New Evidence in Oncology is an independent medical news reporting service providing educational updates on current medical events. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsors. Support for the development and distribution of this report was provided by Boehringer Ingelheim Oncology, Gilead Sciences Canada Inc., Hoffmann-La Roche Oncology and Lundbeck Oncology. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information. No claims or endorsements are made for any products, uses, or doses presently under investigation. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate understanding of current trends in oncology for physicians and allied healthcare providers.

INSIDE THIS ISSUE

LEUKEMIAS AND LYMPHOMAS
Balancing Toxicity and Efficacy in the Treatment of High-Risk, Elderly, and Unfit Patients with CLL

BREAST CANCER
New Strategies in the Treatment of HER2-Positive Breast Cancer

Updates in APL: Reducing Early Death and Therapy-Related Myeloid Neoplasms and Improving First-Line Treatments

A Delicate Balance
Between Efficacy and Toxicity

Interviews with Dr. Matthew Seftel and Dr. Sunil Verma
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 February 2014 issue presents coverage from the following key conferences: the 15th International Workshop on Chronic Lymphocytic Leukemia, the 6th International Symposium on Acute Promyelocytic Leukemia, and the European Cancer Congress 2013. This issue reports on topics of general interest and key studies testing novel agents that target specific molecular pathways for the treatment of chronic lymphocytic leukemia, acute promyelocytic leukemia, non-Hodgkin lymphoma, and breast cancer. The development of targeted therapeutics for these diseases has not only led to improved efficacy, but also to reduced toxicity in some cases — an ideal balance when it comes to the patient’s quality of life. We would like to thank Dr. Matthew Seftel for his Canadian Perspective and Dr. Sunil Verma for his Investigator Commentary.

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

Addendum: Lymphoma Canada’s follicular lymphoma treatment guidelines

The following is the final list of authors who will be developing Lymphoma Canada’s follicular lymphoma treatment guidelines: Dr. John Kuruvilla, Dr. Sarit Assouline, Dr. David Hodgson, Dr. David MacDonald, Dr. Douglas Stewart, and Dr. Joseph Connors.
Contents

LEUKEMIAS & LYMPHOMAS

Chronic lymphocytic leukemia

Balancing Toxicity and Efficacy in the Treatment of High-Risk, Elderly, and Unfit Patients with Chronic Lymphocytic Leukemia

8

- Phase Ib study of idelalisib (GS-1101) plus chlorambucil with or without rituximab in patients with relapsed or refractory CLL. (Coutre SE, et al. iwCLL 2013)
- A phase II study of idelalisib (GS-1101) in combination with rituximab in treatment-naïve patients ≥65 years with CLL or SLL. (Lamanna N, et al. iwCLL 2013)
- The Bruton tyrosine kinase inhibitor, ibrutinib, promotes a high frequency of durable responses in relapsed/refractory and older treatment-naïve chronic lymphocytic leukemia patients: final results of a phase Ib/II study. (Furman RR, et al. iwCLL 2013)
- Salvage therapies in patients with first relapse after fludarabine, cyclophosphamide, and rituximab for chronic lymphocytic leukemia: the French CLL Intergroup experience. (Fornecer L-M, et al. iwCLL 2013:5.5)
- Bendamustine and rituximab as first or second line therapy in elderly patients with chronic lymphocytic leukemia. (Gozzetti A, et al. iwCLL 2013:4.15)
- Update on a phase I study of the selective PI3Kδ inhibitor, idelalisib, in combination with rituximab, bendamustine, or BR in patients with relapsed/refractory chronic lymphocytic leukemia. (Barrientos JC, et al. iwCLL 2013:4.22)
- Kinetics of blood cell subpopulations during treatment with obinutuzumab (GA101) plus chlorambucil (Clb), rituximab plus Clb versus Clb alone in patients with CLL and coexisting medical conditions: stage 1 results of the CLL11 trial. (Goede V, et al. iwCLL 2013:4.14)

38 Detection of Minimal Residual Disease in Clinical Trials of Chronic Lymphocytic Leukemia: Summary of the Presentation by Dr. Michael Kneba at iwCLL 2013

42 Initial Chemoimmunotherapy Approaches for Young and Old Patients: Summary of the Presentation by Dr. Michael Hallek at iwCLL 2013

45 How to Approach Relapse in CLL if no Clinical Trial is Available? Summary of the Presentation by Dr. Tadeusz Robak at iwCLL 2013

49 Biology and Treatment of Patients with del(11q) CLL: Summary of the Presentation by Dr. Thorsten Zenz at iwCLL 2013

52 Defining Elderly Patients and How to Evaluate Comorbidity: Summary of the Presentation by Dr. Valentin Goede at iwCLL 2013

55 Optimizing Trial Design in CLL: Biology and Treatment Approaches for 17p-deleted CLL: Summary of the Presentation by Dr. Peter Hillmen at iwCLL 2013
Acute promyelocytic leukemia

Updates on Early Death, Therapy-Related Myeloid Neoplasms, and First-Line Therapies in the Treatment of Acute Promyelocytic Leukemia

60

Early death in APL

• Early death rate in APL remains high: an update on the Lehmann et al. 2011 study (Lehmann, S)
• ATRA delays increase in early death rate in APL from hemorrhage (Tallman, MS)
• High early death rate for patients with APL in Canada (Seftel, M)
• A model to prevent early death in APL (Jillella, A)

66

Therapy-related myeloid neoplasms in APL

• Therapy-related myeloid neoplasms in APL (Montesinos, P)

68

An update on first-line therapies in APL

• The GIMEMA pathway to the cure for APL (Avvisati, G)
• Improvements with risk-adapted PETHEMA protocols in newly diagnosed APL (Sanz, MA)
• Combined ATRA and arsenic trioxide as front-line therapy for APL: experience from China (Hu, J)
• The Australasian Leukaemia and Lymphoma Group APML4 trial (Iland, H)
• Strategies to improve clinical outcome of front-line therapy with ATO, without increasing myelosuppression and by maintaining low toxicity (Mathews, V)
• APL: less is just as good (Burnett, AK)
• Long-term quality of life in patients with APL (Efficace, F)

Canadian Perspective by Dr. Matthew Seftel

BREAST CANCER

New Strategies in the Treatment of HER2-Positive Breast Cancer

80

• Trastuzumab emtansine for HER2-positive metastatic breast cancer: primary results from TH3RESA, a phase III study of trastuzumab emtansine versus treatment of physician’s choice. (Wildiers H, et al. ECC 2013:LBA15)
• Evaluation of everolimus in HER2-positive advanced breast cancer with activated PI3K/mTOR pathway: exploratory biomarker observations from the BOLERO-3 trial. (Jerusalem G, et al. ECC 2013:LBA16)
• Everolimus in combination with letrozole in the treatment of postmenopausal women with hormone receptor positive/HER2-negative advanced breast cancer after failure of endocrine therapy — a phase I study. (Safra T, et al. ECC 2013:1895)
• Bevacizumab preconditioning followed by etoposide and cisplatin (BEEP) is a highly effective treatment for brain metastases of breast cancer progressing from radiotherapy — results of a multicentre phase II study. (Lu YS, et al. ECC 2013:1878)

• Overall and subgroup findings of the aTTom trial: A randomized comparison of continuing adjuvant tamoxifen to 10 years or stopping after 5 years in women with ER-positive or ER-untested early breast cancer. (Rea DW, et al. ECC 2013:1860)

Investigator Commentary

92

An Interview with Dr. Sunil Verma on the First Results from the TH3RESA Study at ECC 2013

New Evidence in Oncology | February 2014
Contributors

Canadian Perspective

Matthew Seftel, MBChB, MPH, MRCP(U.K.), FRCPC

Dr. Seftel is a hematologist/oncologist based at Princess Margaret Hospital in Toronto. He is a member of the Leukemia Group and leads the Allogeneic Blood and Marrow Transplantation Program. He is an Associate Professor at the University of Toronto in the Division of Internal Medicine. He is actively involved in clinical trials and outcomes-based research related to hematological malignancies and blood and marrow transplantation.
Investigator Commentary

**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*.
LEUKEMIAS & LYMPHOMAS
Leukemias

Chronic lymphocytic leukemia

Balancing Toxicity and Efficacy in the Treatment of High-Risk, Elderly, and Unfit Patients with Chronic Lymphocytic Leukemia

Although first-line chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) has markedly improved outcomes in younger, fit patients with chronic lymphocytic leukemia (CLL), nearly all patients eventually relapse or become refractory.1 High risk patients characterized by fludarabine-refractory disease or the presence of certain genetic aberrations, such as deletions on the short arm of chromosome 17 [del(17p)], are also known to be resistant to FCR therapy.2,3 Furthermore, elderly and unfit patients are not suitable candidates for FCR because this treatment results in substantial toxicity, including increased risk of infections due to marked immunosuppression and prolonged cytopenias.1 To make matters worse, these special patient populations have been heavily underrepresented in clinical trials, and to date, there is no evidence to support a standard of care for them.2,3

In addition to developing novel agents with reduced toxicity, considerable research efforts have been made to optimize therapy for high-risk, elderly, and unfit patients with CLL, with a particular focus on striking a balance between efficacy and toxicity. While a number of questions still remain, considerable progress has been made in optimizing clinical trials in the CLL setting, and data are now beginning to accumulate for these special patient populations.

At the 15th biennial International Workshop on CLL (iwCLL), a well-established and premier scientific meeting addressing exciting topics at the forefront of CLL research, experts from around the world presented on novel research findings as well as general topics of interest, such as optimizing clinical trials and the treatment of special patient populations. The following provides a brief summary of some of these presentations:

**Novel research findings:**

- Preliminary findings from a phase Ib study demonstrated that treatment with combinations of idelalisib with chlorambucil (Clb) and idelalisib with Clb and rituximab are well tolerated and effective in inducing durable responses in the majority of patients with heavily pretreated relapsed or refractory CLL.
- In a phase II trial, idelalisib in combination with rituximab had an acceptable safety profile and was found to be highly active in treatment-naïve, elderly patients with CLL or small lymphocytic lymphoma.
- Updated results from a phase I trial found that ABT-199, a novel, selective, potent BCL-2 inhibitor, was found to be highly active in patients with relapsed or refractory CLL independent of high risk factors [i.e., del(17p) or fludarabine-refractory disease]. However, additional dosing and scheduling modifications are being explored to minimize the risk of dose-limiting tumour lysis syndrome.
- In a multicohort phase Ib/II trial, ibrutinib, an oral inhibitor of Bruton tyrosine kinase, was found to be highly active, well tolerated, and result in a high frequency of durable responses in patients with CLL, including relapsed/refractory patients, those with high-risk disease, or older treatment-naïve patients.
- In a retrospective study, bendamustine and rituximab (BR) was found to be an effective salvage regimen after first-line therapy with FCR in a cohort of high-risk patients with relapsed and refractory CLL.
• An Italian study demonstrated that BR is an extremely effective first- or second-line therapy in elderly patients with CLL.

• Updated results from a phase I trial demonstrated that idelalisib, a first-in-class, highly selective, oral inhibitor of PI3Kδ, in combination with bendamustine, rituximab, or BR was well tolerated for up to three years and resulted in durable responses in the majority of patients with heavily pretreated or refractory CLL.

• The initial results of a phase II trial indicated that combination therapy with ofatumumab and bendamustine induced high response rates and an acceptable safety profile in patients with previously untreated CLL who are inappropriate for fludarabine-based therapy, and patients with relapsed CLL.

• Stage Ia and Ib analyses of the phase III CLL11 trial revealed that GA101, a novel type II anti-CD20 monoclonal antibody (mAb), may have superior B-cell depleting activity than rituximab when each mAb is used in combination with Clb, which may result in enhanced recovery of bone marrow function and increased clinical efficacy.


Coutre SE, et al. iwCLL 2013

Phase Ib study of idelalisib (GS-1101) plus chlorambucil with or without rituximab in patients with relapsed or refractory CLL

Background

In earlier phase I trials, idelalisib (GS-1101), a first-in-class, highly selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit delta (PI3Kδ), demonstrated significant activity as monotherapy and combination therapy with bendamustine, rituximab, or both. Given that the current National Comprehensive Cancer Network (NCCN) guidelines recommend chlorambucil with or without rituximab (Clb ± R) as a treatment option for relapsed or refractory chronic lymphocytic leukemia (CLL), a phase Ib trial was conducted to evaluate the safety and efficacy of adding idelalisib to chlorambucil (I-Clb) and Clb + R (I-Clb + R) in patients with relapsed or refractory CLL. Coutre and colleagues presented the preliminary findings from this ongoing trial at iwCLL 2013.1

Study design

• In this phase Ib combination study, patients with heavily pretreated relapsed or refractory CLL were continuously treated with idelalisib at a dose of 150 mg twice daily for 48 weeks in combination with either:
  ◊ Chlorambucil (10 mg/m² on days 1–7 for 3–12 cycles); or
  ◊ Clb + R (Clb: 10 mg/m² on days 1–7 for 3–12 cycles and R: 375 mg/m² on day 1 of cycles 1–6).

• The inclusion criteria were:
  ◊ Age ≥18 years;
  ◊ Relapsed or refractory CLL requiring treatment, as per 2008 iwCLL criteria;
  ◊ Absolute neutrophil count (ANC) ≥1,000/µL and platelet count ≥75,000/µL, unless due to marrow infiltration with CLL;
Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2 times the upper limit of normal; Total serum bilirubin <2 mg/dL; Serum creatinine <2 mg/dL.

- The primary end point was safety.
- The secondary end point was efficacy (i.e., overall response rate [ORR] and progression-free survival [PFS]).
- Response was assessed by the investigators based on scheduled computed tomography (CT) evaluations at weeks 8, 16, 24, 36, and 48, and in accordance with the published criteria of the 2008 iwCLL.
- After 48 weeks, patients who were still benefiting from treatment were eligible to continue idelalisib as part of an extension study (NCT01090414).

**Key findings**

**Baseline characteristics and disposition**

- A total of 29 patients were enrolled between March 2012 and August 2012.
- Most baseline characteristics were well balanced in both treatment arms (I-Clb vs. I-Clb + R):
  - Median age (range): 63 years (53–77) vs. 68 years (41–82);
  - Male: 93% vs. 71%;
  - Bulky adenopathy: 60% vs. 57%;
  - Refractory to rituximab: 60% vs. 57%;
  - Rai stage, I–II/III–IV: 40%/60% vs. 57%/43%;
  - World Health Organization performance score, 0−1/2−3: 100%/0% vs. 100%/0%;
  - Immunoglobulin heavy chain variable (IgHV) unmutated: 80% vs. 86%;
  - Deletion of chromosome 17 p [del(17p)] and/or TP53 mutation: 47% vs. 14%;
  - Prior therapies (median [range]): 3 (1–8) vs. 3 (1–6);
  - Prior therapy type:  
    - Rituximab: 93% vs. 100%;
    - Fludarabine: 80% vs. 57%;
    - Bendamustine: 33% vs. 50%;
    - Chlorambucil: 7% vs. 7%;
    - Anthracyclines/anthracenedione: 13% vs. 7%.
- In the primary study, patients received idelalisib for a median of 9.2 months (range: 0.9−12.3).

**Safety**

- Among all patients in both treatment groups, the top three all-grade treatment-emergent AEs were diarrhea (52%), pyrexia (38%), and cough (35%). (Table 1)
- In general, fewer patients treated with I-Clb experienced all-grade treatment-emergent AEs (with ≥15% incidence) vs. those treated with I-Clb + R: (Table 1)
  - I-Clb: diarrhea (40%), cough (40%), febrile neutropenia (33%), chills (33%), pyrexia (20%), fatigue (20%), nausea (20%), dyspnea (20%), and insomnia (20%);
  - I-Clb + R: diarrhea (64%), pyrexia (57%), fatigue (43%), rash (36%), cough (29%), nausea (29%), constipation (29%), abdominal pain (29%), pneumonia (29%), dyspnea (21%), insomnia (21%), decreased appetite (21%), and peripheral edema (21%).
- The most common grade ≥3 treatment-emergent AEs occurring in ≥15% of patients were (Table 1):  
  - All patients: febrile neutropenia (21%) and diarrhea (17%);
  - I-Clb: febrile neutropenia (33%) and diarrhea (27%);
  - I-Clb + R: fatigue (21%) and pneumonia (21%).
Overall, in all patients, the incidences of treatment-emergent laborator abnormalities (all-grade/grade ≥3) were (Table 1):
- Neutropenia: 76%/59%;
- Thrombocytopenia: 55%/28%;
- Anemia: 52%/17%;
- ALT/AST elevations: 38%/10%.
- The incidences of all-grade and grade ≥3 neutropenia, thrombocytopenia, and anemia were higher in patients treated with I-Clb vs. those treated with I-Clb + R. (Table 1)
- Conversely, the incidence of ALT/AST elevations (all-grade/grade ≥3) was lower in patients treated with I-Clb vs. those treated with I-Clb + R. (Table 1)
- The most common serious AEs (n ≥2) were: (Table 2)
  - All patients: febrile neutropenia (17%), diarrhea (14%), pneumonia (10%), and pyrexia (10%);
  - I-Clb: febrile neutropenia (27%), diarrhea (13%), and pneumonia (13%);
  - I-Clb + R: diarrhea (14%) and pyrexia (14%).

### Table 1. Treatment-emergent adverse events* and laboratory abnormalities

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Idelalisib + Clb, n (%)</th>
<th>Idelalisib + Clb + R, n (%)</th>
<th>All patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (40)</td>
<td>4 (27)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (20)</td>
<td>0</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Cough</td>
<td>6 (40)</td>
<td>0</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (20)</td>
<td>0</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (20)</td>
<td>0</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (13)</td>
<td>0</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (13)</td>
<td>0</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (20)</td>
<td>0</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (33)</td>
<td>5 (33)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (20)</td>
<td>0</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (7)</td>
<td>0</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Chills</td>
<td>5 (33)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (13)</td>
<td>1 (7)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>2 (13)</td>
<td>0</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>4 (29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory abnormalities</th>
<th>Idelalisib + Clb, n (%)</th>
<th>Idelalisib + Clb + R, n (%)</th>
<th>All patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>13 (87)</td>
<td>11 (73)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (67)</td>
<td>5 (33)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (60)</td>
<td>3 (20)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>ALT/AST elevation</td>
<td>4 (27)</td>
<td>0</td>
<td>7 (50)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Clb = chlorambucil; R = rituximab
*Occurring in ≥15% of all patients

### Table 2. Serious adverse events (n ≥2)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Idelalisib + Clb, n (%)</th>
<th>Idelalisib + Clb + R, n (%)</th>
<th>All patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>4 (27)</td>
<td>1 (7)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (13)</td>
<td>2 (14)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>P. Jiroveci Pneumonia</td>
<td>2 (13)</td>
<td>1 (7)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (7)</td>
<td>2 (14)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Clb = chlorambucil; R = rituximab
• The three AEs that led to study drug discontinuation were:
  ◦ I-Clb: diarrhea (n = 1) and febrile neutropenia (n = 1);
  ◦ I-Clb + R: acute respiratory failure (n = 1).
• The three deaths in this study were due to sepsis (n = 2) and respiratory failure (n = 1).

**Preliminary efficacy**

• The ORR for all patients was 79%, with 10% achieving a complete response (CR) and 69% achieving a partial response (PR). (Table 3)

![Table 3. Best response](image)

<table>
<thead>
<tr>
<th>Best response*†</th>
<th>I-I-Clb, n (%)</th>
<th>I-I-Clb + Clb + R, n (%)</th>
<th>All patients, n (%)</th>
<th>Del(17p) and/or TP53 mutation, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 15</td>
<td>N = 14</td>
<td>N = 29</td>
<td>N = 9</td>
</tr>
<tr>
<td>ORR</td>
<td>10 (67)</td>
<td>13 (93)</td>
<td>23 (79)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (7)</td>
<td>2 (14)</td>
<td>3 (10)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (60)</td>
<td>11 (79)</td>
<td>20 (69)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (27)</td>
<td>1 (7)</td>
<td>5 (17)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not done</td>
<td>1 (7)</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

*Clb = chlorambucil; CR = complete response; del(17p) = deletion of chromosome 17p; ORR = overall response rate; PD = progressive disease; PR = partial response; R = rituximab; SD = stable disease
†Intention-to-treat analysis

• The median time to response for all patients was 1.9 months (range: 1.8–6.0).
• The ORR for patients treated with I-Clb was 67% (CR: 7%; PR: 60%) and for those treated with I-Clb + R, the ORR was 93% (CR: 14%; PR: 79%). (Table 3)
• Among the nine patients with a del(17p) and/or TP53 mutation, the ORR was 56% (CR: 11%; PR: 44%).
• Median PFS has not yet been reached in the entire study population or any subgroup. (Figure 1)

![Figure 1. Progression-free survival*](image)
Key conclusions

- The combinations of idelalisib with chlorambucil and idelalisib with Clb + R have induced responses in 79% of patients with heavily pretreated relapsed or refractory CLL.
- The responses are durable; only one patient [with del(17p)/TP53 mutation] has progressed.
- Both combinations are well tolerated, with infrequent discontinuations due to AEs.
- Chlorambucil and rituximab are suitable for idelalisib combination trials.


Lamanna N, et al. iwCLL 2013

A phase II study of idelalisib (GS-1101) in combination with rituximab in treatment-naïve patients ≥65 years with CLL or SLL

Background
Idelalisib (GS-1101) is a targeted, highly selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit delta (PI3Kδ). In a phase I trial, idelalisib demonstrated significant activity when combined with rituximab in heavily pretreated patients with relapsed or refractory chronic lymphocytic leukemia (CLL).1 Subsequently, a phase II trial was conducted to evaluate the efficacy and safety of idelalisib in combination with rituximab in treatment-naïve, elderly patients with CLL or small lymphocytic lymphoma (SLL). The findings of this study were presented at iwCLL 2013.2

Study design
- In this phase II, single-arm, open-label study, treatment-naïve, elderly (i.e., ≥65 years) patients with CLL or SLL requiring therapy, as per 2008 iwCLL criteria, were treated with idelalisib (150 mg twice daily for 48 weeks) and rituximab (375 mg/m² weekly for 8 cycles).
- Patients who completed 48 weeks of treatment without progression could continue to receive idelalisib as part of an extension study.
- The primary endpoint was overall response rate (ORR).
- The secondary endpoints included progression-free survival (PFS), safety, and duration of response.
- Response and progression assessments (at weeks 0, 8, 16, 24, 36, 48, and per standard of care thereafter) were investigator determined and based on the 2008 iwCLL criteria.

Study design

Primary study: 101-08

Subject accrual: October 2010 through April 2012

Rituximab (375 mg/m²) weekly x 8

Idelalisib (150 mg bid) x 48 weeks

Therapy continues as long as patient receives benefit

Extension study: 101-99
Key findings

Baseline characteristics and disposition

- A total of 64 patients were enrolled with the following baseline characteristics:
  - CLL/SLL: 92%/8%;
  - Median age: 71 years (range: 65–90);
  - Male: 63%;
  - Rai stage III/IV: 42%;
  - Lymph nodes ≥5 cm: 11%;
  - World Health Organization performance score of 0/1: 98%;
  - Deletion of chromosome 17p [del(17p)] and/or TP53 mutation: 14%;
  - Deletion of chromosome 11q [del(17p)]: 16%.

- In the primary study, 97% and 67% of patients completed the study at 8 and 48 weeks, respectively.

- Approximately 33% of patients discontinued the study due to adverse events (AEs; n = 17), death (n = 3), or withdrawn consent (n = 1).

- A total of 40 patients (63%) have entered the extension study, and as of May 2013, seven patients discontinued the extension study due to AEs (n = 6) or withdrawn consent (n = 1).

- The median time on idelalisib was 14.1 months (range: 1−30+).

Efficacy

- The ORR was 97%, with 19% of patients achieving a complete response (CR) and 78% achieving a partial response (PR). (Table 1)

- Of note, the ORR of patients with a del(17p) and/or TP53 mutation was 100% (CR: 33%; PR: 67%). (Table 1)

- The median time to response was 1.9 months (range: 1.6−5.7).

- By week 16, 24 of 26 patients with B symptoms had their symptoms resolved.

- At 24 months, the estimated PFS was 93%, and there was no progression on study treatment. (Figure 1)

Safety

- Over the 48-week treatment period, hematological responses were evident in 100% of patients with anemia (17/17) and neutropenia (S/5), and in 94% (16/17) of those with thrombocytopenia.

- The median absolute lymphocyte count decreased from 38,600/µL (range: 1,000−188,600) at baseline to 2,700/µL (range: 700−28,100) at week 48 of treatment.

