INSIDE THIS ISSUE

BREAST CANCER
New HER2-targeted Agents are Efficacious and Well Tolerated

LUNG CANCER
Afitinib and Dacomitinib — Irreversible EGFR-TKIs Show Promise for the Treatment of NSCLC

LEUKEMIAS AND LYMPHOMAS
New Protocols for the Treatment of Indolent Lymphomas, AML, and Myelodysplastic Syndrome

MELANOMA
Novel Agents Offer a Renewed Sense of Hope for the Treatment of Melanoma

A Closer Look
Emerging Data in Oncology

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

Our September 2012 issue presents coverage from the following key conferences that took place over the past six months: the 4th Annual Canadian Conference On Lymphoproliferative Disorders (CCOLD), the 38th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT), the Annual Meeting of the Canadian Blood and Marrow Transplant Group (CBMTG), and the Annual Meeting of the American Society of Clinical Oncology (ASCO). This issue reports on key studies of novel agents and treatment strategies for breast cancer, leukemias and lymphomas, and lung cancer. It also provides the Canadian oncologist’s perspective on recent findings in the breast cancer and hemato-oncology fields, as well as an article on the clinical management of metastatic melanoma. In addition, this issue has spotlight articles by Dr. Michael Hallek and the Lymphoma Foundation Canada (LFC) on treatments for leukemias and lymphomas. We would like to thank Dr. Sunil Verma and Dr. Douglas Stewart for their Canadian perspectives. We would also like to thank Dr. Kimberly Blackwell, Dr. Barbara Eichhorst, Dr. Michael Hallek, Dr. Tony Mok, Dr. Arnon Nagler, and Dr. Mathias Rummel for their investigator commentaries.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research. Slide presentations on various topics are available for download.
New targeted agents demonstrate greater efficacy and tolerability for the treatment of HER2-positive breast cancer

- Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer (Blackwell KL, et al. ASCO 2012: Abstract LBA1)
- Cardiac tolerability of pertuzumab compared with placebo when combined with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study (Ewer M, et al. ASCO 2012: Abstract 533^)
- An open-label, randomized, phase III trial comparing taxane-based chemotherapy with lapatinib or trastuzumab as a first-line therapy for women with HER2-positive metastatic breast cancer (Gelman KA, et al. ASCO 2012: Abstract LBA671)
- Cardiac safety in a phase II study of trastuzumab emtansine (T-DM1) following anthracycline-based chemotherapy as adjuvant or neoadjuvant therapy for early-stage HER2-positive breast cancer (Dang CT, et al. ASCO 2012: Abstract S32)

Canadian perspective by Dr. Sunil Verma

Investigator Commentary

An interview with Dr. Kimberly Blackwell on the implications of the EMILIA study for patients with metastatic breast cancer

Investigator Commentaries

An Interview with Dr. Mathias Rummel on the use of bendamustine in CLL, iNHL, and MCL

An Interview with Dr. Barbara Eichhorst on the use of bendamustine in CLL

Spotlight on Fludarabine-refractory CLL

Management of Fludarabine Refractory Patients with CLL: Summary of the Presentation by Dr. Michael Hallek at CCOLD

^Denotes abstracts that were granted an exception in accordance with ASCO’s Conflict of Interest Policy.
Investigator Commentary

63
An Interview with Dr. Michael Hallek on the treatment of unfit patients with CLL

66
Intravenous Busulfan Is a Safe and Effective Option for Conditioning Regimens Prior to Transplant in Acute Myeloid Leukemia

• High-dose chemotherapy followed by allogeneic stem cell transplantation in high-risk relapsed and refractory aggressive NHL: results of a prospective study of the German high-grade NHL study group (Glass B, et al. ASCO 2012: Abstract 8004)

• Allogeneic stem cell transplantation for patients over age 65 years with acute myeloid leukemia and myelodysplastic syndrome (Conter HJ, et al. ASCO 2012: Abstract 6529)


• Intravenous busulfan plus cyclophosphamide versus total body irradiation plus cyclophosphamide conditioning for alloSCT from matched unrelated donors: a survey on behalf of the ALWP-EBMT (Nagler A, et al. EBMT 2012: Abstract O345)

• Intravenous versus oral busulfan administration results into a dramatic reduction of veno-occlusive disease (VOD) incidence in a randomized trial assessing fresh frozen plasma plus heparin versus heparin-alone as anti-VOD prophylaxis (Yannaki E, et al. EBMT 2012: Abstract P633)

• Busulfan-based versus total body irradiation-based myeloablative conditioning in patients with acute myeloid leukemia: reduction of acute GVHD incidence, mucositis, and duration of hospitalization (Bucher C, et al. EBMT 2012 : Abstract O121)

Investigator Commentaries

76
An Interview with Dr. Arnon Nagler on his study examining intravenous busulfan-based conditioning prior to autologous transplant in AML

80
An Interview with Dr. Arnon Nagler on his study comparing intravenous busulfan plus cyclophosphamide versus total body irradiation plus cyclophosphamide conditioning for allogeneic transplant in AML

Spotlight on Lymphoma Foundation Canada

82

LUNG CANCER

86
The Irreversible EGFR-TKIs Afatinib and Dacomitinib Show Promise for the Treatment of NSCLC


• Afatinib monotherapy in patients with metastatic squamous cell carcinoma of the lung progressing after erlotinib/gefitinib and chemotherapy: interim subset analysis of the LUX-Lung 5 trial (Kim JH, et al. ASCO 2012: Abstract 7558)

• First-line dacomitinib (PF-00299804), an irreversible pan-HER tyrosine kinase inhibitor, for patients with EGFR-mutant lung cancers (Kris MG, et al. ASCO 2012: Abstract 7530)

• An interim analysis of the LUX-Lung 5 trial: afatinib monotherapy in metastatic NSCLC following progression on chemotherapy and erlotinib/gefitinib (Schuler MH, et al. ASCO 2012: Abstract 7557)

Investigator Commentary

102
An Interview with Dr. Tony Mok on the LUX-Lung 3 study

MELANOMA

108
Novel Agents Offer a Renewed Sense of Hope for the Treatment of Melanoma

• Canadian Perspective on the Clinical Management of Metastatic Melanoma
Contributors

Canadian Perspectives

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, and Lancet Oncology.

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

Investigator Commentary

Kimberly L. Blackwell, MD
Dr. Kimberly Blackwell is a medical oncologist, Professor of Medicine, and Assistant Professor of Radiation Oncology at Duke University Medical Center in Durham, North Carolina, U.S. She is the Director of the Breast Cancer Program at the Duke Cancer Institute and serves on the national Scientific Advisory Board of the Susan G. Komen for the Cure. She received her undergraduate degree in bioethics at Duke University, and her medical degree at Mayo Clinic Medical School. Afterwards, Dr. Blackwell completed an internal medicine internship and residency, and a hematology-oncology fellowship at Duke University Medical School. In addition to maintaining an active clinical practice, she has served as a principal investigator on many clinical trials in breast cancer. Her research interests include breast cancer angiogenesis, breast cancer in younger women, endocrine therapy, and HER2-targeted therapy. Dr. Blackwell has authored or co-authored over 40 articles or book chapters appearing in journals such as Clinical Cancer Research, the Journal of Clinical Oncology, Cancer, Radiation Research, and Molecular Cancer Therapeutics. In the past year, she has reviewed for several grant committees and peer-reviewed journals.

Tony Mok, MD
Dr. Tony Mok studied medicine at the University of Alberta and subsequently completed his fellowship training at the Princess Margaret Hospital in Toronto. After practising oncology and internal medicine for seven years in Toronto, Dr. Mok became an Assistant Professor in the Department of Clinical Oncology at the Chinese University of Hong Kong in 1996. He became a full professor in 2007. He holds an honorary professorship at the Guangdong Provincial People’s Hospital in Guangdong, China, and a guest professorship at the Peking University School of Oncology. He is heavily involved in several professional societies and committees, including being President-elect of the International Association for the Study of Lung Cancer. Dr. Mok is the Associate Editor of several journals and has published over 130 articles in peer-reviewed journals.
Mathias J. Rummel, MD, PhD

Mathias J. Rummel is the head of the Department for Hematology at the Clinic for Hematology and Medical Oncology at the Justus-Liebig University-Hospital, Giessen, Germany. Professor Rummel studied medicine at J.W. Goethe University Hospital in Frankfurt, Germany, obtaining his licence to practice medicine in 1995. Following this, he completed his doctoral degree and residency, obtained board certification in internal medicine, and was awarded his PhD from J.W. Goethe University Hospital. Professor Rummel’s current research focuses on novel treatment approaches in hematological malignancies, most notably follicular and other indolent lymphomas as well as hairy cell leukemia and also immune thrombocytopenic purpura (ITP). He is the chair of the Study group indolent Lymphomas (StiL) and principal investigator of several ongoing clinical trials in leukemias, lymphomas, and ITP. He is actively involved in a number of professional scientific societies, he is a reviewer for a number of journals, and has several published book chapters and papers to his credit.

Barbara F. Eichhorst, MD

Dr. Eichhorst graduated from the University of Munich School of Medicine in 1997, having completed a doctoral thesis in the field of hematology that focused on evaluating the signal transduction pathways of Hodgkin cells. She became a consultant in internal medicine after finishing an internship at Klinikum Grosshadern in the Department of Internal Medicine III at the University of Munich. Shortly after its founding, Dr. Eichhorst became a leading member of the German CLL Study Group and has served as the group’s secretary since 2005. She has published several papers on the treatment of chronic lymphocytic leukemia (CLL) and has acted as principal investigator for several phase II and III clinical trials that evaluated treatment optimization in CLL. Dr. Eichhorst is currently an Associate Professor at the University of Cologne and a consultant in hematology and internal oncology at the University Hospital of Cologne.

Arnon Nagler, MD, MSc

Arnon Nagler is Professor of Medicine at the Tel Aviv University, Tel Aviv, Israel, and the Director of both the Division of Hematology and the Bone Marrow Transplantation and Cord Blood Bank at the Chaim Sheba Medical Center, Tel Hashomer, Israel. Dr. Nagler received his medical training at the Hebrew University-Hadassah Medical School, Jerusalem, Israel, specializing in hematology at the Rambam Medical Center, Haifa, Israel. He carried out a postdoctoral research fellowship in hematology and bone marrow transplantation at Stanford University Hospital in Palo Alto, California, U.S. Dr. Nagler has been working in the fields of bone marrow transplantation for hematological malignancies, including non-Hodgkin lymphoma, and hemato-oncology, for the last 20 years. In Israel, Dr. Nagler established the first public cord blood bank and performed the first cord blood transplantations from related and unrelated donors in genetic and malignant hematological disease. His main clinical interests include stem cells, bone marrow transplantation, hematological malignancies, cord blood biology, and adoptive cell-mediated immunotherapy. Dr. Nagler has written numerous articles, reviews, and chapters for peer-reviewed journals, and is the principal investigator for a number of clinical studies. He serves on the Editorial Board of several journals and is a Section Editor for Leukemia.

Michael Hallek, MD

Dr. Michael Hallek is Professor of Medicine, and Director and Chair of the Department of Internal Medicine I at the University of Cologne in Cologne, Germany, where he oversees internal medicine, hematology, hemostaseology, oncology, intensive care, infectious diseases, and immunology. From 1994–2005, Dr. Hallek was head of the Gene Therapy Program at the Gene Center of the University of Munich and of the Clinical Cooperation Group for Gene Therapy at the National Centre for Research on Environment and Health (GSF) in Munich. In 2007, Dr. Hallek was appointed Director of the Center of Integrated Oncology (CIO), the joint comprehensive cancer centre of the Universities of Cologne and Bonn. Since 1994, he has been Chair of the German CLL Study Group. Dr. Hallek is the principal investigator for the CLL-8 clinical trial.
BREAST CANCER
New targeted agents demonstrate greater efficacy and tolerability for the treatment of HER2-positive breast cancer

This year in Canada, breast cancer is expected to remain the most commonly diagnosed form of female malignancy, accounting for 26% of all new cases, and the second leading cause of cancer death in women.1 Approximately 20% to 25% of breast cancers are classified as human epidermal growth factor receptor 2 (HER2)-positive, which has historically been associated with an aggressive phenotype and a poor prognosis.2

The relatively recent advent of a humanized monoclonal antibody that binds and inhibits HER2, trastuzumab, has transformed therapy and improved outcomes for patients with HER2-positive breast cancer.2

New HER2-targeted agents have been developed that work through different mechanisms of action. For instance, trastuzumab emtansine (T-DM1) is a modification of trastuzumab that stably links the antibody to a potent antimicrotubule agent, DM1, which is selectively delivered to and subsequently released within HER2-positive breast cancer cells.3 A different humanized monoclonal antibody, pertuzumab, is the first in a new class of drugs known as HER2 dimerization inhibitors.4 Pertuzumab inhibits HER2 signalling by targeting the extracellular domain involved in its dimerization with all other members of the HER family of receptors. The small molecular inhibitor, lapatinib, is a dual tyrosine kinase inhibitor that binds to an intracellular domain common to the HER1 and HER2 proteins, thus preventing receptor auto-phosphorylation and signalling.5

At the 2012 ASCO Annual Meeting, results were presented from several ongoing clinical trials testing the efficacy and safety of these new HER2-directed agents as complementary or alternative therapies to trastuzumab in various breast cancer settings. This article summarizes six of those presentations.

• Primary results from the phase III EMILIA trial revealed superior efficacy and safety of T-DM1 vs. capecitabine and lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

• Analysis of safety data from the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study provided evidence that combining pertuzumab with trastuzumab and docetaxel in patients with HER2-positive MBC did not increase the frequency of cardiac adverse events.

• In addition, patients in the CLEOPATRA trial reported no detrimental effects of pertuzumab with trastuzumab and docetaxel on the health-related quality-of-life assessment.

• Interim analysis of an open-label, phase III trial indicated that taxane-based chemotherapy was significantly more effective when combined with trastuzumab than with lapatinib as a first-line therapy for women with HER2-positive MBC.

• Evaluation of the HER2-directed component of neo-adjuvant therapy for operable breast cancer showed lapatinib was just as effective as trastuzumab. Combining the two agents may be more effective for the patient population with HER2-positive tumours.

• In a phase II study of adjuvant or neoadjuvant therapy for early-stage HER2-positive breast cancer, T-DM1 following anthracycline-based chemotherapy was not associated with a significant development of cardiac toxicity.

Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer

Background
The clinical efficacy and safety of the human epidermal growth factor receptor 2 (HER2)-directed treatments, trastuzumab emtansine (T-DM1) and lapatinib in combination with capecitabine, for metastatic breast cancer (MBC) have been well studied. Currently, the only approved combination therapy for trastuzumab-refractory HER2-positive MBC is capecitabine and lapatinib. Primary results from the EMILIA trial build on findings from two phase II trials in which T-DM1 was well tolerated and effective in patients with MBC who had received prior HER2-directed treatments and chemotherapies. A retrospective analysis of archival tumour samples from those same studies indicated that confirmed HER2-positive status was associated with a higher objective response rate (ORR).¹ EMILIA is designed to compare the safety and efficacy of T-DM1 vs. capecitabine plus lapatinib, in order to determine the viability of T-DM1 as an alternative therapy for patients with trastuzumab-refractory HER2-positive MBC.²

Study design
- EMILIA is a multicentre, international, randomized, open-label, two-arm, phase III clinical trial (NCT00829166).
- Patients (n = 980) who were first-, second-, or third-line with centrally confirmed HER2-positive locally advanced breast cancer (LABC) or MBC were randomized and treated in this trial.
- All patients had tumours that had either progressed while receiving treatment for metastatic disease or recurred within six months of completing adjuvant trastuzumab and had received a prior taxane and trastuzumab but had received no prior treatment with either capecitabine or lapatinib.
- The results of this trial, which enrolled patients from February 2009 to October 2011, are reported as of the cut-off date of January 14, 2012, although some patients in each group (capecitabine plus lapatinib [n = 125] and T-DM1 [n = 182]) were still receiving treatment.
- Patients received one of the following treatments until disease progression or unmanageable toxicity:
  - T-DM1 (n = 490) at a dosage of 3.6 mg/kg intravenously once every three weeks (q3w);
  - Capecitabine plus lapatinib (n = 488) at the respective dosages for capecitabine (1,000 mg/m² orally twice a day, on days 1–14 q3w) and lapatinib (1,250 mg orally each day).
- The primary endpoints were progression-free survival (PFS) assessed by an independent review committee (IRC), overall survival (OS), and safety.
- The secondary endpoints were PFS assessed by the investigator, objective response rate (ORR), duration of response (DOR), and the patient-reported outcome of time to symptom progression.
- The targeted number of events to be observed (n = 508) for the final analysis of PFS was met at the time of reporting.
- Final analysis of OS was not yet mature, and is planned when 632 events have been observed.

EMILIA study design

**HER2+ (central)**
LABC or MBC (n = 980)
Prior taxane and trastuzumab
Progression on metastatic tx or within 6 months of adjuvant tx

**Capecitabine**
1,000 mg/m² orally bid, days 1–14 q3w
+ Lapatinib
1,250 mg/day orally qd

**T-DM1**
3.6 mg/kg iv q3w

1:1

PD
PD

bid = twice a day; HER2+ = human epidermal growth factor receptor 2-positive; iv = intravenously; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; PD = progressive disease; q3w = dosage given every 3 weeks; qd = every day; T-DM1 = trastuzumab emtansine; tx = treatment
Key findings

• After a median follow-up of 12.4 months for capecitabine plus lapatinib and 12.9 months for T-DM1, T-DM1 significantly extended the duration of PFS, as assessed by the IRC, by 3.2 months compared with capecitabine plus lapatinib (9.6 vs. 6.4 median months, hazard ratio [HR] = 0.650; 95% CI [confidence interval]: 0.55–0.77; p <0.0001).

• The results of PFS assessed by the investigator (HR = 0.658; 95% CI: 0.56–0.77; p <0.0001) were consistent with the assessment of the IRC. (Figure 1)

• Subgroup analyses of PFS by patients’ baseline characteristics revealed T-DM1 was better than capecitabine plus lapatinib for nearly every category, except for those who were 65 years or older (HR = 1.06; 95% CI: 0.68–1.66). (Table 1)

• Patients with presence of visceral disease (n = 138) showed improved PFS with T-DM1 versus capecitabine plus lapatinib, however, this did not reach statistical significance (HR = 0.96; 95% CI: 0.71–1.30).

• Patients in the T-DM1 group had a statistically significant increase in ORR over those in the capecitabine plus lapatinib group (43.6% vs. 30.8%, a difference of 12.7% [95% CI: 6.0–19.4%]; p = 0.0002). (Figure 2)

• The DOR was longer in patients treated with T-DM1 compared with capecitabine plus lapatinib (12.6 months [95% CI: 8.4–20.8] vs. 6.5 months [95% CI: 5.5–7.2]). However, the difference was not statistically analyzed due to the hierarchal design of the trial. (Figure 2)

• Although OS results are not yet mature, an interim analysis showed a trend favouring T-DM1, with a median OS that had not yet been reached, compared with 23.3 months for capecitabine plus lapatinib (HR = 0.621 [95% CI: 0.48–0.81]; p = 0.0005). (Figure 3)

• At one-year and two-year follow-ups, OS trends were in favour of T-DM1 (one-year: 84.7% vs. 77.0%; two-year: 65.4% vs. 47.5%). The efficacy stopping boundary had not yet been reached (HR = 0.617 or p = 0.0003).

Figure 1. Progression-free survival by independent and investigator review

![Graph showing progression-free survival by independent and investigator review.](image-url)
Table 1. PFS subgroup analyses

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Total n</th>
<th>X + L Median, months</th>
<th>T-DM1 Median, months</th>
<th>HR (95% CI)</th>
<th>T-DM1 better</th>
<th>X + L better</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>991</td>
<td>6.4</td>
<td>9.6</td>
<td>0.66 (0.56–0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>World region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>270</td>
<td>5.7</td>
<td>8.5</td>
<td>0.70 (0.51–0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>317</td>
<td>6.4</td>
<td>10.9</td>
<td>0.56 (0.41–0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>404</td>
<td>6.9</td>
<td>9.6</td>
<td>0.73 (0.56–0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of prior chemotherapeutic regimens for MBC or unresectable LABC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>609</td>
<td>6.7</td>
<td>10.3</td>
<td>0.68 (0.55–0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>382</td>
<td>5.7</td>
<td>8.5</td>
<td>0.63 (0.49–0.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of visceral disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>669</td>
<td>5.7</td>
<td>9.6</td>
<td>0.55 (0.45–0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>322</td>
<td>10.2</td>
<td>8.5</td>
<td>0.96 (0.71–1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>853</td>
<td>6.0</td>
<td>9.8</td>
<td>0.62 (0.52–0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>138</td>
<td>8.1</td>
<td>7.0</td>
<td>1.06 (0.68–1.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER and PR status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+</td>
<td>545</td>
<td>7.1</td>
<td>9.0</td>
<td>0.72 (0.58–0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER– and PR–</td>
<td>426</td>
<td>5.6</td>
<td>10.3</td>
<td>0.56 (0.44–0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Line of therapy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>118</td>
<td>5.7</td>
<td>10.8</td>
<td>0.51 (0.30–0.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>361</td>
<td>6.8</td>
<td>9.6</td>
<td>0.69 (0.53–0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>512</td>
<td>6.5</td>
<td>9.0</td>
<td>0.69 (0.55–0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER– = estrogen receptor negative; ER+ = estrogen receptor positive; HR = hazard ratio; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; n = number of patients; PR– = progesterone receptor negative; PR+ = progesterone receptor positive; T-DM1 = trastuzumab emtansine; X + L = capecitabine and lapatinib

* Defined as any systemic therapy, including endocrine or chemotherapy

- Time-to-symptom progression, a patient-reported outcome, occurred later in the T-DM1 group (7.1 vs. 4.6 median months, HR = 0.80; 95% CI: 0.67–0.95; p = 0.0121). (Table 2)

- A total of five AEs leading to death on treatment occurred in the capecitabine plus lapatinib arm compared with one in the T-DM1 arm.

- A higher percentage of patients in the capecitabine plus lapatinib group compared with the T-DM1 group experienced grade ≥3 non-hematologic AEs of nearly every kind, except for increased aspartate aminotransferase and alanine aminotransferase, which were higher in the T-DM1 group. (Table 4)

- The safety data for grade ≥3 hematologic AEs revealed that a greater percentage of patients in the capecitabine plus lapatinib group experienced neutropenia and febrile neutropenia, while a greater percentage of the T-DM1 group experienced anemia and thrombocytopenia.

Table 2. Patient-reported outcomes: time to symptom progression

<table>
<thead>
<tr>
<th>Time to symptom progression</th>
<th>X + L (n = 445)</th>
<th>T-DM1 (n = 450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>4.6</td>
<td>7.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80 (0.67–0.95)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0121</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; n = number of patients; T-DM1 = trastuzumab emtansine; X + L = capecitabine and lapatinib

- Overall, the number of all-grade adverse events (AEs) was similar between the two treatment groups. However, the percentage of patients experiencing grade ≥3 AEs (57.0% vs. 40.8%) and AEs leading to treatment discontinuation (10.7% vs. 5.9%) were higher in those treated with capecitabine plus lapatinib. (Table 2)
**Figure 2. Objective response rate and duration of response**

**ORR**

Difference: 12.7% (95% CI: 6.0–19.4); \( p = 0.0002 \)

<table>
<thead>
<tr>
<th></th>
<th>X + L</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>30.8%</td>
<td>43.6%</td>
</tr>
<tr>
<td>120/389</td>
<td>173/397</td>
<td></td>
</tr>
</tbody>
</table>

**DOR**

Median, months (95% CI)

- X + L: 6.5 (5.5–7.2)
- T-DM1: 12.6 (8.4–20.8)

**Figure 3. Overall survival: interim analysis**

Median (months) No. events

<table>
<thead>
<tr>
<th></th>
<th>X + L</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.3</td>
<td>129</td>
<td>NR 94</td>
</tr>
</tbody>
</table>

Stratified HR = 0.621 (95% CI: 0.48–0.81); \( p = 0.0005 \)

Efficacy stopping boundary: \( p = 0.0003 \) or HR = 0.617

CI = confidence interval; ORR = objective response rate; DOR = duration of response; No. = number; T-DM1 = trastuzumab emtansine; X + L = capecitabine and lapatinib
Key conclusions

- T-DM1 offered a significant and clinically meaningful improvement in PFS over capecitabine and lapatinib.
- Other endpoints, such as ORR, DOR, and the safety profile, support T-DM1 as an active and well tolerated novel therapy for patients with HER2-positive MBC.

Cardiac tolerability of pertuzumab compared with placebo when combined with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study

**Background**
In patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC), therapy with anthracyclines, trastuzumab, and especially their concomitant administration, has been associated with cardiac dysfunction. Cardiotoxicity related to trastuzumab therapy is not well understood but, in contrast to anthracycline-induced cardiac injury, the majority of trastuzumab-related cardiac events are reversible after treatment discontinuation.

Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA), a phase III trial, tested the safety and efficacy of combining docetaxel and trastuzumab with pertuzumab, a HER2 dimerization inhibitor with a distinct binding epitope, or placebo as a first-line therapy for patients with HER2-positive MBC. The addition of pertuzumab significantly improved progression-free survival compared with placebo, from 12.4 to 18.5 months.1 At ASCO 2012, Ewer and colleagues presented their analysis of the CLEOPATRA study for cardiac tolerability of this novel treatment regimen.

**Study design**
- CLEOPATRA is a randomized, double-blind, placebo-controlled, phase III trial (NCT00567190).
- Patients (n = 808) with centrally confirmed HER2-positive MBC were enrolled; 804 patients were included in the safety population.
- Patients received one of two treatment regimens:
  - Pertuzumab plus trastuzumab and docetaxel (pertuzumab group); or
  - Placebo plus trastuzumab and docetaxel (placebo group).
- Study drugs were administered intravenously once every three weeks until disease progression or unmanageable toxicity:
  - Pertuzumab/placebo: 840 mg initial dose, 420 mg subsequent doses;
  - Trastuzumab: 8 mg/kg initial dose, 6 mg/kg subsequent doses;
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated (≥6 cycles recommended).
- Inclusion criteria were a baseline left ventricular ejection fraction (LVEF) ≥50%, no history of congestive heart failure, and no LVEF decline to <50% during/after prior trastuzumab.
- LVEF was assessed by echocardiography or multigated acquisition (MUGA) scanning at baseline, every nine weeks during treatment, at discontinuation, and up to three years thereafter.
- Adverse events (AEs) were monitored continuously and graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (NCI-CTCAE v3.0).
- Symptomatic left ventricular systolic dysfunction (LVSD) was reported as a serious adverse event and graded according to the NCI-CTCAE v3.0 and New York Heart Association (NYHA) classifications.
Key findings
- The incidence of any cardiac disorder (grade ≥1) as assessed by the investigators was similar for both groups: placebo group (16.4%) and pertuzumab group (14.5%).
- Two patients in the placebo arm of the study died due to myocardial infarction.
- LVSD grade ≥1 was the most frequent cardiac AE and more common in patients treated in the placebo group compared with the pertuzumab group (8.3% vs. 4.4%). (Table 1)

At the time of data cut-off for this analysis, eight of the 11 symptomatic LVSD events (seven events in the placebo group vs. four events in the pertuzumab group) had resolved; none were fatal.
- All patients who developed symptomatic LVSD had one or more potential cardiac risk factors (prior exposure to anthracyclines, trastuzumab, and radiation, smoking, diabetes, hypertension, etc.). (Table 2)

- Compared with the overall patient population, only prior anthracycline (hazard ratio [HR] = 2.21; 95% confidence interval [CI]: 1.27–3.86; p = 0.0053) and prior radiation (HR = 2.43; 95% CI 1.37–4.31; p = 0.0025) exposures were identified as potentially important risk factors in patients who developed symptomatic LVSD.
- However, prior anthracycline and radiation exposures had no influence on the overall analysis of the time to first asymptomatic or symptomatic LVSD event.
- LVEF decline to <50% and by ≥10% points from baseline was more frequent in the placebo group (6.6% vs. 3.8%), but most patients in both the placebo (72.0%) and pertuzumab (86.7%) groups recovered LVEF ≥50% on or after stopping treatment. (Table 3)

### Table 1. LVSD adverse events

<table>
<thead>
<tr>
<th>LVSD, n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n = 397)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-CTCAE all grades</td>
<td>33 (8.3)</td>
<td>18* (4.4)</td>
</tr>
<tr>
<td>NCI-CTCAE grade 2</td>
<td>15 (3.8)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>NCI-CTCAE grade ≥3†</td>
<td>11 (2.8)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Symptomatic LVSD*</td>
<td>7 (1.8)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>3 (0.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>3 (0.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>1 (0.3)</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

LVSD = left ventricular systolic dysfunction; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for Adverse Events; n = number of patients; NYHA = New York Heart Association

* Assessment of NCI-CTCAE grade was missing for one patient.
† All symptomatic LVSD events (n = 11) were reported as LVSD grade ≥3. However, there were five patients with LVSD grade 3 (placebo arm: n = 4; pertuzumab arm: n = 1) that was not deemed to be symptomatic by the investigator.

### Table 2. Comparison of risk factors between symptomatic LVSD and overall patient populations

<table>
<thead>
<tr>
<th></th>
<th>Patients who developed symptomatic LVSD (both arms combined, n = 11)</th>
<th>Entire study population (both arms combined, n = 808)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>55.0 (38–82)</td>
<td>54.0 (22–89)</td>
</tr>
<tr>
<td>&gt;75 years, n (%)</td>
<td>1 (9.1)</td>
<td>19 (2.4)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>72.0 (60–85)</td>
<td>64.9 (39–142)</td>
</tr>
<tr>
<td>Baseline LVEF, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>64.0 (50–85)</td>
<td>65.0 (50–88)</td>
</tr>
<tr>
<td>Past or current smoker, n (%)</td>
<td>3 (27.3)</td>
<td>179 (22.2)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (27.3)</td>
<td>207 (25.6)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0 (0.0)</td>
<td>52 (6.4)</td>
</tr>
<tr>
<td>Prior anthracyclines, n (%)</td>
<td>8 (72.7)</td>
<td>314 (38.9)</td>
</tr>
<tr>
<td>Prior radiotherapy, n (%)</td>
<td>8 (72.7)</td>
<td>346 (42.8)</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; n = number of patients

* On treatment is defined as on or before the day of the latest assessment date within 42 days following the last valid assigned study treatment.
† After stopping treatment is defined as after the day of the latest assessment date within 42 days following the last valid assigned study treatment.

### Table 3. LVEF assessment

<table>
<thead>
<tr>
<th></th>
<th>Placebo + trastuzumab + docetaxel (n = 397)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with post-baseline LVEF assessment, n</td>
<td>379</td>
<td>393</td>
</tr>
<tr>
<td>LVEF decline to &lt;50% and by ≥10% points from baseline, n/N (%)</td>
<td>25/379 (6.6)</td>
<td>15/393 (3.8)</td>
</tr>
<tr>
<td>LVEF recovered to ≥50% on treatment*, n/N (%)</td>
<td>12/25 (48.0)</td>
<td>6/15 (40.0)</td>
</tr>
<tr>
<td>LVEF recovered to ≥50% after stopping treatment†, n/N (%)</td>
<td>6/25 (24.0)</td>
<td>7/15 (46.7)</td>
</tr>
<tr>
<td>Total number of patients with LV EF recovery to ≥50%, n/N (%)</td>
<td>18/25 (72.0)</td>
<td>13/15 (86.7)</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; n/N = number of patients
Key conclusion

- CLEOPATRA provides evidence that pertuzumab, when combined with trastuzumab and docetaxel, does not increase the frequency of overall cardiac disorders compared with placebo.


Cortés J, *et al.* ASCO 2012: Abstract 598^*^

Quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer

**Background**

Several studies in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer have shown that treatment with the combination of two HER2-targeted agents improves efficacy compared with one targeted agent alone. However, in a disease setting like metastatic breast cancer (MBC) where current treatments are not curative, it is not only important to demonstrate that a new therapy provides clinical benefit but also that it does not have an adverse impact on the patient’s health-related quality of life (HRQoL). Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA), a phase III trial, tested the safety and efficacy of combining docetaxel and trastuzumab with pertuzumab, a second anti-HER2 antibody with a distinct binding epitope, or placebo as a first-line therapy for patients with HER2-positive MBC. The addition of pertuzumab significantly improved progression-free survival compared with placebo, from 12.4 to 18.5 months.1

At ASCO 2012, Cortés and colleagues presented their analysis of HRQoL data from the CLEOPATRA study.2

**Study design**

- For information on study design and treatment protocols see Ewer *et al.* on p. 14.

- Female patients completed the Functional Assessment of Cancer Therapy for breast cancer (FACT-B) questionnaire every third cycle of therapy within three days before each tumour assessment until independently determined progressive disease.

- Time to deterioration in the breast cancer subscale (BCS), which measures symptoms and issues relevant in breast cancer, was recorded once patients reported a decrease from baseline of ≥2 points.

- Time to deterioration of HRQoL was measured when a decrease from baseline of ≥5 points occurred in the Trial Outcome Index-Physical/Functional/BCS (TOI-PFB) composite score.

**Key findings**

- Compliance with completion of the FACT-B questionnaire was ≥75% beyond the first year in both treatment arms.

- A similar percentage of patients in both groups experienced deterioration of HRQoL during the study (placebo group: 56.7%; pertuzumab group: 59.5%).

- The median time to deterioration of HRQoL was approximately six cycles of treatment for both groups (hazard ratio [HR] = 0.97; p = 0.7161). (Figure 1)

- At the sixth cycle, the mean reduction in the TOI-PFB score from baseline was –3.5 for the placebo group vs. –3.0 for the pertuzumab group. (Figure 2)

- At subsequent cycles, when most patients had discontinued docetaxel, mean reductions were smaller
suggesting that after an early decline, patients’ scores improved slightly. Overall, mean changes were small in both arms. (Figure 2)

• From around cycle 21 on, the mean change from baseline in TOI-PFB scores improved in the pertuzumab group and worsened in the placebo group.

• However, it should be noted that the number of patients with an evaluable score decreased over time. (Figure 2)

- An exploratory analysis suggested that time to deterioration in the BCS score was delayed in the pertuzumab group (18.3 vs. 26.7 weeks; HR 0.77; \( p = 0.0061 \)). (Figure 3)

- The mean change from baseline in BCS scores remained stable around zero until cycle 21, when it improved thereafter in the pertuzumab group and worsened slightly in the placebo group.

• However, it should be noted that the number of patients with an evaluable score decreased over time. (Figure 4)
Key conclusions

- The combination of pertuzumab with trastuzumab and docetaxel as a first-line therapy for HER2-positive MBC appeared to have no detrimental effect on patient-reported HRQoL.

- Adding pertuzumab to the first-line therapy appears to be associated with a delay in the time to deterioration in the BCS score.

An open-label, randomized, phase III trial comparing taxane-based chemotherapy with lapatinib or trastuzumab as a first-line therapy for women with HER2-positive metastatic breast cancer

Background
Lapatinib, an orally active, reversible inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) tyrosine kinases, is approved for use in combination with capecitabine as therapy for patients who have received prior treatment for HER2-positive locally advanced (LABC) or metastatic breast cancer (MBC). As a first-line therapy for patients with HER2-positive MBC, lapatinib has been shown to improve efficacy over placebo when used in combination with paclitaxel. This trial, presented by Gelmon and colleagues at the ASCO 2012 meeting, was designed to directly compare the efficacy and safety of a first-line therapy using lapatinib or trastuzumab in combination with taxane-based chemotherapy for patients with HER2-positive MBC. 1

Study design
• This was a multicentre, international, open-label, randomized, phase III clinical trial (NCIC CTG MA.31, NCT00667251).
• Patients (N = 636) with MBC and no prior chemotherapy or HER2-targeted therapy for MBC were randomized and treated in this trial.
• Patients received either:
  ◦ Lapatinib with a taxane, followed by lapatinib monotherapy (LTax/L);
  or
  ◦ Trastuzumab with a taxane followed by trastuzumab monotherapy (TTax/T).
• The dosages of study drugs administered for the first 24 weeks of therapy were a taxane:
  ◦ Paclitaxel: 80 mg/m² intravenously (iv) weekly for the first three weeks, then once every four weeks for six courses;
  or
  ◦ Docetaxel: 75 mg/m² iv on day 1, then once every three weeks (q3w) for eight courses (plus granulocyte colony-stimulating factor prophylaxis for patients taking lapatinib).
• In combination with a HER2-directed agent:
  – Lapatinib: 1,250 mg orally each day;
  or
  – Trastuzumab: 4 mg/kg iv initial dose, then 2 mg/kg iv weekly or 8 mg/kg iv initial dose, then 6 mg/kg iv q3w.
• Following the first 24 weeks of treatment, patients received monotherapy with the HER2-directed agent, lapatinib (1,500 mg orally each day) or trastuzumab (6 mg/kg iv q3w), corresponding to their initial therapy for four years or until progressive disease (PD).
• The primary endpoint of this study was progression-free survival (PFS) as determined by Response Evaluation Criteria In Solid Tumors 1.0 or death from any cause and analyzed by intent to treat (ITT).
• A secondary analysis of PFS was performed with patients who had centrally confirmed HER2-positive tumours.
• The secondary endpoints of this study were overall survival (OS) and safety.
• Further analyses will include treatment exposure, incidence of and time to central nervous system (CNS) metastases, response rates, among others but were not reported at this presentation.

