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Recent Advances in the Treatment of Leukemia, Lymphoma, and Myeloma

A Review of Selected Presentations From
the 52nd American Society of Hematology
Annual Meeting and Exposition
December 4–7, 2010
Orlando, Florida

With expert commentary by
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PIM Postgraduate Institute for Medicine

Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and other health care professionals who treat patients with leukemia, lymphoma, or myeloma.

Statement of Need/Program Overview

Current research efforts in leukemia, lymphoma, and myeloma focus on novel agents, new potential roles for already approved therapies, new combinations of existing therapies, biomarkers that enable identification of the patient subgroups most likely to respond to a particular therapy, and use of cytogenetics and other prognostic factors to help predict outcome and guide treatment decisions. The annual meeting of the American Society of Hematology (ASH) is one of the premier outlets for the release of new clinical data on these various efforts, and as such it is an extremely important event for oncologists and hematologists. With the multitude of presentations made at this meeting, there is a need for supplementary materials that distill information, cull the most important breakthrough findings, and summarize data for subsequent integration into clinical care.

Educational Objectives

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

- Integrate prognostic factors into treatment decisions for patients with lymphoma, leukemia, and multiple myeloma
- Identify factors influencing the choice of treatment for patients with lymphoma, leukemia, and multiple myeloma
- Describe the most recent data on treatment options for both newly diagnosed and recurrent lymphoma, leukemia, and multiple myeloma

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Recent Advances in the Treatment of Leukemia, Lymphoma, and Myeloma

Highlights From the 52nd American Society of Hematology Annual Meeting and Exposition
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332 A Phase II Study of Lenalidomide for Previously Untreated Deletion (del) 5q Acute Myeloid Leukemia (AML) Patients Age 60 or Older Who Are Not Candidates for Remission Induction Chemotherapy (Southwest Oncology Group Study S0605)[1]

MA Sekeres, H Gundacker, J Lancet, A Advani, S Petersdorf, JL Liesveld, D Mulford, T Norwood, CL Willman, AF List, FR Appelbaum

To evaluate the safety and efficacy of single-agent lenalidomide, Sekeres and colleagues conducted a phase II study in 37 untreated older patients with acute myeloid leukemia (AML) and the del(5q) cytogenetic abnormality (with or without other abnormalities).[1] Induction therapy included lenalidomide 50 mg/day for up to 28 days without cytotoxic or growth factor therapies. At day 28, bone marrow assessments were conducted; those patients with stable disease or better received lenalidomide 10 mg/day for 21 days of a 28-day cycle.

The median age of the patients was 74 years (range, 60–94 years), 57% were female, 89% were white, and 51% had prior myelodysplastic syndrome (MDS). Pretreatment cytogenetic studies were available for 29 patients: 2 patients had del(5q) detected by fluorescence in situ hybridization, 5 patients had isolated del(5q), and 22 patients had complex karyotypes that included 3 or more abnormalities. Of the 37 patients, 7 exhibited toxicities (infection, renal, respiratory, gastrointestinal, and rash) that necessitated their removal from the study, and 4 died (due to respiratory conditions [n=2], cardiac conditions [n=1], and febrile neutropenia [n=1]). Grade 4 nonhematologic toxicities occurred in 5 additional patients (hypocalcemia [n=2], fatigue [n=2], and infection [n=1]). The induction protocol was completed by 14 patients (38%). Following induction therapy, 13 patients (35%) had stable disease, with 8 patients entering postremission therapy. Four patients (11%) achieved complete response (CR) or incomplete response after induction therapy. Of these 4 patients, relapse occurred after 1, 2, and 4 months; the fourth patient died 13 months after CR. The authors reported that 33 of the 37 patients have died; these patients had a median overall survival (OS) of 2 months (95% confidence interval [CI], 1–4 months). The remaining 4 patients had a follow-up time between 6 and 23 months.

Sekeres and associates concluded that lenalidomide used as a monotherapy has modest efficacy in patients older than 60 years with del(5q) AML. In the future, the researchers will combine lenalidomide with other therapies such as cytotoxic or hypomethylating agents in an effort to improve outcomes in this difficult-to-treat patient population.

210 A Phase 1 Trial of Oral Ponatinib (AP24534) in Patients with Refractory Chronic Myelogenous Leukemia (CML) and Other Hematologic Malignancies: Emerging Safety and Clinical Response Findings[2]

J Cortes, M Talpaz, D Bixby, M Deininger, N Shah, IW Flinn, M Mauro, T O'Hare, S Hu, R Kan, VM Rivera, T Clackson, F Haluska, H Kantarjian

Although many patients with chronic myelogenous leukemia (CML) benefit from treatment with tyrosine kinase inhibitors (TKIs), there are limited treatment options for patients who have failed 2 or more TKIs or who have the T315I mutation.[3,4] Therefore, Cortes and colleagues investigated the use of ponatinib (AP24534),[2] an oral TKI with potent activity against BCR-ABL variants, T315I mutants, and multiple kinases.[5] In this ongoing, open-label, phase I trial, patients with refractory hematologic malignancies received a single daily dose of ponatinib (2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 45 mg, or 60 mg, with intrapatient dose escalation) in an effort to assess safety, optimal dosing, and anti-leukemic activity. As of October 2010, 74 patients were enrolled in the study

(median age, 56 years; 53% male). Diagnoses included CML (60 patients), Philadelphia chromosome-positive (Ph-positive) acute lymphoblastic leukemia (4 patients), AML (6 patients), and 4 other hematologic malignancies. Of the CML/Ph-positive acute lymphoblastic leukemia patients, 95% were resistant to 2 or more TKIs, and 65% were resistant to 3 or more TKIs. At study entry, 63% of patients had at least 1 BCR-ABL mutation (40 of 64 patients), and 8% had 2 or more BCR-ABL mutations (8 of 64 patients).

The most common adverse events associated with ponatinib were thrombocytopenia (23%; grade 3/4, 16%), rash (22%; grade 3/4, 1%), arthralgia (15%), headache (15%), increased lipase (14%; grade 3/4, 7%), nausea (12%), fatigue (11%), myalgia (11%), pancreatitis (10%; grade 3/4, 4%), neutropenia (10%; grade 3/4, 7%), vomiting (10%), dry skin (10%), and anemia (10%). At 45 mg, the dose-limiting toxicities included rash (1 patient) and elevated pancreatic enzymes/pancreatitis (1 patient). At 60 mg, dose-limiting toxicities were elevated pancreatic enzymes/pancreatitis (4 patients) and fatigue with increased alanine transaminase (2 patients). As of October 2010, 48 patients (65%) were still in the study (mean duration of 322 days).

Of the 38 chronic-phase CML patients, complete hematologic response was achieved in 36 patients (95%), major cytogenetic response was achieved in 25 patients (66%), and complete cytogenetic response was achieved in 20 patients (53%; Table 1). Of the 9 chronic-phase CML patients with confirmed T315I mutation, all 9 achieved complete hematologic response and major cytogenetic response, while 8 (89%) achieved complete cytogenetic response; 78% of all chronic-phase CML patients and 89% of chronic-phase CML patients with T315I mutation remained in response at 1 year. Major molecular response occurred in 16 of the 38 (42%) chronic-phase CML patients and in 7 of the 9 (78%) chronic-phase CML patients with the T315I mutation. Of the 17 advanced-phase CML patients, major hematologic response was achieved in 6 patients (35%), major cytogenetic response was achieved in 4 patients (24%), and complete cytogenetic response was achieved in 2 patients (12%). Of the 5 advanced-phase CML patients with confirmed T315I mutation, 1 (20%) achieved major hematologic response, 1 achieved major cytogenetic response (20%), and none achieved complete cytogenetic response. Based upon the efficacy and safety data, the authors determined that 45 mg once daily is the recommended dose of ponatinib for the phase II study that was initiated in September 2010.

Table 1. Ponatinib in CML: Phase I Data[2]

	Complete Hematologic Response	Major Cytogenetic Response	Complete Cytogenetic Response
Chronic-Phase CML (n=38)	95%	66%	53%
Advanced-Phase CML (n=17)	35%	24%	12%

CML=chronic myelogenous leukemia.

4027 Prognostic Factors of Long-Term Outcomes In Low- or Int-1-Risk MDS with del5q Treated with Lenalidomide (LEN): Results From a Randomized Phase 3 Trial (MDS-004)[6]

P Fenaux, A Giagounidis, O Beyne-Rauzy, G Mufti, M Mittelman, P Muus, P te Boekhorst, G Sanz, M Cazzola, J Backstrom, T Fu, E Hellström-Lindberg

Transfusion dependence is a negative predictor of OS and disease progression.[7] Fenaux and associates sought to determine which factors were predictive of AML-free survival and OS during lenalidomide treatment.[6] To address this aim, they analyzed patient data from the MDS-004 study[8] after prolonged follow-up. MDS-004 was a randomized, double-blind, phase III study that found that lenalidomide (5 mg or 10 mg) induced significant red blood cell–transfusion independence in red blood cell–transfusion-dependent patients with low-risk or intermediate-1–risk MDS and del(5q). In the present study, the researchers combined data from patients randomized to receive lenalidomide 5 mg or lenalidomide 10 mg, but placebo patient data were excluded because the majority of these patients crossed over to lenalidomide 5 mg during the open-label phase of the study. The authors evaluated potential baseline risk factors using a Cox proportional hazard model. The time-dependent covariates on AML-free survival and OS were red blood cell–transfusion independence lasting at least 26 weeks and cytogenetic response.

A total of 138 patients received 1 or more doses of lenalidomide. The median age was 68 years (range, 36–86 years), and most patients (74%) were female. An isolated del(5q) abnormality was detected in 66% of patients, and 28% had 1 or more additional cytogenetic abnormalities. Using the World Health Organization International Prognostic Scoring System, 43% of patients were low/intermediate risk, 32% were high/very high risk, and 25% had missing data. The duration of lenalidomide treatment was 12.9 months (range, 0.3–36.7 months). During the long-term follow-up, 31 patients (22%) progressed to AML (median time to AML progression, 4.01 years;

95% CI, 3.17–4.03) resulting in a 3-year cumulative AML-progression rate of 34.8%. In addition, 66 patients (48%) died (median OS, 3.68 years); the 3-year OS rate was 56.0%.

