# Advances in the Management of Hematologic Malignancies: Highlights from the 2012 ASCO Annual Meeting

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### INTRODUCTION
This newsletter highlights key experimental and clinical data presented at the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago, Illinois. Participants will be provided with an overview of the most recent advances in the treatment of cancer, as well as specific updates and outcomes of ongoing clinical trials, synthesized into a concise learning opportunity by experts in the field.

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

### 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

With the theme "Collaborating to Conquer Cancer" the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, held in Chicago, Illinois provided the largest international multidisciplinary forum for cutting-edge cancer research. In an effort to improve the lives of cancer patients, both in terms of quality and quantity, clinicians from around the world gathered to hear the most current advances in cancer research. Further optimization of current treatments and the development of important novel therapies continued to be intense areas of investigation. Data and information from notable ASCO presentations on hematological malignancies are included in this newsletter.

## LYMPHOMA UPDATE

### *Indolent Non-Hodgkin Lymphoma*

There are approximately 25,000 new cases per year of indolent and mantle cell lymphomas (MCL) in the United States alone. Although there is increased knowledge about the biology of these diseases, the clinical management and incorporation of new therapies is challenging because of the inherent complexity of indolent non-Hodgkin lymphomas (NHL) and the marked clinical and biological heterogeneity, within and between individual subtypes. Furthermore, none of these diseases are curable with standard treatments. Most patients relapse and undergo sequential therapies with cumulative toxicities that may limit their future treatment options. Clearly, there is a need to move away from traditional sequential cytotoxic therapy towards better therapeutic options that are more durable and less toxic.

**BR vs R-CHOP in Indolent and Mantle Cell Lymphoma**

Bendamustine, a purine analog/alkylator hybrid chemotherapeutic agent with possible bifunctional properties, has been approved for the treatment of rituximab-refractory indolent lymphoma.[1,2] Rituximab is a chimeric monoclonal antibody against the CD20 antigen. When bendamustine was combined with rituximab, in patients with relapsed indolent and MCL, both patient populations benefitted with greater than 90% overall response rate (ORR) and median duration of response (DOR) from 21 to 24 months.[3,4]

The German StiL NHL1 study was a multicenter, randomized, phase III, German national trial that enrolled 549 indolent and MCL patients between September 2003 and August 2008. The trial compared bendamustine plus rituximab (BR) to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in newly diagnosed patients in need of therapy. Preliminary analysis of the trial data including a comprehensive safety analysis was presented at the American Society of Hematology (ASH) Annual Meeting in 2009.[5] At the ASCO 2012 plenary session, Dr Rummel and his colleagues presented updated long-term results of this trial.[6]

This trial was originally designed as a BR non-inferiority trial. Patients were randomized to 6 cycles of BR (bendamustine at 90 mg/m$^2$ days 1-2 and rituximab at 375 mg/m$^2$ day 1) or R-CHOP (cyclophosphamide 750 mg/m$^2$ day 1, doxorubicin 50 mg/m$^2$ day 1, vincristine 1.4 mg/m$^2$ day 1, prednisone 100 mg days 1-5, and rituximab 375 mg/m$^2$ day). The primary objective of this study was non-inferiority of BR vs R-CHOP (defined as a decrease of less than 10% in progression-free survival [PFS] after 3 years). Secondary objectives included response, time to next treatment, overall survival (OS), acute vs late toxicities, infectious complications, and stem cell mobilization capacity in younger patients. At the time of data analysis, 514/549 symptomatic patients were evaluable for response and toxicity. The patient characteristics in both arms of the trial were well matched with a median age of 64 years in each arm (**Table 1**).

**Table 1. Histology breakdown for the StiL trial.**

| | BR N = 261 | R-CHOP N = 253 | Median Age (years) |
|---|---|---|---|
| Follicular (54%) | 139 | 140 | 60 |
| Mantle cell (18%) | 45 | 48 | 70 |
| Marginal zone (13%) | 37 | 30 | 66 |
| Waldenström's (8%) | 22 | 19 | 64 |
| SLL (4%) | 10 | 11 | 68 |
| Unclassifiable (2%) | 7 | 5 | 69 |

BR, bendamustine 90 mg/m$^2$ day 1-2, rituximab 375 mg/m$^2$ day 1; R-CHOP, rituximab 375 mg/m$^2$ day 1; cyclophosphamide 750 mg/m$^2$ day 1, doxorubicin 50 mg/m$^2$ day 1, vincristine 1.4 mg/m$^2$ day 1, prednisone 100 mg days 1-5; SLL, small lymphocytic lymphoma

A summary of the hematological toxicities revealed a significant difference between neutropenia (grade 3 and 4) in the BR treated patients (29%) compared to R-CHOP treated patients (69%). Conversely, lymphocytopenia was more profound for the BR group (74%) vs the R-CHOP group (43%). There were no severe anemias or thrombocytopenias

in either group. Overall, there were more non-hematological toxicities with R-CHOP. These included alopecia (R-CHOP, 253 patients vs BR, 0 patients), parasthesias (R-CHOP, 73 patients vs BR, 18 patients), stomatitis (R-CHOP, 47 patients vs BR, 16 patients), and infectious complications (R-CHOP, 127 patients vs BR, 96 patients). There were more skin-erythema and skin allergic reactions reported in the BR group. The differences in the toxicities were all statistically significant. Thus, BR had a more favorable tolerability profile than did R-CHOP. There was no difference in the number of secondary malignancies occurring between the 2 treatment groups (BR, 20 patients [1 myelodysplastic syndromes (MDS)] vs R-CHOP, 23 patients [1 acute myeloid leukemia (AML)]) with a mean follow-up of 4 years. Transformations into an aggressive lymphoma were infrequent in both treatment groups.

Response rates were comparable between the 2 arms with a slightly better complete response (CR) for BR than R-CHOP (**Table 2**). With a median follow-up of 45 months, PFS was superior with BR (median PFS for BR, 69.5 months vs 31.2 months for R-CHOP) (**Figure 1**). With the exception of marginal zone lymphoma, the PFS benefit with BR was maintained in all histological subtypes. The PFS benefit with BR was independent of age. Progression-free survival was significantly prolonged with BR compared with R-CHOP regimen ($P < 0.001$) in patients with normal LDH, while in the elevated LDH group PFS was numerically, but not significantly increased with BR compared to R-CHOP ($P = 0.118$).

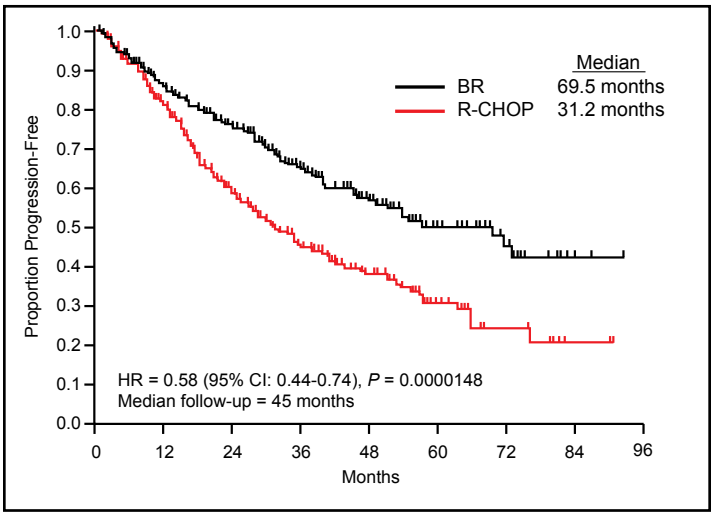
**Table 2. Response of indolent and mantle cell lymphoma to BR and R-CHOP (the StiL trial).**

| | BR n = 261 | R-CHOP n = 253 | *P* |
|---|---|---|---|
| ORR | 92.7% | 91.3% | |
| CR | 39.8% | 30% | 0.021 |
| SD | 2.7% | 3.6% | |
| PD | 3.5% | 2.8% | |

ORR, overall response rate; CR, complete response; SD, stable disease; PD, progressive disease; BR, bendamustine rituximab; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab

In patients with follicular lymphoma (FL), both Follicular Lymphoma International Prognostic Index (FLIPI) subgroups defined by 0-2 factors (favorable) and 3-5 factors (unfavorable) had a longer PFS with the BR regimen than

**Figure 1. Progression-free survival in newly diagnosed patients with indolent and mantle cell lymphomas treated with bendamustine plus rituximab (BR) or CHOP plus rituximab (R-CHOP).[6]**




with R-CHOP ($P = 0.043$ and $P = 0.068$ for the favorable and unfavorable FLIPI subgroups, respectively). To date, the superiority of PFS with the bendamustine plus rituximab regimen has not translated into OS difference. However, with 43 and 45 deaths in the BR and R-CHOP arms, respectively, a longer observation time may be needed to observe a true difference in OS in this indolent patient population.

Seventy four salvage treatments have been initiated in the BR group compared with 116 in the R-CHOP group; notably, of those in the R-CHOP group 52 patients received BR as a salvage regimen. The use of BR did not appear to have stem cell depletion properties when compared to R-CHOP although more extensive evaluation of stem cell mobilization and collection following bendamustine therapy is needed.

Overall, the results from the German StiL NHL1 trial indicate that BR treatment in patients with previously untreated indolent lymphoma, and elderly patients with MCL results in superior PFS and improved tolerability compared to R-CHOP. These results support the use of BR as a frontline regimen for indolent B-cell lymphomas and non-transplant eligible MCL patients. However, longer follow-up and additional studies are needed to confirm the positive results and to determine the degree of long-term toxicities, the ability to mobilize stem cells after BR therapy for those patients needing a hematopoietic stem cell transplant (HSCT), and evaluate any benefit to OS.

**R-CVP vs R-CHOP vs R-FM for Advanced-Stage FL**

Follicular lymphoma is the most common of the indolent NHLs comprising about one-fifth of all NHL, and the second-most-common form of NHL overall.[7] At the time of diagnosis, patients are typically stage III or IV, but are generally asymptomatic. The median survival is 8 to 10 years, although survival times range from a few years to decades. The optimal chemotherapy regimen for patients with advanced active FL has not been determined.

Dr Federico and colleagues reported a phase III trial of rituximab with 3 chemotherapy regimens for previously untreated patients with advanced-stage FL. The FOLL05 trial from the Fondazione Italiana Linfomi consortium compared R-CHOP to rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) and rituximab plus fludarabine and mitoxantrone (R-FM).[8]

The primary endpoint of the study was time to treatment failure (TTF), which was defined as failed induction therapy, withdrawal due to unacceptable toxicity or shift to another therapy, progressive or relapsed disease or death in partial response (PR)/CR from any cause other than FL. From February 2006 to September 2010, 534 patients with active disease were randomized and stratified by FLIPI (0-2 vs 3-5) into the 3 treatment arms (178 patients for each treatment arm). Due to exclusions, there were 168 patients evaluable in the R-CVP treatment arm, 165 patients in the R-CHOP arm, and 178 patients in the R-FM arm with all 504 patients eligible for intent-to treat (ITT) analysis. Patient characteristics were well balanced in each arm of the study. Median patient age was 56 years (range 30-75), 92% of patients had stage III-IV disease, 37% had a FLIPI score of 3-5, and 27% with FLIPI2 score of 3-5.

Hematologic toxicity was more pronounced in the treatment arm containing fludarabine (R-FM arm) with marked differences in neutropenia and thrombocytopenia. Neutropenia was also greater in the R-CVP compared to the R-CHOP arm of the study. Grade 3/4 neutropenia increased with time and with each subsequent cycle in all 3 arms of the study. Thirty deaths were observed, 17 in the R-FM arm, 9 in the R-CHOP arm, and 4 in the R-CVP arm. A higher number of secondary malignancies were detected in patients who received R-FM (8%) compared to R-CHOP (3%) and R-CVP (2%).

Response rates were similar in all 3 treatment arms with a CR of 67% for R-CVP, 72% for R-CHOP, and 72% for the R-FM group. The ORR was 88%, 93%, and 91% for the R-CVP, R-CHOP, and R-FM groups, respectively. The OS was 95% at 3 years and the TTF was 56% at 3 years of follow-up.

Overall, R-CHOP and R-FM were superior to R-CVP as evaluated by the primary endpoint, TTF. In terms of toxicity, R-CHOP and R-CVP were found to be less toxic than R-FM. Dr Federico concluded his presentation by indicating the comparison of chemotherapy regimens for previously untreated patients with advanced-stage FL found that the R-CHOP combination of therapeutic agents was associated with the best risk/benefit ratio.

**R-CHOP vs CHOP Plus $^{131}$Iodine-Tositumomab for FL**

The Southwest Oncology Group (SWOG) and the Cancer and Leukemia Group B (CALGB) compared the safety and efficacy of 2 immunochemotherapy regimens in a phase III trial enrolling 554 advanced FL patients (bulky stage II, III, or IV) between 3/1/2001 and 9/15/2008. The patients were randomized to either 6 cycles of standard chemotherapy with R-CHOP[9] or 6 cycles of CHOP, followed by a dosimetric infusion of $^{131}$iodine-tositumomab ($I^{131}T$) (CHOP-RIT) followed 1 to 2 weeks later by a therapeutic infusion of $I^{131}T$ sufficient to deliver a total body dose of 75 cGy.[10] An exploratory subset analysis and comparison of 3 prognostic models were presented by Dr Press.[11]

The objective of this trial was to compare PFS and OS after frontline therapy of FL with R-CHOP (n = 279) or CHOP-RIT (n = 275). Patients were stratified by β2 microglobulin (β2M) level. The patient characteristics were well balanced between the 2 immunochemotherapeutic arms with a median age of 53-54 years with over half of the patients with elevated β2M (an adverse prognostic factor).

Overall, both arms of the trial were well tolerated, with no statistically significant difference in grade 4 toxicity, treatment-related mortality, and secondary malignancies or AML. Compared with CHOP-RIT, patients who received R-CHOP experienced more grade 3/4 febrile neutropenia (16% vs 10%, $P = 0.05$) but less grade 3/4 thrombocytopenia (2% vs 18%, $P < 0.0001$).

At a median follow-up of 4.9 years, the estimated 5-year PFS was 60% with R-CHOP and 66% with CHOP-RIT. The estimated 5-year OS was 92% with R-CHOP and 86% with CHOP-RIT.

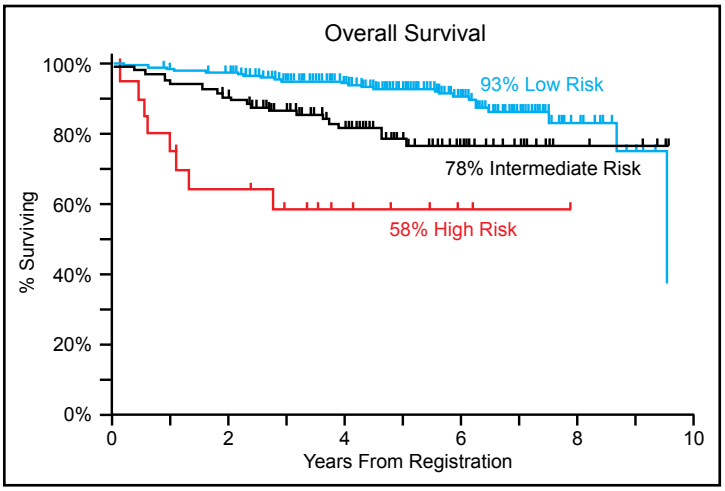
The authors suggest that although $I^{131}T$ will not replace rituximab as initial therapy of FL, the agent may prove beneficial as consolidation after R-CHOP, with or without additional rituximab maintenance.

