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Highlights from the 10th International Conference on Malignant Lymphoma: A Review of Selected Presentations

June 4–7, 2008
Lugano, Switzerland

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Faculty
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Highlights from the 10th International Conference on Malignant Lymphoma

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Large-cell Lymphoma

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is becoming a standard part of the diagnosis, staging, surveillance, and prognosis of malignant lymphomas. However, many unanswered questions preclude FDG-PET from being commonly used in lymphoma management. Issues such as universal availability, equipment variation, standardization of interpretation, and potential differences among treatment protocols comprise the basis of uncertainty surrounding this technology. Sehn and associates from the British Columbia Cancer Agency (BCCA), Vancouver, Canada, presented two studies that support the use of FDG-PET during therapy to drive risk-adapted treatment algorithms. The first was in patients with limited-stage diffuse large B-cell lymphoma (DLBCL)[1] and the second in those with advanced-stage aggressive non-Hodgkin lymphoma (NHL).[2] In 2005, BCCA recommended that all patients with limited-stage DLBCL undergo FDG-PET scanning following three cycles of standard every-3-week cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP). The objective of this recommendation was to identify chemosensitive patients, regardless of clinical risk factors, who could be treated with chemotherapy alone. A retrospective analysis of the initial 65 prospective patients identified in the BCCA Lymphoid Cancer Database was undertaken to assess outcome of patients with limited-stage DLBCL treated according to the FDG-PET–based algorithm. Patients were at least 16 years of age, with newly diagnosed, biopsy-proven DLBCL showing limited-stage disease (stage I/II, <10 cm, no B symptoms, encompassable in a single radiation field). FDG-PET was performed following three cycles of R-CHOP. All scans were performed at a single center and reviewed according to NHL International Harmonization Project guidelines.[3] FDG-PET–negative patients were offered one additional cycle of R-CHOP, whereas FDG-PET–positive patients receive involved-field radiation therapy (IFRT). Median follow-up was 17 months (range, 3–30). After three cycles of R-CHOP, 49 patients (75%) were FDG-PET–negative and 16 patients (25%) were FDG-PET–positive. No clinical factors predicted FDG-PET status. Of the 49 FDG-PET–negative patients, 47 completed treatment with one additional cycle of chemotherapy, 1 received IFRT due to poor chemotherapy tolerance, and 1 died of toxicity before receiving any more treatment. Only 1 of 49 FDG-PET–negative patients relapsed but the patient was still alive with disease after salvage therapy. All 16 FDG-PET–positive patients received IFRT. There were three relapses, all of which were outside the radiation field, and there were two deaths from lymphoma. The 2-year estimated progression-free survival (PFS) was 93% overall (97% and 83% for FDG-PET–negative and FDG-PET–positive patients, respectively, P=.04). The 2-year overall survival (OS) was 97% for FDG-PET–negative and 76% for FDG-PET–positive patients (P=.12). The conclusion is that four cycles of R-CHOP are suffi-

cient therapy for patients with limited-stage DLBCL who are FDG-PET–negative after three cycles and they can be spared additional radiation. Although, in general, the FDG-PET–negative patients had superior PFS and OS than those who were –positive, longer follow-up is needed to determine any long-term differences.

A second retrospective analysis followed 120 patients identified in the BCCA Cancer Lymphoid Database with newly diagnosed, advanced stage, aggressive NHL treated with R-CHOP. FDG-PET was performed at least 3 weeks following completion of therapy. Those with a residual mass at least 2 cm on computed tomography (CT) were radiated if positive on FDG-PET. Radiation was not given to those who were FDG-PET–negative. A third cohort of patients was FDG-PET–positive but did not receive radiation. Patients with residual abnormalities on CT greater than or equal to 2 cm in diameter who received consolidation radiation to sites of FDG-PET positivity appeared to have an outcome similar to patients with a negative posttherapy FDG-PET. The 2-year PFS was similar for FDG-PET–positive patients who received radiation therapy (87%) and FDG-PET–negative patients (81%), and was significantly better than FDG-PET–positive patients who did not receive radiation therapy (40%; $P<.001$). These data suggested that radiation might benefit select patients who are FDG-PET–positive.

Follicular Lymphoma

143 A Phase II Trial of Extended Induction Galiximab Plus Rituximab in Previously Untreated Follicular Lymphoma: Initial Report of CALGB 50402

Galiximab is a primatized immunoglobulin G1 monoclonal antibody hypothesized to induce antibody-dependent cellular cytotoxicity (ADCC) in malignant B cells in NHL following binding to CD80, a transmembrane glycoprotein transiently expressed on activated B cells and antigen-presenting cells[4] and involved in activation and regulation of T cells.[5] A phase I/II single-agent study in relapsed/refractory follicular NHL demonstrated that galiximab is well-tolerated; the most common drug-related adverse effects were grade 1/2 fatigue, nausea, headache (10–30% of patients) and grade 3 axillary pain in 1 patient (3%).[6] The maximum tolerated dose (MTD) was not achieved at tested doses (125, 250, 375, or 500 mg/m^2/week 3 4 [4 doses total]). Tumor burden was reduced in 49% of the patients on this study, and an overall response (OR) rate of 11% (4/37 patients) was reported with two complete responses (CR) and one partial response (PR) at a dose of 375 mg/m^2 (n=21) and one PR at 500 mg/m^2 (n=10). Event-free survival (EFS) for responders was reported up to 31 months. In a second phase I/II trial of galiximab and rituximab in relapsed follicular lymphoma (FL) reported by Leonard and colleagues,[7] an OR rate of 66% (19% CR, 14% unconfirmed complete response [CRu], 33% PR) was noted at a dose of 500 mg/m^2. In this study, patients were a median of 61 years old; 88% had stage III–IV and 23% had favorable Follicular Lymphoma International Prognostic Index (FLIPI) risk disease, 41% favorable intermediate—41% and 36% poor-risk disease, and 40% were rituximab-naive. The median duration of response was 12.4 months and the median time to progression (TTP) was 12.2 months.