The researchers found a reduced risk of AML progression and death in patients with red blood cell–transfusion independence for at least 26 weeks (hazard ratio [HR], 0.547; *P*=.022; HR, 0.49; *P*=.008; respectively), lower baseline ferritin levels (HR, 1.01; *P*=.004; HR, 1.01; *P*=.004), and a younger age (HR, 1.03; *P*=.014; HR, 1.04; *P*=.004). The authors conclude that achievement of red blood cell–transfusion independence, lower baseline ferritin levels, and younger age are predictive factors for longer AML-free survival and OS in low-risk and intermediate-1–risk del5q MDS patients treated with lenalidomide.

985 Results of PX-171-003-A1, an Open-label, Single-arm, Phase 2 (Ph2) Study of Carfilzomib (CFZ) in Patients (pts) with Relapsed and Refractory Multiple Myeloma (MM)[9]

DS diCapua Siegel, T Martin, M Wang, R Vij, AJ Jakubowiak, S Jagannath, S Lonial, V Kukreti, NJ Bahlis, M Alsina, AA Chanan-Khan, G Somlo, F Buadi, FJ Reu, JA Zonder, K Song, E Stadtmauer, AF Wong, M Vallone, Y-L Chang, M Kauffman, RZ Orlowski, AK Stewart, SB Singhal

In this study by diCapua Siegel and coworkers, all patients had evidence of relapsed and progressive multiple myeloma (MM), and 65% had been refractory to treatment with bortezomib at some point.[9] Further, all patients had relapsed after at least 2 previous lines of treatment; these must have included bortezomib and an immunomodulatory agent (either thalidomide or lenalidomide). Carfilzomib was administered for 12 cycles, on days 1, 2, 8, 9, 15, and 16; during cycle 1, the dose was 20 mg/m^2; it was 27 mg/m^2 for the remaining cycles. The median patient age was 63 years (range, 37–87 years), patients had a median duration of MM of 5.4 years (range, 0.5–22.3 years), and 69% of patients had an International Staging System (ISS) disease stage of II/III. Most patients (83%) had experienced disease progression by 60 days after their last therapy. A total of 257 patients were considered evaluable for this analysis.

Overall, carfilzomib was associated with a 24% overall response rate (ORR), the primary endpoint of the study. However, slightly more patients (34%) achieved clinical benefit (overall response or minimal response). The median duration of overall response was 8.3 months. Most of the responses were partial responses (PR; 18.7%) or very good PRs (VGPR; 5.1%); a CR was achieved by 0.4%. Although carfilzomib was active even among bortezomib-refractory patients, both the proportion of responding patients (17%) and the median duration of overall response (7.8 months) were decreased. The overall response to carfilzomib was observed regardless of whether patients were considered to be low or high risk. For example, similar proportions of patients achieved an overall response regardless of bone marrow involvement (<50% vs ≥50% involvement: 24% vs 26%), number of previous chemotherapy lines (<5 vs ≥5 lines: 25% vs 24%), cytogenetics (good vs poor: 24% vs 28%), and baseline peripheral neuropathy (absent or present: 26% vs 24%). The median progression-free survival (PFS) was 3.7 months (95% CI, 2.8–4.6), and the median OS was 15.5 months (95% CI, 12.7–19.0).

Grade 3/4 hematologic toxicities—including thrombocytopenia (27%), anemia (22%), lymphopenia (18%), and neutropenia (10%)—were the most frequent treatment-emergent adverse events. The incidence of new onset grade 3/4 peripheral neuropathy was low (<1%). Most patients (82%) discontinued treatment, either due to disease progression (57%) or adverse events (12%). A minority of patients (16%) completed all 12 intended cycles of carfilzomib.

862 Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma: Initial Results of Phase I/II MMRC Trial[10]

AJ Jakubowiak, D Dytfeld, S Jagannath, DH Vesole, TB Anderson, BK Nordgren, D Lebovic, KE Stockerl-Goldstein, KA Griffith, MA Hill, CK Harvey, AM Dollard, R Ott, SL Kelley, J Barrickman, M Kauffman, R Vij

Jakubowiak and colleagues reported the results of a phase I/II study designed to determine the maximum tolerated dose of carfilzomib, lenalidomide, and dexamethasone and to evaluate its safety and efficacy in patients with newly diagnosed MM.[10] This is the first published study to evaluate carfilzomib in the frontline MM setting.

The combination of carfilzomib, lenalidomide, and dexamethasone was administered in 28-day cycles. During the phase I portion of this trial, only carfilzomib was dose escalated, whereas both lenalidomide (25 mg on days 1–21) and dexamethasone (40 mg weekly during cycles 1–4 and 20 mg weekly during cycles 5–8) were kept at constant doses. Carfilzomib was initiated at 20 mg/m^2, with a maximal planned dose of 27 mg/m^2 and a decrease to 15 mg/m^2 as needed; it was administered on days 1, 2, 8, 9, 15, and 16 of each cycle. After a toxicity assessment, the study protocol was amended with the addition of a higher carfilzomib dose (36 mg/m^2), and the total phase I trial enrollment was increased to 35 patients. Overall, 36 patients are expected to be treated at the maximum tolerated dose during the phase I/II study. Patients who achieved a PR or better after 4 or more cycles could

proceed to stem cell collection and autologous stem cell transplantation (ASCT); these patients were offered the option of continuing treatment with the carfilzomib-based combination. Following the completion of 8 cycles, patients continued to receive maintenance doses of the combination (carfilzomib on days 1, 2, 15, and 16; lenalidomide on days 1–21; and dexamethasone weekly), administered at the dosage tolerated.

This analysis included data from 24 enrolled patients (4, 14, and 6 patients at carfilzomib doses of 20 mg/m^2, 27 mg/m^2, and 36 mg/m^2); of these patients, toxicity data were available for 21. The maximum tolerated dose had not yet been reached at the time of this analysis. One dose-limiting toxicity was observed; this patient experienced nonfebrile neutropenia at the 27-mg/m^2 carfilzomib dose, which required lenalidomide dose reduction. Of the 23 patients who continued on therapy, the majority (n=20) had no need for dose modifications. Reversible hematologic toxicities included grade 3/4 neutropenia (n=3), grade 3/4 thrombocytopenia (n=3), and grade 3 anemia (n=2). Grade 3 nonhematologic adverse events included glucose elevations related to dexamethasone (n=5), deep vein thrombosis (n=1), fatigue (n=1), and mood alteration (n=1). Even after prolonged therapy, only 2 cases of peripheral neuropathy were reported, both of which were grade 1 in severity.

After a median of 4 months of treatment (range, 1–8), 19 patients who completed 1 or more treatment cycles were found to be evaluable for response. All of these patients had a PR or greater; 63% had VGPR or better, and 37% had a CR or near CR. This response was rapid, with the majority of patients (n=17) achieving a PR after the first treatment cycle. None of the evaluable patients had experienced disease progression in the follow-up period. After a median of 4 treatment cycles, a total of 7 patients proceeded to stem cell collection (median 6.3 × 10^6 CD34+ cells/kg collected).

622 A Phase 3 Study Evaluating the Efficacy and Safety of Lenalidomide Combined with Melphalan and Prednisone in Patients ≥ 65 Years with Newly Diagnosed Multiple Myeloma (NDMM): Continuous Use of Lenalidomide Vs Fixed-duration Regimens[11]

A Palumbo, M Delforge, J Catalano, R Hajek, M Kropff, MT Petrucci, Z Yu, L Herbein, JM Mei, CJ Jacques, MA Dimopoulos

Palumbo and colleagues reported an updated interim analysis of the MM-015 study, a randomized, double-blind, multicenter phase III trial of 459 elderly (≥65 years of age) patients with newly diagnosed MM.[11] The safety and efficacy of lenalidomide were investigated in both the induction and maintenance settings.

Patients were stratified by age and disease stage and were then randomized into 3 treatment arms. All patients first received nine 28-day cycles of induction therapy followed by maintenance treatment. Patients were randomized to receive either MPR-R (n=152; 0.18 mg/kg melphalan on days 1–4; 2 mg/kg prednisone on days 1–4; and 10 mg/day lenalidomide on days 1–21 induction therapy followed by 10 mg/day lenalidomide on days 1–21 maintenance therapy), MPR (n=153; 0.18 mg/kg melphalan on days 1–4; 2 mg/kg prednisone on days 1–4; and 10 mg/day lenalidomide on days 1–21 induction therapy followed by placebo on days 1–21 maintenance therapy), or MP (n=154; 0.18 mg/kg melphalan on days 1–4; 2 mg/kg prednisone on days 1–4; and placebo on days 1–21 induction therapy followed by placebo on days 1–21 maintenance therapy). Baseline patient characteristics were well balanced between the 3 treatment arms, and approximately half of patients (48–51%) had ISS stage III disease. The median Karnofsky performance score was 80–90%. This second interim analysis was conducted with 70% of events reported, after a median follow-up of 21 months. The study was unblinded in May 2010 based on a recommendation of the Data Safety and Monitoring Board; therapy was continued in the current treatment arms.

Patients in the MPR-R arm experienced a prolonged median PFS compared with the MPR arm and a significantly prolonged median PFS compared with the MP arm (31 months vs 14 months and 13 months, respectively; HR, 0.398; P<.0000001 for MPR-R vs MP). Importantly, this improvement was also observed in patients ages 65–75 years (not reached vs 14.7 months and 12.4 months, respectively; HR, 0.315; P<.001 for MPR-R vs MP). PFS was also found to favor MPR-R versus MP across several other patient groups, including patients with ISS stage I/II disease, with creatinine clearance of 60 mL/min or higher, with beta-2-microglobulin levels less than or equal to 5.5 mg/L, and with a Karnofsky performance score of 90 or higher. In contrast, there was no significant difference in OS between the 3 treatment arms, either in the overall patient group or in a patient subgroup analysis. At the beginning of maintenance therapy, a comparison of patients in the MPR-R and MPR arms showed that the continuation of lenalidomide maintenance therapy was associated with a significantly reduced risk of disease progression (HR, 0.314; P<.001) as compared with placebo. More patients in the MP and MPR arms, compared with MPR-R, required salvage therapy (most commonly lenalidomide or bortezomib).

Compared with the MP arm, patients who received lenalidomide in either the MPR-R or MPR arms had a higher frequency of grade 3/4 adverse events. Grade 4 hematologic adverse events, which were more common with lenalidomide therapy, included anemia,

neutropenia, and thrombocytopenia. Grade 3/4 nonhematologic adverse events more common with lenalidomide included infections, pulmonary embolism, deep vein thrombosis, fatigue, and rash. Overall, these occurred more often during the induction phase compared with the maintenance phase. As a result, patients in the MPR-R and MPR arms exhibited higher rates of treatment discontinuation due to toxicity during induction therapy.

