Advances in the Management of B-Cell Lymphoma: Highlights from the 56th American Society of Hematology Annual Meeting and Exposition

Editors
Christopher R. Flowers, MD, MSc
Associate Professor, Hematology and Oncology
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Julie M. Vose, MD, MBA
Neumann M. and Mildred E. Harris Professor
Chief, Division of Oncology/Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

This activity is supported by an independent educational grant from Celgene Corporation.
TABLE OF CONTENTS (CLICK THE SECTION YOU WISH TO VIEW)

INTRODUCTION ........................................................................................................................................ 1

NON-HODGKIN B-CELL LYMPHOMA ..................................................................................................... 1

   Diffuse Large B-Cell Lymphoma ........................................................................................................... 1
      R-CHOP With or Without Radiotherapy in Previously Untreated DLBCL ........................................ 1
      DA-EPOCH-R in Previously Untreated DLBCL/BCL-U With MYC Rearrangement ......................... 2
      Lenalidomide vs Investigator’s Choice in Relapsed/Refractory DLBCL ............................................... 3
      Brentuximab Vedotin in CD30-Undetectable DLBCL ....................................................................... 5

   Mantle Cell Lymphoma ........................................................................................................................... 5
      Lenalidomide Plus Rituximab in Previously Untreated MCL ............................................................. 5
      Rituximab Maintenance After HDT-ASCT in MCL: LyMa Trial .................................................... 7
      Lenalidomide Monotherapy in Relapsed/Refractory MCL .............................................................. 8
      Ibrutinib Plus Rituximab in Relapsed/Refractory MCL ................................................................... 8

   Investigational Agents and Strategies in B-Cell Lymphomas .............................................................. 9
      Nivolumab in B-Cell Lymphomas .................................................................................................... 9
      Anti-CD20 Targeted Therapy Plus PI3K-Delta Inhibition ................................................................. 10
      Dual PI3K-Delta and PI3K-Gamma Inhibition in Relapsed/Refractory B-Cell Lymphoma ............... 11
      CAR T-Cells in Relapsed/Refractory Aggressive B-Cell Lymphoma ............................................... 12
      Utility of Interim PET Scans in Aggressive Lymphomas: PETAL Trial ............................................ 13

HODGKIN LYMPHOMA .............................................................................................................................. 14

   Frontline Therapy .................................................................................................................................... 14
      Early Consolidation With Brentuximab Vedotin Following ASCT: AETHERA Trial ......................... 14
      Frontline Brentuximab Vedotin in Older Patients ............................................................................. 15

   Relapsed/Refractory Disease ................................................................................................................ 16
      Pembrolizumab in Relapsed/Refractory Classic Hodgkin Lymphoma ............................................ 16
      Nivolumab in Relapsed/Refractory Classic Hodgkin Lymphoma ..................................................... 17

CONCLUSION ........................................................................................................................................ 18

POST-TEST ............................................................................................................................................ 19

REFERENCES ........................................................................................................................................ 19
 Advances in the Management of B-Cell Lymphoma:  
Highlights from the 56th American Society of Hematology Annual Meeting and Exposition

MEDIA: CONFERENCE HIGHLIGHTS  
Estimated time to complete activity: 1.0 hour  

INTRODUCTION  
Written by expert faculty from across the US, this interactive Conference Highlights will highlight clinical updates, research, and best practices in managing patients with B-cell lymphoma.

EDITORS  
Christopher R. Flowers, MD, MSc  
Associate Professor, Hematology and Oncology  
Winship Cancer Institute  
Emory University School of Medicine  
Atlanta, Georgia

Julie M. Vose, MD, MBA  
Neumann M. and Mildred E. Harris Professor  
Chief, Division of Oncology/Hematology  
Department of Internal Medicine  
University of Nebraska Medical Center  
Omaha, Nebraska

TARGET AUDIENCE  
The target audience for this activity is hematologist/oncologists, medical oncologists, hematopathologists, oncology pharmacists, and other allied healthcare professionals caring for patients with B-cell lymphoma.

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

• Describe and evaluate current practice and future approaches in the management of patients with B-cell malignancies
• Analyze the strengths and weaknesses of clinical trials of agents designed to improve efficacy and safety outcomes in newly diagnosed and relapsed/refractory disease
• Identify ongoing clinical trials of significance in B-cell malignancies
• Better communicate the latest therapeutic treatment advances with patients and caregivers

DESIGNATION OF CREDIT  
PHYSICIAN CONTINUING EDUCATION

Accreditation Statement
Educational Concepts Group, LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation Statement
Educational Concepts Group, LLC designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

METHOD OF PARTICIPATION
There are no fees for participating and receiving CME credit for this activity. During the period Monday, January 26, 2015 through Monday, January 25, 2016, participants must 1) read the educational objectives and faculty disclosures 2) study the educational activity 3) complete the post-test and evaluation.

CME CREDIT
Physicians who complete the post-test with a score of 80% or better may view and print their credit letter via the website, www.ecgcme.com.
**POLICY ON DISCLOSURE**

It is the policy of ECG that the faculty, authors, planners, and other persons who may influence content of this CME activity disclose all relevant financial relationships with commercial interests in order to allow ECG to identify and resolve any potential conflicts of interest.

The Following Faculty Members Have Declared Relevant Financial Relationships

<table>
<thead>
<tr>
<th>Name</th>
<th>Grants/Research Support</th>
<th>Consultant Fees</th>
</tr>
</thead>
</table>

**STAFF DISCLOSURE**

Planners and managers at ECG have no relevant financial relationships to disclose.

**ACKNOWLEDGEMENT**

The editors wish to thank Sara R. Fagerlie, PhD, CCMEP and Anne Jacobsen, MPH, CCMEP, CMPP for assistance in writing this document.

**DISCLOSURE OF OFF-LABEL USE**

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. ECG does not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity do not necessarily represent the views of ECG. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

**DISCLAIMER**

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Please refer to the official prescribing information for each product or consult the Physicians’ Desk Reference for discussion of approved indications, contraindications, and warnings.

**ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT**

This activity is supported by an independent educational grant from Celgene Corporation.

**CME INQUIRIES**

For further information, please contact:
Educational Concepts Group, LLC
1300 Parkwood Circle SE, Suite 325
Atlanta, Georgia 30339
Phone: 1.866.933.1681 | Fax: 1.866.933.1692
www.ecgcme.com

None of the contents may be reproduced in any form without prior written permission from the publisher. This activity may be accessed at www.ecgcme.com.
INTRODUCTION
The 2014 American Society of Hematology (ASH) Annual Meeting, held in San Francisco, California, featured research with potential implications for the management of B-cell malignancies. Several studies explored new options for enhancing response to the current standards of care in non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma. Investigators also explored options for moving away from cytotoxic chemotherapy toward chemotherapy-free regimens in certain B-cell lymphomas. Furthermore, a number of novel immunotherapies showed promising efficacy in both untreated and relapsed disease. Highlights from the 2014 ASH Annual Meeting are summarized below.

