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Recent Advances in the Treatment of Hematologic Malignancies

A Review of Selected Presentations from the
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Target Audience

This activity has been designed to meet the educational needs of hematologist and oncologists involved in the management of patients with hematologic malignancies.

Statement of Need/Program Overview

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

Educational Objectives

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

- Describe how to integrate prognostic factors into treatment decisions for patients with hematologic malignancies, including lymphoma, leukemia, myelodysplastic syndromes (MDS), and multiple myeloma
- Identify factors influencing the choice of treatment for patients with MDS and leukemia
- Outline the most recent data on treatment options for both newly diagnosed and recurrent multiple myeloma.

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Introduction

Readers perusing the 2008 American Society of Hematology (ASH) abstracts selected for the accompanying review cannot help but be impressed by not only how far we have come in the last few years in the treatment of patients with leukemias, lymphomas and myeloma, but also how far there is to go. The days of empiric mixing and matching of conventional cytotoxics, once the subject of many ASH presentations, has been replaced by studies reporting on a series of novel agents which, when demonstrated to have clinical activity, are rapidly combined with other active drugs. Such regimens are rapidly being brought to frontline therapy, increasing the likelihood of further clinical benefit. This series of events has been quite impressive in multiple myeloma where, until the availability of the new generation of agents, complete remissions were uncommon and there was limited evidence that outcome was being improved. The immunomodulatory drugs, thalidomide and lenalidomide, and bortezomib have not only demonstrated impressive single-agent activity, but also in various combination regimens, the induction of responses in as many as 100% of patients in some series, including a significant number of patients attaining a complete remission. Whereas randomized trials have failed to demonstrate a role for early stem cell transplant, the addition of agents such as bortezomib prior to transplant improves outcome following the procedure. Importantly, however, the availability of new treatment options should continue to prolong the survival of these patients and may limit the need for transplant in multiple myeloma in the future.

Novel approaches have also markedly improved the outcome for patients with chronic myelogenous leukemia (CML). In years past, the only options were hydroxyurea, interferon, or bone marrow transplantation. The tyrosine kinase inhibitors have revolutionized our approach to CML, first with imatinib, and now the relative roles for dasatinib and nilotinib are being better characterized. The next major breakthrough will be when an agent that has efficacy in patients with the drug-resistant T315I mutation is discovered.

For decades, there was no effective approach for patients with myelodysplastic syndromes. Thus, supportive care was the comparator for most clinical trials. Azacitidine and decitabine now offer effective treatment options for select patients with the potential for prolonged survival. Data from ASH suggest that combinations with histone deacetylase inhibitors may further improve patient outcome. Unfortunately, improvements in the therapy of acute myelogenous leukemia have been slow in coming.

The ASH meetings provided important data on the role of both relatively standard agents as well as novel compounds in the non-Hodgkin lymphomas and chronic lymphocytic leukemia (CLL). There was a time when a controversy raged about the preferred purine analog for the treatment of CLL, a so-called "Therapeutic Beauty Contest" (*J Clin Oncol.* 1992;10:868-871.): There was the fludarabine camp (which obviously won), the cladribine supporters, and then there were those who insisted that pentostatin was associated with superior efficacy and less toxicity. In 1996, I published an editorial entitled "Ennui or not ennui, that is the question" (*Ann Oncol.* 1996;7:767-769.) in which I bemoaned the large number of clinical trials comparing different purine analog-based regimens in CLL and NHL with a disturbing lack of progress. However, at the recent ASH, I was actually pleased to see just one more such trial. The controversy about the role of pentostatin compared with fludarabine in CLL should now be put to rest, with no apparent advantage for the former over fludarabine-based therapy in either efficacy or safety. Now we can move on to address more innovative questions.

Published 7 years ago were the first data showing that rituximab, when added to CHOP (R-CHOP), improved the survival of patients with DLBCL, thus providing the first evidence in decades of an advance in therapy and resulting in a new standard of care. Subsequent randomized trials also showed a prolongation of survival with this and other chemoimmunotherapy regimens in patients with follicular NHL, the first time that one regimen was superior to another in this disease.

The safety and efficacy of rituximab in NHL rapidly led to its use in patients with CLL. Rituximab has become a standard component of the therapy for patients with CLL, based largely on phase II studies and historical comparisons. Yet, until recently, prospective randomized trials were lacking. However, the CLL-8 study in previously untreated patients and the REACH trial in those who were relapsed or refractory convincingly demonstrated the clinical benefit of adding rituximab to the combination of fludarabine and

cyclophosphamide. Hopefully, these data will lead to the approval of rituximab by regulatory agencies for CLL. The widespread clinical use of rituximab stimulated the development of other potentially more effective anti-CD20 monoclonal antibodies. Interesting data were also presented at ASH for ofatumumab, a humanized anti-CD20 which binds to a different epitope on CD20 than rituximab.

Despite recent successes, new strategies are still needed to both increase efficacy in patients with indolent NHL with higher risk disease and reduce toxicity for patients for whom aggressive therapy might be unnecessary or not well tolerated. One promising strategy that was presented at the ASH meetings was of biological doublets. Friedberg and his colleagues presented the long-term follow-up of a phase II combination of galiximab with rituximab in relapsed and refractory follicular NHL, demonstrating 20% long-term progression-free survival with no adverse effects. Czuczman et al from the CALGB provided impressive data with this double antibody combination as initial treatment for follicular NHL—the first of a succession of such doublets that were studied in this patient population. Based on CD80 expression on Reed-Sternberg cells, galiximab is also being studied by the CALGB in Hodgkin lymphoma. Hopefully, such innovative biologic approaches will provide a less toxic way to improve the outcome of lymphoma patients.

Other interesting drugs discussed at ASH included bendamustine, a bifunctional molecule which is either the newest old drug or the oldest new drug for CLL and NHL, depending on your perspective. Although developed almost 40 years ago in the German Democratic Republic, it has only relatively recently emigrated to the United States and is now approved for CLL and rituximab-refractory follicular and low-grade NHL. At ASH, Knauf and coworkers updated their data demonstrating superiority for bendamustine over chlorambucil in previously untreated patients with CLL. Nevertheless, it is clearly time to stop whipping that old dog, chlorambucil, every time a company with a CLL drug wants FDA approval. Until now, there was no other FDA-approved comparator for initial therapy— no, fludarabine has never received that blessing! We now have both alemtuzumab and bendamustine, benchmarks against which newer agents should be compared. Data from the German CLL Study Group also demonstrated interesting results for the combination of bendamustine and rituximab in relapsed/refractory CLL.

Rummel and coworkers updated their important R-CHOP versus R-bendamustine study for previously untreated follicular and mantle cell NHL patients. With additional follow-up, the results with bendamustine continue to compare very favorably with the standard arm. Nevertheless, before this regimen can actually replace R-CHOP, longer follow-up for progression-free and overall survival, as well as the incidence of secondary malignancies and histologic transformation, is warranted.

Lenalidomide, a second generation immunomodulatory drug, has also shown activity in both relapsed/refractory CLL and NHL. The data presented at ASH in relapsed and refractory mantle cell lymphoma (MCL) are particularly encouraging. CALGB is currently conducting a combination of bortezomib with lenalidomide in relapsed and refractory MCL. However, the reported activity in previously untreated patients with CLL presented at ASH was modest with no complete remissions. Nevertheless, the more important role for this drug will likely be in combinations. For example, we are currently evaluating bendamustine plus lenalidomide in patients with CLL and other B-cell malignancies.

These are exciting times, as evidenced by the select abstracts that follow. Clinical research has fortunately moved away from non-specific cytotoxic therapy to more innovative targeted drugs based on lymphoma immunology and biology. Rationale development of combinations of newer agents will hopefully, someday, not only prolong survival, but will also lead to a cure for the heretofore incurable. To reach this goal, however, requires a dedication to enter patients into clinical research studies with correlative science that provides further insights into the biology and genetics of these tumors, leading to newer and more effective treatment strategies. Hopefully, we will see some of these presented at ASH meetings in the not too distant future.

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Recent Advances in the Treatment of Hematologic Malignancies

Myeloma Studies

93 Safety and Efficacy of Novel Combination Therapy with Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide in Newly Diagnosed Multiple Myeloma: Initial Results from the Phase I/II Multi-Center EVOLUTION Study

S Kumar, IW Flinn, SJ Noga, P Hari, RM Rifkin, NS Callander, M Bhandari, JL Wolf, C Gasparetto, A Krishnan, DD Grosman, J Glass, EA Sahovic, H Shi, IJ Webb, P Richardson, SV Rajkumar

Regimens comprised of various combinations of bortezomib (V), dexamethasone (D), cyclophosphamide (C), and/or lenalidomide (R), have previously been shown to be active as front-line therapy for patients with newly diagnosed multiple myeloma (MM).[1,2] Regimens which include all 4 of these drugs in combination (VDCR) may result in more profound responses for these patients, especially as they all belong to different classes of drugs. The EVOLUTION study is an on-going phase I/II trial, of which the phase I dose-escalation phase is reported here. Kumar and colleagues evaluated the safety of the VDCR combination as front-line therapy for MM.[3]

A total of 25 patients with MM were included in this analysis. All patients had previously untreated and measurable disease and a Karnofsky performance score 50% or higher. Patients who exhibited peripheral neuropathy that was grade 2 or higher, renal insufficiency, low absolute neutrophil counts (<1,000 cells/mm^3), low platelet counts (<70,000 cells/mm^3), or elevated liver enzymes were excluded from the study. Patients received up to eight 21-day cycles of treatment, including bortezomib (1.3 mg/m^2 intravenously on days 1, 4, 8, and 11), dexamethasone (40 mg orally on days 1, 8, and 15), lenalidomide (15 mg orally on days 1–14), and cyclophosphamide (100–500 mg/m^2 orally on days 1 and 8). Dose escalation of cyclophosphamide occurred at 100, 200, 300, 400, and 500 mg/m^2, based on the dose-limiting toxicity. The median treatment duration was 6 cycles (range, 3–12 cycles).

The primary study objective was to determine the maximum tolerated dosage of cyclophosphamide in combination with VDR. For this assessment, the maximum tolerated dosage was defined as the highest cyclophosphamide dose in combination treatment, which resulted in 1 or less dose-limiting toxicity in a total of 6 patients. The patients were enrolled in a 3 + 3 dose escalation study design. Dose escalation was based on dose-limiting toxicities, including low platelet counts (<25,000 cells/mm^3 lasting >7 days or any platelet count <10,000 cells/mm^3), neutropenia (grade 4 lasting >7 days), a cyclophosphamide-related nonhematologic toxicity grade 3 or higher, or any adverse event that resulted in a treatment delay of more than 2 weeks. At the 100, 200, 300, 400, and 500 mg/m^2 dose level of cyclophosphamide, the number of patients enrolled was 3, 4, 4, 8, and 7, respectively; the number of patients actually treated was 3, 4, 4, 7, and 7.

The median patient age was 61 years (range, 49–79 years), and approximately half of the population was male (52%). Most patients had immunoglobulin (Ig) G-type myeloma (60%), although some patients had IgA-type myeloma (20%), λ light chain-type myeloma (12%), or κ light chain-type myeloma (8%). Most patients had either ISS stage I (48%) or stage II (48%) disease. Almost half of the patients (44%) had a Karnofsky performance status 80% or lower, and most were eligible for autologous stem cell transplant (ASCT) at baseline (88%).

The study reported that the maximum tolerated dosage for cyclophosphamide was not reached in this study. Two patients experienced a dose-limiting toxicity, 1 of

who was treated with 400 mg/m^2 cyclophosphamide and exhibited grade 4 febrile neutropenia, while the other was treated with 500 mg/m^2 and had grade 3 herpes zoster virus reactivation, despite prophylactic antiviral management. Thus, the investigators concluded that the recommended phase II dose of cyclophosphamide in this combination was 500 mg/m^2.

The most common nonhematologic adverse events of grade 3 or higher that were attributed to treatment included peripheral neuropathy (16%), fatigue (4%), nausea (4%), and diarrhea (4%). A total of 10 patients (40%) experienced a hematologic toxicity of grade 1 or higher. However, the hematologic toxicity was not observed to be cumulative.

The investigators also reported encouraging responses to therapy in their phase I population. At the time of the report, all 25 patients had an unconfirmed OR to therapy (Table 1). Of these, 20% were a stringent complete response (CR), 36% were a CR or better, and 68% were VGPR or better. By treatment cohort, similar rates of CR were observed among all cyclophosphamide treatment groups, but more VGPR were noted at the higher cyclophosphamide dosages.

158 Superior Complete Response Rate and Progression-Free Survival after Autologous Transplantation with Up-Front Velcade-Thalidomide-Dexamethasone Compared with Thalidomide-Dexamethasone in Newly Diagnosed Multiple Myeloma

M Cavo, P Tacchetti, F Patriarca, MT Petrucci, L Pantani, M Ceccolini, M Galli, F Di Raimondo, C Crippa, E Zamagni, P Tosi, F Narni, S Bringhen, V Montefusco, M Offidani, S Buttignol, A Levi, A Gorgone, A Brioli, MC Pallotti, T Spadano, N Pescosta, L Baldini, A Ledda, T Caravita, A Falcone, A Zaccaria, G Perrone, A Petrucci, A Palumbo, M Boccadoro, M Baccarani

For patients with newly diagnosed MM, thalidomide plus dexamethasone is the most frequently used induction treatment prior to ASCT. However, its use is associated with only a very low CR rate (≤10%). Therefore, these patients have a need for additional therapies to improve their induction regimen, in order to increase response rates, allow for adequate collection of patient stem cells, and result in a lower toxicity profile. Here, Cavo and colleagues assessed the safety and efficacy of the addition of bortezomib to thalidomide plus dexamethasone as induction and consolidation therapy in patients with newly diagnosed MM who were undergoing ASCT.[4]

Table 1. EVOLUTION: Best Unconfirmed Response to Treatment

Response*	n (%)
sCR	5 (20)
≥CR	9 (26)
≥VGPR	17 (68)
≥PR	25 (100)

ORR 100%

*Response rates to date (Nov 25, 2008) in 25 evaluable patients. Median treatment duration: 6 cycles (range, 3–12).

CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent CR; VGPR=very good PR.

In this phase III multicenter study, a total of 460 patients with newly diagnosed MM were randomized to receive induction therapy with bortezomib combined with dexamethasone plus thalidomide or dexamethasone plus thalidomide alone. After patients received three 21-day cycles of induction therapy, they underwent stem cell harvest, followed by double ASCT with melphalan. Patients then continued in their randomization arms to receive consolidation therapy with bortezomib combined with dexamethasone plus thalidomide or dexamethasone plus thalidomide alone. After two 35-day consolidation cycles, all patients received maintenance therapy with dexamethasone. The baseline patient characteristics were well balanced between both treatment arms. The majority of patients in each arm were male (60%), and the median patient age was 56 years. Approximately half of the patient population had ISS stage I disease, while the other half had ISS stage II/III disease. This current interim analysis contained data from evaluable patients following the first ASCT.

Patients who had the addition of bortezomib to their induction therapy achieved a significantly superior rate of CR plus near CR, the primary study endpoint, compared with patients who did not receive bortezomib (32% vs 12%, *P*<.001). More patients receiving bortezomib also achieved at least a VGPR or at least a partial response (PR). Of note, although 4.7% of patients in the dexamethasone plus thalidomide arm experienced disease progression, no patient receiving bortezomib had progressive disease (*P*=.001). The bortezomib induction combination remained significantly superior even among poor prognostic patient subgroups including patients with low platelet cell count, an ISS score of 3, and poor cytogenetic abnormalities.
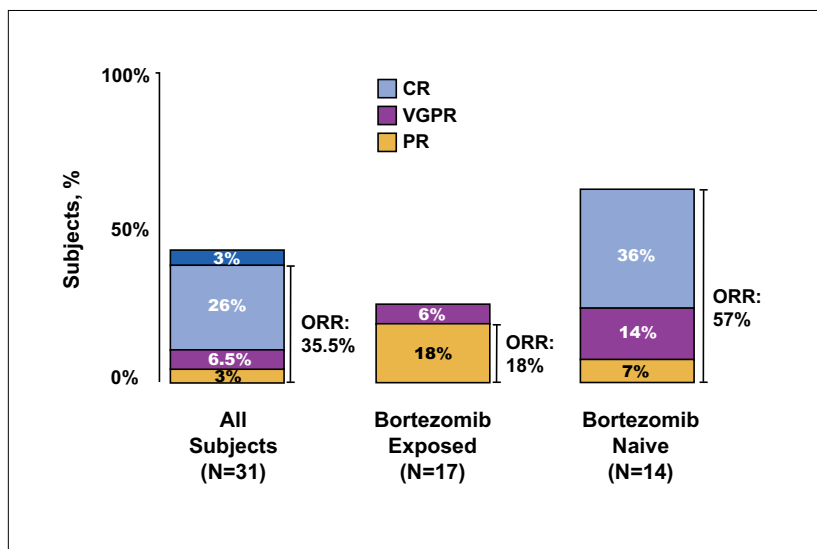
Figure 1. PX-171-004: response summary; 90% of responses occurred by the end of Cycle 2.

CR=complete response; ORR=overall response rate; PR=partial response; VGPR=very good PR.

A higher incidence of adverse events, including grade 3/4 peripheral neuropathy and skin rash, were observed in the bortezomib treatment arm. However, 95% of patients who experienced grade 3/4 peripheral neuropathy continued therapy. Interestingly, there were significantly fewer discontinuations among patients receiving the bortezomib combination compared with patients receiving standard therapy. Cavo and colleagues concluded that the addition of bortezomib to standard dexamethasone plus thalidomide induction therapy was safe, and significantly active in patients with newly diagnosed MM.

865 Initial Results of PX-171-004, an Open-Label, Single-Arm, Phase II Study of Carfilzomib (CFZ) in Patients with Relapsed Myeloma (MM)

R Vij, M Wang, R Orlowski, AK Stewart, S Jagannath, V Kukreti, J Taylor, D Guhrman, S Cruickshank, R Schwartz, L Kunkel, D Siegel, the Multiple Myeloma Research Consortium (MMRC)

Carfilzomib is a novel anticancer agent that selectively inhibits a single subunit of the proteasome. This selective proteasome inhibition allows carfilzomib to have minimal activity against off-target proteases, unlike the more promiscuous proteasome inhibitor bortezomib.[5,6] Also, unlike the reversible activity of bortezomib, when carfilzomib binds to its target proteasome subunit, it forms an irreversible adduct that leads to a more sustained proteasome inhibition. These characteristics allow carfilzomib to display activity in bortezomib-resistant cell lines and animal xenograft models.[5,7] Several phase I trials have been conducted to evaluate single-agent carfilzomib in

relapsed/refractory MM. The PX-171-004 study, reported here by Vij and colleagues, was initiated to evaluate the efficacy of carfilzomib in a less heavily pretreated population, including bortezomib-naïve patients.[8]

This phase II, open-label, single-arm study included 31 patients with relapsed/refractory MM who failed 3 or fewer prior treatments. Carfilzomib (20 mg/m²) was administered on the first 2 days of each of 3 consecutive weeks, for up to twelve 28-day cycles. The median patient age was 60 years, and patients had a median of 3.3 years since time of diagnosis. Over half (55%) of patients had prior bortezomib exposure, of whom most (82%) had received bortezomib as part of combination therapy.

Overall, approximately one-third of patients (35.5%) had an OR to carfilzomib therapy; of these, 3% were a CR, 6.5% were a VGPR, and 26% were a PR. The majority of responses (90%) occurred within the first 2 cycles of carfilzomib therapy. Importantly, the rate of OR was higher in patients who were bortezomib-naïve compared with patients with a prior history of bortezomib (57% versus 18%, respectively; Figure 1). Related to this, bortezomib-naive patients had a longer median duration of carfilzomib therapy compared to those patients with prior bortezomib exposure (271 vs 99 days, respectively). Although the median time to progression (TTP) had not yet been reached, the Kaplan-Meier estimates showed a trend for improved TTP in the bortezomib-naive group compared with patients who had prior bortezomib exposure or the overall treatment population.

Although hematologic adverse events were frequently reported, the majority were mild in severity. Grade 3/4 hematologic adverse events included neutropenia (10%), anemia (6.5%), and thrombocytopenia (6.5%). Similarly,

most nonhematologic adverse events were also mild, and the only grade 3/4 nonhematologic event reported was dyspnea (6.5%). Two cases of tumor lysis syndrome occurred in bortezomib-naive patients. This led to a study protocol amendment to administer prophylactic hydration and allopurinol, after which no new cases were reported.

The investigators concluded that carfilzomib was highly active in the relapsed/refractory MM population, and this efficacy was particularly apparent in patients who had not previously received bortezomib. Carfilzomib was well tolerated, thus allowing a lengthy duration of therapy. The authors reported that this study is ongoing, with planned completion in 2009.

866 Pomalidomide (CC4047) Plus Low-Dose Dexamethasone (Pom/Dex) is Highly Effective Therapy in Relapsed Multiple Myeloma

MQ Lacy, SR Hayman, MA Gertz, JB Allred, SJ Mandrekar, A Dispenzieri, SR Zeldenrust, S Kumar, PR Greipp, JA Lust, SJ Russell, F Buadi, RA Kyle, PL Bergsagel, R Fonseca, V Roy, J Mikhael, AK Stewart, SV Rajkumar

Pomalidomide is a novel immunomodulator with structural similarity to thalidomide and lenalidomide (Figure 2). However, pomalidomide is associated with more potent immunosuppression and fewer adverse events.[9] Two previous phase I studies have shown that single-agent pomalidomide is associated with an OR rate of 50–54% in patients with relapsed/refractory MM.[10,11] Here, Lacy and colleagues evaluated the safety and efficacy of pomalidomide in combination with low-dose dexamethasone for the treatment of relapsed/refractory MM patients.[12]

In this phase II single-arm study, 60 patients with relapsed/refractory MM were included. Most patients (60%) were male, and the average patient age was 65.5 years. A total of 72% of patients had ISS stage II/III disease, and nearly half (45%) had grade 1/2 neuropathy. Patients had relapsed/refractory disease, and the majority of patients (72%) had failed 2 or more prior chemotherapies; 65% had failed a prior stem cell transplant. A total of 60% of patients had previous immunomodulatory drug exposure. Patients received oral pomalidomide (2 mg/day) on days 1–28, and oral dexamethasone (40 mg/day) on days 1, 8, 15, and 22. Aspirin was administered daily to prevent deep vein thrombosis (DVT).

After a median follow-up of 4 months, a 58% rate of OR was observed among the patient population. These included 1 stringent CR (sCR; 2%), 14 VGPRs (23%),
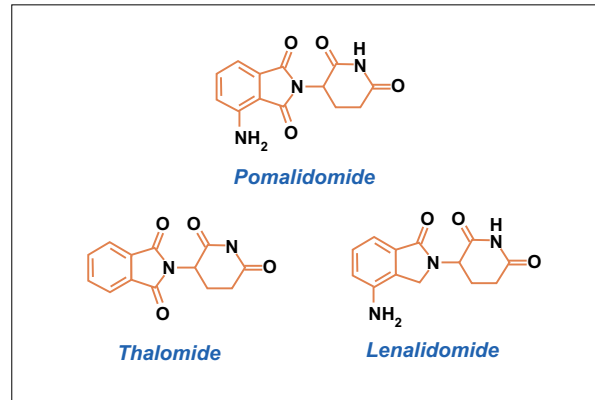
Figure 2. Molecular structure of thalidomide, lenalidomide, and pomalidomide.

and 20 PRs (33%). Importantly, 29% of lenalidomide-refractory patients achieved a response. The majority of patients (66%) exhibited a decrease 25% or greater in monoclonal protein.

The most frequently reported hematologic toxicity was anemia (80%) which was primarily grade 1/2 in severity. Although neutropenia occurred at a lower frequency (52%), 32% of these cases were grade 3/4. Grade 3/4 nonhematologic toxicities occurred in 28% of patients, primarily due to fatigue. One death occurred during the study, due to pneumonia while the patient was neutropenic. No incidences of DVT or pulmonary embolism were reported. Pomalidomide dose reductions occurred in 13% of the patients, mainly due to neutropenia and neuropathy, while dexamethasone dose reductions occurred in 32%.

Lacy and colleagues concluded that pomalidomide, when combined with low-dose dexamethasone, had a relatively good safety profile and was highly active in patients with relapsed/refractory MM. No DVT events occurred during the study, likely due to the use of low-dose dexamethasone, in addition to prophylactic aspirin. Future studies will include a phase II trial of pomalidomide combined with dexamethasone specifically in lenalidomide-refractory and bortezomib-refractory patients.

871 Vorinostat Plus Bortezomib for the Treatment of Relapsed/Refractory Multiple Myeloma: Early Clinical Experience

D Weber, AZ Badros, S Jagannath, D Siegel, V Richon, S Rizvi, J Garcia-Vargas, D Reiser, KC Anderson

Vorinostat is a potent member of the histone deacetylase (HDAC) class of drugs.[13] Like other HDACs, vorino-

stat induces cell growth arrest and cell death, or apoptosis.[14] A previous preclinical study showed that when combined with bortezomib, vorinostat had an additive-to-synergistic effect in a MM cell line.[15] Another preclinical study showed that vorinostat enhanced the sensitivity of MM cells to proteasome inhibition.[16] In this current study, Weber and colleagues analyzed the results of 2 small clinical trials which evaluated vorinostat in combination with bortezomib for the treatment of relapsed/refractory MM.[17]

The 2 studies included were phase I, multi-center, open-label trials. The major inclusion criteria were similar between the 2 studies, and included patients with measurable serum or urine monoclonal protein and an Eastern Cooperative Oncology Group (ECOG) performance status 0–2. Both studies had a dose escalation design. In the first study, patients received vorinostat (200 mg or 400 mg daily on days 1–14) plus bortezomib (0.7–1.3 mg/m² on days 1, 4, 8, and 11, or days 4, 8, 11, and 15). In the second study, patients were administered vorinostat (100/200 mg once daily or 400/500 mg once daily on days 4–11) plus bortezomib (1.0–1.3 mg/m² on days 1, 4, 8, and 11). In both trials, dexamethasone (20 mg/day) was permitted with disease progression. The primary study objectives of both trials were to determine the maximum tolerated dose, as well as to determine any safety or efficacy outcomes. Dose-limiting toxicities were calculated as any nonhematologic toxicity grade 3 or higher (except controllable grade 3 fatigue or gastrointestinal events), or any hematologic toxicity grade 4 or higher.