An extension of this study was an exploratory subgroup analysis designed to determine whether subgroups of patients benefitted from either immunochemotherapeutic arms. The objectives were 3-fold: 1. to identify the prognostic factors predicting PFS and OS using a univariate and multivariate Cox regression model; 2. to compare 3 mutivariable prognostic factors (FLIPI1, FLIPI2, and a lab-based risk model) and, 3. to explore whether any subgroup benefitted more from treatment with R-CHOP or CHOP-RIT. The prognostic value of 3 multi-variable models was compared.[11]

Of the 7 factors that were statistically associated with greater PFS (hemoglobin [12], max lymph node size [≥ 6 cm], performance status [≥ 1], β2M, lactate dehydrogenase (LDH), number of lymph node areas [> 4], stage [II-III vs IV]), only β2M had a statistically significant association with treatment arm and PFS ($P = 0.02$). No factors had a statistically significant association with OS and treatment arm. Both FLIPI and FLIPI2 models were able to predict PFS and OS. However, there was no statistically significant interaction between the treatment arm and outcome with respect to risk levels. The third model based strictly on lab values showed that β2M, LDH, and hemoglobin were all significantly associated with PFS and OS in the univariate models. Only β2M and LDH remained independent for both PFS and OS in the multivariate models, and were selected for the lab-based model. The lab-based model performed at least as well as the FLIPI models for separating the high- risk (both β2M and LDH high) from low-risk patients for both PFS and OS (**Figure 2**).

Overall, the clinical outcomes are similar with either R-CHOP or CHOP-RIT. FLIPI, FLIPI2, and LDH + β2M models were all strong predictors of patient outcomes. Both FLIPI and FLIPI2 models were highly associated with PFS and OS in this trial, although the lab-based model using the risk factors of β2M and LDH had similar prognostic value to FLIPI and FLIPI2 was easier to perform. The retrospective subanalyses hypothesized that the low-risk patients may have superior outcomes with the CHOP-RIT whereas the high-risk patients may have superior outcomes with R-CHOP.

**Figure 2. A lab-based model using β2 microglobulin and lactate dehydrogenase levels predicted overall survival in follicular lymphoma patients treated with CHOP plus rituximab or CHOP plus $^{131}$iodine-tositumomab.**




**Rituximab Dosing Strategies for Low Tumor Burden FL: The RESORT Trial**

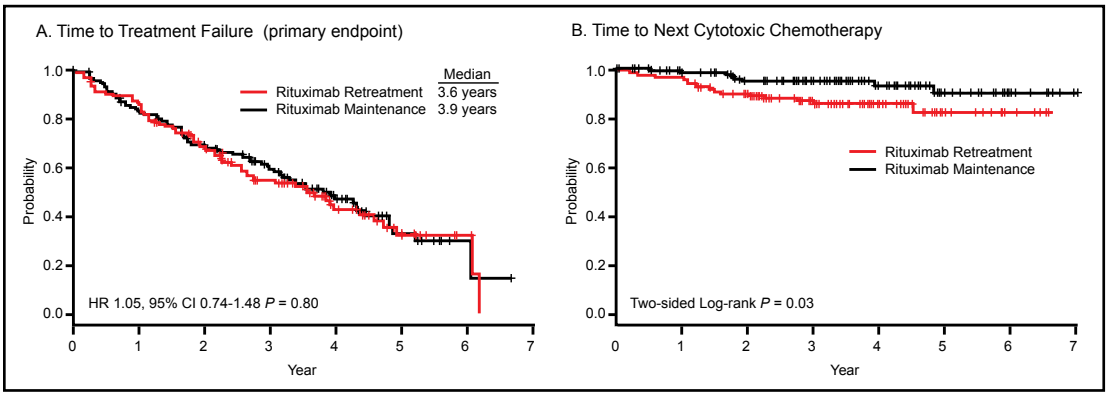
Follicular lymphoma is classified as low tumor burden (LTB) by the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria if a nodal or extranodal tumor mass is less than 7 cm in diameter, involvement includes less than 3 nodal sites with a diameter of more than 3 cm, and systemic symptoms, splenic enlargement, serous effusion, local risk of compression (epidural, ureteral, etc), leukemia, and cytopenias are absent.

The standard therapeutic approach for patients with LTB follicular lymphoma (LTBFL) has been "watch and wait" with initiation of chemotherapy upon the development of high tumor burden. This paradigm was based on 3 randomized trials that failed to show an OS advantage for immediate chemotherapy treatment vs the watch and wait strategy.[12,13] However, based on the relative safety and high activity of rituximab, investigators from the Eastern Cooperative Oncology Group (ECOG) initiated a study to investigate the efficacy of 2 rituximab dosing strategies in patients with indolent lymphoma who previously were untreated, but not necessarily newly diagnosed. Results for the FL patients in this phase III study, Rituximab Extended Schedule or Re-Treatment Trial (RESORT), were reported at the ASH Annual Meeting in December 2011 and at the ASCO/ASH 2012 Joint Session by the Study Chair Dr Brad Kahl.[14,15]

Enrolled patients received rituximab (375 mg/m$^2$ weekly for 4 weeks) as induction. If a CR or PR was achieved, patients were randomly assigned to either maintenance rituximab (MR) at 375 mg/m$^2$ every 12 weeks or retreatment rituximab (RR) where 375 mg/m$^2$ was given weekly for 4 weeks only when progression occurred. The primary endpoint was TTF, defined as progression within 6 months of last rituximab, no response to RR, initiation of alternative therapy, or inability to complete rituximab therapy.

The study enrolled 129 non-FL patients and 384 FL patients. Of the 384 FL patients, 274 (71%) responded to induction rituximab and were subsequently randomized to the 2 treatment strategies (RR, n = 134; MR n = 140). The median follow-up time was 3.8 years. For the primary endpoint of TTF, there was no difference between regimens, with a median of 3.6 years in the RR group and 3.9 years in the MR group (HR 1.05, 95% CI 0.74-1.48, *P* = 0.80; **Figure 3**).There was a statistically significant difference in the percentage of patients at 3 years who had not yet required first cytotoxic therapy (86% with RR and 95% with MR; HR 2.5, 95% CI 1.08-5.77, *P* = 0.027).

**Figure 3. The RESORT trial. (A) Time to treatment failure and (B) time to next cytotoxic chemotherapy for low tumor burden follicular lymphoma patients treated with maintenance rituximab or rituximab retreatment.**




Quality of life (QOL) and anxiety were measured with standardized scales at baseline, months 3, 6, 12, 24, 36, and 48 and at the time of treatment failure. The ratings at 1 year showed no difference.

Grade 3/4 toxicity occurred in less than 5% of patients. There was 1 case of progressive multifocal leukoencephalopathy in the MR group and 1 death in each group. The mean total number of rituximab doses administered per patient during the study period (including the induction regimen) was 4.5 in the RR group compared with 15.8 in the MR group.

Dr Kahl concluded his presentation by stating a RR strategy was as effective as the MR strategy for previously untreated LTBFL patients for the endpoint of TTF. If the decision is made to use rituximab for LTBFL, the RR approach is superior to MR, based on the excellent outcome where 86% of patients were chemotherapy-free at 3 years, the lack of a QOL difference between the 2 strategies, and decreased use of healthcare resources because fewer doses of rituximab are required with RR. Therefore, RR proved to be the superior strategy if opting for rituximab monotherapy in LTBFL.

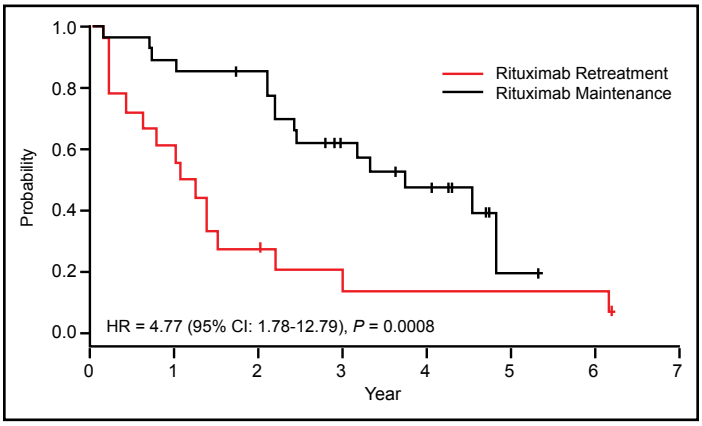
**Rituximab Dosing Strategies for SLL and MZL, Subset Analysis of the RESORT Trial**

A subgroup exploratory analysis of non-FL patients with small lymphocytic lymphoma (SLL) and marginal zone lymphomas (MZL) in the RESORT trial was presented by Williams and colleagues on behalf of ECOG co-investigators.[16]

Data from 129 non-FL patients, 55 SLL and 74 marginal zone lymphoma (MZL) were included in the analysis. The combined ORR of the non-FL patients (SLL, splenic MZL, extranodal MZL, nodal MZL, and other B-cell lymphomas) was 39% (n = 50) compared to 70% for LTBFL (*P* < 0.001). The ORR was 51% (n = 36/71) for MZL and 22% (n = 12/55) for SLL patients. The non-FL combined CR was 7% (n = 9) with the majority of the patients achieving stable disease (SD; n = 71/129, 59%). Three patients (2%) progressed through rituximab treatment.

With the exception that more males were enrolled on the MR arm, patient characteristics were well-balanced between the MR and RR randomized treatment arms. At the time of randomization (with a median follow-up of 4.3 years), the number of patients in CR and PR were comparable (CR/CR unconfirmed [CRu]): 19% RR vs 17% MR; PR: 81% RR vs 83% MR). In terms of the primary study endpoint TTF, there was a significant benefit for the maintenance strategy in the non-FL subpopulation (**Figure 4**). With a median follow-up of 4.3 years, TTF was 3.74 years for MR vs 1.07 year for RR (*P* = 0.0002; HR 4.95). This benefit of MR was also true for the

**Figure 4. RESORT trial subgroup analysis. Time to treatment failure in small lymphocytic leukemia (SLL) and marginal zone lymphoma (MZL) for patients treated with maintenance rituximab or rituximab retreatment.**




secondary endpoint of time to first cytotoxic therapy with all of the MR patients remaining free of cytotoxic therapy, versus 70% for RR.

Overall, in contrast to what was found for FL, maintenance therapy with rituximab was superior to RR for TTF in previously untreated, LTB non-follicular indolent B-cell lymphoma patients who achieved a CR or PR with rituximab monotherapy. This was also true for time to cytotoxic therapy where at 3 years no MR patient had received cytotoxic therapy. Thus, for FL, retreatment with rituximab is the recommended strategy for responding patients, whereas for non-follicular indolent lymphoma patients, the maintenance with rituximab strategy is an acceptable approach in patients responding to weekly x 4 rituximab. Future analyses with more patients are needed to confirm these results in MZL. In addition, the low ORR of SLL to weekly x 4 rituximab in this and earlier studies suggests that other strategies will be preferable for this subtype of indolent lymphoma.

**Lenalidomide vs Lenalidomide Plus Rituximab in Recurrent FL, CALGB 50401 Trial**

Lenalidomide is an immunomodulatory agent with numerous anti-tumor effects[17] and with approved indications for multiple myeloma (MM) and MDS. The drug has also been studied in B-cell disorders such as chronic lymphocytic leukemia (CLL). Preclinical evaluations have shown lenalidomide enhances rituximab-induced apoptosis and activates NK cells, enhancing antibody-dependent cellular cytotoxicity (ADCC) and providing a synergistic effect that may overcome tumor resistance to rituximab.[18] Lenalidomide is active in recurrent FL.[19] In a randomized trial in relapsed, rituximab-naïve or -sensitive, FL patients, the ORR was 49% when patients were given 8 doses of rituximab.[20] Lenalidomide and rituximab are active as single agents in FL and other B-cell lymphomas, although combination strategies have not been previously assessed in a randomized fashion. Based on these observations, a randomized phase II trial was designed by Dr Leonard and his North American collaborators to evaluate lenalidomide compared to lenalidomide plus rituximab in patients with recurrent FL.[21]

Initially designed to evaluate 3 regimens, rituximab alone (375 mg/m$^2$ weekly x 4), lenalidomide alone (15 mg cycle 1, then escalated to 20 mg and 25 mg cycles 2-12, administered days 1-21 q 28 days x 12 cycles), or the combination of lenalidomide plus rituximab (same dosing). The rituximab alone arm was discontinued due to slow accrual. The primary objective of the study was the ORR, and secondary objectives included CR and event-free survival (EFS) to provide benchmarks for future study and to examine the toxicity profiles of both of the therapies. The key eligibility criteria included recurrent FL, prior therapy with rituximab alone or in combination with chemotherapy, and time to progression (TTP) of ≥ 6 months from the last rituximab dose.

Of the 94 recurrent FL patients who met eligibility criteria, 89 patients received at least 1 dose of therapy and were evaluable. Therefore, 45 patients were randomized to the lenalidomide alone arm and 44 to the lenalidomide plus rituximab arm of the study. The baseline characteristics included a median age of 63 years (range 34-89) and the majority of patients with intermediate- or high-risk FLIPI.

Grade 3/4 adverse events (AE) were most commonly neutropenia, fatigue, and thrombosis (lenalidomide 16%; lenalidomide plus rituximab, 4%; $P = 0.158$). The full regimen was completed by 33% of patients on lenalidomide alone and 59% on lenalidomide plus rituximab, with the difference mainly due to more progressions or non-responders in the lenalidomide alone group. In both arms approximately 19% of subjects discontinued therapy early due to AE.

The ORR was 51.1% (13% CR) for the lenalidomide arm and 72.7% (36.4% CR) for the combination arm. With a median follow-up of 1.5 years (range 0.1-3.6 years), median EFS was 1.2 years for lenalidomide and 2.0 years for lenalidomide plus rituximab ($P = 0.0063$).

Overall, lenalidomide had significant activity as a single agent or in combination with rituximab in patients with recurrent FL. The ORR was greater with the combination of the 2 agents and was more active than lenalidomide alone in patients with recurrent FL, but had similar toxicity. A trend toward lower thrombosis risk with lenalidomide plus rituximab may relate to greater anti-tumor efficacy. This combination regimen warrants further study in FL including investigation for its use as a backbone for future non-cytotoxic treatment regimens.

## *Aggressive Non-Hodgkin Lymphoma*

### Radiotherapy for Elderly Patients With DLBCL

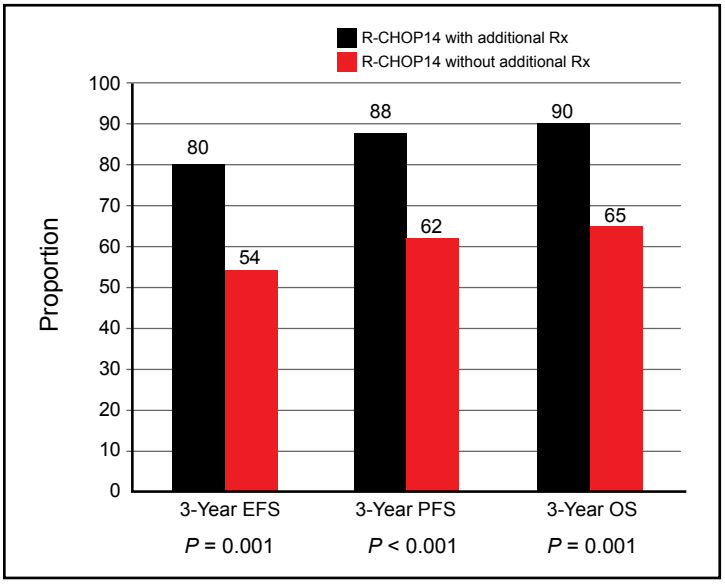
Diffuse large B-cell lymphoma (DLBCL) is the most common NHL histology, comprising approximately one-third of all adult lymphomas. Diffuse large B-cell lymphoma is associated with an aggressive natural history, and, if left untreated, median survival is less than 1 year. Treatment with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was the mainstay of DLBCL therapy for several decades. The pivotal GELA study, found that the addition of rituximab to CHOP (R-CHOP) significantly improved OS compared to CHOP alone, and established R-CHOP given every 21 days (R-CHOP21) as standard therapy for DLBCL.[22] Several trials have explored the possible advantage of dose-intense CHOP-based regimens in combination with rituximab; however, although the addition of rituximab to the standard CHOP therapy has improved outcomes, the universal optimal intensive dosing schedule in the era of rituximab in DLBCL has not been identified.

Dr Held and colleagues have undertaken a non-randomized phase II extension of the RICOVER-60[23] trial named RICOVER-60-no-Rx trial.[24] Immunochemotherapy consisted of 6 cycles R-CHOP14 plus 2 additional rituximab doses in the RICOVER-60-no-Rx trial. Radiotherapy (Rx) was mandatory for bulky (> 7.5 cm) and extranodal disease in the RICOVER-60 trial; however, no radiotherapy was given in the RICOVER-60-no-Rx trial. Patients with CD20+ DLBCL stages I-IV, ages 61-80 years were eligible. Of the 306 elderly patients treated in RICOVER-60 with 6 cycles of R-CHOP14 with 2 additional rituximab doses, 117 were assigned to receive Rx to their bulky disease.

