Advances in the Management of B-Cell Lymphoma: Highlights from the 55th American Society of Hematology Annual Meeting and Exposition

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MEDIA: NEWSLETTER
Estimated time to complete activity: 1.0 hour
Release date: Monday, February 3, 2014 | Expiration date: Monday, February 2, 2015

INTRODUCTION
The 2013 American Society of Hematology (ASH) Annual Meeting held in New Orleans, Louisiana, provided a comprehensive review of key experimental and clinical data presented at the conference. Included in this newsletter are highlights from the conference covering advances in the management of B-cell lymphoma.

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TARGET AUDIENCE
The target audience for this activity is medical oncologists caring for patients with B-cell lymphoma.

EDUCATIONAL OBJECTIVES
At the conclusion of this activity, participants should be able to:

• Describe the importance of diagnostic and pathologic evaluation of B-cell lymphoma
• Understand the rationale for the development and integration of treatment strategies in B-cell lymphoma
• Examine clinical trial results of treatment regimens, both containing novel agents and combinations, in patients with B-cell lymphoma

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ACKNOWLEDGEMENT

The editors wish to thank Lisa van Devender, PharmD and Sara R. Fagerlie, PhD, CCMEP for assistance in writing this document.

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ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT

This activity is supported by an educational grant from the following: Genentech

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INTRODUCTION
At the 2013 American Society of Hematology (ASH) Annual Meeting, held in New Orleans, Louisiana, clinicians from around the world presented meaningful data in B-cell malignancies. A number of novel targeted therapies are demonstrating promising efficacy in both untreated and relapsed disease. Moreover, new studies designed to move away from standard cytotoxic chemotherapy in certain types of non-Hodgkin lymphoma (NHL) were included in this year’s meeting. Results of these studies are highlighted in this newsletter.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
Chlorambucil vs Obinutuzumab/Chlorambucil vs Rituximab/Chlorambucil, CLL11 Trial
Although the majority of patients with CLL are of advanced age, these patients have not been well represented in clinical trials. Additionally, patients with certain comorbidities are also often excluded from clinical trials. Extrapolating the clinical trial data to patients who may not be candidates for the investigated treatments can be challenging for the practicing oncologist. For example, the FCR regimen (fludarabine, cyclophosphamide, and rituximab) has demonstrated superior results in randomized trials of CLL patients in the frontline and relapsed settings, but is associated with considerable adverse events (AEs) in older patients, as well as, those patients with comorbidities. A number of exciting new therapies have recently received FDA approval for CLL; however, selecting the initial therapy for older patients and those with comorbidities remains challenging.

During the plenary session at the 2013 ASH Annual Meeting, Dr Goede from the German CLL Study Group reported results for the CLL11 trial, a large, phase III, randomized study, which investigated the efficacy and safety profile of chlorambucil alone compared with chlorambucil plus obinutuzumab (GA101), a type 2 monoclonal antibody to CD20, or rituximab in less fit patients with CLL. The study included 781 previously untreated CLL patients with comorbidities. The Cumulative Illness Rating Scale (CIRS) was used to distinguish between physically fit and non-fit patients. Untreated CLL patients with a CIRS total score greater than 6 and/or an estimated creatinine clearance (CrCl) less than 70 mL/min were eligible for the study. Patients were randomized at a ratio of 1:2:2 to chlorambucil alone (0.5 mg/kg PO day 1, 15 q28 days, x 6 cycles; n = 118), obinutuzumab plus chlorambucil (100 mg IV day 1, 900 mg day 2, 1000 mg day 8, day 15 of cycle 1, 1000 mg day 1 cycles 2-6; n = 233), or rituximab plus chlorambucil (375 mg/m² IV day 1 cycle 1, 500 mg/m² day 1 cycles 2-6; n = 233). The primary endpoint for this study was investigator-assessed progression-free survival (PFS), and secondary efficacy endpoints included response rates, minimal residual disease (MRD), and overall survival (OS).

Initial results showed that the combination of chlorambucil with either obinutuzumab or rituximab improved response rates and PFS compared with chlorambucil alone. The second stage of the CLL11 study directly compared obinutuzumab/chlorambucil with rituximab/chlorambucil. Treatment arms were well balanced according to baseline characteristics. Median patient age was 74 years (range 39-89) for the obinutuzumab-containing arm and 73 years (range 40-90) for the rituximab-containing arm. Over 40% of patients were 75 years or older (46% obinutuzumab/chlorambucil, 42% rituximab/chlorambucil). The median CIRS score was 8 (at least 3 comorbidities of increased severity).

Patients treated with obinutuzumab/chlorambucil had an overall response rate (ORR) of 78%, compared with that of 65% in patients treated with rituximab/chlorambucil (P < 0.0001), and there were more complete remissions in the obinutuzumab/chlorambucil group than in the rituximab/chlorambucil group (21% vs 7%, respectively). The partial response (PR) rate was 58% in each treatment arm. In terms of MRD, the percentage of MRD-negative patients was 19.5% vs 2.6% (P < 0.0001) for bone marrow and 37.7% vs 3.3%
(P < 0.0001) for blood in obinutuzumab/chlorambucil vs rituximab/chlorambucil, respectively. In this head-to-head comparison, median PFS was 26.7 months for obinutuzumab/chlorambucil compared with 15.2 months for rituximab/chlorambucil (P < 0.0001; Figure 1). The PFS benefit of obinutuzumab/chlorambucil over rituximab/chlorambucil was retained in all pre-planned subgroup analyses.

