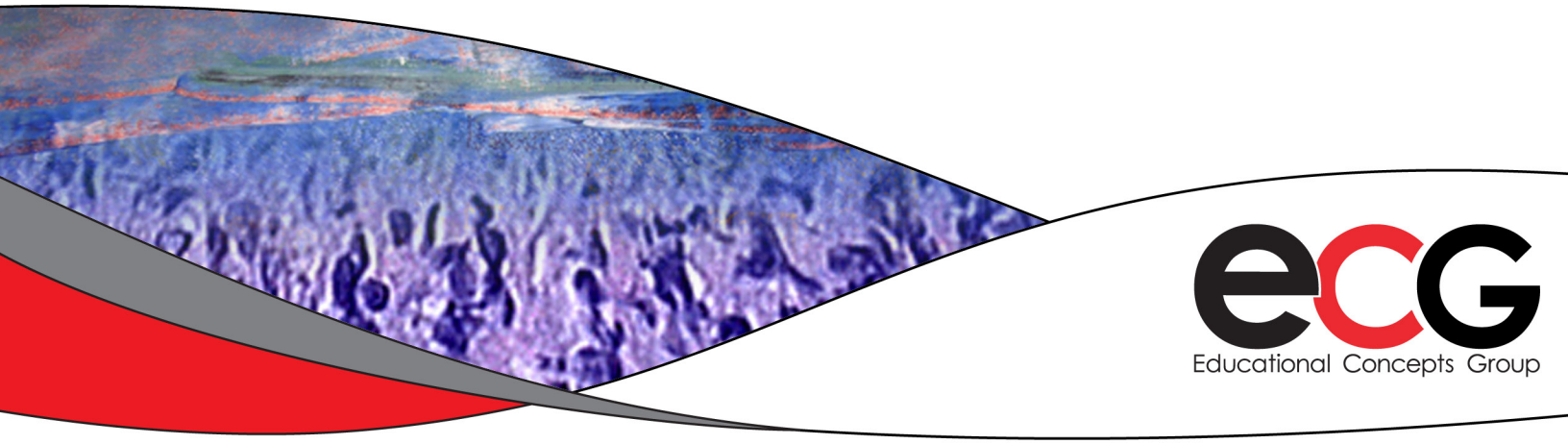

Advances in the Management of B-Cell Lymphoma: Highlights from the 54th American Society of Hematology Annual Meeting and Exposition

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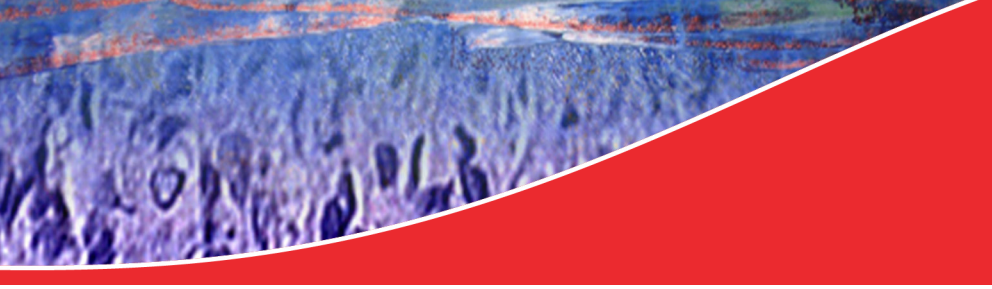

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HIGHLIGHTS FROM THE 54TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING AND EXPOSITION

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INTRODUCTION
This newsletter covers major plenary sessions, key symposia, and targeted oral and poster presentations on B-cell lymphoma presented during the 54th American Society of Hematology (ASH) Annual Meeting, December 8-11, 2012 in Atlanta, Georgia. This newsletter will describe the importance of diagnostic and pathologic evaluation of B-cell lymphoma, review the rationale for the development and integration of treatment strategies in B-cell lymphoma, and examine clinical trial results of treatment regimens, both containing novel agents and combinations, in patients with B-cell lymphoma.

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TARGET AUDIENCE
The intended audience for this activity is community-based hematologists, hematologist-oncologists, medical oncologists, and oncology specialty pharmacists 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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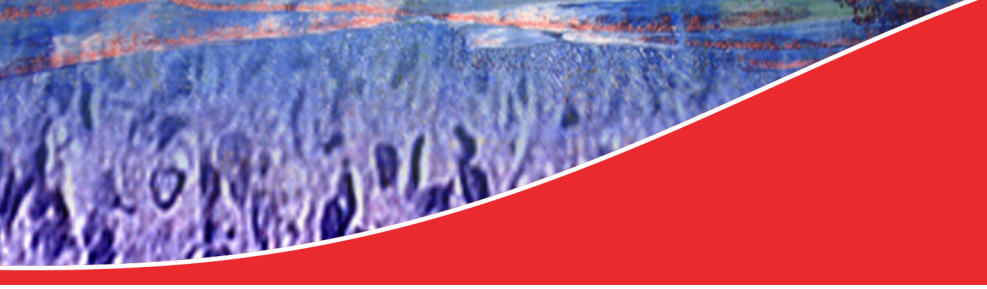

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) comprises a heterogeneous group of malignancies with differing clinical patterns and treatment responses. A growing number of therapeutic agents have become available in recent years that offer improved strategies for managing various types of NHL. Numerous presentations at the 54th American Society of Hematology (ASH) Annual Meeting and Exposition revealed exciting and encouraging findings from recent NHL clinical trials.

