

## Highlights in B-Cell Malignancies From the 2012 American Society of Hematology (ASH) Meeting

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A Review of Selected Presentations From the 2012  
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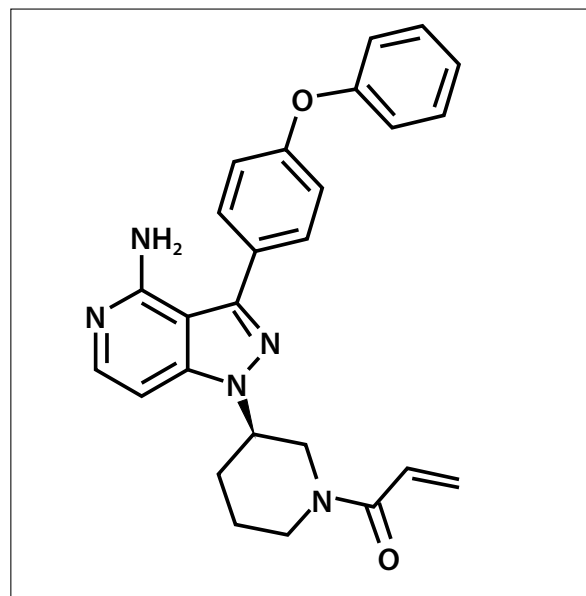
# Highlights in Chronic Lymphocytic Leukemia

**189 The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Promotes High Response Rate, Durable Remissions, and Is Tolerable in Treatment Naïve (TN) and Relapsed or Refractory (RR) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Patients Including Patients With High-Risk (HR) Disease: New and Updated Results of 116 Patients in a Phase Ib/II Study<sup>1</sup>**

JC Byrd, RR Furman, S Coutre, IW Flinn, JA Burger, KA Blum, JP Sharman, B Grant, JA Jones, WG Wierda, W Zhao, NA Heerema, AJ Johnson, A Tran, F Clow, L Kunkel, DF James, S O'Brien

Bruton's tyrosine kinase (BTK) is critical for lymphoma cell survival and proliferation. BTK is an essential part of the B-cell receptor (BCR) signaling pathway in normal and malignant B cells.<sup>2</sup> Ibrutinib (PCI-32765) is a selective, oral inhibitor to BTK (Figure 1). In chronic lymphocytic leukemia (CLL) cells, ibrutinib promotes apoptosis while inhibiting cell proliferation, migration, and adhesion.<sup>3</sup> Fludarabine-based therapy has improved outcomes in younger CLL patients, but in elderly patients, it is not tolerated as well and is associated with significant risk of cellular immune suppression as well as myelosuppression, thus limiting its use. Moreover, virtually all elderly CLL patients eventually relapse, and effective salvage regimens are lacking.

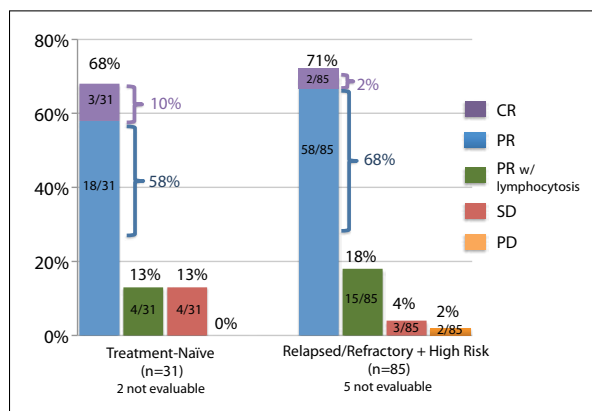
To address the need for improved treatment for elderly CLL patients, a multicohort, phase Ib/II trial (PCYC-1102-CA) of ibrutinib monotherapy in this patient population was conducted. The mature data, presented by Dr. John C. Byrd and colleagues, show that ibrutinib induced a high frequency of disease control lasting beyond 22 months in both treatment-naïve and relapsed or refractory CLL and small lymphocytic leukemia (SLL).<sup>1</sup> The patients were ages 65 years or older. Those with relapsed or refractory disease had received at least 2 prior therapies. For high-risk patients, relapse within 2 years following combination chemoimmunotherapy or the genetic marker del17p was required. Patients were enrolled into 5 cohorts that received oral ibrutinib at fixed doses of 420 mg or 840 mg daily until



**Figure 1.** Ibrutinib (PCI-32765) is a selective, oral inhibitor to Bruton's tyrosine kinase.

progressive disease (PD). The primary objective was to determine the safety of the dosing regimens. Secondary objectives included drug efficacy, pharmacokinetics/pharmacodynamics, and long-term safety. Response criteria were based on International Workshop on CLL (IWCLL) 2008 criteria, with modifications based on current practice.<sup>4,5</sup> One such modification included categorization of a partial response (PR) by all other criteria but without resolution of lymphocytosis as "PR with lymphocytosis." The NHL International Working Group (IWG) criteria were applied to SLL cases.<sup>6</sup>

For the 31 evaluable treatment-naïve patients, an overall response rate (ORR) of 68% was observed and included 10% complete responses (CRs; Figure 2). For the 85 evaluable relapsed/refractory and high-risk patients, the ORR was 71%, including 2% CRs. Responses appeared to be independent of factors indicating poor risk, including advanced-stage disease, 3 or more prior lines of therapy, elevated  $\beta$ 2-microglobulin, and cytogenetics. Estimated 22-month progression-free survival (PFS) rates were 96% for treatment-naïve patients and 75% for the relapsed or refractory and high-risk patients. Estimated overall survival (OS) rates for the



**Figure 2.** In a phase Ib/II study, ibrutinib was associated with an overall response rate of 68% and a CR rate of 10% in 31 evaluable, treatment-naïve chronic lymphocytic leukemia patients. CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease. Adapted from Byrd JC et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 189.

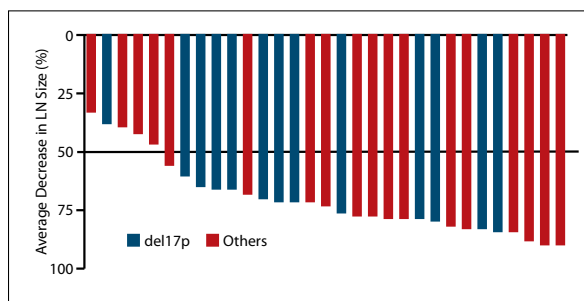
same 2 patient populations, respectively, were 96% and 83%. Median PFS and OS data are forthcoming.

The majority of adverse events (AEs) were grade 1/2. The most common were diarrhea (54%), fatigue (29%), upper respiratory tract infection (29%), rash (28%), nausea (26%), and arthralgias (25%). The most common ibrutinib-related AEs were diarrhea (28%), fatigue (18%), nausea (13%), and rash (8%). Hematologic toxicity of at least grade 3 was relatively uncommon. At a median follow-up of 16 months for all enrolled patients, there was no evidence of cumulative toxicity and no long-term safety concerns. Among 116 patients, 7 discontinued treatment due to an AE. Immunoglobulin (Ig) A increased significantly at 3, 6, and 12 months ( $P < .005$  for each time point).

### 187 The Btk Inhibitor Ibrutinib (PCI-32765) in Combination With Rituximab Is Well Tolerated and Displays Profound Activity in High-Risk Chronic Lymphocytic Leukemia (CLL) Patients<sup>7</sup>

JA Burger, MJ Keating, WG Wierda, J Hoellenriegel, A Ferrajoli, S Faderl, S Lerner, G Zacharian, X Huang, DF James, JJ Buggy, HM Kantarjian, SM O'Brien

Conventional chemoimmunotherapy induces relatively short remissions and poor outcomes in CLL patients with high-risk disease, particularly in cases of disease relapse. Patients with high-risk CLL show inferior responses to standard chemoimmunotherapy compared with patients with low-risk disease. CLL patients treated with ibrutinib monotherapy typically show delayed responses or stable disease (SD) due to persistent lymphocytosis,



**Figure 3.** In a phase II trial of patients with high-risk chronic lymphocytic leukemia, a regimen of ibrutinib plus rituximab reduced LN size by at least 50% in most patients, including those with del17p. CR=complete response; LN=lymph node; PD=progressive disease; PR=partial response; SD=stable disease. Adapted from Burger JA et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 187.

which arises from the redistribution of tissue-resident CLL cells into the peripheral blood. Based on data showing responses to ibrutinib treatment in high-risk CLL patients,<sup>8</sup> a single-center, phase II clinical trial of ibrutinib plus rituximab was conducted.<sup>7</sup> The trial accrued 40 patients who received oral ibrutinib (420 mg daily) plus rituximab (375 mg/m<sup>2</sup> weekly) for the 4 weeks in cycle 1. For cycles 2–6, patients received daily ibrutinib plus monthly rituximab, followed by daily ibrutinib monotherapy thereafter. Patients were required to have high-risk disease defined by del17p or TP53 mutation, relapsed CLL with del11q, or a PFS lasting less than 36 months after first-line chemoimmunotherapy.

Patients were a median age of 65 years (range, 35–82 years) and had received a median of 2.5 prior therapies (range, 0–8). Patients had a median Rai stage of 4 (range, 1–4) and a median  $\beta$ 2-microglobulin level of 4.2 mg/L (range, 2.2–12.3 mg/mL). The Ig heavy chain variable region was wild-type in 32 patients, mutated in 1 patient, and of unknown status in the remaining patients. Twenty patients had del17p or TP53 mutation, and 13 patients had del11q. Lymphocytosis peaked after 1 week of combination therapy and declined to approximately 50% of baseline after approximately 12 weeks; the decrease appeared to be accelerated by the addition of rituximab. During the same time frame, normal hematopoiesis improved, as reflected in a gradual increase in hemoglobin levels in anemic patients and normalization of platelet counts. One patient died from an unrelated infectious complication, and 1 patient withdrew consent prior to the start of therapy. With a median follow-up of 4 months, 38 patients remained on study therapy without PD, comparing favorably to the historic control of patients previously treated at the same center. As assessed by computed tomography (CT) scan in 31 evaluable patients, most patients, including those with del17p, showed a reduction in lymph node size of

at least 50%, including patients with del17p (Figure 3). Similarly, most patients showed a reduction in spleen size. Based on a response assessment at 3 or 6 months, 1 patient had a CR and 32 patients had a PR, yielding an ORR of 83%. In addition, 3 patients had a PR with persistent lymphocytosis.