Table 1. Response assessment

<table>
<thead>
<tr>
<th></th>
<th>All patients, n (%) N = 64</th>
<th>Del(17p) and/or TP53 mutation, n (%) n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>62 (97)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>CR</td>
<td>12 (19)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>PR</td>
<td>50 (78)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*CR = complete response; del(17p) = deletion on the short arm of chromosome 17; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Table 2. All-cause adverse events occurring in ≥25% of patients in the primary and extension studies

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Any grade, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea*</td>
<td>35 (55)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27 (42)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (38)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>24 (38)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Chills</td>
<td>23 (36)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (33)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (27)</td>
<td>11 (17)</td>
</tr>
</tbody>
</table>

*Ten patients reported as grade 3 colitis, including six lacking any adverse event of grade ≥3 diarrhea (median time to grade 3 diarrhea/colitis: 9 months).
In the primary study, the incidences of grade ≥3 laboratory abnormalities were:
- Neutropenia: 28%.
- Transaminase elevations: 23%.
- Anemia: 3%.
- Thrombocytopenia: 2%.
- Serious AEs occurred in 58% of the patients, with diarrhea (16%), pneumonia (16%), and colitis (11%) being the most frequent. (Table 3)

The AEs that led to discontinuations (n = 23; patients may have had >1 AE) in the primary and extension studies were diarrhea/colitis (n = 8), other (n = 8), respiratory disorders (n = 5), rash (n = 3), anemia (n = 2), and ALT/AST elevations (n = 1). (Table 4)

The five deaths in this study were due to pneumonia/sepsis (n = 1), pneumonia/metastatic melanoma (n = 1), pneumonitis (n = 2), and myocardial infarction (n = 1).

### Table 3. Serious adverse events occurring in >1 patient

<table>
<thead>
<tr>
<th>SAE</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>37 (58)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Colitis</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*SAE = serious adverse event*

### Table 4. Adverse events leading to discontinuations

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>&lt;24 weeks (n = 10*), n</th>
<th>24–48 weeks (n = 67*), n</th>
<th>&gt;48 weeks (n = 7), n</th>
<th>Total (n = 23*), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/colitis</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>8 (13)</td>
</tr>
</tbody>
</table>

*ALT = alanine aminotransferase; AST = aspartate aminotransferase

*Patients may have >1 adverse event.

### Key conclusions

- **Idelalisib in combination with rituximab has an acceptable safety profile and is highly active in treatment-naïve, elderly (i.e., ≥65 years) patients with CLL or SLL, achieving an ORR of 97% and PFS (at 24 months) of 93%.

- These results support further evaluation of idelalisib in front-line CLL.

### References:


Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory CLL

### Background

In patients with chronic lymphocytic leukemia (CLL), overexpression of B-cell CLL/lymphoma 2 (BCL-2) leads to an evasion of apoptosis and chemoresistance, suggesting that targeting BCL-2 may be a promising strategy for treating CLL. ABT-199 is a selective, potent, orally bioavailable BCL-2 inhibitor that was found to have higher affinity for BCL-2 than for BCL-XL, BCL-W, and MCL-1. In preclinical studies, ABT-199 has shown activity as a single agent in a wide range of BCL-2-expressing hematologic malignancies. Based on these preclinical findings, a phase I trial of ABT-199 was initiated in patients with relapsed or refractory CLL/small lymphocytic lymphoma (SLL) or non-Hodgkin lymphoma. The updated findings from the CLL/SLL arm of this ongoing phase I trial were presented at iwCLL 2013.1
Study design

- This study is a first-in-human, open-label, dose-escalation, multicentre, international, phase I trial evaluating the safety and pharmacokinetics profile of ABT-199 (GDC-0199) in patients with relapsed or refractory CLL/SLL.
- The inclusion criteria were:
  - Measurable disease requiring therapy;
  - Relapsed after, or refractory to, standard fludarabine or alkylator-based regimen;
  - Eastern Cooperative Oncology Group Performance Status 0 or 1;
  - Adequate bone marrow function (neutrophil count ≥1,000/µL; platelets ≥50,000/µL);
  - Adequate renal (calculated creatinine clearance >50 mL/min) and hepatic function.
- The exclusion criteria were:
  - Prior autologous or allogeneic stem cell transplant;
  - Active infection.

- Eligible patients received an initial single oral dose of ABT-199 (cohort 1: 200 mg; cohorts 2–8: 50 mg), which was followed by a 7-day off-drug period, and then, continuous once daily dosing until disease progression or unacceptable toxicity.
- After cohort 1, the initial dose was reduced and daily dosing was modified to include a two- or three-step weekly dose escalation to the target dose for each cohort (150–1,200 mg).
- The coprimary end points were to:
  - Assess safety and pharmacokinetics;
  - Determine the maximum tolerated dose and recommended phase II dose.
- The secondary end points included objective response rate (ORR), duration of response, time to tumour progression, progression-free survival, overall survival, biomarkers, and pharmacogenetics.

### Study design

#### Day –7

- **50 mg**

#### Week 1

- **50 mg**

#### Week 2

- **100/150 mg**

#### Final dose

---

### ABT-199 doses (mg), weekly escalation

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients enrolled, n</th>
<th>Initial dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>200§</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>50*</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>50*</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>50*</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>

*Three patients (one patient in cohorts 2, 3, and 5) received an initial dose of 20 mg.
†A dose of 100 mg was administered at week 2 in cohorts 2–5.
‡Cohort 6 had an extra step prior to final dosing at week 4.
§Target dose.
Key findings

- As of July 4, 2013, 56 patients were enrolled, of which 61% (n = 34) are active in the study.
- The baseline characteristics of the overall study population were:
  - Age, median (range): 67 years (36–86);
  - Male: 73%;
  - Diagnosis of CLL/SLL: 88%/12%;
  - Lymphocyte count >5.0 × 10⁹/L: 57%;
  - Bulky nodes ≥5 cm/≥10 cm: 50%/14%;
  - Prior therapies, median (range): 4 (1–10);
  - Prior fludarabine treatment: 61%;
  - Fludarabine-refractory: 32%;
  - Deletion of chromosome 17p [del(17p)]: 38%;
  - Deletion of chromosome 11q [del(17p)]: 10%.
- The median time on study in each group of patients was 10 months (range: 0.03–21.0).
- The reasons for discontinuation were progressive disease (n = 12), adverse events (AEs; n = 8), and other (n = 2).

Safety

- The most common nonhematological all-grade AEs occurring in ≥20% of patients were diarrhea (46%), nausea (43%), fatigue (34%), upper respiratory tract infection (29%), and cough (25%). (Table 1)
- The most common grade 3/4 AEs occurring in ≥2 patients were neutropenia (41%), thrombocytopenia (11%), and tumour lysis syndrome (TLS; 11%). (Table 1)
- Serious AEs included febrile neutropenia (n = 3), laboratory TLS (n = 2), clinical TLS (n = 1), acute renal failure (n = 1), and sudden death (n = 1).
- The major dose-limiting toxicity (DLT) was TLS, which occurred in all patients in cohort 1 (n = 3) and in three patients with the modified dosing schedule (i.e., cohorts 2, 4, and 8).

Preliminary efficacy

- Of the 56 evaluable patients, 20% achieved a complete response (CR) and 64% achieved a partial response (PR) for an ORR of 84%. (Table 2)
- Patients with ultra-high risk CLL had ORRs comparable to that of the entire study population [del(17p) CLL: 82%; fludarabine-refractory CLL: 78%]. (Table 2)
- Computed tomography assessments revealed a gradual decrease of nodal size with a median time to 50% reduction of 1.4 months (range: 0.7–13.7) for the entire study population. (Figure 1)
- Antitumour activity (i.e., percent change from baseline) of ABT-199 was observed in all tumour compartments, as demonstrated by the median times to 50% reduction in lymphocyte count (12 days [range: 1–43]) and bone marrow infiltrate (5.6 months [range: 1.9–17.4]). (Figure 2)
- While minimal residual disease (MRD) was not a pre-specified end point, it was assessed in eight out of 11 patients with a CR or CR with incomplete marrow recovery, of which 5 patients were MRD-negative.

<table>
<thead>
<tr>
<th>Table 1. Adverse events in the overall study population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
</tr>
</tbody>
</table>

| **Adverse event** | **Grades 3/4 (≥2 patients), n (%)** |
| Neutropenia | 23 (41) |
| Thrombocytopenia* | 6 (11) |
| Tumour lysis syndrome† | 6 (11) |
| Hyperglycemia | 5 (9) |
| Anemia | 4 (7) |
| Febrile neutropenia | 4 (7) |
| Hypophosphatemia | 2 (4) |

*Includes patients with autoimmune thrombocytopenia.
†Tumour lysis syndrome includes three events from cohort 1; two clinical events and one laboratory TLS occurred in cohorts 4 and 8, and cohort 2, respectively.

<table>
<thead>
<tr>
<th>Table 2. Response assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response</strong></td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR*</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
</tr>
</tbody>
</table>

*Three patients had confirmatory computed tomography imaging assessments at <8-week intervals (i.e., 5, 6, and 7 weeks).

**CLL = chronic lymphocytic leukemia; CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease**

New Evidence in Oncology | February 2014 17
Figure 1: Best percent change from baseline in nodal size, as assessed by CT scan*

![Graph showing best percent change from baseline in nodal size](image)

CT = computed tomography

*CT assessment occurred at minimum after 6 weeks of treatment in 52 evaluable patients.

Figure 2: Changes from baseline in lymphocyte count and bone marrow infiltrate*

![Graph showing changes from baseline in lymphocyte count and bone marrow infiltrate](image)

CLL = chronic lymphocytic leukemia

*Assessments of lymphocyte count and bone marrow infiltrate occurred at minimum after 6 weeks of treatment in 32 and 34 evaluable patients, respectively.

†Data represents patients with a lymphocyte count >5x10⁹/L at baseline.

‡ Patient had 70% infiltrate at baseline and at week 24.

§ Patient did not have CLL infiltrate at baseline.
In Supportive Care Oncology

Background
Chemoimmunotherapy regimens such as fludarabine, cyclophosphamide, rituximab (FCR) have markedly improved outcomes in younger, fit patients with chronic lymphocytic leukemia (CLL). However, virtually all CLL patients relapse after fludarabine-based therapies; thus, effective salvage regimens that induce durable remissions are needed. Ibrutinib, an oral inhibitor of Bruton tyrosine kinase (BTK), promotes apoptosis and inhibits proliferation, migration, and adhesion in CLL cells. Furman and colleagues presented data from a large, multicohort phase Ib/II trial of ibrutinib in treatment-naïve or relapsed/refractory patients with CLL or small lymphocytic lymphoma (SLL) (PCYC 1102; NCT01105247).1

Study design
• Between May 2010 and July 2011, 116 patients with CLL or SLL were enrolled and given ibrutinib monotherapy.
• Thirty-one patients aged ≥65 were treatment-naïve (TN). Twenty-seven of these patients received 420 mg/day of ibrutinib, and four patients received 840 mg/day.
• Eighty-five patients had relapsed/refractory (R/R) disease, including high-risk patients (n = 24) who were defined as having disease progression within 24 months after initiation of a chemoimmunotherapy regimen or failure to respond. In the R/R group, 51 patients were given 420 mg/day of ibrutinib, and 34 patients received 840 mg/day.

Key findings
• The primary objective was to determine the safety of the two dosing regimens.
• Secondary end points measured were overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and pharmacokinetics/pharmacodynamics.

Key conclusions
■ ABT-199 is highly active in patients with relapsed or refractory CLL independent of high risk factors [i.e., del(17p) or fludarabine-refractory disease], achieving an ORR of 84%.
■ Treatment with ABT-199 resulted in some cases of dose-limiting TLS; additional dosing and scheduling modifications are being explored to minimize the risk of TLS.
  • A titrated dosing scheme combined with more aggressive prophylaxis, monitoring, and management may provide adequate protection for patients.
■ A phase II single-agent study of ABT-199 in patients with del(17p) CLL and phase III combination therapy studies of ABT-199 with rituximab or obinutuzumab (GA101) in patients with relapsed or refractory CLL have begun enrolling.


Furman RR, et al. iwCLL 2013

The Bruton tyrosine kinase inhibitor ibrutinib promotes a high frequency of durable responses in relapsed/refractory and older treatment-naïve chronic lymphocytic leukemia patients: final results of a phase Ib/II study

Background
Chemoimmunotherapy regimens such as fludarabine, cyclophosphamide, rituximab (FCR) have markedly improved outcomes in younger, fit patients with chronic lymphocytic leukemia (CLL). However, virtually all CLL patients relapse after fludarabine-based therapies; thus, effective salvage regimens that induce durable remissions are needed. Ibrutinib, an oral inhibitor of Bruton tyrosine kinase (BTK), promotes apoptosis and inhibits proliferation, migration, and adhesion in CLL cells. Furman and colleagues presented data from a large, multicohort phase Ib/II trial of ibrutinib in treatment-naïve or relapsed/refractory patients with CLL or small lymphocytic lymphoma (SLL) (PCYC 1102; NCT01105247).1

Study design
• In the TN group, baseline characteristics were:
  ○ Median age: 71, ≥70 years: n = 23 (74%);
  ○ Male: 61%;
  ○ Eastern Cooperative Oncology Group (ECOG) status: 0–1: 100%;
  ○ Median absolute lymphocyte count (ALC): 41.1 x 10^9/L;
  ○ β2-microglobulin >3.0 mg/L: n = 8 (26%);

Key findings

Baseline characteristics and disposition
• In the TN group, baseline characteristics were:
  ○ Median age: 71, ≥70 years: n = 23 (74%);
  ○ Male: 61%;
  ○ Eastern Cooperative Oncology Group (ECOG) status: 0–1: 100%;
  ○ Median absolute lymphocyte count (ALC): 41.1 x 10^9/L;
  ○ β2-microglobulin >3.0 mg/L: n = 8 (26%);
High-risk Rai stage III/IV: n = 17 (55%);

- Prognostic markers:
  - Immunoglobulin heavy chain variable region (IgHV) unmutated: n = 15 (48%);
  - del(17p13.1)+: n = 2 (6%);
  - del(11q22.3)+: n = 1 (3%).

In the R/R group, baseline characteristics were:
- Median age: 66, ≥70 years: n = 30 (35%);
- Male: 76%;
- ECOG status 0–1: 98%;
- Median ALC: 8.9 x 10^9/L;
- β2-microglobulin >3.0 mg/L: n = 39 (46%);
- High-risk Rai stage III/IV: n = 52 (61%);

- Prognostic markers:
  - IgHV unmutated: n = 65 (76%);
  - del(17p13.1)+: n = 29 (34%);
  - del(11q22.3)+: n = 29 (34%).

- Median of four prior therapies.

Patient disposition was as follows:
- Median time on treatment: 21.3 months for TN, 16.3 months for R/R;
- Median time on study: 22.1 months for both groups;
- Patients still on treatment: 26 (84%) for TN, 53 (62%) for R/R.

Safety
- The majority of adverse events (AEs) have been grade ≤2 in severity, most commonly diarrhea (57%), fatigue (33%), upper respiratory tract infection (32%), peripheral edema (28%), nausea (27%) and arthralgias (27%).

- Grade ≥3 AEs were reported in 48% and 74% of patients in the TN and R/R groups, respectively. (Table 1)

- The frequency of the most common grade ≥3 AEs are shown in figure 1.

- Ibrutinib-related grade ≥3 AEs were reported in 16% and 28% of patients in the TN and R/R groups, respectively. (Table 1)

- Eleven AEs were reported leading to ibrutinib dose reduction (one in the TN group and 10 in the R/R group). (Table 1)

- Eight deaths were reported within 30 days of the final dose, all in the R/R group. (Table 1)

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>TN ≥65 years n = 31</th>
<th>R/R n = 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE grade ≥3</td>
<td>15 (48)</td>
<td>63 (74)</td>
</tr>
<tr>
<td>Any ibrutinib-related AE grade ≥3</td>
<td>5 (16)</td>
<td>24 (28)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Ibrutinib-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs leading to ibrutinib dose reduction</td>
<td>1 (3)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Deaths within 30 days of final dose</td>
<td>0</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

AE = adverse event; R/R = relapsed/refractory; TN = treatment-naive

Efficacy
- The ORRs were 71% in the TN group and 75% in the R/R group. (Figure 2)

- Among those patients whose initial response was classified as partial response with lymphocytosis (PR-L), the majority achieved classic response by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (69% [9/13] and 78% [38/49] in the TN and R/R groups, respectively).

- The combined ORRs including the PR-L group were 84% and 88% in the TN and R/R groups, respectively.

- Overall, the estimated PFS at 26 months was 96.3% and 73.6% in the TN and R/R groups, respectively. (Figure 3)

- When stratified by mutation status, the estimated PFS at 26 months was 92.2% for patients without del(17p) or del(11q), 72.9% for patients with del(11q), and 53.1% for patients with del(17p). (Figure 3)

- Overall, the estimated OS at 26 months was 96.6% and 77.5% in the TN and R/R groups, respectively. (Figure 4)

- When stratified by mutation status, the estimated OS at 26 months was 92.6% for patients without del(17p) or del(11q), 81.3% for patients with del(11q), and 59.6% for patients with del(17p). (Figure 4)
Figure 1. Frequency of grade ≥3 adverse events

Figure 2. Best overall response

ORR = (CR + PR)

CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; PR-L = partial response with lymphocytosis; R/R = relapsed/refractory; SD = stable disease; TN = treatment-naive
Figure 3. Progression-free survival

Figure 4. Overall survival

del(11q) = deletion on the long arm of chromosome 11; del(17p) = deletion on the short arm of chromosome 17; PFS = progression-free survival; R/R = relapsed/refractory; TN = treatment-naive

del(11q) = deletion on the long arm of chromosome 11; del(17p) = deletion on the short arm of chromosome 17; OS = overall survival; R/R = relapsed/refractory; TN = treatment-naive
Background

Fludarabine, cyclophosphamide, rituximab (FCR) chemoimmunotherapy is recommended as first-line therapy for fit patients with chronic lymphocytic leukemia (CLL). However, few data are available regarding the outcomes of patients salvaged in the second line after first-line FCR.

The objective of this study was to assess the management and outcomes of CLL patients at the time of first salvage after first-line therapy with FCR.\(^1\)

Study design

- This was a retrospective analysis of 132 CLL patients who were treated in 14 French centres and, after having relapsed following first-line FCR, received any second-line treatment for active disease.
- The primary outcomes were progression-free survival (PFS) and overall survival (OS) after second-line therapy.

Key findings

- At the time of first-line FCR, the median patient age was 60.5 years. The majority of patients were male (69.7%) with Binet stage B or C disease (82.7%).
- Based on their characteristics at the time of relapse, a high percentage of patients were classified as high risk or ultra-high risk. (Figure 1, Table 1)
- At first relapse, the majority of patients received bendamustine plus rituximab (BR) as second-line therapy (n = 62). The next two most frequently administered therapies were alemtuzumab-based therapy (n = 22) and rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) (n = 15). (Figure 1)
- Median PFS after second-line therapy was 18 months for BR, 11 months for R-CHOP, and 6 months for alemtuzumab-based therapies. (Figure 2)
- Multivariate analysis indicated that only the type of chemotherapy was significantly associated with PFS.
- OS was significantly improved in patients treated with BR compared to those treated with R-CHOP or alemtuzumab-based therapies (p = 0.0015). (Figure 3)
- For patients treated with BR, PFS did not differ significantly for ultra-high risk patients or for patients with 17p deletion compared with that of the rest of the patient population.
- In multivariate analysis of data for patients treated with BR, no parameter was significantly associated with PFS or OS.
- After second-line therapy, the median OS of patients who had received first-line FCR and were subsequently deemed FCR-refractory and had a PFS lasting <36 months was 3.5 years, which was significantly worse than the median OS of the rest of the patient population (not reached, p = 0.007). (Figure 4)
Figure 1. Patient characteristics at time of relapse and second-line therapies used

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH del(11q) (n = 80)</td>
<td>31</td>
</tr>
<tr>
<td>del(17p) (n = 93)</td>
<td>27</td>
</tr>
<tr>
<td>Complex karyotype (n = 68)</td>
<td>41</td>
</tr>
<tr>
<td>Bulk &gt;5 cm (n = 114)</td>
<td>31</td>
</tr>
<tr>
<td>TTNT after FCR</td>
<td></td>
</tr>
<tr>
<td>&lt;24 months</td>
<td>34.2</td>
</tr>
<tr>
<td>&lt;36 months</td>
<td>57</td>
</tr>
<tr>
<td>PFS after FCR</td>
<td></td>
</tr>
<tr>
<td>&lt;24 months</td>
<td>48</td>
</tr>
<tr>
<td>&lt;36 months</td>
<td>74</td>
</tr>
</tbody>
</table>

Alem-based = alemtuzumab-based therapy; BR = bendamustine, rituximab; del(11q) = deletion on the long arm of chromosome 11; del(17p) = deletion on the short arm of chromosome 17; FCR = fludarabine, cyclophosphamide, rituximab; FISH = fluorescence in situ hybridization; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-Clb/R-CD = rituximab, chlorambucil/rituximab, cyclophosphamide, dexamethasone; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-HDMP = rituximab, high-dose methylprednisolone; TTNT = time to next treatment; w/o R = without rituximab

Table 1. Patient characteristics at the time of relapse for the three most frequently used second-line therapies

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BR (n = 62), %</th>
<th>R-CHOP (n = 15), %</th>
<th>Alem-based (n = 22), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR-refractory</td>
<td>9.7</td>
<td>20</td>
<td>27.3</td>
</tr>
<tr>
<td>High risk*</td>
<td>46.8</td>
<td>46.7</td>
<td>86.4</td>
</tr>
<tr>
<td>Ultra-high risk†</td>
<td>34</td>
<td>40</td>
<td>81.8</td>
</tr>
<tr>
<td>IgHV unmutated</td>
<td>42.6</td>
<td>23</td>
<td>57.1</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>25</td>
<td>60</td>
<td>40.1</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>14.7</td>
<td>66.7</td>
<td>26.7</td>
</tr>
<tr>
<td>Binet stage C</td>
<td>45.1</td>
<td>33.3</td>
<td>42.8</td>
</tr>
<tr>
<td>Bulky tumour (&gt;5cm)</td>
<td>13.3</td>
<td>40</td>
<td>27.3</td>
</tr>
<tr>
<td>AlloBMT</td>
<td>8</td>
<td>26.7</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Alem-based = alemtuzumab-based therapy; AlloBMT = allogeneic bone marrow transplantation; BR = bendamustine, rituximab; Del(11q) = deletion on the long arm of chromosome 11; Del(17p) = deletion on the short arm of chromosome 17; FCR = fludarabine, cyclophosphamide, rituximab; IgHV = immunoglobulin heavy chain variable region; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

*High risk: FCR-refractory, del(17p), PFS <24 months.
†Ultra-high risk: FCR-refractory, del(17p), or PFS <24 months with treatment indication.

Figure 2. Progression-free survival after second-line therapy
Figure 3. Overall survival after second-line therapy

Figure 4. Overall survival stratified by progression-free survival after first-line FCR

Key conclusions

- BR appears to be an effective salvage regimen after FCR first-line therapy in this cohort, which was largely composed of high-risk relapsed and refractory patients.

- These data are important, as BR is now used as a backbone chemoimmunotherapy for the evaluation of new molecules.

- Prognosis for patients with early relapse remains poor, with a median OS of 3.5 years.

Bendamustine and rituximab as first- or second-line therapy in elderly patients with chronic lymphocytic leukemia

Background
The current standard therapy for fit young patients with chronic lymphocytic leukemia (CLL) is fludarabine, cyclophosphamide, rituximab (FCR); however, this therapy can induce unacceptable myelotoxicity and increase the risk of infection in elderly patients. Since the median age at diagnosis for patients with CLL is 72, the majority of patients cannot tolerate FCR. Bendamustine is an alkylator that has a unique mechanism of action and it has yielded good clinical efficacy and acceptable tolerability in patients with various hematologic malignancies. The aim of this study was to investigate the safety and efficacy of bendamustine and rituximab (BR) in elderly patients with CLL as first- or second-line therapy.1

Study design
• Twenty-six patients with CLL were enrolled at three hematological centres in Tuscany, Italy.
• Six cycles of BR were given.
  ◦ Rituximab was given at a dose of 375 mg/m² intravenously (iv) on day three of the first cycle, and then 500 mg/m² iv was given on day one of each subsequent cycle.
  ◦ Bendamustine was given at a dose of 70 mg/m² iv on days one and two of the first cycle, and on days two and three of subsequent cycles.
• Antibiotics prophylaxis was given on days 1–10 of each cycle.