The Cancer and Leukemia Group B (CALGB) Lymphoma Committee initiated a program to study a series of targeted doublets in previously untreated patients with follicular NHL and low to intermediate FLIPI risk. The first of these doublets was rituximab and galiximab. The goal of the study, reported at the 10th annual International Conference on Malignant Lymphoma (ICML), was to determine the OR and CR rate and TTP after upfront combination therapy of galiximab plus rituximab. Secondary objectives were safety and to study the associations between OR, CR, and TTP with respect to Fc receptor receptor polymorphism status. Patients were previously untreated, FL grade 1, 2, or 3a (World Health Organization [WHO] classification) without known histologic transformation, with stage III, IV, or bulky stage II and CD20-positive disease. Induction therapy was given as four weekly infusions of rituximab and galiximab, with extended induction every other month for four additional infusions.

On this well-tolerated regimen; the most frequent adverse events were fatigue, pain, cytokine release/allergy, rash, transient hypotension, and chills, with only three cases of grade 2 infections.

Table 1. Association of FLIPI With ORR and CR Rate with Galiximab And Rituximab In Patients With Previously Untreated Follicular Lymphoma

FLIPI Score	ORR (*P*=.0059)	CR (*P*=.03)
0–1	11 (92%)	9 (75%)
2	20 (80%)	12 (48%)
3–5	12 (55%)	6 (27%)

CR=complete response; FLIPI=Follicular Lymphoma International Prognostic Index; ORR=overall response rate.

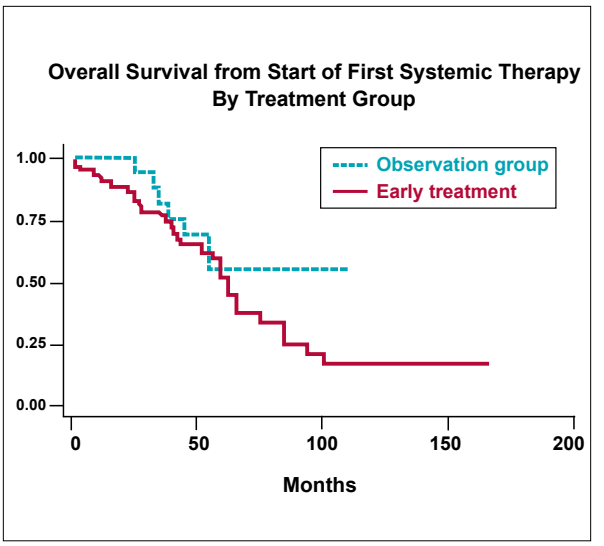

Figure 1. Kaplan-Meier analysis of 97 patients with asymptomatic mantle cell lymphoma followed from start of first systemic therapy at the Weill-Cornell Medical Center, New York, since 1997. Patients are divided into two cohorts: observation group (n=31) and early treatment (n=66).

Overall there were 48% grade 2 and 13% grade 3 adverse events. There were no grade 4 or 5 events reported. The OR rate was 70% (44% CR/CRu) but appeared to be influenced by FLIPI score (Table 1). Median PFS had not been reached at 1.8 years' median follow-up and appeared to correlate primarily with FLIPI score (low and intermediate not reached; high 1.62 years).

Mantle Cell Lymphoma

011 Initial Observation Without Therapy in Patients With Asymptomatic, Newly Diagnosed Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an incurable aggressive NHL with a median survival reported to be only 3–4 years, although more recent data suggest that this figure may be an underestimate. Nevertheless, although some patients require immediate treatment because of the extent of disease or disease-related symptoms, others exhibit a more indolent course. Initial treatment approaches vary from R-CHOP to more aggressive programs, some including stem cell transplantation. Martin and colleagues from Weill-Cornell Medical Center, New York, reported long-term outcomes of asymptomatic MCL patients followed at their institution since 1997.[8] A surprising observation is that there is a subset of patients who are asymptomatic, and who may be followed for extended periods with no initial therapy.

The observation group (OG) was composed of patients with time-to-first-systemic-therapy (TTT) of greater than 3 months from diagnosis. OS comparisons were made using the log-rank test and potential predictors of treatment group were evaluated by logistic regression. Clinical information and dates of diagnosis and first therapy were available in 97 patients of a total of 181. The OG included 31 patients (32%), whereas 66 were in the early-treatment group (ETG). Median age at diagnosis was 58 years (range, 40–81) for the OG and 65 years (range, 44–89) for the ETG. In the OG, 14 patients (44%) were followed for longer than a year without requiring therapy, with 3 observed for at least 5 years. In the ETG, median TTT was 1 month (range, 0–128). Median OS of all 97 patients was 68 months (95% confidence interval [CI], 61–101), and that of the ETG was 64 months (95% CI, 45–85). With a median of 55 months' follow-up, the median OS for the OG was not reached and was statistically superior to that for the ETG (*P*=.0038; Figure 1). One third of patients with MCL in this analysis followed a more indolent course, characterized by their ability

to undergo more than a 3-month observation period following diagnosis, with a large proportion under observation for more than 1 year. In the OG only performance status (PS) predicted early treatment (OR, 9.9; *P*=.006 for PS>0), but this difference disappeared on multivariate analysis. Thus, prolonged observation in select, asymptomatic patients may be an appropriate approach.

116 Immunochemotherapy in Advanced Mantle Cell Lymphoma Is Not Superior to Chemotherapy Alone—50 Months Update of the OSHO Phase III Study

Rituximab plus chemotherapy is an accepted standard for treatment of advanced FL and DLBCL. In MCL, however, the role of immunochemotherapy remains controversial. A prospective randomized trial was conducted by the East German Study Group Hematology/Oncology to compare the safety and efficacy of mitoxantrone, chlorambucil, and prednisolone (MCP) versus MCP plus rituximab in advanced indolent and MCL.[9] CR and OR rates did not differ between the arms, and at a median follow-up of 50 months, MCP plus rituximab failed to demonstrate superiority over chemotherapy alone (Table 2).

Table 2. Response Rates and Survival in Mantle Cell Lymphoma Patients Treated With R-MCP or MCP

	R-MCP (n=44)	MCP (n=46)	*P* value
RR	71%	63%	.5074
CR	32%	15%	.0822
PFS, median	20 mo	18 mo	.2400
PFS at 50 months	26%	11%	
EFS, median	18 mo	13 mo	.1383
EFS at 50 months	23%	9%	
OS, median	56 mo	50 mo	.5176
OS at 50 months	56%	52%	

CR=complete response; EFS=event-free survival; MCP=mitoxantrone, chlorambucil, and prednisone; OS=overall survival; PFS=progression-free survival; R-MCP=rituximab plus MCP; RR=response rate.

