

**Advances in the Management of Hematologic Malignancies:
Highlights from the 2010 American Society of Clinical
Oncology Annual Meeting**

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Table of Contents *(click the section you wish to view)*

| | |
|---|-----------|
| Introduction | 1 |
| Chronic Myeloid Leukemia (CML) | 1 |
| Follicular Lymphoma (FL) | 4 |
| Multiple Myeloma (MM) | 5 |
| Chronic Lymphocytic Leukemia (CLL) | 8 |
| Acute Myeloid Leukemia (AML) | 9 |
| Acute Lymphoblastic Leukemia (ALL) | 10 |
| Non-Hodgkin’s Lymphoma (NHL) | 10 |
| Hodgkin’s Lymphoma (HL) | 12 |
| References | 12 |
| Post-Test | 13 |
| Upcoming ECG Hematology Activities | 14 |

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ACKNOWLEDGEMENT

The editors wish to thank Jason Everly, PharmD, BCOP, a paid employee of ECG, for assistance in writing this document.

ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT

This activity is supported by educational grants from Allos Therapeutics, Inc., Bristol-Myers Squibb Company, Celgene Corporation, and Genentech BioOncology & Biogen Idec.

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Target Audience

The intended audience for this initiative is 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 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 parameters

Media: Newsletter

Estimated time to complete activity: 1.5 hours

Release date: July 8, 2010

Expiration date: July 7, 2011

This activity may be accessed at www.educationalconcepts.net

INTRODUCTION

The 46th Annual Meeting of the American Society of Clinical Oncology (ASCO) was held in Chicago, Illinois from June 4-8, 2010. The theme of the meeting was "Advancing Quality Through Innovation". This newsletter highlights pivotal data presented on chronic myeloid leukemia (CML), follicular lymphoma (FL), and multiple myeloma (MM). Additionally, data presented on chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), non-Hodgkin's (NHL), and Hodgkin's lymphoma (HL) are summarized.

CML

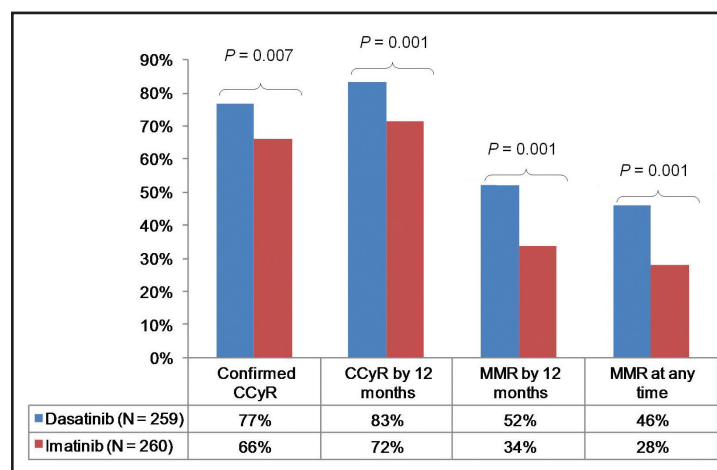
Dasatinib Induces Superior Responses Compared to Imatinib in Newly Diagnosed Patients

Dr Kantarjian, of The University of Texas, MD Anderson Cancer Center, Houston, Texas, presented the results of the dasatinib vs imatinib trial in treatment-naïve chronic phase CML patients (CP-CML) (DASISION, CA180-056).^{1,2} After a minimum follow-up of 12 months, the confirmed complete cytogenetic response (confirmed CCyR) rate was 77% for patients assigned dasatinib compared with 66% for imatinib ($P = 0.007$). The time to complete cytogenetic response (CCyR) was shorter for dasatinib patients than imatinib patients (HR 1.5, $P < 0.001$), with more than half of dasatinib patients (54%) achieving CCyR within 3 months. Dasatinib therapy was associated with a low rate of progression to accelerated phase (AP) or blast crisis (BC). The safety profiles of the 2 treatments were similar.

The DASISION trial was a phase III, multinational study that enrolled 519 patients with newly diagnosed CP-CML. Patients were randomly assigned to receive dasatinib 100 mg PO qday (N = 259) or imatinib 400 mg PO qday (N = 260). The primary endpoints were confirmed CCyR (CCyR detected in 2 consecutive assessments) and CCyR (no Philadelphia chromosome-positive [Ph⁺] metaphases in the bone marrow) by 12 months. Baseline demographic characteristics, disease characteristics, and risk stratification were well

balanced between the 2 treatment groups. Response rates are shown in **Figure 1**.

Figure 1. DASISION Response Rates



Importantly, responses were faster with dasatinib, with 54% at CCyR at 3 months and 73% at 6 months compared with 31% and 59% for imatinib. "With short follow-up, dasatinib therapy was associated with superior efficacy as measured by faster and higher rates of confirmed CCyR, CCyR, and molecular response rate (MMR)" Dr Kantarjian said adding "dasatinib may improve the long-term outcomes among patients with newly diagnosed CP-CML." Progression to AP/BC occurred in 5 patients who were receiving dasatinib (1.9%) and in 9 patients who were receiving imatinib (3.5%). Commonly reported adverse events (of all grades) with dasatinib and imatinib included superficial edema (9% and 36%), nausea (8% and 20%), rash (11% and 17%), and muscle inflammation (4% and 17%). Overall rates of fluid retention observed in the study were 19% with dasatinib and 42% with imatinib. Pleural effusions were seen only in the dasatinib arm (10%).

Results from this trial clearly demonstrate that dasatinib yields significantly higher and faster rates of CCyR and MMR vs the current standard of care, imatinib. Longer follow-up is needed to see if dasatinib therapy improves the long-term outcomes in patients with newly diagnosed CP-CML.

4-Year Data Confirm Efficacy of Dasatinib in Imatinib-Resistant or Imatinib-Intolerant CP-CML

Dr Shah, of the University of California, San Francisco, presented the 4-year follow-up results from a phase III randomized, open-label, dose-optimization study (CA180-034) of dasatinib in CP-CML patients resistant or intolerant to imatinib.³ Progression-free survival (PFS) and overall survival (OS) was 66% and 82%, respectively, at 48 months. The rate of transformation to AP/BC was 4% at 48 months. Additionally, achievement of CCyR at 6 and 12 months was predictive for superior PFS at 48 months.