Key findings
• After median follow-up times of 12.9 months in the lapatinib arm and 14 months in the trastuzumab arm, ITT analysis indicated that the median time of PFS in the LTax/L arm (8.8 months [95% confidence interval (CI): 8.3–10.6]) was inferior compared with the TTax/T arm (11.4 months [95% CI: 10.8–13.7]), hazard ratio (HR) = 1.33 (95% CI: 1.06-1.67); p = 0.01. (Figure 1)
• The secondary analysis of PFS, which only included patients with centrally-confirmed HER2-positive tumours, also showed that LTax/L was inferior to TTax/T (9.0 vs. 13.7 median months, HR = 1.48 [95% CI: 1.15–1.92]; p = 0.003).
NCIC CTG MA.31 study design

Women with HER2-positive (central or local lab) MBC and no prior chemotherapy or HER2-targeted therapy in the metastatic setting

• Standard inclusion including mandatory central HER2 testing
• Standard exclusion
• Prior (neo)adjuvant chemotherapy/trastuzumab allowed (>12 months)
• No CNS metastases

Randomize 1:1

EXPERIMENTAL ARM
24 weeks Lapatinib plus Taxane

STANDARD ARM
24 weeks Trastuzumab plus Taxane

Primary Outcome: PFS

Sample Size: ~600 (536 centrally confirmed HER2+ patients)

CNS = central nervous system; HER2 = human epidermal growth factor receptor 2; HER2+ = HER2-positive; MBC = metastatic breast cancer; PD = progressive disease; PFS = progression-free survival

• No difference in OS was detected between the treatment arms when comparing LTax/L with TTax/T, regardless of whether it was analyzed by ITT (HR = 1.1 [95% CI: 0.75–1.61]; p = 0.62) or by HER2-positive status (HR = 1.25 [95% CI: 0.81–1.93]; p = 0.32). (Figure 2)

• Safety data profiles differed between the two treatment arms:
  ◦ Overall, more serious adverse events (SAEs) were reported in the LTax/L group (136 vs. 78), with a greater number of cases of diarrhea (32 vs. 5).
  ◦ A higher frequency of two grade ≥3 adverse events (AEs), diarrhea (19.3% vs. 1.3%) and rash (8.9% vs. 0.3%), occurred in patients taking LTax/L.
  ◦ A greater percentage of patients treated with TTax/T experienced a decrease ≥20% of LVEF from baseline over the course of the study. (Table 1)
  ◦ A total of 10 deaths on treatment took place in the TTax/T arm compared with five deaths in the LTax/L arm.

Figure 1. PFS: analysis of intent-to-treat and centrally confirmed HER2+ populations

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HER2+ = HER2-positive; HR = hazard ratio; LTax/L = Lapatinib plus Taxane followed by Lapatinib; No. = Number; PFS = progression-free survival; TTax/T = Trastuzumab plus Taxane followed by Trastuzumab
Figure 2. Overall survival: analysis of intent-to-treat and centrally confirmed HER2+ populations

Table 1. LVEF decrease from baseline while on treatment

<table>
<thead>
<tr>
<th>Week</th>
<th>LTax/L (n = 312)</th>
<th>TTax/T (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute decrease (%)</td>
<td>Absolute decrease (%)</td>
</tr>
<tr>
<td></td>
<td>0–&lt;20</td>
<td>20 or more</td>
</tr>
<tr>
<td>12</td>
<td>255</td>
<td>158 (62)</td>
</tr>
<tr>
<td>24</td>
<td>199</td>
<td>126 (63)</td>
</tr>
<tr>
<td>36</td>
<td>145</td>
<td>95 (66)</td>
</tr>
<tr>
<td>48</td>
<td>72</td>
<td>43 (60)</td>
</tr>
<tr>
<td>60</td>
<td>42</td>
<td>28 (67)</td>
</tr>
<tr>
<td>72</td>
<td>26</td>
<td>14 (54)</td>
</tr>
</tbody>
</table>

0–<20 = 0 to less than 20; LTax/L = lapatinib plus taxane followed by lapatinib; n = number of patients; TTax/T = trastuzumab plus taxane followed by trastuzumab

Key conclusions

- Patients receiving TTax/T compared with LTax/L had a statistically significant increase in PFS, as indicated by median differences of 2.6 months for the ITT population and 4.7 months in those with centrally confirmed HER2-positive tumours.
- The two therapies produced different safety data profiles with diarrhea and rash occurring more frequently with LTax/L while a greater percentage of TTax/T patients experienced a ≥20% decrease in LVEF.

**Evaluation of lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer: NSABP protocol B-41**

**Background**

The standard neoadjuvant therapy for human epidermal growth factor receptor 2 (HER2)-positive operable breast cancer is administration of doxorubicin and cyclophosphamide combined with weekly paclitaxel and trastuzumab leading up to surgery. Lapatinib, combined with a cytotoxic agent, is used to treat patients with metastatic breast cancer (MBC) whose tumours have progressed on trastuzumab. Even though lapatinib and trastuzumab are both HER2-directed agents, they operate through different mechanisms of action and can have synergistic activity. The authors of this phase III clinical trial attempted to determine whether substitution of or addition to the HER2-targeted component of standard neoadjuvant therapy, trastuzumab, with lapatinib might improve outcomes for patients with HER2-positive operable breast cancer.

**Study design**

- This interventional trial was a multicentre, international, randomized, open-label, phase III design (NCT00486668).
- Patients (N = 529) were accrued for the trial from July 2007 to June 2011.
- Inclusion criteria for patients in this study were a palpable tumour ≥2 cm, diagnosis by core needle biopsy, left ventricular ejection fraction ≥50%, and confirmation of a HER2-positive tumour.
- All patients received part of the standard neoadjuvant treatment regimen. It consisted of doxorubicin and cyclophosphamide followed by weekly paclitaxel, combined with trastuzumab, lapatinib, or both trastuzumab and lapatinib.
- The study drugs were administered as follows:
  - Doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² intravenously (iv) every 21 days for cycles 1–4;
  - Weekly paclitaxel (80 mg/m² iv on days 1, 8, and 15 every 28 days for cycles 5–8).
- While taking weekly paclitaxel, patients were also administered the HER2-targeted agents:
  - Trastuzumab: 4 mg/kg iv initial dose, 2 mg/kg iv subsequent dose weekly until one week before surgery;
  - Lapatinib: 1,250 mg orally each day until one day before surgery;
  - Trastuzumab plus lapatinib: trastuzumab (same dosage) and lapatinib (750 mg orally each day until one day before surgery).
- The primary endpoint was pathologic complete response (pCR) in the breast.
- Secondary outcome measures were complete clinical response (cCR), pCR in the breast and negative nodes, and toxicities (cardiac and non-cardiac).

**NSABP B-41 study design**

![NSABP B-41 study design diagram](image)

Endpoints: pCR, cardiac events, PFS, OS

+ = plus; → = followed by; AC = doxorubicin and cyclophosphamide; HER2 = human epidermal growth factor receptor 2; L = lapatinib; OS = overall survival; pCR = pathologic complete response; PFS = progression-free survival; R = randomize; T = trastuzumab; WP = weekly paclitaxel
**Key findings**

- The percentage of patients who fully completed the protocol-defined neoadjuvant therapies was significantly different between the treatment groups (trastuzumab = 78%, lapatinib = 68%, trastuzumab plus lapatinib = 63%; \( p = 0.01 \)).
- However, the percentage of patients who at least started the fourth cycle of HER2-directed treatment was not significantly different between groups (trastuzumab = 82%, lapatinib = 73%, trastuzumab plus lapatinib = 72%; \( p = 0.082 \)).
- The percentage of patients reaching a cCR decreased when they were treated with lapatinib compared with trastuzumab (69.9% vs. 82%, \( p = 0.014 \)).
- The combination of trastuzumab plus lapatinib compared with trastuzumab (76.8% vs. 82.0%, \( p = 0.3 \)) did not confer any difference in the percentage of patients with a cCR. (Figure 1)
- Lapatinib or trastuzumab plus lapatinib neoadjuvant therapies compared with the standard of trastuzumab did not significantly change the percentage of patients achieving a pCR in the breast (lapatinib vs. trastuzumab: 53.2% vs. 52.5%; \( p = 0.99 \); trastuzumab plus lapatinib vs. trastuzumab: 62% vs. 52.5%; \( p = 0.095 \)). (Figure 2)
- When the treatment groups were divided by hormone receptor status (positive or negative) and compared, there was no difference in the percentage of patients achieving a pCR in the breast. (Figure 3)
- The percentage of patients with a pCR in the breast and negative nodes remained unchanged in the trastuzumab vs. lapatinib groups (49.4% vs. 47.4%) and was marginally increased in the trastuzumab plus lapatinib group vs. trastuzumab alone (60.2% vs. 49.4%, \( p = 0.056 \)). (Figure 4)
- Dividing the treatment groups into two categories of HER2 expression levels by immunohistochemistry (IHC), IHC low (0+, 1+, and 2+) and IHC 3+, revealed that a greater percentage of patients with IHC 3+ levels of HER2 attained a pCR when treated with trastuzumab plus lapatinib compared with trastuzumab (71% vs. 54.7%; \( p = 0.006 \)). (Figure 5)
- An interaction of pCR with IHC levels was detected in the trastuzumab plus lapatinib vs. trastuzumab groups (\( p = 0.021 \)).
- Overall grade \( \geq 3 \) adverse events (AEs), more specifically grade 3 diarrhea (trastuzumab = 2%, lapatinib = 20%, trastuzumab plus lapatinib = 27%; \( p < 0.001 \)), occurred with greater frequency in patients from both of the lapatinib-treated groups compared with trastuzumab.
- Differences in the percentage of patients experiencing febrile neutropenia, hepatic toxicity, or congestive heart failure between treatment arms were not significant.

![Figure 1. Complete clinical response](image1)

![Figure 2. Pathologic complete response in the breast](image2)
Figure 3. Pathologic complete response in the breast by hormone receptor status

Figure 4. Pathologic complete response in the breast and negative nodes

Figure 5. Pathologic complete response in the breast based on HER2 overexpression levels

Key conclusions

- Substitution of lapatinib for trastuzumab in neo-adjuvant therapy for operable breast cancer was equally as efficacious as trastuzumab in nearly every outcome measure except for cCR.

- The combination of the two HER2-directed agents, trastuzumab and lapatinib, may be more effective than trastuzumab alone as a neoadjuvant therapy for patients with operable breast cancer that express high levels of HER2 protein.

- The main difference in AEs was an increased frequency of diarrhea for both of the lapatinib-containing treatment regimens compared with the standard trastuzumab regimen.

References:
Cardiac safety in a phase II study of trastuzumab emtansine (T-DM1) following anthracycline-based chemotherapy as adjuvant or neoadjuvant therapy for early-stage HER2-positive breast cancer

Background
Trastuzumab emtansine (T-DM1) has demonstrated clinical activity and favourable safety when used as a single agent in several studies of patients with metastatic breast cancer (MBC). As a result, there is considerable interest in exploring its use in patients with early-stage disease. However, monitoring the frequency and severity of cardiac dysfunction with the use of T-DM1 is of special interest given the cardiotoxicity associated with trastuzumab treatment and that women with early-stage breast cancer can expect long-term survival. At ASCO 2012, Dang and colleagues presented an assessment of the cardiac safety and clinical feasibility of T-DM1 following anthracycline-based chemotherapy in the adjuvant or neoadjuvant setting for early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer in this phase II study.1

Study design
• TDM4874g (NCT01196052) is a single-arm, open-label, phase II study of T-DM1 in patients with early-stage HER2-positive breast cancer.
• Patients (N = 153) were enrolled in this study from October 2010 to June 2011.
• As of the clinical cut-off date, 148 patients had received at least one dose of T-DM1.

TDM4874g study design

- A pre-chemotherapy left ventricular ejection fraction (LVEF) ≥55% by multigated acquisition (MUGA) scan/echocardiography (ECHO) was required for enrolment.
- Patients were administered one of two chemotherapy regimens:
  - Doxorubicin (A)/cyclophosphamide (C) – AC (A: 60 mg/m²; C: 600 mg/m² once every two weeks [q2w] or q3w for four cycles);
  - 5-fluorouracil (F)/epirubicin (E)/cyclophosphamide (C) – FEC (F: 500 mg/m²; E: 100 mg/m²; C: 600 mg/m² q3w for three to four cycles).
- Followed by the HER2-directed agent:
  - T-DM1 (3.6 mg/kg q3w intravenously [iv]; up to 17 cycles).
- The primary endpoints were safety and an allowable incidence rate of pre-specified cardiac events ≤6% following initiation of T-DM1 treatment.
- A pre-specified cardiac event was defined as death from a cardiac cause or severe congestive heart failure (CHF) (New York Heart Association [NYHA] class III or IV) with a decrease in LVEF of ≥10 absolute percentage points from baseline to an LVEF <50%.

AC = doxorubicin plus cyclophosphamide; ECHO = echocardiogram; FEC = 5-fluourouracil/epirubicin/cyclophosphamide; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; q2w = once every 2 weeks; q3w = once every 3 weeks; qw = once weekly; RT = radiation therapy; T-DM1 = trastuzumab emtansine

* Patients were allowed to enroll before or after chemotherapy period 1.
† Dose reductions to 3.0 mg/kg and 2.4 mg/kg were permitted for toxicity.
‡ Starting with cycle 5 of T-DM1.
§ Radiation was indicated as per investigator’s discretion; safety was evaluated after the first 20 patients had been treated with concurrent T-DM1 and RT, until confirmation of concurrent RT and T-DM1 safety, additional patients were given sequential RT.
** Number of T-DM1 cycles were reduced in accordance with the number of trastuzumab cycles received (maximum of 17 cycles of HER2-directed therapy).
Key findings

- The mean LVEF of patients (n = 147) pre-chemotherapy was 67.1% and changed very little over the course of treatment, although the values had greater variation approaching the end of treatment due to the fact that fewer patients had reached that point at clinical cut-off. (Figure 1)

- There were no symptomatic decreases in LVEF but 2.0% of patients experienced an asymptomatic decrease in LVEF. (Table 1)

- Neither pre-specified cardiac events nor T-DM1 discontinuations due to cardiac adverse events (AEs) had occurred at this time but 3.4% of patients experienced T-DM1–related cardiac AEs, such as atrial fibrillation, tricuspid valve incompetence, or palpitations.

- The most common all-grade T-DM1–related AEs were nausea, headache, epistaxis, asthenia, and pyrexia. (Table 2)

Figure 1. Mean LVEF in T-DM1–treated patients over time

Table 1. Cardiac adverse events

<table>
<thead>
<tr>
<th>Cardiac adverse events</th>
<th>All cardiac-evaluable patients (N = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol prespecified cardiac events, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Symptomatic decrease in LVEF, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asymptomatic decrease in LVEF,* n (%)</td>
<td>3 (2.0)*</td>
</tr>
<tr>
<td>T-DM1 discontinuations due to cardiac AEs, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T-DM1–related cardiac AEs, n (%)</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Atrial fibrillation (grade 4)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Tricuspid valve incompetence (grade 2)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Palpitations (all grade 1)</td>
<td>3 (2.1)</td>
</tr>
</tbody>
</table>

AEs = adverse events; LVEF = left ventricular ejection fraction; n/N = number of patients; RT = radiation therapy; T-DM1 = trastuzumab emtansine

* After the end of the T-DM1 cycle 4, patients may have received optional chemotherapy, RT, trastuzumab, or surgery prior to recommencing T-DM1 treatment. Some patients missed protocol-specified LVEF assessments.

Table 2. Most common T-DM1–related adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades with incidence &gt;15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>27.0</td>
</tr>
<tr>
<td>Headache</td>
<td>31</td>
<td>20.9</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25</td>
<td>16.9</td>
</tr>
<tr>
<td>Asthenia</td>
<td>23</td>
<td>15.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>15.5</td>
</tr>
<tr>
<td>Grade ≥3 with incidence &gt;5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>7.4*</td>
</tr>
<tr>
<td>Increased AST</td>
<td>10</td>
<td>6.8*</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>9</td>
<td>6.1*</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; n = number of patients; T-DM1 = trastuzumab emtansine

* All grade 3

Key conclusion

- Early results indicate that T-DM1 following anthracycline-based chemotherapy was not associated with cardiac toxicity in patients with early-stage HER2-positive breast cancer.

An interview with Dr. Kimberly Blackwell on the implications of the EMILIA study for patients with metastatic breast cancer

New Evidence: What outcomes are sought for patients who are being treated for metastatic breast cancer (MBC)?

Dr. Blackwell: When considering outcomes for patients who are being treated for MBC, we are not only thinking about length of life but also quality of life (QoL). It is a balance between keeping the breast cancer under control with treatment and not hurting the patient. We are moving beyond the old days of cancer care when the patient had to get really sick first, from the associated toxicities of treatment, in order to live longer. This new approach to care is slowly becoming a reality for the treatment of breast cancer and, for all practical purposes, other solid tumours as well.

New Evidence: What factors should be considered when selecting treatment for these patients?

Dr. Blackwell: There is still a real art to treating patients who are facing breast cancer. Even though we have many published treatment guidelines and approvals by regulatory bodies, such as the U.S. Food and Drug Administration, that drive our decision-making, we recognize that they are all built on population-based studies. The challenge is to take these population-based results and apply them to each individual patient sitting in our clinics. When I started treating patients with MBC 15 years ago, we had no human epidermal growth factor receptor 2 (HER2)-targeted treatment options. By the end of 2012, we will hopefully have four HER2-targeted agents — trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) — to pick and choose from, thus allowing us to achieve that therapeutic balance for each individual patient. Treatment-related decisions are made not only by talking to the patient about the data as they relate to large populations of women, but also by considering what is important to the patient, known as patient-assigned goals.
**New Evidence:** What is trastuzumab resistance and how significant a problem is it when treating patients with breast cancer?

**Dr. Blackwell:** Trastuzumab resistance in the treatment of breast cancer is quite difficult to define. Until we have a better understanding of the biology and more precise sequential biopsy samples from patients who progress or relapse after receiving trastuzumab, I do not think we will have a good idea. Right now, our clinical practice is driven by the agents that patients have received and not necessarily by how well they will work. I am not sure that we can call it trastuzumab resistance if patients relapse locally or in the brain two years after receiving a year of trastuzumab treatment. It may just be that we should have kept on administering trastuzumab or that the treatment prevented the cancer from returning everywhere else but the brain. For now, we will just have to do the best we can in the clinic to figure out which treatments work and have a good understanding of the patient populations being accrued in clinical trials before widely using new drugs.

**New Evidence:** What was the rationale for the EMILIA study?

**Dr. Blackwell:** In the EMILIA study, we chose lapatinib and capecitabine as the control arm because the indication for their use is in patients who have progressed on trastuzumab and taxane-based chemotherapy. Consequently, this combination was thought to be an appropriate first-, second-, or third-line therapy for patients with MBC. The experimental arm included the use of only one drug, T-DM1. Since T-DM1 retains all of the properties of its parent antibody, trastuzumab, it made more sense to use a comparator that was already considered a very active agent in these patients. We wanted to include a broad range of patients by enrolling some who had received no prior treatment for MBC to, in this case, a third of our patients who had already received up to two years of treatment. The two main endpoints of this study were progression-free survival (PFS) and overall survival (OS). For the purpose of developing a less toxic therapy, this study also performed an extensive assessment of the patient’s QoL. It was well recognized that although lapatinib and capecitabine form an active combination, the combination is also associated with a lot of toxic side effects, in particular, diarrhea, rash, nausea, and vomiting. In terms of QoL, the other important consideration was comparing T-DM1, which is given intravenously once every three weeks, to the orally administered, daily pills regimen of lapatinib and capecitabine.

**New Evidence:** Please describe the unique mechanism of action employed by the new antibody-drug conjugate technology in T-DM1.

**Dr. Blackwell:** One of the most exciting aspects of the EMILIA study was that it provided the first proof-of-concept of an antibody-drug conjugate for the treatment of a solid tumour. These antibody-drug conjugates have been the holy grail of cancer therapy. That is to say, if we could design a drug that would only target the cancer cells and not the host’s cells, we could make something really toxic to the tumour while having minimal impact on the patient. T-DM1 was designed to do exactly that because it is composed of a chemotherapeutic agent, DM1, bound to an antibody, trastuzumab, which targets the overexpressed HER2 receptor on breast cancer cells. In the wake of the results from EMILIA, the antibody-drug conjugate concept has received a lot of attention because it could have widespread applicability for the treatment of many other diseases beyond solid tumours. It took close to two decades of research to understand how to properly bind a toxin to an antibody through a stable linker molecule such that the toxin would only be released within the target cell. In the case of T-DM1, it was the culmination of a lot of basic research in lysosomal biology. Now that we understand it, I believe the door has been swung wide open to the development of other antibody-drug conjugates.

**New Evidence:** How did the efficacy of T-DM1 compare with lapatinib and capecitabine in this trial?

**Dr. Blackwell:** The use of T-DM1 improved PFS by 3.6 months over lapatinib and capecitabine. This was a statistically significant result in which the study had met its endpoint, triggering an analysis of OS independent of how many deaths had actually occurred. At that point, median OS had not been reached for T-DM1 compared with 23.3 months in the control arm. The study narrowly missed the early overall efficacy stopping boundary for OS (hazard ratio [HR] = 0.617 or \( p = 0.0003 \)) since the HR was 0.621 and the \( p \)-value was 0.0005. At the time of the analysis, there was an absolute difference of 18% in OS at the two-year mark. This is the largest difference we have ever seen in an MBC trial and with additional follow-up, we would expect the pre-defined OS endpoint to be met as well.
**New Evidence**: Why did T-DM1 provide a significant improvement in PFS for every patient subgroup analyzed except for those without visceral disease or those who were 65 years or older?

**Dr. Blackwell**: The simplest reason for not having seen as much of a beneficial effect with T-DM1 in patients without visceral disease is that the presence of visceral disease is easily measured whereas its complete absence is much more difficult to ascertain. We did allow for an evaluable disease in the study. For example, a patient could have had bone-only disease and a pleural effusion. About one third of patients in the study were classified as being without visceral disease. Typically, this means their disease is more difficult to measure, therefore, determining PFS in this subgroup may have been done with a little less precision. As far as elderly patients are concerned, they only constituted about one seventh of the total patient population. This was a much smaller subgroup, which is usually prone to more variability. When looking at the absolute difference in PFS between study arms for both of these subgroups, it certainly appears as though T-DM1 is favoured.

**New Evidence**: How did the safety profile of T-DM1 compare with lapatinib and capecitabine in this study?

**Dr. Blackwell**: The safety profile for T-DM1 certainly supported the idea that an antibody-drug conjugate can directly deliver chemotherapy while sparing normal tissues from toxicity. One of the measurements we look at is adverse events (AEs) leading to treatment discontinuation. The percentage of patients in the control arm (10.7%) who experienced these kinds of events was almost double that seen in patients in the experimental arm (5.9%) of this study. For lapatinib and capecitabine, treatment discontinuation can largely be attributed to an increase in diarrhea, hand-foot syndrome, vomiting, and nausea. T-DM1 occasionally produced elevations in alanine aminotransferase and aspartate aminotransferase that were typically asymptomatic and resolved once the drug was stopped. We also saw grade 4 thrombocytopenia in about 3% of patients who were given T-DM1. This strange occurrence, which was identified early on in drug development, needs to be monitored and is currently under investigation. In the clinic, the sequelae of AEs associated with lapatinib and capecitabine treatment have a greater impact on the patient’s QoL than some of these laboratory abnormalities seen with T-DM1. Time to symptom progression and scores on the Functional Assessment of Cancer Therapy-Breast scale both showed a significant delay in the worsening of the QoL for those patients in the T-DM1 arm.

**New Evidence**: What was the cardiac toxicity profile of T-DM1 in the EMILIA study?

**Dr. Blackwell**: Although it was quite a concern when trastuzumab showed early signs of increasing the incidence of cardiac events, we recognize now that these are fairly infrequent but still need to be monitored. In the control versus experimental arms of EMILIA, only 1.6% and 1.7% of patients, respectively, had a decline in their left ventricular ejection fraction. This indicates that even though the toxin is being delivered to cells expressing the HER2 protein, it does not appear to be reaching the myocardium. It is thought that T-DM1 only delivers the drug to cells that express at least two million copies of HER2 compared with normal cellular expression of approximately 10,000 copies of this protein. The reason for occasional incidents of cardiotoxicity with T-DM1 is still unknown but this drug does not appear to cause an increased signal over what is normally seen with trastuzumab alone.

**New Evidence**: Are there any disadvantages to T-DM1 compared with other therapies available?

**Dr. Blackwell**: Treatment with T-DM1 is just a 30-minute infusion, no pre-medications are required, and patients do not lose their hair. In fact, when some of my patients and I were interviewed by the press, we had a unique problem because everyone was worried about how their hair was going to look. It dawned on me that up until that point, none of the patients I had ever been interviewed with still had their own hair. The fact is the toxicity of T-DM1 is not something that the patient has to monitor because it can be tracked by laboratory values.
**New Evidence:** Will there still be a role for lapatinib and capecitabine in the treatment of HER2-positive MBC?

**Dr. Blackwell:** This goes back to the art of oncology but I think lapatinib remains an approved and active agent for patients with HER2-positive MBC. If T-DM1 is approved, I believe it will be a preferred agent but there is still a role for lapatinib in patients who have progressed on T-DM1. Lapatinib also remains the only HER2-targeted agent that is approved in combination with endocrine therapy. This is a patient population that is not typically treated with chemotherapy, thus lapatinib is still a viable option prior to receiving chemotherapy for MBC.

**New Evidence:** Considering the results from the EMILIA and Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trials, can you discuss how T-DM1 and pertuzumab might fit into clinical algorithms for the treatment of HER2-positive MBC?

**Dr. Blackwell:** It is important to point out that CLEOPATRA was a different kind of study than EMILIA. CLEOPATRA was conducted in patients with first-line MBC and roughly 80% of them had never received trastuzumab. This is in stark contrast to the EMILIA study where 100% of the patients had previously received trastuzumab, only to have disease progression or relapse. Although both agents were studied in the MBC domain, they should drive clinicians to utilize them in different settings. The CLEOPATRA study indicates that pertuzumab should be used in addition to trastuzumab and chemotherapy for patients who have not received trastuzumab, whereas the EMILIA study points to the use of T-DM1 over lapatinib in patients who have progressed after having previously received trastuzumab and a taxane. The logical progression would be to use pertuzumab and trastuzumab in the first-line metastatic setting and then to use T-DM1 once patients have already seen those agents. Currently, I am unaware of any clinical trials testing the efficacy and safety of administering T-DM1 in earlier stages of breast cancer, but there is obviously a lot of discussion about T-DM1 being used in the adjuvant setting. The priority trial right now is the Adjuvant Pertuzumab and Herceptin In Initial Therapy of Breast Cancer (APHINITY) trial, which is testing the addition of pertuzumab. However, T-DM1 could also be used for patients who have progressed following pertuzumab therapy in a study like APHINITY.

**New Evidence:** What are the clinical factors that drive these decisions?

**Dr. Blackwell:** As clinicians, we like to see evidence of efficacy and broad coverage of patient populations for new drugs. It should be stated that these drugs are going to be quite expensive, adding a significant cost to the treatment of HER2-positive MBC. Currently in my clinical practice, I will be limiting the use of both these drugs to the same patient populations in which they were tested. We should have the results soon from a phase III clinical trial called MARIANNE, which enrolled a patient population that is comparable to CLEOPATRA, comparing trastuzumab plus chemotherapy versus T-DM1 alone versus T-DM1 plus pertuzumab. The results from that trial will set the stage for how we should treat first-line MBC. Until then, I think pertuzumab and trastuzumab should be used first followed by T-DM1 in the metastatic setting.
In Supportive Care Oncology

Canadian perspective interview with Dr. Sunil Verma

New Evidence:

What is known about the mechanism for trastuzumab resistance in breast cancer?

Dr. Verma: Our understanding of resistance to trastuzumab-based therapy is limited because patients tend to respond even after disease progression. There may be an expression of p95, a truncated HER2 receptor. There may also be a role for MUC4, an extracellular protein that could inhibit trastuzumab from binding to the human epidermal growth factor receptor 2 (HER2). There are also some downstream resistance pathways, such as upregulation of the mTOR and PI3K-Akt pathways, which the immune modulatory effects of trastuzumab may be unable to overcome. We are continually addressing how to treat these patients through clinical trials with new agents and combination therapies, but there is no prototype of trastuzumab-resistant breast cancer that can be properly examined. Therefore, trastuzumab resistance remains an ill-defined term. All we can say is that these patients, even after disease progression, continue to derive some benefit from HER2-targeted therapy with either trastuzumab or lapatinib.

New Evidence:

How is lapatinib used in your clinical practice?

Dr. Verma: We use lapatinib as a second- or third-line therapy for our patients who have had up to one or two lines of previous trastuzumab-based therapy in the metastatic setting. For patients who have progressed on taxanes and trastuzumab, lapatinib has shown to be effective when given in combination with capecitabine. The challenge with capecitabine and lapatinib is the associated toxicity profile because patients have higher rates of grade 3/4 diarrhea and rash. Lapatinib is also effective when given in combination with letrozole for hormone receptor-positive, HER2-positive breast cancer and in combination with trastuzumab as a totally targeted combination approach.

New Evidence:

What was the rationale for the EMILIA trial?

Dr. Verma: Our standard approach to treatment for patients whose breast cancer has progressed on taxanes and trastuzumab in the metastatic setting includes capecitabine and lapatinib. At times, we may consider using other chemotherapies with trastuzumab instead to treat these patients. In previous phase II trials, a new drug called trastuzumab emtansine (T-DM1) has shown response rates of approximately 30% to 40% for patients with HER2-positive metastatic breast cancer (MBC). T-DM1 is an antibody-drug conjugate that is composed of the antibody, trastuzumab, linked to DM1, a potent cytotoxic microtubule inhibitor, through a stable linker molecule. In the EMILIA trial, we wanted to see how effective and safe T-DM1 was compared with the standard treatment of capecitabine and lapatinib in a randomized, phase III trial.
**New Evidence:** What are your impressions of the efficacy data and safety profile for T-DM1 in the EMILIA trial?

**Dr. Verma:** The results of the EMILIA trial show that T-DM1 is a game changer. It is more effective than capecitabine and lapatinib in terms of prolonging progression-free survival (PFS) and it shows a trend towards improving overall survival (OS). T-DM1 also has fewer serious side effects than standard treatment, which can improve the quality of life for patients with MBC. Many of the side effects that our patients find debilitating were not seen in those treated with T-DM1. For example, we did not see any hair loss, febrile neutropenia, or infections. About 5% of patients did develop grade 3/4 transaminitis — elevations in their liver enzymes — and there was an approximately 15% rate of grade 3/4 thrombocytopenia, but the risk of significant bleeding was quite low.

**New Evidence:** How does T-DM1 compare with trastuzumab in terms of the risk for cardiotoxicity?

**Dr. Verma:** Most of the concerns in the past over increased cardiotoxicity with trastuzumab have been in the context of patients who were previously treated with anthracyclines or when trastuzumab was administered in close proximity with anthracyclines. Previous phase II trials for T-DM1 have indicated that there is no clear increase in cardiotoxicity with this agent. There were some data presented at the ASCO meeting from the TDM4874g phase II trial that showed T-DM1 had a manageable cardiac safety profile, even after anthracycline treatment. The authors of this study examined the use of T-DM1 following anthracycline-based chemotherapy for patients with breast cancer in either the adjuvant or neoadjuvant settings. They found very little change in patients’ mean left ventricular ejection fraction over the course of treatment and few cardiac adverse events, none of them leading to treatment discontinuation at the time of analysis. The cardiac safety data for T-DM1 from EMILIA, in which cardiotoxicity was one of the secondary endpoints, also showed that there were no increased rates of cardiac adverse events over the standard treatment of capecitabine and lapatinib. However, in terms of the full cardiotoxic profile for T-DM1, we still need to study the drug further, including more studies in the early-stage breast cancer setting, to see how it compares with a taxane plus trastuzumab.

**New Evidence:** Which patients would benefit most from this new antibody-drug conjugate T-DM1?

**Dr. Verma:** The eligibility criteria in the EMILIA study were for patients who had progressed on treatment with a taxane and trastuzumab. Therefore, if it is approved, treatment with T-DM1 would be appropriate for patients who have progressed on those treatments, either taxanes in the adjuvant setting or trastuzumab in the adjuvant and metastatic settings. This antibody-drug conjugate, T-DM1, allows us to deliver targeted therapy without significant side effects that would impact the patient’s quality of life. The reason for this is that chemotherapy is directed right to the cancer cell without exposing normal tissues to as much of the cytotoxic agent, essentially decreasing the amount of free drug exposure to the patient. This form of precision chemotherapy allows for greater efficacy without significant toxicity. It is the first in class for such an approach in solid tumours and will offer patients with HER2-positive MBC a therapy that is well tolerated and efficacious.

**New Evidence:** What was the rationale for the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study?

**Dr. Verma:** The CLEOPATRA study was designed to evaluate whether we can improve on the efficacy seen with the standard treatment of a taxane plus trastuzumab for patients with HER2-positive MBC. The treatment for the control arm of this study was docetaxel plus trastuzumab plus a placebo and the experimental arm was docetaxel plus trastuzumab plus pertuzumab. Pertuzumab is a monoclonal antibody that prevents the dimerization of HER2 and HER3 and it appears to be synergistic with trastuzumab. The question to be answered was can we combine the two HER2-directed agents with a chemotherapy backbone of a taxane for the treatment of patients in the first-line metastatic setting as part of a randomized, phase III trial.

**New Evidence:** What are your impressions of the cardiac safety of pertuzumab in this trial?

**Dr. Verma:** The results for the CLEOPATRA study, first presented in San Antonio, were very impressive. There was an improvement in PFS from 12.5 months with docetaxel and trastuzumab to about 18 months when pertuzumab was added to the combination. The data on cardiac safety suggest that the addition of pertuzumab, while increasing efficacy, does not increase the cardiac toxicity over taxanes and trastuzumab.
**New Evidence**: What are the advantages of combining two HER2-targeted agents over administering just one for the treatment of HER2-positive MBC?

**Dr. Verma**: The reason for combining two different HER2-targeted agents as a treatment approach is that complete blockade of the HER2 receptor is needed. Trastuzumab alone does not block the potent dimerization of HER2 and HER3, which leads to an increased signal transduction cascade and aggressiveness of the breast cancer. Pertuzumab on its own is not that efficacious but the synergy of both agents is clearly showing greater efficacy over trastuzumab alone. Blocking this receptor dimerization is clinically important and the data showing extended PFS are evidence of that. We have some data that indicate the combination of trastuzumab with lapatinib is also very effective but the lapatinib toxicity profile limits its ability to be combined with chemotherapy. This also makes it difficult to study as a combination therapy. There are not many phase III trials studying the combination of trastuzumab and lapatinib with chemotherapy and I think these are still needed.

---

**New Evidence**: Is pertuzumab available in Canada and how would you use this new drug in your clinical practice?

**Dr. Verma**: Pertuzumab, recently approved by the U.S. Food and Drug Administration, is not available at this time in Canada because it is currently going through the Health Canada review process. However, we do have clinical studies, which will be opening soon, to evaluate this drug in the metastatic setting and to see if benefit will transfer to the adjuvant setting. The trial in the adjuvant setting, called Adjuvant Pertuzumab and Herceptin In Initial Therapy of Breast Cancer (APHINITY), will be opening in a number of centres across the country. As long as pertuzumab is approved, funded, and available, I think this will be the new standard treatment approach for patients in the first-line setting. The one challenge with pertuzumab is that the current level of evidence for its safety and efficacy is solely based upon its combination with docetaxel. I think that may limit our use of this drug to a certain degree but results from future studies will address whether or not we can change the chemotherapy backbone. There are studies ongoing to see whether we can combine pertuzumab with paclitaxel, other taxanes, and other chemotherapies like vinorelbine.

---

**New Evidence**: What other breast cancer trial results presented at ASCO 2012 could have a significant impact on clinical practice in Canada?

**Dr. Verma**: In terms of HER2-positive breast cancer, there were a couple of other key presentations, one of which looked at a taxane with lapatinib versus a taxane with trastuzumab. This was the MA31 clinical trial presented by Dr. Karen Gelmon. The authors showed that a taxane plus trastuzumab was superior to a taxane plus lapatinib in prolonging PFS, but there was no significant difference in OS between the treatment arms. This trial was really informative and solidifies the idea that trastuzumab may be better than lapatinib in the first-line, metastatic setting.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-41 trial, presented by Dr. André Robidoux, examined the combination of weekly paclitaxel with lapatinib, trastuzumab, or both drugs following the standard treatment of doxorubicin and cyclophosphamide in the neoadjuvant setting. The authors found that lapatinib and trastuzumab were equally effective but the toxicity profile favoured the trastuzumab arm. Similar to previously reported neoadjuvant studies, the combination of lapatinib and trastuzumab was superior to the single HER2-targeted strategy.

Another metastatic breast cancer trial, the Cancer and Leukemia Group B (CALGB) study, looked at ixabepilone versus weekly paclitaxel versus weekly nanoparticle albumin-bound (nab)-paclitaxel. It showed that weekly paclitaxel was superior to ixabepilone and may be just as good as weekly nab-paclitaxel. The challenge in that study was that 98% of the patients received bevacizumab, so the interpretation of the study is somewhat diluted by this fact. However, there was no incremental benefit of nab-paclitaxel over paclitaxel, so this is also a significant study result that may have an impact on clinical practice.