The updated median PFS in obinutuzumab/chlorambucil, rituximab/chlorambucil, and chlorambucil alone was 26.7, 16.3, and 11.1 months, respectively. Regarding OS, treatment with obinutuzumab/chlorambucil resulted in an OS benefit compared with chlorambucil only (HR 0.41, P = 0.002), whereas there was no difference between the rituximab/chlorambucil and chlorambucil treatment arms (HR 0.66; P = 0.112). The OS data for the head-to-head comparison between obinutuzumab/chlorambucil and rituximab/chlorambucil was not significantly different (HR 0.66; P = 0.084), and longer follow-up may be needed.

The rate of AEs was higher in patients who received obinutuzumab/chlorambucil compared with those who received rituximab/chlorambucil (70% vs 55%), which was mainly due to an increased incidence of infusion-related reactions with obinutuzumab (20% vs 4%, respectively). Notably, these reactions occurred during the first infusion and not during subsequent infusions. However, it is important for physicians to be aware of such infusion-related reactions associated with obinutuzumab therapy and to perform prophylactic measures and monitor patients rigorously during the first infusion. Neutropenia also occurred more often in patients treated with obinutuzumab/chlorambucil than those treated with rituximab/chlorambucil (33% vs 28%). Infections occurred in 7% of patients in both groups.

As first-line treatment of CLL patients with comorbidities, obinutuzumab with chlorambucil demonstrated prolongation of OS compared with chlorambucil alone, and had superior PFS, complete response (CR) rates, and MRD rates compared with chlorambucil/rituximab at the tested doses. These data represent a potentially practice-changing treatment advance for this patient population.

**MAINTENANCE THERAPY IN FOLLICULAR LYMPHOMA (FL)**

**Rituximab Maintenance Therapy: 6-Year Follow-Up of the PRIMA Study**

The phase III PRIMA study was designed to investigate the potential benefit of 2 years of rituximab maintenance in patients with FL responding to 1 of 3 non-randomized, first-line immunochemotherapy treatments. The study demonstrated that at 36 months of follow-up there was a significant reduction in risk of disease progression or death in favor of patients randomized to 2 years of rituximab maintenance compared to those on observation (75% vs 58%, HR 0.55; P < 0.0001). Updated 6-year follow-up data were presented by Dr Salles.
The aims of the updated analysis of PRIMA were to determine:

- If the initial benefit achieved with R maintenance for PFS and time to next treatment (TTNT) extended with 3 years of additional follow up
- How initial patient characteristics and induction treatment impact PFS
- If there is an OS benefit with prolonged follow up
- The response rate to second-line treatment after progression
- The incidence of histological transformation at relapse

From December 2004 to April 2007, 1217 patients were enrolled and complete data were available for 1193 patients. The majority of patients received R-CHOP induction (N = 885), and those who responded to induction therapy were stratified based on their immunochemotherapy regimen and response and randomized to observation or rituximab maintenance, 1 infusion (375 mg/m$^2$) every 8 weeks for 2 years. A total of 1018 randomized patients were analyzed (513 observation, 505 rituximab maintenance). All initial pre-treatment characteristics were well balanced between treatment arms. At the time of randomization, 39% of patients had a CR, 32% had a complete response, unconfirmed (CRu), and 28% had a PR.

With a median follow-up of 73 months from randomization, 6-year PFS was significantly higher in the rituximab maintenance arm compared to the observation arm (59.2% vs 42.7%, respectively, $P < 0.0001$; HR 0.58; Figure 2). This PFS benefit held regardless of the induction therapy regimen (R-CHOP induction 62.9% vs 44.5%, $P < 0.0001$; R-CVP induction 49.7% vs 38%, $P = 0.05$, maintenance vs observation, respectively) or FLIPI score. The rate of histological transformation did not appear to differ between the 2 treatment arms (24 patients in observation arm vs 16 patients in maintenance arm). At the time of the data cut-off, OS remained similar for the 2 groups (88.7% rituximab maintenance vs 87.4% observation).

Relevant causes of death included lymphoma (n = 28 observation vs 28 maintenance), second malignancies (19 observation vs 6 maintenance); and infections (4 observation vs 7 maintenance). For patients who required salvage treatment, a response was achieved by 79% of patients in the observation arm and 76% in the rituximab maintenance arm.

Overall, 3 years of additional follow-up supported a sustained and persistent PFS benefit of 2-year rituximab maintenance therapy after immunochemotherapy. No additional or unexpected long-term toxicities were observed and second-line treatment efficacy appeared to be similar between the 2 study arms.

**Rituximab Maintenance Therapy: SAKK 35/03 Study**

Results of another maintenance trial, SAKK 35/03, were also presented at ASH. This study evaluated event-free survival (EFS) in 165 patients with follicular lymphoma randomized to either short-term maintenance rituximab (375 mg/m$^2$ every 2 months x 4) or long-term maintenance (375 mg/m$^2$ every 2 months
for a maximum of 5 years or until disease progression, relapse, or unacceptable toxicity. Although the study did not meet the primary endpoint of EFS, long-term rituximab maintenance doubled the median PFS (7.4 years long-term vs 3.5 years short-term; **Figure 3**) without leading to increased undue toxicity.

