

EDUCATIONAL CONCEPTS GROUP



Clinical Treatment Advances in Hematologic Malignancies: Updates from the 14th Congress of the European Hematology Association

Editors

Harry P. Erba, MD, PhD

Associate Professor of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan

Robert E. Marcus, MA, FRCP, FRCPath

Consultant Haematologist, Lead Cancer Clinician
Kings College Hospital
Consultant Haematologist
London Oncology Clinic
London, United Kingdom

This activity is supported by educational grants from



This activity is sponsored by

EDUCATIONAL
CONCEPTS GROUP



Table of Contents *(click the section you wish to view)*

Introduction	1
Chronic Lymphocytic Leukemia	1
Clinical Implications of Biological Markers in Chronic Lymphocytic Leukemia.....	1
Risk-Adapted Therapy in Chronic Lymphocytic Leukemia	3
Single-Agent Ofatumumab, a Novel CD20 Monoclonal Antibody, Results in High Response Rates in Patients With Fludarabine-Refractory Chronic Lymphocytic Leukemia (CLL) also Refractory to Alemtuzumab or With Bulky Lymphadenopathy	5
Phase I Study of RO507275 (GA101) in Relapsed/Refractory Chronic Lymphocytic Leukemia	6
Follicular Lymphoma	7
Follicular Lymphoma: Is Watch and Wait Still an Option? (Pro & Con)	7
Pro.....	7
Con	8
Brief Chemoimmunotherapy Rituximab (R)-FND ± R Maintenance is Effective and Safe in Newly Diagnosed Follicular Lymphoma Elderly Patients: An Intergruppo Italiano Linfomi (IIL) Randomized Trial.....	9
Diffuse Large B-Cell Lymphoma	10
Developing New Treatments for Diffuse Large B-Cell Lymphoma	10
Treatment Options for Relapsing Patients.....	12
Multiple Myeloma	13
Experimental Agents Knocking at the Door of Myeloma Treatment.....	13
Treatment Options for Myeloma in 2009.....	15
Chronic Myelogenous Leukemia	17
Nilotinib 800 mg Daily in Early Chronic Phase Chronic Myeloid Leukemia: 12 Months Results of a Phase II Trial of the GIMEMA CML Working Party	17
Dasatinib 100 mg Once Daily for Chronic Phase Chronic Myeloid Leukemia (CML-CP) Following Imatinib Failure: Long-Term Follow-Up From Study CA180-034	18
Molecular Responses of the SPIRIT Phase III Trial of the French CML Group Comparing Imatinib (IM) 400 mg to Higher Dose Imatinib or Combination With Interferon or Cytarabine for the Treatment of Newly Diagnosed Chronic Phase (CP) Chronic Myeloid Leukaemia (CML) Patients (Pts).....	19
Early Molecular Response to First-Line Imatinib Therapy is Predictive for Long-Term PFS and EFS in CP-CML– An Interim Analysis of the Randomized German CML Study IV	19
Acute Myelogenous Leukemia	20
Clinical Trial Update in Elderly Patients–MRC.....	20
Clinical Trial Update in Elderly Patients–HOVON-SAKK	20
Clinical Trial Update in Elderly Patients–EORTC-GIMEMA.....	21

ACCREDITATION INFORMATION

PHYSICIAN CONTINUING EDUCATION ACCREDITATION STATEMENT

Educational Concepts Group, LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

DESIGNATION OF CREDIT

Educational Concepts Group, LLC designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PHARMACIST CONTINUING EDUCATION



Educational Concepts Group, LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of activity: Knowledge-based

Educational Concepts Group, LLC designates this continuing education activity for 1.5 contact hours (0.15 CEUs) (UPN 199-000-09-030-H01-P).

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME/CE credit for this activity. During the period July 28, 2009 through July 27, 2010, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test and activity evaluation form.

CME/CE CREDIT

Physicians and pharmacists who complete the post-test with a score of 70% or better may view and print their credit letter or statement of credit via the website, www.educationalconcepts.net.

FACULTY DISCLOSURE STATEMENT

All faculty participating in continuing education activities sponsored by ECG are expected to disclose to the audience any real or apparent commercial financial affiliations related to the content of their presentations/materials.

ECG HAS DECLARED THE FOLLOWING FINANCIAL RELATIONSHIPS

ECG receives educational grants from pharmaceutical industry and other commercial sources. Planners, managers, and other staff members at ECG have no relevant financial relationships to disclose.

None of the contents may be reproduced in any form without prior written permission from the publisher. This activity may be accessed at www.educationalconcepts.net.

THE FOLLOWING FACULTY MEMBERS HAVE DECLARED RELEVANT FINANCIAL RELATIONSHIPS

Harry P. Erba, MD, PhD

Speakers' Bureau

Bristol-Myers Squibb Company, Celgene Corporation, Cephalon, Eisai Inc., Novartis, Pharmion

Grants/Research Support

Cell Therapeutics, Cephalon, Eli Lilly and Company, Genzyme Corporation, Kanisa, Novartis, Wyeth Pharmaceuticals, Xanthus

Consultant Fees

Genzyme Corporation

Robert E. Marcus, MA, FRCP, FRCPath

Consultant Fees, Honorarium, Speakers' Bureau
Mundipharma, Roche

ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT

This activity is supported by educational grants from Celgene Corporation and Merck & Co., Inc.

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Please refer to the official prescribing information for each product or consult the *Physicians' Desk Reference* for discussion of approved indications, contraindications, and warnings.

DISCLOSURE OF OFF-LABEL USE

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. Educational Concepts Group, LLC (ECG) does not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity do not necessarily represent the views of ECG. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

CME/CE INQUIRIES

For further information, please contact:

Educational Concepts Group, LLC
1300 Parkwood Circle SE, Suite 325
Atlanta, Georgia 30339

Phone: 1.770.933.1681 | Fax: 1.770.933.1692
www.educationalconcepts.net



Target Audience

The target audience for the program includes hematologists, medical oncologists, hematologist oncologists, oncology specialty pharmacists, and oncology nurses charged with the care of patients with hematologic malignancies.

Learning Objectives

Upon completion of this educational activity, participants should be better able to:

- Describe the potential role of novel treatment strategies in the management of hematologic malignancies
- Compare available treatment options for patients with hematologic malignancies in respect to efficacy and toxicity parameters
- Describe the proposed mechanism of action of new and emerging therapeutic agents utilized to improve remission and survival rates for patients with hematologic malignancies
- Discuss implications of updated safety and efficacy data for clinically available treatment options for patients with hematologic malignancies

Statement of Need

Inclusive of lymphoma, multiple myeloma, and leukemia, an estimated 140,000 new hematologic malignancy cases are expected to be diagnosed in the United States in 2009. Even with treatment advancements for these hematologic malignancies, approximately 53,000 individuals will die secondary to their malignancy. The treatment of hematologic malignancies remains a challenge for many healthcare professionals and patients despite recent gains made in the management of these diseases. Determining which treatment approach is most appropriate for a given patient requires careful consideration of patient-specific characteristics, physician expertise, and available health-system resources. While difficult, these decisions require knowledge of current clinical and experimental data in order for the appropriate utilization of therapeutic agents and strategies in clinical practice. This educational program provides participants with an overview of the most recent advances in the treatment of hematologic malignancies, as well as specific updates and outcomes of ongoing clinical trials, synthesized into a concise learning opportunity by experts in the field. The cutting-edge data these experts will present will provide practitioners with the information they need to incorporate new therapeutic strategies into their patient care decisions. As a result, it will lead to improved response and survival rates for patients with hematologic malignancies while minimizing adverse events and maintaining or improving patient quality of life.

Media: Newsletter

Estimated time to complete activity: 1.5 hours

Release date: July 28, 2009

Expiration date: July 27, 2010

INTRODUCTION

The 14th Congress of the European Hematology Association (EHA) was held June 4-7, 2009 in Berlin, Germany. With over 2,000 abstracts submitted, this congress endeavored to promote not only excellence in clinical practice and research, but also in hematology education. This newsletter summarizes the following areas of hematologic malignancies as presented by experts in their respective fields.

Featured Content:

- Chronic Lymphocytic Leukemia
- Follicular Lymphoma
- Diffuse Large B-Cell Lymphoma
- Multiple Myeloma
- Chronic Myelogenous Leukemia
- Acute Myelogenous Leukemia

CHRONIC LYMPHOCYTIC LEUKEMIA

Clinical Implications of Biological Markers in Chronic Lymphocytic Leukemia

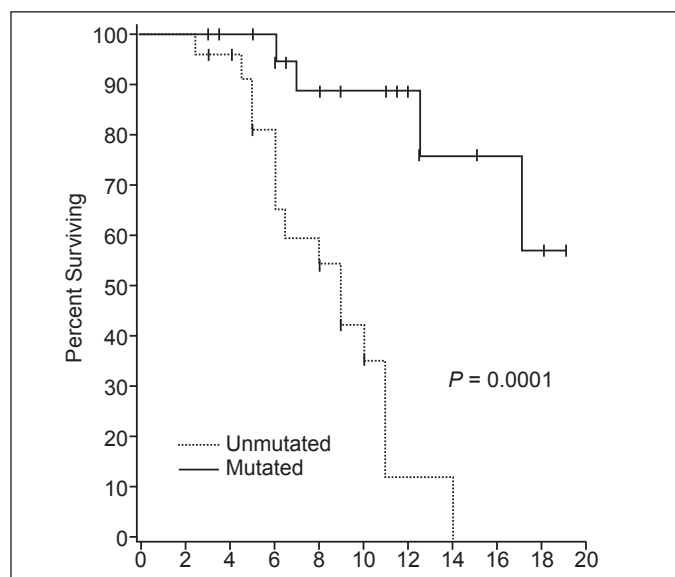
R. Rosenquist

Department of Genetics and Pathology, Uppsala University
Uppsala, Sweden

The most common leukemia in the world is chronic lymphocytic leukemia (CLL). The decision of when to treat CLL is based upon a myriad of disease- and patient-specific characteristics, including clinical stage, symptoms, disease burden, age, comorbid illnesses, prognostic factors, and available treatment options. Multiple novel prognostic factors have been identified recently, adding to the complexity of treatment decision-making. Prognostic markers can be categorized into 3 major categories: 1. DNA-based (immunoglobulin gene analysis); 2. flow cytometry-based; and 3. RNA-based markers. In addition, for prognostic markers to impact survival outcome, markers should have the following characteristics: 1. robust standard assay that can be applied to multicenter studies; 2. confirmed repeatedly by independent cohorts; and 3. can be applied prospectively in new trials.

DNA-Based Markers—During the 1990s, investigators discovered that CLL cells displayed a diverse somatic hypermutation status and that approximately 50% of patients have an immunoglobulin variable heavy-chain region gene (IgVH) mutation. Studies have shown that unmutated IgVH genes are associated with more aggressive disease and poor prognosis (**Figure 1**).