---

**New Evidence**: What is the biggest challenge that Canadian oncologists face when treating breast cancer?

**Dr. Verma**: The biggest challenge that Canadian oncologists face is related to the cost of the drugs because, even though the benefit that we are seeing is quite significant, the cost of paying for such therapies can also be significant. We do need to ensure that we are utilizing these treatments in an evidence-based manner. We also need to assess the patient’s receptor status with a biopsy of metastatic disease upon relapse because that really guides us in our ability to give the appropriate therapy. That being said, I do think Canadian oncologists should be very proud because we are offering the best possible treatments to our patients. Many of the studies that were presented at ASCO had a Canadian impact. For instance, I am the senior author on the EMILIA study. Dr. Karen Gelmon, from the British Columbia Cancer Agency, is the first author on the MA31 clinical trial. In addition, Dr. André Robidoux, from the Breast Cancer Research Centre at l’Université de Montréal, is the first author on the NSABP B-41 study. This year’s ASCO annual meeting certainly had a true Canadian flavour.
LEUKEMIAS & LYMPHOMAS
New Hope for Patients with Chronic Lymphocytic Leukemia and indolent non-Hodgkin Lymphoma

In June 2012, a beacon paper presenting the perspective of Canadian experts on bendamustine for the treatment of chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (NHL), and mantle cell lymphoma (MCL) was published in Current Oncology. The paper came at a crucial and strategic time as bendamustine has very recently been approved in Canada. It highlights and summarizes the latest research in the field, providing an important background for physicians dealing with hematologic malignancies and for patients with these conditions.

The paper compiles results from the first-line and relapsed-setting studies that show a promising role for bendamustine in CLL, indolent NHL, and MCL treatment. In the first-line setting for CLL, bendamustine monotherapy produced a better response in patients and improved progression-free survival (PFS) as compared with chlorambucil. It was also found to be effective with manageable toxicities in elderly patients with comorbidities when given in combination with rituximab. In relapsed patients, bendamustine monotherapy showed similar efficacy to fludarabine treatment, and was highly effective and well tolerated in high-risk relapsed patients when used along with rituximab. In Canada, patients with CLL currently have an effective standard treatment available that includes FCR (fludarabine, cyclophosphamide, rituximab) and FR (fludarabine, rituximab). However, patients are not all always eligible for the standard treatment and may not tolerate it due to many factors, including associated toxicities and patient comorbidities. Bendamustine may come as an answer to an unmet need for an effective and safe therapeutic agent.

In Canada, the standard treatment for patients with indolent NHL is R-CVP (rituximab, cyclophosphamide, vincristine, prednisone). However, R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin) is also an acceptable alternative. In patients who were treated with bendamustine in combination with rituximab, better PFS and significantly less toxicities were observed as compared with R-CHOP. In light of these findings, bendamustine in combination with rituximab is replacing R-CHOP in many countries as the standard first-line treatment. The use of bendamustine monotherapy in patients who did not respond or relapsed shortly after rituximab treatment resulted in a good overall response rate. Administered in combination with rituximab, bendamustine was safe and showed a better response and longer PFS in relapsed patients as compared with FR.

In August 2012, bendamustine was approved in Canada for the treatment of patients with CLL who had not received any prior therapy and in patients with relapsed indolent NHL who did not respond to rituximab, or whose cancer progressed during or shortly after rituximab therapy. This additional therapeutic option, that will soon be available, brings new hope to patients with CLL and indolent NHL and their healthcare providers. The Lymphoma Foundation Canada will continue its advocacy efforts across the provinces to ensure patients have equal access to treatments, including bendamustine, throughout Canada.
New Protocols for the Treatment of Indolent Lymphomas, Acute Myeloid Leukemia, and Myelodysplastic Syndrome

Combination Therapies for the Treatment of Indolent, Follicular, and Mantle Cell Lymphomas

Bendamustine hydrochloride, a bifunctional alkylating agent, has shown clinical activity in a number of cancers, including breast cancer, small-cell lung cancer, multiple myeloma, chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (NHL), and mantle cell lymphoma (MCL). In light of the growing importance of nitrogen mustards as anticancer agents, bendamustine was developed to improve tolerability without sacrificing clinical activity. Although used extensively for more than 40 years, bendamustine was not studied systematically in lymphoproliferative disorders until the 1990s. Bendamustine is currently approved in the United States and Europe for the first-line treatment of CLL and relapsed indolent NHL.\(^1\) It has recently been approved in Canada in patients with relapsed indolent B-cell NHL who did not respond to or progressed during or shortly following treatment with a rituximab regimen; and in patients with symptomatic CLL who have received no prior treatment.

Achieving effective and durable disease control through the use of agents with minimal toxicity is the overarching goal of treatment. With this approach, the aim is to improve progression-free survival (PFS), overall survival (OS), and quality of life. Despite the abundance of treatment options, indolent NHL and MCL remain incurable with standard therapies.\(^1\)

The standard initial treatment for patients with indolent NHL varies across North America, with both R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) being widely accepted options. However, higher complete response rates and improvements in PFS have been reported with R-CHOP compared with R-CVP.\(^1\)

A phase III study by the German Study Group for Indolent Lymphomas (StiL) compared six cycles of bendamustine plus rituximab (BR) (bendamustine dose: 90 mg/m\(^2\)) with six cycles of R-CHOP in 549 treatment-naïve patients with indolent NHL, MCL, and follicular lymphoma (FL). At the time of initial analysis, the median observation time was 32 months. Although the overall response rates were similar in the two groups, PFS, event-free survival (EFS), and time to next treatment were significantly longer after BR than after R-CHOP (PFS 54.8 months versus 34.8 months; \(p = 0.0002\); EFS: 54 months versus 31 months; \(p = 0.0002\); time to next treatment: median not reached versus 40.7 months; \(p = 0.0002\)). Additionally, when compared with R-CHOP, BR was associated with lower rates of hematologic toxicity, infectious complications, and peripheral neuropathy. Significant differences in hematologic toxicities were observed for neutropenia grade 3/4 (10.7% with BR versus 46.5% with R-CHOP, \(p < 0.0001\)) and for leukopenia grade 3/4 (12.1% with BR versus 38.2% with R-CHOP; \(p < 0.0001\)). A lower number of infectious complications (95 with BR versus 121 with R-CHOP, \(p = 0.0403\)) and peripheral neuropathy (18 with BR versus...
73 with R-CHOP, p < 0.0001) were observed in the BR group. Alopecia was also less common in the BR group (15% versus 62% with R-CHOP); however, a greater number of erythematous skin reactions were reported in the BR group (p = 0.0122).²

At ASCO 2012, studies were presented that highlight emerging strategies using bendamustine in the treatment of indolent lymphoma and MCL. This article reports on three of those studies.

- Updated analysis results from the StiL NHL 1-2003 study indicate that BR is an effective first-line therapy for patients with indolent lymphoma and MCL. Specifically, PFS was significantly improved with BR compared with R-CHOP, with BR showing a better side-effect profile.
- A predictive model analysis of the StiL NHL 1-2003 study demonstrated that BR is a cost-effective alternative to R-CHOP.
- A phase III trial demonstrated that R-CVP was associated with an inferior three-year time-to-treatment failure compared with R-CHOP and fludarabine, mitoxantrone plus rituximab (R-FM) in patients with untreated, advanced FL.


Bendamustine plus rituximab versus R-CHOP as first-line treatment in patients with indolent and mantle cell lymphomas: updated results from the StiL NHL1-2003 study

Background
At ASCO 2012, Rummel and colleagues presented an updated analysis of results (cut-off date of October 31, 2011) from the German Study Group for Indolent Lymphomas (StiL) NHL 1-2003 study.¹²

Study design
- Previously untreated patients with indolent lymphoma and mantle cell lymphoma (MCL) were randomized to receive BR (bendamustine plus rituximab) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for a maximum of six cycles as follows:
  - BR: intravenous (iv) bendamustine 90 mg/m² on days 1 to 2 of each 28 day cycle, plus iv rituximab 375 mg/m² on day 1 of each cycle;²
  - R-CHOP: iv cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², and rituximab 375 mg/m² on day 1 of each 21-day cycle. Oral prednisone 100 mg was administered on days 1 to 5 of each cycle.²
- Patients included in the study were >18 years with previously untreated CD20-positive lymphoma entities including:
  - Grade 1/2 follicular lymphoma (FL) (n = 279);
  - Waldenström’s macroglobulinemia (n = 41);
  - Small lymphocytic lymphoma (SLL) (n = 21);
  - Nodular and generalized marginal zone lymphoma (MZL) (n = 67);
  - MCL (n = 93).
- All lymphomas were stage III or IV with histologies not older than six months.
- The primary endpoint was progression-free survival (PFS), further defined as a decrease of <10% after three years.
- Secondary endpoints included a comparison of overall response rate (ORR), complete response (CR), event-free survival (EFS), and overall survival (OS) between study arms, and toxicity.
Key findings

Baseline characteristics and disposition

- Of the 549 patients randomized in the study, 514 patients were evaluable; BR (n = 261) and R-CHOP (n = 253).
- Median age of all patients across treatment arms was 64 years, with other patient characteristics being well balanced between the arms.
- The majority of patients evaluated (54%) presented with FL (n = 279).

Efficacy

- At a median follow-up of 45 months, PFS was significantly prolonged for patients in the BR group (69.5 months) compared with 31.2 months for R-CHOP (log-rank PFS; \( p = 0.0000148 \); hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.44–0.74). (Figure 1)
- The PFS benefit of BR was independent of age:
  - In patients \( \leq 60 \) years (n = 199), PFS with BR was 71.6 months vs. 30.9 months with R-CHOP (\( p = 0.0022 \), HR 0.52, 95% CI 0.33–0.79);
  - In patients aged >60 years, (n = 315), PFS was 53.6 months vs. 31.5 months with R-CHOP (\( p = 0.0022 \), HR 0.62, 95% CI 0.45–0.84).
- An exploratory analysis demonstrated that, with the exception of MZL, the PFS benefit of BR was maintained in all histological subtypes:
  - Significantly, in patients with FL (n = 279), PFS was not yet reached in the BR group compared with 40.9 months in the R-CHOP group (\( p = 0.0072 \); HR 0.61, 95% CI 0.42–0.87). (Figure 2);

**Figure 1. Progression-free survival after treatment with BR or R-CHOP in patients with indolent and MCL (median follow-up 45 months)**

\[
\text{BR Median 69.5 months} \\
\text{R-CHOP Median 31.2 months}
\]

**Figure 2. Progression-free survival in patients with follicular lymphoma after treatment with BR or R-CHOP**

- Follicular lymphoma International Prognostic Index (FLIPI) subgroups defined as low (0–2 factors) (n = 152) and high (3–5 factors) (n = 127) had longer PFS with BR than with R-CHOP (\( p = 0.0428 \) and \( p = 0.0679 \) for low and high FLIPI subgroups, respectively);
In patients with MCL (n = 93), PFS was significantly prolonged in the BR group at 35.4 months compared with 22.1 months in the R-CHOP group (p = 0.0061; HR 0.50, 95% CI 0.29–0.81);

For patients with Waldenström’s macroglobulinemia (n = 41), a significant difference in PFS of 69.5 vs. 28.1 months was noted between the BR and R-CHOP groups respectively (p = 0.0033; HR 0.33, 95% CI 0.11–0.64).

For patients with normal lactic dehydrogenase (LDH) (62%), PFS was significantly prolonged with BR compared with R-CHOP (p <0.001); in patients with elevated LDH (38%), PFS was numerically, but not significantly increased with BR compared with R-CHOP (p = 0.1182).

ORR was comparable between the BR and R-CHOP groups (92.7% vs. 91.3%, respectively). (Table 1)

A significant difference in CR was observed between the BR group (39.8%) and the R-CHOP group (30.0%), p = 0.021. (Table 1)

OS did not differ between the treatment arms, with 43 and 45 deaths in the BR and R-CHOP arms, respectively. OS after five years was 80.1% for BR and 77.8% for R-CHOP.

Salvage treatments were initiated in 86 patients in the BR group compared with 128 in the R-CHOP group. Of those in the R-CHOP group, 52 patients received BR as a salvage regimen. Salvage treatment was at the discretion of the patient’s physician.

The number of patients receiving autologous stem cell transplantation as a salvage regimen was higher in the R-CHOP group compared with the BR group (13% vs. 5%, respectively).

Secondary malignancies were observed in 20 patients in the BR group compared with 23 in the R-CHOP group, with one hematological malignancy in each group (one myelodysplastic syndrome in the BR group, and one acute myeloid leukemia in the R-CHOP group).

Safety

Grade 3/4 neutropenia was observed in 29% of patients in the BR group (n = 77) compared with 69% in the R-CHOP group (n = 173). (Table 2)

Notably, grade 3/4 lymphocytopenia was more pronounced in the BR group compared with the R-CHOP group (74% vs. 43%, respectively). (Table 2)

Alopecia, a well-known adverse event in patients receiving R-CHOP, was not reported in patients in the BR group (p <0.0001). (Table 3)

Paresthesias, stomatitis, and infectious complications were more common in the BR group but was not dose limiting. (Table 3)

Skin toxicity was reported more often in the BR group but was not dose limiting. (Table 3)
Table 3. Non-hematological adverse events (all CTC grades) in patients with indolent and MCL treated with BR or R-CHOP

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>BR (n = 261) (n)</th>
<th>R-CHOP (n = 253) (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>–</td>
<td>+++</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>18</td>
<td>73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16</td>
<td>47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Erythema</td>
<td>42</td>
<td>23</td>
<td>= 0.0122</td>
</tr>
<tr>
<td>Allergic reaction (skin)</td>
<td>40</td>
<td>15</td>
<td>= 0.0003</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>96</td>
<td>127</td>
<td>= 0.0025</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>8</td>
<td>= 0.0190</td>
</tr>
</tbody>
</table>

BR = bendamustine plus rituximab; CTC = common toxicity criteria; MCL = mantle cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Key conclusions

■ In patients with previously untreated indolent lymphoma, and in elderly patients with MCL, BR demonstrates a significant PFS benefit and improved tolerability compared with R-CHOP.

■ BR can therefore be considered an effective first-line therapy for patients with FL, indolent lymphoma, and MCL.

References:

Su W, et al. ASCO 2012: Abstract 6553

Cost-effectiveness analysis of bendamustine plus rituximab versus R-CHOP in treatment-naive patients with indolent lymphoma and mantle cell lymphoma

Background
Su and colleagues conducted an analysis of the cost-effectiveness of bendamustine plus rituximab (BR) with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in treatment-naive patients with indolent or mantle cell lymphoma (MCL) from the perspective of a third-party healthcare payer in the United States. The results of the analysis were presented at ASCO 2012.

Study design
- A discrete event simulation was developed for a mixed population of patients with MCL or indolent lymphoma.
- For each population, two arms were simulated, each containing 1,000 identical patients with MCL or indolent lymphoma treated with BR or R-CHOP as per the StiL (Study Group for Indolent Lymphomas) NHL (non-Hodgkin lymphoma) 1-2003 trial.
- Baseline patient characteristics (obtained from the StiL NHL 1-2003 trial) included age, sex, disease stage, Mantle Cell Lymphoma International Prognostics Index, and laboratory values (including lactate dehydrogenase level, hemoglobin, and white blood cell count).
- Overall response (OR), overall adverse events (AEs), overall survival (OS), and second-line treatments were assigned based on the StiL NHL 1-2003 trial (n = 549, primarily stage IV MCL and indolent lymphoma).
• Direct medical costs and utilities were estimated based on U.S. databases and published literature. Costs and benefits were discounted at 3% per annum.

• Base case model predictions were performed by selecting regression models that had a best fit to progression-free survival (PFS).

• Model clinical measures included response to treatment, PFS, survival (total life years), and quality-adjusted life years (QALYs).

• Model economic measures were defined as treatment, additional medications, care costs, and costs associated with AEs.

• The incremental cost-effectiveness ratio (ICER) represented the cost per additional QALY gained from BR.

**Key findings**

• In the base case, the model predicted longer mean PFS for BR than for R-CHOP for both MCL (49.8 vs. 28.6 months) and indolent lymphoma (67.9 vs. 51.0 months), respectively.

• QALYs per patient were higher for BR than R-CHOP in MCL (3.51 vs. 2.68 years) and indolent lymphoma (4.42 vs. 3.58 years).

• Predicted life years per patient were also higher for BR than for R-CHOP in both MCL (5.03 vs. 4.41 years) and indolent lymphoma (6.07 vs. 5.39 years).

• In the model outcomes for 10-year costs per patient, initial treatment costs were higher for treatment with BR compared with R-CHOP; however, R-CHOP was associated with higher subsequent treatment and AE costs. (Figure 1)

• Mean per patient costs for MCL were $115,191 for BR compared with $100,261 for R-CHOP, respectively. (Figure 1)

• For indolent lymphoma, mean per patient costs were $134,814 for BR and $110,065 for R-CHOP. (Figure 1)

• Higher complete response and partial response rates for BR than for R-CHOP affected subsequent treatment costs, which were lower for BR by $21,632 for MCL and $24,961 for indolent lymphoma; AE costs were lower by $10,113 and $10,570, respectively. (Figure 1)

• As calculated per patient, ICERS for BR compared with R-CHOP were $18,161 per QALY for MCL and $29,549 for indolent lymphoma. Sensitivity analysis indicated a 98.3% probability that BR would be cost-effective at ≤$50,000 compared with R-CHOP for the overall patient population. (Figure 2)
Key conclusion

In patients with MCL or indolent lymphoma, the model demonstrates that BR is a cost-effective alternative to R-CHOP, in addition to providing patients with more QALYS. Alternative regression models confirmed the robustness of these results.

References:


R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: final results of the FOLL05 trial from the Fondazione Italiana Linfomi

Background

The optimal chemotherapy regimen for patients with advanced, active follicular lymphoma (FL) has not yet been established. Federico and colleagues conducted a phase III study comparing the efficacy of regimens of R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), and R-FM (rituximab, fludarabine, mitoxantrone) in this patient population. The final results of this study were presented at ASCO 2012.1

Study design

- Previously untreated patients with advanced FL (n = 534) were randomly assigned to receive eight cycles (every 21 days) of R-CVP, or six cycles (every 21 days) of R-CHOP or R-FM as follows:
  - R-CVP: intravenous (iv) prednisone 40 mg/m² on days 1 to 5, plus cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², and rituximab 375 mg/m² on day 1;
  - R-CHOP: iv prednisone 100 mg/m² on days 1 to 5, plus cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², and rituximab 375 mg/m² on day 1;
R-FM: iv fludarabine 25 mg/m² on days 1 to 3, plus mitoxantrone 10 mg/m² and rituximab 375 mg/m² on day; no maintenance therapy with rituximab was allowed.

- The primary end point was time-to-treatment failure (TTF). TTF events included failure of induction therapy, progressive disease or relapse, withdrawal due to unacceptable toxicity, shifting to another therapy after at least one cycle, and overall survival (OS).
- Overall response rate (ORR) was defined as complete response (CR) plus partial response (PR).
- In order to show a hazard ratio (HR) between each of the experimental arms and standard arm of 0.53, 534 patients were recruited (n = 178 per arm) with four years of accrual and one year of follow-up.

**Study design**

**Baseline characteristics and disposition**

- Between February 2006 and September 2010, 534 patients were enrolled 30 of whom were subsequently excluded due to violation of inclusion criteria.
- The intent-to-treat (ITT) population (n = 504) was as follows: R-CVP (n = 168), R-CHOP (n = 165), and R-FM (n = 171).

- The ITT population had the following baseline characteristics:
  - The median age of patients was 56 years (range: 30–75 years), with 33% over the age of 60 years;
  - Sixty-three percent (63%) of patients had stage IV disease, and 92% had stage III/IV disease;
  - Thirty-seven (37%) had 3–5 follicular lymphoma international prognostic index (FLIPI) scores and 27% had 3–5 FLIPI2 scores.

**Efficacy**

- At a median follow-up of 34 months (range: 1–70 months), 212 events for TTF were recorded across all treatment arms. Both R-CHOP and R-FM were shown to be superior to R-CVP across defined TTF events. (Figure 1 and Table 1)
- The rate of three-year TTF was significantly lower with R-CVP than with R-CHOP (45% vs. 63%, p = 0.007) or with R-FM (45% vs. 59%, p = 0.020). (Figure 1)

- At the end of induction treatment, ORR for the entire study group was 91% and was similar across groups (p = 0.247).
- At a median follow up of 34 months, the three-year OS rate was similar for the R-CVP, R-CHOP, and R-FM groups (98%, 95%, and 93%, respectively).

**Key findings**

**Baseline characteristics and disposition**

- Between February 2006 and September 2010, 534 patients were enrolled 30 of whom were subsequently excluded due to violation of inclusion criteria.
- The intent-to-treat (ITT) population (n = 504) was as follows: R-CVP (n = 168), R-CHOP (n = 165), and R-FM (n = 171).
Safety
- The most common AE was grade 3/4 neutropenia. Patients treated with R-FM had a higher incidence compared with R-CVP (63.5% vs. 27.7%, \( p < 0.001 \)) and R-CHOP (50%, \( p = 0.015 \)). (Figure 2)
- Secondary malignancies were registered as late events in 23 patients (2%, 3%, and 8% in R-CVP, R-CHOP, and R-FM, respectively).

<table>
<thead>
<tr>
<th>Status</th>
<th>R-CVP (n = 168)</th>
<th>R-CHOP (n = 165)</th>
<th>R-FM (n = 171)</th>
<th>Total ITT population (n = 504)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Censored</td>
<td>82 (42)</td>
<td>105 (64)</td>
<td>105 (61)</td>
<td>292 (58)</td>
</tr>
<tr>
<td>&lt;PR</td>
<td>19 (11)</td>
<td>10 (6)</td>
<td>14 (8)</td>
<td>43 (8)</td>
</tr>
<tr>
<td>Therapy shift</td>
<td>9 (5)</td>
<td>4 (2)</td>
<td>7 (4)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>3 (2)</td>
<td>5 (3)</td>
<td>2 (1)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Relapse</td>
<td>55 (33)</td>
<td>40 (24)</td>
<td>38 (22)</td>
<td>133 (26)</td>
</tr>
<tr>
<td>Death in CR/PR</td>
<td>–</td>
<td>1 (1)</td>
<td>5 (3)</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

Overall log rank test, \( p = 0.002 \)

CR = complete response; ITT = intent-to-treat; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; R-FM = rituximab, fludarabine, mitoxantrone

Figure 2. Adverse events (grade ≥3) in patients with FL treated with R-CVP, R-CHOP, or R-FM

Fl = follicular lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; R-FM = rituximab, fludarabine, mitoxantrone

Key conclusions
- This trial showed that R-CVP was associated with an inferior three-year TTF compared with R-CHOP and R-FM.
- OS was similar among study arms, but R-FM was associated with a higher rate of secondary malignancies.
- The investigators concluded that R-CHOP had the best risk/benefit ratio.

In patients with either advanced indolent non-Hodgkin lymphoma (NHL) or mantle cell lymphoma (MCL), the goal of treatment is to achieve effective and durable disease control using agents that minimize toxicity, with the aim of optimizing progression-free survival (PFS), overall survival (OS), and quality of life (QoL). Although upfront therapy for patients with indolent NHL varies across North America, R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) are widely accepted options. Most Canadian centres tend to prefer R-CVP for the majority of patients with indolent lymphoma.

The German Study Group for Indolent Lymphomas (StiL) by Rummel et al. compared six cycles of bendamustine plus rituximab (BR) with six cycles of R-CHOP in treatment-naive patients with indolent NHL and MCL. Results indicated that PFS was markedly improved with BR compared with R-CHOP, despite BR showing a better adverse-event profile. Although this study had a non-inferiority design, it is scientifically valid to use the results to conclude that BR is superior to R-CHOP based upon the large sample size, intention-to-treat analysis, and non-overlapping confidence intervals surrounding the PFS estimates of the two treatment arms. As stated earlier, most centres in Canada use R-CVP instead of R-CHOP as first-line therapy of indolent NHL. Nevertheless, R-CHOP is the more appropriate comparator for BR because it confers longer PFS than R-CVP for patients with indolent lymphoma, and is the most commonly used regimen for MCL. The difference in PFS rates would likely have been even more dramatic if BR had been compared with R-CVP instead of R-CHOP. Although there was no difference in OS reported between groups, given the long median survival for indolent NHL (i.e., longer than 15 years for patients with follicular NHL under 60 years of age), major improvements in OS were not expected from this study, nor are they necessary to change practice as long as the dramatic improvement in PFS does not come at a cost of higher toxicity.

Treatment safety is a key consideration in the management of indolent lymphoma. In Canada, R-CVP is used in favour of R-CHOP because of its more tolerable toxicity profile. The doxorubicin in R-CHOP is associated with neutropenia, infection, stomatitis, and alopecia, all of which affect QoL and general well-being. The vincristine in both R-CHOP and R-CVP may cause bothersome peripheral neuropathy; something not seen with BR. Although the safety of BR compared with R-CVP was not evaluated in the StiL study, the results show that BR is very well tolerated, perhaps to a similar degree as one might expect with R-CVP. Therefore, we can extrapolate findings from the StiL study and expect a change in practice in Canada from R-CVP to BR. In my opinion, a major improvement in PFS, as seen with BR, without obvious or significant worsening in toxicity, is sufficient to change practice.

Should any patients with either indolent NHL or MCL not receive BR as initial therapy? To answer this question, it is important to look at which patients were excluded from the StiL study. Although these patients likely have a higher risk for toxicity, comorbidities would need to be severe not to justify its use outside of clinical trials. Clinicians will likely be swayed by the significant PFS and toxicity advantages BR demonstrated in this study, and use BR in situations where they currently feel comfortable using R-CVP. In some situations this may require dose modifications, similar to those commonly used for other chemotherapy regimens. From the study results it is clear that age alone should not be a deterrent to using BR. In fact, PFS and safety benefits of BR were independent of age, thus supporting the use of a BR regimen across age groups, including patients older than 60 years.

Su and colleagues conducted an analysis of the cost-effectiveness of BR compared with R-CHOP based on the results from the StiL Group, conducted by Rummel et al. Analyses of cost-effectiveness such as this one can be problematic in that they are highly influenced by many assumptions as well as the method of modelling. As both treatments had a very high response rate (over 90%), all patients were eligible for maintenance treatment. Consequently, it is therefore somewhat difficult to comprehend the differences in the overall cost of maintenance treatment. Additionally, subsequent treatments after relapse were included as part of this analysis; however, the choice of subsequent treatments for relapsed indolent NHL is variable and controversial, and the justification for the assumptions used in the analysis is questionable.
and unclear. A final concern with this analysis is that the U.S. cost estimates and data are taken from the 2009 StiL results, but not the updated 2012 analysis. In 2009, the PFS advantage was not as significant as in 2012; therefore, bendamustine may be even more cost-effective than indicated in the results of this modelling analysis.

This methodology used by Su et al. is not robust as it is hard to be exact, and is not necessarily transferable to Canadian costs. At most, one can suggest that the cost-effectiveness of BR seems to be within an acceptable range of approximately $50,000 compared with R-CHOP. The costs of R-CVP and R-CHOP are probably comparable. The cost of adverse events may be lower with R-CVP, and the administration costs of R-CHOP may be higher due to more frequent use of granulocyte colony-stimulating factor. However, the greatest cost differential between these two regimens is probably the cost of subsequent therapies, which is somewhat higher with R-CVP within the first five years after treatment due to a higher relapse rates.

The study by Federico et al. comparing fludarabine, mitoxantrone plus rituximab (R-FM), R-CVP, and R-CHOP provides some insight into current upfront therapies in patients with advanced follicular lymphoma. Higher PFS was seen after the more intensive R-FM and R-CHOP regimens compared with R-CVP. However, in patients with indolent NHL, QoL and toxicity are highly important factors influencing treatment decisions. Although Federico et al. concluded that R-CHOP has the best risk-benefit ratio, this conclusion is controversial. The small sample size and short follow-up preclude adequate evaluation of late complications, tolerance of subsequent therapies, and of course, OS. While hair loss, stomatitis, and neutropenia following R-CHOP are important early toxicities for patients, the even more serious toxicities that appear later need to be considered. For example, clinicians are concerned about delayed secondary myelodysplastic syndrome (MDS)/leukemia and cardiotoxicity following anthracyclines, and prolonged immune suppression, poor marrow reserve, and secondary MDS/leukemia following fludarabine/mitoxantrone. These very serious complications would not have been captured in this study because of the relatively short follow-up.

Canadian physicians are unlikely to be significantly influenced by the results of the study by Federico et al. Given the improved efficacy and safety profile of BR, Canadian physicians are likely to recommend the use BR over R-CVP once it becomes available for patients with indolent NHL and MCL. Provincial funding and cost considerations will probably be the major factors affecting timing of this change in practice.
An Interview with Dr. Mathias Rummel on the use of bendamustine in CLL, indolent NHL, and MCL

At the CBMTG 2012 Annual Meeting, New Evidence spoke with Dr. Mathias Rummel, head of the Department of Hematology at the Clinic for Hematology and Medical Oncology at the Justus-Liebig University Hospital, Giessen, Germany

General:

**New Evidence:** Please describe bendamustine’s unique mechanism of action.

**Dr. Rummel:** Bendamustine was developed over 50 years ago in the former East Germany. The chemical structure of bendamustine is that of an alkylator owing to the inclusion of a nitrogen mustard group. However, the compound also includes a benzimidazole ring, which is similar to that found in purine analogues such as fludarabine and cladribine. Bendamustine, therefore, is not purely an alkylator or purine analogue, but also appears to be in a class of its own. Currently, we believe bendamustine functions more as an alkylator than a purine analogue. However, *in vitro* studies show that bendamustine is active in cell lines that are refractory to other alkylators. The mechanism of action (MoA) of bendamustine is therefore unique compared with that of other chemotherapeutic agents.

**New Evidence:** Please discuss the infusion rate and administration of bendamustine.

**Dr. Rummel:** It is recommended that bendamustine be infused within 30 to 60 minutes. This short infusion time is very important as it is necessary to achieve a high peak concentration of the drug early on in the infusion since bendamustine has a very short half-life. The product information does recommend infusing bendamustine with 500 mL of fluid; however, in my opinion, this is too much fluid to be given over such a short infusion time.

**New Evidence:** How do you manage skin and hematologic toxicities seen with bendamustine?

**Dr. Rummel:** Hematologic toxicity is the key toxicity associated with bendamustine; however, studies have shown the incidence of hematologic toxicity to be manageable and much lower than that observed with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone). In contrast to other alkylating agents, growth factors are not needed with the use of bendamustine. Skin toxicities, including rash and skin reactions, are occasionally observed with bendamustine. These skin toxicities occur in approximately 5% to 10% of patients; however, they are rarely dose limiting. In Germany, skin reactions following bendamustine are not often, if ever, reported and are thought to be very rare. In the United States, there have been three cases of Stevens-Johnson syndrome in which allopurinol and antibiotics were given to the patients. It is, therefore, unclear whether skin toxicities are a concern with the use of bendamustine.
New Evidence: What are your recommendations for the use of bendamustine in patients with renal impairment?

Dr. Rummel: A major advantage of bendamustine is the ability to use it in patients with renal insufficiency. In my practice, we also give bendamustine to patients with multiple myeloma, including those with low creatinine clearance. In the United States, caution is recommended with the use of bendamustine in patients with a creatinine clearance below 40 mL/minute. However, this caution, on the part of the Federal Drug Administration, is based on a lack of data in this patient population. In Germany, bendamustine is routinely used in patients with renal insufficiencies and is the preferred agent in these patients.

New Evidence: What is the rate of secondary malignancies with the use of bendamustine?

Dr. Rummel: When one considers that bendamustine has properties of an alkylating agent, one would expect there to be a higher rate of secondary malignancies with this agent. However, in both of our studies using bendamustine plus rituximab (BR) in patients with non-Hodgkin lymphoma (NHL), BR did not increase the rate of secondary malignancies. In the study comparing upfront BR with R-CHOP, the rate of secondary malignancies was comparable across groups (20 patients in the BR group and 23 patients in the R-CHOP group after four years of follow-up). In addition, we have not observed an increased risk of myelodysplastic syndrome (MDS) in patients given BR. Whether bendamustine increases the risk of MDS will need to be examined in trials with longer follow-up.

New Evidence: Where else do you see a role for bendamustine?

Dr. Rummel: In addition to its use in chronic lymphocytic leukemia (CLL) and NHL, we believe that BR is a very good treatment option for patients with relapsed diffuse large B-cell lymphoma (DLBCL) in elderly patients who are not eligible for high-dose treatment or autologous stem cell transplant. A randomized study in Japan showed response rates of around 70% in patients with DLBCL; BR is therefore a very effective option in these patients. While we do not yet have a similar study in Germany, in our practice we all give a bendamustine-based regimen to patients with relapsed DLBCL who cannot tolerate a high-dose treatment approach.

CLL:

New Evidence: What are the advantages of bendamustine as a treatment for CLL?

Dr. Rummel: We know that fludarabine plus cyclophosphamide and rituximab (FCR) is supported by the most evidence for the treatment of CLL. However, if patients are not fit enough for FCR, BR is a very good alternative for first-line treatment as well as in the relapsed setting. Given that BR appears to be very efficacious, the German CLL Study Group undertook a randomized comparison of FCR versus BR in the CLL10 study: this study is now closed and we are awaiting results. The objective of the CLL10 study is to show that BR is as effective as FCR but with lower toxicities. Interestingly, in Germany, we have a registry for lymphoproliferative diseases in which it has been documented that BR is the preferred first-line treatment for CLL and not FCR. The German experience is that we are confident with the use of BR given its efficacy in CLL, despite the fact that the evidence for this regimen is not as good as that for FCR.

New Evidence: What dose and what regimen of bendamustine do you recommend using in CLL in the front-line and relapsed settings?

Dr. Rummel: Currently, I use BR for the treatment of CLL in the first-line and the relapsed settings. Bendamustine by itself was shown to be effective in rituximab-refractory patients with indolent lymphomas, and it has achieved registration in that indication. However, the real value of bendamustine is to use it before patients become refractory to rituximab. Consequently, we are investigating BR as first-line and second-line treatment of CLL.

If one uses BR, the recommended dose is 90 mg/m² given on two consecutive days. While this dose is lower than the official dose of 120 mg/m² every three weeks (in rituximab-refractory patients), I think that dose is too high. We therefore use 90 mg/m² because bendamustine is not excessively hematotoxic at that dose. Worldwide, our colleagues are following our recommended dose of 90 mg/m² when combined with rituximab on two consecutive days. However, in patients with relapsed CLL who have been pre-treated with fludarabine-containing regimens, we start with a dose of 70 mg/m².
**New Evidence:** In which patients with CLL do you use bendamustine?

**Dr. Rummel:** As I have extensive experience using BR, I prefer to use this regimen in my clinical practice as first-line treatment of CLL. I use BR particularly in those patients who have been pre-treated with a fludarabine-based regimen. Other than in patients who do not tolerate bendamustine or are experiencing severe hematotoxicities or skin reactions after the first or second cycle, I cannot think of a situation where bendamustine would not be beneficial. In addition, one can give this agent to very elderly and frail patients as it is often easier to administer two short infusions of bendamustine than to ask patients to swallow at least 10 tablets of chlorambucil. However, based purely on the current evidence, I do officially recommend using FCR over BR in the first-line setting for fit patients with CLL.

**Indolent NHL & MCL:**

**New Evidence:** What is the advantage of bendamustine as a treatment for indolent NHL and MCL?

**Dr. Rummel:** The advantage of bendamustine is that one can avoid using an anthracycline-containing regimen in places that would typically use R-CHOP as first-line treatment. In countries such as England and Canada, some clinicians believe using R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) is sufficient; however, in most countries, R-CHOP is used more frequently than R-CVP. In comparison with R-CHOP, BR is less toxic and better tolerated by patients. In addition, there is less hair loss with BR and overall, patients experience fewer side effects with BR than with R-CHOP. An additional advantage of bendamustine is that it does not result in organ toxicities, while these are often a concern with anthracycline-containing compounds.

**New Evidence:** In which patients with indolent NHL and MCL do you use bendamustine?

**Dr. Rummel:** In my clinical practice, I recommend BR as first-line treatment in nearly all indolent lymphomas. In patients with MCL and in younger patients, I would plan a more aggressive approach such as high-dose cytarabine followed by a stem cell transplant. This aggressive approach is being used in my hospital in younger patients with MCL. However, an aggressive approach is not meaningful in indolent and follicular lymphoma (FL), or in patients with mucose-associated lymphoid tissue (MALT) or small lymphocytic lymphoma (SLL). For these typical indolent lymphoma patients, I recommend BR as the preferred treatment regimen.

**New Evidence:** What regimen of bendamustine do you recommend using in indolent NHL?

**Dr. Rummel:** Thus far, 90 mg/m² is considered to be the preferred and optimal dose of bendamustine for the treatment of indolent NHL. However, a higher dose of bendamustine has never been tested in this patient population. If a higher dose of bendamustine were to result in a complete response of approximately 40%, then using a higher dose should be considered to improve treatment success. Results of future clinical trials should aid in determining the optimal treatment dose of bendamustine in this setting.

**New Evidence:** Describe the efficacy results of your study using BR in patients with indolent NHL.

**Dr. Rummel:** We have conducted a phase III trial examining the efficacy and safety of first-line treatment with BR versus R-CHOP in 514 patients with different histologies. The majority of patients had FL (50% of patients); the remaining patients had MCL, MALT, and Waldenström’s macroglobulinemia. We started the trial in 2003 and planned to assess the statistics for the total patient group because, in the majority of cases, one would treat these patients with R-CHOP as the standard approach. Interestingly, the trial was planned using a non-inferiority design with the idea that the efficacy of BR and R-CHOP would be comparable. However, the final results demonstrated that the efficacy of BR was superior to
R-CHOP. The difference in efficacy was large and clinically meaningful, because it was not only statistically significant with a hazard ratio of 0.58 ($p < 0.0001$), but also the median progression-free survival (PFS) was 69 months after BR compared with 31 months after R-CHOP. When looking at a subgroup of patients with FL, the median PFS after BR has not yet been reached and was 41 months after treatment with R-CHOP. This difference in PFS in patients with FL was statistically significant in favour of BR.

