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A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2014 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2014 American Society of Hematology Annual Meeting and Exposition • December 6-9, 2014 • San Francisco, California

Special Reporting on:

- The AETHERA Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Progression Following Autologous Stem Cell Transplant for Hodgkin Lymphoma
- PD-1 Blockade With the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Preliminary Results From a Phase Ib Study (KEYNOTE-013)
- Brentuximab Vedotin in Combination With Bendamustine for Patients With Hodgkin Lymphoma Who Are Relapsed or Refractory After Frontline Therapy
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- Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides or Sézary Syndrome: Final Results Show Significant Clinical Activity and Suggest Correlation With CD30 Expression
- Rituximab Maintenance Versus Wait and Watch After Four Courses of R-DHAP Followed By Autologous Stem Cell Transplantation in Previously Untreated Young Patients With Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective LyMa Trial, a LYSA Study
- Results of a Phase II Trial of Brentuximab Vedotin as First Line Salvage Therapy in Relapsed/Refractory HL Prior to AHCT

PLUS Meeting Abstract Summaries

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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

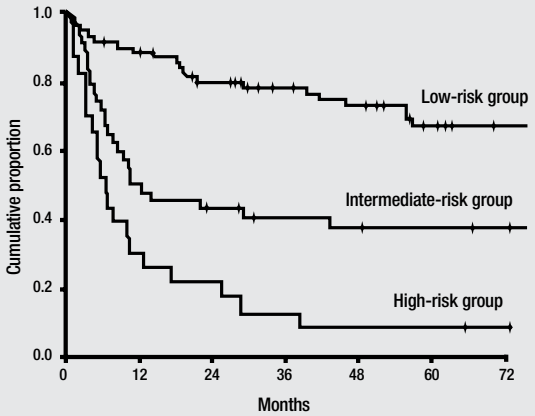
There will be an estimated 9,190 new cases of Hodgkin lymphoma (HL) in the US in 2014.[3] HL is considered a highly curable disease; however, up to 10% of patients are refractory to frontline therapy, and up to 30% of patients will eventually relapse.[4,5] The standard approach for relapsed HL is autologous 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.[7] 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.[1,2,6,8-16]

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

- Refractory disease or early relapse after frontline therapy[2,8-11]
- Extranodal disease at pre-ASCT relapse[2,8,10-12]
- B symptoms at pre-ASCT relapse[1,8-11,13]
- Lack of chemoresponsiveness pre-ASCT[1,2,13]
- Residual disease at time of ASCT[1]
- Positive FDG-PET scan pre-ASCT[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[1,9]

Progression-free survival based on a prognostic model using risk groups[1,*]



*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 chemosensitive disease at the time of ASCT.[1]

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The AETHERA Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Progression Following Autologous Stem Cell Transplant for Hodgkin Lymphoma

Autologous stem cell transplantation (ASCT) can achieve cures in approximately 50% of patients with relapsed or refractory Hodgkin lymphoma (HL).[1-3] However, over the last 2 decades, most randomized trials of patients with aggressive lymphomas have failed to demonstrate improved efficacy outcomes from the novel ASCT regimens. Brentuximab vedotin is an antibody-drug conjugate consisting of an anti-CD30 monoclonal antibody and a protease-cleavable linker bound to the microtubule-disrupting agent monomethyl auristatin E (MMAE). In a pivotal phase 2 trial, the drug demonstrated manageable toxicity and induced objective responses in 75% of patients with relapsed or refractory HL after ASCT.[4] Brentuximab vedotin is approved for treating HL in patients who have failed ASCT and patients who have failed at least 2 prior chemotherapy regimens and are not candidates for ASCT.[5]

The randomized, placebo-controlled, phase 3 AETHERA (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) study was conducted to assess whether consolidation therapy with brentuximab vedotin could reduce the risk for disease progression in HL patients after ASCT. Results from the study were presented at the 2014 American Society of Hematology (ASH) meeting by Dr Craig Moskowitz.[6] The trial enrolled 329 patients at 78 sites in North America. Eligible patients had received at least 2 prior systemic therapies and were at risk for disease progression after transplant. Prior to randomization, patients were stratified based on primary refractory disease, relapse within 12 months after frontline therapy, or relapse with extranodal involvement 12 months or later after frontline therapy. After salvage therapy, patients received ASCT and were then randomized to receive either brentuximab vedotin or matched placebo beginning 30 to 45 days after transplant. Patients received up to 16 doses of brentuximab vedotin (1.8 mg/kg) or placebo administered every 21 days. Imaging was performed every 3 months for the first year and then at 18 and 24 months. Patients who progressed on the placebo arm were permitted to receive brentuximab vedotin treatment as part of a companion study, thus potentially improving the efficacy outcomes observed in the placebo arm. The trial's primary objective was progression-free survival (PFS), with secondary endpoints of overall survival (OS) and safety.

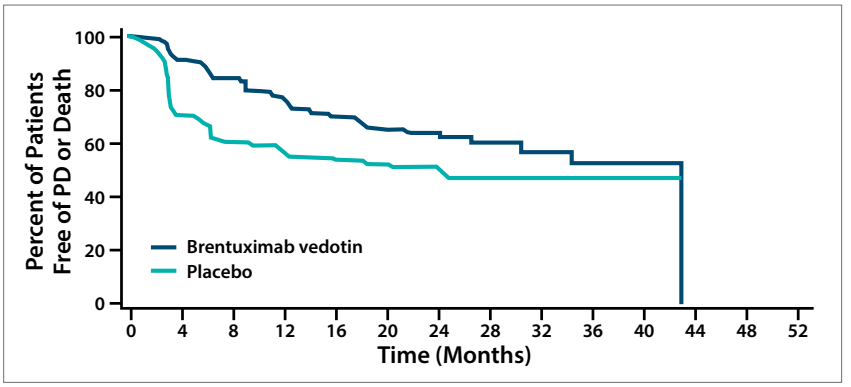

Figure 1. Progression-free survival based on independent review in the phase 3 AETHERA trial. AETHERA, A Phase 3 Study of Brentuximab Vedotin (SGN-35) in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant. Data from Moskowitz CH et al. ASH abstract 673. *Blood*. 2014;124(suppl 21).[6]

Patients had a median age of 33 years (range, 18-76 years), and approximately half were male. Nearly half had received 2 or more prior salvage therapies, and 60% had primary refractory HL. Nearly half of the patients in each arm had completed treatment. Reasons for treatment discontinuation included progressive disease (15% in the brentuximab vedotin arm vs 42% in the placebo arm), adverse events (AEs; 33% vs 6%, respectively), and patient decision (5% vs 2%, respectively).

The analysis conducted by an independent review board was based on imaging scans that were taken at 24 months after the initiation of study treatment. In contrast, the investigators continued to perform clinical lymphoma assessments of patients after 24 months. Based on independent review, the median PFS was 43 months with brentuximab vedotin vs 24 months with placebo (hazard ratio [HR], 0.57; 95% CI, 0.40-0.81; *P*=.001; Figure 1). Two-year PFS rates were 63% vs 51%, respectively. Based on investigator review, median PFS was not reached with brentuximab vedotin vs 16 months with placebo (HR, 0.50; 95% CI, 0.36-0.70), with 2-year PFS rates of 65% and 45%, respectively. The study therefore reached its primary endpoint

ABSTRACT SUMMARY Positron Emission Tomography (PET) Guided Therapy of Aggressive Lymphomas—A Randomized Controlled Trial Comparing Different Treatment Approaches Based on Interim PET Results (PETAL Trial)

Imaging by ^{18}F-FDG-PET has been explored as a means to reveal response to treatment after repeated cycles of chemotherapy. Although studies investigating this concept have yielded variable results, inconsistencies in imaging procedures could contribute to the variation in outcomes. The PETAL (Positron Emission Tomography Guided Therapy of Aggressive Non-Hodgkin's Lymphomas) trial was conducted to determine whether response rates could be improved by switching to a more aggressive treatment regimen for patients with unfavorable interim PET imaging results (Abstract 391). The study enrolled patients aged 18 to 80 years with newly diagnosed aggressive lymphoma and a positive baseline PET. Patients received 2 cycles of R-CHOP followed by interim PET. In an effort to provide more consistent imaging results, interim PET scanning was performed during the 3-week interval following the second treatment cycle. To avoid altered glucose biodistribution, no G-CSF was administered after the second R-CHOP cycle, and SUV-based PET interpretation was used to improve the objectivity of image analyses (Lin C et al. *J Nucl Med*. 2007;48:1626-1632). Patients with a favorable interim PET result were randomized to receive 4 additional cycles of R-CHOP with or without 2 additional doses of rituximab. Patients with an unfavorable PET result were randomized to receive 6 additional cycles of R-CHOP or a more intensive regimen. Rituximab was omitted in patients with CD20-negative disease. Among the 926 patients enrolled, 107 (13%) had an unfavorable interim PET scan. The interim PET results were highly predictive of outcomes, with a 2-year time to treatment failure of 79% with favorable results vs 47% for unfavorable results (HR, 3.4; 95% CI, 2.6-4.6; *P*<.0001). In patients with CD20-positive lymphoma and a favorable interim PET result, additional rituximab doses failed to improve the risk for treatment failure compared with 6 doses (HR, 1.2; 95% CI, 0.8-2.1). For patients with an unfavorable interim PET result, switching to the more intensive treatment did not improve the risk for treatment failure (HR, 1.6; 95% CI, 0.9-2.7), CR rate (50% vs 31%; *P*=.10), or OS (HR, 1.0; 0.5-2.1). An interim PET scan performed after only 2 treatment cycles predicted OS (HR, 3.9; 95% CI, 2.7-5.7; *P*<.0001).

Table 1. Response According to Risk Factors in the AETHERA Trial

Number of Risk Factors	n	PFS Hazard Ratio (95% CI)	OS Hazard Ratio (95% CI)
≥1	329	0.57 (0.40-0.81)	1.15 (0.67-1.97)
≥2*	280	0.49 (0.34-0.71)	0.94 (0.53-1.67)
≥3*	166	0.43 (0.27-0.68)	0.92 (0.45-1.88)

*Ad hoc analysis.

AETHERA, A Phase 3 Study of Brentuximab Vedotin (SGN-35) in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant; OS, overall survival; PFS, progression-free survival.

Data from Moskowitz CH et al. ASH abstract 673. *Blood*. 2014;124(suppl 21).[6]

based on both analyses. Kaplan-Meier analysis based on prior response to treatment showed a benefit from treatment with brentuximab vedotin for all subgroups, including patients with primary refractory disease (n=196), patients who relapsed before 1 year (n=107), and patients who relapsed with extranodal involvement at 1 year or later (n=26). A stronger benefit with brentuximab vedotin appeared to correspond to the number of risk factors, such as disease that was refractory to frontline therapy or that relapsed within 12 months of frontline therapy, most recent salvage therapy resulting in a partial response (PR) or stable disease, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, and 2 or more salvage therapies (Table 1).

After a median follow-up of 24.4 months, 2-year OS was 88% for both treatment arms (*P*=.62). No difference in OS was observed between the 2 treatment arms, but 85% of patients in the placebo arm received subsequent treatment with brentuximab vedotin. Final OS data will be presented in 2016.