Figure 1. Survival Based on IgVH Mutational Status



However, the Scandinavian group reported a population-based cohort study that revealed a novel subset that expressed an IgVH3-21 gene, with a frequency of about 10%. These IgVH3-21 patients had mutated IgVH genes, but the clinical course followed an unmutated disease course of poor prognosis. Interestingly, the subset had almost identical complementarity determining region 3 (CDR3) with one lambda light-chain gene, IgLV3-21, in > 50% of patients.

The findings of a “stereotyped” B-cell receptor (BCR) in non-related IgVH3-21 CLL patients have been confirmed by others. Further, several additional subsets with stereotyped heavy-chain CDR3s have been identified. These subsets include IgVH1/5/7, IgVH3-21, IgVH4-34, and IgVH1-69. Stamatopoulos et al demonstrated that > 20% of CLL cases belonged to stereotyped subsets. An important finding is that these stereotyped subset patients had a poor prognosis compared to non-stereotyped subsets, which was independent of somatic mutational status.

Flow Cytometry Markers—One of the flow cytometry markers is CD38. Prior studies demonstrated that cases with greater than 30% CD38+ cells typically had unmutated IgVH genes. However, recent studies have shown less stringent correlation with great heterogeneity in cases with between 0 to 20% CD38+ cells.

Another prognostic marker ZAP-70, can be assayed by several different methods, including flow cytometry. Several

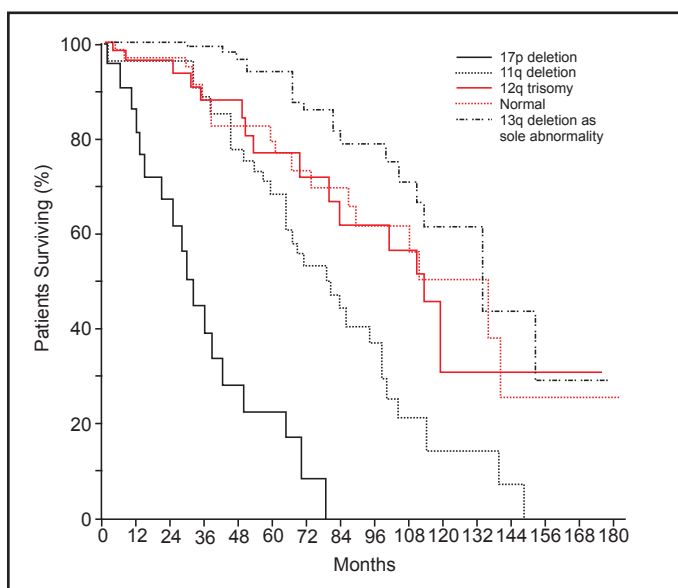


studies have shown upregulation of the ZAP-70 marker in unmutated CLL cells, thus correlating ZAP-70-positive cases with poor prognosis. However, Rassenti et al reported that ~ 25% of the cases have discordant mutational status and ZAP-70 expression. Patients with deletion of 11q or 17p sequences can be ZAP-70-negative despite having unmutated IgVH.

RNA-Based Markers—One of the RNA-based prognostic markers being investigated is lipoprotein lipase (LPL), using real-time polymerase chain reaction (RT-PCR). Several studies demonstrated that LPL is highly expressed in unmutated CLL. Several chromosomal aberrations in CLL have been identified to correlate with prognosis (**Figure 2**). Recently, the role of TP53 mutation has been reinforced in CLL because the majority of cases of 17p deletion also displayed this mutation. Additionally, approximately 4-5% of cases displayed TP53 mutation in the absence of 17p deletion.

Another interesting genetic aberration is telomere length. Studies demonstrated that shorter telomere length is associated with unmutated CLL cells and that longer length is associated with mutation. Furthermore, patients with 11q and 17p deletions demonstrated shorter telomere length and poor prognosis. In conclusion, several prognostic markers have a strong correlation with prognosis, while others may require further analysis.

Figure 2. Survival Based on Five Genetic Categories



Bibliography

- Bomben R, Dal Bo M, Capello D, et al. Molecular and clinical features of chronic lymphocytic leukaemia with stereotyped B cell receptors: results from an Italian multicentre study. *Br J Haematol*. 2009;144:492-506.
- Damle RN, Wasil T, Fais F, et al. IgV gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood*. 1999;94:1840-1847.
- Dicker F, Herholz H, Schnittger S, et al. The detection of TP53 mutations in chronic lymphocytic leukemia independently predicts rapid disease progression and is highly correlated with a complex aberrant karyotype. *Leukemia*. 2009;23:117-124.
- Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000;343:1910-1916.
- Fais F, Ghiotto F, Hashimoto S, et al. Chronic lymphocytic leukemia B cells express restricted sets of mutated and unmutated antigen receptors. *J Clin Invest*. 1998;102:1515-1525.
- Ghia EM, Jain S, Widhopf GF, et al. Use of IGHV3-21 in chronic lymphocytic leukemia is associated with high-risk disease and reflects antigen-driven, post-germinal center leukemogenic selection. *Blood*. 2008;111:5101-5108.
- Ghia P, Stamatopoulos K, Belessi C, et al. Geographic patterns and pathogenetic implications of IGHV gene usage in chronic lymphocytic leukemia: the lesson of the IGHV3-21 gene. *Blood*. 2005;105:1678-1685.
- Ghiotto F, Fais F, Valetto A, et al. Remarkably similar antigen receptors among a subset of patients with chronic lymphocytic leukemia. *J Clin Inv*. 2004;113:1008-1016.
- Grabowski P, Hultdin M, Karlsson K, et al. Telomere length as a prognostic parameter in chronic lymphocytic leukemia with special reference to VH gene mutation status. *Blood*. 2005;105:4807-4812.
- Hamblin TJ, Davis Z, Gardiner A, et al. Unmutated IgV(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood*. 1999;94:1848-1854.
- Hamblin TJ, Orchard JA, Gardiner A, et al. Immunoglobulin V genes and CD38 expression in CL. *Blood*. 2000;95:2455-2457.
- Heintel D, Kienle D, Shehata M, et al. High expression of lipoprotein lipase in poor risk B-cell chronic lymphocytic leukemia. *Leukemia*. 2005;19:1216-1223.

Juliusson G, Oscier DG, Fitchett M, et al. Prognostic subgroups in B-cell chronic lymphocytic leukemia defined by specific chromosomal abnormalities. *N Engl J Med.* 1990;323:720-724.

Krober A, Bloehdorn J, Hafner S, et al. Additional genetic high-risk features such as 11q deletion, 17p deletion, and V3-21 usage characterize discordance of ZAP-70 and VH mutation status in chronic lymphocytic leukemia. *J Clin Oncol.* 2006;24:969-975.

Krober A, Seiler T, Benner A, et al. V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. *Blood.* 2002;100:1410-1406.

Mansouri M, Sevov M, Fahlgren E, et al. Differential RNA and protein levels of lipoprotein lipase in chronic lymphocytic leukemia patients with mutated and unmutated IGHV genes. *Leuk Lymphoma.* 2007;48:S47.

Messmer BT, Albesiano E, Efremov DG, et al. Multiple distinct sets of stereotyped antigen receptors indicate a role for antigen in promoting chronic lymphocytic leukemia. *J Exp Med.* 2004;200:519-525.

Opezzo P, Vasconcelos Y, Settegrana C, et al. The LPL/ADAM29 expression ratio is a novel prognosis indicator in chronic lymphocytic leukemia. *Blood.* 2005;106:650-657.

Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. *N Engl J Med.* 2004;351:893-901.

Roos G, Krober A, Grabowski P, et al. Short telomeres are associated with genetic complexity, high-risk genomic aberrations, and short survival in chronic lymphocytic leukemia. *Blood.* 2008;111:2246-2252.

Schroeder HW, Jr, Dighiero G. The pathogenesis of chronic lymphocytic leukemia: analysis of the antibody repertoire. *Immunol Today.* 1994;15(6):288-294.

Stamatopoulos K, Belessi C, Moreno C, et al. Over 20% of patients with chronic lymphocytic leukemia carry stereotyped receptors: pathogenetic implications and clinical correlations. *Blood.* 2007 Jan 1;109(1):259-270.

Thorselius M, Krober A, Murray F, et al. Strikingly homologous immunoglobulin gene rearrangements and poor outcome in VH3-21-using chronic lymphocytic leukemia patients independent of geographic origin and mutational status. *Blood.* 2006;107:2889-2894.

Thunberg U, Johnson A, Roos G, et al. CD38 expression is a poor predictor for VH gene mutational status and prognosis in chronic lymphocytic leukemia. *Blood.* 2001;97:1892-1894.

Tobin G, Thunberg U, Johnson A, et al. Somatic mutated IgV(H)3-21 genes characterize a new subset of chronic lymphocytic leukemia. *Blood.* 2002;99:2262-2264.

Tobin G, Thunberg U, Karlsson K, et al. Subsets with restricted immunoglobulin gene rearrangement features indicate a role for antigen selection in the development of chronic lymphocytic leukemia. *Blood.* 2004;104:2879-2885.

Widhopf GF, Rassenti LZ, Toy T, et al. Chronic lymphocytic leukemia B cells of more than 1% of patients express virtually identical immunoglobulins. *Blood.* 2004;104:2499-2504.

Wiestner A, Rosenwald A, Barry TS, et al. ZAP-70 expression identifies a chronic lymphocytic leukemia subtype with unmutated immunoglobulin genes, inferior clinical outcome, and distinct gene expression profile. *Blood.* 2003;101:4944-4951.

Zenz T, Krober A, Scherer K, et al. Monoallelic TP53 inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. *Blood.* 2008;112:3322-3329.

Risk-Adapted Therapy in Chronic Lymphocytic Leukemia

P. Hillmen

St James's University Hospital

Leeds, United Kingdom

Until recently, the CLL4 trial provided the basis for standard conventional chemotherapy regimens for patients with untreated CLL. The trial compared chlorambucil, fludarabine alone, or fludarabine + cyclophosphamide (FC) in untreated CLL. The results clearly demonstrated that, compared to either single-agent, the FC combination yielded superior response rates (**Table 1**).

Table 1. Response by Treatment in CLL4*

Treatment	n	CR	nPR	PR
Chlorambucil	366	7	19	46
Fludarabine	181	15	27	38
FC	182	38	22	34

*n indicates number of patients; CR, complete response; nPR, nodular partial response; PR, partial response.



Also, a significant difference in 5-year progression-free survival (PFS) was detected between the FC (37%) treatment arm and either the fludarabine alone (10%) or the chlorambucil (10%) treatment arms ($P < 0.00005$). Additionally, a hazard ratio comparison between the FC treatment arm and the chlorambucil treatment arm significantly favored the FC group in all subgroup categories other than the poor-risk group. Furthermore, these results have been verified by other investigators.

However, the trial did not demonstrate a significant difference in overall survival (OS) between the treatment groups. A potential explanation for this discrepancy between the PFS and the OS may be due to patients who were previously treated with chlorambucil being treated with either FC or other nucleoside analog-containing regimens upon relapse. Thus, the survival for patients treated with the first-line chlorambucil may be disproportionately extended due to the use of other nucleoside analog-containing therapies upon relapse.

