

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2012 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 54th Annual Meeting and Exposition • December 8–11, 2012 • Atlanta, Georgia

Special Reporting on:

- The Addition of Bevacizumab to Standard Therapy With R-CHOP in Patients With Previously Untreated Diffuse Large B-Cell Lymphoma Is Associated With an Increased Rate of Cardiac Adverse Events: Final Analysis of Safety and Efficacy Outcomes From the Placebo-Controlled Phase 3 MAIN Study
- Brentuximab Vedotin Administered Concurrently With Multi-Agent Chemotherapy as Frontline Treatment of ALCL and Other CD30-Positive Mature T-Cell and NK-Cell Lymphomas
- Mature Results From ECOG Study E1405—A Phase II Study of VcR-CVAD With Maintenance Rituximab for Previously Untreated Mantle Cell Lymphoma
- Rituximab Dose-Dense Chemotherapy Followed by Intensified High-Dose Chemotherapy and Autologous Stem Cell Transplantation (HDC+ASCT) Significantly Reduces the Risk of Progression Compared to Standard Rituximab Dose-Dense Chemotherapy as First Line Treatment in Young Patients With High-Risk (aaBIPI 2-3) Diffuse Large B-Cell Lymphoma (DLBCL): Final Results of Phase III Randomized Trial DLCL04 of the Fondazione Italiana Linfomi (FIL)
- Brentuximab Vedotin Demonstrates Significant Clinical Activity in Relapsed or Refractory Mycosis Fungoides With Variable CD30 Expression
- Frontline Therapy With Brentuximab Vedotin Combined With ABVD or AVD in Patients With Newly Diagnosed Advanced Stage Hodgkin Lymphoma
- Safety and Efficacy of Ibrutinib in the Treatment of DLBCL, Follicular Lymphoma (FL), and MCL

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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CD30-directed therapy

Important Safety Information

BOXED WARNING

Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS™ (brentuximab vedotin).

Contraindication:

Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity.

Warnings and Precautions:

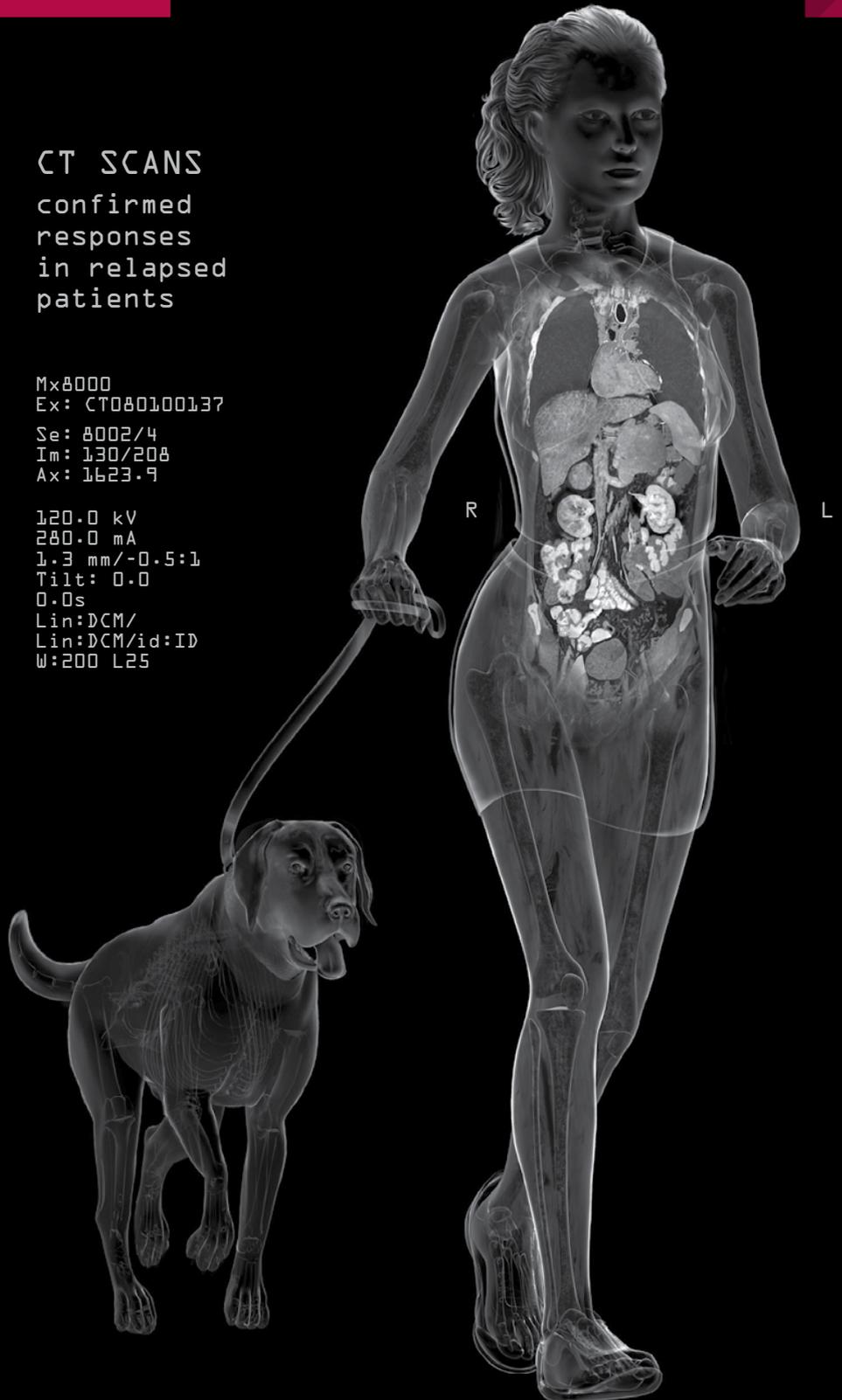
- **Peripheral neuropathy:** ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. Treating physicians should monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.
- **Infusion reactions:** Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an infusion reaction occurs, the infusion should be interrupted and appropriate medical management instituted. If anaphylaxis occurs, the infusion should be immediately and permanently discontinued and appropriate medical management instituted.
- **Neutropenia:** Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions or discontinuation. Prolonged (≥ 1 week) severe neutropenia can occur with ADCETRIS.
- **Tumor lysis syndrome:** Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and these patients should be monitored closely and appropriate measures taken.

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responses
in relapsed
patients

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After multiple failures, single-agent response

Indicated for the treatment of:

- Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT)¹
- HL in patients who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens¹

HL: 73% objective response rate (ORR) (95% CI: 65%-83%)¹

32%
complete remission
(95% CI: 23%-42%)¹

40%
partial remission
(95% CI: 32%-49%)¹

N = 102, 15-77 years (median: 31 years)¹

- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 multiagent chemotherapy regimen¹

sALCL: 86% ORR (95% CI: 77%-95%)¹

57%
complete remission
(95% CI: 44%-70%)¹

29%
partial remission
(95% CI: 18%-41%)¹

N = 58, 14-76 years (median: 52 years)¹

The indications for ADCETRIS™ (brentuximab vedotin) are based on response rate. There are no data available demonstrating improvement in patient-reported outcomes or survival with ADCETRIS.¹



Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on the last page of this ad.

REFERENCE: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc; 2012. US/BVP/2011/0104e

Important Safety Information (continued)

- **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has been reported in ADCETRIS™ (brentuximab vedotin)-treated patients. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture or brain biopsy. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- **Stevens-Johnson syndrome:** Stevens-Johnson syndrome has been reported with ADCETRIS. If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- **Use in pregnancy:** Fetal harm can occur. Pregnant women should be advised of the potential hazard to the fetus.

Adverse Reactions:

ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting.

Drug Interactions:

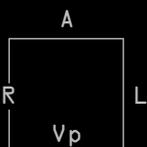
Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.



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CD30-DIRECTED
ADCETRIS[™]
brentuximab vedotin

Brief Summary of Prescribing Information

(see Package Insert for full Prescribing Information)

**WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
JC virus infection resulting in PML and death can occur in patients
receiving ADCETRIS.**

Indications and usage

These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with ADCETRIS.

ADCETRIS[™] (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.

ADCETRIS is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

Contraindications

Pulmonary toxicity: Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids.

Warnings and precautions

Peripheral neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. In the HL and sALCL clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS.

Infusion reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

Neutropenia

Complete blood counts should be monitored prior to each dose of ADCETRIS and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Prolonged (≥ 1 week) severe neutropenia can occur with ADCETRIS. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions, or discontinuations.

Tumor lysis syndrome

Tumor lysis syndrome may occur. Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

Progressive multifocal leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression.

Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture or brain biopsy. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

Stevens-Johnson syndrome

Stevens-Johnson syndrome has been reported with ADCETRIS. If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy.

Use in pregnancy

There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus.

Adverse reactions

ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions ($\geq 10\%$), regardless of causality, were neutropenia, anemia, thrombocytopenia, lymphadenopathy, peripheral sensory neuropathy, peripheral motor neuropathy, headache, dizziness, fatigue, pyrexia, chills, pain, edema peripheral, upper respiratory tract infection, nausea, diarrhea, abdominal pain, vomiting, constipation, rash, pruritus, alopecia, night sweats, dry skin, cough, dyspnea, oropharyngeal pain, arthralgia, myalgia, back pain, pain in extremity, muscle spasms, insomnia, anxiety, decreased appetite and weight decreased.

ADCETRIS was studied in 102 patients with HL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 27 weeks (range, 3 to 56 weeks). The most common adverse reactions ($\geq 20\%$), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting. The most common serious adverse reactions experienced by patients with HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%).

ADCETRIS[™] (brentuximab vedotin) was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 24 weeks (range, 3 to 56 weeks). The most common adverse reactions ($\geq 20\%$), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain. The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%).

Drug interactions

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5.

