anti-leukemia therapy, and duration of response.
- An exploratory sub-study was performed to assess alternative administration approaches for the first infusion of obinutuzumab, and the first cohort is presented here.

**Key findings**

- This is an ongoing safety study that is still enrolling patients, and some patients are still on treatment.
- There were 513 treated subjects in the overall safety population:
  - Previously untreated: n = 303;

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**Study design**

- Patients with previously untreated or relapsed/refractory CLL (planned sample size: 800 patients)
- 6 cycles of obinutuzumab ± chemotherapy (dependent on patient fitness)
- Treated – overall safety population (N = 513)
- Relapsed/refractory patients with CLL
- Cohort 1: lower C1D1 dose and infusion rate (N = 238)*
  - C1D1: 25 mg obinutuzumab (12.5 mg/hour)/ C1D2: 975 mg obinutuzumab
  - If unchanged IRRs†
    - Keep the lower C1D1 dose and rate regimen for all subsequent patients
  - If reduced IRRs†
    - Cohort 2: dexamethasone premedication:
      - 20 mg dexamethasone 12 hours before C1D1 + corticosteroids 1 hour before C1D1
      - C1D1: 100 mg obinutuzumab (25 mg/hour)/ C1D2: 900 mg obinutuzumab; Current N = 86
  - Cohort 3: IDMC can recommend another first infusion administration schedule

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*C = cycle; CLL = chronic lymphocytic leukemia; D = day; IDMC = independent data monitoring committee; IRR = infusion-related reaction

*Cohort 1 was assessed by IDMC after 150 patients had completed cycle 1 of study treatment.
†Threshold changes of IRRs discussed by IDMC based on clinical evidence with standard regimen available to date and according to observed treatment discontinuations and grade 3/4 adverse events.
• The median treatment exposure was 12.1 weeks (range: 0.1–24.1 weeks).
• Baseline characteristics of the overall safety population:
  - Median age was 68.0 years (range: 34.0–90.0 years) with 60.8% and 25.7% aged ≥65 years and ≥75 years, respectively;
  - Most subjects were male (64.1%) with Binet stage B (48.3%) or C (35.5%) disease, with bulky disease ≥5 cm (60.2%);
  - There were 269 fit vs. 244 unfit subjects.
• AEs reported in the overall safety population, n (%):
  - Any treatment-related AE: 460 (89.7);
  - Serious AE: 176 (34.3);
  - Grade ≥3 AE: 294 (57.3);
  - Grade ≥3 IRR: 87 (17.0);
  - AEs leading to obinutuzumab discontinuation: 44 (8.6);
  - Deaths: 7 (1.4);
  - Tumour lysis syndrome (TLS; including one uncoded case at time of analysis): 31 (6.0).
• The most frequently reported (≥5%) grade ≥3 AEs were:
  - G-mono: 26 (44.1%) patients overall, six (10.2%) neutropenia, three (5.1%) TLS, and three (5.1%) hypotension;
  - G-FC: 59 (64.8%) patients overall, 35 (38.5%) neutropenia, 14 (15.4%) thrombocytopenia, nine (9.9%) anemia, six (6.6%) febrile neutropenia, six (6.6%) lymphopenia, and five (5.5%) leukopenia;
  - G-B: 196 (60.1%) patients overall, 89 (27.3%) neutropenia, 35 (10.7%) thrombocytopenia, 23 (7.1%) TLS, 21 (6.4%) anemia, 19 (5.8%) febrile neutropenia, 19 (5.8%) leukopenia, and 19 (5.8%) lymphopenia;
  - G-Clb: 13 (35.1%) patients overall, four (10.8%) neutropenia, three (8.1%) anemia, dyspnea, and hypotension, and two (5.4%) for anemia, dyspnea, and hypotension.
• Overall, 26 (5.1%) patients experienced grade ≥3 infections or infestations: five (5.5%) G-FC, 18 (5.5%) G-B, and three (8.1%) G-Clb.
• TLS was experienced by 23 (7.1%) patients in the G-B group compared with three (5.1%) in the G-mono group, three (3.3%) in the G-FC group, and two (5.4%) in the G-Clb group.
• One death due to obinutuzumab-related TLS (cycle 1, day 13, TLS, and febrile neutropenia) occurred in an 80-year-old, a previously untreated patient with chronic renal failure (creatinine clearance: 44.28 mL/min), receiving G-B.
• Analyses are ongoing to assess the risk of TLS with different chemotherapy regimens.
• Cohort 1 was made up of 238 previously untreated patients.
  - The median age of cohort 1 was 66.0 years (34.0–84.0 years); the majority of patients were male (63.0%) with Binet stage B (49.2%) or C (32.8%) CLL, and 138 were fit vs. 100 unfit.
  - The median observation time was 4.4 months (range: 0.5–9.4 months) and the median exposure time was 14.2 weeks (range: 0.1–24.1 weeks), which were representative of the overall safety population (3.91 months [range: 0–9.4 months] and 12.1 weeks [range: 0.1–24.1 weeks], respectively).
  - Most patients in cohort 1 received G-B (63.0%) or G-FC (25.6%).
  - IRRs were reported in 132 (55.5%) patients and were predominantly grade 1 or 2.
  - In the overall population, serious IRRs and grade ≥3 IRRs were reported in 10.1% and 16.4% of patients, respectively. (Table 1)

### Table 1. Overview of obinutuzumab-related IRRs and withdrawals during cycle 1*

<table>
<thead>
<tr>
<th>n (%)</th>
<th>GREEN cohort 1</th>
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<tr>
<td></td>
<td>G-B (n = 150)</td>
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<tr>
<td>IRR</td>
<td>132 (55.5)</td>
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<tr>
<td>Serious IRR†</td>
<td>24 (10.1)</td>
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<tr>
<td>Grade ≥3 IRR †</td>
<td>39 (16.4)</td>
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<td>IRRs leading to obinutuzumab discontinuation</td>
<td>4 (1.7)</td>
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<tr>
<td>Withdrawal in cycle 1</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>Patient deaths in cycle 1§</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>

*11 (13.9%) patients discontinued obinutuzumab treatment in cohort 1 overall.
†IRR: a treatment-related adverse event occurring during or within 24 hours of obinutuzumab infusion.
§Not due to IRR.

G-B = obinutuzumab, bendamustine; G-Clb = obinutuzumab, chlorambucil; G-FC = obinutuzumab, fludarabine, cyclophosphamide; G mono = single-agent obinutuzumab; IRR = infusion-related reaction.
In cohort 1, 31 (13.0%) patients discontinued obinutuzumab treatment:
- Twenty-two (9.2%) patients discontinued due to intolerability, of which four (1.7%) were due to IRRs (three in the G-mono group and one in the G-FC group);
- Two (0.8%) patients died during the treatment period, three (1.3%) patients discontinued treatment due to administrative/other reasons, one (0.4%) patient withdrew due to disease progression, two (0.8%) patients were withdrawn based on investigator decision, and one (0.4%) patient withdrew consent;
- Thirteen patients withdrew from treatment during cycle 1.
- Based on a medical review (cutoff date: November 14, 2014) other AEs leading to obinutuzumab discontinuations were neutropenia (n = 6), hepatic events (n = 4), and metabolic events (n = 4; TLS and cytokine release).
- The currently observed IRR profile from this preliminary safety analysis of obinutuzumab in cohort 1 was in line with that seen for obinutuzumab in similar patient populations.
- IRRs were most frequent on cycle 1, day 1, with a peak of 12.6% of patients with any grade IRR at 1–2 hours: (Figure 1)
- Grade ≥3 IRRs were less frequent on day 2 compared with day 1, and most common at >5 hours.
- IRRs appeared to occur slightly later in treatment in GREEN vs. historical comparisons.
- The most frequent signs and symptoms of IRRs in the GREEN cohort 1 included chills (17.2%), pyrexia (16.0%), TLS (7.6%), nausea (8.4%), and vomiting (5.9%).
- Grade ≥3 IRRs experienced by ≥1% of patients were TLS (6.7%), hypotension (2.5%), hypertension (2.1%), and thrombocytopenia (1.7%).
- These results were in line with the findings from the CLL11, GALTON, and GAGE studies;
- The main exceptions were a higher frequency of TLS in GREEN (6.7% vs. 0%, 2.4%, and 1.0% in the CLL11, GALTON, and GAGE studies, respectively) and a higher incidence of hypotension and dyspnea in CLL11 (5.0% each vs. 2.5% and 0.4% in GREEN, respectively).
- The most frequent serious IRRs (≥1%) in GREEN were TLS (3.4%) and pyrexia (1.3%).

**Figure 1. Occurrence of IRRs during the first dose of obinutuzumab**

Values at the limit of time range are included within the lower range (e.g., 1–2 h means >1 h to ≤2 h). Only the first IRR per category (all grades, grade 3/4) per patient is included.
Key conclusions

- Preliminary safety data from the GREEN study were in line with the known safety profile of obinutuzumab, and no new safety signals were reported.

- These data suggest that the use of a lower initial dose and slower infusion rate on cycle 1, day 1, leads to more manageable IRRs and a reduction in subjects with grade ≥3 IRRs compared with previous studies.
  - As expected, the frequency and severity of IRRs decreased following cycle 1.
  - Although there appeared to be fewer grade ≥3 IRRs, as the number of discontinuations during cycle 1 was comparable with previous obinutuzumab studies, further improvement in IRR rates will be examined in cohort 2 by optimizing treatment administration and assessing dexamethasone premedication (12 hours prior to the first infusion).

- Analyses are ongoing to assess the risk of TLS with different chemotherapy regimens.

- Further safety data from the study will be presented at a later timepoint.


Noninferior pharmacokinetics with comparable safety and response rates for subcutaneous, compared with intravenous, rituximab in combination with FC in patients with untreated CLL: part 2 of the phase Ib SAWYER study

Background

SAWYER is a two-part, phase Ib study investigating subcutaneous (sc) rituximab compared with intravenous (iv) rituximab, both in combination with fludarabine and cyclophosphamide (FC), in patients with previously untreated chronic lymphocytic leukemia (CLL). Data from part 1 of the SAWYER study was presented previously and predicted that fixed-dose rituximab sc 1,600 mg would achieve noninferior serum trough concentrations (C_{trough}) compared with four-weekly rituximab iv 500 mg/m², the standard dose and dosing interval for patients with CLL. The aim of part 2 of the study was to formally confirm the pharmacokinetic (PK) noninferiority of fixed-dose rituximab sc 1,600 mg to standard rituximab iv 500 mg/m².

Study design

- SAWYER is a two-part, open-label, parallel-group, multicentre study.
- In part 2, 176 adult patients with untreated CD20+ B-cell CLL requiring treatment according to the International Workshop on Chronic Lymphocytic Leukemia criteria were randomized 1:1 to receive rituximab iv or sc in combination with FC, stratified by Binet stage and FC administration route (oral or iv).
  - In Cycle 1, all patients received rituximab iv 375 mg/m²; in cycles 2–6, patients received either rituximab iv 500 mg/m² or rituximab sc 1,600 mg fixed dose (the sc dose was determined in part 1 of the SAWYER trial).
  - Patients will be followed for up to 48 months after their last rituximab administration.
- The primary endpoint was to establish noninferiority (lower boundary for the 90% CI for the geometric mean ratio [GMR] C_{trough,sc}/C_{trough,iv} being above the pre-specified noninferiority margin of 0.8) in observed rituximab C_{trough} at cycle 5 (pre-dose cycle 6) between rituximab sc 1,600 mg and rituximab iv 500 mg/m².
- Secondary endpoints were to evaluate additional PK parameters (including area under the curve [AUC] at cycle 6), safety, overall response rate (ORR), and complete response rate (CRR; including complete response [CR] and CR with incomplete bone marrow recovery).
• Serial blood samples were collected during treatment and after treatment completion for the assessment of PK parameters ($C_{\text{trough}}$, AUC). $C_{\text{trough}}$ was analyzed at cycle 5, day 29 (cycle 6 pre-dose) for noninferiority, and AUC was analyzed at cycle 6.

• Tumour response was assessed by the investigator based on peripheral blood count, physical examination, computed tomography scan, B-symptoms, and bone marrow assessment (if applicable).

• Safety assessments included monitoring of adverse events (AEs), laboratory assessments (hematology, biochemistry, and immunogenicity), vital signs, and electrocardiography.

• Statistically, a sample size of 170 (85 patients per arm) was determined for the primary endpoint based on 80% power, with a one-sided alpha of 0.05 and a 20% drop-out rate:
  - $C_{\text{trough}}$ analysis was based on logarithmic values of observed $C_{\text{trough}}$ adjusted for tumour load; a standard non-inferiority margin of 0.8 was used for the GMR of $C_{\text{trough}}$ (sc/iv).

• Efficacy endpoint analyses were exploratory with no formal statistical testing.

Key findings

• A total of 176 patients were randomized (iv arm, n = 88; sc arm, n = 88) and 145 patients completed treatment (iv, n = 72; sc, n = 73).
  - At enrollment, 68% of patients received iv FC.

• Patient baseline characteristics were well balanced between treatment groups, with the exception of more male patients (71% vs. 60%) in the rituximab sc group.

• The median age was 59 years (range: 25–74 years) in the rituximab sc group compared with 60 years (range: 28–78 years) in the rituximab iv group.

• PK data for the $C_{\text{trough}}$ noninferiority analysis at cycle 5 were available for 69 patients in the iv arm and 65 patients in the sc arm.

• The adjusted GMR $C_{\text{trough,sc}}$:$C_{\text{trough,iv}}$ was 1.53 at cycle 5 (pre-dose cycle 6); the lower limit of the 90% confidence interval (CI) was 1.27, which was above the pre-specified noninferiority margin. (Figure 1)

  - Geometric mean $C_{\text{trough}}$ Values were 97.5 µg/mL and 61.5 µg/mL for rituximab sc and rituximab iv, respectively.

Figure 1. Geometric mean ratio ($C_{\text{trough,sc}}$:$C_{\text{trough,iv}}$) for rituximab by treatment cycle in the PK population
• The adjusted cycle 6 GMR of AUCsc:AUCiv was 1.10 (90% CI: 0.98–1.24).
  - The geometric mean AUC was 4,089 µg•day/mL for rituximab sc and 3,630 µg•day/mL for rituximab iv.
• Subgroup analyses explored PK parameters:
  - For C\textsubscript{trough} at cycle 5 and AUC at cycle 6, the GMR showed no monotonic change as the body surface area (BSA) increased, confirming that patients with a high BSA were not underexposed;
  - There was no effect of sex on exposure determined by C\textsubscript{trough} at cycle 5 or AUC at cycle 6.
• Investigator-assessed ORR after three months’ follow-up (intent-to-treat population) was 85% (75/88; 95% CI: 76–92%) and 81% (71/88; 95% CI: 71–88%), respectively, in the sc and iv arms.
  - CRRs were 26% (23/88; 95% CI: 17–37%) and 33% (29/88; 95% CI: 23–44%), respectively; any CR not confirmed by both clinical and bone marrow assessment was considered a partial response.
• The overall safety profile for rituximab sc was similar to rituximab iv, with no unexpected AEs. (Table 1)
  - The overall incidence of AEs across all treatment cycles was 96% in the sc arm and 91% in the iv arm.
  - Rates of grade ≥3 AEs were 69% and 71%, respectively, and rates of serious AEs were 29% and 33%, respectively.
• Of the individual grade ≥3 AEs reported, only neutropenia (56% sc vs. 52% iv) and leukopenia (14% sc vs. 12% iv) occurred in >10% of patients.
  - Grade ≥3 infections occurred in 13% of sc patients and 10% of iv patients.
• The rate of administration-related reactions (ARRs; AEs occurring during/within 24 hours of rituximab administration and considered rituximab-related by the study investigator) was similar between arms (44% sc vs. 45% iv), and most were grade 1/2. (Table 2)
  - During cycle 1, when all patients received iv rituximab, 36% of patients in the iv arm and 26% of patients in the sc arm experienced an ARR.
  - During cycles 2–6, the incidence of ARRs was 19% (16/84 patients) in the iv arm and 26% (22/85 patients) in the sc arm.
• The most common ARRs (all grades) occurring in ≥5% of patients in either treatment group were injection-site erythema (sc arm only), nausea, pyrexia, and chills.

<table>
<thead>
<tr>
<th>Table 1. Overview of safety (safety population)</th>
<th>Rituximab 1600 mg sc + FC (n = 85)</th>
<th>Rituximab 500 mg/m² iv + FC (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, n (%)</td>
<td>82 (96)</td>
<td>81 (91)</td>
</tr>
<tr>
<td>Leading to treatment withdrawal</td>
<td>9 (11)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Leading to dose modification/interruption</td>
<td>21 (25)</td>
<td>26 (29)</td>
</tr>
<tr>
<td>Any SAE, n (%)</td>
<td>25 (29)</td>
<td>29 (33)</td>
</tr>
<tr>
<td>SAE leading to death</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>SAE leading to treatment withdrawal</td>
<td>3 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>SAE leading to dose modification/interruption</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Severe AEs (grade 3/4)</td>
<td>59 (69)</td>
<td>63 (71)</td>
</tr>
</tbody>
</table>

AE = adverse event; FC = fludarabine, cyclophosphamide; iv = intravenous; SAE = serious adverse event; sc = subcutaneous

<table>
<thead>
<tr>
<th>Table 2. Summary of administration-related reactions (safety population)</th>
<th>Rituximab 1600 mg sc (n = 85)</th>
<th>Rituximab 500 mg/m² iv (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ARR, n (%)</td>
<td>37 (44)</td>
<td>40 (45)</td>
</tr>
<tr>
<td>Grade 3/4 ARRs, n (%)</td>
<td>6 (7)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Most common ARRs (≥5% of patients in either group), n (%)</td>
<td>9 (11)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Chills</td>
<td>7 (8)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (2)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Injection-site erythema</td>
<td>3 (4)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (2)</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

ARR = administration-related reaction; iv = intravenous; sc = subcutaneous
Key conclusions

- Rituximab sc 1,600 mg achieved noninferior serum $C_{\text{trough}}$ compared with rituximab iv 500 mg/m² when given every four weeks.

- The AUC of rituximab after sc administration was also at least as high as after iv administration.

- For $C_{\text{trough}}$ at cycle 5 and AUC at cycle 6, the GMR showed no monotonic change as the BSA increased, confirming that patients with a high BSA were not underexposed.

- Comparable ORRs and CRRs were achieved with rituximab sc and rituximab iv in combination with FC, and these were within the expected range for a comparable CLL population treated with rituximab iv in combination with FC.

  - Together with previously reported efficacy data in lymphoma, SAWYER part 2 ORR and CRR suggest that switching to the sc route does not impair the anti-B-cell activity of rituximab.

- There were no unexpected AEs; the overall safety profile of rituximab sc 1,600 mg was similar to rituximab iv 500 mg/m².

  - The overall incidence of ARRs was similar following rituximab sc or iv administration and most were grade 1/2.

- Rituximab sc 1,600 mg provides a more convenient and less resource-intensive option for patients with CLL.


Updated efficacy and overall safety in the phase III RESONATE™ trial of ibrutinib versus ofatumumab in previously treated CLL/SLL

Background

The implications of various prognostic factors and new genetic markers associated with high risk in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are not yet fully understood. Ibrutinib, a first-in-class Bruton’s tyrosine kinase inhibitor, is a once-daily single agent approved by the U.S. Food and Drug Administration for CLL patients who have received at least one prior therapy and for CLL patients with deletion 17p [del(17p)]. At ASH 2014, updated efficacy results, relative to genetic features and prior treatment exposure, and adverse event (AE) data were presented for the phase III RESONATE™ (PCYC-1112) study of ibrutinib versus ofatumumab.1

Study design

- The RESONATE™ (PCYC-1112) trial was a randomized, two-arm, phase III trial comparing ibrutinib to ofatumumab treatment:

  - Ibrutinib (n = 195): 420 mg orally once daily until progressive disease (PD) or unacceptable toxicity;

  - Ofatumumab (n = 196): initial dose of 300 mg intravenously followed by 11 doses of 2,000 mg over 24 weeks.

- Inclusion criteria for patients in this study were:

  - Diagnosis of CLL/SLL;
  - At least one previous therapy;
  - Eastern Cooperative Oncology Group performance status 0–1;
  - Measurable lymph node disease (>1.5 cm) by computed tomography (CT) scan;

- The primary endpoints were progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and safety.

- PFS and response assessments were conducted according to the International Workshop on CLL criteria with the 2012 clarification for treatment-related lymphocytosis and are presented per investigator assessment.
Longer-term follow-up safety data focused on ibrutinib.
- Ofatumumab treatment (and the AE reporting period) was complete at publication of the interim analysis.
- Analysis of immunoglobulin heavy chain variant (IGHV) genes was performed by a central laboratory; complex karyotype was determined by the investigator.
- The entire coding regions of Notch1, SF3B1, MYD88, and TP53 were sequenced by next generation sequencing.

Key findings
- Baseline characteristics were similar for both groups (ibrutinib vs. ofatumumab):
  - Median age was 67 years, with 40% vs. 41% of patients ≥70 years old;
  - Median number of prior therapies (range) was 3 (1–12) vs. 2 (1–13);
  - Del(17p) was detected in 32% vs. 33% of patients and del(11q) in 33% vs. 31%;
  - Gene mutations at baseline: NOTCH1, 29% vs. 30%; SF3B1, 31% vs. 30%; TP53, 50% vs. 46%; and MYD88, 2% (both groups).
- Median follow-up was 16 months for ibrutinib vs. 12 months for ofatumumab.
- Ibrutinib treatment significantly lengthened PFS (median not reached vs. 8.1 months; HR = 0.106, 95% CI: 0.073–0.153, \( p < 0.001 \)). (Figure 1)
The 12-month PFS rate was significantly improved for ibrutinib vs. ofatumumab (84% vs. 18%, \( p < 0.001 \)).

OS was significantly improved for ibrutinib vs. ofatumumab at interim analysis (HR = 0.43, \( p = 0.005 \)), when 57 patients had crossed over following progressive disease (PD), which was confirmed by the independent review committee (IRC).

The 12-month OS rate was 90% for ibrutinib. A total of 168 out of 195 patients randomized to ibrutinib were alive at the time of analysis.

Best ORR was 90% for ibrutinib compared with 25% for ofatumumab (\( p < 0.0001 \)). (Figure 2)

Median time to initial response was 3 months for both ibrutinib (range, 2–17) and ofatumumab (range, 2–9) consistent with first CT assessment.

Median time to best response was 5 months (range, 2–17) for ibrutinib and 3 months (range, 2–9) for ofatumumab.

Median time to complete response (CR)/CR with incomplete bone marrow recovery (CRi) with ibrutinib was 11 months (range, 6–17). One patient receiving ofatumumab achieved CR at 8 months.

Most patients experienced a transient increase in blood lymphocyte counts that frequently resolved with continued ibrutinib treatment and patients achieved deeper responses.

The 12-month PFS rate and ORR were significantly improved with ibrutinib vs. ofatumumab regardless of baseline genet-ics, including del(17p), del(11q), and genetic mutations (e.g., SF3B1 and Notch1), complex karyotype, or number of prior therapies.

Notch1, complex karyotype, unmutated IGHV, del(17p), and del(11q) were associated with inferior PFS for patients treated with ofatumumab.

There was a significant difference in PFS with and without del(17p) for ofatumumab-treated (\( p = 0.039 \)) but not ibrutinib-treated (\( p = 0.396 \)) patients. (Figure 3)

Patients in the ibrutinib arm treated in second-line therapy experienced better outcomes (\( p = 0.046 \)) than those salvaged in later lines of therapy. (Figure 4)

ORR was 100% for ibrutinib-treated patients who had received one prior therapy vs. two (79%) or \( \geq \)three (78%) prior therapies (\( p = 0.002 \). (Table 1)

### Table 1. ORR in ibrutinib-treated patients by number of prior lines of therapy

<table>
<thead>
<tr>
<th>Number of prior lines of therapy</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100*</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>( \geq 3 )</td>
<td>78</td>
</tr>
</tbody>
</table>

ORR = overall response rate

*\( p = 0.002 \) for ibrutinib-treated patients who had received one prior therapy vs. two or \( \geq \)three prior therapies.

---

**Figure 2. Best overall response**

![Figure 2. Best overall response](image-url)

\( ORR = CR + CRi + nPR + PR-L + PR \)

*\( p < 0.0001 \) for ibrutinib vs. ofatumumab.

5 patients for ibrutinib and 17 for ofatumumab were nonevaluable for response but included in denominator (ITT population).

CR = complete response; CRi = complete response with incomplete marrow recovery; ITT = intent to treat; nPR = nodular partial response; ORR = overall response rate; PD = progressive disease; PR = partial response; PR-L = partial response with lymphocytosis; SD = stable disease.
There was no significant difference in ORR or PFS between ibrutinib-treated patients with and without lymphocytosis. (Figure 5)

In terms of AEs, the most frequently reported preferred terms were diarrhea, fatigue, cytopenia, constipation, and pneumonia over the 16-month follow-up.

Most AEs were grade 1. The most frequent grade 3/4 AEs for ibrutinib were neutropenia (18%), pneumonia (9%), thrombocytopenia (6%), anemia (6%), and hypertension (6%).

Over 16 months of follow-up, atrial fibrillation of any grade occurred in 13 (7%) ibrutinib-treated patients, which includes three additional patients reported since interim analysis.

- One patient discontinued due to atrial fibrillation.
- Of note, prior medical history of atrial fibrillation was reported more frequently for ibrutinib (5.6%) than ofatumumab (2.6%).

Bleeding AEs occurred in 48% of patients; the majority were grade 1 (40%), with grade 2 events in 6%, grade 3 in 2%, and grade 4 in 1%. The most frequently reported terms were petechiae, contusion, and increased tendency to bruise.

Tumour lysis syndrome (TLS) occurred in two patients randomized to ibrutinib and was not considered related to treatment by investigator. Both patients experienced TLS in the setting of disease progression on study days 534 and 242, 5 days and 11 days, respectively, after discontinuation of ibrutinib.

Dose reductions due to an AE and discontinuations due to AE/unacceptable toxicity occurred in 6% and 7% of ibrutinib-treated patients, respectively.
Figure 5. No significant difference in PFS with or without lymphocytosis for ibrutinib

Key conclusions

■ Ibrutinib significantly improved PFS, OS, and ORR relative to ofatumumab in patients with CLL/SLL who had received ≥1 prior therapy.

■ Patients in the ibrutinib arm treated after only one prior therapy experienced better outcomes than those salvaged in later lines of therapy, while the presence of del(17p) did not confer inferior outcomes in ibrutinib-treated patients.

■ The updated results for ibrutinib-treated patients, with 16 months of follow-up, are consistent with previously published phase II single-agent results.

■ These results provide further evidence of the robust clinical activity of ibrutinib in patients with CLL regardless of high-risk baseline genetics.


In vivo evidence that ibrutinib deregulates chemokine receptor CXCR4 surface membrane expression and signaling, along with inhibiting B-cell antigen receptor signaling, as causes for defective homing and impaired retention of CLL cells in tissues

Background

The Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib is approved by the U.S. Food and Drug Administration for the treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma in patients who have received at least one prior therapy. Patients receiving ibrutinib treatment often develop lymphocytosis and concomitant reduced organomegaly. Although the mechanism is unknown, it is believed that these actions of ibrutinib are due to egress of CLL cells from lymphoid compartments. Migration and interaction of CLL cells with protective niches is correlated with overexpression of surface membrane chemokine receptor CXCR4 (smCXCR4). Surface expression and phosphorylation of CXCR4 is regulated by BTK and
PIM kinases. This study investigated the effect of ibrutinib on CLL cell distribution using TCL1-192 cells, a clonal murine cell line that mimics aggressive CLL and experiences active B-cell antigen receptor (BCR) signaling.1

Study design
• This study was divided into three parts:
  ◦ Part I: Two weeks following TCL1-192 cell engraftment, mice received one oral gavage treatment with either control vehicle or ibrutinib 25 mg/kg. The number of CLL cells in peripheral blood was measured at 1, 4, and 24 hours after oral treatment.
  ◦ Part II: Two weeks after TCL1-192 cell engraftment, mice were treated for 4 weeks with either control vehicle or ibrutinib 25 mg/kg, administered by oral gavage. Following 4 weeks of treatment, tumour cells were collected from treated mice and transferred into recipient mice that were treated with either control vehicle or 25 mg/kg of ibrutinib for 5 days before cell transfer. Tumour cell analysis was performed at 24 and 72 hours after cell transfer to recipient mice.
  ◦ Part III: Following TCL1-192 cell engraftment, mice were treated with either control vehicle or ibrutinib 25 mg/kg by oral gavage. Treatment started at two weeks (early disease) or 4 weeks (late disease) after TCL1-192 cell engraftment. Prolonged survival was documented.

Key findings
Part I
• Compared to mice receiving control vehicle treatment, mice receiving ibrutinib 25 mg/kg had:
  ◦ An increased number of CLL cells in peripheral blood after 1, 4, and 24 hours of oral treatment;
  ◦ A higher percentage of divided cells in circulating CD19+CD5+ cells 1 hour post treatment; and
  ◦ A significantly decreased number of CLL cells in peripheral blood that contained a higher percentage of divided cells after 4 weeks of daily ibrutinib treatment.
• CXCR4 surface membrane levels and signaling were rapidly decreased in ibrutinib-treated TCL1-192 leukemic cells.
• Compared with mice receiving control treatment, mice treated with ibrutinib showed impaired CXCR4 internalization in response to chemokine CXCL12 stimulation and defective CXCR4 recycling to the cell surface membrane. These results were recapitulated in vitro in TCL1-192 cells.
• Impairments in CXCR4 internalization and recycling were correlated with a reduction of phosphorylated CXCR4 and a reduction of total BTK and PIM1 kinase protein levels.

Part II
• Ibrutinib-treated TCL1-192 leukemic cells displayed a markedly impaired ability to re-enter lymphoid tissues. (Figure 1)
  ◦ At 24 hours after tumour cell injection into recipient mice, the cells exposed to ibrutinib remained in peripheral blood rather than moving to the spleen.
At 72 hours after tumour cell injection, ibrutinib-treated recipient mice had higher numbers of circulating tumour cells in peripheral blood compared to control.

- Treatment with ibrutinib for 4 weeks significantly blocked the growth of TCL1-192 cells in the spleen and lymph nodes.
- After 4 weeks of treatment, ibrutinib-treated mice showed less tumour cell infiltration in the spleen, lymph nodes, liver, and bone marrow compared to vehicle-treated mice.

**Part III**
- Mice treated with ibrutinib at early and late disease stages had prolonged survival compared to vehicle-treated mice. (Figure 2)

**Figure 2. Survival in mice receiving ibrutinib at early and late disease stages**

![Figure 2](image)

**TCL1-192 = transferrable, antigenic-specific murine B-cell clone**

**Key conclusions**

- Treatment with ibrutinib lowered the expression of smCXCR4 on TCL1-192 cells by blocking CXCR4 internalization and recycling.

- Ibrutinib continuously promoted emigration of tumour cells into circulation in TCL1-192 cell-engrafted mice and also prevented CLL cells from homing back to tissue niches.

- For tumour cells remaining in lymphoid tissues, treatment with ibrutinib blocked BCR and CXCR4 signaling, as well as the growth of those tumour cells.

- Ibrutinib prolonged the survival of mice treated at early and late stages of disease.

Patterns of use of anticoagulation and/or antiplatelet agents in patients with CLL treated with single-agent ibrutinib

**Background**
Ibrutinib is a first-in-class, oral, covalent inhibitor of Bruton's tyrosine kinase (BTK) that has shown single-agent efficacy and an acceptable safety profile in patients with chronic lymphocytic leukemia (CLL). While BTK is expressed in platelets, bleeding diathesis has not been reported in patients with hereditary BTK deficiency (X-linked agammaglobulinemia). Patients with CLL often have comorbidities requiring anticoagulants and/or antiplatelet agents, which can increase bleeding risk. The objective of this study was to report the pattern of use of these agents and describe bleeding adverse events (AEs) observed in two trials of single-agent ibrutinib in patients with CLL.

**Study design**
- An analysis of data from the ibrutinib phase II PCYC-1102 trial and an interim analysis of the randomized phase III PCYC-1112 (RESONATE™) study of ibrutinib vs. ofatumumab was performed to determine the use of concomitant anticoagulants and/or antiplatelet therapy in these studies of patients with CLL.
- Major bleeding was defined as any grade ≥3 bleeding event or hemorrhage of any grade resulting in one of the following: intraocular bleeding causing loss of vision, need for at least two units of red blood cell transfusion, hospitalization, prolonged hospitalization, or any intracranial hemorrhage.

**Key findings**
- At baseline, the median age of patients was 68 years (range: 37–84 years) in the PCYC-1102 trial, and 67 years (range: 30–86 years) and 67 years (range: 37–88 years) in the RESONATE™ ibrutinib arm and ofatumumab arm, respectively.
- Baseline platelet count was <100 x 10^9/L in 41% of ibrutinib-treated patients in the two studies.
- Median follow-up was 21.1 months (range: 16.5–22.1 months) for PCYC-1102 and 9.6 months (range: 0.3–16.6 months) and 9.2 months (range: 0.1–16.5 months) for the RESONATE™ ibrutinib arm and ofatumumab arm, respectively.