A second, era-sequential analysis of standard treatment programs at the Memorial Sloan-Kettering Cancer Center, New York, evaluated the role of rituximab and functional imaging (FI) with gallium or FDG-PET in MCL.[10] Patients had been treated since 1994 with sequential chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT). Rituximab was added to induction and as posttransplant maintenance therapy. In the prospective-study phase of this analysis, patients were treated with four cycles of induction with biweekly CHOP with (n=59) or without (n=20) rituximab followed by FI. Patients with a positive scan (n=16) received three cycles of consolidation with ifosfamide, carboplatin, and etoposide plus rituximab (R-ICE), whereas those with a negative scan (n=43; vs those who did not have FI, n=20) received two cycles of consolidation with ICE without (n=20) or with rituximab (n=42). Patients eligible for transplant underwent conditioning with either total body irradiation, cyclophosphamide, and etoposide or carmustine, cytarabine, etoposide, and melphalan. In this analysis, 28 patients did not and 51 did receive rituximab maintenance therapy following the high-dose therapy and ASCT. Outcomes were analyzed by Kaplan-Meier method and comparisons were by log rank. The median EFS was 4.75 years and the median OS has yet to be reached. Patients who never received rituximab (n=20) had similar outcomes to those who did (n=59). Similarly, there was no impact of rituximab maintenance. In contrast, FI status (positive vs negative) following induction with four cycles of CHOP with or without rituximab was correlated with both EFS (*P*=.04) and OS (*P*<.001).

135 All B Lymphoma Subtypes Do Not Share Similar Outcomes After Front-line R-CHOP Plus Bortezomib Treatment: A Randomized Phase 2 Trial From the Groupe d'Étude des Lymphomes de L'Adulte

The French Groupe d'Étude des Lymphomes de L'Adulte investigated another immunochemotherapeutic approach, R-CHOP plus the proteasome

inhibitor bortezomib, in a frontline phase II trial in patients with various B-cell lymphoma subtypes, including MCL, beginning in January 2005.[11] The trial enrolled 49 patients (median age, 63 years): 11 with DLBCL without adverse factors, 5 with FL with histologic transformation, 3 with MCL, 11 with FL, 2 with mucosa-associated lymphoid tissue lymphoma, 8 with marginal zone lymphoma, 6 with small lymphocytic lymphoma (SLL), and 3 with lymphoplasmacytic lymphoma. Patients were assigned on a randomized basis to receive a planned six cycles of R-CHOP (21-day cycle) plus one of two two-arm dosing schedules of bortezomib, either on days 1, 4, 8, and 11 at 1 mg/m^2 (step 1) or 1 and 8 at 1.3 mg/m^2 or on the same days at 1.3 mg/m^2 or 1.6 mg/m^2, respectively (step 2). The primary endpoint was CR after six cycles. Grade 3–4 thrombocytopenia and leukopenia occurred in 14% and 41% of patients, respectively. Grade 2 neurotoxicity occurred in 11 patients (9 in step 2) and grade 3–4 neurotoxicity occurred in 10 patients (9 in step 2). Forty patients achieved CR/CRu (19 CRs in step 1; 21 CRs in step 2), with 5 achieving PR, 1 experiencing stable disease, and 2 experiencing progressive disease. The investigators found that the CR/CRu rates varied according to lymphoma subtype, with 74% of patients with small-cell lymphomas, 72% of patients with FL, 94% of patients with large-cell lymphomas, and 100% of patients with MCL achieving CR. Therefore, R-CHOP plus bortezomib is considered an effective regimen, particularly in patients with MCL or large-cell lymphomas. Dose-limiting neurotoxicity is the primary cause for caution in future research.

Hodgkin Lymphoma

Hodgkin lymphoma represents one of the success stories of modern hematology/oncology, as approximately 85% of patients can be cured with initial radiation and/or chemotherapy. Nevertheless, many patients still fail to respond to, or relapse following, initial treatment, and effective approaches are needed for these patients. This problem was emphasized by an elegant analysis of OS in patients who relapsed following ASCT presented by Horning and coworkers.[12] An international group of five transplant centers and the Center for International Blood and Marrow Transplant Research pooled their data on 756 patients and evaluated OS according to the time from transplantation to disease progression. Patients with the most recent transplants showed the worst OS: 0.7 months for those who relapsed at 0–3 months after transplant versus 1 year for those who relapsed after 3–6 months. At the 1-year cut-off, median survival was approximately 2 years. This analysis demonstrated that survival following relapse within the first year after transplantation is so poor that this time-point should be considered as a stratification point for clinical trials. Thus, patients who relapse prior to 3 months should be considered for clinical trials of novel therapeutics.

The role of FDG-PET in the management of HL is also a critical issue. The German Hodgkin Study Group (GHSG) recently completed a trial in patients with advanced-stage HL that compared eight cycles of escalated cyclophosphamide, doxorubicin, etoposide, vincristine, bleomycin, procarbazine, and prednisone (BEACOPP) with six or eight cycles of time-condensed baseline BEACOPP. The aim was to identify the negative predictive value of FDG-PET in patients with residual tumor mass larger than 2.5 cm after BEACOPP.[13] Of 817 patients enrolled in the study, 311 were eligible for FDG-PET evaluation; of these 245 (79%) were FDG-PET–negative and 66 (21%)–positive. The negative predictive value (proportion of patients without progression or relapse within 12 months) was 0.958% (95% CI, 0.931–0.985%). In 244 of 245 cases with FDG-PET–negative residual masses, no irradiation was given. In the 62 of 66 cases still FDG-PET–positive, additional radiation therapy was administered. Progression and relapse rates were significantly better in patients with a FDG-PET–negative versus –positive residual mass (P=.0053). FDG-PET–negative patients, assessed as PR by CT, experienced an outcome similar to those in CR. Importantly, the proportion of patients receiving radiation therapy decreased from 70%, as reported in a prior study, to 12% in the current study. There was no significant difference in PFS between this study and previous GHSG trials for advanced-stage Hodgkin lymphoma (P=.266). If these data are confirmed in the final analysis, only FDG-PET–positive advanced-stage patients might benefit from additional radiation therapy after BEACOPP. Additional studies are planned by

the GHSG to study the role of earlier FDG-PET in directing therapy of advanced-stage HL.