An AE of any grade occurred in 98% of patients in the brentuximab vedotin arm and 89% of patients in the placebo arm. AEs of grade 3 or higher were more common with brentuximab vedotin than placebo. Consistent with previous reports, peripheral neuropathy was the most common AE in the brentuximab vedotin arm, occurring in 56% of patients (vs 16% in the placebo arm). Grade 3 peripheral neuropathy occurred in 13% of the treatment arm vs 1% of the placebo arm. No grade 4 peripheral neuropathy was observed. Among patients receiving brentuximab vedotin, the median time to resolution of peripheral neuropathy was 23.4 weeks, and symptoms resolved in 85% of these patients after treatment delays, dose reductions, or treatment cessation. Other common AEs observed in the brentuximab vedotin arm included neutropenia (occurring in 35% vs 12% in the placebo arm), upper respiratory tract infection (26% vs 23%, respectively), and fatigue (24% vs 18%, respectively). Two notable deaths occurred during the study in patients receiving treatment with brentuximab vedotin. One patient developed acute respiratory distress syndrome arising from pneumonia caused by infection with *Staphylococcus aureus* and multiple organ failure on day 40 of treatment. Another patient died from acute pancreatitis, a known complication of brentuximab vedotin.

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PD-1 Blockade With the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Preliminary Results From a Phase Ib Study (KEYNOTE-013)

The programmed cell death (PD-1) receptor is a member of the CD28 family. It is expressed on the surface of activated T cells and has 2 ligands: PD-L1 and PD-L2.[1] In hosts without lymphoma, the PD-1/PD-L1 pathway contributes to tolerance of self antigens. In tumors, PD-1 plays a major role in avoiding destruction by the immune system through negative regulatory mechanisms. Many tumor types express PD-L1, which binds to PD-1 receptors on activated T cells and induces T-cell exhaustion. Blockade of the PD-1/PD-L1 interaction has shown very promising results in several types of cancer, including HL.[2] Classical HL is characterized by the presence of rare Reed-Sternberg cells surrounded by a mixture of inflammatory cells, which are mostly ineffective. The genes encoding the PD-1 ligands PD-L1 and PD-L2 are located on chromosome 9p24.1, which is commonly amplified in classical HL.[3] PD-L1 is expressed on Reed-Sternberg cells in more than 85% of classical HL cases.[3] In addition, nearly half of all HL patients are infected with the Epstein-Barr virus, which further increases expression of the PD-1 ligands. Blockade of PD-1 may therefore be an effective strategy for treating classical HL.

ABSTRACT SUMMARY Brentuximab Vedotin Monotherapy and in Combination With Dacarbazine in Frontline Treatment of Hodgkin Lymphoma in Patients Aged 60 Years and Above: Interim Results of a Phase 2 Study

HL patients aged 60 years and older have significantly inferior outcomes compared with younger patients, and standard ABVD treatment is associated with increased toxicities, often leading to dose reductions and reduced efficacy (Evens AM et al. *Oncology*. 2008;22[12]:1369-1379). In a retrospective analysis of patients ages 60 years and older, brentuximab vedotin monotherapy yielded an ORR of 53% and a CR rate of 40%, and it was well tolerated (Fanale MA et al. ASH abstract 3687. *Blood*. 2012;120[21 suppl]). To expand the available treatment options, brentuximab vedotin as a single agent or combined with chemotherapy was evaluated as first-line therapy in elderly patients (Abstract 294). All patients were ages 60 years or older, treatment-naive, and had not received conventional first-line treatment for HL (because they were ineligible or because they had declined). Treatments consisted of brentuximab vedotin monotherapy (1.8 mg/kg on day 1), the same treatment combined with dacarbazine (375 mg/m^2 on day 1), or brentuximab vedotin combined with bendamustine (90 mg/m^2 on days 1 and 2). Preliminary data were presented for the cohorts receiving brentuximab vedotin monotherapy and brentuximab vedotin plus dacarbazine. Among the 27 patients who received brentuximab vedotin alone, the ORR was 93%, including 70% CRs, and 7% of patients achieved stable disease. The median PFS was 10.5 months (range, 2.6+ to 14.3 months), and the median duration of response was 9.1 months (range, 0.3+ to 13.14 months). Patients received a median 8 cycles of treatment (range, 3-23 cycles). The most common reasons for discontinuing treatment were progressive disease (41%) and AEs (37%). No grade 4 AEs or AE-related deaths occurred. AEs leading to discontinuation included 7 grade 3 cases of peripheral sensory neuropathy, peripheral motor neuropathy, and orthostatic hypotension. Among the 14 evaluable patients receiving brentuximab vedotin plus dacarbazine, all achieved some level of tumor reduction. The combination of brentuximab vedotin plus dacarbazine was well tolerated, with 3 reports of grade 3 AEs: *Clostridium difficile* colitis, hypotension, and hyperglycemia. The treatment cohort of brentuximab vedotin combined with bendamustine is currently enrolling patients.

Pembrolizumab is a humanized monoclonal antibody with high affinity for PD-1 that blocks binding of both PD-L1 and PD-L2. It has demonstrated activity and durable responses in multiple tumor types.[4-6] It was recently approved for patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab or—in patients with *BRAF* V600 mutations—after ipilimumab plus a *BRAF* inhibitor. Pembrolizumab was investigated in a cohort of classical HL patients included in the KEYNOTE-013 (A Trial of Pembrolizumab [MK-3475] in Participants With Blood Cancers [MK-3475-013]) study, and results from the HL patients were presented by Dr Craig Moskowitz.[7] This ongoing, multicenter, open-label, phase 1b clinical trial enrolled patients with a variety of hematologic malignancies. The classical HL patients were heavily pretreated and had received brentuximab vedotin, which failed. Patients had nodular sclerosing or mixed-cellularity HL and were relapsed or refractory to treatment with brentuximab vedotin. They were ineligible for transplant, or prior ASCT had been unsuccessful. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, no autoimmune disease, and no interstitial lung disease. Patients received pembrolizumab (10 mg/kg) every 2 weeks for up to 24 months until disease progression or intolerable toxicity. Responses were assessed at week 12 and every 8 weeks thereafter. The study's primary endpoint was complete response (CR) rate, with secondary endpoints including ORR, PFS, and safety.

Thirty-one patients had been enrolled at the time of the presentation at ASH 2014, with data available for 29 patients. Patients had a median age of 32 years (range, 20-67 years). Bulky lymphadenopathy was present in 31% of patients, and 52% had received 5 or more prior therapies for their advanced HL. In most patients (69%), prior ASCT was unsuccessful; the remaining patients were ineligible (28%) or had refused transplant (3%). After a median follow-up of 153 days (range, 1-341 days), 9 patients had discontinued treatment after disease progression (n=7), an AE (n=1), or a CR (n=1). Twenty patients (69%) remained on therapy, and 1 patient (3%) subsequently underwent stem cell transplantation.

Nearly all patients had some evidence of tumor shrinkage. Among the 29 evaluable patients, the ORR based on investigator review was 66% (Table 2). The treatment was generally well tolerated. Sixteen patients (55%) experienced 1 or more treatment-related AEs of any grade. The most common treatment-related AEs of any grade included hypothyroidism and pneumonitis, each observed in 3 patients (10%), and constipation, diarrhea, nausea, hypercholesterolemia, hypertriglyceridemia, and hematuria, each observed in 2 patients (7%). Laboratory abnormalities were mostly of short duration. Grade 3 AEs included 1 case each of axillary pain, hypoxia, joint swelling, and pneumonitis. No patients experienced more than 1 grade 3 AE. There were no grade 4 events, and no deaths.

Table 2. Response in a Phase 1B Trial of Pembrolizumab

	n (%)
Overall response rate	19 (66)
Complete remission	6 (21)
Partial remission	13 (45)
Stable disease	6 (21)
Clinical benefit rate	25 (86)
Progressive disease	4 (14)

Data from Moskowitz CH et al. ASH abstract 290. *Blood*. 2014;124(21 suppl).[7]

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Brentuximab Vedotin in Combination With Bendamustine for Patients With Hodgkin Lymphoma Who Are Relapsed or Refractory After Frontline Therapy

HL patients who achieve a CR before undergoing ASCT have improved outcomes.[1,2] Although standard salvage therapies show high ORRs, the CR rates vary from 20% to 60%, and significant toxicities may arise.[1-5] Both brentuximab vedotin and bendamustine have shown high single-agent activity in relapsed and refractory HL, with each therapy yielding a CR rate of approximately 33%.[6,7] Both drugs have manageable safety profiles. Their mechanisms of action are distinct: Brentuximab vedotin binds to CD30, followed by internalization and subsequent release of its MMAE toxin, and bendamustine is a DNA-alkylating agent.

The combination of these 2 drugs was explored in a phase 1/2 expansion study of patients with relapsed or refractory HL, presented by Dr Ann LaCasce.[8] The phase 1 study was designed to determine safety and tolerability and to identify the optimal dose of bendamustine. Patients initially received bendamustine (90 mg/m^2) on days 1 and 2 and brentuximab vedotin (1.8 mg/kg) on day 1 of a 21-day cycle. Reduced bendamustine dosing was planned if 4 or more patients experienced a dose-limiting toxicity, which was defined as any toxicity occurring during the first treatment cycle that required a dose delay of at least 14 days. If fewer than 2 patients achieved a CR, the trial would be halted. The primary objective of the phase 2 expansion phase was to determine the dose that achieved the best duration of response and PFS.

Patients were assessed for response with a combined positron emission tomography (PET)/computed tomography (CT) scan after cycles 2 and 4 and before ASCT. Patients received up to 6 cycles of combination therapy and had the option to undergo stem cell transplantation any time after cycle 2. After the transplant, patients could receive brentuximab vedotin monotherapy for up to 16 doses. Responses were assessed by CT scan every 3 months. Enrolled patients were adults with relapsed or refractory classical HL after frontline therapy and an ECOG performance status of 0 to 2. The 54 enrolled patients had a median age of 37 years (range, 27-51 years), and 57% were male. Nearly all patients (98%) had an ECOG performance status of 0 or 1. The median time since HL diagnosis was 13.8 months (range, 8.8-20.4 months). At diagnosis, 54% of patients had stage III or IV disease. Half of the patients had primary refractory disease, and half had relapsed. Nearly all patients had received the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as their first-line treatment.

Patients received a median 2 cycles of therapy (range, 1-6 cycles) during the phase 1 study. No dose-limiting toxicities were observed during cycle 1, and therefore the original dosing schedule was used for the phase 2 study. Ninety-six percent of patients experienced a treatment-emergent AE, 41% experienced an AE of grade 3 or higher, 22% experienced a serious AE, and 17% discontinued treatment owing to an AE. The majority of AEs were infusion-related, including the

ABSTRACT SUMMARY Preliminary Results of a Phase I Study of Nivolumab (BMS-936558) in Patients With Relapsed or Refractory Lymphoid Malignancies

Nivolumab is a fully human monoclonal antibody that blocks the PD-1 receptor and has demonstrated clinical efficacy in various solid tumors. Nivolumab is being evaluated in an open-label, dose-escalation, phase 1 study of patients with relapsed or refractory lymphoid malignancies (Abstract 291). Nivolumab (1 mg/kg or 3 mg/kg) was administered every 2 weeks for up to 2 years. Thirteen patients were treated during the dose-escalation portion of the trial, and 69 patients were treated with 3 mg/kg during the dose-expansion phase. (Data for an additional 23 patients with classical HL treated in the dose-expansion phase were presented separately.) Lymphoma subtypes included mycosis fungoides (n=13), follicular lymphoma (n=10), DLBCL (n=11), other B-cell lymphomas (n=8), peripheral T-cell lymphoma (PTCL; n=5), and other T-cell lymphomas (n=3). The study also included 27 patients with multiple myeloma. Fifteen patients (18%) experienced a grade 3 AE, with the most common being anemia (4%), leukopenia (2%), decreased lymphocyte count (2%), and decreased platelet count (2%). Grade 4 AEs included pustular rash and sepsis, each occurring in 1 patient (1%). Two patient deaths occurred: 1 from pneumonitis and 1 from acute respiratory distress syndrome. The incidence and severity of drug-related AEs were similar across tumor types. The ORRs were 28% for the B-cell lymphoma patients, including 7% CRs, and 17% for the T-cell lymphoma patients, with no CRs. Although no CRs or PRs were observed for the 27 multiple myeloma patients, the rate of stable disease was 67%. For the 10 patients with follicular lymphoma and the 11 patients with DLBCL, nivolumab monotherapy induced ORRs of 40% and 36%, respectively. Phase 2 studies are being conducted in these B-cell lymphoma subtypes.