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**Study design**

**PCYC-1102**

N = 132
Nonrandomized study of patients with CLL receiving ibrutinib monotherapy

- TN aged ≥65 years n = 31
- R/R n = 101

**PCYC-1112 (RESONATE™)**

N = 391
Randomized study of patients with R/R CLL/SLL

- Ibrutinib n = 195
- Ofatumumab n = 196

CLL = chronic lymphocytic leukemia; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; TN = treatment-naive
• Among 327 patients treated with single-agent ibrutinib, 175 (54%) received concomitant anticoagulant or antiplatelet therapy. (Table 1)
  - The most frequent concomitant anticoagulant was low molecular weight heparin (LMWH) (15%);
  - Seventy patients (21%) received concomitant acetylsalicylic acid (ASA).
• In the RESONATE™ ibrutinib arm, eight of the 10 patients with atrial fibrillation (at the time of interim analysis) received concomitant anticoagulant or antiplatelet therapy with:
  - LMWH alone (n = 3);
  - ASA alone (n = 1);
  - LMWH and ASA (n = 1);
  - Dabigatran and ASA (n = 1);
  - ASA and clopidogrel (n = 1);
  - LMWH, warfarin, and ASA (n = 1);
• The most common bleeding AEs were grade 1 petechiae and contusion, occurring in 13% and 20% of patients in the PCYC-1102 trial and 13% and 11% of patients in the RESONATE™ trial, respectively. (Figure 1)
• No grade 4/5 bleeding events were reported.
• Bleeding AEs led to discontinuation of ibrutinib in four patients (1%) from the two studies (three patients in PCYC-1102 and one patient in the RESONATE™ ibrutinib arm), all due to major bleeding.
• In PCYC-1102, major bleeding occurred in three to six of 132 patients (5%). (Figure 2)
  - Most bleeding events occurred early, during the first three to six months of therapy.
• In the ibrutinib arm of RESONATE™, major bleeding occurred in two of 195 patients (1%) vs. three of 191 patients (2%) in the ofatumumab arm. (Figure 2)

---

**Table 1. Overall concomitant use of anticoagulation and antiplatelet therapy**

<table>
<thead>
<tr>
<th>Concomitant treatment, n (%)</th>
<th>PCYC-1102 All treated patients N = 132</th>
<th>RESONATE™ All treated patients (ibrutinib arm) n = 195</th>
<th>Total N = 327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anticoagulant or antiplatelet</td>
<td>77 (58)</td>
<td>98 (50)</td>
<td>175 (54)</td>
</tr>
<tr>
<td>Anticoagulant only</td>
<td>10 (8)</td>
<td>25 (13)</td>
<td>35 (11)</td>
</tr>
<tr>
<td>Both anticoagulant or antiplatelet</td>
<td>13 (10)</td>
<td>17 (9)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>23 (17)</td>
<td>42 (22)</td>
<td>65 (20)</td>
</tr>
<tr>
<td>LMWH</td>
<td>14 (11)</td>
<td>34 (17)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>6 (5)</td>
<td>4 (2)*</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Heparin</td>
<td>3 (2)</td>
<td>5 (3)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>—</td>
<td>3 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>—</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>—</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Alteplase†</td>
<td>1 (1)</td>
<td>—</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Antiplatelet only</td>
<td>54 (41)</td>
<td>56 (29)</td>
<td>110 (34)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>67 (51)</td>
<td>73 (37)</td>
<td>140 (43)</td>
</tr>
<tr>
<td>ASA</td>
<td>33 (25)</td>
<td>37 (19)</td>
<td>70 (21)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>—</td>
<td>7 (4)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dipyridamole/ASA</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Nonaspirin NSAIDs</td>
<td>46 (35)</td>
<td>45 (23)</td>
<td>91 (28)</td>
</tr>
</tbody>
</table>

ASA = acetylsalicylic acid; NSAIDs = nonsteroidal anti-inflammatory drugs

*Four patients who received vitamin K antagonists in the RESONATE™ ibrutinib arm were not receiving these agents at the time of study entry.
†Thrombolytic agent used to open a thrombosed catheter.
As in PCYC-1102, most bleeding events occurred within the first three to six months of ibrutinib treatment.

- Major bleeding AEs occurred in eight of 327 ibrutinib-treated patients (2%) across the two studies (Table 2):
  - Of 175 patients receiving concomitant anticoagulant or antiplatelet therapy, five had major bleeding events.
  - Three of the five received concomitant anticoagulation with warfarin or LMWH.
  - Specific anticoagulation/antiplatelet use in the five included anticoagulant alone (LMWH, n = 1), antiplatelet agent alone (ASA, n = 1; nonsteroidal anti-inflammatory drug [NSAID], n = 1), and both an anticoagulant and antiplatelet (ASA and warfarin, n = 1; NSAID, heparin, and LMWH, n = 1).
  - Three of the eight who experienced major bleeding events were not taking concomitant anticoagulant or antiplatelet therapy.
  - One of the three had a baseline platelet count of 2 x 10^9/L.
  - One of the three had an acquired von Willebrand deficiency.
  - One of the eight had perioperative hemorrhage (postoperatively at the location of excision of a nonmalignant skin lesion), in which ibrutinib was not held prior to the excision.
  - Three of the eight had thrombocytopenia at baseline, two of whom had thrombocytopenia at the time of the bleeding event.
  - In the RESONATE™ ofatumumab arm, three patients had major bleeding events, one grade 2 hemoptysis, one grade 3 epistaxis, and one grade 1 epistaxis.

---

**Figure 1. Bleeding events in >3% of patients by grade**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>Contusion</td>
<td>Ecchymosis</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Epistaxis</td>
<td>Tendency to bruise</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Blood blister</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2. Frequency of bleeding events by time to new event onset**

- As in PCYC-1102, most bleeding events occurred within the first three to six months of ibrutinib treatment.
- Major bleeding AEs occurred in eight of 327 ibrutinib-treated patients (2%) across the two studies (Table 2):
- Of 175 patients receiving concomitant anticoagulant or antiplatelet therapy, five had major bleeding events.
- Three of the five received concomitant anticoagulation with warfarin or LMWH.
- Specific anticoagulation/antiplatelet use in the five included anticoagulant alone (LMWH, n = 1), antiplatelet agent alone (ASA, n = 1; nonsteroidal anti-inflammatory drug [NSAID], n = 1), and both an anticoagulant and antiplatelet (ASA and warfarin, n = 1; NSAID, heparin, and LMWH, n = 1).
- Three of the eight who experienced major bleeding events were not taking concomitant anticoagulant or antiplatelet therapy.
- One of the three had a baseline platelet count of 2 x 10^9/L.
- One of the three had an acquired von Willebrand deficiency.
- One of the eight had perioperative hemorrhage (postoperatively at the location of excision of a nonmalignant skin lesion), in which ibrutinib was not held prior to the excision.
- Three of the eight had thrombocytopenia at baseline, two of whom had thrombocytopenia at the time of the bleeding event.
- In the RESONATE™ ofatumumab arm, three patients had major bleeding events, one grade 2 hemoptysis, one grade 3 epistaxis, and one grade 1 epistaxis.
### Table 2. Summary of baseline characteristics and major bleeding events in patients treated with ibrutinib

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient</th>
<th>Age, years/ Sex</th>
<th>Number of lines of prior therapy</th>
<th>Event/ Study day</th>
<th>AE grade</th>
<th>Action taken</th>
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<th>Prior anticoagulant or antiplatelet therapy and use</th>
<th>Confounding factors</th>
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<th>PLT count within 30 days of bleed (x 10^3/µL)</th>
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<td>Warfarin for atrial fibrillation; aspirin for HTN/CAD prophylaxis</td>
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<td>Postoperative hemorrhage at site of excision of skin lesion/ D18</td>
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<td>History of HTN; ibrutinib not held before skin biopsy procedure</td>
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CAD = coronary artery disease; DVT = deep vein thrombosis; GI = gastrointestinal; HTN = hypertension; INR = international normalized ratio; PE = pulmonary embolism

*Denotes bleeding adverse events that led to discontinuation of ibrutinib.
Key conclusions

- Concomitant anticoagulation or antiplatelet therapy was common in the PCYC-1102 and RESONATE™ studies of single-agent ibrutinib and use did not frequently result in major bleeding events.

- Most bleeding AEs were grade 1, were observed early in treatment, and did not lead to frequent treatment discontinuation (4/327; 1%).

- Major bleeding events were uncommon in patients receiving single-agent ibrutinib (8/327; 2%) and were typically confounded by various factors (e.g., concomitant anticoagulant and/or antiplatelet treatment, and/or prior history of chronic gastrointestinal bleeds, acquired von Willebrand deficiency, or intermittent epistaxis).

- Although there were no major bleeding events in patients receiving non-warfarin oral anticoagulants, the number of patients receiving these agents was small.

- Precautions on concomitant use of anticoagulants and antiplatelet agents, along with adherence to appropriate perioperative drug-withholding guidelines as applied in the RESONATE™ study and similarly reflected in the ibrutinib label, resulted in a small number of major bleeding complications.


Barrientos JC, et al. ASH 2014:4696

Hematologic and immunologic function and patient well-being for the phase III RESONATE™ study of ibrutinib versus ofatumumab in relapsed/refractory CLL/SLL

Background

Ibrutinib is a new treatment option approved by the U.S. Food and Drug Administration for chronic lymphocytic leukemia (CLL) patients with ≥1 prior therapy, as well as patients with del(17p) CLL. Previously reported results from the phase III RESONATE™ (PCYC-1112) study of ibrutinib versus ofatumumab in patients with relapsed/refractory (R/R) CLL or small lymphocytic lymphoma (SLL) demonstrated a 78% reduction in risk of progression by an independent review committee (IRC) and 57% reduction in risk of death with ibrutinib. These results prompted the independent data monitoring committee to recommend that all patients randomized to ofatumumab be provided access to ibrutinib.

At ASH 2014, Barrientos et al. reported measures of patient well-being, including hematologic, immunologic, and quality-of-life parameters, from the phase III RESONATE™ (PCYC-1112) study of ibrutinib versus ofatumumab in patients with R/R CLL or SLL.1

Study design

- Patients with CLL/SLL after ≥1 prior therapy were randomized 1:1 to:
  - Ibrutinib, 420 mg/day until progression or unacceptable toxicity; or
  - Ofatumumab, according to package insert for up to 24 weeks.
- Secondary efficacy endpoints included hematologic improvement (sustained improvement ≥56 days without transfusions or growth factors) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).
- Exploratory endpoints included disease-related symptoms, serum immunoglobulin, patient-reported outcomes (PROs) by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), and medical resource utilization.
- This analysis presents updated data as of the June 20, 2014 cut-off. Data for ofatumumab beyond 24 weeks were limited. At the time of the analysis, 122 patients randomized to ofatumumab crossed over to ibrutinib.

Key findings

- Median age was 67 years in both arms and approximately 40% of patients were ≥70 years of age.
The ibrutinib and ofatumumab arms were balanced in terms of cytogenetic abnormalities (del(17p), 32%) and Rai stage (stage III/IV, 57%).

Of the 391 patients enrolled in the trial, 63% had cytopenias at baseline consisting of thrombocytopenia (35%), anemia (45%), and neutropenia (20%).

In patients on ibrutinib with any baseline cytopenia, 73% showed sustained improvement in hemoglobin, 82% in platelets, and 44% in absolute neutrophil count (Figure 1).

In the ibrutinib arm, 80% of patients with baseline cytopenias showed sustained improvement in blood counts compared to 45% on ofatumumab ($p < 0.0001$).

The white blood cell (WBC) differential demonstrated an increase in the proportion of neutrophils and a decrease in the percentage of lymphocytes over time. (Figure 2)

In the ibrutinib arm, the relative proportion of B cells decreased over time, while that of T cells (both CD4+ and CD8+ subsets) and NK cells increased over time. (Figure 3)

No significant decrement was observed in serum immunoglobulins (IgA, IgG, IgM) during follow-up on the ibrutinib arm.

More patients achieved a clinically meaningful improvement in FACIT-F (increase of ≥3 points) with ibrutinib than ofatumumab (56% vs. 43%; odds ratio = 1.69; $p = 0.0101$). (Figure 4)

An improvement in EORTC Fatigue Subscale Score from baseline to week 24 with ibrutinib (n = 117) vs. ofatumumab (n = 87) was observed (median, −11 vs. 0).

A larger proportion of patients treated with ibrutinib compared to ofatumumab showed clinically meaningful improvement on EORTC QLQ-C30 global health scores (47% vs. 40%; odds ratio = 1.3; $p = 0.2049$).

Following transient increase in peripheral lymphocyte count (ALC) in the ibrutinib arm, the ALC declined over time to a median of 50% below baseline at 24 weeks and continued to decrease to normal (<4 × 10⁹ g/L) at later time points.

Although ibrutinib showed initial increase in ALC, reduction in ALC from baseline was similar between the two arms at later time points.

A ≥50% reduction in lymph node based on IRC-assessed computed tomography (CT) scans was observed more frequently with patients on ibrutinib than those on ofatumumab (92% vs. 14%, $p < 0.0001$).

A ≥50% reduction in estimated volume of splenic enlargement based on IRC assessment of CT was more common with ibrutinib than ofatumumab (85% vs. 54%, $p < 0.0001$).

Improvement in disease-related symptoms (defined by change of at least one grade post-baseline reported for at least two consecutive assessments) was seen more often with ibrutinib than with ofatumumab for weight loss (100% vs. 87%), fatigue (79% vs. 64%), night sweats (89% vs. 77%), abdominal pain/discomfort (96% vs. 75%), and anorexia (100% vs. 64%).

Hospitalizations in the first 30 days occurred less frequently with ibrutinib than ofatumumab (0.087 vs. 0.184 events/patient; $p = 0.0198$).

Figure 1. Improvement in median hemoglobin and platelets over time in patients with baseline cytopenias
- Growth factor usage after day 30 occurred more frequently with ofatumumab than ibrutinib.
- Most adverse events (AEs) were grade 1 in severity.
- At a median treatment duration of 16 months and 5 months for ibrutinib and ofatumumab, respectively, the most frequently observed AEs throughout the entire follow-up were diarrhea (52%), fatigue (33%), and nausea (31%), with new onset of these events being less frequent after the first 6 months.
- New episodes of diarrhea (all grades) declined over time from 47% at > 0–6 months to 3% at >18–24 months.
- The most frequently observed grade ≥3 AEs throughout the entire follow-up were neutropenia (18%), pneumonia (11%), and hypertension (6%).
- Grade ≥3 atrial fibrillation occurred in seven patients (4%) over the entire follow-up, resolving in six patients and leading to ibrutinib discontinuation in one patient.

Figure 2. Effect of ibrutinib vs. ofatumumab on WBC count differential over time

Figure 4. Improvement in FACIT-F by treatment arm

FACIT-F = functional assessment of chronic illness therapy-fatigue
Figure 3. Percentage of lymphocytes over time

**T cells**

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<th>Ofatumumab</th>
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*p < 0.05 for change from baseline.

**B cells**

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**NK cells**

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*n = 183 169 168 155 153 149 73 169 151 127*
In Supportive Care Oncology

Key conclusions

■ Ibrutinib led to significant improvements in hematologic function and disease burden compared to ofatumumab when administered to patients who were previously treated for CLL/SLL.

■ No significant decrement in immunoglobulin levels was observed; the relative proportion of normal immune cells increased, while the proportion of CD19+ B cells decreased.

■ A survival benefit with ibrutinib, together with sustained improvements in hematologic endpoints and PRO, suggest that ibrutinib restores quality of life while prolonging survival.


The addition of rituximab abrogates ibrutinib-induced lymphocytosis and promotes more rapid decrease in absolute lymphocyte counts in patients with relapsed CLL

Background

The Bruton tyrosine kinase inhibitor ibrutinib has proved to be an effective targeted therapy in patients with chronic lymphocytic leukemia (CLL). A multicentre phase Ib/II study of ibrutinib in 85 patients with relapsed CLL or small lymphocytic lymphoma (SLL) showed an overall response rate (ORR) of 71% with an additional 15 to 20% of patients having a partial response with lymphocytosis. A phase II trial of ibrutinib in combination with rituximab in 40 high-risk CLL patients conducted at the MD Anderson Cancer Center demonstrated an ORR of 95%. However, efficacy of ibrutinib in combination with rituximab vs. ibrutinib alone has not been directly compared.

A randomized study of ibrutinib vs. ibrutinib plus rituximab in patients with relapsed CLL was designed to compare long-term progression-free survival (PFS). In this study, the working hypothesis was that the addition of rituximab may abrogate ibrutinib-induced lymphocytosis and accelerate response of other biomarkers, including plasma levels of chemokines CCL3 (MIP-1α) and CCL4 (MIP-1β), which are known to reflect the activation status of CLL cells.1

Study design

• Patients were randomized to receive ibrutinib alone (Arm A) or ibrutinib plus rituximab (Arm B).
  ◯ Patients in Arm A were treated with ibrutinib (420 mg) orally, once daily, continuously throughout the study.
  ◯ Patients randomized to Arm B received ibrutinib starting on day 1 or day 2, and rituximab (375 mg/m²) was administered intravenously on days 1, 8, 15, and 22 (cycle 1), then monthly during cycles 2–6.
  ◯ Inclusion criteria required patients to have previously treated CLL or small lymphocytic lymphoma, or treated or untreated high-risk disease (deletion 17p [del(17p)] or TP53 mutation).
  ◯ Serial blood samples were drawn at pre-treatment, then weekly during the first month, and monthly until five or six months.
  ◯ Plasma levels of CCL3 and CCL4 were measured at pre-treatment, one week, one month, three months, and five or six months of follow-up by enzyme-linked immunosorbent assay.
  ◯ Statistical significance was determined by a paired t-test.
T cells were counted before initiation of treatment and after six months. Results are presented as median with interquartile range of percentage of change in T-cell counts (i.e., \([\text{post-treatment measurement} - \text{baseline measurement}] / \text{baseline measurement} \times 100\%\)). Statistical significance was determined by a paired t-test or two sample t-test.

A linear, mixed effects model with randomly varying intercepts and slopes was constructed for each absolute lymphocyte count (ALC) measured repeatedly over time using SAS PROC MIXED. Models included an unstructured covariance and the Kenward-Rogers degrees of freedom adjustment to take into account unequally spaced unbalanced data. Models over at least four months of measurements included both linear and quadratic components.

Patient accrual began in December 2013 with an enrolment goal of 208 patients: At the time of presentation, there were 104 patients enrolled; Analysis was performed on 93 patients who had at least one month of follow-up as of July 2013; the following graphs represent data from 104 patients who had at least one month of follow-up as of October 2013.

**Key findings**

- Baseline characteristics of the patient population as of October 2014 (Arm A vs. Arm B):
  - Age, years: 64 (range: 46–80) vs. 63.5 (range: 42–77);
  - Male, n (%): 35 (67) vs. 32 (62);
  - Del(17p), n (%): 13 (25) vs. 19 (37);
  - Immunoglobulin heavy chain variant unmutated, n (%): 32 (62) vs. 36 (69);
  - Absolute lymphocyte count (x10^3/µL): 25.0 (range: 0.5–205.1) vs. 27.6 (0.7–146.9).
- A mixed model with quadratic trend confirmed a curvature pattern in ALC for Arm A during the first month of treatment, consistent with lymphocytosis; in Arm B, no statistically significant changes in ALC were observed during this initial period. (Figure 1)
- The same model demonstrated an ALC downward trend for both arms over a period of at least four months. Patients on Arm B experienced a more rapid decrease in ALC (\(p = 0.03\) for the linear component; \(p = 0.002\) for the quadratic component).

**Figure 1. Changes in absolute lymphocyte count during treatment**

<table>
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<th>Arm A (n = 104)</th>
<th>Arm B (n = 104)</th>
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<tr>
<td>ALC ≥4000/µL at 4 months</td>
<td>36 (92%)</td>
<td>21 (70%)</td>
</tr>
<tr>
<td>ALC &lt;4000/µL at 4 months</td>
<td>3 (8%)</td>
<td>9 (30%)</td>
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<tr>
<td>Total n of patients at 4 months</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td>ALC ≥4000/µL at 6 months</td>
<td>31 (89%)</td>
<td>18 (64%)</td>
</tr>
<tr>
<td>ALC &lt;4000/µL at 6 months</td>
<td>4 (11%)</td>
<td>10 (36%)</td>
</tr>
<tr>
<td>Total n of patients at 6 months</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>ALC ≥4000/µL at 9 months</td>
<td>16 (73%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>ALC &lt;4000/µL at 9 months</td>
<td>6 (27%)</td>
<td>9 (53%)</td>
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<tr>
<td>Total n of patients at 9 months</td>
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<td>17</td>
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</table>

**Figure 2. Changes in hemoglobin concentration and platelet count**
The number of patients ranged from 52, between zero and four weeks, to 24 and 22 at 36 weeks, for Arms A and B, respectively.

- Descriptive analysis suggested that Arm B had more patients with normal ALC following four, six, and nine months of treatment. (Figure 1)
- Platelet count and hemoglobin concentration demonstrated upward trends in both arms. (Figure 2)
- Both treatment regimens resulted in significant reduction of CCL3, CCL4, and β2-microglobulin levels in one week. (Figure 3)

CCL3 and CCL4 plasma levels were measured in plasma samples from 37 patients in Arm A and 41 patients in Arm B who had at least one month follow-up as of June 2013.

- Amounts of CD3+ and CD3+/CD4+ cells decreased significantly ($p = 0.0007$ and $p = 0.0002$, respectively, by paired t-test) in patients in Arm B, but not in Arm A. (Figure 4)
- Patients treated with combination therapy had significantly higher reduction in CD3+, CD3+/CD4+, and CD3+/CD8+ T cells compared with patients treated with ibrutinib alone ($p = 0.03$, $p = 0.0008$, and $p = 0.01$, respectively, by two sample t-test).

**Key conclusions**

- In this ongoing, randomized study, there are currently 104 patients enrolled (52 patients in each arm); the accrual goal is 208 patients.

- An initial analysis suggests that addition of rituximab to ibrutinib abrogates the transient lymphocytosis and is associated with faster clearing of the bloodstream of leukemia cells in patients with relapsed CLL.
  - These results are consistent with recently published findings from the study of ibrutinib in combination with rituximab for patients with high-risk CLL.

- T-cell counts declined significantly after six months of treatment in patients receiving ibrutinib in combination with rituximab compared with patients treated with ibrutinib alone.
  - Clinical implications of this finding will be investigated.

- Both treatment regimens improved platelet counts and hemoglobin levels, while significantly reducing CCL3, CCL4, and β2-microglobulin levels.

Efficacy and safety of ibrutinib in patients with relapsed or refractory CLL/SLL with 17p deletion: results from the phase II RESONATE™-17 trial

Background
Patients with chronic lymphocytic leukemia (CLL) with deletion 17p [del(17p)] follow an aggressive clinical course and demonstrate a median survival of less than 2 years in the relapsed/refractory (R/R) setting. Ibrutinib, a first-in-class Bruton’s tyrosine kinase (BTK) inhibitor, has been approved for previously treated patients with CLL and for patients with del(17p) CLL.

At ASH 2014, O’Brien et al. reported results from the primary analysis of the phase II RESONATE™-17 (PCYC-1117-CA) study, designed to evaluate the efficacy and safety of single-agent ibrutinib for treatment of patients with R/R del(17p) CLL or small lymphocytic lymphoma (SLL).¹

Study design
• RESONATE™-17 was a phase II, open-label, single-arm, multicentre, international study.
• Key eligibility criteria:
  - Patients with CLL/SLL;
  - Documentation of del17p13.1 in peripheral blood by fluorescence in situ hybridization (FISH) analysis (>7% positive cells);
  - R/R disease after 1–4 prior lines of therapy;
  - Eastern Cooperative Oncology Group performance status 0–1;
  - Measurable nodal disease.
• Ibrutinib was given at 420 mg orally once daily until unacceptable toxicity or disease progression (N = 144).

Key findings
• Baseline characteristics of the 144 patients treated with ibrutinib were as follows:
  - Diagnosis of CLL/SLL: 95%/5%;
  - Median age (range), years: 64 (36–89);
  - Rai Stage III or IV: 63%;
  - Bulky disease ≥5 cm/≥10 cm: 49%/10%;
  - Median percentage of del(17p) cells (range): 65.5% (7.5–96.5%);
  - Median absolute lymphocyte count (ALC) x 10⁹/L (range): 33(0.4–385), with 57% of patients with ALC ≥25 x 10⁹/L;
  - Beta-2 microglobulin levels were ≥3.5 mg/L in 78% of patients;

PCYC-1117 (RESONATE™-17)

CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; po = per os (orally); PS = performance status; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma

¹Cut-off for del (17p) was >7% positive cells.
Lactate dehydrogenase levels were ≥250 U/L in 53% of patients;
- Median number of prior therapies (range): 2 (1–7).
- The investigator-assessed ORR was 83%, including 17% of patients achieving partial response with lymphocytosis (PR-L). IRC-assessed ORR was 65%. (Figure 1)
- Best response (ORR + PR-L) by IRC without second confirmatory computed tomography (CT) scan was 74% (95% CI: 66–80%).
- Median DOR was not reached, and the 12-month DOR rate was 88.3%.

There was sustained hematologic improvement in patients with:
- Any baseline cytopenia: 77% (70/91);
- Baseline neutropenia (ANC ≤1.5 x 10^9/L): 85% (22/26);
- Baseline anemia (hemoglobin ≤11g/dL): 52% (33/63);
- Baseline thrombocytopenia (platelets ≤100 x 10^9/L): 72% (42/58).
- At a median follow-up of 11.5 months, median PFS was not reached. At 12 months, 79.3% were alive and progression-free. (Figure 2)

---

**Figure 1. Overall response: investigator and IRC assessments**

**Figure 2. Progression-free survival**

*Median follow-up: 11.5 months.

---

**Ibrutinib**

<table>
<thead>
<tr>
<th>(N = 144)</th>
<th>CR</th>
<th>CRi</th>
<th>PR-L</th>
<th>PR</th>
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</thead>
<tbody>
<tr>
<td><strong>Responders (%):</strong></td>
<td>83%</td>
<td>17%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>SD</td>
<td>63%</td>
<td>11%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>4%</td>
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**Ibrutinib**

<table>
<thead>
<tr>
<th>(N = 144)</th>
<th>PR-L</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders (%):</strong></td>
<td>65%</td>
<td>4%</td>
</tr>
<tr>
<td>SD</td>
<td>60%</td>
<td></td>
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<tr>
<td>PD</td>
<td>24%</td>
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**N 12-month PFS rate**

<table>
<thead>
<tr>
<th>Overall Del(17p) quartiles†</th>
<th>144</th>
<th>79.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>35</td>
<td>85%</td>
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<tr>
<td>25–50%</td>
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<td>81%</td>
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<tr>
<td>50–75%</td>
<td>33</td>
<td>83%</td>
</tr>
<tr>
<td>≥75%</td>
<td>39</td>
<td>69%</td>
</tr>
</tbody>
</table>

---

**CLL = chronic lymphocytic leukemia; PFS = progression-free survival**
• Progressive disease was reported in 20 patients (13.9%). Richter’s transformation was reported in 11 of these patients (7.6%), and 10 out of 11 of these cases occurred within the first 6 months.
• Median OS was not reached, and the 12-month OS rate was 83.5%. (Figure 3)
• At the time of analysis, 30% of patients had discontinued treatment due to various reasons including progression (13%), AE/unacceptable toxicity (11%), patient withdrawal (2%), investigator decision (3%), or death (1%).
  ◦ Among patients who discontinued due to unacceptable toxicity, 10 (7%) eventually had fatal events (pneumonia, sepsis, myocardial or renal infarction, and health deterioration).
• The most frequently reported treatment-emergent adverse events (TEAE) of any grade, regardless of attribution, were:
  ◦ Diarrhea: 36% (2% grade 3-4);
  ◦ Fatigue: 31% (1% grade 3-4);
  ◦ Cough: 24% (<1% grade 3-4); and
  ◦ Arthralgia: 22% (1% grade 3-4). (Table 1)
• Neutropenia (14%), anemia (8%), and hypertension (8%) were the most frequently reported grade 3-4 TEAEs. (Table 1)
• Any grade ≥3 infection AE (in >1 patient) occurred in 24% of patients, the most being pneumonia (10%) and urinary tract infection (3%).
• Skin cancers (squamous or basal cell carcinoma) were reported in 5% of patients, and 1% had non-skin cancer.
• Atrial fibrillation of any grade was reported in 11 patients (8%; 3.5% grade 3-4), major bleeding in 7 patients (5%, all grade 2 or 3), and tumour lysis syndrome in 1 patient (<1%).

**Figure 3. Overall survival***

![Overall survival graph](image)

<table>
<thead>
<tr>
<th>Months</th>
<th>Number at risk</th>
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<tbody>
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<tr>
<td>11</td>
<td>114</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
</tr>
</tbody>
</table>

*Median follow-up: 11.5 months.
†Based on % of CLL cells with del(17p) at baseline.
CLL = chronic lymphocytic leukemia; OS = overall survival

**Table 1. Treatment-emergent adverse events (≥15% of patients) regardless of attribution**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ibrutinib (N = 144)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Any grade, %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31</td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
</tr>
<tr>
<td>Nausea</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>17</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15</td>
</tr>
</tbody>
</table>

*TEAEs were reported in all patients receiving study drug.
TEAE = treatment-emergent adverse event
Key conclusions

- Ibrutinib is efficacious with a favourable risk-benefit profile in the largest prospective study in del(17p) CLL/SLL.
  - Best response (ORR including PR-L) was 83% (based on investigator-assessed ORR);
  - Median PFS and DOR were not reached at a median follow-up of 11.5 months;
  - The 12-month PFS was 79%, consistent with previously observed efficacy.

- PFS outcomes were favourable compared to that of frontline del(17p) CLL treated with fludarabine, cyclophosphamide, and rituximab, or alemtuzumab (median PFS: 11 months).

- The safety profile was consistent with previous reports for ibrutinib.

- Ibrutinib appears to be effective in patients with del(17p) CLL/SLL.


Thompson PA, et al. ASH 2014:22

Complex karyotype is a stronger predictor than del(17p) for inferior outcomes in relapsed or refractory CLL patients treated with ibrutinib-based regimens

Background

The Bruton’s tyrosine kinase inhibitor ibrutinib has improved the outcomes of patients with relapsed/refractory chronic lymphocytic leukemia (CLL). Dur- able responses have been observed in the majority of patients, with a progression-free survival (PFS) of approximately 75% at 26 months. In patients with CLL with deletion 17p [del(17p)], which remains a high-risk group, the median PFS is 28.1 months. Approximately two of every three cases of del(17p) CLL are associated with complex metaphase karyotype, which is defined as the presence of at least three unrelated abnormalities. The objective of this study was to assess the prognostic relevance of complex metaphase karyotype in ibrutinib-treated patients.1

Study design

- This study included a total of 100 patients with CLL treated with ibrutinib-based regimens at the MD Anderson Cancer Center (MDACC) from July 2010 to June 2013.
- These patients were treated with ibrutinib alone (n = 50), ibrutinib plus rituximab (n = 36), or ibrutinib plus bendamustine and rituximab (BR; n = 14).
- Response rates, event-free survival (EFS), and overall survival (OS) were assessed according to baseline characteristics.
- Eight patients were censored for EFS analysis due to planned allogeneic stem cell transplants.
- Lipopolysaccharide stimulation was used for metaphase analysis. Sufficient metaphases were achieved in 65 of 72 patients.
- Clonality was defined according to the 2009 International System for Human Cytogenetic Nomenclature (ISCN) guidelines.

Key findings

- At baseline, the patients’ median age was 65 (range: 35–83) years, 60% had Rai stage III-IV disease, with 52% having bulky adenopathy ≥5 cm, and patients had received a median of two (range: 1–12) prior therapies.
- Analysis by fluorescence in situ hybridization (FISH) was completed for 94 patients, revealing that 48% had del(17p), 28% had del(11q), and 24% had other karyotype. Out of 65 patients tested, the presence of complex metaphase karyotype was detected in 42%.
- Median follow-up in surviving patients was 27 months (range: 11–48 months).
- In the total cohort, the overall response rate (ORR) was 95%, including a complete response (CR) rate of 16%.
By treatment regimen, the ORR and CR rates respectively were:
- Ibrutinib: 94% and 12%;
- Ibrutinib plus rituximab: 94% and 8%;
- Ibrutinib plus BR: 100% and 50%.

The multivariable analysis of CR rate showed a hazard ratio (HR) of 13.9 (95% CI: 2.8–69.0; \( p = 0.001 \)) for patients who received ibritunib plus BR.

