



**Clinical Treatment Advances in Hematologic Malignancies:  
Updates from the 15th Congress of the  
European Hematology Association**

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### **Target Audience**

The intended audience for this initiative includes hematologists, medical oncologists, hematologist-oncologists, oncology specialty pharmacists, and oncology nurses charged with the care of patients with hematologic malignancies.

### **Learning Objectives**

Upon completion of this educational activity, participants should be better able to:

- Discuss implications of updated efficacy and safety data for clinically available treatment options for patients with hematologic malignancies
- Describe the potential role of new therapeutic agents or strategies into clinical practice to improve remission and survival rates for patients with hematologic malignancies
- Describe the proposed mechanisms of action of new and emerging therapeutic agents in development for the management of patients with hematologic malignancies
- Differentiate treatment regimens based upon efficacy and toxicity parameter

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## INTRODUCTION

The 15th Congress of the European Hematology Association (EHA), held in Barcelona, Spain, brought together hematology professionals from around the world to discuss and disseminate important clinical information. Highlights from select EHA clinical presentations are included in this newsletter.

## LYMPHOMA UPDATE

### Non-Hodgkin Lymphoma

In 2010, nearly 66,000 new cases of non-Hodgkin lymphoma (NHL) will be diagnosed in the United States, and, despite the numerous treatment advances, NHL will cause more than 20,000 deaths. Non-Hodgkin lymphoma comprises a heterogeneous group of lymphoproliferative malignancies subdivided by histological type and clinical behavior.<sup>1</sup> Prognosis for NHL has improved significantly over the past 2 decades, however, numerous questions on optimal therapy remain.

#### *Rituximab Maintenance Improves Outcomes for Patients With Follicular Lymphoma*

Rituximab in combination with chemotherapy has improved disease-free survival (DFS) and overall survival (OS) rates for patients with newly diagnosed follicular lymphoma (FL).<sup>2</sup> Despite the efficiency of disease control with rituximab and chemotherapy, FL, which accounts for approximately 20% of all NHLs, remains incurable.

Previous studies had suggested that maintenance therapy with rituximab may provide a clinical benefit.<sup>3</sup> Therefore, the Group d'Etudes de Lymphomes de L'Adulte (GELA) conducted the phase III, multicenter randomized trial, Primary Rituximab and Maintenance (PRIMA). The study enrolled 1217 patients with untreated FL and high tumor burden.<sup>4</sup> Patients were treated with 8 cycles of rituximab (R) plus 8 cycles of cyclophosphamide, vincristine, prednisone (CVP), 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or 6 cycles of fludarabine, cyclophosphamide, mitoxantrone (FCM). In total,

1018 patients who responded to primary induction therapy were randomized to maintenance therapy with rituximab (375 rituximab mg/m<sup>2</sup> IV, every 8 weeks for 2 years, n = 505) or observation (n = 513). The primary endpoint of the study was progression-free survival (PFS). After a median follow-up of 25 months from randomization, a planned interim analysis was conducted. Results of this interim analysis were reported by Salles et al.<sup>5</sup>

**Table 1: Observation vs rituximab maintenance in patients with newly diagnosed follicular lymphoma**

Response at the end of maintenance	Observation, % n = 398	Rituximab, % n = 389
CR	47.7	66.8
PR	7.3	7.2
SD	0.3	0
PD	40.7	20.3
Patients converting from PR or SD to CR/CRu	30	45

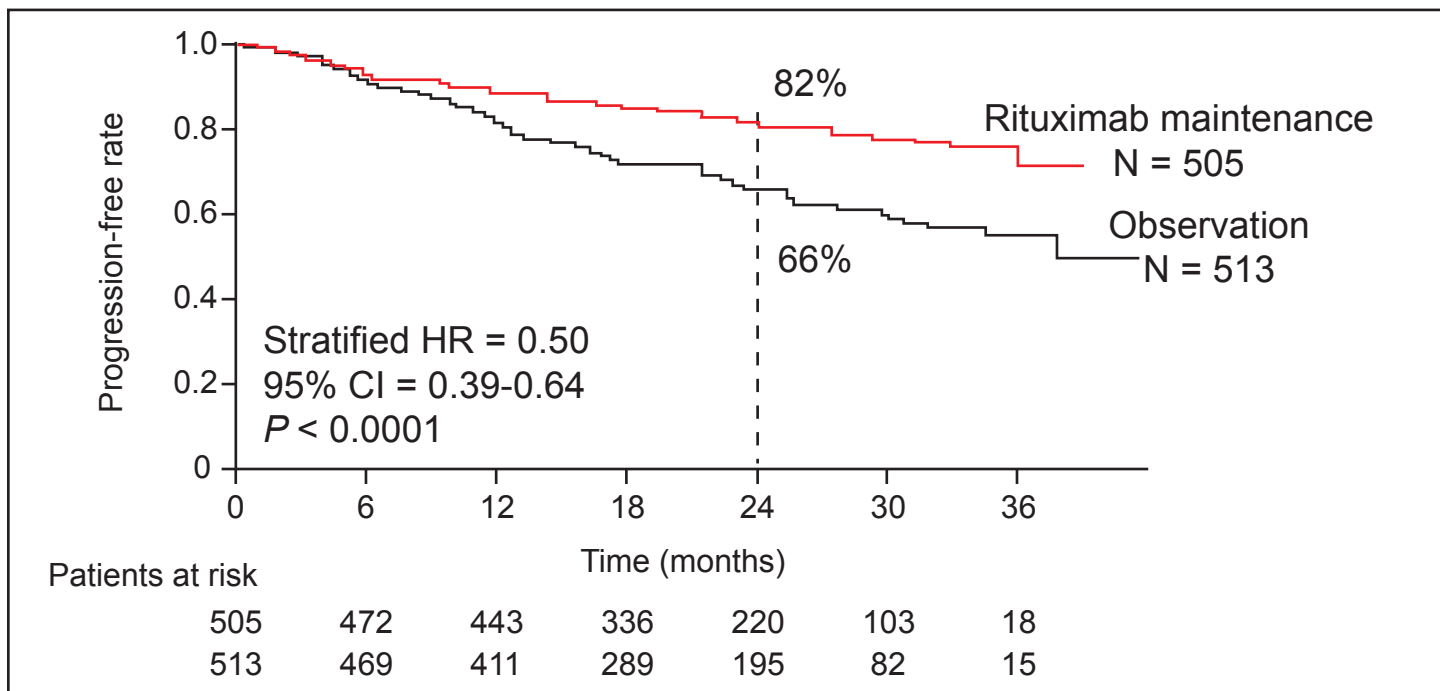
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CRu, CR unconfirmed; PFS, progression-free survival.

At the end of rituximab maintenance 66.9% of patients remained in complete response (CR) compared to 47.7% in the observation arm. Rituximab maintenance resulted in fewer patients with progressive disease (PD) (20.3% rituximab maintenance vs 40.7% observation) (**Table 1**).

Rituximab maintenance reduced the risk of progression by 50%. Progression-free survival at 24 months was 82% with rituximab maintenance versus 66% for patients on observation (HR = 0.50, 95% CI [0.39-0.64],  $P < 0.0001$ ) (**Figure 1**). The benefit of rituximab maintenance was consistent when patients were analyzed by age, Follicular Lymphoma International Prognostic Index (FLIPI), or response to induction therapy. Patients on rituximab maintenance also had increased time to next anti-lymphoma treatment (HR = 0.51,  $P = 0.0003$ ) and next



**Figure 1: Progression-free survival in follicular lymphoma patients treated with rituximab maintenance or observation**



chemotherapy treatment (HR = 0.60,  $P = 0.0011$ ). At the time of data cut-off, 34 patients (3.3%) had died. Longer follow-up is needed to evaluate the effects of rituximab maintenance on OS.

More patients on rituximab maintenance reported adverse events (any grade, 52% vs 35%, grade 3/4, 23% vs 16%) and grade 3/4 neutropenia (4% vs < 1%). On the maintenance arm, 10 patients withdrew for toxicity-related reasons compared to 1 patient on the observation arm. However, there were no major differences in quality of life as assessed by the European Organization for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-30).

Overall, 2 years of rituximab maintenance significantly improved PFS in patients with untreated FL responding to induction immunochemotherapy, and the benefit was seen in all major subgroups. Toxicity was moderately increased in patients on rituximab maintenance, but this did not impact quality of life scores.

### R-MCP vs MCP in Advanced Follicular Lymphoma

An early report comparing mitoxantrone, chlorambucil, and prednisolone (MCP) with and without rituximab in patients with advanced FL demonstrated that the addition of rituximab to MCP resulted in a significant survival advantage for patients with advanced FL.<sup>6</sup> Long-term follow-up of that study in patients with advanced FL was presented by Herold et al.<sup>7</sup>

**Table 2: Long-term outcomes of R-MCP vs MCP in patients newly diagnosed with FL**

	R-MCP n = 105	MCP n = 96	P
ORR	92.4%	75%	0.0009
CR	49.5%	25%	0.0004
Median PFS	86 months	35 months	0.0001
Median TTNT	NR	29 months	< 0.0001
Median OS	NR	108 months	0.0278

R, rituximab; MCP, mitoxantrone, chlorambucil, prednisolone; ORR, overall response rate; CR, complete response; PFS, progression-free survival; TTNT, time to next treatment; OS, overall survival; NR, not reached.

Patients with advanced stage symptomatic CD20-positive indolent NHL and mantle cell lymphoma (N = 358) were randomized to either 8 cycles every 4 weeks of MCP (mitoxantrone, 8 mg/m<sup>2</sup> IV, days 1-2; chlorambucil, 3 x 3 mg/m<sup>2</sup> orally, day 1-5; prednisolone, 25 mg/m<sup>2</sup> PO, days 1-5) or MCP with rituximab (375 mg/m<sup>2</sup>, day 1). Study endpoints included overall response rate (ORR), CR, PFS, event-free survival (EFS), time to next treatment (TTNT), OS, and toxicity.

After a median follow-up of 5 years, the ORR and CR rates were significantly higher with R-MCP compared to MCP. Median PFS and OS were also significantly better with R-MCP (**Table 2**).

This long-term follow-up demonstrates the superiority of immunochemotherapy over chemotherapy alone in advanced FL, with the addition of rituximab to chemotherapy significantly prolonging PFS, EFS, and OS. However, the optimal chemotherapy combination to use with rituximab remains unclear and needs to be further evaluated.

### ***Lenalidomide Monotherapy in DLBCL***

Diffuse large B-cell lymphoma (DLBCL) is the most common NHL histology. The pivotal GELA study, LNH98.5, which randomized R-CHOP to CHOP in newly diagnosed elderly DLBCL patients, established R-CHOP as the standard of care for patients with DLBCL.<sup>8</sup> Despite the marked improvement in survival with modern therapy, relapse in NHL remains a significant problem. Lenalidomide is a potent thalidomide analogue approved for the treatment of multiple myeloma and myelodysplastic syndromes. Two phase II studies (NHL-002 and NHL-003) have demonstrated activity of lenalidomide monotherapy in relapsed aggressive B-cell lymphoma.<sup>9-10</sup> Czuczman et al evaluated the safety and efficacy of lenalidomide monotherapy in patients with relapsed DLBCL by conducting a subset analysis of the 2 trials.<sup>11</sup>

In total, 49 patients with aggressive B-cell lymphoma with measurable disease ( $\geq 2$  cm), and at least 1 prior therapy were enrolled on NHL-002 and 217 patients were enrolled on NHL-003. Patients with DLBCL

histology include 26 patients from NHL-002 and 108 patients from NHL-003 (N = 134). Patients received 25 mg oral lenalidomide on days 1-21 of a 28-day cycle. In NHL-002, treatment continued for up to 52 weeks and in NHL-003 treatment continued until disease progression. The primary endpoint was ORR. Secondary endpoints included duration of response (DOR), PFS, and safety.

In the pooled subset, the median age was 66 years (range, 21-87), median time from diagnosis was 2.3 years (range, 0.3-21.1), and more male patients (61%) were enrolled. Patients had failed a median of 3 prior regimens (range, 1-10), and 39% of patients had received a SCT.

The ORR was 26% with 9% achieving a CR or unconfirmed CR (CRu). In patients, refractory to their last therapy, 16.1% had a response, and 29% of patients with prior SCT had a response. The median duration of response was 6.0 months, but was better (10.4 months) in patients achieving a CR or CRu.

The most common grade 3 and 4 adverse events were neutropenia (22.4% and 13.4%), thrombocytopenia (15.7% and 5.2%), and anemia (6% and 0.7%).

Overall, the data suggests that lenalidomide monotherapy is active in a proportion of relapsed or refractory DLBCL patients. Additional studies are needed to determine which patients are most likely to benefit from this treatment, optimize the treatment regimen, and explore combination therapy with lenalidomide.