In general, the combination treatment was very well tolerated. The most common AEs were diarrhea, bone pain, and fatigue. Toxicities of grade 3 (n=11) or grade 4 (n=2) were mostly transient and considered unrelated to study treatment. Two patients discontinued treatment due to aspergillosis or oral ulcers. Biomarker analysis showed a rapid reduction and normalization of plasma levels of the chemokines CCL3 and CCL4, which are secreted by CLL cells in a BCR-dependent manner.

### 1802 Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Blocks Hairy Cell Leukemia (HCL) Survival, Proliferation, and BCR Signaling: A New Therapeutic Approach for HCL<sup>9</sup>

M Sivina, RJ Kreitman, E Arons, JJ Buggy, F Ravandi, JA Burger

Hairy cell leukemia is an indolent B-cell malignancy genetically characterized by the *BRAF* mutation V600E.<sup>10</sup> Although state-of-the-art treatment with purine analogs typically induces durable CRs, most patients eventually progress, and many develop resistance to treatment. BCR signaling is directly involved in the pathogenesis and progression of many B-cell malignancies. The BCR signaling cascade leads to downstream activation of BTK, which in turn activates chemokine receptors and adhesion molecules involved in B-cell migration and tissue homing. Based on the established importance of BCR signaling in B-cell malignancies, its role in HCL and the activity of ibrutinib were explored in 2 HCL cell lines, ESKOL and HC-1, as well as in primary HCL cells.<sup>9</sup>

BTK protein expression was observed in the 2 HCL cell lines. Significant, dose-dependent inhibition of growth and reduction in S-phase length were observed with ibrutinib concentrations of 0.5  $\mu$ M, 1  $\mu$ M, and 5  $\mu$ M. Consistent with a reduction in BCR activation, ibrutinib at a concentration of 1  $\mu$ M inhibited BCR-mediated production of phospho-ERK, phospho-AKT, CCL3, and CCL4. Analysis of primary HCL cells from 8 patients showed that ibrutinib induced apoptosis, significantly reducing cell viability at 48 hours. Ibrutinib also reduced BCR signaling and activation in primary HCL cells, with levels of BTK, ERK, AKT, CCL3, and CCL4 significantly reduced.

### 191 Combinations of the Selective Phosphatidylinositol 3-Kinase-Delta (PI3Kdelta) Inhibitor Gs-1101 (CAL-101) With Rituximab and/or Bendamustine Are Tolerable and Highly Active in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL): Results From a Phase I Study<sup>11</sup>

SE Coutre, JP Leonard, RR Furman, JC Barrientos, S de Vos, IW Flinn, MT Schreeder, ND Wagner-Johnston, JP Sharman, TE Boyd, NH Fowler, LM Holes, BJ Lannutti, DM Johnson, LL Miller, TM Jahm

Phosphoinositide 3-kinase delta (PI3K $\delta$ ) is a major driver of proliferation and survival in B cells and has been directly implicated in the survival of CLL cells.<sup>12</sup> GS-1101 (CAL-101), now known as idelalisib, is an orally available small molecule with high selectivity for the PI3K $\delta$  isoform. When administered in doses of at least 100 mg twice daily, idelalisib monotherapy has demonstrated considerable activity in patients with heavily pretreated CLL.<sup>13</sup> Therefore, a phase I study was designed to evaluate 28-day cycles of idelalisib plus rituximab and/or bendamustine in patients with previously treated CLL.<sup>11</sup> For the idelalisib plus rituximab (GR) regimen, patients received idelalisib plus rituximab (375 mg/m<sup>2</sup> weekly) for 8 doses. For the idelalisib plus bendamustine (GB) regimen, patients received bendamustine (90 mg/m<sup>2</sup> on days 1 and 2) for 6 cycles. Idelalisib was administered to initial cohorts in the GR or GB arms at 100 mg twice daily, and the dose was increased in later cohorts to 150 mg twice daily. Patients in the idelalisib/rituximab/bendamustine (GBR) arm received idelalisib (150 mg twice daily) plus 6 cycles of rituximab (375 mg/m<sup>2</sup> on day 1) and bendamustine (90 mg/m<sup>2</sup> on days 1 and 2). Tumor response was evaluated based on standard criteria.<sup>4</sup> Chemokine and cytokine plasma levels were assessed at baseline and on day 28 of each cycle using multiplexed bead suspension arrays.

The study enrolled 51 patients with CLL. The majority of patients in each treatment arm had bulky adenopathy. Nearly all of the patients had received prior rituximab, and approximately 43% of patients across all arms had received prior bendamustine. In the GR, GB, and GBR arms, 37%, 71%, and 47% of patients, respectively, had refractory disease. AEs of grade 3 or higher and laboratory abnormalities were generally consistent with those described for each of the single agents. In the GR, GB, and GBR arms, the most common AEs of at least grade 3 were neutropenia (observed in 32%, 76%, and 67% of patients in each arm, respectively) and thrombocytopenia (observed in 5%, 35%, and 20% of patients in each arm, respectively). A reduction in lymphadenopathy was observed in 93–100% of evaluable patients in

each arm, and lymph node shrinkage was rapid. In the GR, GB, and GBR arms, investigator-reported ORRs were 78%, 82%, and 87%, respectively. At a minimum follow-up of 40 weeks for each arm, 1-year PFS rates were 74%, 88%, and 87%, respectively. Disease-associated chemokines and cytokines were commonly elevated at baseline, with significant reductions observed after treatment. The authors noted that the favorable safety profile and lack of overlapping toxicities among the therapeutic agents enabled the delivery of idelalisib at a full dose of 150 mg twice daily when combined with rituximab and/or bendamustine. Phase III trials of idelalisib in combination with rituximab or bendamustine plus rituximab have been initiated.<sup>14,15</sup>

### 192 Monotherapy With Subcutaneous (SC) Injections of Low Doses of Humanized Anti-CD20 Veltuzumab Is Active in Chronic Lymphocytic Leukemia (CLL)<sup>16</sup>

M Kalaycio, G Negrea, R Elstrom, C Farber, H Horne, WA Wegener, DM Goldenberg

Veltuzumab is a second-generation, humanized, anti-CD20, monoclonal antibody that differs from the chimeric rituximab in terms of structure, function, and improved preclinical properties. In patients with NHL, intravenous antibody administration can be avoided by administering 4 subcutaneous injections of low-dose veltuzumab every other week.<sup>17</sup> However, patients with CLL have high levels of circulating leukemic cells. Therefore, the possible requirement of more frequent and prolonged dosing in CLL patients was investigated in a multicenter, phase I/II study.<sup>16</sup> The study evaluated the safety, tolerability, pharmacokinetics, and preliminary efficacy of subcutaneous veltuzumab in patients with previously untreated (n=13) or relapsed (n=7) CD20-positive CLL. Patients' ages ranged from 53–93 years. Patients initially received the drug based on the NHL dosing schedule, with 4 doses administered every other week at 80 mg, 160 mg, or 320 mg (cohort 1; cumulative dose range, 320–1,280 mg). After protocol amendment, subsequent patients received 16 doses administered twice per week at levels of either 160 mg or 320 mg (cohort 2; cumulative dose range, 2,560–5,120 mg). Twenty patients were enrolled into cohort 1 (n=11) or cohort 2 (n=9). Thirteen patients were treatment-naïve. Among the 7 patients who had received 1–6 prior treatments, 6 had received prior rituximab. Fourteen patients had Rai intermediate-risk scores, and 16 patients had 1 or more B symptoms.

Veltuzumab was well tolerated, with transient injection-site reactions of grade 1/2 only. One patient developed bacterial meningitis and withdrew from the study during treatment. A second patient with a complicated medical history developed malignant hypertension, transient ischemia

attack, and pneumonia 6 months after treatment. No other serious AEs or grade 3/4 events were reported. One patient who had previously received rituximab therapy had antibodies to veltuzumab at study entry. Thirteen patients showed a decrease in circulating leukemic cells of 50% or greater from baseline, and 3 patients achieved absolute lymphocyte count (ALC) values of less than 4,000 cells/ $\mu$ L. Mean maximum concentration (C<sub>max</sub>) values in cohort 1 at dose levels of 80 mg, 160 mg, and 320 mg were 1.8  $\mu$ g/mL, 4.5  $\mu$ g/mL, and 30.8  $\mu$ g/mL, respectively. In cohort 2, at dose levels of 160 mg or 320 mg, mean C<sub>max</sub> values were 36.2  $\mu$ g/mL and 199.5  $\mu$ g/mL, respectively. Based on IWCLL criteria, 3 patients had a PR, including 2 who were relapse-free at 12 and 24 months; among the 12 patients who had SD as best response, 4 remained relapse-free for 6–12 months. Three patients had PD by the first evaluation, and 2 patients withdrew consent prior to any response assessment. Therefore, 15 of 18 patients (83%) achieved either PR or SD with veltuzumab treatment. Veltuzumab appeared active in all dose groups. Treatment responses and ALC decreases appeared similar regardless of dose level or dosing schedule.

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## Commentary: Chronic Lymphocytic Leukemia

Susan M. O'Brien, MD

There were many noteworthy presentations in chronic lymphocytic leukemia (CLL) at the 2012 American Society of Hematology (ASH) meeting. Interesting data were presented on ibrutinib, idelalisib, ABT-199, and velvuzumab.

Dr. John Byrd presented follow-up data for ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, in patients with CLL.<sup>1</sup> There are now several agents in clinical trials whose mechanism of action is inhibition of the B-cell receptors. A CLL cell is a B cell, and when the B-cell receptor on either a normal B cell or a malignant B cell is ligated, that cell receives a very strong survival and proliferative signal. It makes sense that in B-cell malignancies, interference with that signaling could have a laudatory effect on the disease. Earlier data from this study were presented at the 2012 Congress of the European Hematology Association.<sup>2</sup> The analysis presented at the 2012 ASH meeting is based on longer follow-up. This longer follow-up is quite relevant because over time, the response categories have changed. B-cell receptor inhibitors have an interesting mechanism of action; initially, they produce a very dramatic and brisk reduction in lymph nodes or tumor bulk, but at the same time, they cause lymphocytosis. The lymphocyte count increases. To some extent, there appears to be a compartment shift, where the cells are coming out of the lymph nodes and entering the blood. Preclinical data from Burger and colleagues show that ibrutinib interferes with the chemokines that hold the cells close to the stroma.<sup>3</sup> The effect goes beyond a compartment shift, however, which would involve even higher lymphocyte counts than are seen based on the very rapid reduction in the lymph node mass. There must also be some kind of direct cellular effect.

