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A Summer of Hematologic Science

Highlights from the 45th Annual Meeting of the American Society of Clinical Oncology, the 14th Congress of the European Hematology Association, and the 2009 Pan Pacific Lymphoma Conference

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Statement of Need/Program Overview

Data are emerging on novel agents as well as new combination regimens for the treatment of hematologic malignancies. This monograph reviews some of the salient new data recently presented at international meetings of hematologists/oncologists.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of hematologic malignancies
- Review the results of these new study findings including current clinical trials evaluating therapy in the treatment of hematologic malignancies
- Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with hematologic malignances in an effort to improve current prognosis
- Identify future research directions for all therapies in hematologic malignancies

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A Summer of Hematologic Science

Highlights from the 45th Annual Meeting of the American Society of Clinical Oncology, the 14th Congress of the European Hematology Association and the 2009 Pan Pacific Lymphoma Conference

The early summer of 2009 offered 3 opportunities for the hematology community to come together and share data; the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO), the 14th Congress of the European Hematology Association (EHA), and the 2009 Pan Pacific Lymphoma Conference (PPLC). These 3 meetings provided updated information on the biology, genetics, prognosis, and treatment of patients with leukemias, lymphomas, and multiple myeloma that will have a major impact on patient management.

Leukemia

The search for valid prognostic factors in leukemia was a central theme at both the ASCO and EHA meetings. Several studies demonstrated the value of genetic markers as prognostic indicators of outcome.

At ASCO, Cancer and Leukemia Group B (CALGB) investigators presented the results of a pretreatment genetic analysis of patients enrolled on therapeutic studies in an attempt to correlate gene expression with outcome in patients with cytogenetically normal acute myeloid leukemia (CN-AML). Schwind and colleagues described miR-181a expression as a prognostic marker in CN-AML. They analyzed 184 patients under the age of 60 years (median, 45 years) and showed that increased levels were associated with a higher complete response rate (CR; 97% vs 76%), 5 year disease-free survival (DFS; 69% vs 23%), and overall survival (OS; 70% vs 30%). However, this benefit was restricted to the molecular high risk group, where it predicts outcome independently of other variables including CEBPA mutations.[1] Marcucci and coworkers constructed a new molecular risk classification of younger, de novo CN-AML patients (ie, low-risk group [FLT3-ITD negative (neg)/NPM1 mutated (mut)] and high-risk group [FLT3-ITD positive (pos) or NPM1 wild type (wt)], FLT3-ITD/NPM1-only classification).[2] This abstract builds on the group's prior observation that CEBPA mutations determined prior to therapy identify CN-AML patients with different outcomes, improving the validity of molecular risk-based classification for this patient population.[3] Taking data collected from 143 CN-AML patients enrolled on CALGB treatment protocols 9621 and 19808, these authors were able to show that the prognostic classification of younger de novo CN-AML patients is improved by adding CEBPA and WT1 mutation and ERG expression testing. Such mutational analyses are already in place for clinical trials, access to validated testing for general use has yet to be achieved. Becker and colleagues for the CALGB presented convincing data at ASCO supporting the role of the NPM1 gene mutation as an independent prognostic factor for older patients as well.[4] They compared the mutational status of the gene with clinical outcome in 189 CN-AML patients (162 de novo and 27 secondary cases of prior hematological basis) with a median age of 69 years (range, 60–83 years). Patients had been entered into 1 of 2 trials sponsored by the CALGB; studies CALGB 9720 (n=106) and CALGB 10201 (n=83). Both of these protocols evaluated standard-dose (100 mg/m^2/d) cytarabine (AraC)/daunorubicin (DN)-based induction followed by consolidation with either 1 cycle of standard-dose AraC/DN/etoposide (study 9720), or 2 cycles of intermediate-dose (2 g/m^2/d) AraC (study 10201). NPM1 mutations predicted clinical outcome in this older CN-AML population with more CRs (85% vs 45%, P<.0001) and longer relapse-free survival in patients with de novo disease (3-year rate of 23% for NPM1 mutated patients versus 10% in patients with no mutation, P=.02). OS rates were also improved in the NPM1mut population compared with the wild-type patients; 3-year rate of 34% versus 7% (P<.0001).

Therapeutic advances have lagged behind our understanding of the biology of AML. Developing treatment options for AML were presented at ASCO by the Eastern Cooperative Oncology Group (ECOG) and the

M.D. Anderson Cancer Center. Fernandez and ECOG colleagues presented data from a randomized trial of daunorubicin dose intensification in 657 patients aged 18–60 years (median, 48 years)[5]. An earlier investigation indicated that anthracycline dose intensification may be beneficial in some patients with AML, although there was no significant improvement in OS.[6] In contrast, the data from this prospective randomized study show that high-dose daunorubicin (HDD; 90 mg/m^2/day for 3 days), when combined with standard dose cytarabine (100 mg/m^2/day for 7 days) as induction therapy resulted in a significantly higher CR rate (70.6% vs 57.3%, *P*=.0003) than did the standard dose of daunorubicin (SDD; 45 mg/m^2/day for 3 days). Following induction, patients achieving a CR received either an allogeneic transplant or high dose cytarabine prior to autologous stem cell transplant. OS was the primary endpoint of this study and was determined from the time of induction randomization. Median OS was 23.7 months for the HDD cohort and 15.7 months for the SDD group, representing a significant difference (*P*=.005). There was no difference in the demographics of each group, and the death rates during induction were similar (5.4% vs 5.0%). However, beneficial effects were seen primarily in patients under the age of 55 years, and with low risk features by cytogenetics, FLT3+, or MLL+. The authors concluded that these data support the use of higher dose anthracyclines as standard of care in younger AML patients.

Garcia-Manero and colleagues reported preliminary phase II data with sapacitabine, a novel nucleoside analog.[7] This molecule has already shown promise in relapsed or refractory AML and MDS and has the advantage of being orally bioavailable. In a multi-center, open label, randomized phase II study, previously treated patients with MDS and elderly patients with AML who were untreated or in first relapse were randomized to receive one of 3 dosing regimens of sapacitabine; 200 mg or 300 mg bid for 7 days every 3–4 weeks and 400 mg bid for 3 days per week every 3–4 weeks. At time of the presentation, 20 patients had achieved at least 30 days of therapy and an ORR of 31% in elderly AML patients older than 70 years with previously untreated disease was observed. At the highest dose level (400 mg bid), the response rate was 35% with 25% CRs. The therapy was well tolerated at all 3 doses and the authors concluded that it is safe and effective.

CLL

New developments in CLL therapy were presented at both ASCO and EHA meetings, from initial clinical experience with novel agents to results from international Phase III studies. At EHA, Knauf and colleagues updated their data from a prospective randomized phase III trial comparing bendamustine, a bifunctional alkylating agent, with chlorambucil as frontline therapy in patients with CLL Binet stage B/C disease.[8] Patients received either 100 mg/m^2 bendamustine for 2 days or 0.8 mg/kg chlorambucil days 1 and 15, for up to 6 cycles, with cycles delivered every 4 weeks. The primary endpoints of the study were ORR and progression-free survival, with secondary endpoints of OS and safety. A total of 319 patients were randomized, but only 312 received study medication. The median age was 64 years and the median number of cycles was 6 per patient. The ORR and CR were both significantly higher with bendamustine than with chlorambucil (68% vs 31%, *P*<.0001; and 31% vs 2%, respectively). The relative median durations of response were 21.8 and 8.0 months for bendamustine and chlorambucil, respectively (*P*<.0001). As of the time of the meeting there had been no significant difference observed in the OS between the 2 groups. Such convincing data support the use of bendamustine as first-line therapy for patients with CLL.

Also at EHA, Susan O'Brien, from the MD Anderson Cancer Center, updated the 5-year follow-up data from a phase III trial that compared fludarabine/cyclophosphamide combination (FC) alone or in combination with oblimersen, a bcl-2 antisense oligonucleotide, in patients with relapsed/refractory CLL who had received at least 2 cycles of fludarabine prior to study entry.[9] These investigators were able to obtain follow-up information on 97% of the patients enrolled in the study (120 patients received oblimersen-FC, and 121 received FC alone). The oblimersen-FC therapy improved the 5-year survival rate (25% vs 15%), but this was not significant. However, within the oblimersen-FC group, patients who had responded to prior fludarabine therapy had a significantly longer survival than those who were refractory to that drug (hazard ratio=.60; *P*=.038; Figure 1).

At ASCO, Kipps and co-workers reported an interim analysis of an international clinical study designed to determine the efficacy of the fully human anti-CD20 ofatumumab in CLL.[10] They presented data on 138 patients who were either refractory to fludarabine and alemtuzumab (DR) or refractory to fludarabine alone, but with bulky disease, in other words larger than 5 cm lymphadenopathy (BFR) and, thus, unlikely to respond to alemtuzumab. Patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions at 3 doses; dose 1, 300 mg, doses 2–12, 2000 mg. The primary endpoint was ORR assessed by the 1996 National Cancer Institute Working Group Criteria.[11] Dr. Kipps reported that disease symptoms abated in a large group of patients over a minimum of a 2-month period (Table 1). Of note, hematologic parameters were improved in patients with

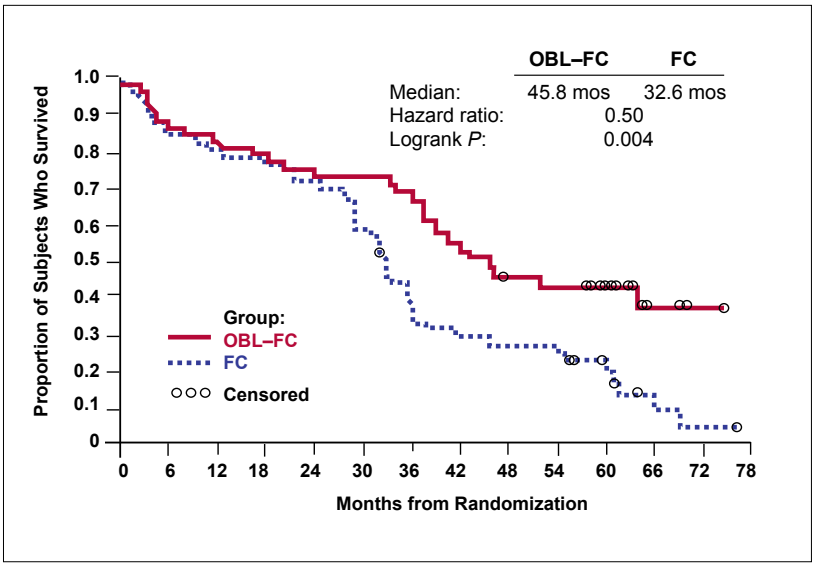

Figure 1. Five-year survival in fludarabine sensitive patients receiving fludarabine/cyclophosphamide (FC) with or without oblimersen (OBL).