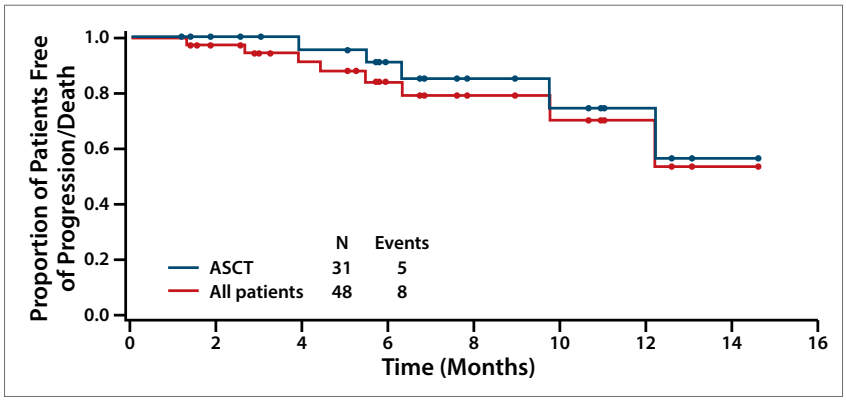

Figure 2. Progression-free survival in a phase 1/2 expansion study of brentuximab vedotin plus bendamustine in patients with relapsed or refractory Hodgkin lymphoma. Adapted from LaCasce A et al. ASH abstract 293. *Blood*. 2014;124(suppl 21).[8]

ABSTRACT SUMMARY Interim Safety Analysis: A Phase I Trial of High Dose Therapy and Autologous Stem Cell Transplantation Followed by Infusion of Chimeric Antigen Receptor Modified T-Cells (19-28z CAR-T) Directed Against CD19+ B-Cells for Relapsed and Refractory Aggressive B-Cell Non-Hodgkin Lymphoma (B-NHL)

Although the majority of patients with DLBCL are cured with standard first-line therapy, many patients relapse or have primary refractory disease. Even after high-dose chemotherapy followed by ASCT, poor rates of PFS have been observed in relapsed or refractory patients. To improve cure rates, a novel cellular approach is under investigation using patient T cells modified with the 19-28z chimeric antigen receptor (CAR). The 19-28z CAR consists of an antibody fragment that binds to CD19, which is expressed on the surface of most malignant B cells, combined with the costimulatory receptor CD28. T cells engineered to express the CAR can kill tumor cells expressing CD19. Preliminary results from a phase 1 study investigating this method were presented (Abstract 677). After undergoing BEAM chemotherapy and ASCT, patient T cells were collected via apheresis and modified to express the 19-28z CAR. The modified T cells were infused into the patient on days 2 and 3 after stem cell transplantation. The 6 treated patients had a median age of 64 years and had received a median 2 prior lines of therapy. All patients had achieved a PR, which continued at the time of study admission. All patients achieved a CR based on PET imaging following study treatment. No autoimmune complications were observed. At a median follow-up of 9 months (range, 1-18 months), all patients remained in CR. Cytokine-release syndrome is a potential complication of this treatment and was a dose-limiting toxicity following modified T-cell infusion at a dose level of 1×10^7 CAR-modified T cells/kg. Three patients were subsequently treated at the lower dose level of 5×10^6 CAR-modified T cells/kg with no dose-limiting toxicities observed. The study continues to enroll patients for treatment at the lower dose level.

most common AEs of dyspnea (15%), chills (13%), and flushing (13%). The majority of reactions occurred within 24 hours of the cycle 2 infusion and were considered related to both drugs. Delayed hypersensitivity reactions also occurred, the most common being rash, which was observed in 14 patients up to 22 days after the drug infusion. As a result, the protocol was amended to include mandatory premedication with corticosteroids and antihistamines.

Table 3. Response in a Trial of Brentuximab Vedotin Plus Bendamustine

	n (%)
Best clinical response*	
Complete remission	40 (83)
Partial remission	6 (13)
Stable disease	1 (2)
Progressive disease	1 (2)
Objective response	46 (96)

*Before autologous stem cell transplantation.
Data from LaCasce A et al. ASH abstract 293. *Blood*. 2014;124(suppl 21).[8]

Among the 48 evaluable patients, 40 (83%) achieved a CR and 6 (13%) achieved a PR, yielding an overall response rate (ORR) of 96% (95% CI, 85.8%-99.5%; Table 3). Most of the CRs (85%) were achieved at cycle 2 restaging. Thirty-three patients underwent stem cell collection, and all but 1 patient had a successful stem cell mobilization using granulocyte-colony stimulating factor alone or in combination with plerixafor. The median number of apheresis sessions was 2 (range, 1-5), with a median CD34-positive cell yield of 4.0×10^6 cells/kg (range, 1.7×10^6 to 11.8×10^6 cells/kg). Among the 33 patients who underwent stem cell mobilization, 17 did so after 2 treatment cycles, and the median time to platelet and neutrophil engraftment was less than 2 weeks. After a median follow-up of 5 months, the median PFS and the median duration of response were not reached (Figure 2). Among the 31 patients who had undergone ASCT, there were 5 adverse events. One patient died of septic shock on day 13 during transplantation. Among the 4 patients with disease progression, 3 were receiving brentuximab vedotin monotherapy. Dr LaCasce concluded that, with the addition of premedications to reduce the incidence of infusion-related reactions, the combination of brentuximab vedotin plus bendamustine has a manageable safety profile and showed promising efficacy in patients with relapsed or refractory HL after first-line therapy.

In a separate study, brentuximab vedotin was also explored in combination with ABVD or AVD chemotherapy.[9] The multicenter, phase 1, dose escalation study enrolled treatment-naive HL patients aged 18 to 60 years with stage IIA bulky disease or stage IIB through IV disease. Treatment consisted of six 28-day cycles, with brentuximab vedotin and chemotherapy administered on days 1 and 15 of each cycle. The brentuximab vedotin dose ranged from 0.6 mg/kg to 1.2 mg/kg, with the latter dose chosen for the AVD expansion cohort. Patients had a median age of 32.5 years, and 75% were male. Nearly half of patients had stage IV disease.

The combination of brentuximab vedotin plus bleomycin led to pulmonary toxicity in 11 of the 25 patients (44%) randomized to ABVD. The pulmonary toxicity resolved in 9 patients but was fatal in the other 2 patients. Eight patients discontinued bleomycin and completed treatment with AVD plus the antibody. No pulmonary toxicities occurred in the 26 patients randomized to brentuximab vedotin plus AVD. Both combinations yielded high response rates; the CR was 95% with ABVD and 96% with AVD. Long-term data were available after a median follow-up of 45 months (range, 32-54 months) for the ABVD group and a median follow-up of 36 months (range, 9-42 months) for the AVD group. The 3-year event-free survival was 79% with bleomycin and 92% without it, and the 3-year OS was 92% vs 100%, respectively. The study showed that brentuximab vedotin should not be combined with bleomycin but can be combined safely with AVD. Brentuximab vedotin plus AVD showed a high level of activity, and responses were durable in treatment-naive HL patients.

ABSTRACT SUMMARY Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma—Preliminary Safety, Efficacy and Biomarker Results of a Phase I Study

PD-1 activity has been implicated in locally suppressing immunity in Hodgkin lymphoma. The gain of chromosome 9p24.1 and infection with Epstein-Barr virus increase the expression of PD-L1 and PD-L2 (Yamamoto et al. *Blood*. 2008;111[6]:3220-3224). Nivolumab blocks the PD-1 ligand binding site, thereby unlocking the antitumor activity of T cells. Given the importance of PD-1 activity in HL malignancy, nivolumab was evaluated in a dose-escalation and cohort expansion phase 1 clinical trial of patients with relapsed or refractory classical HL or multiple myeloma, with results for the latter patients reported separately (Abstract 289; Ansell et al. *N Engl J Med*. 2015;372(4):311-319). Patients with classical HL received nivolumab at 3 mg/kg every 2 weeks until confirmed tumor progression or excessive toxicity. The primary endpoint was safety. The 23 classical HL patients were heavily pretreated: 87% had received 3 or more prior treatments, 78% had received prior ASCT, and 78% had received prior treatment with brentuximab vedotin. Drug-related AEs of any grade were observed in 78% of patients. Drug-related grade 3/4 AEs occurred in 22% of patients. Serious AEs included 1 occurrence each of grade 3 myelodysplastic syndrome, grade 3 pancreatitis, and grade 2 lymph node pain. The ORR was 87%, including 17% CRs, with the remaining 13% of patients achieving stable disease. The 24-week PFS was 86% (95% CI, 62%-95%). All patients experienced a reduction in tumor burden. The 18 patients who were refractory to treatment with brentuximab vedotin had an ORR of 89%, including 1 patient who achieved a CR. At the time of the presentation at ASH 2014, median OS had not been reached (range, 21+ weeks to 75+ weeks). Among the patients who discontinued treatment, 6 chose to undergo stem cell transplantation, 4 had disease progression, and 2 had toxicity. In all 10 patients who underwent biomarker analysis, the copy number of PD-L1 and PD-L2 in their Reed-Sternberg cells was increased. The US Food and Drug Administration has granted nivolumab breakthrough therapy designation in HL.

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Ibrutinib Monotherapy in Relapsed/Refractory Follicular Lymphoma (FL): Preliminary Results of a Phase 2 Consortium (P2C) Trial

Ibrutinib is an orally available, covalent inhibitor of Bruton's tyrosine kinase (BTK), a downstream component of the B-cell receptor signaling pathway.[1] By inhibiting B-cell receptor signaling, ibrutinib induces cells to undergo apoptosis. Ibrutinib is approved for treating patients with mantle cell lymphoma or chronic lymphocytic leukemia who have received at least 1 prior treatment and for patients with chronic lymphocytic leukemia characterized by 17p deletion.[2] In the initial phase 1 study of ibrutinib in patients with relapsed or refractory B-cell malignancies, full occupancy of the BTK active site was demonstrated at a dose of 2.5 mg/kg.[3] However, the maximum tolerated dosage was not reached with dose escalation to 12.5 mg/kg, and a dose of 560 mg/kg was recommended for phase 2 studies of non-Hodgkin lymphoma. In a phase 1 study that included 16 patients with follicular lymphoma, ibrutinib yielded an ORR of 44% and included 19% CRs.[4] At a dosage of 2.5 mg/kg or higher, the ORR was 55% and the median duration of response was 13.4 months.[4]

To further explore the activity of ibrutinib in follicular lymphoma, a phase 2 study was conducted at 6 treatment centers. Preliminary results were presented by Dr Nancy Bartlett at the 2014 ASH meeting.[5] Key eligibility criteria included grade 1, 2, or 3a relapsed or refractory follicular lymphoma, at least 1 prior chemotherapy treatment, and an ECOG performance status of 0 to 2. An absolute neutrophil count of at least 750/mm^3 and a platelet count of at least 30,000/mm^3 were required. Patients received ibrutinib (560 mg daily) with continuous dosing during 28-day cycles until disease progression or unacceptable toxicity. Baseline evaluations included peripheral blood analysis and lymph node biopsy. Patients were restaged based on CT imaging on day 1 of cycle 3, then every 3 cycles. Lymph node biopsy was performed upon disease progression. The study had a 1-stage binomial design with no formal interim analysis. Thirty-six evaluable patients were required to test the null hypothesis that the true ORR was less than or equal to 20%. The study's primary endpoint was ORR; however, imaging results were not included in the formal response analysis. Secondary endpoints included safety and tolerability, as well as OS, PFS, time to response, and duration of response. Biomarker studies, including somatic mutation analysis, were planned to compare molecular profiles from tumor samples collected at baseline and upon disease progression. Metabolic and proteomic profiling was planned for plasma samples collected from a subset of patients on day 8 of cycle 1 and after completion of cycle 2.

