

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2015 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2015 American Society of Hematology Annual Meeting and Exposition • December 5-8, 2015 • Orlando, Florida

Special Reporting on:

- Five-Year Survival Data Demonstrating Durable Responses From a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma
- Post Transplant Outcome of a Multicenter Phase II Study of Brentuximab Vedotin as First Line Salvage Therapy in Relapsed/Refractory HL Prior to AHCT
- Targeted BEACOPP Variants in Patients With Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma: Final Analysis of a Randomized Phase II Study
- TARC Predicts PET-Normalization and Event Free Survival in Relapsed/Refractory Hodgkin Lymphoma Patients Treated With Brentuximab Vedotin
- First Multicenter, Randomized Phase 3 Study in Patients (Pts) With Relapsed/Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL): Alisertib (MLN8237) Versus Investigator's Choice (LUMIERE trial; NCT01482962)
- Brentuximab Vedotin in Combination With Dacarbazine or Bendamustine for Frontline Treatment of Hodgkin Lymphoma in Patients Aged 60 Years and Above: Interim Results of a Multi-Cohort Phase 2 Study
- Randomized Phase 2 Open-Label Study of R-CHOP ± Bortezomib in Patients (Pts) With Untreated Non-Germinal Center B-Cell-like (Non-GCB) Subtype Diffuse Large Cell Lymphoma (DLBCL): Results From the Pyramid Trial (NCT00931918)
- Updated Efficacy and Safety Data From the AETHERA Trial of Consolidation With Brentuximab Vedotin After Autologous Stem Cell Transplant (ASCT) in Hodgkin Lymphoma Patients at High Risk of Relapse

PLUS Meeting Abstract Summaries

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ADCETRIS[®]

brentuximab vedotin | for injection

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:

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

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. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.
- **Anaphylaxis and infusion reactions:** Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy.
- **Hematologic toxicities:** Prolonged (≥ 1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with ADCETRIS. Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.
- **Serious infections and opportunistic infections:** Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Closely monitor patients during treatment for the emergence of possible bacterial, fungal or viral infections.
- **Tumor lysis syndrome:** Closely monitor patients with rapidly proliferating tumor and high tumor burden.
- **Increased toxicity in the presence of severe renal impairment:** The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment.
- **Increased toxicity in the presence of moderate or severe hepatic impairment:** The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment.
- **Hepatotoxicity:** Serious cases of hepatotoxicity, including fatal outcomes, have occurred with ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first dose of ADCETRIS or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant

NOW APPROVED

for the treatment of patients with classical Hodgkin lymphoma (HL) at high risk of relapse or progression as post-auto-HSCT consolidation.¹

VISIT ADCETRIS.com to:

- ▶ Get full Prescribing Information
- ▶ Download a patient brochure
- ▶ Request a visit from a Seattle Genetics representative

medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. 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. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- **Pulmonary toxicity:** Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.
- **Serious dermatologic reactions:** Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with

ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- **Embryo-fetal toxicity:** Fetal harm can occur. Advise pregnant women of the potential hazard to the fetus.

Most Common Adverse Reactions:

ADCETRIS was studied in 329 patients with classical HL at high risk of relapse or progression post-auto-HSCT in a placebo-controlled randomized trial. The most common adverse reactions ($\geq 20\%$) in the ADCETRIS-treatment arm (167 patients), regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea.

Drug Interactions:

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE).

Use in Specific Populations:

MMAE exposure and adverse reactions are increased in patients with moderate or severe hepatic impairment or severe renal impairment. Avoid use.

Please see brief summary of Prescribing Information on following page and full Prescribing Information at ADCETRIS.com.

Reference: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; August 2015.

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ADCETRIS® (brentuximab vedotin) for injection, for intravenous use

Brief Summary: see package insert for complete prescribing information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.****INDICATIONS AND USAGE****Classical Hodgkin Lymphoma (HL) Post-auto-HSCT Consolidation**

ADCETRIS® (brentuximab vedotin) for injection is a CD30-directed antibody-drug conjugate indicated for the treatment of classical HL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.

DOSAGE AND ADMINISTRATION**Dosage Recommendations**

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until a maximum of 16 cycles, disease progression or unacceptable toxicity. Initiate ADCETRIS treatment within 4-6 weeks post-auto-HSCT or upon recovery from auto-HSCT.

The recommended dose is 1.8 mg/kg up to 180 mg. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to 120 mg. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (CLcr <30 mL/min).

Dose Modification

Peripheral Neuropathy: 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: The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles in patients who experience Grade 3 or 4 neutropenia in the previous cycle. In patients with recurrent Grade 4 neutropenia despite the use of G-CSF prophylaxis, consider discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg.

CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

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 relapsed classical 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.

Anaphylaxis and 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.

Hematologic Toxicities

Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. 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. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses.

Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Patients should be closely monitored during treatment for the emergence of possible bacterial, fungal or viral infections.

Tumor Lysis Syndrome

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

Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CLcr) <30 mL/min].

Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

Hepatotoxicity

Serious cases of hepatotoxicity, including fatal outcomes, have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. 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. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

Pulmonary Toxicity

Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

Serious Dermatologic Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

Embryo-Fetal Toxicity

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 classical 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**Summary of Clinical Trial Experience in Classical HL Post-auto-HSCT Consolidation (Study 3)**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ADCETRIS was studied in 329 patients with classical HL at high risk of relapse or progression post-auto-HSCT in a randomized, double-blind, placebo-controlled clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks or placebo for up to 16 cycles. Of the 329 enrolled patients, 327 (167 brentuximab vedotin, 160 placebo) received at least one dose of study treatment. The median number of treatment cycles in each study arm was 15 (range, 1–16) and 80 patients (48%) in the ADCETRIS-treatment arm received 16 cycles.

Standard international guidelines were followed for infection prophylaxis for herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Pneumocystis jirovecii* pneumonia (PCP) post-auto-HSCT. Overall, 312 patients (95%) received HSV and VZV prophylaxis with a median duration of 11.1 months (range, 0-20) and 319 patients (98%) received PCP prophylaxis with a median duration of 6.5 months (range, 0-20).

The most common adverse reactions (≥20%) in the ADCETRIS-treatment arm of Study 3, regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea.

Most Commonly Reported (≥10% in the ADCETRIS arm) Adverse Reactions in Study 3

Adverse Reaction	ADCETRIS Total N = 167 % of patients			Placebo Total N = 160 % of patients		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Blood and lymphatic system disorders</i>						
Neutropenia*	78	30	9	34	6	4
Thrombocytopenia*	41	2	4	20	3	2
Anemia*	27	4	-	19	2	-
<i>Nervous system disorders</i>						
Peripheral sensory neuropathy	56	10	-	16	1	-
Peripheral motor neuropathy	23	6	-	2	1	-
Headache	11	2	-	8	1	-
<i>Infections and infestations</i>						
Upper respiratory tract infection	26	-	-	23	1	-
<i>General disorders and administration site conditions</i>						
Fatigue	24	2	-	18	3	-
Pyrexia	19	2	-	16	-	-
Chills	10	-	-	5	-	-
<i>Gastrointestinal disorders</i>						
Nausea	22	3	-	8	-	-
Diarrhea	20	2	-	10	1	-
Vomiting	16	2	-	7	-	-
Abdominal pain	14	2	-	3	-	-
Constipation	13	2	-	3	-	-
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	21	-	-	16	-	-
Dyspnea	13	-	-	6	-	1
<i>Investigations</i>						
Weight decreased	19	1	-	6	-	-
<i>Musculoskeletal and connective tissue disorders</i>						
Arthralgia	18	1	-	9	-	-
Muscle spasms	11	-	-	6	-	-
Myalgia	11	1	-	4	-	-
<i>Skin and subcutaneous tissue disorders</i>						
Pruritus	12	1	-	8	-	-
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	12	1	-	6	-	-

*Derived from laboratory values and adverse reaction data

Additional Important Adverse Reactions**Peripheral neuropathy**

In Study 3, 67% of patients treated with ADCETRIS experienced any grade of neuropathy. The median time to first onset of any grade was 14 weeks (range, 0.1–47), of Grade 2 was 27 weeks (range, 0.4–52) and of Grade 3 was 34 weeks (range, 7–106). The median time from onset to resolution or improvement of any grade was 23 weeks (range, 0.1–138), of Grade 2 was 24 weeks (range, 1–108) and of Grade 3 was 25 weeks (range, 2–98). Of the patients who reported neuropathy, 59% had complete resolution and 41% had residual neuropathy (26% partial improvement, 15% no improvement) at the time of their last evaluation.

Infusion reactions

Two cases of anaphylaxis were reported in the dose-finding trials. In Study 3, infusion-related reactions were reported in 25 patients (15%) in the ADCETRIS-treated arm and 3 patients (2%) in the placebo arm. Grade 3 events were reported in 3 of the 25 ADCETRIS-treated patients who experienced infusion-related reactions. No Grade 4 infusion-related reactions were reported. The most common adverse reactions (≥2%) associated with infusion-related reactions were nausea (4%), chills (4%), dyspnea (2%), headache (2%), pruritus (2%), rash (2%), back pain (2%), and vomiting (2%).

Pulmonary Toxicity

In a trial in patients with classical HL 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. The concomitant use of ADCETRIS with bleomycin is contraindicated.

Cases of pulmonary toxicity have also been reported in patients receiving ADCETRIS. In Study 3, pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm. A causal association with single-agent ADCETRIS has not been established.

Serious adverse reactions

In Study 3, serious adverse reactions, regardless of causality, were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were pneumonia (4%), pyrexia (4%), vomiting (3%), nausea (2%), hepatotoxicity (2%) and peripheral sensory neuropathy (2%).

Dose modifications

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients in Study 3 were neutropenia (22%), peripheral sensory neuropathy (16%), upper respiratory tract infection (6%), and peripheral motor neuropathy (6%).

Discontinuations

Adverse reactions led to treatment discontinuation in 32% of ADCETRIS-treated patients in Study 3. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (14%), peripheral motor neuropathy (7%), acute respiratory distress syndrome (1%), paraesthesia (1%) and vomiting (1%).

Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: febrile neutropenia.

Hepatobiliary disorders: hepatotoxicity.

Infections: PML, serious infections and opportunistic infections.

Metabolism and nutrition disorders: hyperglycemia.

Gastrointestinal disorders: Pancreatitis (including fatal outcomes). Consider the diagnosis of pancreatitis for patients presenting with severe abdominal pain.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes).

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes.

Immunogenicity

Patients with classical HL and sALCL Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 timepoints) and 30% developed transiently positive antibodies (positive in 1 or 2 post-baseline timepoints). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ADCETRIS with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

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

In vitro data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

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%.

P-gp Inhibitors: Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE.

Patients who are receiving P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

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.

Risk Summary

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 classical 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.

Animal Data

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 classical 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

Avoid the use of ADCETRIS in patients with severe renal impairment (CL_{cr} <30 mL/min).

The kidney is a route of excretion for monomethyl auristatin E (MMAE). The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CL_{cr} >50-80 mL/min; n=4), moderate (CL_{cr} 30-50 mL/min; n=3) and severe (CL_{cr} <30 mL/min; n=3) renal impairment. In patients with severe renal impairment, the rate of Grade 3 or worse adverse

reactions was 3/3 (100%) compared to 3/8 (38%) in patients with normal renal function. Additionally, the AUC of MMAE (component of ADCETRIS) was approximately 2-fold higher in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, \geq Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function.

Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment.

The liver is a route of clearance for MMAE. The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. In patients with moderate or severe hepatic impairment, the rate of \geq Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function. Additionally, the AUC of MMAE was approximately 2.2-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (MMAE) have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5, or 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

PATIENT COUNSELING INFORMATION

• Peripheral neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness.

• Fever/Neutropenia

Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

• Infusion reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion.

• Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

• Progressive multifocal leukoencephalopathy

Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

• Pulmonary Toxicity

Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath.

• Pancreatitis

Advise patients to contact their health care provider if they develop severe abdominal pain.

• Pregnancy and Nursing

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy. Advise patients to report pregnancy immediately. Advise patients to avoid nursing while receiving ADCETRIS.



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Five-Year Survival Data Demonstrating Durable Responses From a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma

Approximately half of Hodgkin lymphoma (HL) patients who receive salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (SCT) will develop relapsed or progressive disease. Brentuximab vedotin is an antibody-drug conjugate that selectively delivers the microtubule-disrupting agent monomethyl auristatin E (MMAE) to CD30-positive cells. In a pivotal phase 2 trial of 102 patients with relapsed or refractory HL after autologous SCT, brentuximab vedotin yielded an overall response rate (ORR) of 75%, with complete responses (CRs) observed in 34% of patients.^{1,2} The most common treatment-related adverse event (AE) was peripheral sensory neuropathy, which occurred in 42% of patients. Other treatment-related AEs included nausea (35%), fatigue (34%), neutropenia (19%), diarrhea (18%), pyrexia (14%), vomiting (13%), arthralgia (12%), pruritus (12%), myalgia (11%), peripheral motor neuropathy (11%), and alopecia (10%). The toxicity profile was considered manageable.

Final results of this trial incorporating 5-year follow-up were reported at the 2015 American Society of Hematology (ASH) meeting.³ The median observation time for all enrolled patients from the first dose of brentuximab vedotin was 35.1 months (range, 1.8-72.9 months). The patients received a median of 9 cycles of brentuximab vedotin (range, 1-16).

The estimated 5-year overall survival (OS) was 41% (95% CI,

31%-51%), and median OS was 40.5 months (95% CI, 28.7-61.9 months; Figure 1). Median progression-free survival (PFS) was 9.3 months (95% CI, 7.1-12.2 months).

By the end of the study, 15 patients remained in remission, with a median observation time of 69.5 months (range, 66.5-72.9 months). Among the patients still in remission by the end of the study, 13 achieved a CR as best response. The ORR was 72%, with 33% CRs. The 34 patients who achieved a CR had received a median of 13.5 cycles of brentuximab vedotin. Thirteen of these patients (38%) remained in remission at study end. The median response duration was not reached in the patients who achieved a CR, and ranged from 2 to 71.6+ months. Thirteen of the 34 CR patients (38%) remained in remission at the time of study closure. Among the 6 CR patients who proceeded to allogeneic SCT as consolidation, 4 patients (67%) remained in CR. In the remaining 28 CR patients who did not receive allogeneic SCT as consolidation, 9 patients (32%) remained in CR with no subsequent therapy.

The most common treatment-related AEs were peripheral sensory neuropathy, fatigue, nausea, neutropenia, and diarrhea. Peripheral neuropathy occurred in 55% of patients; it resolved completely in 73% and improved in 14%. There were ongoing symptoms of grade 1 peripheral neuropathy in 20% and grade 2 in 7%. No patients experienced ongoing symptoms of grade 3 or higher. The most common grade 3 or higher AEs

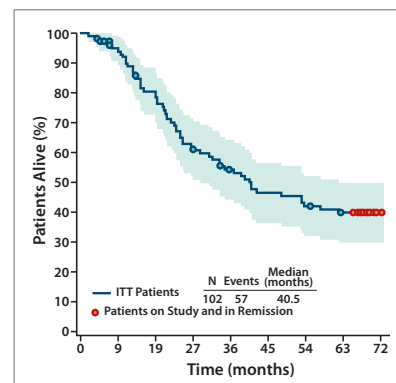


Figure 1. Overall survival in a 5-year follow-up analysis of the pivotal phase 2 trial of brentuximab vedotin. ITT, intent-to-treat. Adapted from Chen R et al. Five-year survival data demonstrating durable responses from a pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma [ASH abstract 2736]. *Blood*. 2015;126(suppl 23).²

included neutropenia (20%), peripheral sensory neuropathy (8%), thrombocytopenia (8%), and anemia (6%).

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Post Transplant Outcome of a Multicenter Phase II Study of Brentuximab Vedotin as First Line Salvage Therapy in Relapsed/Refractory HL Prior to AHCT

Dr Robert Chen presented the preliminary results from a prospective, multicenter, phase 2 trial investigating brentuximab vedotin as first-line salvage therapy prior to SCT in HL patients who failed induction chemotherapy.² Eligible patients were ages 10 years or older with histologically documented, CD30-positive HL at relapse or after a failed response to induction chemotherapy. Radiographically measurable disease and adequate organ function were also required. The study excluded patients who had received any second-line salvage therapy and those with prior autologous or allogeneic hematopoietic SCT.

Patients initially received 2 cycles of brentuximab vedotin (1.8 mg/kg) with 3 weeks between cycles followed by positron emission tomography (PET) or computed tomography imaging. Patients with a CR, partial response (PR), or stable disease received 2 more cycles of brentuximab vedotin. Patients who achieved a CR then underwent stem cell mobilization followed by transplant. Patients with stable disease or progressive disease received further salvage chemotherapy. Patients with a PR were given the option of proceeding to SCT or receiving further salvage chemotherapy. The primary endpoint was ORR.

The 37 patients had a median age of 34 years (range, 11-67 years). Sixty-five percent of patients had primary refractory disease, and 35% had relapsed within 7 months of induction chemotherapy. Induction chemotherapy for 92% of the patients was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), and 24% had received prior radiation.

Table 1. Response to Brentuximab Vedotin and Subsequent Chemotherapy

	Best Response to Brentuximab Vedotin (n=37)	Response to Combination Therapy ^a After Brentuximab Vedotin (n=18)
Overall response rate	68%	89%
Complete response	35%	56%
Partial response	32%	33%
Stable disease	27%	6%
Progressive disease	5%	6%

^aChemotherapy regimens consisted of ifosfamide, carboplatin, and etoposide; dexamethasone, ifosfamide, cisplatin, and etoposide; ifosfamide, gemcitabine, and vinorelbine; and gemcitabine, navelbine, and doxorubicin.

Adapted from Chen R et al. Post transplant outcome of a multicenter phase 2 study of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT [ASH abstract 519]. *Blood*. 2015;126(suppl 23).²

ABSTRACT SUMMARY A Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) Monotherapy in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma

Venetoclax is an oral inhibitor of BCL-2, an antiapoptotic protein that is commonly overexpressed in non-Hodgkin lymphoma. An open-label, dose-escalation, multicenter, phase 1 study evaluated the safety, pharmacokinetics, and efficacy of venetoclax monotherapy in patients with relapsed or refractory non-Hodgkin lymphoma (Abstract 254). In the dose-escalation cohorts, venetoclax was administered once daily in doses starting at 200 mg and reaching a maximum level of 1200 mg. For evaluation in a safety cohort that included 15 patients with follicular lymphoma and 21 with DLBCL, venetoclax was escalated stepwise from 400 mg to 800 mg, and then to 1200 mg. The most common grade 3/4 treatment-emergent AEs in all patients were anemia (16%), neutropenia (12%), thrombocytopenia (9%), and fatigue (6%). Thirty-three percent of patients experienced at least 1 serious AE. The maximum tolerated dose was not reached. Grade 3 and 4 neutropenia were the only dose-limiting toxicities, occurring in 2 DLBCL patients receiving 600 mg. The ORR for the 106 non-Hodgkin lymphoma patients at all doses was 47%, including 13% CRs. The ORR was 75% in mantle cell lymphoma, 38% in follicular lymphoma, and 18% in DLBCL patients. The responses in follicular lymphoma and mantle cell lymphoma were durable.

After treatment with brentuximab vedotin, the ORR was 68% and included 35% CRs (Table 1). Univariate analysis did not reveal any differences in outcomes based on age, sex, disease stage, response to induction, or

the presence of B symptoms or bulky disease. Among the 18 patients who did not achieve a CR after treatment with brentuximab vedotin and who subsequently received salvage chemotherapy, the ORR was 89%, with a CR

ABSTRACT SUMMARY Brentuximab Vedotin Plus Bendamustine: A Highly Active Salvage Treatment Regimen for Patients With Relapsed or Refractory Hodgkin Lymphoma

Brentuximab vedotin and bendamustine are safe and active when administered as monotherapy to patients with relapsed or refractory HL. A single-arm, 2-stage, open-label, phase 1/2 study investigated the safety and efficacy of brentuximab vedotin plus bendamustine in HL patients with primary refractory disease or in first relapse (Abstract 3982). Patients received 2 to 6 cycles of combination therapy and additional cycles of brentuximab vedotin for up to 16 total doses. Optional autologous SCT was permitted any time after cycle 2. The 55 treated patients had a median age of 36 years (range, 19-79 years). Infusion-related reactions were observed in 58% of the patients, a higher rate than expected. A protocol amendment requiring premedication with corticosteroids and antihistamines reduced the severity of infusion-related reactions. Forty patients underwent autologous SCT following successful stem cell collection, and 1 patient underwent bone marrow harvest owing to failure of granulocyte-colony stimulating factor. After approximately 15 months of follow-up from the first dose of study treatment and 13 months from autologous SCT, the 2-drug combination yielded an ORR of 93%, including 76% CRs. The estimated 18-month PFS rate was 75%. An early trend suggested a benefit from brentuximab vedotin consolidation therapy after autologous SCT.

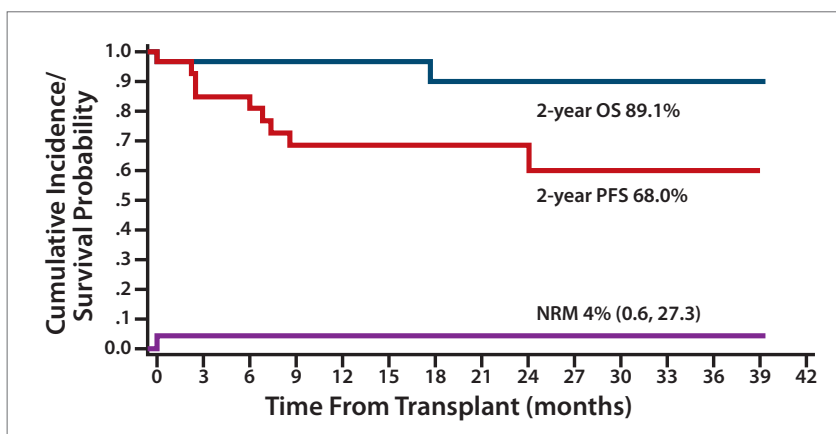


Figure 2. Outcome after transplant among the 31 patients enrolled from the City of Hope. NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival. Adapted from Chen R et al. Post transplant outcome of a multicenter phase 2 study of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT [ASH abstract 519]. *Blood*. 2015;126(suppl 23).²

rate of 56%. Among the 32 patients who proceeded to stem cell mobilization and autologous SCT, 72% had a

CR, 25% had a PR, and 3% had stable disease. Salvage regimens included brentuximab vedotin only (47%),

and brentuximab vedotin followed by either chemotherapy (50%) or radiation (3%).