### ***Hodgkin Lymphoma***

#### ***ABVD Cycle Number and IFRT Dose***

Outcomes for patients with newly diagnosed favorable Hodgkin lymphoma (HL) are generally quite good. However, the optimal number of chemotherapy cycles and dose of radiotherapy remain unclear. Therefore, the German Hodgkin Study Group (GHSg) conducted an international prospectively randomized multicenter trial comparing 2 and 4 cycles of adriamycin, bleomycin,



vinblastine, and dacarbazine (ABVD) and 20 Gy or 30 Gy involved field radiotherapy (IFRT). Results of this non-inferiority study were presented by Engert et al.<sup>12</sup>

Patients were randomized into 4 arms: 4 cycles of ABVD + 30 Gy IFRT; 4 cycles of ABVD + 20 Gy IFRT; 2 cycles ABVD + 30 Gy IFRT; 2 cycles of ABVD + 20 Gy IFRT. Patients were equally balanced for age, gender, stage, histology, performance status, and risk factors.

Comparing cycles of chemotherapy, a CR/CRu was achieved in 97% of patients treated with 4 cycles of ABVD and 97% of patients treated with 2 cycles of ABVD. There was also no significant difference between 5-year PFS ( $P = 0.24$ ). More hematologic toxicity occurred with 4 cycles compared with 2 cycles. In addition, alopecia, nausea, and infection were all higher with 4 ABVD cycles. More patients on 4 cycles of ABVD (52%) had grade 3/4 adverse events compared to 2 cycles (33%). Therefore, 2 cycles of ABVD was less toxic and was not inferior to 4 cycles.

When patients receiving 20 Gy were compared to patients receiving 30 Gy, both had good response (CR/CRu 99% with 30 Gy vs 97% with 20 Gy). Progression-free survival was not different between 20 Gy and 30 Gy ( $P = 0.93$ ). Dysphagia, mucositis, alopecia, and the presence of at least one grade 3/4 toxicity were more common in patients receiving 30 Gy. Therefore, there were less acute toxicities with 20 Gy and no difference in response or PFS.

When all 4 arms were compared, there was no significant difference in terms of OS, freedom from treatment failure (FFTF), and PFS.

Taken together, the reduced intensity regimen of 2 cycles of ABVD and 20 Gy IFRT was effective and not inferior to 2 cycles of ABVD with 30 Gy IFRT or 4 cycles of ABVD with 20 or 30 Gy IFRT. Therefore, the reduced intensity regimen is a reasonable option for patients with newly diagnosed favorable HL.

### ***Dacarbazine in Favorable HL***

Although 2-4 cycles of ABVD IFRT is generally regarded as standard therapy for early favorable HL, the impact of bleomycin and dacarbazine in this combination is unclear. To determine the minimum required cytotoxic drugs, the GHSG compared 2 cycles of ABVD to 2 cycles of ABV, AVD, or AV in a multicenter prospective trial. A total of 1710 patients were enrolled into this study. However, due to more events (progressive disease, relapse, and death) the AV arm was closed in 2005 and the ABV arm was closed in 2006. A descriptive analysis of the closed arms was performed on the initially randomized patients and results were presented by Borchmann et al.<sup>13</sup>

When ABVD (198 patients) was compared to ABV (191 patients) the CR/CRu rate was 97.5% for ABVD compared to 95.8%. Compared to the ABVD arm, more patients progressed (3.1% ABV vs 1.0% ABVD), and died (4.2% ABV vs 2.5% ABVD) on the ABV arm. The 4-year FFTF was significantly lower with ABV (84.5%) compared to ABVD (93.5%) ( $HR = 2.26, P = 0.01$ ). Four-year OS was also lower with ABV (95.9%) compared to ABVD (98.4%), but the difference was not significant ( $HR = 1.64, P = 0.36$ ).

When ABVD (167 patients) was compared to AV (156 patients) the CR/CRu rate was 97.0% for ABVD compared to 91.0% for AV. More patients progressed on the AV arm (5.8% AV vs 1.2% ABVD), but more deaths occurred on the ABVD arm (3.0% vs 1.9% on the AV arm). The 4-year FFTF was significantly lower with AV (75.3%) compared to ABVD (92.3%) ( $HR = 2.81, P < 0.001$ ). Four-year OS was not different between the 2 arms (98.1% ABVD vs 98.7% AV,  $HR = 0.61, P = 0.49$ ).

Overall, in terms of response and FFTF, both AV and ABV were inferior to standard therapy. This suggests that dacarbazine is essential to the current treatment regimen of 2-4 cycles ABVD with IFRT.

Non-inferiority analysis of the AVD regimen with IFRT is ongoing. A total of 143 events are needed to determine non-inferiority and 45 events have occurred. The final analysis on the AVD arm is expected in 3 to 4 years.

## T-Cell Lymphoma

### Romidepsin in Relapsed CTCL and PTCL

Romidepsin is a novel pan-histone deacetylase (HDAC) inhibitor recently approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients with one prior systemic therapy. The efficacy and safety of single-agent romidepsin were evaluated in 317 patients with CTCL and peripheral T-cell lymphoma (PTCL) from 3 studies (GPI-04-0001, NCI 1312, GPI-05-0002). The primary endpoint for the CTCL studies was ORR, and was assessed by a composite endpoint including skin, blood, lymph nodes, and viscera. The primary endpoint for PTCL studies was the rate of CR. Duration of response and safety were evaluated for all patients. Results were presented by Coiffier et al.<sup>14</sup>

Patients were heavily pretreated with a median of 2 to 4 prior therapies. The ORR was 35% for CTCL patients and 38% for PTCL patients. The median DOR for CTCL patients was 13.7 months (in NCI1312) and 15 months (in NCI1312) and 10 months for PTCL patients.

The most common CTCL treatment-related adverse events were nausea (67%; 3% ≥ grade 3), fatigue (49%; 10% ≥ grade 3) and vomiting (34%; 2% ≥ grade 3). For PTCL, the most common adverse events were nausea (53%; 3% ≥ grade 3), thrombocytopenia (44%; 21% ≥ grade 3), and fatigue (43%; 7% ≥ grade 3). Thrombocytopenia and neutropenia occurred more often in PTCL patients compared with CTCL patients.

Therefore, single agent romidepsin had efficacy with manageable toxicity as a salvage therapy for both PTCL and CTCL.

### Pralatrexate in Relapsed/Refractory PTCL

Pralatrexate is a novel antifolate recently approved by the U.S. Food and Drug Administration (FDA) for relapsed or refractory PTCL. Approval was based on the pralatrexate in relapsed or refractory peripheral T-cell lymphoma (PROPEL) trial. Coiffier et al analyzed the PROPEL data to determine if early response is prognostic for survival.<sup>15</sup>

**Table 3: Landmark analysis from the completion of cycle 1 in pralatrexate-treated PTCL responders and non-responders**

	Per ICR N = 90		Per Investigators N = 95	
	Responders	Non-responders	Responders	Non-responders
N	20	70	33	62
Median subsequent survival	17.6 months	13.4 months	21.3 months	8.6 months
HR (95% CI)	0.69 (0.33-1.43)		0.46 (0.24-0.84)	
P	0.32		0.01	

PTCL, peripheral T-cell lymphoma; ICR, independent central review.

Landmark analysis from the completion of cycle 1 was performed. At the landmark time point, study day 53 (the approximate end of cycle 1), surviving patients were categorized as responding or not responding. Survival was subsequently measured to the landmark and compared between categories via the Cox model.

The ORR was 29% (32/109) per independent central review (ICR) and 39% (43/109) per investigator assessment. By the landmark time point, there were 90 patients with an assessment per ICR, and 95 with an assessment per investigator. Of these, there were 20 responders per ICR and 33 responders per investigator. Responders and nonresponders were matched by demographics (gender, race, age, weight) and disease characteristics (mean time since diagnosis, histopathology per central review, baseline cutaneous involvement, ECOG performance status, number of prior regimens, number of prior systemic regimens). Overall survival was 14.5 months. Patients who experienced tumor response during cycle 1 had a 31% (per central review) and 54% (per investigator) reduction in risk of death. As assessed by the investigators, the landmark analysis (**Table 3**) demonstrated that early responses to pralatrexate strongly correlated with prolonged survival ( $P = 0.01$ ).



## LEUKEMIA UPDATE

### Chronic Myelogenous Leukemia

#### Dasatinib vs Imatinib in Newly Diagnosed CML-CP

Dasatinib is a highly potent BCR-ABL kinase inhibitor, inducing high rates of complete cytogenetic response (CCyR) in chronic myelogenous leukemia (CML) following imatinib failure, resistance, or intolerance. A single arm phase II trial suggested that dasatinib may safely induce high rates of CCyR and major molecular response (MMR) in newly diagnosed CML patients.<sup>16</sup> Because a significant proportion of patients with CML-chronic phase (CP) fail to achieve an optimal response with imatinib, an international randomized phase III trial (DASISION, CA180-056) was conducted comparing dasatinib (100 mg daily) to imatinib (400 mg daily) in newly diagnosed CML patients. Results were reported by Bacarani et al during the EHA Presidential Symposium.<sup>17</sup>

**Table 4: Response and outcomes of dasatinib vs imatinib in newly diagnosed CML-CP patients**

	Dasatinib n = 259	Imatinib n = 260	P
CCyR at 12 months, %	83	72	0.0011
Confirmed CCyR at 12 months, %	77	66	0.0067
MMR at 12 months, %	46	28	< 0.0001
MMR at any time, %	52	34	< 0.00003
Median time to MMR, months	9.2	6.3	< 0.00001
Progression to AP or BP, %	1.9	3.5	NR
12-month OS, %	97.2	98.8	NS

CML-CP, chronic myelogenous leukemia-chronic phase; CCyR, complete cytogenetic response; MMR, major molecular response; AP, accelerated phase; BP, blastic phase; OS, overall survival; NR, not reported; NS, not significant.

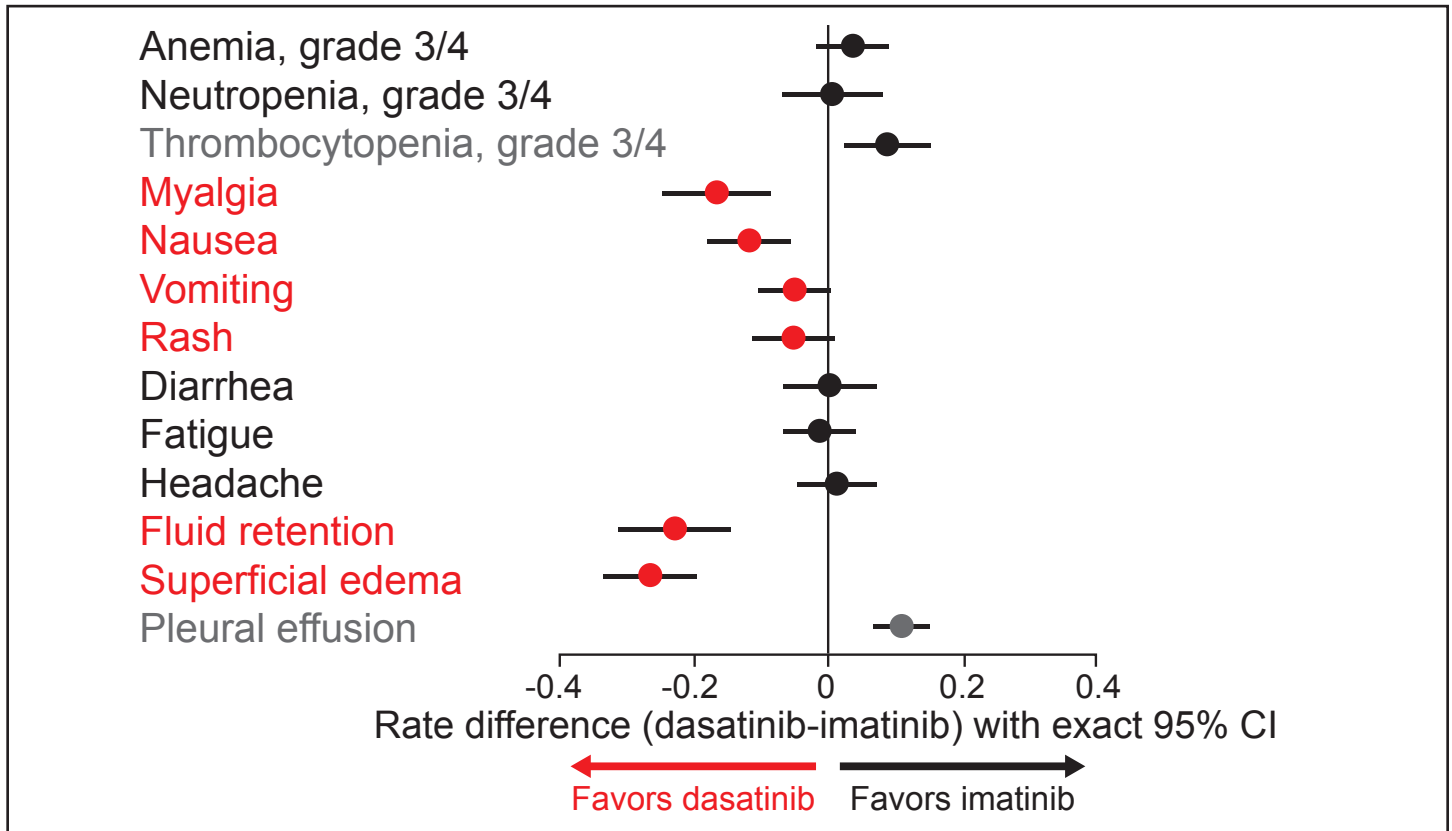
In total, 519 adults with Philadelphia Chromosome positive CML-CP stratified by Hasford Risk Scores, were randomized. The primary endpoint was rate of

confirmed CCyR by 12 months. Secondary endpoints included CCyR and MMR rates. Baseline patient characteristics were well balanced.