FOLLICULAR LYMPHOMA

Frontline Therapy

LENALIDOMIDE + RITUXIMAB

Follicular lymphoma (FL) is the most common subtype of indolent lymphoma and comprises about 22% of all NHL. This subtype is characterized by diffuse lymphadenopathy, involvement of bone marrow, splenomegaly, and less commonly, other extranodal sites of involvement.[1] The optimal treatment for newly diagnosed indolent NHL has not been determined and continues to evolve.

Lenalidomide, which has single-agent activity in relapsed indolent NHL, enhances rituximab-induced apoptosis in preclinical models.[2,3] Given concomitantly with rituximab, lenalidomide has demonstrated activity in patients with relapsed mantle cell lymphoma (MCL) as well as patients with chronic lymphocytic leukemia (CLL).[4,5] Dr Nathan Fowler from MD Anderson Cancer Center reported the final results of a study that evaluated lenalidomide + rituximab for untreated indolent lymphoma.[6]

The primary endpoint of this phase II, single-arm study was overall response rate (ORR). After a 30-patient pilot phase, the study was expanded to enroll 110 patients including FL (n = 50), small lymphocytic lymphoma (SLL; n = 30), and marginal zone lymphoma (MZL; n = 30) subtypes. Enrolled patients received lenalidomide 20 mg/day on days 1-21 + rituximab 375 mg/m^2 on day 1 of each 28-day cycle x 6 cycles. Prophylactic growth factors and antithrombotics were not utilized aside from aspirin in patients at high risk for thrombosis.

As data emerged from the leukemia study groups that improved response occurred with continued drug therapy, patients were allowed to receive up to 12 cycles of the same regimen if they were deriving clinical benefit. Approximately 50% of patients had high tumor burden according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.

The ORR was 90% in evaluable patients (n = 103) and 85% in the intent-to-treat (ITT) population (n = 110). **Table 1.** Similar ORR and complete response (CR)/complete response unconfirmed (CRu) rates were shown for FL patients stratified by bulk of disease. Nearly all FL patients demonstrated molecular response with the absence of detectable *BCL-2* by polymerase chain reaction. At a median follow-up of 22 months, projected 3-year progression-free survival (PFS) was 81% in FL patients (n = 46), 89% in MZL patients (n = 27), and 66% in SLL patients (n = 30).

Among all patients, grade ≥ 3 neutropenia occurred in 41% and thrombocytopenia occurred in 6%. The most common grade ≥ 3 non-hematologic toxicities included fatigue, pain, rash, nausea, diarrhea, and constipation. Secondary malignancies occurred in 5 patients.

In conclusion, high overall and complete response rates were shown with a combination of lenalidomide + rituximab as initial treatment for indolent NHL. Durable remissions were observed in the majority of patients. Phase III randomized trials in untreated FL are underway.

Table 1. Response Rates

	SLL (n = 30)	MZL (n = 27)	FL (n = 46)*	All Patients	
				Evaluated (n = 103)	ITT (n = 110)
ORR, n (%)	24 (80)	24 (89)	45 (98)	93 (90)	93 (85)
CR/CRu	8 (27)	18 (67)	40 (87)	66 (64)	66 (60)
PR	16 (53)	6 (22)	5 (11)	27 (26)	27 (25)
SD, n (%)	4 (13)	3 (11)	1 (2)	8 (8)	8 (7)
PD, n (%)	2 (7)	0	0	2 (2)	2 (2)

ORR = overall response rate; CR/CRu = complete response/complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease; ITT = intent-to-treat.
*7 patients not evaluable for response: 5 due to adverse event in cycle 1, 1 due to non-compliance, 1 due to withdrawal of consent.

BENDAMUSTINE + RITUXIMAB vs R-CHOP or R-CVP

Bendamustine, a unique alkylating agent with a multifaceted mechanism of action, has shown clinical activity in patients with disease refractory to conventional alkylator chemotherapy. In the recent STiL-NHL-1 study, which compared bendamustine + rituximab (BR) with rituximab,

cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in indolent NHL and MCL, BR was associated with a higher CR rate than R-CHOP (40% vs 30%) and a significantly higher PFS (70 months vs 31 months; $P = 0.0001$).[7]

Dr Ian Flinn of the Sarah Cannon Research Institute presented the results of the BRIGHT study, which compared BR with R-CHOP or rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) as frontline therapy in patients with advanced indolent NHL or MCL.[8] Patients were randomized to 6 cycles of BR (bendamustine 90 mg/m^2/day on days 1 and 2 + rituximab 375 mg/m^2 on day 1 of a 28-day cycle) or standard R-CHOP/R-CVP (R-CHOP or R-CVP determined by investigator prior to randomization). At the investigator's discretion, patients could receive up to 8 cycles of treatment.

The primary objective of this study was to determine whether BR therapy was non-inferior to standard treatment (R-CHOP or R-CVP) in CR rate as frontline treatment. Of 447 randomized patients, 419 patients (BR n = 213; R-CHOP/R-CVP n = 206) were evaluable for efficacy. Randomized groups were well matched for age, sex, Eastern Cooperative Oncology Group (ECOG) status, lymphoma type, and Ann Arbor stage.