The activity of B-cell receptor inhibitors may require an updated approach to assessing patient outcome. For example, a patient who is 2–3 months into treatment

could have an 80% reduction in tumor bulk, which is quite dramatic in such a short period of time. This patient would not, however, qualify as a responder according to standard International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Working Group Criteria. According to those guidelines, partial remission (PR) requires a 50% reduction in baseline lymphocytosis. A new response criteria, known as nodal responses, includes patients who have 50% reduction in nodal disease, including the spleen, but do not meet the IWCLL criteria for a PR because their lymphocyte count is either elevated above baseline or has decreased by less than 50%. These patients are sometimes now referred to as having a PR with lymphocytosis.

Interestingly, as the data for ibrutinib were presented over a year's time, we saw that the overall response rate was quite high at 80–90%. At early follow-up, the PR rate started at 20–25%, but it has now increased over time as the lymphocytosis resolves and the IWCLL criteria for PR are met.

In the ASH presentation, Dr. Byrd reported data for 2 different populations: a relapsed/refractory population and treatment-naïve patients older than 65, in whom chemoimmunotherapy—such as fludarabine, cyclophosphamide, and rituximab (FCR)—may produce greater toxicity. Oral ibrutinib was administered at doses of 420 mg or 840 mg daily among 5 cohorts until progressive disease. After follow-up of approximately 2 years, the relapsed/refractory patients had a PR rate of 71% and a PR with lymphocytosis rate of 18%. Adding those 2 rates together, essentially 90% of the patients had at least 50% reduction in tumor bulk, an impressive outcome in a very refractory population. In the treatment-naïve group, the overall response rate was 68%, and an additional 13% of patients had a PR with lymphocytosis, for a total response rate of approximately 80%. The estimated progression-free survival (PFS) at 26 months was 75% for the relapsed/refractory group

and 96% in the treatment-naïve group. These responses occurred with very minimal toxicity. There was 1 patient in the treatment-naïve group who progressed and died.

An interesting finding in this study is that some of the known prognostic factors that predict a poor response to a chemotherapy-based regimen or a shorter PFS did not appear to be correlated with response to ibrutinib. The most important prognostic factor is probably the 17p deletion; CLL patients with this deletion have the worst prognosis and do not respond well to chemotherapy. In this study of ibrutinib, patients with the 17p deletion did just as well as patients without it. The most common side effect was mild diarrhea, but it was often self-limited and resolved during the treatment course. In addition, ibrutinib was not myelosuppressive, which is important because the most common complications in CLL patients—who present with baseline immunologic defects—are myelosuppression and infection. Not only is ibrutinib not myelosuppressive, but there are some sustained increases in platelet count and hemoglobin in patients who started the study cytopenic. These data are exciting, and ibrutinib is now being studied in pivotal registration trials.

Dr. Jan Burger presented results from a trial examining ibrutinib and rituximab in a relapsed/refractory high-risk cohort, defined as patients with either an 11q or a 17p deletion or who had progressed within 3 years of frontline chemoimmunotherapy.<sup>4</sup> The patients received 420 mg/day of ibrutinib in a flat dose and rituximab at the standard dose of 375 mg/m<sup>2</sup> weekly for the first 4 weeks and then monthly for 4 additional months. Afterward, treatment with rituximab ended, but treatment with ibrutinib continued indefinitely. In this trial, as in the one presented by Dr. Byrd,<sup>1</sup> ibrutinib was continued until the patient showed signs of progression.

The follow-up on this trial was limited. However, it is conceivable that if an antibody is added to ibrutinib, there will be a much more rapid reduction in lymphocytosis because rituximab immediately reduces the lymphocyte count. One might expect to see standard IWCLL responses much faster when an antibody—or chemotherapy—is added. The advantage of adding an agent like rituximab is that it is a nonchemotherapy regimen that is also nonmyelosuppressive and relatively nontoxic. In his study, Dr. Burger reported initial lymphocytosis that decreased very quickly. At an early follow-up of 3–6 months, the overall response rate using standard criteria was 83% percent, with another 8% of patients achieving a PR with lymphocytosis. Again, this response rate is approximately 90%.

At 3–6 months, there was a dramatic difference between single-agent ibrutinib and the ibrutinib/rituximab combination. In the single-agent study, the true PR rate was approximately 25%—again, because of lymphocytosis—whereas with the combination, the PR rate was 80%.<sup>1,4</sup> There is no

question that when rituximab was added to ibrutinib, the response was much more rapid. We do not yet know whether these responses will be deeper and/or more durable because the follow-up in this study was fairly short.

Dr. Mariela Sivina presented results from a preclinical trial examining the in vitro effects of ibrutinib on the cells in hairy cell leukemia.<sup>5</sup> BTK signaling appears to be important in hairy cell leukemia, as it is in CLL and lymphoma.<sup>6</sup> This study found BTK expression in hairy cells, as well as significant inhibition of hairy cell growth and proliferation with ibrutinib in a dose-dependent fashion. The authors also looked at the effects of ibrutinib on BCR signaling, and ibrutinib reduced the level of BCR-induced phosphorylated ERK. The pathway was clearly being inhibited because some of the downstream kinases were not being phosphorylated, as would be expected with signaling through the B-cell receptor.

This study suggests that ibrutinib might be an active agent in hairy cell leukemia, although it has not been used in that disease yet. The irony is that hairy cell leukemia is a disease that has almost as many treatments as there are patients. It is very rare, and there are several treatments that work, including purine analogs and monoclonal antibody toxins. Recently, there were some interesting data showing that all of these patients have a *BRAF* mutation. The *BRAF* inhibitor vemurafenib was approved by the US Food and Drug Administration (FDA) in 2011 for the treatment of patients with melanoma whose tumors have V600E mutations in the *BRAF* gene.<sup>7,8</sup> It would be interesting to combine vemurafenib, which is an oral drug, with ibrutinib, another oral drug, to create a nontoxic oral combination for hairy cell leukemia. First, it would be necessary to obtain clinical data with single-agent ibrutinib in this disease.

There are multiple B-cell receptor inhibitors in clinical trials. One such agent is GS-1101, which was formerly known as CAL-101 and recently received the official name of idelalisib. Idelalisib targets a different kinase in the B-cell receptor pathway—PI3K $\delta$ —from ibrutinib. Idelalisib is an oral agent given twice a day. Previous data on single-agent idelalisib in refractory patients have shown very high overall response rates of 80–90%, with true PRs in approximately 25% of patients.<sup>9,10</sup> It appears that the lymphocytosis may be somewhat prolonged with this agent, and therefore data for idelalisib in combination with another agent would be of interest. That being said, patients with CLL can have very high lymphocyte counts—200,000–300,000 cells/mm<sup>3</sup>—and be asymptomatic. To some extent, initial lymphocytosis is a cosmetic problem. Obviously, we hope to see PRs and then potentially even CRs with longer follow-up.

At the 2012 ASH meeting, Dr. Coutre presented results from a study combining idelalisib with rituximab

and/or bendamustine, the chemotherapeutic agent, in patients with relapsed/refractory CLL.<sup>11</sup> As in the trial of rituximab and ibrutinib by Dr. Burger,<sup>4</sup> here the antibody and/or the chemotherapy were given for a finite period of time upfront, and then the idelalisib was continued indefinitely until the patient progressed. The study showed that with any of the combinations, the response rate using standard IWCLL criteria varied from 78–87%. There were still some patients who had a lymph node response, but that response was largely abrogated by the combination. This study had not reached a median PFS; at 1-year, the PFS rate was 69%, so these responses appeared to be very durable. The most common adverse event was fever. Elevation of transaminases has been seen in phase I studies of idelalisib.<sup>12</sup> In this combination trial, any-grade elevated transaminases occurred in 37% of patients, and grade 3/4 elevated transaminases occurred in 10%. In the single-agent trials of idelalisib, grade 3/4 elevated transaminase resolved when the drug was held.<sup>12</sup> The drug was then resumed at a lower dose. It was rare for elevated transaminase to require discontinuation of idelalisib. These data are encouraging, and idelalisib is being studied in several trials that might lead to FDA approval.

Dr. Matthew Davids presented trial results on the oral agent ABT-199, a Bcl-2 mimetic that is mostly a Bcl-2 inhibitor.<sup>13</sup> Another BH3 mimetic, ABT-263, was previously shown to inhibit multiple Bcl-2 family members, such as Bcl-2 and Bcl-xl, but not Mcl-1.<sup>14</sup> The dosing of ABT-263 was limited due to thrombocytopenia that appeared to be caused by binding to Bcl-xl in platelets. ABT-199 was expressly engineered to remove the Bcl-xl inhibition. It is not a B-cell receptor inhibitor, so the initial response is a reduction in lymphocytosis. An interesting finding in this study was that the reduction in lymphocytosis was so dramatic that the CLL patients experienced tumor lysis syndrome. To minimize this toxicity, the dosing schema was revised so that treatment started with a lower dose that was slowly escalated. Tumor lysis is an interesting toxicity. Although it can be a problem, it is also an encouraging sign because it indicates that the drug is having a brisk effect on the disease. Among the 37 evaluable patients in this study with relapsed CLL, the overall response rate using standard criteria was 81%. This is a striking response rate to an oral, single agent in patients with CLL. Thus far, tumor lysis is the only major toxicity; thrombocytopenia has not been significant.

Veltuzumab is an anti-CD20 antibody that is similar to rituximab but engineered to have improved preclinical properties. Dr. Matt Kalaycio presented results from a study of monotherapy with subcutaneous veltuzumab in CLL.<sup>15</sup> This approach might be very relevant in CLL. Rituximab in combination with chemotherapy has completely changed the treatment for CLL, because of

the synergy between the 2 therapies. Single-agent rituximab is a very weak drug in CLL compared to follicular lymphoma. For example, in one of the original trials of relapsed low-grade lymphoma patients, the follicular lymphoma patients had a 50% response rate with single-agent rituximab, and the patients with small lymphocytic lymphoma—which would be essentially equivalent to CLL—had about a 15% response rate.<sup>16</sup> A more effective anti-CD20 for CLL would be useful.