In 2008, results of the German CLL8 trial in first-line treatment and the REACH trial in relapsed CLL changed the standard treatment for the treatment of CLL. Both trials showed that treatment with fludarabine, cyclophosphamide, rituximab (FCR) was superior to treatment with FC.

The German CLL8 trial investigated treatment comparison between FCR and FC in patients with untreated CLL. The primary endpoint was PFS and secondary endpoints included OS. Response to treatment showed a doubling of the complete response (CR) rate by FCR compared to FC (**Table 2**).

Table 2. Response to Treatment in CLL8*

Response	FC	FCR	<i>P</i> value
CR	22.9%	44.5%	< 0.01
nPR	4.9%	2.8%	0.15
PR	50.4%	39.6%	< 0.01

*CR indicates complete response; nPR, nodular partial response; PR, partial response; FC, fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab.

Additionally, a significant difference in the primary endpoint was detected; the median PFS was 42.8 months in the FCR group compared to 32.3 months in the FC group ($P = 0.000007$). Similarly, in the treatment of relapsed CLL patients, the REACH trial also demonstrated that the median PFS was greater with the FCR treatment group (30.6 months) compared to the FC treatment group (20.6 months) ($P = 0.0002$).

However, several important questions remained regarding the use of FCR in previously untreated CLL patients. Is FCR deliverable to all patients? Is FCR adequate and appropriate therapy for all patients? Is FCR necessary for all patients? Which patients benefit most from FCR since FCR may not be affordable for all patients?

In the German CLL8 trial, only 10% of the patients were aged ≥ 70 years and were of good performance status. The overall response rate (ORR) in both treatment arms was high (FCR 98% vs FC 97%) but CR was higher with FCR (33%) compared to FC (15%) in patients ≥ 70 years of age. However, significantly more patients in the FCR treatment group (46.8% all cycles) had dose reductions compared to patients in the FC treatment group (27.3% all patients) ($P < 0.01$), suggesting that FCR may be more appropriate for healthy fit patients. Furthermore, fludarabine may not be appropriate for all patients, such as those with renal insufficiency, autoimmune hemolysis during previous fludarabine exposure, cardiac insufficiency, or neurologic disorders. Thus, for patients who may not tolerate FCR, other regimens are being investigated to address these questions. Separate trials are ongoing to investigate rituximab + chlorambucil, ofatumumab + chlorambucil, and GA101, a third generation anti-CD20 antibody, + chlorambucil in the treatment of patients with untreated CLL.

Stilgenbauer et al presented FCR response data by genetic analyses (**Table 3**). The study demonstrated that FCR provides a good CR rate in patients with del(11q) while providing no benefit over FC for patients with del(17p).

Table 3. CLL8 Complete Responses by Genetic Analyses*

Parameter	n	FC	FCR	<i>P</i> value
All Patients	817	27%	52%	< 0.001
17p-	43	4.5%	19%	0.185
11q-	136	13.8%	61.5%	< 0.001
+12q	56	25%	75%	< 0.001
13q- single	211	31.2%	52%	0.003
normal	131	30.9%	40.8%	0.274
VH mutated	215	27.8%	55.1%	< 0.001
VH unmutated	364	21.8%	46.4%	< 0.001

*FC indicates fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab.

Pettitt et al investigated alemtuzumab + steroid (methylprednisolone) in patients with 17p deletions and presented the results at this congress. The CR for all patients was 24% and for de novo patients was 37%. In conclusion, FCR is considered the standard of care for patients with newly diagnosed CLL as treatment results in increased response rates and prolonged PFS. Co-morbidity and not age should be the determining factor for treatment, as patients ≥ 70 years who are healthy should be considered for intensive therapy. Additionally, prospective randomized trials are needed to better elucidate treatment options for patients with 17p deletions.

Bibliography

Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. *Lancet*. 2007;370:230-239.

Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood*. 2006;107:885-891.

Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol*. 2007;25:793-798.

Hallek M, Fingerle-Rowson G, Fink AM, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). *Blood*. 2008;112. Abstract 325.

Pettitt R, Matutes E, Dearden C, et al. Results of the phase II NCRI CLL206 trial of alemtuzumab in combination with high-dose methylprednisolone for high-risk (17p-) CLL. *Haematologica*. 2009;94(s2). Abstract 351.

Robak T, Moiseev SI, Dmoszynska A, et al. Rituximab, fludarabine, and cyclophosphamide (R-FC) prolongs progression-free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the International Randomized Phase III REACH Trial. *Blood*. 2008;112. Abstract LBA-1.

Stilgenbauer S, Zenz T, Winkler D, et al. Genomic aberrations, VH mutation status and outcome after fludarabine and cyclophosphamide (FC) or FC plus rituximab (FCR) in the CLL8 trial. *Blood*. 2008;112. Abstract 781.

Single-Agent Ofatumumab, a Novel CD20 Monoclonal Antibody, Results in High Response Rates in Patients With Fludarabine-Refractory Chronic Lymphocytic Leukemia (CLL) also Refractory to Alemtuzumab or With Bulky Lymphadenopathy

B. Wierda

*The University of Texas, MD Anderson Cancer Center
Houston, USA*

Patients with fludarabine-refractory CLL, especially those with bulky (> 5 cm) lymphadenopathy, have a poor outcome with available salvage regimens. The ORR with salvage regimens in this patient population is ~ 20%, with a median time-to-failure (TTF) of 2 to 3 months.

Ofatumumab is a human monoclonal antibody that targets the CD20 antigen at a different epitope than rituximab. Ofatumumab showed clinical activity in a pilot CLL study with an ORR of up to 50%. The aim of this study was to evaluate the efficacy and safety of ofatumumab in patients with fludarabine-refractory CLL who were also refractory to alemtuzumab (FA-ref) or ineligible for alemtuzumab due to bulky lymphadenopathy (BF-ref). This was an international, open-label, single-arm clinical trial and the planned interim analysis was presented.

Patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions. The primary endpoint was ORR. The secondary endpoints included duration of response (DR), PFS, OS, and safety. A total of 138 patients were enrolled, of which 59 patients were FA-ref and 79 patients were BF-ref. **Table 4** provides a summary of baseline patient characteristics.

Table 4. Baseline Patient Characteristics*

Characteristic	FA-ref	BF-ref
Median Age (range)	64 (41-86) years	62 (43-84) years
Median Duration of CLL (range)	6 (1-18.6)	6 (0.7-18)
Rai Stage III/IV	54%	70%
ECOG PS 1-2	53%	67%
Lymph Nodes > 5 cm	93%	100%
Median Prior Therapies	5	4
Prior Rituximab Exposure	59%	43%

*FA-ref indicates fludarabine-refractory CLL also refractory to alemtuzumab; BF-ref, fludarabine-refractory CLL ineligible for alemtuzumab due to bulky lymphadenopathy.



The ORR in FA-ref and BF-ref was 58% and 47%, respectively. The median PFS was 5.7 months and 5.9 months in FA-ref and BF-ref, respectively (**Table 5**).

Table 5. Clinical Outcomes*

Outcome	FA-ref	BF-ref
Overall Response Rate	58%	47%
Time-to-Relapse	1.8 months	1.8 months
Duration of Response	7.1 months	5.6 months
Progression-Free Survival	5.7 months	5.9 months
Overall Survival	15.4 months	13.7 months

*FA-ref indicates fludarabine-refractory CLL also refractory to alemtuzumab; BF-ref, fludarabine-refractory CLL ineligible for alemtuzumab due to bulky lymphadenopathy.

A landmark analysis at week 12 showed a significant difference in OS between responders (not reached) versus non-responders (9.8 months) in FA-ref patients ($P = 0.04$) and between responders (not reached) versus non-responders (10.2 months) in BF-ref patients ($P < 0.0001$). The most common adverse event was infusion-related reactions in 60% of the patients. The most common grade 3/4 adverse events were infections. Early death occurred in 6 patients (4 FA-ref and 2 BF-ref), none of which were considered related to ofatumumab. In conclusion, ofatumumab as a single-agent produced good response rates in patients with fludarabine-refractory CLL.

Bibliography

- Coiffier B, Lepage S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood*. 2008;111:1094-1100.
- Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. 2002;99:3554-3561.
- Osterborg A, Kipps T, Mayer J, et al. Single-agent ofatumumab, a novel CD20 monoclonal antibody, results in high response rates in patients with fludarabine-refractory chronic lymphocytic leukemia (CLL) also refractory to alemtuzumab or with bulky lymphadenopathy. *Haematologica*. 2009;94(s2). Abstract 494.

Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008;112(4):975-980.

Teeling J, French R, Cragg MS, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood*. 2004;104:1793-1800.

Teeling J, Mackus, WJ, Wiegman L, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol*. 2006;177:362-371.

Phase I Study of RO507275 (GA101) in Relapsed/Refractory Chronic Lymphocytic Leukemia

T. Lamy
CHU Rennes
Rennes, France

GA101 is the first humanized glycoengineered type II monoclonal anti-CD20 antibody. In vitro studies have shown that glycoengineering results in an increased ADCC activity compared to rituximab. This was an open-label, multicenter, phase I/II clinical trial to explore GA101 clinical activity in patients with no treatment options in CLL. The primary objective was safety, and additional objectives included pharmacokinetics, response rates, and PFS. Patients received GA101 on days 1, 8, and 22 and every 3 weeks for a total of 9 infusions. The dose escalated based on a standard 3 + 3 design (**Table 6**).

Table 6. Phase I Dose-Escalation Cohorts

Cohort Group	GA101 Dose Dose 1/Doses 2-9
1	400/800 mg
2	800/1200 mg
3	1200/2000 mg
4	1000/1000 mg

A total of 13 patients were enrolled, with a median age of 64 years. Baseline patient characteristics are shown on **Table 7**.

Table 7. GA101 Baseline Patient Characteristics (N = 13)

Characteristic	GA101
Median Age (range)	64 (46-81) years
Median Duration of CLL (range)	8 (2.8-15.7) years
Median Prior Therapies	
Prior Rituximab	62%
Prior Fludarabine	100%
Prognostic Factors	
Cytogenetics	17p- (n = 2), 11q- (n = 1), 13q- (n = 1), +12 (n = 2)
IgVH Status	Mutated (n = 2), IgVH3-21 (n = 1), unmutated (n = 7)

Nine out of 13 patients experienced grade 3/4 neutropenia during treatment, with 1 patient experiencing febrile neutropenia. Serious adverse events were reported as follows: grade 4 febrile neutropenia in the 400/800 mg cohort; in the 800/1200 mg cohort, grade 3 bronchitis, thrombocytopenia, and grade 4 neutropenia; and in the 1200/2000 mg cohort, grade 3 tumor lysis syndrome. Responses were observed in 7 of 11 evaluable patients.

Table 8 provides response rates based on dosing cohort.