The trial enrolled 670 heavily pre-treated patients with resistant (N = 497) or intolerant (N = 173) to imatinib who were randomized to 1 of 4 dasatinib treatment arms: 100 mg PO qday (N = 167), 50 mg PO BID (N = 168), 140 mg PO qday (N = 167), and 70 mg PO BID (N = 168). An earlier report showed that compared with 70 mg PO BID, 100 mg PO qday maintained efficacy while reducing toxicity.⁴ At 4 years, the OS was 82% (95% CI: 76%-88%) and PFS was 66% (95% CI: 57%-74%) confirming the efficacy of dasatinib 100 mg PO qday. However, efficacy outcomes were similar across arms at 4-year follow-up. Complete cytogenetic response to dasatinib at 6, 12 months predictive of 4-year PFS ($P < 0.001$, $P < 0.001$, respectively). Pleural effusion (all grades) occurred in 10% of patients by 12 months, 14% by 24 months, 6% between 24 and 36 months, and 3% between 36 and 48 months. Neutropenia and thrombocytopenia (grade 3/4) occurred primarily within the first 12 months of treatment (34% and 22% by 12 months, 1.2% and 0.6% between 12 and 24 months, 0.6% and 0.6% between 24 and 36 months, and 0% and 0.6% between 36 and 48 months, respectively).

Results from this trial demonstrate that the 100 mg qday dosing dasatinib offers the most favorable 4-year risk-benefit profile than other tested doses for CP-CML patients resistant or intolerant to imatinib.

Nilotinib Yields Superior 12-Month MMR Rates Compared to Imatinib in Newly Diagnosed CP-CML

Dr Larson, of the University of Chicago, Chicago, Illinois, presented the 18- and 24-month results from the trial evaluating the safety and efficacy of the selective oral BCR-ABL inhibitor nilotinib in newly diagnosed Ph+ CML (ENESTnd).⁵ Results from the primary analysis with median follow-up of 13.8 months were recently published in *The New England Journal of Medicine*.⁶ With longer follow-up, rates of MMR and CCyR remain superior for nilotinib vs imatinib. Molecular responses continue to improve over time with nilotinib and there are lower event rates (progression or death) with nilotinib vs imatinib. Overall survival rates remain similar. Grade 3/4 adverse events with nilotinib were similar to imatinib.

The ENESTnd trial was a phase III, randomized, open-label, multicenter study, that enrolled 846 patients with chronic-phase Ph+ CML in a 1:1:1 ratio to receive nilotinib (at a dose of either 300 mg or 400 mg PO BID) or imatinib (at a dose of 400 mg PO qday). The response to treatment is shown in **Table 1**.

Table 1. ENESTnd Response to Treatment

| Response | Nilotinib 300 mg PO BID (N = 282) | Nilotinib 400 mg PO BID (N = 282) | Imatinib 400 mg PO qday (N = 282) |
|---------------------|---|---|---|
| MMR | | | |
| 12 months (ITT) | 44%* | 43%* | 22% |
| 18 months (N = 525) | 69% | 63% | 36% |
| 24 months (N = 145) | 86% | 88% | 48% |
| CCyR | | | |
| 12 months (ITT) | 80%* | 78%† | 65% |
| 18 months (N = 442) | 99% | 99% | 89% |
| Overall (ITT) | 85%† | 82%‡ | 74% |

ITT, intent-to-treat.

* $P < 0.0001$ vs imatinib arm.

† $P < 0.001$ vs imatinib arm.

‡ $P = 0.017$ vs imatinib arm.

Both nilotinib and imatinib were well tolerated overall. Rates of discontinuation due to adverse events or laboratory abnormalities were 7% for nilotinib 300 mg BID, 12% for nilotinib 400 mg BID, and 9% for imatinib 400 mg qday. Gastrointestinal and fluid-retention events were more frequent among patients receiving imatinib, whereas dermatologic events and headache were more frequent in those receiving nilotinib. Discontinuations due to aminotransferase and bilirubin elevations were low in all 3 study groups. No sudden deaths occurred with either treatment.

Nilotinib appears more effective than imatinib in the front-line setting. Further follow-up is needed to assess the durability of responses, the development of treatment resistance, and the side-effect profile of nilotinib in the front-line setting. On June 17, 2010, the U.S. Food and Drug Administration approved nilotinib for the treatment of adult patients with newly diagnosed Ph+ CP-CML.

Bosutinib Active in Imatinib-Resistant or Imatinib-Intolerant CML

Dr Cortes, of The University of Texas, MD Anderson Cancer Center, Houston, Texas, reported the preliminary results of an open label phase I/II study that investigated the efficacy and safety of bosutinib, an orally bioavailable dual SRC/ABL tyrosine kinase inhibitor; not active against the T315I ABL mutation, in patients with CP-CML who failed treatment with imatinib.⁷ With a median follow-up of 23.8 months, the majority of patients had a response to bosutinib and response occurred regardless of imatinib resistance or intolerance. The median PFS and OS were not reached. Treatment was generally well tolerated with low incidence of hematologic toxicity with gastrointestinal toxicity and rash being the most frequent adverse events.

Data was presented on 299 patients, 72% of whom were imatinib-resistant and 28% were imatinib-intolerant. Patients had prior therapy with agents other than imatinib, including interferon and stem cell transplant. Bosutinib was administered orally at

a dose of 400, 500, or 600 mg/day. Of 109 patients evaluable for hematological response, 91% had a complete response (CR). Of 214 patients evaluable for cytogenetic response, 64% achieved a major cytogenetic response, 50% of which were complete. Among evaluable patients, 151 were analyzed for a molecular response. Of these, 32% achieved a MMR, and 52% of these had a complete molecular response. The best response to bosutinib in imatinib resistance or intolerance patients is shown in **Table 2**.