In most previous studies, veltuzumab was administered intravenously. In the study by Kalaycio and colleagues, administration was subcutaneous.<sup>15</sup> Patients did not receive pretreatment with antihistamines or steroids because the infusion reactions seen with most intravenous monoclonal antibodies were not expected, and they did not occur. The only adverse events seen were grade 1/2 injection site reactions. The activity of veltuzumab was disappointing. Among the 20 patients in the study, 13 were treatment-naïve. Expectations would be high that treatment-naïve patients would benefit from any kind of treatment. However, there were only 3 partial responses reported, a low rate. It was not specified whether these partial responses were among the treatment-naïve patients, but I suspect they were. Although the total number of patients was small, the results of the trial can be considered disappointing. Veltuzumab monotherapy was not toxic, but there was nothing to suggest that it would be better than established treatments, such as single-agent rituximab.

### Acknowledgment

*Dr. O'Brien has received research support from Pharmacia and Gilead.*

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## Highlights in Mantle Cell Lymphoma, NHL, Follicular Lymphoma, DLBCL, and Indolent Lymphoma

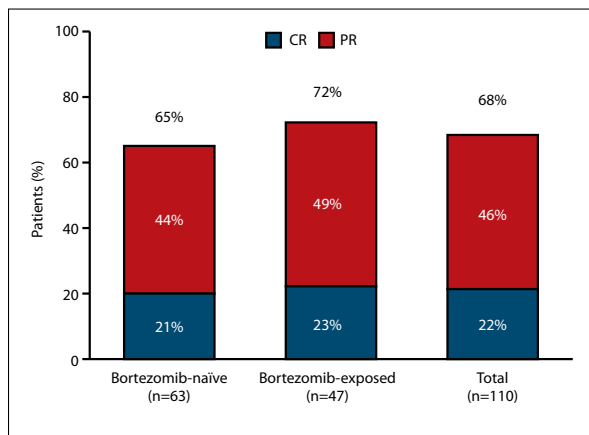
### 904 Interim Results of an International, Multicenter, Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Relapsed or Refractory Mantle Cell Lymphoma (MCL): Durable Efficacy and Tolerability With Longer Follow-Up<sup>1</sup>

M Wang, SA Rule, P Martin, A Goy, R Auer, BS Kahl, W Jurczak, RH Advani, JEE Romaguera, J McGreivy, F Clow, M Stevens-Brogan, L Kunkel, KA Blum

Mantle cell lymphoma is an aggressive subtype of NHL characterized by high response rates to initial therapy frequently followed by relapse with acquired resistance to chemotherapy and short response durations to conventional treatment. The PCYC-1104-CA trial is an ongoing, international, multicenter, open-label, phase II study of single-agent ibrutinib (560 mg/day until PD) in patients with relapsed or refractory mantle cell lymphoma.<sup>1</sup> The study's primary objective is ORR, with secondary objectives including duration of response (DOR), PFS, OS, safety, and tolerability. Two cohorts were enrolled in parallel based on prior treatment with the proteasome inhibitor bortezomib. The bortezomib-naïve cohort enrolled 58 patients who had never received bortezomib plus 7 patients who received fewer than 2 cycles of bortezomib. The bortezomib-exposed cohort enrolled 50 patients who had received at least 2 cycles of the drug. Eligible patients

had confirmed mantle cell lymphoma, measurable disease, and cyclin D1+ or t(11;14). Following their most recent treatment regimen, they had failed to achieve a PR or better or had experienced PD. They had received 1–5 prior lines of therapy for mantle cell lymphoma. Patients were permitted to have an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0–2, but most patients had a score of 0 or 1. Median age was 68 years (range, 40–84 years), and 89 patients (77%) were male. Most patients (n=61; 53%) had received at least 3 prior treatment regimens. The median time since diagnosis was 42 months (range, 3–224 months). Thirty-three patients (29%) had received prior therapy with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate and cytarabine (hyper-CVAD), 11 patients (10%) had received a prior stem cell transplant, and 27 patients (23%) had received prior lenalidomide. A high-risk mantle cell lymphoma International Prognostic Index (MIPI) score was recorded for 57 patients (49%); a bulky mass, defined as 10 cm or larger, was observed for 15 patients (13%), and refractory disease was present in 52 patients (45%).

With a median follow-up of 9.2 months, the ORR for the combined cohorts was 68% and included 22% complete responses (CRs) (Figure 4). For the bortezomib-exposed cohort (n=47), the ORR was 72% and included 23% CRs; for the bortezomib-naïve cohort (n=63), the ORR was 65% and included 21% CRs. ORRs ranging

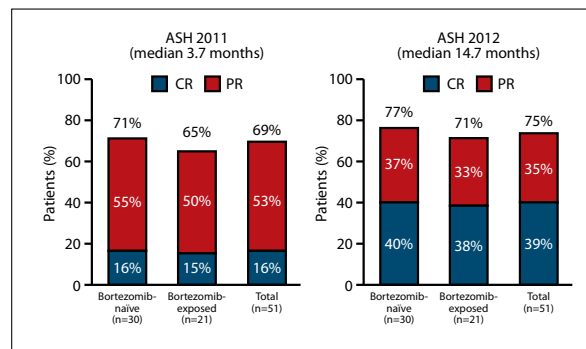


**Figure 4.** In a phase II trial of patients with relapsed or refractory mantle cell lymphoma, ibritinib was associated with an overall response rate of 68% and a complete response rate of 22% at a median follow-up of 9.2 months. CR=complete response; PR=partial response. Adapted from Wang M et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 904.

from 63–76% were observed for patients with baseline characteristics such as bulky disease (64%), refractory disease (65%), and 3 or more prior treatment regimens (66%).

As presented at ASH in 2011, preliminary results in 51 evaluable patients from the study had shown rapid nodal responses, including CRs, in relapsed and refractory mantle cell lymphoma patients.<sup>2</sup> The longer follow-up on these patients showed an increase in ORR from 69% at a median follow-up of 3.7 months to 75% at a median follow-up of 14.7 months (Figure 5). As seen with the longer follow-up, ORR increased from 71% to 77% for patients in the bortezomib-naïve cohort and from 65% to 71% in the bortezomib-exposed cohort. Notably, the proportion of patients with CRs increased with the longer follow-up, from 16% to 39% for the combined cohorts, with similar increases observed within each cohort. For the 110 evaluable patients, the median time to response was 1.9 months for patients who achieved a PR (range, 1.4–1.9 months) and 5.5 months for patients who achieved a CR (range, 1.7–16.4 months). The authors concluded that the longer follow-up demonstrated the durability of responses achieved with ibritinib monotherapy and that the single agent elicited an unprecedented ORR in patients with relapsed or refractory mantle cell lymphoma.

Treatment-emergent AEs occurring in at least 15% of subjects included diarrhea (35%), fatigue (32%), upper respiratory tract infection (23%), nausea (21%), rash (21%), dyspnea (20%), and peripheral edema (15%). Neutropenia was the most common AE of grade 3 or higher; it occurred in 11% of patients. Anemia, diarrhea, dyspnea, pneumonia, and thrombocytopenia each occurred in 5% of patients. Grade 4 treatment-related AEs included neutropenia (5%), hyperuricemia (2%), and pancytopenia (1%). One case of grade 5 pneumonia was considered treatment-related.



**Figure 5.** In an updated analysis of a phase II study of ibritinib in relapsed or refractory mantle cell lymphoma, the longer follow-up on these patients showed an increase in overall response rate from 69% with a median follow-up of 3.7 months to 75% with a median follow-up of 14.7 months. ASH=American Society of Hematology; CR=complete response; PR=partial response. Adapted from Wang M et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 904.

A study presented at the 2013 United States & Canadian Academy of Pathology Annual Meeting examined BTK inhibition and response prediction in mantle cell lymphoma cells. Immunoblotting showed that primary mantle cell lymphoma cells expressed higher levels of phospho-BTK compared to resting B cells purified from healthy donors, which suggests that lymphoma cells may be more susceptible to BCR inhibition than healthy B cells.<sup>3</sup> The authors used an MTT assay to evaluate the effect of ibritinib on 3 mantle cell lymphoma cell lines: Jeko-1, Granta-519, and Mino. Ibrutinib reduced the activity of ERK1/2 and AKT in the Jeko-1 cells in a dose-dependent manner. No reduction was seen in the Mino or Granta-519 cells. A reduction in AKT activity corresponded to the pretreatment Ki67 index, and therefore the highly proliferative mantle cell lymphoma cells may be especially sensitive to BTK inhibition. The anti-tumor effects of ibritinib were mediated primarily by specific BTK inhibition, suggesting that genetic knockdown of BTK effectively reduced the growth of Jeko-1 cells.

### 304 The BCL-2-Specific BH3-Mimetic ABT-199 (GDC-0199) Is Active and Well-Tolerated in Patients With Relapsed Non-Hodgkin Lymphoma: Interim Results of a Phase I Study<sup>4</sup>

MS Davids, AW Roberts, MA Anderson, JM Pagel, BS Kahl, JF Gerecitano, DE Darden, CE Nolan, LA Gressick, J Yang, BJ Chyla, TA Busman, AM Graham, E Cerri, SH Enschede, RA Humerickhouse, JF Seymour

Bcl-2 is highly expressed in indolent NHL, mantle cell lymphoma, and certain aggressive lymphomas, and thus

represents a promising therapeutic target. Navitoclax, a first-generation inhibitor of Bcl-2, showed activity in indolent lymphoma; however, its therapeutic use in NHL was limited due to concomitant inhibition of Bcl-xL and consequent dose-limiting thrombocytopenia. ABT-199 is an orally bioavailable, second-generation BH3 mimetic that inhibits Bcl-2 with an inhibition constant (K<sub>i</sub>) of less than 0.10 nM but shows a 500-fold reduction in inhibition of Bcl-xL (K<sub>i</sub>=48 nM). ABT-199 has demonstrated antitumor activity against human cell lines and xenograft models representing NHL, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma.<sup>5</sup>

As presented by Dr. Matthew S. Davids and colleagues, a phase I dose-escalation trial using a modified Fibonacci design was undertaken in patients with relapsed or refractory NHL.<sup>4</sup> The study's primary objectives were to determine the safety, pharmacokinetics, and maximum tolerated dose (MTD) of ABT-199; to recommend a dose for a phase II trial; to assess drug efficacy; and to evaluate biomarkers in this patient population. The patients were adults who required therapy, had an ECOG PS of 0–1, and had adequate bone marrow function. They received ABT-199 on week 1, day 7, followed by continuous dosing until PD or unacceptable toxicity. Based on concerns of potential tumor lysis syndrome, the dosing strategy included a lead-in period of 2–3 weeks with step-wise increases to the target dose. For the first 4 cohorts, the starting doses were, respectively, 50 mg, 100 mg, 200 mg, and 200 mg, with target cohort doses of 200 mg (n=3), 300 mg (n=3), 400 mg (n=4), and 600 mg (n=7).