Adapted from O'Brien et al. *Haematologica*. 2009; 94[suppl.2]:141, Abstract 0357.

Table 1. Disease Symptom Abatement with Ofatumumab in Patients with Fludarabine-refractory Chronic Lymphocytic Leukemia (CLL) Who Are Also Refractory to Alemtuzumab or with Bulky Lymphadenopathy

	FA-ref		BF-ref	
Improvement in Clinical Parameter from Baseline to Week 24	**N***	**n(%)†**	**N***	**n(%)†**
Complete resolution of B-symptoms	31	15 (48)	46	29 (63)
Complete resolution of lymphadenopathy (<1 cm nodes)	55	9 (16)	74	8 (11)
≥50% reduction in lymphadenopathy	55	34 (62)	74	36 (49)
Complete resolution of splenomegaly	30	14 (47)	46	16 (35)
Complete resolution of hepatomegaly	18	9 (50)	21	11 (52)
Neutrophil count from $<1.5 \times 10^9$/L to $\geq 11.5 \times 10^9$/L	19	1 (5)	17	5 (29)
Hemoglobin from ≤11 g/dL to >11 g/dL	26	8 (31)	42	11 (26)
Improvement in platelet count from $\leq 100 \times 10^9$/L to 50% increase or $>100 \times 10^9$/L	29	12 (41)	44	17 (39)

*Total number of patients with abnormal baseline parameters; †number of patients with improvement (lasting for at least 2 months) from baseline to week 24.

FA-ref=fludarabine- and alemtuzumab-refractory; BF-ref=bulky fludarabine-refractory.

Adapted from Kipps et al. *J Clin Oncol.* 2009; 27(suppl):366s, Abstract 7043.

abnormal baseline values; platelet counts in particular showed substantial increases. Patients with thrombocytopenia at baseline (n=73) showed count increases of over 35% after 8 weeks of therapy, corresponding with similar improvement in hemoglobin levels. This analysis was also presented at EHA by Dr. Anders Osterborg.[12]

Wierda and colleagues also presented data on a subset of patients from this trial who were fludarabine and alemtuzumab-refractory or BFR CLL patients who had prior exposure to rituximab.[13] This analysis was performed since it was unknown whether prior exposure to one anti-CD20 antibody (rituximab) had any influence on response to ofatumumab. In the patient group analyzed (n=138), the ORR was 58% in the DR group and 47% in the BFR group (99% CI). Prior exposure to rituximab had no apparent detrimental effect; both ORR

Table 2. Phase II Study of Ofatumumab in Refractory CLL: An Interim Analysis

	Refractory to Fludarabine and Alemtuzumab* (n=59)	Bulky Fludarabine Refractory† (n=79)
All patients		
ORR	58%	47%
Median PFS	5.7 months	5.9 months
Median OS	13.7 months	15.4 months
Prior Rituximab exposure		
ORR	54%	44%
Median PFS	5.5 months	7.1 months
Median OS	15.5 months	13.7 months

*Double-refractory to fludarabine-containing and alemtuzumab-containing regimens.

†Bulky fludarabine-refractory: inappropriate for alemtuzumab due to bulky nodes.

Adapted from Wierda et al. *J Clin Oncol.* 2009;27(suppl):366s (abstract 7044).

and PRF were similar in the patients with or without prior rituximab treatment (Table 2). This analysis was also presented at EHA.[14]

Lenalidomide is a second generation immunomodulatory drug with demonstrated activity in patients with relapsed or refractory CLL. Two interesting studies focusing on the safety aspects of lenalinomide were presented at the EHA meeting. Firstly, Wendtner and colleagues investigated a dosing schedule for lenalidomide designed to decrease the risk of tumor lysis syndrome (TLS) observed in a prior phase II trial in patients with relapsed or fludarabine refractory CLL and high risk cytogenetics and/or bulky disease treated with an initial dose of 10 mg/day.[15] In the current interim analysis, 30 patients with fludarabine-refractory disease and prior alkylating-agent therapy were treated with a starting dose of lenalidomide 2.5 mg/day, which was increased by 5 mg increments every 28 to a maximum dose of 25 mg/day. Prophylaxis against TLS with 300 mg/day allopurinol and oral hydration was begun 3 days before lenalidomide therapy and continued for 3 cycles. As of the 15 mg dose level, the investigators had detected only one case of laboratory TLS at the 2.5 mg level. Further dose escalation is underway.

A second paper correlated the occurrence of lenalidomide-associated tumor flare with clinical outcome.[16] This syndrome is characterized by a rapid, often painful, enlargement of nodes with a lymphocytosis, which are transient. A prospective analysis was undertaken of 45 patients with relapsed or refractory disease enrolled in a phase II study who received lenalidomide at 1 of 2 doses: 25-mg/day for 21 days of a 28 day cycle without prophylaxis against tumor flare or 10 mg daily with dose escalations in 5 mg increments every 1–2 weeks until a maximum dose of 25 mg/day was achieved (n=16). The latter group also received oral prednisone during days 1–14 of cycle prophylaxis against tumor flare. Clinically significant tumor flare occurred in 30 patients, but no patient discontinued treatment. The incidence of tumor flare was equal between the two groups, but in the 8 patients who achieved a CR, 7 developed tumor flare. This suggestion that lenalidomide-related tumor flare in CLL may be correlated to response requires further confirmation.

Promising data were reported at ASCO and EHA on novel compounds at initial stages of investigation in CLL. Preliminary data were presented at both meetings on ABT-263, an orally bioavailable BH3 mimetic. Two phase I studies in 72 CLL patients were summarized by Wierda and colleagues at EHA and Wilson and colleagues at ASCO.[17,18] The patients had a median of 4 prior regimens and 4 of the 43 CLL/small lymphocytic lymphoma (SLL) patients experienced a partial response (PR), with clinical activity also noted in a number of others. Their data demonstrate that the molecule is well tolerated, and dose optimization is ongoing. GA-101 is the first humanized and glycoengineered monoclonal anti-CD20 antibody to proceed into clinical trials and to date has been well-tolerated with evidence of potential clinical benefit; 64% ORR in the first 13 patients with 1 CR, 6 PRs, and 4 patients who experienced stable disease.[19]

CML

Imatinib has altered the treatment paradigm for patients with CML with durable responses in the majority of cases. Other drugs are also available for resistant or relapsed cases, including dasatinib and nilotinib. However, in many patients, other agents are eventually needed. Cortes and coworkers presented preliminary data on a novel agent under investigation in CML that has intriguing potential in this disease. Omacetaxine mepesuccinate is a first-in-class cetaxine with demonstrated clinical activity as a single agent in a range of hematologic malignancies.[20] Omacetaxine is a subcutaneous therapy with a novel mechanism of action in that it has targeted binding to and inhibits protein translation of specific oncoproteins acting independently of tyrosine kinase inhibitors, thus offering potential clinical benefit to patients who have developed resistance to such therapy. This trial included 66 patients, 40 in chronic phase, 16 in accelerated phase, and 10 in blast phase, with T315I positive CML who had

Table 3. Endpoint Results of Four Trials with Decitabine Using a 3 Day (D-0007 and EORTC-06011) or 5 Day Regimen (DACO-020 and ID03-0180)

OUTCOME	D-OOO7 (N=89)	EORTC -06011 (N=119)	DACO-020 (N=99)	ID03-0180 (N=93)
Median # cycles	3	4	5	7 (check)
% Improvement	30	34	43	65
CR	9	13	15	37
PR	8	6	1	2
HI	13	15	27	26
Median time to response *	2.9 (1.4–3.2)	3.8 (3.0–5.7)	2.0 (1.4–2.8)	2.8 (2.2–3.6)
Median duration of best response *	9.9 (7.9–11.1)	8.6 (6.1–12.6)	NE (4.2–NE)	12.2 (10.3–22.2)
Time to AML or death*	10.0 (7.6–11.2)	8.8 (6.3–11.9)	12.1 (9.7–16.4)	15.2 (11.3–22.2)
PFS*	7.3 (5.2–9.7)	6.6 (4.7–8.5)	8.1 (6.7–9.9)	9.2 (6.8–12.6)
OS*	12.8 (10.3–16.1)	10.1 (8.0–14.0)	17.8 (13.8–NE)	20.3 (14.6–26.3)

*Months (95% CI).