Among the 41 patients registered, 1 patient withdrew before initiating treatment. Two patients stopped treatment

ABSTRACT SUMMARY Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study (OMB110928)

For DLBCL patients who fail first-line R-CHOP, standard second-line treatment is chemotherapy followed by high-dose therapy and ASCT. However, salvage chemotherapy plus rituximab after failure of first-line chemotherapy plus rituximab yields poor event-free survival rates (Gisselbrecht C et al. *J Clin Oncol*. 2010;28[27]:4184-4190). Ofatumumab binds to CD20 and has shown efficacy in rituximab-resistant lymphoma cell lines as well as in patients with relapsed or refractory intermediate-grade B-cell lymphoma when combined with chemotherapy (Matasar MJ et al. *Blood*. 2013;122[4]:499-506). To address the need for more effective salvage regimens, the phase 3 ORCHARRD (Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy Followed by Autologous Stem Cell Transplant in Relapsed or Refractory Diffuse Large B Cell Lymphoma) study evaluated the combination of ofatumumab plus DHAP vs R-DHAP in patients with relapsed or refractory, CD20-positive DLBCL (Abstract 630). Prior to randomization, patients were stratified for risk factors. Treatment included DHAP plus either ofatumumab (1000 mg) or rituximab (375 mg/m^2) administered on day 1 and day 8 of cycle 1, and on day 1 of cycles 2 and 3. Patients who showed a response after cycle 2 received the third cycle of treatment followed by high-dose therapy and ASCT. The study randomized 447 patients with a median age of 57 years. The 2 treatment arms failed to show a significant difference in PFS (*P*=.27), 2-year event-free survival (*P*=.27), or OS (*P*=.25). Response to salvage treatment also did not differ significantly between the 2 arms. The ORR was 38% for the ofatumumab plus DHAP arm (including 15% CRs) and 42% for the R-DHAP arm (including 22% CRs). Approximately one-third of patients in each arm underwent on-protocol ASCT. Clinically relevant toxicities were comparable for both treatments.

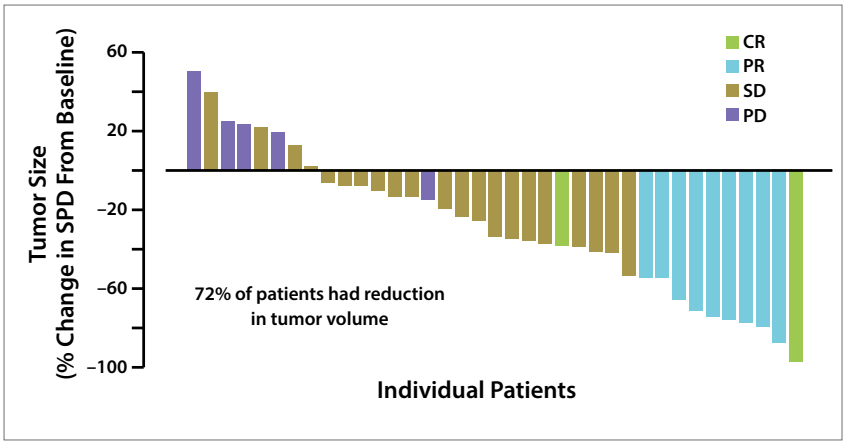

Figure 3. Maximum tumor volume reduction in a phase 2 trial of ibrutinib monotherapy in relapsed/refractory follicular lymphoma. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Bartlett NL et al. ASH abstract 800. *Blood*. 2014;124(21 suppl).[5]

during cycle 1 and were not evaluated for response; however, all 40 patients who initiated therapy were included in the analyses. Patients had a median age of 64 years (range, 46-82 years), and 52.5% had a Follicular Lymphoma International Prognostic Index score of 3 or higher. One-fourth of patients had elevated lactate dehydrogenase levels, 10% had B symptoms, and 63% met at least 1 of the Groupe d'Etude des Lymphomes Folliculaires criteria at study entry. The median number of prior therapies was 3 (range, 1-11), and 25% of patients had received 1 prior therapy. Forty-five percent of patients were refractory to rituximab (defined as no objective response to the drug or relapse within 6 months), and 35% of patients were refractory to their most recent treatment.

Median follow-up was 10.2 months (range, 3.9-18.4 months). The ORR based on a CT scan was 28% (95% CI, 15%-44%), including 2 CRs (5%) and 9 PRs (23%). The CRs were observed after cycle 5 and cycle 11, and both patients had a positive PET scan after cycle 2. Three patients with a PR and 1 patient with stable disease had negative PET/CT results after cycle 2. A better ORR was observed for patients who were sensitive to rituximab (42%; 8 of 19 patients) compared with patients whose disease was refractory to rituximab (6%; 1 of 18 patients). A reduction in tumor volume was observed in 72% of patients (Figure 3), suggesting that BTK signaling is an oncologic driver in a significant proportion of patients. Patients had received a median 8 treatment cycles (range, 1-19+ cycles). Treatment was discontinued due to progressive disease (n=18), an AE (n=2), refusal of further therapy (n=2), and death (n=1). Among the 11 patients who exhibited a response, the median time to response was 2.8 months (range, 1.8-7.4 months), and the median duration of response was not reached. Three of these patients developed progressive disease (at 2.5 months, 4.7 months, and 11.6 months). The remaining 8 patients had ongoing responses ranging from 5.5 months to 14.2 months. One-year PFS was 50.1% (95% CI, 35.3%-71.1%).

Among the 40 follicular lymphoma patients who initiated treatment with ibrutinib, 5 deaths occurred. Three patients died from progressive disease and 1 patient died from gastric hemorrhage. One patient died from pneumonia but had received only 1 week of therapy and had extensive bilateral pleural effusions at baseline. Ibrutinib treatment was well-tolerated overall, with no unexpected AEs reported. One patient with known liver cirrhosis died during treatment cycle 5 from an upper gastrointestinal tract bleeding event that was considered related to the presence of gastric varices. A least 1 grade 3/4 AE occurred in 35% of patients. Grade 3/4 AEs occurring in at least 1 patient included neutropenia (7.5%), anemia (5%), lymphopenia (5%), and infection (5%).

A correlative study examined the relationship between response and PET scans performed at baseline; on cycle 1, day 8; and on cycle 3, day 1. The maximum standardized uptake value (SUV_{max}, a marker of tumor glucose metabolism), peak SUV, metabolic tumor volume, and total lesion glycolysis were evaluated at baseline; cycle 1, day 8; and week 8 in all patients. Correlations with response and PFS were evaluated for the absolute values obtained at each time point and for the change in values for baseline vs cycle 1, day 8 and for baseline vs week 8. SUV_{max} on cycle 1, day 8 was shown to correlate with response (P=.04) and PFS (P=.003). PFS was worse for patients with SUV_{max} of at least 12.7 on cycle 1, day 8 (P=.15).

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Autologous Hematopoietic Stem Cell Transplantation (AHCT) in Patients With Chemotherapy-Sensitive, Relapsed/Refractory (CSRR) Human Immunodeficiency Virus (HIV)-Associated Lymphoma (HAL): Results From the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0803)/AIDS Malignancy Consortium (AMC-071) Trial

HIV-related lymphoma remains a significant health problem; the risk for developing HL or non-Hodgkin lymphoma is 11 to 17 times greater in people with HIV.[1] The introduction of combination antiretroviral therapy (cART) in 1996 profoundly changed HIV treatment by achieving dramatic reductions in viral load and corresponding decreases in HIV symptoms. By enabling the recovery of T-cell mediated immunity and decreasing the risk for opportunistic infections, cART therapy also allowed patients with HIV-related lymphoma to receive standard lymphoma treatments. Standard treatments have continued to demonstrate success in HIV-infected patients, and in the late 1990s, ASCT was first attempted in patients with HIV-related lymphoma. However, published studies of ASCT for HIV-related lymphoma are limited by several factors: Many studies are retrospective, the use of various preparative regimens limits the ability to compare results across trials, and posttransplant therapy is variable. Moreover, HIV infection remains an exclusion criterion for the majority of ASCT trials, and most transplants for HIV-infected lymphoma patients are performed at centers with extensive HIV expertise, thus limiting the availability of stem cell transplantation for these patients.

To address the need for increased access to ASCT for HIV-infected patients, the Blood and Marrow Transplant Clinical Trials Network and the AIDS Malignancy Consortium conducted a phase 2 multicenter trial. Results were presented by Dr Joseph Alvarnas. The trial enrolled 43 patients with treatable HIV-1 infection and aggressive lymphoma that was chemotherapy-sensitive, relapsed, or refractory.[2] Patients with concurrent opportunistic infections were excluded. Patients received the modified BEAM regimen, consisting of carmustine (300 mg/m^2 on day -6), etoposide (100 mg/m^2 twice daily on days -5 to -2), cytarabine (100 mg/m^2 on days -5 to -2), and melphalan (140 mg/m^2 on day -1). Patients underwent ASCT on day 0 and received standard supportive care until discharge. cART therapy was withheld during the BEAM regimen and was resumed following resolution of any gastrointestinal toxicities. Azidothymidine was prohibited based on its myelosuppressive effects. The trial's primary endpoint was OS at 1 year, with secondary endpoints of PFS, lymphoma-free survival, ORR, disease response, transplant-related mortality, hematopoietic recovery, and complications after transplant.

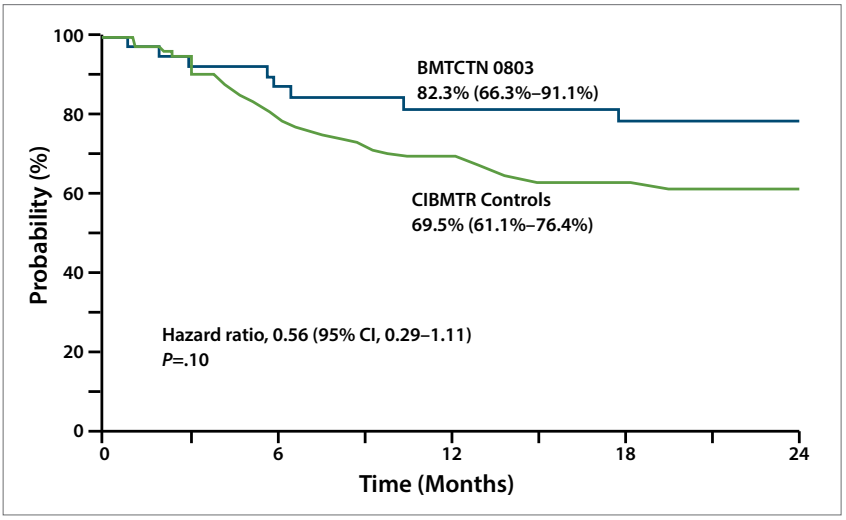

Figure 4. Progression-free survival in a phase 2, multicenter trial of autologous hematopoietic stem cell transplantation in patients with HIV-1 infection and lymphoma. BMTCTN, Blood and Marrow Transplant Clinical Trials Network; CIBMTR, Center for International Blood and Marrow Transplant Research. Adapted from Alvarnas J et al. ASH abstract 674. *Blood*. 2014;124(21 suppl).[2]

Patients had a median age of 46.9 years, and the majority of patients were male. Lymphoma subtypes

included diffuse large B-cell lymphoma (DLBCL; 43%), HL (37.5%), Burkitt or Burkitt-like lymphoma (17.5%), and plasmablastic lymphoma (5%). Most patients (95%) had a Karnofsky score of at least 80%. Prior to transplant, 75% of patients were in CR, 20% were in PR, and 5% had relapsed or progressive disease. The pretransplant HIV viral load was undetectable in 31 patients (77.5%). In patients with detectable HIV, median viral load prior to transplant was 84 copies/mL. The median CD4-positive cell count was 250.5 cells/μL (range, 39-17,000 cells/μL).

