A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 13th International Conference on Malignant Lymphoma
A Review of Selected Presentations From the 13th International Conference on Malignant Lymphoma • June 17-20, 2015 • Lugano, Switzerland

Special Reporting on:
• Preliminary Efficacy and Safety of Brentuximab Vedotin and AVD Chemotherapy Followed by Involved-Site Radiotherapy in Early Stage, Unfavorable Risk Hodgkin Lymphoma
• Response-Adapted Therapy Based on Interim FDG-PET Scans in Advanced Hodgkin Lymphoma: First Analysis of the Safety of Deescalation and Efficacy of Escalation in the International RATHL Study (CRUK/07/033)
• Sequential Brentuximab Vedotin and AVD for Older Hodgkin Lymphoma Patients: Initial Results From a Phase 2 Multicenter Study
• Addition of Thiopeta and Rituximab to Antimetabolites Significantly Improves Outcome in Primary CNS Lymphoma: First Randomization of the IELSG32 Trial
• Analysis of Primary-Refractory Hodgkin Lymphoma Pts in a Randomized, Placebo-Controlled Study of Brentuximab Vedotin Consolidation After Autologous Stem Cell Transplant
• Early FDG-PET Adapted Treatment Improves the Outcome of Early FDG-PET-Positive Patients With Stages I/II Hodgkin Lymphoma (HL): Final Results of the Randomized Intergroup EORTC/LYSA/FIL H10 Trial
• Brentuximab Vedotin Plus AVD for Non-Bulky Limited Stage Classical Hodgkin Lymphoma: A Phase 2 Trial
• Rituximab, Bendamustine and Cytarabine (RBAC500) as Induction Therapy in Elderly Patients With Mantle Cell Lymphoma: A Phase 2 Study From the Fondazione Italiana Linfomi

PLUS Meeting Abstract Summaries

With Expert Commentary by:
Craig H. Moskowitz, MD
Steven A. Greenberg Chair in Lymphoma Research
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

ON THE WEB: hematologyandoncology.net

Indexed through the National Library of Medicine (PubMed/MEDLINE), PubMed Central (PMC), and EMBASE
CD30 plays a dual role in HRS cell survival: CD30 stimulates NF-κB signaling critical to HRS cell survival, and it triggers CD30L-expressing bystander cells in the cHL tumor microenvironment to support HRS cell survival and proliferation.\textsuperscript{1-10}

CD30 activates both the canonical and alternative NF-κB pathways in anaplastic large cell lymphoma cells.\textsuperscript{7} CD30 activates both the classical and alternative NF-κB pathways in anaplastic large cell lymphoma cells.\textsuperscript{6} CD30-MEDIATED CROSSTALK PROMOTES TUMOR PROGRESSION\textsuperscript{1}

CD30 IS CRITICAL TO MALIGNANT HRS CELL SURVIVAL\textsuperscript{2}

CD30 plays a dual role in HRS cell survival: CD30 stimulates NF-κB signaling critical to HRS cell survival, and it triggers CD30L-expressing bystander cells in the cHL tumor microenvironment to support HRS cell survival and proliferation.1-10

CD30-MEDIATED CROSSTALK PROMOTES TUMOR PROGRESSION1

HRS cells extend actin- and tubulin-based protrusions out into the cHL tumor microenvironment; this allows CD30-dependent crosstalk between HRS cells and surrounding bystander cells, which include T-cells, mast cells, and eosinophils.1,3,11,12 The bidirectional signaling via CD30 and CD30L is proposed to be critical to establishing cHL tumor growth and HRS cell proliferation.1,5 Disrupting this crosstalk would deprive HRS cells of important pro-survival signals, making CD30 an essential target in disease elimination.3

Learn more and DOWNLOAD informational slides at ScienceofCD30.com
Preliminary Efficacy and Safety of Brentuximab Vedotin and AVD Chemotherapy Followed by Involved-Site Radiotherapy in Early Stage, Unfavorable Risk Hodgkin Lymphoma

Two types of standard therapy exist for unfavorable early-stage Hodgkin lymphoma: 4 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and involved field radiotherapy at 30 Gy, or 2 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) followed by 2 cycles of ABVD plus involved field radiotherapy at 20 Gy. However, the ABVD regimen fails in as many as 20% of patients, and combining ABVD with BEACOPP increases toxicity. Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE). CD30 is expressed on Hodgkin lymphoma cells but not on most noncancerous cells, thereby limiting the toxicity associated with this therapy. After brentuximab vedotin binds to CD30, the MMAE moiety is released, which disrupts microtubule assembly and leads to apoptosis. Based on its efficacy and safety in patients with relapsed or refractory CD30-positive leukemia or lymphoma, brentuximab vedotin was granted accelerated approval by the US Food and Drug Administration in 2011.

Dr Craig Moskowitz presented preliminary results of a study that investigated the addition of brentuximab vedotin to doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy followed by 30 Gy involved site radiation therapy (ISRT) in patients with early-stage Hodgkin lymphoma. The primary objective of the study was to evaluate safety, with a focus on pulmonary toxicity. Secondary objectives included evaluating the prognostic capability of interim $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging and assessing efficacy. All patients had stage I or II classical Hodgkin lymphoma, plus at least 1 of the following risk factors: a bulky mediastinal mass; an erythrocyte sedimentation rate (ESR) of at least 50 mm/hour in the absence of B symptoms or an ESR of at least 30 mm/hour in the presence of B symptoms; extranodal involvement; 3 or more sites of involved lymph nodes, as defined by the German Hodgkin Study Group; or infradiaphragmatic disease.

Treatment consisted of brentuximab vedotin (1.2 mg/m$^2$) plus doxorubicin (25 mg/m$^2$), vinblastine (6 mg/m$^2$), and dacarbazine (375 mg/m$^2$). Patients underwent PET-computed tomography (CT) imaging after treatment cycles 2 and 4 and were evaluated based on Deauville scoring. Patients with a Deauville score of 1 to 3 received ISRT (30 Gy). Patients with a Deauville score of 4 or 5 underwent biopsy for the evaluation of active Hodgkin lymphoma. Patients with a negative biopsy received ISRT (30 Gy), and those with active disease were removed from the study. The 28 patients who received treatment had a median age of 31 years (range, 18-59 years), and 53% were male. All of the patients had stage II Hodgkin lymphoma, and 11 patients (37%) had stage IIB bulky disease or extranodal involvement, which was classified as advanced stage based on German Hodgkin Study Group criteria. Unfavorable risk factors included B symptoms (47%), ESR of at least 50 without B symptoms or at least 30 with B symptoms (67%), at least 3 involved nodal sites (67%), extranodal involvement (47%), and bulky disease measuring at least 10 cm (47%).

Three patients had grade 3 peripheral neuropathy, and one had grade 3 hypertension. Patients received mandatory prophylactic treatment with granulocyte-colony stimulating factor, and 5 patients experienced grade 3 febrile neutropenia. Pulmonary function was assessed based on the percent change in carbon monoxide diffusing capacity. Dr Moskowitz observed that there was no clinically meaningful correlation between pulmonary dysfunction and brentuximab vedotin treatment or radiotherapy (Figure 1).

After the second treatment cycle, FDG-PET results were negative in 89% of patients and positive in 11%. Patients with a positive FDG-PET scan had a Deauville score of 4 (Table 1). In comparison, in the RAPID (Randomised Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages I/A IA/IIA Hodgkin’s Disease) study, FDG-PET imaging after 3 cycles of ABVD was negative in 74.6%. Of the 3 patients with positive scans after the second treatment cycle, 2 had negative scans after cycle 4. After cycle 4, 2 patients had positive FDG-PET scans and showed active disease on biopsy, including 1 patient with Gy zone lymphoma, and were removed from the study.