The incidence of CCyR by 12 months (83% dasatinib vs 72% imatinib,  $P = 0.0011$ ) and confirmed CCyR (77% dasatinib vs 66% imatinib,  $P = 0.0067$ ) were higher with dasatinib. The MMR rates at 12 months (46% dasatinib vs 28% imatinib,  $P < 0.0001$ ) and best response (52% dasatinib vs 34% imatinib,  $P < 0.00003$ ) were also higher with dasatinib. The time to achieve a MMR was also more rapid with dasatinib (median time to MMR: 6.3 months dasatinib vs 9.2 months imatinib,  $HR = 2.01$ ,  $P < 0.0001$ ). Dasatinib was superior across low, intermediate, and high-risk patients. Progression to accelerated or blastic phase was lower with dasatinib (1.9% vs 3.5%). However, there was no difference in OS between the 2 arms (12-month OS, 97.2% dasatinib vs 98.8% imatinib) (**Table 4**).

Treatment discontinuation was 15.5% with dasatinib and 18.6% with imatinib. Hematologic toxicity included anemia (10% dasatinib vs 7% imatinib), neutropenia (21% dasatinib vs 20% imatinib), and thrombocytopenia (19% dasatinib vs 10% imatinib). Grade 3/4 bleeding occurred in 1 patient on dasatinib and 2 patients on imatinib. Non-hematologic toxicity (any grade) included fluid retention (19% dasatinib vs 42% imatinib [including pleural effusion, 10% dasatinib vs 0% imatinib]), nausea (8% dasatinib vs 20% imatinib), vomiting (5% dasatinib vs 10% dasatinib), myalgia (6% dasatinib vs 12% imatinib), muscle inflammation (4% dasatinib vs 17% imatinib), and rash (11% dasatinib vs 17% imatinib) (**Figure 2**). Grade 3/4 non-hematologic adverse events were rare.

**Figure 2: Adverse events with first-line dasatinib or imatinib treatment in patients with chronic phase CML**



**Table 5: Imatinib 400 mg daily vs nilotinib at 300 mg and 400 mg BID in newly diagnosed CML-CP patients**

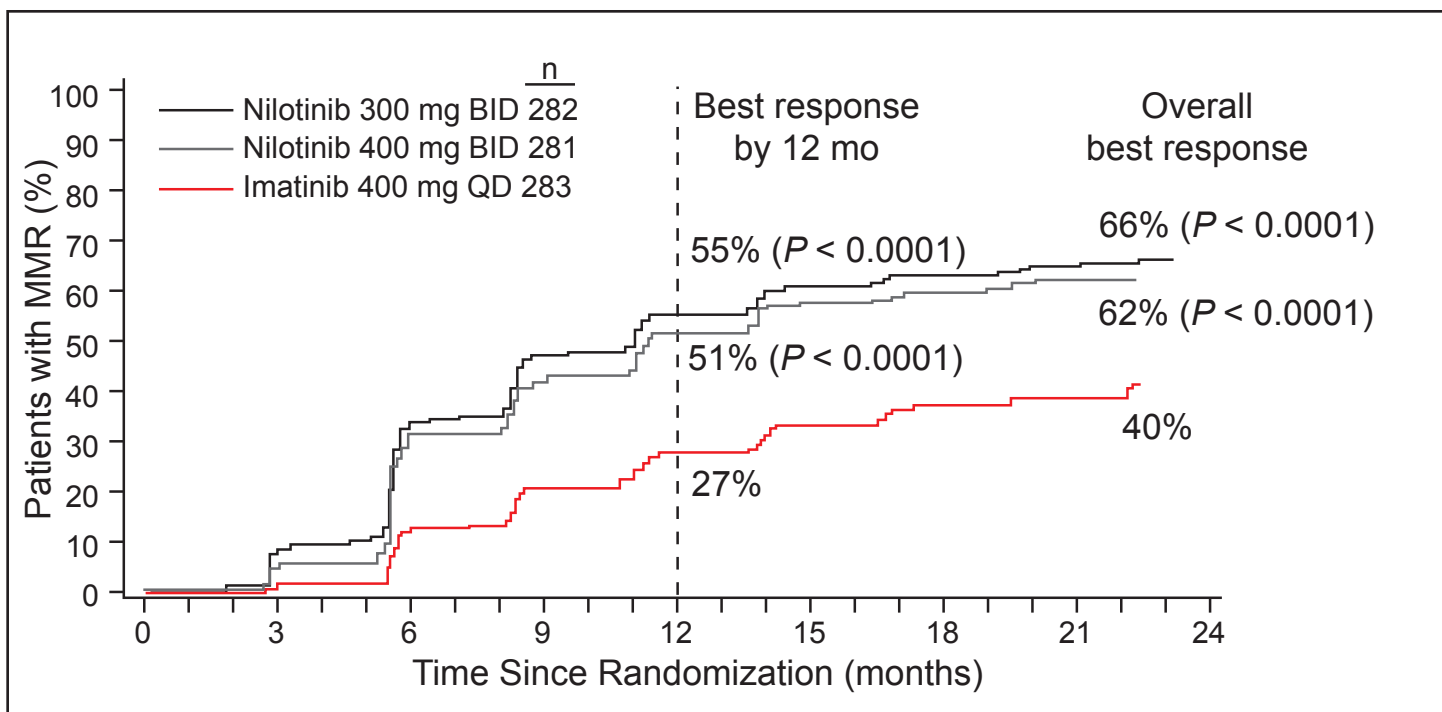
	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg daily n = 283
MMR at 12 months, %	44*	43*	22
Overall Best Response MMR, %	66*	62*	40
CCyR Best Response at 12 months, %	80*	78 <sup>†</sup>	65
Suboptimal Response, %	2	2	11
Treatment Failure, %	3	2	8
Progression to AP/BC, %	0.7 <sup>‡</sup>	0.4 <sup>§</sup>	4.2
18-month OS, %	98.5	99.3	96.9
Median time on treatment, months	18.6	18.5	18.1
Median dose intensity, mg/day (range)	593 (186-656)	779 (232-800)	400 (206-800)

CML-CP, chronic myelogenous leukemia-chronic phase; CCyR, complete cytogenetic response; MMR, major molecular response; AP, accelerated phase; BP, blastic phase; OS, overall survival.

\*vs imatinib,  $P < 0.0001$  <sup>†</sup>vs imatinib,  $P < 0.001$  <sup>‡</sup>vs imatinib,  $P = 0.006$  <sup>§</sup>vs imatinib,  $P = 0.003$ .



**Figure 3: Cumulative incidence of MMR with nilotinib vs imatinib in newly diagnosed CML-CP**



Taken together, these data demonstrate that once daily dasatinib results in significantly improved CCyR and MMR for first-line therapy in CML-CP patients. Overall, in both treatment arms, 12-month survival was high and therapies were generally well-tolerated. More time is needed to determine if the high response rates with dasatinib lead to improved long-term survival.

#### **Nilotinib vs Imatinib in Newly Diagnosed CML-CP**

Nilotinib is another potent 2nd generation tyrosine kinase inhibitor with proven efficacy in relapsed CML. A randomized phase III trial (ENESTnd) directly compared imatinib (400 mg daily) to nilotinib (300 mg BID and 400 mg BID). Primary analysis with 13.8-month follow-up suggested nilotinib was superior to imatinib.<sup>18</sup> Results after 18.5 months of follow-up were reported at EHA by Hochhaus et al.<sup>19</sup>

A total of 845 patients with newly diagnosed CML-CP were randomized to nilotinib 300 mg BID, nilotinib 400 mg BID, or imatinib (400 mg daily). The primary

endpoint of the study was MMR at 12 months and the secondary endpoint was durable MMR at 24 months. Patients were well matched for baseline characteristics.

Rates of MMR at 12 months were superior for nilotinib 300 mg and 400 mg BID compared with imatinib. Superior rates of MMR at 12 months were observed in both nilotinib arms compared with the imatinib arm (**Table 5**). This superiority held across all Sokal risk groups. The best overall MMR was also significantly higher in the nilotinib arms compared to the imatinib arm (**Figure 3**). The cumulative incidence of CCyR rates by 12 months were also significantly higher in patients treated with nilotinib 300 mg BID (80%,  $P < 0.0001$ ) and nilotinib 400 mg BID (78%,  $P < 0.0001$ ) compared with imatinib (65%). Molecular responses were deeper for nilotinib, with more patients achieving BCR-ABL transcript level reductions of  $\leq 0.01\%$  and  $\leq 0.0032\%$  compared to imatinib.

Treatment failure occurred more frequently on imatinib (8% imatinib vs 3% nilotinib 400 mg BID or 2% nilotinib 300 mg BID), and progression to advanced disease was significantly lower for both nilotinib 300 mg BID ( $P = 0.006$ ) and nilotinib 400 mg BID ( $P = 0.003$ ) (**Table 5**). Estimated 18-month OS was not different between the arms (**Table 5**).

Nausea, muscle spasms, diarrhea, vomiting, and edema were more common with imatinib. Rash, headache, pruritus, and alopecia were more common with nilotinib. Grade 3/4 adverse events were rare.

With a median follow-up of 18.6 months, nilotinib induced higher response rates compared with imatinib, and the depth of response was more robust. Adverse events for both medications were manageable. Based on these data, the FDA approved nilotinib on June 21, 2010 for first-line therapy of adult patients with newly diagnosed Philadelphia Chromosome positive CML-CP.

#### **Imatinib With Pegylated $IFN\alpha$ -2b**

Imatinib at 400 mg daily is the current standard of care for newly diagnosed CML. However, some studies have suggested that response rates may be improved using increased imatinib doses or imatinib in combination with interferon $\alpha$  ( $IFN\alpha$ ). Simonsson et al compared imatinib at 400 mg daily to imatinib combined with pegylated interferon $\alpha$ -2b (PEG-IFN) in newly diagnosed CML patients with intermediate or low Sokal Scores who achieved a complete hematological response after treatment with imatinib at 400 mg daily for 3 months.<sup>20</sup> The primary objective of the study was the MMR rate at 12 months.

**Table 6: Imatinib vs imatinib with PEG-IFN in newly diagnosed CML**

	Imatinib, % n = 56	Imatinib + PEG-IFN, % n = 56	<i>P</i>
CCyR at 12 months	83.9	91.1	
MMR at 12 months	53.6	82.1	0.002
MMR for patients who continued treatment for 12 months	57.7	90.9	0.012

CML, chronic myelogenous leukemia; CCyR, complete cytogenetic response; MMR, major molecular response; PEG-IFN, pegylated interferon $\alpha$ .

A total of 112 patients with a complete hematological response were randomized. Significantly more patients achieved a complete MMR at 12 months on imatinib with PEG-IFN compared to imatinib alone ( $P = 0.002$ ) (**Table 6**). The MMR rate also increased with longer duration of PEG-IFN treatment.

No unusual adverse events were reported. Four patients (8%) in each arm discontinued treatment.

These data suggest that imatinib with PEG-IFN is effective, yielding significantly higher MMR rates compared to imatinib alone.