310 Maintenance Treatment with Lenalidomide After Transplantation for Myeloma: Final Analysis of the IFM 2005-02[12]

M Attal, VC Lauwers, G Marit, D Caillot, T Facon, C Hulin, P Moreau, C Mathiot, M Roussel, C Payen, H Avet-Loiseau, J Luc Harousseau

Attal and colleagues reported the final analysis of the Intergroupe Francophone du Myelome (IFM) 2005-02 study, which aimed to evaluate the safety and efficacy of lenalidomide as maintenance therapy following ASCT in younger MM patients (<65 years).[12] Significant PFS benefit with lenalidomide was demonstrated in the first interim analysis,[13] and this study was unblinded in June 2010 following recommendation by the Data Safety and Monitoring Board. This prospective, placebo-controlled, phase III trial enrolled 614 MM patients with nonprogressive disease within 6 months of first-line ASCT. All patients received 2 cycles of consolidation therapy with 25-mg/day lenalidomide on days 1–21 of 28 days. Following stratification for beta-2-microglobulin level at baseline, presence of chromosome 13 deletion, and VGPR or better following ASCT, patients were randomized to receive either 10–15 mg/day lenalidomide (n=307) or placebo (n=307) maintenance therapy until evidence of disease relapse. Baseline characteristics were well balanced between the 2 treatment arms. Median age was 55 years, and nearly half of patients (43–48%) had ISS stage I disease. The majority of patients (79% in each arm) had only 1 ASCT, and the remaining 21% had 2 ASCT treatments. The median time from diagnosis to randomization was 10 months (range, 8–12) in each arm, and the median time from ASCT to consolidation was 4 months (range, 3–5) in each arm.

Results in this final analysis confirmed that patients treated with lenalidomide maintenance experienced significantly longer PFS compared with patients receiving placebo (HR, 0.5; *P*<.00000001). This benefit was observed across all patient subgroups, regardless of baseline beta-2-microglobulin levels, presence of the chromosome 13 deletion, and type of induction regimen used. PFS was significantly associated with the degree of response both prior to and after consolidation therapy. HRs more heavily favored lenalidomide among patients reaching PR or stable disease prior to consolidation (HR, 0.46; 95% CI, 0.32–0.66; *P*<.00001) and a CR after consolidation therapy (HR, 0.31; 95% CI, 0.14–0.68; *P*=.021). In fact, the response achieved following consolidation therapy was found to be highly prognostic for PFS (VGPR vs no response; *P*=.001). There was no difference in OS between patients who received lenalidomide versus placebo maintenance therapy.

Overall, lenalidomide maintenance therapy was well tolerated, although these patients had a higher rate of treatment discontinuation due to adverse events compared with those treated with placebo (21% vs 15%). Some of the grade 3/4 adverse events that occurred more frequently with lenalidomide maintenance therapy included neutropenia, thrombocytopenia, anemia, and skin disorders. Secondary hematologic malignancies (10 vs 2) and nonhematologic malignancies (6 vs 1) were also more frequent in the lenalidomide maintenance arm compared with placebo.

37 Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB 100104[14]

PL McCarthy, K Owzar, KC Anderson, CC Hofmeister, DD Hurd, H Hassoun, S Giralt, EA Stadtmauer, PG Richardson, DJ Weisdorf, R Vij, JS Moreb, NS Callander, K van Besien, T Gentile, L Isola, RT Maziarz, DA Gabriel, A Bashey, H Landau, T Martin, MH Qazilbash, D Levitan, B McClune, V Hars, J Postiglione, C Jiang, E Bennett, SS Barry, L Bressler, M Kelly, M Sexton, C Rosenbaum, H Parameswaran, MC Pasquini, MM Horowitz, TC Shea, SM Devine, C Linker

Data from the third intent-to-treat analysis were reported from the Cancer and Leukemia Group B (CALGB) 100104 study by McCarthy and coworkers.[14] A total of 568 patients with Durie-Salmon stage I–III MM younger than 70 years were enrolled in this double-blind, placebo-controlled, phase III clinical trial. All patients had achieved stable disease or better after 2 or more cycles of induction therapy, and were within 1 year of having initiated MM treatment; all patients also had adequate stem cell count ($\geq 2 \times 10^6$ CD34+ cells/kg).

Patients underwent a single ASCT with 200 mg/m^2 melphalan and were restaged on days 90–100. Patients who had a CR, a PR, or stable disease were randomized to receive either 10-mg/day lenalidomide (n=231) or placebo (n=229), which were administered until disease progression. Prior to randomization, patients were stratified according to beta-2-microglobulin baseline levels and the use of thalidomide or lenalidomide during induction therapy. Baseline characteristics were similar in the 2 treat-

ment arms. Almost three-quarters (74%) of patients had received lenalidomide or thalidomide as induction therapy prior to study enrollment.

Lenalidomide maintenance therapy was associated with a 60% reduction in the risk of disease progression. Significantly fewer patients in the lenalidomide arm experienced an event as compared with the placebo arm (19.9% vs 41.5%; *P*<.0001). The median time to disease progression, the primary endpoint of the study, was also significantly improved with lenalidomide compared to placebo (42.3 vs 21.8 months; *P*<.0001). The time to disease progression benefit associated with lenalidomide was observed across the characteristics used to stratify patients. Median OS did not significantly differ between the 2 treatment arms; however, the investigators suggested that this similarity could be due to study unblinding and patient crossover (78.2% of eligible patients in the placebo arm crossed over to receive lenalidomide). Significantly more patients treated with lenalidomide experienced grade 3 or higher adverse events compared with patients treated with placebo, including both hematologic toxicities (45% vs 11%; *P*<.0001) and nonhematologic toxicities (33% vs 25%; *P*=.0350). Grade 3 or higher hematologic toxicities included neutropenia, thrombocytopenia, febrile neutropenia, and anemia. Grade 3 or higher nonhematologic toxicities included infections, fatigue, rash, and diarrhea. A higher proportion of patients in the lenalidomide arm discontinued study treatment due to adverse events (12% vs 1%) and to reasons other than adverse events (20% vs 7%). A total of 5 new cases of acute myelogenous leukemia or MDS were reported; of these, 2 patients were not treated with lenalidomide, and 1 patient treated with lenalidomide had also received prior breast cancer therapy.

858 Efficacy and Toxicity of Rituximab and Brief Duration, High Intensity Chemotherapy with Filgrastim Support for Burkitt or Burkitt – Like Leukemia/Lymphoma: Cancer and Leukemia Group B (Calgb) Study 10002[15]

DA Rizzieri, JL Johnson, JC Byrd, G Lozanski, BL Powell, TC Shea, S Nattom, E Hoke, BD Cheson, R Larson

Patients with Burkitt leukemia and lymphoma who are treated with high-dose metabolite therapy and intensive alkylator therapy over a short period may have improved outcomes. Rizzieri and colleagues evaluated the addition of rituximab plus growth factor support to an intensive chemoimmunotherapy regimen in patients with untreated Burkitt leukemia/lymphoma.[15] They also examined the patterns of relapse when prophylactic cranial irradiation was not administered. The study enrolled 105 patients with a median age of 43 years (range, 19–79; 27% >60 years), and 69% were male. Disease was intermediate risk or high risk in 46% of patients.

Patients were treated with cyclophosphamide 200 mg/m^2 for 5 days and prednisone 60 mg/m^2 for 7 days; cycles were started on day 8 and were delivered every 21 days. Cycles 2, 4, and 6 included ifosfamide 800 mg/m^2 on days 1–5, methotrexate 1.5 g/m^2 infused over 1 day with leucovorin rescue, vincristine 2 mg on day 1, Ara-C 1 gm/m^2 on days 4 and 5, etoposide 80 mg/m^2 on days 4 and 5, and dexamethasone 10 mg/m^2 on days 1–5. Cycles 3, 5, and 7 included the same doses of methotrexate, vincristine, and dexamethasone, but also included cyclophosphamide 200 mg/m^2 intravenous (IV) on days 1–5 and doxorubicin 25 mg/m^2 on days 4 and 5. Filgrastim was administered at 5 µg/kg/day each cycle until recovery of neutrophil counts. Rituximab was administered on day 8 of cycle 2 at 50 mg/m^2 and on days 10 and 12 at 375 mg/m^2; during cycles 3–7, it was infused only on day 8 of each course at 375 mg/m^2. All 7 courses of therapy were completed by 75 of the 105 patients.

The median follow-up of survivors was 3.2 years. A CR was achieved in 83% of patients, with 87% of these patients maintaining CR at follow-up (Table 2). The 2-year event-free survival (77%) and OS (80%) favored patients younger than 60 years (event-free survival, 87%; OS, 87%). The study also found that 2-year event-free survival and OS were better for low-risk patients (90%, 92%) versus high-risk patients (55%, 55%). Central nervous system (CNS) relapse occurred in 4 patients (4%). Treatment-related death (CNS bleed [n=1], infections [n=4], and respiratory failure [n = 2]) occurred in 7 patients (6.8%). Almost all patients experienced hematologic toxicities; the most common grade 3/4 nonhematologic toxicities were infection (72%), stomatitis/upper gastrointestinal toxicity (66%), fatigue (26%), nausea/vomiting (20%), pulmonary or CNS bleeding (11%), rash or erythema multiforme (10%), diarrhea (10%), dyspnea (10%), and neurologic disruptions (8%). The authors concluded that high-intensity chemotherapy administered with rituximab and growth factor support induces a lasting high rate of remission with tolerable side effects in patients with Burkitt leukemia and lymphoma.

593 ^{90}Yttrium Ibritumomab Tiuxetan as First Line Treatment for Follicular Lymphoma. First Results from an International Phase II Clinical Trial[16]

CW Scholz, A Pinto, W Linkesch, O Linden, A Viardot, U Keller, G Hess, K Lerch, F Frigeri, M Arcamone, B Frericks, C Pott, A Pezzutto

Radioimmunotherapy (RIT) with ^{90}Yttrium ibritumomab tiuxetan improves remission rates in follicular lymphoma when given as consolidation after both mild and aggressive chemotherapy regimens.[17] Scholz and associates sought to determine if chemotherapy is needed before

Table 2. Rituximab Plus Growth Factor Added to an Intensive Chemotherapy Regimen in Patients With Untreated Burkitt Leukemia/Lymphoma[15]

Variable	<60 Years n=77	≥60 Years n=28	All Patients N=105
Completing ≥6 Cycles	84% (64)	52% (16)	76% (80)
Reason Tx Ended Early			
Progression	1% (1)	–	1% (1)
Adverse Event/Refusal	8% (6)	18% (5)	10% (11)
Death	4% (3)	21% (6)	9% (9)
Other	4% (3)	4% (1)	4% (4)
Complete Remission	86% (66)	75% (21)	83% (87)
CNS Relapse	1% (1)	10% (3)	4% (4)*
2-Year Event-Free Survival (95% CI)	87% (77–93%)	53% (33–70%)	77% (68–85%)
2-Year Overall Survival (95% CI)	87% (77–93%)	61% (40–76%)	80% (70–86%)

*According to International Prognostic Index scoring, 2 patients were low/intermediate and 1 patient was high. Scoring was not available for 1 patient.

