Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

August 2011 www.clinicaladvances.com Volume 9, Issue 8, Supplement 17

Faculty

Elizabeth Ashforth, PhD
Principal
Chado Healthcare Consulting, LLC
Beverly Hills, California

Bruce D. Cheson, MD
Deputy Chief
Division of Hematology-Oncology
Head of Hematology
Lombardi Comprehensive
Cancer Center
Georgetown University Hospital
Washington, DC

Summer Happenings in Hematology 2011

Highlights in Hematologic Malignancies From the 2011 American Society of Clinical Oncology Annual Meeting, the 16th Congress of the European Hematology Association, and the 11th International Conference on Malignant Lymphoma

A CME Activity
Approved for 1.25
AMA PRA
Category 1
Credit(s)™

Release date: August 2011
Expiration date: August 31, 2012
Estimated time to complete activity: 1.25 hours
Project ID: 8383

Sponsored by the Postgraduate Institute for Medicine

Supported through an educational grant from
Celgene Corporation

Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologists, nurses, and other health care professionals involved in the management of patients with hematologic malignancies.

Statement of Need/Program Overview: The treatment of hematologic malignancies continues to evolve rapidly, and clinicians must be able to integrate the most recent therapeutic advances into their practice in order to maximize the benefit for their patients. The management of patients requires careful consideration of the available options, analysis of the most recent data and treatment guidelines, the impact of assays used to monitor patients, and management strategies for potential toxicities. Several new studies in hematologic malignancies were presented at the 2011 American Society of Clinical Oncology Annual Meeting, the 16th Congress of the European Hematology Association, and the 11th International Conference on Malignant Lymphoma. This educational activity has been planned to provide a summary of the most important data and provide recommendations for the integration of this information into clinical practice.

Educational Objectives

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

- Analyze the benefits and limitations of current treatment strategies for hematologic malignancies
- Interpret recent clinical data in the management of hematologic malignancies
- Define strategies for integrating recent clinical data into clinical practice
- Identify ongoing clinical trials that are expected to impact clinical practice

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Millennium Medical Publishing. PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: The Postgraduate Institute for Medicine designates this journal-based CME activity for a maximum of 1.25/*AMA PRA Category 1 Credit(s)*™/. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure of Conflicts of Interest: Postgraduate Institute for Medicine (PIM) assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high-quality CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest or a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Disclosures:
Elizabeth Ashforth, PhD—No real or apparent financial relationships to disclose
Bruce D. Cheson, MD—Consultant: Cephalon

The following PIM planners and managers, Jan Hixon, RN, BSN, MA, Trace Hutchison, PharmD, Julia Kimball, RN, BSN, Samantha Mattiucci, PharmD, Jan Schultz, RN, MSN, CCMEP, and Patricia Staples, MSN, NP-C, CCRN, hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months. Jacquelyn Matos: No real or apparent conflicts of interest to report.

Method of Participation

There are no fees for participating in and receiving CME credit for this activity. During the period August 2011 through August 31, 2012, participants must read the learning objectives and faculty disclosures and study the educational activity.

PIM supports Green CE by offering your Request for Credit online. If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID 8383. Upon registering and successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately. Processing credit requests online will reduce the amount of paper used by nearly 100,000 sheets per year.

Media: Monograph

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. PIM, Millennium Medical Publishing, and Celgene Corporation do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, Millennium Medical Publishing, and Celgene Corporation. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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

Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Summer Happenings in Hematology 2011

Highlights in Hematologic Malignancies From the 2011 American Society of Clinical Oncology Annual Meeting, the 16th Congress of the European Hematology Association, and the 11th International Conference on Malignant Lymphoma

Elizabeth Ashforth, PhD
Principal
Chado Healthcare Consulting, LLC
Beverly Hills, California

While global attention to William and Kate met fever pitch this summer, the hematology community focused its attention on back-to-back meetings of the American Society of Clinical Oncology (ASCO), the European Hematology Association (EHA), and the International Conference on Malignant Lymphoma (ICML), which took place in Chicago, London, and Lugano, Switzerland, respectively. The paparazzi attention to these meetings may not have matched the media frenzy surrounding the new Duke and Duchess during their visits to Canada and the United States, but there were still plenty of new data to be excited about.

Myelofibrosis

Two groups presented data at the ASCO meeting from the phase III analysis of ruxolitinib in patients with myelofibrosis (MF). A key characteristic of MF is dysregulated signaling of the Janus kinase/signal transducer and activator of transcription (JAK-STAT).[1] Ruxolitinib is a selective inhibitor of the JAK1 and JAK2 pathways, with previously demonstrated clinical activity in this disease, which currently has no viable treatment options.[2] The 2 papers presented at the ASCO meeting represented 2 separate randomized, phase III trials of ruxolitinib in patients with intermediate-2 or high-risk MF. (Risk factors include thrombocytopenia, anemia, red cell transfusion requirement, circulating blasts, leukocytosis, unfavorable karyotype, constitutional symptoms, and older age. Intermediate-2 risk is defined as the presence of 2–3 factors, and high risk is defined as 4 or more factors.) Verstovek and colleagues reported on the COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment) trial, in which 309 patients were randomized to receive placebo or ruxolitinib 15 mg or 20 mg orally twice a day depending on baseline platelet count (100–200 × 10^9/L or >200 × 10^9/L, respectively).[3] This study was also presented at the Presidential Symposium at the EHA meeting.[4] The primary endpoint was the proportion of patients who experienced reduced spleen volume of at least 35% at week 24 of therapy, as assessed by blinded review of spleen magnetic resonance imaging (MRI) or computed tomography (CT). Significantly more patients had a greater decrease in total symptom score on the ruxolitinib arm than on the placebo arm (46% vs 5%, respectively; P<.0001). However, overall survival (OS) at 60 weeks was quite high and not different between the 2 treatment groups (93.5% ruxolitinib vs 90.9% placebo). Ruxolitinib was well-tolerated; the most frequent adverse event was grade 3/4 anemia and grade 1/2 thrombocytopenia.

Harrison and colleagues reported data from the COMFORT-II study, in which 219 patients were randomized to either ruxolitinib (15 or 20 mg; n=146) or the best available therapy (n=73).[5] In this study, the primary endpoint was spleen volume reduction of at least 35%, as assessed by MRI at week 48. Secondary endpoints were durability of spleen response, changes in symptom burden, and survival. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Fatigue, molecular and serum biomarkers, and transfusion dependence were also assessed. A total of 219 patients were randomized to this study. The primary endpoint of response rate was 28.5% versus 0% (ruxolitinib vs best available therapy at week 48 of therapy; P<.0001), with corresponding rates of 31.9% and 0% reported at week 24 (secondary endpoint). Median time to response was 12.29 weeks, and of the 69 patients who had achieved the primary endpoint at any time during the study, 44 (64%) had done so by the first planned study assessment at 12 weeks. The percent change in spleen volume at any

time during the study was significantly better for the ruxolitinib cohort (best response of 97% reduction vs 35% for the best available therapy cohort; *P*<.0001). An analysis of the EORTC QLQ-C30 scores from baseline to week 48 showed an overall improvement associated with ruxolitinib for measures of appetite loss, insomnia, dyspnea, pain, and fatigue, with improvements seen by week 8 that were maintained through week 48. Ruxolitinib showed a very similar adverse event profile to that seen in the COMFORT-I study and, overall, Harrison and colleagues concluded that this therapeutic has the potential to offer an improved treatment option in MF.

Acute Myeloid Leukemia

Two phase III studies in acute myeloid leukemia (AML) were presented at the ASCO meeting. Dr. Faderl and colleagues reported data from the CLASSIC 1 (A Study of Clofarabine and Cytarabine for Older Patients With Relapsed or Refractory Acute Myelogenous Leukemia) trial of clofarabine and cytarabine compared to cytarabine alone in older patients with relapsed or refractory AML.[6] In this study, patients aged 55 years or older were randomized to receive clofarabine 40 mg/m^2/day intravenously (IV) for 5 days plus cytarabine 1 g/m^2/day IV for 5 days (n=162) or cytarabine 1 g/m^2/day IV for 5 days (n=158) for a maximum of 3 cycles. The 2 treatment groups were well balanced, with patients stratified for relapsed or refractory disease. The primary endpoint of the study was OS, with secondary endpoints of objective response rate, event-free survival (EFS), complete response (CR) rate, duration of response, and safety. Objective response rate and 4-month EFS were superior for the combination cohort (objective response rate: 47% vs 23%; *P*<.0001: EFS: 38% vs 17%; *P*<.0001). In addition, the CR rate was 35% in the combination cohort compared to 18% for cytarabine monotherapy (*P*=.0005). The response rates were very similar between relapsed or refractory patients. However, the primary endpoint was not met in this study; median OS was 6.6 months for clofarabine plus cytarabine and 6.4 months for cytarabine alone (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.778–1.28; *P*=.9951). Whereas the combination regimen was associated with a 47% reduction in the risk of disease progression or death (HR, 0.63; 95% CI, 0.49–0.80; *P*=.0001), early mortality was higher (16 deaths vs 5 and 24 vs 17 when compared to cytarabine monotherapy at days 30 and 60, respectively).

A second phase III study in AML, undertaken by the Eastern Cooperative Oncology Group (ECOG) and presented by Dr. Thomas at ASCO, reported a positive result in older patients with newly diagnosed disease treated with decitabine.[7] Older patients with AML have limited treatment options since they typically have high relapse rates and poor response to therapy, and they are less able to tolerate intensive chemotherapy regimens than younger patients. DNA hypermethylation has been linked to AML, and decitabine—a demethylation agent—has shown activity in a phase II trial of older patients with AML.[8] The patients (N=485) were randomized to receive decitabine 20 mg/m^2/day IV over 1 hour for 5 days every 4 weeks (n=242) or, as comparison, supportive care (n=28) or low-dose cytarabine (20 mg/m^2/day subcutaneously for 10 days every 4 weeks (n= 215). Patients were stratified by ECOG performance status (0–1 vs 2), age (65.9 vs 70 years), and cytogenetic risk (intermediate vs high), and they received therapy until disease progression, death, or unacceptable toxicity occurred. The primary endpoint of the study was OS, with remission rates and safety as secondary endpoints. EFS, relapse-free survival, and pharmacokinetics were also assessed. Patients received a median of 4 cycles (range: 1–29) of decitabine and 2 cycles (range: 1–30) of cytarabine, and the median treatment duration was 4.4 and 2.4 months, respectively. At the protocol-defined clinical cutoff (396 deaths), the 3-year OS was similar between the treatment arms when all patients were included; median OS was not statistically longer with decitabine (7.7 vs 5.0 months; HR, 0.85; 95% CI, 0.69–1.04; *P*=.108). Similar median OS results were found at ad hoc analysis undertaken at 446 deaths; decitabine was associated with survival of 7.7 months versus 5.0 months (HR, 0.82; 95% CI, 0.68–0.99; *P*=.037). However, a subgroup analysis demonstrated that decitabine treatment was associated with significant benefit in OS for patients aged 75 years or older, patients diagnosed with de novo AML, and patients with bone marrow blasts exceeding 30%, intermediate-risk cytogenetics, or ECOG performance status of 2 (Table 1). Higher response rates were found with decitabine treatment when compared with either supportive care or low-dose cytarabine (Table 2). Rates of adverse events were similar between decitabine and cytarabine treatment but lower with supportive care; overall, more than 50% of patients experienced treatment-related grade 3/4 adverse events. In all cohorts, 5% of patients experienced infections, including febrile neutropenia, pneumonia, urinary tract infection, sepsis, septic shock, bronchopneumonia, thrombocytopenia, anemia, and neutropenia. In conclusion, this study showed that decitabine treatment may offer benefit to certain subgroups of elderly patients with newly diagnosed AML.