Median follow-up for the 32 patients was 20.9 months (range, 10.1-41.1 months). At 18 months, the OS rate was 96.9% and the PFS rate was 71.9%. Nonrelapse mortality at day 100 was 3.1%. Twenty-five patients were treated at the City of Hope National Medical Center. These patients had a longer median follow-up of 24.2 months (range, 10.1-39.6 months). At 2 years, OS was 89.1% and PFS was 68.0% (Figure 2). Nonrelapse mortality at day 100 was 4%. The PFS rates were 76.5% for patients who achieved a CR prior to SCT vs 50.0% for those who did not ($P=.047$). Patients who received brentuximab vedotin alone as first-line salvage therapy had a PFS of 84.6%, whereas patients who received brentuximab vedotin plus chemotherapy had a PFS of 54.5% ($P=.036$).

All toxicities were grade 1 or 2. The most common AEs were stomatitis (60%), gastrointestinal toxicity (44%), and hepatic toxicity (24%). The combination of brentuximab vedotin plus bleomycin has been associated with an increase in pulmonary toxicity. In the current study, the only pulmonary toxicity events were grade 1, and they occurred in 8% of patients.

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Targeted BEACOPP Variants in Patients With Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma: Final Analysis of a Randomized Phase II Study

Escalated BEACOPP chemotherapy consists of bleomycin, vincristine, procarbazine, and prednisolone plus increased doses of etoposide, doxorubicin, and cyclophosphamide. The regimen has significantly improved tumor control and OS in patients with advanced-stage HL, with a recent study yielding an OS of 95.3% after 6 courses of escalated BEACOPP followed by PET-guided radiotherapy.¹ However, the regimen is associated with severe treatment-related morbidity in approximately 60% of patients. AEs include hematologic toxicities, such as severe infections and the need for transfusions, and nonhematologic toxicities, particularly of the nervous system. A primary objective of the German Hodgkin Study Group (GHSG) has been to reduce the intensity of BEACOPP while maintaining its efficacy.

Brentuximab vedotin has demonstrated efficacy and tolerability in HL. A phase 2 study of 102 heavily pretreated patients with relapsed or refractory HL yielded an ORR of 72%, including a CR rate of 33%, following treatment with brentuximab vedotin monotherapy for up to 16 cycles.² After a median observation time of 35.1 months (range, 1.8-72.9 months), the estimated 5-year OS rate was 41%, and the median OS was 40.5 months. These positive outcomes prompted the evaluation of brentuximab vedotin in combination with chemotherapy regimens derived from BEACOPP.³ The BEACOPP variants were adjusted to minimize toxicity by eliminating vincristine and bleomycin. Both MMAE and vincristine interfere with microtubule formation, and vincristine is also associated with neuropathy. Brentuximab vedotin has been associated with neurotoxicity. Bleomycin was omitted based on the potential for severe

pulmonary toxicity when combined with brentuximab vedotin.⁴

The regimen known as BrECAPP included etoposide, doxorubicin, and cyclophosphamide plus brentuximab vedotin, procarbazine, and prednisone. The BrECADD regimen eliminated procarbazine and prednisone while retaining dacarbazine and dexamethasone and adding brentuximab vedotin. These regimens were evaluated in a randomized phase 2 study. Results from the final analysis were presented by Dr Peter Borchmann. The study's primary objective was the CR rate at the end of treatment. Enrolled patients were ages 18 to 60 years and had advanced-stage HL. Patients were randomized to 2 cycles of BrECAPP or BrECADD and underwent interim staging by PET or computed tomography. After interim staging, patients with progressive disease were removed from the study. Patients with stable disease or better received 4 more cycles of the same regimen, and those with a positive PET scan then received radiotherapy.

The study then randomly assigned 49 patients to BrECAPP and 52 to BrECADD. The CR rates were 86% for BrECAPP and 88% for BrECADD. Estimates of 18-month PFS were 95.0% for BrECAPP and 88.6% for BrECADD. To compare the BEACOPP variants with escalated BEACOPP, the researchers provided data from the GHSG HD15 trial. The full dose at cycle 6 was given to 60% of patients in the BrECAPP arm and 69% of patients in the BrECADD arm. In comparison, 50% of patients received the full dose of escalated BEACOPP at cycle 6 in the GHSG HD15 trial. The proportions of patients receiving the lowest dose at cycle 6 were 17% for BrECAPP, 8% for BrECADD, and 15% for escalated BEACOPP. Brentuximab vedotin was reduced or stopped in cycle 5 or cycle 6 in 8% of patients.

Grade 3/4 hematologic toxicities were reported in 80% of the BrECAPP arm and 83% of the BrECADD arm. In comparison, grade 3/4 hematologic toxicities were reported in 93% of patients receiving escalated BEACOPP in the

ABSTRACT SUMMARY Initial Results of US Intergroup Trial of Response-Adapted Chemotherapy or Chemotherapy/Radiation Therapy Based on PET for Non-Bulky Stage I and II Hodgkin Lymphoma (HL) (CALGB/Alliance 50604)

To further refine the use of interim PET, the US Intergroup conducted a phase 2 clinical trial for patients with newly diagnosed, nonbulky, stage I or II HL (Abstract 578). The 164 enrolled patients received 2 cycles of ABVD followed by PET. A Deauville score of 1 to 3 was considered negative. PET-negative patients received 2 more cycles of ABVD. PET-positive patients received 2 cycles of escalated BEACOPP plus 3060 cGy of involved-field radiation therapy. After a median follow-up of 2.1 years, 8 of 131 PET-negative patients relapsed or progressed. The estimated 3-year PFS for these patients was 92%. Among the 13 patients with PET-positive disease, 3 patients relapsed and 1 committed suicide. For these patients, the estimated 3-year PFS was 66%. The authors projected that the trial was likely to meet its primary objective of a 3-year PFS of at least 85% for PET-negative patients, but was unlikely to meet its secondary objective of improving 3-year PFS for PET-positive patients.

Table 2. Grade 4 Hematologic Toxicities With BEACOPP Variants

Toxicity	BrECAPP (n=50)	BrECADD (n=52)	HD18* (n=630)
Anemia	6%	0%	10.2%
Thrombocytopenia	40%	29%	47.0%
Infection	2%	2%	2%
Total	40%	29%	50.5%

*HD18 is a separate, ongoing trial from the German Hodgkin Study Group. Patients are scheduled to receive 6 cycles of BEACOPP.

BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BrECAPP, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, and prednisone; BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Adapted from Borchmann P et al. Targeted BEACOPP variants in patients with newly diagnosed advanced stage classical Hodgkin lymphoma: final analysis of a randomized phase II study [ASH abstract 580]. *Blood*. 2015;126(suppl 23).³

GHSB HD18 trial. Grade 3/4 nonhematologic toxicities were observed in 8% and 2% of patients receiving BrECAPP or BrECADD, respectively, vs 14.7% of patients who received 6 cycles of escalated BEACOPP in trial HD18. One patient in the BrECADD arm experienced a grade 3 event that resolved completely, accounting for the 2% rate of grade 3/4 nonhematologic toxicity.

An analysis of grade 4 hematologic toxicities suggested that the regimens containing brentuximab vedotin were

associated with fewer complications than escalated BEACOPP (Table 2). In patients who received BrECAPP, BrECADD, or escalated BEACOPP, grade 4 anemia occurred in 6%, 0%, and 10.2%, respectively, and grade 4 thrombocytopenia occurred in 40%, 29%, and 47%. Grade 4 infection occurred in 2% of patients in all 3 treatment groups. Among patients receiving the BEACOPP variants, there were no reports of grade 4 neuropathy. Grade 1 to 3 sensory neuropathy occurred in

23% of the BrECAPP arm and 9% of the BrECADD arm, vs 1% of the escalated BEACOPP patients in HD18. All treatment-related neuropathy resolved completely, as did a single report of grade 3 motor neuropathy. A new trial, HD21, will compare 6 cycles of BrECADD vs 6 cycles of escalated BEACOPP in patients with advanced HL.

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TARC Predicts PET-Normalization and Event Free Survival in Relapsed/Refractory Hodgkin Lymphoma Patients Treated With Brentuximab Vedotin

The cysteine-cysteine thymus and activation-related chemokine (TARC), which is also known as CCL17, binds to chemokine receptors CCR4 and CCR8 and is normally produced by antigen-presenting cells.¹ In HL, the chemokine is secreted by Reed-Sternberg cells and attracts TH₂ T cells to the microenvironment. Based on its high expression levels in Reed-Sternberg cells, TARC is promising as a biomarker for predicting response to treatment in HL patients. In an analysis of serum samples of patients from several GHSB studies, lower baseline TARC was associated with a higher rate of PET negativity after 2 cycles of treatment, whereas a high level

was associated with primary refractory disease.² The findings support those of a prospective study that described a correlation between TARC levels in plasma and response to treatment.³ In another study, circulating CD163 (a marker of tumor-associated macrophages) and TARC were predictive of disease extent and response to treatment in newly diagnosed HL.⁴ Other biomarkers of interest in HL include interleukin (IL) 1, IL-6, IL-10, IL-2R, and soluble CD30.⁵⁻⁸

Dr Alison Moskowitz presented updated results from a nonrandomized, open-label, single-center, phase 2 study that aimed to increase the proportion of negative PET scans before autologous

SCT in HL patients who had failed first-line therapy.^{9,10} Enrolled patients had relapsed or refractory HL and had failed 1 prior doxorubicin-containing chemotherapy regimen. All patients received brentuximab vedotin (1.2 mg/kg on days 1, 8, and 15) for two 28-day cycles. Patients with a negative PET scan proceeded to high-dose therapy and autologous SCT. Patients with a positive PET scan received 2 cycles of an augmented regimen of ifosfamide, carboplatin, and etoposide (ICE). Patients who received augmented ICE received a second PET scan and either proceeded to high-dose therapy plus autologous SCT or further treatment to address persistent PET

abnormalities. A negative PET scan was defined as a Deauville score of 1 or 2.

The updated results incorporated a median posttransplant follow-up of 33 months (range, 20-43 months) for the 45 treated patients. In 76% of patients, PET scans were negative. The rate of event-free survival was highest for patients who were PET-negative after receiving brentuximab vedotin plus augmented ICE and was slightly lower for patients who were PET-negative after brentuximab vedotin alone (Figure 3). Patients who had persistent abnormalities on a PET scan after receiving brentuximab vedotin plus ICE showed the lowest rate of event-free survival, at approximately 50%.

Serum samples were collected at baseline and after 2 cycles of brentuximab vedotin. TARC decreased by approximately 82% from a baseline median level of 8250 pg/mL to a median of 1027 pg/mL after 2 cycles of brentuximab vedotin. A greater reduction in TARC following 2 cycles of brentuximab vedotin was associated with an increased likelihood of PET normalization (odds ratio, 5.82). The median serum level of TARC was 1027 pg/mL after 2 cycles of brentuximab vedotin. Among the 6 patients with progressive disease, all had TARC serum levels above the median after receiving brentuximab vedotin. One patient with a TARC level below the median after treatment died from infection.