At the time of the interim report, 17 patients had received treatment with ABT-199. Their median age was 71 years (range, 35–85 years). Patients had received a median 3 prior therapies (range, 1–7), and 6 patients had bulky adenopathy. The most common AEs experienced by 3 or more patients were nausea, occurring in 41%; diarrhea, dyspepsia, extremity pain, and fatigue, each occurring in 24%; and anemia, constipation, upper respiratory tract infection, and cough, each occurring in 18%. Grade 3/4 AEs occurring in more than 1 patient included anemia (18%) and neutropenia (12%). There have been no reports of treatment-related thrombocytopenia, dose-limiting toxicities (DLTs), or tumor lysis syndrome related to ABT-199 treatment. At a median follow-up of 2.8 months (range, 1.2–10.8 months), 14 patients remained on-study and 3 patients had discontinued due to PD. Of the 15 patients who had completed at least 1 week 6 assessment, reductions of greater than 50% in target lesions have been observed in 8 patients (53%), including 6 of 6 patients with mantle cell lymphoma, 1 of 2 patients with Waldenström's macroglobulinemia, and 1 of 2 patients with DLBCL. Five patients with follicular lymphoma were evaluated, of whom 3 had rituximab-refractory disease. With a median time-on-study of

6.4 months (range, 3.5–10.8 months), 4 of 5 follicular lymphoma patients showed nodal disease reductions that ranged from 18–40%. Dose escalation to identify the optimal dosing regimen and MTD is continuing.

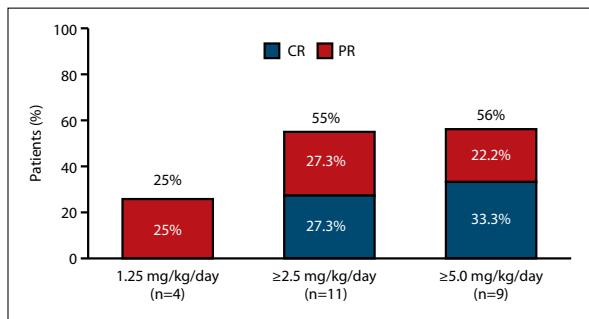
### 156 The Bruton's Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Is Active and Tolerated in Relapsed Follicular Lymphoma<sup>6</sup>

NH Fowler, RH Advani, JP Sharman, SM Smith, J McCreiby, L Kunkel, V Troung, C Zhou, TE Boyd

Dr. Nathan Fowler and colleagues presented long-term tolerability and sustained activity of ibrutinib monotherapy in patients with follicular lymphoma.<sup>6</sup> A phase I study enrolled adult patients with relapsed or refractory B-cell lymphoma and included 16 patients with follicular lymphoma. The study followed a dose escalation protocol in which oral ibrutinib was escalated to the MTD or 3 dose levels above complete occupancy of the active site in BTK. Five cohorts received ibrutinib intermittently in doses ranging from 1.25–12.5 mg/kg daily on a cycle of 28 days on the drug followed by 7 days without the drug, and 2 cohorts received continuous daily ibrutinib dosed at 8.3 mg/kg or in a fixed dose of 560 mg. Tumor assessment occurred every 2 cycles and was based on the Revised Response Criteria for Malignant Lymphoma.<sup>7</sup> The trial's primary objectives were to establish the study drug safety and MTD; to determine ibrutinib pharmacokinetics; and to measure the pharmacodynamic parameters, including drug occupancy of BTK. The secondary objective was to evaluate tumor response.

For the subgroup of patients with follicular lymphoma, baseline characteristics of interest included median age of 60 years (range, 41–71 years) and median time from diagnosis of 54 months (range, 19–186 months). Patients had received a median 3 prior therapies (range, 1–5), and all of the patients had received prior rituximab. Forty-four percent of patients had Follicular Lymphoma International Prognostic Index (FLIPI) scores indicating high-risk disease, and 44% of patients had stage IV disease at diagnosis.

The ORR was 44% and included 4 patients (25%) with a CR. The median DOR was 12.3 months. The median time to first response was 4.7 months (range, 2–12 months) for all follicular lymphoma patients, 4.6 months (range, 2–11 months) for patients who achieved a PR, and 11.5 months (range, 5–12 months) for patients who achieved a CR. A comparison of outcomes for patients who received ibrutinib at 2.5 mg/kg or greater (n=11) versus 5 mg/kg or greater (n=9) suggested a trend toward improved PFS for the higher dosages (median PFS, 13.4 months vs 19.6 months, respectively). The CR rate was highest among patients who received daily dosages of at least 5 mg/kg compared with the lower dosages (Figure 6). At the time of the presentation,



**Figure 6.** In a phase I trial examining different dosages of ibrutinib, a daily dosage of at least 5 mg/kg was associated with the highest complete response rate among patients with relapsed or refractory B-cell lymphoma. CR=complete response; PR=partial response. Adapted from Fowler NH et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 156.

2 patients were still responding to ibrutinib at 25 and 29 months. The authors recommended an ibrutinib dose of 560 mg daily for future studies in follicular lymphoma patients.

Treatment-emergent AEs occurring in at least 25% of patients included diarrhea (50%), fatigue (44%), nausea (38%), cough (31%), and myalgia (25%). Grade 3 AEs included 1 event of each of the following: anemia, neutropenia, pancytopenia, anxiety, hypersensitivity, hypokalemia, hypophosphatemia, non-cardiac chest pain, pneumonia, and vomiting. Investigators reported 1 case of grade 4 hypokalemia and 1 case of myelodysplastic syndrome that occurred 29 days after the last dose of ibrutinib. DLTs included grade 2 neutropenia and grade 4 hypokalemia in 1 patient in the 2.5 mg/kg intermittent dosing cohort and 1 case of grade 3 hypersensitivity reaction in the 8.3 mg/kg intermittent dosing cohort. However, no DLTs were observed in the 12 mg/kg intermittent cohort, and the MTD was not reached. BTK occupancy, determined for all 56 patients in the phase I study, showed 100% occupancy of the BTK active site at 2.5 mg/kg daily.<sup>8</sup>

### 686 The Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), Has Preferential Activity in the ABC Subtype of Relapsed/Refractory De Novo Diffuse Large B-Cell Lymphoma (DLBCL): Interim Results of a Multicenter, Open-Label, Phase 2 Study<sup>9</sup>

WH Wilson, JF Gerecitano, A Goy, S de Vos, VP Kenkre, PM Barr, KA Blum, AR Shustov, RH Advani, J Lih, M Williams, R Schmitz, Y Yang, S Pittaluga, G Wright, LA Kunkel, J McGreivy, S Balasubramanian, M Cheng, D Moussa, JJ Buggy, LM Staudt

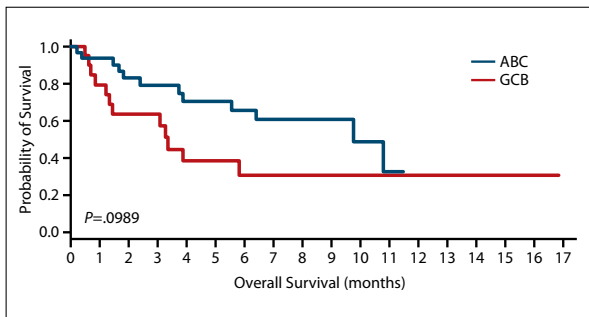
DLBCL comprises 2 molecular subtypes: activated B-cell-like (ABC) and germinal center B-cell-like

(GCB). Of the 2 subtypes, ABC is associated with significantly reduced PFS and OS despite current therapies, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).<sup>10</sup> In contrast to GCB DLBCL cell lines, the survival of ABC DLBCL cell lines requires "chronic active" BCR signaling mediated by BTK.<sup>11</sup> In the BCR subunit CD79B, gain-of-function mutations have been observed in 21% of ABC versus 5% of GCB DLBCL tumors. MYD88, an adapter for Toll-like receptors, also promotes the survival of ABC DLBCL cell lines; similarly, the MYD88 mutation, L265P, results in constitutive activation and is common in ABC DLBCL tumors but rare in GCB DLBCL.

Based on the different behaviors of the 2 DLBCL subtypes, a multicenter, open-label, phase II study (PCYC-1106-CA) was conducted based on the hypothesis that patients with ABC DLBCL would show a superior response to the BTK inhibitor. Interim results were presented by Dr. Wyndham Wilson and colleagues.<sup>9</sup> Patients with relapsed or refractory DLBCL received ibrutinib (560 mg) daily to progression in a 28-day cycle. The study's primary objective was to evaluate ORR in the 2 DLBCL subtypes, with response determined by the investigator based on NHL IWG Criteria.<sup>7</sup> The secondary objective was to evaluate the drug's safety and tolerability. Central gene expression profiling was used to stratify patients into separate cohorts of ABC versus GCB disease subtype.

The trial enrolled 70 patients with a median age of 63 years (range, 28–92), including 50 men (71%). The median time from diagnosis was 19 months (range, 5–332 months); patients had received a median 3 prior regimens (range, 1–7); 59% of patients had an International Prognostic Index (IPI) score indicating high-risk disease; and 54% of patients had refractory disease. Patient characteristics were generally similar in patients with ABC DLBCL versus those with GCB DLBCL. Treatment-emergent AEs were consistent with previously reported data. Grade 5 sepsis, dyspnea, and pneumonia were reported.

In the ITT population of 70 patients, an ORR of 23% was observed and included 9% CRs. Of the 60 patients evaluable for response, an ORR of 41% was observed for ABC DLBCL (n=29), and a single PR was observed in the patients with GCB DLBCL (n=20), yielding an ORR of 5% ( $P=.007$ ). No PRs or CRs were observed in the patients with an unclassified disease subtype (n=21). At the time of the presentation, all 4 patients who remained on study treatment had the ABC DLBCL subtype. OS rates in the ITT populations were 9.76 months (range, 3.88–not reached) for ABC DLBCL and 3.35 months (range, 1.22–not reached) for GCB DLBCL (Figure 7). Data from 29 ABC DLBCL patients in this trial and 10 patients from a separate ongoing trial<sup>12</sup> were pooled for mutational analysis and showed



**Figure 7.** In a phase II study of ibrutinib in patients with diffuse large B-cell lymphoma, overall survival rates were 9.76 months (range, 3.88–not reached) for patients with ABC disease and 3.35 months (range, 1.22–not reached) for patients with GCB disease. ABC=activated B-cell–like; GCB=germinal center B-cell–like. Adapted from Wilson WH et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 686.

responses in patients regardless of CD79B mutational status. All 4 patients who had mutations in both CD79B and MYD88 responded to ibrutinib treatment, showing that the MYD88 L265P mutation does not prevent ibrutinib activity. However, patients harboring only the latter mutation did not respond to treatment (n=4;  $P=.0286$ ). Mutations in CARD11, an oncogene in DLBCL,<sup>13</sup> also conferred resistance to ibrutinib treatment.