Hodgkin Lymphoma

At the ICML, Dr. Evens and associates presented findings from the phase III US Intergroup Trial E2496 that had

Table 1. Subgroup Analysis of Overall Survival in Elderly Patients Newly Diagnosed With AML: Decitabine Versus Low-Dose Cytarabine or Supportive Care

Subgroup Analysis Median OS (months)	Decitabine (n=242)	Low-Dose Cytarabine or Supportive Care (n=243)	HR (95% CI)	*P* Value
All patients	7.7	5.0	0.82 (0.68–0.99)	.037
Age ≥75 years	6.3	4.5	0.72 (0.54–0.98)	.035
De novo AML	8.2	5.2	0.71 (0.56–0.91)	.006
>30% Bone marrow blasts	7.1	4.3	0.72 (0.57–0.91)	.005
Intermediate-risk cytogenetics	9.4	6.0	0.78 (0.61–0.99)	.044
ECOG PS 2	5.3	3.6	0.65 (0.44–0.95)	.025

AML=acute myeloid leukemia; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; OS=overall survival.

Data from Thomas XG et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;29:504s. Abstract 6504.[7]

Table 2. Response Rates to Decitabine Compared to Low-Dose Cytarabine or Supportive Care in Elderly Patients Newly Diagnosed With AML

	Decitabine (n=242)	Treatment of Choice (n=243)	Low-Dose Cytarabine (n=215)	Supportive Care (n=28)
CR + CR with incomplete platelet recovery	17.8%*	7.8%*	8.4%	3.6%
CR with incomplete blood count recovery	9.9%	2.9%	2.8%	3.6%

*P=.001; HR, 2.5 (95% CI, 1.40–4.78).

AML=acute myeloid leukemia; CI=confidence interval; CR=complete response; HR=hazard ratio.

Data from Thomas XG et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;29:504s. Abstract 6504.[7]

compared doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and Stanford V in patients with advanced-stage Hodgkin lymphoma (HL).[9] The patients (N=812) were randomized to receive ABVD for 6–8 cycles, with radiotherapy for bulky mediastinal disease or the Stanford V regimen (12 weeks of chemotherapy followed by consolidation radiotherapy). There was no difference between the arms in efficacy. The current study population was a subset of the overall trial that included 43 patients aged 60 years or older, 23 of whom had received ABVD. This subgroup had a higher proportion of mixed cellularity histology than did the group younger than 60 years old, and fewer patients in the older population had an ECOG performance status of 0. Otherwise, the treatment arms were well balanced for age (median 65 years), and the majority of patients had stage 3 disease.

The 2 regimens were well-tolerated, with neutropenia being the most common grade 3/4 toxicity. Other grade 4 toxicities included dyspnea (n=3), motor and sensory neuropathy (n=2 each), hypoxia (n=1), constipation (n=1), infection (n=1), and myalgia (n=1). The treatment-related mortality rate was the same for both regimens (5% overall, n=1 for each treatment; pulmonary with ABVD and infection with Stanford V). At least 1 dose reduction occurred per protocol in 84% of elderly patients. There was no significant difference in outcome measures between the treatment arms (overall response rate [ORR], CR rate, OS, or time to progression, relapse, or failure-free survival. However, an analysis of the entire patient population did show that the 3-year progression-free survival (PFS; 55% vs 76%; P=.0014) and OS (69% vs 93%; P<.0001) were significantly decreased among

elderly patients even though there was no difference in ORR and CR rate compared with younger patients. Dr. Evens and associates concluded that the apparent difference in PFS and OS might be a reflection of a difference in the disease biology in the elderly requiring novel therapeutic approaches.

Dr. Chen and coworkers presented an update at ASCO on the phase II trial of brentuximab vedotin in patients with relapsed or refractory HL.[10] This study was presented previously at the American Society of Hematology meeting in 2010, the ASCO presentation being an update based on additional patient follow-up. Brentuximab vedotin, formerly known as SGN-35, is an antibody-drug conjugate that consists of an anti-CD30 (brentuximab) and 3–5 units of the antimitotic agent monomethyl auristatin, which is responsible for the agent's antitumor activity through disruption of tubulin within tumor cells. This study was a phase II, single-arm, multicenter study evaluating the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory HL after autologous stem cell transplant. The therapy is given as a 30-minute outpatient IV infusion of 1.8 mg/kg every 3 weeks for up to 16 cycles. The primary endpoint was ORR per an independent review facility. It was previously reported that 75% of patients achieved an objective response, including 34% with complete remission; median duration of response for all responding patients was 6.7 months, and the duration of response for patients achieving a CR had yet to be reached.[11] Updated data presented at ASCO, based on additional patient follow-up, reported an estimated 12-month OS of 89% for all patients. Median duration of response in patients with a CR was 20.5 months, and 21 patients with a CR were alive and free of progression at the time of the last analysis prior to the meeting. Patient follow-up is ongoing. However, these encouraging data helped to support the unanimous recommendation in July 2011 by the US Food and Drug Administration's Oncologic Drugs Advisory Committee for the accelerated approval of brentuximab vedotin in refractory HL.

Non-Hodgkin Lymphoma

Follicular Lymphoma

The PRIMA (Primary Rituximab and Maintenance) study was a large, multinational trial in which patients with untreated follicular lymphoma were treated with 1 of 3 chemoimmunotherapy regimens at the choice of the treating physician: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), rituximab plus cyclophosphamide, vincristine, and prednisolone (R-CVP), and fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) with a randomization to rituximab maintenance or observation. Thus, it was not specifically designed to determine the optimal chemotherapy regimen to use in combination with rituximab in follicular non-Hodgkin lymphoma (NHL). This study enrolled 1,202 patients with follicular NHL. Every patient received 8 cycles of induction therapy. Patients who achieved a CR, CR unconfirmed (CRu), or partial response (PR) were then randomized to receive 2 years of rituximab maintenance therapy or observation alone. Efficacy outcomes were reported before the ICML; a significant increase in PFS was observed with rituximab maintenance.[12] At the ICML this summer, Dr. Morschhauser presented an analysis of the choice of induction chemotherapy regimen.[13]

Baseline characteristics were well balanced among patients receiving R-CHOP (n=881), R-CVP (n=268), and R-FCM (n=44). The ORR was slightly higher in the R-CHOP arm, as was the CR/CRu rate (Table 4). The PFS at a median follow-up of 42 months was 66.5%

Table 3. Response Rates to Various Chemotherapy Regimens in Follicular NHL: Results From the PRIMA and FOLL05 IIL Studies

The PRIMA Study[12]

	R-CHOP (n=881)	R-CVP (n=268)	R-FCM (n=44)
ORR	94.4%	86.9%	79.5%
CR/Cru	68.1%	53.7%	63.6%
PR	26.3%	33.2%	15.9%
SD	1.2%	5.2%	0%
PD	1.7%	4.9%	9.0%

The FOLL05 IIL Study[14]

	R-CHOP	R-CVP	R-FM
CR	71%	66%	70%
PR	23%	21%	21%
SD/PD	5%	10%	6%

CR=complete response; Cru=complete response unconfirmed; ORR=overall response rate; PD=progressive disease; PR=partial response; PRIMA=Primary Rituximab and Maintenance; SD=stable disease; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP=rituximab plus cyclophosphamide, vincristine, and prednisolone; R-FCM=rituximab plus fludarabine, cyclophosphamide, and mitoxantrone; R-FM=rituximab plus fludarabine and mitoxantrone.

Data from Morschhauser F et al. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22. Abstract 022.[13]

Table 4. The Impact of ASCT on PFS and OS After Chemotherapy With R-CHOP in Patients With Advanced High-Risk Diffuse NHL (SWOG Study 9704)

	CHOP ± R for 1 Cycle + ASCT (n=125)	CHOP ± R for 3 Cycles (n=128)	HR (95% CI)	*P* Value
2-Year PFS rate	69%	56%	1.72 (1.18–2.51)	.005
2-Year OS rate	74%	71%	1.24 (0.81–1.91)	.16

ASCT=autologous stem cell transplant; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CI=confidence interval; HR=hazard ratio; NHL=non-Hodgkin lymphoma; OS=overall survival; PFS=progression-free survival; R=rituximab; SWOG=Southwest Oncology Group.

Data from Stiff PJ et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;29:504s. Abstract 8001.[17]

(R-CHOP), 48.9% (R-CVP), and 58.9% (R-FCM), and the OS was 93.2% (R-CHOP), 88.3% (R-CVP), and 74.1% (R-FCM). The choice of chemotherapeutic regimen did not affect PFS in the observation arm, whereas R-CHOP induction was associated with a PFS benefit in the rituximab maintenance arm. In a Cox regression multivariate analysis adjusted by prognostic factors, improved PFS was significantly associated with randomization to the rituximab maintenance arm (*P*<.0001), age older than 60 years (*P*=.0013), female sex (*P*=.013), low Follicular Lymphoma International Prognostic Index (FLIPI) score (*P*<.0001), and R-CHOP or R-FCM induction therapy (*P*=.0029). Grade 3/4 adverse events were reported in 18% of patients receiving R-CHOP, 17% of patients receiving R-CVP, and 25% of patients receiving R-FCM. Serious adverse events were reported in 23%, 22%, and 27% of R-CHOP, R-CVP, and R-FCM patients, respectively. Rates of infection of any grade were low and balanced between the arms. Overall, the authors concluded that even though toxicity was similar between R-CHOP and R-CVP, ORR and PFS were improved with the R-CHOP regimen. It will be interesting to see if this trend is maintained when OS data are available.

A second large study in follicular lymphoma was presented by Dr. Federico and colleagues at ICML.[14] In this multicenter trial, known as FOLL05 IIL (Phase III Multicentric IIL Study, Three Randomized Arms [R-CVP vs R-CHOP vs R-FM] for Treatment of Patients With Stage II–IV Follicular Lymphoma), 534 patients with treatment-naïve stage II–IV follicular lymphoma were randomized to receive 8 doses of rituximab with 8 cycles of CVP (R-CVP), 6 cycles of CHOP (R-CHOP), or 6 cycles of fludarabine 25 mg/m^2 on days 1–3 and mitoxantrone 10 mg/m^2 on day 1 (R-FM). All patients received the same dose of rituximab. Baseline characteristics were similar across treatment groups; median age was 56 years (range: 30–75 years), 37% had a FLIPI score greater than 2, and at least 90% of patients in each arm had stage III/IV disease. The endpoint of the study was time to treatment failure. Dr. Federico presented data at a median follow-up of 25 months. At this point, the 3-year time to treatment failure rate was 47%, 57%, and 60% for patients receiving R-CVP, R-CHOP, and R-FM, respectively (R-CHOP vs R-CVP: *P*=.022; R-FM vs R-CVP: *P*=.008; R-FM vs R-CHOP: *P*=NS). In addition, both R-CHOP and R-FM were associated with higher response rates than R-CVP (Table 4). With 25 reported deaths in the evaluable population, 3-year OS for the entire group was approximately 94% (97%, 96%, and 92% for R-CVP, R-CHOP, and R-FM, respectively). Toxicity was mainly hematologic; with 56% of patients reporting grade 3/4 neutropenia. R-FM was associated with a higher incidence of both hematologic and non-hematologic toxicities and, notably, more secondary malignancies (AML/myelodysplastic syndrome [MDS] and other tumors). Dr. Federico concluded that although R-CHOP and R-FM were superior to R-CVP in this study in terms of antitumor activity, R-FM was associated with a less acceptable toxicity profile, including increased secondary malignancies, that preclude its use in this population of patients.