Table 8. Response by Dosing-Cohorts

Response	400/800 mg	800/1200 mg	1200/1200 mg	1000/1000 mg
Complete Response		1 patient		
Partial Response	2 patients	1 patient	3 patients	
Stable Disease	1 patient	1 patient		2 patients

In conclusion, GA101 is well-tolerated in patients with CLL and has a similar safety profile to that seen in patients with NHL. The ORR of 64% is encouraging and a phase II study is to be initiated in the future.

Bibliography

- Cartron G, Lamy T, Morschhauser F, et al. Phase I study of RO507275 (GA101) in relapsed/refractory chronic lymphocytic leukemia. *Haematologica*. 2009;94(s2). Abstract 495.
- Hallek M, Cheson B, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111:5446-5456.

Salles G, Morschhauser F, Cartron G, et al. A phase I/II study of RO5072759 (GA101) in patients with relapsed/refractory CD20+ malignant disease. *Blood*. 2008;112. Abstract 234.

FOLLICULAR LYMPHOMA

Follicular Lymphoma: Is Watch and Wait Still an Option? (Pro & Con)

Pro

M. van Oers
Academic Medical Center
Amsterdam, The Netherlands

In regard to the question of approach to treatment of asymptomatic patients with follicular lymphoma (FL), the proponent speaker discussed reasons for watchful waiting as an option. First, FL has a relatively long median survival and, currently, there is no curative treatment. There are new treatments for FL that demonstrated increased PFS but this did not necessarily equate to improved OS. Thus, the international consensus for the indication for treatment of advanced FL is as follows:

- Symptomatic disease
- Bulky disease, impairing organ function
- Disease progression
- Histological transformation

Several trials have addressed a “watch and wait” approach to FL. A summary of trials demonstrated that there is no advantage in the treatment of asymptomatic patients compared to watch and wait.

Additionally, in a study by Ardeshtna et al, patients with low-grade lymphoma (75% had FL) with a median age of 61 years were randomized to receive chlorambucil or observation. With a median follow-up of 16 years, the median time-to-treatment in the watch and wait arm was 31 months and the actuarial chance of not requiring chemotherapy at 10 years was 19%. Furthermore, an OS comparison between observation and chlorambucil was identical.

On the other hand, is watch and wait still an option for patients with a poor prognosis? Can patients with a poor prognosis be identified early within the disease progression for treatment?

There are several prognostic factors in FL, such as the Follicular Lymphoma International Prognostic Index (FLIPI) score, gene expression profiles (GEP) of IR1 and IR2, and



polymorphism markers. However, reproducibility is still suboptimal, and all of the markers have shown to be relevant to survival on treatment but are not a requirement for treatment. Also, all of the trials included patients with an indication for treatment after an unknown period of the “watch and wait” approach. Thus, there are still no molecular markers predicting requirements for treatment.

Lastly, can watch and wait increase the risk of FL transformation to an aggressive lymphoma? In a study by Horning et al, the investigators retrospectively compared the histologic transformation of FL between the watch and wait period and treatment. The results showed that there was no difference in transformation risk between the 2 groups. Also, in a randomized, prospective study by Al-Tourah et al, the risk of transformation in FL patients who were treated with radiation, chemotherapy, or observation was not different between the 3 treatment groups ($P = 0.3$). In conclusion, in 2009 watchful waiting is still an option because there is no evidence for benefit of immediate treatment or reliable prognostic factors to define early treatment.

Con

C. Buske

Department of Internal Medicine, University of Munich
Munich, Germany

For the treatment of asymptomatic FL patients, the standard of therapy has changed due to the introduction of rituximab. Watch and wait was a strategy during the era of conventional “toxic” chemotherapy where providing “toxic” therapy should not have been an option in asymptomatic patients. However, with the introduction of targeted antibody therapy, the OS has significantly improved, perhaps approaching cure, as demonstrated by Fisher et al and Hiddemann et al. Thus, the benefit of watch and wait is not so clear with availability of therapy like rituximab monotherapy.

Prior to disease progression, can patients with a poor prognosis be identified early for treatment initiation? The answer is that the FLIPI score can be used to differentiate risk groups for treatment. In a study by Buske et al, approximately 1/3 of the patients failed treatment who had high FLIPI scores after R-CHOP therapy. Thus, the FLIPI score can define a high-risk group that can be identified for early treatment. Additionally, GEP in FL predicts survival based on the molecular features of tumor-infiltrating immune cells.

Lastly, can the risk of transformation be delayed by early therapy? Montoto et al demonstrated that high tumor

burden increases the risk of transformation. In addition, this trial showed that low hemoglobin level ($P = 0.03$), high LDH level ($P < 0.0001$), high-risk FLIPI score ($P = 0.01$), and older age ($P = 0.005$) were all associated with increased risk of transformation. With transformation, the median survival was only 1.2 years. Thus, without treatment, the risk of developing high tumor burden is increased; therefore, treatment should be used as a preventative measure.

Bibliography

- Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:5165-5169.
- Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*. 2003;362:516-522.
- Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15:1110-1117.
- Buske C, Hoester E, Dreyling M, et al. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. *Blood*. 2006;108:1504-1508.
- Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med*. 2004;351:2159-2169.
- Fisher RI, LeBlanc M, Press OW, et al. New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol*. 2005;23:8447-8452.
- Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106:3725-3732.
- Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1984;311:1471-1475.

Montoto S, Davies A, Matthews J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol.* 2007;25:2426-2433.

O'Brien ME, Easterbrook P, Powell J, et al. The natural history of low-grade non-Hodgkin's lymphoma and the impact of a no initial treatment policy on survival. *Q J Med.* 1991;80:651-660.

Portlock CS, Rosenberg SA. No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic type. *Ann Intern Med.* 1979;90:10-13.

Young RC, Longo DL, Glatstein E, et al. The treatment of indolent lymphomas: watchful waiting versus aggressive combined modality treatment. *Semin Hematol.* 1988;25:11-16.

Brief Chemoimmunotherapy Rituximab (R)-FND ± R Maintenance is Effective and Safe in Newly Diagnosed Follicular Lymphoma Elderly Patients: An Intergruppo Italiano Linfomi (IIL) Randomized Trial

U. Vitolo
Department of Oncology and Hematology, Azienda Ospedaliera-Universitaria
San Giovanni Battista
Torino, Italy

To maintain efficacy and reduce toxicity in the treatment of elderly patients with FL, a clinical trial with short chemoimmunotherapy was performed. This was a prospective, multicenter, randomized, open-label, phase III clinical trial in patients with untreated advanced-stage FL. The primary objective of the study was to compare the efficacy of rituximab maintenance versus observation in elderly patients (age ≥ 61 years) with advanced-stage FL who were responsive to brief chemoimmunotherapy R-FND (rituximab, fludarabine, mitoxantrone, dexamethasone) plus rituximab maintenance therapy. The secondary objectives included response rates, incorporating molecular response determined by RT-PCR analysis of the BCL-2 gene, OS, and safety. Patients received 4 courses of R-FND (rituximab 375 mg/m² on day 0, fludarabine 25 mg/m² on days 1-3, mitoxantrone 10 mg/m² on day 1, dexamethasone 10 mg/m² on days 1-3) every 28 days/cycle followed by 4 weekly courses of rituximab 375 mg/m². Then, patients experiencing a partial response (PR) or better were randomized to receive rituximab maintenance every 2 months for 4 doses.

A total of 234 patients were eligible for the study, 209 patients were randomized to maintenance or observation. **Table 9** provides information on the baseline characteristics.

Table 9. Baseline Patient Characteristics*

Characteristic	R-FND
Median Age, (range) ≥ 70 years	66 (60-75) years 23%
Grade	
I	36%
II	58%
IIla	6%
Stage	
II	14%
III	21%
IV	65%
B Symptoms	18%
LDH > Normal	18%
Positive Bone Marrow	55%
FLIPI	
Low	11%
Intermediate	34%
High	55%
Concomitant Illness	
0	41%
1	36%
≥ 2	23%

*R-FND indicates rituximab, fludarabine, mitoxantrone, dexamethasone; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index.

The ORR after R-FND was 92%, with a CR of 55% and a PR of 37%. After rituximab maintenance therapy, the ORR was 87%, with a 69% CR and a PR of 18%. Rituximab maintenance therapy was able to convert 41% of the PR patients from R-FND to CR. Additionally, PCR negativity (molecular response) increased from 61% after R-FND to 75% after maintenance therapy. The most common adverse events were hematologic, including neutropenia, anemia, and thrombocytopenia. After a median follow-up of 19 months, 2-year OS and PFS were 93% and 74%, respectively. In conclusion, brief treatment with R-FND with rituximab maintenance was able to achieve a high CR rate and prolonged PFS.



Bibliography

Vitolo U, Ladetto M, Boccomini C, et al. Brief chemoimmunotherapy rituximab (R)-FND ± R maintenance is effective and safe in newly diagnosed follicular lymphoma elderly patients: an Intergruppo Italiano Linfomi (IIL) randomized trial. *Haematologica*. 2009;94(s2). Abstract 1041.

DIFFUSE LARGE B-CELL LYMPHOMA

Developing New Treatments for Diffuse Large B-Cell Lymphoma

M. Shipp
 Dana-Farber Cancer Institute, Harvard Medical School
 Boston, USA

To improve the survival of patients with diffuse large B-cell lymphoma (DLBCL), different chemotherapy agents have been combined and compared in several randomized phase III clinical trials. These studies have demonstrated that OS of different intensive chemotherapy regimens are equivalent and do not impact OS. However, a clinical classification system, the International Prognostic Index (IPI), was developed to identify prognosis based on clinical characteristics (**Table 10**). Unfortunately, the IPI classification system did not provide treatment guidance for patients with a poor prognosis.

Table 10. International Prognostic Index

Risk	Risk Factors	5-Year Survival
Low	0, 1	73%
Low-Intermediate	2	51%
High-Intermediate	3	43%
High	4, 5	26%

Subsequently, with the identification of the molecular B-cell surface antigen CD20, rituximab-based (anti-CD20 antibody) combination regimens showed improved OS in both elderly (GELA Trial) and in young patients (MInt Trial). In addition, studies were conducted to further understand the intrinsic molecular heterogeneity of the disease so that additional targeted agents can be identified.