By stratifying EFS in all patients according to FISH, the EFS of patients with neither del(17p) nor del(11q) was significantly different compared with that of patients with del(17p) \( (p = 0.014) \). (Figure 1)

Figure 1. Event-free survival in all patients according to FISH

In an analysis including all patients, the EFS of patients with a complex karyotype was significantly different from that of patients without a complex karyotype \( (p < 0.0001) \). (Figure 2)

The multivariable analysis of EFS:
- Complex karyotype: HR = 5.3 (95% CI: 1.5–19.2; \( p = 0.011 \));
- Fludarabine-refractory disease: HR = 1.7 (95% CI: 0.6–4.7; \( p = 0.317 \));
- Del(17p) on FISH: HR = 0.9 (95% CI: 0.2–3.6; \( p = 0.887 \)).

In a comparison of OS according to FISH in all patients, the OS was not significantly different between patients with neither del(17p) nor del(11q) and patients with del(17p) \( (p = 0.054) \). (Figure 3)

The OS according to the presence of complex karyotype was significantly different between patients with and without complex karyotype \( (p = 0.006) \). (Figure 4)

The OS according to FISH in patients without complex karyotype was similar between patients with neither del(17p) nor del(11q) and patients with del(17p) \( (p = 0.52) \).

The OS of patients without fludarabine-refractory disease was significantly higher than that of patients with fludarabine-refractory disease \( (p = 0.009) \). (Figure 5)

The multivariable survival analysis:
- Fludarabine-refractory disease: HR = 6.4 (95% CI: 1.8–22.8; \( p = 0.004 \));
- Complex karyotype: HR = 5.7 (95% CI: 1.5–22.2; \( p = 0.011 \));
- Beta-2-microglobulin \( \geq 4.0 \): HR = 3.0 (95% CI: 0.9–9.8; \( p = 0.076 \));
- Del(17p) by FISH: HR = 0.9 (95% CI: 0.3–3.2; \( p = 0.981 \)).

The survival of patients after progression during ibritunib treatment is shown in Figure 6.
**Key conclusions**

- **Complex karyotype** is a more important predictor of outcome than del(17p) assessed by FISH.
- **Patients without complex karyotype** have a low rate of disease progression, including those with del(17p).
- **Most progressions** during ibrutinib therapy occur after 12 months, with a short survival after progression.
- **Patients with complex karyotype** represent an ideal group in which to study novel treatment approaches.

As chronic lymphocytic leukemia (CLL) is a genetically heterogeneous disease affecting patients with a range of ages and fitness levels, multiple treatment options are necessary in order to safely and effectively treat this diverse population of patients.

One significant challenge for the frontline treatment of CLL is the lack of effective treatments for high-risk patients, including patients with 17p deletions [del(17p)]. Another key unmet need is the availability of effective yet tolerable therapies for patients with comorbidities who are not well enough to receive intensive treatments such as fludarabine, cyclophosphamide, and rituximab (FCR). Currently, FCR is the gold standard for the frontline treatment of young and fit patients with CLL; however, due to its associated toxicities, only approximately 25% of the patients I treat are eligible to receive FCR as dosed in the landmark study. These eligible patients are generally less than 65 years of age, are fit, have normal kidney function, and have minimal comorbidities. For patients unable to tolerate FCR, there are other frontline treatment options that could be considered. Chlorambucil plus rituximab may be a good option for patients who are considerably older and unfit. Chlorambucil plus obinutuzumab is a more effective treatment option for these less fit patients, however, it is not yet reimbursed in Canada. Another potential treatment option for fit older patients, or for less fit patients, is bendamustine plus rituximab (BR).

Several studies evaluating BR in frontline treatment of CLL were presented at the American Society of Hematology (ASH) 2014 meeting, including a key study by Eichhorst et al., who presented the final analysis of the phase III CLL10 trial.1 This randomized, open-label, multicentre trial was designed to test the non-inferiority of BR regarding efficacy and its potentially better tolerability compared with FCR in first-line therapy of physically fit CLL patients without del(17p). The most notable result from this trial was the finding that FCR was superior to BR in terms of efficacy, with more complete remissions and minimal residual disease-negative results achieved in the overall patient population. In terms of overall survival, there was no difference noted between the FCR and BR arms at a median follow-up of 37.1 months. Interestingly, although patients younger than 65 years had significantly prolonged progression-free survival (PFS) in the FCR arm compared to the BR arm, there was no statistically significant difference in PFS between treatment arms in patients older than 65 years. The authors noted that the older patients in the study were unable to receive as many complete cycles of FCR treatment, which was likely a contributor to the lack of superiority of FCR in these patients. Although FCR demonstrated superior efficacy overall, it was also associated with significantly greater toxicity. In the overall population, more patients in the FCR arm experienced grade 3–4 thrombocytopenia, neutropenia, and infections. An even more sizeable difference in toxicities was observed between treatment arms in patients over 65 years. In these patients, 48% in the FCR arm experienced grade 3–4 infections compared with only 21% in the BR arm. However, it is important to note that both FCR and BR are intensive and toxic regimens, with grade 3–4 neutropenia being relatively frequent with both regimens. The marked difference in grade 3–4 infections is an important result as it indicates that approximately 50% of patients in the FCR arm would require admission to hospital as part of their treatment, which is an unacceptably high incidence and a deterrent to such treatment for most patients.

The authors concluded that since BR shows inferior efficacy versus FCR in this randomized phase III controlled trial, FCR remains the standard frontline therapy for fit patients with CLL. However, given the significantly higher toxicity of FCR and comparable efficacy of BR in patients older than 65 years, BR may be considered as an alternative frontline therapy in fit older patients. The Alberta guidelines recommend BR as the preferred frontline therapy for fit patients with CLL who are older than 65 years, and the updated results from the CLL10 study reinforces that BR is an appropriate therapy to choose for these patients. As there was no statistically significant difference in PFS in these older patients, there is not a sufficiently meaningful improvement to justify the extra toxicity of the FCR regimen. We can also start to extrapolate from these data and consider BR as an alternative therapy for patients who have a history of infection or who are considered at higher risk of infection, as suggested by the authors. BR may also be an alternative in younger patients who are less fit, although this was not tested in this study and could not be confidently concluded from these results. Based on my experience in lymphoma patients, the use of BR in patients with renal dysfunction appears to be safer than with fludarabine-based treatments. For this reason BR may also be preferred over fludarabine-based treatments for CLL patients with renal impairment.
To date, several therapies for the frontline treatment of CLL have demonstrated efficacy and safety in CLL patients who cannot tolerate FCR therapy. Results from the CLL10 trial presented at ASH 2014 show that BR has similar efficacy and better tolerability than FCR in fit patients who are older than 65 years, suggesting it should be the preferred regimen in this population of patients. As several other novel agents are being investigated in clinical trials, both as monotherapy and in combination with current chemoimmunotherapy regimens, it will be interesting to see how these new therapies will change the CLL treatment landscape by providing additional treatment options for patients with a variety of fitness levels and for those with higher risk disease.


Despite significant advances in treatment over the past decade, chronic lymphocytic leukemia (CLL) remains incurable, with patients requiring multiple treatments over the course of the disease. In the relapsed setting, there is a higher probability that patients will have trouble with treatment-related toxicities, as they are typically older, have more comorbidities, and their disease has progressed. Additionally, compared to treatment in the first-line setting, fewer patients respond to currently available therapy, and the depth and duration of response is often decreased. This highlights the need for additional therapeutic options that are not only effective in this population of CLL patients, but also have low or manageable associated toxicities. There also remains a need for effective treatments in both the first-line and relapsed settings for patients with high-risk disease. These include patients with deletions of chromosome 17p [del(17p)], patients with multiple cytogenetic abnormalities, and patients with bulky disease. Several studies evaluating the safety and efficacy of ibrutinib in patients with relapsed CLL were presented at the American Society of Hematology (ASH) Annual Meeting in 2014, and provide support for the use of this novel agent in these relapsed and high-risk patients.

The long-term efficacy and safety results, from the phase III RESONATE™ trial comparing ibrutinib with ofatumumab in previously treated patients with CLL were presented by Brown et al. All patients in this study had relapsed or refractory CLL, including many patients with high-risk features who typically respond poorly to standard treatments. For instance, 57% of patients had advanced stage disease, 32% had del(17p), and 71 of 298 patients presented with three or more cytogenetic abnormalities. Patients were also heavily pretreated, with 49% having received three or more prior therapies. In addition, the population in this study was older than typically seen in clinical trials, with 40% of patients being older than 70 years. Together, these patient characteristics are representative of the relapsed/refractory patients I see in practice.

Although the median follow-up time of the ibrutinib arm was only 16 months, this trial showed important progression-free survival (PFS) and overall survival (OS) results. The investigator-assessed median PFS was 8.1 months in the ofatumumab arm, which is approximately the expected PFS for this population of patients, while the median PFS was not reached in the ibrutinib arm. This result was statistically significant, with a hazard ratio of 0.106 and a p-value of less than 0.001. As superior results were achieved in the ibrutinib arm, an independent data safety monitoring board mandated that patients treated with ofatumumab cross over to the ibrutinib arm if they developed progressive disease. OS was significantly better in the ibrutinib arm than in the ofatumumab arm, with 18-month OS rates of 85% and 78% respectively, despite 61% of patients in the ofatumumab arm having crossed over and been censored at that time. The overall efficacy results for ibrutinib compare favourably to ofatumumab and are independently good in comparison to other approved therapies for relapsed/refractory CLL in Canada.
making the results from this trial clinically meaningful.

The overall response rate (ORR) was significantly higher in the ibrutinib arm than in the ofatumumab arm. In the ibrutinib arm, most patients experienced a transient increase in blood lymphocyte counts early on in treatment that frequently resolved with continued ibrutinib treatment. This pattern of lymphocytosis is commonly seen with ibrutinib and other B-cell receptor pathway inhibitors, and it is caused by the redistribution of cells from the marrow and lymph nodes to the peripheral blood. The early development of lymphocytosis does not appear to be clinically significant, and it had no impact on ORR or PFS in this trial; however, it is important that physicians are aware of this pattern.

With regard to safety, the adverse events (AEs) experienced with ibrutinib were fairly predictable, based on what was already observed in phase II clinical trials, and manageable. The most common AE experienced with ibrutinib was diarrhea, which was mostly low-grade and occurred early in treatment, as very few patients had late-onset diarrhea. Neutropenia was the most common grade 3/4 AE, occurring in 18% of patients. Bleeding AEs occurred in 48% of patients treated with ibrutinib, the vast majority being grade 1 or 2, with 3% of patients experiencing grade 3 or 4 events. In addition, atrial fibrillation occurred in a small percentage of patients treated with ibrutinib (7%), but prior medical history of atrial fibrillation was reported more frequently for ibrutinib (5.6%) than ofatumumab (2.6%).

Results from the RESONATE™ trial demonstrate that ibrutinib was efficacious in all patients and is particularly promising in those with high-risk features; particularly promising in those with high-risk features; in the ibrutinib arm, most patients experienced a transient increase in blood lymphocyte counts early on in treatment that frequently resolved with continued ibrutinib treatment. This pattern of lymphocytosis is commonly seen with ibrutinib and other B-cell receptor pathway inhibitors, and it is caused by the redistribution of cells from the marrow and lymph nodes to the peripheral blood. The early development of lymphocytosis does not appear to be clinically significant, and it had no impact on ORR or PFS in this trial; however, it is important that physicians are aware of this pattern.

Safety results in this trial were similar to the RESONATE™ trial, with diarrhea (36%) and fatigue (31%) of any grade commonly reported, and in a smaller fraction of patients, atrial fibrillation of any grade (8%) and hemorrhage (5%; all grade 2 or 3) were reported. More information is needed to better understand, predict, and best manage bleeding and atrial fibrillation events, and it will be important to educate patients and physicians about the risk of these AEs. In order to minimize some of the AEs that occur during treatment, the dose modifications recommended in the product monograph should be followed. Additionally, although this was not discussed in the abstract, there are a number of important drug interactions with ibrutinib. Therefore, when using ibrutinib in patients taking concomitant medications, modifications to these medications must be considered.

Another valuable analysis of the phase III RESONATE™ study by Barrientos et al. reported measures of patient well-being, including hematologic, immunologic, and quality-of-life parameters.4 Overall, this was a very interesting analysis as it suggests that ibrutinib is not only effective in treating patients with relapsed or refractory CLL, but it is also well tolerated and results in improved patient and disease outcomes. This study reported sustained improvements in hemoglobin, platelets, and absolute neutrophil counts in patients in the ibrutinib arm with any baseline cytopenias. Overall, improvement in blood counts occurred in more patients in the ibrutinib arm than the ofatumumab arm (80% vs. 45% of patients with baseline cytopenias; p <0.0001). Patients in both the ibrutinib and ofatumumab arms also experienced significant increases in other immune cells, including CD4+ and CD8+ T cells, and Natural Killer cells, and a significant decrease in B cells. There is overall immune dysregulation in CLL, and over time, the majority of patients will have low immunoglobulin levels, which may be exacerbated by certain therapies. In the ibrutinib arm, no significant decreases in serum immunoglobulins were observed during follow-up. This is an important finding because the consequence of a decrease in immunoglobulins is an increase in the risk of infection.

Patient-reported outcomes are another important piece
of data when assessing ibrutinib. Overall, patients reported improvements in outcomes that are important to them, including fatigue. In this trial, more patients in the ibrutinib arm than in the ofatumumab arm had clinically meaningful improvement in fatigue based on the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F; increase of ≥3 points) and the European Organization for Research and Treatment of Cancer (EORTC) Fatigue Subscale Score. Another important disease-related outcome was the measure of hospitalizations in the first 30 days of treatment, which occurred less frequently in the ibrutinib arm than in the ofatumumab arm. Growth factor usage after day 30 also occurred less frequently with ibrutinib than ofatumumab, signaling an improvement in blood counts with ibrutinib treatment.

This study measuring patient well-being suggests that ibrutinib will be a dominant strategy not only for the control of CLL, but also in terms of improving other parameters such as quality of life. I look forward to seeing the final published results of this study with more comparative data. As 61% of patients in the ofatumumab arm crossed over to the ibrutinib arm in this study, this may have decreased the power to show statistically significant improvements between arms in this analysis.

Given the results of these studies together, ibrutinib has proved to be highly effective in patients with relapsed CLL and has a manageable toxicity profile. Ibrutinib is a desirable therapeutic option for relapsed CLL patients who are not likely to have a good response to standard chemotherapies. This includes patients who received a strong chemoimmunotherapy upfront, such as fludarabine plus rituximab or fludarabine and cyclophosphamide plus rituximab, and had a duration of response of less than three years. In these patients, switching to another chemoimmunotherapy may be suboptimal; therefore, ibrutinib would be a suitable option for these patients. It will also be important to utilize ibrutinib in high-risk CLL patients, especially if they have relapsed and their disease has progressed. I feel comfortable using ibrutinib in patients that I think would benefit from this agent. With the recent approval of ibrutinib by Health Canada for patients with CLL who have received at least one prior therapy, including those with del(17p), it is expected that hematologists will look at the current evidence and work with local and provincial agencies to try to gain access to ibrutinib for patients who need it. This is a very exciting time in terms of expected advances in our ability to manage CLL. There are a number of novel agents in clinical trials with promising results. I am hopeful that future therapies will provide improved responses to treatment, prolonged treatment-free intervals and better quality of life for patients with CLL, while also having less expected toxicity than that of current therapies.


Canadian Perspective by Dr. Cynthia Toze — The Use of Bendamustine Plus Rituximab in Relapsed CLL

Chronic lymphocytic leukemia (CLL) is a disease where the optimal type and order of treatment have not been determined in the relapsed setting. When determining which treatment regimen to use in this setting, we consider multiple factors, including age, fitness, comorbidities, prognostic markers, and first-line therapies.

In British Columbia (B.C.), from 2004 to 2013, the median age of patients with CLL who ever required treatment was 62 years (range: 25–97 years) in our database, including all CLL patients who had fluorescence in situ hybridization (FISH) testing. In the CLL patient population requiring therapy, in order to determine fitness we take a history, do a physical exam, look at performance status (e.g., Eastern Cooperative Oncology Group score), and review laboratory data, including blood counts, creatinine clearance, and liver function tests. Comorbid illness also needs to be considered. Possible comorbidities in this patient population include hypertension, cardiac abnormalities (e.g., atrial fibrillation), and adult-onset diabetes. While renal dysfunction is uncommon, it is important when consid-
ering treatment options (e.g., fludarabine cannot be given to patients with impaired renal function) and whether dose adjustments are required.

In addition to comorbidities, patients with relapsed CLL are also predisposed to hematological toxicities, particularly patients who have low blood counts prior to starting therapy. Knowing the cause of low blood counts may impact treatment decisions. Management is different for patients with autoimmune cytopenias compared with those with marrow that is packed with CLL. In the relapsed setting, we also look at prognostic markers, which are similar to those used upfront and include cytogenetics by FISH. In addition, a deep response (e.g., complete remission) and a prolonged response to first-line therapy suggest a patient will likely do well with their next treatment regimen unless there is a new, concerning FISH abnormality such as deletion 17p [del(17p)], del(11q), or transformation.

In B.C., if patients progress following a long duration of response to their first-line treatment we may repeat the same regimen. However, in many cases we may elect to use bendamustine plus rituximab (BR) once the patient has progressed, especially if the duration of response to the first-line therapy was suboptimal. In the relapsed setting, BR has been shown to be well tolerated in patients of a variety of ages and in patients with comorbidities.

The rationale for using BR in the relapsed setting comes from the phase II trial by Fischer and colleagues in the German CLL Study Group.1 This study looked at the safety and efficacy of BR in patients with relapsed and/or refractory CLL. The overall response rate was 59.0%, which was a good response rate in this group of patients. In fludarabine-refractory and fludarabine-sensitive patients, the overall response rates were 45.5% and 60.5%, respectively. Patients in the study with del(11q) as well as patients with other abnormalities, did fairly well. Patients with del(17p) by FISH did not do as well as others. The median event-free survival was 14.7 months. In terms of adverse events (AEs), severe infections occurred in 12.8% of patients, which was not unexpected given these patients are already immunocompromised. Grade 3 or 4 AEs included neutropenia, thrombocytopenia, and anemia that occurred in 23.1%, 28.2%, and 16.6% of patients, respectively. Again, we expected these hematologic toxicities in this group of patients when treating with chemotherapeutic agents.

Similar to the protocol used in the Fischer study, the B.C. protocol for relapsed patients is bendamustine at 70 mg/m² on days 1 and 2, which may be combined with rituximab if appropriate, given every 28 days for a maximum of six cycles. We like to start at the lower dose of 70 mg/m², which is fairly well tolerated in the relapsed setting, in order to get an idea of how the patient is responding. If they are doing well, then we would consider escalating the dose up to 100 mg/m², if tolerated.

If patients had terrible performance status, significant renal impairment, or hepatic impairment, they would not receive any type of intravenous chemotherapy, including BR. Other patients that we would not treat with BR in the relapsed setting are those with del(17p), where BR has not been shown to be effective. Also, as per the B.C. protocol, patients with creatinine clearance less than 40 mL/min, aspartate transaminase or alanine transaminase greater than 2.5 times the upper limit of normal (ULN), or total bilirubin greater than 1.5 times the ULN would not be treated with BR.

Treatment for patients with relapsed or refractory CLL is likely going to change as targeted agents and newer antibodies are coming down the pipeline. Some agents of interest when used in combination with bendamustine are ofatumumab, obinutuzumab, and ibrutinib. Results of the Helios trial, which is a phase III, randomized, double-blind, placebo-controlled trial evaluating the role of ibrutinib in combination with BR in previously treated CLL/SLL patients, will be of interest and will be presented at ASCO this year. We will have to look closely at the results of upcoming clinical trials to make decisions on which combinations to use, and in which order, to provide optimal treatment for our patients.

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

Dr. Knauf: With standard chemoimmunotherapy, we are currently able to achieve very high overall response rates (ORRs) of around 95%. However, despite improvements in response, there is no plateau in progression-free survival (PFS), and we continue to see a continuous decline in survival. A major goal of treatment should therefore be to prolong PFS; this is of utmost importance to patients as it increases the time off treatment without symptoms. In addition, progress is being made in identifying genetically or immunologically defined subgroups of patients who respond differently to treatment. There is therefore a need for personalized treatment that is tailored according to the needs and wishes of individual patients.

New Evidence: What are the factors you consider in making treatment decisions for patients with CLL?

Dr. Knauf: There are two main considerations used to make treatment decisions: these include disease-related and patient-related factors. Disease-related factors include cytogenetics, the speed at which the disease is progressing, and the stage of the disease. Patient-related factors include comorbidities, biological age, defining natural life expectancy, and the wishes of the patient. For example, we will not eradicate the disease in a patient who is 85 years old; however, treatment goals may be different in a younger patient. The examination of factors such as deletion of chromosome 17p [del(17p)], TP53 mutations, del(11q), lymphocyte doubling time, B-symptoms, and obstructive lymphadenopathy is being seen as increasingly important in clinical practice.

New Evidence: In clinical practice, what percentage of patients is eligible for treatment with fludarabine, cyclophosphamide, rituximab (FCR)?

Dr. Knauf: It is important to note that when looking at the entire patient population with CLL, there is a significant portion of patients who do not currently need treatment. When restricting patients to those requiring treatment, around 25% to 30% are eligible for FCR. We currently use the Cumulative Illness Rating Scale (CIRS) to identify patients eligible for FCR; however, there is no international consensus on how to measure patient fitness. The CIRS is a reasonable method in which to measure patient fitness, but it is fairly subjective and based mainly on clinical experience. The modified version of the CIRS is more suitable for use in this patient population.
**New Evidence:** What are the issues with using fludarabine-based regimens for the treatment of CLL?

**Dr. Knauf:** There is a high risk of infections with the use of fludarabine-based regimens, even long after completing treatment. We know from the CLL10 study that there is an increased risk of infections with FCR, even six months after completion of treatment. These infection risks are higher than those seen with chlorambucil or bendamustine-based regimens. In addition, there is a high proportion of patients over 70 years who have chronic lung disease and diabetes and are at high risk of serious infections. Fludarabine-based regimens should also not be used in patients with decreased kidney function. Therefore, patients with these comorbidities are not the best candidates for FCR.

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**New Evidence:** What treatment options would you consider in patients who would not be able to tolerate FCR?

**Dr. Knauf:** In Germany, our registry data shows that around 70% of patients with CLL are treated with bendamustine plus rituximab (BR). From these data, we know that only 5% of patients receive chlorambucil and around 25% of patients receive FCR or low-dose FCR (FCR-Lite). I do not use FCR or FCR-Lite in many patients and mainly use these regimens in clinical trials. Even in very fit patients, I prefer to give BR to most patients and would only consider FCR for those with unmutated immunoglobulin heavy chain variable (IGHV) status. Even for patients with unmutated IGHV status, we need to consider the toxicity and the high risk for secondary malignancies with FCR.

If BR is used initially, the patient is subjected to lower toxicity and there are a lot of treatment alternatives available that can be used three to four years later when they relapse. In the majority of cases, patients can be retreated with BR at relapse, whereas FCR seldom can be given again to patients once they have relapsed.

There is a small population of patients who are frail or who do not want to receive intravenous (iv) infusions; in these patients, I would give chlorambucil or obinutuzumab plus chlorambucil. However, it should be taken into account that for obinutuzumab plus chlorambucil, the PFS is historically similar to that of bendamustine monotherapy. I would also not add obinutuzumab to chlorambucil in a frail patient with known pronounced allergic disposition, given possible severe infusion-related reactions. Finally, it is difficult to monitor patients given chlorambucil as monotherapy; these patients might have comorbidities and could be taking other interacting medications that cannot be adequately monitored. Ultimately, if a patient is fit enough to tolerate rituximab, I assume they should be able to tolerate bendamustine. Alternatively, they can be given a reduced dose of bendamustine (i.e., 50% to 70% of the standard dose) in combination with rituximab (BR Lite), thus providing an attractive treatment option in these patients.

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**New Evidence:** Please describe your recently published German registry study.

**Dr. Knauf:** The data registry in Germany includes around 5,000 patients with lymphatic neoplasias. Within this group of patients, we identified those with CLL and compared those given BR to those given FCR. Given this was a registry study, data were collected prospectively and patients were not randomized. Those treated with BR were around eight years older than those treated with FCR. In addition, the mean Charlson Comorbidity Index score was higher for patients treated with BR, meaning these patients were less fit than those in the FCR group. Results of our study showed ORRs and complete response (CR) rates were similar between groups and, after adjusting for age, PFS and OS curves were superimposable.

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**New Evidence:** Why do you think BR is used most frequently in Germany?

**Dr. Knauf:** Bendamustine is used very frequently in Germany because physicians have been using it for over fifty years and are therefore familiar with how to use it. It is also easy to administer, well tolerated, and has proven to be efficacious in patients with CLL. Given that rituximab has become a backbone in the treatment of CLL, we usually give bendamustine with rituximab. Bendamustine monotherapy is only given when there is a known allergic disposition to rituximab or to those patients with serious infusion-related toxicities. If I did not have access to BR, I would still give bendamustine monotherapy in preference to FCR to most patients, given that I do not see many young and fit patients with CLL.
New Evidence: The results of the CLL10 trial were presented at the ASH 2014 Annual Meeting. Please provide your perspective on the data from this study.

Dr. Knauf: Results of the CLL10 study demonstrated superior PFS for FCR versus BR (median of 55.2 months vs. 41.7 months; HR = 1.626, \( p < 0.001 \)). There was no difference in the survival curves between groups, with differences in outcomes shown only for PFS in younger patients. In addition, it is important to note that the median age of patients with CLL at first-line treatment is between 72 to 74 years. In the CLL10 study, the median age was 61 years; this trial is therefore not representative of the general population.

In addition, FCR proved to be more toxic than BR, with greater rates of neutropenia and infection; these results are in line with what we see in clinical practice. Although I was surprised by the high infection rate in the FCR arm, a significant proportion occurred after treatment and after a longer follow-up. Therefore, the immunosuppressive effect of FCR must be longer than that of BR, which can be explained by the immunosuppressive effects of cyclophosphamide. We also observed late-onset cytopenias with FCR due to stem cell damage, which may be linked to the higher rate of secondary myelodysplastic syndrome that occurs after fludarabine-based regimens. The negative effect of fludarabine on T cells may also explain the higher infection rate with FCR.

Given the late-onset infections that occur with FCR, we should monitor patients for a longer duration following treatment. It is also important to use antibiotic prophylaxis, which was not part of the protocol in the CLL10 study. In patients with compromised lung function or a history of infections, it is of particular importance to give antibiotics as prophylaxis. I would also consider giving granulocyte colony-stimulating factor (G-CSF) on a case-by-case basis after the first cycle of FCR. Conversely, in patients treated with BR, I do not generally use prophylactic antibiotics or G-CSF.

Given the fact that the patients in the CLL10 study were younger than the typical CLL patient population and considering the greater toxicity of FCR, it is not correct to conclude that FCR should be given in preference to BR. The CLL10 results have therefore not changed my practice as I continue to give BR in preference to FCR to the majority of patients with CLL. Despite recent results from the CLL10 study, the use of FCR continues to decline rapidly in our registry. Therefore, in clinics, hematologists appear to interpret the CLL10 results differently than the scientific community. It is therefore more accurate to conclude that FCR is a treatment option, but it should not be considered the standard of care in these patients.

New Evidence: How do you see the treatment of CLL evolving, given the new agents on the horizon?

Dr. Knauf: There are three new agents that show promise in the treatment of CLL; these include ibrutinib, idelalisib, and ABT-199. Although these agents are exciting, CR rates are low, demonstrating the continuing need for classic chemotherapy. To overcome the low CR rates, we could start by treating with BR or FCR and then give one of these new agents as consolidation or maintenance. To examine this strategy, we are conducting a study that includes the use of BR in a debulking phase, followed by consolidation and maintenance with ABT-199.

Another promising agent is obinutuzumab, which has proven efficacy when combined with chlorambucil. There is a need to examine obinutuzumab in combination with agents other than chlorambucil to determine whether it should be used in preference to rituximab when combined with chemotherapy. We are currently examining obinutuzumab in combination with the investigator’s choice of chemotherapy backbone; in this trial, there are 80 patients being treated with obinutuzumab plus bendamustine.
New Evidence: What are the key unmet needs in the treatment of chronic lymphocytic leukemia (CLL)?

Dr. Wendtner: Despite recent improvements to treatment, there is currently no cure for CLL and prognosis remains poor in certain subgroups of patients. These subgroups include those with high-risk cytogenetics, such as deletion of chromosome 17p [del(17p)], TP53 mutations, and complex karyotypes. Elderly patients, those with comorbidities, and those refractory to fludarabine also tend to demonstrate poor outcomes to available treatments. New options are therefore needed to improve the outcome for these patients.

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

Dr. Wendtner: In both clinical trials and in community practice, I use the Cumulative Illness Rating Scale (CIRS) to determine patient fitness. Although the CIRS is not the ideal tool for this setting, it can be done quickly and provides some consistency across patients. The modified version also takes into account the number of dysfunctions per organ, as well as the number of organs with dysfunctions. The CLL10 study used this modified version of the CIRS and included patients with a score of 6 or less in the study. Other tools can also be used to determine patient fitness, such as the Eastern Cooperative Oncology Group (ECOG) performance status assessment. Overall, no matter what tools are used to determine fitness, the most important factor to consider is renal function. In clinical practice, around 10% to 20% of patients are considered to be very fit and are therefore eligible for treatment with fludarabine, cyclophosphamide, rituximab (FCR), based on the CIRS.

New Evidence: Please describe the rationale and design of the CLL10 study.

Dr. Wendtner: Given the need for new treatment options with improved efficacy and safety, the CLL10 study compared bendamustine, rituximab (BR) to the standard treatment, FCR, in the frontline setting. Overall, baseline characteristics were well matched between groups. However, there were more elderly patients and more cases of unmutated immunoglobulin heavy chain variable region (IGHV) in the BR arm.
**New Evidence:** Please describe the efficacy results of the study.

**Dr. Wendtner:** Although overall response rates were identical in both groups, more of the patients treated with FCR attained complete response and minimal residual disease negativity than those treated with BR. In addition, the median progression-free survival (PFS) was significantly longer in patients treated with FCR compared to BR (55.2 months vs. 41.7 months; HR = 1.626; \(p < 0.001\)). Although there was no difference in overall survival between groups, longer follow-up duration would generally be needed to detect a difference.

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

**Dr. Wendtner:** Results of the CLL10 study demonstrated very high rates of grade 3/4 neutropenia with FCR (84.2% FCR vs. 59.0% BR; \(p < 0.001\)) that were even higher than those seen in the CLL8 study. These rates of neutropenia remained high even 12 months after treatment and translated into higher grade 3/4 infection rates with FCR versus BR (39.1% vs. 26.8%; \(p < 0.001\)).

Per cycle, dose reductions were more frequent in the BR arm; however, we were able to give the full six cycles in this arm. With FCR we were able to use the full dose, but we were not able to use it for as many cycles. In regards to long-term toxicities, there was a trend for more cases of secondary acute myeloid leukemia and myelodysplastic syndrome for FCR (n = 6) versus BR (n = 1); however, this difference was not statistically significant.

**New Evidence:** Please describe the efficacy and safety results in patients older than 65 years.

**Dr. Wendtner:** After stratifying efficacy results by age category we saw no difference in PFS between groups in patients older than 65 years (not reached FCR vs. 48.5 months BR; \(p = 0.170\)). In regards to safety results, there was a doubling of infection rates with FCR, with 47.7% of patients older than 65 years experiencing grade 3 or 4 infections with FCR versus 20.6% with BR (\(p < 0.001\)). In addition, elderly patients experienced greater dose reductions and discontinuation rates with FCR, with a median of four cycles given of FCR compared to six cycles of BR. Given these results, it is clear that FCR is too toxic for elderly patients and BR should be the preferred treatment in these patients.

**New Evidence:** Given the results of this study, in which patients would you currently recommend giving BR as first-line treatment?

**Dr. Wendtner:** In fit patients younger than 65, I would still give FCR upfront, given that we can expect cure rates over 80% in these patients. Previous to the CLL10 study, we would also give FCR to fit elderly patients (>65 years of age). However, given the CLL10 results, we would now give a full dose of BR to patients older than 65 years of age and would consider reducing the dose as needed. The difficulty now is to determine when to give this reduced dose of BR versus giving obinutuzumab plus chlorambucil. Chlorambucil is given orally and is therefore difficult to use in the elderly, who cannot be easily monitored for compliance. If quick control over the disease is needed, BR is also the better option as it takes four to six weeks for chlorambucil to work. However, there may be a place for chlorambucil plus an antibody in very frail patients.

**New Evidence:** How have results of the CLL10 study impacted the updated German CLL guidelines and future clinical trials?

**Dr. Wendtner:** The updated German treatment guidelines for CLL still recommend use of FCR in fit patients younger than 65 years. For fit patients older than 65 years, the guidelines now recommend using BR. These recommendations have influenced the design of upcoming clinical trials. For example, the CLL13 trial will give FCR or BR based on an age cut-off of 65 years. In addition, combining new drugs will be easier with a less toxic backbone like BR rather than FCR. For example, BR plus ABT-199 or ibrutinib will be much less toxic than adding these agents to FCR.
An Interview with Dr. Susan O’Brien on the RESONATE™-17 Study

At the ASH 2014 Annual Meeting, New Evidence spoke with Dr. Susan O’Brien, Professor in the Department of Leukemia at the University of Texas, MD Anderson Cancer Center in Houston, Texas, about results from the RESONATE™-17 study examining the safety and efficacy of ibrutinib for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) in patients with chromosome 17p deletion [del(17p)].