B = Bendamustine 70 mg/m² iv
R = Rituximab 375 mg/m² iv

iv = intravenously
Key findings

- The median age of patients was 72 years.
- The majority of patients were male (65%) with previously treated CLL (65%).
- Disease characteristics were as follows:
  - Rai stage III/IV: n = 18 (69%);
  - Immunoglobulin heavy chain variable region (IgHV) unmutated: n = 16 (61.5%);
  - Fluorescence in situ hybridization:
    - N/13q−/+12 deletions: n = 20 (77%);
    - 17p−/11q− deletions: n = 6 (23%);
  - Eastern Cooperative Oncology Group (ECOG) performance status:
    - 0: n = 9; 1: n = 15; 2: n = 3.
- A median of six (range: 3–6) cycles of BR was given and the median follow-up was 18 months.
- Hematological toxicities were reported in 17 patients, of which 10 were grade 3/4 (38%). (Table 1)
- Nonhematological toxicities were mild, with grade 1 gastrointestinal toxicity reported in 19 patients (73%) and grade 1 cutaneous toxicity reported in five patients (19%). (Table 1)
- Grade 3/4 pneumonia was reported in four patients (15%). (Table 1)

- The overall response rate (ORR) was 84% in the entire study population, and 100% in previously untreated patients. A complete response was observed in 6 patients (23%), and a partial response was observed in 16 patients (61%). (Table 2)
- The median progression-free survival (PFS) for patients treated in the first-line setting has not been reached; PFS for patients treated at first relapse was 17 months.
- No differences were seen in response or PFS in patients with del(11q), trisomy 12, or del(13q) abnormalities.
- Patients with del(17p) or unmutated IgHV had lower rates of response.

<table>
<thead>
<tr>
<th>Table 1. Reported toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological toxicity</td>
</tr>
<tr>
<td>N = 26</td>
</tr>
<tr>
<td>Nonhematological toxicity</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Response rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
</tbody>
</table>

CR = complete response; ORR = overall response rate; PR = partial response

Key conclusions

- BR is extremely effective in the treatment of elderly patients with CLL.
- Hematological toxicity was the most important toxicity reported; however, it can be easily managed with growth factors and antibiotic prophylaxis.


Barrientos JC, et al. iwCLL 2013:4.22

Update on a phase I study of the selective PI3Kδ inhibitor, idelalisib, in combination with rituximab, bendamustine, or BR in patients with relapsed or refractory chronic lymphocytic leukemia

Background

Idelalisib (GS-1101) is a targeted, highly selective, oral inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3Kδ) that inhibits proliferation and induces apoptosis of B cells in many B-cell malignancies. Phase I studies of idelalisib demonstrated significant activity as monotherapy. At iwCLL 2013, Barrientos and colleagues presented an update that examined the safety and efficacy of idelalisib in combination with bendamustine and/or rituximab in patients with CLL.1
Study design

- Eligibility criteria included age ≥18 years and relapsed or refractory CLL requiring treatment.
- The primary end point was safety; secondary end points, as determined by intention-to-treat (ITT) analysis, included overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS).
- Patients (n = 52) were randomized to one of three treatment arms (see study design for dosages):
  - Idelalisib plus rituximab (I + R);
  - Idelalisib plus bendamustine (I + B); or
  - Idelalisib plus bendamustine and rituximab (I + BR).
- Patients remained on study for 48 weeks, at which point those who continued to benefit from treatment, as determined by iwCLL 2008 and Cheson 2012 response criteria, were given the option of joining the extension study.
- Patients in the extension study received idelalisib monotherapy continuously.

Key findings

Patient characteristics and disposition

- The median age of patients in this study was 64 years.
- The majority of patients were male (57%) with a median of three prior therapies.
- Disease characteristics were as follows:
  - Bulky adenopathy (≥1 node with diameter ≥5 cm): 65% of patients;
  - Refractory disease (defined as progression within six months of last therapy): 52% of patients;
  - Deletion on short arm of chromosome 17 [del(17p)] and/or TP53 mutation: 21% of patients.
- Of the 52 patients originally enrolled, 31 completed the study protocol and enrolled in the extension study.
- The most common reasons for discontinuation from the primary study were disease progression (10%), adverse events (AEs) (10%), and death (10%).
- Nineteen patients remain on the extension study; the most common reasons for discontinuation were disease progression (8%) and AEs (8%).
- The median dosing duration over the course of the primary and extension studies was 18 months.

Safety

- The most common treatment-emergent AEs of any grade were pyrexia (48%), diarrhea (40%), fatigue (33%), cough (31%), and nausea (27%). (Table 1)
- The most common AEs of grade ≥3 included febrile neutropenia (15%), pneumonia (14%), and diarrhea (14%). (Table 1)
- The recorded hematotoxicities and laboratory abnormalities (any grade/grade ≥3) included neutropenia (73%/50%), thrombocytopenia (44%/12%), anemia (42%/15%), and alanine aminotransferase/aspartate aminotransferase elevations (35%/10%). (Table 1)
- The most common serious AEs were febrile neutropenia, pneumonia, and pyrexia (each occurred in 12% of patients). (Table 2)

Efficacy

- ORR for all patients was 83%; 89% for I + R, 78% for I + B, and 87% for I + BR.
  - ORR for patients with del(17p) or TP53 mutations was 73%. (Figure 1)
- For all patients, median DOR was 27 months.
  - When stratified by mutation status, median DOR was 19 months for patients with del(17p) or TP53 mutations, and has not yet been reached in patients with neither mutation.
- For all patients, median PFS was 28 months.
  - When stratified by mutation status, median PFS was 20 months for patients with del(17p) or TP53 mutations, and has not yet been reached in patients with neither mutation. (Figure 2)
### Table 1. Adverse events and selected lab abnormalities

<table>
<thead>
<tr>
<th>Adverse event, &gt;10% (N = 52)</th>
<th>Any grade, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>None</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Chills</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab abnormalities</th>
<th>Any grade, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>73</td>
<td>50</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Anemia</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>ALT/AST elevation</td>
<td>35</td>
<td>10</td>
</tr>
</tbody>
</table>

ALT/AST = alanine aminotransferase/aspartate aminotransferase

### Table 2. Serious adverse events in n ≥2 and adverse events leading to study drug discontinuation

<table>
<thead>
<tr>
<th>Serious adverse event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Colitis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

AE = adverse event; ALT = alanine aminotransferase

<table>
<thead>
<tr>
<th>AE (any grade) leading to drug discontinuation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT elevation</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>1</td>
</tr>
<tr>
<td>Colitis</td>
<td>1</td>
</tr>
<tr>
<td>Colon cancer recurrent</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>1</td>
</tr>
<tr>
<td>Rash papular</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
</tr>
</tbody>
</table>

### Figure 1. Overall response rate

![Graph showing overall response rate](image)

CI = confidence interval; del(17p) = deletion on the short arm of chromosome 17; I + B = idelalisib plus bendamustine; I + BR = idelalisib plus bendamustine, rituximab; I + R = idelalisib plus rituximab; ITT = intention-to-treat; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; TP53mut = tumour protein p53 mutation

*Response by iwCLL criteria (Hallek 2008)

†ITT analysis

‡Del(17p) only (n = 1), TP53 only (n = 6), del(17p) + TP53 (n = 4)
**Key conclusions**

- Combinations of idelalisib with rituximab and/or bendamustine induced overall responses in >80% of patients with heavily pretreated or refractory CLL.
- Idelalisib combination therapies were well tolerated for up to three years, with minimal overlapping toxicities when combined with chemoimmunotherapy and infrequent discontinuations due to AEs.
- The responses were durable despite frequent prior exposure to combination agents (bendamustine and rituximab), with a median DOR of 27 months.
- Phase III trials of idelalisib in combination with rituximab or BR for the treatment of relapsed/refractory CLL are currently underway.


Offner F, et al. iwCLL 2013:4.29

**Ofatumumab and bendamustine combination therapy in patients with untreated and relapsed chronic lymphocytic leukemia: initial results of the phase II study OMB115991**

**Background**

Ofatumumab is currently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. In vitro experiments with ofatumumab and bendamustine have shown synergistic anti-tumour activity when both agents are used together compared with the individual agents used alone. Study OMB115991 was designed to investigate the safety and efficacy of ofatumumab plus bendamustine in two populations: patients with untreated CLL who were unfit for fludarabine-based therapy and patients with relapsed CLL.

---

**Figure 2. Progression-free survival**

**Key conclusions**

- Combinations of idelalisib with rituximab and/or bendamustine induced overall responses in >80% of patients with heavily pretreated or refractory CLL.
- Idelalisib combination therapies were well tolerated for up to three years, with minimal overlapping toxicities when combined with chemoimmunotherapy and infrequent discontinuations due to AEs.
- The responses were durable despite frequent prior exposure to combination agents (bendamustine and rituximab), with a median DOR of 27 months.
- Phase III trials of idelalisib in combination with rituximab or BR for the treatment of relapsed/refractory CLL are currently underway.


Offner F, et al. iwCLL 2013:4.29

**Ofatumumab and bendamustine combination therapy in patients with untreated and relapsed chronic lymphocytic leukemia: initial results of the phase II study OMB115991**

**Background**

Ofatumumab is currently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. In vitro experiments with ofatumumab and bendamustine have shown synergistic anti-tumour activity when both agents are used together compared with the individual agents used alone. Study OMB115991 was designed to investigate the safety and efficacy of ofatumumab plus bendamustine in two populations: patients with untreated CLL who were unfit for fludarabine-based therapy and patients with relapsed CLL.³
Study design

- Study OMB115991 was a phase II, open-label, single-arm, multicentre study.
- The primary outcome was overall response rate (ORR) as determined by investigator evaluation, according to the 2008 National Cancer Institute Working Group guidelines.
- Secondary outcomes included complete response (CR) rate, safety, and tolerability.
- Patients received pre-medications of acetaminophen (1,000 mg or equivalent), an antihistamine (50 mg diphenhydramine or equivalent), and a glucocorticoid (equivalent to 50 mg prednisolone) prior to ofatumumab therapy.
- Patients received monthly intravenous infusions of ofatumumab (cycle 1: 300 mg on day 1 and 1,000 mg on day 8; cycles 2-6: 1,000 mg on day 1 every 28 days) in combination with bendamustine on days 1 and 2, every 28 days for up to six cycles.
- Patients with previously untreated CLL received an initial dose of 90 mg/m². Patients with relapsed CLL received an initial dose of 70 mg/m².
- A dose reduction of bendamustine, but not ofatumumab, was required for toxicity. Previously untreated patients required a bendamustine dose reduction to 60 mg/m² and relapsed patients required a reduction to 50 mg/m².
- Patients were evaluated for response and safety at the start of each cycle of treatment and at every three-month follow-up visit until progression, or until three years after the last dose of study treatment.

Key findings

Patient characteristics

- The study enrolled a total of 97 patients: 44 patients with previously untreated CLL and 53 patients with relapsed CLL.
- The median ages of patients in the previously untreated and relapsed groups were 62.5 and 68.0 years, respectively.
- Patients in the relapsed group had received a median of one prior therapy.
- Disease characteristics for each group were as follows (previously untreated/relapsed):
  - Modified high-risk Rai stage: 32%/57%;
  - Binet stage C: 27%/47%;
  - Median serum β₂-microglobulin (mg/L): 3.6/4.8;
  - Median lymphocyte count (GL/L): 67.6/50.0;
  - 17p deletion: 5%/12%;
  - 11q deletion: 18%/29%;
  - Immunoglobulin heavy chain variable region (IgHV) unmutated: 66%/72%;
  - Zeta-chain-associated protein kinase 70 (ZAP70) positive: 82%/85%;
- The majority of patients completed all six treatment cycles (previously untreated: 89%; relapsed: 85%).

Efficacy

- Investigator-assessed ORRs were 95% (CR = 43%) in the previously untreated population and 74% (CR = 11%) in the relapsed population. (Table 1)
- By computed tomography evaluation, ORR was 82% (CR = 27%) in the previously untreated population and 70% (CR = 9%) in the relapsed population.

**Study design**

- **Patients with untreated CLL** (n = 40)
  - Up to six monthly iv infusions of ofatumumab* in combination with up to six cycles of iv infusions of bendamustine!
  - Follow-up/PD

- **Patients with relapsed CLL** (n = 40)
  - Up to six monthly iv infusions of ofatumumab* in combination with up to six cycles of iv infusions of bendamustine!

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

*Cycle 1: 300 mg day 1 and 1,000 mg day 8; subsequent cycles: 1,000 mg day 1, every 28 days.
†90 mg/m², days 1 and 2, every 28 days.
‡70 mg/m², days 1 and 2, every 28 days.
For the patients who had an investigator-assessed CR and had minimal residual disease (MRD) analysis performed, MRD negativity was 56% for the previously untreated population and 0% for the relapsed population.

The median time to response was 0.95 months for both groups.

As of the data cutoff (Feb. 28, 2013), the following end points of duration of response, progression-free survival (PFS), time to progression, overall survival (OS), and time to next therapy were not yet mature.

**Safety**

- Adverse events (AEs) classified as grade ≥3 included neutropenia (previously untreated group: n = 16 and relapsed group: n = 29), rash (previously untreated group: n = 2), and thrombocytopenia (relapsed group: n = 4). (Table 2)

- No deaths occurred in the previously untreated group, and four deaths occurred in the relapsed group, two of which were considered by the investigators to be possibly related to study treatment:
  - One patient died of pneumonia and hemolytic anemia 15 days after the latest dose of study treatment.
  - One patient died of sepsis four days after the latest dose of study treatment.
  - The most frequently reported infections were upper respiratory tract infections (20% of previously untreated patients and 15% of relapsed patients), and lower respiratory tract infections (16% of previously untreated patients and 19% of relapsed patients).
  - Grade ≥3 infections occurred in 11% and 15% of previously untreated and relapsed patients, respectively.
  - In the relapsed group, three patients had serious AEs of infection that were fatal.
  - Infusion reactions occurred in 68% of previously untreated patients and 60% of relapsed patients. Infusion reactions occurred primarily during cycles 1 and 2 and were generally considered mild to moderate. (Figures 1 & 2)
  - Grade ≥3 infusion reactions occurred in 11% of previously untreated patients and 8% of relapsed patients. (Figures 1 & 2)
  - Two patients from the previously untreated study population were discontinued from further study treatment due to infusion reactions (delayed type hypersensitivity reaction and anaphylaxis).

---

### Table 1. Summary of overall response rate

<table>
<thead>
<tr>
<th></th>
<th>Previously untreated population: ofatumumab + bendamustine 90 mg/m²</th>
<th>Relapsed population: ofatumumab + bendamustine 70 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After 3 cycles (N = 42)*</td>
<td>After 6 cycles (N = 39)#</td>
</tr>
<tr>
<td>Overall response, n (%)</td>
<td>15 (36)</td>
<td>19 (49)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>CRi</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>30 (61)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>nPR</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

**Responders, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Yes (CR + CRi + nPR + PR)</th>
<th>No</th>
<th>95% CI for (CR + CRi + nPR + PR)#</th>
<th>95% CI for (CR + CRi + nPR + PR)#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>38 (90)</td>
<td>4 (10)</td>
<td>(77.38, 97.34)</td>
<td>(77.38, 97.34)</td>
</tr>
<tr>
<td></td>
<td>38 (97)</td>
<td>1 (3)</td>
<td>(86.52, 99.94)</td>
<td>(86.52, 99.94)</td>
</tr>
<tr>
<td></td>
<td>42 (95)</td>
<td>2 (5)</td>
<td>(84.53, 99.44)</td>
<td>(84.53, 99.44)</td>
</tr>
<tr>
<td></td>
<td>42 (86)</td>
<td>7 (14)</td>
<td>(72.76, 94.06)</td>
<td>(72.76, 94.06)</td>
</tr>
<tr>
<td></td>
<td>37 (82)</td>
<td>8 (18)</td>
<td>(67.95, 92.00)</td>
<td>(67.95, 92.00)</td>
</tr>
<tr>
<td></td>
<td>39 (74)</td>
<td>14 (26)</td>
<td>(59.67, 84.74)</td>
<td>(59.67, 84.74)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow; nPR = nodular partial response; PD = progressive disease; PR = partial response; SD = stable disease

*N is the number of patients who completed study treatment at cycle 1, 2, and 3.

†N is the number of patients who completed all six cycles of study treatment.

‡95% exact binomial confidence interval for CR + CRi + nPR + PR.
Table 2. Summary of common (≥5%) grade 3, 4, or 5 serious adverse events up to 60 days after last dosing

<table>
<thead>
<tr>
<th>Event</th>
<th>Previously untreated population: ofatumumab + bendamustine 90 mg/m² (N = 44)</th>
<th>Relapsed population: ofatumumab + bendamustine 70 mg/m² (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Any event, n (%)</td>
<td>15 (34)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (16)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Figure 1. Infusion reactions in the previously untreated safety population

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Patients (n)</th>
<th>All grades (n)</th>
<th>Grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1D1</td>
<td>44</td>
<td>23</td>
<td>1 (4)</td>
</tr>
<tr>
<td>C1D2</td>
<td>44</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
<td>43</td>
<td>30</td>
<td>1 (3)</td>
</tr>
<tr>
<td>C3</td>
<td>42</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>C4</td>
<td>40</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>C5</td>
<td>40</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>C6</td>
<td>39</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 2. Infusion reactions in the relapsed population

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Patients (n)</th>
<th>All grades (n)</th>
<th>Grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1D1</td>
<td>53</td>
<td>21</td>
<td>3 (6)</td>
</tr>
<tr>
<td>C1D2</td>
<td>53</td>
<td>27</td>
<td>1 (2)</td>
</tr>
<tr>
<td>C2</td>
<td>50</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>C3</td>
<td>49</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>C4</td>
<td>49</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>C5</td>
<td>48</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>C6</td>
<td>45</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

C = cycle; D = day
Key conclusions

- Ofatumumab in combination with bendamustine is an effective and tolerable therapy, providing high response rates and an acceptable safety profile for patients with previously untreated CLL who are unfit for fludarabine-based therapy and for patients with relapsed CLL.

- Longer follow-up is required to determine time-to-event end points such as PFS and OS.


Goede V, et al. iwCLL 2013:4.14

Kinetics of blood cell subpopulations during treatment with obinutuzumab (GA101) plus chlorambucil (Clb), rituximab plus Clb versus Clb alone in patients with CLL and coexisting medical conditions: stage 1 results of the CLL11 trial

Background

Reducing the leukemic burden and restoring normal hematopoietic function are important goals when treating chronic lymphocytic leukemia (CLL). The CLL11 study, a large, randomized, prospective phase III trial in treatment-naïve CLL patients with coexisting medical conditions, compared patient outcomes and safety associated with obinutuzumab (GA101) plus chlorambucil (G-Clb) or rituximab plus chlorambucil (R-Clb) treatment versus chlorambucil (Clb) alone. At iwCLL 2013, Goede and colleagues described the changes in lymphocytes, hemoglobin, platelets, and neutrophils from baseline to end of treatment, as observed in stage 1a and 1b analyses of the CLL11 study.1

Key findings

- Patient characteristics at baseline (% of patients) were as follows for the chlorambucil, G-Clb, and R-Clb groups, respectively:
  - Binet stage A: 20%, 23%, and 21%;
  - Binet stage B: 42%, 41%, and 43%;
  - Binet stage C: 37%, 36%, and 36%;
  - Lymphocyte count ≥25 x 10^9/L: 84%, 76%, and 71%;
  - Lymphocyte count ≥100 x 10^9/L: 37%, 24%, and 26%.

- All groups received a median of 6 cycles of treatment.

- Median total dose of chlorambucil received was 384 mg, 370 mg, and 400 mg for the chlorambucil, G-Clb, and R-Clb groups, respectively.

- Lymphocyte counts decreased faster and to a greater extent in the G-Clb and R-Clb groups compared to that in the chlorambucil group. The fastest lymphocyte depletion was observed in the G-Clb group. (Figure 1)

- Trends toward improvements in hemoglobin levels and platelet counts were observed in the G-Clb and R-Clb groups compared to the chlorambucil group. (Figures 2 and 3)

- Absolute neutrophil counts decreased below baseline with all three regimens. (Figure 4)

- There were no changes in the median IgA, IgG, or IgM levels from baseline to end of treatment in any treatment arm.
Key conclusions

- Ofatumumab in combination with bendamustine is an effective and tolerable therapy, providing high response rates and an acceptable safety profile for patients with previously untreated CLL who are unfit for fludarabine-based therapy and for patients with relapsed CLL.
- Longer follow-up is required to determine time-to-event end points such as PFS and OS.

Eligibility criteria (786 patients enrolled):
- Previously untreated CLL with comorbidities
- Total CIRS score >6 and/or CrCl <70 mL/min

Randomized to treatment 1:2:2*
(6 cycles of 28 days)

Chlorambucil (Clb)†
GA101 + chlorambucil (G-Clb)
Rituximab + chlorambucil (R-Clb)

Stage 1a
G-Clb vs. Clb
Stage 1b
R-Clb vs. Clb
Stage 2
G-Clb vs. R-Clb

CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; GA101 = obinutuzumab
*Randomization to Clb was closed after 118 patients and continued in a 1:1 ratio to the G-Clb and R-Clb arms.
†Patients with progressive disease were allowed to cross to the G-Clb treatment group.

Figure 1. Lymphocyte counts during treatment*

Figure 2. Hemoglobin levels during treatment*

*C = cycle; Clb = chlorambucil; D = day; G-Clb = GA101 (obinutuzumab) + chlorambucil; R-Clb = rituximab + chlorambucil
*Numbers under boxes represent the median value (g/L).
Figure 3. Platelet counts during treatment*

Figure 4. Absolute neutrophil counts during treatment*

Key conclusion

- The data suggest that GA101 may have superior B-cell depleting activity than that of rituximab, which could result in enhanced recovery of bone marrow function and increased clinical efficacy.

Established efficacy in the first-line setting for EGFR M+ metastatic lung adenocarcinoma¹,²

GIOTRIF demonstrated superior PFS vs. pemetrexed/cisplatin in the first-line setting in LUX-Lung 3, the largest, open-label, phase III trial in EGFR M+ metastatic lung adenocarcinoma¹,².*

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

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


¹ Comparative clinical significance unknown.

See additional safety information on page 96
Detection of Minimal Residual Disease in Clinical Trials of Chronic Lymphocytic Leukemia: Summary of the Presentation by Dr. Michael Kneba at iwCLL 2013

Introduction
As treatments for chronic lymphocytic leukemia (CLL) improve and become more effective, more patients are achieving long-lasting clinical remissions. Accordingly, a complete eradication of CLL is an obvious and desirable end point, and measurement of residual disease (i.e., minimal residual disease [MRD]) is becoming increasingly important, as assessments of complete remission (CR) at the clinical and morphological level are no longer sensitive enough to assess outcome. MRD is a very sensitive measure of tumour load that takes advantage of the biological features of the disease to determine the number of CLL cells remaining during or after treatment (i.e., when the patient is in remission). If residual CLL cells are a major cause of relapse, then achieving lower levels of MRD should, in theory, be associated with better outcomes. Indeed, several studies have demonstrated that MRD levels independently predict progression-free survival (PFS) and overall survival (OS) in patients with CLL, suggesting that MRD levels may be used as an early indicator of treatment efficacy in clinical trials of new therapies. Although MRD is increasingly being used as an end point in clinical trials, the wide variety of MRD techniques and different sampling sources used in these trials makes it difficult to interpret and compare outcomes. Therefore, it is essential that assays used for MRD detection are harmonized before MRD can be widely used as an end point in clinical trials.

Approaches for detecting MRD
MRD can be quantified by using two distinct approaches — polymerase chain reaction (PCR) or flow cytometry. Current international guidelines recommend the use of either 4-colour flow cytometry or allele-specific oligonucleotide PCR, as these methods have been shown to be reliably and reproducibly sensitive in detecting low levels of MRD (i.e., at a threshold of $10^{-4}$). While both techniques have their respective advantages and disadvantages, flow cytometry has the advantages of being simpler, quicker, and less expensive than PCR, thereby making it more suitable for routine use. On the basis of these advantages, an international consortium led by the European Research Initiative in CLL (ERIC) developed a standardized 4-colour flow cytometry MRD assay that can be reliably performed by most centres to guide therapy and assess response in the context of clinical trials. This 4-colour assay demonstrated comparable detection sensitivity to allele-specific oligonucleotide PCR, and is effective in detecting CLL cells in either bone marrow or peripheral blood samples independent of the treatment used. Although the 4-colour assay is now widely accepted and used in several clinical trials, it does have limitations, and considerable efforts have been made by ERIC to further improve and standardize flow cytometric detection of MRD. At iwCLL 2013, two abstracts addressed two important aspects for the use of MRD detection in clinical trials of CLL, namely: (1) the technical aspects of flow cytometry, and (2) the optimal sampling material and time points.