Table 2. Best Response to Bosutinib in Imatinib Resistance or Intolerance Patients

| Response | Imatinib Resistant | Imatinib Intolerant |
|--------------|--------------------|---------------------|
| Hematologic* | (N = 75) | (N = 34) |
| Overall | 92% | 97% |
| Complete | 88% | 97% |
| Cytogenetic | (N = 158) | (N = 56) |
| Major | 60% | 73% |
| Complete | 46% | 59% |
| Molecular | (N = 108) | (N = 43) |
| Major | 54% | 49% |
| Complete | 30% | 40% |

*Includes unconfirmed hematologic response.

Duration of major cytogenetic response was similar between imatinib-resistant and imatinib-intolerant patients. Additionally, median PFS or OS was not reached in either imatinib-resistant or imatinib-intolerant patients. Gastrointestinal symptoms were the most frequent nonhematologic adverse events. Thrombocytopenia was the most frequent grade 3/4 hematologic toxicity (24%). Treatment was associated with minimal fluid retention.

Early data indicate that bosutinib is more effective than imatinib in the front-line setting. Additional follow-up will provide information about the potential long-term benefits or disadvantages of bosutinib therapy. Moving forward, encouraging results with the dual

BCR-ABL and Src-family kinase inhibitors demonstrate that the CML treatment landscape is evolving rapidly. Studies will be necessary to evaluate the sequencing of treatment options and combinations of agents.

FL **Reduced Risk of Disease Progression With Front-Line Rituximab Maintenance**

Dr Salles, of the Université de Lyon, Lyon, France, presented the long-awaited results from the Primary Rituximab and Maintenance (PRIMA) study in newly diagnosed patients with advanced stage FL requiring therapy.⁸ At first interim analysis, results demonstrated a 2-year PFS advantage in patients who received rituximab (R)-maintenance therapy after induction immunochemotherapy (HR, 0.50; 95% CI, 0.39-0.64; $P < 0.001$).

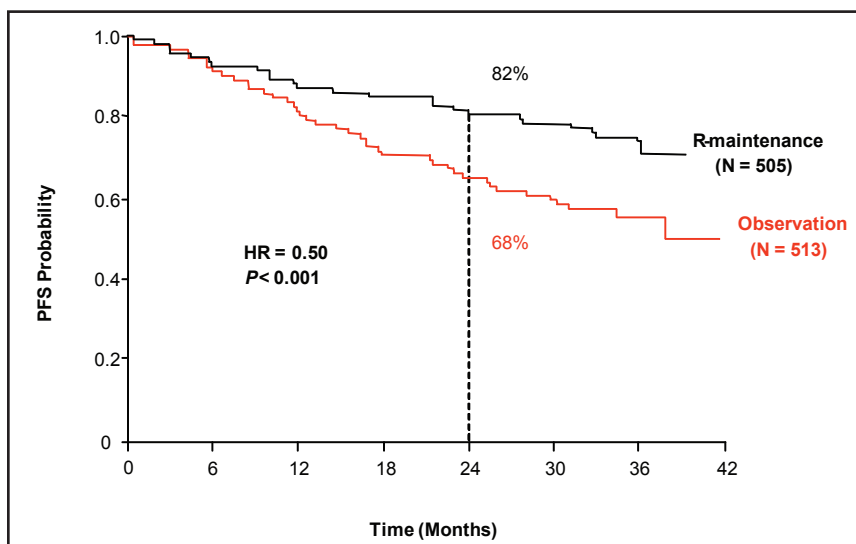
Sponsored by the Group d'Études de Lymphomes de l'Adulte (GELA) this international, multicenter, randomized, phase III trial enrolled 1,217 patients from December 2004 to April 2007. Primary endpoint of the study was an increase in median PFS by 45% in the R-maintenance arm of the study. Of the 1,207 evaluable patients, three-quarters underwent R-CHOP (rituximab plus cyclophosphamide, daunorubicin, vincristine, prednisone) induction therapy and 1,018

patients responded to treatment. Of those, 513 were randomly assigned to undergo observation and 505 were randomly assigned R-maintenance therapy (375 mg/m² IV rituximab every 8 weeks for 2 years). Progression-free survival is shown in **Figure 2**.

"Patients who received rituximab maintenance had a significantly reduced risk for tumor progression by 50%" Dr Salles said adding that R-maintenance "should be considered a new standard of care for FL patients in need of treatment." R-maintenance decreased the risk for starting a new anti-lymphoma treatment by 39% (HR, 0.61; $P < 0.0003$). Patients benefited from rituximab regardless of age, FLIPI score, type of induction therapy, or whether they had achieved a complete or partial response from induction therapy. R-maintenance therapy was well tolerated, and there was no impact on quality of life, Dr Salles reported. The most commonly reported adverse effects were infections (grade ≥ 2 ; 37% in the rituximab arm and 22% in the observation arm). Sixteen percent of patients in the observation arm reported grade 3/4 adverse events vs 22% in the rituximab arm.

Although a different R-maintenance administration schedule was used, results from the PRIMA study confirm the findings from the E1496 study,⁹ and it has now established the benefit of R-maintenance in patients with FL who were initially treated with rituximab in combination with chemotherapy.

Figure 2. PRIMA PFS



Rituximab Maintenance for Patients With Relapsed Disease After Autologous Transplant Reduces Risk of Disease Progression

Dr Pettengell, of St George's University of London, London, England, presented the results from the European Group for Blood and Marrow Transplantation study (EBMT-LYM-1), which examined the role of rituximab for in vivo purging and as maintenance after autologous stem cell transplant (ASCT).¹⁰ At 5 years, PFS was significantly higher for patients

receiving R-maintenance (59.4% vs 42.0%) resulting in 35% reduction in risk of next relapse (HR, 0.65; 95% CI, 0.46-0.90; $P = 0.01$). No difference was noted in OS for the patients receiving R-maintenance (HR, 0.88; 95% CI, 0.54-1.45; $P = 0.6$). The role of rituximab given prior to collecting cells for transplantation is much less certain.