137 Isotype-selective Histone Deacetylase Inhibitor MGCD0103 Demonstrates Clinical Activity and Safety in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma

MGCD0103 is an oral, isotype-selective inhibitor of histone deacetylase (HDAC) with demonstrated antitumor activity in a variety of cancers.[14] Younes and colleagues reported a multicenter phase II trial with this agent in adults with relapsed or refractory Hodgkin lymphoma.[15] Study objectives were to assess the safety and efficacy of MGCD0103 in patients with relapsed or refractory classic Hodgkin lymphoma and to identify potential biomarkers and/or predictive markers of efficacy or toxicity. There were 38 patients who received either 110 mg (n=23) or 85 mg (n=15) of MGCD0103 thrice weekly in 4-week cycles. In this heavily pretreated population, 31 patients (82%) had undergone transplantation previously, 4 patients (13%) had both autologous and allogeneic transplantation, and the median number of prior therapies was five (range, 3–10).

Of 20 evaluable patients treated with the dose of 110 mg, 2 (9%) achieved a CR and 6 (26%) a PR (OR, 35%). CT data showed that 17 (85%) experienced tumor reduction, with 12 patients (60%) having a decrease of 25% or more. Among the 15 patients enrolled at a starting dose of 85 mg, 2 (13%) attained a PR and 1 (7%) achieved stable disease for at least 6 cycles; the overall disease control rate (CR + PR + stable disease) in this group was 20%. Preliminary data from the 10 patients in the 85-mg cohort evaluable for efficacy showed that 7 (70%) experienced at least a 25% decrease. There were fewer serious drug-related adverse events at the dose of 85 mg. The most commonly reported hematologic adverse event was thrombocytopenia at both starting doses (17% at 85 mg and 20% at 110 mg). Four patients (17%) discontinued the study due to an adverse event at the starting dose of 110 mg compared to 3 (20%) at the dose of 85 mg. The median duration of therapy for responders was 6.1 cycles (range, 3–12) and the median time to response in this group was 2.2 cycles (range, 1–4.4). The median duration of therapy for all enrolled patients was 4 cycles (range, 1–12).

141 Objective Responses in a Phase I Dose-escalation Study Of SGN-35, a Novel Antibody–Drug Conjugate Targeting CD30, in Patients With Relapsed or Refractory Hodgkin Lymphoma

SGN-35 comprises an anti-CD30 antibody conjugated to monomethyl auristatin E (MMAE). It binds to CD30 leading to antibody-drug conjugate internalization, MMAE release, and subsequent binding to tubulin, prompting cell cycle arrest and apoptosis;[16] Hodgkin lymphoma is a model disease for this novel therapy due to CD30 expression on Reed-Sternberg cells. A multicenter phase I dose-escalation study was conducted in patients with refractory or recurrent CD30-positive hematologic malignancies to define the safety and MTD of SGN-35,[17] which was administered as a 2-hour outpatient intravenous infusion every 21 days at 0.1–2.7 mg/kg. Secondary study objectives were to determine the pharmacokinetic profile, immunogenicity, and antitumor activity. Of 39 patients, 36 had Hodgkin lymphoma, 2 had systemic anaplastic large-cell lymphoma, and 1 had angioimmunoblastic T-cell lymphoma. The median number of prior chemotherapy regimens was three (range, 1–7), and 29 patients (74%) previously underwent ASCT. Infusions were tolerated well. The most common related adverse events were grades 1 or 2 fatigue, cough, and diarrhea. At doses greater than or equal to 1.2 mg/kg, clinical benefit was reported in 19 patients (86%) and objective response in 10 patients (45%). CR as assessed by the Cheson criteria was observed in 5 patients (23%). The study is continuing to accrue patents, with the goal of determining the MTD. An evaluation of a weekly dosing regimen has also been initiated.

Burkitt Lymphoma

The 10th ICML coincided with the 50th anniversary of the discovery of Burkitt lymphoma (BL).[18] Standard therapy is effective but usually involves intensive combination chemotherapy resulting in high treatment-related toxicity and mortality, espe-

cially in the older population. The two strategies outlined here, which were presented at the ICML, suggest it is possible to maintain high efficacy in BL with substantially less toxicity than that historically observed with standard treatment.

008 New Developments in the Management of Burkitt's Lymphoma

The German Multicenter Study Group for Adult acute lymphoblastic leukemia (GMALL) investigators, led by Dr. Dieter Hoelzer, developed a novel protocol for adult B-cell acute lymphoblastic leukemia (B-ALL)/BL and other high-grade lymphomas based on high-dose methotrexate (HDMTX) and high-dose anthracycline with rituximab.[19] Patients less than 55 years of age received two cycles of high-dose anthracycline (2 g/m^2) and HDMTX (1.5 g/m^2) and patients over 55 years received a dose-reduced regimen without high-dose anthracycline and with methotrexate at 500 mg/m^2.

There were 332 patients with BL (32 with Burkitt-like lymphoma), B-ALL, or DLBCL evaluable for response after the first two cycles of therapy. The median age was 36 years for BL, 46 years for B-ALL, and 35 years for DLBCL; 18%, 41%, and 12% were older than 55 years, respectively. The CR rate was 90% in BL, 83% in B-ALL, and 69% in DLBCL; death on study occurred in 3%, 11%, and 0% of patients, respectively. The OS at 3 years was 91% for BL, 79% for B-ALL, and 90% for DLBCL. There was no difference in OS between patients with BL (93%) and Burkitt-like NHL (91%). Major reported grade 3/4 toxicity was hematologic (28–37%) and mucositis (28–37%).

009 A Prospective Study of Dose-adjusted EPOCH With Rituximab in Adults With Newly Diagnosed Burkitt Lymphoma: a Regimen With High Efficacy and Low Toxicity

Twenty-three treatment-naive patients (HIV-negative, n=15), received dose-adjusted etoposide, doxorubicin, vincristine, prednisone, cyclophosphamide (EPOCH) plus rituximab infusional therapy for six cycles or for three to six cycles up to one cycle beyond CR for a maximum of three cycles in HIV-positive patients (n=8).[20] The regimen was well tolerated, with reported significant toxicities of one case of tumor lysis syndrome and fever/neutropenia in 22% of cycles. Neutropenia (absolute neutrophil count <500/µL) was reported for 45% of cycles. There were no treatment-related deaths. CR was reported for all patients. As of June 2008, the median follow-up was 28 months and EFS was reported at 96%.