**Figure 3. Progression-free survival in the SAKK 35/03 trial, evaluating short-term and long-term rituximab maintenance in patients with follicular lymphoma.**

**Consolidation With **$^{90}$**Y Ibritumomab Tiuxetan vs Rituximab Maintenance**

Patients with FL can achieve long-term survival, but disease progression typically occurs between 3 and 5 years after initial treatment. Consolidation with $^{90}$Y ibritumomab tiuxetan (ibritumomab) after initial therapy, mainly in the pre-rituximab era, demonstrated significant improvement in PFS and TTNT, and maintenance with rituximab has also shown a substantial PFS benefit for patients treated with chemotherapy or immunochemotherapy, as noted above. The Spanish Intergroup conducted a randomized, phase II study (ZAR2007) comparing consolidation with ibritumomab to rituximab maintenance in patients with FL responding to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

From June 2008 to July 2010, 146 patients (median age 55 years) were enrolled and 124 patients who achieved a CR after R-CHOP were randomized 1:1 to receive ibritumomab ($N = 64$, 0.4 mCi/Kg IV, total dose capped at 32 mCi) or rituximab ($N = 62$, 375 mg/m$^2$ IV every 8 weeks for 2 years). Key inclusion criteria were histologically confirmed FL grade 1, 2, or 3a, age 18 to 75 years, Ann Arbor stage II, III, or IV, and need of treatment according to modified GELF criteria. The main study endpoint was PFS from randomization.

After a median follow-up of 37 months from randomization, the 36-month PFS was higher for patients treated with rituximab (63% ibritumomab vs 77% rituximab; HR = 0.517, 95% CI: 0.269-0.996, $P = 0.044$). For patients in a PR after R-CHOP, more patients converted to a CR with rituximab maintenance compared to ibritumomab consolidation (18/27, 67% with rituximab vs 12/30, 40% with ibritumomab, $P = 0.06$) and fewer relapsed/progressed with rituximab (12/30 40% vs 3/27 11%, respectively; $P = 0.01$). However, there was no difference between the 2 treatment arms in terms of TTNT or OS.

Grade 3/4 neutropenia occurred in 6 of 64 cases (9%) and grade 3/4 thrombocytopenia in 5 of 64 cases (8%) in the ibritumomab arm, compared with 2 of 62 cases (3%) and 0 of 62 cases (0%), respectively, in the rituximab arms. Infections occurred in significantly more patients who received rituximab maintenance (13%) than those who received ibritumomab consolidation (2%). No deaths from toxicity occurred, but 7 patients died due to disease progression or disease-related causes.

Results of this study showed that rituximab maintenance was superior to consolidation with ibritumomab in terms of PFS, although no significant differences were observed regarding TTNT or OS.

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NOVEL REGIMENS IN NHL

Immunomodulatory Agents

Lenalidomide With Rituximab in Mantle Cell Lymphoma (MCL)

The initial treatment for MCL is not standardized, and conventional chemoimmunotherapies are generally not curative. The immunomodulatory agent lenalidomide is FDA-approved for the treatment of recurrent MCL. A number of studies have addressed single-agent lenalidomide, including the EMERGE trial that demonstrated an ORR of 28% and a CR of 8%. Combination therapy with lenalidomide plus rituximab suggested an increased response rate compared with lenalidomide monotherapy. Therefore, Ruan and colleagues tested the efficacy of lenalidomide with rituximab in untreated MCL patients.

The phase II study included patients with untreated MCL and adequate organ function who had tumor mass ≥ 1.5 cm, low-intermediate risk Mantle Cell Lymphoma International Prognostic Index (MIPI), or high-risk MIPI (if a patient refused or was not a candidate for chemotherapy). The primary study objective was ORR. This study included an induction phase and a maintenance phase. During the induction phase (cycles 1 to 12), lenalidomide (20 mg) was administered daily on days 1-21 of a 28-day cycle, and standard-dose rituximab was administered weekly x 4 during cycle 1, then once every other cycle for a total of 9 doses. During the maintenance phase (cycle 13 to disease progression), lenalidomide at 15 mg daily was administered on days 1-21 of a 28-day cycle, with rituximab given once every other cycle until disease progression. Thirty-two subjects were enrolled (median age 65 years; male:female ratio 3:1). All patients had extensive disease, and MIPI scores were evenly distributed among low-, intermediate-, and high-risk patients (34%, 32%, and 34%, respectively). Symptomatic lymphadenopathy (44%) and cytopenias (22%) were the most common indications for treatment.

In the intent-to-treat (ITT) analysis, the ORR was 81% (Table 1). Of the 30 evaluable patients, the ORR was 87% and CR occurred in 57% of patients. The quality of response appeared to improve with time with continued treatment. A significant number of patients with PR appeared to improve to CR between 6 and 12 months on therapy and were able to maintain their response quality. With a median follow-up of 16 months, the 12-month PFS was 93.2% (95% CI: 75.5%, 98.3%).

Table 1. Efficacy of lenalidomide plus rituximab in mantle cell lymphoma.

<table>
<thead>
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<th>Response</th>
<th>No. of Patients</th>
<th>ITT</th>
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<tr>
<td>ORR</td>
<td>26</td>
<td>81%</td>
<td>87%</td>
</tr>
<tr>
<td>CR</td>
<td>16</td>
<td>53%</td>
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<td>SD</td>
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<tr>
<td>PD</td>
<td>2</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td>2</td>
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</tr>
<tr>
<td>Median follow up</td>
<td>16 months (range 7-27)</td>
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<tr>
<td>Median time to PR</td>
<td>3 months (range 3-13)</td>
<td></td>
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<tr>
<td>Median time to CR</td>
<td>11 months (range 3-22)</td>
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</table>

*Treatment was discontinued in 2 patients due to tumor flare without progression before tumor response evaluation.

No, number; ITT, intent-to-treat; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Treatment was generally well tolerated and AEs were fairly typical for lenalidomide therapy. Grade 3/4 hematologic toxicities included neutropenia (47%), thrombocytopenia (16%), and anemia (6%), whereas grade 3/4 non-hematologic toxicities included rash (22%), tumor flare (9%), and serum sickness associated with rituximab (7%). These inflammatory reactions generally occurred during first cycles of treatment and resolved with supportive care.