The preliminary efficacy results included 20 patients who had completed 4 cycles of therapy and 5 patients who were continuing treatment. Two patients with primary-refractory disease after treatment cycle 4 were off-study; 1 patient was removed from the study owing to grade 3 peripheral neuropathy after 1 cycle of brentuximab vedotin plus AVD; 1 patient elected to receive proton beam radiotherapy instead of ISRT; and 1 patient refused ISRT after...
In summary, the combination of brentuximab vedotin plus chemotherapy was well tolerated. Approximately 90% of patients showed negative imaging scans after 2 and 4 treatment cycles. Activity was observed in patients with bulky disease. An additional 29 patients will be added to the study for treatment with the same combination of brentuximab vedotin and AVD for 4 cycles, plus 20 Gy ISRT.

### References


Response-Adapted Therapy Based on Interim FDG-PET Scans in Advanced Hodgkin Lymphoma: First Analysis of the Safety of Deescalation and Efficacy of Escalation in the International RATHL Study (CRUK/07/033)

Although BEACOPP has demonstrated greater activity than ABVD for first-line treatment of Hodgkin lymphoma patients, long-term toxicity and secondary malignancies are a concern. Deescalation of therapy for patients who are responding well could provide efficacy while reducing toxicities, particularly those associated with bleomycin. In a study of 77 consecutive, newly diagnosed patients with stage I to IV Hodgkin lymphoma, interim FDG-PET after 2 cycles of chemotherapy predicted progression-free survival (PFS) as accurately as FDG-PET after completion of ABVD treatment. Moreover, regression analysis revealed that early imaging results predicted response to treatment more accurately than established prognostic factors. These findings are supported by an earlier retrospective study that investigated the prognostic utility of FDG-PET after 2 or 3 cycles of treatment.

The RATHL (Response-Adjusted Therapy for Hodgkin Lymphoma) study evaluated whether patients with advanced Hodgkin lymphoma who did not show early evidence of response on a PET scan would benefit from escalation of therapy using the BEACOPP regimen. The study enrolled adults with Ann Arbor stage III to IV Hodgkin lymphoma or stage II Hodgkin lymphoma with bulky disease or multiple involved sites. Patients underwent an initial FDG-PET scan for staging followed by 2 cycles of ABVD. The latter was given at full dose and on schedule, regardless of blood counts, to maximize treatment intensity. Within 10 to 14 days after ABVD treatment cycle 2, patients underwent another FDG-PET scan. The quality and consistency of imaging were ensured by measures such as central review of results within each participating country and consistent reporting based on the 5-point Deauville scale. Patients with a positive imaging result after the second cycle of ABVD received either 4 cycles of BEACOPP every 14 days or 3 cycles of escalated BEACOPP every 3 weeks on a nonrandomized basis. These patients underwent a third FDG-PET scan. Those with a positive result received radiation therapy or salvage treatment, and those with a negative result received either 2 more cycles of BEACOPP-14 or 1 cycle of escalated BEACOPP without radiation therapy. Patients with a negative imaging result after ABVD cycle 2 were randomized to receive 4 cycles of either ABVD or AVD. The omission of radiation therapy for these patients

ABSTRACT SUMMARY GADOLIN: Primary Results of a Phase III Study of Obinutuzumab Plus Bendamustine Compared With Bendamustine Alone in Patients With Rituximab-Refractory Indolent Lymphoma

To expand the treatment options available for patients with rituximab-refractory, indolent NHL, the phase 3 GADOLIN (A Study to Investigate the Efficacy and Safety of Bendamustine Compared With Bendamustine+RO5072759 [GA101] in Patients With Rituximab-Refractory, Indolent Non-Hodgkin’s Lymphoma) study investigated the combination of bendamustine plus obinutuzumab, a novel anti-CD20 antibody, followed by maintenance with obinutuzumab (abstract 123). Patients with rituximab-refractory, CD20-positive, indolent NHL were randomized to receive bendamustine (120 mg/m²) on days 1 and 2 for 6 cycles of 28 days each or bendamustine (90 mg/m²) on the same schedule plus obinutuzumab (1000 mg) on days 1, 8, and 15 during cycle 1, then on day 1 of cycles 2 to 6. In the combination group, patients without progressive disease after therapy went on to receive maintenance with obinutuzumab (1000 mg) every 2 months for 2 years or until disease progression. Among the 143 patients who started maintenance therapy, 35 patients completed treatment. Patients had a median age of 63 years (range, 21-87 years). Approximately 40% of patients in each arm had a high Follicular Lymphoma International Prognostic Index score. The median number of prior therapies was 2 (range, 1-10). The study met its primary endpoint, demonstrating a median PFS of not reached (95% CI, 22.5 months-not reached) for bendamustine plus obinutuzumab vs 14.9 months (95% CI, 12.8-16.6 months) for bendamustine monotherapy (HR, 0.55; 95% CI, 0.40-0.74; P=.0001). The incidence of AEs and serious AEs was similar in both treatment arms, with the exception of more serious cases of pneumonia in patients receiving bendamustine monotherapy (5.1% vs 2.6%), and more infusion-related reactions in patients receiving the combination (1.5% vs 4.1%).
was recommended but not required. The study’s primary endpoint was 3-year PFS in patients who obtained a negative imaging scan after ABVD cycle 2. This endpoint was designed to demonstrate noninferiority of AVD in comparison with ABVD.

Among the 1214 patients registered in the study, 77 withdrew before the second FDG-PET scan. The registered patients had a median age of 33 years; 41% were stage II, 31% were stage III, and 28% were stage IV. The International Prognostic Score (IPS) was 3 or higher in 37%. Among 1137 imaging scans available after ABVD cycle 2, 84% were negative. The study randomized 952 patients to treatment with ABVD or AVD. Deauville scores and patient characteristics were well balanced between the 2 arms. Only 4% of patients received consolidation radiation therapy.

At a median follow-up of 36.3 months, 3-year PFS for the intent-to-treat (ITT) population was 85.4% (95% CI, 81.6%-88.5%) for ABVD and 84.4% (95% CI, 80.7%-87.6%) for AVD (P=.53; hazard ratio [HR], 1.11; 95% CI, 0.79-1.54; Figure 2). Three-year overall survival (OS) was also similar for both arms (ABVD, 97.0% [95% CI, 94.5%-98.4%] vs AVD, 97.5% [95% CI, 95.1%-98.7%]). For the entire study group of 1214 patients, 3-year PFS was 82.5% (95% CI, 80.1%-84.7%), and OS was 95.4% (95% CI, 93.8%-96.6%). For patients with a negative imaging scan after ABVD cycle 2, prognostic factors for treatment failure included advanced initial disease stage (P=.01) and high-risk IPS (P=.05). Factors not prognostic for treatment failure included tumor bulk, B symptoms, and Deauville score. Continued bleomycin treatment beyond cycle 2 was associated with significantly more toxicity. Patients treated with ABVD after randomization were more likely to experience febrile neutropenia, infections, or respiratory complications compared with patients randomized to AVD. A similar number of deaths occurred in both arms. For patients with positive FDG-PET results after ABVD cycle 2, 74% had a negative imaging result following treatment with a BEACOPP regimen. Among these patients, 3-year PFS was approximately 70%, and 3-year OS was approximately 87%, with no difference observed for the nonrandomized comparison between the 2 BEACOPP treatment regimens. Dr Johnson concluded that omission of bleomycin following a negative interim FDG-PET scan after 2 cycles of ABVD decreased toxicity while maintaining efficacy.