CI=confidence interval; CNS=central nervous system; Tx=treatment.

applying RIT with ^{90}Yttrium ibritumomab tiuxetan for the treatment of follicular lymphoma.[16] This prospective phase II multicenter study enrolled patients older than 50 years with previously untreated follicular lymphoma (stage III or IV disease) who exhibited a clinical need for treatment (tumor lesions increasing at least 50% in the last 6 months, B symptoms, and bulky disease up to 10 cm). ^{90}Yttrium ibritumomab tiuxetan was administered as a single dose of 15 MBq/kg (0.4 mCi/kg).

At the time of the report, 59 patients were enrolled in the study. At the 6-month follow-up, 25 patients (45%) achieved complete remission and 22 patients (40%) achieved partial remission. At the 12-month follow-up, 52% of patients were in complete remission, and 20% were in partial remission. Of the 33 patients who reached at least 18 months of follow-up, 52% were still in complete remission, 9% were in partial remission, and 36% were off the study (either in observation or new treatment). The PFS was 17.9 months after a median follow-up of 23 months; progression to high-grade lymphoma occurred in 3 patients. Polymerase chain reaction analysis revealed BCL2-IgH translocation in peripheral blood and bone marrow samples of 49% of the patients (28 of 57 patients); 6 months after RIT, 19 of 26 evaluated patients were negative (molecular remission rate of 73%).

No severe acute toxicity or febrile episodes were observed. Some patients exhibited thrombocytopenia (grade 3, n=13; grade 4, n=1) and neutropenia (grade 3, n=13; grade 4, n=0). Anemia occurred in 5 patients (grade 1/2). All other adverse events were grade 1 or 2. Two deaths occurred during the observation period; these patients were off-study due to progressive disease, and the deaths were attributed to progressive lymphoma and pancreatic carcinoma. Colon adenocarcinoma, oral cavity squamous carcinoma, and renal cancer occurred in 3 additional patients during the course of the study, but the authors thought it unlikely that these cancer cases were causally linked to RIT therapy.

The researchers concluded that RIT with ^{90}Yttrium ibritumomab tiuxetan induced high rates of clinical and molecular remission with adverse events of limited severity; however, the duration of remission remains to be determined. They suggest that this treatment may be a useful option as a first-line therapy in older or frail patients with follicular lymphoma.

594 ^{90}Y-Ibritumomab Tiuxetan (Zevalin®) Consolidation of First Remission In Advanced-Stage Follicular Non-Hodgkin's Lymphoma: Updated Results After a Median Follow-up of 66.2 Months From the International, Randomized, Phase III First-Line Indolent Trial (FIT) In 414 Patients[18]

A Hagenbeek, J Radford, A Van Hoof, U Vitolo, AZS Rohatiner, G Salles, P Soubeyran, H Tilly, AB Delaloye, WLJ van Putten, F Morschhauser

Hagenbeek and associates provided an update of results from the phase III FIT (First-line Indolent Trial) trial.[18] In the FIT trial, previously untreated patients with advanced stage follicular lymphoma were randomized to receive 0.4 mCi/kg (maximum dose of 32 mCi) of ^{90}Y-ibritumomab tiuxetan (207 patients) or observation (202 patients) within 3 months of completing initial induc-

tion therapy (chemotherapy only, 86%; rituximab plus chemotherapy, 14%). After a median follow-up of 3.5 years, the patients treated with ^{90}Y-ibritumomab tiuxetan had significantly improved PFS compared to the observation group (36.5 months vs 13 months; $P<.0001$).[19] The authors of the present study extended these results by reporting data from a median follow-up of 66.2 months.

Five-year PFS was significantly better in the ^{90}Y-ibritumomab tiuxetan-treated group compared to the observation group (47% vs 29%, respectively; HR, 0.51; 95% CI, 0.39–0.65; $P<.0001$), with a median PFS of 49 months in the ^{90}Y-ibritumomab tiuxetan group versus 14 months in the observation group. For those patients who achieved CR/CR unconfirmed after induction, the 5-year PFS was 57% for the ^{90}Y-ibritumomab tiuxetan group (median not yet reached at 92 months) versus 43% for the observation group (median of 31 months; HR, 0.61; 95% CI, 0.42–0.89). For those patients who achieved a PR after induction, the 5-year PFS was 38% for the ^{90}Y-ibritumomab tiuxetan group (median of 30 months) versus 14% for the observation group (median of 6 months; HR, 0.38; 95% CI, 0.27–0.53). The patients who received rituximab plus chemotherapy during induction had a 5-year PFS of 64% in the ^{90}Y-ibritumomab tiuxetan group compared to 48% in the observation group (HR, 0.66; 95% CI, 0.30–1.47). The ORR to second-line treatment was 79% versus 78% (^{90}Y-ibritumomab tiuxetan group vs observation group, respectively). There was no significant difference in the 5-year OS for the ^{90}Y-ibritumomab tiuxetan group (93%) versus the observation group (89%; $P=.561$). At the time of their report, 40 patients had died (^{90}Y-ibritumomab tiuxetan group, n=18; observation group, n=22). There was no significant difference in the number of patients who developed secondary malignancies ($P=.19$) or MDS/AML ($P=.063$) between the 2 groups.

The authors concluded that this extended 5-year follow-up confirms that ^{90}Y-ibritumomab tiuxetan consolidation results in a significant increase in PFS. The authors note that rescue treatment with rituximab may explain why there is no difference in the OS between groups (63 of 82 patients in the ^{90}Y-ibritumomab tiuxetan group and 102 of the 122 patients in the observation group received rituximab-containing treatments after progression).

428 A Phase 2, Double-Blind, Placebo-Controlled Trial of Rituximab + Galiximab Vs Rituximab + Placebo In Advanced Follicular Non-Hodgkin's Lymphoma (NHL)[20]

I Bence-Bruckler, D Macdonald, PJ Stiff, B McKinney, KL Ruffner, L Wilson, M Whiteley, B Kahl

Galiximab is a primatized chimeric monoclonal immunoglobulin G_1 antibody that specifically binds CD80, an immune coregulatory protein. In vitro, galiximab directly mediates antibody-dependent cell-mediated toxicity against CD80-positive malignant B cells. Ex vivo, galiximab can modulate immune signaling within the tumor microenvironment.

In a phase II study, Bence-Bruckler and colleagues evaluated rituximab plus galiximab versus rituximab plus placebo for patients with relapsed or refractory (grade I–IIIa) follicular non-Hodgkin lymphoma (NHL).[20] Patients were randomized according to age (≤60 years vs >60 years), prior rituximab treatment, and baseline tumor bulk (diameter of largest lesion ≤7 cm vs >7 cm). On days 1, 8, 15, and 22, patients received rituximab (375 mg/m^2) plus galiximab (500 mg/m^2) or rituximab plus placebo. Patients were followed every 3 months for 2 years, and every 6 months thereafter. The study enrolled 337 patients (rituximab plus galiximab, 175 patients; rituximab plus placebo, 162 patients). There were comparable baseline patient demographics and disease characteristics in each treatment group. The median follow-up time was 13.8 months.

Compared to the rituximab group, the rituximab plus galiximab group had a 26% reduction in the hazard for disease progression or death (HR, 0.738; 95% CI, 9.0–14.7). The median PFS in the rituximab plus galiximab group was 12.0 months (95% CI, 9.0–14.7) compared to 9.0 months (95% CI, 8.9–10.5) in the rituximab group. There was no significant difference in the ORR (51% vs 48%; rituximab plus galiximab vs rituximab, respectively; $P=.455$) or CR (20% vs 15%; $P=.251$) between groups. In patients who were rituximab-naïve or who had a bulky tumor, elevated lactate dehydrogenase (>1 × the upper limit of normal), or involved bone marrow, the researchers noted a trend toward a larger PFS effect with treatment.

There was a trend towards more adverse events in the rituximab plus galiximab group versus the rituximab group for pyrexia (18% vs 11%), headache (13% vs 7%), cough (10% vs 6%), upper respiratory infection (8% vs 4%), insomnia (8% vs 4%), neutropenia (6% vs 3%), muscle spasms (5% vs <1%), and oropharyngeal pain (4% vs 1%). No significant differences were observed for grade 3/4 adverse events or serious adverse events between groups. During the study, no antigaliximab antibodies were detected. Ten deaths occurred in the rituximab plus galiximab group compared to 17 deaths in the rituximab group (HR, 0.549; 95% CI, 0.248–1.217; $P=.135$). The authors concluded that rituximab plus galiximab was well tolerated in patients with relapsed or refractory follicular NHL, with a trend toward improved PFS.

430 Inotuzumab Ozogamicin (CMC-544) In Patients with Indolent B-Cell NHL That Is Refractory to Rituximab Alone, Rituximab and Chemotherapy, or Radioimmunotherapy: Preliminary Safety and Efficacy From a Phase 2 Trial[21]

A Goy, J Leach, WC Ehmann, K Ando, K Hatake, K Tobinai, T Feldman, S Hua, ADG Volkert, ER Vandendries, M Ogura

Phase I trial data indicate that inotuzumab ozogamicin (CMC-544), a humanized anti-CD22 antibody conjugated to a cytotoxic antitumor antibiotic (calicheamicin), is safe and effective in refractory or heavily pretreated patients.[22,23] In this phase II trial, Goy and associates assessed the safety and efficacy of inotuzumab ozogamicin for the treatment of relapsed or refractory patients with indolent B-cell NHL.[21] These patients had progressed after treatment with 2 or more systemic therapies, and had no response or progression within 6 months of rituximab-containing therapy or within 12 months of anti-CD20 RIT. Inotuzumab ozogamicin (1.8 mg/m^2) was administered every 28 days for 4 to 8 cycles. The dose and frequency were adjusted according to any observed toxicities. The researchers presented preliminary results from 53 patients with CD22-positive indolent B-cell NHL (follicular, n=45 patients; marginal zone, n=5; small lymphocytic lymphoma, n=3). The median duration of follow-up was 6.2 months, 5.9 months, and 5.3 months, respectively. The majority of follicular lymphoma patients (56%) were high risk, 27% were intermediate risk, and 18% were low risk.

