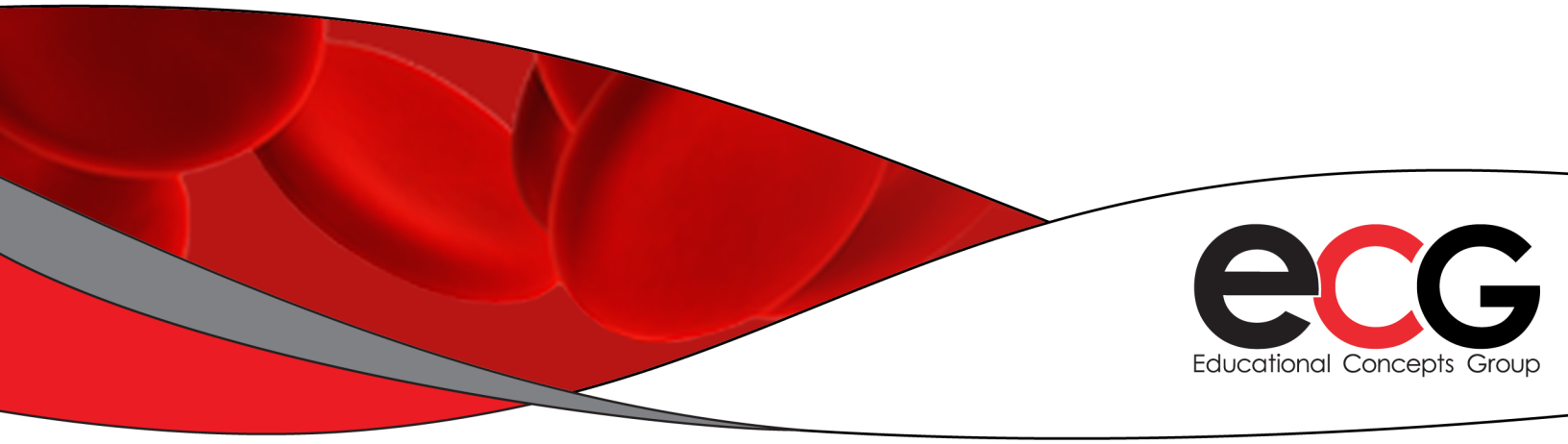

Advances in the Management of Hematologic Malignancies: Highlights from the 2013 ASCO Annual Meeting

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INTRODUCTION
The 2013 American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago, Illinois, provided a comprehensive review of key experimental and clinical data presented at the conference. Included in this newsletter are highlights from the conference covering major plenary sessions, oral sessions, and select poster presentations resulting in a detailed summary of current and developing therapy options in hematologic malignancies.

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TARGET AUDIENCE
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EDUCATIONAL OBJECTIVES
At the conclusion of this activity, participants should be 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

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INTRODUCTION

"Building Bridges to Conquer Cancer" was the theme at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting, held in Chicago, Illinois. This conference provided the largest international multidisciplinary forum for cutting-edge cancer research and sought to facilitate diffusion of the latest hematologic research. Clinicians from around the world gathered to hear the most up-to-date advances in cancer research in an effort to improve the lives of cancer patients, both in terms of quality and quantity. Further optimization of current treatments and the development of important novel therapies continued to be intense areas of investigation. Data from notable ASCO presentations on hematological malignancies are highlighted in this newsletter.

MULTIPLE MYELOMA

The introduction of new therapeutic agents over the past decade has improved responses and prolonged survival in patients with multiple myeloma (MM); however, nearly all MM patients eventually relapse. A number of promising clinical trials designed to further optimize frontline therapy for newly diagnosed MM patients or develop novel treatment strategies for relapsed/refractory disease were presented at ASCO 2013.

Newly Diagnosed

MPR vs MEL200 ASCT Followed by Lenalidomide vs Observation

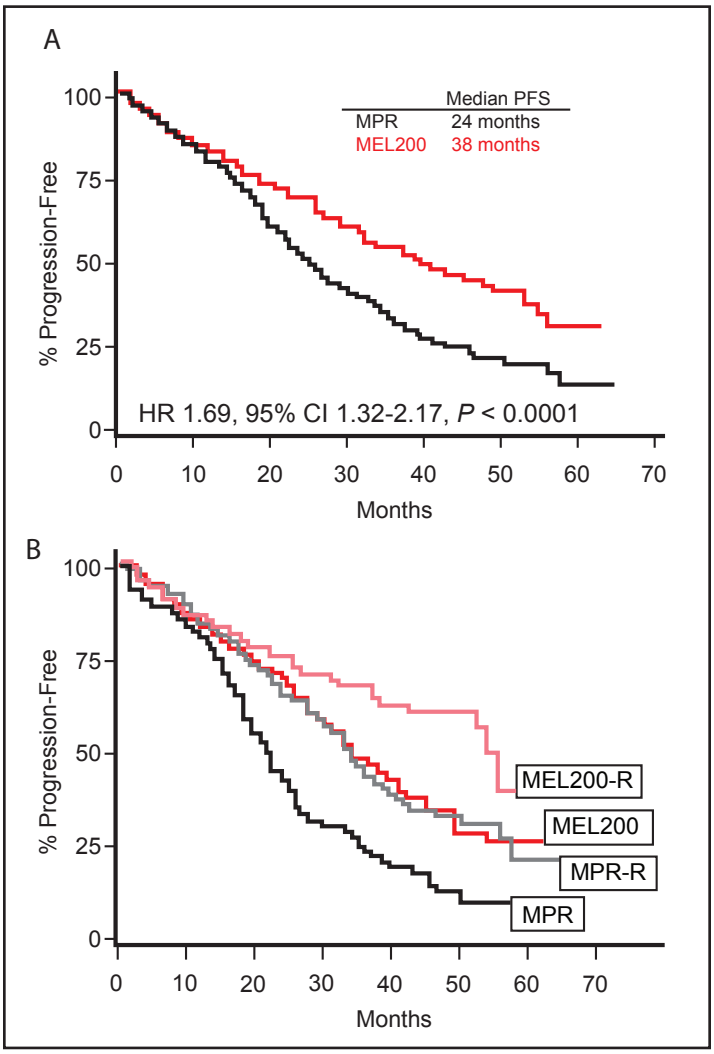
Autologous stem cell transplant (ASCT) clearly has a positive impact on MM patient survival. However, with the proven efficacy of novel anti-myeloma agents such as the immunomodulatory agents, lenalidomide, thalidomide and pomalidomide, and proteasome inhibitors, bortezomib and carfilzomib, the optimal timing of transplant remains an active area of discussion and examination. Therefore, Boccadoro and colleagues designed a phase III trial of newly diagnosed MM patients 65 years or younger, comparing melphalan, prednisone, and lenalidomide (MPR) to high-dose melphalan conditioned ASCT (MEL200).[1]

The study included 402 patients (≤ 65 years) from 62 healthcare centers. All patients received 4, 28-day courses of lenalidomide (25 mg/day) and dexamethasone (40 mg/day) (Rd) upfront. Patients were then randomized to MPR (melphalan, 0.18 mg/kg/day, days 1-4; prednisone, 2 mg/kg/day, days 1-4; lenalidomide, 10 mg/day, days 1-21) or MEL200 (200 mg/m^2 on day -2 followed by stem cell support on day 0). Patients received 6 cycles of MPR (28-day courses) or tandem MEL200. Patients from each arm underwent a second randomization to lenalidomide maintenance (10 mg/day, days 1-21) or placebo. The median age on each arm was 58 years, and 23% of patients on the MPR arm, and 24% on the MEL200 arm had ISS stage III disease status.

With a median follow-up of 49 months, progression free survival (PFS) was significantly longer with MEL200 (n = 200; PFS, 38 months) compared to MPR (n = 202; PFS, 24 months) (**Figure 1A**). There was no significant difference in overall survival (OS) with 5-year OS rates of 71% vs 62% for MEL200 and MPR treatment arms, respectively.

In maintenance, there was no difference in response rates between lenalidomide and placebo. However, with a median follow-up of 32 months from the start of maintenance, median PFS was significantly longer with lenalidomide maintenance (37 months with lenalidomide maintenance vs 26 months with no maintenance, HR = 0.50; $P < 0.0001$). The benefit with lenalidomide was found regardless of age (> 60 vs ≤ 60 years), complete response (CR, yes vs no), or high-risk cytogenetics (yes vs no of t[4;14], t[14;16], and del 17p). Moreover, 5-year OS was significantly longer with lenalidomide (75% lenalidomide vs 58% placebo, HR = 0.62, $P = 0.02$). When all arms were analyzed, those receiving MEL200 and maintenance lenalidomide had the best outcomes (**Figure 1B**).

Figure 1. Progression-free survival of newly diagnosed MM patients treated with lenalidomide/dexamethasone induction followed by (A) MPR or MEL200 (B) with or without lenalidomide maintenance.



MM, multiple myeloma; MPR, melphalan, prednisone, lenalidomide; MEL200, high-dose melphalan conditioned autologous stem cell transplant; MPR-R, MPR followed by lenalidomide maintenance; MEL200-R, MEL200 followed by lenalidomide maintenance.

The most common adverse event (AE) associated with maintenance therapy was neutropenia. Anemia, thrombocytopenia, infections, and cutaneous toxicities were also observed. Grade 3/4 deep vein thrombosis (DVT) occurred in 2% of patients and 4% of patients developed second primary malignancies (SPM).

Overall, this study demonstrated that early transplant significantly prolonged PFS compared to MPR; however, no difference in OS has been detected. Moreover, lenalidomide maintenance significantly reduced the risk of progression independently from the previous treatment and the OS at 60 months was significantly increased in patients receiving lenalidomide.