Effect of other drugs on ADCETRIS

CYP3A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions. Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

Effect of ADCETRIS on other drugs

Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

Use in specific populations

Pregnancy

Pregnancy Category D. There are no adequate and well-controlled studies with ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption ($\geq 99\%$), post-implantation loss ($\geq 99\%$), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with HL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

Nursing mothers

It is not known whether brentuximab vedotin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADCETRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

The safety and effectiveness of ADCETRIS have not been established in the pediatric population. Clinical trials of ADCETRIS included only 9 pediatric patients and this number is not sufficient to determine whether they respond differently than adult patients.

Geriatric use

Clinical trials of ADCETRIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Safety and efficacy have not been established.

Renal impairment

The kidney is a route of excretion for MMAE. The influence of renal impairment on the pharmacokinetics of MMAE has not been determined.

Hepatic impairment

The liver is a route of clearance for MMAE. The influence of hepatic impairment on the pharmacokinetics of MMAE has not been determined.

Overdosage

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

Dosage and administration

General dosing information

The recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. Do not administer as an intravenous push or bolus. Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

Dose modification

Peripheral Neuropathy: Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.2 mg/kg. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, ADCETRIS should be discontinued.

Neutropenia: Neutropenia should be managed by dose delays and reductions. The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg may be considered.

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The Addition of Bevacizumab to Standard Therapy With R-CHOP in Patients With Previously Untreated Diffuse Large B-Cell Lymphoma Is Associated With an Increased Rate of Cardiac Adverse Events: Final Analysis of Safety and Efficacy Outcomes From the Placebo-Controlled Phase 3 MAIN Study

Vascular endothelial growth factor (VEGF) plays a significant role in lymphoma growth, with over-expression of VEGF associated with poor patient prognosis.¹⁻³ Treatment of patients with diffuse large B-cell lymphoma (DLBCL) or peripheral T-cell lymphoma with the anti-VEGF antibody bevacizumab has shown promising results as a monotherapy or when used in combination with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).^{1,4,5} The MAIN (MabThera + Avastin in NHL Aggressive) study assessed whether patients with previously untreated CD20+ DLBCL had improved outcomes when bevacizumab was added to standard R-CHOP therapy.⁶ This placebo-controlled, double-blind, phase III trial planned to enroll 1,060 patients to be followed for 60 months in order to detect a 27% reduction in the risk of progression-free survival (PFS). Inclusion criteria included previously untreated DLBCL, an International Prognostic Index (IPI) score of at least 2 or bulky disease irrespective of IPI, and normal cardiac function.

Patients were randomized to receive either placebo or bevacizumab. Bevacizumab was administered at 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. Both placebo-treated and bevacizumab-treated patients received either 8 cycles of R-CHOP21 (80% of patients) or 6 cycles of R-CHOP14 (20% of patients) fol-

lowed by 2 cycles of rituximab. At the end of treatment, patients in the placebo arm were observed until month 12, while patients in the bevacizumab arm received bevacizumab 15 mg/kg every 3 weeks until month 12. Treatment arms were balanced for baseline patient characteristics, including hypertension, cardiac risk factors, and baseline left ventricular ejection fraction. The median age of patients was 61 years, half of the patients in each treatment arm had bulky disease, and 65% of patients had elevated lactate dehydrogenase.

There were 787 patients enrolled in the study from July 2007 to June 2010. In May 2010, there was an increased number of left ventricular ejection fraction adverse events (defined as $\geq 20\%$ absolute decline from baseline and/or a decline of $\geq 10\%$ from baseline to $< 50\%$) observed in patients treated with bevacizumab. As such, the independent Data and Safety Monitoring Board determined that there was an unfavorable benefit-risk profile for patients in the bevacizumab plus R-CHOP treatment arm, so treatment with bevacizumab was discontinued and further enrollment was halted. The study was completed as a safety follow-up of the enrolled patients.

A total of 781 patients were treated, with a median follow-up of 27 months. The median PFS was not significantly different between treatment arms (placebo plus R-CHOP, 42.9 months vs bevacizumab plus

R-CHOP, 40.2 months; hazard ratio [HR], 1.09; $P=.49$). Early survival data indicate that the addition of bevacizumab to R-CHOP did not significantly improve survival (placebo plus bevacizumab, 83 deaths [20.9%] vs bevacizumab plus R-CHOP, 82 deaths [21%]). The median overall survival has not yet been reached in either treatment arm.

Grade 3/4 adverse events occurred in 55% of patients in the placebo plus R-CHOP arm and in 58% of patients in the bevacizumab plus R-CHOP arm. More patients in the bevacizumab arm had serious adverse events (57% vs 45%, respectively). There were 18 patients in the placebo arm (5%) and 32 patients in the bevacizumab arm (98%) who had grade 5 adverse events that resulted in death. Twice as many patients discontinued treatment with bevacizumab compared to placebo (23% vs 11%, respectively). Patients in the bevacizumab plus R-CHOP arm had increased rates of hypertension (bevacizumab arm, 16% vs placebo arm, 4%) and bleeding (19% vs 8%, respectively). Patients in the bevacizumab plus R-CHOP arm also had increased rates of cardiac events when compared to patients in the placebo plus R-CHOP arm (Table 1). Patients treated with bevacizumab had higher rates of left ventricular ejection fraction (18% vs 8%; odds ratio [OR], 2.51; 95% confidence interval [CI], 1.60–3.93) and congestive heart failure adverse events

Table 1. Outcomes of Congestive Heart Failure Events

	Bevacizumab + R-CHOP (n=395)	R-CHOP (n=386)
Patients with CHF event, n	25	64
Total CHF events,* n	27	68
• Resolved, no sequelae, n (%)	43 (63)	21 (78)
• Resolved, with sequelae, n (%)	9 (13)	1 (4)
• Unresolved, n (%)	14 (21)	4 (15)
• Death, n (%)	2 (3)	1 (4)
Median CHF duration, months (95% CI)	7.8 (5.2–12.8)	3.5 (1.9–9.0)

*26 grade 3 or higher events in the bevacizumab arm, 6 grade 3 or higher events in the control arm.

CHF=congestive heart failure; CI=confidence interval; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Data from Seymour JF et al. The addition of bevacizumab to standard therapy with R-CHOP in patients with previously untreated diffuse large B-cell lymphoma is associated with an increased rate of cardiac adverse events: final analysis of safety and efficacy outcomes from the placebo-controlled phase 3 MAIN study. Paper presented at the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 58.

Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCLnet)

In a randomized international study of 455 patients (aged <65 years) with untreated MCL, an alternating course of 3× CHOP and 3× dexamethasone, cytarabine, and cisplatin (DHAP) plus rituximab followed by high-dose cytarabine (10 Gray TBI, 4×1.5 g/m² cytarabine, 140 mg/m² melphalan) and SCT (experimental arm) significantly improved response rates, time to treatment failure, and overall survival compared to the control arm (6 courses of R-CHOP followed by myeloablative radiochemotherapy and ASCT; Abstract 151). The overall response was 95% in the experimental arm and 90% in the control arm ($P=.19$). The experimental arm had a significantly higher complete response rate (36% vs 25%, respectively; $P=.012$). The number of transplants was similar in both arms (80% vs 83%), with similar overall response rates (98% vs 97%) and complete remission rates (61% vs 62%) following transplantation. Patients in the experimental arm had a longer time to treatment failure (88 months) than patients in the control arm (46 months; $P=.0382$; HR, 0.68). This was primarily due to a lower number of relapses after response (experimental arm, n=44 vs control arm, n=88). Following ASCT, the complete remission rate was not significantly different between the 2 treatment arms, but remission duration was longer in the experimental arm (84 months vs 49 months, respectively; $P=.0001$). In addition, overall survival was significantly longer in the experimental arm (not reached vs 82 months; $P=.045$). Increased rates of grade 3/4 hematologic toxicity, renal toxicity, and grade 1/2 nausea and vomiting occurred in the experimental arm.

(16.2% vs 6.5%; OR, 2.79; 95% CI, 1.72–4.54). Among the congestive heart failure adverse events, 26 events in the bevacizumab arm and 6 events in the placebo arm were grade 3 or higher. The median duration of the congestive heart failure adverse events was 7.8 months in the bevacizumab arm and 3.5 months in the placebo arm. Patients in the placebo arm had fewer unresolved congestive heart failure events (placebo arm, 14.8% vs bevacizumab arm, 20.6%) and were more likely to resolve these events without sequelae (77.8% vs 63.2%, respectively). In addition, patients aged 65 years or older had a higher rate of congestive heart failure adverse events relative to younger patients (bevacizumab arm, 20% vs 14%; placebo arm, 9.3% vs 4.7%). When the cumulative doxorubicin dose was at least 200 mg/m², the congestive heart failure adverse events increased in both the bevacizumab and placebo treatment arms. When the doxorubicin dose increased to at least 300 mg/m², these events further increased in the bevacizumab arm. There were 3 fatal congestive heart failure-related adverse events in the study (placebo, 1 of 386 patients; bevacizumab arm, 2 of 395 patients).

Overall, adding bevacizumab to R-CHOP was associated with an increased risk of left ventricular ejection fraction and congestive heart failure adverse events in patients with DLBCL. Furthermore, the risk of congestive heart failure events was greater for patients aged 65 years and older. Bevacizumab also increased the rate of doxorubicin-associated cardiac adverse events. As a result, the study investigators concluded that bevacizumab should not be used in conjunction with R-CHOP for the treatment of patients with DLBCL.