In the intent-to-treat population, 32 (59%) patients discontinued therapy. The majority of these discontinuations were due to adverse events (13 patients, 24%), including 10 cases of thrombocytopenia and 4 cases of neutropenia. The most common treatment-related adverse events (all grades) were thrombocytopenia (63%), neutropenia (49%), increased aspartate aminotransferase (47%), nausea (41%), fatigue (37%), leukopenia (33%), lymphopenia (33%), and decreased appetite (28%). The most common grade 3/4 adverse events included thrombocytopenia (45%), neutropenia (29%), lymphopenia (12%), and leukopenia (6%). Serious adverse events occurred in 6 patients (pyrexia [n=2], hydronephrosis leading to sepsis and death [n=1], upper abdominal pain [n=1], pneumonia [n=1], abdominal distension [n=1], urinary retention [n=1], and abnormal hepatic function [n=1]).

The ORR was 50% in all refractory indolent lymphoma patients (21 of 42 patients), 58% in follicular lymphoma patients (21 of 36 patients), and 85% in patients who discontinued treatment due to an adverse event. A CR was observed in 19% of all patients (8 of 42 patients) and in 22% of follicular lymphoma patients (8 of 36 patients). Of the 21 follicular lymphoma patients who had an ORR, 4 experienced relapse or progression. The median PFS in both the intent-to-treat population and the follicular lymphoma subgroup was 11.1 months. The OS rate was 87% (95% CI, 71–94%) at 6 months and 64% (95% CI, 34–83%) at 12 months; the median OS for all patients in the intent-to-treat population had not yet been reached.

856 Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab In Patients with Relapsed Follicular, Indolent and Mantle Cell Lymphomas—Final Results of the Randomized Phase III Study NHL 2-2003 on Behalf of the StiL (Study Group Indolent Lymphomas, Germany)[24]

MJ Rummel, U Kaiser, C Balser, MB Stauch, W Brugger, M Welslau, N Niederle, C Losem, H Ballo, E Weidmann, U von Gruenhagen, L Mueller, M Sandherr, J Vereschagina, A Hinke, J Barth

Fludarabine plus rituximab is an effective treatment option for patients with relapsed or refractory follicular, other indolent, or mantle cell lymphomas. However, several phase II studies suggest that bendamustine plus rituximab is also efficacious in this patient population.[25,26] Rummel and associates presented the final results of a phase III study investigating the use of bendamustine plus rituximab versus fludarabine plus rituximab as a first-relapse therapy for patients with low-grade NHL.[24] The patients were randomized to receive rituximab 375 mg/m^2 (day 1) plus either bendamustine 90 mg/m^2 (days 1 and 2) or fludarabine 25 mg/m^2 (days 1–3) every 28 days, with a maximum of 6 cycles. The final analysis included 208 patients (follicular, 47%; mantle cell, 21%; Waldenströms, 12%; marginal zone, 8%; lymphocytic, 8%; unclassifiable, 5%). There were 109 patients in the bendamustine plus rituximab group and 99 patients in the fludarabine plus rituximab group. The median age of the patients was 68 years (range, 38–87 years), patients had a median of 1 prior therapy (range, 1–7). Most patients had stage IV (71.6%, bendamustine plus rituximab group; 60.6%, fludarabine plus rituximab group) and stage III (21.1%, bendamustine plus rituximab group; 25.3%, fludarabine plus rituximab group) disease. A median of 6 treatment cycles were administered in each group.

During the median observation time of 33 months, patients in the bendamustine plus rituximab group had significantly longer PFS than patients in the fludarabine plus rituximab group (30.4 months vs 11.2 months, respectively; HR, 0.51; 95% CI, 0.34–0.67; P<.0001). Both the ORR and the CR rate were significantly better in the bendamustine plus rituximab group versus the fludarabine plus rituximab group (ORR, 82% vs 49%;

P<.0001; CR, 39% vs 16%; *P*=.0004). However, the OS did not differ significantly between the 2 groups: it was 63.6 months in the bendamustine plus rituximab group versus 49.2 months in the fludarabine plus rituximab group (HR, 0.76; 95% CI, 0.50–1.15; *P*=.1932). In addition, there was no significant difference in the duration of remission between treatment groups (36.5 months, bendamustine plus rituximab group vs 27.5 months, fludarabine plus rituximab group; HR, 0.74; 95% CI, 0.45–1.19; *P*=.2074). There were no significant differences in the rates of adverse events or serious adverse events. Grade 3/4 hematologic toxicities were similar in both treatment groups (leukocytopenia, 13.6% of bendamustine plus rituximab treatment cycles vs 14.2% of fludarabine plus rituximab treatment cycles; neutropenia, 14.0% vs 14.5%; thrombocytopenia, 2.2% vs 2.8%; and anemia, 1.6% vs 2.0%). The researchers determined that bendamustine plus rituximab and fludarabine plus rituximab have similar safety profiles, but bendamustine plus rituximab treatment results in significantly improved PFS, ORR, and CR. The authors concluded that bendamustine plus rituximab is more effective than fludarabine plus rituximab in the treatment of relapsed indolent lymphoma.

589 R-CHOP Versus (vs) CHOP Followed by Maintenance Rituximab (MR) Vs Observation In Older Diffuse Large B-Cell Lymphoma (DLBCL) Patients (pts): Long-Term Follow-up of Intergroup E4494 / C9793[27]

VA Morrison, F Hong, TM Habermann, RI Fisher, BD Cheson, B Kahl, SJ Horning, BA Peterson

Morrison and colleagues presented updated long-term results[27] of an intergroup trial comparing cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) to CHOP with or without maintenance rituximab.[28] The study enrolled 632 patients older than 60 years with previously untreated CD20-positive diffuse large B-cell lymphoma. During the induction phase, patients were randomized to receive CHOP plus rituximab 375 mg/m^2 (R-CHOP; days -7, -3, and -2 before cycles 3, 5, and 7 if given) versus CHOP for 2 cycles beyond the best response (6–8 cycles total). The responders (415 patients) to R-CHOP or CHOP were randomized to receive maintenance rituximab every 6 months for 2 years starting 4 weeks after the last cycle (n=207 patients) or observation (n=208 patients). Results from a median follow-up of 9.4 years from the start of induction therapy (546 patients; 267 R-CHOP, 279 CHOP) and 9.0 years from maintenance (352 patients; 174 maintenance rituximab, 178 observation) were presented.

R-CHOP significantly prolonged the 9-year failure-free survival compared to CHOP (35% vs 25%, respectively; HR, 0.71; 95% CI, 0.55–0.92; *P*=.008; Figure 1). However, the 9-year OS was not significantly different (44% vs 37%; *P*=.11). High-risk patients had a significant difference in the effect of induction therapy for failure-free survival (HR, 0.61; 95% CI, 0.51–0.93; *P*=.02) but not OS. Maintenance rituximab improved failure-free survival (HR, 0.70; 95% CI, 0.53–0.93; *P*=.014) but not OS (HR, 0.89; 95% CI, 0.66–1.20; *P*=.45). There was a relationship between induction and maintenance therapies; maintenance rituximab improved failure-free survival after CHOP (HR, 0.56; 95% CI, 0.38–0.82; *P*=.003) but not after R-CHOP (HR, 0.97; 95% CI, 0.64–1.47; *P*=.89). However, there was no difference in OS for CHOP plus maintenance rituximab versus R-CHOP plus maintenance rituximab. The median time to failure after maintenance randomization was 9.5 years for CHOP plus maintenance rituximab and 2.0 years for CHOP with observation (*P*=.003); the median time to failure was 8.5 years for R-CHOP plus maintenance rituximab and 7.5 years for R-CHOP plus observation (*P*=.79). In an analysis of treatment failures that occurred within the first 2 years, the most failures occurred in the CHOP with observation group (CHOP plus observation, 73%; CHOP plus maintenance rituximab, 47%; R-CHOP plus observation; 38%; R-CHOP plus maintenance rituximab, 36%). The researchers concluded that initial therapy with R-CHOP led to improved disease-free survival and failure-free survival compared to CHOP in diffuse large B-cell lymphoma patients older than 60 years. The time to failure, but not OS, was lengthened with maintenance rituximab after CHOP, but not R-CHOP.

961 Complete Remissions with Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma[29]

AR Shustov, R Advani, P Brice, NL Bartlett, JD Rosenblatt, T Illidge, J Matous, R Ramchandren, MA Fanale, JM Connors, Y Yang, EL Sievers, DA Kennedy, B Pro

There is a significant need for viable treatment options for patients with systemic anaplastic large cell lymphoma, a CD30-expressing subtype of peripheral T-cell lymphoma that is particularly aggressive. Brentuximab vedotin (SGN-35) is an antibody drug conjugate: monomethyl auristatin E (MMAE) is conjugated to an anti-CD30 monoclonal antibody; lysosomal degradation releases MMAE inside CD30-positive malignant cells, where it induces cell-cycle arrest and apoptosis of the tumor cell. Shustov and colleagues presented the interim results of an open-label,

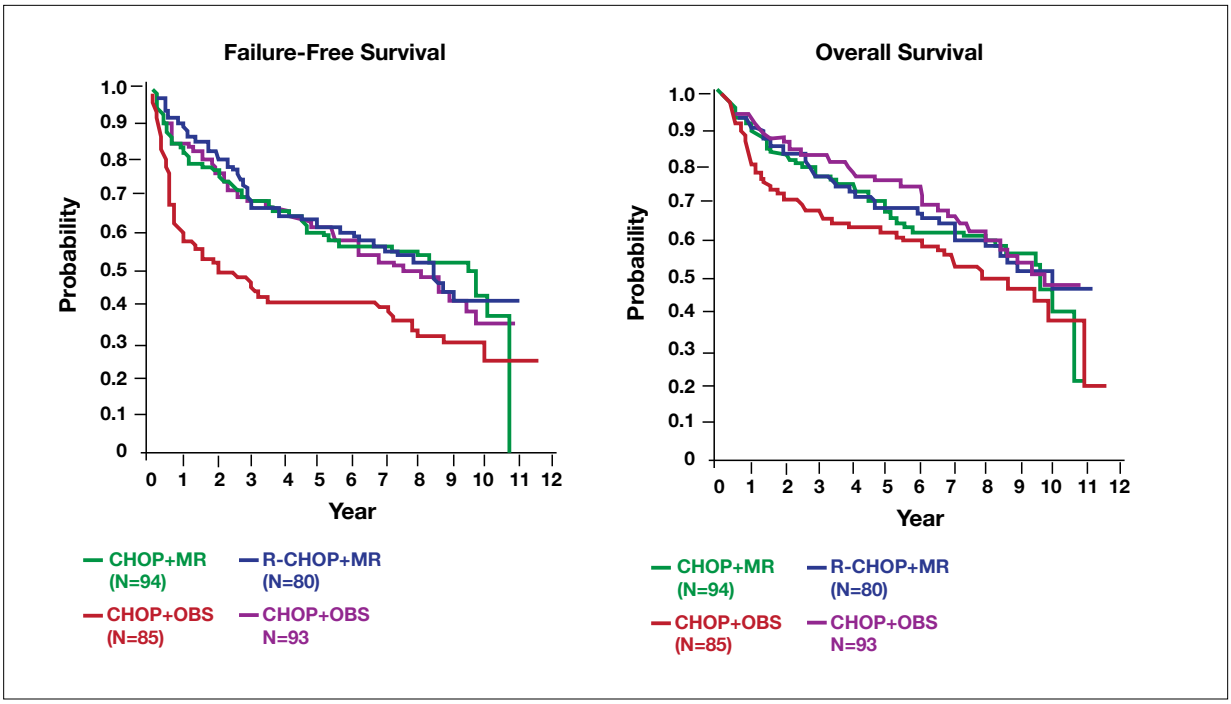

Figure 1. Results from long-term follow-up of Intergroup E4494/C9793, a trial examining R-CHOP versus CHOP followed by maintenance rituximab versus observation in older diffuse large B-cell lymphoma patients.

CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; MR=maintenance rituximab; OBS=observation; R-CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab.

Data from Morrison VA et al. *Blood* (ASH Annual Meeting Abstracts). 2010;116: Abstract 589.

multicenter phase II study of the safety and efficacy of brentuximab vedotin for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma.[29] This study enrolled 58 patients with relapsed or refractory systemic anaplastic large cell lymphoma, measurable disease (≥1.5 cm fluorodeoxyglucose-avid), and Eastern Cooperative Oncology group (ECOG) performance status of 0–1. Every 3 weeks, patients received brentuximab vedotin 1.8 mg/kg as a 30-minute IV infusion for up to 16 cycles (median 6; range, 1–16). The median age of the patients was 52 years (range, 14–76), and 53% were female. There was bone marrow involvement at baseline in 14% of patients, and 72% of patients were anaplastic lymphoma kinase (ALK)-negative. In terms of treatment history, 62% were refractory to frontline therapy, 50% were refractory to the most recent treatment, and 24% were nonresponsive to prior treatment. The median number of prior chemotherapy treatments was 2 (range, 1–6); 26% failed prior autologous hematopoietic stem cell transplant.

According to an independent review facility, the ORR was 86% (95% CI, 75–94); complete remission occurred in 53% of patients, partial remission occurred in 33% of patients, 5% of patients had progressive disease, 3% of patients had stable disease, and the remaining patients were histologically ineligible or not evaluable. The median duration of the ORR, the median duration of complete remission, the median PFS, and the median OS were not yet reached at the time of the presentation. A tumor burden reduction was observed in 97% of patients. B symptom resolution occurred in 14 of the 17 patients with symptoms at baseline. Both the ALK-negative and ALK-positive patients achieved similar ORRs (88% vs 81%, respectively), and complete remission was achieved in at least 50% of these patients (50% of ALK-negative vs 63% of ALK-positive). After treatment, 14 of the 58 patients had subsequent stem cell transplants. The most common adverse events were nausea (38%), peripheral sensory neuropathy (38%), fatigue (34%), pyrexia (33%), diarrhea (29%), neutropenia (21%), and rash (21%). Grade 3/4 adverse events occurred in 60% of patients: neutropenia (grade 3, 12%; grade 4, 9%), peripheral sensory neuropathy (10%; 0%), thrombocytopenia (9%; 5%), and anemia (7%; 0%). No deaths occurred during the study. Eleven patients (19%) discontinued therapy, 5 due to treatment-related adverse events (11%).

763 Intensive Chemotherapy and Immunotherapy, without Brain Irradiation, In Newly Diagnosed Patients with Primary CNS Lymphoma: Results of CALGB 50202[30]

JL Rubenstein, JL Johnson, SH Jung, BD Cheson, LD Kaplan

The treatment of patients with primary central nervous system lymphoma (PCNSL) can be challenging because whole brain irradiation may result in impaired neurocognitive function, particularly in patients older than 60 years. Therefore, Rubenstein and associates conducted a study to assess an intensive chemotherapy-alone treatment for patients with PCNSL.[30] For the remission induction therapy (14-day cycle, 8 cycles), patients received methotrexate 8 g/m^2 IV over 4 hours (day 1), leucovorin 100 mg/m^2 every 6 hours until methotrexate was less than 0.05 mM (day 2), rituximab 375 mg/m^2 IV cycles 1–6 (day 3), and temozolomide 150 mg/m^2 orally (days 7–11 in odd cycles only). Patients who achieved CR following induction therapy received intensive consolidation therapy with etoposide 40 mg/kg continuous IV infusion over 96 hours (days 1–4) and cytarabine 2 gm/m^2 IV over 2 hours every 12 hours for 8 doses (days 1–4).

The study enrolled 45 newly diagnosed patients with PCNSL (95.6% large B-cell lymphoma); the median age was 61 years (range, 12–76 years), and 48.9% were male. The median ECOG performance score was 1, 27.9% of patients had elevated lactate dehydrogenase (LDH), 48.8% had elevated CSF protein, 46.5% had deep brain lesions, and 23.3% had positive cerebrospinal fluid cytology. Following induction, 64% of patients achieved CR and went on to the consolidation phase. The median follow-up was 3.6 years. There were 21 cases of disease progression, 1 treatment-related mortality (sepsis following consolidation therapy), 1 fatality secondary to sepsis (off-protocol), and 1 fatality secondary to lung cancer at 4.5 years. The median PFS had not yet been reached, but the estimated 2-year PFS was 57%, and the estimated 3-year PFS was 52%. The median OS had not yet been reached, but the estimated 2-year OS was 73%, and the estimated 3-year OS was 71% (Figure 2). The researchers noted that patients with ECOG performance scores of 2 had significantly reduced event-free survival compared to those with ECOG performance scores of 0–1 (P<.01). Event-free survival was similar in older (>60 years) and younger (<60 years) patients (P=.51). Hematologic adverse events (grade 3, 13%; grade 4, 58%; grade 5, 0%) included neutropenia (4%; 53%; 0%) and thrombocytopenia (7%; 49%; 0%). Nonhematologic adverse events included infection (18%, 0%, 2%), aspartate aminotransferase (18%; 4%, 0%), and neurotoxicity (4%; 0%; 0%).

The authors of the study concluded that this induction and consolidation protocol resulted in a CR of 64%, had comparable efficacy in older and younger patients, and was associated with minimal treatment-related neurotoxicity. In addition, the estimated 2-year PFS of 57% was comparable to combined-modality programs with reduced-dose whole brain irradiation.

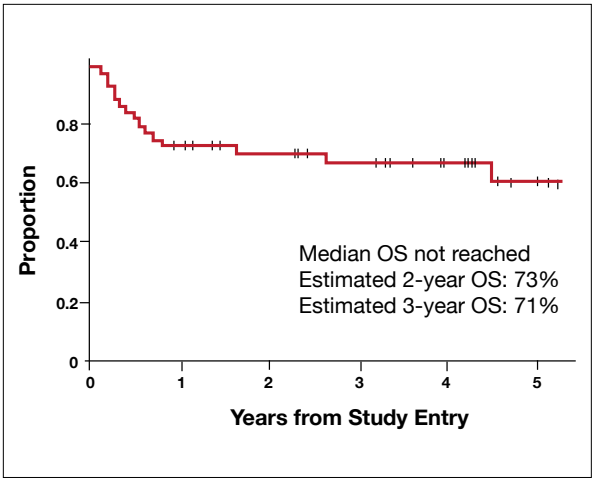

Figure 2. Overall survival from the CALGB 50202 trial, which studied intensive chemotherapy and immunotherapy, without brain irradiation, in newly diagnosed patients with primary central nervous system lymphoma.

OS=overall survival.

Data from Rubenstein JL, Johnson JL, Jung SH, et al. Intensive chemotherapy and immunotherapy, without brain irradiation, in newly diagnosed patients with primary CNS lymphoma: results of CALGB 50202. *Blood* (ASH Annual Meeting Abstracts). 2010;116: Abstract 763.

415 A Randomized Phase III Trial of ABVD Vs. Stanford V +/- Radiation Therapy In Locally Extensive and Advanced Stage Hodgkin's Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496)[31]

LI Gordon, F Hong, RI Fisher, NL Bartlett, JM Connors, RD Gascoyne, H Wagner, PJ Stiff, BD Cheson, M Gospodarowicz, R Advani, B Kahl, JW Friedberg, KA Blum, TM Habermann, J Tuscano, R Hoppe, SJ Horning

The implementation of combined chemotherapy regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) provided a significant advance in oncology treatment by greatly improving clinical outcomes of advanced Hodgkin lymphoma (HL). Overtime, newer treatments such as the Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone) were developed to add targeted radiation to sites of disease,

Table 3. ABVD Versus Stanford V in Hodgkin Lymphoma[31]

	CR + CCR	Partial Response	Stable Disease	Progression
ABVD	72	7.7	7.9	<1
STANFORD V	69	7.4	10.3	2

P=NS

ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; CR=complete response; CCR=complete cytogenetic response; NS=not significant.

reduce duration of chemotherapy, and reduce toxicity while maintaining efficacy.[32,33] To compare the Stanford V approach with the ABVD approach, Gordon and associates conducted a randomized, phase III intergroup trial in patients with locally extensive or advanced HL.[31] The primary endpoint of the trial was failure-free survival; the study was designed with sufficient power to detect a 33% improvement in failure-free survival for Stanford V versus ABVD.

The study enrolled 812 treatment-naïve patients with locally extensive HL (Ann Arbor Stage I-IIA/B) with bulky mediastinal disease or advanced HL (Ann Arbor Stage III or IV). The median age of the patients was 33 years, and 53% were men. Stage of disease, cell type, extranodal involvement, and risk factors were similar in each arm of the study. The patients were randomized to receive either 6–8 cycles of ABVD (n=404 patients; only patients with bulky mediastinal disease received 36 Gy of radiation) or 12 weeks of Stanford V (n=408 patients; only patients with sites >5 cm or with macroscopic splenic disease received 36 Gy of radiation).