### 1643 A Phase I Trial of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Combination With Rituximab (R) and Bendamustine in Patients With Relapsed/Refractory Non-Hodgkin's Lymphoma (NHL)<sup>14</sup>

KA Blum, B Christian, JM Flynn, SM Jaglowski, JA Jones, K Maddocks, JC Byrd

In a phase I study of patients with relapsed B-cell malignancies, ibrutinib yielded an ORR of 43%, with responses seen in DLBCL, follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma.<sup>15</sup> In a phase II study of mantle cell lymphoma patients, ibrutinib yielded an ORR of 67%, with ibrutinib treatment extended over 1 year in some responding patients.<sup>2</sup> The combination of rituximab plus bendamustine has also proven effective, with ORRs of up to 92% observed in patients with relapsed or refractory NHL.<sup>16</sup> In light of these results, a phase I study was conducted to examine the combination of rituximab, bendamustine, and ibrutinib in patients with relapsed or refractory NHL, including DLBCL, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and transformed NHL. Patients with untreated mantle cell lymphoma who were not candidates for autologous stem cell transplantation (ASCT) were also eligible. Prior treat-

ment with ASCT or the study drugs was permitted. As presented by Dr. Kristie A. Blum and colleagues, patients received rituximab (375 mg/m<sup>2</sup> on day 1), bendamustine (90 mg/m<sup>2</sup> on days 1 and 2), and escalating doses of ibrutinib (280 mg or 560 mg daily) every 28 days for 6 cycles.<sup>14</sup> Six patients were enrolled at each dose level. Responding patients could continue ibrutinib monotherapy after cycle 6 until PD or unacceptable toxicity. Responses were assessed after cycles 3 and 6 based on NHL IWG criteria.<sup>7</sup>

The study enrolled 11 patients with a median age of 72 years (range, 45–84 years) and a median 3 prior treatments (range, 0–10). Patient characteristics of interest included stage III or IV disease (82%), extranodal involvement (64%), IPI of at least 3 (55%), and bulky adenopathy, with a lesion of at least 5 cm (45%). Nine patients completed at least 2 cycles of therapy (median, 3 cycles; range, 1–6) with ibrutinib dosed at either 280 mg/d (n=6) or 560 mg/d (n=3). Two patients experienced PD prior to completing the first cycle of treatment and were replaced. At the time of reporting, 6 patients continued to receive protocol treatment. One patient with mantle cell lymphoma who was receiving ibrutinib at the lower dose discontinued treatment due to grade 3 neutropenia lasting longer than 14 days after cycle 4.

The ORR was 38% in 8 evaluable patients; restaging scans were not yet available for 3 patients who were continuing on study treatment. Responses included 2 CRs and 1 PR, all in patients with mantle cell lymphoma.

No DLTs were observed. Grade 3/4 AEs included lymphopenia (64%), neutropenia (27%), and thrombocytopenia (18%), plus pancreatitis, vomiting, shingles, and rash (each occurring in 9%). Ibrutinib dose reductions from 280 mg to 140 mg were required in 3 patients for thrombocytopenia, pancreatitis, and rash. Bendamustine dose reductions to 60 mg/m<sup>2</sup> were required in 1 patient due to grade 3 thrombocytopenia. The study is continuing to accrue patients in the 560 mg ibrutinib cohort and in expansion cohorts.

### 153 Mature Results From ECOG Study E1405 – A Phase II Study of VcR-CVAD With Maintenance Rituximab for Previously Untreated Mantle Cell Lymphoma<sup>17</sup>

BS Kahl, H Li, MR Smith, RD Gascoyne, DT Yang, E Paietta, RH Advani, SJ Horning

Modified rituximab plus hyperCVAD (modified R-hyperCVAD) is a well tolerated therapeutic regimen that has produced high response rates in patients with mantle cell lymphoma.<sup>18</sup> Bortezomib is a proteasome inhibitor with demonstrated activity in relapsed or refractory mantle cell lymphoma.<sup>19</sup> The addition of bortezomib to R-hyperCVAD therapy with 5-year maintenance

rituximab yielded a CR rate of 77%, ORR of 90%, and 3-year PFS of 63%.<sup>20</sup> Supported by these results, the new regimen, VcR-CVAD with maintenance rituximab, was tested for safety and efficacy in trial E1405. Dr. Brad Kahl and colleagues presented results from this trial.<sup>17</sup>

Eligible patients had histologically confirmed, treatment-naïve mantle cell lymphoma, an ECOG PS of 0–2, and adequate end organ function. The VcR-CVAD with maintenance rituximab regimen included bortezomib (1.3 mg/m<sup>2</sup>, days 1 and 4), rituximab (375 mg/m<sup>2</sup>, day 1), cyclophosphamide (300 mg/m<sup>2</sup> intravenously over 3 hours every 12 hours, days 1–3 for a total of 6 doses), doxorubicin (50 mg/m<sup>2</sup> continuous infusion over 48 hours, days 1–2), vincristine (1 mg, day 3), and dexamethasone (40 mg, days 1–4). Patients received treatment every 21 days for 6 cycles, and all patients received granulocyte-colony stimulating factor support. Patients who achieved a CR or PR were given weekly maintenance rituximab for 4 consecutive weeks every 6 months for 2 years or they could choose ASCT. The trial's primary endpoint was the rate of CR as determined by positron emission tomography scanning following VcR-CVAD. Secondary endpoints included ORR, PFS, and OS in the subgroup receiving maintenance rituximab, PFS and OS in the subgroup receiving ASCT, and toxicity. Seventy-seven patients were enrolled from May 2007 through October 2008, with 2 patients excluded based on central pathology review. Patients were a median age of 62 years (range, 40–76 years). Most (77%) were male, and nearly all had an ECOG PS of 0–1 (96%). Most patients had stage III or IV disease (92%), and 19% had high-risk disease based on the MIPI score. Among the 75 patients, 67 completed treatment, and of these, 44 received maintenance rituximab therapy and 22 received ASCT consolidation.

VcR-CVAD induction therapy yielded an ORR of 94% and a CR rate of 68% in the eligible population of 75 patients (Table 1). Among the 20 responses considered a PR, 11 were recorded as such due to a lack of patient evaluation after therapy. In the 64 patients with a complete final response assessment, the CR rate was 80%. At a median follow-up of 3.6 years, the 3-year PFS was 73% for patients who received maintenance rituximab and 74% for the study cohort of 75 patients. The 3-year OS was 88%, with no difference between the 2 post-induction treatment arms.

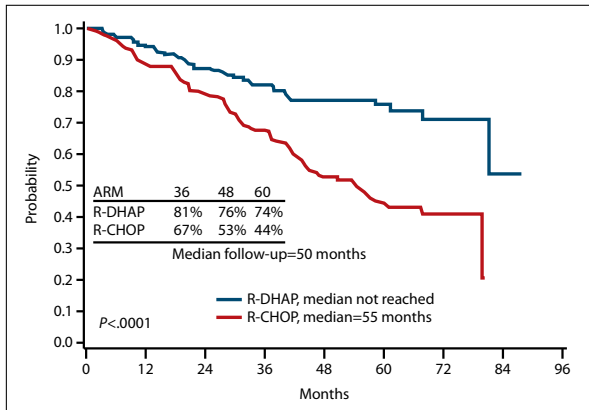
Toxicity data for VcR-CVAD showed that the majority of grade 3/4 AEs were of hematologic origin, consistent with previous reports. Grade 4 non-hematologic AEs included non-neutropenic infection (1%) and fatigue (1%). Grade 3 non-hematologic AEs included fatigue (9%), hyperglycemia (9%), anorexia (5%), dehydration (4%), and diarrhea (4%). No cases of grade 3/4 peripheral neuropathy and no deaths were reported. No serious toxicities developed during maintenance rituximab treatment, although the rate of grade 3/4 neutropenia was higher than anticipated.

## 151 Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net)<sup>21</sup>

O Hermine, E Hoster, J Walewski, V Ribrag, N Brousse, C Thieblemont, R Bouabdallah, H Dohner, P Feugier, R Forspointner, C Haioun, M Kneba, M Hänel, O Casasnovas, RH Mertelsmann, M Hallek, A Bosly, M Nowacki, W Klapper, C Gisselbrecht, B Coiffier, M Unterhalt, W Hiddemann, MH Dreyling

Dr. Olivier Hermine and colleagues presented final data reflecting long-term follow-up from the Younger Trial of the European Mantle Cell Lymphoma Network, which examined sequential R-CHOP/rituximab plus dexamethasone, Ara-C, and cisplatin (R-DHAP) treatment in patients ages 65 years or younger with previously untreated stage II–IV mantle cell lymphoma.<sup>21</sup> Patients in arm A (n=248) received 6 cycles of R-CHOP followed by stem cell mobilization and subsequent myeloablative radiochemotherapy (12 Gray total body irradiation) plus cyclophosphamide (2 doses at 60 mg/kg) and ASCT. Patients in arm B (n=249) received 3 cycles of R-CHOP, then 3 cycles of R-DHAP followed by stem cell mobilization and subsequent myeloablation that included high dose Ara-C (4 doses of 1.5 g/m<sup>2</sup>) and melphalan (140 mg/m<sup>2</sup>) and ASCT. The primary endpoint was time to treatment failure (TTF), with secondary endpoints of response rates, OS, and toxicity.