Adapted from O'Brien et al, *Haematologica*. 2009; 94[suppl.2]:141 abstract. 0357

failed tyrosine kinase therapy; all had failed prior imatinib and 80% had failed more than 2 prior tyrosine kinase inhibitors. Omacetaxine was well-tolerated with transient myelosuppression as the most frequent adverse event. A complete hematologic response (CHR) rate of 85% with median response duration of 8.9 months was reported for chronic phase patients with a major cytogenetic response (MCyR) rate of 15% and a median response duration 6.1 months. In the accelerated-phase patients, a CHR rate of 31% was reported with a median duration 4.1 months. The MCyR rate was 6% for this population, with a median response duration of 1.8 months. Finally, a CHR rate of 20% with a median duration of 3.3 months was observed for blast phase patients. Similar data were also presented at EHA.[21] This new agent offers promise to patients with an unfavorable mutation rendering them resistant to currently available therapies.

MDS

The management of immune thrombocytopenia has changed recently with the development of thrombopoietin receptor antagonists that stimulate platelet production.[23] However, the role of such agents in patients with myeloid malignancies has not been well studied. At ASCO, Sekeres and colleagues reported a phase II trial of romiplostim, an Fc-peptide fusion protein, in patients with myelodysplastic syndrome (MDS).[22] In an open label study in 28 patients with low or intermediate-1 risk MDS, 750 µg romiplostim was administered as 1 of 3 dosing schedules: weekly or biweekly subcutaneous injections (QWSC or Q2WSC), or biweekly intravenous injections (Q2WIV). The mean platelet baseline count at study entry was less than 50 x 10^9/L and the mean age was 71 years. Twenty three patients completed at least 8 weeks of treatment, during which romiplostim was well tolerated. The most common adverse events were fatigue and headache (both 18%). Importantly, there was no evidence of neutralizing antibodies developing to either romiplostim or endogenous thrombopoietin. Of the patients who completed therapy, 15 (65%) achieved a platelet response as assessed by the IWG 2006 response criteria[23] and 14 (61%) did not need a platelet transfusion during this period. The authors concluded that romiplostim is well tolerated and effective in managing platelet counts in MDS patients following intravenous or subcutaneous administration, although the study was clearly too small to be able to identify the preferred route of administration.

A second paper included a retrospective analysis of different schedules of decitabine, based on data from 4 clinical trials, each of which had used 1 of 2 dose schedules: 20 mg/m^2 intravenous once daily for 5 days or 15mg/m^2 intravenous every 8 hours for 3 days q6 weeks.[24] Clinical endpoints common to each study were analyzed (ie, overall improvement rates, time to development of AML or death, progression-free survival [PFS] and OS; Table 3). Overall improvement rates were determined using the IWG 2006 criteria and for all 4 trials this was 30% or higher irrespective of the dosing schedule. The duration of improvement (CR, PR or HI) ranged from 9.2–11.3 months and correlated with the number of cycles of decitabine. Patients in one study who received the greatest median number of cycles (7) showed the highest rates of CR (37%),

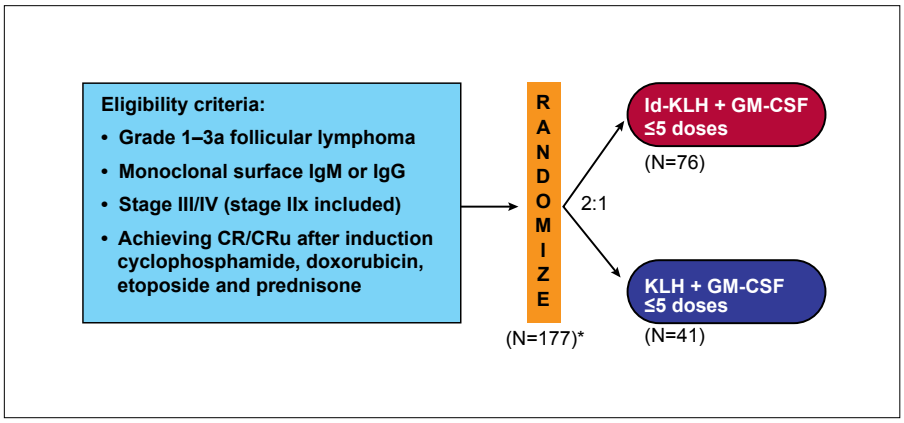

Figure 2. Phase III BV301 trial of idiotype vaccine (Id-KLH) in follicular lymphoma in first complete remission: study design.

*A total of 60 patients failed to maintain CR/CRu and did not receive the study drug.

Adapted from Schuster et al. *J Clin Oncol.* 2009; 27(suppl):793s (abstract 2).

Table 4. Outcome Associated with Idiotype Vaccine (Id-KLH) in Patients with Follicular Lymphoma in First Complete Remission

	Id-KLH (n=76)	KLH (n=41)	*P* Value	HR
Median DFS	44.2 months	30.6 months	.047	0.62
Median OS	Not reached	Not reached	.7	0.7
OS rate	95%	91%		

Note: Median follow-up time was 56.6 months.

Adapted from Schuster et al. *J Clin Oncol.* 2009; 27(suppl):793s (abstract 2).

overall improvement (65%), and the longest time to AML or death (15.2 months). PFS was also longer in this group (9.2 months), although OS was comparable to the other patient groups. This analysis indicated that increasing the number of cycles of decitabine with the 5-day regimen may effectively allow greater exposure to therapy with an associated clinical benefit.

Non-Hodgkin Lymphomas

Hematologic disease was highlighted at the plenary session of the ASCO meeting where Dr. Stephen Schuster of the University of Pennsylvania School of Medicine presented data from an 8-year phase III study of anti-idiotype vaccine therapy (BiovaxID) in follicular lymphoma patients in first CR.[25] Previous phase II studies suggested that patients who developed cellular and humoral responses to anti-Id vaccines had a longer PFS. However, 2 recent large phase III, placebo-controlled trials failed to show an overall clinical benefit to the administration of the vaccine. BiovaxID is a patient-specific tumor derived idiotype (Id) protein conjugated with keyhole limpet hemocyanin (KLH) which functions as a carrier protein. It is administered with GM-CSF, which serves as an immune stimulant.[26] This prospective randomized double-blind, placebo-controlled, study accrued previously untreated patients with grade 1–3a follicular lymphoma and stage III/IV disease, with surface IgG or IgM. Patients received chemotherapy (PACE: prednisone, doxorubicin, cyclophosphamide, etoposide) and those who achieved a CR or complete response unconfirmed (CRu) were stratified by, and randomized, on a 2:1 basis to receive either vaccination with Id-KLH/GM-CSF or the control, which was KLH alone with GM-CSF (Figure 2). The primary endpoint was DFS; secondary endpoints were safety, OS, and immunologic and molecular responses. Of 234 patients considered for the study, 177 patients were randomized and 60 were excluded, as CR/CRu was not maintained for more than 6 months as per protocol. The intent-to-treat population was considered to be those 117 remaining patients who received more than 1 vaccine dose; 76 patients received active therapy (Id-KLH/GM-CSF) and 41 patients received placebo (KHL/GM-CSF). At the time of the presentation, median follow-up time was 56.6 months (range 12.6–89.3 months) and median survival had yet to be reached (Table 4). The median time to relapse post-randomization for the active treatment was 44.2 months compared to 30.6 months for

Table 5. Grade 3/4 Adverse Events Observed in a Phase III Trial of Idiotype Vaccine (Id-KLH) in Patients with Follicular Lymphoma in First Complete Remission

	Id-KLH (n=76)		KLH (n=41)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Cardiovascular	1 (1%)	1 (1%)	1 (2%)	0
Constitutional	2 (3%)	0	0	0
Dermatology	4 (5%)	0	1 (2%)	0
Gastrointestinal	3 (4%)	0	1 (2%)	0
Pain	5 (7%)	0	6 (15%)	0
Secondary Malignancy	0	1 (1%)	1 (2%)	0

Schuster et al. *J Clin Oncol.* 2009; 27(suppl):793s (abstract 2).

the placebo group (*P*=.047; HR=.62). OS was 95% for patients receiving Id-KLH with GM-CSF versus 91% in the control arm (NSD). Id-KLH in combination with GM-CSF was well tolerated (Table 5). Dr. Schuster concluded that this therapy represents an opportunity to utilize a patient's immune system to enhance the effectiveness of traditional chemotherapy. Further studies are planned in different histologic variants and as maintenance therapy in follicular disease.

At ASCO, Ghielmini and colleagues presented the long-term follow-up data of a randomized trial designed to evaluate the optimal dosing schedule of rituximab in patients with follicular lymphoma.[27] A total of 202 patients (64 chemotherapy naive, 138 pre-treated) were treated with 4 weekly doses of rituximab (375 mg/m²). Following response assessment patients exhibiting a complete or partial response, or stable disease were randomized either to no further treatment (n=78) or rituximab maintenance (4 doses of 375 mg/m² every 2 months). At a median follow-up of 9.4 years, 25% of patients remained event-free in the prolonged therapy arm versus fewer than 10% in the control arm (*P*=.0007), but with no difference in OS (*P*=.09). An analysis of prognostic factors revealed that having received consolidation rituximab was the only significant influence on outcome (*P*=.008; HR, 0.58; CI, 0.44–0.87). There was no long-term toxicity observed. Secondary malignancies were reported in 11 patients in the observation arm and 10 in the consolidation group (Table 6). Dr. Ghielmini concluded that, on the basis of these observations, the optimal way to administer rituximab is on a prolonged schedule. This benefit was limited mostly to patients who achieved an initial complete or partial response. Notably, previously untreated patients who respond to induction have a 45% chance of remaining in remission at 8 years. Based on these data, prolonged rituximab is safe and effective and may prolong survival in this patient population beyond the end of treatment, independent of other prognostic factors.