Among the 43 enrolled patients, 40 underwent ASCT. The 3 patients who did not undergo stem cell transplantation had experienced lymphoma progression and were not included in the study analysis. All patients mobilized adequate numbers of hematopoietic stem cells, and the median stem cell dose was 3.9×10^6 cells/kg. After 24 months of follow-up, the estimated 1-year OS was 86.6% (95% CI, 70.8%-94.2%), estimated 1-year PFS was 82.3%, and the risk for progression at 1 year was 12.5% (Figure 4). Disease responses assessed at day 100 after transplant showed a CR rate of 92.3%, with 1 patient (2.6%) in PR, 2 patients (5.1%) with relapsed or progressive disease, and 1 patient (2.6%) who died on day 64 and was therefore not evaluable. Five patients died within 1 year of undergoing ASCT: 3 from recurrent or persistent disease, 1 from fungal infection, and 1 from cardiac arrest. The projected nonrelapse mortality rate at 12 months was 5.2%. The median time to neutrophil engraftment was 11 days (range, 9-32 days), and the median time to platelet recovery was 18 days (range, 9-176 days). At 100 days posttransplant, 28.9% of patients had recovered hematologic function, one of the trial's secondary endpoints; this rate increased to 75% by 1 year after ASCT.

Posttransplant toxicities were recorded through 1 year after the procedure. AEs of grade 3 or higher were observed in 15 patients (37.5%) and included grade 4 toxicities in 2 (5%). Nine patients experienced a total of 13 grade 3 to 5 AEs; infections and sepsis were the most common events. Seventeen patients developed at least 1 infection after ASCT, with 42 infectious events of any grade and 9 severe infections. Trial results were compared with outcomes collated in the Center for International Blood and Marrow Transplant Research database, which has results from 151 lymphoma patients without HIV. Most of these control patients (93%) had undergone ASCT within 2 years of the HIV patients in the current study, and patients were also matched for age, performance status, disease subtype, and disease stage. No significant differences emerged between the 2 patient groups based on overall mortality, treatment failure, or transplant-related mortality. Moreover, rates of PFS and OS were similar between the HIV-infected patients and the uninfected patients.

ABSTRACT SUMMARY Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor, Shows Activity in Patients With Relapsed/Refractory T-Cell Lymphoma

Approved agents for relapsed PTCL and cutaneous T-cell lymphoma have ORRs in the range of 25% to 35%. Duvelisib (IPI-145) is an oral inhibitor of phosphoinositide-3-kinase δ and γ isoforms, which are expressed in leukocytes and are key regulators of growth, survival, and other cellular functions. Duvelisib was evaluated in 35 patients with relapsed or refractory PTCL (n=16) and cutaneous T-cell lymphoma (n=19; Abstract 803). The dosages of duvelisib ranged from 25 mg twice daily to 100 mg twice daily, with the majority of patients receiving 75 mg twice daily. Patients had a median age of 64 years (range, 34-86 years) and had received a median 4 prior therapies (range, 1-11). The 31 evaluable patients yielded an ORR of 42%, with ORRs of 53% in PTCL and 33% in cutaneous T-cell lymphoma. The median time to response was 1.9 months (range, 1.5-3.8 months). For PTCL patients, the median PFS was 8.3 months, and the median duration of response was not reached. For cutaneous T-cell lymphoma patients, the median PFS was 4.5 months, and the median duration of response was 8.1 months. Ten patients were evaluated with early PET imaging, and an early reduction in SUV generally corresponded with persistent response. The 4 patients who did not show an early PET response did not go on to develop a response. The safety profile was consistent with prior reports, with the most common AE being transaminase elevation. Most AEs were manageable. Three deaths occurred within 30 days of treatment, including 1 from disease progression.

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Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides or Sézary Syndrome: Final Results Show Significant Clinical Activity and Suggest Correlation With CD30 Expression

CD30, the target of brentuximab vedotin, is expressed uniformly in the malignant cells of HL and anaplastic large cell lymphoma (ALCL). Systemic ALCL is an aggressive subtype of mature T-cell lymphoma. Approximately half of systemic ALCL patients relapse after frontline treatment, and a phase 2 study was conducted to investigate the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory systemic ALCL.[1] Results presented by Dr Barbara Pro. Patients received brentuximab vedotin (1.8 mg/kg) every 3 weeks for up to 16 cycles. Survival and disease status were assessed every 3 months for the first 2 years, every 6 months during years 3 to 5, and annually thereafter. The study enrolled 58 patients, who had received a median 2 prior systemic chemotherapy regimens (range, 1-6). Seventy-two percent of patients had *ALK*-negative disease and 62% had primary refractory disease. In 26%, prior ASCT had been unsuccessful. Based on investigator assessment, the ORR was 83%, with 66% CRs. After discontinuation, 18 patients (31%) underwent a hematopoietic stem cell transplantation (allogeneic in 9 patients and autologous in 9 patients), and 12 patients received additional cycles of brentuximab vedotin, including 8 patients who relapsed after the first course. For the 4-year survival analysis, the median observation time from the first dose was 46.3 months (range, 0.8-57.7 months). The estimated 4-year survival rate was 64% (95% CI, 51%-76%). Median PFS based on investigator assessment was 20.0 months (95% CI, 9.4 months-not reached). Among the 38 patients with a CR, 19 (50%) remained progression-free. Of these 19 patients, 11 had undergone consolidative stem cell transplantation and 8 had received no further therapy. Therefore, long-term remissions occurred with and without consolidative stem cell transplantation. A randomized phase 3 study, ECHELON-2 (A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas), is evaluating brentuximab vedotin combined with cyclophosphamide, doxorubicin, and prednisone as first-line treatment for patients with CD30-positive, mature T-cell lymphomas, including systemic ALCL.[3]

CD30 expression is uniform in ALCL cells. In mycosis fungoides and Sézary syndrome, however, the level of expression differs and can vary even within the same patient. In a study presented at ASH 2012 by Dr Youn Kim, brentuximab vedotin had clinical activity in mycosis fungoides and Sézary syndrome, but there was no correlation between levels of CD30 expression and treatment efficacy.[4] Based on promising results from this study, brentuximab vedotin was investigated in the same patient population in an investigator-initiated phase 2 trial, with final results presented by Dr Kim at ASH 2014.[5] CD30 expression levels in the skin as a percentage of total mononuclear cell infiltrate were evaluated by immunohistochemistry. At least 2 skin biopsies were obtained from each patient, and the maximum CD30 level obtained from analysis was used to categorize expression levels for each patient and then to group patients into 3 cohorts of CD30 expression levels. All patients, regardless of CD30 expression levels, were treated with up to 8 cycles of brentuximab vedotin (1.8 mg/kg) every 3 weeks. An optional extension of treatment for up to 8 additional cycles was permitted in patients who showed clinical improvement. The tumor microenvironment was evaluated by immunohistochemistry for CD8, CD20, CD163, FoxP3, and PD-1. CD30 antigen coexpression was evaluated by multispectral image analysis. The study's primary objective was to achieve an ORR of at least 35%, with secondary endpoints including biomarker expression and safety.

All 32 patients enrolled in the study received at least 1 dose of brentuximab vedotin. Patients had a median age of 62 years (range, 20-87 years). Most patients (88%) had advanced-stage disease and the adverse prognostic features of large-cell transformation and/or folliculotropism (90%). Patients had received a median 3 prior therapies (range, 1-13). CD30 expression levels were below 10% in 43% of patients, between 10% and 50% in 43% of patients, and greater than 50% in 13% of patients. Among the 30 patients evaluated for response, the ORR was 70%. Responses were seen for all disease stages, including stage IB (n=4; 75%), stage IIB (n=18; 78%), and stage IV/Sézary syndrome (n=8; 50%). One patient achieved a CR, and 19 patients achieved a PR. Based on the best percent change shown by the skin-modified severity-

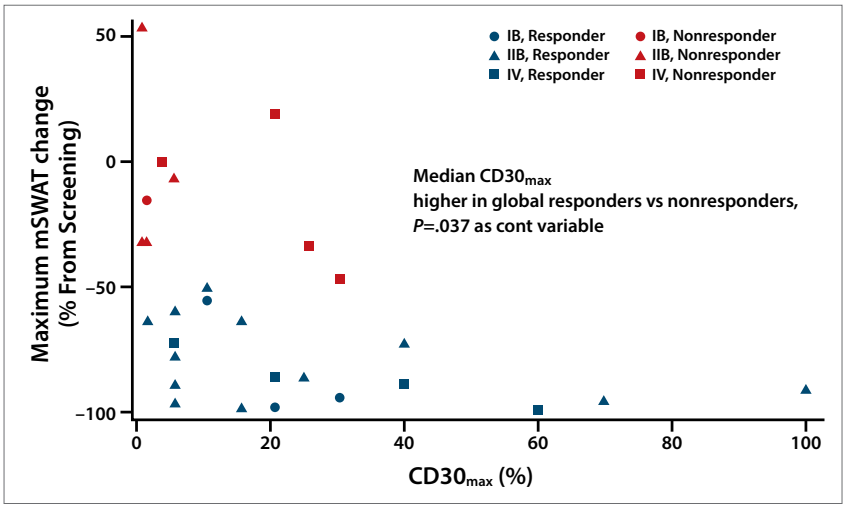

Figure 5. Correlation between levels of CD30 expression and response in a phase 2 trial of brentuximab vedotin in mycosis fungoides or Sézary syndrome. Adapted from Kim YH et al. ASH abstract 804. *Blood*. 2014;124(21 suppl).[5]

weighted assessment tool (mSWAT) score, 21 patients achieved an improvement of at least 50%. Median best mSWAT reduction was 73%, and 8 patients showed an mSWAT reduction of greater than 90%. Median time to response was 6.6 weeks (range, 3.0-27.0 weeks), and Kaplan-Meier estimates showed continuing responses in 90% of patients at 6 months and 79% of patients at 12 months. Kaplan-Meier estimates also showed PFS rates of 79% at 6 months and 54% at 12 months; event-free survival rates were 61% and 28%, respectively, at those time points. Imaging demonstrated that brentuximab vedotin was active across all compartments of the disease, and was associated with dramatic improvements in the skin, blood compartment, and lymph nodes.