Serum TARC levels below 1027 pg/mL correlated with an increased likelihood of event-free survival (2-year event-free survival rates: 94% vs 67%; $P=.044$). The highest rates of event-free survival were seen in patients with negative PET scans before SCT and in patients with a positive PET scan and a TARC serum level below 1027 pg/mL. A low level of serum TARC appeared to offset the negative predictive value of a positive PET scan before SCT.

This study also included an analysis of cytokines and chemokines (Table 3). Elevated baseline interferon γ and IL-10 correlated with the presence of

Table 3. Changes in Levels of Cytokines and Chemokines After Brentuximab Vedotin

Cytokine/ Chemokine (normal)	Before Brentuximab Vedotin (pg/mL)		After Brentuximab Vedotin (pg/mL)	
	Median	Range	Median	Range
IL-6 (<17.4)	2.27	0.10-154	1.41	0.09-34
IL-10 (<2)	0.38	0.09-112	0.45	0.14-18
TNF α (<5.6)	2.55	0.55-15.15	2.25	0.58-22
IFN- γ (<2)	8.66	1.45-1554	9.01	2.62-113
TARC (<500)	8250	236-220,773	1027	241-34,453

IFN- γ , interferon gamma; IL-6, interleukin 6; IL-10, interleukin 10; TARC, thymus and activation-related chemokine; TNF α , tumor necrosis factor alpha.

Adapted from Moskowitz AJ et al. TARC predicts PET-normalization and event free survival in relapsed/refractory Hodgkin lymphoma patients treated with brentuximab vedotin [ASH abstract 180]. *Blood*. 2015;126(suppl 23).¹⁰

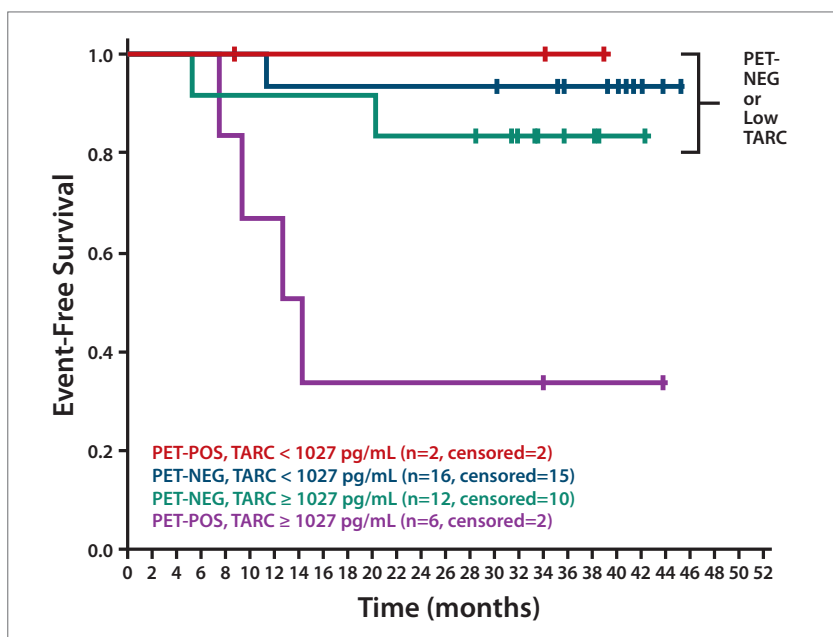


Figure 3. Interim levels of TARC predicted PET-normalization and event-free survival in patients with relapsed/refractory Hodgkin lymphoma treated with brentuximab vedotin. NEG, negative; PET, positron-emission tomography; POS, positive; TARC, thymus and activation-related chemokine. Adapted from Moskowitz AJ et al. TARC predicts PET-normalization and event free survival in relapsed/refractory Hodgkin lymphoma patients treated with brentuximab vedotin [ASH abstract 180]. *Blood*. 2015;126(suppl 23).¹⁰

extranodal disease. Elevated IL-10 and tumor necrosis factor α correlated with an increased likelihood of B symptoms.

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First Multicenter, Randomized Phase 3 Study in Patients (Pts) With Relapsed/Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL): Alisertib (MLN8237) Versus Investigator's Choice (LUMIERE trial; NCT01482962)

Alisertib is an investigational, orally administered, selective inhibitor of Aurora A kinase.¹⁻³ In phase 2 trials, alisertib monotherapy demonstrated antitumor activity with favorable tolerability in peripheral T-cell lymphoma (PTCL), yielding an ORR of 30%.^{4,5} Dr Owen O'Connor presented results from the international, multicenter, open-label, phase 3 LUMIERE (Alisertib [MLN8237] or Investigator's Choice in Patients With Relapsed/Refractory Peripheral T-Cell Lymphoma) study, which investigated the efficacy and safety of alisertib monotherapy in adult patients with relapsed or refractory PTCL.⁶ Patients had measurable disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Demographic and baseline characteristics were well balanced between the 2 treatment arms. The median age was 63 years (range, 19-86 years), and two-thirds were male. Patients had received treatment with at least 1 prior conventional systemic cytotoxic therapy but not with the study drugs. The study randomly assigned 138 patients to alisertib and 133 to the comparator arm.

Alisertib was administered at 50 mg twice daily on days 1 to 7 in 21-day cycles. Patients in the comparator arm received 1 of 3 therapies—pralatrexate, gemcitabine, or romidepsin—as selected by their physician. (Gemcitabine is currently not approved for use in

hematologic malignancies.) Treatment continued until disease progression or unacceptable toxicity. Patients with stable disease or better could continue treatment for up to 2 years. The primary endpoints were ORR and PFS. Secondary endpoints were OS, CR rate, duration of response, and safety.

The study design included adaptive sample size reassessment with 2 interim analyses and a final analysis. For the first interim analysis, ORR was evaluated for the first 74 patients. The second interim analysis of ORR included the first 146 patients.

The ORRs were 35% (19% CRs) for alisertib vs 46% (28% CRs) for the comparator arm. The comparator treatments of pralatrexate (n=45), gemcitabine (n=22), and romidepsin (n=18) yielded ORRs of 44%, 36%, and 61%, respectively. Median PFS was 115 days for the alisertib arm vs 104 days for the comparator arm (hazard ratio [HR], 0.87; 95% CI, 0.64-1.16; $P=.177$; Figure 4). After elimination of patients who did not meet eligibility criteria based on central pathology review, the PFS rates were 120 days in the alisertib arm vs 104 days in the comparator arm. Median OS was

ABSTRACT SUMMARY Brentuximab Vedotin With RCHOP As Frontline Therapy in Patients With High-Intermediate/High-Risk Diffuse Large B Cell Lymphoma (DLBCL): Results From an Ongoing Phase 2 Study

A multicenter, randomized, phase 2 study investigated 6 cycles of R-CHOP plus brentuximab vedotin (1.2 or 1.8 mg/kg) as first-line therapy in patients with high-intermediate or high-risk DLBCL (Abstract 814). Tumors were assessed at baseline for CD30 expression. Among the 51 patients, 71% had stage IV disease, 37% were high risk, and 63% were high/intermediate risk. After the first 10 patients experienced significant neurotoxicity with 1.8 mg/kg of brentuximab vedotin, the remaining patients received the 1.2 mg/kg dose. The most common grade 3/4 AEs were neutropenia (33%), febrile neutropenia (31%), and anemia (24%). ORRs were similar in the CD30-negative and CD30-positive patients. Among the 25 evaluable patients with CD30-positive disease, 84% obtained an objective response, including 76% CRs. Median PFS for the CD30-negative patients was 18 months vs not reached for the CD30-positive patients. Estimated 12-month and 15-month PFS rates for CD30-positive patients were both 83%. For CD30-negative patients, these rates were 62% and 54%, respectively. ORR was not impacted by the presence of Epstein-Barr virus. The trial has been amended to add a cohort evaluating brentuximab vedotin plus R-CHOP in order to eliminate the toxicity associated with vincristine.

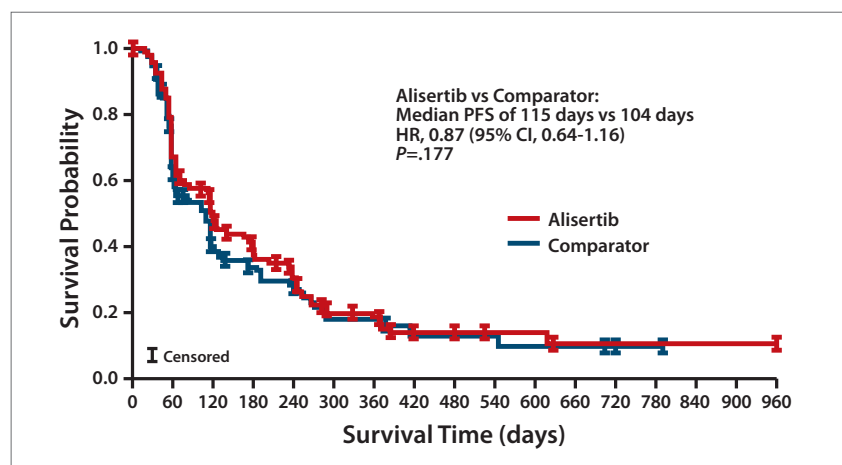


Figure 4. PFS in the intent-to-treat population of a phase 3 study comparing alisertib vs investigator's choice in patients with relapsed/refractory peripheral T-cell lymphoma. HR, hazard ratio; PFS, progression-free survival. Adapted from O'Connor OA et al. First multicenter, randomized phase 3 study in patients (pts) with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL): alisertib (MLN8237) versus investigator's choice (LUMIERE trial; NCT01482962) [ASH abstract 341]. *Blood*. 2015;126(suppl 23).⁶

13.6 months for alisertib vs 12.1 months for comparator treatment (HR, 0.96; 95% CI, 0.70-1.33; $P=.338$). Estimated 2-year OS was 35% for both arms.

Treatment-related AEs were 88% in the alisertib arm vs 94% in the compara-

tor arm. Treatment-related AEs of grade 3 or higher were reported in 70% vs 68% of patients, respectively. Treatment-related serious AEs were reported in 34% vs 32%. AEs leading to discontinuation were observed in 9% vs 14% of

patients. On-study deaths occurred in 8% vs 12%. In the alisertib arm, anemia, neutropenia, and diarrhea were the most common AEs of any grade and of grade 3 or higher.

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Brentuximab Vedotin in Combination With Dacarbazine or Bendamustine for Frontline Treatment of Hodgkin Lymphoma in Patients Aged 60 Years and Above: Interim Results of a Multi-Cohort Phase 2 Study

Older patients with HL have an inferior outcome.¹ Dr Christopher Yasnchak presented interim results from a multicohort phase 2 study of brentuximab vedotin in HL patients ages 60 years or older.² Results from a monotherapy arm (cohort A) were published previously.³ Brentuximab vedotin monotherapy yielded an ORR of 92%, including 73% CRs, among 27 patients. All patients achieved stable disease or better. Median PFS was 10.5 months (range, 2.6+ to 22.3+ months). The therapy was generally well tolerated, with serious AEs observed in 22% of

patients. No deaths occurred within 30 days of treatment cessation.