In the first trial, the maximum tolerated dose was not reached, and therefore the highest dose (400 mg daily vorinostat plus 1.3 mg/m² bortezomib) was selected for future study. In the second trial, the maximum tolerated dose was determined to be 400 mg daily vorinostat plus 1.3 mg/m² bortezomib. The most frequently reported treatment-related adverse events were similar in both trials and included gastrointestinal symptoms, thrombocytopenia, and fatigue. High rates of discontinuations were reported in both trials (72% and 87%).

A similar rate of OR occurred in the 2 trials (38% and 43%). This was only slightly reduced when the subset of patients with prior bortezomib exposure was analyzed; only PRs were achieved in bortezomib-refractory patients. Disease progression was observed in no more than 10% of patients in both trials.

Weber and colleagues concluded that vorinostat combined with bortezomib was safe and active in patients with relapsed/refractory MM. Importantly, this combination was active even in patients with prior bortezomib exposure. Larger studies will be needed to further evaluate the clinical efficacy of this combination.

1740 Effect of Venous Thrombotic Events on Overall Survival in Multiple Myeloma: Analysis of Thrombotic Events Occurring in E4A03 A Randomized Trial of Lenalidomide Plus High-Dose Dexamethasone (RD) Versus Lenalidomide Plus Low-Dose Dexamethasone (Rd) in Newly Diagnosed Multiple Myeloma, a Trial Coordinated by the Eastern Cooperative Oncology Group (ECOG)

S Jacobus, S Kumar, NS Callander, R Abonour, R Fonseca, D Siegel, P Greipp, SV Rajkumar

Lenalidomide plus dexamethasone therapy is frequently associated with venous thrombotic events.[18,19] Although the rate of venous thrombotic events can reach approximately 20%, thromboprophylaxis, erythropoietin avoidance, and use of low-dose dexamethasone can help to reduce these occurrences.[20] Here, Jacobus and colleagues sought to determine the impact of venous thrombotic events on the overall survival (OS) of patients with newly diagnosed MM.[21] The investigators analyzed the incidence of venous thrombotic events which occurred in the ECOG E4A03 trial, a phase III study comparing lenalidomide (25 mg/day) plus standard-dose dexamethasone (40 mg days 1–4, 9–12, and 17–20) versus lenalidomide (25 mg/day) plus low-dose dexamethasone (40 mg days 1, 8, 15, and 22) in newly diagnosed MM patients.

In the ECOG E4A03 study, 445 patients with untreated, symptomatic MM were randomized to either treatment arm. After study initiation, the trial protocol was amended to require mandatory aspirin as prophylactic therapy for thromboembolic events. The amendment further recommended that stronger thromboprophylaxis, including warfarin or low molecular weight heparin, be used in patients randomized to the standard-dose dexamethasone arm. Patients were followed over a median of 30 months.

Overall, venous thrombotic events occurred in 19% of the study participants; more patients in the standard dexamethasone arm experienced an event compared to the low-dose dexamethasone arm (25.6% vs 11.4%). Similarly, a significantly higher rate of venous thrombotic events occurred during the first 4 treatment cycles in the standard dexamethasone arm versus the low-dose dexamethasone arm (20.2% vs 8.6%, $P<.01$). The protocol amendment did not significantly alter the rate of event occurrence. The median time to venous thrombotic event was similar between both the standard-dose and low-dose dexamethasone groups (2.2 vs 2.8 months). Age and albumin status were the only baseline characteristics which significantly differed between patients who did or did not experience a venous thrombotic event.

Table 2. Venous Thrombotic Event as Time Varying Covariate in Cox PH Model

		Hazard Ratio (95% CI)	Wald *P*-value
OS			
Univariate	VTE	1.59 (1.01–2.49)	.045
Adjusted	VTE	1.46 (0.93–2.29)	.100
	SCT	0.40 (0.23–0.70)	.001
PFS			
Univariate	VTE	1.51 (1.10–2.08)	.011
Adjusted	VTE	1.38 (0.99–1.90)	.050
	SCT	0.46 (0.31–0.68)	<.001

CI=confidence interval; OS=overall survival; PFS=progression-free survival; SCT=stem cell transplantation; VTE=venous thrombotic event.

The investigators found that patients who experienced a venous thrombotic event had a significantly higher hazard ratio of death (HR, 1.59; 95% confidence interval [CI], 1.01–2.49; *P*=.045; Table 2). A landmark analysis at 4 months found that the 2-year probability of OS was slightly shorter among patients who had experienced a venous thrombotic event compared with those who had not (80.9% vs 87.2%). Similarly, the 2-year probability of progression-free survival (PFS) was also decreased (46.0% vs 54.9%). A lower proportion of patients who developed a venous thrombotic event received ASCT within 6 months of being off study.

Interestingly, there was a trend for more patients who developed a venous thrombotic event to achieve at least a PR compared with patients who did not experience one (82.3% vs 74.3%), although this difference did not reach statistical significance (*P*=.148). However, patients who experienced a venous thrombotic event did exhibit significantly higher rates of some grade 3–5 toxicities. These toxicities included cardiac ischemia (4.9% vs 0.8%; *P*=.002), non-neuropathic weakness (13.4% vs 6.4%; *P*=.039). Other grade 3–5 toxicities which also occurred more frequently in patients with a venous thrombotic event included hyperglycemia (14.6% vs 7.5%), infection or pneumonia (17.1% vs 11.1%), and fatigue (18.3% vs 10.5%).

Jacobus and colleagues concluded from this data that development of a venous thrombotic event may negatively affect survival of patients with newly diagnosed MM. However, it was clear that venous thrombotic events were associated with a higher rate of grade 3–5 adverse events. Therefore, prophylactic treatment to prevent venous thrombotic events is an important intervention in these patients.

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Commentary on Myeloma Presentations

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The past few years have seen rapid progress in the field of MM with introduction of novel agents contributing to improved outcome for patients with this disease.[1] Use of the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs) have resulted in response and survival rates not seen with the past treatment approaches. Recent clinical trials have focused on developing combination regimens and approaches that can enhance the depth of response while improving on the safety and tolerability of the treatment in the setting of newly diagnosed MM. This effort has been paralleled by early-phase clinical trials exploring other novel drugs in the setting of relapsed MM.

The E4A03 clinical trial comparing 2 different doses of dexamethasone in combination with lenalidomide in newly diagnosed MM is pivotal in that it has changed the field in many ways.[2] This trial clearly demonstrated that using high dose steroids combined with a novel agent can lead to poorer outcomes despite higher response rates, highlighting its deleterious effect on survival. This has led to a practice change, with high-dose steroids being abandoned as part of treatment regimens for untreated MM. The other important focus of this trial is the role of this well-tolerated regimen for management of untreated MM. This regimen, used as an induction therapy prior to ASCT, resulted in an unprecedented 3-year survival of 92%, or when used as primary therapy without ASCT, can lead to a 3-year survival of nearly 80%. These results have led to the widespread adoption of this regimen as the initial therapy choice for MM.

To further improve initial treatment responses, Cavo and colleagues examined the impact of adding bortezomib to a thalidomide and dexamethasone combination as pre-ASCT therapy in patients with newly diagnosed MM.[3] The aim of the study was to examine if the depth of response can be improved prior to ASCT using a well-tolerated regimen that does not interfere with the ability to collect stem cells. The addition of bortezomib clearly led to deeper responses (higher CR and VGPR rates) both

going into ASCT as well as after 1 or 2 ASCTs without significant increase in the toxicities, with the exception of peripheral neuropathy and skin rash. As with other phase III trials in newly diagnosed MM incorporating the novel agents, the reduction in early mortality was remarkable with 2-year survival of 96% in the 3-drug arm.

Clearly, these approaches have improved the depth of response and curbed early mortality among patients with newly diagnosed MM—2 important milestones on the way to a potential cure for this disease. It remains controversial if a cure is a necessary goal for treatment approaches in MM or whether disease control over a long period of time will be sufficient, especially if cure-targeted strategies are associated with considerable toxicity. Recent data suggests that an intensive approach may be warranted, at least in a group of patients with high-risk myeloma, and that development of novel combinations that can lead to deeper treatment responses, defined by more stringent criteria and possibly molecular methods, need to be continued. The results of the EVOLUTION trial presented at the ASH meeting represent such an effort.[4]

Given the encouraging results of the various combinations of novel agents, either among themselves or with conventional drugs such as alkylating agents, this randomized phase II trial is studying two 3-drug regimens (bortezomib + lenalidomide + dexamethasone, or bortezomib + cyclophosphamide + dexamethasone) alongside a regimen incorporating all 4 of these drugs. The results of the phase I portion of this trial that estimated the maximum tolerated dose of cyclophosphamide in combination with bortezomib, lenalidomide, and dexamethasone showed an unprecedented 100% rate of response, which included a highly impressive 36% CR rate. Even more striking was the 20% sCR rate seen among these patients, representing a deeper degree of response. This trial continues to accrue patients to the phase II portion in all the 3 arms, and future results will give a better sense of the durability of these responses and the long-term outcome for these patients. While the success of these trials is evident, the continued relapses that are seen with these highly effective combinations highlight the need for new drug development. The results of phase II trials examining new agents in the setting of relapsed MM offer a glimpse of the future for this field and included pomalidomide, a new generation IMiD, as well as carfilzomib, a proteasome inhibitor. The phase II trial of pomalidomide enrolled 60 patients with relapsed MM who had 1–3 prior regimens.[5] The overall response rate (ORR) to the combination of pomalidomide and dexamethasone was 58%, including a 25% VGPR, and the regimen was very well tolerated with a manageable toxicity profile. Moreover, the response rate among patients who were previously refractory to lenalid-

omide was 29%, opening up a possible future choice for this group of patients.

The phase II trial of carfilzomib, an irreversible inhibitor of cellular proteasome, enrolled 31 patients with relapsed myeloma who have had 3 or less prior therapies, stratifying them based on prior bortezomib exposure.[6] The responses were relatively rapid, occurred within 2 cycles with an ORR of 36%, and were higher among those previously not exposed to bortezomib. Results from another study incorporating a novel class of drugs—HDAC inhibitors—were very encouraging.[7] The addition of vorinostat, an HDAC inhibitor, to bortezomib, resulted in disease responses with acceptable tolerability in patients who had relapsed while on or were refractory to previous bortezomib therapy.

Clearly, these drugs open up new avenues for patients whose myeloma has become nonresponsive to the drugs currently in the armamentarium. So, where do we go from here? Future trials, currently ongoing and those being designed are asking several important questions. Can we improve upon the initial treatment of myeloma and potentially get to minimal residual tumor state or even complete elimination of the malignant clone, either by developing novel combinations of available drugs or by continuous application of 1 or more drugs? How do we manage patients whose disease has grown refractory to current drugs: new potent drugs, agents that can reverse the resistance to current drugs, or combinations of new and old drugs? What is the role of ASCT in the current day and age? These are all questions of which the answers will move us ahead in the field and eventually allow patients with myeloma to live a normal life.

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Lymphoma Studies

3 Fostamatinib Disodium (FosD), an Oral Inhibitor of Syk, is Well-Tolerated and Has Significant Clinical Activity in Diffuse Large B Cell Lymphoma (DLBCL) and Chronic Lymphocytic Leukemia (SLL/CLL)

JW Friedberg, J Sharman, J Schaefer-Cutillo, PB Johnston, S De Vos, A LaCasce, JP Leonard, LD Cripe, R Sinha, SA Gregory, J Sweetenham, JM Vose, AM Lowe, R Levy, MA Shipp

DLBCL and follicular lymphoma (FL) cells exhibit overactivated B-cell receptor (BCR) signaling.[22] The increased activity of these signaling pathways culminates in enhanced cellular survival, as well as upregulated activity of downstream BCR targets. One such target is Syk, a downstream kinase that is triggered by BCR activation.[23] Syk is an attractive target in non-Hodgkin lymphoma (NHL), as these cells exhibit enhanced Syk activation and expression.[24,25] Fostamatinib is an investigational oral ATP competitor agent that acts as a Syk inhibitor. To date, the safety of fostamatinib has been demonstrated in humans. Here, Friedberg and colleagues further evaluated the safety and efficacy of fostamatinib in the setting of relapsed/refractory NHL.[26]

This was a phase I/II trial. The phase I portion enrolled 13 patients to receive 1 of 2 fostamatinib doses, either 200 mg or 250 mg, both administered twice daily. All patients had relapsed/refractory NHL, and several histologies were included in the study, including DLBCL (n=3), FL (n=5), mantle cell lymphoma (MCL; n=3), and CLL/SLL (n=2). Patients were eligible for the study regardless of prior therapy (2 patients had ASCT, 4 patients had radioimmunotherapy). The median patient age was 74 years.

During this phase I portion, dose-limiting toxicities were evident in patients receiving 250 mg twice daily. These toxicities included neutropenia, thrombocytopenia, and diarrhea. Therefore, the investigators chose the 200 mg twice daily dose as the dosage to use for the phase II portion of the trial.

During the phase II phase, 68 patients with relapsed/refractory NHL received fostamatinib as determined during the phase I phase. Patients had undergone a median number of 5 prior therapies. DLBCL and CLL/SLL patients achieved a greater number of responses to treatment compared to other histologies (FL and MCL). This included 1 CR experienced by a DLBCL patient. In the entire 68 patient cohort, the most frequently reported serious adverse event was febrile neutropenia (n=5). Overall,

the commonly occurring treatment-related adverse events included diarrhea (41%), fatigue (41%), neutropenia (31%), anemia (27%), thrombocytopenia (24%), hypertension (22%), and nausea (21%). The authors noted a transient increase in circulating white blood cells in CLL patients following fostamatinib therapy, but found this spike returned to normal levels after the first month of therapy.