From October 1999 to April 2006, 280 of a planned 420 rituximab-naïve patients with relapsed FL in first ($n = 16$), second ($n = 222$), or third remission ($n = 41$) who achieved either a complete remission ($n = 83$) or a very good partial remission ($n = 196$) to induction chemotherapy, with limited bone marrow infiltration ($< 25\%$ B-lymphocytes), underwent randomization (2 x 2 design) to rituximab in vivo purging (375 mg/m² IV weekly for 4 doses), and R-maintenance (375 mg/m² IV every 8 weeks for 2 years) after ASCT ($N = 69$), rituximab in vivo purging followed observation after ASCT ($N = 72$), R-maintenance after ASCT ($n = 69$), or observation alone ($n = 70$). The 5-year PFS rates by ITT analysis for in vivo purging vs none and R-maintenance vs none are shown in **Table 3**.

Table 3. EBMT-LYM-1 PFS by ITT

| | 5-year PFS by ITT | HR | 95% CI | P value |
|-----------------------------------|-------------------|------|-----------|---------|
| Rituximab in vivo purging vs none | 54.1% vs 48% | 0.81 | 0.58-1.13 | 0.20 |
| R-maintenance vs none | 59.4% vs 42% | 0.85 | 0.48-0.90 | 0.01 |

No difference in OS for the patients receiving R-maintenance (HR, 0.88; 95% CI, 0.54-1.45; $P = 0.6$) was observed. The 5-year PFS rates for the patient groups are as follows: rituximab in vivo purging and R-maintenance after ASCT; 62.8%, rituximab in vivo purging followed observation after ASCT; 55.0%, R-maintenance after ASCT; 48.0%, and observation; 37.6% (HR, 0.78; 95% CI, 0.68-0.93; $P = 0.004$). Although a significant finding was noted, the statistical methodology utilized is debatable and the result is much less supported by the data. Thus, uncertainty remains regarding the role of rituximab given prior to collecting cells for transplantation.

Rituximab maintenance after ASCT in rituximab-naïve FL patients in second or third remission improves PFS. Thus, the role of maintenance rituximab following autograft is strongly supported. Additional studies are needed to see if rituximab maintenance for longer than 2 years would produce better outcomes or more toxic effects.

MM **Lenalidomide Maintenance Following ASCT Prolongs TTP**

Dr McCarthy, of Roswell Park Cancer Institute in Buffalo, New York, presented the results of the phase III intergroup study of lenalidomide vs placebo maintenance therapy following single ASCT for MM (CALGB 100104).¹¹ Lenalidomide maintenance therapy following ASCT was associated with 58% reduction in progression or death vs placebo (HR, 0.42, 95% CI, 0.27-0.67, $P < 0.001$). Findings of this trial were consistent with interim results of the randomized IFM2005-2 trial.¹²

In the CALGB 100104 trial, 568 patients were enrolled from April 2005 to July 2009 from 46 centers. Patients with \geq stable disease ($N = 418$) were randomized double-blind at day 100-110 post-ASCT to lenalidomide (starting 10 mg PO qday with dose adjustments to 5-15 mg after 3 months) or placebo until disease progression, after stratification by diagnostic β -2 microglobulin. Drug was held for \geq grade 3 toxicity, restarted at resolution to \leq grade 2, and was de-escalated by 5 mg or maintained at 5, 10, or 15 mg/day as tolerated.

There was an estimated 58% lower chance of disease progression in the maintenance patients compared to the placebo patients. The OS rate is also higher among the lenalidomide patients, but the difference is not statistically significant and longer follow-up is needed. The independent Data and Safety Monitoring Committee report of a planned interim analysis in

November 2009 led to the announcement the study had met its primary endpoint and should be halted early and unblinded in December 2009. At that time the majority of placebo arm patients chose to switch to lenalidomide maintenance. The most common grade 3-5 adverse events experienced by patients receiving lenalidomide or placebo in the study were neutropenia (42% vs 7%), thrombocytopenia (12% vs 3%), and infections (7% vs 2%). There was no difference in the rate of grade 5 adverse events between the 2 arms of the study (2% vs 2%).

Rd Induction → MPR vs MEL200 → Lenalidomide Maintenance vs Observation: Updates From the Phase III Trial

Dr Palumbo, of the University of Torino, AOU San Giovanni Battista, Torino, Italy, presented results from a phase III study in which patients (< 65 years old) with MM received lenalidomide, melphalan, and prednisone (MPR) or melphalan plus ASCT (MEL200) following an induction treatment of lenalidomide plus low-dose dexamethasone (Rd).¹³ In the final phase of the trial, which is still ongoing, half of the patients will receive maintenance lenalidomide therapy. At a median follow-up of 14 months, 1-year PFS was 91% for both the MPR and MEL200 arms ($P = 0.77$). Additionally, 1-year OS for the MPR arm was 97% compared to 98% ($P = 0.27$) for the MEL200 arm.

A total of 402 patients received 4, 28-day cycles of Rd (lenalidomide 25 mg PO qday on days 1-21 and dexamethasone 40 mg PO qday days 1, 8, 15, and 22) as an induction therapy. Patients were then randomized to receive either 6, 28-day courses of MPR (melphalan 0.18 mg/kg and prednisone 2 mg/kg on days 1-4 and lenalidomide 10 mg PO qday on days 1-21) or tandem autologous stem cell transplant (MEL200). Upon completion of this regimen, patients were randomized to either continuous lenalidomide or no continuous therapy until relapse.

Following the Rd induction phase (N = 370), 6% of patients achieved a CR, 31% achieved a VGPR, and 49% achieved a PR. After randomization, 55% of those who

received at least 3 cycles of MPR (64/117) achieved at least a VGPR, with 13% (15/117) achieving a CR. Fifty-three percent of patients who received the first of the tandem autologous stem cell transplant (MEL200) (65/122) achieved at least a VGPR, with 16% (20/122) ($P = 0.82$) achieving a CR. With a relatively short follow-up of only 14 months, 91% of patients in both the MPR and MEL200 arms had not seen their disease progress ($P = 0.77$). Some 97% of patients in the MPR arm were still alive at 14 months, while 98% of patients in the MEL200 arm were still alive ($P = 0.27$).