Outcome of 164 elderly patients prospectively treated without Rx in the RICOVER-60-no-Rx was compared with the historical data of 306 patients from RICOVER-60. There was a difference in the patient characteristics; patients in R-CHOP-no Rx group were older (71 vs 69 years; $P = 0.018$), more frequently in advanced stages (60% vs 50%; $P = 0.037$), and with extranodal involvement (63% vs 53%; $P = 0.024$), while bulky disease was more frequent in R-CHOP14-Rx group (35% vs 29%; $P = 0.038$).

With a median observation time of 39 months, patients who received additional Rx in R-CHOP14 had longer 3-year EFS (80% vs 54%; $P = 0.001$), PFS (88% vs 62%; $P < 0.001$), and OS (90% vs 65%; $P = 0.001$) compared to R-CHOP14-no RX (**Figure 5**). This was largely due to patients with bulky disease in R-CHOP14-no Rx group having worse outcomes after 6 cycles of R-CHOP if they achieved less than a CR with R-CHOP induction therapy.

**Figure 5. Three-year event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) in elderly patients with bulky DLBCL treated with R-CHOP14 with or without additional radiotherapy (Rx).**




Overall, within the rituximab era, the addition of Rx to bulky disease does not improve the outcome of elderly patients in CR/CRu after completion of R-CHOP14 immunochemotherapy. However, for patients with bulky disease who do not achieve a CR or CRu, Rx appears to be beneficial. By restricting radiotherapy to patients not achieving a CR/CRu, 43% of the patients with bulky disease could be spared radiotherapy exposure.

**BR in Relapsed/Refractory DLBCL**

Dr Ogura and colleagues conducted an open-label, multicenter, single arm, phase II study to examine the safety, efficacy, and pharmacokinetic parameters of BR in patients with relapsed/refractory DLBCL.[25] The primary endpoint was ORR. Complete response rate, PFS, safety, tolerability, and pharmacokinetic parameters were examined as secondary endpoints. Patients with histologically confirmed DLBCL who satisfied the inclusion and exclusion criteria were eligible to enroll in the trial in which bendamustine was given at 120 mg/m$^2$ on days 2 and 3 in up to 6 cycles in 21-day intervals. Rituximab was given at 375 mg/m$^2$ on day 1 in up to 6 cycles with the same 21-day interval. The severity of the adverse reactions dictated the reduction or discontinuation of bendamustine.

A total of 63 patients were enrolled with 59 patients evaluable. The median age of the patients was 67 (range 36-75) years with 37 patients over 65 years. The majority (64.4%) of patients experienced at least 1 prior therapy and 57 patients (96.6%) were previously treated with rituximab-containing combination chemotherapy. Eight (13.6%) patients had prior peripheral blood autologous stem cell transplant (ASCT). Patients received a median of 4 (range, 1-6) treatment cycles with 16 (27.1%) patients completing 6 treatment cycles. Disease progression (n = 15) and failure to meet criteria to start the next cycle (n = 13) were the most common reasons for early discontinuation.

In 59 evaluable patients, the ORR was 62.7% with a 37.3% CR rate. The median PFS was 6.7 months. The most common grade 3/4 hematologic AE included a reduction in CD4 lymphocytes (66.1%), neutropenia (54.2%), and thrombocytopenia (10.2%). Four (6.8%) patients discontinued therapy due to serious AE (cytomegalovirus infection, infection, pneumonia, and pneumonia/respiratory failure). Overall, these results suggest that BR is a promising salvage regimen and should be furthered evaluated in patients with relapsed/refractory DLBCL after R-CHOP.

## *T-Cell Lymphoma*

**Bendamustine in Refractory/Relapsed T-Cell Lymphomas, BENTLY Trial**

Between 10% and 15% percent of all patients with NHL have a T-cell lymphoma subtype. Peripheral T-cell lymphomas (PTCLs) are a relatively rare and heterogeneous group of clinically aggressive diseases associated with poor outcome. In the past decade, an increasing number of studies have focused specifically on PTCL with the intention of understanding immunobiology of the disease and to develop new and more efficacious treatment strategies.

Dr Gressin and colleagues designed a prospective, multicenter, open-label, phase II study of bendamustine treatment in patients with relapsed or refractory T-cell lymphomas.[26] The objective of this study, the BENTLY trial, was to investigate the efficacy and safety of bendamustine as a single agent in the treatment of relapsed or refractory PTCL patients. The study enrolled 60 patients between the ages of 43 and 87 years with any type of histologically proven PTCL or mycosis fungoides (MF) stage IIB or more. Registered patients were treated with bendamustine administered at a dose of 120 mg/m$^2$ IV on days 1-2, every 3 weeks for a total of 6 cycles. Treatments were discontinued given evidence of partial disease (PD), unacceptable toxicity, or refusal by the patient. A cycle delay and a dose reduction occurred as a result of the development of grade 4 hematologic or 3/4 non-hematologic toxicity after any cycle. If toxicity continued, the treatment was stopped. Safety was assessed at every cycle.

Treatment response was assessed using the International Workshop Criteria (IWC) for NHL. The primary endpoint was ORR. Secondary endpoint included DOR, PFS, and OS. In the ITT population, the best ORR was 50%, with 28% CR (**Table 3**). Median DOR, PFS, and OS were 3.6, 4.0, and 6.0 months, respectively.

**Table 3. Response of relapsed/refractory PTCL patients to bendamustine.**

| Response after 3 cycles, N = 60 | n (%) |
|---|---|
| ORR (CR + CRu +PR) | 30 (50) |
| CR+ CRu | 17 (28) |
| PR | 13 (22) |
| SD | 3 (5) |
| PD | 27 (45) |
| Median DOR, months (range) | 3.5 (1-21) |

PTCL, peripheral T-cell lymphoma; CR, complete response; CRu, complete response unconfirmed; ORR, overall response rate; PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response

Bendamustine dose reductions were necessary in 15 patients mainly due to: hematologic toxicities (n = 7), infections (n = 3), and fatigue (n = 2). The most common non-hematologic grade 3/4 AE were infections, skin reactions, mucositis, and arrhythmia. All were reversible. Death secondary to infection occurred in 3 patients.

In summary, bendamustine is active in high-risk refractory and relapsed T-cell lymphoma with manageable and reversible hematological toxicities. The results showed an ORR of 50% with CR in 28%. However, the DOR was short. The role for bendamustine as a bridge to transplant needs to be determined in future studies.

## *Hodgkin Lymphoma*

### ABVD vs BEACOPP in Stage III-IV High-Risk HL

The optimal treatment approach for advanced stage Hodgkin lymphoma (HL) is controversial. A combined modality treatment and multiagent chemotherapy combination of adriamycin doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has been standard initial therapy for advanced stage HL for over 25 years with earlier trials demonstrating efficacy with a 5-year failure-free survival (FFS) rate of 61% and a 5-year OS of 73%.[27] The intense bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen was developed by the German Hodgkin Study Group to improve on standard therapy by intensifying treatment and substituting the active agent etoposide for vinblastine and dacarbazine. However, BEACOPP is highly myelosuppressive and associated with a risk of secondary malignancies. Thus, the challenge remains to develop or amend multi-agent modalities to increase positive response rates and lessen the observed toxicities. Modifications of the BEACOPP protocol have been sought to maintain or improve efficacy of this drug combination and reduce the observed adverse effects. To this end, Dr Carde and his international collaborators conducted a randomized phase III trial comparing ABVD to BEACOPP in stage III-IV high-risk HL. The preliminary results of this highly anticipated international EORTC 20012 intergroup randomized phase III clinical trial were presented at ASCO 2012.[28]

From January 2003 to January 2010 this trial accrued 549 high-risk patients under the age of 60 and an international prognostic score of 3 or higher. The study compared 8 cycles of ABVD (n = 275) to BEACOPP (n = 275). Radiation therapy was not included in the treatment schema. The primary endpoint was EFS. Additional endpoints included CR, PFS, OS, QOL, and secondary malignancies.

Discontinuations occurred in 16% of patients in the ABVD arm and 19% of the BEACOPP arm. The major reasons for discontinuation were relapse and disease progression in the ABVD group and toxicity in the BEACOPP arm. Toxicities leading to treatment discontinuation were mainly respiratory in the ABVD arm and hematologic and infections in the BEACOPP arm. There were a total of 56 deaths (33 ABVD and 23 BEACOPP) mostly due to toxicity with 27% of the deaths occurring within the first 3 months of treatment. The secondary malignancy rate was relatively low and similar for both groups with a cumulative incidence at 4 years of 4.7% for ABVD vs 3.4% for BEACOPP.

Complete response to treatment was approximately the same for each group (~ 82%). With a relatively short median follow-up of 3.8 years, the primary endpoint of EFS was 63.7% with ABVD compared to 69.3% with BEACOPP (HR = 0.86, 95% CI[0.64 to 1.15], $P = 0.312$). The PFS was 69.4% for the ABVD and 84% for the BEACOPP favoring the BEACOPP arm of the study. Overall survival was not significantly different (86.7% ABVD vs 90.3 BEACOPP).

Results from this trial demonstrate that EFS was similar between treatment arms. However, more progressions/relapses were observed with the ABVD arm, while early discontinuations were more frequent with BEACOPP therapy. Given lack of conclusive survival benefit the routine use of BEACOPP cannot be justified since most patients do well with ABVD or respond to secondary therapy. Longer follow-up will be needed to assess late relapses and delayed toxicities.

### Retreatment With Brentuximab Vedotin in CD30+ Hematologic Malignancies

Brentuximab vedotin is an anti-CD30 antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent, monomethyl auristatin E (MMAE). Brentuximab vedotin selectively delivers MMAE into CD30-expressing cells. In phase I studies, brentuximab vedotin demonstrated significant activity with a favorable safety profile in patients with relapsed or refractory CD30-positive lymphomas. A phase II monotherapy pivotal study demonstrated a 75% ORR with a CR of 34% in relapsed or refractory HL patients.[29] Similarly, an ORR of 86% with a median DOR of 12.6 months was observed in systemic anaplastic large cell lymphoma

(sALCL) patients.[30] Based on these studies brentuximab vedotin was FDA approved for the treatment of HL after failure of ASCT or at least 2 prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT and sALCL after failure of at least 1 prior multi-agent chemotherapy regimen. Dr Bartlett and her colleagues initiated a phase II trial to investigate whether patients who have previously responded to brentuximab vedotin could achieve another response with retreatment.[31]

The study recruited 24 patients with CD30-positive hematologic malignancies, who achieved response with prior brentuximab vedotin treatment and subsequently relapsed after discontinuing treatment. Brentuximab vedotin was administered at 1.8 mg/kg every 21 days IV and the antitumor activity was assessed by the investigator. The median age of the 14 HL patients and 8 sALCL (5 ALK-negative) was 34 years, with a range of 16-72 years. Patients had received a median of 4 prior systemic therapies (range 2-12). Median time since the previous brentuximab vedotin treatment was 6.9 months. The median number of brentuximab vedotin retreatment cycles was 7.

Common AE observed in more than 15% of patients were peripheral sensory neuropathy (46%), nausea (42%), fatigue (38%), and diarrhea (33%). The most common grade 3/4 AE were anemia, fatigue, and hyperglycemia observed in 3 patients each. Of the 11 patients who had pre-existing peripheral neuropathy (PN), 3 (27%) had worsening of the condition with retreatment.

A 70% ORR was observed with an 8.8-month median DOR. Among patients with HL (n = 15), 3 achieved a CR, 6 a PR, 2 had stable disease, and 27% had disease progression. Among the 8 patients with sALCL, 5 achieved a CR, 1 had PD, and 2 were not yet evaluated. Of the 8 patients exhibiting CR in retreatment, previous best responses to brentuximab vedotin treatment were 4 PR and 4 CR. Median duration of retreatment response was 10.8 months (range 0+ to 10.8). To date, 11 patients remain on the retreatment trial and recruitment of new patients is ongoing.

These results are promising and suggest that retreatment with brentuximab vedotin results in clinically meaningful activity. Enrollment to the phase II retreatment study is ongoing. Questions remain regarding timing and duration of retreatment and if the retreatment should be ongoing or punctuated by periods of no treatment.

**Everolimus for Relapsed/Refractory Classical HL**

Dysregulation of the PI3Kinase/AKT mTOR pathway has been implicated in the pathogenesis of HL. Everolimus, an oral mTOR inhibitor, has shown activity and acceptable toxicities in patients with relapsed/refractory HL.[32] Given these early results, Dr Johnston and collaborators designed a single-arm, open-label, phase II study to confirm the safety and efficacy of everolimus in adults with relapsed/refractory classical HL who progressed after high-dose chemotherapy with ASCT or a gemcitabine, vinorelbine, or vinblastine-containing regimen.[33]

A total of 55 patients were enrolled in this multicenter, phase II study and were given 10 mg daily until disease progression or unacceptable toxicity. Tumor assessments were performed at baseline and every 12 weeks, responses were monitored by PET/computer tomography (CT) with contrast or CT with contrast. The primary endpoint was ORR per modified response criteria for malignant lymphoma.

Of the 42 currently evaluable patients, 64% were women and the median age was 32.5 years. Almost 60% of the patients had received a prior ASCT, and 95% were pretreated with gemcitabine, vinorelbine, or vinblastine. Seventy-one percent of the patients had disease progression during previous therapies or discontinued previous treatment due to progression. Of the 42 evaluable patients, 23 patients discontinued treatment, most commonly due to disease progression (n = 11). The ORR was 38% (**Table 4**), and median PFS was 7.2 months.

**Table 4. Response of pre-treated classical Hodgkin lymphoma patients to everolimus.**

| Best overall response, N = 42 | n (%) |
|---|---|
| ORR (CR + PR) | 16 (38.1) |
| CR | 3 (7.1) |
| PR | 13 (30.9) |
| SD | 12 (28.6) |
| PD | 6 (14.3) |
| Unknown | 8 (19.0) |

CR, complete response; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

The most common hematologic AE were thrombocytopenia (42.9%) and anemia (23.8%); the most common nonhematologic AE were fatigue (47.6%), rash (28.6%), cough (23.8%), dyspnea (23.8%), and headache (21.4%).

In this study, everolimus demonstrated acceptable tolerability and promising efficacy in the first 42 heavily pretreated, relapsed/refractory classical HL patients. Future studies are needed to confirm these preliminary results and to evaluate the long-term responses to everolimus.

## MULTIPLE MYELOMA

The introduction of new therapeutic agents over the past decade has improved responses and prolonged survival in patients with MM. However, nearly all MM patients go on to experience relapsed disease. A number of clinical trials designed to further optimize therapy for newly diagnosed patients or to develop novel treatment strategies for relapsed/refractory MM were presented at ASCO 2012.