In contrast to the earlier results, the current study showed a correlation between high levels of CD30 expression and increased likelihood of response (P=.037; Figure 5). All 5 of the patients with CD30 maximum expression observed in at least 40% of malignant cells experienced a response, and all of the patients with nonresponsive disease had CD30 expression levels below 40%. Moreover, the response rate was 17% for patients with CD30 expression levels below 5% and 83% for patients with CD30 expression levels of 5% or higher. Some patients responded to brentuximab vedotin despite a lack of CD30 expression by immunohistochemistry; however, multispectral imaging revealed quantifiable CD30 expression in 19 of 20 patients with negligible CD30 expression by immunohistochemistry. Clinical response did not correlate to expression of CD8 or Foxp3, or to the presence of PD-1–positive T cells, B cells, or macrophages in the baseline tissue microenvironment. However, an abundance of tumor-associated macrophages showed significant coexpression of CD30, which may affect the activity of the study drug. Tumor-associated macrophages, detected by expression of CD163, were the most abundant infiltrating cells, representing a median 40% of the total infiltrate. These macrophages play an important role in tumor development in several tumor types, and the depletion of macrophages was shown to slow tumor development in a mouse xenograft model of cutaneous T-cell lymphoma. To distinguish between CD30 expression by neoplastic vs infiltrating cells, coexpression of CD30/CD8 or CD30/CD163 was assessed. Coexpression of CD30 was observed in 9.7% of CD163-positive macrophages (range, 1.0%-40.9%). In CD8-positive cytotoxic T cells, coexpression of CD30 was observed in 1.7% of cells (range, 0.2%-14.8%). Given the abundance of tumor-associated macrophages expressing significant levels of CD30, the mechanism of action of clinical response may be affected by these cells. The most common treatment-related AEs of any grade in the safety population of 32 patients were peripheral neuropathy (66%), fatigue (47%), and nausea (28%). Grade 3/4 AEs included neutropenia (13%), skin eruptions (9%), and peripheral neuropathy (3%). Some cases of peripheral neuropathy were irreversible.

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Rituximab Maintenance Versus Wait and Watch After Four Courses of R-DHAP Followed By Autologous Stem Cell Transplantation in Previously Untreated Young Patients With Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective LyMa Trial, a LYSA Study

Mantle cell lymphoma accounts for approximately 6% of non-Hodgkin lymphoma cases.[1] The disease follows a variable course, and there is no consensus regarding optimal frontline treatment. Most patients eventually relapse, and the median OS is approximately 5 to 7 years. The German Low Grade Lymphoma Study Group showed that the addition of rituximab to CHOP (R-CHOP; rituximab 375 mg/m^2 on day 1, cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, and prednisone 100 mg on days 1-5) induction chemotherapy prolongs survival in previously untreated mantle cell lymphoma patients.[2] In older mantle cell lymphoma patients, maintenance rituximab prolonged OS in those who responded to induction R-CHOP.[3] Dr Steven Le Gouill presented the first interim analysis from the LyMa (Randomized, Open-Label, Phase III Study Efficacy of Rituximab Maintenance Therapy in Patients 18 to 65 Years, First-Line Treatment for Mantle Cell Lymphoma) trial of rituximab maintenance after chemotherapy and ASCT in previously untreated, young mantle cell lymphoma patients.[4] The trial enrolled patients aged 65 years or younger. Patients received 4 courses of R-DHAP (rituximab 375 mg/m^2 on day 1, dexamethasone 40 mg on days 1 to 4, cytarabine 2000 mg/m^2 on day 2, and cisplatin 100 mg/m^2 on day 1). Patients who responded received R-BEAM conditioning followed by ASCT.[5] Patients were then randomized to observation or rituximab maintenance (375 mg/m^2 once every 2 months for 3 years). Patients with no response after 4 courses of R-DHAP were permitted to receive 4 subsequent courses of R-CHOP. The trial's primary objective was event-free survival at 4 years, with secondary endpoints including PFS, OS, and CR rate.

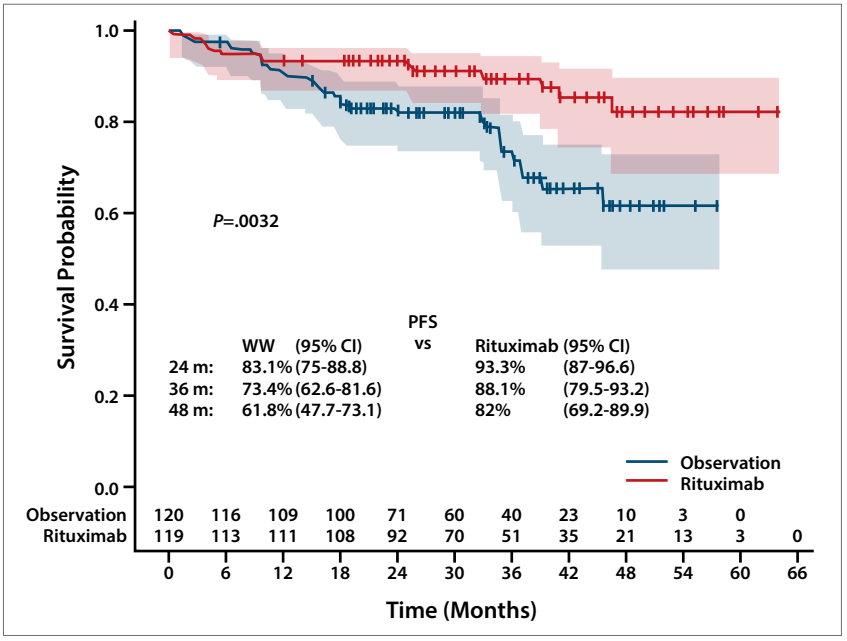

Figure 6. Progression-free survival (PFS) in a phase 3 trial comparing rituximab maintenance therapy with a watch-and-wait (WW) approach in mantle cell lymphoma. Adapted from Le Gouill S et al. ASH abstract 146. *Blood*. 2014;124(21 suppl).[4]

Patients had a median age of 57 years (range, 27-65), and 78.9% were male. The Mantle Cell Lymphoma International Prognostic Index (MIPI) score was low in 53.2% of patients, intermediate in 24.7%, and high in 19.4%. Among the 299 enrolled patients, 266 (89%) received 4 complete courses of R-DHAP, and 6.7% of patients received R-CHOP. Among the 257 patients (86%) who underwent ASCT after induction, 239 (92.7%) achieved a CR and were randomized to observation or rituximab maintenance. Patient characteristics were well balanced between the 2 randomization arms based on age, sex, blastoid presentation, disease stage, and MIPI score.

Few toxic or infectious events were observed during the maintenance period. After a median follow-up of 34.3 months, the interim analysis of survival rates from the time of randomization showed an improvement in 4-year event-free survival of 80.4% (95% CI, 67.2%-88.7%) in the rituximab arm compared with 61.8% (95% CI, 47.7%-73.1%) in the observation arm (*P*=.0057). PFS was also significantly improved with rituximab maintenance therapy (82%

[95% CI, 69.2%-89.9%] vs 61.8% [95% CI, 47.7%-73.1%] with observation; *P*=.0032; Figure 6). However, OS was similar between the 2 arms (83.4% [95% CI, 70.2%-91.1%] vs 83.6% [95% CI, 72.8%-90.5%]; *P*=.7175). Ancillary studies of minimum residual disease and ^{18}F-fluorodeoxyglucose (FDG)-PET will be performed in 2015, and final results from the study are expected in 2016.

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Results of a Phase II Trial of Brentuximab Vedotin as First Line Salvage Therapy in Relapsed/Refractory HL Prior to AHCT

Approximately 20% to 30% of HL patients relapse after induction therapy with ABVD or are refractory to treatment.[1-4] Although standard first-line salvage regimens have high response rates, they are associated with significant toxicities, including grade 3/4 thrombocytopenia and febrile neutropenia. In addition, transfusions of peripheral red blood cells or platelets are often necessary, and stem cell mobilization sometimes fails. In a pivotal phase 2 trial, brentuximab vedotin yielded an ORR of 75%, including 34% CRs, in patients with relapsed or refractory HL after ASCT.[5] The only reported grade 4 AE was neutropenia, which occurred in 6% of patients. In an effort to provide a less toxic alternative to current regimens, brentuximab vedotin was investigated as first-line salvage therapy prior to ASCT in a prospective, multicenter, phase 2 trial of HL patients.[6] Results were presented by Dr Robert Chen. Patients in this study were ages 10 years or older, and they had histologically documented, CD30-positive HL at relapse. Other inclusion criteria included failure to achieve induction with prior therapy, radiographically measurable disease, and adequate organ function. Patients were excluded if they had received any second-line salvage therapy or had undergone stem cell transplantation.

Brentuximab vedotin (1.8 mg/kg) was administered in the outpatient setting every 3 weeks for up to 4 cycles. Radiographic assessment with CT or PET was performed after 2 cycles. Patients who achieved a CR, PR, or stable disease after 2 cycles received an additional 2 cycles of treatment. Patients then underwent both CT and PET or a combined CT-PET scan. Patients whose imaging demonstrated a CR then underwent ASCT; patients with a PR could continue directly to stem cell transplantation or receive further salvage chemotherapy. Patients who developed progressive disease received salvage chemotherapy and were removed from

ABSTRACT SUMMARY A Phase 1 Evaluation of Duvelisib (IPI-145), a PI3K-δ,γ Inhibitor, in Patients With Relapsed/Refractory iNHL

Duvelisib was evaluated in a study of patients with indolent non-Hodgkin lymphoma (Abstract 802). Pharmacodynamic studies and observed clinical activity supported an optimal biologic dose of 25 mg twice daily with continuous dosing in a 28-day cycle. Expansion cohorts escalated the dosage to 75 mg twice daily. Among the 36 enrolled patients, 18 were treated with 25 mg twice daily, the dosage that was selected for phase 2 and phase 3 studies. Sixteen patients received the drug at 75 mg twice daily, and 2 patients received other doses. For the patients treated at 25 mg twice daily, the median age was 63 years, and the median number of prior therapies was 3. The median time on treatment was 11.8 months. Seven patients discontinued treatment owing to AEs, and 4 discontinued owing to disease progression. The ORR was 72%, including a CR rate of 33%. The median time to response was 1.8 months, and three-fourths of patients who responded did so by their first assessment. The 13 patients with follicular lymphoma yielded an ORR of 69%, including 38% CRs. CT scans showed that all patients exhibited lymph node reduction. This reduction was at least 50% among 13 of the 17 patients treated continuously at 25 mg twice daily. Median PFS and median OS were not reached. At 24 months, PFS was 69% and OS was 89%. Duvelisib demonstrated an acceptable safety profile. At the dosage of 25 mg twice daily, the most common grade 3 AEs were diarrhea (32%) and transaminase elevation (32%). The most common grade 4 AEs were neutropenia (11%), pneumonia (5%), and transaminase elevation (5%).

Table 4. Response in a Phase 2 Trial of Brentuximab Vedotin as First-Line Salvage Therapy in Relapsed/Refractory Hodgkin Lymphoma

	Best Response (%)	Best Response at Cycle 2 (%)	Response at Cycle 4 or End of Treatment (%)
Overall response	69	67	61
Complete response	36	36	36
Partial response	33	31	25
Stable disease	28	31	27
Progressive disease	3	3	11

Data from Chen RW et al. ASH abstract 501. *Blood*. 2014;124(suppl 21).[6]

the trial. The study's primary endpoint was ORR, with secondary endpoints of toxicity, stem cell mobilization rate, engraftment, and biomarker assessment. A Simon optimal 2-stage design was used to assess ORR. After the first stage, 12 of 23 patients (52%) had to achieve a CR or PR to continue with the trial. The second stage was designed to accrue up to 37 patients, and investigation would proceed if the response rate reached 60% (23 or more CRs or PRs).

The trial enrolled 37 patients with a median age of 34 years (range, 11-67 years). Approximately half of patients had stage III or IV disease. Sixty-five percent had primary refractory disease. B symptoms at baseline were found in 62%, and 86% had bulky disease (defined as a tumor mass greater than 5 cm). ABVD was the first-line treatment in 92%, and 35% of patients had relapsed within 7 months of their first-line treatment. The 36 evaluable patients showed an ORR of 69%, including 36% CRs and 33% PRs (Table 4). All of the 13 patients who achieved a CR did so after the second treatment cycle and sustained the CR through the end of cycle 4. There were 12 patients who achieved a PR as their best response, which occurred after cycle 2 in 11 and persisted through the end of treatment in 9. Based on univariate analysis, no differences in response rates emerged in terms of age, sex, disease stage, response to induction treatment, bulky disease, or B symptoms.