Among all randomized and evaluable patients, the CR rate was higher for BR than R-CHOP/R-CVP and statistically non-inferior (31% vs 25%, respectively; $P = 0.0225$). The ORR was 97% for BR vs 91% for R-CHOP/R-CVP. **Table 2.** Complete response rates for indolent NHL were similar between BR and R-CHOP/R-CVP; however, in MCL, BR was statistically superior (51% vs 24%, respectively; $P = 0.018$).

The combination of BR was associated with a higher incidence of nausea and vomiting, pyrexia, chills, drug hypersensitivity, decreased appetite, rash, and pruritus. Conversely, R-CHOP and R-CVP were associated with a higher incidence of constipation, paresthesia, peripheral neuropathy, and alopecia. The R-CHOP regimen was associated with a higher incidence of febrile neutropenia and mucosal inflammation, with significantly more grade 3/4 neutropenia in patients treated with R-CHOP/R-CVP. A greater degree of lymphocytopenia was associated with BR. Whereas dose delays were more common for BR-treated patients, dose reductions were less common.

The CR rate of the BR treatment regimen was statistically non-inferior to the R-CHOP/R-CVP regimen in patients with previously untreated indolent NHL and MCL, and the ORR was high for both treatment groups. The adverse event profile for BR was distinct from that of R-CHOP/R-CVP.

Table 2. Response Rates

Evaluable: IRC	BR % (n = 213)	R-CHOP/R-CVP % (n = 206)	*P* value (Non-Inferior)	*P* value (Superior)
CR (95% CI)	31 (25.3-38.2)	25 (19.5-31.7)	0.0225	0.1269
PR	65	66		
ORR (CR + PR)	97 (93.3-98.7)	91 (86.0-94.4)		

IRC = independent review committee; CR = complete response; PR = partial response; ORR = overall response rate.

Relapsed/Refractory Therapy

REFOLL STUDY

Follicular lymphoma has an indolent course, with treatments ranging from single-agent chemotherapy (CHT) or monoclonal antibodies to high-dose therapy with stem cell transplantation (HSCT). In relapsed patients, the efficacy of salvage treatments may be affected by the type and intensity of previous treatments. Therefore, it is not known whether a definite sequence of treatments throughout the disease course is optimal for outcome.

Results of an observational, multicenter study conducted by the Fondazione Italiana Linfomi (FIL) were presented by Dr Giuseppe Rossi. The REFOLL study sought to retrospectively analyze any effect of the type of frontline treatment on the outcome of second-line treatments in patients with relapsed FL and to identify an optimal sequence of frontline and salvage treatments.[9]

This study enrolled 582 patients with FL at first relapse from 25 institutions; 548 patients were included in the study. Patients had received the following therapies as frontline treatment:

- Alkylating agents (AA) = 22%
- Anthracycline-containing CHOP or CHOP-like regimens +/- rituximab (AC) = 61%
- Nucleoside analogue-containing regimens (NA) = 17%

Rituximab was added to therapy in 284 patients. Patients receiving AA had maintenance rituximab after frontline CHT more often compared with those receiving AC- or NA-based CHT.

Salvage treatment was the same frontline CHT program in 271 patients (AA = 20%; AC = 18%; NA = 14%), included autologous HSCT in 151 patients (29%) or MoAB/radioimmunoconjugate without CHT in 101 patients (19%). The primary endpoint was time to next treatment (TTNT) after relapse; secondary endpoints were PFS and overall survival (OS).

The median TTNT was 41 months, and 37% of patients were free of a third-line treatment at 5 years. Among frontline treatments, AC +/- rituximab was associated with a better TTNT after any salvage than either AA +/- rituximab or NA +/- rituximab. The addition of rituximab to frontline CHT did not adversely impact the efficacy of salvage treatments. Regarding salvage therapy, patients receiving autologous HSCT had a significantly better outcome when compared with any other treatment +/- rituximab. The TTNT after relapse was significantly better in patients receiving frontline AC CHT +/- rituximab followed by autologous HSCT as salvage. Progression-free survival after relapse was 35% at 5 years and OS from diagnosis was 88% at 5 years.

In his closing remarks, Dr Rossi noted that frontline AC-containing chemotherapy obtained a better TTNT than either AA- or NA-containing therapies. Moreover, second-line treatment programs that include HSCT obtained the best TTNT compared with any other regimens. He emphasized that this study highlights the concept that in FL patients, the efficacy of prior therapy may significantly impact the outcome of subsequent therapy. The confounding factor in this study is the retrospective nature of the analysis. The fact that patients who had anthracycline-based chemotherapy followed by HSCT at relapse had the best outcome could easily relate to selection bias rather than the treatment sequence.

ENZASTAURIN IN FL

The B-cell receptor (BCR) is critical for the development and persistence of B-cell NHL. Protein kinase C beta (PKCβ) has been identified as a key signaling hub downstream of the BCR, constituting a potentially valuable therapeutic target in B-cell NHL.[10] Whereas overexpression of this enzyme is implicated in the pathogenesis of B-cell lymphoma, low PKCβ expression is associated with improved outcomes in patients with diffuse large B-cell lymphoma (DLBCL).[11,12] Enzastaurin (ENZ), an oral serine/threonine kinase inhibitor, targets the PKCβ and PI3K/AKT pathways to inhibit tumor cell proliferation, induce apoptosis, and suppress tumor-induced angiogenesis. Single-agent ENZ has been shown to have activity in refractory DLBCL and MCL.[13,14]

Dr Lee Schwartzberg from The West Clinic presented the updated results of a study that evaluated ENZ in patients with FL.[15] The primary objective of this study was evaluation of ORR. Secondary objectives were assessment of PFS, time to response, duration of response (DOR), safety of ENZ, and correlation of biomarkers with ORR and PFS.