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Brentuximab Vedotin Administered Concurrently With Multi-Agent Chemotherapy as Frontline Treatment of ALCL and Other CD30-Positive Mature T-Cell and NK-Cell Lymphomas

CD30 is a molecule that is expressed by systemic anaplastic large cell lymphoma (sALCL) and other mature T-cell and natural killer (NK)-cell lymphomas. Treatment of CD30+ lymphomas (including sALCL) with anthracycline-containing regimens results in response rates of 76–88%, but complete remission rates are only 39–53%.¹⁻³ In addition, the number of patients who remain disease-free or progression-free after 5 years is relatively low. Brentuximab vedotin is an antibody drug conjugate that primarily targets cells that express the CD30 molecule. Brentuximab vedotin comprises the CD30-specific monoclonal antibody cAC10 and the antitubulin agent monomethyl auristatin E, which are attached by a protease-cleavable linker. A recent phase II study of brentuximab vedotin for the treatment of difficult-to-treat patients with relapsed or refractory sALCL resulted in an objective response rate of 86%, with a complete remission rate of 57%.⁴

This phase I, open-label, multicenter trial enrolled 39 patients with higher-risk sALCL (ALK⁻ or ALK⁺ with IPI scores ≥ 2) or other CD30+ mature T-cell and NK-cell lymphomas.⁵ The primary goal of the study was to determine the safety of combination brentuximab vedotin plus cyclophos-

phamide, doxorubicin, and prednisone (CHP) for the frontline treatment of CD30+ T-cell and NK-cell lymphomas, including sALCL. In addition,

the investigators sought to determine the recommended dose of brentuximab vedotin when used as a combination therapy with CHP. Patients

Differences in Quality of Life Between Bendamustine Plus Rituximab Compared With Standard First-Line Treatments in Patients With Previously Untreated Advanced Indolent Non-Hodgkin's Lymphoma or Mantle Cell Lymphoma

In a randomized study of 447 previously untreated patients with indolent non-Hodgkin Lymphoma (NHL) or MCL (Abstract 155), bendamustine plus rituximab significantly improved global health status/quality of life compared to R-CHOP/R-CVP (3.6 vs -5.1; $P=0.005$). Among patients with indolent NHL, the mean change in global health status score was significantly higher for patients treated with bendamustine plus rituximab compared to patients treated with R-CHOP/R-CVP (2.1 vs -6.3; $P=.0021$). For patients with MCL, the mean change in the global health status score was not significantly higher with bendamustine plus rituximab treatment, despite a numerically higher score (10.9 vs 1.6; $P=.0654$). The patient quality of life scores for most aspects of functioning and symptoms, as measured by the QLQ-C30 questionnaire, were improved with bendamustine plus rituximab compared to R-CHOP/R-CVP. The mean change from baseline of cognitive, physical, role, and social functioning scales decreased in both treatment groups. In addition, there were larger reductions in symptom scales, indicating a greater improvement in patients receiving bendamustine plus rituximab compared to R-CHOP/R-CVP. These improvements were observed for appetite loss (-2.9 vs -1.1 for R-CHOP/R-CVP), pain (-5.6 vs -1.7, respectively), and constipation (-0.7 vs 1.8, respectively). In contrast, a deteriorating effect was observed for dyspnea (0.8 vs 4.8), fatigue (0.5 vs 7.2), and financial difficulties (0.9 vs 1.3), with bendamustine plus rituximab exhibiting less deterioration than R-CHOP/R-CVP. Patients treated with R-CHOP/R-CVP had larger reductions in mean scores with regard to insomnia (-2.1 vs -6.7, respectively), diarrhea (0.5 vs -1.3, respectively), and nausea/vomiting (1.8 vs 0.9, respectively).

were randomized to receive 2 cycles of brentuximab vedotin 1.8 mg/kg every 3 weeks followed by 6 cycles of CHOP or 6 cycles of brentuximab vedotin 1.8 mg/kg plus standard-dose CHP every 3 weeks. Patients who responded to therapy were treated with single-agent brentuximab vedotin every 3 weeks for an additional 10 cycles. Data on brentuximab vedotin plus CHP were presented.

Of the 26 patients treated with brentuximab vedotin and CHP (15 female; median age, 55.5 years), 19 patients had sALCL (ALK⁻, n=16), 2 patients had peripheral T-cell lymphoma, 2 patients had angioimmunoblastic T-cell lymphoma, 2 patients had adult T-cell leukemia/lymphoma, and 1 patient had enteropathy-associated T-cell lymphoma. More than half of the patients had advanced-stage disease (n=18) or IPI scores of at least 2 (n=17).

The maximum tolerated dose of brentuximab vedotin plus CHP was not exceeded, as evidenced by the 1 grade 3 rash among 6 patients. Treatment-emergent adverse events that occurred in more than 30% of patients (any grade; Figure 1) included nausea (62%), peripheral sensory neuropathy (62%), diarrhea (58%), fatigue (54%), alopecia (46%), dyspnea (38%), constipation (35%), cough (35%), and febrile neutropenia (31%). Among the 18 patients (69%) who developed peripheral neuropathy, 16 had peripheral sensory neuropathy, 3 had muscular weakness, 2 had peripheral motor neuropathy, 1 had burning sensation, 1 had paresthesia (grade 3), 1 had peripheral sensorimotor neuropathy, and 1 patient had peroneal nerve palsy. The median time to onset of peripheral neuropathy was 12.5 weeks (n=18 patients) for any grade, 23 weeks (n=11 patients) for grade 2, and 32.6 weeks (n=2 patients) for grade 3. Peripheral neuropathy was managed with dose delays in 4 patients and dose reductions in 7 patients. The most common grade 3 or higher adverse events included

Table 2. Best Response by Disease Diagnosis

Outcome	sALCL (n=19)	Other Mature T-Cell and NK-Cell Lymphomas (n=7)	Total (N=26)
Objective Response Rate, n (%)	19 (100)	7 (100)	26 (100)
• Complete Response, n (%)	16 (84)	7 (100)	23 (88)
• Partial Response, n (%)	3 (16)	—	3 (12)
Median PFS, months (95% CI)	—	—	Not reached (4+ to 13+)
Median OS, months (95% CI)	—	—	Not reached (4+ to 13+)

CI=confidence interval; NK=natural killer; OS=overall survival; PFS=progression-free survival; sALCL=systemic anaplastic large cell lymphoma.

Data from Fanale MA et al. Brentuximab vedotin administered concurrently with multi-agent chemotherapy as frontline treatment of ALCL and other CD30-positive mature T-cell and NK-cell lymphomas. Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 60.

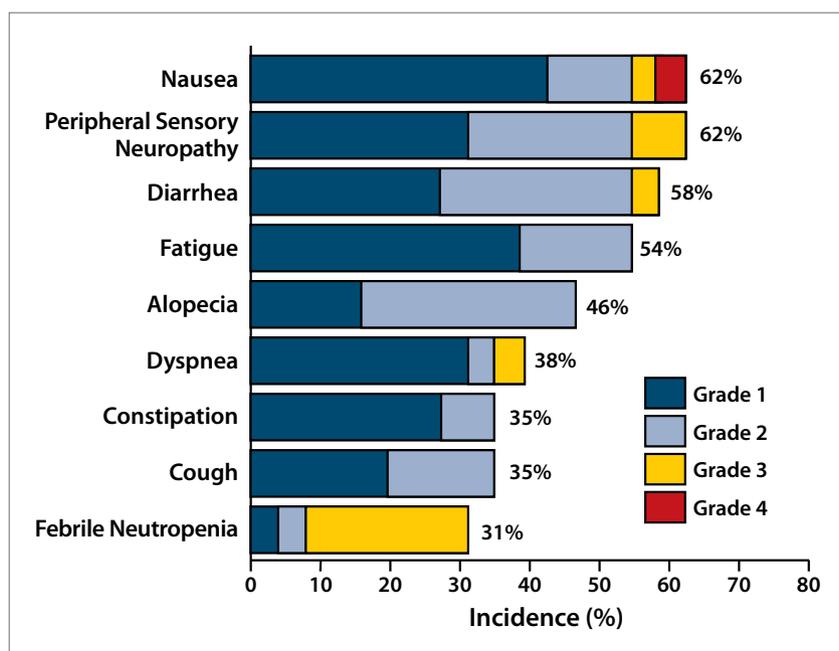


Figure 1. Summary of Adverse Events by Grade.

Data from Fanale MA et al. Brentuximab vedotin administered concurrently with multi-agent chemotherapy as frontline treatment of ALCL and other CD30-positive mature T-cell and NK-cell lymphomas. Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 60.

febrile neutropenia (19%), nausea (8%), neutropenia (8%), and pulmonary embolism (8%). Treatment discontinuation due to adverse events occurred in 6 patients (23%). There were no infusion-related reactions.

Clinical response was assessed in 23 patients at the end of 6 cycles of brentuximab vedotin plus CHP and in 3 patients who discontinued treat-

ment before cycle 6 (Table 2). Of the 26 patients, 21 received single-agent brentuximab vedotin after combination therapy. Eight patients remain in treatment. An objective response was achieved in 100% of patients. Complete remission was achieved in 23 patients (88%), which included 16 patients with sALCL and 7 patients with other CD30+ lymphomas. Two

patients experienced disease progression. The median PFS and overall survival have not yet been reached. The investigators concluded that frontline treatment of sALCL and other CD30+ T-cell and NK-cell lymphomas with brentuximab vedotin 1.8 mg/kg plus CHP every 3 weeks had a manageable safety profile and promising clinical efficacy. A phase III study of brentuximab vedotin plus CHP versus CHOP alone for the frontline treat-

ment of mature T-cell lymphomas is scheduled to begin in 2013.