The current analysis provided data evaluating brentuximab vedotin in combination with dacarbazine or bendamustine.^{2,4} Patients in cohort B received brentuximab vedotin (1.8 mg/kg, day 1) for up to 16 cycles, plus dacarbazine (375 mg/m², day 1) for up to 12 cycles. Cohort C also received brentuximab vedotin (1.8 mg/kg, day 1) for up to 16 cycles, plus bendamustine (90 mg/m², days 1 and 2) for up to 6 cycles. Additional cycles of brentuximab vedotin were permitted for patients showing a clinical benefit. After 9 patients in cohort C received

treatment, the protocol was amended to reduce the starting dose of bendamustine from 90 mg/m² to 70 mg/m².

Enrolled patients had treatment-naïve classical HL and were ages 60 years or older. They were ineligible for first-line conventional combination therapy or had declined it. Patients had measurable disease of at least 1.5 cm and an ECOG performance status of 0 to 3. Patients enrolled in cohort C had a creatinine clearance rate of at least 40 mL/min. At the data cutoff, 27 patients had been treated in cohort A, and all were off treatment. Among the 22 patients treated in cohort B, 2 remained

ABSTRACT SUMMARY Addition of Etoposide to CHOP Is Associated With Improved Outcome in Adult Anaplastic Large Cell Lymphoma Patients: A Nordic Lymphoma Group Study

A population-based study was conducted to analyze outcome and risk factors in adult anaplastic large T-cell lymphoma (ALCL) patients from the Swedish and Danish Lymphoma Registries (Abstract 340). The analysis included 371 patients, with a median follow-up of 7.2 years. ALK-positive patients were younger than ALK-negative patients (median age, 44 vs 66 years; $P < .001$). Five-year OS rates were 78% for the ALK-positive patients vs 37% for those who were ALK-negative. Multivariate analysis revealed that treatment with CHOP, compared with CHOP plus etoposide, was an independent risk factor associated with reduced OS (HR, 1.85; 95% CI, 1.18-2.89; $P = .007$). An increasing IPI score was also associated with inferior OS (HR for each increment, 1.79; 95% CI, 1.52-2.12; $P < .001$). For the 108 patients who had received treatment with CHOP plus etoposide, multivariate analysis revealed 3 independent risk factors for OS: increased age (HR for ages 41-60 years, 2.71; 95% CI, 1.45-5.05; $P = .001$; HR for ages 61-75 years, 7.34; 95% CI, 2.10-25.5), ALK negativity (HR, 2.54; 95% CI, 1.12-5.76; $P = .026$), and elevated lactate dehydrogenase (HR, 2.24; 95% CI, 1.08-4.67; $P = .031$).

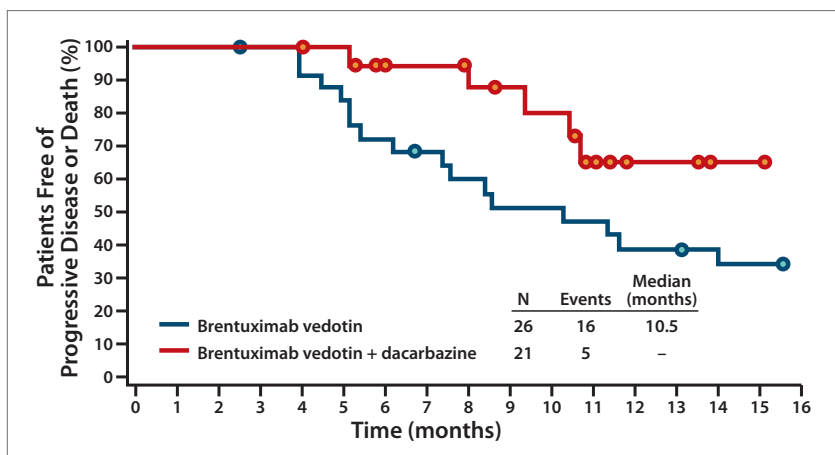


Figure 5. Interim analysis of progression-free survival for brentuximab vedotin plus dacarbazine vs brentuximab vedotin alone in a phase 2 trial. PD, progressive disease. Adapted from Yasenchak CA et al. Brentuximab vedotin in combination with dacarbazine or bendamustine for frontline treatment of Hodgkin lymphoma in patients aged 60 years and above: interim results of a multi-cohort phase 2 study [ASH abstract 587]. *Blood*. 2015;126(suppl 23).²

on treatment. Among the 20 patients treated in cohort C, 11 continued treatment with brentuximab vedotin monotherapy. Tolerability of bendamustine did not meet the study goals, and use of the drug was discontinued.

The median ages were 78 years in cohort A, 69 years in cohort B, and 75 years in cohort C. In all cohorts, most patients had an ECOG performance status of 0 or 1 and stage III/IV disease. Bulky disease was present in 22% of cohort A,

9% of cohort B, and 5% of cohort C. B symptoms were present in 33%, 41%, and 50%, respectively, and conventional chemotherapy was contraindicated in 52%, 86%, and 85%. Significant comorbidities and impaired functional status were noted in all 3 cohorts.

The ORRs were 92% in cohort A and 100% in cohorts B and C. Rates of CR were 73%, 67%, and 81%, respectively. With median observation times of 23.1 months for cohort A and

13.4 months for cohort B, estimates of 12-month PFS were 38% and 66%, respectively (Figure 5). The observation time for cohort C was only 4.6 months, precluding meaningful estimates of PFS.

In cohort A, patients received a median 8 cycles of treatment. In cohort B, patients received a median 12.5 cycles of brentuximab vedotin and a median 12 cycles of dacarbazine. In cohort C, patients received a median 3.5 cycles of brentuximab vedotin and a median 3.5 cycles of bendamustine. The most common reason for treatment discontinuation was an AE, as reported in 41% of cohorts A and B and 25% of cohort C. Other reasons for discontinuation in cohorts A, B, and C included progression after a CR or PR (41%, 14%, 0%, respectively), investigator decision (4%, 18%, 5%), and patient decision (11%, 18%, 15%).

All patients in the study experienced an AE. Rates of serious AEs were 22% in cohort A, 9% in cohort B, and 60% in cohort C. Treatment-related AEs of grade 3 or higher were reported in 48%, 36%, and 65% of patients in cohorts A, B, and C, respectively. AEs leading to treatment discontinuation were reported in 41% of patients in cohorts A and B and 25% of patients in cohort C. Brentuximab vedotin plus bendamustine was associated with more types of AEs and more grade 3/4 AEs compared with brentuximab vedotin plus dacarbazine. Peripheral neuropathy was more frequent in cohort B compared with cohort C; however, patients in cohort B had received more cycles of brentuximab vedotin (median 12.5 cycles vs 3.5 cycles). Within the 30-day safety period, 2 deaths occurred, both in cohort C and both considered unrelated to study treatment.

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Randomized Phase 2 Open-Label Study of R-CHOP ± Bortezomib in Patients (Pts) With Untreated Non-Germinal Center B-Cell-like (Non-GCB) Subtype Diffuse Large Cell Lymphoma (DLBCL): Results From the Pyramid Trial (NCT00931918)

Dr John Leonard presented results from the PYRAMID (Study to Assess the Effectiveness of RCHOP With or Without VELCADE in Previously Untreated Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma Patients) trial, an open-label, randomized phase 2 study that evaluated efficacy and safety of the standard regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) vs R-CHOP plus bortezomib (VR-CHOP) in patients with treatment-naïve non-germinal center B-cell (GCB) diffuse large B-cell lymphoma (DLBCL).¹ Enrolled patients had centrally or locally confirmed non-GCB DLBCL based on the Hans immunohistochemistry method.² Patients had measurable disease and an ECOG performance status of 0 to 2. Their median age was 64 years (range, 10-85 years). The study's primary endpoint was PFS, with secondary endpoints of OS, ORR, CR, and toxicity. The study randomly assigned 91 patients to R-CHOP and 92 patients to VR-CHOP. At least 6 treatment cycles were completed by 86% of the R-CHOP arm and 85% of the VR-CHOP arm. The median follow-up was 34 months for both arms.

The ORR was 98% in the R-CHOP arm vs 96% in the VR-CHOP arm, with CR rates of 49% vs 56%, respectively. Rates of negative ¹⁸F-fluorodeoxyglucose PET scans at the end of treatment were 53% with R-CHOP and 59% with VR-CHOP.

The 2-year PFS rates were 78% for R-CHOP vs 82% for VR-CHOP (HR, 0.73; *P*=.611). Two-year OS probability was 88% with R-CHOP vs 93% with VR-CHOP (HR, 0.75; *P*=.763; Figure 6). Survival outcomes were similar when analyzed by International Prognostic Index (IPI) score.

No new safety signals emerged in the toxicity analysis of R-CHOP (n=100) vs VR-CHOP (n=101). AEs of grade 3 or higher occurred in 71% of the R-CHOP group and 79% of the VR-CHOP group. Drug-related AEs of grade 3 or higher occurred in 55% vs 68%, respectively. One patient died in each arm. Neutropenia occurred

at similar rates in both arms, whereas thrombocytopenia and anemia were more common with VR-CHOP. The most common nonhematologic AEs of any grade in both arms were fatigue, nausea, peripheral neuropathy, alopecia, and constipation. The most common AE of grade 3 or higher was neutropenia, occurring in approximately 50% of patients in both arms. Grade 3 or greater thrombocytopenia and anemia were more common in patients who received treatment with bortezomib. The only grade 3 or higher nonhematologic AE was hypokalemia, occurring in approximately 10% of patients in each arm.

In the current study, patients who

ABSTRACT SUMMARY Interim Analysis of a Phase 2 Study of Bortezomib Plus Rituximab Maintenance Therapy in Patients With Mantle Cell Lymphoma Status Post Autologous Stem Cell Transplantation

A multicenter, phase 2 trial evaluated bortezomib plus rituximab maintenance therapy in patients with mantle cell lymphoma in CR after autologous SCT (Abstract 1961). The primary endpoint was disease-free survival after 2 years of maintenance therapy. The study accrued 16 patients, and 15 were eligible for analysis. The 2-year disease-free survival was 100%, and the 2-year OS was 100%. No patients relapsed or died. The treatment was well tolerated. Grade 3/4 AEs potentially related to treatment included neutropenia in 4 patients, lymphopenia in 3, and pneumonia and skin infection, each in 1 patient. Grade 2 AEs potentially related to treatment included thrombocytopenia in 2 patients and neutropenia, anemia, arthralgia, peripheral sensory neuropathy, pruritus, and hypertension, each in 1 patient. Peripheral neuropathy toxicities included grade 1 sensory neuropathy in 4 patients, grade 1 motor neuropathy in 1, and grade 2 sensory neuropathy in 1. In an analysis of 12 patients for minimal residual disease (MRD), the relative CCND1 mRNA level never exceeded 12% of the control (JVM2), and the majority of the samples were below 5%. There were few inpatient fluctuations.