In this open-label, single-arm, phase II study conducted in the US and Germany, patients with grade 1/2 and stage III/IV measurable FL, either chemonaïve or relapsed after 1 regimen, received ENZ 500 mg once daily (1125 mg loading dose on day 1) up to 3 years or until progression, withdrawal, or toxicity. Of 66 patients enrolled, 58 comprised the per-protocol population. The study was amended over time to allow patients deriving clinical benefit from ENZ to remain on study. Three patients completed 3 years of therapy and went off-trial, while 7 patients remain on therapy and 56 patients have discontinued treatment, mostly because of progressive disease. The median overall exposure was 10.8 months.

The ORR was 26%, whereas CR and PR were 4% and 23%, respectively. The median PFS was 18.1 months (1-year PFS 59%; 2-year PFS 42%), median time to response was 4.9 months, and median DOR was 22.2 months. According to response rate by subgroup, there was no significant difference in response rate based on prior CHT, FLIPI score, or bone marrow biopsy.

Enzastaurin was well tolerated in this population, with only 2 grade 3 adverse events (AEs) (cough and decreased hemoglobin). The most commonly occurring AEs were fatigue, diarrhea, nausea, and cough. There were no drug-related deaths.

The biomarker analysis evaluated FL-specific biomarkers and ENZ mechanism of action biomarkers (including PKCβ2). No significant correlations were observed with ORR or PFS for any FL-specific markers. However, for ORR, there was significance with PKCβ2 expression. Twenty four patients comprised the PKCβ2 biomarker population. The ORR and PFS were essentially identical in the subgroup population

versus the study population (25% vs 26%, and 18.1 months vs 18.1 months, respectively). Using a predetermined cutpoint, the ORR for low expression was 41.7% (n = 12), whereas the ORR for high expression was 8.3% (n = 12), yielding a statistically significant odds ratio of 0.031 (95% CI 0.001-0.86). Of the 3 patients who completed 3 years of study drug, all showed low expression of PKCβ2.

Dr Schwartzberg concluded that exploration of lymphoma and ENZ mechanism of action and biomarkers will be continued in lymphoma studies, including the ENZ phase III PRELUDE trial pending final results in 2013.

MANTLE CELL LYMPHOMA

Frontline Therapy

R-CHOP → MYELOABLATIVE CHEMOTHERAPY and HSCT vs ALTERNATING R-CHOP/R-DHAP →TBI + ARA-C + MELPHALAN and HSCT

Mantle cell lymphoma is a distinct subtype of malignant lymphoma characterized by the chromosomal translocation t(11;14). Although MCL outcome has improved during the last few decades, this type of lymphoma is associated with an aggressive clinical course and a median survival < 5 years. A 2005 landmark trial by the European MCL Network suggested radiochemotherapy + autologous HSCT consolidation in first remission significantly prolonged PFS.[16] Furthermore, the French GELA/Lysa study showed that R-CHOP + R-DHAP exhibited an ORR of 95% and a CR rate of 61% following TBI + ara-C + melphalan (TAM) and autologous HSCT. The event-free survival in this study was 84 months and survival was 75% at 5 years.[17]

Final results of the MCL Younger Trial (European MCL Network) were presented by Dr Olivier Hermine from the University of Paris Descartes.[18] This trial compared 6 courses of R-CHOP followed by myeloablative radiochemotherapy + HSCT consolidation (Arm A) with alternating courses of 3x R-CHOP and 3x R-DHAP followed by TBI + cytarabine + melphalan (TAM) + HSCT (Arm B) consolidation. The primary endpoint was time to treatment failure (TTF) defined as failure of initial therapy, progression, or death.

From July 2004 to May 2010, 497 patients ≤ 65 years were randomized in 4 countries; of these, 465 patients were evaluable (Arm A n = 33; Arm B n = 232). After a median follow-up of 53 months, TTF was longer in Arm B than Arm A (46 months vs 88 months, $P = 0.0382$). After induction, ORR was similar in both arms (90% vs 95%; $P = 0.11$); however, CR and CR/CRu rates were significantly higher in Arm B (25% vs 36%; $P = 0.0077$; 39% vs 55%; $P = 0.0013$). Stem cell transplantation was performed and documented at the same rate in both groups (Arm A 83%; Arm B 80%). Following transplantation, ORR and CR rates were comparable in both arms (97% vs 98%; 62% vs 61%). Although the CR rate after HSCT was similar in both arms, remission duration after HSCT was superior in Arm B (49 months vs 84 months; $P = 0.0001$). At the time of final analysis, OS was superior in Arm B (NR vs 82 months; $P = 0.045$). The percentage of patients who were negative for minimal residual disease (MRD) within the first year following HSCT was significantly higher in Arm B than Arm A (54% vs 77%; $P < 0.001$).

After induction, safety was comparable between both arms, with the exception of increased grade 3/4 hematological toxicity (hemoglobin, white blood cells, platelets, neutrophils; $P < 0.001$); renal toxicity (creatinine grade 1/2 and grade 3/4; $P < 0.001$); and nausea and vomiting (grade 1/2; $P < 0.001$) in Arm B.