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Mature Results From ECOG Study E1405—A Phase II Study of VcR-CVAD With Maintenance Rituximab for Previously Untreated Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a moderately aggressive B-cell lymphoma that is typically in the advanced stage at the time of diagnosis. MCL is incurable and there is currently no standardized treatment regimen. Treatment with modified R-hyperCVAD (rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone every 21 days with rituximab plus high-dose methotrexate-cytarabine for a total of 6–8 cycles) results in a high overall response rate in patients with MCL.¹ In 2004, bortezomib was incorporated into the induction phase of R-hyperCVAD (VcR-CVAD), which resulted in a 3-year PFS of 63%.² The safety and efficacy of adding bortezomib and maintenance rituximab to R-hyperCVAD (VcR-CVAD with MR) was assessed in patients with MCL in the phase II Eastern Cooperative Oncology Group (ECOG) E1405 study.³

Between May 2007 and October 2008, 75 previously untreated patients with histologically-confirmed MCL, performance scores of 0–2, and sufficient end-organ function were enrolled in the study. At enrollment, the median age

of patients was 62 years (range, 40–76 years), 77% were male, 92% had stage III/IV disease, 40% had elevated lactate dehydrogenase, and 5% of patients had blastic histology. Patients had a

Mantle Cell Lymphoma International Prognostic Index (MIPI) risk of 37% (low), 36% (intermediate), 19% (high), and 8% (unknown). The treatment regimen was as follows: bortezomib

Response Adapted Therapy for Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL) Based on Early [18F] FDG-PET Scanning: An Eastern Cooperative Oncology Group Study (E3404)

The efficacy of switching from R-CHOP to rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) was assessed in an ECOG study of patients with DLBCL (Abstract 687). There were 78 eligible patients with stage III, IV, or bulky 2 DLBCL (58 male patients; median age, 62 years; 13% IPI 0–1, 31% IPI 2, 37% IPI 3, and 19% IPI 4–5). Patients with a PET scan positive for fluorodeoxyglucose (FDG)-avid tumor after 3 cycles of R-CHOP were treated with a total of 4 cycles of R-CHOP followed by 4 cycles of R-ICE. PET-negative patients received a total of 6 cycles of R-CHOP. Among the 74 patients who underwent a midtreatment PET scan, 12 patients (16%) were scored as positive and 62 patients (84%) were scored as negative. At the end of treatment, 13% of patients were positive and 87% of patients were negative. The 2-year PFS of patients PET-positive at midtreatment was 45% (90% CI, 21%–67%), while patients PET-negative at midtreatment had a 2-year PFS of 77% (90% CI, 67%–85%). In addition, PET-positive patients had reduced 3-year overall survival compared to PET-negative patients (67% [90% CI, 40%–84%] vs 93% [90% CI, 85%–97%], respectively). The 5-year overall survival was 87% (90% CI, 78%–92%). While switching patients who were PET-positive at midtreatment to R-ICE met the predefined threshold for promising results (a 2-year PFS of at least 45% for patients PET-positive), the investigators noted that the use of early PET scanning for the determination of treatment modification should only be used in clinical trials.

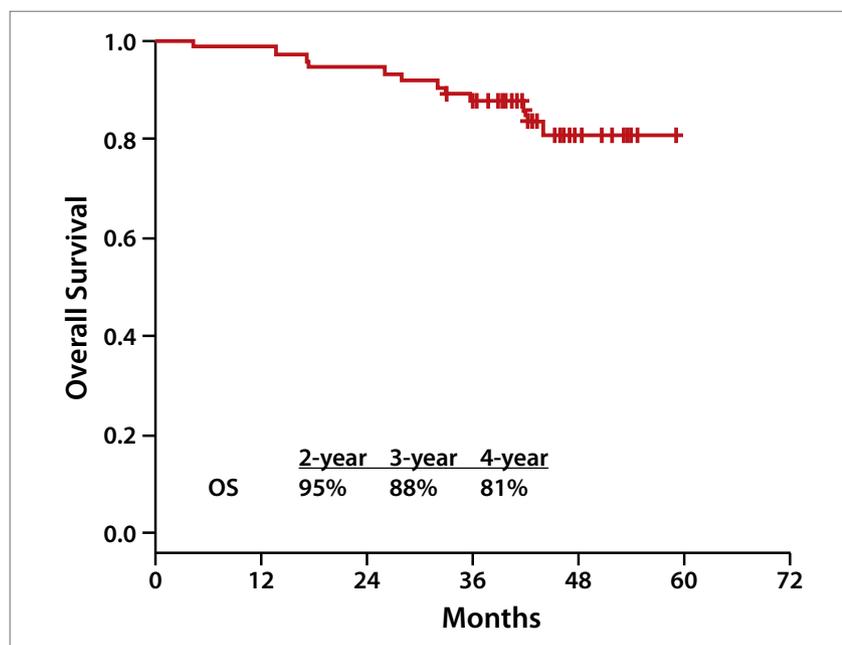


Figure 2. Overall Survival (N=75).

Data from Kahl BS et al. Mature results from ECOG Study 1405- a phase II study of VcR-CVAD with maintenance rituximab for previously untreated mantle cell lymphoma. Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 153.

1.3 mg/m² on days 1 and 4, intravenous (IV) rituximab 375 mg/m² on day 1, cyclophosphamide 300 mg/m² every 12 hours on days 1–3, doxorubicin 50 mg/m² as a continuous infusion over 48 hours on days 1–2, IV vincristine 1 mg on day 3, and dexamethasone 40 mg on days 1–4. Each cycle was conducted every 21 days for 6 cycles. In addition, all patients received granulocyte-colony stimulating factor (G-CSF) support. If patients reached stable disease, partial response, or complete response, then maintenance rituximab was administered as 4 weekly treatments every 6 months for 2 years. As an alternative to maintenance rituximab, patients could choose to receive high-dose chemotherapy plus autologous SCT off protocol. The primary endpoint of the study was the rate of complete response (positron emission tomography [PET]-negative, marrow-negative). The investigators considered a complete response rate of 75% to be promising.

A total of 67 patients completed VcR-CVAD induction therapy. Patients discontinued treatment due to progression (n=2), adverse events (n=4), and

patient preference (n=2). The overall response rate was 97% (73 of 75 patients) and the complete response rate was 68% (51 of 75 patients). Of the 20 patients who achieved a partial response (26%), 11 patients had no bone marrow evaluation and/or PET imaging following therapy. Of the 66 patients eligible for maintenance therapy, 44 patients received the planned maintenance rituximab and 22 patients chose to go off protocol and received SCT consolidation. After a median follow-up of 3.6 years, the PFS among all 75 patients was 77% at 2 years, 74% at 3 years, and 50% at 4 years. In a comparison of response duration between maintenance rituximab and SCT, the PFS was similar for both cohorts through year 3. Among all patients, the median overall survival was 95% at 2 years, 88% at 3 years, and 81% at 4 years (Figure 2), with no difference in overall survival between the maintenance remission arm and the SCT arm.

The primary adverse effect of the induction treatment regimen was myelosuppression. Grade 3 adverse events that occurred in more than 20% of patients included anemia (31%), thrombocyto-

penia (23%), and neutropenia (16%). The most common grade 4 adverse events were thrombocytopenia (43%) and neutropenia (68%). There were no incidences of grade 3/4 neuropathy. In addition, there were no serious adverse events during maintenance rituximab; the most common grade 3/4 adverse event was neutropenia (9–11%). No treatment-related deaths occurred.

Overall, induction with VcR-CVAD in patients with MCL was well tolerated and resulted in a high overall response rate (97%) and a high complete response rate (68–80%). In addition, the 3-year PFS and overall survival rates were high, with maintenance rituximab as durable as SCT consolidation for remission. The investigators indicated that maintenance rituximab likely enhanced remission duration and rituximab appears to be a viable option for maintenance in patients with MCL. The investigators noted that they are adopting maintenance rituximab as the treatment standard for their older patients with MCL. ECOG recently initiated a randomized intergroup trial (E1411) evaluating first-line bortezomib added to conventional chemotherapy in patients over 60 years of age.⁴

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Rituximab Dose-Dense Chemotherapy Followed by Intensified High-Dose Chemotherapy and Autologous Stem Cell Transplantation (HDC+ASCT) Significantly Reduces the Risk of Progression Compared to Standard Rituximab Dose-Dense Chemotherapy as First Line Treatment in Young Patients With High-Risk (aaIPI 2-3) Diffuse Large B-Cell Lymphoma (DLBCL): Final Results of Phase III Randomized Trial DLCL04 of the Fondazione Italiana Linfomi (FIL)

When DLBCL patients younger than 65 years were treated with R-CHOP14, those with intermediate-to-high IPI scores had a PFS of only 54% compared to 82% for patients with low-to-intermediate IPI scores.¹ Overall, younger patients with high-risk DLBCL who are treated with standard R-CHOP often have unsatisfactory results. However, data from phase II studies suggest that high-dose chemotherapy with autologous SCT may provide a better outcome for these patients.² This prospective, randomized, phase III trial (DLCL04) was designed by the Fondazione Italiana Linfomi to determine if rituximab dose-dense chemotherapy followed by high-dose chemotherapy (HDC) plus autologous SCT (R-CHOP + R-HDC + SCT) would increase the 2-year PFS over standard rituximab dose-dense chemotherapy (R-CHOP alone).³

The multicenter study enrolled and randomized 399 patients from June 2005 through September 2010. Patients were eligible for enrollment if they were aged 18–65 years, had previously untreated DLBCL, and an age-adjusted IPI score of 2 or 3. Patients in the non-SCT arms (R-CHOP alone arms) received R-CHOP14 for 8 cycles or R-MegaCHOP14 (1,200 mg/m² cyclophosphamide, 70 mg/m² doxorubicin, standard-dose vincristine, and prednisone) for 6 cycles. Patients in the SCT arms (R-CHOP + R-HDC + SCT) received R-CHOP14 for 4 cycles plus

R-HDC (rituximab, high-dose cytarabine, mitoxantrone, and dexamethasone) followed by carmustine, etoposide, cytarabine, and melphalan (BEAM) and autologous SCT, or R-MegaCHOP14 for 4 cycles plus R-HDC plus BEAM and autologous SCT (R-MegaCHOP14 + R-HDC + SCT). All patients received G-CSF support. The baseline patient characteristics were well balanced among treatment groups. The median age of patients was 49 years (range, 18–65 years) and 54% of patients were male. There were patients with stage II (6%), stage III

(29%), and stage IV (65%) disease. The majority of patients had elevated lactate dehydrogenase values (89% of patients), and the ECOG performance score was greater than 1 in 43% of patients. The age-adjusted IPI score was 2 in 74% of patients and 3 in 26% of patients.