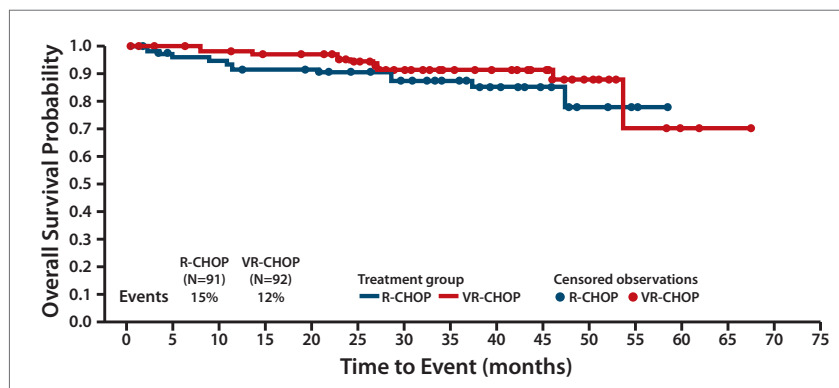


Figure 6. Probability of overall survival in the PYRAMID trial. The difference between the treatment arms did not reach statistical significance ($P=.763$). PYRAMID, Study to Assess the Effectiveness of RCHOP With or Without VELCADE in Previously Untreated Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma Patients; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; V, bortezomib. Adapted from Leonard JP et al. Randomized phase 2 open-label study of R-CHOP \pm bortezomib in patients (pts) with untreated non-germinal center B-cell-like (non-GCB) subtype diffuse large cell lymphoma (DLBCL): results from the PYRAMID trial [ASH abstract 811]. *Blood*. 2015;126(suppl 23).¹

ABSTRACT SUMMARY The Combination of Brentuximab Vedotin (Bv) and Bendamustine (B) Demonstrates Marked Activity in Heavily Treated Patients With Relapsed or Refractory Hodgkin Lymphoma (HL) and Anaplastic Large T-Cell Lymphoma (ALCL): Results of an International Multi Center Phase I/II Experience

A multicenter phase 1/2 study investigated the addition of brentuximab vedotin to bendamustine in heavily pretreated patients with relapsed or refractory HL and ALCL (Abstract 586). Patients were enrolled at 3 centers from August 2012 to November 2015. In phase 1 of the trial, brentuximab vedotin (day 1) was escalated from 1.2 mg/kg to 1.8 mg/kg, and bendamustine (days 1 and 2) was escalated from 70 mg/m² to 100 mg/m² in 5 cohorts, with treatment administered in 21-day intervals for a maximum of 6 cycles. Phase 2 used the recommended doses from phase 1 (brentuximab vedotin 1.8 mg/kg [day 1] plus bendamustine 90 mg/m² [days 1 and 2]). The trial enrolled 27 patients in phase 1 and 19 patients in phase 2. For the 46 patients, median age was 36 years (range, 30-70 years), and the majority of patients were male. Patients had received a median 6 prior therapies (range, 1-16). For all dose levels combined, the ORR was 69%, including 20% CRs. Responses were observed in more than 50% of patients who had received either agent separately prior to study enrollment. The preliminary duration of response was 4.4 months (range, 2.3-10.3 months). In the phase 1 vs phase 2 patients, the most common grade 3/4 AEs were neutropenia (15% vs 16%, respectively), anemia (22% vs 0%), thrombocytopenia (19% vs 0%), and lung infection (11% vs 21%).

received standard R-CHOP performed better than expected, demonstrating a 2-year PFS of 78%. In a previous study, patients with activated B-cell DLBCL based on gene expression profiling had a 3-year PFS rate of only 40% after treatment with standard R-CHOP.³ However, in a more recent study of patients with non-GCB DLBCL, R-CHOP yielded a 2-year PFS rate of 77%.⁴ Dr Leonard concluded by suggesting that the prospective selection process may have inadvertently excluded patients likely to have less favorable outcomes.

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Updated Efficacy and Safety Data From the AETHERA Trial of Consolidation With Brentuximab Vedotin After Autologous Stem Cell Transplant (ASCT) in Hodgkin Lymphoma Patients at High Risk of Relapse

AETHERA (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) is a placebo-controlled, randomized phase 3 study that investigated consolidation treatment with brentuximab vedotin after autologous SCT in 329 HL patients at high risk of relapse or progression.¹ The study met its primary endpoint by demonstrating improved PFS with brentuximab vedotin vs placebo by independent review (42.9 months vs 24.1 months; HR, 0.57; $P=.001$). The most common AEs in the brentuximab vedotin treatment arm were peripheral sensory neuropathy (56% vs 16% for placebo) and neutropenia (35% vs 12% for placebo).

Dr John Sweetenham presented updated safety and efficacy results from the AETHERA trial, reflecting approximately 3 years of follow-up.² Patients had a median age of 33 years (range, 18-76 years). Approximately 60% of patients in both arms had refractory disease, and one-third had relapsed within 12 months of their prior treatment. Salvage therapy before autologous SCT was associated with a CR rate of 37% to 38%, a PR rate of 34% to 35%, and a stable disease rate of 28%. One-third of patients had extranodal involvement upon relapse before autologous SCT, and 24% to 28% had B symptoms after first-line therapy.

The PFS rate at 24 months was 65% (95% CI, 57%-72%) for brentuximab vedotin vs 45% (95% CI, 37%-52%) for placebo. At 36 months, the PFS rate was 61% (95% CI, 53%-68%) vs 43% (95% CI, 36%-51%), respectively (Figure 7). The median PFS

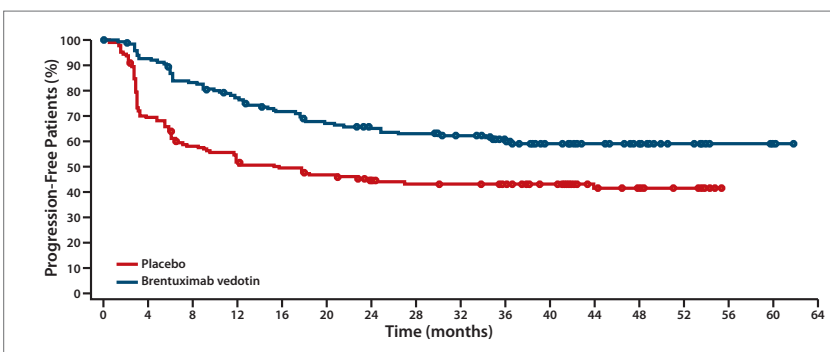


Figure 7. Progression-free survival 3 years after randomization among patients in the AETHERA trial. AETHERA, A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant. Adapted from Sweetenham J et al. Updated efficacy and safety data from the AETHERA trial of consolidation with brentuximab vedotin after autologous stem cell transplant (ASCT) in Hodgkin lymphoma patients at high risk of relapse [ASH abstract 3172]. *Blood*. 2015;126(suppl 23).²

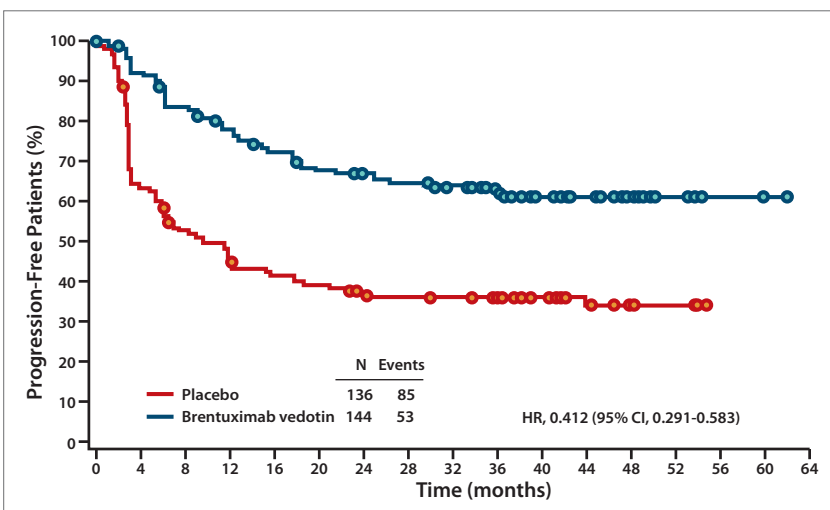


Figure 8. Progression-free survival among patients with 2 or more risk factors in an updated analysis of the AETHERA trial. AETHERA, A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant; HR, hazard ratio. Adapted from Sweetenham J et al. Updated efficacy and safety data from the AETHERA trial of consolidation with brentuximab vedotin after autologous stem cell transplant (ASCT) in Hodgkin lymphoma patients at high risk of relapse [ASH abstract 3172]. *Blood*. 2015;126(suppl 23).²

had not been reached for the brentuximab vedotin arm and was 15.8 months

for the placebo arm (HR, 0.52). Subgroup analyses showed superior PFS for

ABSTRACT SUMMARY Updated Data for the PD-1 Inhibitors Nivolumab and Pembrolizumab

An ongoing phase 1 study is evaluating the efficacy of nivolumab in 23 patients with relapsed or refractory HL. Twenty-three HL patients received nivolumab in the dose expansion cohort (Abstract 583). The ORR was 87%, including 22% CRs and 65% PRs. After a median follow-up of 101 weeks, median PFS and median duration of response had not been reached. Median rates of OS were 91% at 1 year and 83% at 1.5 years. Treatment-emergent AEs of interest included 1 event each of grade 3 colitis and grade 3 pneumonitis. Three patients discontinued treatment owing to AEs, 2 of which were considered related to nivolumab treatment. Pembrolizumab was evaluated in the open-label, multicenter phase 1b KEYNOTE-013 (A Trial of Pembrolizumab [MK-3475] in Participants With Blood Cancers [MK-3475-013]) trial. Results from an expansion cohort study were presented at the 2015 ASH meeting (Abstract 584). Among the 31 patients with relapsed or refractory classical HL, the ORR was 65%, including 16% CRs. The size of target lesions was reduced in 90% of patients. At 24 weeks, PFS was 69%, and 71% of patients had a response duration of 24 weeks or longer. Treatment-related AEs of any grade occurred in 68% of patients, and treatment-related AEs of grade 3 occurred in 16%. Two patients discontinued treatment owing to an AE.

brentuximab vedotin vs placebo among patients with a PR prior to autologous SCT (HR, 0.459; 95% CI, 0.272-0.773), those with stable disease before autologous SCT (HR, 0.390; 95% CI, 0.390-0.686), and those with 2 or

more risk factors (HR, 0.412; 95% CI, 0.291-0.583; Figure 8).

Among patients receiving brentuximab vedotin, 112 developed peripheral neuropathy, for a rate of 67%. Peripheral neuropathy was grade 3 in 22 patients.

There were no reports of grade 4. The peripheral neuropathy resolved or improved in 99 patients (88%), and completely resolved in 74 (66%). Secondary malignancies were reported in 3% of the brentuximab vedotin arm vs 1% of the placebo arm. Following subsequent poststudy treatment with brentuximab vedotin to treat relapse, the ORR was 86% for the 7 evaluable patients in the brentuximab vedotin arm and 67% for the 61 evaluable patients in the placebo arm. Patients in the AETHERA study remain in long-term follow-up, and final analysis for OS is planned for 2020.

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Highlights in Lymphoma From the 2015 ASH Meeting: Commentary

Robert W. Chen, MD

Presentations at the 2015 American Society of Hematology (ASH) meeting provided insight into the management of several lymphoma subtypes, including Hodgkin lymphoma, peripheral T-cell lymphoma (PTCL), anaplastic large-cell lymphoma, and mantle cell lymphoma. Studies evaluated therapies such as brentuximab vedotin, bendamustine, bortezomib, venetoclax, and alisertib, and attempted to refine existing regimens.