NON-HODGKIN B-CELL LYMPHOMA
Diffuse Large B-Cell Lymphoma
R-CHOP With or Without Radiotherapy in Previously Untreated DLBCL
The role of radiotherapy (RT) following chemotherapy in patients with limited-stage diffuse large B-cell lymphoma (DLBCL) is controversial. The German UNFOLDER trial recently closed early due to an excess risk of relapse among patients with bulky DLBCL who were treated with R-CHOP without RT. In 2005, the LySA/GOELAMS Group initiated the prospective, randomized, multicenter, phase III 02-03 trial to examine whether adding RT after 4 to 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) would improve outcomes for patients with non-bulky, limited-stage, previously untreated DLBCL (abstract 393).

The trial enrolled 336 patients with non-bulky (< 7 cm), limited-stage, histologically proven CD20+ DLBCL. Patients were randomly assigned to treatment with R-CHOP plus RT (n = 151) or R-CHOP alone (n = 150). The R-CHOP schedule varied according to baseline modified International Prognostic Index (IPI) score. Patients with no adverse prognostic factors (IPI score = 0) received 4 consecutive cycles of R-CHOP, and patients with at least 1 risk factor (IPI score ≥ 1) received 6 consecutive cycles. Two additional cycles of R-CHOP followed by RT was recommended for patients who achieved less than a complete response (CR). The primary endpoint was overall survival (OS). In the current analysis, 301 patients were evaluable for response.

After 4 cycles of chemoimmunotherapy, 85% of patients assigned to R-CHOP plus the RT arm and 82% of patients assigned to R-CHOP alone achieved a CR. Among patients who achieved a partial response (PR, n = 43) after 4 cycles of R-CHOP, 37 patients (86%) received 2 additional cycles of R-CHOP plus RT, and 6 patients received additional treatment with other regimens. With the additional treatment, 40 patients achieved CR.

After a median follow-up of 51 months, there was no advantage to adding RT to R-CHOP (Table 1). In an intent-to-treat (ITT) analysis, the 5-year event-free survival (EFS) was 87% with R-CHOP alone and 91% with R-CHOP plus RT (HR, 0.55; P = 0.13). For patients in CR after 4 cycles of R-CHOP, the 5-year EFS was 89% for patients treated with R-CHOP alone, compared with 91% for patients treated with R-CHOP plus RT (HR, 0.59; P = 0.24).
Table 1. Outcomes with R-CHOP with and without radiotherapy in patients with previously untreated diffuse large B-cell lymphoma.

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>R-CHOP Plus Radiotherapy</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year EFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>87%</td>
<td>91%</td>
<td>0.55</td>
<td>0.13</td>
</tr>
<tr>
<td>Patients with CR after R-CHOP</td>
<td>89%</td>
<td>91%</td>
<td>0.59</td>
<td>0.24</td>
</tr>
<tr>
<td>5-year OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>90%</td>
<td>95%</td>
<td>0.60</td>
<td>0.32</td>
</tr>
<tr>
<td>Patients with CR after R-CHOP</td>
<td>92%</td>
<td>94%</td>
<td>0.54</td>
<td>0.31</td>
</tr>
</tbody>
</table>

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; EFS, event-free survival; CR, complete remission; OS, overall survival.

Patient outcomes were excellent and similar in both groups, with a 5-year OS of 90% for patients treated with R-CHOP and 95% for those treated with R-CHOP plus RT (HR, 0.60; P = 0.32) in the ITT analysis. Among patients with CR after R-CHOP, the 5-year OS without and with RT was 92% and 94%, respectively (HR, 0.54; P = 0.31).

In a multivariate analysis of response stratified by baseline characteristics, higher IPI scores significantly predicted worse EFS (P = 0.0015) and worse OS (P = 0.001). Twenty patients relapsed during the follow-up period, with no difference between the treatment groups in the risk of relapse (P = 0.27). The median time to relapse was 21 months. There were 16 deaths due to progressive disease (n = 9), toxicity (n = 1), other cancers (n = 2), and unrelated/unknown reasons (n = 4).

Findings from the phase III 02-03 trial suggest that RT should be reserved for the small proportion of patients with non-bulky, limited-stage DLBCL who do not achieve a CR following R-CHOP.

**DA-EPOCH-R in Previously Untreated DLBCL/BCL-U With MYC Rearrangement**

Approximately 10% of patients with DLBCL exhibit the MYC rearrangement (MYC-R), a genetic alteration associated with poor response to treatment with R-CHOP. Outcomes are especially poor for patients who harbor the “double-hit” of MYC and BCL2 translocations.⁴

In 2011, Dunleavy and colleagues showed that MYC-R did not adversely affect response to treatment with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab).⁴ In that retrospective analysis of 108 patients with previously untreated DLBCL who received DA-EPOCH-R, the 2-year EFS was 83% in patients with MYC-R-positive disease and 76% in MYC-R-negative cases (P = nonsignificant).⁴ To prospectively validate the activity of DA-EPOCH-R in aggressive MYC-R-positive B-cell lymphoma, Dunleavy and colleagues conducted a multicenter phase II trial (abstract 395).⁵

The phase II study enrolled 52 patients with previously untreated DLBCL (86%) or B-cell lymphoma-unclassifiable (BCL-U) (14%). The median age was 61 years; 71% of patients were male. Most patients had poor prognostic factors, including stage III or IV disease (73%) and IPI scores of 3-5 (65%). All patients harbored a MYC translocation confirmed by fluorescence in situ hybridization (FISH) or conventional cytogenetics. In addition, BLC2 was rearranged in 45% in cases tested by FISH (n = 31) and BLC2 was overexpressed in 56% of cases evaluated by immunohistochemistry (IHC, n = 43).
All patients received 6 cycles of DA-EPOCH-R. At a median follow-up of 14 months, progression-free survival (PFS) was 79% and the OS was 77% for all patients, suggesting clinical activity in patients with MYC-R-positive DLBCL and BCL-U (Table 2).

The effects of BCL2 abnormalities were mixed. The BCL2 rearrangement did not adversely affect PFS at 14 months (87%; \(P = 0.23\)). In contrast, patients with high BCL2 expression, as measured by IHC, had a lower PFS rate after 14 months (64%; \(P = 0.044\)). Because the combination of MYC and BCL2 translocations and the combination of MYC and BCL2 overexpression may have different biological origins and different clinical implications, additional data are needed from larger studies to clarify how these entities may affect outcomes associated with DA-EPOCH-R and other therapies.

Table 2. Outcomes with DA-EPOCH-R in patients with MYC-rearranged diffuse large B-cell lymphoma or B-cell lymphoma-unclassifiable.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DLBCL/BCL-U</th>
<th>(P) (vs all patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS at 14 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>BCL2 rearrangement</td>
<td>87%</td>
<td>0.23</td>
</tr>
<tr>
<td>BCL2 overexpression</td>
<td>64%</td>
<td>0.044</td>
</tr>
<tr>
<td>OS at 14 months (all)</td>
<td>77%</td>
<td></td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab; DLBCL, diffuse large B-cell lymphoma; BCL-U, B-cell lymphoma-unclassifiable.

Preliminary findings suggest a potential role for the DA-EPOCH-R regimen in patients with MYC-R-positive DLBCL and BCL-U, although longer-term follow-up is required. The phase II trial is ongoing and remains open to patient accrual.

Lenalidomide vs Investigator’s Choice in Relapsed/Refractory DLBCL

Diffuse large B-cell lymphoma is a biologically diverse form of NHL with 3 main molecular subtypes: germinal center B-cell (GCB), activated B-cell (ABC), and class III. While the prognosis for patients with relapsed/refractory DLBCL is poor, with fewer than 10% of patients achieving a durable remission with current salvage therapies, the prognosis for patients with ABC-DLBCL is worse than that for other DLBCL subtypes.