These studies demonstrate that efficacy in the treatment of BL can be maintained with less toxicity than encountered with previous aggressive chemotherapy programs.

Table 3. Bendamustine in Refractory/Relapsed Non-Hodgkin Lymphoma (NHL)

NHL Grade	No. Patients	CR, %	ORR, %	Dose, mg/m^2; Schedule
Indolent	62[1]	15	82	50–60; d1–5
Indolent	52[2]	11	3	120; d1–2
Aggressive	18[3]	16	44	120; d1–2
Indolent, MCL, transformed	77[4]	34	77	120; d1–2
Indolent, MCL	100[5]	17	75	120; d1–2

CR=complete response; MCL=mantle cell lymphoma; ORR=overall response rate.

Data taken from:
1. *J Cancer Res Clin Oncol.* 2002;128:603-609.
2. *Anticancer Drugs.* 2001;12:725-729.
3. *Ann Oncol.* 2002;13:1285-1289.
4. *J Clin Oncol.* 2008;26:204-212.
5. *Blood.* 2007;110: Abstract 1351.

Emerging Therapies and Novel Agents in B-cell NHL

302 Bendamustine Plus Rituximab Versus CHOP Plus Rituximab in the First-line Treatment of Patients With Indolent and Mantle Cell Lymphomas—Interim Results of a Randomized Phase III Study of the STIL

Bendamustine is an alkylating agent with a nitrogen mustard group and a purine-like benzimidazole ring. This drug has demonstrated efficacy in several

solid tumors, multiple myeloma, and indolent NHL (Table 3). At the ICML, Rummel and colleagues provided an update on a large, randomized, multicenter phase III trial of bendamustine with rituximab (B-R) compared with R-CHOP as first-line therapy for indolent FL and MCL.[21] This study, begun in 2003, has accrued 483 patients, of whom 331 are evaluable (B-R, n=173; R-CHOP, n=158). ORR is similar for both treatment arms (94% vs 97% for B-R and R-CHOP, respectively), as is CR (45% and 40%). The B-R arm appears to have a more favorable safety profile, demonstrated by a lower rate of infectious complications (19% with B-R vs 41% with R-CHOP) and complete lack of alopecia compared with 40% occurrence with R-CHOP. Moreover, R-CHOP is correspondingly more hematologically toxic; WHO grade 3/4 leukopenia was 41% in patients treated with R-CHOP and only 12% in those treated with B-R. The study continues to follow patients and a full analysis is expected at the end of 2009 (2-year follow-up after last patient is recruited).

379 Bendamustine vs Fludarabine as Second-line Treatment for Patients With Chronic Lymphocytic Leukemia—First Interim Results of a Randomized Study

Nierdele and colleagues presented initial data from a small, randomized study comparing bendamustine with fludarabine as second-line therapy for patients with chronic lymphocytic leukemia (CLL).[22] Ninety-six patients were randomized to receive either treatment and 89 were evaluable for an interim analysis. ORR was 78% (bendamustine, n=46) versus 65% (fludarabine, n=43) and clinical CR rates were 29% and 10% for bendamustine and fludarabine, respectively. After median follow-up of 2 years, median PFS was 83 weeks for bendamustine and 64 weeks for fludarabine. Nonhematologic toxicities were similar for both treatments (15% grade 3/4 infections); however, there was slightly more hematologic toxicity with bendamustine. These authors concluded that bendamustine may be a feasible option for patients with relapsed CLL.

Finally, two presentations of preliminary data with B-R in relapsed disease confirm previously published results reported by Rummel and associates[23] and Robinson and colleagues.[24] Mohren and coworkers reported preliminary data from a small study (n=12) of B-R in relapsed or refractory NHL.[25] The OR rate was 80% with four CRs, one PR, and one minimal response. One of the patients remained in CR for 33 months. The regimen was tolerated well, with no toxicity-related treatment delays or mortality, and only one grade 3 /4 hematologic toxicity. A second small study of B-R in relapsed B-cell lymphoma or MCL (n=48) demonstrated an OR rate of 85%, determined in 40 evaluable patients.[26] The PFS was 1 year and median OS was 14 months. The B-R regimen was well tolerated, with reversible myelosuppression as the major reported toxicity.

102 Tamatinib Fosdium, an Oral SYK Inhibitor, Has Significant Clinical Activity in B-Cell Non-Hodgkin Lymphoma

Subgroups of DLBCLs, based on specific molecular signatures and underlying genetic and cellular abnormalities, have been identified by genetic profiling and other molecular techniques. The so-called B-cell receptor (BCR) DLBCLs have high levels of B-cell transcription factors expressed, including Bcl-6 and other, more frequent, Bcl-6 translocations. It has been shown that spleen tyrosine kinase (SYK)[27] is intimately involved in BCR signaling in BCR DLBCLs, thus revealing a novel and exciting clinically relevant target (Figure 2). Friedberg and coworkers presented the first data from a clinical trial of tamatinib fosdium, the first oral SYK inhibitor.[28] Thirteen patients of mixed histologies were enrolled into the study; FL (n=5), CLL (n=2), MCL (n=3), and DLBCL (n=3). Patients received 200 mg or 20 mg twice daily following response evaluation at day 57, when 1 patient showed a PR and 3 patients had progressive disease, the data safety monitoring board decided to begin a phase II study using a twice-daily dose of 200 mg. Sixty-eight patients with relapsed/refractory disease were then enrolled into three cohorts: DLBCL (n=23), FL (n=21), and "Other" (n=24; 11 cases of SLL/CLL, 9 MCL, 1 lymphoplasmacytic lymphoma, and 1 marginal zone lymphoma). Tamatinib fosdium was tolerated well, with neutropenia and thrombocytopenia as the most prominent serious adverse events. There were no significant gastrointestinal effects and no