**New Evidence**: Describe the safety results of your study using BR in patients with indolent NHL.

**Dr. Rummel**: In our phase III study in patients with indolent NHL, BR was better tolerated than R-CHOP in the first-line setting. Results demonstrated that BR was less hematotoxic than R-CHOP and less granulocyte colony-stimulating factor (G-CSF) was administered with BR (20% of all cycles with R-CHOP versus 4% of all cycles with BR). In addition, hair loss occurred with R-CHOP but was not reported after treatment with BR. Neurotoxicities and stomatitis were also more common with R-CHOP than with BR. Although we did observe more skin toxicities and infections with BR, these were not dose limiting.

**New Evidence**: As a result of studies in indolent NHL, do physicians in Germany routinely use BR instead of R-CHOP in the first-line setting?

**Dr. Rummel**: In Germany, bendamustine is by far the most common approach for the first-line treatment of indolent lymphoma. This use of BR has changed from 10 years ago when R-CHOP was the standard approach. After we presented the results of our phase III study using first-line BR, clinicians in Germany were convinced of the efficacy and safety of this regimen. Of course, the situation in Germany is unique because bendamustine has been registered for more than 20 years, and it is fully approved and reimbursed.

**New Evidence**: Describe the design of your study using BR in relapsed indolent lymphoma.

**Dr. Rummel**: The aim of our phase III study in relapsed indolent lymphoma was to examine the efficacy and safety of BR in this setting. Based on the recommendations of our steering committee and the results of a previous study that showed FR was an effective salvage treatment, we decided to use FR as the comparator. In the FR treatment group, we used a three-day regimen of fludarabine based on a recommendation from a previous study by Czuczman, *et al.* published in 2005. In this previous study, dose reductions were recorded due to an unexpected high rate of toxicity when a five-day regimen was used. It is therefore possible that the lower dose of FR used in our study may have impacted the results.

In our study, most patients were pre-treated with a CHOP-based regimen and the majority had previously been given rituximab. In addition, around 10% of patients were pre-treated with bendamustine or fludarabine as first- or second-line treatment. In total, we allowed participants to have received a maximum of three regimens prior to recruitment.

**New Evidence**: Describe the results of your study using BR in relapsed indolent lymphoma.

**Dr. Rummel**: In our study in the relapsed setting, it was a surprise that BR was so much more effective than FR. Our study demonstrated an 82% overall response rate (ORR) with BR, which is what would be expected in relapsed disease. However, after treatment with FR, we saw only a 49% ORR. Therefore, FR was very ineffective in inducing a sufficient response in the relapsed setting. In patients who achieved a response after FR, remission duration was very similar to BR. However, owing to the low ORR achieved with FR, PFS was by far inferior with FR compared with BR. Overall, the median PFS was approximately 30 months with BR, compared with 11 months for FR.
New Evidence: Please describe your standard treatment for fit patients with chronic lymphocytic leukemia (CLL).

Dr. Eichhorst: The CLL8 phase III clinical trial compared immunochemotherapy with fludarabine plus cyclophosphamide and rituximab (FCR) versus chemotherapy with fludarabine plus cyclophosphamide (FC) as a first-line treatment for patients with CD20-positive CLL. This study was the first to show a benefit in overall survival (OS) in one treatment group compared with another. The addition of rituximab to FC as a first-line treatment improved response and progression-free survival (PFS) as well as OS in physically fit patients. Based on the results of CLL8, we treat our fit patients with six cycles of FCR.

New Evidence: What are your criteria for determining patient eligibility for aggressive treatments such as FCR?

Dr. Eichhorst: I personally recommend using the cumulative illness rating scale (CIRS), which rates according to whether there are comorbidities in organ systems. A score of 0 indicates the organ system is not compromised, whereas a score of 4 indicates a life-threatening illness or impairment. To be considered for FCR, a patient should have an overall CIRS score of 6 or less and no score of 4 in any organ system. In addition, I think it is important to estimate physical fitness by checking to see if the patient is able to perform daily functions, such as dressing themselves. Patients who have a CIRS score of 6 or less, are able to perform daily functions, and have normal creatinine clearance would receive FCR. If patients have impaired renal function, they would not be eligible for FCR because the chemotherapeutic agents would not be metabolized properly, resulting in prolonged toxicity.

New Evidence: Do you use age as a criterion for determining fitness? Please describe.

Dr. Eichhorst: We do not consider age a criterion for determining patient fitness, but instead focus more on physical aspects and the CIRS score. It is natural that with increasing age, patients will have increasing comorbidities and impaired renal function. According to the above criteria, physically fit patients over 80 years of age are rare, so generally they would not be treated with FCR.

New Evidence: What percentage of your patients is not eligible for aggressive treatments such as FCR?

Dr. Eichhorst: The majority of patients at my centre, which is a university centre, are physically fit and eligible to receive FCR but this is not the norm. In general, less than half of patients with CLL are physically fit and could receive FCR.

New Evidence: What type of patients should not be given fludarabine?
**Dr. Eichhorst:** In fit patients, in combination with cyclophosphamide and rituximab, there is no reason not to give fludarabine. With FCR we have not seen an increase in autoimmune hemolysis; however, with fludarabine monotherapy there is an increase.

**New Evidence:** What treatment do you offer patients who are borderline fit/unfit?

**Dr. Eichhorst:** So far, in elderly and unfit patients, there is no clinical evidence to show that any chemoimmunotherapy is superior to chlorambucil in terms of OS. Thus, in unfit patients with severe comorbidities we give chlorambucil monotherapy, which is delivered orally. As we do not have fludarabine as oral therapy, it means that patients with comorbidities must come to the clinic for five days for infusions, making the treatment relatively complicated for them. Oral chlorambucil is a more straightforward treatment for these patients.

**New Evidence:** What treatment do you offer patients with mild-to-moderate renal dysfunction?

**Dr. Eichhorst:** Bendamustine is suitable for use in patients with renal insufficiency. So we use a lot of bendamustine plus rituximab (BR) in patients with mild renal dysfunction, who are not eligible for FCR. If these patients received FCR as a first-line treatment then relapsed after two years, I would recommend BR. Also in patients who received chlorambucil as first-line treatment and then subsequently relapsed, bendamustine or BR might be considered.

**New Evidence:** In which patients do you offer bendamustine?

**Dr. Eichhorst:** Because BR induces higher rates of myelotoxicity than bendamustine alone this regimen it is too toxic for some unfit patients. For those patients, bendamustine monotherapy might be considered. In unfit patients with a high lymphocyte count, bendamustine alone might be given for the first course of treatment. When their leukocyte count comes down, rituximab could be added for the second or third cycle of treatment.

**New Evidence:** Are there any patients who are too frail to be given BR?

**Dr. Eichhorst:** We would not give BR to patients with severe comorbidities or with a CIRS score of 4 in any organ system. For example, if a patient has heart problems, the need to give fluid with bendamustine infusions might result in congestive heart failure. Also, patients who have a history of myelosupression with infection would need to be careful with the combination of BR because it can cause some hematological toxicities.

**New Evidence:** What dosing regimen of bendamustine do you use?

**Dr. Eichhorst:** For first-line therapy in combination with rituximab, we give 90 mg/m² of bendamustine on days 1 and 2, two consecutive days, and repeat every 28 days for a total of six cycles. In the relapsed setting, we give 70 mg/m² on days 1 and 2 for six cycles. We give rituximab on day 0 of the first cycle and on day 1 of the second cycle, similar to FCR (375 mg/m² for the first cycle and then 500 mg/m² for cycles two through six). For first-line bendamustine monotherapy, we give 100 mg/m² on days 1 and 2. In relapsed treatment, we reduce the bendamustine dose to 80 mg/m² as monotherapy. In a clinical trial of heavily pretreated patients the dose was reduced to 60 mg/m², which might mean that the dose would need to be reduced further in patients with pre-existing myelotoxicities.

**New Evidence:** What are the advantages of bendamustine as a treatment for CLL?

**Dr. Eichhorst:** One of the advantages of bendamustine is that it can be given to patients with renal function impairment. If the patient has few other comorbidities, then treatment with BR may be a good option. Also, treatment with bendamustine may have less hematological toxicity and lower rates of infection than treatment with FCR, but this is not yet proven.

**New Evidence:** Do you have any safety concerns with the use of bendamustine?
**Dr. Eichhorst:** Combination therapy with BR can cause some myelotoxicities. In follicular lymphoma, we have seen some allergic reactions to bendamustine and some fever during administration. Although it is rare, we do see some skin reactions. When treating patients with bendamustine, physicians should not administer allopurinol concomitantly on the days of infusion because this might cause severe epidermal damage, specifically toxic epidermal necrolysis. Usually we give allopurinol before administration of bendamustine but stop on the day of infusion and then restart on days following infusion.

**New Evidence:** What treatments do you offer patients with relapsed CLL?

**Dr. Eichhorst:** Patients who relapse early (two years or less after first-line treatment) have a poor prognosis. Independent of cytogenetics, we aim for allogeneic stem cell transplant (SCT) in these patients. We often give alemtuzumab with or without dexamethasone, or fludarabine plus alemtuzumab prior to transplantation as well as rituximab with dexamethasone, cytarabine, and cisplatin. For patients without a 17p deletion we can also use BR. It is important that the patient will have very good partial response or complete response before proceeding to allogeneic SCT.

In patients who relapsed after more than two years after first-line treatment, first-line therapy can be repeated, but a switch to BR is also possible. This is a common practice. Also, patients who relapse later they are usually older and have more comorbidities, so it makes sense to leave BR for second-line treatment.

**New Evidence:** What is the efficacy of bendamustine in patients with cytogenetic abnormalities?

**Dr. Eichhorst:** According to a phase II clinical trial, patients with 11q deletions respond very well to bendamustine treatment; however, patients with a 17p deletion do not respond. It is important that you detect a TP53 deletion or mutation prior to treatment because these patients will have a poor prognosis with bendamustine. To test for the deletion we use fluorescence *in situ* hybridization (FISH). For detection of TP53 mutation a molecular cytogenetic analysis is necessary. This is an expensive evaluation but it is important since it has implications for treatment decisions. Even in unfit patients, we do this examination because these patients should not be treated with chlorambucil or bendamustine.

**CLL10 study:**

**New Evidence:** Please describe the design of the CLL10 study.

**Dr. Eichhorst:** The CLL10 study is a phase III clinical trial comparing FCR with BR as first-line treatment in physically fit patients with CLL. The primary outcome measure is PFS rate after 24 months. In addition, the study will look at whether BR is less toxic than FCR. With FCR, we see severe infections in 25% of patients and sometimes we see prolonged leukocytopenia. The hypothesis of the study is that BR may be better tolerated with lower rates of neutropenia and leukocytopenia and therefore may result in a lower rate of severe infection.

Patients included in the study had Binet stage C disease or stage B or A disease showing symptoms and requiring treatment. Other patient characteristics include a CIRS score of 6 or less, normal renal function, and no 17p deletion as detected by FISH. The patient criteria are similar to those of the CLL8 study with the exception of the 17p deletion as an exclusion criterion.

The study started in September 2008 and finished recruitment in June 2011. The interim analysis will be done in 2013 and we should have the interim results at the end of 2013.

**New Evidence:** How generalizable will the study population be to a real-life setting?

**Dr. Eichhorst:** Approximately 15% to 20% of the study participants are over 70 years of age. This is in contrast to the real-life setting where more than 50% of patients are over 70 years of age at onset. When treatment is required, 60% to 70% of patients are over 70 years old.

**New Evidence:** How might results of the CLL10 study influence practice?

**Dr. Eichhorst:** We expect that treatment with BR will be as effective as FCR; therefore, we think that BR will become the new standard of treatment in most fit patients. In patients who do not tolerate BR due to allergic reactions we would switch to FCR.
AT LUNDBECK CANADA, WE’RE COMMITTED TO SUPPORTING PATIENTS WITH CLL AND iNHL.

Lundbeck Oncology: our new line of attack

Find out more, contact Lundbeck at 1 800 586-2325.
Spotlight: Fludarabine-refractory CLL

Management of Fludarabine Refractory-Patients with CLL:
Summary of the Presentation by Dr. Michael Hallek at CCOLD

As part of the chronic lymphocytic leukemia (CLL) session at CCOLD 2012, Dr. Michael Hallek, Professor of Medicine, and Director and Chair of the Department of Internal Medicine at the University of Cologne, Germany, presented data on selecting therapy for fludarabine-refractory patients with CLL.

Heterogeneity of CLL
Heterogeneity in chronic lymphocytic leukemia (CLL) applies to the patient, to the disease, and to the treatment options. Patients vary in age (though in general, CLL patients tend to be older), fitness level, and presentation of comorbidities; these factors impact the ability of the patient to tolerate therapy. The disease itself varies in stage at diagnosis, which will affect treatment decisions; in turn, these treatment decisions impact the clinical course of the disease. For CLL in particular, it seems that there is a large discordance globally around approaches to treatment. Guidelines for the treatment of CLL do not exist and are difficult to devise for this disease state because of the varying outcomes based on the selection of initial therapy. The choice of first- and second-line therapies therefore has a significant impact on patient outcomes and on subsequent therapeutic options.

Fludarabine-refractory CLL and patients at high risk of relapse following FC/FCR
The definition of fludarabine-refractory disease can be relatively vague and confusing, with numerous variations being included in clinical trials and protocols. The most widely accepted definition is that from MD Anderson, which defines refractory disease as treatment failure or disease progression within six months of the last anti-leukemic therapy. Patients who relapse within six months after treatment with fludarabine and cyclophosphamide (FC) or fludarabine, cyclophosphamide, and rituximab (FCR) are considered to be fludarabine refractory, generally have a worse prognosis, and are classified as having high-risk disease. The definition of a high-risk CLL patient has been developed to justify the use of allogeneic stem cell transplantation (SCT). According to this definition, patients can be classified as high risk if they are refractory to purine analog-based therapy or to autologous hematopoietic stem cell transplantation.

Minimal residual disease (MRD) following treatment has been linked to prognosis in CLL as well and the CLL8 study provided evidence for superior survival in patients treated with FCR compared with FC. A recent multivariate analysis of the CLL8 data suggested that the quality of response, as assessed by both clinical parameters and MRD, is extremely important with respect to outcomes. Patients can be categorized by MRD into low (<10^-5), intermediate (10^-5 to <10^-2), and high-level (≥10^-2) groups. Patients with low MRD have a better prognosis, as evidenced by data demonstrating that low MRD levels during and after therapy are associated with longer progression-free survival (PFS) and overall survival (OS; p <0.0001). Furthermore, FCR is more efficient at inducing low MRD than FC. These
data suggest that the ability to identify high-risk patients could allow for optimization of therapy. High-risk patients who relapse within two years of completing FCR therapy can almost entirely be defined by the following criteria:

- High MRD levels of $\geq 10^{-2}$
- Intermediate MRD levels of $\geq 10^{-4}$ to $<10^{-2}$ and one of the following:
  - 17p deletion;
  - p53 mutation;
  - Unmutated IgVH.

These criteria allow for the separation of patients into high- and low-risk groups with very distinct times to progression, with low-risk patients having a significantly longer PFS. (Figure 1)

**Figure 1. CLL8 patients at high and low risk of progression**

The separation of patients into high- and low-risk groups is also correlated with significant differences in OS. High-risk patients had a median OS of 57 months from the time they first enrolled in the CLL8 trial compared with low-risk patients, where the median OS has not been reached. (Figure 2) These data suggest that if a patient does not respond well to FCR or a similar regimen, or if the patient relapses within two years, OS is likely to be less than five years. Research efforts should be focused on improving the survival rates in this higher risk group of patients. CLLM1 is a recently initiated phase III multicentre, double-blind, placebo-controlled trial that will examine the efficacy and safety of lenalidomide as maintenance therapy for high-risk CLL patients following first-line therapy with FCR, bendamustine (B), bendamustine plus rituximab (BR), or alemtuzumab-based regimens.

**Figure 2. Overall survival of high- and low-risk CLL8 patients**

There are no guidelines for the use of second-line therapies in high-risk CLL and treatments vary worldwide. A number of treatment options have been explored — these are summarized below.

**Single-agent rituximab**

Single-agent rituximab administered at conventional doses has shown very low activity in CLL. Following rituximab monotherapy, the median duration of response is approximately 21 weeks and the median PFS is approximately 14 weeks.² Single-agent rituximab in a maintenance setting also yields disappointing results.³ Rituximab alone in the relapsed CLL setting is therefore not a very efficient agent; however, in combination with chemotherapy, rituximab can be quite potent.

**Rituximab with methylprednisolone**

In an interesting approach to improving the efficacy of single-agent rituximab in the refractory CLL setting, Castro, *et al.* administered rituximab at the standard dose of 375 mg/m² weekly in combination with three daily doses of 1 g/m² methylprednisolone every four weeks.⁴ This higher cumulative dose of rituximab has been well tolerated by patients who were cytopenic and may not have been able to tolerate a cytotoxic regimen, as is often the case in relapsed elderly CLL patients. This regimen has been shown to be effective in improving platelet and hemoglobin counts; however, while response rates were high, they were not durable. Given the results, there may be some utility in the use of rituximab in combination with methylprednisolone, depending on the clinical situation.
Ofatumumab

Wierda, et al. evaluated the efficacy of another anti-CD20 antibody, ofatumumab, used at higher doses in the CLL setting. While response rates were around the 50% mark, there were few complete responses and the duration of response was short, with a median PFS of 5.5 months and a median OS of 14.2 months.

Alemtuzumab

In the final example of antibodies used in the treatment of CLL, alemtuzumab, while capable of inducing remissions alone or in combination with steroids, results in short-lived remissions. In a study by Stilgenbauer, et al. the time-to-treatment failure (TTF) was less than 12 months after treatment with alemtuzumab, with an OS of approximately 18 months. These examples collectively demonstrate that the use of anti-CD20 antibodies, alone or in combination with steroids, may provide a short-term solution in the treatment of relapsed CLL but the remissions are not sustained.

Alemtuzumab plus dexamethasone (CLL20)

In an attempt to optimize therapy with anti-CD20 antibodies, Stilgenbauer, et al. evaluated standard doses of alemtuzumab plus oral dexamethasone at a high dose (40 mg), followed by either alemtuzumab maintenance or allogeneic transplantation in ultra high-risk CLL patients in a phase II study (CLL20) conducted by the German CLL Study Group (GCLLSG). At the time of the most recent data analysis presented at ASH 2011, the median OS was estimated to be approximately 12 to 18 months, which is similar to what is observed with alemtuzumab monotherapy. These data suggest that the addition of dexamethasone does not fundamentally alter the clinical course of the disease.

FCR

In patients who have not been exposed to rituximab in first-line therapy, a rituximab-containing regimen could be of value in the relapsed setting as shown by Robak, et al. A study of FCR versus FC in relapsed CLL patients showed good response rates (24.3% versus 13%, respectively) and a significantly longer TTF interval (30.6 months versus 20.6 months, respectively; p <0.05). These data suggest that FCR is a reasonable option in fludarabine-refractory patients.

Bendamustine plus rituximab

The combination of BR is similar in principle to FCR, although BR is not cross-refractory or cross-resistant with fludarabine. BR is a very active regimen that has demonstrated efficacy in most molecular subgroups including trisomy 21, del(13q), and del(11q), but not in patients with del(17p). Furthermore, BR has demonstrated activity in fludarabine-refractory patients as well as those previously treated with rituximab or alemtuzumab. (Table 1) These results suggest that BR is a suitable treatment option for patients who have failed FCR.

Allogeneic transplant

Allogeneic SCT is often offered to refractory CLL patients once other treatment options have been exhausted. Within the last decade or so, treatment-related mortality following allogeneic SCT hovered in the range of 40% for CLL patients. Novel regimens that allowed for reduced intensity conditioning regimens (RICs) have lowered treatment-related mortality rates to approximately 20%. While impressive improvements have been realized, allogeneic SCT remains to be optimized in this population and it is for this reason that it is not offered first line or to low-risk patients. However, allogeneic transplantation is one approach to overcome dismal chromosomal aberrations such as del(17p) or a p53 dysfunction. One important question that has arisen and resulted in considerable debate is whether it is necessary for patients to achieve a good remission prior to transplantation, and there is a lack of clear

---

Table 1. Bendamustine and rituximab as second-line therapy for CLL

<table>
<thead>
<tr>
<th>Population Description</th>
<th>n</th>
<th>Missing</th>
<th>CR</th>
<th>PR/nPR</th>
<th>SD</th>
<th>PD</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients who were naïve to fludarabine</td>
<td>15</td>
<td>3 (20.0)</td>
<td>4 (26.7)</td>
<td>8 (53.3)</td>
<td>0</td>
<td>0</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Total number of patients who were sensitive to fludarabine</td>
<td>38</td>
<td>2 (5.3)</td>
<td>3 (7.9)</td>
<td>20 (52.7)</td>
<td>10 (26.3)</td>
<td>3 (7.9)</td>
<td>23 (60.5)</td>
</tr>
<tr>
<td>Total number of patients who were refractory to fludarabine</td>
<td>22</td>
<td>1 (4.5)</td>
<td>0</td>
<td>10 (45.5)</td>
<td>9 (40.9)</td>
<td>2 (9.1)</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td>Previous therapies with rituximab and/or alemtuzumab</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td>0</td>
<td>6 (60.0)</td>
</tr>
</tbody>
</table>

CLL = chronic lymphocytic leukemia; CR = complete response; nPR = nodular partial response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease
consensus on this topic. Despite this, common practice is to proceed to SCT in most patients who have failed numerous lines of therapy.

**Promising new agents**

There are numerous new agents in development for the treatment of CLL. New agents include anti-CD20 antibodies such as GA101, anti-CD37 antibodies, CDK inhibitors, immunomodulatory drugs such as lenalidomide, and inhibitors of specific signalling pathways which include the Bcl2 antagonist ABT-263, the phosphatidylinositol 3 kinase delta (PI3Kδ) inhibitor CAL-101, the bruton tyrosine kinase (BTK) inhibitors PCI-32765, the Syk inhibitor fostamatinib, and the multi-tyrosine kinase inhibitor dasatinib.

**Lenalidomide**

Several small phase II trials have demonstrated response rates of approximately 30% to 60% following single-agent lenalidomide in relapsed/refractory CLL.14-18 The most interesting observation is that patients who respond to lenalidomide tend to have durable responses. Therefore, while lenalidomide appears to be effective in a select group of patients, the duration of response may be long.

**Navitoclax**

Navitoclax is a Bcl2 inhibitor currently under development and not yet available in clinical practice. This agent has shown some promise in a number of international trials. High-risk patients with enlarged lymph nodes show some benefit from several cycles of treatment. In one small study, a patient realized a 92% reduction in lymphadenopathy after seven cycles of navitoclax. The partial response (PR) rate in this study was 31% and the responses were durable, with a median PFS of 25 months.19

**Modulation of B cell receptor signaling pathways**

The most interesting recent development in the treatment of CLL is the attempt to pharmacologically modify the B cell receptor signalling pathway. This strategy is critical in CLL because B cell signalling drives not only normal B cells but also malignant B cells. This pathway remains relevant even in patients who have p53 mutations. The CLL cell is one in which the concept of oncogene addiction is well demonstrated. CLL cells seem to remain completely dependent on the B cell receptor signalling pathway because once inhibited, the cell undergoes cell death. Elements of the B cell receptor signalling pathway include SARC kinases, BTK, and PI3Kδ. Inhibitors of these pathways are currently being studied in clinical trials and early results demonstrate promising safety and activity.

**GS-1101**

GS-1101 (CAL-101) is an inhibitor of PI3Kδ. Data were presented at ASH 2011 that evaluated the safety and clinical efficacy of this agent as monotherapy or in combination with rituximab, fludarabine, bendamustine, or BR in CLL patients.20 Both lymph node responses and overall responses improved when GS-1101 was used in combination with other agents. The highest response rates were observed with GS-1101 plus rituximab (84%) and GS-1101 plus BR (86%). (Figure 3)

---

**Figure 3. GS-1101 combination therapies substantially increase overall response rates**

<table>
<thead>
<tr>
<th>GS-1101 combination therapy</th>
<th>LNR**</th>
<th>OR†</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
<th>LNR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-1101 monotherapy (n = 55)</td>
<td>84% n = 46</td>
<td>84% n = 16</td>
<td>84% n = 16</td>
<td>71% n = 5</td>
<td>71% n = 5</td>
<td>79% n = 11</td>
<td>79% n = 11</td>
<td>84% n = 12</td>
<td>86% n = 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR (n = 19)</td>
<td>24% n = 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GF (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GB (n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRB (n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Decrease by ≥50% in the nodal SPD
†Response by IWCLL criteria (Hallek M. Ann Oncol. 2008;19 Suppl 4:iv51-3.)

B = bendamustine; CI = confidence interval; CLL = chronic lymphocytic leukemia; G = GS-1101; IWCLL = international working group on CLL; LNR = lymph node response; OR = overall response; R = rituximab;
F = fludarabine; SPD = sum of the product of the diameters
PCYC-1102-CA

PCI-32765 is a BTK inhibitor and has been studied by O’Brien, et al. at two dose levels (420 and 840 mg) in relapsed/refractory CLL.21 Preliminary data were presented at ASH 2011. PCI-32765 was very well tolerated with no grade 4 toxicities reported. The most commonly reported adverse event (AE) was diarrhea, which is common with these types of inhibitors. Reports of diarrhea were primarily mild, reaching grade 3 in severity in only a few cases. All other AEs were mild (grade 1 or 2) and easily managed, with grade 3 toxicities being rare. Almost all patients enrolled in this study experienced a significant decrease in tumour burden of greater than 50%, including patients with high-risk disease features. The overall response rate (ORR) for all patients studied was 67%, with high response rates of 61% to 74% in all subgroups, including elderly patients (older than 70 years of age), patients with very large lymph nodes, patients with del(17p) and del(11q), patients with unmutated IgVH, patients with very high beta 2 microglobulin, and patients who were purine analog refractory (i.e., those who relapsed within 12 months of completing therapy). Furthermore, preliminary analyses suggest that response rates are durable, with approximately 90% of patients being free of progression at one year at both dose levels. When one looks at the PFS data for patients with del(17p), over 70% remain progression free at one year, a finding that has never been previously reported. These data need to be confirmed by larger studies with longer follow-up times. However, if these data can be confirmed, the findings could represent a major shift in CLL management.

The role of fitness in managing CLL

Having evaluated several therapeutic options in refractory CLL patients, one needs to determine how to apply these therapies in clinical practice. It is important to evaluate a patient’s physical fitness in order to select a treatment that balances efficacy and tolerability. Physical fitness appears to be a better predictor than age alone in selecting treatments for CLL patients. Gribben and colleagues classify patients using a comprehensive geriatric assessment (CGA)22 which is based on creatinine clearance and the cumulative illness rating score (CIRS).23 The CGA classifies patients into three categories:

- Go go: suitable for standard treatment;
- Slow go: suitable for reduced treatment;
- No go: suitable for supportive care.

The CIRS, while subjective, is fairly reproducible and has been tested in the geriatric setting. It evaluates a patient systematically. Fourteen organ systems are each assigned a score ranging from 0 for “no problem” to 4 for “extremely severe problems or organ failure.” The sum of the individual scores is taken to determine the CIRS. In GCLLSG protocols, the cutoff for the inclusion of patients is a CIRS of 6 or less.

A proposed algorithm for selecting second-line treatments

The selection of second-line treatment for CLL patients is based on the duration of response to first-line therapy and on fitness. A proposed algorithm is depicted in Table 2.

Duration of response is divided into two categories. The first category includes refractory patients (those who relapsed within six months), those who progressed within two years, or those who did respond at all. The second category includes patients who progressed after two years. Fitness, based on the CGA, includes fit patients (go go) or less fit patients (slow go).

Table 2. The selection of second-line therapies for CLL

<table>
<thead>
<tr>
<th>Response to first-line therapy</th>
<th>Fitness</th>
<th>Standard Therapy</th>
<th>Alternatives (trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory or progression within two years</td>
<td>Go go</td>
<td>• Alemtuzumb-dexamethasone</td>
<td>• Lenalidomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fludarabine + alemtuzumab</td>
<td>• BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FCR followed by allogeneic SCT</td>
<td>• BR in combination with kinase inhibitors</td>
</tr>
<tr>
<td>Slow go</td>
<td>Change therapy (if possible, enroll in a trial)</td>
<td>• Alemtuzumab for del(17p) patients</td>
<td>• FCR lite</td>
</tr>
<tr>
<td>Progression after two years</td>
<td>All</td>
<td>Repeat first-line therapy</td>
<td>BR</td>
</tr>
</tbody>
</table>

BR = bendamustine and rituximab; FCR = fludarabine, cyclophosphamide, rituximab; FCR lite = fludarabine, cyclophosphamide, rituximab at reduced doses; SCT = stem cell transplantation
In early relapsed patients who are fit, allogeneic transplantation should be given serious consideration following treatment to induce a remission. It is not important how the remission is achieved and any of the therapies discussed can be used, such as alemtuzumab plus dexamethasone, fludarabine plus alemtuzumab, FCR, or any of the experimental therapies. The patient should then be started on a transplant protocol. The selection of therapy for less fit patients becomes challenging because these patients do not meet the criteria for allogeneic transplant. In these situations, a change in therapy from what was used first line is necessary. Options for second-line treatment include alemtuzumab, FCR at reduced doses, BR, bendamustine, lenalidomide, ofatumumab, and high-dose rituximab.

In patients who relapse two or more years after first-line therapy, data suggest repeating the first-line treatment. The two-year cutoff has been evaluated extensively and data analyses from the CLL8 study suggest that patients who relapse after two years have better outcomes. While a Gaussian distribution is expected, if a patient presents with relapsed disease at four or more years after initial therapy, one can confidently repeat this therapy and expect that the patient will do well again.

Questions from the Audience

Question #1:
You had reported that 40/143 (29%) patients who turned out to be high risk, which is considerably more than those with del(17p) so there must be something additionally wrong with those patients. Has your team been working on gene array studies or some underlying molecular biology rationale to be able to identify those patients?

Answer:
That is a wonderful question and I honestly do not have the answer, but it is precisely what we are now trying to determine in order to characterize these patients using the techniques that you refer to (i.e., microarrays). There are some 6q deletions in this group but this is not a major contributor. Currently, we simply do not know the answer. In the meantime, we use MRD-negativity as a surrogate marker in this group of patients. I am relatively confident that with all the novel genetic defects that we are discovering in CLL, including Notch and SF3B1, some of these molecular aberrations might be useful to characterize high-risk patients. We are actively searching our database and we will do the sequencing or molecular analysis in these patients. Maybe in the next two or three years I will be able to share the data with you.

Question #2:
How is MRD-negativity defined?

Answer:
There is a consensus paper from the European Research Initiative in CLL (ERIC) that defines the threshold or MRD-negativity as one in 10,000 leukocytes by four colour flow cytometry. In the CLL8 study we applied this technique but we also compared it to PCR and we did a very systematic analysis of these two techniques in both the blood and bone marrow. The results were published in a paper by Sebastien Bottcher and showed that you can use four colour flow cytometry from the blood. It is equally as sensitive as it was for the bone marrow. There were a few discordances in some cases but it was usually less than 5%. Therefore, the blood seems to be sufficient for the clinical assessment of MRD with four colour flow cytometry. This will likely be a key parameter for future clinical studies because it is a surrogate endpoint that you can read immediately after treatment.

Question #3:
This is a practical question as it was very enticing the see that data on lenalidomide. How do you use it in clinical practice? Do you start with lower doses and increase?

Answer:
If the patient has a residual tumour load, as is the case for most of our patients, I would start at doses as low as 5 or 10 mg. In the more fragile, elderly patients I start with 5 mg only. I never start with the full dose. I then slowly increase the dose monthly in 5 mg increments if the blood counts are stable. As soon as I observe the platelets dropping or I see other problems, I reduce the dose. You would be ill-advised to start with 25 mg in a CLL patient because that patient will experience acute problems.
New Evidence: What is your standard treatment for fit patients with chronic lymphocytic leukemia (CLL)?

Dr. Hallek: The current standard for the treatment of physically fit patients with CLL is a combination of fludarabine, cyclophosphamide, and rituximab (FCR). In some cases where the fitness of the patient is somewhat reduced, we may use a combination of bendamustine and rituximab (BR).

New Evidence: What are your criteria for determining patient eligibility for aggressive treatments such as FCR?

Dr. Hallek: Before making decisions about the optimal treatment for patients with CLL we first need to determine their physical fitness. In the clinic, a thorough physical exam is a good first step. In clinical trials we use two methods to determine fitness, the Cumulative Illness Rating Score (CIRS), which evaluates comorbidities in different organ systems, as well as creatinine clearance, which measures kidney function. If a patient has a CIRS score greater than six or a creatinine clearance greater than 60 to 70 mL/min, this is an indication to reduce the treatment intensity. We do not use age as a criterion to influence treatment decisions either in our practice or within clinical trials.

New Evidence: What percentage of your patients is not eligible for aggressive treatments such as FCR?

Dr. Hallek: In a university or academic centre, the majority (80% to 90%) of our patients are very fit and able to receive standard therapies. From previous studies we know that at the age of 70 years, around 60% to 70% of patients will be fit enough to tolerate aggressive treatments. By the age of 80 years, however, only 30% to 40% of patients are able to tolerate more aggressive therapies. Therefore, in western countries most patients aged 70 years or younger can tolerate aggressive treatments. However, in clinical trials that include patients from Russia and other less developed countries, the number of fit patients is reduced.
**New Evidence:** What type of patients should not be given fludarabine?

**Dr. Hallek:** Although many patients may tolerate fludarabine as monotherapy, it is important to follow the guidelines discussed earlier for determining patient fitness when considering giving FCR or fludarabine plus rituximab (FR). In addition, caution should be exercised in giving fludarabine-containing combination regimens to patients who are severely immunosuppressed. Finally, there are rare side effects in patients previously treated with fludarabine such as skin or kidney toxicities. In these cases, patients should not be retreated with fludarabine.

---

**New Evidence:** What treatment do you offer patients who fall in between the fit and unfit categories?

**Dr. Hallek:** We tend to categorize these patients as “slow-go” and generally offer them chlorambucil as a first-line treatment in Germany. We are conducting trials on new regimens such as chlorambucil plus rituximab or chlorambucil plus GA-101. In my opinion, chlorambucil plus an antibody will become the new standard treatment in these “slow-go” patients. It is unclear whether we should intensify the chemotherapy component of this regimen by using bendamustine instead of chlorambucil in these patients. It makes sense to give BR to patients who are slightly less fit and to give chlorambucil with or without rituximab to patients who truly fill the criteria of the “slow-go” category. In Germany, we have a lot of experience using bendamustine; however, there is a need for clinical trials using bendamustine in the elderly population.

---

**New Evidence:** What treatment do you offer patients with mild-to-moderate renal dysfunction?

**Dr. Hallek:** In patients with renal dysfunction we would give chlorambucil rather than fludarabine. BR is another option in these patients as bendamustine has not been shown to have a lot of nephrotoxicity.

---

**New Evidence:** In which patients do you offer bendamustine? Do you give bendamustine as monotherapy or as part of a combination regimen?

**Dr. Hallek:** There is now enough evidence to suggest that patients will benefit from the addition of rituximab to chemotherapy. We therefore always give bendamustine in combination with rituximab, even in patients with reduced fitness. The ongoing CLL10 trial will determine whether BR is equivalent to FCR in physically fit patients. However, we need to examine BR in a patient population that is less fit to determine whether this is the best regimen for them. Currently we give BR as second-line treatment to patients who have relapsed after FCR.

---

**New Evidence:** Are there any patients who are too frail to be given BR?

**Dr. Hallek:** There are patients whom we classify as “no-go” who tend to have a very short life expectancy; these patients should not be given BR. For example, we may decide not to treat a patient who has a severe heart insufficiency and a life expectancy of less than one year.

---

**New Evidence:** What dosing regimen of bendamustine do you use?

**Dr. Hallek:** More studies are needed to examine the dosing of bendamustine in CLL. For first-line treatment we recommend 90 mg/m² of bendamustine when combined with rituximab. Based on a small second-line trial showing relatively high toxicity with bendamustine, we now use 70 mg/m² of this agent in the relapsed setting. We typically give bendamustine for a total of six cycles; however, in the elderly or in “slow-go” patients, there are occasional myelotoxicities that require early discontinuation after three to four cycles of treatment.
**New Evidence:** What are the advantages of bendamustine as a treatment for CLL?

**Dr. Hallek:** The advantage of bendamustine, in general, is that it does not result in alopecia. In addition, bendamustine is relatively easy to administer as it involves a maximum of two days of infusion and there is a short infusion time. Bendamustine is therefore well tolerated and is a convenient treatment for patients with CLL.

---

**New Evidence:** Do you have any safety concerns with the use of bendamustine?

**Dr. Hallek:** The safety concern with bendamustine is long-term myelosupression. For example, you may see neutropenia at three weeks that subsequently resurfaces again at around five to six weeks. In these patients it is often dangerous to continue treatment with bendamustine. Aside from the importance of managing myelosupression, bendamustine is very well tolerated in patients with CLL.