Lenalidomide is an immunomodulatory agent that has demonstrated single-agent activity in patients with relapsed/refractory DLBCL. In one retrospective analysis, the overall response rate (ORR) to lenalidomide was significantly higher among patients with the non-GCB subtype of DLBCL than among those with GCB-DLBCL (53% vs 9%, respectively; \(P = 0.006\)). In a phase II trial, Czuczman and colleagues compared the efficacy and safety of single-agent lenalidomide to the investigator’s choice of therapy for patients with relapsed/refractory DLBCL, including patients with the GCB, non-GCB, and ABC subtypes (abstract 628).

The phase II trial enrolled 107 patients with DLBCL relapsed/refractory to 2 or more prior therapies, including a rituximab-based chemoimmunotherapy regimen and at least 1 additional treatment or stem cell transplant (SCT). Prior to randomization, a central pathology laboratory determined DLBCL subtype (GCB vs non-GCB). Patients were stratified by DLBCL subtype and then randomly assigned to treatment
with lenalidomide (25 mg/day every 21 days) \((n = 52)\) or investigator’s choice (gemcitabine, rituximab, etoposide, or oxaliplatin monotherapy) \((n = 55)\). At the time of progression, 29 patients in the investigators choice arm crossed over to treatment with lenalidomide. The primary study endpoint was ORR. Secondary endpoints included PFS, OS, and DLBCL subtype analysis using gene expression profiling (GEP).

Baseline characteristics were similar in both treatment arms and across all DLBCL subtypes. The median age in the lenalidomide group was 69 years, and 59% of patients were male. The patients had been heavily pretreated, with 49% of patients receiving 3 or more prior anticancer therapies and 26% with prior SCT.

In the entire study cohort, lenalidomide was associated with a nonsignificant trend toward improved ORR compared with investigator’s choice \((28\% \text{ vs } 12\%; P = 0.079)\). The trend was consistent across all DLBCL subgroups.

Lenalidomide improved the median PFS compared with investigator’s choice \((13.6 \text{ weeks vs } 7.9 \text{ weeks}; HR, 0.64; P = 0.041)\). Patients with ABC DLBCL (as assessed by GEP) experienced the greatest magnitude of benefit with lenalidomide (Figure 1).

**Figure 1.** Progression-free survival of patients with relapsed or refractory DLBCL subtypes assessed by gene expression profiling (GEP) or immunohistochemistry (IHC).
There was no difference in OS between the lenalidomide and investigator’s choice arms (31.0 weeks vs 24.6 weeks; HR, 0.91; \( P = 0.673 \)). Among patients with ABC, however, there was a nonsignificant trend toward improved OS with lenalidomide relative to investigator’s choice (108 weeks vs 19 weeks; HR, 0.47; \( P = 0.144 \)).

All patients experienced at least 1 treatment-related adverse event (AE). The most common grade 3/4 hematologic AEs in the lenalidomide arm were neutropenia (43%), anemia (19%), thrombocytopenia (17%), and leukopenia (4%). Grade 3/4 non-hematologic events were infrequent in the lenalidomide arm, and included dyspnea (6%), hypokalemia (4%), fatigue (4%), and hypercalcemia (4%).

Overall, single-agent lenalidomide showed strong antitumor activity in patients with heavily pretreated DLBCL. Subtype analysis by GEP revealed a more pronounced clinical benefit from lenalidomide in the ABC subtype, which supports the potential role of GEP-guided treatment in DLBCL.

According to the study investigators, the use of lenalidomide in combination with other agents active against ABC-DLBCL may provide further clinical benefit for this poor-risk subtype of DLBCL. The phase III ROBUST trial is currently using GEP to compare the efficacy and safety of R-CHOP plus lenalidomide or placebo in patients with previously untreated ABC-DLBCL.

**Brentuximab Vedotin in CD30-Undetectable DLBCL**

Approximately 14% to 25% of DLBCL express CD30. Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated via protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE). A phase II study examined the potential role of brentuximab vedotin monotherapy in patients with CD30 levels who were visually undetectable by standard IHC (abstract 629). Preliminary results indicated a modest degree of clinical activity with brentuximab vedotin in patients with CD30-undetectable DLBCL. As expected, however, the activity was lower in patients with undetectable CD30 than in CD30-positive DLBCL, including lower ORR (31% vs 44%), shorter median duration of response (1.8 months vs 5.6 months), and shorter median PFS (1.4 months vs 4.0 months). Further studies will examine the mechanisms underlying the modest activity of brentuximab vedotin in CD30-undetectable DLBCL, which may include tumor heterogeneity, CD30 expression below the threshold of IHC sensitivity, and beneficial effects on the tumor microenvironment.

**Mantle Cell Lymphoma**

**Lenalidomide Plus Rituximab in Previously Untreated MCL**

To date, there has not been a defined gold-standard frontline therapy for patients with previously untreated mantle cell lymphoma (MCL). Conventional chemotherapy is commonly active but rarely curative, indicating a potential role for other treatment approaches. Lenalidomide is FDA-approved for the treatment of recurrent MCL, where it shows activity as a single agent and in combination with rituximab. 

In a phase II trial, Ruan and colleagues evaluated the efficacy of lenalidomide plus rituximab in patients with untreated MCL (abstract 625). The multicenter phase II study enrolled patients with untreated MCL and adequate organ function who had a tumor mass 1.5 cm or larger, low-intermediate risk MCL IPI (MIPI), or high-risk MIPI (if the patient refused or was not a candidate for chemotherapy). The treatment protocol involved 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 each 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 (15 mg) was administered daily on days 1-21 of each 28-day cycle, with rituximab given once every other cycle until disease progression. The primary study endpoint was ORR.

Thirty-eight patients were enrolled (median age 65 years; 71% male). All patients had stage III-IV disease, 89% had bone marrow involvement, and 37% of patients had elevated lactate dehydrogenase levels. MIPI scores were evenly distributed among low-, intermediate-, and high-risk groups (34%, 34%, and 32%, respectively). Symptomatic lymphadenopathy (53%), cytopenias (18%), and bulky disease (5 cm or larger) (13%) were the most common indications for treatment. At the time of analysis, 6 patients remained in treatment in the induction phase, and 23 patients remained in treatment in the maintenance phase.

The ORR was 84% in the ITT analysis (Table 3). Among the 36 evaluable patients, the ORR was 89%, with 58% of patients achieving a CR. The median time to PR was 3 months (range, 3 to 13 months), and the median time to CR was 11 months (range, 3 to 22 months).

### Table 3. Efficacy of lenalidomide plus rituximab in mantle cell lymphoma.

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of Patients</th>
<th>ITT (n = 38)</th>
<th>Evaluable (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>32</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>CR</td>
<td>21</td>
<td>55%</td>
<td>58%</td>
</tr>
<tr>
<td>PR</td>
<td>11</td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median follow-up</th>
<th>26 months (range, 5-38 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to PR</td>
<td>3 months (range, 3-13 months)</td>
</tr>
<tr>
<td>Median time to CR</td>
<td>11 months (range, 3-22 months)</td>
</tr>
</tbody>
</table>

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

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

With a median follow-up of 26 months, the 24-month PFS was 84.6%. There was no difference in PFS by baseline MIPI score ($P = 0.38$). The 24-month OS was 92.4%.