Dr. Friedberg presented an intriguing paper at ICML describing an outcome analysis in patients with stage I follicular lymphoma from the National LymphoCare Study database.[15] The National LymphoCare Study is a multicenter, longitudinal, observational study designed to collect information on treatment regimens and outcomes for patients with newly diagnosed follicular lymphoma in the United States. Whereas guidelines suggest that radiation therapy should be considered as first-line therapy, only a third of patients are treated in that manner. Dr. Friedberg reported outcome data for a group of 467 patients, median age 61 years (range: 25–86 years), with varying histologic grades (44% grade 1, 26% grade 2, 18% grade 3, and 12% not otherwise specified). Of these patients, 206 were considered rigorously staged (they had undergone CT

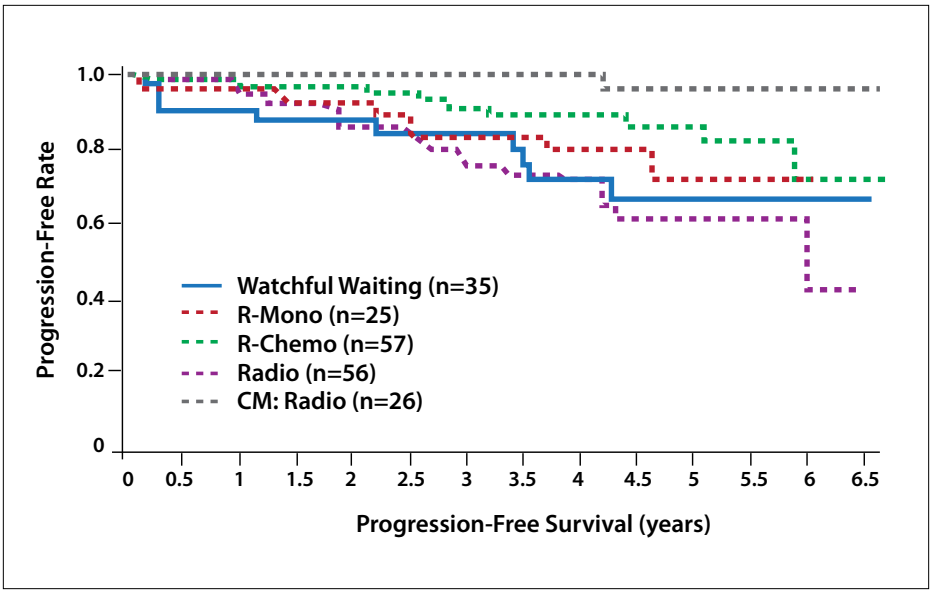

Figure 1. Outcome analysis in follicular lymphoma: progression-free survival in 206 rigorously staged patients from the National LymphoCare Study.

R-Mono=rituximab monotherapy; R-Chemo= rituximab and chemotherapy; Radio=radiation therapy alone; CM:Radio=radiation therapy combined with other treatment.

Adapted with permission from Friedberg J et al. *Ann Oncol* (ICML Annual Meeting Proceedings). 2011;22:90: Abstract 026.[15]

with or without positron emission tomography [PET] and bone marrow biopsy; 128 had undergone PET and bone marrow biopsy). Treatment modalities were reported as watchful waiting (18%), rituximab monotherapy (12%), rituximab and chemotherapy (29%), radiation therapy alone (28%), and radiation therapy combined with other treatment (13%). A Cox regression analysis of outcome—measured as PFS adjusted for age, grade, elevated lactate dehydrogenase (LDH) levels, and hemoglobin below 12 g/dL—revealed that radiation therapy alone was not superior to watchful waiting (HR, 0.9; CI, 0.3–2.2), but other treatments were (HR, 0.3; CI, 0.1–0.9; Figure 1). Of note, rituximab in combination with chemotherapy showed a statistically improved PFS compared to watchful waiting (HR, 0.2; CI, .05–0.6). Finally, there was no difference in outcome in patients who were staged by PET (n=128) or by CT (n=78). The best results were in the chemoradiation and rituximab plus chemotherapy groups, followed by rituximab alone and observation. The worst outcome was experienced by patients treated with radiation therapy alone. The result of this analysis raises the question of what the optimal therapy is for this patient population; however, Dr. Friedberg and colleagues questioned whether radiation alone was the best choice for this group of patients.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a potentially curable malignancy; but, with R-CHOP—the current standard of care—the average cure rate of patients with advanced-stage disease hovers around 50–60%. Second-line therapy tends to rely on regimens such as rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE) or dexamethasone, high-dose cytarabine, and cisplatin (DHAP) with autologous stem cell transplant (ASCT). This summer, several independent groups presented results from studies designed to address whether ASCT should be used upfront rather than at the time of relapse. In addition, the benefit of intensity of chemotherapy was evaluated in DLBCL. Overall, these investigations did not support the use of ASCT upfront, nor did they show that more chemotherapy is necessarily better in DLBCL.

At the ASCO meeting, Dr. Cunningham and associates reported the results of a phase III trial enrolling 1,080 treatment-naïve DLBCL patients who were randomly assigned in equal numbers (540 patients in each arm) to receive either 8 cycles of R-CHOP-21 or 6 cycles of R-CHOP-14 plus supportive care followed by 2 cycles of single-agent rituximab.[16] Each cohort was similar with respect to median age, B symptoms, bulky disease, disease stage, and International Prognostic Index (IPI). More than half of the patients were 60 years or older; none were younger than 19 years.

After a median follow-up of 37 months and 237 deaths, there was no difference in PFS between the groups. OS was comparable in the R-CHOP-21 arm (81%) and the R-CHOP-14 arm (83%). There was also no significant difference in the objective response rate among patients receiving R-CHOP-21 (88%) compared with those in the R-CHOP-14 arm (90%). In addition, patient status at 39 months (measured by death, survival without progression, survival with progression or relapse, deaths without documented progression, and progression or relapse followed by death) was virtually identical for

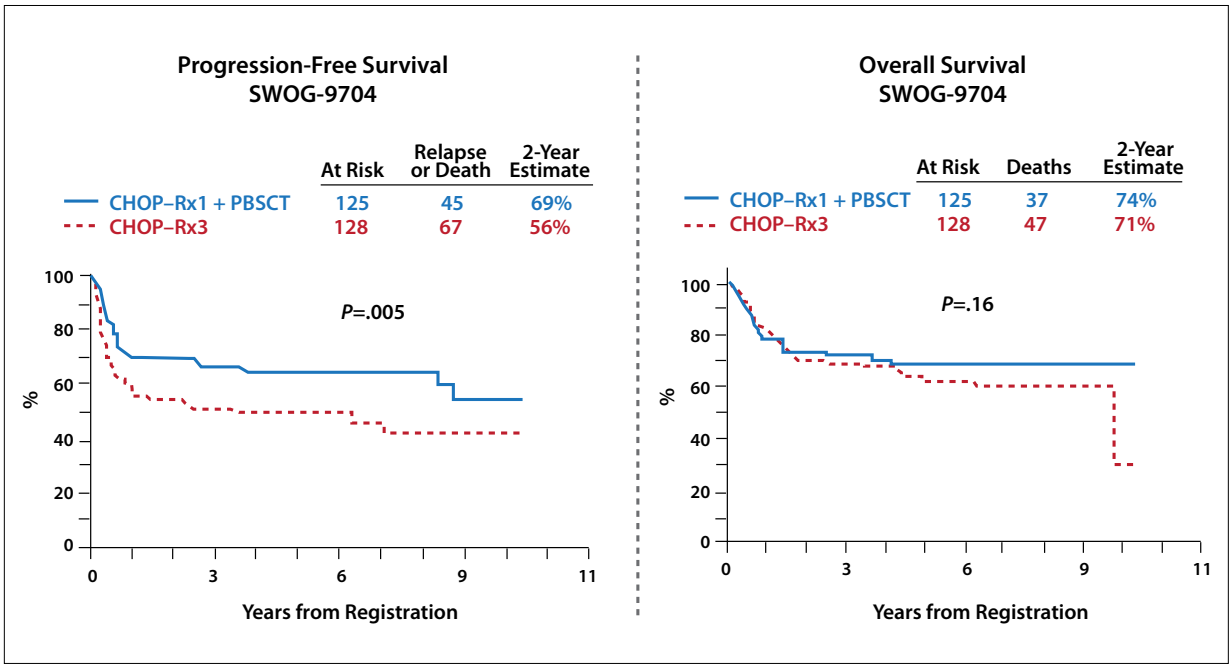

Figure 2. Overall outcome (progression-free survival and overall survival) in a phase III US/Canadian intergroup study that compared 8 cycles of CHOP with and without rituximab to 6 cycles followed by ASCT in 370 patients with aggressive non-Hodgkin lymphoma at high-intermediate risk or high risk based on age-adjusted International Prognostic Index scoring.

ASCT=autologous stem cell transplant; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; R=rituximab; SWOG=Southwest Oncology Group; PBSCT=peripheral blood stem cell transplant.

Adapted with permission from Stiff PJ et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;29:504S. Abstract 8001.[17]

the 2 groups. Dr. Cunningham noted that benefit from accelerated R-CHOP-14 was similar across all subgroups, including patients older than age 60, patients with high IPI score, and patients with MIB1 status and the non-germinal center phenotype—2 presumed predictors of prognosis in this disease. Although grade 3/4 nonhematologic toxicities were comparable in the 2 trial arms, neutropenia and febrile neutropenia were significantly more frequent in patients receiving the 21-day regimen, probably due to primary prophylaxis with granulocyte colony-stimulating factor being administered to patients receiving accelerated treatment. In contrast, thrombocytopenia was significantly more frequent in the R-CHOP-14 arm, presumably as a consequence of greater therapeutic intensity. Toxicities, progressive disease, death, and patient choice contributed substantially to early termination of treatment in the accelerated arm (58 patients) and with standard treatment (107 patients). Dr. Cunningham concluded that CHOP-14 for 6 cycles is not superior to CHOP-21 for 8 cycles.