#### **Imatinib, 400 mg vs Imatinib 800 mg vs Imatinib + $IFN\alpha$**

Optimal imatinib dose remains an important question in the treatment of CML. Some studies have suggested that higher doses of imatinib yield more rapid induction of molecular and cytogenetic remissions. Therefore, the German CML Study Group compared imatinib 800 mg (IM800) with standard dose imatinib (IM400) with or without interferon (IM +  $IFN$ ) in newly diagnosed CML-CP. Results were reported by Hehlmann et al.<sup>21</sup>



**Table 7: IM800 vs IM400 vs IM400 + IFN $\alpha$  in CML-CP**

	IM800 n = 259	IM400 n = 246	IM400 + IFN $\alpha$ n = 253
MMR at 12 months	59%	44%	46%
Median Time to MMR	28 months	43 months	48 months
Time to Optimal Molecular Response	31.3 months	47.5 months	42.5 months

CML-CP, chronic myelogenous leukemia-chronic phase; MMR, major molecular response; IM800, imatinib 80 mg daily; IM400, imatinib 400 mg daily; IFN $\alpha$ , interferon $\alpha$ .

The primary objective of the study was MMR at 12 months and cytogenetic remission, OS, and adverse events. A total of 1022 were enrolled and 1012 were evaluable for survival analysis. The patients were well matched for baseline characteristics. However, observation time was lower for the IM800 arm (median 28 months IM800 vs 43 months IM400 and 48 months IM + IFN). More patients on IM800 (59%) achieved an MMR at 12 months than with IM400 (44%,  $P = 0.0001$ ) or IM+IFN (46%,  $P = 0.0009$ ). Time to MMR was also shorter with IM800 (median 10.1 months) compared to IM400 (18.0 months) or IM + IFN (16.5 months). Optimal molecular response (< 0.01% BCR-ABL transcript) was reached more rapidly with IM800 (median: 31.3 months IM800 vs 47.5 months IM400 vs 42.5 months IM + IFN) (**Table 7**). Complete cytogenetic response was also reached faster with IM800 ( $P < 0.01$ ). The more rapid achievement of MMR with IM800 was observed in low- and intermediate-risk patients, but not in high-risk patients. For all patients, 5-year OS was 92% and 5-year PFS was 90% with no significant differences in OS and PFS between the arms.

The actual dose delivered for IM800 was 628 mg/day (range 208-800 mg/day). Grade 3/4 thrombocytopenia (8% vs 4-5%), edema (all grades) (36% vs 20-27%), and gastrointestinal AE (all grades) (43% vs 29-33%) were more common with IM800. Neurological AEs (21% vs 13-15%) and fatigue (18% vs 13-16%) were more common with IM400 + IFN.

These data suggest that IM800 is more effective than IM400 or IM + IFN and well tolerated when dose adjusted.

**IM400 vs IM600 vs IM400 + Ara-C vs IM400 + PEG-IFN**  
 Guilhot et al also conducted a multicenter randomized phase III trial comparing IM400, imatinib 600 mg/day (IM600), IM400 with cytarabine (Ara-C), and IM400 with PEG-IFN.<sup>22</sup> In total, 636 patients with a median age of 51 years (range 18-78) were stratified by Sokal Risk scores. Patients were randomized 1:1:1:1 to IM400 (n = 159), IM600 (n = 160), IM400 plus Ara-C (20 mg/m<sup>2</sup>/day, days 15-28 of a 28-day cycle, n = 158), and IM400 plus PEG-IFN (90  $\mu$ g/week, n = 159). Median follow-up was 47 months (range 3-73 months). Sokal Score distribution included 33% low, 40% intermediate, and 27% high.

**Table 8: IM400 vs IM600 vs IM400 + Ara-C vs IM400 + PEG-IFN in CML-CP**

	IM400 n = 159	IM600 n = 160	IM400 + Ara-C n = 158	IM400 + PEG-IFN n = 159
CHR, %	89	89	95	91
CCyR at 12 months, %	58	65	70	66%
MMR at 12 months, %	38	49	46	57*
MMR at 24 months, %	43	53	54	64*
Optimal MR at 12 months, %	14	17	15	30 <sup>†</sup>
Optimal MR at 24 months, %	21	26	26	38 <sup>†</sup>
Undetectable molecular residual disease, %	9	8	8	16 <sup>†</sup>
Treatment discontinuations, n	55	58	148	133

CML-CP, chronic myelogenous leukemia-chronic phase; CHR, complete hematologic response; CCyR, complete cytogenetic response; MMR, major molecular response; MR, molecular response; IM400, imatinib 400 mg daily, IM600, imatinib 600 mg daily; Ara-C, cytarabine; PEG-IFN, pegylated IFN $\alpha$ .  
 \*vs IM400,  $P = 0.0006$  <sup>†</sup>vs IM400,  $P = 0.001$ .

Patients on IM400 plus PEG-IFN had higher rates of CCyR and MMR, but treatment discontinuation was also more common with this combination (133 patients) (**Table 8**). Discontinuations were most common with IM400 + Ara-C (148 patients) and were lower with both IM400 (55 discontinuations) and IM600 (58 discontinuations). The majority of imatinib discontinuations were due to failure, whereas the majority of Ara-C and PEG-IFN discontinuations were due to toxicity.

Patients exposed to IFN more than 12.6 months had better rates responses compared to patients who were treated with PEG-IFN less than 4 months (MMR, 82% vs 48%; SMR 49% vs 23%; undetectable molecular residual disease 20% vs 8%). The median dose of imatinib during the first year was 400 mg daily for IM400 (all arms) and 590 mg daily for IM600. The median dose delivered for PEG-IFN was 54 µg per week (range, 11-66), and the median delivered Ara-C dose was 24 mg per day (range, 10-40).

Grade 3/4 neutropenia and thrombocytopenia occurred more frequently with the combination arms. Cramps, musculoskeletal pain, and edema were more common with IM600. Nausea and vomiting were more common with IM400 plus Ara-C, and flu-like symptoms, pruritus, and skin rash were more common with IM400 plus PEG-IFN.

In this study, the combination of imatinib with PEG-IFN yielded the best response. Toxicity was relatively manageable toxicity; however, the majority of patients discontinued treatment. As the previous 3 trials demonstrate, studies examining imatinib dose and combination therapy have yielded conflicting results. A meta-analysis may be needed to clarify the role of imatinib dose escalation and imatinib combination therapy in CML front-line therapy.

## Acute Myeloid Leukemia

### Subdivision of Intermediate-Risk Patients

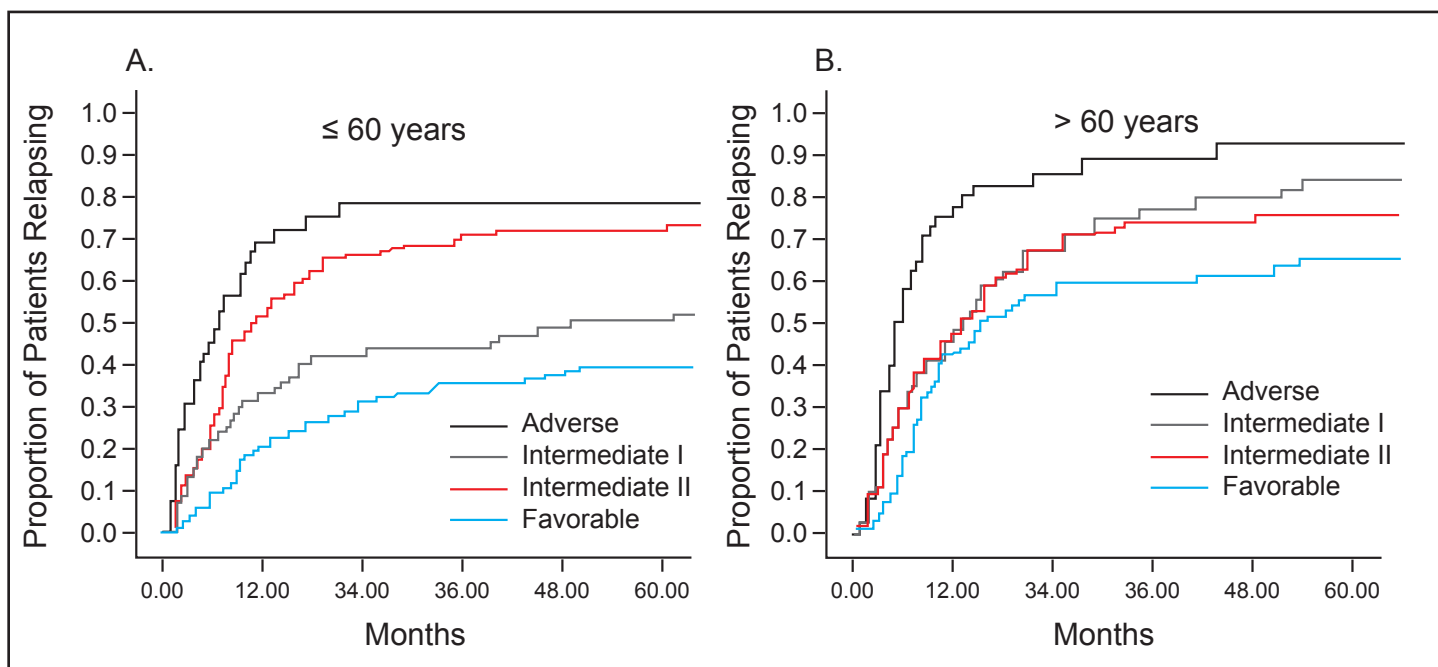
Acute myeloid leukemia (AML) is the most common type of leukemia among adults. Cytogenetic aberrations and molecular mutations in nucleophosmin (*NPM1*), CCAAT/enhancer binding protein (*CEBPA*), and *fms*-related tyrosine kinase (*FLT3*) have a significant impact on prognosis of AML patients. Based on cytogenetic and molecular classification, patients are currently divided into favorable, intermediate, and unfavorable (or adverse) risk groups. There is generally consensus regarding the prognostic value of the favorable and unfavorable risk classification. However, the intermediate risk group is heterogeneous. Therefore, the European LeukemiaNet (ELN) recently recommended a subdivision of intermediate-risk patients into intermediate I and the predicted less favorable intermediate II groups. The intermediate I group includes patients with a normal karyotype and mutated *NPM1/FLT3-internal tandem duplication (ITD)+*, wild type (wt) *NPM1/FLT3-ITD+*, or wt *NPM1/FLT3-ITD-*. Intermediate II includes patients with t(9;11)(p22;q23); *MLL3-MLL* or other cytogenetic abnormalities not classified as favorable or adverse.<sup>23</sup> The ELN risk classification is outlined in **Table 9**.

**Table 9: New AML risk classification recommended by the European LeukemiaNet group**

Risk Group	Cytogenetics
Favorable	<ul style="list-style-type: none"> <li>• T(8;21)122;q22); RUNX1-RUNX1T1</li> <li>• Inv16(p13.1;q22) or t(16;16)(p13.1;q22);CBFB-MYH11</li> <li>• Mutated NPM1 without FLT3-ITD (normal karyotype)</li> <li>• Mutated CEBPA (normal karyotype)</li> </ul>
Intermediate-I	<ul style="list-style-type: none"> <li>• Mutated NPM1 and FLT3-ITD (normal karyotype)</li> <li>• Wild-type NPM1 and FLT3-ITD (normal karyotype)</li> <li>• Wild-type NPM1 without FLT3-ITD (normal karyotype)</li> </ul>
Intermediate-II	<ul style="list-style-type: none"> <li>• t(9;11)(p22;q23); MLL3-MLL</li> <li>• Cytogenetic abnormalities not classified as favorable or adverse</li> </ul>
Adverse	<ul style="list-style-type: none"> <li>• Inv(3)(q21q26.2) or t(3;3)(q21;q26.2);RPN1-EV1</li> <li>• t(6;9)(p23;q34): DEK-NUP214</li> <li>• t(v;11)(v;q23); MLL rearranged</li> <li>• -5 or del(5q); -7</li> <li>• Abnormal 17p</li> <li>• Complex karyotype</li> </ul>



**Figure 4: Intermediate I and II sub-classification is prognostic for relapse-free survival for patients 60 years and younger, but not for patients over the age of 60 years**



To assess the prognostic value of the new ELN reporting system for correlation between cytogenetic and molecular genetic data, 1557 patients enrolled in the AML96 trial of the Study Alliance Leukemia were evaluated and reported by Rollig et al.<sup>24</sup>

Under the ELN classification, 27% were favorable risk, 30% were intermediate I, 20% were intermediate II, and 23% were adverse. There was no difference in the rate of complete remission for patients classified as intermediate I compared to intermediate II. With a median follow-up of 8.3 years, time to relapse was significantly different between intermediate I and intermediate II ( $P = 0.003$ ) for patients 60 years and younger. However, the time to relapse was significantly longer for intermediate II rather than intermediate I (**Figure 4A**). Overall survival in patients 60 years and younger was also similarly divided in 4 prognostic groups with intermediate II being significantly more favorable than intermediate I ( $P = 0.039$ ). For patients over the age of 60 years, there were no significant differences in time to relapse (**Figure 4B**) and OS between intermediate I and Intermediate II. Survival

was not different between intermediate I and Intermediate II patients who underwent allogeneic stem cell transplant.