Relapsed/Refractory

Pomalidomide Plus Low-Dose Dexamethasone vs High-Dose Dexamethasone in MM

Patients who have exhausted treatment options with bortezomib and lenalidomide or thalidomide have a poor prognosis. Pomalidomide is a third generation immunomodulatory agent, and, when combined with dexamethasone, has high activity in MM patients after multiple lines of therapy.[2,3,4,5] In February 2013, pomalidomide was Food and Drug Administration (FDA) approved for the treatment of MM patients who have received at least 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.[6] Results from a phase III study comparing pomalidomide with low-dose dexamethasone to high-dose dexamethasone were presented by Dr Weisel on behalf of Dr San-Miguel and colleagues.[7]

This phase III, multicenter, randomized, open-label study included 455 patients who had failed lenalidomide and bortezomib after at least 2 consecutive cycles of each (alone or in combination) and were refractory to their last prior therapy. Patients were randomized (2:1) to receive pomalidomide (4 mg/day, days 1-21 of a 28-day cycle) plus dexamethasone (40 mg/day, days 1, 8, 15, and 22) or high-dose dexamethasone (40 mg, days 1-4, 9-12, and 17-20). Patients over the age of 75 years were given half the dose of dexamethasone (20 mg) in both arms of the study. The therapy continued until disease progression or unacceptable toxicity. Patients who progressed on high-dose dexamethasone were eligible to enter a companion trial where they were eligible to receive pomalidomide treatment. The primary endpoint

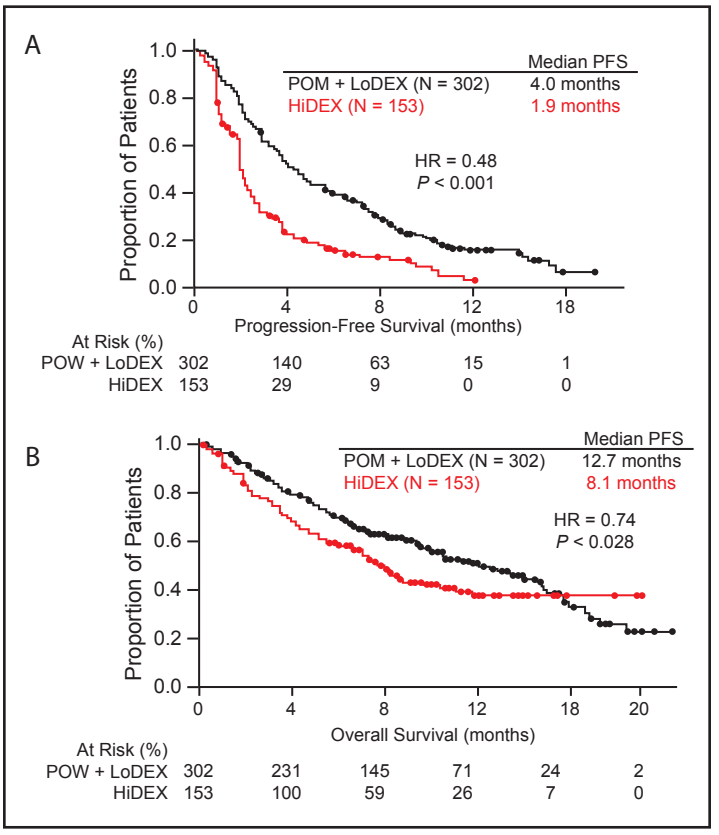
of the study was PFS, and secondary endpoints included OS, overall response rate (ORR; ≥ partial response [PR]), duration of response (DOR), and safety.

Study arms were well matched for age (median 64 and 65 years), median time from initial diagnosis (5.3 and 6.1 years), ECOG status, international staging system (ISS) disease status, and the proportion of patients with compromised renal function. Patients had received a median of 5 prior therapies (2-17), and 75% of patients had been given treatment with lenalidomide, bortezomib, and an alkylating agent.

A planned interim analysis found that with a median follow-up of 4 months, pomalidomide plus low-dose dexamethasone significantly extended median PFS (3.6 vs 1.8 months, HR = 0.45, $P < 0.001$). Median OS was not reached for pomalidomide/dexamethasone compared to 7.8 months for high-dose dexamethasone (HR = 0.53, $P < 0.001$). The OS benefit was observed despite 29% of high-dose dexamethasone patients receiving therapy after progression. The trial met the primary endpoint of PFS, crossed the upper O'Brien-Flemming superiority boundary for OS, and the Data Monitoring Committee recommended crossover from high-dose dexamethasone to pomalidomide with or without dexamethasone independent of disease progression.

The ORR was higher in patients who had received pomalidomide plus low-dose dexamethasone (31% vs 10%, $P < 0.001$). The response achieved was independent of the type of drug the patient was refractory to or prior treatment. With a median follow-up of 10 months, median PFS was significantly longer with pomalidomide and dexamethasone (PFS, 4.0 vs 1.9 months; HR = 0.48; $P < 0.001$) (**Figure 2A**). Despite 50% of patients crossing over on the study and all patients on the control receiving salvage pomalidomide, median OS was significantly longer with pomalidomide (12.7 months vs 8.1 months; $P < 0.028$) (**Figure 2B**). This OS benefit extended to all subgroups analyzed.

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) in relapsed/refractory MM patients treated with pomalidomide plus low-dose dexamethasone (POM + LoDEX) or high-dose dexamethasone (HiDEX).



Hematologic toxicity was common with 48% of patients having grade 3/4 neutropenia and 9% of patients experiencing febrile neutropenia. Grade 3/4 anemia (33%) and thrombocytopenia (22%) were also common. Grade 3/4 infections occurred in 30% of patients. Other less common grade 3/4 AEs included bone pain (7%), fatigue (5%), asthenia (4%), and glucose intolerance (3%). One percent of patients developed grade 3/4 DVT/pulmonary embolism (PE) or peripheral neuropathy (PN). Discontinuations due to AEs occurred in 9% of patients on the pomalidomide/dexamethasone arm and 10% of patients on high-dose dexamethasone.

In conclusion, this updated analysis reconfirms that pomalidomide with the low-dose dexamethasone regimen significantly improved PFS over high-dose dexamethasone. Moreover, OS was significantly prolonged with pomalidomide, despite 50% of patients crossing over.

Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone

Proteasome-mediated protein degradation is critical to cell function and survival. Proteasome inhibition causes apoptosis in myeloma cells and the proteasome has proven to be an effective target for myeloma therapy. The proteasome inhibitor, carfilzomib, is an active anti-myeloma agent both as a monotherapy and in combination. In August 2012, carfilzomib was FDA approved for the treatment of MM patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy.[8,9,10] Interim results from a phase Ib/II trial combining carfilzomib with lenalidomide, and low-dose dexamethasone (CRd) in relapsed or progressive MM revealed promising safety and efficacy profiles.[11] Among all patients, the ORR was 62.5%, the clinical benefit response rate was 75.0%, and the median DOR and PFS were 11.8 and 10.2 months, respectively. Further study was recommended at the maximum planned CRd dose (carfilzomib 27 mg/m^2, lenalidomide 25 mg, dexamethasone 40 mg).
Dr Wang and colleagues presented final results on the safety and efficacy of the overall study population and the maximum planned dose (MPD) cohort in relapsed/refractory MM.[12]

The trial enrolled 84 patients (40 in phase Ib and 44 in a phase II dose expansion) with symptomatic and measurable MM progressing after 1 to 3 prior lines of therapy. Patients must have achieved at least a minimal response (MR) to a prior therapy. The primary endpoint of the phase Ib portion of the study was safety and the determination of maximum tolerated dose (MTD). Secondary endpoints for the phase Ib/II study included ORR, DOR, and PFS. Patients were treated with carfilzomib (IV, days 1, 2, 8, 9, 15, 16 at 20 mg/m^2 on cycles 1 and 2 and at 27 mg/m^2 thereafter), lenalidomide (25 mg/day on days 1-21 of a 28-day cycle), and oral dexamethasone (40 mg once weekly). Responses were assessed on day 15 of cycle 1 and on day 1 of all subsequent cycles.

Median patient age was 61.5 (43-86) years, and the majority of patients had an ECOG performance status of 0 or 1. The median time since initial diagnosis was 3.1 (0-22) years. High-risk cytogenetics were found in 26% of patients. Patients had received a median of 2 prior therapies (range, 1-5), and 40% of the patients were refractory to the last treatment regimen (20.2% to bortezomib, 34.5% to lenalidomide, and 9.5% to both).

With a median follow-up of 32.7 months, the ORR was 69%. Patients at the maximum planned dose had an ORR of 76.9% (**Table 1**). The median DOR was 18.8 months overall and 22.1 months for the MPD cohort. The median time to a response was 1.0 month. Median PFS was 11.8 months for the overall study population and 15.4 months for patients treated at the MPD.

Table 1. Reponses in relapsed/refractory MM to carfilzomib, lenalidomide, and low-dose dexamethasone (CRd).

Best Response	Maximum Planned Dose N = 52	Overall N = 84
ORR	76.9%	69.0%
≥ CR sCR	5.7% 3.8%	4.8% 3.6%
≥ VGPR	42.2%	40.5%
≥ MR	76.9%	75%
Median TTR, months (range)	1.0 (0-5)	1.0 (0-30)
DOR, months	22.1	18.8
Median PFS, months	15.4	11.8

MM, multiple myeloma; ORR, overall response rate; CR, complete response; sCR, stringent CR; VGPR, very good partial response; MR, minimal response; TTR, time to response; DOR, duration of response; PFS, progression-free survival.

The majority of grade 3/4 AEs were hematologic and included neutropenia (36.9%), lymphopenia (31%), and thrombocytopenia (25%). Peripheral neuropathy occurred in 18 patients (21.4%) with only 1 patient experiencing a grade 3 event. Three deaths occurred during treatment or within 30 days of treatment discontinuation; the primary cause in all 3 was progressive disease. In 1 of these patients, a secondary cause of death (colonic stenosis) was deemed possibly related to the study treatment. The safety and tolerability profile of the MPD cohort was consistent with the overall results.

Overall, CRd treatment provided robust, rapid, and durable responses in patients with relapsed or refractory MM, including 35% of the patients who were refractory to lenalidomide. Additional CRd studies in other MM patient populations are ongoing.

The CRd combination is also highly active as treatment for newly diagnosed MM. The final results from extended follow-up of a phase I/II trial employing CRd in 53 newly diagnosed MM patients were presented at ASCO by Dr Jakubowiak and colleagues.[13] Response rates in the upfront setting were very high with 87% of patients achieving at least a VGPR and 55% of patients attaining a stringent complete response (sCR). Furthermore, 22 of 24 patients (92%) with a sCR were negative for minimal residual disease (MRD). Progression-free survival at 2 years was 94% and 2-year OS was 98%. Taking together, these studies suggest that the CRd regimen is highly active in both newly diagnosed and relapsed or refractory MM.