Dr Hermine concluded that the regimen of alternating R-CHOP/R-DHAP followed by TAM + HSCT significantly improves TTF, extends survival, and exhibits a reasonable safety profile. He further suggested this regimen be considered as a new standard in patients ≤ 65 years with MCL.

Relapsed/Refractory Therapy

IBRUTINIB IN RELAPSED/REFRACTORY MCL

B-cell receptor signaling is required for tumor expansion and proliferation. Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway. Targeted inhibition of BTK is a contemporary investigational treatment approach for B-cell malignancies.[19] Ibrutinib, a first-in-class, orally administered inhibitor of BTK, induces apoptosis and inhibits cellular migration and adhesion in malignant B-cells.

Dr Michael Wang of MD Anderson Cancer Center presented results of an interim analysis of an ongoing, international, multicenter, open-label, phase II, single-agent trial of ibrutinib. Between February 2011 and July 2012, 115 patients with relapsed or refractory MCL who were either bortezomib-naïve (n = 65) or bortezomib-exposed (≥ 2 cycles of bortezomib) (n = 50) were enrolled.[20] A total of 111 patients were treated with ibrutinib 560 mg daily in continuous 28-day cycles until

disease progression. Tumor response was assessed every 2 cycles according to the revised International Working Group for NHL criteria. The primary endpoint was ORR.

The ORR was 65% in the bortezomib-naïve group (PR 44%, CR 22%) and ORR was 72% in the bortezomib-exposed group (PR 49%, CR 23%). Responses to ibrutinib increased with longer time on study treatment. Time to PR ranged from 1.4 to 9.1 months (median 1.9 months), whereas CR ranged from 1.7 to 16.4 months (median 5.5 months). Increased CR and PR rates were observed with longer follow-up of the initial 51 patients presented at the 53rd ASH Annual Meeting and Exposition. Median time on study treatment was 3.7 months in 2011 vs 14.7 months in 2012; ORR was 69% vs 74.5%, while CR rate was 16% vs 35.3%, respectively. The improved response with longer follow-up was termed the "phenomenon of incremental response" by the investigators. Overall, responses have been durable, with a median PFS of 13.9 months and a median DOR not reached.

Ibrutinib was generally well tolerated, and treatment-emergent AEs occurring in ≥ 15% of patients consisted of diarrhea, fatigue, upper respiratory tract infections, nausea, rash, dyspnea, and peripheral edema. Neutropenia, thrombocytopenia, or anemia occurred at rates of < 20%. The majority of AEs were grade 1 or grade 2.

Dr Wang concluded that ibrutinib demonstrated an unprecedented ORR as a single-agent in patients with relapsed or refractory MCL and that the final results of this study will be forthcoming.

LENALIDOMIDE in RELAPSED MCL: THE EMERGE STUDY

In the relapsed setting, patients with MCL frequently develop chemoresistance and have a poor overall prognosis with limited treatment options. No standard therapy exists for patients who have failed bortezomib. Results of a phase II, multicenter, single-arm, open-label study, which examined lenalidomide in 134 MCL patients with relapsed/refractory MCL previously exposed to bortezomib, were presented by Dr Andre Goy of the John Theurer Cancer Center.[21] Patients received lenalidomide 25 mg po on days 1-21 of a 28-day cycle, and were required to have failed prior treatment with anthracycline (or mitoxantrone), cyclophosphamide, rituximab, and bortezomib, and to have relapsed/progressed ≤ 12 months after last dose of bortezomib or were refractory after ≥ 2 cycles of bortezomib. Patients were followed via computed tomography (CT) scan every 90 days. The primary endpoints were ORR and DOR.

In this study population, 63% were ≥ 65 years of age, 93% had stage III/IV MCL, and 60% were refractory to prior bortezomib. Patients were heavily pretreated and had received multiple treatments. The ORR to single-agent lenalidomide was 32% by investigator review and 28% by central review, whereas CR/CRu was 16% by investigator review and 8% by central review. **Table 3.** By central review, the median DOR was 16.6 months and the maximum DOR was 29+ months at data cut-off. By central review, the median time to response was 2.2 months and the median PFS was 4.0 months; the median OS was 19.0 months. The median daily dose of lenalidomide was 23.5 mg/day and the median duration of treatment was 95 days.

The most common grade 3/4 AEs leading to dose reductions, interruptions, or discontinuations were neutropenia and thrombocytopenia; the other most common grade 3/4 AEs were anemia, pneumonia, and fatigue. Grade 1/2 AEs that occurred in ≥ 10% of patients were tumor flare reaction (10%) and rash (22%). Eighteen deaths (13%) occurred within the last 30 days of the last dose of lenalidomide; 14 of these were attributed to progressive disease.

Dr Goy concluded that the EMERGE trial confirmed a rapid and durable efficacy and a manageable safety profile with lenalidomide in MCL patients who failed prior therapies including bortezomib.

Table 3. Efficacy Outcomes

Efficacy Parameter (n = 134)	Central Review n (%)	Investigator Review n (%)
ORR*	37 (28)	43 (32)
CR/CRu	10 (8)	22 (16)
PR	27 (20)	21 (16)
SD	39 (29)	36 (27)
PD	35 (26)	43 (32)
Median DOR, months (95% CI)	16.6 (7.7-26.7)	18.5 (12.8-26.7)
Median DOR for CR/CRu, months (95% CI)	16.6 (16.6-NR)	26.7 (16.8-NR)

ORR = overall response rate; CR/CRu = complete response/complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease; DOR = duration of response. *No response assessments were available for 23 patients (central review) and 12 patients (investigator review).