These data suggest that the new ELN risk classification may be applicable for prognostic purposes in patients 60 years or younger. However, further investigation is needed in a larger data set to determine the role of this classification in guiding therapeutic decisions.

#### **GO-FLAI Induction Therapy for CD33+ Patients Under 65 Years**

CD33 is a cell surface antigen that is expressed on greater than 90% of AML blasts and is a major target for antibody-based therapy. Gemtuzumab ozogamicin (GO) is a monoclonal antibody linking CD33 to the cytotoxic calichamine. At the time of this presentation, GO was approved for the treatment of elderly patients with CD33+ AML. Interim results of a multicenter prospective clinical trial evaluating low-dose gemtuzumab ozogamicin with fludarabine, cytarabine, and idarubicin (GO-FLAI) was reported by Candoni et al.<sup>25</sup>

Primary endpoints of the study included feasibility, safety, efficacy (CR + PR), OS, and DFS. Newly diagnosed AML patients (all FAB subtypes except M3), aged 18-65 years, with a WHO performance status of 0 to 2 or Karnofsky score of 70 or higher, and CD33 positivity of 20 or higher were included in the trial. Patients were treated with GO-FLAI induction (fludarabine, 25 mg/m<sup>2</sup>, days 1-5; Ara-C, 2 g/m<sup>2</sup>, days 1-5; idarubicin 10 mg/m<sup>2</sup>, days 1, 3, and 5; GO 3 mg/m<sup>2</sup>, day 6) followed by consolidation with idarubicin and Ara-C and high-dose Ara-C. Hematopoietic stem cell transplant (HSCT) was planned for all high-risk AML patients (age > 60 years, secondary AML, WBC > 30 x 10<sup>9</sup>/L, complex or adverse karyotype, or MDR overexpression) in first complete remission after consolidation.

To date, 124 patients with a median age of 51 years (range, 18-65) have been enrolled on the study, and 118 patients were evaluable for response. The majority of patients had high-risk disease (69%) and M4 or M5 subtype (42%).

After induction, the ORR was 86% with 83% of evaluable patients achieving a CR. Of the standard-risk patients 34 of 38 (89%) achieved a CR, and 64 of 86 (74%) high-risk patients achieved a CR. One-year OS was 83%. After a median follow-up of 17 months, 89 out of 124 (72%) patients remained alive. Of those patients still alive, 82% were in complete cytogenetic remission. In total 85 (68%) patients underwent autologous (n = 20) or allogeneic (n = 65) stem cell transplant (SCT). The relapse rate for patients undergoing allogeneic SCT was 13% and the relapse rate for patients undergoing autologous SCT was 20%. Median OS has not been reached (1-year OS, 83%; 2-year OS, 66%; 3-year OS, 61%). One-year DFS was 74% and 2-year DFS was 58%. There was no difference in DFS for patients with WBC greater than vs less than 30,000 cells/mm<sup>3</sup>, de novo vs secondary AML and *FLT3* positive vs negative patients. Patients over the age of 56 years, however, had significantly shorter DFS.

The median time to a neutrophil count greater than 1 x 10<sup>9</sup>/L was 23 days (range, 19-39) and platelet count over 50 x 10<sup>9</sup>/L was 24 days (range, 18-43). Patients were hospitalized a median of 31 days (range, 22-59). Common extra-hematologic toxicity included fever during GO infusion (46%), neutropenic fever (47%), bacteremia (25%), mucositis (17.5%), HSV infections (18%), enteritis (12.5%), and liver toxicity (7.5%). Treatment-related mortality occurred in 8.5% of patients (6 after allo-BMT, and 5 after consolidation).

Taken together, these data suggest that the combination of intensive chemotherapy combined with targeted therapy and stem cell transplantation yields high complete remission rate with manageable toxicity. However, further analysis is needed to determine long-term outcomes and efficacy in comparison to other treatment regimens.

*Note: On June 21, 2010 gemtuzumab ozogamycin (GO) was voluntarily removed from the market after a recent study in 627 AML patients found no overall benefit of the addition of GO to standard therapy.*

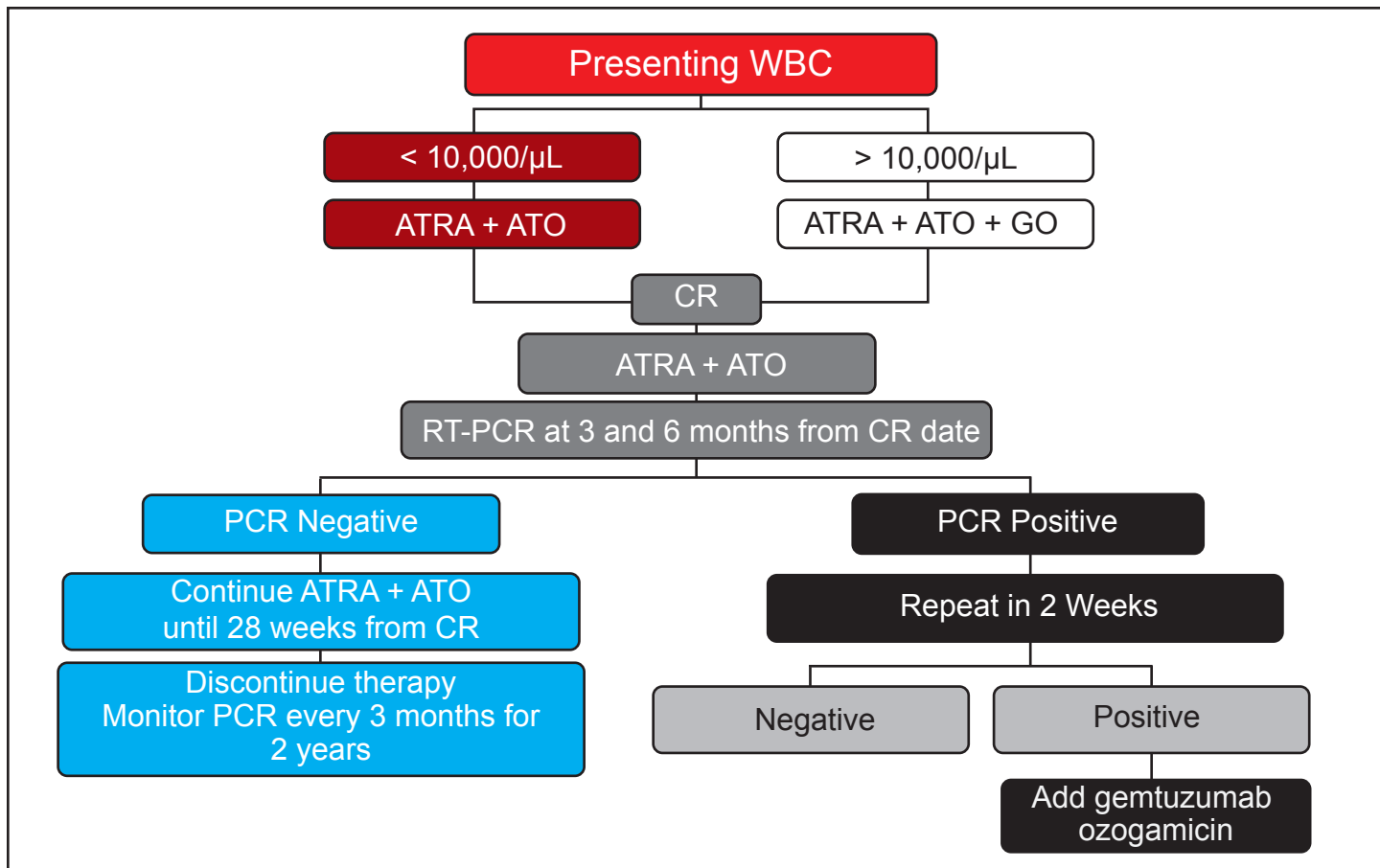
### ***Elacytarabine in Late-Stage AML, Phase II***

Elacytarabine is a novel cytotoxic nucleoside analogue. The mechanism of action of elacytarabine is similar to cytarabine, but cellular uptake is independent of nucleoside transporters. Historically, patients receiving second salvage therapies have a low CR rate and survival (less than 2 months).<sup>26</sup> Therefore, O'Brien et al evaluated the efficacy and safety of elacytarabine in patients with late stage AML in an open-label multicenter trial.<sup>27</sup>

The study included relapsed or refractory AML patients with a performance status between 0 and 2 who had received 2 previous chemotherapy regimens. Response and survival were compared to historical controls.<sup>26</sup> The population was matched for 6 adverse prognostic factors and distributed into 4 risk groups based on those factors (low, 1-2 adverse factors; intermediate 1, 3 adverse factors; intermediate 2, 4 adverse factors;



**Figure 5: Study schema ATRA + ATO with or without GO**



and high, 5-6 adverse factors). Sixty-four patients received elacytarabine monotherapy (2000 mg/m<sup>2</sup>, continuous IV infusion, days 1-5 every 3 weeks). The median patient age was 58 years (range 25-82), and 49% of patients were high-risk. Patients were followed for relapse and survival for at least 6 months.

The CR/CRp rate with elacytarabine was 18%, higher than the historical control rate of 2.5% ( $P < 0.001$ ). The median time to CR/CRp was 34 days (range, 28-126 days). The median duration of CR/CRp was 92 days (range, 6-218+). A total of 10 patients proceeded to hematopoietic stem cell transplant. Overall survival was 5.3 months for all patients and 10.9 months for those patients who achieved a CR or CRp. The 6-month OS rate was 44% .

The most common grade 3/4 hematological adverse events included thrombocytopenia, leukopenia, neutropenia, febrile neutropenia, anemia, and lymphopenia. Common nonhematological toxicity included fatigue (11.5%), increase in aspartate aminotransferase (8.2%), hypokalemia (8.2%), hyperbilirubinemia (6.6%), hyponatremia (6.6%), diarrhea (4.9%), nausea (4.9%), and dyspnea (4.9%).

Overall, the efficacy of elacytarabine in this highly pretreated population is promising, especially when compared to historical controls, and the toxicity profile appears manageable. This study has led to a recently opened randomized, multicenter study comparing elacytarabine to investigator's choice in patients with late stage AML (2-3 prior regimens).

### **ATRA + ATO With or Without GO in APL**

All trans retinoic acid (ATRA) in combination with chemotherapy is the current standard of care for front-line treatment of patients with acute promyelocytic leukemia (APL, AML M3). However, some challenges with APL remain, including a high rate of early deaths, a 20-30% relapse rate, and the development of APL therapy-related myelodysplastic syndromes.<sup>28</sup> Arsenic trioxide (ATO) has proven to be an effective therapy for relapsed APL and recent data suggests that ATO in combination with ATRA and daunorubicin yields high durable remission rates.<sup>29</sup> Single agent activity of GO had been demonstrated in relapsed APL patients,<sup>30-31</sup> and GO with ATRA yielded high CR rates and more durable remissions than ATRA alone.<sup>32</sup> Therefore, Ravandi et al examined the efficacy and safety of ATRA plus ATO with or without GO in newly diagnosed APL patients.<sup>33</sup>

Overall, 92 patients with newly diagnosed APL and a performance status of 2 or less were enrolled. The first 47 patients received ATRA (45 mg/m<sup>2</sup> daily) and ATO (0.15 mg/kg daily beginning on day 10 of ATRA) (cohort 1). High-risk patients (WBC ≥ 10 × 10<sup>9</sup>/L) received GO 9 mg/m<sup>2</sup> on the first day of induction. In July 2007 the study was amended (cohort 2, n = 45) to ATRA (45 mg/m<sup>2</sup> daily) and ATO (0.15 mg/kg daily) concomitantly on day 1 of induction. High-risk patients also received GO 9 mg/m<sup>2</sup> on day 1, and any time during induction if their WBC rose above 30 × 10<sup>9</sup>/L. Consolidation included 4 courses of ATO administered 5 consecutive days per week for 4 weeks every other month and ATRA for 2 weeks followed by 2 weeks rest for a total of 28 weeks after CR. Monitoring for PML-RARα fusion gene using reverse transcriptase-polymerase chain reaction (RT-PCR) was conducted after induction and throughout consolidation and follow up. If confirmed RT-PCR positive, GO 9 mg/m<sup>2</sup> was administered with ATRA and ATO every 4-5 weeks (based on recovery of counts) until negative (**Figure 5**).