**References**


**Figure 2.** Intent-to-treat analysis of progression-free survival in PET-negative patients in the RATHL study. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine; RATHL, Response-Adjusted Therapy for Hodgkin Lymphoma. Adapted from Johnson PW et al. Response-adapted therapy in the RATHL study. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; RATHL, Response-Adjusted Therapy for Hodgkin Lymphoma.
Sequential Brentuximab Vedotin and AVD for Older Hodgkin Lymphoma Patients: Initial Results From a Phase 2 Multicenter Study

Elderly Hodgkin lymphoma patients, usually defined as ages 60 years and older, have inferior outcomes compared with younger patients. In a recent study, 5-year failure-free survival was 74% in patients younger than 60 years and 48% in those ages 60 or older (P=.002). Five-year OS was 90% vs 58%, respectively (P<.0001). Advanced age at presentation is a strong negative risk factor and is influenced by numerous biologic factors, including a greater likelihood of presenting with advanced-stage disease and more aggressive histology. Elderly patients typically present with comorbidities, are less tolerant of intense chemotherapy regimens, and experience more severe toxicity. These characteristics often lead to dose reductions or the elimination of agents such as bleomycin. Adding to the difficulty of determining the best treatment approach for this population, elderly patients have been underrepresented in clinical trials. Although population-based studies show that patients ages 60 years or older constitute 15% to 30% of the population, they represent approximately 5% to 10% of patients in Hodgkin lymphoma clinical trials. This reduced enrollment of elderly patients is partly attributable to study exclusion criteria based on age, comorbidities, and poor performance status.

Brentuximab vedotin has demonstrated efficacy in relapsed or refractory Hodgkin lymphoma patients after autologous stem cell transplant (SCT), yielding an objective response rate (ORR) of 75%, including 34% complete responses (CRs). In advanced Hodgkin lymphoma, brentuximab vedotin improved efficacy when added to ABVD or AVD (although use with bleomycin led to unacceptable levels of toxicity). Brentuximab vedotin is currently being tested in combination with dacarbazine in elderly Hodgkin lymphoma patients. Early trials of brentuximab vedotin included 16 elderly patients, with a median age of 66 years (range, 60-82 years). These patients demonstrated an ORR of 56% and a median OS of 12.4 months, similar to the results seen in younger patients. However, elderly patients exhibited higher rates of anemia (30% vs 10%), sensory peripheral neuropathy (60% vs 46%), fatigue (58% vs 43%), and grade 3/4 adverse events (AEs; 70% vs 56%).

Dr Andrew Evens presented initial results of a multicenter, phase 2 study investigating sequential brentuximab vedotin and AVD as first-line treatment in elderly Hodgkin lymphoma patients. After initial imaging to assess disease stage, patients received 2 cycles of brentuximab vedotin (1.8 mg/kg every 3 weeks). Patients then received an interim FDG-PET scan. Patients who demonstrated a CR, a partial response (PR), or stable disease received 6 cycles of AVD. Patients then underwent either FDG-PET or a CT scan. Those with a CR or PR received 4 cycles of consolidation brentuximab vedotin (1.8 mg/kg every 3 weeks).

The study incorporated a Simon 2-stage design with a planned enrollment of 48 patients. Part 1 of the study required 20 evaluable patients, with 12 CRs required after 3 cycles of AVD for continuation to the second stage. Revised Cheson criteria and Deauville scoring were used to evaluate FDG-PET and CT scans. The first 26 enrolled patients had a median age of 69 years (range, 60-88 years). The median Eastern Cooperative Oncology Group (ECOG) performance

ABSTRACT SUMMARY Nivolumab in Patients With Relapsed or Refractory Lymphoid Malignancies and Classical Hodgkin Lymphoma: Updated Results of a Phase 1 Study (CA209-039)

A phase 1 dose escalation and expansion study evaluated nivolumab in patients with relapsed or refractory lymphoid malignancies and classical Hodgkin lymphoma. Previous results were published in early 2015 (Ansell SM et al. N Engl J Med. 2015;372(4):311-319). An updated analysis provided data on patients with Hodgkin lymphoma (n=23), B-cell NHL (n=31), T-cell NHL (n=23), multiple myeloma (n=27), and chronic myelogenous leukemia (n=1; abstract 010). Patients were heavily pretreated. Median follow-up was 76 weeks. The most common drug-related AEs were fatigue and rash, and 5% of patients experienced serious pneumonitis. The CR rate was 4% among multiple myeloma patients, with 63% showing stable disease. Among the T-cell NHL patients, the PR rate was 17%, and 43% had stable disease. B-cell NHL patients had a CR rate of 10%, a PR rate of 16%, and a stable disease rate of 52%. In Hodgkin lymphoma patients, the CR rate was 26%, with a PR in 61% and stable disease in 13%. In Hodgkin lymphoma patients, the median duration of response was not reached (range, 2 to 91+ months) after a median follow-up of 86 weeks. Responses were ongoing in 50%. Median PFS for Hodgkin lymphoma patients was 92.1 weeks.
score was 1; however, 15% of patients had an ECOG performance score of 2, representing some frailty. The median IPS was 4 (range, 2-7), and the median cumulative illness rating scale (CIRS) grade was 5, including 52% of patients with CIRS grades of 3 or 4.

Of the 26 enrolled patients, 6 were not evaluable. One of the first 5 patients in the study experienced grade 5 pancreatitis following the second dose of brentuximab vedotin. The estimated overall incidence of acute pancreatitis is approximately 0.16% to 0.25% among patients receiving brentuximab vedotin.12 Three patients withdrew from the study owing to pneumonitis and diarrhea, hepatotoxicity, and wound infection. One patient withdrew consent, and 1 patient refused further treatment owing to toxicity after 1 cycle of ABVD. These 6 patients had a mean CIRS score of 15 (range, 11-19). Among all other patients, the mean CIRS score was 5 (range, 0-14).

After the first 2 full cycles of brentuximab vedotin, the 20 evaluable patients had an ORR of 85% and a CR rate of 30% (Figure 3). After the first 3 cycles of AVD, the ORR increased to 95%, and the CR rate was 70%. After 6 cycles of AVD, the ORR was 95%, and the CR rate increased to 95%. Results following the consolidation treatment with brentuximab vedotin are forthcoming.

The most common nonhematologic AE was peripheral neuropathy, occurring in 65% of patients. Nausea, diarrhea, and cough each occurred in 54% of patients. Grade 3 or 4 AEs were observed in 46% and 31% of patients, respectively. The most common grade 3/4 AE was infection (occurring in 15%). Grade 2 peripheral neuropathy was observed in 31% of patients. Fifteen percent of patients had discontinued based on grade 2 infusion reaction, hepatotoxicity, or pneumonitis; or grade 3 wound infection. Twelve percent discontinued owing to grade 2 peripheral neuropathy, and 12% refused additional treatment. After a median follow-up of 14 months, 92% of patients were still alive, and 95% of evaluable patients were disease-free. Based on the achievement of at least 12 CRs among the first 20 evaluable patients, the study is continuing with the second stage.

References

Addition of Thiotepa and Rituximab to Antimetabolites Significantly Improves Outcome in Primary CNS Lymphoma: First Randomization of the IELSG32 Trial

Primary central nervous system (CNS) lymphoma is a rare and aggressive form of non-Hodgkin lymphoma (NHL). Current treatment consists of chemotherapy plus radiation. The Radiation Therapy Oncology Group (RTOG) 93-10 study was the first multicenter trial to demonstrate improved survival over historical reports of radiation therapy alone.\(^1\) In the study, 102 newly diagnosed patients received treatment consisting of high-dose methotrexate (2.5 g/m\(^2\)), vincristine, procarbazine, and intraventricular methotrexate (12 mg), followed by consolidation treatment with whole brain irradiation (45 Gy) and subsequent high-dose cytarabine. The regimen yielded an ORR of 94%, including 58% CRs. Median PFS was 24.0 months, and median OS was 36.9 months. Median OS was longer in patients younger than 60 years vs those 60 years and older (50.4 months vs 21.8 months; \(P<.001\)). Since this study, other chemotherapy regimens have been investigated in primary CNS lymphoma patients. Efforts to improve cure rates by increasing therapeutic intensity must be balanced against the need to limit toxicity. Severe neurotoxicity often accompanies treatment, particularly in elderly patients. In the RTOG 93-10 study, 53% of patients experienced grade 3/4 toxicity during induction chemotherapy. In addition, 15% of patients experienced severe delayed neurotoxicity, and 8 of these patients died.\(^1\)