DIFFUSE LARGE B-CELL LYMPHOMA

Frontline Therapy

RESPONSE-ADAPTED THERAPY BASED ON PET SCANNING

Imaging with 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been used increasingly as a non-invasive tool for the management of patients with lymphoma, for risk stratification and tailored therapy.[22] A persistently positive PET scan after just a few cycles of therapy may be predictive of a poor clinical outcome in DLBCL. Dr Lode Swinnen of Johns Hopkins University stated that about one-third of patients remain PET-positive after 2 to 4 cycles, with ≤ 20% 2-year PFS for such patients. Dr Swinnen presented results of an ECOG Study (E3404), which used a response-adapted strategy for patients with DLBCL based on early PET scanning.[23]

Eligible patients were previously untreated, had DLBCL stage III, IV, or bulky II, measurable disease, adequate organ reserve, and were HIV-negative. A PET/CT scan was performed before treatment and again after 3 cycles of R-CHOP; a fourth cycle of R-CHOP was given while the scan was centrally reviewed and scored as positive or negative.

Patients who were persistently PET-positive received 4 cycles of rituximab + ifosfamide-carboplatin-etoposide (R-ICE) for a total of 8 cycles chemotherapy (4x R-CHOP + 4x R-ICE), while those who were PET-negative received 2 more cycles of R-CHOP (total of 6 cycles). The primary study objective was to estimate 2-year PFS after R-ICE for patients who remain PET-positive after 3 cycles of R-CHOP. Secondary endpoints were 1) the proportion of mid-treatment PET-positive patients who became PET-negative after 4 cycles of R-ICE, and 2) PFS of mid-treatment PET-negative patients. PET interpretation criteria were negative (0, 1+, 2+) or positive (3+, 4+).

At mid-treatment PET scan, 12/74 patients (16%) were positive and 62/74 patients (84%) were negative. At the end of treatment, 10/74 patients (13%) were positive and 65/74 patients (84%) were negative. Two-year PFS was 45% for interim PET-positive patients and 77% for interim PET-negative patients, all of whom had had their treatment switched to R-ICE. Three-year OS was 67% for interim PET-positive patients and 93% for interim PET-negative patients.

Dr Swinnen concluded that the 2-year PFS for mid-treatment PET-positive patients given 4 additional cycles of R-ICE met the threshold to be considered promising, but the confidence interval was wide due to the smaller than expected number of mid-treatment PET-positive patients. Additionally, the inter-observer variability in the interpretation of mid-treatment PET scans in this study implies that treatment modification based on early PET scanning should remain but only be used in the setting of a clinical trial.

YOUNG HIGH-RISK DLBCL PATIENTS

Diffuse large B-cell lymphoma is the most common NHL in the United States, and accounts for approximately 30% of new lymphoma diagnoses in adults.[24] Despite remarkable progress in improving patient survival in many patients with DLBCL, the prognosis in young patients with R-CHOP remains unsatisfactory. Although most randomized phase III trials have failed to show a survival benefit for high-dose chemotherapy and HSCT consolidation, the addition of rituximab + high-dose chemotherapy (R-HDC) + HSCT consolidation in the subset of poor-prognosis DLBCL patients suggests improved outcomes.[25] The final results of a trial conducted by the Fondazione Italiana Linfomi (FIL) were presented by Dr Umberto Vitolo.[26]

The aim of this multicenter, randomized, phase III trial was to evaluate if intensification with R-HDC followed by BEAM + HSCT after 4 courses of rituximab-dose-dense chemotherapy (R-CHOP-14 and R-MegaCHOP-14: cyclophosphamide 1200 mg/m^2 + doxorubicin 70 mg/m^2 + standard-dose vincristine and prednisone) improves prognosis of newly diagnosed young DLBCL patients at high risk compared with a full course of rituximab-dose-dense chemotherapy.

Patients were stratified according to age-adjusted IPI (aaIPI) and randomized to receive:

- R-CHOP-14 x 8 cycles
- R-MegaCHOP-14 x 6 cycles
- R-CHOP-14 x 4 cycles + R-HDC, then BEAM + HSCT
- R-MegaCHOP-14 x 4 cycles + R-HDC, then BEAM + HSCT

The primary endpoint was an increase of 2-year PFS from 50% of the standard dose-dense arm (R-dose-dense chemotherapy) to 65% in the experimental arm. Of 412 enrolled patients, 399 were eligible and randomized (R-HDC + HSCT n = 199; R-dose-dense n = 200). According to the type of chemotherapy, 203 patients were randomized to R-CHOP-14 and 196 patients were randomized to R-MegaCHOP-14. The median age of patients was 49

years (range 18 to 65 years) and DLBCL stage II/III/IV was 6%/29%/65%, with clinical characteristics well balanced between those treated with or without HSCT.

Complete response was achieved by 76% of patients in the R-HDC + HSCT arm vs 72% in the R-dose-dense arm. After a median follow-up of 41 months, 3-year PFS was achieved by 71% of patients treated with R-HDC + HSCT vs 58% of those treated with R-dose-dense ($P = 0.008$). No difference in 3-year PFS was observed between R-CHOP-14 and R-MegaCHOP-14. By aa-IPI score, 3-year PFS for R-HDC + HSCT vs R-dose-dense arms were 75% vs 65%, for score 2 (n = 295) and 60% vs 46%, for score 3 (n = 104).