The investigators concluded that the novel Syk inhibitor fostamatinib was safe and active in the setting of heavily pretreated relapsed/refractory NHL. Notably, patients with either DLBCL or CLL/SLL histologies seemed to benefit more from this therapy. Together, these data add to the rationale for targeting this pathway in NHL.

262 Confirmation of the Efficacy and Safety of Lenalidomide Oral Monotherapy in Patients with Relapsed or Refractory Mantle-Cell Lymphoma: Results of an International Study (NHL-003)

PL Zinzani, TE Witzig, JM Vose, CB Reeder, R Buckstein, C Haioun, R Bouabdallah, J Polikoff, P Guo, A Ervin-Hayes, D Pietronigro, JB Zeldis, MS Czuczman

268 Confirmation of the Efficacy and Safety of Lenalidomide Oral Monotherapy in Patients with Relapsed or Refractory Diffuse Large-B-Cell Lymphoma: Results of an International Study (NHL-003)

MS Czuczman, JM Vose, PL Zinzani, CB Reeder, R Buckstein, C Haioun, R Bouabdallah, J Polikoff, P Guo, A Ervin-Haynes, D Pietronigro, JB Zeldis, TE Witzig

Aggressive lymphoma is associated with poor survival, mainly due to relapse or no response-to-initial therapy. Lenalidomide, a derivative of thalidomide, is an immunomodulatory drug that has been investigated for its activity in various forms of hematologic malignancies, including NHL.[27] In a phase II, single-arm, multi-center trial, lenalidomide monotherapy was found to be active in relapsed/refractory patients with aggressive NHL.[28] These 2 presentations reported the results of an international trial (NHL-003) evaluating single-agent lenalidomide in various NHL subtypes.

In the first study, Zinzani and colleagues reported on the activity of lenalidomide monotherapy in patients with MCL.[29] All 39 patients included in this analysis had measurable MCL disease, with an ECOG performance score of 2 or higher. Lenalidomide (25 mg daily) was administered on days 1–21 of a 28-day cycle, and the
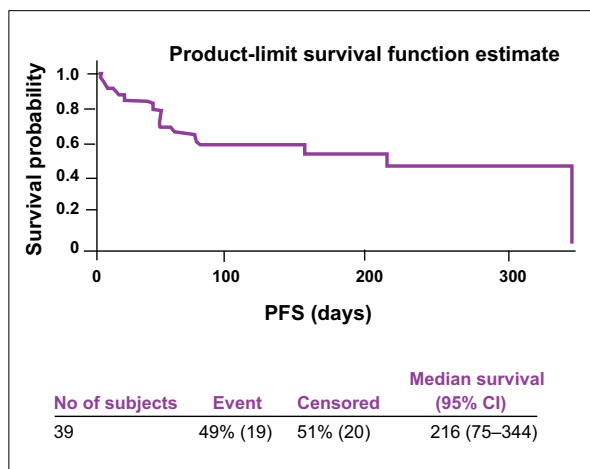
Figure 3. Kaplan-Meier estimate for PFS for lenalidomide in mantle cell lymphoma (n=39).

CI=confidence interval; PFS=progression-free survival.

treatment cycles were continued until intolerable toxicity or disease progression occurred. Nearly three-quarters of this MCL population were male (74%), and the median patient age was 66 years. Extranodal sites were apparent in 28% of patients, and patients had an IPI score of 1 (15%), 2 (39%), 3 (36%), or 4 (10%). Patients had a median number of 3 prior therapies, although this ranged up to 8 previous treatments. The majority of these were standard therapy (77%), although they also included ASCT (33%) and bortezomib-based therapy (23%).

An OR rate of 41% was observed in the MCL patient population, of which 13% was a CR/unconfirmed CR (CRu) and 28% was a PR. While the median duration of response was not reached, the median PFS was 216 days (95% CI, 75–344 days; Figure 3). Hematologic toxicities were the most frequently reported grade 3/4 adverse events, including neutropenia (52%), thrombocytopenia (26%), anemia (13%), febrile neutropenia (11%), and leukopenia (8%). Grade 3 fatigue was also experienced in 10% of patients. Over one-third of patients (38%) required a dose reduction, most frequently due to neutropenia or thrombocytopenia.

In the second study, Czuczman and colleagues evaluated the activity of lenalidomide monotherapy in patients with DLBCL.[30] As in the previous report, patients received lenalidomide monotherapy (25 mg daily) on days 1–21 of a 28-day cycle; treatment cycles were only interrupted due to intolerable toxicity or disease progression. A total of 73 DLBCL patients were evaluable in this analysis. Most patients were male (67%), and the median patient age was 67 years. Patients had received a median of 3 (but up to 6) prior therapies, and had gone a median of 2 years from diagnosis to lenalidomide treatment.

A 29% rate of OR was observed in DLBCL patients. Of these, 4% were CRs and 25% were PRs. Disease stabilization occurred in 15% of patients. Similar with the study in MCL patients, hematologic toxicities were the most frequent grade 3/4 adverse events. These included neutropenia (32%), thrombocytopenia (15%), and anemia (7%).

Together, the results of the NHL-003 study show that lenalidomide is active in both MCL and DLBCL patient populations. Importantly, this study included heavily pretreated patients who typically have a poor prognosis. Therefore, lenalidomide may represent an effective treatment alternative for patients with relapsed/refractory MCL or DLBCL.

1003 FLIPI Score is Applicable and Predictive of Response to Upfront Immunotherapy in CALGB 50402: Phase II Trial of Extended Induction Galiximab ([G] Anti-CD80 Monoclonal Antibody) Plus Rituximab

MS Czuczman, JP Leonard, JL Johnson, S-H Jung, E His, JC Byrd, BD Cheson

1004 Durable Responses in Patients Treated with Galiximab (Anti-CD80) in Combination with Rituximab for Relapsed or Refractory Follicular Lymphoma: Long-Term Follow-Up of a Phase II Clinical Trial

JW Friedberg, A Younes, DC Fisher, LI Gordon, JO Moore, MS Czuczman, TP Miller, PJ Stiff, BD Cheson, A Forero-Torres, B McKinney, JP Leonard

The majority of patients with indolent B-cell lymphomas are treated with rituximab, either as single-agent therapy or in combination with chemotherapy. Recent effort has focused on the use of biologic therapies in combination with rituximab to enhance the antitumor effect of the drug.[31] The benefit of this combination is that patients have a reduced risk of experiencing the broad-ranging adverse events associated with systemic chemotherapy administration. Additionally, the introduction of biologic agents adds other targets into the arsenal against these lymphomas. The monoclonal antibody galiximab is one such possible biologic agent. Galiximab is directed against CD80, a molecule expressed on activated B cells.[32] Previously, in a phase I/II study, galiximab in combination with rituximab was found to be safe and active in relapsed/refractory FL.[33] Here, 2 studies which further

Table 3. CALGB 50402: Association Between FLIPI Score and PFS

FLIPI Score	% Progressed	Median PFS
0–1	0	Not reached
2	24	Not reached
3–5	59	1.62 years

FLIPI=follicular lymphoma international prognostic index;
PFS=progression-free survival.

evaluate galiximab in the setting of indolent B-cell lymphoma are discussed.

In the first presentation, Czuczman and colleagues reported the results of the CALGB 50402 study, a phase II trial which aimed to evaluate the activity of the combination of galiximab plus rituximab in an extended induction schedule (weekly 34, then every 2 months 34).[34] Patients included had previously untreated FL. Of the 61 evaluable patients, 61% were male and the median patient age was 57 years. Patients had a baseline Follicular Lymphoma International Prognostic Index (FLIPI) score of low risk (20.3%), intermediate risk (42%), or high risk (37%). The majority of patients (93%) had stage III/IV disease. Only 13% of patients experienced an adverse event following therapy. The CALGB 50402 study reported an OR rate of 70%, which included a 44% rate of CR/CRu and a 26% rate of PR. Interestingly, more than 10% of patients experienced a delayed initial response of 8–14 months following initiation of therapy, and more than 15% of patients converted from a PR to a CR after 9 months or more of treatment.

Czuczman and colleagues further noted an apparent association between FLIPI score and the response rate. Patients with a low risk FLIPI score had a higher rate of OR compared to intermediate risk or high risk (92%, 80%, and 55%, respectively). A similar trend was noted in the rate of CR as well (75%, 48%, and 27%, respectively). OR was not found to be associated with other baseline characteristics, including age, gender, disease stage, bulky disease, or marrow involvement. Importantly, PFS also seemed to be associated with FLIPI score (Table 3). At a median follow-up of 2.17 years, 67% of patients were progression-free. The proportion of patients who had progressed on therapy increased with worsening FLIPI score (0%, 24%, and 59% for low risk, intermediate risk, and high risk, respectively.

In the second presentation, Friedberg and colleagues reported a long-term follow-up of the previously published phase II study which evaluated the combination of galiximab plus rituximab in patients with relapsed/refractory FL.[33,35] In this study, patients had received galiximab (500 mg/m² weekly for 4 weeks)

concurrently with a standard dose of rituximab (375 mg/m² every week for 4 weeks). Patients were not permitted to receive maintenance therapy. A total of 64 patients were included (mean age 59 years). The majority of patients had stage III/IV disease (88%), and a FLIPI score of low risk (27%), intermediate risk (39%), or high risk (34%). Just over half of patients had received prior rituximab (58%), although no rituximab-refractory patients were included. Here, Friedberg and colleagues reported results after a median follow-up of 45 months (range, 9–59 months).

The median PFS was 12.2 months; 20% of patients remained progression-free after 2 years. Approximately one-third of patients (37%) did not require any additional lymphoma treatment for at least 2 years following therapy with galiximab plus rituximab. Patients who achieved a CR were more likely to remain progression-free after 2 years. The duration of response patients had experienced in prior therapy was not associated with their response to galiximab plus rituximab. Pharmacokinetics did not differ significantly between patients who were long-term responders and those who were not. Over the long-term follow-up, no late opportunistic infections, secondary malignancies, or infusion-associated deaths were reported.

Together, these 2 studies indicate that galiximab is an effective biologic agent in combination with rituximab for the treatment of both untreated and relapsed/refractory FL. Importantly, this combination is associated with long-term efficacy and safety, and it seems patients with a better FLIPI score may benefit more from treatment.

2596 Bendamustine Plus Rituximab Versus CHOP Plus Rituximab in the First-Line Treatment of Patients with Follicular, Indolent and Mantle Cell Lymphomas: Results of a Randomized Phase III Study of the Study Group Indolent Lymphomas (StiL)

MJ Rummel, U von Gruenhagen, N Niederle, H Ballo, E Weidmann, M Welslau, G Heil, C Balser, HA Duerk, M Stauch, D Koofahl-Krause, U Kaiser, W Knauf, W Brugger

A previous phase II study which evaluated the combination of bendamustine plus rituximab in patients with relapsed/refractory indolent or MCL has shown promising activity, including an OR rate of 90%.[36] Of these responses, 60% were a CR. Therefore, Rummel and colleagues conducted a follow-up phase III study to compare the efficacy of bendamustine plus rituximab compared with CHOP plus rituximab as front-line therapy for patients with FL, MCL, or indolent lymphoma.[37]

A total of 546 patients were randomized to receive rituximab (375 mg/qm on day 1) plus either bendamustine (90 mg/qm on days 1 and 2, every 28 days) or standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) every 21 days. Treatment was continued for a maximum of 6 cycles. The second interim analysis of this phase III multicenter study is reported here, for which 437 patients are evaluable for response. The median patient age was 64 years. Lymphoma histologies were equally distributed between treatment groups, including FL (52%), MCL (20%), and other indolent subtypes (28%). The median follow-up was 28 months for both treatment groups.

The primary study endpoint, median even-free survival (EFS), had not yet been reached in the bendamustine arm, and was 39 months in the CHOP arm; this difference was not statistically significant. The OR rate was similar between both treatment groups (94% vs 93% for patients receiving bendamustine vs CHOP). Similarly, the rate of CR was also similar among treatment arms (41% vs 33%). Fewer adverse events were reported in the bendamustine arm.

The authors concluded that the second analysis of this study demonstrated that bendamustine plus rituximab is noninferior to CHOP plus rituximab. However, the improved safety profile associated with bendamustine may point toward bendamustine plus rituximab being a preferable regimen.

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Commentary on Lymphoma Presentations

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Therapy for NHL remains challenging. The heterogeneity of the disease results in a variety of treatment approaches depending on the clinical setting. With aggressive lymphomas, many patients can be cured, but new approaches are needed to overcome resistant disease and to reduce toxicity. For indolent lymphoma types, most individuals can live an extended time with disease, but are generally not cured. Development of more effective and better-tolerated treatments would be of significant value with respect to improving survival and quality of life. Several presentations at ASH 2008 provided new information on novel treatment approaches which offer the promise of potentially helping to address current unmet needs in lymphoma management.

Rituximab, the chimeric anti-CD20, has demonstrated the utility of monoclonal antibody therapy for B-cell lymphomas. As a single agent, rituximab is an effective treatment for indolent lymphoma and is active in most other B-cell malignancies. The precise role of rituximab in various treatment settings continues to be explored. Subsequently, various groups have explored the potential utility of other monoclonals, including human and humanized anti-CD20s, as well as antibodies directed against other tumor targets.