Treatment was generally well tolerated and AEs were fairly typical for lenalidomide therapy. Grade 3/4 hematologic toxicities included neutropenia (50%), thrombocytopenia (13%), and anemia (11%), whereas grade 3/4 non-hematologic toxicities included rash (26%), tumor flare (11%), fatigue (8%), and serum sickness associated with rituximab (7%).

Data from this phase II study warrant further evaluation of the non-cytotoxic combination of lenalidomide and rituximab as frontline therapy for patients with previously untreated MCL. The lenalidomide/rituximab combination may represent a potential backbone regimen for the inclusion of additional novel agents in the setting of upfront MCL treatment.
Rituximab Maintenance After HDT-ASCT in MCL: LyMa Trial

For younger patients with previously untreated MCL, a myeloablative consolidation regimen containing high-dose cytarabine followed by autologous SCT (ASCT) has emerged as the new standard of care. The Lysa group initiated the phase III LyMa study to examine the potential benefit of rituximab maintenance after high-dose cytarabine-based induction chemotherapy and ASCT in patients aged 65 years and younger with previously untreated MCL (abstract 146).

The trial included patients aged 18 to 65 years with newly diagnosed MCL. All patients received 4 courses of induction chemotherapy with R-DHAP (rituximab 375 mg/m^2, cytarabine 2 g/m^2 every 12 hours for 2 doses, dexamethasone 40 mg on days 1-4, and cisplatin 100 mg/m^2 on day 1. Patients with a very good partial response (VGPR) or better then proceeded to ASCT with rituximab (500 mg/m^2) plus BEAM (BCNU, etoposide, cytarabine, melphalan) conditioning. Patients who did not achieve a VGPR after 4 cycles of R-DHAP could receive 4 cycles of standard R-CHOP before ASCT. Patients who achieved a CR or PR after ASCT were randomly assigned to rituximab maintenance therapy (375 mg/m^2 every 2 months for 3 years) or observation. The primary study endpoint was EFS at 4 years.

From September 2008 to August 2012, 299 patients enrolled (median age, 57 years; 79% male). The distribution of MIPI scores indicated low-, intermediate-, and high-risk disease in 53%, 28%, and 20% of patients, respectively.

In the induction phase, 266 patients (89%) completed 4 cycles of R-DHAP. The CR and PR rates were 81.4% and 15.5%, respectively. Among 20 patients who received 4 additional cycles of R-CHOP, the CR and PR rates were 42% and 37%, respectively. In total, 257 patients underwent ASCT, with most patients achieving a CR (92.7%) or PR (6.9%). Of these, 239 patients were randomized to rituximab maintenance (n = 119) or observation (n = 120).

After a median follow-up of 34.3 months from randomization, the 4-year EFS was significantly higher in the rituximab maintenance arm compared to the observation arm (80.4% vs 61.8%, respectively, \( P < 0.0057 \) (Figure 2).

In an ITT analysis of the full study cohort, the 4-year PFS was 67.7% and the 4-year OS was 77.0%, suggesting durable disease control with the LyMa protocol of R-DAHP followed by R-BEAM and ASCT. The 4-year PFS also significantly favored rituximab maintenance compared to observation (82% vs 61.8%).

![Figure 2. Event-free survival in the LyMa study of rituximab maintenance vs watch-and-wait following autologous stem cell transplant in MCL.](image-url)
respectively, \( P < 0.0038 \). However, the 4-year OS was nearly identical in the rituximab maintenance and observation groups (83.4% vs 83.6%, respectively, \( P < 0.7175 \)). Rituximab maintenance was well-tolerated, with few reports of treatment-related toxicities or infectious events.

Overall, these interim findings from the phase III LyMa trial support the use of rituximab maintenance therapy after ASCT as a potential new standard of care for younger patients with MCL. The final analysis of the LyMa trial is expected in the second quarter of 2016. Ancillary studies will examine minimal residual disease and disease control as measured by FDG-PET.

**Lenalidomide Monotherapy in Relapsed/Refractory MCL**

The phase II MCL-002 (SPRINT) study demonstrated the efficacy of single-agent lenalidomide in patients with advanced relapsed/refractory MCL (abstract 626). The phase II trial was the first randomized, controlled trial to evaluate single-agent lenalidomide versus the investigator’s choice of other single-agent therapy in this patient population. In the trial, 254 patients were randomly assigned to treatment with lenalidomide (n = 170) or investigator’s choice (n = 84). Lenalidomide significantly improved median PFS compared with investigator’s choice (8.7 months vs 5.2 months, respectively; HR, 0.61; \( P = 0.004 \)). Lenalidomide compared with investigator’s choice also significantly improved ORR (40% vs 11%; \( P < 0.001 \)) and CR/CR unconfirmed (5% vs 0%; \( P < 0.043 \)). These results support the role of lenalidomide in the management of patients with advanced relapsed/refractory MCL.

**Ibrutinib Plus Rituximab in Relapsed/Refractory MCL**

Single-agent oral ibrutinib is currently approved as a treatment for patients with MCL who have received at least 1 prior therapy. Ibrutinib has been shown to induce a transient increase in circulating MCL lymphocytes during the initial phase of tumor reduction. During this so-called compartmental shift, MCL cells are driven out of their home microenvironment and into the peripheral blood circulation. Wang and colleagues hypothesized that the MCL lymphocytes, newly exposed by an ibrutinib-induced compartmental shift, might be vulnerable to intravenous treatment with rituximab (abstract 627).

The single-center phase II study examined the safety and efficacy of targeted therapy with ibrutinib plus rituximab in 50 patients with relapsed CD20-positive MCL. All patients (median age, 67 years; 76% male) had good performance status and organ function. Patients received a median of 3 prior lines of therapy (range, 1 to 9). Common previous therapies included hyper-CVAD (64%), bortezomib (36%), and lenalidomide (20%). Most patients had low- (44%) or intermediate-risk (44%) MIPI scores.

All patients received oral ibrutinib 560 mg daily. Rituximab (375 mg/m\(^2\)) was given in 4 weekly loading doses during the first 28-day cycle, followed by 1 dose in cycles 3 to 8. After cycle 8, patients continued rituximab therapy with 1 dose every other cycle for up to 2 years. Ibrutinib was given continuously until disease progression or treatment intolerance.

Among evaluable patients (n = 46), the ORR was 88% and included CR for 40% of patients (Figure 3). A lower level (< 50%) of the Ki-67 proliferation marker was a strong predictor of response. Patients with lower Ki67 levels were significantly more likely than those with higher levels (≥ 50%) to achieve an overall response (100% vs 50%, respectively; \( P = 0.0001 \)) or a CR (56% vs 1%; \( P = 0.006 \)).
With a median follow-up of 11 months, the median PFS had not been reached in the overall study cohort. In the analysis of PFS by baseline Ki-67 expression, the median PFS was not reached for patients with a Ki-67 index < 50%, compared with 13.6 months among patients with a Ki-67 index ≥ 50% (P = 0.0001).