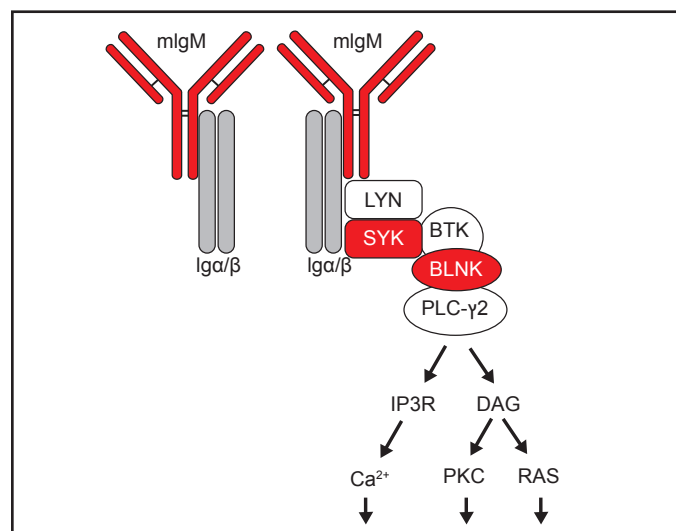
One of the molecular targets identified was a Protein Kinase-C-β (PKCβ) signaling pathway. Immunohistochemistry studies of primary DLBCL have shown that expression of PKCβ correlates with poor prognosis and outcome. PKCβ is a serine/threonine kinase that activates I_k inhibitor kinase (I_kK), the initial step of the pro-survival NF_κB pathway. PKCβ is

also a critical component of the vascular endothelial growth factor (VEGF) signaling pathway. This was an important discovery in that VEGF-mediated tumor angiogenesis has been linked with poor prognosis in DLBCL. To determine clinical efficacy, single-agent enzastaurin, an oral PKCβ inhibitor, was investigated in a phase II multicenter trial in patients with relapsed/refractory DLBCL. Of note, the study demonstrated that a small subset of patients (7%) remained progression-free for up to and over 5 years. Thus, multicenter phase III trials of standard induction therapies with enzastaurin as initial therapy have been initiated.

From transcriptional profiling, several subsets of DLBCL have been identified that suggest a reliance on different pathways for survival. One of the subsets identified for potential target is the BCR subtype. An important factor of the BCR DLBCL subtype was that these tumors had increased expression of multiple B-cell transcription factors, including BCL-6, and increased incidence of BCL-6 translocations. Additionally, BCR DLBCL tumors also exhibited selective coordinate regulation of BCL-6 target genes, and BCR tumors were significantly sensitive to a highly selective BCL-6 peptide inhibitor (BPI), a potential therapeutic target.

Studies have highlighted the role of BCR-mediated survival signals that recruit and activate spleen tyrosine kinase (SYK) and downstream pathways. SYK is a cytoplasmic protein kinase, expressed in most hematopoietic cells, that plays important roles in early B-cell development and mature B-cell function as a downstream mediator of BCR (**Figure 3**). In murine models, tonic BCR signaling or loss of BCR from the cell surface triggered apoptosis of B cells.

Figure 3. B-Cell Receptor (BCR) Signaling Pathway



In recent studies, the role of SYK-dependent tonic BCR survival signals in primary DLBCL and tumor cell lines was evaluated with the competitive SYK inhibitor, R406. The investigators demonstrated that R406 induced apoptosis of BCR-type DLBCL cell lines. Therefore, a phase I/II trial of an oral SYK inhibitor, fostamatinib disodium (FosD), was conducted and results published. The study demonstrated clear evidence of activity in DLBCL and follow-up studies are in the planning stages. In conclusion, several challenges remain in identifying signaling candidates for targeted therapy.

Bibliography

- Chen L, Monti S, Juszczynski P, et al. SYK-dependent tonic B-cell receptor signaling is a rational treatment target in diffuse large B-cell lymphoma. *Blood*. 2008;111:2230-2237.
- Fisher RI, Gaynor ER, Dahlborg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993;328:1002-1006.
- Friedberg JW, Sharman J, Schaefer-Cuttillo J, et al. Fostamatinib disodium (FosD), an oral inhibitor of SYK, is well-tolerated and has significant clinical activity in diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (SLL/CLL). *Blood*. 2008;112: Abstract 3.
- Hans CP, Weisenburger DD, Greiner TC, et al. Expression of PKC-beta or cyclin D2 predicts for inferior survival in diffuse large B-cell lymphoma. *Mod Pathol*. 2005;18:1377-1384.
- Klein U, Dalla-Favera R. Germinal centres: role in B-cell physiology and malignancy. *Nat Rev Immunol*. 2008;8:22-33.
- Kraus M, Alimzhanov MB, Rajewsky N, et al. Survival of resting mature B lymphocytes depends on BCR signaling via the Ig alpha/beta heterodimer. *Cell*. 2004;117:787-800.
- Lam KP, Kuhn R, Rajewsky K. In vivo ablation of surface immunoglobulin on mature B cells inducible gene targeting results in rapid cell death. *Cell*. 1997;60: 1073-1083.
- Monti S, Savage KJ, Kutok JL, et al. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. *Blood*. 2005;105:1851-1861.
- Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomized controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379-391.
- Polo JM, Dell'Oso T, Ranuncolo SM, et al. Specific peptide interference reveals BCL6 transcriptional and oncogenic mechanisms in B-cell lymphoma cells. *Nat Med*. 2004;10:1329-1335.
- Polo JM, Juszczynski P, Monti S, et al. Transcriptional signature with differential expression of BCL6 target genes accurately identifies BCL6-dependent diffuse large B cell lymphomas. *Proc Natl Acad Sci USA*. 2007;104:3207-3212.
- Robertson MJ, Kahl BS, Vose JM, et al. Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2007;25:1741-1746.
- Rueda D, Thome M. Phosphorylation of CARMA1: the link(er) to NK-kappaB activation. *Immunity*. 2005;23:551-553.
- Saijo K, Mecklenbrauker I, Santana A, et al. Protein kinase C beta controls nuclear factor kappaB activation in B cells through selective regulation of the IkappaB kinase alpha. *J Exp Med*. 2002;195:1647-1652.
- Shinohara H, Yasuda T, Aiba Y, et al. PKC beta regulates BCR-mediated IKK activation by facilitating the interaction between TAK1 and CARMA1. *J Exp Med*. 2005;193:1377-1384.
- Sommer K, Guo B, Pomerantz JL, et al. Phosphorylation of the CARMA1 linker controls NK-kappaB activation. *Immunity*. 2005;23:561-574.
- Su TT, Guo B, Kawakami Y, et al. PKC-beta controls I Kappa B kinase lipid raft recruitment and activation in response to BCR signaling. *Nat Immunol*. 2002;3:780-786.
- Suzuma K, Takahara N, Suzuma I, et al. Characterization of protein kinase C beta isoform's action on retinoblastoma protein phosphorylation, vascular endothelial growth factor-induced endothelial cell proliferation, and retinal neovascularization. *Proc Natl Acad Sci USA*. 2002;99:721-726.
- Teicher BA, Menon K, Alvarez E, et al. Antiangiogenic and antitumor effects of a protein kinase C beta inhibitor in murine lewis lung carcinoma and human Calu-6 non-small-cell lung carcinoma xenografts. *Cancer Chemother Pharmacol*. 2001;48:473-480.
- Yoshiji H, Kuriyama S, Ways DK, et al. Protein kinase C lies on the signaling pathway for vascular endothelial growth factor-mediated tumor development and angiogenesis. *Cancer Res*. 1999;59:4413-4418.



Treatment Options for Relapsing Patients

C. Gisselbrecht

Institut d'Hematologie, Hopital Saint Louis

Paris, France

Patients with DLBCL who relapse or fail to achieve primary response have a poor survival outcome. Salvage therapy with high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) is the standard treatment for chemosensitive patients; however, the outcome is poor in the absence of transplantation. For instance, in a long-term follow-up study (LNH98-5 trial) that compared R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) versus CHOP, patients who received CHOP as the first-line therapy who then received a rituximab-containing salvage regimen at relapse achieved significantly longer survival than patients who received chemotherapy alone. However, for patients who received R-CHOP as the first-line therapy, addition of rituximab at relapse did not affect survival compared to chemotherapy alone. Thus, the question still remains regarding the optimal salvage regimen in the post-rituximab era.

To answer this question, a prospective study was conducted by the HOVON group. In the study, patients with relapsed or refractory DLBCL received a salvage regimen of DHAP (cisplatin-cytarabine-dexamethasone)-VIM (etoposide-ifosfamide-methotrexate)-DHAP with or without rituximab, and followed by ASCT. Analysis demonstrated that the rituximab-containing group (75%) had a significantly greater ORR than those receiving chemotherapy alone (54%) ($P \leq 0.01$) after 2 courses of chemotherapy. Also a significant increase in 24 months failure-free survival (FFS) was observed in the rituximab-containing group (50%) compared to the chemotherapy alone group (24%) ($P < 0.001$); however, the OS was not significantly different between the 2 treatment groups.

In a separate trial, the CORAL intergroup study compared R-ICE (ifosfamide, carboplatin, etoposide) and R-DHAP in patients with relapsed/refractory DLBCL. Responding patients received BEAM (carmustine, etoposide, cytarabine, melphalan) and ASCT and were randomized between observation and maintenance with rituximab for 1 year.

Table 11 provides responses to treatment after first-line and salvage therapy for both treatment arms. The study demonstrated that there was no difference in response rates between the 2 salvage treatment arms. The ORR was 63.5% and 62.8% for the R-ICE and R-DHAP treatment arms, respectively. The toxicity profiles were similar between the

2 treatment arms, except R-DHAP patients required more platelet transfusions than the R-ICE group (57% vs 35%, respectively). Significant factors that affected response were as follows: relapse/refractory < 12 months; secondary IPI > 1; and prior rituximab therapy. A significant difference was detected in 3-year EFS between the 2 treatment groups. Similar to response rates, relapse < 12 months, prior rituximab therapy, and IPI 2 to 3 significantly affected 3-year EFS.

Table 11. Treatment Responses*

	After First-Line Treatment		
Response	R-ICE (n = 202)	R-DHAP (n = 194)	All (n = 396)
CR/CRu	65%	64%	65%
PR	20%	19%	20%
	After Salvage Treatment		
	R-ICE (n = 197)	R-DHAP (n = 191)	
ORR	63.5%	62.8%	

*R indicates rituximab; ICE, ifosfamide, carboplatin, etoposide; DHAP, cisplatin-cytarabine-dexamethasone; CR, complete response; CRu, unconfirmed complete response; PR, partial response; ORR, overall response rate.

In conclusion, a new pattern of relapses in refractory patients after rituximab is now observed, and identifying the optimal salvage regimen with rituximab first-line use requires further study.

Bibliography

- Blay J, Gomez F, Sebban C, et al. The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of PARMA trial. *Blood*. 1998;92:3562-3568.
- Cilley J, Winter JN. Radioimmunotherapy and autologous stem cell transplantation for the treatment of B-cell lymphomas. *Haematologica*. 2006;91:114-120.
- Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23:4117-4226.
- Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. *J Clin Oncol*. 2009;27. Abstract 8509.

Guglielmi C, Gomez F, Philip T, et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the PARMA trial. *J Clin Oncol.* 1998;16:3264-3269.

Krishnan A, Nademanee A, Fung HC, et al. Phase II trial of a transplantation regimen of yttrium-90 ibritumomab tiuxetan and high-dose chemotherapy in patients with non-Hodgkin's lymphoma. *J Clin Oncol.* 2008;26:90-95.

Shimoni A, Zwas ST, Oksman Y, et al. Yttrium-90-ibritumomab tiuxetan (Zevalin) combined with high-dose BEAM chemotherapy and autologous stem cell transplantation for chemo-refractory aggressive non-Hodgkin's lymphoma. *Exp Hematol.* 2007;35:534-540.