One such agent, galiximab, is directed toward the CD80 antigen which is widely expressed on B-cell and other malignancies. After an initial phase I/II study of this agent in FL,[1] a subsequent multicenter study was conducted in combination with rituximab[2] and long-term follow-up from this trial was recently presented.[3] These data confirmed an ORR of this regimen of 64% in recurrent FL, with 20% of patients demonstrating PFS of greater than 2 years and no late toxicities.

Based on these promising results, the Cancer and Leukemia Group B conducted CALGB 50402, which explored the use of an extended induction regimen of galiximab plus rituximab as initial treatment for FL.[4] An ORR of 70% was reported, including CR/CRu rates of 44%. Importantly, in low risk patients as defined by FLIPI, ORR was 92% with 75% CR. These data suggest that combination biologic therapy (without chemotherapy) may be an effective and well-tolerated approach as initial and subsequent management for selected indolent lymphoma patients. Further studies of this combination, specifically to assess the contribution of galiximab to the activity of the regimen, are ongoing.

Another important emerging agent in the treatment of various hematologic malignancies is lenalidomide, an immunomodulatory agent with a wide range of potential antitumor activities, possibly including anti-angiogenic effects. Zinzani and colleagues reported on a confirmatory study employing single-agent lenalidomide in patients with relapsed MCL and a median of 3 prior therapies. The ORR was 41%, including 13% CR/CRu.[5] Principal toxicities were cytopenias that were managed with dose reductions. In a similar study in other aggressive lymphoma subtypes, an ORR of 29% was described by Czuczman and coworkers.[6]

These data, combined with those in indolent lymphoma and CLL, suggest that lenalidomide may play a valuable role in a variety of lymphoid tumors. Ongoing studies are exploring combinations with rituximab and chemotherapy. This oral agent may also potentially be useful in "maintenance" treatment approaches following chemoimmunotherapy.

At the plenary session of ASH 2008, Friedberg and colleagues presented data from a recent study of fostamatinib disodium, an oral small molecule inhibitor of Syk that has been previously explored in autoimmune disease. Activity of Syk is involved in signaling of the BCR, important in the biology of normal and malignant B cells. While this pathway has been specifically implicated in the pathogenesis of a subset of DLBCLs, it is potentially relevant to other lymphoma subtypes as well. In a phase I/II study, toxicity, principally neutropenia, was manageable. While numbers of patients in each subset were small, activity was noted in several lymphoma groups including DLBCL (ORR, 21%), SLL/CLL (ORR, 54%) and objective responses were also noted in some patients with MCL and FL. These data suggest that this compound warrants further development in lymphoma both as a single agent and in rational combinations.

Finally, a recent addition to the armamentarium of approved agents in lymphoid malignancies is the chemotherapeutic compound bendamustine, which is effective in CLL, refractory FL and other settings.[8]

Rummel and colleagues have presented additional data from their ongoing randomized study of bendamustine and rituximab versus CHOP plus rituximab (CHOP-R) as initial treatment for a variety of indolent lymphomas (predominantly follicular).[9] With median follow-up of 28 months, efficacy appears comparable with bendamustine and rituximab (B-R) and CHOP-R including ORR (94% and 93%), CR (41% and 33%) and similar EFS. Less hematologic toxicity and no total alopecia was observed in the B-R group. While further follow-up is needed and ongoing, these data suggest that the bendamustine-rituximab combination may prove to be a useful upfront regimen with comparable efficacy and better tolerability than standard approaches.

Results from ASH 2008 highlighted the array of novel therapeutics and promising new strategies that are in development for the treatment of lymphoid malignancies. Ongoing efforts with these approaches are focused on determining the optimal setting for the use of new drugs, including combination with standard approaches. Given their potential to improve efficacy and tolerability of treatment, participation in clinical trials of these and other regimens should be encouraged with the aim of improving outcomes for all patients with lymphoma and related diseases.

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Leukemia Studies

44 A Phase II Study of Lenalidomide in Previously Untreated, Symptomatic Chronic Lymphocytic Leukemia (CLL)

C Chen, H Paul, W Xu, V Kukreti, S Trudel, E Wei, ZH Li, J Brandwein, M Pantoja, C Leung-Hagensteijn

The immunomodulatory agent lenalidomide has displayed promising efficacy in relapsed/refractory CLL.[38,39] However, there are few data available on lenalidomide in the setting of newly diagnosed CLL. Here, Chen and colleagues report a preliminary analysis of the safety and efficacy of single-agent lenalidomide in patients with previously untreated, symptomatic CLL.[40] Symptomatic CLL was defined as having at least 1 of the following: low hemoglobin or platelet counts, symptomatic lymphadenopathy, hepatomegaly

or splenomegaly, fatigue/weight loss/sweats/fever, or a lymphocyte doubling time of less than 12 months.

A total of 25 patients were enrolled in this phase II study. The initial starting dose of lenalidomide was 10 mg/day, with weekly 5 mg dose escalations to a final target dose of 25 mg/day. Treatment was administered on days 1–21 of a 28-day cycle. However, toxicity in the first 2 patients required a study protocol amendment in which the starting dose was lowered to 2.5 mg/day, and the target dose was lowered to 10 mg/day; the dose escalation was slowed to once monthly. Nonresponding patients were allowed to continue escalation up to 25 mg/day. The median patient age was 60 years, and most patients (64%) were male. A total of 40% of patients had stage III/IV disease.

Over half of patients (56%) had a PR, and 40% of patients exhibited stable disease. No CRs were reported. The median patient follow-up was 10.1 months (range, 2.9–20.6 months), over which the median number of cycles was 7 (range, 3–21) and the median tolerated dose was 10 mg/day.

Nearly one-third of patients required a dose reduction, and 5 patients discontinued study treatment. Grade 3/4 neutropenia was the most frequently occurring hematologic event (64%). The only grade 3/4 nonhematologic toxicity reported was infection, which occurred in 3 patients. The most common adverse events overall were fatigue and tumor flare. Tumor flare occurred most commonly during the first week of the study, and steroids were required in 40% of patients to control the symptoms.

These preliminary results suggest that lenalidomide is safe and active in previously untreated CLL.

181 High and Early Rates of Cytogenetic and Molecular Response with Nilotinib 800 mg Daily as First Line Treatment of Ph-Positive Chronic Myeloid Leukemia in Chronic Phase: Results of a Phase 2 Trial of the GIMEMA CML Working Party

G Rosti, F Castagnetti, A Poerio, M Breccia, L Levato, A Capucci, M Tiribelli, F Stagno, A Zaccaria, T Intermesoli, B Martino, M Bocchia, M Cedrone, F Bartucci, F Palandri, G Gugliotta, N Testoni, G Alimena, G Martinelli, F Pane, G Saglio, M Baccarani

Nilotinib is a tyrosine kinase inhibitor with activity against the Bcr-Abl, Kit, and PDGFR kinases.[41] To date, its investigation has been limited to drug-resistant CML, for which it shows high potency.[42] Here, Rosti and colleagues evaluated the efficacy of nilotinib in the treatment of previously untreated CML on behalf of the Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) CML Working Party.[43]

In this phase II, open-label, multicenter study, nilotinib (400 mg twice daily) was administered to 73 patients. All patients had previously untreated, Philadelphia chromosome (Ph)-positive CML in chronic phase. No dose escalation was allowed in this current study. Nilotinib was administered for a median of 337 days (range, 185–467 days). The median patient age was 51 years and nearly half of all patients (51%) were male. Using the Sokal scale, patients either had low risk (45%), intermediate risk (41%) or high risk (14%) disease. Variant translocations were further identified in 14% of the study population. All patients had a minimum follow-up of no more than 6 months, and 44% of patients had a minimum follow-up of no more than 1 year.

During the first 3 months of treatment, 78% of patients exhibited a complete cytogenetic response. This increased to 96% of patients between 4–6 months of therapy. Accordingly, the rate of major molecular response also increased over the study period, from 3% during month 1 to 66% during month 6. Over this time period, the majority of patients were receiving either the full dose of drug (800 mg daily), or just under the full drug dose (600–799 mg daily). At 6 months, 75% of patients were receiving 800 mg of nilotinib. Age did not significantly impact the rate of complete cytogenetic response, although more patients 65 years of age or older required a dose reduction during the first 6 months of treatment.

The only grade 3 nonhematologic adverse events reported were skin rash (5%), bone or muscle pain (4%), and pruritus (4%). Several grade 3/4 biochemical abnormalities were noted, including bilirubin (16%), alanine aminotransferase (ALT; 8%), aspartate aminotransferase (AST; 3%), lipase (8%), and amylase levels (4%). Grade 3/4 neutropenia and thrombocytopenia occurred in 4% and 3% of patients, respectively.

Rosti and colleagues concluded that nilotinib results in high rates of response as front-line therapy in CML. The majority of adverse events were grade 1/2 in severity, suggesting this high dose intensity is safe in this patient population.

182 Efficacy of Dasatinib in Patients (Pts) with Previously Untreated Chronic Myelogenous Leukemia (CML) in Early Chronic Phase (CML-CP)

J Cortes, S O'Brien, G Borthakur, D Jones, F Ravandi, C Koller, O Mesina, A Ferrajoli, J Shan, H Kantarjian

Like nilotinib, dasatinib is a multi-targeted kinase inhibitor with activity against Bcr-Abl and Src.[44] Also similar to nilotinib, dasatinib has mainly been investigated for its activity in relapsed/refractory CML, for which it shows a

high rate of benefit.[45] Here, Cortes and colleagues report the results of a study evaluating dasatinib in the front-line treatment of CML.[46]

A total of 50 patients with previously untreated CML in chronic phase were enrolled in this study. Patients were randomized to receive dasatinib at either 50 mg twice daily or 100 mg once daily. The median patient age was 45 years, and three-quarters of patients were Sokal low risk. The median study follow-up reported here was 2 years. During that time, all but 1 patient (98%) achieved a complete cytogenetic response. A major molecular response was observed in 34% and 48% of patients at 12 and 18 months, respectively. Two patients achieved a complete molecular response; one of these was confirmed. The 2-year EFS was 81%.

Grade 3/4 neutropenia (21%), thrombocytopenia (11%), and anemia (9%) occurred only transiently. The most frequently reported grade 3/4 nonhematologic adverse events included pruritus (13%), fatigue (6%), neuropathy (4%), and memory impairment (4%). A total of 4 patients stopped therapy, 1 due to toxicity, 1 due to patient choice, and 2 due to loss of response. Importantly, 2 other patients lost response due to noncompliance.

The investigators concluded that dasatinib was a safe and highly effective therapy in the front-line treatment of CML. The authors reported continued accrual to this trial.

330 Bendamustine in Combination with Rituximab (BR) for Patients with Relapsed Chronic Lymphocytic Leukemia (CLL): A Multicenter Phase II Trial of the German CLL Study Group (GCLLSG)

K Fischer, S Stilgenbauer, CD Schweighofer, R Busch, J Renschler, M Kiehl, L Balleisen, MJ Eckart, AM Fink, J Kilp, M Ritgen, S Böttcher, M Kneba, H Döhner, BF Eichhorst, M Hallek, CM Wendtner, the German CLL Study Group

The alkylating agent bendamustine, which also has properties of a purine analog, is highly active as a single-agent in multiple malignancies, including CLL. Several clinical trials of bendamustine monotherapy in relapsed/refractory CLL have shown OR rates of 56% to 78%, with accompanying rates of CR as high as 30%.[47-51] A preclinical study showed that combination of rituximab with bendamustine sensitized CLL cell lines to the cytotoxic effects of bendamustine, suggesting this may be an important potential treatment strategy.[52] In fact,

this combination was shown to be safe and promising in a clinical study of MCL and low-grade NHL, including FL, marginal zone lymphoma (MZL), and SLL.[36] Therefore, Fischer and colleagues initiated a study which was the first to investigate the efficacy and safety of the bendamustine plus rituximab combination in patients with relapsed/refractory CLL.[53]

This phase II, prospective, multicenter, open-label single-arm study included 81 patients. Patients received bendamustine (70 mg/m² on days 1 and 2 every 4 weeks for 6 cycles) and rituximab (375 mg/m² on day 0 of cycle 1, followed by 500 mg/m² on day 0 of cycles 2–6). Most patients (66.7%) were male, and the mean patient age was 66.7 years. Patients had Binet stage A (12.7%), stage B (34.2%), or stage C (53.1%) disease. All patients had relapsed/refractory CLL, and had a median of 2 prior therapies. A majority of patients (63.3%) had immuno-globulin heavy chain (IgV_H) unmutated disease.

Hematologic toxicities were among the most frequently reported adverse events grade 3 or higher, and included neutropenia (12.2%), thrombocytopenia (9.1%), and anemia (6.1%). A total of 17 infections grade 3 or higher also occurred, 3 of which were fatal. Other nonhematologic adverse events grade 3 or higher included fatigue (0.6%), cytokine release syndrome (0.6%), bed-sores (0.3%), acute myocardial infarction (0.3%), dehy-dration (0.3%), and thrombophlebitis (0.3%).

A total of 62 patients were evaluable for response. Over three-quarters of patients (77.4%) had a response to therapy; of these 14.5% had CR/CRu, 1.6% a nPR, and 61.4% a PR (Table 4). A minimal residual disease (MRD) level of less than $10E^{-4}$ was measured in 2 of 30 evaluable patient blood samples, and 0 of 12 evaluable patient bone marrow samples.