The study found similar response rates and toxicity in each treatment group. In the ABVD treatment group, 72% achieved CR plus complete cytogenetic response, and 7.7% achieved PR (Table 3). In the Stanford V treatment group, 69% achieved CR plus complete cytogenetic response, and 7% achieved PR. Neutropenia was the most common grade 3/4 adverse event in both groups. More patients in the Stanford V treatment group experienced grade 3 lymphopenia (78%, Stanford V vs 42%, ABVD; *P*<.001) and grade 3/4 sensory neuropathy (10%, Stanford V vs 3%, ABVD; *P*<.001). Grade 5 adverse events occurred in less than 1% of both groups. Secondary cancers developed in 12 patients after ABVD and in 14 patients after Stanford V. The 5-year failure-free survival was 73% and 71% (ABVD and Stanford V, respectively; *P*=.29). The OS was also similar between the 2 treatment groups: 88% for ABVD and 87% for Stanford V (*P*=.87; HR, 0.97; 95% CI, 0.65–1.44). Overall, patients with locally extensive disease (Stage I, II) had better failure-free survival and OS compared to patients with advanced disease (Stage III, IV); the failure-free survival and OS did not vary by treatment type for patients with advanced disease. The researchers concluded that ABVD (advanced HL) and ABVD plus radiation (locally extensive disease with bulky mediastinal disease) should remain the standard of care because the Stanford V regimen did not meet the study requirement of 33% improvement in failure-free survival. For some patients, particularly older patients with compromised cardiac and lung function, Stanford V with radiation is a viable treatment alternative.

283 Results of a Pivotal Phase 2 Study of Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma[34]

R Chen, AK Gopal, SE Smith, SM Ansell, JD Rosenblatt, R Klasa, JM Connors, A Engert, EK Larsen, DA Kennedy, EL Sievers, A Younes

Approximately half of HL patients who undergo ASCT relapse, and those patients with refractory or relapsed HL have a poor prognosis.[35-37] Since one characteristic of HL is the presence of CD30+ Hodgkin Reed-Sternberg cells, Chen and associates assessed the efficacy and safety of the antibody-drug conjugate brentuximab vedotin (SGN-35), which causes apoptotic death of CD30-expressing tumor cells, in patients with relapsed or refractory HL.[34] In this phase II multicenter study, 102 patients who had previously received ASCT were treated with brentuximab vedotin 1.8 mg/kg every 21 days (30-minute outpatient infusion) for up to 16 cycles. The median age of the patients was 31 years (range, 15–77 years), and 54% were female. At baseline, the ECOG performance status was 0 (41%) or 1 (59%), the median number of prior chemotherapy treatments was 3.5 (range, 1–13), 71% of patients had primary refractory disease, and 42% of patients were refractory to the most recent treatment.

After a median duration of 27 weeks (range, 3–54 weeks) of brentuximab vedotin treatment (median number of cycles, 9 [range, 1–16 cycles]), 96 patients (94%) had achieved tumor reduction. Thirty-five patients had B symptoms at baseline; 29 of these patients (83%) had

resolution of symptoms at a median of 3 weeks (range, <1–16 weeks). The ORR was evaluated by an independent review facility according to the Revised Response Criteria for Malignant Lymphoma. The ORR was 75% (95% CI, 65–83), with 34% CR and 40% PR. Stable disease was observed in 22% of patients, and progressive disease was observed in 3% of patients. The median OS had not yet been reached, but the estimated 12-month OS was 88%. According to the independent review facility, the median PFS was 25.1 weeks, the median duration of overall response was 29 weeks (95% CI, 16–52), and the median duration of CR was not yet determined.

The most common treatment-related adverse events included peripheral sensory neuropathy (47%), fatigue (46%), nausea (42%), upper respiratory tract infection (37%), diarrhea (36%), pyrexia (29%), neutropenia (22%), vomiting (22%), and cough (21%). Grade 3 or higher adverse events occurred in 55% of patients. The grade 3/4 treatment-related adverse events were neutropenia (grade 3, 14%; grade 4, 6%), peripheral sensory neuropathy (8%; 0%), thrombocytopenia (6%; 2%), and anemia (5%; 1%). The median time to onset of grade 2 peripheral neuropathy was 27.3 weeks (approximately 9 cycles of treatment); when the treatment was discontinued or the dose was reduced, 68% of these patients had resolution or improvement of symptoms (median time to improvement or resolution, <2 months). Adverse events led to discontinuation in 20% of patients. No deaths were attributed to treatment.

419 Final Analysis: Phase II Study of Oral Panobinostat In Relapsed/Refractory Hodgkin Lymphoma Patients Following Autologous Hematopoietic Stem Cell Transplant[38]

A Sureda, A Younes, D Ben-Yehuda, T-C Ong, JL Kaufman, C Le Corre, J Gallagher, A Shen, A Engert

In another study of patients with refractory or post-ASCT relapsed HL, Sureda and colleagues assessed the efficacy of panobinostat, an oral pan-deacetylase inhibitor that increases acetylation of proteins in multiple pathways involved in oncogenesis.[38] In this prospective, phase II study, adults with classic HL with progressive disease after ASCT and at least 1 site of measurable nodal disease received oral panobinostat 40 mg 3 times per week, every week, in 21-day cycles. The dose was modified according to the development of adverse events, and response was assessed by computed tomography/magnetic resonance imaging every 2 cycles. The study enrolled 129 patients (median age, 32 years; 63 women), the majority of whom had nodular sclerosing/mixed cellularity HL (96%). Patients had received a median of 4 prior systemic regimens (range, 2–7), and 41% of patients did not have a response to the last systemic therapy. The majority of the patients (66%) had experienced a relapse less than 12 months after their first ASCT, and 79% had received additional systemic therapies after their first ASCT.

The median duration of treatment with panobinostat was 132 days (range, 5–614 days); 110 patients (85%) exited the study. Reasons for discontinuation included disease progression (65 patients, 50%), adverse events (21 patients, 16%), withdrawal of consent (11 patients, 9%), new cancer therapy (11 patients, 9%), protocol deviation (1 patient, 1%), and death (1 patient, 1%). The median time to response was 10 weeks (range, 4–51 weeks). According to investigator assessment, 106 patients (82%) achieved disease control (defined as CR [4%], PR [23%], or stable disease [55%]). Overall response (defined as CR or PR) occurred in 35 patients (27%). Progressive disease was seen in 14 patients (11%), and 9 patients (7%) were not evaluable. Tumor reduction was observed in 77% of patients. The median PFS (investigator assessment, 6.1 months; central assessment, 6.7 months) and duration of response (investigator assessment, 6.9 months; central assessment, 6.7 months) were greater than 6 months. The median OS had not yet been reached, but the estimated 12-month OS was 78%. Treatment-related hematologic adverse events included thrombocytopenia (any grade, 85%; grade 3/4, 79%), anemia (38%; 21%), neutropenia (26%; 21%), and leukopenia (10%; 5%). The thrombocytopenia was reversible with dosing changes, and only 5% of patients stopped treatment because of this adverse event. The most common nonhematologic adverse events included diarrhea (any grade, 66%; grade 3/4, 3%), nausea (60%; 1%), fatigue (38%; 9%), vomiting (33%; 3%), and decreased appetite (25%; 3%). There were no drug-related deaths.

The researchers noted that their primary endpoint of an ORR greater than 15% was reached; the ORR was 27%. Further, they suggested that there is an absence of cross-resistance to conventional chemotherapy because response was observed in all poor prognosis groups. They also found that the response was durable and the safety profile was manageable. Patients are currently being enrolled in a phase III maintenance trial.

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Commentary

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The 2010 American Society of Hematology (ASH) meeting was long on interesting abstracts on the management of patients with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), acute and chronic leukemias, and multiple myeloma, but longer still on topics of controversy.

Acute Leukemias and Chronic Myelogenous Leukemia

Molecular lesions are present even in cytogenetically normal acute myeloid leukemia (AML) and are of prognostic importance. Adding to the list of FMS-like tyrosine kinase-3 and nucleophosmin is now Tet oncogene family member 2 mutations, as presented at ASH in a study from the Cancer and Leukemia Group B (CALGB). Since AML tends to be a disease of older persons—a population that fares poorly with standard 7+3 chemotherapy—new approaches are needed. Fortunately, a large number of agents are being evaluated, including clofarabine, lenalidomide, cloretazine, azacytidine, decitabine, sapacitabine, and bortezomib.[1] How they will be best integrated into future treatment paradigms remains to be determined.[2]

For patients with Philadelphia chromosome-positive (Ph-positive) acute lymphoblastic leukemia, several studies at ASH confirmed the beneficial role of incorporating a tyrosine kinase inhibitor (TKI).[3,4] However, which TKI will be preferred in the future is under investigation.

For chronic myelogenous leukemia (CML), most patients respond nicely to one of several available TKIs. However, there is no effective treatment for patients whose cells exhibit the T315I mutation. Ponatinib appears to be a solution to that problem. In the phase I data presented at ASH from 74 patients mostly with CML or Ph1-positive acute lymphoblastic leukemia, 95% of patients achieved a complete hematologic response, and 53% of patients achieved a complete cytogenetic response. Importantly, all patients with T315I had a complete hematologic response, and 89% had a complete cytogenetic response. The drug was well tolerated and should afford a treatment option for this previously poor-risk group of patients.[5]

Multiple Myeloma

Incorporation of novel agents, such as bortezomib and lenalidomide, into initial treatment strategies for myeloma has altered conventional approaches to these patients. Unfortunately, the optimal regimen remains unclear. At ASH, studies supported 2 observations with important clinical implications: First, 4 drugs (dexamethasone, cyclophosphamide, bortezomib, and lenalidomide) did not appear to be superior to a variety of 3-drug combinations.[6] Second, lenalidomide maintenance following induction treatment appears to prolong failure-free and overall survival.[7]

Follicular Lymphoma/Low-Grade NHL

Patients with follicular lymphoma (FL) and low-grade NHL are usually highly responsive to treatment, yet these remain incurable disorders. Studies from decades ago failed to demonstrate benefit from early intervention in the absence of specific indications for treatment, leading to a watch-and-wait approach.[8] However, at ASH, results were presented from a 3-arm randomized trial in which patients with stages II–IV, asymptomatic, non-bulky FL received either watch-and-wait, weekly rituximab for 4 doses alone, or 4 doses of weekly rituximab followed by 2 years of maintenance.[9] The time to next therapy and the progression-free survival (PFS) were significantly longer with the last group. However, the follow-up was relatively short, and there was no survival advantage. Importantly, data regarding responsiveness to second-line therapy (first systemic treatment for watch-and wait, second systemic treatment for rituximab-treated patients) were not available. Whether this approach should become standard is up for debate.