Dr Ruan addressed potential criticisms of this study, pointing out that all subjects had at least one indication for treatment and that patient...
demographics were reflective of the MCL population. She concluded that this combination biologic approach appears to be safe and effective as initial therapy for MCL. Identification of the optimal duration of therapy remains to be determined. Given the efficacy and lack of compound AEs, further evaluation of this combination is warranted.

The combination of rituximab and lenalidomide was also investigated in other studies. In a phase II study, this combination was tested in 30 relapsed/refractory and previously untreated patients with indolent NHL (iNHL). This combination was active with high response rates, particularly in patients with FL. Durable remission was observed even in heavily pretreated/rituximab-refractory patients. In another phase II study of 40 patients with relapsed/refractory indolent B-cell or MCL (39 were FCGRIIIa-158F carriers), the combination of lenalidomide and rituximab yielded a 46% ORR and 2-year PFS after a 4-week course of rituximab and continuous lenalidomide. These data suggest that the combination of lenalidomide and rituximab may have efficacy beyond untreated MCL.

**BTK Inhibitors**

**Ibrutinib + R-CHOP in CD20-Positive B-Cell NHL**

R-CHOP is the currently accepted standard of care for several NHL subtypes, including diffuse large B-cell lymphoma (DLBCL), MCL, and FL. Despite the good initial results observed with R-CHOP for the treatment of NHL, a substantial number of DLBCL patients still either fail to respond or relapse after initial remission. Given the promising clinical activity of the Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib in a variety of relapsed or refractory B-cell malignancies, the combination of ibrutinib with standard R-CHOP chemotherapy was investigated in patients with previously untreated NHL by Younes and colleagues.

An open-label, nonrandomized, multicenter, 2-part study that combined ibrutinib with R-CHOP was conducted. The primary objective of this phase Ib study was to determine the recommended phase II dose of ibrutinib in combination with standard R-CHOP therapy in treatment-naïve patients with CD20-positive DLBCL. Secondary objectives included safety, ORR, pharmacokinetics, and pharmacodynamic biomarkers.

Part 1 of this study was dose escalation and Part 2 was dose expansion. In Part 1, the maximum tolerated dose was not reached and the recommended Part 2 dose was established at ibrutinib 560 mg + R-CHOP. No significant pharmacokinetic interactions were observed. In Part 2 (involving only patients with DLBCL; N = 18), the median age was 53 years (range 22-77), 56% were male, and 67% had stage IV disease. All patients received the planned 6 cycles of ibrutinib 560 mg + R-CHOP; 4 patients required dose reduction for ibrutinib, 2 patients required dose reduction for doxorubicin, and 7 patients required dose reduction for vincristine.

Of the 22 evaluable patients in both Parts 1 and 2, the ORR was 100% (91% CR, 9% PR). The most common AEs ≥ grade 3 were neutropenia (67%), febrile neutropenia (22%), thrombocytopenia (11%), and anemia (11%). The expanded ibrutinib 560 mg + R-CHOP cohort is ongoing to further explore the safety and efficacy of this combination. Based on the promising early results, a randomized phase III trial of R-CHOP +/- ibrutinib is ongoing in de novo, treatment-naïve DLBCL patients.

**Ibrutinib in Relapsed or Refractory Waldenström’s Macroglobulinemia**

Waldenström’s macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized primarily by the infiltration of lymphoplasmacytic cells into bone marrow and the demonstration of IgM monoclonal gammopathy. Whole genome sequencing has revealed highly prevalent somatic mutations in WM. The MYD88 L265P mutation is present in over 90% of patients with WM, and MYD88 has been shown to bind to BTK in L265P expressing cells, and ibrutinib induces apoptosis of
WM cells bearing MYD88 L265P. Moreover, WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis syndrome)-like mutations in CXCR4, present in about 30% of patients with WM, induce BTK activity and confer decreased sensitivity to ibrutinib-mediated growth suppression in WM cells. Therefore, the efficacy and tolerability of ibrutinib, along with the impact of MYD88 L265P and WHIM-like CXCR4 mutations, was evaluated in relapsed or refractory WM by Treon and colleagues.

In this phase II study, 63 symptomatic WM patients (median age 63 years; range 44-86) were enrolled to receive ibrutinib 420 mg daily for 2 years or until disease progression or unacceptable toxicity. Patients had received a median of 2 prior therapies (range 1-8). The most common reason for treatment initiation was anemia (87%), although multiple reasons could apply for a single patient going on therapy.

There was a rapid decline in IgM levels, with best response going from 3610 mg/dL to 1260 mg/dL ($P = 0.00001$; median of 9 cycles). Equally impressive was the fact that hemoglobin levels rose from 10.5 mg/dL to 13.4 mg/dL ($P = 0.00001$; median of 9 cycles). Bone marrow biopsy at 6 months showed a reduction from 62.5% to 36.8% at cycle 6 ($P = 0.0005$). For extramedullary disease following ibrutinib (patients with baseline and cycle 6 CT scans), improvement in adenopathy occurred in 67.7% of patients, with stable disease in 25.8%.

With a median follow up of 9 cycles (range 1-18), the best ORR$^{21}$ to ibrutinib was 83%, with a major response rate (MRR) occurring in 64% of patients.

Overall, ibrutinib was very well tolerated, with the majority of AEs being neutropenia and thrombocytopenia, which occurred in predominantly heavily pretreated patients. At a median of 9 cycles of ibrutinib, 55 (87.3%) participants continue on therapy.

In patients who underwent tumor sequencing, attainment of major responses was impacted by mutations in CXCR4, but not MYD88 L265P. The ORR was 80% for patients with wild-type CXCR4 vs 30% for those with WHIM-like CXCR4 mutations. Patients with wild-type CXCR4 also showed decreases in serum IgM, improvements in hemoglobin, and increased peripheral lymphocytosis.