Hodgkin Lymphoma

There were several presentations on brentuximab vedotin, which provided both updated analyses and results from

new trials. I presented data from a 5-year follow-up analysis of the pivotal phase 2 study of brentuximab vedotin in relapsed Hodgkin lymphoma.¹ The study was published in 2012, and showed an overall response rate of 75%.² It led to accelerated approval from the US Food and Drug Administration (FDA).

In the original study, approximately 50% of patients developed peripheral neuropathy. After 5 years, the peripheral neuropathy resolved or improved in 88% of these patients. In 73% of patients, it resolved completely. Therefore, most of the neuropathies seen with brentuximab vedotin were reversible and did not interfere with a patient's life after treatment.

The 5-year overall survival in this study was 41%, and the progression-free survival (PFS) was 22%. The median overall survival was 40.5 months. (In contrast, before brentuximab vedotin was available, the median overall survival among patients who had failed an autologous transplant was approximately 10 to 27 months.) Approximately a third of the patients obtained a complete remission, and these patients had even better outcomes. Their 5-year overall survival was 64%, and their 5-year PFS was 54%. It is encouraging to be able to tell patients who have achieved a complete response that their chance of being alive in 5 years is approximately 60%.

I presented results from a study evaluating the posttransplant outcome of brentuximab vedotin as frontline salvage therapy.³ This study in the pre-transplant population was prompted by the exciting data from the pivotal study showing that brentuximab vedotin had a high response rate in post-transplant patients.² Typical frontline salvage therapies include multiagent combination chemotherapy, such as ifosfamide, carboplatin, and etoposide (ICE). Although ICE has a high response rate, it is associated with significant toxicity. Brentuximab vedotin also has a high response rate, but with far less toxicity.

The dosage of brentuximab vedotin was 1.8 mg every 3 weeks given for a total of 4 cycles. Patients who achieved a complete response or a very good partial response went directly to transplant. Patients who achieved only stable disease, progressive disease, or a partial response received second-line salvage therapy, such as ICE. The overall response rate was 68%, with 35% complete responses, which is similar to the pivotal trial. Among the 37 patients, 32 were able to proceed to transplant. Among the patients who proceeded to transplant, 72% achieved complete remission at the time of transplant. It is known that patients who undergo transplant while in complete remission have a better outcome than patients not in complete remission.

Approximately half of the patients who proceeded to transplant were receiving brentuximab vedotin alone. Those patients were therefore spared the multiagent salvage chemotherapy strategy. In the study, the stem cell mobilization rate was unaffected, and engraftment was not delayed. We also presented data for 2 years after transplant. The 2-year overall survival post-transplant was 89%, and the PFS was 68%, which compares favorably with historical controls. Among the patients who proceeded to transplant while in complete remission, the 2-year PFS was even better, at 77%.

Before the study, concerns had been raised regarding whether a complete response achieved with brentuximab vedotin is equivalent to a complete response achieved with ICE chemotherapy, and whether the posttransplant outcome—specifically, PFS—would be affected if patients received brentuximab vedotin alone. In the study, patients who received brentuximab vedotin alone achieved a higher rate of 2-year PFS, at 85%. Patients who received brentuximab vedotin as a salvage regimen only and proceeded to transplant had a very good outcome posttransplant.

Dr Alison Moskowitz presented a study evaluating whether levels of cysteine-cysteine thymus and activation-related chemokine (TARC) predict PET normalization.⁴ As in the previous study, brentuximab vedotin was used as the first-line salvage regimen, but at a different dosage: 1.2 mg weekly (compared with 1.8 mg every 3 weeks). The response rates, including PFS, were similar to the ones we reported in the previous trial. The focus of this study, however, was to identify biologic correlates to response. TARC levels were

measured before and after treatment with brentuximab vedotin. They found that a reduction in TARC levels was associated with the rate of PET-negative complete responses. In addition, a TARC level less than 1026.7 pg/mL at the end of brentuximab vedotin therapy was associated with improved event-free survival after transplant. These data have positive implications for the future. It would be useful to rely on a blood test, instead of imaging, to confirm complete remission or predict for a good outcome after transplant. A larger study is needed to confirm these results.

Dr John Sweetenham presented updated efficacy and safety data from the AETHERA trial, a randomized, placebo-controlled, phase 3 study evaluating consolidation with brentuximab vedotin after transplant in patients with Hodgkin lymphoma.⁵ When AETHERA was presented in 2014, it showed that brentuximab vedotin improved PFS.⁶ The analysis at the 2015 ASH meeting provided updated efficacy and safety data drawn from approximately 3 years of follow-up. The median PFS in the placebo

ABSTRACT SUMMARY Evaluation of the Regimen Brentuximab Vedotin Plus ESHAP (BRESHAP) in Refractory or Relapsed Hodgkin Lymphoma Patients: Preliminary Results of a Phase I-II Trial From the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO)

A phase 1/2 trial was conducted to evaluate the dose-limiting toxicity, maximum tolerated dose, and ORR with brentuximab vedotin plus etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) chemotherapy as second-line treatment in patients with relapsed or refractory HL prior to autologous SCT (Abstract 582). Brentuximab vedotin was administered on day 1 at 0.9 mg/kg, 1.2 mg/kg, or 1.8 mg/kg in conjunction with ESHAP every 21 to 28 days followed by autologous SCT. After transplant, patients received brentuximab vedotin monotherapy. All 9 patients enrolled in the phase 1 portion of the trial had a CR. Severe AEs included nonneutropenic fever that resolved in 1 to 3 days, pneumothorax that resolved in 1 day, and febrile neutropenia that resolved in 7 days. Two AEs of grade 4 neutropenia and 1 of grade 4 thrombocytopenia occurred. No dose-limiting toxicity was observed, and the maximum tolerated dose of brentuximab vedotin was defined as 1.8 mg/kg every 21 days in combination with ESHAP. The phase 2 portion included 36 patients. Stem cells were collected in 24 patients, and no mobilization failures occurred. In the 24 patients evaluable for pretransplant response, the ORR was 96%, with 83% metabolic CRs. The majority of grade 3/4 AEs were hematologic, and toxicity was manageable.

arm was 15.8 months, and it was not yet reached in the brentuximab vedotin arm. The 3-year PFS was 61% with brentuximab vedotin vs 43% with placebo. Peripheral neuropathy was seen in 67% of patients receiving brentuximab vedotin. By the end of this follow-up period, the neuropathy improved in 88% and completely resolved in 55%.

To summarize, the Kaplan-Meier curves for PFS are plateauing and clearly separating, indicating that the improvement seen with brentuximab vedotin could possibly translate into an overall survival advantage. Any neuropathy usually resolves. Overall, these follow-up results are very promising.

Dr Christopher Yasnchak presented data from a study of brentuximab vedotin plus dacarbazine or bendamustine in frontline treatment of elderly patients (≥ 60 years) with Hodgkin lymphoma.⁷ The standard treatment, ABVD, is associated with poor outcomes in elderly patients. In a previous study of elderly patients, single-agent brentuximab vedotin was associated with a high overall response rate (92%) and complete response rate (73%).⁸ However, the PFS was only 10.5 months, and the 1-year PFS was 38%. The current study attempted to improve PFS by adding an additional agent.

In the brentuximab vedotin/dacarbazine arm, the overall response rate was 100%, and the complete response rate was 67%. The 1-year PFS was 66%. Therefore, the addition of dacarbazine to brentuximab vedotin improved 1-year PFS by 28%. The toxicity was well-tolerated. This promising combination merits further study as upfront treatment for elderly patients with Hodgkin lymphoma.

In the brentuximab vedotin/bendamustine arm, the dose of bendamustine was reduced from 90 mg/m² to 70 mg/m² based on toxicity. The overall response rate was 100%, and the complete response was 81%, higher than the dacarbazine combination. This arm started later than the other, and the duration of

response was not available. Toxicity was common in the bendamustine arm, with 65% of patients experiencing a grade 3 or higher adverse event. There were 2 deaths on study within 30 days, although they were deemed unrelated to treatment. The toxicity led the authors to conclude, and I would agree, that the brentuximab vedotin/bendamustine combination was not suitable in this population at the tested dose.

Dr Peter Borchmann presented data for a study of targeted BEACOPP variants.⁹ In Germany, escalated BEACOPP is a standard regimen for patients with advanced Hodgkin lymphoma. In the United States, ABVD is the standard regimen because it is associated with less toxicity than escalated BEACOPP. The aim of the study by Dr Borchmann was to decrease toxicity while maintaining efficacy by substituting brentuximab vedotin for certain agents. They evaluated 2 different regimens in 104 patients. The BrECAPP regimen added brentuximab vedotin while removing vincristine and bleomycin. The BrECADD regimen added brentuximab vedotin, removed vincristine, bleomycin, procarbazine, and prednisone, and added dexamethasone and dacarbazine, which is associated with less gonadotoxicity than procarbazine.

The primary endpoint of the study, PET-negative complete response, was similar in both treatment arms, at 86% for BrECAPP and 88% for BrECADD. PFS at 18 months was 95.0% vs 88.6%, respectively.

The regimens differed in terms of toxicity. The rate of grade 3/4 hematologic toxicity was 80% with BrECAPP vs 83% with BrECADD. Grade 3/4 organ toxicities occurred in 8% vs 2% of patients, respectively. No patients in the BrECADD arm developed grade 4 anemia, whereas it occurred in 6% of patients in the BrECAPP arm. Grade 4 thrombocytopenia occurred in 40% of the BrECAPP arm and 29% of the BrECADD arm. In the BrECADD arm, no patients developed severe neurotoxicity, compared with 1 patient in the

BrECAPP arm. The authors concluded that BrECADD was a safer regimen and the one to use in future studies. I agree that BrECADD is preferable to BrECAPP. However, the rate of grade 3/4 hematologic toxicity seen in the BrECADD arm was still very high, at 83%. In addition, only 69% of patients in the BrECADD arm received the full treatment dose by the end of the study. The overall toxicity seen with the BrECADD regimen is still high compared with ABVD, and it would not be a popular regimen to use in the United States.

Dr Ramon Garcia-Sanz presented results from a phase 1/2 study of brentuximab vedotin plus etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) in the first salvage setting.¹⁰ The primary endpoint was complete response rate at the time of transplant. The study population consisted of Hodgkin lymphoma patients who had an inadequate response to frontline treatment and required salvage therapy. The study used the standard ESHAP regimen. Brentuximab vedotin was added at 3 different doses: 0.9 mg/kg, 1.2 mg/kg, and 1.8 mg/kg. The phase 1 portion of the study found no dose-limiting toxicity to brentuximab vedotin. Therefore, 1.8 mg/kg, the standard dose, was used in the phase 2 portion.

Among the 17 evaluable patients, the complete response rate was high, at 94%. There were no difficulties with stem cell collection. There were high rates of hematologic toxicity, but that was expected with the ESHAP regimen. The authors concluded that the combination of brentuximab vedotin and ESHAP was safe, can induce a high complete response rate, and has the typical hematologic toxicity expected with the ESHAP regimen.

Dr Ann LaCasce presented a study evaluating brentuximab vedotin plus bendamustine as first-line salvage therapy in Hodgkin lymphoma patients.¹¹ An interesting aspect of this study is that the patients also received brentuximab vedotin as maintenance therapy while

they were awaiting stem cell transplant. This study is the first to evaluate patients who received brentuximab vedotin before and after transplant.