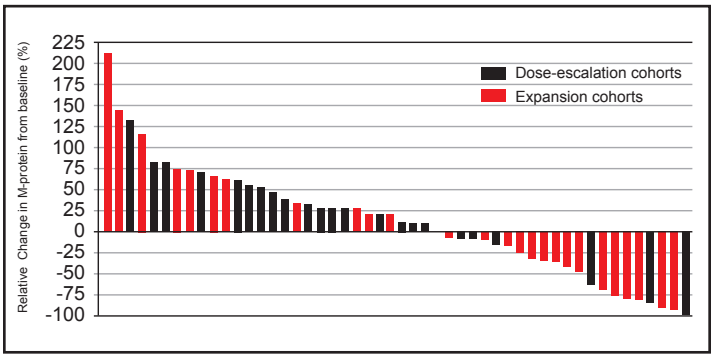
Ixazomib (MLN9708)

Ixazomib is an orally bioavailable second-generation proteasome inhibitor reported to have a shorter proteasome dissociation half-life and improved pharmacokinetics compared with bortezomib. Activity of ixazomib alone and in combination with lenalidomide and dexamethasone has been demonstrated in phase I/II trials.[14,15] Updated results of the fully enrolled single-agent ixazomib weekly dosing study were presented by Dr Kumar and colleagues.[16]

The study enrolled 60 patients subdivided into 3 dose escalation cohorts. MLN9708 was administered at doses of 0.24 to 3.95 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, for up to 12 cycles. The MTD identified in the phase I single-agent studies was 2.97 mg/m^2. An additional 31 patients were stratified into 4 expansion cohorts groups of relapsed and refractory (n = 11), bortezomib-relapsed (n = 10), proteasome inhibitor-naïve (n = 6), and prior carfilzomib therapy (n = 4). The median patient age was 64 years. Patients had received a median of 4 (range, 1-13) prior therapies and had a median time of 5 years from MM diagnosis.

For the 50 evaluable patients, 9 achieved a PR or better (ORR = 18%) and 10 (20%) achieved an MR or better. Of the 10 responding patients, 4 remained in response at the time of presentation with disease control duration of up to 9.8 months and 9 of those 10 had prior proteasome inhibitor exposure. Among the 31 response-evaluable patients given the MTD of ixazomib, the ORR was 26% and 9 patients (29%) achieved a MR or better. The majority of patients experiencing a reduction in the M-protein levels were in the expansion cohorts (with a third of the patients showing ≥ 25% reduction) (**Figure 3**). Pharmacokinetic studies found MLN9708 is rapidly absorbed and has a half-life of 4 to 11 days, supporting the weekly dosing schedule.

Figure 3. Best M-protein response of relapsed/refractory MM patients treated with ixazomib (MLN9708).



Dose-limiting toxicity included grade 3 skin and gastrointestinal events. Common drug-related AEs included thrombocytopenia (43%), diarrhea

(38%), and nausea (38%). Grade 3/4 AEs included thrombocytopenia (33%), diarrhea (17%), and neutropenia (18%). Peripheral neuropathy occurred in 20% of patients with only 2% grade 3/4.

In conclusion, the MTD of 2.97 mg/m^2 of ixazomib was relatively well tolerated and associated AEs were mainly hematologic and gastrointestinal. These data suggest that ixazomib has clinical activity in relapsed and/or refractory MM patients. Based on these results, a phase III trial has been initiated examining weekly dosing of ixazomib plus lenalidomide and low-dose dexamethasone compared to placebo, lenalidomide, and low-dose dexamethasone.

Daratumumab

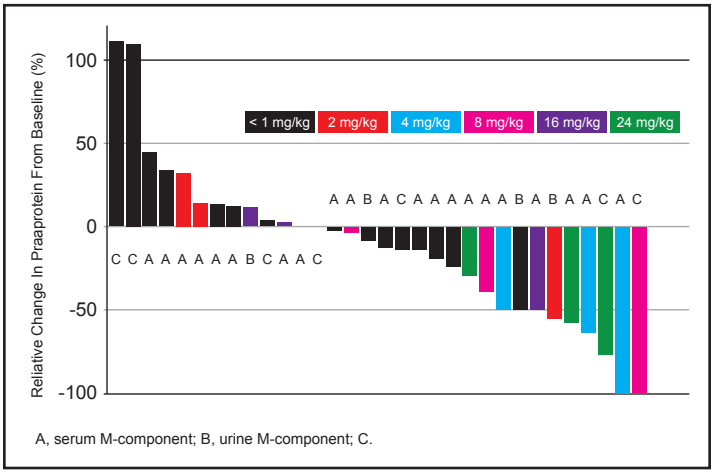
CD38 is widely expressed in humans and highly expressed in a number of tumor cells including myeloma. Daratumumab is a human anti-CD38 monoclonal antibody with broad-spectrum killing activity. Preliminary safety and efficacy data from a dose-escalation study of daratumumab in patients with relapsed or refractory MM have shown that the single-agent was active in heavily pretreated patients.[17] At ASCO 2013, Dr Lokhorst updated safety and efficacy data from a phase I/II monotherapy trial in relapsed or refractory MM patients.[18]

The primary objectives of this study were to establish the safety and pharmacokinetic profile of daratumumab and to examine the efficacy and immunogenicity of daratumumab. The dose-escalation study consisted of a classic 3+3 scheme, starting at a low dose of 0.005 mg/kg up to 24 mg/kg weekly over 8 weeks. All patients were heavily pretreated and had received lenalidomide and bortezomib, and the majority of patients were refractory to both of these agents.

The maximal change in paraprotein levels in response to daratumumab occurred in the higher dose groups (**Figure 4**). The PFS has not been met for the patients receiving the 4 to 24 mg/kg doses and was very short in patients receiving lower doses. In the 32 patients who received 8 weeks of daratumumab monotherapy up to 24 mg/kg, 47% had a reduction in paraprotein levels. This reduction was concomitant with a clinical response where 5 patients achieved a PR and 5 achieved a MR. At a dose of 4 mg/kg, 67% of patients (8/12; 5 PR, 3 MR) achieved a clinical response.

The most common AEs reported were infusion-related, which occurred predominantly during the first full infusion. Across all dose groups, 44% of the patients had grade 1-3 infusion-related AEs, of which 2 were grade 3. Serious AEs included grade 3 and 4 anemia and thrombocytopenia, grade 2 cytokine release syndrome, and grade 2 and 3 bronchospasm.

Figure 4. Best M-protein response in relapsed/refractory MM patients treated with daratumumab.



These preliminary data suggest daratumumab is active with manageable toxicity in a heavily pretreated MM population, and the investigators concluded that further study is warranted.

Minimal Residual Disease

Deep Sequencing Method for MRD

Relapsed disease remains a persistent problem in MM patients with most relapses due to persistence of residual tumor cells. Molecular-based methods

analyzing VDJ rearrangements of IgH genes used to detect MRD in MM are highly specific and sensitive but identification is time-consuming, labor-intensive, and applicable to only 50 to 60% of cases. Thus, new techniques are needed to clearly define response to treatment. Recently, deep sequencing of the B and T receptor loci by massive parallel sequencing from patient samples has been found to be highly sensitive and specific in detecting a unique 300 bp VDJ rearranged sequence. Using this technology, Dr Martinez-Lopez and his Spanish consortium compared the prognostic value of traditional response criteria and MRD measurements in a cohort of uniformly treated MM patients.[19]

Bone marrow samples were obtained from 68 patients from the Spanish Myeloma Group trials at diagnostic and post-treatment time points. All patients were in CR or VGPR at the post-treatment time point. Sequencing was used to identify clonal rearrangements of immunoglobulin (IgH-VDJ, IgH-DJ, and IgK) genes in the diagnostic samples. Minimal residual disease was assessed in follow-up samples and analyzed for concordance between sequencing and multiparameter flow cytometry methods. The prognostic value was then assessed with each method using traditional response criteria. The objectives of the study were to compare the results of immunoglobulin deep sequencing to immunophenotyping by multiparameter flow cytometry and to study the prognostic value of MRD assessment by deep sequencing of the IgH and IgK genes.

The sequencing assay detected a myeloma-specific gene rearrangement in diagnostic samples from 61 of 68 (90%) patients. Minimal residual disease was analyzed at the follow-up time points in 56 of the 59 patients (n = 77 samples). A high correlation ($r^2 = 0.90$) in detection of MRD was observed between multiparameter flow cytometry and the sequencing methods with 34 of 46 samples positive by both techniques. Nine samples were MRD-negative by both techniques and 3 were discordant (2 negative by sequencing and positive by flow cytometry, 1 positive by sequencing and negative by flow cytometry). As expected, there was improved OS and PFS in the MRD-negative group versus the MRD-positive group.

Overall, MRD assessment by immunoglobulin deep sequencing was found to be feasible in most MM patients. Assessment of MRD by sequencing is a useful method for patient risk stratification and can be used to determine molecular CR in MM patients. In the future, the use of sequencing for the detection of MRD may contribute to the design of patient-specific treatment approaches such as de-escalation of therapy for MRD-negative patients or continuous or escalation of treatment for MRD-positive patients.

LYMPHOMA UPDATE

Non-Hodgkin Lymphoma

The National Cancer Institute estimates that there will be over 69,000 new cases of and more than 19,000 deaths due to non-Hodgkin lymphoma (NHL) in the USA alone in 2013.[20] The combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the currently accepted standard of care for a number of the most common B-cell malignancies, including several NHL subtypes, such as DLBCL, mantle cell lymphoma (MCL), and follicular lymphoma (FL).[21,22] While incorporation of new agents and regimens (R-CHOP, R-bendamustine, radioimmunotherapy, and maintenance regimens) have prolonged PFS and OS, additional strategies are needed to prevent relapse and treat those patients refractory to frontline therapy or relapsing after initial response.

Ibrutinib With R-CHOP in CD20+ NHL

Despite high response rates and improved OS with R-CHOP treatment of B-cell NHL, a proportion of patients still either fail to respond or relapse after initial remission. Bruton's agammaglobulinemia tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase essential in B-lymphocyte development, differentiation, and signalling. Mutations in *Btk* result in X-linked agammaglobulinemia in humans and

X-linked immunodeficiency in mice both leading to B-lymphocyte-specific defects. BTK is expressed and functional across B-cell malignancies, including NHL. Ibrutinib (PCI32765) is an orally bioavailable small-molecule, irreversible, selective BTK inhibitor. Ibrutinib binds to and inhibits BTK activity, preventing B-cell activation and B-cell-mediated signalling and inhibiting the growth of malignant B-cells that overexpress BTK. Ibrutinib has demonstrated single-agent activity in a variety of relapsed or refractory B-cell malignancies with limited toxicity, making it an appealing drug to combine with standard R-CHOP chemotherapy in patients with previously untreated NHL. [23] Results from a phase Ib trial using ibrutinib with R-CHOP immunochemotherapy were presented by Dr Younes and his international colleagues at the Lymphoma Session at ASCO 2013.[24]

The primary objective of this study was to determine the recommended phase II dose and the dose-limiting toxicities of ibrutinib in combination with standard R-CHOP therapy in treatment-naïve NHL patients. The secondary objectives were to assess the safety profile, evaluate the pharmacokinetics and pharmacodynamic biomarkers of ibrutinib in the presence of R-CHOP, and determine the ORR.