**PI3K Inhibitors**

**Idelalisib in Double-Refractory Indolent B-Cell NHL**

Phosphatidylinositol 3-kinases (PI3K) are a family of lipid kinases involved in various signaling cascades downstream of B-cell receptors. Activation of the PI3K signaling pathway contributes to cell proliferation, motility, survival, and angiogenesis, all of which are important aspects of tumorigenesis.$^{25}$ Like the majority of protein kinase inhibitors, all existing PI3K inhibitors bind competitively in the ATP-binding pocket of the catalytic domain, which has enabled the development of both pan-PI3K- and isoform-specific inhibitors (Table 2),$^{26,27}$ Two PI3K inhibitors being studied in relapsed/refractory NHL include idelalisib, a selective oral inhibitor of PI3K-delta (PI3K$\delta$), and copanlisib (Bay 80-6946), which has significant activity against PI3K-alpha (PI3K$\alpha$) and PI3K$\delta$ isoforms.

**Table 2. Class I PI3K isoforms.**

<table>
<thead>
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<th>Class I PI3K Isoform</th>
<th>Cellular Expression</th>
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<td>Alpha (α)</td>
<td>Broad</td>
<td>Insulin signaling and angiogenesis</td>
</tr>
<tr>
<td>Beta (β)</td>
<td>Broad</td>
<td>Platelet function</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Leukocytes</td>
<td>Neutrophil and T-cell function</td>
</tr>
<tr>
<td>Gamma (γ)</td>
<td>Leukocytes</td>
<td>B-cell signaling, development, and survival</td>
</tr>
</tbody>
</table>

Although alkylating agents with rituximab are the current standard of care for the treatment of iNHL, this type of lymphoma eventually becomes refractory. In particular, once iNHL becomes “double-refractory” to alkylating agent-rituximab combinations, few data are available on beneficial therapeutic options, indicating
a patient population with an unmet clinical need. Idelalisib demonstrated promising activity in relapsed/refractory iNHL in a phase I study, and a phase II study was thus undertaken to evaluate this agent in patients with double-refractory iNHL. In this single-arm study, 125 patients with previously treated iNHL who were refractory (lack of response to, or progression of lymphoma within 6 months of completion of therapy, documented by imaging) to both an alkylating agent and rituximab received idelalisib 150 mg PO BID until disease progression or intolerance. The primary endpoint was ORR.

Enrolled patients had a median age of 64 years and were 64% male and 36% female. iNHL subtypes included FL (58%), small lymphocytic lymphoma (SLL, 22%), marginal zone lymphoma (MZL, 12%), and lymphoplasmacytic lymphoma/WM (8%). The median number of prior therapies was 4 (range 2-12), and the median time since completion of last regimen was 3.9 months. All patients were refractory to rituximab and 99% were refractory to an alkylating agent. Median duration of idelalisib treatment was 6.6 months. At followup, 32% of patients remained on treatment, and 68% had discontinued.

The ORR was 57%, with 71 responders, of which 7 (6%) had a CR, 63 (50%) had a PR, and 1 (1%) had a minor response (MR). Median time to response was 1.9 months, and median time to CR was 3.7 months. In terms of lymph node response, 90% of patients experienced some improvement in tumor burden, whereas a decrease of 50% or more from baseline was documented in 57% (Figure 4). Among responders, median duration of response (DOR) was 12.5 months. Median PFS for all patients was 11.0 months and median OS was 20.4 months.

The most common AEs (total %/≥ grade 3 %) were diarrhea (43/13), fatigue (30/2), nausea (30/2), cough (29/0), pyrexia (28/2), dyspnea (18/3), rash (13/2), and pneumonia (11/7). Grade ≥ 3 neutropenia occurred in 27% of patients, thrombocytopenia in 6%, and anemia in 2%. Grade ≥ 3 ALT/AST elevations, which occurred in 16 patients, were reversible with drug interruption. Twenty percent of patients discontinued therapy due to AEs.

In this study, idelalisib demonstrated high response rates in double-refractory iNHL, with responses independent of number of prior treatments, degree of refractoriness, and histologic subtype. Idelalisib was well tolerated and had an acceptable safety profile. Results of this study suggest that idelalisib may provide meaningful disease control in patients with double-refractory iNHL.

Copanlisib (Bay 80-6946) in Relapsed/Refractory, Indolent, or Aggressive Lymphoma

A phase I dose-escalation study established the maximum tolerated dose of copanlisib and reported promising activity in FL. An open-label, phase II study was undertaken to further investigate the efficacy and safety of this agent in patients with indolent or aggressive lymphoma subtypes. A total of 67 patients were enrolled in this study (33 indolent, 34 aggressive) and treated with copanlisib 0.8 mg/kg as a 1-hour infusion on days 1, 8, and 15 of a 28-day cycle.
Patients continued therapy until disease progression or unacceptable toxicity. Responses were assessed every 2 cycles, according to the Cheson or iwCLL criteria. The primary endpoint was ORR up to 16 weeks after the last patient had initiated therapy.

Patients were similarly distributed among indolent and aggressive cohorts with respect to gender (52% female), median age (68 yr, range 22-90), and ethnicity (76% Caucasian) and were heavily pretreated (median number of prior therapies: 3). Indolent lymphoma subtypes included FL (16, 48%), CLL (14, 42%), and MZL (3, 9%); aggressive lymphoma subtypes included DLBCL (15, 44%), MCL (7, 21%), and transformed (6, 18%). The median number of prior chemotherapy lines was 3.