Shimoni A, Zwass T, Oksman Y, et al. Ibritumomab tiuxetan (Zevalin) followed by high-dose chemotherapy and autologous stem-cell transplantation results in improved survival of patients with chemo-refractory non-Hodgkin's lymphoma expected to have poor outcome with standard pre-transplant conditioning. *Blood.* 2006;108. Abstract 3052.

Vellenga E, van Putten WL, van't Veer MB, et al. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. *Blood.* 2008;111:537-543.

Winter JN, Inwards D, Spies S, et al. 90Y ibritumomab tiuxetan (Zevalin; 90YZ) doses calculated to deliver up to 1500 cGy to critical organs may be safely combined with high-dose BEAM and autotransplant in NHL. *Blood.* 2006;108. Abstract 3807.

MULTIPLE MYELOMA

Experimental Agents Knocking at the Door of Myeloma Treatment

N.C. Munshi

Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School
Boston, USA

Currently approved novel multiple myeloma agents (eg, thalidomide, bortezomib, lenalidomide) target the multiple myeloma bone marrow microenvironment to overcome conventional drug resistance. These agents are effective in the relapsed/refractory setting and are being incorporated in first-line treatment therapy as combinations. Also, studies have investigated using these agents in combination to improve outcome (**Table 12**). As seen in the table, responses are approaching or equal to 100%.

Table 12. Phase I/II Combination Studies*

Efficacy	CRD	VRD	VCRD	VCD/VTD
ORR	85%	100%	100%	96%
≥ nCR	NR	44%	36%	35%
≥ VGPR	32%	74%	68%	56%
Median OS		Not Reached		86% at 12 months

*CRD indicates cyclophosphamide, lenalidomide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone; VCRD, bortezomib, cyclophosphamide, lenalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; ORR, overall response rate; nCR, near complete response; VGPR, very good partial response; OS, overall survival.

Additionally, there are new agents being investigated in clinics. Carfilzomib specifically inhibits the chymotrypsin-like (ChT-L) activity of proteasome, similar to bortezomib; however, carfilzomib is an irreversible inhibitor of the proteasome. Two phase II studies investigated carfilzomib in either relapsed/refractory or relapsed multiple myeloma patients. In the relapsed/refractory study (PX-171-003), patients were required to have had at least 2 prior lines of therapy that must have included bortezomib or thalidomide and/or lenalidomide. The median number of prior therapies was 5. The ORR was 13% and clinical response (≥ minimal response) was 26%, with 5 patients achieving a PR and 5 patients achieving a minimal response. The duration of response (DR) was 8 months. The most common adverse event was hematologic toxicity. However, patients did not experience neuropathy as was seen with bortezomib.

In the relapsed study (PX-171-004), patients were enrolled who had received 1-3 prior lines of therapy. Patients were stratified into bortezomib-naïve, bortezomib-responsive (> 6 months response), and bortezomib-nonresponsive (< 6 months response). The ORR for all patients (N = 31) was 36%, with 10% very good partial response (VGPR), and 26% with a PR. In the bortezomib-naïve patients (n = 13), the ORR was 57%, with 7% CR, 14% VGPR, and 36% PR. In the bortezomib-exposed patients (n = 17), the ORR was 18%, which were all PR. In both studies, no grade 3/4 peripheral neuropathy was detected.

Pomalidomide is a new immunomodulatory drug currently in phase II studies. In comparison to thalidomide, pomalidomide has more potent immune modulation activities, especially in T cell/NK cell costimulation and ADCC activity. A phase II study with pomalidomide + dexamethasone was conducted in patients with relapsed/refractory multiple myeloma to assess efficacy and safety.



The study goals were to investigate responses, DR, OS, PFS, and toxicity. A total of 60 patients were enrolled, with a median age of 65 years (range, 35-88 years). Seventy-two percent of the patients were \geq ISS stage II, and 45% of the patients had neuropathy at baseline. Also, 60% of the patients had treatment with prior immunomodulatory-based therapy and 33% were treated with prior bortezomib.

Panobinostat is a pan-deacetylase inhibitor (pan-DACi) that interferes with epigenetic and nonepigenetic pathways in cancer. This was a phase Ib trial investigating panobinostat + bortezomib in relapsed/refractory multiple myeloma patients. The most common adverse event was hematologic toxicity. Of the 14 evaluable patients, 1 achieved an immunofixation negative CR, 1 VGPR, and 3 PR. Two of the PR patients had been refractory to previous bortezomib therapy. In conclusion, preliminary results suggest panobinostat + bortezomib combination is safe and showed encouraging efficacy.

Another combination under investigation is based on the preclinical model of perifosine, an Akt inhibitor. Since Akt is an antiapoptotic protein, its inhibition by perifosine and caspase-9 activation by bortezomib induces synergistic cell death. Phase I/II studies have demonstrated efficacy and safety, and phase III studies are ongoing comparing perifosine + bortezomib versus bortezomib alone.

Lastly, gene expression profiling studies are likely to identify targets of drug sensitivity versus resistance and provide treatment guidance to tailor therapy for patients. For instance, microRNA expression profiles can identify distinct subgroups with different survival outcome. In conclusion, the goal of multiple myeloma treatments has continued to progress from simple palliation to improvement in survival.

Bibliography

- Bensinger W, Jagannath S, Vescio R, et al. A phase II study of bortezomib (Velcade), cyclophosphamide (Cytosan), thalidomide (Thalomid) and dexamethasone as first-line therapy for multiple myeloma. *Blood*. 2008;112. Abstract 94.
- Chauhan D, Catley L, Li G, et al. A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from bortezomib. *Cancer Cell*. 2005;8:407-419.
- Chauhan D, Li G, Hideshima T, et al. Heat shock protein-27 confers drug resistance in multiple myeloma cells. *Blood*. 2003;102:3379-3386.
- Chauhan D, Li G, Hideshima T, et al. Hsp27 overcomes bortezomib/proteasome inhibitor PS-341 resistance in lymphoma cells. *Cancer Res*. 2003;63:7174-6177.
- Davies FE, Dring A, Cheng L, et al. Insights into the multistep transformation of MGUS to myeloma using microarray expression analysis. *Blood*. 2003;102:4504-4511.
- Hideshima T, Catley L, Yasui H, et al. Perifosine, an oral bioactive novel alkylphospholipid, inhibits Akt and induces in vitro and in vivo cytotoxicity in human multiple myeloma cells. *Blood*. 2006;107:4053-4062.
- Hideshima T, Podar K, Chauhan D, et al. p38MAPK inhibition enhances PS-341 (bortezomib)-induced cytotoxicity against multiple myeloma cells. *Oncogene*. 2004;23:8766-8776.
- Jagannath S, Vij S, Stewart G, et al. Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM). *J Clin Oncol*. 2009;27. Abstract 8504.
- Kumar S, Hayman S, Buadi F, et al. Phase II trial of lenalidomide (Revlimid) with cyclophosphamide and dexamethasone (RCd) for newly diagnosed myeloma. *Blood*. 2008;112. Abstract 91.
- Kumar S, Flinn IW, Noga S, et al. Safety and efficacy of novel combination therapy with bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in newly diagnosed multiple myeloma: initial results from the phase I/II multi-center EVOLUTION study. *Blood*. 2008;112. Abstract 93.
- Lacy M, Hayman S, Gertz M, et al. Pomalidomide (CC4047) plus low-dose dexamethasone (pom/dex) is highly effective therapy in relapsed multiple myeloma. *Blood*. 2008;112. Abstract 866.
- Richardson P, Lonial S, Jakubowiak A, et al. Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: encouraging efficacy in high risk groups with updated results of a phase I/II study. *Blood*. 2008;112. Abstract 92.
- Richardson P, Wolf J, Jakubowiak A, et al. Phase I/II results of a multicenter trial of perifosine (KRX-0401) + bortezomib in patients with relapsed or relapsed/refractory multiple myeloma who were previously relapsed from or refractory to bortezomib. *Blood*. 2008;112. Abstract 870.
- Vij R, Wang M, Orłowski R, et al. PX-171-004, a multicenter phase II study of carfilzomib (CFZ) in patients with relapsed myeloma: an efficacy update. *J Clin Oncol*. 2009;27. Abstract 8537.
- Weber D, Badros A, Jagannath S, et al. Vorinostat plus bortezomib for the treatment of relapsed/refractory multiple myeloma: early clinical experience. *Blood*. 2008;112. Abstract 871.

Treatment Options for Myeloma in 2009

J. Blade

Hematology and Oncology Institute, University of Barcelona
Barcelona, Spain

The introduction of high-dose therapy followed by ASCT and the incorporation of novel agents has resulted in higher antimyeloma effect and prolonged survival outcome. For young patients, ASCT as part of first-line therapy is the gold standard. Induction therapy with novel agents (ie, thalidomide/dexamethasone) has replaced traditional therapy. **Table 13** provides the CR rate with novel agents pre- and post-ASCT.

Table 13. Complete Response Rate With Novel Induction Regimen in ASCT*

Regimen	Pre-ASCT	Post-ASCT
Thalidomide/Dexamethasone	6%	23-34%
Bortezomib/Dexamethasone	12%	33%
PAD-1	24%	43%
VTD	21-30%	43-49%
Total Therapy III	NR	56% at 2 years

*ASCT indicates autologous stem-cell transplantation; PAD-1, bortezomib, adriamycin, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

Regarding the question of single versus tandem ASCT, 5 prospective randomized studies have been conducted. Several studies have demonstrated superiority with tandem ASCT, with an improved CR rate and improved EFS and OS. However, a recent study demonstrated that single ASCT followed by thalidomide maintenance is superior to tandem ASCT for both relapse rate and OS (**Table 14**).

Table 14. A Summary Single vs Tandem ASCT Clinical Trials

Trial	N	Response (%)	EFS (mo)	OS (mo)
Attal et al	399	42 vs 50	25 vs 30 ($P = 0.03$)	48 vs 58 ($P = 0.01$)
Cavo et al	321	33 vs 47 ($P = 0.008$)	23 vs 35 ($P = 0.001$)	65 vs 71
Sonneveld et al	303	13 vs 32 ($P < 0.001$)	24 vs 27 ($P = 0.006$)	50 vs 55
Ferland et al	227	37 vs 39	31 vs 34	57 vs 73
Abdelkefi et al	202	68 vs 54 ($P = 0.04$)	85 vs 57 ($P = 0.02$)	85 vs 65 ($P = 0.04$)

*ASCT indicates autologous stem-cell transplantation; EFS, event-free survival; OS, overall survival.

For patients who were not eligible for transplantation, the addition of novel agents has improved response rates.

Table 15 provides a summary of results from these studies. For instance, the French IFM study 01-01 demonstrated a superior median OS advantage with MPT treatment (45.3 months) versus MP (27.7 months) ($P = 0.033$). Additionally, the VISTA trial demonstrated superior 3-year OS with VMP compared to MP (72% vs 59%, respectively; $P = 0.0032$).