Interestingly, a high proportion of fludarabine refractory patients had an OR (7 of 9 patients), although none of these was a CR. Conversely, 29 of 41 fludarabine sensitive patients achieved an OR, 4 of which were CRs. Genetic CLL subtype also seemed to affect response. Of 13 patients with the 11q- alteration, 12 had an OR, 1 of which was a CR. All 8 patients with +12 achieved an OR, 1 of which was a CR. Three-quarters of IgV_H unmutated patients had an OR (74.4%), but less than half of patients with 17p- disease had an OR (44.4%).

From these results, Fischer and colleagues concluded that the combination of bendamustine plus rituximab was active in relapsed/refractory CLL. This combination was relatively safe, with manageable toxicities. The authors reported that a follow-up analysis will be performed to evaluate the duration of response as well as the long-term safety of the combination. Although this and other studies have restricted the investigation of bendamustine plus rituximab in relapsed/refractory CLL, future trials will

Table 4. Bendamustine and Rituximab for CLL: Response Rates

Response	N	%
ORR	48	77.4
CR (CRu)	9 (4)	14.5
nPR	1	1.6
PR	38	61.4
SD	11	17.7
PD	3	4.8

Best Response (N=62 *).

*4 patients excluded due to violation of enrollment criteria, 13 patients not yet evaluable.

CR=complete response; CRu=CR unconfirmed; nPR=nodal PR; ORR=overall response; PD=progressive disease; PR=partial response; SD=stable disease.

also be conducted to test this combination as front-line CLL therapy.

557 Impact of Post-Remission Treatments in Patients Aged 65–70 Years with De Novo AML: A Comparison of Two Concomitant Randomized ALFA Trials with Overlapping Age Inclusion Criteria

R Itzykson, C Gardin, C Pautas, X Thomas, P Turlure, E Raffoux, C Terré, S Castaigne, H Dombret, N Boissel

Older AML patients treated with intensive chemotherapy have a poor prognosis. Currently, there is no standard post-remission therapy for this patient population. Two similar ALFA trials were conducted to evaluate post-remission treatment strategies in acute myelogenous leukemia (AML) patients. ALFA 9801 focused on patients between 50–70 years of age with de novo AML, while ALFA 9803 included patients 65 years of age or older with either de novo or secondary AML.[54,55] Here, Itzykson and colleagues compared the overall outcome and impact of these treatment strategies on patients aged 65–70 years from both trials.[56]

Both ALFA trials included a frontline randomization between the anthracyclines idarubicin or daunorubicin, each in combination with the antimetabolic agent cytarabine (AraC), as induction therapy. Following this, the trials differed in their post-remission chemotherapy

strategies. The post-remission strategy of ALFA 9801 consisted of 2 cycles of idarubicin or daunorubicin in combination with AraC. In ALFA 9803, the post-remission strategy contained a second randomization between a standard AraC cycle and 6 anthracycline-based ambulatory consolidation cycles, each in combination with idarubicin or daunorubicin.

This study only analyzed the 211 patients from both trials (76 from ALFA 9801 and 135 from ALFA 9803) who were between 65 and 70 years of age. The baseline characteristics were similar between the patients from each study, including performance status (PS), white blood cell count, French-American-British (FAB), and the prognosis of the karyotype of their disease.

Among the total 211 patients, 62% achieved a CR. Although there was a trend for a higher rate of CR in ALFA 9801 compared with ALFA 9803, this difference was not statistically significant (70% vs 57%, respectively, P=.17). Approximately one-third of patients had resistant disease (26% in ALFA 9801 and 36% in ALFA 9803).

Overall, the particular trial had no significant impact on median OS (13.5 vs 14.4 months in trials 9801 and 9803, respectively). There was also no significant difference in the median OS experienced by patients receiving the various post-remission therapies. In univariate analysis, only an unfavorable karyotype significantly impacted OS (HR, 1.8; 95% CI, 1.3–2.6).

The authors concluded from this comparison that patients between 65–70 years of age experienced no difference in survival outcome between the post-remission treatment strategies evaluated. Thus, continued exploration of alternative post-remission strategies is important in this older patient population.

2091 Bendamustine Versus Chlorambucil as First-Line Treatment in B Cell Chronic Lymphocytic Leukemia: An Updated Analysis from an International Phase III Study

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Although frontline treatment for CLL consists of alkylating agents, purine analogs, or their combination, there is still a large need for new therapeutic options in patients with advanced CLL. The dual action purine analog and alkylating agent bendamustine has been shown to have high activity in a variety of hematologic malignancies,
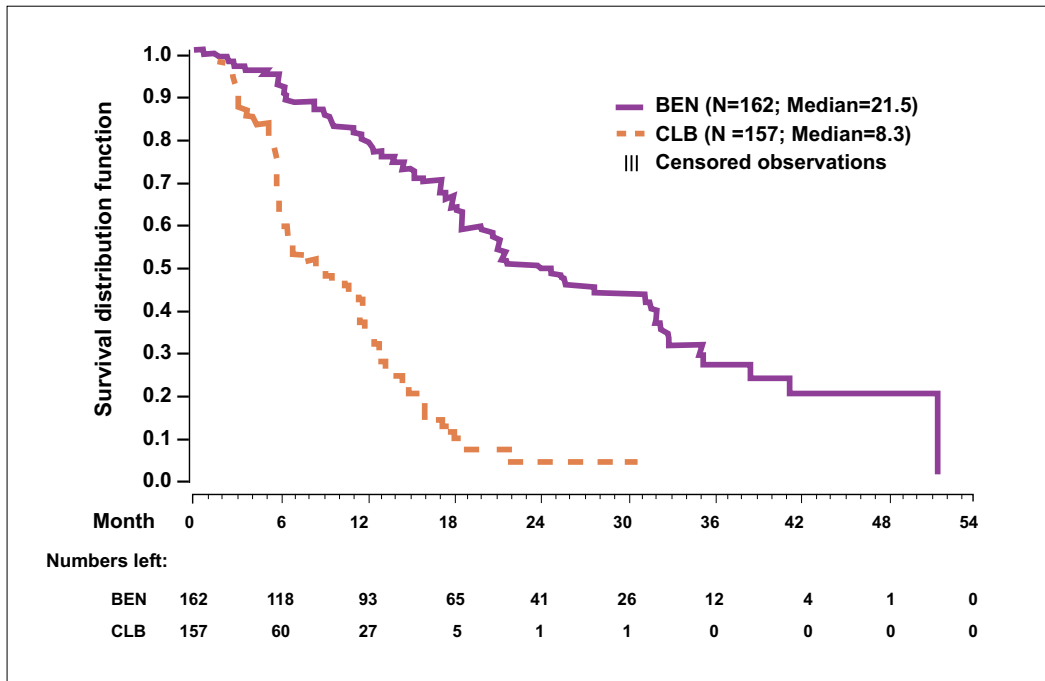
Figure 4. Bendamustine (BEN) versus chlorambucil (CLB) for first-line treatment of B-cell chronic lymphocytic leukemia: Kaplan-Meyer plot of progression-free survival.

including CLL.[47-51] These phase I and II clinical trials of single-agent bendamustine have shown that this drug can produce response rates as high, or higher, than those observed with the standard therapy chlorambucil. These data prompted Knauf and colleagues to conduct a phase III study to compare bendamustine with chlorambucil as frontline therapy for CLL.[57]

In this open-label multi-center study, 319 patients were randomized to a 1:1 ratio to receive either bendamustine (100 mg/m^2 daily on days 1 and 2, every 4 weeks) or chlorambucil (0.8 mg/kg on days 1 and 15, every 4 weeks). Patients were stratified according to treatment center and Binet stage. After 3 cycles of treatment, patients were assessed for response, at which point those with a CR or PR were recommended for 2 additional cycles of treatment. Patients received a mean of 4.8 cycles of therapy in the bendamustine arm and 4.6 in the chlorambucil treatment arm. Included patients had symptomatic Binet stage B or C CLL disease that was previously untreated and a World Health Organization PS of between 0–2. Only patients who were 75 years of age or younger were included. The baseline characteristics were evenly distributed between the treatment groups; 61–63% of patients were male, and the mean patient age was 63 years. Patients were followed for a median duration of 29.2 months.

Significantly, over twice as many patients in the bendamustine arm achieved an OR compared with the chlorambucil arm (67% vs 30%, respectively; P<.0001). Of these, 32% of the responses in the bendamustine arm were a CR, whereas 2% in the chlorambucil arm was a CR. A similar proportion of PRs were observed in each treatment arm (25% vs 26%, respectively). In both arms, more patients with Binet stage B disease had a clinical response compared with Binet stage C. Interestingly, the durations of CR and PR were longer in the bendamustine arm versus the chlorambucil arm (CR, 27 vs 8.15 months, respectively; PR, 18.6 vs 8.1 months, respectively). Patients receiving bendamustine also experienced a significantly longer median PFS compared with those receiving chlorambucil (21.5 vs 8.3 months, respectively, P<.0001; Figure 4).

While a similar proportion of patients in the bendamustine and chlorambucil arms experienced any adverse event (88.2% vs 80.1%), more patients in the bendamustine arm experienced a grade 3/4 adverse event (52.8% vs 31.1%). Hematologic toxicities were the most common, including neutropenia (23.0%), leukopenia (14.3%), thrombocytopenia (11.8%), lymphopenia (6.2%), and anemia (1.9%).

Knauf and colleagues concluded that bendamustine provided a significant and substantial clinical benefit compared with chlorambucil when used as frontline CLL therapy. Although a higher rate of adverse events was associated with bendamustine, these were manageable and of short duration.

3656 A Phase I Trial of the Epigenetic Modulator, Vorinostat, in Combination with Azacitidine (AzaC) in Patients with the Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): A Study of the New York Cancer Consortium

LR Silverman, A Verma, R Odchimar-Reissig, A LeBlanc, V Najfeld, J Gabrilove, L Isola, I Espinoza-Delgado, J Zwiebel

Azacitidine is a hypomethylating agent which leads to a reversal of epigenetic gene silencing.[58] Azacitidine is active in both MDS, as well as nonproliferative AML, where it is associated with improved survival.[59] However, responses associated with single-agent azacitidine are notably slow, thus requiring a median of 3–4 cycles before initial response is achieved. Preclinical in vitro studies have suggested that the HDAC inhibitor vorinostat is synergistic with azacitidine, resulting in an increased amount of reactivation of epigenetically silenced genes.[60] It has also been shown that the sequence in which these drugs are combined is important, and azacitidine should be administered prior to vorinostat. Silverman and colleagues initiated a phase I study to evaluate the safety of this combination in patients with MDS or AML, as well as to evaluate patient response.[61]

A total of 21 patients were evaluated in this study, in a 3+3 dose escalating de-escalating design. Of these patients, 20 had MDS and 8 had AML. Azacitidine was administered at doses of either 55 or 75 mg/m² daily, while vorinostat was administered at either 200 or 300 mg twice daily for between 7–14 days. A total of 171 cycles were administered to patients, with a mean of 5 cycles per patient (range, 1–17). Eight patients discontinued the study treatment due to progression (n=1), relapse (n=2), comorbidities (n=2), or withdrawal of consent (n=3).

During the first cycle, no grade 3/4 nonhematologic toxicities were reported; however, several patients experienced grade 2 anorexia (31.6%) and fatigue (57.9%). The severity of fatigue (grade 1 vs grade 2) was associated with the scheduled duration of vorinostat (7 days vs 14 days, respectively).

A response rate of 86% was observed among the patients. Of these, 53% were a CR/complete response with incomplete blood count recovery (CRi; 9 were a CR, 2 were a CRi). Of the 12 patients identified with high-risk disease, 83% achieved a response. Interestingly, in 57% of patients the abnormal MDS/AML clone persisted. The authors noted that this suggested the combination of azacitidine plus vorinostat had a modulating effect on the clone.

Silverman and colleagues concluded that the combination of azacitidine plus vorinostat was safe in patients with AML and MDS. Further, this combination appeared active, with a high rate of CR and OR. A 55 mg/m² dose of azacitidine was chosen for future phase II studies in combination with various dosages of vorinostat.

References for the above section of Presentation Summaries begin on page 29.

Commentaries on Leukemia Summaries

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Lenalidomide is a widely used and effective drug in the treatment of MM and MDS. This drug has now become an extremely promising agent in the treatment of CLL because of its unique mechanism of action. Lenalidomide is an immunomodulatory compound and also appears to affect the stromal cells in the bone marrow. The work of Chen and her colleagues[1] from Toronto, Canada, demonstrates that although lenalidomide as a single agent has beneficial activity in previously untreated patients with CLL, its safest and most effective dose has yet to be clearly defined.

Chen and colleagues started their study using a daily oral 10-mg dose for 21 days in each 28-day cycle, (with a plan to increase to a maximum of 25 mg/day) but they encountered serious toxicities (tumor lysis syndrome requiring dialysis; neutropenic sepsis leading to death) in their first 2 patients. The study was interrupted and was resumed after the starting doses were reduced to 2.5 mg/day for 21 days in each 28-day cycle with an allowance of slowly increasing it to a targeted maximum of 10 mg/day.

The preliminary results confirm that lenalidomide has activity in CLL and that it can be administered safely when it is started at a low dose and increased slowly if the patient is able to tolerate it. The next phase of exploring the true role of this new drug in CLL will be to test it in combination with other agents. The most likely candidates that could be combined with lenalidomide are monoclo-

nal antibodies such as rituximab and chemotherapy drugs such a bendamustine or fludarabine.