“At present there is evidence that the MEL200 regimen seems to be better for high-risk patients” Dr Palumbo said adding “longer follow-up is needed to assess PFS and OS.” The most common grade 3 or 4 adverse events were neutropenia (Rd 9%, MPR 48%, MEL200 84%), thrombocytopenia (Rd 3%, MPR 8%, MEL200 84%), infection (Rd 5%, MPR 0%, MEL200 17%), and gastrointestinal events (Rd 0%, MPR 0%, MEL200 22%).

VMPT + VT Superior to VMP in Newly Diagnosed Elderly Patients

Dr Palumbo, of the University of Torino, AOU San Giovanni Battista, Torino, Italy, presented the results of the multicenter, open-label, nonrandomized, phase I/II trial, evaluating the 4-drug combination, bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by bortezomib and thalidomide (VT) maintenance compared to bortezomib, melphalan, and prednisone (VMP) in patients with relapsed/refractory myeloma. After a median follow-up of 26.5 months, response rates were superior with VMPT/VT compared to VMP in terms of PR or better and VMPT/VT was associated with higher rates of CR or VGPR. Additionally, the 3-year PFS was superior for the VMPT/VT arm compared to the VMP arm ($P = 0.006$).

Sponsored by the Gruppo Italiano Malattie Ematologiche Ddell'Adulto (GIMEMA) Italian Multiple Myeloma Network, the trial enrolled 511 patients, median age 66 years (range 38-79), with relapsed or refractory myeloma. Patients were randomized to receive either induction therapy of VMPT followed by

VT maintenance or VMP induction with no maintenance. Patients in the VMPT arm received 9, 6-week cycles of bortezomib at 1.3 mg/m² twice-weekly in cycles 1-4 and once-weekly in cycles 5-9, melphalan at 9 mg/m² daily, prednisone at 60 mg/m² on days 1-4, and thalidomide at 50 mg on days 1-42 followed by maintenance with bortezomib at 1.3 mg/m² on days 1 and 15 and thalidomide at 50 mg daily every 3 weeks. Patients in the VMP arm received the same doses and schedule for the first 9 cycles without maintenance. In March 2007, both VMPT and VMP schedules were changed to once-weekly bortezomib infusion. Best response to treatment is shown in **Table 4**.

Table 4. Best Response Rates to Treatment

| Response | VMP (N = 253) | VMPT → VT (N = 250) | P value |
|----------|------------------|------------------------|---------|
| CR | 24% | 38% | < 0.001 |
| ≥ VGPR | 50% | 59% | 0.03 |
| ≥ PR | 81% | 89% | 0.01 |

Sixty-nine percent of patients in the VMPT/VT arm did not need second-line therapy at 3 years vs 55% in the VMP arm ($P = 0.006$). “Based on the results of this trial, VMPT/VT should become the new standard of care for newly diagnosed elderly myeloma patients” Dr Palumbo said. Dr Palumbo also suggested that “the results of this trial indicate that weekly administration of bortezomib is superior to the drug’s standard dosing schedule, because weekly dosing seems to reduce the incidence of peripheral neuropathy.” Overall, VMPT resulted in a higher incidence of grade 3/4 neutropenia and cardiac complications. The incidence of grade 3/4 peripheral neuropathy was 8% in VMPT/VT and 5% in VMP ($P = 0.19$).

Better Disease Control With Before and After ASCT With Low-Dose Bortezomib, Thalidomide, Dexamethasone (vTD) in Newly Diagnosed Multiple Myeloma

Dr Moreau, of the Hôpital de Nantes, Nantes, France, presented the results of the IFM2007-2 randomized

trial that compared the efficacy and safety of standard-dose bortezomib and dexamethasone (VD) with vTD as induction therapy in newly diagnosed MM patients. Significantly higher rates of ≥ VGPR vTD combination were observed compared to VD induction and ASCT. Significantly lower incidence of grade ≥ 2 peripheral neuropathy was noted with vTD vs VD ($P = 0.03$). Fatigue, anemia, and gastrointestinal problems were the most common grade 3/4 adverse events with similar incidence between treatment arms.

The trial enrolled 199 newly diagnosed patients; 100 received 4, 21-day cycles vTD (bortezomib 1 mg/m² on days 1, 4, 8, 11, thalidomide 100 mg PO days 1-21, and dexamethasone 40 mg PO on days 1-4 and 8-11) and 99 received 4 cycles VD (bortezomib 1.3 mg/m² on days 1, 4, 8, 11, and dexamethasone 40 mg PO on days 1-4 and 8-11). The 2 groups were well balanced in regards to initial prognostic parameters. On an ITT basis, the results are shown in **Table 5**.

Table 5. Response Rates to VD vs vTD

| | VD (N = 99) | vTD (N = 100) |
|-------------------------|----------------|------------------|
| Response after 2 cycles | | |
| CR | 6% | 4% |
| CR + nCR | 16% | 15% |
| ≥ VGPR | 20% | 22% |
| ≥ PR* | 78% | 90% |
| Response after 4 cycles | | |
| CR | 12% | 13% |
| CR + nCR | 22% | 32% |
| ≥ VGPR* | 35% | 51% |
| ≥ PR | 81% | 90% |
| Response after ASCT | | |
| CR | 33% | 30% |
| CR + nCR | 54% | 61% |
| ≥ VGPR* | 59% | 73% |
| ≥ PR | 84% | 90% |

*Statistically significant at an alpha level of 0.05.

Priming with granulocyte colony-stimulating factor alone for stem collection failed and cyclophosphamide mobilization required more frequently with vTD vs VD (21% vs 6%, $P = 0.003$). Additionally, the stem cell collection failure rate was 1% with VD vs 2% with vTD. There was no difference regarding toxicity between the 2 arms of the study, except for peripheral neuropathy. Grade > 2 peripheral neuropathy occurred in 28% of the cases in the VD arm vs 18% in vTD ($P = 0.03$), and treatment was interrupted due to peripheral neuropathy in 4 cases of the VD arm vs 0 in the vTD arm ($P = 0.12$).