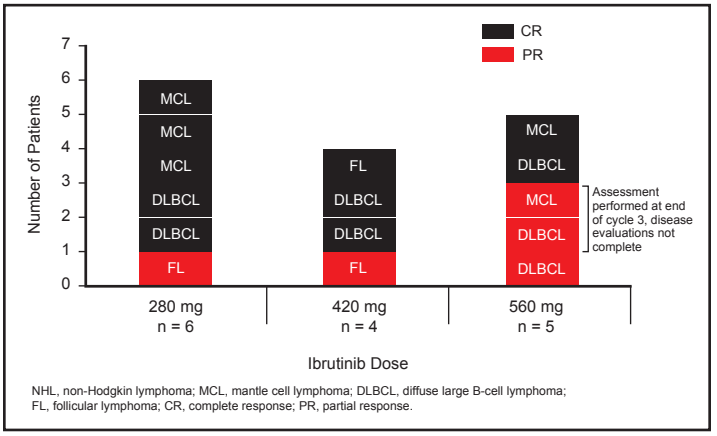
This 2-part study included a dose escalation study with patients receiving an oral daily dose of ibrutinib (280, 420, or 560 mg) in combination with standard-dose R-CHOP (rituximab, cyclophosphamide, doxorubicin, and vincristine on day 1, prednisone on days 1-5 of each 21-day cycle; n = 3 patients per dose). Patients were given up to 6 cycles of standard R-CHOP with daily ibrutinib beginning on day 3. Part 2 included a dose expansion study at the recommended phase II dose of ibrutinib (560 mg; n = 15 patients) focused on patients with newly diagnosed treatment-naïve DLBCL.

Seventeen patients with either DLBCL, MCL, or FL were enrolled in the first part of the study. Patients had a median age of 65 (range 46-81) years and 59% were male. NHL subtypes included: 47% DLBCL, 29% MCL, and 24% FL.

Three patients had dose-limiting toxicity: 1 with transient syncope (grade 3) and 1 with periorbital cellulitis (grade 3) in the 280 mg cohort and 1 patient had gastritis (grade 2) in the 560 mg cohort. The MTD was not reached, and the recommended phase II dose was the highest tested ibrutinib dose, 560 mg.

The ORR in evaluable patients was 100% with 67% CR and 33% PR. In the 560 mg group, 3 patients experienced a PR whereas 2 patients achieved a CR (**Figure 5**). All patients were evaluated by positron emission tomography (PET) and computed tomography (CT).

Figure 5. Response of newly diagnosed CD20-positive B-cell NHL to ibrutinib with R-CHOP.



NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CR, complete response; PR, partial response.

Neutropenia and thrombocytopenia (any grade) were experienced by all patients at the 280 or 420 mg ibrutinib dose and 50% of patients at the 560 mg dose. In the dose expansion study, 7 of 15 patients (46.7%) experienced neutropenia and 6 patients (40%) developed thrombocytopenia. Other AEs included vomiting, anemia, nausea, fatigue, headache, constipation, diarrhea, and dizziness. Grade 3/4 neutropenia occurred in 15 of 17 patients with febrile neutropenia occurring in 2 patients (from the 280 mg cohort). Fifteen patients completed all 6 cycles.

The addition of R-CHOP to the treatment regimen did not affect the pharmacokinetics of ibrutinib. The exposure levels of ibrutinib with R-CHOP were

consistent with data from previous single-agent studies in other B-cell malignancies. Ibrutinib did not alter vincristine (CYP3A4) substrate pharmacokinetics.

In conclusion, no new early toxicities were noted with the addition of ibrutinib to R-CHOP. An expansion cohort using 560 mg ibrutinib is being initiated to further explore the safety of this combination in newly diagnosed untreated DLBCL.

Idelalisib With Rituximab and/or Bendamustine in Previously Treated Indolent NHL

The combination of bendamustine with rituximab in patients with relapsed indolent and MCL yields response rates greater than 90% in both patient populations with a median DOR of 21 to 24 months.[25,26] Phosphoinositide 3-kinase (PI3K) plays a critical role in a number of key pathways known to be dysregulated in indolent NHL. PI3K-delta (PI3Kδ) is highly expressed in in many B-cell malignancies and its signaling is critical for activation, proliferation and survival of B-cells. Idelalisib is a highly selective oral inhibitor of PI3Kδ. Preclinical studies have suggested that idelalisib inhibits proliferation, homing, and retention of malignant B-cells. It has also been shown to induce apoptosis in many B-cell malignancies. Early studies have suggested that idelalisib is active in recurrent indolent NHL.[27,28] To assess safety and efficacy, Dr Leonard and his US collaborators designed a 3-pronged phase I study of continuous idelalisib (100 or 150 mg bid) with (375 mg/m^2 weekly x 8 doses), idelalisib with bendamustine (90 mg/m^2 x 2, for 6 cycles), or idelalisib with rituximab and bendamustine.[29]

The study enrolled 79 patients with relapsed/refractory indolent NHL (FL, small lymphocytic lymphoma [SLL], marginal zone lymphoma). The median age of the participants was 61 (37-84) years, 66% were male, half of the patients had bulky adenopathy, and 40% had refractory disease. Patients had received a median of 3 prior regimens (range, 1-11) with 97% having prior rituximab exposure. The primary focus of this study was to examine the safety and toxicity of the combination regimen.

The predominant AEs were fever, nausea, fatigue, rash, cough, and other gastrointestinal symptoms, and most of these were grade 1 and 2. Idelalisib has been associated with liver enzyme abnormalities and 56% had elevated ALT/AST with 16.5% being grade 3 or higher. A comparison between cohorts revealed an AE distribution similar to single-agent studies (**Table 2**).

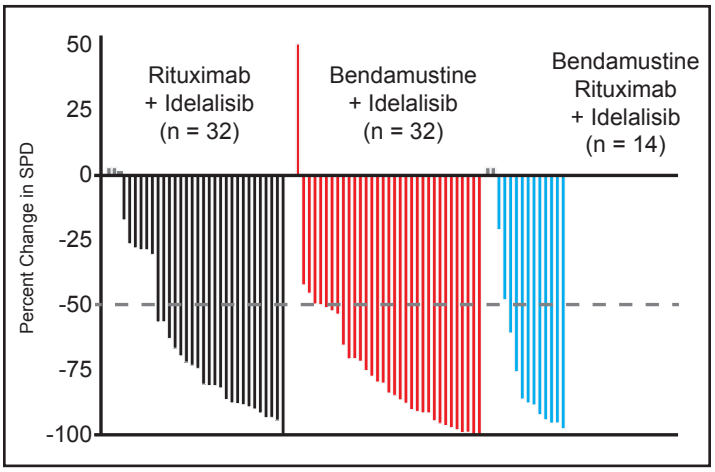
Table 2. Grade 3 or higher adverse events (AEs) by cohort in patients with indolent NHL treated with rituximab/idelalisib, bendamustine/idelalisib, or bendamustine/rituximab/idelalisib.

Grade ≥ 3 AEs	Rituximab + Idelalisib n = 32	Bendamustine + Idelalisib n = 33	Bendamustine + Rituximab + Idelalisib n = 14
Pneumonia	3 (9%)	9 (27%)	2 (14%)
Diarrhea	4 (13%)	1 (3%)	1 (7%)
Rash	1 (3%)	2 (6%)	3 (21%)
Fatigue	1 (3%)	2 (6%)	0
Pyrexia	0	1 (3%)	1 (7%)
≥ Grade 3 Lab Abnormality			
Transaminase Elevation	5 (16%)	8 (24%)	0
Neutropenia	11 (34%)	15 (45%)	6 (43%)
Anemia	2 (6%)	5 (15%)	1 (7%)
Thrombocytopenia	1 (3%)	4 (12%)	1 (7%)

All but 2 patients (1 progression and 1 not evaluable) had some tumor shrinkage, and the majority had at least a PR regardless if they were treated with 2 or 3 drugs (**Figure 6**). By combining all the cohorts, the ORR was 78% with a 26% CR rate. The DOR at 24 months was 69%. At 24 months, PFS at 24 months was 62.5% and was comparable across cohorts.

Forty-six percent (n = 37) of patients completed all 48 weeks of the study, and 44% (35) of those enrolled in the extension phase of this study. Twenty-eight patients (35%) remain on the study extension. Reasons for discontinuation of the extension phase (n = 7) were disease progression, AE, death, investigator choice, and one undefined factor.

Figure 6. Best nodal response of previously treated indolent NHL patients to rituximab/idelalisib, bendamustine/idelalisib or bendamustine/rituximab/idelalisib.



Overall, idelalisib in combination with rituximab, bendamustine, or both in relapsed or refractory indolent NHL was active with manageable side effects. A phase III trial evaluating the efficacy of idelalisib in combination with bendamustine and rituximab is ongoing.

Idelalisib With Everolimus, Bortezomib, or Bendamustine/Rituximab in Previously Treated MCL

In patients with relapsed or refractory MCL, idelalisib has an ORR of 40% and a PFS of 22% at 1 year.[30] Everolimus is a mammalian target of rapamycin (mTOR) inhibitor with an associated ORR of 30% in MCL.[31] The addition of everolimus and idelalisib in vitro to MCL cell lines results in an additive inhibition of pAKT and decreased cell viability. In MCL the combination of bendamustine and rituximab results in response rates between 75% and 90%,[25,26] and bortezomib yields an ORR of 30% in relapsed MCL.[32] To investigate the safety and efficacy of idelalisib combinations, Dr Wagner-Johnston and her colleagues initiated a phase I study evaluating continuous idelalisib (150 mg bid) in 3 drug combinations with: 1) everolimus (10 mg po daily), 2) bortezomib (1.3 mg/m^2 SC day 1, 8, 15 per 28-day cycle), and 3) rituximab (375 mg/m^2, on day 1) and bendamustine (90 mg/m^2 x 2), for 6 cycles.[33]

Patients with measurable disease and adequate hematologic, renal, and hepatic function who had at least 1 prior chemotherapy and rituximab treatment regimen were eligible for this study. Disease response was assessed at weeks 0, 8, 16, and 24 and every 12 weeks thereafter. The primary endpoint of this study was safety with secondary endpoints that included assessment of pharmacokinetics and clinical activity. Patients who continued to benefit were eligible for enrollment in an extension study consisting of continuous idelalisib (150 mg bid).