In 2008, bendamustine was FDA-approved for the treatment of CLL on the basis of the results of a large randomized trial comparing this drug versus chlorambucil in previously untreated patients. Updated results of that randomized trial reported by Knauf and colleagues,[2] with a median duration of 29 months of follow-up, confirmed the superiority of bendamustine over chlorambucil in overall remission rate and PFS. All toxicities associated with bendamustine were reported to be manageable.

These updated results confirm that bendamustine has become a proven and effective drug in the treatment of CLL. The next phase of exploration of enhanced activity of bendamustine will be in combination with rituximab, which is exactly the topic of the work presented by Fischer and colleagues.[3] These investigators tested the combination of bendamustine and rituximab in relapsed or refractory CLL. Previously treated CLL patients who have relapsed or refractory disease are known to have poor prognosis and low incidence of response to most therapeutic agents. The fact that Fischer and colleagues were able to achieve a 14% CR rate and a 63% PR rate in such a population demonstrates that the combination of bendamustine and rituximab deserves to be tested in the frontline therapy of CLL.

Over the past 10 years, imatinib has been in clinical use as a dramatically effective therapy in chronic phase CML, but it has been recognized that a small proportion of patients develop resistance to imatinib. The most likely explanations for the development of resistance to imatinib are mutations in tyrosine kinase domain of Bcr-Abl and the overexpression of Bcr-Abl protein due to the amplification of Bcr-Abl gene. It is in this context, therefore, that 2 drugs—dasatinib and nilotinib—have been approved by the FDA for treatment of CML patients who have become resistant to imatinib. The interest, therefore, is now shifting to study these 2 drugs in patients who have not been treated with imatinib. Nilotinib is a second generation ATP-competitive Bcr-Abl inhibitor, and it inhibits platelet-derived growth factor receptor (PDGFR) but does not inhibit Src-family kinases (SFK). It is 10–50 times more potent than imatinib in inhibiting the proliferation of wild-type Bcr-Abl cell lines and most of Bcr-Abl mutants. Rosti and colleagues provide an impressive report on the results of nilotinib therapy in previously untreated CML patients.[4]

Dasatinib is a dual Src-family kinase/Abl kinase inhibitor and a multi-target kinase inhibitor of Bcr-Abl, SFK, and PDGFR. It is more potent than imatinib. Like nilotinib, dasatinib also is capable of inhibiting proliferation of wild-type and most Bcr-Abl mutant cell lines. Cortes and colleagues[5] demonstrate the efficacy of dasatinib in previously untreated CML patients.

As a natural result of these observations with nilotinib and dasatinib in frontline CML, it is expected that the next level of investigation might be directed to find out whether patients would become refractory or resistant just as it has been seen with imatinib, and to observe what long-term toxicities might emerge. These success stories might also follow with other new drugs which will be effective against the T315I mutant of Bcr-Abl, a heretofore unconquered form of CML.

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MDS Studies

221 Final Results from a Phase I Combination Study of Lenalidomide and Azacitidine in Patients with Higher-Risk Myelodysplastic Syndromes (MDS)

MA Sekeres, AF List, D Cuthbertson, R Paquette, D Latham, M Afable, K Paulic, TP Loughran, JP Maciejewski

Immunomodulatory agents, including lenalidomide, are thought to act in MDS through a variety of mechanisms. These include inhibition of angiogenesis, growth arrest of chromosome 5–deleted hematopoietic tumor cells, increased cytolysis, and enhanced NKT cell expansion.[62-64] Several phase II trials have shown single-agent lenalidomide is active in MDS.[65,66] Likewise, the DNA hypomethylating agent azacitidine, which leads to the transcription of previously methylated and silenced genes, has also been found to be active in MDS.[59,67] Here, Sekeres and colleagues sought to determine if the combination of these 2 agents with unique mechanisms of action would improve on their respective single-agent response rates.[68]

The target population of this study was MDS patients with higher risk disease, meaning they had an expected survival of less than 1.5 years and a high rate of AML. These patients had an IPSS score of intermediate-2 or high. Notably, this higher risk disease group accounts for approximately 29% of the MDS population in the United States.[69] The primary objective of this study was to determine the maximum tolerated dose and dose-limiting toxicity of lenalidomide combined with azacitidine in patients with higher risk MDS. This was a phase I trial which enrolled patients in a 3+3 study design with increasing disease of each drug. Dose-limiting toxicities included a nonhematologic adverse event grade 3 or higher, febrile neutropenia, grade 4 neutropenia, or an inability to initiate the scheduled day 1 of cycle 2 within 28 days because of toxicity. Azacitidine was administered at a dosage of 75 mg/m^2 on days 1–5 or 50 mg/m^2 on days 1–5 and 8–12. Lenalidomide was given at a dosage of 5 or 10 mg daily, either on days 1–14 or days 1–21. Dose reductions were allowed as needed. The median patient age was 68 years, and 66.7% were male. The median time from diagnosis to study initiation was 5 weeks. Patients had intermediate-1 (n=3), intermediate-2 (n=9), or high (n=6) risk disease.

No dose-limiting toxicities occurred during the study. Within the first 8 weeks, the median neutrophil count decrease was 26%, while the median platelet decrease was 0% (mean was 24% decrease). Grade 3/4 nonhematologic toxicities included febrile neutropenia, cardiac events, and central nervous system hemorrhage. Other less frequent toxicities included monocular blindness, basal cell skin carcinoma, shortness of breath, perforated appendix, and renal failure.

A 72% OR rate was observed in response to the combination treatment. Of these, 39% were a CR and 6% were a PR (Table 5).

Sekeres and colleagues concluded that the combination of azacitidine plus lenalidomide was relatively safe, and not as toxic as the authors had anticipated. From this phase I study, the investigators chose azacitidine (75 mg/m^2 on days 1–5) plus lenalidomide (10 mg on days 1–21) as the optimal dose for future study. Importantly, the high rate of response observed in this preliminary study suggests that future trials are needed to further confirm these results.

222 Oral (PO) and Intravenous (IV) Clofarabine for Patients (Pts) with Myelodysplastic Syndrome (MDS)

S Faderl, G Garcia-Manero, F Ravandi, G Borthakur, Z Estrov, DA Thomas, V Gandhi, W Plunkett, A Byrd, M Kwari, HM Kantarjian

As patients with higher risk MDS have a poor prognosis, much effort has been focused on improving treatment strategies for these individuals. One drug, clofarabine, is a second generation deoxyadenosine analog.[70] It can be administered either orally or intravenously. Clofarabine

Dosing Cohort	AZA Dose	LEN Dose	IPSS Risk Group	Grade 3/4 Nonheme Toxicities	Maximum Response
1	75 mg/m² SC days 1-5	5 mg PO days 1-14	1 Int-1 2 Int-2	2	2 CR 1 progression
2	75 mg/m² SC days 1-5	5 mg PO days 1-21	2 Int-2 1 High	2	1 CR 1 PR, 1 HI
3	75 mg/m² SC days 1-5	10 mg PO days 1-21	1 Int-2 2 High	0	2 CR, 1 stable disease
4	50 mg/m² SC days 1-5, 8-12	5 mg PO days 1-14	1 Int-1 2 Int-2	2	2 CR, 1 stable disease
5	50 mg/m² SC days 1-5, 8-12	5 mg PO days 1-21	2 Int-2 1 High	6	1 HI 1 stable disease 1 progression
6	50 mg/m² SC days 1-5, 8-12	10 mg PO days 1-21	1 Int-1 1 Int-2 1 High	3	1 HI 2 BM CR

Table 5. Lenalidomide (LEN) + 5-Azacitidine (AZA) for Higher Risk MDS: Responses

BM=bone marrow; CR=complete response; HI=hematologic improvement; IPSS=international prognostic scoring system; PO=oral; PR=partial response; SC=subcutaneous

has been evaluated for frontline treatment of AML, resulting in an OR in nearly half of patients, many of which had a CR.[71] Early studies also suggested that clofarabine is active in the setting of MDS as well.[72] Here, Faderl and colleagues evaluated the efficacy and safety of clofarabine in MDS, and further compared the oral and systemic routes of administration.[73]

Patients eligible for this study had MDS of IPSS intermediate risk-1 or higher, an ECOG PS of 2 or lower, and exhibited normal organ function. Patients could not have received any prior intensive chemotherapy, although targeted and biological therapies were allowed. Oral clofarabine was administered at 40 mg/m² daily over 5 days, but this was reduced to 30 mg/m² after the first 6 patients. Patients receiving intravenous clofarabine were randomized to receive either 15 mg/m² or 30 mg/m² daily doses over 5 days. For both administration routes, courses were repeated every 4–6 weeks with no dose escalations permitted. A maximum of 12 courses were allowed, and growth factor use was permitted. The median age for patients receiving oral and intravenous clofarabine was 70 years and 67 years, respectively. The median number of prior therapies in both groups was 1, but ranged up to 4.

The OR rate for oral clofarabine was 48%, of which 28% had CRs and 8% experienced a hematologic improvement. A 50% and 33% rate of OR was observed in the intravenous 15 mg/m² and 30 mg/m² groups, respectively. Of these, 35% and 25% had a CR, respectively. Patients needed a similar number of courses to respond (median of 1 course in both oral and intravenous groups, ranging up to 3 courses in both groups). Interestingly, patients who had failed a prior hypomethylation therapy also responded in this study (OR of 33%, 26%, and 11% in oral, 15 mg/m² intravenous, and 30 mg/m² intravenous, respectively). However, patients without a history of hypomethylation use had a longer OS, though this did not reach statistical significance (11.27 months vs 6.51 months, P=.2445).

Several grade 3 or higher toxicities were reported. Increased liver enzymes occurred more frequently in patients receiving oral clofarabine, including ALT (24%), AST (16%), and bilirubin (12%). Toxicities also occurred more frequently in patients receiving 30 mg/m² intravenous clofarabine, such as edema (25%) and skin rash (19%). Importantly, acute renal failure occurred in 8%, 10%, and 19% of patients receiving oral clofarabine, 15 mg/m² intravenous clofarabine, and 30 mg/m² intravenous clofarabine, respectively.

The authors concluded that clofarabine was active in MDS patients, and especially noted that lower doses were associated with improved responses. Current studies are underway to continue evaluating the optimal dosage of clofarabine in this patient population.

224 Effect of Romiplostim in Patients (Pts) with Low or Intermediate Risk Myelodysplastic Syndrome (MDS) Receiving Azacitidine

H Kantarjian, F Giles, P Greenberg, R Paquette, E Wang, J Gabrilove, G Garcia-Manero, J Gray, K Hu, J Franklin

Thrombocytopenia is a frequent occurrence in MDS, occurring in up to two-thirds of patients.[74] Associated hemorrhagic complications can lead to a 20% mortality rate. Thrombocytopenia is often caused by the use of hypomethylating agents. Romiplostim is an Fc-peptide fusion protein, or peptibody that was recently approved for the treatment of chronic immune thrombocytopenic purpura.[75,76] Although it has no homology with erythropoietin, it leads to platelet production through a similar mechanism. Previously, romiplostim was shown to improve platelet counts in up to half of patients with low risk MDS who were experiencing severe thrombocytopenia.[77] Here, Kantarjian and colleagues investigated the benefit of adding romiplostim to hypomethylating agents in MDS patients.[78]

In this phase II, multicenter, double-blind study, 40 patients receiving azacitidine were randomized to 3 treatment arms—romiplostim at 500 mg weekly, at 750 mg weekly, or placebo. All treatments were administered for 4 cycles. No other concurrent MDS therapies were allowed, except for best supportive care. Patients with low or intermediate-1/2 risk MDS were enrolled in this study. However, the IPSS score was unbalanced between treatment arms, with more patients having intermediate-2 risk disease contained in the placebo arm and more patients having intermediate-1 risk disease in the romiplostim arms.

Although romiplostim resulted in improved thrombocytopenia compared with placebo, this difference did not reach statistical significance. The rate of clinically significant thrombocytopenic events was 85%, 62%, and 71% in patients receiving placebo, low dose, and high dose romiplostim, respectively. Similarly, the incidence of platelet transfusions decreased with increasing use of romiplostim (69%, 46%, and 36% in placebo, low dose, and high dose romiplostim, respectively). Over time, patients receiving romiplostim exhibited higher platelet counts.

Kantarjian and colleagues concluded that romiplostim was well tolerated when administered with azacitidine. Although it seemed to have activity in these MDS patients, the lack of statistical significance suggests future studies are needed to confirm these findings.

226 Low Dose Decitabine Versus Best Supportive Care in Elderly Patients with Intermediate or High Risk MDS Not Eligible for Intensive Chemotherapy: Final Results of the Randomized Phase III Study (06011) of the EORTC Leukemia and German MDS Study Groups

P Wijermans, S Suciu, L Baila, U Platzbecker, A Giagounidis, D Selleslag, B Labar, H Salih, F Beeldens, P Muus, T de Witte, M Lübbert

Decitabine, a similar agent to azacitidine, is currently approved for the treatment of MDS.[79] In this study, Wijermans and colleagues compared low-dose decitabine with best supportive care in patients with primary or secondary MDS.[80]

Patients 60 years of age or older with intermediate- or high-risk MDS or chronic myelomonocytic leukemia (CMML) were included in this phase III study. Eligible patients had a blast cell count of 11–30% or no more than 10% blast cell count plus poor cytogenetics. A total of 233 patients were randomized to receive either best supportive care or decitabine (15 mg/m^2 every 8 hours on days 1–3, every 6 weeks). No dose reductions were allowed, and up to 8 cycles of treatment were administered. A median of 4 cycles was administered. Patients with progressive disease at any point discontinued therapy. Patients spent a longer time on therapy in the decitabine arm compared with the best supportive care arm (180 days vs 112 days, respectively).