**Table 10: Adverse events in APL patients treated with ATRA and ATO with or without GO**

Toxicity, N = 92	Grade 3, n	Grade 4, n
ATRA syndrome	5	1
Pain (back, headache, etc)	5	0
Renal failure	5	0
Cardiac (AFIB, MI)	4	0
Neurology (cerebrovascular ischemia)	1	1
Dermatology/rash/hand-foot	2	0
Elevated liver enzymes	2	0
Hemorrhage/bleeding	2	0
Nausea/vomiting	2	0
Edema	0	1
Constipation	1	0
Esophagitis	1	0
Respiratory failure/pulmonary embolism	1	0

APL, acute pro-myelocytic leukemia; ATRA, all-trans retinoic acid, ATO, arsenic trioxide; GO, gemtuzumab ozogamycin, AFIB, atrial fibrillation; MI, myocardial infarction.

The median patient age was 46 years (range, 14-81 years). Patients had a median presenting WBC of 2.7 × 10<sup>9</sup>/L (range, 0.4-131.4 × 10<sup>9</sup>/L), and a median platelet count of 36 × 10<sup>9</sup>/L (range, 7-261 × 10<sup>9</sup>/L). Thirty percent of patients had high-risk disease (WBC ≥ 10.0 × 10<sup>9</sup>/L).

Of all 92 patients, 90 (98%) achieved a CR (27/28 high-risk [98%]; 63/64 low-risk [98%]). Two patients died at induction, both over the age of 60. The CR rate was the same before and after the amendment to the protocol. The median time to CR was 29 days (range, 19-60 days) and the median days to a molecular CR was 122 days (range 20-271 days). In total, there were 9 deaths and 12 progression events, but remission was generally durable. Event-free survival was better, although not significantly, for patients with low-risk APL (*P* = 0.058) and under the age of 60 (*P* = 0.064). Responses were durable with 36 patients alive and in CR 3 or more years (25 low-risk; 9 high-risk) and 21 patients alive and in CR 5 or more years (12 low-risk; 9 high-risk).



Grade 3/4 adverse events are outlined in **Table 10** and include ATRA syndrome, pain, renal failure, and cardiac symptoms. Early death was due to respiratory failure (n = 1, day 9) and multi-organ failure (n = 1, day 24). Other deaths on the study included 2 patients with active APL (1 CNS, 1 unknown) and 5 patients in remission (unrelated metastatic cancer, 4 patients; pneumococcal meningitis post SCT, 1 patient).

Overall, the combination of ATRA and ATO with or without GO (depending on disease risk) was effective with high CR rates and durable response. More studies are needed to determine the contribution of GO and direct comparison of this regimen to current standards.

### MULTIPLE MYELOMA UPDATE

This year, more than 20,000 new cases of multiple myeloma (MM), the second most common hematologic neoplasm, will be diagnosed in the

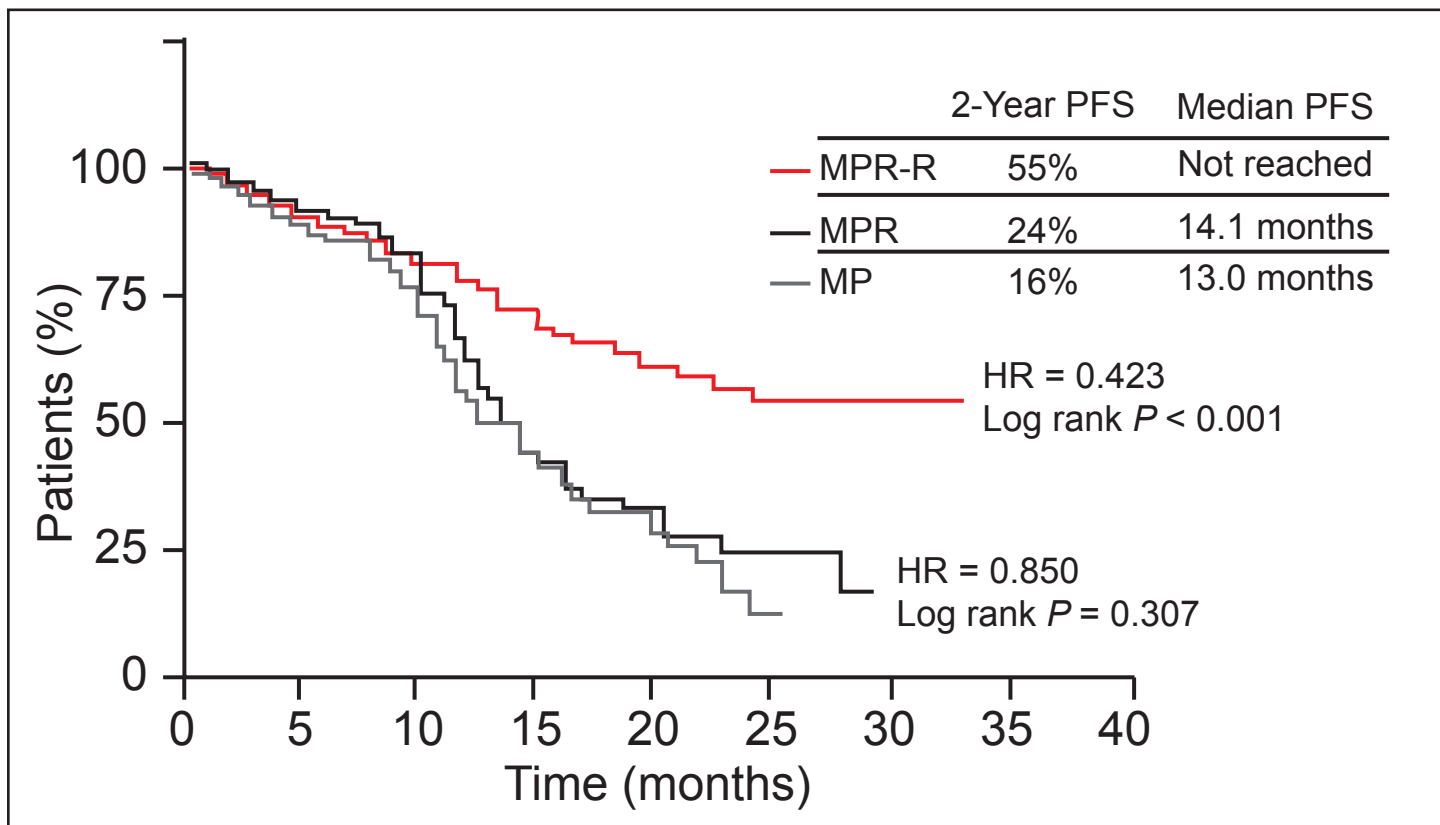
United States.<sup>1</sup> An increased understanding of MM pathogenesis has led to a plethora of data and numerous novel treatment options. However, further optimization of MM treatment is needed in order to maximize efficacy and minimize toxicity for a broad range of patients.

### Newly Diagnosed

#### MP vs MPR vs MPR-R, Phase III, SCT Ineligible

Lenalidomide is an active agent in patients with MM. To test the efficacy of lenalidomide with melphalan and prednisone in newly diagnosed SCT ineligible patients, Palumbo et al conducted a randomized phase III multicenter trial on 459 patients with newly diagnosed MM who were 65 years old or older or ineligible for a HSCT.<sup>34</sup>

Figure 6: Progression-free survival of newly diagnosed patients treated with MP vs MPR vs MPR-R



**Table 11: MP vs MPR vs MPR-R in newly diagnosed, SCT ineligible patients**

	MPR-R N = 152	MPR N = 153	MP N = 154	P (MPR-R vs MP)
ORR (> PR)	77%	68%	50%	< 0.001
CR	16%	11%	4%	< 0.001
> VGPR	32%	33%	12%	< 0.001
Median time to 1st response	2 months	2 months	3 months	< 0.001
Median PFS	NR	14.1 months	13.0 months	< 0.001
2 year PFS	55%	24%	16%	< 0.001

MP, melphalan, prednisone; MPR, MP + lenalidomide; MPR-R, MPR with continued lenalidomide; ORR, overall response rate; PR, partial response; CR, complete response; VGPR, very good partial response; PFS, progression-free survival; NR, not reached.

Patients were randomized between melphalan (0.18 mg/kg, days 1-4) and prednisone (2 mg/kg, days 1-4) (MP), MP with lenalidomide (10 mg/day, days 1-21) (MPR), or MPR followed by continued lenalidomide treatment (10 mg/day on days 1-21) (MPR-R). The median age for each arm was approximately 71 years, and 25% of patients were over 75 years. Approximately 50% of patients had stage III disease (MPR-R: 49%, MPR: 48%, MP: 51%).

The ORR was 77% for MPR-R, 68% for MPR, and 50% for MP (MPR-R vs MP,  $P < 0.001$ ). The CR rate (16% for MPR-R, 11% for MPR, and 4% for MP; MPR-R vs MP,  $P < 0.001$ ) and very good partial response (VGPR) rate (32% MPR-R, 33% MPR, and 12% MP; MPR-R vs MP,  $P > 0.001$ ) were significantly better with MPR-R compared to MP (**Table 11**).

The number of patients achieving a VGPR or better increased over time, and continuous treatment was important for improvement to a VGPR. With a median follow-up of 21 months, PFS was significantly longer for MPR-R (not reached for MPR-R vs 13.0 months MP, HR = 0.423,  $P < 0.001$ ) (**Figure 6**). Subgroup analysis for PFS demonstrated that MPR-R provided a

significant benefit for all subgroups except patients over the age of 75 years. This is likely due to the higher discontinuation rate for patients on MPR over the age of 75 years and the lower cumulative dose intensity delivered (**Table 12**). Overall survival was not significantly different between the arms (12-month OS, 92-93%; 24-month OS, 75-82%).

**Table 12: Discontinuation rate and cumulative dose intensity with MP and MPR + MPR-R**

	MPR + MPR-R	MP
Discontinuation rate		
65 – 75 years	17%	10%
> 75 years	34%	16%
Cumulative dose intensity		
65-75 years	88%	97%
> 75 years	56%	97%

MP, melphalan, prednisone; MPR, MP + lenalidomide; MPR-R, MPR with continued lenalidomide.

The incidence of grade 3/4 adverse events was higher with MPR-R compared to MP. Hematologic toxicity included anemia, thrombocytopenia, neutropenia, and febrile neutropenia. Deep vein thrombosis (DVT) or pulmonary embolism (PE) also occurred more frequently in the MPR-R arm (3% MPR-R vs 1% MP). Administration of granulocyte-colony stimulating factor (G-CSF) (66% vs 31%), platelet infusions (35% vs 18%), and overall discontinuations (20% vs 8%) were higher with MPR-R compared to MP.

Landmark analysis after induction (9 cycles) comparing MPR-R to MPR demonstrated that continuous lenalidomide therapy provided a significant benefit (HR = 0.314,  $P < 0.0001$ ). Continuous lenalidomide was safe with few grade 3/4 adverse events (thrombocytopenia, 4%; neutropenia, 3%; DVT, 3%; rash, 1%; fatigue, 1%).

These data suggest that continuous lenalidomide provides a significant clinical benefit, similar to recently reported results at the American Society of



Clinical Oncology.<sup>35-36</sup> Given these results, MPR-R is a reasonable option for transplant ineligible patients with the greatest benefit observed in patients aged 65-75 years. However, further follow-up is required to determine if the increase in PFS translates into improved OS.

### **VMPT → VT vs VMP, Phase III, SCT Ineligible**

Palumbo and colleagues also compared the combination of bortezomib, melphalan, and prednisone (VMP) to the 4-drug combination bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance therapy with bortezomib and thalidomide in a phase III randomized study.<sup>37</sup>

**Table 13: VMP vs VMPT followed by VT in newly diagnosed MM patients**

	VMP, % n = 253	VMPT → VT, % n = 250	P
CR	24	38	0.0008
≥ VGPR	50	59	0.03
≥ PR	81	89	0.01
3-year PFS	40	54	0.006
3-year TTNT	55	69	0.006
3-year OS	84	86	0.60

VMP, bortezomib, melphalan, prednisone; VMPT → VT, bortezomib, melphalan, prednisone, thalidomide followed by bortezomib and thalidomide maintenance; CR, complete response; VGPR, very good partial response; PFS, progression-free survival; TTNT, time to next treatment; OS, overall survival.

The trial included 511 patients 65 years or older who were ineligible for SCT and had creatinine levels 2.5 mg/dL or less. The trial was amended early on to use weekly doses of bortezomib rather than twice weekly. Induction therapy included 9, 5-week cycles of bortezomib (1.3 mg/m<sup>2</sup>, days 1, 8, 15, 22), melphalan (9 mg/m<sup>2</sup>, days 1-4), and prednisone (60 mg/m<sup>2</sup>, days 1-4) with or without thalidomide (50 mg/day). The VMPT arm was followed by maintenance with bortezomib (1.3 mg/m<sup>2</sup>, days 1, 15) and thalidomide (50 mg/day) until relapse (VMPT → VT).