One option for reducing neurotoxicity is to replace brain radiation with high-dose chemotherapy supported by autologous SCT. Dr Andrés Ferreri presented results of the International Extranodal Lymphoma Study Group (IELSG) 32 trial, which investigated rituximab and thiotepa for consolidation chemotherapy.\(^2\) Rituximab, an anti-CD20 monoclonal antibody, has demonstrated efficacy in diffuse large B-cell lymphoma (DLBCL) and other types of NHL; it has single-agent activity in patients with relapsed disease and can be combined with chemotherapy.\(^3\) Thiotepa is a lipophilic alkylating agent with high antineoplastic activity. The IELSG32 trial examined the addition of rituximab, with or without thiotepa, to standard antimetabolite chemotherapy. The primary endpoints were CR rate and 2-year failure-free survival. The study enrolled 224 patients with histologically proven primary CNS lymphoma and measurable disease from 52 sites in 5 countries. Patients were randomized into 3 arms to receive four 3-week cycles of treatment. Autologous stem cells were collected after the second treatment cycle. Responses were assessed after treatment cycles 2 and 4. After completion of this treatment, patients with disease that did not respond were removed from the study. Patients with a response were randomly assigned to consolidation therapy consisting of either whole brain radiation therapy or autologous SCT.

The age limit for trial enrollment was 65 years for patients with an ECOG performance score of 0 to 3, and 70 years for those with an ECOG score of 0 to 2. All patients had histologically or cytologically confirmed lymphoma exclusively confined to the CNS and at least 1 measurable lesion. The study included 224 patients, with a median age of approxi-
HIGHLIGHTS IN LYMPHOMA FROM THE 13TH INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA

More than half (61%) were male, and approximately 20% of patients in each arm. Treatment following the initial randomization for induction therapy was as follows. In arm A, 75 patients received methotrexate (3.5 g/m² on day 1) and cytarabine (2 g/m² twice daily on days 2 and 3). In arm B, 69 patients received the same treatment plus rituximab (375 mg/m² on day 5). In arm C, 75 patients received MATRix therapy consisting of the same treatment as arm B plus thiopeta (30 mg/m² on day 4). Patient characteristics were well balanced among the 3 treatment arms. Patients in arms A, B, and C received 74%, 86%, and 91% of planned chemotherapy courses, respectively. The relative dose intensity of thiopeta was 76%. The most commonly reported AEs were infective complications. Patients in the MATRix arm exhibited a higher incidence of grade 4 hematologic toxicity, including neutropenia (P=.01) and thrombocytopenia (P=.0001). Overall, toxicity resulted in dose interruptions in 21 patients (9%) and death in 13 patients (6%). No significant differences in rates of death or infection were observed across the 3 arms.

ORRs in arms A, B, and C were 53%, 74%, and 87%, respectively, with significant differences between arm A vs B (P=.01), arm A vs C (P=.00001), and arm B vs C (P=.05). The CR rates for arms A, B, and C were 23%, 30%, and 49%, reflecting significant improvement for arm C vs arm B (P=.02) or vs arm A (P=.0007). Therefore, the MATRix regimen was superior to antimetabolite therapy alone or with rituximab. Subgroup analysis demonstrated that MATRix therapy was significantly more active than the other regimens regardless of the patient’s IELSG risk. After a median follow-up of 21 months (range, 5-60 months), 50% of patients remained failure-free, including 32% in arm A, 54% in arm B, and 65% in arm C (Figure 4). Two-year OS rates in arms A, B, and C were 40% ±6%, 58% ±6%, and 66% ±6%, respectively. Data from the second randomization investigating whole brain radiation therapy vs autologous SCT consolidation therapy will be presented at a later date.

In a discussion of this study, Dr Tracy Batchelor commented that the IELSG32 provides important insights for treating this challenging type of lymphoma. Part of the study’s strength is derived from the well-balanced patient characteristics, including the stratification based on IELSG risk scores. The study was further strengthened by the use of consensus-based response criteria, which were developed by the International Primary CNS Lymphoma Collaborative Group and required centralized pathology and radiology review. Dr Batchelor also underscored the superior outcomes achieved with the MATRix regimen in the absence of significant increases in toxicity or infectious complications as compared with results of the IELSG20 trial, which investigated high-dose methotrexate with or without high-dose cytarabine. Dr Batchelor concluded that MATRix induction therapy is feasible and safe, and that it demonstrated superior outcomes compared with the other 2 treatment arms and did not interfere with stem cell collection.

References

Knowing the risk factors can change the way you see your patients with Hodgkin lymphoma.
Although half are cured by transplant,\(^1,^2\) relapse may be closer than you think for some

There will be an estimated 9,050 new cases of Hodgkin lymphoma (HL) in the US in 2015.\(^3\) HL is considered a highly curable disease; however, up to 10% of patients are refractory to frontline therapy, and up to 30% of patients will eventually relapse.\(^4,^5\) The standard approach for relapsed HL is autologous stem cell transplantation (ASCT), which has a 5-year progression-free survival rate of approximately 50%.\(^1,^2,^6\)

Among those who relapse after ASCT, prognosis has traditionally been poor, with a median survival of 1.3 years following relapse.\(^6,^7\) Further, the majority of relapses occur within 1 year.\(^8\) As advances continue in the treatment of HL, utilization of clinical prognostic factors may help identify a group of patients who are at high risk of relapse.\(^1,^2,^8,^9,^10\)

**Risk factors that may help identify patients who will relapse following ASCT**

- Refractory disease or early relapse after frontline therapy\(^8,^11\)
- Extramedullary disease at pre-ASCT relapse\(^8,^10,^12\)
- B symptoms at pre-ASCT relapse\(^8,^10,^12\)
- Lack of chemoresponsiveness pre-ASCT\(^2,^13\)
- Residual disease at time of ASCT\(^7\)
- Positive FDG-PET scan pre-ASCT\(^4,^14-16\)
- Bulky disease pre-ASCT\(^2,^12\)
- Higher disease stage at relapse\(^8,^9\)
- Anemia pre-ASCT\(^8,^9\)
- >1 relapse or >2 prior regimens\(^1,^8\)

**Progression-free survival based on a prognostic model using risk groups\(^5,^*\)**

![Graph showing progression-free survival based on a prognostic model using risk groups](image)

*High, intermediate and low risk were defined as patients with 0-1, 2 or 3 risk factors, respectively. The 3 factors incorporated into the model were B symptoms at pre-ASCT relapse, transplantation in CR and chemoresistant disease at the time of ASCT.\(^7\)

References:

The AETHERA (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) trial was the largest randomized, placebo-controlled study to investigate relapsed and refractory Hodgkin lymphoma. This international, phase 3 study randomized 329 patients to receive 16 cycles of brentuximab vedotin (1.8 mg/kg) or placebo intravenously every 3 weeks, starting 30 to 45 days after autologous SCT. Based on independent review, PFS significantly improved from 24.1 months for the placebo arm to 42.9 months in the brentuximab vedotin arm (P=0.0013; HR, 0.57; 95% CI, 0.40-0.81). A benefit was observed across subgroups.

Primary-refractory disease is an important risk factor for progression following autologous SCT, with a historical 2-year PFS of less than 40%. Three-year OS from the time of autologous SCT or salvage therapy improved from approximately 45% for patients treated between 1979 and 1995 to approximately 65% for patients treated between 1994 and 2012. The improvement can be partially explained by the fact that 43% of patients from the earlier study did not receive salvage therapy, whereas all of the patients treated during the later time frame did. Among patients in the AETHERA study, 60% had primary-refractory Hodgkin lymphoma. Dr Craig Moskowitz presented results of a post-hoc analysis of PFS, OS, and AEs in patients with primary-refractory Hodgkin lymphoma who received early brentuximab vedotin consolidation therapy or placebo during the study.