Standardizing multiparameter flow cytometry for MRD detection in clinical trials
In the development of the 4-colour assay, the following three CLL-specific antibody combinations were identified as having the lowest interlaboratory variation and false-detection rates: (1) CD5/CD19/CD20/CD38; (2) CD5/CD19/CD81/CD22; and (3) CD5/CD19/CD79b/CD43. Since at least two of the three combinations need to be used to detect MRD in addition to an initial screening test and contamination control, the 4-colour assay requires four to five tests to be performed. Additionally, this procedure may be unnecessary for many patients with an obvious presence of CLL, and it may be difficult for unspecialized laboratories to interpret the results. Therefore, to further improve the efficiency and sensitivity of flow cytometric MRD detection, multiparameter assays that use six or more colours simultaneously are being developed and tested. Indeed, ERIC recently published a harmonized approach for a 6-colour assay that is more sensitive, requires only two tests, fewer reagents and cells, and has a simpler analysis protocol. Furthermore, other groups have tested 8- and 10-colour assays; however, these methodologies need to be standardized and validated in larger studies.
At iwCLL 2013, Rawstron and colleagues presented an update on the recent collaborative efforts of ERIC in the E.U., U.S., and Australia.² Given that flow cytometry protocols used at different laboratories vary with respect to sensitivity, reproducibility, costs, and speed, ERIC developed: (1) a standardized, single test, 8-colour assay, and (2) guidelines for MRD detection in CLL using multiparameter (i.e., 4- to 10-colour) flow cytometry. The 8-colour assay was found to reliably detect residual CLL down to a level of 0.003% (3 × 10⁻⁶), which is sensitive enough to detect MRD negativity at the required threshold of 0.01% (10⁻⁴), as recommended by the iwCLL guidelines.³ The ERIC consortium also presented their guidelines for MRD detection in CLL using multiparameter flow cytometry approaches that are simple, reproducible, cost-effective, and can be adapted to most laboratories with cytometers that detect at least four colours. These standardized guidelines will aid in collecting reliable MRD data in future clinical trials.

**Sampling issues in clinical trials**

While both peripheral blood and bone marrow samples can be used for MRD assessments in CLL trials, peripheral blood should only be used at least 3 months after completing therapy, as certain therapies (e.g., alemtuzumab, rituximab, and other antibodies targeting CLL) deplete cells in peripheral blood.³,⁸ Despite this recommendation, it is still not entirely clear what sampling material and time points are the most predictive of outcome.⁵,⁸

Furthermore, according to the current iwCLL guidelines, to document a clinical CR in clinical trials, both a bone marrow aspirate and trephine biopsy must be performed.³,⁸ However, trephine biopsies cause significant discomfort to the patient, and immunohistochemical assessments of biopsy samples are subjective and have low sensitivity for detecting residual disease.⁸ Thus, the significance of using trephine biopsies is questionable, particularly because more sensitive assays that quantify residual disease are available.⁵,⁸

To deal with these sampling issues, Rawstron and colleagues set out to: (1) compare MRD assessments in peripheral blood and bone marrow aspirates at 3 and 6 months after treatment cessation, and (2) determine whether trephine biopsies are necessary for response assessment in clinical trials. The preliminary findings were presented at iwCLL 2013.⁸ Using flow cytometry, as per ERIC guidelines, it was determined that detection of residual disease in peripheral blood samples was less sensitive than bone marrow aspirate at 3 and 6 months after treatment cessation. Additionally, at 3 months after treatment cessation, assessments of trephine biopsies provided virtually no additional information in patients who had >1% CLL cells in peripheral blood or <0.01% CLL cells in bone marrow aspirates. These findings suggest that bone marrow aspirate at 3 months after treatment cessation remains the optimal source for MRD assessment, and that in a substantial proportion of CLL patients, trephine biopsies appear unnecessary for clinical response assessment.

**Application of flow cytometric detection of MRD in clinical trials**

The randomized German CLL Study Group (GCLLSG) CLL8 trial was the first to use the standardized 4-colour flow cytometry protocol developed by ERIC to determine the prognostic significance of MRD in determining the outcome of patients with CLL.⁵ The main finding of this trial was that, in patients with CLL, MRD negativity was associated with longer PFS and OS independent of previously established prognostic risk factors (e.g., chromosome 17p deletion, IgHV mutation, etc.) and treatment received (i.e., fludarabine and cyclophosphamide [FC] vs. FC plus rituximab [FCR]). Although this finding is pivotal in supporting the use of MRD as a surrogate marker of treatment efficacy before clinical response can be evaluated, several other important observations were made that further our understanding of the applicability of MRD in clinical trials.

One interesting observation was that MRD kinetics can be used to track response during and after therapy. Using peripheral blood samples, the investigators assessed MRD status prior to treatment (i.e., initial staging), after three cycles of treatment (i.e., interim staging), and three months after treatment cessation (i.e., final restaging) (Figure 1). MRD levels were similar prior to treatment in both arms, but after three cycles of therapy, more patients in the FCR arm achieved MRD negativity than those in the FC arm (26% vs. 8%) (Figure 1). After completion of therapy, the proportion of MRD-negative patients more than doubled in both treatment arms (FCR: 63% vs. FC: 35%) (Figure 1). These findings were also corroborated by MRD levels in bone marrow at final restaging (FCR: 44% vs. FC: 28%) (Figure 1). While tracking MRD kinetics during treatment revealed that FCR had higher efficacy than FC, the more interesting finding was that patients from both treatment arms who achieved MRD negativity at both interim staging and final restaging had similar median PFS (64 and 69 months, respectively).³ This finding suggests that tracking MRD kinetics during treatment may be a useful indicator of outcome independent of the treatment regimen.

Another interesting finding was that lower levels of MRD after treatment were associated with longer PFS regardless of the sampling material (i.e., peripheral blood or bone marrow) used to quantify MRD levels (Figure 2).⁴,⁵ That is, when patients were stratified according to three subgroups of MRD levels (i.e., <10⁻⁴, ≥10⁻⁴ to <10⁻⁵, and >10⁻⁵), it was determined that there was an inverse relationship between MRD level and time to progression.³ This finding highlights the prognostic significance of MRD levels per se. Furthermore, even though current iwCLL guidelines define MRD negativity at a threshold of 10⁻⁴, this threshold does not equate to complete disease eradication, and therefore, the predictive
value of MRD assessments can be further improved with more sensitive techniques that can measure MRD at lower levels. 3, 4

Lastly, it was found that the predictive value of MRD appears to be independent of clinical response. When MRD levels were compared between patients who achieved a partial remission versus those who achieved a CR, it was found that partial responders who attained a low-level MRD had a similar risk of progression as complete responders at the same MRD level (Figure 3). 5 These data further support the independent prognostic significance of MRD levels, and suggest that MRD should be assessed in all responding patients. 4, 5

Since the CLL8 trial, other clinical trials have included MRD as an end point. For example, in the ongoing CLL 10 trial (NCT00769522) of FCR versus bendamustine and rituximab in patients with previously untreated CLL, MRD is defined as a secondary end point. 10 In CLL10, MRD testing is conducted not only at the end of the study, but also throughout (i.e., after three cycles of treatment, two months after treatment, and every three months until two years after final staging). 10

Conclusion
In conclusion, there is evidence to support the idea that MRD may be a used as a surrogate marker to compare treatment efficacy prior to the availability of clinical end point data. Due to significant efforts on behalf of the ERIC consortium to standardize flow cytometric detection of MRD, MRD is now being considered by regulatory agencies (e.g., the U.S. Food and Drug Administration) as a meaningful end point for clinical trials, which would not only decrease the duration of follow-up required, but also accelerate the approval of novel therapies for CLL. 7
Figure 2. CLL8 trial: PFS in patients grouped by MRD levels assessed in (A) peripheral blood and (B) bone marrow at final restaging

MRD = minimal residual disease; PFS = progression-free survival

The inserted pie charts represent frequency distributions at each MRD level.

Figure 3. CLL8 trial: PFS in patients grouped by clinical response and MRD levels assessed in peripheral blood at final restaging

CR = complete remission; MRD = minimal residual disease; PFS = progression-free survival; PR = partial remission

The inserted pie charts represent frequency distributions at each MRD level.

References:
**Introduction**

Chronic lymphocytic leukemia (CLL) is a disease that occurs predominantly in elderly patients; the median age of patients with CLL is 72 years. As a result, patients with CLL are characterized as having an increased number of comorbidities, with most patients presenting with some degree of comorbidities. This observation has led physicians to begin to prioritize patient fitness over age when considering treatment options for CLL, and a consensus paper by the International Workshop on CLL on this topic will shortly be published.

**Therapy for fit patients**

An important consideration in the treatment of fit patients with CLL is the selection of the first therapy received, since response to first-line therapy is a very important determinant of patient outcome. Patients with a complete response (CR) to first therapy have better outcomes than those who progress or have stable disease after first therapy. Additionally, if a minimal residual disease (MRD)-negative state is achieved after first-line therapy, overall survival (OS) is much higher. This is illustrated in the recently published update to the CLL8 trial, where OS was substantially longer for patients at low risk for early relapse compared to those at high risk (Figure 1).

Since first-line therapy is so crucial for patients with CLL, in the ongoing CLLM1 trial, we have adopted the strategy of giving a chemotherapy or chemoimmunotherapy that will achieve the best possible response in young, fit patients, and then measuring MRD and other progression markers to identify the high-risk population. These high-risk patients usually have a very short time to next progression and have very poor outcomes, so they are then placed on maintenance therapy (in the case of the CLLM1 trial, lenalidomide versus placebo) (Figure 2). The goal of this strategy is to control the patient’s remission if first response is insufficient.

The choice of therapy for first-line treatment is still under debate, although the addition of an anti-CD20 antibody to chemotherapy does appear to be superior to chemotherapy alone. In the update to the CLL8 trial, patients treated with fludarabine, cyclophosphamide, rituximab (FCR) had a slight increase in OS compared to those treated with FC. The comparison between FCR and bendamustine, rituximab (BR) is not well determined at this time; the CLL10 trial is in the process of comparing these two therapies directly, however the data are not yet finalized. While the following is not a truly fair comparison, when previous studies investigating either FCR or BR are compared, a complex picture emerges. The overall response rates (ORR) observed with both therapies are similar, but the CR rate with BR therapy is half of what is observed with FCR, and progression-free survival (PFS) is slightly less with BR than with FCR as well (Table 1).

However, BR appears to cause less toxicity than FCR, particularly with the incidence of neutropenia and infections (Table 2). With the current data, it appears that FCR is preferable to increase efficacy in fit patients, but if adverse events are a concern, BR may be preferable. The results of the CLL10 trial will confirm these hypotheses.
Therapy for unfit patients

FCR and BR are not indicated for unfit patients with CLL, therefore other therapies must be considered. Chlorambucil is less immunosuppressive than fludarabine, however the CLL5 study showed that chlorambucil was not better than fludarabine with respect to OS in older patients (>65 years) with CLL. Nonetheless, the efficacy of chlorambucil can be improved with the addition of anti-CD20 antibodies. Specifically, the addition of rituximab to chlorambucil (R-Clb) improves both CR and ORR. A novel type II anti-CD20 monoclonal antibody, obinutuzumab (GA101), has a different mechanism of action than rituximab that increases direct cell death and antibody-dependent cell-mediated cytotoxicity while lowering complement-dependent cytotoxicity. The phase I and II studies suggest that GA101 is more efficient than rituximab. The phase III CLL11 trial investigated the safety and efficacy of GA101 plus chlorambucil (G-Clb), R-Clb, and chlorambucil alone in older patients with CLL and comorbidities, who usually are excluded from clinical trials (Figure 3). Patient characteristics were similar between the three groups, with a median age of 72 to 74 years and a median Cumulative Illness Rating Scale score of 8. It is also important to note that 21–29% of patients had a creatinine clearance <50 mL/min. Disease characteristics were also similar between groups. The major finding of this study thus far is that ORR, CR, and MRD are higher in the R-Clb and G-Clb groups compared with those in the chlorambucil alone group (Table 3). While G-Clb and R-Clb have not yet been directly compared, it appears as if G-Clb improves these parameters to a greater extent than does R-Clb. PFS is also improved in the G-Clb and R-Clb groups compared with that in the chlorambucil alone group, and again it appears that G-Clb is more efficient than R-Clb. The most prevalent side effects seen in the G-Clb and R-Clb groups were neutropenia and infusion-related reactions.

Translation into clinical practice

The current first-line therapies for CLL are listed in Table 4. Treatment is not recommended for inactive or low-stage disease. If the disease is active or is at an advanced stage, the patient's fitness and genetic risk should be assessed (specifically 17p deletion and p53 mutation). FCR is the...
preferred treatment for first-line therapy in fit patients with no genetic abnormalities, and allogeneic stem cell transplant is recommended for fit patients with genetic abnormalities. In unfit patients with no genetic abnormalities, R-Clb is the recommended treatment, although the CLL11 trial suggests that G-Clb may replace R-Clb in the near future. For unfit patients with genetic abnormalities, it is difficult to determine a standard treatment; however, some options currently being used include alemtuzumab, ofatumumab, ibrutinib, and high-dose rituximab.

Figure 3. CLL11 study design

Table 3. End-of-treatment response rates: stage I of the CLL11 trial

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Stage Ia</th>
<th>Stage Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clb (n = 106)</td>
<td>G-Clb (n = 212)</td>
<td>Clb (n = 110)</td>
</tr>
<tr>
<td>Response rate*, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>30.2</td>
<td>75.5</td>
</tr>
<tr>
<td>CR†</td>
<td>0</td>
<td>22.2</td>
</tr>
<tr>
<td>PR‡</td>
<td>30.2</td>
<td>53.3</td>
</tr>
<tr>
<td>SD</td>
<td>21.7</td>
<td>4.7</td>
</tr>
<tr>
<td>PD</td>
<td>25.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>22.6</td>
<td>16.0</td>
</tr>
<tr>
<td>MRD-negative§, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0 (0/80)</td>
<td>31.1 (41/132)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0 (0/30)</td>
<td>17.0 (15/88)</td>
</tr>
</tbody>
</table>

ASO-RQ-PCR = allele-specific oligonucleotide real-time quantitative polymerase chain reaction; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; GA101 = obinutuzumab; G-Clb = GA101, chlorambucil; MRD = minimal residual disease; ORR = overall response rate; PD = progressive disease; PR = partial response; R-Clb = rituximab, chlorambucil; SD = stable disease

*Not reached by cut-off in 12 patients in stage Ia Clb arm, 26 patients in G-Clb arm, eight patients in stage Ib Clb arm, and 16 patients in the R-Clb arm; as assessed by International Workshop on CLL criteria.
†Includes CR with incomplete hematologic recovery.
‡Includes nodular PR.
§As measured by central laboratory assessment (ASO-RQ-PCR); bone marrow samples were usually only taken from patients thought to be in CR.
Table 4. Current first-line therapy of CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>Del(17p)/p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go-go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td>Slow-go</td>
<td>No</td>
<td>Clb + anti-CD20 mAb (R or GA101)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Alem, HD R or O, ibrutinib?</td>
</tr>
</tbody>
</table>

Alem = alemtuzumab; Allo-SCT = allogeneic stem cell transplantation; Clb = chlorambucil; del(17p) = deletion on the short arm of chromosome 17; FCR = fludarabine, cyclophosphamide, rituximab; HD = high dose; mAb = monoclonal antibody; O = ofatumumab; p53mut = p53 mutation; R = rituximab


References:

How to Approach Relapse in CLL if no Clinical Trial is Available?
Summary of the Presentation by Dr. Tadeusz Robak at iwCLL 2013

Chronic lymphocytic leukemia (CLL) is an incurable disease at present, and patients will inevitably require second or subsequent lines of therapy upon relapse. There are many current treatment options available for relapsed/refractory patients, and new therapies will likely change our treatment strategies in the near future. However, this plethora of options leads to confusion when deciding on a treatment strategy for an individual patient (Figure 1).

The International Workshop on CLL (iwCLL) expert panel published the widely accepted definitions of relapsed CLL and refractory CLL. Relapsed CLL is defined as disease progression after a period of six months or more, having previously achieved a complete or partial response. Refractory CLL is defined as failure to respond to purine analog-based therapy or stem cell transplantation, or disease progression within six months of such therapy.1 Criteria that are used to select treatments for second or subsequent lines of therapy include genetic status, previous treatments, and patient fitness. At present, deletions on the short arm of chromosome 17 [del(17p)] and TP53 mutations are known to influence treatment outcomes; in the near future, mutations in genes such as NOTCH1, splicing factor 3B subunit 1, and baculoviral IAP repeat-containing protein 3 may also be important to evaluate before treatment is selected.

Previous treatments are a very important consideration for the success of a second or subsequent line of therapy. For example, alkylating agents are not recommended for second or subsequent lines of therapy if they were used as first-line therapy; rather, purine analogs appear to be more effective in this case. Other considerations include the number of previous therapies, the response to the last therapy, and response duration.2

New Evidence in Oncology | February 2014 45
Patient fitness also has an impact on the choice of therapy. In the U.S., rituximab is used in the majority of patients, but the drug with which it is combined changes depending on patient fitness. For fit (‘go-go’) patients, the most frequently used therapy is fludarabine, cyclophosphamide, rituximab (FCR) in both the first line and subsequent lines of therapy. In unfit (‘slow-go’) patients, rituximab monotherapy is the most often used treatment; chlorambucil is also frequently used. Patients who are somewhat fit (‘go-go/slow-go’) are most frequently treated with bendamustine, rituximab (BR) (Table 1).

Patients with fludarabine-refractory CLL are a special problem for clinicians, as they respond poorly to other treatments and the optimal treatment is unknown. The introduction of immunotherapy to fludarabine regimens has substantially reduced the number of patients who become fludarabine-refractory. However, little is known about how to manage those patients who are refractory to FCR or who have early relapse after FCR treatment.

Three recent studies have reported the frequency and efficacy of each type of second-line therapy used after first-line FCR. In the CLL8 study, 22% of patients who relapsed were initially administered FCR. One third of patients treated with FCR relapsed within three years, and 20.3% of patients given FCR or fludarabine, cyclophosphamide (FC) required second-line therapy within six months. The second-line therapies chosen to treat these patients were quite heterogeneous, despite the fact that the patient population in the study was quite homogeneous. After initial FCR, the most frequent second-line therapy was BR, followed by FCR and R-CHOP. The choice of therapy was also dependent on the length of initial remission; FCR retreatment, BR, and bendamustine alone were common therapies that were administered if remission was >24 months. Patients were typically administered R-CHOP, CHOP, alemtuzumab, or BR if they relapsed earlier. A Czech study found that relapsed patients who had received FCR as first-line therapy had higher overall response rates

### Table 1. Choice of treatment and fitness of CLL patients in the U.S.*

<table>
<thead>
<tr>
<th>Go-Go</th>
<th>Go-Go/Slow-Go</th>
<th>Slow-Go</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line (%)</td>
<td>2nd line (%)</td>
<td>3rd line (%)</td>
</tr>
<tr>
<td>FCR: 31</td>
<td>BR: 14</td>
<td>R: 12</td>
</tr>
<tr>
<td>FC: 2</td>
<td>B: 10</td>
<td>Cib: 4</td>
</tr>
<tr>
<td>FR: 4</td>
<td>Other: 10</td>
<td>CR: 5</td>
</tr>
<tr>
<td>F: 2</td>
<td></td>
<td>CibR: 0</td>
</tr>
<tr>
<td>2nd + line (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCR: 10</td>
<td>BR: 24</td>
<td></td>
</tr>
<tr>
<td>FC: 2</td>
<td>B: 18</td>
<td></td>
</tr>
<tr>
<td>FR: 2</td>
<td>Other: 20</td>
<td></td>
</tr>
<tr>
<td>F: 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*B = bendamustine; C = cyclophosphamide; Cib = chlorambucil; CLL = chronic lymphocytic leukemia; F = fludarabine; R = rituximab

*Source: Synovate 2011
(ORR) and longer progression-free survival (PFS) following subsequent therapy than those who had relapsed after FCR in the second or subsequent line of therapy. Finally, a French study followed 132 patients who had a first relapse after FCR as first-line therapy. The most frequently used second-line therapy was BR, which was also associated with the longest PFS (median of 18 months compared with 11 months for R-CHOP and six months for alemtuzumab-based therapies) (Table 2).

Many therapies have recently been tested for the treatment of patients with relapsed/refractory CLL. Rituximab is used both in monotherapy and in combination therapies to treat patients with relapsed CLL. While doses as low as 375 mg/m² have been shown to be effective for increasing response rates, a dose-escalation study found that high-dose rituximab monotherapy (2,250 mg/m²) resulted in a greater ORR than with lower doses (375 mg/m² and 500 mg/m²). Rituximab can also be combined with many other therapies in relapsed patients; for example, ORR and complete response (CR) rates are higher and PFS is longer for patients treated with FCR than for those treated with FC. In the U.S., the combinations of rituximab and high-dose methylprednisolone (HDMP) and R-CHOP are also common. However, the most effective combination therapy appears to be BR, which has shown excellent results in clinical trials with high ORR and CR with the exception of patients with del(17p)] (Figure 2).

Table 2. Salvage therapies in first relapse after FCR:
French CLL Intergroup experience

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>62</td>
<td>18</td>
</tr>
<tr>
<td>Alemtuzumab-based regimens</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>FCR</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>R-DHAP</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, rituximab; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP = rituximab, dexamethasone, cytarabine, cisplatin
Adapted from Fornecker L-M, et al. iwCLL 2013;5.5.

Bendamustine monotherapy was originally tested in a small number of patients with CLL and was found to be effective. Subsequently, many studies have used bendamustine in combination therapies and achieved lasting remissions. However, the best results have been observed with bendamustine in combination with rituximab and mitoxantrone.

Alemtuzumab is a drug that has established activity against CLL in patients with a p53 mutation. It has been approved specifically for use in patients who have been previously treated with alkylating agents and who have failed fludarabine therapy. While alemtuzumab is not particularly effective on its own, when combined with fludarabine, ORR improves dramatically.

Alemtuzumab is no longer commercially available, but can be procured through the Campath Distribution Program, which will provide alemtuzumab free of charge.

Ofatumumab was indicated for patients who are refractory to both fludarabine and alemtuzumab; ORR was 58% in those patients, and 47% in patients who were refractory to fludarabine with bulky adenopathy. However, median PFS was relatively short (six months), and median overall survival was one year.

Figure 2. Rituximab and bendamustine in relapsed CLL

11q– = deletion on the long arm of chromosome 11; 17p– = deletion on the short arm of chromosome 17; CLL = chronic lymphocytic leukemia; CR = complete response; F = fludarabine; IgHV = Immunoglobulin heavy chain variable region; nPR = nodular partial response; ORR = overall response rate; PR = partial response
Other treatment combinations for fludarabine-refractory patients include R-CHOP, rituximab, dexamethasone, cytarabine, cisplatin (R-DHAP), HDMP (especially in patients with cytopenia), high dose dexamethasone (HDDM) plus rituximab, and rituximab plus cyclophosphamide and dexamethasone (particularly in patients with autoimmune cytopenias). Allogeneic stem cell transplantation is also an option for younger patients with non-response or early relapse, or for patients with del(17p) or p53 abnormalities requiring treatment.

There are several treatment guidelines written by international societies for CLL, including iwCLL and the European Society for Medical Oncology.1,18 As such, the decision of which therapy to use is very heterogeneous among physicians, and drug availability in the patient’s country plays a role in this decision. In the U.S., 16% of patients receive lenalidomide as third-line therapy, but this drug is unavailable in Poland and other developing countries (Figure 1). Rituximab is also frequently used in the U.S. as a first-line combination therapy and in monotherapy as a second or subsequent line of therapy (Figure 1). Cost is another issue, particularly in developing countries. A list of average wholesale prices for common regimens is provided in Table 3.

The treatment choice in routine practice for relapsed patients with CLL depends on patient fitness, biology of disease, response to previous treatments, and cost of treatment. The initial treatment may be repeated if the previous response was long, but in refractory or early relapse patients, the initial regimen should be changed and treatment within clinical trials should be offered whenever possible. Allogeneic stem cell transplantation should also be recommended for eligible patients who are refractory to purine analogs or who have del(17p).


Table 3. Cost of common regimens used for CLL: average wholesale price*

<table>
<thead>
<tr>
<th>Single-agent therapy</th>
<th>Cost ($)</th>
<th>Chemoimmunotherapy</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil (12-month supply)</td>
<td>2,038</td>
<td>FR</td>
<td>37,590</td>
</tr>
<tr>
<td>Fludarabine (iv)</td>
<td>7,200</td>
<td>FCR</td>
<td>43,599</td>
</tr>
<tr>
<td>Fludarabine (oral)</td>
<td>23,136</td>
<td>FCR-“lite”</td>
<td>83,080</td>
</tr>
<tr>
<td>Rituximab (4 weeks)</td>
<td>20,260</td>
<td>BR</td>
<td>83,094</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>52,704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab (12-week supply)</td>
<td>74,340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab (12 doses)</td>
<td>119,704</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine, rituximab; iv = intravenous

*All prices are for six cycles unless otherwise indicated.

In patients with chronic lymphocytic leukemia (CLL), deletion on the long arm of chromosome 11 [del(11q)] is associated with progressive disease. The incidence of del(11q) is rare in early stage disease (approximately 6–10%), but at the time of first treatment indication, approximately 20% of patients with CLL have del(11q). Incidence of this deletion has likely been underreported, as fluorescence in situ hybridization has made this deletion easier to detect in recent years. The reported incidence of del(11q) in patients with refractory disease varies between studies; however, the high proportion of patients with 17p deletion [del(17p)] heavily biases this cohort, so it is difficult to determine the actual incidence of del(11q) in this patient population.