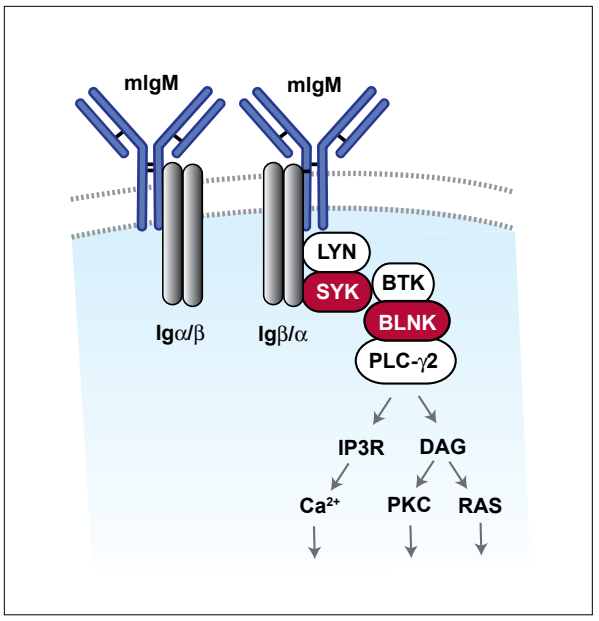

Figure 2. SYK (spleen tyrosine kinase) amplifies BCR signal and initiates downstream events.

alopecia. Eight patients in phase II required dose modification to 150 mg twice daily. The OR rate was 21% for DLBCL, 10% for FL, and 54% for the SLL/CLL cohort. Further studies with this agent are planned

099 SGN-40 Shows Evidence of Activity in Patients With Relapsed Non-Hodgkin Lymphoma: Final Results of a Phase I Dose-escalation Study

SGN-40 is a humanized monoclonal antibody that binds to CD40, triggers proapoptotic signal transduction, and mediates effector cell function (ie, antibody-dependent cellular phagocytocis and cytotoxicity).[29] A multicenter phase I study was conducted to assess the safety, MTD, pharmacokinetic profile, and antitumor activity of SGN-40 in patients with relapsed NHL. Fifty patients with various histologic subtypes of NHL were enrolled and were heavily pretreated, with a median of three prior therapies (range, 1–8). Treatment with SGN-40 was tolerated well, and a MTD was not reached, with 2 patients experiencing dose-limiting toxicities (conjunctivitis with transient loss of visual acuity and grade 3 elevation of alanine aminotransferase). Six patients (12%) achieved objective responses (5 PRs and 1 CR) and 13 patients (26%) achieved stable disease. Three responses were ongoing at the final clinical evaluation, up to 2 years after completing treatment. Two additional patients who discontinued SGN-40 due to toxicity achieved durable CRs after withdrawal from the study and without subsequent treatment. The median OS was 10.5 months (range, 0.1–16.9).

098 GA101, a Novel Therapeutic Type II CD20 Antibody With Outstanding Anti-Tumor Efficacy in Non-Hodgkin Lymphoma Xenograft Models and Superior B-cell Depletion

GA101 is derived by humanization of the murine B-Ly1 antibody and is characterized by a high CD20 binding affinity with reduced complement-dependent cytotoxicity and strong direct induction of cell death when compared to classic type I anti-CD20 antibodies such as rituximab. GA101 demonstrated significant antitumor efficacy in other NHL models. At the ICML, Umana and coworkers presented data showing that GA101 induced tumor remissions in NHL xenografts in severe combined immunodeficiency mice.[30] By contrast, rituximab at higher doses was able only to slow tumor progression. Similar results have been seen in MCL models, and in hCD20 transgenic mice, GA101 has greater B-cell depleting activity than rituximab, which extends into the peripheral lymphoid compartments. Primate studies comparing B-cell depletion as an in vivo measure of efficacy for GA101 and rituximab showed similar activity. The unique binding mode and the induction of CD20-dependent cell death by GA101 may be responsible for the greater B-cell depletion with GA101. This molecule represents a novel class of CD20 antibody with potentially improved efficacy when compared to existing CD20 antibodies, which may translate into clinical benefit.

145 Lumiliximab in Combination With FCR for the Treatment of Relapsed Chronic Lymphocytic Leukemia: Results from a Phase I/II Multicenter Study

Lumiliximab is a chimeric (macaque-human) anti-CD23 monoclonal antibody in clinical development

as a potential agent for relapsed CLL. Previously published studies have shown that lumiliximab monotherapy is well tolerated, can achieve and maintain CD23 receptor occupancy, and has clinical activity demonstrated as changes in absolute lymphocyte count, although there were no confirmed responses observed, according to the National Cancer Institute.[31] Byrd and colleagues reported the results from a phase I/II, multicenter study conducted to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide, and rituximab (L+FCR) in patients with relapsed CLL.[32] Thirty-one patients received either 375 mg/m^2 (n=3) or 500 mg/m^2 (n=28) of L+FCR for up to six 28-day cycles. The median number of prior regimens was two (range, 1–10), 74% of the patients had Rai stage I/II disease at study entry, and the median age was 58 years. The OR rate was 65%, with a CR rate of 52% and a PR rate of 13%. Of note, 5 of 8 patients with deletion 11q22.3 achieved CR. PFS for all patients was 19.3 months, with a median follow-up of 16.8 months (range, 1.5–37.6). The median PFS for all responders was 23.4 months and 30.4 months for patients who achieve CR. CD23 receptor occupancy on CLL cells and possible effects of elevated serum CD23 were evaluated using a semiquantitative flow cytometry method and enzyme-linked immunosorbent assay, respectively. L+FCR was found to sustain CD23 receptor occupancy and was not affected by elevated levels of serum CD23. A large, randomized, global study of L+FCR versus FCR (LUCID) is currently enrolling patients to further evaluate the safety and efficacy of this regimen.

Emerging Therapies and Novel Agents in T-cell NHL

138 Pralatrexate produces a High and Durable Complete Response Rate in Patients With Chemotherapy Resistant T-Cell Lymphomas

Pralatrexate (PDX) is a novel folate analog inhibitor with improved membrane transport and polyglutamylation in tumor cells compared with methotrexate, and with improved cytotoxicity in a variety of preclinical models, including a number of lymphoid histologies. O'Connor and coworkers updated their results of a phase I study of PDX in patients with a variety of histologies of NHL using either an every-other-week or a weekly schedule.[33] The MTD of PDX on a weekly schedule was 30 mg/m^2 weekly x 6 weeks every 7 weeks. The dose-limiting toxicity was primarily thrombocytopenia. In the clinical trial reported at ICML there were 24 (20 evaluable) patients with B-cell NHL and 34 (22 evaluable) with T-cell NHL. There were only two PRs in the patients with B-cell NHL, for a disappointing response rate of 10%. However, among the patients with T-cell NHL there were six CRu/CRs and four PRs, including three that became negative on FDG-PET scan, for a response rate of 45%, with six of the responses in patients refractory to the immediate prior treatment. These responses lasted from over 2 to over 21 months and were all longer than patient response to the last prior therapy. PDX was also found to be synergistic with gemcitabine and bortezomib, two other active drugs in T-cell NHL, and various combinations are in development for clinical trials.