The post-hoc analysis included 99 patients from the brentuximab vedotin arm and 97 patients from the placebo arm. Patients had a median age of 31 to 33 years (range, 18-68 years). Approximately 57% of patients in each arm had at least 3 risk factors, which included primary-refractory Hodgkin lymphoma, a PR or stable disease as the best response to salvage therapy prior to autologous SCT, 2 or more previous salvage therapies, extranodal disease at relapse prior to SCT, and B symptoms after failure of first-line therapy.

Approximately half of the patients had completed treatment. Reasons for discontinuation included progressive disease (20% in the treatment arm vs...
43% in the placebo arm) and an AE (26% vs 6%). Based on ITT analysis, maintenance therapy with brentuximab vedotin improved PFS compared with placebo in the 196 patients with primary-refractory disease (HR, 0.55; Figure 5). Brentuximab vedotin showed efficacy in the subpopulations of patients who relapsed within 12 months of first-line therapy (n=107; HR, 0.50) and patients who relapsed after 12 months with extranodal disease (n=26; HR, 0.30). Brentuximab vedotin improved PFS in patients with or without extranodal involvement (HR, 0.37 and HR, 0.61, respectively) and with or without B symptoms (HR, 0.36 and HR, 0.63, respectively). Maintenance with brentuximab vedotin improved PFS compared with placebo in patients who had received more than 2 prior systemic therapies (HR, 0.39; Figure 6). Further analysis based on the number of risk factors continued to show a PFS benefit with brentuximab vedotin (HR, 0.55 for >1 risk factor; HR, 0.47 for >2; and HR, 0.40 for >3).

Dr Moskowitz emphasized that previously, patients with at least 2 risk factors would have been considered candidates for allogeneic SCT. The efficacy observed with brentuximab vedotin in this study, however, suggests that allogeneic SCT may no longer be necessary for these patients. No difference in OS was observed between the 2 randomized treatment arms (HR, 1.19; 95% CI, 0.62-2.29). The actual OS is likely to be longer than the 3 years anticipated when the study was designed, and the study is mandated to continue to estimate OS. Three-year OS was 81% with brentuximab vedotin and 79% with placebo, which compares favorably with historical controls. The most common AEs of any grade in the brentuximab vedotin arm were peripheral sensory neuropathy (58% vs 8% with placebo), neutropenia (34% vs 10%), and peripheral motor neuropathy (26% vs 0%). Among the AEs of grade 3 or higher, peripheral sensory neuropathy and motor neuropathy occurred at rates of 11% and 8%, respectively, among patients treated with brentuximab vedotin. No cases were reported in the placebo arm.

Figure 5. Intent-to-treat analysis of progression-free survival in patients with primary-refractory Hodgkin lymphoma from the AETHERA trial. Adapted from Moskowitz CH et al. Analysis of primary-refractory Hodgkin lymphoma pts in a randomized, placebo-controlled study of brentuximab vedotin consolidation after autologous stem cell transplant [ICML abstract 120]. Hematol Oncol. 2015;33(suppl 1):165.6

Figure 6. A subanalysis of AETHERA showing progression-free survival in patients with primary-refractory Hodgkin lymphoma who had received more than 2 previous treatments. Adapted from Moskowitz CH et al. Analysis of primary-refractory Hodgkin lymphoma pts in a randomized, placebo-controlled study of brentuximab vedotin consolidation after autologous stem cell transplant [ICML abstract 120]. Hematol Oncol. 2015;33(suppl 1):165.6

References

5. Memorial Sloan Kettering Cancer Center: Data on file.
Early FDG-PET Adapted Treatment Improves the Outcome of Early FDG-PET-Positive Patients With Stages I/II Hodgkin Lymphoma (HL): Final Results of the Randomized Intergroup EORTC/LYSA/FIL H10 Trial

A positive FDG-PET scan after 2 cycles of chemotherapy strongly predicts progression in Hodgkin lymphoma patients. Dr John Raemaekers presented late-breaking results from the H10 trial, which investigated the modification of therapy based on results from early FDG-PET scans. The H10 trial was conducted by the European Organisation for Research and Treatment of Cancer (EORTC), the Lymphoma Study Association (LYSA), and the Italian Lymphoma Foundation (FIL). The primary objective was to determine whether chemotherapy alone was as effective as combined modality therapy in patients with stage I or II Hodgkin lymphoma who had negative FDG-PET scans after 2 cycles of ABVD therapy. However, a preplanned interim futility analysis showed that it was unlikely that the primary objective could be met.

Accrual continued to investigate the secondary objective, which was to determine whether a change from ABVD therapy to escalated BEACOPP could improve the outcome of patients with stage I or II Hodgkin lymphoma who had a positive FDG-PET scan after 2 cycles of ABVD. The primary endpoint was PFS. The study enrolled patients ages 15 to 70 years with previously untreated, stage I or II Hodgkin lymphoma, with supradiaphragmatic disease. Patients with nodular lymphocyte–predominant Hodgkin lymphoma were excluded. FDG-PET scans were centrally reviewed, with a Deauville score of 1 or 2 indicating a negative result. The original statistical analysis anticipated a need for 248 patients with a positive FDG-PET result and 77 events to yield a predicted 50% 5-year PFS with standard treatment of ABVD plus involved node radiation therapy and a predicted 70% 5-year PFS with escalated BEACOPP plus involved node radiation therapy. An interim analysis, however, showed that the number of events was much lower than expected. Therefore, in 2010, the number of patients included in the study was increased to achieve 355 patients with a positive FDG-PET result.

Patients were categorized as favorable or unfavorable. The latter group included those 50 years or older, as well as those with at least 4 involved nodal areas, mediastinal bulk, an ESR of at least 50 mm/hour without B symptoms, or an ESR of at least 30 mm/hour with B symptoms. Patients were divided into 2 treatment arms based on favorable vs unfavorable status. All patients initially received 2 cycles of ABVD and then underwent FDG-PET imaging. Half of the patients in each arm then received standard combination therapy consisting of ABVD: 1 cycle for the favorable group or 2 cycles for the unfavorable group. All patients also received involved node radiation therapy (30 Gy), regardless of the imaging result. The other half of patients in both arms received tailored treatment based on the FDG-PET scan result. In the favorable arm, patients with a negative scan received 2 cycles of ABVD without radiation, whereas patients with a positive scan received 2 cycles of escalated BEACOPP plus involved node radiation therapy (30 Gy). In the unfavorable arm, patients with a negative scan received 4 cycles of ABVD and no radiation, and patients with a positive scan received 2 cycles of escalated BEACOPP plus involved node radiation therapy (30 Gy).

The study enrolled 1950 patients, with 754 categorized as favorable and 1196 as unfavorable. Among the favorable-risk patients, 371 were randomized to standard treatment, and 14% had a positive FDG-PET scan. Among the 376 randomized to experimental treatment, 11% had a positive FDG-PET scan. In the unfavorable-risk cohort, 583 received standard treatment, and 595 received the experimental treatment. A positive FDG-PET result was seen in 23% of the standard arm and 21% of the experimental arm, yielding a total of 361 FDG-PET–positive patients for the entire study population. The median follow-up was 4.5 years.

Among the 361 patients with a positive PET scan, 188 received standard ABVD, and 142 received escalated BEACOPP. Patients in the escalated BEACOPP arm demonstrated an increase in grade 3/4 neutropenia (53.5% vs 30.3% in the ABVD arm), thrombocytopenia (19.7% vs 0%), and anemia (4.9% vs 0%). Patients in the escalated BEACOPP arm also experienced more grade 3/4 infections, including febrile neutropenia (23.9% vs 1.1%) and infection without neutropenia (11.2% vs 1.1%). ITT analysis for ABVD vs escalated BEACOPP treatment demonstrated improved outcomes for the latter, based on disease progression or relapse (18.8% vs 7.7%), death (9.4% vs 4.1%), and the first incidence of progression/relapse or death (21.4% vs 9.5%). Five-year PFS was significantly improved by intensification of chemotherapy for patients with a positive scan after 2 cycles of ABVD, with 5-year PFS of 91% for escalated BEACOPP plus involved node radia-
tion therapy vs 77% for ABVD plus involved node radiation therapy (Figure 7). The difference in 5-year OS was not significant.