How best to approach patients with more advanced disease was a topic of the PRIMA (Primary Rituximab and Maintenance) study, presented at the 2010 American Society of Clinical Oncology (ASCO) meeting by Salles and coworkers.[10] Patients receiving chemoimmunotherapy followed by rituximab maintenance experienced a longer PFS than those who were merely observed. At ASH, the PRIMA investigators presented interesting data on the potential role for fluorodeoxyglucose (FDG)/positron emission tomography (PET) scans in post-treatment assessment.[11] The outcome for patients with a negative PET scan following induction was excellent (74% 3-year PFS); however, those with a positive study experienced a 3-year PFS of only 32%.

Validation of this potentially powerful prognostic test is warranted.

Since FL is a disease characterized by repeated relapses, new agents are needed to treat each recurrence, thus prolonging survival. New and exciting drugs in clinical trials include CAL-101, an oral PI3-kinase inhibitor, with a response rate of 62% in indolent NHL and 62% in mantle cell lymphoma, but with no responses in diffuse large B-cell lymphoma (DLBCL).[12] Fowler and colleagues[13] updated their work with an oral Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, which blocks pathways downstream from the B-cell receptor. Responses were achieved in 60% of chronic lymphocytic leukemia/small lymphocytic lymphoma, 75% of mantle cell lymphoma, 25% of FL, and 37.5% of DLBCL. Data on inotuzumab, a drug-antibody conjugate with an anti-CD22 monoclonal antibody linked to the toxin calicheamicin, was reported by Goy and associates[14] in 43 patients with indolent NHL. The ORR was 53% in all patients, and 66% in those with FL (n=35). Trials are in development featuring combinations with these agents.

In another randomized phase II trial, 337 patients with relapsed or refractory FL received either rituximab plus placebo or rituximab plus galiximab, a primatized anti-CD80 antibody. There was no significant difference between the groups in complete response (CR) or overall response, with a trend toward prolonged PFS for the combination.[15] However, in the frontline setting, CALGB investigators found the combination of galiximab and rituximab to be highly active, with an overall response rate (ORR) of 92% in patients with low-risk disease according to the Follicular Lymphoma International Prognostic Index (FLIPI), 80% in patients with intermediate-risk disease, and even 55% in patients with high-risk disease, with CR rates of 75%, 48%, and 27%, respectively.[16] Unfortunately, the future of this antibody is uncertain. Encouraging data from a recent CALGB study presented at ASH by Grant and coworkers of rituximab plus epratuzumab (anti-CD22) demonstrated an ORR of 84.2%, with a 33.3% CR across FLIPI groups.[17]

Other studies of new approaches unfortunately provided disappointing results. Coiffier and colleagues[18] randomized 676 patients with relapsed or refractory follicular NHL to rituximab alone or with bortezomib. Although the addition of bortezomib was associated with a longer PFS and a higher response rate, the doublet failed to meet its primary objective of a 33% increase in PFS, and it was associated with increased toxicity.

Diffuse Large B-Cell NHL

Cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) has remained the standard regimen for patients with DLBCL for more than 8 years.[19] At ASH, Morrison and colleagues representing the US Intergroup presented 9.4-year follow-up of 632 older patients with advanced-stage DLBCL treated with CHOP or R-CHOP with a secondary randomization to maintenance rituximab or observation.[20] The previously observed advantage for R-CHOP in PFS and disease-free survival persisted; however, there were a comparable number of failures within 2 years. Maintenance benefitted only patients initially treated with CHOP alone. Friedberg and Southwest Oncology Group (SWOG) coworkers failed to demonstrate benefit with R-CHOP followed by I-131 tositumomab consolidation in advanced stage DLBCL.[21] A study of its efficacy in earlier-stage patients is being planned.

Attempts to improve on R-CHOP have been largely unsuccessful. Preliminary data from the German High-grade Lymphoma study group suggested that R-CHOP given every 2 weeks (R-CHOP-14) was superior[22]; however, 2 subsequent studies from the United Kingdom and France failed to support this impression.[23,24] In the pre–rituximab era, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) with intrathecal methotrexate and followed by sequential consolidation by high-dose methotrexate, rituximab, ifosfamide, and etoposide was shown to be superior to CHOP.[25] At ASH, a randomized trial of R-CHOP versus ACVBP plus rituximab (R-ACVBP) in 380 patients younger than 60 years showed similar ORR and CR rates between the arms.[26] However, the PFS (86.8% vs 73.4%) and overall survival (92.2% vs 83.8%) at 3 years favored R-ACVBP. Nonetheless, R-ACVBP was significantly more toxic with respect to myelosuppression and mucositis. It is not clear whether such a regimen will be adopted in North America. In an ongoing US trial (CALGB-50303), dose-adjusted etoposide, prednisone, vincristine, and doxorubicin plus rituximab (R-EPOCH) is being compared with R-CHOP. Future studies might better focus on patients with high International Prognostic Index scores, for whom none of these regimens is satisfactory.

Whether central nervous system prophylaxis is beneficial in patients with DLBCL has been a subject of controversy. Studies from SWOG suggested no benefit for this approach.[27] This impression was confirmed at ASH by Schmitz and coworkers from the German High-Grade Lymphoma Study Group (GHGLSG).[28] They reported the likelihood of a central nervous system event of only 2.3% in 2,797 patients ages 60 years or younger. They were unable to identify any specific risk factors that would justify the use of central nervous system prophylaxis. Indeed, they were unable to demonstrate a lower incidence of central nervous system recurrence in patients who actually received central nervous system prophylaxis. These data

supported their previous data in older patients.[29] Thus, the aggregate of data provides compelling support against the routine use of this therapy.

T-Cell NHLs

The peripheral T-cell NHLs (T-NHL) have long been neglected because they represent only 10% of NHLs, and there have been no effective treatment options. Although CHOP is the most commonly used regimen, results are disappointing, with the notable exception of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (ALCL).[30,31] Adding a drug such as etoposide failed to benefit older patients, and the prolongation of PFS in younger patients did not translate into a survival advantage.[32] CHOP plus alemtuzumab induces a high response rate, but with an unacceptable number of opportunistic infections.[32] The combination of CHOP-bortezomib was reported at ASH[33] to induce an ORR of 76%, with 65% CRs in 46 untreated patients, data that warrant confirmation. Other drugs with modest activity include bevacizumab, denileukin diftitox, gemcitabine, lenalidomide, nelarabine, pentostatin, and thalidomide. Fortunately, there are now several effective new agents that have rekindled interest in clinical trials in these patients. O'Connor and associates were the first to suggest activity for the antifol pralatrexate in patients with T-NHL.[34] In the subsequent pivotal, multicenter PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma) study trial, 109 patients with relapsed and refractory disease were accrued, and the drug achieved an ORR of 29%, with 11% CRs and a median PFS of 3.5 months.[35] Combinations of pralatrexate with a variety of other agents are in development. Romidepsin is one of the numerous histone deacetylase inhibitors in clinical trials. In early studies, the response rate was 38% in patients with all histologic subgroups of peripheral T-cell lymphoma.[36] At ASH, Coiffier and colleagues[37] presented results from a pivotal trial, which included 131 patients with relapsed and refractory T-NHL. The response rate was 26%, with 15% CRs. Other drugs with activity described at ASH included the farnesyltransferase inhibitor tipifarnib[38] and the purine nucleoside phosphorylase inhibitor forodesine.[39] Monoclonal antibodies have also demonstrated activity in T-NHL, including KW-0761, a humanized antibody that targets the chemokine receptor (CCR4), which is present in cutaneous T-cell lymphoma, peripheral T-cell lymphoma, and adult T-cell leukemia/lymphoma (ATL). Yamamoto conducted a phase I study with this antibody and reported 31% ORR with 13% CR.[40] At ASH, Ishida and associates[41] presented data on 27 patients with relapsed/refractory ATL and reported an ORR of 54% with 27% CR. These results appear superior to combination chemotherapy in untreated patients and will be pursued further.

Brentuximab vedotin (SGN-35) stimulated the most excitement of the new drugs. This drug-antibody conjugate consists of an anti-CD30 monoclonal antibody linked to dolastatin 10 monomethyl auristatin E (MMAE), an inhibitor of tubulin, which is internalized into tumor cells, where the MMAE is released, resulting in cell cycle arrest and apoptosis. In 58 patients with relapsed and refractory ALCL, another CD30-positive disease, the response rate was 87%, with 57% CR; 95% of patients experienced some tumor regression. The duration of response ranged from 4 to 36 weeks, with ongoing responses in 18 patients.[42] The drug was well-tolerated, with neutropenia and peripheral sensory neuropathy being the most frequent adverse effects. It is hoped that this drug will be on a fast track to approval. Doublets of these various drugs are being developed with the goal of moving them to initial treatment, replacing CHOP.

Hodgkin Lymphoma

Given the high cure rate with HL, there are several new goals of therapy: increasing efficacy in poor-risk patients, decreasing toxicity in good-risk patients, and identifying better strategies for relapsed and refractory patients. Unfortunately, 2 studies failed to show progress in the initial treatment of HL. The US Intergroup comparison of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with Stanford V failed to show any advantage for the latter in the population as a whole,[43] or even in the subset with bulky disease.[44]

However, the German Hodgkin's Study Group presented the HD-15 trial, which showed that the use of fluorodeoxyglucose positron emission tomography scans reduced the number of patients exposed to radiation therapy from 70% in earlier studies to 11%, with no compromise in outcome.[45]

For the first time in many years, HL was also the focus of a high level of interest in new therapies. Brentuximab vedotin was reported to induce a response rate of 75%, with 34% CR in patients with relapsed and refractory disease; 94% of patients experienced some reduction in tumor burden. The median PFS was longer than 7 months. Myelosuppression and peripheral neuropathy were the most common severe adverse effects.[46] This impressive agent is being evaluated post–autologous transplant, is being combined with ABVD and other agents, and is expected to rapidly move into frontline treatment. Another agent that may find its way into the Hodgkin's armamentarium is the histone deacetylase inhibitor panobinostat. Sureda and coworkers presented data on 129 patients, all of whom had failed at least frontline therapy

and autologous stem cell transplantation. Overall, 27% of patients responded; there were mostly partial remissions with a median PFS longer than 6 months.[47]

Conclusion

These reports from ASH should provide optimism that new and exciting targeted drugs will lead to a future of improved outcome and reduced toxicities for lymphoma patients. Participation in clinical trials is essential if this progress is to continue.

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