---

**New Evidence:** What treatments do you offer patients with relapsed CLL?

**Dr. Hallek:** In the relapsed setting there is no standard treatment for patients with CLL. In patients with a long remission of more than two years following first-line treatment, we repeat treatment with the same agent. In patients with a short remission following first-line treatment with FCR or BR, we usually give patients the regimen they did not receive as first-line treatment. If a patient is young and physically fit but does not respond to first-line treatment, we often will consider transplant. In less fit patients with a short relapse following upfront treatment, chlorambucil or bendamustine is a reasonable option in combination with rituximab.
Intravenous Busulfan Is a Safe and Effective Option for Conditioning Regimens Prior to Transplant in Acute Myeloid Leukemia

High-dose chemotherapy, reduced-intensity conditioning, and allogeneic stem cell transplantation (alloSCT) have shown limited efficacy in patients with relapsed or refractory high-risk, aggressive non-Hodgkin lymphoma (NHL). The role of the graft-versus-lymphoma effect in alloSCT in this population is unclear.1

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) primarily affect older patients, with the highest rate of mortality in patients over the age of 65 years. These patients typically do not respond well to chemotherapy, have a higher incidence of poor-risk disease, and are at increased risk of graft-versus-host disease (GVHD), relapse, and non-relapse mortality. AlloSCT represents a potentially curative approach for AML and MDS in this population.2

Oral busulfan is a standard agent used as part of conditioning regimens prior to autologous transplant in the treatment of AML.3–6 However, there are a number of disadvantages with the oral formulation of busulfan, including inconvenient dosing, variations in absorption, risk of poor engraftment and relapse, as well as an increased risk of veno-occlusive disease (VOD).

In contrast to the oral formulation of busulfan, the intravenous (iv) formulation is more predictable.1–6 It is therefore easier for nurses and doctors to administer and there is less risk of engraftment issues, relapse, and toxicities. Increasingly, studies are examining the outcome of patients treated with iv busulfan-based conditioning regimens as an alternative to oral busulfan.

Data from studies examining conditioning regimens with a focus on the use of iv busulfan were presented at EBMT 2012 and ASCO 2012. This article reports on two studies from ASCO and four studies from EBMT:

• A prospective study of the German high-grade non-Hodgkin lymphoma study group demonstrated excellent results in patients with early relapse or primary refractory aggressive B-cell and T-cell lymphomas with lymphoma-debulking (high-dose) chemotherapy followed by alloSCT.

• A study examining outcomes in patients >64 years with AML and MDS receiving alloSCT demonstrated that although a significant minority achieve long-term disease control, relapse is still the greatest risk to mortality in this population.

• A retrospective survey of patients with AML receiving an iv busulfan-based conditioning regimen prior to ASCT demonstrated that VOD of the liver was uncommon after ASCT using this regimen, and translated into a lower incidence of non-relapse mortality (NRM).

• A retrospective survey of patients with AML at first allograft transplanted from an unrelated donor who received either total body irradiation (TBI) plus cyclophosphamide (TBI/Cy) or iv busulfan plus cyclophosphamide (Bu/Cy). Results demonstrated that induction of remission, leukemia-free survival, and OS were significantly higher with Bu/Cy, with no differences in engraftment rate or incidence of acute GVHD (aGVHD).

• A prospective randomized trial measuring the incidence of VOD with iv vs. oral busulfan administration, and fresh-frozen plasma plus heparin-alone as anti-VOD prophylaxis, reported that the improved pharmacokinetics of iv busulfan led to a dramatic decrease in the incidence of VOD.

• A study comparing busulfan-based vs. TBI-based myeloblastic conditioning in patients with AML demonstrated that the use of the non-targeted iv busulfan regimen resulted in a lower incidence of aGVHD, and less toxicity and morbidity.

**Background**

At ASCO 2012, Glass and colleagues presented results from their prospective, randomized phase II study examining the efficacy of using lymphoma-directed myeloablative conditioning prior to allogeneic stem cell transplantation (alloSCT) in patients with high-risk, aggressive non-Hodgkin lymphoma (NHL).¹

**Study design**

- Patients with primary refractory disease, early relapse (<12 months) or relapse ≥12 months of aggressive B-cell (n = 61) or T-cell (n = 23) lymphomas after high-dose chemotherapy and autologous SCT (ASCT) were enrolled between June 2004 and March 2009.
- All patients received the following myeloablative conditioning regimen:
  - Fludarabine 25 mg/m² weekly for five weeks, beginning nine weeks prior to alloSCT;
  - Busulfan 4 mg/kg weekly for three weeks, beginning seven weeks prior to alloSCT;
  - Cyclophosphamide 60 mg/kg weekly for two weeks, beginning four weeks prior to alloSCT.
- Anti-thymoglobulin (ATG) was optional in the six weeks leading up to the alloSCT.
- Following alloSCT, prophylaxis for GVHD was short-term mycophenolatemofetil (MMF) on weeks 1 to 4 and tacrolimus (weeks 1–28); patients were also randomized to receive rituximab on weeks 3 to 6 and 25 to 28, or no rituximab as part of the graft-versus-host disease (GVHD) prophylaxis regimen.
- The primary endpoints were overall survival (OS) at one year, and the determination of the impact of prophylactic rituximab on the incidence of acute GVHD (aGVHD).
- Secondary endpoints included progression-free survival (PFS), non-relapse mortality (NRM), and the overall relapse rate.

**Key findings**

**Baseline characteristics and disposition**

- The median age of the study population was 48.5 years (range: 20–64 years).
• Before being enrolled in the study, 45 patients (54%) had previously received high-dose chemotherapy and ASCT.

• In patients with aggressive B-cell lymphoma (n = 61), 49 (80%) had received prior treatment with rituximab.

• During myeloablative conditioning, 35 patients (42%) also received optional ATG.

• No significant differences were noted in the results between the B-cell (n = 61) and T-cell (n = 23) lymphoma groups, and as such they are reported together.

• Prior to alloSCT, the majority of patients (57%) had a remission period of <three months, while 29% had a remission duration of >12 months.

• Patients (n = 57 [68%]) received a 10/10 human leukocyte antigen loci compatible graft.

• Donor types for alloSCT were:
  - Matched related (n = 23);
  - Mismatched related (n = 1);
  - Matched unrelated (n = 34);
  - Mismatched unrelated (n = 26).

**Efficacy**

• In the overall study population (n = 84), OS at one year was 52.1% and 41.6% at three years (95% confidence interval [CI]: 31–52); PFS was similar at 48.3% at one year and 39.7% (95% CI: 29–50) at three years. (Figure 1)

• Patients with a remission duration of >12 months (n = 24) experienced significantly longer PFS at three years than patients with a relapse in ≤12 months (n = 60) (57.2% vs. 32.8%; p = 0.0483).

**Figure 1.** Overall survival and progression-free survival in patients with high-risk relapsed and refractory aggressive NHL

- A high incidence of GVHD >grade 1 (>65%) was observed; this was not affected by the use of prophylactic rituximab (p = 0.7413).

- A significant difference in the incidence of GVHD >grade 1 was noted between patients who were administered optional ATG (n = 35) during the conditioning regimen and those not receiving ATG (44.7% vs. 75.5%; p = 0.0072).

- Higher grades of GVHD (moderate and severe) were associated with a longer PFS at three years (46.8%) when compared with no or mild GVHD (30.2%), p = 0.0204. (Figure 2)

**Figure 2.** Progression-free survival by incidence of GVHD (>grade 1) in patients with refractory or relapsed aggressive NHL receiving alloSCT

- NRM in all patients (n = 84) was 35.2% at one year.

- Patients receiving alloSCT from a matched related or matched unrelated donor plus ATG had the best outcome (NRM at one year 10.3% vs. 57.2%; PFS at three years 64.7% vs. 17.5%; p = 0.0001). (Figures 3 and 4)

- The relapse rate was 28.5% with the latest relapse occurring at day 327 following alloSCT.

**Figure 3.** Incidence of non-relapse mortality at one year by donor type and use of ATG
In Supportive Care Oncology

Figure 4. Progression-free survival by donor match type and use of ATG during pre-alloSCT conditioning regimen

Key conclusions

- Lymphoma-debulking (high-dose) chemotherapy followed by alloSCT demonstrates excellent results in patients with early relapse or primary refractory aggressive B-cell and T-cell lymphomas.

- Evidence of graft-vs.-lymphoma activity was shown in this setting.

- For patients with a fully matched related or unrelated donor, the results compare favourably with high-dose chemotherapy plus autoSCT or alloSCT following reduced-intensity conditioning.


Conter HJ, et al. ASCO 2012: Abstract 6529

Allogeneic stem cell transplantation for patients over age 65 years with AML and MDS

Background

At ASCO 2012, Conter and colleagues presented outcomes from patients older than 64 years treated with allogeneic stem cell transplantation (alloSCT) at the MD Anderson Cancer Center from 1996 until December 2011.1

Study design

- Patients >64 years (n = 182) received an alloSCT for either acute myeloid leukemia (AML, n = 143) or myelodysplastic syndrome (MDS, n = 39).

- Disease factors included the current state of disease (e.g., active, relapse, complete remission), cytogenetics, and molecular analysis.

- Patients underwent preparative regimens that included fludarabine and melphalan (n = 85), fludarabine and busulfan (n = 61), and fludarabine and idarubicin (n = 13).

- Immunosuppression regimens included tacrolimus and mini-methotrexate (n = 147), tacrolimus and mycophenolate (n = 8), and post-transplant cyclophosphamide (n = 16).

- Outcomes of interest were overall survival (OS), progression-free survival (PFS), incidence of acute and chronic graft-versus-host disease (GVHD), transplant-related mortality (TRM), and incidence of relapse, which were estimated from the date of transplant.

- Median follow-up for patients still living (n = 63) was 13 months (n = 63; range: 0.2–117 months).

Key findings

Baseline characteristics and disposition

- The median patient age was 67 years (range: 65–79 years).

- It was determined that 92% of patients had either poor risk or intermediate risk factors (50% and 42%, respectively).
• The majority of patients (66%, n = 120) had refractory or untreated disease at the time of alloSCT. An additional 21 patients (12%) had primary induction failure at transplantation.

• Among the patients receiving alloSCT, 38 (21%) were categorized as complete remission (CR1), with another 15 patients (8%) categorized as CR2 or CR3.

• Donor types for alloSCT were:
  ‧ Matched related (n = 87);
  ‧ Matched unrelated (n = 73);
  ‧ Mismatched unrelated (n = 17).

**Efficacy**

• Actuarial OS was estimated to be 45% at one year, 28% at three years, and 21% at five years. (Figure 1)

**Figure 1. Actuarial overall survival of patients receiving alloSCT for AML or MDS**

![](image1)

- In patients ≥65 years, OS at three years was 30% compared with 20% for all patients (p = 0.06);
- OS was notably higher for patients with CR disease status vs. active disease status (38% vs. 27%, respectively).
- PFS of patients achieving a CR vs. no CR is presented in Figure 2.
- Grade 2–4 acute GVHD developed in 26% of patients, while 35% developed chronic GVHD. Limited GVHD was reported in 13% of patients, while 17% developed extensive GVHD.
- Overall incidence of GVHD is presented in Figure 3.
- The cumulative incidence of 100-day, one-year, and three-year treatment-related mortality (TRM) was 14%, 18%, and 21%, respectively.
- The actuarial incidence of relapse was 46% at one year and 53% at three and five years.

**Figure 2. Progression-free survival in patients receiving alloSCT by patients with complete remission versus no complete remission**

![](image2)

**Figure 3. Incidence of GVHD in patients treated with alloSCT**

![](image3)

**Key conclusions**

- Although a significant minority of patients >64 years of age may achieve long-term disease control, relapse is still the greatest risk to mortality.
- New approaches are needed to reduce TRM, GVHD, and relapse in this cohort of patients.

Outcomes after ASCT in patients with AML using intravenous busulfan-based conditioning regimen: a survey on behalf of the ALWP-EBMT

Background
Historically, busulfan has been the mainstay of the busulfan plus cyclophosphamide (Bu/Cy) pre-stem cell transplantation conditioning regimen. However, the absorption of oral busulfan varies, with wide inter- and intra-patient variability. In contrast, intravenous (iv) busulfan has more predictable pharmacokinetics and a favourable toxicity profile. No data are available in the literature reporting the use of iv busulfan in the autologous hematopoietic stem-cell transplantation (ASCT) setting.

To assess this, Nagler and colleagues performed a survey on behalf of the Acute Leukemia Working Party of EBMT (ALWP-EBMT). The survey included 209 patients with acute myeloid leukemia (AML) who received iv busulfan as part of the conditioning regimen. The findings of this study were presented at EBMT 2012.

Study design
- Of the 209 patients included, 113 were male (46%) and the median age at transplant was 50.4 years.
- A total of 185 patients (88.5%) were transplanted in first complete remission (CR1), 20 (9.5%) in second remission (CR2), and four (2%) in third remission (CR3).
- Cytogenetic intermediate-risk AML was exhibited by 72% of patients, while 12% and 3% had good risk and poor risk, respectively.
- Conditioning was myeloablative in all cases.

Key findings
- Overall survival (OS), leukemia-free survival (LFS), and relapse incidence (RI) at three years were 57 ± 4%, 49 ± 4%, and 45 ± 3%, respectively. (Figures 1 and 2)
- Four patients (1.9%) had veno-occlusive disease (VOD) (moderate = 2, severe = 2) at median day 16 (range, 10–47), and one of the patients died from VOD.
- Non-relapse mortality (NRM) at three years was low (6 ± 1%).
- In a multivariate analysis, the only prognostic factor found to be significant for OS, LFS, RI, and NRM was age (over 50 years vs. under 50 years) (47 ± 5%, 38 ± 5%, 52 ± 5%, 10 ± 3% vs. 68 ± 5%, 76 ± 4%, 32 ± 5%, and 0%, respectively; \( p < 0.05 \)).

Key conclusion
- These results suggest that, similar to the allogeneic setting, VOD occurs infrequently after ASCT using iv busulfan in the conditioning regimen, translating into a low incidence of NRM.

Intravenous busulfan plus cyclophosphamide versus total body irradiation plus cyclophosphamide conditioning for alloSCT from matched unrelated donors: a survey on behalf of the ALWP-EBMT

**Background**
Two treatment protocols are traditionally used prior to allogeneic transplant in acute myeloid leukemia (AML).1,2 One protocol uses total body irradiation (TBI) plus cyclophosphamide, and the second protocol uses oral busulfan plus cyclophosphamide (By/Cy). The TBI protocol is considered to be significantly more toxic, increasing the risk of cataracts and heart damage. However, a number of studies have shown the TBI regimen to improve leukemia-free survival (LFS) and overall survival (OS) compared with the oral busulfan regimen.

Nagler and colleagues conducted a study with the rationale that using intravenous (iv) busulfan would reduce the toxicity of the conditioning regimen, improving outcomes compared with the TBI plus cyclophosphamide (TBI/Cy) regimen. The results were presented at EBMT 2012.3

**Study design**
- In this observational registry-based retrospective study, TBI/Cy was compared with iv Bu/Cy conditioning prior to allogeneic stem cell transplantation (alloSCT) from human leukocyte antigen (HLA)-matched unrelated donors in 169 adult patients with AML in first relapse (Rel 1).
- TBI/Cy was given to 95 patients and Bu/Cy was given to 74 patients.
- The median age was 38 years and 42 years in the TBI/Cy vs. Bu/Cy groups, respectively (p <0.005).
- French-American-British classification, cytogenetic risk, time from diagnosis to alloSCT, donor gender, and cytomegalovirus sero status did not differ between the groups.
- Median year of alloSCT was 2004 vs. 2007 for TBI/Cy vs. Bu/Cy, respectively (p <0.001).
- Anti-thymoglobulin (ATG) was used in 35% vs. 71% in the TBI/Cy and Bu/Cy groups, respectively (p <0.0001).
- Eighty percent and 78% of the TBI/Cy and Bu/Cy groups received peripheral blood stem cell grafts, while 22% and 20% received bone marrow (BM) grafts, respectively (p = 0.8).
- Median follow-up was 23 (range: 1–125) and 27 (range: 1–120) months in the TBI/Cy and Bu/Cy groups, respectively.

**Key findings**
- Engraftment in both groups was similar: 17 (10–33) and 16 (6–31) days in the TBI/Cy and Bu/Cy groups, respectively (p = 0.23).
- Acute graft-versus-host disease (≥grade 2) incidence did not differ between the two groups: 33% vs. 37% for the TBI/Cy vs. Bu/Cy, respectively.
- Death before day 100 occurred in 38% vs. 25% of patients with TBI/Cy vs. Bu/Cy, respectively (p = 0.25).
- Two-year non-relapse mortality was similar between the two groups (28 ± 5% vs. 19 ± 5%, respectively [p = 0.2]).
- The two-year relapse rate was 54 ± 5% vs. 50 ± 6%, respectively (p = 0.56).
- Induction of remission post-alloSCT was higher with Bu/Cy vs. TBI/Cy: 72% vs. 54% (p = 0.02).
- Two-year LFS was also higher with the Bu/Cy vs. TBI/Cy groups: 23 ± 6% vs. 18 ± 4 %, respectively (p = 0.045).
- Two-year OS was significantly higher with Bu/Cy vs. TBI/Cy: 37 ± 6% vs. 21 ± 5%, respectively (p = 0.013).
- The main cause of death was disease relapse: 53% and 60% with TBI/Cy vs. Bu/Cy, respectively (p = 0.49).
- VOD and infection-related deaths did not differ between the groups.
- In a multivariate analysis, the interval from diagnosis to transplant (greater than vs. less than 16 months) was the most significant prognostic factor for relapse, LFS, and OS (25 ± 8% vs. 59 ± 4% [p = 0.004], 48 ± 9% vs. 17 ± 3% [p = 0.002] and 41 ± 7% vs. 20 ± 4% (p = 0.003), respectively) (Figures 1 and 2).
- Age, cytogenetic risk groups, and use of ATG were not significant prognostic factors for survival.
In Supportive Care Oncology

Figure 1. Leukemia-free survival in patients with AML treated with Cy/TBI versus Bu/CY

<table>
<thead>
<tr>
<th>Bu/Cy</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Year &gt;2004</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Diagnosis-treatment &gt;12 months</td>
<td>0.69</td>
<td></td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia; ATG = anti-thymoglobulin; Bu/Cy = busulfan plus cyclophosphamide; CI = confidence interval; HR = hazard ratio; TBI/Cy = total body irradiation plus cyclophosphamide

Figure 2. Overall survival in patients with AML treated with Cy/TBI versus Bu/CY

<table>
<thead>
<tr>
<th>Bu/Cy</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Year &gt;2004</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Diagnosis-treatment &gt;12 months</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia; ATG = anti-thymoglobulin; Bu/Cy = busulfan plus cyclophosphamide; CI = confidence interval; HR = hazard ratio; TBI/Cy = total body irradiation plus cyclophosphamide

Key conclusions

- This study suggests that patients with AML in first relapse undergoing unrelated transplantation post-transplant, iv Bu/Cy vs. TBI/Cy induced higher remission rates resulting in better LFS and OS.
- The advantage in favour of the iv Bu/Cy regimen is possibly due to a lower overall toxicity and improved capacity for salvage therapy.

References:
Intravenous versus oral busulfan administration results into a dramatic reduction of VOD incidence in a randomized trial assessing fresh frozen plasma plus heparin versus heparin-alone as anti-VOD prophylaxis

**Background**
Monitoring early complications is an important consideration and is part of the management of patients during autologous stem cell transplant (ASCT). Yannaki and colleagues prospectively measured the incidence of veno-occlusive disease (VOD) with intravenous (iv) versus oral busulfan administration, in a randomized trial assessing fresh-frozen plasma plus heparin versus heparin alone as anti-VOD prophylaxis. Results were presented at the 2012 EBMT meeting.¹

**Study design**
- Patients (n = 336) were prospectively studied for risk factors and VOD incidence in relation to anti-VOD prophylaxis. The patients had consecutively undergone hematopoietic cell transplantation (HCT) between March 2004 and March 2011.
- Patients were randomized to receive heparin (Group A), or two fresh-frozen plasmas (FFP) per day plus heparin (Group B).
- Alpha tau (AT) and protein C levels were measured every week up to day 28.
- Patients with a median age of 36 years underwent autologous (n = 152) or allogeneic (sibling = 117, volunteer = 61, alternative = 6) HCT from blood (n = 315), bone marrow (n = 19), or cord blood (n = 3) following mainly myeloablative conditioning (292/336).
- The majority of patients were transplanted at advanced disease.
- Patients were randomized into Group A (n = 164) and Group B (n = 172). The baseline characteristics were similar between the two groups.

**Key findings**
- The cumulative VOD incidence was 2% (7/336 patients, 5/7 were severe, and 2/7 were moderate).
- The VOD-associated mortality was 57%.
- Anti-VOD prophylaxis was not shown to influence VOD incidence (Group A: 3/7, Group B: 4/7).
- All patients with lethal VOD had more than one known risk factor.
- In busulfan-conditioned patients, VOD-incidence was 50% (3/6) and 2.5% (3/119) with oral and iv administration, respectively, without there being a difference in VOD-induced mortality.
- Multivariate analysis demonstrated the allo-HCT (odds ratio [OR]: 14.1, \( p = 0.04 \) vs. auto-HCT) and oral busulfan (OR: 75.4, \( p < 0.001 \) vs. iv busulfan) as factors significantly associated with VOD.
- Significant reductions in AT/protein C levels were observed compared with baseline, both in VOD (ATd14–28/protein-C:d21–28, \( p = 0.03 \)) and no-VOD patients (ATd7–21/protein-C:d0–21, \( p = 0.00002 \)).
- However, VOD subjects had lower AT (d14–28) and protein C (d0–d28) values vs. no-VOD individuals (\( p = 0.02 \)).

**Key conclusions**
- **Overall,** the improved pharmacokinetics of iv busulfan lead to a dramatic decrease in VOD incidence.
- **The drop of natural anticoagulants occurs independently of VOD and their higher reduction at VOD represents an epiphenomenon.**
- **Replenishment with fresh frozen plasma, although it may correct the anticoagulant values, cannot stem the syndrome’s progression.**

Busulfan-based versus total body irradiation-based myeloablative conditioning in patients with AML: reduction of acute GVHD incidence, mucositis, and duration of hospitalization

**Background**

The effect of busulfan plus cyclophosphamide (Bu/Cy) versus cyclophosphamide, VP16, and total body irradiation (TBI) on acute graft-versus-host disease (aGVHD) has been evaluated in patients receiving bone marrow transplant (BMT) but not in patients receiving peripheral blood stem cell transplants (PBSCT). Bucher and colleagues conducted a study assessing the incidence of aGVHD after busulfan-based versus TBI-based myeloablative conditioning in patients with acute myeloid leukemia (AML). The results of this study were presented at the 2012 EBMT meeting.

**Study design**

- Data from 96 patients with consecutive AML undergoing non-T-depleted human leukocyte antigen (HLA)-identical PBSCT after myeloablative conditioning were included in the study, with a timeframe of January 2001 to January 2011.
- Patients (n = 54) received 12 Gy TBI (plus Cy [n = 26]; plus Cy/VP16 [n = 28]) and 42 patients received non-targeted full dose intravenous (iv) busulfan (Bu/Cy [n = 7] or CyBu [n = 35]).
- Methotrexate/CyA was used for GVHD prophylaxis.
- The TBI and iv busulfan groups were comparable for all relevant pre-transplant risk factors except for year of transplant (median 2004 vs. 2008; \( p < 0.001 \)) and age at transplant (41.6 years vs. 50.0 years; \( p < 0.001 \)), reflecting the gradual introduction of busulfan-based regimens and increased age limits at the institution in which the study was conducted.

**Key findings**

- The cumulative incidence of aGVHD at day 100 was 67.3% in the TBI group and 38.6% in the iv busulfan group (\( p < 0.001 \)).
- The median onset of aGVHD was 12 (6–45) days in the TBI group and 17 (7–1,463) days in the iv busulfan group (\( p = 0.04 \)).
- Overall survival (OS) at two years post-transplant was similar (56.8% vs. 53.7%; \( p = 0.78 \)).
- The Cox regression analysis after correction for age, remission status, year of transplant, and cytomegalovirus (CMV) status confirmed a significant aGVHD risk reduction (RR = 0.4 [0.18–0.90; \( p = 0.028 \)]) for the iv busulfan group without influence on transplant-related mortality (TRM) and OS.
- In the TBI group, the median duration of clinical mucositis was 12 days (0–30 days), whereas in the iv busulfan group it was five days (0–19 days; \( p < 0.001 \)).
- The cumulative median dose of morphine used for mucositis-related pain was 269 mg (0–3,055 mg) in the TBI group vs. 36 mg (0–483 mg) in the iv busulfan group (\( p < 0.001 \)).
- Reduced morbidity resulted in a significant reduction of in-hospital stay from a median of 27 days (mean 34.9 [95% confidence interval (CI): 29.2–42.3]) in the TBI group to a median of 21 days in the iv busulfan group (mean 24.5 [95% CI 21.6–27.4], \( p = 0.014 \)).

**Key conclusion**

- Compared with TBI, the use of the non-targeted iv busulfan regimen demonstrated a lower incidence of aGVHD, less toxicity and morbidity, as well as a shortened in-hospital stay.

**References:**

New Evidence: Please discuss the rationale for your study.

Dr. Nagler: Oral busulfan is a standard agent used as part of conditioning regimens prior to autologous transplant in the treatment of acute myeloid leukemia (AML). However, there are a number of disadvantages of the oral formulation of busulfan. The oral formulation is given in individual tablets of 2 mg. Therefore, if you need to give a patient 2 mg/kg of busulfan for four days, the patient will often need to take over 100 tablets per day. In addition, if the patient is not able to keep the tablets down, some of the medication will be lost. Another disadvantage of the oral formulation of busulfan is that the absorption is not predictable and varies from patient to patient. In patients absorbing less than expected, engraftment may not occur, the risk of relapse is greater, and in those receiving more than required, toxicities may result. To manage the differences in absorption, blood levels of the drug can be taken and dose adjustments made to ensure optimal drug delivery; however, this is a laborious and complicated process. The final and most important disadvantage of oral busulfan is the risk of veno-occlusive disease (VOD) of the liver.

In contrast to the oral formulation of busulfan, the intravenous (iv) formulation is much more predictable. It is therefore easier for nurses and doctors to administer and there is less risk of engraftment issues, relapse, and toxicities. The rationale of our study was therefore to examine the outcome of patients treated with iv busulfan-based conditioning regimens as an alternative to oral busulfan.
New Evidence: Please describe the design and patient population used in your study.

Dr. Nagler: Our study was a retrospective survey based on a database including all transplant centres in Europe. The database is managed by the Acute Leukemia Working Party of the European Cooperative Group for Blood and Marrow Transplantation (ALWP-EBMT). Database managers are able to track the number of transplants performed in AML in Europe and can approach individual centres for additional data.

Our study included patients over 18 years of age with AML who had received their first autograft between 2003 and 2009. Patients must have received iv busulfan alone or in combination with other agents and had to be in remission at the time of transplant. A total of 209 patients were included in the study, with a median age of 50.4 years. Out of 209 patients, 108 received iv busulfan in combination with cyclophosphamide, 39 received iv busulfan in combination with melphalan, and two patients received iv busulfan monotherapy.

New Evidence: Please discuss the results of your study.

Dr. Nagler: In our study, after three years of follow up, overall survival (OS), leukemia-free survival (LFS), and relapse incidence (RI) were 57%, 49%, and 45%, respectively. These outcomes are superior to those seen in historical studies using oral busulfan as part of conditioning regimens in AML. For example, a study by Chantry, et al. based on data from the United Kingdom, demonstrated an OS of 32% and progression-free survival (PFS) of 28% after 10 years of follow up after autologous transplantation.1 Although our study is based on a shorter follow-up duration, outcomes with iv busulfan appear promising. In addition, LFS was particularly good in patients younger than 50 years and outcomes appeared comparable in patients after the first or second complete response.

New Evidence: How does the rate of VOD in this study compare with that of patients receiving oral busulfan?

Dr. Nagler: In our study, only 1.9% (4/209) of patients had VOD after treatment with iv busulfan prior to transplant. A study by Kashyap, et al. performed a retrospective comparison of oral versus iv busulfan as part of conditioning regimens prior to transplant.2 The incidence rate of VOD was found to be 8% (5/61) after iv busulfan and 33% (10/30) after oral busulfan. A second study by Sobocinski, et al. performed a matched-pair analysis of patients receiving oral and iv busulfan prior to transplantation.3 Results of the study showed the overall incidence of VOD was 4.6% (4/83) with iv busulfan and 20.3% (38/149) with oral busulfan (p <0.001). Although the factors used to determine VOD vary between centres, the percentage of patients with VOD after conditioning with iv busulfan appear to be much lower than in those receiving oral busulfan.

New Evidence: How common is the use of iv busulfan versus oral busulfan in conditioning regimens prior to autologous stem cell transplant?

Dr. Nagler: Given the difficulties with the oral formulation of busulfan, most centres now use the iv formulation. However, the iv formulation of busulfan is more expensive than the oral formulation. Therefore, some centres have developed strict guidelines on checking blood levels of busulfan and are therefore able to regulate the levels of oral busulfan to ensure they are appropriate.
New Evidence: In what patients and in which settings do you give busulfan in your clinical practice?

Dr. Nagler: In our practice we give busulfan to most patients with leukemia prior to transplant. However, we tend to use allogeneic rather than autologous transplant in our centre. An alternative conditioning regimen is total body irradiation (TBI) plus cyclophosphamide. However, this regimen is prone to a number of toxicities associated with radiation. In addition, it requires that radiation facilities are available at the treatment centre. In Israel, we do not use TBI for patients with AML. Most transplants are allogeneic and use iv busulfan plus cyclophosphamide or reduced intensity conditioning (RIC) with iv busulfan plus fludarabine. In addition, a new agent called treosulfan is being explored in combination with fludarabine at our centre. A study by Shimoni, et al. compared treosulfan with RIC (busulfan plus fludarabine) conditioning regimens in patients with AML and myelodysplastic syndrome (MDS). The study demonstrated comparable efficacy and toxicity of the two regimens.

New Evidence: How might the results of your study impact clinical practice?

Dr. Nagler: In the last 10 to 15 years, there has been a decrease in the use of autologous transplant. Since the availability of RIC, most centres now prefer to use allogeneic transplant. With RIC, reduced chemotherapy results in a less toxic regimen and the donor immune system is able to attack the leukemia. Allogeneic transplant is therefore seen as more efficient than autologous transplant for the treatment of AML. However, given the availability of less toxic but effective conditioning regimens, autologous transplantation may become more useful in the future. There is now a growing interest in revisiting the role of autologous transplantation in relatively good-risk patients who are not usually candidates for allogeneic transplantation in first complete remission.

New Evidence: Do you have any further comments on this study?

Dr. Nagler: It is important to mention that this was a single-arm registry study and was therefore not a randomized comparison. Results therefore need to be interpreted with caution. As a next step it would be interesting to compare autologous to haploidentical and cord transplants performed in patients without human leukocyte antigen compatible siblings or unrelated donors (30% to 40% of donors).

References:
BUSULFEX® (busulfan) Injection is indicated for use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation, including: acute lymphocytic leukemia, acute non-lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and myelodysplastic syndrome.

In any regimen utilizing BUSULFEX®, the patient’s disease status should either be refractory to other therapies or carry sufficiently high risk for recurrence of disease, so that progenitor cell transplant is the treatment of choice, in the opinion of a qualified physician.

WARNINGS

BUSULFEX® (busulfan) Injection is a potent cytotoxic drug that results in profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents and in the management of patients with severe pancytopenia. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The most frequent, serious consequence of treatment with BUSULFEX® at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Frequent complete blood counts, including white blood cell differentials, and quantitative platelet counts should be monitored during treatment and until recovery is achieved. Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for prevention and management of infections during the neutropenic period. Platelet and red blood cell support should be employed as medically indicated.

Busulfan may be a human carcinogen. Several cases of leukemia have occurred 5–8 years following oral busulfan treatment. Caution should be exercised when administering the recommended dose of BUSULFEX® to patients with a history of seizure disorder, head trauma, or receiving other potentially epileptogenic drugs.

Special populations

Busulfan can cause fetal harm when administered to a pregnant woman. It is not known whether this drug is excreted in human milk. BUSULFEX® has not been administered to patients with hepatic insufficiency. However, patients who have received prior radiation therapy, greater than three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease with the recommended BUSULFEX® dose and regimen.

Please see Product Monograph for a complete listing of warnings, precautions and contraindications, including further information about special populations.

ADVERSE REACTIONS (see Product Monograph for full listing)

The most common adverse events observed in patients treated with BUSULFEX® (busulfan) were: nausea (97%), stomatitis (96%), vomiting (91%), fever (87%), anorexia (80%), diarrhea (80%), insomnia (80%), headache (69%), anxiety (65%), hypomagnesemia (64%), abdominal pain (62%), hypokalemia (58%), hyperglycemia (57%), anemia (56%), tachycardia (50%) and rash (50%). In addition to these adverse events, 62% of patients experienced grade 3 anemia, while 96% and 91% of patients experienced grade 4 leukopenia and thrombocytopenia, respectively.

Patients undergoing high-dose busulfan therapy followed by hematopoietic progenitor cell transplantation experience a wide range of adverse events. These may result from their disease, prior therapy, concomitant cytotoxic drugs or other medications, as well as from busulfan.

Hepatic veno-occlusive disease (HVOD) developed in 5.8% (6/103) (1 of 42 autologous and 5 of 61 allogeneic patients) of patients treated with BUSULFEX® in these studies and was fatal in 1.9% (2/103) (2 of 61 allogeneic patients, one of which had a prior transplant). The incidence of HVOD per the Jones’ criteria was 3.8% (4/103). Hepatic veno-occlusive disease was reported in 17% of patients treated with high-dose oral busulfan in the transplant setting; 5–6% of patients died. Serum transaminases, alkaline phosphatase, and bilirubin should be monitored regularly for early detection of hepatotoxicity.

Other than the expected bone marrow suppression often resulting in opportunistic infections that can be lethal, most clinically relevant adverse events are for the liver, lung and brain.

Post-Marketing Adverse Drug Reactions:

The following additional adverse events have been spontaneously reported during the post-marketing use of BUSULFEX®: febrile neutropenia; tumor lysis syndrome; thrombotic micro-angiopathy (TMA); severe bacterial, viral (e.g., cytomegalovirus viraemia) and fungal infections; and sepsis. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Please consult Product Monograph for complete prescribing information.

For questions, please contact Medical Information at 1-877-341-9245.
Investigator Commentary

An Interview with Dr. Arnon Nagler on his study comparing intravenous busulfan plus cyclophosphamide versus total body irradiation plus cyclophosphamide conditioning for allogeneic transplant in AML

At the EBMT 2012 Annual Meeting, New Evidence spoke with Dr. Arnon Nagler, Professor of Medicine at Tel Aviv University and Director of the Hematology Division and Cord Blood Bank at Chaim Sheba Medical Center, Tel Hashomer, Israel on his study examining intravenous busulfan-based conditioning prior to autologous transplant in acute myeloid leukemia.

New Evidence: Please discuss the rationale for your study.

Dr. Nagler: There are two treatment protocols traditionally used prior to allogeneic transplant in acute myeloid leukemia (AML). One protocol uses total body irradiation (TBI) plus cyclophosphamide and the second protocol uses oral busulfan plus cyclophosphamide. The TBI protocol is considered to be significantly more toxic, increasing the risk of cataracts and heart damage. However, a number of studies have shown the TBI regimen to improve leukemia-free survival (LFS) and overall survival (OS), compared to the oral busulfan regimen.1,2

Oral busulfan is a standard agent used as part of conditioning regimens prior to autologous transplant in the treatment of AML. However, there are a number of disadvantages of the oral formulation of busulfan. The oral formulation is given in individual tablets of 2 mg. Therefore, if you need to give a patient 2 mg/kg of busulfan for four days, the patient will often need to take over 100 tablets per day. In addition, if the patient is not able to keep the tablets down, some of the medication will be lost. Another disadvantage of the oral formulation of busulfan is that the absorption is not predictable and varies from patient to patient. In patients absorbing less than expected, engraftment may not occur, risk of relapse is greater, and in those receiving more than required, toxicities may result. To manage the differences in absorption, blood levels of the drug can be taken and dose adjustments made to ensure optimal drug delivery; however, this is a laborious and complicated process. The final and most important disadvantage of oral busulfan is the risk of veno-occlusive disease (VOD) of the liver.

In contrast to the oral formulation of busulfan, the intravenous (iv) formulation is much more predictable. It is therefore easier for nurses and doctors to administer and there is less risk of engraftment issues, relapse, and toxicities. The rationale for our study is that using iv busulfan would reduce the toxicity of the conditioning regimen, improving outcomes compared with the TBI plus cyclophosphamide regimen.
**New Evidence:** Please describe the design and patient population used in your study.

**Dr. Nagler:** Our study was a retrospective survey based on a database including all transplant centres in Europe. The database is managed by the Acute Leukemia Working Party of the European Cooperative Group for Blood and Marrow Transplantation (ALWP-EBMT). Database managers are able to track the number of transplants performed in AML in Europe and can approach individual centres for additional data.

Our study included patients at first allograft transplanted from an unrelated donor who received either TBI plus cyclophosphamide (TBI/Cy) or iv busulfan plus cyclophosphamide (Bu/Cy). Data included 169 patients with AML transplanted between 2000 and 2010. The median age was 38 years in the TBI/Cy arm and 42 years in the Bu/Cy arm.

**New Evidence:** Please discuss the results of your study.

**Dr. Nagler:** In our study there was no difference in the engraftment rate and incidence of acute graft-versus-host disease (aGVHD) between the TBI/Cy and Bu/Cy groups. However, induction of remission, LFS, and OS were significantly higher in the Bu/Cy group compared with the TBI/Cy group \((p < 0.05)\). The superior efficacy demonstrated in the Bu/Cy group is surprising and we do not have a good explanation for these findings. The difficulty is that these are registry data and we are therefore missing information on factors that may influence results. For example, we do not have data on the treatments used at relapse, patient blood counts, and number of salvage therapies given. We are now going back to the treatment centres to gather this additional information. Our plan is to incorporate these data into our next analysis to improve the quality of the results.