Dr. Stiff, on behalf of the Southwest Oncology Group (SWOG), presented the long-awaited results from a randomized phase III US/Canadian intergroup study that compared 8 cycles of CHOP with and without rituximab to 6 cycles followed by ASCT in 370 patients with high-intermediate or high-risk age-adjusted IPI aggressive NHL (SWOG 9704).[17] In this relatively high-risk group of patients, 62% had stage IV disease, 85% had an elevated LDH, and 32% had high-IPI grade disease (following age adjustment). Histology leaned toward B-cell lymphoma (89% vs 11% T-cell lymphoma). Median age was 51 years, and 59% of patients were men. Following induction therapy (rituximab was included for most patients with B-cell CD20-positive lymphomas, as the trial began in the pre-rituximab era), patients experiencing a PR or better after 5 cycles were stratified by risk and randomized to receive 1 additional cycle of CHOP (with or without rituximab as appropriate) followed by ASCT with total body irradiation or carmustine-based regimens, or an additional 3 cycles of CHOP (with or without rituximab). Of the 370 patients who enrolled, 253 patients were eligible to proceed to the randomized part of the study. Not surprisingly, grade 3/4 toxicities were more common with transplant versus standard

therapy, including infection (50% vs 13%, respectively), gastrointestinal effects (26% vs 5%, respectively), and metabolic toxicities (13% vs 1%, respectively). Dr. Stiff reported that, although there was a trend for improved PFS for the ASCT arm (Figure 2), there was no difference in OS, which was 74% for chemotherapy plus ASCT versus 71% for chemotherapy alone (Table 4). However, the estimated 2-year PFS rate was 69% with ASCT compared with 56% with induction therapy alone (HR, 1.72; 95% CI, 1.18–2.51; *P*=.005). Dr. Stiff noted that since 18% of relapsed patients from the standard chemotherapy arm were alive and disease-free following ASCT, it could be that subsequent therapies beyond the study protocol have influenced the survival analyses. It was also noted that the benefit of ASCT appeared to be evident primarily in patients with high-IPI disease (2-year PFS 75% with ASCT vs 41% chemotherapy alone). In addition, the 2-year OS rates in these patients were 82% and 64%, respectively. However, in patients with a high-intermediate IPI score, 2-year PFS rates were 66% with ASCT versus 63% with chemotherapy alone, and 2-year OS rates were 75% and 70%, respectively. Although these results suggest a benefit of ASCT in patients with high-risk IPI, this study was not powered to support such an analysis. Thus, it is likely that ASCT will remain an option for relapsed patients for practical reasons until clinical data indicate otherwise.

A number of prospective, randomized trials have tested high-dose therapy followed by ASCT as first-line therapy for younger patients with aggressive B-cell lymphoma, mostly in the pre-rituximab era, limiting the relevance of those data. In a more recent study, the German High-Grade Non-Hodgkin's Lymphoma Study Group undertook a comparison of 8 cycles of a conventional regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab and etoposide (R-CHOEP-14) to 4 courses of cyclophosphamide at doses of 1,500 mg/m^2, 4,500 mg/m^2, and 6,000 mg/m^2; doxorubicin 70 mg/m^2; vincristine 2 mg/m^2; etoposide at doses of 600 mg/m^2, 960 mg/m^2, and 1,480 mg/m^2; and prednisone 500 mg, plus rituximab 375 mg/m^2 (R-MegaCHOEP) followed by transplantation of autologous blood stem cells in patients.[18,19] All received 6 infusions of rituximab. Dr. Schmitz reported the results from the trial, which enrolled 263 evaluable patients, median age 47.5 years, with CD20-positive aggressive B-cell lymphoma. Patients were randomized to 8 cycles of R-CHOEP-14 (n=130 patients) or 4 cycles of R-MegaCHOEP (n=132 patients).

After a median follow-up of 43 months, the CR rates were similar (78.7% R-CHOEP-14 vs 71.4% R-MegaCHOEP) as were 3-year EFS (69.5% vs 61.4%; *P*=.14), PFS (73.7% vs 69.8%), and OS rates (84.6% vs 77%; *P*=.13). Dr. Schmitz reported that OS was significantly

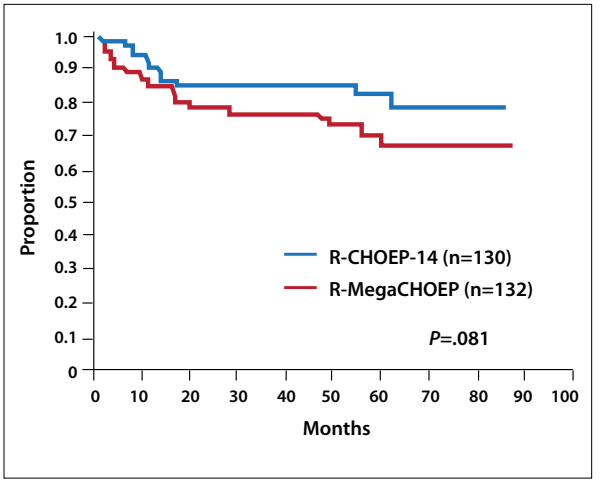

Figure 3. Overall survival in patients with CD20-positive, aggressive B-cell lymphoma and age-adjusted International Prognostic Index score of 2 treated with R-CHOEP or R-MegaCHOEP.

R-CHOEP=cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab and etoposide.

Adapted with permission from Schmitz N et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8002.[18]

better for patients with an age-adjusted IPI of 2 who received conventional chemotherapy (91% vs 77.1%; *P*=.13), an outcome related to inferior lymphoma control (Figure 3). Importantly, only 57% of the patients in the R-MegaCHOEP arm completed therapy due to toxicity; there were more frequent adverse events—most commonly, infection, mucositis, nausea, diarrhea, vomiting, and arrhythmia—and more deaths (n=32 vs 21). Overall, the conclusion was made that R-MegaCHOEP followed by ASCT was not superior to R-CHOEP-14.

Dr. Vitolo and coworkers from the Italian Lymphoma Foundation presented a paper at the ICML describing the results from a randomized phase III trial comparing 2 dose-dense regimens: R-CHOP-14 and R-MegaCHOP-14.[20] The rationale behind this study is that although R-CHOP is considered the standard of care in young patients with high-risk DLBCL, outcomes remain unsatisfactory. The Italian Lymphoma Foundation undertook this phase III study designed to evaluate intensified, rituximab plus dose-dense chemotherapy (R-CHOP-14 or R-MegaCHOP-14) with or without high-dose chemotherapy in combination with ASCT. A total of 399 eligible patients received 8 cycles of R-CHOP-14 (arm A), 6 cycles of R-MegaCHOP-14 (1,200 mg/m^2 cyclophosphamide, 70 mg/m^2 doxorubicin, and standard vincristine/prednisone; arm B), 4 cycles of R-CHOP-14 with high-dose cytarabine, mitoxan-

trone, and dexamethasone plus carmustine, etoposide, cytosine arabinoside, and melphalan (BEAM), and ASCT (arm C), or 4 cycles of R-MegaCHOP-14 with high-dose cytarabine, mitoxantrone, dexamethasone, BEAM, and ASCT (arm D). The comparisons for analysis were R-CHOP-14 (arms A and C) versus R-MegaCHOP-14 (arms B and D) and "dose-dense" (arms A and B) versus "high-dose chemotherapy" with ASCT (arms C and D). Dr. Vitolo reported data from 392 patients (median age, 49 years; range: 18–63 years). The majority of patients (65%) had stage IV disease, but only 21% had bone marrow involvement. Overall responses were similar in the high-dose chemotherapy with ASCT arms (ORR, 78%; CR/CRu, 75%) and dose-dense arms (ORR, 82.5%; CR/Cru, 72.5%). When the R-CHOP and R-MegaCHOP arms were compared, the outcomes in the R-CHOP arm were better in terms of ORR (84% vs 76%), CR/CRu (77% vs 70%), and PR (7% vs 6%). At a median follow-up of 24 months, the 2-year PFS significantly favored the high-dose chemotherapy plus ASCT arms (71% vs 59%; *P*=.0128), but with no clear survival benefit. In comparison, there was no significant difference with the use of R-CHOP (64%) or R-MegaCHOP (65%). Thus, Dr. Vitolo and colleagues concluded that in young patients with high-risk DLBCL, a more aggressive dose-dense chemotherapy is not necessarily the means to provide a significant benefit.

At ASCO, Dr. Milpied and colleagues from the Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS) presented the preliminary analysis of a multicenter, randomized controlled trial comparing R-CHOP-14 or rituximab high-dose therapy (R-HDT) in 340 adults with DLBCL.[21] The previously untreated patients, median age 49 years, had CD20-positive, DLBCL stage III–IV or stage I–II with bulky disease and were randomized to receive 1 of 2 strategies: either R-CHOP-14 for 4 courses, with an additional 4 courses if they responded as determined by PET, or 2 courses of high-dose, cyclophosphamide, epirubicin, vindesine, and prednisone (CEEP) therapy 15 days apart with rituximab 375 mg/m^2 on day 1 and then rituximab on day 22. Cycle 3 included high-dose methotrexate (3 g/m^2) plus cytarabine (100 mg/m^2). Those who responded went on to BEAM and ASCT. Unresponsive patients received 3 cycles of DHAP and ASCT. Of the 340 patients, 312 were eligible for evaluation (156 patients in each arm). Patient characteristics were well balanced, although a slightly higher percentage of patients in the R-HDT group had a poor performance status. An interim analysis showed that more patients in the R-CHOP-14 arm achieved a negative PET scan (67%) than in the R-HDT arm (56%) following 4 courses of R-CHOP-14 and the first 3 courses of R-HDT. However, the intent-to-treat analysis showed no difference in objective response rates (about 80%), and at a median follow-up of 27 months, the 3-year EFS showed that R-CHOP-14 (56%) was superior to R-HDT (41%). The 3-year PFS rate was 80% for both groups, and the 3-year OS rates were similar (85% vs 82% for R-CHOP-14 and R-HDT, respectively). High-dose therapy did not compensate for a bad prognosis of bone marrow involvement; there was no significant difference in PFS between patients who had a positive PET scan and those who did not. Dr. Milpied concluded that R-HDT is clearly not superior to R-CHOP-14 for patients with an intermediate negative PET scan, and R-CHOP-14 for 8 courses could be regarded as a standard of care for young adults with CD20-positive DLBCL responding to 4 courses of therapy.

Dr. Gisselbrecht and coworkers reported the final data from a second randomized study from France, the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study, at ASCO and ICML.[22,23] This study is the first trial to compare salvage therapies and evaluate maintenance post-ASCT in patients with CD20-positive relapsed/refractory DLBCL. A total of 481 patients with CD20-positive DLBCL in first relapse or refractory after first therapy were randomized to receive 3 cycles of R-ICE or 3 cycles of rituximab plus DHAP. Responders went on to receive BEAM and ASCT and then were further randomized between observation and rituximab maintenance every 2 months for 1 year. The primary endpoint of the induction phase was ORR, and the primary endpoint of the maintenance phase was EFS at 2 years post-transplant. The median age for each arm of the maintenance phase was 51 years, and the majority of patients were men (62% and 83% for rituximab vs observation, respectively) with stage III/IV disease and an age-adjusted IPI of 0–1 (84% and 81% for rituximab vs observation, respectively). At the completion of the induction phase before ASCT, at a median follow-up of 45 months, there was no difference in ORR (51.5% vs 56.5%), EFS (29% vs 33%), or OS (48% vs 51% for R-ICE and R plus DHAP, respectively). However, fewer adverse events were reported among patients receiving R-ICE. A strong negative predictor of outcome was prior rituximab therapy. In the maintenance phase, survival rates were similar between the 2 arms (rituximab vs observation) for median EFS (57.6% vs 58.2%; *P*=.735) and median PFS (57.6% vs 58.2%; *P*=.8314). There was no difference in OS. In multivariate analyses, a high IPI score significantly affected EFS, PFS, and OS (*P*=.0004), and interestingly, in the rituximab arm, 4-year EFS was significantly improved among female patients as compared to male patients (63% vs 37%; *P*=.01), which was reflected in an improved