Bortezomib, Lenalidomide, and Dexamethasone Combination Therapy Highly Active in Newly Diagnosed Patients

Dr Richardson, of the Harvard Medical School, Boston, Massachusetts, presented the longer follow-up results of a prospective, multicenter phase I/II trial of bortezomib, lenalidomide, and dexamethasone (VRD) combination therapy for newly diagnosed myeloma patients.¹⁴ Results demonstrate that all patients achieved PR or better with high rates of CR, near CR (nCR), or VGPR. The estimated 2-year OS rate (with option for autologous stem cell transplantation [ASCT] if in PR after 4 cycles) was 95%. VRD related toxicities were mostly low grade and manageable with only 1 patient experiencing a grade 3 sensory peripheral neuropathy. Phase III trials are ongoing.

Sixty-six patients were enrolled in the trial and received 24 weeks of the VRD regimen (lenalidomide 15-25 mg PO on days 1-14, bortezomib 1.0-1.3 mg/m² IV on days 1, 4, 8, 11, and dexamethasone 40 mg PO during cycles 1-4 and 20 mg PO during cycles 5-8 on days 1, 2, 4, 5, 8, 9, 11, 12). Importantly, 91% of patients had International Staging System (ISS) stage I/II disease and del 13q as the most frequently observed chromosomal abnormality. After the initial therapy, patients who responded to treatment could receive an autologous stem cell transplant or maintenance therapy. Best response to VRD is shown in **Table 6**.

Table 6. Best Response to VRD

| Response | All Patients (N = 66), % (90% CI) | Phase II Patients (N = 35), % (90% CI) |
|-----------------|-----------------------------------|--|
| CR + nCR | 39 (29-50) | 57 (42-71) |
| CR + nCR + VGPR | 67 (56-76) | 74 (59-86) |
| At least PR | 100 (96-100) | 100 (92-100) |

Responses improved in 75% of patients from cycle 4-8 and in 53% of patients during maintenance. Median time to best overall response (OR) was 2.1 months. The estimated 2-year PFS and OS with VRD ± ASCT were 68% and 95%, respectively. The 24-month PFS rate significantly higher with baseline ISS stage I vs II/III disease ($P = 0.02$). Of particular interest, in post hoc analysis of 53 patients without progression at short follow-up (1-year), PFS was similar with vs without ASCT ($P = 0.84$). The most frequent grade 3/4 adverse events were neutropenia (14%) and lymphopenia (14%). One patient experienced grade 3 sensory peripheral neuropathy, 6% of patients experienced deep vein thrombosis or pulmonary embolism, and there were no treatment-related deaths.

CLL

Front-Line Lenalidomide Monotherapy Effective in Elderly Patients With CLL

Dr Badoux, of The University of Texas, MD Anderson Cancer Center, Houston, Texas, presented the results of an investigator-initiated phase II study of lenalidomide as front-line monotherapy in elderly patients with CLL.¹⁵ With a median follow-up of 23 months, the OR rate was 62%, and 15% of patients achieved a CR. Data suggests that the quality of response improves with time. The estimated 2-year OS and PFS rates were 90% and 60%, respectively.

A total of 60 patients (≥ 65 years old) with untreated CLL and had indications for therapy were enrolled and received 5 mg/day of lenalidomide for the first 56 days of treatment and then titrated up to 25 mg/day

by 5 mg increments for days 1-21 of each cycle (28 days) as tolerated. Median age was 71 years (range, 66-85). Eighteen patients had Rai stage III-IV disease, 20 patients had deletion of 17p or 11q by FISH analysis, and 33 of 55 patients had unmutated IgVH genes. The OR rate for all patients was 62%. Nine patients (15%) achieved a CR, 3 (5%) a nodular partial response (nPR), and 25 (42%) PR. A rise in median IgG levels from 724 mg/dL at baseline to 941 mg/dL after 15 cycles of therapy ($P < 0.001$) was also observed. The most common grade 3/4 adverse events reported in the study were neutropenia (38% of cycles), thrombocytopenia (14% of cycles), and anemia (< 1% of cycles). There were no grade 3/4 tumor lysis or tumor flare reactions whereas 30 patients experienced grade 1/2 tumor flare. Grade 3/4 infections were observed in 15% of patients.

This encouraging data suggests that lenalidomide monotherapy offers a reasonable risk-benefit profile in elderly patients with CLL. Further studies are ongoing to evaluate the activity of lenalidomide alone or in combination with chemotherapy in this setting. Moving forward, further correlative studies are needed to further clarify the impact of lenalidomide-induced immunomodulation in CLL.

AML
EFS in Patients (> 60 Years Old) in CR1 is Highly Dependent Upon FLT3 and NPM1 Status

Dr Niederwieser, of the University of Leipzig, Leipzig, Germany, presented the results of a study on behalf of the East German Study Group for Hematology and Oncology examining the influence of FLT3 and NPM1 mutations on outcome of elderly pts (> 60 years old) and to further evaluate outcomes following chemotherapy or stem cell transplantation.¹⁶ Results indicate that FLT3 and NPM1 status does not influence OS of AML patients > 60 years old. However, the event-free survival (EFS) of patients in CR1 is highly dependent upon mutation status and is increased

by allogeneic stem cell transplant (aSCT) rather than chemotherapy by reducing relapse incidence.

Of the 498 patients who were enrolled in the trial, 357 were evaluable and 53% achieved a CR after induction therapy. FLT3-ITD and NPM1 status was available in 158 patients of whom 97 were in CR1 (75 patients with FLT3wt and 22 with FLT3-ITD). Overall survival of the 158 patients was 33% at 2 years. Mutation status did not significantly influence OS, but did influence the EFS of patients. Patients with FLT3wt (N = 75) and NPM1mut/FLT3wt (N = 33) had better EFS than the rest post-induction therapy. The EFS at 2 years stratified by mutation status for the 97 patients in CR1 after induction therapy are shown in **Table 7**. Additionally the effect of aSCT or chemotherapy on outcomes is shown.