New Evidence: What are the key unmet treatment needs for patients with CLL?

Dr. O’Brien: There are certain groups of patients that achieve long remissions following chemoimmuno-therapy, such as those with immunoglobulin-heavy chain variable (IGHV) mutations. We are currently collecting minimal residual disease (MRD) data to determine whether a cure is possible for these patients. However, although those without the IGHV mutation may experience several years of remission, there is no suggestion of a plateau in survival curves in this patient group. In addition, in the subgroup of patients without IGHV mutations, those with del(11q) or del(17p) experience even shorter progression-free survival (PFS). More effective treatment options are therefore needed for patients without IGHV mutations. In addition, there is a need for more effective treatments in the relapsed setting, where achieving complete responses (CRs) is more challenging. In patients with del(17p), outcomes in the relapsed setting are particularly dire, with a median survival of less than two years.

Ibrutinib is a once-daily orally administered breakthrough therapy that inhibits the Bruton tyrosine kinase (BTK) enzyme. In the relapsed setting, phase II studies have demonstrated a median PFS of 28 months in patients with del(17p). This is a fantastic outcome, given that standard frontline therapies only achieve a PFS of 11 to 12 months in these patients.

New Evidence: Recent evidence suggests that ibrutinib is effective in a wide range of patients. Given the current standard approaches to treatment, what have studies to date told us about the treatment of patients with del(17p)?

Dr. O’Brien: Unfortunately, standard treatment options, such as the combination of fludarabine, cyclophosphamide, rituximab (FCR), have not yielded positive outcomes for patients with del(17p). Given these findings, the U.S. Food and Drug Administration (FDA) gave ibrutinib accelerated approval for the upfront treatment of patients with del(17p). This decision was based on data using ibrutinib in the relapsed setting, which was even stronger than outcomes using standard agents in the front-line setting. Health Canada has also approved ibrutinib in the frontline setting in patients with del(17p).
**New Evidence:** Please describe the mechanism of action of ibrutinib.

**Dr. O’Brien:** We know that if you ligate the B-cell receptor (BCR), you will provide a strong proliferative signal to the cell; interfering with this signal is therefore beneficial in treating CLL. BTK is one of the enzymes in this pathway that is inhibited by ibrutinib. Treatment with ibrutinib results in a reduction in the size of lymph nodes by preventing adherence to the stroma and forcing cells into circulation where they die off over time. A preliminary increase in lymphocyte count is seen in some patients when treated with BCR inhibitors (such as ibrutinib and idelalisib), combined with a reduction in the size of lymph nodes. This phenomenon of the increase in lymphocytosis was initially thought to represent drug resistance, but is now known to be a sign of treatment response. It is therefore important that physicians recognise this pattern and understand that it is consistent with a response.

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**New Evidence:** Please describe the design and rationale of the RESONATE™-17 study.

**Dr. O’Brien:** There is currently an unmet need in CLL patients with del(17p) for effective treatment options. Given this unmet need, we initiated a phase II study examining the efficacy and safety of ibrutinib in relapsed and refractory patients with del(17p). Patients were given ibrutinib (420 mg per day) orally until unacceptable toxicity or progression. The primary analysis was conducted 12 months following inclusion of the last patient.

One of the goals of the study was to obtain accelerated approval of ibrutinib in a broader group of patients, including those with del(17p). However, as this study was in progress, the FDA gave approval for the frontline treatment of patients with del(17p) based on the phase II trial of all relapsed patients. This is the first time I have seen the FDA give approval in the upfront setting based on data obtained only in the relapsed setting, which is an amazing outcome.

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

**Dr. O’Brien:** The median age of patients included in the study was 64 years, 48% of whom were 65 years or older, and they had received a median of two (range: 1–7) prior therapies. This was therefore a group of patients with a poor prognostic outcome. However, it is important to note that the presence of del(17p) is a more important prognostic factor than any other baseline characteristic. Given that these patients had del(17p), they were at a significant disadvantage in terms of treatment outcome.

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

**Dr. O’Brien:** This was the largest study conducted in patients with del(17p) specifically. The overall response rate (ORR) was 82.6% and included 17.4% partial responses with lymphocytosis. CRs, including those with incomplete bone marrow recovery (CRi) were reported in three patients. At a median follow-up of 13 months, the median PFS and duration of response (DOR) had not been reached. At 12 months, 79.3% were alive and 88.3% of responders were progression-free. Given that standard frontline therapies for these patients, such as FCR or alemtuzumab, only achieve a PFS of 11 to 12 months, results of the current study are extremely promising.

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

**Dr. O’Brien:** The most frequently reported adverse events (AEs) were diarrhea, fatigue, cough, and arthralgia. However, these were easily managed and were consistent with those seen in previous studies. Atrial fibrillation was reported in a total of 11 patients, 3.5% of which were grades 3 to 4. In clinical practice, we examine vital signs at each visit; however, initial screening for this would not be necessary as patients would experience and report symptoms if they experienced this side effect.
**New Evidence:** Given the results of this and previous studies, in which patients would you use ibrutinib if it were available?

**Dr. O’Brien:** Ibrutinib can be used in a wide range of patients for the treatment of CLL. It is important to screen patients for del(17p) prior to making treatment decisions in both the upfront and relapsed settings. I would use ibrutinib in any patient with del(17p), in either of these settings. It would also be reasonable to use ibrutinib in patients with TP53 mutations, even though this would technically be considered off label. I would also consider giving ibrutinib upfront to patients with unmutated IGHV and to those with del(11q). Finally, it would be reasonable to use ibrutinib in elderly patients, given that it has a good safety profile. Results of a study comparing ibrutinib to chlorambucil in elderly patients may result in approval in this setting. It may be useful to combine ibrutinib with an anti-CD20 antibody such as ofatumumab, rituximab, or obinutuzumab. Adding an antibody may result in deeper and faster remissions, especially where lymphocyte counts are initially high.

In young and fit patients with mutated IGHV, FCR remains the best treatment option; however, we might consider reducing the total number of cycles by adding ibrutinib for these patients. This is one strategy being considered as part of a clinical trial at the MD Anderson Cancer Center to reduce myelosuppression and potential long-term toxicities such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). A potential combination for this approach would be FC plus obinutuzumab and ibrutinib for a total of three cycles, with additional obinutuzumab combined with ibrutinib, depending on MRD status.

**New Evidence:** With the advent of new therapies like ibrutinib, what will be the role of allogeneic stem cell transplantation (ASCT)?

**Dr. O’Brien:** Previously, we would have recommended ASCT in young/fit patients with del(17p) after first remission. With the availability of ibrutinib, we would no longer move to ASCT in these patients. The role of transplantation is therefore expected to diminish over time as future patients with del(17p) are treated upfront with ibrutinib. However, if a patient relapsed while on ibrutinib, I would still recommend transplantation as there is little data on cross-resistance from one BTK inhibitor to another.

**New Evidence:** Overall, what are the advantages of an agent like ibrutinib for the treatment of CLL?

**Dr. O’Brien:** The main advantage of ibrutinib is that it has an excellent safety profile. Given that patients are generally immunosuppressed due to their disease, standard chemoinmunotherapy often results in additional myelosuppression and infections. Given that ibrutinib is not myelosuppressive and in fact improves cytopenias, this is a tremendous advantage. In addition, ibrutinib has very few direct side effects and is well tolerated by most patients.

Another advantage of ibrutinib is its effectiveness in patients with del(17p). In the frontline setting, approximately 5% to 10% of patients have this deletion, which increases to 30% to 50% in the relapsed setting. In the relapsed setting, studies show ibrutinib is far more effective for these patients than standard treatments. In patients with mutated IGHV, where 10-to-12–year remission times are possible, the value of ibrutinib is less clear. However, a small phase II trial in patients greater than 65 years old shows only one patient progressing after ibrutinib at three years. In addition, other trials are comparing bendamustine, rituximab (BR) and FCR to ibrutinib. Results of these trials will further determine the usefulness of ibrutinib in other patient groups with CLL.
TREANDA is indicated for treatment of patients with relapsed indolent B-cell non-Hodgkin lymphoma (NHL) who did not respond to or progressed during or shortly following treatment with a rituximab regimen and for the treatment of patients with symptomatic chronic lymphocytic leukemia (CLL) who have received no prior treatment.

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

- Contraindication in patients hypersensitive to mannitol
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We have created an animated video aimed at helping children better understand cancer in the family and help them cope with the situation. If you think that this video could be helpful for your patient, it is located at http://www.lundbeck.com/ca/en/therapeutic-areas/oncology.
Acute Leukemias

Chemotherapy-Free or -Reduced Options Improve Treatment Outcome in Acute Promyelocytic Leukemia and Show Promise in Acute Myelogenous Leukemia

Despite significant advances in the treatment of acute promyelocytic leukemia (APL) and acute myelogenous leukemia (AML), there remains an unmet need. In APL, although all-trans retinoic acid (ATRA) in combination with anthracyclines has resulted in cure rates as high as 80%, exposure to anthracyclines is associated with a high frequency of hematological toxicity, as well long-term adverse events such as cardiotoxicity and secondary tumours.1 Furthermore, there is a need for more effective treatments in high-risk patients (white blood cell counts [WBC] >10 x10^9/L). In relapsed/refractory (R/R) AML, patients have limited treatment options, and typically have a poor prognosis and limited overall survival.

The past several years have witnessed significant advances that have addressed these unmet needs. The success of arsenic trioxide (ATO) plus ATRA in the relapsed setting has led the way to the phase III study by Lo-Coco et al., which showed that ATO in combination with ATRA was noninferior to idarubicin plus ATRA in the treatment of low-to-intermediate–risk APL patients (WBC ≤10 x10^9/L) in the front-line setting.2 In addition, this treatment was associated with a lower frequency of hematological toxicities. ATO has also improved the outcomes of high-risk patients treated with this agent during induction and consolidation using the Iland et al. protocol. The Iland et al. study showed that not only did the inclusion of ATO in induction and consolidation reduce the need for anthracyclines, but it also eliminated the need for high-dose cytarabine in high-risk patients.3

The success of chemotherapy-free or -reduced approaches is not limited to APL. Large molecules that target receptors, such as antibodies, and small molecules designed to inhibit intracellular proteins or signalling pathways have also changed treatment approaches, and in some cases have the potential to eliminate chemotherapy. One example of a small molecule inhibitor is the promising antiapoptotic BCL2 inhibitor venetoclax (ABT-199). Venetoclax is being investigated in the treatment of several cancers, including chronic lymphocytic leukemia (CLL), NHL, and AML. In AML, a recent phase II study in untreated patients unfit for chemotherapy and R/R patients showed that venetoclax was clinically active in these patient populations, a finding that supports further studies of this agent in this setting.4 The demonstrated activity of venetoclax in AML confirms an important role for BCL2 in AML, and is consistent with findings from other settings such as in CLL where BCL2 is also known to play an important role in the etiology of the disease.

At the American Society of Hematology (ASH) 2014 Annual Meeting, investigators presented studies on ATO in first-line APL, the use of hematopoietic stem cell transplantation (HCT) in relapsed patients with APL, long-term follow-up of patients treated with ATO plus ATRA, and the use of venetoclax in R/R AML. The following is a report on six presentations presented at ASH 2014:

- The updated results from the Italian-German APL0406 trial showed improved outcomes with ATRA plus ATO versus ATRA plus chemotherapy in non-high-risk APL.

- A study that investigated ATRA, ATO, and idarubicin as initial therapy for APL showed that incorporation of ATO during induction and consolidation allowed substantial reductions in total anthracycline exposure and eliminated the need for high-dose cytarabine in patients with high-risk disease.
• A long-term follow-up in patients with newly diagnosed APL treated with ATRA plus ATO showed that this combination therapy resulted in good long-term survival.

• A study on HCT as a salvage strategy for relapsed APL showed that autologous HCT has excellent long-term results in selected patients with a second complete response (CR).

• A study on survivorship in APL showed that patients with APL who maintained a CR for at least three years had a very low incidence of late relapse.

• A phase II study of venetoclax in patients with AML demonstrated clinical activity in heavily pretreated AML patients with limited treatment options.


Acute Promyelocytic Leukemia

Platzbecker U, et al. ASH 2014:12

Improved outcome with all-trans retinoic acid (ATRA) plus arsenic trioxide vs. ATRA plus chemotherapy in non-high-risk acute promyelocytic leukemia: updated results of the Italian-German APL0406 trial on the extended final series

Background

The combination of ATRA and arsenic trioxide (ATO) has recently been shown to be at least noninferior and possibly superior to standard ATRA plus chemotherapy (CHT) in the front-line management of patients with low/intermediate-risk APL. The results from the extended and final series of 276 patients (162 patients were in the previous report), with the last case being enrolled into the study in January 2013, were presented at ASH 2014.1

Study design

• This was a phase III, randomized, prospective trial (APL0406) initiated by the Italian GIEMME that included participation by the German Study Alliance Leukemia (SAL) and AML Study Group (AMLSG) multicentre groups.

• The study period was from October 2007 to January 2013, with 276 patients enrolled:
  - Patients enrolled between October 2007 and September 2010: n = 162;
  - Patients enrolled between January 2010 and January 2013: n = 114;
  - Eligible (genetically confirmed) patients: n = 270;
  - Patients evaluable for induction: n = 254.

• The study was designed to assess noninferiority between the groups at a margin of difference of 5%.

• The primary study objective was event-free survival (EFS) at two years.

• The secondary objectives included complete response (CR), overall survival (OS), and cumulative incidence of relapse (CIR) at two years, as well as the toxicity profile and kinetics of minimal residual disease.

• Eligible patients were newly diagnosed adults who were 18 years or older but under 71 years, had genetically confirmed, non-high-risk APL (white blood cell [WBC] ≤ 10 x 10⁹/L).

• Patients were randomized to receive either:
  - ATRA-ATO (n = 131): induction treatment with ATRA plus ATO (45 mg/m² ATRA plus 0.15 mg/kg of ATO daily until CR, after which ATO was given five days/week in a cycle of four weeks on four weeks off, for a total of four courses, while ATRA was given for two weeks on two weeks off, for a total of seven courses);²
  - ATRA-CHT (n = 139): Standard induction treatment with AIDA (ATRA plus idarubicin) followed by three cycles of anthracycline-based consolidation together with ATRA, and low-dose chemotherapy and ATRA given for maintenance.³
Key findings

- Baseline characteristics were similar between groups (ATRA-ATO vs. ATRA-CHT):
  - Median age, years: 46 vs. 46;
  - Risk, low/intermediate, %: 40/60 vs. 38/62.
- The median follow-up was 36.0 months (range: 1–75 months).
- Induction outcomes (ATRA-ATO vs. ATRA-CHT):
  - Number of patients: 122 vs. 132;
  - Achieved a CR, n (%): 122 (100) vs. 128 (97);
  - Deaths, n: 0 vs. 4;
  - No resistance occurred in either arm.
- The causes of induction deaths in the ATRA-CHT arm were ischemic stroke (n = 1, day 14), differentiation syndrome (n = 2, days 16 and 20), and bronchopneumonia (n = 1, day 28).
- Hematologic toxicity results are shown in Figure 1.
- Other toxicities (ATRA-ATO vs. ATRA-CHT):
  - QTc prolongation, %: 11 vs. 2 (p = 0.002);
  - Hepatic toxicity (grade 3/4), %: 62 vs. 6 (p <0.001);
  - These toxicities were managed with temporary discontinuation and dose modification of ATO.
- Post-induction outcomes (ATRA-ATO vs. ATRA-CHT):
  - Relapse, n: 2 vs. 10;
  - Death in CR, n: 1 vs. 4;

Figure 1. Hematologic toxicity
• The causes of death in CR were bronchopneumonia (n = 1 in each arm), hemorrhagic shock, pulmonary embolism, and secondary myelodysplastic syndrome (n = 1 for each in the ATRA-CHT arm).

• In the final series, EFS was 98% in the ATRA-ATO arm compared with 84.9% in the ATRA-CHT arm (p ≤ 0.001). (Figure 2)

• Results for secondary objectives in the final series (ATRA-ATO vs. ATRA-CHT):
  ◦ OS, %: 99.1 vs. 94.4 (p = 0.01); (Figure 3)
  ◦ Disease-free survival (DFS), %: 98 vs. 87.9 (p = 0.002); (Figure 4)
  ◦ CIR, %: 1.1 vs. 9.4 (p = 0.005). (Figure 5)

Figure 2. Event-free survival

![Event-free survival graph](image1)

Figure 3. Overall survival

![Overall survival graph](image2)
Key conclusions

- Compared with ATRA-CHT, ATRA-ATO resulted in significantly higher EFS, DFS, and OS.
- ATRA-ATO had higher anti-leukemic efficacy and significantly reduced hematologic toxicity.
- These results add support to ATRA-ATO as the new standard of care in non-high-risk APL.

In Supportive Care Oncology

Iland HJ, et al. ASH 2014:375

All-trans retinoic acid, intravenous arsenic trioxide, and idarubicin as initial therapy for acute promyelocytic leukemia

Background
The combination of all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy has traditionally been regarded as the gold standard for induction and consolidation in previously untreated acute promyelocytic leukemia (APL) patients, with arsenic trioxide (ATO) usually reserved for relapse. In an attempt to improve anti-leukemic efficacy while limiting reliance on anthracyclines for all risk categories of APL, the Australasian Leukaemia and Lymphoma Group (ALLG) incorporated ATO into an ATRA plus reduced chemotherapy backbone, and the results of an interim analysis with a median follow-up of two years have been published. Here, we report results of the protocol-specified final analysis, conducted when all surviving patients had been followed for at least two years after completion of consolidation.

Study design
• The APML4 treatment protocol:
  - Induction: ATRA (45 mg/m² days 1–36), idarubicin (12 mg/m² days 2, 4, 6, 8), ATO (0.15 mg/kg days 9–36), and prophylactic prednisone (1 mg/kg days 1–10), plus aggressive hemostatic support;
  - Consolidation: ATRA and ATO, continuous in cycle 1 and intermittent in cycle 2;
  - Maintenance: ATRA, 6-mercaptopurine, and methotrexate every three months for two years plus molecular monitoring by quantitative reverse transcriptase-polymerase chain reaction.
• The historical control for the APML4 trial was the APML3 trial that gave patients ATRA + idarubicin for both induction and consolidation, followed by maintenance with ATRA, 6-mercaptopurine, and methotrexate.

Key findings
• Between November 2004 and September 2009, 124 evaluable patients were accrued.
• Baseline patient characteristics (range):
  - Age, years: 44 (range: 3–78);
  - Median white blood cell count (WCC), x 10⁹/L: 2.4 (range: 0.1–85.8);
  - Median platelet count, x 10⁹/L: 22 (2–173);
  - Sanz risk category, n:
    - High: 23;
    - Intermediate: 67;
    - Low: 33;
    - Unknown: 1.
• Median follow-up in this final analysis was 4.2 years.
• There were 124 evaluable patients accrued between November 2004 and September 2009; there were four (3.2%) early deaths (up to day 36) and two withdrawals before hematologic complete remission (HCR) assessment.
  - Early deaths were due to myocardial infarction (n = 1, day 1), cerebral hemorrhage (n = 2, days 3 and 7), and seizures and cerebral edema (n = 1, day 30).
• Grade 3/4 non-hematological adverse events (AEs):
  - Differentiation syndrome in 14% of patients during induction, and frequent but reversible biochemical hepatic and gastrointestinal toxicity;
  - QTc prolongation >500 msec occurred in 14% of patients during induction, but there were no cases of ventricular arrhythmias or torsades de pointe;
  - Significant neurological and cutaneous toxicity were infrequent.
• Severe AEs were less common during the chemotherapy-free consolidation cycles, especially cycle 2.
• The frequency of grade 3/4 neutropenia was 100% during induction, 62% in consolidation cycle 1, and 27% in consolidation cycle 2; grade 3/4 thrombocytopenia only occurred during induction (100%), not during consolidation.
• HCR was achieved by 118 (95%) patients; there were two withdrawals in HCR and four in molecular CR (MCR).
• MCR was achieved by 116 (94%) patients.
• Disease-free survival (DFS) was 95% at eight years from a documented HCR. (Figure 1)
Event-free survival (EFS) was 90% and overall survival (OS) was 94% eight years from the start of ATRA therapy. (Figures 2 and 3)

Multivariate analysis:
- There were significant associations of ≥2 additional cytogenetic abnormalities ($p = 0.04$ for DFS) and age >70 years ($p = 0.0002$ for EFS, $p = 0.005$ for OS);
- Sanz risk category was correlated with EFS ($p [\text{trend}] = 0.003$) and OS ($p [\text{trend}] = 0.02$);
- There were no significant associations for WCC, FLT3 mutations, PML breakpoint, or PML-RARA after induction. (Table 1)
- The cumulative incidence of relapse at five years (± standard error of the mean) was 4.6% (± 2.0%) for all patients, 4.5%
(± 2.2%) for patients with WCC ≤10 x 10⁹/L, and 5.3% (± 5.1%) for patients with WCC >10 x 10⁹/L.

- Competing risks were relapse, death in remission, and failure to achieve MCR.

- When compared with the APML3 trial, APML4 was associated with substantial and statistically significant improvements in survival (APML3 vs. APML4):
  - DFS: 79% vs. 95% (HR = 0.21, 95% CI: 0.07–0.59, p = 0.001);
  - EFS: 72% vs. 90% (HR = 0.34, 95% CI: 0.16–0.69, p = 0.002);
  - OS: 83% vs. 94% (HR = 0.35, 95% CI: 0.14–0.91, p = 0.02).

- The significance of trial assignment was retained in multivariate analysis when APML3 and APML4 data were combined. (Table 2)

**Figure 2. Event-free survival**

**Figure 3. Overall survival**

**Table 1. APML4 multifactor analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reference Comparator</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤70</td>
<td>&gt;70</td>
<td>51.3 (8.48–311)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sanz risk category Low</td>
<td>Intermediate  High</td>
<td>18.9 (1.62–220)</td>
<td>0.003 (trend)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤70</td>
<td>&gt;70</td>
<td>31.5 (3.77–264)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sanz risk category Low</td>
<td>Intermediate  High</td>
<td>5.13 (0.39–67.9)</td>
<td>0.02    (trend)</td>
</tr>
<tr>
<td>DFS</td>
<td>Additional cytogenetic abnormalities 0–1</td>
<td>5.19 (0.87–31.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

WCC, FLT3 mutations, PML breakpoint, and PML-RARA after induction NS

**Table 2. APML3 plus APML4 multifactor analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comparator</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>Trial APML4</td>
<td>16.0 (4.74–53.9)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Sanz risk category   Intermediate</td>
<td>High</td>
<td>3.53 (1.07–11.6)</td>
<td>0.02 (trend)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>Trial APML4</td>
<td>13.9 (3.50–55.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sanz risk category   Intermediate</td>
<td>High</td>
<td>2.14 (0.53–8.71)</td>
<td>0.04 (trend)</td>
</tr>
<tr>
<td>DFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial APML4</td>
<td>0.21 (0.07–0.59)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Sanz risk category   Intermediate</td>
<td>High</td>
<td>5.86 (0.75–45.8)</td>
<td>0.005 (trend)</td>
</tr>
</tbody>
</table>

APML = acute promyelocytic leukemia; DFS = disease-free survival; EFS = event-free survival; NS = not significant; OS = overall survival; PML = promyelocytic leukemia; PML-RARA = promyelocytic leukemia gene-retinoic acid receptor alpha; WCC = white blood cell count
Key conclusions

- Mature data indicate that the APML4 regimen is feasible, tolerable, and highly effective, with a low early death rate and absence of deaths in remission.
- All survival endpoints were significantly superior to the previous APML3 regimen.
- Incorporation of ATO during induction and consolidation allowed substantial reductions in total anthracycline exposure and eliminated the need for high-dose cytarabine in patients with high-risk disease.
- These results support the inclusion of ATO in both induction and consolidation as the standard of care for the initial therapy of patients with high-risk and standard-risk APL.


Long-term follow-up in patients with newly diagnosed acute promyelocytic leukemia treated with all-trans retinoic acid plus arsenic trioxide

Background

The combination therapy of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) for patients with newly diagnosed acute promyelocytic leukemia (APL) has yielded high efficacy in clinical trials. However, there are few studies focusing on the long-term follow-up of survival and complications, which was the objective of this study.1

Key findings

- The ten-year overall survival (OS) was 86.3%. (Figure 1)
  - Early death rate was 7.4% (16/217);
  - Complete remission (CR) rate was 91.7% (199/217);
  - Median follow-up was 72 months.
- The ten-year event-free survival (EFS), disease-free survival (DFS), and cumulative incidence of relapse (CIR) were 78.0%, 87.0%, and 12.0%, respectively. (Figures 2–4)
  - DFS and CIR were analyzed in 199 patients with CR.
  - OS, EFS, DFS, and CIR stratified by Sanz risk category and white blood cell (WBC) count are given in Table 1.
- High WBC count was the only unfavourable prognostic factor for remission duration and led to significant differences between low-to-intermediate and high-risk groups in EFS (82.1% vs. 63.9%, \( p = 0.016 \)), DFS (90.6% vs. 73.1%, \( p = 0.008 \)) and CIR (8.0% vs. 26.9%, \( p = 0.003 \)).
- For the 112 patients who received health assessment, there were no significant long-term complications associated with ATRA plus ATO therapy, except for higher incidence of grade-1 liver dysfunction (15.2%) and hepatic steatosis (42.9%) compared with healthy controls (both \( p <0.001 \)).
The arsenic concentration results revealed no general retention of arsenic in patients during the long-term follow-up:

- Plasma and urine: Arsenic levels quickly returned to normal right after the cessation of ATO, to even lower than that of healthy controls ($p < 0.001$ and $p = 0.004$, respectively);
- Hair and nails: Arsenic levels slowly decreased to normal after six months off ATO, with no significant difference compared with healthy controls.

- QoL was satisfactory in almost all patients.
  - Mean values (95% confidence interval) for global health status, functional scale, and symptom scale were 79.2 (76.0–82.5), 92.7 (91.0–94.5), and 6.9 (5.3–8.5), respectively.
  - Main complaints were mild to moderate weakness (55.4%), difficulty remembering things (41.1%), and financial difficulties (33.0%).

### Study design

<table>
<thead>
<tr>
<th>Therapy stage</th>
<th>Medication</th>
<th>Dosage</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>ATRA</td>
<td>25 mg/m²/day</td>
<td>Until CR</td>
</tr>
<tr>
<td></td>
<td>ATO</td>
<td>0.16 mg/kg/day</td>
<td>Until CR</td>
</tr>
<tr>
<td></td>
<td>IDA (if WBC $&gt;10 \times 10^9/L$)</td>
<td>8 mg/m²/day</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>Supportive care if necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
<td>DA: DNR</td>
<td>45 mg/m²/day</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>Ara-C</td>
<td>100 mg/m²/day</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td>Ara-C ‘pulse’</td>
<td>1 g/m² every 12 hours</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>HA: HHT</td>
<td>2 mg/m²/day</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>Ara-C</td>
<td>100 mg/m²/day</td>
<td>7 days</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>ATRA</td>
<td>25 mg/m²/day</td>
<td>28 days</td>
</tr>
<tr>
<td>(5 cycles)</td>
<td>ATO</td>
<td>0.16 mg/kg/day</td>
<td>28 days</td>
</tr>
<tr>
<td></td>
<td>6-MP or</td>
<td>100 mg/day</td>
<td>28 days</td>
</tr>
<tr>
<td></td>
<td>MTX</td>
<td>15 mg/week</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

6-MP = mercaptopurine; APL = acute promyelocytic leukemia; Ara-C = cytarabine; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CR = complete remission; DA = DNR + Ara-C; DNR = daunorubicin; HA = HHT + Ara-C; HHT = homoharringtonine; MTX = methotrexate
### Table 1. Survival results stratified by Sanz risk category and WBC count

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>EFS</th>
<th>DFS</th>
<th>CIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sanz risk category, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>89.7</td>
<td>82.4</td>
<td>89.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>88.2</td>
<td>81.8</td>
<td>91.0</td>
<td>8.0</td>
</tr>
<tr>
<td>High</td>
<td>78.4</td>
<td>63.9</td>
<td>73.1</td>
<td>26.9</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.165</td>
<td>0.048</td>
<td>0.029</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>WBC-based, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-to-intermediate</td>
<td>88.8</td>
<td>82.1</td>
<td>90.6</td>
<td>8.0</td>
</tr>
<tr>
<td>High</td>
<td>78.4</td>
<td>63.9</td>
<td>73.1</td>
<td>26.9</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.069</td>
<td>0.016</td>
<td>0.008</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*CIR = cumulative incidence of relapse; DFS = disease-free survival; EFS = event-free survival; OS = overall survival; WBC = white blood cell*

### Key conclusions
- The combination therapy of ATRA plus ATO was associated with good long-term survival, particularly for low-to-intermediate risk patients.
- There were few long-term complications, with the exception of liver dysfunction and hepatic steatosis.
- There was no significant arsenic retention, with levels returning to normal after at most six months off ATO.
- The QoL results were satisfactory.


**Hematopoietic stem cell transplantation as a successful salvage strategy for relapsed acute promyelocytic leukemia: a Mayo Clinic series**

### Background
Relapse after all-trans retinoic acid (ATRA)-based induction therapy is relatively uncommon in patients with acute promyelocytic leukemia (APL); long-term follow-up studies have estimated a 15% to 25% relapse rate. Autologous and allogeneic hematopoietic stem cell transplantation (HCT) has been used as an effective salvage strategy. The outcomes of patients with relapsed APL who underwent HCT in a single institution study were presented at ASH 2014.1

### Study design
- The Mayo Clinic transplant database was retrospectively reviewed to identify all patients with relapsed APL who underwent HCT from 1996 to 2013 at three Mayo Clinic sites.
- Data were abstracted at diagnosis and at relapse.
- The aims of this study were to report the descriptive characteristics of patients, with a focus on HCT outcomes.

### Key findings
- A total of 15 patients with relapsed APL who underwent HCT were identified.
- At baseline, the median age was 36 years (range: 19–63 years), there were nine male and six female patients, the Sanz risk score was high for four patients, intermediate for eight patients, and low for two patients.
- The median follow-up from diagnosis was 8.8 years (range: 1.7–17 years).
- Two (13%) deaths were recorded, one from relapse.
- Induction regimens at diagnosis:
  - ATRA plus anthracycline-based therapy was given to 14 (93%) patients;
  - Anthracycline-based therapy without ATRA was given to one patient (7%).
- Relapse:
  - All relapsed patients had achieved a complete remission (CR) after induction;
  - Median time to relapse was 1.6 years (range: 0.6–3.9 years);
● Ten (67%) patients had a medullary relapse (hematologic: n = 7, cytogenetic: n = 2, and molecular: n = 1);
● Three (20%) patients had additional extramedullary (EM) disease (central nervous system [CNS]: n = 2, myeloid sarcoma: n = 1), and two (13%) patients presented with EM disease only (CNS: n = 2).
● Salvage regimens included ATRA in five (33%) patients and arsenic trioxide (ATO) in eight (53%) patients.

● At HCT:
  ● The median age of patients was 38 years (range: 23–68 years);
  ● Thirteen (87%) patients were transplanted in CR2 and two (13%) had persistent disease (PD), with one of them in third relapse;
  ● Four (27%) patients received allogeneic HCT and 11 (73%) received autologous HCT. (Table 1)

● Allogeneic HCT:
  ● Four (27%) patients with a median age of 37 years (range: 33–49 years) underwent allogeneic HCT;
  ● Two (50%) patients received myeloablative (MA) conditioning and two received reduced-intensity conditioning (RIC);
  ● The two patients who underwent MA HCT had PD at the time of transplant, while one patient in CR3 received RIC;
  ● Two (50%) patients developed acute graft-versus-host disease (GVHD) while two (50%) had extensive stage chronic GVHD;
  ● At a median follow-up of 2.6 years (range: 0.3–10.9 years), three (75%) patients remained alive and disease-free; one patient died of infectious complications within 100 days of transplant.

● Autologous HCT:
  ● Eleven (73%) patients with a median age of 40 years (range: 23–68 years) underwent autologous HCT with MA conditioning;
  ● Seven (64%) patients were in molecular remission at the time of HCT, two (18%) patients transplanted before 2004 were in cytogenetic remission, and information about the type of remission was unavailable for two patients;
  ● At a median follow-up of 6.8 years (range: 0.5–16 years) after HCT, ten (91%) patients were alive and in remission; one (9%) patient had a documented relapse at 175 days after HCT and died of disease-related complications.