Patients treated with everolimus and idelalisib (n = 18) had a median age of 68 (56-80) years and had received a median of 4 (1-7) prior therapies, 61% had bulky adenopathy, and 61% had refractory disease. Patients treated with bortezomib and idelalisib (n = 11) had a median age of 73 (56-79) years and had received a median of 4 prior therapies. Bulky adenopathy was found in 73%, and 27% of patients were treatment-refractory.

The ORR was 39% (7/18) for the everolimus/idelalisib cohort including 2 CR. Five patients were not evaluable because of progression, fever/neutropenia, acute respiratory distress syndrome, or pneumonia. The ORR for the patients given bortezomib and idelalisib was 46%. For the smaller group of patients (n = 4) who received bendamustine, rituximab, and idelalisib, the ORR was 100%. The median PFS for all cohorts was 8.1 months.

In comparison to a prior everolimus single-agent study, grade 3 or higher AEs were more pronounced with the combination of everolimus and idelalisib. Notably 10/18 patients required dose reductions of everolimus. There were also no unexpected AEs in the bortezomib/idelalisib or bendamustine/rituximab/idelalisib cohorts.

Two patients in each of the everolimus/idelalisib and bendamustine/rituximab/idelalisib cohorts had ongoing CRs, but there were no durable responses in

the bortezomib arm. Further trials involving idelalisib combinations will include bendamustine/rituximab, rituximab/lenalidomide, and a Syk inhibitor.

Lenalidomide in Relapsed/Refractory MCL Post-Bortezomib

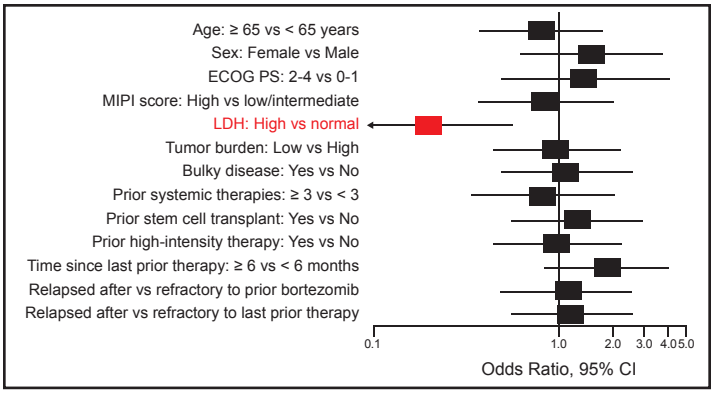
Relapsed/refractory MCL is characterized by frequent chemo resistance, lack of durable responses, and limited treatment options. Consequently, there is currently no standard of care available for patients not responding to bortezomib, and new therapeutic options are needed for patients who relapse. The immunomodulatory agent, lenalidomide, has established anti-tumor and anti-proliferative effects.[34,35,36,37] A combined analysis of 206 relapsed or refractory MCL patients treated with lenalidomide monotherapy in 3 separate studies (NHL-002, NHL-003, and MCL-001) found an ORR of 32% (10% CR/CRu) with a median DOR of 16.6 months. Median PFS was 5.4 months, and median OS was 23.9 months.[35,38,39,40] At ASCO 2013, a subgroup analysis of the MCL-001 trial examining predictors of response in relapsed/refractory MCL patients after bortezomib was presented by Dr Williams and colleagues.[41]

MCL-001 is a phase II, open-label, single-arm, multicenter trial of single-agent lenalidomide in 134 MCL patients who had relapsed, progressed, or were refractory to bortezomib. Exploratory analyses of ORR and DOR was based on subgroups that were predefined and prospectively conducted. Patients were divided into subgroups based on demographic and clinical status, baseline clinical disease characteristics, and prior anti-lymphoma treatment. A mulitvariate logistic regression model evaluated the possible baseline factors predictive of response.

Patients with relapsed/refractory MCL (N = 134) had a median age of 67 (43-83) years, 81% were male (n = 108), and 93% had stage III-IV disease. High tumor burden was noted in 57% of patients, and 33% had bulky disease. Patients were heavily pretreated and had received a median of 4 prior therapies (range, 2-10).

The ORR as assessed by a central review committee was 28% (7.5% CR/CRu) and DOR was 16.6 months (95% CI, 7.7-26.7). Lenalidomide treatment provided consistent ORR and DOR across all subgroups analyzed by demographics, baseline disease status, and prior therapy. Interestingly, high vs normal baseline LDH was the only significant predictive factor by univariate and multivariate logistic regression analysis of ORR (multivariate odds ratio = 0.193; $P = 0.002$) (**Figure 7**).

Figure 7. Univariate logistic regression analysis of overall response rate in relapsed or refractory mantle cell lymphoma patients treated with lenalidomide after prior bortezomib therapy.



Overall, single-agent lenalidomide provided clinical benefit in some patients with relapsed/refractory MCL post-bortezomib. LDH was the only pretreatment factor predictive of response. Additional studies are necessary to determine whether this is a reliable prognostic factor across trials of lenalidomide and/or across trials of relapsed MCL.

Utility of Post-Therapy Surveillance Scans in DLBCL

The optimal follow-up strategy for patients with DLBCL in remission is unclear. Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend evaluation every 3-6 months for 5 years, and CT scans no more often than once per 6 months for the first 2 years after completion of therapy and then only as clinically indicated. Due to the risks associated with scans (radiation exposure, false positives, patient anxiety, and the high cost) prudent

surveillance taking into account associated risks while increasing relapse detection and overall patient survival is needed. Therefore, Dr Thompson from the Mayo Clinic and colleagues from the University of Iowa and Université de Lyon designed a study to assess the utility of surveillance scans in a multi-institutional cohort of patients in remission for DLBCL.[42]

The study enrolled 644 newly diagnosed DLBCL patients treated with anthracycline-based immunochemotherapy and needing no further treatment as recommended by the treating physician. Patients were followed every 6 months for the first 3 years and then annually thereafter. Upon relapse, medical records were re-reviewed for clinical details and relationship to planned follow-up and surveillance scans.

Median patient age was 63 years (range 18-92), 54% were men, and 58% were over the age of 60 years. Of the original cohort of 644 patients, 12 died from toxic death, 72 patients experienced refractory disease, 12 patients were given unplanned consolidative therapy, and the surveillance status was unavailable in 11 patients, leaving 537 patients for post-treatment observation.

From those 537 patients, 109 (20%) relapsed and 380 remain in remission (41 died from other causes and 7 are in unknown disease status). Timing of relapse was unavailable for 9 patients leaving 100 patients. Of those 100, 62% of patients presented to their physician earlier than a planned follow-up visit due to symptoms. The remaining 38% of patients were detected at a routine visit. Of the 38 patients with relapse detected at a planned visit, 26 had clinical features of relapse. The remaining 12 patients were asymptomatic and their relapse was detected solely by scan.

Of the 12 asymptomatic patients who had relapse detected solely by planned surveillance scan, 4 patients had relapse of low-grade or other subtype and 8 had DLBCL relapse. Upon re-review, 4 of these 8 patients had equivocal/positive PET scans at the end of therapy. Thus, surveillance scanning detected DLBCL relapse prior to clinical manifestations in only 8 of 537 patients (1.5%).

Overall, the vast majority of DLBCL relapses occurred outside of the planned follow-up visits and were generally accompanied by symptoms, physical exam, or laboratory abnormalities. Thus, routine surveillance scans post-therapy provided little benefit in terms of detection of DLBCL relapse. Ideally, a randomized prospective trial should be completed to determine the optimal strategy for scanning in this population of patients.

Hodgkin Lymphoma

Routine Surveillance Imaging in First Complete Remission

Routine surveillance imaging for patients in complete remission from classical Hodgkin lymphoma (HL) is common practice. Theoretically, routine surveillance imaging offers the benefit of detecting asymptomatic relapse and early initiation of second-line therapy. However, there is no evidence to suggest that there is a survival benefit from routine surveillance in classical HL. The risks associated with routine surveillance include unnecessary harm from false-positive workup, patient anxiety, significant radiation exposure, and high costs.[43,44] The recommendations for routine surveillance varies widely. The NCCN guidelines recommend CT scans every 6 to 12 months for 2 to 3 years whereas the European Society of Medical Oncology (ESMO) and the International Working Group (IWG) advise against routine image surveillance. Several studies have shown that few relapses are detected by routine surveillance alone and 80% of the relapses are discovered by the patient or their physician and not by surveillance alone.[45,46,47] To compare clinical surveillance to routine surveillance imaging, Dr Pingali and colleagues performed a retrospective chart review of newly diagnosed classical HL patients from 3 tertiary care centers.[48]

Patients must have achieved a complete remission at the end of first-line therapy and had a minimum

of 2 years follow-up to be included in the analysis. The primary objective of this study was to compare OS of HL patients in first complete remission who were monitored by routine surveillance imaging vs clinical surveillance. The secondary objectives were to compare the success of the salvage regimen in each group and the costs of both methods of screening.

Patients (N = 241) were stratified by the surveillance strategy employed; either patients were monitored by planned routine surveillance imaging (n = 164) or by clinical surveillance (n = 77). Surveillance for the routine imaging group included radiological surveillance, clinical exam, and laboratory tests. Surveillance for the clinical surveillance group included only clinical exam and laboratory values with scans obtained as indicated based on signs and symptoms. Baseline patient characteristics, prognostic features, treatment records, and outcomes were collected.

Patient characteristics were similar for both groups in terms of age, sex, stage of disease, B-symptoms, bulky disease, Hasenclever Index, and median follow-up. However, with regard to frontline therapy, the vast majority of patients (92%) in the routine surveillance imaging group had received doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy, and only 57% of the clinical surveillance group received ABVD. Four of the 164 (2%) patients in the routine surveillance imaging group had been given the Stanford V regimen compared to 36% of the patients in the clinical surveillance group.

With a follow-up of 8 years, the OS was similar in both groups ($P = 0.74$), with 5 (3.8%) deaths (1 from relapsed HL) in the routine surveillance imaging group and 4 (5.3%) in the clinical surveillance group. Six (4.6%) relapses occurred in the routine surveillance imaging group, and 4 of those were detected by routine surveillance imaging. Five (6.6%) relapses occurred in the clinical surveillance group ($P = 0.64$ for relapse at 5 years). All relapsed patients achieved a second CR with second-line therapy.