**Architecture and genes**

While the size of the deletion varies between patients, one region that is deleted in almost all patients with del(11q) is the ataxia telangiectasia mutated (ATM) gene (Figure 1). \(^1\) ATM is a key kinase in the DNA damage response pathway, which is involved in the early stage of the cellular response to DNA damage. Many patients with del(11q) also have a mutation on the remaining allele for ATM, which is a strong indication that this gene is responsible for the phenotype of this deletion.\(^4\)^\(^7\) The functional consequence of del(11q) and ATM mutation in patients with CLL is an impaired DNA damage response.\(^5\) However, the overall incidence of ATM mutation in patients with del(11q) is approximately 30–50%, suggesting that it may not be the only region that is important to consider in patients with del(11q).

Another mutation that is common in patients with del(11q) is the baculoviral IAP repeat-containing protein 3 (BIRC3) gene. BIRC3 is a regulator of nuclear factor kappa-light chain enhancer of activated B cells (NFκB); mutation of BIRC3 results in increased NFκB activity, which confers increased cell survival. BIRC3 mutation is also common in CLL patients with refractory disease.\(^8\) A few studies have shown a strong impact on clinical outcome in patients with this mutation; however, BIRC3 mutation was quite rare in the samples studied.\(^3\)^\(^8\) More data need to be generated to determine how this mutation fits into the pathogenesis of del(11q) in CLL.

**Figure 1. ATM deletion occurs in the majority of patients with 11q deletion**

ATM = ataxia telangiectasia mutated; FDX1 = ferredoxin 1; RDX = radixin; YAC = yeast artificial chromosome

With the discoveries of new mutations in CLL, researchers are now beginning to examine associations between mutations, which can be a very useful way of determining the biology of the disease. One observation that has been confirmed by many groups is that there is a very strong association between del(11q) and mutation of the splicing factor 3B subunit 1 (SF3B1) gene. Another association that has been clearly shown is that most patients with del(11q) have unmutated immunoglobulin heavy chain variable region status. The reasons for these associations are still unknown.

**Clinical impact**

In patients with CLL, del(11q) is associated with early progression and poor prognosis. With more intense treatment it may be possible to overcome this, but the data supporting this argument are still preliminary. Massive lymphadenopathy is also associated with del(11q), although the mechanism for this is unclear. A number of retrospective analyses and clinical trials suggest that patients with del(11q) may particularly benefit from more intense first-line treatment. For example, a German study showed a 100% response rate in patients with del(11q) treated with fludarabine and cyclophosphamide, compared with a 69% response rate in patients treated with fludarabine alone. In the CLL8 study, overall response rate, progression-free survival, and overall survival (OS) were all higher in del(11q) patients receiving chemoimmunotherapy compared to those receiving chemotherapy (Table 1). It is important to note that these data are slightly biased because patients with p53 mutations were not excluded from this group. Patients with del(11q) have the shortest time to treatment when patients are stratified by genetic abnormalities (Figure 2). Additionally, most patients with this deletion will require treatment. However, OS in patients with del(11q) is higher than in patients with del(17p), and this difference is even greater when patients are given chemoimmunotherapy.

The presence of ATM mutation has a strong clinical impact on patients with del(11q), with OS being much worse in del(11q) patients with the mutation compared to those without the mutation (Figure 3). However, ATM is challenging to study because it is a large gene with many possible mutations. Additionally, the presence of a mutation does not guarantee that the protein encoded by the gene will be defective. This means that the functional consequences of the mutation must be determined, which is difficult. Mutations must be examined thoroughly before clinical consequences are inferred.

**Therapeutic consequences**

Genetic abnormalities such as del(11q) are commonly thought of as markers, which have a predictive use in CLL. However, these mutations can also be thought of as vulnerabilities of the cancer cells that can be used to improve treatment (i.e., used diagnostically). By collecting CLL cell samples with known genotypes and treating them with many different compounds, it is possible to discover patterns of drug sensitivities that are specific to different genotypes. The goal of this research is to find an optimal treatment for patients based on their disease genotype. These data can also be used to learn about a drug’s mechanisms of action. For example, our lab has found that kinase inhibitors cause a very similar phenotype in many different patients. Additionally, preliminary data may have identified a few compounds that appear to have preferential activity in patients with del(11q).

<table>
<thead>
<tr>
<th>Table 1. CLL8 results for all and del(11q) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rates</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>All (n = 817)</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>Del(11q) (n = 142)</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>ORR</td>
</tr>
</tbody>
</table>

| Progression-free survival                          |
|                                                   |
| Chemotherapy (%)                                  | Chemoimmunotherapy (%) | Hazard rate (95% CI) | p value |
| All (n = 817)                                      | 45                  | 65                  | 0.56 (0.46–0.69) | <0.0001 |
| Del(11q) (n = 142)                                | 32                  | 64                  | 0.34 (0.24–0.61) | <0.0001 |

| Overall survival                                   |
|                                                   |
| Chemotherapy (%)                                  | Chemoimmunotherapy (%) | Hazard rate (95% CI) | p value |
| All (n = 817)                                      | 83                  | 87                  | 0.67 (0.48–0.92) | 0.012   |
| Del(11q) (n = 142)                                | 83                  | 94                  | 0.42 (0.18–0.97) | 0.036   |

CI = confidence interval; CR = complete response; Del(11q) = deletion on the long arm of chromosome 11; ORR = overall response rate

Open questions/the future

While much has been learned about del(11q) in CLL, there are still many remaining questions to be answered. The biological basis of the clinical presentation of del(11q) is still unclear, and the biology of cases where ATM is unmutated in del(11q) is not well defined. While the clinical usefulness of diagnosing del(11q) in routine practice is still up for discussion, it is exciting to see clinical trials targeting specific genotypes, including one for del(11q).

References:
Defining Elderly Patients and How to Evaluate Comorbidity: Summary of the Presentation by Dr. Valentin Goede at iwCLL 2013

A large proportion of patients with chronic lymphocytic leukemia (CLL) are older at the time of diagnosis, with 70% of patients being at least 65 years old and 43% of patients being at least 75 years old. The purpose of defining or categorizing elderly CLL patients initially was to identify those patients who would not benefit from any treatment (no-go patients). However, this has changed with the introduction of more intense treatments for CLL; now the purpose of categorizing elderly patients is to identify patients that may benefit from milder treatments (slow-go) and those who can tolerate more intense therapy (go-go) (Figure 1).

In the past, age alone was used to stratify patients. For example, in the CLL4 and CLL5 trials, age 65 was the cutoff between more and less intense treatments. This concept completely ignores the heterogeneity inherently present in the elderly population. The rate of decline of many physiological and pathological attributes varies tremendously within the aging population. These include declining physiological function, increased comorbidities, polymedication, decreased mobility, decreased cognition, decreased nutrition, and decreased ability to perform life activities.

Today the Cumulative Illness Rating Scale (CIRS) is used to evaluate comorbidities in elderly patients and thereby determine patient fitness. CIRS separates patients into go-go, slow-go, or no-go categories. Patients are rated on a scale from 0 to 4 in 14 different clinical categories, the sum of which is the total CIRS score (Table 1). It was first proposed in 1968, but was not used until nearly 30 years later by an investigator who found good inter-rater reliability with a modified version of the scale. This version was validated a few years later by Parmelee et al. who used the scale to predict remaining life expectancy and dependency in a large cohort of geriatric patients. Subsequently, guidelines for the scale were developed and electronic versions were created. The validity and reliability of CIRS have been demonstrated repeatedly since then.

Identifying the CIRS score to use as a cutoff for determining treatment of patients with CLL is challenging. The CLL8 and CLL11 trials used a CIRS score of 6 as the cutoff, wherein the CLL8 trial included patients with CIRS ≤ 6 and the CLL11 trial included patients with CIRS >6. These two patient populations were found to be different with

---

Figure 1. Why define elderly CLL patients?

```plaintext
BR = bendamustine, rituximab; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; F = fludarabine; FC = fludarabine, cyclophosphamide; FCR = fludarabine, cyclophosphamide, rituximab
```
respect to age: the median age of the CLL11 cohort was 72–74 (depending on treatment arm), while the median age of the CLL8 cohort was 61. There were also differences in the number of comorbidities and performance status.\textsuperscript{10,11} This does not tell you whether patients are eligible for standard treatment.

However, the CIRS score is a good predictor of overall survival (OS). In the CLL8 trial, patients were stratified by CIRS score (0–3 and 4–6) and OS was measured. The cohort with CIRS 4–6 had a lower OS than that of the 0–3 group.\textsuperscript{12} Further analysis of the CIRS score was performed as well, where patients were stratified by the number of comorbidities present (\textit{CAT\textsubscript{NUM}}) as well as the category score (\textit{CAT\textsubscript{SCO}}) for certain relevant comorbidities (e.g., blood pressure, respiratory, and upper gastrointestinal) (Table 1). When this was done, differences in OS between groups were even greater than in the previous analysis (Figure 2).\textsuperscript{12} The CIRS score appears to be a good predictor of OS in patients with CLL, as it is independent of age and other factors affected by CLL.\textsuperscript{12}

Unfortunately, the ability of the CIRS score to predict toxicity in patients with CLL is quite poor. In the CLL8 study, there was no correlation between CIRS score and the number of grade 3/4 adverse events (AEs); however, there was a relationship observed between \textit{CAT\textsubscript{SCO}} and the number of AEs (Table 2).\textsuperscript{12} In the CLL5 trial, there was no correlation between CIRS and toxicity (the cohort had CIRS scores of 0–6).\textsuperscript{13} Additionally, in the Q-Lite trial there was no difference in progression-free survival when patients were stratified by CIRS score (≤6 and ≥7, patients with a CIRS score of 0–13 were included in the study).\textsuperscript{14}

\begin{table}[h]
\centering
\caption{The CIRS score}
\begin{tabular}{|l|l|l|}
\hline
Organ system & If illness/impairment present, please specify: & Score \\
\hline
Heart & & \\
Blood pressure & & \\
Vascular & & \\
Respiratory & & \\
Ear/nose/throat & & \\
Upper gastrointestinal & & \\
Lower gastrointestinal & & \\
Liver & & \\
Renal & & \\
Genitourinary & & \\
Musculoskeletal & & \\
Endocrine/metabolic & & \\
Neurological & & \\
Psychiatric & & \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{CIRS score and toxicity}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textit{CAT\textsubscript{NUM}} & \textit{CAT\textsubscript{SCO}} & 0–3 & 4+ & \textit{p value} \\
\hline
0–1 & 2–4 & & & \\
69 & 63 & n.s. & 66 & 81 & <0.001 \\
\hline
\end{tabular}
\end{table

\textsuperscript{*GCLLSG CLL8 trial FCR/FC; 2009 data set, patients with CIRS 0–6.}

Adapted from Goede V, et al. EHA Congress 2012.
The CIRS score has both strengths and weaknesses. Existing guidelines have proven sufficiently reliable in geriatric medicine, and the score predicts remaining life expectancy in elderly patients, which is a useful tool. The CIRS score also helps to select patients with comorbidities. Additionally, CLL researchers are already comfortable using this scale. However, the CIRS score is not a good tool for predicting toxicity. It is also unclear which version of the scale should be used for patients with CLL, which guidelines to follow, and how to best evaluate the scores. Because of this, alternative approaches are currently being developed (Table 3) using a combination of age, biochemical markers (such as creatinine clearance), performance scores, and scales targeting specific comorbidities (e.g., the New York Heart Association scale for cardiac impairment).

Clearly, the categorization process for elderly patients is becoming more complicated, and it is important to determine how to improve this situation in the future. Adding to this problem is the fact that there are many new clinical trials currently investigating new therapies for CLL, but few of these trials are capturing fitness in their patients. If or when these treatments become available, it will be unknown if they are appropriate for elderly patients. Also, the heterogeneity of fitness tools will make it difficult to compare between trials. To address this problem, Dr. Hallek and Dr. Gribben have started a new iwCLL initiative to better define fitness in CLL. The first step in this initiative was to host a consensus workshop of CLL researchers from many countries and research groups, with a focus on elderly/unfit patients with CLL. The key questions asked were:

- Will a tool to stratify fitness in CLL still be needed in the era of targeted therapy?
- What capabilities should such a tool have?
- Do currently available tools have these capabilities?
- Which tool can currently be recommended for clinical research and routine practice?
- What research should be done to develop a broadly accepted tool?

The group concluded that to allow treatment tailoring, an ideal tool would predict life expectancy (independent of CLL), risk of toxicity, and risk of intercurrent illness during therapy. In routine practice, clinical judgment is the standard, as there is so far no proof that such a tool will result in greater benefit. In clinical trials, the group encourages study groups to develop or explore their own concepts, but believes that iwCLL should also define a core panel of assays that should be run in all CLL trials. The next steps for this initiative include coordinating an analysis of available CIRS data, harmonizing CIRS methodology among researchers, and re-testing the reliability of CIRS in CLL. They also plan to conduct an observational study with the core assay panel, once developed, to test its effectiveness in categorizing elderly patients with CLL.

### Table 3. Current alternative approaches

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIALTO</td>
</tr>
<tr>
<td>Treatment</td>
<td>B-Ofa vs. Clb-Ofa</td>
</tr>
<tr>
<td>F(CR) ineligibility criteria</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td></td>
</tr>
<tr>
<td>WHO Performance Status 2 or 3</td>
<td></td>
</tr>
<tr>
<td>Cardiac impairment (NYHA II)</td>
<td></td>
</tr>
<tr>
<td>Respiratory impairment (GOLD II)</td>
<td></td>
</tr>
<tr>
<td>Renal impairment (eGFR &lt;30 mL/min)</td>
<td></td>
</tr>
<tr>
<td>Any other significant comorbidity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RESONATE-2</td>
</tr>
<tr>
<td>Treatment</td>
<td>PCI vs. Clb</td>
</tr>
<tr>
<td>F(CR) ineligibility criteria</td>
<td></td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;70 mL/min</td>
<td></td>
</tr>
<tr>
<td>Plt &lt;100 G/L</td>
<td></td>
</tr>
<tr>
<td>Hb &lt;10 g/dL</td>
<td></td>
</tr>
<tr>
<td>ECOG 1–2</td>
<td></td>
</tr>
</tbody>
</table>

References:
Deletion on the short arm of chromosome 17 [del(17p)] is a serious problem in chronic lymphocytic leukemia (CLL); patients with del(17p) have very poor outcomes and low survival. There is no convincing evidence that the standard treatment for fit patients with CLL (fludarabine, cyclophosphamide, rituximab [FCR]) improves survival in patients with del(17p).\(^1,2\) Because of this, the suitability of FCR as a control in future clinical trials involving patients with del(17p) is under debate.

The main issue with del(17p) in CLL is the loss of p53. Since p53 regulates apoptosis caused by DNA damage, the loss of p53 results in an inappropriate response to radiation therapy and chemotherapy. New agents are being developed that cause cell death through p53-independent mechanisms. To date, the agents in clinical trials for patients with del(17p) include antibodies and glucocorticoids.

In the U.K., the phase II CLL206 trial (CamPred) examined the combination of alemtuzumab and methylprednisolone for 16 weeks in 39 CLL patients who had del(17p) or who were relapsed/refractory.\(^3\) In this study, the dose of methylprednisolone (1.0 g/m\(^2\)/day for 5 days, every 28 days for 4 cycles) was very high. The overall response rate (ORR) was higher than expected; 82% of patients had a response, and over a third of patients achieved complete response (CR) (Table 1). Five patients who achieved CR also achieved minimal residual disease (MRD)-negative remission. Progression-free survival (PFS) was higher than is usually seen in patients with del(17p), but still disappointing given the high response rate observed (Figure 1). When separated by response, patients who achieved CR had better outcomes than those who did not. Patients who achieved MRD negativity had a longer PFS than those who did not; however, it still was not a lasting remission, as PFS for this group was 23.5 months, and most patients had progressed after two to three years (Figure 1). Patients in this trial also had the option of stem cell transplantation. A group of eight patients with advanced disease received a transplant, and six of those patients died after the transplant. This demonstrates that transplants are not necessarily beneficial for this group of patients. This may be particularly true after alemtuzumab therapy, which depletes the donor T cells that are required for immune reconstruction after transplant. The remaining two patients are alive, well, and in remission as of last follow-up. Transplantation can still be an effective option, but getting these patients through the transplant procedure is difficult.

The German CLL Study Group and the French Cooperative Group on CLL and Waldenstrom macroglobulinemia conducted a similar trial, combining alemtuzumab and glucocorticoids (CLL20). Patients were treated with alemtuzumab and oral dexamethasone. The steroid dose was much lower than what was used in the CamPred trial, and treatment was given for 12 weeks instead of 16.\(^4\) After the induction period, this study gave patients the option of transplant or alemtuzumab maintenance for up to two years. PFS was much lower in patients with del(17p)-relapsed or fludarabine-refractory disease than that in first-line patients with del(17p) disease, with first-line patients having a median PFS of just 18 months. OS followed the same pattern, with few patients surviving past three years of follow-up.

When the combination of alemtuzumab and steroids are given as front-line therapy, better responses are observed than with other treatments (Table 2).\(^5,6\)

### Table 1. NCRI CLL206 study: final response data*

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>32/39</td>
<td>82</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>14/39</td>
<td>36</td>
</tr>
<tr>
<td>PR</td>
<td>18/39</td>
<td>46</td>
</tr>
<tr>
<td>SD</td>
<td>1/39</td>
<td>3</td>
</tr>
<tr>
<td>PD</td>
<td>6/39</td>
<td>15</td>
</tr>
<tr>
<td>BM MRD negative</td>
<td>9/25*</td>
<td>36</td>
</tr>
</tbody>
</table>

BM = bone marrow; CR = complete response; CRi = complete response with incomplete marrow recovery; MRD = minimal residual disease; NCRI = National Cancer Research Institute; OR = overall response; PD = progressive disease; PR = partial response; SD = stable disease

*Only 5/9 patients who achieved MRD negativity were in CR/CRi.
However, PFS and OS are still quite low in patients with del(17p), particularly in relapsed/refractory patients.

An upcoming trial in the U.K. is the CamDexRev trial, which started recruitment a few months ago. Patients will be treated with a reduced steroid (dexamethasone) dose, compared to the CamPred trial, as well as lenalidomide (a potential therapy for patients with del(17p)) and alemtuzumab. After the induction phase, patients suitable for transplant will receive one, and patients ineligible for transplant will be randomized to no treatment or lenalidomide maintenance (Figure 2). Since alemtuzumab is no longer commercially available, the trial was modified and just reopened, with alemtuzumab being replaced by ofatumumab. The trial is open to relapsed/refractory patients and patients with del(17p).

Novel agents have been developed to target del(17p). They include idelalisib, ibrutinib, and ABT-199. Idelalisib is an inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta that inhibits proliferation and induces apoptosis in many B-cell malignancies. A study of idelalisib monotherapy enrolled 31% of patients with del(17p). Patients in this study had either relapsed or refractory disease, and had received multiple prior treatments. It appeared that patients with del(17p) responded to idelalisib in the same way as patients without del(17p) (Figure 3). However, median PFS was shorter in patients with del(17p) than in those without the deletion, so the response to idelalisib monotherapy was not durable.

Another study combined ofatumumab and idelalisib for 48 weeks, followed by idelalisib maintenance therapy for the...
treatment of patients with relapsed/refractory CLL. Although there were only seven patients in this trial with del(17p) and/or p53 mutated (p53mut) disease, response rates in these patients appeared to be similar to that in the entire study population. Furthermore, PFS and duration of response (DOR) were similar for patients regardless of their del(17p) or p53 mutational statuses; however, the sample size was very small (Figure 4). Perhaps idelalisib combination therapy is an appropriate treatment for patients with del(17p), but more data are needed to confirm this hypothesis.

Idelalisib has also been combined with bendamustine, rituximab, or both agents (BR), although it is unclear how the chemotherapy is useful, since patients with del(17p) should be insensitive to chemotherapy. Nevertheless, it was again

Figure 2. CLL210 updated design: maintenance phase

Figure 3. Idelalisib monotherapy: best on-treatment change in tumour size (ITT analysis, N = 55)
observed that the response of patients with del(17p)/p53mut was similar to that of those without del(17p)/p53mut. PFS with idelalisib combination therapy is possibly better than what has been shown in previous trials of idelalisib alone, although the difference is small. However, PFS in those with del(17p)/p53mut was lower compared to that in the rest of the cohort from this study.

The combination of idelalisib and rituximab has also been examined as front-line therapy. A relatively small number of patients had del(17p) in this trial (9 out of 64), but all of them responded to treatment, with three in CR. While the final results of this study have not been completed, at this point there is no difference in PFS between patients with del(17p) and patients without del(17p). Looking at the data so far, idelalisib combined with a CD20 antibody appears to be very beneficial for CLL patients with del(17p).

Ibrutinib is an inhibitor of Bruton tyrosine kinase (BTK) that promotes apoptosis and inhibits proliferation, migration, and adhesion in CLL cells. A phase I/II trial examined ibrutinib monotherapy in 29 patients with relapsed/refractory del(17p) disease. Ibrutinib as a monotherapy seemed to be effective, although half of the patients have relapsed after two years (Figure 5). However, this is a better result than what has been seen previously. It is possible that ibrutinib may be more effective if given earlier on in disease progression. The upcoming RESONATE-17 study will be the first to investigate ibrutinib exclusively in patients with del(17p).

Ibrutinib combination therapy has also been investigated. In a phase II study, ibrutinib and rituximab were given to 40 patients. Again, no difference was observed in the response
between patients with and without del(17p) (Figure 6). Only six months of data have been collected at this point in the study, so no conclusions can be made, but the data are encouraging for this combination in front-line trials.

Another very promising drug is the Bcl-2 inhibitor, ABT-199. A phase I trial examined, among others, 17 patients with del(17p); 82% responded and 2 were in CR (Table 3).12 Another study with this drug (M13-982) will investigate patients with del(17p) exclusively and is now in recruitment. The data for ABT-199 are compelling at this stage, and promise to change the way we treat CLL.

Table 3. Responses in ABT-199–treated CLL patients

<table>
<thead>
<tr>
<th>Responses</th>
<th>All CLL, n (%)</th>
<th>del(17p), n (%)</th>
<th>Fludarabine Refractory, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>47 (84)</td>
<td>14 (82)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (20)</td>
<td>2 (12)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Partial response*</td>
<td>36 (64)</td>
<td>12 (71)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1 (2)</td>
<td>1 (6)</td>
<td>–</td>
</tr>
<tr>
<td>D/C prior to first (6W) assessment</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>3 (17)</td>
</tr>
</tbody>
</table>

CLL = chronic lymphocytic leukemia; CT = computerized tomography; D/C = discontinued; del(17p) = deletion on the short arm of chromosome 17

*3 patients had confirmatory CT imaging assessments at less than an 8-week interval (5, 6, and 7 weeks).

Adapted from Seymour JF, et al. iwCLL 2013.

The presence of del(17p) is an indication for allogeneic stem cell transplantation, as these patients have very good outcomes after transplant.11 However, no difference in survival after transplantation based on 17p status has been observed. This may be due to the timing of the transplant (before or after initial therapy), which is still under debate.

In conclusion, chemoimmunotherapies are ineffective in patients with del(17p) and are possibly unsuitable to use as a control in trials with these patients. One of the challenges of phase III trials is finding a standard treatment for del(17p) disease. Therapies that work independently of p53, such as antibodies and steroids, yield better responses than chemoimmunotherapy, but are not a solution to this disease. However, this should still be considered standard treatment in this population because clinicians have the most experience with this type of therapy. Allogeneic stem cell therapy can be effective in CLL with del(17p), but there are concerns over toxicity. The novel therapies discussed here are very promising, and upcoming trials will show how these new therapies can best be used to treat CLL patients with del(17p).

Leukemias

Acute promyelocytic leukemia

Updates on Early Death, Therapy-Related Myeloid Neoplasms, and First-Line Therapies in the Treatment of Acute Promyelocytic Leukemia

Since the first description of acute promyelocytic leukemia (APL) by Dr. Hillestad in 1957, prognosis of APL has been transformed from highly fatal to highly curable.1 This transformation has been made possible by several key discoveries over the past several decades. These include the sensitivity of most APL cells to all-trans retinoic acid (ATRA), the high response rates observed in APL patients treated with anthracyclines, and the superior efficacy observed when ATRA is combined with anthracyclines. Combining anthracyclines with ATRA has been shown to result in remission rates higher than 90% and cure rates of about 80% in first-line treatments.2 Further progress has come from the development of a chemotherapy-free approach leading to equally effective outcomes but with much lower hematological toxicity.3

Despite this impressive progress, several unmet needs remain in the treatment of APL. A high early death (ED) rate due mostly to hemorrhage continues to be the most significant challenge facing health professionals today,4 with ED rates as high as 30% reported in population-based studies.5 In addition, therapy-related myeloid neoplasms (t-MN) and a high frequency of hematological toxicity resulting from intensive chemotherapy regimens pose significant challenges as well.