Brentuximab vedotin was associated with a low rate of hematologic and nonhematologic AEs. Grade 3/4 hematologic AEs included neutropenia (5%) and lymphopenia (6%). No patients required growth factors, peripheral red blood cell transfusions, or platelet transfusions. The most common grade 3/4 nonhematologic AE was rash (occurring in 5%); aspartate transaminase elevation, hyperuricemia, tumor lysis syndrome, pruritus, and elevated creatinine each occurred in 1 patient (3%). Based on previous reports of AEs associated with brentuximab vedotin, the occurrence of rash was unexpected. Rashes of grade 1, 2, and 3 were observed in 24%, 11%, and 5% of patients, respectively. No grade 4 rash was reported.

Among the 37 patients enrolled in the study, 33 (89%) proceeded to ASCT. One patient received allogeneic stem cell transplantation, and 3 patients were refractory to salvage therapy. Of the 33 patients who underwent ASCT, 17 (52%) received brentuximab vedotin as their only salvage treatment, and 16 (48%) received additional salvage chemotherapy. At the time of the stem cell transplantation, 24 patients (73%) were in CR, 8 (26%) were in PR, and 1 (3%) had stable disease. For stem cell mobilization, patients were primed with granulocyte colony–stimulating factor plus cyclophosphamide or plerixafor. The median number of days to neutrophil engraftment was 11 (range, 10-12), and the median number of days to platelet engraftment was 13 (range, 9-23), consistent with results observed in other studies. Because the presence of increased numbers of CD68-positive macrophages is associated with a higher risk of relapse after ABVD induction and ASCT, tumor samples taken prior to treatment in the current study were tested for the presence of CD68 by immunohistochemistry.[7] All of the tumors showed some level of CD68 staining, consistent with the fact that in nearly all enrolled patients, ABVD or a related treatment had failed prior to study entry. However, no correlation was observed between the level of CD68 expression at baseline and response to brentuximab vedotin. In this phase 2 trial, patients who did not achieve a CR after 2 cycles of treatment showed a risk of progression. Therefore, the trial protocol was amended so that patients who fail to achieve a CR after 2 cycles of brentuximab vedotin dosed at 1.8 mg/kg will then receive 2 cycles of brentuximab vedotin at 2.4 mg/kg. Twenty patients have been added to the study to test brentuximab vedotin following the revised protocol.[8]

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Highlights in Lymphoma From the 2014 ASH Meeting

Craig H. Moskowitz, MD

Potential practice-changing studies made 2014 a banner year for lymphoma at the American Society of Hematology (ASH) meeting. Presentations included results from 4 randomized trials, which evaluated brentuximab vedotin as consolidation therapy after transplantation; ofatumumab combined with dexamethasone, cytarabine, and cisplatin (DHAP); use of positron emission tomography (PET) to guide selection of therapy; and rituximab consolidation therapy after 4 cycles of rituximab plus DHAP (R-DHAP) and transplantation. Additional clinical trials of brentuximab vedotin evaluated its use as first salvage therapy and in combination with bendamustine. Several studies focused on novel treatment approaches, such as the checkpoint inhibitors and chimeric antigen receptor (CAR)–modified T cells.

Randomized Clinical Trials

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 a randomized, placebo-controlled, double-blind study of brentuximab vedotin in the treatment of Hodgkin lymphoma patients at risk for progression following autologous stem cell transplantation.[1] It is the first placebo-controlled, phase 3 study in this setting. The impetus for the study is that only 50% of patients who undergo transplantation for Hodgkin lymphoma are cured,[2-5] a rate that has been at a plateau for the past 20 years. It was hoped that the addition of brentuximab vedotin posttransplant in a consolidation fashion could improve this outcome.

The study included 329 patients at 78 sites across North America and Europe. Patients were stratified upfront based on poor risk factors, including primary refractory disease, remission duration of less than 12 months, and late relapse with extranodal involvement. All patients received salvage chemotherapy. Patients with no evidence of disease progression were eligible to receive brentuximab vedotin posttransplant for up to 1 year. Patients who were randomly assigned to placebo were eligible to enroll in a companion study to receive brentuximab vedotin free of charge. The study population had unexpectedly poor risk: 60% had primary refractory Hodgkin lymphoma, and 45% had required more than 1 salvage regimen to achieve chemosensitive disease.

The primary endpoint of the study was progression-free survival. At 24 months, the progression-free survival for the patients who received brentuximab vedotin consolidation therapy was 65%, compared with 45% among the patients who received placebo (hazard ratio, 0.5; $P<.0001$). There was no difference in overall survival, but one was not expected based on the short follow-up and the crossover design, which led to 85% of the placebo patients subsequently receiving brentuximab vedotin.

When this study was originally designed in 2009, the median survival for Hodgkin lymphoma patients in whom stem cell transplantation had failed was 26 months.[6] In 2015, the median survival is now longer than 4 years. This improvement can be attributed to new and novel agents, including brentuximab vedotin, the checkpoint inhibitors, and the histone deacetylase inhibitors. It will take several more years for a difference in overall survival to emerge in the AETHERA patient population. However, the study results will likely make consolidation therapy with brentuximab vedotin the standard of care in this patient population.

The international, multicenter, randomized phase 3 ORCHARRD (Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy Followed by Autologous Stem Cell Transplant in Relapsed or Refractory Diffuse Large B Cell Lymphoma) study had disappointing results.[7] This study was presented by Dr Gustaaf van Imhoff, for a consortium led by the Hemato-Oncology Cooperative (HOVON) group. This random assignment trial compared ofatumumab vs rituximab salvage chemoimmunotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma. Patients were randomly assigned to receive rituximab and DHAP chemotherapy or ofatumumab and DHAP chemotherapy followed by stem cell transplantation and follow-up. Treatment was given for 3 cycles. The primary endpoint was progression-free survival, and the secondary endpoints were overall survival and response. It was expected that the addition of ofatumumab, as opposed to rituximab, would improve pretreatment response rates and thereby increase progression-free survival. The study had 90% power to detect a 15% improvement in 2-year progression-free survival (from 25% in the rituximab arm to 40% in the ofatumumab arm).

The ORCHARRD trial, with data for 447 patients, is one of the largest performed in the salvage setting. The baseline characteristics were well balanced between the treatment arms. The overall response rate for rituximab and DHAP chemotherapy was 42%, vs 38% for ofatumumab and chemotherapy. Rates of complete response, partial response, and stable disease were similar between the treatment arms. Median 2-year progression-free survival was poor in both treatment arms: 26% with rituximab and 21% with ofatumumab. There were similar numbers of deaths, almost

all of which were related to lymphoma. Based on the results of this study, rituximab and DHAP chemotherapy should continue to be the standard of care.

The randomized PETAL (Positron Emission Tomography Guided Therapy of Aggressive Non-Hodgkin's Lymphomas) trial evaluated PET-guided therapy for aggressive lymphoma.[8] This interesting study incorporated prospective evaluation of interim PET scanning based on the δ standardized uptake value (SUV) to risk-stratify patients into different treatment arms. Nearly all the patients had diffuse large B-cell lymphoma. They received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for 2 cycles, followed by an interim PET scan. Using the δ SUV of 66% as a cutoff, patients were randomized. Those with a negative PET scan could receive continued R-CHOP with or without a few extra doses of rituximab, and those with a positive PET scan could receive R-CHOP or an aggressive combination chemotherapy regimen similar to that used in Burkitt lymphoma.

Use of a δ SUV of 66% as a cutoff led to a significant difference in outcome between patients with a negative PET scan and those with a positive PET scan. Time to treatment failure was significantly longer in patients with a favorable PET scan. Unfortunately, the use of more aggressive therapy in patients with a positive PET scan at the interim evaluation did not improve outcome compared to standard R-CHOP–based treatment. The conclusion of this study is that interim PET continues to be an important prognostic tool to risk-stratify patients into different types of therapy. However, the use of more aggressive chemotherapy in patients who have an abnormal PET scan at interim restaging did not improve outcome.

The Lymphoma Study Association presented the first interim analysis of a phase 3 trial comparing rituximab consolidation therapy vs observation after R-DHAP chemotherapy and autologous stem cell transplantation among younger patients with mantle cell lymphoma.[9] All patients received 4 cycles of R-DHAP. Those who achieved a complete response or partial response were subsequently transplanted. Those patients (n=238) were then randomly assigned to receive 2 years of consolidative rituximab given in a bimonthly schedule (12 doses) or to undergo observation. Notably, patients who achieved less than a partial response to R-DHAP could receive additional R-CHOP to allow transplantation. The primary endpoint was event-free survival at 4 years after randomization. The patient population was typical for mantle cell lymphoma transplantation studies, with a median age of 57 years. The 2-year event-free survival was 93.2% in the rituximab arm vs 81.5% in the watch-and-wait arm (hazard ratio, 2.1; *P*=.01). Patients who received rituximab consolidation therapy had a 2-year overall survival of 93.4% vs 93.9% in the watch-and-wait arm.

It is interesting that the regimen used in this study mirrors the rituximab consolidative strategy used in patients who are ineligible for transplantation. Whether this approach will become the standard of care posttransplant is a matter of debate. However, this study did achieve its primary endpoint of improvement in progression-free survival.

The Checkpoint Inhibitors

Likely the most exciting data in lymphoma management presented at the 2014 ASH meeting were the study results of the checkpoint inhibitors nivolumab and pembrolizumab. In classical Hodgkin lymphoma, there is frequent amplification on chromosome 9p24.1, consisting of upregulation of the programmed death-1 (PD-1) receptor ligands and the Janus kinase 2 (JAK2). There is a hypothesis that classical Hodgkin lymphoma may have a genetically driven dependence on PD-1, an idea that appears to be supported by the results of these clinical trials.

Nivolumab is a fully human immunoglobulin (Ig) G4 anti–PD-1 antibody that blocks the interaction between the PD-1 receptor and its ligands, PD-L1 and PD-L2. Dr Philippe Armand presented results from a phase 1 trial of 23 patients with Hodgkin lymphoma who received 3 mg/kg of nivolumab.[10] The primary endpoint was safety and tolerability, and the secondary endpoint was response rate. Typical for the Hodgkin lymphoma population, these patients were heavily pretreated; 78% had undergone a prior transplantation, and 78% had previously received brentuximab vedotin. Eight patients had received more than 6 prior regimens.

There were no drug-related grade 4 events. One patient developed pancreatitis, and there were several cases of pneumonitis and colitis. In general, however, the safety profile was similar to that seen in solid tumors. The overall response rate was 87%, which included a 17% complete response rate. Several patients had stable disease. Evaluation of the median duration of response in these patients is ongoing. All of the 10 patients who were evaluated for the 9p24 abnormality had it. This study shows that nivolumab can be safely administered and can achieve a high response rate in this patient population.[10,11]

Pembrolizumab is also being evaluated extensively in Hodgkin and non-Hodgkin lymphomas. Pembrolizumab is a humanized IgG4 antibody against PD-1. As with nivolumab, there is a dual ligand blockade of both PD-L1 and PD-L2. Pharmacokinetics suggest a dosing schedule of every 2 weeks or every 3 weeks. Pembrolizumab has already been approved by the US Food and Drug Administration for patients with melanoma.[12] In a phase 1b trial, pembrolizumab was administered to patients in whom transplantation was unsuccessful or unsuitable because of primary progressive disease.[13] Of note, in all of these patients, previous therapy with brentuximab vedotin had failed. The primary endpoint was the complete response rate. Secondary endpoints were response rate and safety. Among the 29 patients enrolled in the study, 20

patients are still receiving therapy. The median duration of response had not been reached at the time the data were presented.