Although R-CHOP given every 21 days (R-CHOP-21) is the standard therapy for previously untreated patients with diffuse large B-cell lymphoma, investigators from the German High-grade Lymphoma Study Group have suggested that a more intensive approach, R-CHOP-14, might be a more effective strategy. At ASCO, Cunningham and colleagues presented results from a phase III trial comparing R-CHOP-14 with R-CHOP-21 in this patient population.[28] Patients were randomized to receive 8 cycles of R-CHOP-21 or 6 cycles of R-CHOP-14 plus G-CSF, with 2 additional cycles of single-agent rituximab. Randomization was stratified by age (≤60 years vs >60 years), WHO performance status (0–1 vs 2) and LDH level (normal vs elevated). The primary endpoint was overall survival; secondary endpoints included failure-free survival, toxicity and response to therapy. The investigators presented an interim analysis from 831 patients of a total of over 1,000 randomized to the study with a median follow-up of 17 months. The patient characteristics were comparable between the arms: IPI score of 4 or higher, 17% versus 15%; stage III/IV disease, 63% versus 62%; B symptoms, 44% versus 47%; bulk disease, 51% versus 48%. Median age is 61 years in both arms. There was no apparent difference in the proportion of patients completing study therapy between the 2 groups (82% of patients in the R-CHOP-21 arm vs 89% in the R-CHOP-14 arm). Toxicities in the arms were similar with the higher rates of neutropenia and febrile neutropenia in the R-CHOP-21 arm, but more thrombocytopenia with R-CHOP-14. CR/CRu were 47% in both arms of the study leading to the conclusion that R-CHOP-21 is as safe and effective as R-CHOP-14. Although the data were not sufficiently mature to present failure-free or overall survival, Dr. Cunningham stated that CR rates usually correlate with those outcomes, suggesting that a major difference between the arms will be unlikely.

Autologous stem cell transplantation is a standard of care for patients with diffuse large B-cell NHL who relapse after initial treatment. However, the optimal re-induction strategy is undefined. Gisselbrecht and co-workers presented the updated results from the international CORAL study comparing rituximab, ifosfamide, etoposide, carboplatinum (R-ICE) and rituximab, dexamethasone, aracytine and cisplatin (R-DHAP) as conditioning therapy for CD20-positive, chemosensitive DLBCL patients prior to autologous stem cell transplantation (ASCT).[29] Responding patients then received BEAM and ASCT with a

Table 6. Long-term Follow-up of Single-agent Rituximab in SAKK 35/98 Study

Grade 3/4 Adverse Events	Standard	Prolonged
Asthenia	0%	4%
Other non-hematologic adverse events	3%	8%
Neutropenia	16%	17%
Second malignancices	12	10
Infection	1	2

Adapted from Ghielmini et al. *J Clin Oncol.* 2009;27(suppl): abstract 8512.

Table 7. R-ICE Versus R-DHAP Followed By ASCT and Maintenance Rituximab or Observation in Relapsed DLBCL (CORAL Study); Efficacy

ORR	%	*P* Value
All Patients (n=388) CR/CRu	63% 38%	–
R-ICE (n=197) R-DHAP (n=191)	63.5% 63%	–
No Prior Rituximab (n=122) Prior Rituximab (n=124)	83% 51%	<.0001
Relapsed > 12 mo (n=140) Refractory < 12 mo (n=106)	88% 46%	<.0001
sIPI 0-1 (n=160) sIPI 2-3 (n=76)	71% 52%	<.0002

Adapted from Gisselbrecht et al. *J Clin Oncol.* 2009; 27(suppl):793s (abstract 8509).

secondary randomization to observation or maintenance with standard-dose rituximab for 12 months. The intent-to-treat analysis was performed on the initial 396 patients randomized on the study of whom 202 received R-ICE and 194 received R-DHAP. Patients with prior exposure to rituximab had more refractory disease and adverse prognostic factors. Two hundred and six patients underwent ASCT with 90 serious adverse events reported in the R-ICE arm compared to 120 in the R-DHAP arm. Overall, there was no difference in response rates between the 2 treatment arms (63%). Factors significantly influencing response rate (*P*<.0001) included refractory disease less than 12 months from completion of therapy, secondary IPI more than 1, and prior exposure to rituximab. There was no significant difference in PFS between R-ICE and R-DHAP at 3 years; 42% versus 45% *P*=.4416, and OS; 56% in both arms, *P*=.4899 (Table 7). Survival outcomes were influenced by prior treatment with rituximab and early relapse. Longer follow-up is obviously necessary to evaluate the second randomization, but the authors concluded that at this point there was no difference in the clinical benefit derived from R-ICE and R-DHAP in this patient population.

The efficacy of lenalidomide in a number of clinical settings was presented at the 3 meetings. At ASCO, Dueck and colleagues presented interim results from a phase II study in patients with relapsed and refractory T-cell NHL (TCL).[30] Patients were given oral lenalidomide 25 mg daily on days 1–21 of each 28-day cycle and treatment continued until disease progression, death, or unacceptable toxicity. The primary endpoint was ORR, and secondary endpoints were safety, CR and PR rates, PFS, and OS. In the first 23 evaluable patients the overall response rate was 30% (all partial responses). Median PFS was 96 days (range, 8–696 days) and median OS was 241 days (range, 8–696+ days). The therapy was tolerated as expected, and the most common grade 4 adverse event was thrombocytopenia (33.3%).

Witzig and colleagues presented the final results from the NHL-001 study at ASCO[31] and the PPLC.[32] This study is a phase II multicenter trial of lenalidomide monotherapy in patients with relapsed and refractory indolent NHL. In this study, 25 mg of lenalidomide was self-administered orally once a day for 21 days of every 28-day cycle. The primary endpoint was ORR with secondary endpoints of duration of response, PFS, and safety. Forty-three patients were enrolled in the intent-to-treat analysis, the median age was 63 (range, 42–89 years), and median time from diagnosis was 4.4 years (range, 0.4–24 years). The ORR was 23%, including 7% CR/CRu and 16% PR. Responses were durable (16.5 months); however, at the time of the presentation the median duration of response had not been reached. Seven of 10 responses are ongoing at 15–28 months. These observations may support additional investigation of lenalidomide in the maintenance setting.

Lenalidomide oral monotherapy has also been investigated in a second phase II study in patients with aggressive lymphomas (Study NHL-003) from which several papers were presented over the summer describing the results from various sub-set interim analyses. The efficacy and safety of lenalidomide in patients with relapsed or refractory mantle cell lymphoma (MCL) were presented at EHA[33] and the PPLC[34] by Zinzani and colleagues, and at ASCO by Reeder and colleagues.[35] Fifty-four patients with Mantle Cell Lymphoma were accrued into this study from a total of 218, and were evaluable for response. As with study NHL-001, patients received 25 mg lenalidomide orally for days 1–21 of each 28-day cycle and ORR (CR, Cru and PR) was the primary endpoint. Twenty-three patients (43%) responded to lenalidomide with

Table 8. Sub-set Analysis of a Phase II Study of Lenalidomide in Patients with Aggressive Lymphomas (Study NHL-003); Response in Patients with Mantle Cell Lymphoma

	n	ORR N (%)	CD/Cru N (%)	PR N (%)
MCL (all patients)	54	23 (43)	9 (17)	14 (26)
MCL (prior to bortezomib)	17	9 (53)	3 (18)	6 (35)
MCL (prior to stem cell transplant)	14	8 (57)	2 (14)	6 (43)

Adapted from Zinzani et al, *Haematologica*. 2009; 94[suppl.2]:394 abstract. 0978.

Table 9. Efficacy Outcome of Bortezomib/Bendamustine/Rituximab (VBR) in Relapsed/Refractory Follicular Lymphoma: The VERTICAL Study

Bendamustine Dose Level	N (%) (n=15)		
	ORR	CR	PR
50 mg/m^2 (n=3)	3 (100%)	2 (67%)	1 (33%)
70 mg/m^2 (n=6)	3 (50%)	2 (33%)	1 (17%)
90 mg/m^2 (n=6)	6 (100%)	4 (67%)	2 (33%)

Adapted from Matous et al. *J Clin Oncol.* 2009; 27(suppl): (abstract 8550).

9 patients (17%) achieving a CR or CRu (Table 8). Median DR had yet to be reached. The therapy was well tolerated and consistent with prior observations with this therapy. Witzig and associates described an analysis of the DLBCL patient subset from the same study and reported an ORR of 30% (31/103 patients) evaluable for response.[36] As with the analysis in MCL, the median duration of response had not been achieved and tolerability in this patient sub-set was again consistent with prior observations. Overall, lenalidomide may have a place in the treatment of aggressive lymphomas either alone or in combination with other agents. These data were also presented at EHA by Haloun and colleagues.[37]

Lenalidomide has also been studied in combination with other agents. A presentation from the M. D. Anderson Cancer Center, at ASCO, reported encouraging data with lenalidomide in combination with rituximab in patients with previously untreated indolent lymphoma. Fowler and colleagues presented data on 17 patients.[38] There were no grade 4 adverse events and no hematologic grade 3/4 toxicities, or tumor flare. In the 13 evaluable patients, an objective response was seen in 11 (85%), with a CR in 10 patients (77%). One patient had PR and one had stable disease. None of the patients experienced disease progression while receiving therapy. DeRoock and colleagues also presented data at the PPLC from a different combination study of lenalidomide and rituximab in patients with relapsed/refractory indolent NHL.[39] Of the 11 evaluable patients, 8 (73%) achieved an objective response (4 CRu and 4 PR). Nine patients had been heavily pre-treated (defined as >3 courses of chemotherapy) of whom 6 (67%) showed a response.