In a Cox model of the 4 treatment arms, assuming R-CHOP-14 as a reference, the risk of relapse was significantly reduced in both HSCT arms, with a major effect in the R-CHOP-14 + R-HDC + HSCT arm (HR = 0.56; 95% CI = 0.35-0.91) and a slight minor HR reduction in the R-MegaCHOP-14 + R-HDC + HSCT arm (HR = 0.68; 95% CI = 0.42-1.08). The 3-year OS was 81% vs 79% for R-HDC + HSCT vs R-dose-dense arms and 80% for both the R-CHOP-14 and R-MegaCHOP-14 arms.

Grade 3/4 hematological (ie, neutropenia and thrombocytopenia) and grade 3/4 extrahematological toxicities occurred at higher rates in the R-HDC + HSCT arm than in the R-dose-dense arm. Treatment-related deaths occurred in 6 R-HDC + HSCT patients and in 4 R-dose-dense patients.

Dr Vitolo concluded that R-dose-dense chemotherapy followed by R-HDC + BEAM + HSCT significantly reduced the risk of progression compared with standard R-dose-dense chemotherapy in young patients with DLBCL without adding significant toxicity. It should be noted that no OS difference was found and none of the study arms could be considered standard of care in the US. The PFS in the R-HDC + BEAM + HSCT arm was similar to that in the transplant arm of the SWOG 9704 study, which included a large population of poor prognosis patients.

LENALIDOMIDE + R-CHOP

Clinical trial data have shown that salvage therapy has minimal impact on OS in patients with aggressive B-cell lymphomas. Lenalidomide has demonstrated significant single-agent activity and durable responses in patients with relapsed/refractory aggressive B-cell lymphomas.[27,28] Results of a phase I study demonstrated that lenalidomide in combination with R-CHOP does not result in dose delays or increased toxicity.[29] Lenalidomide + R-CHOP combination development strategies include maintenance following R-CHOP and/or concomitant use with R-CHOP.

Dr Grzegorz Nowakowski of the Mayo Clinic presented phase II results of lenalidomide in combination with R-CHOP-21 (R2-CHOP) in adult patients with newly diagnosed CD20-positive DLBCL or grade 3 FL.[30] Patients were treated with lenalidomide 25 mg po days 1-10 of the cycle. Of 51 patients enrolled, 25% were > 70 years old, 61% were stage IV, 92% had DLBCL, and 8% had FL grade 3.

For 47 evaluable patients, the ORR and CR were 98% and 83%. At 1 year, PFS was 73%. Since enrolled patients represented a relatively high-risk group, the investigators compared PFS in R2-CHOP-21 with PFS in a contemporary cohort of 87 consecutive patients with DLBCL from the Mayo Clinic Lymphoma Database who were treated with standard R-CHOP-21 alone. The PFS was 62% at 12 months and was inferior to R2-CHOP.

Treatment was generally well tolerated. The major toxicity was hematological and, although neutropenia and thrombocytopenia were common, they were of short duration and generally not associated with infectious or bleeding complications. Thrombosis occurred in 1 patient and there was 1 death on the study, caused by perforation/sepsis. R-CHOP dose intensity was maintained with the addition of lenalidomide.

The combination of lenalidomide with standard R-CHOP-21 chemotherapy (R2-CHOP-21) appears promising, with favorable ORR and CR rates and PFS in elderly high-IPI patients. Dr Nowakowski concluded that a randomized trial will be required to evaluate R2-CHOP vs R-CHOP (ECOG 1412 in development).

Relapsed/Refractory Therapy

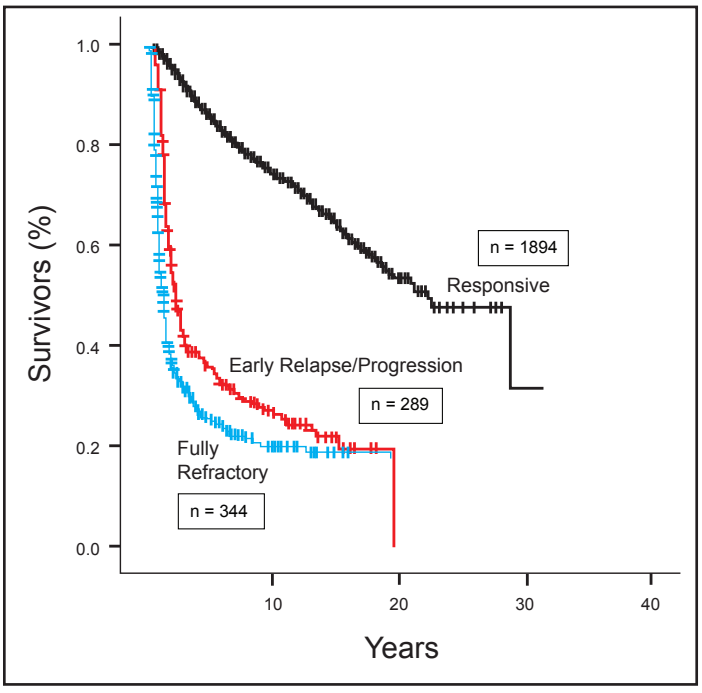
IMPACT OF REFRACTORY DISEASE

Refractory disease is probably the most relevant clinical challenge in NHL, and its prediction and management is a focus in biological and clinical research. The true incidence of refractory NHL is not well established, and little is known about the long-term outcome of refractory vs responsive NHL patients. An extensive analysis of a series of 3,542 newly diagnosed NHL patients was conducted over the last 3 decades. Patients were identified for stable or progressive disease (fully refractory, FR) and for transient response with disease progression within 6 months (early progression, EP) following frontline chemotherapy.