### *Frontline Treatment*

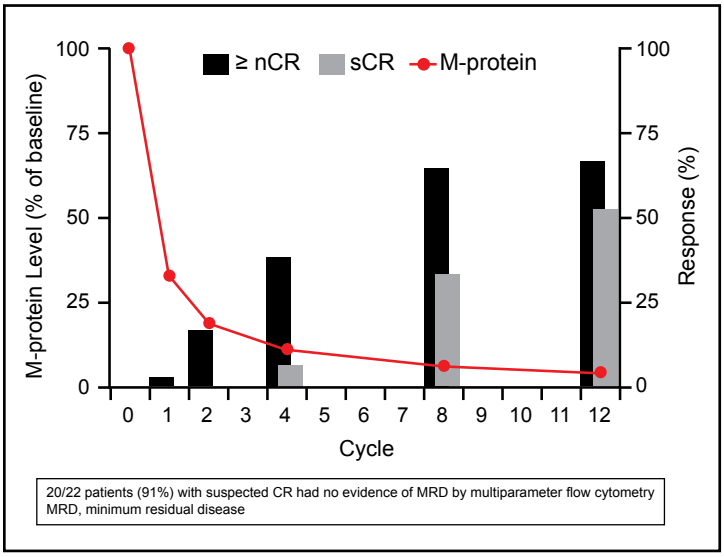
**Carfilzomib, Lenalidomide, and Dexamethasone**

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. Carfilzomib is a novel epoxyketone proteasome inhibitor that has demonstrated efficacy with manageable toxicity in early clinical trials.[34,35] A phase IIB, carfilzomib single agent trial that enrolled heavily pretreated MM patients showed good efficacy, tolerability and durability.[36] The safety and efficacy of carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) was examined in a phase I/II study demonstrating that this combination provided rapid reduction of disease (68% after 1 cycle), very good responses, evidence of improved depth of response over time, and good tolerability.[37] The clinical significance of these response rates with a longer follow-up of 13 months was examined by Jakubowiak and collaborators in newly diagnosed MM patients.[38]

The primary objective of the phase I study was to examine the maximum tolerated dose (MTD) of the CRd regimen Secondary objectives included ORR, DOR, PFS, OS, tolerability, and toxicity and the impact of the CRd combination on stem cell mobilization. The study included 53 newly diagnosed MM patients. The treatment schema included 8 induction cycles of carfilzomib (20 mg/m$^2$, 27 mg/m$^2$ [phase I], and 36 mg/m$^2$ IV on days 1, 2, 8, 9, 15, and 16), lenalidomide (25 mg PO, days 1-21), and dexamethasone (40/20 mg PO weekly, cycles 1-4/5-8) followed by 16 maintenance CRd cycles and lenalidomide off protocol.

The median patient age was 59 years with 43% of patients 65 years or older. Sixty percent had ISS stage II or III disease and 33% had unfavorable cytogenetics. The ORR was 94% with 65% achieving a very good partial response (VGPR) or better and 53% achieving a stringent CR (sCR), CR, or near CR (nCR). There was a rapid decline in M protein and an increase in nCR and sCR with time. More than 50% of patients achieved a sCR with 12 cycles (**Figure 6**). There was no evidence of minimum residual disease (MRD) in 20/22 (91%) patients with suspected CR.

**Figure 6. Stringent CR (sCR), ≥ near complete response (nCR), and M-protein levels in multiple myeloma patients treated with carfilzomib, lenalidomide, and dexamethasone (CRd).**




High response rates were observed in all ISS stages and irrespective of cytogenetic status. In the 28 patients who received a median of 12 cycles of therapy, 98% achieved a PR or better, 81% achieved a VGPR or better, and 62% achieved a CR or better, and 42% achieved a sCR. With a median follow-up of 13 months, the PFS was 97% and 92% at 12 and 24 months, respectively, with only 2 patients

progressing. In the 19 patients who received 12 or more cycles of CRd, 100% have achieved a VGPR or better and 70% have achieved a sCR, CR, or nCR. Twenty-four patients proceeded to stem cell harvest and ASCT, and all stem cell collections were successful.

Hematologic toxicity included thrombocytopenia, anemia, and neutropenia. Non-hematologic toxicity included infection, hyperglycemia, abnormal liver function tests, edema, diarrhea, rash, muscle cramping, dyspnea, phlebitis, fatigue, PN, reduced renal function, constipation, mood alterations, and deep vein thrombosis (DVT) or pulmonary embolism (PE). Dose modifications were required. Two PNs were limited to grade 1 and 2. There were no treatment discontinuations due to toxicity during maintenance and limited dose modifications were made.

Overall, the CRd combination was well tolerated and highly active and compares favorably to the best currently available frontline therapies. Responses to CRd were deep and rapid, continued to improve with time, and were durable. All patients who achieved sCR remained on CRd with sustained sCR.

**Cyclophosphamide, Carfilzomib, Thalidomide, and Dexamethasone**

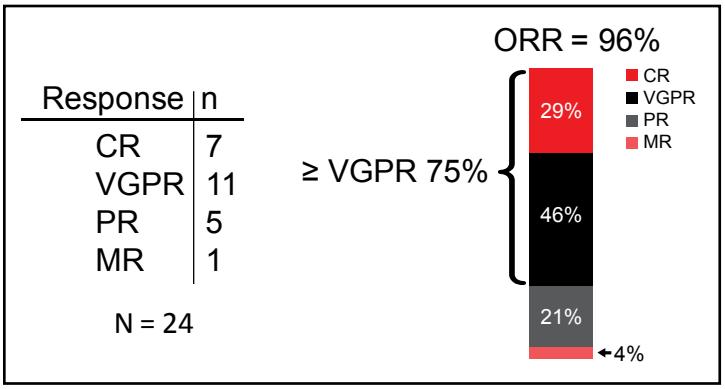
A phase I/II trial was designed by Mikhael and colleagues to evaluate the novel combination of cyclophosphamide, carfilzomib, thalidomide, and dexamethasone (CYCLONE) in patients with newly diagnosed MM prior to a HSCT.[39] The objectives of the study were to establish the MTD of carfilzomib in combination with the other agents, assess response, PFS, OS, toxicity, and the ability to mobilize stem cells. For the phase II portion of this trial, the primary endpoint of the study was the ability of patients to achieve at least a VGPR.

Newly diagnosed myeloma patients with measurable disease and prior to transplant were eligible for a phase I safety study to test the dose of carfilzomib. This trial included 3 patients to test tolerability, and all 3 patients responded (2 VGPR and 1 PR) and successfully had their stem cells collected. No dose-limiting toxicities (DLTs) were observed.

These results led to the phase II study at a planned carfilzomib dose of 20 mg/m$^2$. Patients were given carfilzomib (dose escalation of 15-27 mg m$^2$) on days 1, 2, 8, 9, 15, and 16, thalidomide 100 mg every day for 28 days, cyclophosphamide 300 mg/m$^2$ days 1, 8, and 15 for 28 days, and dexamethasone 40 mg days 1,8,15, and 22 for 28 days.

Twenty-seven patients were enrolled. The median age was 65 (27-74) years with 52% female patients. The majority of patients had an ECOG score of 0 and were ISS stage I. All but one patient was still alive. The ORR for evaluable patients (n = 24) was 96% with 29% CR, 46% VGPR, 21% PR, and 4% marginal response after 4 cycles of CYCLONE therapy (**Figure 7**).

**Figure 7. Response of newly diagnosed multiple myeloma patients to cyclophosphamide, carfilzomib, thalidomide, and dexamethasone (CYCLONE).**




Grade 3 toxicity was reported in 52% of patients and 14% experienced a grade 4 toxicity. Grade 3/4 toxicities occurring in more than 5% of patients included fatigue, neutropenia, lymphopenia, thromboembolism, and myopathy. Toxicities of any grade seen in more than 20% of patients included fatigue, constipation, lethargy, and thrombocytopenia. Seven patients developed grade 1 sensory neuropathy; no higher grade than 2 or painful neuropathy was reported. Tumor lysis syndrome developed in 1 case in the first treatment cycle. All patients advancing to HSCT successfully collected stem cells.

Overall, the 4-drug CYCLONE regimen was highly effective with an ORR of 96% (≥ VGPR 75% after only 4 cycles). CYCLONE therapy was well tolerated and had manageable toxicity in newly diagnosed patients with MM. Especially notable was the low incidence of neuropathy and depth of response after 4 cycles. Given the limited toxicity an extension of this regimen at higher doses of carfilzomib (20/45 mg/m$^2$) has been initiated.

In another study, frontline therapy with carfilzomib (36 mg/m$^2$) and melphalan-prednisone also proved to be a tolerable and effective combination in elderly MM patients. The ORR was 92% including 42% of patients achieving at least VGPR.[40]

**MLN9708, Lenalidomide and Dexamethasone**
Second-generation proteasome inhibitors are now being tested in phase I-II clinical trials. MLN9708 is a selective, orally bioavailable agent reported to have a shorter proteasome dissociation half-life and improved pharmacokinetics and antitumor activity compared with bortezomib. Analysis of 20S proteasome inhibition and markers of the unfolded protein response confirmed that MLN9708 has greater pharmacodynamic effects in tissues than bortezomib. MLN9708 is active in both solid tumor and hematologic preclinical xenograft models.[41] Based on previous clinical experience, Dr Richardson and collaborators combined the proteasome inhibitor MLN9708 with the immunomodulatory agent lenalidomide plus dexamethasone in a phase I/II clinical trial of previously untreated MM patients.[42]

The objectives of the phase I study was safety, tolerability, MTD, and recommended phase II dose and PK levels of MLN9708, in combination with lenalidomide and dexamethasone. Phase II objectives were to determine the rate of CR, VGPR, ORR, PFS, and the safety profile.

Twenty-nine previously untreated MM patients with measurable disease received oral MLN9708 (phase 1: 1.68-3.95 mg/m$^2$, days 1, 8, and 15, lenalidomide 25 mg, days 1-21, and dexamethasone, 40 mg days 1, 8, 15, and 22, for up to 12, 28-day cycles). The overall median age was 66 years (range 34-86) and 55% were in ISS stage II/III.

In phase I, the MLN9708 MTD was determined as 2.97 mg/m$^2$ and the recommended phase II dose was 2.23 mg/m$^2$; for phase II, the dose was converted to a 4.0 mg fixed-dose based on population PK results. Phase I patients received a median of 6 treatment cycles (range 1-11). Phase II patient treatment (range 1-2 cycles) is ongoing.

Grade 3 or higher hematologic toxicity was reversible and included anemia and thrombocytopenia. Grade 3/4 nonhematologic toxicity included erythematous rash, fatigue, nausea, syncope, and vomiting. All-grade drug-related PN was seen in 14 (21%) patients. Three patients discontinued therapy due to AE.

Of the 46 response-evaluable patients (phase I + phase II), 98% achieved PR or better, including 12 (26%) CR, 21 (46%) ≥ VGPR, and 9 (20%) VGPR. The ORR was 98% in 45 patients who had received at least 4 cycles of therapy (**Table 5**).

**Table 5. Response of previously untreated MM patients to MLN9708, lenalidomide, and dexamethasone.**

| Response, N = 46* | n (%) |
|---|---|
| ORR | 45 (98) |
| CR | 12 (26) |
| ≥ VGPR | 21 (46) |
| VGPR | 9 (20) |

MM, multiple myeloma; ORR, overall response rate; CR, complete response; VGPR, very good partial response. *Phase I + phase II patients

Thus, in this phase I/II study the combination of oral MLN9708 given weekly with standard-dose lenalidomide and dexamethasone in previously untreated MM appears to be well tolerated with manageable and reversible toxicities. The 98% ORR in patients who received ≥ 4 cycles of therapy was impressive, with no progressions among the response-evaluable patients.

## *Relapsed/Refractory MM*

Clinical research into the treatment of MM patients with relapsed and refractory disease is of paramount concern because nearly all MM patients eventually progress. Unfortunately, MM patients who are refractory to both bortezomib and immunomodulatory drugs have poor response and outcome.[43] Fortunately, early results with promising new agents provide optimism for this important clinical need.

**Pomalidomide With or Without Low-Dose Dexamethasone**
Pomalidomide is a third generation immunomodulatory agent. Recent encouraging results demonstrate that pomalidomide with dexamethasone has activity in MM patients after multiple lines of therapy.[44,45] At ASCO 2012, Dr Vij and colleagues presented results for MM patients refractory to lenalidomide, bortezomib, or both, as well as dual-refractory disease after ASCT.[46]

In this phase II study 221 patients were randomized between pomalidomide (n = 108) alone or pomalidomide with low-dose dexamethasone (n = 113). Patients in the pomalidomide monotherapy arm with progressive disease had the option to add low-dose dexamethasone (61/108). Pomalidomide was administered at 4 mg for 21 days of a 28-day cycle. The median patient age was 63 years (61 years for the pomalidomide only cohort and 64 years for

pomalidomide with dexamethasone). Patients had received a median of 5 cycles (range 1-17) of therapy. All patients had received prior lenalidomide and bortezomib. The primary endpoint of this phase II study was PFS and the secondary endpoints included ORR, safety, DOR, and OS.

The ORR in the ITT population was 9% for pomalidomide alone and 30% for pomalidomide with low-dose dexamethasone. An MR or better was achieved in 25% of patients on pomalidomide alone and 45% of patients on pomalidomide with dexamethasone (**Table 6**). Median time to response was 2.9 months with pomalidomide alone and 1.9 months with pomalidomide and dexamethasone. Median DOR had not been reached in the pomalidomide alone arm and 7.4 months with pomalidomide and low-dose dexamethasone. Disease control (≥ SD) was achieved in 76% of all patients. Median OS was 13.6 months with pomalidomide alone and 14.4 months for pomalidomide with dexamethasone.

**Table 6. Response and outcomes of relapsed or refractory MM patients to pomalidomide or pomalidomide with dexamethasone, ITT population.**

| | Pomalidomide n = 108 | Pomalidomide + dex n = 113 |
|---|---|---|
| ORR | 9% | 30% |
| DOR | NR | 7.4 months |
| ≥ MR | 25% | 45% |
| Median PFS | 2.5 months | 3.8 months |
| Median OS | 13.6 months | 14.4 months |

MM, multiple myeloma; ORR, overall response rate; DOR, duration of response; MR, marginal response; PFS, progression-free survival; OS, overall survival; dex, dexamethasone; NR, not reached

Subset analysis of refractory patients limited to the pomalidomide plus dexamethasone arm divided patients into 4 populations: lenalidomide- (n = 87), bortezomib- (n = 82), or dual-refractory (n = 69). Sixty-two percent were refractory to both lenalidomide and bortezomib and had received prior transplant. The ORR was similar for all 4 populations regardless of which drugs the patients were refractory to with the response rates varying from 25% to 34%. The toxicities were mainly hematological.

Overall, pomalidomide with or without dexamethasone was active in heavily pretreated advanced MM patients, including those refractory to lenalidomide, bortezomib, or both agents. Low-dose dexamethasone improved the efficacy of pomalidomide and was generally well-tolerated. The subset analysis revealed that the response rates and duration were comparable in patients with disease refractory to lenalidomide, bortezomib, or both, and in patients who had received a prior ASCT. Similarly, survival outcomes were consistent across the groups. These results suggest a lack of cross-resistance between pomalidomide and lenalidomide, and confirm activity not only in bortezomib-refractory patients but also those for whom transplant has failed.

**Panobinostat, Bortezomib, and Dexamethasone in Relapsed and Bortezomib-Refractory MM, PANORAMA 2**

Panobinostat is an oral pan-deacetylase inhibitor that increases acetylation of proteins involved in multiple oncogeneic pathways.[47] Panobinostat and bortezomib have synergistic antimyeloma activity. In a phase Ib study the combination of panobinostat and bortezomib demonstrated efficacy in MM patients including a subset of patients that were refractory to bortezomib.[48] Based on this study, a PANORAMA 2 trial was initiated to examine the role of panobinostat and bortezomib plus dexamethasone in MM patients with bortezomib-refractory disease.[49]

In the phase I study, patients received 8, 3-week cycles of panobinostat, bortezomib, and dexamethasone. Patients experiencing clinical benefit could proceed to 6-week cycles with panobinostat, bortezomib, and dexamethasone until disease progression. The primary endpoint of the study was OR, including CR, nCR, and PR, and secondary endpoints included PFS, TTP, OS, MR, TTR, and DOR.

Fifty-five patients were treated on the phase II study. The median age was 61. The range of prior treatments varied from 2 to 11 with 35 (64%) patients having previous ASCT. Of the original 55 patients, 6 (11%) patients were ongoing, and 49 (89%) patients were off treatment at the time of the analysis.

The ORR (including CR, nCR, and PR) occurred in 17 (31%) patients. Sixteen (29%) patients obtained a PR with only 1 patient obtaining an nCR. Minimal response was observed in 11 (20%) patients. Responses were typically observed after 1 to 2 cycles.

In terms of safety of this drug combination, common AE of any grade included thrombocytopenia (64%), fatigue (56%), diarrhea (69%), nausea (60%), and anemia (44%). Common grade 3/4 AE included thrombocytopenia (62%), fatigue (15%), anemia (15%), pneumonia (16%), and diarrhea (20%). Only 1 patient (2%) experienced grade 3/4 PN. The thrombocytopenia was manageable and reversible.

Thus, panobinostat in combination with bortezomib plus dexamethasone has clinical activity with manageable toxicities in heavily pretreated, bortezomib-refractory MM patients.