Table 15. A Summary of Front-Line Trials, Not Eligible for SCT*

Trial	Regimen	ORR (%)	CR (%)	EFS	OS
Rajkumar et al	Thal/Dex vs Dex	63 vs 46	7.7 vs 2.6	22.6 vs 6.5 months	29 mo vs NR
Facon et al	MPT vs MP	76 vs 35	13 vs 2	HR 0.56 (MPT favor)	51.6 vs 33.2 months
Hulin et al	MPT vs MP	62 vs 31	7 vs 1	24.1 vs 19 mo	45.3 vs 27.7 months
Palumbo et al	MPT vs MP	76 vs 47	15.5 vs 2.4	54 vs 27% at 2 years	80 vs 64% at 3 years
San Miguel et al	MPV vs MP	71 vs 36	30 vs 4	24 vs 16.6 months	82.6 vs 69.5% at 2 years
Palumbo et al	MPR	81	24	92% at 1 year	100% at 1 year
Ludwig et al	Thal/Dex vs MP	68 vs 51	14 vs 7	43 vs 25 months	58 vs 45 months
Rajkumar et al	Len/Dex vs Len/dex	82 vs 70	-	87 vs 75% at 2 years	-

*SCT indicates stem-cell transplantation; Thal or T, thalidomide; Dex, dexamethasone; M, melphalan; P, prednisone; V, bortezomib; NR, not reached.

For relapsed/refractory multiple myeloma patients, treatment decisions should include the following considerations: 1. components of initial therapy; 2. degree or duration of response to primary therapy; and 3. the possibility of high-dose therapy followed by ASCT in chemosensitive relapse patients. Additional considerations include the type of relapse, previous toxicity, age, and performance status. Similar to what has been seen in first-line therapy, the addition of novel agents has significantly improved outcome for relapsed/refractory patients (**Table 16**).



Table 16. A Summary of Relapsed/Refractory Trials*

Trial	Regimen	ORR (%)	CR (%)	EFS	OS
Richardson et al	Bort vs Dex	38 vs 18	6 vs 1	6.2 vs 3.5 months	80 vs 66% at 1 year
Orlowski et al	Bort + Doxil vs Bort	44 vs 41	4 vs 2	9.3 vs 6.5 months	76 vs 65% at 15 months
Weber et al	Len/Dex vs Dex	61 vs 19.9	14.1 vs 0.6	11.1 vs 4.7 months	29.6 vs 20.2 months
Dimopoulos et al	Len/Dex vs Dex	60.2 vs 24	15.9 vs 3.4	11.3 vs 4.7 months	NR vs 20.6 months

*Bort indicates bortezomib; Dex, dexamethasone; Len, lenalidomide; NR, not reached.

Bibliography

Abdelkefi A, Ladeb S, Torjman L, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. *Blood*. 2008;111:1805-1810.

Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem cell transplantation for multiple myeloma. *N Engl J Med*. 2003;49:2495-2502.

Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous transplantation for multiple myeloma. *J Clin Oncol*. 2007;25:2434-2441.

Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.

Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma. *Lancet*. 2007;370:1209-1218.

Fernand JP. High-dose therapy supported with autologous blood stem cell transplantation in multiple myeloma: long-term follow-up of prospective studies of the MAG group. *Haematologica*. 2005;90. Abstract 40.

Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma. *Haematologica*. 2006;91:1498-1506.

Hulin C, Tacon T, Rodon P, et al. Comparison of melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients > 75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized double-blind, placebo controlled trial, IFM 01-01. *Blood*. 2007;110. Abstract 75.

Ludwig H, Tothova E, Hajek R, et al. Thalidomide-dexamethasone compared to melphalan-prednisone in elderly patients with multiple myeloma. *Blood*. 2009;113:3435-3442.

Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. *Br J Haematol*. 2005;129:755-762.

Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol*. 2007;25:3892-3901.

Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood*. 2008;112:3107-3114.

Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA-Italian Multiple Myeloma Network. *J Clin Oncol*. 2007;25:4459-4465.

Popat R, Oakervee HE, Curry N, et al. Long-term follow-up of PAD for untreated multiple myeloma. *Haematologica*. 2007;97. Abstract 725.

Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Group. *J Clin Oncol.* 2006;24:431-436.

Rajkumar SV, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2008;26. Abstract 8504.

Rajkumar SV, Rosinol L, Hussein M, et al. A multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone versus dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol.* 2008;26:2171-2177.

Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood.* 2007;110:3557-3560.

Rosinol L, Cibeira MT, Martinez J, et al. Thalidomide/dexamethasone (TD) vs. bortezomib (Velcade)/thalidomide/dexamethasone (VTD) vs. VBMCP/VBAD/Velcade as induction regimen prior autologous stem cell transplantation (ASCT) in younger patients with multiple myeloma (MM): first results of a prospective phase III PETHEMA/GEM trial. *Blood.* 2008;112. Abstract 244.

Rosinol L, Oriol A, Mateos MV, et al. A phase II trial of alternating bortezomib and dexamethasone as induction regimen prior autologous stem cell transplantation in younger patients with multiple myeloma: efficacy and clinical implications of tumour response kinetics. *J Clin Oncol.* 2007;25:4452-4458.

San Miguel JF, Schlag R, Khuageva N, et al. A phase 3 study comparing bortezomib-melphalan-prednisone (VMP) with melphalan-prednisone (MP) in newly diagnosed multiple myeloma. *Blood.* 2007;110. Abstract 76.

Sonneveld P, van der Holt B, Segeren CM, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON24 trial. *Haematologica.* 2007;92:928-935.

Weber D, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007;357:2133-2142.

CHRONIC MYELOGENOUS LEUKEMIA

Nilotinib 800 mg Daily in Early Chronic Phase Chronic Myeloid Leukemia: 12 Months Results of a Phase II Trial of the GIMEMA CML Working Party

G. Rosti

Department of Hematology and Oncological, Bologna
Bologna, Italy

Imatinib 400 mg daily is a standard treatment for CML in the early chronic phase. Despite the successes observed with imatinib-based therapy, a small cohort of patients fails to obtain a stable complete cytogenetic response (CCyR). Therefore, continued investigation into treatment alternatives is necessary. The aim of this study was to investigate the safety and the efficacy of nilotinib 400 mg twice daily (BID) in CML. This was an open-label, single-stage, multicenter, phase II trial in patients with early chronic phase, Ph+ CML. A total of 73 patients were enrolled in the study, with a median (range) age of 51 years (18-83). Thirty-six percent of the patients were ≥ 60 years of age, and 14% had high Sokal risk score.

The mean daily nilotinib dose was 784 mg (280-800 mg) with dose interruption occurring in 52% of the patients. The cumulative CCyR rate within 12 months was 100%, and a major molecular response (MMR), defined as a BCR-ABL:ABL ratio $\leq 0.1\%$ at 12 months was 77% (**Table 17**).

Table 17. Response to Treatment (N = 73)

	3 months	6 months	12 months
Major Molecular Response	52%	66%	85%
Complete Hematologic Response	100%	99%	97%
Cytogenetic Response			
Complete	78%	96%	96%
Partial	7%	3%	1%

The most common adverse events were skin rash (42%), bone/muscle/joint pain (41%), and headache (30%). Within 3 months, neutropenia and thrombocytopenia (\geq grade 2) were observed in 14% and 4%, respectively. In conclusion, the trial supports the hypothesis that in early chronic phase, Ph+ CML patients, the response to nilotinib is achieved early.



Bibliography

Rosti G, Castagnetti F, Breccia M, et al. Nilotinib 800 mg daily in early chronic phase chronic myeloid leukemia: 12-months results of a phase 2 trial of the GIMEMA CML Working Party. *Haematologica*. 2009;94(s2). Abstract 1090.

Dasatinib 100 mg Once Daily for Chronic Phase Chronic Myeloid Leukemia (CML-CP) Following Imatinib Failure: Long-Term Follow-Up From Study CA180-034

A. Hochhaus

Universitätsmedizin Mannheim, Universität Heidelberg Mannheim, Germany

Previous results from the CA180-034 phase III dose-optimization study have demonstrated that dasatinib 100 mg once daily (QD) maintains efficacy while significantly minimizing toxicity. Despite dasatinib's short half-life (3.6 hours), its high potency may allow intermittent BCR-ABL inhibition to result in clinical efficacy. Additionally, recent data suggest that the cytogenetic response to a second-line tyrosine-kinase inhibitor at 12 months is predictive of long-term survival. Thus, the objective of this study was to evaluate the long-term efficacy and safety of dasatinib 100 mg QD in patients with chronic phase CML following resistance, suboptimal response, or intolerance to imatinib.

Patients were randomized using a 2 x 2 factorial design to 1 of 4 treatment arms: 100 mg QD (n = 167), 70 mg BID (n = 168), 140 mg QD (n = 167), or 50 mg BID (n = 168). Response rates are shown on **Table 18**.

Table 18. Dasatinib Response Rates at Last Assessment*

Response	100 mg QD	70 mg BID	140 mg QD	50 mg BID
CHR [†]	92%	88%	87%	92%
MCyR	63%	61%	63%	61%
CCyR [†]	50%	53%	50%	49%
MMR [‡]	39%	40%	40%	40%

*QD indicates once daily; BID, twice daily; CHR, complete hematologic response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response.

[†]CHR and CCyR were last assessed at 24 months per protocol.

[‡]MMR was last assessed at 30 months.

For the dasatinib 100 mg QD treatment group, CCyR in all patients previously exposed to imatinib at 6, 12, and 24 months was 39%, 45%, and 50%, respectively. For patients who experienced resistance or suboptimal response to imatinib, CCyR at 6, 12, and 24 months was 34%, 40%, and 45%, respectively. For the 100 mg QD group, 3-year PFS was 73% (**Table 19**).

Table 19. Progression-Free and Overall Survival by Treatment Groups*

	100 mg QD (n = 167)	70 mg BID (n = 168)	140 mg QD (n = 167)	50 mg BID (n = 168)
PFS				
12 month	91%	87%	87%	86%
24 month	81%	76%	75%	76%
36 month	73%	67%	60%	72%
OS				
12 month	96%	94%	96%	96%
24 month	91%	88%	94%	91%
36 month	87%	80%	84%	84%

*QD indicates once daily; BID, twice daily; PFS, progression-free survival; OS, overall survival.

The landmark analysis of PFS according to response at 12 months is shown on **Table 20**.

Table 20. Landmark Analysis of PFS at 12 Months*

	Estimated PFS at 36 months	95% CI
MMR	94%	89-98%
CCyR	88%	78-98%
PCyR	81%	71-91%
Other CyR	54%	43-64%

*PFS indicates progression-free survival; MMR, major molecular response; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response.

Compared to other treatment arms, the dasatinib 100 mg QD group experienced the lowest rates of drug-related pleural effusion and cytopenias. Additionally, the 100 mg QD group had the lowest treatment interruption, reduction, and discontinuation rates. In conclusion, response to dasatinib 100 mg QD at 12 months was predictive for PFS at 36 months.

Bibliography

Christopher LJ, Cui D, Wu C, et al. Metabolism and disposition of dasatinib after oral administration to humans. *Drug Metab Dispos*. 2008;36:1357-1364.