These challenges and more were recently addressed at the 6th international symposium on APL, which was held in October 2013 in Rome. Held once every four years, this international gathering of APL experts presented a rare opportunity to learn about the latest progress in the biology and management of APL. The following is a report covering several presentations made at the conference:

• **Early death in APL:**
  - An update from the Swedish Acute Leukemia Registry examined whether ED rates have improved in a new 2007–2012 cohort of patients. The study could not definitively conclude that diagnosis and supportive care measures in the 2007–2012 cohort were improved compared with those in the 1997–2006 cohort.
  - A study examining the hypothesis that delays in ATRA therapy contribute to a high ED rate found that ATRA was delayed often, with delays occurring in ordering but not in procurement and administration.
  - A population-based analysis found that ED rates previously reported in the SEER (Surveillance, Epidemiology, and End Results) and Swedish registries were similar to those in the Canadian Cancer Registry.
  - An analysis of a proactive program implemented to decrease the rate of EDs showed the program to be highly successful.

• **t-MN in APL:**
  - A presentation reviewed available data on the incidence, outcomes, and prognostic factors of t-MN development in APL. A recent study was highlighted, showing that t-MN may be responsible for as much as 2% of deaths in patients treated for APL.

• **Update on first-line therapies in APL:**
  - A review of the GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto) experience with APL treatment highlighted the recent study by Lo-Coco et al. showing that arsenic trioxide (ATO) plus ATRA is non-inferior to ATO plus chemotherapy in patients with APL who are of low or intermediate risk.
A presentation highlighted the ongoing LPA2012 clinical trial by the PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) group. The study is aimed at improving patient outcomes by utilizing the prognostic factor CD56.

In a presentation of the current use of ATO as first-line therapy in China, several studies demonstrated the long-term safety of ATO in APL.

A study comparing the outcomes of the APML4 phase II trial, which used ATO in induction and consolidation, with those of the APML3 trial, which used ATRA plus anthracyclines instead, showed that the addition of ATO allows for anthracyclines to be reduced significantly and eliminates the need for high dose cytarabine in high risk patients.

A study on the long-term efficacy and safety of single-agent ATO in newly diagnosed patients with APL showed that ATO was effective and safe, with no evidence of secondary malignancies observed after a median follow-up of 60 months.

The conclusion of a study comparing the approach of the Medical Research Council to treating newly diagnosed APL patients with that of the Spanish group (PETHEMA) was that the absence of cytarabine and etoposide in the Spanish approach did not compromise hematological/molecular responses or cure rates.

The first evidence-based data on long-term cancer survivorship issues, focusing on health-related quality of life in APL, showed that APL patients had worse role limitations due to physical health and emotional problems than the general population.


Early death in APL

Background
The risk of early death (ED) from severe hemorrhage has been recognized as the most significant cause of treatment failure in newly diagnosed patients with acute promyelocytic leukemia (APL). While the advent of all-trans retinoic acid (ATRA) therapy greatly improved the management of coagulopathy in APL by reducing the risks of complications such as severe bleeding, recent population-based studies have shown that ED rates have remained high despite ATRA therapy. In addition, these studies have identified a major discrepancy between ED rates reported in clinical trials (~3–14%) and those reported from real-world data (17–29%). The following is a summary of four presentations on ED in APL delivered at the 6th International Symposium on APL, which was held in Rome in 2013.

Early death rate in APL remains high: an update on the Lehmann et al. 2011 study (Lehmann, S)

In 2011, a population-based study by Lehmann et al. reported an ED rate of 29% in a cohort of newly diagnosed patients with APL (1997–2006) in the Swedish Acute Leukemia Registry. Utilizing the same registry, this update examined a subsequent cohort of patients with APL from 2007 to 2012. Data used for analysis included registry data, age, gender, World Health Organization (WHO) performance status, results of diagnostic procedures and genetic analyses, limited laboratory data (e.g., hemoglobin, white blood cells, platelets), treatment intention, transplantation, and outcomes (e.g., complete response, relapse, survival). Analysis revealed several key findings. ED rates were slightly reduced in the 2007 to 2012 cohort compared with the 1997 to 2006 cohort (Figure 1), with improvement restricted only to low/intermediate risk patients (Figure 2). Analysis of diagnosis and supportive care revealed common delays in the diagnosis and start of treatment, as well as evidence for non-optimal supportive care in ED patients. However, these observations were also seen in non-early death patients, with any differences failing to be statistically significant. The authors could not definitively conclude that diagnosis and supportive care measures in the 2007 to 2012 cohort were improved compared with those in the 1997 to 2006 cohort.
Rapid and aggressive supportive care consists of immediate ATRA therapy at the earliest suspicion of APL, aggressive transfusions of cryoprecipitate, platelets, and fresh frozen plasma, and frequent daily monitoring. In 2012, Altman et al. examined the hypothesis that delays in ATRA therapy contribute to ED rate, specifically those that occur as a result of hemorrhage. This retrospective analysis of 204 newly diagnosed patients with APL between 1992 and 2009 examined the following timing intervals before ATRA administration: 1. Initial presentation to suspicion of APL; 2. Suspicion of APL to ordering ATRA; 3. Ordering ATRA to its administration; 4. Presentation to ordering ATRA; 5. Presentation to ATRA administration.

The study found the ED rate to be 11% within 30 days, with hemorrhage accounting for 61% of EDs. ATRA was ordered in only 31% of patients on the day APL was suspected. A significant finding was that in high risk patients, a delay in ATRA administration by three to four days after APL was suspected was associated with an ED rate of 80% (p = 0.01) (Table 1).

Overall, ATRA was found to be delayed often, even at experienced centres, with delays occurring in ordering but not procurement and administration. The delays in ATRA administration appeared to contribute to early hemorrhagic death in high risk patients. The findings of this study suggest that ED rates may be reduced if ATRA is administered in the ER immediately at first suspicion, and thus, educating health care providers should be a high priority.

The population-based analysis by Paulson et al. examined whether previous observations of high ED rate in the SEER (Surveillance, Epidemiology, and End Results) and Swedish registries, as well as the previously reported increase in incidence of APL, would also be observed in the Canadian Cancer Registry. The study sought to determine the national incidence of APL in Canada, the rates of ED and overall survival in APL, and finally, to compare the national outcomes of patients with APL with those at leukemia referral centres.

Analysis conducted on 399 cases identified in the Canadian Cancer Registry from 1993 to 2007 demonstrated that the incidence of APL was low and stable (0.083/100,000), with no reported increase in incidence during the years analyzed. Consistent with previous population-based studies, the ED rate was high at the population level compared to what had been reported in clinical trials, with older patients showing poor outcomes (ED rates for: all patients = 21.8%; <50 years old = 10.6%; ≥50 years old = 35.5%) (Table 2). In addition,
In Supportive Care Oncology

The study by Jillella et al. was prompted after a very high ED rate (7/19 = 37%) among patients treated between July 2005 and June 2009 at the Georgia Regents University Cancer Center in Augusta, Georgia. Jillella and colleagues implemented a proactive program to decrease EDs based on: a comprehensive review of patient charts, information obtained from APL conferences, and identifying bleeding, differentiation syndrome (DS), and infection as the main causes of death in the first month of APL diagnosis.

A treatment strategy with the following components was initiated in 2010: 1. A short and simple treatment algorithm; 2. Quick diagnosis; 3. Ad hoc meeting and treatment planning; 4. Rapid initiation of therapy; 5. Aggressive management of coagulopathy; 6. Prevention, early recognition, and management of DS; and 7. Prophylaxis and aggressive treatment of infections. The strategy also included a proactive communication effort with affiliate centres that included providing an algorithm, a discussion with the treating physician about a treatment plan, and very frequent follow-up (three to four times during the first ten days). Of the 27 patients treated post strategy and algorithm implementation, all have remained alive after a median follow-up of 400 days (Figure 3).

Based on these results, Jillella et al. have initiated a larger trial to demonstrate the efficacy of this approach. The study aims to accrue 150 patients with APL over three years and will prospectively assess 30-day mortality using this strategy, collect survival data, and educate health professionals on the approach to reduce the ED rate.

Jillella and colleagues concluded that ED in APL can and should be prevented. The strategy implemented by this study has already been validated in Brazil, Chile, Uruguay, and Mexico, where ED rates were reduced from 32% to 15%. Focus should be on expediting diagnosis and treatment, and proactively managing the three main causes of death. The authors suggested that several factors may contribute to a high ED rate, including lack of awareness of issues by treating oncologists, inadequate supervision at large treatment centres, and physician’s ego, apathy, and unwillingness to seek advice.

References:
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
Background and objectives

This presentation reviewed available data on the incidence, outcomes, and prognostic factors of therapy-related myeloid neoplasm (t-MN) development in acute promyelocytic leukemia (APL), based on a 2010 study by Montesinos et al., and discussed the current consensus and controversies on management approaches. In contrast to extensive reports on the incidence of t-MN after treatment of lymphomas and solid tumours, reports on its occurrence in acute myeloid leukemia (AML) and in particular, APL, have been few. Much about t-MN, including causation and true incidence, remains unknown. It is unclear how immunological and environmental factors, and exposure to anti-leukemic agents (e.g., alkylating topoisomerase inhibitors) are related to t-MN development, and whether oncogenic mechanisms of the primary tumour predispose patients to its development.

t-MN incidence

The incidence of t-MN in patients who have experienced first complete remission (CR) from all-trans retinoic acid (ATRA) plus anthracycline-based chemotherapy has been previously reported in only two studies, ranging from 0.97% to 6.5%. A shortcoming of these studies, however, was the absence of cumulative incidence by competing risk analysis. The study by Montesinos et al. in 2010 sought to determine the cumulative incidence of t-MN in three trials (LPA96, LPA99, and LPA2005) of the PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) group. A total of 1,025 patients enrolled from 1996 to 2008 were treated with ATRA and anthracycline-based induction and consolidation therapy. The cumulative incidence of t-MN among these patients was determined to be 2.2% (17/918) after a median follow-up of 77 months (Figure 1). An update on this analysis showed a crude incidence of 1.8% (25/1,402). The study also found that the median time interval from APL diagnosis to t-MN diagnosis was 43 to 46 months (range: 13–74 months), consistent with previous reports. Three patients were still on maintenance treatment when t-MN developed. The estimated incidence provided in this study is likely to be a more accurate representation of t-MN incidence given that the previous reports from La Sapienza University (GIMEMA 0389 [incidence = 6.5%; median follow-up >24 months]) and from European APL studies (APL91 and 93 [incidence = 0.97%; median follow-up of 51 months]) were not based on cumulative risk.

Figure 1. Cumulative incidence of t-MN in patients with APL treated on the PETHEMA trials: LPA96, LPA99, and LPA2005

APL = acute promyelocytic leukemia; PETHEMA = Programa para el Estudio de la Terapéutica en Hemopatía Maligna; t-MN = therapy-related myeloid neoplasm
Prior treatments and genetic abnormalities
Consistent with previous reports, the majority of patients had complete or partial deletions of chromosomes five and seven, which has previously been reported to be associated with prior alkylating agent treatments. However, this study did not find an association between these chromosome aberrations and prior alkylating agent treatments. In addition, the chromosome rearrangement of the mixed lineage leukemia (MLL)/11q23 gene region, which has been previously associated with topoisomerase II inhibitor treatment, was less frequently observed in the study despite all patients in the PETHEMA trials being treated with this class of inhibitors (e.g., idarubicin and mitoxantrone). These findings support the recent reclassification of t-MN into a single entity by the World Health Organization, in contrast to the earlier classification in which t-MN was categorized as either alkylating-agent or topoisomerase-II-inhibitor related.

Outcome, prognosis, and treatment
The outcome of patients who developed t-MN was shown to be very poor, with patients who developed either type of t-MN (myelodysplastic syndrome [MDS] and AML) in this study showing similar median overall survival of 19% at five years (Figure 2).1 A multivariate analysis revealed that age (HR = 8.89; p = 0.001) and relapse score (HR = 0.34; p = 0.005) were two independent prognostic factors. There were no specific treatment recommendations with respect to managing t-MN after APL. Three out of six patients with AML receiving induction treatment achieved a CR; three of these patients proceeded to allogeneic stem cell transplantation (SCT). Eight out of 10 patients diagnosed with MDS progressed to developing leukemia after a median of nine months, with two out of six patients who had received chemotherapy proceeding to allogeneic SCT. Three patients received only supportive care, and one patient received azacytidine.

ATO and t-MN
The presenters noted that in contrast to the established association between chemotherapy treatment and t-MN development, arsenic trioxide (ATO) has not been associated with t-MN development, although environmental arsenic exposure has been shown to be associated with a predisposition to malignancies. In a study by Hu et al. in 2009, an analysis of 80 patients in CR after ATO plus ATRA (median follow-up of 70 months) revealed no cases of secondary neoplasia.2

Summary
The results of this study are consistent with previous reports that the development of t-MN after ATRA plus chemotherapy is a relatively infrequent occurrence. However, due to very poor prognosis of patients with t-MN, t-MN contributes to almost 2% of APL deaths. The pathogenesis of the disease remains unknown, as well as the relationship between dose intensity of chemotherapy and the incidence of t-MN. Future approaches to reduce the incidence of t-MN should include prognostic factors as well as risk-adapted strategies.

Since daunorubicin was first demonstrated to be effective in APL by Bernard et al. in 1973,1 the GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto) research group has played a leading role in developing treatment approaches to APL. GIMEMA conducted several studies in the 80's and early 90's examining the roles of daunorubicin, idarubicin, and idarubicin in combination with cytarabine in the treatment of APL. Results from these studies showed high complete response (CR) rates ranging from 67% to 82%. Given that single-agent idarubicin in those studies led to the highest CR rate, the lowest rate of resistance, and the lowest rate of induction death (82%, 3.5%, 14.5%, respectively), the group conducted the first study combining all-trans retinoic acid (ATRA) with idarubicin (AIDA protocol).2 Together with two other studies that followed (AIDA 0493 and AIDA 2000), the group demonstrated CR rates as high as 94%, induction death rates as low as 5%, and virtually no detection of resistance.3,4

Despite high efficacy shown with ATRA plus idarubicin, reports have also shown a high frequency of hematological toxicity and evidence of long-term toxicities including secondary malignancies and cardiotoxicities. These safety concerns prompted the GIMEMA group to utilize a chemotherapy-free approach in APL using ATRA in combination with arsenic trioxide (ATO) in a phase III clinical trial recently published in the New England Journal of Medicine in 2013.5 This study, conducted in collaboration with the German AML Study group and Study Alliance for Leukemia, compared the efficacy and safety of ATRA plus ATO with those of ATRA plus chemotherapy in newly diagnosed APL patients of low/intermediate risk. The study demonstrated hematologic CR rates in the ATRA plus ATO group and ATRA plus chemotherapy group of 100% and 95%, respectively (p = 0.12). The two-year event-free survival rates in the ATRA plus ATO group and ATRA plus chemotherapy group were 97% and 86%, respectively (p = 0.02) (Figure 1). Although patients in the ATRA plus ATO group experienced more QTc prolongation (16% vs. 0%; p <0.001), more frequent grade 3 or 4 hepatic toxic effects (63% vs. 6%; p <0.001), and more frequent hyperleukocytosis (47% vs. 24%; p = 0.007), hematological toxicity was significantly lower in the ATRA plus ATO group (Figure 2).

Figure 1. Event-free and overall survival estimates

![Event-free and overall survival estimates](image-url)

<table>
<thead>
<tr>
<th>Months since diagnosis</th>
<th>Probability of event-free survival</th>
<th>Probability of overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>36</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Number at risk:
- ATRA + ATO: 76, 75, 72, 28, 5
- ATRA + chemo: 77, 66, 65, 27, 7
- ATRA + ATO: 77, 73, 73, 29, 5
- ATRA + chemo: 79, 69, 69, 29, 7

Source: Lo-Coco et al., 2013

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; chemo = chemotherapy

An update on first-line therapies in APL

The GIMEMA pathway to the cure for APL (Avvisati, G)
Several trials by the PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatia Maligna) group have demonstrated that risk-adapted treatment has improved patient outcomes by means of lowering relapse rates and improving disease-free survival (DFS) and overall survival (OS) rates in low, intermediate, and high risk patients. Following up on these results, the PETHEMA group is currently conducting the LPA2012 clinical trial aimed at improving patient outcomes by utilizing the prognostic factor CD56. CD56 was recently shown by Montesinos et al. in 2011 to be an independent adverse prognostic factor for relapse in patients with APL treated with an ATRA plus idarubicin-based regimen (5-year cumulative incidence of relapse = 22% for CD56+ vs. 10% for CD56--; p = 0.006). The LPA2012 trial was based on the LPA2005 trial that used the AIDA protocol for induction and risk-adapted consolidation treatment with idarubicin (cycle 1), mitoxantrone (cycle 2), and idarubicin (cycle 3), but with the following modifications: 1) Extended combination of ATRA plus idarubicin plus cytarabine for patients of intermediate risk; 2) Dose reduction of idarubicin for elderly and intermediate risk groups; and 3) Risk upgrading for patients positive for CD56 expression (Figure 3).

Figure 2. Hematological toxic effects

Figure 3. LPA2012 risk-adapted design
Recent clinical practice in China: role of arsenic trioxide in front-line treatment

Recent studies from China have explored the role of arsenic trioxide (ATO) in induction therapy for newly diagnosed patients with acute promyelocytic leukemia (APL). The study by Hu et al. published in 2009 examined the long-term effects of incorporating ATO into induction therapy. The study showed that the five-year event-free survival (EFS) and overall survival (OS) rates were 89.2% and 91.7%, respectively (Figure 4). The toxicity profile was mild and reversible, with long-term follow-up revealing no secondary neoplasms. Consistent with the long-term safety results of this trial, the study by Wang et al. in 2011 found no evidence of secondary malignancies or chronic arsenic toxicity. The study followed 54 newly diagnosed APL patients treated with ATO over a median follow-up of 39 months. The five-year leukemia-free survival rate was 93.4 ± 4.7% and the five-year cumulative incidence of relapse was 6.8 ± 4.7%.8

ATRA plus ATO treatment in pediatric APL: experience from China

Several other studies have explored the role of ATO in pediatric patients. The study by Zhou et al. in 2010 showed that single-agent ATO (0.2 mg/kg for children 4–6 years old; 0.16 mg/kg for children >6 years old) led to an OS rate of 83.9% and an EFS rate of 72.7% after a median follow-up time of 53 months (Figure 5).9 Long-term follow-up revealed no chronic ATO toxicity or secondary tumours. In 2010, a study by Wang et al. examined the efficacy and safety of ATO (0.15–0.17 mg/kg) in induction, followed by anthracycline-based consolidation and ATO for maintenance in 35 newly diagnosed pediatric patients. The study reported three early deaths during induction treatment, with 30 patients achieving CR. With a follow-up ranging from 10 to 108 months, the five-year EFS and OS rates among all patients were 80.3% and 82.7%, respectively. Finally, a study by Luo et al. in 2009 showed that a less intensive, modified PETHEMA protocol from the LPA99 trial that included ATO in induction led to improved outcomes in pediatric patients (age ≤14 years) when compared with those on an in-house protocol.11 Patients treated on the modified PETHEMA protocol showed a significant improvement in the 3.5-year EFS rate (79.6% vs. 37.5%; p = 0.012), a reduced frequency of sepsis during treatment (7.7% vs. 77.8%; p = 0.0015), and reduced hospitalization costs (median US$: 4,700 vs. 20,000; p <0.0001) compared with those treated on the previous protocol.

Summary

ATRA plus ATO is currently the mainstay of front-line treatment for newly diagnosed APL in China, with promising outcomes in adult and pediatric patients with APL of low/intermediate risk. The role of chemotherapy is dependent on risk stratification, as it remains important for high risk patients.
The acute promyelocytic leukemia 4 (APML4) phase II study of newly diagnosed patients with APL compared the outcomes of treatment with arsenic trioxide (ATO), idarubicin, and all-trans retinoic acid (ATRA) in induction, ATRA and ATO in consolidation, and methotrexate (MTX), ATRA, and 6-mercaptopurine (6-MP) in maintenance, with the outcomes of the previous APML3 trial, providing an historical control. In the APML3 trial, idarubicin and ATRA were used in induction and consolidation, followed by the same maintenance regimen used in the APML4 trial (i.e., MTX, ATRA, and 6-MP). The updated results presented at the conference showed that after a median potential follow-up of 4.2 years among 124 evaluable patients, the early death (ED) rate was 3.2% (4/124), the hematologic complete remission (CR) rate was 95% (118/124), and the molecular CR rate was 100% in all 112 patients who completed consolidation treatment. Patients treated with the APML4 protocol showed a significant improvement compared with the historical control (APML3) with respect to freedom from relapse (95% vs. 80%; $p = 0.002$), disease-free survival (DFS; 95% vs. 79%; $p = 0.001$), event-free survival (EFS; 90% vs. 72%; $p = 0.002$) and overall survival (OS; 94% vs. 83%; $p = 0.02$).

In contrast to the APML3 trial, the results of the APML4 trial showed no significant impact of FLT3 mutation status on OS rate (wildtype = 94% vs. mutated = 94%; $p = 0.95$). In addition, age (≤ 60 years vs. >60 years) and white blood cell counts (WBC >10 x $10^9$/L vs. ≤10 x $10^9$/L) had no significant impact on the five-year rates of DFS, EFS, and OS in the APML4 trial. This updated analysis showed that the APML4 regimen was feasible, tolerable, highly effective, and was associated with a low ED rate, as well as the absence of death in remission. The addition of ATO in the APML4 regimen significantly improved all survival endpoints compared with those observed with the APML3 regimen. Furthermore, the successful addition of ATO to induction and consolidation treatment has allowed anthracyclines to be reduced significantly, and has eliminated the need for high dose cytarabine in high risk patients.
Strategies to improve clinical outcome of front-line therapy with ATO, without increasing myelosuppression and by maintaining low toxicity (Mathews, V)

This presentation reviewed the recent 2010 study by Mathews et al. examining the long-term efficacy and safety of single-agent arsenic trioxide (ATO) in newly diagnosed acute promyelocytic leukemia (APL) patients, and described strategies currently being explored to improve the outcome of ATO treatment. The long-term follow-up of ATO as a single agent in APL showed that after a median follow-up of 60 months, the five-year Kaplan-Meier estimates for event-free survival (EFS) and overall survival were 69% ± 5.5% and 74.2% ± 5.2%, respectively (Figure 6). The authors concluded that the ATO regimen was well tolerated, with the rate of cytopenia occurring at approximately 6% post induction. Most side effects were found to be self-limiting, with no evidence of major long-term side effects, secondary malignancies, or long-term retention of ATO. However, ATO as a single agent was shown to be inadequate in high risk patients due to an increase in the incidence of relapse in that category.

A study published in 2009 by Thirugnanam et al. was highlighted, showing that relapsed patients with APL who were induced with an ATO-based regimen had superior outcomes if they received consolidation treatment with autologous stem cell transplantation compared with ATO plus all-trans retinoic acid (EFS = 83.33 % vs. 34.45%; p = 0.01).

Recently, efforts have been made to understand differences between APL cells from newly diagnosed APL patients and APL cells from relapsed APL patients, with the goal of creating more effective ATO-based regimens that would increase efficacy without increasing myelosuppression. Early findings indicate that relapsed APL cells have higher CD34 expression and lower CD13 and CD38 expression than newly diagnosed APL cells. In addition, there is higher expression of genes associated with stem cell and adhesion pathways in relapsed APL cells than in newly diagnosed APL cells. The evidence presented showed that relapsed APL cells may be protected from ATO-induced apoptosis by mesenchymal stem cells. Current work with various agents including bortezomib is exploiting these observations in an effort to nullify the protective effect of mesenchymal stem cells on relapsed APL cells (Figure 7).
Dr. Burnett summarized a recently published trial comparing the approach of the Medical Research Council (MRC) to treating newly diagnosed acute promyelocytic leukemia (APL) patients with that of the Spanish group (PETHEMA) (Figure 8). The study found that the MRC approach of using cytarabine in induction and consolidation resulted in similar efficacy outcomes to those of the Spanish approach. CR rates between the two arms were similar (93%), and the five-year relapse-free and overall survival rates were also similar between the Spanish and MRC approaches (81% vs. 82% and 85% vs. 83%, respectively) (Figure 9). However, the MRC approach was associated with more supportive care and hospitalization (81.8 vs. 63 days; \( p < 0.0001 \)). The conclusions of this study were that the absence of cytarabine and etoposide in the Spanish approach did not compromise hematological/molecular responses or cure rates, and although idarubicin in the Spanish approach is considered more myelosuppressive, it resulted in fewer hospitalizations. In support of this observation were quality of life assessments showing benefit with the Spanish approach. Dr. Burnett concluded by briefly summarizing an ongoing randomized clinical trial started in 2009 comparing the chemotherapy-free approach of arsenic trioxide plus all-trans retinoic acid (ATRA) with the AIDA protocol (ATRA plus idarubicin) in newly diagnosed APL patients. High risk patients in this trial would receive gemtuzumab ozogamicin with induction treatment. Results of this trial are still pending.