No maintenance therapy was used for the VMP arm. Patients were well-matched for age, β2 microglobulin levels, and chromosome abnormalities.

Response was better in the VMPT → VT arm, with 38% of patients achieving a CR on this arm compared to 24% of patients on the VMP arm ( $P = 0.0008$ ). In addition more patients on the VMPT → VT achieved a VGPR or better (59% VMPT → VT vs 50% VMP,  $P = 0.03$ ) and a PR or better (89% VMPT → VT vs 81% VMP,  $P = 0.01$ ). Partial responses were achieved rapidly (> 50% within the first month). However, achievement of a CR took considerably longer, emphasizing the importance of keeping patients on treatment. With a median follow-up of 26.5 months, TTNT ( $P = 0.006$ ) and PFS ( $P = 0.006$ ) were significantly better with VMPT → VT, but 3-year OS was not different (VMPT → VT, 86% vs VMP, 84%;  $P = 0.6$ ) (**Table 13**).

Grade 3/4 hematologic toxicity included neutropenia, thrombocytopenia, and anemia. Neutropenia was more common in the VMPT → VT arm ( $P = 0.02$ ). Grade 3/4 nonhematological events included sensory neuropathy, infections, cardiac events, and thromboembolic events and occurred more frequently on the VMPT → VT arm. Significantly more patients on the VMPT → VT had grade 3/4 cardiac events (5% VMP vs 10% VMPT → VT,  $P = 0.04$ ) and thromboembolic events (3% VMP vs 5% VMPT → VT,  $P = 0.05$ ). More patients on the VMPT → VT arm discontinued treatment because of adverse events (16% VMP vs 21% VMPT → VT).

Patients who received twice weekly bortezomib had similar CR rates and PFS, but once weekly bortezomib significantly lowered the rates of PN (14% twice weekly vs 2% once weekly) and discontinuation (16% twice weekly vs 4% once weekly). When the total delivered dose was analyzed, the delivered dose of weekly bortezomib was similar to twice weekly bortezomib (41 mg/m<sup>2</sup> twice weekly vs 40 mg/m<sup>2</sup> once weekly).

Achievement of CR had the greatest impact on outcome for both treatment arms. Subgroup analysis demonstrated that patients with the high-risk cytogenetics, t(4:14) and t(14;16) had similar PFS compared to patients with standard-risk cytogenetics ( $P = 0.99$ ). However, outcomes for patients over 75 years was not different between the 2 treatment arms.

Overall, the 4-drug VMPT combination followed by VT maintenance improved response and PFS; however, to date, no difference in OS has been detected and longer follow-up is needed. Reduction of the bortezomib dose from twice weekly to once weekly yielded similar response rates and significantly reduced the rate of peripheral neuropathy.

#### ***MPT vs MP, Meta Analysis, SCT Ineligible***

Several randomized clinical trials comparing melphalan, prednisone, and thalidomide to melphalan and prednisone in patients ineligible for HSCT have been conducted. Results from those trials have been mixed, some showing a clinical benefit with the addition of thalidomide and others demonstrating no benefit. Therefore, Waage et al conducted a meta-analysis of 6 randomized from Italy (GIMEMA,  $N = 331$ ),<sup>38</sup> France (IFM 321,  $N = 229$ ),<sup>39</sup> Netherlands/Belgium (HOVON,  $N = 333$ ),<sup>40</sup> Nordic countries (NMSG,  $N = 35$ ),<sup>41</sup> and Turkey (TMSG,  $N = 114$ ).<sup>42</sup>

The daily dose of thalidomide between the trials ranged from 100-400 mg. A total of 1685 patients were analyzed (816 MPT, 869 MP). The addition of thalidomide significantly improved PFS (HR = 0.67, 95% CI [0.55-0.8]). Median PFS was 20.4 months with MPT versus 14.9 months with MP ( $P < 0.001$ ). Overall survival was better with MPT (median OS 39.3 months with MPT vs 32.7 months with MP,  $P = 0.085$ ), but the difference was not significant (HR = 0.82, 95% CI [0.66-1.02]).

Therefore, the addition of thalidomide to melphalan and prednisone results in significantly longer PFS. Overall survival is increased with the addition of thalidomide, but this difference is not significant.

#### ***Relapsed/Refractory***

##### ***Carfilzomib in Bortezomib-Naïve and Bortezomib-Treated Patients***

Protein degradation in the proteasome is critical to cell function and survival. Proteasome inhibition causes apoptosis in myeloma cells and, given the activity of bortezomib in MM, the proteasome is an effective target for myeloma therapy. Previous reports have suggested that carfilzomib is active in relapsed disease.<sup>43-45</sup>

The activity and safety of carfilzomib in relapsed or refractory MM patients following 1-3 prior therapies was tested in a phase II study (PX-171-004). Carfilzomib was administered intravenously on days 1, 2, 8, 9, 15, and 16 every 28 days for up to 12 cycles. Carfilzomib was given at 20 mg/m<sup>2</sup> (cohort 1,  $N = 95$ ) or 20 mg/m<sup>2</sup> for cycle 1 followed by 27 mg/m<sup>2</sup> in all remaining cycles (cohort 2,  $N = 60$ ). There were 2 populations entered on the study, bortezomib-naïve and bortezomib-treated patients. The primary endpoint was ORR and secondary endpoints included duration of response, PFS, TTP, OS, and safety. Stewart et al reported the results from 155 patients.<sup>46</sup>

For bortezomib-treated patients in cohort 1 (20 mg/m<sup>2</sup> carfilzomib,  $n = 34$ ), the ORR was 21% with a clinical benefit rate (CBR) ( $\geq$  marginal response [MR]) of 33%. Median TTP for these patients was 8.1 months (95% CI, 2.8-11.1) and the median duration of response was 8.5 months for patients with an MR or better (95% CI, 7.3-NE months) and 11.5 months for patients with a PR or better (range 7.2-15.2 months).



**Table 14: Response of relapsed or refractory MM patients to carfilzomib**

	Bortezomib-Treated		Bortezomib-Naïve	
	Cohort 1	Cohort 1	Cohort 1	Cohort 2
N	34	53	53	53
ORR	21%	45%	55%	55%
CBR	33%	58%	62%	62%
Median TTP	8.1 months	8.3 months	11.5 months	11.5 months
Median DOR (> MR)	8.5 months	8.3 months	11.5 months	11.5 months
Median DOR (> PR)	11.5 months	10.2 months	11.5 months	11.5 months

MM, multiple myeloma; ORR, overall response rate; CBR, clinical benefit rate; DOR, duration of response; TTP, time to progression.

For bortezomib-naïve patients in cohort 1 (n = 53), the ORR was 45% and CBR was 58%. For bortezomib-naïve patients in cohort 2 (n = 53), the ORR was 55% and the CBR was 62%. Median TTP for bortezomib-naïve patients in cohort 1 was 8.3 months and 11.5 months for cohort 2. The median DOR for bortezomib-naïve patients achieving an MR or better in cohort 1 was 8.3 months and 11.5 months for cohort 2. The median DOR for bortezomib-naïve patients achieving a PR or better in cohort 1 was 10.2 months and 11.5 months for cohort 2 (**Table 14**).

Common grade 3 or higher adverse events included pneumonia (11%), anemia (9.7%), neutropenia (9.7%), thrombocytopenia (9.0%), and fatigue (5.2%). Five patients died on study (2 due to progressive disease, 2 due to AE related to study treatment, and 1 due to AE unrelated to study treatment). Forty-five percent of patients had grade 1/2 peripheral neuropathy at baseline. In total 15% of patients developed treatment-emergent neuropathy. Only 1% of patients developed grade 3 neuropathy, and no patients had grade 4 neuropathy. The rate of treatment discontinuations for PN was 0.6% (1/155).

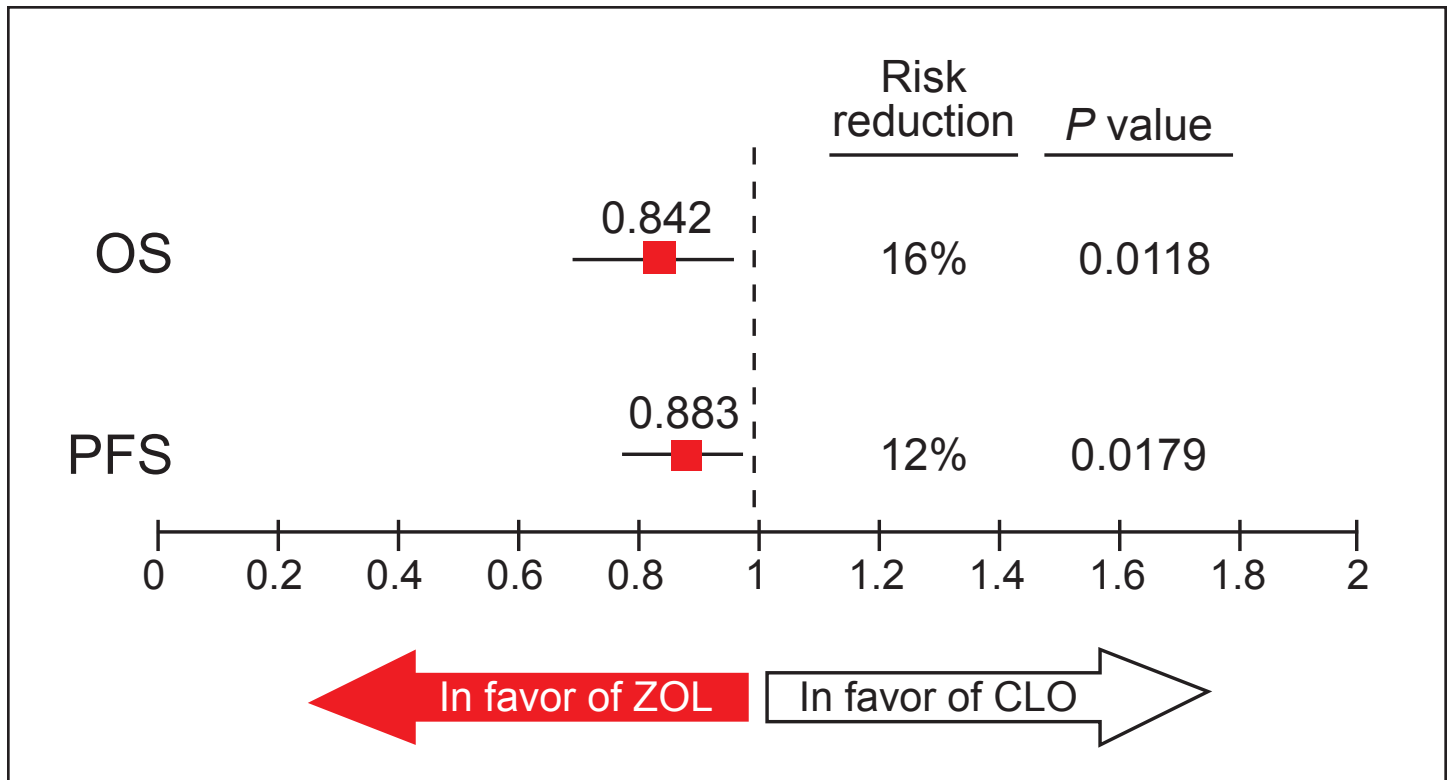
Overall, single-agent carfilzomib is active in relapsed and/or refractory MM. Approximately 25% of patients remain on study and 25% have completed 12 full cycles, and the trial is ongoing at the 27 mg/m<sup>2</sup> dose of carfilzomib.