Table 7. EFS at 2 Years Stratified by Mutation Status

| Mutation Status | 2-year EFS | P value |
|------------------------------------|------------|---------|
| After Induction Therapy | | |
| FLT3-ITD vs FLT3wt | 27% vs 51% | < 0.01 |
| NPM1mut/FLT3wt vs NPM1mut/FLT3-ITD | 69% vs 34% | 0.01 |
| FLT3-ITD vs FLT3wt | | |
| Post aSCT | 59% vs 43% | 0.04 |
| Post chemotherapy | 40% vs 15% | |
| NPM1mut/FLT3wt vs NPM1mut/FLT3-ITD | | |
| Post aSCT | 62% vs 74% | 0.01 |
| Post chemotherapy | 51% vs 11% | |

Although limited by a small sample size, this data suggests a subgroup of elderly AML patients who achieve a CR following induction therapy and are NPM1mut / FLT3wt will have more favorable outcomes. Conversely, the subgroup of patients who achieve a CR following induction therapy and are NPM1mut / FLT3-ITD receive “less aggressive” therapy, do poorly and represent a subgroup that should be targeted for new therapeutic trials.

ALL **Vincristine Sulfate Liposomes Are Effective Treatment for Relapsed/Refractory Adult ALL Patients With Limited Treatment Options**

Dr O'Brien, of The University of Texas, MD Anderson Cancer Center, Houston, Texas, presented the results of the phase II open-label, multicenter study that evaluated the safety and efficacy of weekly doses of vincristine sulfate liposomes injection (VSLI) in adult patients with Philadelphia chromosome-negative (Ph-) ALL in second relapse or who failed 2 lines of chemotherapy (RALLY trial).¹⁷ Results demonstrate a 35% OR rate, with 13 of 65 subjects (20%) experiencing a CR. The median OS was 4.6 months and treatment-associated toxicities were predictable and manageable.

The trial enrolled 65 heavily pretreated patients who received VSLI 2.25 mg/m² with no dose cap (highest dose delivered was 5.5 mg) IV weekly over 1 hour. Median age was 32 years old, 43% had prior stem cell transplantation, 20% had extramedullary disease, 100% had prior vincristine exposure, and 82% had prior neuropathy. The response rate was 35%, with 12 CR/CRi (CRs with incomplete neutrophil or platelet recovery), 6 bone marrow blast responses, and 9 partial remissions. Median CR/CRi duration was 5.3 months (range, 0.3-6.5). Ten responders received subsequent stem cell transplant. Median OS was 4.6 months for the entire population. Median OS in complete responders was 7.4 months, with 5 patients having an OS > 1 year. The most common related adverse events of grade ≥ 3 were febrile neutropenia (32%), neuropathy (22%), diarrhea (5%), and constipation (2%), which is similar to standard vincristine sulfate.

Results from this trial demonstrate preliminary evidence of anti-leukemic activity of VSLI in an advanced, heavily pre-treated, adult ALL population. Further studies are ongoing.

Outcome With Hyper-CVAD and Imatinib Remains Superior to Hyper-CVAD Alone

Dr Thomas, of The University of Texas, MD Anderson Cancer Center, Houston, Texas, presented the long-term outcomes associated with hyper-CVAD (fractionated cyclophosphamide, vincristine [VCR], doxorubicin, dexamethasone alternating with methotrexate and cytarabine) and imatinib therapy for de novo or minimally treated Ph+ ALL.¹⁸ Results continue to demonstrate that outcome with hyper-CVAD and imatinib remains favorable compared with hyper-CVAD alone; 3-yr CR duration and OS rates were 68% vs 24% and 54% vs 15%, respectively, ($P < 0.001$).

From 2001-2006, 45 patients with imatinib naïve de novo or minimally treated Ph+ ALL were treated with hyper-CVAD¹⁹ and imatinib (600 mg PO on days 1-14 of induction, 600 mg PO continuous courses 2-8, 800 mg PO during 24 months of maintenance therapy with monthly vincristine-prednisone interrupted by 2 intensifications [hyper-CVAD and imatinib], then imatinib indefinitely). With a median follow-up of 77 months, the CR rate was 93% and the molecular CR rate prior to aSCT was 52%. The 3-year OS in de novo patients ≤ 40 years old and ≤ 60 years old was superior for patients who had undergone aSCT vs no aSCT (90% vs 33%, $P = 0.05$; 77% vs 57%, $P = 0.01$, respectively). Additionally, the 3-yr CR duration rate was 76% for patients who achieved a molecular CR prior to aSCT vs 63% who did not ($P = 0.2$). Neither CD20 expression nor additional chromosomal aberrancies influenced outcome. Dr Thomas concluded that recent data favors aSCT in first CR, particularly in younger patients, and that second or later-generation tyrosine kinase inhibitors may further improve outcome.

NHL **Diffuse Large B-Cell Lymphoma**

Preliminary results suggest that rituximab plus gemcitabine and oxaliplatin (R-GemOx) is an active salvage regimen for relapsed/refractory diffuse large

B-cell lymphoma (DLBCL) patients not candidates for high-dose therapy.²⁰ Dr Haioun, of the Hôpital Henri Mondor, Créteil, France, presented results from the phase II trial that was designed to evaluate the efficacy of R-GemOx as salvage therapy for relapsed/refractory DLBCL patients too frail or unable to receive high-dose chemotherapy. Results demonstrate that salvage therapy R-GemOx has a favorable safety profile and produced a high objective response rate (ORR) (60%) in patients with relapsed/refractory DLBCL who were not candidates for high-dose therapy. Patients who relapsed < 1 year (from last treatment) and had previous rituximab treatment had the lowest probability of response to R-GemOx salvage therapy.