**Bendamustine, Bortezomib, and Dexamethasone in Elderly MM**

Despite the therapeutic advances already discussed, treatment options for elderly patients with relapsed/refractory MM are limited and prognosis is poor. In 2 studies of MM patients over the age of 65, the median survival at progression after first-line treatment was between 9 and 13 months.[50,51] Dr Rodon and colleagues conducted a phase II trial using a triple combination therapy to address the need for more robust therapies in older adults with MM in first relapse.[52]

Elderly symptomatic MM patients who were in relapse or refractory to first-line therapy and had measurable disease were eligible for this trial. The triple drug combination included bendamustine (70 mg/m$^2$ IV, days 1 and 8), bortezomib (1.3 mg/m$^2$ IV, days 1, 8, 15, and 22), and dexamethasone (20 mg, days 1, 8, 15, and 22). The induction phase consisted of 4 consecutive 28-day cycles. Patients achieving at least a PR continued into the consolidation phase of 2 additional cycles. If response was sustained patients entered the maintenance phase with the same regimen. The total length of regimen was 72 weeks. Response was evaluated every 2 months. The primary endpoint of the study was the response at the end of cycle 4. The secondary endpoints were ORR, response at the consolidation and maintenance phases, time to best response, PFS, OS, and toxicity.

The analysis was restricted to the first 4 cycles (induction phase) and included 73 patients. The median time from diagnosis was 29 months. The median age was 75.8 years. Response was evaluated according to IMWG criteria and at the end of 4 cycles.

Eight (10.9%) patients achieved a CR, 9 (12.3%) a VGPR, 25 (34.2%) a PR, 10 (13.6%) patients had SD, and 11 progressed during the induction phase. Overall response was 67.1% plus 6 minor responses.

At 4 months, there were 11 deaths. Toxicity was mild overall. Adverse events were mainly neutropenia, sepsis, DVT, and gastrointestinal. Nine patients experienced PNs (5 pre-existing). The triple drug combination was stopped in 20 patients for lack of efficacy or toxicity.

In summary, the triplet combination analyzed in this study showed modest activity and was generally tolerable in elderly patients with MM in first progression. These results are similar or slightly less favorable than other triple drug combinations containing cyclophosphamide, and a longer follow-up is required to assess the durability of the responses and OS.

## *Immunotherapeutic Targets in Myeloma*

Numerous cytokines and cell surface antigens are critical for interaction of the myeloma cell with the bone marrow microenvironment. Disruption of these interactions by antibody targeting inhibits these interactions, thus inhibiting myeloma cell proliferation. A number of these agents are in the myeloma immunotherapy development pipeline; 3 such monoclonal antibodies were discussed at the 2012 ASCO Annual Meeting in a Special Session Clinical Science Symposium.

**Siltuximab (α-IL-6 Antibody) Plus Bortezomib vs Bortezomib**

Siltuximab is a chimeric mouse: human anti-interleukin-6 (IL-6) monoclonal antibody with potential therapeutic benefit in patients with MM. Preclinical studies of siltuximab in combination with bortezomib suggest an additive effect in MM cell lines. Dr Robert Orlowski and his international collaborators designed a phase II randomized, double blind, placebo-controlled study to evaluate the safety and efficacy of siltuximab plus the proteasome inhibitor, bortezomib, compared with placebo plus bortezomib in patients with relapsed/refractory MM after 1 to 3 prior treatment lines, but no prior bortezomib exposure.[53]

Two hundred and eighty six patients were randomized 1:1 to siltuximab plus bortezomib (n = 142) or to placebo plus bortezomib (n = 144). Siltuximab was administered at 6 mg/kg and bortezomib at 1.3 mg/m$^2$ was given IV on days 1, 4, 8,

11, 22, 25, 29, 32 for a maximum of 4, 42-day cycles. This was subsequently reduced to q1w for 35-day cycles. Bortezomib was stopped for patients with PD/intolerability. The primary endpoint was a 50% improvement in PFS by EBMT criteria. Secondary endpoints included ORR, OS, and safety. The baseline demographics and disease characteristics were well balanced between the 2 treatment arms although the bortezomib/siltuximab group were slightly older with more bone marrow plasmacytosis.

The AE were similar between the arms, with neutropenia and thrombocytopenia increased in the siltuximab/bortezomib arm of the study.

Progression-free survival was 245 days for siltuximab/bortezomib and 232 days for bortezomib/placebo. The ORR/CR rate was 55%/11% for siltuximab and bortezomib and 47%/7% bortezomib and placebo. Minimal response was achieved in 6% of the patients in the siltuximab/bortezomib arm vs 10% in the bortezomib/placebo arm.

Overall, despite strong preclinical rationale to pursue the inhibition of IL6 in MM patients, the combination of siltuximab and bortezomib increased hematologic toxicity and did not improve outcomes over bortezomib with placebo. Suboptimal dose or schedule of siltuximab may have contributed to the less than favorable results.

**Daratumumab (α-CD38 mab)**
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. An ongoing first-in-human dose-escalation study has shown an acceptable safety profile.[54] A multicenter phase I/II efficacy trial was devised by Dr Torben Plesner and co-workers.[55]

Patients with previously diagnosed MM requiring systemic therapy and considered relapsed or refractory to at least 2 different prior lines of therapy and not eligible for salvage ASCT were enrolled in this trial. Daratumumab was administrated over a 9-week period encompassing 2 pre-doses and 7 full-doses. The doses range from 0.005 mg/kg to 24 mg/kg.

The most common AE were pyrexia (31%), cough (21%), hypo/hypertension (7%/14%), and nausea (14%). Monocytopenia (21%), lymphocytopenia (21%), free hemoglobin (17%), anemia (17%), hemolysis (14%), and thrombocytopenia (7%) were also noted across all cohorts. Five serious AE were related to daratumumab. Most of the dose-limiting AE were noted in the early part of the study prior to prophylactic steroid administration. Data from 23 patients including the 4 mg/kg group were collected.

Preliminary efficacy evaluation was based on best paraprotein response as reflected by change in serum and/or urine M-component. For groups ≤ 1 mg/kg, 3/17 patients achieved a reduction in serum M-component (12%, 14%, 19%), in the 2 mg/kg group, 1/3 patients had a reduction in urine M-component (55%), and in the 4 mg/kg group, 3/3 patients had a reduction in the serum M-component of 49%, 55, and 64%, respectively. In the 4 mg/kg group a marked reduction in the percentage of plasma cells in the bone marrow was seen in all patients (80%, 89%, and 97%). Eighteen of 29 heavily pretreated MM patients receiving 8 weeks of monotherapy up to a dose of 16 mg/kg experienced a marked reduction in M-component and the corresponding responses were: PR (7 patients), minimal response (4 patients), and SD (7 patients). Remarkably, biochemical responses were accompanied by clearance of myeloma cells from the bone marrow. The MTD has not yet been reached and the associated toxicities were manageable.

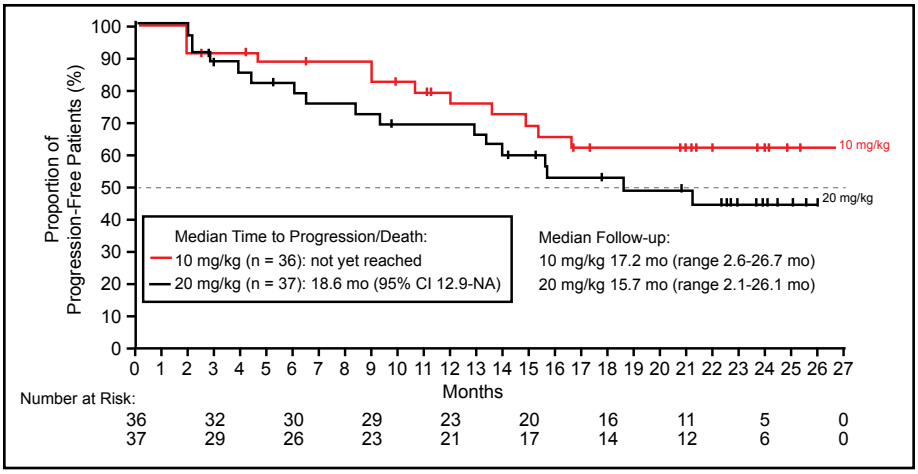
Thus, these promising results demonstrate that daratumumab is a highly active treatment that resulted in reductions in M-component and bone marrow plasma cells. Future studies are needed, including studies on continuous dosing and multi-drug combinations.

**Elotuzumab (α-CS1 Ab) With Lenalidomide and Low-Dose Dexamethasone**
The cell surface glycoprotein, CS1, is highly expressed on plasma and MM cells. Clinical studies have suggested that elotuzumab monotherapy is safe and capable of stabilizing disease.[56] In a xenograft mouse MM model, elotuzumab induced significant antibody-dependant cytotoxicity against primary myeloma cells in the presence of either autologous or allogeneic peripheral lymphocytes. This effect was significantly enhanced when peripheral blood mononuclear effector cells were pretreated with lenalidomide.

The safety and efficacy of elotuzumab in combination with lenalidomide and low-dose dexamethasone has been examined in phase I and phase II studies. The phase I study included 28 patients who had received 1 or more prior therapies. Dose escalation of elotuzumab (5, 10, or 20 mg/kg) in

combination with lenalidomide and low-dose dexamethasone was examined. There were no DLTs in the dose escalation and MTD was not reached. With a median follow-up of 16 months, 10 patients remain on study. The most common treatment-emergent AE were fatigue (64%), diarrhea (57%), anemia (46%), nausea (46%), constipation (43%), and neutropenia (30%). The ORR was 82% with a VGPR rate or better of 43%. For lenalidomide-naïve patients the response rate was 95%. Median PFS was not reached after a median follow-up of 16.4 months.[57]

**Figure 8. Progression-free survival of relapsed/refractory lenalidomide-naïve multiple myeloma patients to elotuzumab, lenalidomide, and low-dose dexamethasone.**




Dr Phillippe Moreau and colleagues presented the results from a randomized phase II study of elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma.[58] The study included 73 relapsed MM patients with measurable disease who had received 1 to 3 prior therapies not including lenalidomide. The primary objective of the study was ORR, and secondary objectives included safety, PFS, pharmacokinetics, and immunogenicity. Patients were randomized to receive 10 or 20 mg/kg IV elotuzumab (days 1, 8, 15, and 22 for cycles 1-2; days 1 and 15 for subsequent cycles) in combination with lenalidomide (25 mg, daily, days 1-21) and dexamethasone (40 mg, weekly).

The ORR was 84% (92% with 10 mg/kg elotuzumab vs 76% with 20 mg/kg elotuzumab) with 41% of patients achieving a VGPR (47% 10 mg/kg vs 35% 20 mg/kg), and 12% achieving a CR or sCR (14% 10 mg/kg vs 11% 20 mg/kg). The median time to response was 1 month (range 0.7-17.5 months). After a median follow-up of 14.1 months, median PFS was not reached with 10 mg/kg elotuzumab (**Figure 8**). For patients with high-risk myeloma, subset analysis suggested that the combination of elotuzumab, lenalidomide, and dexamethasone was similarly active in patients with high-risk myeloma as in patients with standard-risk disease.

Grade 3/4 AE were reported in 56% of patients. There was no treatment-related mortality. The most common treatment-emergent AE were muscle spasms, fatigue, diarrhea, and constipation. Neutropenia (16%), thrombocytopenia (16%), lymphopenia (19%), and anemia (12%) were the most common grade 3/4 AE. Patients were premedicated with methylprednisone (50 mg, IV), diphenhydramine (25-50 mg PO or IV), ranitidine (50 mg, IV), and acetaminophen (650-1000 mg PO) 30 to 60 minutes prior to elotuzumab infusion. Premedication appeared to mitigate the incidence and severity of infusion reactions, which were generally manageable. Grade 3 infusion reactions were reported in only 2 of 73 (3%) patients.

Overall, these very promising results suggest that the combination of elotuzumab with lenalidomide and dexamethasone is a safe and active regimen in lenalidomide-naïve patients. The 10 mg/kg regimen appeared equally effective as the 20 mg/kg elotuzumab dose, and the lower dose has been incorporated into a phase III trial comparing elotuzumab (10 mg/kg) in combination with lenalidomide and dexamethasone to lenalidomide and dexamethasone.

## LEUKEMIA UPDATE

### *Acute Myeloid Leukemia*

**Azacitidine and Gemtuzumab Ozogamicin as Induction and Post-Remission Therapy in Older Previously Untreated Non-M3 AML Patients**

A particular challenge in AML is managing the disease in the older adult population. Typically, with age, the response rates to standard chemotherapy decrease and toxicities and early death rates increase. Data summarized from 5 SWOG trials indicate that patients younger than 56 years of age have a complete remission rate of 65% and a 30-day mortality risk of 2.7%; whereas, patients over the age of 75 years have a complete remission rate of 33% and a mortality risk of

31.6%.[59] Thus, one goal of managing the disease in older adults is to apply novel therapeutics to attempt to reduce the toxicities and increase the response rate.

Both azacitidine and gemtuzumab ozogamicin (GO) have single-agent activity. Preclinical data suggests that when combined, these 2 agents may act synergistically to have increased cytotoxic activity against AML cells. Based on this information, Nand and colleagues conducted a phase II trial combining these two agents to address the safety and efficacy of a less toxic treatment regimen intended for older patients in the outpatient setting.[60] Patients were stratified by risk with results presented from the good risk cohort only.

Newly diagnosed non-M3 AML patients, 60 years or older, with a white cell count of 10,000/μL or higher were treated with hydroxyurea 1500 mg bid followed by azacitidine 75 mg/m$^2$/day subcutaneous or intravenous (IV) injection given on days 1-7 followed by GO 3 mg/m$^2$ on day 8. Induction treatment was repeated on day 14 if the patient's marrow showed residual disease. Patients with persistent disease on day 28 were removed from the protocol. Consolidation identical to the induction treatment was given to patients achieving a CR, followed by 4 cycles of azacitidine 75 mg/m$^2$, days 1-7, given every 28 days.

Eighty-three patients entered the study and 79 were evaluable. The median age of the patients was 71 years (60-89) and 49 patients were males. Cytogenetic evaluation was available for 27 patients. Sixteen patients had a normal karyotype, 2 had a single abnormality, and 9 had a complex karyotype. Twenty-three of the 79 patients achieved a CR, and 12 achieved a CR with incomplete hematologic recovery (CRi) (CR + CRi = 44%, 95% CI 33%-56%). Median OS was 11 months and median relapse-free survival (RFS) for patients achieving a CR/CRi was 8 months. Six patients (8%) died within 30 days of registration (3 due to disease progression). Treatment-related toxicity was modest with a 30-day mortality of 8%. In 27 patients, the main non-hematologic toxicity was neutropenic fever (grade 3 or higher).

Overall, the combination of hydroxyurea, azacitidine, and GO can be administered in the outpatient setting, was associated with a low induction mortality, and achieves results, which compare favorably with standard chemotherapy AML. Although these results are encouraging, it was felt that a cytogenetic evaluation for all the patients should be completed in order to fully evaluate the trial.

**Fludarabine, Cytarabine, Filgrastim, and Gemtuzumab Ozogamicin in Patients With Newly Diagnosed Core-Binding Factor AML**

The general approach to managing patients with AML is to stratify patients based on karyotype and molecular aberrations. Core binding factor (CBF) leukemias result from translocations involving RUNX1(CBFα) t(8;21) or CBFβ (inv16). Core binding factor leukemias have an exquisite sensitivity to high-dose cytarabine (HiDAC) in consolidation and typically have a favorable prognosis. A retrospective analysis of the MD Anderson Cancer Center (MDACC) data reveals that there is good EFS with the addition of a FLAG-based regimen, which is a combination of fludarabine mg/m$^2$ IV on days 1 to 5, cytarabine (A) 2 g/m$^2$ IV daily on days 1 to 5, and granulocyte colony stimulating factor (G-CSF; G) 5 μg/kg body weight. A recent subgroup analyses of CBF AML15 data suggested improved outcomes with the addition of GO for CBF AML patients. Given this data, Dr Borthakur and his colleagues at MDACC designed a trial combining GO with the FLAG-based regimen.[61]

The addition of GO to the induction phase was at 3 mg/m$^2$ IV on day 1. Of the 50 patients enrolled in the study, 20 patients had an inversion on chromosome 16 (inv[16]) and 30 carried a translocation between chromosome 8 and 21 t(8:21). With a median follow-up of 34 months, the overall CR rate was 82% (CR = 80% for inv [16] and 81% for t[8;21]), EFS rates of 74% and RFS rates of 83% (**Table 7**). These results compare favorably to historical MDACC data, with only 3/50 patients relapsing when GO was added compared to 8/22 in the FLAG only regimen.