103 International Trial Confirms Romidepsin Efficacy in Refractory CTCL Patients

Romidepsin is a bicyclic depsipeptide antibiotic isolated from the bacterium *Chromobacterium violaceum*. Following intracellular activation, it binds to and inhibits HDAC, resulting in altered gene expression and the induction of cell differentiation, cell cycle arrest, and apoptosis. It also inhibits hypoxia-induced angiogenesis and depletes several heat shock protein 90–dependent oncoproteins. To confirm reported activity in cutaneous T-cell lymphoma, a single-arm, open-label phase II study was conducted in 96 patients, accrued from 36 international sites, with stages 1B–1VA disease who had failed more than one prior systemic therapy.[34] Romidepsin was administered at 14 mg/m^2 on days 1, 8, and 15 every 28 days. The primary endpoint was response rate determined by a combination of imaging, circulating malignant T-cell counts, and a skin-scoring instrument. In 73 evaluable patients, the most frequent adverse events were nausea (51%), fatigue (27%), vomiting (22%), anorexia (11%), aguesia (11%), and headache (11%). Serious adverse events were considered possibly, probably, or likely related to treatment in 14 patients with no deaths attributed to the study drug. The OR rate was 34% with four cytogenic CRs, 21 PRs, 42 patients with

stable disease, and 6 patients with progressive disease. The median time to response was 6 weeks and the median duration of response was 5 months (range, 2+–21 months).

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Commentary

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The 10th ICML held in Lugano, Switzerland, June 2–7, 2008, included presentations reflecting major changes in our concepts of lymphoma biology, diagnosis and classification, prognosis, and therapy. The original REAL (Revised European American Lymhoma) classification, revised as the WHO classification, was the first to incorporate biology, immunology, and clinical features. Harris and coworkers described the revised WHO classification of 2001, which will be published in September 2008. Several new entities were recognized, including primary cutaneous follicle center-cell lymphoma; diffuse large B-cell NHL not otherwise specified; primary extranodal diffuse large B-cell NHL; virus-associated aggressive B-cell NHL (eg, Epstein-Barr virus, human herpesvirus 8); high-grade B-cell NHL, unclassifiable, between diffuse large B-cell NHL and BL; and B-cell lymphoma, unclassifiable, between BL and classic Hodgkin lymphoma, as well as a number of subtypes of T-cell NHL. As a result, there are now more than 60 recognized lymphoma entities. Over the past 15 years, several clinically relevant prognostic scoring systems have been in use, for example the International Prognostic Index (IPI) for DLBCL, the FLIPI for follicular NHL, and the International Prognostic Score for Hodgkin lymphoma. Federico and coworkers presented their initial data on the F2, a revised FLIPI that bases its predictions on ß2-microglobulin, hemoglobin, age, bone marrow involvement, and tumor bulk. Other studies have looked at molecular markers of disease. Winter and associates from the Eastern Cooperative Oncology Group previously showed that the addition of rituximab to CHOP had improved the outcome in DLBCL patients with tumors that were Bcl-6–negative but with no effect on the Bcl-6–positive cases.[1] These researchers updated and expanded these data at the ICML and included evaluation of p21, a cyclin-dependent kinase inhibitor that is a downstream effector of p53. Rituximab appeared to benefit patients with p21-positive DLBCL but not those with p21-negative tumors. When combining the various markers, the best outcome was in patients with Bcl-2–negative/p21-positive tumors, whereas those with Bcl-2–positive/p21-negative patients had the worst outcome. Results with other combinations were intermediate between the two.[2] Dr. Gilles Salles described the work of the Lunenberg Consortium, who identified seven biologic and genetic factors with clinical relevance: expression of Ki-67, MUM1, Bcl-2, Bcl-6, CD5, CD10, and HLA-DR. When validated, these markers will be incorporated into a prognostic system to predict outcome and, eventually, direct treatment.

Apparently, lymphomas cannot live by lymphoid cellular characteristics alone, a point emphasized by Dr. Randy Gascoyne in his Keynote lecture at the ICML. An increasing body of evidence supports the importance of the tumor microenvironment, such as the presence or absence of lymphoma-associated macrophages and other effector cells, such as regulatory T cells.[3] Not only do these cells and various cytokines support lymphoma growth and survival, they may also predict response to various agents, such as rituximab,[4] and provide novel targets for anti-lymphoma therapy.

Much of the focus of the meeting was directed at new treatments and the use of functional imaging with FDG-PET in prognosis and risk-adapted therapy. Drugs of interest included bendamustine,[5] tamatinib fosdium,[6] and various HDAC inhibitors. Of note were impressive results in the challenging T-cell NHLs with PDX and romidepsin. In addition, a number of biologic approaches stimulated interest. Based on the success of rituximab in B-cell malignanices, multiple companies have been developing human/humanized anti-CD20 monoclonal antibodies that differ with regard to the tightness of binding to CD20; the CD20 epitope to which binding occurs; or the amount of ADCC, CDC, or apoptosis induced. Preliminary data were presented at ICML regarding GA-101, a type II anti-CD20 agent, that in vitro appears to be more potent than

rituximab.[7] Additional anti-CD20 antibodies in clinical trials include ofatumumab, PRO131921, and veltuzumab.[8] Other antibodies of interest discussed at the meeting include galiximab (anti-CD80), SGN-40, and lumiliximab (anti-CD23). Galiximab was studied by the CALGB in combination with rituximab in previously untreated follicular NHL, with impressive results in patients with low to intermediate FLIPI scores. It is now under investigaton by the CALGB in Hodgkin lymphoma as well because of the expression of the antigen on Reed-Sternberg cells. Other agents take therapy beyond the standard antibody, such as SGN-35, an anti-CD30 antibody-drug (auristatin) conjugate. The latter has shown impressive initial results in relapsed and refractory Hodgkin lymphoma.