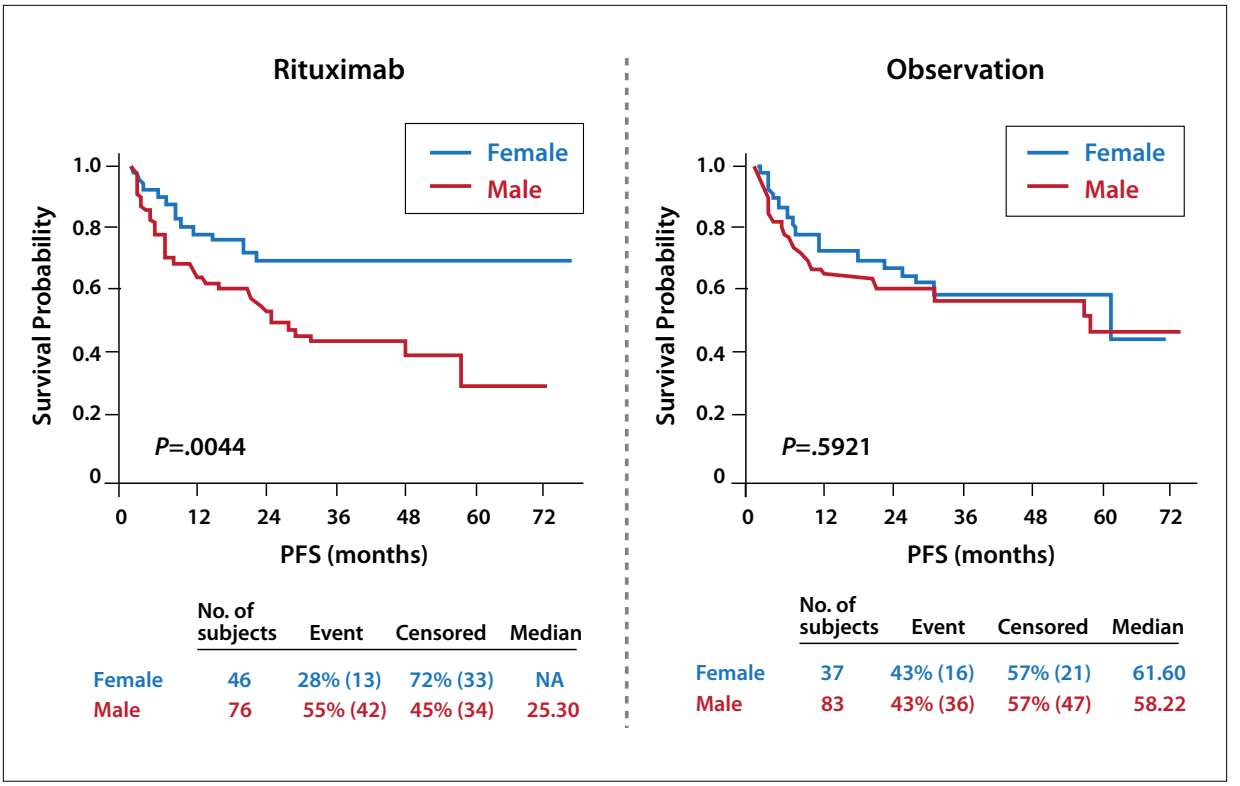

Figure 4. The CORAL study: overall survival by gender, stratified by maintenance treatment modality (rituximab maintenance vs observation).

CORAL=Collaborative Trial in Relapsed Aggressive Lymphoma; NA=not available; PFS=progression-free survival.

Adapted with permission from Gisselbrecht C et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8004.[22]

OS for women (Figure 4). Serious adverse events were slightly higher in the rituximab arm (21%) as compared to the observation arm (13%). However, there was no difference in serious adverse events during the time period from transplantation to day 100 of follow-up. Dr. Gisselbrecht concluded that the induction phase of this trial demonstrated no difference between R-ICE and R plus DHAP, and the maintenance phase showed no difference between rituximab and observation. However, women have a significant advantage in survival in rituximab maintenance, an observation that he believes warranted further evaluation.

Mantle Cell Lymphoma

A curative therapy for mantle cell lymphoma (MCL) in elderly patients remains a challenge. Induction therapy with R-CHOP is generally considered the standard regimen, but this approach typically achieves remissions of short duration only. Maintenance therapy with different regimens is under evaluation by many groups; at EHA, one of the Presidential Symposium presentations described such an evaluation with interferon-alfa (IFN) maintenance. Dr. Kluin-Nelemans presented data from the European MCL Elderly trial, in which different induction regimens, as well as the role of maintenance therapy with IFN, were evaluated.[24] In this multinational study, patients were randomized to receive 8 cycles of 3-times-weekly R-CHOP or 6 cycles of 4-times-weekly rituximab, fludarabine, and cyclophosphamide (R-FC). Patients who experienced a CR/CRu or PR underwent a second randomization between rituximab maintenance (375 mg/m^2 every 2 months) or IFN 2a or 2b (regular IFN weekly 3 × 3 million international units or pegylated IFN 1 × 1 µg/kg). Both maintenance arms were continued until disease progression occurred. Dr. Kluin-Nelemans reported that out of 308 patients randomized for maintenance therapy, data from 223 patients were currently evaluable. All patients in the study were ineligible for high-dose therapy with stage II–IV MCL. Median age was 70 years (68% male), and 79% had stage IV disease (48% intermediate-risk and 43% high-risk IPI). Following induction therapy, 61%

Table 5. Phase II Study of Romidepsin in PTCL: Patient Characteristics of Responders and the Complete Study Population

	CR/CRu (n=17)	Other (n=113)
Age in years, median (range)	62 (37–78)	61 (20–83)
Stage III/IV disease, n (%)	13 (77)	78 (69)
PTCL subtype, n (%)		
PTCL-NOS	9 (53)	60 (53)
AITL	4 (24)	23 (20)
ALK-1–negative ALCL	4 (24)	17 (15)
Bone marrow disease, n (%)	6 (35)	30 (27)
International Prognostic Index, n (%)		
<2	2 (12)	29 (26)
≥2	15 (88)	84 (74)
Number of prior systemic therapies, n (%)		
≤2	10 (59)	72 (64)
>2	7 (41)	41 (36)
Refractory to last prior systemic therapy, n (%)	7 (41)	42 (37)
Prior stem cell transplant, n (%)	2 (12)	19 (17)

AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large cell lymphoma; CR/CRu=complete response/complete response unconfirmed; PTCL=peripheral T-cell lymphoma; PTCL-NOS=peripheral T-cell lymphoma not otherwise specified.

Data from Horwitz S et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;29:504S. Abstract 8033.[26]

of the study population experienced a CR/Cru. After a median follow-up of 30 months, patients randomized to receive rituximab maintenance had a significantly longer remission duration compared to those who received IFN (51 vs 24 months; *P*=.0117; HR, 0.56; 95% CI, 0.36–0.88), and OS was not different between the 2 maintenance arms. However, further analysis revealed that patients who had received R-CHOP as induction therapy (58% of the total study population) appeared to have a survival advantage after rituximab maintenance (3-year OS after maintenance with IFN 85% vs 70% for patients who had not received R-CHOP; *P*=.0375). In comparison, patients in CR/CRu or PR after induction who did not receive any maintenance (n=106) had a poor outcome (median remission duration, 26 months; 3-year OS, 52%). Not surprisingly, hematologic grade 3/4 toxicity was higher in the IFN arm (leukocytopenia 36% vs 17%; thrombocytopenia 16% vs 7%) but non-hematologic grade 3/4 toxicity was rare apart from infections (7% IFN; 7% rituximab). R-FC followed by rituximab resulted in the highest infection rate (all grades: 48% vs 30%). Overall, 61% of patients on IFN stopped maintenance versus 30% on rituximab. The authors concluded that rituximab maintenance following R-CHOP induction should be considered the new standard for elderly patients with MCL, and efforts should continue to evaluate new regimens and new agents in the induction phase.

Central Nervous System Lymphoma

The outcome for patients with central nervous system (CNS) lymphoma is grim; median survival is less than 6 months, and there is currently no standard of care. Radiotherapy and intrathecal therapy are typically palliative. However, several studies have indicated that high-dose methotrexate with additional chemotherapy or ASCT improves patient outcome. Dr. Fischer presented data from a prospective, multicenter phase II study in 30 immunocompetent patients with CNS relapse of aggressive lymphoma who received systemic and intrathecal chemotherapy followed by high-dose chemotherapy with ASCT (HD-ASCT).[25] Induction chemotherapy consisted of 2 cycles of high-dose methotrexate 4 g/m^2 IV (day 1), ifosfamide 2 g/m^2 IV (days 3–5), and intrathecal liposomal cytarabine 50 mg (day 6), and 1 cycle of high-dose cytarabine 3 g/m^2 (days 1–2), thiotepa 40 mg/m^2 IV (day 2), and intrathecal liposomal cytarabine 50 mg (day 3). Patients who did not show disease progression then received carmustine 400 mg/m^2 IV (day -5), thiotepa 2 × 5 mg/kg IV (days -4 to -3), and etoposide 150 mg/m^2 IV (days -5 to -3) prior to ASCT. Thirty patients (median age, 58 years; range: 29–65) were enrolled, 3 with T-cell lymphoma and 27 with aggressive B-cell lymphoma. The median time to CNS relapse was 8.6 months (range: 3–80 months); this relapse was intracerebral in 24 patients and meningeal in 13 patients; 6 individuals also had systemic disease. All patients had been heavily pretreated; prior therapy was CHOP-based in 29 patients, and 26 had received rituximab.

Of the 30 patients enrolled in the study, CNS disease responded to induction therapy in 22 (73%); 10 had a CR, 12 had PR, 2 had stable disease, and 4 showed disease progression. Only 2 patients were not evaluable for response. At the time of the meeting, Dr. Fischer was able to report on 23 patients who had proceeded

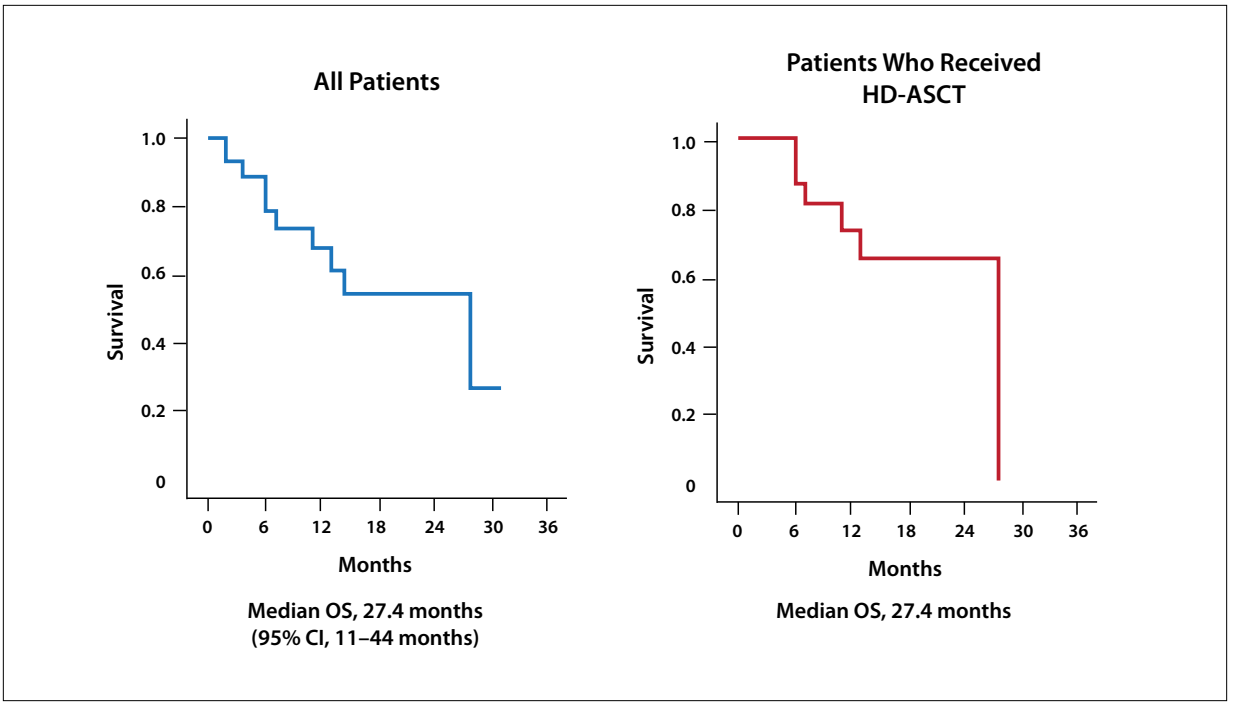

Figure 5. Overall survival in patients with central nervous system relapse of aggressive lymphoma treated with systemic and intrathecal chemotherapy followed by high-dose chemotherapy with ASCT. A) All patients enrolled in the study (n=30). B) Patients who had proceeded to high-dose chemotherapy and ASCT (n=23).