Preliminary efficacy results showed an ORR of 71% for MCL and 50% for T-cell lymphoma. A striking and somewhat unexpected finding was that in 4 patients with T-cell lymphoma, 1 CRu, and 1 PR was achieved. Patients with varying histologies did receive ongoing treatment, suggesting long-term remissions. The majority of patients did show a decrease in lymph nodes. The most frequently occurring AEs were hyperglycemia, hypertension, fatigue, diarrhea, nausea, neutropenia, and anemia. Gastrointestinal (GI) AEs were minor and self-limiting, and hematologic toxicities were also minor. A total of 43 patients (64%) discontinued therapy (13 indolent, 30 aggressive).

Copanlisib demonstrated encouraging preliminary efficacy results, with significant activity in FL, CLL, MCL, PTCL, and DLBCL. This agent showed an acceptable safety profile consistent with prior studies, and no unexpected toxicity in relapsed/refractory lymphoma. Further studies of copanlisib are planned and ongoing in indolent and aggressive NHL.

**PKC Inhibitors**

**Enzastaurin in DLBCL: The PRELUDE Trial**

Protein kinase C beta (PKCβ), a member of a closely related family of enzymes with serine/threonine kinase activity, is the major PKC isoform expressed in normal and malignant B-cells. PKCβ is required for B-cell receptor signaling, activation of NFκB, and VEGF-mediated angiogenesis. Overexpression of PKCβ mRNA and protein is associated with a poor outcome in patients with DLBCL. Patients with DLBCL and an IPI score of 3-5 at diagnosis are at high risk of treatment failure despite the use of R-CHOP. Enzastaurin, a potent and selective competitive inhibitor of PKCβ, was associated with freedom from disease progression in a phase II trial in a small subgroup of patients with relapsed/refractory DLBCL. Results of the phase III multinational, randomized, double-blind PRELUDE study compared post-induction therapy with enzastaurin to placebo in patients with DLBCL at high risk of relapse, in first remission following R-CHOP.

Patients with a histologic diagnosis of DLBCL were randomized 2:1 to receive either enzastaurin 500 mg daily or an identical placebo as maintenance therapy for a planned duration of 3 years from time of randomization. Key inclusion criteria included pre-treatment IPI score ≥ 3, stage III or IV disease, and CR/CRu or negative FDG-PET scan after R-CHOP-14 or R-CHOP-21. The primary endpoint was disease-free survival (DFS), defined as lack disease progression or death; secondary endpoints included OS and EFS.

A total of 866 patients were enrolled, and 758 patients were randomized to treatment (enzastaurin n = 504; placebo n = 254). Median age at enrollment was 64 years (range 21-89); at diagnosis, 64% of enzastaurin patients and 67% of placebo patients had stage IV disease. In the ITT population, there was no significant difference between enzastaurin and placebo for DFS (HR 0.92, 95% CI: 0.689, 1.216; P = 0.541). DFS, OS, and EFS values at 24 and 48 months were not significantly different between treatment arms.

Treatment-emergent AEs possibly related to enzastaurin and significantly different (P < 0.001) between enzastaurin and placebo were chromaturia (18.5% vs 0.4%), QTc prolongation (10.8% vs 3.6%), and diarrhea (10.3% vs 2.8%). There were no significant differences in the number of patients with at least...
1 grade 3 or higher AE between treatment arms. Biomarker analyses, using molecular subtypes of DLBCL (germinal center B cell-like [GCB] and non-germinal center B cell-like [non-GCB]) showed no significant difference between treatment groups for DFS. The investigators concluded that enzastaurin, compared with placebo, did not improve DFS, EFS, or OS in patients with CR after initial treatment for DLBCL. Safety results of the PRELUDE study were consistent with the established safety profile of enzastaurin when used as single-agent therapy in lymphoma and other cancers. Furthermore, cell of origin (GCB vs non-GCB) was not prognostic for DFS in patients with CR.

Monoclonal Antibodies
Brentuximab Vedotin in Relapsed/Refractory CD30-Positive B-Cell Lymphomas
CD30, originally identified as a cell-surface marker of classical Hodgkin lymphoma, is expressed by several types of NHL, including a subset of DLBCL. In 2 recent studies that looked at over 1300 patients with newly diagnosed DLBCL, CD30 was expressed in approximately 14-25% of patients. Interestingly, both series showed that CD30 expression in DLBCL was a favorable prognostic factor, and both ABC and GCB subtypes had patients who expressed CD30. Hu et al also found that the CD30-positive subset of DLBCL did appear to have a unique gene expression profile. Patients with relapsed or refractory DLBCL have a very poor outcome. As shown in the CORAL study, autologous transplant appears to have less efficacy in the rituximab era, with a 3-year EFS of 21%. The median OS in DLBCL patients failing second-line therapy is approximately 4 months.

Brentuximab vedotin, a CD30-directed antibody that is conjugated to a tubulin disrupting agent, is indicated for the treatment of Hodgkin lymphoma after failure of autologous stem cell transplant and for systemic anaplastic large cell lymphoma after failure of chemotherapy. The efficacy of brentuximab vedotin in patients with relapsed/refractory CD30-positive NHLs was reported by Bartlett and colleagues. Patients were treated with standard-dose brentuximab 1.8 mg/kg IV every 3 weeks and were allowed to continue treatment until disease progression or unacceptable toxicity, and were restaged after cycle 2, cycle 4, and then every 3 cycles. The primary endpoint of the study was ORR, and a key secondary endpoint was correlation of CD30 expression with response.