Enrolled patients were a median age of 55 years (range, 30–66 years), 79% were male, 81% had stage IV disease, 37% had B symptoms, 96% had an ECOG PS of 0–1, and 14% had an MIPI index indicating high-risk disease. Following induction therapy, arms A and B showed similar ORRs (90% vs 95%, respectively; *P*=.11). However, arm B showed an increased rate of CRs (36% vs 25%; *P*=.0077), and an increase in the combined rate of confirmed CR plus CRu (55% vs 39%; *P*=.0013). ASCT was administered to 80% of patients in arm A and 83% of patients in arm B, with subsequent ORRs of 97–98% and similar CR rates of 61–63%. With a median follow-up of 53 months, median TTF was superior for patients who received R-DHAP (88 months vs 46 months; HR, 0.68; *P*=.0382), due largely to a higher number of patients who relapsed after CR, CRu, or PR in arm A (88 patients vs 44 patients). The median remission duration was



**Figure 8.** Long-term follow-up from the Younger Trial of the European Mantle Cell Lymphoma Network, which examined sequential R-CHOP/R-DHAP treatment in patients with previously untreated stage II–IV mantle cell lymphoma, showed that the median remission duration was increased with the R-DHAP regimen. Adapted from Hermine O et al. *Blood* (ASH Annual Meeting Abstracts). 2012;120: Abstract 151.

also increased with the R-DHAP regimen (55 months vs not reached;  $P < .0001$ ; Figure 8). The rate of ASCT-related deaths in remission was 3% in both arms. With a median follow-up of 54 months, median OS was not yet reached in either arm but appeared superior for arm B ( $P = .0485$ ).

Hematologic toxicities of any grade that were significantly more frequent in arm B during induction therapy included leukopenia, neutropenia, anemia, thrombocytopenia ( $P < .001$  for each), and febrile neutropenia ( $P = .025$ ). Other toxicities that were significantly increased in arm B during induction therapy included elevated creatinine, nausea, and vomiting ( $P < .001$  for each), weight loss ( $P = .048$ ), and fatigue ( $P = .011$ ). During ASCT, any grade of elevated creatinine ( $P < .001$ ), nausea ( $P = .039$ ), and mucositis ( $P = .002$ ) was more frequent in arm B; any grade of constipation ( $P < .001$ ) or liver toxicity ( $P < .001$ ) was more frequent in arm A.

### 154 What Is the Best Combination of First-Line and Salvage Treatments in Follicular Lymphoma? Results of the Multicenter Study “Refol” by the Fondazione Italiana Linfomi (FIL) On 548 Patients<sup>22</sup>

G Rossi, L Marcheselli, C Bottelli, A Tucci, A Dondi, S Luminari, L Arcaini, M Merli, A Pulsoni, C Coccomini, B Puccini, M Micheletti, G Martinelli, A Rossi, VR Zilliloi, V Bozzoli, M Balzarotti, S Bolis, MG Cabras, M Frederico

Due to the difficulty of implementing clinical trials to test several treatment sequences, the Fondazione Italiana Linfomi conducted a retrospective study, REFOLL, to examine the effect of the type of first-line treatment on the outcome of

second-line treatments received by patients with relapsed follicular lymphoma, with the larger aim of identifying the optimal sequence of first-line and salvage treatments in follicular lymphoma patients.<sup>22</sup> The study’s primary endpoint was time to next treatment (TTNT) after first relapse, with secondary endpoints of PFS after relapse and OS. The study included patients with a histologic follicular lymphoma diagnosis who received first-line treatment with alkylating agents (AA), either alone or in combination; anthracycline-containing regimens (AC); or regimens containing nucleoside analogs (NA).

Of the 548 patients, 22% had received AA, 61% had received AC, and 17% had received NA therapy; in addition, 52% had received rituximab as part of their first-line therapy. Of the 512 patients included for the combined first- and second-line therapy analysis, 20% had received AA, 19% had received AC, and 14% had received NA, all either with or without rituximab. In addition, 29% of patients received ASCT, and 18% received rituximab and radioimmunotherapy as their second-line treatment. Patients were a median age of 58 years (range, 24–84 years); 86% of patients had Ann Arbor stage III or IV disease; 38% of patients had a FLIPI score indicating high-risk disease; 66% had experienced a CR after their first-line therapy; and the response to first-line therapy was greater than 12 months in 58% of patients. TTNT for the entire group was 41 months (95% confidence interval (CI), 34–47 months). AC with or without rituximab was associated with a superior TTNT after any salvage regimen compared with either of the other treatments with or without rituximab (HR, 0.70;  $P = .006$ ) and remained significant after adjusting for age, stage, and year of diagnosis (HR, 0.73;  $P = .021$ ). Addition of rituximab to first-line therapy did not impact the relative efficacy of salvage treatments.

ASCT was associated with an improved outcome in comparison to any other second-line treatment with or without rituximab (HR range, 1.79–2.40). Examination of the patients who received second-line ASCT versus those who did not showed that 43% of the ASCT patients were younger than 60 years versus only 9% of the other patients ( $P < .001$ ). However, the ASCT patients also were more likely to have stage III or IV disease (31% vs 18%;  $P = .020$ ) and were less likely to have a DOR of 12 months or longer (25% vs 36%;  $P = .014$ ). Other patient and treatment characteristics also differed between patients who had received second-line ASCT and those who had not; however, the only factors that influenced TTNT were the type of first-line treatment of AC ( $P = .041$ ) and DOR less than 12 months ( $P = .035$ ).

Comparison of the efficacies for the various combinations of first- and second-line treatments by multiple Cox regression analysis showed that the TTNT was superior in patients who received first-line AC, with or without rituximab, followed by ASCT in comparison to any other treatment sequence (HR range, 1.97–3.21). Factors that independently influenced TTNT after HSCT included

rituximab maintenance therapy (HR, 0.57; 95% CI, 0.39–0.84;  $P=.005$ ), first-line DOR less than 12 months (HR, 0.60; 95% CI, 0.46–0.78;  $P<.001$ ), and stage III or IV disease at diagnosis (HR, 1.92; 95% CI, 1.25–2.94;  $P=.003$ ). Five-year OS was 89% (95% CI, 85–91%).

### 901 Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study<sup>23</sup>

NH Fowler, SS Neelapu, FB Hagemester, P McLaughlin, LW Kwak, JE Romaguera, MA Fanale, LE Fayad, RZ Orłowski, M Wang, F Turturro, Y Oki, LC Lacerte, F Samaniego

Dr. Nathan Fowler presented the results of a phase II, single-arm study examining the efficacy and safety of lenalidomide and rituximab in patients with untreated, advanced-stage, indolent NHL.<sup>23</sup> The patient histologies included small lymphocytic lymphoma, follicular lymphoma, and marginal zone lymphoma. The regimen consisted of 20 mg/day of lenalidomide on days 1–21 and 375 mg/m<sup>2</sup> of rituximab on day 1 of each 28-day cycle for 6 cycles. (Patients with evidence of tumor response received 12 cycles.) To reduce the incidence of tumor flare, lenalidomide was initiated at 10 mg in patients with small lymphocytic lymphoma.

Among the 46 evaluable patients with follicular lymphoma, 78% had a FLIPI score of 2 or higher, and 52% met the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria for high tumor burden. The overall response rate for the evaluable follicular lymphoma patients was 98%, with 87% CR or CRu. Partial response was seen in 11%, and stable disease was seen in 2%.

Grade 3 or higher neutropenia occurred in 40% of all patients, and thrombocytopenia occurred in 4% of patients. The most common grade 3 or higher nonhematologic toxicities included rash ( $n=8$ ), muscle pain ( $n=7$ ), fatigue ( $n=3$ ), and thrombosis ( $n=3$ ). There were 2 episodes of neutropenic fever, and 6 patients discontinued treatment due to adverse events.

### 905 Phase II Multicenter Study of Single-Agent Lenalidomide in Subjects With Mantle Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: The MCL-001 "EMERGE" Study<sup>24</sup>

A Goy, R Sinha, ME Williams, SK Besisik, J Drach, R Ramchandren, MJ Robertson, I Avivi, JM Rowe, R Herbrecht, A Van Hoof, M Egyed, L Zhang, S Cicero, T Fu, TE Witzig

Patients with relapsed mantle cell lymphoma often develop chemoresistance and have a poor prognosis. Dr. Andre Goy presented results of the phase II, multicenter, single-arm

MCL-001 EMERGE (A Study to Determine the Efficacy and Safety of Lenalidomide in Patients With Mantle Cell NHL Who Have Relapsed or Progressed After Treatment With Bortezomib or Are Refractory to Bortezomib) study, which evaluated the safety and efficacy of single-agent lenalidomide in mantle cell patients who had relapsed or who were refractory to bortezomib.<sup>24</sup> Lenalidomide was administered at 25 mg/day orally on days 1–21 of a 28-day cycle. Patients continued treatment until disease progression, unacceptable toxicity, or withdrawal.

In this heavily pretreated population, lenalidomide achieved an ORR of 28% (CR/CRu 8%) according to independent central review. The median duration of response was 16.6 months (95% CI, 7.7–26.7). ORR according to investigator assessment was higher at 32% (CR/CRu 16%), with a median duration of response of 18.5 months. According to central review, the median time to response was 2.2 months (CR was achieved at 3.7 months). The median PFS was 4.0 months (95% CI, 3.6–5.6), and the median OS was 19.0 months (95% CI, 12.5–23.9). The most common grade 3/4 AEs were neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (8%), and fatigue (7%). Dose reductions were required in 38% of patients. Treatment was discontinued due to an adverse event (primarily myelosuppression) in 19% of patients.

### 3687 Retrospective Analysis of the Safety and Efficacy of Brentuximab Vedotin in Patients Aged 60 Years or Older With Relapsed or Refractory CD30+ Hematologic Malignancies<sup>25</sup>

MA Fanale, NL Bartlett, A Forero-Torres, A Younes, RW Chen, JW Friedberg, JV Matous, AR Shustov, SE Smith, J Zain, MM O'Meara, AK Gopal

Brentuximab vedotin exhibited significant antitumor activity and durability of response in a retrospective analysis of 40 patients with relapsed or refractory CD30+ lymphomas.<sup>25</sup> Patients were ages 60 years and older; the median age was 66 years. The study population included patients with systemic anaplastic large cell lymphoma (sALCL) ( $n=22$ ), Hodgkin lymphoma ( $n=15$ ), and other CD30+ lymphomas ( $n=3$ ) from 7 clinical studies. Among all patients, the ORR was 83%, with a CR rate of 45%. Among sALCL patients, the ORR was 100%, with a CR rate of 50% and a median duration of response of 13 months. Patients with HL achieved an objective response of 56%; the complete response rate was 38%, and the median duration of response was not yet reached. Discontinuation due to AEs was reported in 30% of patients. Treatment-related serious adverse events occurred in 20% of patients; change in mental status was the most common. Patients ages 60 and older were more likely to experience AEs such as treatment-emergent fatigue (58% vs 43%), peripheral neuropathy (60% vs



46%), and anemia (30% vs 10%). Grade 3 adverse events were more common in patients ages 60 years or older (70% vs 56%), and included neutropenia (25%), anemia (20%), and peripheral sensory neuropathy (15%).