The routine surveillance imaging group received a mean number of 4.25 scans and the clinical surveillance group received a mean of 1.14 scans. The study found that 17.6 scans were needed to detect 1 relapse in the clinical surveillance group and 123.8 scans were required to detect 1 relapse in the routine surveillance imaging group. Assuming the costs of $5190 per CT scan and $6600 per PET/CT scan, an average of $18,896 extra charges were incurred per routine surveillance patient amounting to $593,698 additional charges per relapse in the routine surveillance imaging group.

Overall, this small retrospective study suggests that routine surveillance imaging did not provide an obvious OS benefit and resulted in substantial cost increase. Prospective studies are warranted, but together these observational studies in DLBCL and HL suggest that routine surveillance imaging to detect radiologically evident but clinically silent relapsed lymphoma are of limited value. Additional studies must also provide evidence that early action and specific therapies can change outcomes for this apparently small population of patients.

T-Cell Lymphoma

CID-ATT With Radiotherapy vs CHOP/Radiotherapy in Extranodal NK/T-Cell Lymphoma, Nasal Type

Between 10% and 15% of NHL patients have a T-cell lymphoma subtype. Extranodal NK/T-cell lymphoma nasal type (ENKL) is a rare lymphoid neoplasm characterized clinically by aggressive, nonrelenting destruction of the midline structures of the palate and nasal fossa and a poor prognosis.[49,50] This disease has a distinctive ethnic and geographical distribution with a global prevalence in Asia, accounting for 7% to 10% of all NHLs. Anthracycline-based chemotherapy in addition to radiotherapy (RT) has not been shown to improve survival outcomes. However, several recent phase II trials have suggested that concurrent chemoradiation is a feasible and effective treatment for the management of localized ENKL. To gain more insight into how to better manage this disease, Dr Lin

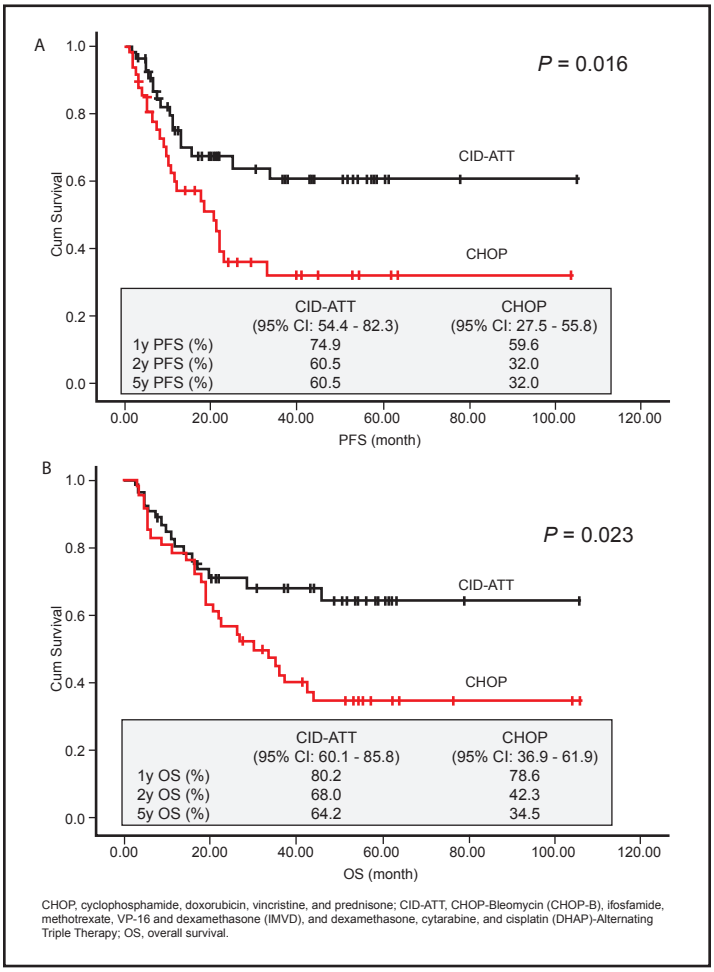
and colleagues designed a prospective phase II/III study in patients with ENKL.[51]

The overall aim of this study was to prospectively compare the efficacy and survival of patients given either a CHOP-based alternating triple therapy or a standard CHOP regimen as first-line treatment. The alternating therapy consisted of 1) CHOP-Bleomycin (CHOP-B), 2) ifosfamide, methotrexate, VP-16 and dexamethasone (IMVD), and 3) dexamethasone, cytarabine, and cisplatin (DHAP)-alternating triple therapy (CID-ATT). The CID-ATT was defined as the sequential administration of CHOP-B, IMVD, and DHAP, given in alternating sequence for a total of 6 courses (21-day cycles). Both cohorts of patients received RT (50-55Gy) after the chemotherapy regimens. With each DHAP cycle, all patients received prophylactic granulocyte colony-stimulating factor, interleukin-11 and thrombopoietin. The primary objective of the study was to evaluate OS. Secondary objectives included the analyses of PFS, response rate, and toxicity of the CID-ATT regimen in early ENKL.

Patients (16-70 years) with ENKL (N = 109 patients) were randomized to receive CID-ATT (n = 54) or CHOP regimen (n = 55) from January 2006 to January 2012. The patient characteristics in both arms of the trial were well matched. The vast majority of the patients completed treatment: 88.9% in the CID-ATT plus RT group and 85.5% in the CHOP plus RT group.

Overall response rates were significantly higher with CID-ATT (92.6%, 50/54 vs 61.8%, 34/55; $P < 0.001$). Compared to the CHOP group, the CID-ATT group had a much higher CR rate (87%, 47/54 patients) vs CHOP (52.7%, 29/55; $P < 0.001$). Progression-free survival was significantly longer with CID-ATT compared to standard CHOP (1-year PFS 74.9% vs 59.6%, 3-year PFS 60.5% vs 32.0%, 5-year PFS 60.5% vs 32.0%, $P = 0.016$) (**Figure 8A**). With a median follow-up of 40.3 months, OS was significantly prolonged with CID-ATT compared with CHOP (1-year OS 80.2% vs 78.6%, 3-year OS 68.0% vs 42.3%, 5-year OS 64.2% vs 34.5%, $P = 0.023$) (**Figure 8B**).

Figure 8. (A) Progression-free survival and (B) overall survival of extranodal NK/T-cell lymphoma, nasal type patients treated with CID-ATT with radiotherapy vs CHOP with radiotherapy.



CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CID-ATT, CHOP-Bleomycin (CHOP-B), ifosfamide, methotrexate, VP-16 and dexamethasone (IMVD), and dexamethasone, cytarabine, and cisplatin (DHAP)-Alternating Triple Therapy; OS, overall survival.

As expected, grade 3/4 neutropenia and thrombocytopenia, was common in both arms especially after patients received DHAP. Other grade 3/4 non-hematologic toxicities noted during chemotherapy were infections (45% CID-ATT vs 11% CHOP) and nausea/vomiting (20% CID-ATT vs 2% CHOP) as well as hepatic, cardiac, and neurologic toxicity (< 9% for each). The most common cause of death was disease progression and relapse (27.8% CID-ATT vs 60% CHOP), infection (1.9% CID-ATT vs 0% CHOP), and liver dysfunction (0% CID-ATT vs 1.8% CHOP).

Overall, the CID-ATT regimen was superior to CHOP as induction therapy followed by RT for untreated early stage ENKL and is a promising treatment regimen for rare and aggressive NHL subtypes.

LEUKEMIA

Chronic Lymphocytic Leukemia

Idelalisib in Relapsed or Refractory CLL

According to the National Cancer Institute, approximately 15,680 patients will be diagnosed with chronic lymphocytic leukemia (CLL) in the US and 4,580 will succumb to the disease in 2013. Currently, CLL treatment includes combination of chemotherapy and immunotherapy. While fludarabine-based therapy for CLL is effective, it carries significant risk of morbidity and mortality for elderly patients. Thus, older CLL patients, as well as, treatment-refractory patients represent a high priority for new therapeutic approaches. The PI3K pathway is hyperactive in CLL with the PI3Kδ isoform a predominant hyperactive subtype, making idelalisib an attractive targeted agent. Dr Brown and her collaborators designed a phase I clinical trial exploring idelalisib treatment in patients with previously treated hematologic malignancies. Results of 54 patients with CLL were presented.[52]

Patients were enrolled into multiple oral idelalisib dosing cohorts ranging from 50 mg bid to 350 mg bid for up to 48 weeks. Patients who demonstrated clinical benefit were eligible to enroll in an extension study until they no longer responded to idelalisib treatment. The 6 dose cohorts were assessed at weeks 0, 8, 16, 24, and every 12 weeks thereafter.

Of the 54 CLL patients, 83% were males and patients had a median age of 63 (range, 37-82) years. In terms of disease status, 70% of the patients were refractory to their most recent therapy, and all patients were heavily pretreated (median prior therapies, 5 [range, 2-14]). Bulky lymphadenopathy was noted in 80% of the patients, and 37% had splenomegaly. Baseline hematopoietic profiles revealed that 63% of the patients had thrombocytopenia, 46% had anemia, and 28% had neutropenia prior to enrolling in this trial. High risk unmutated IgHV genetics were documented in 91% of the CLL patients. Less than 30% had del(17p) with a TP53 mutation, del(11q), and/or NOTCH1 mutation. Twenty-five (46%) CLL patients completed 48 weeks of treatment, and 23 patients enrolled in the extension study.

Idelalisib was well tolerated with no dose-limiting toxicities. The most common AEs were fatigue, diarrhea, pyrexia, cough, back pain, rash, and pneumonia. The major reason for discontinuation was progressive disease.

Pharmacokinetic studies suggest idelalisib effectively inhibited its target. In vivo inhibition of phosho-AKT levels were consistent with targeted inhibition and resulted in profound nodal response. Based on best nodal response, 150 mg of idelalisib was chosen as the recommended phase II dose.

Lymph node response was detected in 81% of patients, and the ORR was 72%. Strikingly, the tumor burden decreased concomitantly with a rise in lymphocyte values. The median time to response was 1 month and the median DOR was 16.8 months. The PFS for all the patients was 17.1 months, and median OS was not reached.

In summary, idelalisib rapidly induced durable responses in heavily pretreated and refractory CLL patients. Half of the patients with relapsed or refractory CLL experienced rapid and prolonged tumor shrinkage, and toxicity was manageable. The study group concludes that given the observed substantial clinical activity of idelalisib further clinical development in CLL is justified. Three phase III trials studying the efficacy of idelalisib are currently enrolling patients testing idelalisib in drug combinations with rituximab, bendamustine/rituximab, and ofatumumab.