### *Effect of Bisphosphonates on Outcomes, Zoledronic Acid vs Clodronate*

Bisphosphonates are often used for the management of MM patients with bone lesions. Some studies have suggested that bisphosphonates may have anticancer effects.<sup>47-48</sup> However, the effect of various bisphosphonates on outcomes has not been tested rigorously. Therefore, the Medical Research Council (MRC) IX myeloma trial randomized newly diagnosed MM patients to either zoledronic acid (4 mg IV, dose adjusted based on renal function, every 3-4 weeks) or clodronate (1600 mg PO daily) plus antimyeloma (intensive or non-intensive) therapy. Primary endpoints included OS, PFS, and ORR. Secondary endpoints included skeletal-related events and safety. Results of this study, which was conducted at 121 centers and enrolled 1960 newly diagnosed MM patients (stage I, II, or III), were presented in the Presidential Symposium by Morgan et al.<sup>49</sup>

Zoledronic acid increased OS by 5.5 months compared to clodronate (median OS: 50 months with zoledronic acid vs 44.5 months with clodronate,  $P = 0.04$ ). In a Cox proportional hazards model adjusting for chemotherapy and minimization factors, zoledronic acid had a significant effect on PFS (HR = 0.883,  $P = 0.0179$ ) and OS (HR = 0.842,  $P = 0.0118$ ) (**Figure 7**). In patients receiving intensive myeloma therapy, the number of patients achieving a VGPR or better was similar between the clodronate and zoledronic acid arms. For patients receiving non-intensive chemotherapy, more patients achieved a VGPR or better on the zoledronic acid arm ( $P = 0.03$ ). Zoledronic acid also significantly reduced the rate of skeletal related events (27% zoledronic acid vs 35.3% clodronate,  $P = 0.0004$ ). This also held true for patients who had no bone lesions at baseline. In addition, new osteolytic lesions were reduced with zoledronic acid. When OS was adjusted for skeletal-related events, the significant impact of zoledronic acid on OS remained (HR = 0.850,  $P = 0.0178$ ) suggesting that zoledronic acid may be having an anti-myeloma effect.

**Figure 7: Overall and progression-free survival in multiple myeloma patients treated with zoledronic acid (ZOL) vs clodronate (CLO)**



There was no difference in the number of patients with acute renal failure, thromboembolic events, or infection. There was an increase in osteonecrosis of the jaw among patients treated with zoledronic acid (intensive pathway: 3.8% zoledronic acid vs 0.4% clodronate,  $P < 0.0001$ ; non-intensive: 3.3% zoledronic acid vs 0.2% clodronate,  $P = 0.0009$ ).

Overall, zoledronic acid compared to clodronate significantly improved the length of PFS and OS and reduced the number of skeletal-related events. Adverse events were similar among the 2 bisphosphonates with the exception of osteonecrosis of the jaw, which occurred more frequently in patients on zoledronic acid. Although more studies are needed, in addition to the effects on skeletal-related events, zoledronic acid may provide an anti-myeloma effect.

### CONCLUSION

The 15th EHA Congress, held in Barcelona, Spain, proved to be an exciting forum to discuss and disseminate novel clinical information on hematologic malignancies. Numerous studies were presented including important phase III trials in NHL, CML, and MM that may influence practice.

### REFERENCES

1. Pohlman B, Advani R, Duvic M, et al. Final results of a phase II trial of belinostat (PXD101) in patients with recurrent or refractory peripheral or cutaneous T-cell lymphoma. *ASH Annual Meeting Abstracts*. 2009;114(22):920.
2. Bendandi M. Aiming at a curative strategy for follicular lymphoma. *CA Cancer J Clin*. 2008;58(5):305-317.
3. van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol*. 2010;28(17):2853-2858.



4. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: Results of the Gela-Goelams FL2000 study. *Blood*. 2008;112(13):4824-4831.
5. Salles G, Catalano J, Feugier P, et al. Rituximab maintenance for 2-years significantly improves the outcome of patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy: results of the PRIMA study. *Haematologica*. 2010;95(S2):557.
6. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German study group hematology and oncology study. *J Clin Oncol*. 2007;25(15):1986-1992.
7. Herold M, Maschmeyer G, Lakner V, et al. Sustained survival advantage after a median follow-up of 5 years for immunochemotherapy (R-MCP) versus chemotherapy alone (MCP) in advanced follicular lymphoma – update of the Osho#39 trial. *Hematologica*. 2010;95(S2):575.
8. Coiffier B, Gisselbrecht C, Bosly A, et al. 10 years follow-up of the GELA LNH98.5 study, first randomized study comparing R-CHOP to CHOP chemotherapy in patients with diffuse large B-cell lymphoma. *ASH Annual Meeting Abstracts*. 2009;114(22):3741.
9. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-hodgkin's lymphoma. *J Clin Oncol*. 2008;26(30):4952-4957.
10. Witzig TE, Vose JM, Zinzani PL, et al. Durable responses after lenalidomide oral monotherapy in patients with relapsed or refractory (R/R) aggressive non-hodgkin's lymphoma (a-NHL): results from an international phase 2 study (CC-5013-NHL-003). *ASH Annual Meeting Abstracts*. 2009;114(22):1676.
11. Czuczman M, Vose J, Zinzani PL, et al. Lenalidomide monotherapy is clinically active in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL): a pooled analysis of data from 2 phase II studies (nhl-002/003). *Hematologica*. 2010;95(S2):574.
12. Engert A, Pluetschow A, Eich H, et al. Two cycles of ABVD followed by involved field radiotherapy with 20 gray (Gy) is the new standard of care in the treatment of patients with early-stage hodgkin lymphoma: final analysis of the randomized German Hodgkin Study Group (GHSg) HD10 study. *Haematologica*. 2010;95(S2):1145.
13. Borchmann P, Diehl V, Goergen H, et al. Dacarbazine is an essential component of ABVD in the treatment of early favourable hodgkin lymphoma: results of the second interim analysis of the GHSg HD13 trial. *Hematologica*. 2010;95(S2):1146.
14. Coiffier B, Horwitz S, Whittaker S, et al. Romidepsin experience in 317 patients with T-cell lymphomas. *Hematologica*. 2010;95(S2):572.
15. Coiffier B, Zinzani PL, Gisselbrecht C, et al. Pralatrexate activity in patients with relapsed/refractory peripheral T-cell lymphoma (ptcl): relationship between response at cycle 1 and subsequent survival. *Hematologica*. 2010;95(S2):305.
16. Kantarjian H, Pasquini R, Lévy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily. *Cancer*. 2009;115(18):4136-4147.
17. Baccarani M, Shah N, Kantarjian H, et al. Dasatinib compared to imatinib in patients with newly diagnosed chronic-phase chronic myelogenous leukemia (CML-CP): results from the randomized phase 3 DASISION trial. *Hematologica*. 2010;95(S2):560.
18. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib demonstrates superior efficacy compared with imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase: results from the international randomized phase III ENESTND trial. *ASH Annual Meeting Abstracts*. 2009;114(22):LBA1.
19. Hochhaus A, Lobo C, Pasquini R, et al. Continued superiority of nilotinib vs imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd beyond 1 year. *Hematologica*. 2010;95(S2):1113.
20. Simonsson B, Gedde-Dahl, Markevärn M, et al. Major molecular response rate at one year is higher if pegylated interferon alpha-2b is added to imatinib in non-HR chronic myeloid leukemia patients in imatinib induced complete hematological remission. *Hematologica*. 2010;95(S2):1110.
21. Hehlmann R, Jung-Munkwitz S, Lauseker M, et al. Treatment optimization by high dose imatinib: Randomized comparison of imatinib 800 mg vs. Imatinib 400 mg vs. Imatinib 400 mg ifn in newly diagnosed bcr-abl positive chronic phase (cp) CML with regard to MMR at month 12. The German CML-study IV. *Hematologica*. 2010;95(S2):1111.
22. Guilhot F, Preudhomme C, Guilhot J, et al. Significant improvement of molecular responses with pegylated form of interferon  $\alpha$ 2a in combination with imatinib (IM) in chronic myeloid leukaemia (CML) patients (pts) report of a phase III trial. *Hematologica*. 2010;95(S2):1112.
23. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. January 21, 2010 2010;115(3):453-474.
24. Röllig C, Thiede C, Aulitzky W, et al. Long-term outcome of AML patients according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system in a cohort of 1507 patients. *Hematologica*. 2010;95(S2):546.

25. Candoni A, Martinelli G, Gherlinzoni F, et al. Low dose gemtuzumab ozogamicin plus fludarabine, cytarabine, idarubicin (GO-FLAI) as induction therapy in cd33-positive acute myeloid leukemia (AML) patients younger than 65 years. Interim results from a phase III multicenter prospective clinical trial (MYFLAI07-NCT.00909168). *Hematologica*. 2010;95(S2):548.
26. Giles F, O'Brien S, Cortes J, et al. Outcome of patients with acute myelogenous leukemia after second salvage therapy. *Cancer*. 2005;104(3):547-554.
27. O'Brien S, Rizzieri D, Vey N, et al. A phase II multicentre study with elacytarabine in late stage acute myeloid leukaemia. *Haematologica*. 2010;95(S2):549.
28. Latagliata R, Petti MC, Fenu S, et al. Therapy-related myelodysplastic syndrome-acute myelogenous leukemia in patients treated for acute promyelocytic leukemia: an emerging problem. *Blood*. February 1, 2002 2002;99(3):822-824.
29. Powell BL. Effect of consolidation with arsenic trioxide (AS<sub>2</sub>O<sub>3</sub>) on event-free survival (EFS) and overall survival (OS) among patients with newly diagnosed acute promyelocytic leukemia (APL): North American intergroup protocol C9710. *J Clin Oncol (Meeting Abstracts)*. 2007;25(18\_suppl):2.
30. Takeshita A, Yamakage N, Shinjo K, et al. CMC-544 (inotuzumab ozogamicin), an anti-CD22 immun-conjugate of calicheamicin, alters the levels of target molecules of malignant B-cells. *Leukemia*. 2009;23(7):1329-1336.
31. Estey EH, Thall PF, Giles FJ, et al. Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside. *Blood*. 2002;99(12):4343-4349.
32. Lo-Coco F, Cimino G, Breccia M, et al. Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood*. 2004;104(7):1995-1999.
33. Ravandi F, Cortes J, Faderl S, et al. Outcome of patients with newly diagnosed acute promyelocytic leukemia (APL) treated with the combination of all-trans retinoic acid (ATRA), arsenic trioxide (ATO), with or without gemtuzumab ozogamicin (GO). *Hematologica*. 2010;95(S2):545.
34. Palumbo A, Dimopoulos M, Delforge M, et al. A phase 3 study to determine the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients = 65 years with newly diagnosed multiple myeloma (NDMM). *Hematologica*. 2010;95(S2):566.
35. Attal M, Cristini C, Marit G, et al. Lenalidomide maintenance after transplantation for myeloma. *J Clin Oncol (Meeting Abstracts)*. 2010;28(15 suppl):8018.
36. McCarthy PL, Owzar K, Anderson KC, et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. *J Clin Oncol (Meeting Abstracts)*. 2010;28(15 suppl):8017.
37. Palumbo A, Bringhen S, Rossi D, et al. A prospective randomized trial of rtezomib-melphalan-prednisone-thalidomide followed by continuous bortezomib-thalidomide for initial therapy of multiple myeloma: effect of age and co-morbidities. *Hematologica*. 2010;95(S2):568.
38. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet*. 2006;367(9513):825-831.
39. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (ifm 99-06): a randomised trial. *Lancet*. 2007;370(9594):1209-1218.
40. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma [published online ahead of print May 2010]. *Blood*.
41. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 study. *J Clin Oncol*. 2010;28(19):3160-3166.
42. Waage A, Palumbo A, Hulin C, et al. MP versus MPT for previously untreated elderly patients with multiple myeloma: A meta analysis of survival of 1682 individual patient data from 6 randomized clinical trials. *Hematologica*. 2010;95(S2):567.
43. O'Connor OA, Stewart AK, Vallone M, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. *Clinical Cancer Research*. 2009;15(22):7085-7091.
44. Wang L, Siegel D, Kaufman JL, et al. Updated results of bortezomib-naive patients in PX-171-004, an ongoing open-label, phase ii study of single-agent carfilzomib (cfz) in patients with relapsed or refractory myeloma (MM). *ASH Annual Meeting Abstracts*. 2009;114(22):302.
45. Siegel D, Wang L, Orłowski RZ, et al. PX-171-004, an ongoing open-label, phase II study of single-agent carfilzomib (CFZ) in patients with relapsed or refractory myeloma (MM); updated results from the bortezomib-treated cohort. *ASH Annual Meeting Abstracts*. 2009;114(22):303.



46. Stewart K, Siegel D, Wang M, et al. Results of PX-171-004, an ongoing open-label, phase II study of carfilzomib in patients with relapsed and/or refractory multiple myeloma (R/R MM) with or without prior bortezomib exposure. *Hematologica*. 2010;95(S2):1099.
47. Aviles A, Nambo MJ, Neri N, Castaneda C, Cleto S, Huerta-Guzman J. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Med Oncol*. 2007;24(2):227-230.
48. McCloskey EV, Dunn JA, Kanis JA, MacLennan IC, Drayson MT. Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *Br J Haematol*. 2001;113(4):1035-1043.
49. Morgan G, Davies F, Gregory W, et al. Zoledronic acid (ZOL) prolongs time to first skeletal-related event (SRE) and survival versus clodronate in newly diagnosed multiple myeloma (MM): MRC myeloma IX trial results. *Hematologica*. 2010;95(S2):562.



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