Treatment was completed by 76% of patients (n=151) in the R-CHOP + R-HDC + SCT arms (including R-CHOP14 + R-HDC + SCT and R-MegaCHOP14 + R-HDC + SCT) and 88% (n=177) of patients in the R-CHOP alone arms (including R-CHOP14 and

Long-Term Remissions Observed in an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

Brentuximab vedotin selectively induces apoptosis in CD30+ cells. In a phase II study of 58 patients with relapsed or refractory sALCL, a durable complete response was achieved in 59% of patients (n=34) treated with brentuximab vedotin 1.8 mg/kg every 3 weeks for up to 16 cycles (Abstract 2745). Among the 58 patients enrolled in the study (median age of 52 years, 57% male), 72% had ALK- disease, 62% had primary refractory disease, and 26% had failed prior autologous SCT. Patients were observed for a median of 22.8 months. As was previously reported, the overall response rate was 86%. The median duration of objective response was 13.2 months; the median duration of response for patients who achieved complete remission has not been reached. At the time of presentation, 53% of patients (18 of 34 patients) who achieved complete response were in continued remission. For all patients, the median PFS was 14.6 months, but the median overall survival had not yet been reached. The estimated overall 2-year survival rate was 63%. ALK+ and ALK- patients achieved similar PFS survival (14.6 months vs 14.3 months, respectively). The most common adverse events were peripheral neuropathy (57%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%). Grade 3 peripheral neuropathy occurred in 17% of patients and was managed with dose delays or dose reductions. Improvement or resolution in peripheral neuropathy occurred in 88% of patients (29 of 33 patients).

R-MegaCHOP14). Complete remission was achieved in 75% of patients (R-CHOP + R-HDC + SCT, 76%; R-CHOP alone, 72%). The highest complete response rate was achieved in the R-CHOP + R-HDC + SCT arm (82% vs R-MegaCHOP + R-HDC + SCT, 69%; R-CHOP, 71%; R-MegaCHOP, 73%). Overall, partial remission was achieved by 7% of patients, and 16% of patients did not respond to treatment.

After a median follow-up of 41 months, the 3-year PFS was 71% (95% CI, 64–76) in the R-CHOP + R-HDC + SCT arms and 58% (95% CI, 50–65) in the R-CHOP alone arms ($P=.008$; HR, 0.63; 95% CI, 0.45–0.89). There was no difference in 3-year PFS between patients who received R-CHOP14 and those who received R-MegaCHOP14 (65% vs 64%, respectively; $P=.7317$). When patients were stratified according to age-adjusted IPI scores, patients with a score of 2 had a 3-year PFS of 75% in the R-CHOP + R-HDC + SCT arms (95% CI, 65–81) versus 65% in the R-CHOP alone arms (95% CI, 56–72; $P=.031$). Patients with an age-adjusted IPI score of 3 had a 3-year PFS of 60% in the R-CHOP + R-HDC + SCT arms (95% CI, 45–71) and 46% in the R-CHOP alone arms (95% CI, 32–59; $P=.122$). Among all arms, the 3-year overall survival was 79% (95% CI, 74–83). There was no significant difference in the 3-year overall survival between the R-CHOP + R-HDC + SCT and R-CHOP alone treatment arms (81% [95% CI, 74–86] vs 79% [95% CI, 72–84], respectively; $P=.8008$) or between the R-CHOP and R-MegaCHOP arms (80% [95% CI, 74–85] vs 80% [95% CI, 73–85]; $P=.6842$).

The investigators performed a Cox-model analysis with 4 arms using the R-CHOP14 arm as a reference point. The risk of relapse was reduced in both arms that included SCT. This risk was lowest in the R-CHOP14 + R-HDC + SCT arm (HR, 0.56; 95% CI, 0.35–0.91; $P=.025$). There was a slight reduction in the risk of relapse in the R-MegaCHOP14 + R-HDC + SCT arm (HR, 0.68; 95%

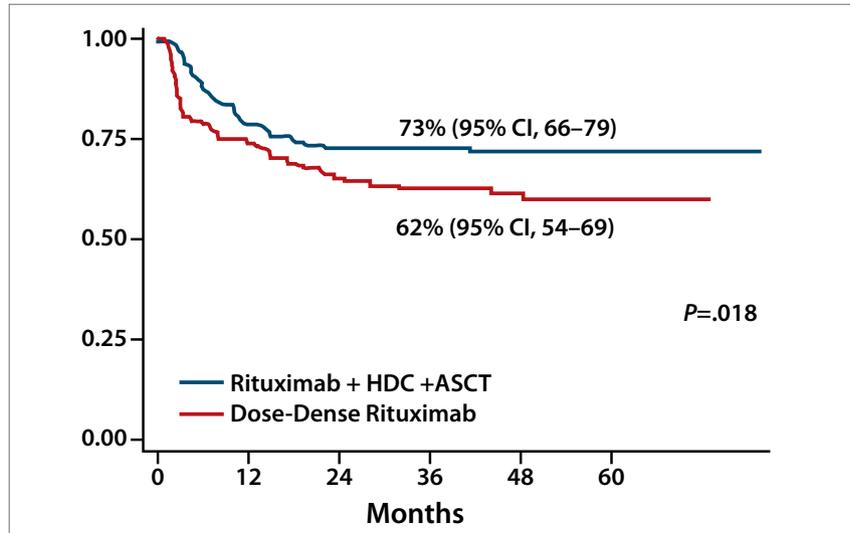


Figure 3. Progression-free survival (PFS) at 3 years among 371 patients with any response following 4 courses of chemotherapy.

ASCT=autologous stem cell transplant; CI=confidence interval; HDC=high-dose chemotherapy.

Data from Vitolo U et al. Rituximab dose-dense chemotherapy followed by intensified high-dose chemotherapy and autologous stem cell transplantation (HDC+ASCT) significantly reduces the risk of progression compared to standard rituximab dose-dense chemotherapy as first line treatment in young patients with high-risk (aaIPI 2-3) diffuse large B-cell lymphoma (DLBCL): final results of phase III randomized trial DLCL04 of the Fondazione Italiana Linfomi (FIL). Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 688.

CI, 0.42–1.08; $P=.109$). In subgroup analyses performed according to the type of dose-dense chemotherapy, age, sex, age-adjusted IPI, and bone marrow involvement, the HRs favored R-CHOP + R-HDC + SCT over R-CHOP alone. Among patients with any response after 4 courses of chemotherapy, those who went on to transplant had a 3-year PFS of 73%, compared with 62% for patients who did not receive a transplant (Figure 3; $P=.018$).

Treatment-related deaths occurred in 6 patients in the R-CHOP + R-HDC + SCT arms and in 4 patients in the R-CHOP alone arms. More patients experienced grade 3/4 gastrointestinal toxicities in the R-CHOP + R-HDC + SCT arms (47 patients) compared to the R-CHOP alone arms (18 patients). Grade 3/4 cardiac events occurred in 3 of 199 patients in the R-CHOP + R-HDC + SCT arms and in 1 of 200 patients in the R-CHOP alone arms. Both the SCT and non-SCT arms each had 2 neurological and 14 infection-related grade 3/4 adverse events.

Overall, treatment with rituximab dose-dense chemotherapy followed by

rituximab high-dose chemotherapy and BEAM with SCT (R-CHOP14 + R-HDC + SCT or R-MegaCHOP14 + R-HDC + SCT) improved PFS compared to standard dose-dense chemotherapy (R-CHOP14 or R-MegaCHOP14) in patients aged 65 years or younger with high-risk DLBCL without significantly increasing toxicity.

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Brentuximab Vedotin Demonstrates Significant Clinical Activity in Relapsed or Refractory Mycosis Fungoides With Variable CD30 Expression

Brentuximab vedotin received accelerated approval from the US Food and Drug Administration (FDA) in 2011 for the treatment of relapsed Hodgkin lymphoma and sALCL. Treatment with brentuximab vedotin resulted in high response rates in patients with Hodgkin lymphoma or sALCL^{1,2}; both of these diseases have CD30 expression on tumor cells. In contrast, mycosis fungoides/Sézary syndrome (MF/SS) has variable CD30 expression on neoplastic cells, ranging from 0–50%, depending on the transformation status. In the present study, the investigators assessed the response rate of brentuximab vedotin in MF/SS patients and evaluated whether there is a correlation between CD30 expression and treatment response (Figure 4).³

For inclusion in this exploratory study, patients were required to be over 18 years of age with MF/SS stages I–IV, an ECOG performance status of 2 or lower, and at least 1 prior systemic therapy. The study enrolled 20 patients, each of whom received at least 1 dose of the study medication. Patients were divided into treatment groups according to the percentage of CD30+ lymphoid cells (<10%, 10–50%, and >50%) and were then treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks for up to 8 cycles. For patients with a partial response and ongoing clinical improvement, there was an optional extension of up to 8 additional treatment cycles. For patients with a complete response, 2 additional treatment cycles were allowed. CD30 expression levels were assessed in the skin by immunohistochemistry using the BerH2 antibody. CD30 expression levels were expressed as the percent

positive of total lymphoid infiltrate in skin biopsies. Both CD30 expression and clinical outcomes were confirmed by independent review.

The study participants had a median age of 59 years (range, 20–88 years); 13 of the 20 patients were men. Most patients had stage IIB or higher disease (18 of 20 patients), 13 patients had large cell transformation, 8 patients had folliculotropic MF, and 3 patients had both large cell transformation and folliculotropic MF. Patients were treated with a median of 6 prior systemic therapies (range, 1–15 therapies). Seven patients had baseline

CD30 expression levels of less than 10%, 10 patients had CD30 levels between 10% and 50%, and 3 patients had CD30 levels greater than 50%.