Bendamustine has significant single agent activity in various lymphoid malignancies. More recent studies are looking at combinations including this drug. Matous and colleagues presented final results from the VERTICAL dose-finding study of bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma at ASCO.[40] Patients received 5 35-day cycles of constant doses of bortezomib (1.6 mg/m^2 on days 1, 8, 15, and 22) and rituximab (375 mg/m^2 on days 1, 8, 15, and 22 for cycle 1 and on day 1 only for cycles 2–5. Bendamustine was administered at 50, 70, or 90 mg/m^2 and the dose escalation continued based on toxicities. Data from 16 patients with a median of 3 prior therapies (range, 1–13) were reported (4 at the 50 mg/m^2 dose and 6 each at 70 mg/m^2 and 90 mg/m^2). There was 1 dose limiting toxicity at the 70 mg/m^2 dose of bendamustine and one at the 90 mg/m^2 dose (grade 3 thrombocytopenia requiring dose delay). The regimen was well-tolerated and evidence of significant antitumor activity was observed (Table 9). Enrollment has been completed in the phase II portion of the study, with a highest planned dose of 90 mg/m^2 bendamustine. Rigacci and colleagues presented data from a study of bendamustine alone (60–90 mg/m^2) or in combination with rituximab (375 mg/m^2)[41]; 122 patients with a median age of 65 (range, 31–87) and of mixed diagnosis were evaluated after receiving 498 cycles of therapy. All had been heavily pre-treated, the median number of prior treatments was 3 (range 1–80), with 50 patients (41%) having experienced more than 3 chemotherapy regimens. Ninety-seven patients were evaluable for response. The overall response rate was 81%; 5 patients achieved a CR and 52 patients had a PR or stable disease. An analysis of the impact of bendamustine dose or schedule showed that response was independent of both parameters. Of note, all the patients (n=9) with MCL achieved a response. In addition, 22 of the 23 patients with indolent non-follicular lymphoma and 13 of 15 with follicular lymphoma obtained a response. Twenty six of 31 (84%) patients with CLL also achieved response. Patients had been observed for a median period of 7 months (range, 1–36). Therapy was well tolerated with manageable hematologic toxicity consistent with prior

observations (grade 3-4 thrombocytopenia and neutropenia in 7 and 14 patients respectively). The authors confirmed that bendamustine therapy, alone or combination with rituximab, offered a potential therapeutic approach in this heavily pre-treated population. Finally, Weidman and colleagues presented a study designed to evaluate the safety and efficacy of bendamustine in combination with rituximab in elderly patients (≥80 years) with aggressive B-cell lymphomas who were not eligible for R-CHOP or who declined aggressive treatment.[42] Patients with stage I/II disease received 4 cycles of rituximab (375 mg/m^2, day 1) and bendamustine (120 mg/m^2, days 2 and 3) every 21 days, followed by involved field irradiation; patients with stage III/IV disease received 6 cycles of the same treatment followed by 2 consolidating administrations of rituximab. Data were presented from 10 evaluable patients from a total of 13 enrolled in the study (9 male, 4 female) with a median age of 85 years (range, 80–89 years). Nine of the 10 (90%) patients achieved a response: 6 (60%) had a CR, 3 (30%) had a PR, and 1 (10%) had progressive disease. An intent-to-treat analysis of all 13 patients estimated that OS at 2 years was 56%, with a mean observation time of 17.3 months (range, 1–49 months) and a mean PFS of 14.4 months. The therapy was well tolerated; only 1 grade 4 toxicity (neutropenia; 2%) was observed in 46 evaluable treatment cycles; grade 3 toxicities were mild and manageable (leukopenia, 7%; neutropenia, 4%; thrombopenia, 2%; infections, 7%; nausea/vomiting, 4%; diarrhea, 2%; and renal insufficiency, 2%). From this study it appears that the bendamustine/rituximab combination offers a potential alternative treatment for aggressive lymphomas in elderly patients who are not eligible for R-CHOP.

New Agents in Lymphoma

Dr. Bruce Cheson presented preliminary data from an international study evaluating the safety and efficacy of YM155, a survivin suppressant, in DLBCL.[43] Two studies were initiated that included patients with DLBCL; a phase I study in patients with solid tumors or NHL refractory to other appropriate therapies, and a phase II study in refractory DLBCL. Forty-three DLBCL patients were enrolled overall; 2 in the phase I study (n=1 relapsing DLBCL and n=1 refractory DLBCL), and 41 in the phase II study (refractory DLBCL patients). YM155 was administered at 4.8 mg/m^2/day (phase I) and at 5 mg/m^2/day (phase II) as a 168-hour continuous infusion in a 21-day cycle. Treatment could be continued until disease progression or unacceptable toxicity. Dr. Cheson presented data on the initial 37 patients from both studies who have completed therapy and remain on follow-up. Median age was 65 years (range, 23–80) years and 68% were male. Responses were noted in 3 patients all of whom had received 2 prior regimens. Two responders were refractory to their last regimen and one had relapsed approximately 2 years after stem cell transplant (SCT). One patient completed 5 total cycles and proceeded to SCT (disease-free >3.7 years post SCT). A second patient completed 7 total cycles and proceeded to SCT. The third remained in remission for 1.5 years before disease progression. The most common treatment-related grade 3/4 adverse events included fatigue, anemia and neutropenia, hemoglobin decrease and deep vein thrombosis, and fever and bacteremia (8% each). The authors concluded that the observed single-agent, anti-tumor activity in relapsed/refractory DLBCL patients warrants further clinical investigation most likely in combination with rituximab, given the in vitro synergy between the agents (Astellas Pharmaceuticals Inc., unpublished data).

At EHA, Johnson and colleagues presented initial results with CMC-544: a conjugate of anti-CD22 and the toxin calicheamicin.[44] A short dose escalation of the agent given as monotherapy to patients with follicular lymphoma and DLBCL was followed by an expanded cohort of patients at the maximum tolerated dose to assess the therapy in combination with rituximab. CMC-544 was tolerated well with the main toxicity being manageable thrombocytopenia. The response rates are sufficiently encouraging to support further clinical investigation.

Zain and colleagues presented a paper at ASCO that described early clinical data with bellinostat (PXD101), a small molecule pan-histone deacetylase inhibitor (HDAC).[45] This study was a phase I, open-label, dose escalation trial in patients with relapsed/refractory lymphoma (NHL and Hodgkin's disease). Fifteen patients were treated, with median age of 53 years (range 21–70) and a range of malignant disease (33% MCL, 33% Hodgkin disease and 33% other lymphomas). Stable disease was observed in 7 of 10 evaluable patients, including all the MCL patients and 3 of 4 patients with Hodgkin's disease. Median duration of treatment was greater than 77 days (range 62 to >282 days). There were no responses according to the Cheson criteria; however, tumor shrinkage was observed in 3 patients in the range of 43–49%, and the therapy was well tolerated with only mild hematologic toxicity, suggesting that further clinical evaluation of bellinostat is warranted. Finally, Witzig and colleagues presented data at EHA, which demonstrated that everolimus, an oral HDAC inhibitor, has activity in relapsed NHL and Hodgkin lymphoma.[46] In a group of 145 patients (77 with aggressive NHL, 41 indolent NHL, 8 T-cell NHL, and 17 Hodgkin lymphoma) ORR was 33% (48/145 patients with 5 CRs and 43 PRs). Median time to progression was 4.3 months and median duration of response was 6.8 months. Everolimus was well tolerated and the authors believed that this study provided proof of concept that intervention of the mTOR pathway has therapeutic potential.

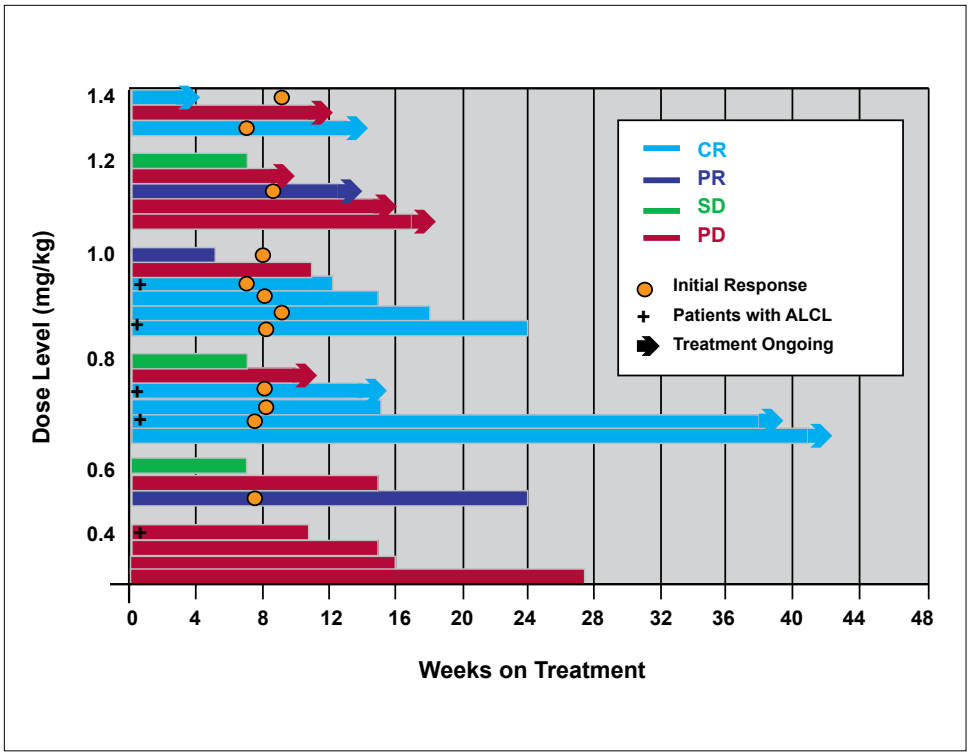

Figure 3. Response and treatment duration in patients with relapsed or refractory Hodgkin's lymphoma or systemic anaplastic large cell lymphoma treated with SGN-35 antibody-drug conjugate.