References
2. Raemaekers J. Early FDG-PET adapted treatment improves the outcome of early FDG-PET-positive patients with stages I/II Hodgkin lymphoma (HL): final results of the randomized intergroup EORTC/LYSA/FIL H10 trial. Late-breaking abstract presented at: the 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland.

Brentuximab Vedotin Plus AVD for Non-Bulky Limited Stage Classical Hodgkin Lymphoma: A Phase 2 Trial

Although ABVD plus radiation therapy is the standard of care for early-stage Hodgkin lymphoma, toxicities relating to bleomycin and radiation are a concern. In a phase I study of brentuximab vedotin plus ABVD or AVD, unacceptable levels of pulmonary toxicity were seen with ABVD but not AVD. Dr Jeremy Abramson presented results of a phase 2 study investigating brentuximab vedotin plus AVD in limited-stage, nonbulky Hodgkin lymphoma.

The study enrolled adults with previously untreated, stage I or II classical Hodgkin lymphoma. They had nonbulky disease, an ECOG performance score of 0 to 2, and adequate organ and bone marrow function. All patients received 2 doses of brentuximab vedotin (1.2 mg/kg) given 14 days apart, followed by a PET-CT scan to assess single-agent activity in previously untreated disease. Patients with progressive disease were eliminated from the study. Patients without disease progression then received 2 cycles of AVD plus brentuximab vedotin (1.2 mg/kg) administered on days 1 and 15 of a 28-day cycle. Patients then received a PET-CT scan. Patients with progressive disease were removed from the study; those with a PR or CR received an additional 2 or 4 cycles of AVD plus brentuximab vedotin. The study’s primary endpoint was the CR rate. Responses were evaluated based on revised Cheson criteria, and a negative imaging result was defined by a Deauville score of 1 to 3. Secondary endpoints included the response to brentuximab vedotin monotherapy, PFS, and OS. The study was designed to include 34 patients to demonstrate a CR rate of 94% with 91% power and an α error of 0.10.

The 34 enrolled patients had a median age of 36 years (range, 20-75 years), and half were male. The most common histology was nodular sclerosis (occurring in 54%), followed by classical Hodgkin lymphoma not otherwise specified (24%), mixedcellularity disease (12%), and lymphocyte-rich disease (12%). Patients had stage IA (18%), IIA (71%), or IIB (12%) disease, and risk was classified as early favorable in 62% and early unfavorable in 38%. One patient was HIV-positive. Ninety-four percent of patients completed treatment. One patient discontinued owing to an AE. There was 1 death, which occurred in an elderly woman who developed neutropenic sepsis during combination therapy.

Figure 7. Progression-free survival among PET-positive patients in the H10 trial of stage I/II Hodgkin lymphoma. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; HR, hazard ratio; INRT, involved node radiation therapy; PET, positron emission tomography; PFS, progression-free survival. Adapted from Raemaekers J. Early FDG-PET adapted treatment improves the outcome of early FDG-PET-positive patients with stages I/II Hodgkin lymphoma (HL): final results of the randomized intergroup EORTC/LYSA/FIL H10 trial. Late-breaking abstract presented at: the 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland.
ABSTRACT SUMMARY Updated Results of a Phase 2 Trial of Brentuximab Vedotin Combined With RCHOP in Frontline Treatment of Pts With High Intermediate/High-Risk DLBCL

A randomized, phase 2 study investigated the addition of brentuximab vedotin to R-CHOP therapy in patients with high/intermediate-risk or high-risk DLBCL (abstract 092). Patients received 6 cycles of standard R-CHOP therapy plus brentuximab vedotin (1.2 mg/kg or 1.8 mg/kg) administered every 21 days. The 53 enrolled patients had a median age of 67 years (range, 21-81 years), and 96% of patients had stage III/IV disease. CD30 expression at baseline was positive (≥1%) in 47%, negative in 45%, and not available in 8%. Several treatment-emergent grade 3/4 AEs were more common with the higher dose of brentuximab vedotin. Grade 3 peripheral sensory neuropathy and grade 3 peripheral motor neuropathy were more common with the higher dose. Grade 4 febrile neutropenia occurred at the higher dose, but only grades 1 to 3 were observed at the lower dose. Response rates for the 51 evaluable patients were similar for the 2 doses of brentuximab vedotin, yielding an ORR of 80%, including 67% CRs. Although numerical improvements in CR and PFS rates were noted in both CD30-positive and CD30-negative disease, longer follow-up is needed to confirm these findings. Based on toxicity concerns, the study was amended to remove vincristine from treatment and will continue with brentuximab vedotin (1.8 mg/kg) added to R-CHP.

Figure 8. One-year progression-free survival in a phase 2 trial of brentuximab vedotin plus AVD for nonbulky limited stage classical Hodgkin lymphoma. AVD, doxorubicin, vinblastine, and dacarbazine; PFS, progression-free survival. Adapted from Abramson JS et al. Brentuximab vedotin plus AVD for non-bulky limited stage classical Hodgkin lymphoma: a phase 2 trial [ICML abstract 087]. Hematol Oncol. 2015;33(suppl 1):146.

After 2 cycles of brentuximab monotherapy, the CR rate was 53% and the PR rate was 47%. All of the enrolled patients then received combination therapy. After the 2 subsequent cycles of brentuximab vedotin plus AVD, 97% experienced a CR. One patient, the elderly woman who died of sepsis, was not included in the evaluation, but she had achieved a CR after brentuximab vedotin monotherapy. After the end of study treatment, all patients had received a total of 4 cycles of brentuximab vedotin plus AVD, and the CR rate was 91%. One patient had progressive disease, and 2 patients were not evaluable. At the end of treatment, 8 patients had imaging scans that were interpreted as positive, with a Deauville score of 4 or 5 based on central review. Seven of the scans had been interpreted by the local investigator as Deauville X, indicating observation of new FDG activity that was considered unrelated to the baseline Hodgkin lymphoma. One of these patients received 2 further cycles of AVD alone and proceeded to a confirmed CR. Six of the patients received a brief follow-up scan that yielded a confirmed CR. After a median follow-up of 14 months, 1-year PFS was 94% (95% CI, 77%-99%; Figure 8), and 1-year OS was 97% (95% CI, 81%-100%).

The most common AE of any grade was peripheral central neuropathy, followed by fatigue, nausea, and constipation. Of the 25 patients who experienced peripheral neuropathy, symptoms were grade 1 or 2 in 17 patients and grade 3 in 8. No grade 4 cases were reported. After a median follow-up of 9 months, approximately 30% of patients continued to experience neurotoxicity, including 2 patients with grade 3 symptoms. High rates of febrile neutropenia led to a mandate for the use of growth factors in all patients. Thereafter, the incidence of febrile neutropenia decreased. The most common hematologic toxicities were neutropenia and anemia. A follow-up study will investigate the combination of brentuximab vedotin plus doxorubicin and dacarbazine, with the goal of eliminating toxicities associated with vinblastine.

References

Rituximab, Bendamustine and Cytarabine (RBAC500) as Induction Therapy in Elderly Patients With Mantle Cell Lymphoma: A Phase 2 Study From the Fondazione Italiana Linfomì

The combination of rituximab, bendamustine, and cytarabine (R-BAC) was investigated in 40 elderly patients with MCL, half of whom had previously untreated disease. Patients received rituximab (375 mg/m² on day 1), bendamustine (70 mg/m²) on days 2 and 3, and cytarabine (800 mg/m²) given by 2-hour continuous infusion on days 2, 3, and 4. The regimen induced an ORR of 100% and estimated 2-year PFS rates of 95% ±5% for previously untreated patients and 70% ±10% for relapsed or refractory patients. After a median follow-up of 60 months (range, 45-72 months), 5-year PFS was 66% and 5-year OS was 73% for the cohort of previously untreated patients. However, 87% of patients experienced grade 3/4 thrombocytopenia, which was generally transient, and 12% experienced febrile neutropenia.