<table>
<thead>
<tr>
<th>Table 1. Outcomes at hematopoietic stem cell transplantation</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at HCT (range), years</td>
<td>38 (23–68)</td>
</tr>
<tr>
<td>Disease status at HCT</td>
<td></td>
</tr>
<tr>
<td>CR2</td>
<td>13 (87)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Type of HCT</td>
<td></td>
</tr>
<tr>
<td>Allogeneic</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Autologous</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Conditioning regimen</td>
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<tr>
<td>Myeloablative</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Median follow-up since HCT (range), years</td>
<td>4.5 (0.3–16.3)</td>
</tr>
<tr>
<td>Disease status at last follow-up</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>13 (86)</td>
</tr>
<tr>
<td>Relapsed disease</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Unable to assess</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Alive at last follow-up</td>
<td>13 (87)</td>
</tr>
</tbody>
</table>

CR = complete remission; HCT = hematopoietic stem cell transplantation; PD = persistent disease

Key conclusions

- This single institution study reaffirmed the efficacy of HCT for APL patients with medullary and EM relapse.
- Autologous HCT has excellent long-term results in selected patients in CR2.
- Allogeneic HCT was used in patients with high risk (i.e., multiple relapses) and PD at the time of HCT and may be preferable to autologous HCT in patients with molecularly detectable disease.

Shetty AV, et al. ASH 2014:954

Survivorship in acute promyelocytic leukemia (APL): outcomes of APL patients after maintaining complete remission for at least three years

**Background**

The outcome for patients with APL has improved over time, most recently with the non-chemotherapeutic approach of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) that yields superior results to conventional chemotherapy. The purpose of this study was to investigate the survivorship outcomes of APL patients who maintained complete remission (CR) for at least three years when treated with either chemotherapy or non-chemotherapy-based regimens (i.e., potentially cured).1

**Study design**

- Charts were reviewed of patients with APL treated at The University of Texas MD Anderson Cancer Center in Houston, Texas, from January 1991 to December 2010, who achieved and maintained first complete remission (CR) for at least three years.

- Patients were divided into two groups:
  - Chemotherapy: Patients treated with anthracycline-based chemotherapy as part of their treatment regimen;
  - No chemotherapy: Patients treated with ATRA plus ATO (with or without gemtuzumab ozogamicin).

- CR was defined as <5% bone marrow blasts and promyelocytes, absolute neutrophil count ≥1 x 10^9/L, and a platelet count ≥100 x 10^9/L.

- Relapse from CR was defined as >10% bone marrow blasts plus abnormal promyelocytes, appearance of extramedullary disease, and detection of PML-RARA (promyelocytic leukemia gene-retinoic acid receptor alpha) by reverse transcriptase-polymerase chain reaction analysis (molecular relapse).

**Key findings**

- Between 1991 and 2010, 253 patients with APL were treated at The University of Texas MD Anderson Cancer Center.

- CR was achieved by 229 (91%) patients, including 140 (61%) patients who maintained first CR for at least three years.

- There were 89 patients who did not reach CR for at least three years:
  - Seventy-five patients were treated with chemotherapy and 14 with no chemotherapy;
  - Fifty-eight patients were alive and in CR (too early): three in the chemotherapy cohort and 55 in the no chemotherapy cohort;
  - Twenty patients died or 11 relapsed before three years;
  - Twenty-three (10%) patients relapsed (median CR1 duration was one year [range: 0.4–2.9 years]); eleven of these patients are alive (eight in the no chemotherapy cohort and three in the chemotherapy cohort);
  - Twenty patients (9%) died (eight in the chemotherapy cohort and 12 in the no chemotherapy cohort);
  - Causes of death were relapse (n = 3), secondary malignancy (n = 2), infection (n = 1), cardiac (n = 1), and others (n = 12, including loss to follow-up).

- The median time to last follow-up from the three-year mark was 41 months (range: 3–132 months).

- Baseline characteristics of patients in CR for at least three years:
  - The median age of the patients in the no chemotherapy group was 46 years (range: 10–81 years) and in the chemotherapy group it was 40 years (range: 13–63 years);
  - Overall comorbidities included hypertension (23%), cardiac disease (15%), diabetes (15%), and pulmonary disease (8%);
  - The median number of concomitant medications per patient was one (range: 0–20).

- The most frequent comorbidities present at three years from CR were (no chemotherapy vs. chemotherapy), n (%):
  - Hypertension: 38 (37) vs. 8 (22);
  - Cardiac (including congestive heart failure [CHF], myocardial infarction [MI], and arrhythmias): 16 (15) vs. 2 (6);
  - Diabetes: 26 (25) vs. 2 (6).
• At last follow-up there were 84 (60%) patients with new comorbidities (70 patients in the no chemotherapy cohort and 14 in the chemotherapy cohort).

• The most frequent comorbidities at last follow-up were (no chemotherapy vs. chemotherapy), n (%):
  - Hypertension: 41 (39) vs. 8 (22);
  - Cardiac (including CHF, MI, and arrhythmias): 17 (16) vs. 3 (8);
  - Diabetes: 29 (28) vs. 5 (14);
  - Hematologic: 14 (13) vs. 0.

• Late relapses occurred in four of 140 (3%) patients who were alive in CR at three years (chemotherapy: n = 3; no chemotherapy: n = 1):
  - CR1 duration was 3.6, 4.1, 4.2, and 9.7 years;
  - One patient had extramedullary disease (central nervous system involvement) at relapse;
  - At relapse, median white blood cell count was 6.1 x 10^9/L (range: 0.8–9.5 x 10^9/L), platelets were 91 x 10^9/L (range: 24–292 x 10^9/L), and median age was 41 years (range: 29–48 years).
  - First salvage therapy was ATRA plus ATO (n = 3) and idarubicin and cytarabine (n = 1);
  - All four patients achieved CR2 (no stem cell transplantation in CR2);
  - Three were alive in CR2 at 39, 67, and 171 months from first relapse.

• There were a total of 18 secondary malignancies in the 140 patients who achieved CR (15 in the no chemotherapy cohort and 3 in the chemotherapy cohort). (Table 1)

• Causes of death included relapse (n = 1), secondary malignancy (n = 8), cardiac (n = 5), and other causes (n = 5).
  - Cardiac causes included CHF and MI;
  - Other causes included renal failure, pulmonary embolism, and unknown causes due to loss to follow-up.

• The median overall survival and relapse-free survival had not yet been reached. (Figures 1 and 2)

### Table 1. Secondary malignancies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No chemotherapy (n = 104)</th>
<th>Chemotherapy (n = 36)</th>
<th>Total (N = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of malignancies, n (%)</td>
<td>15 (14)</td>
<td>3 (8)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Time to second malignancy, years (range)</td>
<td>4 (3–10)</td>
<td>5 (4–6)</td>
<td>4 (3–10)</td>
</tr>
<tr>
<td>Type of second malignancy, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>—</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Prostate</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

*Other malignancies included thyroid (n = 1), renal cell carcinoma (n = 1), sarcoma (n = 3), skin (n = 2), pancreatic (n = 1), and non-small cell lung cancer (n = 1).

**Figure 1. Overall survival**

**Figure 2. Relapse-free survival**

NR = not reached
**Key conclusions**

- Patients with APL who maintained CR for at least three years had a very low incidence of late relapse.
- New medical problems, including heart disease and secondary malignancies, occurred in nearly two-thirds of patients. The extent to which prior therapies contributed to these comorbidities requires further evaluation.
- Survival for APL patients in remission after three years was very favourable.
- APL patients who maintain CR for at least three years require ongoing medical care and long-term surveillance.


**Acute Myelogenous Leukemia**

Konopleva M, et al. ASH 2014:118

A phase II study of venetoclax (ABT-199/GDC-0199) in patients with acute myelogenous leukemia

**Background**

BCL2 has been implicated in hematologic malignancies and associated with drug resistance and poor prognosis in patients with acute myelogenous leukemia (AML). Patients with relapsed/refractory (R/R) AML have poor prognosis with limited overall survival. Venetoclax is a selective, potent, orally bioavailable small molecule BCL2 inhibitor. Venetoclax has demonstrated pre-clinical efficacy, inhibiting the growth of AML cell lines or AML-patient derived primary cells systemically engrafted into immunocompromised mice. The current study evaluated venetoclax monotherapy in patients with high-risk R/R AML and those unfit for chemotherapy.1

**Study design**

- This was a phase II, open-label, multicentre study evaluating venetoclax monotherapy in patients with R/R AML or as frontline treatment in patients unfit for intensive therapy.
- The primary objective was to evaluate preliminary efficacy.
- The secondary objectives were to evaluate preliminary safety and to assess pharmacokinetics (PK) and pharmacodynamics.
- The study also had an exploratory objective, which was to evaluate biomarkers that may serve as surrogates for clinical endpoints.
- Patients received venetoclax (20 mg) on week 1, day 1, with daily escalation to a final target dose of 800 mg on day 6, and daily thereafter until progression or withdrawal.
- Patients without a complete response (CR) or CR with incomplete blood count recovery (CRi) at first assessment (end of week 4) were able to escalate to 1,200 mg.
- Adverse events (AEs) were reported according to National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.0).
- Responses were evaluated using the revised guidelines of the International Working Group for AML.
- Blood samples for PK analysis were collected:
  - During week 1, days 1–6, eight hours after dosing;
  - At week 6, day 1, intense PK was done from pre-dose to eight hours post-dose.
Key findings

- There were 32 patients enrolled in the study, including 16 (50%) male patients; 30 patients had R/R AML and two patients were unfit for chemotherapy.
- The median age at baseline was 71 years (range: 19–84 years).
- Eleven (34%) patients had a history of myelodysplastic syndrome and two (6%) patients had a history of myeloproliferative neoplasms.
- Fourteen (44%) patients had received more than three prior treatment regimens and 24 (75%) had received prior hypomethylating agents.
- Isocitrate dehydrogenase (IDH) mutations were reported in 11 (35%) patients and six (18%) patients had FMS-like tyrosine kinase-3-internal tandem duplication (FLT3-ITD) mutations.
- Molecular marker and cytogenetic testing was done at the investigator sites; 8/32 patients did not have IDH mutational testing done at the site.
- Overall, an objective response (CR + CRi) was achieved by six (19%) patients:
  - CR, n (%): 2 (6);
  - CRi, n (%): 4 (13).
- One patient with an IDH mutation in exon 3 had a dose interruption for 20 days after week 4 and achieved CRi at week 24.
- Anti-leukemic activity was shown in six (19%) patients:
  - ≥50% blast reduction with two cell line recovery transfusion independence, n (%): 2 (6);
  - ≥50% blast reduction with one cell line recovery, n (%): 2 (6);
  - ≥50% blast reduction with no hematologic recovery, n (%): 2 (6).
- Treatment failure (i.e., progressive disease and less than partial response) occurred in 20 (63%) patients.
- In patients with IDH mutations, an objective response was achieved by four (36%) patients, stable disease (i.e., ≥50% blast reduction with one cell line recovery) by two (18%) patients, progressive disease by four (36%) patients, and marrow aplasia was seen in one (9%) patient.
- The mean time on venetoclax was 63 days (range: 13–246 days).
- Biologic activity and biomarker correlates at end of week 4 are shown in Figure 1.
- Preliminary findings (n = 12) suggest BH3 (Bcl-2 homology domain 3) profiling might identify patients who respond favourably.
- The most common AEs of all grades in ≥20% of patients were nausea (n = 18, 56%), diarrhea (n = 17, 53%), and vomiting (n = 13, 41%).
- The most common grade 3/4 AEs occurring in ≥3 patients were febrile neutropenia (n = 9, 28%) and pneumonia (n = 10, 31%). (Table 1)
- The most common serious AEs reported in ≥3 patients were febrile neutropenia (n = 8, 25%) and pneumonia (n = 6, 19%). (Table 1)
- There were no reported events of clinical or laboratory tumour lysis syndrome.
- At the time of analysis, 31 (97%) patients had discontinued study treatment due to AEs (n = 1, 3%), disease progression (n = 28, 88%), withdrawn consent (n = 1, 3%), and proceeding to transplant (n = 1, 3%); one patient was still active.
- There were no AEs leading to death.
- Pharmacokinetics of venetoclax in AML:
  - The peak plasma concentration (C_max) was 3.77 µg/mL (standard deviation [SD]: 1.82 µg/mL) and C_max/dose was 0.005 µg/mL/mg (SD: 0.002 µg/mL/mg);
  - The time to reach C_max was 6.5 hours (SD: 1.5 hours);
  - The area under the curve at 24 hours (AUC24) was 60.6 µg*hr/mL (SD: 42.9 µg*hr/mL) and the AUC24/dose was 0.076 µg*hr/mL/mg (SD: 0.054 µg*hr/mL/mg).
Six patients came off study prior to first assessment and one had unevaluable bone marrow.

BM = bone marrow; CR = complete response; CRi = complete response with incomplete blood count recovery; FLT3 = FMS-related tyrosine kinase 3; IDH = isocitrate dehydrogenase; ITD = internal tandem duplication

Table 1. Grade 3/4 AEs and serious adverse events

<table>
<thead>
<tr>
<th>Grade 3/4 AEs (in ≥3 patients)</th>
<th>N = 32 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 AE</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious AEs (in ≥3 patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious AE</td>
<td>27 (94)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

Key conclusions

- Preliminary efficacy results demonstrate clinical activity in heavily pretreated AML patients with limited treatment options, and patients with IDH mutations may be particularly sensitive.

- Biologic activity included objective responses, transfusion independence, and blast reductions.

- Venetoclax monotherapy has an acceptable safety profile in patients with R/R AML and those unfit for chemotherapy.

- Venetoclax is being evaluated in AML in combination with hypomethylating agents and chemotherapy while exploring predictive biomarkers.

Acute promyelocytic leukemia (APL) is a highly curable leukemia characterized by the presence of the translocation t(15,17)(q22,q12) in the majority of patients. Initial presentation is often complicated by coagulopathy. A high index of suspicion, prompt specialist referral, and management of coagulopathy and commencement of disease-directed therapy can significantly reduce early death rates and improve outcomes. Since the 1990's, APL has most often been treated with a combination of chemotherapy and the vitamin A derivative, all-trans retinoic acid (ATRA). Although this approach reduced the early death rate due to coagulopathy and significantly reduced relapse rates, the toxicity (both long- and short-term) related to chemotherapy remains a challenge, particularly in older patients and those with comorbidities.

Over the last few years, the use of arsenic trioxide (ATO) and ATRA in the upfront setting has been assessed in a number of trials. At the 2014 Annual Meeting of the American Society of Hematology (ASH), the updates of a number of studies were presented. Platzbecker and colleagues presented results from the extended series of patients enrolled in a prospective, randomized, phase III trial of 276 patients with newly diagnosed low/intermediate-risk APL (presenting white blood cell count [WCC] of ≤ 10 x 10⁹/L) comparing ATRA plus ATO with ATRA plus chemotherapy.¹ In the ATRA plus ATO arm, induction therapy was ATRA plus ATO given daily for a minimum of 35 days or until complete response (CR) based on bone marrow morphology (maximum 60 days). After CR, patients were given consolidation treatment of 28 weeks of ATO and ATRA. This included four cycles of ATO on a four weeks on and four weeks off schedule and seven cycles of ATRA on a two weeks on and two weeks off schedule. In the ATRA plus chemotherapy arm, standard induction of ATRA plus idarubicin was given, followed by three cycles of anthracycline-based consolidation with ATRA, and low-dose chemotherapy and ATRA for maintenance for two years. The primary endpoint of the trial was event-free survival (EFS) at two years.

The results of this study were quite remarkable: after a median follow-up of 36 months, patients in the ATRA plus ATO arm had an EFS rate of 98% compared with 84.9% for ATRA plus chemotherapy (p ≤ 0.001). The overall survival (OS) and disease-free survival (DFS) were also significantly higher in the ATRA plus ATO arm compared with the ATRA plus chemotherapy arm (99.1% vs. 94.4% [p = 0.01] and 98% vs. 87.9% [p = 0.002], respectively). The relapse rate was lower in the ATRA plus ATO arm compared with the ATRA plus chemotherapy arm (1.1% vs. 9.4% [p = 0.005], respectively).

In terms of safety, during induction, therapy with ATRA plus ATO was associated with fewer incidences and shorter duration of significant cytopenia compared with ATRA plus chemotherapy. The incidence of differentiation syndrome was comparable. The toxicities that occurred with significantly higher frequency with ATRA plus ATO included QTc prolongation and hepatotoxicity. However, these toxicities were managed with temporary discontinuation and dose modification of ATO as well as more intensive monitoring specific to these toxicities. It should also be noted that the tolerability to these drugs improved through cycles of consolidation. More importantly, while there were cases of QTc prolongation there were no cases of ventricular arrhythmia or torsades de pointes.

Another study presented at ASH 2014 that reported on an ATRA plus ATO regimen was the final analysis of the APML4 trial.² This was a non-randomized study of 124 patients with newly diagnosed APL who were treated with ATRA plus ATO combined with idarubicin (IDA). All patients, regardless of risk category, received ATRA, ATO, and IDA as induction therapy until CR followed by two cycles of consolidation therapy with ATRA plus ATO, and two years of maintenance with ATRA, 6-mercaptopurine, and methotrexate. This was a well-designed study, although not randomized, looking at upfront treatment of APL using ATRA plus ATO. Compared with the APML3 trial, which used ATRA plus IDA for induction and consolidation (without ATO), the DFS, EFS, and OS were all significantly higher in the APML4 trial. These results suggest that using ATRA plus ATO in induction and consolidation, and removing chemotherapy from consolidation, increases survival benefit in patients with APL and reduces the risk of relapse. The advantage of this regimen was the use of ATRA, ATO, and IDA upfront, avoiding the use of chemotherapy consolidation. The disadvantages to the design of the study were first, the role of anthracycline during induction treatment for low/intermediate risk patients is questionable based on the results of the APL0406 study.³ Second, two years of maintenance treatment was given in this regimen. The role of maintenance in combination with ATRA and ATO is questionable particularly in low/intermediate-risk patients based on the results of APL0406.³
Overall, the data for relapse risk were interesting and encouraging (4–5% at five years) and did not significantly vary based on presenting WCC. Historically in trials of ATRA plus chemotherapy a greater risk of relapse with high-risk patients has been noted. The results of this study suggest this might not be the case with ATRA plus ATO, which is very encouraging.

The long-term safety of ATRA plus ATO was reported in a follow-up study in patients with newly diagnosed APL. In this study, Zhu and colleagues followed 217 patients with newly diagnosed APL who were treated with ATRA plus ATO combination therapy between 2001 and 2010. Of these patients, 112 had health assessments for long-term complications and quality of life; arsenic retention in their plasma, urine, hair, and nails was also quantified. This study was important because it helps health care providers understand the tolerability of giving these agents in terms of quality of life and clearance of arsenic. It was quite encouraging to see that arsenic was cleared quickly from the plasma and urine, returning to normal levels right after ATO was stopped, and in the hair and nails arsenic levels slowly decreased to normal after six months following the end of ATO therapy. This information will be reassuring to both physicians and patients. However, there was a higher incidence of grade 1 liver dysfunction and hepatic steatosis (15.2% and 42.9%, respectively). Based on these results, patients treated on this regimen should receive ongoing follow-up of their liver function tests, even on completion of therapy.

In general, the advantage of reducing or eliminating chemotherapy from the treatment of APL is the reduction or elimination of the adverse events (AEs) associated with chemotherapy. These AEs include grade 3/4 cytopenia, hospitalization, neutropenic sepsis, and cardiotoxicity related to anthracycline use, and secondary myelodysplastic syndrome/acute myelogenous leukemia. A second advantage is that older patients can be treated on this regimen with dose modifications, if required. The potential disadvantages of ATRA plus ATO regimens are QTc prolongation, which requires close monitoring (especially as patients get older), and hepatotoxicity.

In British Columbia, the combination of ATO plus ATRA for induction and consolidation is used for first-line treatment of all low/intermediate-risk patients with APL, as described by Platzbecker et al. For high-risk patients (presenting WCC >10 x 10⁹/L), the same regimen is used except for the addition of anthracycline (daunorubicin) in induction. We started using ATO plus ATRA in the spring of 2014 based on the preliminary results of the APL0406 trial that were presented at ASH in 2012. Patients receiving therapy are closely monitored during induction therapy for signs of differentiation syndrome. They receive prophylactic prednisone (0.5 mg/kg) for the duration of induction therapy. If leukocytosis (WCC >10 x 10⁹/L) occurs, hydroxyurea is commenced to maintain WCC at less than ten. At the earliest signs of differentiation syndrome, prednisone is discontinued and dexamethasone is commenced. If the clinical concern is significant, then ATRA and ATO are held.

To monitor for QTc prolongation, electrocardiograms are performed at least once or twice a week during induction and more frequently if there is a concern about QTc prolongation; electrolytes are optimized to reduce the risk of QTc prolongation. QTc prolongation is reversible and can be managed by dose reduction or holding doses. To monitor for hepatotoxicity, liver function tests are done a minimum of twice a week, more frequently if a patient develops any derangement of their liver function tests. During consolidation, the same monitoring protocol is continued. Liver function tests are monitored even on completion of all therapy, with routine monthly blood work in particular for patients who developed hepatotoxicity during therapy.

An Interview with Dr. Uwe Platzbecker on the APL0406 Study

**New Evidence:** What are the key unmet needs of patients with APL?

**Dr. Platzbecker:** Although the majority of patients with APL can be cured with conventional chemotherapy, a considerable number of patients are lost to therapy in the early phase due to treatment-related toxicities such as bleeding and infections. In addition, patients may suffer from long-term toxicity from chemotherapy, including cardiac problems and secondary hematologic malignancies. Therefore, a key unmet need of patients with APL is the availability of an effective therapy with reduced toxic effects. There is also a need to improve the speed of initial treatment delivery for patients with APL. APL is a life-threatening disease where therapeutic intervention is an emergency; however, it is often not recognized or it is misdiagnosed in the emergency room. In these cases, there is a delayed transfer to a specialized centre and thus therapy cannot be delivered immediately.

**New Evidence:** Please describe the importance of early treatment of APL.

**Dr. Platzbecker:** It is critical for patients with APL to receive treatment early as this would abrogate the occurrence of life-threatening complications. For this reason it is recommended that patients with signs and symptoms of APL receive therapy immediately while the diagnosis is being confirmed genetically.

**New Evidence:** Is ATRA plus ATO the current standard upfront treatment of APL in low/intermediate-risk patients in Europe? What is the current standard upfront treatment in high-risk patients?

**Dr. Platzbecker:** There is enough scientific evidence to support that ATRA plus ATO should be used to treat patients with low/intermediate-risk APL; however, due to reimbursement issues, it is not the currently registered first-line treatment for these patients. In high-risk patients with APL, the standard upfront treatment is anthracycline and cytarabine supplemented with ATRA.

**New Evidence:** What are the possible advantages of ATRA plus ATO over ATRA plus chemotherapy for the treatment of APL?

**Dr. Platzbecker:** There are several advantages to treating APL with ATRA plus ATO over ATRA plus chemotherapy. Firstly, ATRA plus ATO is associated with less toxicity than ATRA plus chemotherapy. Importantly, there is a significant reduction in thrombocytopenia and neutropenia in patients treated with this regimen. Secondly, this combination produces a greater anti-leukemic effect and a decrease in the relapse rate compared to ATRA plus chemotherapy. Lastly, ATRA plus ATO can be given on an outpatient basis in the consolidation phase.
**New Evidence:** Please describe the rationale and design of the APL0406 study.

**Dr. Platzbecker:** As ATO alone or in combination with ATRA has shown high efficacy and reduced toxicity in pilot studies, this phase III, multicentre trial was conducted to evaluate the noninferiority of ATRA plus ATO compared with ATRA plus chemotherapy in patients with low/intermediate-risk APL. Patients in this study were randomly assigned to receive either ATRA plus ATO for induction and consolidation therapy or standard ATRA-idarubicin induction therapy, followed by three cycles of consolidation therapy with ATRA plus chemotherapy, and maintenance therapy with low-dose chemotherapy and ATRA. Noninferiority was confirmed if the difference between the rates of event-free survival (EFS) at 2 years in the two groups was not greater than 5%.

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**New Evidence:** Please describe the efficacy results for the extended and final series of patients.

**Dr. Platzbecker:** The results from the extended and final series were consistent with the previous efficacy results published in 2013 in *The New England Journal of Medicine*. The data demonstrate that ATRA plus ATO improves the EFS and overall survival in patients compared with ATRA plus chemotherapy. There are also significantly more relapses with the ATRA plus chemotherapy regimen.

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**New Evidence:** Please describe the safety results of the study for the extended and final series of patients.

**Dr. Platzbecker:** In this study, we see a significant decrease in thrombocytopenia and neutropenia in patients treated with ATRA plus ATO; however, this treatment was also associated with more frequent hepatic events. These events were easily managed by delaying ATO treatment until liver enzyme levels were normalized, followed by a 50% ATO dose reduction.

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**New Evidence:** Do the results of the extended cohort support the use of ATRA plus ATO as the standard upfront treatment in this patient group? Did the results of the study change the standard of care in Germany?

**Dr. Platzbecker:** Yes, these results provide strong support for the use of ATRA plus ATO as the upfront treatment in low/intermediate-risk APL. However, in Germany, we are restricted to the label of ATO. Therefore, although scientific evidence for the use of ATRA plus ATO is recognized and appreciated, it has not yet been adopted as the standard of care. Nevertheless, there is currently a trend towards gaining access to ATO on a case-by-case basis.

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**New Evidence:** If ATRA plus ATO were used first-line, what treatment would you give in the relapsed setting?

**Dr. Platzbecker:** This has not yet been explored, and may be difficult to examine, as relapse is a rare event. In patients who relapse late after ATRA plus ATO treatment, I would consider retreating with this same therapy.

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**New Evidence:** Do you recommend giving maintenance treatment to patients with APL?

**Dr. Platzbecker:** Maintenance therapy is the standard of care in the chemotherapy-based treatment regimen. There are data from randomized trials that suggest maintenance therapy can be abandoned if an intensive treatment is used; however, this remains debatable. I would always recommend maintenance therapy, and this could be individually titrated based on the patient’s tolerability.

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**New Evidence:** What are the next steps in improving the treatment of patients with APL? What about in high-risk patients?

**Dr. Platzbecker:** The next steps in improving the treatment of patients with APL will be to evaluate the real-life data and to learn more about the applicability of this new regimen. For high-risk patients with APL, the next step should be to construct a randomized trial specifically in this subgroup of patients with APL.
An interview with Dr. Stephen Couban on the Canadian consensus article which outlined recommendations for the management of newly diagnosed and relapsed acute promyelocytic leukemia in adults

**New Evidence:** How many patients with acute promyelocytic leukemia (APL) do you see in your clinic every year? What is the prognosis for patients with APL?

**Dr. Couban:** My clinic in Nova Scotia treats about five to seven patients with new or relapsed APL every year. The rarity of the disease presents greater challenges in smaller centres than in larger centres such as those in Toronto and Vancouver. These challenges include maintaining knowledge about treatment advances, and making sure the leukemia team is always ready to recognize and treat APL patients immediately. Despite its rarity, APL has witnessed major improvements over the past decade; prognosis for patients today is very good. However, the high rate of early death due to bleeding complications remains a significant challenge. Complicating matters is the fact that clinical trials in APL usually exclude patients with significant bleeding complications and therefore underestimate the number of patients that die from this disease.

**New Evidence:** What are the standard first- and second-line treatments for APL in Canada and how do they differ from other places like the United States and Europe?

**Dr. Couban:** This has become an increasingly complicated question due to several treatment approaches in first- and second-line treatment, and in low/intermediate-risk and high-risk APL. For patients who relapse, there is an international consensus that arsenic trioxide (ATO), with or without all-trans retinoic acid (ATRA), should be the treatment. There are a number of treatment options to choose from after ATO-induced remission in the relapsed setting, with special circumstances ultimately dictating which option is best. These options include more ATO and allogeneic and autologous hematopoietic stem cell transplants. One question that remains unanswered is what treatment option should be used for patients who relapse after ATO-induced second remission. This question will take on greater significance as ATO becomes more widely used in the first-line setting. With respect to risk categories, there is consensus in Canada and around that world that high-risk patients with APL should receive treatments that include ATO, ATRA, and chemotherapy. In Canada, and in some other parts of the world, chemotherapy-based protocols that include ATO have become widely implemented. For patients with low/intermediate-risk APL, many of us in Canada have embraced the recent results of the Lo-Coco et al. trial which demonstrated the benefits of a chemotherapy-free approach of ATO plus ATRA in this patient group. This is not an option in some parts of the world due to restrictions on the use of ATO or the lack of availability altogether.
New Evidence: What are the unmet needs in APL treatment? What challenges are the physicians and the patients facing?

Dr. Couban: There are three basic unmet needs in APL. The first is raising and maintaining awareness with health care professionals regarding the treatment of APL. This is especially challenging given the rarity of the disease and the difficulties that Canadian geography present in disseminating information. The second unmet need is to ensure that patients entering the clinical setting receive vital treatment immediately. This is especially problematic in settings that are not leukemia centres. We know that initiating treatment with ATRA and blood products within the first few hours of a suspected diagnosis of APL is vital to the survival of the patient. The third unmet need in APL is the challenge of interpreting emerging data from clinical trials, and applying this information to make decisions about chemotherapy and ATO for individual patients.

New Evidence: The Canadian consensus article highlighted the need for more aggressive supportive measures as soon as a patient is suspected of having APL.¹ These were aggressive blood transfusions, immediate ATRA therapy, and frequent monitoring. Why are aggressive supportive measures very early on so critical?

Dr. Couban: There is a general consensus that early supportive care measures with ATRA, platelets, cryoprecipitate, and plasma are important because mortality from bleeding and/or thrombosis is high in the first 24 hours after a patient presents with symptoms. So by providing supportive care and ATRA therapy as soon as a suspected diagnosis is made, without waiting for a definitive diagnosis, we hope to reduce the risk of mortality.

New Evidence: What steps can medical institutions and physicians employ to help meet this challenge?

Dr. Couban: Institutions can meet this challenge in three steps:

1) By creating awareness of the disease with physicians, nurses, and medical technologists;
2) By instituting protocols that trigger immediate therapy based on suspicion, before diagnostic certainty; and
3) By starting immediate supportive care with blood products as well as with ATRA therapy.

With respect to the last step, one limitation has been that some centres may not have some of these agents. This has resulted in some centres sending ATRA to the clinic by taxi or transporting the patient by ambulance to appropriate centres that have the necessary agents.

New Evidence: ATRA in combination with anthracyclines (± cytarabine) has been the standard approach in the treatment of low/intermediate-risk and high-risk APL. The recent phase III clinical trial by the Italian group, GIMEMA, showed that ATO plus ATRA in low/intermediate-risk APL was equally effective. What are the key advantages and disadvantages of ATRA/anthracycline-based approaches?

Dr. Couban: The key advantages of anthracycline-based approaches are well established, with many studies demonstrating their efficacy in APL. And unlike ATO, anthracyclines do not pose immediate cardiac risks (prolonged QT interval). The disadvantages are the hair loss, hematological toxicity, increased risk of fever, and long-term chronic heart issues that are associated with anthracyclines.

New Evidence: What are the key advantages and disadvantages of ATO plus ATRA in low/intermediate-risk APL?

Dr. Couban: Unlike chemotherapy-based approaches, ATO is not associated with hair loss, and can be given to patients on an outpatient basis in a manner that is at least as effective as chemotherapy-based approaches. The lower risk of hematological toxicity associated with ATO means less time spent in the hospital. The main disadvantage with ATO is the risk of a prolonged QT interval during treatment.
**New Evidence**: What kind of an impact do you foresee this consensus article¹ having on the way oncologists treat APL in Canada?

**Dr. Couban**: Our aim with this consensus article is to raise awareness within the Canadian medical community about APL, which will hopefully bring forth a discussion about diagnostic and therapeutic issues.


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An interview with Dr. Matthew Seftel, co-author of the Canadian consensus article outlining recommendations for newly diagnosed and relapsed acute promyelocytic leukemia in adults

**New Evidence**: How many patients with acute promyelocytic leukemia (APL) do you see in your clinic in a year? What is the prognosis for patients with APL?

**Dr. Seftel**: My institution sees approximately two APL patient referrals per month. Personally, I treat about two to three newly diagnosed APL patients in my clinic per year, in addition to some 20 patients on active treatment or follow-up. The outlook for APL patients is good and has been dependent on timely referral and early, aggressive supportive care. Approximately 75% of patients can expect to be cured, with greater cure rates expected in low-risk patients and younger patients. Older patients have a poorer prognosis, likely because of delayed diagnosis or lower tolerance for intensive therapy. Although prognosis is very positive for APL patients, several aspects of APL treatment can still be improved, such as preventing and managing complications from bleeding, differentiation syndrome, and infections, as well as reducing relapse rates and long-term complications from treatments.

**New Evidence**: What are the unmet needs in APL treatment? What challenges are physicians and patients facing?

**Dr. Seftel**: Firstly, outcomes of APL can be further improved with respect to the unacceptably high early death rates (i.e., within the first month after diagnosis) from coagulopathy, differentiation syndrome, and infection. Secondly, population-based studies on long-term outcomes are limited due to the rarity of the disease, and we need more data about “real-world” outcomes. Thirdly, there is a need for clinical trials that investigate new treatments to improve the standard of care, and should focus on high-risk and older patients. Finally, unequal access to financially expensive but effective treatments, such as arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), remains an issue.
**New Evidence**: Please describe the rationale for this Canadian consensus APL paper.¹

**Dr. Seftel**: The objective of the paper was to address what we perceived as an unmet need in the current knowledge about diagnosis and treatment of APL. APL is a rare disease for which successful treatment crucially depends on prompt diagnosis and excellent supportive care. Deficiencies in appropriate supportive care remain a challenge. Furthermore, new data on novel treatment approaches have been released since the publication of the last evidence-based guideline. Therefore, we assembled Canadian authors with extensive experience in research or treatment related to APL. Our aim was to update current guidelines, based on recently published literature, and to provide recommendations suited to the Canadian medical landscape.