Hochhaus A, Kim DW, Kantarjian HM, et al. Dasatinib 100 mg once daily for chronic phase chronic myeloid leukemia (CML-CP) following imatinib failure: long-term follow-up from study CA180-034. *Haematologica*. 2009;94(s2). Abstract 1091.

Martinelli G, Soverini S, Iacobucci I, et al. Intermittent targeting as a tool to minimize toxicity of tyrosine kinase inhibitor therapy. *Nat Clin Pract Oncol*. 2009;6:68-69.

O'Hare T, Walter DK, Stoffregen E, et al. In vitro activity of BCR-ABL inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant ABL kinase domain mutants. *Cancer Res.* 2005;65:4500-4505.

Shah NP, Kantarjian H, Kim DW, et al. Intermittent target inhibition with dasatinib (100 mg once daily) preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol.* 2008;26:3204-3212.

Shah NP, Kasap C, Weier C, et al. Transient potent BCR-ABL inhibition is sufficient to commit chronic myeloid leukemia cells irreversibly to apoptosis. *Cancer Cell.* 2008;14:485-493.

Tam CS, Kantarjian H, Garcia-Manero G, et al. Failure to achieve a major cytogenetic response by 12 months defines inadequate response in patients receiving nilotinib or dasatinib as second or subsequent line therapy for chronic myeloid leukemia. *Blood.* 2008;112:516-518.

Molecular Responses of the SPIRIT Phase III Trial of the French CML Group Comparing Imatinib (IM) 400 mg to Higher Dose Imatinib or Combination With Interferon or Cytarabine for the Treatment of Newly Diagnosed Chronic Phase (CP) Chronic Myeloid Leukaemia (CML) Patients (Pts)

P. Rousselot

Centre Hospitalier de Versailles
Versailles, France

This was a prospective, randomized, multicenter, open-label, phase III trial comparing standard imatinib 400 mg daily (n = 187) to imatinib 600 mg daily (n = 171), imatinib 400 mg daily plus cytarabine (Ara-C) (subcutaneous) 20 mg/m²/d (n = 165), or imatinib 400 mg daily plus pegylated interferon-2α (Peg) (n = 170). As of May 2009, a total of 681 patients with a median age of 50 years (18-79 years) were enrolled. At 42 months, EFS for imatinib 400 mg, imatinib 600 mg, imatinib + Ara-C, and imatinib + Peg was 93%, 93%, 92%, and 93%, respectively. MMR, defined as BCR-ABL:ABL ≤ 0.1%, with at least 18 months of follow-up was 45%, 58%, 59%, and 68%, respectively. A significant difference was detected in MMR between the imatinib 400 mg group and the imatinib + Peg group (P = 0.0001) (**Table 21**).

Table 21. Response by Treatment Groups*

Response	IM 400 mg (n = 167)	IM 600 mg (n = 171)	IM + Ara-C (n = 185)	IM + Peg (n = 170)
MMR	41%	52%	53%	62% [†]
OMR	19%	25%	19%	36% [‡]
CMR	4%	7%	5%	15% [§]

*IM indicates imatinib; Ara-C, cytarabine; Peg, pegylated interferon-2α; MMR, major molecular response; OMR, optimal molecular response; CMR, complete molecular response.

[†]P = 0.001; IM 400 vs IM + Peg.

[‡]P < 0.001; IM 400 vs IM + Peg.

[§]P = 0.0013; IM 400 vs IM + Peg.

In conclusion, the superiority of the imatinib + Peg treatment was confirmed, with a complete molecular response (CMR) of 15% at 18 months. Currently, the optimal dose and schedule of Peg is being investigated.

Bibliography

Rousselot P, Preudhomme C, Guilhot J, et al. Molecular responses of the SPIRIT phase III trial of the French CML Group comparing imatinib (IM) 400 mg to higher dose imatinib or combination with interferon or cytarabine for the treatment of newly diagnosed chronic phase (CP) chronic myeloid leukaemia (CML) patients (pts). *Haematologica.* 2009;94(s2). Abstract 1093.

Early Molecular Response to First-Line Imatinib Therapy is Predictive for Long-Term PFS and EFS in CP-CML—An Interim Analysis of the Randomized German CML Study IV

M. Muller

Universitaetsmedizin Mannheim
Mannheim, Germany

Despite favorable hematologic and cytogenetic response data, patients on first-line imatinib therapy may relapse. Thus, the aim of this study (CML Study IV) is to evaluate the predictive impact of early molecular response for long-term PFS and EFS. This was a prospective, randomized, multicenter trial in patients with chronic phase CML. Patients were recruited from July 2002 to December 2005. Patients received either standard imatinib dose (400 mg/day), imatinib 800 mg/day, or combination with low-dose Ara-C or interferon-α. A total of 710 patients with a median age of 54 years (16-84 years) was enrolled. The results are presented from a planned interim analysis. The estimated 5-year PFS in patients achieving a molecular response of 10% BCR-ABL¹⁵ after 3 months was 93% versus 86% in patients not achieving a response (P = 0.053). To help



improve the comparability of results, an international scale (IS) has been established recently which is anchored to 2 key points defined in the IRIS trial: a common baseline (100% BCR-ABL¹⁵) and major molecular response (0.1% BCR-ABL¹⁵). Definition of the IS currently relies on relating results directly or indirectly to the Adelaide international reference laboratory. A more robust definition of the IS requires the development of internationally accredited reference reagents. Additional data are presented in **Table 22**.

Table 22. Predictive Impact of Molecular Response*

	Estimated 5-year PFS		Estimated 5-year EFS	
	Yes	No	Yes	No
10% BCR-ABL ¹⁵ after 3 months	93%	86%	88%	71%
	$(P = 0.053)$		$(P = 0.013)$	
1% BCR-ABL ¹⁵ after 12 months	96%	87%	94%	66%
	$(P = 0.011)$		$(P = 0.0001)$	
1% BCR-ABL ¹⁵ after 18 months	96%	85%	96%	76%
	$(P = 0.0045)$		$(P = 0.0002)$	
0.1% BCR-ABL ¹⁵ after 18 months	96%	96%	95%	88%
	$(P = 0.9)$		$(P = 0.22)$	

*PFS indicates progression-free survival; EFS, event-free survival.

In conclusion, prospective molecular surveillance of CML shows that early response predicts stable remissions on first-line imatinib therapy. After 3 months of treatment, PCR data starts to be predictive for PFS and EFS.

Bibliography

Muller MC, Hanfstein B, Erben P, et al. Early molecular response to first line imatinib therapy is predictive for long term PFS and EFS in CP-CML—an interim analysis of the randomized German CML Study IV. *Haematologica*. 2009;94(s2). Abstract 1094.

ACUTE MYELOGENOUS LEUKEMIA

Clinical Trial Update in Elderly Patients—MRC

R. Hills

University of Wales College of Medicine
Cardiff, United Kingdom

The speaker began with a general description of the acute myelogenous leukemia (AML)16 trial, indicating that this trial is an intensive treatment for patients to improve initial response, to determine the optimal number of courses, to investigate the role of reduced-intensity chemotherapy transplant, and to evaluate maintenance with demethylation therapy. For the intensive therapy, patients were randomized to either standard daunorubicin + Ara-C x 2 courses or daunorubicin + clofarabine x 2 courses. With a response of PR or better after course 1, patients were randomized again to receive 1 course of daunorubicin + Ara-C or observation. Then, if mini-allograft was not planned, patients were further randomized to receive azacitidine maintenance or observation. The expected target is 800 patients and as of June 2009, a total of 777 patients were enrolled. Preliminary results showed the ORR of 65%, with 75% in de novo AML, 49% in secondary AML, and 70% in myelodysplastic syndrome (MDS) patients.

For patients who were not candidates for intensive treatment, the AML14 trial demonstrated that low-dose Ara-C is a standard therapy. Thus, AML16 will investigate new agents against the standard low-dose Ara-C for non-intensive treatment.

Clinical Trial Update in Elderly Patients—HOVON-SAKK

G. Ossenkoppele

VU University Medical Center
Amsterdam, The Netherlands

The HOVON-SAKK AML43 trial is a dose-intensity trial in patients ≥ 61 years comparing daunorubicin 45 mg/m² + Ara-C (DNR-45) or daunorubicin 90 mg/m² + Ara-C (DNR-90) in cycle 1 with Ara-C alone in cycle 2 for both treatment arms. In postinduction, patients can be additionally randomized to receive gemtuzumab ozogamicin or observation.

A total of 813 patients have been enrolled and preliminary baseline characteristics are provided in **Table 23**.

Table 23. Baseline Patient Characteristics*

Characteristic	DNR-45 (n = 411)	DNR-90 (n = 402)
Median Age, (range)	67 (60-79) years	67 (60-83) years
≤ 65 years	36%	37%
66-70 years	38%	36%
> 70 years	26%	27%
White Blood Cell		
≤ 20	66%	68%
20-100	25%	24%
> 100	9%	8%

*DNR-45 indicates daunorubicin 45 mg/m² + cytarabine; DNR-90, daunorubicin 90 mg/m² + cytarabine.

The preliminary CR rate in the DNR-45 treatment group was 54% after induction, with 35% and 19% after cycle 1 and cycle 2, respectively. In the DNR-90 group, the CR rate was 64%, with 52% after cycle 1 and 13% after cycle 2. The adverse events in both arms so far are similar and unremarkable. Additionally, preliminary results showed that with postinduction therapy, there was not a difference in OS and DFS between the gemtuzumab treatment and observation arms.

Clinical Trial Update in Elderly Patients–EORTC-GIMEMA

*S. Amadori
Tor Vergata University Hospital
Rome, Italy*

Current ongoing trials by EORTC/GIMEMA include the following:

- Untreated AML (intensive therapy)
 - AML17-phase III (completed)
 - AML1208-phase I (in preparation)
- Untreated AML (non-intensive therapy)
 - AML19-phase II/III (phase II completed and phase III ongoing)
- Advanced AML
 - AML1107-phase II (ongoing)

AML17 is a randomized, open-label, multicenter, phase III trial comparing gemtuzumab plus standard chemotherapy versus standard chemotherapy alone in patients between 61-75 years of age. The primary endpoint was OS and is undergoing final analysis with completion of accrual.

AML1208 is a phase I, multicenter trial investigating the combination of RAD001 (mTOR inhibitor) with MICE induction and mini-ICE consolidation therapy in elderly AML patients.

AML19 is a sequential phase II/III trial with single-agent gemtuzumab ozogamicin. The phase II trial has been completed and phase III trial is still recruiting patients. For the phase II trial, a total of 56 patients were enrolled and received either gemtuzumab on days 1 and 8 (GO 1-8) or gemtuzumab on days 1, 3, and 5 (GO 1-3-5). The ORR in the GO 1-8 treatment arm was 22% and in the GO 1-3-5 treatment arm was 24%. Infection (52% GO 1-8; 31% GO 1-3-5) and febrile neutropenia (11% GO 1-8; 31% GO 1-3-5) were the most common adverse events seen in both treatment arms.



**Click here to take
the *post-test***