To improve this regimen, a new protocol with a lower cytarabine dose was tested in elderly, treatment-naive MCL patients. Study results were presented by Dr Carlo Visco. The single-arm, multicenter, phase 2 study enrolled patients older than 65 years who were eligible for autologous SCT and patients ages 60 to 65 who were not candidates for SCT. Patients with a history of indolent disease were excluded. To minimize toxicity, the cytarabine dose was reduced to 500 mg/m², and therefore this regimen was named R-BAC500. The study included assessments for minimum residual disease (MRD) and comprehensive geriatric assessment, as well as central pathology review.

The primary objectives were the CR rate (based on FDG-PET and Cheson 2007 criteria) and the safety of R-BAC500. Secondary objectives included the rate of molecular response, PFS, OS, and duration of response. Treatment consisted of a maximum 6 cycles of R-BAC500 for patients who showed evidence of a response, based on FDG-PET after cycles 2 and 4, without any relevant toxicities. Patients underwent a final imaging scan and MRD evaluation at the end of treatment, and MRD evaluations every 6 weeks thereafter.

The enrolled patients had a median age of 71 years (range, 61-79 years), and three-fourths were male. Most patients had a performance status of 0 or 1 and Ann Arbor stage III or IV disease. MCL International Prognostic Index scores were low in 16%, intermediate in 40%, and high in 44%. All 57 enrolled patients received at least 2 cycles of treatment. After the first 2 cycles, 4 patients discontinued owing to toxicity or an AE. Thirty-six patients (63%) completed 6 cycles of treatment. Discontinuations were attributed to toxicity or an AE in 11 cases, progressive disease in 1, and decision by the physician and/or patient in 5. Hematologic toxicity was acceptable. Grade 3 or 4 AEs included leukopenia (17% and 27%, respectively), neutropenia (14% and 35%), febrile neutropenia (5% and 1%), thrombocytopenia (16% and 36%), and anemia (12% and <1%). Therefore, the rate of grade 3/4 thrombocytopenia was reduced considerably by decreasing the dose of cytarabine.
CR of 93%. At a median follow-up of 22 months (range, 15-38 months), Kaplan-Meier survival analysis yielded a 2-year PFS of 80% ± 5% (Figure 9) and a 2-year OS of 89% ± 4%. Subgroup analysis based on prognostic factors showed that early relapse was more likely in patients with blastoid histology compared with those showing classic or pleomorphic histology (P < .001). At the end of therapy, MRD analysis by means of nested PCR performed on 39 available samples yielded negative results in 51% of bone marrow samples and 77% of peripheral blood samples.

References


Nonhematologic toxicity was generally acceptable, with the most common AEs of any grade being fatigue (25%), nausea/vomiting (21%), and infusion-related reactions (21%). The end-of-treatment ORR was 96%, including a

from 800 mg/m² to 500 mg/m². The rate of grade 4 occurrences decreased from 64% to 36%. Platelet transfusions were needed during 29% of 303 treatment cycles, and 49% of patients underwent at least 1 platelet transfusion.

Nonhematologic toxicity was generally acceptable, with the most common AEs of any grade being fatigue (25%), nausea/vomiting (21%), and infusion-related reactions (21%). The end-of-treatment ORR was 96%, including a

Highlights in Lymphoma From the 13th International Conference on Malignant Lymphoma: Commentary

Craig H. Moskowitz, MD
Steven A. Greenberg Chair in Lymphoma Research
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

The 13th International Conference on Malignant Lymphoma (ICML) was held in June 2015. Several exciting abstracts were presented. The most important studies were on patients with Hodgkin lymphoma, mostly in the untreated setting. In addition, there were presentations in non-Hodgkin lymphoma that may impact clinical practice.

**Hodgkin Lymphoma**

Dr Jeremy Abramson presented the results from a phase 2 study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy in 34 patients with early-stage Hodgkin lymphoma. The study included patients with favorable and unfavorable characteristics, but without bulky disease. The patients represented the typical population. Interestingly, the patients received a lead-in cycle of brentuximab vedotin given at 1.2 mg/kg on days 1 and 15, followed by an exploratory positron emission tomography (PET) scan. This cycle was followed by standard chemotherapy, which included brentuximab vedotin and AVD.
Although the median follow-up was short, this chemoimmunotherapy program produced very high complete response rates: 97% at cycle 2 and 91% at end of treatment. Nearly all patients had a negative PET scan at the conclusion of treatment. There was significantly more neurotoxicity with the combination of brentuximab vedotin and AVD. Importantly, this study showed that the combination of brentuximab vedotin and AVD likely requires growth factor support with pegfilgrastim or filgrastim.

The group from Memorial Sloan Kettering Cancer Center presented results of a study that also enrolled patients with early-stage Hodgkin lymphoma, albeit ones with unfavorable stage 1 or 2 disease, with or without tumor bulk. The study evaluated brentuximab vedotin and AVD for 4 cycles of chemotherapy followed by involved-site radiation. Twenty-eight patients received treatment. In general, the treatment was well tolerated. As in the study by Dr Abramson,1 mild to moderate neuropathy was reported. A complete response was seen in 26 patients. Of the 2 patients who did not achieve a complete response, 1 patient had diffuse large B-cell lymphoma on repeat biopsy. In patients with tumor bulk, the relapse rate is between 15% and 20%.3 The results of this study are therefore promising and warrant further investigation. The study is being continued with a decrease in the amount of radiation therapy, from 30 Gy to 20 Gy, in a new cohort of approximately 30 patients.

Another study in early-stage Hodgkin lymphoma was presented by Dr John Raemaeker.5 The H10 intergroup trial was a collaboration among the European Organisation for Research and Treatment of Cancer, the Lymphoma Study Association, and the Fondazione Italiana Linfomi group. In 2010, a preplanned interim futility analysis suggested that the trial was unlikely to meet the primary objective of showing noninferiority for chemotherapy alone compared with combined-modality treatment in patients with negative PET scans after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).7 That part of the study was discontinued. The ICML analysis addressed the secondary objective, which was to determine whether an early change from ABVD to intensified treatment with escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) could improve outcome in unfavorable, early-stage patients with a positive PET scan after 2 cycles of ABVD.4

The experimental arm showed improvement that was highly statistically significant. The 5-year progression-free survival (PFS) improved from 77% to 91% with the crossover to escalated BEACOPP. The 5-year overall survival improved from 89% to 96%. The authors concluded that, despite some increased toxicity, intensifying chemotherapy in patients with early PET-positive scans should be an option for Hodgkin lymphoma patients with stage 1 or 2 unfavorable, early-stage disease in the combined modality therapy setting.

A phase 2, multicenter study presented by Dr Andrew Evens enrolled older Hodgkin lymphoma patients (>60 years).6 The study evaluated sequential treatment with brentuximab vedotin followed by AVD and then a short course of consolidation with additional brentuximab vedotin. It was a typical patient population for an older group with Hodgkin lymphoma, and most of the patients had an abnormal comorbidity score. Among the 26 patients enrolled in the first stage of the study, 20 were evaluable for response.