**New Evidence**: Who was involved and what expertise did the panel have in APL?

**Dr. Seftel**: The panel consisted of me and Dr. Andre Schuh, both of us based at Princess Margaret Hospital in Toronto, Ontario, Dr. Michael Barnett at the University of British Columbia, Dr. Stephen Couban at Dalhousie University in Halifax, Nova Scotia, Dr. Brian Leber at McMaster University in Hamilton, Ontario, and Dr. John Storring at the McGill University Health Centre in Montreal, Quebec. All panel members have extensive experience in APL clinical trials and research, as well as in the treatment of APL.

**New Evidence**: Please describe the methodology.

**Dr. Seftel**: The objective of the study was to update existing international guidelines with recently published literature. Based on the needs of the APL medical community in Canada, we focused on three areas: supportive care, the use of ATO in first-line treatment, and the role of hematopoietic stem cell transplantation (HSCT) in the relapsed setting. We performed a systematic review using formal search criteria in PubMed and in abstracts submitted to the annual meetings of the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association. Publications were excluded if they were published before 2009, if they included treatment with ATO as a single agent in induction and consolidation, or if they examined the role of ATO in maintenance.

**New Evidence**: What were the recommendations for how patients with suspected APL should be approached?

**Dr. Seftel**: Regarding supportive care, several recent publications highlight the importance of supportive care in improving overall outcomes in APL. However, we were unable to generate recommendations about new interventions, as there have been no compelling publications on this topic since 2009. Therefore, our recommendations followed previous guidelines and included aggressive transfusion support to manage coagulopathy and early ATRA therapy based on clinical or laboratory suspicion of APL.

**New Evidence**: What were the recommendations for how ATO should be used in induction and consolidation for newly diagnosed APL patients?

**Dr. Seftel**: The panel was able to provide an update for first-line treatments in low/intermediate-risk APL because of the Lo-Coco et al. study, recently published in 2013.² The results of this phase III study comparing ATRA plus ATO with ATRA plus idarubicin were convincing. We therefore recommended ATRA plus ATO for the first-line treatment of low/intermediate-risk APL patients.
We also recognised that there was a need to recommend a regimen for high-risk APL. For this group we recom-
mended the regimen used in the Iland et al. study. This approach combines ATRA, ATO, and idarubicin in the
first-line treatment of APL (ATRA, ATO, and idarubicin in induction; ATRA and ATO in consolidation). The alterna-
tive regimen for high-risk patients, as outlined by the Powell et al. study, uses ATO as part of consolidation only,
which we thought was a disadvantage. Furthermore, the Iland et al. platform was a more intuitive approach to
use because of medical practice patterns in Canada, where idarubicin and ATRA are the most commonly chosen
remission induction agents rather than the combination of daunorubicin, cytarabine, and ATRA.

New Evidence: What were the recommendations for using HSCT in patients with relapsed APL?

**Dr. Seftel:** Because of relatively few new data on the subject, the recommendations were not substantially different
from those published in 2009 by the European LeukemiaNet and the National Comprehensive Cancer Network.
Overall, we predict a much lower need to consider autologous or allogeneic HSCT in APL today, given the success
of ATRA plus ATO in controlling the disease in both the frontline and relapsed settings. After relapse, allogeneic
HSCT should only be considered after failure to induce a second molecular complete remission (CR) with ATO.
In those patients who achieve a second molecular CR after ATO, consolidation with autologous HSCT remains a
reasonable approach.

New Evidence: How do you see this consensus paper impacting how oncologists treat APL in Canada? What kind
of an impact will this consensus paper have on how oncologists treat APL in Canada?

**Dr. Seftel:** This consensus paper updates the previously published, five-year-old guideline on APL. Our recom-
mendations are an up-to-date, evidence-informed aid to guide Canadian health care providers on the management
of adult patients with APL.

arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-80; quiz 752. 4.Powell BL, Moser B, Stock W, et
al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup
For induction of remission and consolidation of APL refractory to or relapsed from retinoid and anthracycline therapy, and where APL shows the presence of the t(15;17) translocation or PML-RARα gene expression.

PART OF THE LUNDBECK ONCOLOGY PORTFOLIO

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

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

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

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

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

*CR (complete remission) was defined as cellular bone marrow aspirate with <5% blasts, peripheral blood leukocyte count ≥3,000/mm³ or absolute neutrophil count ≥1,500/mm³, and platelet count ≥100,000/mm³.

APL = acute promyelocytic leukemia; PML-RARα = promyelocytic leukemia-retinoic-acid-receptor alpha

We have created an animated video aimed at helping children better understand cancer in the family and help them cope with the situation. If you think that this video could be helpful for your patient, it is located at http://www.lundbeck.com/ca/en/therapeutic-areas/oncology.
Efficacy and Safety of Single-Agent and Combination Therapies in Patients with non-Hodgkin and Hodgkin Lymphomas

Standard treatments for indolent non-Hodgkin lymphoma (iNHL) and mantle cell lymphoma (MCL) include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone). These regimens are associated with high toxicities and some patients do not respond to treatment or relapse after initial therapy. Bendamustine in combination with rituximab (BR) was shown to be more efficacious and better tolerated than R-CHOP in patients with iNHL and MCL.1 The StiL NHL 1-2003 and BRIGHT trials have shown that in patients with iNHL and MCL, BR led to improved progression-free survival (PFS) and non-inferior complete response (CR) rates compared with R-CHOP/R-CVP.1,2

Phase I and II studies of patients with NHL have also shown a promising role for the single agent obinutuzumab (GA101).3-6 The GAUDI study showed that obinutuzumab plus chemotherapy resulted in response rates of 93% to 96% in patients with relapsed/refractory follicular lymphoma (FL), supporting phase III investigation.7

MCL is a rare but aggressive B-cell malignancy generally observed in elderly patients. Despite recent advances in therapy, it remains difficult to treat with frequent chemoresistance in the relapsed or refractory setting. MCL patients that are fit to receive high-dose regimens undergo induction therapy with rituximab and chemotherapy (Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone [Hyper-CVAD]/CHOP/bendamustine) followed by consolidation with autologous stem cell transplantation (ASCT). Another treatment option for MCL is ibrutinib—a first-in-class, once-daily, oral, covalent inhibitor of Bruton’s tyrosine kinase — which has been approved in the United States, the European Union, and other countries for patients with MCL who have received at least one prior line of therapy. Ibrutinib demonstrated durable single-agent efficacy in a phase II study of patients with MCL who had received one to five prior therapies.8

Patients with relapsed/refractory Hodgkin lymphoma (HL) usually undergo salvage chemotherapy after frontline therapy, followed by ASCT. However, efficacy and safety of the salvage chemotherapy are suboptimal, with the need for more therapeutic options.

At the 2014 American Society of Hematology (ASH) Annual Meeting, New Evidence covered many studies that provided new information on these topics. The following abstracts are covered in this section:

• The maintenance phase results of the phase 1b GAUDI study showed that in previously untreated patients with FL, first-line induction with obinutuzumab plus CHOP (G-CHOP) or obinutuzumab plus bendamustine (G-B) followed by obinutuzumab maintenance was well tolerated. Complete response rates were high and most patients were progression-free at 32 months.

• A multicentre, randomized, phase III study demonstrated better efficacy, without increased risk of secondary neoplasia, for BR compared with R-CHOP as first-line treatment in patients with indolent lymphomas or MCL. These results confirm the high anti-lymphoma activity of the BR regimen and support the use of BR as a preferred first-line treatment for indolent lymphoma.

• The prospective phase II trial by the LYSA group investigated the RiBVD regimen (rituximab, bendamustine, bortezomib [Velcade®], and dexamethasone) in elderly patients with MCL and found it to be a highly effective and well-tolerated first-line treatment.

• A retrospective analysis of patients with MCL showed that those receiving R-Hyper-CVAD chemotherapy in the frontline setting have a significantly higher rate of peripheral blood stem cell (PBSC) mobilization failure and collect significantly fewer CD34+ PBSCs when compared to patients treated with R-CHOP or BR. R-Hyper-CVAD should be used
with caution in patients with newly diagnosed MCL who are eligible for ASCT.

- The StiL, NHL 7-2008 trial (MAINTAIN) confirmed the efficacy and safety of BR when followed by 2 years of standard maintenance therapy with rituximab in patients with previously untreated advanced FL.

- Updated safety and efficacy results from the international, multicentre, open-label phase II trial of daily oral ibrutinib in relapsed or refractory MCL showed durability of responses with ibrutinib. Moreover, the longer follow-up did not reveal any new adverse events.

- The MCL2001 (SPARK) study showed that single-agent ibrutinib is highly efficacious and well tolerated in patients with MCL who progressed after a rituximab-containing regimen and bortezomib therapy. These results were consistent with previous ibrutinib studies, without any new safety signals.

- The multicentre, randomized phase III study NHL 2-2003 compared the efficacy and safety of BR vs. fludarabine plus rituximab (FR) in patients with relapsed FL, other indolent lymphomas, or MCL. The 8-year follow-up results showed that BR was more efficacious than FR, with higher overall and complete response rates, a longer PFS, and better overall survival.

- A multicentre, open-label, single-arm, phase II study showed the efficacy and safety of BR across a wide range of patient subgroups with relapsed/refractory MCL. These results could allow the BR regimen to act as a backbone to which other active agents can be added for improving anti-lymphoma activity.

- A study showed that most patients with relapsed/refractory indolent B-NHL and MCL displayed prolonged lymphocytopenia and low CD4+ T-cell counts, for at least 7–9 months, after the completion of bendamustine with or without rituximab. As this may increase the risk of opportunistic infections, the need for prophylaxis against Pneumocystis pneumonia and varicella zoster virus for at least 7–9 months should be taken into consideration.

- A phase I/II, single-arm, two-stage, open-label study showed that the outpatient regimen of brentuximab vedotin in combination with bendamustine was safe with premedication in patients with HL who are either relapsed or refractory after frontline therapy, and the very high CR rate observed on combination treatment compared favourably with historical data. The regimen also had no adverse impact on stem cell mobilization or engraftment. These results suggest that the regimen may represent a promising approach for maximizing responses prior to ASCT in these patients.


Dyer MJS, et al. ASH 2014:1743

**Obinutuzumab (GA101) in combination with CHOP or bendamustine for the first-line treatment of follicular non-Hodgkin lymphoma: final results from the maintenance phase of the phase Ib GAUDI study**

**Background**

Chemoimmunotherapy based on rituximab is the standard-of-care treatment for advanced follicular lymphoma (FL). However, some patients do not respond to treatment or relapse after an initial response. Obinutuzumab (GA101) is an anti-CD20 monoclonal antibody, which triggers increased direct cell death and antibody-dependent cellular cytotoxicity *in vitro* compared with rituximab.

In the open-label, phase Ib GAUDI study (NCT00825149), induction with obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) or obinutuzumab plus fludarabine and cyclophosphamide (G-FC) followed by obinutuzumab maintenance was associated with encouraging efficacy and safety outcomes for relapsed/refractory FL. The GAUDI study also showed the safety and efficacy of G-CHOP or obinutuzumab plus...
Bendamustine (G-B) followed by obinutuzumab maintenance in patients with previously untreated FL: no new safety signals were identified, and the overall response rate at the end of induction was more than 92% for both arms, with complete response (CR) rates of 37% (G-B) and 35% (G-CHOP).

At ASH 2014, Dyer et al. report data from the maintenance phase of GAUDI for the first-line FL population, in which patients responding to induction G-CHOP or G-B received obinutuzumab as maintenance therapy.1

**Study design**

- Eligibility criteria included age >18 years, previously untreated CD20+ B-cell FL, at least one bidimensionally measurable lesion, life expectancy >12 weeks, Eastern Cooperative Oncology Group performance status 0–2, and no disease transformation.
- During induction, patients received obinutuzumab (intravenous [iv] 1000 mg, cycle 1 days 1 and 8; day 1 of each cycle thereafter) plus either standard CHOP (every 3 weeks, 6–8 cycles) or bendamustine (iv 90 mg/m² every 4 weeks, 4–6 cycles).
  - The first infusion of obinutuzumab 1000 mg iv was administered at a slow initial rate (50 mg/h vs. 100 mg/h for subsequent infusions).
  - Premedication with oral acetaminophen/paracetamol and an antihistamine was given about 30 minutes before each obinutuzumab infusion.

  - Chemotherapy backbone was selected at investigator discretion.
  - Patients with a CR or partial response (PR) were eligible for maintenance with obinutuzumab. Maintenance treatment was started 12 weeks after the last chemoinmunotherapy dose. Obinutuzumab was administered iv at 1000 mg once every 3 months, for up to 2 years or until disease progression (PD).
  - Patients who completed maintenance were followed for 2 years after their last obinutuzumab dose or until PD or the start of new anti-lymphoma treatment.
  - The primary endpoint was safety. Secondary endpoints included progression-free survival (PFS), response rates, and B-cell depletion and recovery after the end of treatment (EOT; the date when treatment, including maintenance, was completed or discontinued).
  - The data cut-off date for this analysis was January 10, 2014.
  - All reported data are from the maintenance phase, but for clarity each cohort of patients is referred to by their treatment assignment during induction phase.

**Key findings**

- The overall safety population comprised the 81 patients who started induction (G-B: n = 41; G-CHOP: n = 40). (Figure 1)

  - Baseline characteristics were balanced between arms. The median observation times from study start were 31 months (G-B) and 33 months (G-CHOP).

**Figure 1. Patient disposition**

*Patient was not eligible to enter maintenance owing to an ongoing infection at the time the first maintenance infusion was due.

G-B = obinutuzumab, bendamustine; G-CHOP = obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone
• The maintenance safety population comprised 72 patients (n = 36 in each arm), most of whom completed maintenance. There were 17 discontinuations due to adverse events (AEs)/intercurrent illness (n = 9), PD (n = 5), administrative/other (n = 2), and death (n = 1). (Figure 1)

• During two years of maintenance, most patients had AEs: G-B, 100% (grade ≥3: 44%); G-CHOP, 78% (grade ≥3: 31%). Treatment-related AEs were reported for 53% of patients.

• Most common AEs:
  - All grade: cough (G-B: 17% of patients; G-CHOP: 11%);
  - Grade ≥3: neutropenia (G-B: 14%; G-CHOP: 0%);
  - Treatment-related: lower respiratory tract infection (RTI; G-B: 3%; G-CHOP: 11%), and urinary tract infection (G-B: 6%; G-CHOP: 8%).
  - The grade ≥3 AEs mainly reflected infections and cytopenia. (Table 1)

• AEs led to dose delays in 17% (G-B) and 6% (G-CHOP) of patients.

• Three patients (G-B: n = 1; G-CHOP: n = 2) experienced treatment-related AEs during, or within 24 hours of, an infusion (all grade 1–2).

• One patient (G-CHOP; aged 64 years) died during maintenance due to an obinutuzumab-related AE (RTI [unknown pathogen] leading to fatal sepsis with lactic acidosis).

• At EOT, all patients in the overall safety population with data available (G-B: n = 41; G-CHOP: n = 39) had experienced B-cell depletion. (Table 2)

  - As median follow-up time and treatment duration were similar (32 months), only 22 patients (28%) had a B-cell assessment 6–9 months after EOT; all were B-cell depleted.
  - B-cell counts in six of 12 patients (G-B: n = 2; G-CHOP: n = 4) assessed 9–24 months after EOT recovered; five patients recovered without PD, one recovered with PD (G-CHOP).

### Table 1. Adverse events during maintenance by induction arm

<table>
<thead>
<tr>
<th>AE</th>
<th>G-B (n = 36)</th>
<th>G-CHOP (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>26 (72)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (11)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (11)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>11 (31)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (11)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>12 (33)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Cough</td>
<td>6 (17)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Grade ≥3 AEs, n (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>6 (17)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>6 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related AEs (all grades)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>8 (22)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>1 (3)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (6)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>1 (3)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>5 (14)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>2 (6)</td>
<td>6 (17)</td>
</tr>
</tbody>
</table>

*System Order Classes with overall occurrence ≥25%; Preferred Terms with overall occurrence ≥10%.

†System Order Classes with overall occurrence ≥5%; Preferred Terms with overall occurrence ≥5%.

‡System Order Classes with overall occurrence ≥10%; Preferred Terms with overall occurrence ≥5%.

Analysis included all patients who started the induction phase (maintenance safety population).

### Table 2. B-cell deletion after end of treatment by induction arm

<table>
<thead>
<tr>
<th>B-cell depletion, n (%)</th>
<th>G-B (n = 41)</th>
<th>G-CHOP (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT, n</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Yes</td>
<td>41 (100)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
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<tr>
<td>EOT to 6 months follow-up after EOT, n</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Yes</td>
<td>31 (100)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>No</td>
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<td>6–9 months follow-up after EOT, n</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>No</td>
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<td>0</td>
</tr>
<tr>
<td>9–12 months follow-up after EOT, n</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (86)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>No</td>
<td>1 (14)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>12–18 months follow-up after EOT, n</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (100)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>2 (50)</td>
</tr>
<tr>
<td>18–24 months follow-up after EOT, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>No</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

Analysis included all patients who started the induction phase (overall safety population).

EOT = end of treatment (defined as the date when treatment, including maintenance, was completed or discontinued; G-B = obinutuzumab, bendamustine; G-CHOP = obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone

AEs = adverse events; G-B = obinutuzumab, bendamustine; G-CHOP = obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone
Key conclusions

- Maintenance treatment with obinutuzumab monotherapy after obinutuzumab plus chemotherapy induction was generally well tolerated.
  - No new safety signals emerged during maintenance treatment with obinutuzumab.
  - Infections occurred in 17% (G-B) and 14% (G-CHOP) of patients.
  - Clinically relevant neutropenia occurred in 14% of patients who received G-B induction, but it was not observed in patients who received G-CHOP induction.
  - Median IgG, IgA, and IgM levels remained within the normal range during maintenance.
- CR rates at the end of maintenance were high (G-B: 61%; G-CHOP: 70%) and most patients were progression-free at 32 months (G-B: 92%; G-CHOP: 84%).

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment in patients with indolent and mantle cell lymphomas: 7-year updated results from the StiL NHL1 study

Background
This multicentre, randomized, phase III study compared bendamustine plus rituximab (BR) and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line treatment in patients with indolent lymphomas or mantle cell lymphomas (MCL). The primary endpoint (progression-free survival [PFS]), response rates, and toxicities were published in The Lancet in 2013.

At ASH 2014, Rummel et al. presented updated results for overall survival (OS), time to next treatment (TTNT), and secondary malignancies (sNPL). The median follow-up period was 78 months.1

Study design
• Patients with indolent lymphomas or MCL were randomized to receive BR or R-CHOP for a maximum of 6 cycles.
• The primary endpoint was PFS; secondary endpoints included OS, TTNT, and sNPL.

Key findings
• In this analysis, 514 randomized patients were evaluable (BR, n = 261; R-CHOP, n = 253).
• Patient characteristics were well balanced between arms; median age was 64 years.
• TTNT was significantly prolonged with BR compared with R-CHOP (HR = 0.53, 95% CI: 0.40–0.68; p <0.0001). (Figure 1)
• Median TTNT was not yet reached in the BR group vs. 42.3 months in the R-CHOP group.
• The difference in OS between the treatment arms was not statistically significant, with estimated 10-year survival rates of 67.4% for BR and 60.1% for R-CHOP.
• In patients with indolent lymphomas (excluding MCL), a trend toward longer survival for the BR group could be observed, with estimated 10-year survival rates of 71.9% for BR and 61.5% for R-CHOP (HR = 0.70, 95% CI: 0.48–1.04; p = 0.076). (Figure 2)
• No difference in OS was found in the subgroup of patients with MCL (n = 95; HR = 1.28, 95% CI: 0.69–2.39; p = 0.429). (Figure 3)
• A total of 36 sNPL were observed in the BR group compared with 42 in the R-CHOP group, with two hematological malignancies in BR vs. five in R-CHOP (two cases of myelodysplastic syndrome in each group; two cases of acute myeloid leukemia and one case of chronic myelogenous leukemia in R-CHOP). (Table 1)

Table 1
<table>
<thead>
<tr>
<th>Malignancy Type</th>
<th>BR (n=36)</th>
<th>R-CHOP (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological malignancies</td>
<td>2 cases</td>
<td>5 cases</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>2 cases</td>
<td>1 case</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>1 case</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Time to next treatment

HR = bendamustine, rituximab; CI = confidence interval; HR = hazard ratio; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
**Figure 2. Overall survival in patients with indolent lymphoma**

**Figure 3. Overall survival in patients with mantle cell lymphoma**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>72</td>
<td>40</td>
</tr>
<tr>
<td>84</td>
<td>30</td>
</tr>
<tr>
<td>96</td>
<td>20</td>
</tr>
<tr>
<td>108</td>
<td>10</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>132</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = 0.70 (95% CI: 0.48–1.04)

$p = 0.076$

HR = 1.28 (95% CI: 0.69–2.39)

$p = 0.429$

**Key conclusions**

- In patients with previously untreated indolent lymphomas, and in elderly patients with MCL, BR demonstrates a PFS and TTNT benefit over R-CHOP.
- Furthermore, even with a longer follow-up, there is no indication that treatment with BR increases the risk of sNPL.
- In patients with indolent lymphomas treated with BR, a trend toward a survival benefit was found.
- These results confirm the high anti-lymphoma activity of the BR regimen and support the use of BR as a preferred first-line treatment in indolent lymphoma.

Frontline therapy with the RiBVD regimen elicits high clinical and molecular response rates and long PFS in elderly patients with mantle cell lymphoma: final results of a prospective phase II trial by the LYSA group

Background
The standard of care for first-line therapy in elderly patients with mantle cell lymphoma (MCL) in Europe is eight cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP-21) followed by rituximab maintenance. However, complete clinical (CR) and molecular responses (MR) to therapy remain suboptimal. Regimens combining rituximab with bendamustine and, more recently, the proteasome inhibitor bortezomib (Velcade®) with CHOP (VcR-CAP) have demonstrated superior CR rates and progression-free survival (PFS) compared to R-CHOP.

At ASH 2014, Gressin et al. reported data from the prospective phase II trial by the LYSA (Lymphoma Study Association) group investigating the RiBVD regimen (rituximab, bendamustine, bortezomib [Velcade®], and dexamethasone) in elderly patients with MCL.

Study design
All patients aged 65 or older with a diagnosis of MCL were treated with the RiBVD regimen if they fulfilled the inclusion criteria: Ann Arbor stage II–IV, performance status <3, no other neoplasm, no active human immunodeficiency virus, hepatitis B virus (HBV), or hepatitis C virus infections, no renal (creatinine clearance >20 mL/min) or cardiac dysfunction, and no diabetes.

The treatment strategy was as follows:
- The RiBVD regimen was administered every 4 weeks with rituximab 375 mg/m² intravenously (iv) on day 1, bendamustine 90 mg/m² iv on days 1 & 2, dexamethasone 40 mg iv on day 2, and bortezomib (Velcade®) 1.3 mg/m² subcutaneously on days 1, 4, 8 and 11.
- Primary prophylaxis with valacyclovir was mandatory for Herpes virus reactivation, but there was no recommendation for bacterial prevention.
- Patients were scheduled to receive a total of 6 cycles, if they achieved at least partial response (PR) at 4 cycles.
- The International Working Group (IWG) criteria, with and without fluorodeoxyglucose-positron emission tomography (FDG-PET), were used to define responses after 4 and 6 cycles. FDG-PET response was evaluated in each centre with the five-point scale visual method of Deauville.
- Molecular responses were evaluated centrally by real-time quantitative polymerase chain reaction (RQ-PCR) using patient specific immunoglobulin heavy chain (IGH) variable, diversity and joining (VDJ) targets.

Study design

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

Prevention: viral infection YES (valacyclovir) — pneumocystosis NO

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Evaluation</th>
<th>Interim</th>
<th>Final</th>
<th>PR</th>
<th>MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td></td>
<td>28 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagrams:

- C = cycle; D = day; iv = intravenous; MRD = minimal residual disease; PET = positron emission tomography; sc = subcutaneous
• The primary objective was to improve median PFS by 6 months over the current median PFS of 18 months obtained with R-CHOP when given without maintenance.

• Secondary objectives were to investigate toxicity and response after 4 and 6 cycles, overall survival (OS), and prognostic factors of survival.

**Key findings**

• Of the total of 76 patients who were recruited in one year (from November 2011 to December 2012), 74 were evaluable (two patients were excluded because of HBV positivity [n = 1] or misdiagnosis [n = 1]).

• Clinical characteristics of the 74 patients were:
  - Median age: 73 years (64–83);
  - Sex ratio, male/female: 49/25;
  - Ann Arbor stage II/III-IV: 4/70;
  - ECOG 0-1/2: 63/11;
  - MIPI score, low/intermediate/high: 3/19/50

• Out of the 55 (73%) cases reviewed for pathology, 54 were cases of MCL: 45 were classic form, and nine were pleomorphic.

• After 4 cycles, the ORR was 86.5% and the CR/ unconfirmed complete response (CRu) was 56.5%. (Table 1)
  - After 6 cycles, the CR/CRu increased to 75.5%, and the PR rate was 8%.
  - The complete MR rates after 6 months in blood and bone marrow samples were 85% and 74%, respectively. (Figure 1)
  - At a median follow-up of 24 months, the PFS was 70% and the OS was 80%. (Figures 2 and 3)

• Minimal residual disease (MRD) negativity in the blood at the end of treatment appeared to be the main prognostic factor of survival.

• Toxicities were essentially hematologic, with grade 3 or 4 neutropenia and thrombocytopenia in 51% and 36% of the cases, respectively.

• The main grade 3 or 4 extra-hematologic toxicities were asthenia (19%), neuropathy (14%), and global cardiac toxicity (7%).

### Table 1. Clinical responses (IWC 2007)

<table>
<thead>
<tr>
<th></th>
<th>Without PET scan</th>
<th>With PET scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interim</td>
<td>Final</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>64 (86.5)</td>
<td>62 (84)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>42 (56.5)</td>
<td>56 (75.5)</td>
</tr>
<tr>
<td>PR</td>
<td>22 (30)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Failure*</td>
<td>10 (13)</td>
<td>12 (16)</td>
</tr>
</tbody>
</table>

*Includes death, progressive disease, stable disease, refusal, and toxicity.

15 not done: CR/PR = 4 + 1, Failure = 10.

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

Figure 1. Interim and final molecular response

**Table 1. Clinical responses (IWC 2007)**

<table>
<thead>
<tr>
<th>Diagnosis (n = 54)</th>
<th>After 4 cycles (n = 53)</th>
<th>End of treatment (n = 50)</th>
<th>Peripheral blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg: 87% (n = 46)</td>
<td>85% (n = 43)</td>
<td></td>
<td>Neg: 87% (n = 46)</td>
</tr>
</tbody>
</table>

**Bone marrow**

Quantitative range = 10⁴
Sensitivity = 10⁻⁵

Pos: 18% (8/44)
16% (7/43)
Neg: 75% (n = 33)
74% (n = 32)

MRD = minimal residual disease; Neg = negative; Pos = positive; Pos NQ = positive not quantifiable
The RiBVD regimen is an effective first-line therapy for elderly patients with MCL. It showed a high CR rate, a high rate of MRD negativity, and good survival.

Toxicities were mild and manageable.

RiBVD is proving to be one of the best first-line treatments for elderly patients before maintenance.


Hyper-CVAD induction chemotherapy is associated with higher rates of stem cell mobilization failure in mantle cell lymphoma

Background
Mantle cell lymphoma (MCL) is an aggressive lymphoma generally seen in older patients. Patients with MCL deemed fit for high-dose regimens undergo induction therapy with rituximab and chemotherapy (e.g., Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone [Hyper-CVAD]/ cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]/bendamustine) followed by consolidation with autologous stem cell transplantation (ASCT).

Rituximab-Hyper-CVAD (R-Hyper-CVAD) is a dose-intense regimen with high response rates for MCL when used in the upfront setting (overall response rate [ORR] 97%; complete response [CR] 38%). R-bendamustine and R-CHOP are contemporary regimens with similar efficacy (ORR 85%–93%). In a recent randomized phase II trial (SWOG 1106), accrual to the Hyper-CVAD arm was stopped due to higher than expected rates of peripheral blood stem cell (PBSC) mobilization failure.

At ASH 2014, Salhotra et al. presented a retrospective analysis assessing the efficacy of autologous CD34+ hematopoietic stem cell (HSC) recovery after frontline chemotherapy with R-Hyper-CVAD versus R-CHOP or R-bendamustine (BR).
**Study design**

- The authors retrospectively analyzed data from 91 patients at City of Hope with newly diagnosed MCL who received upfront chemotherapy with R-Hyper-CVAD (n = 45, 49%) compared to R-CHOP or BR (n = 46, 51%) for success of stem cell collection.
- The primary endpoint was successful stem cell collection defined as the ability to collect ≥2.1 million CD34+ cells/kg.
- Secondary endpoints included number of days of apheresis, use of plerixfor as mobilization salvage, and total number of CD34+ cells collected.

**Key findings**

- There was no baseline difference between the two groups in terms of demographic profile (age/sex ratio) and time from diagnosis to start of CD34+ HSC collection (median 5.5 months). (Table 1)
- The majority of patients had stage IV (84%) disease at diagnosis and most of the HSC collections (88%) were done in the plerixafor era (post 2009).
- The majority of patients (81%) who successfully collected adequate numbers of HSCs underwent high-dose chemotherapy and ASCT.

---

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 91)</th>
<th>R-Hyper-CVAD (N = 45)</th>
<th>Other chemotherapy (N = 46)</th>
<th>Comparison p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient gender</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 0.62</td>
</tr>
<tr>
<td>Female</td>
<td>21 (23)</td>
<td>9 (20)</td>
<td>12 (26)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70 (77)</td>
<td>36 (80)</td>
<td>34 (74)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at collection completion (range), years</strong></td>
<td>58 (36–74)</td>
<td>56 (40–68)</td>
<td>62 (36–74)</td>
<td>Wilcoxon Rank Sum, p &lt; 0.01</td>
</tr>
<tr>
<td><strong>Time from diagnosis to collection (range), months</strong></td>
<td>5.5 (2.3–69.4)</td>
<td>4.5 (2.3–65.3)</td>
<td>6.4 (3.9–69.4)</td>
<td>Wilcoxon Rank Sum, p &lt; 0.01</td>
</tr>
<tr>
<td><strong>Stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 0.40</td>
</tr>
<tr>
<td>I</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (4)</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8 (9)</td>
<td>2 (4)</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>76 (84)</td>
<td>39 (87)</td>
<td>37 (81)</td>
<td></td>
</tr>
<tr>
<td><strong>Bone marrow involvement at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 0.73</td>
</tr>
<tr>
<td>No</td>
<td>22 (24)</td>
<td>9 (20)</td>
<td>13 (28)</td>
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<tr>
<td>Yes</td>
<td>67 (74)</td>
<td>35 (78)</td>
<td>32 (70)</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment after chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 0.06</td>
</tr>
<tr>
<td>Auto transplant</td>
<td>81 (89)</td>
<td>37 (82)</td>
<td>44 (96)</td>
<td></td>
</tr>
<tr>
<td>Allo transplant</td>
<td>4 (4)</td>
<td>4 (9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>No transplant</td>
<td>6 (7)</td>
<td>4 (9)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Mozobil era (08/16/2009)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 0.12</td>
</tr>
<tr>
<td>Pre</td>
<td>11 (12)</td>
<td>8 (18)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>80 (88)</td>
<td>37 (82)</td>
<td>43 (93)</td>
<td></td>
</tr>
<tr>
<td><strong>Mozobil usage</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 1.00</td>
</tr>
<tr>
<td>No</td>
<td>59 (65)</td>
<td>29 (64)</td>
<td>30 (65)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (35)</td>
<td>16 (36)</td>
<td>16 (35)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of collections (range)</strong></td>
<td>3 (1–9)</td>
<td>4 (1–9)</td>
<td>3 (2–8)</td>
<td>Wilcoxon Rank Sum, p = 0.21</td>
</tr>
<tr>
<td><strong>Total CD34+ (range), x 10^6 cells</strong></td>
<td>5.0 (0.3–100.5)</td>
<td>4.5 (0.3–100.5)</td>
<td>5.3 (0.7–76.6)</td>
<td>Wilcoxon Rank Sum, p = 0.05</td>
</tr>
<tr>
<td><strong>Total CD34+ (Failure rate)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s Exact, p = 0.05</td>
</tr>
<tr>
<td>&lt;2.1 x 10^6 cells</td>
<td>10 (11)</td>
<td>8 (18)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>≥2.1 x 10^6 cells</td>
<td>81 (89)</td>
<td>37 (82)</td>
<td>44 (96)</td>
<td></td>
</tr>
</tbody>
</table>

Hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone
On intent-to-treat analysis, the CD34+ HSC collection failure rate (defined by collection of <2.1 million CD34+ cells/kg) was 18% in the Hyper-CVAD arm and 4% in the control arm.