**Table 7. FLAG with GO in newly diagnosed CBF AML with a median 34-month follow up.**

| | FLAG + GO N = 50 |
|---|---|
| CR | 82% |
| CRp | 4% |
| EFS | 74% |
| RFS | 83% |
| Induction death | 4% |
| Death in CR | 6% |

CBF, core binding factor; FL, fludarabine; A, cytarabine; G, G-CSF; I, idarubicin; GO, gemtuzumab ozogamicin; CR complete response; EFS, event-free survival; RFS, relapse-free survival.

Thus, this study suggests that the addition of GO to the FLAG regimen for CBF AML may produce favorable clinical results.

## *Acute Lymphoblastic Leukemia*

### Anti-CD19 Blinatumomab in Adult Patients With Relapsed/Refractory B-Precursor ALL

Outcomes for adults with relapsed or refractory acute lymphoblastic leukemia (ALL) are poor. The majority of relapsed/refractory ALL patients fail to achieve a CR, and if the patient manages to achieve a CR, it is generally short-lived with a median survival of 4 to 5 months. Moreover, response rates are typically 20-30%, and treatment-related mortality rate is high. Very few patients are eligible for a HSCT and for those who do go to transplant the morbidity and mortality is high (20-30%) Thus, novel strategies to improve outcomes for these patients are urgently needed. Dr Topp and his collaborators explored third generation antibody technology involving a construct of 2 antibodies (against CD19 and CD3) joined by a small linker to enable T-cells to target, lyse, and destroy the tumour cells. Thus, blinatumomab is a bispecific T-cell engager antibody designed to direct cytotoxic T-cells to CD19-expressing tumour cells.

Blinatumomab has been examined in 2 clinical trials. The first phase I trial explored the use of blinatumomab in a dose-dependent manner in NHL patients where it was found that 4 out of 5 patients who had NHL with bone marrow infiltration had clearance of their bone marrow.[62] A subsequent phase II trial designed to study the poor prognostic indicator MRD in positive B-precursor ALL found that blinatumomab was well-tolerated, and conversion from MRD+ to MRD- was possible with an 80% MRD response in evaluable patients.

Thus, an open-label, multicenter, exploratory phase II study in relapsed/refractory B-precursor ALL patients was designed by Dr Topp and his colleagues to evaluate the efficacy and safety of blinatumomab.[63] The primary endpoint was the rate of hematological CR or CR with partial hematological recovery (CRh) within 2 cycles of blinatumomab treatment. The dose-finding run-in phase consisted of 3 cohorts and after determining the safest cohort the extension phase was implemented, which involved blinatumomab at 5 µg/m$^2$/day in week 1 followed by 15 µg/m$^2$/day thereafter. Blinatumomab was administered by continuous IV infusion for 28 days followed by a 14-day treatment-free interval for up to 5 cycles. Three additional cycles of treatment were given to responding patients or they could proceed to bone marrow transplantation.

Thirty-six patients have been enrolled in this trial (all cohorts) with 23 currently evaluable (cohorts 2a and 3). The most common treatment-emergent AE were pyrexia (67%), headache (33%), and tremor (33%). Grade 3 or higher AE included epilepsy, hypertension, infections, confusion, and thrombocytopenia. Cytokine release syndrome (CRS) was observed in 2 patients with high tumour burden and no previous cytoreductive therapy. Six patients experienced fully reversible CNS AE. One patient died due to a fungal infection.

Seventeen out of 23 treated patients (74%) reached a hematological CR/CRh and an MRD response (MRD level $< 10^{-4}$) within the first 2 cycles (**Table 8**). With a median observation time of 4.5 months, duration of hematological CR in responding patients (n = 25) was 8.9 months. The OS in this patient cohort is 9.0 months (with a median follow-up of 10.7 months).

**Table 8. Response of adult patients with relapsed/refractory B-precursor ALL to 2 cycles of blinatumomab by cohort.**

| Cohort | All cohorts, n (%) N = 36 | Cohorts 2a + 3, n (%) N = 23 |
|---|---|---|
| CR + CRh | 26 (72) | 17 (74) |
| CR | 16 (44) | 11 (48) |
| CRh | 10 (28) | 6 (26) |
| Non-responder | 7 (19) | 5 (22) |
| Not evaluable | 3 (8) | 1 (4) |

CR, complete response; CRh, CR with partial hematological recovery

In summary, a well-tolerated blinatumomab dose regimen has been established with observed hematologic and molecular remissions. A global phase II study has been initiated to confirm these positive results.

### Inotuzumab Ozogamicin in Refractory-Relapsed ALL

Inotuzumab ozogamicin (IO) is a humanized anti-CD22 antibody conjugated to calicheamicin. It binds with high affinity resulting in rapid internalization of the antibody-antigen complex upon binding to CD22 releasing

calicheamicin inside the cell. Calicheamicin is a potent cytotoxic antitumor antibiotic that binds DNA inducing double-stranded DNA breaks cumulating in apoptosis of tumour cells. CD22 is a B-lymphoid cell specific antigen expressed on both normal and malignant B-cells, and in more than 90% of adult patients with ALL.

Based on encouraging anti-tumour activity, Jabbour and colleagues previously reported that 48 relapsed/refractory ALL patients treated with IO (1.3 mg/m$^2$ in 6 patients, increased to 1.8 mg/m$^2$ in the remaining 42 patients).[64] In 46 evaluable patients, the ORR was 61% with 20% achieving a CR, 30% achieving a CRp, and 11% achieving a CRi. With a median follow-up of 4 months, median OS is 5 months for censored patients. Median PFS was 4 months. Most AE were grade 1/2, with many related to allergic reaction. Patients with the Philadelphia chromosome (Ph) or t(4;14) had a lower likelihood of response. Thus, IO is an active agent in relapsed ALL warranting further evaluation. Given these encouraging preliminary results, Jabbour and colleagues from MDACC assessed the efficacy and regimen-related toxicity of weekly IO in refractory-relapsed CD22 positive ALL.[65]

Twenty-seven evaluable patients with refractory-relapsed ALL received a total IO dose of 1.8 mg/m$^2$ IV (given at 0.8 mg/m$^2$ on day 1, 0.5 mg/m$^2$ on day 8 and 15) with a possibility to repeat every 3 to 4 weeks. Patients who responded to therapy continued on this regimen for up to 8 weeks. CD22 was expressed in more than 50% of blasts in all patients and greater than 90% in 20 patients. Eleven patients received IO as salvage 1, 6 as salvage 2, and 10 had received 3 or more salvage regimens. Two patients had a prior allogeneic HSCT before IO.

With an ORR of 14/27 (52%), 3/27 patients (11%) achieved CR, 8/27 (30%) achieved CRp (CR with platelet count of < 100 x 10$^9$/L), 3/27 (11%) had CRi (marrow CR), 11/27 (41%) were resistant, and there were 2/27 (7%) deaths. The median OS was 7 months and there was no difference when the data was censored for those patients who received a transplant (**Table 9**). As expected, patients in first salvage had better outcomes.

Drug fever occurred in 26% of patients with 4 patients (15%) having grade 3/4 fever. Mild hypotension (grade 1/2) occurred in 15% of patients. Grade 1/2 liver enzyme abnormalities (SGPT/SGOT) abnormalities were noted in 22% of patients and 7% had grade 3/4 abnormalities. Grade 1/2 bilirubin abnormalities and lipase/amylase abnormalities were each noted in 1 patient (4%).

**Table 9. Response of relapsed or refractory CD22 positive ALL patients to weekly inotuzumab ozogamicin.**

| | Response N = 27 |
|---|---|
| ORR, n (%) | 14 (52) |
| CR, n (%) | 3 (11) |
| CRp, n (%) | 8 (30) |
| CRi, n (%) | 3 (11) |
| Resistant, n (%) | 11 (41) |
| Median OS | 7 months |
| Early death, n (%) | 2 (7) |

ALL, acute lymphocytic leukemia; CR, complete response; CRp, CR with platelet count < 100 x 109/L; CRi, CR with incomplete hematologic recovery; OS, overall survival.

Overall, IO has impressive single-agent activity in relapsed-refractory ALL and appears to be safe in the allogeneic transplant setting.

## *Chronic Myeloid Leukemia*

### Dasatinib vs Imatinib in Newly Diagnosed CML-CP, DASISION 3-Year Follow-Up

The use of imatinib has greatly improved the outcome of patients with chronic myeloid leukemia (CML). However, the majority (55%) of CML patients do not achieve complete molecular response (CMR) on imatinib even with long-term therapy (> 6 years).[66] A significant proportion of patients with CML-CP fail to achieve an optimal response with imatinib due to imatinib failure, resistance, or intolerance. Therefore, in the last few years other tyrosine kinase inhibitors (TKIs) have been examined with the overall goal to induce significantly faster and deeper cytogenetic and molecular responses. The 3 TKIs indicated for CML and reviewed here are dasatinib, imatinib, and nilotinib.

Dasatinib is a highly potent novel BCR-ABL kinase inhibitor that induces high rates of complete cytogenetic response (CCyR) in CML following imatinib resistance, intolerance, or failure. A significant proportion of patients with chronic phase (CP) CML fail to achieve an optimal response with imatinib. An international randomized phase III

trial (DASISION, CA180-056) was conducted comparing dasatinib (100 mg daily) to imatinib (400 mg daily) in newly diagnosed patients with CML-CP patients. Dasatinib treatment resulted in higher 12-month rates of CCyR and major molecular response (MMR).[67] By 12 months, confirmed CCyR rates for dasatinib were 77% compared to 66% for imatinib ($P = 0.001$), meeting the primary endpoint. Dasatinib as compared with imatinib induced significantly higher and faster rates of confirmed CCyR and MMR with few patients transforming to accelerated phase (AP)/blast phase (BP) CML. Achieving a CCyR within 12 months has been associated with better long-term, PFS; therefore, dasatinib, which was associated with a faster and deeper molecular responses, may improve the long-term overall outcomes among patients with newly diagnosed CML-CP.

A minimum 3-year follow-up of the DASISION phase III trial was presented at this year's ASCO meeting.[68] Treatment-naïve CML-CP patients (N = 519) from 108 centers and 26 countries were randomized to dasatinib (100 mg QD, n = 259) or imatinib (400 mg QD, n = 260) and stratified by EURO (Hasford) risk score. The primary endpoint was confirmed CCyR by 1 year.

Approximately the same number of patients in either study arm, 183/258 (71%) for dasatinib and 179/258 (69%) for imatinib are still on treatment, with 93% of patients on follow-up for survival. In terms of efficacy, MMR continues to be the major endpoint for first-line CML therapy and there is an advantage of dasatinib over imatinib over 3 years in this regard. Major molecular response rates were higher for dasatinib in all Hasford risk groups (high 73% vs 56%; intermediate 61% vs 50%; low 73% vs 56%). The molecular response with dasatinib is superior with a greater than 3 log reduction in BCR-ABL transcripts. Of the patients who achieved MMR at 12 months on dasatinib vs imatinib, 97% vs 92% had maintained their MMR at 24 months, respectively. Importantly, deeper responses as measured by $MR^4$ (BCR-ABL levels ≤ 0.01%) and $MR^{4.5}$ (BCR-ABL levels ≤ 0.0032%) indicating 4 log and 4.5 log reductions compared to standardized baseline transcripts were observed. By 36 months, there was an improvement of molecular response rates in dasatinib over imatinib; 35% vs 22% for $MR^4$ and 22% vs 12% for $MR^{4.5}$ after 3 years, dasatinib compared to imatinib, respectively. This difference continued to increase over time (**Figure 9**).

**Figure 9. Cumulative incidence of $MR^4$ and $MR^{4.5}$ in CML patients treated with dasatinib or imatinib.**

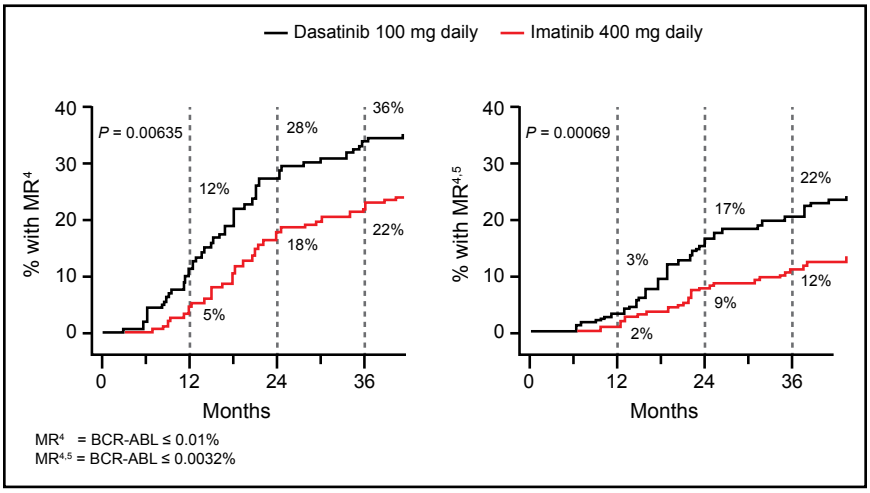
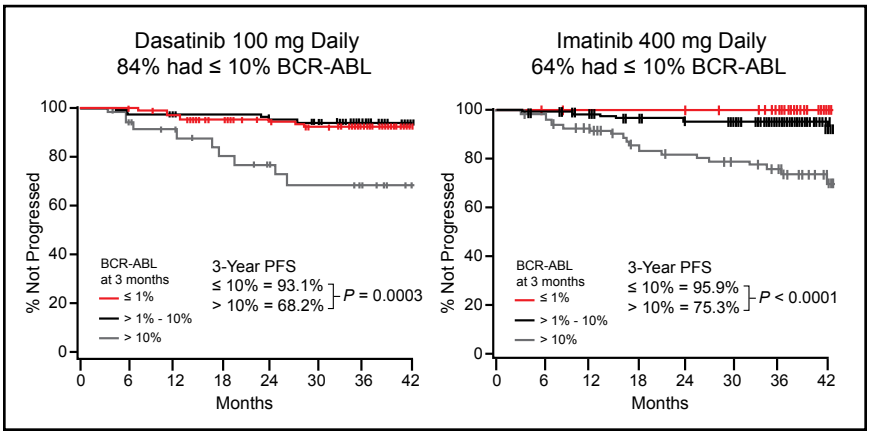



**Figure 10. Progression-free survival (PFS) according to BCR-ABL level at 3 months in CML patients treated with dasatinib or imatinib.**




Faster responses were also observed in patients receiving dasatinib. The median time to CCyR and MMR was 3.2 vs 6.0 and 15 vs 36 months, respectively. In an ITT analysis, fewer patients receiving dasatinib (n = 9; 3.5%) transformed to AP/BP vs imatinib (n = 15; 5.8%). Overall survival and PFS were similar for both groups. However, there was a difference between dasatinib and imatinib in PFS as indicated by BCR-ABL level at 3 months (**Figure 10**).

There were a few additional AE reported between 12 and 24 months in both arms, with grade 3/4 nonhematologic AE rates 1% or less. Patients receiving dasatinib had a lower transformation rate and higher molecular responses than those patients receiving imatinib, supporting the use of dasatinib as first treatment in newly diagnosed CML-CP.

**Nilotinib vs Imatinib in Newly Diagnosed CML-CP, ENESTnd 3-Year Follow-Up**

Nilotinib is a potent second generation TKI with proven efficacy in CML. A randomized phase III trial (ENESTnd) directly compared imatinib (400 mg daily) to nilotinib (300 mg bid and 400 mg bid) in newly diagnosed CML-CP. Follow-up at 24 months was presented at ASCO 2011.[69] It was found that nilotinib showed superior efficacy compared to imatinib and nilotinib was well tolerated. Patients receiving nilotinib had significantly lower rates of progression to AP/blast crisis (BC) and fewer CML-related deaths. Longer follow-up is needed to confirm the more rapid and deeper molecular responses observed with nilotinib, which may prevent the development of emerging mutations and disease progression.[70] Thus, Kantarjian and his global colleagues performed a 3-year follow-up of the ENESTnd trial comparing imatinib (400 mg daily) to nilotinib (300 mg bid and 400 mg bid) in newly diagnosed CML-CP.[71]

A total of 846 patients from 217 centers and 35 countries with newly diagnosed CML-CP were randomized to nilotinib 300 mg bid, nilotinib 400 mg bid, or imatinib 400 mg, daily. The primary endpoint of the study was MMR at 12 months and the secondary endpoint was durable MMR at 24 months. Patients were well matched for baseline characteristics.