Treatment with ibrutinib and rituximab was well tolerated. Grade 1 hematologic toxicities included anemia (30%) and thrombocytopenia (25%). Treatment-emergent non-hematologic toxicities in more than 15% of patients included fatigue, diarrhea, myalgia, and dyspnea. Grade 3 atrial fibrillation occurred in 6 patients, all of whom had cardiovascular risk factors or a history of cardiovascular disease.

Based on these promising preliminary results of the ongoing phase II trial, ibrutinib plus rituximab is a highly efficacious and well-tolerated combination in patients with relapsed MCL. Patients with Ki67 < 50% appear especially likely to benefit from the combination, with an ORR of 100%.

**Investigational Agents and Strategies in B-Cell Lymphomas**

**Nivolumab in B-Cell Lymphomas**

Programmed death 1 (PD-1) is an immune-checkpoint receptor that interacts with its ligands, PD-L1 and PD-L2, to block T cell activation and attenuate the host antitumor response. Nivolumab is a fully human monoclonal antibody that blocks anti-PD-1 activity, potentiates T cell activity, and restores antitumor immunity in multiple solid tumors types. In a phase I dose-escalation trial, Lesokhin and colleagues evaluated the safety and efficacy of nivolumab in patients with relapsed or refractory B-cell lymphoma and other hematologic malignancies (abstract 291).

The trial included 105 patients with relapsed or refractory B-cell lymphoma (n = 31), multiple myeloma (n = 27), T-cell lymphoma (n = 23), Hodgkin lymphoma (n = 23), and chronic myelogenous leukemia (n = 1). Patients were heavily pretreated, with two-thirds of patients having received 3 or more prior therapies. Patients had no history of stem cell or organ allografting, immune checkpoint blockade, or autoimmune disease.

Patients received nivolumab (1 mg/kg or 3 mg/kg) on weeks 1 and 4, and then every 2 weeks for up to 2 years. The primary study endpoint was safety. Safety and efficacy outcomes for patients with Hodgkin lymphoma were reported separately (see nivolumab in relapsed/refractory classic Hodgkin lymphoma, abstract 289).

Among 82 patients evaluable for safety, 51 (62%) reported AEs of any grade. Treatment-related AEs occurred with similar incidence and severity regardless of tumor type.
The most common AEs included fatigue (13%), pneumonitis (11%), pruritus (9%), rash (9%), pyrexia (7%), and anemia, diarrhea, decreased appetite, and hypocalcemia in 6% of patients each. The majority of pneumonitis cases were mild, with no clear association between pneumonitis and prior radiation (n = 28) or prior treatment with brentuximab (n = 9) or gemcitabine. Grade 3 AEs included anemia (4%), leukopenia (2%), decrease lymphocyte count (2%), and decreased platelet count (2%). Grade 4 events included 1 case each of rash and sepsis. There were 2 grade 5 events, including 1 case of pneumonitis and 1 case of acute respiratory distress syndrome.

Responses were seen across multiple tumor types (Table 4). The ORR was 40% in follicular lymphoma (FL), 40% in peripheral T-cell lymphoma, 36% in DLBCL, and 17% in cutaneous T-cell lymphoma. Two patients achieved a CR, including 1 patient (10%) with FL and 1 patient (9%) with DLBCL.

Table 4. Best response to nivolumab by tumor type.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphoma (n = 29)</td>
<td>28%</td>
<td>7%</td>
<td>21%</td>
<td>48%</td>
</tr>
<tr>
<td>FL (n = 10)</td>
<td>40%</td>
<td>10%</td>
<td>30%</td>
<td>60%</td>
</tr>
<tr>
<td>DLBCL (n = 11)</td>
<td>36%</td>
<td>9%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>T-cell lymphoma (n = 23)</td>
<td>17%</td>
<td>0%</td>
<td>17%</td>
<td>43%</td>
</tr>
<tr>
<td>Mycosis fungoides (n = 13)</td>
<td>15%</td>
<td>0%</td>
<td>15%</td>
<td>69%</td>
</tr>
<tr>
<td>PTCL (n = 5)</td>
<td>40%</td>
<td>0%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>Multiple myeloma (n = 27)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>67%</td>
</tr>
<tr>
<td>PMBCL (n = 2)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

No patients with multiple myeloma had an objective response, although 67% achieved stable disease. Two patients had primary mediastinal B-cell lymphoma, and both patients achieved stable disease in the absence of an objective response.

Based on these phase I results showing promising activity in patients with B-cell lymphoma, multicenter phase II trials of nivolumab are currently underway in patients with FL and DLBCL.

**Anti-CD20 Targeted Therapy Plus PI3K-Delta Inhibition**

Ublituximab (TG-1101) is an investigational anti-CD20 antibody that demonstrates stronger antibody-dependent cell-mediated cytotoxicity (ADCC) compared to the anti-CD20 antibody rituximab based on enhanced affinity to a unique epitope on the CD20 antigen. TGR-1202 is an oral, once-daily phosphatidylinositol 3-kinase (PI3K)-delta inhibitor whose side effect profile does not appear to include the hepatotoxicity commonly observed with other PI3K-delta inhibitors. In a phase I study, Lunning and colleagues presented early data indicating clinical activity with the combination of ublituximab plus TGR-1202 in patients with heavily pretreated, relapsed or refractory NHL or chronic lymphocytic leukemia (CLL, abstract 801).21
The phase I dose-escalation study enrolled 21 patients (median age, 64 years) with CLL or small lymphocytic lymphoma (SLL; n = 7), DLBCL (n = 7), FL (n = 5), or Richter’s transformation (n = 1). Patients had received a median of 3 prior lines of therapy. All patients were treated with ublituximab (600 mg to 900 mg) on days 1, 8, and 15 of cycles 1 and 2, followed by maintenance therapy. TGR-1202 was given at 800 mg once daily in the first dosing cohort and increased in subsequent cohorts. The primary endpoints were safety and dose limiting toxicity (DLT).

One patient with CLL experienced a DLT (neutropenia) after treatment with ublituximab 600 mg plus TGR-1202 800 mg. No other DLTs were reported. Adverse events were generally mild and included infusion-related reactions on day 1 of treatment (48%), neutropenia (38%), diarrhea (29%), and nausea (29%). No patients experienced TGR-1202-related hepatotoxicity.

Among 15 patients evaluable for response, 80% showed a reduction in tumor burden at the first efficacy assessment. The ORR was 40% for all patients, with most of the responses occurring in patients with CLL/SLL (ORR, 80%) or DLBCL (ORR, 40%). Enrollment for the phase I study is ongoing.

**Dual PI3K-Delta and PI3K-Gamma Inhibition in Relapsed/Refractory B-Cell Lymphoma**

Duvelisib is an investigational, oral, once-daily dual inhibitor of PI3K-delta and PI3K-gamma. By targeting both the delta and gamma isoforms of the PI3K family of kinases, duvelisib inhibits the survival of malignant B-cell and T-cells and disrupts the tumor microenvironment. New data from an ongoing phase I trial suggested clinical activity in patients with relapsed/refractory indolent NHL and other advanced hematologic malignancies (abstract 802).

The phase I trial enrolled 36 patients with relapsed/refractory FL, marginal zone lymphoma and Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma. All patients were treated with duvelisib (15 mg bid to 75 mg bid) given continuously in 28-day cycles. Half of the patients (n = 18) were treated with duvelisib 25 mg bid, which was the dose selected for further development in phase II and III trials. The primary study endpoint was safety.