To date, 68 patients with variable CD30 expression have been enrolled in this study (DLBCL n = 50; other B-cell n = 18). The median age of all patients was 55 years and 92% of patients had an ECOG performance status of 0 or 1. The median percent of CD30-positive malignant cells was 25% in DLBCL cohort and 45% in other B-cell cohort. Median soluble CD30 (normal < 30 ng/mL) was 199 ng/mL in the DLBCL cohort and 381 ng/mL in the other B-cell cohort. The majority of patients in this study were refractory to frontline therapy (74% DLBCL, 89% other B-cell) as well as their most recent prior therapy (82% DLBCL, 72% other B-cell). Patients had a median of 2 prior systemic therapies (range 1-6) in the DLBCL cohort and 3 (range 1-19) in the other B-cell cohort.

The ORR to brentuximab vedotin was 42% in the DLBCL cohort and 22% in the other B-cell cohort (Table 3). Patients received a median of 4 treatment cycles and 8 patients remain on treatment. Of the patients evaluated, 81% achieved tumor reduction. Tumor reduction plotted against CD30 expression did not show a response expression relationship.

The safety profile of brentuximab vedotin was similar to what has been observed in previous studies. Treatment-emergent AEs included fatigue (49%), neutropenia (40%), nausea (38%), diarrhea (37%), pyrexia (29%), and anemia, decreased appetite, and peripheral sensory neuropathy (24% each). Serious AEs included 3 cases of pneumonia and 2 cases each of anemia, febrile neutropenia, neutropenia, and thrombocytopenia. The primary reason for treatment discontinuation was progressive disease (PD) (38 patients).
The investigators concluded that brentuximab shows promising antitumor activity in relapsed/refractory DLBCL, with responses across a broad range of CD30 expression. The safety profile of this agent was consistent with labeled indications. An additional cohort of DLBCL patients with undetectable CD30 expression is currently enrolling.

**Reactive Oxygen Species (ROS) Suppression Imexon in Relapsed/Refractory B-Cell NHL**

Cancer cells must endure higher levels of stressors and are therefore more dependent on stress support pathways. The increased oxidative stress intrinsic to cancer cells results from a tipping of the balance between production of ROS versus their removal by antioxidant defense systems. Glutathione is one key contributor to ROS defenses. It has been hypothesized that the difference in oncogenic stress and anti-stress responses between the tumor and normal cells can be exploited therapeutically either by augmenting oncogenic stress or by blocking the anti-stress response. The precedent for this therapeutic approach in lymphoma comes from evidence of reduction-oxidation (redox) alterations, including the identification of a subset of DLBCL and overexpressing of genes involved in oxidative phosphorylation as well as mitochondrial function. Additional studies have suggested antioxidant gene expression, most notably glutathione-related genes, to be associated with prognosis in DLBCL. It was therefore hypothesized that therapy with the pro-oxidant molecule imexon would increase oxidative stress beyond the lymphoma cellular threshold, eliciting cell death and thus representing a novel targeted approach.

The mechanism of action of imexon links to its ability to bind and deplete cellular thiols, most notably glutathione. This decreases the cell’s ability to scavenge ROS, increases mitochondrial permeability, and leads to cytochrome C release and subsequently apoptosis. The phase I experience of imexon comes from 3 single-agent studies, as well as 3 additional studies combining imexon with cytotoxic agents. These studies demonstrated a 90-minute half-life ($T_{1/2}$) of imexon, as well as tolerable and reversible AEs that were most commonly gastrointestinal in origin. Although these studies enrolled a minority of lymphoma patients, a PR was noted in one FL patient.

A phase II multicenter study was developed to further investigate the clinical efficacy of imexon in patients with relapsed/refractory NHL who had otherwise normal organ function and a G6PD $\geq$ lower level of normal. Twenty-two patients (9 FL, 5 DLBCL, 3 MCL, 2 transformed follicular, 2 CLL, 1 Burkitt) with a median age of 64 years were enrolled and received imexon $1000 \text{ mg/m}^2 \text{ IV x 5 days of a 21-day cycle up to 1 year}$. Median number of prior treatment regimens was 4 (range 1 to 8). Of the 20 evaluable patients, the ORR was 30%, the PR was 30%, and stable disease was achieved by 35%. Of the 6 responses, 2 occurred in patients with DLBCL and 4 occurred in patients with FL. After a median followup of 11.3 months, the median PFS was 2.1 months in all patients and 5.5 months in FL patients. To date, the OS is 22 months. Common AEs included GI (91%), fatigue (91%), fever (46%), cough

### Table 3. Best clinical response to brentuximab vedotin by disease diagnosis in CD30-positive NHL.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DLBCL N = 50</th>
<th>Other B-cell N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>42%</td>
<td>22%</td>
</tr>
<tr>
<td>CR</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>PR</td>
<td>26%</td>
<td>11%</td>
</tr>
<tr>
<td>SD</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>PD</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>Median DOR, mos (min, max)</td>
<td>5.8 (0+, 22.7+)</td>
<td>5.0 (1.4, 12.2+)</td>
</tr>
<tr>
<td>Median duration of CR, mos (min, max)</td>
<td>11.5 (1.4, 22.7+)</td>
<td>NR (8.5, 12.2+)</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>4.0 (1.6, 5.0)</td>
<td>2.9 (1.3, 4.8)</td>
</tr>
</tbody>
</table>

ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response; PFS, progression-free survival; DLBCL, diffuse large B-cell lymphoma.
(30%), anemia (50%), thrombocytopenia (36%), and neutropenia (23%); common serious AEs were sepsis (9%), respiratory infection (9%), and vomiting (9%).

In an effort to identify a predictive biomarker, the investigators developed studies that identified redox-related genes whose expression correlated with OS in patients with B-cell lymphoma. Combining the expression values of the 13 most significant genes into a single formula, a Redox Signature Score was generated, which reflected multiple components of the redox environment and also predicted survival. In an attempt to apply these data to the imexon-treated patients, Barr et al identified pre-treatment tumor biopsies from 13 patients. Of these 13 patients, 2 achieved PR, 5 achieved stable disease, and 6 experienced disease progression. It was found that patients with higher scores were more likely to respond to imexon (Figure 5).