ASCT=autologous stem cell transplantation; CI=confidence interval; OS=overall survival.

Adapted with permission from Fisher L et al. *J Clin Oncol* (2011 ASCO Annual Meeting Proceedings). 2011;29:504S.[25]

to HD-ASCT.[25] In this group, a 70% response was seen overall for CNS-based disease (11 CR; 5 patients without progression; 7 remain to be evaluated). Systemic lymphoma responded in 3 patients (2 CR and 1 PR). At a median follow-up of 12.6 months, median PFS was not reached. An analysis of all patients shows a median OS of 27.4 months (95% CI, 11–44 months); for the HD-ASCT patients only, OS was 27.4 months (Figure 5). Toxicities associated with induction chemotherapy were manageable; grade 3/4 toxicities included leukopenia (50% for methotrexate/ifosfamide; 85% AraC/thiotepa), thrombopenia (27% and 54%, respectively) and infection (27% and 19%, respectively). Following HD-ASCT, mucositis and infection were observed (33% and 61%, respectively). One patient died due to septic diverticulitis, and 1 developed persistent fecal incontinence. Dr. Fischer concluded that these results indicate promising PFS and OS with a feasible, highly active treatment that has manageable toxicity. Whereas the additional benefit of ASCT to the high-dose chemotherapy was not clear, this study is the first prospective evaluation of HD-ASCT in this setting. Prolonged follow-up will assess its curative potential.

Peripheral T-Cell Lymphoma

Romidepsin, a potent histone deacetylase inhibitor, has recently become available in the United States for the treatment of peripheral T-cell lymphoma (PTCL). At ASCO, Dr. Horwitz presented a subset analysis of patients from a phase II study in relapsed or refractory PTCL who had achieved a CR/CRu.[26] Patients with relapsed/refractory PTCL had received romidepsin 14 mg/m^2 as a 4-hour IV infusion on days 1, 8, and 15 every 28 days. Dr. Horwitz reported that the CR/CRu rate was 13%, and the median time to CR/CRu was 4 months (range: 2–9 months). All patients who achieved CR/CRu were representative of the overall patient population; most patients were older than 60 years and had received more than 2 prior systemic therapies (Table 5). Duration of response had yet to be reached at the data cut-off prior to the ASCO meeting, but the longest duration of response was in excess of 26 months, and 94% of the responding patients (16/17) had not progressed at a median follow-up of 8.2 months. The adverse event profile was similar for all groups of patients; the most common grade 3/4 toxicities were thrombocytopenia (24%), neutropenia (20%), and anemia (10%). Dr. Horwitz concluded that romidepsin

could achieve a durable response in patients with relapsed/refractory PTCL with manageable toxicity, even in individuals with advanced disease or those who have received multiple prior therapies.

A second paper at the ICML described preliminary data from an open-label, multicenter, phase II study of bendamustine in relapsed or refractory T-cell lymphoma, the BENTLY (Bendamustine in Patients With Refractory or Relapsed T-cell Lymphoma) trial.[27] Dr. Damaj presented data on the initial 38 patients enrolled in the study (median age, 64 years at diagnosis; range: 38–87 years), who had each received 120 mg/m^2 of bendamustine as a 1-hour infusion on days 1–2 of a 21-day cycle for 3 cycles. The median number of prior therapies was 2 (range: 1–3), and best response to prior therapy was CR/Cru (n=13), PR (n=10), or stable disease (n=3). With bendamustine, the ORR in this group was 47%, with 29% achieving a CR/CRu (n=11). PR was observed in 7 patients (18%), and 20 patients (53%) experienced disease progression. At the time of the analysis for the presentation, median duration time for responders was 157 days (range: 14–350 days). Bendamustine was well tolerated in this group of patients, the most frequent adverse events being neutropenia and thrombopenia (28 and 18 episodes of grade 3/4 events, respectively). In addition, 35 episodes of sepsis were reported in 23 patients. The authors concluded that these early data appear to support the use of bendamustine in future regimens for PTCL.

Systemic Anaplastic Large Cell Lymphoma

The initial treatment of patients with ALK-positive anaplastic large cell lymphoma (ALCL) achieves long-term, disease-free survival in 60–70% of patients, although the outcome in those who are ALK-negative is clearly inferior. However, the prognosis is poor for both groups in the relapsed/refractory setting. A new therapy, brentuximab vedotin, has emerged with demonstrated efficacy in relapsed and refractory patients.[28] Dr. Shustov presented updated results from a phase II study of brentuximab vedotin at the ICML.[29] In this study, 58 patients with relapsed/refractory systemic ALCL (median age, 52 years) received 1.8 mg/kg brentuximab vedotin by IV infusion every 21 days for up to a maximum of 16 cycles. Patients had received a median of 2 prior systemic therapies; 62% were refractory to frontline therapy, 50% were refractory to their most recent therapy, and 22% had never responded to any therapy. All but 1 patient had an ECOG status of 0–1, 33 were male, and 72% were ALK-negative. Dr. Shustov reported that 86% of patients achieved an objective response, with a median duration of 12.6 months. The CR rate was 57%, with a median CR duration of 13.2 months. The overall median PFS was 13.3 months, and median OS had yet to be reached. Tumor shrinkage was observed in 97% of the 22 patients who went on to stem cell transplant; the procedure did not impact PFS. Brentuximab vedotin was well tolerated; the most common adverse event was peripheral sensory neuropathy, which occurred in 36% of patients (events were primarily grades 1 and 2; there were no grade 4 events). Dose delays or dose reductions to 1.2 mg/kg were able to manage most adverse events, and in the case of peripheral neuropathy, 81% of patients experienced resolution or some improvement, while 48% had complete resolution of all events. This study is ongoing, with 9 patients (16%) remaining on study. Due to these encouraging data, a frontline study in systemic ALCL is planned. As was the case for HL, brentuximab vedotin was recommended in July 2011 for approval for the treatment of relapsed/refractory ALCL by the US Food and Drug Administration's Oncologic Drugs Advisory Committee.

Multiple Myeloma

Lenalidomide has significantly improved the prognosis for patients with multiple myeloma (MM). However, with the extended patient survival, there has been a suggestion of secondary primary malignancies (SPM) in long-term survivors. Whether this observation was a result of the drug or reflects the known association of aging with the development of malignancies is unclear and was the subject of several abstracts over the summer. One of the most notable was a retrospective analysis of pooled data from 11 clinical studies in which 3,839 patients with relapsed/refractory MM received up to 24 months of lenalidomide therapy.[30] Dr. Durie and colleagues had compared data from these studies with expected background incidence of all invasive cancers reported from the US Surveillance, Epidemiology, and End Results (SEER) database for 2003–2007. The incidences of SPM and incidence rate per 100 person-years were compared from both sets of data, although by SEER definition, nonmelanoma skin cancers and in situ malignancies were excluded. The median age at study entry was 64 years (range: 29–92 years) and the study treatments included lenalidomide monotherapy (n=729; 19.1%) and lenalidomide/dexamethasone combination (n=3,083; 80.9%). Median treatment duration was 5 months (range: 0.03–58.27 months), with 313 (8.2%) patients receiving therapy for 24 months or more. Dr. Durie reported that 57 SPMs were found in this patient population; 8 cases of MDS, 1 AML, 2 B-cell malignancies, and 46 solid tumors. Of these cases of SPM, 22 were in the group of patients who had 24 months or more of lenalidomide treatment (n=313). These cases (4 MDS, 1 AML, 17 solid tumors) represent 7% of the population who had been treated with lenalidomide for over 24 months, and the

overall SPM incidence rate was 2.35 for treatment of 24 months or longer. The standardized incidence ratio was 0.77 (CI, 0.43–1.28). These rates compare favorably with the incidence rate for all invasive cancers reported from SEER (range: 1.3–2.2 per 100 person-years for all subjects in the age range of 60–85+ years). Dr. Durie and colleagues concluded that their analysis demonstrated that lenalidomide-based therapy for relapsed/refractory MM, including treatment durations of 24 months or more, is associated with no significant increase in the rate of SPM compared to incidence rates for invasive malignancies reported by SEER.

A similar analysis, based on a smaller group of patients, was also reported at the EHA and ASCO meetings by Dr. Dimopoulos and coworkers.[31,32] In this study, 740 patients with relapsed/refractory MM were randomized to lenalidomide/dexamethasone or placebo/dexamethasone. There was a significantly longer median OS with lenalidomide/dexamethasone than with placebo/dexamethasone (HR, 0.607; 95% CI, 0.459–0.803; *P*<.001). The SPM incidence rate among 23,838 MM patients in the US SEER Cancer Registries (1973–2000) were used to calculate expected SPM (the rates for MDS were not available). The incidence of SPM with the lenalidomide-treated patients was 1.71 per 100 person years, which was comparable to the SEER data. There were no cases of AML, 2 cases of MDS, and 6 cases of solid tumors. Noninvasive, nonmelanoma skin cancer was reported in 11 patients receiving lenalidomide/dexamethasone and 2 patients receiving lenalidomide and placebo. Interestingly, there was a significantly longer median time to development of SPM in the lenalidomide/dexamethasone-treated patients compared to the placebo combination (HR, 0.355; 95% CI, 0.292–0.431; *P*<.001).

A third analysis also compared the incidence of SPM in a small group of MM patients treated with lenalidomide as first-line therapy to patients in the SEER database.[33] In this study, reported by Dr. Rosi and colleagues, 72 newly diagnosed patients with MM were treated with continuous lenalidomide. At 6 years of follow-up, ORR was 90%, CR/near CR was 53%, and 4-year OS was 82% (2-year EFS; 97.2%). The incidence of SPM was 16% (n=110) with no cases of AML or MDS. As with the reports from Dr. Durie and Dr. Dimopoulos, these observations are consistent with the SEER data.

Emerging Therapies

It would not be possible to summarize current events in hematology without mentioning emerging therapies, especially those targeting newly identified specific pathways of disease.