Patients were stratified according to cytogenetic profile (good vs intermediate vs poor vs unknown), IPSS score (intermediate-1 vs intermediate-2 vs high risk), type of MDS (primary vs secondary), and study center. Baseline characteristics were relatively similar between the 2 treatment groups, including median age (69–70 years), gender (64% male), and ECOG PS (12-15% PS of 2). Over one-third of patients in each arm had a high risk IPSS score (37–39%), and nearly half had poor cytogenetics (45–48%).

Decitabine treatment produced a markedly improved rate of response compared with best supportive care. Although no patients in the best supportive care arm achieved a CR or PR, 13% and 6% achieved a CR and PR in the decitabine arm. Similarly, only 2% of patients in the best supportive care arm experienced hematologic improvement, compared with 15% in the decitabine arm. The median response duration was 8.5 months. This improved response translated into a statistically significant increase in median PFS in the decitabine arm compared with the best supportive care arm (6.6 months vs 3 months, P=.004)

During the study, more patients receiving decitabine than best supportive care experienced adverse events, including febrile neutropenia (26% vs 7%), grade 1/2 nausea (28% vs 16%), and grade 1/2 vomiting (16% vs 9%). A similar proportion of patients died in each arm during the study (24% vs 22%). However, patients died from different reasons between treatments. For example, 18% of patients in the best supportive care arm died due to progression, compared with 6% in the decitabine arm. In contrast, 8% of patients in the decitabine arm died due to toxicity, compared with an unknown percentage in the best supportive care arm. The time to AML or death was similar between the 2 treatment arms (8.8 vs 6.1 months in the decitabine vs best supportive care arm, respectively).

Wijermans and colleagues concluded that decitabine had an acceptable safety profile in elderly patients with high-risk MDS. Its use was associated with improved response and PFS compared with best supportive care. The authors stated that the optimal schedule and dosage of decitabine in this setting still remains to be determined.

3629 Effects of Azacitidine (AZA) vs Conventional Care Regimens (CCR) in Elderly (≥75 Years) Patients (Pts) with Myelodysplastic Syndromes (MDS) from the AZA-001 Survival Trial

JF Seymour, P Fenaux, LB Silverman, GJ Mufti, E Hellström-Lindberg, V Santini, AF List, SD Gore, J Backstrom, D McKenzie, CL Beach

Recently, the phase III study AZA-001 showed that the DNA hypomethylating agent azacitidine is the first agent to significantly extend OS in patients with higher risk MDS. As the currently available cytotoxic therapies are poorly tolerable and largely ineffective, especially in older (≥75 years) MDS patients, there is a need for new treatment options for these patients. Therefore, Seymour and colleagues performed a subgroup analysis of the AZA-001 study, focusing on the effect of azacitidine in patients 75 years of age and older.[81]

In the AZA-001 trial, higher risk MDS patients (intermediate-2 risk or high risk IPSS score) were preselected by the study investigators to receive either best supportive care only, low dose cytarabine, or intensive chemotherapy. Subsequently, patients were randomized to receive azacitidine (75 mg/m^2 daily on days 1–7, every 28 days) or a conventional care regimen which was to continue with their initial therapy. Of the entire AZA-001 study population (n=358), 24% (n=87) were 75 years of age or older. Most of the patients who were randomized to the conventional care regimen arm received best supportive care, suggesting that clinicians are reluctant to use active cytotoxic treatment in this elderly population.

After a median follow-up of 17.7 months, patients receiving azacitidine experienced a prolonged survival compared to conventional care (median OS not reached vs 10.8 months, respectively, *P*=.0193). Additionally, the 2-year OS rate was significantly higher in the azacitidine arm (55% vs 15%, *P*=.0003). Twice as many elderly patients in the azacitidine arm who were transfusion-dependent became transfusion-independent compared to the conventional care arm (44% vs 22%, respectively). This outcome coincided with more patients receiving azacitidine achieving a hematologic improvement (58% vs 39%, respectively).

In this elderly population, azacitidine was generally well tolerated. Hematologic toxicities included anemia (42%), neutropenia (66%), and thrombocytopenia (71%), and occurred at a higher rate than in the conventional care arm. Similarly, more infections occurred in the azacitidine arm compared to the conventional care arm (79% vs 60%). More patients discontinued therapy in the azacitidine arm compared to the conventional care arm (13% vs 8%, respectively).

The authors concluded that azacitidine continued to be a beneficial therapy even in elderly higher risk MDS patients. Although adverse events were associated with its use, it was considered to be generally well tolerated in this patient population.

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Commentary on MDS Summaries

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The development of agents with the capacity to enhance platelet production in patients with MDS is a very important area of clinical research in MDS. One of these agents (romiplostim) was recently approved by the FDA for patients with immune thrombocytopenia purpura (ITP), but its use is currently not recommended for patients with MDS. Romiplostim and other similar drugs could be used in 2 different fashions in MDS: as primary single-agent therapy in patients with lower risk disease with thrombocytopenia, or as an adjunct to supportive care in patients receiving primary therapy to minimize the complications of therapy-induced thrombocytopenia.

The preliminary results of single-agent therapy with romiplostim in MDS were presented at ASH 2007.[1] Although these were encouraging, there was evidence of transient increases in marrow blasts and potential marrow fibrosis in a small subset of patients. This study was followed by another randomized trial exploring its use as an adjunct to hypomethylating-based therapy: romiplostim at 2 different doses—500 or 750 µg weekly versus placebo in patients receiving azacitidine with significant thrombocytopenia.[2] Preliminary results presented during the meeting indicated a modest effect on thrombocytopenic events (85% for placebo vs 62–71% for treatment arms). Platelet transfusion needs dropped from 69% to 36–46%. The combination was safe. These initial results are encouraging, but further data are needed with azacitidine and also decitabine before recommendations can be made. This is particularly important as romiplostim is available in the United States for ITP.

The hypomethylating agents, both azacitidine and decitabine, are standard care in patients with higher risk disease. That said, there is no standard of care for patients that lose response or fail to benefit from this class of agents. One potential approach is the use of clofarabine, an agent available orally and intravenously, both upfront or at the time of hypomethylating failure in MDS. The first of such studies was presented by Faderl and colleagues.[3] In total, 61 patients were treated with different doses, schedules, and routes of clofarabine; 64% of the patients had received prior hypomethylating-based therapy. CR/CRp was observed in 25 (41%) patients. Of importance, 4 patients achieved a CR after hypomethylating failure and 4 additional patients had clinical benefit (ORR 20%). Induction mortality was approximately 10%. This data is of importance as it points toward the first potentially active alternative for a nonhypomethylating-based approach in MDS.

The survival study of decitabine was one of the most highly anticipated studies at ASH 2008. Although both azacitidine and decitabine are approved in the United States, criteria for their approval was based on response data and not survival.[4] For European approval, a survival benefit is required. Therefore, following the experience with azacitidine,[5] a large randomized study of decitabine was conducted in Europe with survival in MDS as its primary endpoint.[6] In total, 223 patients with higher risk MDS were randomized to receive decitabine (15 mg/m^2 TID for 3 days) versus supportive care. Unfortunately, no effect on survival was observed (HR, 0.88; *P*=.38), although PFS was better for decitabine-treated patients

(0.55 vs 0.25 years; HR, 0.68; P=.004) These results are a major setback for the development of decitabine in MDS and will have a significant impact for the development and comparators of further therapies in patients with higher risk MDS. These negative results could be explained, in part, as due to the design of the study (ie, limited number of cycles of therapy planned), the dose and schedule of decitabine used (3-days vs 5-day),[7] and by the fact that significant fraction of patients (40%) received less than 3 cycles of therapy. A randomized study comparing azacitidine with decitabine, with survival as a primary endpoint, will be the only way to establish the role of these agents and the superiority of one versus the other.

One of the most important characteristics of the hypomethylating agents is that their toxicity profile is low enough that they can be potentially combined with multiple other compounds. Mechanistically, combination epigenetic therapies (hypomethylating agent with an HDAC inhibitor) are rational approaches, but other combinations are being studied. At ASH 2008, Sekeres and colleagues reported the initial results of a phase I study of azacitidine with lenalidomide.[8] Interest in the combination stems from the fact that both agents are active in MDS. The investigators reported that the combination has activity in patients with higher risk MDS, with myelosuppression being frequently observed. Although these are very preliminary results, they indicate a potential role for such a combination to be confirmed in further studies.

Last year, a randomized study of azacitidine versus a menu of conventional care demonstrated that treatment with azacitidine was associated with a significant improvement in survival.[5] The results of this study are now being re-analyzed in a number of subset analyses. One of these studies was presented at ASH 2008 by Seymour and colleagues: the effect of azacitidine in patients older than 75 years treated on the study.[9] This evaluation is important because the median age of patients with MDS is approximately 75 years old, and therefore younger patients treated on the study may not fully be representative of the actual MDS patient population. In total, 87 patients (24% of the total group) of the AZA-001 study were 75 years old or older.[5] The OS for azacitidine-treated patients was not reached compared to a duration of 11 months for the supportive group (HR, 0.48; P=.01); OS at 2 years was 55% versus 15% (P=.0003). No significant drug discontinuation was observed in this group of elderly patients. These results clearly confirm the role of azacitidine in older patients with MDS.

These are exciting times for patients and researchers in MDS. The new supportive care interventions, second line agents, and combination strategies should translate into better outcomes for our patients.

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Recent Advances in the Treatment of Hematologic Malignancies

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

1. In a study by Kumar and colleagues, what was the maximum tolerated dosage of cyclophosphamide in combination with VDR?

   a. 100 mg/m^2
   b. 300 mg/m^2
   c. 400 mg/m^2
   d. Not reached

2. According to the initial results of the PX-171-004 study which evaluated carfilzomib, presented by Vij and colleagues, which of the following statements is TRUE?

   a. The rate of OR was higher in patients with a prior history of bortezomib compared with patients who were bortezomib-naive.
   b. The rate of OR was higher in patients with newly diagnosed MM.
   c. The rate of OR was higher in patients with no prior history of bortezomib compared with patients who had previously been treated with bortezomib.
   d. The rate of OR was similar among all patient subgroups.

3. In a study by Lacy and colleagues, pomalidomide plus low-dose dexamethasone produced what rate of OR in patients with relapsed/refractory MM?

   a. 23%
   b. 33%
   c. 58%
   d. 64%

4. Which of the following agents is an oral inhibitor of the Syk kinase?

   a. Vorinostat
   b. Fostamatinib disodium
   c. Pomalidomide
   d. Carfilzomib

5. According to a study by Zinzani and colleagues that evaluated lenalidomide monotherapy in relapsed/refractory MCL, which of the following statements is FALSE?

   a. Although a 41% rate of OR was observed, none achieved a CR.
   b. A 41% rate of OR was observed, of which 13% was a CR/CRu.
   c. The median duration of response was not reached.
   d. The median PFS was 216 days.

6. According to a phase III StiL study by Rummel and colleagues, which of the following statements is TRUE regarding treatment in patients with FL and MCL?

   a. Patients in the CHOP arm had not reached a median EFS.
   b. Patients in the bendamustine arm had a significantly superior OR.
   c. Bendamustine plus rituximab is noninferior to CHOP plus rituximab.
   d. More adverse events were reported in the bendamustine arm.

7. In a study by Rosti and colleagues, what proportion of patients achieved a complete cytogenetic response between 4–6 months of therapy with nilotinib?

   a. 42%
   b. 56%
   c. 78%
   d. 96%

8. In a German CLL Study Group trial by Fischer and colleagues, the investigators found what combination of drugs to be active in relapsed/refractory CLL?

   a. Bendamustine plus rituximab
   b. Fostamatinib plus rituximab
   c. Bendamustine plus chlorambucil
   d. Dasatinib plus rituximab

9. In the final results of a study by Sekeres and colleagues, what was the OR rate observed in response to lenalidomide plus azacitidine?

   a. 39%
   b. 66%
   c. 72%
   d. 86%

10. Which of the following agents is a fusion protein that improves platelet counts by increasing platelet production?

    a. Clofarabine
    b. Romiplostim
    c. Nilotinib
    d. Dasatinib

Evaluation Form Recent Advances in the Treatment of Hematologic Malignancies

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

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

1. Extent to Which Program Activities Met the Identified Objectives
After completing this activity, I am now better able to:

- Describe how to integrate prognostic factors into treatment decisions for patients with hematologic malignancies, including lymphoma, leukemia, MDS, and multiple myeloma   1 2 3 4 5
- Identify factors influencing the choice of treatment for patients with MDS and leukemia   1 2 3 4 5
- Outline the most recent data on treatment options for both newly diagnosed and recurrent multiple myeloma   1 2 3 4 5

2. Overall Effectiveness of the Activity
The content presented:
- Was timely and will influence how I practice   1 2 3 4 5
- Enhanced my current knowledge base   1 2 3 4 5
- Addressed my most pressing questions   1 2 3 4 5
- Provided new ideas or information I expect to use   1 2 3 4 5
- Addressed competencies identified by my specialty   1 2 3 4 5
- Avoided commercial bias or influence   1 2 3 4 5

3. Impact of the Activity
Name one thing you intend to change in your practice as a result of completing this activity: _____

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

Additional comments about this activity: _____
_____

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

1	2	3	4	5	6	7	8	9	10

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