In the 25 mg bid-dosing cohort, 7 patients (37%) discontinued treatment due to AEs, and 4 patients (21%) discontinued due to disease progression. The median duration of duvelisib treatment was 11.8 months.

Responses were observed across all dosing groups. The ORR was 72% among 18 evaluable patients treated with duvelisib 25 mg bid. This included 6 patients (33%) who achieved a CR. The median time to response was 1.8 months. Moreover, the response rates were similar across all tumor types. For example, the ORR was 69% and the CR as 38% among patients with FL.

At 24 months, the PFS was 69% and the OS was 89%. The median PFS and median OS had not been reached.

Duvelisib 25 mg bid was well tolerated with an acceptable safety profile. The most common grade 3 AEs in this dosing cohort were diarrhea (32%), increased ALT or ALT levels (32%), neutropenia (11%), and pneumonia (11%). Grade 4 AEs included neutropenia (11%), pneumonia (5%), and increased ALT or AST levels (5%). The liver enzyme elevations were the most common AEs leading to treatment discontinuation (11%).
Based on early evidence of clinical activity in indolent NHL, phase II and III trials evaluating duvelisib 25 mg bid given as monotherapy or in combination with rituximab are currently underway in this patient population.

**CAR T-Cells in Relapsed/Refractory Aggressive B-Cell Lymphoma**

High-dose therapy followed by autologous stem cell transplantation (HDT-ASCT) is an established standard of care for patients with relapsed/refractory DLBCL. Despite the possibility of cure for many of these patients, approximately half will relapse following transplantation. New therapies are needed to improve patient prognosis following HDT-ASCT.

Chimeric antigen receptor (CAR) T-cell therapy is an emerging immunotherapeutic approach in which the patient’s own T-cells are isolated, redirected with a synthetic receptor to recognize a tumor-specific antigen or protein, and reinfused into the patient. Treatment with autologous T-cells expressing the 19-28z CAR specific to the CD19 antigen has shown activity in patients with relapsed/refractory B-cell acute lymphoblastic leukemia.²³

Researchers are evaluating a range of methods to enhance tumor susceptibility to CAR-mediated T-cell killing.²⁴ Sauter and colleagues hypothesized that myeloablative chemotherapy and ASCT may prime the tumor microenvironment for optimal response to CAR T-cell therapy. HDT and ASCT briefly eliminate regulatory T-cells and myeloid-derived suppressor cells, allowing for the maximum expansion of 19-28z CAR T-cells. To test this hypothesis, investigators initiated a phase I trial of 19-28z CAR T-cell therapy administered immediately following HDT-ASCT in relapsed/refractory aggressive B-cell NHL (abstract 677).²⁵

The ongoing phase I trial is enrolling patients with positron emission tomography (PET)-positive disease following 2 or more cycles of salvage chemotherapy and/or bone marrow involvement at the time of relapse or refractory disease. At the time of the analysis, 7 patients (median age, 64 years) had been treated with 19-28z CAR T-cells. Patients were heavily pretreated, having received a median of 2 prior lines of therapy (range, 2 to 4 lines).

Patients underwent apheresis for T cells and were admitted to the bone marrow transplant service for BEAM-conditioned HDT followed by ASCT. After ASCT on day 0, patients received pegfilgrastim on day 1 and 19-28z CAR T-cell therapy split on days 2 and 3. The primary study objective was to assess the maximum tolerated dose (MTD) of the 19-28z CAR T-cell infusion.

All patients engrafted neutrophils by day 9-10 after transplant and achieved a PET-negative CR. No autoimmune complications were observed.

After a median follow-up of 9 months, the PFS was 100%. By comparison, the estimated 1-year PFS in this historically poor-risk patient group is 40-50%.

Treatment with 19-28z CAR T-cells (5 x 10⁶/kg) was safe, with no dose-limiting toxicities (DLTs) in 6 patients. One patient developed cytokine release syndrome, which included fever, hypotension, and neurologic sequelae, at the higher dose level of 19-28z CAR T-cells (1 x 10⁷/kg).

Based on these promising preliminary findings, the phase I study is continuing patient enrollment at the lower dose level for 19-28z CAR T-cells (5 x 10⁶/kg).
Utility of Interim PET Scans in Aggressive Lymphomas: PETAL Trial

Positron emission tomography imaging identifies areas of increased glucose uptake and metabolism, indicating the presence of active disease in patients with aggressive lymphoma. Pre- and post-treatment PET scans are routine in the management of aggressive lymphomas, but the potential role of interim PET scanning during treatment is not well characterized. The randomized PETAL trial examined the value of interim PET imaging after the first 2 cycles of R-CHOP in this patient population (abstract 391).

The trial enrolled 926 patients with newly diagnosed aggressive B-cell or T-cell lymphoma who were starting treatment with R-CHOP and showed active disease on baseline PET imaging. Patients with cerebral, Burkitt, and lymphoblastic lymphomas were not eligible for the trial.

All patients with aggressive B-cell lymphoma began treatment with R-CHOP and received an interim PET scan within 3 weeks of completing the second cycle of chemoimmunotherapy. A favorable PET response was defined as a reduction of > 66% in the standardized uptake value (SUV), a quantitative measure of (18) F-FDG metabolism, compared to the baseline PET scan.

After 2 cycles of R-CHOP, 107 patients (13%) had an unfavorable interim PET scan and were randomly assigned to treatment with 6 additional cycles of R-CHOP or a more intensive regimen that included hyperfractionated alkylating agents and high doses of methotrexate and cytarabine. Patients with a favorable interim PET scan (n = 746; 87%) were randomly assigned to treatment with 4 additional cycles of R-CHOP with or without 2 additional courses of rituximab. The primary study endpoint was time to treatment failure (TTF).

Among patients with an unfavorable interim PET scan, there was no advantage to switching to a more intensive cytotoxic regimen. Patients who switched did not have a significant increase in the CR rate compared with those who continued on R-CHOP (50% vs 31%; P = 0.10). In addition, switching to more intensive treatment had no effect on TTF (HR, 1.6; 95% CI: 0.9-2.7) or OS (HR, 1.0; 95% CI: 0.5-2.1).

Switching to a more aggressive cytotoxic regimen significantly increased the risk of grade 3/4 AEs. Compared with patients who remained on R-CHOP with or without additional rituximab, patients who switched to more aggressive therapy were significantly more likely to report grade 3/4 leukopenia (80%; P = 0.0221 vs the other treatment arms), thrombocytopenia (57%; P < 0.0001), infection (46%; P = 0.0086), and mucositis (38%; P = 0.0034).

The study also found no advantage to adding 2 additional courses of rituximab after 6 cycles of R-CHOP in patients with a favorable interim PET scan. Compared with 6 cycles of R-CHOP alone, 6 cycles of R-CHOP plus 2 cycles of rituximab did not prolong the median TTF (HR, 1.2; 95% CI: 0.8-2.1).

The interim PET scan was highly predictive of patient outcomes. The 2-year probability of freedom from treatment failure was 79% among patients with a favorable interim PET scan, compared with 47% for those with an unfavorable interim scan (HR, 3.4; 95% CI: 2.6-4.6; P < 0.0001). A favorable interim PET scan result was also highly predictive of better OS (HR, 3.9; P < 0.0001).