**New Evidence:** What are the advantages of iv busulfan in this setting?

**Dr. Nagler:** As discussed above, the TBI/Cy regimen is limited by a large number of toxicities. Therefore, providing an effective alternative to TBI/Cy is important in this patient group. We also know that iv busulfan is less toxic than oral busulfan. Therefore, the iv Bu/Cy regimen may be a good alternative to TBI/Cy in patients with AML. Our study shows that iv Bu/Cy is at least as effective as TBI/Cy. Although our study has a number of limitations, it is reassuring that we could use iv Bu/Cy in patients unable to tolerate the TBI/Cy regimen, knowing that efficacy will not be compromised. In addition, in centres where radiation facilities are not available, iv Bu/Cy may be a reasonable alternative.

**New Evidence:** Do you still use TBI as part of your conditioning regimens in your clinic?

**Dr. Nagler:** Although many treatment centres do use TBI for conditioning prior to allogeneic transplant in AML, our centre does not use TBI in this setting. In our clinic, we use TBI mainly in acute lymphoblastic leukemia. Most transplants in our clinic are allogeneic and use iv busulfan plus cyclophosphamide or reduced intensity conditioning (RIC) with iv busulfan plus fludarabine. In addition, a new agent called treosulfan is being explored in combination with fludarabine at our centre. A study by Shimoni, et al. compared treosulfan with RIC (busulfan plus fludarabine) conditioning regimens in patients with AML and myelodysplastic syndrome. The study demonstrated comparable efficacy and toxicity of the two regimens.

**References:**
A number of initiatives are currently underway in support of LFC’s corporate mission. These include:

**General Practitioner (GP) Education Program:**
- Delayed diagnosis for individuals is an issue and can affect the outcome for some patients.
- LFC’s hope is that GP education on the signs and symptoms of lymphoma will mean patients will be diagnosed earlier. This program will be an online, accredited continuing medical education (CME) program.

**Consistency of Care for Lymphoma Patients Nationwide:**
- Identifying gaps in care, treatment options, and related demographics and geography issues for lymphoma patients is an important step in understanding how to improve consistency of care across the nation. To this end, LFC is in the process of creating a Report Card on Lymphoma in Canada.
- LFC is working with its Scientific Advisory Board and the medical community to develop National Lymphoma Treatment Guidelines to ensure consistent protocols for all lymphoma patients regardless of where they live in Canada.

**Support for New Treatment Options**
- LFC is grateful to be able to participate in patient submissions to the pan-Canadian Oncology Drug Review (pCODR), and is currently working on the third submission this year. Through surveys sent across Canada, LFC has collected qualitative and quantitative data to help inform the submissions.
- LFC, in collaboration with several stakeholders, was instrumental in obtaining Ontario Government approval for rituximab to be funded for relapsed refractory follicular lymphoma patients. Our advocacy work to support access to treatment across Canada continues as new treatment options are being developed.

**Commitment to Research**
- LFC has supported lymphoma research in Canada since the organization began, and continues to support research through funding of two two-year research fellowships.
- In 2012, thanks to a generous gift of gratitude, LFC will be providing two additional significant research grants to Princess Margaret Hospital and Odette Cancer Centre at Sunnybrook Health Sciences Centre.
Innovative Patient Support

- The online community of “people helping people” includes shared stories as well as patient blogs featured at www.lymphoma.ca.
- The website also includes information on third party events across Canada, and updates to the community through LFC’s newsletter, the LFC LEAFlet.

Increased Awareness

- Increasing awareness of lymphoma, including signs and symptoms, as well as ensuring patients know about LFC and the support that is available to them is a priority for LFC.
- Stay tuned for new awareness campaigns launching through 2012.

Expanded Resources Across Canada

- LFC is growing!
- Recent staff additions include a full-time Quebec Regional Coordinator and Marketing Communication Coordinator, with additional staff to be hired in Fall 2012.

LFC provides an annual summary of our activities and financials, available at www.lymphoma.ca.

Key Dates

LFC has a number of events in the coming months. Please visit www.lymphoma.ca for more information. Highlights include:

- Golf tournament:
  Aug 21, 2012 at Eagle’s Nest Golf Club, Maple, ON
- Ontario Health Care and Patient Symposium:
  September 29, 2012 in Toronto, ON
- Quebec Health Care and Patient Symposium:
  November 12, 2012 in Montreal, QC

How to Help

There are many ways to help LFC. These include patient referrals, involvement in events, connecting with LFC on lymphoma-related activities and stories in your community, as well as through donations. Please contact LFC for more information on how to get involved.

For more information, please visit the LFC’s website at: www.lymphoma.ca
Charitable Business Number: 87346 1040 RR0001
LUNG CANCER
The Irreversible EGFR-TKIs Afatinib and Dacomitinib Show Promise for the Treatment of NSCLC

In 2012, lung cancer is expected to remain the second most frequently diagnosed form of cancer, accounting for 14% of new cases, and the leading cause of cancer death among men (27%) and women (26%) in Canada. Non-small cell lung cancer (NSCLC) is the most common classification for this disease, representing approximately 85% of all lung cancers. Usually, patients with NSCLC are diagnosed at an advanced stage of disease and prognosis is poor.

In recent years, treatment for NSCLC has targeted the epidermal growth factor receptor (EGFR). Erlotinib and gefitinib, the first generation of reversible EGFR-tyrosine kinase inhibitors (TKIs), have produced modest response rates in unselected patient populations. Patients achieving the best response rates with these agents had tumours carrying certain EGFR mutations, such as in-frame deletions in exon 19 or point mutations in exon 21 (e.g., L858R), that confer sensitivity to treatment. In a number of trials, monotherapy with erlotinib or gefitinib has been more effective than first-line chemotherapy for this subgroup of patients. However, most of these patients eventually develop acquired resistance and disease progression while on treatment.

Consequently, a second generation of EGFR TKIs, which offers irreversible inhibition, has been developed for the treatment of NSCLC. Afatinib inhibits the tyrosine kinase activity of both EGFR and human epidermal growth factor receptor-2 (HER2), while dacomitinib can inhibit all catalytically active members of the EGFR tyrosine kinase family — EGFR, HER2, and HER4.

In this article, we report results shared at the ASCO 2012 annual meeting from trials that investigated the efficacy and safety of afatinib and dacomitinib for the treatment of NSCLC:

• LUX-Lung 3, a phase III study, found that afatinib’s adverse events were manageable and it was more effective than pemetrexed plus cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harbouring EGFR-activating mutations.

• The Advanced Research for Cancer targeted pan-HER therapy (ARCHER) study is a phase III trial investigating the use of dacomitinib, an irreversible pan-HER tyrosine kinase inhibitor, vs. erlotinib for the treatment of patients with advanced NSCLC.

• Two interim analyses of the first stage of a phase III trial called LUX-lung 5 showed that afatinib monotherapy provided clinically relevant disease control for most patients with metastatic NSCLC (all patients and a subset with squamous histology) who had disease progression after prior chemotherapy and treatment with either erlotinib or gefitinib.

• A phase II trial demonstrated that dacomitinib is a tolerable and efficacious first-line treatment for patients with lung cancer carrying EGFR exon 19 or 21 mutations.

References:
### Background
Certain epidermal growth factor receptor (EGFR) mutations define a subgroup of patients with lung cancer whose tumours are more sensitive to treatment with reversible EGFR-tyrosine kinase inhibitors (TKIs) than standard first-line chemotherapy. In a phase II study of afatinib, this orally bioavailable and irreversible TKI of EGFR and human epidermal growth factor receptor-2 (HER2) had efficacy in treating lung adenocarcinomas harbouring EGFR mutations. However, afatinib has not been directly compared with pemetrexed and cisplatin, a highly effective and well tolerated combination chemotherapy, for the first-line treatment of patients with advanced-stage lung adenocarcinoma that is EGFR mutation-positive. Yang and colleagues designed the LUX-Lung 3 trial in order to make this comparison of treatments and presented the results at ASCO 2012.1

### Study design
- **LUX-Lung 3 was a multinational, randomized, open-label, phase III study.**

- Following central laboratory testing for EGFR mutations, eligible patients (n = 345) with treatment-naïve, stage IIIB/IV lung adenocarcinoma were randomized at a ratio of 2:1 to either afatinib (n = 230) or pemetrexed/cisplatin (n = 115).

- The dosages for each study drug were:
  - Afatinib: 40 mg orally once daily;
  - Pemetrexed/cisplatin: (pemetrexed: 500 mg/m²; cisplatin: 75 mg/m² intravenously once every 21 days, up to six cycles).

- The primary endpoint for this study was progression-free survival (PFS) as determined by an independent review committee in Solid Tumors 1.1.

- Secondary endpoints included overall response rate (ORR), duration of response (DOR), safety, and patient-reported outcomes.

### Key findings
- After a median follow-up of 16.4 months, 221 PFS events had occurred among all randomized patients (afatinib: 152 events; pemetrexed/cisplatin: 69 events). (Figure 1)

- The LUX-Lung 3 trial met its primary endpoint since the median time of PFS was significantly extended for patients taking afatinib compared with pemetrexed/cisplatin (11.1 vs. 6.9 months; HR = 0.58 [95% CI: 0.43–0.78]; p = 0.0004). (Figure 1)

- The median time of PFS was also significantly prolonged in a subset of patients with the common EGFR mutations Del19/L858R who were treated with afatinib vs. pemetrexed/cisplatin (13.6 vs. 6.9 months; HR = 0.47 [95% CI: 0.34–0.65]; p < 0.0001). (Figure 1)
• Analysis of PFS by patient subgroup favoured treatment with afatinib compared with pemetrexed/cisplatin for nearly every characteristic, except for those classified as current/ex-smokers (HR = 1.04 [95% CI: 0.54–1.98]) where the two treatments were equally effective. (Figure 2)

Figure 2. Progression-free survival subgroup analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Number of patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>345</td>
<td>0.58 (0.43–0.78)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>121</td>
<td>0.61 (0.37–1.01)</td>
</tr>
<tr>
<td>Female</td>
<td>224</td>
<td>0.54 (0.38–0.78)</td>
</tr>
<tr>
<td>Age at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>211</td>
<td>0.53 (0.36–0.76)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>134</td>
<td>0.64 (0.39–1.03)</td>
</tr>
<tr>
<td>Race stratification factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Asian</td>
<td>96</td>
<td>0.68 (0.39–1.19)</td>
</tr>
<tr>
<td>Asian</td>
<td>249</td>
<td>0.34 (0.18–0.67)</td>
</tr>
<tr>
<td>EGFR mutation category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del19/L858R (common)</td>
<td>108</td>
<td>0.47 (0.34–0.65)</td>
</tr>
<tr>
<td>Del19</td>
<td>170</td>
<td>0.38 (0.18–0.44)</td>
</tr>
<tr>
<td>L858R</td>
<td>136</td>
<td>0.73 (0.46–1.17)</td>
</tr>
<tr>
<td>Baseline ECOG score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>133</td>
<td>0.30 (0.31–0.82)</td>
</tr>
<tr>
<td>1</td>
<td>211</td>
<td>0.63 (0.43–0.91)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>256</td>
<td>0.47 (0.33–0.67)</td>
</tr>
<tr>
<td>&lt;15 pack year/stop ≥1 year</td>
<td>30</td>
<td>0.50 (0.39–1.34)</td>
</tr>
<tr>
<td>Other: current/ex-smoker</td>
<td>79</td>
<td>1.04 (0.34–3.98)</td>
</tr>
</tbody>
</table>

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor

• ORR was greater in the afatinib group compared with the pemetrexed/cisplatin group, among all patients (56.1% vs. 22.6%; p < 0.001) and patients with common EGFR mutations (60.8% vs. 22.1%; p < 0.0001). (Figure 3)

• The median DOR was prolonged for patients who took afatinib compared with pemetrexed/cisplatin (11.1 vs. 5.5 months). (Figure 3)

• A longitudinal analysis of the difference in mean scores over time for a questionnaire evaluating the patient’s quality of life (QoL) favoured treatment with afatinib compared with pemetrexed/cisplatin in every category. (Figure 4)

Figure 4. Quality of life: difference in mean scores

Difference in mean scores

Global health status/QoL 3.28
Overall health 3.52
QoL 3.13
Physical functioning 4.83
Role functioning 4.50
Emotional functioning 0.85
Cognitive functioning 3.24
Social functioning 1.18

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor

• Significant delays in time to deterioration of two lung cancer-related symptoms, cough (HR = 0.60, p = 0.0072) and dyspnea (HR = 0.68, p = 0.0145) were seen in patients taking afatinib vs. pemetrexed/cisplatin.

• The percentage of patients experiencing drug-related adverse events (AEs) of any grade, AEs leading to discontinuation, and serious AEs (SAEs) were similar between treatment groups.
• A few patients (n = 4 [1.7%]) treated with afatinib had drug-related SAEs leading to death compared with none on pemetrexed/cisplatin.

• The most frequent drug-related, all-grade AEs with greater than 20% difference between treatment arms were:
  - Afatinib: diarrhea (95.2%), rash/acne (89.1%), stomatitis/mucositis (72.1%), paronychia (56.8%), and dry skin (29.3%);
  - Pemetrexed/cisplatin: nausea (65.8%), decreased appetite (53.2%), fatigue (46.8%), vomiting (42.3%), neutropenia (31.5%), and anemia (27.9%). (Table 1)

| Table 1. Most frequent drug-related adverse events (>20% difference between treatment arms) |
|-----------------------------------------------|---------------------------------|---------------------------------|
| **Adverse Event**                         | **Afatinib (n = 229)** | **Pemetrexed/Cisplatin (n = 111)** |
|                                          | **All Grades^† n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **All Grades^† n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** |
| Diarrhea                                 | 218 (95.2)             | 33 (14.4)        | 0                 | 17 (15.3)             | 0                 | 0                 |
| Rash/acne*                               | 204 (89.1)             | 37 (16.2)        | 0                 | 7 (6.3)               | 0                 | 0                 |
| Stomatitis/mucositis*                    | 165 (72.1)             | 19 (8.3)         | 1 (0.4)           | 17 (15.3)             | 1 (0.9)           | 0                 |
| Paronychia                               | 130 (56.8)             | 26 (11.4)        | 0                 | 0                    | 0                 | 0                 |
| Dry skin                                 | 67 (29.3)              | 1 (0.4)          | 0                 | 2 (1.8)               | 0                 | 0                 |
| Nausea                                   | 41 (17.9)              | 2 (0.9)          | 0                 | 73 (65.8)             | 4 (3.6)           | 0                 |
| Decreased appetite                       | 47 (20.5)              | 7 (3.1)          | 0                 | 59 (53.2)             | 3 (2.7)           | 0                 |
| Fatigue*                                 | 40 (17.5)              | 3 (1.3)          | 0                 | 52 (46.8)             | 14 (12.6)         | 0                 |
| Vomiting                                 | 39 (17.0)              | 7 (3.1)          | 0                 | 47 (42.3)             | 3 (2.7)           | 0                 |
| Neutropenia                              | 2 (0.9)                | 1 (0.4)          | 0                 | 35 (31.5)             | 17 (15.3)         | 3 (2.7)           |
| Anemia                                   | 7 (3.1)                | 1 (0.4)          | 0                 | 31 (27.9)             | 5 (4.5)           | 2 (1.8)           |

*Grouped term; †No grade 5 events for the presented adverse events

n = number of patients
**Key conclusions**

- Afatinib is a clinically relevant first-line treatment option, having significantly improved the time of PFS, rates of response, time to symptom worsening, and QoL for patients with EGFR mutation-positive, advanced-stage lung adenocarcinoma compared with the chemotherapeutic combination of pemetrexed/cisplatin.

- The safety profile for afatinib was consistent with previous studies of the drug and AEs were manageable with a low treatment discontinuation rate.


Boyer M, et al. ASCO 2012: Abstract TPS7615

**ARCHER: dacomitinib (PF-00299804) versus erlotinib for advanced non-small cell lung cancer — a randomized double-blind phase III study**

**Background**

Patients with advanced non-small cell lung cancer (NSCLC) who received dacomitinib, an irreversible tyrosine kinase inhibitor (TKI) of all catalytically active members of the human epidermal growth factor receptor (HER) family, had significantly prolonged progression-free survival (PFS) compared with erlotinib in a previous phase II trial. This drug was beneficial across several clinical and molecular subgroups of patients, including those with KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) wild-type (WT) tumours. Based on these results, a larger phase III clinical trial known as ARCHER (Advanced Research for Cancer targeted pan-HER therapy) was designed to better compare the efficacy of dacomitinib with erlotinib in two patient populations with NSCLC: (a) all enrolled patients with advanced NSCLC, and (b) patients with KRAS WT NSCLC. At ASCO 2012, Boyer and colleagues presented a quick look at the rationale and design of ARCHER, a trial that is in its early stages of enrollment. (Figure 1)

**Figure 1. Dacomitinib is an irreversible pan-human epidermal growth factor receptor inhibitor**

Inhibition of all kinase-active HER receptors offers potential for a more complete inhibition of HER signalling: receptor dimerization is key to HER family signalling.

<table>
<thead>
<tr>
<th>HER receptor dimers</th>
<th>Inhibition by dacomitinib</th>
<th>Inhibition by registered EGFR-TKis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In vitro kinase assay against wild-type receptor
† Potential benefits — based on preclinical data

**EGFR** = epidermal growth factor receptor (HER1); **HER** = human epidermal growth factor receptor; **IC** = half maximal inhibitory concentration; **TKIs** = tyrosine kinase inhibitors
**Study design**

- ARCHER is a multinational, randomized, double-blinded, controlled phase III clinical trial (NCT01360554).
- This trial plans on recruiting 800 patients with locally advanced or metastatic NSCLC who have had at least one but no more than two previous regimens of chemotherapy.
  - As of May 21, 2012, 322 patients have been enrolled.
- Patients are randomized (1:1) to receive once daily, oral doses of either erlotinib (150 mg) or dacomitinib (45 mg).
- Both treatments are self-administered on an empty stomach without scheduled breaks and patients are assessed every 28 days.

**Key findings**

- The objective of this study is to investigate whether treatment with dacomitinib is superior to erlotinib with respect to PFS in either of the co-primary populations.
- The study will be considered positive if the stratified log-rank test for PFS is significant at the time of the final analysis for either of the two co-primary populations (all patients: \( p < 0.015 \); KRAS WT patients: \( p < 0.01 \)).
- An interim analysis of PFS for futility will be conducted after 33.3% and 39% of PFS events have occurred in the KRAS-WT group and the all-patients group, respectively, but the study will not be stopped for efficacy based on comparison of PFS at that time.
- The secondary objectives of this trial are to compare the following measures between treatment arms for both patient populations:
  - Overall survival, overall response rate, and duration of response;
  - Safety and tolerability of treatment;
  - Patient-reported outcomes of health status, quality of life, and disease-/treatment-related symptoms.
- This trial also seeks to determine the following factors:
  - KRAS and HER family genotypes of each patient’s tumour tissue;
  - Plasma levels of dacomitinib and its circulating metabolites for the evaluation of steady-state pharmacokinetics.

**ARCHER study design**

**Endpoints**

- Primary: PFS*
- Secondary: OS,†
- best overall response (RECIST), safety, PRO

**Co-primary patient populations**

In patients who have previously had at least one (and no more than two) chemotherapy regimens for advanced disease within the two co-primary populations:

- All patients with advanced NSCLC
- Patients with NSCLC that is confirmed KRAS WT

**Stratification**

- Never-smokers vs. ever-smokers
- Adenocarcinoma vs. nonadenocarcinoma
- East Asian vs. non-East Asian/Indian
- ECOG PS 0/1 vs. 2

**Trial design**

- Double-blind, randomized, phase III, global

**Dacomitinib 45 mg QD**

**Erlotinib 150 mg QD**

- Advanced NSCLC 1–2 prior chemotherapies; ECOG PS 0–2
- Tissue available (determination of molecular markers not required prior to dosing)

* Based on independent radiologic review
† The study is adequately powered to show difference in OS

ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of patients; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors

**Key conclusion**

ARCHER is a randomized, double-blinded, phase III clinical trial designed to compare dacomitinib with erlotinib for the treatment of patients with locally advanced or metastatic NSCLC who have had at least one prior chemotherapy regimen.

Background

Patients with squamous non-small cell lung cancer (NSCLC) have limited treatment options. For those with acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors, it is unclear whether sustained EGFR family blockade offers any benefit upon disease progression. In this study, afatinib, an irreversible inhibitor of human epidermal growth factor receptor-1 (HER1) and HER2 tyrosine kinases, was evaluated for efficacy and safety in patients with metastatic NSCLC who had failed chemotherapy and erlotinib or gefitinib. At ASCO 2012, Kim and colleagues presented results of a prespecified interim analysis of LUX-Lung 5 that described a subset of patients with squamous NSCLC treated in the first part of this trial.

Study design

- LUX-Lung 5 is a multicentre, randomized, open-label, two-stage, phase III trial.
- Eligibility criteria for this trial included:
  - Patients with pathologically confirmed stage IIIB or IV NSCLC with lesions measurable by Response Evaluation Criteria in Solid Tumors 1.1;
  - Disease progression after at least one line of cytotoxic chemotherapy (platinum-based or pemetrexed) and treatment with erlotinib or gefitinib for advanced or metastatic disease.
- This study was designed with a two-part treatment regimen:
  - Part A:
    - Patients were enrolled from April 2010 to May 2011;
    - All patients received a continuous 50 mg oral dose of afatinib once daily;
    - Two dose reductions (50 mg/day starting dose to 40 mg/day and 30 mg/day) were permitted in patients experiencing certain adverse events (AEs).
  - Part B:
    - Patients who show complete response, partial response, or stable disease (SD) for ≥12 weeks followed by progressive disease (PD) after part A of the trial will be randomized, at a 2:1 ratio, to receive one of two therapies:
      - Afatinib (40 mg/day) plus paclitaxel weekly (n ≈ 234 patients).
      - Investigator’s choice of chemotherapy (n ≈ 117 patients).
- The primary endpoint for this trial was progression-free survival (PFS).
- The secondary endpoints were objective response (OR), defined as complete or partial response, and overall survival.

Key findings

- The results presented here are from an interim analysis of patients with squamous NSCLC treated in part A of this trial.
- The majority of the patients treated with afatinib had tumours classified as adenocarcinoma (n = 985), while fewer had tumours with squamous (n = 91) or other (n = 77) histologies. (Figure 1)
• Median PFS for patients treated with afatinib in the squamous histology subset was 3.7 months, similar to the adenocarcinoma subset.
  - Forty-two patients (46.2%) had PFS ≥ three months.
  - Thirteen patients (14.3%) had PFS ≥ six months. (Figure 2)
• In the squamous histology subset, patients’ response to treatment was 4.4% with an OR, 56.0% with SD, 24.2% with PD, and 15.4% were not evaluable. (Table 1)
• In the group of patients (n = 31) with PD on prior erlotinib or gefitinib with no intervening chemotherapy, 10 patients achieved confirmed disease control on afatinib (two with partial response and eight with SD).
• The most commonly reported grade 3 AEs were diarrhea (13.2%) and rash/acne (12.1%). (Table 2)
• The safety profile for afatinib in the squamous histology subset was similar to that observed for the whole trial.

![Figure 1. Patient disposition in Part A](image1)

![Figure 2. Progression-free survival for patients with adenocarcinoma or squamous tumour histology](image2)
Key conclusion

- Afatinib monotherapy demonstrated encouraging activity in the squamous histology subset of treatment-refractory patients with NSCLC, meriting further evaluation.

First-line dacomitinib (PF-00299804), an irreversible pan-HER tyrosine kinase inhibitor, for patients with EGFR-mutant lung cancers

**Background**

Dacomitinib irreversibly inhibits human epidermal growth factor receptor-1 (HER1), HER2, and HER4, and shows superior activity versus reversible epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors in EGFR-mutant lung cancer models, including resistant forms. This open-label phase II study evaluated dacomitinib as first-line treatment for patients with lung cancer. Kris and colleagues presented results of their study concerning the sub-cohort of patients with sensitizing EGFR exon 19 or exon 21 mutations.

**Study design**

- This phase II trial was a multicentre, Fleming single-stage design.
- Patients included in the EGFR-mutant cohort of this study had to meet the following criteria:
  - Have stage IIIB/IV lung adenocarcinoma;
  - Received no prior systemic treatment for lung cancer;
  - Have EGFR mutation.
- Patients received dacomitinib orally once daily continuously at 45 mg or 30 mg with the option to escalate to 45 mg, and were evaluated every 28 days.
- The primary endpoint was the progression-free survival (PFS) rate at four months.
- Other endpoints included overall PFS and partial response (PR) rate.

**Key findings**

- Patients enrolled in this study were classified into cohort A or B, and subcategorized as follows:
  - Cohort A:
    - Patients with EGFR-mutant lung cancer (n = 53);
    - Never-smokers (<100 cigarettes) and former light-smokers (<10 pack years) with ≥15 years since last cigarette (n = 36).
  - Cohort B:
    - HER2 gene mutation or amplification (n = 17).
- The majority of patients with EGFR-mutant lung cancer enrolled in this study were female (n = 36), of Asian (n = 28) or Caucasian (n = 23) descent, and had no prior smoking history (n = 41).
- The majority of patients with EGFR-mutant lung cancer also had EGFR mutations in exon 19 (n = 25) or 21 (n = 21), while seven patients had other EGFR mutations. (Table 1)

**Table 1. Types of epidermal growth factor receptor mutations**

<table>
<thead>
<tr>
<th>EGFR mutation(s)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>53</td>
</tr>
<tr>
<td>Exon 19 and 21 mutations</td>
<td>46</td>
</tr>
<tr>
<td>Exon 19</td>
<td>25</td>
</tr>
<tr>
<td>Exon 21</td>
<td>21</td>
</tr>
<tr>
<td>Other EGFR mutation(s)</td>
<td>7</td>
</tr>
<tr>
<td>G719S (exon 18) and E709A (exon 18)</td>
<td>1</td>
</tr>
<tr>
<td>G719S (exon 18) and R776H (exon 20)</td>
<td>1</td>
</tr>
<tr>
<td>T790M (exon 20) and E746,49del (exon 19)</td>
<td>1</td>
</tr>
<tr>
<td>T790M (exon 20) and L858R (exon 21)</td>
<td>2</td>
</tr>
<tr>
<td>S768_D770dupSVD (exon 20)</td>
<td>1</td>
</tr>
<tr>
<td>A767_V769dupASV (exon 20)</td>
<td>1</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor; n = number of patients

- After four months of treatment, the PFS rates for groups of patients in cohort A were:
  - EGFR exon 19 or 21 mutations: 96% (95% confidence interval [CI]: 84–99);
  - Other EGFR mutations: 63% (95% CI: 14–89);
  - All patients in cohort A: 77% (95% CI: 67–84). (Table 2)

- At one year, patients with EGFR exon 19 or 21 mutations exhibited a PFS rate of 74% (95% CI: 58–85) compared with 21% (95% CI: 1–60) for patients with other EGFR mutations.
- Patients with mutations in EGFR exon 19 or 21 had the following median durations of PFS, which did not differ significantly between the two groups:
  - Exon 19: 16.4 months (95% CI: 12.4–23.8);
  - Exon 21: 18.3 months (95% CI: 11.0–24.8). (Figure 1)
- Patients with EGFR exon 19 or 21 mutations who received dacomitinib had a PR rate of 74% (95% CI: 59–86). These PR rates were not significantly different between the two mutation subgroups (exon 19 = 72%; exon 21 = 76%). (Table 3)
• The rest of the patients with EGFR exon 19 or 21 mutations attained stable disease (SD) (n = 11) or had disease progression (PD) (n = 1) on dacomitinib. (Table 3)

• Of the seven patients who had lung cancer with other EGFR mutations, two had a PR, three reached SD, one had PD, and one was indeterminate. (Table 3)

• The best tumour changes from baseline for each patient with a mutation in EGFR exon 19 or 21 are shown in Figure 2.

• For all patients in cohort A, common adverse events included grade 3/4 dermatitis acneiform (17%) and diarrhea (14%).

• Three patients with EGFR exon 19 or 21 mutations discontinued treatment due to drug-related toxicity.

### Table 2. Progression-free survival rate at study time points

<table>
<thead>
<tr>
<th>Study time point</th>
<th>EGFR exon 19 and 21 mutations (n = 46)</th>
<th>Other EGFR mutations (n = 7)</th>
<th>All patients in cohort A (N = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months*</td>
<td>96 (84–99)</td>
<td>63 (14–89)</td>
<td>77 (67–84)</td>
</tr>
<tr>
<td>6 months</td>
<td>84 (70–92)</td>
<td>42 (6–77)</td>
<td>–</td>
</tr>
<tr>
<td>9 months</td>
<td>84 (70–92)</td>
<td>21 (1–60)</td>
<td>–</td>
</tr>
<tr>
<td>12 months</td>
<td>74 (58–85)</td>
<td>21 (1–60)</td>
<td>–</td>
</tr>
</tbody>
</table>

* Primary endpoint

CI = confidence interval; EGFR = epidermal growth factor receptor; n = number of patients

### Figure 1. Progression-free survival for epidermal growth factor receptor exon 19 vs. exon 21 mutation

Exon 19 median PFS = 16.4 months (95% CI: 12.4–23.8)
Exon 21 median PFS = 18.3 months (95% CI: 11.0–24.8)

Number of patients at risk:
Exon 19: 25, 23, 18, 13, 7, 2, 0
Exon 21: 21, 17, 13, 10, 6, 2, 1

CI = confidence interval; PFS = progression-free survival
Table 3. Radiologic responses

<table>
<thead>
<tr>
<th>Best response to dacomitinib</th>
<th>EGFR exon 19 and exon 21 mutations (n = 46) n (%)</th>
<th>Other EGFR mutations (n = 7) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>34 (74)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Exon 19 PR (n = 25)</td>
<td>18 (72)</td>
<td>N/A</td>
</tr>
<tr>
<td>Exon 21 PR (n = 21)</td>
<td>16 (76)</td>
<td>N/A</td>
</tr>
<tr>
<td>SD</td>
<td>11 (24)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0</td>
<td>1 (14)</td>
</tr>
</tbody>
</table>

CR = complete response; EGFR = epidermal growth factor receptor; n = number of patients; N/A = not applicable; PD = progressive disease; PR = partial response; SD = stable disease

Figure 2. Best tumour changes from baseline for patients with an epidermal growth factor receptor exon 19 or 21 mutation

Key conclusions

- Dacomitinib was efficacious and well tolerated for the treatment of patients with EGFR exon 19- or 21-mutant lung cancer. Further research is planned for the drug in this patient population.

- Since dacomitinib demonstrated preclinical activity against either HER2-mutant or HER2-amplified tumours, a cohort of patients with these types of lung cancer was added to this trial.

Background

Treatment options are limited for patients with squamous non-small cell lung cancer (NSCLC). For those with acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), it is unclear whether sustained EGFR family blockade offers any benefit upon disease progression. In this study, afatinib, an irreversible inhibitor of human epidermal growth factor receptor-1 (HER1) and HER2 tyrosine kinases, was evaluated for efficacy and safety in patients with metastatic NSCLC who had failed chemotherapy as well as erlotinib or gefitinib. At ASCO 2012, Schuler and colleagues presented results of a prespecified interim analysis of LUX-Lung 5 for all patients with NSCLC treated in the first part of this trial.

Study design

- LUX-Lung 5 is a multicentre, randomized, open-label, two-stage, phase III trial.
- For information on study design and treatment protocols see Kim et al. on p. 92–93.
- Available tumour samples were collected for central EGFR mutation testing; local mutation data were also collected.

Key findings

- The results presented here are from an interim analysis of all patients with NSCLC treated in part A of this trial. At the time of analysis, some patients remained on treatment (n = 99).
- The majority of patients had tumours in the lung classified as adenocarcinoma (85.4%), while the rest had tumours with squamous (7.9%) or other (6.7%) histologies.
- The majority of patients enrolled in this trial were female (56.7%), Asian (42.5%), or Caucasian (39.4%), and were never smokers (53.6%).
- Patients’ best responses to prior erlotinib or gefitinib therapies were primarily stable disease (SD) (41.6%), followed by partial response (30.6%) or complete response (1.5%). The rest of the patients had progressive disease (PD) (20.1%) on prior treatment. (Table 1)
- Median progression-free survival (PFS) for all patients on afatinib monotherapy was 3.3 months. (Figure 1)
- Among all patients on afatinib monotherapy, some achieved disease control (63.7%) with the majority of those reaching SD (56.1%) or an objective tumour response (7.6%). Other patients had PD (24.1%) or their tumour response was not evaluable (0.9%). (Table 2)

### Table 1. Patients’ clinical characteristics

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response to prior erlotinib/gefitinib (investigator reported)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>17 (1.5)</td>
</tr>
<tr>
<td>PR</td>
<td>353 (30.6)</td>
</tr>
<tr>
<td>SD</td>
<td>480 (41.6)</td>
</tr>
<tr>
<td>PD</td>
<td>232 (20.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>43 (3.7)</td>
</tr>
<tr>
<td>Not available</td>
<td>28 (2.4)</td>
</tr>
</tbody>
</table>

Central EGFR mutation status

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>110 (9.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>49 (4.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>35 (3.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>26 (2.3)</td>
</tr>
</tbody>
</table>

| CR = complete response; EGFR = epidermal growth factor receptor; n = number of patients; PD = progressive disease; PR = partial response; SD = stable disease |

### Table 2. Best overall tumour response in patients given afatinib (50 mg/day)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of treated patients</td>
<td>1,154 (100.0)</td>
</tr>
<tr>
<td>Disease control</td>
<td>735 (63.7)</td>
</tr>
<tr>
<td>OR</td>
<td>88 (7.6)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>PR</td>
<td>87 (7.5)</td>
</tr>
<tr>
<td>SD</td>
<td>647 (56.1)</td>
</tr>
<tr>
<td>PD</td>
<td>278 (24.1)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>10 (0.9)</td>
</tr>
</tbody>
</table>

| CR = complete response; n = number of patients; OR = objective response; PD = progressive disease; PR = partial response; SD = stable disease |
• For centrally confirmed EGFR mutation-positive patients (n = 49), PFS was 4.2 vs. 2.6 months for EGFR mutation-negative patients (n = 35). (Figure 2)

• When applying clinical enrichment criteria for patients with acquired resistance to EGFR-targeted treatment, PFS was significantly prolonged for those with enrichment (4.2 vs. 2.8 months; p < 0.0001). (Figure 3)

• The most common grade 3 adverse events were diarrhea (16.8%) and rash/acne (10.5%). (Table 3)
Figure 3. Progression-free survival by clinical enrichment for acquired resistance to EGFR-targeted treatment

Table 3. Frequency of adverse events of all grades occurring in >10% of patients

<table>
<thead>
<tr>
<th>Afatinib</th>
<th>All grades, n (%)</th>
<th>Grade 3, n (%)</th>
<th>Grade 4, n (%)</th>
<th>Grade 5, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>983 (85.2)</td>
<td>194 (16.8)</td>
<td>4 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Rash/acne*</td>
<td>802 (69.5)</td>
<td>121 (10.5)</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>586 (50.8)</td>
<td>57 (4.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nail effect*</td>
<td>381 (33.0)</td>
<td>49 (4.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>331 (28.7)</td>
<td>63 (5.5)</td>
<td>3 (0.3)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>306 (26.5)</td>
<td>41 (3.6)</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>246 (21.3)</td>
<td>13 (1.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>235 (20.4)</td>
<td>57 (4.9)</td>
<td>9 (0.8)</td>
<td>22 (1.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>211 (18.3)</td>
<td>23 (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>181 (15.7)</td>
<td>11 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>176 (15.3)</td>
<td>8 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>158 (13.7)</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>149 (12.9)</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ocular effect*</td>
<td>129 (11.2)</td>
<td>6 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Grouped term
AE = adverse event; n = number of patients

Key conclusions

- Afatinib monotherapy provided a clinically meaningful benefit in this large, treatment-refractory NSCLC trial.
- Those clinically enriched for acquired resistance to EGFR TKIs achieved prolonged disease control upon continued EGFR family blockade.

IF ONE OF US CAN COME UP WITH AN IDEA TO HELP OUR PATIENTS, WHAT COULD ALL OF US COME UP WITH?
New Evidence spoke with Dr. Tony Mok, from the Department of Clinical Oncology at the Chinese University of Hong Kong, about the results of the LUX-Lung 3 study which examined afatinib, an irreversible epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, versus platinum-based chemotherapy as a first-line treatment for patients with EGFR-mutation positive, non-small cell lung cancer (NSCLC). Dr. Mok was on the steering committee for the study and was also a co-investigator.

**New Evidence:** What was the rationale for the LUX-Lung 3 trial?

**Dr. Mok:** In 2006/2007, we were performing the Iressa Pan-Asia Study (IPASS). At that time, we wanted to know how we could get afatinib, a second generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), registered on the market as well as how we could prove it was efficacious. When the study was designed, chemotherapy was still the standard of care. We wanted to prove that afatinib was better than the most efficacious chemotherapy regimen available at that time. We, therefore, decided to use a biomarker-selected population and compare afatinib with pemetrexed plus cisplatinum.

**New Evidence:** Please describe the design of the study.

**Dr. Mok:** This was a biomarker-selected study in which we focused on patients with an EGFR mutation. There are the so-called “common” mutations in exon 19 and exon 21, and there are also “other” mutations. We knew that exon 19 and exon 21 mutations would likely have more sensitivity to afatinib. However, because afatinib could have efficacy on the “other” mutations as well, we included them in the study. Consequently, we selected patients with any EGFR mutation. The study included both Asian and non-Asian patients, the first study to do so, randomized to either a standard dose of afatinib of 40 mg daily or a chemotherapy regimen (pemetrexed/cisplatinum) at the standard dose. The primary endpoint was progression-free survival (PFS).