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## Commentary

Luhua (Michael) Wang, MD

The 2012 American Society of Hematology (ASH) Annual Meeting and Exposition featured many exciting presentations. There were several important abstracts on B-cell malignancies.

Dr. Michael Wang presented the preliminary results from a phase II study on the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib in relapsed or refractory mantle cell lymphoma.<sup>1</sup> This international trial was conducted in 18 sites, including 9 in the United States and 9 in Europe. At a median follow-up of 9.2 months, the overall response rate (ORR) for the combined cohorts was 68%, including 22% complete responses (CRs).

Dr. Nathan Fowler presented phase I study results on ibrutinib in 16 patients with relapsed follicular lymphoma.<sup>2</sup> The ORR was 44% and included 4 patients (25%) with a CR. The median duration of response was 12.3 months. At the time of the presentation, 2 patients were still responding to ibrutinib, one at 25 months and the other at 29 months. No dose-limiting toxicities were observed in the 12 mg/kg intermittent cohort, and the maximum tolerated dose was not reached.

Interim results of a multicenter, open-label, phase II study showed that ibrutinib has preferential activity in the ABC subtype of relapsed/refractory diffuse large B-cell lymphoma (DLBCL).<sup>3</sup> Of the 60 patients evaluable for response in this trial, an ORR of 41% was observed for ABC DLBCL (n=29), and a single partial response (PR) was observed in patients with GCB DLBCL (n=20), yielding an ORR of 5% (P=.007). No PRs or CRs were

observed in the patients with an unclassified disease subtype (n=21). Overall survival (OS) was 9.76 months (range, 3.88–not reached) for the ABC DLBCL group and 3.35 months (range, 1.22–not reached) for the GCB DLBCL group.

Dr. Kristie Blum presented the results of a phase I trial of ibrutinib in combination with rituximab and bendamustine in patients with relapsed/refractory non-Hodgkin lymphoma (NHL), including DLBCL, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and transformed NHL.<sup>4</sup> Patients with untreated mantle cell lymphoma who were not candidates for autologous stem cell transplant (ASCT) were also eligible. Patients received rituximab, bendamustine, and escalating doses of ibrutinib (280 mg/day or 560 mg/day) every 28 days for 6 cycles. Nine patients completed at least 2 cycles of therapy (median, 3 cycles; range, 1–6) with ibrutinib dosed at either 280 mg/day (n=6) or 560 mg/day (n=3). The ORR was 38% in 8 evaluable patients, including 2 CRs and 1 PR, all in patients with mantle cell lymphoma. No dose-limiting toxicities were observed. Grade 3/4 adverse events (AEs) included lymphopenia (64%), neutropenia (27%), and thrombocytopenia (18%), plus pancreatitis, vomiting, shingles, and rash (each occurring in 9%). The study is continuing to accrue patients in the 560-mg ibrutinib cohort and in expansion cohorts.

Lenalidomide is another agent showing promising results in mantle cell lymphoma. Dr. Andre Goy presented results of the phase II MCL-001 EMERGE (A Study to Determine the Efficacy and Safety of Lenalidomide in Patients With Mantle Cell NHL Who Have Relapsed or Progressed After Treatment With Bortezomib or Are Refractory to Bortezomib) trial.<sup>5</sup> This study evaluated the safety and efficacy of single-agent lenalidomide in mantle cell lymphoma patients who had relapsed or who were refractory to bortezomib. According to independent central review, lenalidomide achieved an ORR of 28%, with a CR/unconfirmed CR of 8%.

Dr. Nathan Fowler presented the results of a phase II, single-arm study examining the efficacy and safety of lenalidomide and rituximab in patients with untreated, advanced-stage, indolent NHL.<sup>6</sup> In this study, the 46 evaluable patients with follicular lymphoma had an ORR of 98%, which is one of the best responses seen with an oral agent in follicular lymphoma. The rate of CR/CR unconfirmed was 87%. PR was achieved by 11%, and stable disease was seen in 2%.

ABT-199, an orally bioavailable, second-generation Bcl-2 inhibitor, is another active and well-tolerated drug in patients with relapsed NHL. Dr. Matthew Davids presented the interim results of a phase I dose-escalation trial with ABT-199 that enrolled 17 patients with relapsed or refractory NHL.<sup>7</sup> The most

common AEs were nausea (41%); diarrhea, dyspepsia, extremity pain, and fatigue (each occurring in 24%); and anemia, constipation, upper respiratory tract infection, and cough (each occurring in 18%). Grade 3/4 AEs included anemia (18%) and neutropenia (12%). Among the 15 patients who had completed at least 1 week 6 assessment, reductions of greater than 50% in target lesions were observed in 8 (53%), including 6 of 6 patients with mantle cell lymphoma, 1 of 2 patients with Waldenström's macroglobulinemia, and 1 of 2 patients with DLBCL. Among the 5 patients with follicular lymphoma, 4 showed nodal disease reductions that ranged from 18–40%. Three of these patients had rituximab-refractory disease.

For previously untreated mantle cell lymphoma, Dr. Brad Kahl presented the mature results from the Eastern Cooperative Oncology Group (ECOG) study E1405 (Phase II Study of VcR-CVAD With Maintenance Rituximab).<sup>8</sup> The regimen in this trial consisted of bortezomib (1.3 mg/m<sup>2</sup>, days 1 and 4); rituximab, cyclophosphamide, doxorubicin, and vincristine (1 mg on day 3); and dexamethasone. Patients who achieved a CR or PR were given weekly maintenance rituximab for 4 consecutive weeks every 6 months for 2 years, or they could choose to undergo ASCT. Seventy-five patients, with a median age of 62 years (range, 40–76 years), were enrolled from May 2007 through October 2008. Among the patients who completed treatment, 44 received maintenance rituximab therapy and 22 received ASCT consolidation. VcR-CVAD induction therapy yielded an ORR of 94% and a CR rate of 68% in 75 patients. At a median follow-up of 3.6 years, the 3-year PFS was 73% for patients who received maintenance rituximab and 74% for the study cohort of 75 patients. The 3-year OS was 88%, with no difference between the 2 post-induction treatment arms. Toxicity data for VcR-CVAD showed that the majority of grade 3/4 AEs were of hematologic origin, consistent with previous reports. No cases of grade 3/4 peripheral neuropathy and no deaths were reported.

Dr. Olivier Hermine presented final data from the Younger Trial of the European Mantle Cell Lymphoma Network.<sup>9</sup> Alternating courses of 3 × cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and 3 × dexamethasone, Ara-C, and cisplatin plus rituximab (R-DHAP) followed by a high-dose Ara-C-containing myeloablative regimen and ASCT (arm B, n=249) increased OS when compared to 6 courses of CHOP plus rituximab (R-CHOP) followed by myeloablative radiochemotherapy and ASCT (arm A, n=248) in patients with previously untreated stage II–IV mantle cell lymphoma. Following induction therapy, arms A and B showed similar ORRs (90% vs 95%, respectively; *P*=.11). However, arm B showed an increased rate of CRs

(36% vs 25%;  $P=.0077$ ) and an increase in the combined rate of confirmed plus unconfirmed CRs (55% vs 39%;  $P=.0013$ ). ASCT was administered to 80% of patients in arm A and 83% of patients in arm B, with subsequent ORRs of 97–98% and similar CR rates of 61–63%. At a median follow-up of 53 months, median time to treatment failure was superior for patients who received R-DHAP (88 months vs 46 months; hazard ratio [HR], 0.68;  $P=.0382$ ). The median remission duration was also increased with the R-DHAP regimen (55 months vs not reached;  $P<.0001$ ). The rate of ASCT-related deaths in remission was 3% in both arms. At a median follow-up of 54 months, median OS was not yet reached in either arm but appeared superior for arm B ( $P=.0485$ ).

Dr. Michelle Fanale presented a retrospective analysis of the safety and efficacy of brentuximab vedotin, an antibody-drug conjugate comprised of the microtubule-disrupting agent monomethyl auristatin E conjugated to an antibody that binds human CD30, in patients ages 60 years or older with relapsed or refractory CD30+ hematologic malignancies, including systemic anaplastic large cell lymphoma (sALCL) ( $n=22$ ) and Hodgkin lymphoma ( $n=15$ ) (median age, 66.5 years and 68.0 years, respectively).<sup>10</sup> Three patients (8%) were diagnosed with other CD30+ lymphomas and were a median age of 62.0 years. All of the sALCL patients and 53% of the Hodgkin lymphoma patients achieved an objective response (CR rate, 50% and 40%, respectively). The ORR was 78%, with 43% of patients achieving a CR. At the time of the analysis, the median duration of response was 13.0 months for sALCL patients and not reached for Hodgkin lymphoma patients. Treatment-emergent AEs of grade 3 or higher (incidence  $\geq 20\%$ ) included neutropenia and anemia. Serious AEs were reported in 53% of patients, with the most common being mental status changes (10%). AEs leading to treatment discontinuation occurred in 30% of patients.

To determine the best combination of first-line and salvage treatments in follicular lymphoma, the Fondazione Italiana Linfomi (FIL)<sup>11</sup> conducted a retrospective multicenter study, REFOLL, which included 548 patients with a histologic follicular lymphoma diagnosis who received first-line treatment with alkylating agents, either alone or in combination; anthracycline-containing regimens; or regimens containing nucleoside analogs. Comparison of the efficacies for the various combinations of first-line and second-line treatments by multiple Cox regression analysis showed that the time to next treatment was superior in patients who received first-line anthracycline, with or without rituximab, followed by ASCT in comparison to any other treatment sequence (HR range,

1.97–3.21). Factors that independently influenced time to next treatment after high-dose therapy with stem cell transplantation included rituximab maintenance therapy (HR, 0.57; 95% CI, 0.39–0.84;  $P=.005$ ), first-line duration of response less than 12 months (HR, 0.60; 95% CI, 0.46–0.78;  $P<.001$ ), and stage III or IV disease at diagnosis (HR, 1.92; 95% CI, 1.25–2.94;  $P=.003$ ). Five-year OS was 89% (95% CI, 85–91%).

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