Idelalisib and Rituximab in Older Treatment-Naïve CLL or SLL

The high response rates and relative tolerability of idelalisib monotherapy in relapsed CLL patients along with the observation of rapid decrease in tumor burden with concomitant rise in blood lymphocyte counts suggested a potential benefit of combination treatment. O'Brien and colleagues examined the efficacy and safety of idelalisib with rituximab in newly diagnosed CLL or SLL patients 65 years or older.[53]

This phase II single arm open-label study enrolled 64 patients (59 CLL and 5 SLL) with a median age of 71 (65-90) years. The median β2 microglobulin levels were 4.0 mg/L (1.9-15.8). Nine patients had either a del(17p) or a TP53 mutation. Cytopenias were also present. Patients were given rituximab at 375 mg/m^2 weekly for 8 cycles and idelalisib at 150 mg bid continuously for 48 weeks. Patients completing 48 weeks without progression could continue to receive idelalisib on an extension study. Responses and progression were based on investigator assessment and assessments were completed at weeks 0, 8, 16, 24, 36, 48, and as needed thereafter. The primary endpoint of this trial was ORR and the secondary endpoints were DOR, PFS, and safety.

As of May 2013, 62/63 patients completed 8 weeks of treatment, and 43 patients completed 48 weeks. The extension study enrolled 40 (63%) patients and 33 were on the study as of the time of analysis.

The ORR was 97% with 19% CR and 78% PR. Median time to response was 1.9 months (range 1.0-6.5) (**Table 3**). Response to treatment included rapid lymph node mass reduction and a decrease in lymphocyte counts. Of note, 6/6 patients with del(17p) responded (1 CR, 5 PR) and 3 remain on treatment for more than 21 months. A significant improvement in cytopenias was noted and there were no significant reductions in neutrophil counts. With a median of 14.1 months on study, there have been no on-study relapses, and PFS at 24 months is 93%.

Table 3. Response and progression-free survival of newly diagnosed CLL or SLL patients 65 years or older treated with rituximab and idelalisib.

	Idelalisib/Rituximab N = 54
ORR	97%
CR	19%
PR	78%
TTR	1.9 months
24-month PFS	93%

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; ORR, overall response rate; CR, complete response; PR, partial response; TTR, time to response; PFS, progression-free survival.

The most frequent grade 3/4 AEs were diarrhea (23% reported as colitis in 10 patients), pyrexia (3%), nausea (2%), rash (98%), cough (2%), and pneumonia (17%). The most common grade 3/4 laboratory abnormality was transaminase elevations (23%) and neutropenia (28%). Serious AEs occurred in 37 (58%) patients and included hospitalization for diarrhea, colitis, and pneumonia. Twenty-one patients (33%) discontinued treatment (17 due to AEs, 3 deaths, 1 withdrew consent). Adverse events leading to discontinuation included diarrhea/colitis, respiratory disorders, rash, anemia, and altered ALT/AST levels. Infections in the first 48 weeks were noted in 67% of the patients, and there were 5 deaths on study (pneumonia/sepsis, pneumonia/metastatic melanoma, pneumonitis, and myocardial infarction).

In summary, these results suggest that idelalisib with rituximab is highly active in treatment-naïve CLL. To date no responding patients have relapsed and further investigation of this combination is planned.

Obinutuzumab Plus Chlorambucil or Rituximab Plus Chlorambucil vs Chlorambucil Alone

Although chemoimmunotherapy is the standard of care for young physically fit CLL patients, the elderly patient populations with pre-existing medical

conditions represent a challenge for oncologists. There is no conclusive evidence to suggest that any available treatments are superior to single-agent chlorambucil.[54] Thus the challenge remains to develop new treatment modalities that minimize associated toxicities and produce increased positive responses. Encouraging results from a phase II trial suggest efficacy with the combination of chlorambucil and anti-CD20 antibodies.[55,56] Obinutuzumab (GA101) is a type 2 monoclonal antibody to CD20 containing a glyco-engineered Fc region and enhanced antibody-dependent cell-mediated cytotoxicity with lower complement-dependent cytotoxicity. In addition, there are encouraging clinical data analyzing the combination of chemotherapy with obinutuzumab.[57,58] Continuing along this line of investigation, Dr Goede and his colleagues from the German CLL study group designed a phase III clinical trial (CLL11) comparing chlorambucil plus obinutuzumab to chlorambucil monotherapy and rituximab with chlorambucil in previously untreated CLL.[59]

The study included 780 previously untreated CLL patients. Eligibility criteria included untreated CLL patients with comorbidities as assessed with a Cumulative Illness Rating Scale (CIRS) total score greater than 6 and/or an estimated creatinine clearance (CrCl) less than 70 mL/min. Patients were randomized at a ratio of 1:2:2 to chlorambucil alone (0.5 mg/kg po day 1, 15 q28 days, x 6 cycles; n = 118), obinutuzumab plus chlorambucil (100 mg IV day 1, 900 mg day 2, 1000 mg day 8, day 15 of cycle 1, 1000 mg day 1 cycles 2-6; n = 238), or rituximab plus chlorambucil (375 mg/m^2 IV day 1 cycle 1, 500 mg/m^2 day 1 cycles 2-6; n = 233). The primary endpoint for this study was investigator-assessed PFS.

The treatment arms were well balanced. For the pairwise comparison of chlorambucil to obinutuzumab with chlorambucil (n = 356), patients had a median age of 73 years, a median CIRS score of 8, and a median CrCl of 61.1 mL/min. For the comparison of chlorambucil to rituximab with chlorambucil (n = 356), patients had a median age of 73 years, CIRS score of 8, and CrCl of 62.1 mL/min.

The ORR was higher with obinutuzumab/chlorambucil vs chlorambucil (75.5% vs 30.2%) and rituximab/chlorambucil vs chlorambucil (65.9% vs 30.0%). Median PFS was 10.9 months for control chlorambucil compared to 23.0 months for obinutuzumab with chlorambucil (HR = 0.14, $P < 0.0001$) and 15.7 months for rituximab chlorambucil vs 10.8 months with chlorambucil (HR = 0.32, $P < 0.0001$) (**Table 4**). The PFS benefit held true across subgroups of patients when subdivided by CIRS score, CrCl, β2 microglobulin, and chromosomal abnormalities. Although the observation time was short with a median follow-up of 14.2 and 15.3 months, the OS rates were comparable in both groups.

Relevant AEs included neutropenia, anemia, thrombocytopenia, and infection in both arms of the study. Notably, there were no infusion-related reactions in the chlorambucil control arm of the study but there were grade 3/4 reactions in the obinutuzumab plus chlorambucil and chlorambucil vs rituximab arms of the study (21% vs 4%, respectively) (**Table 4**).

In conclusion, the combination of chlorambucil with either anti-CD20 (obinutuzumab or rituximab) antibody improved response rates and PFS compared to chlorambucil alone. A direct comparison between obinutuzumab and rituximab will be examined in stage II of this study.

Chronic Myeloid Leukemia

Mutation Analysis in CML; Impact of Baseline Mutations on Response to Ponatinib

Last year, 3 new agents, bosutinib, ponatinib, and omacetaxine mepesuccinate, were FDA approved for the treatment of various phases of chronic myeloid leukemia (CML) resistant to frontline treatment.[60,61,62] The multi-targeted TKI, ponatinib, was specifically approved based on activity against the imatinib-,

Table 4. Reponses and AEs in elderly CLL patients treated with chlorambucil alone vs obinutuzumab plus chlorambucil (stage Ia) or chlorambucil alone vs rituximab with chlorambucil (stage Ib).

Total stage I N = 589	Stage Ia		Stage Ib	
	Chlorambucil n = 118	Chlorambucil Obinutuzumab n = 238	Chlorambucil n = 118	Chlorambucil Rituximab n = 233
Median observation, months	13.6	14.5	14.2	15.3
ORR, %	30.2	75.5	30.0	65.9
CR, %	0	22.2	0	8.3
Median PFS, months	10.9	23.0	10.8	15.7
HR (95% CI) *P*	0.14 (0.09-0.21) < 0.0001		0.32 (0.24-0.44) < 0.0001	
Grade 3-5 AE during treatment, %	41	67	41	46
Infusion-related reaction	-	21	-	4
Neutropenia	15	34	15	25
Infections	11	6	11	8

AE, adverse events; ORR, overall response rate; CR, complete response; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

dasatinib-, and nilotinib-resistant mutation, T315I.[63,64] Because *BCR-ABL1* kinase domain mutations are often the cause of TKI failure, Deininger and colleagues evaluated the impact of baseline mutations on the response to ponatinib as well as the end of treatment mutation status in patients discontinuing treatment.[65]

The original study included heavily pretreated CML patients or Ph+ acute lymphoblastic leukemia (ALL) resistant or intolerant to dasatinib or nilotinib or with T315I confirmed at baseline (N = 267). At baseline 26 unique mutations were detected. There were no mutations detected in 51% of patients, 1 mutation detected in 39%, and 2 or more mutations found in 10% of patients. Responses were observed regardless of baseline mutation status. Major cytogenetic response (MCyR) rates were observed in 56% of all patients, 49% of patients with no baseline mutations, 70% of patients with T315I mutation, and 57% of patients with other mutations (**Figure 9**). Durable responses to ponatinib were observed regardless of baseline mutation. For CML-chronic phase (CP) patients in MCyR, 91% were estimated to remain in response at 12 months. Resistance to ponatinib was not correlated to any single mutation in CML-CP patients.

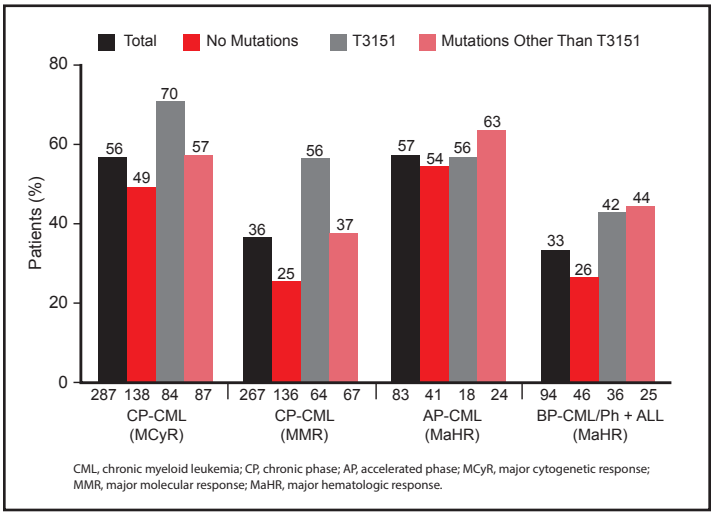
Overall, responses to ponatinib were observed regardless of baseline mutation status or disease stage, and durable responses were noted for patients in CP. At therapeutic doses, no single mutation conferring resistance to ponatinib has been observed to date.