**New Evidence:** What is the mechanism of action of afatinib?

**Dr. Mok:** We know that patients with an EGFR mutation have an oncogenic addiction to EGFR signalling. By having a tyrosine kinase that binds to the adenosine triphosphate (ATP) pocket, we are able to inhibit the EGFR signal. This has been proven with the first-generation, or reversible, EGFR-TKIs erlotinib and gefitinib. Afatinib was designed to bind irreversibly using a covalent bond to the ATP binding pocket. In other words, it has the potential to increase the efficacy of EGFR inhibition by binding more permanently. In preclinical data, there is evidence that afatinib may inhibit signalling in the T790M mutation at exon 20, which is a known resistance mechanism, and that may prolong disease control.

**New Evidence:** In addition to the type of binding, are there other differences between afatinib and erlotinib or gefitinib?

**Dr. Mok:** Another difference is that afatinib is a pan-HER (human epidermal growth factor receptor) inhibitor. There are four receptor sites called HER1 (EGFR), HER2, HER3, and HER4. There is no intracellular domain in HER3 but there are intracellular domains in HER1, HER2, and HER4. In addition to inhibiting HER1, afatinib may also inhibit HER2 and HER4. Basically, afatinib is a pan-HER inhibitor whereas erlotinib and gefitinib are predominantly HER1 inhibitors. As a result, afatinib may potentially have high efficacy and more specific efficacy in a very small proportion of patients with a HER2 mutation.
**New Evidence:** Please describe the patients that were included in the LUX-Lung 3 study.

**Dr. Mok:** The main inclusion criterion for the study was that patients had to have an established EGFR mutation on the basis of a Therascreen test. They had sufficient tissue available for testing and were confirmed to have one of the 29 mutations in the Therascreen test. Of course, there were other criteria such as the patients being healthy, have measurable disease, and good performance status. The patient profiles were similar to those of patients I see in practice.

**New Evidence:** What did the results of the study show in the overall patient population? What were the results in terms of overall response rate (ORR)?

**Dr. Mok:** The primary endpoint of this study was PFS. For the afatinib arm the median PFS was 11.1 months versus 6.9 months in the chemotherapy arm. We had a hazard ratio (HR) of 0.58 that confirmed the improvement over standard chemotherapy, which is what we expected. The degree of difference was compatible with all the other major randomized studies comparing EGFR-TKIs with chemotherapy in this population with mutations.

For ORR, there was an independent review and an investigator review. For the independent review, the films were sent to a blinded reviewer who did not know the case histories and was only looking at x-rays. In this situation the ORR was 56.1% in the afatinib arm versus 22.6% in the chemotherapy arm; this was statistically significant. On the other hand, in the investigator review, the ORR was 69.1% in the afatinib arm versus 44.3% in the chemotherapy arm. In general, the investigator tended to interpret more generously.

**New Evidence:** In your opinion, how important was the independent review?

**Dr. Mok:** I think the independent review was important to give the assurance that there was no investigator bias. For example, an investigator may know a patient has a mutation and the patient is on chemotherapy. The investigator may, therefore, have the tendency to say there is a slight progression and switch the patient to the EGFR-TKI. While, if the patient is actually on the EGFR-TKI, then slight progression may not be so bad, just a tiny bit of an increase that the investigator may say is marginal so they can keep the patient on the EGFR-TKI because they will benefit from the drug. There is an investigational bias in order to help and protect the patient, to provide the best service to the patient.

**New Evidence:** Please describe the results for patients with common mutations (deletion 19 and L858R)?

**Dr. Mok:** The common mutations refer to the exon 19 deletion and the exon 21 point mutation. In total, there were about 308 patients that fulfilled this description. As expected in a sense, this classification of patients was more sensitive to EGFR-TKIs. In the afatinib arm (204 patients), there was a median PFS of 13.6 months and the chemotherapy arm was exactly the same as the overall population at 6.9 months. The HR was 0.47, which was a bit lower compared with the overall population.

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

**Dr. Mok:** The main toxicities related to afatinib are diarrhea, skin rash, and stomatitis. Those are the non-hematological toxicities. Overall, there were about 14% of patients that had grade 3 diarrhea. The majority of patients (95%) had some kind of diarrhea, so this is a significant toxicity with this drug. Skin rash was similar. About 16% of patients had grade 3 rash but the majority had some kind of skin rash. The other major toxicity was stomatitis (soreness in the mouth). Grade 3 stomatitis was experienced by 8.3% of patients. These non-hematological toxicities are manageable and improve over time but the doctor or the investigator using the drug has to pay attention to these toxicities. The hematological toxicities — neutropenia and anemia — were worse in the chemotherapy arm when compared with afatinib.

**New Evidence:** How do you manage patients with grade 3 rash or diarrhea?

**Dr. Mok:** They need to be caught early on and efforts need to be made to avoid them developing grade 3 rash or diarrhea, which is severe. For skin rash, they are given a prophylactic cream as well as a steroid cream and antibiotics ahead of time. When the rash gets severe, either hold off on the drug for a few days or reduce the dose.

Diarrhea is similar. Do not allow the patient to get up to six or seven bowel movements a day. When they get to two or three stools a day, advise them to take anti-diarrheal medication and then see how it progresses. If the diarrhea worsens, hold off on the drug for a few days.
**New Evidence:** Please describe the quality of life results of the study.

**Dr. Mok:** I do not have the full details of the quality of life results because they will be disclosed at the European Society for Medical Oncology (ESMO) 2012 Congress. However, we can look at the rough estimations using the European Organisation for Research and Treatment of Cancer quality of life questionnaire. Responses to this 30-question questionnaire show there is a significant improvement in functioning including physical function, role function, emotional function, and cognitive function. All of these demonstrate a trend toward improvement with afatinib. The other way to look at it is in terms of cough, pain, and shortness of breath. For all of these cancer-related symptoms, patients in the afatinib arm took a longer time to deteriorate.

**New Evidence:** For emotional functioning, there was a smaller difference between treatment arms than in other areas of functioning. Can you comment on the impact of afatinib versus chemotherapy on emotional functioning?

**Dr. Mok:** The questionnaire is not an exact science, it just tells how the patient interprets their current situation; their emotions are a very subjective thing. I don’t have the exact score from each individual question so I may not be able to go into detail. However, in general, how I interpret the smaller difference between treatment arms is that patients either had improved emotional status in both the afatinib and the chemotherapy arms or they felt equally bad in both the chemotherapy and afatinib arms. One way or the other, it tells us there is not much difference in emotional functioning in either arm. It does not imply whether the drug worked or not. I am sure that in the afatinib arm, skin rash and diarrhea had an impact on the patients’ emotions to a certain extent. In the chemotherapy arm, patients had fatigue and some numbness in the fingertips as adverse effects, which may affect their emotional status. I think it is more complex than just one little dot on a graph but, at this moment, I do not know which answer is correct.

**New Evidence:** The LUX-Lung 3 study used centralized mutation testing. Can you comment on the advantages and disadvantages of on-site versus centralized testing?

**Dr. Mok:** For a clinical trial, centralized testing will give a uniform sensitivity and specificity because we want accuracy. If the same standard method is used, then it can be assured that the finding of a positive mutation is consistent between the two arms. This provides the accuracy needed for clinical trials. However, the major disadvantage is that it takes time to retrieve the tumour tissue, send it to the central lab, and wait for the results. Sometimes the patient does not want to wait. In my opinion, because EGFR mutation testing has to be done in order to help out with clinical decisions, I would encourage all major cities to have their own laboratory, or a few of them in the city. Even though a hospital may not have on-site testing, they can have access to a lab that can do the testing in the city. Although it may not be centralized testing, the hospital can send it to the reference lab closest to them.

**New Evidence:** How might the results of this study change your clinical practice?

**Dr. Mok:** Although this is a positive study, afatinib is not currently available. It is pending Food and Drug Administration (FDA) approval and then, after FDA approval, it will take a little while before it comes to Hong Kong. So, in the short term, I do not see any major changes in my clinical practice. However, knowing that there will be one extra drug that works well in our armamentarium is very encouraging and we look forward to the future. Now, a much bigger topic is how we are going to choose which drug to use in the first line because at this moment there is no major randomized study that compares one EGFR-TKI with another. There is one ongoing study, LUX-Lung 7, but those data may not be available for a little while. At this moment it is dealer’s choice.

**New Evidence:** What makes afatinib a good candidate for first-line treatment?

**Dr. Mok:** First of all, LUX-Lung 3 is a randomized study that proves afatinib works better than chemotherapy and has established its efficacy. There is a PFS of 13.6 months in a randomized, controlled, registration study, which are impressive data and quite encouraging. On the other hand, once the drug is available, whether it is going to change everyone’s practice is still doubtful.

**New Evidence:** For the 10% of patients with mutations other than the common mutations, what do you feel is the best treatment option for them?
**Dr. Mok:** For patients with “other” mutations, there are data on other reversible EGFR-TKIs. The data are scanty, mostly case control, but there is a certain degree of tumour response. For afatinib, in addition to the LUX-Lung 3 trial, the LUX-Lung 2 trial has documentation on about 20 patients who have atypical mutations. In general, the data give us the impression that even with afatinib, the response rate is lower and the PFS is shorter. This has recently been reported in LUX-Lung 2, which was published in *Lancet Oncology*. So afatinib may have an edge but I don’t think we can say conclusively that one drug is better than another in terms of atypical mutations, based on the existing studies. When there is only a small sample size in a non-comparative setting, then we can only say that it is a hypothetical advantage, not a conclusive advantage.

**New Evidence:** As a first-line treatment, how do you think reversible EGFR-TKIs will compare with irreversible EGFR-TKIs?

**Dr. Mok:** From the existing data, afatinib may have an edge in terms of longer PFS. However, this still has to be tested and proven in a randomized, comparative study. This is being undertaken in LUX-Lung 7 in which afatinib is being compared with gefitinib. On the other hand, there is a difference in the toxicity profiles of the two drugs. Skin rash and diarrhea incidence are documented in the IPASS (Iressa Pan-Asia Study) trial and a number of similar studies, and there is actually numerically less diarrhea or grade 3 skin rash using the first-generation EGFR-TKIs. So basically when the data come out, we will have to look at the advantages and the tradeoffs in terms of toxicity.

**New Evidence:** Patients have acquired resistance to reversible EGFR-TKIs. Can you comment on patients acquiring resistance to afatinib?

**Dr. Mok:** All patients will eventually develop resistance to EGFR-TKIs, including afatinib. We know that this is not a curative medication. With afatinib, PFS at six months is longer but patients will become resistant. There are some phase 2 data on the combination of afatinib plus cetuximab that have actually induced a response in 36% of patients who failed a first-generation EGFR-TKI. Now whether the same efficacy is going to show with patients who have failed afatinib, we do not know yet. There have been discussions over the years on how best to investigate the combination of afatinib plus cetuximab. I am still waiting for the final design of an upcoming study but I know that all patients will get afatinib and then when they have disease progression, they will proceed with afatinib plus cetuximab.

**New Evidence:** PFS was twice as long in the afatinib arm compared with the chemotherapy arm. Is this clinically meaningful?

**Dr. Mok:** Yes, of course. This is the seventh randomized study comparing EGFR-TKIs with chemotherapy in mutation-positive patients and consistently the HR is in the range of 0.5 to 0.6. This study falls in the same pattern for HR.

**New Evidence:** In your opinion, what are the next steps to further extend PFS in patients with NSCLC?

**Dr. Mok:** Well, that is a philosophical question because we have to define progression. Right now we define progression using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, which were actually defined initially for chemotherapy drugs. For EGFR-TKIs, to maximize the duration of usage we have to define progression. That is being investigated in a number of trials, including the IMPRESS study, which will treat patients with an EGFR-TKI beyond RECIST progression.

**New Evidence:** Do you consider PFS a good outcome measure in NSCLC?

**Dr. Mok:** At this point, PFS is the best measure we can use because patients do cross over to the efficacious drug. If the cancer is driven by an oncogenic driver, patients can take afatinib in either the first-line or second-line setting. If they take it as first-line treatment they will benefit and if they take it as second-line treatment they will benefit, meaning there will be no overall survival difference. For that reason, there is no other way, apart from PFS, to document the efficacy of the drug.
MELANOMA
Canadian Perspective on the Clinical Management of Metastatic Melanoma

Teresa Petrella, MD, FRCPC;1 Scott Ernst, MD, FRCPC;2 Alan Spatz, MD;3 Joel Claveau, MD, FRCPC;4 Ralph Wong, BSc, MD, FRCPC;5 Michael Smylie, MD, FRCPC6

1Division of Medical Oncology/Hematology, Odette Cancer Centre, Toronto, Ontario; 2Division of Medical Oncology, London Regional Cancer Program, London, Ontario; 3Department of Pathology, Jewish General Hospital, Montreal, Quebec; 4Centre Hospitalier Universitaire de Quebec, Quebec City, Quebec and Hotel-Dieu de Quebec, Quebec City, Quebec; 5Cancer Care Manitoba, Winnipeg, Manitoba; 6Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, Alberta

Medical Writer: Diana Stempak, MSc, PhD, New Evidence

Corresponding Author: Dr. Teresa Petrella, Division of Medical Oncology/Hematology, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, T2-041, Toronto, ON, M4N 3M5
Telephone: 416-480-5248 • Fax: 416-480-6002 • Email: teresa.petrella@sunnybrook.ca

Metastatic melanoma is almost invariably incurable and the prognosis for patients with this disease is quite dismal. Historically, the median survival time for a patient with metastatic melanoma is six to nine months and the five-year overall survival (OS) rate is less than 5%. Until recently, there were few treatment options available for metastatic melanoma and those available demonstrated low efficacy and significant toxicity. The discovery, development and recent approval of novel agents such as vemurafenib (a selective BRAF inhibitor) and ipilimumab (a novel immunotherapeutic agent) has resulted in patients experiencing prolonged survival with manageable adverse events. In the case of vemurafenib, the importance of selecting patients in this new era of personalized medicine has been underscored. While challenges exist to implementing rapid, efficient biomarker testing, this is an essential component of therapy that will improve outcomes in this traditionally difficult-to-treat population. The recent approval of these new agents necessitates a shift in the treatment paradigm and in attitude. As a result, a renewed sense of hope now exists in a therapeutic area that was previously burdened by poor outcomes.

Background

In 2012, 5,800 new cases of melanoma will have been diagnosed in Canada and 970 deaths will have been attributed to this disease.1 In the past several decades, the incidence rates for melanoma have significantly increased, particularly in males.2,3 The lifetime probability of developing melanoma is one in 85 for females and one in 67 for males and the five-year relative survival for melanoma is 90%.4

Melanoma, if detected early, is highly curable by appropriate surgery, but in patients with high-risk features (tumour thickness [depth greater than 4 mm], ulceration, high mitotic rate or regional node involvement) the risk of developing metastases can be very high (30% to 80%).6 Of these patients, 10% to 40% will present with metastases to the central nervous system (CNS) including the brain.7 Melanoma can metastasize to almost every major organ and tissue. (Table 1) The most common initial sites of distant metastases are the skin and soft tissue, and lymph nodes.8 The most common sites of visceral metastases are the lung, brain, liver, gastrointestinal tract, and bone.9 The prognosis for patients with metastatic melanoma is quite dismal as the disease is almost invariably incurable.5,10 Historically, the median survival time for patients with metastatic melanoma is six to nine months and the five-year overall survival (OS) rate is less than 5%.10 Until
recently, there were few treatment options available for metastatic melanoma and those available demonstrated low efficacy and significant toxicity. Without question, metastatic melanoma is a devastating disease with a need for novel treatment strategies that has been unmet until the discovery and development of novel agents such as BRAF (v-raf murine sarcoma viral oncogene homologue B1) inhibitors (vemurafenib and dabrafenib) and novel immunotherapies (ipilimumab).

The purpose of this paper is to present a general discussion and summary on the clinical management of metastatic melanoma in Canada. New therapies such as vemurafenib and ipilimumab will be discussed, as well as promising new agents and/or combinations that are being explored in clinical trials. The goal is to raise awareness in the oncology community about new treatment approaches to metastatic melanoma, and to highlight the importance of rapid coordination and testing for biomarkers that are the targets for a more personalized approach to cancer therapy. With recent notable improvements in outcomes in patients with metastatic melanoma, the prognosis of this disease may not be as dismal as it was in the past. While this paper is evidence-based, it does not reflect a systematic literature review and is not meant to be used as a consensus guideline.

### The Evolution of Cancer Therapy: From Chemotherapy to Personalized Medicine

Systemic chemotherapy was introduced well over 60 years ago as an approach to treating cancer by directly killing tumour cells. These agents function by varying mechanisms such as damaging deoxyribonucleic acid (DNA), impairing DNA repair, inhibiting microtubule formation and acting as alkylating agents. However, the cytotoxic effects are not limited to tumour cells alone, they also target any rapidly dividing cell in the body including bone marrow cells, hair follicles, and gut mucosal cells resulting in the classic side effects of myelosuppression, mucositis, alopecia, nausea, and vomiting.

The last decade has seen an emergence of therapies targeting the molecular and cellular changes specific to cancer such as specific cell signals and receptors, rather than all rapidly dividing cells. Used as monotherapy or in combination with other agents, these targeted therapies have significantly improved patient outcomes and the safety of treatment over previously accepted standards. Almost every malignancy can be divided into molecular subsets that vary in prognosis, natural history, and response to treatment. Research has now yielded an increasing number of available targeted therapies that are uniquely effective in small subpopulations of each tumour type.

With these recent advances, the term *personalized medicine* has been coined and there has been a prominent shift in the general healthcare field as well as in oncology. The goal is to understand the relevant characteristics underlying a particular individual’s disease, which include both disease and host factors, and tailor therapy to that individual or disease. In other words, it is the use of the right drug, at the right dose, for the right patient, at the right time. While significant advances have been made in a number of tumour types, little change has been realized in the treatment of metastatic melanoma until very recently. Today, metastatic melanoma is at the forefront of the movement toward personalized medicine. To better understand how these new treatments fit into the treatment paradigm, it is important to look at how melanoma can be classified.

### Classification of Melanoma

Different approaches can be taken to classify melanoma based on clinical, histological, and epidemiological characteristics. Historical classification by histologic subtypes included superficial spreading, nodular, lentigo maligna, and acral lentiginous. Melanoma can also be studied based on non-cutaneous sites (e.g., uveal tract of the eye and mucosal surfaces). In the past, efforts to classify melanoma into biological subtypes have had little impact on the clinical management of the disease and, in particular, on the management of metastatic melanoma. Cytotoxic and immunological therapies that have been available to date did not target specific pathways in cells, and most were not effective in controlling the disease regardless of the primary origin of the disease. In spite of the identification of a wide variety of genetic abnormalities and potential molecular targets in melanoma, effective targeted agents are required in order to advance patient outcomes.
In more recent years, emerging molecular data have provided strong genetic support for the notion of biologically distinct melanoma subtypes as mutations in oncogenes, tumour suppressor genes, and others have been discovered. Mutated oncogenes include NRAS (neuroblastoma RAS viral (v-ras) oncogene homologue), BRAF, c-KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue), GNAQ (guanine nucleotide binding protein (G protein), q polypeptide), and GNA11 (guanine nucleotide-binding protein subunit alpha-11). Tumour suppressor genes that are mutated include PTEN (phosphatase and tensin homologue), P53, and others. Some of these molecular alterations appear to be linked to the degree of sun exposure, histology, and physical location of the primary melanoma. The incidence of some of these mutations is summarized in Table 2. While the prognostic importance of many of these markers has not yet been demonstrated, the prognostic significance of BRAF has recently been shown. The presence of a BRAF mutation may be associated with poorer survival in patients with metastatic melanoma. It is suggested that BRAF-targeted therapy may transform the more aggressive tumour biology conferred by BRAF mutations into a more favourable phenotype similar to patients with amplified human epidermal growth factor 2 (HER2) in breast cancer who are treated with HER2-targeted therapies.

These mutations are emerging targets for therapy and because the mutations are generally mutually exclusive, melanoma can be molecularly classified into distinct subtypes which will differ in the response to therapy. Melanoma is a heterogeneous disease and should no longer be treated as homogenous entity.

### Treating Metastatic Melanoma in the Past

Over the last three decades, there have been few developments in more effective treatment strategies for metastatic melanoma. Systemic approaches that have been evaluated to date for metastatic disease include cytotoxic chemotherapy as single agents and in multi-drug combinations including dacarbazine (DTIC), temozolomide and platinum agents (carboplatin, paclitaxel, and protein-bound paclitaxel) and immunotherapies including the cytokines interferon-α (IFN) and interleukin-2 (IL-2). Treatment with DTIC, alone or in combination, has resulted in low response rates, rare durable responses, and no impact on survival. Though response rates for single agent IL-2 have been low, treatment with IL-2 had attracted some attention because of reports of durable responses in complete responders. The combination of chemotherapy with immunotherapy (biochemotherapy) resulted in increased response rates as observed in numerous phase III trials, but survival benefit has not been demonstrated while toxicity was significantly increased.

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Incidence (%)</th>
<th>Type of melanoma</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>40–50</td>
<td>Cutaneous</td>
<td>Found most frequently in sites where sun damage is intermittent and not chronic</td>
<td>22</td>
</tr>
<tr>
<td>NRAS</td>
<td>15–30</td>
<td>Cutaneous</td>
<td>NRAS mutations are mutually exclusive of BRAF mutations</td>
<td>23, 24</td>
</tr>
<tr>
<td>c-KIT</td>
<td>5–10</td>
<td>Acral and mucosal</td>
<td>Found more frequently in chronic sun damaged skin</td>
<td>25</td>
</tr>
<tr>
<td>GNAQ and GNA11</td>
<td>80</td>
<td>Uveal (almost exclusively)</td>
<td>Uveal melanomas are very rare</td>
<td>16</td>
</tr>
</tbody>
</table>

BRAF = v-raf murine sarcoma viral oncogene homologue B1; c-KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue; GNA11 = guanine nucleotide-binding protein subunit alpha-11; GNAQ = guanine nucleotide binding protein (G protein), q polypeptide; NRAS = neuroblastoma RAS viral (v-ras) oncogene homologue

### A New Era for the Treatment of Metastatic Melanoma

The heterogeneity of melanoma underscores the need for patient-specific diagnostic and treatment approaches, and the recognition of the heterogeneity of the disease is precisely what has driven recent clinical advances. The two leading agents that are changing the landscape of melanoma therapy are the highly selective BRAF inhibitor, vemurafenib, and the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibody, ipilimumab. Additional targets and new agents against these targets are currently being studied in phase III trials. These will be briefly addressed later in this paper. Further-
more, molecules are under development in each of these two drug classes and various combinations remain to be explored as synergies may become evident between different classes of drugs as well as between agents within the same class. Even for patients whose melanomas contain mutant BRAF, decisions about therapy with an inhibitor versus ipilimumab will need to be individualized.

The selection of the most appropriate course of treatment is dependent on a number of factors that include, but are not limited to, the presence of a molecular target, tumour burden, rapidly versus slowly progressing disease, presence of brain metastases, performance status, and the ability to tolerate treatment. The current standard of care for metastatic melanoma in Canada is clinical trials and this will continue to be the case as combination therapies are investigated to further improve outcomes. For example, the recent observation that ipilimumab improves survival in patients with metastatic melanoma suggests the possibility of combining CTLA-4 blockade with BRAF inhibition. BRAF inhibition seems to enhance antigen presentation that may potentiate activity when the two agents are used together.

**BRAF: A Key Target for the Treatment of Metastatic Melanoma**

BRAF is a RAS-(guanine nucleotide binding protein) activated serine/threonine protein kinase. It plays a central role in regulating the MAPK (mitogen-activated protein kinase) signalling pathway that normally regulates cell growth, division, and differentiation. The MAPK signalling pathway has long been associated with human cancers due to frequent oncogenic mutations identified in RAF (rapidly growing fibrosarcoma) family members. The V600E activating mutation in BRAF is the most common mutation accounting for over 90% of BRAF mutations although other activating mutations are known (e.g., BRAF V600K and BRAF V600R). It significantly increases the kinase activity of BRAF resulting in uncontrolled cell growth, reduced apoptosis, increased invasiveness, and increased metastatic potential. V600E inhibition leads to inhibition of MAPK activation and, therefore, to growth arrest, apoptosis, and reversal of the malignant phenotype, making this an ideal target on which to focus therapeutic strategies. In 2002, it was discovered that approximately 50% of human melanomas harbour an activating mutation in BRAF, raising the possibility that melanoma could be amenable to targeted therapy. While a number of agents with some BRAF inhibitory activity have been studied in oncology, recent efforts have been focusing on the highly selective BRAF inhibitors. Vemurafenib is one such agent that has recently been approved by Health Canada. Other selective BRAF inhibitors include dabrafenib (GSK2118436), which has been shown to be effective in phase II and phase III trials.

**Vemurafenib: A Novel Selective BRAF Inhibitor**

The first selective BRAF inhibitor to be developed in the clinical setting is vemurafenib (PLX4032). Vemurafenib is a small molecule inhibitor that binds potently to and selectively inhibits the BRAF V600 oncogenic mutation. Preclinical studies of vemurafenib in cell lines that were positive for the BRAF mutation demonstrated vemurafenib’s ability to inhibit extracellular signal regulated kinase (ERK) activation, arrest the cell cycle, selectively inhibit cell growth and proliferation, and induce apoptosis leading to cell death.

In a phase I dose escalation study, vemurafenib was administered to 55 patients with solid tumours and to 32 patients with BRAF V600E mutation-positive metastatic melanoma in the extension phase of the study. All 32 patients in the extension phase received the recommended phase II dose of 960 mg twice daily. In the extension phase, vemurafenib was found to have high single-agent clinical activity with unprecedented response rates of 81% in patients, including those who had previously received multiple lines of chemotherapy, as well as at metastatic sites such as bone and liver that are typically...
refractory. A clear impact on progression-free survival (PFS) was also observed but these findings were only seen in patients with the V600E mutation. Patients who had wild-type BRAF had no evidence of tumour regression. As of August 2011, as presented at the ECCO/ESMO meeting, the OS estimate for the patients included in the extension phase was 13.8 months.

The efficacy of vemurafenib in previously treated patients was confirmed in a phase II trial (BRIM-2) of 132 patients with BRAF V600E mutation-positive metastatic melanoma. The confirmed overall response rate (ORR) assessed by an independent review committee (IRC) was 53% (95% confidence interval [CI]: 44–62), with 6% achieving a complete response (CR) and 47% achieving a partial response (PR). Additionally, four of the 10 patients who had a BRAF V600K mutation had a PR to vemurafenib. The median PFS was 6.8 months (95% CI: 5.6–8.1) and the median OS was 15.9 months (95% CI: 11.6–18.3).

In a phase III trial (BRIM-3) comparing first-line therapy of vemurafenib to DTIC, 675 patients with unresectable stage IIIIC/ stage IV melanoma with the V600E BRAF mutation were treated. Vemurafenib was associated with statistically significantly improved OS and PFS compared with DTIC. (Figures 2 and 3)

The key efficacy results for BRIM-3 are summarized in Table 3.

![Figure 2. BRIM-3 overall survival](image1)

**Table 3. Key efficacy results for BRIM-3, a phase III trial of vemurafenib versus DTIC in previously untreated advanced stage metastatic melanoma patients**

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib (n = 337)</th>
<th>DTIC (n = 338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>Not reached*†</td>
<td>Not reached*</td>
</tr>
<tr>
<td>OS rate at 6 months</td>
<td>84</td>
<td>64</td>
</tr>
<tr>
<td>(95% CI: 78–89)</td>
<td></td>
<td>(95% CI: 56–73)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.3</td>
<td>1.6</td>
</tr>
<tr>
<td>(N = 549; vemurafenib n = 275; DTIC n = 274)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best ORR (N = 439; vemurafenib n = 219; DTIC n = 220)</td>
<td>106/219 (48% [95% CI: 42–55])</td>
<td>12/220 (5% [95% CI: 3–9])</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>2/219 (1)</td>
<td>0/220 (0)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>104/219 (47.5)</td>
<td>12/220 (5.5)</td>
</tr>
</tbody>
</table>

*An inadequate number of patients were evaluated after seven months of follow-up in either study group to provide reliable Kaplan–Meier estimates of the survival curves at the time of presentation of this study at the 2011 meeting of the American Society of Clinical Oncology (ASCO) or at the time of publication in the New England Journal of Medicine.†*In an updated analysis with a median follow-up of 6.21 months (range: 0.4–13.9 months) in the vemurafenib arm, the median OS has not been reached (95% CI: 9.59 months–not reached).*CI = confidence interval; CR = complete response; DTIC = dacarbazine; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response
In the interim analysis (data cut-off December 20, 2010), vemurafenib was associated with a relative reduction of 63% in the risk of death (HR for death = 0.37 [95% CI: 0.26–0.55; p <0.001]) and with a relative reduction of 74% in the risk of tumour progression (HR for tumour progression = 0.26 [95% CI: 0.20–0.33; p <0.001]). The median time to response in the vemurafenib group was 1.45 months compared with 2.7 months in the DTIC group and the difference in the confirmed response rates was highly significant (p <0.001).

In the vemurafenib group, 10 patients were later found to have BRAF V600K mutations; of these patients, four had a PR (40%). Benefit was observed in all subgroups studied including patients with poor prognosis including those with M1c disease or elevated lactate dehydrogenase (LDH). Vemurafenib consistently improved PFS, OS, and best ORR in this patient population.45

A total of 618 patients (92%) in the BRIM-3 study underwent at least one assessment for toxic effects. (Table 4) The most common adverse events (AEs) in the vemurafenib group were cutaneous events, arthralgia, and fatigue. Grade 2 or 3 photosensitivity skin reactions were observed in 12% of the patients and it was noted that grade 3 photosensitivity reactions characterized by blistering could have been prevented with the application of sunblock. As expected, the most common severe toxic effects in the DTIC group were fatigue, nausea, vomiting, and neutropenia. AEs resulted in dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group and in 44 of 282 patients (16%) in the DTIC group. In the vemurafenib group, 61 patients (18%) developed cutaneous AEs with a cutaneous squamous-cell carcinoma or keratoacanthoma, or both. All lesions were treated by simple excision.45

Vemurafenib has also shown promise in the treatment of patients with melanoma metastatic to the brain that harbours a BRAF mutation. Preliminary results suggest that vemurafenib is well tolerated and that it has activity in metastatic melanoma that has metastasized to the brain.47 A phase II study is currently ongoing to confirm these results. Furthermore, in a recent phase II trial, dabrafenib was also shown to have activity in melanoma that is metastatic to the brain, suggesting that there is a role for BRAF inhibition in the treatment of such patients.48

BRAF Resistance

It has become evident that metastatic melanoma can become resistant to BRAF inhibition and a number of mechanisms have been proposed. (Table 5)

Novel drug combinations, such as BRAF inhibitors plus MEK inhibitors or BRAF inhibitors plus PI3K/AKT inhibitors, are being evaluated in clinical trials with the hope of circumventing resistance mechanisms. It is also thought that combining BRAF and MEK inhibition may reduce the formation of squamous-cell carcinomas.28

### Table 4. Grade 2 and 3 adverse events from the BRIM-3 trial*45

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Vemurafenib (n = 336)</th>
<th>DTIC (n = 282)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>61 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma†</td>
<td>40 (12)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Keratoacanthoma§</td>
<td>27 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>26 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>21 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Other adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>71 (21)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44 (13)</td>
<td>38 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (5)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (5)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

*Most adverse events were mild to moderate. Those listed are of grade 2 or higher and were reported in more than 5% of patients in either study group.
†One patient in the DTIC group who was treated with vemurafenib in error was included in the vemurafenib group for the assessment of adverse events.
§Three patients with keratoacanthomas that were assessed by the investigator as grade 1 were included among the grade 2 keratoacanthomas.

<table>
<thead>
<tr>
<th>Form of resistance</th>
<th>Potential mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rewiring of signalling systems</td>
<td>• Switching to either CRAF or ARAF to reactivate the MAPK pathway28</td>
</tr>
<tr>
<td></td>
<td>• Activation of tyrosine kinase receptors such as PDGFRα30 with subsequent signalling through other growth pathways (PI3K/AKT)35</td>
</tr>
<tr>
<td>Changes in other genes</td>
<td>• NRAS mutations26,27</td>
</tr>
<tr>
<td></td>
<td>• Loss of PTEN24</td>
</tr>
<tr>
<td></td>
<td>• Overexpression of COT as a MEK activator26,27</td>
</tr>
<tr>
<td></td>
<td>• MEK mutation23</td>
</tr>
</tbody>
</table>

DTIC = dacarbazine

AKT = v-akt murine thymoma viral oncogene homologue; ARAF = v-raf murine sarcoma 3611 viral oncogene homologue B1; BRAF = v-raf murine sarcoma viral oncogene homologue B1; CRAF = MAP3K8/Tpl2 (tumour progression locus 2); MEK = dual-specificity mitogen-activated protein kinase; NRAS = neuroblastoma RAS viral (v-ras) oncogene homologue; PDGFR = platelet derived growth factor receptor; PI3K = phosphatidylinositol 3-kinase; PTEN = phosphatase and tensin homologue

### Table 5. Mechanisms of resistance to BRAF inhibitors

<table>
<thead>
<tr>
<th>Form of resistance</th>
<th>Potential mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Switching to either CRAF or ARAF to reactivate the MAPK pathway28</td>
<td></td>
</tr>
<tr>
<td>• Activation of tyrosine kinase receptors such as PDGFRα30 with subsequent signalling through other growth pathways (PI3K/AKT)35</td>
<td></td>
</tr>
<tr>
<td>• Activation of IGF-1R to promote survival28</td>
<td></td>
</tr>
<tr>
<td>• Dimerization of BRAF variants</td>
<td></td>
</tr>
<tr>
<td>• NRAS mutations26,27</td>
<td></td>
</tr>
<tr>
<td>• Loss of PTEN24</td>
<td></td>
</tr>
<tr>
<td>• Overexpression of COT as a MEK activator26,27</td>
<td></td>
</tr>
<tr>
<td>• MEK mutation23</td>
<td></td>
</tr>
</tbody>
</table>

AKT = v-akt murine thymoma viral oncogene homologue; ARAF = v-raf murine sarcoma 3611 viral oncogene homologue B1; BRAF = v-raf murine sarcoma viral oncogene homologue B1; CRAF = MAP3K8/Tpl2 (tumour progression locus 2); MEK = dual-specificity mitogen-activated protein kinase; NRAS = neuroblastoma RAS viral (v-ras) oncogene homologue; PDGFR = platelet derived growth factor receptor; PI3K = phosphatidylinositol 3-kinase; PTEN = phosphatase and tensin homologue
Immune Modulation to Treat Metastatic Melanoma

There are several examples of the successful use of monoclonal antibodies as targeted therapies in cancer including HER2 blockade by trastuzumab in breast cancer and CD20 blockade by rituximab in lymphomas. Extensive research efforts have focused on using antibodies to control immune checkpoints that diminish and extinguish anti-tumour immune responses.\textsuperscript{10} Immunological therapies for metastatic melanoma, including the use of cytokines, tumour vaccines, adoptive immunotherapy, and combinations, have been extensively studied but none have shown an impact on OS.\textsuperscript{49}

Cytotoxic T-lymphocyte antigen 4, CD152 (CTLA-4) is a member of the immunoglobulin super-family. It is expressed on a subset of activated human T lymphocytes and regulatory T-cells, and plays a critical role in the control of activated T-cells. As a negative regulator of the immune system, it plays an important role in endogenous and vaccine-induced anti-tumour immunity. Resting lymphocytes do normally express CTLA-4 but expression is transiently up-regulated upon binding of the T-cell receptor. Up-regulation of CTLA-4 on the surface of cytotoxic T-cells results in inhibition of proliferation of these cells. Cytotoxic T lymphocytes (CTLs) are key to a melanoma-specific anti-tumour response.\textsuperscript{49} (Figure 4)

Ipilimumab: A Novel Anti-CTLA-4 Antibody

Host immune function has long been observed to play a role in the development and regulation of melanoma growth. In an effort to exploit this interaction, potential immunotherapies have been developed such as IL-2, IFN, and most recently, ipilimumab — a fully humanized monoclonal antibody which is specific against CTLA-4.\textsuperscript{49} Blocking CTLA-4 with monoclonal antibodies was initially shown to induce regression of established tumours in several mouse models.\textsuperscript{10} Phase I and II clinical trials showed long-lasting responses, prompting Hodi and colleagues to conduct a phase III clinical trial in patients with stage IV melanoma who were pretreated. Participants were randomized to receive ipilimumab (3 mg/kg), a glycoprotein 100 (gp100) peptide vaccine or both ipilimumab and gp100 once every three weeks for four treatments. Patients who were treated with ipilimumab experienced an improvement in OS, PFS, and ORR.\textsuperscript{51} The key efficacy results for this trial are summarized in Table 6.
Additionally, a phase III trial was conducted that compared DTIC plus ipilimumab versus DTIC plus placebo in previously untreated patients with metastatic melanoma. Patients received ipilimumab at a dose of 10 mg/kg plus DTIC at a dose of 850 mg/m² or DTIC plus placebo every three weeks for four cycles followed by DTIC (850 mg/m²) alone every three weeks through week 22. At week 24, patients with stable disease or an objective response who did not have a dose-limiting AE were eligible for maintenance therapy consisting of placebo or ipilimumab every 12 weeks until progression, toxicity, or the end of the study.\textsuperscript{52} The OS results from this ongoing study are similar to the previous phase III trial and are summarized in Table 7 and Figure 5.