Adapted from Bartlett et al, *J Clin Oncol.* 27:15s, 2009 (suppl;abstract 8500).

Hodgkin Lymphoma

Advances in therapy for Hodgkin lymphoma were featured at all 3 meetings over the summer with novel therapies demonstrating effectiveness in several studies. SGN-35 is one such therapy that consists of an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E (MMAE). It binds to CD30 expressed on tumor cells, leading to internalization, MMAE release, and subsequent binding to tubulin, prompting cell cycle arrest and apoptosis.[47] Hodgkin lymphoma is a model disease for these agents because of the characteristic CD30 expression by Reed-Sternberg cells.

Preliminary data have been presented in recent years demonstrating clinical activity in lymphoma.[48] At ASCO, Dr. Nancy Bartlett presented the results of a phase I multicenter, dose escalation study of SGN-35 in patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma (sALCL).[49] SGN-35 was administered weekly at doses of 0.4–1 mg/kg (2-hr intravenous infusions) for 2 28-day cycles (6 doses) after which they were restaged using the Cheson criteria to determine whether treatment could continue (stable disease or better). Thirty-four patients were enrolled, with a median age of 34 (range, 13–82), 29 had Hodgkin lymphoma and 5 had sALCL. ECOG performance status was 0-1 for 30 patients (88%) and 2 for 4 patients (12%), and the median number of prior therapies was 5 (range, 1–13). SGN-35 was generally well tolerated; dose-limiting toxicities were observed in 1 of 6 patients at 1.0 mg/kg (grade 3 diarrhea) and 2 of 6 patients at 1.4 mg/kg (grade 4 hyperglycemia and grade 3 diarrhea). The MTD was exceeded at 1.4 mg/kg and is now being determined at lower doses. In the 27 evaluable patients, ORR was 48% (n=13) with CR seen in 37% of patients (n=10). In the patients with Hodgkin lymphoma (n=22) ORR was 41% (n=9) and CR was 27% (n=6). A PR was recorded for 3 patients and stable disease in 11, with only 3 patients showing disease progression. The median duration of response was at least 16 weeks (range, 0.1+ to 27.1+ weeks; Figure 3). This study was also reported at the EHA congress by Younes and colleagues.[50] Panobinostat (LBH589) is another novel therapy showing promise in a variety of tumors including Hodgkin lymphoma.[51] Panobinostat is a pan-deacetylase inhibitor that targets epigenetic and other oncogenic pathways.[52] Preliminary data from an open-label phase II study in patients with Hodgkin lymphoma were presented at EHA by Dr. Younes and colleagues.[53] In this study, 30 patients with either refractory disease or who progressed after ASCT received 40 mg oral doses of panobinstat 3 times weekly in a 21-day cycle. Treatment continued to the point of

disease progression or intolerance to therapy, with dose delay and or modification being permitted. Of the first 30 patients enrolled on the study, preliminary data were available for 14 who had completed treatment. Of these, 6 showed tumor reductions in the range of 18–68%. The therapy was well tolerated with the more common adverse events being grade 3 or 4 thrombocytopenia (6/14), which was managed by dose reduction or delay, diarrhea (6/14), and nausea (8/14). Pharmacodynamic activity was monitored by measuring the programmed cell death protein 1(PD-1) on CD8 positive T cells at predetermined time points after therapy, which was decreased significantly in all cases. Overall, this therapy appears to be well tolerated and exerts a measurable anti-tumor effect in this heavily pretreated population.

Peripheral T Cell Lymphoma

Dr. Owen O'Connor presented data from the PROPEL study, the largest prospective study in patients with relapsed or refractory peripheral T cell lymphoma (PTCL).[54] This nonrandomized, open-label phase II study was designed as the pivotal trial for pralatrexate, a novel targeted antifolate therapy. Pralatrexate is an analog of folate and inhibits dihydrofolate reductase, accumulating in cancer cells leading to apoptosis and cell death.[55] Patients with histologically confirmed PTCL, ECOG performance status of 2 or lower and who had shown disease progression after 1 or more prior treatment received 30 mg/m^2 of pralatrexate intravenously weekly for 6 of 7 weeks, supplemented with vitamin B12 and folic acid. The primary endpoint was ORR and the secondary endpoints were response duration, PFS and OS with response assessment undertaken by independent central review using International Workshop Criteria. A total of 115 patients were enrolled with 109 evaluable for efficacy. The patients were heavily pre-treated with a median of 3 prior systemic regimens (range, 1–12). The therapy was tolerated well, the most common grade 3/4 adverse events were thrombocytopenia (32% of patients); mucositis (22%); neutropenia (20%), and anemia (17%). Twenty-six patients had to discontinue therapy because of adverse events, most frequently mucositis (6%) or thrombocytopenia (5%). The ORR by central review was 28% (n=30) and 8 patients (7% overall) had a CR, 20 patients (18%) had a PR, and 23 (21%) had stable disease (Table 10). The median duration of response was 9.4 months, with 7 responses exceeding 300 days. Importantly, 17 of 69 patients who had not responded to their last prior treatment and 5 of 26 who did not have evidence of response to any prior treatments, responded to pralatrexate. Overall, pralatrexate may offer an effective therapy for this poorly treated patient population irrespective of their prior therapy.

Table 10. PROPEL: Pralatrexate in Patients With Relapsed/Refractory Peripheral T-Cell Lymphoma

Efficacy (assessed by Central Review, International Workshop Criteria)	Number of Patients, % (n=109)
Overall response rate	30 (28%)
Complete response	8 (7%)
Complete response unconfirmed	2 (2%)
Partial response	20 (18%)
Stable disease	23 (21%)
Median duration of response	9.4 months
Median progression-free survival	108 days
Median overall survival	14.7 months

Adapted from O'Connor et al. *J Clin Oncol* 2009; 27(suppl):449s (abstract 8561).

Multiple Myeloma

Advances in multiple myeloma (MM) therapy were prominent at all 3 summer meetings. At ASCO, Palumbo and colleagues presented data from an Italian phase III study designed to determine whether VMPT (bortezomib, melphalan, prednisone, and thalidomide); 9 6-week cycles of bortezomib (1.3 mg/m^2), melphalan (9 mg/m^2), prednisone (60 mg/m^2), and thalidomide (50 mg), is superior to VMP; 9 6-week cycles of bortezomib (1.3 mg/m^2), melphalan (9 mg/m^2) prednisone (60 mg/m^2) in relapsed refractory MM.[56] Five hundred and eleven patients were enrolled from 58 Italian centers. They had symptomatic disease, organ damage or measurable disease and were 65 years or older, or younger than 65 years and not transplant-eligible. There were 500 newly diagnosed MM patients who were 65 years or older, randomly assigned to receive VMPT (N=247) or VMP (N=253) and the primary end point was PFS on an intent-to-treat basis. In the VPMT arm there were 450 patients (median age, 71 years); 221 in the VPMT arm and 229 in the VMP cohort. The best response rates (CR, VGPR, and PR) were 51% for VPMT-treated patients and 42% for VMP for a median of 5 treatment cycles (P=.06). However, CR rates alone were 35% and 21% for VPMT and VMP cohorts respectively (P=.001). Time to response and progression-free survival were superior in the VPMT group at a median follow up of 16.1 months. The 3-year OS was 90% in the VMPT group (n=177) and 89% in the VMP group (n=177; P=.81). Subgroup analyses did not show any statistical difference between response, PFS, and either ISS (international staging system) or chromosomal abnormalities

(t(4;14), t(14;16), or del17) between the VMPT and VMP groups. The incidence of grade 3/4 adverse events was similar in both groups. The most frequent adverse events were neutropenia, thrombocytopenia, peripheral neuropathy, and infection. These authors concluded that VMPT appears to be the superior regimen in terms of response rates, but more follow-up is needed to assess PFS and OS.

A second abstract from EHA involved a retrospective analysis of 2 phase III trials with the goals of determining whether lenalidomide and dexamethasone therapy confers a survival benefit to patients with MM.[57] Data were pooled from trials MM-009 and MM-010, which had a median follow-up of 48 months; the studies were analyzed to determine Kaplan-Meier survival estimates for patients achieving a PR or better. Study MM-009 was a phase III, multicenter, double-blind trial in 354 patients with relapsed or refractory MM. Patients received 40 mg of dexamethasone daily on days 1–4, 9–12, and 17–20 every 28 days and were randomized to receive either 25 mg lenalidomide or placebo daily on days 1–21 every 28 days. Study MM-010 was a companion study of identical design run in Canada, Europe, and Australia.[58] A comparison was made between patients receiving continuous treatment and those discontinuing treatment due to adverse events or disease progression. Although the authors acknowledge that this analysis should be confirmed in a prospective study, the results indicate that continued treatment with lenalidomide and dexamethasone has a statistically significant impact on OS.

A series of studies suggest that a number of newer agents hold promise in MM. At ASCO, Jagannath and colleagues presented final results of an open-label, single-arm, phase II study of carfilzomib in patients with relapsed and refractory MM.[59] Carfilzomib is, mechanistically, a proteasome inhibitor that is highly selective for unique active sites within the proteasome. As such, it has activity very similar to bortezomib, but with the unique advantage of minimal cross-reactivity with other catalytic sites within the proteasome or across other protease classes.[60] This study enrolled heavily pretreated refractory MM patients who have failed all proven agents; relapsed from at least 2 prior therapies, failed bortezomib therapy and at least 1 immunomodulator (thalidomide or lenolidomide), and refractory to last treatment. Carfilzomib was administered as a 20 mg/m^2 dose by IV infusion on days 1, 2, 8, 9, 15, and 16 every 28 days for up to 12 cycles. Forty six patients were enrolled and 39 completed at least 1 cycle of therapy, had measurable M-protein, and were evaluable for response. A durable PR and minimal response (MR; 19%) were observed in 26 patients (Figure 6). Median PFS was 5.1 months and the response duration was 7.4 months. Carfilzomib was well tolerated; a low rate of peripheral neuropathy was observed (10%; 4/39 patients completed 12 cycles). The study has since been opened to include a dose escalation after the first cycle and the sample size has been increased to 250 patients.