Rates of MMR at 12 months were superior for nilotinib 300 mg and 400 mg bid compared with imatinib.[72,73] The superiority of MMR with nilotinib extended to 36 months (73% nilotinib 300 mg vs 70% nilotinib 400 mg vs 53% imatinib, $P < 0.0001$) (**Table 10**). This superiority held across all Sokal risk groups. The best overall MMR was also significantly higher in the nilotinib arms compared to the imatinib arm. More patients achieved an $MR^4$ (BCR-ABL < 0.01%; 50% nilotinib 300 mg, 44% nilotinib 400, 26% imatinib, $P < 0.0001$) and $MR^{4.5}$ (BCR-ABL < 0.0032%; 32% nilotinib 300 mg, 28% nilotinib 400, 15% imatinib, $P < 0.0001$). Progression to AP/BC was significantly lower for both nilotinib 300 mg bid ($P = 0.0059$) and nilotinib 400 mg bid ($P = 0.0185$) compared to imatinib. Estimated 36-month PFS and OS were high and not significantly different between the arms. Longer follow-up demonstrated that compared to imatinib, nilotinib resulted in superior rates of MMR, $MR^4$, and $MR^{4.5}$ in addition to fewer progressions to AP/BP.

**Table 10. Imatinib 400 mg daily vs nilotinib at 300 mg and 400 mg bid in newly diagnosed CML-CP patients.**

| | Nilotinib 300 mg bid n = 282 | Nilotinib 400 mg bid n = 281 | Imatinib 400 mg daily n = 283 |
|---|---|---|---|
| Cumulative MMR at 3 yr, % | 73* | 70* | 53 |
| Overall best response MMR, % | 66* | 62* | 40 |
| $MR^4$ (BCR-ABL < 0.01%) by 3 yr, % | 50* | 44* | 26 |
| $MR^{4.5}$ (BCR-ABL < 0.0032%) by 3 yr, % | 32* | 28† | 15 |
| Progression to AP/BC, n (%) | 9 (3.2)‡ | 6 (2.1)§ | 19 (6.7) |
| 36-month OS, % | 95.1 | 97.0 | 94.0 |

CML-CP, chronic myeloid leukemia-chronic phase; MR, molecular response; MMR, major molecular response; AP, accelerated phase; BC, blast crisis; OS, overall survival; yr, years
*vs imatinib, $P < 0.0001$; †vs imatinib, $P < 0.003$; ‡vs imatinib, $P = 0.0496$; §vs imatinib, $P = 0.0076$.

Mutational analysis found that twice as many patients on imatinib developed mutations during treatment (11 mutations on nilotinib 300 mg, 11 on nilotinib 400 mg, and 21 on imatinib 400 mg). Overall, both TKIs were well-tolerated and there were no new safety signals observed in the third year of follow-up.

This encouraging 3-year trial review of nilotinib vs imatinib in newly diagnosed CMP-CP patients indicates that the more rapid and deeper molecular responses observed with nilotinib may prevent the development of emerging mutations and disease progression.

**Imatinib Switch to Nilotinib vs Continued Imatinib in CML-CP, ENESTcmr 12-Month Follow-Up**

As mentioned, nilotinib induced significantly faster and deeper molecular responses and significant freedom from progression vs imatinib in the ENESTnd trial. Achieving these deeper molecular responses may increase patient eligibility for future TKI discontinuation studies. With the ultimate goal of a cure (ie, treat with TKI and then discontinue) this study was designed to determine whether those patients achieving a CCyR but not a CMR could benefit from being switched from imatinib to nilotinib. This summary of ENESTcmr trial includes a minimum 12-month follow-up on all patients.[74]

CML-CP patients (n = 207) who achieved a CCyR but were still BCR-ABL positive by RQ-PCR after at least 24 months on imatinib were randomized 1:1 to nilotinib (400 mg bid [n = 104]) or continuation of imatinib (400 or 600 mg QD [n = 103]). The primary endpoint was confirmed CMR (undetectable BCR-ABL by RQ-PCR with a sample sensitivity of ≥ 4.5 logs in 2 consecutive samples). Secondary endpoints included the analyses of molecular responses (MMR, $MR^4$, $MR^{4.5}$, and CMR), BCR-ABL ratio over time, and safety.

The study was well-balanced in terms of patient disposition. The rate of confirmed CMR (undetectable BCR-ABL) was higher in the nilotinib arm compared to imatinib by 12 months (12.5% vs 5.8%). Rate of CMR (undetectable BCR-ABL in at least 1 sample) by 12 months was significantly higher on nilotinib vs imatinib (23.1% vs 10.7%; $P = 0.02$). The confirmed CMR was also slightly greater for those patients switched to nilotinib (12.5% vs 5.8%; $P = 0.108$) but this was not statistically significant. Rates of MMR, $MR^4$, $MR^{4.5}$, and CMR were superior in patients who were switched to nilotinib; twice as many patients achieved MMR, $MR^4$, $MR^{4.5}$, and CMR on nilotinib and these patients had significantly shorter times to achieve these responses. Patients switched to nilotinib had a median 0.5-log reduction in BCR-ABL from baseline vs no change in patients who continued on imatinib. Twice as many patients achieved deeper molecular responses after switching to nilotinib vs staying on imatinib which may increase these patients' eligibility to discontinue the TKI in the future.

**Bosutinib vs Imatinib in Newly Diagnosed CML-CP Patients, BELA Trial 30-Month Update**

Bosutinib (SKI-066) is an orally active, dual competitive inhibitor of the SRC and ABL tyrosine kinases and has minimal activity against platelet-derived growth factor receptor or c-KIT.[75] A phase I/II study designed to evaluate bosutinib in patients with imatinib-resistant or imatinib-intolerant CML-CP demonstrated good response rates with a PFS and OS of 79% and 92%, respectively.[76] Preliminary results from the phase III BELA trial in patients with newly diagnosed CML-CP showed a higher rate of MMR with bosutinib (61%) compared with imatinib (50%).[77] Fewer disease transformations to AP or BP with bosutinib (n = 4) vs imatinib (n = 13) was found. The objective of the BELA trial was to compare the efficacy and safety profile of bosutinib to imatinib in patients newly diagnosed with CML-CP. These updated results were presented by Dr Gambacorti-Passerini.[78]

The BELA trial is an open-label, phase III study that randomized patients (N = 502) with bosutinib or imatinib and then stratified by Sokal risk. The treatment dose was 500 mg/day of bosutinib and 400 mg/day imatinib, and a dose escalation to 600 mg/day with either drug was permitted for lack of efficacy. The primary endpoint was the rate of CCyR at 12 months. The secondary and exploratory endpoint included time to response, DOR, EFS, time to and rate of transformation to AP/BP CML, safety, and OS. Patient characteristics were well balanced between the 2 arms of the study with a median age of 47 and 48 years for bosutinib and imatinib, respectively.

At 30 months, CCyR rates were 56% (140/250) for bosutinib and 61% for imatinib (153/252). Cumulative CCyR rates at 30 months were 79% (197/250) for bosutinib and 81% (204/252) for imatinib. At 30 months, MMR rates were approximately the same (45% vs 43% for bosutinib and imatinib, respectively). Kaplan-Meier EFS estimates at 30 months were 88% (95% CI, 82%-92%) for bosutinib and 86% (95% CI, 80-90%) for imatinib. The EFS included 8 and 15 patients in the bosutinib and imatinib arms who transformed to AP/BP CML. Transformation to AP/BP occurred in 4% of patients on bosutinib and 6% of patients on imatinib. Median on treatment EFS and OS were not reached.

There were a total of 9 and 13 deaths in the patients receiving bosutinib vs imatinib, respectively. Both TKIs were safe and tolerable. Treatment with bosutinib was associated with a higher incidence of gastrointestinal toxicities. In contrast, the administration of imatinib was associated with higher incidences of musculoskeletal events. Neutropenia occurred in both patient populations whereas the incidence of anemia and thrombocytopenia were the same for both treatments.

Thus, longer follow-up of this study continues to show good efficacy for bosutinib after a 30-month review. Consistent with earlier reports, bosutinib showed a distinct and manageable safety profile.

**Ponatinib in CML and Ph+ ALL, PACE Trial**

Ponatinib is a novel, synthetic, orally active TKI and a potent multi-targeted kinase inhibitor. Ponatinib primarily targets BCR-ABL, an abnormal tyrosine kinase that is the hallmark of CML and Philadelphia chromosome positive (Ph+) ALL. Ponatinib has potent kinase inhibitor activity and was designed to inhibit the enzymatic activity of BCR-ABL with very high potency and broad specificity. This experimental

oral drug candidate was intended to target not only native BCR-ABL, but also its isoforms that carry mutations that confer resistance to treatment with existing TKIs, including the T315I mutation for which an effective therapy does not exist. A phase I study demonstrated significant clinical activity and identified a MTD of 45 mg/day with DLT resulting in pancreatitis. Given these results, the current PACE trial was designed by Dr Cortes and his colleagues to identify the efficacy of ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation.[79]

A total of 449 CML-CP, CML-AP, CML-BP or Ph+ ALL heavily pretreated patients have been entered into the trial and stratified into 1 of 6 cohorts depending if they are resistant or intolerant to dasatinib or nilotinib or T315I mutation status. The primary endpoint for patients in CP was the rate of major cytogenetic response (MCyR). The primary endpoint for the advanced diseases included the rate of major hematologic response. Secondary endpoints included MMR. The median age of patients with CML-CP, CML-AP, and CML-BP, or Ph+ ALL was 54 to 60 years and the median time since diagnosis was 7 years (CML-CP and CML-AP) and 2 years (CML-BP or Ph+ ALL). Greater than 50% of patients remain on study and the majority of these patients are from the CML-CP cohort where 69% of the patients remain on study. Only 11% of patients have discontinued therapy due to AE. The most common reason for discontinuation of therapy in patients with CML-CP was thrombocytopenia whereas the most common reason for discontinuation in patients with CML-BP was progressive disease. Only 18% of patients died on therapy, and 5 were possibly related to the study drug. The majority of patients were heavily pretreated going into this study with the majority of patients having received at least 2 prior TKIs.

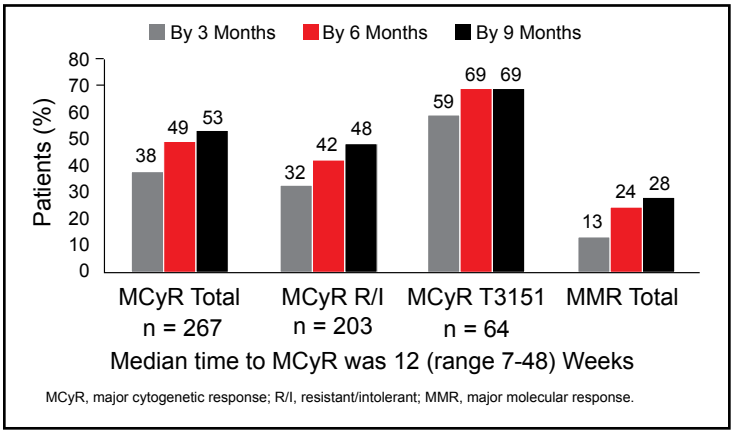
With a median follow-up of 10 months, more than 50% of the patients in the CML-CP cohort had achieved a MCyR. Subgroup analysis found that 70% of the patients who carry the T315I mutation achieved a MCyR whereas only 49% of those without the mutation achieved a MCyR. In the CML-AP cohort where the primary endpoint was major hematologic response (MaHR), almost 60% of patients had achieved this response. In the AP cohort, 58% of the patients achieved a MaHR whereas only 34% of the CML-BP/Ph+ ALL patients achieved the primary endpoint response (**Table 11**). Generally for CML, the responses to the TKI therapy improved over time and this same trend holds true for ponatinib. Thirty-eight per cent of the total patients achieved a MCyR after 3 months of therapy and this increased to 49% and 53% in the subsequent 6 and 9 months. This rapid response was also observed in the other cohorts and it was especially true for those patients with the T315I mutation (59% at 3 months, 69% at 6 and 9 months). This trend held for the rate of MMR. (**Figure 11**) Ponatinib is also effective in the patients with advanced disease. In the CML-AP, 20-33% of patients have achieved a CCyR.

**Table 11. Responses of pretreated CML-CP, CML-AP, CML-BP, and Ph+ ALL to ponatinib.**

| | CML-CP n/N (%) | CML-AP n/N (%) | CML-BP/Ph+ ALL n/N (%) |
|---|---|---|---|
| Primary endpoint | MCyR | MaHR | MaHR |
| Dasatinib or nilotinib resistant/intolerant | 99/203 (49) | 39/65 (60) | 17/48 (35) |
| T315I mutation | 45/64 (70) | 9/18 (50) | 15/46 (33) |
| Total | 144/267 (54) | 48/83 (58) | 32/94 (34) |

CML-CP, chronic myeloid leukemia-chronic phase; Ph, Philadelphia chromosome; ALL, acute lymphoblastic leukemia; MCyR, major cytogenetic response; MaHR, major hematopoietic response; AP, accelerated phase; BC, blast crisis; OS, overall survival

**Figure 11. Response of heavily pretreated chronic phase (CP) CML patients to ponatinib.**




MCyR, major cytogenetic response; R/I, resistant/intolerant; MMR, major molecular response.

Ponatinib was well tolerated with transient and manageable AE (majority were grade 1 or 2). The most common AE were dermatological (most were rashes and dry skin). Pancreatitis occurred in 7% of the patients, which resulted in 1 discontinuation of therapy.

In conclusion, this pivotal phase II trial assessing ponatinib, a novel, orally active TKI with broad kinase specificity demonstrated that ponatinib exhibited robust anti-leukemic activity in this heavily pretreated population, with 54% achieving a MCyR rate in CML-CP. Responses were observed regardless of mutation status or disease stage and the responses appear to improve over time. The responses were durable: in CML-CP, 93% of the patients are predicted to remain in MCyR at 1 year. Ponatinib has a favorable safety profile. Ponatinib may indeed be an important new treatment for CML and Ph+ ALL patients who are resistant or intolerant to dasatinib or nilotinib or who have the T315I mutation.

## *Chronic Lymphocytic Leukemia*

### Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Treatment-Naïve CLL

Chronic lymphocytic leukemia remains an incurable disease, with all patients who require therapy destined to relapse. Fludarabine-based therapy for CLL is highly effective; however, it carries significant risk of morbidity and mortality in the elderly patients. Thus, older CLL patients represent a high priority for new therapeutic approaches. Bruton's agammaglobulinemia tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase essential in B-lymphocyte development, differentiation, and signaling. 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 all non T-cell hematopoietic lineages and is highly expressed in CLL. Ibrutinib (PCI32765) is an orally bioavailable small-molecule potent irreversible selective inhibitor of BTK that binds to and inhibits BTK activity, preventing B-cell activation and B-cell-mediated signaling and inhibiting the growth of malignant B-cells that over-express BTK.

A phase I/II single agent study in relapsed or refractory CLL patients demonstrated a high frequency of durable response.[80] Interim results of a phase IB/II trial of Ibrutinib in treatment-naïve relapsed or refractory CLL and small lymphocytic leukemia (SLL) were presented by Dr Byrd and his colleague at last year's ASCO meeting.[81] An update was provided by these authors at this year's ASCO meeting focusing on a subset of CLL patients who had not received prior treatment.[82]

Results were presented for the phase Ib/II trial evaluating 2 doses of single-agent ibrutinib in treatment-naïve CLL patients with active disease requiring transplant by iwCLL guidelines. Two cohorts, consisting of untreated patients 65 years and older treated with 2 doses of ibrutinib were analyzed. Twenty-six treatment-naïve patients were treated with ibrutinib (420 mg/day continuous dosing until progression) for a median follow-up of 14.4 months. Subsequently, 5 treatment-naïve patients were treated with 840 mg/day of ibrutinib with a median follow-up of 7.4 months. This higher dose cohort was discontinued because there was 100% of the BTK occupancy at the lower dose and the responses and toxicities were the same as the lower dose. The primary endpoints of the study were safety, response rate, and PFS.