Dr Corrado Tarella from the University of Torino presented the findings of this retrospective review.[31] Data were collected on patients referred and treated at 2 Italian centers between 1984 and 2012. Among 3,068 patients undergoing primary therapy for lymphoma, 78% were responsive and 22% were refractory, including 12% FR and 10% with EP. The overall incidence of refractory disease was comparable between the 2 treatment centers. In the T-cell and B-cell subtypes, the rate of refractory disease was 41% and 20%. T-cell NHL is thus associated with a poorer prognosis than B-cell NHL. Within B-cell subtypes, refractory patients were more frequently observed among DLBCL patients (23%) than FL patients (13%). Factors that were most significantly ($P < 0.001$) associated with treatment response were intermediate-high risk IPI presentation and the addition of rituximab. The addition of rituximab decreased the rate of refractoriness from 28% to 16% among DLBCL patients, and from 49% to 12% among MCL patients. These factors maintained their independent predictive values in multivariate regression analysis.

At a median follow-up of 8 years, OS was significantly poorer for patients who were FR (median survival 1.3 years), compared with EP patients; both refractory subgroups had a poorer OS compared with responsive patients, whose median survival was 22.2 years. **Figure 1.**

Figure 1. Overall Survival



Non-Hodgkin's lymphoma refractory to primary treatment is highly predictive of poor outcome in the short-term, both in patients treated with and without rituximab. Patients responsive to frontline therapy have a prolonged life expectancy, whereas patients who are refractory have a much shorter life expectancy. Dr Tarella added that the short life expectancy of refractory patients suggests that alternative therapies including allogeneic transplantation be considered.

IBRUTINIB IN ABC SUBTYPE OF DLBCL

In recent years, gene expression profiling studies have distinguished 2 molecular subtypes for DLBCL, termed activated B-cell like (ABC) and germinal center B-cell like (GCB). More recently, a third subgroup of DLBCL, primary mediastinal B-cell lymphoma (PMBL), was identified. These subgroups utilize different oncogenic pathways and have distinct clinical features.[32] Patients with GCB DLBCL have demonstrated a higher probability of PFS and OS than patients with ABC DLBCL.[33] Thus, much work is yet to be done to improve survival with the ABC subtype.

A key characteristic of the ABC subtype is activation of the NF-κB transcription factor. Since the identification of the DLBCL subtypes, questions have arisen regarding what is responsible for the activation of NF-κB and whether there are mutations in the ABC subtype lymphomas within the BCR signaling pathway. A constitutively active MYD88 mutant (L265P) is frequent in ABC DLBCL tumors but rare in GCB DLBCL; CD79B and MYD88 L265P mutations often coexist in ABC DLBCL tumors. Dr Wyndham Wilson from the National Cancer Institute presented the interim results of a study that evaluated whether ibrutinib would be more active in ABC than GCB and assessed the association of CD79B and MYD88 mutations with response.[34]

In this multicenter, open-label, phase II study, 70 patients with relapsed/refractory de novo DLBCL were treated with ibrutinib 560 mg PO qday until disease progression (28-day cycle). The primary endpoint was ORR categorized by molecular type. Molecular subtypes were ABC (n = 29), GCB (n = 20), unclassifiable (n = 16), and unknown (n = 5). In the ITT population, the ORR was 23% (16/70). Per protocol ORR was 41% in the ABC group, compared with 5% in the GCB group. There was a clear trend toward improved OS in the ABC group vs the GCB group (9.76 months vs 3.35 months). Ibrutinib was well tolerated, with treatment-emergent AEs consistent with data reported in other ibrutinib studies; no discontinuations occurred secondary to toxicity.

An analysis of mutation subgroups CD79B, MYD88, and CARD11 was also conducted, which included 29 ABC cases from the present study and 10 ABC cases from a pilot study of ibrutinib (PCYC-04753). The CD79B mutant ABC DLBCL showed a 71% (5/7) response to ibrutinib. Moreover, the MYD88 L265P mutation without the CD79B mutation predicts ibrutinib resistance in ABC DLBCL.

Dr Wilson concluded that ibrutinib induced a high response rate in relapsed/refractory ABC DLBCL, but showed marginal activity in GCB DLBCL, supporting the use of the ABC subtype as a biomarker for activity. Ibrutinib response did not require CD79B mutant, suggesting that BCR pathway addiction can occur by other means in ABC DLBCL. Furthermore, tumors with only MYD88 L265P mutation were resistant to ibrutinib, suggesting a BCR-independent pathway to ABC DLBCL.

CONCLUSION

Results from a variety of studies on FL, MCL, and DLBCL were presented at the 54th ASH Annual Meeting and Exposition, many of which show promise in the quest to refine and improve treatment outcomes for this group of hematologic malignancies. The 55th ASH Annual Meeting and Exposition will be held December 7-10, 2013 in New Orleans, Louisiana. Please see *www.educationalconcepts.net* for additional CME programs.

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