The median reduction in skin modified severity weighted adjustment tool (mSWAT) scores at the time of best clinical response was 65%. The overall response rate was 70% (14 of 20 patients), with a median time to response of 6 weeks (range, 3–18 weeks) and a median follow-up time of 36 weeks (range, 6–55 weeks). There was no significant difference in response rate when patients were grouped according to baseline CD30 expression

Retrospective Analysis of the Safety and Efficacy of Brentuximab Vedotin in Patients Aged 60 Years or Older With Relapsed or Refractory CD30+ Hematologic Malignancies

In a retrospective analysis of 40 patients aged 60 years or older with relapsed or refractory CD30+ lymphomas, treatment with brentuximab vedotin exhibited significant antitumor activity and durability of response (Abstract 3687). The analysis included patients with a median age of 66 years and sALCL (22 patients), Hodgkin lymphoma (HL; 15 patients), or other CD30+ lymphomas (3 patients) from 7 clinical studies. The overall response rate was 83% and the complete response rate was 45%. Among sALCL patients, the overall response rate was 100%, the complete response rate was 50%, and the median duration of response was 13 months. Among patients with HL, the objective response rate was 56%, the complete response rate was 38%, and the median duration of response was not yet reached. Efficacy data were comparable to what was observed in patients younger than 60 years. Treatment-emergent fatigue (58%), peripheral neuropathy (60%), and anemia (30%) occurred more frequently in patients 60 years or older compared to patients younger than 60 years (43%, 46%, and 10%, respectively). Treatment-related serious adverse events occurred in 20% of patients; mental status change was the most frequent serious adverse event reported. Overall, grade 3 adverse events were more common in patients at least 60 years of age (≥ 60 years, 70% vs <60 years, 56%). The most common grade 3 adverse events in patients aged 60 years or older included neutropenia (25%), anemia (20%), and peripheral sensory neuropathy (15%). Discontinuation due to adverse events occurred in 30% of patients. A phase II study of frontline brentuximab vedotin in patients aged 60 years or older is currently underway.

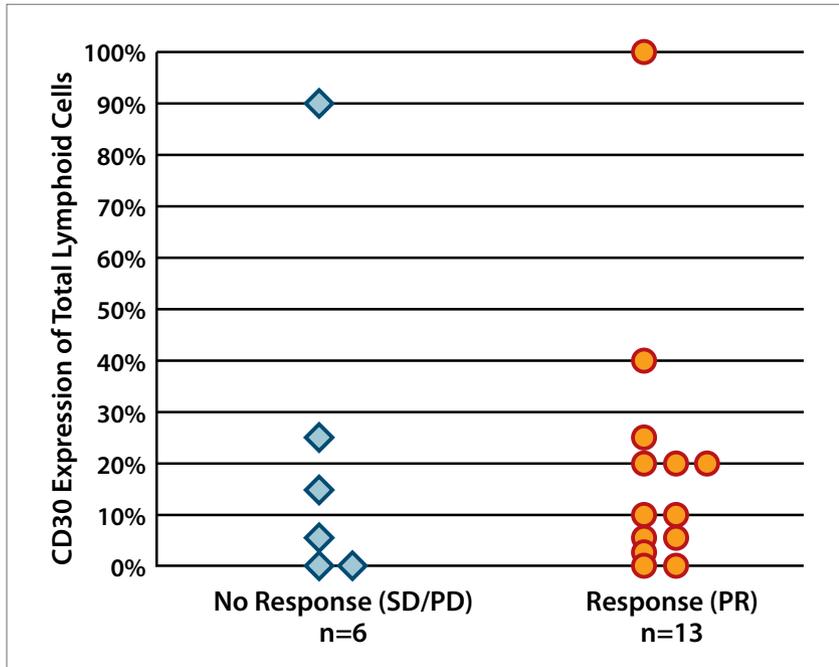


Figure 4. Routine immunohistochemistry (IHC) reveals no correlation of clinical response to brentuximab vedotin and CD30 expression in patients with mycosis fungoides/Sézary syndrome.

PD=progressive disease; PR=partial response; SD=stable disease.

Data from Krathen M et al. Brentuximab vedotin demonstrates significant clinical activity in relapsed or refractory mycosis fungoides with variable CD30 expression. Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 797.

(<10%, 71%; 10–50%, 70%; >50%, 67%). Responses were observed in all clinical stages of disease (stage IB, 2 partial responses; stage IIB, 10 partial responses and 1 stable disease; stage IVA/B, 2 partial responses and 4 cases of progressive disease). No patients achieved complete response. There was no correlation between response and sex, age, large cell transformation, folliculotropism, or baseline soluble CD30. The median event-free survival was 31 weeks (range, 4–61+ weeks). A Kaplan-Meier survival probability analysis estimated that at a median follow-up of 46 weeks, a median of 78% of responses were ongoing at 6 months. The median PFS has not yet

been met; however, 73% of patients were progression-free at 6 months.

A quantitative image analysis of CD30 staining was performed on pretreatment biopsy samples from 16 patients. All samples had detectable CD30 on lymphoid cells. Of note, 12 of the samples tested positive by quantitative image analysis, but were negative for CD30 by routine immunohistochemistry. The investigators speculated that this was likely due to the low sensitivity of standard immunohistochemistry when detecting CD30. In addition, 3 tumors that developed during treatment with brentuximab vedotin also tested positive for CD30 by quantitative

image analysis. There was no correlation between clinical response and CD30 expression levels (immunohistochemistry, $P=.17$; quantitative image analysis, $P=.74$).

The most common treatment-related grade 1/2 adverse events included peripheral neuropathy (78%), fatigue (61%), decreased appetite (28%), and nausea (22%). There were a number of treatment-related grade 3/4 adverse events, including rash (n=3), neutropenia (n=2), lymphocytosis (n=1), peripheral neuropathy (n=1), pruritus (n=1), pneumonia (n=1), hyperglycemia (n=1), sepsis (n=1), acute renal failure (n=1), leukopenia (n=1), and thrombocytopenia (n=1). The patient with pneumonia experienced respiratory failure and subsequent death. Onset of neuropathy occurred at a median of 14 weeks (range, 6–39 weeks), with resolution or improvement occurring after a median of 24 weeks (range, 6–46+ weeks).

The investigators concluded that brentuximab vedotin had significant clinical activity in patients with MF/SS who had relapsed or were refractory to 1 or more previous treatments. In addition, patients were responsive to treatment regardless of their CD30 expression.

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Frontline Therapy With Brentuximab Vedotin Combined With ABVD or AVD in Patients With Newly Diagnosed Advanced Stage Hodgkin Lymphoma

A regimen consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is often used as a frontline treatment for Hodgkin lymphoma (HL). Up to 30% of patients with advanced stage HL require salvage treatment following ABVD.¹ Since HL is associated with CD30+ Hodgkin Reed-Sternberg cells, treatment with brentuximab vedotin, an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to monomethyl auristatin E, may be efficacious for patients with advanced HL. Patients with relapsed or refractory HL who were treated with brentuximab vedotin alone achieved an objective response rate of 75% and a complete response of 33%.² This phase I, open label, dose-escalation study assessed the safety of brentuximab vedotin in combination with ABVD or AVD for frontline therapy of patients with advanced HL.³

Patients aged 18–60 years were eligible for the study if they had previously untreated HL with stage IIA bulky disease or stage IIB–IV disease. On days 1 and 15, patients were treated with brentuximab vedotin (0.6 mg/kg, 0.9 mg/kg, or 1.2 mg/kg) plus standard doses of ABVD or brentuximab vedotin (1.2 mg/kg) plus AVD every 28 days for up to 6 cycles. A dose-limiting toxicity period was implemented, which was defined as any toxicity in cycle 1 that necessitated a delay of 7 or more days of standard ABVD or AVD therapy. The investigators used the Revised Response Criteria for Malignant Lymphoma to assess antitumor activity.⁴ Deauville criteria were used for the fluorodeoxyglucose (FDG)-PET interpretation; uptake above liver background was considered positive.

Table 3. Summary of Adverse Events of Grade 3 or Higher

	ABVD With Brentuximab Vedotin N=25 (%)	AVD With Brentuximab Vedotin N=26 (%)
Neutropenia	20 (80)	20 (77)
Anemia	5 (20)	3 (12)
Febrile neutropenia	5 (20)	2 (8)
Pulmonary toxicity	6 (24)	0
Syncope	3 (12)	2 (8)
Dyspnea	3 (12)	1 (4)
Pulmonary embolism	3 (12)	0
Fatigue	1 (4)	1 (4)
Leukopenia	1 (4)	1 (4)

Grade 3 or higher adverse events occurring in more than 1 patient overall, regardless of relationship.

ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD=doxorubicin, vinblastine, and dacarbazine.

Data from Ansell SM et al. Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma. Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 798.

Among the 51 patients treated, the median age was 33 years (range, 18–59 years) and 73% of patients were male. All patients had an ECOG status score of 0 or 1, 17% of patients had bulky disease, and 25% of patients had an IPS score of 4 or higher. Most patients had stage IV disease (45%); 6% had stage IIA bulky, 16% had stage IIB, 16% had stage IIIA, and 18% of patients had stage IIIB disease. In the first treatment arm (and in combination with ABVD), 6 patients received brentuximab vedotin 0.6 mg/kg, 13 patients received a dose of 0.9 mg/kg, and 6 patients received 1.2 mg/kg of brentuximab vedotin. In the second arm, 26 patients received 1.2 mg/kg of brentuximab vedotin plus AVD. No dose-limiting toxicity was observed for up to 1.2 mg/kg of brentuximab vedotin in either treatment arm. Adverse events occurring in at least 20% of patients included nausea (ABVD arm, 76% vs AVD arm, 77%), neutropenia (80% vs 77%, respec-

tively), peripheral sensory neuropathy (72% vs 73%, respectively), vomiting (60% vs 42%, respectively), fatigue (44% vs 50%, respectively), and constipation (48% vs 35%, respectively). Grade 3 or higher adverse events occurring in more than 1 patient overall (Table 3) included neutropenia (ABVD, 80% vs AVD, 77%), anemia (20% vs 12%, respectively), febrile neutropenia (20% vs 8%, respectively), and pulmonary toxicity (24% vs 0%, respectively). Of note, 44% of patients in the ABVD arm (11 of 25 patients) discontinued bleomycin due to pulmonary toxicity (n=9), interstitial lung disease (n=1), or pneumonitis (n=1). There were 2 deaths related to pulmonary toxicity; in the other 9 patients, events resolved after a median of 2.6 weeks. The investigators noted that these events usually occurred between cycles 3 and 4. Of these 11 patients, 8 patients discontinued bleomycin and finished their treatment with AVD and brentuximab vedotin. No patients in

the AVD arm experienced pulmonary toxicity. There was a similar rate of peripheral neuropathy in both arms (ABVD arm, 72% vs AVD arm, 77%); there were no grade 4 or 5 events. Discontinuation of brentuximab vedotin due to peripheral neuropathy occurred in 6 out of 51 patients. Overall, there were 5 patients in the ABVD arm and 2 patients in the AVD arm who discontinued brentuximab vedotin due to adverse events.