Five patients of the total 31 patients (16%) discontinued therapy and there were no deaths. The AE were low-grade in severity and reversible (most common diarrhea, nausea, and fatigue). Grade 3 or 4 hematologic toxicity was rare, and the majority of the toxicities were grades 1 or 2. Ten per cent of patients experienced infections.

The ORR was 74% for treatment-naïve patients with 10% of the patients attaining a CR, 65% achieving a PR, and 13% with nodal response by iwCLL guidelines. Patients who had thrombocytopenia or anemia at baseline had a sustained improvement in their hematological function. At 15 months the PFS rate was 96%. Continuous daily dosing was well tolerated allowing for extended treatment.

Overall the use of ibrutinib as a single agent holds great promise and given the efficacy of ibrutinib, further evaluation as a first-line treatment approach in elderly CLL patients is warranted.

### Bruton's Tyrosine Kinase Inhibitor Ibrutinib With Bendamustine/Rituximab in Relapsed/Refractory CLL

The availability of effective, safe, and specific monoclonal antibodies has dramatically altered treatment strategies for B-cell malignancies. Previous studies have suggested that the use of bendamustine, an alkylating agent, in combination with the chimeric monoclonal antibody against the CD20 antigen, rituximab, produces an ORR of 59% in relapsed/refractory CLL. Dr O'Brien and colleagues presented interim data from a trial combining the BTK inhibitor ibrutinib with bendamustine and rituximab (BR) in relapsed/refractory CLL patients.[83] Patients with a diagnosis of CLL or SLL with adequate end-organ function requiring treatment per iwCLL guidelines who had received 1 to 3 prior therapies were eligible for this study. Ibrutinib was

given to relapsed/refractory CLL patients at a dose of 420 mg orally daily for 28-day cycles until disease progression. Bendamustine was administered 70 mg/m$^2$ on days 1 and 2 combined with rituximab at 375 mg/m$^2$ on day 0 for cycle 1 and 500 mg/m$^2$ on day 1 for subsequent courses for cycles 2-6 (maximum of 6 cycles). The objective of this study was to evaluate the safety and ORR. Response was evaluated according to iwCLL criteria.

This phase Ib/II study enrolled 30 patients (CLL, n = 29; SLL n = 1) with a median age of 61.5 years (range 41-82). Forty six percent of patients were Rai stage III/IV and the median number of prior therapies was 2 (range 1-3). Thirty-seven (13%) of the patients were considered refractory (treatment free interval < 12 month) to a purine analog containing regimen or B, respectively. Bulky disease was present in 53% of the patients.

Adverse events have been consistent with that expected with BR (most commonly diarrhea, nausea, fatigue and headache). Grade 3/4 neutropenia and thrombocytopenia have been noted in 23% and 7% of patients, respectively. Grade $\geq$ 3 non-hematologic AE potentially related to ibrutinib included rash (10% or 3 patients), fatigue, tumor lysis, and cellulitis (7% or 2 patients each). There were no grade 3/4 infusion reactions. There have been no discontinuations due to AE and no deaths were reported.

The ORR was 93% (28/30 patients; CR 13%, PR 80%). An additional 3% of patients achieved a nodal response with residual lymphocytosis. The responses appear independent of high-risk clinical or genomic features. An analysis of best responses by risk features revealed the ORR for patients with a deletion of 11q was 100% whereas the ORR for patients with a deletion of 17p was 71%. Patients with β2M 3 mg/L, LDH > ULN or purine analog refractory had an ORR between 91 and 94%. Patients who were bendamustine refractory had an ORR of 75%.

Thus, ibrutinib (PCI-32765) in combination with BR, is highly active. The high ORR, low rate of PD, and reasonable tolerability compares very favorably with historical controls, warranting phase III investigation of this combination.

**Bruton's Tyrosine Kinase Inhibitor Ibrutinib With Ofatumumab in CLL and SLL**

Ofatumumab is a fully humanized type I CD20 monoclonal antibody that has been approved by the FDA for the treatment of fludarabine- and alemtuzumab- refractory CLL. Compared to rituximab, ofatumumab has been reported to have increased complement-dependent cytotoxicity (CDC), ADCC, and apoptosis, as well as a slower off-rate for CD20 binding.[84,85] In fludarabine- and alemtuzumab-refractory CLL ofatumumab treatment resulted in a 58% ORR.[86] A phase Ib/II study evaluating the safety, tolerability, toxicity, and efficacy of the BTK inhibitor ibrutinib combined with ofatumumab in patients with CLL and SLL and related diseases was presented by Dr Jaglowski and colleagues at ASCO 2012.[87]

This single institution study evaluated the use of ibrutinib (420 mg/day for 28 days during cycle 1) and ofatumumab (300 mg day 1 of cycle 2, followed by 2000 mg on days 1, 8, 15, 22 of cycle 3, then on day 1 of cycles 5-8 until disease progression). The primary objectives were toxicity of the combination and response (CR + PR) at 1 year. Patients with refractory CLL/SLL following at least 2 prior therapies, including a purine-nucleoside analog with less than 10% CD20 expression on CLL cells and with adequate end-organ function were eligible for this study. Twenty-seven patients (CLL, n = 22; SLL, n = 1; PLL, n = 1; Richter's, n = 3) were enrolled in the study, and all received 6 cycles of treatment. The median age was 66 (range 51-85), 9 patients were Rai stage III/IV. Patients had received a median of 3 (range 2-10) prior therapies, 15 (56%) had bulky disease (> 5 cm), and 11 patients (41%) were purine-nucleoside analog refractory. Poor-risk molecular features were common in this cohort with 10 (37%) patients displaying del(17p) and 9 (33%) with the del(11q).

There were no grade 3 or 4 infusion reactions, neutropenia, or thrombocytopenia. The majority of AE were grade 1/2. Grade 3/4 AE included anemia (11%), pneumonia (11%), urinary tract infection (7%), and hyponatremia (7%).

Remarkably, the ORR was 100% for all 24 CLL/SLL/prolymphocytic leukemia (PLL) patients and 23/24 (96%) achieved PR and 1/24 (4%) attained a CR within 6 cycles. Two out of 3 Richter's patients achieved a PR. Among the patients with cytopenias before treatment, 67% of those patients with thrombocytopenia, 56% of those patients with anemia, and 50% of those patients with neutropenias had sustained improvement in their counts. With a median follow-up of 6.5 months (range 5.3-10.2 months), 23 CLL/SLL/PLL patients and 1 Richter's patient remain on study, 1 CLL/SLL patient went to transplant in PR, and 2 radiotherapy patients progressed.

Therefore, the combination of ibrutinib and ofatumumab was well tolerated and highly active (100% ORR irrespective of genomics) in patients with heavily pretreated relapsed/refractory CLL/SLL. The favorable safety profile, rapid onset of response, and durable remissions that have been observed in this trial make this combination and other treatment sequences worthy of future study.

**Ofatumumab and Lenalidomide in Patients With Relapsed CLL**

Lenalidomide is an oral immunomodulatory drug with numerous immunological and tumor cell microenvironment effects leading to inhibition of malignant cell growth.[88] Both lenalidomide and ofatumumab have shown single-agent activity in relapsed CLL. Based on encouraging reports of lenalidomide in relapsed and refractory CLL and the activity of ofatumumab and lenalidomide as monotherapy, Falchi and co-workers from MDACC evaluated the efficacy and tolerability of this combination in patients with relapsed CLL.[89]

This phase II trial enrolled 36 patients with relapsed CLL. Patients who had relapsed CLL/SLL, were symptomatic with indications for treatment, had adequate liver and renal function, and received prior purine analogue-based therapy (fludarabine) and with Zubrod/WHO performance status of 0-2 were eligible for this trial. Ofatumumab was given weekly for 4 weeks (300 mg IV week 1; 1000 mg weeks 2-4), monthly during months 2-6, and every other month during months 7-24. Lenalidomide, 10 mg PO/day, started on day 9 and continued for 24 months until disease progression. Responses were assessed (2008 IWG criteria) at month 3, 6, and every 6 months.

Thirty four of the 36 patients were evaluable. Median patient age was 64 (34-82) years, and patients had received a median of 2 (1-8) prior treatments. Fifty-nine percent of patients had Rai stage III-IV disease, median β2M level was 4.1 mg/dL (1.7-16), and 62 % of the patients had unmutated *IgHV*. Twenty-six percent harbored a deletion (17p), 12% del(11q), 21% del(13q), and 9% of the patients had trisomy 12. Chromosomal abnormalities were absent in 15% of the patients. Fludarabine refractory patients represented 29% (10/34) of the population.

The ORR was 65% (22/34 patients), 7/34 patients (21%) achieved a CR including 4 MRD-negative CR, and 15/34 patients (44%) achieved a PR. With a median time of 11 (2-24) months on therapy, 12 of 36 patients have ongoing responses and remain on therapy and 29 (85%) are alive. With a median follow-up of 13 months, median DOR has not been reached.

Seven patients discontinued therapy despite ongoing response due to HSCT (3 patients), toxicity (2 patients), and physician's choice (2 patients). Three patients lost their response and discontinued therapy. No deaths occurred on therapy; however, 6 deaths occurred after therapy discontinuation. Neutropenia (16 patients, 47%), thrombocytopenia (3 patients, 9%), and anemia (2 patients, 6%) represented the grade 3/4 hematologic toxicities. A grade 4 PE was noted in 1 patient while on erythropoiesis-stimulating agents and another patient had a grade 3 infusion reaction to ofatumumab. Fourteen grade 3 infections occurred: pneumonia (4), fever/bacteremia (5), parotitis (1), cellulitis (2), HZV (1), and CNS toxoplasmosis (1). A grade 1/2 tumor flare reaction occurred in 8 patients (24%).

As the primary objectives of this phase II trial were to evaluate the efficacy and tolerability of lenalidomide in combination with ofatumumab, it can be concluded that this drug combination was well tolerated inducing durable responses in 65% of the pretreated patients with recurrent CLL.

## *Myelofibrosis*

**Ruxolitinib vs Best Available Therapy, COMFORT-II Analysis of JAK2 V617F Allele Burden**

Myeloproliferative neoplasms, including primary myelofibrosis (PMF), essential thrombocythemia (ET), and polycythemia vera (PV), are a group of clonal stem cell-derived diseases characterized by splenomegaly, bone marrow fibrosis, and debilitating symptoms. Outside of allogeneic HSCT, treatment regimens for myelofibrosis (MF) are largely palliative. Signaling of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is critical for proper hematopoietic cell function. Approximately 50% of PMF patients have inactivating mutations in Janus kinase 2 (JAK2). The *Jak2* V617F gain-of-function mutation occurs in over 95% of PV patients and approximately 50% of patients with ET and PMF.[90] The *Jak2* V617F-mutated allele has been linked to lower rates of survival, higher leukocyte counts, higher hemoglobin levels, and an increased risk of splenomegaly.[91]

Verstovsek and colleagues presented results of a phase III trial (COMFORT-I) at the ASCO meeting in 2011 comparing ruxolitinib (15 or 20 mg) to placebo in patients with intermediate-2 or high-risk PMF, post-polycythemia

vera-MF, or post-essential thrombocythemia MF. The trial demonstrated that the JAK inhibitor, ruxolitinib, significantly improves spleen size and symptom burden with limited and manageable toxicity in patients with MF.[92] Ruxolitinib was also compared to best available therapy in a separate 2 to 1 open-label multicenter randomized phase III study (COMFORT-II trial) also presented at ASCO 2011.[93] Overall, ruxolitinib demonstrated marked improvements in spleen size and QOL measures with manageable and limited toxicity. Based on the promising results from 2 COMFORT studies, ruxolitinib, a potent JAK1/2 kinase inhibitor was FDA approved for the treatment of intermediate or high-risk MF.[94,95,96]

Further analyses of the results from the COMFORT-II trial included an exploratory endpoint designed to assess the changes in *JAK2* V617F allele burden as a metric of molecular response to ruxolitinib or best available treatment. An additional objective was to analyze the correlation between changes in *JAK2* V617F allele burden with spleen size reduction in patients with MF from the COMFORT-II study. These results were presented at ASCO 2012 by Dr Vannucchi and colleagues.[97]

In total, 214 COMFORT-II patients with allele burden data at baseline and at 48 weeks and spleen volume measurement by magnetic resonance imaging (MRI) or computed tomography (CT) scan were included in this analysis. Based on the patient's absolute allele burden, the patients were divided into 3 groups (< 10%, 10% to < 20%, ≥ 20%). Allele burden was measured from blood samples using allele specific quantitative real time polymerase chain reaction (qPCR). Data was presented as a percentage of V617F mutant to nonmutant allele in each individual sample.

Most patients received benefit from ruxolitinib treatment regardless of the presence or absence of the *JAK2* V617F mutation or degree of allele burden reduction. Patients with the *JAK2* V617F mutation who received ruxolitinib had greater reductions in allele burden. Similarly, a greater allele burden response corresponded with greater reductions in spleen volume in ruxolitinib-treated patients. There was no concrete relationship identified at week 48 in ruxolitinib-treated patients between baseline allele burden and change in spleen volume. The kinetics of patient allele burden reduction was gradual over the course of the 48-week study. Additional studies and longer follow-up is needed to determine the extent of allele burden reduction.

## CONCLUSION

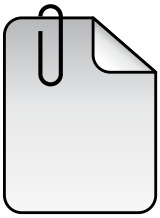
At ASCO 2012, results from several hematological malignancy trials revealed several key areas that may affect clinical practice.

In the lymphomas, BR demonstrates superiority to R-CHOP. These results support the use of BR as frontline regimen for indolent B-cell lymphomas and non-transplant eligible MCL patients. R-CHOP combination of therapeutic agents was associated with the best risk/benefit ratio in advanced stage FL. Clinical outcomes are similar and excellent with either R-CHOP or CHOP-RIT in FL and β2M and LDH had similar prognostic value to FLIPI and FLIPI2 but were easier to perform. Retreatment with rituximab appeared to be superior strategy if opting for rituximab monotherapy in LTBFL whereas maintenance therapy with rituximab was superior in terms of TTF in previously untreated LTB non-FL patients. Lenalidomide has significant activity as a single agent or in combination with rituximab in patients with recurrent FL but further studies are needed to confirm the potential of this combination as a backbone to future non-cytotoxic treatments. Bendamustine as a single agent is active in CLL and BR is a promising salvage regimen for patients with relapsed/refractory DLBCL after R-CHOP and warrants more research. Radiotherapy to bulky disease does not improve the outcome of elderly DLBCL patients in CR/CRu after completion of R-CHOP14 immunochemotherapy, but appears to be beneficial for patients with bulky disease not achieving CR/CRu.

For MM, data presented at ASCO 2012 suggest that advances in the treatment of MM have been made with novel proteasome inhibitors, histone deacetylase inhibitors, novel immunomodulatory drugs, and signal transduction modulators. While clinical studies are in the early stages, some antibodies such as daratumumab and elotuzumab are demonstrating efficacy in combination with current therapies such as lenalidomide and bortezomib.

In the leukemias, the next-generation TKIs demonstrated excellent efficacy and tolerability in CML, with faster and deeper molecular responses than imatinib and very low rates of disease progression. Acute myeloid leukemia remains without effective therapy in older patients; however, the addition of GO to azacitidine and to FLAG-based regimens compared favorably with standard chemotherapy or slightly better and warrant further studies. Early trials of 2

well-tolerated, antibody targeted therapies (blinatumomab and IO) for ALL show promising clinical results that need to be further examined. In CLL, the BTK inhibitor, ibrutinib, shows promise as a single agent and in combination with BR. Ofatumumab is highly active warranting further investigations in combination. The durable responses observed with ofatumumab plus lenalidomide also deserve attention and future study. Finally, the JAK2 inhibitor, ruxolitinib, is superior to the standard of care in improving splenomegaly and constitutional symptoms in MF.



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