Reports of newer agents were also presented at EHA, where 2 papers were presented with intriguing data in relapsed/refractory MM. Richardson and colleagues presented a phase I study of tanespimycin and bortezomib in relapsed/refractory disease. Tanespimycin is an Hsp90 inhibitor which prevents optimal functioning of signal transduction proteins critical for myeloma cell growth and drug resistance.[61] Seventy two patients received bortezomib by intravenous bolus (0.7–1.3 mg/m^2) followed by a 1-hour infusion of tanespimycin (100–340 mg/m^2) in a 21-day cycle on days 1, 4, 8, and 11. Response rates of 41%, 20%, and 14% were observed in patient groups who were bortezomib naive, pretreated, and refractory, respectively. Notably, a response rate of 56% was reported in a sub-group of individuals who were bortezomib naive and had up to 3 prior therapies. The most severe adverse events (>grade 3) were thrombocytopenia (25%), diarrhea, anemia, and fatigue (all 7%), back pain, and AST elevation (4% each); there was no grade 3 or 4 peripheral neuropathy, and only 4.2% of patients had neutropenia (2.8%, >grade 3). All adverse events were manageable with dose reduction and appropriate supportive care. This therapeutic combination is clearly active and well tolerated in this patient group and a phase III study of tanespimycin and bortezomib versus monotherapy with bortezomib is ongoing.

A final study with a novel proteasome inhibitor NPI-0052 was reported at ASCO. This molecule is unique in that it acts as a proteosome inhibitor but is a non-peptide and appears to have a slightly different cellular activity than bortezomib, which may confer improved efficacy on the molecule with a better safety profile.[62] Hofmeister and colleagues reported a small phase I dose escalation study in patients with relapsed/refractory disease. Seventeen patients were treated with intravenous NPI-0052 weekly for 3 weeks in 4-week cycles with doses ranging from 0.025 mg/m^2 to 0.6 mg/m^2, without reaching a MTD. The therapy was well tolerated; drug-related adverse events were mild-to-moderate fatigue, nausea, and diarrhea. Of note, NPI-0052 does not appear to induce peripheral neuropathy or myelosuppression. Two patients remained on the study for over 6 months and 1 year with stable disease and did not experience any significant toxicity. The dose escalation was able to continue on to a planned phase II dose for relapsed/refractory disease, and additional trials in MM are being initiated.

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Commentary

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This summer was notable for 3 meetings providing important new information and thoughtful perspectives on the biology, diagnosis and therapy of patients with hematologic malignancies: ASCO, the Pan Pacific Lymphoma Conference (PPLC), and the European Society of Hematology (EHA) meeting. Some of the studies resolved or created controversies, others were practice changing, while data on a large number of new drugs and combinations offered promise for the future.

Leukemia

Traditionally, the 2 most important negative prognostic factors in acute myeloid leukemia were older age and abnormal cytogenetics. However, patients with apparently normal chromosomes still had a markedly variable course. At ASCO, CALGB investigators shed light on this issue with several presentations demonstrating the importance of newly identified molecular/genetic features, including NPM1 mutations and microRNA 181a (mIR-181a) expression. Previous data have shown that in younger patients without FLT-ITD, NPM mutations predict outcome; Becker and colleagues looked at this finding in older patients and came to a similar conclusion. The same investigators have recently published that CEBPA mutation was a favorable predictor in cytogenetically normal patients and a unique microRNA profile. CEBPA encodes a protein member of the basic region leucine zipper (bZIP) transcription factor family necessary for myeloid differentiation. At ASCO, Schwind and colleagues also showed that mIR-181a had a positive impact independent of CEBPA mutational status. Finally, Marcucci and colleagues presented a new molecular-genetic classification of cytogenetically normal AML young patients, including FLT3, NPM1, CEBPA, WT1 mutations, ERG and BAALC expression, concluding that prognostic classification is improved by adding CEBPA and WT1 mutation and ERG testing, although standardization is needed.

Although we are gaining a better understanding of the differences amongst morphologically similar patients, there has been limited improvement in therapeutic outcome in decades. Until new, effective agents become available, it is important to optimize current regimens. Towards this end, ECOG investigators reported at ASCO the results of a randomized phase III trial comparing 2 doses of adriamycin in a 7+3 schedule, 45 mg/m^2 and 90 mg/m^2. Not only was the complete remission (CR) rate significantly improved (70.6% vs 57.3%), but so was the median overall survival of 23.7 versus 15.7 months. However, it appeared that this benefit was restricted to patients younger than 55 years old, with lower risk cytogenetics, and with no impact on those patients who were FLT3-positive. Thus, this study defined a new standard regimen for younger patients, but with considerable room for improvement.

At ASCO and EHA there was a major focus on chronic lymphocytic leukemia (CLL). Regimens such as fludarabine and rituximab, with or without cyclophosphamide induce responses in 90% of previously untreated patients, yet relapse is inevitable and new treatment approaches are needed. Given the favorable safety profile of rituximab in this disease, several second- and third-generation anti-CD20 monoclonal antibodies are in development. The most widely studied is ofatumumab, which binds to a different epitope on CD20 than rituximab. At EHA, Kipps and colleagues and Wierda and colleagues presented data demonstrating efficacy with this antibody in patients who were either refractory to both fludarabine and alemtuzumab or who were fludarabine refractory and with bulky lymphadenopathy, making them poor candidates for alemtuzumab therapy. Responses were observed in about half the patients in either group. Whereas the investigators demonstrated similar activity in patients who had been previously treated with rituximab as those who had not, there was no information as to the activity in patients whose disease was refractory to that antibody. Ofatumumab is currently under evaluation by the U.S. Food and Drug Administration (FDA) and will hopefully be available as another treatment option for these patients. Activity has also been demonstrated in patients with follicular and low-grade non Hodgkin lymphoma (NHL)and further development is under way.

Ga101 is the first humanized type II anti-CD20 actively studied in clinical trials. At EHA Carton and coworkers reported the results of their phase I/IIa study in patients with a variety of B-cell malignancies, including CLL/SLL, demonstrating important activity. Whether either of these anti-CD20 antibodies will supplant

rituximab will require demonstration either of superior activity, or efficacy in patients resistant to rituximab.

Almost half a century ago, William Dameshek, one of the pioneers of the field of Hematology proposed that CLL was not a lymphoproliferative disorder but was, instead, a lymphoaccumulative disease in which the malignant cells were not growing out of control but, instead they did not die. Subsequent research confirmed that the processes that activate what we now know as apoptosis, or programmed cell death, are defective in CLL. In the past few years an increasing number of small molecules that target various apoptotic pathways have entered clinical trials. Oblimersen sodium first demonstrated a survival improvement in combination with fludarabine and cyclophosphamide in patients with relapsed disease, with data updated at the EHA by O'Brien and colleagues. Newer agents include ABT-263, an orally available BH3 mimetic that inhibits a number of Bcl-2 family proteins. At EHA Wierda and coworkers presented data from two phase I trials demonstrating safety and efficacy with this agent, which is now being combined with other drugs, including anti-CD20 monoclonal antibodies.

Increasing attention is being directed towards bendamustine, either the oldest new drug or newest old drug in the treatment of lymphoid malignancies. Knauf and colleagues updated their phase III trial in which bendamustine outperformed chlorambucil in untreated CLL, confirming the superior efficacy and safety of this agent compared with chlorambucil, and demonstrating it to be another effective, initial option for this disease. A trial comparing B-R with FCR is underway and may redefine our approach to this disease.

Non-Hodgkin's Lymphoma (NHL)

The addition of rituximab to standard cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) provided the first evidence for an improvement in the outcome of patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. Nevertheless, a third of patients in the former group are not cured of the disease, and none of the latter. One approach to improving the outcome of patients with DLBCL was to intensify the CHOP regimen. The German High Grade Lymphoma Study Group previously compared CHOP vs CHOP plus etoposide (CHOEP), each administered every 14 or 21 days. The CHOEP-14 results proved superior. However, when rituximab was subsequently added to CHOP-14 or CHOEP-14, the outcomes were comparable, failing to support a role for etoposide. Whether R-CHOP-14 is superior to R-CHOP-21 has not yet been resolved. However, at ASCO, Cunningham and coworkers presented preliminary data from a similar comparison. Complete and overall response rates were comparable between the arms. Although the data were not sufficiently mature to present progression-free or overall survival data, the authors did note that CR rates generally predicted time-dependent endpoints. Thus, we should not be optimistic that there will be a substantial difference between the curves. A similar comparison is under study by the GELA group.

Patients with DLBCL who are old and have comorbidities, including cardiac dysfunction, present a therapeutic challenge. Data from EHA with R-bendamustine suggested promising activity in this population and this combination warrants further study.

Few new agents have demonstrated activity in relapsed/refractory DLBCL. At ASCO, Cheson and colleagues presented the first data with YM-155, a survivin antagonist, showing modest activity in DLBCL; however, planned combinations with rituximab are likely to be more effective. Lenalidomide has also induced responses in about a quarter of patients with this histology, and combination strategies incorporating this agent are warranted.