In summary, quantitative interim PET analysis predicted outcome in patients with aggressive lymphomas. However, findings from the PETAL trial do not support a change in the standard cytotoxic regimen for poor interim PET responders, as switching to a more aggressive regimen did not improve response or survival outcomes for these patients.
HODGKIN LYMPHOMA
Frontline Therapy

Early Consolidation With Brentuximab Vedotin Following ASCT: AETHERA Trial

Approximately half of patients with Hodgkin lymphoma are cured with high-dose chemotherapy and ASCT. For those who remain at risk for progression, however, no new therapies have been able to demonstrate improved prognosis following ASCT over the past 20 years.

Brentuximab vedotin is a CD30-targeted antibody that is currently FDA-approved for the treatment of patients with Hodgkin lymphoma after failure of ASCT, or after failure of 2 or more combination chemotherapy regimens in patients who are not candidates for transplant. The phase III AETHERA trial evaluated whether early consolidation with brentuximab vedotin could prevent disease progression following ASCT in patients with relapsed and difficult-to-treat Hodgkin lymphoma (abstract 673).  

The multicenter AETHERA trial included 329 patients with Hodgkin lymphoma. All patients were at high risk for post-transplant disease progression based on 1 of 3 eligibility criteria: refractory to frontline therapy, relapsed within 12 months of frontline therapy, or relapsed 12 months or longer after frontline therapy with extranodal disease. Patients received salvage therapy and achieved remission or stable, non-progressing disease at the time of transplant.

Patients were randomly assigned to treatment with best supportive care plus 16 cycles of brentuximab vedotin 1.8 mg/kg every 3 weeks (n = 165) or placebo (n = 164) for up to 1 year. Patients who progressed on placebo were eligible to leave the trial and receive brentuximab vedotin as part of another study. The primary study endpoint was PFS by independent review. Baseline characteristics were similar in both treatment groups. The median age in the brentuximab vedotin group was 33 years (range, 18 to 71 years); 46% of patients were male. The majority of patients (60%) were refractory to frontline therapy. Approximately 43% of patients had received 2 or more prior systemic salvage therapies.

The median follow-up was 24.4 months. Brentuximab vedotin was associated with a significant improvement in PFS at 2 years compared with placebo as determined by investigator review (65% vs 45%; HR = 0.50, 95% CI: 0.36-0.70). An independent review of PFS showed a similar advantage with brentuximab vedotin compared with placebo (63% vs 51%; HR = 0.57, 95% CI: 0.40-0.81, P = 0.001). A subgroup analysis of PFS favored treatment with brentuximab vedotin across all patient subgroups.

There was no difference in OS between the brentuximab vedotin and placebo groups (P = 0.62). However, the assessment of OS was confounded by the fact that 85% of patients in the placebo group crossed over to brentuximab vedotin. In addition, other patients underwent allogeneic SCT and/or received subsequent salvage therapy at the time of progression.

The most common AEs in the brentuximab vedotin arm were peripheral sensory neuropathy (56%), neutropenia (35%), upper respiratory tract infection (26%), fatigue (24%), peripheral motor neuropathy (23%), nausea (22%), cough (21%), and diarrhea (20%). Most AEs were manageable through dose reductions or delays, although 33% of patients discontinued treatment with brentuximab vedotin due to AEs. Two deaths occurred within 40 days of brentuximab vedotin dosing.
The AETHERA trial is the first phase III trial in the lymphoma population to demonstrate that maintenance therapy after ASCT improves PFS. According to the study authors, maintenance therapy with brentuximab vedotin may become the standard of care for patients with Hodgkin lymphoma who undergo ASCT.

**Frontline Brentuximab Vedotin in Older Patients**

Brentuximab vedotin is also under evaluation as a single agent and in combination with dacarbazine in patients aged 60 years or older with previously untreated Hodgkin lymphoma (abstract 294). Forero-Torres and colleagues presented interim findings from an ongoing phase II trial showing strong antitumor activity with brentuximab vedotin in this difficult-to-treat patient population.

The phase II trial enrolled patients aged 60 years or older with treatment-naïve classic Hodgkin lymphoma who were ineligible for, or declined, conventional frontline combination therapy. Patients were randomly assigned to treatment with brentuximab vedotin as a single agent (n = 27) or in combination with dacarbazine (n = 18). All patients received brentuximab vedotin 1.8 mg/kg every 3 weeks for up to 16 cycles, or more cycles for patients achieving stable disease or better. Patients in the combination group also received dacarbazine 375 mg/m² on day 1 for cycles 1-12 only. The primary endpoint was ORR.

Among patients treated with single-agent brentuximab vedotin, the median patient age was 78 years (range, 64-92 years; 52% male). The majority of patients had late-stage disease; the stages at diagnosis were I (4%), II (33%), III (26%), and IV (37%). Most patients also had mild (26%) or moderate (44%) renal impairment.

All patients (100%) achieved tumor reduction with brentuximab vedotin monotherapy (Figure 4). The ORR was 93%, including a CR in 70% of patients. The median duration of response was 9.1 months, and the median PFS was 10.5 months.

**Figure 4. Tumor reduction and response to (A) brentuximab vedotin (BV) monotherapy and (B) BV in combination with dacarbazine... in patients aged 60 years or older with treatment-naïve classic Hodgkin lymphoma.**

![Figure 4](image)

Treatment-related AEs in the brentuximab vedotin monotherapy group included peripheral sensory neuropathy (n = 7), peripheral motor neuropathy (n = 2), rash (n = 2), and 1 case each of anemia, aspartate aminotransferase (AST) elevation, asthenia, neutropenia, orthostatic hypotension, generalized rash, and maculopapular rash. Twelve patients discontinued treatment due to AEs.
Patients treated with brentuximab vedotin plus dacarbazine had similar baseline demographics. The median patient age was 72.5 years (range, 62 to 87 years; 72% male). Most patients (56%) had normal renal function; others had mild (28%), moderate (6%), or severe (11%) renal impairment.

Among 14 patients evaluable for efficacy after treatment with combination therapy, all patients (100%) achieved tumor reduction with brentuximab vedotin plus dacarbazine. The ORR was 93%. At the time of the analysis, 83% of patients remained on treatment with combination therapy.

The combination of brentuximab vedotin plus dacarbazine was well tolerated. The most common grade 1-2 AEs were peripheral sensory neuropathy (33%), nausea (33%), diarrhea (28%), constipation (28%), fatigue (22%), alopecia (22%), arthralgia (22%), and headache (22%). One patient developed grade 3 hyperglycemia, and 2 serious AEs included colitis and hypotension.

Preliminary results from this phase II trial show robust clinical activity with frontline brentuximab vedotin alone and in combination with dacarbazine in older patients with Hodgkin lymphoma. A third arm of the ongoing trial will evaluate brentuximab vedotin plus bendamustine with the goal of identifying the optimal frontline regimen for this patient population.

Brentuximab vedotin is also under evaluation in combination with other agents in the frontline setting, including ABVD and AVD (abstract 292). Data from a long-term study of brentuximab vedotin in combination with ABVD or AVD demonstrated an unacceptably high rate of pulmonary toxicity (44%) in patients who received bleomycin, although the AVD regimen was safe and active in combination with brentuximab vedotin. The phase III ECHELON-1 study will compare AVD plus brentuximab vedotin with ABVD in patients with newly diagnosed, advanced-stage classical Hodgkin lymphoma.