### Table 6. Key efficacy results for a phase III study of ipilimumab and gp100 in pretreated stage IV melanoma patients\textsuperscript{51}

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab plus gp100 (n = 403)</th>
<th>Ipilimumab alone (n = 137)</th>
<th>gp100 alone (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up time for OS (months)</td>
<td>21.0</td>
<td>27.8</td>
<td>17.2</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>10.0 (95% CI: 8.5–11.5)</td>
<td>10.1 (95% CI: 8.0–13.8)</td>
<td>6.4 (95% CI: 5.5–8.7)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>2.76 (95% CI: 2.73–2.79)</td>
<td>2.86 (95% CI: 2.76–3.02)</td>
<td>2.76 (95% CI: 2.73–2.83)</td>
</tr>
<tr>
<td>PFS rate at week 12 (%)</td>
<td>49.1 (95% CI: 44.1–53.9)</td>
<td>57.7 (95% CI: 48.9–65.5)</td>
<td>48.5 (95% CI: 39.6–56.7)</td>
</tr>
<tr>
<td><strong>Best ORR, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.2)</td>
<td>2 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>22 (5.5)</td>
<td>13 (9.5)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>SD</td>
<td>58 (14.4)</td>
<td>24 (17.5)</td>
<td>13 (9.6)</td>
</tr>
<tr>
<td>PD</td>
<td>239 (59.3)</td>
<td>70 (51.1)</td>
<td>89 (65.4)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CR = complete response; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

### Table 7. Overall survival results for a phase III study of DTIC plus ipilimumab versus DTIC plus placebo in previously untreated metastatic melanoma patients\textsuperscript{52}

<table>
<thead>
<tr>
<th></th>
<th>DTIC plus ipilimumab (n = 250)</th>
<th>DTIC plus placebo (n = 252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>11.2 (95% CI: 9.4–13.6)</td>
<td>9.1 (95% CI: 7.8–10.5)</td>
</tr>
<tr>
<td>One-year OS (%)</td>
<td>47.3</td>
<td>36.3</td>
</tr>
<tr>
<td>Two-year OS (%)</td>
<td>28.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Three-year OS (%)</td>
<td>20.8</td>
<td>12.2</td>
</tr>
</tbody>
</table>

CI = confidence interval; DTIC = dacarbazine; OS = overall survival
As the first assessment of progression occurred at week 12 after the true median, the median values for PFS were similar in the two groups. After the first tumour assessment, the Kaplan–Meier curves separated. (Figure 6) However, the PFS curves for the two groups subsequently became divergent as patients were followed. The best ORR was 15.2% in the DTIC plus ipilimumab group and 10.3% in the DTIC plus placebo group \((p = 0.09)\). The median duration of response among all patients with a CR or PR was 19.3 months (95% CI: 12.1–26.1) in the DTIC plus ipilimumab group and 8.1 months (95% CI: 5.19–19.8) in the DTIC plus placebo group \((p = 0.03)\).52 (Figure 7) However, it should be noted that the treatment arms of these first-line and second-line phase III trials were considerably different. Further research is warranted to identify and validate the optimal treatment regimen regarding ipilimumab dosing and scheduling as well as combinations.

A distinctive observation of ipilimumab is the variable response patterns, which include a slow, steady decline in baseline lesions, response after an initial increase in the number of lesions, and delayed response in index lesions accompanied by the appearance of new lesions. Although the first two types of responses would be captured using the standard Response Evaluation Criteria In Solid Tumours (RECIST), the last two atypical responses would likely be classified as progressive disease by RECIST. Patients being treated with ipilimumab may have delayed responses or durable stable disease even after apparent disease progression, therefore new immune-related response criteria have been proposed and may be necessary to avoid premature treatment withdrawal.53

While no specific molecular targets exist for ipilimumab, investigating predictive markers to identify patients who are most likely to benefit as long-term survivors should be a priority.49 Such markers could be useful in identifying responders despite early progression, providing clinicians and patients with the confidence to continue treatment.53

Immune-related adverse events (irAEs) are common in patients treated with ipilimumab and may occur in up to 60% of patients.33 The most common irAEs include dermatologic, gastrointestinal (diarrhea), endocrine, and hepatic toxicities. The majority of these irAEs are grade 1/2, non-life threatening, and easily managed. However, the more serious grade 3/4 irAEs can be difficult to manage by healthcare practitioners who lack experience with this drug. Prompt medical attention, early administration of corticosteroids, and close patient follow-up are critical to the management of irAEs.51 In the phase III first-line trial, early treatment discontinuation was primarily due to disease progression; however, significantly more patients discontinued treatment owing to drug-related AEs in the DTIC plus ipilimumab group (36%) than in the DTIC plus placebo group (4%).52

**Figure 6. Progression-free survival for a phase III study of DTIC plus ipilimumab versus DTIC plus placebo in previously untreated metastatic melanoma patients**

![Figure 6](image1.png)

**Figure 7: Duration of response for a phase III study of DTIC plus ipilimumab versus DTIC plus placebo in previously untreated metastatic melanoma patients**

![Figure 7](image2.png)

**Positioning Vemurafenib and Ipilimumab in Clinical Practice**

Over the past few years, there have been major advances in melanoma research and the clinical management of this disease will dramatically shift with the approvals of vemurafenib and ipilimumab. These drugs differ from one another by mechanism, treatment course, clinical outcomes, and AEs, as summarized in Table 8.

Data suggest a potentially synergistic benefit to combining vemurafenib and ipilimumab.30 It has been observed that non-specific inhibitors of the MAPK pathway, such as MEK inhibitors, may reduce T-cell function, and treatment with vemurafenib has been shown to increase melanoma differentiation, antigen expression, and improve antigen-specific T-cell recognition.30 A clinical trial exploring the synergism of these two agents has begun to accrue patients but until this...
trial is complete, the decision to use vemurafenib versus ipilimumab should be determined by patient circumstance.\(^3\)

Additionally, dual pathway blockade may be one way to circumvent resistance to vemurafenib. Evidence currently suggests that the MAPK pathway is activated in order to bypass the BRAF blockade. Targeting this pathway further downstream in the cascade can be achieved using MEK inhibitors such as GSK1120212 (trametinib). Using MEK inhibitors in combination with BRAF inhibitors could theoretically prolong response duration, and also possibly prevent some of the side-effects of the BRAF inhibitors.\(^5\) Phase I/II data suggest that combining the BRAF inhibitor GSK2118436 (dabrafenib) and the MEK inhibitor GSK1120212 (trametinib) is safe and has a lower incidence of adverse events associated with each agent alone. Long-term durability data are pending and are anxiously awaited.\(^5\) Results of phase III trials are anticipated.

### Table 8. Comparing and contrasting vemurafenib and ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>• Vemurafenib is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.(^4)</td>
<td>• Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.(^5)</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>• Inhibition of V600 mutated BRAF</td>
<td>• CTLA-4 blockade</td>
</tr>
</tbody>
</table>
| **Treatment course** | • Rapid onset of action (median time to response is 1.45 months).\(^4\)  
  • Best ORR is 48% in the phase III pivotal study of previously untreated patients (BRIM-3).\(^5\) | • Time course for response is variable.  
  • Best ORR is 15.2% in a phase III study of previously untreated patients.\(^2\)  
  • Allowance is needed for non-clinically significant progression of the disease prior to observing a clinical response.\(^9\) |
| **Clinical outcomes** | • The median PFS was reproducible in phase II and III studies and was reported to be:  
  – 6.8 months in BRIM-2\(^4\)  
  – 5.3 months in BRIM-3.\(^4\)  
  • Statistically significant benefit in OS compared with DTIC in BRIM-3, with a strong hazard ratio of 0.37 (95% CI: 0.26–0.55; \(p<0.001\)) with the median OS not yet reached.\(^4\) | • With the median duration of response among patients achieving a CR or PR 19.3 months, long-term responses are possible.\(^2\)  
  • For ipilimumab monotherapy in pretreated patients, the median PFS was 2.86 months and the median OS was 10.1 months.\(^5\)  
  • The OS benefit was reproduced when ipilimumab was combined with DTIC in previously untreated patients (median OS 11.2 months).\(^2\) |
| **Tolerability and AEs** | • Treatment was relatively well tolerated and AEs easily managed.\(^4\)  
  • The most common AEs were cutaneous events, arthralgia, and fatigue.\(^4\)  
  • AEs resulted in dose modification or interruption in 38% in the vemurafenib group compared with 16% in the DTIC group\(^6\) and treatment discontinuation was 7% in the vemurafenib group compared with 4% in the DTIC group.\(^4\) | • irAEs occurred in up to 60%.\(^5\)  
  • Drug-related AEs were a common reason for treatment discontinuation in patients treated with DTIC plus ipilimumab (36%) compared with DTIC plus placebo (4%).\(^2\) |

CI = confidence interval; DTIC = dacarbazine; OS = overall survival; AEs = adverse events; CR = complete response; PFS = progression-free survival; PR = partial response; irAE = immune-related adverse events; ORR = overall response rate.
Other Molecular Targets in Development for Metastatic Melanoma

A number of other molecular targets have been identified in melanoma patients. These include c-KIT, BRAF, MEK, NRAS, PI3K, Akt, mTOR, and GNAC. Several pharmacological inhibitors targeting mutated signal transduction molecules are being explored in clinical trials in genetically defined subgroups of patients with melanoma.57,58 (Table 9) Of these, the BRAF and c-KIT inhibitors are furthest in development at the moment.27

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Drug</th>
<th>Clinical Trial Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>Sorafenib</td>
<td>Phase III (completed)</td>
</tr>
<tr>
<td></td>
<td>RAF-265</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>XL-281</td>
<td>Phase II</td>
</tr>
<tr>
<td>Selective</td>
<td>Vemurafenib</td>
<td>Phase III (completed)</td>
</tr>
<tr>
<td></td>
<td>PLC5092</td>
<td>Phase I-II</td>
</tr>
<tr>
<td></td>
<td>GSK2118436 (dabrafenib)</td>
<td>Phase III (completed)</td>
</tr>
<tr>
<td>MEK</td>
<td>AZD6244</td>
<td>Phase II (completed)</td>
</tr>
<tr>
<td></td>
<td>PD0325901</td>
<td>Phase I (completed)</td>
</tr>
<tr>
<td></td>
<td>GSK1120212</td>
<td>Phase III (completed)</td>
</tr>
<tr>
<td>c-KIT</td>
<td>Imatinib</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td>Phase II (ongoing)</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>Phase II</td>
</tr>
<tr>
<td>NRAS</td>
<td>R115777</td>
<td>Phase II (completed)</td>
</tr>
<tr>
<td>PI3K</td>
<td>GDC0941</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>XL147</td>
<td>—</td>
</tr>
<tr>
<td>Akt</td>
<td>MK-2206</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>GSU690693</td>
<td>—</td>
</tr>
<tr>
<td>mTOR</td>
<td>Tenselimum</td>
<td>Phase II (completed)</td>
</tr>
<tr>
<td>GNAC</td>
<td>MEK inhibitors</td>
<td>—</td>
</tr>
<tr>
<td>CDK4</td>
<td>PDO32991</td>
<td>—</td>
</tr>
</tbody>
</table>

(Adapted from Eggermont, et al. 2010 and Flaherty, et al. 2010)

Biomarker Screening

An important component of personalized medicine is the use of predictive biomarkers to aid in selecting patients who have a greater likelihood of responding to a given therapeutic modality. For metastatic melanoma specifically, this would lead to improved outcomes in this traditionally difficult-to-treat population while reducing the likelihood of exposing patients to potentially ineffective therapy and unnecessary side effects. In general terms, there are several criteria that should be met to successfully implement biomarker testing.

While highly efficacious in a subset of patients, immunotherapy for melanoma currently lacks needed predictive biomarkers for efficacy and toxicities.30 However, it is known that vemurafenib therapy requires the identification of patients with the BRAF mutation much the same way as is now routinely being done for breast cancer (HER2) and chronic myeloid leukemia (BCR-ABL).37 The commercially available cobas® 4800 BRAF V600 Mutation Test was approved by Health Canada in November 2011. The cobas® test is a real-time polymerase chain reaction assay designed to detect the BRAF V600E mutation. It is highly selective for V600E; however, it also detects other BRAF V600 mutations with less sensitivity.30 The test is robust, rapid, and accurate providing a higher sensitivity in detecting the V600E mutation than Sanger sequencing.30 Health Canada
Vemurafenib and other BRAF-selective inhibitors should only be prescribed to patients who harbour the BRAF mutation. Recently, several studies have described the challenges of treating non-BRAF V600E melanoma cell lines with a BRAF inhibitor. These studies have demonstrated that BRAF inhibitors can paradoxically induce, rather than inhibit, RAF/MEK signalling in NRAS or wild-type BRAF tumours through the formation of RAF dimers, in a RAS-dependent manner thus stimulating cell proliferation. These studies underscore the need to carefully select the right patient population on the basis of BRAF mutational status before treating with BRAF selective inhibitors.

Despite the clear need for mutation testing in metastatic melanoma, a number of challenges and barriers exist. Some of these are unique to metastatic melanoma and others are more general and apply to other therapeutic areas. These include funding of the molecular test, turnaround time, logistical issues surrounding sample collection and handling, and timing of the test amongst others. There are also different models for biomarker screening that ought to be considered including a central reference centre model that uses a single imposed platform versus a network of reference centres and different platforms. Funding and availability of the test will be governed provincially. It is likely that testing will require some centralization as not all treatment centres have a molecular or skin pathologist. Strategies will need to be implemented to allow for efficient testing in order to avoid treatment delays. Furthermore, multiplexing of tests for various biomarkers will be important particularly in melanoma because there is a limited amount of tissue available. This tissue may be limited to the original melanoma, which can be very small and it may be difficult to obtain more. Multiplexing allows for the screening of an array of mutations at once (BRAF, cKIT, NRAS, and GNAQ amongst others). This should be done for high-risk patients before they become metastatic. Given that the incidence of BRAF mutations is approximately 50%, fast and accurate testing is especially critical in order to initiate vemurafenib in a timely fashion, particularly in rapidly progressing disease.

**A Foundation to Build On**

Recently, melanoma has earned the designation as “an unlikely poster child for personalized cancer therapy.” As new agents transition from the clinical trial context to widespread clinical practice, their use, including the management of AEs, will require optimization. Furthermore, new strategies will be needed to treat patients in whom resistance to BRAF inhibitors develops. Rational combination with other agents including other targeted therapies and immune therapies is one approach to overcome drug resistance. It is very likely that within the next several years, melanoma patients will be routinely screened for the presence of a panel of specific markers to determine the most appropriate therapeutic approaches that will undoubtedly have a positive impact on outcomes.

The key message is that metastatic melanoma is no longer the dismal disease it once was. With the recent approval of these new agents, a shift in the treatment paradigm and in attitude is needed. There now exists a renewed sense of hope in a therapeutic area that was previously burdened by poor outcomes.

**Acknowledgments**

The authors acknowledge medical writing support from Diana Stempak MSc, PhD of New Evidence; this support was funded by Hoffman La-Roche.

**Conflict of Interest Disclosures**

Dr. Petrella is an advisor and consultant for Bristol-Meyers Squibb, Glaxo SmithKline, Hoffmann-La Roche, and Merck. Dr. Ernst is an advisory board member for Bristol-Meyers Squibb and Hoffmann-La Roche. Dr. Claveau is a consultant and investigator for Bristol-Meyers Squibb, Glaxo SmithKline, Hoffmann-La Roche, Merck, and Novartis. Dr. Spatz and Dr. Wong do not have any conflicts of interest to disclose.

**References:**

BUSULFEX® (BUSULFAN) INJECTION IS A POTENT CYTOTOXIC DRUG THAT RESULTS IN PROFOUND MYELOSUPPRESSION AT THE RECOMMENDED DOSAGE. IT SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A QUALIFIED PHYSICIAN WHO IS EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS AND IN THE MANAGEMENT OF PATIENTS WITH SEVERE PANCYTOPENIA. APPROPRIATE MANAGEMENT OF THERAPY AND COMPLICATIONS IS ONLY POSSIBLE WHEN ADEQUATE DIAGNOSTIC AND TREATMENT FACILITIES ARE READILY AVAILABLE.

INDICATIONS AND CLINICAL USE

BUSULFEX® (busulfan) Injection is indicated for use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation, including: acute lymphocytic leukemia, acute non-lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and myelodysplastic syndrome.

In any regimen utilizing BUSULFEX®, the patient’s disease status should either be refractory to other therapies or carry sufficiently high risk for recurrence of disease, so that progenitor cell transplant is the treatment of choice, in the opinion of a qualified physician.

CONTRAINDICATIONS

BUSULFEX® (busulfan) Injection is contraindicated in patients who are sensitive, allergic or intolerant of the drug or its vehicle.

Special Populations
For use in special populations, see Safety Information: Special Populations.

WARNINGS

BUSULFEX® (busulfan) Injection is a potent cytotoxic drug that results in profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents and in the management of patients with severe pancytopenia. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The most frequent, serious consequence of treatment with BUSULFEX® at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Frequent complete blood counts, including white blood cell differentials, and quantitative platelet counts should be monitored during treatment and until recovery is achieved. Absolute neutrophil counts <0.5 x 10^9/L at a median of 4 days post transplant occurred in 100% of patients and recovered at median day 10 following transplant (median neutropenic period of 6 days). Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for prevention and management of infections during the neutropenic period. Thrombocytopenia (<25,000/mm^3 or requiring platelet transfusion) at a median of 5–6 days occurred in 98% of patients. Anemia (hemoglobin <8.0 g/dL) occurred in 69% of patients. Platelet and red blood cell support should be employed as medically indicated.

Busulfan may be a human carcinogen. Several cases of leukemia have occurred 5-8 years following oral busulfan treatment. Ovarian suppression and amenorrhea commonly occur in premenopausal women undergoing chronic, low-dose busulfan therapy for chronic myelogenous leukemia. Sterility, azospermia and testicular atrophy have been reported in male patients. Bronchopulmonary dysplasia with pulmonary fibrosis is a rare complication following chronic busulfan therapy. The average onset of symptoms is after 4 years of therapy (range 4 months to 10 years).

Special Populations

Pregnancy: Busulfan can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If BUSULFEX® is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for busulfan in human and animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Hepatic Insufficiency: BUSULFEX® has not been administered to patients with hepatic insufficiency. However, patients who have received prior radiation therapy, greater than three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease with the recommended BUSULFEX® dose and regimen.

PRECAUTIONS

General: At the recommended dosage of BUSULFEX® (busulfan), profound myelosuppression is universal, and can be manifested as neutropenia, thrombocytopenia, anemia or a combination thereof. The patient should be monitored for signs of local or systemic infection or bleeding and their hematologic status evaluated frequently. Caution should be exercised when administering the recommended dose of BUSULFEX® to patients with a history of seizure disorder, head trauma, or receiving other potentially epileptogenic drugs. It is recommended that phenytoin be administered prophylactically to such patients. Seizures have been reported with high dose oral busulfan treatment.

Information for Patients: The increased risk of a second malignancy should be explained to the patient.

Monitoring: Patients receiving BUSULFEX® should be monitored daily with a complete blood count, including differential count and quantitative platelet count, until engraftment has been demonstrated. To detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase, and bilirubin should be evaluated daily through transplant day 28.

Drug Interactions: There are no known or manifest interactions with antifungal agents (fluconazole), known glutathione transferase (GST) inhibitors (itraconazole) and 5-HT3 antineutemetics such as odansetron (Zofran®) and granisetron (Kytril®). It has been reported that phenytoin increases the clearance of busulfan by 10% or more, possibly due to the induction of GST. Since virtually all patients are empirically treated with anticonvulsants (phenytoin,
Administration

**BUSULFEX® (busulfan)** should be administered intravenously via a central venous catheter as a two-hour infusion every 6 hours x 4 consecutive days for a total of 16 doses. All patients should be premedicated with phenytoin to prevent seizures, as busulfan is known to cross the blood brain barrier. Antiemetics of the 5-HT3 class should be administered prior to the first dose of BUSULFEX® and continued on a fixed schedule through administration of BUSULFEX® or considered through completion of the preparative regimen.

The usual adult dose of BUSULFEX® in combination with cyclophosphamide as a preparative regimen prior to bone marrow or peripheral blood progenitor cell replacement support is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower. For obese or severely obese patients, dosing based on adjusted ideal body weight could be considered. Ideal body weight (IBW) should be calculated as follows: (height in cm - 91.4) / 2.3 (height < 152); IBW (kg, men) = 50 + 0.91 x (height - 152). Adjusted ideal body weight (AIBW) should be calculated as follows: AIBW = IBW + 0.25 x (actual weight - IBW). Cyclophosphamide in combination with BUSULFEX® was given on each of two days as a one-hour infusion at 60 mg/kg beginning on BMT day -3, six hours following the 16th dose of BUSULFEX®.

**Stability and Storage Recommendations:**

Unopened vials of BUSULFEX® Injection must be stored under refrigerated conditions between 2 - 8 °C (36 - 46 °F).

BUSULFEX® diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is stable at room temperature (25 °C) for up to 8 hours but the infusion must be completed within that time. BUSULFEX® diluted in 0.9% Sodium Chloride Injection, USP is stable at refrigerated conditions (2-8 °C) for up to 12 hours but the infusion must be completed within that time.

**FREEZING OF DILUTED PREPARATIONS OF BUSULFEX® IS NOT RECOMMENDED.**

**Reconstituted Solutions:**

Preparation for Intravenous Administration: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Discard unused portion. BUSULFEX® must be diluted prior to use with either 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D5W). The diluent quantity should be 10 times the volume of BUSULFEX® Injection, so that the final concentration is approximately 0.5 mg/mL.

By way of example, for a 70 kg patient, the amount of drug to be administered would be calculated as follows:

\[
(70 \text{ kg patient}) \times (0.8 \text{ mg/kg}) / (6 \text{ mg/mL}) = 9.3 \text{ mL BUSULFEX® (56 mg total dose)}.
\]

To prepare the final solution for infusion, add 9.3 mL of BUSULFEX® to 93 mL of diluent (normal saline or D5W) as calculated below:

\[
(9.3 \text{ mL BUSULFEX®}) \times (10) = 93 \text{ mL of either diluent plus the 9.3 mL of BUSULFEX® to yield a final concentration of busulfan of 0.54 mg/mL (9.3 mL x 6 mg/mL / 102.3 mL = 0.54 mg/mL)}.
\]

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing. DO NOT put the BUSULFEX® Injection into an intravenous bag that does not contain normal saline or D5W. Always add the BUSULFEX® to the diluent, not the diluent to the BUSULFEX®. Mix thoroughly by inverting several times.

Infusion pumps should be used to administer the diluted BUSULFEX® solution. Set the flow rate of the pump to deliver the entire prescribed BUSULFEX® dose over two hours. Prior to and following each infusion, flush the catheter line with approximately 5 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. DO NOT infuse concomitantly with another intravenous solution of unknown compatibility. WARNING: BUSULFEX® SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION OR BOLUS.
Parenteral Products:

**Intravenous Injection**

1) 0.9% Sodium Chloride Injection USP

<table>
<thead>
<tr>
<th>Vial (mL)</th>
<th>Volume of Diluent to be Added (mL) (for a 70 kg patient)</th>
<th>Approximate Available Volume (for a 70 kg patient)</th>
<th>Nominal Concentration per mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>93</td>
<td>102</td>
<td>0.5 mg</td>
</tr>
</tbody>
</table>

2) 5% Dextrose Injection, USP

<table>
<thead>
<tr>
<th>Vial (mL)</th>
<th>Volume of Diluent to be Added (mL) (for a 70 kg patient)</th>
<th>Approximate Available Volume (for a 70 kg patient)</th>
<th>Nominal Concentration per mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>93</td>
<td>102</td>
<td>0.5 mg</td>
</tr>
</tbody>
</table>

By way of example, for a 70 kg patient, the amount of drug to be administered would be calculated as follows:

(70 kg patient) x (0.8 mg/kg) / (6 mg/mL) = 9.3 mL BUSULFEX® (56 mg total dose).

To prepare the final solution for infusion, add 9.3 mL of BUSULFEX® to 93 mL of diluent (normal saline or D5W) as calculated below:

(9.3 mL BUSULFEX®) x (10) = 93 mL of either diluent plus the 9.3 mL of BUSULFEX® to yield a final concentration of busulfan of 0.54 mg/mL (9.3 mL x 6 mg/mL / 102.3 mL = 0.54 mg/mL).

**Special Instructions:**

**Preparation and Administration Precautions:** As with other cytotoxic compounds, caution should be exercised in handling and preparing the solution of BUSULFEX®. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If BUSULFEX® or diluted BUSULFEX® solution contacts the skin or mucosa, wash the skin or mucosa thoroughly with water.

**DO NOT USE POLYCARBONATE SYRINGES OR POLYCARBONATE FILTER NEEDLES WITH BUSULFEX®.**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

For further reconstitution information, please refer to Product Monograph.

**SUPPLEMENTAL PRODUCT INFORMATION**

**ADVERSE REACTIONS**

**Summary of the Incidence (≥20%) of Hematologic Adverse Events in Patients Who Received BUSULFEX® Prior to Autologous or Allogeneic Hematopoietic Progenitor Cell Transplantation (n=103) Through Blood and Marrow Transplant Day +28**

<table>
<thead>
<tr>
<th>HEMATOLOGICAL ADVERSE EVENTS</th>
<th>PERCENT INCIDENCE (# PATIENTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (6.5 - 7.9 g/dL)</td>
<td>62 (64)</td>
</tr>
<tr>
<td>Grade 4 (&lt;6.5 g/dL)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

**HEMATOLOGICAL ADVERSE EVENTS**

**PERCENT INCIDENCE (# PATIENTS)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PERCENT INCIDENCE (# PATIENTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (1.0 x 10^9 – 1.9 x 10^9 cells/L)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 4 (&lt;1.0 x 10^9 cells/L)</td>
<td>96 (99)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (25 x 10^3 – 49 x 10^9 cells/L)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Grade 4 (&lt;25 x 10^9 cells/L)</td>
<td>91 (94)</td>
</tr>
<tr>
<td>Median number of Platelet transfusions per patient</td>
<td></td>
</tr>
<tr>
<td>Autologous (n=41)</td>
<td>3</td>
</tr>
<tr>
<td>Allogeneic (n=60)</td>
<td>6</td>
</tr>
<tr>
<td>Median number of Red Blood Cell transfusions per patient</td>
<td></td>
</tr>
<tr>
<td>Autologous (n=37)</td>
<td>3</td>
</tr>
<tr>
<td>Allogeneic (n=53)</td>
<td>4</td>
</tr>
</tbody>
</table>

**NON-HEMATOLOGICAL ADVERSE EVENTS**

**PERCENT INCIDENCE**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PERCENT INCIDENCE (# PATIENTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BODY AS A WHOLE</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>87</td>
</tr>
<tr>
<td>Headache</td>
<td>69</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>62</td>
</tr>
<tr>
<td>Anemia</td>
<td>56</td>
</tr>
<tr>
<td>Chills</td>
<td>47</td>
</tr>
<tr>
<td>Pain</td>
<td>41</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>32</td>
</tr>
<tr>
<td>Edema General</td>
<td>27</td>
</tr>
<tr>
<td>Inflammation at Injection Site</td>
<td>23</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>22</td>
</tr>
<tr>
<td>CARDIOVASCULAR SYSTEM</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>50</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>27</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>23</td>
</tr>
<tr>
<td>DIGESTIVE SYSTEM</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>97</td>
</tr>
<tr>
<td>Stomatitis (Mucositis)</td>
<td>96</td>
</tr>
<tr>
<td>Vomiting</td>
<td>91</td>
</tr>
<tr>
<td>Anorexia</td>
<td>80</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>80</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>40</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
</tr>
<tr>
<td>Rectal Disorder</td>
<td>24</td>
</tr>
<tr>
<td>METABOLIC AND NUTRITIONAL SYSTEM</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>64</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>58</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>57</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>43</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>37</td>
</tr>
<tr>
<td>Edema</td>
<td>37</td>
</tr>
<tr>
<td>SGPT Elevation</td>
<td>25</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>21</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>80</td>
</tr>
<tr>
<td>Anxiety</td>
<td>65</td>
</tr>
<tr>
<td>Dizziness</td>
<td>26</td>
</tr>
<tr>
<td>Depression</td>
<td>20</td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>44</td>
</tr>
<tr>
<td>Cough</td>
<td>36</td>
</tr>
<tr>
<td>Lung Disorder</td>
<td>34</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>27</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>23</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
</tr>
<tr>
<td>SKIN AND APPENDAGES</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>50</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29</td>
</tr>
</tbody>
</table>
Percent Incidence of Non-hematologic Adverse Events Reported in a Review of 43 Publications Using High-Dose Oral Busulfan as a Conditioning Regimen Prior to Hematopoietic Progenitor Cell Transplant

<table>
<thead>
<tr>
<th>NON-HEMATOLOGIC ADVERSE EVENTS</th>
<th>PERCENT INCIDENCE (# PATIENTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis/Stomatitis</td>
<td>85 (483/571)</td>
</tr>
<tr>
<td>Fever</td>
<td>83 (37/457)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>72 (52/722)</td>
</tr>
<tr>
<td>Rash</td>
<td>67 (38/57)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58 (28/49)</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>45 (187/413)</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>35 (301/848)</td>
</tr>
<tr>
<td>Infection</td>
<td>31 (128/407)</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>15 (149/968)</td>
</tr>
<tr>
<td>Hepatic veno-occlusive disease</td>
<td>13 (153/1186)</td>
</tr>
<tr>
<td>Intestinal pneumonitis</td>
<td>11 (45/415)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (15/462)</td>
</tr>
</tbody>
</table>

Hematologic: At the indicated dose and schedule, BUSULFEX® produced profound myelosuppression in 100% of patients. Severe leukopenia occurred in 92% of patients, thrombocytopenia in 86%, and anemia in 50%. Following hematopoietic progenitor cell infusion, recovery of neutrophil counts to ≥500 cells/mm³ occurred at median day 10 and 13, for autologous and allogeneic patients respectively.

Gastrointestinal: Gastrointestinal toxicities were frequent and generally considered to be related to the drug. Few were categorized as serious. Mild/moderate nausea occurred in 93% of patients and mild/moderate vomiting in 91% throughout blood and marrow transplant Day +28; nausea was severe in 4%. The incidence of vomiting during BUSULFEX® administration (BMFT Day -7 to -4) was 38% (39/103). Stomatitis was severe in 13% of patients, and mild/moderate in 83% of patients. Severe esophagitis was considered life-threatening and occurred in 16% of patients and was mild/moderate in 64%. Diarrhea was severe in 6% of patients and mild/moderate in 74%. Mild/moderate constipation occurred in 31% of patients; ileus developed in 7% and was severe in 2%. Forty percent (40%) of patients reported mild/moderate dyspepsia. Twenty percent (2%) of patients experienced mild/moderate nausea, and mild/moderate rectal discomfort occurred in 24% of patients. One patient (1%) developed gastrointestinal bleeding which was severe and considered serious.

Hepatic: Hyperbilirubinemia was observed in 37% of patients; it was life-threatening in 3% and associated with veno-occlusive disease, severe in 8%, and mild/moderate in 26%. It was associated with graft versus host disease in six patients. Severe serum glutamic oxaloacetic transaminase (SGPT) elevations occurred in 2% of patients. There were mild/moderate increases in serum glutamic oxaloacetic transaminase (SGPT) in 23% and in SGOT in 10%. Alkaline phosphatase increases were mild/moderate in 12% of patients. Mild/moderate jaundice developed in 8% of patients; it was associated with graft versus host disease in six patients. Mild/moderate veno-occlusive disease in 4%. Mild/moderate hepatomegaly developed in 5% of patients.

Hepatic Veno-occlusive Disease: Hepatic veno-occlusive disease (HVOD) is a recognized potential complication of conditioning therapy prior to transplant. Six of 103 patients (6%) experienced HVOD. It was fatal in 2%, severe in 2% and moderate in 2%. After BMT day +28, an additional 3% developed graft versus host disease that was considered serious.

Edema: Seventy-one percent (71%) of patients exhibited some form of edema, hypervolemia, or weight increase; all events were mild/moderate. One patient (<1%) developed moderate capillary leak syndrome.

Infection/Fever: Although 39% of patients (40/103) experienced one or more episodes of infection, 83% (33/40) were rated as mild or moderate. Pneumonia was fatal in 1% and life-threatening in 3% of patients. Other infections were considered severe in 3% of patients. Fever was reported in 87% of patients; it was mild/moderate in 84% and severe in 3%. 47% of patients experienced chills which were mild/moderate in 46% and severe in 1%.

Cardiovascular: Mild/moderate tachycardia was reported in 50% of patients. Other rhythm abnormalities which were all mild/moderate, included atrial fibrillation (3%), atrial flutter (2%), paroxysmal atrial tachycardia (1%), and paroxysmal atrial fibrillation (1%). Mild/moderate hypertension occurred in 27% of patients, usually associated with the central venous catheter. One patient (1%) experienced a severe femoral artery thrombosis, which was controlled with coagulation therapy. Hypertension was reported in 25% of patients and was severe in 1%. Hypokalemia occurred in 17% of patients and was severe in 2%. Mild/moderate hypokalemia was reported in 23% of patients. Other cardiovascular events included mild cardiomegaly, mild ECG abnormality, moderate pericardial effusion, moderately decreased ejection fraction, and moderate pericarditis; all were reported at an incidence of <3% and mainly in the post-cyclophosphamide phase.

Pulmonary: Mild/moderate dyspnea occurred in 22% of patients and was severe in 2%.

One patient (1%) experienced severe hyperventilation; and in 4% (4 additional patients), it was mild/moderate. Respiratory failure occurred in two patients (2%), either in conjunction with HVOD and cerebral hemorrhage or pneumonia. Mild/moderate rhinorrhea and cough were reported in 44% and 36% of patients, respectively; most events were mild. Epistaxis events were mild in 22% of patients and moderate in 1%. Alveolar hemorrhages were severe in 1% and life-threatening in 1% of patients. Other pulmonary events that were mild/moderate included abnormal breath sounds (34%), pharyngitis (27%), hiccup (17%), asthma (7%), atelectasis (3%), pleural effusion (3%), and hypoxia (1%).

Neurologic: The most commonly reported events involved nonspecific, global disturbances, but the central nervous system: headache (1%), confusion (2%), hallucinations (1%), and cerebrovascular accident (1%). One patient (1%) developed a mild seizure while receiving cyclophosphamide; however, 99% of patients were prophylactically treated with phenytoin.

Renal: Creatinine was mild/moderate in 17% of patients. BUN was increased in 2% of patients and to a severe degree in 1%. 13% of patients experienced dysuria, 11% oliguria, and 9% hematuria; all were mild/moderate except for 1% severe hematuria. Moderate renal insufficiency was reported in 2% of patients.

Skin: Mild/moderate rash (50%) and pruritus (29%) were reported; both conditions were predominantly mild. Alopecia was mild in 12% of patients and moderate in 3%. Mild vesicular rash was reported in 8% of patients and mild/moderate maculopapular rash in 7%.

Metabolic: Hyperglycemia was observed in 57% of patients and was severe in 5%. More than half of the patients experienced some electrolyte disturbance, usually a decrease, and none were considered serious. Hypoglycemia was mild/moderate in 64% of patients. Gastrointestinal toxidynia was mild/moderate in 57% and severe in 1%, hypocalcemia was mild/moderate in 40% and severe in 3%; hypophosphatemia was mild/moderate in 21%, hypernatremia was mild/moderate in 3%.

Other: Other events reported include: headache (mild/moderate 65%, severe 4%), abdominal pain (mild/moderate 61%, severe 2%), asthenia (mild/moderate 56%, severe 1%), unspecified pain (mild/moderate 31%, severe 1%), injection site inflammation (mild/moderate 23%) or injection site pain (mild/moderate 17%), chest pain (mild/moderate 23%), back pain (mild/moderate 18%), myalgia (mild/moderate 17%), and arthralgia (mild/moderate 13%).

Post-Marketing Adverse Drug Reactions: The following additional adverse events have been spontaneously reported during the post-marketing use of BUSULFEX®: fever, thrombocytopenia, leukopenia, severe neutropenia; tumor lysis syndrome; thrombotic microangiopathy (TMA); severe bacterial, viral (e.g., cytomegalovirus infection) and fungal infections; and sepsis. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

SYMPTOMS AND TREATMENT OF OVERDOSE:

The principal toxic effect is profound bone marrow hypoplasia/aplasia and pancytopenia but the central nervous system, liver, lungs, and gastrointestinal tract may be affected. There is no known antidote to busulfan overdose, other than hematopoietic progenitor cell transplantation. The hematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated. In the absence of hematopoietic progenitor cell transplantation, the recommended dosage for BUSULFEX® (busulfan) would constitute an overdose of busulfan. Survival after a single 140-mg dose of Myleran® Tablets in an 18 kg, 4-year-old child has been reported. Inadvertent administration of a greater than normal dose of oral busulfan (2.1 mg/kg; total dose of 23.3 mg/kg) occurred in a 2-year-old child prior to a scheduled bone marrow transplant without sequelae. An acute dose of 2.4 g was fatal in a 10-year-old boy. There has been one report that busulfan is dialyzable, thus dialysis should be considered in the case of an overdose. Busulfan is metabolized through conjugation with glucuronide, thus administration of glucuronide may be considered.

Product Monograph available from Medical Information at 1-877-341-9245.

Date of issuance: January 20, 2012. © 2012 Otsuka Canada Pharmaceutical, Inc.

*BUSULFEX® is a registered Trade Mark of Otsuka Pharmaceutical Co., Ltd., used under license by Otsuka Canada Pharmaceutical Inc.

2250 Alfred-Nobel Boulevard, suite 301
Saint-Laurent, Quebec
H4S 2C9

Otsuka Canada Pharmaceutical Inc.