The overall response rate to the brentuximab vedotin lead-in was 85%, with 30% of patients having a complete response based on PET imaging. After 3 cycles of AVD, the response rates improved to 95% for overall response and 70% for complete response. This difficult patient population lacks a standard of treatment. Sequential therapy with brentuximab vedotin and AVD may offer these patients a higher cure rate. It is extremely unlikely that a randomized study can be performed in this older population because it constitutes no more than 10% of patients with Hodgkin lymphoma.7

Dr Peter Johnson presented results for the RATHL (Response-Adjusted Therapy for Hodgkin Lymphoma) study in advanced-stage Hodgkin lymphoma.8 This study was the most important one presented at the 13th ICML, and the results are practice-changing. Many studies in advanced-stage Hodgkin lymphoma are employing a PET-adapted approach to management. This strategy is based on data from nearly a decade ago showing that patients who have a negative PET scan after 2 cycles of ABVD do extremely well, whereas those with a PET-avid scan have a PFS rate between 25% and 40%.6,9 The RATHL study aimed to determine whether bleomycin can be eliminated from further treatment in patients who have a PET-negative response after 2 cycles of ABVD, and whether the addition of a BEACOPP-based chemotherapy regimen will improve PFS in patients who have a PET-avid response after 2 cycles of ABVD.

Among the 1200 patients enrolled in the study, more than 900 had an interim PET2-negative scan. These patients showed no difference in response to ABVD or AVD. The treatments were associated with similar complete response rates and death rates. The treatment arms shared nearly identical rates of 3-year PFS (85.4% for ABVD vs 84.4% for AVD) and overall survival (85.3% for ABVD vs 84.6% for AVD). The study showed that bleomycin can be removed from the ABVD program in patients with a PET-negative response after 2 months of upfront ABVD treatment.

There were 174 patients with PET2-positive scans. These patients were subsequently treated with either BEACOPP-14 or escalated BEACOPP. In this group, 3-year PFS was 68% and OS was 86%, with no difference in the nonrandomized compar
The results suggest that it is safe to omit bleomycin in patients who have a favorable response to ABVD. In patients with a positive interim PET scan, it seems reasonable to convert treatment to escalated BEACOPP. In a similar study from the Southwest Oncology Group (SWOG), patients with PET-avid disease after 2 cycles of ABVD were converted to escalated BEACOPP and had a 2-year PFS of 62%.

Several studies provided data on relapsed Hodgkin lymphoma. An analysis of the AETHERA (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) dataset focused on primary-refractory Hodgkin lymphoma. In this treatment program, patients first underwent transplant. Beginning 30 to 45 days after transplant, patients were randomly assigned to either brentuximab vedotin maintenance or placebo. In this very unfavorable patient population, there was a marked improvement in PFS (hazard ratio, 0.5) in patients who received the maintenance treatment with brentuximab vedotin. This approach will likely become the standard of care in this setting.

Dr John Timmerman presented an update of a phase 1 trial of single-agent nivolumab in relapsed/refractory lymphoid malignancies and classical Hodgkin lymphoma. A previous report of this trial, published in January 2015, showed a response rate of 87% (17% complete responses and 70% partial responses). At the 13th ICML, Dr Timmerman reported that nivolumab was associated with a median time to progression of 92 weeks in patients with relapsed or refractory Hodgkin lymphoma, which is outstanding in this unfavorable population. This study will likely lead to approval of nivolumab in this setting.

### Non-Hodgkin Lymphoma

Several presentations in non-Hodgkin lymphoma could also be practice-changing. A study presented by Dr Andrés Ferreri was conducted by the International Extranodal Lymphoma Study Group. This international, randomized, phase 2 trial addressed the tolerability and efficacy of adding rituximab and thiotepa to methotrexate and Ara-C as induction therapy for patients with primary central nervous system lymphoma. With 219 patients, this study is the largest performed in this population. All patients were HIV-negative, and they ranged in age from 18 to 70 years. They were randomly assigned to 1 of 3 arms: standard treatment with methotrexate and Ara-C; methotrexate, Ara-C, and rituximab; or methotrexate, Ara-C, rituximab, and thiotepa (known as the MATRix regimen). The data suggested that the MATRix regimen was the most active, with a complete response rate of 49% and an overall response rate of 87%. Similar data have been reported from single-institution studies. With the results of this large, multicenter study, induction therapy with the MATRix regimen may become the standard of care after the data are peer-reviewed and published.

Another practice-changing study, GADOLIN (A Study to Investigate the Efficacy and Safety of Bendamustine Compared With Bendamustine+R05072759 [GA101] in Patients With Rituximab-Refractory, Indolent Non-Hodgkin’s Lymphoma), was presented by Dr Bruce Cheson. This phase 3 trial compared obinutuzumab [GA101] plus bendamustine vs bendamustine alone as induction therapy in approximately 400 patients with rituximab-refractory, indolent non-Hodgkin lymphoma. The obinutuzumab/bendamustine arm also received obinutuzumab maintenance therapy for up to 2 years, whereas the single-agent bendamustine arm did not receive maintenance therapy. The primary endpoint was PFS. The induction phase used a higher daily dose of bendamustine in the single-agent arm (120 mg/m²) than in the combination arm (90 mg/m²). Interestingly, the response rates were similar after induction therapy. The maintenance phase is marked by a separation of PFS curves on the Kaplan-Meier plot, reflecting a marked improvement for the patients who received additional treatment. Median PFS as assessed by independent review was not reached in the combination arm vs 14.9 months in the single-agent arm. There was no difference in overall survival. The adverse events were fairly similar with both regimens.

Dr Stephen Schuster presented results from an interesting study evaluating chimeric antigen receptor (CAR)-modified T cells in non-Hodgkin lymphoma patients with relapsed/refractory CD19-positive disease. Subtypes included diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Several centers in the United States are studying CAR-modified T cells. In this study of heavily pretreated patients, CAR T-cell therapy was associated with durable responses. Some complete responses were seen in patients with diffuse large B-cell lymphoma and follicular lymphoma. A drawback to the use of CAR-modified T cells is an associated toxicity known as cytokine-release syndrome, which can necessitate admission to an intensive care unit. In the study, cytokine-release syndrome was generally grade 2 and caused no deaths.

My conclusion from this study is that although the results are early, the therapy appears promising. Many applications are possible. There is the potential for long-term remissions in patients who are heavily pretreated. Further research is needed to determine which diseases are most likely to respond to CAR-modified T cells, and whether the therapy should be administered.
early or late in the management course. This therapy can be associated with significant toxicity. There is a learning curve for administration and prediction of outcome. Large, multicenter studies are underway using several different techniques and cellular products.

Dr Carlo Visco presented a large trial in older patients (60 to 80 years) with mantle cell lymphoma. This group previously reported results from a study evaluating a combination of rituximab, bendamustine, and cytara- bine (R-BAC). The study presented at the ICML evaluated a regimen entitled R-BAC 500, in which the dose of cytarabine was reduced to avoid the potential for increased toxicity in this elderly patient population. The trial included 57 patients from 29 centers. The patients reflected the typical elderly population with mantle cell lymphoma. Interestingly, the overall response rate was 96%, and the complete response rate was 93%. Minimal residual disease was also assessed; it was negative in 76% of patients with peripheral blood samples and in 59% of patients with bone marrow samples. At a median follow-up of 22 months, the 2-year PFS was approximately 80%. Unfortunately, this treatment regimen was not efficacious in patients with the blastoid variant of mantle cell lymphoma. However, the authors suggested that the R-BAC 500 regimen was safe in this elderly population and is an option for patients who are not eligible for transplant.

Dr Steven Ansell reported updated phase 2 data of brentuximab vedotin combined with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemothera-py in the frontline management of patients with diffuse large B-cell lymphoma. This planned interim analysis provided data on the 51 treated patients. The disease was considered high/intermediate risk in 62% and high risk in 38%. The overall response rate to brentuximab vedotin and R-CHOP was 80%. A complete response was reported in 67% of patients. There was no significant difference in outcome or complete response rates between the ABC and the GCB subtypes. There were reports of peripheral neuropathy, which has been previously seen with brentuximab vedo-tin, but it was mostly grade 1 or grade 2. The results of this treatment program suggested that brentuximab vedotin plus R-CHOP had encouraging activity. In patients with CD30-positive disease, a randomized study may be warranted.

Disclosure
Dr Moskowitz has received research support from Seattle Genetics, Merck, and Pharmacycles. He is a member of the Scientific Advisory Boards of Seattle Genetics, Merck, and Celgene.

References