Sponsored by GELA, the trial enrolled 49 patients. R-GemOx consisted of 8 cycles every 2 weeks of rituximab 375 mg/m² IV on day 1 followed by gemcitabine 1000 mg/m² IV and oxaliplatin 100 mg/m² IV (over 2 hours after gemcitabine) on day 2. Patients were evaluated after 4 cycles of induction for response. If patients achieved PR or better, then they started consolidation therapy for an additional 4 cycles. The median duration between last treatment and R-GemOx was 14 months and 14% of patients received R-GemOx within 1 year of last treatment.

The 3-year PFS and OS rates were 20.1 and 28.1 months, respectively. Patients receiving rituximab prior to R-GemOx had shorter PFS compared with patients not exposed to rituximab (4.2 vs 11.4 months, respectively; $P = 0.028$). Patients whose delay between last treatment and R-GemOx < 1 year had shorter PFS than those whose delay was ≥ 1 year (3 vs 10 months, respectively; $P = 0.016$). Shortest PFS was seen in patients with previous rituximab exposure and early relapse requiring salvage therapy within 1 year ($P < 0.001$). Neutropenia was the most common toxicity, but the incidence of febrile neutropenia was rare (< 5%). No life-threatening liver, neurologic, or kidney toxicities were observed.

Primary Central Nervous System Lymphoma

Previously, the standard treatment for primary central nervous system lymphoma (PCNSL) has included high-dose methotrexate (HDMTX) followed by whole-brain radiotherapy (WBRT); usually to doses of 45Gy. However, due to the concern of side effects of WBRT (mainly long-term neurotoxicity), its role has been controversial in the existing literature. Dr Thiel, of the Department of Hematology, Charite Campus Benjamin Franklin, Berlin, Germany, presented the results from the G-PCNSL-SG1 non-inferiority trial, which investigated the role of WBRT in patients with PCNSL who have received primary therapy with HDMTX.²¹ Results indicated that the exclusion of WBRT following HDMTX for newly diagnosed patients with PCNSL does not impact OS. However, WBRT was associated with prolonged PFS duration in the ITT population and CR subgroup analyses.

From May 2000 to May 2009, 551 immunocompetent patients were enrolled and randomized to chemotherapy followed by WBRT (arms A1, B1) or chemotherapy alone (A2, B2). Patients achieving a CR received either consolidating WBRT with 45 Gy in 1.5 Gy fractions (arm A1) or no further treatment (A2). Patients without CR received salvage WBRT (B1) or salvage chemotherapy using HD-cytarabine (B2) (4 x 3 g/m²/48 h, x 3 weeks). After randomization, 526 received at least 1 of a planned 6 cycles HDMTX (4 g/m² on day 1, biweekly) and HDMTX plus ifosfamide (1.5 g/m² on days 3-5, biweekly) thereafter. Of those, 66 died on HDMTX, 49 dropped out, 411 entered the post-HDMTX phase (ITT population), and 318 were treated per protocol (PP population). The median OS was 32.4 months in the chemotherapy + WBRT arm (A1 + B1, n = 154) and 37.1 months in the chemotherapy alone arm (A2 + B2, n = 164) ($P = 0.70$). Median PFS was 18.3 and 12 months ($P = 0.13$) for the WBRT group vs the no WBRT group, respectively.

For the ITT population, OS was not statistically different between the 2 groups. The median PFS was 15.5 months in the chemotherapy + WBRT arm and 9.9 months in the chemotherapy alone arm ($P = 0.041$). Late neurotoxicity was examined in PP patients with CR by χ^2 analysis. On clinical evaluation, neurotoxicity was seen in 48.9% of patients in the WBRT arm vs 26% in the no WBRT arm. On neuroradiologic evaluation, neurotoxicity was seen in 72.5% of patients in the WBRT arm vs 41.7% in the non-WBRT arm. Thus, WBRT consolidation following HDMTX was associated with higher incidence of late neurotoxicity than HDMTX alone.

Although no significant difference was seen for OS when WBRT was omitted from HDMTX-based chemotherapy, these results should be interpreted cautiously based on the following study limitations: poor results in terms of response to chemotherapy compared to previously published data for PCNSL, small sample size for a non-inferiority study, and patients with CR or non-CR were equally likely to receive radiation suggesting that response to chemotherapy was not taken into consideration for treatment decisions. For these reasons, these data can only be hypothesis generating at this time and need to be confirmed in future prospective trials.

HL New Agent Show Promising Antitumor Activity for the Treatment of Hodgkin Lymphoma

Dr Sureda, of the Hospital de la Santa Creu, Barcelona, Spain, presented results from an ongoing large phase II study of the potent pandecetylase inhibitor, panobinostat (LBH589) in patients with relapsed/refractory HL after ASCT.²² Panobinostat monotherapy demonstrated durable antitumor activity in heavily pretreated patients (disease control rate, 86%; tumor reduction rate, 71%; and ORR, 26%). Estimated median duration of response was 7.2 months. The most common treatment-related adverse event was reversible thrombocytopenia.

Despite the relative rarity of the patient population, 129 patients from 45 sites in 13 countries were enrolled within 12 months. The median age of patients was 32 years, 66% were male, 96% had nodular sclerosing or mixed cellularity histologic subtype, 90% had an Eastern Cooperative Oncology Group status of 0-1. Importantly, 37% had no response on last therapy and 80% had a prior autologous stem cell transplant. Oral panobinostat was administered at a dose of 40 mg 3 times per week in 21-day cycles. Dose interruptions or modifications were permitted for management of toxicities. Response to panobinostat is shown in **Table 8**.

Table 8. Response to Panobinostat

| Response | N = 129 |
|---------------------------------------|----------|
| ORR (CR + PR), n (%) | 33 (26) |
| Disease control (CR + PR + SD), n (%) | 111 (86) |
| Median TTR, wks (range) | 7 (4-51) |
| Median DOR (by Kaplan-Meier), months | 7.2 |
| Median PFS (by Kaplan-Meier), months | 5.9 |

Common grade 1 and 2 toxicity included diarrhea, nausea, fatigue, anemia, and vomiting. The most common grade 3 and 4 toxicity was reversible thrombocytopenia (77.5%). The final analysis of this study is expected to be available by the end of this year. Panobinostat-based combination clinical trials are currently enrolling patients with relapsed HL.

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