The ICML had 3 notable abstracts reporting data on 3 novel therapies targeting specific cellular activities in lymphoma. Dr. Friedberg and associates presented initial data from a multicenter, phase II trial of a novel aurora-A kinase inhibitor (MLN8237) in patients with aggressive B-cell and T-cell NHL.[34] Aurora-A kinase regulates mitotic function, and its inhibition leads to abnormal cellular proliferation. Dr. Friedberg described data from 48 patients, in which MLN8237 was associated with an ORR of 32%, including 12% CRs and 20% PRs. The most common adverse events (all grades) were neutropenia, fatigue, leukopenia, diarrhea, anemia, and alopecia. The most common grade 3/4 adverse events were febrile neutropenia, neutropenia, stomatitis, pneumonia, and deep vein thrombosis. These data imply that MLN8237 has antitumor activity, and more studies are planned. A second novel therapeutic is PCI-32765, an oral inhibitor of Bruton's tyrosine kinase.[35] Dr. Advani and coworkers presented data from a preliminary study in 56 patients with relapsed/refractory B-cell lymphoma and showed an objective response in 60% of evaluable patients across all dose levels. At a median follow-up of 6 months (range: 1–19 months), the median response duration had yet to be reached. The therapy was well tolerated, and phase II trials of PCI-32765 as monotherapy and in combination are being established.

Dr. Leonard presented data on behalf of his colleagues from a phase I study of CAL-101, a novel isoform-selective inhibitor of phosphatidylinositol 3-kinase in combination with rituximab (RC) or bendamustine (BC) in patients with previously treated B-cell malignancies.[36] To date, 49 patients have been enrolled in the study (28 with indolent NHL, 21 with chronic lymphocytic leukemia). The therapy was tolerated well, with no unexpected toxicities. Data were presented on 35 evaluable patients; preliminary overall response was seen in 19 out of 22 for the NHL patients (9 out of 10 for RC, and 10 out of 12 for BC) and 9 out of 13 for chronic lymphocytic leukemia (4 out of 6 for RC, and 5 out of 7 for BC).

GA101 is a type II, glycoengineered, humanized monoclonal anti-CD20 antibody that has been in clinical evaluation for some time. At the ICML, Dr. Morschhauser reported on a phase I/II trial of this novel therapy in patients with relapsed or refractory indolent NHL.[37] Forty patients were randomized to receive nine 3-week cycles of 400 mg GA101 (low-dose arm; n=22) or 1 infusion of 1,600 mg GA101 (on days 1 and 8) followed by eight 3-week cycles of 800 mg GA101 (high-dose arm; n=18). The primary endpoint of the study was response, assessed 4 weeks after the last infusion. The majority of patients were rituximab-refractory with disseminated disease, and the median number of

prior therapies was 3. The ORR was 55% in the high-dose arm (2 CR, 10 PR) and 17% in the low-dose arm (0 CR, 3 PR). Median PFS for the high-dose and low-dose arms was 11.3 months and 6 months, respectively. The most common adverse events were infusion-related reactions (72% and 73% for the low-dose and high-dose arms, respectively). The most common grade 3/4 adverse events were neutropenia, febrile neutropenia, infusion-related reactions, asthenia, infection, and cytolytic hepatitis. Overall, GA101 was well tolerated in this study, and Dr. Morschhauser noted that of the rituximab-refractory patients, 5 of 10 patients in the high-dose arm and 1 of 12 patients in the low-dose arm responded. This promising activity in such a heavily pretreated population warrants further investigation.

A second phase II study with GA101 in patients with CD20-positive aggressive lymphoma was also reported at the ICML by Dr. Cartron and colleagues.[38] Forty patients, with a median age of 71 years, were randomized to receive 9 low-dose cycles of 400 mg GA101 on days 1, 8, and 22 (n=21) or 9 high-dose cycles starting with a loading dose of 1,600 mg GA101 on days 1 and 8, followed by 800 mg GA101 at all other infusions (n=19). All patients had received prior rituximab treatment, and the median number of prior treatments was 3.

At the time of the presentation, the median response duration had not yet been reached. ORR was 24% in the low-dose arm (2 CR) and 32% in the high-dose arm (0 CR). An analysis of the subset of patients with DLBCL (low dose: n=10; high dose n=15) revealed an ORR of 80% in the low-dose arm and 27% in the high-dose arm (0 CR). Fifteen patients with MCL were also enrolled in the study (low-dose arm=11; high-dose arm=4). In these groups, the ORR was 18% and 50% for the low-dose and high-dose arms, respectively. The ORR in patients refractory to rituximab was lower than for the other subgroups (8% with low-dose GA101 and 25% with high-dose GA101). Not surprisingly, the adverse event profile was more severe in this patient population than reported for the prior study. Grade 3/4 toxicities in the low-dose/high-dose arms included infusion-related reaction (91%/73%), asthenia (24%/16%), anemia (28%/21%), and thrombocytopenia (28%/0%). During administration of the study medication, 14 patients experienced serious adverse events, and 17 deaths were reported (14 due to progressive disease and 3 related to adverse events). Overall, this study demonstrated that GA101 monotherapy has activity and is tolerable in patients with heavily pretreated, aggressive NHL. Ongoing studies with this agent include a phase III trial of bendamustine with or without GA-101 in rituximab-refractory patients.

Acknowledgment

Dr. Ashforth has no real or apparent conflicts of interest to report.

References

1. Levine RL, Wernig G. Role of JAK-STAT signaling in the pathogenesis of myeloproliferative disorders. *Hematology Am Soc Hematol Educ Program*. 2006: 233-239, 510.
2. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor in myelofibrosis. *N Engl J Med*. 2010;363:1117-1127.
3. Verstovsek S, Mesa RA, Gotlib JR, et al. Results of COMFORT-I, a randomized double-blind phase 3 trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504s: Abstract 6500.
4. Verstovsek S, Mesa RA, Gotlib JR, et al. Results of COMFORT-I, a randomized, double-blind phase III trial of the JAK1 and JAK2 inhibitor ruxolitinib (INCB018424) versus placebo for patients with myelofibrosis. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:107: Abstract 0505.
5. Harrison CN, Kiladjian J, Al-Ali HK, et al. Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504s: Abstract 6501.
6. Faderl S, Wetzler M, Rizzieri D, et al. Clofarabine plus cytarabine compared to cytarabine alone in older patients with relapsed or refractory (R/R) acute myelogenous leukemia (AML): results from the phase 3 CLASSIC 1 trial. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504s: Abstract 6503.
7. Thomas XG, Dmoszynska A, Wierzbowska A, et al. Results from a randomized phase 3 trial of decitabine versus supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed AML. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504s: Abstract 6504.
8. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase 2 study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J Clin Oncol*. 2010;28:556-561.
9. Evens AM, Hong F, Gordon LI, et al. Efficacy and tolerability of ABVD and Stanford V for elderly advanced-stage Hodgkin Lymphoma (HL): analysis from the phase 3 randomized US Intergroup Trial E2496. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 107.
10. Chen RW, Gopal AK, Ansell SM, et al. Results from a pivotal phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29(504s): Abstract 8031.
11. Chen RW, Gopal AK, Smith S, et al. Results of a pivotal phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma. *Blood* (ASH Meeting Abstracts). 2010;16: Abstract 293.
12. Salles F, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumor burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomized controlled trial. *Lancet*. 2011;377:42-51.
13. Morschhauser F, Seymour J, Feugier P, et al. Impact of induction chemotherapy regimen on response, safety and outcome in the PRIMA Study. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 022.
14. Federico M, Luminari S, Dondi A, et al. R-CVP vs R-CHOP vs R-FM for the initial treatment of patients with advanced stage follicular lymphoma. Preliminary results of FOLL05 IIL trial. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:128: Abstract 135.
15. Friedberg J, Byrtek M, Link B, et al. Should radiation therapy (XRT) be the standard therapeutic approach for stage I follicular lymphoma (FL)? A comparative effectiveness analysis of the National Lymphocare Study (NLCS). *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:90: Abstract 026.
16. Cunningham D, Smith P, Mouncey P, et al. R-CHOP14 versus R-CHOP21: result of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504s: Abstract 8000.
17. Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade

diffuse aggressive non-Hodgkin lymphoma (NHL). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504S. Abstract 8001.
18. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemoimmunotherapy (R-CHOEP-14) or high-dose therapy (R-Mega-CHOEP) for young, high-risk patients with aggressive B-cell lymphoma: final results of the randomized Mega-CHOEP trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8002.
19. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemoimmunotherapy (R-CHOEP-14) for young, high-risk patients with aggressive B-cell lymphoma: final results of the randomized Mega-CHOEP trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:106: Abstract 073.
20. Vitolo U, Chiappella A, Brusamolino E, et al. A randomized multicentre phase III study for first line treatment of young patients with high-risk (AAIPI 2-3) diffuse large B-cell lymphoma (DLBCL): rituximab (R) plus dose-dense chemotherapy CHOP-=14/MEGACHOP14 with or without intensified high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT): results of DLCL04 trial of Italian Lymphoma Foundation (ILF). *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:106. Abstract 072.
21. Gouill S, Milpied NJ, Lamy T, et al. First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: preliminary results of the GOELAMS 075 prospective multicenter randomized trial. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8003.
22. Gisselbrecht C, Glass B, Laurent DS, et al. Maintenance with rituximab after autologous stem cell transplantation in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL): CORAL final analysis. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8004.
23. Gisselbrecht C, Glass B, Fournier M, et al. Salvage regimen with autologous stem cell transplantation with or without rituximab maintenance for relapsed diffuse large B-cell lymphoma (DLBCL): CORAL final report. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:107: Abstract 075.
24. Kluin-Nelemans J, Hoster E, Vehling-Kaiser U, et al. Rituximab maintenance significantly prolongs duration of remission in elderly patients with mantle cell lymphoma. First results of a randomized trial of the European MCL network. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:107. Abstract 0504.
25. Fischer L, Haenel M, Moehle R, et al. Systemic and intrathecal chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) for CNS relapse of aggressive lymphomas: a potentially curative approach? *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504S. Abstract 8005.
26. Horwitz S, Coiffier B, Foss FM, et al. Complete responses (CR/CRu) on a phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504S. Abstract 8033.
27. Damaj G, Gressin R, Bouabdallah K, et al. Preliminary results from an open-label, multicenter, phase II study of bendamustine in relapsed or refractory T cell lymphoma from the French GOELAMS group: the BENTLY trial. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 126.
28. Francisco JA, Cervany CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. *Blood*. 2003;102:1458-1456.
29. Shustov A, Advani R, Brice P. Durable remissions with SGN-35 (brentuximab vedotin): updated results of a phase 2 study in patients with relapsed or refractory systemic anaplastic large cell lymphoma (SALCL). *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 125.
30. Durie BG, Morgan G, San-Miguel JF, et al. Long-term safety of lenalidomide (LEN) in relapsed/refractory multiple myeloma (RRMM) patients (Pts): analysis of pooled data. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8086.
31. Dimopoulos MA, Weber D, Richardson P, et al. Lenalidomide and dexamethasone (LEN + DEX) treatment in relapsed/refractory multiple myeloma (RR/MM) patients does not increase the risk of second primary malignancies (SPM): analysis of MM-009/010. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:107. Abstract 1009.
32. Palumbo A, Delforge M, Catalano J, et al. Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8002.
33. Rossi AC, Mark TM, Jayabalan PJ, et al. Incidence of second primary malignancies (SPM) after 6-years follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8008.
34. Friedberg J, Mahadevan D, Persky D, et al. Multicenter phase II trial of MLN8237, an investigational inhibitor of aurora A kinase (AAK) in patients with aggressive B-cell and T-cell non-Hodgkin lymphoma. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 152.
35. Advani RH, Sharman JP, Smith SM, et al. The BKT inhibitor PCI-32765 is highly active and well tolerated in patients with relapsed/refractory B-cell malignancies: final results from a phase I study. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 153.
36. Flinn IW, Schreeder MT, Coutre SE, et al. A phase I study of CAL-101, an isoform-selective inhibitor of phosphatidylinositol 3−kinase P110δ, in combination with anti-CD20 monoclonal antibody therapy and/or bendamustine in patients with previously treated B-cell malignancies. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 3064.
37. Salles GA, Morschhauser F, Thieblemont C, et al. Results from a phase I/II study (B020999) of RO5072759 (GA101) monotherapy in relapsed/refractory non-Hodgkin Lymphoma. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 066.
38. Cartron G, Thieblemont C, Solal-Celigny P, et al. Results from a phase 2 study (BO20999) of RO5072759 (GA101) monotherapy in relapsed/refractory aggressive non-Hodgkin lymphoma. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22: Abstract 144.