The median number of cycles of Hyper-CVAD received by patients who failed to collect >2.1 million CD34+ HSCs was 4 (3–8); this was not different from the median number of cycles received by patients who collected successfully [4 (2–8)].

The results of univariate and multivariate analyses are presented in Tables 2 and 3.

### Table 2. Univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at collection ≥58 years old</td>
<td>0.53 (0.14–2.04)</td>
<td>0.36</td>
</tr>
<tr>
<td>Time from diagnosis to collection ≥5.5 months</td>
<td>1.62 (0.42–6.16)</td>
<td>0.48</td>
</tr>
<tr>
<td>Induction therapy: Other, Hyper-CVAD</td>
<td>4.76 (0.95–23.80)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mozobil usage: No, Yes</td>
<td>9.50 (1.88–48.06)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CI = confidence interval; Hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone

### Table 3. Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy: Other, Hyper-CVAD</td>
<td>4.76 (0.95–23.80)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mozobil usage: No, Yes</td>
<td>9.50 (1.88–48.06)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Unadjusted**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at collection ≥58 years old</td>
<td>0.84 (0.17–4.17)</td>
<td>0.83</td>
</tr>
<tr>
<td>Time from diagnosis to collection ≥5.5 months</td>
<td>2.14 (0.41–11.32)</td>
<td>0.37</td>
</tr>
<tr>
<td>Induction therapy: other, HyperCVAD</td>
<td>7.28 (1.01–52.57)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mozobil usage: No, Yes</td>
<td>9.38 (1.73–50.92)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Adjusted for baseline differences**

CI = confidence interval; Hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone

### Key conclusions

- This retrospective analysis confirms observations that Hyper-CVAD induction leads to higher rates of stem cell collection failures.

- Unlike prior published reports, the median number of cycles (4) was similar in the Hyper-CVAD arm in patients who failed to successfully collect HSCs compared with patients who did not.

- No difference was seen in number of days on apheresis or frequency of plerixafor usage.

- Hyper-CVAD is an effective chemotherapy for upfront treatment of MCL; however, its use significantly impairs the ability to subsequently collect HSCs.

- The limitations of this trial included its retrospective design and limited sample size, as all patients were from a single institution.

Bendamustine plus rituximab followed by rituximab maintenance for patients with untreated advanced follicular lymphomas: results from the StiL NHL 7-2008 trial (MAINTAIN)

Background
The StiL Study NHL 7-2008 investigated the role of maintenance duration with rituximab after induction with bendamustine plus rituximab (BR) in the first-line treatment of advanced follicular lymphoma (FL), other indolent lymphomas, or mantle cell lymphoma.

At ASH 2014, Rummel et al. reported the response to BR and its safety, followed by 2 years of rituximab maintenance in patients with FL only.1

Study design
- Patients with FL were treated with a maximum of 6 cycles of BR (bendamustine 90 mg/m² [days 1 & 2], rituximab 375 mg/m²) administered every 28 days plus two more rituximab cycles every 4 weeks.
- All responding patients (complete response [CR] or partial response [PR]) received 2 years of rituximab maintenance treatment (375 mg/m²) administered every 2 months.
- Patients with an ongoing response after 2 years of maintenance were then randomized 1:1 to observation or to 2 more years of rituximab maintenance (i.e., BR plus 2 years vs. 4 years rituximab maintenance).

Key findings
- To date, 612 patients (319 women and 293 men) with FL have been registered (first patient in April 2009, last patient in July 2012). (Table 1)
  - Median age was 61 years;
  - 58% of patients had stage IV disease;
  - Median number of nodal areas was 5;
  - Bone marrow involvement was found in 52% of patients; and 28% presented with splenomegaly.
  - Median lactate dehydrogenase (LDH) was 210 U/L, with 32% of patients having an LDH >240 U/L.
  - Median follicular lymphoma International Prognostic Index (FLIPI) was 3; and
  - The median CD4 count was 491 at induction.
- Of these 511 patients achieving remission, 291 (56.9%) received the full 2 years of rituximab maintenance treatment, and 281 patients were then randomized to observation only (n = 140) or to 2 additional years of rituximab maintenance (n = 141).
- Seventy-nine patients are still undergoing treatment with the planned 2-year standard rituximab maintenance therapy and are not yet randomized.
- Reasons for not receiving the full 2-year course of rituximab maintenance (n = 141) included: death (n = 6); relapse or progressive disease (n = 50); transformation into aggressive lymphoma (n = 4); infection during rituximab maintenance (n = 4); infection during BR induction (n = 1); toxicity (n = 19); secondary malignancies during

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics and response rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Median age (range), years</td>
</tr>
<tr>
<td>Stage IV, n (%)</td>
</tr>
<tr>
<td>Median number of nodal areas</td>
</tr>
<tr>
<td>Bone marrow involvement, n (%)</td>
</tr>
<tr>
<td>Splenomegaly, n (%)</td>
</tr>
<tr>
<td>Median LDH</td>
</tr>
<tr>
<td>LDH &gt;240 U/L, n (%)</td>
</tr>
<tr>
<td>Median FLIPI</td>
</tr>
<tr>
<td>Overall response rate</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
</tbody>
</table>

FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase

Single-agent ibrutinib demonstrates safety and durability of response at 2 years follow-up in patients with relapsed or refractory mantle cell lymphoma: updated results of an international, multicentre, open-label phase II study

Background
Bruton’s tyrosine kinase (BTK) is a critical signaling molecule in the B-cell receptor (BCR) signaling pathway essential for B-cell development, survival, and function. Ibrutinib is a first-in-class, once-daily, orally dosed, covalent inhibitor of BTK approved for treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Previous results of the phase II trial demonstrated durability of responses and favourable safety profile of daily oral ibrutinib in relapsed or refractory MCL at a median follow-up of 15.3 months.

At ASH 2014, Wang et al. presented updated safety and efficacy results of the phase II trial with a median follow-up of approximately 26.7 months.1

Study design
• This international, open-label, phase II study was conducted at 18 sites.

induction or during rituximab maintenance (n = 3 and n = 6, respectively); reactivated hepatitis B (n = 1; patient had not received lamivudine prophylaxis despite mandatory instructions stated in the study protocol); rituximab intolerance (n = 3); removal of patient from trial by investigator for any reason (n = 16); withdrawal of patient consent during BR induction (n = 2) and during the 2-year rituximab maintenance (n = 14); non-compliance (n = 2); lost to follow-up (n = 6); severe comorbidity (dementia, n = 1); and other reasons (n = 3).
• No unexpected toxicity and no progressive multifocal encephalopathy were observed in patients with FL.
• To date, 35 out of 612 (5.7%) patients have developed 38 secondary malignancies.

Key conclusions
• Results of this study confirmed the efficacy of BR in frontline treatment of patients with previously untreated advanced FL. These are in line with results from other studies, such as StiL NHL 1-2003 or the BRIGHT study.
• Rituximab standard maintenance over 2 years for FL appears safe, with no new or unexpected toxicities.
• The role of rituximab maintenance after BR remains under investigation.


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Key findings

- Median treatment duration was 8.3 months; 51 patients (46%) were treated for >1 year, and 22 (20%) were treated for two or more years.

Safety

- Safety results are shown in Table 1 and Figure 1.
- Atrial fibrillation was reported in 12 patients (11%) overall: (Table 1)
  - They were considered grade 3-4 events in 6% of patients and serious adverse events (SAEs) in 6% of patients.
- Second malignancies:
  - Cutaneous malignancies included squamous cell carcinoma (3 patients) and basal cell carcinoma (1 patient).
  - With an estimated median follow-up of 26.7 months, the prevalence rate of all-grade diarrhea was 54%. (Figure 1)
  - No SAE of diarrhea was reported after the 6-month interval.
  - At median follow-up, the prevalence rate of grade ≥3 infections was 28%.
  - SAE infections occurred in 21% of patients, and both grade ≥3 and SAE infections generally decreased over time.
  - Pneumonia was the most common grade ≥3 infection.
- Bleeding events had occurred in 50% of patients at median follow-up.
  - The prevalence rate of all-grade bleeding was highest in first 6-month interval; there were no grade 5 events.
  - The prevalence rate of major bleeding was low, with similar rates across evaluated time intervals.
- Subdural hematomas were reported in four patients: grade 1 in one patient, grade 2 in one patient, and grade 3 in two patients.
  - All cases were associated with falls, head trauma, or both.
  - All four patients received either aspirin or warfarin within 2 days before or on the day of the event.

Efficacy

- Median time to initial response was 1.9 months, median time to complete response (CR) was 5.5 months, and response was independent of patient characteristics and risk factors.
- Best response results are shown in Figure 2.
- Median DOR was 17.5 months (95% CI: 14.9, non-estimable [NE]).

| Table 1. Summary of serious adverse events (≥2% of patients) regardless of attribution |
|---------------------------------------------|-----------------|-----------------|-----------------|
| SAE*, n (%)                                  | Any grade       | Grade 3/4       | Grade 5         |
| Disease progression†                        | 11 (10)         | 3 (3)           | 8 (7)           |
| Pneumonia                                   | 8 (7)           | 7 (6)           | 1 (1)           |
| Atrial fibrillation                         | 7 (6)           | 6 (5)†          | 0               |
| Urinary tract infection                     | 4 (4)           | 3 (3)           | 0               |
| Febrile neutropenia                         | 3 (3)           | 3 (3)           | 0               |
| Abdominal pain                              | 3 (3)           | 3 (3)           | 0               |
| Acute renal failure                         | 3 (3)           | 2 (2)           | 1 (1)           |
| Subdural hematoma                           | 3 (3)           | 2 (2)           | 0               |
| Pyrexia                                     | 3 (3)           | 1 (1)           | 0               |
| Confusional state                           | 3 (3)           | 1 (1)           | 0               |

*Adverse events were updated with an estimated median follow-up of 26.7 months.
†Mantle cell lymphoma reported as a SAE by investigators.
‡One additional patient had a grade 3 atrial fibrillation that was not considered a SAE.
SAE = serious adverse event
• For patients with best response as PR, estimated median DOR was 14.9 months (95% CI: 6.6, 17.5).
• For patients with CR, median DOR was not reached (95% CI: 20.3, NE).
• Median PFS for the all treated population was 13 months (95% CI: 7.0, 17.5). (Figure 3)
• The estimated PFS rate at 24 months was 31% (95% CI: 22.3%, 40.4%).
• Median OS for the all treated population was 22.5 months (95% CI: 13.7, NE). (Figure 4)
• The estimated OS rate at 24 months was 47% (95% CI: 37.1%, 56.9%).
• The most prolonged DOR, PFS, and OS were observed in patients with better prognosis, lower disease burden, and less refractory disease.

Figure 1. Treatment-emergent adverse events (≥15% of patients) regardless of attribution

AEs = adverse events

AEs were updated with an estimated median follow-up of 26.7 months.

AEIs = adverse events
Figure 2. Best response

CR = complete response; PR = partial response

Figure 3. Progression-free survival

Figure 4. Overall survival
Key conclusions

- Results with a median follow-up of 26.7 months demonstrate durability of responses and sustained single-agent activity of continuous ibrutinib in previously treated MCL.
- Approximately one-third of patients remain progression-free at 24 months.
- Additional follow-up time did not reveal an increase in unforeseen AEs.
- Ibrutinib continues to show a favourable risk-benefit profile over time, with a safety profile consistent with that reported previously.


Efficacy and safety of single-agent ibrutinib in patients with mantle cell lymphoma who progressed after bortezomib therapy

Background
Mantle cell lymphoma (MCL) is a rare but aggressive B-cell malignancy that is difficult to treat, particularly in the relapsed setting where median overall survival (OS) is 1 to 2 years. Ibrutinib, a first-in-class, once-daily, oral covalent inhibitor of Bruton’s tyrosine kinase (BTK), has been approved in the United States, the European Union, and other countries for patients with MCL who have received at least one prior line of therapy. Approvals were based on results from a single-agent, single-arm phase Ib/II study of ibrutinib in patients with MCL who had received at least one prior therapy.

At ASH 2014, Wang et al. reported, from the MCL2001 (SPARK) study, the efficacy and safety of single-agent ibrutinib in patients with MCL who had received a rituximab-containing regimen and who received at least two cycles of bortezomib and had progressed during or after bortezomib therapy.1

Study design
- This was a phase II, multicentre, single-arm study, in which patients received ibrutinib 560 mg orally once daily until progressive disease (PD) or unacceptable toxicity.
- The primary endpoint was overall response rate (ORR) in response-evaluable patients, as assessed by an independent review committee (IRC).
- Secondary endpoints included IRC-assessed duration of response, progression-free survival (PFS), OS, and safety.
- Key inclusion criteria:
  - Age ≥18 years, with diagnosis of MCL confirmed by central review prior to enrollment;
  - Received at least one prior rituximab-containing chemotherapy regimen and at least two cycles of bortezomib therapy (single-agent or in combination) with documented PD during or after bortezomib therapy;
  - At least one measurable site of disease;
  - Absolute neutrophil count ≥750/mm³ and platelet count ≥50,000/mm³.
- Key exclusion criteria:
  - Prior treatment with ibrutinib or other BTK inhibitors;
  - More than five prior lines of therapy.

Key findings
- A total of 120 patients were enrolled in the study (38 centres in 7 countries).
- At the time of clinical cut-off for the primary analysis (April 29, 2014), median follow-up was 14.9 months, with median treatment duration of 8 months (range: 0.5–20.9 months).
Eighty-one patients (67.5%) discontinued treatment, mainly due to disease progression in 53 patients (44.2%) and an adverse event (AE) in 8 patients (6.7%).

- ORR by IRC was 62.7%, with a complete response (CR) rate of 20.9%. (Figure 1)
- Subgroup analysis showed that the ORR was independent of age, gender, geographic region, number of prior lines of therapies, baseline extranodal disease, simplified MIPI score, bulky disease, and stage of MCL.
- Median time to best response was 2.14 (range: 1.3–10.6) months: 2.07 (range: 1.3–6.3) months to partial response (PR) and 6.21 (range: 1.9–10.6) months to CR.
- ORR by investigator assessment for response-evaluable patients was 66.4% (95% CI: 57.5–75.2%), with a CR of 18.2%.
- Median duration of response by IRC was 14.9 months (Figure 2), with the median time to first response being 2.1 months (range: 1.3–6.3 months). The median duration of PR was 14.9 months and the median duration of CR was not reached with 53% remaining progression-free at 1 year.

**Figure 1. Best response in the evaluable population by IRC (N = 110)**

![Chart showing best response percentages]

**Figure 2. Kaplan-Meier curve of duration of response by IRC (all-treated population)**

![Chart showing Kaplan-Meier curve]
In Supportive Care Oncology
Progression-free survival (%)

<table>
<thead>
<tr>
<th>Months since first dose</th>
<th>Number at risk</th>
</tr>
</thead>
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<tr>
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IRC = independent review committee; PFS = progression-free survival

Ibrutinib

Median PFS: 10.5 months
PFS rate at 12 months: 47%

Number at risk

Figure 3. Kaplan-Meier curve of progression-free survival by IRC (all-treated population)

Overall survival (%)

<table>
<thead>
<tr>
<th>Months since first dose</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

OS = overall survival

OS = overall survival

Ibrutinib

Median OS: not reached
OS rate at 18 months: 61%

Figure 4. Kaplan-Meier curve of overall survival (all-treated population)

• Kaplan-Meier analyses of PFS and OS are shown in Figures 3 and 4, respectively.

• The majority of AEs were grades 1 and 2. (Figure 5)

• Dose reductions due to AEs occurred in 8 patients (6.7%).

• The most common AEs were fatigue (any grade: 43.3%; grade 3 or 4: 3.3%) and diarrhea (any grade: 42.5%; grade 3 or 4: 2.5%), with the vast majority being grade 1 (grade 1: fatigue 25.8% and diarrhea 30.8%). (Figure 5)

• The majority of bleeding events were grade 1, the most common being contusion (14.2%) and epistaxis (6.7%). Major bleedings were rare (2.5% ≥ grade 3).

• Treatment-related lymphocytosis (absolute lymphocyte count increased ≥50% from baseline and ≥5 × 10^9/L) was observed in 27.5% of patients.

• The percentage of patients with grade ≥3 infections in the first 6 months was 19.2%, and after 6 months was 15.5%.
**Key conclusions**

- **ORR (63%)** and **CR (21%)** rates with single-agent ibrutinib were high and similar to those found in previous studies. Some patients, however, take up to 6.3 months to achieve their initial response and 10.6 months to achieve their best response.

- The majority of AEs were mainly grade 1 and 2 and self-limiting, and few patients discontinued due to AEs (6.7%). No new safety signals were identified.

- These results confirm the clinical efficacy and safety of once-daily ibrutinib in patients with relapsed MCL, providing a high and durable response accompanied with a good tolerability profile.


Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent, or mantle cell lymphomas: 8-year follow-up results of the randomized phase III study NHL 2-2003 on behalf of the StiL

**Background**

Fludarabine plus rituximab (FR) is an established treatment option for patients with relapsed/refractory follicular lymphoma (FL), other indolent lymphomas, or mantle cell lymphoma (MCL).

In 2003, Rummel et al. initiated the multicentre, randomized, phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) to compare the efficacy and safety of bendamustine plus rituximab (BR) versus FR for patients with relapsed FL, other indolent lymphomas, or MCL. At ASH 2014, they reported the 8-year follow-up results.1

**Study design**

- This was an investigator-initiated trial conducted by the cooperative study group StiL at 55 centres in Germany.
- Patients in need of treatment were randomized to rituximab 375 mg/m² (day 1) plus either bendamustine 90 mg/m² (days 1 & 2) or fludarabine 25 mg/m² (days 1–3) every 4 weeks for a maximum of 6 cycles.
- The protocol was amended in July 2006 to allow rituximab maintenance therapy (rituximab 375 mg/m² every 3 months for up to 2 years) in both arms, following regulatory approval in this setting.
- A total of 219 patients, accrued between November 2003 and September 2009, were evaluable for the analysis.

- Inclusion criteria:
  - Patients with one of the following CD20-positive lymphoma entities: FL grade 1 and 2, lymphoplasmacytic lymphoma/immunocytoma (Waldenstrom), small lymphocytic lymphoma (CLL without leukemic phase), nodular and generalized (nodal and extranodal) marginal zone lymphoma, or MCL;
  - Relapsed disease or refractory to previous treatment. Patients refractory to rituximab-, bendamustine-, or purine analog-based therapies were excluded;
  - Defined indication for treatment, except in MCL;
  - Histology not older than 6 months;
  - Stage II (bulky disease 7.5 cm), III, or IV;
  - Age at least 18 years, no upper age limit, WHO 0–2;
  - Written informed consent of the patient.
- Defined indications for treatment: MCL, B-symptoms, hematopoietic failure (Hb <11g/dL, granulocytes <1,500/µL, thrombocytes <100,000/µL), large tumour burden (three areas >5cm or one area >7.5 cm), rapid progression, complications due to disease
- The primary objective was to prove non-inferiority of BR versus FR in patients with relapsed indolent lymphomas or MCL defined as a difference of less than 15% in progression-free survival (PFS) after one year (α = 5%, β = 20%).
The secondary objectives were to compare response rates, time to next treatment, event-free survival, overall survival (OS), acute and late toxicities, and infectious complications.

Key findings
- A total of 219 patients were evaluable for response and toxicity (BR, n = 114; FR n = 105).
- Histological subtypes were distributed equally between the BR and FR arms.
- There were no significant differences in patient characteristics between arms. Patients had received a median of one prior therapy.
- Median follow-up was 96 months.
- There were no significant differences in the rates of alopecia, peripheral neuropathy, stomatitis, nausea and emesis, fatigue, erythema, allergic reactions (skin), or infectious complications between groups. (Table 1)
- Grade 3/4 hematologic toxicities were also similar between arms (BR vs. FR, % of cycles):
  - Neutropenia: 14.0% vs. 14.5%;
  - Leukocytopenia: 13.6% vs. 14.2%;
  - Thrombocytopenia: 2.2% vs. 2.8%;
  - Anemia: 1.6% vs. 2.0%.
- Sixteen patients (14.0%) developed a secondary neoplasia after BR compared with 16 patients (15.2%) after FR.
- The overall response rate was significantly higher with BR than with FR (82% vs. 49%, respectively; \( p < 0.0001 \)).
- The complete response rate with BR was also significantly higher than that with FR (39% vs. 16%; \( p = 0.0004 \)).

Table 1. Toxicities in the BR and FR groups (all CTC grades)

<table>
<thead>
<tr>
<th></th>
<th>BR (n = 109)</th>
<th>FR (n = 99)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Paresthesias</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nausea and emesis</td>
<td>29</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Skin (erythema)</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Allergic reaction (skin)</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Infectious complications</td>
<td>37 (34%)</td>
<td>25 (25%)</td>
<td>0.1765</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; CTC = Common Toxicity Criteria; FR = fludarabine, rituximab

Sixteen patients (14.0%) developed a secondary neoplasia after BR compared with 16 patients (15.2%) after FR.
- The overall response rate was significantly higher with BR than with FR (82% vs. 49%, respectively; \( p < 0.0001 \)).
- The complete response rate with BR was also significantly higher than that with FR (39% vs. 16%; \( p = 0.0004 \)).

Figure 1. Progression-free survival by treatment arm

BR = bendamustine, rituximab; CI = confidence interval; FR = fludarabine, rituximab; HR = hazard ratio; PFS = progression-free survival
• There were significantly more patients with disease progression after treatment with FR than with BR (30% vs. 7%, respectively; \( p < 0.0001 \)).

• Median PFS was significantly prolonged with BR compared with FR (34.3 vs. 12.0 months; HR = 0.54, 95% CI: 0.39–0.73; \( p = 0.000064 \)). (Figure 1)

• The longer PFS translated into a survival benefit with a significantly longer median OS in the BR group than in the FR group (109.7 vs. 49.4 months; HR = 0.64, 95% CI: 0.45–0.91; \( p = 0.012 \)), comprising 55 and 71 deaths in the BR and FR groups, respectively. (Figure 2)

• A subanalysis showed that rituximab maintenance therapy may have added benefit in terms of PFS (HR = 0.52, 95% CI: 0.32–0.85; \( p = 0.0083 \)) and OS (HR = 0.52, 95% CI: 0.29–0.93; \( p = 0.024 \)) in the small group of 44 patients who received this treatment compared with those who did not (\( n = 108 \)). (Figures 3 and 4)

---

**Figure 2. Overall survival by treatment arm**

<table>
<thead>
<tr>
<th></th>
<th>Months (median)</th>
<th>Deaths (events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>114</td>
<td>109.7</td>
</tr>
<tr>
<td>FR</td>
<td>105</td>
<td>49.4</td>
</tr>
</tbody>
</table>

**Figure 3. Progression-free survival by maintenance arm**

<table>
<thead>
<tr>
<th></th>
<th>Months (median)</th>
<th>PFS (events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No maintenance</td>
<td>108</td>
<td>30.5</td>
</tr>
<tr>
<td>Maintenance</td>
<td>44</td>
<td>72.4</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival
Figure 4. Overall survival by maintenance arm

<table>
<thead>
<tr>
<th>HR = 0.52 (95% CI: 0.29–0.93)</th>
<th>n</th>
<th>Months (median)</th>
<th>Deaths (events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No maintenance</td>
<td>108</td>
<td>69.8</td>
<td>57</td>
</tr>
<tr>
<td>Maintenance</td>
<td>44</td>
<td>n.y.r.</td>
<td>14</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; n.y.r. = not yet reached

Key conclusions

- BR was more effective than FR in this setting of relapsed FL, other indolent lymphomas, and MCL due to higher overall and complete response rates, a longer PFS, and an improved OS.

- These data confirm the high anti-lymphoma activity of BR.

- Rituximab maintenance appeared to have additional benefit, but limitations include:
  - Small sample size;
  - Potential selection bias;
  - Unplanned nature of that comparison, and not randomized.


Czuczman MS, et al. ASH 2014:1757

Bendamustine plus rituximab in the treatment of relapsed/refractory mantle cell lymphoma: multivariate analysis and updated final results by subgroup

Background

Most patients with mantle cell lymphoma (MCL) experience an aggressive disease course. Although overall survival (OS) has improved recently, patients have a reported median OS of about 3 to 5 years, depending on the MCL International Prognostic Index (MIPI) score. Relapse is high, and management of relapsed/refractory MCL remains difficult.

A retrospective analysis of 58 patients with relapsed/refractory MCL treated with bendamustine combination therapy (primarily rituximab) in Spain showed an overall response rate (ORR) of 86% and a median progression-free survival (PFS) of 16 months (95% CI: 13.3–18.8).

Czuczman et al. conducted a study of bendamustine plus rituximab (BR) in patients with relapsed/refractory
MCL, with preliminary results previously presented. A multivariate analysis of baseline demographic and disease factors affecting outcomes was conducted along with individual subgroup analyses for best overall response (OR), duration of response (DOR), and PFS. Results were presented at ASH 2014.1

Study design
• This multicentre, open-label, single-arm, phase II study was conducted to evaluate efficacy, tolerability, and safety of BR in adults with relapsed/refractory CD20+ B-cell MCL.
• Relapsed disease was defined as having achieved complete response (CR) with a previous therapy but demonstrating recurrent disease ≥6 months after the last dose.
• Refractory disease was defined as either a lack of CR while undergoing previous therapy or the loss of CR <6 months after the last dose.
• Bendamustine 90 mg/m² was administered on days 1 and 2, and rituximab 375 mg/m² was administered on day 1 of a 28-day cycle. The treatment period was 6 cycles, but patients who did not have disease progression and had not achieved a CR could receive up to 8 cycles.
• Univariate analyses were conducted based on relapsed/refractory status, response to most recent rituximab treatment, MCL International Prognostic Index (MIPI) category, IPI total score, Ann Arbor stage, cyclin D1 status, lactate dehydrogenase (LDH) level, β2-microglobulin level, sex, and race. Fisher’s exact test was used to explore association between best OR and each categorical variable. Variables with a p ≤0.1 were included in a multivariate analysis.
• Logistic regression using the proportional odds model was used to examine overall response based on parameters selected above.
• A step-wise model selection method with entry and stay criteria of p = 0.1 was applied.
• Score test for the proportional odds assumption was conducted. Deviance and Pearson goodness-of-fit statistics were examined.

Key findings
• Forty-five patients received ≥1 cycle of BR. Median age was 70 years, 71% were male, and 82% had stage IV disease.
• Median treatment duration was 6 cycles.
• For the entire cohort, the ORR was 82% (95% CI: 68.0%–92.0%) and the median PFS was 17.2 months (range: 0.03–45.37 months), with a one-year PFS rate of 67%. (Figure 1)
• Overall survival is shown in Figure 2.
• The most common nonhematologic treatment-emergent adverse events (AEs) were nausea (69%), fatigue (56%), decreased appetite (42%), constipation (38%), diarrhea (36%), vomiting (36%), and decreased weight (31%).
• The main treatment-emergent grade 3/4 AEs (>10%) were hematologic: neutropenia (n = 15), lymphopenia (n = 6), and leukopenia (n = 5).
• Univariate analyses for time-to-event endpoints are presented in Table 1. Relapsed/refractory patient status (p = 0.0003), prior response to the most recent rituximab treatment (p = 0.0011), the IPI total score (p = 0.0482), LDH (p = 0.0043), and β2-microglobulin (p = 0.0319) at baseline met the p = 0.1 criterion and were selected and included in multivariate analysis.
• The final logistic regression model had relapsed/refractory patient status and β2-microglobulin as predictors of response, with p = 0.0675 for score test for proportional odds assumption, p = 0.9999 for deviance goodness-of-fit statistic, and p = 0.9796 for Pearson goodness-of-fit statistic.
• The logistic regression analysis showed a significant association between best OR and relapsed/refractory patient status at study entry (p = 0.0013) but a nonsignificant association between best OR and β2-microglobulin (p = 0.0929).
• The estimate of odds ratio between relapsed and refractory MCL was 13.984 (95% CI: 2.805–69.71). The odds for improved best OR were significantly higher in relapsed patients than in refractory patients. The estimate of odds ratio corresponding to a 1 unit increase of β2-microglobulin is 1 (95% CI: 1–1).
• Final data showed ORRs of 90% and 75% in patients with relapsed and refractory MCL, respectively.
• Similarly, median DOR and PFS were longer in the relapsed group. (Table 1)
• Prior response to rituximab and lower MIPI score were also generally aligned with more favourable response and time-to-event results. (Table 1)
Table 1. Univariate analysis of time-to-event endpoints

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median DOR (95% CI), months</th>
<th>Median PFS (95% CI), months</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>19.7 (11.1–38.8)</td>
<td>23.1 (13.2–41.5)</td>
<td>21</td>
</tr>
<tr>
<td>Refractory</td>
<td>15.3 (7.9–35.3)</td>
<td>17.1 (8.3–24.0)</td>
<td>24</td>
</tr>
<tr>
<td>Prior response to the most recent rituximab treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>17.0 (10.7–38.8)</td>
<td>22.1 (13.2–41.5)</td>
<td>19</td>
</tr>
<tr>
<td>Partial response</td>
<td>17.9 (4.9–35.9)</td>
<td>18.1 (4.7–38.7)</td>
<td>9</td>
</tr>
<tr>
<td>MIPI category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 (low risk)</td>
<td>20.6 (14.3–35.5)</td>
<td>23.2 (16.2–40.4)</td>
<td>24</td>
</tr>
<tr>
<td>4–5 (intermediate risk)</td>
<td>11.1 (5.1–21.3)</td>
<td>12.8 (8.3–24.0)</td>
<td>12</td>
</tr>
<tr>
<td>≥6 (high risk)</td>
<td>NC (5.1–NC)</td>
<td>7.9 (2.0–NC)</td>
<td>9</td>
</tr>
</tbody>
</table>

CI = confidence interval; DOR = duration of response; MIPI = Mantle Cell Lymphoma International Prognostic Index; NC = not calculable; PFS = progression-free survival

Key conclusions

- In this study of heavily pretreated older patients with advanced MCL, logistic regression analysis demonstrated a statistically significant difference in best OR to BR treatment between patients with relapsed and refractory status at study entry.
- The ORR was higher in patients with relapsed MCL (90%) and lower in patients with refractory MCL (75%) at baseline. These ORRs are higher than those reported for two single-agent therapies, bortezomib (31%) and lenalidomide (26%), approved for relapsed/refractory MCL.
- BR showed efficacy across a wide range of patient subgroups with relapsed/refractory MCL.
  - In the subgroup of patients with relapsed MCL, CR was more common than partial response (PR), while patients with refractory MCL were more likely to achieve PR than CR. This information may be used to help guide treatment decisions when considering BR in heavily treated MCL patients.
- Data from this study are consistent with previous studies and demonstrate that BR has an acceptable safety profile in the relapsed/refractory MCL setting.
- With an overall median PFS of 17.2 months, the BR regimen was generally well tolerated and may serve as the backbone to which other active agents can be added in study regimens to further improve antilymphoma activity.

Saito H, et al. ASH 2014:3066

Prolonged lymphocytopenia after bendamustine with or without rituximab treatment in patients with relapsed or refractory indolent B-cell and mantle cell lymphoma

**Background**
Bendamustine with or without rituximab has demonstrated remarkable efficacy in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma (B-NHL) and mantle cell lymphoma (MCL). However, previous reports showed that the incidence of lymphocytopenia was higher in patients receiving bendamustine with or without rituximab than in those receiving other conventional cytotoxic chemotherapy regimens such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Opportunistic infections were also triggered, including cytomegalovirus reactivation, hepatitis B virus reactivation, varicella zoster virus infections, and *Pneumocystis* pneumonia (PCP).

The duration until recovery of the decreased lymphocytes and CD4-positive T cells to their baseline levels upon bendamustine treatment is still unclear. This question was addressed in a study by Saito et al. at ASH 2014.1

**Study design**
- This was a retrospective study of 56 consecutive patients with relapsed or refractory indolent B-NHL and MCL who received bendamustine ± rituximab (no rituximab maintenance) at a single institution between 2011 and 2014.
- Peripheral blood lymphocytes and CD4-positive T-cell counts were analyzed at baseline, during, and after bendamustine treatment, as well as the details of infectious events and their correlations.