In a central review of FDG-PET at cycle 2, all 22 ABVD patients and 24 out of 26 AVD patients were PET-negative, but the prognostic value of interim PET results has not yet been established. Prior to the end of treatment, 4 patients withdrew consent or were lost to follow-up. The objective response rate in the remaining 47

patients was 96%. Complete response was achieved in 95% of patients in the ABVD arm and 96% of patients in the AVD arm. One patient in the AVD arm achieved partial response, and 1 death occurred in the ABVD arm.

In conclusion, brentuximab vedotin can be safely combined with AVD. Due to the risk of pulmonary toxicity, the investigators recommend against concomitant treatment with brentuximab vedotin and bleomycin-containing regimens such as ABVD. In addition, no dose-limiting toxicity of brentuximab vedotin in combination with ABVD or AVD was observed at a dose of up to 1.2 mg/kg every 2 weeks. Therefore, the recommended regimen is brentuximab vedotin 1.2 mg/kg every 2 weeks plus AVD. Given the high complete response rates observed

in this study, the investigators are planning a phase III study of brentuximab vedotin plus AVD versus ABVD alone.

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Safety and Efficacy of Ibrutinib in the Treatment of DLBCL, Follicular Lymphoma (FL), and MCL

Ibrutinib is a first-in-class specific inhibitor of Bruton's tyrosine kinase (BTK). BTK is a central mediator in B-cell receptor (BCR) signaling; in the absence of BTK, signal transduction from the BCR to nuclear factor kappa B (NF- κ B) is prevented. Daily, orally-administered ibrutinib covalently binds and inhibits BTK for 24 hours. Three studies investigated the safety and efficacy of ibrutinib in various malignancies.

Wilson and associates assessed the clinical activity of ibrutinib in 2 molecular subtypes of DLBCL (activated B cell-like [ABC] and germinal center B cell-like [GCB]).¹ ABC DLBCL is less likely to be cured with current management options due to chronic active BCR signaling.² Enhanced signaling in the ABC DLBCL cell lines is due to mutations in 2 signaling pathways: gain-of-function mutations in the BCR subunit CD79B and a constitutively active MYD88 mutant (L265P),

which is an adapter for Toll-like receptors. In this open-label, multicenter phase II study, the clinical activity of ibrutinib in ABC and GCB DLBCL was assessed. The study enrolled 70 patients with relapsed or refractory DLBCL (27% relapsed, 54% refractory, 19% unknown). The median age of patients was 64 years (range, 28-92 years), 63% had stage IV disease, and all patients had ECOG scores of 2 or lower. There was a median of 3 prior systemic therapies (range, 1-7) and 23% of patients had a prior SCT. Patients were treated with ibrutinib 560 mg daily.

Interim data were presented. Of the 70 patients who received at least 1 dose of ibrutinib, treatment was well tolerated, with no new safety signals identified. There were 29 patients with the ABC subtype, 20 patients with the GCB subtype, 16 patients with unclassifiable disease, and 5 patients with an unknown subtype (not

arrayed). Among patients with the ABC subtype, the overall response rate was 41% (12 of 29 patients; 95% CI, 21-61%). The complete response rate was 17% and the partial response rate was 24%. For patients with the GCB subtype, the overall response rate was 5%, as only 1 patient achieved a partial response. The median overall survival was 9.76 months (95% CI, 3.88-NR) in the ABC subtype and 3.35 months (95% CI, 1.22-NR) in the GCB subtype (Figure 5). Of note, response to ibrutinib did not require BCR mutations, and there were responses in ABC DLBCL tumors with either mutated CD79B (71%, n=5 patients) or wild-type CD79B (34%, n=10 patients). In addition, 4 of the 5 ABC subtype patients with both CD79B and MYD88 mutations responded to ibrutinib (80%), whereas the 5 patients with only a MYD88 mutation did not ($P=.0286$). In addition, patients with CARD11

mutations did not respond to ibrutinib, indicating that ibrutinib response requires upstream BCR signaling.

Primary follicular lymphoma cells and select subtypes of non-Hodgkin lymphoma (NHL) exhibit chronic activation of the BCR signaling pathway, which suggests that ibrutinib may be efficacious in these patients.³ Fowler and colleagues presented the results of a phase I study of patients with relapsed or refractory B-cell lymphoma who were treated with ibrutinib.⁴ The study enrolled 16 patients with follicular lymphoma and a median age of 60 years (range, 41–71 years). Patients had received a median of 3 prior therapies (range, 1–5), including SCT (6%), anthracyclines (56%), nucleoside analogs (19%), and rituximab (100%). At baseline, the Follicular Lymphoma International Prognostic Index (FLIPI) scores were low risk (19%), intermediate risk (37%), and high risk (44%). Five groups of patients were treated with ibrutinib 1.25–12.5 mg/kg daily using a 28-days-on, 7-days-off intermittent schedule. Two groups of patients received constant treatment with either 8.3 mg/kg or a 560 mg fixed dose of ibrutinib.

The most common treatment-related adverse events included diarrhea (50%), fatigue (44%), nausea (38%), cough (31%), and myalgia (25%). There was 1 case of each of the following grade 3 adverse events: anemia, anxiety, hypersensitivity, hypokalemia, hypophosphatemia, decreased neutrophils, noncardiac chest pain, pancytopenia, pneumonia, and vomiting). There was 1 treatment-related grade 4 hypokalemia and 1 treatment-unrelated case of myelodysplastic syndrome. In the intermittent cohort, 1 patient treated with ibrutinib 2.5 mg/kg experienced dose-limiting toxicity (grade 2 neutropenia and grade 4 hypokalemia) and 1 patient treated with ibrutinib 8.3 mg/kg experienced grade 3 hypersensitivity. No patients in the 12.5 mg/kg cohort experienced a dose-limiting toxicity.

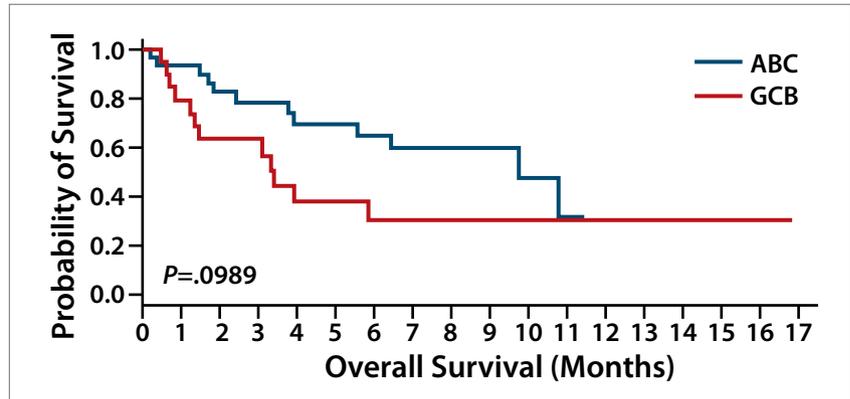


Figure 5. Overall survival in activated B cell-like (ABC) and germinal center B cell-like (GCB) diffuse large B-cell lymphoma (DLBCL).

Data from Wilson WH et al. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCIB32765), has preferential activity in the ABC subtype of relapsed/refractory de novo diffuse large B-cell lymphoma (DLBCL): interim results of a multicenter, open-label, phase 2 study. Paper presented at: the 2012 ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 686.

Overall Survival Benefit for Patients With Relapsed Hodgkin Lymphoma Treated With Brentuximab Vedotin After Autologous Stem Cell Transplant

In a nonrandomized comparison, overall survival of 102 patients with relapsed or refractory HL after autologous SCT who were treated with brentuximab vedotin was compared to an international cohort of 756 patients with relapsed or refractory HL after autologous SCT who were not treated with brentuximab vedotin (Abstract 3701). The median time following SCT was 49.9 months (brentuximab vedotin cohort) and 58.8 months (international cohort). Patients receiving brentuximab vedotin had a significantly longer median overall survival compared to patients in the international cohort (91.49 months vs 27.99 months, respectively; $P < .0001$). Overall survival was not impacted by age, sex, or the time from SCT to relapse. Among those patients treated with brentuximab vedotin who achieved complete remission, the stage of disease at the time of the initial diagnosis significantly affected overall survival ($P = .0004$). In addition, negative PET status after cycles 4 and 7 was associated with improved overall survival and longer PFS. There was a trend toward longer lasting complete remission (>12 months) for patients who achieved complete remission after 4 or fewer cycles of brentuximab vedotin. The results suggest that patients with relapsed or refractory HL after autologous SCT may have improved overall survival and a longer duration of response with brentuximab vedotin treatment. A randomized trial is currently under way to assess the administration of brentuximab vedotin following autologous SCT.

There were 11 patients with follicular lymphoma who were evaluable for clinical response. Patients received ibrutinib for a median of 7 months (range, 0–29 months). The overall response rate was 54.5%. Three patients achieved a complete response and 3 patients achieved a partial response.

The duration of response was 12.3 months and the median PFS was 13.4 months. Among patients treated with at least 5 mg/kg of ibrutinib, there was a trend toward improved PFS (19.6 months), but the overall response rate was similar to the median rate seen in all patients. The investigators con-

cluded that ibrutinib was well tolerated and clinically active in patients with relapsed follicular lymphoma.