Attempts to improve on the activity of rituximab include using it as maintenance following induction therapy. An ECOG/CALGB intergroup, randomized trial demonstrated that there is clearly no place for this approach in patients with DLBCL treated with R-CHOP. However, data for maintenance in follicular lymphoma are conflicting. At ASCO, Ghielmini and colleauges from the Swiss SAKK group presented 8-year follow-up data from a trial in which previously treated and untreated patients with follicular and low-grade NHL received 4 weekly doses of rituximab followed by 4 additional doses at 2-month intervals. The event-free survival advantage persisted over time; however, the difference in survival was not significant and any benefit appeared restricted to patients who had an initial complete remission. At the PPLC, Sonali Smith and Bruce Cheson debated the issue of maintenance, concluding that the currently available published data are mostly irrelevant to current practice as no positive results with this approach following R-chemotherapy are available. What is needed are the data of the extremely important PRIMA study in which patients received chemotherapy plus rituximab and were then randomized to rituximab maintenance or observation. Hopefully, preliminary data may be available at the 2009 ASH meeting.

Bendamustine is becoming an important drug for relapsed and refractory follicular lymphoma. Following impressive data from Germany with single-agent therapy,

Cheson and coworkers presented the aggregate North American experience at the PPLC, with results at least as good as those coming from Germany. Further support for this agent was provided by Rigacci and colleagues at EHA for bendamustine alone and in combination with rituximab. Rummel and coworkers have completed a study in previously untreated patients with follicular and mantle cell lymphoma in which B-R demonstrated efficacy comparable to R-CHOP but with significantly less toxicity. Further follow-up of these data are underway, and B-R may take a place in the initial therapy of these diseases in appropriate patients, including those who are older or have comorbidities.

Other novel bendamustine-containing combinations in development include the Vertical trial regimen, the phase I portion of which was presented at ASCO by Matous and colleagues with bendamustine, bortezomib and rituximab in relapsed or refractory follicular NHL. Not only was the regimen well tolerated, but it had a high level of efficacy. The phase II study of this combination has been recently completed and the data will be available at the 2009 ASH meeting.

Lenalidomide is a second generation immunomodulatory agent with modest single-agent activity in relapsed/refractory follicular NHL. However, Fowler and coworkers at ASCO demonstrated impressive activity when combined with rituximab as initial treatment of patients with this disease. Combinations including lenalidomide with other drugs, such as bendamustine, are in development.

The role of anti-lymphoma vaccines was also an important topic of controversy at ASCO. The idiotype is the only lymphoma-specific target and earlier data suggested that patients with lymphoma who were capable of mounting a cellular or humoral response to anti-idiotype vaccines appeared to exhibit a longer time to progression than those who did not. Following clearly negative studies with Genitope's MyVax and Favrille's FAVId, data from the BioVax phase III trial were presented at the plenary session of ASCO. Enthusiasm for the data was tempered by the fact that a progression-free survival benefit was observed in the vaccine-treated group, but with no survival advantage, and the benefit was only apparent in patients who attained a response that lasted at least a year following intensive induction chemotherapy. How these data will be perceived by regulatory agencies and the general hematology/oncology community remains to be determined.

Peripheral T-cell NHLs have been a previously neglected area therapeutically. CHOP has been the initial standard for initial therapy; however, results with this combination have been disappointing and newer agents are desperately needed. Fortunately, there are now an increasing number of drugs that target this challenging subpopulation of patients. Dr. O'Connor presented an important update on the international PROPEL trial with the novel antifol pralatrexate which will hopefully soon be more widely available. A number of histone deacetylase inhibitors are also in clinical trials, and preliminary data suggest activity for lenalidomide as well. Given the dismal results with currently available regimens, effective new agents could rapidly be moved into frontline strategies.

Hodgkin's Lymphoma

Despite the increasing use of FDG-PET scans in the assessment and management of patients with lymphoma, there is limited guidance as to how to use the information to limit unnecessary therapy for low-risk patients while improving outcome for those at high-risk. One particularly challenging situation is what to do with patients whose scan remains positive after several cycles of treatment. Gallamini and associates treated patients with advanced HL using ABVD and those that were PET-positive after 2 cycles received the intensive BEACOPP regimen; in contrast to the expected progression-free survival of 12% from historical controls, intensification led to 56%. Ongoing and planned North American risk-directed studies in patients with limited-stage, bulky, and advanced stage disease will further evaluate this issue.

A number of new agents have shown promise for patients with relapsed and refractory disease. Nancy Bartlett at ASCO and Anas Younes at the EHA presented exciting data with SGN-35, a drug-antibody conjugate of an anti-CD30 monoclonal antibody with the tubulin poison auristatin. Another agent of interest is panabinostat, a histone deacetyalse inhibitor. The future role for such agents will be to improve the initial approach to this disease.

Multiple Myeloma

The management of patients with multiple myeloma is becoming increasingly effective, but the disease remains incurable. Regimens including various combinations and permutations of thalidomide, lenalidomide, bortezomib, and liposomal doxorubicin were presented at ASCO and EHA. However, we will require randomized trials to determine which regimen is preferable for which patient subset. Unfortunately, a limited number of other new promising agents are being studied. Richardson and coworkers presented initial data from a

phase I trial showing activity with tanespimycin, which disrupts HSP90, important for myeloma cell growth. New proteasome inhibitors are also in clinical trials. Another issue is that the role of stem cell transplantation as part of first-line therapy has become increasingly controversial given that the data on which this paradigm was developed were in an era prior to the availability of the newer, more effective regimens.

Conclusions

These 3 outstanding meetings reinforce the progress being made in the diagnosis, prognosis, treatment, and management of patients with hematologic malignancies. Through rational integration of the knowledge we are gaining in each of these areas, clinicians should be optimistic that the outlook of patients with lymphomas, leukemias, and multiple myeloma will certainly improve.

Highlights in Hematologic Malignancies

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

1 In Knauf and colleagues' EHA presentation of a randomized phase III trial comparing bendamustine with chlorambucil as frontline therapy in CLL patients, they found that:

1. ORR and CR were both higher with bendamustine than with chlorambucil.
2. ORR and CR were both higher with chlorambucil than with bendamustine.
3. ORR was higher with bendamustine and CR was higher with chlorambucil.
4. CR was higher with bendamustine and ORR was higher with chlorambucil.

2. In Wierda's trial of patients who were fludarabine and alemuzumab-refractory or BFR CLL patients who had prior exposure to rituximab, they found that:

1. prior exposure to rituximab had no apparent detrimental effect.
2. prior exposure to rituximab had minimal detrimental effect.
3. prior exposure to rituximab had significant apparent detrimental effect.
4. none of the above.

3. In Wetzler's study of omacetaxine in CML patients of chronic phase, accelerated phase, and blast phase, they found that:

1. the accelerated-phase patients had a CHR rate of 20% with a median duration of 4.1 months.
2. the accelerated-phase patients had a CHR rate of 20% with a median duration of 3.3 months.
3. the accelerated-phase patients had a CHR rate of 31% with a median duration of 4.1 months.
4. the accelerated-phase patients had a CHR rate of 31% with a median duration of 3.3 months.

4. In Schuster's study in follicular lymphoma patients who were randomized to receive either vaccination with Id-KLH/GM-CSF or KLH alone with GM-CSF, researchers found that:

1. OS was 91% for patients receiving Id-KLH with GM-CSF, compared to 95% in the control arm.
2. OS was 95% for patients receiving Id-KLH with GM-CSF, compared to 91% in the control arm.
3. PFS was 91% for patients receiving Id-KLH with GM-CSF, compared to 95% in the control arm.
4. PFS was 95% for patients receiving Id-KLH with GM-CSF, compared to 91% in the control arm.

5. In Dr. Gisselbrecht's international CORAL study:

1. there was no difference in response rates between the R-ICE arm and the R-DHAP arm.
2. there was significant difference in response rates between the R-ICE arm and the R-DHAP arm.
3. there was significant difference in PFS between the R-ICE arm and the R-DHAP arm.
4. none of the above.

6. In Witzig's presentation at EHA about the effects of everolimus in relapsed NHL and Hodgkin lymphoma, they reported that in patients who were treated:

1. median time to progression was 6.8 months and median duration of response was 4.3 months.
2. median time to progression was 5.2 months and median duration of response was 5.5 months.
3. median time to progression was 2.3 months and median duration of response was 6.8 months.
4. median time to progression was 4.3 months and median duration of response was 6.8 months.

7. In Bartlett's presentation at ASCO of the clinical activity of SGN-35 in lymphoma patients, researchers reported that the maximum tolerated dose was

1. 1.2 mg/kg and now being determined at lower doses.
2. 1.4 mg/kg and now being determined at lower doses.
3. 1.6 mg/kg and now being determined at lower doses.
4. 1.8 mg/kg and now being determined at lower doses.

8. In O'Connor's data from the PROPEL study, the most common grade 3/4 adverse event observed from pralatrexate therapy was:

1. thrombocytopenia
2. mucositis
3. neutropenia
4. all of the above

9. Carfilzomib is a proteasome inhibitor that is highly selective for unique active sites within the proteasome.

1. True
2. False

10. The most severe adverse event seen in Richardson's phase I study of tanespimycin and bortezomib in replapsed/refractory multiple myelopma is:

1. thrombocytopenia
2. diarrhea
3. anemia
4. all of the above

Evaluation Form Highlights in Hematologic Malignancies

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)

1. Extent to Which Program Activities Met the Identified Objectives

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

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of hematologic malignancies 1 2 3 4 5
- Review the results of these new study findings including current clinical trials evaluating therapy in the treatment of hematologic malignancies 1 2 3 4 5
- Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with hematologic malignances in an effort to improve current prognosis 1 2 3 4 5
- Identify future research directions for all therapies in hematologic malignancies 1 2 3 4 5

2. 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

3. 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: _____

_____

4. 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 for this activity, please complete the posttest 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 6367. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____

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Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

For Physicians Only

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

☐ I participated in the entire activity and claim 1.5 credits. ☐ I participated in only part of the activity and claim _____ credits.