**Figure 8. MRC AML15 study design**

![Diagram showing MRC and Spanish approach]

**Figure 9. AML15 APL: overall survival**

![Graph showing survival rates]

AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; MRC = Medical Research Council
Dr. Efficace presented the first evidence-based data on long-term cancer survivorship issues focusing on health-related quality of life (HRQoL) in acute promyelocytic leukemia (APL) patients. The main objective of the study was to investigate long-term HRQoL in APL patients from two trials (AIDA 0493 and AIDA 2000) previously conducted by GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto). Patients in both trials were treated with all-trans retinoic acid plus idarubicin. After a median time from diagnosis of 13 years, a preliminary comparison between APL patients and the general population revealed that APL patients had worse outcomes for role limitations due to physical health and emotional problems. The study also showed that a greater percentage of older APL patients (≥30 years) experienced moderate-to-severe symptoms than did younger APL patients (<30 years). These symptoms included fatigue (40% vs. 14%), pain (23% vs. 7%), numbness (19% vs. 4%), and sleep disturbance (28% vs. 18%). In addition, fatigue was the most prevalent symptom reported in 67% of patients several years after treatment (Figure 10), which greatly affected mental and physical HRQoL outcomes. Given the modern success of APL treatment, continued research into survivorship issues will be an essential step in optimizing approaches to long-term follow-up care of APL patients.

Figure 10. Symptom prevalence

References:
Introduction

Tremendous progress has been made over the past decade in the treatment of acute promyelocytic leukemia (APL). Cure rates are now expected at about 80% after first-line therapy.1 One of today’s most significant challenges in the treatment of APL is the high early death (ED) rate, which has persisted despite the widespread use of all-trans retinoic acid (ATRA) over the last decade.2 This issue is also one we face in Canada. Not only are the observations that have been made in the U.S. and Europe likely to be true here, but our own analysis of the Canadian Cancer Registry shows that the ED rate is high as well.3 Moreover, in Canada we face the challenge of the geographic makeup of the country, where patients may need to travel great distances to reach leukemia centres. Immediate administration of ATRA and complex supportive care may not be readily available. The resulting delay in definite diagnosis and treatment may be a contributing factor in high ED rates. To balance this challenge, the Canadian health care infrastructure has the components to improve ED in APL. The distribution of experienced leukemia centres in each province and universal health insurance for hospital-based care mean that treatment outcomes should not be compromised.

One approach that may help reduce the ED rate involves the dissemination of management strategies by physicians experienced in the care of patients with APL. To help with this, several APL experts from across Canada are currently working on a Canadian-specific APL guideline to help achieve consensus and improve knowledge regarding APL treatment. This guideline should create further awareness on issues regarding APL treatment, especially early treatment and supportive care, and will hopefully lead to improved outcomes.

The 6th International Symposium on Acute Promyelocytic Leukemia

The 6th International Symposium on APL covered several key areas in APL including persistent high early ED rates, new findings on the incidence of therapy-related myeloid neoplasms (t-MN), and significant developments in first-line therapies from around the world.

Early death in acute promyelocytic leukemia

Despite the achievement of high cure rates in APL, the frequency of ED remains high, as pointed out in the results of the Lehmann et al. study. The updated study, which examined a 2007–2012 cohort of patients with APL in the Swedish registry, found little improvement in the rates of ED — consistent with the results of an earlier study on the 1997–2006 patient cohort.2 These surprising results become even more significant given the highly organised Swedish health care system, and suggest that the availability of ATRA may have reached the limit of reducing early mortality in a real-world population outside of clinical trials. Furthermore, the results might suggest that the effort to educate and disseminate information on how to reduce early mortality has not been successful. These sobering findings suggest that further improvements in outcomes may require new strategies to reduce early mortality.

The high rate of ED reported in the Lehmann et al. study is also consistent with our recent study here in Canada that showed a high early mortality in APL.3 However, our findings showed some differences when compared to population-based studies including those based on the SEER (Surveillance, Epidemiology, and End Results) and Swedish registries. One of the main objectives of the study was to determine the national incidence of APL in Canada, which would show whether the incidence of APL has increased over time as other studies have demonstrated. The study not only showed that the incidence of APL was not increasing in Canada, but that it was also rather low (0.083/100,000). An explanation for the low incidence of APL may perhaps be due to the ethnic demographics of Canada; for example, there is a lower representation of people from the Mediterranean and Latin American regions — both known for a high incidence of APL. A second explanation may be due to the possibility of biased reporting to the Canadian Cancer Registry. However, bias is unlikely to be a significant factor for several reasons. First, the registry employs the International Classification of Diseases for Oncology coding for all APL diagnoses, a process that is similar to how APL is coded in other national registries. Second, all provinces are required to report new cancer diagnoses to the national registry. Third, if under-reporting were an underlying reason for low incidence, we would expect a slow increase in reported incidence in the ATRA era — a period when the profile of this leukemia sub-type has increased. The fact that the incidence of APL has been stable in Canada suggests consistent reporting over the past 15 years.
The persistence of a high ED rate in APL has been shown in several population-based studies. However, it remains unclear which treatment-related risk factors are contributing to this issue. The study by Tallman et al. examined the hypothesis that a delay in ATRA administration may be a contributing factor. Their results showed that the administration of ATRA is often delayed. Revealing this problem allows us to now focus on educating referral centres here in Canada. Peripheral hospitals need to begin early discussion on the management of APL when this diagnosis is first suspected. Any suspicion of APL on morphological or clinical grounds should lead to the immediate initiation of ATRA without waiting for genetic confirmation, along with referral to a leukemia centre. Although these steps seem like simple interventions, there are some challenges. First, the rarity of APL means that the ER physician or internist is unlikely to have ever encountered a prior case of APL. Second, the median age at diagnosis for patients with APL is 50 years; for patients older than this, physicians may suspect a wider range of underlying conditions such as myelodysplastic syndrome or other sub-types of acute myeloid leukemia (AML), making it possible that a true APL case will be overlooked. This is consistent with studies showing that outcomes, including early death, are worse with older patients.

One of the most effective approaches to deal with the challenge of reducing the ED rate in APL is the communication-based model proposed in a study by Jillella et al. The model, which has been shown to be effective in Latin American countries, demonstrated that good communication and education decreased the ED rate in newly diagnosed APL patients. This model could also be successful in Canada. In addition to communicating diagnostic and treatment algorithms through Canadian-specific guidelines, improving communication with referral sites as implemented in this study would likely reduce ED rates here in Canada. Interestingly, this approach would probably improve outcomes in other leukemias as well.

First-line therapy in acute promyelocytic leukemia

There were several new developments in first-line therapies. One of the most significant was the recent publication of the Lo-Coco et al. study demonstrating non-inferiority of arsenic trioxide (ATO) plus ATRA compared with a standard anthracyclines-based approach in patients with low/intermediate risk APL. This study showed that a chemotherapy-free approach of ATO plus ATRA resulted in a high rate of molecular remission, and was associated with a much lower risk of hematological toxicity.

There are several important challenges ahead. First, it is important to determine how ATO could be built into a regimen for high-risk patients since the Lo-Coco study only addresses low/intermediate APL patients. Second, longer follow-up is required to determine the frequency of late relapses at sites beyond the bone marrow, particularly central nervous system relapses, and to determine the frequency of t-MN. Finally, the health economics of introducing ATO remains unclear since ATO is likely to be more expensive to purchase, but would result in less hospitalization time due to lower hematological toxicity. A recent study presented at the 2013 American Society of Hematology Annual Meeting examining the cost-effectiveness of ATRA plus ATO compared to ATRA plus idarubicin in Canada may help clarify this issue. Based on the results of the Lo-Coco et al. study, anthracycline-based therapy for APL is likely to be phased out, at least for high-risk APL patients.
At least in the context of clinical trials, ATRA plus ATO appears to achieve the main goals of reducing therapy-related deaths and reducing the risk of APL relapse.

The APML4 trial by Iland et al. was a key phase II trial that examined the role of ATO within the platform of the AIDA protocol (ATRA plus idarubicin) in induction and consolidation. The study showed that adding ATO to the AIDA regimen was not only feasible with good outcomes, but the positive results also extended to high-risk patients. Interestingly, FLT3 (fms-related tyrosine kinase 3) mutations and diagnostic white blood cell count had no impact on major endpoints, implying that the addition of ATO rendered these prognostic factors irrelevant.

Two important questions were addressed in the presentation by Dr. Burnett of the National Cancer Research Institute (NCRI): 1) What is the role of cytarabine in first-line treatment? and 2) How should the chemotherapy-free approach of ATO plus ATRA be incorporated into treating high-risk patients?. The first question was addressed in the recent MRC AML 15 trial by Burnett et al. that compared the NCRI approach of using additional chemotherapy (cytarabine/etoposide) to the less intense PHEMA approach (no cytarabine or etoposide). This randomized study challenges the idea that intensification of chemotherapy is effective. Not only was lower intensity chemotherapy just as effective, but the NCRI approach was more likely to be toxic in early and late stages of therapy. The NCRI is now addressing the efficacy of ATO in high-risk APL patients in a clinical trial that compares ATO plus ATRA with the AIDA protocol in newly diagnosed APL patients. High-risk patients receive gemtuzumab ozogamicin (GO) in addition to ATO plus ATRA. The decision to add GO to therapy for high-risk patients is a logical one, and may likely prove to be the solution for treating high-risk APL patients.

BREAST CANCER
Breast cancer

New Strategies in the Treatment of HER2-Positive Breast Cancer

Overexpression of the human epidermal growth factor receptor 2 (HER2) protein is detected in the tumours of approximately 20% of patients with breast cancer, conferring an aggressive phenotype that historically resulted in poor clinical outcome.1 The landmark development of trastuzumab, a humanized monoclonal antibody targeting HER2, and other anti-HER2 agents such as lapatinib, a reversible HER2 tyrosine kinase inhibitor, have changed the course of HER2-positive disease; however, a subset of patients will still relapse.1 Given this clinical reality, new anti-HER2 agents with different mechanisms of action have been developed. Recently, the antibody-drug conjugate trastuzumab emtansine was shown to improve progression-free survival (PFS) and overall survival (OS) compared with capecitabine plus lapatinib in the phase III EMILIA study of previously treated patients with HER2-positive advanced breast cancer (ABC).2

A different approach that has also been taken has been to elucidate the molecular mechanisms mediating resistance to HER2 blockade.1 The phosphatidylinositol 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR) signaling transduction pathway is commonly deregulated in breast cancer and represents a potential target. Everolimus, a mTOR kinase inhibitor, has shown some encouraging antitumour activity when used in combination with trastuzumab and chemotherapy in phase I studies of HER2-positive ABC.1 Currently, everolimus is being studied in two ongoing phase III trials in the HER2-positive ABC setting: BOLERO-1 (NCT00876395) and BOLERO-3 (NCT01007942).

The following abstracts were presented at the 2013 European Cancer Congress (ECC), some of which pertain to the ongoing development of trastuzumab emtansine and everolimus:

• Primary results from TH3RESA, a phase III study of trastuzumab emtansine versus treatment of physician’s choice in HER2-positive ABC, have demonstrated improved efficacy and favourable safety with trastuzumab emtansine.

• Patients with HER2-positive ABC in the BOLERO-3 study who have biomarkers indicative of PI3K/mTOR pathway activation may have derived greater benefit from the addition of everolimus to trastuzumab and vinorelbine.

• Preliminary results from a phase II study showed significant prolongation of PFS, with an acceptable toxicity profile, with the addition of everolimus to an aromatase inhibitor in post-menopausal women with ER+/HER2– ABC who have progressed following previous endocrine therapy.

• Results of a multicentre, phase II study have shown that bevacizumab preconditioning followed by etoposide and cisplatin (BEEP) is a highly effective treatment for brain metastases of breast cancer progressing from radiotherapy.

• The aTTom study has shown that continuing tamoxifen to year 10 rather than just to year 5 produces further reductions in breast cancer recurrence and may help reduce breast cancer mortality in women with ER-positive or ER-untested early breast cancer.

Trastuzumab emtansine for HER2-positive metastatic breast cancer: primary results from TH3RESA, a phase III study of trastuzumab emtansine versus treatment of physician’s choice

Background
Trastuzumab emtansine, an antibody-drug conjugate comprising the cytotoxic agent DM1 linked to trastuzumab, is approved in Canada for patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) previously treated with trastuzumab and a taxane, separately or in combination. There is no clear standard of care for patients with progressive disease (PD) after ≥2 HER2-directed regimens for MBC. TH3RESA is an ongoing phase III study evaluating trastuzumab emtansine versus treatment of physician’s choice (TPC) in this patient population. At ECC 2013, Wildiers and colleagues presented the final analysis of progression-free survival (PFS) and the first interim analysis of overall survival (OS) for this study.1

Study design
• Patients with centrally confirmed HER2-positive unresectable locally advanced breast cancer (LABC) or MBC with PD after ≥2 HER2-directed regimens, including trastuzumab and lapatinib, in the unresectable recurrent/metastatic setting and a taxane (any setting) were randomized 2:1 to trastuzumab emtansine (3.6 mg/kg intravenous [iv] every three weeks [q3w]) or TPC, respectively.
• After EMILIA2 data were reported, which showed a significant improvement in median PFS and OS with trastuzumab emtansine than with capcitabine plus lapatinib, crossover from TPC to trastuzumab emtansine was allowed post-progression.
• Co-primary end points were PFS by investigator assessment and OS.
• Key secondary end points were objective response rate (ORR) by investigator assessment and safety.

Key findings
Baseline characteristics and disposition
• By the Feb 11, 2013 clinical data cutoff, 602 patients were randomized: 404 patients to the trastuzumab emtansine arm and 198 patients to the TPC arm. A total of 44 patients in the TPC arm have crossed over to trastuzumab emtansine after documented PD.
• Patients’ baseline characteristics were well balanced between the two treatment arms (trastuzumab emtansine vs. TPC), including:
  - Age (<65 years): 85.4% vs. 82.8%;
  - Race (white): 80.4% vs. 81.3%;
  - ECOG Performance Status 0/1: 44.8%/49.8% vs. 41.4%/51.0%;
  - Disease extent (MBC/unresectable LABC): 96.8%/3.2% vs. 94.4%/5.6%.
  
Study design

<table>
<thead>
<tr>
<th>HER2-positive (central) advanced breast cancer* (N = 600)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥2 prior HER2-directed therapies for advanced breast cancer</td>
</tr>
<tr>
<td>• Prior treatment with trastuzumab, lapatinib, and a taxane</td>
</tr>
<tr>
<td>Trastuzumab emtansine 3.6 mg/kg q3w iv (n = 400)</td>
</tr>
<tr>
<td>TPC† (n = 200)</td>
</tr>
<tr>
<td>Trastuzumab emtansine† (optional crossover)</td>
</tr>
</tbody>
</table>

• Stratification factors: world region, number of prior regimens for advanced breast cancer,1 presence of visceral disease
• Coprimary end points: PFS by investigator and OS
• Key secondary end points: ORR by investigator and safety

HER2 = human epidermal growth factor receptor 2; iv = intravenous; MBC = metastatic breast cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; q3w = every 3 weeks; TPC = treatment of physician’s choice

*Advanced breast cancer includes MBC and unresectable locally advanced/recurrent breast cancer.
†TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
‡First patient in: September 2011. The study was amended September 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive trastuzumab emtansine after documented PD.
§Excluding single-agent hormonal therapy.

Wildiers H, et al. ECC 2013:LBA15
Trastuzumab emtansine for HER2-positive metastatic breast cancer: primary results from TH3RESA, a phase III study of trastuzumab emtansine versus treatment of physician’s choice
• Patients in each treatment arm had received a median of 4 prior regimens (excluding hormonal therapy) in the recurrent/metastatic setting, and the majority (75.1%) had visceral disease.

• TPC comprised HER2-directed regimens (83.2%) and single-agent chemotherapy (16.8%). (Table 1)
  ◦ Of the HER2-directed regimens, the majority contained trastuzumab, with chemotherapy plus trastuzumab (68.5%) being the most frequently used of all regimens.
  ◦ The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.

• A greater proportion of patients from the TPC arm discontinued the study than those from the trastuzumab emtansine arm (36.9% vs. 21.0%).
  ◦ The reasons for study discontinuation (TPC vs. trastuzumab emtansine) were death (22.2% vs. 15.1%), withdrawal by patient (13.1% vs. 4.7%), physician’s decision (1.0% vs. 0.5%), and other (0.5% vs. 0.7%).

Efficacy

• At a median follow-up of 7.2 months in the trastuzumab emtansine arm and 6.5 months in the TPC arm, median PFS by investigator assessment was significantly longer with trastuzumab emtansine than with TPC (6.2 vs. 3.3 months; stratified HR = 0.528 [95% CI: 0.422–0.661], p < 0.0001). (Figure 1)
  ◦ The increased benefit with trastuzumab emtansine remained similar when median PFS with trastuzumab emtansine was compared with that for patients who received trastuzumab-containing regimens (6.2 vs. 3.2 months; stratified HR = 0.558 [95% CI: 0.437–0.711], p < 0.0001).

• PFS benefit with trastuzumab emtansine was consistent across subgroups, including age, visceral involvement, and number of prior regimens.
• At an observed 21% of targeted events, the first interim OS analysis showed a similar trend of benefit with trastuzumab emtansine compared with TPC (median: not reached vs. 14.9 months; stratified HR = 0.552 [95% CI: 0.369–0.826], p = 0.0034), but the efficacy stopping boundary (HR <0.363 or p <0.0000013) was not crossed. (Figure 2)

• The ORR by investigator assessment in patients with measurable disease was significantly improved with trastuzumab emtansine compared with TPC (31.3% vs. 8.6%; difference: 22.7% [95% CI: 16.2–29.2%], p <0.0001). (Figure 3)

![Figure 1. Progression-free survival by investigator assessment](image1)

![Figure 2. First interim overall survival analysis](image2)

![Figure 3. ORR by investigator assessment in patients with measurable disease](image3)
Safety

- The percentage of patients experiencing adverse events (AEs) of any grade was slightly higher in the trastuzumab emtansine arm vs. the TPC arm (93.5% vs. 88.6%).
- Of the AEs of any grade (trastuzumab emtansine vs. TPC):
  - More thrombocytopenia (15.1% vs. 3.3%) was reported with trastuzumab emtansine.
  - More diarrhea (9.9% vs. 21.7%), neutropenia (5.5% vs. 21.7%), and abdominal pain (6.5% vs. 12.5%) were reported with TPC.
  - Fewer grade $\geq 3$ AEs overall were reported for trastuzumab emtansine vs. TPC (32.3% vs. 43.5%), (Table 2)
  - More grade $\geq 3$ thrombocytopenia (4.7% vs. 1.6%) was reported with trastuzumab emtansine.
  - More grade $\geq 3$ neutropenia (2.5% vs. 15.8%), febrile neutropenia (0.2% vs. 3.8%), and diarrhea (0.7% vs. 4.3%) were reported with TPC.
- The TPC arm reported higher incidences of AEs leading to treatment discontinuation (10.9% vs. 6.7%) and AEs leading to dose reduction (19.6% vs. 9.4%).

| Table 2. All-grade and grade $\geq 3$ adverse events |
|---------------------------------|-----------------|-----------------|-----------------|
| **TPC (n = 184)** | **Trastuzumab emtansine (n = 403)** | |
| **Nonhematologic AEs** | | |
| Diarrhea | 21.7 | 4.3 | 9.9 |
| Abdominal pain | 12.5 | 2.7 | 6.5 |
| AST increased | 5.4 | 2.2 | 8.4 |
| Fatigue | 25.0 | 2.2 | 27.0 |
| Asthenia | 15.8 | 2.2 | 15.6 |
| Cellulitis | 3.3 | 2.2 | 1.2 |
| Pulmonary embolism | 2.2 | 2.2 | 0.5 |
| Dyspnea | 9.2 | 1.6 | 9.9 |
| **Hematologic AEs** | | |
| Neutropenia | 21.7 | 15.8 | 5.5 |
| Febrile neutropenia | 3.8 | 3.8 | 0.2 |
| Anemia | 10.3 | 2.7 | 8.9 |
| Leukopenia | 6.0 | 2.7 | 0.7 |
| Thrombocytopenia | 3.3 | 1.6 | 15.1 |

AEs = adverse events; AST = aspartate aminotransferase; TPC = treatment of physician’s choice

*Grade 5 subarachnoid hemorrhage was reported for one patient with grade 4 thrombocytopenia, grade 4 tumour hemorrhage was reported for one patient with grade 3 thrombocytopenia. The incidences of grade $\geq 3$ hemorrhage of any type were 2.2% for trastuzumab emtansine and 0.5% for TPC.

Key conclusions

- Trastuzumab emtansine demonstrated improved efficacy compared with TPC.
  - The ORR was 31.3% vs. 8.6%, $p < 0.0001$.
  - There was a significant improvement in PFS (HR = 0.528; $p <0.0001$) and a clear and consistent treatment effect across subgroups.
  - The interim OS analysis favoured trastuzumab emtansine (HR = 0.552; $p = 0.0034$), but the efficacy stopping boundary was not crossed.
- Safety favoured trastuzumab emtansine, with fewer grade $\geq 3$ AEs and fewer discontinuations and dose reductions due to AEs compared with those for TPC.
- These data reaffirm the results from the EMILIA study, demonstrating a consistent benefit with trastuzumab emtansine in patients with previously treated HER2-positive advanced breast cancer.

References:
Background
In BOLERO-3 (NCT01007942), a randomized, double-blind, placebo-controlled, phase III trial, everolimus 5 mg daily combined with weekly trastuzumab and vinorelbine significantly prolonged progression-free survival (PFS) versus placebo in patients with trastuzumab-resistant human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer previously treated with a taxane (HR = 0.78 [95% CI: 0.65–0.95]).1 At ECC 2013, Jerusalem and colleagues explored correlations between key members of the phosphatidylinositol 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR) pathway and everolimus efficacy in a subset of patients from this study for the identification of potential predictive biomarkers.1

Study design
• Patients (N = 569) with locally advanced or metastatic HER2-positive breast cancer that was trastuzumab resistant were randomized 1:1 to receive vinorelbine (25 mg/m² weekly) plus trastuzumab (2 mg/kg weekly; 4 mg/kg loading dose on day 1, cycle 1) in combination with either everolimus (5 mg orally (po) daily) or a placebo (po daily), until progressive disease or intolerable toxicity.

Key findings
• Archival tumour samples were available for biomarker analysis from 283/569 patients. Of 283 available patients, 262 had evaluable data for one or more of the measured biomarkers.
• This biomarker population was representative of the trial population in terms of demographics, clinical characteristics, and efficacy outcomes.

N = 569
• Locally advanced or metastatic HER2-positive breast cancer
• Prior taxane required
• Trastuzumab resistance
  – Adjuvant: progression on or within 12 months of trastuzumab
  – Metastatic: progression within four weeks of trastuzumab
• Measurable disease only

HER2 = human epidermal growth factor receptor 2; po = orally
*Following 4 mg/kg loading dose on day 1, cycle 1.
• None of the known prognostic factors were significantly imbalanced between the arms.

• Patients with high pS6 level (optimal histology (H)-score cut-point: ≥75th percentile) derived more benefit with everolimus (HR = 0.48 [95% CI: 0.24–0.96]). (Figure 1 and Table 1)

Similarly, patients with low PTEN level (optimal H-score cut-point: <20th percentile) derived more benefit with everolimus (HR = 0.41 [95% CI: 0.20–0.82]), with a median PFS gain of 18 to 19 weeks (41.9 weeks vs. 23.1 weeks). (Figure 2 and Table 2)

In contrast, patients with low pS6 or normal to high PTEN did not appear to derive any benefit from addition of everolimus (HR = 1.14 [95% CI: 0.77–1.68] and HR = 1.05 [95% CI: 0.75–1.45], respectively). (Tables 1 and 2)

• A trend of enhanced everolimus treatment benefit was observed in patients with PIK3CA mutations (~20% of the population) and in those with activated PI3K pathway, defined as harbouring either PIK3CA mutation or low PTEN level. (Table 3)

Significant treatment-marker interactions were detected for PTEN and pS6 (p = 0.01 and p = 0.038, respectively), but not for PIK3CA (p = 0.32).