The investigators of this study concluded that imexon has antitumor activity in relapsed/refractory heavily pretreated NHL as well as manageable and reversible toxicities. They also contend that intratumoral expression of redox-related genes may predict for responses to imexon.

**Figure 5. Redox signature score and response to imexon in patients with relapsed or refractory B-cell non-Hodgkin lymphoma.**

**DOUBLE-HIT LYMPHOMA (DHL) Impact of Induction Regimen and Consolidative Stem Cell Transplantation**

Double hit lymphoma is a high-grade B-cell lymphoma characterized by dual gene rearrangements of **MYC** and either **BCL2** or **BCL6**. Most cases of **MYC/BCL2** DHL morphologically resemble DLBCL or BCL, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BL). This subset of lymphoma is associated with very poor outcomes. Patients with dual rearrangement-defined DHL typically have a poor prognosis with R-CHOP-based chemoinmunotherapy, with a median survival of less than 2 years. While it is important to note that there are some patients with DHL who are able to achieve a durable complete remission, this entity represents an uncommon and biologically aggressive subset of lymphoma.

Gandhi and colleagues designed a retrospective study that sought to: 1) determine if alternative therapeutic strategies (DA-EPOCH-R, R-Hyper CVAD, CODOX-M/IVAC +/- R) are more efficacious in this high-risk cohort, 2) determine if consolidative autologous stem cell transplantation (SCT) in first complete remission improves upon PFS and OS compared with R-CHOP, and 3) evaluate predictors of outcomes using univariate and multivariate analysis. Cases diagnosed between 2000 and 2012 across 15 study centers were considered. The study population consisted of HIV-negative patients over 18 years old who had a **MYC** rearrangement plus a **BCL2** and/or **BCL6** rearrangement, defined by fluorescence in situ hybridization (FISH). Institutional investigators abstracted relevant clinical and treatment-related data through chart review.

A total of 106 cases were analyzed. The median age at diagnosis was 60 years old (range 19-86), and 59% were male. An IPI of 3-5 was seen in 67% of patients, and 27% had an antecedent or concurrently diagnosed low-grade lymphoma. The majority of DHLs were defined by a **BCL2** rearrangement (77%), while 10% demonstrated a **BCL6** rearrangement, and 12% had the triple-hit genotype. Histology findings were 53% with DLBCL, 42% with BCL unclassifiable, and 5%...
with Burkitt-like. The most frequently used induction regimens were R-CHOP (36 patients, 33%) and R-EPOCH (33 patients, 31%). Induction regimens were variably consolidated with SCT in first CR, with a total of 14 transplants performed in CR1.

Median PFS was 16.2 months, whereas median OS was 34.8 months; however, these data are immature, with median followup in survivors of only 23 months. At 2 years, approximately 40 patients are alive. Response rates of separate induction regimens showed that dosage-adjusted EPOCH-R was superior in achieving CR compared with R-CHOP \( (P = 0.005) \), and trended toward significance compared with R-Hyper-CVAD and CODOX-M \( (P = 0.03) \). Collectively, the alternative regimens are superior to R-CHOP in achieving CR. Dose-adjusted EPOCH-R was associated with less frequent occurrence of PD compared with both R-CHOP and R-Hyper-CVAD and CODOX-M.

Evaluation of individual regimens in the absence of SCT showed no significant difference in PFS; similarly, in the absence of a consolidated transplant, there was no difference among regimens with respect to OS. When evaluating patients who were able to achieve first CR with induction chemotherapy, the subsequent consolidative autologous SCT appeared to improve OS compared with observation alone. However, this survival benefit was not statistically significant and may be a reflection of the small number of patients able to undergo SCT. The characteristics of patients who were transplanted did not appear to be significantly different with respect to either patient profile or disease parameters, compared with those observed following achievement of CR.

Univariate analysis to assess predictors for OS showed that an IPI of 3-5 was the only significant pretreatment factor \( (P < 0.001) \). Interestingly, neither the triple-head genotype nor DHL defined by \( BCL2 \) or \( BCL6 \) impacted OS. With respect to treatment and response-related factors, consolidated SCT compared with all patients (not just those achieving CR) as well as PD were each significant \( (P = 0.02 \text{ and } P = 0.0001, \text{ respectively}) \).

Multivariate analysis showed that only PD was a significant predictor of OS \( (P < 0.0001) \).

This study illustrated that the type of induction regimen does not clearly improve PFS and OS compared with R-CHOP among patients with DHL; however dose-adjusted EPOCH-R may be associated with improved rates of CR and less frequent occurrence of progressive disease. Consolidative autologous SCT CR1 may improve OS, but is not statistically significant compared with observation alone. Finally, the nature of DHL, as determined by \( BCL2 \) or \( BCL6 \), or the presence of a triple-hit lymphoma, does not impact survival.

**CONCLUSION**

Results of numerous studies presented at the 2013 ASH Annual Meeting demonstrated promise in the treatment of a variety of NHL subtypes. While no exceptional breakthroughs in the lymphoma field were cited at this meeting, further understanding about the biology of this disease continues to enhance treatment strategies. Therapies that target key cellular pathways, such as the PI3K pathway, continue to show promise in the treatment of B-cell malignancies. Encouraging data related to the use of kinase inhibitors in FL offer new insight into treatment and prognosis of this subtype. Updated study results about prolonged maintenance therapy with rituximab after immunochemotherapy demonstrated favorable survival rates.
REFERENCES