Relapsed/Refractory Disease

Pembrolizumab in Relapsed/Refractory Classic Hodgkin Lymphoma

Pembrolizumab is a monoclonal antibody that targets PD-1 to block its interaction with the PD-L1 and PD-L2 ligands. As a result, pembrolizumab disarms the PD-1-mediated immune checkpoint system and stimulates a potent antitumor immune response. In September 2014, pembrolizumab became the first PD-1 inhibitor to gain FDA approval for the treatment of patients with unresectable or metastatic melanoma whose disease has progressed following prior therapies. The agent is currently under evaluation in a range of other tumor types.

The phase Ib KEYNOTE-013 trial evaluated the safety and efficacy of pembrolizumab in patients with heavily pretreated classic Hodgkin lymphoma (abstract 290). The trial included 31 patients (median age, 32 years) with relapsed or refractory classic Hodgkin lymphoma who had been treated with a median of 4 prior therapies. In addition, all patients had failed prior treatment with brentuximab vedotin, and 69% had relapsed following prior ASCT.

All patients received pembrolizumab (10 mg/kg) administered intravenously every 2 weeks. Treatment response was assessed with imaging beginning at week 12. The primary study endpoint was CR.
Twenty-nine patients were included in the analysis presented. The median age of patients was 32 years and the median number of prior therapies was 4. All patients had prior brentuximab failure and 20% had prior transplant failure. The researchers first assessed response with imaging at week 12. The median duration of follow-up was 153 days.

The clinical benefit rate (CBR), indicating response or stable disease, was 86% among 29 evaluable patients (Table 5). The ORR was 66%, including 21% of patients who achieved CR. The median time to response was 12 weeks. The median duration of response was not reached, with responses ongoing for 17 of 19 responding patients (89%).

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 29)</th>
<th>Transplant ineligible or refused (n = 9)</th>
<th>Transplant failure (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>66%</td>
<td>44%</td>
<td>75%</td>
</tr>
<tr>
<td>CR</td>
<td>21%</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>PR</td>
<td>45%</td>
<td>22%</td>
<td>55%</td>
</tr>
<tr>
<td>SD</td>
<td>21%</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>CBR</td>
<td>86%</td>
<td>78%</td>
<td>90%</td>
</tr>
<tr>
<td>PD</td>
<td>14%</td>
<td>22%</td>
<td>10%</td>
</tr>
</tbody>
</table>

ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; CBR, clinical benefit rate; PD, progressive disease.

There were no grade 4 AEs and no treatment-related deaths with pembrolizumab treatment. Sixteen patients (55%) reported treatment-related AEs, although most were mild. The most common AEs were hypothyroidism (10%) and pneumonitis (10%). Three patients (10%) reported a total of 4 grade 3 AEs (axillary pain, hypoxia, joint swelling, and pneumonitis).

Chromosome 9p24.1 amplification is a structural alteration that is commonly found in patients with classical Hodgkin lymphoma and results in the overexpression of PD-L1 and PD-L2. Among 10 patient samples that were evaluable for PD-L1 expression, 100% were PD-L1 positive. These data indicate that the PD-1 signaling pathway is active in classical Hodgkin lymphoma and may be especially vulnerable to PD-1 inhibition.

**Nivolumab in Relapsed/Refractory Classical Hodgkin Lymphoma**

Patients with relapsed/refractory classical Hodgkin lymphoma were included as part of a phase I dose-escalation study of nivolumab in lymphoma and multiple myeloma (see nivolumab in B-cell lymphomas, abstract 291). However, due to the potential vulnerability of classical Hodgkin lymphoma to PD-1 blockade, these patients were assessed as an independent cohort (abstract 289). The safety and efficacy results in the Hodgkin lymphoma cohort were also published simultaneously in the *New England Journal of Medicine*.

The classical Hodgkin lymphoma cohort included 23 patients who failed aggressive frontline therapy, including treatment with brentuximab vedotin and/or ASCT. More than one-third of patients (35%) had received 6 or more prior systemic therapies. The median patient age was 35 years. Patients received nivolumab (3 mg/kg) by IV infusion every 2 weeks until disease progression or excessive toxicity. The primary study objective was safety. Secondary endpoints included ORR, PFS, and expression of immunomodulatory proteins in tumor biopsies.
All patients achieved a reduction in tumor burden (Figure 5). The ORR was 87% and included a CR in 4 patients (17%) and a PR in 16 patients (70%). Three additional patients (13%) achieved stable disease. No patient experienced disease progression.

Among responding patients, 60% of responses occurred in the first 8 weeks of treatment with nivolumab. The 24-week PFS was 86%. At the time of the analysis, 11 patients (48%) had ongoing responses. Among 12 patients who discontinued treatment, 6 patients (26%) went on to SCT, 4 patients (17%) had disease progression, and 2 patients (9%) discontinued due to AEs.

An analysis of cytogenetic abnormalities found 9p24.1 amplification with PD-L1/PD-L2 copy gain in 100% of 10 tumor samples. Furthermore, an immunohistochemistry analysis was positive for PD-L1, PD-L2, and pSTAT3 expression in 100% of Hodgkin RS cells. These findings support the hypothesis that classical Hodgkin lymphoma has a genetically driven dependence on the PD-1 signaling pathway and a vulnerability to PD-1 blockade.

Nivolumab administration was safe in this patient cohort. The most common AEs of any grade (78%) included rash (22%), decreased platelet count (17%), and diarrhea, nausea, pruritus, fatigue, and pyrexia (13% each). Five patients (22%) each reported 1 treatment-related grade 3 AEs, including decreased lymphocyte count, increase lipase, stomatitis, myelodysplastic syndrome, and pancreatitis. No drug-related grade 4 or grade 5 AEs were reported.

In summary, nivolumab demonstrated substantial anti-cancer activity in patients with relapsed or refractory classic Hodgkin’s lymphoma, including a reduction in tumor burden at 1 or more efficacy assessments in 100% of patients. As a result of these promising phase I data, the FDA has granted nivolumab breakthrough therapy designation in Hodgkin lymphoma. A phase II trial is currently evaluating nivolumab in patients with Hodgkin lymphoma who relapsed after ASCT.

CONCLUSION
The 2014 ASH Annual Meeting provided a wealth of new insights with potential implications for clinical practice. Several trials examined strategies for enhancing response to standard cytotoxic therapy, as well as emerging options for chemotherapy-free regimens in patients with DLBCL, MCL, and other B-cell lymphomas. Investigators also addressed important questions regarding the optimal use of frontline brentuximab vedotin in Hodgkin lymphoma, including the role of early consolidation after ASCT and the safety and efficacy of treatment in older patients.

Immunotherapies with novel mechanisms of action, such as CART-cell therapy and agents that target the PI3K and PD-1 signaling pathways, continue to show promise in the treatment of B-cell malignancies. Genetic and molecular analyses provided support for the use of PD-1 blockade in classic Hodgkin
lymphoma in particular, due to a common chromosomal abnormality in this tumor type that confers vulnerability to PD-1-targeted therapy. Future studies will clarify the role of new and emerging therapies for patients across the spectrum of B-cell lymphomas.

The 2015 ASH Annual Meeting will be held December 5-8, 2015, in Orlando, Florida. Additional information can be obtained at http://www.hematology.org/Annual-Meeting/Archive.aspx.

REFERENCES