The original rate of infusion reaction in this study was high, at 58%. Grade 3 reactions occurred in 32% of patients. This rate of infusion reaction is higher than that seen with brentuximab vedotin or bendamustine alone. When this complication became apparent, the study design was amended to add corticosteroids and antihistamines as premedication. This strategy reduced the rate of grade 3 reactions to 17%.

The brentuximab vedotin/bendamustine regimen was efficacious. The overall response rate was 93%, with 73% complete responses. At 18 months, the PFS was 75%. The study also provided outcome data for after transplant. The 18-month PFS was 83%. Stem cells were collected without incident in 95% of patients.

Dr Carmelo Carlo-Stella presented results of a study evaluating bendamustine plus gemcitabine and vinorelbine in the first salvage setting.¹² Bendamustine, gemcitabine, and vinorelbine were given every 3 weeks for a total of 4 cycles in 59 patients. The response rate was good, with an overall response of 83% and 73% complete responses. The long-term outcome, however, was less positive. The 2-year PFS was 51%, which appears lower than what the historical control would be. The regimen was safe. Stem cell collection was not possible in only 3.5% of patients. There was no engraftment delay.

Dr Stephen Ansell presented an update to a previous phase 1 study evaluating the PD-1 inhibitor nivolumab in patients with Hodgkin lymphoma.¹³ As reported at the 2014 ASH meeting, the overall response was 87% in the heavily pretreated population. This follow-up analysis showed that the responses were very durable. The median PFS has not yet been reached. The response was fairly durable even among patients who discontinued treatment owing

to remission or toxicity. Most of the immunologic toxicity—rash, diarrhea, and colitis—resolved after nivolumab was discontinued. There were poor outcomes, however, among the 5 patients who responded to nivolumab and then proceeded to allogeneic transplant. Three of these patients died from veno-occlusive disease (VOD) or graft-vs-host disease (GVHD). There appeared to be a higher incidence of VOD and acute GVHD.

T-Cell Lymphoma

Dr Owen O'Connor presented results from LUMIERE, a large, randomized, phase 3 study comparing the oral kinase A inhibitor alisertib vs pralatrexate, romidepsin, or gemcitabine in patients with treatment-naïve PTCL.¹⁴ In a phase 2 trial, alisertib was associated with a good response rate in patients with relapsed T-cell lymphoma.¹⁵ LUMIERE had 2 different endpoints: overall response rate and PFS. The results were disappointing. The response rate was 35% for alisertib

vs 46% for the other therapies. PFS was 120 days for alisertib and 104 days for the other therapies. The results from this study indicate that alisertib should not be used in the management of frontline peripheral T-cell lymphoma.

Dr Fredrik Ellin presented results from a retrospective, population-based study that added etoposide to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).¹⁶ Data were gathered from the Swedish and Danish Registry for patients with anaplastic large-cell lymphoma (ALCL). Among the 371 patients, one-third were ALK-positive. This study confirmed previous data showing that ALK-positive patients have better outcomes.¹⁷ The 5-year PFS was 64% for ALK-positive patients vs 32% for ALK-negative patients. Patients with a high score on the International Prognostic Index had a worse outcome. An interesting finding was that the addition of etoposide increased overall survival, with a hazard ratio of 0.48. This large study is the first to show this improvement. A caveat to consider is that this study was retrospective, not prospective.

ABSTRACT SUMMARY Bortezomib Maintenance Therapy After Induction With R-CHOP, ARA-C and Autologous Stem Cell Transplantation in Newly Diagnosed MCL Patients, Results of a Multicenter Phase II HOVON Study

Maintenance therapy with bortezomib after autologous SCT in mantle cell lymphoma patients was investigated in a phase 2 study (Abstract 339). Patients with newly diagnosed mantle cell lymphoma received 3 cycles of R-CHOP followed by 2 cycles of high-dose cytarabine plus rituximab; then carmustine, etoposide, cytarabine, and melphalan (BEAM); and, for patients with a PR or CR, autologous SCT. Patients with a CR or PR after transplant with adequate platelet and neutrophil counts were randomized to maintenance bortezomib (1.3 mg/m² once every 2 weeks for 24 months) or no further treatment. The patients had a median age of 57 years (range, 34-66 years), and 78% were male. Mantle cell lymphoma IPI scores were low in 57%, intermediate in 32%, and high in 10%. Sixty eligible patients were randomly assigned to receive bortezomib maintenance or no further treatment. Among the 30 patients who received bortezomib maintenance, 15 completed the 2 years of treatment. Reasons for discontinuation included excessive toxicity (n=6), disease progression or relapse (n=4), nonadherence (n=3), and second malignancy (n=1). With a median follow-up of 50 months, median 4-year event-free survival for all patients in the intent-to-treat population was 61%, and median 4-year OS was 78%. Median 4-year event-free survival was 72% without bortezomib vs 71% with bortezomib. Rates of 4-year OS were 90% vs 93%, respectively.

A phase 1/2 study presented by Dr Ahmed Sawas evaluated the addition of brentuximab vedotin to bendamustine in a population of heavily pretreated patients with relapsed/refractory Hodgkin lymphoma or ALCL.¹⁸ The study evaluated brentuximab vedotin at doses of 1.2 mg/kg or 1.8 mg/kg and bendamustine at doses of 70 mg/m², 80 mg/m², or 90 mg/m². No dose-limiting toxicities were found, so that at the end of the trial, the dose was 1.8 mg/kg for brentuximab vedotin and 90 mg/m² for bendamustine.

The aim of the study, to show that the combination of brentuximab vedotin plus bendamustine was safe, was met. The overall response rate was 67%, and the complete response rate was 19%. These response rates are low, but it should be noted that the patients were heavily pretreated. Many patients had prior exposure to brentuximab vedotin.

Dr John Leonard presented a study that added bortezomib to R-CHOP in patients with diffuse large B-cell lymphoma (DLBCL).¹⁹ It is known that patients with the ABC subtype of DLBCL have inferior outcomes to R-CHOP chemotherapy. The ABC subtype of DLBCL relies heavily on the NF-kappa-B pathway. Bortezomib is a proteasome inhibitor, but it also downregulates NF-kappa-B downstream. This study randomized patients with the ABC subtype to receive R-CHOP only or R-CHOP plus bortezomib. The goal was to show that PFS would be better for patients who received bortezomib. Unfortunately, the study did not meet this goal. The addition of bortezomib was associated with a nonsignificant improvement in complete response, at 59% vs 53%, and in PFS, at 82% vs 78%. Thrombocytopenia was more common in the bortezomib arm.

The rate of PFS among the patients who received R-CHOP without bortezomib was 78%, which is high for patients with the ABC subtype of DLBCL. The authors sug-

gested that the improvement seen with bortezomib failed to meet significance because this prospective study was unable to enroll high-risk patients. Patients who had significant disease burden and disease kinetics were unable to wait for completion of study screening procedures and ultimately could not enroll in this trial.

Dr Christopher Yasenachak presented results from a study evaluating R-CHOP plus brentuximab vedotin in DLBCL.²⁰ The 3-year PFS for patients receiving R-CHOP is approximately 70%.²¹ This rate is lower, at 55%, among patients who have a high-risk International Prognostic Index (IPI) score. In an attempt to improve this rate, the study added brentuximab vedotin to R-CHOP. A prior study showed that brentuximab vedotin, an anti-CD30 antibody-drug conjugate, was effective in CD30-negative patients in the relapsed/refractory setting.²² In the current study presented at ASH, the complete response rate was 76% in CD30-positive patients vs 63% in CD30-negative patients. The 50-month rate of PFS was 83% in CD30-positive patients vs 54% in CD30-negative patients. Therefore, the addition of brentuximab vedotin to R-CHOP appeared to increase complete response and PFS in CD30-positive DLBCL patients with a high-risk IPI score. These promising results have led to a larger, randomized phase 2 study comparing R-CHOP vs R-CHOP plus brentuximab vedotin.

Dr John Gericitano presented the results of a phase 1 trial evaluating the safety, tolerability, and response of the BCL2 inhibitor venetoclax in a variety of lymphoma subtypes, including DLBCL, mantle cell lymphoma, follicular lymphoma, Waldenström macroglobulinemia, and marginal zone lymphoma.²³ The study found that venetoclax was well tolerated. Responses were seen at all dose levels in mantle cell lymphoma but at only the higher dose levels for DLBCL and follicular lymphoma. It worked particularly well in mantle cell lymphoma, where the overall response rate was 75%.

The overall response rate was 100% in Waldenström macroglobulinemia and 67% in marginal zone lymphoma. In follicular lymphoma and DLBCL, however, a higher dose was needed to obtain a response. The overall response rates were 18% for DLBCL and 38% for follicular lymphoma. An interesting finding is that complete responses appeared to be durable, lasting several weeks to months. Venetoclax is an exciting agent, particularly for mantle cell lymphoma and marginal zone lymphoma. For DLBCL and follicular lymphoma, venetoclax will probably need to be combined with other agents to improve response rates. Since venetoclax is so well tolerated, it should work well in combination with other therapies.

Mantle Cell Lymphoma

Dr Jeanette Doorduijn presented results from the HOVON (Hemato-Oncologie voor Volwassenen Nederland) trial, which examined whether bortezomib administered posttransplant can increase event-free survival.²⁴ The enrolled patients had untreated mantle cell lymphoma. They received 3 cycles of R-CHOP and 2 cycles of rituximab plus Ara-C. They underwent transplant with a BEAM regimen. They were then randomly assigned to receive placebo or bortezomib at 1.3 mg/m² given intravenously once a week, every 2 weeks, for 2 years. Although the study began with 140 patients, the randomized group included 60 patients.

At the end of the study, for all patients, the 4-year PFS was 61%, and the overall survival was 78%. The 4-year event-free survival was similar for both arms, at 72% without bortezomib vs 71% with bortezomib. The overall survival was 90% vs 93%, respectively. The study therefore showed that bortezomib did not improve event-free survival. However, there were 2 limitations to this study. The first is that the treatment arms were not well balanced. In the placebo arm, 70% of patients had a low-risk MIPI score vs 50% in the bort-

ezomib arm. Another limitation is that only half the patients in the bortezomib arm completed treatment. Therefore, it cannot be concluded based on this study alone that posttransplant bortezomib maintenance therapy is not effective.

I presented results from an interim analysis of a multicenter study evaluating whether bortezomib and rituximab can increase event-free survival after transplant in patients with mantle cell lymphoma.²⁵ This study was not randomized. All patients received bortezomib at 1.3 mg/kg subcutaneously once a week for 4 weeks every 3 months and rituximab at 375 mg/m² once a week for 4 weeks every 6 months. We also assessed minimal residual disease, by using intrapatient quantifiable CCND1 mRNA.

The interim analysis showed a 2-year event-free survival of 100%. The intrapatient quantifiable CCND1 messenger mRNA level did not vary by more than 5%, showing that this method provides reliable monitoring of minimal residual disease. Thus far, this treatment appears safe and promising. This study is the only one evaluating rituximab plus bortezomib maintenance posttransplant. More follow-up is needed.

Disclosure

Dr Chen is a consultant for Seattle Genetics, Millennium, and Genentech, and a member of their speakers bureaus. He has received research funding from Seattle Genetics and Millennium.

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