The treatment program was well tolerated, with few extramedullary side effects. The clinical benefit rate was 86%, including a complete response rate of 21% and a partial response rate of 45%. Among the 6 patients with stable disease, a few have been receiving treatment for nearly a year.

Like nivolumab, pembrolizumab demonstrates outstanding activity in patients with heavily pretreated Hodgkin lymphoma. Drug development with pembrolizumab is continuing, and a registration trial will be initiated this year.[14]

In non-Hodgkin lymphoma, a study presented by Dr Alexander Lesokhin evaluated nivolumab in patients with refractory lymphoid malignancies.[15] Among the 69 patients enrolled, 23 had multiple myeloma, 23 had T-cell lymphoma, and 23 had B-cell lymphoma. The patients were heavily pretreated. The safety profile was similar to that seen in patients with Hodgkin lymphoma. The response rates were more muted, though still intriguing. There was a 40% response rate in follicular lymphoma, and a 36% response rate in diffuse large B-cell lymphoma. There appeared to be little activity in patients with multiple myeloma or T-cell lymphoma. Clinical trials are now evaluating nivolumab in different aspects of non-Hodgkin lymphoma management.[16,17]

Brentuximab Vedotin

Presentations at the 2014 ASH meeting included several studies evaluating brentuximab vedotin in various aspects of management. Dr Robert Chen presented phase 2 data of single-agent brentuximab vedotin as first salvage therapy in patients with relapsed and refractory Hodgkin lymphoma.[18] In this interesting study, all patients received standard-dose brentuximab vedotin for 2 cycles and then underwent restaging. Patients with a complete response were subsequently transplanted. Patients who did not achieve a complete response received 2 more cycles of brentuximab vedotin followed by chemotherapy, if necessary.

The results were similar to those in other single-agent studies with brentuximab vedotin in the relapsed setting.[19] The complete response rate was 36%, and the partial response rate was 33%. This overall response rate of 69% is intriguing and better than expected for single-agent presalvage therapy. Unfortunately, none of the patients converted from a partial response to a complete response after the first restaging. The investigators have amended the protocol, and an ongoing study is evaluating a dose-augmented version of brentuximab vedotin in patients who did not achieve a complete response after the first restaging.[20] Based on the results of the study by Dr Chen, as well as a study from the Memorial Sloan Kettering Cancer Center,[21] there is likely to be broad use of brentuximab vedotin as single-agent salvage therapy for patients with Hodgkin lymphoma.

Dr Ann LaCasce presented results of a study that combined brentuximab vedotin with bendamustine as first salvage therapy in patients with Hodgkin lymphoma.[22] In this multicenter study, patients received standard-dose brentuximab vedotin and bendamustine initially in a phase 1 design and then in an expansion cohort. Interestingly, there were several reports of infusion reactions that required steroid use and, at times, fluid and vasopressors. Eventually, the dosing and schedule was worked out, and patients tolerated the treatment fairly well.

Among the 48 patients in this study, 40 achieved a complete response (which occurred at the first restaging in 34). Stem cell collection was adequate. Several patients had undergone transplantation, although follow-up was too short to assess outcome. With the results of this study, the regimen of bendamustine and brentuximab vedotin will likely become another option for salvage therapy in Hodgkin lymphoma.

Novel Treatment Approaches

There were several presentations on novel treatment approaches that may have implications for the management of non-Hodgkin lymphoma. Dr Craig Sauter from the Memorial Sloan Kettering Cancer Center presented results from an interim analysis of a phase 1 trial of high-dose therapy and autologous stem cell transplantation followed by infusion of CAR-modified T cells directed against CD19 for relapsed and refractory aggressive non-Hodgkin lymphoma.[23] In this study, patients with diffuse large B-cell lymphoma who were eligible for transplantation received standard salvage chemotherapy. If they achieved a partial response, but showed residual PET-avid disease at restaging, they were eligible to receive CAR-modified T cells posttransplant; 6 patients were included in this arm. All 6 patients had a normal PET scan and remained in remission at the time of the study presentation. CAR-modified T-cell therapy was associated with several different adverse events, including cytokine release syndrome that required anti–interleukin 6 therapy. This study is ongoing, but if the results hold, they could have implications for the management of diffuse large B-cell lymphoma in the relapsed setting.

Dr Nancy Bartlett presented data on ibrutinib monotherapy in patients with relapsed and refractory follicular lymphoma.[24] Ibrutinib has changed the management landscape for chronic lymphocytic leukemia, and it is now making inroads in the management of diffuse large B-cell lymphoma. In this study, ibrutinib was given at 560 mg/day in a continuous dosing, 28-day schedule. Patients had grade 1, 2, or 3A follicular lymphoma. They had all received at least 1 prior chemotherapy regimen. Patients underwent a lymph node biopsy before treatment and then again if they showed disease progression after response. The primary endpoint was overall response rate. Secondary endpoints included safety and survival.

Among the 40 patients included in the analysis, 45% were refractory to rituximab, and 35% were refractory to their most recent treatment. Their median age was 64 years. The median follow-up was short, at 10 months. The overall response rate was 28%, which is disappointing based on this agent's activity in other lymphomas. A waterfall plot, however, provided stronger data: 72% of the patients experienced a reduction in tumor volume. The 1-year progression-free survival was 50%. It is not known whether these results will lead to further development of ibrutinib in other treatment programs.

Dr Steven Horwitz presented results from a study on duvelisib (also known as IPI-145) in patients with relapsed and refractory T-cell lymphoma.[25] Duvelisib is an oral phosphoinositide-3 (PI-3) kinase δ/ϒ inhibitor. At doses of 25 mg twice daily, it suppresses activity of the PI-3 kinases δ and ϒ. The primary endpoints of this study were the pharmacodynamic parameters and the tumor response. Enrollment included 16 patients with peripheral T-cell lymphoma and 19 patients with cutaneous T-cell lymphoma. Among all evaluable patients in the trial, the overall response rate was 42%, which is high for this disease. The overall response rate was 53% for patients with peripheral T-cell lymphoma (which included 2 complete responses), and 33% for patients with cutaneous T-cell lymphoma.

The median time on study was 8.3 months for patients with peripheral T-cell lymphoma and 14.7 months for patients with cutaneous T-cell lymphoma. The median overall survival was 8.4 months in peripheral T-cell lymphoma, and it had not been reached in cutaneous T-cell lymphoma. The major toxicity was abnormalities in liver function tests at any grade, which occurred in 54% of patients. Grade 4 abnormalities were seen in 2 patients. The authors concluded that the pharmacodynamic response as assessed by PET scan at cycle 1, day 22 may predict for clinical response. The safety was generally well tolerated, and there was clear efficacy in patients with T-cell lymphoma. These results warrant further testing for the optimal dosing of duvelisib and the use of this agent in combination with other active agents in T-cell disease.

Disclosure

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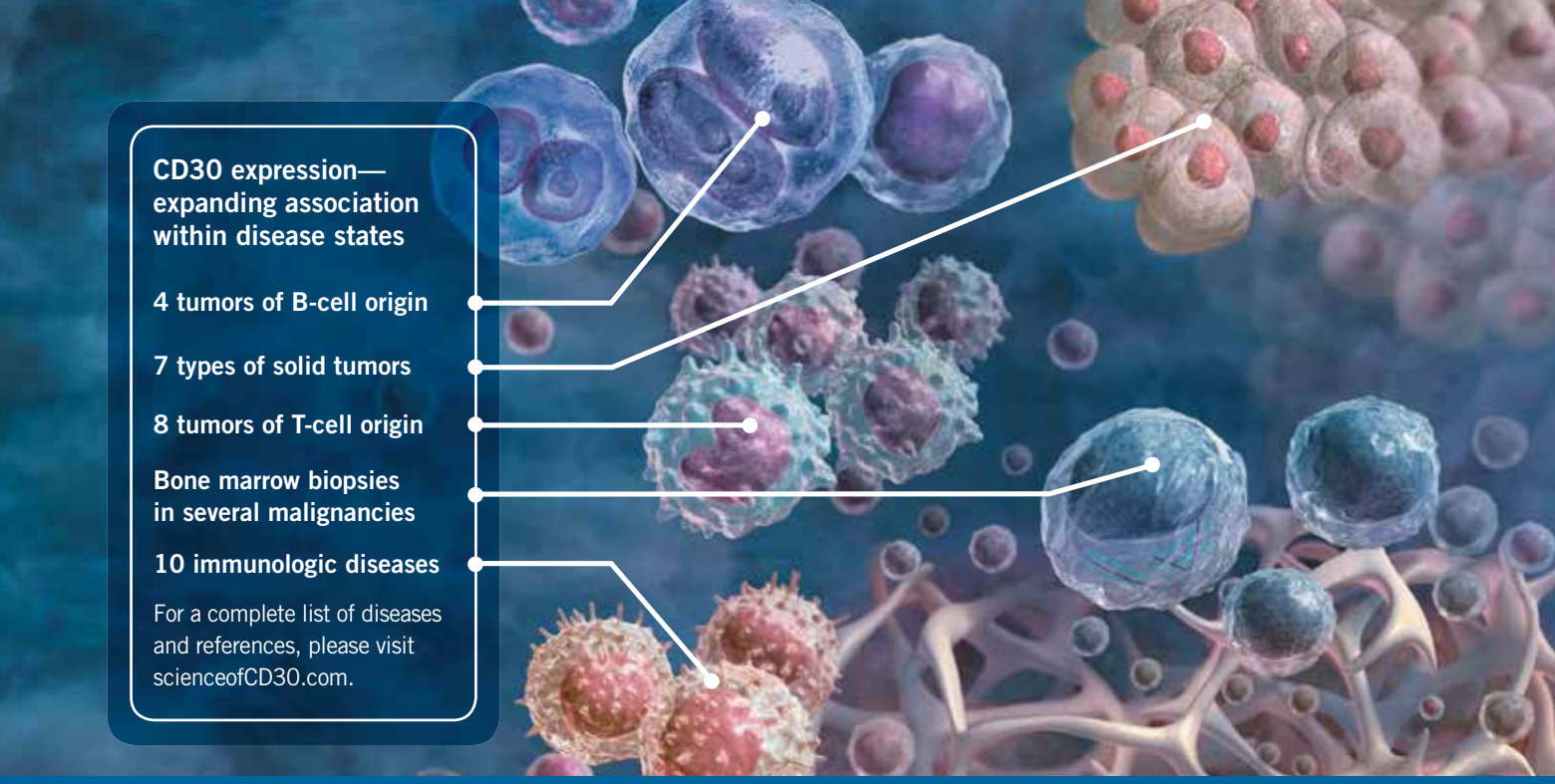

CD30: a valuable clinical marker

Diagnosis—the clinical relevance of CD30: Screening for CD30 can assist with the differential diagnosis of CD30-expressing tumors.[1,2] Immunophenotyping improves diagnostic accuracy by 10% to 45% for a number of major lymphoma subtypes.[3] Because of the unique expression characteristics of CD30, diagnostic screening may also assist in the distinction between different types of germ cell tumors.[4,5]

Prognosis—the prognostic value of CD30: In several types of non-Hodgkin lymphoma, levels of CD30 expression correlate with overall survival (OS). Five-year OS for peripheral T-cell lymphoma, not otherwise specified is 32%, but if ≥80% of the cells are CD30-positive, OS is only 19%. Determining CD30 expression can therefore facilitate a risk-adapted approach to treatment.[2,6-8]

For more information on CD30 expression, and to download an educational presentation on CD30, visit scienceofCD30.com

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