Myelodysplastic Syndrome

Lenalidomide With or Without EPO

Therapeutic options for patients with myelodysplastic syndrome (MDS) are mainly supportive of palliative treatments aimed at improving symptoms and quality of life. Stem cell transplantation has a curative potential but is only an option for a minority of patients and high-dose chemotherapy has poor efficacy with high toxicity. In lower risk MDS patients without del(5q), erythropoietic stimulating agents (ESA) as the first-line treatments of anemia yield responses of 40%-50% with a median response duration of 2 years.[66,67,68] Used

Figure 9. Response rates by baseline mutation status in heavily pre-treated CML patients treated with ponatinib.



CML, chronic myeloid leukemia; CP, chronic phase; AP, accelerated phase; MCyR, major cytogenetic response; MMR, major molecular response; MaHR, major hematologic response.

as a second-line treatment in ESA refractory patients, lenalidomide gives red blood cell (RBC) transfusion independence in 27% of lower-risk MDS without del(5q).[69] In vitro studies have shown an additive effect of lenalidomide and ESAs on response of erythroid progenitors.[70] Dr Toma and colleagues from the Groupe Francophone des Myélodysplasies designed a randomized, prospective, multicenter, open-label phase II clinical trial combining lenalidomide with or without EPO for low-risk patients.[71]

The inclusion criteria for this study included low-risk MDS patients, without a del(5q), transfusion dependent, ESA failure after 12 consecutive weeks, or relapse after response. Patients were randomized to receive lenalidomide alone (10 mg/day for 21 days and every 28 days thereafter) or lenalidomide plus erythropoietin (EPO; 60,000U per week) for 4, 28-day cycles. The primary endpoint was erythroid response (HI-E, IWG 2006 criteria) after 4 treatment cycles. The secondary endpoints were to evaluate RBC transfusion independence, safety, and the duration of the erythroid response.

Between July 2010 and June 2012, 132 patients were enrolled in this study; 3 patients were excluded leaving 129 evaluable patients. Median patient age was 73 (45-88) years. Patient characteristics were well matched between the groups.

An intention to treat analysis of the 129 patients found that that the erythroid response was greater in the lenalidomide plus EPO arm compared to lenalidomide alone (40.0% vs 23.4%, $P = 0.043$). There was no significant difference in RBC transfusion independence in the lenalidomide plus EPO vs lenalidomide alone (24.6% vs 14.1%, $P = 0.13$) (**Table 5**).

Table 5. Lenalidomide with or without EPO in lower-risk MDS patients with anemia resistant to ESA.

	Lenalidomide + EPO n = 65	Lenalidomide n = 64	*P*
Erythroid response	40.0%	23.4%	0.043
RBC transfusion independence	24.6%	14.1%	0.13

MDS, myelodysplastic syndrome; ESA, erythroid stimulating agents; EPO, erythropoietin; RBC, red blood cell.

Grade 3/4 serious AEs occurring before the end of the 4th cycle included infections, myelosuppression, DVT, and cardiovascular and gastrointestinal disorders, but there was no significant difference in occurrence between the arms. Thirty-three patients discontinued treatment early, but this was not different between the 2 arms. Reasons for discontinuation included toxicity (n = 24), death (n = 6), and consent withdrawal (n = 3).

Ancillary analysis using the 29-gene expression profile signature of bone marrow mononuclear cell RNA from 50 patients (23 responders and 27 non-responders) found that in responders vs non-responders analysis, 19 genes were downregulated (transcription, signaling, and DNA repair) and 8 genes were upregulated (splicing and apoptosis). In the entire cohort, a cereblon gene promoter polymorphism predicted erythroid response to lenalidomide.[72]

Table 6. All causes of death in patients who received an ablative marrow transplant with Bu/Flu conditioning and post-transplant prophylaxis with cyclophosphamide.

Cause of Death	Related, n n = 45	Unrelated, n n = 47	Total, n (%) N = 92
Relapsed or progressive disease	9	6	15 (16%)
Non-relapse mortality	7	8	15 (16%)
Bacterial infection	2	3	5 (5%)
Respiratory viral infection	1	2	3 (3%)
Diffuse alveolar hemorrhage	2	0	2 (2%)
Stroke	0	1	1 (1%)
Multi-organ failure	0	1	1 (1%)
GVHD	1	1	2 (2%)
Venocclusive disease	1	0	1 (1%)

GVHD, graft-vs-host disease; Bu, busulfan; flu, fludarabine; CI, confidence interval; BMT, bone marrow transplant; NHL, non-Hodgkin lymphoma.

Overall, lenalidomide with erythropoietin yielded significantly higher responses in lower risk MDS patients with anemia resistant to ESA. There was no difference, however, in RBC transfusion independence. Finally, response to lenalidomide was predicted by a cereblon gene promoter polymorphism.

Stem Cell Transplant

Myeloablative Busulfan/Fludarabine Conditioning and Short-Course, Single-Agent GVHD Prophylaxis With High-Dose, Post-Transplantation Cyclophosphamide

The clinical efficacy of both busulfan/fludarabine conditioning and post-transplant high-dose cyclophosphamide as graft-vs-host (GVHD) prophylaxis have been independently shown in multiple single-center hematopoietic stem cell transplant studies.[73,74] Kanakry and his collaborators sought to combine these 2 promising strategies in a multi-institutional clinical trial.[75]

The study enrolled patients with a high-risk hematologic malignancy who were 65 years or older with an ECOG performance status of 2 or lower. Patients must have had an HLA-matched donor. Busulfan (130 mg/m^2/dose, IV) was given in pharmacokinetically adjusted doses to achieve a targeted steady-state concentration. Fludarabine was given at a dose of 40 mg/m^2/dose, IV. Both agents were administered on transplant days -6 to -3 prior to bone marrow infusion on day 0. Cyclophosphamide (50 mg/m^2/dose, IV) was given days +3 and +4 and was administered as sole GVHD prophylaxis. The primary endpoint of the study was the incidence of grade 3/4 acute GVHD. The secondary endpoints were non-relapse mortality at 100 days and 1 year, disease-free and OS, and incidence of chronic GVHD.

Ninety-two patients (median age 49, range 21-65) received HLA-matched allografts. The majority of the patients (74%) were diagnosed with a myeloid malignancy (AML, MDS, CMML) with ALL as the second most common disease (37%). Three-quarters of the patients were in morphologic CR, 27% with MRD and 25% with active disease at the time of transplant. In terms of donor and graft characteristics, the median donor age was 51 years for related donors and 32 for unrelated donors. Twenty-seven percent of the female into male transplants, a known independent risk factor for GVHD, were performed. Nearly half of the donors and recipients had documented cytomegalovirus serology mismatch. Median follow-up was 565 days for all patients and 794 days for patients alive at last update.

Grade 3/4 treatment-related toxicities up to day 100 were low and the major toxicity was mucositis (21%). Primary graft failure occurred in 5% of the patients. The cumulative incidence of grade 2-4 acute GVHD was 51% (42% and 60% in those patients who had a related vs unrelated donor, respectively). In contrast, grade 3/4 GVHD was low with a cumulative incidence of 15%, and chronic GVHD was 14%. Non-relapse mortality was 9% at 100 days and 16% at 1 year with no difference between the donor groups. Deaths were attributed to relapsed or progressive disease and non-relapse mortality including bacterial and respiratory infections, diffuse aveolar hemorrhage, stroke, multi-organ failure, GVHD, and venocclusive disease (**Table 6**).

At 2 years, the EFS was 62% and this was similar for both donor types. The EFS stratified by disease status revealed that 2-year EFS for patients in a CR, with MRD, or with active disease was 80%, 50%, and 33%, respectively. Overall survival at 2 years was 67% (79%, 50%, and 54% for patients with CR, MRD, and active disease, respectively).

Overall, this multi-institutional trial demonstrated that post-transplant high-dose cyclophosphamide as a single-agent GVHD prophylaxis can be safely and effectively combined with busulfan and fludarabine myeloablative conditioning. The combination yielded low levels of grade 3/4 acute GVHD and low treatment-related mortalities. This combination provided effective disease control with favorable EFS and OS.

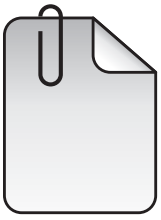
CONCLUSION

ASCO 2013 provided an excellent venue for the distribution of important hematology clinical trial information that may positively impact clinical practice.

In MM, data presented suggest that advances in the treatment of MM have been made with novel immunomodulatory drugs and first and second generation proteasome inhibitors. While clinical studies are in the early stages, results are also promising with antibodies such as daratumumab demonstrating efficacy.

In the lymphomas, the combination of ibrutinib-R-CHOP has a reasonable safety and toxicity profile and promising response rates in DLBCL patients. Idelalisib-based combination therapy was highly active and well tolerated in patients with relapsed/refractory indolent NHL with observed durable responses. In previously treated MCL patients, the combination of bendamustine, rituximab, and idelalisib produced encouraging response rates. Single-agent lenalidomide provided clinical benefit in some patients with relapsed/refractory MCL post-bortezomib, particularly those with lower LDH levels. The CID-ATT regimen was found to be superior to CHOP in induction therapy for untreated early stage ENKL. The costs incurred with routine surveillance imaging and the potential risks to the patients are significant without an obvious OS benefit in HL patients. Similarly, routine surveillance scans post-therapy provided little apparent benefit in terms of detection of DLBCL relapse.

In the leukemias, idelalisib induced relatively rapid responses in heavily pretreated and refractory CLL patients. In older patients, idelalisib plus rituximab is highly active as frontline therapy in treatment-naïve patients with CLL. The combination of chlorambucil with an anti-CD20 antibody (either rituximab or obinutuzumab) proved beneficial to previously untreated elderly CLL patients with significant comorbidities and was superior to chlorambucil alone. In lower-risk MDS patients with anemia resistant to ESA, erythroid response was significantly higher in those patients given lenalidomide and EPO compared to lenalidomide alone. In CML, durable responses to ponatinib were observed regardless of baseline mutation status or disease stage in heavily pretreated CML patients. It is postulated that early introduction of ponatinib may suppress the emergence of single *BCR-ABL1* mutations and as a result the development of compound mutations. Finally, post-transplant high-dose cyclophosphamide as a single-agent GVHD prophylaxis can be safely and effectively combined with busulfan and fludarabine myeloablative conditioning in the hematopoietic stem cell transplant setting.



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