Commentary

Bruce D. Cheson, MD

Deputy Chief
Division of Hematology-Oncology
Head of Hematology
Lombardi Comprehensive Cancer Center
Georgetown University Hospital
Washington, DC

Sometimes I ask myself what it is that I expect out of national and international meetings. When I was younger, it was mostly to learn something I did not already know. Now that I have become older, albeit perhaps not wiser, it is often to confirm what I had already expected. The 2011 American Society of Clinical Oncology (ASCO) meeting, and to a lesser extent the 11th International Conference on Malignant Lymphoma (ICML), clearly provided the material for this possibility. For years I have been unable to accept the concept that "more is better." We have reached a plateau in results of the intensification of conventional agents, especially in diffuse large B-cell lymphoma (DLBCL), although the same can probably be said of follicular non-Hodgkin lymphoma (NHL) as well.[1] The Southwest Oncology Group (SWOG)-led high priority comparison of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with 3 more intensive regimens concluded that none were better than CHOP, but they were more toxic and expensive.[2] The German High-Grade Non-Hodgkin's Lymphoma Study Group conducted a series of studies suggesting that rituximab plus CHOP (R-CHOP) delivered every 14 days (R-CHOP-14) should be the new standard, although it had never been directly compared with R-CHOP-21.[3,4] A Groupe d'Etude des Lymphomes de l'Adulte (GELA) study which concluded that R-CHOP administered every 14 days was no better than R-CHOP every 21 days in untreated DLBCL was considered by some to be flawed.[5] However, Cunningham and coworkers[6] at ASCO presented the results of a large study in which the 2 regimens were delivered appropriately; again, there was no benefit for the more intensive regimen. Several studies went the next step to incorporate intensive regimens or even high-dose therapy with autologous stem cell transplant as part of an initial treatment strategy, yet were unable to demonstrate benefit for this approach; in several studies discussed in this monograph, high-dose therapy improved progression-free survival, but a survival advantage was not apparent.[7-10] Further lessons in DLBCL were learned from the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) trial, in which patients with relapsed/refractory DLBCL were randomized to rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE) or rituximab plus dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) prior to autologous stem cell transplantation with a secondary randomization to post-transplant rituximab maintenance or observation.[11] The maintenance had no effect and, for unclear reasons, appeared to be detrimental to male patients.

Other findings of little surprise in follicular lymphoma were that radiation did not appear to improve the outcome of patients with limited-stage disease[12] and that R-CHOP appears superior to rituximab plus cyclophosphamide, vincristine, and prednisolone (R-CVP) and to fludarabine-based regimens.[13,14] However, the recent data with bendamustine-rituximab may limit the relevance of the latter studies.[15]

In chronic lymphocytic leukemia (CLL), high-dose therapy with autologous stem cell transplantation has been proposed as part of initial therapy for patients with adverse risk factors, such as those with 11q deletion and 17p deletion abnormalities. At ICML, Dreger and colleagues[16] presented an historical comparison of fludarabine, cyclophosphamide, and rituximab (FCR) versus high-dose therapy, which confirmed the recent randomized trial by Sutton and coworkers[17] demonstrating that high-dose therapy was no more effective than FCR, even in this high-risk group, and should be put to rest as a treatment option. Instead, the focus of clinical research should be the incorporation of newer agents into frontline therapy to enhance the activity of conventional regimens.

The meetings generated continued interest in the variety of new and effective novel agents in NHL, Hodgkin lymphoma, and CLL. Lenalidomide has provided another effective component of the armamentarium in NHL and myeloma. However, recent concerns about an association with secondary malignancies has led to longer discussions with patients, rewriting of informed consents,

and obvious concern for patient welfare given the apparent beneficial effect of long-term maintenance. A trio of abstracts at ASCO raised questions about that association—the overall risk was extremely low (<1%) and not clearly higher than expected, and it was associated with unfavorable baseline cytogenetics.

Of the new agents, those that have stimulated the greatest interest include the drug-antibody conjugate brentuximab vedotin, which has demonstrated remarkable activity in relapsed/refractory Hodgkin lymphoma (HL) and anaplastic large cell lymphoma. In NHL, several drugs that inhibit intracellular pathways continue to engender considerable interest, including CAL-101 and PCI-32765. The data on all of these agents have confirmed their initial promise, and a number of new trials combining them with other drugs are under way.

Unfortunately, there was less optimism for patients with acute myeloid leukemia. There were no presentations at either the ASCO meeting or the European Hematology Association (EHA) congress of novel new agents with good efficacy and a tolerable safety profile.

The meeting that engendered the greatest interest, but of which there has been limited general information to date, actually took place the day prior to the opening of the ICML. The availability of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning has far outpaced our knowledge of how to use this technology. Thus, a closed workshop was held to discuss how to integrate FDG-PET into the management of patients with lymphoma. In the morning were discussions regarding staging, and in the afternoon, on response assessment and follow-up. Of the few issues on which consensus was attained that day, the one of greatest immediate clinical relevance was that since PET was already being used to assess response in certain lymphoma histologies, it should be incorporated into staging for relevant lymphomas, as already published in 2007. However, all present at the meeting—clinicians, nuclear medicine physicians, and radiologists alike—concluded that there is no apparent role for interim PET in DLBCL. Its role in HL, as published by Gallamini and coworkers,[18] was validated at ICML by an international validation study, by Gallamini and associates.[19] This observation lends strong support to several international risk-adapted studies in HL where decisions on treatment are based on interim PET results. Surveillance PET scans were also discouraged because of a lack of data to support related clinical benefit, the high frequency of false positive results, their cost, and increased radiation exposure. The possibility that PET can replace a staging bone marrow biopsy was suggested for HL because of the infrequency of bone marrow biopsy–positive, PET-negative patients and the fact that most bone marrow biopsy–positive patients have systemic symptoms and other evidence for stage IV disease; but, because of the frequency of histologic discordance, this approach is not yet a consideration in NHL. There was no support for omitting the bone marrow biopsy in NHL because of the likelihood of discordant histologies. No official publication is planned as a consequence of this meeting. However, important questions were identified, with ways to obtain the data directed at arriving at the answers. Additional communications will take place over the next few months, and it is hoped that some conclusions will be presented when this group meets again at the 12th ICML to be held in 2 years hence, once again in the beautiful lakeside town of Lugano.

Acknowledgment

Dr. Cheson is a consultant for Cephalon.

References

1. Watanabe T, Tobinai K, Shibata T, et al. Phase II/III study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP-21) versus two-week R-CHOP (R-CHOP-14) for untreated indolent B-cell non-Hodgkin lymphoma: Japan Clinical Oncology Group (JCOG) 0203 trial. *J Clin Oncol*. In press.

2. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *New Engl J Med*. 1993;328:1002-1006.

3. Pfreundschuh M, Trümper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood*. 2004;104:634-641. Epub 2004 Mar 11.

4. Pfreundschuh M, Trümper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood*. 2004;104:626-633. Epub 2004 Feb 24.

5. Delarue R, Tilly H, Salles G, et al. R-CHOP14 compared to R-CHOP21 in elderly patients with diffuse large B-cell lymphoma: results of the interim analysis of the LNH03-6B GELA study. *Blood* (ASH Meeting Abstracts). 2009;114:169: Abstract 406.

6. Cunningham D, Smith P, Mouncey P, et al. R-CHOP14 versus R-CHOP21: result of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504s: Abstract 8000.

7. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemoimmunotherapy (R-CHOEP-14) or high-dose therapy (R-Mega-CHOEP) for young, high-risk patients with aggressive B-cell lymphoma: final results of the randomized Mega-CHOEP trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;19:504S: Abstract 8002.

8. Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP + R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL). *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504S: Abstract 8001.

9. Le Gouill S, Milpied NJ, Lamy T, et al. First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: preliminary results of the GOELAMS 075 prospective multicenter randomized trial. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2011;29:504S: Abstract 8003.

10. Vitolo U, Chiappella A, Brusamolino E, et al. A randomized multicentre phase III study for first line treatment of young patients with high-risk (AAIPI 2-3) diffuse large B-cell lymphoma (DLBCL): rituximab (R) plus dose-dense chemotherapy CHOP-=14/MEGACHOP14 with or without intensified high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT): results of

DLCL04 trial of Italian Lymphoma Foundation (ILF). *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:106. Abstract 072.
11. Gisselbrecht C, Glass B, Fournier M, et al. Salvage regimen with autologous stem cell transplantation with or without rituximab maintenance for relapsed diffuse large B-cell lymphoma (DLBCL): CORAL final report. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:107: Abstract 075.
12. Friedberg J, Byrtek M, Link B, et al. Should radiation therapy (XRT) be the standard therapeutic approach for stage I follicular lymphoma (FL)? A comparative effectiveness analysis of the National Lymphocare Study (NLCS). *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:90: Abstract 026.
13. Federico M, Luminari S, Dondi A, et al. R-CVP vs R-CHOP vs R-FM for the initial treatment of patients with advanced stage follicular lymphoma. Preliminary results of FOLL05 IIL trial. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:128: Abstract 135.
14. Morschhauser F, Seymour J, Feugier P, et al. Impact of induction chemotherapy regimen on response, safety and outcome in the PRIMA study. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:89 Abstract 022.
15. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Blood* (ASH Meeting Abstracts). 2009;114:168-169: Abstract 405.
16. Dreger P, Busch R, Stilgenbauer S, et al. FCR vs autologous stem cell transplantation as first-line treatment for chronic lymphocytic leukemia (CLL): a comparison of two prospective studies of the GCLLSG. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:123: Abstract 121.
17. Sutton L, Chevret S, Tournihlac O, et al. Autologous stem cell transplantation as a first-line treatment strategy for chronic lymphocytic leukemia: a multicenter, randomized, controlled trial from the SFGM-TC and GFLLC. *Blood*. 2011;117:6109-6119.
18. Gallamini A, Hutchings M, Avigdor A, Polliack A. Early interim PET scan in Hodgkin lymphoma: where do we stand? *Leuk Lymphoma.* 2008;49:659-662.
19. Gallamini A, Barrington S, Biggi A, et al. International validation study of interpretation rules and prognostic role of interim-PET scan in advanced stage Hodgkin lymphoma. *Ann Oncol* (ICML Annual Meeting Abstracts). 2011;22:107: Abstract 047.

Notes


H&O