A third study of ibrutinib focused on patients with relapsed or refractory MCL.⁵ Patients with MCL often relapse and acquire resistance to conventional chemotherapy. A preliminary study revealed that relapsed and refractory MCL patients achieved rapid responses to ibrutinib.⁶ Wang and associates presented the interim results of an international, multicenter, phase II study of ibrutinib in previously treated patients with relapsed or refractory MCL.⁶ Patients who were either bortezomib-naïve (n=65) or bortezomib-exposed (n=50) received orally-administered ibrutinib 560 mg daily in continuous 28-day cycles until disease progression.

The most common treatment-related adverse events included diarrhea (35%), fatigue (32%), upper respiratory tract infection (23%), nausea (21%), rash (21%), dyspnea (20%), and peripheral edema (15%). The most common adverse events of grade 3 or higher included neutropenia (11%), anemia (5%), diarrhea (5%), dyspnea (5%), pneumonia (5%), and

thrombocytopenia (95%). Treatment-related grade 4 events included neutropenia (5%), hyperuricemia (2%), and pancytopenia (1%). There was 1 incident of grade 5 pneumonia.

Of the 109 patients evaluable for efficacy, the median age was 68 years (range, 40–84 years) and the median number of prior treatments was 3 (range, 1–6). Bulky disease was present in 13% of patients, 77.4% had stage IV disease, 48.7% had a high-risk MIPI score, and 44.3% of patients had refractory disease. After a median time on treatment of 6 months (range, 0.7–6.6 months), the overall response rate was 66.1% (bortezomib-naïve, 65.1%; bortezomib-exposed, 67.4%). The complete response rate was 19.3% and the partial response rate was 46.8%; complete and partial response rates were similar between groups. The median duration of response, PFS, and overall survival have not yet been reached. The 8-month duration of response was 65%, the 12-month estimation of PFS was 53%, and the overall survival was 67%. Responses to ibrutinib increased with longer time on study treatment. A pivotal study to evaluate

ibrutinib in patients with relapsed or refractory MCL with prior bortezomib exposure is currently under way.

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Commentary

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In both of the frontline brentuximab vedotin trials presented at the 2012 American Society of Hematology (ASH) meeting, there were very high levels of responses observed for high-risk lymphoma patient populations. I presented the results of our frontline CD30-positive T-cell lymphoma protocol, which enrolled patients who had high-risk disease, either high-risk systemic anaplastic large cell lymphoma (sALCL) or high-risk CD30-positive peripheral T-cell lymphoma (PTCL).¹ These are patients who typically can have a 5-year survival rate of 25%. Based on the pivotal trial data,² we knew that brentuximab vedotin induces very high levels of remission for patients who have sALCL at the mid-50% range. Even at this time, with multiple years of follow-up, the median duration of remission for patients entering complete remission has not been reached. Ideally, we would want to treat patients in a frontline setting, induce a higher rate of complete remission, and lower the chance of potential relapse, rather than treat patients when they have already had disease relapse. This trial was designed to examine 2 different treatment approaches. One approach looked at a sequential treatment, and these data were previously presented at the European Society for Medical Oncology (ESMO) in October.³ The presentation at the 2012 ASH meeting focused on a concurrent-based treatment approach, which is the treatment approach that we are moving forward

with for the phase III frontline trial. Patients received treatments in a combination, which included brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone (CHP) for 6 cycles, followed by additional maintenance cycles that were given a total of 10 times with brentuximab vedotin. All patients responded, and 84% of patients entered into complete remission. The follow-up remains short at 9 months, but we have not seen a significant rate of disease relapse thus far. The side effects were also quite manageable. What particularly piqued our interest was the fact that 7 patients who had T-cell lymphoma of other types had very promising levels of response, and all had gone into complete remission. These patients did not have 100% expression of CD30; rather, they had CD30 expression that generally ranged from approximately 20–80%. Given these encouraging efficacy and safety data, a phase III study comparing the standard of care regimen cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) to brentuximab vedotin plus CHP in the frontline treatment of mature T-cell lymphomas has recently commenced.⁴ With this trial, we hope to determine the lower limit of CD30 expression that is needed in order to respond to this treatment approach.

The other frontline study involving brentuximab vedotin was presented by Ansell and associates.⁵ This study also showed high levels of response at the end of treatment.

Additionally, it showed positron emission tomography (PET)-negativity after just 2 cycles of treatment. The percentage of patients who were PET-negative after 2 cycles of treatment was very high in both arms (100% for patients who received doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] in combination with brentuximab vedotin and 92% for patients who received brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine [AVD]). Complete remission rates were 95% in the brentuximab vedotin plus ABVD group and 92% in the brentuximab vedotin plus AVD arm. Of note, 44% of patients in the brentuximab vedotin plus ABVD arm experienced pulmonary toxicity, interstitial lung disease, or pneumonitis, which led to the deaths of 2 patients. As a result, bleomycin was discontinued and the trial was amended so that all further patients received brentuximab vedotin plus AVD. This trial highlights the importance of treating patients with any type of new combination via a clinical trial. For example, if one physician is treating several patients and they did develop pulmonary toxicity, the physician might think it is a sporadic event rather than an actual significant adverse event related to a drug combination. Moving forward, data from this trial support further evaluation of brentuximab vedotin administered concomitantly with AVD in previously untreated

advanced-stage Hodgkin lymphoma patients to potentially improve the current standard of care. The frontline phase III randomized trial of brentuximab vedotin plus AVD versus ABVD is preparing to begin enrollment.⁶ It will enroll a larger number of patients and have a longer follow-up with a primary endpoint of progression-free survival (PFS).

Krathen and colleagues presented data on brentuximab vedotin in patients with relapsed or refractory mycosis fungoides (MF).⁷ The overall response rate was 68%, which was impressive. There was a lower limit set in terms of how much CD30 expression was needed in order to enroll (10%). Only 2 patients had more than 50% expression, whereas 7 patients had less than 10% expression. Clinical response did not correlate with CD30 expression by routine immunohistochemistry or image analysis. I think that there is still a lot to be learned from targeting CD30 expression, and this study supports the need for further investigation of brentuximab vedotin in other diseases.

In patients with mantle cell lymphoma (MCL), Hermine and associates within the European Mantle Cell Lymphoma Network (MCLnet) compared 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy and autologous stem cell transplant (ASCT) versus alternating courses of 3× CHOP and 3× dexamethasone, cytarabine, and cisplatin (DHAP) plus rituximab followed by a high-dose cytarabine-containing myeloablative regimen and ASCT.⁸ As anticipated, there was a better level of response for patients who received the DHAP-based treatment in combination with rituximab. It increased the complete remission rate by approximately 10% and improved PFS. The time to treatment failure was 88 months for patients who received the DHAP-based treatment compared to approximately 46 months for patients who received the

R-CHOP-based treatment. This was to be expected, because even if there was not such a great split between the complete remission rates in the 2 treatment approaches, one could postulate that the patients who received the most intensive treatment would have a more durable complete remission after transplant.

A trial by Kahl and colleagues looked at the incorporation of bortezomib into modified R-hyperCVAD, which consists of rituximab fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.⁹ One advantage was that this regimen could be used for older patients as well, and patients as old as 80 years were treated. High response rates were demonstrated, and complete remission rates were high, at 68%. The 3-year PFS was also high for this patient population, and 75% of patients remain in remission.

The study by Swinnen and coworkers showed that there is much interest in using PET to predict outcomes.¹⁰ The investigators evaluated the efficacy of switching from R-CHOP to rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) in 78 eligible patients with stage III, stage IV, or bulky stage II DLBCL. A total of 6 cycles of R-CHOP was administered to PET-negative patients. There were 74 patients who underwent a midtreatment PET scan; 12 patients (16%) were scored as positive and 62 patients (84%) were scored as negative. At the end of treatment, 13% of patients were positive and 87% of patients were negative. The 2-year PFS was 45% among patients who were PET-positive at midtreatment, compared with 77% among patients who were PET-negative. PET-positive patients had reduced 3-year overall survival compared to PET-negative patients. However, in terms of a standard of care treatment approach, it would not be recommended to have a patient switched over to more inten-

sive treatment just because they had PET-positivity.

Abexinostat is a novel, broad-spectrum hydroxamic acid-based inhibitor of histone deacetylase (HDAC) with potential antineoplastic activity. It induces apoptosis and cell cycle arrest in various human tumor cell lines and inhibits tumor growth in several lymphoma xenograft models. Data were particularly positive for patients with follicular lymphoma in the trial of abexinostat presented by Evens and associates.¹¹ These patients had the highest level of response, in the mid-60% range. The response for patients with MCL was lower, at approximately 30%. Overall, the response rates seen with the HDAC inhibitor were a bit higher for follicular lymphoma compared to other HDAC inhibitors, such as panobinostat. Abexinostat may be suitable for further study in follicular lymphoma, particularly in combination with other agents. Abexinostat was well tolerated and had several advantages, including an oral dosing schedule and the ability to be combined with other agents.

Several different studies of ibrutinib were presented. Ibrutinib is a first-in-class specific inhibitor of Bruton's tyrosine kinase (BTK), which is known to be expressed in chronic lymphocytic leukemia, small lymphocytic lymphoma, MCL, DLBCL, follicular lymphoma, and multiple myeloma. Fowler and colleagues presented on ibrutinib in follicular lymphoma,¹² Wang and coworkers discussed ibrutinib in MCL,¹³ and Wilson and associates presented on ibrutinib in diffuse large B-cell lymphoma (DLBCL).¹⁴ There was a high response rate across the board for this drug. For patients with follicular lymphoma, the response rate was approximately 55%. For patients with MCL, the response rate was even higher, in the 70% range. That mirrors what has already been published from the phase I data experience; the paper by Advani and colleagues that was recently published in the *Journal*

of *Clinical Oncology* showed an overall response rate of approximately 60%.¹⁵ What is interesting about ibrutinib, particularly for patients with follicular lymphoma, is that some patients did not reach their maximum level of response right away. The side effect profile is very positive, so ibrutinib may be a good fit for combination treatment, particularly with other targeted agents.

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