**Key findings**
- Thirty-one (55%) patients were male and 25 (45%) were female, with a median age of 63 years (range: 36–86).
- Patients had the following diagnosis, n (%):
  - Follicular lymphoma (FL): 20 (35);
  - MCL: 14 (25);
  - Transformed FL: 9 (16);
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue: 5 (9);
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma: 4 (7);
  - Nodal marginal zone lymphoma: 2 (4);
  - Lymphoplasmacytic lymphoma: 1 (2);
  - Low-grade B-NHL, unclassifiable: 1 (2).
- The median number of prior regimens administered was 2 (range: 1–9).
- A total of 23 (41%) of the 56 patients received bendamustine in combination with rituximab, while the rest (33 [59%]) received bendamustine without rituximab.
- The median number of bendamustine cycles was 4 (range: 1–6).
- The median follow-up period was 9.1 months (range: 0–33 months).
- Median lymphocyte and CD4-positive T-cell count nadirs during observation were 365/µL (range: 20–1310/µL) and 93/µL (range: 7–178/µL), respectively.
- Significantly decreased lymphocyte counts (median: 260 vs. 410/µL) were detected in the patients who received bendamustine with rituximab compared with those who received bendamustine without rituximab (*p* = 0.03).
- In the comparison between 1 month and 7–9 months after the completion of bendamustine without rituximab, lymphocyte counts were significantly increased (median: 565 vs. 1125/µL, *p* = 0.003). On the other hand, with rituximab, lymphocyte counts were not significantly increased (median: 600 vs. 780/µL, *p* = 0.07).
- Results for lymphocyte and CD4-positive T-cell counts are shown in Figure 1.
- Although no statistical significances were detected between lymphocytopenia and incidence of infectious events, all infectious events occurred within 9 months after completion of bendamustine in patients who received no treatment after bendamustine during follow-up.
- Infectious complications are shown in Table 1.
Figure 1. Lymphocyte and CD4-positive T-cell counts

Table 1. Infectious complications

<table>
<thead>
<tr>
<th>Patients affected, n (%)</th>
<th>During bendamustine</th>
<th>During observation*</th>
<th>During subsequent treatments</th>
<th>Total follow-up†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytomegalovirus antigenemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>4 (7)</td>
<td>2 (4)</td>
<td>9 (16)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Cytomegalovirus disease (colitis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Pneumocystis pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Varicella zoster virus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Hepatitis B virus reactivation‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Other infections§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>15 (25)</td>
<td>8 (13)</td>
<td>18 (32)</td>
<td></td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td></td>
</tr>
</tbody>
</table>

*After the completion of bendamustine.

*During observation: the period between the completion of bendamustine and starting the next treatment.
†Total follow-up: the period between the completion of bendamustine and the last follow-up.
‡Hepatitis B virus (HBV) reactivation without clinical symptoms and liver damage was detected in the patients with HBs antigen (-) and anti-HBc antibody (+) during monitoring of serum HBV DNA. After administration of entecavir treatment, HBV DNA became undetectable.
§Other infections: During bendamustine: fever (n = 9), febrile neutropenia (n = 2), sepsis (n = 1), urinary tract infection (n = 1), oral mucositis (n = 1), mycosis (n = 1). During observation: fever (n = 6), influenza virus infection (n = 1), sinusitis (n = 1).

Key conclusions

- This analysis revealed that the majority of relapsed or refractory patients with indolent B-NHL and MCL showed prolonged lymphocytopenia and low CD4-positive T-cell counts, for at least 7–9 months, after the completion of bendamustine with or without rituximab.
- The prophylaxis against PCP and varicella zoster virus deserves consideration for at least 7–9 months after bendamustine treatment.
- Further investigations are needed to confirm these results.

LaCasce A, et al. ASH 2014:293

Brentuximab vedotin in combination with bendamustine for patients with Hodgkin lymphoma who are relapsed or refractory after frontline therapy

Background
Patients with Hodgkin lymphoma (HL) who have relapsed/refractory disease after frontline therapy typically undergo salvage chemotherapy followed by high-dose conditioning and autologous stem cell transplantation (ASCT). Patients who achieve complete remission (CR) on salvage therapy prior to ASCT have improved outcomes. Standard salvage chemotherapy regimens produce variable CR rates (19%-60%) and are associated with significant toxicities in the first relapse setting. Brentuximab vedotin and bendamustine have independent mechanisms of action and are highly active with manageable safety profiles when administered as single agents to patients with HL who relapse after ASCT (brentuximab vedotin: 34% CR; bendamustine: 33% CR).

At ASH 2014, LaCasce et al. presented data from the phase I/II, single-arm, two-stage, open-label study that was designed to evaluate the safety and efficacy of brentuximab vedotin in combination with bendamustine for the treatment of patients with HL in first relapse.1

Study design
- Patients received an outpatient intravenous infusion of brentuximab vedotin 1.8 mg/kg on day 1 with bendamustine 90 mg/m² on days 1 and 2 of a 3-week cycle for up to 6 cycles. Patients could undergo ASCT any time after cycle 2 and then resume treatment post-transplant with brentuximab vedotin as monotherapy for up to 16 total doses.
- Phase I (N = 10) was designed to determine the recommended dose of bendamustine in combination with brentuximab vedotin and to assess its safety and tolerability. The dose of bendamustine was to be de-escalated if ≥4/10 patients experienced dose-limiting toxicity (DLT), defined as any cycle 1 toxicity requiring a dose delay of ≥14 days. The trial was to stop if <2 patients achieved CR.
- During phase II (expansion, N = 40+), bendamustine was administered at the recommended dose to assess the CR rate of the combination therapy. Response was assessed by the investigator per Cheson 2007.
- The main eligibility criteria were: ≥18 years old, classical HL, relapsed/refractory disease after frontline chemotherapy, and ECOG performance status 0–2.

Key findings
- A total of 54 patients with a median age of 37 years (range: 27–51) were enrolled. Fifty percent of patients had relapsed disease and 50% of patients had primary refractory disease after frontline therapy.

Study design

<table>
<thead>
<tr>
<th>Screening/ Baseline</th>
<th>Combination Therapy</th>
<th>Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin + bendamustine (2 to 6 cycles)</td>
<td>Up to 16 total cycles brentuximab vedotin</td>
<td>Additional cycles brentuximab vedotin</td>
</tr>
<tr>
<td>Response Assessment Days 15-21 CT/PET Cycles 2, 4, and pre-ASCT</td>
<td>Optional ASCT (any time after cycle 2)</td>
<td>Response Assessment CT q3 months</td>
</tr>
</tbody>
</table>

ASCT = autologous stem cell transplantation; CT = computed tomography; iv = intravenous; PET = positron emission tomography
- A median of 13.8 months (range: 8.8–20.4) had elapsed since initial diagnosis.
- No DLTs were observed in cycle 1, thus the recommended dose of bendamustine in combination with brentuximab vedotin was 90 mg/m².
- Patients received a median of 2 cycles (range: 1–6) of the combination therapy.
- The main toxicities observed with the combination treatment were infusion-related reactions (IRRs). (Figure 1)
  - Dyspnea (15%), chills (13%), and flushing (13%) were the most common symptoms; hypotension requiring vasopressor support also occurred.
  - The majority of reactions occurred within 24 hours of cycle 2 infusion and were considered related to both agents.
  - Delayed hypersensitivity reactions also occurred, the most common of which was rash (14 patients up to 22 days after infusion).
  - The protocol was amended to require premedication with corticosteroids and antihistamines, which decreased the severity of the IRRs. (Figure 2)

**Figure 1. Adverse events on combination therapy**

![Figure 1. Adverse events on combination therapy](image)

*Grade 3 IRR per NCI CTCAE 4.03: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; NCI = National Cancer Institute; SAE = serious adverse event; TEAE = treatment-emergent adverse event

**Figure 2. The effect of premedication* on infusion-related reactions**

![Figure 2. The effect of premedication* on infusion-related reactions](image)

*IRR = infusion-related reaction; SAE = serious adverse event

*Protocol was amended to require premedication with corticosteroids and antihistamines.*
• The CR rate of combination therapy was 83% and the overall objective response rate (ORR) was 96%. The majority of CRs (34/40) were achieved after 2 cycles of combination therapy. (Table 1)

Table 1. Best response on combination therapy

<table>
<thead>
<tr>
<th>Best clinical response*</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>40 (83)</td>
<td>69.8, 92.5</td>
</tr>
<tr>
<td>PR</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>46 (96)</td>
<td>85.8, 99.5</td>
</tr>
</tbody>
</table>

*Prior to ASCT.

ASCT = autologous stem cell transplantation; CI = confidence interval; CR = complete remission; ORR = objective response rate; PD = progressive disease; PR = partial remission; SD = stable disease

• Stem cell mobilization and collection data are presented in Table 2.

Table 2. Stem cell mobilization and collection

<table>
<thead>
<tr>
<th>Medan number of apheresis sessions, (range)</th>
<th>N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD34+ cell yield (x 10^6 cells/kg), (range)</td>
<td>4.0 (1.7–11.8)</td>
</tr>
</tbody>
</table>

>2 x 10^6 cells collected, n

<table>
<thead>
<tr>
<th>32*</th>
</tr>
</thead>
</table>

*Patient with 1.7 x 10^6 cells collected was able to undergo transplant with engraftment.

• First-line mobilization (granulocyte colony-stimulating factor [G-CSF] alone or combined with plerixafor) was successful in all but one patient (patient underwent bone marrow harvest due to failure of G-CSF [rescue plerixafor not used]).

• About half of patients who underwent mobilization (17/33) did so after two treatment cycles.

• Median time to platelet and neutrophil engraftment was less than 2 weeks.

• Median PFS was not reached. (Figure 3)

• There were four progressions and one death subsequent to ASCT (eight events overall).

• Median response duration was also not yet estimable.

Figure 3. Progression-free survival

Key conclusions

• The outpatient regimen of brentuximab vedotin in combination with bendamustine:
  • Had a manageable safety profile with premedication for IRRs;
  • Induced a response rate (83% CR, 96% ORR) that compares favourably to historical data;
  • Has had no adverse impact on stem cell mobilization or engraftment to date.

• This combination therapy represents a promising salvage regimen for patients with HL who have relapsed/refractory disease after frontline therapy.

The principal unmet need for patients with indolent non-Hodgkin lymphoma (iNHL) and mantle cell lymphoma (MCL) is the lack of a curative therapy. Once patients need treatment, our goals are to have our patients live as long as possible on therapies that are maximally effective with the least toxicity. With treatment, many patients with iNHL are living 10 to 15 years, so having safe and effective treatment regimens that give patients a reasonable quality of life is important both during treatment and in the long term.

When selecting the first line of therapy, for the majority of patients we use bendamustine plus rituximab (BR) for follicular lymphoma (FL) and most indolent lymphomas. One exception to using BR upfront would be in patients with FL grade 3b, which is rare; at our centre we are still using R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). Another exception would be its use in very frail, or very ill, patients for whom the treatment-related potential toxicity of BR might be excessive, particularly neutropenia and risk of infection, as well as general fatigue and nausea. For those patients, we could use chlorambucil and rituximab or sometimes R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), which in some respects may be less myelosuppressive. However, in some elderly patients using R-CVP, it can also be associated with toxicity; the prednisone can result in significant adverse events (AEs) related to hyperglycemia, indigestion, and emotional lability, as well as symptoms of withdrawal upon cessation, and the vincristine can cause neuropathy and constipation.

The shift to BR occurred about two years ago when funding was approved based on the StiL-1 clinical trial data. The StiL-1 trial compared the use of BR versus R-CHOP as first-line treatment in patients with iNHL and MCL. The results of this trial showed that progression-free survival (PFS) was significantly prolonged in the BR group (69.5 months) compared with the R-CHOP group (31.2 months) at a median follow-up of 45 months. At the ASH 2014 Annual Meeting, the results of this study were updated with a median follow-up of 78 months.

In terms of efficacy, the PFS benefit that was seen at 45 months held through the longer follow-up period. There was also a time-to-next-treatment (TTNT) benefit, with the median TTNT not yet reached for the BR group compared with 42.3 months for the R-CHOP group. However, there was no survival difference between groups.

In terms of toxicities, both those occurring during treatment and over the long term are important, and secondary neoplasms are of particular interest. There was no real difference in the occurrence of secondary neoplasms between the two groups (36 cases in the BR group vs. 42 cases in the R-CHOP group). Looking at the hematologic toxicities, the risk of myelodysplasia and acute myelogenous leukemia did not seem to be of concern. This study was in upfront patients; therefore, the effect of prior therapies could not be evaluated. These data were reassuring, especially given the long follow-up, and they confirm our use of BR as the standard treatment in iNHL patients.

Ongoing trials in the upfront or relapsed setting are investigating the addition of a B-cell receptor downstream-acting molecule to BR, such as a Bruton’s tyrosine kinase inhibitor (e.g., ibrutinib) or a phosphoinositide 3-kinase inhibitor (e.g., idelalisib), which are known to have single-agent activity in indolent lymphoma. After completion of chemotherapy, the use of these agents as maintenance until progression or unacceptable toxicity is being studied. This is a whole new area we are learning about, not only in terms of efficacy, but also in terms of AEs. Quality of life will become very important if patients end up taking long-term daily medication to prevent their lymphoma from relapsing.

An Interview with Dr. Mathias Rummel on the Use of Bendamustine for the Treatment of Indolent NHL and MCL

At the ASH 2014 Annual Meeting, New Evidence spoke with Dr. Mathias Rummel, head of the Department of Hematology at the Clinic for Hematology and Medical Oncology at the Justus-Liebig University Hospital, Giessen, Germany, about the results of three studies using bendamustine for the treatment of indolent non-Hodgkin lymphoma (iNHL) and mantle cell lymphoma (MCL).

New Evidence: What are the unmet needs in the management of first-line iNHL and MCL?

Dr. Rummel: Until recently, standard treatments for iNHL and MCL included rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and, in some countries, rituximab, cyclophosphamide, vincristine, prednisone (R-CVP). Unfortunately, these regimens are associated with significant organ toxicities. Given that the typical patient is over 60 years of age, the tolerability of these regimens is of concern. Although there are many new agents under development, there is currently insufficient data to justify their use in the front-line setting. New regimens are therefore needed that can be used in patients unable to tolerate standard therapies.

New Evidence: What first-line treatment do you give to patients with iNHL and MCL?

Dr. Rummel: Although there is greater familiarity with the use of R-CHOP to treat iNHL and MCL, I prefer to give bendamustine plus rituximab (BR) in this setting. Currently I use BR in patients with these diseases, regardless of age or comorbidities. Although some might give chlorambucil to very frail patients, these patients often have difficulty swallowing pills.

New Evidence: Briefly describe the efficacy and safety results of the StiL-1 trial.

Dr. Rummel: The StiL-1 trial was conducted from 2003 to 2008, with results based on a follow-up duration of 45 months being published in The Lancet in 2013. These results showed that the BR arm had progression-free survival (PFS) that was superior to that of the R-CHOP arm (69.5 months vs. 31.2 months, respectively; \( p < 0.0001 \)). BR was also better tolerated than R-CHOP, with lower rates of alopecia, hematological toxicities, and infections. At the ASH 2014 meeting, we presented updated results based on a follow-up of 78 months.

The most recent analysis provided longer-term results for time to next treatment (TTNT), overall survival (OS), and secondary malignancies. Median TTNT was not reached in the BR arm and was 42.3 months in the R-CHOP arm. This finding is of high clinical significance as it means that the majority of patients in the BR arm have not yet needed a second treatment. In addition, we saw a strong trend towards longer OS with BR versus R-CHOP in the patient subgroup with iNHL. The estimated 10-year survival rate was 71.9% with BR versus 61.5% with R-CHOP in these iNHL patients (\( p = 0.076 \)).
In the Lancet publication (2013), we demonstrated an improved safety profile with BR compared to R-CHOP. With the long-term follow-up, there was no difference in secondary malignancies between groups, with numerically fewer secondary neoplasms in the BR arm (36/261) than in the R-CHOP arm (42/253).

**New Evidence:** Discuss the treatments given as salvage therapy in each arm of the StiL-1 trial.

**Dr. Rummel:** Salvage treatment was not predefined in the study protocol and was therefore the choice of the investigator. Approximately half of patients given R-CHOP initially were subsequently treated with BR. The remainder were given a wide variety of treatments such as fludarabine-based regimens, radiation, and transplantation. After treatment with BR, 31% of patients were given R-CHOP, 22% were retreated with BR, and the rest were given other treatment options. For a patient to be given BR a second time, they needed to have a long response duration following initial therapy of around 2.5 years.

**New Evidence:** What do these follow-up data add to the previously published findings?

**Dr. Rummel:** There are only few studies that present such long-term results. Given that longer observation is needed to examine the potential OS benefit and the rate of secondary malignancies, these recent results from the StiL-1 study are clinically meaningful.

**New Evidence:** Do the StiL-1 results strengthen the recommendation to use BR as the standard upfront treatment for iNHL and MCL?

**Dr. Rummel:** The long-term results do strengthen the recommendation to use BR upfront for iNHL and MCL; it is very rare that there is a reason not to use BR in these patients.

**Maintenance treatment:**

**New Evidence:** What maintenance regimen do you currently use to treat patients with iNHL and other histological subtypes?

**Dr. Rummel:** For the treatment of follicular lymphoma (FL), I currently give rituximab maintenance for two years, every three months, in the relapsed setting and for two years, every two months, in the upfront setting. However, there are currently no data to support the use of rituximab maintenance following BR induction; this question is addressed by the ongoing MAINTAIN trial. I do not use maintenance therapy in other disease subtypes given the lack of data showing its effectiveness.

**New Evidence:** What have studies to date told us about the benefit of rituximab maintenance following chemo-immunotherapy induction for the treatment of iNHL?

**Dr. Rummel:** The value of maintenance rituximab for the treatment of iNHL remains an unanswered question. The PRIMA study demonstrated improved PFS following two years of maintenance rituximab in patients with FL; however, there was no improvement in OS. Despite the improved disease control demonstrated in the study, the lack of an OS improvement is disappointing. However, there are some studies in the relapsed setting that show maintenance can improve survival. Maintenance therapy is therefore a reasonable option in relapsed disease, but its value in the front-line setting remains unanswered.
New Evidence: Please describe the rationale and design of the MAINTAIN trial.

Dr. Rummel: Although rituximab maintenance therapy has been examined following R-CHOP and other induction regimens, it is unclear whether it is effective following upfront treatment with BR. Examining the efficacy of maintenance therapy following induction with BR is therefore an unanswered question that the MAINTAIN study aims to address.

When we began the MAINTAIN trial in 2008, physicians were highly motivated to give maintenance therapy in FL given the initial results of the PRIMA study. However, after a longer follow-up in the PRIMA study, no difference in OS between groups was found. We would therefore have used a different design than the one in the MAINTAIN study to determine whether rituximab maintenance should be used at all in the upfront setting. Given the mindset in 2008, we therefore designed the study to determine whether 2 or 4 years of maintenance should be given following BR in FL. The use of maintenance therapy in other disease subtypes, such as marginal zone lymphoma, Waldenström macroglobulinemia, small lymphocytic lymphoma, and MCL, is also being examined. In the latter subtypes, the study will compare the efficacy of two years of maintenance rituximab versus observation. It will be interesting to see the results of the study in these different subtypes, as there is a lack of data on the use of maintenance in these disease states. However, in the current analysis presented at ASH 2014, we only included patients with FL.

New Evidence: Please describe the efficacy results following BR induction in the FL subgroup of the MAINTAIN study.

Dr. Rummel: Results from the MAINTAIN trial demonstrate a 93.6% overall response rate (ORR) and a 39.6% complete response (CR) rate following BR in patients with FL. These results support those from the StiL-1 and BRIGHT studies. Although there have been no unexpected safety signals thus far, 70 patients have yet to be randomized for the maintenance phase and it is too early to examine these data.

Relapsed setting:

New Evidence: What treatment regimen do you currently give to patients with relapsed/refractory iNHL?

Dr. Rummel: The regimen used for the treatment of relapsed/refractory iNHL depends on a number of factors, such as the number and type of previous therapies, response to treatment, age, and comorbidities. If BR was given upfront, I would use a different regimen such as R-CHOP if relapse occurred early, or repeat treatment with BR in the case of a long remission duration following the prior BR regimen. If the patient was not given BR upfront, I would use BR in the relapsed setting. In patients who are young and fit, I would consider high-dose therapy followed by transplantation if the relapse occurs shortly after the previous treatment. Other treatment options include rituximab monotherapy and fludarabine-based regimens. For patients who do not respond to second-line therapy, prognosis is very poor and there is a need for additional treatment options in this group.

New Evidence: Please describe the patient population participating in the StiL-2 study.

Dr. Rummel: Patients included in the StiL-2 study had a median age of 67 years and a median of one previous treatment, with some patients having had two or more previous treatment lines. Given that the study was initiated in 2003, R-CHOP was the most frequent upfront treatment and was used in over 50% of patients. Around 15% of patients were pretreated with BR and 10% with fludarabine-based regimens.
**New Evidence:** Please describe the rationale for the three-day regimen of fludarabine used in the study.

**Dr. Rummel:** A study by Czuczman, et al., published in 2005 in the *Journal of Clinical Oncology*, demonstrated an ORR of 90% with fludarabine plus rituximab (FR) for the treatment of FL. Although the study showed high response rates with FR, hematotoxicity was highly documented with the five days of fludarabine and was consequently reduced to a three-day regimen. We therefore wanted to avoid this toxicity and followed the treatment modification of that study by reducing the duration of fludarabine to three days in the StiL-2 study.

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**New Evidence:** Please describe the efficacy and safety results of the StiL-2 study.

**Dr. Rummel:** Results of the StiL-2 study showed ORRs of 82% in the BR arm compared with only 49% in the FR arm ($p < 0.0001$). The CR rate with BR was also significantly higher than that with FR (39% vs. 16%; $p = 0.0004$). The poor ORRs in the FR arm also translated into inferior PFS and OS compared to those in the BR arm. The median PFS was 34.3 months in the BR arm and 12.0 months in the FR arm ($p = 0.000064$). In addition, OS was 109.7 months in the BR arm and only 49.4 months in the FR arm ($p = 0.012$). The substantially inferior response to FR is surprising and clearly shows that FR is not sufficiently effective in this patient population.

Given that we used a three-day instead of five-day regimen of fludarabine, hematotoxicity was reasonable in the FR arm. Both arms were relatively well tolerated, with no major differences in safety signals between arms.

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**New Evidence:** Please describe the maintenance phase in the sub-study of StiL-2.

**Dr. Rummel:** Based on the results of studies showing a benefit of rituximab maintenance in the relapsed setting, we amended the protocol after July 2006 so that all patients who responded to BR or FR were treated with two years of maintenance therapy. In the subanalysis, we compared the 44 patients given maintenance after July 2006 to those patients responding to treatment prior to this date; the latter were not given maintenance. Those treated with maintenance rituximab achieved an improved median PFS of 72.4 months versus 30.5 months ($p = 0.0083$), which translated into a difference in median OS (not reached versus 69.8 months, respectively; $p = 0.024$). Although the subanalysis includes a small sample size, the improved outcome with maintenance therapy is clinically meaningful and justifies giving maintenance in the relapsed setting.

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**New Evidence:** Given the results from the StiL-2 study, is BR your preferred regimen in the relapsed setting?

**Dr. Rummel:** In patients not previously treated with BR or with a long response following initial treatment with BR, I would choose to give BR subsequently to most patients in the relapsed setting. Where response to initial treatment is short, I would move to transplant in young patients or other regimens in those ineligible for transplant. However, given the median age in the relapsed population, very few patients would be eligible for transplant.
The Evolution of CLCCO Into a National Symposium

The Importance of Attending CLCCO — Perspectives from Canada’s Lung Experts

Interviews with:

Dr. Barbara Melosky (BC Cancer Agency, Vancouver, BC), Dr. Sunil Verma (Sunnybrook Odette Cancer Centre, Toronto, ON), Dr. Wojciech Morzycki (NS Cancer Centre, Halifax, NS)

Barbara Melosky, MD, FRCP(C)
Dr. Barbara Melosky is a Clinical Associate Professor of Medicine at the University of British Columbia and a medical oncologist at the British Columbia Cancer Agency in Vancouver. She graduated from medical school at the University of Manitoba, and did a residency in internal medicine and an oncology fellowship at the University of British Columbia. Dr. Melosky is currently working in the fields of lung and gastrointestinal malignancies with a special interest in the side effects of targeted therapy. She sits on the Executive Committee for the Lung Disease Site NCIC Clinical Trials Group and is the annual Chair of the Canadian Lung Cancer Conference.

Sunil Verma, MD, MSEd, FRCPC
Dr. Sunil Verma is a medical oncologist and the Chair of Breast Medical Oncology at the Sunnybrook Odette Cancer Centre in Toronto, Ontario. He is also an Associate Professor at the University of Toronto. Dr. Verma completed his medical degree and postgraduate training in internal medicine and medical oncology at the University of Alberta. He completed a fellowship in breast cancer at the University of Toronto and a master’s degree in medical education at the University of Southern California. Dr. Verma is internationally recognized for his educational leadership and research in breast and lung cancers. He has led and created numerous innovative educational projects in oncology and won several teaching and mentoring awards. Dr. Verma’s research interests include reducing the toxicity of systemic treatment, developing novel therapies for breast and lung cancers, and medical education. He is the principal investigator for many clinical trials in breast and lung cancers, including an international phase III trial in breast cancer, and has authored or co-authored articles appearing in publications such as the *Journal of Clinical Oncology, Cancer, The Oncologist, Lancet Oncology, Lancet*, and *The New England Journal of Medicine*.

Wojciech Morzycki, MD, FRCPC
Dr. Wojciech Morzycki is a medical oncologist with the Nova Scotia Cancer Centre at the QEII Health Sciences Centre in Halifax, and he is an Associate Professor in the Division of Medical Oncology at Dalhousie University’s Faculty of Medicine. He completed his internal medicine training at Dalhousie University and medical oncology training at the University of Ottawa. Dr. Morzycki’s main clinical focus is on thoracic malignancies.
New Evidence: How long has the Canadian Lung Cancer Conference (CLCCO) been around?

Dr. Melosky: This is our fifteenth year. It is now held annually in Vancouver during the first week of February.

New Evidence: How did you get the idea for CLCCO?

Dr. Melosky: There was a need for a conference specifically for lung cancer. It was an idea put forward initially by Lilly Oncology. It started as the Western Canadian Lung Cancer Conference with only medical oncologists. Today, CLCCO has over 500 attendees from across Canada. Many sponsors support CLCCO by providing educational grants.* Our diamond sponsors are Lilly and Boehringer Ingelheim.†

New Evidence: What are the objectives and goals of CLCCO?

Dr. Melosky: The goal of CLCCO is to have a multidisciplinary meeting for all health care practitioners who are interested in improving the treatment and management of lung cancer patients, and to make it a highly educational event that is CME certified, while keeping everyone involved and engaged. The program has general sessions for all attendees and then breaks out into parallel sessions for each specialty, such as medical oncologists, respirologists, radiation oncologists, thoracic surgeons, and oncology nurses.

Additionally, CLCCO aims to:
• Review new approaches to the treatment of non-small cell lung cancer (NSCLC);
• Discuss the role of radiation oncology in the management of NSCLC; and
• Update surgical options in NSCLC therapy.

New Evidence: How has CLCCO grown over the years?

Dr. Melosky: The first meeting was in Kelowna and was chaired by Dr. Charlie Butts. I started to chair it several years ago. We had many colleagues from Ontario and Quebec attend so we decided to change the name to the Canadian Lung Cancer Conference.

Dr. Morzycki: This conference has grown significantly from a regional to a national symposium.

Dr. Verma: In many ways the growth of CLCCO has mirrored the growth in lung cancer treatment. CLCCO is the ideal venue to discuss more treatment options. It is remarkable how far the meeting has come and how far the treatment of lung cancer has come across the country.

New Evidence: Would you recommend that your colleagues attend CLCCO? Why?

Dr. Morzycki: Yes, I would. It is a fantastic event that allows you to meet your colleagues from across Canada and hear about the differences in clinical practices in each province. It offers educational opportunities for all health care practitioners, not just medical oncologists and radiation oncologists, but also oncology nurses and pharmacists.

Dr. Verma: Yes, CLCCO is a premier conference. It is of international caliber. It is a great platform to learn, network, and discuss the future of lung cancer treatment options.

Dr. Melosky: Definitely. Our guest speakers provide a wealth of expertise and knowledge to optimize the care of lung cancer patients. There have been exciting advances in the treatment, diagnosis, and staging of lung cancer. I believe that this is a very informative and timely meeting.

New Evidence: Will you use the information presented at CLCCO in your practice?

Dr. Morzycki: Absolutely, yes. The topics presented this year were germane, and I look forward to incorporating certain aspects into my practice.

Dr. Verma: Most definitely. The discussions and presentations have clear clinical practice applications. The sessions are great platforms for discussion. It is interesting to hear the data presented and hear about clinical practice patterns across the country.
**New Evidence:** Is there anything you plan to do differently as a result of CLCCO?

**Dr. Verma:** Yes, I think we need to apply a greater involvement of multidisciplinary care. I am also looking forward to hearing more about clinical trials in immunotherapy and other novel therapies currently in various stages of development.

**Dr. Morzycki:** Patient advocacy was a big theme at this year’s meeting and it plays a large part in the treatment of the patient. Our centre in Halifax would like to work towards applying a greater involvement of multidisciplinary care, which is why we have nurses from our centre attending the conference this year.

**New Evidence:** What is your favourite thing about CLCCO?

**Dr. Melosky:** My favorite thing about the meeting is the sense of humour we all have. I especially enjoy the spirit of comradery during the debates.

**Dr. Morzycki:** Venue, atmosphere, location, and scientific aspect.

**Dr. Verma:** Meeting with colleagues from across the country.

**New Evidence:** What makes CLCCO unique and different from other conferences?

**Dr. Melosky:** As a single day meeting in Vancouver that is multidisciplinary, this unique meeting is a great learning experience and a lot of fun.

**Dr. Morzycki:** The scientific aspect of CLCCO is unique because this conference focuses only on lung cancer, which allows attendees to focus and dive deeper within one disease state. It also brings together health care practitioners and partners who are all striving to improve patient care and improve the treatment of lung cancer.

**Dr. Verma:** The venue, logistics, and the leadership that Dr. Barb Melosky brings. You can see her passion for the conference and lung cancer. It is an international conference but also an intimate meeting, which makes it interactive and enjoyable. I truly enjoy hearing about regional differences and sharing our Ontario experiences with colleagues.

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Safety and effectiveness in patients <18 years of age have not been established.

Contraindications:

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

Most serious warnings and precautions:

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

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

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

Other relevant warnings and precautions:

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

- Risk of extravasation.

- Cardiac disorders have been reported.

- Risk of ECG changes, including QTc prolongation.

- Risk of hypertension.

- Risk of tumor lysis syndrome.

- Risk of increase in liver enzymes and bilirubin levels.

- The use of live attenuated vaccines should be avoided.

- Risk of infusion reactions and anaphylaxis.

- Potential risk to reproductive capacity.

- Risk of skin reactions. One case of toxic epidermal necrolysis (TEN) was reported.

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- Potential risk to reproductive capacity.

- Risk of skin reactions. One case of toxic epidermal necrolysis (TEN) was reported.

Most serious warnings and precautions:

- APL Differentiation Syndrome: Can be fatal. At first signs or symptoms, high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated.

- Acute Cardiac Toxicities (Rhythm Disturbance): Can cause potentially fatal QT prolongation and complete atrioventricular block. Patients with syncope, rapid or irregular heartbeat should be hospitalized for monitoring. Serum electrolytes should be assessed and treatment interrupted. Special electrocardiogram and electrolyte monitoring is required.

- Concomitant drug use: Avoid use of drugs that prolong the QT interval or disrupt electrolyte levels.

Other relevant warnings and precautions:

- Tumor lysis syndrome.

- Carcinogenesis of arsenic trioxide.

- Increased heart rate.

- Hyperleukocytosis.

- Elevated transaminases.

- Peripheral neuropathy.

- Fertility, embroyotoxicity and teratogenicity.

- Presence of arsenic in semen (use condom during treatment and for 3 months after stopping treatment).

- Patients with renal or hepatic impairment.

- Monitoring of electrocardiograms, laboratory parameters (potassium, calcium, magnesium, glucose, hematologic, hepatic, renal, coagulation), serious arsenic toxicity in the obese, and for hypoxia and development of pulmonary infiltrates and pleural effusion in all patients.

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† Based on results from two open-label, single-arm trials, one multicentre (n=40) and one single-centre (n=12). Tri xenox dose: multicentre trial: 0.15 mg/kg daily; single-centre trial: 5.10, or 15 mg or 0.15 mg/kg daily (median dose of 0.16 mg/kg/day; the recommended daily dose is 0.15 mg/kg. Treatment continued until CR or for a maximum of 60 days for induction and 25 days for consolidation.  

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Contraindications:

- Pregnancy and nursing mothers.

- APL Differentiation Syndrome: Can be fatal. At first signs or symptoms, high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated.

- Acute Cardiac Toxicities (Rhythm Disturbance): Can cause potentially fatal QT prolongation and complete atrioventricular block. Patients with syncope, rapid or irregular heartbeat should be hospitalized for monitoring. Serum electrolytes should be assessed and treatment interrupted. Special electrocardiogram and electrolyte monitoring is required.

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Moving Forward
Providing Safer Treatment Options

Interviews with Dr. Knauf, Dr. Moreau, Dr. O’Brien, Dr. Platzbecker, Dr. Plesner, Dr. Rummel, and Dr. Wendtner