Table 1. Analysis of progression-free survival by pS6 levels and treatment

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>Events</th>
<th>Median PFS, weeks (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus/pS6 high</td>
<td>23</td>
<td>15</td>
<td>29.4 (18.1–55.1)</td>
<td>0.48 (0.24–0.96)</td>
</tr>
<tr>
<td>Placebo/pS6 high</td>
<td>22</td>
<td>20</td>
<td>17.1 (11.7–24.0)</td>
<td></td>
</tr>
<tr>
<td>Everolimus/pS6 low</td>
<td>66</td>
<td>47</td>
<td>24.9 (23.6–31.0)</td>
<td>1.14 (0.77–1.68)</td>
</tr>
<tr>
<td>Placebo/pS6 low</td>
<td>77</td>
<td>57</td>
<td>30.0 (24.0–36.1)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; pS6 = phosphorylated ribosomal protein S6

Table 2. Analysis of progression-free survival by PTEN levels and treatment

<table>
<thead>
<tr>
<th>Subgroup defined by low or normal PTEN level</th>
<th>Therapy</th>
<th>n (# of events)</th>
<th>Median PFS, weeks (95% CI)</th>
<th>HR (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-score ≥50</td>
<td>Everolimus</td>
<td>100 (72)</td>
<td>30.1 (24.3–35.6)</td>
<td>0.97 (0.71–1.33)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>108 (85)</td>
<td>30.0 (24.0–35.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-score &lt;50</td>
<td>Everolimus</td>
<td>15 (11)</td>
<td>41.4 (17.3–66.9)</td>
<td>0.52 (0.21–1.26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>14 (11)</td>
<td>23.7 (10.6–25.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroups defined by optimal cut-point of PTEN level (20th percentile)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-score ≥20th percentile</td>
<td>Everolimus</td>
<td>89 (67)</td>
<td>30.1 (24.0–35.3)</td>
<td>1.05 (0.75–1.45)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>100 (78)</td>
<td>30.1 (24.0–36.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-score &lt;20th percentile</td>
<td>Everolimus</td>
<td>26 (16)</td>
<td>41.9 (24.0–53.1)</td>
<td>0.41 (0.20–0.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>22 (18)</td>
<td>23.1 (12.1–24.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; H-score = histology score; PFS = progression-free survival; PTEN = phosphatase and tensin homolog

*p Treatment-biomarker interaction.
†PTEN optimal cut-point selected as ≥ and < 20th percentile (H-score = 100).
Table 3. Analysis of progression-free survival by PIK3CA mutational status and treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Biomarker</th>
<th>n</th>
<th>Events</th>
<th>Median PFS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>PIK3CA mutant</td>
<td>15</td>
<td>9</td>
<td>5.52 (*)</td>
<td>0.65* (0.29–1.45)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>21</td>
<td>19</td>
<td>6.74 (4.83–7.59)</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>PIK3CA wildtype</td>
<td>69</td>
<td>51</td>
<td>6.83 (5.32–8.18)</td>
<td>0.98 (0.67–1.44)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>77</td>
<td>56</td>
<td>5.72 (5.22–7.79)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha

*Not evaluable due to small sample size/event number.

Key conclusions

- Patients in BOLERO-3 with biomarkers indicative of PI3K/mTOR pathway activation may derive greater benefit from addition of everolimus to trastuzumab and vinorelbine.
- These observations are consistent with the hypothesis that mTOR inhibition attenuates trastuzumab resistance resulting from PI3K/mTOR pathway activation.
- The results and clinical implications of this exploratory analysis need further validation and investigation.


Safra T, et al. ECC 2013:1895

Everolimus in combination with letrozole in the treatment of postmenopausal women with hormone receptor positive/HER2-negative advanced breast cancer after failure of endocrine therapy — a phase I study

Background

Approximately 75% of advanced breast cancers (ABC) in post-menopausal women are estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2–). Currently, there is an unmet medical need for new treatment modalities after failure of endocrine therapy. Activation of the mTOR pathway is a key adaptive change driving endocrine resistance. Preclinical and early clinical data suggest a synergism between RAD001 (everolimus) and letrozole resulting in restoration of sensitivity to endocrine therapy.1

Study design

- This was a multicentre, Israeli, open-label, phase II study evaluating treatment with everolimus (oral 10 mg/day) combined with letrozole (oral 2.5 mg/day) in post-menopausal women with ABC after progression on tamoxifen and/or anastrozole and/or letrozole and/or fulvestrant and/or exemestane.
- The objectives were to assess overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and the safety profile of the combination after failure of one or more endocrine therapies. Analysis was performed on the intent-to-treat population.

Key findings

- A total of 73 patients were enrolled.
- The patients’ baseline characteristics included:
  - Median age: 55 (28–80) years;
  - All had ABC with one to three metastatic sites;
  - Patients were previously exposed to a median of 2 (1–5) lines of hormonal therapy; 54% to letrozole.
• At the time of analysis, the median follow-up was 12.23 (2–22) months.
• Responses to treatment were:
  ◦ ORR: 19% (15/73);
  ◦ DCR: 58% (43/73); and
  ◦ Progressive disease: 25% (18/73).
• PFS was 7.9 (1–22) months, while 25% (18/73) of patients are still on treatment.
• OS is too early to evaluate, with 78% of patients still alive.
• Commonly observed all-grade toxicities included: stomatitis (50%), weakness (50%), weight loss (30%), anorexia (27%), anemia (28%), hyperlipidemia (23%), diarrhea (19%), myalgia/arthralgia (16%), and pneumonitis (10%).

Lu YS, et al. ECC 2013:1878

Bevacizumab preconditioning followed by etoposide and cisplatin (BEEP) is a highly effective treatment for brain metastases of breast cancer progressing from radiotherapy — results of a multicentre phase II study

Background
The management of brain metastasis of breast cancer progressing from whole brain radiotherapy remains a severe challenge. The investigators hypothesized that starting bevacizumab (BE) one day before chemotherapy could further enhance the activity of etoposide (E) and cisplatin (P), two of the cytotoxic agents that have moderate activity in brain metastases of breast cancer, by increasing drug delivery into tumour tissue via bevacizumab-induced vascular normalization. At ECC 2013, Lu and colleagues presented results of this multicentre phase II study.1

Study design
• This trial is registered with ClinicalTrials.gov (NCT01281696).
• Breast cancer patients with brain metastases and progression of brain lesions after whole brain radiotherapy were enrolled.
• Treatment was given in 21-day cycles: patients received bevacizumab 15 mg/kg on day 1, etoposide 70 mg/m^2/day from day 2 to day 4, and cisplatin 70 mg/m^2 on day 2 (BEEP regimen), for a maximum of six cycles.
• The primary end point was a centrally assessed objective central nervous system (CNS) response, defined as a ≥50% reduction in the volumetric sum of all measurable CNS lesions in the absence of increasing steroid use, development of a new CNS lesion, or progressive neurologic symptoms, and no progressive extra-CNS diseases.
• An objective CNS response rate of 30% was assumed and 15% as a minimum interest, and using a Simon’s optimum two-stage design with a significance level α of 0.15 and a power of 80%, a total of 31 assessable patients were required.
• Serial dynamic contrast enhancement-magnetic resonance imaging (DCE-MRI) one hour, 24 hours, and 21 days after bevacizumab infusion were performed in selected suitable patients who had consented to the DCE-MRI study.

Key findings

Baseline characteristics and disposition
• A total of 35 patients were enrolled from January 2011 to January 2013.
• All patients were included for safety and efficacy analysis (reported by intent-to-treat analysis). Data cut-off was July 31, 2013.
• Some of the patients’ baseline clinical characteristics included:

References:
Median age: 54.3 (range: 33.4–75.0) years;
Estrogen receptor (ER)/human epidermal growth factor receptor 2 (HER2) status:
- ER+HER2−: six patients;
- ER+HER2+: nine patients;
- ER−HER2+: 14 patients; and
- ER−HER2−: six patients.

Eastern Cooperative Oncology Group Performance Status:
- 0–1: 16 patients;
- 2: eight patients;
- 3: 11 patients.

Median number of extra-CNS metastatic sites: 2 (range: 0–3);
Median number of prior lines of chemotherapy in metastatic setting: 3 (range: 1–8);
Six patients had been exposed to cisplatin and four patients had been exposed to etoposide treatment for metastatic disease before entering this study.

The median number of treatment cycles delivered was six (range: 1–6).

Eighteen patients (51.4%) needed dose reductions of etoposide to 60 mg/m² and cisplatin to 60 mg/m², and three patients discontinued from treatment due to toxicity. (Table 1)

Safety
- The most frequent grade 3/4 toxicities per treatment cycle included neutropenia (30.8%), leukopenia (16.0%), infection with normal absolute neutrophil count or grade 1/2 neutropenia (15.4%), thrombocytopenia (7.7%), and anemia (7.1%). (Table 1)
- One patient died of infection and one patient died of tracheoesophageal fistula. The latter patient had extensive mediastinal lymph node metastases, but her CNS tumours completely resolved after three cycles of BEEP.
- Due to the high incidence of grade 3/4 neutropenia, the protocol was amended to mandate prophylactic filgrastim 300 µg/day for three days after BEEP treatment. After the amendment, the incidence of grade 3/4 neutropenia decreased from 37% to 12% per cycle.

Efficacy
- In total, 27 patients (77.1%; 95% CI: 59.9–89.6) achieved an objective CNS response.
- The best volumetric CNS responses were: (Table 2)
  - ≥80% reduction: 13 patients (37.1%);
  - 50–<80% reduction: 14 patients (40.0%);
  - 20–<50% reduction: six patients (17.1%);
  - Non-evaluable: two patients (5.7%).
- Six patients had non-CNS disease progression while CNS tumours remained under control.

All patients were also evaluated by exploratory analysis for best CNS response according to modified Response Evaluation Criteria in Solid Tumours (RECIST):
- 21 patients (60.0%) achieved an objective CNS response, with two (5.7%) complete responses and 19 (54.3%) partial responses.
- 12 patients (34.3%) had stable disease, and tumour status was non-evaluable for two patients (5.7%).
- Median progression-free survival (PFS) was 6.2 months (95% CI: 4.9–7.5) and six patients were censored. (Figure 1A)
• Median CNS-PFS was 7.1 months (95% CI: 6.4–7.8) and seven patients were censored. (Figure 1B)
• Median overall survival was 9.8 months (95% CI: 6.5–13.1) and 11 patients were censored. (Figure 1C)
• Eight patients received serial DCE-MRI on the study.
• In general, tumour vascular normalization could be observed at 2.5 hours after starting bevacizumab infusion (one hour after infusion completion), but became much more obvious at 24 hours after infusion, as demonstrated by changes in DCE-MRI parameters. (Table 3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2.5 hours</th>
<th>24 hours</th>
<th>21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Peak (%)</td>
<td>$-12.8 \pm 4.6^*$</td>
<td>$-24.7 \pm 7.9^{**}$</td>
<td>$-27 \pm 8.6^{**}$</td>
</tr>
<tr>
<td>Δ Slope (%)</td>
<td>$-46.6 \pm 26.5^*$</td>
<td>$-65.8 \pm 20.6^{**}$</td>
<td>$-52.8 \pm 27.7^*$</td>
</tr>
<tr>
<td>Δ IAUC$_{60}$ (%)</td>
<td>$-27.9 \pm 15.4^*$</td>
<td>$-55.5 \pm 11.1^{**}$</td>
<td>$-58.1 \pm 15^{**}$</td>
</tr>
<tr>
<td>Δ Ktrans (%)</td>
<td>$-46.6 \pm 27.6^*$</td>
<td>$-63.9 \pm 31.2^{**}$</td>
<td>$-78.2 \pm 23.9^{**}$</td>
</tr>
</tbody>
</table>

Table 3. Changes in DCE-MRI parameters after bevacizumab infusion

DCE-MRI = dynamic contrast enhancement-magnetic resonance imaging

*$p <0.05$, statistically significant as compared with baseline.

$^{**}p <0.05$, statistically significant as compared with 2.5 hours.

Figure 1. Probabilities of (A) PFS, (B) CNS-PFS, and (C) OS

- Tumour vascular normalization effects were more obvious at 24 hours compared with that at 2.5 hours after bevacizumab infusion.
- By giving bevacizumab one day before etoposide and cisplatin, the BEEP regimen appears highly effective in brain metastases of breast cancer progressing from previous whole brain radiotherapy.
- Further studies of this concept are warranted.

Key conclusions

Background
Tamoxifen given for five years after surgery for estrogen receptor (ER)-positive early breast cancer reduces recurrence and breast cancer mortality and is more effective than treatment for shorter durations. However, it is uncertain what advantage there may be to extending tamoxifen treatment to 10 years. At ECC 2013, Rea and colleagues presented the overall and subgroup findings of the aTTom study.1

Study design
• A total of 6,953 women with ER+ (n = 2,755) or ER-untested (n = 4,198) invasive breast cancer from 176 U.K. centres, who were relapse-free after five years of prior adjuvant tamoxifen, were randomized to stop tamoxifen or continue to year 10.
• Annual follow-up recorded compliance, recurrence, mortality, and hospital admissions.

Key findings
• Allocation to continue tamoxifen to year 10 reduced breast cancer recurrence compared with that after just five years of tamoxifen (10 vs. 5 years of tamoxifen: 614/3,470 vs. 711/3,486; rate ratio (RR) = 0.86 [95% CI: 0.77–0.96], p = 0.006). (Figure 1)
• This reduction in breast cancer recurrence was time dependent, based on the number of years from the start of treatment (10 vs. 5 years of tamoxifen): (Figure 2)
  ◦ Years 5–6: RR = 1.11 (95% CI: 0.89–1.37);
  ◦ Years 7–9: RR = 0.85 (95% CI: 0.71–1.02);
  ◦ Years 10–14: RR = 0.72 (95% CI: 0.59–0.87);
  ◦ Years 15+: RR = 0.83 (95% CI: 0.56–1.24).
• Overall, longer treatment trended towards reduced breast cancer mortality, but was not significant (10 vs. 5 years of tamoxifen: 426 vs. 466 breast cancer deaths; RR = 0.91 [95% CI: 0.80–1.04], p = 0.2). (Figure 3)
  ◦ Compared with breast cancer mortality in the 5-year tamoxifen group, a reduction in breast cancer mortality with 10 years of tamoxifen was only observed at 10–14 years from the start of treatment (RR = 0.78 [95% CI: 0.64–0.95]). (Figure 3)
• All-cause mortality was not significantly different between the 10-year and 5-year groups (944 vs. 995 deaths; RR = 0.95 [95% CI: 0.87–1.04], p = 0.2).
• In the 10-year tamoxifen group, there were more endometrial cancers (102 vs. 47, p <0.0001), but there was no difference in the number of endometrial cancer deaths between the two groups (10 vs. 5 years of tamoxifen: 31 vs. 23, p = 0.27).

Figure 1. Breast cancer recurrence by duration of treatment with tamoxifen
### Key conclusions

- **aTTom confirms the recently reported findings of the complementary ATLAS study** — continuing tamoxifen to year 10 rather than just to year 5 produces further reductions in breast cancer recurrence.

- **Continuing tamoxifen beyond 5 years also reduces breast cancer mortality:** while there is no effect in years 5–9, there is a 22% reduction after year 10.

- **Endometrial cancer risk is increased with longer tamoxifen,** but the observed increase in endometrial cancer deaths is numerically small and statistically non-significant.

- **The magnitude of the benefit of continuing tamoxifen beyond 5 years makes this an appropriate option for almost all women with ER-positive early breast cancer.**

An Interview with Dr. Sunil Verma on the First Results from the TH3RESA Study at ECC 2013

Following the 2013 European Cancer Congress (ECC) in Amsterdam, New Evidence interviewed Dr. Sunil Verma for his impressions of the first results from the TH3RESA study, which evaluated the efficacy and safety of trastuzumab emtansine compared with those of a treatment of physician’s choice (TPC) for patients with advanced breast cancer.

New Evidence: Please describe the study design of TH3RESA.

Dr. Verma: TH3RESA was a multi-national, phase III study investigating the efficacy and safety of trastuzumab emtansine as compared with those of TPC for patients with previously treated human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer. Around 600 patients were randomized in a 2:1 manner to trastuzumab emtansine and TPC, respectively.

New Evidence: What were the main characteristics of the patient population in this study?

Dr. Verma: The main characteristics of the patient population in the TH3RESA study were that patients had to have been previously treated with at least two or more HER2-directed therapies, including trastuzumab and lapatinib, and had to have received prior treatment with a taxane. This was a more heavily pretreated population compared with patients who were in the EMILIA study.

New Evidence: Given that the control arm for TH3RESA comprised treatment of physician’s choice (TPC), what were the main treatments that physicians chose to use?

Dr. Verma: In the TPC arm, about 83% of patients received combination therapy that included a HER2-directed agent, which was primarily composed of chemotherapy plus trastuzumab (68.5%). The rest of the HER2-directed therapies in the TPC arm were lapatinib plus trastuzumab (10.3%), hormonal therapy plus trastuzumab (1.6%), or chemotherapy plus lapatinib (2.7%). Approximately 17% of patients received single-agent chemotherapy. The most commonly used chemotherapies were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.

New Evidence: Does this represent what is practised in Canada for this patient population?

Dr. Verma: It depends on where you live in Canada. In Ontario, for instance, physicians are only allowed two lines of anti-HER2 therapy in the metastatic setting. In this case, patients in Ontario who have fulfilled the same criteria as the TH3RESA study (i.e., ≥2 lines of HER2-directed therapy) would likely receive single-agent chemotherapy. In some other parts of the country, physicians have access to more than two lines of anti-HER2 therapy, and those same patients would likely receive a combination of chemotherapy plus an anti-HER2 agent.
New Evidence: How did the fact that many different treatments were allowed as comparators affect the interpretation of the results?

Dr. Verma: In many ways, this was a very practical study because patients in the comparator arm were receiving treatments that would normally be offered to them. This was also an important study because one of the discussion points for the EMILIA study was not knowing how the results for trastuzumab emtansine would have compared if patients in the control arm had received chemotherapy plus trastuzumab instead of capcitabine plus lapatinib. With TH3RESA, we can now make that comparison, and having that flexibility allows the interpretation of the results to be even more practical.

New Evidence: Please describe the efficacy results for trastuzumab emtansine versus TPC, in terms of the coprimary end points of progression-free survival (PFS) and overall survival (OS).

Dr. Verma: The analysis presented at ECC 2013 showed that median PFS improved from 3.3 months with TPC to 6.2 months with trastuzumab emtansine, with a hazard ratio (HR) of 0.528, which was statistically significant. Across the patient subgroups, PFS benefit with trastuzumab emtansine was still observed regardless of age, race, world region, baseline performance status, estrogen receptor status, visceral involvement of disease, number of prior lines of therapy, and the presence or absence of brain metastasis at baseline. Furthermore, trastuzumab emtansine significantly prolonged median PFS, from 3.2 to 6.2 months, when compared with those who received a trastuzumab-containing regimen as part of the TPC arm.

The first interim OS analysis was also presented, although data are still immature. The median OS was 14.9 months for TPC and was not yet reached for trastuzumab emtansine. The HR was 0.552 (95% CI: 0.369–0.826; \( p = 0.0034 \)), but the efficacy stopping boundary (HR <0.363 or \( p <0.0000013 \)) was not crossed.

New Evidence: How did the objective response rate (ORR) of the trastuzumab emtansine arm compare with that of the TPC arm?

Dr. Verma: The ORR by investigator assessment was 8.6% with TPC and significantly improved to 31.3% with trastuzumab emtansine, a difference of 22.7% (\( p <0.0001 \)).

New Evidence: Given that 80% of patients in the TPC arm received a trastuzumab-based regimen, were the efficacy results for trastuzumab emtansine expected?

Dr. Verma: Yes, the results were what we had expected; trastuzumab emtansine offers patients with HER2-positive advanced breast cancer improved outcomes compared to those with chemotherapy plus an anti-HER2 agent, regardless of which anti-HER2 agent is used. The data from this trial and EMILIA² have shown that, for patients who have progressed on chemotherapy plus trastuzumab or lapatinib, physicians should consider trastuzumab emtansine.

New Evidence: How did the general safety profile of trastuzumab emtansine compare with that of TPC in this trial?

Dr. Verma: Overall, the safety profile was more favourable with trastuzumab emtansine than with TPC. Fewer grade \( \geq 3 \) adverse events (AEs) were reported in patients who received trastuzumab emtansine compared with those who received TPC, with incidences of 32% vs. 43%, respectively. Also, the trastuzumab emtansine arm reported fewer AEs that led to treatment discontinuation or to dose reduction compared with those in the TPC arm. Overall, trastuzumab emtansine was better tolerated than TPC. However, the key AEs that were observed with trastuzumab emtansine included thrombocytopenia and liver transaminase elevations.
**New Evidence:** Was the safety profile for trastuzumab emtansine in this trial expected based on previous trials with trastuzumab emtansine in HER2-positive metastatic breast cancer?

**Dr. Verma:** Yes, the observed safety profile of trastuzumab emtansine in this trial was consistent with what has been previously observed. Trastuzumab emtansine has an excellent safety profile. That being said, it is still important to monitor platelets and liver function tests of patients who are receiving this drug and physicians need to modify the dosing based on these parameters.

**New Evidence:** What main conclusions can be drawn from the TH3RESA study, based on the data that were presented at ECC 2013?

**Dr. Verma:** The results of the TH3RESA study have reaffirmed the conclusions from the EMILIA study. In other words, trastuzumab emtansine provided consistent efficacy benefit and tolerability compared with chemotherapy plus an anti-HER2 agent, which in this case was mainly trastuzumab. Furthermore, the benefit with trastuzumab emtansine was observed in patients who had prior therapy with trastuzumab, lapatinib, and a taxane, demonstrating the efficacy of trastuzumab emtansine for treating HER2-positive advanced breast cancer in and beyond the second line of therapy.

**New Evidence:** How would you use trastuzumab emtansine in your clinical practice and where do you see trastuzumab emtansine best fitting into the lines of treatment for HER-positive breast cancer based on the results from TH3RESA as well as the previously reported results from the EMILIA study?

**Dr. Verma:** Trastuzumab emtansine is not currently funded, but it has been approved by Health Canada. At present, we have two key patient subgroups who are candidates for this therapy. The first is for patients who had received adjuvant trastuzumab but then relapsed within six months of completion of their trastuzumab-containing therapy; I would consider using trastuzumab emtansine in the first-line setting for these patients. The second is for patients who have progressed on first-line anti-HER2 therapy; I would consider using trastuzumab emtansine in the second-line setting. The results of EMILIA are very much in line with this.

The role for trastuzumab emtansine in the first-line setting is still being assessed in the MARIANNE study, which is comparing trastuzumab emtansine plus pertuzumab vs. trastuzumab emtansine plus placebo vs. trastuzumab plus a taxane. Also, we do not currently have prospective data for the use of trastuzumab emtansine after patients have received chemotherapy plus trastuzumab and pertuzumab, but based on the treatment profile of these agents, trastuzumab emtansine would also make a very reasonable second-line option for these patients.


**Indications & clinical use**

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. The indication is based on complete response rate. The duration of remission has not been determined. The response rate of other acute myelogenous leukemia subtypes has not been examined. There is limited clinical data on use in geriatric patients. Caution is needed in these patients. Safety and effectiveness in patients <5 years of age have not been studied. There is limited clinical data on use in pregnancy. See Contraindications and precautions.

**Contraindications**

- Pregnancy and nursing mothers.

**Most serious warnings and precautions**

- APL Differentiation Syndrome: Can be fatal. At first signs or symptoms, high-dose steroids (dexamethasone 10 mg intravenously 60 mg or 15 mg intravenously 80 mg) 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, embryotoxicity 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) in patients; serious arsenic toxicity in the obese, and for hypoxia and development of pulmonary infiltrates and pleural effusion in all patients.

**For more information**

Please consult the Product Monograph at http://www.lundbeck.com/upload/ca/en/files/pdf/pm/Trisenox.pdf for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 514-844-8515 or 1-800-586-2325.

† Based on results from two open-label, single-arm trials, one multicentre (n=40) and one single-centre (n=10). Trisenox 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 0.15 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.
At Roche, we’ve had HER2-positive breast cancer in our sights for years. As with any cancer, when it metastasizes, this aggressive form of the disease can pose an even greater challenge. For these reasons, and for all the people this condition affects, Roche is committed to research in HER2-positive metastatic breast cancer.

Clinical use not discussed elsewhere in the piece:
A validated test is required to identify EGFR mutation status. Clinical effectiveness was based on progression-free survival and objective response. No overall survival benefit was demonstrated. Safety and efficacy of Giotrif have not been established in patients with EGFR mutations other than exon 19 deletions and the exon 21 L858R point mutation. Close monitoring and proactive management of diarrhea is essential for successful Giotrif treatment. In clinical trials, more grade ≥3 adverse events were reported for patients ≥65 years than <65 years. Treatment of children or adolescents with Giotrif is not recommended.

Most serious warnings and precautions:

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

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

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

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

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

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

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

LEUKEMIAS AND LYMPHOMAS
Balancing Toxicity and Efficacy in the Treatment of High-Risk, Elderly, and Unfit Patients with CLL

BREAST CANCER
New Strategies in the Treatment of HER2-Positive Breast Cancer

Updates in APL: Reducing Early Death and Therapy-Related Myeloid Neoplasms and Improving First-Line Treatments

Interviews with Dr. Matthew Seftel and Dr. Sunil Verma

A Delicate Balance
Between Efficacy and Toxicity