The abstract with perhaps the most disappointing results was presented by Levy and colleagues.[9] This randomized, phase III trial was designed to confirm preliminary results suggesting clinical benefit from tumor-specific, anti-idiotype vaccine therapy. In this trial, patients were randomized to receive chemotherapy with cyclophosphamide, vincristine, and prednisone followed by either anti-idiotype vaccination or control immunotherapy. Although, as in previous reports, patients who were able to mount an immune response to the vaccine had an improved outcome, there was no demonstrable overall difference between the two treatment arms. Another phase III vaccine trial, not presented at these meetings, was also negative, leaving questions about the future of this approach.

In the absence of effective therapies, response criteria are rather irrelevant. However, with the increasing number of effective agents, the ability to compare the results of clinical trials becomes critical. In 1999, an international workshop was convened and subsequently published the International Working Group recommendations for response assessment in NHL, which were then adapted for Hodgkin lymphoma as well. The availability of FDG-PET was largely responsible for a recent revision of these guidelines.[10,11] The optimal use of FDG-PET was discussed and debated at the ICML meeting. Several studies, including those from the BCCA and the GHSG, demonstrated that FDG-PET can limit the number of patients exposed to unnecessary radiation therapy without compromising outcome. The number of publications and presentations regarding this technology have far surpassed our ability to utilize it intelligently in patient management. Numerous risk-adapted studies are ongoing to determine whether functional imaging can successfully alter treatment, leading to patient benefit: for early stage patients, limiting the amount of therapy to reduce toxicity, and, in those with advanced stage disease, modifying treatment in nonresponding patients to improve outcome.

Major lessons learned from the 10th ICML included the importance of international collaborations to improve classification, prognosis, and development of novel, effective therapeutics as well as identifying who will respond to them. Integrating these areas in a rational fashion will certainly lead to an improved outcome for patients with malignant lymphomas.

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Notes

Highlights from the 10th International Conference on Malignant Lymphoma

CME Post-Test: *Circle the correct answer for each question below.*

1. In the BCCA retrospective anaylsis of patients with limited-stage DLBCL treated with R-CHOP who underwent FDG-PET scanning, how many additional cycles of R-CHOP were considered sufficient therapy when patients displayed FDG-PET–negative disease after three cycles?

   a. 0 b. 1 c. 2 d. 3

2. In the phase I/II trial of galiximab by Leonard and colleagues, what was the median duration of response?

   a. 6.2 months
   b. 12.2 months
   c. 12.4 months
   d. 13.0 months

3. In the study of patients with MCL by Martin and colleagues, what characterized indolent disease?

   a. Patients' ability to undergo observation for 1 month following diagnosis
   b. Patients' ability to undergo observation for 3 months following diagnosis
   c. Patients' ability to undergo observation for 1 year following diagnosis
   d. None of the above

4. According to the analysis of survival of patients with Hodgkin lymphoma who relapsed following ASCT by Horning and colleagues, which of the following statements is untrue?

   a. Patients who relapsed at 0–3 months had overall survival of 0.7 months.
   b. Patients who relapsed after 3–6 months had overall survival of 1 year.
   c. Patients who relapsed after 6 months had overall survival of 3 years.
   d. At the 1-year cut-off, median survival was approximately 2 years.

5. Which of the following is true about the HDAC inhibitors MGCD0103 and romidepsin?

   a. MGCD0103 is safe for use in patients with classic B-cell Hodgkin lymphoma.
   b. Romidepsin is associated with a median duration of response of 5 months in patients with refractory CTCL.
   c. In total, at two dose levels, 8 patients achieved PR with MGCD0103 therapy.
   d. Nausea was the most frequent adverse event reported in patients who received romidepsin.
   e. All of the above

6. Which of the following was not a finding of the phase III trial of bendamustine plus rituximab versus R-CHOP in patients with indolent FL or MCL?

   a. Forty percent of patients who received R-CHOP experienced alopecia.
   b. ORR was similar for both treatment arms.
   c. Bendamustine plus rituximab was associated with a CR rate of 75%.
   d. R-CHOP was associated with a CR rate of 40%.
   e. Bendamustine plus rituximab was associated with WHO grade 3/4 leukocytopenia in 12% of patients.

7. What was the ORR among patients with DLBCL who received tamatinib fosdium in the trial by Friedberg and coworkers?

   a. 21%
   b. 10%
   c. 54%
   d. 22%
   e. 55%

8. Five of 8 patients with what chromsome deletion who received lumiliximab in the phase I/II study conducted by Byrd and colleagues achieved CR?

   a. 5q
   b. 8p21.3
   c. 11q22.3
   d. 6q21
   e. 9p21

9. How many patients with chemotherapy-resistant T-cell NHLs achieved CRu/CR while receiving therapy with pralatrexate?

   a. 3 b. 4 c. 5 d. 6 e. 7

10. At what dose was romidepsin administered in the phase II trial in patients with refractory cutaneous t-cell lymphoma?

    a. 14 mg/m^2 on days 1, 8, and 15 every 28 days
    b. 14 mg/m^2 on days 1, 8, and 16 every 28 days
    c. 12 mg/m^2 on days 1, 8, and 15 every 28 days
    d. 15 mg/m^2 on days 1, 8, and 15 every 28 days
    e. 15 mg/m^2 on days 1, 8, and 16 every 28 days

Evaluation Form

Highlights from the 10th International Conference on Malignant Lymphoma

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
(1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree)

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

• Describe new insights into the natural history of lymphoma	1 2 3 4 5
• Outline findings of clinical trials related to treatment of lymphoma	1 2 3 4 5
• Identify future research directions for treatment of lymphoma	1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

• Was timely and will influence how I practice	1 2 3 4 5
• Enhanced my current knowledge base	1 2 3 4 5
• Addressed my most pressing questions	1 2 3 4 5
• Provided new ideas or information I expect to use	1 2 3 4 5
• Addressed competencies identified by my specialty	1 2 3 4 5
• Avoided commercial bias or influence	1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity:

_____

Please list any topics you would like to see addressed in future educational activities:

_____

Additional comments about this activity: _____

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by project ID 5718. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Posttest Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____

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For Physicians Only:

I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1.0 credits.

☐ I participated in only part of the activity and claim _____ credits.

Project ID: 5718-ES-34

Notes


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